Heterocyclic analogs of nucleosides: synthesis and biological evaluation of some 1-(3-thianyl)uracil and 9-(3-thianyl)adenine derivatives[1]

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This paper is dedicated to Professor David B. MacLean

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The 1-(3-thianyl)uracil (**9**) and 9-(3-thianyl)adenine (**14**) nucleoside analogs have been prepared from the key intermediate, (±)-(3β,5β)-3-amino-5-(hydroxymethyl)thiane (**6**). Analog **9** was converted into a mixture of diastereomeric sulfoxides (**10**) that afforded, by a Pummerer reaction, a mixture of (±)-1-{(2′β,3′β,5′β)-2′-acetoxy-5′-(acetoxymethyl)thian-3′-yl}-2,4(1*H*,3*H*)-pyrimidinedione (**11***a*) and its 6′-β isomer (**11***b*). The EI mass spectra of the nucleoside analogs are discussed. The uracil nucleoside analogs have been evaluated also for their anti-HIV and antitumor activities.

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On a préparé le 1-(3-thianyl)uracile (**9**) et la 9-(3-thianyl)adénine (**14**), des analogues de nucléosides, à partir de l'intermédiaire clé, (±)-(3β,5β)-3-amino-5-(hydroxyméthyl)thiane (**6**). On a transformé l'analogue **9** en un mélange de sulfoxydes diastéréoisomères (**10**) qui, par réaction de Pummerer, conduit à un mélange de la (±)-1-{(2′β,3′β,5′β)-2′-acétoxy-5′-(acétoxyméthyl)thian-3′-yl}-2,4(1*H*,3*H*)-pyrimidinedione (**11***a*) et son isomère 6′-β (**11***b*). On discute des spectres de masse en IE des analogues de nucléoside. On a aussi évalué les analogues nucléoside de l'uracile pour leurs activités anti-HIV et antitumorale.

[Traduit par la rédaction]

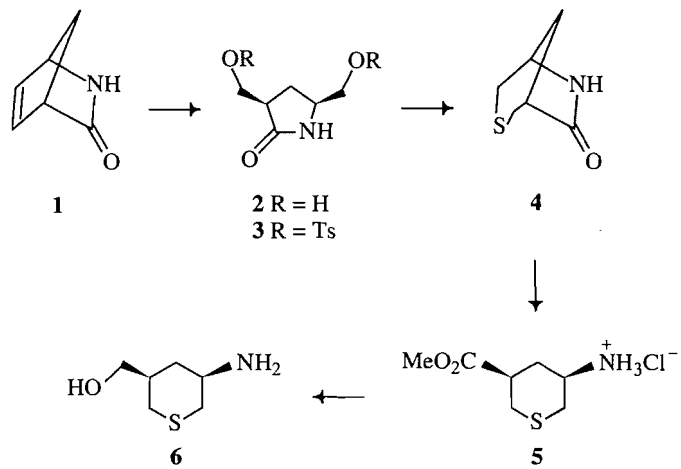
Introduction

Nucleoside analogs have received much attention as a result of their antiviral (1) and antitumor (2) activities. Interest in replacement of the carbohydrate moiety by other heterocycles was recently stimulated by the announcement of the potent anti-HIV activity of the 1,3-oxathiolanyl nucleoside BCH-189 by Belleau and co-workers (3). The chemistry and biological activity of 1,3-oxathiolanyl (4), 1,3-dioxolanyl (5), oxolanyl (6), thiolanyl (7), and pyrrolidinyl (8) nucleosides have been reported by several groups. Nucleosides derived from 1,4- dioxane, 1,4-oxathiane, and 1,4-oxazine have also been prepared and their antiviral activities determined (9).

We have published the results of studies of the synthesis, structure, and antitumor activities of nucleoside analogs having 1,4-oxathianyl, 1,4-dithianyl, 1,4-dioxanyl, 1,4-oxazinyl, 1,4-thiazinyl, and 1,3-thiazolidinyl groups replacing the sugar ring (10). As part of this ongoing project, we wished to prepare the 3-thianyl nucleosides **9**, **10**, and **14**, and to determine their activities against HIV and a variety of human cancers. It was anticipated that **9**, **10**, and **14** would have antitumor properties similar to those of our earlier six-membered heterocyclic analogs, but that they should prove to be more stable *in vivo* since the base ring is not attached by a glycosidic linkage.

Results and discussion

Since our analogs do not involve a glycosidic linkage, the pyrimidine- or purine-ring system had to be constructed on an aminothiane already possessing the desired *cis* stereochemistry. *cis*-3-Amino-5-(hydroxymethyl)thiane (**6**) was prepared as shown in Scheme 1 from the known bicyclic lactam **1** (11). This lactam was prepared as a racemate, and, consequently, our analogs were also racemic; however, **1** can be obtained in optically pure form from a microbiological resolution (12), and is available commercially now in both enantiomeric forms.[3]



SCHEME 1

Ozonolysis of **1** followed by reduction with sodium borohydride afforded the diol **2**, which was converted directly into ditosylate **3** (57.5% overall). Double displacement with sodium sulfide in hot *N*,*N*-dimethylformamide gave the bicyclic thianelactam **4**, in 68% yield after recrystallization, with the required *cis*-3,5 stereochemistry in place. The lactam was esterified using methanol containing concentrated aqueous hydrochloric acid. It is noteworthy that initial attempts to perform this reaction under anhydrous conditions were unsuccessful, but that addition of even a small amount of water promoted a facile, complete conversion of **4** into **5**. The crystalline amino alcohol **6** then could be obtained in 93% yield by reduction with lithium borohydride.

Synthesis of uracil derivatives

Preparation of the uridine analogs **9** and **10** is shown in Scheme 2. The required acylisocyanate **7** was made by a literature method (13), and condensed with **6** in *N*,*N*-dimethylformamide–benzene in the cold, to afford the acylurea derivative **8** in 78% yield. Cyclization was effected by brief boiling in 2 N

[1]This paper is gratefully dedicated to Professor David B. MacLean, teacher and colleague of one of us (W.A.S.).

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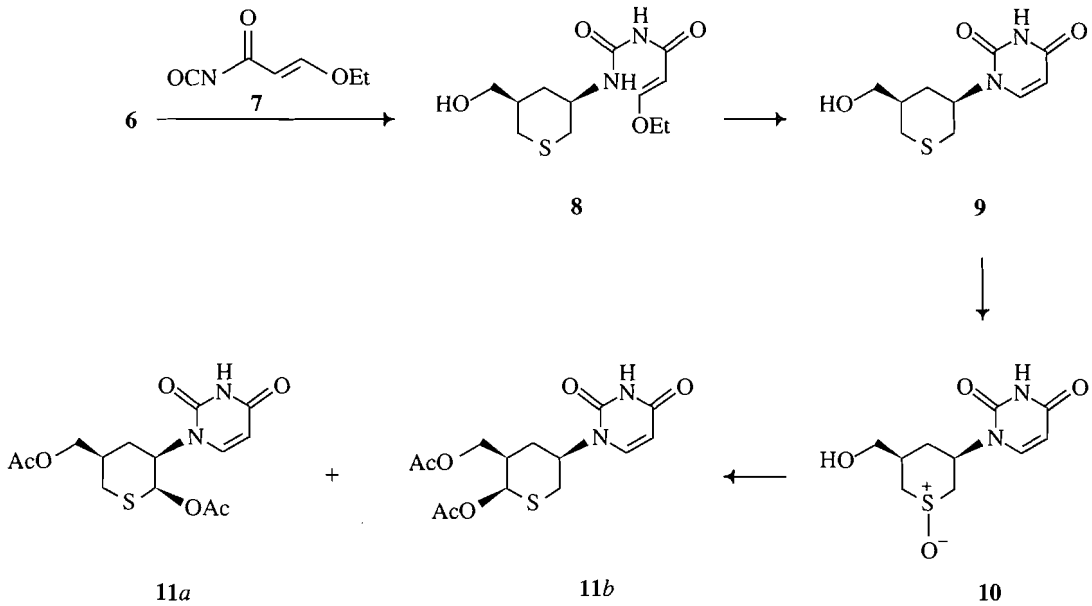


SCHEME 2

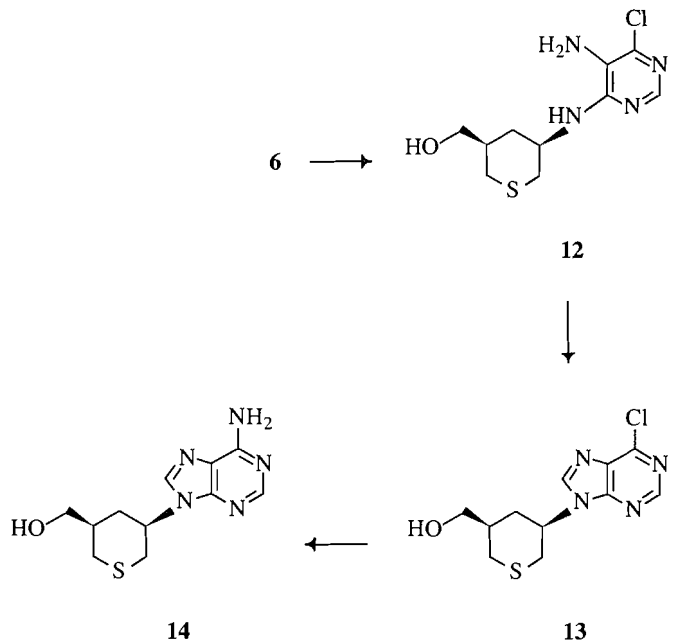
sulfuric acid, to give the nucleoside analog **9** as a crystalline solid.

We also wished to prepare the sulfoxide **10**. Treatment of **9** with sodium metaperiodate in ice-cold water gave **10** as an unresolvable mixture of diastereomers. Although the ^{1}H nmr spectrum of **10** was complicated by overlap of all the signals, even at 400 MHz, assignment of the signals attributable to the major and minor products was possible using a COSY experiment. The major product was identified as the axial sulfoxide by the downfield shift of the ^{1}H NMR signals of the axial protons, H-3′ and H-5′, relative to those of the minor product, as well as by the smaller chemical-shift differences between the signals of the geminal-proton pairs, H-2′$_{ax}$/H-2′$_{eq}$ and H-6′$_{ax}$/H-6′$_{eq}$ (see ref. 14). Because of signal overlap, nmr integration could not be used to estimate the axial:equatorial ratio of **10**. Treatment of **10** with *tert*-butyldimethylsilyl chloride provided the corresponding primary silyl ether derivative, in whose nmr spectrum the signals of the vinylic H-5 protons of the major and minor components were well separated. Integration of these signals allowed the axial:equatorial ratio of **10** to be estimated as 12:5.

We explored the use of the Pummerer reaction to install oxygen functionality at C-6′ of our analog. Treatment of **10** with hot acetic anhydride in the presence of *p*-toluenesulfonic acid afforded a 1:1 mixture of regioisomeric products **11***a*,*b* in 65% yield, which co-eluted on silica gel chromatography. The products were identified as 2′- and 6′-axial acetoxy derivatives by ^{1}H nmr spectroscopy in deuterated pyridine solution, which showed no axial–axial couplings for the thioketal-type protons. Partial purification of the 2′-acetoxy isomer **11***a* was achieved by recrystallization from *N*,*N*-dimethylformamide–isobutanol; this sample was useful for achieving a complete assignment of the ^{1}H nmr spectrum. Because of the difficulty in effecting separation of **11***a* and **11***b*, and the low solubility of these compounds, further elaboration of them was not pursued.

Synthesis of adenine derivatives

As shown in Scheme 3, **6** was condensed with 5-amino-4,6-dichloropyrimidine in 1-butanol at reflux temperature (11), to give **12** (88%). The purinyl ring was completed by treatment

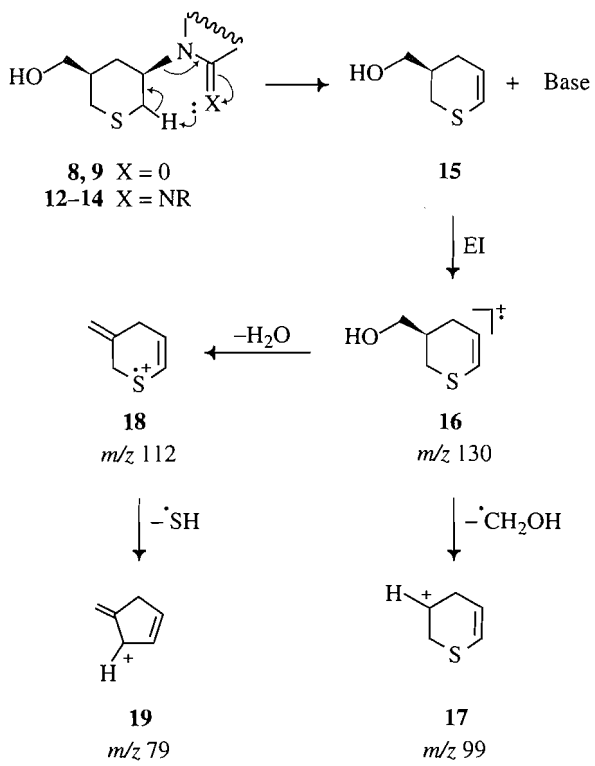


SCHEME 3

with triethyl orthoformate under acid catalysis, followed by brief exposure to 0.5 N hydrochloric acid (15); chloropurine derivative **13** precipitated from solution in 64% yield. Subsequent displacement of chloride by methanolic ammonia in a glass bomb at 75°C gave the desired analog (**14**) of adenosine in 41% yield after recrystallization from 2-propanol.

Anti-HIV and antitumor assays

Nucleoside analogs **9** and **10** were submitted to the U.S. National Cancer Institute (N.C.I.) for anti-HIV screening by the soluble-formazan assay in human T4 lymphocytes (16). The IC_{50} value for each compound was found to be $>10^{-3}$ M in this system. These compounds were screened also by N.C.I. against a panel of human leukemia, lung cancer, colon cancer, CNS



SCHEME 4

cancer, melanoma, ovarian cancer, and renal cancer cell cultures; analog **9** displayed weak activity (GI_{50} 5.6×10^{-5} M) against CNS cancer SNB-75 cells, but **9** and **10** were inactive otherwise ($GI_{50} > 10^{-4}$ M) in this assay. In none of these tests was any significant toxicity observed.

Compounds **9**, **10**, and **11***a* were screened also against HIV in MT-4 T-cells, by both reverse transcriptase assay and indirect immunofluorescence detection of viral p24 antigen.[4] No significant anti-HIV activity was found in these tests.

Mass-spectral observations

Routine EI mass spectra revealed an interesting common fragmentation for the thiane derivatives **8**, **9**, and **12–14**. These molecules afforded weak or no molecular ions, and their spectra displayed a sequence of major fragments at *m/z* 130, 112, 99, and 79. This pattern can be explained by a facile *thermal* elimination promoted by Lewis-basic atoms in the substituent side chain, as shown in Scheme 4. A mechanism of this type has recently been proposed by Lafortune et al. (17) to explain the fragmentation of thymidine in SIMS-TOF mass spectrometry. Subsequent electron-impact ionization of the neutral unsaturated product **15** then affords the observed fragments. The molecular formulas of all the proposed fragments have been determined by high-resolution measurements. A transformation of the type **18** → **19** was observed previously in the spectrum of methyl vinyl sulfide (18), which ejects sulfhydryl radical to give allyl cation by alkyl migration.

The thermal character of the initial elimination is suggested by the absence of any fragment ions characteristic of McLafferty or similar reactions of $M^{+\cdot}$. It is also supported by the behavior of the urea **8** under hot- and cold-injection conditions. This compound may produce fragments at *m/z* 99 by two pathways. High-resolution measurements showed the presence of a 1:1 mixture of ion **17** and acylium ion $[C_5H_7O_2]^+$ when the injection probe was heated, while only the product $[C_5H_7O_2]^+$, arising from direct electron-impact ionization of intact **8**, was observed on cold injection.

The Pummerer product **11** appears to fragment by a similar pathway, but competing loss of HOAc complicates analysis of the spectrum. Interestingly, the sulfoxide **10** gives a strong molecular ion and no fragments related to the sequence of Scheme 4, despite the enhanced acidity of its C-2′ protons.

Experimental

The ^{1}H nmr spectra were recorded on a Bruker AM-400 or AC-F 200 spectrometer at 400.136 or 200.132 MHz. The signals due to residual protons in the deuterated solvents indicated were used as internal standards. Chemical shifts are reported in ppm (δ) downfield from the position of tetramethylsilane (TMS). The symbols s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broadened) are used to describe the multiplicity and shape of the signals. The ^{13}C nmr spectra were obtained at 100.6 MHz on the AM-400 spectrometer or at 50.323 MHz on the AC-F 200 spectrometer. The JMOD spin-echo sequence (19) was used to aid in peak identification. Chemical shifts in ppm (δ) downfield from the position of TMS were measured using the solvent signals as internal standards, except for spectra measured in D_2O, where 1,4-dioxane-H_8 (δ 66.5) (20) was added as a standard.

EI mass spectra were recorded on a VG Micromass 7070F mass spectrometer at an ionizing voltage of 70 eV, or on a VG Analytical ZAB-E mass spectrometer, and CI spectra were recorded using NH_3 at ~1 Torr (133.3 Pa) as reagent gas; data are given as *m/z* (% relative intensity). The exact masses were determined under EI conditions. Except where noted, the high-resolution measurements were performed by peak matching using perfluorokerosene as a reference standard, at a resolution of ~4000.

Melting points were determined using a Fisher–Johns apparatus, and are uncorrected. Flash chromatography was performed on Kieselgel 60 (230–400 mesh), and thin-layer chromatography (TLC) was performed on glass plates coated with Kieselgel 60.

The homogeneity of the products was established on the basis of chromatographic, spectroscopic (^{1}H and ^{13}C nmr), and melting-point determinations.

(±)-(3β,5β)-3,5-Bis(p-toluenesulfonyloxymethyl)-1-aza-2-oxocyclopentane (3)

A solution of freshly recrystallized lactam **1** (see ref. 11) (8.2 g, 75 mmol) in dry methanol (300 mL) was purged with oxygen, while being cooled to −60°C in a Dry Ice – acetone bath. Ozone was passed through the solution at −60°C, until TLC analysis (0.5% methanol in ethyl acetate as eluant) and the presence of the blue color of an excess of ozone indicated completion. The temperature of the solution was allowed to rise to −30°C over 20 min, while the excess of ozone was purged with a stream of oxygen. Sodium borohydride (2.84 g, 75 mmol) was added slowly, while the temperature rose to −5°C. Stirring was continued for 1 h, and then Dowex-50 (H^+) ion-exchange resin was added to bring the apparent pH to 5. The mixture was filtered and the filtrate was concentrated. The residual oil was evaporated several times from methanol, and then left overnight on a vacuum pump, to provide diol **2** as a solid (10.01 g, 92%). A sample recrystallized from methanol–ether had mp 91–92°C; ^{1}H nmr (D_2O, 400 MHz) δ: 1.67 (1H, ddd, $J_{4\alpha,4\beta}$ = 13 Hz, J_{vic} = 9 Hz, $J_{vic'}$ = 7 Hz, H-4α), 2.31 (1H, ddd, $J_{4\beta,4\alpha}$ = 13 Hz, J_{vic} = 10 Hz, $J_{vic'}$ = 8 Hz, H-4β), 2.74 (1H, m, H-3), 3.46 (1H, dd, J_{gem} = 12 Hz, $J_{to\,5}$ = 6 Hz, 5-CH_2OH), 3.63 (1H, dd, J_{gem} = 12 Hz, $J_{to\,5}$ = 4 Hz, 5-CH_2OH), 3.68 (1H, dd, J_{gem} = 11 Hz, $J_{to\,3}$ = 5 Hz, 3-CH_2OH), 3.76 (1H, dd, J_{gem} = 11 Hz, $J_{to\,3}$ = 6 Hz, 3-CH_2OH), 3.70–3.80 (1H, m, H-5); ms (EI): 114 (M − CH_2OH)$^+$

[4]We thank Dr. Mark A. Wainberg of the Lady Davis Institute for Medical Research at The Sir Mortimer B. Davis-Jewish General Hospital, Montreal, for conducting these assays.

(100%), 96 (M − CH_2OH − H_2O)$^+$ (80.4%), 84 (M − CH_2O − CH_2OH)$^+$ (36.2%); ms (CI): 146 (M + H)$^+$ (100%), 163 (M + NH_4)$^+$ (6.4%), 291 (2M + H)$^+$ (2%). Exact Mass calcd. for $C_5H_8NO_2$ (M − CH_2OH)$^+$: 114.0555; found (hrms): 114.0551.

Without further purification, **2** (9.929 g, 68.4 mmol) was dissolved in freshly distilled, dry pyridine (200 mL) under an argon atmosphere. 4-Dimethylaminopyridine (0.852 g, 6.97 mmol) was added, and the mixture was cooled in an ice–water bath. *p*-Toluenesulfonyl chloride (28.7 g, 150.5 mmol) was added in several portions, and the mixture was stirred for 1 h. The pyridine was then evaporated under vacuum at 35°C. The residue was dissolved in ethyl acetate (200 mL), and the solution was washed successively with water (50 mL), a saturated aqueous solution of copper sulfate (50 mL), and water (50 mL). The combined aqueous layers were extracted with dichloromethane (50 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated. Flash chromatography (ethyl acetate as eluant) of the residue afforded a sample of **3** (19.4 g, 57.5% overall), which was recrystallized from ethyl acetate; mp 131–132°C; ^{1}H nmr ($CDCl_3$, 200 MHz) δ: 1.62 (1H, ddd, $J_{4\alpha,4\beta}$ = 13.3 Hz, J_{vic} = 9 Hz, J_{vic} = 7 Hz, H-4α), 2.38 (1H, ddd, $J_{4\beta,4\alpha}$ = 13.3 Hz, J_{vic} = 9.6 Hz, J_{vic} = 7.3 Hz, H-4β), 2.43 (3H, s, ArCH_3), 2.45 (3H, s, ArCH_3), 2.61–2.81 (1H, m, H-3), 3.78–3.96 (2H, m, H-5 and 5-C*H*OTs), 4.06 (1H, m, 5-C*H*OTs), 4.08 (1H, dd, J_{gem} = 9.9 Hz, $J_{to\ 3}$ = 6 Hz, 3-C*H*OTs), 4.20 (1H, dd, J_{gem} = 9.9 Hz, $J_{to\ 3}$ = 3.7 Hz, 3-C*H*OTs), 6.21 (1H, br s, NH), 7.33 (2H, d, *J* = 8.4 Hz, aromatic), 7.36 (2H, d, *J* = 8.4 Hz, aromatic), 7.73 (2H, d, *J* = 8.4 Hz, aromatic), 7.78 (2H, d, *J* = 8.4 Hz, aromatic); ^{13}C nmr ($CDCl_3$, 50 MHz) δ: 21.72 (2 × ArCH_3), 26.04 (C-4), 40.81 (C-3), 50.91 (C-5), 69.06 (*C*H_2OTs), 72.21 (*C*H_2OTs), 128.00 (4 × *meta*-aromatic C's), 130.02 (2 × *ortho*-aromatic C's), 130.19 (2 × *ortho*-aromatic C's), 132.23 (2 × *para*-aromatic C's), 132.26 (2 × *para*-aromatic C's), 145.23 (aromatic *C*-S), 145.51 (aromatic *C*-S), 174.26 (C-2). Anal. calcd. for $C_{20}H_{23}NO_7S_2$: C 52.97, H 5.11, N 3.09, S 14.14; found: C 52.81, H 5.13, N 3.13, S 13.88.

(±)-3-Thia-6-aza-7-oxobicyclo[3.2.1]octane (4)

To a solution of ditosylate **3** (17.0 g, 37.5 mmol) in *N*,*N*-dimethylformamide (300 mL) was added sodium sulfide nonahydrate (10.8 g, 45 mmol), and the mixture was stirred at 90°C for 45 min. Heating was stopped, and the solvent was evaporated in vacuo. The residue was taken up in acetone (100 mL), and the resulting suspension was filtered. The filtrate was concentrated to produce an oil that deposited a solid on standing under vacuum. The solid product was collected by filtration and washed with a small amount of ethyl acetate. The filtrate was concentrated and the residue was chromatographed (gradient elution using 0% → 4% methanol in ethyl acetate) to afford further product. The combined solids were recrystallized from ethyl acetate – hexanes to give **4** (3.67 g, 68%); mp 198–200°C (sealed capillary); ^{1}H nmr ($CDCl_3$, 400 MHz) δ: 1.73 (1H, dd, $J_{8ax,8eq}$ = 11.6 Hz, $J_{8ax,5}$ = 1.5 Hz, H-8_{ax}), 2.37 (1H, m, H-8_{eq}), 2.52 (1H, br dd, $J_{2eq,2ax}$ = 12.8 Hz, $J_{2eq,1}$ = 4.5 Hz, H-2_{eq}), 2.59–2.69 (2H, m, H-4_{eq} and H-5), 2.96 (1H, dd, $J_{4ax,4eq}$ = 12 Hz, $J_{4ax,5}$ = 1.5 Hz, H-4_{ax}), 3.03 (1H, d, $J_{2ax,2eq}$ = 12.8 Hz, H-2_{ax}), 3.98 (1H, br dd, $J_{1,8eq}$ = 5.8 Hz, $J_{1,2eq}$ = 4.5 Hz, H-1), 6.31 (1H, br s, NH); ^{13}C nmr (D_2O, 100 MHz) δ: 25.69 (C-4), 30.04 (C-2), 35.76 (C-8), 39.87 (C-5), 50.83 (C-1), 181.51 (C-6). An analytical sample was obtained by sublimation at 0.2 Torr and 110°C. Anal. calcd. for C_6H_9NOS: C 50.32, H 6.34, N 9.78, S 22.39; found: C 50.36, H 6.29, N 9.78, S 22.79.

(±)-(3β,5β)-3-Amino-5-(methoxycarbonyl)thiane hydrochloride (5)

A solution of lactam **4** (3.00 g, 20.95 mmol) in methanol (50 mL) was treated with concentrated hydrochloric acid (0.25 mL), and the mixture was heated at reflux temperature for 12 h. Heating was stopped, and the solvent was evaporated. The residual solid was recrystallized from isoamyl alcohol. The product crystals were washed with ether and dried in vacuo at 110°C to give **5** (4.05 g, 91%); mp 167–168°C; ^{1}H nmr (DMSO-d_6, 400 MHz) δ: 1.49 (1H, apparent q, J_{app} = 12 Hz, H-4_{ax}), 2.30 (1H, br d, $J_{4eq,4ax}$ = 12 Hz, H-4_{eq}), 2.51 (1H, dd, $J_{2ax,2eq}$ = 13.5 Hz, $J_{2ax,3}$ = 12 Hz, H-2_{ax}), 2.61 (1H, dd, $J_{6ax,6eq}$ = 13 Hz, $J_{6ax,5}$ = 12 Hz, H-6_{ax}), 2.70–2.83 (3H, m, H-2_{eq}, H-5 and H-6_{eq}), 3.26 (1H, m, H-3), 3.64 (3H, s, OCH_3), 8.50 (3H, br s, NH_3^+); ^{13}C nmr (DMSO-d_6, 100 MHz) δ: 28.17 (C-6), 29.34 (C-4), 32.11 (C-2), 43.18 (C-5), 49.12 (C-3), 51.98 (OCH_3), 172.50 (C=O). Anal. calcd. for $C_7H_{13}NO_2S$·HCl: C 39.71, H 6.67, N 6.62, S 15.14; found: C 39.78, H 6.65, N 6.59, S 15.87.

(±)-(3β,5β)-3-Amino-5-(hydroxymethyl)thiane (6)

A stirred suspension of **5** (3.5 g, 16.5 mmol) in dry oxolane (40 mL) was treated with a 2 M solution of lithium borohydride in oxolane (15 mL, 30 mmol). The resulting clear solution was heated at reflux temperature for 2 h. The reaction mixture was cooled, methanol (25 mL) was added slowly, and then concentrated hydrochloric acid was added dropwise until the solution was acidic to pH paper; the solvents were evaporated. The residue was dissolved in methanol (50 mL) and the solution was evaporated; the residue was then dissolved in concentrated aqueous ammonia (70 mL). The solution was continuously extracted with chloroform overnight. The dried ($MgSO_4$) extracts were concentrated to yield **6** as a solid (2.27 g, 93%). An analytical sample was obtained by recrystallization from dichloromethane–hexanes; mp 124–125°C; ^{1}H nmr ($CDCl_3$, 400 MHz) δ: 0.85 (1H, apparent q, J_{app} = 12 Hz, H-4_{ax}), 1.55 (3H, br s, OH and NH_2), 1.93–2.04 (2H, m, H-4_{eq} and H-5), 2.23 (1H, dd, $J_{2ax,2eq}$ = 13 Hz, $J_{2ax,3}$ = 12 Hz, H-2_{ax}), 2.33 (1H, dd, $J_{6ax,6eq}$ = 13 Hz, $J_{6ax,5}$ = 10 Hz, H-6_{ax}), 2.56–2.65 (2H, m, H-2_{eq} and H-6_{eq}), 2.98 (1H, dddd, $J_{3,2ax}$ = 12 Hz, $J_{3,4ax}$ = 12 Hz, $J_{3,4eq}$ = 3.5 Hz, $J_{3,2eq}$ = 3 Hz, H-3), 3.45 (1H, dd, J_{gem} = 11 Hz, $J_{to\ 5}$ = 7 Hz, CH_2OH), 3.53 (1H, dd, J_{gem} = 11 Hz, $J_{to\ 5}$ = 6 Hz, CH_2OH); ^{13}C nmr ($CDCl_3$, 50 MHz) δ: 30.16 (C-4), 36.75 (C-6), 38.80 (C-2), 42.32 (C-5), 50.73 (C-3), 67.06 (CH_2OH); ms (EI): 147 (M$^+$) (24.4%), 116 (M − CH_2OH)$^+$ (7.3%), 104 (M − C_2H_5N)$^+$ (12.8%), 86 (M − CH_2SCH_3)$^+$ (100%). Exact Mass calcd. for $C_6H_{13}NOS$: 147.0719; found (hrms): 147.0707. Anal. calcd. for $C_6H_{13}NOS$: C 48.95, H 8.90, N 9.51, S 21.77; found: C 48.80, H 8.91, N 9.31, S 23.12.

(±)-trans-*3-Ethoxy*-N-*[N'-[(3'β,5'β)-5'-(hydroxymethyl)thian-3'-yl]-carbamoyl]propenamide (8)*

Following the procedure of Shealy and O'Dell (13*a*), silver cyanate was dried at 100°C and <1 Torr in the dark for 2 h. A solution of amine **6** (1.47 g, 10 mmol) in dry, distilled *N*,*N*-dimethylformamide (50 mL) was dried over 3 Å molecular sieves under an argon atmosphere until needed. All glassware was dried overnight at 140°C, and assembled while hot, under an argon atmosphere.

A suspension of silver cyanate (4.5 g, 30 mmol) in dry benzene (20 mL) was heated at reflux temperature for 30 min, under an argon atmosphere. A solution of *trans*-3-ethoxypropenoyl chloride (13*b*) (2.00 g, 15 mmol) in dry benzene (10 mL) was added using a syringe, and the mixture was boiled for 45 min. Heating and stirring were stopped, and the suspended solids were allowed to settle for 2 h.

The solution of amine **6** was transferred to a dry flask by cannula, under argon pressure, and cooled to −60°C. A 20-mL portion (~10 mmol) of the acyl isocyanate solution was removed with a syringe, and was added dropwise to the amine over 15 min. The temperature was raised quickly to −30°C. Stirring was continued as the mixture warmed gradually to 23°C overnight. The solvent was then evaporated under high vacuum, and the residue was re-evaporated from ethanol (50 mL). Traces of solvent were removed on the vacuum pump, and the solid product was recrystallized from 95% ethanol to afford **8** (2.26 g, 78%); mp 171–172°C; IR ν_{max} (KBr): 3510 (sh, OH), 3310, 3230 (sh, NH), 2980 (vinyl CH), 1700, 1670, 1605 (s, C=O), 1530, 1510 (C=C) cm^{-1}; ^{1}H nmr ($CDCl_3$, 400 MHz) δ: 1.11 (1H, apparent q, J_{app} = 12 Hz, H-4_{ax}), 1.37 (3H, t, *J* = 7 Hz, CH_3), 1.56 (1H, br s, OH), 2.00–2.13 (2H, m, H-4_{eq} and H-5), 2.29 (1H, dd, $J_{2ax,2eq}$ = 13 Hz, $J_{2ax,3}$ = 11 Hz, H-2_{ax}), 2.43 (1H, dd, $J_{6ax,6eq}$ = 12.5 Hz, $J_{6ax,5}$ = 11 Hz, H-6_{ax}), 2.64 (1H, br d, $J_{2eq,2ax}$ = 13.5 Hz, H-2_{eq}), 2.87 (1H, ddd, $J_{6eq,6ax}$ = 13 Hz, $J_{6eq,5}$ = 2 Hz, $J_{6eq,2eq}$ ~1.5 Hz, H-6_{eq}), 3.48 (1H, dd,

[5]For the Exact Mass determinations of peaks at *m/z* 99 and 79 in compounds **8** and **9**, peak matching to $C_2H_6O_2$ = 74.03678 and CH_2Cl_2 = 83.9536 was used for calibration.

J_{gem} = 10.5 Hz, $J_{to\ 5}$ = 7 Hz, CH_2OH), 3.55 (1H, dd, J_{gem} = 10.5 Hz, $J_{to\ 5}$ = 5.5 Hz, CH_2OH), 3.96 (2H, q, J = 7 Hz, OCH_2CH$_3$), 3.92–4.05 (1H, m, H-3), 5.32 (1H, d, J = 12 Hz, C(O) CH=), 7.64 (1H, d, J = 12 Hz, =CHO), 8.69 (1H, d, $J_{to\ 3}$ = 7.5 Hz, CHN*H*C=O), 9.35 (1H, br s, C(O)NHC(O)); ^{13}C nmr ($CDCl_3$, 100 MHz) δ: 14.45 (CH_3), 30.25 (C-4), 33.26 (C-6), 35.46 (C-2), 42.29 (C-5), 49.24 (C-3), 67.19 (O*C*H$_2$CH$_3$), 67.45 (CH$_2$OH), 97.80 (=*C*C(O)N), 154.32 (NC(O)N), 162.86 (=CHO), 168.19 (=C*C*(O)N); ms (EI): 288 (M^+) (2.5%), 159 ($C_6H_{11}N_2O_3$)$^+$ (68.7%), 130 ($C_6H_{10}OS$)$^+$ (64.4%), 112 (C_6H_8S)$^+$ (22.4%), 99 (O=CC=COEt)$^+$ and (C_5H_7S)$^+$ (83.9%), 79 (C_6H_7)$^+$ (13.2%), 71 (C_4H_7O)$^+$ (100%). Exact Mass calcd. for $C_{12}H_{20}N_2O_4S$: 288.1149; found (hrms): 288.1145. Exact Mass calcd. for $C_5H_7O_2$: 99.0446; found (hrms)[5]: 99.0453. Exact Mass calcd. for C_5H_7S: 99.0268; found (hrms)[5]: 99.0275. Exact Mass calcd. for C_6H_7: 79.0548; found (hrms)[5]: 79.0541. Anal. calcd. for $C_{12}H_{20}N_2O_4S$: C 49.98, H 6.99, N 9.71, S 11.12; found: C 49.73, H 6.82, N 9.62, S 11.37.

*(±)-1-{(3′β,5′β)-5′-(Hydroxymethyl)thian-3′-yl}-2,4(1H,3H)-pyrimidinedione (**9**)*

Enol ether **8** (1.90 g, 6.59 mmol) was suspended in a mixture of concentrated sulfuric acid (4 mL) and water (20 mL), and the reaction mixture was heated at reflux temperature for 30 min. The resulting solution was cooled, and neutralized with 1 M sodium hydroxide. The water was evaporated, and the residue was extracted with 95% ethanol (3 × 75 mL). The extracts were filtered and the filtrate was concentrated to afford a glass. Re-evaporation from toluene–ethanol gave **9** as a powder, which was dried in vacuo (1.53 g, 96%); mp 178–179°C; IR ν_{max} (KBr): 3430 (br, OH), 3176 (NH), 3044 (vinyl C-H), 1687 (C=O) cm^{-1}; ^{1}H nmr (DMSO-d_6, 400 MHz) δ: 1.48 (1H, apparent q, J_{app} = 12 Hz, H-4′$_{ax}$), 1.76 (1H, br d, $J_{4'eq,4'ax}$ = 12 Hz, H-4′$_{eq}$), 1.88 (1H, m, H-5′), 2.23 (1H, dd, $J_{6'ax,6'eq}$ = 12 Hz, $J_{6'ax,5'}$ = 12 Hz, H-6′$_{ax}$), 2.54 (2H, br d, J_{app} = 13 Hz, H-2′$_{eq}$ and H-6′$_{eq}$), 2.88 (1H, dd, $J_{2'ax,2'eq}$ = 12 Hz, $J_{2'ax,3'}$ = 12 Hz, H-2′$_{ax}$), 3.19–3.31 (2H, m, CH_2OH), 4.50 (1H, m, H-3′), 4.68 (1H, dd, J_{vic} = 5 Hz, J_{vic} = 5 Hz, OH), 5.56 (1H, d, $J_{5,6}$ = 8 Hz, H-5), 7.70 (1H, d, $J_{6,5}$ = 8 Hz, H-6), 11.12 (1H, br s, NH); ^{13}C nmr (DMSO-d_6, 100 MHz) δ: 29.27 (C-4′), 30.25 (C-6′), 33.31 (C-2′), 43.51 (C-5′), 54.32 (C-3′), 65.35 (CH$_2$OH), 101.27 (C-5), 141.93 (C-6), 150.69 (C-2), 163.08 (C-4); ms (CI): 485 (2M + H)$^+$ (2%), 260 (M + NH$_4$)$^+$ (10.5%), 243 (M + H)$^+$ (100%), 131 ($C_6H_{10}OS$ + H)$^+$ (34.1%); ms (EI): 130 ($C_6H_{10}OS$)$^+$ (100%), 112 (C_6H_8S)$^+$ (28.5%), 99 (C_5H_7S)$^+$ (32.9%), 79 (C_6H_7)$^+$ (57%). Exact Mass calcd. for $C_6H_{10}OS$: 130.0452; found (hrms): 130.0452. Exact Mass calcd. for C_6H_8S: 112.0347; found (hrms): 112.0339 (pyrimidinedione $C_4H_4N_2O_2$ requires 112.0273). Exact Mass calcd. for C_5H_7S: 99.0268; found (hrms)[5]: 99.0270. Exact Mass calcd. for C_6H_7: 79.0548; found (hrms)[5]: 79.0541. Anal. calcd. for $C_{10}H_{14}N_2O_3S\cdot\frac{1}{2}H_2O$: C 47.80, H 6.02, N 11.15, S 12.76; found: C 47.88, H 5.68, N 11.07, S 12.98.

*(±)-1-{(3′β,5′β)-5′-(Hydroxymethyl)thian-3′-yl}-2,4(1H,3H)-pyrimidinedione S-oxide (**10**)*

To a solution of sulfide **9** (1.00 g, 4.13 mmol) in water (30 mL) at 0°C was added sodium periodate (0.929 g, 4.34 mmol) in a minimum amount of water, and the reaction mixture was stirred for 1 h. An excess of solid sodium bisulfite was added with cooling, and the solution was evaporated. The solid residue was dried in vacuo, and extracted with methanol (3 × 30 mL). The extracts were filtered, the filtrate was evaporated, and the residue was chromatographed by gravity on flash-grade silica, using a chloroform–methanol gradient (10% → 20%) as eluant. No separation of sulfoxide diastereomers was observed. Evaporation of the combined product fractions afforded a glassy oil, which was dissolved in water. The solution was freeze-dried, to afford **10** as an amorphous powder (0.732 g, 69%); mp > 155°C; IR ν_{max} (KBr): 3404 (br, OH), 1685 (C=O), 1101 (S=O) cm^{-1}; ^{1}H nmr (D_2O, 400 MHz) major (axial S=O) diastereomer δ: 1.72 (1H, apparent q, J_{app} = 12 Hz, H-4′$_{ax}$), 1.93 (1H, br d, $J_{4'eq,4'ax}$ = 12 Hz, H-4′$_{eq}$), 2.38 (1H, dd, $J_{6'ax,6'eq}$ = 13.5 Hz, $J_{6'ax,5'}$ = 13 Hz, H-6′$_{ax}$), 2.50 (1H, m, H-5′), 2.92 (1H, dd, $J_{2'ax,2'eq}$ = 14 Hz, $J_{2'ax,3'}$ = 14 Hz, H-2′$_{ax}$), 3.04 (br d, $J_{6'eq,6'ax}$ = 13.5 Hz, H-6′$_{eq}$), 3.18 (1H, m, H-2′$_{eq}$), 3.45–3.56 (2H, m, CH_2OH), 4.96 (1H, m, H-3′), 5.71 (1H, d, $J_{5,6}$ = 8 Hz, H-5), 7.52 (1H, d, $J_{6,5}$ = 8 Hz, H-6); minor (equatorial S=O) diastereomer δ: 1.60 (1H, apparent q, J_{app} = 12 Hz, H-4′$_{ax}$), 1.84 (1H, br d, $J_{4'eq,4'ax}$ = 12 Hz, H-4′$_{eq}$), 1.88–1.98 (1H, m, H-5′), 2.44 (1H, dd, $J_{6'ax,6'eq}$ = 12 Hz, $J_{6'ax,5'}$ = 12 Hz, H-6′$_{ax}$), 2.96 (1H, dd, $J_{2'ax,2'eq}$ = 12 Hz, $J_{2'ax,3'}$ = 12 Hz, H-2′$_{ax}$), 3.45–3.56 (3H, m, CH_2OH and H-6′$_{eq}$), 3.63 (1H, br d, $J_{2'eq,2'ax}$ = 12 Hz, H-2′$_{eq}$), 4.53 (1H, m, H-3′), 5.72 (1H, d, $J_{5,6}$ = 8 Hz, H-5), 7.55 (1H, d, $J_{6,5}$ = 8 Hz, H-6); ^{13}C nmr (D_2O, 100 MHz) major (axial S=O) diastereomer δ: 31.34 (C-5′), 31.87 (C-4′), 45.98 (C-6′), 48.05 (C-3′), 52.31 (C-2′), 64.80 (CH$_2$OH), 102.20 (C-5), 143.71 (C-6), 151.71 (C-2), 166.12 (C-4); minor (equatorial S=O) diastereomer δ: 31.34 (C-4′), 33.30 (C-5′), 45.41 (C-6′), 50.01 (C-3′), 51.35 (C-2′), 64.39 (CH$_2$OH), 102.29 (C-5), 143.10 (C-6), 151.55 (C-2), 166.05 (C-4). Exact Mass calcd. for $C_{10}H_{14}N_2O_4S$: 258.0675; found (hrms): 258.0666. Anal. calcd. for $C_{10}H_{14}N_2O_4S\cdot H_2O$: C 43.47, H 5.84, N 10.14, S 11.60; found: C 43.51, H 5.54, N 10.13, S 11.80.

Treatment of **10** with *tert*-butyldimethylsilyl chloride afforded the corresponding silyl ether derivative (TLC: **10**, R_f = 0.26; silyl ether, R_f = 0.76; using 8:2 (v/v) chloroform–methanol as eluant). The ^{1}H nmr signals attributable to H-5 in the two diastereomers of this derivative were separated sufficiently at 400 MHz (Δδ = 0.098 ppm) to show the diastereomer ratio to be 12:5.

*(±)-1-{(2′β,3′β,5′β)-2′-Acetoxy-5′-(acetoxymethyl)thian-3′-yl}-2,4(1H,3H)-pyrimidinedione (**11**a)*

A mixture of sulfoxide **10** (200 mg, 0.77 mmol), acetic anhydride (15 mL), and *p*-toluenesulfonic acid (cat.) was heated in an oil bath at 100°C under a nitrogen atmosphere for 2.5 h. The excess of acetic anhydride was evaporated under vacuum. The dried residue was adsorbed on a small amount of silica gel, applied to a silica gel column, and chromatographed using a gradient of chloroform–methanol (0% → 2%) as eluant. All of the product fractions could be seen on TLC analysis, using 2% (v/v) methanol in chloroform as eluant, to contain two components (R_f = 0.17 and 0.23) in approximately equal proportions. Evaporation of these fractions afforded a mixture of **11***a* (2′-β) and its 6′-β isomer **11***b* (171 mg, 65%). Recrystallization of this material from isobutanol–*N*,*N*-dimethylformamide effected a partial resolution, affording 22 mg (8.3%) of an 8:1 mixture of **11***a*:**11***b*; ^{1}H nmr (pyridine-d_5, 400 MHz) δ: 1.83 (1H, br d, $J_{4'eq,4'ax}$ = 12.3 Hz, H-4′$_{eq}$), 2.01 (3H, s, CH$_3$-11′), 2.04 (3H, s, CH$_3$-9′), 2.16 (1H, apparent q, J_{app} = 12.4 Hz, H-4′$_{ax}$), 2.45 (1H, m, H-5′), 2.53 (1H, br d, $J_{6'eq,6'ax}$ = 13.4 Hz, H-6′$_{eq}$), 2.76 (1H, dd, $J_{6'ax,6'eq}$ = 13.2 Hz, $J_{6'ax,5'}$ = 11.9 Hz, H-6′$_{ax}$), 4.07 (1H, dd, J_{gem} = 11.0 Hz, $J_{to\ 5'}$ = 6.8 Hz, CH_2OAc), 4.12 (1H, dd, J_{gem} = 11.0 Hz, $J_{to\ 5'}$ = 5.9 Hz, CH_2OAc), 5.32 (1H, ddd, $J_{3',4'ax}$ = 13.2 Hz, $J_{3',2'}$ = 2.4 Hz, $J_{3',4'eq}$ = 3.5 Hz, H-3′), 5.89 (1H, d, $J_{5,6}$ = 8.1 Hz, H-5), 6.44 (1H, d, $J_{2',3'}$ = 2.4 Hz, H-2′), 7.66 (1H, d, $J_{6,5}$ = 8.1 Hz, H-6); ^{13}C nmr (pyridine-d_5, 50 MHz) δ: 20.65 (C-9′ and C-11′), 26.17 (C-4′), 27.94 (C-6′), 40.15 (C-5′), 56.76 (C-3′), 67.66 (C-7′), 71.34 (C-2′), 102.14 (C-5), 141.18 (C-6), 152.26 (C-2), 164.09 (C-4), 169.38 (C-10′), 170.67 (C-8′); ms (EI): 342 (M^+) (3.8%), 282 (M − HOAc)$^+$ (20.1%), 230 (M − pyrimidinedione)$^+$ (13.2%), 222 (M − 2HOAc)$^+$ (28.5%), 113 (pyrimidinedione + H)$^+$ (100%): Exact Mass calcd. for $C_{14}H_{18}N_2O_6S$: 342.0886; found (hrms): 342.0887.

*(±)-5-Amino-6-chloro-4-{[(3′β,5′β)-5′-(hydroxymethyl)thian-3′-yl]-amino}pyrimidine (**12**)*

According to the method of Daluge and Vince (11), a solution of amino alcohol **6** (250 mg, 1.7 mmol), 5-amino-4,6-dichloropyrimidine (563 mg, 3.44 mmol), and triethylamine (1.2 mL, 8.5 mmol) in *n*-butanol (10 mL, dried over 3 Å molecular sieves) was heated at reflux temperature in a nitrogen atmosphere for 24 h. The mixture was cooled, and the solvent was evaporated. The residue was adsorbed on a small amount of silica gel, and applied to a silica gel column. Elution with ethyl acetate afforded **12** as a yellowish solid (412 mg, 88%); mp 177–178°C; ^{1}H nmr (DMSO-d_6, 400 MHz) δ: 1.10 (1H, apparent q,

[6]The overlapping signals at δ 151.20 ppm could be separated by addition of ~20% (v/v) of benzene-d_6 to the sample.

J_{app} = 12.5 Hz, H-4′$_{ax}$), 1.79–1.94 (1H, m, H-5′), 1.94 (1H, br d, $J_{4'eq,4'ax}$ = 12 Hz, H-4′$_{eq}$), 2.22 (1H, dd, $J_{6'ax,6'eq}$ = 13 Hz, $J_{6'ax,5'}$ = 12 Hz, H-6′$_{ax}$), 2.31 (1H, dd, $J_{2'ax,2'eq}$ = 12.5 Hz, $J_{2'ax,3'}$ = 11 Hz, H-2′$_{ax}$), 2.56 (1H, br d, $J_{6'eq,6'ax}$ = 13 Hz, H-6′$_{eq}$), 2.80 (1H, br d, $J_{2'eq,2'ax}$ = 12.5 Hz, H-2′$_{eq}$), 3.20–3.35 (2H, m, CH_2OH), 4.05–4.16 (1H, m, H-3′), 4.61 (1H, dd, $J_{to\ CH_2O}$=5.5 Hz, $J_{to\ CH_2O}$ = 5.0 Hz, OH), 5.05 (2H, br s, ArNH_2), 6.71 (1H, d, $J_{to\ 3'}$ = 7.0 Hz, ArN*H*CH), 7.74 (1H, s, H-2); ^{13}C nmr (DMSO-d_6, 100 MHz) δ: 29.83 (C-4′), 32.22 (C-2′), 35.06 (C-6′), 42.70 (C-5′), 50.22 (C-3′), 65.63 (C-7′), 123.45 (C-4), 136.95 (C-5), 145.54 (C-2), 150.73 (C-6); ms (EI): 274 (^{35}Cl M$^+$) (3%), 146 ($C_4H_5N_4{}^{37}Cl)^+$ (33%), 144 ($C_4H_5N_4{}^{35}Cl)^+$ (100%), 130 ($C_6H_{10}OS)^+$ (11.1%), 112 ($C_6H_8S)^+$ (3.9%), 99 ($C_5H_7S)^+$ (5%), 79 ($C_6H_7)^+$ (10.7%); ms (CI): 277 (^{37}Cl M + H)$^+$ (38.2%), 275 (^{35}Cl M + H)$^+$ (100%). Exact Mass calcd. for $C_{10}H_{15}N_4OSCl$: 274.0655; found (hrms): 274.0653.

*(±)-6-Chloro-9-[(3′β,5′β)-5′-(hydroxymethyl)thian-3′-yl]purine (**13**)*

A solution of **12** (275 mg, 1 mmol), triethyl orthoformate (5 mL), and concentrated hydrochloric acid (0.3 mL) was stirred at 23°C for 1.75 h (see ref. 15). The excess of the orthoformate was evaporated, the last traces being removed under high vacuum. The residue was dissolved in 0.5 M hydrochloric acid (7 mL), and the solution was stirred for 1 h. A white precipitate formed that was isolated by filtration and found to be **13** (183 mg, 64%). The product could be crystallized from water and dried at 78°C and 0.1 Torr; mp 173–174°C; ^{1}H nmr (DMSO-d_6, 400 MHz) δ: 1.90 (1H, apparent q, J_{app} = 12 Hz, H-4′$_{ax}$), 2.01 (1H, m, H-5′), 2.10 (1H, br d, $J_{4'eq,4'ax}$ = 12.2 Hz, H-4′$_{eq}$), 2.38 (1H, dd, $J_{6'ax,6'eq}$ = 13.2 Hz, $J_{6'ax,5'}$ = 11.2 Hz, H-6′$_{ax}$), 2.65 (1H, br d, $J_{6'eq,6'ax}$ = 13.2 Hz, H-6′$_{eq}$), 2.86 (1H, br d, $J_{2'eq,2'ax}$ = 12.7 Hz, H-2′$_{eq}$), 3.22 (1H, dd, $J_{2'ax,2'eq}$ = 12.7 Hz, $J_{2'ax,3'}$ = 11.6 Hz, H-2′$_{ax}$), 3.29 (1H, dd, J_{gem} = 10.7 Hz, $J_{to\ 5'}$ = 6.5 Hz, CH_2OH), 3.33 (1H, dd, J_{gem} = 10.7 Hz, $J_{to\ 5'}$ = 5.5 Hz, CH_2OH), 4.20–4.60 (1H, br, OH), 4.80 (1H, m, H-3′), 8.75 (1H, s, H-8), 8.76 (1H, s, H-2); ^{13}C nmr (DMSO-d_6, 50 MHz)[6] δ: 29.43 (C-4′), 31.22 (C-2′), 34.34 (C-6′), 42.97 (C-5′), 55.08 (C-3′), 65.22 (C-7′), 130.96 (C-5), 145.63 (C-8), 149.05 (C-4), 151.20 (C-2 and C-6); ms (EI): 285 (M + H)$^+$ (4%), 157 (^{37}Cl purine + H)$^+$ (26.9%), 155 (^{35}Cl purine + H)$^+$ (83.8%), 130 ($C_6H_{10}OS)^+$ (100%), 112 ($C_6H_8S)^+$ (39.3%), 99 ($C_5H_7S)^+$ (27.7%), 79 ($C_6H_7)^+$ (46.4%); ms (CI): 287 (^{37}Cl M + H)$^+$ (38.6%), 285 (^{35}Cl M + H)$^+$ (100%), 251 (M − H_2S + H)$^+$ (6.4%), 131 ($C_6H_{10}OS$ + H)$^+$ (11.6%). Exact Mass calcd. for $C_{11}H_{14}N_4OSCl$ (M + H)$^+$: 285.0577; found (hrms): 285.0577.

*(±)-6-Amino-9-[(3′β,5′β)-5′-(hydroxymethyl)thian-3′-yl]purine (**14**)*

Chloropurine **13** (100 mg, 0.35 mmol) was suspended in methanol (3 mL) in a Pyrex tube. The suspension was cooled to −78°C and anhydrous ammonia was bubbled in until the solution volume was increased to ~5 mL. The tube was sealed, and heated at 75°C for 40 h. The solvent was evaporated under a stream of nitrogen to leave **14** as a solid, which was recrystallized from isopropanol and dried over potassium hydroxide at 0.1 Torr and 61°C (38 mg, 41%); mp 213–215°C; ^{1}H nmr (DMSO-d_6 + D_2O, 400 MHz) δ: 1.81 (1H, apparent q, J_{app} = 12 Hz, H-4′$_{ax}$), 1.90–2.07 (2H, m, H-4′$_{eq}$ and H-5′), 2.34 (1H, dd, $J_{6'ax,6'eq}$ = 12 Hz, $J_{6'ax,5'}$ = 12 Hz, H-6′$_{ax}$), 2.62 (1H, br d, $J_{6'eq,6'ax}$ = 12 Hz, H-6′$_{eq}$), 2.77 (1H, br d, $J_{2'eq,2'ax}$ = 12 Hz, H-2′$_{eq}$), 3.15 (1H, dd, $J_{2'ax,2'eq}$ = 12 Hz, $J_{2'ax,3'}$ = 12 Hz, H-2′$_{ax}$), 3.21–3.36 (2H, m, CH_2OH), 4.63 (1H, m, H-3′), 8.16 (1H, s, H-8), 8.25 (1H, s, H-2); ^{13}C nmr (DMSO-d_6, 100 MHz)[7] δ: 29.55 (C-4′), 31.66 (C-2′), 34.76 (C-6′), 43.06 (C-5′), 54.24 (C-3′), 65.30 (CH_2OH), 118.80 (C-5), 139.34 (C-8), 148.86 (C-4), 151.62 (C-2), 155.39 (C-6); ms (EI): 266 (M + H)$^+$ (2%), 136 (adenine + H)$^+$ (100%), 130 ($C_6H_{10}OS)^+$ (15.3%), 112 ($C_6H_8S)^+$ (7.7%), 99 ($C_5H_7S)^+$ (12.4%), 79 ($C_6H_7)^+$ (16.2%); ms (CI): 266 (M + H)$^+$ (100%), 136 (adenine + H)$^+$ (8.2%). Exact Mass calcd. for $C_{11}H_{16}N_5OS$ (M + H)$^+$: 266.1076; found (hrms): 266.1079.

[7]The signal attributable to C-8 at δ 139.34 ppm was prone to saturation. Accordingly, this spectrum was acquired using a power-gated sequence employing a 3-μs pulse and a 10-s relaxation delay between pulses.

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