IJPSR (2013), Vol. 4, Issue 4 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 30 December, 2012; received in revised form, 21 February, 2013; accepted, 15 March, 2013

SYNTHESIS AND ANTIMICROBIAL EVALUATION OF CHROMONES BEARING 1, 5-BENZO THIAZEPINYL MOIETY

R.V. Dengle*[1] and R. N. Deshmukh [2]

Department of Chemistry, Vivekanand College, Kolhapur – 416002, Maharashtra, India
Department of Chemistry, Bharati Vidyapeeth's College of Engineering, Kolhapur- 416013, Maharashtra, India

Keywords:
1,5-Benzothiazepines, Antimicrobial, Chromones, Bischalcone

Correspondence to Author:

Dr. R.V. Dengle

Associate Professor, Department of Chemistry, Vivekanand College, Kolhapur – 416002, Maharashtra, India

E-mail: drrameshdengle@gmail.com

ABSTRACT: 1, 5-Benzothazepinyl chromones were synthesized starting from 2, 4-diacyl phenol. The 2, 4-diacyl phenol was condensed with aryl aldehydes to obtain bis-chalcones[1a-d]. The bis-chalcones on cyclocondensation with equimolar amount of 2-aminothiophenol gave 1, 5-benzothiazepinyl chalcones[2a-d]. The chalcones on oxidative cyclisation in DMSO - I_2 yielded the titled compounds[3a-d]. The microbial evaluation of the representative 1, 5-benzothiazepinyl chromones has also been performed.

INTRODUCTION: 1, 5-Benzothiazepines are valuable structural units in the field of medicinal chemistry due to their significant pharmacological properties [1].

Number of biological activities have been associated with 1,5-benzothiazepine skeleton such as antihypertensive [2], anti-ischemic [3], analgesic [4], cardiovascular [5], platelets aggregation inhibitor [6], calcium antagonists [7]. It has been observed that incorporation of 1.5-benzothiazepine unit has resulted in the compounds with enhanced biological activities like anti-inflammatory [8], anticancer [9], vasodilation [10], antifungal [11], anti HIV [12], antimicrobial [13].

QUICK RESPONSE CODE

IJPSR:
ICV (2011)- 5.07

Article can be accessed online on:
www.ijpsr.com

Chromones occurs widely in number of natural products and are proved to be versatile molecules owing to their pharmacodynamics. chromones and its derivatives found to have wide range of biological properties including anti-inflammatory, analgesic, antimicrobial, antitumor and anticancer.

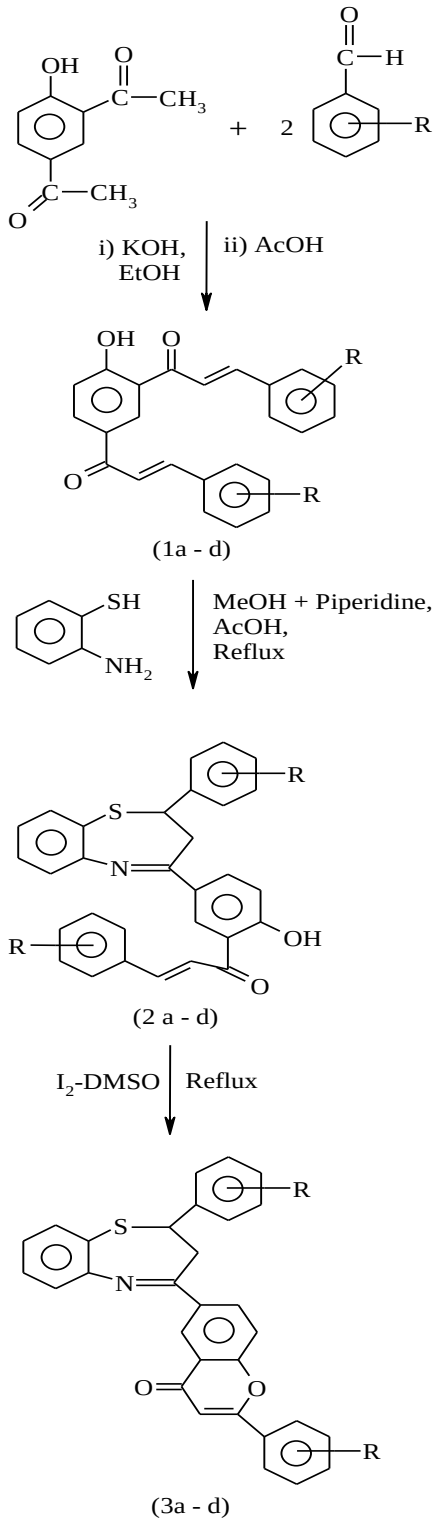
Keeping in mind the broad spectrum of biological activities shown by 1,5-benzothiazepines and chromones, we thought to combine these two privileged structures within a molecular frame work to obtain better pharmacological properties.

To obtain the target molecules we preferred to start the synthetic route with simple and easily available precursor that is 2,4-diacylphenol. 2,4-diacylphenol on reaction with aryldehydes in 1:2 mole proportion yielded bis-chalcones.

Bis-chalcones on cyclocondensation with 2-aminothiophenol in presence of catalytic amount of piperdine in methanol at reflux condition give 1,5-benzothiazepines.

These 2,4-disubstituted 1,5-benzothiazepines contain chalcone skeleton as one of the substitutions which on oxidative cyclisation in I_2-DMSO system, finally cyclise to give the desired target molecules, which contain both chromone and 1,5-benzothiazepine as a part of its structure. The synthesis pathway leading to the title compounds is given in scheme 1.

Scheme 1 :



Where, R = H, CH_3, OCH_3, Cl.

MATERIALS AND METHODS: Melting points were recorded with open capillary method and are uncorrected. All the synthesized products were characterized with the help of their IR, NMR spectra and elemental analysis. IR spectra were recorded on a Perkin Elmer spectrophotometer using KBr discis. NMR spectra were obtained from Bruker AMX-500 FT NMR spectrometer, in $CDCl_3$ using TMS as an internal standard.

Synthetic Procedure: (1a - d) synthesis of 2,4-di-(3'-aryl-acrylo)-phenol. (Bis-chalcone). A mixture of 2,4-diacylphenol (0.01 mole) and aromatic aldehyde (0.02 mole) was dissolved in ethanol (50 ml) and was added a solution of potassium hydroxide in a portion, keeping the temperature below 10°C. The reaction flask was corked and kept at room temperature for 48 hours. The contents of the flask was then poured over ice containing acetic acid. The solid thus obtained was filtered, washed with water and crystallised from acetic acid. The melting point, yields and solvents for crystallisation are listed in **table 1**.

To a mixture of bischalcone, 2,4-bis-(3'-aryl-acryl) phenol (0.01 mole) and 2-amino-benzenethiol (0.01 mole) in methanol was added 2-3 drops of piperidine and it was refluxed for four hours. It was acidified with glacial acetic acid (10 ml) and further refluxed for two hours and cooled. The reaction mixture was left overnight at room temperature. The solid thus obtained was filtered. In a few cases it was necessary to pour the reaction mixture in water and solid thus obtained was filtered and crystallized from methanol-acetic acid mixture. Purity of the product was checked by TLC. The melting points, yields and solvent for crystallization are listed in **table 2**.

A solution of 1-[2'-hydroxy-5'-(2''-aryl-2,3-dihydro-1,5-benzothiazepine -4'-yl)-phenyl]-3-aryl-2-propen-1-ones (0.01 mole) in DMSO containing iodine (1-2 crystals) was refluxed for 10-15 minutes. The reaction mixture was cooled to room temperature and poured on crushed ice with stirring. The solid thus obtained was filtered, washed with 10% sodium thiosulphate solution followed by water. It was then dried and crystallized from DMSO-ethanol mixture. Purity of the product was checked by TLC. Melting points, yields, solvents for crystallization are listed in **table 3**.

TABLE 1 : DATA OF COMPOUNDS 1a - d.

Compounds	R	Solvent for crystallization	M.P. [°C]	Yield [%]
1a	H	Ethanol + AcOH	152	85
1b	CH_3	AcOH	148	84
1c	OCH_3	AcOH	142	86
1d	Cl	AcOH	210	80

(2a-d) synthesisof 1-[2'-hydroxy-5'-(2''-aryl-2,3-dihydro-1, 5-benzothiazepine-4'-yl)-phenyl)-3-aryl-2-propen-1-ones.

TABLE 2 : DATA OF COMPOUNDS 2a - d.

Compounds	R	Solvent for crystallization	M.P. [°C]	Yield [%]
2a	H	Methanol	172	68
2b	CH_3	Methanol + AcOH	162	60
2c	OCH_3	Methanol + AcOH	178	72
2d	Cl	Methanol + AcOH	240	65

[3a -d] synthesis of 2-aryl-2,3-dihydro-4-[2'-aryl-chromon-6'-yl)-1,5-benzothiazepenes.

TABLE 3 : DATA OF COMPOUNDS 3a - d.

Compounds	R	Solvent for crystallization	M.P. [°C]	Yield [%]
3a	H	DMSO + EtOH	282	86
3b	CH_3	DMSO + EtOH	262	80
3c	OCH_3	DMSO + EtOH	284	86
3d	Cl	DMSO + EtOH	294	78

Microbial evaluation of the representative compounds: The newly synthesized compounds have been screened for microbial activity using filter paper disc method. The solution of the compounds were prepared in acetone at 250 ppm and 500 ppm concentrations. The discs of Whatman filter paper 6 mm diameter were dipped out from the test solution of different concentrations. After evaporation of acetone in the aseptic conditions, the treated discs were placed on the Czepel Dox agar medium seeded with pathogens disc, placed in acetone served as control. The plates were incubated at 26°C □ 5°C for a week. The inhibitory or stumulatory zones in mm were recorded. Carbendazim (Bavastin) and streptomycin sulphate were used as standard for *Aspergillus, Flavus, Helminthosporium oryzae* and *Xanthomonas compestris, Bacillus subtilis* respectively. The results of antifungal and antibacterial activities are recorded in table 4.

Table 4 : Result of Microbial Screening

Products	A		B		C		D	
	I	II	I	II	I	II	I	II
3a	-1	-2	-2	-2	-2	-4	-2	-3
3c	-2	-3	-2	-2	-3	-4	-2	-3
3d	-2	-3	-2	-3	-3	-4	-2	-4
Carbendazim (Bavastin)	-4	-7	-3	-5				
Streptomycin sulphate					-3	-5	-4	-6

A = *Aspergillus flavus,* B = *Helminthosporium oryzae,* C = *Xanthmononas compestris,* D = *Bacillus subtilis,* - = Inhibitory in ppm : I = 250, II = 500.

Spectral data of selected compounds:

(1C) : IR (KBr, Cm^{-1}) 3150-3180 (OH), 1650-1660 (C=0) .^{1}HNMR ($CDCl_3$) δ3.75 - 3.85 (6H, S, OCH_3), δ6.75 - 8.7 (15H, m, ArH), δ13.45 (1H, S, phOH) (2C): IR (KBr, Cm^{-1}) 3150 - 3180 (OH), 1620 - 1630 (C=0), 1585 - 1600 (C=N).

^{1}H NMR ($CDCl_3$) δ3.14 - 3.48 (2H, m, -CH-CH_2-), δ3.76 (3H, S, OCH_3) δ3.87 (3H, S, OCH_3), δ5.15 (1H, dd, -CH-CH_2-), δ6.82 (17H, m, ArH), δ15.38 (1H, S, p0H).

(3C): IR (KBr, Cm^{-1}) 1610 - 1640 (C=0), 1580 - 1600 (C=N), ^{1}H NMR ($CDCl_3$) δ3.71 - 3.85 (2H, m, -CH-CH_2), δ3.88 (3H, S, OCH_3), δ3.91 (3H, S, OCH_3), δ5.14 (1H, dd, -CH-CH_2-), δ6.81 - 8.87 (16H, m, ArH).

RESULTS AND DISCUSSION: We describe herein the synthesis of 1,5-benzothiazepines. For the synthesis of target compounds. First, the bis-chalcones 1a - d were prepared by the reaction of 2,4-diacylphenol with aryl aldehydes in presence of ethanol and 40% aqueous KOH. The condensation of 2,4-diacyl-phenol with arylaldehydes in presence of 40% KOH afforded bis-chalcones.

Cyclocondensation of compounds 1a - d with equimolar amount of 2-aminothiophenol in methanol and 2 - 3drops of piperidine gave 1,5-benzothia zepinyl chalcones 2a - d. The 1, 5-benzo thiazepinyl chalcones on oxidative cyclisation in I_2-DMSO and (1-2 crystals of iodine) gave the target compounds 3a - d (Scheme 1). The structure of the synthesized compounds was confirmed by M.P., IR and PMR spectra. The synthesized compounds were screened for antifungal and antibacterial activities. The results are summarized in Table 1, Table 2, Table 3 and Table 4.

CONCLUSION: In conclusion, novel chromones bearing 1, 5-benzothiazepinyl moiety were prepared. For the synthesis oxidative cyclisation with I_2-DMSO was used because time required was short, products obtained were pure, and simple experimental conditions. The antimicrobial activity of these compounds was evaluated against various bacteria and fungi. Compounds showed a moderate degree of antimicribial activity. Among them compound 3C was found to be most active against all the microorganisms employed both for antibacterial and antifungal activity.

ACKNOWLEDGEMENT: The author thanks to Vivekanand College, Kolhapur, Bharati Vidyapeeth College of Engineering, Kolhapur and Department of Chemistry, Shivaji University, Kolhapur for their support.

REFERENCES :

1. Bariwal JB, Upadhyay KD, Manvar AT, Trivedi JC, Singh JS, Jain KS, Shah AK, Eur J Med Chem,2008; 43: 2279-2290.
2. Inove H, Konda M, Hashiyama T, Otsuka H, Takashashi K, Gaino M, Date T, Aoe K, Takeda M, Murata S, Narita H, NagaoT J. Med Chem,1991;34: 675-687.
3. Ooisihi A, Takeda M. Nakajima H, Nagao , Jpn Kokai Tokkyo Koho Jp 61262, 1986, S20, Chem. Abstr,1987; 106 :1494478b.
4. Satyanarayanan K, Rao MNA, Indian J PharmSci,1993; 55:230.
5. Nagao T, Sato M,Nakajima A, Kiyomoto, Chem Pharma Bull, 1973; 21:92-97
6. Weiss K., Fitscha P, Gazso A, Gludovac H, Prog Clin.Biol.Res,1989;301 **:353.**
7. Chaffman M, Brogden RN, Drugs, 1985; 29: 387-454
8. Dunn JP, Ackerman NA, Tomolonis AJ, J Med Chem, 1986; 29: 2326-2329
9. Gradishar WJ,Jordan VC,Clin J Oncol, 1997; 15:840-852
10. Nagao T, Sato Y, Iwasawa T, Takada R, Ishida, Jpn J Pharmacol, 1972;22:467-478
11. Dandia A, Singha R, Khaturia S, Cheminfor, 2007; 38 (36):236.
12. Giuliano G, Luana P, Valeria A, Eur J Med Chem,1999: 34 (9): 701.
13. Nikalje AG., Mane RA, InglePB, Ind J Het Chem, 2006 15(3): 309-310.

How to cite this article:
Dengle RV and Deshmukh RN: Synthesis and Antimicrobial evaluation of Chromones bearing 1, 5-benzo thiazepinyl moiety. *Int J Pharm Sci Res* 2013; 4(4); 1495-1498.