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MILD AND EFFICIENT METHOD TO OBTAIN GLYCOSYL SULFONES OF MERCAPTOTRIAZOLE

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Thioglycosides of mercaptotriazoles in the piranose and furanose series were oxidized to sulfones by a mild and efficient oxidation method, using $KMnO_4/CuSO_4$ in acetonitrile. The structural assignement of the newly synthesized compounds was based on their ^1H, ^{13}C-NMR, I.R. and mass spectra.

INTRODUCTION

Sulfones are an important class of synthetic intermediates, which are, for example, used for C–C bond formation and stereocontrolled functional group transformations.[1–3] In carbohydrate chemistry, glycosyl sulfones have been used for the preparation of functionalized glycals as well as O- and C-glycosides.[4-6] A number of biologically important oligosaccharides having C-glycosyl linkages have been synthesized using glycosyl sulfones under samarium mediated reductive reaction conditions with excellent anomeric stereocontrol.[7-9] Apart from being used as glycosyl donors, glycosyl sulfones have also been used as potential glycosyltransferase inhibitors.[10] The replacement of the naturally occurring *O*-glycosidic linkages by *S*-glycosides is an approach practiced in the synthesis of carbohydrate containing compounds as an avenue to enhance the stability of the glycosidic linkage towards enzymatic hydrolysis whilst retaining vital molecular recognition interactions with biological targets. Starting from this point of vue, Supuran & all recently synthetized a series of thioglycosides, sulfoxides and sulfones of 4-(4-Mercaptomethyl-[1,2,3]triazol-1-yl)-benzenesulfonamide with glucose and galactose as sugar moieties and studied the activity of the new compounds as inhibitors for carbonic anhydrase by reference to the activity of some known drugs such as brinzolamide (BRZ), dorzolamide (DRZ) and acetazolamide (AZA).[11] The glycosides of 5-substituted 3-mercapto 1,2,4-triazols as well as all the triazols and their congeners are little mentioned

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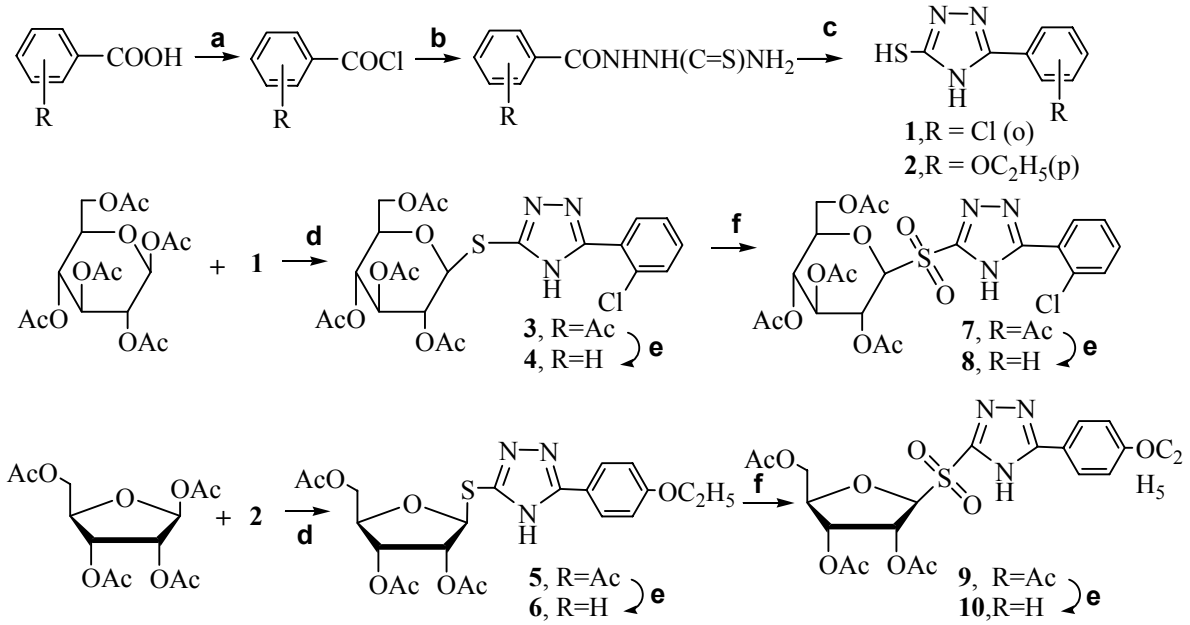
in literature, and the corresponding sulfones are completely unmentioned, providing a strong argument for the study of the synthesis possibilities by simple, efficient and economic methods, in order to test their physiological properties.

RESULTS AND DISCUSSION

A first step in obtaining glucosylsulfones of mercaptotriazols by oxidation of the thioether is the synthesis of the corresponding glycosides. As the mercaptotriazols (**1**) and (**2**) are not commercially available reagents, they were obtained starting from substituted aromatic acids, following the sequence: acid, acid chloride, aroylthiosemicarbazide, 3 mercapto 5(R)-1,2,4 triazol (**Scheme 1**). The procedure and the conditions for separation and puriffication were previously described for similar compounds.[13]



Scheme 1 – The synthesis of 3-mercapto-5-substituted-1,2,4-triazols and their corresponding glycosil sulfones: **a**)SO_2Cl_2/CCl_4, 50°C; **b**) $_2HNNHC(=S)NH_2$,CCl_4,r.t. **c**)EtOH,NaOH (5%),78°C **d**) $BF_3.Et_2O$/DCM,0°C→r.t.**e**)MeOH/Na,r.t. **f**) $CuSO_4/KMnO_4$, CH_3CN,r.t. or m-CPBA/DCM,r.t.

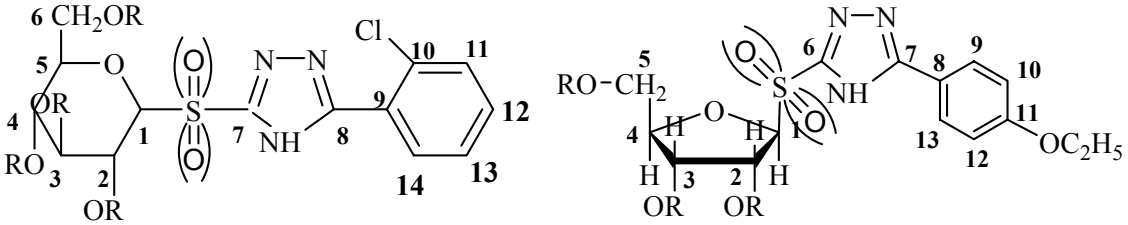
The synthesis of S-glycosides starting from 3-mercapto-1,2,4- or 1,2,3-triazols or their congeners 2-mercapto-1,3,4 oxadiazols or 2-mercapto-1,3,4 thiadiazols is poorly represented in literature, a review from 2006 is presenting an exhaustive summary of the up-to-date literature.[14] Thus 2-thioxo-1,3,4-oxadiazoles and 2-thioxo-1,3,4-thiadiazoles were reacted with tetra-O-acetyl-D-glucopyranosyl bromide in the presence of potassium hydoxide to yield thioglucoside and N-glucosyl derivatives.[15] The coupling of 3-mercapto-5-substituted-1-H-1,2,4-triazole with acetohalosugars in the presence of K_2CO_3 in DMF at room temperature afforded N,S-di-β-glycosides in good yield. On the other hand the regioselective formation of the S-β-thioglycosides was achieved by performing the glycosilation reactions in the presence of triethylamine.[16]

3-Phenyl-1,2,4-triazolin-5-thione was reacted with acetobromglucose or acetobromxylose in the presence of NaOH to give the thioglycopyranoside and thioxylopyranoside respectively.[17] When 5-phenyl-1,3,4-oxa or thiadiazolin-2-thione was coupled with acetobromxylose in the presence of NaOH in acetone, they gave only the S-glycoside derivatives.[17,18] The common feature of these methods is the use of per-O-acylglycosyl halides as glycosilating agents.

The use of peracetylated aldohexoses or aldopentoses as glycosil donors is illustrated in a single reference:[9] glycosilation of 3-mercapto-1,2,4-triazole with 1-O-acetyl-2,3,5-tri-O-benzoyl-D-ribofuranose and respectively 2-acetamido-1,3,4,6-tetra-O-acetyl-D-glucose under Hillbert-Johnson-Bikofer conditions (TMSOTf as promoter) led to the N^1-,N^4-,S- glycosyl and N^1,S-diglycosyl derivatives.

The glycosilation of mercaptotriazols (**1**) and (**2**) was conducted under Ferrier conditions,[20] using freshly distilled $BF_3.Et_2O$ as promoter, in anhydrous dichloromethane, under Argon atmosphere. Pentaacetylglucose and tetraacetylribose respectively (dried at 50 ^{0}C and 7 mm Hg) were used as glycosyl donors. The products obtained are exclusively the β-S-glycosides (**3**) and (**5**) (**Scheme 1**).

The nature of the glycosidic linkage was confirmed by spectral analysis, from the chemical shifts of the C7 carbon atoms in compounds (**3**),(**4**) in the ^{13}C-NMR spectrum. These chemical shifts were centered at the 150-160 ppm regions for the above mentioned carbon atoms. In case the tautomeric form of the mercaptotriazols (thione form) had reacted, N-glycosides would have been obtained and the chemical shift of the same carbon atoms would be placed in the 160-170 ppm range.[21] The geometry of the anomeric centers is β and is assured by the assisting acetate protective groups at C2, both for the pyranose and the furanose forms. The exclusive formation of S-β-glycosides was then investigated by ^{1}H-NMR spectroscopy, being confirmed by the $J_{1,2}$ coupling constants, that are greater than 8Hz for the pyranose forms and respectively less than 4Hz for the furanose forms. The large J values between H_2, H_3, H_4 and H_5 confirm the $^4C_1$ conformation of pyranose ring. The numbering of the carbon atoms in the pyranose and furanose derivatives (used in the NMR spectra description) is presented in the formulae in **Scheme 2.**

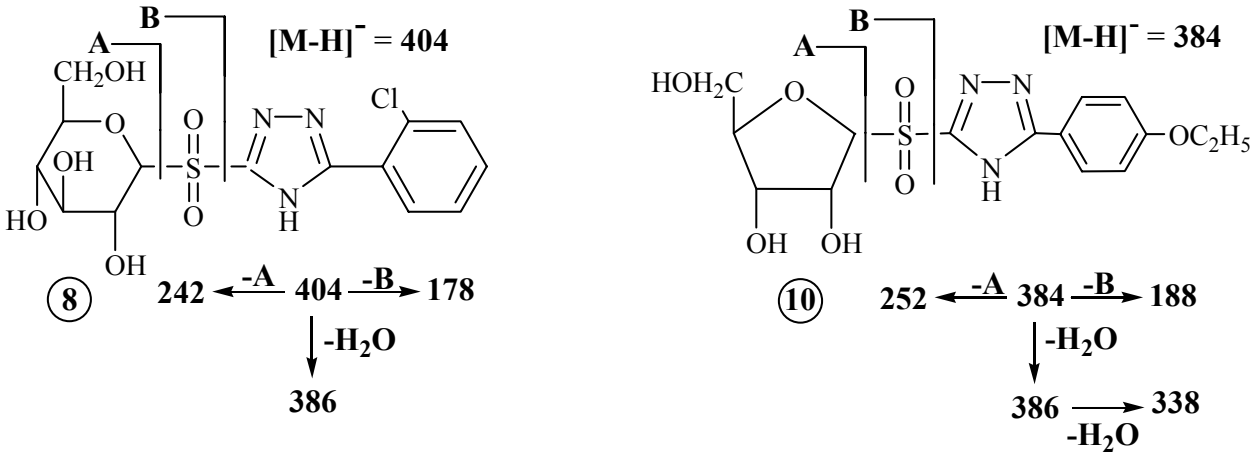


Scheme 2 – The carbon atoms numbering in the pyranose and furanose derivatives used in NMR description.

Due to the importance of sulfones, a number of oxidizing agents for the sulfur atom were tried over time, including metachloroperoxybenzoic acid (m-CPBA),[22] tert-butyl hydroperoxide or H_2O_2 in the presence of complexes $CpMo(CO)_3Cl$, $CpMoO_2Cl$,[23] dioxiranes,[24] 30% hydrogen peroxide and tantalum(V) chloride as catalyst,[25] tetra-n-butylammonium oxone,[26] osmium tetraoxide (OsO_4),[27] $PhIO/RuCl_2$-(PPh_3),[28] $RuCl_3/NaIO_4$, or HIO_4[29] and $HOF.CH_3CN$.[30] Though many methods are available for the oxidation of sulfides to sulfones, they were less investigated for the preparation of glycosilsulfones. For this purpose, the agents mentioned in literature include: metachloroperoxybenzoic acid (m-CPBA), magnesium bis(monoperoxyphthalate) (MMPP),[31] dimethyldioxirane (DMDO),[32] $KMnO_4$/acetic acid,[15] and $RuCl_3/NaIO_4$.[5] The most often cited method for oxidating thioglycosides to thiosulfones is the one using $NaIO_4$ and catalytic amounts of $RuCl_3$. Unfortunately this method is unappropriate for the oxidation of S-glycosil mercaptotriazoles, due to the coordination of the Ruthenium to the Nitrogen atom from the triazole ring. The oxidation of the thioglycosides to sulfones was achieved successfully using m-CPBA as oxidizing agent, but this also presents some downsides like the partial solubility of m-CPBA in dichloromethane and the difficulty to remove secondary products (m-chlorobenzoic acid) form the reaction mixture. The efficiency of the oxidation depends on the number of oxidizing agent equivalents used in the reaction, in general 5-8 eq ensure the complete transformation of the starting material.[22] Sulfoxides are formed as intermediates (as a mixture of diastereoisomers) and they are observed in TLC inspection (Kiesselgel F_{254}) at lower Rf values than the corresponding sulfones (eluent is presented in experimental part). The coexistence of sulfoxides and sulfones after the total consumption of the starting material at TLC inspection is an indication of the quality of m-CPBA used. This compound decomposes in time, even if kept at low temperatures. Good results were obtained if the commercially available m-CPBA (10 eq, ALDRICH) was solved in 10-15 mL $CHCl_3$, then repeatedly washed with a 10% aqueous solution of $NaHCO_3$, in order to remove the metachlorobenzoic acid. The chloroformic solution containing only m-CPBA is then washed with water, dried over Na_2SO_4, filtered and concentrated to half the initial volume. The solution obtained is then engaged in the reaction. Obtaining glycosilsulfones using $KMnO_4/CuSO_4$ mixture (1.5:1, as molar ratio) in CH_3CH/H_2O as oxidizing agent, under conditions that do not affect

protective groups such as acetate, benzyl or benzylidene, was only recently reported.[33] Modifying this method for S-glycosides of mercaptotriazoles showed that the use of 3eq oxidizing agent compared to the starting sulfide should complete the reaction in 24 h. As compared to the m-CPBA method, the subsequent workover of the reaction mixture is more facile, avoiding the use of chlorinated solvents, reducing agents and repeated crystallizations for the purification of the products. Other methods for the oxidation of thioglycosides also present many major downsides, like strongly acidic reaction conditions, or the use of high temperatures.

The synthesized sulfones were investigated in I.R., emphasizing the bands corresponding to the sulfur-oxygene bond valence vibrations, both symmetrical 1154 cm^{-1} (for compound **7**) and 1158 cm^{-1} (for compound **9**), and asymmetrical 1375 cm^{-1} (for **7** and **9**). MS^2 spectra for compounds **8** and **10** were performed in negative ion mode and present the characteristic fragmentation for sulfones,[34] thus confirming, along with the NMR, the structures of the obtained compounds, **Scheme 3.**



Scheme 3 – Diagnosis fragments resulting from MS^2 spectra of compounds **8** and **10.**

Hydrolisis of the compounds **3**, **5**, **7**, **9**, was performed under Zemplen conditions,[35] and the control of total deprotection was performed by inspection of IR spectra of the isolated and purified **4**, **6**, **8**, **10**. The absence of the valence vibration of the carbonyl group at 1760-1780 cm^{-1}, corroborated with the presence of a broad band at 3400-3600 cm^{-1} are sufficient evidence for probing the completion of the deprotection reaction. All S-glycosides and their corresponding sulfones are characterized by melting point, mass spectrometry and ^{1}H-NMR and ^{13}C-NMR. For the assignment of the chemical shifts of compound **8**, the **NMR** measurements were performed at 90 ^{o}C (363K).

EXPERIMENTAL

Analysis

The proton spectra were recorded on a Varian Gemini 300MHz or Inova 400 MHz spectrometers. Mass spectrometry was performed on a High Capacity Ion Trap (HCIT) Ultra PTM mass spectrometer (Bruker Daltonik, Bremen, Germany). The HCT mass spectrometer is interfaced to a PC running the Compass integrated software package under WindowsXP, which includes EsquireControl and Hystar modules for instrument tuning, control and spectrum acquisition, and DataAnalysis software for storing the ion chromatograms and processing the MS data. The samples were infused into MS by online syringe pump electrospray at a constant flow rate of 250 μL/h. Nitrogen at a flow rate of 5 L/min was employed at 250 °C for desolvation and as a nebulizer gas at 7 p.s.i. The instrument was set to operate in the negative or positive ion mode under 3.0 kV ESI potential. For MS analysis the sample was dissolved to a concentration of about 5 pmol/μL, in MeOH/H_2O (1:1 v/v). The UV spectra were recorded on a CECIL CE7200 spectrophotometer. The infrared spectra were recorded using JASCO-FT/IR-4200 apparatus (single beam) in KBr pallets. Melting points were recorded on a Boetius apparatus S30A/G (Nagema).

Reagents and materials

4-Ethoxybenzoic acid, thiosemicarbazide, sodium hydroxide, potassium permanganate, copper (II) sulfate pentahydrate, glucose, 1,2,3,5-Tetra-O-acetyl-β-D-ribofuranose, 3-chloroperoxybenzoic acid (77%), acetic anhydride, sodium acetate and acetonitrile were puchased from Aldrich. Boron trifloride-diethyl ether complex aquired from Merck Suchardt OHG.Amberlite IR-120 (16-45 mesh) was purchased from Fluka Chemie GmbH. Methanol, toluene, methylene chloride and chloroform were furnished by Chimopar (Romania). 1,2,3,4,6-penta-O-acetyl-β-D-glucopyranose was synthesized from glucose and acetic anhydride according to literature.[12]

The thin layer chromatography (TLC) was performed on Kieselgel (Merck, Darmstadt) F_{254} aluminium sheets. The separation of intermediates and products was done by flash

chromatography, using silicagel 230-400 mesh (Aldrich). For reaction monitoring the chromatograms were developed with a solution of H_2SO_4 20% in EtOH and heating the plate at 120 ^oC for 1 min. For flash chromatographic (FC) separation the plates were developed with a prepared solution (2.1 g ammonium molibdate, 0.1 g cerium (II) sulphate, 3.1 mL conc. sulphuric acid, 47 mL water).The methylene chloride was distilled over P_2O_5 under argon atmosphere and the Lewis acid ($BF_3.Et_2O$) used in the glycosilation reactions was freshly distilled before use.

Procedures

General procedure for the glycosilation reaction:

To a cooled (0 ^oC) solution of 1.5 mmol 3-mercapto-5-substituted-1,2,4-triazole and 1 mmol of fully acetylated sugar in methylene chloride (10 mL), 0.63 ml of boron trifloride ethyl ether complex (5 mmol) is added dropwise during 1 hour under argon. The reaction mixture is slowly left to reach room temperature. When TLC control indicated the complete consumption of the acetylated sugar, the reaction mixture is again cooled to 0 ^0C (ice bath) and 3 mL of triethylamine is added dropwise under strong stirring. The reaction mixture is diluted to 50 mL with DCM, washed with 20% $NaHCO_3$ solution, and the organic layer is repeatedly washed with water. After separation, the organic layer is dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product is isolated from crude by FC.

General procedure for the oxidation reaction:

To a solution of thioglycoside (1.0 mmol) in CH_3CN/H_2O (6:1 v/v; 10 mL), 1g of oxidizing agent as fine powder ($KMnO_4$:$CuSO_4.5H_2O$=1.5:1) is added. The reaction mixture is stirred at room temperature until TLC control indicates the disappearance of the starting material. The reaction mixture is concentrated under reduced pressure and the crude mass is repeatedly extracted with chloroform. The organic layer is concentrated under reduced pressure to furnish an almost pure product. Analytical samples are prepared by FC.

General procedure for the deacetylation reaction:

To a stirred solution of acetylated compound (1 mmol) in dry MeOH (10 mL), 50 mg metallic sodium is added. After TLC control indicates the complete deprotection of the starting material, the reaction mixture is acidified (pH~6-7) with Amberlite H^+ IR 120 resin. After filtering the resin, the solvent is evaporated under reduced pressure and the residue is purified by FC.

(1) ***3-mercapto-5(o-chloro-phenyl)-1,2,4-triazole:*** (white cryst. H_2O); Yield(overall) = 60%; **M.p.**(^oC) = 198-199; **U.V.**(λ_{max}(nm),$\varepsilon_{max,}$MeOH): 252.95(14819); **I.R.**(cm^{-1})**:** 560, 696, 734, 752, 970, 1050, 1084, 1102, 1236, 1256, 1264, 1434, 1482, 1508, 1568, 1588, 1604, 2904, 2980, 3012; **(+)ESI-HCIT-MS,** $[M+H]^+$ = 212**,** $[M+Na]^+$ = 234, $[M+K]^+$ = 250

(2) ***3-mercapto-5-p-ethoxy-phenyl-1,2,4-triazole*** (white cryst. H_2O); Yield(overall) = 64%; **M.p.**(^oC) = 225-227; **U.V.**(λ_{max}(nm),$\varepsilon_{max,}$MeOH): 260.08(14348); **I.R.**(cm^{-1})**:** 622, 760, 866, 1078, 1176, 1204, 1282, 1312, 1326, 1436, 1462, 1502, 1616, 2936, 3412; **(+)ESI-HCIT-MS,** $[M+Na]^+$ = 244.3

(3) ***S-(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosyl)-3-mercapto-5(o-chloro-phenyl)-1,2,4-triazole*****;** (white cryst. MeOH); Yield = 73%; R_f = 0.42 (Tol:AcOEt = 1:1); FC(SiO_2) Tol:AcOEt = 1.2:1; **M.p.**(^oC) = 118-120; **(+)ESI-HCIT-MS:** $[M+H]^+$ = 541**,** $[M+Na]^+$ = 564, $[M+K]^+$ = 580

^{1}H-NMR (300MHz, $CDCl_3$, δ(ppm), J(Hz)); ^{13}C-NMR (75MHz, $CDCl_3$, δ(ppm)) see reference [20]

(4) ***S-(β-D-glucopyranosyl)-3-mercapto-5(o-chloro-phenyl)-1,2,4-triazole*****;** (white cryst. MeOH); Yield = 92%; R_f = 0.56 (AcOEt:MeOH = 4:1); FC(SiO_2) AcOEt :MeOH = 8.5:1.5; **M.p.**(^oC) = 200-202;

(+)ESI-HCIT-MS: $[M+H]^+$ = 406**,** $[M+Na]^+$ = 428, $[M+K]^+$ = 444

^{1}H-NMR (300 MHz, DMSO-d^6, δ(ppm), J(Hz)): 7.81 (dd, 1H, $J_{11,12}$=6.3, $J_{11,13}$=2.6; **H_{11}**); 7.60 (dd, 1H, $J_{14,13}$=7.3, $J_{14,12}$=2.1; **H_{14}**); 7.48 (m, 2H, **H_{12}**, **H_{13}**); 5.11 (d, 1H, $J_{1,2}$=9.5; **H_1**); 3.63 (dd, 1H, $J_{6a,6b}$=12.1, J_{6a5}=1.0; **H_{6a}**); 3.46 (dd, 1H, $J_{6b,6a}$ =12.1, $J_{6b,5}$=5.0; **H_{6b}**); 3.28-3.16 (m, 3H, **H_3**, **H_4**, **H_5**); 3.16 (dd, 1H, $J_{2,1}$=9.5, $J_{2,3}$=8.7; **H_2**).

^{13}C-NMR (DMSO-d^6, 75 MHz, δ(ppm)): 157.45 (1C, **C_7** or **C_8**); 153.21 (1C, **C_8** or **C_7**); 131.50 (1C, **C_{10}**); 131.33; 131.04; 130.44; 127.34 (4C, **C_{11}**, **C_{12}**, **C_{13}**, **C_{14}**); 128.49 (1C, **C_9**); 85.50 (1C, **C_1**); 81.22; 78.88; 69.55 (3C, **C_3**, **C_4**, **C_5**); 72.80 (1C, **C_2**); 60.71 (1C, **C_6**).

(7) ***(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosyl)-5(o-chloro-phenyl)-1,2,4-triazole sulfone*** (white cryst. MeOH); Yield = 95%; R_f = 0.30 (Tol:AcOEt = 1:1); FC(SiO_2) Tol:AcOEt = 1:1**, M.p. (^oC)** = 198-200;

(+)ESI-HCIT-MS: $[M+H]^+$ = 574.50

^{1}H-NMR (400 MHz, $CDCl_3$, δ(ppm), J(Hz)): 8.35 (bs, 1H, **H_{13}**); 7.45-8.6 (3m, 3H, **H_{10}**, **H_{11}**, **H_{12}**); 5.78 (dd, 1H, $J_{2,1}$=$J_{2,3}$=9.0; **H_2**); 5.38 (dd, 1H, $J_{3,2}$=$J_{3,4}$=9.0; **H_3**); 5.05 (dd, 1H, $J_{4,3}$= $J_{4,5}$ =9.0; **H_4**); 4.97 (d, 1H, $J_{1,2}$=9.0; **H_1**); 4.12-4.04 (m, 2H, **H_{6a}, H_{6b}**); 3.82 (bs, 1H, **H_5**); 2.08, 2.02, 2.00, 1.85 (4s, 12H, 4xCH_3CO)

^{13}C-NMR (100 MHz, $CDCl_3$, δ(ppm)): 170.47; 170.30; 169.23; 169.19 (4C, 4xCH_3CO); 158.90 (1C, **C_7** or **C_8**); 154.97 (1C, **C_8** or **C_7**); 132.64; 132.18; 131.51; 127.96 (4C, **C_{13}-C_{10}**); 88.35 (1C, **C_1**); 76.57 (1C, **C_5**); 73.51 (1C, **C_3**); 67.44 (1C,**C_4**); 66.71 (1C, **C_2**); 61.51 (1C, **C_6**); 20.62; 20.59; 20.51; 20.39 (4C,4xCH_3CO)

(8) ***(β-D-glucopyranosyl)-5-(o-chloro-phenyl)-1,2,4-triazole sulfone*** (white cryst. MeOH); Yield = 85%; R_f = 0.10 (Tol:AcOEt = 1:1); FC(SiO_2) AcOEt:MeOH = 4:1; **M.p.**(^oC) = 118-120 **(-)ESI-HCIT-MS:** $[M-H]^-$ = 404.0

^{1}H-NMR (300 MHz, DMSO-d^6, δ(ppm), J(Hz); T=363^{o}K): 7.78 (d, 1H, **H_{13}**); 7.66-7.43 (m, 3H, **H_{10}-H_{12}**); 4.68 (m, 3H, $J_{1,2}$=9.3; **H_1**); 3.73(d, 1H, $J_{2,1}$=$J_{2,3}$= 9.3; **H_2**); 3.58 (dd, 1H, $J_{6a,5}$=2.4; $J_{6a,6b}$=11.6; **H_{6a}**); 3.42 (dd, 1H, $J_{6b,5}$=2.4; $J_{6b,6a}$=11.6;**H_{6b}**); 3.36 (dd, 1H, $J_{3,4}$=$J_{3,2}$=9.3;**H_3**); 3.28 (dddd,1H,1H, $J_{5,6a}$=2.4, $J_{5,6b}$=5.5, $J_{5,4}$=10.0;**H_5**); 3.16 (dd, 1H, $J_{4,5}$=10.0 $J_{4,3}$= 9.3;**H_4**)

^{13}C-NMR (75 MHz, DMSO-d^6, δ(ppm), T=363^{o}K): 131.41;130.40; 130.36; 127.0 (4C, **C_{10}-C_{13}**); 91.23 (1C, **C_1**); 81.77 (1C, **C_5**); 77.53 (1C, **C_3**); 69.51 (1C, **C_4**); 69.13 (1C, **C_2**); 61.51 (1C, **C_6**)

(5) ***S-(2',3',5'-tri-O-acetyl-β-D-ribofuranosyl)-3-mercapto-5-p-ethoxy-phenyl-1,2,4-triazole;*** (white cryst. EtOH); Yield = 73%; R_f = 0.34 (Tol:AcOEt = 1:1.1); FC(SiO_2) AcOEt:MeOH = 1:1; **M.p.(^oC)** = 92-94; **(+)ESI-HCIT-MS:** $[M+H]^+$ = 480.0

^{1}H-NMR (300MHz, $CDCl_3$, δ(ppm), J(Hz)): 11.8 (bs, 1H, **H**N); 7.91 (d, 2H, $J_{9,10}$ =$J_{13,12}$=8.1; H_9, **H_{13}**); 6.94 (d, 2H, $J_{10,9}$ =$J_{12,13}$=8.1; **H_{10}**, **H_{12}**); 5.75 (d, 1H, $J_{1,2}$=4.0; **H_1**); 5.53 (dd, 1H ,$J_{2,1}$=4.0,$J_{2,3}$=5.7;**H_2**); 5.43 (dd, 1H, $J_{3,2}$=$J_{3,4}$=5.7; **H_3**); 4.39 (m, 2H, **H_4**, **H_{5a}**); 4.22 (m, 1H, **H_{5b}**); 4.07 (q, 2H, O**CH_2**CH_3); 2.12; 2.11; 2.09 (3s, 3H, CO**CH_3**); 1.43 (t, 3H, OCH_2**CH_3**);

^{13}C-NMR (75MHz, $CDCl_3$, δ(ppm)): 171.09, 169.57 (3C, 3x**CO**CH_3); 160.61 (1C, **C_{11}**); 127.97 (2C, **C_9, C_{13}**); 120.71 (1C, **C_8**); 114.71 (2C, **C_{10}, C_{12}**); 86.58 (1C, **C_1**); 80.69 (1C, **C_4**); 74.63 (1C, **C_2**); 71.01 (1C, **C_3**); 63.59 (1C, O**CH_2**CH_3); 63.10 (1C, **C_5**); 20.93; 20.54 (3C, 3xCO**C**H_3); 14.76 (1C, O**CH_2CH_3**)

(6) ***S-β-D-(ribofuranosyl)-3-mercapto-5-p-ethoxy-phenyl-1,2,4-triazole)****; (*white cryst. $CHCl_3$); Yield = 87%; R_f = 0.54 (AcOEt:MeOH = 5:1); FC(SiO_2):AcOEt; **M.p.(^oC)** = 74-76; **(+)ESI-HCIT-MS:** $[M+H]^+$ = 354.2

^{1}H-NMR (300MHz, DMSO-d$_6$, δ(ppm), J(Hz), T=298^{o}K): 7.90 (d, 2H, $J_{9,10}$ =$J_{13,12}$=8.4; **H_9**, **H_{13}**); 7.05 (d, 2H, $J_{10,9}$ =$J_{12,13}$ =8.4;**H_{10}**, **H_{12}**); 5.59 (d, 1H, $J_{1,2}$=4.5;**H_1**); 4.09 (m, 3H, H_2, O**H_2**CH_3); 3.99-3.83 (m, 2H, **H_3**, **H_4**); 3.49 (m, 2H, **H_{5a}**, **H_{5b}**); 1.35 (t, 3H, OCH_2C**H_3**);

^{13}C-NMR (75MHz, DMSO-d$_6$, δ(ppm)): 159.97 (1C, **C_{11}**); 127.66 (1C, **C_{13}, C_9**); 120.46 (1C, **C_8**); 114.87 (2C, **C_{10}**, **C_{12}**); 88.87 (1C, **C_1**); 85.37 (1C, **C_4**); 75.44 (1C, **C_2**); 70.63 (1C, **C_3**); 3.36 (1C, O**C**H_2CH_3); 61.79 (1C, **C_5**); 14.64 (1C, OCH_2**C**H_3).

(9) ***(2',3',5'-tri-O-acetyl-S-β-D-ribofuranosyl) 5-p-ethoxy-phenyl-1,2,4-triazole sulfone,*** (white cryst. MeOH); Yield = 85%; R_f = 0.30 (Tol: AcOEt = 1:1.1); FC(SiO_2): Tol: AcOEt = 1:1; **M.p**.(^{o}C) = 126-128; **(+)ESI-HCIT-MS:** $[M+H]^+$ = 511, $[M+Na]^+$ = 534, $[M+K]^+$ = 550

^{1}H-NMR (400 MHz, CDCl$_3$, δ(ppm), J(Hz)): 7.92 (d, 2H, $J_{9,10}$=8.2, **H_9**, **H_{13}**); 6.94 (d, 2H, $J_{10,9}$=8.2; **H_{10}**, **H_{12}**); 6.03 (d, 1H,$J_{1,2}$=5.5; **H_1**); 5.50 (dd, 1H, J_{21}=$J_{2,3}$=5.5;**H_2**); 4.52-4.41 (m, 2H, **H_4**, **H_3**); 4.20-4.00 (m, 4H, **H_{5a}**, **H_{5b}**, O**H_2**CH_3); 2.11-2.00 (3s, 9H , 3x COC**H_3**); 1.42 (t, 3H, OCH_2C**H_3**)

^{13}C-NMR (100 MHz, CDCl$_3$, δ=ppm): 170.03; 169.48; 169.16 (3C, 3x **C**OCH_3); 161.63 (1C, **C_6**); 156.13 (1C, **C_7**); 128.67 (2C, **C_{10}**, **C_{12}**); 115.07 (2C, **C_9**, **C_{13}**); 81.52 (1C, **C_3**); 71.16 (1C, **C_2**); 70.44 (1C, **C_1**); 63.75 (1C, **C_5**); 62.38 (2C, **C_4**, O**C**H_2CH_3); 20.91; 20.44; 20.39 (3C, 3x **C**H_3CO)

(10) ***(2',3',5'-tri-O-acetyl-S-β-D-ribofuranosyl) 5-p-ethoxy-phenyl-1,2,4-triazole sulfone;*** (white cryst. H_2O); Yield = 88%; R_f = 0.30 (AcOEt); FC(SiO_2): AcOEt; **M.p.**(^{o}C) = 98; **(+)ESI-HCIT-MS:** $[M+H]^+$ = 385, $[M+Na]^+$ = 408, $[M+K]^+$ = 424

^{1}H–NMR (400 MHz, DMSO- d^6, δ(ppm), J(Hz)): 7.98 (d, 2H, $J_{9,10}$=8.9; **H_9**, **H_{13}**); 7.11 (d, 2H, $J_{10,9}$=8.9, **H_{10}**, **H_{12}**); 5.04 (d, 1H, $J_{1,2}$=2.8; **H_1**); 4.50 (dd, 1H, $J_{2,1}$=2,8; $J_{2,3}$=4.9; **H_2**); 4.11 (q, 2H, O**C**H_2CH_3); 3.92-3.88 (m, 1H, **H_4**); 3.80 (dd, 1H, $J_{3,2}$=4.9, $J_{3,4}$=6.5; **H_3**); 3.43 (dd, 1H, $J_{5a,5\ b}$=11.8; $J_{5a,4}$=4.0; **H_{5a}**); 3.37 (dd, 1H, $J_{5b,5a}$=11.9; $J_{5b,4}$=6.4; **H_{5b}**); 1.35 (t, 3H, OCH_2C**H_3**)

^{13}C-NMR (100 MHz, DMSO-d^6, δ(ppm)): 166.07 (1C, **C_6**); 160.80 (1C, **C_7**); 128.83 (2C, **C_{10}**, **C_{12}**); 115.13 (2C, **C_9**, **C_{13}**); 97.27 (1C, **C_1**); 86.05 (1C, **C_4**); 71.39 (1C, **C_3**); 70.59 (1C, **C_2**); 63.40 (1C, O**C**H_2CH_3); 61.85 (1C, **C_5**); 14.61 (1C, OCH_2**C**H_3).

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