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Synthesis and Antimicrobial Activity of 3-Amino-5-sugarimino-1, 2, 4-thiadiazolines

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ABSTRACT

A series of 3-amino-5-sugarimino-1, 2, 4-thiadiazolines have been synthesized by oxidative cyclization of sugar-3-amidinothiocarbamides by using bromine. These amidino thiocarbamides were prepared by interaction of guanidine and sugar isothiocynates. Guanidine itself plays an important role as antifungal, anticancer activities when it links with glycosides its acivity increased. These newly synthesized compounds have pharmaceutical uses. The identities of these newly synthesized compounds have been established on the basis of usual chemical transformation and IR, ^{1}H NMR, and Mass spectral studies. The synthesized compounds were screened for their in vitro antimicrobial activities using human pathogens.

Keywords: Sugar isothiocynates, guanidine, sugar-3-amidinothiocarbamides, 1, 2, 4-thiadiazolines, antimicrobial activity.

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INTRODUCTION

Heterocyclic compounds having three hetero atoms in ring posses a wide range of pharmacological behaviours. Thiadiazolines belongs to these category have spectrum of biological and technological applications. 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. This class of compounds also used as antifungal[1], antitumor[2], anticancer[3], antiviral[4] and anti malerial activity[5]. Such significant values have focused our interest on the studies towards these compounds.

In this communication series of 3-amino-5-sugarimino-1, 2, 4-thiadiazolines (IV) have been synthesized by oxidative cyclization of sugar-3-amidinothiocarbamides (III) by using bromine. These amidino thiocarbamides were prepared by interaction of guanidine (I) and sugar isothiocynates(II).

The IR, ^{1}H NMR and Mass[7-8] spectral analysis and elemental analysis (Table 1) indicate the product and design the structure as 3-amino-5- Sugarimino-1, 2, 4-thiadiazolines (IV).

MATERIALS AND METHODS:-

The reagent grade chemicals were obtained from commercial sources and purified by either distillation or recrystallization before use. 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 CDCl3 on Bruker DRX-300 of NMR spectrometer 300 MHz. The Mass spectra were recorded on Waters UPLC-TQD Mass Spectrometer. Optical rotations were measured on Equip-Tronics EQ 800 Digital Polarimeter in CHCl3. Purity of synthesized compounds has been checked by thin layer chromatography. It was performed on E. Merck pre-coated silica gel plates.

Procedure:-

Sugar isotiocyanates(I) was prepared by the known method, by refluxing Sugar bromide(0.001 M, 1.1 g in 40ml) with lead isothiocyante in xylene for about 4 hrs. This Sugar isothiocynate (0.001 M, 1.1 g in 20 ml) was mixed with guanidine (II) in ethanolic medium (0.001 M, 0.12 g in 20 ml). This mixture was refluxed for 2.30 h. in water bath which results in Sugar-3-amidinothiocarbamides (III) .After that it is kept for solvent evaporation which affords a sticky mass which is isolated by ethanol-water system. It was purified by ethanol-water. Sugar-3-amidinothiocarbamides (III) is then subjected to oxidative cyclization by using bromine in

chloroform it was kept overnight at room temperature which was basified to yield 3-amino-5-Sugarimino-1, 2, 4-thiadiazolines (IV). It gives charring test. (Scheme I).

Scheme I

R-Br+ Pb (SCN)$_2$ —xylene,4 h→ R-NCS + $PbBr_2$

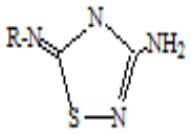
Sugar bromide Lead isothiocynate Sugar isothiocynates(Ia-g) Lead Bromide

Scheme II

RNCS + NH_2-C(=NH)-NH_2 —Ethanol, Refluxed, 2.30h→ R—NHCSNHC(=NH)NH$_2$

Sugar isothiocynates(Ia-g) guanidine (II) Sugar-3-amidinothiocarbamides(IIIa-g)

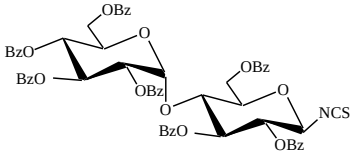
↓ Br_2 in Chloroform



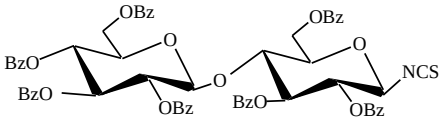
3-amino-5- Sugarimino-1, 2, 4-thiadiazolines(IVa-g)

Where, Sugar isothiocynates=

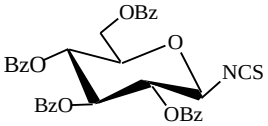
Ia)hepta-*O*-benzoyl maltosl isothiocynate,



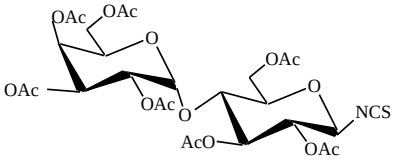
Ib)hepta-*O*-benzoyl lactosyl isothiocynate,

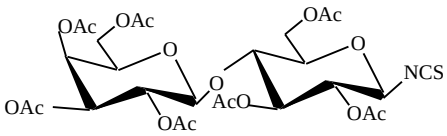


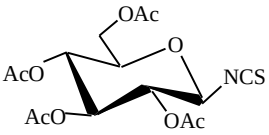
Ic) tetra-*O*-benzoyl glucosyl isothiocynate,



Id) hepta-*O*-acetyl maltosyl isothiocynate,



Ie)hepta-*O*-acetyl lactosyl isothiocynate, 

If)tetra-*O*-acetyl glucosyl isothiocynate. 

RESULTS AND DISCUSSION

Herein, we report the synthesis of various 3-amino-5- Sugarimino-1, 2, 4-thiadiazolines(IVa-g**)** by interaction of Sugar substituted isothiocynates(Ia-g**)** and guanidine (II**)** in ethanol medium. All products were crystallized from ethanol before recording the physical data (Table-1). The purity of compounds were checked by TLC. The spectral analysis15-17 IR, 1H NMR and Mass spectra of the product were observed. Optical rotation of the product was also recorded**. IV(a-g).**

Spectral Data:-

IIIa:- IR(KBr cm^{-1}): 3510 (N-H), 3062 (Aromatic C-H), 2920 (Aliphatic C-H), 1730 (C=O), 1452 (C=N), 1068 (C=S), 1269 (C-O), 1351(C-N), 1177 and 1026 (Characteristics of maltose), 709.80(Mono substituted benzene**);**

^{1}H NMR ($CDCl_3$, ppm): δ 9.25 (H, s, N-H), 1.574(2H, s, aliphatic NH_2)8.054-7.260 (39H, m, Aromatic proton), 4.871-3.894 (14H, m, maltosyl proton)

IIIe:- IR(KBr cm^{-1}): 3298 (N-H str.), 2980, 2941 (Aliphatic C-H str.), 1745 (C=O str..), 1514 (C=N str.), 1059 (C=S str.), 1371 (C-O str.), 1351(C-N), 1223 and 952 (Characteristics of lactose);

^{1}H NMR ($CDCl_3$, ppm): δ 9.20-9.25(H, s, N-H), 1.574(2H, s, aliphatic NH_2)3.767-2.120 (20H, m, aliphatic proton), 5.648-3.9 (14H, m, lactosyl proton).

Mass (m/z): 738(M^+), 657(M^+-CH_2N_2S), 547(M^+-CH_2N_2S,CHN_2,AcOH), 504(M^+-CH_2N_2S,CHN_2,AcOH, CHN_2, AcO, CH_3CO), 412(M^+-CH_2N_2S,CHN_2,AcOH, CHN_2, AcO, CH_3CO, 2COCH).

IIIf:- IR(KBr cm^{-1}): 3317 (N-H str.), 2964 (Aliphatic C-H str.), 1745 (C=O str..), 1519 (C=N str.), 1037 (C=S str.), 1371 (C-O str.), 1351(C-N), 1136 and 947 (Characteristics of glucose**);**

^{1}H NMR ($CDCl_3$, ppm): δ 9.20-9.25(H, s, N-H), 1.574(2H, s, aliphatic NH_2), 2.184-2.020(12H, m, aliphatic) 5.588-3.861(7H, m, glucosyl ring);

Mass (m/z): 406 (M^+-CN_2H_2), 336 (M^+- CN_2H_2,CHN_2S), 231 (M^+- CN_2H_2,CHN_2S,2AcOH), 148(M^+- CN_2H_2,CHN_2S,2AcOH,CH_2).

Table 1:- **3-amino-5- Sugar imino-1, 2, 4-thiadiazolines (IVa-f) (Scheme 1).**

Sr. No.	Product	m.p. (^oC)	Yield (%)	Analysis(%) found(required)		Rf Value	$[\alpha]_D^{31}$ (c, in $CHCl_3$]
				N	S		
1.	IIIa	172	93	4.68 (4.87)	2.76 (2.78)	0.60	-134.30^o (0.5 in $CHCl_3$)
2.	IIIb	154	89	4.57 (4.85)	2.75 (2.77)	0.79	-129.37 (0.5 in $CHCl_3$)
3.	IIIc	129	60	8.0 (8.06)	4.47 (4.60)	0.74	-136.36^o (0.5 in $CHCl_3$)
4.	IIId	132	81	8.0 (8.06)	4.47 (4.60)	0.79	-102.30 ^{o} (0.5 in $CHCl_3$)
5.	IIIe	154	84	7.66 (7.77)	4.40 (4.44)	0.72	-178.12 ^{o} (0.5 in $CHCl_3$)
6.	IIIf	148	73	10.87 (10.95)	6.18 (6.26)	0.69	-169.23 ^{o} (0.5 in $CHCl_3$)

C and H analysis were found satisfactory in all cases.

Antibacterial activity:-

Amikasin (100 µg/ml) was used as standard for antibacterial activity. The compounds were screen for antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, *Proteus vulgaris and Pseudomonas aeruginosa* in nutrient agar medium. Amikasin (100 µg/ml) was used as standard for antibacterial activity. The results are presented in Table 2.

It has been observed that some of these compound exhibited interesting microbial activities. IIIa, IIIc, IIId and IIIe exhibited most significant activity against *S. aureus.* All the other compounds exhibited low to moderate activity. (Table2).

Table2: Antimicrobial activities of novel 3-amino-5- Sugarimino-1, 2, 4-thiadiazolines

Compounds	Antibacterial**				Antifungal**	
	E. coli	*S. aureus*	*P. vulgaris*	*Ps. aeruginosa*	*C. albicance*	*A. niger*
IIIa	13	13	13	17	18	14
IIIb	14	16	12	14	15	16
IIIc	17	14	12	14	15	16
IIId	12	16	20	13	17	14
IIIe	18	17	12	15	15	16
IIIf	13	15	15	18	16	18
Amikacin	19	23	22	24	-	-
Fluconazole	-	-	-	-	25	26

**zone of inhibition in mm (15 or less) resistance, (16-20mm) moderate and (more than 20mm) sensitive. *Escherichia coli* (*E.* coli), *Staphalococcus aureus* (*S.* aureus), *Proteus vulgaris* (*P.* vulgaris), *Psudomonas auriginosa* (*Ps. auriginosa*), *Candida albicancs* (*C. albicancs*) and *Aspergillus niger* (*A. niger*).

Antifungal activity:-

The compounds were screen for antifungal activity against *Aspergillus niger* and *Candida*

albicance in potato dextrose agar medium fluconazole (100 µg/ml) as standard for antifungal activity.

The results of antifungal activities are also tabulated in Table2. IIIa, IIId and IIIf are effective towards *Candida albicance*. IIIb, IIIc, IIIe and IIIf inhibited *Aspergillus niger*. While other compounds inhibited moderate to low activity.

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.

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