RESEARCH ARTICLE Am. J. PharmTech Res. 2016; 6(5) ISSN: 2249-3387

AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Synthesis, Characterization and Biological Evaluation of New Glycosyl Thiocarbamides Derived from Glycosylamines

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ABSTRACT

Thiourea and urea are important functional groups in various natural products and drug intermediates. They are used as neutral receptor for various anions (anion complexation) and building blocks for various heterocycles. Sugar-based thioureas are a new class of molecules promising for many biological applications. Here, we have synthesized a new range of 1-β-D-glycosyl-3-aryl thiocarbamides by the interaction of various glycosylamines with aryl isothiocyanates. The structure of title compounds were confirmed by their IR, NMR mass spectral data and elemental analysis. The newly synthesized compounds were screened for their in vitro antimicrobial activities using standard cup plate method against bacteria *E. coli, P. aeruginosa, S. aureus* and fungi *A. niger, T. viride.* The title compounds exhibited mild to moderate antimicrobial activities.

Keywords: 1-β-D-glycosyl-3-aryl thiocarbamides, glycosylamines, aryl isothiocyanates, drug intermediates.

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Received 05 August 2016, Accepted 16 August 2016

Please cite this article as: Jadhao SU *et al.*, Synthesis, Characterization and Biological Evaluation of New Glycosyl Thiocarbamides Derived from Glycosylamines. American Journal of PharmTech Research 2016.

INTRODUCTION

The chemistry of thiourea and their derivatives of saccharides are extensively elaborated and documented for their biological properties. Glycosyl thioureas have been widely used as important intermediate in the synthesis of nuclieoside anologs[1-2]. Urea and thiourea derivatives possess many promising biological activities, such as herbicidal[3], antimicrobial[4], antioxidant[5], antiviral[6], anti-HIV[7] and antitumor[8] activity, while urea derivatives exhibit antimalarial[9] and antidiabetic activities[10]. Thiourea and urea derivatives have been used as purification agents for organic and inorganic effluents, industrial, agricultural and mining wastes[11], spinning mixtures, paper and paints, as well as wrinkle proofing agents for cotton and cotton polyester fabrics[12].

In view of these observations, we have designed new compounds incorporating the above pharmacophores together in order to prepare molecules having enhanced antimicrobial activity.

Therefore, we have synthesized new 1-β-D-glycosyl-3-aryl thiocarbamides by the interaction of various glycosylamines with aryl isothiocyanates in order to investigate their antibacterial and antifungal activities.

MATERIALS AND METHOD

Materials

The reagent grade chemicals were obtained from commercial sources and purified by either distillation or recrystallization before use.

Methods

Method employed in the present experiments for the synthesis of 1-β-D-glycosyl-3-aryl thiocarbamides is conventional refluxing for one hour.

Experimental

Melting points of all synthesized compounds were determined using open capillary tube on Mac digital melting point apparatus and were uncorrected. IR spectra were recorded in solid phase KBr disks on SHIMADZU IR affinity-1 FTIR spectrometer and 1H NMR spectra in DMSO-d6 on AVANCE ll 400 NMR spectrometer 400 MHz. The Mass spectra were recorded on WATERS, Q-TOF MICROMASS (LC-MS) instrument. Optical rotations were measured on Equip-Tronics EQ 801 Digital Polarimeter in DMSO. Purity of synthesized compounds has been checked by thin layer chromatography. It was performed on E.Merck pre-coated silica gel plates.

General experimental procedure

Preparation of glycosylamines (1a-d)

Glycosylamines (1a-d) were prepared by passing a current of ammonia (generated by warming concentrated aqueous ammonia) in icecold methanolic suspension of various sugars (0.001M).

Preparation of aryl isothiocyanates (2 & 3)

The aryl isothiocyanates prepared as usual by the oxidative decomposition of ammonium aryl dithiocarbamates with help of lead nitrate.

Preparation of 1-β-D-glycosyl-3-aryl thiocarbamides (4a-d & 5a-d)

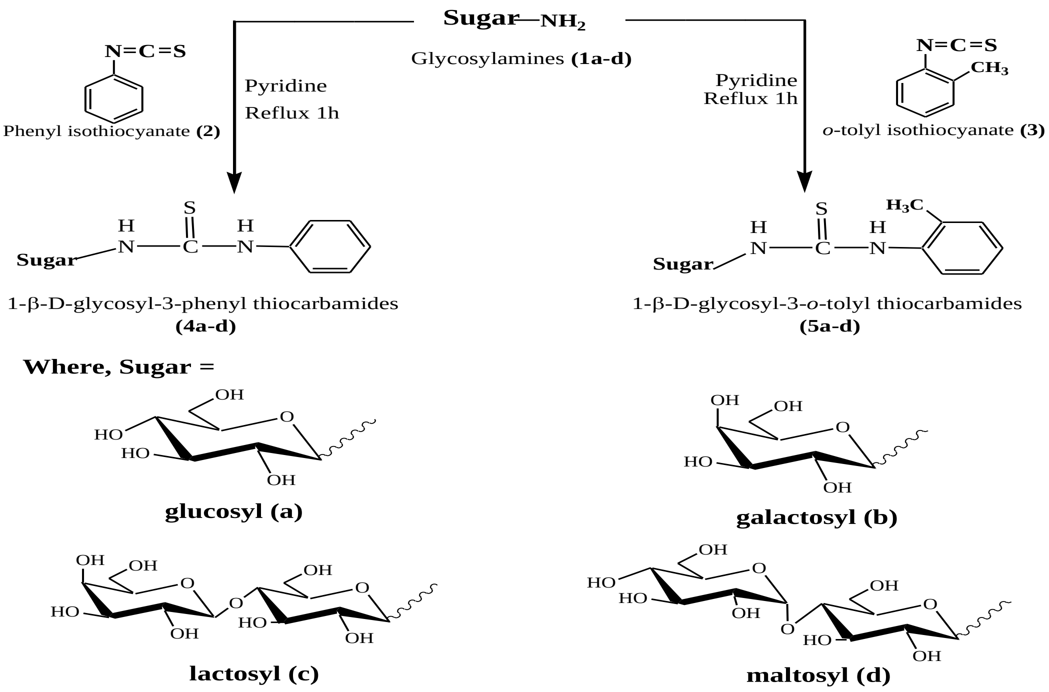
A pyridine solution of Glucosylamine **(1a)** (0.001M, 0.179g in 10 ml) was mixed with solution of phenyl isothiocyanate **(2)** (0.001M, 0.135g in 10 ml) and mixture was refluxed for 1 h on heating mental. Afterwards, the pyridine was distilled off and resultant was triturated several times with petroleum ether (60-80°C) to afforded a white solid **(4a)**. The product was crystallized from chloroform-petroleum ether. The % yield, m.p., optical rotation and R_f values are shown in **Table.1**

Table 1: Physical Characterization of 1-β-D-glycosyl-3-aryl thiocarbamides (4a-d & 5a-d)

Sr.no.	**Compounds**	**Yield (%)**	**M. p. (°C)**	**Elemental analysis (%): Found (Req.)**		**$[\alpha]^{32}_D$**	**R_f (7:3 EtOAc: pet. Ether)**
				N	S		
1.	4a	88.26	138	8.89 (8.91)	10.17 (10.20)	+76.2°	0.62
2.	4b	89.38	160	8.86 (8.91)	10.18 (10.20)	+67.4°	0.67
3.	4c	82.35	141	5.86 (5.88)	6.70 (6.73)	+57.3°	0.72
4.	4d	73.60	129	5.84 (5.88)	6.71 (6.73)	+34.3°	0.69
5.	5a	77.55	149	8.51 (8.53)	9.73 (9.76)	+ 93.85°	0.74
6.	5b	73.46	172	8.50 (8.53)	9.71 (9.76)	+107.48	0.68
7.	5c	77.93	150	5.70 (5.71)	6.52 (6.54)	+85.83°	0.70
8.	5d	87.30	139	5.68 (5.71)	6.50 (6.54)	+93.85°	0.77

Scheme 1

Compounds **4a-d & 5a-d**were also prepared by similar method. **(Scheme 1)**



Antimicrobial activity

The antimicrobial activity of newly synthesized compounds were tested in *vitro* against a selected gram positive, gram negative bacteria and fungi are presented in **Table.2** using cup plate agar diffusion method[13-15] by measuring the inhibition zone in mm. The compounds were taken at a concentration of 1mg/mL using Dimethyl Sulphoxide (DMSO) as solvent. Amikacin (100µg/ mL) was used as standard for antibacterial activity and Fluconazole (100µg/ mL) as standard for antifungal activity. The compounds were screen for antibacterial activity against *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* by using Muler Hinton agar medium and antifungal activity against *Aspergillus niger* and *Trichoderma viride* were determined by using Potato Dextrose Agar medium. These sterilized agar media were poured into Petri dishes and allowed to solidify. On the surface of the media microbial suspensions were spread with the help of sterilized cotton swab. After incubation the well was punched by using sterile stainless steel cork borer of 6mm diameter. Into these wells were added 0.1mL portion of the test compounds in solvent. The drug solution was allowed to diffuse for an hour into the medium. The plate was incubated at 37°C for 24 h and 30°C for 48 h for antibacterial and for antifungal activities respectively. The zone of inhibition observed around the cups after respective incubation was measured. The results are presented in Table 2.

Escherichia coli (E. coli), Staphylococcus aureus (S. aureus), Psudomonas aeruginosa (Ps. Aeruginosa), Aspegillus niger (A.niger), Trichoderma viride (T. viride).

RESULTS AND DISCUSSION

The synthesis of title compounds was accomplished by reacting glycosylamines with aryl isothiocyanates in pyridine solvent for 1 h. the progress of the reaction was monitored by TLC. The resulting title compounds **4a-d & 5a-d** were obtained in high yield. The chemical structures of the title compounds **4a-d & 5a-d** were deduced by IR, ^{1}H NMR, mass spectral analysis[16-18] & elemental analysis, the results of which are given below:

Spectral Characterization:

1-β-D-glucosyl-3-phenyl thiocarbamide (4a)

IR (KBr cm^{-1}): υ 3203 (O-H), 3116 (N-H), 3034 (Ar C-H), 2924 (Ali C-H), 1361 (C-N), 1070 (C=S), 933 (characteristic of glucose). **^{1}H NMR (DMSO-D$_6$, ppm)**: δ 7.25-7.18 (5H, m, ArH), 6.28 and 5.34 (2H, s, NH), 5.30-4.29 (4H, m, hydroxyl proton), 4.25-3.98 (7H, m, glucosyl proton). **Mass (m/z)**: 314 (M$^+$), 315 (M$^+$+1), 297, 288, 279, 230, 229, 221, 206, 178. (Found: C, 49.64; H, 5.73; N, 8.89; S, 10.17 calcd for $C_{13}H_{18}O_5N_2S$; C, 49.67; H, 5.77; N, 8.91; S, 10.20%).

1-β-D-galactosyl-3-*o*-tolyl thiocarbamide (5b)

IR (KBr cm^{-1}): υ 3273 (O-H), 3219 (N-H), 3032 (Ar C-H), 2918 (Ali C-H), 1354 (C-N), 1071 (C=S), 1024 and 907 (characteristic of galactose). **^{1}H NMR (DMSO-D$_6$, ppm)**: δ 7.36-7.30 (4H, m, ArH), 6.27 and 5.31 (2H, s, NH), 4.84-4.53 (4H, m, hydroxyl proton), 4.47-3.98 (7H, m, galactosyl proton), 2.39 (3H, s, CH_3). **Mass (m/z)**: 328 (M$^+$), 314, 288, 271, 256, 241, 230, 206, 178. (Found: C, 51.18; H, 6.10; N, 8.51; S, 9.73 calcd for $C_{14}H_{20}O_5N_2S$; C, 51.21; H, 6.14; N, 8.53; S, 9.76%).

1-β-D-lactosyl-3-phenyl thiocarbamide (4c)

IR (KBr cm^{-1}): υ 3235 (O-H), 3111 (N-H), 3034 (Ar C-H), 2916 (Ali C-H), 1365 (C-N), 1070 (C=S), 1000 and 974 (characteristic of lactose). **^{1}H NMR (DMSO-D$_6$, ppm)**: δ 7.27-7.16 (5H, m, ArH), 6.68 and 5.59 (2H, s, NH), 5.84-3.67 (7H, m, hydroxyl proton), 3.65-3.48 (14H, m, lactosyl proton) ppm. **Mass (m/z)**: 476 (M$^+$), 463, 450, 412, 387, 373, 344, 329. (Found: C, 47.87; H, 5.90; N, 5.86; S, 6.70 calcd for $C_{19}H_{28}O_{10}N_2S$; C, 47.89; H, 5.92; N, 5.88; S, 6.73%).

1-β-D-maltosyl-3-*o*-tolyl thiocarbamide (5d)

IR (KBr cm^{-1}): υ 3334 (O-H), 3136 (N-H), 3020 (Ar C-H), 2956 (Ali C-H), 1345 (C-N), 1074 (C=S), 1039 and 921 (characteristic of maltose). **^{1}H NMR (DMSO-D$_6$, ppm)**: δ 7.26-7.20 (5H, m, ArH), 6.35 and 5.45 (2H, s, NH), 5.30-4.29 (7H, m, hydroxyl proton), 4.25-3.98 (14H, m, maltosyl proton), 2.35 (3H, s, CH_3). **Mass (m/z)**: 490 (M$^+$), 476, 464, 450, 412, 387, 373, 344, 329. (Found: C, 48.95; H, 6.14; N, 5.70; S, 6.52 calcd for $C_{20}H_{30}O_{10}N_2S$; C, 48.97; H, 6.16; N, 5.71; S, 6.54%).

ANTIMICROBIAL STUDIES:

Antibacterial activity:

The compounds were screened for antibacterial activity against *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* in muller Hinton agar medium. Amikacin (100 µg/ml) was used as standard for antibacterial activity. The result are presented in Table 2.

Compounds **4c** and **5d**, were found to be active against *Escherichia coli*, **4c** and **5a** exhibited significant activity against *Staphylococcus aureus* and **4b**, **5a** and **5c**, active towards *Pseudomonas aeruginosa*. All other compounds exhibited low to moderate activity.

Antifungal activity:

The compounds were screened for antifungal activity against *Aspergillus niger* and *Trichoderma viride* in potato dextrose agar medium. Fluconazole (100 µg/ml) was used as standard for antifungal activity.

The results of antifungal activities are also tabulated in **Table 2**. Compound **4d** was most effective against *Aspergillus niger*. **4a, 4b** and **5d** actively inhibited *Trichoderma viride*. The other compounds exhibited low to moderate activity.

Table 2: Antimicrobial activities of 1-β-D-glycosyl-3-aryl thiocarbamides (3ia-d & 3iia-d)

Sr.no.	**Compounds**	**Antimicrobial activity****				
		Antibacterial activity			**Antifungal activity**	
		E. coli	*S. aureus*	*Ps. aeruginosa*	*A. niger*	*T. viride*
1.	4a	18	10	12	10	23
2.	4b	06	12	24	11	20
3.	4c	22	22	10	10	17
4.	4d	8	12	04	20	14
5.	5a	18	26	22	10	10
6.	5b	10	18	10	09	10
7.	5c	08	18	26	09	10
8.	5d	20	16	10	11	23
9.	Amikacin	25	24	27	-	-
10.	Fluconazole	-	-	-	24	25

**Zone of inhibition measured in mm, (15 or less) resistance, (16-20 mm) moderate and (more than 20 mm) sensitive.

CONCLUSION

The newly synthesized 1-β-D-glycosyl-3-aryl thiocarbamides exhibited comparable antibacterial and antifungal activities against the organisms tested. The method adopted in this investigation is simple, efficient and inexpensive and is useful in synthesizing pharmacologically important molecules.

ACKNOWLEDGEMENT

Authors are grateful to SAIF, Chandigarh for providing the spectral data and Dr. S. G. Bhadange, Principal, Shri Shivaji College, Akola for encouragement and providing necessary facilities.

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