Asian Journal of Chemistry; Vol. 33, No. 1 (2021), 127-131

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2021.22967

Synthesis and Antimicrobial Studies of Novel *N*-Glycosyl Hydrazino Carbothioamide

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Received: 27 August 2020; *Accepted*: 5 October 2020; *Published online*: 10 December 2020; AJC-20188

In view of applications of *N*-glycosylated compounds in medicinal chemistry and in many other ways, herein the synthesis of novel *N*-glycosyl hydrazino carbothioamides is reported. New N-glycosyl hydrazino carbothioamides were synthesized by the condensation of per-*O*-acetyl glycosyl isothiocyanate with different aromatic hydrazides. The newly synthesized compounds were characterized by using the IR, ^{1}H NMR and mass spectral studies. Antimicrobial evaluation of the synthesized *N*-glycosyl hydrazino carbothioamide was also examined. Antimicrobial activities of the synthesized compound were evaluated against bacteria *E. coli*, *P. aeruginosa*, *S. aureus*, *S. pyogenus* and fungi *C. albicans*, *A. niger* and *A. clavatus*. All the *N*-glycosyl hydrazino carbothioamides exhibit promising antimicrobial activity.

Keywords: Glycosyl isothiocyanates, Nicotinic acid hydrazide, *N*-Glycosyl hydrazino carbothioamide, Antimicrobial activity.

INTRODUCTION

The chemistry of thiocarbamide is broadly developed and well documented. Sugar thiocarbamide derivatives have been found to posses wide applications in industry as carbohydrate based detergent [1] and in medicine as an anticancer agents [2] and antifungal agents [3]. Heterocyclic thiocarbamides are known to exhibit antiviral, anti-tuberculosis, fungicidal and herbicidal activities [4]. These compounds arouse interest as potential biologically active substances and versatile intermediate for preparing various derivatives.

Hydrazide derivatives constitute an important class of compounds which have found wide utility in organic synthesis and gained great important due to diverse biological properties including antibacterial, antifungal, anti-inflammatory, anti-malarial and anti-tubercular activities [5]. Isoniazid is a well known anti-mycobacterial agents and exhibits good activities against tuberculosis [6]. Nicotinic acid derivatives have also been investigated as an agent for the prevention or delay of onset type 1 diabetes mellitus and also shows antibacterial, antioxidant, anti-inflammatory and anticarcinogenic activities [7]. Benzhydrazides have been reviewed to possess analgesic, antiviral, anti-convulsant, antioxidant, vasodilator, anti-tumour, antimicrobial, anti-tubercular, antidepressant, antimalarial and anti-inflammatory activities [8].

In view of earlier works [9-13] on biologically important glycosyl derivatives and also due to wide applications of hydrazide derivatives, it was of great interest to synthesize novel *N*-glycosyl hydrazino carbothioamide derivatives by reacting per-*O*-acetyl glycosyl isothiocyanate and different aromatic hydrazides to explore the possibilities of some altered biological activity. The antimicrobial activities of newly synthesized compounds have also been evaluated.

EXPERIMENTAL

Melting points were recorded on electrothermal melting point apparatus and are presented without correction. IR spectra were recorded on a Perkin-Elmer Spectrum RXI (4000-450 cm^{-1}) FTIR spectrometer. The ^{1}H NMR spectra were obtained on a Bruker DRX-300 (300 MHz FT-NMR) NMR spectrometer. The sample were dissolved in $CDCl_3$ and TMS solution was used as an internal standard. The mass spectra were recorded on Jeol SX-102 Mass spectrometer. TLC was performed in E. Merck per coated silica gel plates and detected by exposure under short UV light.

Synthesis: The key intermediate per-*O*-acetyl glycosyl isothiocyanate was synthesized in three steps. The first step is the acetylation of sugar with acetic anhydride and catalytic amount of perchloric acid. The product was brominated in HBr in AcOH. The per-*O*-acetyl glycosyl bromide was subjected

to nucleophilic substitution reaction with $Pb(SCN)_2$ in boiling dry xylene to yield per-*O*-acetyl glycosyl isothiocyanate (**Scheme-I**).

Synthesis of per-*O*-acetyl glycosyl hydrazino carbothioamide: A solution of per-*O*-acetyl glycosyl isothiocyanate (**1/4/6**) and different aromatic hydrazide (**2a-c**) in toluene was refluxed on heating mental for 5-6 h. The reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated in vacuum and the resultant sticky residue was triturated with petroleum ether (60-80 ºC) to afford solid which was crystallized from aqueous ethanol (**Scheme-II**).

Spectral data

2-Isonicotinoyl-*N*-tetra-*O*-acetyl glucosyl hydrazine carbothioamide (3a): Yield: 78%, m.p. 120-122 ºC, m.w.: 526, $[\alpha]_D$ (c, 0.03 in $CHCl_3$): +180º, R_f (7:3:: EtOAc:Pet. ether): 0.93. IR (KBr, ν_{max}, cm^{-1}): 3309.96 (N-H), 2901.04 (C-H, aliph.), 3016.77 (C-H, arom.), 1751.42 (C=O), 1373.36 (C-N), 1226.77 (C=S), 895-1041(glucose unit). ^1H NMR ($CDCl_3$, δ ppm): 3.82-5.61 (m, 7H, glucose unit, 1.99-2.21 (m, 12H, $4COCH_3$), 7.60-7.66 (m, 2H, pyridine-H), 8.74- 8.77 (m, 2H, pyridine- H), 8.0 (s, 1H, CONHR). Mass: 526(M^+), 331, 211, 169,122, 109, 106, 79, 59. Elemental analysis: calcd. (found) % for $C_{21}H_{26}N_4O_{10}S$: C, 47.90 (47.70); H, 4.98 (4.70); N, 10.64 (10.50); S, 6.09 (6.00).

2-Nicotinoyl-*N*-tetra-*O*-acetyl glucosyl hydrazine carbothioamide (3b): Yield: 80%, m.p. 90-92 ºC, m.w.: 526, $[\alpha]_D$ (c, 0.03 in $CHCl_3$): +183.3º, R_f (7:3:: EtOAc:Pet. ether): 0.71. IR (KBr, ν_{max}, cm^{-1}): 3309 (N-H), 2901 (C-H, aliph.), 3016 (C-H, arom.), 1751(C=O), 1373 (C-N), 1226 (C=S), 895-1041 (glucose unit). ^1H NMR ($CDCl_3$, δ ppm): 3.82-5.61 (m,7H, glucose unit), 1.99-2.21 (m, 12H, $4COCH_3$), 7.26-7.41(m, 1H, pyridine-H), 8.121-8.141 (m, 1H, pyridine-H), 8.75 (m, 1H, pyridine-H), 8.98 (m, 1H, pyridine-H), 8.7 (s, 1H, CONH), 1.24-1.31(s, 1H, NH). Mass: 526(M^+), 331, 211, 169, 109, 106, 79, 59. Elemental analysis: calcd. (found) % for $C_{21}H_{26}N_4O_{10}S$: C, 47.90 (47.70); H, 4.98 (4.70); N, 10.64 (10.50); S, 6.09 (6.00).

2-Benzoyl-*N*-tetra-*O*-acetyl glucosyl hydrazine carbothioamide (3c): Yield: 78%, m.p. 60-62 ºC, m.w.: 525, $[\alpha]_D$ (c, 0.03 in $CHCl_3$): +176.66º, R_f (7:3:: EtOAc:Pet. ether): 0.61. IR (KBr, ν_{max}, cm^{-1}): 3309 (N-H), 2901 (C-H, aliph.), 3016 (C-H, arom.), 1751 (C=O), 1373 (C-N), 1226 (C=S), 895-1041(glucose unit). ^1H NMR ($CDCl_3$, δ ppm): 3.82-5.61 (m, 7H, glucose unit), 1.99-2.21 (m, 12H, $4COCH_3$), 7.26-7.43 (m, 1H, aromatic-H), 7.45-7.53 (m, 2H, aromatic-H), 7.74-7.82 (m, 2H, aromatic-H), 8.7 (s, 1H, CONH), 2.0 (s, 1H, NH). Mass: 525(M^+), 619, 559, 331, 211, 169, 109, 105, 78, 58. Elemental analysis: calcd. (found) % for $C_{22}H_{27}N_3O_{10}S$: C, 50.28 (50.10); H, 5.18 (5.10); N, 8.00 (7.80); S, 6.10 (6.00).

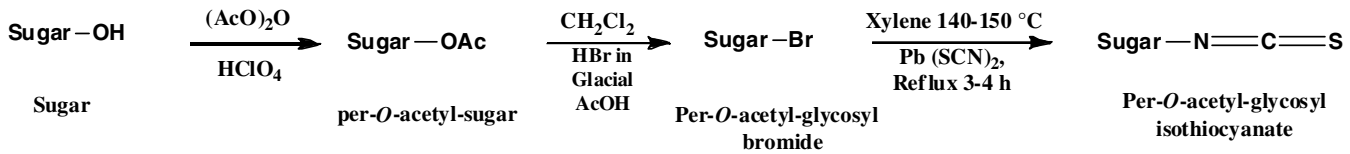
2-Isonicotinoyl-*N*-hepta-*O*-acetyl lactosyl hydrazine carbothioamide (5a): Yield: 75%, m.p. 135-137 ºC, m.w.: 814, $[\alpha]_D$ (c, 0.03 in $CHCl_3$): +216º, R_f (7:3:: EtOAc:Pet. ether): 0.86. IR (KBr, ν_{max}, cm^{-1}): 3294 (N-H), 2985 (C-H, aliph.), 3109 (C-H, arom.), 1751 (C=O), 1373 (C-N), 1226 (C=S), 902.72-1049 (lactose unit). ^1H NMR ($CDCl_3$, δ ppm): 3.76-5.53 (m, 14H, lactose unit), 1.96-2.15 (m, 21H, $7COCH_3$), 7.60-7.66 (m, 2H, pyridine-H), 8.74-8.77 (m, 2H, pyridine-H), 8.0 (s, 1H, -CONHR). Mass: 814(M^+), 331, 211, 169,122, 109, 106, 79, 59. Elemental analysis: calcd. (found) % for $C_{33}H_{42}N_4O_{18}S$: C, 48.65 (48.40); H, 5.20 (5.10); N, 6.88 (6.70); S, 3.94 (3.75).

2-Nicotinoyl-*N*-hepta-*O*-acetyl lactosyl carbothioamide hydrazine (5b): Yield: 85%, m.p. 92-94 ºC, m.w.: 814, $[\alpha]_D$ (c, 0.03 in $CHCl_3$): +220º, R_f (7:3:: EtOAc:Pet. ether): 0.62.IR (KBr, ν_{max}, cm^{-1}): 3279 (N-H), 2978 (C-H, aliph.), 3279 (C-H, arom.), 1751 (C=O), 1373 (C-N), 1226 (C=S), 902-1049 (lactose unit). ^1H NMR ($CDCl_3$, δ ppm): 3.76-5.53 (m, 14H, lactose unit), 1.96-2.15 (m, 21H, $7COCH_3$), 7.26-7.41 (m, 1H, pyridine-H), 8.12-8.14 (m, 1H, pyridine-H), 8.75 (m, 1H, pyridine-H), 8.98 (m, 1H, pyridine-H), 8.7 (s, 1H, CONH), 1.24-1.31 (s, 1H, NH). Mass: 814(M^+), 331, 211, 169, 109, 106, 79, 59. Elemental analysis: calcd. (found) % for $C_{33}H_{42}N_4O_{18}S$: C, 48.65 (48.50); H, 5.20 (5.12); N, 6.88 (6.78); S, 3.94 (3.70).

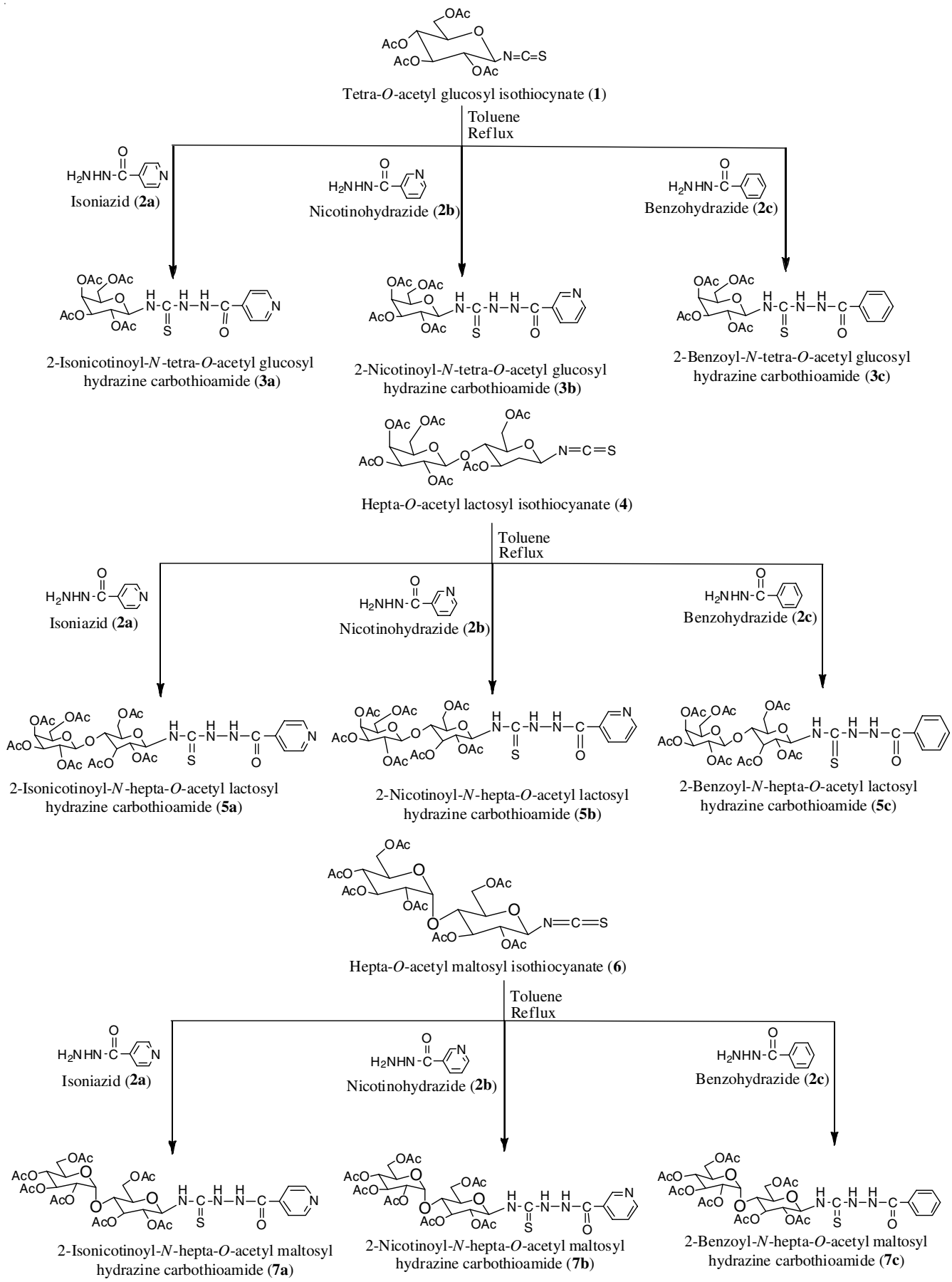
2-Benzoyl-*N*-hepta-*O*-acetyl lactosyl hydrazine carbothioamide (5c): Yield: 79%, m.p. 70-72 ºC, m.w.: 813, $[\alpha]_D$ (c, 0.03 in $CHCl_3$): +223.3º, R_f (7:3:: EtOAc:Pet. ether): 0.81. IR (KBr, ν_{max}, cm^{-1}): 3309 (N-H), 2901 (C-H, aliph.), 3016 (C-H, arom.), 1751 (C=O), 1373 (C-N), 1226 (C=S), 895-1041 (glucose unit). ^1H NMR ($CDCl_3$, δ ppm): 3.76-5.53 (m, 14H, lactose unit), 1.96-2.15 (m, 21H, $-COCH_3$), 7.26-7.43 (m, 1H, aromatic-H), 7.45-7.53 (m, 2H, aromatic-H), 7.74-7.82 (m, 2H, aromatic-H), 8.7 (s, 1H, CONH), 2.0 (s, 1H, NH). Mass: 813(M^+), 619, 559, 331, 211, 169, 109, 105, 78, 58. Elemental analysis: calcd. (found) % for $C_{34}H_{43}N_3O_{18}S$: C, 50.18 (50.00); H, 5.33 (5.10); N, 5.16 (5.11); S, 3.94 (3.62).

2-Isonicotinoyl-*N*-hepta-*O*-acetyl maltosyl hydrazine carbothioamide (7a): Yield: 77%, m.p. 147-149 ºC, m.w.: 814, $[\alpha]_D$ (c, 0.03 in $CHCl_3$): +200º, R_f (7:3:: EtOAc:Pet. ether): 0.75. IR (KBr, ν_{max}, cm^{-1}): 3294 (N-H), 2962 (C-H, aliph.), 3109 (C-H, arom.), 1751 (C=O), 1373 (C-N), 1234 (C=S), 902-1041 (maltose unit). ^1H NMR ($CDCl_3$, δ ppm): 3.93-5.41 (m, 14H, maltose unit), 1.99-2.14 (m, 21H, $7COCH_3$), 7.60-7.66 (m, 2H, pyridine-H), 8.74-8.77 (m, 2H, pyridine-H), 8.0 (s, 1H, -CONHR). Mass: 814(M^+), 331, 211,122, 169, 109, 106, 79, 59. Elemental analysis: calcd. (found) % for $C_{33}H_{42}N_4O_{18}S$: C, 48.65 (48,53); H, 5.20 (5.15); N, 6.88 (6.63); S, 3.94 (3.73).

2-Nicotinoyl-*N*-hepta-*O*-acetyl maltosyl hydrazine carbothioamide (7b): Yield: 82%, m.p. 95-97 ºC, m.w.: 814, $[\alpha]_D$ (c, 0.03 in $CHCl_3$): +203º, R_f (7:3:: EtOAc:Pet. ether): 0.58. IR (KBr, ν_{max}, cm^{-1}): 3294 (N-H), 2962 (C-H, aliph.), 3109 (C-H, arom.), 1751 (C=O), 1373 (C-N), 1234 (C=S), 902-1041(maltose unit). ^1H NMR ($CDCl_3$, δ ppm): 3.93-5.41



Scheme-I: Synthesis of key intermediate per-*O*-acetyl glycosyl isothiocyanate



Scheme-II: Synthetic route of per-*O*-acetyl glycosyl hydrazino carbothioamides

(m, 14H, maltose unit), 1.99-2.13 (m, 21H, -$COCH_3$), 7.26-7.41 (m, 1H, pyridine-H), 8.12-8.14 (m, 1H, pyridine-H), 8.75 (m, 1H, pyridine-H), 8.98 (m, 1H, pyridine-H), 8.7 (s, 1H, CONH), 1.24-1.315 (s, 1H, NH). Mass: 814(M^+), 331, 211, 169, 109, 106, 79, 59. Elemental analysis: calcd. (found) % for $C_{33}H_{42}N_4O_{18}S$: C, 48.65 (48.58); H, 5.20 (5.19); N, 6.88 (6.73); S, 3.94 (3.89).

2-Benzoyl-*N*-hepta-*O*-acetyl maltosyl hydrazine carbothioamide (7c): Yield: 77%, m.p. 74-76 ºC, m.w.: 813, $[\alpha]_D$ (c, 0.03 in $CHCl_3$): +203.3º, R_f (7:3:: EtOAc:Pet. ether): 0.70. IR (KBr, ν_{max}, cm^{-1}): 3294 (N-H), 2962 (C-H, aliph.), 3109 (C-H, arom.), 1751 (C=O), 1373 (C-N), 1234 (C=S), 902-1041 (maltose unit). ^1H NMR ($CDCl_3$, δ ppm): 3.93-5.41 (m, 14H, maltose unit), 1.99-2.13 (m, 21H, -$COCH_3$), 7.26-7.43 (m, 1H, aromatic-H), 7.45-7.53 (m, 2H, aromatic-H), 7.74-7.82 (m, 2H, aromatic-H), 8.7 (s, 1H, CONH), 2.0 (s, 1H, NH). Mass: 813(M^+), 331, 169, 109, 105, 78, 58. Elemental analysis: calcd. (found) % for $C_{34}H_{43}N_3O_{18}S$: C, 50.18 (50.08); H, 5.33 (5.17); N, 5.16 (5.03); S, 3.94 (3.79).

Antimicrobial activity: The antimicrobial activity of newly synthesized compounds were tested against a panel of selected Gram-positive (*S. aureus*, *S. pyogenus*) and Gram-negative (*E. coli*, *P. aeruginosa*) bacteria and also few fungi (*C. albicans*, *A. niger*, *A. clavatus*) in comparison with reference drugs ampicillin, gentamycin, chloramphenicol, ciprofloxacin, norfloxacin for antibacterial activity and nystatin, greseofulvin for antifungal activity using broth dilution method [14]. The lowest concentration inhibiting growth of the organism is recorded as the MIC.

RESULTS AND DISCUSSION

Per-*O*-acetyl-glycosyl hydrazino carbothioamides were synthesized by the condensation of substituted aromatic hydrazides and per-*O*-acetyl glycosyl isothiocyanate in toluene for 5-6 h. The reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated in vacuum and resultant sticky residue was triturated with petroleum ether (60-80 ºC) to afford the product. The products were crystallized from aqueous ethanol. Structure of newly synthesised compounds were confirmed by using the IR, ^1H NMR and mass spectral studies.

The IR spectra of the compounds showed strong characteristic absorption of glycosyl unit in the range of 910-895 and 1400-1000 cm^{-1} for stretching vibration of C-H bond. The stretching band for acetyl C=O also appeared in the region 1750-1749 cm^{-1}. The absorption bands for C=S and C-N have been appeared in the region 1234-1226 and 1373-1300 cm^{-1}, respectively. ^1H NMR spectrum of the synthesized compounds shows the characteristic of glycosyl protons at δ 5.6-3.7 ppm and resonance signals for aromatic protons at δ 7.41-8.77 ppm, while the acetyl protons appeared at δ 1.96-2.21 ppm. Pyridine proton are appeared at δ 7.60-7.66 and δ 8.74-8.77 ppm.

Antimicrobial activity: The synthesized compounds were tested for their antibacterial activities against *E. coli*, *P. aeruginosa*, *S. aureus* and *S. pyogenus* using gentamycin, ampicillin, chloramphenicol, ciprofloxacin and norfloxacin as the standard drugs. All the synthesized compounds tested for antibacterial activity were found to be moderately active against *E. coli* and *P. aeruginosa*. Compounds **3a** and **5c** were found equally potent, compounds **3b** and **5a** found to have exceptional activity, while compounds **3c**, **7a**, **7b** and **7c** exhibited moderate activity against *S. aureus* comparison with ampicillin standard drug. Compounds **3c**, **5a** and **5b** were found equally potent, whereas compounds **3a**, **3b**, **5c**, **7a**, **7b** and **7c** were found to be moderately active against *S. pyogenus* comparison with ampicillin, chloramphenicol and ciprofloxacin standard drugs.

The synthesized compounds were also tested for their antifungal activities against *C. albicans*, *A. niger* and *A. clavatus* using nystatin and greseofulvin as standard drugs. Compounds **3a**, **3b**, **5a** and **7b** were found equally potent, compound **3c** found to have exceptional activity while compounds **5b**, **5c**, **7a** and **7c** were weakly active against *C. albicans* as compare to standard drug greseofulvin. All the synthesized compounds were found to be inactive against *A. niger* and *A. clavatus* (Table-1).

TABLE-1
ANTIMICROBIAL ACTIVITIES OF SYNTHESIZED COMPOUNDS (MINIMAL INHIBITION CONCENTRATION, μg/mL)

Compound	Bacteria				Fungi		
	E. coli MTC 443	*P. aeruginosa* MTCC 441	*S. aureus* MTCC 96	*S. pyogenus* MTCC 442	*C. albicans* MTCC 227	*A. niger* MTCC 282	*A. clavatus* MTCC 1323
3a	125	200	250	250	500	>1000	>1000
3b	150	250	125	200	500	>1000	>1000
3c	200	200	500	50	200	>1000	>1000
5a	250	200	125	100	500	>1000	>1000
5b	200	250	100	50	1000	>1000	>1000
5c	200	250	250	125	1000	>1000	>1000
7a	250	125	500	200	1000	>1000	>1000
7b	200	125	500	500	500	>1000	>1000
7c	250	125	500	500	1000	>1000	>1000
Gentamycin	0.05	1	0.25	0.5	–	–	–
Ampicillin	100	–	250	100	–	–	–
Chloramphenicol	50	50	50	50	–	–	–
Ciprofloxacin	25	25	50	50	–	–	–
Norfloxacin	10	10	10	10	–	–	–
Nystatin	–	–	–	–	100	100	100
Greseofulvin	–	–	–	–	500	100	100

Conclusion

Newly synthesized *N*-glycosyl hydrazino carbothioamides **3a-c**, **5a-c** and **7a-c** were successfully synthesized and characterized on the basis of IR, ^{1}H NMR and mass spectral studies. Most of the synthesized *N*-glycosyl hydrazine carbothioamides exhibited comparable antibacterial and antifungal activities against highly pathogenic organisms.

ACKNOWLEDGEMENTS

The authors are thankful to Centre of Excellence, Department of Chemistry, Saurashtra University, Rajkot, India for providing spectral data and Microcare Laboratory, Surat, India for conducting the antimicrobial activities.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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