International Journal of Advance Research, IJOAR .org
Volume 1, Issue 11, November 2013, Online: ISSN 2320-9178

SPECTRAL STUDIES AND SYNTHESIS OF 10-SUBSTITUTED 6A, 7-DIHYDRO-6H-7-(3-CHLOROPHENYL) - 6-(4-METHOXYPHENYL) - [1] BENZOPYRANO [3, 4-C][1,5]-BENZOTHIAZEPINES

Prerna Jain, Ved Prakash Bairwa, B.S. sharma

Dept. of chemistry, Govt. R.R. College Alwar (Raj.) India.
lect.prernajain@gmail.com

Abstract-

1,5- benzothiazepine nuclei has tremendous biological activities. The patent drug diltiazem having 1,5-benzothiazepine nuclei used in cardiac ailment. 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-(3-chlorobenzylidine) chromanone in dry toluene containing piperidine or trifluoroacetic acid in catalytic amount to give respective 10-substituted 6a, 7-dihydro-6H-7-(3-chlorophenyl)- 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 micro analytical data of elements and spectroscopic studies based on IR, H1 NMR, and mass spectra.

Keywords:

2-Aminobenzenethiols, 1,5-benzothiazepine, benzylidene chromanone, biological activities.

Introduction

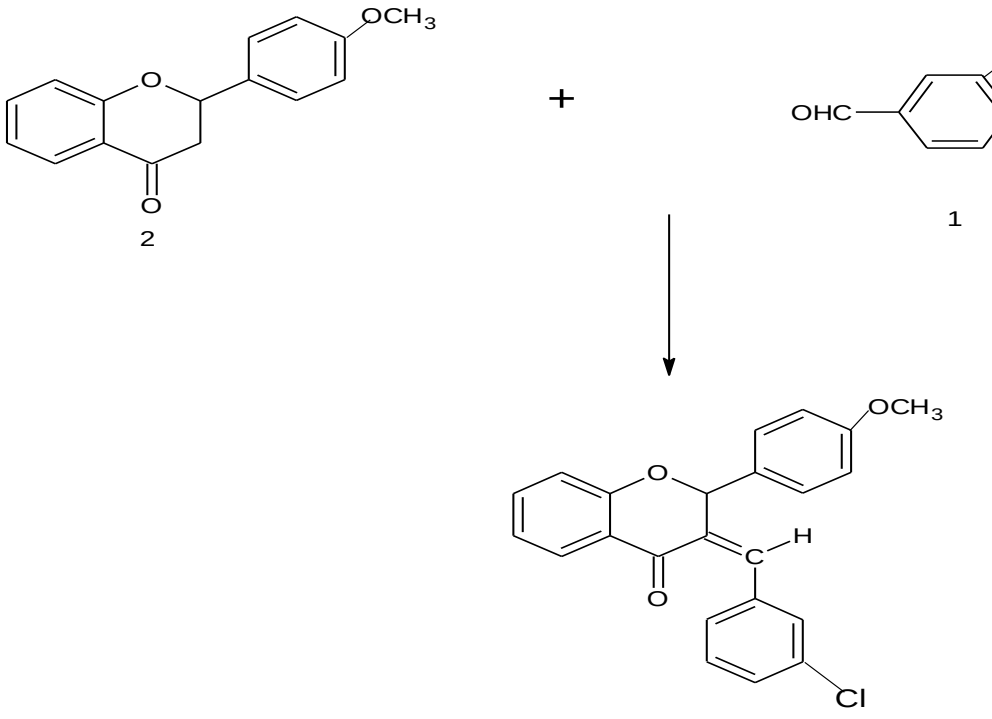
1,5-benzothiazepine nuclei has attracted attention towards medicinal chemistry. Due to its tremendous biological activities such as coronary vasodilator[1] , anti HIV[2], Calcium channel blocker[3], antihypertensive[4], antifungal[5] ,antibacterial[6], anticancer[7]etc. The benzothiazepine nuclei as drugs have been patented such as diltiazem[8]. Due to various biological activities of 1,5-benzothiazepine, great efforts have been made to synthesise 1,5-benzothiazepine derivatives.

Incorporation of substituents in fused benzene ring and in fused heterocyclic ring enhances biological activities[9,10,11]. It has been observed that incorporation of chlorine in benzothiazepine nuclei enhances anti-bacterial activities.

Result and discussion

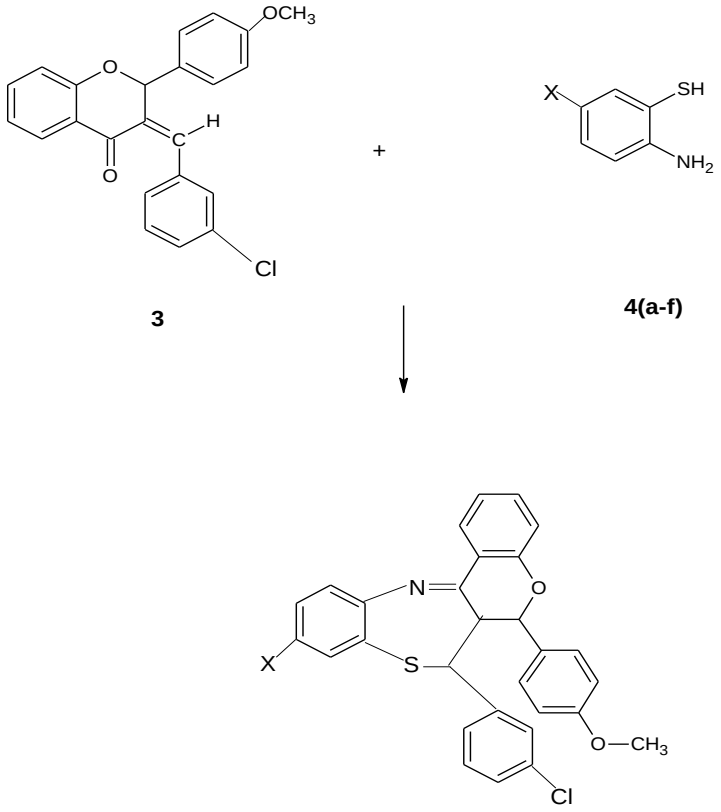
The synthesis of 10-substituted 6a, 7-dihydro-6*H*-7-(3-chlorophenyl)- 6-(4-methoxyphenyl)- [1] benzopyrano [3,4-c][1,5]- benzothiazepines was carried in two steps-

Step-I – 3-chlorobenzaldehyde **[1]** is reacted with 4-methoxy flavanone**[2]** to give 3-(3-chlorobenzylidine) flavanone**[3].**



3-(3-chlorobenzylidene)flavanone

Step II- In this step equimolar quantities of 3-(3-chlorobenzylidine)flavanone and 5-substituted-2-aminothiophenols were refluxed for about 6 hours in dry toluene containing trifluoroacetic acid as catalyst. The product **[5]** was obtained in good yield.



3 **4(a-f)**

5(a-f)

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

SPECTRAL ANALYSIS:

The IR spectra of all the 6 compounds showed strong absorption in the region 1615-1606 cm^{-1} which indicates the presence of C=N. Absence of absorption peak around 1680 and 3400-3100 cm^{-1} indicates that both precursors have reacted to give the target compound.

In H^1-NMR spectra of 5a-5f, the double doublet at δ =3.70 (J_1=12.3Hz, J_2 =1.1Hz) may be assigned to C_{6a}. A doublet at δ=4.98 (J==12.2) may be assigned to C_7-H. The multiplet at δ=6.04-8.26 may be assigned to 15 aromatic protons. Appearence of singlet at 3.87 may be assigned to 3 protons of OCH_3 group. In compound 3f a quartet at 3.76 and a triplet at 1.36 may be assigned to protons of OC_2H_5 group.

The mass spectra of compounds(5a-f)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	120-122	0.74	58	$C_{29}H_{21}NO_2SClF$ (501.5)	69.72 (69.39)	4.34 (4.18)	6.57 (6.38)
5b	Cl	111-113	0.72	64	$C_{29}H_{21}NO_2SCl_2$ (518)	67.29 (67.18)	4.40 (4.05)	6.29 (6.17)
5c	Br	122-125	0.78	68	$C_{29}H_{21}NO_2SClBr$ (562.5)	61.98 (61.86)	4.02 (3.73)	5.78 (5.68)
5d	CH_3	110-112	0.70	45	$C_{30}H_{24}NO_2ClS$ (497.5)	72.57 (72.36)	4.95 (4.82)	6.58 (6.43)
5e	OCH_3	108-110	0.68	59	$C_{30}H_{24}NO_3ClS$ (513.5)	70.67 (70.10)	4.93 (4.67)	9.47 (9.34)
5f	OC_2H_5	112-114	0.69	64	$C_{31}H_{26}NO_3ClS$ (527.5)	70.94 (70.52)	5.06 (4.92)	9.34 (9.10)

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

Compd.	^{1}HNMR (δ, ppm)					
	C_{10}-XH	C_6-H	C_{6a} -H	C_7-H	Aromatic Protons	$C_{4''}$ –OCH_3-H
5a	--	4.90(d, J=1.1)	3.67(dd,J_1=12.2, J_2=1.2)	4.96	6.01 - 8.29	3.87
5b	-	4.91(d, J=1.1)	3.68(dd,J_1=12.1, J_2=1.1)	4.97	6.24 - 8.23	3.86
5c	-	4.89(d, J=1.0)	3.65(dd,J_1=12.1, J_2=1.0)	4.96	6.13 - 8.21	3.86
5d	2.32(s.3H)	4.91(d, J=1.0)	3.66(dd,J_1=12.1, J_2=1.1)	4.97	6.15 - 8.20	3.87
5e	3.82(s, 3H)	4.90(d, J=1.2)	3.69(dd,J_1=12.2, J_2=1.2)	4.97	6.11 - 8.23	3.88
5f	3.76(q,2H) 1.36(t,3H)	4.90(d,J=1.1)	3.68(dd,J_1=12.1, J_2=1.2)	4.96	6.15 - 8.20	3.87

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 onDRX-300 MHz Bruker,Switzerland NMR using $CDCl_3$ as solvent. The mass spectra were recorded on JMS-T100LC, Accu TOF (DARTMS) mass spectrometer.

10-fluoro- 6a, 7-dihydro-6H-7-(3-chlorophenyl)- 6-(4-methoxyphenyl)- [1] benzopyrano [3,4-c][1,5]- benzothiazepine(5a)-

2-amino-5-fluro benzenethiol (0.14gm,0.001mol) and 2-(4-anisyl)-3-(3-chlorobenzylidene) (0.37gm,0.001mol) were dissolved in dry toluene (15ml) separately and mixed. Trifluoroacetic acid (1ml) was added as catalyst and refluxed for 3 hours . The mixture was cooled and excess toluene was removed under reduced pressure to obtain light yellow solid. The crude solid was crystallized with methanol. Purity was checked by TLC and spectra were recorded of 10-fluoro- 6a, 7-dihydro-6H-7-(3-chlorophenyl)- 6-(4-methoxyphenyl)- [1] benzopyrano [3,4-c][1,5]- benzothiazepine.[5a, m.p. 120-22^{o}C,yield 0.29gm]

Acknowledgment:

The authors wish to thank the Head, Department of chemistry, Govt. R.R. Autonomous college, alwar and UGC, New Delhi for providing facilities to work. We also thanks to SAIF, Central drug research institute, Lucknow for providing analytical facilities.

REFERENCES:

1. K.Hirano, H.Kanaide, S.Abe and M.Nakamura, Effects of diltiazem on calcium concentrations in the cytosol and on force of contractions in porcine coronary arterial strips: Br. J. Pharmac., **101,** 273-280 (1990).
2. Grandolini G, Perioli L, Ambrogi V, 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(1999)
3. K.S.Atwal, S.Z.Ahmed, D.M.Floyd, S.Moreland and A.Hedberg, (cis) – 3- methyl – 1,5- benzothiazepine – 4 – ones: potent analogs of the calcium channel blocker diltiazem: Bioorg. Med. Chem. Lett., 3, 2797-2800 (1993).
4. J.F.Burris, M.R.Weir, S.Oparil, M.Weber, W.J.Cady and W.H.Stewart, An assessment of diltiazem and hydrochlorothiazide in hypertension: application of factorial trial design to a multicenter clinical trial of combination therapy: J. Am. Med. Assoc., **263,** 1507-1512 (1990).
5. A. Dandia, R. Singh, and S. Khaturia, Efficient microwave enhanced solvent free synthesis of potent antifungal agents: Fluorinated benzothiazepine fused β-lactam derivatives: J. fluorine Chem., 128, 524-529(2007).
6. Fabrizio micheli**,** Fabio Degiorgis, Aldo Feriani, Alfredo paio, Alfonso pozzan, Paola Zarantonella, and Pierfausto seneci, A combinatorial approach to [1,5]Benzothiazepine derivatives as potential antibacterial agents: J. Comb. Chem., 3(2), 224-228 (2001).
7. Anoop K. Sharma, Gajendra singh, Ashok K. Yadav and L. Prakash, Improved method for the synthesis of new 1.5-Benzothiazepine derivatives as analogues of anticancer Drugs: molecules, 2(9),129-134(1997).

8. E.Mogilnicka, A.Czyrak and J.Maj, Dihydropyridine calcium channel antagonists reduce immobility in the mouse behavioral despair test; antidepressants facilitate nifedipine action: Inst. Pharmacol, pol. Acad. sci. 31-343 krakow, pol: Eur. J. Pharmacol., **138,** 413-16 (1987).

9. V. Ambrogi, G. Grandolini, L. Perioli, G.M. DeMia, M. Ricci, and L. Tuttobello, Studies on annelated 1,4-benzothiazines and 1,5-benzothiazepines. IV. Synthesis and biological activity of new 1-substituted derivatives of 4H-s-triazolo[3,4-c]-1,4-benzothiazine and 4,5-dihydro-s-triazolo[3,4-d]-1,5-benzothiazepine: Eur. J. Med. Chem., 26, 835-838 (1991).

10. A.N. Garg, T. Chandra, Archana, A.B. Jain, and A. Kumar, Synthesis and evaluation of some new substituted benzothiazepine and benzoxazepine derivatives as anticonvulsant agents: Eur. J. Med. Cem.,(2010). In Press, Corrected Proof.

11. V. Ambrogi, G. Grandolini, C. Rossi, and M.C. Tiralti, 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 (1987).