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MICROWAVE ASSISTED SYNTHESIS OF 3-(2-BENZOYL-6-HYDROXY-3-METHYL BENZO[b] FURAN-5-YL)-5-(ARYL)-4, 5-DIHYDRO-1*H*-PYRAZOLE CARBOTHIOAMIDES AND THEIR ANTIBACTERIAL ACTIVITY

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Abstract:
A series of 3-(2-Benzoyl-6-hydroxy-3-methyl benzo[b] furan-5-yl)-5-(aryl)-4, 5-dihydro-1*H*-pyrazole carbothioamides have been prepared by the reaction of (*E*)-1-(2-Benzoyl-6-hydroxy-3-methylbenzo[b]furan-5-yl)-3-aryl-2-propen-1-ones with thiosemicarbazide in the presence of sodium hydroxide under microwave irradiation. The structures of newly synthesized compounds have been confirmed on the basis of elemental analysis, IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral data. All the compounds were screened for their antibacterial activity.

Keywords: Microwave irradiation, chalcone, pyrazoline, benzofuran.

Introduction

A number of pyrazoline derivatives have been shown to exhibit a broad spectrum of biological and pharmaceutical activities which include anti-inflammatory[1-2], antibacterial[3], analgesic[4], antifungal[5], anticancer[6] and anticonvulsant[7] activities. Many 1-Thiocarbamoyl-3,5-diphenyl-2-pyrazolines are reported to have antimycobacterial[8], antidepressant[9] and monoamine oxidase inhibitory activities [10-11]. Benzofuran derivatives are also associated with vide variety of physiological activities such as antihistaminic [12], anti-inflammatory [13,] estrogenic and anti-implantation[14]activities. In order to know the combined effect of both pyrazoline and benzofuran moieties on physiological activity, we have taken up the synthesis of 3-(2-Benzoyl-6-hydroxy-3-methylbenzo[b]furan-5-yl)-5-(aryl)-4,5-dihydro-1*H*-pyrazole carbothioamides**(3a-g)**.

Recently microwave assisted organic synthesis (MAOS) has gained popularity as a non-conventional technique for rapid organic synthesis[15]. It is eco-friendly, economical and is believed to be a step towards green chemistry. Synthesis and biological evaluation of benzofurans and dihydropyrazole carbothioamides have been a topic of special interest to organic and medicinal chemists. In continuation of our earlier work on microwave assisted synthesis[16-18] of biodynamic heterocycles and to explore their biological activity, herein we report the microwave assisted synthesis of novel benzofuranyl pyrazolines with possible antibacterial activity.

Results and discussion

The required starting material 5-Acetyl-2-benzoyl-6-hydroxy-3-methyl benzofuran[19, 20] **(1)** was synthesized by the reaction of 4, 6-diacetylresorcinol[21] with ώ- bromoacetophone[22] (1:1) in the presence of anhydrous K_2CO_3 under microwave irradiation. The desired (*E*)-1-(2-Benzoyl-6-hydroxy-3-methylbenzo[b] furan-5-yl)-3-aryl-2-propen-1-ones **(2a-g)** were synthesized by the condensation of 5-Acetyl-2-benzoyl-6-hydroxy-3-methyl benzofuran**(1)** with aromatic/hetero aromatic aldehydes in the presence of sodium methoxide under microwave irradiation. Several 3-(2-Benzoyl-6-hydroxy-3-methylbenzo[b]furan-5-yl)-5-(aryl)-4,5-dihydro-1*H*-pyrazole carbothio-amides **(3a-g)** were synthesized by the reaction of (*E*)-1-(2-Benzoyl-6-hydroxy-3-methyl benzo[b]furan-5-yl)-3-aryl-2-propen-1-ones with thiosemicarbazide in the presence of sodium hydroxide under microwave irradiation in excellent yields. The synthesis of **3a-g** was also carried out under conventional heating. Yields obtained under conventional heating (62-76%) as compared to microwave irradiation (80-90%), demonstrating that the effect of microwave irradiation.

Experimental

Melting points were determined on Polmon MT 96 melting point apparatus and are uncorrected. IR Spectra were measured on Shimadzu FTIR-8400S. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in DMSO-d_6 on Avance 300, spectrometer. Elemental analysis was recorded on Thermo Finnigan CHNS analyzer. Mass spectra were recorded on LCMS-2010A Shimadzu spectrophotometer. The purity of the compounds was checked by TLC using precoated silica gel plates (F-254), Merck. Microwave irradiation was carried out in Multisynth series microwave system (Milestone).

Scheme:

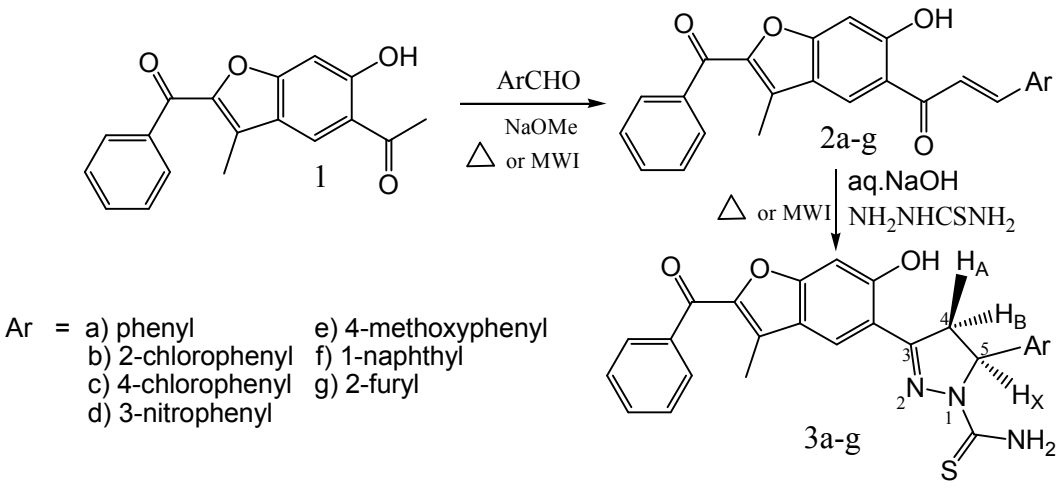

Table1: Analytical data of 3-(2-Benzoyl-6-hydroxy-3-methylbenzo[b]furan-5-yl)-5-(aryl)-4,5-dihydro-1*H*-pyrazole carbothioamides (3a-g)

Compound	M.P. (°C)	Conventional heating		Microwave irradiation	
		Time (hr)	Yield (%)	Time (min)	Yield (%)
3a	50	8	76	5	82
3b	255	8	65	5	86
3c	185	8	65	5	85
3d	242	8	62	5	80
3e	240	10	65	5	82
3f	205	8	62	6	83
3g	245	8	66	5	90

Synthesis of (E)-1-(2-Benzoyl-6-hydroxy-3-methylbenzo[b]furan-5-yl)-3-aryl-2-propen-1-ones (2a-g)

a) Conventional method

A mixture of 5-Acetyl-2-benzoyl-6-hydroxy-3-methyl benzofuran **(1) (**0.01 mol), appropriate aromatic / hetero aromatic aldehydes (0.01mol), sodium methoxide (0.04 mol) and ethanol (20ml) was stirred for 16 hr at room temperature. After completion of reaction as indicated by TLC, the reaction mixture was poured on to crushed ice and neutralized with dil.HCl. The solid separated was filtered and recrystallized from methanol as yellow powder.

b) Microwave irradiation method

A mixture of 5-Acetyl-2-benzoyl-6-hydroxy-3-methyl benzofuran **(1) (**0.001 mol), appropriate aromatic / hetero aromatic aldehydes (0.001mol), sodium methoxide (0.004 mol) and ethanol (5 ml) was taken in a quartz tube and inserted into teflon vial with screw capped and subjected to microwave irradiation at the constant temperature 70°C for 5 min. After completion of reaction as indicated by TLC, the reaction mixture was poured on to crushed ice and neutralized with dil.HCl. The solid separated was filtered and recrystallized from methanol as yellow powder.

Synthesis of 3-(2-Benzoyl-6-hydroxy-3-methylbenzo[b]furan-5-yl)-5-(aryl)-4,5-dihydro-1*H*-pyrazole carbothioamides (3a-g):

a) Conventional heating method

A mixture of (*E*)-1-(2-Benzoyl-6-hydroxy-3-methylbenzo[b]furan-5-yl)-3-aryl-2-propen-1-ones (0.001mol), thiosemicarbazide (0.001mol), aq. NaOH (0.08g) in 1 ml of water and ethanol (10 ml), was taken in a 25ml round bottomed flask and the reaction mixture was refluxed for 8-

10hrs. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with cold water and neutralized with dil. HCl. The precipitate thus formed was filtered and recrystallized from methanol as yellow powder.

b) Microwave irradiation method

A mixture of (*E*)-1-(2-Benzoyl-6-hydroxy-3-methylbenzo[b]furan-5-yl)-3-aryl-2-propen-1-ones (0.001mol), thiosemicarbazide (0.001mol), aq. NaOH (0.08g) in 1 ml of water and DMF (5 ml) was taken in a quartz tube and inserted into teflon vial with screw capped and subjected to microwave irradiation at the constant temperature 120°C for 5-6 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with cold water and neutralized with dil. HCl. The precipitate thus formed was filtered and recrystallized from methanol as yellow powder.

IR, ^{1}H-NMR, ^{13}C-NMR, mass spectral data and elemental analysis

3-(2-Benzoyl-6-hydroxy-3-methylbenzo[b]furan-5-yl)-5-(phenyl)-4,5-dihydro-1*H*-pyrazole carbothioamide (3a):

IR (KBr): 3434 (OH), 3276 (NH_2); 1637(C=O), 1596(C=N), 1564, 1448, 1373, 1344 (C=S) 1294, 1247, 1149, 1097(C-O-C) cm^{-1}. ^{1}H-NMR(300 MHz, $CDCl_3$) : δ 2.57 (s, 3H, CH_3), 3.47(dd, 1H, H_A), 4.09(dd, 1H, H_B), 6.0(dd, 1H, H_X) 6.37 (s, 2H, NH_2) 7.01 (s, 1H, C_7-H), 7.26-7.77 (m, 8H, Ar-H) 8.03-8.05 (m,2H, Ar-H), 8.27 (s, 1H, C_4-H), MS: $[M+H]^+$, m/z=456 (100%),447(5%),397(5%), 383(20%), 295(10%),180(5%), 106(10%). Anal. Calcd. for $C_{26}H_{21}N_3O_3S$: C, 68.57; H, 4.61; N, 9.23%, Found: C, 68.43; H, 4.72; N, 9.31%.

3-(2-Benzoyl-6-hydroxy-3-methylbenzo[b]furan-5-yl)-5-(o-chlorophenyl)-4,5-dihydro-1*H*-pyrazole carbothioamide (3b):

IR (KBr):3444(OH), 3265(NH_2); 1637 (C=O), 1596(C=N), 1562, 1473, 1446, 1377, 1344 (C=S), 1294, 1247, 1184, 1149, 1097 cm^{-1} (C-O-C). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.58 (s, 3H, CH_3), 3.36(dd, 1H, H_A) 4.18 (dd, 1H, H_B) 6.40 (dd, 1H, H_X) 7.12-7.61 (m, 11H, Ar-H, NH_2), 10.06 (s, 1H, OH).^{13}C-NMR (75 MHz, DMSO-d6): δ 10.04, 60.22, 98.79, 115.1, 122.08, 123.62, 126.05, 127.66, 128.69, 128.93, 129.26, 129.87, 130.63, 132.81, 137.77, 139.88, 147.94, 156.31, 158.43, 176.05, 184.72, 190.42. MS: $[M]^+$, m/z=489 (60%),292(100%), 214(40%). Anal. Calcd. for $C_{26}H_{20}N_3O_3ClS$: C, 63.73; H, 4.08; N, 8.58%, Found: C, 63.70; H, 4.11; N, 8.67%,

3-(2-Benzoyl-6-hydroxy-3-methylbenzo[b]furan-5-yl)-5-(p-chlorophenyl)-4,5-dihydro-1*H*-pyrazole carbothioamide (3c):

IR (KBr): 3467(OH), 3251(NH_2); 3145, 1629 (C=O), 1598(C=N), 1560, 1488, 1473, 1460, 1342 (C=S), 1292, 1247, 1182, 1149, 1091 cm^{-1} (C-O-C). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.57 (s, 3H, CH_3), 3.39-3.45(dd, 1H, H_A) 4.04-4.14 (dd, 1H, H_B) 6.06-6.10 (dd, 1H, H_X) 6.38 (s, 2H, NH_2) 7.18-7.64 (m, 9H, Ar-H), 8.04-8.06 (d, 2H, Ar-H), 10.37(s, 1H, OH). MS $[M]^+$, m/z=489 (20%), 472(7%), 455(4%), 430(5%), 413((18%), 400(8%), 367(17%), 350.7(4%), 294(5%),105(7%). Anal. Calcd. for $C_{26}H_{20}N_3O_3ClS$: C, 63.73; H, 4.08; N, 8.58%, Found: C, 63.81; H, 4.17; N, 8.64%.

3-(2-Benzoyl-6-hydroxy-3-methylbenzo[b]furan-5-yl)-5-(m-nitrophenyl)-4,5-dihydro -1*H*-pyrazolecarbothioamide (3d):

IR (KBr): 3458(OH), 3286(NH_2); 1631 (C=O), 1596(C=N), 1562, 1529, 1477, 1446, 1346 (C=S), 1294, 1247, 1149, 1097 cm^{-1} (C-O-C). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.55 (s, 3H, CH_3), 3.44(dd, 1H, H_A) 4.15-4.27 (dd, 1H, H_B),) 6.2 (dd, 1H, H_X) 6.50 (s, 2H, NH_2) 7.18 (s, 1H, C_7-H), 7.51-7.54 (m, 3H, Ar-H) 7.90-8.40 (m,7H, Ar-H) 9.98(s, 1H, OH). .MS: $[M+H]^+$, m/z=501 (100%), 485(10%), 471(20%), 451(10%) ,412(10%), 391(25%), 324(30%), 295(10%), 279(30%). Anal. Calcd. for $C_{26}H_{20}N_4O_5S$: C, 62.40; H, 4.00; N, 11.20%, Found: C, 62.31; H, 4.11; N, 11.29%.

3-(2-Benzoyl-6-hydroxy-3-methylbenzo[b]furan-5-yl)-5-(p-methoxyphenyl)-4,5-dihydro-1*H*-pyrazolecarbothioamide (3e):

IR (KBr): 3413(OH), 3261NH_2), 1631(C=O), 1596(C=N), 1554, 1514, 1492, 1460, 1369, 1342 (C=S), 1292, 1247, 1180, 1145, 1101cm^{-1} (C-O-C). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.63 (s, 3H, CH_3), 3.78 (s,3H, OCH_3) 3.46(dd, 1H, H_A) 4.06(dd, 1H, H_B), 6.04 (dd, 1H, H_X),6.33(s, 2H, NH_2), 6.88(d, 2H, Ar-H), 7.18(d, 2H, Ar-H) 7.26 (s, 1H, C_7-H), 7.50-7.64 (m, 4H, Ar-H), 8.05 (d, 2H, Ar-H), 10.12(s, 1H, OH). ^{13}C-NMR (75 MHz, DMSO-d6): δ 9.48, 28.9, 43.5, 54.6, 61.2, 121.8, 126.2, 126.5, 127.7, 128.8, 131.9, 133.5, 137.1, 148.0, 156.1, 156.8, 158.2, 158.3, 175.8, 184.4. MS: $[M]^+$, m/z=485 (10%), 466(20%), 455(25%), 426(22%), 410(20%), 394(20%), 350(30%), 293(28%) 278(10%). Anal. Calcd. for $C_{27}H_{23}N_3O_4S$: C, 66.81; H, 4.74; N, 8.65%, Found: C, 66.75; H, 4.75; N, 8.71%.

3-(2-Benzoyl-6-hydroxy-3-methylbenzo[b]furan-5-yl)-5-(α-naphthyl)-4,5-dihydro-1*H*-pyrazolecarbothioamide (3f):

IR (KBr): 3483(OH), 3276(NH_2); 1629 (C=O), 1596(C=N), 1560, 1475, 1458, 1444, 1344 (C=S) , 1292, 1245, 1149, 1099 cm^{-1} (C-O-C). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.50 (s, 3H, CH_3), 3.42(dd, 1H, H_A) 4.28 (dd, 1H, H_B) 6.52 (dd, 1H_X) 7.15 (s, 1H, C_7-H), 7.34-7.91 (m, 11H, Ar-H) 7.48-7.67 (m,4H, Ar-H) 7.93-7-96 (d, 2H, Ar-H), 8.27 (s, 1H, C_4-H), 8.32(s, 2H, NH_2) 10.15(s, 1H, OH). MS: $[M+H]^+$, m/z=506(100%),489(10%), 460(5%0, 447(5%), 430(10%), 417(15%). Anal. Calcd. for $C_{30}H_{23}N_3O_3S$: C, 71.28; H, 4.55; N, 8.31, Found: C, 71.39; H, 4.64; N, 8.40%.

3-(2-Benzoyl-6-hydroxy-3-methylbenzo[b]furan-5-yl)-5-(2-furyl)-4,5-dihydro-1*H*-pyrazolecarbothioamide (3g):

IR (KBr): 3446, (OH), 3261 (NH_2), 1635 (C=O), 1596(C=N), 1569, 1477, 1456, 1380, 1346 (C=S), 1292, 1245, 1211, 1147, 1101 cm^{-1}(C-O-C). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.60 (s, 3H, CH_3), 3.70(dd, 1H, H_A) 3.90 (dd, 1H, H_B) 6.24 (dd, 1H_X), 6.35 (d,1H,H H_α -furyl), 6.52 (d,1H, H_β-furyl), 7.16 (s,1H,C_7-H), 7.26-7.61 (m, 7H, Ar-H, NH_2), 8.04-8.06(d, 2H, Ar-H) 10.02 (s, 1H, OH). MS:$[M]^+$,m/z =445 (20%), 428(8%), 411(10%), 393(35%), 386(50%), 369(30%), 358(12%), 293(12%), 279(10%), 264(6%), 249(5%), 169(10%), 165(5%), 153(5%), 140(5%), 115(5%), 109(10%), 105(100%),94(6%), 81(16%), 77(75%), 73(10%), 65(5%), 59(18%), 51(10%), 43(10%). Anal. Calcd. for $C_{24}H_{19}N_3O_4S$: C, 64.71; H, 4.26; N, 9.43%. Found: C, 64.80; H, 4.34, N, 9.52%,

Antibacterial Activity

The activity was determined using cup-plate agar diffusion method[23] by measuring the inhibition zone in mm. All the compounds were screened for their antibacterial activity against a variety of bacterial strains such as Bacillus subtilis (ATCC-6633), staphylococcus aureus (ATCC-29737), Escherichia coli (ATCC-10536) Pseudomonas aeruginosa (ATCC-27853) using streptomycin, Tetracycline, Chloramphenicol, Carbenicillin respectively as standard drug. Nutrient Agar was used as a culture medium. A 1mg/ml solution in dimethylformamide was used. DMF showed no inhibition zones.

The agar medium was inoculated with bacterial cultures tested. After 24 hours of incubation at 37^{o}C, the diameter of inhibition zone (mm) was measured. Streptomycin (25 µg/well) used against Bacillus subtilis, Tetracycline (30 µg/well) used against S.aureus, Chloramphenicol (25 µg/well) used against E. coli, Carbenicillin (100 µg/well) used against pseudomonas aeruginosa as a references (as standard) for antibacterial activity. The results of the antibacterial activity are given in Table2. 3-(2-Benzoyl-6-hydroxy-3-methylbenzo[b]furan-5-yl)-5-(aryl)-4,5-dihydro-1*H*-pyrazole carbothioamides 3b, 3e and 3g exhibited good antibacterial activity.

Table2. Antibacterial activity of some synthesized compounds and inhibition zones

Compound No.	**Gram Positive Bacteria**		**Gram Negative Bacteria**	
	Bacillus subtilis (ATCC-6633)	Staphylococcus aureus (ATCC-29737)	Escherichia coli (ATCC-10536)	Pseudomonas aeruginosa (ATCC-27853)
3a	10.0 mm	10 mm	8 mm	- ve
3b	11.5 mm	11 mm	8 mm	8 mm
3c	8 mm	9mm	- ve	- ve
3d	8 mm	10 mm	- ve	8mm
3e	9 mm	8 mm	9 mm	9 mm
3f	10.5mm	10 mm	8 mm	- ve
3g	9 mm	10 mm	9 mm	8 mm
Standard	22 mm Streptomycin	15 mm Tetracycline	13 mm Chloramphenicol	13 mm (Carbenicillin)

Conclusions:

In conclusion, we have successfully synthesized new 3-(2-Benzoyl-6-hydroxy-3-methylbenzo[b]furan-5-yl)-5-(phenyl)-4,5-dihydro-1*H*-pyrazole carbothioamides under microwave irradiation conditions. This methodology provides an easier facile and environmentally benign synthesis in which the reaction time is reduced with better yields. The compounds 3b, 3e and 3g exhibited good antibacterial activity.

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