RESEARCH PAPER | Pharma | Volume : 4 | Issue : 1 | Jan 2014 | ISSN - 2249-555X

Spectral studies and synthesis of 10-substituted 6a, 7-dihydro-6H-7-(4-hydroxyphenyl) - 6-(4-methoxyphenyl) -[1] benzopyrano[3, 4-c][1,5]- benzothiazepines

KEYWORDS: Substituted 2-Aminobenzenethiols, 4-hydroxybenzylidene chromanone, trifluoroacetic acid.etc.

Ved Prakash Bairwa	Prerna Jain	B.S. sharma
Dept. of chemistry, Govt. R.R. CollegeAlwar (Raj.) India.	Dept. of chemistry, Govt. R.R. CollegeAlwar (Raj.) India.	Dept. of chemistry, Govt. R.R. CollegeAlwar (Raj.) India.

ABSTRACT *Diltiazem and clentiazem having 1,5-benzothizepine nuclei shows various biological activities so we are going to synthesize new 1,5-benzothizepine derivatives. For the synthesis of substituted 1,5- benzothiazepines, equimolar proportion of 5-substituted-2-amino benzenethiols, the substituents being fluoro,Chloro, bromo, methyl, methoxy, and ethoxy were reacted with 2-(4-anisyl)-3-(4 hydroxybenzylidine)chromanone in dry toluene containing trifluoroacetic acid in catalytic amount to give respective 10-substituted 6a, 7-dihydro-6H-7-(4-hydroxyphenyl)- 6-(4-methoxyphenyl)- [1] benzopyrano [3,4-c][1,5]- benzothiazepines. The products were conveniently obtained by refluxing for 3 hours in good yield. The structural investigations are based on the result of microanalytical data of elements and spectroscopic studies based on IR, H^1 NMR, and mass spectra.*

1.Introduction

1,5-benzothiazepine derivatives have been reported to be well know chemotherapeutic agent because of their various pharmacological and biological activities such as anti HIV[1], Calcium channel blocker[2,3], antifeedant[4], anticonvulsant[5], antibacterial[6,7], anticancer[8] , CNS activity[9] etc. Due to various biological activities of 1,5-benzothiazepine, great efforts have been made to synthesize 1,5-benzothiazepine derivatives. Incorporation of substituents in fused benzene ring and in heterocyclic ring enhances biological activities[10,11].

By the survey of literature it was found that acid catalysed condensation[12] of flavanone and substituted benzaldehyde gives substituted arylidene flavanone in good yield as **scheme 1**.

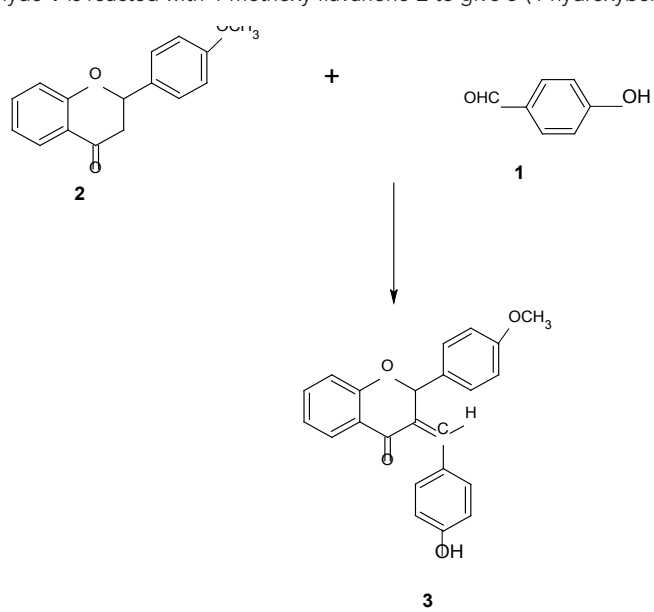
The synthesis of the title compounds were carried out by the reaction of Substituted 2-Aminobenzenethiol and 2-(4-anisyl)-3-(4 hydroxybenzylidine)chromanone.

2.Result and discussion

Acid catalysed condensation of 4-hydroxybenzaldehyde **1** with flavanone **2** afforded 3-(4-hydroxybenzalidene)-flavanone **3** which was reacted with six 5-substituted-2-aminobenzenethiols **4a-f** the substituents being fluoro,Chloro, bromo, methyl, methoxy, and ethoxy to give the title compounds On refluxing the precursors 1 and 2 for 3 hr, the products were obtained in yield of 60-70% in acidic medium –toluene containing trifluoroacetic acid .

The synthesis of 10-substituted 6a, 7-dihydro-6*H*-7-(4-hydroxyphenyl)- 6-(4-methoxyphenyl)- [1] benzopyrano [3,4-c] [1,5]- benzothiazepines was carried in two steps-

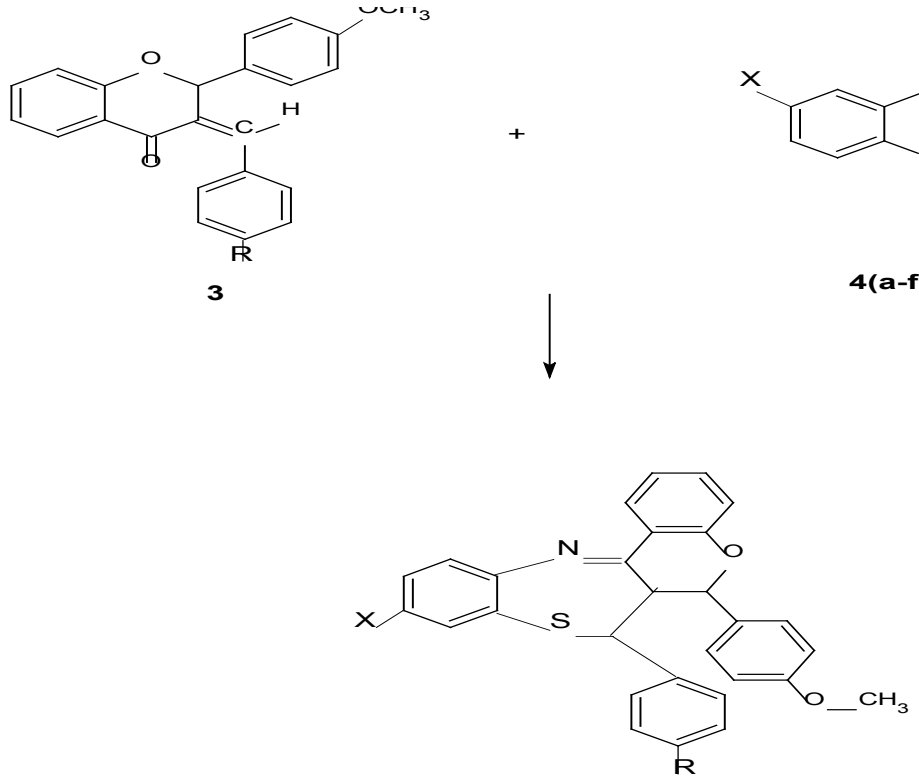
Step-I – 4-hydroxybenzaldehyde **1** is reacted with 4-methoxy flavanone **2** to give 3-(4-hydroxybenzylidine) flavanone **3.**



Scheme I

Step II- In this step equimolar quantities of 3-(4-hydroxybenzylidine)flavanone **3** and 5-substituted-2-aminothiophenols **4a-f** were refluxed for about 3 hours in dry toluene containing trifluoroacetic acid as catalyst. The product **5a-f** was obtained in good yield.

Volume : 4 | Issue : 1 | Jan 2014 | ISSN - 2249-555X



Scheme II

Compd	5a	5b	5c	5d	5e	5f
X	F	Cl	Br	CH_3	OCH_3	OC_2H_5
R	OH	OH	OH	OH	OH	OH

3. Spectral analysis:
The IR spectra of all the 06 compounds showed strong absorption in the region 1615-1606 cm^{-1}which indicates the presence of C=N. Absence of absorption peak around 1680 cm^{-1} indicates that both precursors have reacted to give the target compound. The peak at 3400-3300 cm^{-1} confirms the presence the OH group.

In ^{1}H-NMR spectra of **5d** , the absorption at δ 3.76 as a singlet may be assigned to 3 protons of OCH_3 group and the absorption at 2.37 as a singlet integrated for three protons indicated the presence of methyl group in **5d**. Two singlet equivalent to 3H each at δ 3.83 and 3.89 indicated the presence of two methoxyl groups in the product **5e**. In ^{1}H-NMR spectra of 5f , the absorption at δ 3.82 as a quartet equivalent to 3H and a triplet at 2.18 with the same value of J= 6 Hz may be assigned to protons of OC_2H_5 group. In ^{1}H-NMR spectra of **5a-5f**, a broad single at δ 7.09- 8.05 may be assigned to hydroxyl proton.

The mass spectra of compounds **5b** showed M^+ peak and [M +2] peak . The [M+2] peak was found to be about 1/3 of M+ peak which indicates the presence of chlorine.

Table-I Characterisation data of Compounds 5a-f

Compoud NO.	R	M.P. °C	Rf	Yield %	Molecular Formula (Mol. Wt.)	Elemental Analysis % Found (Calcd)		
						C	H	O
5a	F	138	0.70	52	$C_{29}H_{22}NO_3SF$ (483)	72.42 (72.05)	4.34 (4.55)	9.57 (9.93)
5b	Cl	153	0.68	61	$C_{29}H_{22}NO_3SCl$ (499.5)	69.69 (69.67)	4.48 (4.40)	9.29 (9.61)
5c	Br	145	0.78	66	$C_{29}H_{22}NO_3SBr$ (544)	64.38 (63.97)	4.10 (4.04)	8.98 (8.82)
5d	CH_3	142	0.70	48	$C_{30}H_{25}NO_3S$ (479)	75.57 (75.15)	5.95 (5.22)	10.58 (10.02)

Volume : 4 | Issue : 1 | Jan 2014 | ISSN - 2249-555X

5e	OCH_3	147	0.89	64	$C_{30}H_{25}NO_4S$ (495)	72.87 (72.72)	5.93 (5.05)	12.47 (12.93)
5f	OC_2H_5	154	0.65	58	$C_{31}H_{27}NO_4S$ (509)	73.94 (73.08)	5.46 (5.30)	12.34 (12.57)

Table-II – Characteristic Data of Compounds 5a-f

Compd.	^{1}HNMR (δ, ppm)					
	C_{10}-XH	C_6-H	C_{6a} -H	C_7-H (d,J=12.2)	Aromatic Protons	OCH_3(s-3H)
5a	-	6.34(d, J=1.2)	7.09(dd,J_1=12.2, J_2=1.2)	6.82	6.18 - 8.12	3.76
5b	-	6.37(d, J=1.0)	7.12(dd,J_1=12.2, J_2=1.0)	6.80	6.12 - 8.14	3.82
5c	-	6.38(d, J=1.1)	7.07(dd,J_1=12.1, J_2=1.2)	6.77	6.14 - 8.21	3.86
5d	2.37(s,3H)	6.40(d, J=1.2)	7.14(dd,J_1=12.1, J_2=1.1)	6.70	6.04 - 8.12	3.76
5e	3.87(s,3H)	6.37(d, J=1.1)	7.06(dd,J_1=12.3, J_2=1.1)	6.88	6.08 - 8.16	3.83,3.89
5f	3.82(q,2H J=6Hz) 2.18(t,3H j=6Hz)	6.32(d,J=1.2)	7.10(dd,J_1=12.2, J_2=1.2)	6.76	6.16.-.8.22	3.81

4.Experimental Section:
All the melting points were determined in open capillary tubes and were uncorrected .The purity of the compounds was checked by TLC on silica gel G coated glass plates using benzene –methanol-ammonia (7:2:1) as solvent system .The IR spectra were recorded on potassium bromide pellets using Perkin-Elmer RX1 FT IR spectrometer (range:4000-450 cm^{-1}). The H^1 –NMR spectra were recorded on Bruker avance 400 (FT NMR) using $CDCl_3$ as solvent. The mass spectra were recorded on JMS-T100LC, Accu TOF (DARTMS) mass spectrometer. The spectral and elemental analysis were carried out at the Sophisticated Analytical Instrumentation Facility, Central Drug Research Institute, Lucknow.

4.1 Synthesis of 5-substituted-2-aminobenzenethiols 4a-f.
Six 5-substituted-2-aminobenzenethiols **4a-f**, were prepared by literature reported methods

4.2 Synthesis of 3-(4-hydroxybenzylidene) -2-(4-methoxyphenyl)- flavanone 3.
Equimolar quantities of 4-methoxyflavanone and 4-hydroxybenzaldehyde, **3** were dissolved in ice-cold ethanol saturated with dry HCl gas. To this reaction mixture dry hydrogen chloride gas was passed with stirring till the colour changed from light yellow to purple red and the mixture was kept in refrigerator for 24 hr . the crude thus obtained was crystallized from dry ethanol to afford the flavanone, 3-(4-hydroxybenzylidene) -2-(4-methoxyphenyl)- flavanone (**3**, yellow crystals, m.p. 130^{0}C, yield 53%)

4.3 General procedure for the preparation of 10-substituted- 6a, 7-dihydro-6H-7-(4-hydroxyphenyl)-6-(4-methoxyphenyl)-[1] benzopyrano [3,4-c][1,5]- benzothiazepine5a-f.
5-substituted-2-aminobenzenthiols **4a-f** and 3-(4-hydroxybenzylidene) -2-(4-methoxyphenyl)- flavanone **3** were dissolved in dry toluene separately and mixed. Trifluoroacetic acid was added as catalyst and refluxed for 3 hours . The mixture was cooled and excess toluene was removed under reduced pressure to obtain crude solid. The crude solid was crystallized with methanol gave the title compounds. The analytical and spectral data of **5a-f** are given in the **Table I** and **II**

5.Acknowledgment:
The authors wish to thank Principal R.R. Govt. college alwar and Shri G.K. Sharma Head Dept.of chemistry for providing necessary facilities. One of them (BSS) is grateful to UGC new delhi for the award of a minar research project. Another auther (VPB) also grateful to UGC new delhi for the award of RGNF fellowship also thank to CDRI Luck now for some of the analytical and spectral work .

REFERENCE
1. Grandolini, G., Perioli, L., & Ambrogi, V., (1999), Synthesis of some new 1,4-benzothiazine and 1,5-benzothiazepine tricyclic derivatives with structural analogy with TIBO and their screening for anti-HIV activity, Eur. J. Med. Chem.,34,701-709. | 2. Atwal, K.S., Bergey, J.L., Hedberg, A., & Moreland, S., (1987), Synthesis and biological activity of novel calcium channel blockers: 2,5-dihydro-4-methyl-2-phenyl-1,5-benzothiazepine-3-carboxylic acid esters and 2,5-dihydro-4-methyl-2-phenyl-1,5-benzodiazepine-3-carboxylic acid esters, J. Med. Chem., 30, 635-640. | 3. Atwal, K.S., Ahmed, S.Z., Floyd, D.M., Moreland, S., & Hedberg, A., (1993), (cis) – 3- methyl – 1,5- benzothiazepine – 4 – ones: potent analogs of the calcium channel blocker diltiazem, Bioorg. Med. Chem. Lett., 3,(12), 2797-2800. | 4. Reddy, J.R., Ashok, D., & Sharma, P.N., (1993), Synthesis of 4,6-bis(2'-substituted- 2',3'-dihydro-1,5-benzothiazepine-4'-yl) resorcinol as potential antifeedants, Indian J. Chem., 32B, 404. | 5. Sarro, G.D., Chimirri, A., Sarro, A.D., Gitto, R., Grasso, S., & Zappala, M., (1995), 5H-[1,2,4] oxadiazolo [5,4-d] [1,5] benzothiazepines as anticonvulsant agents Eur. J. Med.Chem. 30, 925-929. | 6. Ambrogi,V., Grandolini,G., Perioli, L., Rossi, C., Ricci, M., & Tuttobello, L., (1990), Synthesis, antibacterial and antifungal activities of several new benzo-naphtho- and quinolino-1,4-thiazine and 1,5- thiazepine derivatives, Eur. J.Med. Chem., 25, 403-411. | 7. Fabriziomicheli, Degiorgis, F., Feriani, A., Paio, A., Pozzan, A., Zarantonella, P., & Pierfaustoseneci, (2001). A combinatorial approach to [1,5] Benzothiazepine derivatives as potential antibacterial agents, J. Comb. Chem., 3(2), 224-228 . | 8. Sharma, A.K., Singh, G., Yadav A.K., & Prakash L., (1997), Improved Method for the Synthesis of New 1,5-Benzothiazepine Derivatives as Analogues of Anticancer Drugs, Molecules, 2, 129 – 134. | 9. Ambrogi, V., Grandolini, G., Rossi, C., & Tiralti, M.C., (1987), Studies on annelated 1,4-benzothiazines and 1,5-benzothiazepines.III. synthesis and CNS activity of some p- substituted derivatives of the novel heterocyclic system 4,5- dihydro-5-thiazolo[3,4-d]-1,5-benzothiazepine, Farmaco.Ed.Sci.,42, 573. | 10. Pant, S., Sharma, P., Sharma, B.S., & Pant, U.C., (2007), Syntheses of 1,5-benzothiazepines: Part XXXIII- Syntheses and antimicrobial studies of 10-substituted-6-(4-methoxyphenyl)-6H-6a,7-dihydro-7-(4-methoxyphenyl/3,4-dimethoxyphenyl) [1] benzopyrano-[3,4c] [1,5]benzothiazepines, Indian J. Chem., 46B, 1537-1544. | 11. Pant, S., Sharma, P., & Pant, U.C., (2008), Syntheses of 1,5-benzothiazepines: part XXXVI - Syntheses and antimicrobial evaluation of 2-(2-chlorophenyl)-4-(4-chlorophenyl/2-thienyl)-2,5-dihydro-8-substituted-1,5-benzothiazepines, Phosphorus Sulfur and Silicon and the Related Elements, 183 (12), 2974–2983. | 12. Pant, U.C., Chandra, H., goyal, S., Sharma, P., & Pant S., (2006), Syntheses of 1,5-benzothiazepines: part XXX - Syntheses and antimicrobial studies of 10-substituted-6a,7-dihydro-6H-7-(4-fluorophenyl)-6-phenyl[1]benzopyrano[3,4-c]1,5-benzothiazepines, Indian J. of Chem., 45B (3), 752-757.