Journal of Multidisciplinary Engineering Science and Technology (JMEST)
ISSN: 2458-9403
Vol. 6 Issue 12, December - 2019

Microwave-Assisted Synthesis of some chromene compounds and Their Biological Activity Assessment

Thi Thanh Mai Nguyen
Faculty of Chemistry
Hanoi University of Industry, Vietnam
thanhmai73@haui.edu.vn

***Abstract*—Five new chromen compounds have been synthesized by condensation reaction of some amines with 6-butoxy-2-oxo-2H-chromene-4-carbaldehyde (4) 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, 1H-and 13C-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; microwave-assisted method

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.

Experimetal

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. 1H-NMR (500 MHz), 13C-NMR (125 MHz) spectra were recorded on an AVANCE AMX 500 FT-NMR Spectrometer (BRUKER, German) at 500.13 MHz, using DMSO-d6 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 [5,6,7]

Procedure A (under refluxing condition). A mixture of 6-butoxy-2-oxo-2H-chromene-4-carbaldehyde 4 or 3-acetyl-6-substituted-2H-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

Procedure B (under microwave-assisted and solvent-free conditions) [1,7,8] A mixture of 6-butoxy-2-oxo-2H-chromene-4-carbaldehyde 4 (2.5mmol), and five drops of acetic acid, stirred for 30 minutes at 60 - 70°C and then mixed carefully with amines (5mmol) in an MW tube and irradiated by using the MW program as follows. Power: 120W; hold time: 3 – 5 minutes; temperature: 100°C. After completion of the reaction, the mixture was treated with water (10ml), and the precipitate was washed with water (50ml) several times; washed and crystallized from ethanol (30ml) and dried to give pure chromenes 5a-e Results of the above synthesis were represented in table 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).

- Compound 5b

^{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).

- Compound 5c

^{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).

- Compound 5d

1HNMR (DMSO-d6, 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””). 13C NMR (DMSO-d6, 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 (CH2); 14.1 (CH3).

- Compound 5e

1HNMR (DMSO-d6, 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, OCH3); 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””). 13C NMR (DMSO-d6, 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 (CH2); 13.9 (CH3); 55.7 (OCH3).

III . 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-2H-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), 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 1H-NMR spectra of compounds 8a-f showed singlet signals at δ = 8.21 – 8.65 ppm (H-4) and 8.10 – 8.96 ppm (Ha) 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 13C-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.

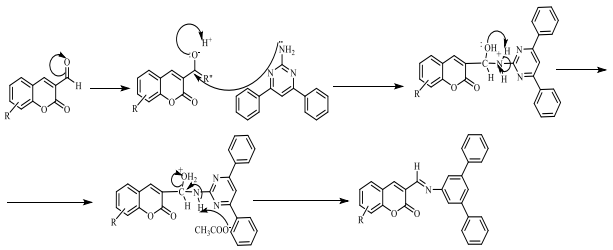
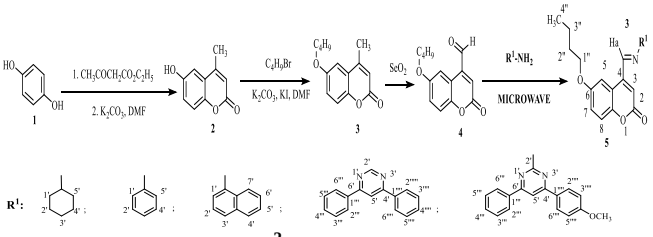


Fig. 1: The proposed mechanism for the formation of compound **5**



R^2: Cl, Br, H.

Fig.2: Synthesis of chromene derivatives

TABLE I. PHYSICAL PARAMETERS OF COMPOUNDS **5A-E**

Entry	Melting point (°C)		Yield (%)		IR spectrum (cm^{-1})		
	A	**B**	**A**	**B**	$\nu_{C=O}$	$\nu_{C=N}$	ν_{C-O}
5a	80-82	80-82	76	80	1722	1557	1051
5b	71-72	71-72	72	80	1709	1530	1043
5c	92-93	92-93	75	84	1725	1541	1105
5d	130-132	130-132	69	84	1707	1530	1158
5e	126-127	126-127	67	75	1752	1569	1179

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

Table II. Response of various micro-organisms to substituted chromenes 5a-E

Entry	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

Compounds **5a-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, Compounds (5a-e) were screened for their antibacterial and antifungal activities against *Enterobacter coli*, *Staphylococcus aureus* and *Candida albicans* by the disc diffusion method (Table 2). Almost all compounds had antifungal activities. Compound 5e showed the best antibacterial and antifungal activity in 150 µg/mL concentration. Other compounds were less antibacterial active, except compound 5b, this compound had activity against E. coli in 100µg/mL concentration.

ACKNOWLEDGMENT

Financial support for this work was provided by Scientific Research Fund- Hanoi University of Industry.

REFERENCES

[1] Nguyen Dinh Thanh, Nguyen Thi Thanh Mai. Synthesis of N-tetra-O- acetyl-β-D-glucopyranosyl-N'-(4',6'-diarylpyrimidin-2'-yl) thioureas, Carbohydrate Research., 344, 2399 – 2405 (2009).

[2] Anshu Chaudhary, Pramod Kumar Sharma, Prabhakar Verma and Rupesh Dudhe. Synthesis of novel pyrimidine derivative And its biological evaluation Pharmaceutica Drug Research., 20(2), 123 – 140 (2011).

[3] Keahav C. Patel and HimanShu D. Patel. Synthesis and Biological Evaluation of Coumarinyl Sydnone Derivatives, E-Journal of Chemistry., 8(1) 113 – 118 (2011).

[4] Vahid Vahabi and Farhad Hatamjafari. Microwave Assisted Convenient One-Pot Synthesis of Coumarin Derivatives via Pechmann Condensation Catalyzed by FeF3 under Solvent-Free Conditions and Antimicrobial Activities of the Products, J. Molecules., 19, 13093 – 13103 (2014).

[5] A. M. Hamil, M. Abdelkarem, M. Hemmet, and M. M. El-ajaily. Synthesis of a New Schiff Base: 2-[2-(E)-(2-hydroxyphenyl)-ethylidene]aminoethyl)ethanimidoyl]phen, International Journal of ChemTech Research., 4(2), 682 – 685 (2012).

[6] J. H. Pandya and K. J. Ganatra. Synthesis, Characterization And Biological Evaluation Of Bis-Bidentate Schiff Base Metal Complexes, Inorganic Chemistry: An Indian Journal., 3(3), 182 – 187 (2008).

[7] Gayathri Rajamanickam, Suresh Selvaraj, and Thirumurthy Rajendran. Synthesis, characterization and pharmacological evaluation of some potent 2-(substituted phenylimino) quinoxaline-3-one for their analgesic activity, Journal of Chemical and Pharmaceutical Research., 7(7), 961 – 966 (2015).

[8] S. G. Naruka and S. S. Mahajan. Conventional and microwave assisted synthesis and QSAR studies of coumarylchancones as potent antimicrobial agents, International Journal of Research in Farmacy and Chemistry., 1(4), 2231 – 2781 (2011).