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Facile synthesis of polynuclear heterocycles and acyclic C-nucleosides via α-substituted cinamonitrile (II)

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ABSTRACT

2-Amino-3-cyanothiophene derivative **(II)** react with formic acid, and carbon disulphide to afford the newly constructed derivatives **(1)** and **(2)** respectively. Compound **(1)** form the corresponding 4-hydrazino derivative **(4)** after its chlorination followed by the treatment of the formed 4-choloro-derivative with hydrazine hydrate (99%). While the 2- hydrazino-derivative **(6)** was obtained upon the methylation of compound **(2)** with methyl iodide followed by reacting the collected 2-methylthio-derivative **(5)** with hydrazine hydrate (1:3; 99%). The S-glycosides are produced when 2, 4-dithione derivative 2′ reacted with 2',3',4', 6'-tetra-*O*-acetyl-β-D-gulcopyranosyl or galactopyranosyl bromide in dry acetone with stirring at room temperature to afford **(7a,b)**. The acyclic C-nucleosides **(12a-c)** and **(13a-c)** were obtained when 2- and 4- hydrazino derivatives reacted with aldo-sugars either aldohexsoses or aldopentoses such as D- glucose, D-galactose and D-xylose.

KEYWORDS

Cinamonitrile derivatives;
Thienopyrimidine derivatives;
C-glycosides;
N-glycosides;
S-glycosides.

INTRODUCTION

The large numbers of thienopyrimidine derivatives are of considerable chemical and pharmacological importance[1-3]. Several of these compounds have anti-tumor[4], anti-viral[5], anti-cancer[6], antipyretic[7], anti-inflammatory[8], anti-histamenic[9], anti-microbial[10], anti-fungal[11], and analgesic[12] activities. In view of these facts and in continuation of our work[13-18], we report here synthesis of some novel thienopyrimidine derivatives and acyclic C-, N-, and S-glycosides using α-substituted cinamonitrile[19] **(II)** as starting material.

RESULT AND DISCUSSION

From the point of view, α-substituted cinamonitriles[1] are very important classes of compounds which considered the key for the synthesis of a new series of heterocyclic organic compounds containing the thienopyrimidine moiety. Thus, refluxing compound **(II)**[19] with formic acid and few drops of conc. hydrochloric acid lead to the formation of the pyrimidone **(1)**. The IR spectrum of compound **(1)** confirmed its structure. It reveales the appearance of peak at 1666 cm^{-1} corresponding to amedic carbonyl group and no absorption peak at CN region. Reaction of pyrimidinone **(1)** with phosphorus oxychloride in dry dioxane yielded 4-chloro derivative **(3)**. The IR spectrum of compound **(3)** showed absence of amedic carbonyl group. Its mass spectrum showed characteristic fragmentation pattern confirming the presence of chlorine atom in its structure. (See experimental)

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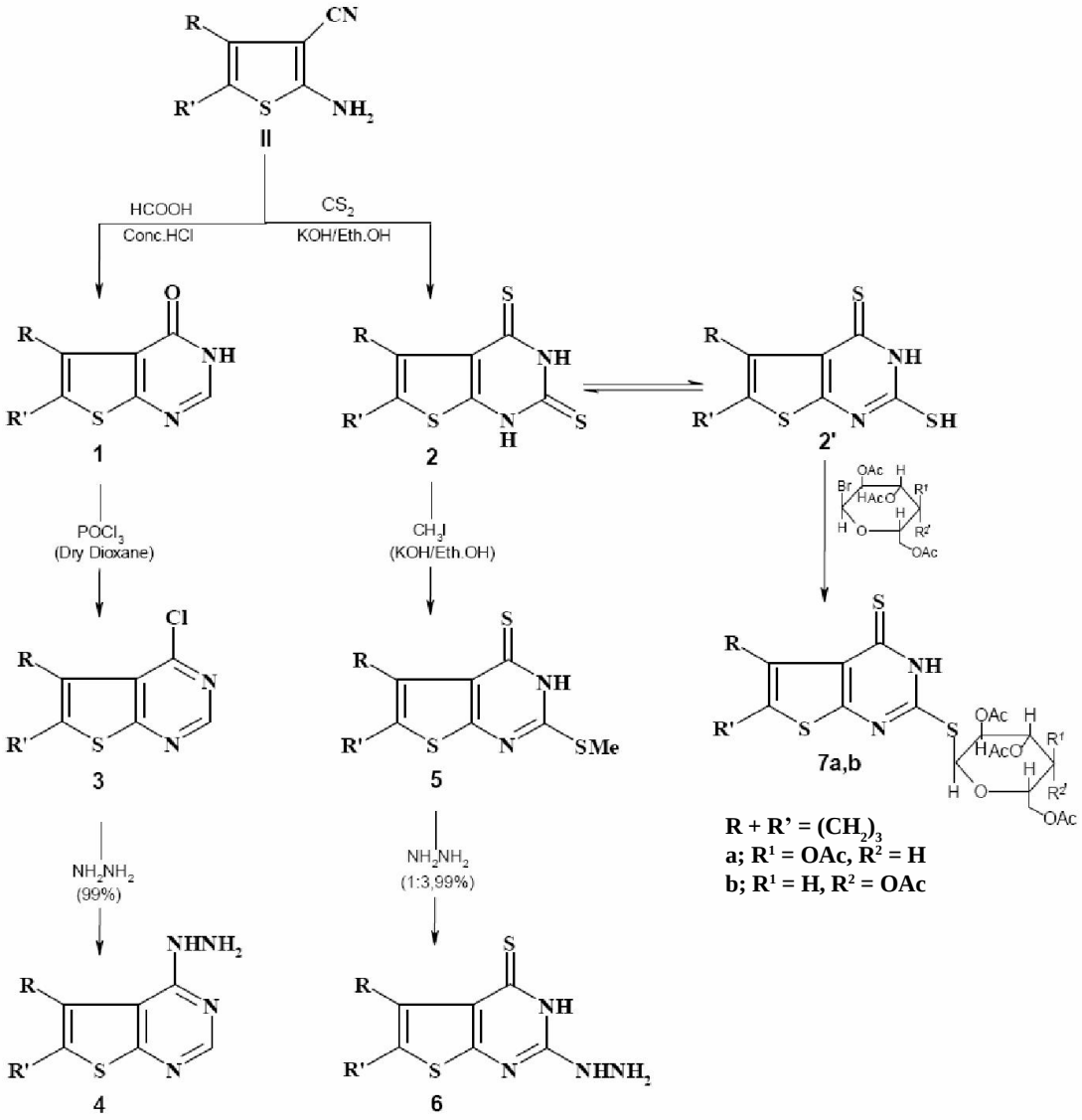
On reacting chloro derivative **(3)** with hydrazine hydrate (99%), 4-hydrazino- derivative **(4)** was obtained. The IR spectrum of compound **(4)** showed a strong absorption bands at 3313, 3295 cm^{-1} characteristic to NH_2 group. On the other hand, heating compound **(II)** with pyridine and carbon disulphide, in water bath at 80 °C, the di-thione derivative **(2)** was produced. The IR spectrum of di-thione **(2)** confirmed its structure. It reveals the absence of both peaks corresponding to NH_2 and CN, instead, peaks corresponding to NH- and CS- appears at 3395 cm^{-1} and 1238 cm^{-1} respectively. Methylation of compound **(2)** with methyl iodide in presence of alcoholic potassium hydroxide solution leads to the formation of the 2-methyltio derivative **(5)**. Refluxing 2-methylthio derivative **(5)** with hydrazine hydrate (1:3; 99 %) in the presence of dioxane, afforded 2-hydrazino- derivative **(6)**. The spectroscopic analyses (IR, NMR, MS) conformed the structure of derivative **(6)**. See experimental (Scheme 1).

Recently, a number of S-glycosides have emerged that possess interesting cytotoxic activity[20]. Many researchers described the synthesis and in vitro cytotoxic activity of series of heterocyclic thioglycosides including pyrimidine nucleosides which showed promising activity against DNA and RNA viruses[21]. Motivated by the forgoing information, our present investigation aims to synthesis some of thioglycosides. Thus, the 2-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyl or galactopyranosylthio)-3,5,6,7-tetrahydro-4H-



Scheme 1

cyclopenta[4,5]thieno[2,3-*d*]pyrimidine-4-thione **(7a,b)** were obtained via the formation of the potassium salt of compounds **(2')** followed by its treatment with a solution of 2',3',4',6'-tetra-*O*-acetyl-D-gulcopyranosyl or galactopyranosyl bromide in dry acetone with stirring at room temperature. Scheme 1.

The elemental analysis and the spectral data of derivatives **(7a,b)** confirmed there structure. (See Experimental)

The biological activities of C- and N- glycosides have been of increasing interest as many of them have useful applications[20,21]. Based on this fact, we aimed to prepare a series of newly synthesized heterocyclic nucleoside analogues. Thus, heating under reflux compound **(4)** or **(6)** with aldo-sugares mainely D-glucose, D-galactose and D-xylose in boiling dioxane in the presence of catalytic amount of piperidine, the acyclic *N*-nucleosides **(8a-c)** and **(9a-c)** were obtained in satisfactory yield (65-69%).

On other hand, stirring at room temperature compounds **(8a-c)** or **(9a-c)** with an equimolecular amounts of pyridine and acetic anhydride afforded the corresponding tetra- or penta-O-acetate derivatives **(10a-c)** or **(11a-c)** Scheme 2.

De-protection of the protected acyclic C-nucleosides **(10a-c)** or **(11a-c)** could be achieved when stirred in methanolic sodium methoxide solution at room temperature, the free acyclic C-nucleosides **(12a,b)** or **(13a,b)** were produced in moderate yield (Scheme 2). The structure assignments of the produced free acyclic C-nucleosides **(12a,b)** or **(13a,b)** are confirmed on their elemental analysis and the spectral data. (See Experimental).

EXPERIMENTAL

Solid compounds were re-crystallized to constant melting points and dried in vacuum in drying pistol containing sodium hydroxide.

All melting points are uncorrected and were taken in open capillaries on a Gallen Kamp Apparatus.

Micro analyses were carried out at the Micro analytical unite National Research Centre and Faculty of Science, Cairo University.

IR spectra were carried out on FT/IR 300 E Jasco using KBr discs.

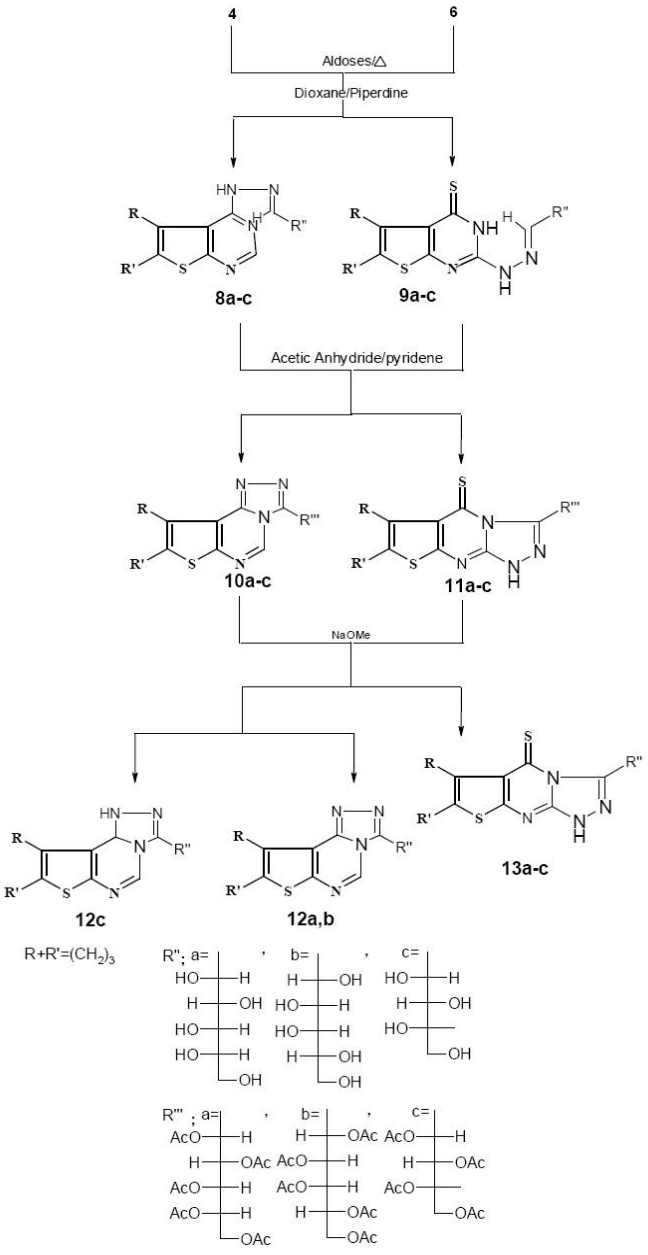
^{1}H-NMR spectra were measured in DMSO or $CDCl_3$, using Joel Ex. 270 NMR spectrometer. Signals were measured with reference to TMS as an internal standard.

The Mass spectra were recorded on Finnigan SSQ 7000 spectrometer.

All reactions were followed up by TLC using $CHCl_3$/MeOH (9:1, v/v) and/or ethyl acetate/Benzene (7:3) and detected under UV Lamp.

3,5,6,7-Tetrahydro-4*H*-cyclopenta[4,5]thieno[2,3-*d*]pyrimidin-4-one (1)

A mixture of compound **(II)** (1.64 g, 10 mmole),



Scheme 2

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TABLE 1 : Physical data for the products (1-13a-c)

No.	m.p. °C	Yield % / Solvent	M.F.(M.wt.)	C%	H%	N%
1	289-291	70 / Dioxane	$C_9H_8N_2OS$ / 192.2387	56.23 / 56.18	4.19 / 3.88	14.57 / 14.49
2	>300	73 / Dioxane	$C_9H_8N_2S_3$ / 240.3713	44.97 / 44.76	3.35 / 3.29	11.65 / 11.59
3	256-258	68 / Ethanol	$C_9H_7N_2ClS$ / 210.6841	51.31 / 48.00	3.35 / 3.70	13.30 / 13.25
4	283-285	64 / Dioxane	$C_9H_{10}N_4S$ / 206.2687	52.41 / 52.36	4.89 / 4.77	27.16 / 26.65
5	288-290	58 / DMF	$C_{10}H_{10}N_2S_3$ / 254.3979	47.21 / 47.11	3.96 / 3.94	11.01 / 10.67
6	286-288	66 / Dioxane	$C_9H_{10}N_4S_2$ / 238.3347	45.35 / 45.12	4.23 / 3.50	23.51 / 23.45
7a	164-166	64 / Benzene	$C_{23}H_{26}N_2O_9S_3$ / 570.6586	48.41 / 47.97	4.59 / 4.56	4.91 / 4.88
7b	181-183	66 / Benzene	$C_{23}H_{26}N_2O_9S_3$ / 570.6586	48.41 / 48.11	4.59 / 4.56	4.91 / 4.88
8a	264-266	80 / Dioxane	$C_{15}H_{20}N_4O_5S$ / 368.4093	48.90 / 48.88	5.47 / 5.45	15.21 / 14.77
8b	269-271	76 / Dioxane	$C_{15}H_{20}N_4O_5S$ / 368.4093	48.90 / 48.88	5.47 / 5.45	15.21 / 14.77
8c	256-258	78 / Dioxane	$C_{14}H_{18}N_4O_4S$ / 338.3833	49.69 / 49.66	5.36 / 4.66	16.56 / 16.51
9a	268-270	77 / Dioxane	$C_{15}H_{20}N_4O_5S_2$ / 400.4753	44.99 / 44.78	5.03 / 4.55	13.99 / 13.85
9b	260-262	73 / Dioxane	$C_{15}H_{20}N_4O_5S_2$ / 400.4753	44.99 / 44.78	5.03 / 4.55	13.99 / 13.85
9c	278-270	75 / Dioxane	$C_{14}H_{18}N_4O_4S_2$ / 370.44933	45.39 / 45.27	4.90 / 4.87	15.12 / 14.56
10a	131-133	65 / Methanol	$C_{25}H_{28}N_4O_{10}S$ / 576.5768	52.08 / 51.86	4.89 / 4.86	9.72 / 9.51
10b	137-139	66 / Methanol	$C_{25}H_{28}N_4O_{10}S$ / 576.5768	52.08 / 51.86	4.89 / 4.86	9.72 / 9.51
10c	126-128	64 / Methanol	$C_{22}H_{24}N_4O_8S$ / 505.5141	52.37 / 52.11	4.79 / 4.75	11.11 / 10.88
11a	154-156	67 / Ethanol	$C_{25}H_{28}N_4O_{10}S_2$ / 608.6428	49.33 / 49.10	4.64 / 4.55	9.21 / 8.75
11b	161-163	63 / Ethanol	$C_{25}H_{28}N_4O_{10}S_2$ / 608.6428	49.33 / 49.10	4.64 / 4.55	9.21 / 8.75
11c	146-148	66 / Ethanol	$C_{22}H_{24}N_4O_8S_2$ / 536.5801	49.24 / 49.10	4.51 / 4.47	10.44 / 10.37
12a	276-278	71 / Dioxane	$C_{15}H_{18}N_4O_5S$ / 366.3934	49.17 / 48.86	5.95 / 5.96	15.29 / 15.26
12b	280-282	76 / Dioxane	$C_{15}H_{18}N_4O_5S$ / 366.3934	49.17 / 48.86	5.95 / 5.96	15.29 / 15.26
12c	278-280	74 / Dioxane	$C_{14}H_{18}N_4O_4S$ / 338.3833	49.69 / 49.67	5.36 / 5.14	16.56 / 16.57
13a	283-285	73 / Dioxane	$C_{15}H_{18}N_4O_5S_2$ / 398.4594	45.21 / 45.10	4.55 / 4.38	14.06 / 13.45
13b	284-286	77 / Dioxane	$C_{15}H_{18}N_4O_5S_2$ / 398.4594	45.21 / 45.10	4.55 / 4.38	14.06 / 13.45
13c	287-289	75 / Dioxane	$C_{14}H_{16}N_4O_4S_2$ / 368.4334	45.64 / 45.56	4.38 / 4.15	15.21 / 15.11

formic acid (10 ml) and conc. hydrochloric acid (1 ml) was refluxed for 6 hours. The reaction mixture was allowed to cool to room temperature and precipitate so-formed was filtered-off, washes with water several tine, dried and re-crystallized to afford the title compound as white powder. IR (cm^{-1}, υ):3418 (br. NH), 2989 (CH alkyl) and 1668 (amidic CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 2.30 (m, 2H, CH_2), 2.85 (m, 4H, $2CH_2$), 8.04(s,1H, CH) and 9.11 (br. s, 1H, NH, D_2O exchangeable). Its MS (m/z), 192 [M, 100%].

1,5,6,7-Tetrahydro-2*H*-cyclopenta[4,5]thieno[2,3-*d*]pyrimidine-2,4(3*H*)-dithione (2)

To a solution of compound **(II)** (1.64g, 10 mmole) in pyridine (5 mL), carbon disulfide (1.2 ml) was added and the mixture was heated on a water bath for 4 hours. After cooling, methanol (15 ml) was added and the obtained solid was collected by filtration, washed with methanol to give di-thion derivative **(2)** as pale yellow powder. IR (cm^{-1}, υ):3422 (br, NH), 2988 (CH alkyl) and 1235, 1240 (2CS); ^{1}H- NMR (DMSO-d_6,) δppm: 2.18 (t, 2H, CH_2), 2.48 (m, 2H, CH_2), 2.75(t, 2H, CH_2) and 12.25 (br. s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) δ ppm: 22.60, 24.33, 26.10 ($3CH_2$), 124.8, 131.3, 136.5, 149.5 (thiophene ring carbon atoms), 178.4, 180.1 (2C=S); Its MS (m/z), 240[M, 100%].

4-Chloro-6,7-dihydro-5*H*-cyclopenta[4,5]thieno[2,3-*d*]pyrimidine (3)

A mixture of compound **(1)** (1.92 g, 10 mmole) and phosphorous oxychloride (3ml) in dry dioxane (15ml) was heated under reflux for 4 hours. The reaction mixture was cooled and poured on ice water (100 ml).

The solid so-formed was collected by filteration, washed several time by water, dried and re-crystallized to give the title compound as white powder. IR (cm^{-1}, υ):3424 (br. NH) and 2992 (CH alkyl); ^{1}H-NMR (DMSO-d_6) δ ppm: 2.32 (m, 2H, CH_2), 2.78 (m, 4H, $2CH_2$), 8.11 (s, 1H, CH) and 9.32 (br. s, 1H, NH, D_2O exchangeable). Its MS (m/z): 210 and 212 [M, (100%, 38%)].

4-Hydrazino-6,7-dihydro-5*H*-cyclopenta[4,5]thieno [2,3-*d*]pyrimidine (4)

A mixture of compound **(3)** (2.10 g, 10 m.mole) and hydrazine hydrate (99%, 3ml) in dioxane/ethanol (3:1, 20 ml) was heated under reflux for 3 hours. The reaction mixture was cooled to room temperature whereby, solid precipitate was formed. The solid so-formed was collected by filtration, washed several time by water, dried and re-crystallized to give the title compound as shiny colorless powder. IR (cm^{-1}, υ):3420 (br. NH), 3330, 3334(NH_2) and 2989 (CH alkyl); ^{1}H-NMR (DMSO-d_6) δ ppm: 2.32 (m, 2H, CH_2), 2.80 (m, 4H, $2CH_2$), 8.11 (s, 1H, CH), 8.25 (br. s., 2H, NH_2, D_2O exchangeable), 9.32 (br. s, 1H, NH, D_2O exchangeable) and 9.45 (br. s, 1H, NH, D_2O exchangeable). Its MS (m/z): 206 and [M, 100%].

2-(Methylthio)-3,5,6,7-tetrahydro-4*H*-cyclopenta [4,5]thieno[2,3-*d*]pyrimidine-4-thione (5)

To a wormed ethanolic potassium hydroxide solution (prepared by dissolving potassium hydroxide (0.56 g, 10 m. mole) in ethanol (50 ml.)) was added compound **(2)** (2.40g, 10 m. mole). The heating was continued for 30 minutes and the mixture was allowed to cool to room temperature. Methyl Iodide (1.72, 12 m. Mole) then was added. The reaction mixture was stirred at 40°C for 8-10 hours (under TLC control). The solvent was evaporated under reduced pressure and the crude product was filtered off, washed several time with water, dried, and re-crystallized to give the title compound as yellow needle crystals. IR (cm^{-1}, υ):3426 (br. NH), 2991, 2988 (CH alkyl) and 1240(CS); ^{1}H-NMR (DMSO-d_6) δ ppm: 2.26 (m, 2H, CH_2), 2.35 (m, 2H, CH_2), 2.48 (s, 3H, SCH_3), 2.77 (m, 2H, CH_2), 9.32 (br. s, 1H, NH, D_2O exchangeable) and 10.12 (br. s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) δ ppm: 14.32 (SCH_3), 21.66, 23.12, 25.13 ($3CH_2$), 124.2, 130.8, 136.0, 149.3 (thiophene ring carbon atoms), 159.1(C-S), 177.4 (C=S); Its MS (m/z), 253 [M, 100%].

2-Hydrazino-3,5,6,7-tetrahydro-4*H*-cyclopenta [4,5]thieno[2,3-*d*]pyrimidine-4-thione (6)

A mixture of compound **(5)** (2.53 g, 10 m.mole) and hydrazine hydrate (99%, 8ml) in dioxane/ethanol (3:1, 30 ml) was heated under reflux for 4 hours. The reaction mixture was cooled to room temperature whereby, solid precipitate was formed. The solid so-formed was collected by filtration, washed several time by water, dried and re-crystallized to give the title compound as pale yellow powder. IR (cm^{-1}, υ):3422 (br. NH), 3333, 3337(NH_2) and 2980 (CH alkyl); ^{1}H-NMR (DMSO-d_6) δ ppm: 2.30 (m, 2H, CH_2), 2.80 (m, 4H, $2CH_2$), 7.65 (br. s., 2H, NH_2, D_2O exchangeable), 9.40 (br. s, 1H, NH, D_2O exchangeable) and 10.22 (br. s, 1H, NH, D_2O exchangeable) . Its MS (m/z): 238 and [M, 100%].

2-(2‘,3‘,4‘,6‘-Tetra-*O*-acetyl-β-D-glycopyrano-sylthio)-3,5,6,7-tetrahydro-4*H*-cyclopenta [4,5]thieno[2,3-*d*]pyrimidine-4-thione (7a,b)

General procedure

To an ethanolic potassium hydroxide solution (prepared by dissolving potassium hydroxide (0.56 g, 10 m. mole) in ethanol (30 ml.)), was added compound **(2)** (2.40g, 10 m.mole). The mixture was stirred at room temperature, whil a solution of 1-bromo- 2,3,4,6-tetra-O-acetyl-a-D-gluco-/or galactopyranosyl bromide (15 m. mole) in acetone (30 ml) was added drop wisely. The reaction mixture was continued to stirrer at room temperature for 18 hours (under TLC control). The solvent was evaporated under reduced pressure and the solid so formed was filtered off, washed with ethanol/ water mixture (3:1), dried, and re-crystallized to afford the title compounds in good yield.

2-(2‘,3‘,4‘,6‘-Tetra-*O*-acetyl-β-D-glucopyrano-sylthio)-3,5,6,7-tetrahydro-4*H*-cyclopenta [4,5]thieno [2,3-*d*]pyrimidine-4-thione (7a)

It was obtained from compound **(2)** and (2,3,4,6-tetra-O-acetyla- β-D- glucopyranosyl)-bromide as a pale yellow powder; IR(cm^{-1}, υ): 3385 (br., NH), 2988 (CH alkyl), 1725 (CO), 1245 (CS); ^{1}H-NMR ($CDCl_3$) δ ppm.:1.95(s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.12(s, 3H, CH_3), 2.15(s, 3H, CH_3), 2.26 (m, 2H, CH_2), 2.35 (m, 2H, CH_2), 2.80 (m, 2H, CH_2), 4.02 (m,1H, H-5‘),

4.22 (m, 2H (H-6', H-6")), 4.38 (t, *J*= 9.45 Hz, 1H, H-4'), 4.96 (t, 1H, *J*= 9.45 Hz,H-2'), 5.25 (t, 1H, *J*= 9.45 Hz, H-3'), 5.94 (d, 1H, *J* = 9.45 Hz, H-1'), 10.36 (br.s, 1H, NH); ^{13}C- NMR: 20.33, 20.65, 20.8, 23.1(4 CH_3), 23.80, 24.1, 26.75 and 29.75 (4CH_2), 60.26 (C-6'), 65.1 (C-3'), 66.9(C-2'), 68.15 (C-4'), 77.0 (C-5'), 85.9 (C-1'), 124.76, 131.23, 136.15 and 148.85 (Thiophene ring carbon atoms), 158.10 (C-S), 170.7, 170.9,171.0 and 171.2 (4C=O), 178.03 (C=S); Its MS (m/z), 584 [M, 83%].

2-(2',3',4',6'-Tetra-*O*-acetyl-β-D-galctopyranosylthio)-3,5,6,7-tetrahydro-4*H*-cyclopenta [4,5]thieno [2,3-*d*]pyrimidine-4-thione (7b)

It was obtained from compound **(2)** and (2,3,4,6-tetra-O-acetyla- β-D- galacto-pyranosyl)-bromide as a pale yellow powder; IR(cm^{-1}, υ): 3385 (br., NH), 2988 (CH alkyl), 1725 (CO), 1245 (CS); ^{1}H-NMR ($CDCl_3$) δ ppm.: 1.95(s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.12(s, 3H, CH_3), 2.15(s, 3H, CH_3), 2.26 (m, 2H, CH_2), 2.35 (m, 2H, CH_2), 2.80 (m, 2H, CH_2), 4.02 (m,1H, H-5'), 4.22 (m, 2H (H-6', H-6")), 4.38 (t, *J*= 9.45 Hz, 1H, H-4'), 4.96 (t, 1H, *J*= 9.45 Hz,H-2'), 5.25 (t, 1H, *J*= 9.45 Hz, H-3'), 5.94 (d, 1H, *J* = 9.45 Hz, H-1'), 10.36 (br.s, 1H, NH); ^{13}C- NMR: 20.33, 20.65, 20.8, 23.1(4 CH_3), 23.80, 24.1, 26.75 and 29.75 (4CH_2), 60.26 (C-6'), 65.1 (C-3'), 66.9(C-2'), 68.15 (C-4'), 77.0 (C-5'), 85.9 (C-1'), 124.76, 131.23, 136.15 and 148.85 (Thiophene ring carbon atoms), 158.10 (C-S), 170.7, 170.9,171.0 and 171.2 (4C=O), 178.40 (C=S); Its MS (m/z), 584 [M, 86%].

4-Glycosylhydrazino-6, 7-dihydro-5*H*-cyclopentenothieno [2,3*d*]pyrimidine (8a-c) and/or 2-Glycosylhydrazino-3,5,6,7-tetrahydrocyclopentenothieno[2,3-d]- pyrimidin-4(H)-one (9a-c)

General procedure

A mixture of compound **(4)** (2.06g, 10 m.mole) and or compound **(6)** (2.40g, 10 m.mole) and the appropriate monosaccharide (10 m mole), dioxane (30 ml), ethanol (10 ml) and a catalytic amounts of piperidine was stirred under reflux for 6-8 hours. The reaction mixture was allowed to cool to room temperature. The precipitate so-formed was filtered-off, washes with ethanol, dried and re-crystallized from proper solvent to afford the title compounds in good yield.

4-Glucosylhydrazino-6,7-dihydro-5*H*-cyclopentenothieno[2,3-*d*]pyrimidine (8a)

It was obtained from compound **(4)** and D-glucose (1.80g, 10 mmol) as yellow crystals. Its IR (cm^{-1}, υ): 3448(broad OH), 3333 (NH) and 2980 (CH alkyl). ^{1}H-NMR (DMSO-d_6) δ ppm: 2.35 (m, 2H, CH_2), 2.85 (m, 4H, CH_2), 3.70 (m, 5H, 5OH, D_2O exchangeable OH-2'-OH-6'), 4.00 (m, 1H, H-5'), 4.35 (m, 2H, H-6', H-6"), 4.55 (m, 1H, H-4'), 4.67 (m, 1H, H-3'), 5.40 (m, 1H, H-2'), 7.50 (m, 1H, H-1'), 7.90 (s, 1H, CH), 11.02 (br. s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) δ ppm: 27.9, 28.2, 28.6 and 28.9 (CH_2); 67.8, 68.3, 69.1 and 69.4 (CH); 138.6, 138.8, 139.1, 139.6, 140.4, 141.11 and 141.8 (Thienopyrimidone carbon atoms and glucose C-1' carbon atom). Its MS (m/z), 438 [M, 73%].

4-Galactosylhydrazino-6,7-dihydro-5*H*-cyclopentenothieno[2,3-*d*]pyrimidine (8b)

It was obtained from compound **(4)** and D-galactose (1.80g, 10 mmol) as yellow crystals. Its IR (cm^{-1}, υ): 3500(broad OH), 3335 (NH) and 2986 (CH alkyl). ^{1}H-NMR (DMSO-d_6) δ ppm: 2.33 (m, 2H, CH_2), 2.83 (m, 4H, CH_2), 3.75 (m, 5H, 5OH, D_2O exchangeable OH-2'-OH-6'), 4.32 (m, 1H, H-5'), 4.37 (m, 2H, H-6', H-6"), 4.58 (m, 1H, H-4'), 4.70 (m, 1H, H-3'), 5.40 (m, 1H, H-2'), 7.50 (m, 1H, H-1'), 7.77 (s, 1H, CH), 7.90 (s, 1H, CH) & 11.02 (br. s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) δ ppm: 27.9, 28.2, 28.6 and 28.9 (CH_2); 67.8, 68.3, 69.8 and 70.0 (CH); 138.6, 138.8, 139.1, 139.6, 140.4, 141.6 and 141.8 (Thienopyrimidine carbon atoms and glucose C-1' carbon atom). Its MS (m/z), 368 [M, 77%].

4-Xylosylhydrazino-6,7-dihydro-5*H*-cyclopentenothieno[2,3-*d*]pyrimidine (8c)

A mixture of compound **(4)** (2.06 g, 10 mmole) and D-xylose (1.50 g, 10 mmole) as orange crystals. Its IR (cm^{-1}, υ): 3449(broad OH), 3330 (NH) and 2984 (CH alkyl). ^{1}H-NMR (DMSO-d_6) ppm: 2.30 (m, 2H, CH_2), 2.85 (m, 4H, 2CH_2), 3.50 (m, 4H, 4OH, D_2O exchangeable, OH-2'-OH-5'), 4.25 (q, 1H, J = 6Hz, H-4'), 4.45 (m, 2H, H-5', H-5"), 4.65 (d, 1H, J = 5Hz, H-3'), 5.85 (dd, 1H, J=7.5Hz, H-2'), 7.45 (d, 1H, J = 4Hz, H-1'), 7.97 (s, 1H, CH) & 11.11 (br. s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) δ ppm: 27.9,

28.2, 28.6 and 28.9 (CH_2); 67.8, 69.1 and 69.4 (CH); 138.6, 138.8, 139.1, 139.6, 140.4 and 141.8 (Thienopyrimidone carbon atoms and glucose C-1‘ carbon atom). Its MS (m/z), 386 [M+, 81%].

2-Glucosylhydrazino-3,5,6,7-tetrahydro-4*H*-cyclopentenothieno[2,3-*d*]pyrimi-dine-4-thione (9a)

It was obtained from compound **(6)** (2.40g, 10 mmol) and D-glucose (1.80g, 10 mmol) as yellow shiny crystals. Its IR (cm^{-1}, υ): 3445(broad OH), 3335 (NH), 2980 (CH alkyl) and 1239 (C-S). ^{1}H-NMR (DMSO-d_6) δ ppm: 2.35 (m, 2H, CH_2), 2.85 (m, 4H, CH_2), 3.70 (m, 5H, 5OH, D_2O exchangeable OH-2‘-OH-6‘), 4.00 (m, 1H, H-5‘), 4.35 (m, 2H, H-6‘, H-6“), 4.55 (m, 1H, H-4‘), 4.67 (m, 1H, H-3‘), 5.40 (m, 1H, H-2‘), 7.50 (m, 1H, H-1‘), 11.02 (br. s, 1H, NH, D_2O exchangeable) and 11.15 (br. s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) δ ppm: 27.9, 28.2, 28.6 and 28.9 (CH_2); 67.8, 68.3, 69.1 and 69.4 (CH); 138.6, 138.8, 139.1, 139.6, 140.4 and 141.8 (Thienopyrimidone carbon atoms and glucose C-1‘ carbon atom) and 178.1 (CS). Its MS (m/z), 400 [M+, 81%].

2-Galactosylhydrazino-3,5,6,7-tetrahydro-4*H*-cyclopentenothieno[2,3-*d*]pyrimi-dine-4-thione (9b)

It was obtained from compound **(6)** and D-galactose (1.80g, 10 mmol) as yellow crystals. Its IR (cm^{-1}, υ): 3447(broad OH), 3340, 3335 (2NH), 2986 (CH alkyl) and 1240 (C-S). ^{1}H-NMR (DMSO-d_6) δ ppm: 2.33 (m, 2H, CH_2), 2.83 (m, 4H, CH_2), 3.75 (m, 5H, 5OH, D_2O exchangeable OH-2‘-OH-6‘), 4.32 (m, 1H, H-5‘), 4.37 (m, 2H, H-6‘, H-6“), 4.58 (m, 1H, H-4‘), 4.70 (m, 1H, H-3‘), 5.40 (m, 1H, H-2‘), 7.50 (m, 1H, H-1‘), 11.02 (br. s, 1H, NH, D_2O exchangeable) and 11.15 (br. s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) δ ppm: 27.9, 28.2, 28.6 and 28.9 (CH_2); 67.8, 68.3, 69.1 and 69.4 (CH); 138.6, 138.8, 139.1, 139.6, 140.4 and 141.8 (Thienopyrimidone carbon atoms and glucose C-1‘ carbon atom) and 178.3 (CS). Its MS (m/z), 400 [M+, 83%].

2-Xylosylhydrazino-3,5,6,7-tetrahydro-4*H*-cyclopentenothieno[2,3-*d*]pyrimi-dine-4-thione (9c)

A mixture of compound **(6)** (2.06 g, 10 mmole) and D-xylose (1.50 g, 10 mmole) as orange crystals. Its IR (cm^{-1}, υ):3445 (broad OH), 3344, 3340 (2NH), 2984 (CH alkyl) and 1239 (C-S). ^{1}H-NMR (DMSO-d_6) δ ppm: 2.30 (m, 2H, CH_2), 2.85 (m, 4H, $2CH_2$), 3.50 (m, 4H, 4OH, D_2O exchangeable, OH-2‘-OH-5‘), 4.25 (q, 1H, J = 6Hz, H-4‘), 4.45 (m, 2H, H-5‘, H-5“), 4.65 (m, 1H, H-3‘), 5.85 (dd, 1H, J=7.5Hz, H-2‘), 7.50 (d, 1H, J = 4.5Hz, H-1‘), 11.11 (br. s, 1H, NH, D_2O exchangeable) and 11.35 (br s, 1H, NH, D_2O exchangeable. ^{13}C-NMR (DMSO-d_6) δ ppm: 27.9, 28.2, 28.6 and 30.1 (CH_2); 67.8, 68.3, 69.1 and 69.4 (CH); 138.6, 138.8, 139.1, 139.6, 140.4 and 141.8 (Thienopyrimidone carbon atoms and xylose C-1‘ carbon atom) and 178. 01(CS). Its MS (m/z), 370[M, 90%].

3-(O-Acetylglycosyl)-8,9-dihydro-10H-cyclo-pentenothieno[3,2-*c*][1,2,4]tri-azolo[4,3-*c*]pyrimidine (10a-c) and/or 3-(O-Acetylglycosyl)-1,6,7,8-tetrahydro- cyclopentenothieno-[2,3-*d*][1,2,4]tri-azolo[4,3-a]pyrimidin-5-(5H)-thion (11a-c)

General procedure

A solution of compounds **(8a-c)** (10 mmole) and/or compounds **(9a-c)** (10 mmole) in a mixture of acetic anhydride-pyridine (20 ml: 20 ml) was stirred at room temperature for overnight them it was poured into water. The reaction mixture was then extracted with chloroform several times and after the removal of chloroform under reduced pressure, the formed crystals was re-crystallized from the proper solvent to produce **(10a-c)** or **(11a-c)**.

3-(1‘,2‘,3‘,4‘,5‘-O-pentaacetylglucosyl)-8,9-dihydro-10H-cyclopentenothieno[3,2-*c*][1,2,4]triazolo[4,3-*c*]pyrimidine (10a)

It was obtained from compound **(8a)** (3.68g, 10 mmole) as yellow crystals. Its IR (cm^{-1}, υ): 2988, 2980 (CH alkyl) and 1740-1760 (acetyl carbonyl). ^{1}H-NMR ($CDCl_3$) δ ppm: 1.85 (s, 3H, CH_3), 1.95 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.10 (5, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.35 (m, 2H, CH_2), 2.85 (m, 4H, $2CH_2$), 4.75 (m, 1H, H-4‘), 5.30 (d, 1H, J=10.8 Hz, H-3‘), 5.45 (m, 2H, H_2-5‘), 5.55 (s, 1H, H-2‘), 5.70 (s, 1H, H-1‘) and 7.77 (s, 1H, CH). ^{13}C-NMR ($CDCl_3$) δ ppm: 20.0, 20.5, 20.6, 20.9 and 23.5 (CH_3), 25.3, 27.6, 29.3 and 30.0 (CH_2), 67.2, 67.4, 68.4, 70.9 and 71.1 (CH), 138.0, 139.3, 141.6, 148.3, 155.1, 156.0 and 157.0

(thienopyrimidine carbon atoms and triazol carbon atom) and 168.3, 168.7, 169.4, 170.3 and 171.0 (CO). Its MS (m/z), 576 [M, 93%].

3-(1‘,2‘,3‘,4‘,5‘-O-pentacetylgalactosyl)-8,9-dihydro-10H-cyclopentenothieno [3,2-*c*][1,2,4] triazolo[4,3-*c*]pyrimidine (10b)

It was obtained from compound **(8b)** (3.68g, 10 mmole) as yellow needle crystals. Its IR (cm^{-1}, υ): 2985, 2989 (CH alkyl) and 1740-1760 (acetyl carbonyl). ^{1}H-NMR ($CDCl_3$) δ ppm: 1.80 (s, 3H, CH_3), 1.95 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.35 (m, 2H, CH_2), 2.80 (m, 4H, $2CH_2$), 4.76 (m, 1H, H-4‘), 5.10 (m, 1H, H-1‘), 5.30 5.50 (m, 2H, H_2-5‘), 5.55 (d, 1H, J=7.50Hz, H-3‘), 5.70 (d, 1H, J=7.50Hz, H-2‘) and 7.85 (s, 1H, CH). Its MS (m/z), 576 [M, 78%].

3-(1‘,2‘,3‘,4-O-Tetraacetylxylosyl)-8,9-dihydro-10H-cyclopentenothieno[3,2-*c*][1,2,4]triazolo[4,3-*c*]pyrimidine (10c)

It was obtained from compound **(8c)** (3.38g, 10 mmole) as yellow crystals. Its IR (cm^{-1}, υ): 3340 (NH), 2985, 2989 (CH alkyl) and 1740-1760 (acetyl carbonyl). ^{1}H-NMR ($CDCl_3$) δ ppm: 1.95 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.35 (m, 2H, CH_2), 2.85 (m, 4H, $2CH_2$), 4.15 (s, 1H, CH), 5.25 (m, 1H, H-3‘), 5.40 (m, 2H, H_2- 4‘), 5.65 (m, 1H, H-2‘). and 5.95 (m, 1H, H-1‘). ^{13}C-NMR ($CDCl_3$) δ ppm: 20.2, 20.3, 20.5 and 20.7 (CH_3), 28.1, 29.2, 30.0 and 31.0 (CH_2), 67.1, 68.2, 69.6, 70.6, 71.3 and 73.2 (CH), 139.2, 139.5, 140.3, 140.9 and 141.8 (thieno pyrimidine carbon atoms and triazol carbon atom) and 169.6, 169.7, 169.8 and 170.0 (CO). Its MS (m/z), 505 [M, 81%].

3-(1‘,2‘,3‘,4‘,5‘-O-pentaacetylglucosyl)-3,5,6,7-tetrahydro-4*H*-cyclopenteno-thieno[2,3-*d*]pyrimidine-4-thione (11a)

It was obtained from compound **(9a)** (4.00g, 10 mmole) as yellow crystals. Its IR (cm^{-1}, υ):3333(NH), 2980,2986 (CH alkyl) and 1240(C-S). ^{1}H-NMR ($CDCl_3$) δ ppm: 1.77 (s, 3H, CH_3), 1.89 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 2.05 (5, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.35 (m, 2H, CH_2), 2.80 (m, 2H, CH_2), 2.85 (m, 2H, CH_2), 4.75 (m, 1H, H-4‘), 5.33 (d, 1H, J=10.8 Hz, H-3‘), 5.45 (m, 2H, H_2-5‘), 5.65 (s, 1H, H-2‘), 5.70 (s, 1H, H-1‘) and 11.15 (br.s,1H, NH, D_2O exchangeable). ^{13}C-NMR ($CDCl_3$) δ ppm: 20.0, 20.5, 20.6, 20.9 and 23.5 (CH_3), 25.3, 27.6, 29.3 and 30.0 (CH_2), 67.2, 67.4, 68.4, 70.9 and 71.1 (CH), 139.3, 141.6, 148.3, 155.1, 156.0 and 157.0 (thienopyrimidinethion carbon atoms and triazol carbon atom) and 168.3, 168.7, 169.4, 170.3 and 171.0 (CO) and 178.3 (CS). Its MS (m/z), 608 [M, 100%].

3-(1‘,2‘,3‘,4‘,5‘-O-pentacetylgalactosyl)-3,5,6,7-tetrahydro-4*H*-cyclopenteno-thieno[2,3-*d*]pyrimidine-4-thione (11b)

It was obtained from compound **(9b)** (4.00g, 10 mmole) as yellow crystals. Its IR(cm^{-1}, υ): 2985, 2989 (CH alkyl) and 1740-1760 (acetyl carbonyl). ^{1}H-NMR ($CDCl_3$) δ ppm: 1.80 (s, 3H, CH_3), 1.95 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.35 (m, 2H, CH_2), 2.80 (m, 4H, $2CH_2$), 4.76 (m, 1H, H-4‘), 5.10 (m, 1H, H-1‘), 5.30 5.50 (m, 2H, H_2-5‘), 5.55 (d, 1H, J=7.50Hz, H-3‘), 5.70 (m, 1H, H-2‘) and 10.55 (br.s,1H, NH, D_2O exchangeable). Its MS (m/z), 608 [M, 93%].

3-(1‘,2‘,3‘,4-O-Tetraacetylxylosyl)- 3,5,6,7-tetrahydro-4*H*-cyclopentenothieno[2,3-*d*]pyrimidine-4-thione (11c)

It was obtained from compound **(9c)** (3.70g, 10 mmole) as yellow crystals. Its IR (cm^{-1}, υ): 3340 (NH), 2980, 2985(CH alkyl), 1740-1760 (acetyl carbonyl) and 1239(C-S). ^{1}H-NMR ($CDCl_3$) δ ppm: 2.0 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.35 (m, 2H, CH_2), 2.85 (m, 4H, $2CH_2$), 5.25 (m, 1H, H-3‘), 5.45 (m, 2H, H_2- 4‘), 5.65 (m, 1H, H-2‘), 5.85 (m, 1H, H-1‘) and 10.82 (br.s,1H, NH, D_2O exchangeable). ^{13}C-NMR ($CDCl_3$) δ ppm: 20.2, 20.3, 20.5 and 20.7 (CH_3), 28.1, 29.2, 30.0 and 31.0 (CH_2), 69.6, 70.6 and 71.3 (CH), 139.2, 139.5, 140.3, 140.9, 141.66 and 141.8 (thienopyrimidinethion carbon atoms and triazol carbon atom) and 169.6, 169.7, 169.8 and 170.0 (CO) and 178.1 (CS). Its MS (m/z), 536 [M, 100%].

3-Glycosyl-8,9-dihydro-10H-cyclopentenothieno [3,2-*c*][1,2,4]triazolo[4,3-*c*]pyrimidine (12a-c) or 3-Glycosyl-)-3,5,6,7-tetrahydro-4*H*-cyclopente-nothieno-[2,3-*d*]pyrimidine-4-thione (13a-c)

General procedure

A solution of methanolic sodium methoxide (pre-

pared by dissolving sodium metal (0.23 g, 10m. mole) in absolute methanol (25 ml)) was added to either compounds **(10a-c)** (10 mmole) or **(11a-c)** (10 mmole). The reaction mixture was allowed to stir for eight hours (under TLC control), and then neutralized with hydrochloric acid solution (The neutralization takes place under pH control). The excess of methanol was removed under reduced pressure, whereby a solid was precipitated. The precipitate so-formed was filtered-off, washed with cold water dried and re-crystallized from the proper solvent to produce the title compounds in good yield.

3-Glucosyl-8,9-dihydro-10H-cyclopentenothieno [3,2-*c*][1,2,4]triazolo[4,3-*c*] pyrimidine (12a)

It was obtained from compound **(10a)** (5.76g, 10 mmole) as yellow crystals. Its IR (cm^{-1}, υ): 3460, 3440 (broad OH) and 2920 (CH alkyl). ^{1}H-NMR (DMSO-d_6) δ ppm: 2.35 (m, 2H, CH_2), 2.85 (m, 4H, $2CH_2$), 3.40(m, 5H, 5OH, OH-1'-OH-5', D_2O exchangeable), 3.55 (m, 1H, H-3'), 3.70 (m, 2H, H-5', H-5"),4.20 (m, 1H, H-2'), 4.28 (m, 1H, H-4'), 4.65 (m, 1H, H-1') and 7.75 (s, 1H, CH). Its MS (m/z), 466 [M, 87%].

3-Glalctosyl-8,9-dihydro-10H-cyclopentenothieno [3,2-*c*][1,2,4]triazolo[4,3-*c*] pyrimidine (12b)

It was obtained from compound **(10b)** (5.76g, 10 mmole) as reddish brown crystals. Its IR (cm^{-1}, υ): 3423, 3397 (broad OH), 3250 and 2930 (CH alkyl). ^{1}H-NMR (DMSO-d_6) δ ppm: 2.35 (m, 2H, CH_2), 2.70 (m, 4H, $2CH_2$), 3.65 (m, 5H, 5OH, D_2O exchangeable, OH-1'-OH-5'), 4.35 (m, 2H, CH_2, H_2-5'), 4.55 (m, 3H, 3CH, H-2'-H-4'), 5.25 (m, 1H, CH, H-1') and 7.77 (s, 1H, CH). ^{13}C-NMR (DMSO-d_6) δ ppm: 27.4, 27.6, 28.21 and 28.9 (CH_2), 62.6, 67.0, 67.9 and 69.5 (CH), 103.0, 112.4, 131.2, 131.6, 133.7 and 139.1 (thienopyrimidinethion carbon atoms and triazol carbon atom). Its MS (m/z), 466 [M, 89 %].

3-Xylosyl-8,9-dihydro-10H-cyclopentenothieno [3,2-*c*][1,2,4]triazolo[4,3-*c*] pyrimidine (12c)

It was obtained from compound **(10c)** (5.05g, 10 mmole) as orange crystals. Its IR (cm^{-1}, υ): 3420, 3400 (broad OH), 3335 (NH) and 1980 ((CH alkyl)). ^{1}H-NMR (DMSO-d_6) δ ppm.: 2.25 (m, 2H, CH_2), 2.55 (d, 1H, J=13Hz, CH of the triazol ring), 2.95 (m, 4H, $2CH_2$), 4.10 (m, 4H, 4OH, D_2O exchangeable, OH-1'-OH-5'), 4.35 (dd, 1H, J=10.8 Hz, H-3'), 5.25 (m, 1H, H-1'), 7.78 (s, 1H, CH) and 8.25 (brs, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) ppm: 27.5, 28.6, 30.1 and 30.2 (CH_2), 63.1, 68.9, 69.8 and 70.0 (CH), 112.0, 130.7, 139.0, 143.86, 148.2 and 150.0 (thienopyrimidine carbon atoms and triazol carbon atom). Its MS (m/z), 338 [M, 100%].

3-Glucosyl-8,9-dihydro-10H-cyclopentenothieno [3,2-*c*][1,2,4]triazolo[4,3-*c*] pyrimidine (13a)

It was obtained from compound **(11a)** (6.08g, 10 mmole) as yellow crystals. Its IR (cm^{-1}, υ): 3460, 3440 (broad OH), 2920 (CH alkyl) and 1239 (C-S). ^{1}H-NMR (DMSO-d_6) δ ppm: 2.35 (m, 2H, CH_2), 2.85 (m, 4H, $2CH_2$), 3.40(m, 5H, 5OH, OH-1'-OH-5', D_2O exchangeable), 3.55 (m, 1H, H-3'), 3.70 (m, 2H, H-5', H-5"),4.20 (m, 1H, H-2'), 4.28 (m, 1H, H-2'), 4.65 (m, 1H, H-1') and 7.75 (s, 1H, CH). Its MS (m/z), 398 [M, 88%].

3-Glalctosyl-8,9-dihydro-10H-cyclopentenothieno [3,2-*c*][1,2,4]triazolo[4,3-*c*] pyrimidine (13b)

It was obtained from compound **(11b)** (6.08g, 10 mmole) as yellow crystals. Its IR (cm^{-1}, υ): 3423, 3397 (broad OH), 3250 and 2930 (CH alkyl). ^{1}H-NMR (DMSO-d_6) δ ppm: 2.35 (m, 2H, CH_2), 2.70 (m, 4H, $2CH_2$), 3.65 (m, 5H, 5OH, D_2O exchangeable, OH-1'-OH-5'), 4.35 (m, 2H, CH_2, H_2-5'), 4.55 (m, 3H, 3CH, H-2'-H-4'), 5.25 (m, 1H, CH, H-1') and 11.05 (br. s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) δ ppm: 27.4, 27.6, 28.70 and 28.9 (CH_2), 62.6, 67.0, 67.9 and 69.5 (CH), 103.0, 112.4, 131.2, 131.6, 133.7 and 139.1 (thienopyrimidinethion carbon atoms and triazol carbon atom) and 178.6 (CS). Its MS (m/z), 398 [M, 91%].

3-Xylosyl-8,9-dihydro-10H-cyclopentenothieno [3,2-*c*][1,2,4]triazolo[4,3-*c*] pyrimidine (13c)

It was obtained from compound **(11c)** (3.68g, 10 mmole) as yellowish green crystals. Its IR (cm^{-1}, υ): 3420, 3400 (broad OH), 3335 (NH), 1980 (CH alkyl) and 1240 (C-S). ^{1}H-NMR (DMSO-d_6) δ ppm.: 2.25 (m, 2H, CH_2), 2.95 (m, 4H, $2CH_2$), 4.10 (m, 4H, 4OH, D_2O exchangeable), 4.35 (dd, 1H, J=10.8 Hz, H-3'), 5.25 (m, 1H, H-1') and 8.25 (brs, 1H, NH,

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D_2O exchangeable). ^{13}C-NMR (DMSO-d_6) δ pm: 27.5, 28.6, 30.1 and 30.2 (CH_2), 63.1, 68.9 and 70.0 (CH), 112.0, 130.7, 139.0, 148.2, 148.8 and 150.0 (thienopyrimidine carbon atoms and triazol carbon atom) and 178.4 (CS). Its MS (m/z), 368 [M, 86%].

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