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ScienceDirect
Bioorganic & Medicinal Chemistry 14 (2006) 7476–7481
Bioorganic & Medicinal Chemistry

Design, synthesis and antibacterial activity of novel 1,3-thiazolidine pyrimidine nucleoside analogues

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Received 13 May 2006; revised 3 July 2006; accepted 7 July 2006
Available online 4 August 2006

Abstract—The synthesis of a new class of 1,3-thiazolidine nucleoside analogues in which furanose oxygen atom was replaced with nitrogen atom and 2′-carbon atom with sulfur atom is described. *N-tert*-butoxycarbonyl-2-acyloxy-4-trityloxymethyl-1,3-thiazolidine was coupled with the pyrimidine bases like uracil, thymine, etc. in the presence of lewis acids stannic chloride or trimethyl silyl triflate following Vorbruggen procedure. The antibacterial activity of the novel 1,3-thiazolidine pyrimidine nucleoside analogues is highlighted. All compounds (**7a**–**e**) with free NH group in the pyrimidine moiety showed significant biological activity against all the standard strains used and in that compounds **7d** and **7e** showed significant activity against 14 human pathogens tested.

1. Introduction

The chemical modification of nucleic acid fragments offers a continuous challenge for the organic chemists in search of compounds with antiviral and antibacterial activity.[1] Accordingly considerable efforts have been made to develop new nucleoside analogues likely to exhibit improved activity or decreased toxicity with respect to the 3′-azido 5′-deoxythymidine (AZT). In this context, design of novel ribose rings has resulted in the discovery of effective biologically active agents; in particular promising results have been obtained from new generation of nucleoside analogues where the ribose moiety has been replaced by the alternative heterocyclic rings.[2]

1,3-Thiazolidines are the new class of antimicrobial agents with activity against broad spectrum of Gram-positive pathogens including *Staphylococci*, *Streptococci* and *Enterococci*.[3] These compounds inhibit the protein synthesis in actively growing bacteria. Mechanism of action supports 1,3-thiazolidinone moiety being binded to the bacterial 50 S ribosomal sub units and inhibition of formation of the 70 S ribosomal initiation complex.[4] Thus, it inhibits the bacterial protein synthesis. The 1,3-thiazolidine structure is relatively simple and allows for diverse synthetic modifications.

Based on the above observations, we have carried out the synthesis of the new class of 1,3-thiazolidine nucleoside analogues using Vorbruggen procedure.[5] In our strategy, furanose oxygen atom has been replaced by nitrogen atom and 2′-carbon atom by sulfur atom. Replacement of furanose oxygen atom by nitrogen atom would provide the system with more conformational flexibility.[6] Moreover positive charge associated with protonation to the nitrogen atom on 1,3-thiazolidine ring would be expected to play an important role on the inhibition of viral or cellular enzymes which are essential for viral replication.[7] The newly synthesized 1,3-thiazolidine nucleoside analogues **7a**–**e** showed significant antibacterial activity.

2. Chemistry

Our synthetic strategy was based on the preparation of *N-tert*-butoxycarbonyl-4-methoxycarbonyl-1,3-thiazolidine-2-one **2** followed by the reduction and acylation to give *N-tert*-butoxycarbonyl-2-acyloxy-4-trityloxymethyl-1,3-thiazolidine **5**.

Keywords: 1,3-Thiazolidine nucleosides; Vorbruggen coupling; NOE experiment; Antibacterial activity.
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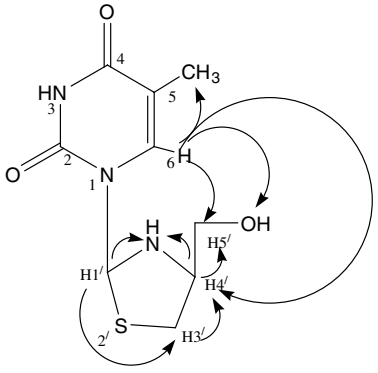
doi:10.1016/j.bmc.2006.07.014

The compound **2** was prepared by condensing di-*tert*-butyl-di-carbonate with L-cystiene methyl ester hydrochloride in the presence of dimethylaminopyridine (DMAP) and triethylamine.[8] The lactam and the ester functional groups were reduced by using lithium triethylborohydride ($Li(Et)_3BH$) at 0 °C to get the *N*-*tert*-butoxycarbonyl-4-hydroxymethyl-1,3-thiazolidine-2-ol **3** in quantitative yield.[9] Protection of primary alcoholic group using trityl chloride in the presence of pyridine gave *N*-*tert*-butoxycarbonyl-4-trityloxymethyl-1,3-thiazolidine-2-ol **4**.[10] Which upon treatment with acetic anhydride, dimethylaminopyridine and triethylamine gave compound **5** (Scheme 1). The compound **5** was coupled with silylated pyrimidine bases in the presence of lewis acids Stannic Chloride or trimethylsilyl triflate (TMS triflate) (Scheme 2). This gave the desired nucleoside analogues (**7a**–**e**) in moderate yield.[11,12] The *N*-*tert*-butoxycarbonyl (Boc) and trityl (T) groups were deprotected by stirring it with trifluoroacetic acid at room temperature which gave the desired products (**7a**–**e**) in excellent yeild.[13]

The proton NMR spectra of the **7b** showed singlet due to the 6H in the region at δ 7.63. The signals due to the NH protons of the pyrimidine moiety appeared downfield in the region at δ 11.27. The 1′-H proton of the 1,3-thiazolidine ring appeared as a singlet in the region at δ 6.8 indicating the attachment of the 1,3-thiazolidine moiety to the pyrimidine base.[14] While triplet due to the 5′-OH protons appeared at δ 4.98. The 5-methyl group appeared in the region at δ 1.71. The 3′H and 4′H appeared in the region between δ 5.9 and 6.4. The NH proton of the 1.3-thiazolidine moiety appeared in the region at δ 4.75. The mass spectra of obtained compounds showed molecular ion peaks, which were consistent with their molecular formulae. The structures of the synthesized compounds were characterized by the IR, ^{1}H NMR, ^{13}C NMR, mass spectra, elemental analysis and NOE experiment.

This modification was envisaged by the formation of nucleosides in enhanced yield and if the sugar moiety carries a 2-α-acyloxy function, the reaction reaches absolute stereospecificity, resulting in the β-ribo or deoxyribonucleosides in contrast to the anomeric mixture routinely obtained by using other methods.[15–17]

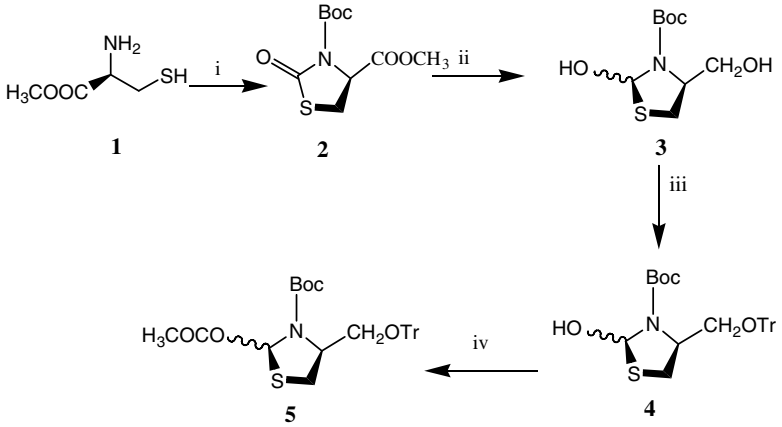


Beta-L-Nucleoside
NOE Correlations from NOESY
Spectra of the compound **7b**

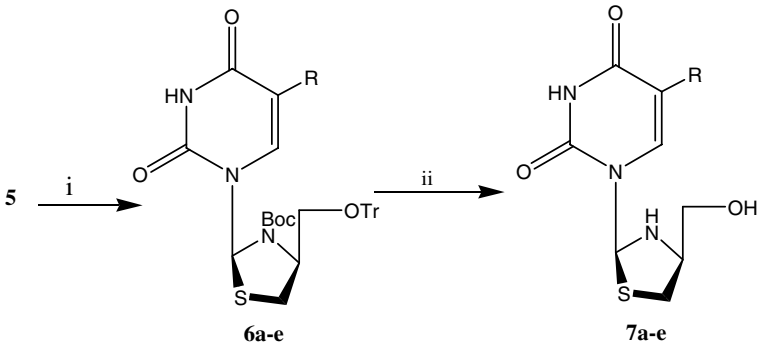
The structure and configuration was obtained through NOE experiment. According to NOE, 6H is giving cross peak to 5-CH_3, 5′-H, 4′-H and OH. 6H and 5′-H cross peak is more stronger compared to 6H to 4′-H. So 5′-H is more nearer to 6H compared to 4′-H. This is possible only in β configuration. The NOE between 6H to 5′-H and 6H to OH suggests that it is L-configuration. In this connection the structure is β-L-Nucleoside.

3. Antibacterial results

The target and intermediate test compounds were passed through a general antibacterial screen. Fourteen human pathogenic bacteria were chosen to evaluate the synthesized nucleoside analogues for antibacterial activity. All compounds were tested at a concentration of 15 mg. The parent molecule **5**, the synthesized nucleosides (**7a**–**e**) and antibiotics Bacitracin and Ciprofloxacin were screened against the bacteria shown in Table 1. The test compounds exhibited quite diverse activities, **7d** and **7e** showed significant activity against Gram +ve and Gram −ve bacteria that was more than that of the parent molecule and the tested antibiotics. The control bacitracin



Scheme 1. Reagents and conditions: (i) $(Boc)_2O$, DMAP, $(Et)_3N$, rt; (ii) $Li(Et)_3BH$, THF, 0 °C; (iii) trityl chloride, pyridine, reflux; (iv) $(CH_3CO)_2O$, DMAP, $(Et)_3N$, rt.



Scheme 2. Reagents and conditions: (i) Silylated pyrimidine base, TMSOTf or $SnCl_4$, CH_3CN, 0 °C; (ii) triflouroacetic acid, rt. Base (a) R=H, uracil; (b) R=CH_3, thymine; (c) R=SH, 5-thiouracil; (d) R=Br, 5-bromouracil; (e) R=Cl, 5-chlorouracil.

Table 1. Antibacterial activity of five newly synthesized nucleoside analogues and antibiotics against human pathogenic bacteria

S. No	Pathogens	5	7a	7b	7c	7d	7e	Bacitracin	Ciprofloxacin
1	*Citrobacter* sp.	12.33 ± 0.17	13.66 ± 0.22	28.50 ± 0.27	12.50 ± 0.39	37.16 ± 0.15	28.66 ± 0.15	0.00 ± 0.00	19.62 ± 0.18
2	*Escherichia coli*	14.50 ± 0.28	17.00 ± 0.00	29.50 ± 0.25	15.16 ± 0.22	36.66 ± 0.15	27.83 ± 0.20	0.00 ± 0.00	0.00 ± 0.00
3	*Klebsiella* sp.	09.83 ± 0.20	10.33 ± 0.16	21.50 ± 0.17	09.50 ± 0.28	32.50 ± 0.13	25.50 ± 0.27	0.00 ± 0.00	20.25 ± 0.16
4	*Proteus mirabilis*	07.50 ± 0.13	08.50 ± 0.27	22.66 ± 0.15	18.00 ± 0.00	28.66 ± 0.25	23.33 ± 0.17	0.00 ± 0.00	18.25 ± 0.16
5	*Pseudomonas aeruginosa*	12.50 ± 0.27	11.50 ± 0.23	34.50 ± 0.13	10.00 ± 0.00	30.66 ± 0.12	27.83 ± 0.27	0.00 ± 0.00	34.25 ± 0.16
6	*S. parathyphi* A	08.50 ± 0.27	13.50 ± 0.21	29.50 ± 0.25	11.50 ± 0.18	34.66 ± 0.12	24.50 ± 0.12	0.00 ± 0.00	27.75 ± 0.16
7	*S. parathyphi* B	06.50 ± 0.28	17.33 ± 0.18	30.66 ± 0.66	16.50 ± 0.19	32.50 ± 0.13	27.83 ± 0.20	0.00 ± 0.00	27.63 ± 0.18
8	*Salmonella typhi*	15.66 ± 0.15	16.50 ± 0.19	27.83 ± 0.20	18.83 ± 0.14	29.50 ± 0.25	19.66 ± 0.11	0.00 ± 0.00	20.25 ± 0.16
9	*S. typhimurium*	10.50 ± 0.12	15.50 ± 0.20	25.50 ± 0.27	12.33 ± 0.15	34.66 ± 0.12	23.33 ± 0.17	0.00 ± 0.00	18.75 ± 0.31
10	*Shigella boydii*	12.66 ± 0.15	17.33 ± 0.18	27.83 ± 0.20	15.50 ± 0.20	37.50 ± 0.07	28.66 ± 0.25	0.00 ± 0.00	17.75 ± 0.16
11	*Shigella flexneri*	07.33 ± 0.17	08.5 ± 0.27	19.66 ± 0.11	10.33 ± 0.16	35.66 ± 0.08	25.50 ± 0.27	0.00 ± 0.00	27.63 ± 0.18
12	*Shigella sonnei*	08.66 ± 0.25	07.66 ± 0.14	21.50 ± 0.17	08.50 ± 0.27	32.50 ± 0.13	37.50 ± 0.07	0.00 ± 0.00	21.75 ± 0.16
13	*Staphylococcus aureus*	7.00 ± 0.00	0.00 ± 0.00	17.33 ± 0.18	0.00 ± 0.00	37.50 ± 0.07	32.50 ± 0.13	26.75 ± 0.84	18.13 ± 0.48
14	*Streptococcus faecalis*	0.00 ± 0.00	6.50 ± 0.30	19.66 ± 0.11	05.50 ± 0.33	38.50 ± 0.12	35.66 ± 0.08	0.00 ± 0.00	0.00 ± 0.00

Zone of inhibition (mean of six replicate ± standard error).
$p < 0.05$.

exhibited no activity towards any of the Gram −ve bacteria and showed activity only against *Staphylococcus aureus* (Gram +ve). Antibacterial activity was maximum against *Streptococcus faecalis* (35.66 mm) and was minimum against *Salmonella typhi* (29.50 mm) in **7e** synthesized nucleoside. In case of **7d** synthesized nucleoside the antibacterial activity was more against *S. faecalis* (38.50 mm) and less against *Proteus mirabilis* (28.66). The antibacterial activity was observed in the parent molecule and all the synthesized nucleosides (**7a**–**e**).

All compounds (**7a**–**e**) with free NH group in pyrimidine moiety showed significant biological activity against all the test bacteria. Further compounds replaced with alkyl group at the 5th position of the pyrimidine moiety might have increased the activity **7b**. There is an important role of the mercapto and halogens attached at the 5th position of the pyrimidine moiety in enhancing the activity.[18] Which reveals that the compounds replaced with different nucleophiles show significant activity. In that compounds replaced with highly electronegative halogens, for example, bromine **7d** and chlorine **7e** show increased activity against all test bacteria. It is interesting to note that both **7d** and **7e** synthesized nucleosides are active against Bacitracin-resistant bacteria. The degree of activity of the parent molecule **5** is generally less than that of all the synthesized nucleosides, but the activity was nearer to the compound **7c.**

4. Conclusion

In conclusion, we have presented short and efficient preparations of the 1,3-thiazolidine nucleoside analogues, which as a consequence of their low toxicity should prove to be important antibacterial agents. The antibacterial activity of these compounds was studied. All compounds (**7a**–**e**) with free NH group in the pyrimidine moiety showed significant biological activity and in that compounds **7d** and **7e** showed significant activity against 14 human pathogens tested. The results of experiments suggest that these nucleosides are good candidate for further investigation on their therapeutic value for management of diseases caused by the test bacteria. Further studies should also explore the relevance of substitutions on the halogen at human cell toxicity and the scope of antibacterial activity.

5. Experimental

5.1. Instrumentation and general materials

All reagents used were of AR grade. THF was distilled from sodium/benzophenone prior to use. Melting points were determined using a Thomas Hoover melting point apparatus and are uncorrected. The ^1H (300 MHz) and ^{13}C NMR (300 MHz) spectra were recorded on a

Bruker 300 NMR spectrometer in $CDCl_3$ and DMSO-d_6 (with TMS for ^1H and DMSO-d_6 for ^{13}C as internal references) unless otherwise stated. MS were recorded on Agluent 1100 ES-MS, Karlsruhe, Germany. Infrared spectra (υ_{max}) were recorded on Perkin Elmer FT-IR spectrophotometer as thin films on KBr plates (for oils) or KBr discs (for solids). Column chromatography was performed on silica gel (230–400 mesh). Microanalyses were obtained with an Elemental Analysensysteme GmbH VarioEL V3.00 element analyzer. The reactions were monitored by thin-layer chromatography (TLC) using aluminium sheets with silica gel 60 F_{254} (Merck). All the reactions were carried out under nitrogen atmosphere.

5.1.1. *N-tert*-Butoxycarbonyl-4-(hydroxyl methyl)-1,3-thiazolidin-2-ol (3). Compound **2** was dissolved in THF (20 ml), cooled to 0 °C and was added 3 equiv of 1 M solution of $Li(Et)_3BH$. The reaction requires 10–60 min to go to completion. Excess of reagent was destroyed by the addition of saturated solution of NH_2Cl aq solution at 0 °C and the reaction mixture was extracted with 15 ml dichloromethane, dried over anhydrous $MgSO_4$ and evaporated to dryness followed by the purification by flash chromatography (hexane/ethyl acetate 7:2) to get the compound **3** as light yellow oil.

Light yellow oil (from EtOAc/hexanes) (0.119 g, 67%); IR (nujol): 1710–1720 (C=O of Boc-ester group), 3200–3220 cm^{-1} (OH). ^1H NMR ($CDCl_3$): δ, 4.24 (dd, J = 8.5, 2.25 Hz, 1H), 3.64 (dd, J = 11.75, 8.5 Hz, 1H), 3.32 (dd, J = 11.75, 2.25 Hz, 1H), 1.51 (s, 9H, Boc ester), 3.88 (t, 2H), 5.2 (2H, s, OH), 6.68 (1H, s, CH): ^{13}C NMR ($CDCl_3$): δ 66.0, 32.3, 86.0, 154.1, 79.8, 28.5, 28.5, 68.5. LC–MS (*m*/*z*) 219.2 (M+1, 55%). Anal. Calcd for $C_9H_{17}NO_4S$: C, 45.95; H, 7.23; N, 5.95; S, 13.6. Found: C, 44.89; H, 7.05; N, 5.86; S, 12.9.

5.1.2. *N-tert*-Butoxycarbonyl-4-(trityloxy methyl)-1,3-thiazolidine-2-ol (4). Compound **3** (4 mmol) and trityl chloride (triphenylmethylchloride) (5 mmol) were dissolved in 20 ml of pyridine. The mixture was heated at 100 °C (steam bath) with swirling for 30 min. The reaction mixture was cooled at room temperature and then poured into 100 ml of ice water. The slurry was stirred vigorously during quenching. The solid was filtered and it was washed thoroughly with water until it is free from pyridine. The solid was dried separately. The white product O-trityl derivative was purified by recrystallization from acetone–toluene.

White solid (from EtOAc/hexanes), (1.05 g, 60%); mp 154–156 °C; IR (nujol): 1710–1720 (C=O of Boc-ester group), 3200–3220 (OH), 1500 cm^{-1} (ArH). ^1H NMR ($CDCl_3$): δ, 4.24 (dd, J = 8.5, 2.25 Hz, 1H), 3.64 (dd, J = 11.75, 8.5 Hz, 1H), 3.30 (dd, J = 11.75, 2.25 Hz, 1H), 3.88 (t, 2H), 1.51 (s, 9H, Boc ester), 6.68 (1H, s, CH), 2 (2H, s, OH), 7.19 (m, 15H, ArH). ^{13}C NMR ($CDCl_3$): δ 66.0, 32.3, 86.0, 154.1, 79.8, 28.5, 85.9, 143.9, 128.3, 129.3, 126.3, 128.3, 143.3, 143.9, 128.3, 129.3, 126.3, 129.3, 129.3, 70.1. LC–MS (*m*/*z*) 429 (M+1, 65%). Anal. Calcd for $C_{27}H_{30}NO_4S$: C, 70.41; H, 6.54; N, 2.93;S, 6.71: Found: C, 69.42; H, 5.53; N, 2.04; S, 6.22.

5.1.3. *N-tert*-Butoxycarbonyl-4-hydroxymethyl-2-acyloxy-1,3-thiazolidine (5). A solution of trityl derivative (**4**) in CH_2Cl_2 was treated with acetic anhydride (2.6 g, 26.3 mmol), triethylamine (2.6 g, 26.3 mmol) and a catalytic amount of 4-DMAP (dimethyl amino pyridine) at room temperature for 3 h. The resultant mixture was washed with 5% HCl, extracted with CH_2Cl_2, evaporated to dryness and purified by silica gel column chromatography with 5% chloroform/ethyl acetate 7:2 to get white solid.

White solid (from EtOAc/hexanes), (0.7493 g, 65%); mp 164–167 °C; IR (nujol): 1710–1720 (C=O of Boc-ester group), 1690 (C=O), 1500 cm^{-1} (Ar H). ^1H NMR ($CDCl_3$): δ, 4.24 (dd, J = 8.5, 2.25 Hz, 1H) 3.64 (dd, J = 11.75, 8.5 Hz, 1H), 3.34 (dd, J = 11.75, 2.25 Hz, 1H), 3.38 (t, 2H), 1.51 (s, 9H, Boc ester), 6.68 (s, 1H, CH), 3.0 (s, 3H, CH_3), 7.19 (m, 15H, ArH). ^{13}C NMR ($CDCl_3$): δ 64.6, 29.0, 89.4, 154.1, 79.8, 28.5, 28.5, 28.5, 85.9, 128.3, 129.3, 126.3, 129.3, 128.3, 129.3, 126.3, 128.3, 143.3, 143.9, 128.3, 129.3, 126.3, 129.3, 129.3, 170.3,20.7; LC–MS (*m*/*z*) 471.6 (M+1, 70%). Anal. Calcd For $C_{30}H_{33}NO_5S$: C, 69.34; H, 6.40; N, 2.70; S, 6.17. Found: C, 68.35; H, 5.42; N, 2.12; S, 6.05.

5.1.4. General procedure for the synthesis of 1,3-thiazolidine nucleoside analogues (7a–e). A mixture of pyrimidine base (2.35 mmol) in HMDS (hexamethyldisilazane) (10 ml) and CH_3CN was heated under reflux for 5 h. After removal of solvent by vacuum pump, a solution of acetate (**5**) (0.786 mmol) in 15 ml CH_3CN was added to the reaction flask containing the silylated pyrimidine bases and then $SnCl_4$ (1.4 mmol) was added dropwise at room temperature. After 16 h, the reaction was quenched with 1 ml of saturated solution of $NaHCO_3$ and the resultant mixture was concentrated. The crude mixture was diluted with 100 ml CH_2Cl_2, washed with 5% $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel column chromatography with 30% ethyl acetate in hexane to give nucleoside analogues. Finally Boc and trityl groups were deprotected by stirring it with trifluoroacetic acid at room temperature to get the desired products (**7a**–**e**) in moderate yield.

5.1.4.1. Procedure for the deprotection of Boc and trityl groups in compounds 6a–e. To a solution of **6a**–**e** (2.34 mmol) in CH_2Cl_2 (2.5 ml) was added TFA (2 ml) under nitrogen atmosphere at RT. After stirring at the same temperature for 24 h, the solvent was evaporated under reduced pressure. Purification of the residue by washing with ether afforded the targeted nucleoside analogues **7a**–**e** in excellent yield.

5.1.4.2. 1-(4-Hydroxymethyl-1,3-thiazolidine-2-yl)-uracil (7a). $[\alpha]_D^{25}$ −146 (*c* 2.5, CH_3OH); white needles (from EtOAc/hexanes), (0.6344 g, 52%); mp 143–146 °C; IR (nujol): 1890 (C=O), 1690 (C=O), 2950 (NH), 3557 cm^{-1} (OH). ^1H NMR (DMSO-d_6): δ, 3.10–3.50 (m, 2H, 2′-H), 3.95–4.10 (m, 2H, 5′-H), 5.01 (t, 1H, 5′-OH), 5.20 (t, 1H, 4′-H), 5.50 (d, J = 7.9 Hz,

1H, 5H), 5.88 (s, 1H, NH), 6.33 (m, 1H, 1′-H), 7.95 (d, 7.9 Hz, 1H, 6-H), 11.20 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 80.5, 34.5, 64.0, 141.3, 102.4, 163.6, 150.9, 65.0. LC–MS (*m*/*z*) 229 (M^+, 87), 175 (15), 153 (7), 95 (38), 83 (8). Anal. Calcd for $C_8H_{11}N_3O_3S$: C, 41.91; H, 4.84; N, 18.33; S, 13.99. Found: C, 41.84; H, 4.75; N, 18.20; S, 13.88.

5.1.4.3. 1-(4-Hydroxymethyl-1,3-thiazolidine-2-yl)-thymine (7b). $[\alpha]_D^{25}$ −121 (*c* 2.5, CH_3OH); white solid (from EtOAc/hexanes), (0.622 g, 58%); mp 148–150 °C; IR (nujol): 1890 (C=O), 1690 (C=O), 2950 (NH), 3557 cm^{-1} (OH). ^{1}H NMR (DMSO-d_6): δ, 1.71 (s, 3H, 5-CH_3), 3.59 (m, 2H, 5′-H), 4.98 (t, 1H, 5′-OH), 4.79 (s, 1H, 6^1 NH), 6.8 (s, 1H, 1′-H), 6.38 (t, 1H, 4′-H), 5.9 (dd, J = 6.3 and 8.8 Hz, 2H, 3′-H), 7.63 (s, 1H, 6-H), 11.27 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 80.8, 34.5, 64.0, 137.5, 110.9, 163.8, 150.9, 65.0. LC–MS (*m*/*z*) 243 (M^+, 92), 175 (15), 167.5 (5), 109 (35), 82 (7). Anal. Calcd for C_8 $H_{11}N_3O_3S$: C, 44.43; H, 5.39; N, 17.27; S, 13.18. Found: C, 44.35; H, 5.25; N, 17.20; S, 13.10.

5.1.4.4. 1-(4-Hydroxymethyl-1,3-thiazolidine-2-yl)-5-thiouracil (7c). $[\alpha]_D^{25}$ −98 (*c* 2.5, CH_3OH); yellow foam (from EtOAc/hexanes), (0.517 g, 55%); IR (nujol): 1890 (C=O), 1690 (C=O), 3557 (OH, NH), 2600 cm^{-1} (SH). ^{1}H NMR (DMSO-d_6): δ 1.5 (s, 1H, SH), 3.10–3.50 (m, 2H, 2′-H), 3.95–4.05 (m, 2H, 5′-H), 5.00 (t, 1H, 5′-OH), 5.20 (t, 1H, 4′-H), 5.85 (s, 1H, NH), 5.95 (m, 1H, 1′-H), 7.95 (s, 1H, 6-H), 11.20 (br s, 1H, NH). ^{13}C NMR δ: 80.1, 34.5, 64.0, 142, 100, 162.4, 150.9, 65.0. LC–MS (*m*/*z*) 261 (M^+, 89), 175 (15), 148.8 (15), 126.9 (35), 98 (6). Anal. Calcd for $C_8H_{11}N_3O_3S_2$: C, 36.77; H, 4.24; N, 16.08; S, 24.54. Found: C, 36.65; H, 4.12; N, 15.98; S, 24.43.

5.1.4.5. 1-(4-Hydroxymethyl-1,3-thiazolidine-2-yl)-5-bromouracil (7d). $[\alpha]_D^{25}$ −152 (*c* 2.5, CH_3 OH); yellow oil (from EtOAc/hexanes), (0.3917 g, 52%); IR (nujol): 1890 (C=O), 1690 (C=O), 2950 (NH), 3557 cm^{-1} (OH). ^{1}H NMR (DMSO-d_6): δ 3.10–3.50 (m, 2H, 2′-H), 3.95-4.05 (m, 2H, 5′-H), 5.00 (t, 1H, 5′-OH), 5.20 (t, 1H, 4′-H), 5.85 (s, 1H, NH), 5.95 (m, 1H, 1′-H), 8.10 (s, 1H, 6-H), 11.20 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 79.8, 34.5, 64.0, 143.5, 94.8, 159.9, 150.9, 65.0. LC–MS (*m*/*z*) 308 (M^+, 75), 232 (8), 175 (15), 168 (35), 147 (6). Anal. Calcd for $C_8H_{10}BrN_3O_3S$: C, 35.04; H, 3.68; N, 20.43; S, 11.69. Found: C, 34.91; H, 3.56; N, 20.31; S, 11.55.

5.1.4.6. 1-(4-Hydroxymethyl-1,3-thiazolidine-2-yl)-5-chlorouracil (7e). $[\alpha]_D^{25}$ −102 (*c* 2.5, CH_3OH).

5.2. Antibacterial activity assay

Antibacterial activity was determined by cup diffusion method on nutrient agar medium. The sterile medium (20 ml) was poured into 9 cm Petri plates. The medium was allowed to cool in a sterile condition and plates were then inculcated with 1×10^5 cfu cultures of test bacteria. The concentration of bacterial cells in the suspension was adjusted to a minimum of 1×10^5 cfu/ml in nutrient broth solution. Agar cup of 5 mm diameter was made in the plates. Each test sample (**5** and **7a**–**e**) was dissolved in dimethyl formamide (DMF), 50 µl of test solution containing 15 mg of the test compound was placed in each cup. The plates were left to stay for an hour in order to facilitate the diffusion of the drug solution. Negative controls were prepared using the same solvent (DMF) employed to dissolve the test compounds.[19] Then the plates were incubated at 37 °C for 24 h. The zone of inhibition if any against the test bacteria was measured in mm. Bacitracin and Ciprofloxacin were used as positive reference to determine the sensitivity of each bacterial species tested.

Acknowledgments

S.N.S. thanks CSIR, Government of India, New Delhi, for Senior Research Fellowship and acknowledges Dr. K. R. Prabhu, senior scientific officer, Department of organic chemistry, IISC, Bangalore, for recording IR, NMR and mass spectra.

Supplementary data

^{1}H NMR and 2D NOESY NMR spectral data of the compound **7b** are provided.

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2006.07.014.

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