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Der Pharma Chemica, 2015, 7(4):185-189
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Synthesis and antimicrobial activity of 3-cyanamidino-5-glycosylimino-1,2,4-thiadiazolines

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ABSTRACT

The synthesis of novel glycosides derivatives and investigation of their chemical and biological behavior have gained more importance in recent decades. 3-cyanamidino-5-glycosylimino-1,2,4-thiadiazolines were synthesized by the oxidative cyclization of glycosyl-3-cyanamidino thiocarbamides. The 1-glycosyl-3-cyanamidino thiocarbamides were prepared by the interaction of glycosyl isothiocynates with dicyanodiamide. The identities of these newly synthesized compounds have been established on the basis of usual chemical transformations and IR, ^{1}H NMR and Mass spectral studies. The synthesized compounds were assayed for their antimicrobial activity most of them possess moderate to significant activity.

Keywords: Glycosyl isothiocynates, dicyanodiamide, 1-glycosyl-3-cyanamidino thiocarbamides, thiadiazolines, antimicrobial activity.

INTRODUCTION

The chemistry of heterocyclic compounds have been an interesting field of study for a long time. The synthesis of novel thiadiazole derivatives and investigation of their chemical and biological behavior have gained more importance in recent decades. Thiocarbamido, amidino thiocarbamido, cyanamidino thiocarmido and thioamido nucleus containing heterocycles. These heterocycles possesses their own identity in pharmaceutical, industrial, agricultural and medicinal sciences.[1-5]

Sugar linked thiadiazolines have a wide range of biologically important uses such as inhibition of replication of HIV, antihypertensive also as potential hypoglycemic agents and antiarrhythmic activities. Also these nucleus containing compounds enhance the potential and therapeutical value of that drug. Hence, there is an evolution in drug, pharmaceutical and medicinal sciences.

The above uses of thiadiazolines and our interest in carbohydrate chemistry promoted us to combine them in a single entity and thus this involves the synthesis of 3-cyanamidino-5-glycosylimino-1,2,4-thiadiazolines (VIa-f).

MATERIALS AND METHODS

Melting points of the synthesized compounds were recorded on electro thermal melting point apparatus and are uncorrected. Specificrotations of the newly synthesized compounds were measured on Equip-Tronic digital polarimeter model no. EQ 801 at 30^0C in $CHCl_3$. IR spectra were recorded on a Shamazdu FTIR spectrophotometer.

^{1}HNMR were obtained on a Bruker DRX-300(300 MHz FT NMR) NMR spectrophotometer in $CDCl_3$ solution with TMS as an internal reference. The MS spectra were recorded on a Jeol SX -102 FAB mass spectrophotometer. Purity of the compounds was checked by thin layer chromatography using Merck silica gel coated aluminum plates and petroleum ether: ethyl acetate as eluent. The glycosyl bromide was prepared according to the literature[10-11].

General Procedure:

*Synthesis of 1-glycosyl-3-cyanamidino thiocarbamides **(IIIa-f):***

A (0.005mol) dicyandiamide (II) was added to a solution of glycosyl isothiocynates (Ia-f) (0.005mol) in 15ml acetone and the reaction mixture were refluxed over boiling water bath for 3hr. After refluxing, the solvent was distilled off and the sticky residue obtained was triturated with petroleum ether (60-80^{0}C) to afford a granular solid **(IIIa-f)**. The products were purified by recrystallization from chloroform-petroleum ether (1:3).

*Synthesis of 3-cyanamidino-5-glycosylimino-1, 2, 4-thiadiazolines **(IVa-f)**:*

1-glycosyl-3-cyanamidino thiocarbamides (IIIa-f) were made into paste with chloroform (2ml) and to it bromine solution in chloroform (20% bromine in chloroform, v/v) was added drop wise with stirring till the evolution of lachrymatory fumes of hydro bromide. An orange red sticky mass thus obtained was allowed to stand for 5-6 h. The sticky mass then subjected to basification which then gives product 3-cynamidino-5-glycosylimino-1, 2, 4-thiadiazolines **(IVa-f).**

(Scheme I).

Spectral Data:

*1-tetra-O-benzoyl-β-D-glucosyl-3-cyanamidino thiocarbamide **(IIIa) :-***

IR(KBr cm^{-1}):3423(N-H str.), 1454.33(C≡N), 3061 (Aromatic C-H), 1730.15 (C=O), 1454.33 (C=N), 1313 (C-O), 704.02(Monosubstituted benzene**);^{1}H NMR** ($CDCl_3$,ppm): δ 8.204-7.426(21H,m, Aromatic proton), 7.368-4.611(7H, m, glucosyl ring), 4.519-4.185 (4H, s, N-H proton),**MASS(m/z):**723(M^++2), 656 (M^+-$C_2N_5H_2$), 579 (TBG$^+$, M^+-$C_8N_5H_7$), 517(M^+-$C_9N_6H_9S$), 475(M^+-$C_9N_6H_9S$,CO_2) .(Found: C, 61.49; H, 5.20; N, 12.37; S, 4.41% Calcd for $C_{37}H_{31}N_5O_9S$: C, 61.58; H, 5.27; N, 12.39; S, 4.40%)

*1-hepta-O-benzoyl-β-D-lactosyl-3-cyanamidino thiocarbamide **(IIId):-***

IR(KBr cm^{-1}):3318 (N-H), 3062 (Aromatic C-H), 1730 (C=O), 1452 (C=N), 1176 (C=S), 1265 (C-O),713 (Monosubstituted benzene**); ^{1}H NMR** ($CDCl_3$,ppm): δ 8.13-5.75 (39H, m, Aromatic proton), 5.66-4.98 (2H, s, aliphatic NH_2), 4.71-1.07 (14H, m,lactosyl protons), **MASS(m/z):**1195(M^+), 1160(HBL$^+$,M-H_3S,C_7H_7N), 949(HBL-$C_9O_2H_{10}N_3$), 845($C_{11}H_{13}N_5O_2S$), 579 (HBL-$C_{14}O_{11}H_{10}N_3$,2 OBz), 151 (HBL-$C_{10}O_3H_{10}N_3$,5 OBz);(Found:C,64.20; H,4.38; N,7.51; S,2.68 % Calcd for $C_{64}H_{53}N_5O_{17}S$: C,64.26; H, 4.43; N,7.53; S,2.67%).

*1-hepta-O-acetyl-β-D-maltosyl-3-cyanamidino thiocarbamide **(IIIe):-***

IR(KBr cm^{-1}):3431 (N-H), 2968 (Aliphatic C-H), 1745 (C=O), 1504 (C=N), 1369 (C-O),1055 (C-S str), 1176 and 1026 (Characteristics of maltose**); ^{1}H NMR** ($CDCl_3$,ppm): δ 5.58-5.21 (4H, s, N-H), 2.11-1.22(21H, s, aliphatic protons),5.24-2.14 (14H, m, maltosyl proton), **MASS(m/z):** 763(M^++2), 732 (M^+-S),701 (M+-S,CNH_2), 659 (HAM$^+$, M^+-$C_3H_4N_5S$), 560(HAM$^+$,M^+-$C_3H_4N_5S$,OAc), 331(TAG$^+$,M^+-$C_9N_5H_4S$,3OAc), 169(TAG-$C_9N_5H_4S$,5OAc). (Found:C,45.68; H,4.98; N,11.84; S,4.23% Calcd for $C_{29}H_{39}N_5O_{17}S$: C,45.72; H, 5.12; N,11.82; S,4.20%).

*3-cyanamidino-5-tetra-O-benzoyl -β-D-glucosylimino-1, 2, 4-thiadiazoline **(IVa):-***

IR (KBr cm^{-1}):3496(N-H str.), 1454.40(C≡N), 3062.96 (Aromatic C-H), 1730 (C=O), 1454.33 (C=N), 1265.30 (C-O), 1176.58 (C=S str), 713.66(Monosubstituted benzene**);^{1}H NMR** ($CDCl_3$,ppm): δ 7.38-7.34(20H,m, Aromatic proton), 5.94-4.51(7H, m, glucosyl ring),8.11-7.62 (2H, s, N-H proton), **MASS (m/z):**719(M^+-2), 693 (M^+-CN), 655(M^+-C_2N_3), 579 (TBG$^+$, M^+-$C_3N_5H_2S$), 288(TBG-2OBz,CO_2,H_2,$C_3N_5H_2S$) .(Found: C, 56.09; H, 3.58; N, 12.48; S, 4.47% Calcd for $C_{37}H_{29}N_5O_9S$: C, 56.13; H, 3.66; N, 12.51; S, 4.45%)

*3-cyanamidino-5-hepta-O- benzoyl -β-D-lactosylimino-1, 2, 4-thiadiazoline **(IV d):-***

IR(KBr cm^{-1}):3062.96(N-H), 2920.23,2852.72 (Ali C-H), 1751 (C=O), 1651 (C=N), 875 (C=S), 1072(C-O); **^{1}H NMR** ($CDCl_3$,ppm): δ 2.12-2.097 (2H, m, NH), 5.35-3.90(21H, s, aliphatic proton), 2.07-1.98 (14H, m, lactosyl protons), **MASS(m/z):**759(M^+), 733(M-CN), 717 (M-CN_2H_2), 691(M-$C_2N_4H_2$), 619(HAL$^+$, M-$C_3N_6H_2S$), 559 (HAL-$C_3N_6H_2S$,OAc), 331(TAG, M-$C_3N_6H_2S$,4OAc), 169(TAG, M-$C_3N_6H_2S$,6OAc, CO_2)(Found:C,64.30; H,4.18; N,7.52; S,2.70% Calcd for $C_{64}H_{40}N_5O_{17}S$: C,64.37; H, 4.27; N,7.54; S,2.68%).

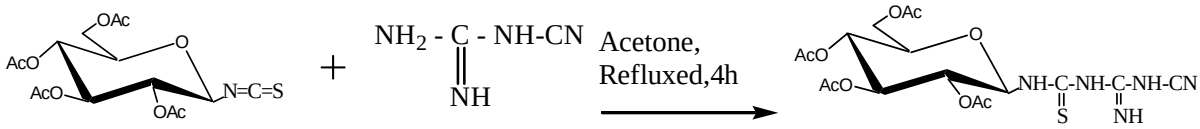
*3-cyanamidino-5-hepta-O- benzoyl -β-D-maltosylimino-1, 2, 4-thiadiazoline (**IVf**):-*
IR(KBr cm^{-1}):3338.72(N-H), 3061.03 (Aromatic C-H), 1743.65 (C=O), 1643 (C=N), 1284.50 (C-O),858(C-S str), 1176 and 1026 (Characteristics of maltose**);** **^{1}H NMR** ($CDCl_3$,ppm): δ 7.54- 7.48 (2H, s, N-H), 8.11-7.62(35H, s, aromatic protons),5.73-4.39 (14H, m, maltosyl proton); **MASS(m/z):**1193(M^+), 1120(M-CN_2SH), 1093(M-$C_2N_3H_2S$), 1053(HBM+, M-$C_2N_5H_2S$), 976(HBM-C_6H_5), 932 (HBM-$C_7H_5O_2$), 579(TBG$^+$, HBM-$C_{27}H_{22}O_8$), 474 (TBG-C_6H_5), 353(TBG-C_7H_5O,$C_7H_5O_2$), 232(HBM-TBG,2$C_7H_5O_2$), 121(HBM-TBG,3$C_7H_5O_2$,$C_8H_7O_2$). (Found:C,45.78; H,4.80; N,11.82; S,4.24% Calcd. for $C_{29}H_{37}N_5O_{17}S$: C,45.84; H, 4.87; N,11.85; S,4.21%).

Antibacterial activity:-
Newly synthesized thiadiazolines were tested against following pathogenic microbes for their antibacterial and antifungal activities using cup plate agar diffusion method[12] like *Escherichia coli*, *Staphylococcus aureus*, *Proteus vulgaris*, *Pseudomonas auriginosa* and *Acinobactor baumani* on agar medium *and Aspergillus niger*, *Candida albicans* in potato dextrose agar medium. The results of antimicrobial activities are also presented in **Table-III and IV.**

It has been observed that some of these compound exhibited interesting microbial activities. Almost all the compounds exhibited moderate to sensitive activities against *Ps. Aeruginosa*, *A. Baumani* and *K. pneumonia* while all compounds exhibited low to moderate activity against *E. Coli*, *S. aureus* all compounds exhibits moderate to sensitive activities against *A. niger* and *C. albicans.*

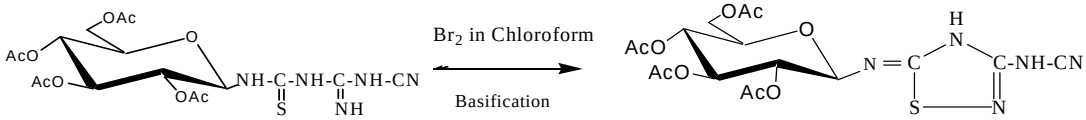
Scheme-I:

A) **Synthesis of 1-glycosyl-3-cyanamidino thiocarbamide (IIIa):**



Tetra-*O*-acetyl-β-D isothiocyanate (Ia) | Dicyanodiamide (II) | 1-tetra-*O*-acetyl-β-D-glucosyl-3-glucosyl cyanamidino thiocarbamide (IIIa)

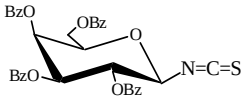
B) **Synthesis of 3-cyanamidino-5-glycosylimino-1, 2, 4-thiadiazoline (IVa):**



1-tetra-*O*-acetyl-β-D-glucosyl-3-thiocarbamide(IIIa) | 3-cyanamidino-5-tetra-*O*-acetyl-β-D-cyanamidino glucosylimino-1, 2, 4-thiadiazoline(IVa)

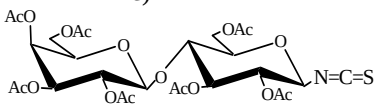
Where,

Ib)



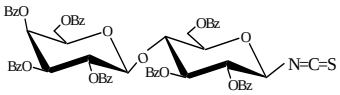
Tetra-*O*-benzoyl-β-D-glucosyl isothiocynate,

Ic)



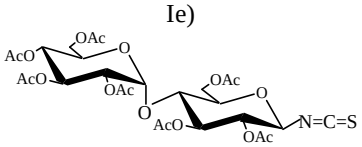
Hepta-*O*-acetyl-β-D-lactosyl isothiocynate,

Id)



Hepta-*O*-benzoyl-β-D-lactosyl isothiocynate,

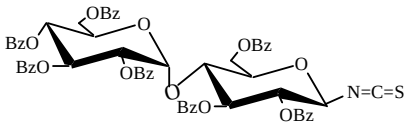
Ie)



Hepta-*O*-acetyl-β-D-maltosyl isothiocynate,

If)

Where, Bz = COC_6H_5, Ac = $COCH_3$



Hepta-*O*-benzoyl-β-D-maltosyl isothiocynate

Table I:-1-glycosyl-3-cyanamidino thiocarbamides (IIIa-f) (Scheme 1). Reactants i) Glycosyl isothiocynates (Ia-f). ii) Dicyanodiamide (II)

Sr. No.	Product	m.p. (°C)	Yield (%)	Analysis (%) found(required)		Rf Value	$[\alpha]_D^{31}$ (c, in $CHCl_3$]
				N	S		
1.	IIIa	142	83	18.96 (18.98)	6.76 (6.75)	0.62	-152.25° (0.5 in $CHCl_3$)
2.	IIIb	96	86	12.37 (12.39)	4.41 (4.4)	0.79	-134.26° (0.5 in $CHCl_3$)
3.	IIIc	118	82	11.83 (11.83)	4.21 (4.20)	0.54	-101.25° (0.5 in $CHCl_3$)
4.	IIId	135	81	7.51 (7.53)	2.68 (2.67)	0.59	-98.01° (0.5 in $CHCl_3$)
5.	IIIe	82	77	11.84 (11.82)	4.23 (4.20)	0.64	-91.30° (0.5 in $CHCl_3$)
6.	IIIf	167	70	7.52 (7.53)	2.69 (2.67)	0.72	-195.45° (0.5 in $CHCl_3$)

Table II:-**3-cyanamidino-5-glycosyl imino-1, 2, 4-thiadiazolines(IVa-f) (Scheme 1).**

Sr. No.	Product	m.p. (°C)	Yield (%)	Analysis(%) found(required)		Rf Value	$[\alpha]_D^{31}$ (c, in $CHCl_3$]
				N	S		
1.	IVa	82	93	5.79 (5.81)	2.65 (2.66)	0.67	-178.30° (0.5 in $CHCl_3$)
2.	IVb	134	89	5.80 (5.81))	2.64 (2.66)	0.80	-138.28 (0.5 in $CHCl_3$)
3.	IVc	148	84	6.35 (6.37)	4.25 (4.30)	0.69	-187.12° (0.5 in $CHCl_3$)
4.	IVd	127	81	8.0 (8.06)	4.57 (4.60)	0.76	-142.30° (0.5 in $CHCl_3$)
5.	IVe	136	86	8.0 (8.06)	4.58 (4.60)	0.69	-198.12° (0.5 in $CHCl_3$)
6.	IVf	130	73	10.87 (10.95)	6.18 (6.26)	0.78	-169.23° (0.5 in $CHCl_3$)

C and H analysis were found satisfactory in all cases.

Table-II: Antimicrobial activities of novel 1-glycosyl-3-cyanamidino thiocarbamides (IIIa-f)

Compounds	**Antibacterial**					**Antifungal**	
	E. coli	*S. aureus*	*K. pneumoniae*	*Ps. aeruginosa*	*A. Baumani*	*A. niger*	*C. albicans*
IIIa	14	12	16	17	16	21	18
IIIb	12	14	13	18	15	19	17
IIIc	13	13	15	18	16	20	18
IIId	12	12	14	18	17	18	15
IIIe	16	12	12	15	16	20	18
IIIf	14	12	12	18	15	17	18
Amikacin	22	24	27	20	29	---	---
Flucanazole	---	---	---	---	---	25	26

TableIV: Antimicrobial activities of novel 3-cyanamidino-5-glycosyl imino-1, 2, 4-thiadiazolines(IVa-f)

Compounds	Antibacterial					Antifungal	
	E. coli	*S. aureus*	*K. pneumoniae*	*Ps. aeruginosa*	*A. Baumani*	*A. niger*	*C. albicans*
IVa	12	12	12	18	16	17	18
IVb	12	12	13	18	16	20	16
IVc	13	12	12	17	16	20	20
IVd	13	12	13	18	17	18	18
IVe	13	12	12	15	16	17	16
IVf	13	12	12	18	15	16	16
Amikacin	22	24	27	20	29	---	---
Flucanazole	---	---	---	---	---	25	26

RESULTS AND DISCUSSION

Several 3-cyanamidino-5-glycosylimino-1, 2, 4-thiadiazolines (VIa-f) have been synthesized by the oxidative cyclization of 1-glycosyl-3-cyanamidino thiocarbamides (Va-f) by using molecular bromine in chloroform. These 1-glycosyl-3-cyanamidino thiocarbamides were synthesized by condensation of dicyanodiamide(V) and various glycosyl isothiocynates (IIIa-f). **(Scheme-I)**.

The reaction was monitored by TLC. The structures of the products were confirmed by IR, ^{1}H NMR and Mass[6-8]spectral analysis and elemental analysis **(Table I & II).** The specific rotations of the product were also recorded[9].

CONCLUSION

Derivatives were synthesized and characterized for their structure elucidation. Various chemical and spectral data supported the structures. Some of the compounds synthesized showed promising antimicrobial activities. The newly synthesized thiadiazolines exhibits 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. The method adopted in the synthesis and investigation is simple, efficient and inexpensive in synthesizing pharmacologically important molecules.

Acknowledgement
Authors are thankful to SAIF, CDRI Chandigarh for providing the spectral data and also to DR. S. G. Bhadange, Principal, Shri Shivaji College, Akola for providing necessary facilities.

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