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Potential Antimicrobial Agents: Trifluoromethyl-10*H*-phenothiazines and Ribofuranosides

Girwar Singh, Neeraj Kumar, Ashok K. Yadav, and A. K. Mishra

Department of Chemistry, University of Rajasthan, Jaipur 302004, India

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ABSTRACT: *The zinc salts of substituted 2-amino benzenethiols, on condensation with 2-chloro-3-nitro-5-trifluoromethyl benzene, in presence of sodium acetate and ethanol and subsequent formylation gave the corresponding 2-formamido-substituted diphenylsulfides. From them substituted 2-trifluoromethyl-10H-phenothiazines have been synthesized via Smiles rearrangement. Ribofuranosides* α- *and* β- *anomers were synthesized by the condensation of phenothiazines with sugar in toluene in presence of* $SnCl_4$ *at 0°C and 155–160°C, respectively.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:481–486, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10165

INTRODUCTION

During the past few years, an effort has been made to synthesize the metabolites of important phenothiazine derivatives, used as antipsychotic agents [1,2], i.e., promazine, chloropromazine, promethazine, fluphenazine, etc. Phenothiazines are associated with a large number of diverse activities, i.e. analgesic [3], anticancer [4], antitumor [5], CNS-depressant [6], antiasthemic [7], antibacterial [8]. Luo et al. [9] have reported phenothiazine nucleosides as antihistamic and antidepressant. Further, the importance of nucleosides against the viral disease AIDS [10] has attracted tremendous interest in this area. A number of reviews regarding general nucleoside chemistry [11,12], as well as aimed more specifically at AIDS [13,14], have been published previously while the opportunistic viral infections associated with AIDS, such as those caused by cytomegalovirus (CMV) and herpes simplex virus (HSV), have initiated additional research into new nucleoside type antiviral agents. This area has been reviewed [15] and will not be induced. Throughout the literature, the location of each has been substituted under considerations described as α-anomer when it lies below the plane of the ring system and β-anomer when it lies above it. In view of the above, we have attempted to prepare some new fluoro-10*H*-phenothiazine derivatives, their ribofuranosides, and have screened them for antimicrobial activity, in the hope to obtain some potential medicinally important compounds.

RESULTS AND DISCUSSION

The zinc salts of 3,6-dimethoxy/3,6-dichloro/3-phenoxy/3-chloro/2-amino benzenethiols (**1a–d**), on condensation with 2-chloro-3-nitro-5-trifluoromethylbenzene (**2**), in presence of sodium acetate and ethanol gave 2-amino-3,6-dimethoxy/3,6-dichloro/3-phenoxy/3-chloro-2′-(3′-nitro-5′-trifluoromethyl)diphenylsulfides (**3a–d**). The formylation of compounds **3** with 95% formic acid, afforded 2-formamido-3,6-dimethoxy/3,6-dichloro/3-phenoxy/3-chloro-2′-(3′-nitro-5′-trifluoromethyl)-diphenylsulfides **4**. Of the various ring-closure methods reported for the synthesis of nuclear substituted

Correspondence to: A. K. Mishra; e-mail: kishoreanant@yahoo.com.
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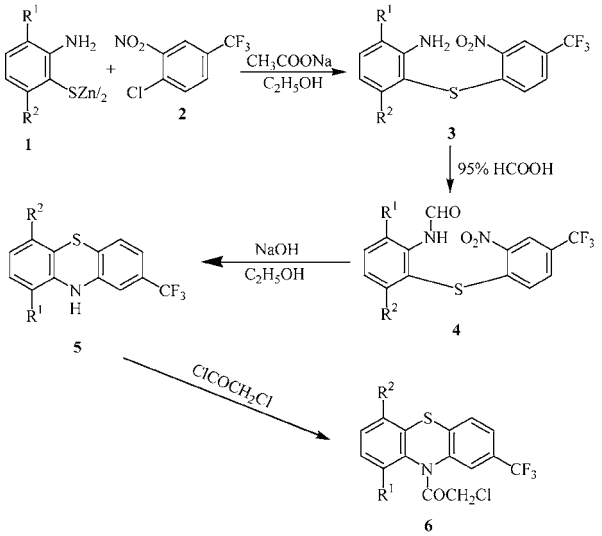
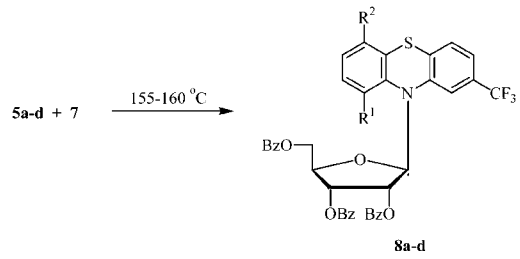
phenothiazines, reaction of diphenylamines with sulfur in the presence of catalyst and Smiles rearrangement of 2-aminophenyl-2′-nitrophenylsulfides followed by ring closure with loss of nitrous acid are quite versatile. Many substituted diphenylamines did not react [16,17] and some halogeno-substituted diphenylamines suffered dehalogenation [18–20]. However, use of dimethyl formamide in the presence of anhydrous potassium carbonate and copper bronze was successful [19]. Zinc salts of the benzenethiols in the presence of sodium hydroxide in ethanol or methanol did not condense with halogeno-nitrobenzenes. We have synthesized 6,9-dimethoxy/6,9-dichloro/6-phenoxy/6-chloro-2-trifluoromethyl-10*H*-phenothiazines (**5**) [21] from compound **4** with NaOH and ethanol via Smiles rearrangement. The combined resonance and inductive mechanisms enforced by the one nitro and halogen atom as in compound **2** activated the Smiles rearrangement as well as the ring closure to such an extent that both the processes were instantaneous and in situ. Chloroacetylation of compounds **5** with chloroacetyl chloride in presence of benzene afforded 10-chloroacetyl-6,9-dimethoxy/6,9-dichloro/6-phenoxy/6-chloro-2-trifluoromethyl-phenothiazines (**6**) (Scheme 1).

Ribofuranosides **8a–d** were prepared by the reaction of compound **5** with β-D-ribofuranose-1-acetate-2,3,5-tribenzoate (**7**) in toluene under vacuum at 160°C. The formation of **8a–d** (β-anomer) may be due to the S_N2-mechanism via neighboring group participation and is in consonance with the earlier report [22,23] (Scheme 2).

Ribofuranosides **8e–h** were synthesized by condensing compound **5** with sugar **7** in presence of



SCHEME 1



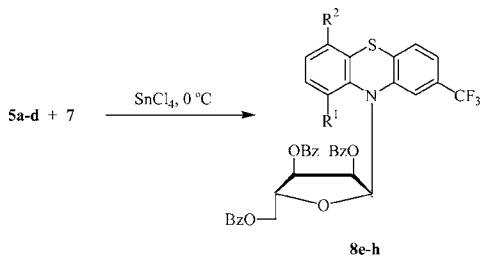
SCHEME 2

$SnCl_4$ at 0°C in 1,2-dichloroethane. The formation of α-anomers is perhaps due to the coordination at $SnCl_4$ to $-OCOCH_3$ group of the sugar moiety, thus permitting selective condensation of α-anomer [24,25] (Scheme 3).

The structure of compounds **5a–d**, **6a–d**, and **8a–h** have been established by elemental analysis (Table 1), IR, ^{1}H NMR (Table 2), and ^{13}C NMR (Table 3) spectral data. The m.p. and yield of all these compounds are presented in Table 1.

IR Spectra

In the IR spectra of compounds **3**, an absorption band in the region 665–650 cm^{-1} was ascribed to >C–S–C< linkage, indicating its formation from condensation of compounds **1** and **2**. This band was also observed in compounds **4–6** and **8** in the region 690–650 cm^{-1}. An abosorption band due to primary amino group appeared in the region 3460–3420 cm^{-1} in compounds **3**. The band in compound **4** at 3380–3130 cm^{-1} was due to >NH stretching vibrations. In compounds **3** and **4**, the strong absorption bands in the regions 1590–1560 cm^{-1} and 1380–1320 cm^{-1} were due to asymmetric and symmetric stretching vibrations of nitro group. Formation of compounds **5** was confirmed by the presence of >NH group absorption in the region 3170–3150 cm^{-1} and the absence of bands due to nitro and carbonyl group. Compounds **6** showed an absorption band in the region 1695–1680 cm^{-1} due to >C=O group. The synthesized compounds showed C=C ring vibrations in the region



SCHEME 3

TABLE 1 Data of Trifluoromethyl-10*H*-phenothiazines and Ribofuranosides

Compound	R^1	R^2	Mol. Formula (Mol. Weight)	m.p. (°C)	Yield (%)	Calcd and Found Values[a]		
						C	H	N
5a	$-OCH_3$	$-OCH_3$	$C_{15}H_{12}F_3NO_2S$ (313)	>350[b]	68	57.51 (57.47)	3.83 (3.79)	4.77 (4.75)
5b	–Cl	–Cl	$C_{13}H_6Cl_2F_3NS$ (336)	323	76	46.43 (46.41)	1.78 (1.75)	4.47 (4.46)
5c	$-OC_6H_5$	–H	$C_{19}H_{12}F_3NOS$ (359)	325–327	78	63.51 (63.47)	3.34 (3.30)	3.90 (3.86)
5d	–Cl	–H	$C_{13}H_7ClF_3NS$ (301.5)	>320[b]	78	51.74 (51.70)	2.32 (2.29)	4.64 (4.61)
6a	$-OCH_3$	$-OCH_3$	$C_{17}H_{13}ClF_3NO_3S$ (403.5)	310–312	80	50.56 (50.51)	3.22 (3.18)	3.47 (3.43)
6b	–Cl	–Cl	$C_{15}H_7Cl_3F_3NOS$ (410.5)	>300[b]	82	43.85 (43.81)	1.70 (1.66)	3.41 (3.39)
6c	$-OC_6H_5$	–H	$C_{21}H_{13}ClF_3NO_2S$ (435.5)	>360[b]	78	57.86 (57.82)	2.98 (2.96)	3.21 (3.18)
6d	–Cl	–H	$C_{15}H_8Cl_2F_3NOS$ (378)	>310[b]	80	47.62 (47.48)	2.12 (2.08)	3.70 (3.66)
8a	$-OCH_3$	$-OCH_3$	$C_{41}H_{31}F_3NO_9S$ (770)	130–132	68	63.90 (63.87)	4.02 (4.01)	1.82 (1.78)
8b	–Cl	–Cl	$C_{39}H_{25}Cl_2F_3NO_7S$ (779)	120–121	70	60.08 (60.04)	3.21 (3.18)	1.80 (1.76)
8c	$-OC_6H_5$	–H	$C_{44}H_{31}F_3NO_8S$ (790)	135–137	69	66.83 (66.82)	3.92 (3.88)	1.77 (1.73)
8d	–Cl	–H	$C_{39}H_{26}ClF_3NO_7S$ (744.5)	140	71	62.86 (62.83)	3.49 (3.46)	1.88 (1.84)
8e	$-OCH_3$	$-OCH_3$	$C_{41}H_{31}F_3NO_9S$ (770)	140–142	70	63.90 (63.87)	4.02 (4.01)	1.82 (1.78)
8f	–Cl	–Cl	$C_{39}H_{25}Cl_2F_3NO_7S$ (779)	130–131	75	60.08 (60.04)	3.21 (3.18)	1.80 (1.76)
8g	$-OC_6H_5$	–H	$C_{44}H_{31}F_3NO_8S$ (790)	145–147	72	66.83 (66.82)	3.92 (3.88)	1.77 (1.73)
8h	–Cl	–H	$C_{39}H_{26}ClF_3NO_7S$ (744.5)	148–190	75	62.86 (62.83)	3.49 (3.46)	1.88 (1.84)

[a]Found values are given in parentheses.
[b]Decomposed.

1600–1580 cm^{-1} and C=N ring vibrations in the region 1450–1420 cm^{-1}. Compounds **3** and **4** showed three sharp and strong bands in the region 1375–1300 cm^{-1}, 1270–1200 cm^{-1}, and 1190–1110 cm^{-1} due to trifluoromethyl group. In compounds **8**, the band in the region δ 3350–3150 cm^{-1} due to >NH completely vanished, suggesting the site of ribosylation at this position. In compounds **8**, the position of other groups (viz. C—Cl and >C=O) appeared in the region 1730–1710 cm^{-1}. Bands due to >C—O—C< linkage were observed in the region 1370–1020 cm^{-1} in compounds **8**.

NMR Spectra

The ^{1}H NMR spectra of compounds **3** showed a multiplet due to aromatic protons in the region δ 6.50–8.20. A broad singlet in the region δ 5.10–5.40 was attributed to NH_2 protons in compounds **8**. Methoxy protons in compounds **3a**, appeared as two singlets at δ 3.70 and 3.95. Compounds **4** showed a multiplet due to aromatic protons in the region δ 6.70–8.10. A broad hump in the region δ 8.15–8.25 was attributed to NH protons in compounds **4a–d**. Compounds **5** showed a multiplet due to aromatic protons in the region δ 6.60–8.10. Methoxy protons in compounds **5a, 6a**, and **8e** showed two singlets in the region δ 3.80–3.95. Phenoxy groups in compounds **5c, 6c, 8c**, and **8g** showed a multiplet in the region δ 6.50–7.30. Compounds **6** showed a multiplet in the region δ 6.80–8.20 due to aromatic protons. A singlet corresponding to two protons in the region δ 4.80–4.95 was attributed due to protons of the chloroacetyl group. The NH signal has disappeared in compounds **8**. Aromatic protons gave signals in the region δ 7.20–8.50 for compounds **8**. The C_1'—H protons of sugar moiety caused a singlet in the region δ 6.42–6.50, confirming the β-configuration of sugar [23]. The α-configuration of the ribofuranosides was confirmed by a doublet at δ 6.40–6.50 (J = 8 Hz) [24] due to C_1'—H, C_4'—H, and C_5'—2H protons of sugar moiety causing a multiplet in the region δ 4.35–4.85, and protons at C_2'—H and C_3'-H appeared in the region δ 5.30–5.90 as multiplet.

In the ^{19}F NMR spectra of compounds **3, 4**, and **8**, signals were observed in the region δ −58.120 to −59.250.

Antimicrobial Activity

The synthesized compounds **5, 6**, and **8** were screened for their antimicrobial activity (according to Bauer et al. [26]) against bacteria and fungi at concentrations of 100 μg/disc, using streptomycin and mycostatin as reference compounds, respectively. These compounds show moderate to fairly good activity against organisms such as *Escherichia coli* (gram −ve bacteria), *Staphylococcus aureus* (gram +ve bacteria), and *Aspergillus niger, Aspergillus flavus, Fusarium oxysporium* (fungi). Compound **5a** showed better activity against *E. coli* than other compounds. Compound **6b** showed significant activity against *S. aureus*. Against *A. niger*, compound **6b** showed better activity than compounds **6** and **8**. Compound **8b** showed better activity against *A. flavus*. Against *F. oxysporium*, compounds **6a** and

TABLE 2 IR, ^{1}H NMR, and ^{19}F NMR Spectral Data of Trifluoromethyl-10*H*-phenothiazines and Ribofuranosides

Compound	*IR (KBr, ν_{max} cm^{-1})*[a]	*^{1}H NMR (δ)*[b]	*^{19}F NMR*
5a	3150 (s, NH), 1320, 1235, 1160 (s, CF_3), 660 (s, C–S–C)	6.80–8.00 (m, Ar–H), 8.20 (s, >NH), 3.80, 3.90 (2s, 6H, 2 × OCH_3)	−58.120
5b	3160 (s, NH), 1350, 1275, 1150 (s, CF_3), 650 (s, C–S–C), 765 (m, C–Cl)	6.70–8.02 (m, Ar–H), 8.30 (s, >NH)	−58.190
5c	3170 (s, NH), 1340, 1250, 1150 (s, CF_3), 670 (s, C–S–C)	6.75–8.10 (m, Ar–H), 8.25 (s, >NH), 6.50–7.10 (m, 5H, OC_6H_5)	−58.210
5d	3165 (s, NH), 1375, 1250, 1170 (s, CF_3), 690 (s, C–S–C)	6.85–8.05 (m, Ar–H), 8.15 (s, >NH)	−58.205
6a	1690 (s, C=O), 1320, 1200, 1150 (s, CF_3), 650 (s, C–S–C), 750 (m, C–Cl)	6.85–8.10 (m, Ar–H), 3.82, 3.95 (2s, 6H, 2 × OCH_3), 4.60 (s, CH_2 of $COCH_2Cl$)	−58.390
6b	1680 (s, C=O), 1300, 1205, 1150 (s, CF_3), 675 (s, C–S–C), 760 (m, C–Cl)	6.80–8.20 (m, Ar–H), 4.70 (s, CH_2 of $COCH_2Cl$)	−58.320
6c	1685 (s, C=O), 1330, 1225, 1190 (s, CF_3), 660 (s, C–S–C), 775 (m, C–Cl)	6.82–8.06 (m, Ar–H), 6.65–7.20 (m, 5H, OC_6H_5), 4.72 (s, CH_2 of $COCH_2Cl$)	−58.360
6d	1695 (s, C=O), 1310, 1260, 1135 (s, CF_3), 685 (s, C–S–C), 765 (m, C–Cl)	6.90–8.10 (m, Ar–H), 4.65 (s, CH_2 of $COCH_2Cl$)	−58.220
8a	1710 (s, C=O), 1345 (s), 1030 (m) (C–O–C) 1370, 1270, 1140 (s, CF_3), 665 (s, C–S–C)	6.95–8.25 (m, Ar–H), 3.85, 3.95 (2s, 6H, 2 × OCH_3), 6.45 (C_1'–H of sugar)	−59.012
8b	1720 (s, C=O), 1350 (s), 1020 (m) (C–O–C) 1345, 1260, 1130 (s, CF_3), 670 (s, C–S–C)	6.90–8.20 (m, Ar–H), 6.42 (C_1'–H of sugar)	−59.140
8c	1730 (s, C=O), 1360 (s), 1040 (m) (C–O–C) 1350, 1245, 1120 (s, CF_3), 680 (s, C–S–C)	6.92–8.15 (m, Ar–H), 6.80–7.20 (m, 5H, OC_6H_5), 6.48 (C_1'–H of sugar)	−59.210
8d	1725 (s, C=O), 1370 (s), 1050 (m) (C–O–C) 1360, 1240, 1130 (s, CF_3), 685 (s, C–S–C)	6.95–8.20 (m, Ar–H), 6.50 (C_1'–H of sugar)	−59.220
8e	1720 (s, C=O), 1340 (s), 1020 (m) (C–O–C) 1365, 1260, 1150 (s, CF_3), 670 (s, C–S–C)	6.92–8.20 (m, Ar–H), 3.80, 3.90 (2s, 6H, 2 × OCH_3), 6.50 (d, C_1'–H of sugar, J = 8 Hz)	−59.250
8f	1710 (s, C=O), 1360 (s), 1030 (m) (C–O–C) 1370, 1250, 1135 (s, CF_3), 675 (s, C–S–C)	6.95–8.10 (m, Ar–H), 6.45 (d, C_1'–H of sugar, J = 8 Hz)	−59.205
8g	1730 (s, C=O), 1365 (s), 1060 (m) (C–O–C) 1360, 1250, 1125 (s, CF_3), 690 (s, C–S–C)	6.90–8.15 (m, Ar–H), 6.70–7.30 (m, 5H, OC_6H_5), 6.48 (d, C_1'–H of sugar, J = 8 Hz)	−59.185
8h	1715 (s, C=O), 1350 (s), 1020 (m) (C–O–C) 1375, 1210, 1110 (s, CF_3), 685 (s, C–S–C)	6.98–8.08 (m, Ar–H), 6.42 (d, C_1'–H of sugar, J = 8 Hz)	−59.198

[a]s = sharp and strong, m = medium.
[b]s = singlet, d = doublet, m = multiplet.

TABLE 3 δ ^{13}C of Ribofuranosides **8a–d** in CH_3OH

	8a	***8b***	***8c***	***8d***		***8a***	***8b***	***8c***	***8d***
C-1	115.4	116.8	115.9	116.6	C-1′	100.80	102.12	103.93	100.52
C-2	132.3	133.4	132.8	132.5	C-2′	78.45	78.62	79.41	78.90
C-3	122.5	122.9	122.2	122.8	C-3′	77.06	77.50	77.86	77.80
C-4	127.6	128.2	128.3	128.4	C-4′	73.60	74.52	73.85	73.77
C-4a	119.5	120.1	119.8	120.3	C-5′	64.08	66.70	66.20	65.90
C-5a	118.6	118.9	118.4	118.7	C=O	167.60	167.70	167.72	167.52
C-6	126.7	127.1	126.9	127.3	Ar(OBr)	126.50–136.52	125.28–136.42	127.06–136.52	125.72–136.86
C-7	122.6	122.8	122.4	122.2					
C-8	126.5	126.8	126.2	126.7					
C-9	116.4	116.4	116.9	116.8					
C-9a	143.5	143.8	143.2	143.6					
C-10a	145.8	146.2	146.4	146.6					

8a showed equal activity. α-Anomer ribofuranosides showed better activity against all tested organisms. Compound **8h** showed better activity (1.20 and 1.21 against *E. coli* and *F. oxysporium*, respecitvely).

EXPERIMENTAL

All the melting points were determined in open capillary tubes and are uncorrected. The IR spectra were recorded on a NICOLET-MEGNA FT-IR 550 spectrophotometer in KBr pellets. The NMR spectra were scanned on a FX 90Q JEOL spectrometer (^{1}H NMR in $CDCl_3$/DMSO-d_6; ^{13}C NMR spectra in CH_3OH, using TMS as internal standard; ^{19}F NMR spectra in $CDCl_3$, using hexafluorobenzene as internal standard). The purity of compounds were checked by TLC using silica gel "G" as adsorbent and visualization was accomplished by UV light/iodine. Zinc mercaptide of 2-amino-benzenethiols were synthesized by reported methods [27].

*2-Amino-3-chloro/3-phenoxy/3,6-dimethoxy/3,6-dichloro-2′-(3′-nitro-5′-trifluoromethyl)-diphenylsulfides (**3a–d**)*

A mixture of **1** (0.005 mol), **2** (0.01 mol), and anhydrous sodium acetate (0.025 mol) in absolute ethanol (15 ml) was refluxed for 7–8 h on a water bath. After cooling, the resultant precipitate was filtered and washed with warm water followed by ethanol. The solid thus obtained was dried and recrystallized from benzene. **3a**: $R^1 = OCH_3$; $R^2 = OCH_3$; m.p. = 195°C; yield 65%; Calc. for $C_{15}H_{13}F_3N_2O_4S$ (374) (Found): C, 48.13 (48.10); H, 3.47 (3.44); N, 7.49 (7.45); IR (KBr, ν_{max} cm^{-1}): 3450 (—NH_2); 1550, 1375 (—NO_2); 1320, 1250, 1150 (—CF_3); 650 (C—S—C); ^{1}H NMR (δ): 6.50–7.30 (Ar—H), 5.10 (NH_2), 4.20 (OCH_3). **3b**: R^1 = Cl; R^2 = Cl; m.p. = 180°C; yield 78%; Calc. for $C_{13}H_7Cl_2F_3N_2O_2S$ (383) (Found): C, 40.73 (40.71); H, 1.83 (1.80); N, 7.30 (7.28); IR (KBr, ν_{max} cm^{-1}): 3420 (—NH_2); 1590, 1380 (—NO_2); 1350, 1230, 1140 (—CF_3); 660 (C—S—C); 750 (C—Cl); ^{1}H NMR (δ): 6.60–8.20 (Ar—H), 5.40 (NH_2). **3c**: $R^1 = OC_6H_5$, R^2 = H; m.p. = 175°C; yield 72%; Calc. for $C_{19}H_{13}F_3N_2O_3S$ (406) (Found): C, 56.16 (56.14); H, 3.20 (3.18); N, 6.90 (6.88); IR (KBr, ν_{max} cm^{-1}): 3460 (—NH_2); 1560, 1340 (—NO_2); 1350, 1220, 1120 (—CF_3); 650 (C—S—C); ^{1}H NMR (δ): 6.80–8.10 (Ar—H), 5.25 (NH_2). **3d**: R^1 = Cl, R^2 = H; m.p. = 185°C; yield 73%; Calc. for $C_{13}H_8ClF_3N_2O_2S$ (348.5) (Found): C, 44.76 (44.72); H, 2.29 (2.27); N, 8.03 (8.01); IR (KBr, ν_{max} cm^{-1}); 3450 (—NH_2); 1565, 1345 (—NO_2); 1340, 1245, 1150 (—CF_3); 665 (C—S—C); 760 (C—Cl); ^{1}H NMR (δ); 6.60–7.9 (Ar—H), 5.30 (NH_2).

*2-Formamido-3-chloro/3-phenoxy/3,6-dimethoxy/3,6-dichloro-2′-(3′-nitro-5′-trifluoromethyl)diphenylsulfides (**4a–d**)*

A solution of **3** (0.05 mol) in 20 ml of 95% formic acid was refluxed on a water bath. After 6 h the resultant solution was poured onto crushed ice. The solid obtained was filtered, washed with water, dried, and recrystallized from ethanol. **4a**: $R^1 = OCH_3$; $R^2 = OCH_3$; m.p. = 160–162°C; yield 70%; Calc. for $C_{16}H_{13}F_3N_2O_5S$ (402) (Found): C, 47.76 (47.72); H, 3.23 (3.21); N, 6.96 (6.93); IR (KBr, ν_{max} cm^{-1}); 3150 (—NH); 1660 (C=O); 1590, 1360 (—NO_2); 1320, 1210, 1110 (—CF_3); 685 (C—S—C); ^{1}H NMR (δ): 6.85–8.00 (Ar—H), 8.20 (NH), 4.06 (OCH_3). **4b**: R^1 = Cl; R^2 = Cl; m.p. = 150–152°C; yield 77%; Calc. for $C_{14}H_7Cl_2F_3N_2O_3S$ (411) (Found): C, 40.87 (40.85); H, 1.70 (1.67); N, 6.81 (6.79); IR (KBr, ν_{max} cm^{-1}); 3160 (NH); 1690 (C=O), 1590, 1340 (—NO_2); 1350, 1250, 1170 (—CF_3); 660 (C—S—C); 750 (C—Cl); ^{1}H NMR (δ): 6.60–8.10 (Ar—H), 8.15 (NH). **4c**: $R^1 = OC_6H_5$; R^2 = H; m.p. = 200–202°C; yield 71%; Calc. for $C_{20}H_{13}F_3N_2O_4S$ (434) (Found): C, 55.30 (55.28); H, 2.99 (2.96); N, 6.45 (6.44); IR (KBr, ν_{max} cm^{-1}): 3130 (NH); 1680 (C=O); 1570, 1320 (—NO_2); 1310, 1205, 1150 (—CF_3); 665(C—S—C); ^{1}H NMR (δ): 6.70–8.05 (Ar—H), 8.25 (NH). **4d**: R^1 = Cl; R^2 = H; m.p. = 187–189°C; yield 79%; Calc. for $C_{14}H_8ClF_3N_2O_3S$ (376.5) (Found): C, 44.62 (44.58); H, 2.12 (2.09); N, 7.44 (7.42); IR (KBr, ν_{max} cm^{-1}): 3180 (NH); 1685 (C=O); 1580, 1185 (—NO_2); 1320, 1260, 1180 (—CF_3); 675 (C—S—C); 760 (C—Cl); ^{1}H NMR (δ): 6.85–8.10 (Ar—H), 8.20 (NH).

*6-Chloro/6-phenoxy/6,9-dimethoxy/6,9-dichloro-2-trifluoromethyl-10H-phenothiazines (**5a–d**)*

Alcoholic solution of sodium hydroxide (0.2 in 10 ml absolute alcohol) was added to an alcoholic solution (20 ml) of **4** (0.005 mol). The reaction mixture darkened immediately. It was refluxed. After 30 min a second portion of sodium hydroxide (0.2 g) in absolute alcohol (10 ml) was added and refluxing was continued for a further 2 h. The mixture was poured onto crushed ice, and the solid was filtered, washed with cold water, dried, and recrystallized from benzene.

*10-Chloroacetyl-6-chloro/6-phenoxy/6,9-dimethoxy/6,9-dichloro-2-trifluoromethylphenothiazines (**6a–d**)*

A solution of chloroacetyl chloride (0.15 mol) in dry benzene (50 ml) was added to a solution of **5** (0.1 mol) in 100 ml of dry benzene at room

temperature with constant stirring and then refluxed for 4 h. After cooling, benzene was removed under reduced pressure and the residue was chilled in ice. The product was separated by filtration, dried, and recrystallized from ethanol.

*N-(2′,3′,5′-tri-O-Benzoyl-β-D-ribofuranosyl)-6-chloro/6-phenoxy/6,9-dimethoxy/6,9-dichloro-2-trifluoromethyl-10H-phenothiazines (**8a–d**)*

Compound **5** (0.01 mol) and β-D-ribofuranose-1-acetate-2,3,5-tribenzoate (**7**) (0.01 mol) in toluene (30 ml) was stirred at 155–160°C under vacuum for 15 min in absence of moisture. The vacuum was broken and the reaction was protected from moisture using a guard tube. Stirring was further continued for 10 h by applying vacuum for 5 min at every hour. The viscous mass thus obtained was dissolved in methanol, boiled for 10 min, and cooled to room temperature. The precipitate was filtered and the filtrate was evaporated to dryness. The viscous residue was dissolved in ether, filtered, concentrated, and kept in refrigerator overnight to get crystalline ribofuranosides.

*N-(2′,3′,5′-tri-O-Benzoyl-α-D-ribofuranosyl)-6-chloro/6-phenoxy/6,9-dimethoxy/6,9-dichloro-2-trifluoromethyl-10H-phenothiazines (**8e–h**)*

Compound **5** (0.01 mol) was refluxed with sugar **7** (0.01 mol) in 1,2-dichloroethane (20 ml) for 4 h under anhydrous conditions. The mixture was cooled to 0°C and a solution of $SnCl_4$ (1.6 ml) was added dropwise with stirring. The completion of reaction was judged by TLC (2–3 h). The mixture was then poured on to saturated $NaHCO_3$ solution, extracted with chloroform, dried over anhydrous $MgSO_4$, and filtered. The removal of solvent gave ribofuranoside.

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