Synthetic and spectral investigation of fluorinated phenothiazines and 4*H*-1,4-benzothiazines as potent anticancer agents

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(Received May 7, 1992; accepted August 6, 1992)

Abstract

The syntheses of fluorinated phenothiazines and fluorinated 1,4-benzothiazines are reported. Fluorinated phenothiazines have been prepared via a Smiles rearrangement of *N*-formylated diphenylsulphides, synthesized in turn by condensation of substituted 2-aminobenzenethiols with 2-chloro-5-trifluoromethylnitrobenzene followed by formylation with formic acid. Fluorinated 4*H*-1,4-benzothiazines have been prepared by the condensation and oxidative cyclization of substituted 2-aminobenzenethiols with *p*-fluorobenzoylacetone in DMSO. The reaction is believed to proceed via an enaminoketone system. IR and NMR spectral investigations are included.

Introduction

Phenothiazines possess a wide spectrum of pharmacological activities. Several derivatives are in clinical use [1]. Phenothiazines also exhibit significant anticancer activities [2–16]. 1,4-Benzothiazines resemble phenothiazines structurally in having a fold along the nitrogen and sulphur axis and therefore are anticipated to possess pharmacological activities similar to phenothiazines. The wide spectrum of applications of phenothiazines and 1,4-benzothiazines has stimulated our interest in their synthesis.

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.

Results and discussion

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

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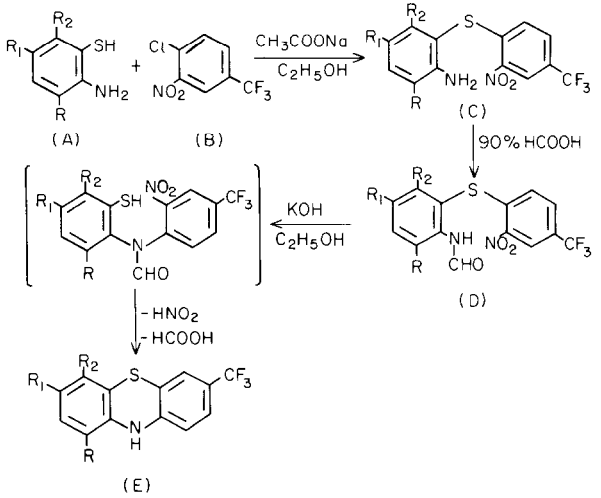
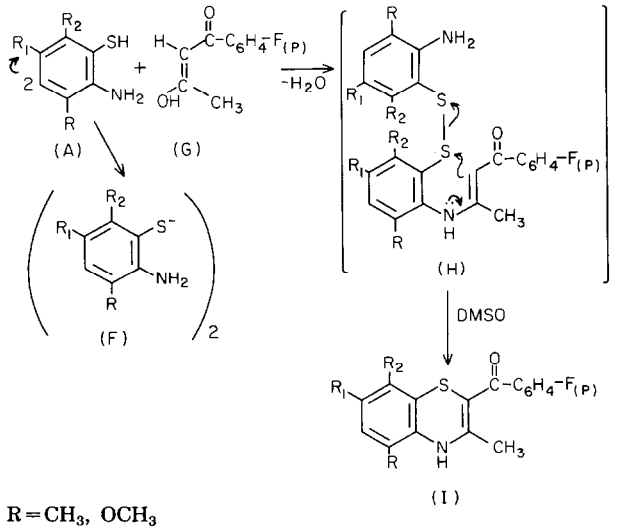
0022-1139/93/$6.00



R = CH_3, OCH_3
R_1 = H, Cl, CH_3
R_2 = Cl, H

Scheme 1.



R = CH_3, OCH_3
R_1 = H, Cl, CH_3
R_2 = Cl, H

Scheme 2.

2-Aminobenzenethiols (A) required in the synthesis of the title compounds have been prepared by the hydrolytic cleavage of 2-aminobenzothiazoles [17, 18]. The benzothiazoles have been prepared by the cyclization of phenylthioureas by bromine in chloroform which in turn were obtained by the action

of ammonium thiocyanate on disubstituted anilines. *p*-Fluorobenzoylacetone has been synthesized from *p*-fluoroacetophenone by its reaction with ethyl acetate and sodium. The experimental details have already been reported elsewhere [6].

Fluorinated phenothiazines have been prepared by the reaction of substituted-2-aminobenzenethiols (A) with 2-chloro-5-trifluoromethylnitrobenzene (B) which resulted in the formation of diphenylsulphides (C), which on formylation with 90% formic acid led to the formyl derivatives (D) which on treatment with alcoholic potassium hydroxide underwent a Smiles rearrangement yielding phenothiazines (E) (Scheme 1).

Fluorinated 4*H*-1,4-benzothiazines have been synthesized by the condensation and oxidative cyclization of substituted 2-aminobenzenethiols (A) with *p*-fluorobenzoylacetone (G) in DMSO. The reaction is believed to proceed through the formation of an intermediate enaminoketone (H). 2-Aminobenzenethiol (A) is readily oxidized to the disulphide (F) [19] which on condensation and cyclization yields 1,4-benzothiazines (I) by the scission of the sulphur–sulphur bond upon attack by the nucleophilic enaminoketone system (Scheme 2).

Experimental

All the melting points are uncorrected. The purity of the synthesized compounds was checked by thin layer chromatography. The infrared spectra of all the compounds have been scanned in KBr discs on a Perkin-Elmer spectrophotometer model 577 and their UV spectra were recorded on a SP 8-100 Pye-Unicam UV–vis spectrophotometer in EtOH. UV and IR spectral data are presented in Table 1.

All the ^{1}H NMR and ^{19}F NMR spectra have been recorded at 90 MHz on a JEOL FX 90Q FT NMR spectrometer using TMS as an internal standard in DMSO-d_6. ^{19}F NMR spectra have been recorded relative to hexafluorobenzene with the ^{19}F signal at -162.9 ppm. ^{1}H NMR and ^{19}F NMR spectral data are presented in Table 2.

Preparation of fluorinated phenothiazines

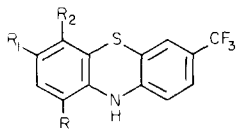
The synthesis of the phenothiazines involves three steps as detailed below:

(a) Preparation of substituted 2-amino-2'-nitro-4'-trifluoromethyldiphenylsulphides (C)

Substituted 2-aminobenzenethiols (A; 0.01 mol) were dissolved in ethanol (20 ml containing 0.01 mol anhydrous sodium acetate) and were added to 2-chloro-5-trifluoromethylnitrobenzene (B; 0.01 mol) in ethanol (10 ml). The reaction mixture was refluxed for 4 h, concentrated and cooled in an ice bath overnight. The solid which separated out was filtered, washed with 30% ethanol and recrystallized from methanol. Physical and analytical data are summarized in Table 3.

TABLE 1

Infrared and UV spectral data for fluorinated phenothiazines and 1,4-benzothiazines



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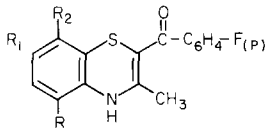


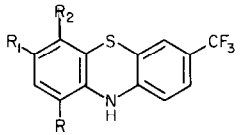
(I)

Comp. No.	R	R_1	R_2	IR spectral data[a]				UV spectral data	Solvent and concentration
				A	B	C	D	λ[nm] (log ε)	
E.1	CH_3	H	Cl	3270	1445 1390	–	1320 1190	282(3.94)	EtOH, 100 ppm, 10 ppm
E.2	CH_3	Cl	H	3320	1430 1370	–	1350 1160	328(3.97)	EtOH, 100 ppm, 10 ppm
E.3	CH_3	CH_3	H	3180	1470 1355	–	1315 1140	376(3.92); 264(4.79)	EtOH, 100 ppm, 10 ppm
I.1	CH_3	H	Cl	3330	1450 1365	1550	1080	448(3.8); 272(4.79)	EtOH, 100 ppm, 10 ppm
I.2	OCH_3	H	Cl	3380	1430 1390	1570	1040	468(3.56); 276(4.67)	EtOH, 100 ppm, 10 ppm
I.3	CH_3	Cl	H	3330	1460 1350	1570	1060	450(3.69); 266(4.87)	EtOH, 100 ppm, 10 ppm
I.4	CH_3	CH_3	H	3290	1435 1340	1575	1030	444(3.79); 264(4.79)	EtOH, 100 ppm, 10 ppm

[a]A, NH stretching vibration; B, CH deformation vibrations of CH_3 group; C, C=O stretching vibrations, and D, C−F stretching vibrations.

TABLE 2

^{1}H and ^{19}F NMR spectral data for fluorinated phenothiazines (E.1–3) and 4*H*-1,4-benzothiazines (I.1–4)[a]



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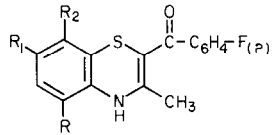


(I)

Comp. No.	R	R_1	R_2	Solvent	δ (ppm)	Multiplicity	Assignment(s)	Solvent δ (ppm)	Assignment
E.1	CH_3	H	Cl	DMSO-d_6	9.63	singlet	NH proton	DMSO −135.466	CF_3 at C-7
					8.24–5.86	multiplet	aromatic protons		
					1.74	singlet	CH_3 protons at C-1		
E.2	CH_3	Cl	H	DMSO-d_6	8.59	singlet	NH proton	DMSO −160.312	CF_3 at C-7
					8.43–7.03	multiplet	aromatic protons		
					2.02	singlet	CH_3 protons at C-1		
E.3	CH_3	CH_3	H	DMSO-d_6	9.81	singlet	NH proton	DMSO −139.484	CF_3 at C-7
					8.44–7.11	multiplet	aromatic protons		
					2.20	singlet	CH_3 protons at C-1		
					2.06	singlet	CH_3 protons at C-3		
I.1	CH_3	H	Cl	DMSO-d_6	8.36	singlet	NH proton	DMSO −105.006	F at C-2
					8.17–6.81	multiplet	aromatic protons		
					2.15	singlet	CH_3 protons at C-3		
					1.83	singlet	CH_3 protons at C-5		
I.2	OCH_3	H	Cl	DMSO-d_6	8.33	singlet	NH proton	DMSO −105.110	F at C-2
					7.79–6.11	multiplet	aromatic protons		
					3.77	singlet	OCH_3 protons at C-5		
					1.77	singlet	CH_3 protons at C-3		

(*continued*)

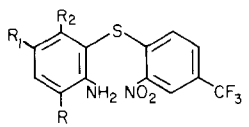
TABLE 2 (*continued*)

Comp. No.	R	R_1	R_2	Solvent	δ (ppm)	Multiplicity	Assignment(s)	Solvent δ (ppm)	Assignment
I.3	CH_3	Cl	H	DMSO-d_6	8.27	singlet	NH proton	DMSO −115.895	F at C-2
					7.98–6.97	multiplet	aromatic protons		
					2.18	singlet	CH_3 protons at C-3		
					1.83	singlet	CH_3 protons at C-5		
I.4	CH_3	CH_3	H	DMSO-d_6	8.08	singlet	NH proton	DMSO −115.490	F at C-2
					7.54–6.78	multiplet	aromatic protons		
					2.34	singlet	CH_3 protons at C-3		
					2.25	singlet	CH_3 protons at C-5		
					2.12	singlet	CH_3 protons at C-7		

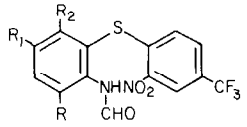
[a]All ^{19}F NMR spectra were relative to hexafluorobenzene with the ^{19}F signal at −162.9 ppm. NMR spectra have been also recorded in the presence of D_2O. In all spectra, the NH proton resonance signal disappeared due to proton–deuterium exchange.

TABLE 3

Physical and analytical data[a] for 2-amino-2'-nitro-4'-trifluoromethyldiphenylsulphides (C) and 2-formamido-2'-nitro-4'-trifluoromethyldiphenylsulphides (D)



(C)



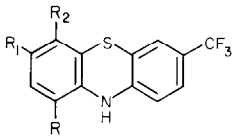
(D)

Comp. No.	R	R_1	R_2	M.p. (°C)	Yield (%)	Molecular formula	Found (%)			Calcd. (%)		
							C	H	N	C	H	N
C.1	CH_3	H	Cl	104	30	$C_{14}H_{10}ClF_3N_2O_2S$	46.58	2.74	7.66	46.34	2.75	7.72
C.2	CH_3	Cl	H	122	30	$C_{14}H_{10}ClF_3N_2O_2S$	46.12	2.74	7.76	46.34	2.75	7.72
C.3	CH_3	CH_3	H	110	42	$C_{15}H_{13}F_3N_2O_2S$	52.89	3.78	8.23	52.63	3.80	8.18
D.1	CH_3	H	Cl	72	90	$C_{15}H_{10}F_3N_2O_3S$	50.94	2.82	7.91	50.70	2.81	7.88
D.2	CH_3	Cl	H	142	38	$C_{15}H_{10}F_3N_2O_3S$	50.46	2.80	7.93	50.70	2.81	7.88
D.3	CH_3	CH_3	H	162	50	$C_{16}H_{13}F_3N_2O_3S$	51.52	3.50	7.52	51.89	3.51	7.56

[a]IR (cm^{-1}): 3400–3380 and 3310–3290 (NH_2 asym. and sym. vibrations in C.1–3); 3310–3190 (NH stretching vibrations in D.1–3); 1585–1550 and 1370–1315 (asym. and sym. vibrations of NO_2 group); 1460–1415 and 1385–1325 (C–H deformation vibrations of CH_3 group); 1645–1630 (C=O stretching vibrations in D.1–3); 1385–1130 (C–F stretching vibrations); 790–710 (C–Cl stretching vibrations in C.1, 2 and D.1, 2).

TABLE 4

Physical and analytical data for fluorinated phenothiazines (E.1–3) and 4*H*-1,4-benzothiazines (I.1–4)



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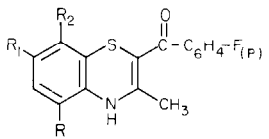

(I)

Comp. No.	R	R_1	R_2	M.p. (°C)	Yield (%)	Molecular formula	Found (%)			Calcd. (%)		
							C	H	N	C	H	N
E.1	CH_3	H	Cl	232	9	$C_{14}H_9ClF_3NOS$	53.58	2.83	4.41	53.24	2.85	4.43
E.2	CH_3	Cl	H	253	42	$C_{14}H_9ClF_3NOS$	53.52	2.86	4.44	53.24	2.85	4.43
E.3	CH_3	CH_3	H	190	39	$C_{15}H_{12}F_3NS$	61.23	4.05	4.76	61.01	4.06	4.74
I.1	CH_3	H	Cl	184	11	$C_{17}H_{13}ClFNOS$	61.54	3.87	4.16	61.16	3.89	4.19
I.2	OCH_3	H	Cl	105	37	$C_{17}H_{13}ClFNO_2S$	58.02	3.72	4.02	58.36	3.71	4.00
I.3	CH_3	Cl	H	152	27	$C_{17}H_{13}ClFNOS$	61.02	3.90	4.21	61.16	3.89	4.19
I.4	CH_3	CH_3	H	172	32	$C_{18}H_{16}FNOS$	69.22	5.13	4.48	69.00	5.11	4.47

(b) Preparation of substituted 2-formamido-2'-nitro-4'-trifluoromethyldiphenylsulphides (D)

The substituted diphenylsulphides (C; 0.01 mol) obtained were refluxed for 4 h in 90% formic acid (20 ml). The contents were then poured out into a beaker containing crushed ice, the separated solid was filtered, washed with water until neutral and recrystallized from benzene. Physical and analytical data are summarized in Table 3.

(c) Preparation of substituted 7-trifluoromethylphenothiazines (E)

To a refluxing solution of the substituted formyl derivatives (D; 0.01 mol) in acetone (15 ml) was added an alcoholic solution of potassium hydroxide (0.2 g in 5 ml ethanol). The contents were heated for 30 min. A second portion of potassium hydroxide (0.2 g in 5 ml ethanol) was added and refluxed for 2 h. The contents were poured out into a beaker containing crushed ice and filtered. The residue obtained was washed with cold water, finally with 30% ethanol and crystallized from benzene. Physical and analytical data are summarized in Table 4.

Preparation of fluorinated 4H-1,4-benzothiazines (I)

To the stirred suspension of a β-diketone (*p*-fluorobenzoylacetone) (G; 0.01 mol) in DMSO (5 ml), substituted 2-aminobenzenethiols (A; 0.01 mol) were added and the resulting mixture was refluxed for 20–30 min. The reaction mixture was cooled to room temperature and the solid phase separated out was filtered, washed with small amount of methanol and crystallized from methanol. The physical and analytical data are summarized in Table 4.

Acknowledgement

We express our sincere thanks to UGC, New Delhi for financial assistance in the form of a research project.

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