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ONE-POT SYNTHESIS OF NEW FLUORINATED 4H-1,4-BENZOTHIAZINES AS POSSIBLE ANTICANCER AGENTS

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SUMMARY

One pot synthesis of fluorinated 4H-1,4-benzothiazines can be effected by the condensation and oxidative cyclization of substituted 2-aminobenzenethiols with β-diketone (p-fluorobenzoylacetone) in DMSO. The reaction is believed to proceed via an enamino-ketone system. The structures have been confirmed by their elemental analyses and spectral studies. p-Fluorobenzoylacetone has been synthesized by Claisen condensation of ethyl acetate with p-fluoroacetophenone.

INTRODUCTION

Benzothiazines find a number of applications in chemotherapy [1-8]. Such a wide spectrum of applications of benzothiazines has stimulated our interest to synthesize fluorinated 4H-1,4-benzothiazines by a one pot method.

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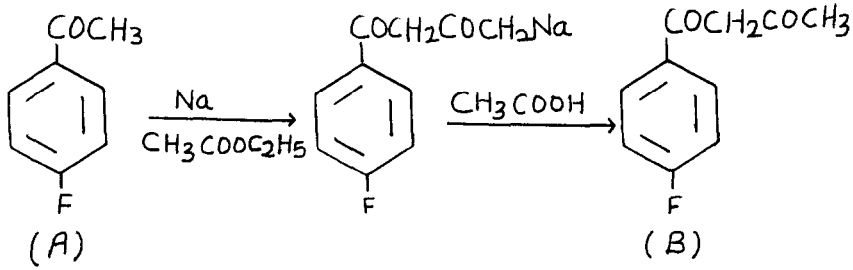
Fluorinated phenothiazines [9-12] (analogues of 4H-1,4-benzothiazines) are most effective drugs and we are designing fluorinated 4H-1,4-benzothiazines as possible anticancer agents.

The tremendous growth in the chemistry of organic fluorine compounds during the last few decades has been due to the unique properties conferred by the fluorine atom on molecules to which it is bonded. 5-Fluoro-uracil and 5-fluorotryptamine are highly effective drugs used in the treatment of cancer.

Keeping the above observations in view, we have undertaken the present investigation to develop one pot synthetic methodology for the title compounds to make them available for anticancer activity screening.

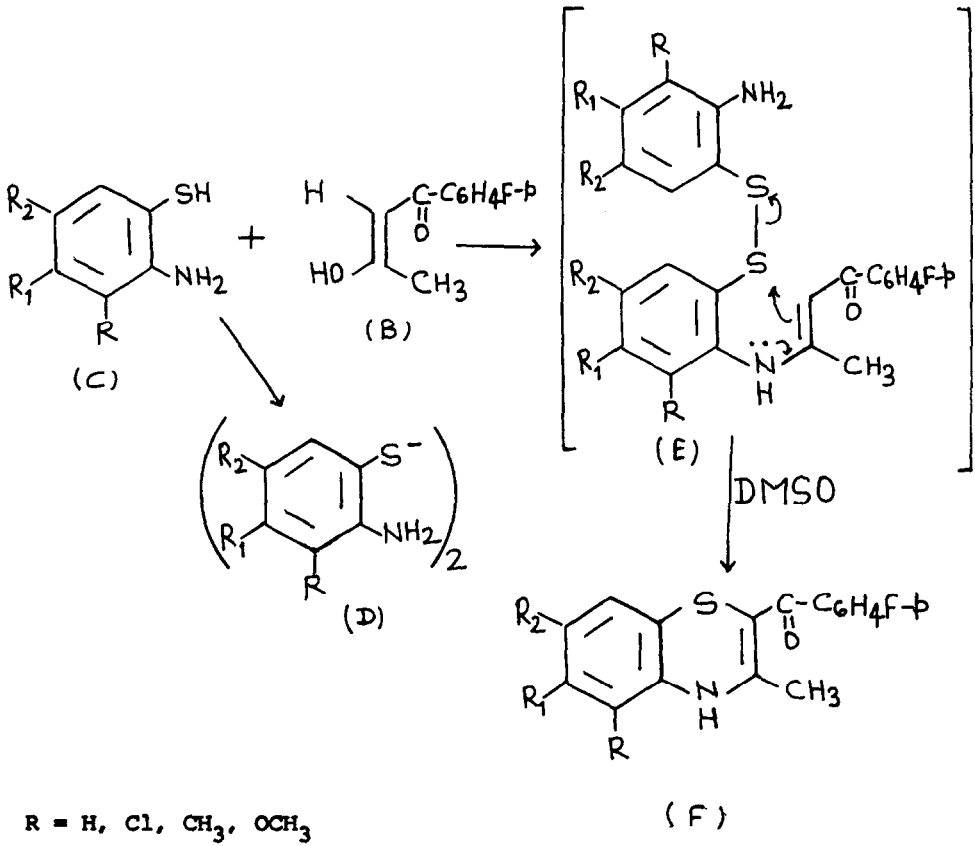
p-Fluorobenzoylacetone has been synthesized from the p-fluoroacetophenone by its reaction with ethyl acetate and sodium below 5 °C (Scheme 1)



Scheme 1

Fluorinated 4H-1,4-benzothiazines have been synthesized by the condensation and oxidative cyclization of substituted 2-aminobenzenethiols with β-diketone (p-fluorobenzoylacetone)

in DMSO. The reaction is believed to proceed through the formation of an intermediate enamino-ketone (E). 2-Amino-benzenethiols (C) are readily oxidized to disulphides (D) under the reaction conditions [13,14] which undergo condensation followed by cyclisation yielding 1,4-benzothiazines (Scheme 2).



R = H, Cl, CH_3, OCH_3

R_1= H, SO_3H

R_2= H, Cl, F, OCH_3, OC_2H_5

Scheme 2

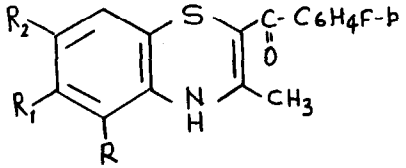
RESULTS AND DISCUSSION

All the melting points are uncorrected. The purity of the synthesized compounds was checked by thin layer chromatography. Infrared spectra of all compounds have been scanned in KBr on Perkin-Elmer spectrophotometer model 577 and their UV spectra were recorded on Perkin-Elmer UV spectrophotometer in EtOH. The IR spectra of all the 4H-1,4-benzothiazines exhibit a single sharp intense peak in the region 3230-3380 cm^{-1} which corresponds to NH stretching vibrations. The sharp band in the region 1575-1610 cm^{-1} is due to C=O stretching vibrations. All the compounds exhibit sharp bands in the region 1350-1480 cm^{-1} due to C-H deformation vibrations of CH_3 group. UV spectral data has been presented in the Table 2 along with the IR spectral data.

All the NMR spectra and ^{19}F spectra have been recorded at 90MHz on Jeol FX 90 Q FT NMR using TMS as an internal standard in polysol and DMSO-d_6. The NMR spectra of all the benzothiazines having allylic linkage ($C=C-CH_3$) exhibit resonance signals in the region 1.92 - 1.78 δ. A singlet in the region 10.63 - 9.06 δ is ascribed to the NH proton in all the compounds. A triplet at 1.42 - 1.20 δ is due to CH_3 protons and quartet centered at 4.26 - 3.70 δ is assigned to CH_2 protons of ethyl group in compound(VIII). The multiplets in the region 8.13 - 6.39 δ are due to aromatic ring protons. ^{19}F NMR spectra of all title compounds exhibit peaks at

TABLE 1

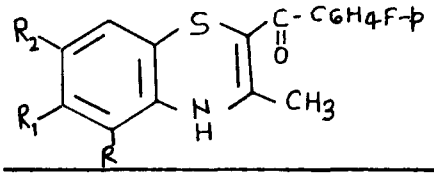
Physical data for fluorinated 4H-1,4-benzothiazines



Comp. No.	R	R_1	R_2	M.P. °C	Yield %	Molecular Formula	% Found C	% Found H	% Found N	% Calcd C	% Calcd H	% Calcd N
I	H	H	H	180-81	65	$C_{16}H_{12}NSFO$	67.22	4.24	4.95	67.36	4.21	4.91
II	Cl	H	H	145-47	57	$C_{16}H_{11}NSFClO$	60.08	3.47	4.41	60.18	3.44	4.38
III	OCH_3	H	H	112-13	48	$C_{17}H_{14}NSFO_2$	64.88	4.46	4.48	64.76	4.44	4.44
IV	CH_3	H	H	109-10	55	$C_{17}H_{14}NSFO$	68.12	4.70	4.72	68.22	4.68	4.68
V	H	SO_3H	H	134	58	$C_{16}H_{12}NS_2FO_4$	57.76	3.58	4.22	57.65	3.60	4.20
VI	H	H	Cl	210-12	70	$C_{16}H_{11}NSFClO$	60.32	3.42	4.35	60.18	3.44	4.38
VII	H	H	F	197-98	65	$C_{16}H_{11}NSF_2O$	63.48	3.61	4.65	63.36	3.63	4.62
VIII	H	H	OC_2H_5	194-95	68	$C_{18}H_{16}NSFO_2$	65.52	3.88	4.22	65.65	4.86	4.25
IX	H	H	OCH_3	176-77	72	$C_{17}H_{14}NSFO_2$	64.58	4.42	4.47	64.76	4.44	4.44
X	H	H	CH_3	220-22	75	$C_{17}H_{14}NSFO$	68.35	4.65	4.70	68.22	4.68	4.68

TABLE 2

Infrared and UV spectral data of fluorinated 4H-1,4-benzothiazines



Comp. No.	R	R_1	R_2	A	B	C	D (cm^{-1})	λ max [nm] (log)	Solvent
I	H	H	H	3260	1590	1475 1350	-	462(3.61), 326(3.64), 296(3.57)	EtOH
II	Cl	H	H	3370	1595	1470 1350	-	442(3.40), 324(3.62), 292(3.60)	EtOH
III	OCH_3	H	H	3380	1600	1475 1355	1260 1040	340(3.58), 298(3.53)	EtOH
IV	CH_3	H	H	3330	1600	1465 1370	-	358(3.55), 306(3.54)	EtOH
V	H	SO_3H	H	3280	1595	1470 1350	-	448(3.47), 326(3.73), 294(3.64)	EtOH
VI	H	H	Cl	3280	1590	1465 1350	-	460(3.47), 332(3.50), 288(3.58)	EtOH
VII	H	H	F	3230	1585	1480 1370	-	460(3.39), 336(3.99), 300(3.57)	EtOH

VIII	H	H	OC_2H_5	3260	1590	1470 1350	1245 1040	464(3.50), 320(3.38), 284(3.37)	EtOH
IX	H	H	OCH_3	3240	1585	1460 1360	1260 1040	464(3.57), 332(3.62), 294(3.64)	EtOH
X	H	H	CH_3	3260	1600	1465 1350	-	424(3.41), 320(3.52), 292(3.55)	EtOH

A = N-H stretching vibrations

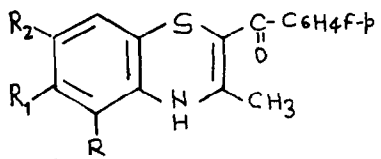
B = C=O (carbonyl) stretching vibrations

C = -CH deformation vibrations

D = C-O-C bonding

TABLE 3

PMR and ^{19}F spectral data of fluorinated 4H-1,4-benzothiazines

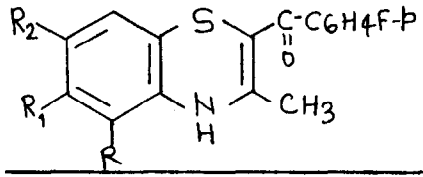


Comp. No.	R	R_1	R_2	Solvent	(ppm)	Multiplicity	Assignment(s)	Solvent	(ppm)	Assignment
I	H	H	H	Polysol	7.81-6.74	multiplets	aromatic protons	Polysol	-105.644	F at C_2
					1.83	singlet	CH_3 protons at C_3			
					9.07	singlet	N-H proton			
II	Cl	H	H	Polysol	7.90-6.79	multiplets	aromatic protons	DMSO	-104.543	F at C_2
					1.96	singlet	CH_3 protons at C_3			
					9.58	singlet	N-H proton			
III	OCH_3	H	H	Polysol	7.90-6.79	multiplets	aromatic protons	DMSO	-104.369	F at C_2
					4.06	singlet	OCH_3 protons at C_5			
					1.92	singlet	CH_3 protons at C_3			
					9.21	singlet	N-H proton			
IV	CH_3	H	H	Polysol	8.13-7.01	multiplets	aromatic protons	DMSO	-105.586	F at C_2
					2.23	singlet	CH_3 protons at C_5			
					1.92	singlet	CH_3 protons at C_3			
					10.63	singlet	N-H proton			
V	H	SO_3H	H	Polysol	7.81-6.65	multiplets	aromatic protons	DMSO	-105.412	F at C_2
					1.83	singlet	CH_3 protons at C_3			
					9.06	singlet	N-H proton			

VI	H	H	Cl	DMSO-d_6	7.86-6.70	multiplets	aromatic protons	DMSO-d_6	-102.921	F at C_2
					1.78	singlet	CH_3 protons at C_3			
					9.38	singlet	N-H proton			
VII	H	H	F	Polysol	7.72-6.56	multiplets	aromatic protons	DMSO	-105.644	F at C_2
					1.78	singlet	CH_3 protons at C_3		-115.374	F at C_7
					9.18	singlet	N-H proton			
VIII	H	H	OC_2H_5	Polysol	7.72-6.39	multiplets	aromatic protons	DMSO	-103.790	F at C_2
					4.26-3.70	quartet	CH_2protons of OC_2H_5 group at C_7			
					1.42-1.20	Triplet	CH_3 protons of OC_2H_5 group at C_7			
					1.78	singlet	CH_3 protons at C_3			
					9.11	singlet	N-H proton			
IX	H	H	OCH_3	Polysol	7.81-6.39	multiplets	aromatic protons	Polysol	-106.223	F at C_2
					3.70	singlet	OCH_3 protons at C_7			
					1.83	singlet	CH_3 protons at C_3			
					9.07	singlet	N-H proton			
X	H	H	CH_3	DMSO-d_6	7.86-6.52	multiplets	aromatic protons	DMSO-d_6	-103.327	F at C_2
					2.19	singlet	CH_3 protons at C_7			
					1.83	singlet	CH_3 protons at C_3			
					9.29	singlet	N-H proton			

TABLE 4

Mass spectral data of fluorinated 4H-1,4-benzothiazines



Comp. No.	R	R_1	R_2	M^+ m/z (Rel. Intensity)
I	H	H	H	285(445.3), 123(1000.0), 95,76,162(550.4), 161,120,284
II	Cl	H	H	319(574.4), 123(1000.0), 95,76,196(131.2), 195,154,119,283 160, 318(67.8)
III	OCH_3	H	H	315(281.7), 123(1000.0), 95,76,192(143.6), 178(67.1), 150, 151,136,300,272,149(59.4),314
IV	CH_3	H	H	299(4.9), 123(1000.0), 95,76,176,161,120,258,243,163,148,298
V	H	SO_3H	H	365, 123(1000.0), 95,76,285(328.6),244,121(54.5),242,178,163, 162(405.7),130
VI	H	H	Cl	319(245.2), 123(1000.0), 95,76,196(336.4),195,160,119,318
VII	H	H	F	303(837.7), 123(1000.0), 95,76,180,139,120,284,161,302(74.5)
VIII	H	H	OC_2H_5	329(306.5), 123(665.8), 95,76,206(1000.0),178(417.0),134, 328, 299,271,176,135
IX	H	H	OCH_3	315(296.6), 123(591.2), 95,76,192(1000.0), 177(65.3), 149(156.7), 108,300,272,314
X	H	H	CH_3	299(368.6), 123(828.3), 95,76,176(1000.0), 161,135,120,298, 283,178,163(78.8)

-102.921 - -106.223 ppm (relative to hexafluorobenzene with ^{19}F signal at -162.9 ppm) due to fluorine at p-position in the benzene ring of side chain at 2-position. However compound(VII) (in Table 1) exhibits an additional signal at -115.374 ppm due to the fluorine at 7-position in the heterocyclic ring system. NMR and ^{19}F spectral data are presented in the Table 3.

Mass spectra of all compounds were recorded on Jeol, JMSD-300 mass spectrometer at 70 eV with 100 amp ionizing current. The mass spectra of all the compounds showed molecular ion peaks corresponding to their molecular weight. Mass spectral data included in the Table 4.

EXPERIMENTAL

Preparation of p-fluorobenzoylacetone

Sodium wire was suspended in ice cold dry ethylacetate (200 ml), contained in a 500 ml three necked flask, fitted with a reflux condenser, mechanical stirrer and dropping funnel. p-Fluoroacetophenone (0.25 mol) was slowly added from the dropping funnel to the ice cold reaction mixture with continuous stirring for 2.0 - 2.5 hrs and allowed to stand overnight. The sodium salt of p-fluorobenzoylacetone was filtered and washed with benzene. It was dissolved in the minimum amount of water and decomposed by dil. acetic acid. The separated oil was extracted with ether

and the ethereal solution after being washed with water was dried over anhydrous sodium sulphate. The ether was evaporated and the residual liquid was distilled under reduced pressure 117°C at 4mm [15].

Preparation of fluorinated 4H-1,4-benzothiazines

To the stirred suspension of β-diketone (p-fluoro-benzoylacetone) (B;0.01 mol) in DMSO (5 ml) was added substituted 2-aminobenzenethiol (C;0.01 mol) and the resulting mixture was refluxed for 30 minutes. The reaction mixture was cooled down to room temperature and solid separated out was filtered, washed with methanol and crystallized from methanol. The physical and analytical data have been recorded in Table 1.

ACKNOWLEDGEMENT

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