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Microwave Assisted Synthesis of Substituted (*Z*)-2-{[1-Phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl]methylene}benzofuran-3(2*H*)-ones and Their Antimicrobial Activity[1]

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Abstract—Aurones, pyrazole and thiophene scaffolds are known for their potential antimicrobial activity. Herein, we have synthesized hybrid compounds containing three substituted (*Z*)-2-{[1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl]methylene}benzofuran-3(2*H*)-ones that had been produced from substituted (*E*)-1-(2-hydroxyphenyl)-3-[1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl]prop-2-en-1-ones in high yields. All synthesized compounds were tested in vitro for their antimicrobial activity. Several of those demonstrated promising activity against some fungal and bacterial strains.

Keywords: antimicrobial activity, aurone, microwave irradiation, pyrazole

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Among flavonoids [1], aurones, (*Z*)-2-benzylidenebenzofuran-3(2*H*)-ones, constitute the less studied subclass that occurs rarely in nature. Aurones are responsible for pigmentation of flowers and fruits, especially for the bright yellow colour of flowers and possess insect antifeedant [2], anticancer [3], anti-inflammatory [4], cytotoxic [5], antibacterial [6], and inhibitory activity against a variety of enzymes and proteins [7]. Only few studies on the antioxidant activity of aurones were documented [8].

Inspired by the pharmacological profile of aurone, thiophene and pyrazole [9–17] skeletons, it was planned to synthesize hybrid molecules containing those building blocks. Our research group has been designing and carrying out innovative synthetic protocols in organic synthesis adopting the eco-sustainable approach [18, 19]. Specifically, the present study is devoted to microwave assisted synthesis and antioxidant screening of benzofuranones or aurones.

RESULTS AND DISCUSSION

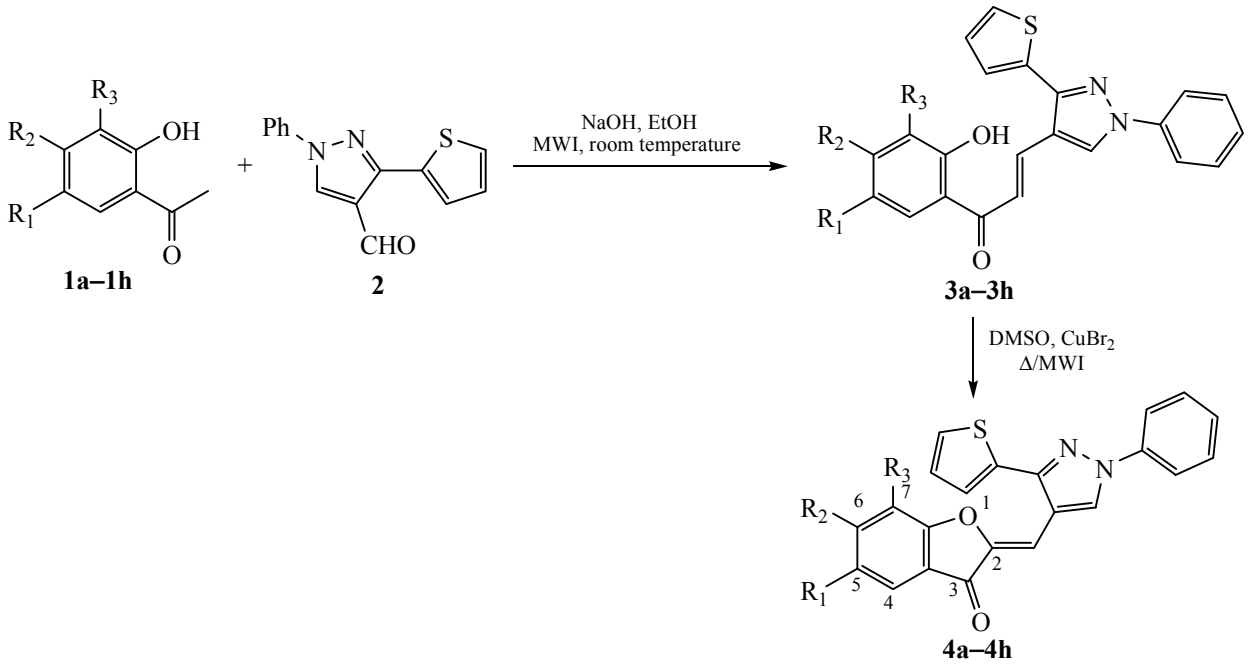
Compounds **2** were synthesized according to the earlier method [20]. Condensation of 2-hydroxyacetophenones **1a–1h** with 1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazole-4-carbaldehyde **(2)** in the presence of an alkali under microwave irradiation gave substituted (*E*)-1-(2-hydroxyphenyl)-3-[1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl]prop-2-en-1-ones **(3a–3h)** in high yields. Subsequently, chalcones **3a–3h** reacted with $CuBr_2$ in the presence of DMSO to give substituted (*Z*)-2-{[1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl]-methylene}benzofuran-3(2*H*)-ones **(4a–4h)** (Scheme 1). At room temperature the reaction did not proceded. Optimum results were obtained at 180°C. Microwave irradiation at 160 W led to optimum results in 5–6 min. The crude product was purified by column chromatography.

Yields obtained with microwave irradiation were higher than those achieved by the conventional heating method (Table 1).

Structures of the synthesized compounds (*Z*)-2-{[1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl]methylene}-

[1] The text was submitted by the authors in English.

Scheme 1. Synthetic route to the title compounds **4a–4h.**



a: $R_1 = R_2 = R_3 = H$, **b**: $R_1 = F$, $R_2 = R_3 = H$, **c**: $R_1 = Cl$, $R_2 = R_3 = H$, **d**: $R_1 = Br$, $R_2 = R_3 = H$, **e**: $R_1 = Me$, $R_2 = R_3 = H$, **f**: $R_1 = Cl$, $R_2 = H$, $R_3 = Cl$, **g**: $R_1 = Cl$, $R_2 = Me$, $R_3 = H$, **h**: $R_1 = H$, $R_2 = OMe$, $R_3 = H$.

benzofuran-3(2*H*)-ones **(4a–4h)** were elucidated by elemental analysis, IR, ^1H and ^{13}C NMR, and mass spectral data. The representative data of the product **4a** were the following. IR spectrum of **4a** demonstrated bands at 1693 cm^{-1} of the C=O group. In ^1H NMR spectrum of **4a** the characteristic benzylidene protone singlet was recorded at 6.99 ppm. Pyrazole proton singlet was recorded at 8.79 ppm. The ^{13}C NMR spectrum of **4a** supported its the formation. In the MS the base peak at 371 corresponded to the respective $[M + H]^{+\cdot}$.

Table 1. Data of synthesis of compounds **4a–4h**

Comp. no.	Conventional heating		MW irradiation	
	time, h	yield, %	time, h	yield, %
4a	2.0	70	5	82
4b	3.0	67	5	84
4c	2.5	63	5	82
4d	3.0	67	6	85
4e	3.0	62	6	82
4f	2.0	67	6	85
4g	2.5	70	5	82
4h	3.0	67	6	80

Antimicrobial activity. All products were screened for their antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa,* and *Escherichia coli* using ampicillin as the standard drug. The activity was determined using the cup plate agar diffusion method by measuring the zone of inhibition in mm. The compounds were screened at the concentration of 50 μg/mL in DMSO. According to the screening data (Table 2) the synthesized compounds **4e**, **4g,** and **4h** showed high antibacterial activity against all tested organisms. Switching the halogens from F to Cl or Br, gave significant enhancement in the levels of activity. Among the other compounds the activity did not depend significantly on the electronic nature of compounds.

Antifungal activity. All products were screened for their antifungal activity against *Aspergillus niger*, *Penicillium italicum* and *Fusarium oxysporum* using griseofulvin as the standard drug. Their activity was determined using the cup plate agar diffusion method by measuring the zone of inhibition in mm. The compounds were screened at a concentration of 50 μg/mL in DMSO. The synthesized compounds **4a**, **4g,** and **4h** showed high antifungal activity (Table 3) against all tested organisms. The unsubstituted compound **4a** demonstrated the highest activity against the fungi.

Table 2. Antibacterial activity of compounds **4a–4h**

Compound	Zone of inhibition, mm			
	gram-positive bacteria		gram-negative bacteria	
	Staphylococcus aureus	*Bacillus subtilis*	*Pseudomonas aeruginosa*	*Escherichia coli*
4a	20	5	9	21
4b	11	3	4	21
4c	16	5	5	25
4d	19	6	9	29
4e	25	8	9	25
4f	08	4	3	9
4g	20	9	10	22
4h	32	17	13	33
Ampicillin	30	12	10	30

The highly electron rich flavonols **4g** and **4h** demonstrated activity that was comparable with that of **4a**. Among the halogen derivates, the bromo substituted compound **4c** exhibited significantly higher activity compared to chloro- and fluoro-substituted compounds, **4b** and **4c** respectively.

EXPERIMENTAL

All solvents and chemicals were obtained commercially, mostly from Sigma-Aldrich, and used without further purification. Melting points were determined in open glass capillaries on a Stuart SMP30 apparatus. The elemental analysis was carried out on a Vario-11 CHN analyzer. IR spectra were recorded in KBr on a Shimadzu FTIR 8400S spectrophotometer in the range of 600–4000 cm^{-1}. ^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance II 300 spectrometer (300 and 75 MHz, respectively) in $CDCl_3$ using TMS as the internal standard. Mass spectra were measured on a Shimadzu LCMS-2020 mass spectrometer. Purity of the compounds was tested by TLC on silica gel 60 F254 (Merck). All microwave irradiation experiments were performed in a multiSYNTH series microwave system (Milestone).

(*Z*)-2-{[1-Phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl]methylene}benzofuran-3(2*H*)-ones (4a–4h) *(general procedure). Conventional method***.** A chalcone **3a–3h** (2 mmol) was dissolved in a solution of $CuBr_2$ (10 mg) in DMSO (10 mL) and refluxed for 2–3 h (Table 1). Upon completion of the reaction (monitored by TLC, EtOAc : hexane, 1 : 4 v/v) the reaction mixture was poured into ice-water and extracted with chloroform (2 × 20 mL). The combined organic layer was washed with 10 mL of water and dried over anhydrous magnesium sulphate. The solvent was evaporated and the residue purified by using silica gel column chromatography to give a pure product **4a–4h**.

Microwave irradiation method. A chalcone **3a–3h** (2 mmol) was dissolved in a solution of $CuBr_2$ (10 mg) in DMSO (2 mL) and subjected to microwave irradiation at 180 W for 5–6 min (Table 1). Upon completion of the reaction (monitored by TLC, EtOAc : hexane, 1 : 4 v/v), the mixture was poured into ice-water and extracted with chloroform (2 ×

Table 3. Antifungal activity of compounds **4a–4h**

Compound	Zone of inhibition, mm		
	Aspergillus nigerzeae	*Penicillium italicum*	*Fusarium oxysporum*
4a	15	23	30
4b	5	8	13
4c	6	7	14
4d	8	16	24
4e	12	19	11
4f	5	21	13
4g	13	25	25
4h	14	26	29
Griseofulvin	12	20	25

20 mL). The combined organic layer was washed with 10 mL water and dried over anhydrous magnesium sulphate. The solvent was evaporated and the residue was purified by using silica gel column chromatography to give the product **4a–4h**.

(*Z*)-2-{[1-Phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl]methylene}benzofuran-3(2*H*)-one (4a) was obtained as pale yellow solid, mp 156–158°C. IR spectrum, ν, cm^{-1}: 752 (C–O–C), 1637 (C=CH), 1693 (C=O). ^{1}H NMR spectrum, δ, ppm: 6.99 s (1H, benzylidene), 7.14–7.16 m (1H, Ar-H), 7.35–7.65 m (8H, Ar-H), 7.83–7.85 d (2H, Ar-H, *J* = 9.03 Hz), 8.25–8.27 m (1H, Ar-H), 8.79 s (1H, pyrazole). ^{13}C NMR spectrum, δ_C, ppm: 110.3, 117.9, 118.9, 120.6, 121.2, 126.9, 127.0, 127.6, 127.9, 129.6, 131.6, 131.6, 133.5, 136.5, 138.7, 139.0, 148.3, 162.5, 184.5. MS: *m/z* 371 $[M + H]^+$. Found, %: C 71.36; H 3.84; N 7.59. $C_{22}H_{14}N_2O_2S$. Calculated, %: C 71.33; H 3.81; N 7.56.

(*Z*)-5-Fluoro-2-{[1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl]methylene}benzofuran-3(2*H*)-one (4b) was obtained as pale yellow solid, mp 155–157°C. IR spectrum, ν, cm^{-1}: 750 (C–O–C), 1632 (C=CH), 1696 (C=O). ^{1}H NMR spectrum, δ, ppm: 6.75 s (1H, benzylidene), 7.14–7.17 m (2H, Ar-H), 7.34–7.40 d (2H, Ar-H, *J* = 3.0 Hz), 7.44–7.46 m (2H, Ar-H), 7.49–7.54 m (2H, Ar-H), 7.82–7.89 m (3H, Ar-H), 8.79 s (1H, pyrazole). ^{13}C NMR spectrum, δ_C, ppm: 108.3, 109.0, 114.2, 118.4, 119.3, 119.9, 120.6, 120.8, 121.9, 122.9, 123.3, 125.1, 126.4, 126.6, 126.8, 127.0, 129.5, 129.6 130.1, 134.2, 139.5 140.6, 142.6, 153.5, 160.0. MS: *m/z* 389 $[M + H]^+$. Found, %: C 68.06; H 3.40; N 7.24. $C_{22}H_{13}FN_2O_2S$. Calculated, % C 68.03; H 3.37; N 7.21.

(*Z*)-5-Chloro-2-{[1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl]methylene}benzofuran-3(2*H*)-one (4c) was obtained as pale yellow solid, mp 150–152°C. IR spectrum, ν, cm^{-1}: 754 (C–O–C), 1640 (C=CH), 1699 (C=O). ^{1}H NMR spectrum, δ, ppm: 6.80 s (1H, benzylidene), 7.12–7.16 m (2H, Ar-H), 7.35–7.54 m (5H, Ar-H), 7.68–7.72 m (1H, Ar-H), 7.819 d (2H, Ar-H, *J* = 8.1 Hz), 8.37 d (1H, Ar-H, *J* = 2.4 Hz), 8.79 s (1H, pyrazole). ^{13}C NMR spectrum, δ_C, ppm: 108.7, 108.9, 119.1, 119.3, 119.6, 120.6, 122.0, 122.3, 122.7, 123.0, 124.3, 125.9, 126.3, 126.6, 129.3, 130.0, 131.8, 132.2, 139.7, 140.4, 141.1, 149.2, 155.3, 168.7. MS: *m/z* 405 $[M + H]^+$. Found, %: C 65.29; H 3.26; N 6.94. $C_{22}H_{13}ClN_2O_2S$. Calculated, %: C 65.26; H 3.24; N 6.92.

(*Z*)-5-Bromo-2-{[1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl]methylene}benzofuran-3(2*H*)-one (4d) was obtained as pale yellow solid, mp 140–142°C. IR spectrum, ν, cm^{-1}: 748 (C–O–C), 802 (C–Br), 1629 (C=CH), 1700 (C=O). ^{1}H NMR spectrum, δ, ppm: 6.80 s (1H, benzylidene), 7.14–7.21 m (2H, Ar-H), 7.35–7.58 m (6H, Ar-H), 7.82 d (2H, Ar-H, *J* = 7.8 Hz), 8.21 s (1H, Ar-H), 8.79 s (1H, pyrazole). ^{13}C NMR spectrum, δ_C, ppm: 108.9, 119.1, 119.3, 120.6, 122.1, 122.8, 122.9, 123.0, 124.3, 125.7, 126.3, 126.4, 128.0, 128.4, 128.6, 129.2, 133.2, 139.8, 140.4, 141.0, 150.2, 155.4, 168.7. MS: *m/z* 451 $[M + H]^+$. Found, %: C 58.83; H 2.94; N 6.25. $C_{22}H_{13}BrN_2O_2S$. Calculated, %: C 58.81; H 2.92; N 6.23.

(*Z*)-5-Methyl-2-{[1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl]methylene}benzofuran-3(2*H*)-one (4e) was obtained as pale yellow solid, mp 154–156°C. IR spectrum, ν, cm^{-1}: 758 (C–O–C), 1618 (C=CH), 1705 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.34 s (3H, CH_3), 6.98 s (1H, benzylidene), 7.13–7.19 m (1H, Ar-H), 7.34–7.39 m (2H, Ar-H), 7.42–7.54 m (5H, Ar-H), 7.82 d (2H, Ar-H, *J* = 8.1 Hz), 8.03 s (1H, Ar-H), 8.77 s (1H, pyrazole). ^{13}C NMR spectrum, δ_C, ppm: 21.8, 108.2, 108.5, 113.7, 118.6, 118.9, 119.2, 120.2, 121.8, 122.2, 122.6, 123.9, 125.3, 125.4, 125.8, 128.8, 129.3, 139.5, 140.0, 140.7, 149.7, 155.0, 159.2, 168.3. MS: *m/z* 385 $[M + H]^+$. Found, %: C 71.87; H 4.21; N 7.31. $C_{23}H_{16}N_2O_2S$. Calculated, %: C 71.85; H 4.19; N 7.29.

(*Z*)-5,7-Dichloro-2-{[1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl]methylene}benzofuran-3(2*H*)-one (4f) was obtained as pale yellow solid, mp 158–160°C. IR spectrum, ν, cm^{-1}: 739 (C–O–C), 1620 (C=CH), 1695 (C=O). ^{1}H NMR spectrum, δ, ppm: 6.88 s (1H, benzylidene), 7.07–7.09 m (1H, Ar-H), 7.32–7.40 m (2H, Ar-H), 7.49–7.54 m (3H, Ar-H), 7.65 d (1H, Ar-H, *J* = 2.4 Hz), 7.80 d (1H, Ar-H, *J* = 8.1 Ar-H), 8.13 d (2H, Ar-H, *J* = 2.4 Hz), 8.69 s (1H, pyrazole). ^{13}C NMR spectrum, δ_C, ppm: 108.3, 119.6, 120.0, 121.9, 122.3, 123.2, 124.3, 125.8, 126.4, 127.0, 127.3, 128.8, 129.3, 130.1, 139.4, 140.6, 142.7, 152.3, 155.3, 168.7. MS: *m/z* 439 $[M + H]^+$. Found, %: C 60.18; H 2.77; N 6.40. $C_{22}H_{12}Cl_2N_2O_2S$. Calculated, %: C 60.15; H 2.75; N 6.38.

(*Z*)-5-Chloro-7-methyl-2-{[1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl]methylene}benzofuran-3(2*H*)-one (4g) was obtained as pale yellow solid, mp 139–141°C. IR spectrum, ν, cm^{-1}: 736 (C–O–C), 1625 (C=CH), 1703 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.34 s (3H, CH_3), 6.80 s (1H, benzylidene), 7.12–7.16 m (2H, Ar-H), 7.35–7.54 m (5H, Ar-H), 7.68–7.72 m (1H, Ar-H), 7.82 d (2H, Ar-H, *J* = 8.1 Hz), 8.79 s (1H, pyrazole). ^{13}C NMR spectrum, δ_C, ppm: 22.1 (CH_3), 108.6, 119.0, 119.3, 120.6, 122.1, 123.0, 124.3, 125.6, 126.6, 128.2, 129.2, 130.0, 130.3, 131.8, 137.8, 139.9,

140.4, 150.3, 155.4, 168.7. MS: *m/z* 419 $[M + H]^+$. Found, %: C 65.97; H 3.62; N 6.71. $C_{23}H_{15}ClN_2O_2S$. Calculated, %: C 65.95; H 3.61; N 6.69.

(*Z*)-5-Methoxy-2-{[1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl]methylene}benzofuran-3(2*H*)-one (4h) was obtained as pale yellow solid, mp 166–168°C. IR spectrum, ν, cm^{-1}: 752 (C–O–C), 1629 (C=CH), 1697 (C=O). ^1H NMR spectrum, δ, ppm: 3.89 s (3H, OCH_3), 6.98 s (1H, benzylidene), 7.13–7.19 (1H, m, H Ar), 7.34–7.39 m (2H, Ar-H), 7.42–7.54 m (5H, Ar-H), 7.82 (2H, d, *J* = 8.1, H Ar), 8.03 (1H, s, Ar-H), 8.77 s (1H, pyrazole). ^{13}C NMR spectrum, δ_C, ppm: 54.9 (OCH_3), 108.2, 108.5, 113.7, 119.2, 120.2, 121.8, 122.2, 122.6, 123.9, 125.3, 125.8, 128.8, 129.3, 139.5, 140.0, 140.7, 149.5, 155.0, 159.1, 168.3. Mass spectrum: *m/z* 401 $[M + H]^+$. Found, %: C 69.01; H 4.06; N 7.03. $C_{23}H_{16}N_2O_3S$. Calculated, %: C 68.98; H 4.03; N 7.00.

Biological activity assay. All synthesized compounds were screened for their antimicrobial activity against two strains of Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*), two strains of Gram-negative bacteria (*Echerichia coli* and *Pseudomonas aeruginosa*), and three strains of fungi (*Aspergillus niger*, *Penicillium italicum*, and *Fusarium oxysporum*). Standard antibiotic drugs *amoxicillin* for bacteria and *mycostatin* for fungi were used at a concentration of 50 μg/mL for comparison. Biological activity of the products was evaluated by the filter paper disc method for 50 μg/mL solutions in DMF. The inhibition zones of microbial growth surrounding the filter paper disc (5 mm) were measured in millimeters at the end of an incubation period of 3 days at 37°C for *E.coli* and at 28°C for other bacteria and fungi. DMF alone showed no inhibition zone.

CONCLUSIONS

A series of new substituted (*Z*)-2-{[1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl]methylene}benzofuran-3(2*H*)-ones **(4a–4h)** have been synthesized by the Vilsmeier–Haack reaction under conventional and microwave irradiation conditions. All products were tested for their in vitro antimicrobial activity. Compounds **4a**, **4e**, **4g,** and **4h** demonstrated higher antimicrobial activity against selected microorganisms than the reference drugs.

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