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SYNTHESIS OF CHROMENE DERIVATIVES USING MICROWAVE-ASSISTED METHOD

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Abstract

Eleven new chromens have been synthesized by condensation reaction of some amines with 6-butoxy-2-oxo-*2H*-chromene-4-carbaldehyde **4** or 3-acetyl-6-substituted-*2H*-chromene-2-one **7** under microwave irradiation. This method offers several advantages: fast reaction rates and significantly high yields. The products were equally available and their structures were confirmed by IR, ^{1}H-and ^{13}C-NMR spectral data. Antimicrobial activities of the obtained compounds have been tested. The results showed that they possess remarkable antimicrobial activities against *Candida albicans*.

Keywords. Chromene; solvent-free; microwave-assisted method.

1. INTRODUCTION

The microwave-assisted organic synthesis method is becoming an increasingly popular method which replaces the classical ones because it proves to be a clean, cheap, and convenient method. This method often affords higher yields in short reaction times and has been extended to almost all areas of chemistry [1]. Numerous organic reactions assisted by microwave have been performed and reviewed in the articles or books. These reactions involved different ones, such as the acylation and alkylation, aromatic nucleophilic substitution, condensation, cycloadditions, heterocyclization, rearrangements, reaction of organometallic compounds, oxidation and reduction [2,4]. On the other hand, chromene derivatives are nowadays an important group of organic compounds that are used as additives to food and cosmetics, optical brightening agentsand dispersed fluorescent and laser dyes [3,4]. Chromenes can be synthesized by methods such as Claisen rearrangement, Perkin and Pechmann reaction as well as Knoevenagel condensation. This paper describes the condensation reaction of some amines with 6-butoxy-2-oxo-*2H*-chromene-4-carbaldehyde **4** or 3-acetyl-6-substituted-*2H*-chromene-2-one **7** under microwave irradiation. Futhermore, the synthesized chromenes were screened for antimicrobial and antifungal activities.

2. EXPERIMENTAL

Melting point was measured by using Thiele's apparatus in capillary and uncorrected. The FTIR-spectra were recorded on Magna 760 FT-IR Spectrometer (NICOLET, USA) in form of mixing with KBr and using reflex-measure method. ^{1}H-NMR (500 MHz), ^{13}C-NMR (125 MHz) spectra were recorded on an AVANCE AMX 500 FT-NMR Spectrometer (BRUKER, German) at 500.13 MHz, using DMSO-d_6 as solvent and TMS as an internal reference, δ in ppm. Bioassays were carried out in Hospital 19-8, Hanoi, Vietnam.

General procedure for the synthesis of nine chromenes [5-7]

Procedure A (under refluxing condition). A mixture of 6-butoxy-2-oxo-*2H*-chromene-4-carbaldehyde **4** or 3-acetyl-6-substituted-2*H*-chromen-2-one **7** (2.5 mmol), amines (5 mmol) and five drops of acetic acid in 5 ml 96% ethanol was refluxed for 20 minutes in home MW oven at 750W, concentrated and cooled. The separated product was filtered and recrystallized from an appropriate solvent to give chromenes **5a-e** and **8a-f**.

Procedure B (under microwave-assisted and solvent-free conditions) [1,7,8] A mixture of 6-butoxy-2-oxo-*2H*-chromene-4-carbaldehyde **4** or 3-acetyl-6-substituted-2*H*-chromene-2-one **7** (2.5mmol), and five drops of acetic acid, stirred for 30 minutes at 60-70 °C and then mixed carefully with amines (5 mmol) in an MW tube and irradiated by using the MW program as follows. Power: 120 W; hold time: 3-5 minutes; temperature: 100 °C.

After completion of the reaction, the mixture was treated with water (10 ml), and the precipitate was washed with water (50 ml) several times; washed and crystallized from ethanol (30 ml) and dried to give pure chromenes **5a-e** and **8a-f**. Results of the above synthesis were represented in table 1.

2.1. Compound 5a

^{1}HNMR (DMSO-d_6, δ, ppm): 8.65 (s, 1H, H-a); 8.41-8.43 (d, 1H, *J* = 8.4 Hz, H-7); 7.37 (s, 1H, H-5); 7.27 - 7.25 (d, 1H, *J* = 7.2 Hz, H-8); 6.79 (s, 1H, H-3); 4.03-4.00 (t, 2H, H-1”); 3.37-3.48 (m, 2H, H-2”); 1.71-1.65 (m, 5H, H1’-H5’); 1.56 (m, 2H, H-3”); 0.97-0.94 (t, 3H, H-4”). ^{13}C NMR (DMSO-d_6, δ, ppm): 160.3 (C=O); 164.1 (C=N); 161.5 (C-6); 110.1-143.2 (aromatic carbons); 19.3 - 68.2 (CH_2); 14.8 (CH_3).

2.2. Compound 5b

^{1}HNMR (DMSO-d_6, δ, ppm): 8.96 (s, 1H, H-a); 8.44-8.45 (d, *J* = 8.2 Hz, 1H, H-8); 7.45 (m, 2H, H-2’& H-4’); 7.50 (1H, H-7); 7.44 (1H, H3’), 7.39 (s, 1H, H-5); 7.29 (2H, H1’ & H5’) 7.03 (s, 1H, H-3); 4.07-4.05 (t, 2H, H-1”); 1.75-1.71 (m, 2H, H-2”); 1.48-1.44 (m, 2H, H-3”); 0.95-0.92 (t, 3H, H-4”). ^{13}C NMR (DMSO-d_6, δ, ppm): 159.5 (C=O); 164.7 (C=N); 162.0 (C-6); 110.5-154.0 (aromatic carbons); 67.5 (C-1”); 32.6 (C2”), 18.6 (C-3”); 14.7 (CH_3).

2.3. Compound 5c

^{1}HNMR (DMSO-d_6, δ, ppm): 9.06 (s, 1H, H-a); 8.67; (d, 1H, d, *J* = 8.0 Hz, H-7’); 8.34 (1H, H-4’); 8.03 (1H, H-1’); 7.96 (1H, H-8); 7.65 (1H, H-3’); 7.64 (1H, H-6’); 7.63 (2H, H2’& H5’); 7.48, (1H, H-7); 7.34 (1H, H-5); 7.17 (s, 1H, H-3); 4.12 (2H, H-1”); 1.77 (2H, H-2”); 1,47 (2H, H-3”); 0.93 (3H, H-4”). ^{13}C NMR (DMSO-d_6, δ, ppm): 155.1 (C=O); 184.7 (C=N); 159.1 (C-6); 110.5 - 154.7 (aromatic carbons); 67-95 (CH_2); 13,6 (CH_3).

2.4. Compound 5d

^{1}HNMR (DMSO-d_6, δ, ppm): 8.44 (s, 1H, H-a); 7,30 (d, *J* = 7.3 Hz, H-7); 8.64 (s, 1H, H-5’); 7.10 (s, 1H, H-5) 8.15-8.22 (d, *J* = 7.2 Hz, 1H, H-8); 6.99 (s, 1H, H-3); 3.32-5.62 (t, 2H, H-1”); 2.49-2.51 (m, 2H, H-2”); 1.26 (2H, H-3”); 0.98 (3H, H-4”); 7.98 (4H, H-2”’, H-6”’& H-2””, H-6””); 7.56 (4H, H-3”’, H-5”’& H-3””, H-5””); 7.29 (2H, H-4”’& H-4””). ^{13}C NMR (DMSO-d_6, δ, ppm): 159.7 (C=O); 163.5 (C=N); 162.5; (C-6); 164.2 (C-4’& C6’); 110.1 - 153.2 (aromatic carbons); 19.3-68.4 (CH_2); 14.1 (CH_3).

2.5. Compound 5e

^{1}HNMR (DMSO-d_6, δ, ppm): 8.22 (s, 1H, H-a); 7.21 (d, *J* = 7.2 Hz, 1H, H-7); 8.55 (s, 1H, H-5’); 6.99 (s, 1H, H-5) 8.15 - 8.22 (d, *J* = 7.2 Hz, 1H, H-8); 6.33 (s, 1H, H-3); 4.21, 4.88 (t, 2H, H-1”); 1.49 - 2.17 (m, 4H, H-2”, H-3”); 0.96 (m, 3H, H-4”); 3.38 (3H, OCH_3); 7.95 (m, 2H, H-2”’& H-6”’); 7.55 (2H, H-3”’ & H-5”’); 7.49 (1H, H4”’) 7.89 (2H, H-2””& H-6””); 7.12 (H-3”” & H-5””). ^{13}C NMR (DMSO-d_6, δ, ppm): 159.4 (C=O); 163.7 (C=N); 161.2 (C-6); 165.2 (C-4’& C6’); 110.0-150.4 (aromatic carbons); 19.0-68.4 (CH_2); 13.9 (CH_3); 55.7 (OCH_3).

2.6. Compound 8a

^{1}HNMR (DMSO-d_6 , δ, ppm): 8.21 (s, 1H, H-4); 7.89 (d, *J* = 8.4 Hz, 1H, H-7’); 7.72 (d, *J* = 7.5 Hz, 1H, H-1’); 7.70 (1H, 1H, H-4’); 7.67 (1H, H-3’); 7.65 (m, 1H, H-5), 7.50 (m, 1H, H-6’); 7.49 (m, 1H, H-7); 7.48 (m, 1H, H-2’); 7.45 (d, *J* = 7.8 Hz, 1H, H-8); 7.46 (m, 1H, H-6); 2.54 (3H, H-b). ^{13}C NMR (DMSO-d_6, δ, ppm): 158.4 (C=O); 195.0 (C=N); 154.5 (C-O); 146 (C-N); 116-134 (aromatic carbons); 29.9 (CH_3).

2.7. Compound 8b

^{1}HNMR (DMSO-d_6, δ, ppm): 8.15 (s, 1H, H-4); 8.02 (d, *J* = 8.4 Hz, 1H, H-5); 7.38 (m, H-6); 7.98 (m, H-7); 7.50 (d, *J* = 7.9 Hz, 1H, H-8); 6.98 (H-1’& H5’); 7.34 (H-2’& H4’); 7.02 (m, H-3’); 2.09 (3H, H-b). ^{13}C NMR (DMSO-d_6, δ, ppm): 159.1 (C=O); 175.6 (C=N); 153.5 (C-O); 136.1 (C-N); 116.1-132.7 (aromatic carbons); 19.5 (CH_3).

2.8. Compound 8c

^{1}HNMR (DMSO-d_6, δ, ppm): 8.01 (s, 1H, H-5); 7.69 (d, *J* = 7.7 Hz, 1H, H-7’); 7.72 (H-1’& H-5’); 7.34 (m, H-2’ & H-4’); 7.07 (m, 2.5, H-3’); 7,55 (d, *J* = 7.9 Hz, H-4); 7.89 (m, 1H, H-7); 7.45 (m, H-8); 2.44 (m, 3H, H-b). ^{13}C NMR (DMSO-d_6, δ, ppm): 159.3 (C=O); 182.1 (C=N); 151.5 (C-O); 136.2 (C-N); 113.4-132.9 (aromatic carbons); 19.5 (CH_3).

2.9. Compound 8d

^{1}HNMR (DMSO-d_6, δ, ppm): 7.56 (s, 1H, H-4); 8.29 (d, *J* = 7.3 Hz, 1H, H-7’); 8.06 (H-1’& H5);

8.10 (1H, H-4'); 7.77 (d, *J* = 8.2 Hz, 1H, H-3'); 7.62 (m, 1H, H-6'); 7.58 (m,1H, H-2'); 7.35 (1H, H-8); 7.62 (d, *J* = 7.22 Hz, 1H, H-7); 2.04 (m, 3H, H-b). ^{13}C NMR (DMSO-d_6, δ, ppm): 159.9 (C=O); 194.7 (C=N); 151.5 (C-O); 147.7 (C-N); 132.3 (C-Cl); 116-134 (aromatic carbons); 19.3 (CH_3).

2.10. Compound 8e

^{1}HNMR (DMSO-d_6, δ, ppm): 8.08 (s, 1H, H-5); 7.69 (d, *J* = 8.4 Hz, 1H, H7'); 7.72 (H-1'& H-5'); 7.34 (m, H-2' & H-4'); 7.07 (m, 1H, H-3'); 7.55 (d, *J* = 7.44 Hz, 1H, H-4); 7.89 (d, *J* = 7.2 Hz, 1H, H-7); 7.25 (m, 1H, H-8); 2,05 (m, 3H, H-b). ^{13}C NMR (DMSO-d_6, δ, ppm): 159.5 (C=O); 179.1 (C=N); 152.5 (C-O); 136.0 (C-N); 113.4 - 134.3 (aromatic carbons); 19.7 (CH_3).

2.11. Compound 8f

^{1}HNMR (DMSO-d_6, δ, ppm): 7.55 (s, 1H, H-4); 8.27 (d, *J* = 7.2 Hz, 1H, H7'); 8.02 (d, *J* = 7.53 Hz, 1H, H-1'); 8.15 (1H, 1H, H-4'); 7.79 (1H, H-3'); 7.63 (m, 1H, H-6'); 7.57 (m, 1H, H-2'); 7.35 (d, *J* = 7.2 Hz, 1H, H-8); 7.54 (1H, H-7); 7.55 (m, 1H, H-6); 2.04 (3H, H-b). ^{13}C NMR (DMSO-d_6, δ, ppm): 159.6 (C=O); 189.5 (C=N); 152.5 (C-O); 147.7 (C-N); 115.1-139.4 (aromatic carbons); 19.7 (CH_3).

3. RESULTS AND DISCUSSION

The derivatives of chromenes could be easily synthesized by nucleophilic addition of corresponding amine compounds to 6-butoxy-2-oxo-*2H*-chromene-4-carbaldehyde **4** or (3-acetyl-6-substituted-2*H*-chromene-2-one **7**. The proposed mechanism for the formation of products was shown in figure 1. We performed this reaction using two different microwave-assisted methods: by refluxing in ethanol and by executing under solvent-free condition in several minutes. We have found that the solvent-free conditions under microwave irradiation offers several advantages because solvents are often expensive, toxic, difficult to remove in case of aprotic dipolar solvents with high boiling point, and are environmentally polluting agents. Moreover, liquid-liquid extraction is avoided in the isolation of reaction products, and the absence of solvent prevents the risk of hazardous explosions when the reaction takes place in a microwave oven. The reactions were usually completed within 3-5 minutes and gave improved yield (55-84 %) over conventional methods in a shorter time. Moreover, the work-up procedure is simply reduced to the recrystallization of product from an appropriate solvent, while the refluxing method of formation of these chromenes involves longer reaction times (20 minutes) and lower yield (63-70 %). The synthetic processes could be represented in figure 2.

The IR spectra of compounds **(5a-e and 8a-f),** contained absorption at 1697-1765 cm^{-1} (C=O pyrone), 1523-1675 cm^{-1} (C=N), and 1023-1275 cm^{-1} (C-O-C, aryl ether). The ^{1}H-NMR spectra of compounds **8a-f** showed singlet signals at δ = 8.21-8.65 ppm (H-4) and 8.10-8.96 ppm (H_a) in **5a-e**, Signals of aromatic protons appeared at δ = 7.44-7.96 ppm, while methyl signals at δ = 2.40-2.40 ppm. The ^{13}C-NMR spectra showed signals of the carbonyl C=O shifted downfield at δ 195.0 ppm. In addition, there were resonance peaks in upfield region at δ = 29.92-39.99 ppm that indicated the presence of methyl groups and δ = 146.93-158.34 ppm belonged to C=C.

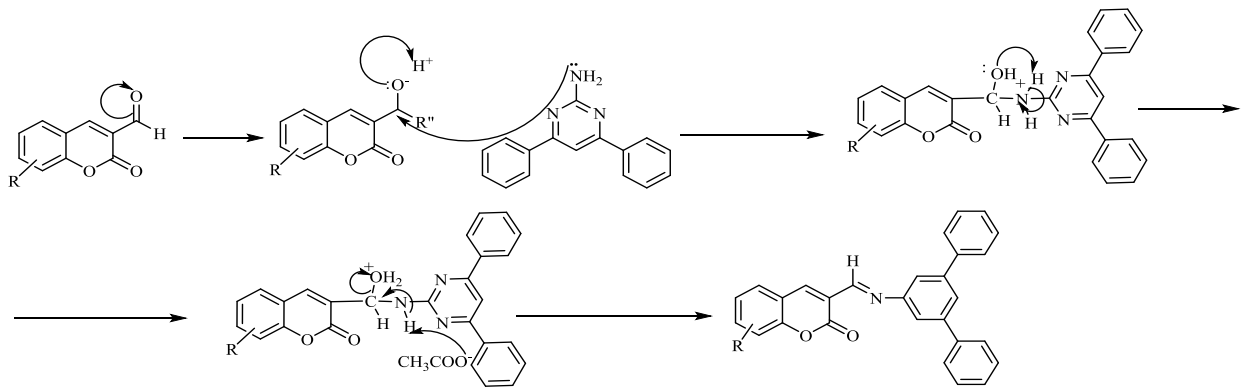
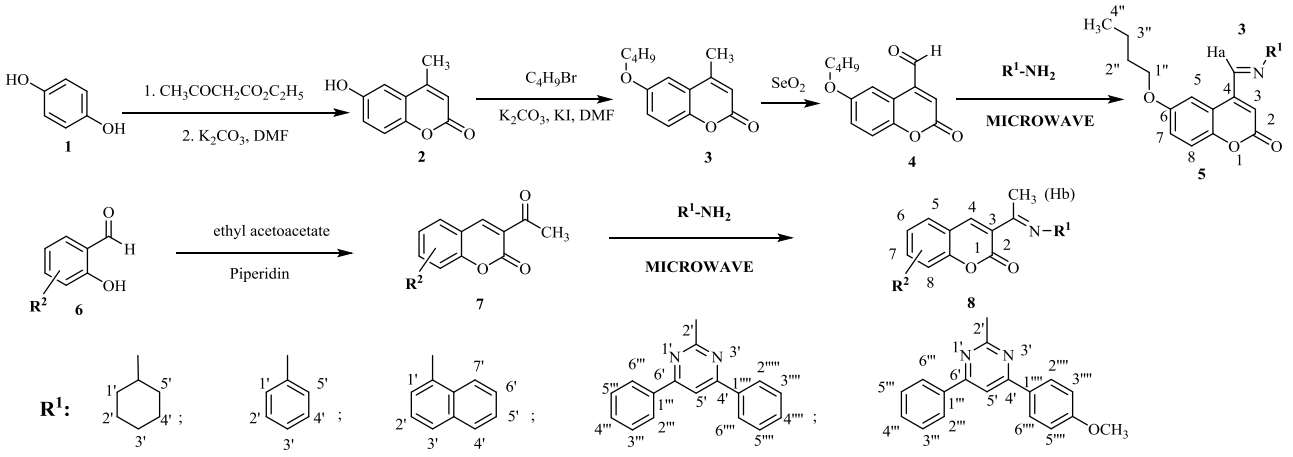


Fig. 1: The proposed mechanism for the formation of compound **5**



5a: $R^1 = C_6H_{11}$, **5b**: $R^1 = C_6H_5$, **5c**: $R^1 = C_{10}H_7$, **5d**: $R^1 = C_{16}H_{11}N_2$, **5e**: $R^1 = C_{17}H_{13}N_2O$
8a: $R^1 = C_{10}H_7$, R^2 = H, **8b**: $R^1 = C_6H_5$, R^2 = H, **8c**: $R^1 = C_6H_5$, R^2 = 6-Cl,
8d: $R^1 = C_{10}H_7$, R^2 = 6-Cl, **8e**: $R^1 = C_6H_5$, R^2 = 6-Br, **8f**: $R^1 = C_{10}H_7$, R^2 = 5-Br

Fig. 2: Synthesis of chromene derivatives

Table 1: Physical parameters of compounds **5a-e** and **8a-f**

Compounds	Melting point (°C)		Yield (%)		IR spectrum (cm^{-1})					
					A			**B**		
	A	**B**	**A**	**B**	$\nu_{C=O}$	$\nu_{C=N}$	ν_{C-O-C}	$\nu_{C=O}$	$\nu_{C=N}$	ν_{C-O-C}
5a	80-82	80-82	76	80	1720	1556	1121	1720	1556	1121
5b	71-72	71-72	72	80	1707	1523	1023	1707	1523	1022
5c	92-93	92-93	75	84	1724	1561	1205	1724	1561	1203
5d	130-132	130-132	69	84	1697	1533	1256	1697	1533	1256
5e	126-127	126-127	67	75	1751	1572	1275	1751	1572	1275
8a	230-232	231-232	66	58	1751	1656	1203	1750	1656	1203
8b	218-219	218-219	68	55	1740	1596	1103	1740	1596	1103
8c	220-221	220-221	70	70	1742	1675	1201	1741	1675	1201
8d	225-226	225-226	65	55	1742	1645	1169	1743	1645	1169
8e	224-225	224-225	66	56	1751	1663	1159	1752	1663	1159
8f	233-234	233-234	63	67	1734	1674	1159	1734	1675	1158

A: under solvent-free microwave method by microwave refluxing method; **B:** under solvent-free microwave method.

Table 2: Response of various micro-organisms to substituted chromenes **5a-e** and **8a-e**

Compounds	Diameter of zone inhibition (mm)					
	E. coli		*S. aureus*		*C. albicans*	
	100 µg/ml	150 µg/ml	100 µg/ml	150 µg/ml	100 µg/ml	150 µg/ml
5a	(-)	(-)	(-)	(-)	25	28
5b	18	(-)	(-)	(-)	25	30
5c	(-)	(-)	(-)	(-)	30	30
5d	(-)	(-)	(-)	(-)	30	30
5e	13	15	22	26	22	32
8a	(-)	17	15	18	35	40
8b	(-)	15	17	19	23	32
8c	(-)	16	13	15	27	32
8d	(-)	16	(-)	(-)	22	27
8e	(-)	16	(-)	14	22	30

Compounds **5a-e** and **8a-e** were screened for their antibacterial and antifungal activities against *Escherichia coli*, *Staphylococcus aureus* and *Candida albicans* by the disc diffusion method (table 2). All tested compounds have antifungal activities, among them compound **8** indicated a remarkable biological activity in concentration of 150 µg/ml. Compound **8a** showed highest antibacterial and antifungal activity.

Chromenes **8a-c** have had significant biological activities against *S.aureus* in concentration 100 µg/ml. Compound **8d** exhibited no antifungal activity against *Staphylococcus aureus*. All chromenes **8a-e** had no biological activities against *Escherichia coli, Staphyl ococcus aureus, Candida albicans* in 100 µg/ml concentration. Compounds **5a-e** were less antibacterial active.

4. CONCLUSIONS

Eleven new compounds of chromene derivatives **5a-e** and **8a-f** have been synthesized from corresponding 6-butoxy-2-oxo-*2H*-chromene-4-carbaldehyde **4** or 3-acetyl-6-substituted-*2H*-chromene-2-one **7** and amines using microwave-assisted methods. Their structures were identified by the combination of IR, ^{1}H- and ^{13}C-NMR spectral data. This method affords the chromene derivatives in moderate to good yields. The tested results showed that they possess remarkable antimicrobial activities against *Candida albicans.*

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