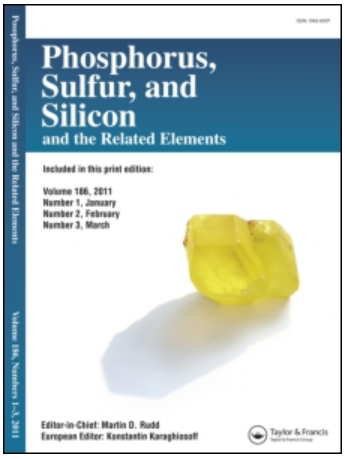

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SYNTHESES OF 1,5-BENZOTHIAZEPINES, PART XVI: SYNTHESES OF 8-ETHOXY/FLUORO–2-CABOXY–4-(FLUORINATED ARYL) – 2,3-DIHYDRO–1,5-BENZOTHIAZEPINES AS PROSPECTIVE CARDIOVASCULAR AGENTS

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Syntheses of fluorinated 8-ethoxy/fluoro–2-carboxy–4-substituted aryl–2,3-dihydro1,5-benzothiazepines having substitutents as chloro, methyl and trifluoromethyl have been achieved by the reaction of 5-ethoxy/-fluoro–2-aminobenzenethiols with fluorinated 3-substituted benzoyl–2-propenoic acids in toluene with catalytic amount of trifluoroacetic acid. The progress of the reactions was monitored by t.l.c. studies. Structures of the title compounds are established by IR, PMR and mass spectral studies and microestimation data of nitrogen.

Keywords: 3-aroyl–2-propenoic acid; pharmacophore; 2,3-dihydro–1,5-benzothiazepine; fluorine

The success in the syntheses of a series of compounds having fluorine, 8-substituted–2-carboxy–4-(4-fluorophenyl)–2,3-dihydro–1,5-benzothiazepines by the reaction of 3-(4-fluorobenzoyl)–2-propenoic acid with 5-substituted–2-aminobenzenethiols reported recently[1] prompted us to attempt the syntheses of analogous 1,5-benzothiazepines having fluorine alongwith chlorine or methyl groups and fluorine as trifiluoromethyl group. Fluorine[1(b)], chlorine[2], methyl[3] and trifluoromethyl groups[4] have been reported recently to be potential pharmacophores when present at different positions in a 1,5-benzothiazepine nucleus or in an analogous nucleus. In our earlier communication[5] the references have been cited to indicate the importance in pharmacology of a substituent in the benzene ring fused with analogus heterocyclic ring as possible pharmacophore. Further, the importance of compounds having 1,5-benzothiazepine nucleus has been realized during the current decade[6–8]. Therefore it was decided to synthesize a number of

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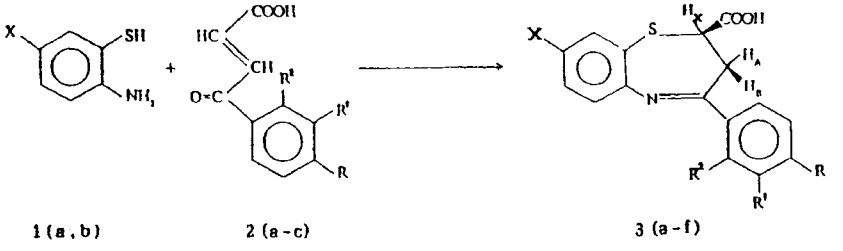
novel benzothiazepine derivatives which were either fluorinated or ethoxy substituted. Compounds **3a, 3b, 3e** and **3f** were tested for possible effects on respiration, cardiovascular systems, and nictitating membrane contraction as well as CNS effects. The compounds, however proved to be without acitvity.

In order to carry out the desired syntheses, the precursors required were fluorinated 3-substituted benzoyl–2-propenoic acids and 5-substituted–2-aminobenzenethiols. Three substituted propenoic acids, 3-(3-trifluoromethylbenzoyl)–2-propenoic acid[9], 3-(3-chloro-4-fluorobenzoyl)–2-propenoic acid[10] and 3-(4-fluoro–2-methylbenzoyl)–2-propenoic acid were prepared by the application of Friedel Crafts reaction by reacting maleic anhydride with trifluoromethylbenzene, 2-chlorofluorobenzene and 3-fluorotoluene respectively in carbon disulphide, in the presence of anhydrous aluminium chloride. The disubstituted fluorobenzenes, 2-chlorofluorobenzene and 3-fluorotoluene were prepared by the BalzShiemann reaction.

3-Aroyl–2-propenoic acids (**2a-c**) were reacted with 5-ethoxy- and 5-fluoro–2-aminobenzenethiols (**1a,b**) in strongly acidic media, using toluene containing trifluoroacetic acid. Higher boiling solvent dry toluene and the catalyst trifluoroacetic acid were used instead of dry hydrogen chloride gas in ethanol used in similar syntheses reported earlier.[1] This method was found to be an improved one as the final products were obtained conveniently in better yields. The purity of the final products was ensured by t.l.c. and then these were subjected to elemental analyses for nitrogen and IR, ^{1}H NMR and mass spectral studies.

The IR spectra of the products (Scheme 1, **3a-f**) showed absence of characteristic keto-carbonyl absorption peak in the range 1675–1670 cm^{-1} and also,



Compd. No.	X	R	R'	R^1
(3) a	F	H	CF_3	H
b	OC_2H_5	H	CF_3	H
c	F	F	Cl	H
d	OC_2H_5	F	Cl	H
e	F	F	H	CH_3
f	OC_2H_5	F	H	CH_3

SCHEME 1

absorption of the primary amino, as two bands in the region 3450–3150 cm^{-1}, was found to be absent. Copresence of absorptions around 1710–1685 cm^{-1}, ν(C=O), a broad absorption in the range 3100–2500 cm^{-1}, characteristic of a hydrogen bonded carboxylic group, C-O streching and O-H bending frequencies in the range 1380–1250 cm^{-1} are assigned to the presence of carboxylic function. The C-F absorption were observed in the range 1190–1140 cm^{-1} (Table II). In the ^1H NMR spectra, absorptions as three double doublets at δ 3.22 - 3.15 (H_A, dd, J_{AB} = 16–15 Hz, J_{AX} = 9–8 Hz, C–3-H_A), 3.85–3.70 (H_B,dd, J_{AB} = 16–15 Hz, J_{BX} = 8.2–7.9 Hz, C–3-H_B), 4.23 - 4.17 (H_X, dd, J_{AX} = 9–8 Hz, J_{BX} = 8.2 - 7.9 Hz, C–2-H_X) in the ABX pattern were charcterized for two methylene protons at C–3 and one methine proton at C–2 in **3a-f** (Table III). The (m/z) $[M]^+$peaks were found to correspond to the calculated values of molecular weight of the compounds **3a-f** (Table I).

TABLE I Physical Constants and analytical data of 8-Substituted-2-carboxy-4-aryl-2,3-dihydro-1,5-benzothiazepines(3a-e)

Compound No.	*X*	*R*	*R^1*	*R^2*	*Molecular Formula [M]⁺, [M+2]⁺*	*m.p. (°C)*	*Rf.*	*Yield (%)*	*N Analysis (%) Found(calcd.)*
3a	F	H	CF_3	H	$C_{17}H_{11}NSO_2F_4$	241	0.62	54	3.81 (3.79)
3b	OC_2H_5	H	CF_3	H	$C_{19}H_{16}NSO_3F_3$ (395, 397)	238	0.56	51	3.58 (3.54)
3c	F	F	Cl	H	$C_{16}H_{10}NSO_2F_2Cl$ (353, 355)	210	0.74	45	(4.00) (3.96)
3d	OC_2H_5	F	Cl	H	$C_{18}H_{15}NSO_3FCl$	197	0.69	48	3.72 (3.69)
3e	F	F	H	CH_3	$C_{17}H_{13}NSO_2F_2$	138	0.79	53	4.23 (4.20)

TABLE II Characteristic IR absorption bands of 8-Substituted-2-carboxy-4-aryl-2,3-dihydro-1,5-benzothiazepines(3a-e)

	-COOH absorption					*Aliphatic*		*Aromatic*	
Compound No.	*ν(C=O)*	*ν(O-H)*	*δ(O-H/ ν(C-O)*	*ν(C=N)*	*ν(C-F)*	*ν(C-H)*	*δ(C-H)*	*ν(C-H)*	*δ(C-H)*
3a	1700s	3090-2600b	1360s, 1300w	1608s	1180s	2930w	1480, 1395w	3080w	820s,740,680w
3b	1710s	3100 2550b	1320s, 1270w	1600s	1190s	2975w	1460, 1380w	3075w	980s,810,660w
3c	1695s	3000-2550b	1340s, 1310w	1605s	1170s	2955w	1450, 1390w	3050w	950s,735,680w
3d	1698s	3080-2570b	1315s, 1290w	1608s	1190s	2940w	1480, 1375w	3076w	960s,780,635w
3e	1708s	3180-2720b	1330s 1260w	1610s	1150s	2960w	1465, 1375w	3065w	880w,820,790s

TABLE III ^{1}H NMR Spectral data of 8-Substituted-2-carboxy-4-aryl-2,3-dihydro-1,5-benzothiazepines(3a-e)

Compound No.	*J in Hz, δ in ppm*						
	C-2-H_X	*C-3-H*		*C-8*	*CH_3*	*COOH*	*Ar-H*
		H_A	*H_B*				
3a	4.20 (J_{AX} = 9, J_{BX} = 8)	3.19 (J_{AB} = 16, J_{AX} = 9)	3.76 (J_{AX} = 16, J_{BX} = 8)	-	-	8.40 (b)	6.8-8.15 (m, 7H)
3b	4.21 (J_{AX} = 9, J_{BX} = 8)	3.20 (J_{AB} = 16, J_{AX} = 9)	3.80 (J_{AB} = 16, J_{BX} = 8)	1.4 (3H, t, J = 7) 3.95 (2H, q, J = 7)	-	8.45 (b)	6.85-8.2 (m, 7H)
3c	4.22 (J_{AX} = 9, J_{BX} = 8)	3.21 (J_{AB} = 16, J_{AX} = 9)	3.82 (J_{AB} = 16, J_{BX} = 8)	-	-	8.36 (b)	6.8-8.1 (m, 6H)
3d	4.23 (J_{AX} = 9, J_{BX} = 8)	3.22 (J_{AB} = 16, J_{AX} = 9)	3.85 (J_{AB} = 16, J_{BX} = 8)	1.35 (3H, t, J = 7) 4.05 (2H, q, J = 7)	-	8.39 (b)	6.77-8.1 (m, 6H)
3e	4.19 (J_{AX} = 9, J_{BX} = 8)	3.16 (J_{AB} = 16, J_{AX} = 9)	3.73 (J_{AB} = 16, J_{BX} = 8)	-	2.55 (3H, s)	8.2 (b)	6.78-7.86 (m, 6H)

EXPERIMENTAL

All the recorded melting points are uncorrected. Progress of the reaction was monitored by using t.l.c. on silica gel 'G' coated plates using toluene: ethylacetate (7:3) as irrigant. IR spectra were recorded in KBr pellets on Perkin Elmer Infracord–577 and Magna FT IR–557 spectrophotometers. Mass spectra were taken on Jeol D–300 (El/Cl) instrument at 70 eV and PMR spectra were recorded in $CDCl_3$ on Jeol 90 MHz FT NMR spectrometer using TMS as internal standard.

3-Aroyl–2-Propenoic acid (2)

o-Cholorofluorobenzene[11] and m-fluorotoluene[12] were prepared in the laboratory by the diazotization of o-chloroaniline and m-toluidine, followed by their fluorobate salt formation with fluroboric acid and then decomposition of the diazonium fluoroborate salt by the literature methods.[11,12]

3-(3-Trifluoromethylbenzoyl)-2-propenoic acid (**2a**) and 3(3-chloro-4-fluorobenzoyl)2-propenoic acid (**2b**) were prepared by literature methods[9,10]. 3-(4-Fluoro-2-methylbenzoyl)-2-propenoic acid (**2c**) was prepared on similar lines.

3-(4-fluoro-2-methylbenzoyl)-2-propenoic acid (2c)

Freshly distilled 3-fluorotoluene (0.1 mol, 11 mL), powdered maleic anhydride (0.105 mol, 10.29 g) and dry carbon disulfide (150 mL) were mixed and kept in an icebath to maintain the temperature below 5°C. Anhydrous aluminium chloride was added in small lots with continuous stirring in a duration of one hr. Stirring was continued for 3 hrs after the addition was completed at room temperature. The reaction mixture was then refluxed on hot water-bath for 6 hrs. The crude solid obtained after distilling out excess of CS_2 was worked up to give yellow crystals after crystallization from hot benzene, m.p. 85–89°C, yield, 16 g (77%); Found : C, 63.21, H, 4.15, $C_{11}H_9O_3F$ requires C, 63.46%, H, 4.32%. IR: 2980–2500 cm^{-1} ν (O-H), 1720 ν (C=O, carboxylic carbonyl), 1670 ν (C=O, ketonic carbonyl), 1610 ν (C=C, Olefinic), 1600,1500 ν(C⋯C, aromatic), 1450, 1415, 1380, 1350, 1320, 1240, 1180 [δ (C-H, aliphatic), δ (O-H), ν (C-O)], 1110 ν (C-F); PMR: δ 2.51 (3H, s, CH_3), 6.71–7.8 (5H, 3 aromatic & 2 olifinic), 8.20 (COO**H**), MS: Calcd. : 208, found : m/z 208 $[M]^+$.

5-Ethoxy and 5-fluoro–2-aminobenzenethiols were prepared from respective anilines by literature reported methods.[13]

2-Carboxy-8-ethoxy-4-(4-fluoro–2-methylphenyl)-2,3-dihydro-1,5-benzothiazepine (3f)

3-(4-Fluoro-2-methyl benzoyl)-2-propenoic acid (0.001 mol, 0.208 g) and 2-amino-5-ethoxy benzenethiol (0.001 mol, 0.169 g) were taken in dry toluene (~ 10 mL) containing catalytic amount (2 drops) of trifluoroacetic acid. The reaction mixture was then refluxed for 12 hrs when its colour changed from light yellow to black. The reaction mixture was cooled and excess solvent was removed under reduced pressure. The residue on crystallization from chloroform and pet ether (60–80) gave light brown coloured crystals of **3f**. mp. 135°, yield 0.216 g. (58%), TLC, Rf. 0.74, Found: N, 3.91, $C_{19}H_{18}NSO_3F$ requires N, 3.89%. **IR**: 3210–2730 cm^{-1} ν (O-H), 1705 ν (C=O), 1610 ν (C=N), 1440, 1410, 1375, 1260, 1230 [δ (C-H, aliphatic), ν (C-O), δ (O-H), ν (C-O-C)], 1140 ν (C-F). PMR [δ 1.38 (3H, t, J=6.0 Hz), 3.95 (2H, q, J=6Hz), C–8-OC**H**$_2$C**H**$_3$], 3.15 (H_A, dd, J_{AB} = 15.0 Hz, J_{AX} = 9 Hz), 3.70 (H_B, dd, J_{AB} = 15.0 Hz, J_{BX} = 8 Hz), 4.17 (H_X, dd, J_{AX} = 9Hz, J_{BX} = 8 Hz), 2.54 (3H, s, C**H**$_3$), 6.76–7.8 (6H, Ar**H**), 8.18 (COO**H**), MS: Calcd.: 359; found: m/z 359 $[M]^+$, 361 $[M+2]^+$.

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References

[1] (a) Upreti, M., Pant, S., Dandia, A., & Pant, U.C. (1996). *Phosphorous, Sulphur & Silicon.*, **113,** 165–171.
(b) references 2–12 cited in (a)

[2] Odawara, A., Ikeo, T., Jpn. Kokai Tokkyo Koho **JP** 06, 183, 978 [94, 183, 978] (C1.A61 K31/55), (1994), Appl. 92/341, 753, (1992), *Chem. Abstr.*, **122,** P96510c; Lochead, A., Muller, J.C., Denys, C., & Dumas, H., Eur. Pat. Appl. EP 338, 892 (C1 C07 D281/10), (1989), FR Appl. 88/5, 131, (1988), *Chem. Abstr.*, (1990), **112,** 158278m.

[3] Atwal, K.S., Ahmed, S.Z., Floyd, D.M., Moreland, S., Hedberg, A. (1993). *Bioorg. Med. Chem. Lett.*, **3(12)** 2797–800r, *Chem. Abstr.*,(1994), **121,** 73051; Das, J., Floyd, D.M., Kimball, S.D., Duff, K.J., Vu, T.C., Lago, M.W., Moquin, R.V., Lee, V.G. (1992). *J. Med. Chem.* **35(4),** 773–780.

[4] Floyd, D.M., Kimball, S.D., Krapcho, J., Das, J., Turk, C.F., Moquin, R.V., Lago, M.W., Duff, K.J., Lee, V.G., White, R.E. (1992).*J. Med. Chem.* **35(4)**, 756–72, 780–793; Kimball, S.D., Hunt, J.T., Barrish, J.C., Das, J., Floyd, D.M., Lago, M.W., Lee, V.G., Spergel, S.H., Moreland, S. (1993). *Bioorg. Med. Chem.* **1(4),** 285–307, *Chem. Abstr.*, (1994), **120,** 152471b; Bailey, L.C., Shroff, A.P., (1974). *Res. Commun. Chem. Pathol. Pharmacol.* **7(1),** 105; Heilman, R.D., Bauer, E.W. & Davanzo, J.P. (1974) *Curr. Ther Res. Clin. Exp.* **16(9),** 1022–32.

[5] Sharma, A., Pant, S., Sharma, C.K. & Pant, U.C. (1996) *Phosphorous Sulphur and Silicon* and refernces therein (In Press).

[6] Ellicolt, J.D., Geeason, J.G., Hill, D.T., PCT Int.Appl. Wo 9504, 534 (C1.A61 K 31/55) (1995). US Appl. 103, 496, (1993), *Chem. Abstr.*, (1995), **123,** 55720 y.

[7] Yanamori, T., Harda, H., oosugi, E., Sakai, K., Eur. Pat. Appl. EP 609, 031 (C1. C07 D323/56)(1994): JP Appl. 93/11, 492 (1993), *Chem. Abstr.*, (1995), **122,** 10074 d.

[8] Nagel, Arthur. A., PCT Int. Appl. WO 9401, 421 (C1. C07 D 267/14) (1994): U.S. Appl. 907, 413 (1992), *Chem. Abstr.*, (1994), **121,** 280684t.
[9] Kameo, K., Ogawa, K., Takeshita, K., Nakike, S., Tomisawa, K.K., Sota, K. (1988), *Chem. Pharm. Bull.*, **36(6),** 2050–60; *Chem. Abstr.*, (1989), **110,** 57257h.
[10] Grelan Pharmaceuticals Co. Ltd. Jpn. Kokai Tokkyo Koho JP 57, 126, 442 [82, 126, 442] (C1.C07 C59/88), (1982), Appl. 81/9, 635, (1981), *Chem. Abstr.*, (1983), **98,** 4308c.
[11] Adams, R, *"Organic Reaction"*, **Vol. V, III**rd Ed., John Wiley & Sons, Inc., U.S.A (1957).
[12] Heilborn, I & Bunburry, H.M. *"Dictionary of Organic Compounds"* Eyre and Spottiswood, London, **Vol.2,** 558 (1953).
[13] Mittal, R.L.,Taunk, P.C. (1971), Montshefte fur chemie, **102,** 760.