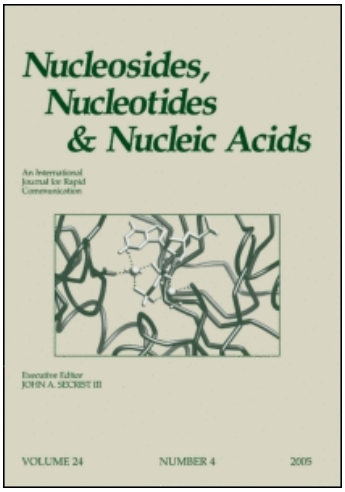


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis and Antimicrobial Activities of Novel Biologically Active Heterocycles: 10H-Phenothiazines, Their Ribofuranosides, and Sulfone Derivatives

Yogesh Dixit[a]; Rahul Dixit[a]; Naveen Gautam[b]; D. C. Gautam[a]
[a] Department of Chemistry, University of Rajasthan, Jaipur, India [b] Department of Chemistry, L. B. S. Government. P. G. College, Jaipur, India

Online publication date: 24 November 2009

To cite this Article Dixit, Yogesh , Dixit, Rahul , Gautam, Naveen and Gautam, D. C.(2009) 'Synthesis and Antimicrobial Activities of Novel Biologically Active Heterocycles: 10H-Phenothiazines, Their Ribofuranosides, and Sulfone Derivatives', Nucleosides, Nucleotides and Nucleic Acids, 28: 11, 998 — 1006
To link to this Article: DOI: 10.1080/15257770903362206
URL: http://dx.doi.org/10.1080/15257770903362206

Nucleosides, Nucleotides and Nucleic Acids, 28:998–1006, 2009

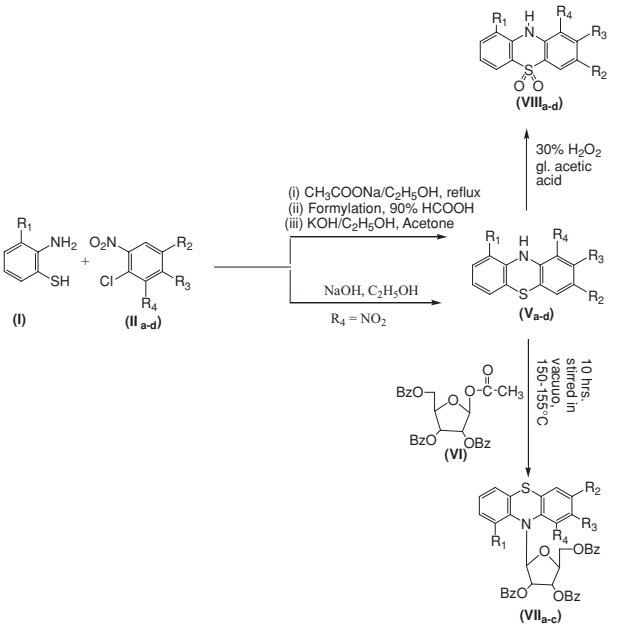
ISSN: 1525-7770 print / 1532-2335 online
DOI: 10.1080/15257770903362206

Taylor & Francis
Taylor & Francis Group

SYNTHESIS AND ANTIMICROBIAL ACTIVITIES OF NOVEL BIOLOGICALLY ACTIVE HETEROCYCLES: 10H-PHENOTHIAZINES, THEIR RIBOFURANOSIDES, AND SULFONE DERIVATIVES

Yogesh Dixit,[1] Rahul Dixit,[1] Naveen Gautam,[2] and D. C. Gautam[1]

[1]*Department of Chemistry, University of Rajasthan, Jaipur, India*
[2]*Department of Chemistry, L. B. S. Government. P. G. College, Kotputli Jaipur, India*



□ *This article deals with the synthesis and antimicrobial activity of a series of novel substituted 10H-phenothiazines, their ribofuranosides, and sulfone derivatives. 10H-Phenothiazines*

Received 21 May 2009; accepted 8 September 2009.
The authors are thankful to the Department of Chemistry and the Department of Botany, University of Rajasthan, Jaipur (India) for providing laboratory facilities. Thanks are also due to UGC, New Delhi for financial support.

Address correspondence to Yogesh Dixit, Department of Chemistry, University of Rajasthan, Jaipur-303004, India. E-mail: yogeshdixit15@yahoo.co.in

were prepared by Smiles rearrangement. These prepared phenothiazines were used as the base to prepare ribofuranosides by treatment with sugar (1-O-acetyl-2,3,5-tri-O-benzoylribofuranose). Sulfone derivatives were prepared by the oxidation of 10H-phenothiazines. The structure of the synthesized compounds was established by elemental analysis and spectroscopic data.

Keywords Antimicrobial activity; phenothiazines; ribofuranosides; Smiles rearrangement

INTRODUCTION

Constructing biologically active molecules such as phenothiazines and their ribofuranosides by molecular modification has been of enormous interest in recent years. A review of the literature on pharmaceutical studies reveals their chemotherapeutic importance. The compounds have been extensively examined as potential antibacterial, antifungal, anti-inflammatory, antitumor, anticancer, anti-herpes, and anti-AIDS agents. A slight change in the substitution pattern in the phenothiazine nucleus causes distinguishable differences in their biological activities.[1–6,8–12,14–24]

Phenothiazines serve as nitrogen and sulfur containing heterocyclic bases for the formation of ribofuranosides by treatment with the appropriate sugar. The formation of sulfone derivatives helps us to investigate the structure of 10H-phenothiazines by the study of the change in infrared and nuclear magnetic resonance (NMR) spectra caused by oxidation of sulfide linkage into sulfones. The Kerby Bauer procedure[7,13] was used for the study of the antimicrobial activity of newly synthesized compounds.

RESULTS AND DISCUSSION

The synthesis of substituted 10H-phenothiazine ($\mathbf{V_a}$) has been carried out by the Smiles rearrangement of substituted 2-formamido-2′-nitrodiphenyl-sulfide ($\mathbf{III_a}$). The formyl derivatives have been prepared from 2-amino-2′-nitrodiphenylsulfide ($\mathbf{II_a}$), which in turn was prepared by the condensation of 2-aminobenzenethiol ($\mathbf{I_a}$) with an o-halonitrobenzene ($\mathbf{II_a}$) in ethanolic sodium acetate solution. 1-Nitrophenothiazines ($\mathbf{V_{b\text{-}d}}$) have been prepared by the condensation of 2-aminobenzenethiols ($\mathbf{I_{a\text{-}b}}$) with o-halonitrobenzenes ($\mathbf{II_{b\text{-}d}}$) containing a nitro group at both *ortho* positions to the reactive halo atom in ethanolic sodium hydroxide solution in which Smiles rearrangement has occurred in situ. The substituted 10H-phenothiazines ($\mathbf{V_{a\text{-}d}}$) dissolved in toluene were then treated with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**VI**) and stirred in vacuo on an oil bath at 150–155°C for 10 hours to yield ribofuranosides ($\mathbf{VII_{a\text{-}c}}$). The sulfone derivatives ($\mathbf{VIII_{a\text{-}d}}$) have been prepared by the oxidation of

TABLE 1 Characterization data of synthesized compounds

Comd. No.	Compound				Yield %	m.p. °C	Molecular formula	% found (calcd.)		
	R_1	R_2	R_3	R_4				C	H	N
IIIa	F	Cl	H	H	85	108	$C_{12}H_8N_2O_2SFCl$	48.02 (48.24)	2.66 (2.68)	9.36 (9.38)
IVa	F	Cl	H	H	75	99	$C_{13}H_8N_2O_3SFCl$	47.89 (47.77)	2.48 (2.45)	8.51 (8.57)
Va	F	Cl	H	H	74	135	$C_{12}H_7NSFCl$	57.11 (57.25)	2.77 (2.78)	5.55 (5.56)
Vb	F	NO_2	H	NO_2	88	358	$C_{12}H_6N_3SO_4F$	46.11 (46.90)	1.95 (1.95)	13.66 (13.68)
Vc	F	Cl	H	NO_2	75	300	$C_{12}H_6N_2SO_2FCl$	48.40 (48.56)	2.01 (2.02)	9.45 (9.44)
Vd	$(CH_3)_2CH$	Cl	H	NO_2	71	260	$C_{15}H_{13}N_2SO_2Cl$	56.07 (56.16)	4.03 (4.05)	8.72 (8.73)
VIIa	F	Cl	H	H	38	111	$C_{38}H_{27}O_7SNFCl$	65.80 (65.56)	3.87 (3.88)	2.02 (2.01)
VIIb	F	NO_2	H	NO_2	41	98	$C_{38}H_{26}O_{11}N_3SF$	60.94 (60.71)	3.44 (3.46)	5.57 (5.59)
VIIc	$(CH_3)_2CH$	Cl	H	NO_2	29	118	$C_{41}H_{33}O_9N_2SCl$	64.52 (64.35)	4.30 (4.31)	3.65 (3.66)
VIIIa	F	Cl	H	H	68	184	$C_{12}H_7NSO_2FCl$	50.59 (50.79)	2.48 (2.46)	4.92 (4.93)
VIIIb	F	NO_2	H	NO_2	65	261	$C_{12}H_6N_3SO_6F$	42.32 (42.47)	1.76 (1.76)	12.39 (12.38)
VIIIc	F	Cl	H	NO_2	71	159	$C_{12}H_6N_2SO_4FCl$	43.63 (43.83)	1.81 (1.82)	8.51 (8.52)
VIIId	$(CH_3)_2CH$	Cl	H	NO_2	60	144	$C_{15}H_{13}N_2SO_4Cl$	50.89 (51.06)	3.67 (3.68)	7.92 (7.94)

TABLE 2 IR, ^{1}H NMR, spectral data, and antimicrobial activity of synthesized compounds

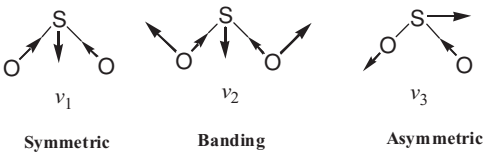
	IR (KBr : υ_{max} cm^{-1})					^{1}H NMR (δ ppm from TMS)				Antibacterial activity		Antifungal activity	
Compound No.	>NH	$\overset{O}{\underset{}{\overset{\|}{N \rightarrow O}}}$	Ar–F	Ar–Cl	C-O-C	^{1}H Singlet	Proton	Ar-H Multiplet	Protons	*S. aureus*	*P. fluorescens*	*A. niger*	*A. flavus*
Va	3410	—	1275	775	—	9.21	1	8.10–7.10	6	0.91	0.92	0.80	0.81
Vb	3340	1560 1340	1280	—	—	9.47	1	7.90–6.50	5	0.95	0.85	0.91	0.86
Vc	3330	1540 1360	1270	760	—	9.31	1	7.80–6.40	5	0.82	0.81	0.96	0.89
Vd	3380	1520 1310	—	740	—	9.71	1	8.65	5	0.86	0.89	0.90	0.81
VIIa	—	—	1280	775	1155	—	—	8.11–7.09	21	0.94	0.97	0.89	0.92
VIIb	—	1555 1340	1283	—	1165	—	—	7.91–6.54	20	0.98	0.87	0.98	0.95
VIIc	—	1520 1310	—	742	1105	—	—	8.22–6.63	20	0.85	0.94	0.96	0.84
VIIIa	3415	—	1278	780	—	9.22	1	8.11–7.13	6	0.92	0.94	0.85	0.88
VIIIb	3344	1565 1345	1282	—	—	9.46	1	7.92–6.49	5	0.86	0.89	0.92	0.95
VIIIc	3337	1542 1360	1272	765	—	9.34	1	7.86–6.41	5	0.94	0.86	0.91	0.95
VIIId	3300	1523 1315	—	743	—	9.72	1	8.20–6.64	5	0.90	0.92	0.89	0.94

Antimicrobial activities are given in term of activity index

$$\text{Activity index} = \frac{\text{Inhibition diameter of test compound}}{\text{Inhibition diameter of standard}}$$

10H-phenothiazines ($\mathbf{V_{a\text{-}d}}$) with 30% hydrogen peroxide in glacial acetic acid (Scheme 1). The structures proposed to the synthesized compounds are well supported by elemental analysis (Table 1) and spectroscopic data.

The characteristic IR bands and ^{1}H NMR data of the synthesized compounds are presented in Table 2.



Compounds $\mathbf{V_{a\text{-}d}}$ exhibit a single sharp peak in the region 3410–3310 cm^{-1} due to the NH- stretching band, which was found absent in compounds $\mathbf{VI_{a\text{-}c}}$, clearly indicating it to be the site of ribosylation. Compounds $\mathbf{VIII_{a\text{-}d}}$ showed three characteristic absorption peak due to asymmetric stretching vibration ν_3 (1380–1370 cm^{-1}), symmetric stretching vibration ν_1 (1195–1140 cm^{-1}), and bending vibration ν_2 (575–520 cm^{-1}) in chloroform solution.

The ^{1}H NMR data of synthesized compounds are presented in Table 2. Compounds $\mathbf{V_{a\text{-}d}}$ showed a singlet due to NH protons, which appeared in the region δ 9.71–9.21 ppm. The ^{1}H NMR spectra of ribofuranosides ($\mathbf{VI_{a\text{-}c}}$) did not show any peak due to NH proton, indicating the formation of ribofuranosides. Molecular ion peaks in the mass spectra of synthesized compounds are observed in accordance with their molecular weights.

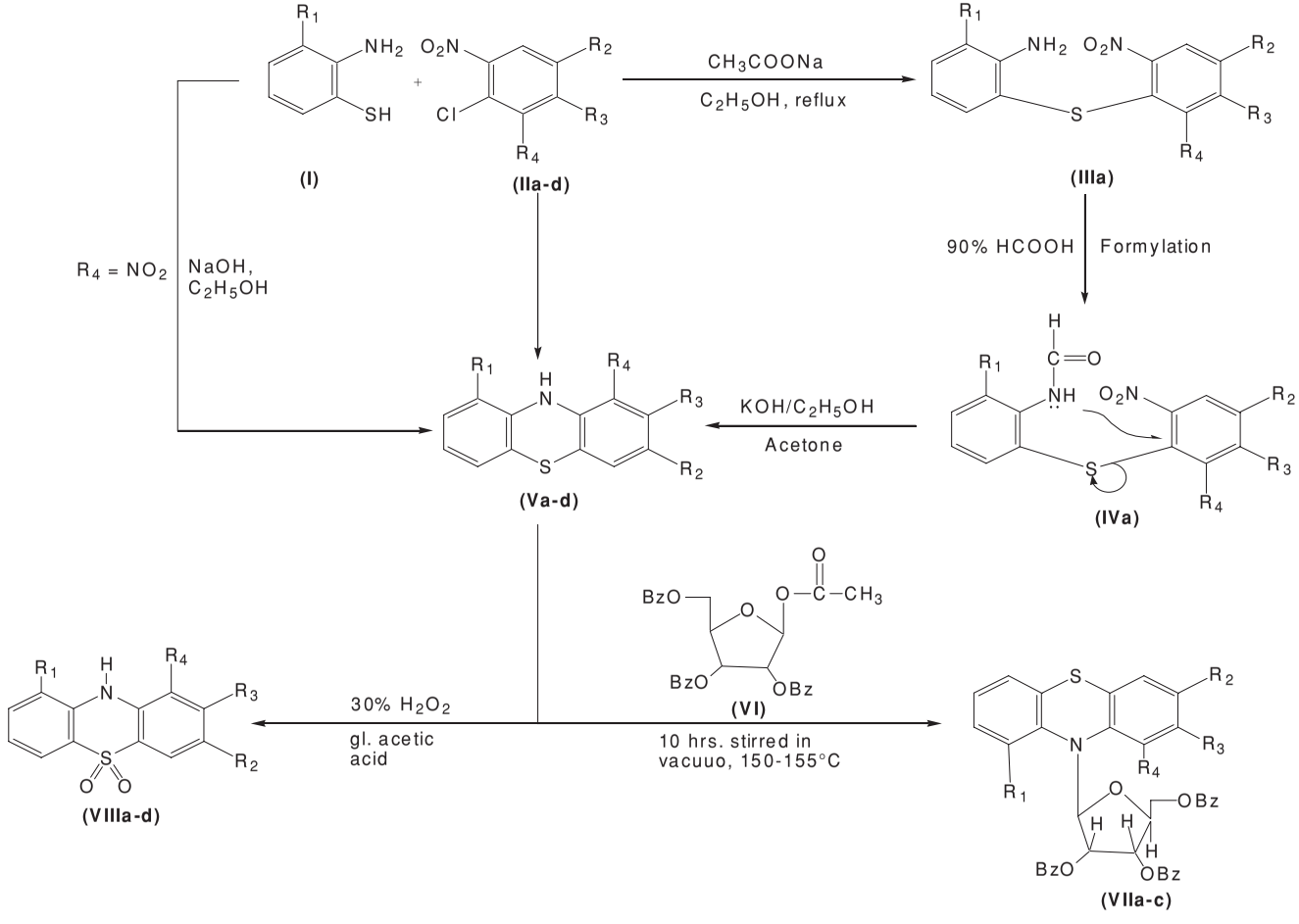
These synthesized compounds were screened for their antimicrobial activities. In the present investigation, the compounds showed good to moderate activity when evaluated against four organisms: *Staphylococcus aureus, Pseudomonas fluorescens, Aspergillus niger,* and *Aspergillus flavus* (see Table 2).

CONCLUSIONS

All these synthesized 10H-phenothiazines, their ribofuranosides, and sulfone derivatives are novel and showed good and moderate antifungal and antibacterial activities against the respective *S. aureas, P. fuoroscens* (bacteria), and *A. niger, A. flavus* (fungi). Hence, these compounds can be used as antifungal and antibacterial drugs after further study and analysis of their biomedical aspects; further biomedical research is required.

EXPERIMENTAL

All melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded in KBr on NICOLET-MEGNA FT-IR



SCHEME 1 Synthesis of substituted 10H-phenothiazines, their ribofuranosides, and sulfone derivatives.

550 spectrometer and the ^{1}H NMR spectra were recorded on JEOL AL-300 spectrometer (300 MHz) in dimethyl sulfoxide (DMSO)-d_6 using tetra methyl silane (TMS) as an internal standard (chemical shifts are measured in δ ppm). Mass spectra were recorded on JEOL SX 102/DA 600 using Argon/Xenon as fast atom bombardment (FAB) gas. The purity of the all synthesized compounds were checked by thin layer chromatography (TLC) using silica gel "G" as adsorbent, visualizing these by ultraviolet (UV) light or an iodine chamber.

Synthesis of 2-Amino-2′-nitro Diphenylsulfide ($\mathbf{III_a}$)

2-Aminobenzenethiol **Ia** (0.1 mole) was dissolved in ethanol (20 mL) containing 0.1 mole of anhydrous sodium acetate in 50 mL round bottom flask and halonitrobenzene **IIa** (0.1 mole) in 10 mL ethanol was added. The reaction mixture was refluxed for 4–5 hours and concentrated in an ice bath overnight. The solid that separated out was filtered, washed with 30% ethanol, and recrystallized from methanol.

Synthesis of 2-Formamido-2′-nitrodiphenylsulfide ($\mathbf{IV_a}$)

The diphenylsulfide $\mathbf{III_a}$ (0.1 mole) obtained was refluxed for 4 hours in 90% formic acid (20 mL). The contents were then poured into a beaker containing crushed ice, the solid separated out was filtered, washed with water until the filtrate was neutralized and crystallized from benzene.

Synthesis of Phenothiazine ($\mathbf{V_a}$)

Formyl derivative $\mathbf{IV_a}$ (0.1 mole) in acetone (15 mL) was refluxed and an alcoholic solution of potassium hydroxide (0.2 gm in 5 mL ethanol) was added. The contents were heated for 30 minutes. A second lot of potassium hydroxide (0.2 gm in 5 mL ethanol) was added to the reaction mixture and further refluxed for 4 hours. The contents were poured into beaker containing crushed ice and were filtered. The residue obtained was repeatedly washed with cold water and finally with 30% ethanol and then crystallized from benzene.

Synthesis of 1-Nitro-10H-phenothiazines ($\mathbf{V_{b\text{-}d}}$)

A mixture of reactive o-halonitrobenzene $\mathbf{II_{b\text{-}d}}$ (0.1 mole), substituted 2-aminobenzenethiol $\mathbf{I_{a\text{-}b}}$ (0.1 mole), sodium hydroxide (0.1 mole), and absolute alcohol (25 mL) was refluxed for 2 hours. The reaction mixture was concentrated on water bath, cooled, and filtered. The

precipitate was washed with hot water and ethanol, then crystallized from acetone.

Synthesis of Substituted N-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl) Phenothiazines (VII$_{a-c}$)

To a concentrated solution of **V$_{a-c}$** (0.002 mole) in toluene, 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose **VI** (0.002 mole) was added and stirred in vacuo on an oil bath at 150–155°C for 15 minutes. The vacuum was broken and the reaction was protected from moisture, by using a guard tube. Stirring was further continued for 10 hours with application of vacuum for 15 minutes after every hour. The melt was dissolved in methanol, boiled for 10 minutes and cooled to room temperature. The precipitate was filtered and the filtrate was evaporated to dryness. The viscous residue thus obtained was dissolved in ether, filtered, concentrated, and kept in a refrigerator overnight to get crystalline ribofuranosides.

Synthesis of Sulfone Derivatives of 10H-Phenothiazines (VIII$_{a-d}$)

To obtain sulfone derivatives of 10H-phenothiazines a solution of substituted 10H-phenothiazines **V$_{a-d}$** (0.01 mole) in 20 mL of 30% glacial acetic acid, 5 mL of 30% hydrogen peroxide was added and refluxed for 15 minutes. Heating was stopped and another lot of 30% hydrogen peroxide (5 mL) was added. The reaction mixture was again refluxed for 3–4 hours. The contents were poured in a beaker containing crushed ice. The yellowish residue obtained was filtered and washed with water and then crystallized from ethanol.

Antimicrobial Activity

All the synthesized compounds were screened for their antibacterial activity against *Staphylococcus aureus* and *Pseudomonas fluoroscens* and antifungal activity against *Aspergillus niger* and *Aspergillus flavus* (Table 2) by the Kerby Bauer procedure (filter paper disc method) using streptomycin (antibacterial) and flucanozole (antifungal) as a standard drug. Natural agar medium for antibacterial activities and standard dextrose agar medium for antifungal activities were used as a medium. From the activity data (Table 2) it may be concluded that the compounds **V$_{a-d}$**, **VII$_{a-c}$**, and **VIII$_{a-d}$** showed good and moderate activity.

The variation in effectiveness of different compound against different organism depends on impermeability of cells of the microbes. The antimicrobial activities of compound given in terms of activity index in Table 2.

REFERENCES

1. Galbraith, F.; Smiles, S. The rearrangement of o-hydroxy sulphones. *J. Chem. Soc.* **1935**, 1234–1238.
2. Kamenov, L.L.; Simov, D.; Golubev, V.B. ESR study of cation radicals of N-substituted phenothiazines. *Theoret. Exp. Chem. J.* **1973**, 7, 115–118.
3. Clercq, E.D. Target for the antiviral and antitumor activities of nucleoside nucleotide and oligonucleotide analogues. *Nucleosides, Nucleotides Nucleic Acid* **1985**, 4, 3–11.
4. Gupta, R.R. (Ed.): *Phenothiazines and 1,4-Benzothiazines–Chemical and Biomedical Aspects*, Elsevier, Amsterdam, 1988.
5. Gupta, A.; Saraswat, V.; Mukherji, S.K.; Gupta, R.R. Synthesis of 5,8-dichloro-3-methyl 4H-1,4-benzothiazine and their conversion into sulphones. *Phosphorus, Sulfur Silicon Relat. Elem.*, **1993**, 85, 101–106.
6. Studenik, C.; Gruber, R.L.; Heistraacher, P. New benzoxazine and benzothiazine derivatives-structure-activity relations in guinea- pig heart and smooth muscle preparation. *Die Pharmazie*, **1999**, 54(5), 330–334.
7. Singh, G.; Swati; Mishra, A.K.; Parkash, L. Synthesis of some novel fluoro substituted benzo(a) phenothiazine and their nucleosides as possible antimicrobial agents. *J. Fluorine Chem.* **1999**, 98, 37–40.
8. Sharma, N.; Gupta, R.; Gautam, D.C.; Gupta, R.R. Synthesis of fluoro phenothiazines via Smiles rearrangement and their conversion into sulfones. *J. Fluorine Chem.* **1999**, 98, 153–157.
9. Gautam, N.; Gupta, R.; Gautam, D.C.; Gupta, R.R. Synthesis of 3-bromo-1-methyl phenothiazines by Smiles rearrangement. *Heterocyclic Commun.* **2000**, 6, 369–374.
10. Kumar, G.; Gupta, V.; Gautam, D.C.; Gupta, R.R. Synthesis of 1- and 3- chlorophenothizines. *Heterocyclic Commun.* **2002**, 8, 447–450.
11. Sharma, P.R.; Gupta, R.; Gupta, V.; Gautam, D.C.; Gupta, R.R. Synthesis of 7-bromo/8,9-dimethyl phenothiazine sulfones. *Heterocyclic Commun.* **2002**, 8, 549–552.
12. Singh, G.; Kumar, N.; Yadav, A.K.; Mishra, A.K. Potential antimicrobial agents; trifluoromethyl 10H-phenothiazines and ribofuranosides. *Heteroatom Chem.* **2003**, 14, 481–486.
13. Collins, C.H.; Lyne, P.M.; Grange, J.O.; Falkinham, J.O. *Microbiological Methods* (8th Ed.), Oxford University Press, London, 2003.
14. Thomas, L.; Gupta, A.; Gupta, V. Synthesis of 2-amino-5-chloro-3-(trifluoromethyl) benzenethiol and conversion into 4H-1,4-benzothiazines and their sulfones. *J. Fluorine Chem.* **2003**, 122, 207–213.
15. Kolaczowski, M.; Michalak, K.; Motoashi, N. Phenothiazines as potent modulaters of yeast multidrug resistance. *International Joural of Antimicrobial Agents* **2003**, 22, 279–283.
16. Gautam, N.; Gautam, D.C. Synthesis of 3-bromo-1-methyl phenothiazine sulfones. *Int. J. Chem. Sci.* **2004**, 2, 84–87.
17. Gautam, N.; Hans, D.; Gautam, D.C. Antifungal activity of some 4H-1,4-benzothiazine compound. *Orient. J. Chem.* **2005**, 21, 299–302.
18. Gautam, N.; Gautam, D.C. Synthesis of 7-bromo-3,5-dimethyl-4H-1,4-benzothiazine sulfones. *Orient. J. Chem.* **2006**, 22, 457–460.
19. Gautam, V.; Sharma, M.; Samarth, R.M.; Gautam, N.; Kumar, A.; Sharma, I.K.; Gautam, D.C. Synthesis of some substituted 10H-phenothiazine, ribofuranosides and their antioxident activity. *Phosphorus, Sulfur Silicon Relat. Elem.*, **2007**, 182, 1381–1392.
20. Dixit, R.; Dixit, Y.; Gautam, N.; Gautam, D.C. Synthesis and antimicrobial activities of new 4H-1,4-benzothiazine. *Indian J. Heterocyclic Chem.* **2007**, 16, 391–394.
21. Dixit, Y.; Dixit, R.; Gautam, N.; Gautam, D.C. Synthesis of bioactive fluorinated 10H-phenothiazines and their sulfone derivatives. *E-Journal of Chemistry* **2008**, 5(S1), 1063–1068.
22. Dixit, R.; Dixit, Y.; Gautam, N.; Gautam, D.C. Synthesis and biological of some new phenothiazines, their sulfones and ribofuranosides. *Phosphorus, Sulfur Silicon Relat. Elem.*, **2008**, 183, 1–12.
23. Dixit, R.; Dixit, Y.; Gautam, N.; Gautam, D.C. Synthesis and antimicrobial activities of novel 4H-1,4-benzothiazine and their sulfones. *Indian J. Heterocyclic Chem.* **2008**, 17, 323–326.
24. Dixit, R.; Gautam, N.; Gautam, D.C. Synthesis of 10H-phenothiazines their sulfones and ribofuranosides as potential chemotherapeutic agents. *Jordan Journal of Chemistry*, **2008**, 3(4), 357–365.