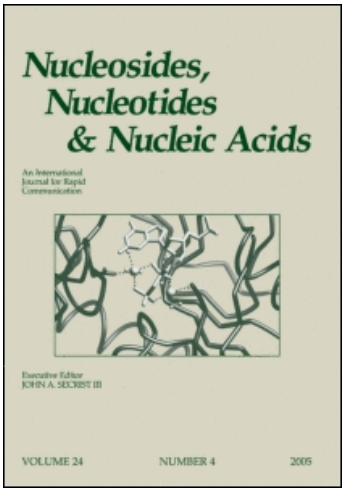

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis and Antiviral Evaluation of Novel 2,3-Dihydroxypropyl Nucleosides from 2- and 4-Thiouracils

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To cite this Article Abdel-Rahman, Adel A. -H. , El-Etrawy, Abd-Allah SH. , Abdel-Megied, Ahmed E. -S. , Zeid, Ibrahim F. and El Ashry, El Sayed H.(2008) 'Synthesis and Antiviral Evaluation of Novel 2,3-Dihydroxypropyl Nucleosides from 2- and 4-Thiouracils', Nucleosides, Nucleotides and Nucleic Acids, 27: 12, 1257 — 1271
To link to this Article: DOI: 10.1080/15257770802086898
URL: http://dx.doi.org/10.1080/15257770802086898

Nucleosides, Nucleotides and Nucleic Acids, 27:1257–1271, 2008

ISSN: 1525-7770 print / 1532-2335 online
DOI: 10.1080/15257770802086898

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SYNTHESIS AND ANTIVIRAL EVALUATION OF NOVEL 2,3-DIHYDROXYPROPYL NUCLEOSIDES FROM 2- AND 4-THIOURACILS

Adel A.-H. Abdel-Rahman,[1] Abd-Allah SH. El-Etrawy,[1] Ahmed E.-S. Abdel-Megied,[1] Ibrahim F. Zeid,[1] and El Sayed H. El Ashry[2]

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□ *Regioselective alkylation of 2-thiouracils* ***1a–c*** *and 4-thiouracils* ***7a,b*** *with 2,3-O-isopropylidene-2,3-dihydroxypropyl chloride (****2****) afforded 2-{[(2,2-Dimethyl-1,3-dioxolan-4-yl) methyl]thio}pyrimidin-4(1H)-ones* ***3a–c*** *and 4-{[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]thio} pyrimidin-2(1H)-ones* ***8a,b,*** *respectively. Further alkylation with* ***2*** *and/or 2,3-O-isopropylidine-1-O-(4-toluenesulfonyl)-glycerol (****4****) gave the acyclo N-nucleosides* ***5a–c*** *and* ***9a,b*** *whose deprotection afforded* ***6a–c*** *and* ***10a,b****. 2-(Methylthio)pyrimidin-4(1H)-ones* ***11a–c*** *and 4-(methylthio)pyrimidin-2(1H)-ones* ***14a,b*** *were treated with* ***2*** *and/or* ***4*** *to give* ***12a–c*** *and* ***15a,b*** *which were deprotected to give* ***13a–c*** *and* ***16a,b****. Pyrimidine-2,4(1H,3H)-dithiones* ***17a–c*** *were treated with two equivalents of* ***2*** *to give 2,4-bis{[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]thio}pyrimidines* ***18a–c****. Deprotection of compounds* ***18a–c*** *gave 2,4-bis[(2,3-dihydroxypropyl)thio]pyrimidines* ***19a-c****. The activity of the deprotected nucleosides against Hepatitis B virus was evaluated and showed moderate inhibition activity against HBV with mild cytotoxicity.*

Keywords Acyclic nucleosides; 2,3-dihydroxypropyl nucleosides; 2-(methylthio) pyrimidin-4(1*H*)-ones; 4-(methylthio)pyrimidin-2(1*H*)-ones; antiviral agents; hepatitis B

INTRODUCTION

The discovery of acyclovir[1] as an antiherpes agent ignited the search for new antiviral nucleosides with acyclic chains, resulting from the absence of bonds in the traditional furanosyl rings, to give seco- to multiseco-acyclonucleosides rings. Thus, many new synthetic schemes for various

Received 21 August 2007; accepted 27 February 2008.
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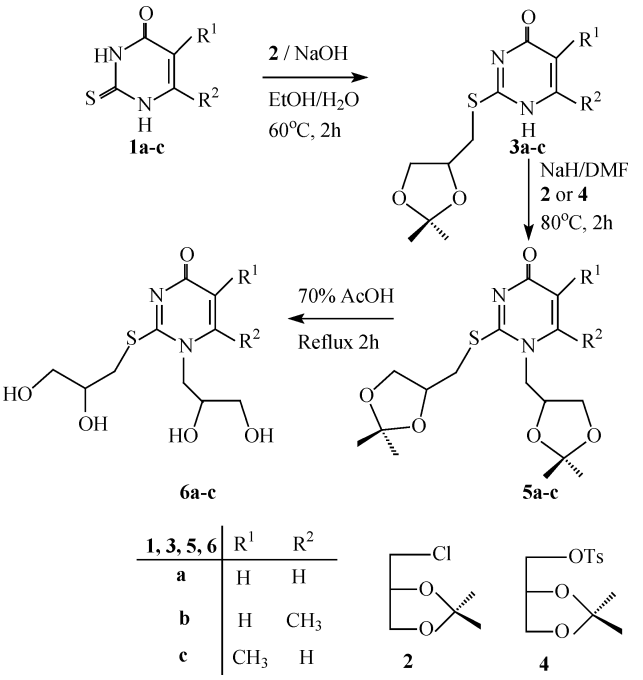
acyclic nucleoside[2] analogues have been discovered and many of these molecules have shown promising antiviral activities.[3] Among them, penciclovir is an acyclic analogue of guanosine and has been approved as an antiviral drug for treating diseases caused by HBV, HSV, and VZV.[4–7] Developments have progressed in the synthesis of acyclic nucleosides whose glycons and aglycons are modified.[2,8–10] Acyclic nucleosides of the tetra-*seco* type showed interesting antiviral activities.[11–18] Although many acyclonucleoside analogues have been synthesized and their activity against Hepatitis B[11,12,18] virus were evaluated, new acyclic nucleosides[2,19] with high activity and low toxicity is still required. Thus, we report here a fast and simple procedure for the alkylation of the modified pyrimidine bases with the objective of synthesizing their divalent acyclic chains and evaluating their antiviral activities.

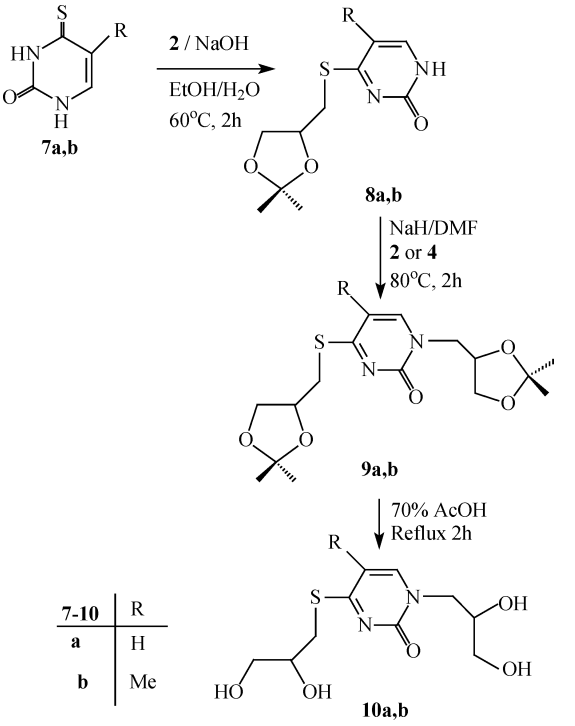
RESULTS AND DISCUSSION

2-Thiouracil derivatives **1a–c**[20] and/or 4-thiouracil derivatives **7a,b**[20] were treated with 2,3-*O*-isopropylidene-2,3-dihydroxypropyl chloride (**2**)[21] and sodium hydroxide in water and ethanol at 60°C to afford 2-{[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]thio}pyrimidin-4(1*H*)-ones **3a–c** in 80–88% yields and 4-{[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]thio}pyrimidin-2(1*H*)-ones **8a,b** in 74–76% yields. Their ^{1}H NMR spectra showed two singlets at the region δ = 1.18–1.20 and 1.32–1.34 corresponding to one isopropylidene group and a broad singlet at δ = 11.17–11.21 corresponding to NH indicating the introduction of one glycerolyl residue under such condition of alkylation. Compounds **3a–c** and/or **8a,b** were treated with **2** and/or 2,3-*O*-isopropylidine-1-*O*-(4-toluenesulfonyl)-glycerol (**4**)[21] in the presence of sodium hydride and DMF to afford 1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-2-{[(2,2-dimethyl-1,3-dioxolan-4-yl)-methyl]thio} pyrimidin-4(1*H*)-ones **5a–c** in 70–78% yields and 1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-4-{[(2,2-dimethyl-1,3-dioxolan-4-yl) methyl]thio}pyrimidin-2(1*H*)-ones **9a,b** in 65–71% yields. Deprotection of compounds **5a–c** and/or **9a,b** were carried out by 70% acetic acid at reflux temperature to give **6a–c** in 73–77% yields and **10a,b** in 88–89% yields. The ^{1}H NMR spectra showed the disappearance of the isopropylidene groups (Schemes 1 and 2).

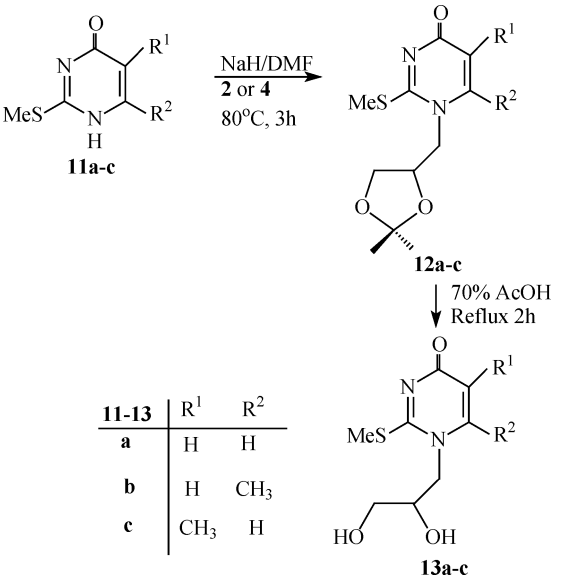
2-(Methylthio)pyrimidin-4(1*H*)-ones **11a–c**[20] and/or 4-(methylthio) pyrimidin-2(1*H*)-ones **14a,b**[20] were treated with **2** and/or **4** in the presence of sodium hydride and in DMF to afford 1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-2-(methylthio)pyrimidin-4(1*H*)-ones **2a–c** in 70–80% yields and 1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-4-(methylthio) pyrimidin-2(1*H*)-ones **15a,b** in 78–80% yields. Deprotection of compounds **12a–c** and/or **15a,b** were carried out by heating in 70% acetic acid to



SCHEME 1 Dialkylation of 2-thiouracils.



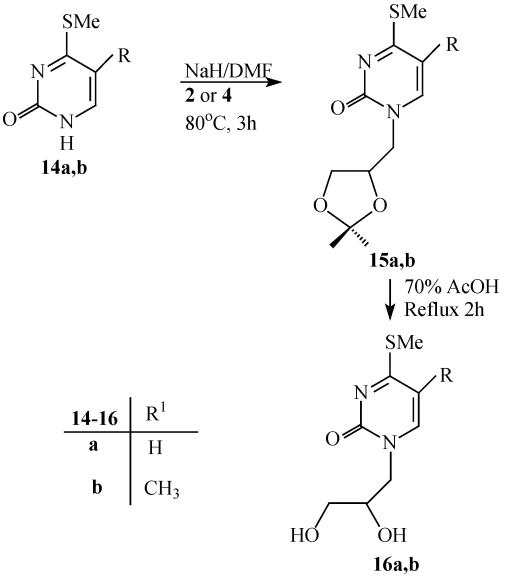
SCHEME 2 Dialkylation of 4-thiouracils.



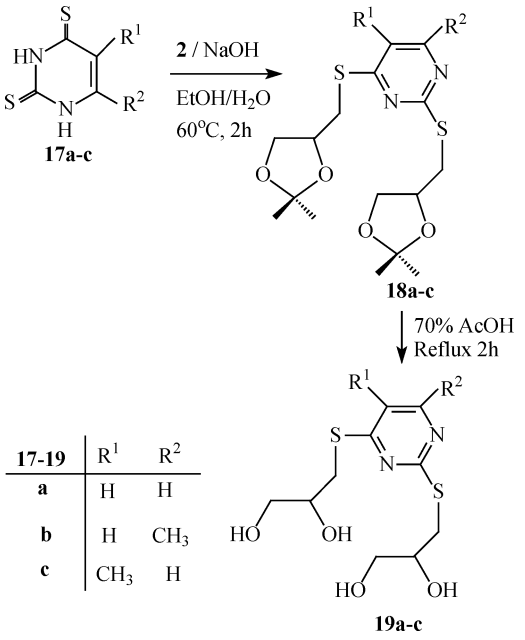
SCHEME 3 Alkylation of 2-(methylthio)pyrimidin-4-ones.

afford 1-(2,3-dihydroxypropyl)-2-(methylthio)pyrimidin-4(1*H*)-ones **13a–c** in 80–84% yields and 1-(2,3-dihydroxypropyl)-4-(methylthio)pyrimidin-2(1*H*)-ones **16a,b** in 87–89% yields (Schemes 3 and 4).

When the pyrimidine-2,4(1*H*,3*H*)-dithiones **17a–c**[20] were reacted with **2** under the same conditions of S-alkylation afforded



SCHEME 4 Alkylation of 4-(methylthio)pyrimidin-2-ones.



SCHEME 5 Alkylation of pyrimidine-2,4-dithiones.

2,4-bis{[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]thio}pyrimidines **18a–c** in 73–79% yields. The ^{1}H NMR spectra confirmed the presence of two glycerolyl residues. Deprotection of compounds **18a–c** gave 2,4-bis[(2,3-dihydroxypropyl)thio]pyrimidines **19a–c** in 80–83% yields (Scheme 5).

The screening, against HBV (Hep G2 2.2.15 cell method),[22–24] indicated that compounds **6a–c**, **13b,c**, and **10a** showed moderate viral replication inhibition and mild cytotoxicity with selective indexes 166.6∼500.0. On the other hand, the compounds **13a**, **19a–c**, **10b**, and **16a,b** showed low inhibition and high cytotoxicity with selectivity index 20.0∼76.9. The drug Lamivudine which is a potent selective inhibitor of HBV replication[23] was used as a standard for the comparative studies (Table 1).

EXPERIMENTAL

Melting points were determined using a Kofler block instrument and are uncorrected. TLC was performed on plastic plates Silica Gel 60_{254} (Merck, layer thickness 0.2 mm). TLC system is (CH_2Cl_2-MeOH 9:1). ^{1}H NMR spectra were recorded on a Bruker AC 250 FT NMR spectrometer at 250 MHz with TMS as an internal standard. ES Mass spectra were obtained from an Esquire 3000plus iontrap mass spectrometer from Bruker Daltonics. The microanalyses were performed at the Microanalytical Unit, Tokyo University,

TABLE 1 Cytotoxic effect (CC_{50}), inhibitory concentration (IC_{50}), and selective index (SI) of compounds **6**, **10**, **13**, **16**, and **19**

Compd No.	HBV DNA IC_{50} (μM)	Hep G2 2.2.15 CC_{50} (μM)	SI
Lamivudine	0.1	100	1000.0
6a	0.5	100	200.0
6b	0.2	100	500.0
6c	0.6	100	166.6
10a	0.6	100	166.6
10b	3.0	100	33.3
13a	1.4	100	71.4
13b	0.5	100	200.0
13c	0.6	100	166.6
16a	1.5	100	66.6
16b	1.3	100	76.9
19a	1.6	100	62.5
19b	1.3	100	76.9
19c	1.7	100	58.8

Japan. Viral screening against HBV was conducted at the National Liver Institute, Menoufia University, Egypt.

2-{[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]thio}pyrimidin-4(1H)-ones 3a-c

General Procedure. A solution of substituted 2-thiouracils **1a–c**[20] (10 mmol), **2**[21] (1.5 g, 10 mmol) and sodium hydroxide (0.4 g, 10 mmol) in mixture of water (10 mL) and ethanol (20 mL) was stirred at 60°C for 2 hours. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography using 5% MeOH in $CHCl_3$ to give **3a–c** in 80–88% yields.

2-{[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]thio}pyrimidin-4(1H)-one **(3a).** Pale yellow syrup (2.1 g, 88%); $R_f = 0.38$; ^{1}H NMR (DMSO-d_6, 250 MHz), δ_H: 1.20 (s, 3 H, CH_3), 1.32 (s, 3 H, CH_3), 3.35–3.45 (m, 2 H, CH_2), 4.15–4.27 (m, 1 H, CH), 4.55–4.68 (m, 2 H, CH_2), 6.67 (d, 1 H, *J* 5.5 Hz, H-5), 8.40 (d, 1 H, *J* 5.5 Hz, H-6), 11.20 (br s, 1 H, NH); MS (ESI): *m/z* = 265 [M + Na]. Anal. calcd. for $C_{10}H_{14}N_2O_3S$: C, 49.57; H, 5.82; N, 11.56. Found: C, 49.50; H, 5.66; N, 11.47%.

2-{[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]thio}-6-methylpyrimidin-4(1H)-one **(3b).** Pale yellow syrup (2.0 g, 80%); $R_f = 0.42$; ^{1}H NMR (DMSO-d_6, 250 MHz), δ_H: 1.18 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3), 2.34 (s, 3 H, CH_3), 3.41–3.51 (m, 2 H, CH_2), 4.20–4.31 (m, 1 H, CH), 4.51–4.69 (m, 2 H, CH_2), 6.57 (s, 1 H, H-5), 11.17 (br s, 1 H, NH); MS (ESI): *m/z* = 279 [M + Na]. Anal. calcd. for $C_{11}H_{16}N_2O_3S$: C, 51.54; H, 6.29; N, 10.93. Found: C, 51.45; H, 6.19; N, 10.88%.

2-{[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]thio}-5-methylpyrimidin-4(1H)-one (**3c**). Pale yellow syrup (2.2 g, 85%); $R_f = 0.41$; ^{1}H NMR (DMSO-d_6, 250 MHz), δ_H: 1.19 (s, 3 H, CH_3), 1.34 (s, 3 H, CH_3), 2.11 (s, 3 H, CH_3), 3.48–3.57 (m, 2 H, CH_2), 4.26–4.31 (m, 1 H, CH), 4.53–4.70 (m, 2 H, CH_2), 8.29 (s, 1 H, H-6), 11.21 (br s, 1 H, NH); MS (ESI): $m/z = 279$ [M + Na]. Anal. calcd. for $C_{11}H_{16}N_2O_3S$: C, 51.54; H, 6.29; N, 10.93. Found: C, 51.43; H, 6.21; N, 10.84%.

1-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]-2-{[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]thio}pyrimidin-4(1H)-ones 5a-c

General Procedure. To a stirred solution of **3a–c** (10 mmol) in dry DMF (10 mL) was added NaH (0.4 g of 60% dispersion in mineral oil, 10 mmol). After almost complete evolution of H_2, the mixture was heated to 100°C for 1 hour, then compound **2**[20] and/or **4**[20] (10 mmol) was added. The reaction mixture was stirred for additional 3 hours (TLC) at 80°C, cooled to room temperature and filtered through silica gel. The solvent was evaporated to dryness at reduced pressure, coevaporated with toluene (3 × 10 mL) and purified by silica gel column chromatography using 2% MeOH in CH_2Cl_2 to afford **5a–c** in 70–78% yields.

1-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]-2-{[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]thio}pyrimidin-4(1H)-one (**5a**). Pale yellow syrup (88% from **2** and 75% from **4**); $R_f = 0.68$; ^{1}H NMR (DMSO-d_6, 250 MHz), δ_H: 1.18 (s, 3 H, CH_3), 1.24 (s, 3 H, CH_3), 1.38 (s, 6 H, 2 CH_3), 3.52–3.62 (m, 2 H, CH_2), 3.90–4.10 (m, 2 H, CH_2), 4.47–4.59 (m, 2 H, 2 CH), 4.98–5.05 (m, 4 H, 2 CH_2), 6.69 (d, 1 H, *J* 5.5 Hz, H-5), 8.47 (d, 1 H, *J* 5.5 Hz, H-6); MS (ESI): $m/z = 379$ [M + Na]. Anal. calcd. for $C_{16}H_{24}N_2O_5S$: C, 53.91; H, 6.79; N, 7.86. Found: C, 53.80; H, 6.69; N, 7.80%.

1-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]-2-{[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]thio}-6-methylpyrimidin-4(1H)-one (**5b**). Pale yellow syrup (71% from **2** and 70% from **4**); $R_f = 0.71$; ^{1}H NMR (DMSO-d_6, 250 MHz), δ_H: 1.20 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3), 1.41 (s, 6 H, 2 CH_3), 2.30 (s, 3 H, CH_3), 3.55–3.69 (m, 2 H, CH_2), 3.90–4.08 (m, 2 H, CH_2), 4.46–4.65 (m, 2 H, 2 CH), 4.90–5.10 (m, 4 H, 2 CH_2), 6.55 (s, 1 H, H-5); MS (ESI): $m/z = 393$ [M + Na]. Anal. calcd. for $C_{17}H_{26}N_2O_5S$: C, 55.12; H, 7.07; N, 7.56. Found: C, 54.99; H, 6.94; N, 7.45%.

1-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]-2-{[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]thio}-5-methylpyrimidin-4(1H)-one (**5c**). Pale yellow syrup (75% from **2** and 71% from **4**); $R_f = 0.73$; ^{1}H NMR (DMSO-d_6, 250 MHz), δ_H: 1.21 (s, 3 H, CH_3), 1.32 (s, 3 H, CH_3), 1.39 (s, 6 H, 2 CH_3), 2.17 (s, 3 H, CH_3), 3.55–3.70 (m, 2 H, CH_2), 3.92–4.08 (m, 2 H, CH_2), 4.47–4.53 (m, 2 H, 2 CH), 4.99–5.12 (m, 4 H, 2 CH_2), 8.21 (s, 1 H, H-6); MS (ESI): $m/z = 393$ [M + Na]. Anal. calcd. for $C_{17}H_{26}N_2O_5S$: C, 55.12; H, 7.07; N, 7.56. Found: C, 55.03; H, 6.96; N, 7.48%.

1-(2,3-Dihydroxypropyl)-2-[(2,3-dihydroxypropyl)thio]pyrimidin-4(1H)-ones 6a–c

General procedure. The isopropylidine derivatives **5a–c** (5.0 mmol) was dissolved in 70% AcOH (5 mL) and the mixture was heated under reflux for 2 hours. The solvent was evaporated under reduced pressure and the residue was coevaporated with H_2O (2 × 3 mL) and ethanol (2 × 3 mL). The residual oil was purified by silica gel column chromatography using 5% MeOH in $CHCl_3$ to give **6a–c** in 73–77% yields.

1-(2,3-Dihydroxypropyl)-2-[(2,3-dihydroxypropyl)thio]pyrimidin-4(1H)-one (**6a**). Pale yellow foam (77%); $R_f = 0.28$; ^{1}H NMR (DMSO-d_6, 250 MHz), δ_H: 3.18–3.31 (m, 2 H, CH_2), 3.55–3.70 (m, 4 H, CH_2, 2 OH), 4.11–4.25 (m, 6 H, 2 CH_2, 2 CH), 4.50 (br s, 2 H, 2 OH), 6.55 (d, 1 H, *J* 5.5 Hz, H-5), 8.33 (d, 1 H, *J* 5.5 Hz, H-6); MS (ESI): *m/z* = 299 [M + Na]. Anal. calcd. for $C_{10}H_{16}N_2O_5S$: C, 43.47; H, 5.84; N, 10.14. Found: C, 43.33; H, 5.55; N, 10.02%.

1-(2,3-Dihydroxypropyl)-2-[(2,3-dihydroxypropyl)thio]-6-methylpyrimidin-4(1H)-one (**6b**). Pale yellow powder (73%); m.p. 150–152°C; $R_f = 0.32$; ^{1}H NMR (DMSO-d_6, 250 MHz), δ_H: 2.34 (s, 3 H, CH_3), 3.29–3.44 (m, 2 H, CH_2), 3.55–3.75 (m, 4 H, CH_2, 2 OH), 4.21–4.42 (m, 6 H, 2 CH_2, 2 CH), 4.73 (br s, 2 H, 2 OH), 6.54 (s, 1 H, H-5); MS (ESI): *m/z* = 313 [M + Na]. Anal. calcd. for $C_{11}H_{18}N_2O_5S$: C, 45.50; H, 6.25; N, 9.65. Found: C, 45.37; H, 6.10; N, 9.43%.

1-(2,3-Dihydroxypropyl)-2-[(2,3-dihydroxypropyl)thio]-5-methylpyrimidin-4(1H)-one (**6c**). Pale yellow powder (75%); m.p. 177–179°C; $R_f = 0.34$; ^{1}H NMR (DMSO-d_6, 250 MHz), δ_H: 2.09 (s, 3 H, CH_3), 3.19–3.27 (m, 2 H, CH_2), 3.45–3.57 (m, 4 H, CH_2, 2 OH), 3.98–4.19 (m, 6 H, 2 CH_2, 2 CH), 4.48 (br s, 2 H, 2 OH), 8.29 (s, 1 H, H-6); MS (ESI): *m/z* = 313 [M + Na]. Anal. calcd. for $C_{11}H_{18}N_2O_5S$: C, 45.50; H, 6.25; N, 9.65. Found: C, 45.26; H, 6.04; N, 9.51%.

4-{[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]thio}pyrimidin-2(1H)-ones 8a,b

General Procedure. As mentioned before for **3a–c**; yield 74–76%.

4-{[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]thio}pyrimidin-2(1H)-one (**8a**). Pale yellow syrup (74%); $R_f = 0.68$; ^{1}H NMR (DMSO-d_6, 250 MHz), δ_H: 1.28 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3), 3.44–3.55 (m, 2 H, CH_2), 4.25–4.31 (m, 1 H, CH), 4.69–4.78 (m, 2 H, CH_2), 6.85 (d, 1 H, *J* 5.5 Hz, H-5), 8.54 (d, 1 H, *J* 5.5 Hz, H-6), 11.22 (br s, 1 H, NH); MS (ESI): *m/z* = 265 [M + Na]. Anal. calcd. for $C_{10}H_{14}N_2O_3S$: C, 49.57; H, 5.82; N, 11.56. Found: C, 49.47; H, 5.63; N, 11.41%.

4-{[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]thio}-5-methylpyrimidin-2(1H)-one (**8b**). Pale yellow syrup (76%); $R_f = 0.70$; ^{1}H NMR (DMSO-d_6, 250

MHz), δ_H: 1.25 (s, 3 H, CH_3), 1.38 (s, 3 H, CH_3), 2.09 (s, 3 H, CH_3), 3.35–3.40 (m, 2 H, CH_2), 4.22–4.30 (m, 1 H, CH), 4.57–4.69 (m, 2 H, CH_2), 8.16 (s, 1 H, H-6), 11.19 (br s, 1 H, NH); MS (ESI): $m/z = 279$ [M + Na]. Anal. calcd. for $C_{11}H_{16}N_2O_3S$: C, 51.54; H, 6.29; N, 10.93. Found: C, 51.40; H, 6.13; N, 10.80%.

1-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]-4-{[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]thio}pyrimidin-2(1H)-ones 9a,b

General Procedure. As mentioned before for **5a–c**; yield 65–71%.

1-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]-4-{[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]thio}pyrimidin-2(1H)-one (**9a**). Pale yellow syrup (67% from **2** and 65% from **4**); $R_f = 0.48$; ^{1}H NMR (DMSO-d_6, 250 MHz), δ_H: 1.19 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3), 1.46 (s, 6 H, 2 CH_3), 3.67–3.75 (m, 2 H, CH_2), 4.11–4.22 (m, 2 H, CH_2), 4.60–4.75 (m, 2 H, 2 CH), 5.12–5.20 (m, 4 H, 2 CH_2), 6.89 (d, 1 H, *J* 5.5 Hz, H-5), 8.53 (d, 1 H, *J* 5.5 Hz, H-6); MS (ESI): $m/z = 379$ [M + Na]. Anal. calcd. for $C_{16}H_{24}N_2O_5S$: C, 53.91; H, 6.79; N, 7.86. Found: C, 53.77; H, 6.57; N, 7.67%.

1-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]-4-{[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]thio}-5-methylpyrimidin-2(1H)-one (**9b**). Pale yellow syrup (71% from **2** and 70% from **4**); $R_f = 0.51$; ^{1}H NMR (DMSO-d_6, 250 MHz), δ_H: 1.21 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3), 1.44 (s, 6 H, 2 CH_3), 2.19 (s, 3 H, CH_3), 3.65–3.72 (m, 2 H, CH_2), 4.09–4.20 (m, 2 H, CH_2), 4.59–4.70 (m, 2 H, 2 CH), 5.07–5.17 (m, 4 H, 2 CH_2), 8.33 (s, 1 H, H-6); MS (ESI): $m/z =$ 393 [M + Na]. Anal. calcd. for $C_{17}H_{26}N_2O_5S$: C, 55.12; H, 7.07; N, 7.56. Found: C, 55.01; H, 6.93; N, 7.43%.

1-(2,3-Dihydroxypropyl)-4-[(2,3-dihydroxypropyl)thio]pyrimidin-2(1H)-ones 10a,b

General Procedure. As mentioned before for **6a–c**; yield 88–89%.

1-(2,3-Dihydroxypropyl)-4-[(2,3-dihydroxypropyl)thio]pyrimidin-2(1H)-one (**10a**). Pale yellow foam (88%); $R_f = 0.67$; ^{1}H NMR (DMSO-d_6, 250 MHz), δ_H: 3.38–3.48 (m, 2 H, CH_2), 4.10–4.29 (m, 1 H, CH), 4.44–4.55 (m, 2 H, CH_2), 4.60 (br s, 2 H, 2 OH), 6.62 (d, 1 H, *J* 5.5 Hz, H-5), 8.39 (d, 1 H, *J* 5.5 Hz, H-6); MS (ESI): $m/z = 299$ [M + Na]. Anal. calcd. for $C_{10}H_{16}N_2O_5S$: C, 43.47; H, 5.84; N, 10.14. Found: C, 43.29; H, 5.57; N, 10.04%.

1-(2,3-Dihydroxypropyl)-4-[(2,3-dihydroxypropyl)thio]-5-methylpyrimidin-2(1H)-one (**10b**). Pale yellow powder (89%); m.p. 156–158°C; TLC (CH_2Cl_2-MeOH 9:1): $R_f = 0.68$; ^{1}H NMR (DMSO-d_6, 250 MHz), δ_H: 2.14 (s, 3 H, CH_3), 3.42–3.47 (m, 2 H, CH_2), 4.16–4.27 (m, 1 H, CH), 4.43–4.59 (m, 2 H, CH_2), 4.75 (br s, 2 H, 2 OH), 8.21 (s, 1 H, H-6); MS (ESI): $m/z = 313$ [M + Na]. Anal. calcd. for $C_{11}H_{18}N_2O_5S$: C, 45.50; H, 6.25; N, 9.65. Found: C, 45.29; H, 6.13; N, 9.49%.

1-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]-2-(methylthio) pyrimidin-4(1H)-ones 12a-c

General Procedure. As mentioned before for **5a–c**; yield 70–80%.

1-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]-2-(methylthio)pyrimidin-4(1H)-one (**12a**). Pale yellow syrup (80% from **2** and 78% from **4**); $R_f = 0.78$; ^{1}H NMR (DMSO-d_6, 250 MHz), δ_H: 1.33 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 2.52 (s, 3 H, SCH_3), 3.55–3.63 (m, 2 H, CH_2), 4.29–4.39 (m, 1 H, CH), 4.75–4.83 (m, 2 H, CH_2), 6.80 (d, 1 H, *J* 5.5 Hz, H-5), 8.45 (d, 1 H, *J* 5.5 Hz, H-6); MS (ESI): $m/z = 279$ [M + Na]. Anal. calcd. for $C_{11}H_{16}N_2O_3S$: C, 51.54; H, 6.29; N, 10.93. Found: C, 51.32; H, 6.14; N, 10.55%.

1-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]-2-(methylthio)-6-methylpyrimidin-4(1H)-one (**12b**). Pale yellow syrup (70% from **2** and **4**); $R_f = 0.79$; ^{1}H NMR (DMSO-d_6, 250 MHz), δ_H: 1.35 (s, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 2.35 (s, 3 H, CH_3), 2.51 (s, 3 H, SCH_3), 3.51–3.62 (m, 2 H, CH_2), 4.29–4.37 (m, 1 H, CH), 4.69–4.79 (m, 2 H, CH_2), 6.62 (s, 1 H, H-5); MS (ESI): $m/z =$ 293 [M + Na]. Anal. calcd. for $C_{12}H_{18}N_2O_3S$: C, 53.31; H, 6.71; N, 10.36. Found: C, 53.22; H, 6.64; N, 10.25%.

1-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]-2-(methylthio)-5-methylpyrimidin-4(1H)-one (**12c**). Pale yellow syrup (77% from **2** and 76% from **4**); $R_f =$ 0.81; ^{1}H NMR (DMSO-d_6, 250 MHz), δ_H: 1.32 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 2.35 (s, 3 H, CH_3), 2.52 (s, 3 H, SCH_3), 3.45–3.64 (m, 2 H, CH_2), 4.33–4.41 (m, 1 H, CH), 4.75–4.85 (m, 2 H, CH_2), 8.27 (s, 1 H, H-6); MS (ESI): $m/z = 293$ [M + Na]. Anal. calcd. for $C_{12}H_{18}N_2O_3S$: C, 53.31; H, 6.71; N, 10.36. Found: C, 53.18; H, 6.67; N, 10.29%.

1-(2,3-Dihydroxypropyl)-2-(methylthio)pyrimidin-4(1H)-ones 13a-c

General Procedure. As mentioned before for **6a–c**; yield 80–84%.

1-(2,3-Dihydroxypropyl)-2-(methylthio)pyrimidin-4(1H)-one (**13a**). Pale yellow foam (84%); $R_f = 0.34$; ^{1}H NMR (DMSO-d_6, 250 MHz), δ_H: 2.52 (s, 3 H, SCH_3), 3.69–3.79 (m, 3 H, CH_2, OH), 4.19–4.29 (m, 3 H, CH_2, CH), 4.68 (br s, 1 H, OH), 6.62 (d, 1 H, *J* 5.5 Hz, H-5), 8.44 (d, 1 H, *J* 5.5 Hz, H-6); MS (ESI): $m/z = 239$ [M + Na]. Anal. calcd. for $C_8H_{12}N_2O_3S$: C, 44.43; H, 5.59; N, 12.95. Found: C, 44.23; H, 5.23; N, 12.65%.

1-(2,3-Dihydroxypropyl)-2-(methylthio)-6-methylpyrimidin-4(1H)-one (**13b**). Pale yellow foam (80%); $R_f = 0.38$; ^{1}H NMR (DMSO-d_6, 250 MHz), δ_H: 2.38 (s, 3 H, CH_3), 2.53 (s, 3 H, SCH_3), 3.69–3.80 (m, 3 H, CH_2, OH), 4.17–4.28 (m, 3 H, CH_2, CH), 4.70 (br s, 1 H, OH), 6.63 (s, 1 H, H-5); MS (ESI): m/z = 253 [M + Na]. Anal. calcd. for $C_9H_{14}N_2O_3S$: C, 46.94; H, 6.13; N, 12.16. Found: C, 46.74; H, 6.02; N, 12.01%.

1-(2,3-Dihydroxypropyl)-2-(methylthio)-5-methylpyrimidin-4(1H)-one (**13c**). Pale yellow powder (84%); m.p. 191–193°C; $R_f = 0.39$; ^{1}H NMR (DMSO-d_6, 250 MHz), δ_H: 2.14 (s, 3 H, CH_3), 2.60 (s, 3 H, SCH_3), 3.65–3.79 (m, 3 H,

CH_2, OH), 4.21–4.33 (m, 3 H, CH_2, CH), 4.89 (br s, 1 H, OH), 8.23 (s, 1 H, H-6); MS (ESI): $m/z = 253$ [M + Na]. Anal. calcd. for $C_9H_{14}N_2O_3S$: C, 46.94; H, 6.13; N, 12.16. Found: C, 46.81; H, 6.05; N, 12.00%.

1-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]-4-(methylthio)pyrimidin-2(1H)-ones 15a,b

General Procedure. As mentioned before for **5a–c**; yield 76–80%.

1-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]-4-(methylthio)pyrimidin-2(1H)-one (**15a**). Pale yellow syrup (78% from **2** and 76% from **4**); $R_f = 0.77$; ^{1}H NMR (DMSO-d_6, 250 MHz), δ_H: 1.32 (s, 3 H, CH_3), 1.39 (s, 3 H, CH_3), 2.54 (s, 3 H, SCH_3), 3.59–3.70 (m, 2 H, CH_2), 4.29–4.37 (m, 1 H, CH), 4.62–4.75 (m, 2 H, CH_2), 6.45 (d, 1H, *J* 5.5 Hz, H-5), 8.10 (d, 1 H, *J* 5.5 Hz, H-6); MS (ESI): $m/z = 279$ [M + Na]. Anal. calcd. for $C_{11}H_{16}N_2O_3S$: C, 51.54; H, 6.29; N, 10.93. Found: C, 51.39; H, 6.17; N, 10.59%.

1-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]-4-(methylthio)-5-methylpyrimidin-2(1H)-one (**15b**). Pale yellow syrup (80% from **2** and 77% from **4**); $R_f = 0.78$; ^{1}H NMR (DMSO-d_6, 250 MHz), δ_H: 1.33 (s, 3 H, CH_3), 1.44 (s, 3 H, CH_3), 2.22 (s, 3 H, CH_3), 2.55 (s, 3 H, SCH_3), 3.49–3.66 (m, 2 H, CH_2), 4.25–4.36 (m, 1 H, CH), 4.63–4.79 (m, 2 H, CH_2), 8.21 (s, 1 H, H-6); MS (ESI): $m/z = 293$ [M + Na]. Anal. calcd. for $C_{12}H_{18}N_2O_3S$: C, 53.31; H, 6.71; N, 10.36. Found: C, 53.18; H, 6.60; N, 10.19%.

1-(2,3-Dihydroxypropyl)-4-(methylthio)pyrimidin-2(1H)-ones 16a,b

General Procedure. As mentioned before for **6a–c**; yield 87–89%.

1-(2,3-Dihydroxypropyl)-4-(methylthio)pyrimidin-2(1H)-one (**16a**). Pale yellow foam (87%); $R_f = 0.38$; ^{1}H NMR (DMSO-d_6, 250 MHz), δ_H: 2.48 (s, 3 H, SCH_3), 3.51–3.69 (m, 3 H, CH_2, OH), 4.09–4.24 (m, 3 H, CH_2, CH), 4.53 (br s, 1 H, OH), 6.56 (d, 1 H, *J* 5.5 Hz, H-5), 8.33 (d, 1 H, *J* 5.5 Hz, H-6); MS (ESI): $m/z = 239$ [M + Na]. Anal. calcd. for $C_8H_{12}N_2O_3S$: C, 44.43; H, 5.59; N, 12.95. Found: C, 44.30; H, 5.33; N, 12.69%.

1-(2,3-Dihydroxypropyl)-4-(methylthio)-5-methylpyrimidin-2(1H)-ones (**16b**). Pale yellow foam (89%); $R_f = 0.39$; ^{1}H NMR (DMSO-d_6, 250 MHz), δ_H: 2.22 (s, 3 H, CH_3), 2.54 (s, 3 H, SCH_3), 3.57–3.71 (m, 3 H, CH_2, OH), 4.11–4.27 (m, 3 H, CH_2, CH), 4.62 (br s, H, OH), 8.30 (s, 1 H, H-6); MS (ESI): $m/z = 253$ [M + Na]. Anal. calcd. for $C_9H_{14}N_2O_3S$: C, 46.94; H, 6.13; N, 12.16. Found: C, 46.88; H, 6.00; N, 12.04%.

2,4-Bis{[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]thio}pyrimidines 18a-c

General Procedure. As mentioned before for **3a–c**; yield 73–79%.

2,4-Bis{[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]thio}pyrimidine (**18a**). Yellow syrup (79%); $R_f = 0.88$; ^{1}H NMR (DMSO-d_6, 250 MHz), δ_H: 1.19 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3), 1.42 (s, 6 H, 2 CH_3), 3.33–3.49 (m, 2 H, CH_2), 3.75–3.84 (m, 2 H, CH_2), 4.25–4.34 (m, 2 H, 2 CH), 4.70–4.84 (m, 4 H, 2 CH_2), 6.46 (d, 1 H, *J* 5.5 Hz, H-5), 8.26 (d, 1 H, *J* 5.5 Hz, H-6); MS (ESI): *m/z* = 395 [M + Na]. Anal. calcd. for $C_{16}H_{24}N_2O_4S_2$: C, 51.59; H, 6.49; N, 7.52. Found: C, 51.43; H, 6.33; N, 7.41%.

2,4-Bis{[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]thio}-6-methylpyrimidine (**18b**). Yellow syrup (73%); $R_f = 0.89$; ^{1}H NMR (DMSO-d_6, 250 MHz), δ_H: 1.23 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3), 1.43 (s, 6 H, 2 CH_3), 2.37 (s, 3 H, CH_3), 3.43–3.52 (m, 2 H, CH_2), 3.78–3.88 (m, 2 H, CH_2), 4.29–4.47 (m, 2 H, 2 CH), 4.75–4.94 (m, 4 H, 2 CH_2), 6.57 (s, 1 H, H-5); MS (ESI): *m/z* = 409 [M + Na]. Anal. calcd. for $C_{17}H_{26}N_2O_4S_2$: C, 52.82; H, 6.78; N, 7.25. Found: C, 52.69; H, 6.63; N, 7.11%.

2,4-Bis{[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]thio}-5-methylpyrimidine (**18c**). Yellow syrup (78%); $R_f = 0.89$; ^{1}H NMR (DMSO-d_6, 250 MHz), δ_H: 1.25 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3), 1.53 (s, 6 H, 2 CH_3), 2.19 (s, 3 H, CH_3), 3.44–3.55 (m, 2 H, CH_2), 3.80–3.90 (m, 2 H, CH_2), 4.27–4.49 (m, 2 H, 2 CH), 4.80–5.00 (m, 4 H, 2 CH_2), 8.33 (s, 1 H, H-6); MS (ESI): *m/z* = 409 [M + Na]. Anal. calcd. for $C_{17}H_{26}N_2O_4S_2$: C, 52.82; H, 6.78; N, 7.25. Found: C, 52.64; H, 6.60; N, 7.10%.

2,4-Bis[(2,3-dihydroxypropyl)thio]pyrimidines 19a-c

General Procedure. As mentioned before for **6a–c**; yield 80–83%.

2,4-Bis[(2,3-dihydroxypropyl)thio]pyrimidine (**19a**). Yellow powder (83%); m.p. 166–168°C; $R_f = 0.28$; ^{1}H NMR (DMSO-d_6, 250 MHz), δ_H: 3.04–3.19 (m, 2 H, CH_2), 3.46–3.58 (m, 6 H, 2 CH_2, 2 OH), 4.05–4.17 (m, 4 H, 2 CH, CH_2), 4.53 (br s, 2 H, 2 OH), 6.50 (d, 1 H, *J* 5.5 Hz, H-5), 8.27 (d, 1 H, *J* 5.5 Hz, H-6); MS (ESI): *m/z* = 315 [M + Na]. Anal. calcd. for $C_{10}H_{16}N_2O_4S_2$: C, 41.08; H, 5.52; N, 9.58. Found: C, 41.00; H, 5.33; N, 9.43%.

2,4-Bis[(2,3-dihydroxypropyl)thio]-6-methylpyrimidine (**19b**). Yellow powder (80%); m.p. 187–189°C; $R_f = 0.30$; ^{1}H NMR (DMSO-d_6, 250 MHz), δ_H: 2.33 (s, 3 H, CH_3), 3.11–3.22 (m, 2 H, CH_2), 3.50–3.62 (m, 6 H, 2 CH_2, 2 OH), 4.15–4.22 (m, 4 H, 2 CH, CH_2), 4.57 (br s, 2 H, 2 OH), 6.53 (s, 1 H, H-5); MS (ESI): *m/z* = 329 [M + Na]. Anal. calcd. for $C_{11}H_{18}N_2O_4S_2$: C, 43.12; H, 5.92; N, 9.14. Found: C, 43.01; H, 5.88; N, 9.04%.

2,4-Bis[(2,3-dihydroxypropyl)thio]-5-methylpyrimidine (**19c**). Yellow powder (82%); m.p. 196–198°C; $R_f = 0.31$; ^{1}H NMR (DMSO-d_6, 250 MHz), δ_H: 2.17 (s, 3 H, CH_3), 3.09–3.23 (m, 2 H, CH_2), 3.49–3.63 (m, 6 H, 2 CH_2, 2 OH), 4.11–4.24 (m, 4 H, 2 CH, CH_2), 4.56 (br s, 2 H, 2 OH), 8.30 (s, 1 H, H-6); MS (ESI): *m/z* = 329 [M + Na]. Anal. calcd. for $C_{11}H_{18}N_2O_4S_2$: C, 43.12; H, 5.92; N, 9.14. Found: C, 43.04; H, 5.84; N, 9.02%.

Preparation and Culture of Hep G2 2.2.15 cells

The required cell line was made by transfection of Hep G2-cells with a plasmid containing multiple tandem copies of the HBV genome (subtype ayw).[21] The 2.2.15 cell line was maintained in RPMI-1640 (Glutamax) culture media containing 100 IU/mL nystatin and 380 μg/mL G418 (geneticin). The transferred HEP G2–2.2.15 cell line was kept in tissue culture flask at 37°C + 5% CO_2. Subcultures were set up after a week by aspiration of the media from culture flask and washing the cells twice by PBS. A 10% versene/trypsin solution was added and the cells were incubated for 1 min. at 37°C.

Cytotoxicity Assay

A colorimetric assay for living cells utilized the colorless substrate 3-(3,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (*MTT*) that is modified to colored product by any living cells, but not by dead cells or tissue culture medium. The cytotoxic effect of the compounds was accessed by culturing the Hep G2–2.2.15 cells in the presence of compounds using a *MTT*-assay.[22,23]

Calculation of IC_{50} and CC_{50}

The 50% inhibitory concentration of antiviral drugs (IC_{50}) was determined by interpolation from the plots of amount of *DNA* copies versus antiviral drug concentration. The 50% cytotoxic effect (CC_{50}) was calculated from the average viability of the cells with concentration of drugs.[23]

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