Asian Journal of Chemistry Vol. 21, No. 8 (2009), 5918-5922

Synthesis of Some Coumarinyl Chalcones of Pharmacological Interest

B.S. JAYASHREE*, SHAKKEELA YUSUF† and D. VIJAY KUMAR
Department of Pharmaceutical Chemistry, Manipal College of Pharmaceutical Sciences, Manipal-576 104, India
Fax: (91)(820)2571998; Tel: (91)(820)2922482
E-mail: jesolar2001@yahoo.co.in

Coumarins are group of secondary plant metabolites found to exhibit important pharmacological activities. Some of their 3-substituted derivatives such as novobiocin, coumaromycin and chartencin are known to exhibit antibacterial activity. The reports on chalcones address their useful biological activity. In the present study, three acetylcoumarins were condensed with different aromatic aldehydes to obtain coumarinyl chalcones. 3-Acetylcoumarins were synthesized by Pachmann reaction and were condensed with different substituted aromatic aldehyde to obtain coumarinyl chalcones (**1**-**12**). The synthesized test compounds were characterized by their TLC, melting point, IR, ^{1}H NMR and Mass spectral studies and evaluated for various pharmacological activities such as, antioxidant, antiinflammatory, analgesic and antibacterial activity. Out of the randomly selected test compounds, none of them exhibited antioxidant activity. However, compounds **7** and **9** exhibited fairly good analgesic activity compared to that of standard diclofenac sodium. Further, three compounds were randomly selected for anti-inflammatory activity and found to be moderately active. Finally, all the test compounds were screened for their antibacterial activity, out of which, few were found to be moderately active against gram positive organisms while compound **10**; a bromo substituted derivative of coumarin has shown zone of inhibition at 18 when compared with that of the standard streptomycin showing inhibition at 10 against *K. pneumonia*. It was found that halogen substitution at 6th position on coumarinyl chalcones has greater influence on analgesic activity than unsubstituted ones, while for antiinflammatory activity unsubstituted ones are more appropriate. Further, compound **10** was found to be active against *K. pneumonia*.

Key Words: Synthesis, Coumarinyl chalcones.

INTRODUCTION

Coumarins are amongst the largest group of secondary plant metabolites found to exhibit various pharmacological activities[1]. The available report on coumarins addresses their useful biological activity[2]. A large number of coumarin derivatives

†Department of Pharmaceutical Sciences, Cheruvandoor Campus, Ettumanoor, Kottayam-686 631, India.

have been reported to possess substantial anticancer[3], anti HIV[4], antibacterial[5], antifungal[6] and antiinflammatory activity[7]. Some of the 3-substituted coumarin derivatives such as novobiocin, coumermycin and chartencin are known to exhibit antibacterial activity[8]. Chalcones are open chain flavonoids in which two aromatic rings are linked by a 3 carbon α,β-unsaturated carbonyl system. There are many interesting chalcones such as combrestatin A4, colchicine, turmeric and podophyllotoxin showing antimitotic activity[9]. Many chalcones with various substitutions on aromatic rings have been reported to possess antibacterial activity[10].

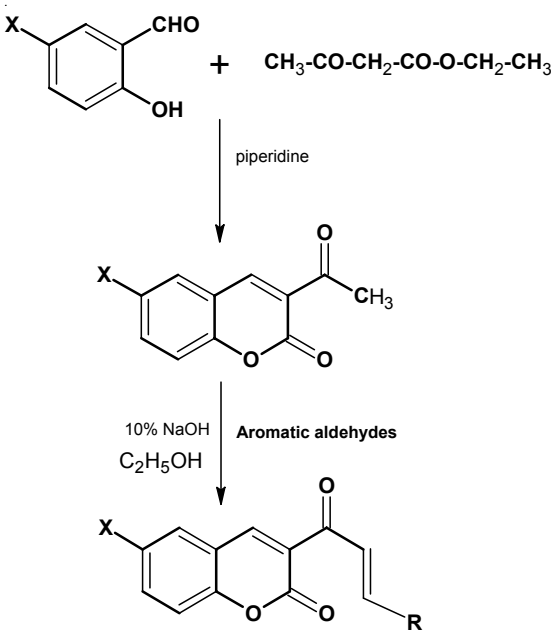
EXPERIMENTAL

Melting points were determined in open capillaries and are found uncorrected. IR spectra were recorded on FTIR spectrophotometer Shimadzu 8700 using KBr disc method. ^{1}H NMR spectra were recorded on AMX-400 using TMS as internal standard and mass spectra was recorded on Joel JMS DX 303 mass spectrophotometer. The purity of the test compounds was determined by TLC using suitable solvent system of different polarity. The physical data of synthesized test compounds are shown in Table-1.

TABLE-1

Compd.	X	R	m.p. (ºC)	Antiinflammatory activity (%)	Analgesic activity (%)
1	H	- C_6H_5	262	52.70	76.00
2	H	-C_6H_4Cl (*o-)*	282	–	78.00
3	H	-C_6H_4-CH_3 (*m-)*	240	–	–
4	H	- CH=CH-C_6H_5	164	–	–
5	H	-C_6H_4-CH_3 (*p-*)	222	–	–
6	H	-C_6H_4-OCH_3 *–(p-)*	213	–	–
7	Cl	-C_6H_4Cl *(o-)*	217	–	92.30
8	Cl	-C_6H_3-$(OCH_3)_2$ *(m- & p-*)	242	46.37	83.00
9	Br	-C_6H_5	218	–	92.30
10	Br	-C_6H_4Cl *(o-*)	218	–	–
11	Br	-CH=CH-C_6H_3-[$(OCH_3)_2$- *m- & p-*]	212	–	–
12	Br	-CH=CH-C_6H_4-(OCH_3-*p-*)	247	50.40	65.00
Standard		Ibuprofen		64.70	
Standard		Diclofenac sodium			74.00

Preparation of 3-acetyl coumarin/substituted 3-acetyl coumarins: To a cooled suspension of mixture of salicylaldehyde or substituted salicylaldehyde (0.5 mol) and ethylacetoacetate (0.5 mol), 10 g of piperidine was added with continuous shaking. The mixture was then maintained at freezing temperature for 2-3 h. A yellow coloured mass so obtained was separated out and washed with cold ethanol, filtered and crystallized from hot glacial acetic acid (Yield 85 %).



Scheme

Preparation of coumarinyl chalcones (1-12): To 1 g of acetyl coumarin in 4 mL of 30 % of sodium hydroxide, a solution of 1 mL of substituted aromatic aldehyde in 5 mL ethanol was added. The red solution so obtained was allowed to stand for 24 h, diluted to 100 mL with water and then acidified with dilute hydrochloric acid. The precipitate so formed was filtered, dried and recrystallized from glacial acetic acid.

Antioxidant activity: The antioxidative activity of some of the selected compounds was done by DPPH* scavenging method[11].

Antiinflammatory activity: The antiinflammatory activity of the synthesized test compounds was determined by carrageenan induced rat paw edema method[12]. The test compounds such as, **1**, **8** and **12** were suspended in 5 % w/v Tween 80 solution and were given orally to the rats at the dose of 100 mg/Kg body weight; after 0.5 h, 0.1 mL of 1 % w/v solution of carrageenan was injected into plantar region of left paw and 0.1 mL of 1 % w/v solution of saline to the right paw of control, standard and treated animals. The paw volumes of both legs of all the groups were measured with plethysmograph at an interval of 1, 2, 3, 4 and 6 h, respectively. Ibuprofen was used as standard and administered according to the test protocol. The activity was reported as % inhibition of paw volume as shown in Table-1.

Analgesic activity: The analgesic activity of synthesized test compounds was determined by acetic acid induced abdominal constriction method[13]. Each test compound was suspended in 5 % Tween 80 and administered orally at the dose of 100 mg/Kg

body weight. After 0.5 h, the pain was induced by intraperitoneal injection with 1 % solution of acetic acid at a dose of 1 mL/100 g body weight and was recorded as writhing episodes after an interval of 10 min. Diclofenac sodium was used as standard at the dose of 7.14 mg/Kg body weight and administered according to the test protocol. The results of the analgesic activity was reported as % inhibition of abdominal constriction as shown in Table-1.

Antibacterial activity: All the synthesized test compounds were screened for their antibacterial activity by agar diffusion method[14] using (Gram +ve) organisms such as *B. subtili* and *S. aureus* and (Gram -ve) organisms such as *E. coli* and *K. pneumonia*. The stock solutions of test compounds and standard drug (streptomycin) were prepared in the concentration of 200 µg/0.1 mL in DMSO and the results were recorded as zone of inhibition as shown in Table-2.

TABLE-2

Compd.	*B. subtilis*	*S. aureus*	*E. coli*	*K. pneumonia*
1	14	10	–	–
2	10	16	13	8
3	8	8	8	–
4	14	17	12	12
5	–	12	8	–
7	–	–	13	12
8	18	15	12	10
9	14	14	12	8
10	14	12	9	18
11	–	14	–	–
12	10	13	15	10
Streptomycin	22	18	15	10

RESULTS AND DISCUSSION

All the synthesized coumarinyl chalcones were purified by TLC and are characterized by their IR, ^{1}HNMR and mass spectral analysis. They were screened for their antioxidant, antiinflammatory, analgesic and antibacterial activity.

It was thought worth-while to carry out antioxidant activity as a preliminary screening method to evaluate antiinflammatory, analgesic and antibacterial activity. However, when few of the test compounds were randomly selected for their antioxidant activity, none of them exhibited the same.

Further, when all the test compounds were screened for their analgesic and antiinflammatory activity, test compounds such as **7** and **9** showed analgesic activity in terms of percentage protection against writhing episodes at 92.30 % each when compared to that of standard diclofinac sodium at 74.00 %. Test compounds such as **7** and **9** had halogen such as chlorine and bromine at 6th position on the coumarinyl nucleus; this suggests that halogen substitution at 6th position has greater influence on analgesic activity than unsubstituted ones.

Three of the test compounds were randomly selected for their antiinflammatory activity such that, each one had different substituent group such as H, Cl and Br groups at 6th position. Out of these test compounds, it was found that the unsubstituted compound showed activity at 52.70 % whereas, compounds **8** (chloro) and **12** (bromo) showed activity at 46.37 and 50.40 %, respectively when compared with that of the standard ibuprofen at 64.70 %. From present study, it was found that the unsubstituted counterpart was more appropriate candidate for expressing anti-inflammatory activity than the halogen substituted counterpart.

Further, all the test compounds were screened for their routine antibacterial activity by agar diffusion method. Out of the test compounds evaluated against four different species such as, *B. subtilis*, *S. aureus*, *E. coli* and *K. pneumonia*, it was found that compounds **2**, **4**, **7**, **8**, **9**, **12** showed moderate activity on all the test organisms excepting *E. coli* as shown in the Table-2. However, the test compound **11** when tested against *S. aureus* showed inhibition very close to that of standard streptomycin. Out of the test compounds showing antibacterial activity, test compound **8** exhibited activity against all organisms almost at par with that of standard streptomycin whereas, compound **12** showed activity on both *E. coli* and *K. pneumonia* compared to that of the standard streptomycin as shown in the Table-2. Further, compound **10**, a bromo substituted derivative of coumarin has shown zone of inhibition at 18 when compared with that of the standard streptomycin showing inhibition at 10 against *K. pneumonia* as shown in the Table-2.

There is a need to study quantitative antibacterial activity along with the properties with respect to compound **10** as it is found to be the most promising test candidate in present antibacterial study.

REFERENCES

1. J.B. Harborne and C.A. William, *Photochemistry*, **55**, 481 (2000).
2. I. Kostova, *Expert Opin. Drug Discov.*, **2**, 1605 (2007).
3. S. Manfredini, R. Bazzanini, P.G. Baraldi, M. Guarneri, D. Simoni, M.E. Marongiu, A. Pani, E. Tramontano and P. La Colla, *J. Med. Chem.*, **35**, 917 (1992).
4. C.C. Chiang, J.F. Mouscadet, H.J. Tsai, C.T. Liu and L.Y. Hsu, *Chem. Pharm. Bull. (Tokyo)*, **55**, 1740 (2007).
5. M. Oblak, M. Kotnik and T. Solmajer, *Curr. Med. Chem.*, **14**, 2033 (2007).
6. S. Sardari, Y. Mori, K. Horita, R.G. Micetich, S. Nishibe and M. Daneshtalab, *Bioorg. Med. Chem.*, **7**, 1933 (1999).
7. K.C. Fylaktakidou, D.J. Hadjipavlou-Litina, K.E. Litinas and D.N. Nicolaides, *Curr. Pharm. Design*, **10**, 3813 (2004).
8. M. Gellert, K. Mizuuchi, M.H. O'Dea, T. Itoh and Jun-Ichi Tomizawa, *Proc. Natl. Acad. Sci. (USA)*, **73**, 4474 (1976).
9. (a) P. Dey, *Curr. Med. Chem.*, **13**, 2909 (2006); (b) http://en.wikipedia.org/wiki/Turmeric (c) K.M. Lokanatha Rai, Y.B. Basavaraju and B. Sadashivamurthy, *Indian J. Pharm. Sci.*, **69**, 116 (2007).
10. Y.B. Vibhute and M.A. Baseer, *Cheminform.*, **34** (2003).
11. M.S. Blios, *Nature*, **181**, 1191 (1958).
12. C.A. Winter, E.A. Risley and G.W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).
13. L.B. Witkin, C.F. Heubner, F. Galdi, O'keefe, P. Spitaletta and A.J. Plummer, *J. Pharmacol. Exp.*, **133**, 400 (1961).
14. H. Richardson, E.H. Emslie-Smith and B.W. Senior, *Appl. Microbiol.*, **16**, 1468 (1968).

(*Received*: 1 August 2008; *Accepted*: 19 May 2009) AJC-7559