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Leishmanicidal activity of phenylene bridged C_2 symmetric glycosyl ureides ☆

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Abstract—A number of phenylene bridged C_2 symmetric glycosyl uerides with ester (**3a**–**f**), alcohol (**4a**–**c**) and acid (**5a**–**d**) functionalities were prepared by addition of glycosyl amino esters with phenyl diisocyanates and their further reaction with $LiAlH_4$ or hydrolysis with LiOH. All the compounds were screened for their in vitro and in vivo antileishmanial activity. Most of the compounds exhibited good activity while two of the compounds **3e** and **3f** reduced the clinical dose of standard drug SSG.

1. Introduction

Leishmaniasis in each of its three clinical forms (cutaneous, mucosal and visceral) is a parasitic disease endemic to American, African and Asian tropical countries.[1] It affects around 12 million people throughout the world, 350 million are at the risk of being infected of which about 1.7 million will be infected each year.[2] Visceral leishmaniasis (VL) or Kala-azar, a disease affecting 61 out of the 88 countries world wide, is caused by kinetoplastid protozoan parasite belonging to the *Leishmania donovani*, which is transmitted to human by the bite of the sand fly.[3,4] In India Bihar is the highly endemic state but the disease has spread to newer areas also.

Attempts to produce an effective vaccine have so far failed. There is lack of interest among the pharmaceutical companies to carry out R&D work due to non-profit nature of this disease.[5,6] Most of the currently used drugs such as glucantine, pentamidine and stibamidine, and amphotericine B develop liver and heart toxicities and after few weeks of treatment these drugs develop resistance.[7] Further, it is also known that these drugs also contribute to increase co-infections leishmaniasis-AIDS.[8] A significant number of patients do not respond satisfactory to the existing drugs.

The important reasons for this include both host and drug factors.[7] No treatment has proven effective in achieving radical cure of VL when associated with HIV infection.[8] Since, chemotherapy is the only weapon in our arsenal, there is an urgent need to develop safer drugs in cost effective manner.

Compounds of both synthetic and natural origin comprising a diverse group of chemical structures have been reported as antileishmanial agents. These include mostly the nitrogen heterocycles; quinolines,[9] acridines,[10] phenothiazines,[11] pyrimidines[12] and purines;[13] and many other class of compounds including anilines,[14] flavonoids,[15] quinones,[16] amino acid esters and amides,[17] amino alcohols,[18] alkyl phospholipids,[19] and certain Pt complexes.[20] Development of most active and selective chemotherapeutic agents could be achieved by rational drug design taking into consideration the biochemical machinery of the parasite. Protozoan parasites of the genus *Leishmania* are prone to oxidative stress or oxidative siege from various ROS.[21] Further, earlier reports indicate that some of the antileishmanial drugs, such as pentavalent antimonials, require an intact cell mediated immune response for expression of their in vivo effect.[22] We have reported that simple amino sugars have immunopotentiating activity[23] and glycosyl urea and many simple sugar derivatives possess property

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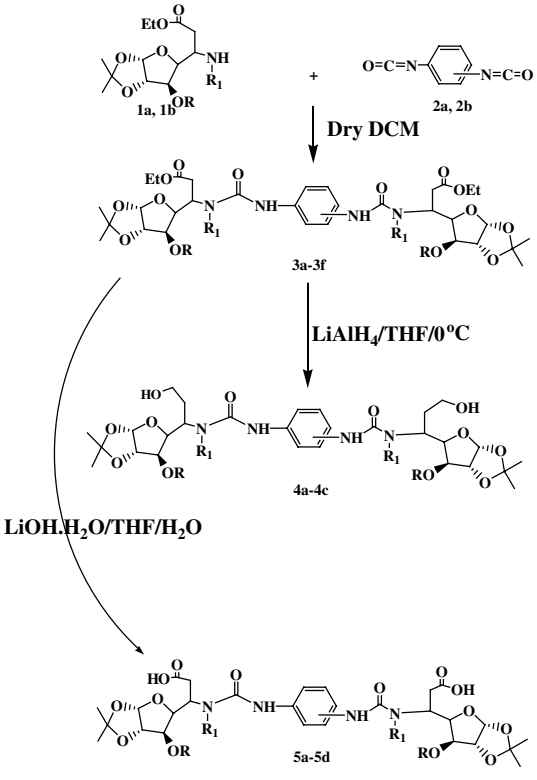
to modulate the enzymes involved in oxidative defense system of the parasite and do possess in vitro antiparasitic activity.[24] Further, many interesting biological properties may arise in the complex machinery of various glycoconjugate.[24] Based on these facts we have designed and synthesised diglycosylated ureides as possible inhibitors of enzymes involved in the defense mechanism of leishmanial parasite. These compounds are evaluated for their leishmanicidal activity alone and as an adjunct to sodium stibogluconate (SSG) against *Leishmania donovani* infection in hamsters.

2. Chemistry

The synthetic strategy of the compounds involves addition of 2 equiv of β-glycosyl β-amino esters (**1a**,**b**)[25] to 1 equiv of 1,3- and 1,4-phenylene diisocynates (**2a**,**b**) resulting in phenylene bridged C_2 symmetric glycosyl ureides[26] (**3a**–**f**) in good to quantitative yields (Scheme 1). The above ureides (**3a**, **3d** and **3e**) on reduction with lithium aluminium hydride resulted in corresponding phenylene bridged glycosyl amino alcohols (**4a**–**c**) in very good yields. Further, the ureides (**3a**, **3b**, **3d** and **3e**) were hydrolysed with $LiOH{\cdot}H_2O$ in THF/water to give the corresponding acids (**5a**–**d**) as shown in Scheme 1. The structures of all the synthesised compounds were determined on the basis of spectroscopic (IR, MS, ^1H ^{13}C NMR) data. The spectroscopic data for prototype compounds are given.[27]

The synthetic strategy chosen is novel in the sense that it is simple, economical, eco-friendly and does not require any special apparatus or work up. The yield in each reaction is almost quantitative and the reactions have been carried out at ambient temperature except during addition and quenching of $LiAlH_4$, which is carried out at 0 °C (Table 1).



Scheme 1.

Table 1. Glycosyl ureidyl esters (**3a**–**f**) and alcohols (**4a**–**c**) and acids (**5a**–**d**)

Compd	R	R_1	Phenylene ring substitution	% Yield (isolated)
3a	CH_3	H	1,4-	95
3b	CH_3	H	1,3-	97
3c	CH_3	CH_2Ph	1,4-	90
3d	CH_2Ph	H	1,4-	95
3e	CH_2Ph	H	1,3-	95
3f	CH_2Ph	CH_2Ph	1,4-	92
4a	CH_3	H	1,4-	85
4b	CH_2Ph	H	1,4-	82
4c	CH_2Ph	H	1,3-	85
5a	CH_3	H	1,4-	80
5b	CH_3	H	1,3-	78
5c	CH_2Ph	H	1,4-	80
5d	CH_2Ph	H	1,3-	75

3. Results and discussion

The in vitro activities against promastigote and amastigotes were determined following the earlier method against promastigotes[28] and macrophages[29] and

Table 2. In vitro antileishmanial activity of compounds against promastigotes and amastigotes

Compd	Concn μg/mL	% Activity against	
		Promastigotes	Amastigotes
3a	50	88	86
	25	82	58
3b	50	Inactive	73
	25	Inactive	ND
3c	50	Inactive	85
	25	Inactive	ND
3d	50	Inactive	64
	25	Inactive	ND
3e	50	87	61
	25	88	57
3f	50	Inactive	47
	25	Inactive	44
4a	50	Inactive	87
	25	Inactive	ND
4b	50	98	65
	25	65	47
4c	50	100	50
	25	100	ND
5a	50	62	36
	25	50	38
5b	50	40	53
	25	57	88
5c	50	62	74
	25	50	ND
5d	50	30	50
	25	40	58
SSG	50	—	75
Pentamidine	5	100	51

ND = not done.

Table 3. Efficacy of compounds alone and in combination with SSG on day 7 pt

Compd	Dose mg/kg ×5 (route)	Replicates (hamsters)	Average % inhibition ± SD
3a	5 (ip)	3 (10)	70 ± 27
3a+SSG	5 (ip)+10 (ip)	3 (12)	72 ± 28
3a	20 (po)	3 (11)	37 ± 21
3a+SSG	20 (po)+10 (ip)	3 (14)	60 ± 21
3b	5 (ip)	1 (4)	32 ± 21
3b+SSG	5 (ip)+10 (ip)	1 (4)	74 ± 26
3c	5 (ip)	1 (4)	26 ± 30
3c+SSG	5 (ip)+10 (ip)	1 (4)	57 ± 51
3d	5 (ip)	1 (4)	0.0
3d+SSG	5 (ip)+10 (ip)	1 (4)	38 ± 41
3e	5 (ip)	3 (10)	72 ± 19
3e+SSG	5 (ip)+10 (ip)	3 (10)	80 ± 17
3e	20 (po)	3 (16)	51 ± 32
3e+SSG	20 (po)+10 (ip)	3 (12)	67 ± 33
3f	5 (ip)	1 (4)	59 ± 43
3f+SSG	5 (ip)+10 (ip)	1 (4)	86 ± 6
4a	5 (ip)	1 (4)	36 ± 35
4a+SSG	5 (ip)+10 (ip)	1 (4)	76 ± 24
4b	5 (ip)	2 (8)	54 ± 43
4b+SSG	5 (ip)+10 (ip)	1 *(4)	56 ± 10
4c	5 (ip)	2 (8)	53 ± 28
4c+SSG	5 (ip)+10 (ip)	1 (4)	50 ± 40
5a	5 (ip)	1 (5)	24 ± 35
5a	20 (po)	2 (7)	60 ± 35
5a+SSG	20 (po)+10 (ip)	1 (4)	69 ± 11
5b	5 (ip)	1 (5)	24 ± 35
5b	20 (po)	2 (7)	60 ± 35
5b+SSG	20 (po)+10 (ip)	1 (4)	69 ± 11
5c	5 (ip)	1 (4)	23 ± 23
5c+SSG	5 (ip)+10 (ip)	1 (4)	30 ± 36
5d	5 (ip)	1 (5)	49 ± 39
5d+SSG	5 (ip)+10 (ip)	1 (4)	89 ± 6
5d	20 (po)	2 (9)	60 ± 31
5d+SSG	20 (po)+10 (ip)	1 (5)	40 ± 24
SSG	10 (ip)	9 (36)	42 ± 26
SSG	20 (ip)	—	85 ± 11

are depicted in Table 2. The in vivo activities were determined according to the method of Gupta et al.[30] and are given in Table 3.

Compounds **3d**, **3e**, **4b**, **4c**, **5a** and **5c** are active against both promastigotes and amastigotes at 50 or 25 μg/mL concentrations. However, compounds **3c** and **4a** are active against amastigote in macrophages, the ex vivo condition only. Therefore, it was thought worthwhile to evaluate all the compounds in vivo against *L. donovani*/hamster model. The efficacies of the compounds alone and in combination with SSG have been presented in the Table 3. The compounds were tested alone and in adjunct therapy with sub curative dose of SSG. Four compounds **3b**, **3e**, **3f**, and **5d** enhanced the efficacy of SSG from 42% to 74–89%. Interestingly the activity of these compounds in combination with SSG was very close to that of the curative dose (20 mg/kg × 5 ip) of the SSG.

As evident from the antileishmanial activity of the compounds in general acids and esters are more active than the corresponding alcohols, which show only marginal activity. It is also clear that compounds with more hydrophobic benzyl substituent (**3e**, **3f** and **5d**) are more potent than those with the less hydrophobic methyl substituent (**3b**, **3c** and **5b**). Further, as adjunctive to SSG acids are enhancing the efficacy of standard drug SSG to a greater extent than the corresponding esters.

These results warrant further comprehensive studies to establish the mode of antileishmanial action of these compounds. The lower doses of the toxic drugs with such adjunctive agents would certainly be beneficial to minimise the side effects. It is evident from these results that by the use these compounds dose of SSG may be reduced, which may be quite helpful in reducing toxicity of the drugs.

4. Conclusion

We have synthesised sugar derivatives flanked by phenylene ureidyl moiety with C_2 symmetry exhibiting significant antileishmanial activity both in vitro and in vivo. The associated antileishmanial activities with this class of compounds has led to a new lead for further exploration and development of better compounds to treat leishmaniasis.

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27. *General procedure for the preparation of compound* **3a**. To a stirring solution of **1a** (1 g, 3.46 mmol) in dry DCM, 1,4-phenyl diisocyanate **2a** (0.27 g, 1.12 mmol) was added and stirring continued for 12 h at room temperature. The solvent was evaporated and the residue thus obtained was chromatographed over SiO_2 using hexane–ethyl acetate (60:40) as eluent to give compound **3a**. Colourless solid, mp 114 °C, yield 95%, $[\alpha]_D$ −33.8 (*c*, 0.18, CH_3OH), FAB MS *m/z* 739 $[M+H]^+$ IR (film) ν_{max} cm^{-1} 3345, 1734, 1656, 1564, 1517. ^1H NMR (200 MHz, $CDCl_3$): δ 7.26 (m, 4H, Ar-H), 5.94 and 5.88 (each d, $J = 3.70$ Hz, 1H, H-1), 4.59 and 4.55 (each d, $J = 3.76$ Hz, 1H, H-2), 4.44 (m, 1H, H-4), 4.13 (q, $J = 7.1$ Hz, 2H, OCH_2CH_3), 3.79 (d, $J = 2.9$ Hz, 1H, H-3), 3.69 and 3.36 (each s, 3H, OCH_3), 2.71 (m, 2H, H-6), 1.73 (s, 1H, NH), 1.47, 1.34 (each s, 6H, $C(CH_3)_2$), 1.24 (t, 3H, OCH_2CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.6, 172.1, 156.3, 134.5, 122.2, 121.6, 112.1, 105.8, 105.3, 84.2, 81.0, 80.6, 71.0, 61.1, 57.9, 47.3, 37.4 (C-6), 27.1, 26.6 ($C(CH_3)_2$), 14.9, 14.85. Anal. Calcd for $C_{34}H_{50}N_4O_{14}\cdot H_2O$: C, 53.96; H, 6.87; N, 7.40. Found C, 53.47; H, 6.63; N, 7.10. *Physical data of* **3c**. Colourless solid, mp 141 °C, yield 90%, $[\alpha]_D$ −75.4 (*c*, 0.11 CH_3OH), FAB MS *m/z* 919 $[M+H]^+$ IR (film) ν_{max} cm^{-1} 3423, 1723, 1652, 1513, 1438. ^1H NMR (200 MHz, $CDCl_3$): δ 7.35–7.09 (m, 7H, Ar-H), 5.93 (d, $J = 3.60$ Hz, 1H, H-1), 4.60 (m, 3H, H-2 and NCH_2Ph), 4.46 (m, 1H, H-4), 4.11 (q, $J = 7.07$ Hz, 2H, OCH_2CH_3), 3.59 (d, $J = 2.50$ Hz, 1H, H-3), 3.37 (s, 3H, OCH_3), 2.80 (m, 1H, H-6_A), 2.40 (m, 1H, H-6_B), 1.57 (s, 1H, NH), 1.39 and 1.31 (each s, 6H, $C(CH_3)_2$), 1.21 (t, $J = 6.98$ Hz, 3H, OCH_2CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.7, 157.3, 139.2, 134.9, 133.6, 132.0, 129.0, 127.5, 121.3, 120.4, 112.2, 109.5, 105.0, 84.0, 81.3, 79.9, 61.4, 57.6, 53.9, 35.8, 27.0, 26.6, 14.4. Anal. Calcd for $C_{48}H_{62}N_4O_{14}\cdot H_2O$: C, 61.53; H, 6.83; N, 5.98. Found C, 61.58; H, 6.53; N, 6.14. Compound **3e**: colourless solid, mp 76 °C, yield 95%, $[\alpha]_D$ −22.8 (*c*, 0.175, CH_3OH), FAB MS *m/z* 891 $[M+H]^+$ IR (film) ν_{max} cm^{-1} 3360, 1729, 1666, 1608, 1546, 1492. ^1H NMR (200 MHz, $CDCl_3$) δ 7.26 (m, 7H, Ar-H), 5.95 (d, $J = 3.74$ Hz, 1H, H-1), 5.56 (m, 1H, NH), 4.69 (d, 1H, $J = 11.6$ Hz, OC CH_APh), 4.61 (d, $J = 3.4$ Hz, 1H, H-2), 4.52 (m, 1H, H-4), 4.43 (d, $J = 11.6$ Hz, 1H, OCH_BPh), 4.11 (q, $J = 7.12$ Hz, 2H, OCH_2CH_3), 3.90 (d, $J = 2.70$ Hz, 1H, H-3), 3.74 (m, 1H, H-5), 2.56 (m, 2H, H-6), 1.77 (m, 1H, NH), 1.45 and 1.29 (each s, 6H, $C(CH_3)_2$), 1.22 (t, $J = 7.10$ Hz, 3H, OCH_2CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.1, 155.6, 139.5, 137.2, 129.6, 128.9, 128.5, 112.2, 105.1, 82.4, 82.0, 80.6, 72.1, 61.1, 47.20, 37.2, 27.1, 26.6, 14.5. Anal. Calcd for $C_{46}H_{58}N_4O_{14}\cdot H_2O$: C, 60.79; H, 6.60; N, 6.16. Found C, 60.82; H, 6.29; N, 5.87. *General method for the preparation of glycosyl ureidyl alcohol* **4c**. To a stirred slurry of lithium aluminium hydride (0.042 g, 1.12 mmol) in anhydrous THF (5 mL), a solution of compound **3a** (1 g, 1.12 mmol) in anhydrous THF was added (10 mL) at 0 °C dropwise and stirring continued for 30 min at the same temperature followed by 4 h at room temperature. Excess of $LiAlH_4$ was quenched with 5% aq NaOH and saturated solution of Na_2SO_4 and reaction mixture filtered over Celite. The solid cake was washed with more THF and the filtrate evaporated under reduced pressure to give a gummy mass. The latter was chromatographed over SiO_2 using chloroform–methanol (95:5) as eluant to give **4c** as colourless solid, mp 139 °C, yield 85%, $[\alpha]_D$ −23.0 (*c*, 0.100, CH_3OH), FAB MS *m/z* 807 $[M+H]^+$ IR (film) ν_{max} cm^{-1} 3387, 1599, 1492, 1360. ^1H NMR (200 MHz, $CDCl_3$): δ 7.33 (m, 7H, Ar-H), 5.94 (d, $J = 3.70$ Hz, 1H, H-1), 4.66 (m, 4H, H-2, H-4, OCH_2Ph), 4.13 (m, 1H, H-5), 3.91 (d, $J = 2.84$ Hz, 1H, H-3), 3.74 (m, 2H, H-7), 1.85 (m, 3H, H-6 and NH), 1.46 and 1.30 (each s, 6H, $C(CH_3)_2$). ^{13}C NMR (50 MHz, $CDCl_3$): δ 156.8, 136.7, 136.5, 129.0, 128.5, 128.3, 128.0, 127.9, 111.7, 111.5, 104.8, 82.3, 81.9, 81.2, 71.8, 58.1, 46.3, 35.4, 27.6, 26.6. Anal. Calcd for $C_{42}H_{54}N_4O_{12}\cdot H_2O$: C, 61.16; H, 6.79; N, 6.79. Found C, 60.81; H, 6.51; N, 6.52. *General procedure for the preparation for glycosyl ureidyl acid* **5d**. Compound **3a** (1.0 g, 1.12 mmol) in THF (5 mL) and $LiOH\cdot H_2O$ (0.094 g, 2.24 mmol) in distilled water was magnetically stirred for 3 h at room temperature. The reaction mixture was neutralised with 2 N HCl at 0 °C. The solvent evaporated under reduced pressure to give a residual mass, which was chromatographed over SiO_2 column using $CHCl_3$–CH_3OH (92:8) as eluant to give **5d** as colourless solid, mp 160 °C $[\alpha]_D$ −20.4 (*c*, 0.170, CH_3OH), FAB MS *m/z* 835 $[M+H]^+$ IR (film) ν_{max} cm^{-1} 3395, 1594, 1515, 1399. ^1H NMR (200 MHz, $CDCl_3$): δ 8.96 (s, 1H, OH), 7.35 (m, 7H, Ar-H), 6.40 (br s, 1H, NH), 5.87 (d, $J = 3.3$ Hz, 1H, H-1), 4.78 (d, $J = 3.6$ Hz, 1H, H-2), 4.69 (d, $J = 11.3$ Hz, 1H, OCH_APh), 4.48 (d, $J = 11.3$ Hz, 1H, OCH_BPh), 4.28 (m, 1H, H-4), 3.88 (d, $J = 2.5$ Hz, 1H, H-3), 3.64 (m, 1H, H-5), 2.43 (m, 2H, H-6), 1.80 (m, 1H, NH), 1.43 and 1.37 (each s, 6H, $C(CH_3)_2$). ^{13}C NMR (50 MHz, $CDCl_3$): δ 174.1, 155.0, 134.7, 129.2, 128.5, 118.4, 110.7, 104.5, 83.5, 81.0, 80.8, 73.0, 45.5, 37.8, 27.8, 26.4. Anal. Calcd for $C_{42}H_{50}N_4O_{14}\cdot H_2O$: C, 59.15; H, 6.10; N, 6.57. Found C, 59.41; H, 5.98; N, 6.40.

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