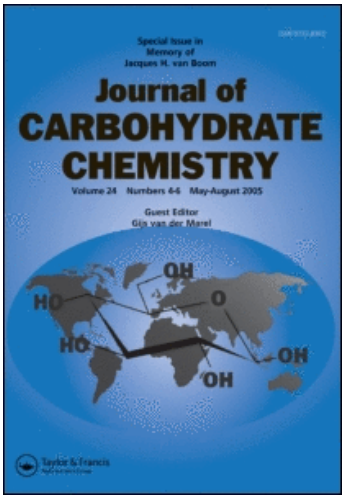

Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

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To cite this Article Elgemeie, Galal H. , Hussein, Mona M. and Al-Khursani, Sheakha A.(2004) 'A Total Synthesis of a New Class of Biazine Thioglycosides', Journal of Carbohydrate Chemistry, 23: 8, 465 — 481
To link to this Article: DOI: 10.1081/CAR-200045262
URL: http://dx.doi.org/10.1081/CAR-200045262

JOURNAL OF CARBOHYDRATE CHEMISTRY
Vol. 23, No. 8–9, pp. 465–481, 2004

A Total Synthesis of a New Class of Biazine Thioglycosides

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CONTENTS

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DOI: 10.1081/CAR-200045262
0732-8303 (Print); 1532-2327 (Online)

ABSTRACT

A new method for the synthesis of bipyridinyl *S*-glycosides **11** and **12** has provided the title compounds in a higher yield. Application of a one-pot glycosylation methodology resulted in an efficient, high-yield synthesis of biazine *S*-glycosides **17–20** An X-ray diffraction analysis of **11** disclosed the conformation of this glycoside as the *S*-glycoside and not the corresponding *N*-form.

Key Words: Bipyridinyl thioglycosides; Biazine thioglycosides; Antimetabolites.

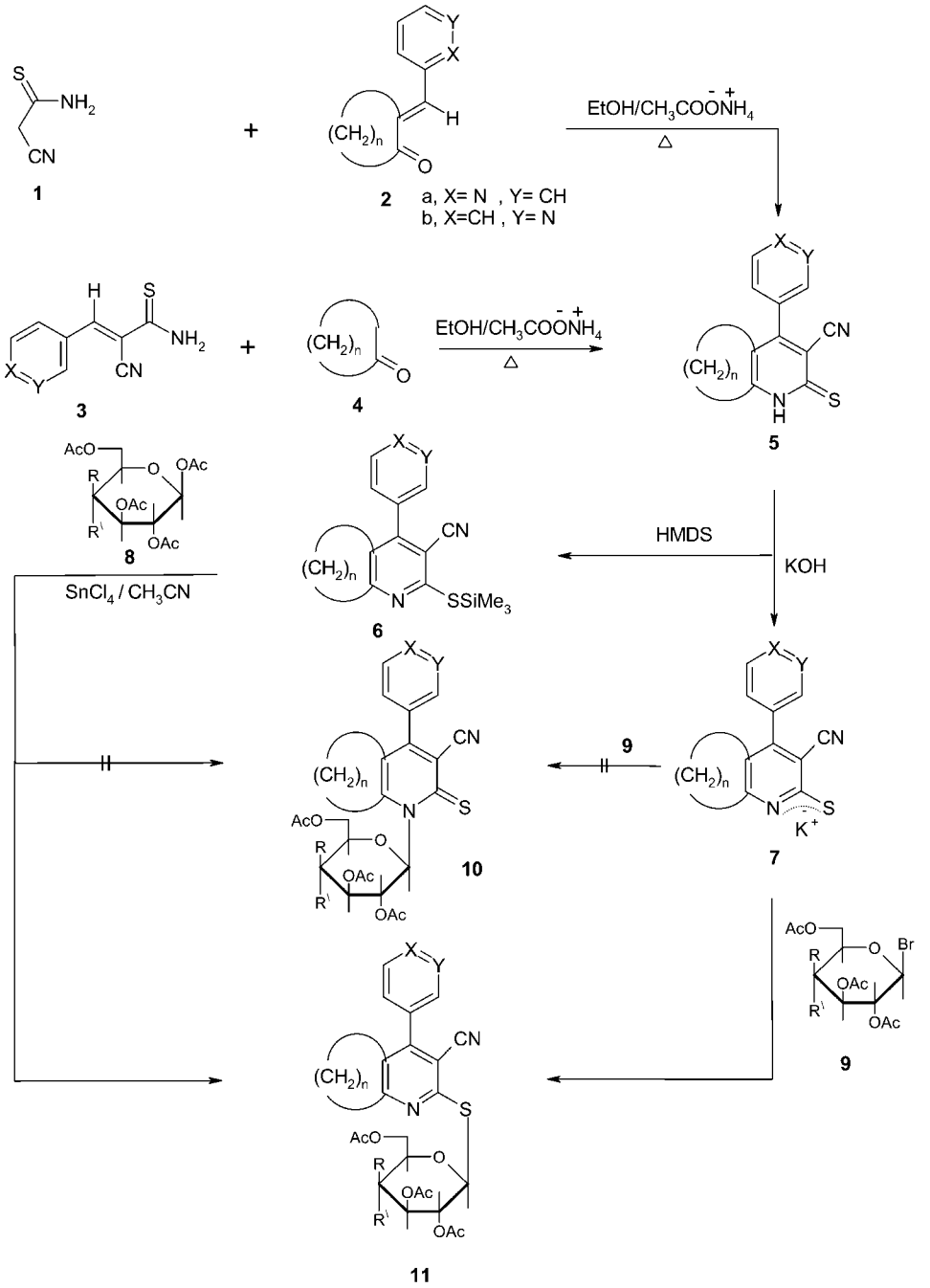
INTRODUCTION

In recent years nucleoside analogues have occupied a significant position in the search for effective antiviral agents, owing to the fact that a large number of unnatural nucleoside derivatives have been shown to inhibit infections caused by viruses.[1] The deazapyrimidine nucleosides constitute a class of analogues with potential biological activity.[2] As a part of our program directed toward the development of new, simple, and efficient procedures for the synthesis of antimetabolites,[3–5] we have recently shown that pyridinethione glycosides exerted inhibitory effects on both DNA- and RNA-containing viruses.[6] On the basis of these findings, it was of interest to prepare modified analogues to search for more effective agents. This part describes the synthesis of nonclassical biheterocyclic glycosides. The latter compounds will be considered as precursors of modified nucleosides.

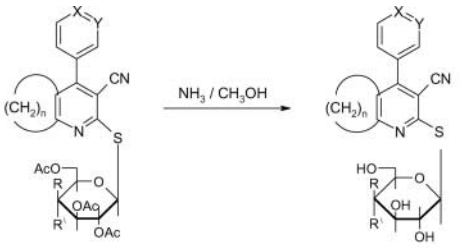
RESULTS AND DISCUSSIONS

Thus, it has been found that pyridinylcyanothioacetamides **3** reacted with cycloalkanones in boiling ethanol containing catalytic amounts of ammonium acetate to give the corresponding mercaptobipyridinyl derivatives **5** (Sch 1). Compounds **5** could also be prepared by the reaction of cyanothiocaetamide with 2-pyridinylmethylene-1-cycloalkanones. The structures of the series of compounds **5** were established on the basis of their elemental analysis and spectroscopic data. Thus, structure **5a** is supported by its mass spectrum, which showed a molecular formula $C_9H_7N_3S$ ($M^+ = 189$). ^{1}H NMR spectroscopy was used to confirm this structure for the product.

The set of compounds **5** reacted with 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- and -galactopyranosyl bromides in the presence of aqueous potassium hydroxide to give the corresponding *S*-glucoside **11a–h** or *S*-galactoside **11i–p**, respectively (Sch 2). It was suggested that the cis(α) sugar reacts by a simple SN_2 reaction to give the β-glycoside product. Although the coupling of **5** with the glycosyl bromides could also give the corresponding *N*-glycosides, the formation of **11** was proved chemically. Reaction of **5** with hexamethyldisilazane (HMDS) in the presence of ammonium sulfate gave the corresponding 2-trimethylsilylthiopyridine **6**, which was subsequently treated with peracetylated sugars in the presence of redistilled $SnCl_4$ to afford the corresponding *S*-glycosyl compounds **11**. A suggested mechanism for the formation of the *S*-glycosides **11** by condensation of silylated base **6** with peracylated sugar in the presence Lewis acid catalyst



Scheme 1.

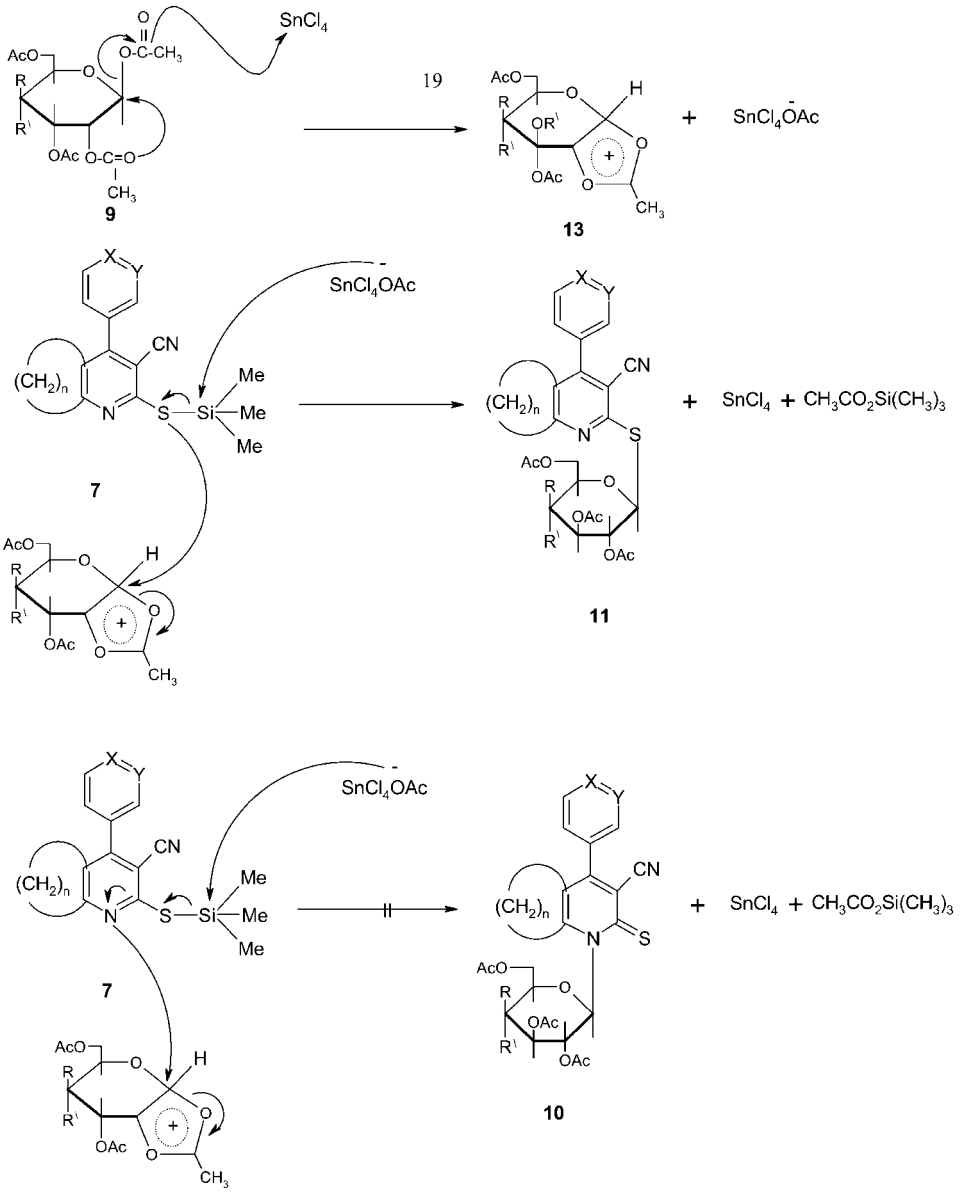


11 12

11		n	X	Y	R	R\
	a,	3	N	CH	H	OAc
	b,	3	CH	N	H	OAc
	c,	4	N	CH	H	OAc
	d,	4	CH	N	H	OAc
	e,	5	N	CH	H	OAc
	f,	5	CH	N	H	OAc
	g,	6	N	CH	H	OAc
	h,	6	CH	N	H	OAc
	i,	3	N	CH	OAc	H
	j,	3	CH	N	OAc	H
	k,	4	N	CH	OAc	H
	l,	4	CH	N	OAc	H
	m,	5	N	CH	OAc	H
	n,	5	CH	N	OAc	H
	o,	6	N	CH	OAc	H
	p,	6	CH	N	OAc	H

12		n	X	Y	R	R\
	a,	3	N	CH	H	OH
	b,	3	CH	N	H	OH
	c,	4	N	CH	H	OH
	d,	4	CH	N	H	OH
	e,	5	N	CH	H	OH
	f,	5	CH	N	H	OH
	g,	6	N	CH	H	OH
	h,	6	CH	N	H	OH
	i,	3	N	CH	OH	H
	j,	3	CH	N	OH	H
	k,	4	N	CH	OH	H
	i,	4	CH	N	OH	H
	m,	5	N	CH	OH	H
	n,	5	CH	N	OH	H
	o,	6	N	CH	OH	H
	p,	6	CH	N	OH	H

Scheme 2.



Scheme 3.

is illustrated in Scheme 3. The structure of the reaction products **11a–p** were established and confirmed by their elemental analyses and spectral data (MS, IR, UV, ^{1}H NMR, ^{13}C NMR). Thus, the analytical data for **11d** revealed a molecular formula $C_{29}H_{31}N_3O_9S$ (M^+ 597). The ^{1}H NMR spectrum showed the anomeric proton as a doublet at δ 6.15 ppm, with a spin-spin coupling constant of 10.50 Hz corresponding to a diaxial orientation of H-1′ and H-2′ protons, indicating the β-configuration. Spectroscopic methods did not identify

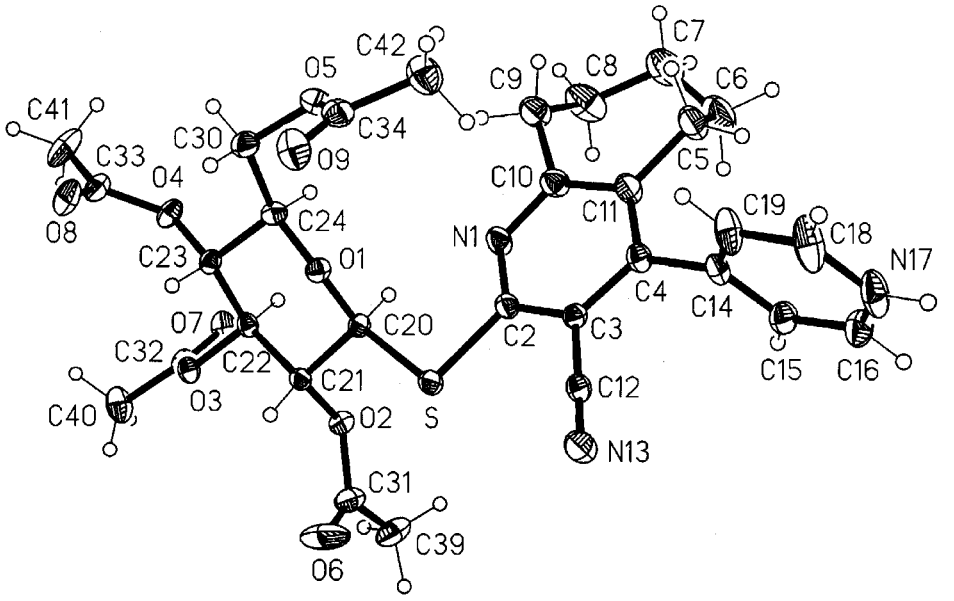


Figure 1. The molecule of **11e** in the crystal.

the product unambiguously as an *N*- or a *S*-nucleoside and therefore an X-ray structure determination was carried out. The X-ray analysis of **11e** (Fig. 1,2)[7] confirms the exclusive presence of the nucleoside in the *S*-form **11** and not the corresponding *N*-nucleoside **10** in the solid state; all H atoms could be located unamiguously, and bond lengths are also consistent with form **11**.

After deprotection of compounds **11a–p** with a saturated solution of ammonia in methanol, the final nucleosides **12a–p** were obtained in almost quantitative yields, the structures of which have been established on the basis of elemental analyses and spectral data (Fig. 2). Thus, the analytical data for **12l** reveal the molecular formula $C_{21}H_{23}N_3O_5S$ (M^+ 429). The ^{1}H NMR spectrum shows the anomeric proton as a doublet at δ 5.68 ($J_{1',2'} = 9.84$ Hz), indicating the presence of only the β-D-configuration.

The series of 4-quinolinyl-3-cyano-2-mercaptopyridine **15** was prepared by the reaction of 4-quinolylmethylidene(cyano)thioacetamide **13** with cycloalkanones **4** in boiling ethanol containing catalytic amounts of ammonium acetate (Scheme 4). The structures of compounds **15** were established on the basis of their elemental analysis and spectral data (MS, IR, ^{1}H NMR). The formation of **15** from **13** and **4** is assumed to proceed via addition of the active methylene group of **4** to the double bond of **13** to give intermediate Michael adducts, which then cyclize via water elimination and oxidation under the reaction conditions to yield **15**.

Compounds **15** reacted with 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- and -galactopyranosyl bromides in the presence of aqueous potassium hydroxide through a Walden inversion to afford the corresponding *S*-glucosides **17a–d** and *S*-galactosides **17e–h**. The structures of the reaction products **17a–h** were established and confirmed on the basis of their elemental analyses and spectral data (MS, IR, UV, ^{1}H NMR, ^{13}C NMR). When compounds **17a–h** were treated with methanolic ammonia at 0°C, the free glycoside

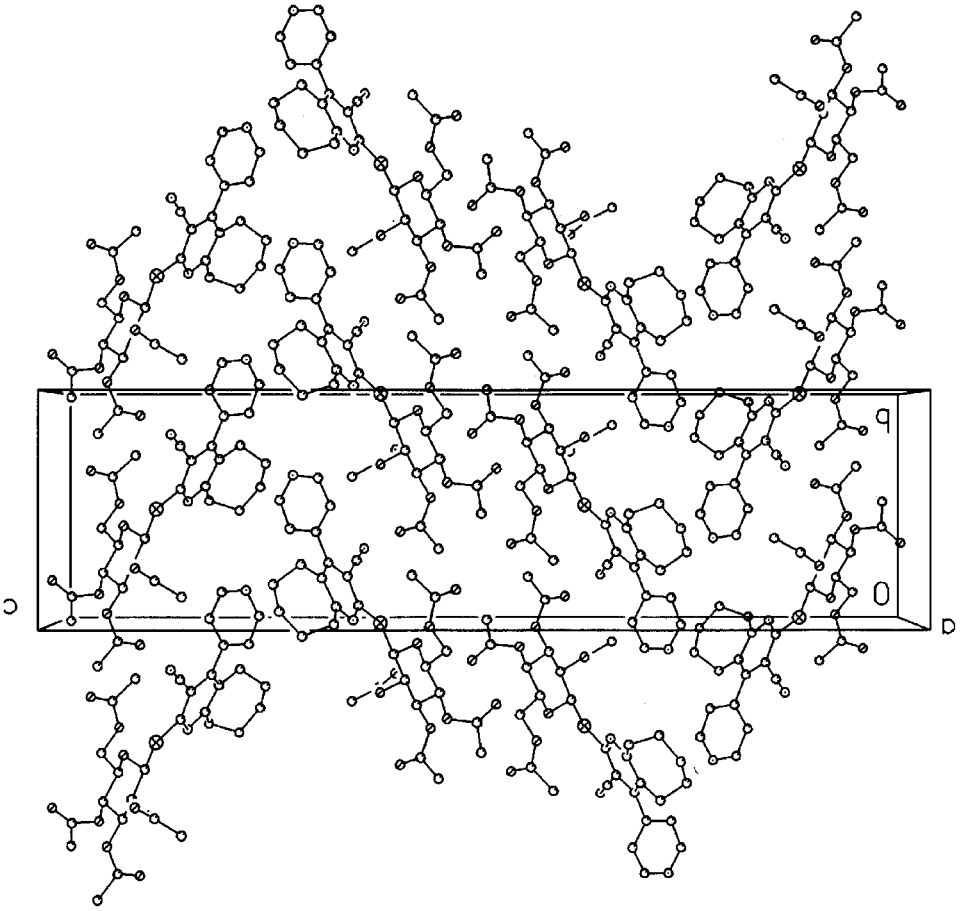
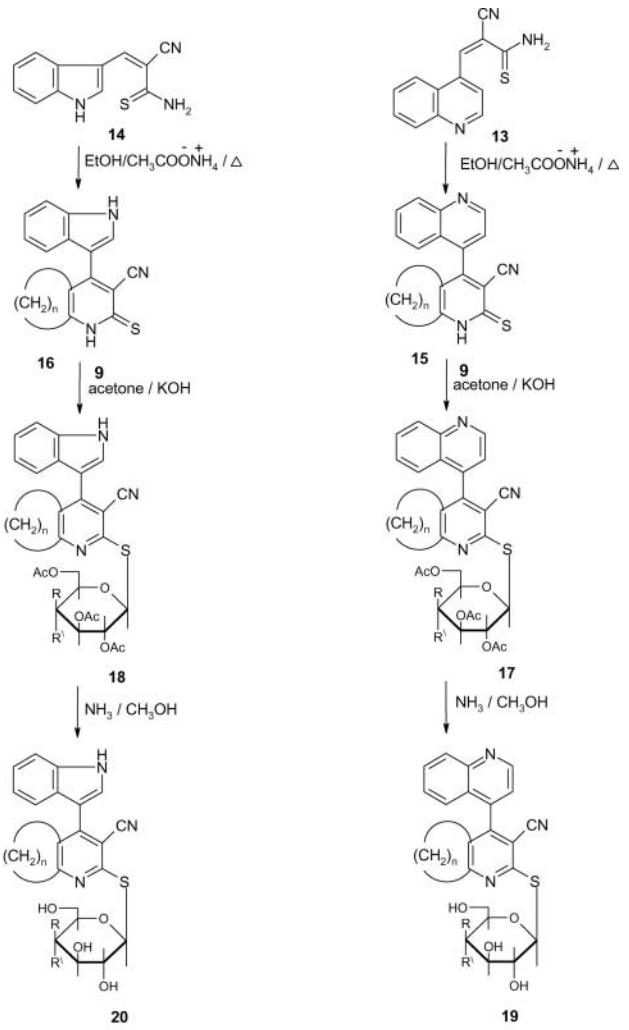


Figure 2. Packing diagram viewed (H atoms have been omitted for clarity).

derivatives **19a–h** were obtained, the structures of which were established on the basis of elemental analysis and spectral data. Thus, the IR spectrum of **19c** showed a characteristic band at 3500–3350 cm^{-1} owing to the hydroxy groups of the glucose moiety. The ^1H NMR spectrum showed the anomeric proton as a doublet at δ 5.58 ($J_{1',2'} = 9.52$ Hz), indicating the presence of only the β-configuration ((Sch 4).

In a simple experimental procedure the 4-indolyl-3-cyano-pyridine- 2(1*H*)thiones **14** were coupled with 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- and -galactopyranosyl bromides in the presence of aqueous potassium hydroxide to give the corresponding *S*-glucosides **18a–d** and *S*-galactosides **18e–h**, respectively. The latter compounds were deacylated by methanolic ammonia to yield the corresponding desired free glycosides **20a–h**. The structure of the products were confirmed and established on the basis of their elemental analysis and spectral data (MS, IR, UV, ^1H NMR and ^{13}C NMR) Table 1.

In summary, we have achieved the synthesis of interesting nonclassical bipyridyl and biazine thioglycosides by the reaction of substituted pyridinethiones with α-halosugars.



17, 18	n	R	R\		n	R	R\
a,	3	H	OAc	e,	3	OAc	H
b,	4	H	OAc	f,	4	OAc	H
c,	5	H	OAc	g,	5	OAc	H
d,	6	H	OAc	h,	6	OAc	H

19, 20	n	R	R\		n	R	R\
a,	3	H	OH	e,	3	OH	H
b,	4	H	OH	f,	4	OH	H
c,	5	H	OH	g,	5	OH	H
d,	6	H	OH	h,	6	OH	H

Scheme 4.

Table 1. Characterization data for compounds **5a–h, 11a–p, 12a–p, 15a–d, 16a–d, 17a–h, 18a–h, 19a–h,** and **20a–h**.

Compd no.	M.p. °C	Yield % color	Cryst. form.	M. F	Analysis: calcd/found % C	H	N	S	M^+ m/z
5a	300	78 Red	EtOH	$C_{14}H_{11}N_3S$	66.2 66.4	4.1 4.4	16.7 16.6	12.5 12.7	253
5b	260	77 Red	EtOH	$C_{14}H_{11}N_3S$	66.4 66.4	4.1 4.4	16.7 16.6	12.5 12.7	253
5c	325	95 Yellow	EtOH	$C_{15}H_{13}N_3$	67.3 67.4	4.8 4.9	15.8 15.7	12.0 11.9	267
5d	259	93 Yellow	EtOH	$C_{15}H_{13}N_3S$	67.1 67.4	4.5 4.9	15.5 15.7	11.8 11.9	267
5e	263	93 Yellow	EtOH	$C_{16}H_{15}N_3S$	68.5 68.3	5.4 5.4	14.9 14.9	11.4 11.4	281
5f	257	92 Yellow	EtOH	$C_{16}H_{15}N_3S$	68.0 68.3	5.3 5.4	14.6 14.9	11.1 11.4	281
5g	290	93 Yellow	EtOH	$C_{17}H_{17}N_3S$	69.2 69.1	5.5 5.8	14.0 14.2	10.8 10.9	295
5h	251	91 Yellow	EtOH	$C_{17}H_{17}N_3S$	69.1 69.1	5.6 5.8	14.0 14.2	11.1 10.9	295
11a	120	85 Brown	DMF	$C_{28}H_{29}N_3SO_9$	57.4 57.6	4.9 5.0	7.1 7.2	5.5 5.5	583
11b	175	82 Red	DMF	$C_{28}H_{29}N_3SO_9$	57.4 57.6	4.8 5.0	7.0 7.2	5.3 5.5	583
11c	202	89 Yellow	DMF	$C_{29}H_{31}N_3O_9S$	58.5 58.3	5.1 5.2	7.1 7.0	5.3 5.4	597
11d	85	85 Brown	EtOH	$C_{29}H_{31}N_3SO_9$	58.3 58.3	5.3 5.2	7.3 7.0	5.6 5.4	579
11e	183	83 Yellow	EtOH	$C_{30}H_{33}N_3O_9S$	59.1 58.9	5.5 5.4	7.0 6.9	5.0 5.2	611
11f	95	92 Yellow	EtOH	$C_{30}H_{33}N_3SO_9$	58.7 58.9	5.2 5.4	6.8 6.9	5.2 5.2	611
11g	190	81 Yellow	DMF	$C_{31}H_{35}N_3SO_9$	59.5 59.5	5.7 5.6	6.8 6.7	5.1 5.1	625
11h	101	94 Yellow	EtOH	$C_{31}H_{35}N_3SO_9$	59.6 59.5	5.4 5.6	6.5 6.7	5.2 5.1	625
11i	200	86 Brown	DMF	$C_{28}H_{29}N_3SO_9$	57.6 57.6	4.9 5.0	7.2 7.2	5.4 5.5	583
11j	175	77 Brown	EtOH	$C_{28}H_{29}N_3SO_9$	57.7 57.6	5.2 5.0	7.1 7.2	5.6 5.5	583
11k	230	95 Yellow	EtOH	$C_{29}H_{31}N_3SO_9$	58.3 58.3	5.1 5.2	7.0 7.0	5.3 5.4	597
11l	180	93 Yellow	EtOH	$C_{29}H_{31}N_3O_9S$	58.1 58.3	5.1 5.2	6.8 7.0	5.2 5.4	597
11m	169	87 Yellow	EtOH	$C_{30}H_{33}N_3SO_9$	58.9 58.9	5.4 5.4	6.8 6.9	5.2 5.2	611

(*continued*)

Table 1. Continued.

Compd no.	M.p. °C	Yield % color	Cryst. form.	M. F	Analysis: calcd/found % C	H	N	S	M^+ m/z
11n	185	78	EtOH	$C_{30}H_{33}N_3SO_9$	58.7	5.2	6.8	5.0	611
		Yellow			58.9	5.4	6.9	5.2	
11o	93	88	DMF	$C_{31}H_{35}N_3SO_9$	59.5	5.5	6.5	5.0	625
		Buff			5.6	5.6	6.7	5.1	
11p	248	94	EtOH	$C_{31}H_{35}N_3SO_9$	59.3	5.4	6.6	4.9	625
		Yellow			59.3	5.6	6.7	5.1	
12a	182	79	EtOH	$C_{20}H_{21}N_3SO_5$	57.8	5.0	10.0	7.5	415
		Red			57.8	5.1	10.1	7.7	
12b	78	89	EtOH	$C_{21}H_{23}N_3SO_5$	58.7	5.3	9.7	7.4	429
		Brown			58.7	5.4	9.8	7.5	
12c	230	89	MeOH	$C_{21}H_{23}N_3SO_5$	58.7	5.3	9.7	7.4	429
		Yellow			58.7	5.4	9.8	7.5	
12d	155	83	EtOH	$C_{21}H_{23}N_3SO_5$	58.5	5.5	9.9	7.4	429
		Yellow			58.7	5.4	9.8	7.5	
12e	191	92	H_2O	$C_{22}H_{25}N_3SO_5$	59.5	5.6	9.4	7.1	443
		Yellow			59.6	5.6	9.5	7.2	
12f	150	85	EtOH	$C_{22}H_{25}N_3SO_5$	59.4	5.5	9.4	7.1	443
		Yellow			59.6	5.6	9.5	7.2	
12g	188	93	EtOH	$C_{23}H_{27}N_3SO_5$	60.3	5.7	9.2	6.9	457
		Yellow			60.4	5.9	9.2	7.0	
12h	135	84	EtOH	$C_{23}H_{27}N_3SO_5$	60.3	5.7	9.2	6.9	457
		Yellow			60.4	5.9	9.2	7.0	
12i	210	89	EtOH	$C_{20}H_{21}N_3SO_5$	57.9	5.0	10.2	7.7	415
		Brown			57.8	5.1	10.1	7.7	
12j	182	86	EtOH	$C_{20}H_{21}N_3O_5S$	57.6	5.0	10.0	7.5	415
		Yellow			57.8	5.1	10.1	7.7	
12k	189	91	DMF	$C_{21}H_{23}N_3SO_5$	58.7	5.3	9.7	7.4	429
		Yellow			58.7	5.4	9.8	7.5	
12l	160	90	EtOH	$C_{21}H_{23}N_3O_5S$	58.6	5.2	9.6	4.7	429
		Yellow			58.7	5.4	9.8	7.5	
12m	185	88	EtOH	$C_{22}H_{25}N_3SO_5$	59.5	5.6	9.4	7.2	443
		Yellow			59.6	5.6	9.5	7.2	
12n	195	78	EtOH	$C_{22}H_{25}N_3SO_5$	59.8	5.7	9.4	7.3	443
		Yellow			59.6	5.6	9.5	7.2	
12o	145	85	EtOH	$C_{23}H_{27}N_3SO_5$	60.5	5.9	9.1	7.1	457
		Brown			60.4	5.9	9.2	7.0	
12p	140	84	EtOH	$C_{23}H_{27}N_3SO_5$	60.5	5.7	9.0	6.9	457
		Yellow			60.4	5.9	9.2	7.0	
15a	250	80	EtOH	$C_{18}H_{13}N_3S$	71.1	4.1	13.8	10.4	303
		Yellow			71.3	4.3	13.9	10.6	
15b	130	95	EtOH	$C_{19}H_{15}N_3S$	71.7	4.9	13.0	9.9	317
		Yellow			71.9	4.7	13.2	10.1	

(*continued*)

Table 1. Continued.

Compd no.	M.p. °C	Yield % color	Cryst. form.	M. F	Analysis: calcd/found % C	H	N	S	M^+ m/z
15c	160	82	EtOH	$C_{20}H_{17}N_3S$	72.5	5.3	12.5	9.9	331
		Yellow			72.5	5.1	12.7	9.7	
15d	205	93	EtOH	$C_{21}H_{19}N_3S$	73.1	5.3	12.1	9.5	345
		Yellow			73.0	5.5	12.2	9.3	
16a	100	79	EtOH	$C_{17}H_{13}N_3S$	69.9	4.6	14.6	11.1	291
		Red			70.1	4.5	14.4	10.9	
16b	144	85	EtOH	$C_{18}H_{15}N_3S$	70.7	4.7	13.9	10.7	305
		Red			70.8	4.9	13.8	10.5	
16c	196	81	EtOH	$C_{19}H_{17}N_3S$	71.4	5.3	13.0	10.1	319
		Yellow			71.5	5.3	13.2	10.0	
16d	160	80	EtOH	$C_{20}H_{19}N_3S$	71.8	5.6	12.6	9.7	333
		Yellow			72.1	5.7	12.6	9.6	
17a	117	98	EtOH	$C_{32}H_{31}N_3SO_9$	60.6	4.8	6.4	5.0	633
		Red			60.7	4.9	6.6	5.1	
17b	98	89	EtOH	$C_{33}H_{33}N_3SO_9$	61.2	5.0	6.4	4.9	647
		Yellow			61.2	5.1	6.5	4.9	
17c	110	92	EtOH	$C_{34}H_{35}N_3SO_9$	61.9	5.2	6.2	4.8	661
		White			61.7	5.3	6.4	4.8	
17d	113	85	.EtOH	$C_{35}H_{37}N_3SO_9$	62.1	5.3	6.3	4.5	675
		Yellow			62.2	5.5	6.2	4.7	
17e	154	80	.EtOH	$C_{32}H_{31}N_3SO_9$	60.5	4.7	6.6	5.1	633
		Red			60.7	4.9	6.6	5.1	
17f	123	70	.EtOH	$C_{33}H_{33}N_3SO_9$	61.0	5.0	6.5	4.7	647
		Orange			61.2	5.1	6.5	4.9	
17g	111	88	EtOH	$C_{34}H_{35}N_3SO_9$	61.5	5.1	6.4	4.9	661
		Yellow			61.7	5.3	6.4	4.8	
17h	242	82	EtOH	$C_{35}H_{37}N_3SO_9$	62.1	5.3	6.0	4.7	675
		Yellow			62.2	5.5	6.2	4.7	
18a	160	89	EtOH	$C_{31}H_{31}N_3SO_9$	59.8	4.9	6.9	5.1	621
		Red			59.9	5.0	6.8	5.2	
18b	110	84	EtOH	$C_{32}H_{33}N_3SO_9$	60.3	5.0	6.4	5.2	635
		Yellow			60.5	5.0	6.6	5.0	
18c	132	90	EtOH	$C_{33}H_{35}N_3SO_9$	60.8	5.3	6.4	4.8	649
		Yellow			61.0	5.4	6.5	4.9	
18d	196	77	EtOH	$C_{34}H_{37}N_3SO_9$	61.3	5.4	6.2	4.9	663
		Yellow			61.5	5.6	6.3	4.8	
18e	180	83	EtOH	$C_{31}H_{31}N_3SO_9$	59.9	4.9	6.7	5.0	621
		Red			59.9	5.0	6.8	5.2	
18f	124	85	EtOH	$C_{32}H_{33}N_3SO_9$	60.3	5.1	6.4	4.8	635
		Orange			60.5	5.2	6.6	5.0	
18g	156	91	EtOH	$C_{33}H_{35}N_3SO_9$	61.2	5.3	6.7	5.1	649
		Yellow			61.0	5.4	6.5	4.9	

(*continued*)

Table 1. Continued.

Compd no.	M.p. °C	Yield % color	Cryst. form.	M. F	Analysis: calcd/found % C	H	N	S	M^+ m/z
18h	150	91 Yellow	EtOH	$C_{34}H_{37}N_3SO_9$	61.3 61.5	5.5 5.6	6.5 6.3	4.9 4.8	663
19a	170	80 Yellow	EtOH	$C_{24}H_{23}N_3SO_5$	61.7 61.9	4.7 4.9	9.1 9.0	6.8 6.9	465
19b	155	80 Yellow	EtOH	$C_{25}H_{25}N_3O_5S$	62.4 62.6	5.3 5.2	8.7 8.8	6.6 6.7	479
19c	152	78 Yellow	EtOH	$C_{26}H_{27}O_5S$	63.0 63.3	5.4 5.5	8.5 8.5	6.3 6.5	493
19d	179	81 Yellow	DMF	$C_{27}H_{29}N_3SO_5$	63.9 63.9	5.5 5.7	8.2 8.3	6.1 6.3	507
19e	143	70 Yellow	EtOH	$C_{24}H_{23}N_3SO_5$	61.8 61.9	4.8 4.9	9.0 9.0	6.7 6.9	465
19f	117	70 Yellow	EtOH	$C_{25}H_{25}N_3O_5S$	62.5 62.6	5.1 5.2	8.9 8.8	6.5 6.7	479
19g	160	84 Yellow	EtOH	$C_{26}H_{27}N_3SO_5$	63.5 63.3	5.4 5.5	8.4 8.5	6.3 6.5	493
19h	154	75 Yellow	EtOH	$C_{27}H_{29}N_3SO_5$	63.9 63.9	5.7 5.7	8.2 8.3	6.1 6.3	507
20a	140	90 Red	EtOH	$C_{23}H_{23}N_3SO_5$	60.7 60.9	5.0 5.1	9.3 9.3	6.9 7.1	453
20b	150	86 Yellow	EtOH	$C_{24}H_{25}N_3SO_5$	61.5 61.7	5.2 5.4	8.9 9.0	7.0 6.9	467
20c	162	79 Yellow	EtOH	$C_{25}H_{27}N_3SO_5$	62.3 62.4	5.4 5.6	8.8 8.7	6.5 6.7	481
20d	160	86 Yellow	EtOH	$C_{26}H_{29}N_3SO_5$	62.8 63.0	5.7 5.9	8.3 8.5	6.7 6.5	495
20e	180	78 Red	EtOH	$C_{23}H_{23}N_3SO_5$	61.0 60.9	5.0 5.1	9.2 9.3	7.0 7.1	453
20f	155	85 Orange	EtOH	$C_{24}H_{25}N_3SO_5$	61.6 61.7	5.3 5.4	9.1 9.0	7.0 6.9	467
20g	160	87 Yellow	EtOH	$C_{25}H_{27}N_3SO_5$	62.2 62.4	5.4 5.6	8.8 8.7	6.6 6.7	481
20h	158	90 Yellow	EtOH	$C_{26}H_{29}N_3SO_5$	62.9 63.0	5.7 5.9	8.3 8.5	6.7 6.5	495

These nucleosides can be utilized as an excellent starting material for the synthesis of other carbohydrate derivatives and for further biological evaluation studies.

ANTIVIRAL ACTIVITY

The anti-HIV activity and cytotoxicity of the condensed pyridine-2-(1*H*)-thione nucleoside derivative are shown in Table 2. Among the acetylated derivatives, compound

Table 2. Comparative potency and selectivity of 3-cyano-2-(2,3,4,6-tetra-*O*-acetyl-β-D-gluco- and -galactopyranosylthio)pyridines **11k**, **18e**, and **19c** as inhibitors of HIV replicain MT-4 cells.

Compd	EC_{50}[a] μM	IC_{50}[b] μM	TI[c] (ratio IC_{50}/EC_{50})
11k	1.86	11.96	6.43
18e	0.19	3.91	20.58
19c	2.43	9.13	3.75

[a]Approximate values for 50% effective concentration of MT-4 cells against the cytopathic effect of HIV (EC_{50}).
[b]Inhibitory concentration for 50% (IC_{50}).
[c]Therapeutic index (IC_{50}/EC_{50}).

11k turned out to be the most selective anti-HIV agent, followed by **18e**. The other compounds were virtually devoid of any anti-HIV activity. Among the free glycoside derivatives, the free nucleoside **19c** proved clearly more active and selective than the corresponding protected derivative. None of the other free sugars showed any selectivity and/or antiviral activity. Because compounds **11**, **12**, and **17–20** belong to a new class of active nucleosides and also were active against HIV, further investigations are needed to determine the mechanism of their action against herpes virus.

BIOLOGICAL PROCEDURE

The series of compounds **11**, **12**, and **17–20** was dissolved in dimethyl sulfoxide and then diluted 1 : 100 in cell culture medium preparing serial half-Log10 dilutions. T_4 Lymphocytes were added, and after a brief interval HIV-1 was added, resulting in 1 : 20 final dilution of the compound. Uninfected cells with the compound served as a toxicity control, and infected and uninfected cells without the compound served as basic controls. Cultures were incubated at 37°C in a % carbon dioxide atmosphere for 6 days. The tetrazolium salt, XTT, was added to all wells, and cultures were incubated to allow formazan color development by viable cells. Individual wells were analyzed spectrophotometrically to quantitate formazan production, and in addition were viewed microscopically for detection of viable cells and confirmation of protective activity. Drug-treated virus-infected cells were compared with drug-treated noninfected cells and with other appropriate controls on the same plate. Data were reviewed in comparison with other tests done at the same time and a determination about activity was made.

EXPERIMENTAL

All evaporations were carried out under reduced pressure at 40°C. IR spectra were obtained (KBr disc) with a Pye Unicam Spectra-1000. ^{1}H NMR and ^{13}C NMR spectra were measured with a Wilmad 270-MHz or a Varian 400-MHz spectrometer for solution in $(CD_3)_2SO$ by using $SiMe_4$ as the internal standard. Mass spectra were recorded with a Varian MAT 112 spectrometer. Analytical data were obtained from the microanalytical data center at Cairo University.

Cycloalkane ring fused 4-pyridinyl-, 4-quinolinyl-, and 4-indolinyl-3-cyanopyridine-2(1*H*)-thiones 5a–h, 15a–d, and 16a-d. To a mixture of **4** and **3** or **13** or **14** (0.01 mol) in ethanol (50 mL), ammonium acetate (3.8 g) was added. The mixture was heated under reflux for 3 hr, and then set aside overnight. The resultant precipitate was filtered off and washed with distilled water several times to dissolve the excess of ammonium acetate. The precipitate was crystallized from the appropriate solvent.

15a. IR (KBr) 3400 (NH), 2220 (CN) cm^{-1}; 1.10 (m, 2H, CH_2), 2.20–2.30 (m, 2H, CH_2), 2.60–2.85 (m, 2H, CH_2), 7.00–8.60 (m, 6H, quinoline-H), 14.00 (s, br, 1H, NH).

15b. IR (KBr) 3330 (NH), 2220 (CN) cm^{-1}; 1.10 (m, 2H, CH_2), 1.50–1.80 (m, 2H, CH_2). 1.70–1.85 (m, 2H, CH_2), 2.30–2.60 (m, 2H, CH_2), 7.00–8.20 (m, 6H, quinoline-H), 13.90 (s, br, 1H, NH).

15c. IR (KBr) 3450, 3400 (NH), 2220 (CN) cm^{-1}; ^{1}H NMR δ_H 1.20–1.59 (m, 2H, CH_2), 1.60–1.78 (m, 4H, $2CH_2$), 2.40–2.52 (m, 2H, CH_2), 3.00–3.10 (m, 2H, CH_2), 7.0–8.22 (m, 6H, quinoline-H), 14.0 (s, br, 1H, NH).

15d. IR (KBr) 3460, 3370, 3300 (NH), 2220 (CN) cm^{-1}; ^{1}H NMR δ^H 1.10–1.18 (m, 2H, CH_2), 1.26–1.80 (m, 2H, CH_2), 1.90–1.95 (m, 2H, CH_2), 2.44 (m, 2H, CH_2), 2.55 (m, 2H, CH_2), 2.80–2.99 (m, 2H, CH_2), 7.0–7.6 (m, 6H, quinoline-H), 13.90 (s, br, 1H, NH).

16a. IR (KBr) 3450, 3400 (NH), 2220 (CN) cm^{-1}; ^{1}H NMR δH 1.19 (m, 2H, CH_2) 2.21–2.32 (m, 2H, CH_2), 2.67–2.80 (m, 2H, CH_2), 7.02–8.68 (m, 5H, indole-H), 12.27 (s, br, 1H, NH), 14.08 (s, br, 1H, NH).

16b. IR (KBr) 3370 (NH), 2218 (CN) cm^{-1}; ^{1}H NMR δ_H 1.21 (m, 2H, CH_2), 1.62–1.93 (m, 2H, CH_2), 1.86–1.96 (m, 2H, CH_2), 2.45–2.62 (m, 2H, CH_2), 7.02–8.37 (m, 5H, indole-H), 11.78 (s, br, 1H, NH), 13.77 (s, br, 1H, NH); ^{13}C NMR δ_C 20.59 (CH_2), 21.50 (CH_2), 25.45 (CH_2), 27.25 (CH_2), 109.08 (CN), 112.27 (C-3), 114.47–136.10 (indole-C), 151.4 (C-5), 152.48 (C-4), 169.00 (C-6), 175.40 (C-2).

16c. IR (KBr) 3520, 3400 (NH), 2210 (CN) cm^{-1}; ^{1}H NMR δ_H 1.29–1.50 (m, 2H, CH_2), 1.58–1.72 (m, 4H, $2CH_2$), 2.47–2.49 (m, 2H, CH_2), 3.02–3.04 (m, 2H, CH_2), 7.06–8.28 (m, 5H, indole-H), 11.60 (s, br, 1H, NH), 13.9 (s, br, 1H, NH); ^{13}C NMR δ_C 24.96 (CH_2), 26.57 (CH_2), 28.43 (CH_2), 31.03 (CH_2), 32.52 (CH_2), 109.74 (CN), 112.21 (C-3), 117.52–135.96 (indole-C), 151.78 (C-5), 157.91 (C-4), 168.70 (C-6), 174.79 (C-2).

16d. IR (KBr) 3370, 3320, 3300 (NH), 2222 (CN) cm^{-1}; ^{1}H NMR δ_H 1.06–1.16 (m, 2H, CH_2), 1.37–1.52 (m, 2H, CH_2), 1.67–1.91 (m, 2H, CH_2), 2.50 (m, 2H, CH_2), 2.50 (m, 2H, CH_2), 2.87–2.96 (m, 2H, CH_2), 7.03–8.02 (m, 5H, indole-H), 11.64 (s, br, 1H, NH), 13.92 (s, br, 1H, NH); ^{13}C NMR δ_C 25.27 (CH_2), 25.4 (CH_2), 25.96 (CH_2), 29.50 (CH_2), 29.92 (CH_2), 30.05 (CH_2), 109.57 (CN), 112.17 (C-3), 116.19–135.91 (indole-C), 152.43 (C-5), 155.48 (C-4), 167.90 (C-6), 175.61 (C-2).

2-(2′, 3′, 4′, 6′-Tetra-*O*-acetyl-β-D-gluco- and galactopyranosylthio)-4-pyridinyl-, 4-quinolinyl-, and 4-indolinyl-cycloalkeno[b]pyridine-3-carbonitriles 11a–p, 17a–h, and 18a–h. General Coupling Procedures. Method A. To a solution of condensed pyridine-2(1H)-thiones **5**, **15**, or **16** (0.01 mol) in aqueous potassium hydroxide [0.56 g, 0.01 mol, in distilled water (6 cm^3)] was added a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- or -galactopyranosyl bromide (4.521 g, 0.011 mol) in acetone (30 cm^3). The reaction mixture was stirred at room temperature for ca. (30 min to 2 hr). The mixture was evaporated under reduced pressure at 40°C and the residue was washed with distilled water to remove the potassium bromide formed. The product was dried and crystallized from the appropriate solvent.

Method B. Condensed pyridine-2(1*H*)-thiones **5** (0.01 mol) was boiled under reflux, with stirring, under anhydrous conditions for 48 hr with hexamethyldisilazane (25 mL) and ammonium sulphate (0.02 g). The excess of hexamethyldisilazane was removed under diminished pressure, providing the silylated bases **7** as a colorless oil. To a solution of silylated base in dry acetonitrile (30 mL) was added a solution of 1,2,3,4,6-penta-*O*-acetyl-α-D-gluco- or galactopyranose (0.011 mol) in dry acetonitrile (20 mL), followed by $SnCl_4$ (1.6 mL). The reaction mixture was stirred at room temperature for ca. (3 to 6 hr), then poured into saturated $NaHCO_3$ solution and extracted with $CHCl_3$. The organic layers were dried over $MgSO_4$, filtered, and concentrated to give the crude glycosides, which were purified by recrystallization from the appropriate solvent.

11a. IR (KBr) 2222 (CN) cm^{-1}; ^1H NMR δ_H 1.66 (m, 2H, CH_2), 1.80 (m, 2H, CH_2), 1.89–2.09 (4s, 12H, 4 × AcO), 2.60 (m, 2H, CH_2), 4.05 (m, 2H, 6′-H2), 4.30 (t, 1H, 5′-H), 5.18 (t, 1H, 4′-H), 5.28 (t, 1H, 3′-H), 5.45 (t-1H, 2′-H), 6.00 (d, 1H, $J_{1',2'} = 10.50$, 1′-H), 7.34–8.60 (m, 4H, pyridine-H), ^{13}C NMR δ_C 20.0–20.20 (4 × CH_3), 21.30–33.20 (3 × CH_2), 61.20 (C-6′), 66.20 (C-4′), 67.50 (C-2′), 71.5 (C-3′), 74.20 (C-5′), 80.91 (C-1′), 107.20 (CN), 115.10 (C-3), 122.50–148.10 (pyridine-C), 151.10 (C-5), 156.10 (C-4), 158.66 (C-6), 162.50 (C-2), 170.00–170.70 (4 CO).

11c. IR (KBr) 2222 (CN) cm^{-1}; ^1H NMR δ_H 1.70 (m, 2H, CH_2), 1.85 (m, 2H, CH_2), 1.90–2.12 (4s, 12H, 4 × AcO), 2.70 (m, 2H, CH_2), 2.90 (m, 2H, CH_2), 4.09 (m, 2H, 6′-H_2), 4.32 (t, 1H, 5′-H), 5.20 (t, 1H, 4′-H), 5.30 (t, 1H, 3′-H), 5.48 (t-1H, 2′-H), 6.09 (d, 1H, $J_{1',2'} = 10.58$, 1′-H), 7.41–8.68 (m, 4H, pyridine-H), ^{13}C NMR δ_C 20.1–20.25 (4 × CH_3), 21.32–33.22 (4 × CH_2), 61.22 (C-6′), 66.22 (C-4′), 67.52 (C-2′), 71.2 (C-3′), 74.22 (C-5′), 80.91 (C-1′), 107.22 (CN), 115.15 (C-3), 122.56–148.11 (pyridine-C), 151.17 (C-5), 156.17 (C-4), 162.70 (C-6), 164.22 (C-2), 170.02–171.10 (4 CO).

11e. IR (KBr) 2218 (CN) cm^{-1}; ^1H NMR δ_H 1.18–1.52 (m, 2H, CH_2), 1.58–1.60 (m, 4H, $2CH_2$), 1.92–2.08 (4s, 12H, 4 × AcO), 2.61–2.80 (m, 2H, CH_2), 3.02–3.12 (m, 2H, CH_2), 4.08 (m, 2H, 6′-H_2), 4.20 (m, 1H, 5′-H), 5.18 (t, 1H, 4′-H), 5.20 (t, 1H, 3′-H), 5.60 (t, 1H, 2′-H), 6.12 (d, 1H, $J_{1'',2''} = 10.20$, 1′-H), 7.08–8.77 (m, 4H, pyridine-H); ^{13}C NMR δ_C 20.12–20.32 (4 × Me), 21.22–36.22 (5 × CH_2), 62.22 (C-6′), 68.12 (C-4′), 69.12 (C-2′), 72.33 (C-3′), 76.08 (C-5′), 80.12 (C-1′), 107.18 (CN), 118.15 (C-3), 123.11–142.80 (pyridine-C), 150.20 (C-5), 151.23 (C-4), 155.22 (C-6), 167.54 (C-2), 170.09–171.20 (4 CO).

11l. IR (KBr) 2225 (CN) cm^{-1}; ^1H NMR δ_H 1.41–1.60 (m, 2H, CH_2), 1.61–1.72 (m, 2H, CH_2), 1.78–1.85 (m, 2H, CH_2), 1.95–2.05 (4s, 12H, 4 × AcO), 2.58–2.66 (m, 2H, CH_2), 4.03 (m, 2H, 6′-H2), 4.35 (m, 1H, 5′-H), 5.25 (t, 1H, 4′-H), 5.32 (t, 1H, 3′-H), 5.55 (t, 1H, 2′-H), 6.15 (d, 1H, $J_{1'',2''} = 10.50$, 1′-H), 7.18–8.80 (m, 4H, pyridine-H). ^{13}C NMR δ_C 20.1–20.4 (4 × Me), 21.20–33.00 (4 × CH_2), 61.20 (C-6′), 66.09 (C-4′), 67.6 (C-2′), 70.05 (C-3′), 74.22 (C-5′), 80.62 (C-1′), 105.22 (CN), 116.51 (C-3), 122.23–149.28 (pyridine-C), 150.13 (C-5), 154.32 (C-4), 165.44 (C-6), 169.21 (C-2), 172.53–172.89 (4 CO).

17b. IR (KBr) 2222 (CN) cm^{-1}; ^1H NMR δ_H 1.97 (m, 2H, CH_2), 1.98 (m, 2H, CH_2), 1.00–2.03 (m, 12H, 4 × AcO), 2.49–2.50 (m, 2H, CH_2), 3.07 (m, 2H, CH_2), 4.18 (m, 3H, 6′-H_2, 5′-H), 5.03 (m, 1H, 4′-H), 5.14 (m, 1H, 3′-H), 5.55 (t, 1H, 2′-H), 6.13 (m, 1H, 1′-H), 6.39–9.07 (m, 6H, quinoline-H); ^{13}C NMR δ_C 20.33–33.09 (4 × CH_2 and 4 × CH_3), 61.84 (C-6′), 68.14 (C-4′), 68.90 (C-2′), 73.21 (C-3′), 75.02 (C-5′), 80.33 (C-1′), 105.03 (CN), 116.23 (C-3), 121.56–149.23 (quinoline-C), 150.56 (C-5), 154.17 (C-4), 162.78 (C-6), 163.99 (C-2), 170.13 (4 CO).

17c. 2212 (CN) cm^{-1}; ^1H NMR δ_H 1.77–1.95 (m, 2H, CH_2), 1.97 (m, 2H, CH_2), 1.98 (m, 2H, CH_2), 2.00–2.02 (4s, 12H, 4 × AcO), 2.22 (m, 2H, CH_2), 3.01 (m, 2H, CH_2), 4.09–4.10 (m, 3H, 6′-H_2, 5′-H), 5.05 (t, 1H, 4′-H), 5.09 (m, 1H, 3′-H), 5.58 (t, 1H, 2′-H), 6.10 (m, 1H, 1′-H), 7.39–9.08 (m, 6H, quinoline-H); ^{13}C NMR δ_C 20.33–31.19 (4 × CH_2), 61.84 (C-6′), 68.93 (C-4′), 69.23 (C-2′), 72.91 (C-3′), 75.62 (C-5′), 80.12 (C-1′), 107.23 (CN), 117.21 (C-3), 121.2–148.50 (quinoline-C), 150.55 (C-5), 153.20 (C-4), 162.11 (C-6), 162.97 (C-2), 171.05 (4 CO).

17d. IR (KBr) 2215 (CN) cm^{-1}; ^1H NMR δ_H 1.05–1.48 (m, 6H, 3 CH_2), 1.85–2.06 (4s, 12H, 4 × AcO), 2.02–2.22 (m, 2H, CH_2), 2.62 (m, 2H, CH_2), 3.12 (m, 2H, CH_2), 4.02–4.17 (m, 3H, 6′-H_2, 5′-H), 5.12 (m. 1H, 3′-H), 5.62 (t, 1H, 2′-H), 6.13 (m, 1H, 1′-H), 7.20–9.12 (m, 6H, quinoline-H); ^{13}C NMR δ_C 20.12–33.20 (6 × CH_2 and 4 × CH_3), 63.25 (C-6′), 68.21 (C-4′), 68.56 (C-2′), 75.91 (C-3′), 72.22 (C-5′), 80.9 (C-1′), 106.25 (CN), 115.78 (C-3), 123.99–148.43 (quinoline-C), 149.78 (C-5), 150.02 (C-4), 154.11 (C-6), 166.20 (C-2), 170.00–171.23 (4 CO).

2-(β-D-Gluco- and galactopyranosylthio)-4-pyridinyl-, 4-quinolinyl- and 4-indolinyl-cycloalkeno[b]pyridine-3-carbonitriles 12a–p, 19a–h, and 20a–h. General Procedures. Dry gaseous ammonia was passed through a solution of protected glycosides **11**, **17**, or **18** (0.5 g) in dry methanol (20 cm^3) at 0°C for ca. 0.5 hr; then the mixture was stirred at 0°C (for ca.) (2 to 6 hr). The mixture was evaporated under reduced pressure at 40°C to give a solid residue, which was crystallized from the appropriate solvent.

12c. IR (KBr) 2225 (CN) cm^{-1}; ^1H NMR δ_H 1.40–1.55 (m, 2H, CH_2), 1.60–1.70 (m, 2H, CH_2), 1.90–2.22 (m, 2H, CH_2), 2.88–2.92 (m, 2H, CH_2), 3.22–3.70 (6H, m, 6′-H_2, 5′-H, 4′-H, 3′-H and 2′-H), 4.50 (s, 2H, 2′-OH and 3′-OH), 5.16 (s, 1H, 4′-OH), 5.38 (s, 1H, 6′-OH), 5.59 (m, 1H, 1′-H), 7.15–8.45 (m, 4H, pyridine-H).

12g. IR (KBr) 2220 (CN) cm^{-1}; ^1H NMR δ_H 1.00–1.33 (m, 2H, CH_2), 1.50–1.77 (m, 6H, 3CH_2), 2.20–2.39 (m, 2H, CH_2), 3.00–3.16 (m, 2H, CH_2), 3.34–3.60 (6H, m, 6′-H_2, 5′-H, 4′-H, 3′-H, and 2′-H), 4.40 (s, 2H, 2′-OH, and 3′-OH), 5.00 (s, 1H, 4′-OH), 5.20 (s, 1H, 6′-OH), 5.50–5.60 (m, 1H, 1′-H), 7.11–8.23 (m, 4H, pyridine-H).

19b. IR (KBr) 2225 (CN) cm^{-1}; ^1H NMR δ_H 1.42–1.58 (m, 2H, CH_2), 1.65–1.72 (m, 2H, CH_2), 1.93–2.20 (m, 2H, CH_2), 2.90–2.96 (m, 2H, CH_2), 3.30–3.68 (6H, m, 6′-H_2, 5′-H, 4′-H, 3′-H, and 2′-H), 4.53 (s, 2H, 2′-OH, and 3′-OH), 5.10 (s, 1H, 4′-OH), 5.30 (s, 1H, 6′-OH), 5.52 (m, 1H, 1′-H), 7.18–9.02 (m, 6H, quinoline-H); ^{13}C NMR δ_C 21.53–33.17 (4 × CH_2), 60.79 (C-6′), 60.90 (C-4″), 69.75 (C-2′), 71.79 (C-3′), 78.67 (C-5′), 81.74 (C-1′), 83.62 (C-3′), 107.22 (CN), 117.09 (C-3), 121.08–148.15 (quinoline-C), 149.99 (C-5), 150.9 (C-4), 158.20 (C-6), 162.35 (C-2).

19c. IR (KBr) 2220 (CN) cm^{-1}; ^1H NMR δ_H 1.08–1.40 (m, 2H, CH_2), 1.58–1.80 (m, 6H, 3CH_2), 2.22–2.40 (m, 2H, CH_2), 3.02–3.10 (m, 2H, CH_2), 3.24–3.69 (6H, m, 6′-H_2, 5′-H, 4′-H, 3′-H, and 2′-H), 4.42 (s, 2H, 2′-OH, and 3′-OH), 5.02 (s, 1H, 4′-OH), 5.22 (s, 1H, 6′-OH), 5.58–5.62 (m, 1H, 1′-H), 7.28–9.05 (m, 6H, quinoline-H), ^{13}C NMR δ_C 25.41–31.17 (6 × CH_2), 60.72 (C-6′), 60.87 (C-4′), 69.73 (C-2′), 71.78 (C-3′), 78.65 (C-5′), 81.72 (C-1′), 83.58 (C-1′), 105.10 (CN), 116.22 (C-3), 121.01–148.18 (quinoline-C), 149.55 (C-5), 150.10 (C-4), 157.11 (C-6), 168.99 (C-2).

20a. IR (KBr) 2225 (CN) cm^{-1}; ^1H NMR δ_H 1.40–1.50 (m, 2H, CH_2), 1.65–1.72 (m, 2H, CH_2), 1.93–2.20 (m, 2H, CH_2), 3.30–3.60 (6H, m, 6′-H_2, 5′-H, 4′-H, 3′-H, and 2′-H), 4.50 (s, 2H, 2′-OH, and 3′-OH), 5.17 (s, 1H, 4′-OH), 5.37 (s, 1H, 6′-OH), 5.59 (m, 1H, 1′-H), 7.10–8.75 (m, 5H, indole-H).

20b. IR (KBr) 2220 (CN) cm^{-1}; ^1H NMR δ_H 1.37–1.45 (m, 2H, CH_2), 1.55–1.67 (m, 2H, CH_2), 1.88–2.09 (m, 2H, CH_2), 2.85–2.99 (m, 2H, CH_2), 3.41–3.70 (6H, m, 6′-H_2, 5′-H, 4′-H, 3′-H, and 2′-H), 4.77 (s, 2H, 2′-OH, and 3′-OH), 5.13 (s, 1H, 4′-OH), 5.47 (s, 1H, 6′-OH), 5.79 (m, 1H, 1′-H), 7.10–8.99 (m, 5H, indole-H).

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