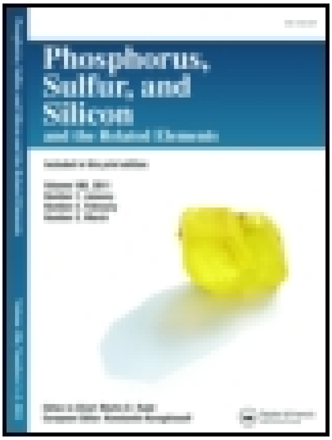

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Synthesis and Anti-Inflammatory Activities of Some Novel S-Pyridyl Glycosides Derivatives

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Synthesis and Anti-Inflammatory Activities of Some Novel S-Pyridyl Glycosides Derivatives

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A series of some new acetylated S-glycosides of pyridine-2-thione derivatives, including D-glucose, D-galactose, D-xylose and L-arabinose derivatives were synthesized. Oxidation of some formed S-glycosides derivatives with H_2O_2 afforded the corresponding sulfones. S-Alkylation of pyridine-2-thione derivatives was performed to furnish the S-acyclo deazauridine derivatives. The entire tested compound showed potent anti-inflammatory activity were potent against edema and in the same time inhibited the prostaglandine formation. It is work mention that all the tested compounds showed high safety margin. The structures of the new synthesized compounds have been proved by IR, ^{1}HNMR, mass spectra and elemental analysis.

Keywords Anti-inflammatory activity; glycoside derivatives; 5,6,7,8- Tetrahydronaphthalene

INTRODUCTION

3-Deazauridine and 3-deazacytidine were found to exert marked inhibitory effects on the growth of neoplastic and bacterial culture[1] and also have antiviral against RNA viruses.[2]Also 3-deazauridine was active against L1210 leukemia cells in vivo.[3] 3-Deazauridine is a potent inhibitor of CTP synthetase (phosphocholine cytidyltransferase). Deaza UTP is a competitive inhibitor of this enzyme with respect to UTP. Deaza UTP is an inhibitor of ribonucleotide reductase activity. The net

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result of the inhibition at these sites is that the cells become deficient in cytidine and deoxycytidine nucleotides, causing inhibition of both RNA and DNA synthesis.[4,5] The importance of such compounds, as intermediates for the synthesis of the biologically active deazafolic acid and 3-deazapyrimidine nucleosides ring system[6,7]prompted our interest in the synthesis and chemistry of this class of compounds. Recently, some new chiral heterocyclic compounds containing pyridine moiety have been reported as anticancer and anti-inflammatory.[8,9] On the other hand, tetrahydronaphthalene incorporated in heterocyclic systems with a wide spectrum of biological activities are known.[10–14] As part of our program of research on the synthesis new uridine and deazauridine glycosides,[15–18] we have herein synthesized some new pyridine S-glycoside derivatives for their evaluation anti-inflammatory activity.

RESULTS AND DISCUSSION

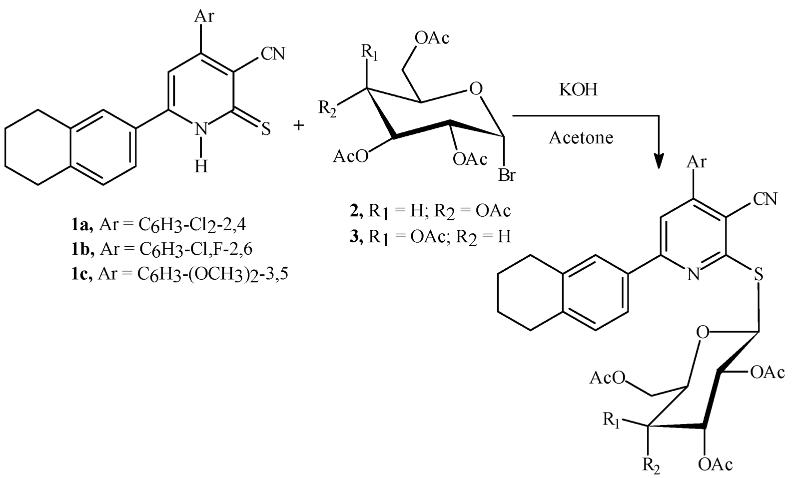
Chemistry

In this study, the synthesis of some new acetylated glycosides of 2-thioxo-3-deazapyrimidine utilizing pyridine-2(1H)-thione **1** as starting materials. Thione derivatives **1** were prepared by the reaction of 6-acetyl-5,6,7,8-tetrahydronaphthalene with arylidenecyanothioacetamide in presence of ammonium acetate according literature method[19]. Compound **1** readily reacted with tetra-*O*-acetyl-α-D-glucopyranosyl bromide **2** or with tetra-*O*-acetyl-α-D-galactopyranosyl bromide **3** in the presence of potassium hydroxide in acetone to yield the corresponding S-glucosides **4a–c** and S-galactosides **5a–c**, respectively (Scheme 1).

Also, reaction of **1** with freshly prepared 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide **6** or with 2,3,4-tri-*O*-acetyl-β-L-arabinopyranosyl bromide **7** in the presence of potassium hydroxide in acetone gave S-xylosides **8a–c** and S-arabinosides **9a–c**, respectively (Scheme 2).

Thin layer chromatography indicated that a single unique compound was produced, and the structures were demonstrated by the elemental analyses and the spectral data. Evidence for the attachment of the sugar moiety to the 2-position was obtained by oxidation of the thio galactosides **5a–c** with hydrogen peroxide in acetic acid,[20] which was yielded the corresponding sulphones **10a–c** as illustrated in Scheme 3.

One the other hand, compound **1c** can be coupled with different classes of acyclic sugar halides namely chloromethylethylether, chloromethylmethylsulfide, and 3-bromo-1-propanol **11a–c** in the presence of sodium hydride in dry acetonitrile to give a series of some pyridine acyclonucleoside analogues **12a–c** (Scheme 4).

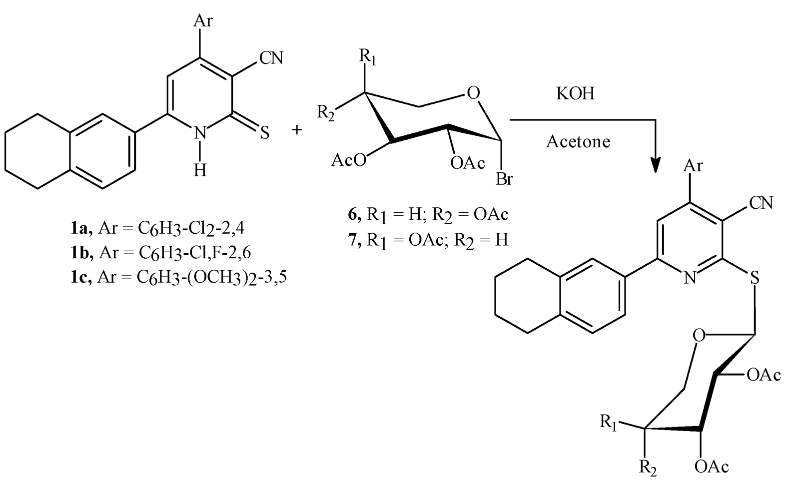


1a, Ar = C_6H_3-Cl_2-2,4
1b, Ar = C_6H_3-Cl,F-2,6
1c, Ar = C_6H_3-$(OCH_3)_2$-3,5

2, R_1 = H; R_2 = OAc
3, R_1 = OAc; R_2 = H

4a, Ar = C_6H_3-Cl_2-2,4; R_1 = H; R_2 = OA
4b, Ar = C_6H_3-Cl,F-2,6; R_1 = H; R_2 = OA
4c, Ar = C_6H_3-$(OCH_3)_2$-3,5; R_1 = H; R_2 = OA
5a, Ar = C_6H_3-Cl_2-2,4; R_1 = OAc; R_2 = H
5b, Ar = C_6H_3-Cl,F-2,6; R_1 = OAc; R_2 = H
5c, Ar = C_6H_3-$(OCH_3)_2$-3,5; R_1 = OAc; R_2 = H

SCHEME 1

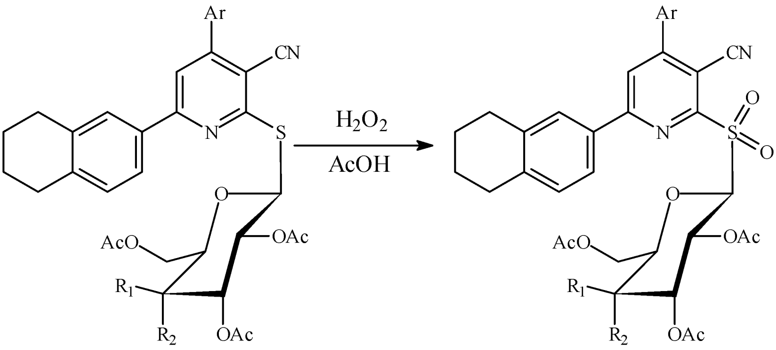


1a, Ar = C_6H_3-Cl_2-2,4
1b, Ar = C_6H_3-Cl,F-2,6
1c, Ar = C_6H_3-$(OCH_3)_2$-3,5

6, R_1 = H; R_2 = OAc
7, R_1 = OAc; R_2 = H

8a, Ar = C_6H_3-Cl_2-2,4; R_1 = H; R_2 = OA
8b, Ar = C_6H_3-Cl,F-2,6; R_1 = H; R_2 = OA
8c, Ar = C_6H_3-$(OCH_3)_2$-3,5; R_1 = H; R_2 = OA
9a, Ar = C_6H_3-Cl_2-2,4; R_1 = OAc; R_2 = H
9b, Ar = C_6H_3-Cl,F-2,6; R_1 = OAc; R_2 = H
9c, Ar = C_6H_3-$(OCH_3)_2$-3,5; R_1 = OAc; R_2 = H

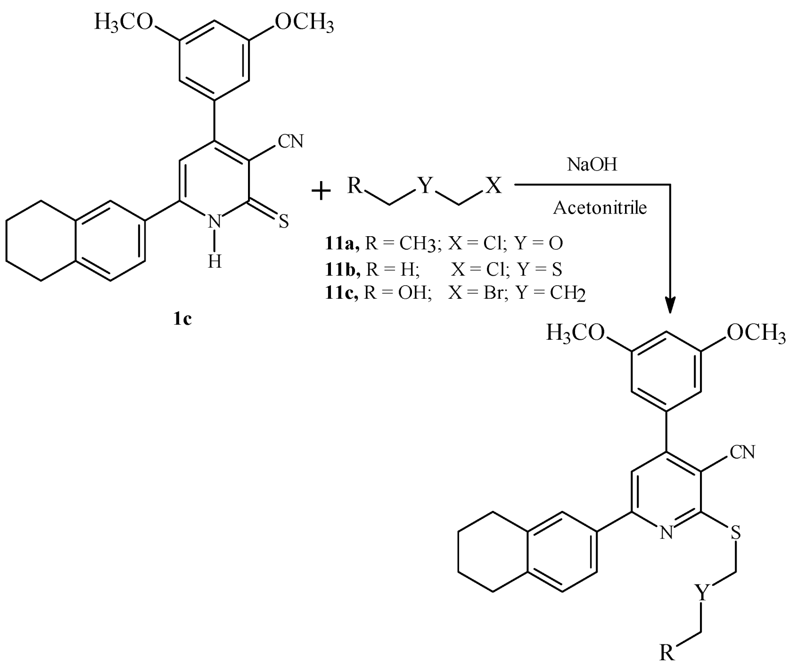
SCHEME 2



5a-c **10a-c**

a, Ar = C_6H_3-Cl_2-2,4; R_1 = OAc; R_2 = H
b, Ar = C_6H_3-Cl,F-2,6; R_1 = OAc; R_2 = H
c, Ar = C_6H_3-$(OCH_3)_2$-3,5; R_1 = OAc; R_2 = H

SCHEME 3



1c

12a, R = CH_3; Y = O
12b, R = H; Y = S
12c, R = OH; Y = CH_2

SCHEME 4

The chemical formulas of the prepared compounds were elucidated with correct elemental analyses and by IR, ^{1}HNMR, ^{13}CNMR as well as mass spectra. The IR spectra of **4a–c**, **5a–c**, **8a–c**, and **9a–c** are characterized by the absence of νas NH and νas SH at 3220−3340 cm^{-1} and by stretching vibration frequencies of the acetate carbonyl in the 1765−1730 cm $^{-1}$ region. The ^{1}HNMR spectral data and their assignments are shown below. All synthesized compounds, **4a–c**, **5a–c**, **8a–c**, and **9a–c** exist predominantly in a chair like configuration and conformation as shown in Schemes 1 and 2. In general, the anomeric proton (H-1$'$) of aldopyranosyl halides[21] and acetylated 1-thioaldopyranoses[22] resonate at relatively lower field than other sugar ring protons. The structures of the synthesized acetylated S-glycopyranosyl derivatives showed the anomeric protons which appear as doublets with large coupling constants at C^1 and C^2 of the carbohydrate residue, corresponding to the diaxial orientation of H-1$'$ and H-2$'$ protons which indicates the presence of only β-configuration in the (D) conformation of compounds **4a–c**, **5a–c**, and **8a–c**, and the α- configuration in the (L) conformation of compounds **9a–c**. Compound **5c** serves as an example, the anomeric proton appear as a doublet at δ 5.83 ppm with spin-spin coupling constant equal to 9.97 Hz, which corresponds to the diaxial orientation of H-1$'$ and H-2$'$ protons indicating the presence of only β-configuration. The other six protons of the galactopyranosyl ring resonates at δ 4.12−5.63 ppm region. The remaining four acetoxy groups appear as four singlets at δ 1.89, 1.96, 1.99, and 2.17 ppm. The ^{13}CNMR spectrum was characterized by a signal at δ 93.1 ppm corresponding to C-1$'$ atom of the β-D-galactopyranose. Four signals appear at δ 169.1, 169.6, 169.7, and 169.9 ppm due to the four acetoxy carbonyl carbon atoms of the sugar moiety, with four additional signals at δ 20.1, 20.2, 20.5, and 20.7 ppm attributed to acetoxy methyl carbons and five signals at δ 61.3, 67.5, 67.9, 69.7 and 71.1 ppm assigned as C-6$'$, C-4$'$, C-2$'$, C-3$'$, and C-5$'$ of galactose, respectively, The nitrile carbon of the pyridine thione appears at 118.1 ppm.

Pharmacological Screening

Anti-Inflammatory Potency

Initially the acute toxicity of the compounds was assayed via the determination of their LD_{50}. All the compounds except **5b** were interestingly less toxic than Valdecoxib® as the reference drug (Table I). The newly synthesized compounds were then pharmacologically screened on male albino rats for their anti-inflammatory potency (Tables II and III). The evaluation of the anti-inflammatory activities

TABLE I Acute Toxicity (LD_{50}) of the Synthesized Compounds

Compound no.	LD_{50} [mg/kg]
5a	2.673 ± 0.010
5b	1.066 ± 0.011
5c	2.212 ± 0.014
5d	3.601 ± 0.012
6a	1.796 ± 0.010
6b	2.214 ± 0.010
6c	2.560 ± 0.010
6d	2.483 ± 0.012
7a	4.176 ± 0.013
7d	3.700 ± 0.010
8a	1.910 ± 0.011
8d	3.115 ± 0.013
10a	3.070 ± 0.012
10d	2.710 ± 0.011
11	3.611 ± 0.013
12a	2.812 ± 0.014
12b	2.813 ± 0.010
Valdicoxib®	1.635 ± 0.014

was based on a strong biological rationale, and this involved the two criteria present in the tested molecules.

Purpose and Rationale

For the determination of the antiphlogistic potency of the synthesized compounds, two standard tests were realized at 25 and 50 mg/kg rat body weight namely, the protection against Carrageenan® induced edema according Winter et al.,[23] and the inhibition of plasma PGE2. The later is known as a good confirming indicator for the Carrageenan® induced rat paw edema.[24]

Regarding the protection against Carrageenan® induced edema, eight compounds namely **5a**, **5b**, **6a**, **6b**, **7a**, **8a**, **11**, and **12b** were found more potent than Valdecoxib®. Where, their protection percentage against carrageenan induced edema at two dose levels 25 and 50 mg/kg are 92.66/95.95, 93.60/98.56, 91.85/98.82, 94.15/96.10, 93.18/93.75, 89.26/98.31, 88.86/97.97, and 93.86/93.81, respectively (Valdecoxib® 80.95/92.98). On the other hand, the inhibition of plasma PGE2 for the compounds **5a**, **5b**, **6a**, and **8a** were found more potent than Valdecoxib® at two tested doses levels 25 and 50 mg/kg. The inhibition percentage for the latter compounds were found as: 99.84/93.56, 91.98/96.75, 80.16/90.62, and 83.76/94.98, respectively.

TABLE II Anti-Inflammatory Potencies of the Synthesized Compounds (Protection against Carrageenan-Induced Edema)

Compound no.	Dose [mg/kg]	Protection against carrageenan-induced edema [%]*
5a	25	92.66 ± 0.084
	50	95.95 ± 0.082
5b	25	93.60 ± 0.088
	50	98.56 ± 0.085
5c	25	−52.16 ± 0.080
	50	
5d	25	−38.66 ± 0.082
	50	
6a	25	91.85 ± 0.075
	50	98.82 ± 0.076
6b	25	94.15 ± 0.080
	50	96.10 ± 0.076
6c	25	−84.16 ± 0.066
	50	
6d	25	−44.80 ± 0.055
	50	
7a	25	93.18 ± 0.066
	50	93.75 ± 0.076
7d	25	47.18 ± 0.080
	50	63.11 ± 0.056
8a	25	89.26 ± 0.060
	50	98.31 ± 0.073
8d	25	55.22 ± 0.055
	50	66.15 ± 0.068
10a	25	53.16 ± 0.078
	50	65.18 ± 0.066
10d	25	55.75 ± 0.069
	50	75.13 ± 0.074
11	25	88.86 ± 0.077
	50	97.97 ± 0.068
12a	25	54.22 ± 0.067
	50	73.14 ± 0.049
12b	25	93.86 ± 0.066
	50	93.81 ± 0.070
Valdicoxib®	25	80.95 ± 0.990
	50	92.98 ± 0.080

*The doses tested were 25, 50 mg and carryout three determinations for each dose.

Pharmacological Screening

Determination of Acute Toxicity (LD_{50})

The LD_{50} for compounds were determined by injected different gradual increased doses of the tested compounds to adult male albino rats, then calculating the dose that caused 50% animal death, according to Austen and Brocklehurst.[25]

TABLE III Anti-Inflammatory Potencies of the Synthesized Compounds (Inhibition of Plasma PGE2)

Compound no.	Dose [mg/kg]	Inhibition of plasma PGE2 [%]*
5a	25	99.84 ± 0.085
	50	93.56 ± 0.092
5b	25	91.98 ± 0.088
	50	96.75 ± 0.105
5c	25	—
	50	46.61 ± 0.090
5d	25	—
	50	31.13 ± 0.085
6a	25	80.16 ± 0.088
	50	90.62 ± 0.100
6b	25	78.62 ± 0.096
	50	82.66 ± 0.087
6c	25	—
	50	77.50 ± 0.086
6d	25	—
	50	36.18 ± 0.088
7a	25	77.41 ± 0.088
	50	81.56 ± 0.086
7d	25	41.16 ± 0.077
	50	54.17 ± 0.091
8a	25	83.76 ± 0.109
	50	94.98 ± 0.110
8d	25	43.18 ± 0.088
	50	62.13 ± 0.078
10a	25	46.31 ± 0.090
	50	61.38 ± 0.110
10d	25	50.99 ± 0.100
	50	71.00 ± 0.098
11	25	76.55 ± 0.078
	50	84.87 ± 0.081
12a	25	47.62 ± 0.065
	50	70.55 ± 0.087
12b	25	82.16 ± 0.076
	50	79.15 ± 0.077
Valdicoxib®	25	77.00 ± 0.084
	50	91.00 ± 0.087

*The doses tested were 25, 50 mg and carryout three determinations for each dose.

Anti-Inflammatory Activity

Procedure. Groups of adult male albino rats (150–180 g), each of 8 animals were orally dosed with tested compounds at a dose level of 25–50 mg/kg 1 h before Carrageenan®challenge. Foot paw edema was induced by subplantar injection of 0.05 ml of 1% suspension of Carrageenan®in saline into the planter tissue of one hind paw. An equal volume of saline was injected to the other hind paw and served as control. Four h after drug administration, the animals were decapitated, blood was collected and the paws were rapidly excised.

The average weight of edema was examined for the treated as well as the control group and the percentage inhibition of weight of edema was also evaluated. Valdicoxib®(5 mg/kg) was employed as standard reference, against which the tested compounds were compared.

Calculation and Evaluation. Thirty min after the rats are challenged by subcutaneous injection of 0.05 ml of 1% solution of carrageenan into the planter side of the lift hind paw. The paw is marked with ink at the level of the lateral malleolus, the paw volume was measured by a sensitive method developed by Webb and Griswold[26] that calculated by interfacing a Mettler DeltaRange top-loading balance with a micro computer.

$$\%\text{Protection} = (\text{A}-\text{B}) \times 100/\text{A}$$
$$\text{A} = \text{the paw volume of non-treated group}$$
$$\text{B} = \text{the paw volume of treated group} \tag{1}$$

Estimation of Plasma Prostaglandin E2 (PGE2)

Procedure. Heparinized blood samples were collected from rats obtained from the previous anti-inflammatory examined groups (n = 8), plasma was separated by centrifugation at 12,000 g for 2 min at 40°C and immediately stored frozen −2°C until use.

The design correlate EIA prostaglandin E2 (PGE2) kit (Merck, Darmstadt, Germany) is a competitive immuno assay for the quantitative determination of PGE2 in biological fluids. The kit uses a monoclonal antibody to PGE2 to bind, in a competitive manner, the PGE2 in the sample after a simultaneous incubation at room temperature. The excess reagents were washed away and the substrate was added, after a short incubation time the enzyme reaction was stopped and the yellow color generated was read on a micro plate reader (DYNATCh, MR 5000) at 405 nm. The intensity of the bound yellow color is inversely proportional to the concentration of PGE2 in either standard or samples.

Calculation and Evaluation. The PGE2 was calculated for the treated and control groups, then the PGE2 percentage inhibition is determined by the following equation:

$$\%\text{Inhibition} = (\text{A}-\text{B}) \times 100/\text{A}$$
$$\text{A} = \text{PGE2 in the control group}$$
$$\text{B} = \text{PGE2 in the treated group} \tag{2}$$

CONCLUSION

All the tested compounds showed potent anti-inflammatory activities at two-dose level except compounds **5c**, **5d**, **6c**, and **6d** only showed activities at 50 mg/kg dose level. Compounds **5b**, **5a**, **8a**, **11**, **6b**, **5a**, and **12b** are more potent than the reference drug Valdecoxib®at in the same time more safe than it except compound 5b. The order of activity (in descending manner) is: **5b**, **5a**, **8a**, **11**, **6b**, **5a**, **12b**, **7a**, **6c**, **10d**, **12a**, **8d**, **10a**, **7d**, **5c**, **6d**, and **5d**.

EXPERIMENTAL

Synthesis

Melting points are uncorrected and were taken on an open glass capillaries Melting point apparatus. Analytical data were obtained from the microanalytical unit, Cairo University, Egypt. IR spectra (KBr discs) were recorded on a Perkin Elmer 1430 spectrophotometer. ^{1}H NMR and ^{13}CNMR spectra were determined on Joel 270 MHz in DMSO-d_6 and the chemical shifts were recorded in ppm relative to TMS. The mass spectra were run 70ev with a Finnegan SSQ GC/ MS spectrometer using EI and Fast Atom Bombardment (FAB) mass spectra on a Kratos MS 50 rf. All reactions were followed by *TLC* (silica gel, aluminum sheets 60 F_{254}, Merck) and Merck Silica gel (0.040−0.063 mm) was used for column chromatography.

4-(Substituted phenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-2-thioxo-1,2-di-hydro-pyridine-3-carbonitrile 1a–c

A suspension of 6-acetyl-5,6,7,8-tetrahydronaphthalene (10 mmol), arylidenecyanothioacetamide (10 mmol) and anhydrous ammonium acetate (15 mmol) in 30 ml ethanol was heated under reflux for 6 h. The resulting product was filtered off and crystallized from the proper solvent to give **1a–c**, respectively.

4-(2,4-Dichlorophenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-2-thioxo-1,2-dihyro-pyridine-3-carbonitrile (1a). Yield (77%), m.p.

266–268°C (dioxane); IR (KBr, cm^{-1}) 3290 (NH), 2230 (CN), 1590 (C=N), 1209 (C=S); ^{1}H-NMR (DMSO-d_6): δ 1.68–1.70 (m, 4H, 2 CH_2), 2.74–2,78 (m, 4H, 2 CH_2), 6.80 (s, 1H, H-5 pyridine), 7.05–7.53 (m, 6H, Ar-H), 10.19 (s, 1H, NH) ppm; MS (EI): m/z 410 (45%) [M^+]. Anal. $C_{22}H_{16}Cl_2N_2S$, Calcd CHN: 64.24; 3.92; 6.81. found: 66.12; 3.71; 6.57.

4-(2-Chloro-6-fluorophenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-2-thioxo-1,2-dihyro-pyridine-3-carbonitrile (1b). Yield (66%), m.p. 279–281°C (ethanol); IR (KBr, cm^{-1}) 3321 (NH), 2219 (CN), 1586 (C=N), 1206 (C=S); ^{1}H-NMR (DMSO-d_6): δ 1.70–1.74 (m, 4H, 2CH_2), 2.78–2.81 (m, 4H, 2CH_2), 6.89 (s, 1H, H-5 pyridine), 7.11–7.59 (m, 6H, Ar-H), 10.37 (s, 1H, NH) ppm; MS (EI): m/z 394 (15%) [M^+], Anal. $C_{22}H_{16}ClFN_2S$, calcd.: CHN: 66.91; 4.08; 7.09, found: 66.74; 3.96; 6.89.

4-(3,5-Dimethoxyphenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-2-thioxo-1,2-dihyro-pyridine-3-carbonitrile (1c). Yield (66%), m.p. 246–247°C (ethanol); IR (KBr, cm^{-1}) 3317 (NH), 2220 (CN), 1589 (C=N), 1207 (C=S); ^{1}H-NMR (DMSO-d_6): δ 1.73–1.76 (m, 4H, 2 CH_2), 2.83–2.86 (m, 4H, 2 CH_2), 3.87 (s, 6H, 2OCH_3), 6.86 (s, 1H, H-5 pyridine), 7.10–7.56 (m, 6H, Ar-H), 10.55 (s, 1H, NH) ppm; MS (EI): m/z 402 (18%) [M^+]. Anal. $C_{24}H_{22}N_2O_2S$, calcd. CHN: 71.62; 5.51; 6.96, found: 71.49; 5.37; 6.77.

Synthesis of Acetylated S-Glycosides 4a–c, 5a–c, 8a–c, and 9a–c—General Procedure

A solution of bromides **2**, **3**, **6**, or **7** (10 mmol) in acetone 50 ml was added to a solution of 2(1H)-pyridine thiones **1a–c** (10 mmol) in water 6 ml containing potassium hydroxide (10 mmol). The reaction mixture was stirred at room temperature for 9 h; complete conversion of starting material to new product was indicated by TLC. The solvent was evaporated under reduced pressure at 40°C. The residue was washed with water to remove potassium bromide. The mixture was filtered, and the filtrate was evaporated to dryness. The residue was crystallized from ethanol to afford colorless crystals of the thioglycosides **4a–c**, **5a–c**, **8a–c**, and **9a–c**

4-(2,4-Dichlorophenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-2-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl thio)-pyridine-3-carbonitrile (4a). Yield (61%), m.p. 170–171°C; IR (KBr, cm^{-1}) 2223 (CN), 1725 (CO ester), 1582 (C=N); ^{1}H-NMR (DMSO-d_6): δ 1.70–1.72 (m, 4H, 2 CH_2), 1.89, 1.97, 1.99, 2.14 (4s, 12H, 4 CH_3CO), 2.82–2.85 (m, 4H, 2 CH_2), 4.22–4.24 (m, 2H, H-6′, 6″), 4.55–4.58 (m, 1H, H-5′), 5.28–5.32 (m, 2H, H-4′ and H-3′), 5.78–5.80 (m, 1H, H-2′), 5.85 (d, $J_{1'-2'}$9.78 Hz, 1H, H-1′), 6.80 (s, 1H, H-5 pyridine), 7.19–7.56 (m, 6H, Ar-H) ppm; MS (FAB): m/z 740 (13%) [M^+]. Anal. $C_{36}H_{34}Cl_2N_2O_9S$, calcd. CHN: 58.30; 4.62; 3.78, found: 58.11; 4.40; 3.59.

4-(2-Chloro-6-fluorophenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-2-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl thio)-pyridine-3-carbo-nitrile (4b). Yield (69%), m.p. 183–185°C; IR (KBr, cm^{-1}) 2220 (CN), 1739 (CO ester), 1586 (C=N); ^{1}H-NMR (DMSO-d_6): δ 1.76–1.78 (m, 4H, 2CH_2), 1.95, 199, 2.01, 2.10 (4s, 12H, 4 CH_3CO), 2.84–2.86 (m, 4H, 2 CH_2), 4.18–4.22 (m, 2H, H-6′, 6″), 4.50–4.54 (m, 1H, H-5′), 5.26–5.29 (m, 2H, H-4′ and H-3′), 5.74–5.77 (m, 1H, H-2′), 5.86 (d, $J_{1'-2'}$9.81 Hz, 1H, H-1′), 6.89 (s, 1H, H-5 pyridine), 7.23–7.51 (m, 6H, Ar-H) ppm; MS (FAB): m/z 724 (22%) [M^+]. Anal. $C_{36}H_{34}ClFN_2O_9S$, calcd. CHN: 59.62; 4.73; 3.86, found: 59.47; 4.52; 3.60.

4-(3,5-Dimethoxyphenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-2–(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl thio)-pyridine-3-carbo-nitrile (4c). Yield (57%), m.p. 206–207°C; IR (KBr, cm^{-1}) 2216 (CN), 1751 (CO ester), 1580 (C=N); ^{1}H-NMR (DMSO-d_6): δ 1.70–1.73 (m, 4H, 2 CH_2), 1.96, 1.98, 2.02, 2.11 (4s, 12H, 4 CH_3CO), 2.86–2.88 (m, 4H, 2 CH_2), 4.24–2.27 (m, 2H, H-6′, 6″), 4.55–4.57 (m, 1H, H-5′), 5.32–5.35 (m, 2H, H-4′ and H-3′), 5.80–5.84 (m, 1H, H-2′), 5.82 (d, $J_{1'-2'}$9.92 Hz, 1H, H-1′), 6.86 (s, 1H, H-5 pyridine), 7.27–7.55 (m, 6H, Ar-H) ppm; MS (FAB): m/z 732 (43%) [M^+]. Anal. $C_{38}H_{40}N_2O_{11}S$, calcd. CHN: 62.28; 5.50; 3.82, found: 62.06; 5.43; 3.65.

4-(2,4-Dichlorophenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-2-(2′, 3′, 4′,6′-tetra-O-acetyl-β-D-galactopyranosyl thio)-pyridine-3-carb-onitrile (5a). Yield (73%), m.p. 115–116°C; IR (KBr, cm^{-1}) 2218 (CN), 1755 (CO ester), 1580 (C=N); ^{1}H-NMR (DMSO-d_6): δ 1.73–1.76 (m, 4H, 2 CH_2), 1.94, 1.98, 2.03, 2.12 (4s, 12H, 4 CH_3CO), 2.85–2.87 (m, 4H, 2 CH_2), 4.21–4.25 (m, 2H, H-6′, 6″ and 1H, H-5′), 4.63 (t, 1H, H-4′), 5.52–5.6 (m, 2H, H-3′ and H-2′), 5.78 (d, $J_{1'-2'}$9.98 Hz, 1H, H-1′), 6.84 (s, 1H, H-5 pyridine), 7.23–7.57 (m, 6H, Ar-H) ppm; MS (FAB): m/z 740 (23%) [M^+]. Anal. $C_{36}H_{34}Cl_2N_2O_9S$, calcd. CHN: 58.30; 4.62; 3.78, found: 58.09; 4.49; 3.50.

4-(2-Chloro-6-fluorophenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-2- (2′,3′,4′,6′-tetra-O-acetyl-β-D-galactopyranosyl thio)-pyridine-3-ca-rbonitrile (5b). Yield (76%), m.p. 168–170°C; IR (KBr, cm^{-1}) 2222 (CN), 1760 (CO ester), 1585 (C=N); ^{1}H-NMR (DMSO-d_6): δ 1.76 (m, 4H, 2 CH_2), 1.96, 1.98, 2.00, 2.18 (4s, 12H, 4 CH_3CO), 2.86–2.90 (m, 4H, 2 CH_2), 4.14–4.18 (m, 2H, H-6′, 6″ and 1H, H-5′), 4.65–4.68 (m, 1H, H-4′), 5.52–5.55 (m, 2H, H-3′ and H-2′), 5.68 (d, $J_{1'-2'}$9.91Hz, 1H, H-1′), 6.80 (s, 1H, H-5 pyridine), 7.22–7.54 (m, 6H, Ar-H) ppm; MS

(FAB): m/z 724 (12%) [M^+]. Anal. $C_{36}H_{34}ClFN_2O_9S$, calcd. CHN: 59.62; 4.73; 3.86, found: 59.52; 4.58; 3.67.

4-(3,5-Dimethoxyphenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-2–(2′,3′,4′,6′-tetra-O-acetyl-β-D-galactopyranosyl thio)-pyridine-3-carbonitrile (5c). Yield (83%), m.p. 218–219°C; IR (KBr, cm^{-1}) 2218 (CN), 1756 (CO ester), 1581 (C=N); ^{1}H-NMR (DMSO-d_6): δ 1.70–1.74 (m, 4H, 2 CH_2), 1.89, 1.96, 1.99, 2.17 (4s, 12H, 4 CH_3CO), 2.84–2.86 (m, 4H, 2 CH_2), 4.12–4.16 (m, 2H, H-6′, 6″), 4.62–4.66 (m, 1H, H-5′), 5.33–5.37 (m, 2H, H-4′ and H-3′), 5.63–5.68 (m, 1H, H-2′), 5.83 (d, $J_{1'-2'}$9.97 Hz, 1H, H-1′), 6.85 (s, 1H, H-5 pyridine), 7.27–7.58 (m, 6H, Ar-H) ppm; ^{13}C-NMR (DMSO-d_6): δ 20.1–20.7 (4 CH_3CO), 22.9–31.2 (4 CH_2), 56.7 (OCH_3), 61.3 (C-6′), 67.5 (C-4), 67.9 (C-2′), 69.7 (C-3), 71.1 (C-5′), 93.1 (C-1′), 118.1 (CN), 118.3 (C-5- pyridine ring), 123.9-164.1 (Ar-C), 169.1–169.9 (4 $COCH_3$) ppm; MS (FAB): m/z 732 (14%) [M^+]. Anal. $C_{38}H_{40}N_2O_{11}S$, calcd. CHN: 62.28; 5.50; 3.82, found: 62.13; 5.29; 3.56.

4-(2,4-Dichlorophenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-2-(2′,3′,4′-tri-O-acetyl-α-D-xylopyranosyl thio)-pyridine-3-carbonitrile (8a). Yield (51%), m.p. 188–189°C; IR (KBr, cm^{-1}) 2220 (CN), 1758 (CO ester), 1586 (C=N); ^{1}H-NMR (DMSO-d_6): δ 1.74–1.78 (m, 4H, 2 CH_2), 1.87, 1.98, 2.03 (3s, 9H, 3 CH_3CO), 2.86–2.90 (m, 4H, 2 CH_2), 4.01 (q, 2H, H-5′, 5″), 4.78–4.82 (m, 1H, H-4′), 4.96 (t, 1H, H-2′), 5.16 (t, 1H, H-3′), 6.19 (d, $J_{1'-2'}$7.33 Hz, 1H, H-1′), 6.80 (s, 1H, H-5 pyridine), 7.27–7.50 (m, 6H, Ar-H) ppm; MS (FAB): m/z 668 (18%) [M^+]. Anal. $C_{33}H_{30}Cl_2N_2O_7S$, calcd. CHN: 59.20; 4.52; 4.18, found: 58.99; 4.37; 3.98.

4-(2-Chloro-6-fluorophenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-2-(2′,3′,4′-tri-O-acetyl-α-D-xylopyranosyl thio)-pyridine-3-carbonitrile (8b). Yield (60%), m.p. 197–198°C; IR (KBr, cm^{-1}) 2224 (CN), 1761 (CO ester), 1580 (C=N); ^{1}H-NMR (DMSO-d_6): δ 1.74–1.79 (m, 4H, 2 CH_2), 1.90, 2.02, 2.03 (3s, 9H, 3 CH_3CO), 2.85–2.88 (m, 4H, 2 CH_2), 4.07 (q, 2H, H-5′, 5″), 4.84-4.88 (m, 1H, H-4′), 4.98 (t, 1H, H-2′), 5.25 (t, 1H, H-3′), 6.17(d, $J_{1'-2'}$7.51 Hz, 1H, H-1′), 6.85 (s, 1H, H-5 pyridine), 7.23–7.58 (m, 6H, Ar-H) ppm; MS (FAB): m/z 652 (32%) [M^+]. Anal. $C_{33}H_{30}ClFN_2O_7S$, calcd. CHN: 60.69; 4.63; 4.29, found: 60.57; 4.45; 4.12.

4-(3,5-Dimethoxyphenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-2–(2′,3′,4′-tri-O-acetyl-α-D-xylopyranosyl thio)-pyridine-3-carbonitrile (8c). Yield (55%), m.p. 164–166°C; IR (KBr, cm^{-1}) 2226 (CN), 1759 (CO ester), 1583 (C=N); ^{1}H-NMR (DMSO-d_6): δ 1.71–1.76 (m, 4H, 2

CH_2), 1.89, 1.99, 2.10 (3s, 9H, 3 CH_3CO), 2.85−2.89 (m, 4H, 2 CH_2), 4.23 (q, 2H, H-5′, 5″), 4.84−4.87 (m, 1H, H-4′), 4.99 (t, 1H, H-2′), 5.26 (t, 1H, H-3′), 6.19 (d, $J_{1'-2'}$7.60 Hz, 1H, H-1′), 6.86 (s, 1H, H-5 pyridine), 7.20−7.52 (m, 6H, Ar-H) ppm; MS (FAB): m/z 660 (44%) [M^+]. Anal. $C_{35}H_{36}N_2O_9S$, calcd. CHN: 63.62; 5.49; 4.24, found: 63.46; 5.27; 4.04.

4-(2,4-Dichlorophenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-2-(2′,3′,4-tri-O-acetyl-α-L-arabinopyranosyl thio)-pyridine-3-carbonitrile (9a). Yield (35%), m.p. 183−184°C; IR (KBr, cm^{-1}) 2223 (CN), 1762 (CO ester), 1589 (C=N); ^{1}H-NMR (DMSO-d_6): δ 1.70−1.75 (m, 4H, 2 CH_2), 1.87, 2.09, 2.15 (3s, 9H, 3 CH_3CO), 2.83−2.86 (m, 4H, 2 CH_2), 3.87 (q, 1H, H-5″), 4.01 (q, 1H, H-5′), 5.15−5.18 (m, 1H, H-4′), 5.22−5.26 (m, 1H, H-3′), 5.39 (d, 1H, H-2′), 6.17 (d, $J_{1'-2'}$9.61 Hz, 1H, H-1′), 6.85 (s, 1H, H-5 pyridine), 7.25−7.55 (m, 6H, Ar-H) ppm; MS (FAB): m/z 668 (16%) [M^+]. Anal. $C_{33}H_{30}Cl_2N_2O_7S$, calcd. CNH: 59.20; 4.52; 4.18, found: 59.06; 4.39; 4.03.

4-(2-Chloro-6-fluorophenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)- 2-(2′,3′,4′-tri-O-acetyl-α-L-arabinopyranosyl thio)-pyridine-3-carbonitr- ile (9b). Yield (20%), m.p. 189−190°C; IR (KBr, cm^{-1}) 2220 (CN), 1758 (CO ester), 1586 (C=N); ^{1}H-NMR (DMSO-d_6): δ 1.7−1.76 (m, 4H, 2 CH_2), 1.90, 2.05, 2.11 (3s, 9H, 3 CH_3CO), 2.83−2.87 (m, 4H, 2 CH_2), 3.83 (q, 1H, H-5″), 4.02 (q, 1H, H-5′), 5.18−5.20 (m, 1H, H-4′), 5.26−5.29 (m, 1H, H-3′), 5.36 (d, 1H, H-2′), 6.21 (d, $J_{1'-2'}$9.47 Hz, 1H, H-1′), 6.80 (s, 1H, H-5 pyridine), 7.24−7.59 (m, 6H, Ar-H) ppm; MS (FAB): m/z 652 (12%) [M^+]. Anal. $C_{33}H_{30}ClFN_2O_7S$, calcd. CHN: 60.69; 4.63; 4.29, found: 60.61; 4.39; 4.09.

4-(3,5-Dimethoxyphenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-2–(2′,3′,4′-tri-O-acetyl-α-L-arabinopyranosyl thio)-pyridine-3-carbonitrile (9c). Yield (16%), m.p. 210−212°C; IR (KBr, cm^{-1}) 2220 (CN), 1755 (CO ester), 1585 (C=N); ^{1}H-NMR (DMSO-d_6): δ 1.70−1.75 (m, 4H, 2 CH_2), 1.88, 1.98, 2.09 (3s, 9H, 3 CH_3CO), 2.85−2.88 (m, 4H, 2 CH_2), 3.79 (q, 1H, H-5″), 4.01 (q, 1H, H-5′), 5.16−5.19 (m, 1H, H-4′), 5.22−5.26 (m, 1H, H-3′), 5.39 (d, 1H, H-2′), 6.23 (d, $J_{1'-2'}$9.67 Hz, 1H, H-1′), 6.80 (s, 1H, H-5 pyridine), 7.26−7.59 (m, 6H, Ar-H) ppm; MS (FAB): m/z 660 (21%) [M^+]. Anal. $C_{35}H_{36}N_2O_9S$, calcd. CHN: 63.62; 5.49; 4.24, found: 63.40; 5.33; 4.12.

Oxidation of thioglycosides 5a–c—General Procedure

A solution of the S-glycosides **5a–c** (1mmol) in 10 ml of glacial acetic acid containing 1ml of 30% hydrogen peroxide was stirred for 20 h at room temperature, then poured into ice-water (200 ml). The separated solid was collected on filtration. The corresponding sulfones **10a–c** was obtained in good yield and high purity.

4-(2,4-Dichlorophenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-2-(2′, 3′,4′,6′-tetra-O-acetyl-β-D-galactopyranosyl sulfonyl)-pyridine-3-carb- onitrile (10a). Yield (53%), m.p. 107–109°C; IR (KBr, cm^{-1}) 2224 (CN), 1750 (CO ester), 1581 (C=N); ^{1}H-NMR (DMSO-d_6): δ 1.69–1.75 (m, 4H, 2 CH_2), 2.02, 2.05, 2.10, 2.14 (4s, 12H, 4 CH_3CO), 2.80–2.85 (m, 4H, 2 CH_2), 4.05–4.15 (m, 2H, H-6′, 6″54–4.58 (m, 1H, H-5′), 5.29 (t, 1H, H-4′), 5.54–5.58 (m, 2H, H-3′ and H-2′), 5.79 (d, $J_{1'-2'}$9.97 Hz, 1H, H-1′), 6.80 (s, 1H, H-5 pyridine), 7.25–7.61 (m, 6H, Ar-H) ppm; MS (FAB): m/z 772 (42%) [M^+]. Anal. $C_{36}H_{34}Cl_2N_2O_{11}S$, calcd. CHN: 55.89; 4.43; 3.62, found: 55.58; 4.26; 3.56.

4-(2-Chloro-6-fluorophenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-2-(2′,3′,4′,6′-tetra-O-acetyl-β-D-galactopyranosyl sulfonyl)-pyridine-3-carbonitrile (10b). Yield (50%), m.p. 139–140°C; IR (KBr, cm^{-1}) 2221 (CN), 1753 (CO ester), 1587 (C=N); ^{1}H-NMR (DMSO-d_6): δ 1.72–1.77 (m, 4H, 2 CH_2), 2.04, 2.07, 2.11, 2.16 (4s, 12H, 4 CH_3CO), 2.83–2.87 (m, 4H, 2 CH_2), 4.01–4.10 (m, 2H, H-6′, 6″), 4.48–4.52 (m, 1H, H-5′), 5.37 (t, 1H, H-4′), 5.59–5.62 (m, 2H, H-3′ and H-2′), 5.86 (d, $J_{1'-2'}$9.95 Hz, 1H, H-1′), 6.80 (s, 1H, H-5 pyridine), 7.18–7.54 (m, 6H, Ar-H) ppm; MS (FAB): m/z 756 (26%) [M^+]. Anal. $C_{36}H_{34}ClFN_2O_{11}S$, calcd. CHN: 57.10; 4.53; 3.70, found: 56.90; 4.46; 3.53.

4-(3,5-Dimethoxyphenyl)-6-(5,6,7,8-tetrahydronaphthalen-2-yl)-2-(2′,3′,4′,6′-tetra-O-acetyl-β-D-galactopyranosyl sulfonyl)-pyridine-3-carbonitrile (10c). Yield (53%), m.p. 146–147°C; IR (KBr, cm^{-1}) 2223 (CN), 1755 (CO ester), 1585 (C=N); ^{1}H-NMR (DMSO-d_6): δ 1.72–1.76 (m, 4H, 2 CH_2), 2.00, 2.03, 2.09, 2.12 (4s, 12H, 4 CH_3CO), 2.84–2.89 (m, 4H, 2 CH_2), 4.00–4.15 (m, 2H, H-6′, 6″), 4.60–4.66 (m, 1H, H-5′), 5.41 (t, 1H, H-4′), 5.62–5.67 (m, 2H, H-3′ and H-2′), 5.86 (d, $J_{1'-2'}$9.96 Hz, 1H, H-1′), 6.80 (s, 1H, H-5 pyridine), 7.23–7.53 (m, 6H, Ar-H) ppm; MS, MS (FAB): m/z 764 (8%) [M^+]. Anal. $C_{38}H_{40}N_2O_{13}S$, calcd. CHN: 59.68; 5.27; 3.66, found: 59.47; 5.12; 3.37.

2-(Substituted)-6-(5,6,7,8-tetrahydronaphthalen-6-yl)-4-(3,5-dimethoxyphenyl) pyridine-3-carbonitrile (12a–c)—General Procedure

To a stirred suspension of 4-(3,5-Dimethoxyphenyl)-6-(5,6,7,8-tetrahydro-naphthalen-2-yl)-2-thioxo-1,2-dihyropyridine-3-carbonitrile **1c** (10 mmol) in dry acetonitrile (50 ml) was added a solution of sodium borohydride (10 mmol) . The mixture was stirred until a clear solution was obtained (30 min). The reaction mixture was cooled to

$0^{\circ}C$ and then acyclic sugar halides, namely chloromethylethyl ether, chloromethyl methyl sulfide, and 3-bromo-1-propanol **11a–c** (10 mmol) was added dropwise into dry acetonitrile (10 ml). The mixture was stirred for 8 h; the solid precipitate was filtered; and the filtrate was removed under reduced pressure. The products were purified by silica gel column chromatography [25−30% EtOAc in petroleum ether (60−80°C)].

2-(Ethoxymethylthio)-6-(5,6,7,8-tetrahydronaphthalen-6-yl)-4-(3,5-di-methoxyphenyl) pyridine-3-carbonitrile (12a). Yield (53%), m.p. 141−143°C; IR (KBr, cm^{-1}) 2223 (CN), 1586 (C=N); ^{1}H-NMR (DMSO-d_6): δ 1.14 (t, 3H, CH_3), 1.73−1.77 (m, 4H, 2 CH_2), 2.83−2.87 (m, 4H, 2 CH_2), 3.49 (q, 2H, OCH_2), 3.87 (s, 6H, 2OCH_3), 5.11 (s, 2H, OCH_2S), 6.81 (s, 1H, H-5 pyridine), 7.15−7.60 (m, 6H, Ar-H) ppm; ^{13}C-NMR (DMSO-d_6): δ 15.01 (CH_3), 23.11, 23.17, 32.37, 32.50 (4 CH_2), 57.39 (2 OCH_3), 67.26 (OCH_2), 76.95 (OCH_2S), 119.08 (CN), 121.00 (CH of pyridine), 120.29−168.26 (Ar-C) ppm; MS (EI): m/z 460 (11%) [M^+]. Anal. $C_{27}H_{28}N_2O_3S$, calcd. CHN: 70.41; 6.13; 6.08, found: 70.28; 5.97; 5.93.

2-[(Methylthio)methylthio]-6-(5,6,7,8-tetrahydronaphthalen-6-yl)-4-(3,5-dimethoxy phenyl) pyridine-3-carbonitrile (12b). Yield (50%), m.p. 166−168°C; IR (KBr, cm^{-1}) 2220 (CN), 1588 (C=N); ^{1}H-NMR (DMSO-d_6): δ 1.75−1.79 (m, 4H, 2 CH_2), 2.17 (s, 3H, CH_3), 2.82−2.87 (m, 4H, 2 CH_2), 3.87 (s, 6H, 2OCH_3), 4.15 (s, 2H, SCH_2), 6.79 (s, 1H, H-5 pyridine), 7.12−7.66 (m, 6H, Ar-H) ppm; ^{13}C-NMR (DMSO-d_6): δ 16.4 (CH_3), 23.15, 23.19, 32.29, 32.40 (4 CH_2), 40.1 (SCH_2), 56.7 (OCH_3), 118.1 (CN), 118.3 (C5-pyridine ring), 123.2−164.3 (Ar-C) ppm; MS (EI): m/z 462 (52%) [M^+]. Anal. $C_{26}H_{26}N_2O_2S_2$, calcd. CHN: 66.18; 5.32; 6.43, found: 66.06; 5.17; 6.31.

2-(3-Hydroxypropylthio)-6-(5,6,7,8-tetrahydronaphthalen-6-yl)-4-(3,5-dimethoxy phenyl) pyridine-3-carbonitrile (12c). Yield (65%), m.p. 178−180°C; IR (KBr, cm^{-1}) 2225 (CN), 1580 (C=N); ^{1}H-NMR (DMSO-d_6): δ 1.73−1.78 (m, 4H, 2 CH_2), 1.90−1.93 (m, 2H, CH2), 2.85−2.88 (m, 4H, 2 CH_2), 3.07 (t, 2H, SCH_2), 3.59 (t, 2H, CH_2OH), 3.89 (s, 6H, 2OCH_3), 6.79 (s, 1H, H-5 pyridine), 7.10−7.61 (m, 6H, Ar-H) ppm; MS (EI): m/z 460 (14%) [M^+]. Anal. $C_{27}H_{28}N_2O_3S$, calcd. CHN: 70.41; 6.13; 6.08, found: 70.19; 5.86; 5.90.

REFERENCES

[1] M. J. Robins, B. L. Currie, R. K. Robins, and A. Bloch, *Proc. Am. Assoc. Cancer Res.*, **10,** 73 (1969).

[2] W. M. Shannon, G. Arnett, and F. M. Schabel, *Antimicrob. Agents Chemother.*, **2,** 159 (1972).
[3] R. R. Copp and V. S. Marquez, *J. Med. Chem.*, **34,** 208 (1991).
[4] M. J. Robins and A. S. K. Lee, *J. Med. Chem.*, **18,** 1070 (1975).
[5] M. Legraverend, Z. C. Nguycn, and E. B. Aurelio, *Nucleosides & Nucleotides*, **5,** 125 (1986).
[6] K. A. Watanabe, U. Reichman, N. Greenberg, C. Lopez, and J. Fox, *J. Med. Chem.*, **27,** 91 (1984).
[7] J. I. Degraw, P. H. Christine, R. L. Kisliuk, Y. Gaumont, F. M. Sirotnak, *J. Med. Chem.*, **33,** 673 (1990).
[8] M. Abo-Ghalia and A. E. Amer, *Amino Acids*, **26**, 283 (2004).
[9] M. Abo-Ghalia, A. E. Amer, and M. M. Abdulla, *Z. Naturforsch.*, **58** (B), 903 (2003).
[10] B. Levant, D. E. Grigoriadis, and E. B. De-Souza, *Eur. J. Pharmacol.*, **278,** 243 (2003).
[11] J. R. Raymond, J. Kim, R. E. Beach, and C. C. Tisher, *Am. J. Physiol.*, **264** (1Pt2), F9–19 (1993).
[12] M. H. Parker, R. Chen, K. A. Conway, D. H. Lee, R. E. Boyed, S. O. Nortey, T. Ross, M. Scott, and A. B. Reitz, *Bioorg. Med. Chem.*, **10,** 3565 (2002).
[13] S. Yous, S. Durieux, E. Belloli, H. Guelzim, C. Bochu, V. Audinot, and D. Lesieur, *Bioorg. Med. Chem.*, **11,** 753 (2003).
[14] K. Bhandari, S. Srivastava, and G. Shankar, *Bioorg. Med. Chem.*, **12,** 4189 (2004).
[15] L. Petersen, T. H. Hansen, N. M. Khalifa, P. T. Jorgensen, E. B. Pedersen, and C. Nielsen, *Monatshefte für Chemie*, **133,** 1031 (2002).
[16] M. Bahgat and N. M. Khalifa, *Acta Poloniae pharmaceutica-Drug Research*, **63,** 181 (2006).
[17] N. M. Khalifa, *J. Biol. Pharm. Sci.*, **2,** 57 (2004).
[18] N. M. Khalifa and A. O. El-nezhawy, *J. Biol. Pharm. Sci.*, **2,** 17 (2004).
[19] A. E. Amr, *Ind. J. Heterocycl. Chem.*, **10,** 49 (2000).
[20] M. F. Abdel-Megeed and M. A. Saleh, *Sulfur Letters*, **6,** 115 (1987).
[21] P. L. Durette and D. Horton, *Carbohydrate Res.*, **18,** 57 (1971).
[22] C. V Holland, D. Horton, M. J. Miller, and N. S. Bhacca, *J. Org. Chem.*, **32,** 3077 (1967).
[23] C. A. Winter, E. A. Risly, and G. W. Nuss, *Proc. Soc. Exp. Bio. Med.*, **111,** 544 (1962).
[24] F. Herrmann, A. Lindemann, J. Gauss, and R. Mertelsmann, *Eur. J. Immunol.*, **20,** 2513 (1990).
[25] K. F. Austen, and W. E. Brocklehurst, *J. Exp. Med.*, **113,** 521 (1961).
[26] E. F. Webb and D. E. Griswold, *J. Pharmacol. Meth.*, **12,** 149 (1984).