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Synthesis and evaluation of antitubercular activity of glycosyl thio- and sulfonyl acetamide derivatives ☆

Samir Ghosh [a], Pallavi Tiwari [a], Shashi Pandey [a], Anup Kumar Misra [a,*], Vinita Chaturvedi [b], Anil Gaikwad [b], Shalini Bhatnagar [b], Sudhir Sinha [b]

[a] Medicinal and Process Chemistry Division, Central Drug Research Institute, Chattar Manzil Palace, Lucknow 226001, UP, India
[b] Drug Target Discovery and Development Division, Central Drug Research Institute, Lucknow 226001, India

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ABSTRACT

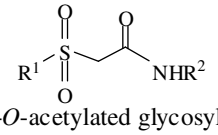
A series of glycosyl thioacetamide and glycosyl sulfonyl acetamide derivatives have been prepared following a convenient reaction protocol and evaluated for their antitubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$. Amongst 32 compounds evaluated **3** compounds were effective in inhibiting mycobacterial growth at MIC of 6.25 μg/mL, **6** compounds at MIC of 3.125 μg/mL and **1** compound at MIC of 1.56 μg/mL. All active compounds were found nontoxic in Vero cell lines and mice bone marrow macrophages.

Mycobacterium tuberculosis, the causative agent of tuberculosis (TB), continues to be the greatest single infectious cause of mortality worldwide, killing roughly two million people annually (one person dies every 10 s).[2] The World Health Organization (WHO) has estimated that one-third of the world's population is infected with Mycobacterium tuberculosis.[3] TB is a leading cause of death amongst people who are HIV-positive (13% of AIDS deaths worldwide).[4] The synergy between tuberculosis and the AIDS epidemic as well as the surge of multidrug-resistant isolates of *M. tuberculosis* has reaffirmed tuberculosis as a primary public health threat.

Although in the recent past, no remarkable breakthrough has been achieved in the discovery of an efficient drug to encounter the TB, quest for the development of better, cheaper and faster drugs continues. In the present context new drugs to treat TB are urgently required, specifically for their use in a shorter treatment regimen and to treat multidrug-resistant and latent disease. Developments of chemotherapeutics that specifically target dormant bacilli and hence provide more effective treatment of latent TB infections are also in great needs.

One of the important strategies for the designing of effective antitubercular agents is to develop inhibitors of Mycobacterial cell-wall biosynthesis. The cell-wall of *Mycobacteria* consist of a wide array of complex fatty acids, such as mycocerosic acid and mycolic acid,[5,6] arabinogalactans and peptidoglycans[7] Earlier, several reports have appeared for the development of inhibitors of fatty acid biosynthesis as antitubercular agents.[8] A number of reports are also available in the literature for the development of carbohydrate-based inhibitors of cell-wall biosynthesis.[9] We have noticed a report from Townsend et al.[10] describing a series of alkyl sulfonyl acetamide derivatives as new class of antitubercular agents. It has been demonstrated that sulfonyl acetamide derivatives can act as inhibitors of the cell-wall biosynthesis by mimicking the transition state of the β-ketoacyl synthase (KAS) catalyzed Claisen reaction step of fatty acid biosynthesis.

Taking the clue from Townsend et al.,[10] we envisioned that designing of per-*O*-acetylated glycosyl sulfonyl acetamide derivatives could be useful in search of antitubercular agents as sulfonyl acetamide region could act as KAS inhibitor and per-*O*-acetylated sugar moiety could serve as a carrier as well as lipophilic tag for the successful inhibition of cell-wall biosynthesis. Besides this, sugar backbone present in the molecules could provide a recognition site as the cell-wall is composed of carbohydrate structures. We re-



R^1 = Per-*O*-acetylated glycosyl; R^2 = H, Alkyl

Figure 1. Proposed inhibitors of cell-wall biosynthesis in *Mycobacteria*.[10]

☆ See Ref. 1.

* Corresponding author. Tel.: +91 522 2612411; fax: +91 522 2623405.
E-mail address: akmisra69@rediffmail.com (A.K. Misra).

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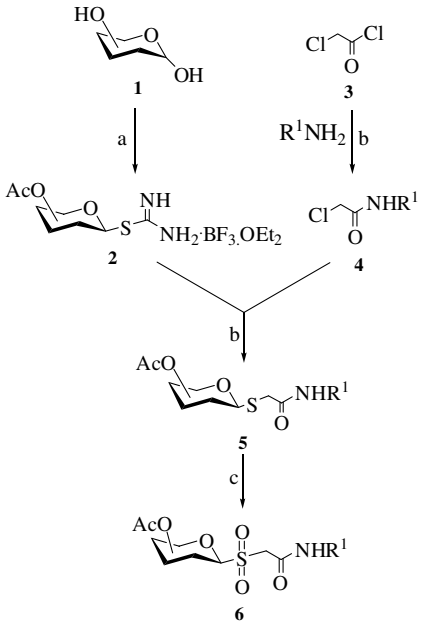

Scheme 1. Reagents and conditions: (a) i—acetic anhydride, $BF_3{\cdot}OEt_2$, rt, 20 min; ii—thiourea, CH_3CN, 70 °C; (b) Et_3N, CH_3CN, rt; (c) *m*-CPBA, CH_2Cl_2, rt.

port herein the synthesis and evaluation of a series of per-*O*-acetylated glycosyl thioacetamide and sulfonyl acetamide derivatives as antitubercular agents. Evaluation of the glycosyl sulfonyl acetamide derivatives has been excluded considering the fact that ionic compounds have poor permeability through the mycobacterial cell-wall (Fig. 1).

A series of glycosyl thioacetamide and glycosyl sulfonyl acetamide derivatives have been prepared and evaluated for their antitubercular activity against *M. tuberculosis* $H_{37}Rv$ strain. A series of per-*O*-acetylated *S*-glycosyl isothiouronium salts (**2**) have been prepared directly from the corresponding free sugars (**1**) in one-pot on treatment with acetic anhydride and boron trifluoride diethyletherate followed by treatment with thiourea at elevated temperature.[11] Treatment of chloroacetamides (**4**)[12] with *S*-isothiouronium salts **2** in the presence of triethylamine furnished glycosyl thioacetamide derivatives (**5a–p**) in satisfactory yields (Scheme 1, Table 1).[13] These glycosyl thioacetamide derivatives were oxidized using *m*-CPBA[14] to furnish glycosyl sulfonyl acetamide derivatives (**6a–p**) in excellent yields (Scheme 1, Table 2).[15]

The glycosyl thioacetamide derivatives (**5a–p**) and glycosyl sulphony lacetamide derivatives (**6a–p**) were evaluated against *M. tuberculosis* $H_{37}Rv$ strains in vitro using the standard Microdilution on Agar Method.[16] The activities of the compounds were evaluated in terms of minimum inhibitory concentrations (MIC; μg/mL). Amongst 32 compounds evaluated, compound **5b** showed MIC

Table 1
Synthesis of glycosyl thioacetamide derivatives (**5a–p**)

Entry	Sugar	R^1–S–CH$_2$–C(=O)–NHR^2	Time (min)[a]	Yield (%)
1	D-Glucose	R^1 = 2,3,4,6-tetra-*O*-acetyl-.β-D-glucopyranosyl; R^2 = H (**5a**)	25	87
2	D-Galactose	R^1 = 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl; R^2 = H (**5b**)	30	85
3	D-Mannose	R^1 = 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl; R^2 = H (**5c**)	30	85
4	D-Ribose	R^1 = 2,3,4-tri-*O*-acetyl-β-D-ribopyranosyl; R^2 = H (**5d**)	30	78
5	D-Xylose	R^1 = 2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl; R^2 = H (**5e**)	30	80
6	D-Arabinose	R^1 = 2,3,4-tri-*O*-acetyl-β-D-arabinopyranosyl; R^2 = H (**5f**)	20	82
7	D-Lactose	R^1 = (2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-(1 → 4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl; R^2 = H (**5g**)	60	90
8	D-Cellobiose	R^1 = (2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-(1 → 4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl; R^2 = H (**5h**)	60	80
9	D-Maltose	R^1 = (2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-(1 → 4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl; R^2 = H (**5i**)	60	82
10	D-Glucose	R^1 = 2,3,4,6-tetra-*O*-acetyl-.β-D-glucopyranosyl; R^2 = C_8H_{17} (**5j**)	30	85
11	D-Arabinose	R^1 = 2,3,4-tri-*O*-acetyl-β-D-arabinopyranosyl; R^2 = C_8H_{17} (**5k**)	25	83
12	D-Lactose	R^1 = (2,3,4,6-tetra-*O*-acetyl-.β-D-galactopyranosyl)-(1 → 4)-2,3,6-tri-*O*-acetyl-.β-D-glucopyranosyl; R^2 = C_8H_{17} (**5l**)	40	87
13	D-Glucose	R^1 = 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl; R^2 = $C_{12}H_{25}$ (**5m**)	25	86
14	D-Arabinose	R^1 = 2,3,4-tri-*O*-acetyl-β-D-arabinopyranosyl; R^2 = $C_{12}H_{25}$ (**5n**)	20	80
15	D-Lactose	R^1 = (2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-(1 → 4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl; R^2 = $C_{12}H_{25}$ (**5o**)	35	88
16	D-Glucose	R^1 = 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl; R^2 = CH_2Ph (**5p**)	30	90

[a] Time taken after formation of *S*-isothiouronium salts.

Table 2
Synthesis of glycosyl sulfonyl acetamide derivatives (**6a–p**)

Entry	Substrates	R^1–S(=O)$_2$–CH$_2$–C(=O)–NHR^2	Time (min)	Yield (%)
1	**5a**	R^1 = 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl; R^2 = H (**6a**)	60	90
2	**5b**	R^1 = 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl; R^2 = H (**6b**)	60	92
3	**5c**	R^1 = 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosyl; R^2 = H (**6c**)	60	87
4	**5d**	R^1 = 2,3,4-tri-*O*-acetyl-β-D-ribopyranosyl; R^2 = H (**6d**)	60	82
5	**5e**	R^1 = 2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl; R^2 = H (**6e**)	60	85
6	**5f**	R^1 = 2,3,4-tri-*O*-acetyl-β-D-arabinopyranosyl; R^2 = H (**6f**)	45	86
7	**5g**	R^1 = (2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-(1 → 4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl; R^2 = H (**6g**)	90	90
8	**5h**	R^1 = (2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-(1 → 4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl; R^2 = H (**6h**)	90	88
9	**5i**	R^1 = (2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-(1 → 4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl; R^2 = H (**6i**)	90	85
10	**5j**	R^1 = 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl; R^2 = C_8H_{17} (**6j**)	60	92
11	**5k**	R^1 = 2,3,4-tri-*O*-acetyl-β-D-arabinopyranosyl; R^2 = C_8H_{17} (**6k**)	50	88
12	**5l**	R^1 = (2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-(1 → 4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl; R^2 = C_8H_{17} (**6l**)	90	94
13	**5m**	R^1 = 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl; R^2 = $C_{12}H_{25}$ (**6m**)	60	93
14	**5n**	R^1 = 2,3,4-tri-*O*-acetyl-β-D-arabinopyranosyl; R^2 = $C_{12}H_{25}$ (**6n**)	50	89
15	**5o**	R^1 = (2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-(1 → 4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranosyl; R^2 = $C_{12}H_{25}$ (**6o**)	120	95
16	**5p**	R^1 = 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl; R^2 = CH_2Ph (**6p**)	100	93

Table 3
Screening of compounds **5a–p** and **6a–p** against *M. tuberculosis* $H_{37}R_v$ strain

Entry	Compound	MIC (μg/mL)	Vero cell/macrophage cytotoxicity
1	**5a**	3.125	NT
2	**5b**	1.56	NT
3	**5c**	3.125	NT
4	**5d**	12.5	ND
5	**5e**	12.5	ND
6	**5f**	>12.5	ND
7	**5g**	>12.5	ND
8	**5h**	>12.5	ND
9	**5i**	>12.5	ND
10	**5j**	>12.5	ND
11	**5k**	>12.5	ND
12	**5l**	>12.5	ND
13	**5m**	>12.5	ND
14	**5n**	3.125	NT
15	**5o**	>12.5	ND
16	**5p**	6.25	ND
17	**6a**	3.125	NT
18	**6b**	3.125	NT
19	**6c**	>12.5	ND
20	**6d**	6.25	NT
21	**6e**	12.5	ND
22	**6f**	12.5	ND
23	**6g**	3.125	NT
24	**6h**	25	ND
25	**6i**	25	ND
26	**6j**	>12.5	ND
27	**6k**	>12.5	ND
28	**6l**	>12.5	ND
29	**6m**	>12.5	ND
30	**6n**	>12.5	ND
31	**6o**	>12.5	ND
32	**6p**	6.25	NT

NT, non toxic; ND, not done.
MIC, minimum inhibitory concentration.

1.56 μg/mL, compounds **5a**, **5c**, **5n**, **6a**, **6b** and **6g** showed MIC 3.125 μg/mL, compounds **5p**, **6d** and **6p** showed MIC 6.25 μg/mL and **18** compounds (**5d–o**, **6c**, **6e**, **6f** and **6j–o**) showed MIC $\geqslant$ 12.5 μg/mL. The active compounds were tested for cytotoxicity against Vero cells and mouse bone marrow macrophages, and all of them were found nontoxic (Table 3).[17] From the activity profile it was observed that the presence of a primary amide functionality might be essential for the effective antitubercular activity. Changes in the stereochemistry in the sugar moiety do not affect much in the MIC values. Although, initially it was believed that sulfonyl acetamide derivatives can mimic the tetrahedral transition state of the β-keto acyl synthase-catalyzed Claisen reaction step[10] in the fatty acid biosynthesis, presence of two loan pair on the sulfur atom in the thioacetamide derivatives (**5a–c**, **5n**, **5p**) may also providing the required geometry to mimic the above-mentioned transition state and thus showing good MIC values.

In conclusion, a series of glycosyl thioacetamide and glycosyl sulfonyl acetamide derivatives have been synthesized following a convenient protocol, which can easily be scaled up for the preparation of compounds in higher quantity. These set of compounds have been evaluated for their antitubercular activities against *Mycobacterium tuberculosis* $H_{37}R_v$, using microdilution on agar method. Some of the compounds (**5a–c**, **5n**, **6a**, **6b** and **6g**) may be considered as potential leads of antitubercular agents. Further optimization of the lead molecules is currently in progress in our laboratory.

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12. *Typical experimental method for preparation of 2-chloroacetamide derivatives (***4***):* To a solution of chloroacetyl chloride (1.0 mmol) in $CHCl_3$ (5 mL) were added amines (1.2 mmol) and triethlyamine (Et_3N; 2.0 mmol) in succession and the reaction mixture was allowed to stir at room temperature for 30 min. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with water. The organic layer was dried (Na_2SO_4) and concentrated to dryness under reduced pressure to yield solid compounds, which were crystallized from EtOH to furnish 2-chloroacetamide derivatives.
13. *Typical experimental method for preparation of glycosyl thioacetamide derivatives (***5a–p***):* A suspension of free carbohydrates (**1a–i**; 10.0 mmol) in acetic anhydride (1.02 mmol/OH) was placed in an ice bath with continuous stirring. To the cold suspension of the reaction mixture was added $BF_3{\cdot}OEt_2$ (1.5 mmol). An exothermic reaction started immediately and the reaction mixture was allowed to stir for 5.0 min. After completion of the per-*O*-acetylation, anhydrous CH_3CN (10.0 mL) was added to the reaction mixture followed by thiourea (2.0 mmol) and the reaction mixture was placed on a preheated oil bath at 80 °C for 15 min with constant stirring. After full consumption of the sugar per-*O*-acetates (TLC; EtOAc), the reaction mixture was cooled to room temperature. To the reaction mixture were added 2-chloroacetamide derivatives (**4**; 1.1 mmol) and Et_3N (5.0 mL) in succession and allowed to stir for appropriate time (Table 1) at room temperature. The solvents were removed and the resulting syrup was diluted with CH_2Cl_2 (100 mL). The organic layer was washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the crude reaction product over SiO_2 using hexane-EtOAc (3:1) furnished pure glycosyl thioacetamide derivatives (**5a–p**) in satisfactory yields (Table 1).
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15. *Typical experimental method for preparation of Glycosyl sulfonyl acetamide derivatives (***6a–p***):* To a solution of glycosyl thioacetamide derivatives (**5a–p**; 1.0 mmol) in CH_2Cl_2 was added *m*-CPBA (1.5 mmol) and the reaction mixture was allowed to stir for appropriate time (Table 2). After completion (TLC; hexane: EtOAc 1:1), the reaction was quenched with aq. $FeSO_4$ solution and extracted with CH_2Cl_2. The organic layer was washed with aq $NaHCO_3$ and water successively, dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the crude reaction product over SiO_2 using hexane-EtOAc (1:1) furnished pure glycosyl sulphonyl acetamide derivatives (**6a–p**) in excellent yields (Table 2).
(2,3,4,6-tetra-O-acetyl-1-sulfonyl-β-D-glucopyranosyl) acetamide (**6a**)*:* $[\alpha]_D^{25}$ – 4.0(*c*1.0, $CHCl_3$); IR (neat): 3462, 3022, 2362, 1751, 1693, 1596, 1370, 1222, 1066, 765 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.68 (br s, 1H, NH_2), 5.84 (br s, 1H, NH_2), 5.25 (t, *J* = 9.0 Hz, 1H, H-2), 5.08 (t, *J* = 9.0 Hz, 1H, H-3), 5.05 (t, *J* = 9.0 Hz, 1H, H-4), 4.62 (d, *J* = 9.0 Hz, 1H, H-1), 4.22–4.20 (m, 2H, H-$6_{a,b}$), 3.79–

3.73 (m, 1H, H-5), 3.51–3.21 (AB_q, J = 15 Hz, 2H, SO_2CH_2), 2.10, 2.07, 2.04, 2.00 (4s, 12H, 4 $COCH_3$); ESI-MS: m/z = 475.9 $[M+Na]^+$; Anal. calcd $C_{16}H_{23}NO_{12}S$ (453.09): C, 42.38; H, 5.11; found: C, 42.16; H, 5.35.

(2,3,4,6-tetra-O-acetyl-1-sulfonyl-β-D-galactopyranosyl) acetamide (**6b**): $[\alpha]_D^{25}$ + 7.0(c1.0, $CHCl_3$); IR (neat): 3460, 3021, 2360, 1752, 1692, 1598, 1372, 1217, 1059, 762, 670 m^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.69 (br s, 1H, NH2), 5.87 (br s, 1H, NH_2), 5.45 (d, J = 3.0 Hz, 1H, H-4), 5.24 (t, J = 9.9 Hz, 1H, H-2), 5.08 (dd, J = 9.9, 3.0 Hz, 1H, H-3), 4.60 (d, J = 9.8 Hz, 1H, H-1), 4.19–4.05 (m, 2H, H-$6_{a,b}$), 4.00–3.96 (m, 1H, H-5), 3.52–3.19 (ABq, J = 16.4 Hz, 2H, SO_2CH_2), 2.16, 2.08, 2.06, 1.99 (4s, 12H, 4 $COCH_3$); ESI-MS: m/z = 475.9 $[M+Na]^+$; Anal. calcd $C_{16}H_{23}NO_{12}S$ (453.09): C, 42.38; H, 5.11; found: C, 42.20; H, 5.30.

(2,3,4,6-tetra-O-acetyl-1-sulfonyl-α-D-mannopyranosyl) acetamide (**6c**):$[\alpha]_D^{25}$ + 36.3(c1.0, $CHCl_3$); IR (neat):3455, 3353, 3022, 2361, 2338, 1753, 1692, 1372, 1321, 1217, 1121, 1050, 760, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz):δ 6.89 (br s, 1H, NH_2), 6.32 (br s, 1H, NH_2), 5.93 (br s, 1H, H-2), 5.48 (dd, J = 9.3, 3.5 Hz, 1H, H-3), 5.38 (br s, 1H, H-1), 5.33 (t, J = 9.2 Hz, 1H, H-4), 4.65–4.60 (m, 1H, H-5), 4.29–4.17 (m, 3H, H-$6_{a,b}$, SCH_2), 4.05 (d, J = 14.7 Hz, 1H, SO_2CH_2), 2.16, 2.11, 2.07, 2.02 (4s, 12H, 4 $COCH_3$); ESI-MS: m/z = 475.9 $[M+Na]^+$; Anal. calcd $C_{16}H_{23}NO_{12}S$ (453.09):C, 42.38; H, 5.11; found:C, 42.20; H, 5.35.

*(2,3,4-tri-O-acetyl-**1**-sulfonyl-β-D-ribopyrano-syl)* acetamide (**6d**): $[\alpha]_D^{25}$ – 15.0(c1.0, $CHCl_3$); IR (neat):3020, 2927, 2361, 2338, 1752, 1692, 1372, 1216, 1045, 760, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz):δ 6.84 (br s, 1H, NH_2), 6.40 (br s, 1H, NH_2), 5.65 (t, J = 2.7 Hz, 1H, H-3), 5.55 (dd, J = 8.3, 3.2 Hz, H-2), 5.13–5.08 (m, 1H, H-4), 4.99 (d, J = 8.3 Hz, 1H, H-1), 4.22–4.10 (m, 2H, H-5_a, SO_2CH_{2a}), 3.99 (d, J = 14.6 Hz, 1H, SO_2CH_{2b}), 3.88–3.81 (m, 1H, H-5_b), 2.16, 2.06, 2.04 (3s, 9H, 3 $COCH_3$); ESI-MS: m/z = 403.9 $[M+Na]^+$; Anal. calcd $C_{13}H_{19}NO_{10}S$ (381.07):C, 40.94; H, 5.02; found:C, 40.75; H, 5.25.

*(2,3,4-tri-O-acetyl-1-sulfonyl-β-D-xylopyranosyl) acetamide (**6e**):* $[\alpha]_D^{25}$ – 45.5 (c1.0, $CHCl_3$); IR (neat):3434, 3021, 2360, 1749, 1641, 1376, 1216, 1044, 762, 670 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz):δ 7.60 (br s, 1H, NH_2), 6.39 (br s, 1H, NH_2), 5.63 (t, J = 8.6 Hz, 1H, H-3), 5.41–5.28 (m, 2H, H-2, H-4), 5.02 (d, J = 9.3 Hz, 1H, H-1), 4.36–4.31 (m, 1H, H-5_a), 4.22–3.88 (ABq, J = 14.6 Hz, 2H, SO_2CH_2), 3.60–3.54 (m, 1 H, H-5_b), 2.09, 2.05 (2s, 9H, 3 $COCH_3$); ESI-MS: m/z = 403.9 $[M+Na]^+$; Anal. calcd $C_{13}H_{19}NO_{10}S$ (381.07):C, 40.94; H, 5.02; found:C, 40.77; H, 5.20.

*(2,3,4-tri-O-acetyl-1-sulfonyl-β-D-arabinopyra-nosyl) acetamide (**6f**):* $[\alpha]_D^{25}$ – 18.0(c1.0, $CHCl_3$); IR (neat): 3464, 3021, 2360, 1751, 1692, 1372, 1217, 1061, 762, 670 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 6.74 (br s, 1H, NH_2), 6.20 (br s, 1H, NH_2), 5.73 (t, J = 9.4 Hz, 1H, H-2), 5.35 (br s, 1H, H-4), 5.21 (dd, J = 9.5, 3.3 Hz, 1H, H-3), 4.86 (d, J = 9.3 Hz, 1H, H-1), 4.24–4.19 (m, 2H, H-5_a, SO_2CH_2), 4.0–3.89 (m, 2H, H-5b, SO_2CH_2), 2.18, 2.07, 2.03 (3s, 9H, 3 $COCH_3$); ESI-MS: m/z = 404.0 $[M+Na]^+$; Anal. calcd $C_{13}H_{19}NO_{10}S$ (381.07): C, 40.94; H, 5.02; found: C, 40.78; H, 5.20.

(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-(1 → 4)-(2,3,6-tri-O-acetyl-1-sulfonyl-β-D-glucopyranosyl) acetamide (**6g**): $[\alpha]_D^{25}$ + 3.0(c1.0, $CHCl_3$); IR (neat): 3464, 3021, 2360, 1753, 1693, 1371, 1216, 1046, 761, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 6.81 (br s, 1H, NH_2), 6.30 (br s, 1H, NH_2), 5.47 (t, J = 9.4 Hz, 1H, H-3), 5.32 (br s, 1H, H-4′), 5.26 (t, J = 8.0 Hz, 1H, H-2), 5.08 (t, J = 10.3 Hz, 1H, H-2′), 4.96 (dd, J = 10.4, 3.2 Hz, H-3′), 4.84 (d, J = 10.0 Hz, 1H, H-1′), 4.63 (d, J = 12 Hz, 1H, H – 6′$_a$), 4.54 (d, J = 7.6 Hz, 1H, H-1), 4.18–4.03 (m, H-4, H-6_a, H – 6′$_b$, SO_2CH_{2a}), H-5, H-5′, H-6_b, SO_2CH_{2b}), 2.12, 2.09, 2.04, 2.03, 2.02, 2.01, 1.93 (7s, 21H, 7 $COCH_3$); ESI-MS: m/z = 764.1 $[M+Na]^+$; Anal. calcd $C_{28}H_{39}NO_{20}S$ (741.2): C, 45.34; H, 5.30; found: C, 45.17; H, 5.50.

(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-(1 → 4)-(2,3,6-tri-O-acetyl-1-sulfonyl-β-D-glucopyranosyl) acetamide (**6h**): $[\alpha]_D^{25}$ – 16.0(c1.0, $CHCl_3$); IR (neat): 3462, 3020, 2361, 2338, 1755, 1692, 1371, 1216, 1046, 760, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 6.77 (br s, 1H, NH_2), 6.21 (br s, 1H, NH_2), 5.49 (t, J = 9.5 Hz, 1H, H-3), 5.29 (t, J = 9.0 Hz, 1H, H-2), 5.15 (t, J = 9.5 Hz, 1H, H-2′), 5.09 (t, J = 9.5 Hz, 1H, H-3′), 4.90 (t,J = 9.5 Hz, 1H, H-4′), 4.86 (d, J = 9.9 Hz, 1H, H-1′), 4.68 (d, J = 11.9 Hz, 1H, H-6_a), 4.55 (d, J = 8.0 Hz, 1H, H-1′), 4.40–4.34 (m, 1H, H-5′), 4.17 (d, J = 14.7 Hz, 1H, SO_2CH_{2a}), 4.14–4.02 (m, 2H, H-4, H-6_b), 3.90 (d, J = 14.7 Hz, 1H, SO_2CH_{2b}), 3.88–3.84 (m, 2H, H-6′$_{a,b}$), 3.72–3.69 (m, 1H, H-5), 2.12, 2.07, 2.02, 1.99, 1.97 (5s, 21H, 7 $COCH_3$); ESI-MS: m/z = 763.9 $[M+Na]^+$; Anal. calcd $C_{28}H_{39}NO_{20}S$ (741.2): C, 45.34; H, 5.30; found: C, 45.15; H, 5.52.

*(2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl)-(1 → 4)-(2,3,6-tri-O-acetyl-**1**-sulfonyl-β-D-glucopyranosyl)* acetamide (**6i**): $[\alpha]_D^{25}$ + 34.0(c1.0, $CHCl_3$); IR (neat): 3470, 3021, 2361, 2339, 1753, 1371, 1217, 1042, 760, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 6.77 (br s, 1H, NH_2), 6.24 (br s, 1H, NH_2), 5.42-5.38 (m, 3H, H-2′, H-3, H-3′), 5.36 (t, J = 7.5 Hz, 1H, H-2), 5.06 (t, J = 7.4 Hz, 1H, H-4′), 4.92 (d, J = 2.0 Hz, 1H, H-1′), 4.87 (d, J = 7.5 Hz, 1H, H-1), 4.71 (d, J = 12 Hz, 1H, H-6_a), 4.27–4.16 (m, 3H, H-4, H-6_b, SO_2CH_{2a}), 4.09–3.99 (m, 2H, H-6′$_{a,b}$), 3.97-3.91 (m, 3H, H-5, H-5′, SO_2CH_{2b}), 2.14, 2.12, 2.10, 2.05, 2.04, 2.00 (6s, 21H, 7 $COCH_3$); ESI-MS: m/z = 763.9 $[M+Na]^+$; Anal. calcd $C_{28}H_{39}NO_{20}S$ (741.2): C, 45.34; H, 5.30; found: C, 45.12; H, 5.55.

*N-Octyl-2-(2,3,4, 6-tetra-O-acetyl-1-sulfonyl-β-D-glucopyranosyl) acetamide (**6j**):* $[\alpha]_D^{25}$ – 5.6(c1.0, $CHCl_3$); IR (neat): 3423, 2929, 2363, 1751, 1592, 1452, 1380, 1352, 1236, 1042, 762, 670 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ *5.45–5.43* (t, J = 9.6 Hz, 1H, H-3), 5.16–5.10 (m, 2H, H-1 and H-2), 4.52–4.49 (m, 1H, H-4), 4.30–4.22 (m, 3H, H-5 and H-6_{ab}), 4.12–4.04 (m, 2H, -SCH_2), 3.91–3.81 (m, 1H, $NHCH_2$), 3.35–3.20 (m, 1H, $NHCH_2$), 2.12, 2.09, 2.03, 2.02 (4s, 12H, 4 $COCH_3$), 1.61–1.52 (m, 2H, –CH_2), 1.28–1.26 (m, 10H, octyl), 0.93–0.86 (m, 3H, CH_3); ESI-MS: m/z = 588.2 $[M+Na]^+$; Anal. calcd $C_{24}H_{39}NO_{12}S$ (565.2): C, 50.96; H, 6.95; found: C, 50.75; H, 7.20.

*N-Octyl-2-(2,3,4-tri-O-acetyl-1-sulfonyl-β-D-ara-binopyranosyl) acetamide (**6k**):* $[\alpha]_D^{25}$ – 10.4(c1.0, $CHCl_3$); IR (neat): 3429, 2927, 2367, 1740, 1592, 1461, 1382, 1351, 1234, 1060, 767 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 5.53 (d, J = 4.2 Hz, 1H, H-4), 5.38–5.26 (m, 3H, H-1, H-2 and H-3), 4.23-4.10 (m, 2H, –SCH_2), 3.83–3.79 (m, 2H, H-5_{ab}), 3.28–3.26 (m, 2 H, $NHCH_2$), 2.11, 2.07, 2.04 (3s, 9H, 3 $COCH_3$), 1.55–1.52 (m, 2H, octyl), 1.26–1.25 (m, 10H, octyl), 0.87–0.84 (m, 3 H, CH_3); ESI-MS: m/z = 516.2 $[M+Na]^+$; Anal. calcd $C_{21}H_{35}NO_{10}S$ (493.2): C, 51.10; H, 7.15; found: C, 50.90; H, 7.34.

N-Octyl-2-[(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-(1 → 4)-2,3,6-tri-O-acetyl-1-sulfonyl-β-D-glucopyranosyl] acetamide (**6l**): $[\alpha]_D^{25}$ – 12.9(c1.0, $CHCl_3$); IR (neat): 3396, 2926, 2857, 2368, 1752, 1591, 1427, 1375, 1229, 1054, 905, 756, 601 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ *5.46–5.39* (t, J = 10.2 and 9.3 Hz, 1H, H-3), 5.33 (d, J = 2.7 Hz, 1H, H-4′), 5.11–5.09 (m, 1H, H-2), 5.07 (d, J = 7.8 Hz, 1H, H-1), 5.03–4.93 (m, 2H, H-2′ and H-4), 4.50 (d, J = 7.8 Hz, 1H, H-1′), 4.41–4.40 (m, 1H, H-3′), 4.13–4.09 (m, 4 H, H-6_{ab} and H-6′$_{ab}$), 4.02–3.99 (m, 1H, H-5), 3.94–3.89 (t, J = 9.0 Hz each, 1H, H-5′), 3.87–3.82 (m, 2 H, SCH_2-), 3.43–3.12 (m, 2H, $NHCH_2$-) 2.19, 2.17, 2.13 (3s, 9H, 3 $COCH_3$), 2.06 (s, 6H, 2 $COCH_3$), 2.01, 1.97 (2s, 6H, 2 $COCH_3$), 1.54–1.51 (m, 2H, octyl), 1.28–1.25 (m, 10H, octyl), 0.92–0.88 (m, 3H, -CH_3); ESI-MS: m/z = 876.2 $[M+Na]^+$; Anal. calcd $C_{36}H_{55}NO_{20}S$ (853.3): C, 50.64; H, 6.49; found: C, 50.47; H, 6.65.

*N-Dodecyl-2-(2,3,4,6-tetra-O-acetyl-1-sulfonyl-β-D-glucopyranosyl) acetamide (**6m**):* $[\alpha]_D^{25}$ – 4.9(c1.0, $CHCl_3$); IR (neat): 3434, 2817, 2368, 1751, 1593, 1383, 1351, 1238, 1042, 766, 603 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ *5.56–5.50* (t, J = 9.3 Hz each, 1H, H-3), 5.15–5.08 (m, 1H, H-2), 4.82 (d, J = 9.9 Hz, 1H, H-1), 4.31–4.23 (m, 2H, H-4 and H-6_a), 4.12–3.99 (m, 2H, H-5 and H-6_b), 3.95–3.82 (m, 2H, -SCH_2), 3.30–3.26 (m, 2H, $NHCH_2$), 2.13, 2.09 (2s, 6H, 2 $COCH_3$), 2.05 (s, 6H, 2 $COCH_3$),1.56–1.52 (m, 2H, CH_2), 1.27–1.25 (m, 18H, dodecyl), 0.91–0.87 (t, J = 6.5 Hz, 3H, CH_3); ESI-MS: m/z = 644.2 $[M+Na]^+$; Anal. calcd $C_{28}H_{47}NO_{12}S$ (621.3): C, 54.09; H, 7.62; found: C, 53.90; H, 7.80.

N-Dodecyl-2-(2,3,4-tri-O-acetyl-1-sulfonyl-β-D-arabinopyranosyl) acetamide (**6n**): $[\alpha]_D^{25}$ – 15.2(c1.0, $CHCl_3$); IR (neat): 3434, 2817, 2368, 1751, 1593, 1383, 1351, 1238, 1042, 766 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 5.49 (d, J = 4.2 Hz, 1H, H-4), 5.34–5.23 (m, 3H, H-1, H-2 and H-3), 4.19–4.07 (m, 2H, -SCH_2), 3.78–3.76 (m, 2H, H-5), 3.25–3.23 (m, 2H, $NHCH_2$), 2.10, 2.05, 2.04 (3s, 9H, 3 $COCH_3$), 1.53–1.50 (m, 2H, dodecyl), 1.26–1.25 (m, 18H, dodecyl), 0.89–0.86 (m, 3H, C$\underline{H}_3$); ESI-MS: m/z = 572.2 $[M+Na]^+$; Anal. calcd $C_{25}H_{43}NO_{10}S$ (549.3): C, 54.63; H, 7.88; found: C, 54.44; H, 8.0.

N-Dodecyl-2-[(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-(1 → 4)-2,3,6-tri-O-acetyl-1-sulfonyl-β-D-glucopyranosyl] acetamide (**6o**): $[\alpha]_D^{25}$ – 8.8(c1.0, $CHCl_3$); IR (neat): 3400, 2927, 2362, 1752, 1592, 1425, 1373, 1230, 1056, 899, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 5.32 (br s, 1H, H-4), 5.22–5.16 (t, J = 9.9 Hz each, 1H, H-3), 4.97–4.90 (m, 3H, H-1′, H-2′ and H-2), 4.52–4.47 (m, 3H, H-3′, H-4′ and H-1), 4.15–4.07 (m, 2H, H-6_{ab}), 4.06–4.02 (m, 1H, H-5), 3.90–3.75 (m, 2H, H-6′$_{ab}$), 3.65–3.61 (m, 1H, H-5′), 3.47–3.16 (m, 4H, SCH_2 and $NHCH_2$), 2.16, 2.13, 2.08, 2.07 (4s, 12H, 4 $COCH_3$), 2.05 (s, 6H, 2 $COCH_3$), 1.97 (s, 3H, $COCH_3$), 1.52–1.47 (m, 2H, CH_2), 1.29–1.26 (m, 18H, dodecyl), 0.92–0.87 (t, J = 6.6Hz, 3H, CH_3); ESI-MS: m/z = 932.2 $[M+Na]^+$; Anal. calcd $C_{40}H_{63}NO_{20}S$ (909.3): C, 52.79; H, 6.98; found: C, 52.60; H, 7.20.

*N-Benzyl-2-(2,3,4,6-tetra-O-acetyl-1-sulfonyl-β-D-glucopyranosyl) acetamide (**6p**):* $[\alpha]_D^{25}$ – 16.3(c1.0, $CHCl_3$); IR (neat): 3417, 2820, 2360, 1593, 1444, 1382, 1350, 1241, 1105, 769 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ *5.17–5.11* (t, J = 9.3 Hz each, 1H, H-3), 5.05–4.99 (m, 3H, H-2 and CH_2Ph), 4.54 (d, J = 10.2 Hz, 1H, H-1), 4.22–4.18 (m, 1H, H-4), 4.07-3.88 (m, 2H, H-6_{ab}), 3.66–3.64 (m, 1H, H-5), 3.50–3.39 (m, 2H, SCH_2), 3.21–3.19 (m, 2H, $NHCH_2$), 1.99 (s, 6H, 2 $COCH_3$), 1.98, 1.97 (2s, 6H, 2 $COCH_3$); ESI-MS: m/z = 566.1 $[M+Na]^+$; Anal. calcd $C_{23}H_{29}NO_{12}S$ (543.1): C, 50.82; H, 5.38; found: C, 50.60; H, 5.60.

16. *Antitubercular activity*[18]: Determination of the MIC (minimum inhibitory concentration) of test compounds or standard anti-TB drugs (rifampicin and isonoiazid) for *M. tuberculosis* $H_{37}Rv$ was done using the "proportion method".[13] Serial twofold dilutions of test compounds were mixed in warm Middlebrook 7H10 agar medium, dispensed in sterile glass tubes (2 mL/tube) and allowed to solidify as "slants". A homogeneous suspension (10 μL, containing 10^5 colony forming units or CFUs) of *M. tuberculosis* $H_{37}Rv$ was spread over the surface of the agar medium in each tube and kept at 37 °C for 4 weeks for appearance of colonies. The minimum concentration of compounds/drugs which completely inhibited bacterial growth was recorded as MIC (μg/mL).
17. *Cytotoxicity measurement*[19]: Selected compounds were tested for their in vitro cytotoxicity against Vero C1008 cells (African Green Monkey kidney cell line) as well as mouse bone marrow-derived macrophages using the described method by Mosmann.[14] 10^4 cells/0.2 mL/well (in DME medium containing 10% foetal bovine serum + antibiotics) were seeded in 96-well tissue culture plates and incubated for 24 h (at 37 °C, 5% CO_2). The medium on top of the cells was replaced with fresh medium containing serial dilutions of test compounds/standard toxic compound/DMSO. After 24 h incubation (37 °C, 5% CO_2), 20 μL MTS reagent (Promega, USA) was added to each well and absorbance was read after 2 h at 490 nm. Absorbance shown by DMSO containing wells was taken to denote 100% cell viability. A compound was considered as toxic if its IC_{50} value (concentration causing 50% inhibition of viability) was 10 times the MIC for *M. tuberculosis* $H_{37}Rv$.

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