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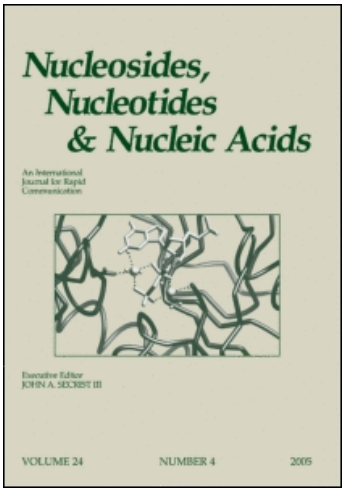

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Synthesis of New Thiolated Acyclonucleosides with Potential Anti-HBV Activity

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Synthesis of New Thiolated Acyclonucleosides with Potential Anti-HBV Activity

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ABSTRACT. Treatment of the sodium salt of compounds **1**, **7** or **12** with chloroethyl methyl ether, 2-chloroethyl toluoylate or 2-(2-chloro ethoxy)ethyl acetate afforded the corresponding derivatives **2**, **3**, **4**, **8**, **9**, **13** and **14**. Ammonolysis of **3**, **4**, **9** and **14** at room temperature gave the corresponding hydroxyalkyl derivatives **5**, **6**, **10**, **11**, and **15**, respectively. Alkylation of 2,4-dithiouracil gave 2,4-dialkylthio pyrimidine.

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INTRODUCTION

Acyclonucleosides are a group of nucleosides which differ only from the parent ribonucleosides by the absence of the ring structure of the pentosyl residue. The general feature of the important members of this class of nucleosides is the absence of one or more of the bonds of the pentose moiety to give an open chain residue *i.e.* they possess portions of the pentose residue. Those nucleosides missing one bond of the furanosyl residue are called *seco*-nucleosides. The terms *diseco-*, *triseco-*, *tetraseco-* and *pentaseco*-nucleoside are given by El Ashry *et al*[1-3] to indicate the number of missing bonds in the respective acyclonucleoside. Also included under this class of nucleosides those heterocycles that are attached to open chain carbohydrate residues.

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A comprehensive review covering the chemistry and antiviral activities of acyclonucleosides is available[4], as are reviews covering the biochemical properties of the potent antiviral agent acyclovir and nucleosides acting as inhibitors of HIV replication[5-8]. Acyclovir (Zovirax)[9-11] has played a key role as a lead compound in this class of nucleosides. Due to the clinical efficacy of acyclovir, a number of purine and pyrimidine acyclic nucleosides were prepared. Recently, acyclic nucleosides of the HEPT type 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine have shown high selectivity towards HIV-1[12], and it was found that replacement of the sulfur atom with a methylene group resulted a new series of potent HEPT analogues, of which MKC-442 (6-benzyl-1-ethoxymethyl-5-isopropyluracil) was found to be extremely potent[13,14]. On the other hand 9-(2-hydroxyethoxymethyl)guanine was shown to has pronounced activity against Type I herpes virus, with low host toxicity[15]. Therefore, a series of new pyrimidine acyclonucleosides are still of great interest to find new active compounds with less prominent side effects than those observed for AZT, FLT and ddC[10].

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RESULTS AND DISCUSSION

In this report we describe the synthesis of the new pyrimidine acyclonucleosides where the 2-oxo group has been replaced by alkylthio groups in the nucleobase moiety. 2-Alkylthio-pyrimidin-4(1H)-ones **1a,b**, **7a,b**, and **12a,b** were synthesized according to Brown *et al*[16] by heating 2-thiouracils with the appropriate alkyl halide in the presence of sodium hydroxide.

In the ^{13}C-NMR spectra of 2-alkylthiouracils, the broadening of the C-6 resonance at 150.48 - 154.22 ppm indicated the existence of a tautomeric equilibrium between N^1-H and N^3-H tautomers[17].

2-Methylthiouracils **1a,b** were alkylated with 2-chloroethylmethylether, 2-chloroethyltoluolylate or 2-(2-chloroethoxy)ethylacetate by the method of Sasaki *et al*[18] to give **2a,b**, **3** and **4a,b** in 78-83% yields after chromatographic purification on silica gel column using 1% MeOH / $CHCl_3$. The TLC shows that there are two

shadow spots above and below the main product that may correspond to N^3-alkylated uracil and the isocytosine derivative produced by nucleophilic substitution in the ammonia solution, respectively. During the chromatographic separation process we could not separate them. Treatment of **3** and **4a,b** with a mixture of methanol and ammonium hydroxide (25%), (1:1) at room temperature for 5-8 h results in complete deprotection of the hydroxy group to give **5** and **6a,b**, which were purified by 5% MeOH / $CHCl_3$ on silica gel column to give 87-89% yields (**Scheme 1**).

2-Ethylthiouracils **7a,b** were alkylated with 2-chloroethylmethylether or 2-chloroethyltoluolylate by the method described previously to give **8a,b** and **9a,b**, which were purified on a silica gel column by using 1% MeOH / $CHCl_3$ to give 81-88% yields. It is also difficult to separate the shadow spots above and below the main product, which again correspond to the N^3-alkylated uracil and isocytosine derivatives. Treatment of **9a,b** with a mixture of methanol and ammonium hydroxide (25%), (1:1) at room temperature for 8 h results in complete deprotection of the hydroxy group to give **10a,b**. In the case of **9b** the TLC shows that there are two spots. The I.R. and ^1H -NMR spectra of the upper spot indicate that the corresponding derivative still has the ethylthio-group whereas with the lower spot the concentrated ammonia solution reacted with ethylthio-group to give the isocytosine derivative **11** (**Scheme 2**).

Repeating the deprotection of **9b** using a concentrated solution of ammonia gas in methanol at room temperature for 1 h results in complete deprotection of the hydroxy group in addition to the formation of the isocytosine derivative which corresponds to the last obtained result (TLC). By increasing the time of the reaction to 2 h, the TLC showed a complete conversion of the upper spot to the lower spot (isocytosine derivative). Thus, we can conclude that the formation of the isocytosine derivative depends on the concentration of ammonia and the time of reaction.

Alkylation of 2-thiouracil derivatives with 2-chloroethylmethylether in the presence of alcoholic sodium hydroxide solution by the method of Brown *et al*[16] gave **12a,b**, which was recrystallized from ethanol to give 70 and 71% yields, respectively. Further alkylation of **12a,b** with 2-chloroethylmethylether or 2-(2-

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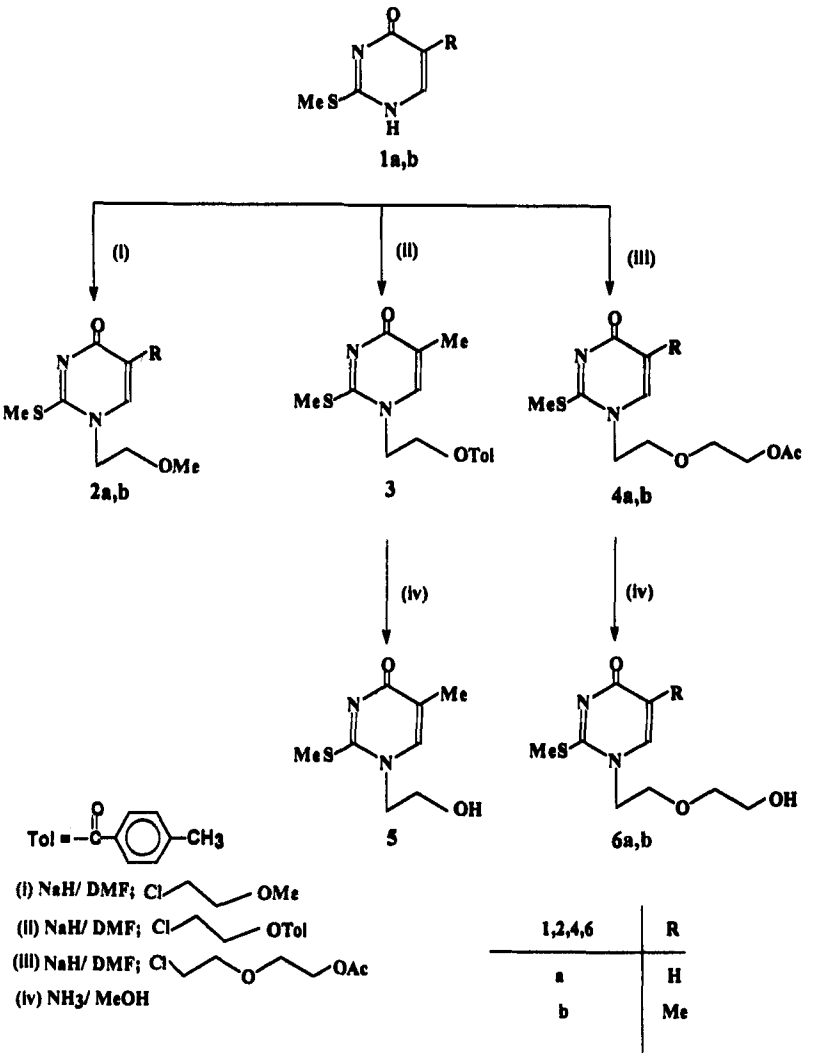

Scheme 1

chloroethoxy)ethylacetate by the method of Sasaki *et al*[18] gave mainly the N^1-alkylated derivatives **13** and **14a,b** in 61-87% yields after chromatographic purification. Deprotection of **14a,b** with a mixture of methanol and ammonium hydroxide (25%), (1:1) gave the corresponding deprotected products **15a,b**, which were purified by column chromatography using 1% MeOH / $CHCl_3$ (**Scheme 3**).

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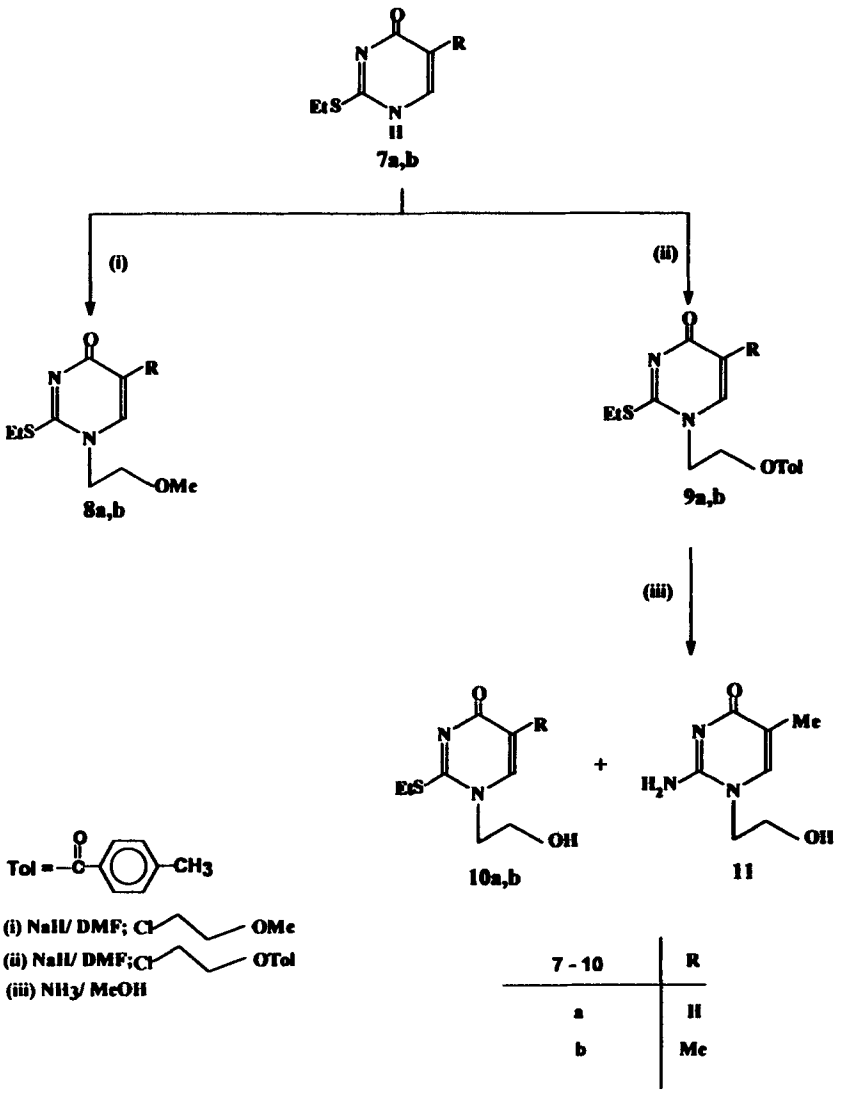

Scheme 2

2,4-Dithiouracil[19] **16** was alkylated with two evaluations of 2-chloroethylmethylether or 2-(2-chloroethoxy)ethylacetate by the method of Sasaki *et al*[18] to give 2,4-dialkylthiopyrimidine derivatives **17** and **18** in 80 and 88% yields, respectively. Treatment of **18** with a mixture of methanol and ammonium hydroxide

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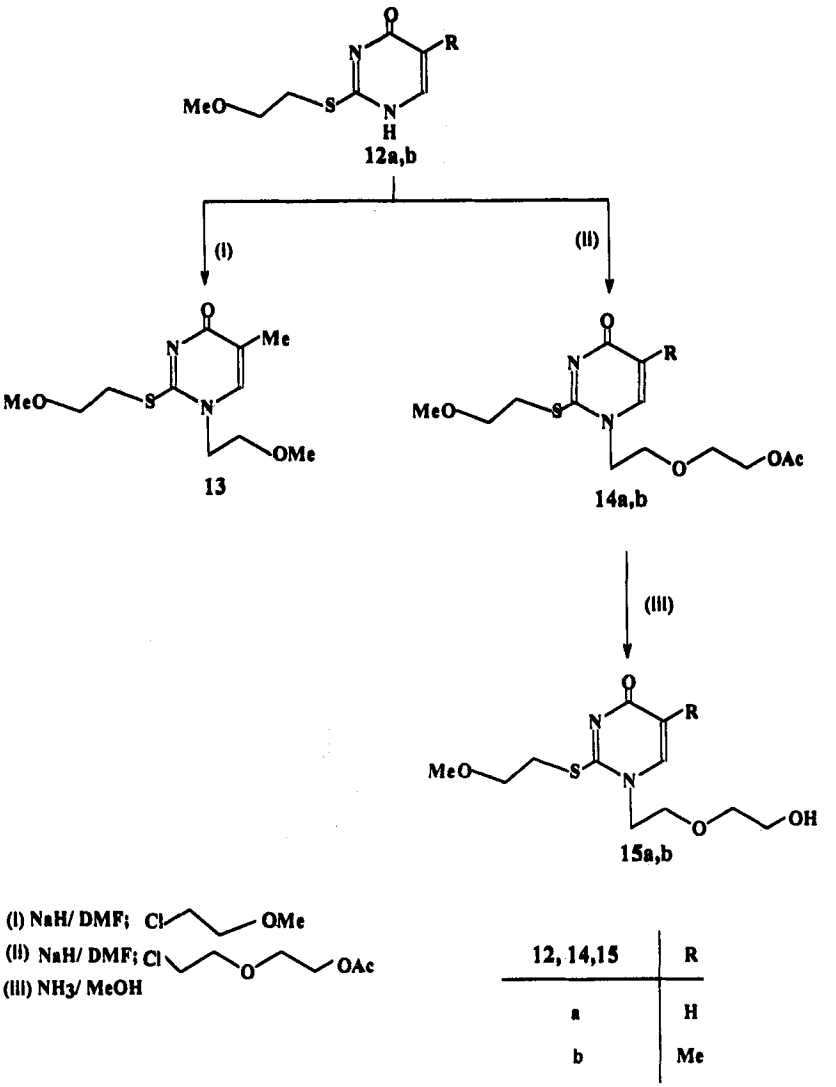

Scheme 3

(25%), (1:1) results in the complete deprotection of the hydroxy group to give **19** in 90% yield after chromatographic purification (**Scheme 4**).

The result of the antiviral assays and cytotoxicity evaluations are presented in table 1. Compounds **2a, 8a,** and **12b** showed moderate viral replication inhibition

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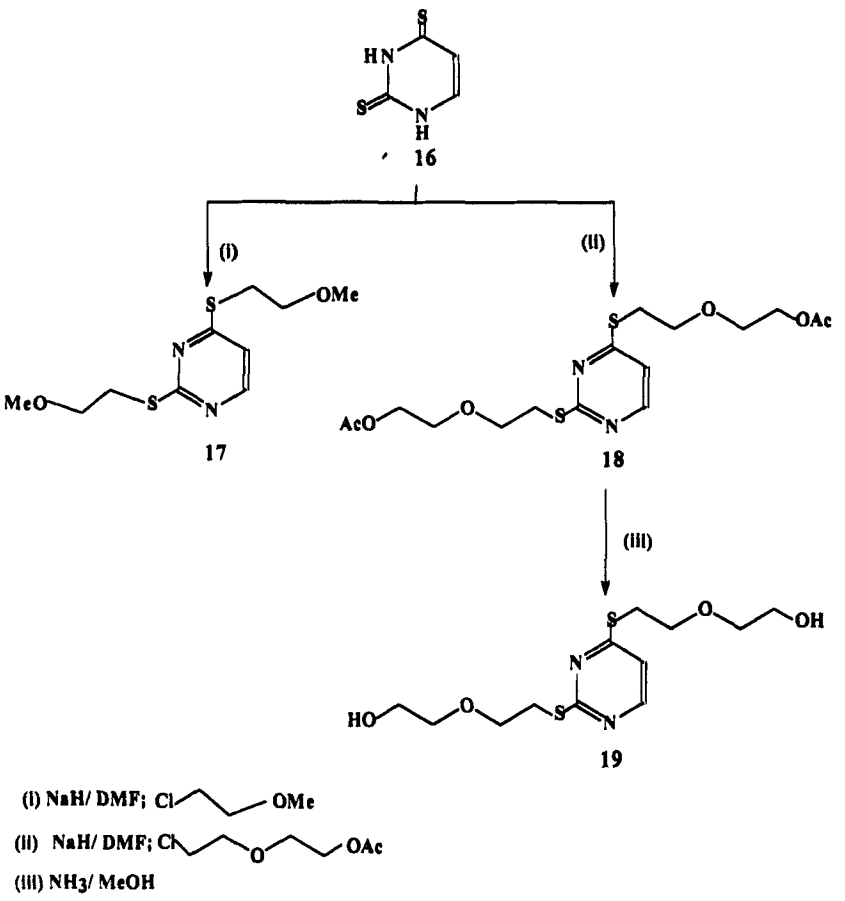

Scheme 4

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Table 1: Inhibition of HBV replication by selected compounds

COMPOUND (10 μM)	% INHIBITION			CYTOTOXICITY (%)
	1 WEEK	2 WEEKS	3 WEEKS	
2a	25.2	13.0	-85.0	4.2
8a	21.6	25.0	-	4.2
10a	83.2	82.1	71.6	13.0
10b	82.5	88.5	73.3	9.8
12b	23.5	17.3	-13.4	2.6
19	79.5	85.5	18.9	17.3

Table 2: UV Spectral Characteristics*

No.	λ_{max} (ϵ)		
	pH 1.0	pH 7.0	pH 13.0
5	235 (8120)	257 (11030)	257 (11140)
6b	245 (7710)	225 (15200) 245 sh (5710)	225 (15200) 242 sh (5720)
10b	258.5 (13200)	258 (13700) 276 sh (8250)	261 (11950)
11	255 (7760)	221 (15200) 255 sh (5780)	221 (15205) 253 sh (5590)
15b	230 sh (33050) 235 (36040) 242 (36700) 250 sh (5600) 313 (5250)	235 (38940) 255 (22140) 275 (5140) 320 (5140) 330 sh (4540)	238 sh (29300) 245.5 (35250) 250 sh (33750) 275 sh (4240) 285 (5450) 295 sh (3350)

* Compounds were dissolved in water and aliquots diluted 10-fold with 0.1 N aqueous HCl , H_2O, or 0.1 N aqueous NaOH solutions.

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and low cytotoxicity. Compounds **10a** and **19** showed high inhibition with moderate cytotoxicity while compound **10b** showed high inhibition with low cytotoxicity.

EXPERIMENTAL SECTION

Melting points were determined in glass capillary tubes on a Buchi apparatus and are uncorrected. UV spectra were recorded on a Norelco Unicom Sp-820 spectrometer. IR spectra were recorded (KBr) on a Pye Unicom Sp-883 Perkin-Elmer Spectrometer. The NMR spectra were recorded on a Bruker AC 250 FT spectrometer. Chemical shifts were reported in ppm relative to TMS as internal, and described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or bs (broad singlet). EI mass spectra were recorded on a varian MAT 311A spectrometer, peak matching $\pm$ 0.009. Silica gel TLC was performed on 60 F-254 precoated plates (Merck). Column chromatography was performed on (Merck) silica gel (0.040-0.063). All solvents were distilled and dried before using. Viral screening against HBV was conducted at the National Liver Institute, Menoufia University, Egypt. Maintenance media were added to the cell culture (Hep G2 2.2.15) together with the tested compounds (final concentration = 10 μM). The supernatant liquid was

collected after one, two and/or three weeks. The DNA replication was estimated by the PCR (polymerase chain reaction) technique. The percentage inhibition could be calculated by the relation between the blanc experiment (containing maintenance media without the tested compounds) and the results obtained after the above mentioned periods. The percentage cytotoxicity could be estimated by the relation between the number of the living and dead cells after three weeks counted by the Haemocytometer.

Preparation of 2-4; *General procedure:*

A mixture of 2-methylthiouracils **1a,b** (10 mmol) and 50% oil-immersed sodium hydride (0.48 g, 20 mmol) in DMF (30 ml) was stirred at 70-80^{0}C for 1 h and cooled to room temperature. Chloroethylmethylether (0.95 g, 10 mmol), 2-chloroethyltoluoylate (1.98 g, 10 mmol) or 2-(2-chloroethoxy)ethylacetate (1.36 g, 10 mmol) was added to the mixture, and stirred at 90^{0}C for 5-10 h . The mixture was evaporated till dryness under reduced pressure and chromatographed on silica gel column with $CHCl_3$/ MeOH (99:1) to give **2-4** in 78-83% yield.

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1-(2-Methoxyethyl)-2-methylthiopyrimidin-4-(1H)-one (2a):

Yield = 1.56 g (78%); as an oil.

^{1}H-NMR ($CDCl_3$) : δ 2.53 (s, 3H, SMe), 3.42 (s, 3H, OMe), 3.72 (m, 2H, CH_2), 4.52 (m, 2H, CH_2), 6.44 (d, 1H, J = 5.6 Hz, 5-H), 8.23 (d, 1H, J = 5.6 Hz, 6-H).

^{13}C-NMR ($CDCl_3$): δ 13.63 (SMe), 58.71 (OMe), 65.11 (CH_2), 70.13 (CH_2), 103.38 (C-5), 156.89 (C-6), 168.07 (C-2), 171.62 (C-4). EI MS: m/z (%) = 200 (M^+, 36). Peak matching of $C_8H_{12}N_2O_2S$ Calc. 200.255 Found 200.251.

1-(2-Methoxyethyl)-5-methyl-2-methylthiopyrimidin-4-one (2b):

Yield = 1.73 g (81%) ; as an oil.

^{1}H-NMR ($CDCl_3$) : δ 2.08 (s, 3H, Me), 2.51 (s, 3H, SMe), 3.42 (s, 3H, OMe), 3.74 (t, 2H, J = 4.6 Hz, CH_2), 4.51 (t, 2H, J = 4.8 Hz, CH_2), 8.04 (s, 1H, 6-H).

^{13}C-NMR ($CDCl_3$): δ 11.74 (5-Me), 13.63 (SMe), 58.63 (OMe), 65.17 (CH_2), 70.15 (CH_2), 112.52 (C-5), 156.13 (C-6), 166.59 (C-2), 168.32 (C-4). EI MS : m/z (%) = 214 (M^+, 33). Peak matching of $C_9H_{14}N_2O_2S$. Calc. 214.282 Found 214.275.

1-(2-Toluoyloxyethyl)-5-methyl-2-methylthiopyrimidin-4-(1H)-one (3):

Yield = 2.58 g (81%); as an oil.

^{1}H-NMR ($CDCl_3$) : δ 2.05 (s, 3H, 5-Me), 2.38 (s, 3H, Me), 2.51 (s, 3H, SMe), 4.46-4.65 (m, 2H, CH_2), 4.71-4.73 (m, 2H, CH_2), 7.21 (d, 2H, J = 7.3 Hz, Ar-H), 7.89 (d, 2H, J = 7.9 Hz, Ar-H), 8.05 (s, 1H, 6-H).

^{13}C-NMR ($CDCl_3$): δ 11.86 (5-Me), 13.85 (SMe), 21.42 (Me), 62.41 (CH_2), 63.94 (CH_2), 112.77 (C-5), 126.95, 128.89, 129.46, 143.58 (Ar-C), 156.58 (C-6), 166.19

(C-2), 166.63 (C-4), 168.67 (C=O). EI MS: m/z (%) = 318 (M^+, 13). Peak matching of $C_{16}H_{18}N_2O_3S$ Calc. 318.389 Found 318.381.

1-[2-(2-Acetoxyethoxy)ethyl]-2-methylthiopyrimidin-4-(1H)-one (4a):

Yield = 2.26 g (83%); as an oil.

^{1}H-NMR ($CDCl_3$): δ 2.08 (s, 3H, COMe), 2.53 (s, 3H, SMe), 3.70-3.78 (m, 4H, 2 CH_2), 4.21-4.25 (m, 4H, 2 CH_2), 6.43 (d, 1H, J = 5.7 Hz, 5-H), 8.23 (d, 1H, J = 5.7 Hz, 6-H).

^{13}C-NMR ($CDCl_3$): δ 13.58 (SMe), 20.48 (COMe), 63.00 (CH_2), 68.74 (2 CH_2), 70.86 (CH_2), 103.32 (C-5), 156.90 (C-6), 168.00 (C-2), 170.51 (C-4), 170.58 (COMe). EI MS: m/z (%) = 272 (M^+, 24). Peak matching of $C_{11}H_{16}N_2O_4S$ Calc. 272.318 Found 272.311.

1-[2-(2-Acetoxyethoxy)ethyl]-5-methyl-2-methylthiopyrimidin-4-(1H)-one (4b):

Yield = 2.23 g (81%); as an oil.

^{1}H-NMR ($CDCl_3$): δ 2.07 (s, 3H, 5-Me), 2.08 (s, 3H, COMe), 2.52 (s, 3H, SMe), 3.72-3.78 (m, 4H, 2 CH_2), 4.21-4.27 (m, 4H, 2 CH_2), 8.06 (s, 1H, 6-H).

^{13}C-NMR ($CDCl_3$): δ 11.82 (5-Me), 13.72 (SMe), 20.55 (COMe), 63.19 (CH_2), 65.24 (CH_2), 68.64 (2 CH_2), 112.64 (C-5), 156.33 (C-6), 166.66 (C-2), 168.49 (C-4), 170.55 (COMe). EI MS: m/z (%) = 286 (M^+, 24). Peak matching of $C_{12}H_{18}N_2O_4S$ Calc. 286.345 Found 286.338.

Preparation of (5) and (6); *General procedure:*

Compounds **3** and **4a,b** (5 mmol) in a stirred mixture of methanol (50 ml) and ammonium hydroxide (25%) (50 ml) were stirred at room temperature for 5-8 h. The resulting solution was evaporated till dryness under reduced pressure. The residue was chromatographed on silica gel column with $CHCl_3$ / MeOH (95:5) to give **5** and **6** in 87-89% yields.

1-(2-Hydroxyethyl)-5-methyl-2-methylthiopyrimidin-4-(1H)-one (5):

Yield = 1.76 g (88%); as an oil.

^{1}H-NMR ($CDCl_3$): δ 2.08 (s, 3H, 5-Me), 2.52 (s, 3H, SMe), 4.26-4.31 (m, 2H, CH_2), 4.51-4.55 (m, 2H, CH_2), 8.05 (s, 1H, 6-H).

^{13}C-NMR ($CDCl_3$): δ 11.95 (5-Me), 13.85 (SMe), 61.11 (CH_2), 68.04 (CH_2), 112.82 (C-5), 156.50 (C-6), 166.96 (C-2), 168.64 (C-4). EI MS: m/z (%) = 200 (M^+, 100). Peak matching of $C_8H_{12}N_2O_2S$ Calc. 200.255 Found 200.247.

1-[2-(2-Hydroxyethoxy)ethyl]-2-methylthiopyrimidin-4-(1H)-one (6a):

Yield = 2.00 g (87%); as an oil.

^{1}H-NMR ($CDCl_3$): δ 2.53 (s, 3H, SMe), 3.60-3.69 (m, 4H, 2 CH_2), 3.71-3.80 (m, 4H.

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2 CH_2), 6.01 (bs, 1H, OH), 6.44 (d, 1H, J = 5.7 Hz, 5-H), 8.23 (d, 1H, J = 5.7 Hz, 6-H).

^{13}C-NMR ($CDCl_3$): δ 13.61 (S-Me), 61.10 (CH_2), 68.74 (CH_2), 72.07 (CH_2), 72.29 (CH_2), 103.30 (C-5), 156.90 (C-6), 168.05 (C-2), 173.48 (C-4). EI MS: m/z (%) = 230 (M^+, 11). Peak matching of $C_9H_{14}N_2O_3S$ Calc. 230.281 Found 230.273.

1-[2-(2-Hydroxyethoxy)ethyl]-5-methyl-2-methylthiopyrimidin-4-(1H)-one (6b):

Yield = 2.17 g (89%); as an oil.

^{1}H-NMR ($CDCl_3$) : δ 2.07 (s, 3H, 5-Me), 2.51 (s, 8H, SMe), 2.59-2.67 (m, 2H, CH_2), 2.73-3.79 (m, 2H, CH_2), 3.70-3.78 (m, 2H, CH_2), 4.53-4.57 (m, 2H, CH_2), 6.01 (bs, 1H, OH), 8.04 (s, 1H, 6-H).

^{13}C-NMR ($CDCl_3$): δ 11.71 (5-Me), 13.61 (SMe), 61.09 (CH_2), 65.27 (CH_2), 68.73 (CH_2), 72.26 (CH_2), 112.57 (C-5), 156.13 (C-6), 166.59 (C-2), 168.36 (C-4). EI MS: m/z (%) = 244 (M^+, 16). Peak matching of $C_{10}H_{16}N_2O_3S$ Calc. 244.307 Found 244.299.

Preparation of (8) and (9); *General procedure:*

Compound **8** and **9** were prepared from **7** as described for **2-4.**

1-(2-Methoxyethyl)-2-ethylthiopyrimidin-4-(1H)-one (8a):

Yield = 1.82 g (85%); as an oil

^{1}H-NMR ($CDCl_3$): δ 1.39 (t, 3H, J = 7.3 Hz, $SCH_2\underline{CH_3}$) 3.12 (q, 2H, J = 7.3 Hz, $S\underline{CH_2}CH_3$), 3.41 (s, 3H, OMe), 3.71 (t, 2H, J = 4.6 Hz, CH_2), 4.50 (t, 2H, J = 4.7 Hz, CH_2), 6.43 (d, 1H, J = 5.6 Hz, 5-H), 8.21 (d, 1H, J = 5.7 Hz, 6-H).

^{13}C-NMR ($CDCl_3$): δ 14.19 ($SCH_2\underline{CH_3}$), 24.77 ($S\underline{CH_2}CH_3$), 58.64 (OMe), 65.04 (CH_2), 70.08 (CH_2), 103.41 (C-5), 156.98 (C-6), 168.05 (C-2), 171.25 (C-4). EI MS: m/z (%) = 214 (M^+, 100). Peak matching of $C_9H_{14}N_2O_2S$ Calc. 214.282 Found 214.277.

1-(2-Methoxyethyl)-2-ethylthio-5-methylpyrimidin-4-(1H)-one (8b):

Yield = 2.01 g (88%); as an oil

^{1}H-NMR ($CDCl_3$): δ 1.38 (t, 3H, J = 7.3 Hz, $SCH_2\underline{CH_3}$), 2.08 (s, 3H, 5-Me), 3.09 (q, 2H, J = 7.4 Hz, $S\underline{CH_2}CH_3$), 3.42 (s, 3H, OMe), 3.72-3.77 (m, 2H, CH_2), 4.50-4.55 (m, 2H, CH_2), 8.05 (s, 1H, 6-H).

^{13}C-NMR ($CDCl_3$): δ 11.81 (5-Me), 14.34 ($SCH_2\underline{CH_3}$), 4.84 ($S\underline{CH_2}CH_3$), 58.74 (OMe), 65.24 (CH_2), 70.27 (CH_2), 112.65 (C-5), 156.38 (C-6), 166.75 (C-2), 168.08 (C-4). EI MS: m/z (%) = 228 (M^+, 100). Peak matching of $C_{10}H_{16}N_2O_2S$ Calc. 228.308 Found 228.299.

1-(2-Toluoyloxyethyl)-2-ethylthiopyrimidin-4-(1H)-one (9a):

Yield = 2.67 g (84%); as a semisolid.

^{1}H-NMR ($CDCl_3$): δ 1.39 (t, 3H, J = 7.3 Hz, $SCH_2\underline{CH_3}$), 2.39 (s, 3H, Me), 3.12 (q, 2H, J = 7.3 Hz, $S\underline{CH_2}CH_3$), 4.61-4.64 (m, 2H, CH_2), 4.68-4.72 (m, 2H, CH_2), 6.42 (d,

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1H, J = 5.7 Hz, 5-H), 7.22 (d, 2H, J = 7.9 Hz, Ar-H), 7.92 (d, 2H, J = 8.1 Hz, Ar-H), 8.22 (d, 1H, J = 5.7 Hz, 6-H).
^{13}C-NMR ($CDCl_3$): δ 14.32 ($SCH_2\underline{CH_3}$), 21.43 (Me), 24.99 ($S\underline{CH_2}CH_3$), 62.43 (CH_2), 63.94 (CH_2), 103.49 (C-5), 126.88, 128.89, 129.52, 143.61 (Ar-C), 157.33 (C-6), 166.20 (C-2), 168.11 (C-4), 171.60 (C=O). EI MS: m/z (%) = 318 (M^+,8). Peak matching of $C_{16}H_{18}N_2O_3S$ Calc. 318.389 Found 318.382.

1-(2-Toluoyloxyethyl)-2-ethylthio-5-methylpyrimidin-4-(1H)-one (9b):
Yield = 1.88 g (81%); as a semisolid.
^{1}H-NMR ($CDCl_3$): δ 1.38 (t, 3H, J = 7.3 Hz, $SCH_2\underline{CH_3}$), 2.05 (s, 3H, 5-Me), 2.39(s, 3H, Me), 3.11 (q, 2H, J = 7.3 Hz, $S\underline{CH_2}CH_3$), 4.58-4.65 (m, 2H, CH_2), 4.70-4.74 (m, 2H, CH_2), 7.22 (d, 2H, J = 7.9 Hz, Ar-H), 7.92 (d, 2H, J = 8.0 Hz, Ar-H), 8.05 (s, 1H, 6-H).
^{13}C-NMR ($CDCl_3$): δ 11.87 (5-Me), 14.41 ($SCH_2\underline{CH_3}$), 21.41(Me), 24.99 ($S\underline{CH_2}CH_3$), 62.40 (CH_2), 63.93 (CH_2), 112.79 (C-5), 126.93, 128.78, 129.46, 143.58(Ar-C), 156.66 (C-6), 166.18 (C-2), 166.66 (C-4), 168.31 (C=O). EI MS: m/z (%) = 332 (M^+, 8). Peak matching of $C_{17}H_{20}N_2O_3S$ Calc. 332.416 Found 332.409.

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Preparation of (10) and (11); *General procedure:*

Compounds **10** and **11** were prepared from **9** as described for **5** and **6**.

1-(2-Hydroxyethyl)-2-ethylthiopyrimidin-4-(1H)-one (10a):
Yield = 1.78 g (89%); as an oil.
^{1}H-NMR ($CDCl_3$): δ 1.39 (t, 3H, J = 7.3 Hz, $SCH_2\underline{CH_3}$), 3.12 (q, 2H, J = 7.3 Hz, $S\underline{CH_2}CH_3$), 3.96 (t, 2H, J = 5.5 Hz, CH_2), 4.49 (t, 2H, J = 5.4 Hz, CH_2), 6.43 (d, 1H, J = 4.5 Hz, 5-H), 8.21 (d, 1H, J = 4.6 Hz, 6-H).
^{13}C-NMR ($CDCl_3$): δ 14.36 ($SCH_2\underline{CH_3}$), 25.08 ($S\underline{CH_2}CH_3$), 61.09 (CH_2), 67.96 (CH_2), 103.56 (C-5), 157.37 (C-6), 174.26 (C-2), 179.07 (C-4). EI MS: m/z (%) = 200 (M^+, 100). Peak matching of $C_8H_{12}N_2O_2S$ Calc. 200.254 Found 200.248.

1-(2-Hydroxyethyl)-2-ethylthio-5-methylpyrimidin-4-(1H)-one (10b):
Yield = 1.22 g (57%); as an oil.
^{1}H-NMR ($CDCl_3$): δ 1.38 (t, 3H, J = 7.3 Hz, $SCH_2\underline{CH_3}$), 2.07 (s, 3H, 5-Me), 3.11 (q, 2H, J = 7.3 Hz, $S\underline{CH_2}CH_3$), 3.96 (t, 2H, J = 4.4 Hz, CH_2), 4.51 (t, 2H, J = 4.6 Hz, CH_2), 8.05 (s, 1H, 6-H).
^{13}C-NMR ($CDCl_3$): δ 12.01 (5-Me), 14.41 ($SCH_2\underline{CH_3}$), 25.06 ($S\underline{CH_2}CH_3$), 61.26 (CH_2), 68.08 (CH_2), 112.88 (C-5), 156.67 (C-6), 167.05 (C-2), 168.36 (C-4). EI MS: m/z (%) = 214 (M^+, 100). Peak matching of $C_9H_{14}N_2O_2S$ Calc. 214.281 Found 214.279.

1-(2-Hydroxyethyl)-2-amino-5-methylpyrimidin-4(1H)-one (11):
Yield = 0.51 g (30%); m.p. 195-197^{0}C.
^{1}H-NMR ($CDCl_3$): δ 1.97 (s, 3H, 5-Me), 4.28 (t, 2H, J = 8.6 Hz, CH_2), 4.72 (t, 2H, J

= 8.6 Hz, CH_2), 6.50 (bs, 1H, OH), 7.21 (d, 1H, J = 7.9 Hz, NH), 7.53 (s, 1H, 6-H), 7.73 (d, 1H, J = 8.1 Hz, NH).
^{13}C-NMR ($CDCl_3$): δ 12.25 (5-Me), 42.28 (CH_2), 66.01 (CH_2), 116.75 (C-5), 150.84 (C-6), 158.27 (C-2), 161.36 (C-4).
IR (KBr film): ν = 3345 and 3171 cm^{-1} (NH_2). EI MS: m/z (%) = 169 (M^+, 2). Peak matching of $C_7H_{11}N_3O_2$ Calc. 169.183 Found 169.179.

Preparation of (12a,b); *General procedure:*

A solution of substituted 2-thiouracils (0.1 mol), chloroethylmethylether (0.1 mol), 1M aq. NaOH (100 ml) and ethanol (200 ml) was stirred at 60^{0}C for 22 h. Half of the ethanol was evaporated and the mixture was allowed to cool. The collected solid, was dried and recrystallized from ethanol.

2-(2-Methoxyethylthio)-pyrimidin-4-(1H)-one (12a):
Yield = 13.0 g (70%); m.p 130-131^{0}C.
^{1}H-NMR ($CDCl_3$) : δ 3.27 (m, 5H, OMe, CH_2), 3.56 (t, 2H, J = 6.2 Hz, CH_2), 6.11 (d, 1H, J = 6.1 Hz, 5-H), 7.87 (d, 1H, J = 6.2 Hz, 6-H), 12.68 (bs, 1H, NH).
^{13}C-NMR ($CDCl_3$): δ 29.16 (SCH_2), 57.78 (OMe), 70.10 (CH_2), 109.69 (bs, C-5), 154.22 (bs, C-6), 162.89 (bs, C-2), 173.90 (C-4). EI MS: m/z (%) = 186 (M^+, 8). Peak matching of $C_7H_{10}N_2O_2S$ Calc. 186.228 Found 186.223.

2-(2-methoxyethylthio)-5-methylpyrimidin-4-(1H)-one (12b):
Yield = 14.2 g (71%); m.p 134-136^{0}C.
^{1}H-NMR ($CDCl_3$): δ 1.87 (bs, 3H, 5-Me), 3.25-3.31 (m, 5H, OMe, CH_2), 3.51-3.56 (m, 2H, CH_2), 7.74 (bs, 1H, 6-H), 12.64 (bs, 1H, NH).
^{13}C-NMR ($CDCl_3$): δ 12.30 (5-Me), 28.99 (SCH_2), 57.75 (OMe), 70.13 (CH_2), 118.87 (bs, C-5), 150.48 (bs, C-6), 158.66 (bs, C-2), 162.98 (C-4). EI MS: m/z (%) = 200 (M^+, 11). Peak matching of $C_8H_{12}N_2O_2S$ Calc. 200.255 Found 200.251.

Preparation of 13 and 14; *General procedure:*

Compound **13** and **14** were prepared from **12** as described for **2-4.**

1-(2-Methoxyethyl)-5-methyl-2-(2-methoxyethylthio)pyrimidin-4-(1H)-one (13):
Yield = 1.83 g (71%); as an oil
^{1}H-NMR ($CDCl_3$): δ 0.86 (s, 3H, 5-Me), 2.11-2.19 (m, 8H, CH_2, 2 OMe), 2.40-2.47 (m, 2H, CH_2), 2.49-2.53 (m, 2H, CH_2), 3.27-3.31 (m, 2H, CH_2), 6.82 (s,1H, 6-H).
^{13}C-NMR ($CDCl_3$): δ 11.85 (5-Me), 29.80 (SCH_2), 58.36 (OMe), 58.78 (OMe), 65.38 (CH_2), 70.28 (CH_2), 71.10 (CH_2), 113.02 (C-5), 156.43 (C-6), 166.87 (C-2), 167.42 (C-4). EI MS: m/z (%) = 258 (M^+, 4). Peak matching of $C_{11}H_{18}N_2O_3S$ Calc. 258.334 Found 258.331.

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1-[2-(2-Acetoxyethoxy)ethyl]-2-(2-methoxyethylthio)-pyrimidin-4-(1H)-one (14a):

Yield = 1.93 g (61%); as an oil.

^{1}H-NMR ($CDCl_3$): δ 2.08 (s, 3H, COMe), 2.88-2.96 (m, 2H, CH_2), 3.38 (m, 5H, OMe, CH_2), 3.63-3.85 (m, 6H, 3 CH_2), 4.21-4.25 (m, 2H, CH_2), 6.45 (d, 1H, J = 5.7 Hz, 5-H), 8.22 (d, 1H, J = 5.7 Hz, 6-H).

^{13}C-NMR ($CDCl_3$): δ 20.44 (COMe), 29.70 (SCH_2), 58.26 (OMe), 63.01 (CH_2), 68.68 (2 CH_2), 70.80 (2 CH_2), 103.59 (C-5), 156.90 (C-6), 168.07 (C-2), 170.44 (C-4), 170.45 (COMe). EI MS: m/z (%) = 316 (M^+ + 1, 33). Peak matching of $C_{13}H_{20}N_2O_5S$ Calc. 316.371 Found 316.366.

1-[2-(2-Acetoxyethoxy)ethyl]-5-methyl-2-(2-methoxyethythio)-pyrimidin-4-(1H)-one (14b):

Yield = 2.88 g (87%); as an oil.

^{1}H-NMR ($CDCl_3$): δ 2.06 (s, 3H, 5-Me), 2.08 (s, 3H, COMe), 3.38 (s, 3H, OMe), 3.63-3.76 (m, 4H, 2 CH_2), 3.85 (t, 2H, J = 4.8 Hz, CH_2), 4.21-4.24 (m, 4H, 2 CH_2), 4.53 (t, 2H, J = 4.9 Hz, CH_2), 8.05 (s, 1H, 6-H).

^{13}C-NMR ($CDCl_3$): δ 11.88 (5-Me), 20.61 (COMe), 29.84 (SCH_2), 58.42 (OMe), 63.24 (CH_2), 65.39 (CH_2), 68.94 (CH_2), 71.13 (CH_2), 113.04 (C-5), 156.50 (C-6), 166.85 (C-2), 167.50 (C-4), 170.65 (COMe). EI MS: m/z (%) = 331(M^+ + 1, 4). Peak matching of $C_{14}H_{22}N_2O_5S$ Calc. 331.398 Found 331.395.

Preparation of (15); *General procedure:*

Compounds **15** was prepared from **14** as described for **5** and **6.**

1-[2-(2-Hydroxyethoxy)ethyl]-2-(2-methoxyethylthio)-pyrimidin-4-(1H)-one (15a):

Yield = 2.38 g (87%); as an oil.

^{1}H-NMR ($CDCl_3$): δ 3.38 (s, 3H, OMe), 3.59-3.69 (m, 4H, 2 CH_2), 3.70-3.85 (m, 6H, 3 CH_2), 4.52 (t, 2H, J = 5.8 Hz, CH_2), 6.46 (d, 1H, J = 5.7 Hz, 5-H), 8.22 (d, 1H, J = 5.7 Hz, 6-H).

^{13}C-NMR ($CDCl_3$): δ 29.45 (SCH_2), 58.04 (OMe), 60.74 (CH_2), 65.12 (CH_2), 68.38 (CH_2), 70.55 (CH_2), 71.83 (CH_2), 103.46 (C-5), 156.87 (C-6), 167.93 (C-2), 170.34 (C-4). EI MS: m/z (%) = 274 (M^+ + 1, 40). Peak matching of $C_{11}H_{18}N_2O_4S$ Calc. 274.334 Found 274.329.

1-[2-(2-Hydroxyethoxy)ethyl]-5-methyl-2-(2-methoxyethylthio)-pyrimidin-4-(1H)-one (15b):

Yield = 2.54 g (88%); as an oil.

^{1}H-NMR ($CDCl_3$): δ 2.07 (s, 3H, 5-Me), 3.32 (m, 2H, CH_2) 3.38 (s, 3H, OMe), 3.59-3.63 (m, 4H, 2 CH_2), 3.73 (m, 2H, CH_2), 3.86 (m, 2H, CH_2), 4.53 (m, 2H, CH_2), 8.04 (s, 1H, 6-H).

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^{13}C-NMR ($CDCl_3$): δ 11.75 (5-Me), 29.66 (SCH_2), 58.27 (OMe), 61.18 (CH_2), 65.36 (CH_2), 68.76 (CH_2), 70.96 (CH_2), 72.28 (CH_2), 112.93 (C-5), 156.33 (C-6), 166.74 (C-2), 167.34 (C-4). EI MS: m/z (%) = 289(M^+ + 1, 1). Peak matching of $C_{12}H_{20}N_2O_4S$ Calc. 289.361 Found 289.360.

Preparation of (17) and (18); *General procedure:*

A mixture of 2,4-dithiouracil **16** (1.46 g, 10 mmol) and 50% oil-immersed sodium hydride (0.096 g, 40 mmol) in DMF (40 ml) was stirred at 70-80^{0}C for 1 h and cooled to room temperature. Then chloroethylmethylether or 2-(2-chloroethoxy)ethylacetate (20 mmol) was added to the mixture and stirred at 90^{0}C for 5 h. The mixture was evaporated till dryness under reduced pressure and chromatographed on silica gel column with $CHCl_3$ / MeOH (99.5:0.5) to give **17** and **18** in 80 and 88% yield, respectively.

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2,4-Bis(2-methoxyethylthio) pyrimidine (17):

Yield = 2.10 g (80%); as an oil.

^{1}H-NMR ($CDCl_3$): δ 3.33-3.41 (m, 10H, 2 OMe, 2 CH_2), 3.62-3.69 (m, 4H, 2 CH_2), 6.82 (d, 1H, J = 5.6 Hz, 5-H), 5.10 (d, 1H, J =5.5 Hz, 6-H).

^{13}C-NMR ($CDCl_3$): δ 28.39 (SCH_2), 29.86 (SCH_2), 58.44 (OMe), 58.48 (OMe), 70.52 (CH_2), 70.89 (CH_2), 114.23 (C-5), 154.10 (C-6), 169.25 (C-2), 170.89 (C-4). EI MS: m/z(%) = 260(M^+, 8). Peak matching of $C_{10}H_{16}N_2O_2S_2$ Calc. 260.368 Found 260.361.

2,4-Bis[2-(2-Acetoxyethoxy)ethylthio]pyrimidine (18):

Yield = 3.56 g (88%); as an oil.

^{1}H-NMR ($CDCl_3$): δ 2.08 (s, 3H, COMe), 2.09 (s, 3H, COMe), 3.34-3.41 (m, 4H, 2 CH_2), 3.70-3.79 (m, 8H, 4 CH_2), 4.22-4.24 (m, 4H, 2 CH_2), 6.85 (d, 1H, J = 5.5 Hz, 5-H), 8.12 (d, 1H, J = 5.6 Hz, 6-H).

^{13}NMR ($CDCl_3$): δ 20.49 (2 COMe), 28.24 (SCH_2), 29.73 (SCH_2), 63.05 (CH_2), 63.10 (CH_2), 68.48 (CH_2), 68.72 (CH_2), 69.10 (CH_2), 69.43 (CH_2), 114.15 (C-5), 154.06 (C-6), 169.13 (C-2), 170.50 (C-4), 170.72 (2 COMe). FAB MS = 405 (M^++1).

2,4-Bis[2-(2-Hydroxyethoxy)ethylthio]pyrimidine (19):

It was prepared from **18** as described for **5** and **6**

Yield = 2.89 g (90%); as an oil.

^{1}H-NMR ($CDCl_3$): δ 3.35-3.42 (m, 4H, 2 CH_2), 3.60-3.67 (m, 4H, 2 CH_2), 3.72-3.80 (m, 8H, 2 CH_2), 6.12 (bs, 1H, OH), 6.85 (d, 1H, J = 5.4 Hz, 5-H), 8.11 (d, 1H, J = 5.4 Hz, 6-H).

^{13}C-NMR ($CDCl_3$): δ 29.92 (SCH_2), 29.55 (SCH_2), 61.17 (2 CH_2), 69.16 (CH_2), 69.50 (CH_2), 72.25 (2 CH_2), 114.30 (C-5), 154.23 (C-6), 169.22 (C-2), 174.15 (C-4). FAB MS = 321 (M^+ + 1)

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