A common route to the synthesis of 1,3,4-oxadiazole -2-thione and 1,2,4-triazole -3-thiols derivatives of trioses and pentoses as models for acyclic C-nucleosides

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Abstract

The 5-(1,2-dihydroxy-ethyl)-3*H*-[1,3,4]oxadiazole-2-thione (**12**) and 1-(5-mercapto-4*H*-[1,2,4]triazole-3-yl)-ethane-1,2-diol (**13**) derived from (±) glyceraldehyde (resembles trioses) have been synthesized from glycerol (**1**) via a common route. The synthesis of the optical active 5-(2,2-dimethyl-[1,3]dioxolan-4-yl)-3*H*-[1,3,4] oxadiazole-2-thione (**17**) and 5-(2,2-dimethyl-[1,3]dioxolan-4-yl)-4*H*-[1,2,4]triazole-3-thiol (**18**) may be achieved by the same common route when the D- glyceraldehyde (**3**) was obtained by cleavage oxidation of 1,2:5,6-Di-*O*-isopropylidene D-mannitol (**15**). Similar derivatives **23** and **24** of D-xylose (**19**) (resembles pentoses) may also be synthesized by the same common route from (tetrahydro-[1,3]dioxino[5,4-d][1,3]dioxin-4-yl)-methanol (**21**). This common route provides a simple synthetic pathway to acyclic C-nucleosides and to less extent to cyclic C-nucleosides.

Keywords:(±)Glyceraldehydes,1,2:5,6-Di-*O*-isopropylidene-D-mannitol,5-(1,2-dihydroxy - ethyl)-3*H*-[1,3,4]oxadiazole-2-thione,1-(5-mercapto-4*H*-[1,2,4]triazole-3-yl)-ethane-1,2-diol, C-nucleosides

Introduction

Hydrazides and related compounds have been described as useful building blocks for the assembly of various heterocyclic rings. Thus, different carbohydrazides were found to be useful as medicines. The synthesis of compounds incorporating both 1,2,4-triazole, and 1,3,4-oxadiazole rings has been attracting widespread attention due to their diverse pharmacological proprieties such as antimicrobial, anti-inflammatory, analgesic and antitumor activities.

Many commonly known cyclic N-nucleosides as well as acyclic analogues have strong biological effects.[1, 2, 3] The less common O-, S- and C-nucleosides are also known to have antiproliferating activity and can be used for antiviral, anti-cancer and anti-aids therapies.[4]

The synthesis of the different kinds of the nucleosides can be performed in any one of the four strategies (A, B, C and D). [5]

Cyclic Sugar   Heterocycle   Acyclic Sugar
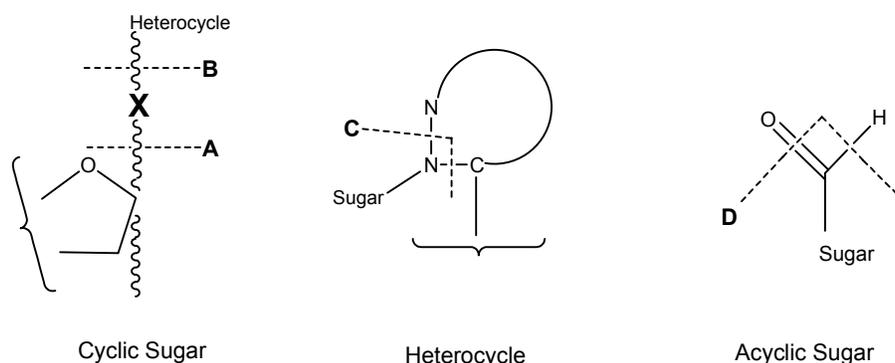
Strategy (A) involves a substitution of the glycosidic link X with a leaving group (e.g. halogen, acetate, etc...) to replace it with the base acting as the nucleophile to build up the desired heterocycles.

Strategy (B) achieving the nucleosides from hetero-sugars (X = S) as in thio-sugars where S acts as nucleophile to react with heterocyclic ring.

Strategy (C) use a sugar containing a base (X = N) as in amino-sugars where N acts as a nucleophile to build up the heterocycles.

Strategy (D) involves nucleophilic addition reaction to the aldehydic carbonyl followed with the lost of water followed by building up the heterocycles.

C-nucleosides are excellent natural products antibiotics and in comparison with the normal nucleosides, they contain no acetal unit and hence they are much more stable compared to normal nucleosides and nucleotides.

The synthetic route to the cyclic C-nucleosides using sugar lactones, while for the acyclic analogue, more often followed strategy (D).

The 1,3,4-oxadiazole derivatives show leprostatic and tuberculostatic properties and exhibit antibacterial, antiproteolytic and anticonvulsant activities. Also they have analgesic, antipyretic, antiphologistic, bactericides, insecticides, fungicidical and several other biological activities. [6]

The relatively simple 1,2,4-triazoles display biological activities such as inhibition of cholinesterase, interference with mitosis and reversible denaturation of serum proteins. The 1,2,4-triazole thiones afford some protection of mice against irradiation with X-rays, and have anti-inflammatory properties. They have appreciable biochemical effects when replacing histidine derivatives in nucleic acids. Also, compounds with a thiourea function NH-(CS)-NH have a strong potential for manufacturing drugs since the SH group can easily converted to their S-substituted derivatives.[7] As a continuation of our investigation of antimicrobial activities of 1,3,4- oxadiazole –thione and 1,2,4–triazole-thiole derivatives , we wish to report a common route to the synthesis of 1,3,4- oxadiazolo–thiones **12, 17**, **23**, and 1,2,4–triazolo-thiols **13**, **18** , **24** as model compounds for acyclic C-nucleosides.

Results and Discussion

Scheme 1 shows the common route for the synthesis of open chain C-nucleosides possessing a 1,3,4-oxadiazolo-2-thione **12** and a 1,2,4-triazolo-3-thiol **13** derived from glycerol. This route initially required a selective protection of the adjacent OH groups of glycerol in order to leave the terminal OH group for further modifications.

Racemic 2,3-*O*-isopropylidene glycerol (**2**) has been prepared in a excellent yield (98%) by refluxing glycerol with an excess of acetone and a catalytic amount of acid when a Dean-Stark apparatus was used to remove the water which formed during the reaction. The amount of acetone may be reduced if chloroform was utilized as a reaction medium. Between the two acids used (concentrated H_2SO_4 or *p*-toluensulfonic acid), the latter was found to be more effective and to give a higher yield.

The (±)-2,3-*O*-isopropylidene glyceric acid (**4**) was prepared by two routes. In the first route, the direct oxidation of (±)-2,3-*O*-isopropylidene glycerol (**2**) with $KMnO_4 / KOH$ gave the potassium salt **6** in 81 % yield, in addition to the starting alcohols.

The second route was achieved by a complete oxidation of the **2** with $CrO_3 /$ pyridine to give the corresponding aldehyde **3**. The crude aldehyde **3** was oxidized with $KMnO_4 / KOH$ then acidified with a mineral acid (HCl) to give a quantitative yield of the corresponding acid **4**.

The (±)-methyl-2,3-*O*-isopropylideneglycerate (**5**) was obtained either by direct esterification of **4** with methanol in presence of conc. H_2SO_4 or by treatment of the potassium salt **6** with methyl iodide in presence of N,N,N',N'-tetramethylethylenediamine (TMED) .

In case the methylation was performed on crude **6**, 1-methoxy-2,3-*O*-isopropylidene glycerol as a side product was isolated. The second route gave a better yield since the latter procedure does not involve the risk of a back hydrolysis of the ester group and the protecting isopropylidene ring.

The racemic hydrazide **7** was prepared in a yield of about 90 % by treating the ester **5** with hydrazine monohydrate (55 %). The product was identified by IR which showed a moderately strong band at 3258 cm⁻¹ region for the free and bonded N-H and a band at 1631 cm⁻¹ for CO-N. The structure **7** was confirmed by ¹H-NMR which exhibited a signal at 8 ppm for N-H and mass spectrometry which showed the fragment M+1 = 161.081 for $C_6H_{12}N_2O_3$.

When the hydrazide **7** was refluxed with CS_2 in absolute ethanol and KOH (0.3 moles) reveled into (±)-5-(2,2-dimethyl-[1,3]dioxolan-4-yl)-3*H*-[1,3,4]oxadiazole-2-thione (**8**). The characteristic bands in IR of this compound showed at regions 1280 cm⁻¹ (C=S) and 1675 cm⁻¹ (C=N). The position of the C=N band suggested that the oxadiazole existed as the thione tautomer **8** rather than the ene-thiol form **8a** which normally exhibited a band at a lower region (in about 1638 cm⁻¹) due to maximum conjugation.[8] Further support for the thione form came from ¹H-NMR which exhibited only one proton as a singlet at lower field 7.01 ppm for N-H and no signal around 13 to 14 ppm where the S-H is normally shown.[9] The product **8** also shown a fragment [M+H] = 203.04 in mass spectrometry.
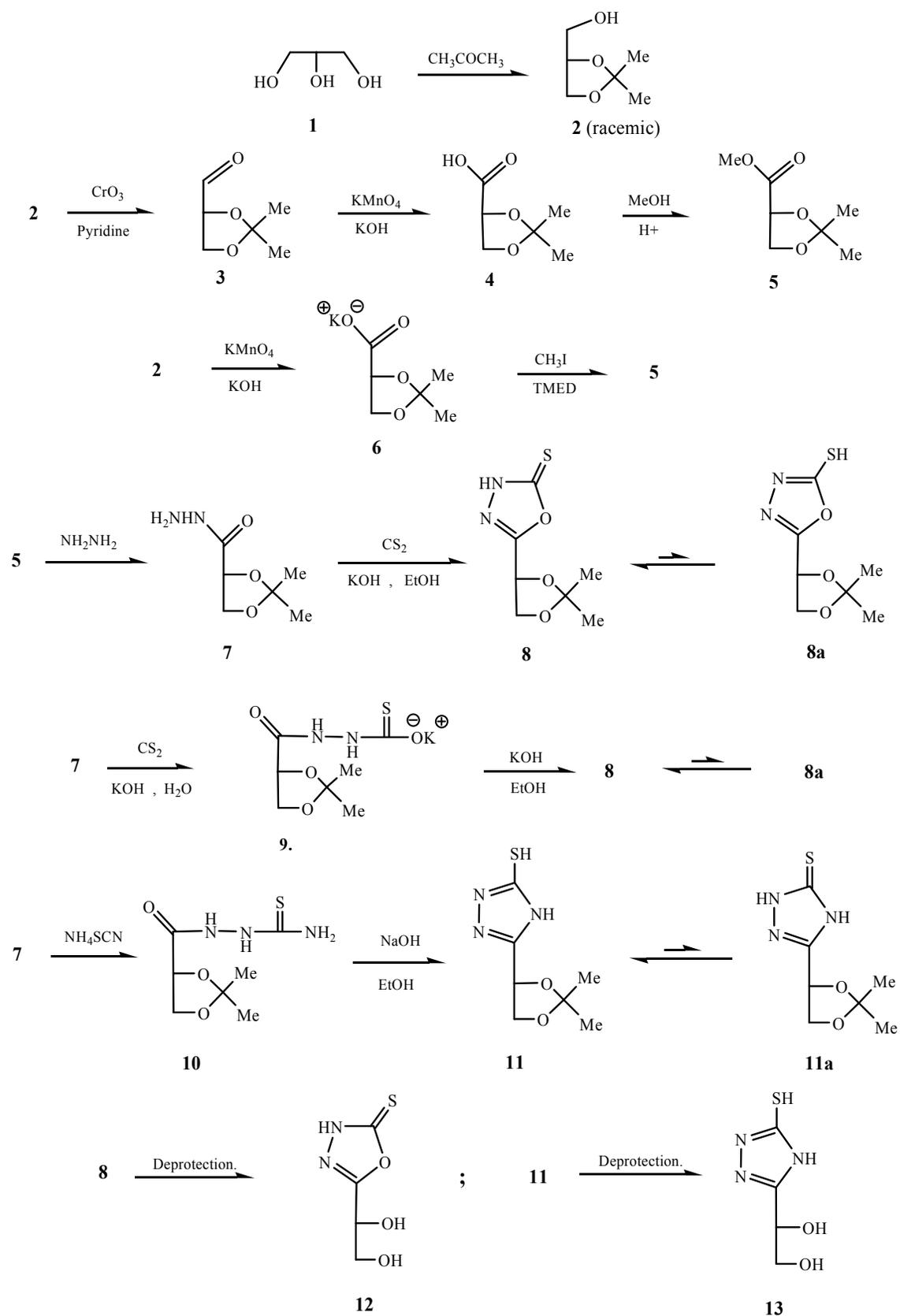
Scheme 1. Common pathway to the synthesis of compounds **12** and **13**

The potassium (±)–2,2-dimethyl-[1,3]dioxolan-4-carboxylic-acid-hydrazide-thio-semi-carbazinate **9** was obtained in a yield 95 % by treatment of the hydrazide **7** with CS_2 in aqueous KOH under reflux for five hours.[10] The IR spectrum of the product exhibited characteristic bands at 3258 cm^{-1} (OCNH), 1580 cm^{-1} (NH), and 1238 cm^{-1} (C=S) .The mass spectrum showed the major fragment [M+1] =259.01 for $C_7H_{11}N_2O_4SK$. When **9** was heated with ethanolic KOH it gave rise to **8**.

The synthesis of the (±)-5-(2,2-dimethyl-[1,3]dioxolan-4-yl)-4*H*-[1,2,4]triazole-3-thiol (**11**) was achieved in two steps from hydrazide **7** .The first step was the preparation of (±)-2,2-dimethyl-[1,3]dioxolan-4-carboxylic-acid-hydrazide-thioformamido-semi-carbazide (**10**) by treating the hydrazide **7** with ammonium thiocyanate in dry benzene under reflux for six hours. The resulting product after isolation showed an IR spectrum which exhibited a broad band centered at 3100 cm^{-1} region for free and bonded N-H ; another band at 1665 cm^{-1} (C=O) and at 1280 cm^{-1} (C=S). Mass spectrum showed a fragment [M+H] =220.07. The second step involved the treatment of **10** with NaOH in absolute ethanol under reflux for five hours to give **11** .IR spectrum exhibited the following characteristic bands 3200 cm^{-1} (NH), 2860-2760 cm^{-1} (SH), and 1670 cm^{-1} (C=N). ^{1}H-NMR showed a singlet at 3.01 ppm for S-H. Mass spectrum exhibited a fragment [M+H] =202.057 attributed for $C_7H_{11}N_3O_2S$. These informations suggested that the triazole **11** found mostly in the thiol form. The synthesis of the optical active oxadiazole **17** and triazole **18** derivatives of D-glyceraldehyde can be achieved according to Scheme 2.
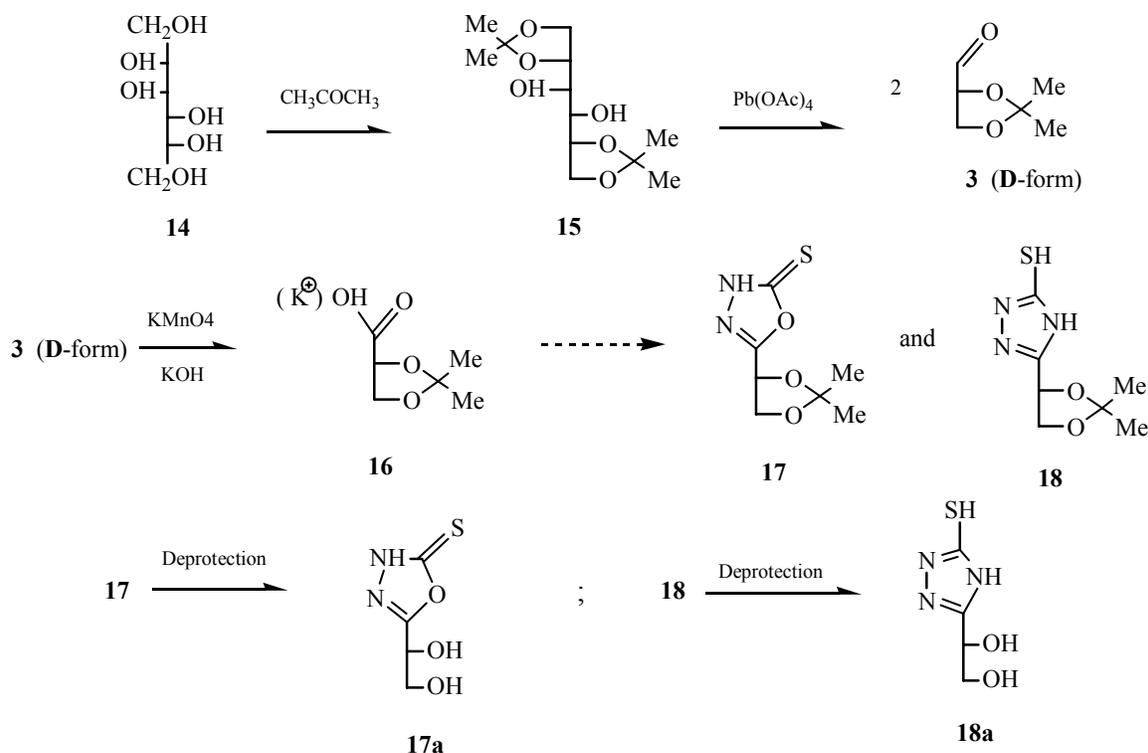
Scheme 2. Common route preparation of D-1,2-O-isopropylidene 1,3,4-oxadiazole (**17**) and 1,2,4-triazole (**18**) thioles from D-mannitol.

The acetonation of D-mannitol (**14**) gave 1, 2:5, 6-Di-*O*-isopropylidene-D-mannitol (**15**).
[11] The oxidation of **15** with lead tetra acetate led to 2,3-*O*-isopropylidene-D-glyceraldehyde (**3a**)
which on oxidation with $KMnO_4$ / KOH followed by acidification with mineral acid to give 2,3-
O-isopropylidene-D-glyceric acid (**16**) which can be used as starting material for preparation of
17 and **18** by following the same steps described in Scheme 1.

For the synthesis of 1, 3, 4-oxadiazole **23** and 1, 2, 4-triazole **24** derived from pentose, e.g.
D-xylose (**19**), Scheme 3 was followed. The reduction of D-xylose (**19**) with $NaBH_4$ afforded D-
xylitol (**20**)[12] which on reaction with formaldehyde gave (tetrahydro-[1,3]dioxino[5,4-
d][1,3]dioxin-4-yl)-methanol (**21**) which on oxidation with $KMnO_4$ gave the corresponding acid
22, which can be used as starting material for the synthesis of **23** and **24** by following reaction
sequence described in Scheme 1.
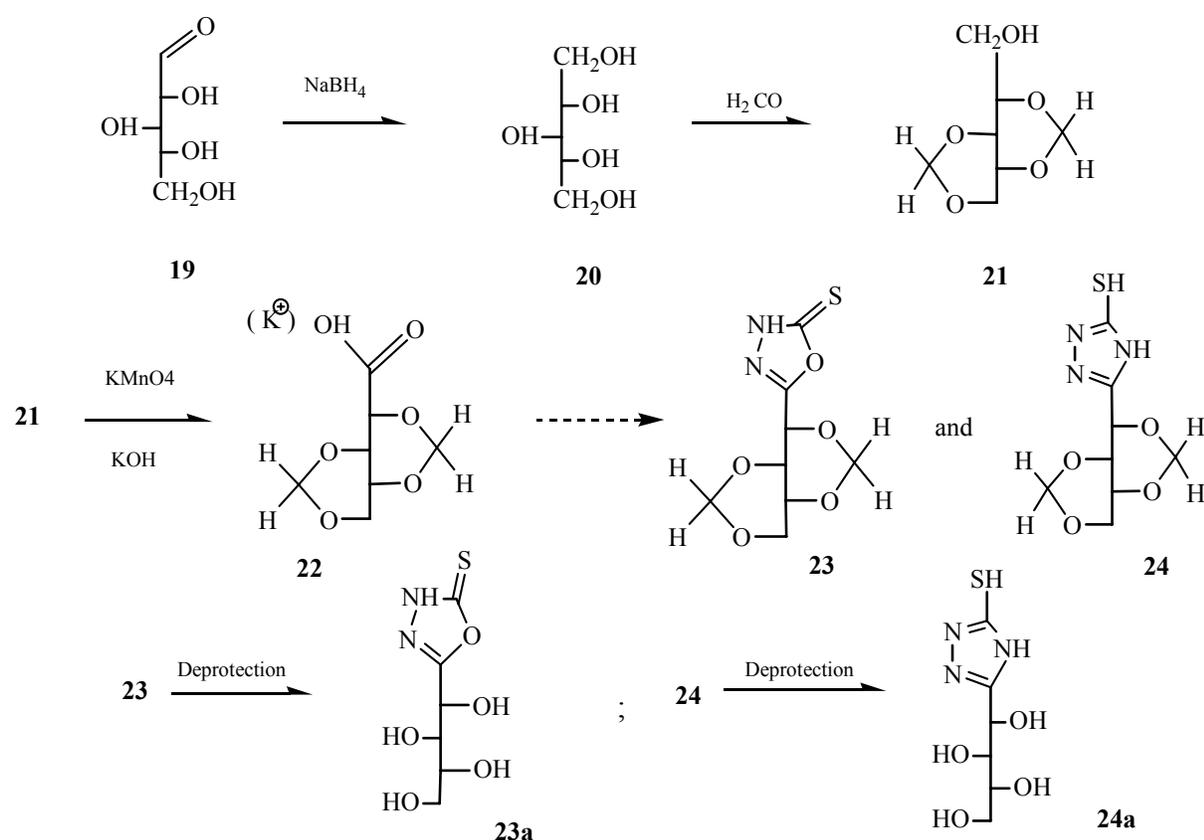
Scheme 3. Common route to the synthesis 1,3,4-oxadiazole (**23**) and 1,2,4-triazole (**24**) thioles
from D-xylose.

Experimental Section

General Procedures. Chemicals were purchased from Fluka and Aldrich. Melting points were determined with a Buchi Apparatus and are uncorrected. The progress of reactions were followed by thin layer chromatography (TLC) prepared in our laboratory using Silica Gel (Merck) on glass (layer thickness 0.25 mm) used without pretreatment. Eluents used volume-to-volume (v/v), and the spots were detected by exposure to iodine vapor for a few minutes. All solvents evaporations were performed in a Buchi rotary evaporator under diminished pressure. The IR spectra were measured as potassium bromide pellets using Perkin-Elmer 1600 FTIR spectrometer. The ^{1}H NMR spectra were obtained using a Bruker AC 250 NMR and were recorded at 250 MHz. Chemicals shifts are reported in part per million δ (ppm) using internal TMS and DMSO-d_6 as solvent . The mass spectra were measured on DX 300-SX102 spectrometer using a FAB (fast atom bombardment) as ionization mode.

(±)-2,2-Dimethyl-[1,3]dioxolan-4-yl-methanol (2). [13] Glycerol (**1**) (15.0 g, 0.16 mol), acetone (400 mL) in petroleum ether b.p. 60-80°C (400 mL) and TsOH (1.0 g) were mixed and heated under reflux for 6 h in which the water formed during the reaction was removed continuously by a Dean-Stark apparatus. The reaction mixture was cooled to room temperature and Na$_2$CO$_3$ (1.3 g) was added gradually. The mixture was stirred for 30 min, filtered, and the filtrate was evaporated to dryness to give the crude product. The crude product was vacuum distilled (10 mm Hg) to give the pure (±)-2,3-O-isopropylidene glycerol (**2**) as a colorless syrup (16.49 g, 76.6%), b.p. 193°C , α_D^{20} = 1.4378. [11]

(±)-2,2-Dimethyl-[1,3]dioxolan-4-carbaldehyde (3) . The racemic mixture **2** (5.0 g, 37 mmol) in CH$_2$Cl$_2$ (2 mL), added to it freshly prepared CrO$_3$ / pyridine /HCl (9.7 g, 0.1 mol) suspended in CH$_2$Cl$_2$ (60mL) .The mixture was kept into an ice bath 0-4°C for 1.5 h with an aid of magnetic stirring (TLC (benzene/chloroform, 3:7 Rf: 0.52 showed the total consumption of glycerol derivative **2**). The CH$_2$Cl$_2$ was evaporated down under vacuum at room temperature, the residue dissolved in dry Et$_2$O and the filtrate and the residue were washed further with ether (1 mL) The combined filtrate and washing were evaporated to dryness under vacuum at room temperature to give a greenish syrup (3.79 g, 75.8 %). mp: 105-110 °C; IR exhibited bands at 2780 cm^{-1} (CH) and 1725 cm^{-1} (>C=O). ^{1}H NMR (250 MHz, TMS) δ (ppm) 1.40 (m, 6H, 2CH$_3$), 4.19(d, 2H, OC-CH$_2$), 4.76 (s, 1H, OC-CH), 9.72 (s, 1H, CHO); MS *m/z*: 131.066 (M$^+$+1), 114.06 (12.97 %); HRMS Calcd for C$_6$H$_{10}$O$_3$: 130.061; Found: 131.070.

(±)-2,2-Dimethyl-[1,3]dioxolan-4-carboxylic acid (4). The aldehyde **3** (0.2 g; 1.53 mmol) in acetone (3 mL) was treated with a solution of KMnO$_4$ (1.25 mg in 7 mL H$_2$O) dropwise at 0°C with the aid of magnetic stirring. The mixture was stirred for 1 h at 20-25°C, the period shown by TLC to complete conversion of the aldehydes to acid [TLC (benzene/ chloroform, 3:7), Rf: 0.17]. A small amount of activated charcoal was added and the reaction mixture was warmed on a water bath at 50°C for 10 minutes . The reaction mixture was then filtered and just acidified with few drops of HCl and extracted with petroleum ether 60-80, and evaporated to dryness to give a white solid,which was recrystallized from light petroleum ether to give colorless needles

(0.15 g, 68%), mp. 68°C ; IR exhibited bands at 2500 cm^{-1} (OH) and 1710 cm^{-1} (>C=O). ^{1}H NMR (250 MHz, TMS) δ (ppm) 1.41 (m, 6H, 2CH$_3$), 4.13(d, 2H, OC-CH$_2$), 4.76 (s, 1H, OC-CH), 11.0 (s, 1H, COOH); MS m/z: 147.051 (M^{+}+1), 129.061 (12.55 %), 114.07 (22.67 %), 101.063 (31.49 %); HRMS Calcd for C$_6$H$_{10}$O$_4$: 146.058; Found: 146.141.

Potassium (±)-2,2-dimethyl-[1,3]dioxolan-4-carboxylate (6) . The racemic mixture **2** (0.4 g, 3.0 mmol) in H$_2$O (40 mL) was added to an aqueous solution (containing KOH, 180 mg in 40 mL H$_2$O). A solution of aqueous KMnO$_4$ (50%) was added dropwise at 0-10 ° C with the aid of stirring until the color of permanganate ion was retained for 30 min. The excess of permanganate was decomposed by addition of MeOH dropwise. Solvents were evaporated to dryness and the residue was suspended in absolute ethanol (100 mL) for two times and again evaporated down to dryness to crude salt (0.48 g) which was used without further purification.

2,2-Dimethyl-[1,3]dioxolan-4-carboxylic acid methyl ester (5)
Method A. From (±)-2,2-dimethyl-[1,3]dioxolan-4-carboxylic acid (4). The acid **4** (1.0 g), methanol (5 mL), toluene (10 mL) and H$_2$SO$_4$ (6 drops) were heated under reflux in an oil bath (105-110 °C) for 4 h. TLC (CHCl$_3$/MeOH, 6:4), Rf: 0.89. The reaction mixture was cooled to room temperature, neutralized with saturated aqueous Na$_2$CO$_3$ solution with the aid of magnetic stirring. Two layers separated, the organic layer was washed with water and dried over MgSO$_4$, filtered and evaporated to dryness to give the ester **5** as colourless syrup (480 mg, 89.5%). IR showed a band at 1740 cm^{-1} characteristic of ester CO, and 2845 cm^{-1} for methoxy group (O-CH$_3$). ^{1}H NMR (250 MHz, TMS) δ (ppm) 1.40 (m, 6H, 2CH$_3$), 3.67(m, 3H, O-CH$_3$), 4.25 (d, 2H, OC-CH$_2$), 4.73 (s, 1H, OC-CH); MS m/z: 161.074 (M^{+}+1), 145.055 (9.95%), 129.057 (19.88 %), 114.06 (29.19 %); HRMS Calcd for C$_7$H$_{12}$O$_4$: 160.074; Found: 161.168.

Method B. From potassium,(±)-2,2-dimethyl-[1,3]dioxolan-4-carboxylate (6). A suspension of potassium-(±)-2,2-dimethyl-[1,3]dioxolan-4-carboxylate (**6**) (300 mg) in MeCN (10 mL) and methyl iodide (1.7 g, 0.60 mol) in the presence of N,N,N',N'-tetra-methylethylenediamine (TMED, 100 mg, 0.04 mol) was stirred vigorously at 50°C for 5 h (TLC CHCl$_3$ / MeOH, 6:4), Rf: 0.90). The reaction mixture was cooled to room temperature and filtered. The residue was washed with a few drops of MeCN. The combined filtrate and washing was evaporated to dryness under reduced pressure to give a light syrup of crude ester **5** (249 mg). Chromatography with a silica gel column (30 cm long) gave the side product methoxy-2,3-*O*-isopropylidene glycerol as colorless syrup, bp 72 °C. The pure ester **5** as colorless syrup (198 mg, 83%, bp 88°C) was recovered. IR showed a band at 1740 cm^{-1} characteristic of ester CO, and 2845 cm^{-1} for methoxy group (O-CH$_3$). ^{1}H NMR (250 MHz, TMS) δ (ppm) 1.41 (m, 6H, 2CH$_3$), 3.67(m, 3H, O-CH$_3$), 4.25 (d, 2H, OC-CH$_2$), 4.73 (s, 1H, OC-CH); MS m/z: 161.074 (M^{+}+1), 147.065 (8.70 %); HRMS Calcd for C$_7$H$_{12}$O$_4$: 160.074; Found: 161.168.

2,2-Dimethyl-[1,3]dioxolan-4-carboxylic acid hydrazide (7). The carboxylic acid methyl ester **5** (0.2 mL, 1.6 mmol) in methanol (1.1 mL) was added to hydrazine hydrate (0.32 mL, 6.4 mmol), and the solution was refluxed in a water bath for 6 h. TLC (CH$_3$Cl / MeOH, 6:4), showed consumption of the ester **5** and formation of the hydrazide **7** (Rf: 0.75). The solvent was removed

in *vacuo* and the residue was dissolved in EtOAc (20 mL); and washed with saturated aqueous NaCl (20 mL), then dried over anhydrous MgSO$_4$ and filtered. The solvent was removed in *vacuo* to afford a white crystalline solid **8** (0.679 g, 89 %), mp 109-113 °C; IR exhibited bands at 3258 cm^{-1} (OC-NH) and 1580 cm^{-1} (RNH$_2$) . ^{1}H NMR (250 MHz, TMS) δ (ppm) 1.40 (m, 6H, 2CH$_3$), 2.00 (s, 1H, NH$_2$), 4.14(d, 2H, OC-CH$_2$), 4.84 (s, 1H, OC-CH), 8.00 (s, 1H, C-NH); MS *m/z*: 161.081 (M$^+$+1), 144.095 (10.56 %),129.06 (19.88 %); HRMS Calcd for C$_6$H$_{12}$N$_2$O$_3$: 160.08; Found: 160.17.

(±)-5-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-3*H*-[1,3,4]oxadiazole-2-thione(8). The hydrazide **7** (300 mg, 0.30 mol) was dissolved in absolute ethanol and CS$_2$ (3 ml, 0.05 moles) and KOH (1.8 g, 0.3 moles in H$_2$O, 20 mL) were added. The reaction mixture was heated under reflux with an aid of magnetic stirring for 3 h, during that time the colour of the solution turned to yellow (H$_2$S evolution took place during the reaction time. TLC (CHCl$_3$ / MeOH, 6:4), Rf: 0.65). Ethanol was distilled off under reduced pressure and the residue was dissolved in H$_2$O, acidified with HCl to pH=2 and extracted with EtOAc (3 x 20 mL). The combined extracts were evaporated to dryness under vacuum to give crystalline solid **8** (0. 275 g, 82 %), mp 165-167 °C. IR cm^{-1}: 1675 (C=N), 1150 (C-O-C), 1280 (C=S). ^{1}H NMR (250 MHz, DMSO-d$_6$) δ (ppm) 1.42 (m, 6H, 2CH$_3$), 3.90 (d, 2H, OC-CH$_2$), 3.93 (s, 1H, OC-CH),7.01 (s, 1H,NH).MS *m/z*: 203.041 (M$^+$+1), 170.07 (16.39 %),156.021 (23.29 %) , 127.65 (37.24 %); HRMS Calcd for C$_7$H$_{10}$N$_2$O$_3$S: 202.041; found: 202.231.

Potassium,(±)–2,2-dimethyl-[1,3]dioxolan-4-carboxylic-acid-hydrazide-thio-semi-carbazinate (9). The hydrazide **7** (150 mg, 0.15 mmol) and carbon disulfide (0.60 mL, 0.15 mmol) were added to a solution containing KOH (560 mg, in 50 mL) and ethanol (50 mL). The mixture was heated under reflux for 5 h (TLC (CHCl$_3$ /MeOH, 6:4), Rf: 0.70). The solvent was evaporated to dryness under reduced pressure to give a yellowish solid, which was dissolved in H$_2$O (300 mL). The solution was acidified with conc. HCl to give a white precipitate, filtered and washed with EtOH. The precipitate recrystallized from chloroform/ethanol to give while needles of the salt **9** (120 mg, 79%), mp 196-197 °C. IR showed bands at 3258 cm^{-1} (OCNH), 1580 cm^{-1} (NH), and 1238 cm^{-1} (C=S). H NMR (250 MHz, TMS) δ (ppm) 1.40 (m, 6H, 2CH$_3$), 2.00 (s, 1H, NH), 4.14(d, 2H, OC-CH$_2$), 4.84 (s, 1H, OC-CH), 8.00 (s, 1H, OC-NH); MS *m/z*: 259.015 (M$^+$+1), 202.909 (21.66 %); HRMS Calcd for C$_7$H$_{11}$KN$_2$O$_4$S: 258.011; Found: 258.340.

(±)-2,2-Dimethyl-[1,3]dioxolan-4-carboxylic-acid-hydrazide-thioformamido-semi-carbazide (10) .The hydrazide **7** (160 mg, 0.01 mol) was added to ammonium thiocyanate (0.01 mol) in dry benzene (10 mL) and the mixture was heated under reflux for 6 h (TLC (CHCl$_3$ / MeOH, 6:4), Rf: 0.60). The solid material obtained on cooling was filtered and recrystallized from methanol (0.58 g, 85 %), mp 145-147 °C. IR cm^{-1}: 3100 (NH), 1665 (CON), 1280 (C=S). ^{1}H NMR (250 MHz, DMSO-d$_6$) δ (ppm) 1.41 (m, 6H, 2CH$_3$), 2.00 (s, 1H, -NH), 2.04 (s, 2H, -NH$_2$) 4.14 (s, 2H, OCH$_2$), 4.84 (s, 1H, OCH), 8.01 (s, 1H, N-NH).MS *m/z*: 220.071 (M$^+$+1), 203.049 (7.73 %),172.152 (21.17 %),159.256 (27.63 %),144.689 (34.25 %),129.152 (41.31%); HRMS Calcd for C$_7$H$_{13}$N$_3$O$_3$S: 219.071; found :219.263.

(±)-5-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-4*H*-[1,2,4]triazole-3-thiol (11). The compound **10** (220 mg, 10 mmol) in 2N-NaOH solution (40 mg NaOH, 10 mmol in 100 mL H_2O) was heated under reflux for 5 h. (TLC ($CHCl_3$/MeOH, 6:4); Rf: 0.55). After cooling, the solution was made acidic with conc. HCl and the precipitate was then recrystallized from absolute ethanol to give crystalline fibres **11** (295 mg, 84 %). IR cm^{-1}: 3200 (NH), 2860-2760 (S-H), 1670 (C=N). ^{1}H NMR (250 MHz, DMSO-d_6) δ (ppm) 1.41 (m, 6H, $2CH_3$), 3.00 (s, 1H, C-SH), 3.63 (s, 1H, C-NH), 4.19 (s, 2H, O-CH_2), 5.18 (s, 1H, O-CH), MS *m/z*: 202.057 (M^++1), 168.084 (16.84 %),101.061 (49.98 %); HRMS Calcd for $C_7H_{11}N_3O_2S$: 201.057;found :201.246.

1, 2:5, 6-di-*O*-isopropylidene-D-mannitol (15). D-Mannitol (**14**) (1.5 g, 0.01 mol) in acetone (60 mL) was added to $ZnCl_2$ (2 g, 0.015 mol). The mixture was stirred vigorously at 20 °C for 3 h (TLC (C_6H_6/$CHCl_3$, 4:6) showed the development of one spot Rf: 0.56). Aqueous K_2CO_3 solution (14 mL, containing 1.52 g, 0.011 mol) was added gradually with the aid of stirring, then filtered and washed with Et_2O/Me_2CO (1:1) (20 mL). Ether (60 mL) was added to the combined filtrate and washing. The ether layer was separated and the aqueous layer was again extracted two times with Et_2O (10 mL, each time).The combined organic layer dried over $MgSO_4$, filtered and evaporated to dryness under vacuum reduced pressure at room temperature to give **15** as white crystals (210 mg, 75%), m.p.117°C,(lit.,119°C). ^{11}

2,3-*O*-isopropylidene-D-glyceraldehyde (3a). 1,2:5,6-Di-*O*-isopropylidene-D-mannitol **15** (260 mg, 0.001 mol), in dry THF (5 mL) and freshly prepared $Pb(OAc)_4$ (543 mg, 0.001 mol) were mixed vigorously for 0.5 h at an ice bath, then for another 0.5 hr at room temperature .TLC (C_6H_6/$CHCl_3$,4:6),Rf:0.80. The reaction mixture was filtered and washed with THF (1 mL) .The THF evaporated down to dryness under vacuum on a warm water bath (50°C) to give a light   syrup of   2,3-*O*-isopropylidene-D-glyceraldehyde **3** (221 mg, 85%), $α_D^{20}$= +1.6.   IR showed a band at   2936 cm^{-1} (=C-H), 1750 cm^{-1} (>C=O), 1082 cm^{-1} (C-O-C). ^{1}H NMR (250 MHz, DMSO-d_6) δ (ppm) 1.41 (m, 6H, $2CH_3$), 4.19 (d, 2H, OC-CH_2), 4.76 (s, 1H, OC-CH), 9.72 (s, 2H, O=CH_2), MS *m/z*: 131.064 (M^++1), 114.068 (13.02 %), 101.064 (22.93 %); HRMS Calcd for $C_6H_{10}O_3$: 130.064; found: 130.145

2,3-*O*-isopropylidene-D-glyceric acid (16). 2,3-O-isopropylidene–D-glyceraldehyde (**3a**) was oxidized with $KMnO_4$/KOH as described for the oxidation of   (±)-(2,2-Dimethyl-[1,3]dioxolan-4-carbaldehyde (**3**). TLC (benzene/ chloroform, 3:7), Rf: 0.17. The reaction mixture give a white solid, which was recrystallized from light petroleum ether to give colorless needles (0.15 g, 68%), mp. 68°C ; IR exhibited bands at 2500 cm^{-1} (OH) and 1710 cm^{-1} (>C=O). ^{1}H NMR (250 MHz, TMS) δ (ppm) 1.41 (m, 6H, $2CH_3$), 4.13(d, 2H, OC-CH_2), 4.76 (s, 1H, OC-CH), 11.0 (s, 1H, COOH); MS *m/z*: 147.051 (M^++1), 129.065 (12.23%), 114.068 (22.43 %), 101.068 (31.27 %); HRMS Calcd for $C_6H_{10}O_4$: 146.058; Found: 146.141.

D-Xylitol (20). D-Xylose (**19**) (6.00 g.) was dissolved in methanol (40 mL) and the $NaBH_4$ (1.2 g) was added in small portions after each production of gas had ceased. The temperature of the reaction mixture was allowed to rise to slightly above 50°C. At the end of the additions, the reaction mixture was allowed to stand for an additional 1 h with continuous stirring (TLC (C_6H_6/MeOH, 7:3), Rf = 0.41 was observed). BIO-RAD (Dowex 50WX8) resin was added

slowly until the production of gas ceased. The mixture was filtered and the filtrate was evaporated to dryness to give yellow syrup. The latter was dissolved in methanol and evaporated to remove boric acid in the form of volatile methyl borate. The crude D-xylitol (**20**) (6.0 g, 98%) was a colorless syrup, crystallized by standing and recrystallized from EtOH/H$_2$O   to give crystalline xylitol (**20**) (5.5 g, 90.4%); m.p.100-105 °C   (lit 102 °C). [11]   IR exhibited bands at 2500 cm^{-1} (OH) and 3645 cm^{-1} (OH),1075 cm^{-1} (CH$_2$-OH). ^{1}H NMR (250 MHz, DMSO-d$_6$) δ (ppm) 2.00 (s, 1H, C-OH), 3.37(s, 1H, C-CH), 3.38 (s, 1H, C-CH), 3.68 (d, 2H, C-CH$_2$);MS *m/z*: 153.05 (M$^+$+1), 135.074 (11.75 %),118.06 (22.86 %); HRMS Calcd for C$_5$H$_{12}$O$_5$: 152.05; Found: 152.15

(Tetrahydro-[1,3]dioxino[5,4-*d*][1,3]dioxin-4-yl)-methanol (21). D-Xylitol **20** (5.0 g) was dissolved in a mixture of formaldehyde (37 %, 1 ml) and conc. HCl (1.0 mL) and maintained at 50°C for 2 days. The reaction mixture was cooled to room temperature, extracted with CHCl$_3$ (6 x 5 ml), dried over anhydrous MgSO$_4$, filtered and evaporated to dryness then absorbed on a column of silica gel (eluents, Benzene/MeOH, 8:2). The product **21** was isolated as colourless needles (1.25 g, 26.5%)**,** m.p.124 °C. IR cm^{-1}: 3450 (OH), 1075 cm^{-1} (CH$_2$-OH), 800(C-O-C). ^{1}H NMR (250 MHz, DMSO-d$_6$) δ (ppm) 2.00 (s, 1H, -OH), 3.01 (s, 1H, OC-CH), 3.66 (d, 2H, OC-CH$_2$), 3.93(d, 2H, OC-CH$_2$), 4.20 (s, 1H, OC-CH), 4.47 (s, 1H, OC-CH), 4.70 (d, 2H, OC-CH$_2$).MS *m/z*: 177.07 (M$^+$+1), 159.07(10.17 %), 145.05 (18.18 %); HRMS Calcd for C$_7$H$_{12}$O$_5$: 176.07; Found: 176.17

Tetrahydro-[1,3]dioxino[5,4-*d*][1,3]dioxin-4-carboxylic acid (22). 2,4:3,5-*O*-dimethylene-xylol (**21**) was oxidized with KMnO$_4$ / KOH as described in the oxidation of   (±)-2,3-*O*-isopropylidene glycerol (**2**)   to give 2,4:3,5-*O*-dimethylene xylitolic acid **(22)** as colorless needles (5.5 g, 90.4%);m.p.100-105 °C.IR exhibited bands at 3645 cm^{-1} (OH), 1710 (>COOH), 1075 (CH$_2$-OH).^{1}H NMR (250 MHz, DMSO-d$_6$) δ (ppm) 3.34 (s, 1H, OC-CH), 3.93(d, 2H, OC-CH$_2$), 4.44 (s, 1H, OC-CH), 4.70 (d, 2H, OC-CH$_2$), 4.99 (s, 1H, OC-CH), 11.00(s, 1H, -COOH).MS *m/z*: 191.05 (M$^+$+1), 173.04 (9.43 %), 159.047 (16.75 %),146.065 (23.55 %); HRMS Calcd for C$_7$H$_{10}$O$_6$: 190.05; Found: 190.15

Deprotection of compounds 8, 11, 17, 18, 23, and 24. [14] Small quantities (0.1 g) of each compounds **8, 11, 17, 18, 23**, and **24** were added to ethanol (95%, 5 mL) and heated under reflux for 3 h in the presence of Amberlyst 15 (wet) ion-exchange resin (0.01 g) The reaction mixture, cooled to room temperature, was filtered, and evaporated to dryness to give the products 5-(1,2-Dihydroxy-ethyl)-3*H*-[1,3,4]oxadiazole-2-thione **(12)** (0.08   g) , 1-(5-Mercapto-4*H*-[1,2,4]triazole-3-yl)-ethane-1,2-diol **(13)** (0.07 g), respectively.

5-(1,2-Dihydroxy-ethyl)-3*H*-[1,3,4]oxadiazole-2-thione(12). Recrystallized from EtOAc/Hex to give a colorless needles (0.08 g; 82 %); m.p 165-167 °C; TLC (CHCl$_3$ / MeOH, 6:4), Rf: 0.65; IR cm^{-1}: 3400 (OH), 3250 (N-H), 1676 (C=N), 1304-1251 (C=S), 1157 (C-O-C).^{1}H NMR (250 MHz, DMSO-d$_6$) δ (ppm) 2.01 (d, 2H, 2OH), 3.33(s, 1H, OC-CH), 3.73 (d, 2H, OC-CH$_2$), 7.02 (s, 1H, C-NH). MS *m/z*: 163.017 (M$^+$+1), 145.012 (11.04 %), 128.01 (21.47 %), 100.098 (38.68 %); HRMS Calcd for C$_4$H$_6$N$_2$O$_3$S: 162.01; Found: 162.17.

1-(5-Mercapto-4H-[1,2,4]triazole-3-yl)-ethane-1,2-diol **(13).** Recrystallized from CH$_2$Cl$_2$/Hex to give pink crystals (0.07 g, 82 %); m.p 135-137 °C; TLC (CHCl$_3$ / MeOH, 6:4), Rf: 0.65; IR cm^{-1}: 3300 (OH), 3200 (NH), 2861-2780 (SH), 1672 (C=N).^{1}H NMR (250 MHz, DMSO-d$_6$) δ (ppm) 2.01 (d, 2H, 2OH), 3.00(s, 1H, -SH), 4.01 (d, 2H, OC-CH$_2$), 4.59 (s, 1H, OC-CH). MS m/z: 162.03 (M$^+$+1), 144.012 (11.66 %), 127.01 (22.07 %), 100.00 (38.66 %); HRMS Calcd for C$_4$H$_7$N$_3$O$_2$S: 161.03; Found: 161.18.

5-(1,2-Dihydroxy-ethyl)-3H-[1,3,4]oxadiazole-2-thione **(17a).** Recrystallized from EtOAc/Hex to give colorless needles (0.064 g, 64 %); m.p 165-167 °C; TLC (CHCl$_3$ / MeOH, 6:4), Rf: 0.65; IR cm^{-1}: 3400 (OH), 3250 (N-H), 1676 (C=N), 1304-1251 (C=S), 1157 (C-O-C).^{1}H NMR (250 MHz, DMSO-d$_6$) δ (ppm) 2.01 (d, 2H, 2OH), 3.33(s, 1H, OC-CH), 3.73 (d, 2H, OC-CH$_2$), 7.02 (s, 1H, C-NH). MS m/z: 163.017 (M$^+$+1), 145.012 (11.04 %), 128.01 (21.47 %), 100.098 (38.68 %); HRMS Calcd for C$_4$H$_6$N$_2$O$_3$S: 162.01; Found: 162.17

1-(5-Mercapto-4H-[1,2,4]triazole-3-yl)-ethane-1,2-diol **(18a).** Recrystallized from CH$_2$Cl$_2$/Hex to give pink crystals (0.056 g, 56 %); m.p 135-137 °C; TLC (CHCl$_3$ / MeOH, 6:4), Rf: 0.65; IR cm^{-1}: 3300 (OH), 3200 (NH), 2861-2780 (SH), 1672 (C=N).^{1}H NMR (250 MHz, DMSO-d$_6$) δ (ppm) 2.01 (d, 2H, 2OH), 3.00(s, 1H, -SH), 4.01 (d, 2H, OC-CH$_2$), 4.59 (s, 1H, OC-CH). MS m/z: 162.03 (M$^+$+1), 144.012 (11.66 %), 127.01 (22.07 %), 100.00 (38.66 %); HRMS Calcd for C$_4$H$_7$N$_3$O$_2$S: 161.03; Found: 161.18.

5-(1,2,3,4-Tetrahydroxy-butyl)-3H-[1,3,4]oxadiazole-2-thione **(23a).** Recrystallized from EtOAc/Hex to give white crystals (0.069 g, 69 %) ; m.p 163-165 °C; TLC (CHCl$_3$ / MeOH, 6:4), Rf: 0.65; IR exhibited bands at 3645 cm^{-1} (OH), 3215 (NH), 1075 (CH$_2$-OH).^{1}H NMR (250 MHz, DMSO-d$_6$) δ (ppm) 2.01 (m, 4H, 4OH), 3.30(s, 1H, OC-CH), 3.38 (s, 1H, OC-CH), 3.40 (s, 1H, OC-CH), 3.68 (d, 2H, OC-CH$_2$), 7.01(s, 1H, -NH).MS m/z: 223.03 (M$^+$+1), 205.032 (8.07 %), 191.032 (14.34 %), 160.023 (28.25 %), 99.096 (55.57 %); HRMS Calcd for C$_6$H$_{10}$N$_2$O$_5$S: 222.03; Found: 222.25.

1-(5-Mercapto-4H-[1,2,4]triazole-3-yl)-butane-1,2,3,4-tetraol **(24a).** Recrystallized from CH$_2$Cl$_2$/Hex to give pale yellow crystals (0.058 g, 58 %); m.p 133-136°C; TLC (CHCl$_3$ / MeOH, 6:4), Rf: 0.65; IR cm^{-1}: 3300 (OH), 3200 (NH), 2860-2760 (SH), 1672 (C=N).^{1}H NMR (250 MHz, DMSO-d$_6$) δ (ppm) 2.01 (m, 4H, 4OH), 3.00(s, 1H, C-SH), 3.38 (s, 1H, OC-CH), 3.63(s, 1H, -NH), 3.68 (s, 2H, OC-CH$_2$), 3.76 (s, 1H, OC-CH), 4.58 (s, 1H, OC-CH). MS m/z: 222.03 (M$^+$+1), 204.042 (8.10 %), 157.04 (29.27 %), 170.043 (23.41 %), 100.096 (54.95 %); HRMS Calcd for C$_6$H$_{11}$N$_3$O$_4$S: 221.03; Found: 221.25

Acknowledgements

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