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 B₆) 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-chlorophenyl 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)-1H-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, 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 SCH₂, CH=N, CH-pyrazole and NH groups, respectively; Scheme 1.

Cyclocondensation of compound 4a with hydrazone halides 5e,f[32-35] 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 CH₃ (triplet) and CH₂.

Scheme 1, Synthesis of some new hydrazones.

Scheme 2, Synthesis of 1,3,4 thidiazoles.
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(q uartet) of ester group, beside a singlet signal at δ 3.27 ppm for methyl protons, two new singlet signals appeared at δ 8.62 & 9.25 ppm related to CH=N and CH-pyrazole, respectively. Similarly, 1,3,4-thiadiazoles 7a-7d were accomplished via the reaction of compound 4b with hydrazonoyl halides 5a-5d [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 lacks 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-d₆) 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-d₆) 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 CH₃ 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 CH₃ and COCH₃ 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 weak 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 1H 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.

### Table 1: Response of various microorganisms to some of synthesized compounds.

| Compd. NO. | 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.
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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\textsubscript{10}H\textsubscript{8}Cl\textsubscript{2}N\textsubscript{2}O\textsubscript{2}S(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-1H-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, ν cm\textsuperscript{-1}): 3039, 2978 (CH), 1735 (C=O), 1597 (C=N); \textsuperscript{1}H NMR: δ 1.50 (t, 3H, J = 7Hz, CH\textsubscript{3}), 3.27 (s, 3H, CH\textsubscript{3}), 4.21 (q, 2H, J = 7Hz, CH\textsubscript{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\textsubscript{29}H\textsubscript{27}N\textsubscript{2}O\textsubscript{2}S (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-1H-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, ν cm\textsuperscript{-1}): 3101, 2978 (CH), 1734 (C=O), 1597 (C=N); \textsuperscript{1}H NMR: δ 4.51 (s, 3H, CH\textsubscript{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\textsubscript{35}H\textsubscript{25}N\textsubscript{2}O\textsubscript{2}S (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)-1H-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, ν cm\textsuperscript{-1}): 3059, 2932 (CH), 1732 (C=O), 1597 (C=N); \textsuperscript{1}H NMR: δ 1.31 (t, 3H, J = 7Hz, CH\textsubscript{3}), 4.35 (q, 2H, J = 7Hz, CH\textsubscript{2}), 7.30-8.14 (m, 13H, Ar-H), 8.67 (s, 1H, CH=N), 9.14 ppm (s, 1H, CH-pyrazole). Anal. Calcd. for C\textsubscript{30}H\textsubscript{28}ClN\textsubscript{2}O\textsubscript{2}S(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)-1H-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, ν cm\textsuperscript{-1}): 3062, 2970 (CH), 1681 (C=O), 1597 (C=N); \textsuperscript{1}H NMR: δ 2.77 (s 3H, COCH\textsubscript{3}), 7.27-7.59 (m, 14H, Ar-H), 7.82 (d, 1H, J = 8 Hz), 8.46 ppm (s, 1H, CH=N). Anal Calcd. for C\textsubscript{32}H\textsubscript{24}ClN\textsubscript{2}O\textsubscript{2}S(599.01): 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)-1H-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, ν cm\textsuperscript{-1}): 3068, 2927 (CH), 1666 (C=O), 1593 (C=N); \textsuperscript{1}H NMR: δ 2.40 (s, 3H, CH\textsubscript{3}), 2.66 (s 3H, COCH\textsubscript{3}), 7.26-7.34 (m, 3H, Ar-H), 7.61-7.78 (m, 7H, Ar-H), 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\textsubscript{34}H\textsubscript{26}ClN\textsubscript{2}O\textsubscript{2}S (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)-1H-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, ν cm\textsuperscript{-1}): 3050, 2935 (CH), 1651 (C=O), 1620 (C=N); \textsuperscript{1}H NMR: δ 7.31-8.24 (m, 19H, Ar-H), 8.45 (s, 1H, CH=N), 9.16 ppm (s, 1H, CH-pyrazole). Anal Calcd. for C\textsubscript{35}H\textsubscript{28}ClN\textsubscript{2}O\textsubscript{2}S (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 acetocetate, 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-1H-pyrazol-4-yl)-2-methyl-6-(benzofuran-2-yl) pyridine-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); ¹H NMR: δ 1.06 (t, 3H, J = 7.5 Hz, CH₃), 2.24 (s, 3H, CH₃), 4.21 (q, 2H, J = 7.5 Hz, CH₂), 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 C₃₂H₂₂N₂O (499.56): C, 76.94; H, 5.04; N, 8.31. Found: C, 76.84; H, 5.14; N, 8.31.

**6-(Benzofuran-2-yl)-4-(1,3-diphenyl-1H-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); ¹H 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 C₅₃H₃₅N₃O (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); ¹H NMR: δ 2.63 (s, 3H, CH₃), 2.89 (s, 3H, COCH₃), 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 C₁₃H₁₁N₂O₂ (469.53): C, 79.30; H, 4.94; N, 8.95. Found: C, 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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في هذه الدراسة، تم تحضير سلسلة جديدة من مشتقات 1,3,4-ثياديازول ابتداءً من بيرازول 4-أ،ب. وهكذا، فإن تفاعل المركب 3 أ،ب مع بنزيل الهيدرازين أعطي مشتقات كرويدايوات 4 أ،ب. عند معالجة المركب 4 أ،ب باشادات الهيدرازونويل 5 أ،ب، تكوّنت مشتقات الهيدرازونويل 6 أ،ب بينما أدي تفاعل المركب 4 أ،ب مع هيدرات الهيدرازونويل 5 أ،ب، تكوّنت مشتقات الهيدرازونويل 7 أ،ب من ناحية أخرى، أمكن تحضير مشتقات البيريدين الجديدة 9 أ،ب من خلال تفاعل الشالكون 8 مع الكواشف النيوكليفية المختلفة مثل الإيثيل أسيتو أسيتات والبنزويل أسيتو نيتريل والأسيتو نيتريل. كما تم اثبات التركيب الكيميائي للمركبات التي تم تحضيرها حديثاً بالتحاليل الطيفية، وتم فحص نشاط بعض المركبات ضد بعض الميكروبات، وأوضحت النتائج أن كل المركبات ليس لها نشاط ما عدا المركب 6 أ والذي كان له نشاط ضعيف ضد تركيبات المختبرة والمركب 6 ب كان له نشاط ضعيف ضد البكتيريا موجبة الجرام باسكلر سبيكلس والمركب 7 ج والذي كان له نشاط ضعيف ضد البكتيريا سالبة الجرام شايروكيا كولاي.