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Short communication

Synthesis and antimicrobial evaluation of 1-(benzofuran-2-yl)-4-nitro-3-arylbutan-1-ones and 3-(benzofuran-2-yl)-4,5-dihydro-5-aryl-1-[4-(aryl)-1,3-thiazol-2-yl]-1*H*-pyrazoles

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ABSTRACT

2-Acetylbenzofuran **1** on treatment with substituted aldehydes affords the corresponding chalcones **2a–c**. Treatment of the chalcones with nitromethane under Michael addition condition furnished the corresponding Michael adducts **3a–c**. Cyclocondensation of the chalcones **2a** and **2b** with thiosemicarbazide under basic refluxing conditions gave 3-(benzofuran-2-yl)-5-(4-aryl)-4,5-dihydropyrazole-1-carbothioamides **4a**,**b**. The pyrazolines **7a–d** were synthesized by treating **4a**,**b** with phenacyl bromides in refluxing ethanol. All the synthesized compounds were screened for their antibacterial and antifungal activities at 100 μg concentration. Some of our compounds showed excellent antimicrobial activities than control drugs.

1. Introduction

Widespread interest in the chemistry of benzofurans in a large number of natural products has attracted due to their biological activities and their potential applications as pharmacological agents. Several benzofuran ring systems bearing various substituents at the C-2 position are widely distributed in nature, e.g., ailanthoidol, is a neolignan derivative, has been reported to have antiviral, antioxidant and antifungal activities [1]. Furthermore, most of compounds prepared from 2-acetylbenzofurans have antimicrobial, antitumor, antiflammatory, fungicidal weed-killing activity, and used for treatment of cardiac arrhythmias [2–9]. On the other hand, compounds including pyrazole nucleus are known to possess analgesic, anti-inflammatory, antipyretic, antiarrhythmic, muscle relaxant, psychoanaleptic, anticonvulsant, hypotensive, monoamine oxidase inhibitor, antidiabetic and antibacterial activities [10–17]. Pyrazole derivative celebrex is a potential anti-inflammatory drug [18]. In addition, 1,3-thiazole derivatives have been reported to possess tuberculostatic, antibacterial and antifungal activities [19–25]. It was also reported that fentiazac, 1,3-thiazole derivative, is potent antinflammatory agent [26] (Fig. 1). Recently, we reported that, some of 3-substituted-5-(benzofuran-2-yl)-pyrazole derivatives showed significant antimicrobial activities towards various microorganisms [27]. In the interest of the above suggestion, and in continuation of our previous work in the synthesis of biologically active heterocycles [28–33], we planned to synthesize 1-(benzofuran-2-yl)-4-nitro-3-arylbutan-1-ones and thiazolyl-pyrazoline derivatives for antimicrobial evaluation.

2. Chemistry

The synthetic route of compounds is outlined in Scheme 1 and Scheme 2. In the present work, 1-(2-benzofuryl)-3-aryl-2-propen-1-ones **2a–c** were prepared by reaction of 2-acetylbenzofuran (**1**) with aromatic aldehyde in accordance with the method described in the literature [34].

The 1-(benzofuran-2-yl)-4-nitro-3-arylbutan-1-ones **3a–c** were prepared by reacting equimolecular amounts of **2a–c** with nitromethane in boiling ethanol and in the presence of piperidine as a basic catalyst (Scheme 1).

On the other hand, the reaction of 1-(2-benzofuryl)-3-aryl-2-propen-1-ones **2a** or **2b** with thiosemicarbazide in refluxing ethanol, in the presence of excess sodium hydroxide, afforded 3-(2-benzofuryl)-5-aryl-1-thiocarbamoyl-2-pyrazolines **4a** and **4b**, respectively. The condensation of pyrazolines **4a** or **4b** with the appropriate 1-aryl-2-bromethanone **5a** or **5b** resulted in the formation of 3-(benzofuran-2-yl)-1-[4-(aryl)-1,3-thiazol-2-yl]-4,5-dihydro-5-aryl-1*H*-pyrazoles **7a–d** through the intermediate **6a–d** (Scheme 2).

Analytical and spectral data (^{1}H NMR, IR, and MS) confirmed the structures of the new compounds.

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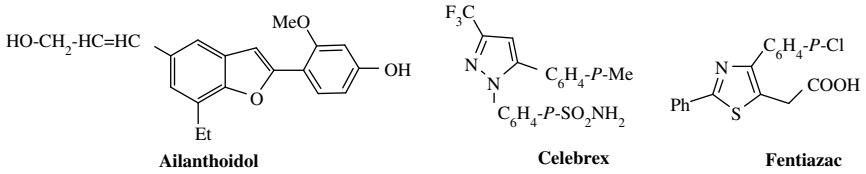


Fig. 1. Chemical structures of ailanthoidol, celebrex and fentiazac.

3. Biology

The synthesized compounds were tested, at 100 μg concentration, for their in vitro antimicrobial activity against the Gram-positive bacteria *Staphylococcus aureus*, *Bacillus subtilis*, the Gram-negative bacteria *Escherichia coli*, and fungi *Candida albicans* and *Aspergillus niger*. The primary screen was carried out by agar disc-diffusion method [35] using nutrient agar medium. Amoxicillin and Flucanazol were used as control drugs. The observed data on the antimicrobial activity of the compounds and control drugs are given in Table 1.

4. Results, discussion and conclusion

In this present work, a series of nine new benzofuran derivatives were synthesized starting from 1-(2-benzofuryl)-3-aryl-2-propen-1-ones **2a**-**c** synthesized according to the literature method [34]. Thus, we have obtained 1-(benzofuran-2-yl)-4-nitro-3-arylbutan-1-ones **3a**–**c** through the treatment of **2a**–**c** with nitromethane under Michael addition conditions. The IR spectra of the latter compounds showed, in each case, stretching band of C=O group in the region 1660–1665 cm^{-1}. Their ^1H NMR spectra revealed, in each case, the signals of two CH_2 groups in the region 2.30–2.33 ppm and 3.50–3.52 ppm in addition to the multiplet signal of CH–Ar in the region 4.29–4.31 ppm.

Several authors have been reported the synthesis of 1-(thiazol-2-yl)pyrazolines from the corresponding methyl ketones [16,24,36]. In the same sense, the reaction of **2a**,**b** with thiosemicarbazide in refluxing ethanol, in the presence of sodium hydroxide, afforded 3-(2-benzofuryl)-5-aryl-1-thiocarbamoyl-2-pyrazolines **4a**, **4b**, respectively. The structures of compounds **4a** and **4b** were confirmed under the bases of their spectral data. For example, The IR spectrum of compound **4a** showed the stretching band of C=S at 1278 cm^{-1} and the absorption bands of NH_2 group at 3475 and 3345 cm^{-1}, its ^1H NMR spectrum showed the signals of H_a, H_b, H_x of pyrazoline ring as doublet of doublet in the regions 3.09–3.30, 4.01–4.10 and 5.59–5.69 ppm, respectively, with coupling constants $J_{ab} = 17.07$, $J_{ax} = 6.30$ and $J_{bx} = 11.05$ Hz, in addition to the D_2O exchangeable signal of amino group at δ 8.34.

The reaction of pyrazoline **4a** or **4b** with 1-aryl-2-bromoethanone **5a**,**b** in refluxing ethanol gave thiazolyl-pyrazolines **7a**–**d** via the non-isolable intermediate **6a**–**d**. In the ^1H NMR spectra of the latter compounds the CH_2 protons of pyrazoline ring resonated as two doublet of doublet signals at 3.23–3.58 ppm (H_a) and 3.80–3.96 ppm (H_b). The CH (H_x) proton appeared as a doublet of doublet at 5.57–5.74 ppm due to vicinal coupling with the two magnetically non-equivalent protons of the methylene group at position 4 of pyrazoline ring ($J_{ab} = 17.0$–17.5 Hz, $J_{ax} = 6.9$–7.4 Hz, $J_{bx} = 11.94$–12.1 Hz). The H_5-proton of thiazole was observed as a singlet in the region 6.79–6.85 ppm. The mass spectra of compounds **7a**–**d** revealed, in each case, a peak corresponding to their molecular ion peaks.

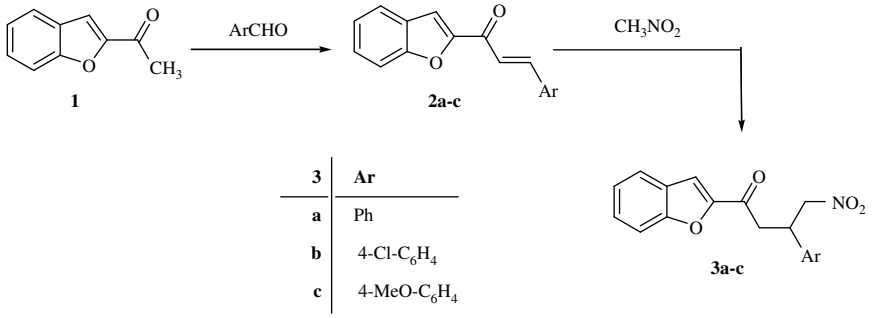
The results of the compounds of preliminary antibacterial testing are shown in Table 1. The results revealed that majority of the synthesized compounds showed varying degrees of inhibition against the tested microorganisms. In general, the inhibitory activity against the Gram-negative bacteria was higher than that of the Gram-positive bacteria. The 1-(thiazol-2-yl)pyrazoline **7a** showed excellent activity against Gram-negative bacteria (inhibitory zone 25 mm), good activity against Gram-positive bacteria (inhibitory zone 20 mm). On the other hand, compounds **3a**–**c** and **7c** showed weak activities against *E. coli*. The antifungal activities of these compounds against *C. albicans* and *A. niger* are shown in Table 1. Compounds **3a**, **3c**, **7c** and **7d** showed inhibition zones and therefore antifungal activities against *C. albicans* more than the reference sample Flucanazol, while compound **3b**, showed similar antifungal activity against *C. albicans*. Most of the tested compounds showed none or weak antifungal activity against *A. niger*.

According to structure–activity relationships (SAR), it can be concluded that benzofuran, pyrazoline, and thiazole moieties are essential for the antimicrobial activity.

5. Experimental

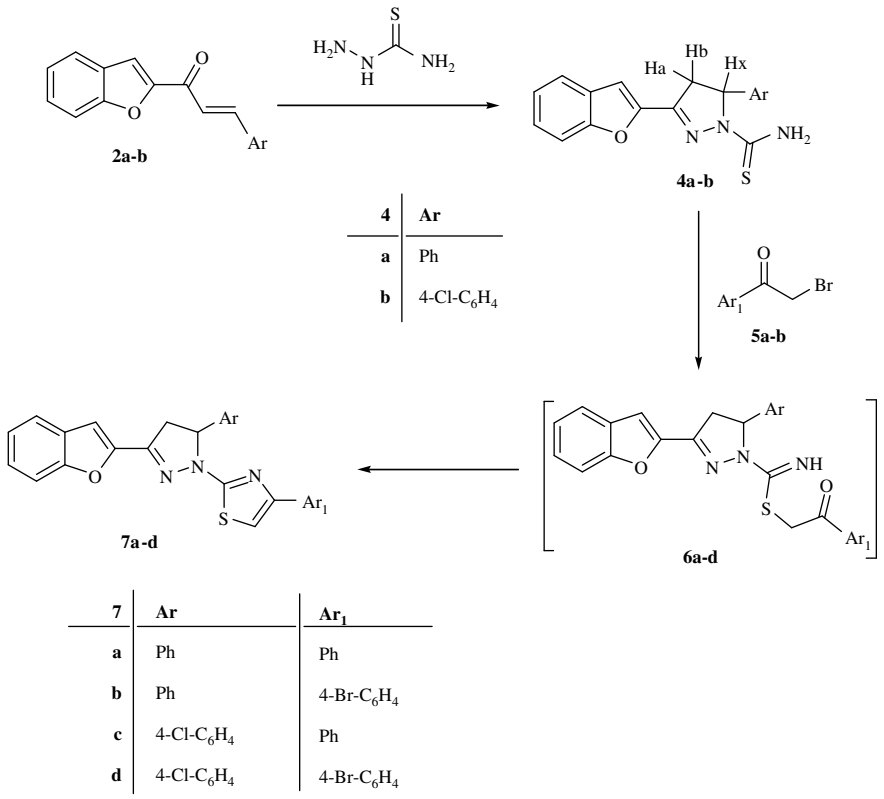
5.1. Chemistry

All melting points were taken on Electrothermal IA 9000 series digital melting point apparatus. The IR spectra (KBr) were recorded on a Shimadzu CVT-04 spectrophotometer. The ^1H NMR spectra were recorded at 270 MHz on a Varian EM-360 spectrometer using TMS as an internal standard. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet. Chemical shift (δ) values are given in parts per million and coupling constants (J) in Hertz. The mass spectra were performed using a Varian MAT CH-5 spectrometer (70 eV). All reactions were followed by TLC (silica gel, aluminum sheets 60 F_{254}, Merck). 2-Acetylbenzofuran (**1**) was prepared according to reported method [37].



3	Ar
a	Ph
b	4-Cl-C_6H_4
c	4-MeO-C_6H_4

Scheme 1. Route to 1-(benzofuran-2-yl)-4-nitro-3-arylbutan-1-ones.



Scheme 2. Synthetic route to 1,3-thiazolyl-pyrazoles.

5.1.1. General procedure for the synthesis of the compounds

*5.1.1.1. 1-(2-Benzofuryl)-3-aryl-2-propen-1-ones (**2a–c**).* A mixture of 2-acetylbenzofuran (0.05 mol) (**1**), appropriate aromatic aldehyde (0.05 mol) and 10% aqueous sodium hydroxide (10 mL) in ethanol (30 mL) was stirred at room temperature for about 3 h. The resulting solid was filtered off, washed with water, dried and crystallized from ethanol [35].

*5.1.1.2. 1-(Benzofuran-2-yl)-4-nitro-3-arylbutan-1-ones (**3a–c**).* A mixture of appropriate 1-(2-benzofuryl)-3-aryl-2-propen-1-ones (**2a-c**) (10 mmol), nitromethane (0.93 g, 15 mmol) and piperidine (0.5 mL) in absolute ethanol (30 mL) was heated at reflux temperature for 3 h, left to cool, the formed solid was filtered off, dried and crystallized from ethanol.

*5.1.1.2.1. 1-(Benzofuran-2-yl)-4-nitro-3-phenylbutan-1-one (**3a**).* M.p. 200–202 °C; Yield, 76%. IR (cm^{-1}): 1660 (C=O, st.). ^1H NMR (DMSO-d_6): 2.32 (d, 2H, CH_2–C=O); 3.50 (d, 2H, CH_2–NO_2); 4.31 (m, 1H, CH–C_6H_5); 6.78 (s, 1H, furan-H); 7.21–7.89 (m, 9H, Ar-H). MS (*m*/*z*): 309 [M^+].

*5.1.1.2.2. 1-(Benzofuran-2-yl)-3-(4-chlorophenyl)-4-nitrobutan-1-one (**3b**).* M.p. 195–196 °C; Yield, 81%. IR (cm^{-1}): 1662 (C=O, st.). ^1H NMR (DMSO-d_6): 2.33 (d, 2H, CH_2–C=O); 3.52 (d, 2H, CH_2–NO_2); 4.29 (m, 1H, CH–C_6H_4–4-Cl); 6.76 (s, 1H, furan-H); 7.22–7.90 (m, 8H, Ar-H). MS (*m*/*z*): 344 [$M^+ + 1$], 343 [M^+].

*5.1.1.2.3. 1-(Benzofuran-2-yl)-3-(4-methoxyphenyl)-4-nitrobutan-1-one (**3c**).* M.p. 170–172 °C; Yield, 78%. IR (cm^{-1}): 1665 (C=O, st.). ^1H NMR (DMSO-d_6): 2.30 (d, 2H, CH_2–C=O); 3.51 (d, 2H, CH_2–NO_2); 3.68 (s, 3H, –OCH_3); 4.30 (m, 1H, CH–C_6H_4–4-OMe); 6.77 (s, 1H, furan-H); 7.21–7.88 (m, 8H, Ar-H). MS (*m*/*z*): 339 [M^+].

*5.1.1.3. 3-(Benzofuran-2-yl)-4,5-dihydro-5-arylpyrazole-1-carbothioamide (**4a**,**b**).* To a suspension of 1-(2-benzofuryl)-3-aryl-2-propen-1-one derivatives **2a**,**b** (0.01 mol) and sodium hydroxide (1.0 g, 0.025 mol) in ethanol (50 mL), thiosemicarbazide (1.1 g, 0.012 mol) was added. The mixture was refluxed for 6 h, then left to cool; the formed solid product was filtered off, washed with ethanol, dried, and then crystallized from ethanol.

*5.1.1.3.1. 3-(benzofuran-2-yl)-4,5-dihydro-5-phenylpyrazole-1-carbothioamide (**4a**).* M.p. 230–231 °C; Yield, 84%. IR (cm^{-1}): 1278 (C=S); 3475, 3345 (NH_2). ^1H NMR (DMSO-d_6): 3.09–3.30 (dd, 1H, H_a); 4.01–4.10 (dd, 1H, H_b); 5.59–5.69 (dd, 1H, H_x); 7.15 (s, 1H, furan-H); 7.21–7.72 (m, 9H, Ar-H); 8.34 (s, D_2O exchangeable, 2H, NH_2) (J_{ab} = 17.07; J_{ax} = 6.30; J_{bx} = 11.09 Hz). MS (*m*/*z*): 321 [M^+].

*5.1.1.3.2. 3-(Benzofuran-2-yl)-5-(4-chlorophenyl)-4,5-dihydropyrazole-1-carbothioamide (**4b**).* M.p. 217–218 °C; Yield, 86%. IR (cm^{-1}): 1276 (C=S); 3472, 3344 (NH_2). ^1H NMR (DMSO-d_6): 3.10–3.30 (dd, 1H, H_a,); 4.00–4.10 (dd, 1H, H_b); 5.59–5.65 (dd, 1H, H_x); 7.10 (s, 1H, furan-H); 7.20–7.71(m, 8H, Ar-H); 8.36 (s, D_2O exchangeable, 2H, NH_2) (J_{ab} = 17.02; J_{ax} = 6.22; J_{bx} = 10.95 Hz). MS (*m*/*z*): 321 [M^+].

Table 1
The in vitro antimicrobial activity of compounds **3**–**7**.

Compounds	Zone of inhibition (mm)				
	S. aureus	*B. subtilis*	*E. coli*	*C. albicans*	*A. niger*
3a	0	0	12	30	0
3b	0	0	12	20	15
3c	0	0	12	25	0
4a	0	0	0	5	0
4b	0	12	15	0	15
7a	17	0	25	0	0
7b	0	0	0	0	0
7c	0	0	12	25	15
7d	0	0	0	25	0
Amoxicillin®	20	20	20	–	–
Flucanazol®	–	–	–	20	20

*5.1.1.4. 3-(Benzofuran-2-yl)-1-(4-(4-aryl)thiazol-2-yl)-5-(4-aryl)-4,5-dihydro-1H-pyrazoles (**7a–d**).* To a suspension of compounds **4a**,**b** (0.01 mol) in ethanol (15 mL) the appropriate 1-aryl-2-bromoethanones **5a** or **5b** (0.01 mol) was added and heated under reflux for 1 h. After cooling, the precipitate was collected by suction filtration and purified by crystallization from methanol.

*5.1.1.4.1. 3-(Benzofuran-2-yl)-4,5-dihydro-5-phenyl-1-(4-phenylthiazol-2-yl)-1H-pyrazole (**7a**).* M.p. 219–220 °C; Yield, 90%. IR (cm^{-1}): 1622 (C═N, st.). ^1H NMR (DMSO-d_6): 3.22–3.57 (dd, 1H, H_a); 3.80–3.95 (dd, 1H, Hb); 5.57–5.74 (dd, 1H, H_x); 6.81 (s, 1H, thiazole-H); 7.34–7.72 (m, 14H, Ar-H); 7.23(s, 1H, furan-H); ($J_{ab} = 17.2$; $J_{ax} = 7.0$; $J_{bx} = 12.1$ Hz). MS (*m*/*z*): 421 [M^+].

*5.1.1.4.2. 3-(Benzofuran-2-yl)-1-(4-(4-bromophenyl)thiazol-2-yl)-4,5-dihydro-5-phenyl-1*H*-pyrazole (**7b**).* M.p. 212–213 °C; Yield, 88%. IR (cm^{-1}): 1618 (C═N, st.). ^1H NMR (DMSO-d_6): 3.23–3.56 (dd, 1H, H_a); 3.80–3.96 (dd, 1H, H_b); 5.57–5.70 (dd, 1H, H_x); 6.79 (s, 1H, thiazole-H); 7.32–7.71 (m, 13H, Ar-H); 7.73 (s, 1H, furan-H); ($J_{ab} = 17.1$; $J_{ax} = 6.94$; $J_{bx} = 11.98$ Hz). MS (*m*/*z*): 501 [$M^+ + 2$]; 500 [$M^+ + 1$]; 499 [M^+].

*5.1.1.4.3. 3-(Benzofuran-2-yl)-5-(4-chlorophenyl)-4,5-dihydro-1-(4-phenylthiazol-2-yl)-1H-pyrazole (**7c**).* M.p. 152–153 °C; Yield, 90%. IR (cm^{-1}): 1624 (C═N, st.). ^1H NMR (DMSO-d_6): 3.25–3.58 (dd, 1H, Ha); 3.82–3.96 (dd, 1H, H_b); 5.58–5.73 (dd, 1H, Hx); 6.85 (s, 1H, thiazole-H); 7.25–7.70 (m, 13H, Ar-H); 7.72 (s, 1H, furan-H); ($J_{ab} = 17.5$; $J_{ax} = 7.04$; $J_{bx} = 12.1$ Hz). MS (*m*/*z*): 456 [$M^+ + 1$]; 455 [M^+].

*5.1.1.4.4. 3-(Benzofuran-2-yl)-1-(4-(4-bromophenyl)thiazol-2-yl)-5-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazole (**7d**).* M.p. 170–171 °C; Yield, 82%. IR (cm^{-1}): 1620 (C═N, st.). ^1H NMR (DMSO-d_6): 3.24–3.57 (dd, 1H, H_a); 3.80–3.92 (dd, 1H, Hb); 5.55–5.74 (dd, 1H, H_x); 6.80(s, 1H, thiazole-H); 7.19–7.71(m, 12H, Ar-H); 7.72(s, 1H, furan-H); ($J_{ab} = 17.2$; $J_{ax} = 7.01$; $J_{bx} = 11.95$ Hz). MS (*m*/*z*): 534 [$M^+ + 2$]; 533 [$M^+ + 1$]; 532 [M^+].

5.2. Biological assays

Preliminary antimicrobial activities of **3**–**7** compounds were tested by Agar disc-diffusion method [35]. Sterile filter paper discs (6 mm diameter) moistened with the test compound solution in DMSO of specific concentration 100 μg were carefully placed on the agar culture plates that had been previously inoculated separately with the microorganisms. The plates were incubated at 37 °C and the diameter of the growth inhibition zones were measured after 24 h in case of bacteria and after 48 h in case of fungi.

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