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Original article

Synthesis and antitumor activity of new dihydropyridine thioglycosides and their corresponding dehydrogenated forms

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ABSTRACT

A number of a new pyridine thioglycosides were synthesized via reaction of piperidinium salts of dihydropyridinethiones with 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- and galactopyranosyl bromide. The antitumor activities of the synthesized compounds were evaluated utilizing two different human cell lines. Some of the tested compounds showed high inhibition of human cell lines. The detailed synthesis, spectroscopic data and antitumor activities for the synthesized compounds were reported.

1. Introduction

The importance of the pyridine ring in the chemistry of biological system has been greatly realized because of their presence as substructure in many natural products of therapeutic importance, involved in oxidation–reduction process. The potent biological activity of various vitamins and drugs [1–4] is primarily contributed by the presence of pyridine ring in their molecular make-up. The pyridine ring is found in the skeleton of many compounds with potent antibacterial, antifungal and anticancer properties [5,6]. Pyridinethiones and related compounds exhibit a wide range of biological activity [7]. Among these activities antitumor and cytotoxic activities of pyridinethiones [8–13] were described. Moreover, a number of sulfur [14,15] containing pyridines are active antimicrobial agents and herbicides [16–18]. On the other hand, thioglycosides have received considerable attention, because they are widely employed as biological inhibitors [19–22], inducers [23] and ligands [24–26] for affinity chromatography for carbohydrate processing-enzymes and proteins. Thiopyridyl glycosides were extensively studied because of their potential activity as glycosyl donors [27]. A number of novel synthesized functionalized pyridinethione glycosides have been shown to exhibit antagonistic activity against human carcinoma cells and HIV-virus [28–30]. Furthermore, the use of dihydropyridine glycosides as P-glycoprotein (Pgp) substrates or inhibitors in the protein glycosylation process was reported [31]. In view of the above facts and our interest [32,33] in the attachment of carbohydrate residues to heterocycles in order to find new biologically active leads, we report here the synthesis and antitumor activity of new thioglycoside derivatives of substituted dihydropyridine and their corresponding dehydrogenated forms.

2. Results and discussion

2.1. Chemistry

In this investigation, we describe the synthesis of dihydropyridine thioglycosides through the reaction of piperidinium salts of dihydropyridine thiolates with 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- or galactopyranosyl bromides. Thus, condensation of arylidenemalononitriles **1a–e** with thiocyanoacetamide or reaction of aromatic aldehydes **2a–e** with thiocyanoacetamide and malononitrile in ethanol containing piperidine at 40 °C gave the corresponding piperidinium salts of 1,4-dihydropyridin-2-thiones **3a–e** following reported procedure [34–36]. Treatment of piperidinium salts **3a–e** with concentrated hydrochloric acid afforded the corresponding 1,4-dihydropyridin-2-thiol derivatives (**3′a–e**). The IR spectra of the thiols **3′a–e** showed characteristic absorption bands at 2205–2228 cm^{-1} corresponding to the CN groups and their ^1H NMR as well as mass spectra agreed with the assigned structures.

When the piperidinium salts **3a–e** were treated with 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- or galactopyranosyl bromide **4a,b** in acetone at 0 °C, the corresponding *S*-glucosides **5a–e** or *S*-galactosides **5f–h**

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were obtained, respectively. The structures of the thioglycosides **5a–h** were proved by means of their spectral data (IR, mass, ^{1}H and ^{13}C NMR) and elemental analyses. The ^{1}H NMR spectrum of **5c** as a representative example showed the anomeric proton as a doublet at δ 5.76 ppm with coupling constant $J_{1'-2'} = 10.4$ Hz indicating that H-1′ is trance-dioxal to H-2′. The other six glucose protons resonated at δ 3.80–5.30 ppm and the four acetyl groups appeared as four singlet peaks at δ 2.03–2.16 ppm and NH_2 group appeared as singlet at δ 5.99 ppm. In addition, its C, H, N analytical data revealed a molecular formula $C_{27}H_{27}BrN_4SO_9$. The ^{13}C NMR spectrum of **5c** revealed the presence of a signal at δ 80.62 ppm corresponding to the C-1′ atom and five signals appearing at δ 62.15, 67.90, 68.32, 69.7 and 74.53 that were assigned to C-6′, C-4′, C-2′, C-3′ and C-5′, respectively. The attachment of the glycosyl residues to the sulfur rather than to the nitrogen atom to give *N*-glucosides **6a–h** has been supported by the value of the chemical shift of the anomeric protons which other wise should appear at a lower field. The anomeric proton of β-*N*-glucosides having an adjacent C═S, was reported [32,37] to appear at higher chemical shift (δ 6.90–7.20 ppm) due to the anisotropic deshielding effect of the C═S. The absence of a peak corresponding to the C═S group in the ^{13}C NMR spectrum indicates that the attachment of the sugar has taken place at the sulfur atom and not on the nitrogen atom which also agreed with the mode of their preparation.

Treatment of the glycosides **5a–h** with saturated solution of ammonia in methanol at room temperature afforded the free glucosides **7a–e** and galactosides **7f–h**. The ^{1}H NMR spectrum of **7a** showed the anomeric proton as a doublet at δ 5.73 ppm with coupling constant $J_{1'-2'} = 10.4$ Hz indicating the β-D-configuration. The signals of the other six glucose protons appeared at δ 3.23–4.14 ppm, while the signals observed at δ 4.73–5.25 ppm and disappeared on rapid exchange with D_2O were assigned as the four hydroxyl groups. Furthermore, the C, H, N analytical data revealed a molecular formula $C_{19}H_{20}N_4SO_5$ (Scheme 1)

Reaction of the piperidinium salts **3a–e** with 2,3,4,6-tetra-*O*-acetyl-α-D-gluco- or galactopyranosyl bromide **4a**,**b** in dry acetone at 30 °C afforded the corresponding aromatized pyridine thioglucosides **8a–c** and thiogalactosides **8d–f**, respectively (Scheme 2). Compounds **8a–f** could be also prepared by heating of dihydrothioglycosides **5a–c** and **5f–h** in ethanol for 5 min, which underwent spontaneous auto-oxidation [38,39] to give the aromatized thioglycosides **8a–f**. The structures of the produced *S*-glycosides were confirmed by their spectral and analytical data which were in agreement with the assigned structures. The formation of *S*-glycosides **8a–f** rather than the corresponding *N*-glycosides were proved by ^{13}C NMR spectroscopy which revealed the absence of the thione carbon (C═S) and the appearance of a signal corresponding to the C–S carbon, whose chemical shift is very close to that of the corresponding *S*-methyl derivative [40,41].

Deacetylation of the thioglycosides **8a–f** using saturated solution of methanolic ammonia at room temperature afforded the free glycoside derivatives **9a–f**. The ^{1}H NMR spectrum of compound **9c**, as a representative example, showed the anomeric proton as a doublet at δ 5.80 ppm. The other six glucose protons resonated at δ 3.25–4.12 ppm. Its ^{13}C NMR spectrum showed the signal at δ 85.28 ppm corresponding to the C-1′ atom and five signals at δ 62.68–75.52 ppm were assigned as the sugar carbons in addition to the signals of the pyridine ring carbons.

2.2. Antitumor activity

The synthesized compounds were tested and evaluated for inhibition using human liver carcinoma cell line (HEPG2) and Human cervix carcinoma cell line (HELA). As shown in Table 1, the administration of prepared compounds significantly increases ($P < 0.05$) the life span of the animals as compared with control group [animals injected with Human liver carcinoma cell line (HEPG2) or Human cervix carcinoma cell line (HELA) alone]. There is a gradual increase in life span using the prepared compounds. The increase in life span was around 25%–69%. The standard reference drug (Cisplatine 2 mg/kg body weight) exhibited 83% ($P < 0.05$) increase in life span of the animals. All the animals in the HEPG2 or HELA injected alone group were dead after 25 or 22 days, respectively. Additionally, the obtained results clearly indicated the effect of substituents in the aryl group on position-4 in the pyridine ring on the antitumor activity.

The results of measurements of effect in treatment with tested compounds on the survival of ascites tumor harboring mice inoculated with (HEPG2) cells line (Table 1) revealed that compound **7e** was the most active exhibiting 69% increase in life span followed by compounds **7h**, **7g** and **9c**. Compounds **9b**, **9e** and **9f** showed moderate activity against the same tumor cell lines.

The results of antitumor measurements of tested compounds with respect to the survival of ascites tumor harboring mice inoculated with (HELA) cells line (Table 1) showed that compounds **7e** having the highest activity with an increase in life span 55% followed by compounds **9e** and **9b**. Compounds **9c**, **8f**, **9f**, **8c**, **7h** and **7g** showed moderate activity with 45–50% increase in life span.

Additionally, the antitumor activity observed for the substituted pyridyl glucopyranosylthio derivative **7e** indicated the importance of both the free hydroxyl glucopyranosylthio and the *p*-methoxy phenyl as well as the conformation of the hydroxyl group at C-4 in the glucose ring, as the activity was reduced when the glucopyranosylthio group was replaced by its corresponding *O*-acetylated derivative **5e**. Moreover, the activity of the substituted glucopyranosylthio derivative was higher than its corresponding galactopyranosylthio analog **7h**.

On the other hand, the results of *In vivo* acute toxicity measurements of synthesized compound with respect to ascites tumor harboring mice inoculated with (HEPG2) cells (Fig. 1) revealed that compound **5e** exhibiting the highest LD50 with 150 μg/kg b.w. followed by compounds **9e**, **9b** and **7g** among the tested series of compounds. For the ascites tumor harboring mice inoculated with (HELA) cells, compound **5e** also showed the highest LD50 with 160 μg/kg b.w. followed by compounds **8e**, **9f**, **9e**, **9c** and **7g** with acute toxicities 120–135 μg/kg b.w.

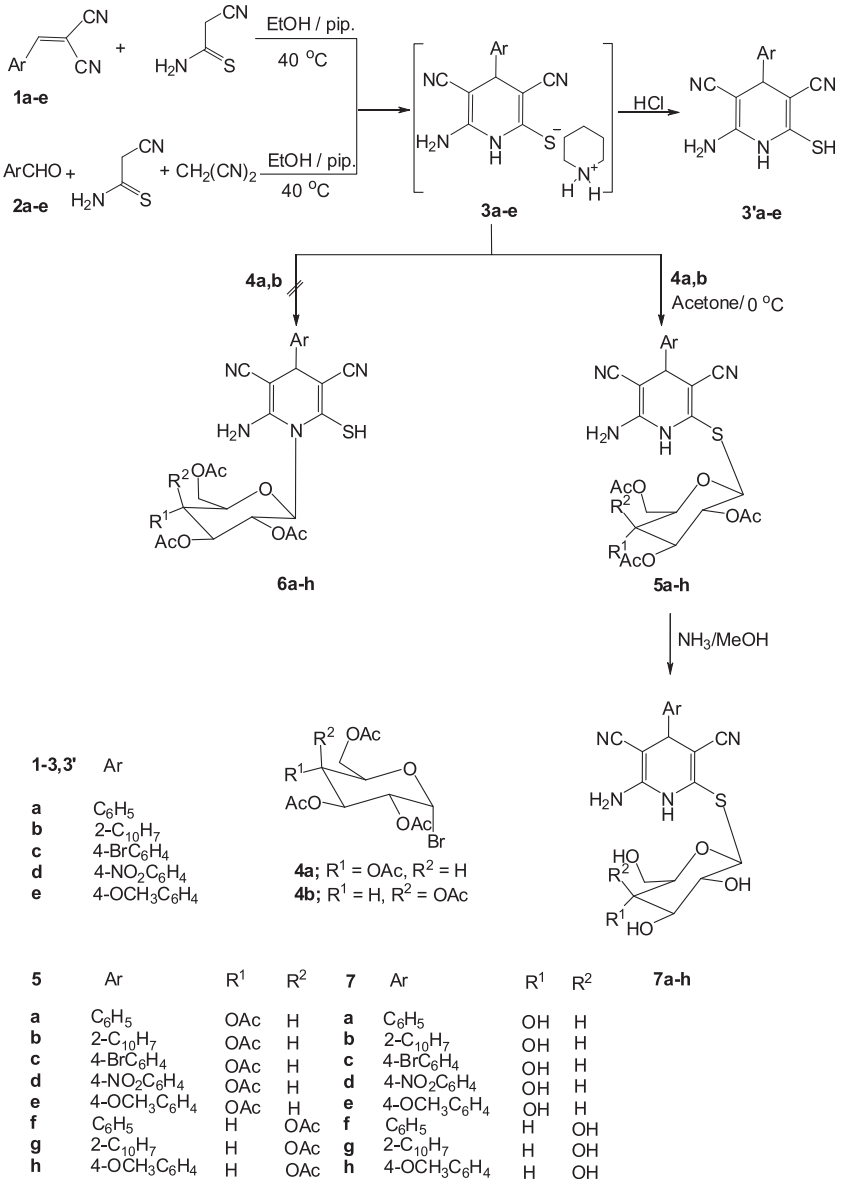
3. Conclusion

From the results of antitumor activity and structure activity relationship, it can be concluded that the effect of the substituent in the aryl group placed at position 4 as well as the glycopyranosylthio moiety in the pyridine ring was obvious. Thus, compound **7e** with free glucopyranosylthio and *p*-methoxy phenyl groups, was the most active against both type of tumor (HEPG2 and HELA) cell lines. Furthermore, all tested compound substituted with free glycopyranosyl moieties showed higher activities than their corresponding acetylated derivatives. Furthermore, compounds **9e** and **9b** containing a 2-naphthayl moiety in their structures exhibited high activity against ascites tumor HELA cell line. On the other hand, the *O*-acetylated glucopyranosylthio derivative **5e** showed the less acute toxicity with respect to both type of tumor (HEPG2 and HELA) cell lines.

4. Experimental

4.1. Chemistry

Melting points were determined on open glass capillaries using an Electrothermal IA 9100 digital melting point apparatus



1-3,3'	Ar
a	C_6H_5
b	2-$C_{10}H_7$
c	4-BrC_6H_4
d	4-$NO_2C_6H_4$
e	4-$OCH_3C_6H_4$

5	Ar	R^1	R^2
a	C_6H_5	OAc	H
b	2-$C_{10}H_7$	OAc	H
c	4-BrC_6H_4	OAc	H
d	4-$NO_2C_6H_4$	OAc	H
e	4-$OCH_3C_6H_4$	OAc	H
f	C_6H_5	H	OAc
g	2-$C_{10}H_7$	H	OAc
h	4-$OCH_3C_6H_4$	H	OAc

7	Ar	R^1	R^2
a	C_6H_5	OH	H
b	2-$C_{10}H_7$	OH	H
c	4-BrC_6H_4	OH	H
d	4-$NO_2C_6H_4$	OH	H
e	4-$OCH_3C_6H_4$	OH	H
f	C_6H_5	H	OH
g	2-$C_{10}H_7$	H	OH
h	4-$OCH_3C_6H_4$	H	OH

Scheme 1. Synthesis of dihydropyridine thioglycosides **5a**–**h** and **7a**–**h**.

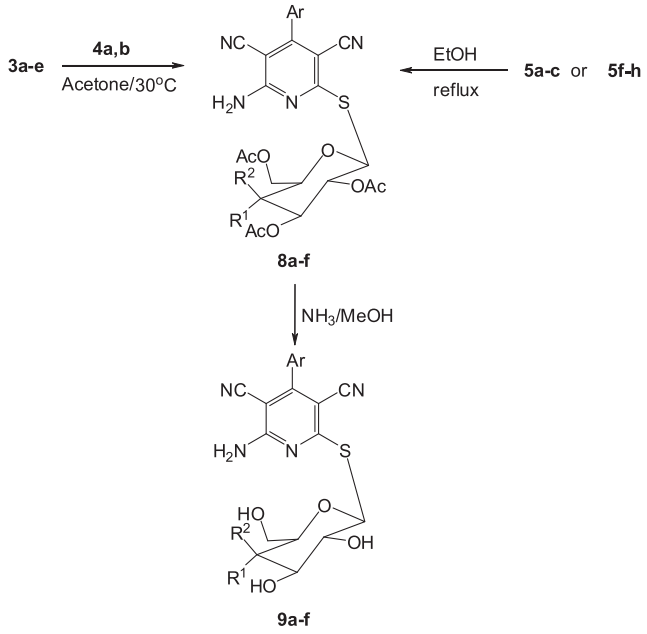
(Shimadzu, Japan) and are uncorrected. IR spectra were recorded as potassium bromide pellets on a Perkin–Elmer 1650 Spectrophotometer, National Research Centre, Cairo, Egypt. ^{1}H NMR and ^{13}C NMR spectra were determined on a Jeol-Ex-300 NMR spectrometer and chemical shifts were expressed as part per million; ppm (δ values) against TMS as internal reference (Faculty of Science, Cairo University, Cairo, Egypt). Mass spectra were recorded by 70 eV El Ms-QP 1000 EX and FAB on a Kratos MS 50 spectrometer. Microanalyses were operated using Mario Elmentar apparatus, Organic Microanalysis Unit, National Research Centre, Cairo, Egypt and the results were within the accepted range of the calculated values. Antitumor activity of the synthesized compounds was measured at the National Cancer Institute, Cairo University, Cairo, Egypt.

*4.1.1. General procedure for the synthesis of 2-amino-4-aryl-6-mercapto 3,5-dicyano-1,4-dihydropyridines (**3′a–e**)*

Method (*A*): Piperidine (0.85 ml, 0.01 mol) was added to a suspension of thiocyanoacetamide (1.0 g, 0.01 mol) and arylidenemalononitrile **1a**–**e** (0.01 mol) in absolute ethanol (30 ml) and the mixture was heated at 40 °C with stirring for 3 h and then left to cool to room temperature. After cooling, the solution of the resulting piperidinium salt **3a**–**e** was acidified with concentrated hydrochloric acid and the obtained precipitate was filtered off, washed with distilled water and crystallized from ethanol to give **3′a**–**e**.

Method (*B*): A mixture of thiocyanoacetamide (1.0 g, 0.01 mol), aromatic aldehyde **2a**–**e** (0.01 mol) and malononitrile (0.66 g, 0.01 mol) in absolute ethanol (30 ml) containing piperidine (0.58 ml, 0.01 mol) was heated at 40 °C with stirring for 3 h and then left to cool at room temperature. After cooling, the solution of the resulting piperidinium salt **3a**–**e** was acidified with concentrated hydrochloric acid and the obtained precipitate was filtered off, washed with distilled water and crystallized from ethanol to give **3′a**–**e**.

*4.1.1.1. 2-Amino-3,5-dicyano-6-mercapto-4-phenyl-1,4-dihydropyridine (**3′a**).* Yield 2.03 g (80%) (brown powder): mp 126–127 °C; IR (KBr) ν_{max} in cm^{-1}: 3319 (NH), 3232 (NH_2), 2211 (CN), 2205 (CN); ^{1}H NMR ($CDCl_3$): δ 4.79 (s, 1H, pyridine H-4), 5.80 (s, 1H, NH), 7.67 (m, 3H, Ar-H), 7.90 (m, 2H, Ar-H), 8.51 (br, 2H, NH_2), 9.65 (s, 1H, SH);



8	Ar	R^1	R^2	9	Ar	R^1	R^2
a	C_6H_5	OAc	H	**a**	C_6H_5	OH	H
b	2-$C_{10}H_7$	OAc	H	**b**	2-$C_{10}H_7$	OH	H
c	4-BrC_6H_4	OAc	H	**c**	4-BrC_6H_4	OH	H
d	C_6H_5	H	OAc	**d**	C_6H_5	H	OH
e	2-$C_{10}H_7$	H	OAc	**e**	2-$C_{10}H_7$	H	OH
f	4-$OCH_3C_6H_4$	H	OAc	**f**	4-$OCH_3C_6H_4$	H	OH

Scheme 2. Synthesis of pyridine thioglycosides **8a–f** and **9a–f**.

^{13}C NMR ($CDCl_3$): δ 76.32 (C-4), 83.40 (C-5), 105.18 (C-3), 112.69 (CN), 114.42 (CN), 126.02–134.12 (Ar-6C), 158.05 (C-6), 159.11 (C-2); *m/z* (%) = 254 (77, [M^+]). Anal. Calcd. for $C_{13}H_{10}N_4S$: C, 61.40; H, 3.96; N, 22.03. Found: C, 61.34; H, 4.00; N, 22.10.

*4.1.1.2. 2-Amino-3,5-dicyano-6-mercapto-4-(naphthalen-2-yl)-1,4-dihydropyridine (**3′b**).* Yield 2.46 g (81%) (brown powder): mp 141–142 °C; IR (KBr) ν_{max} in cm^{-1}: 3311 (NH), 3218 (NH_2), 2220 (CN), 2208 (CN); ^{1}H NMR ($CDCl_3$): δ 4.74 (s, 1H, pyridine H-4), 5.71 (s, 1H, NH), 7.41 (m, 2H, Ar-H), 7.48 (d, 1H, *J* = 8.5 Hz, Ar-H), 7.56 (d, 1H, *J* = 8.2 Hz, Ar-H)7.69 (d, 1H, *J* = 8.2 Hz, Ar-H), 7.76 (s, 1H, Ar-H), 8.21 (d, 1H, *J* = 8.5 Hz, Ar-H), 8.41 (br, 2H, NH_2), 9.84 (s, 1H, SH); *m/z* (%) = 304 (84, [M^+]). Anal. Calcd. for $C_{17}H_{12}N_4S$: C, 67.08; H, 3.97; N, 18.41. Found: C, 67.10; H, 3.90; N, 18.50.

*4.1.1.3. 2-Amino-3,5-dicyano-4-(4-bromophenyl)-6-mercapto-1,4-dihydropyridine (**3′c**).* Yield 2.26 g (68%) (dark yellow powder): mp 132–133 °C; IR (KBr) ν_{max} in cm^{-1}: 3307 (NH), 3241 (NH_2), 2218 (CN), 2208 (CN); ^{1}H NMR ($CDCl_3$): δ 4.81 (s, 1H, pyridine H-4), 5.62 (s, 1H, NH), 7.12 (d, 2H, *J* = 7.8 Hz, Ar-H), 7.76 (d, 2H, *J* = 7.8 Hz, Ar-H), 8.54 (br, 2H, NH_2), 9.80 (s, 1H, SH); ^{13}C NMR ($CDCl_3$): δ 76.37 (C-4), 83.18 (C-5), 105.21 (C-3), 112.51 (CN), 115.17 (CN), 126.16–134.14 (Ar-6C), 158.08 (C-6), 158.82 (C-2)*m/z* (%) = 333 (69, [M^+]). Anal. Calcd. for $C_{13}H_9BrN_4S$: C, 46.86; H, 2.72; N, 16.81. Found: C, 46.79; H, 2.74; N, 16.87.

*4.1.1.4. 2-Amino-3,5-dicyano-6-mercapto-4-(4-nitrophenyl)-1,4-dihydropyridine (**3′d**).* Yield 2.39 g (80%) (yellow powder): mp 125–126 °C; IR (KBr) ν_{max} in cm^{-1}: 3318 (NH), 3236 (NH_2), 2228 (CN), 2215 (CN); ^{1}H NMR ($CDCl_3$): δ 4.71 (s, 1H, pyridine H-4), 5.49 (s, 1H, NH), 7.49 (d, 2H, *J* = 7.8 Hz, Ar-H), 7.90 (d, 2H, *J* = 7.8 Hz, Ar-H), 8.35 (br, 2H, NH_2), 9.98 (s, 1H, SH); ^{13}C NMR ($CDCl_3$): δ 75.87 (C-4), 82.90 (C-5), 105.12 (C-3), 111.71 (CN), 114.18 (CN), 125.92–134.14 (Ar-6C), 158.02 (C-6), 158.69 (C-2); *m/z* (%) = 299 (92, [M^+]). Anal. Calcd. for $C_{13}H_9N_5O_2S$: C, 52.17; H, 3.03; N, 23.40. Found: C, 52.10; H, 2.98; N, 23.32.

*4.1.1.5. 2-Amino-3,5-dicyano-6-mercapto-4-(4-methoxyphenyl)-1,4-dihydropyridine (**3′e**).* Yield 2.45 g (88%) (yellow powder): mp 129–130 °C; IR (KBr) ν_{max} in cm^{-1}: 3309 (NH), 3229 (NH_2), 2217 (CN), 2210 (CN); ^{1}H NMR ($CDCl_3$): δ 3.81 (s, 3H, OCH_3), 4.79 (s, 1H, pyridine H-4), 5.50 (s, 1H, NH), 7.12 (d, 2H, *J* = 7.8 Hz, Ar-H), 7.35 (d, 2H, *J* = 7.8 Hz, Ar-H), 8.49 (br, 2H, NH_2), 9.97 (s, 1H, SH); *m/z*

Table 1
Effect of treatment with different compounds on the survival of ascites tumor harboring mice inoculated with (HEPG2) or (HELA) cells line.

Conc. of compounds (μg/kg b. w.)	Survival time (days) HEPG2	% Increase in life span of animals HEPG2	Survival time (days) HELA	% Increase in life span of animals HELA
Control	25.00 ± 1.95	0	22.00 ± 1.90	0
Cisplatine (2 mg/kg b. w.)	45.00 ± 4.20[a]	83	45.00 ± 4.20[a]	84
5a (10 μg/kg b. w.)	28.00 ± 2.30[a]	29	28.00 ± 2.30[a]	30
5c (10 μg/kg b. w.)	29.00 ± 2.50[a]	31	29.00 ± 2.50[a]	29
5d (10 μg/kg b. w.)	30.00 ± 1.90[a]	34	27.00 ± 1.90[a]	27
5e (10 μg/kg b. w.)	35.00 ± 2.70[a]	39	27.00 ± 2.70[a]	25
5f (10 μg/kg b. w.)	33.00 ± 2.20[a]	34	29.00 ± 2.20[a]	30
5g (10 μg/kg b. w.)	35.00 ± 2.70[a]	38	29.00 ± 2.50[a]	31
5h (10 μg/kg b. w.)	29.00 ± 2.30[a]	30	29.00 ± 2.20[a]	30
7a (10 μg/kg b. w.)	36.00 ± 2.50[a]	43	30.00 ± 2.50[a]	35
7b (10 μg/kg b. w.)	37.00 ± 1.90[a]	50	35.00 ± 1.90[a]	39
7e (10 μg/kg b. w.)	39.00 ± 2.70[a]	69	37.00 ± 2.70[a]	55
7g (10 μg/kg b. w.)	38.00 ± 2.70[a]	60	36.00 ± 2.70[a]	45
7h (10 μg/kg b. w.)	38.00 ± 2.80[a]	63	36.00 ± 2.50[a]	44
8b (10 μg/kg b. w.)	36.00 ± 2.50[a]	49	34.00 ± 2.50[a]	40
8c (10 μg/kg b. w.)	36.00 ± 2.30[a]	48	36.00 ± 2.30[a]	46
8d (10 μg/kg b. w.)	32.00 ± 1.90[a]	43	33.00 ± 1.90[a]	38
8e (10 μg/kg b. w.)	37.00 ± 2.70[a]	50	35.00 ± 2.70[a]	39
8f (10 μg/kg b. w.)	36.00 ± 2.70[a]	48	36.00 ± 1.90[a]	47
9b (10 μg/kg b. w.)	37.00 ± 2.20[a]	58	37.00 ± 2.80[a]	51
9c (10 μg/kg b. w.)	38.00 ± 2.30[a]	60	37.00 ± 2.30[a]	50
9e (10 μg/kg b. w.)	36.00 ± 2.50[a]	57	38.00 ± 2.50[a]	53
9f (10 μg/kg b. w.)	36.00 ± 2.70[a]	56	36.00 ± 2.70[a]	47

Values are mean ± SE.; *n* = 10 mice.
[a] $P < 0.05$ significant with respect to control.

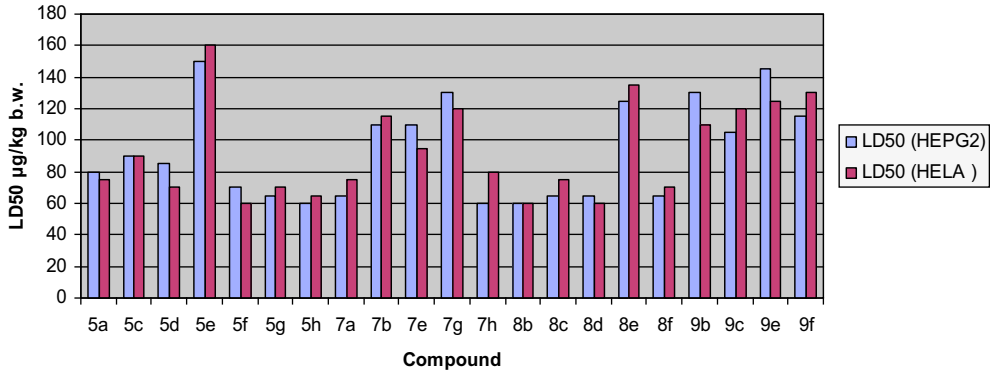


Fig. 1. Acute toxicity of synthesized compounds (LD_{50} µg/kg b.w.).

(%) = 284 (84, [M^+]). Anal. Calcd. for $C_{14}H_{12}N_4OS$: C, 59.14; H, 4.25; N, 19.70. Found: C, 59.22; H, 4.20; N, 19.65.

*4.1.2. General procedure for the synthesis of 2-amino-4-aryl-3,5-dicyano-6-(2′,3′,4′,6′-tetra-O-acetyl-1′-thio-β-D-gluco- or galactopyranosyl)-1,4-dihydropyridines (**5a**–**h**)*

The piperidinium salt **3a**–**e** (0.01 mol) was dissolved in dry acetone (5 ml), then 2,3,4,6-teta-*O*-acetyl-α-D-gluco- or galactopyranosyl bromide **4a**,**b** (4.52 g, 0.011 mol) in dry acetone (20 ml) was added at 0 °C. The reaction mixture was stirred for 25–30 h and the solvent was evaporated under reduced pressure. The residue was washed with distilled water and the obtained crude solid was filtered off, washed with distilled water and dried. The pure product was extracted from the above solid with petroleum ether (80–100). The petroleum ether extract was evaporated under reduced pressure and the obtained solid was crystallized from benzene to give the thioglycosides **5a**–**h**.

*4.1.2.1. 2-Amino-3,5-dicyano-4-phenyl-6-(2′,3′,4′,6′-tetra-O-acetyl-1′-thio-β-D-glucopyranosyl)-1,4-dihydropyridines (**5a**).* Yield 4.27 g (73%) (Pale yellow powder): mp 220–222 °C; $[\alpha]_D$ = +26.4 (c 2, $CHCl_3$); IR (KBr) ν_{max} in cm^{-1}: 3311 (NH), 3212 (NH_2), 2214 (CN), 2201 (CN), 1765 (CO); ^1H NMR ($CDCl_3$): δ 1.90–2.12 (4s, 12H, $4CH_3CO$), 3.80 (dd, 1H, *J* = 2.8 Hz, *J* = 10.5 Hz, H-6′), 3.94 (dd, 1H, *J* = 3.2 Hz, *J* = 10.5 Hz, H-6″), 4.08–4.23 (m, 3H, H-5′, NH and pyridine H-4), 5.12 (m, 1H, H-4′), 5.24 (t, 1H, *J* = 7.4 Hz, H-3′), 5.30 (dd, 1H, *J* = 7.4 Hz, *J* = 10.0, H-2′), 5.75 (d, 1H, $J_{1'-2'}$ = 10.0 Hz, H-1′), 5.80 (s, 2H, NH_2), 7.61 (m, 3H, Ar-3H), 7.91 (m, 2H, Ar-2H); ^{13}C NMR ($CDCl_3$): δ 20.39–20.69 ($4CH_3CO$), 62.35 (C-6′), 67.20 (C-4′), 68.80 (C-3′), 71.79 (C-2′), 75.53 (C-5′), 78.37 (C-4), 80.57 (C-1′), 85.43 (C-5), 106.66 (C-3), 114.21 (CN), 114.95 (CN), 126.19–134.54 (Ar-6C), 158.22 (C-2), 159.36 (C-6), 169.27–170.84 (4C=O); MS (FAB): *m*/*z* (%) = 584 (87, [M^+]). Anal. Calcd. for $C_{27}H_{28}N_4SO_9$: C, 55.47; H, 4.83; N, 9.58. Found: C, 55.40; H, 4.86; N, 9.52.

*4.1.2.2. 2-Amino-3,5-dicyano-4-(naphthalen-2-yl)-6-(2′,3′,4′,6′-tetra-O-acetyl-1′-thio-β-D-glucopyranosyl)-1,4-dihydropyridines (**5b**).* Yield 4.89 g (77%) (Pale yellow powder): mp 204–205 °C; $[\alpha]_D$ = +32.8 (c 2, $CHCl_3$); IR (KBr) ν_{max} in cm^{-1}: 3330 (NH), 3260 (NH_2), 2222 (CN), 2200 (CN), 1750 (CO); ^1H NMR ($CDCl_3$): δ 2.02–2.34 (4s, 12H, $4CH_3CO$), 3.97 (dd, 1H, *J* = 3.2 Hz, *J* = 10.4 Hz, H-6′), 4.09 (dd, 1H, *J* = 3.4 Hz, *J* = 10.4 Hz, H-6″), 4.13–4.28 (m, 3H, H-5′, NH and pyridine H-4), 5.10 (m, 1H, H-4′), 5.20 (t, 1H, *J* = 7.5 Hz, H-3′), 5.39 (dd, 1H, *J* = 7.5, 10.4 Hz, H-2′), 5.78 (d, 1H, $J_{1'-2'}$ = 10.4 Hz, H-1′), 5.88 (s, 2H, NH_2), 7.44 (m, 2H, Ar-H), 7.52 (d, 1H, *J* = 8.5 Hz, Ar-H), 7.59 (d, 1H, *J* = 8.2 Hz, Ar-H), 7.72 (d, 1H, *J* = 8.2 Hz, Ar-H), 7.78 (s, 1H, Ar-H), 8.20 (d, 1H, *J* = 8.5 Hz, Ar-H); ^{13}C NMR ($CDCl_3$): δ 20.10–20.96 ($4CH_3CO$), 62.2 (C-6′), 68.46 (C-4′), 69.77 (C-3′), 71.14 (C-2′), 76.5 (C-5′), 79.57 (C-4), 82.68 (C-1′), 84.51 (C-5), 110.55 (C-3), 113.65 (CN), 113.95 (CN), 125.10–139.60 (Ar-10C), 148.39 (C-2), 159.01 (C-6), 169.14–170.83 (4C=O); MS (FAB): *m*/*z* (%) = 634 (56, [M^+]). Anal. Calcd. for $C_{31}H_{30}N_4SO_9$: C, 58.67; H, 4.76; N, 8.83. Found: C, 58.66; H, 4.73; N, 8.80.

*4.1.2.3. 2-Amino-4-(4-bromophenyl)-3,5-dicyano-6-(2′,3′,4′,6′-tetra-O-acetyl-1′-thio-β-D-glucopyranosyl)-1,4-dihydropyridines (**5c**).* Yield 4.58 g (69%) (Pale yellow powder): mp 215–217 °C; $[\alpha]_D$ = +22.6 (c 2, $CHCl_3$); IR (KBr) ν_{max} in cm^{-1}: 3319 (NH), 3280 (NH_2), 2214 (CN), 2218 (CN), 1759 (CO); ^1H NMR ($CDCl_3$): δ 2.03–2.16 (4s, 12H, $4CH_3CO$), 3.80 (dd, 1H, *J* = 3.2 Hz, *J* = 10.4 Hz, H-6′), 3.89 (dd, 1H, *J* = 3.4 Hz, *J* = 10.4 Hz, H-6″), 4.07–4.30 (m, 3H, H-5′, NH and pyridine H-4), 5.08 (m, 1H, H-4′), 5.24 (t, 1H, *J* = 7.5 Hz, H-3′), 5.30 (dd, 1H, *J* = 7.5 Hz, *J* = 10.4 Hz, H-2′), 5.76 (d, 1H, $J_{1'-2'}$ = 10.4 Hz, H-1′), 5.99 (s, 2H, NH_2), 7.63 (d, 2H, *J* = 7.8 Hz, Ar-2H), 7.66 (d, 2H, *J* = 7.8 Hz, Ar-2H); ^{13}C NMR ($CDCl_3$): δ 20.34–20.67 ($4CH_3CO$), 62.15 (C-6′), 67.9 (C-4′), 68.32 (C-3′), 69.7 (C-2′), 74.53 (C-5′), 78.39 (C-4), 80.62 (C-1′), 83.33 (C-5), 106.53 (C-3), 114.26 (CN), 114.94 (CN), 126.09–134.5 (Ar-6C), 158.20 (C-2), 159.33 (C-6), 169.20–170.80 (4C=O); MS (FAB): *m*/*z* (%) = 663 (42, [M^+]). Anal. Calcd. for $C_{27}H_{27}BrN_4SO_9$: C, 48.88; H, 4.10; N, 8.44. Found: C, 48.87; H, 4.08; N, 8.47.

*4.1.2.4. 2-Amino-3,5-dicyano-4-(4-nitrophenyl)-6-(2′,3′,4′,6′-tetra-O-acetyl-1′-thio-β-D-glucopyranosyl)-1,4-dihydropyridines (**5d**).* Yield 4.22g (67%) (Pale yellow powder): mp 230–232 °C; $[\alpha]_D$ = +20.4 (c 2, $CHCl_3$); IR (KBr) ν_{max} in cm^{-1}: 3328 (NH), 3218 (NH_2), 2216 (CN), 2220 (CN), 1763 (CO); ^1H NMR ($CDCl_3$): δ 2.06–2.13 (4s, 12H, $4CH_3CO$), 3.93 (dd, 1H, *J* = 3.2 Hz, *J* = 10.8 Hz, H-6′), 4.05 (dd, 1H, *J* = 2.8 Hz, *J* = 10.8 Hz, H-6″), 4.10–4.32 (m, 3H, H-5′, NH and pyridine H-4), 5.13–5.40 (m, 2H, H-4′, H-3′), 5.40 (dd, 1H, *J* = 7.6 Hz, *J* = 10. 4 Hz, H-2′), 5.74 (d, 1H, $J_{1'-2'}$ = 10.4 Hz, H-1′), 6.02 (s, 2H, NH_2), 7.60 (d, 2H, *J* = 7.8 Hz, Ar-2H), 8.4 (d, 2H, *J* = 7.8 Hz, Ar-2H). ^{13}C NMR ($CDCl_3$): δ 20.24–20.63 ($4CH_3CO$), 62.19 (C-6′), 67.20 (C-4′), 68.45 (C-3′), 70.55 (C-2′), 75.52 (C-5′), 78.21 (C-4), 80.53 (C-1′), 82.98 (C-5), 106.55 (C-3), 114.65 (CN), 114.97 (CN), 126.14–134.58 (Ar-6C), 158.24 (C-2), 159.56 (C-6), 169.20–170.78 (4C=O); MS (FAB): *m*/*z* (%) = 629 (29, [M^+]). Anal. Calcd. for $C_{27}H_{27}N_5SO_{11}$: C, 51.51; H, 4.32; N, 11.12. Found: C, 51.53; H, 4.29; N, 11.10.

*4.1.2.5. 2-Amino-3,5-dicyano-4-(4-methoxyphenyl)-6-(2′,3′,4′,6′-tetra-O-acetyl-1′-thio-β-D-glucopyranosyl)-1,4-dihydropyridines (**5e**).* Yield 3.63 g (59%) (Pale yellow powder): mp 189–190 °C; $[\alpha]_D$ = +38.4 (c 2, $CHCl_3$); IR (KBr) ν_{max} in cm^{-1}: 3336 (NH), 3238 (NH_2), 2220 (CN), 2200 (CN), 1759 (CO); ^1H NMR ($CDCl_3$) δ in ppm: 2.03–2.12 (4s, 12H, $4CH_3CO$), 3.83 (s, 1H, OCH_3), 3.90 (dd, 1H, *J* = 3.2 Hz, *J* = 10.4 Hz, H-6′), 4.09 (dd, 1H, *J* = 2.8 Hz, *J* = 10.4 Hz, H-

6″), 4.13–4.24 (m, 3H, H-5′, NH and pyridine H-4), 4.55 (t, 1H, J = 8.8 Hz, H-4′), 5.12 (dd, 1H, J = 8.8 Hz, J = 10.3 Hz, H-3′), 5.34 (t, 1H, J = 10.3 Hz, H-2′), 5.76 (d, 1H, $J_{1'-2'}$ = 10.3 Hz, H-1′), 5.99 (s, 2H, NH_2), 7.03 (d, 2H, J = 7.8 Hz, Ar-2H), 7.75 (d, 2H, J = 7.8 Hz, Ar-2H); ^{13}C NMR ($CDCl_3$): δ 20.20–20.60 (4*C*H$_3$CO), 55.35 (OCH_3), 62.15 (C-6′), 67.25 (C-4′), 68.55 (C-3′), 70.59 (C-2′), 75.68 (C-5′), 76.69 (C-4), 81.99 (C-1′), 82.41 (C-5), 106.40 (C-3), 114.62 (CN), 114.89 (CN), 126.15–134.63 (Ar-6C), 158.14 (C-2), 159.59 (C-6), 169.29–170.75 (4C═O); MS (FAB): m/z (%) = 614 (47, [M$^+$]). Anal. Calcd. for $C_{28}H_{30}N_4SO_{10}$: C, 54.72; H, 4.92; N, 9.12. Found: C, 54.70; H, 4.90; N, 9.09.

*4.1.2.6. 2-Amino-3,5-dicyano-4-phenyl-6-(2′,3′,4′,6′-tetra-O-acetyl-1′-thio-β-D-galactopyranosyl)-1,4-dihydropyridines (**5f**).* Yield 3.86 g (66%) (Pale yellow powder): mp 186–188 °C; $[\alpha]_D$ = +36.6 (c 2, $CHCl_3$); IR (KBr) ν_{max} in cm^{-1}: 3335 (NH), 3218(NH_2), 2211 (CN), 2200 (CN), 1758 (CO); ^{1}H NMR ($CDCl_3$): δ 2.04–2.18 (4s, 12H, 4CH_3CO), 3.67 (dd, 1H, J = 2.8 Hz, J = 10.5 Hz, H-6′), 4.88 (dd, 1H, J = 3.2 Hz, J = 10.5 Hz, H-6″), 4.11 (m, 3H, H-5′, NH and pyridine H-4), 5.08 (m, 1H, H-4′), 5.21 (t, 1H, J = 7.4 Hz, H-3′), 5.62 (dd, 1H, J = 7.8 Hz, J = 10.2 Hz, H-2′), 5.73 (d, 1H, $J_{1'-2'}$ = 10.2 Hz, H-1′), 5.79 (s, 2H, NH_2), 7.40 (m, 3H, Ar-3H), 7.80 (m, 2H, Ar-2H); ^{13}C NMR ($CDCl_3$): δ 20.30–20.57 (4*C*H$_3$CO), 62.23 (C-6′), 67.88 (C-4′), 68.31 (C-3′), 71.72 (C-2′), 75.63 (C-5′), 77.24 (C-4), 80.62 (C-1′), 81.59 (C-5), 105.89 (C-3), 114.25 (CN), 114.94 (CN), 126.09–134.90 (Ar-6C), 158.24 (C-2), 159.36 (C-6), 169.20–170.70 (4C═O); MS (FAB): m/z (%) = 584 (41, [M$^+$]). Anal. Calcd. for $C_{27}H_{28}N_4SO_9$: C, 55.47; H, 4.83; N, 9.58. Found: C, 55.46; H, 4.81; N, 9.54.

*4.1.2.7. 2-Amino-3,5-dicyano-4-(naphthalen-2-yl)-6-(2′,3′,4′,6′-tetra-O-acetyl-1′-thio-β-D-galactopyranosyl)-1,4-dihydropyridines (**5g**).* Yield 4.38 g (69%) (Pale yellow powder): mp 213–215 °C; $[\alpha]_D$ = +34.8 (c 2, $CHCl_3$); IR (KBr) ν_{max} in cm^{-1}: 3320 (NH), 3240 (NH_2), 2225 (CN), 2217 (CN), 1760 (CO); ^{1}H NMR ($CDCl_3$): δ 2.05–2.18 (4s, 12H, 4CH_3CO), 3.97 (dd, 1H, J = 3.2 Hz, J = 10.4 Hz, H-6′), 4.14 (dd, 1H, J = 2.4 Hz, J = 10.4 Hz, H-6″), 4.15–4.32 (m, 3H, H-5′, NH and pyridine H-4), 5.10 (m, 1H, H-4′), 5.19 (t, 1H, J = 8.2 Hz, H-3′), 5.40 (dd, 1H, J = 8.2 Hz, J = 10.4 Hz, H-2′), 5.79 (d, 1H, $J_{1'-2'}$ = 10.4 Hz, H-1′), 5.99 (s, 2H, NH_2), 7.24 (m, 1H, Ar-H), 7.36 (d, 1H, J = 8.5 Hz, Ar-H), 7.47 (m, 1H, Ar-H), 7.66 (m, 1H, Ar-H), 7.79 (d, 1H, J = 8.2 Hz, Ar-H), 7.92 (d, 1H, J = 8.2 Hz, Ar-H), 8.25 (d, 1H, J = 8.5 Hz, Ar-H), ^{13}C NMR ($CDCl_3$): δ 20.10–20.96 (4*C*H$_3$CO), 62.32 (C-6′), 68.49 (C-4′), 69.72 (C-3′), 70.79 (C-2′), 76.90 (C-5′), 75.57 (C-4), 81.68 (C-1′), 83.55 (C-5), 110.65 (C-3), 113.61 (CN), 113.95 (CN), 125.10–139.60 (Ar-10C), 148.39 (C-2), 159.21 (C-6), 169.19–170.33 (4C═O); MS (FAB): m/z (%) = 634 (36, [M$^+$]). Anal. Calcd. for $C_{31}H_{30}N_4SO_9$: C, 58.67; H, 4.76; N, 8.83. Found: C, 58.70; H, 4.77; N, 8.81.

*4.1.2.8. 2-Amino-3,5-dicyano-4-(4-methoxyphenyl)-6-(2′,3′,4′,6′-tetra-O-acetyl-1′-thio-β-D-galactopyranosyl)-1,4-dihydropyridines (**5h**).* Yield 4.36 (71%) (Pale yellow powder): mp 220–221 °C; $[\alpha]_D$ = +40.4 (c 2, $CHCl_3$); IR (KBr) ν_{max} in cm^{-1}: 3324 (NH), 3214 (NH_2), 2221 (CN), 2208 (CN), 1751 (CO); ^{1}H NMR ($CDCl_3$): δ 2.04–2.12 (s, 12H, 4CH_3CO), 3.98 (s, 3H, OCH_3), 4.10 (dd, 1H, J = 3.2 Hz, J = 11.2 Hz, H-6′), 4.15 (dd, 1H, J = 2.8 Hz, J = 11.2 Hz, H-6″), 4.24 (m, 3H, H-5′, NH and pyridine H-4), 5.11 (m, 1H, H-4′), 5.18 (t, 1H, J = 7.8 Hz, H-3′), 5.40 (dd, 1H, J = 7.8 Hz, J = 9.8 Hz, H-2′), 5.78 (d, 1H, $J_{1'-2'}$ = 9.8 Hz, H-1′), 5.84 (s, 2H, NH_2), 6.99 (d, 2H, J = 7.8 Hz, Ar-2H), 7.17 (d, 2H, J = 7.8 Hz, Ar-2H). ^{13}C NMR ($CDCl_3$): δ 20.20–20.60 (4CH_3CO), 55.3 (OCH_3), 62.25 (C-6′), 67.35 (C-4′), 69.56 (C-3′), 71.62 (C-2′), 75.54 (C-5′), 75.98 (C-4), 81.85 (C-1′), 82.87 (C-5), 106.49 (C-3), 114.52 (CN); 114.92 (CN), 126.35–134.23 (Ar-6C), 158.34 (C-2), 159.49 (C-6), 169.35–170.42 (4C═O); MS (FAB): m/z (%) = 614 (50, [M$^+$]). Anal. Calcd. for $C_{28}H_{30}N_4SO_{10}$: C, 54.72; H, 4.92; N, 9.12. Found: C, 54.76; H, 4.98; N, 9.11.

*4.1.3. General procedure for the synthesis of 2-amino-4-aryl-3,5-dicyano-6-(1′-thio-β-D-glycopyranosyl)1,4-dihdropyridines **7a–h***

To a solution of saturated mathanolic ammonia (20 ml), glucoside **5a–e** or galactosides **5f–h** (0.01 mol) was added at room temperature. The reaction mixture was stirred at the same temperature for 24 h, and then evaporated under reduced pressure. The residue was treated with distilled water; the formed solid was filtered off, washed with methanol and crystallized from methanol-DMF (4:1) to give free glucosides **7a–e** or free galactosides **7f–h**, respectively.

*4.1.3.1. 2-Amino-3,5-dicyano-4-phenyl-6-(1′-thio-β-D-glucopyranosyl)-1,4-dihdropyridines (**7a**).* Yield 2.08 g (50%) (Pale yellow powder): mp 188–189 °C; $[\alpha]_D$ = +42.8 (c 1.5, MeOH); IR (KBr) ν_{max} in cm^{-1}: 3325-3270 (OH, NH, NH_2), 2219 (CN), 2203 (CN); ^{1}H NMR (DMSO-d_6): δ 3.23 (m, 2H, H-6′, H-6″), 3.29 (m, 1H, H-5′), 3.56 (m, 2H, H-4′, H-3′), 4.14 (dd, 1H, J = 7.8 Hz, J = 10.4 H-2′), 4.73 (m, 1H, OH), 4.83 (s, 1H, pyridine H-4), 4.86 (t, 1H, J = 4.6 Hz, OH), 5.13 (d, 1H, J = 4.5 Hz, OH), 5.25 (t, 1H, J = 4.8 Hz, OH), 5.73 (d, 1H, $J_{1'-2'}$ = 10.4 Hz, H-1′), 6.24 (bs, 2H, NH_2), 6.38 (bs, 1H, NH), 7.18 (m, 3H, Ar-3H), 7.45 (m, 2H, Ar-2H); ^{13}C NMR (DMSO-d_6): δ 61.25 (C-6′), 66.20 (C-4′), 68.20 (C-2′), 73.30 (C-3′), 75.50 (C-5′), 77.17 (C-4), 81.57 (C-1′), 82.93 (C-5), 106.02 (C-3), 115.11 (CN), 115.75 (CN), 126.29–137.44 (Ar-6C), 158.36 (C-2), 159.26 (C-6); MS (FAB): m/z (%) = 416 (37, [M$^+$]). Anal. Calcd. for $C_{19}H_{20}N_4SO_5$: C, 54.80; H, 4.84; N, 13.45. Found: C, 54.85; H, 4.81; N, 13.40.

*4.1.3.2. 2-Amino-3,5-dicyano-4-(naphthalen-2-yl)-6-(1′-thio-β-D-gluco-pyranosyl)-1,4-dihdro pyridines (**7b**).* Yield 2.05 g (44%) (Pale yellow powder): mp 193–194 °C; $[\alpha]_D$ = +39.4 (c 1.5, MeOH); IR (KBr) ν_{max} in cm^{-1}: 3380-3310 (OH, NH and NH_2), 2200 (CN), 2198 (CN); ^{1}H NMR (DMSO-d_6) δ in ppm: 3.25 (m, 2H, H-6′, H-6″), 3.28 (m, 1H, H-5′), 3.53 (m, 2H, H-4′, H-3′), 4.12 (dd, 1H, J = 7.6 Hz, J = 10.2 Hz, H-2′), 4.72 (d, 1H, J = 7.2 Hz, OH), 4.85 (s, 1H, pyridine H-4), 4.88 (t, 1H, J = 4.6 Hz, OH), 5.11 (m, 1H, OH), 5.25 (t, 1H, J = 4.4 Hz, OH), 5.74 (d, 1H, $J_{1'-2'}$ = 10.2 Hz, H-1′), 6.25 (bs, 2H, NH_2), 6.35 (bs, 1H, NH), 7.40 (m, 2H, Ar-H), 7.47 (d, 1H, J = 8.5 Hz, Ar-H), 7.57 (d, 1H, J = 8.2 Hz, Ar-H), 7.67 (d, 1H, J = 8.2 Hz, Ar-H), 7.76 (s, 1H, Ar-H), 8.19 (d, 1H, J = 8.5 Hz, Ar-H). ^{13}C NMR (DMSO-d_6): δ61.2 (C-6′), 68.26 (C-4′), 73.37 (C-2′), 75.82 (C-3′), 76.12 (C-5′), 76.98. (C-4), 80.58 (C-1′), 82.65 (C-5), 110.41 (C-3), 113.32 (CN), 113.87 (CN), 125.10–140.60 (Ar-10C), 148.02 (C-2), 159.10 (C-6); MS (FAB): m/z (%) = 466 (22, [M$^+$]). Anal. Calcd. for $C_{23}H_{22}N_4SO_5$: C, 59.22; H, 4.75; N, 12.01. Found: C, 59.20; H, 4.74; N, 11.96.

*4.1.3.3. 2-Amino-4-(4-bromophenyl)-3,5-dicyano-6-(1′-thio-β-D-gluco-pyranosyl)-1,4-dihdropyridines (**7c**).* Yield 2.48 g (50%) (Pale yellow powder); mp 203–205 °C; $[\alpha]_D$ = +32.8 (c 1.5, MeOH); IR (KBr) ν_{max} in cm^{-1}: 3316-3250 (OH, NH and NH_2), 2224 (CN), 2220 (CN); ^{1}H NMR (DMSO-d_6) δ in ppm: 3.27 (m, 2H, H-6′, H-6″), 3.29 (m, 1H, H-5′), 3.52 (m, 1H, H-4′), 3.88 (m, 2H, H-3′, H-2′), 4.75 (d, 1H, J = 6.8 Hz, OH), 4.86 (s, 1H, pyridine H-4), 4.92 (t, 1H, J = 4.6 Hz, OH), 5.13 (m, 1H, OH), 5.27 (t, 1H, J = 4.4 Hz, OH), 5.73 (d, 1H, $J_{1'-2'}$ = 9.8 Hz H-1′), 6.24 (bs, 2H, NH_2), 6.34 (bs, 1H, NH), 7.29 (d, 2H, J = 7.8 Hz, Ar-2H), 7.78 (d, 2H, J = 7.8 Hz, Ar-2H); ^{13}C NMR (DMSO-d_6): δ 62.19 (C-6′), 67.28 (C-4′), 68.25 (C-2′), 73.50 (C-3′), 75.51 (C-5′), 77.69 (C-4), 80.53 (C-1′), 81.38 (C-5), 106.55 (C-3), 114.65 (CN), 114.87 (CN), 126.14–134.58 (Ar-6C), 158.24 (C-2), 159.56 (C-6); MS (FAB): m/z (%) = 495 (32, [M$^+$]). Anal. Calcd. for $C_{19}H_{19}BrN_4SO_5$: C, 46.07; H, 3.87; N, 11.31. Found: C, 46.09; H, 3.88; N, 11.29.

*4.1.3.4. 2-Amino-3,5-dicyano-4-(4-nitrophenyl)-6-(1′-thio-β-D-gluco-pyranosyl)-1,4-dihdropyridines (**7d**).* Yield 2.68 g (58%) (Pale yellow powder): mp 218–219 °C; $[\alpha]_D$ = +28.8 (c 1.5, MeOH); IR (KBr) ν_{max} in cm^{-1}: 3297-3235 (OH, NH and NH_2), 2213 (CN), 2200 (CN); ^{1}H NMR (DMSO-d_6): δ 3.24 (m, 2H, H-6′, H-6″), 3.26 (m, 1H,

H-5′), 3.52 (m, 1H, H-4′), 3.87–4.14 (m, 2H, H-3′, H-2′), 4.75 (m, 1H, OH), 4.84 (t, 1H, J = 4.6 Hz, OH), 4.84 (s, 1H, pyridine H-4), 5.14 (d, 1H, J = 6.4 Hz, OH), 5.27 (t, 1H, J = 5.8 Hz, OH), 5.72 (d, 1H, $J_{1'-2'}$ = 10.4 Hz, H-1′), 6.22 (bs, 2H, NH_2), 6.32 (bs, 1H, NH), 7.33 (d, 2H, J = 7.8 Hz, Ar-2H), 7.84 (d, 2H, J = 7.8 Hz, Ar-2H); ^{13}C NMR (DMSO-d_6): δ 63.56 (C-6′), 68.08 (C-4′), 69.14 (C-2′), 73.56 (C-3′), 75.45 (C-5′), 77.69 (C-4), 80.53 (C-1′), 81.38 (C-5), 106.10 (C-3), 114.21 (CN), 114.87 (CN), 126.14–131.58 (Ar-6C), 158.24 (C-2), 159.21 (C-6); MS (FAB): m/z (%) = 461 (39, [M$^+$]). Anal. Calcd. for $C_{19}H_{19}N_5SO_7$: C, 49.45; H, 4.15; N, 15.18. Found: C, 49.43; H, 4.11; N, 15.20.

*4.1.3.5. 2-Amino-3,5-dicyano-4-(4-methoxyphenyl)-6-(1′-thio-β-D-gluco-pyranosyl)-1,4-dihdropyridines (**7e**).* Yield 2.72 g (61%) (Pale yellow powder): mp 230–231 °C; [α]$_D$ = +30.2 (c 1.5, MeOH); IR (KBr) ν_{max} in cm^{-1}: 3309-3224 (OH, NH and NH_2), 2224 (CN), 2220 (CN); ^{1}H NMR (DMSO-d_6): δ 3.21 (m, 2H, H-6′, H-6″), 3.23 (m, 1H, H-5′), 3.49 (m, 1H, H-4′), 3.80 (s, 3H, OCH_3), 3.86–4.14 (m, 2H, H-3′, H-2′), 4.73 (t, 1H, J = 6.4 Hz, OH), 4.82 (t, 1H, J = 4.6 Hz, OH), 4.89 (s, 1H, pyridine H-4), 5.12 (m, 1H, OH), 5.26 (t, 1H, J = 4.4 Hz, OH), 5.72 (d, 1H, $J_{1'-2'}$ = 9.8 Hz, H-1′), 6.22 (bs, 2H, NH_2), 6.36 (bs, 1H, NH), 7.28 (d, 2H, J = 7.8 Hz, Ar-2H), 7.82 (d, 2H, J = 7.8 Hz, Ar-2H); ^{13}C NMR (DMSO-d_6): δ 55.38 (OCH_3), 64.16 (C-6′), 68.08 (C-4′), 69.14 (C-2′), 73.56 (C-3′), 75.45 (C-5′), 76.69 (C-4), 80.53 (C-1′), 81.42 (C-5), 106.55 (C-3), 114.15 (CN), 114.67 (CN), 129.44–132.36 (Ar-6C), 158.24 (C-2), 159.56 (C-6); MS (FAB): m/z (%) = 446 (19, [M$^+$]). Anal. Calcd. for $C_{20}H_{22}N_4SO_6$: C, 53.56; H, 4.94; N, 12.49. Found: C, 53.55; H, 4.92; N, 12.50.

*4.1.3.6. 2-Amino-3,5-dicyano-4-phenyl-6-(1′-thio-β-D-galactopyranosyl)-1,4-dihdropyridines (**7f**).* Yield 2.21 (53%) (Pale yellow powder): mp 180–181 °C; [α]$_D$ = +28.6 (c 1.5, MeOH); IR (KBr) ν_{max} in m^{-1}: 3326-2166 (OH, NH and NH_2), 2200 (CN), 2198 (CN); ^{1}H NMR (DMSO-d_6): δ 3.22 (m, 2H, H-6′, H-6″), 3.27 (m, 1H, H-5′), 3.53 (m, 2H, H-4′, H-3′), 4.15 (dd, 1H, J = 7.8 Hz, J = 10.5 Hz, H-2′), 4.76 (t, 1H, J = 4.6 Hz, OH), 4.86 (t, 1H, J = 4.6 Hz, OH), 4.90 (s, 1H, pyridine H-4), 5.14 (m, 1H, OH), 5.27 (t, 1H, J = 4.4 Hz, OH), 5.78 (d, 1H, $J_{1'-2'}$ = 9.8 Hz, H-1′), 6.34 (bs, 2H, NH_2), 6.99 (m, 3H, Ar-3H), 7.31 (m, 2H, Ar-2H); ^{13}C NMR (DMSO-d_6): δ 61.24 (C-6′), 64.90 (C-4′), 70.50 (C-2′), 74.80 (C-3′), 75.50 (C-5′), 76.87 (C-4), 81.57 (C-1′), 82.21 (C-5), 110.02 (C-3), 114.11 (CN), 114.85 (CN), 125.29–137.44 (Ar-6C), 158.30 (C-2), 159.20 (C-6); MS (FAB): m/z (%) = 416 (28, [M$^+$]). Anal. Calcd. for $C_{19}H_{20}N_4SO_5$: C, 54.80; H, 4.84; N, 13.45. Found: C, 54.85; H, 4.80; N, 13.48.

*4.1.3.7. 2-Amino-3,5-dicyano-4-(4-naphthalen-2-yl)-6-(1′-thio-β-D-galacto-pyranosyl)-1,4-dihdropyridines (**7g**).* Yield 2.47 g (53%) (Pale yellow powder): mp 217–217 °C; [α]$_D$ = +32.6 (c 1.5, MeOH); IR (KBr) ν_{max} in cm^{-1}: 3298-3227 (OH, NH and NH_2), 2205 (CN), 2201 (CN); ^{1}H NMR (DMSO-d_6): δ 3.24 (m, 2H, H-6′, H-6″), 3.29 (m, 1H, H-5′), 3.55 (m, 1H, H-4′), 3.93 (m, 2H, H-3′, H-2′), 4.79 (t, 1H, J = 6.6 Hz, OH), 4.84 (t, 1H, J = 4.6 Hz, OH), 4.87 (s, 1H, pyridine H-4), 5.16 (m, 1H, OH), 5.29 (t, 1H, J = 4.8 Hz, OH), 5.73 (d, 1H, $J_{1'-2'}$ = 10.2 Hz, H-1′), 6.29 (bs, 2H, NH_2), 6.37 (bs, 1H, NH), 7.22 (m, 1H, Ar-H), 7.34 (d, 1H, J = 8.5 Hz, Ar-H), 7.45 (m, 1H, Ar-H), 7.54 (m, 1H, Ar-H), 7.55 (d, 1H, J = 8.2 Hz, Ar-H), 7.86 (d, 1H, J = 8.2 Hz, Ar-H), 8.25 (d, 1H, J = 8.5 Hz, Ar-H). ^{13}C NMR ($CDCl_3$): δ62.05 (C-6′), 67.98 (C-4′), 72.88 (C-2′); 75.12 (C-3′), 75.33 (C-5′), 75.98 (C-4), 79.88 (C-1′), 83.14 (C-5), 111.81 (C-3), 112.45 (CN), 114.24 (CN), 123.12–144.62 (Ar-10C), 147.77 (C-2), 160.08 (C-6); MS (FAB): m/z (%) = 466 (69, [M$^+$]). Anal. Calcd. for $C_{23}H_{22}N_4SO_5$: C, 59.22; H, 4.75; N, 12.01. Found: C, 59.23; H, 4.70; N, 11.94.

*4.1.3.8. 2-Amino-3,5-dicyano-4-(4-methoxyphenyl)-6-(1′-thio-β-D-galacto-pyranosyl)-1,4-dihdropyridines (**7h**).* Yield 2.05 g (46%) (Pale yellow powder): mp 200–201 °C; [α]$_D$ = +34.2 (c 1.5, MeOH); IR (KBr) ν_{max} in cm^{-1}: 3350-3268 (OH, NH and NH_2), 2222 (CN), 2218 (CN); ^{1}H NMR (DMSO-d_6): δ 3.20 (m, 2H, H-6′, H-6″), 3.24 (m, 1H, H-5′), 3.47 (m, 1H, H-4′), 3.82 (s, 3H, OCH_3), 3.85 (m, 2H, H-3′, H-2′), 4.72 (t, 1H, J = 4.8 Hz, OH), 4.81 (t, 1H, J = 4.6 Hz, OH), 4.88 (s, 1H, pyridine H-4), 5.20 (m, 1H, OH), 5.26 (t, 1H, J = 4.4 Hz, OH), 5.75 (d, 1H, $J_{1'-2'}$ = 10.4 Hz, H-1′), 6.18 (bs, 2H, NH_2), 6.35 (bs, 1H, NH), 7.31 (d, 2H, J = 7.8 Hz, Ar-2H), 7.85 (d, 2H, J = 7.8 Hz, Ar-2H). ^{13}C NMR (DMSO-d_6): δ 55.68 (OCH_3), 64.66 (C-6′), 67.08 (C-4′), 71.34 (C-2′), 73.46 (C-3′), 75.05 (C-5′), 76.89 (C-4), 80.13 (C-1′), 81.42 (C-5), 106.95 (C-3), 114.05 (CN), 114.67 (CN), 129.40–132.30 (Ar-6C), 158.24 (C-2), 159.26 (C-6); MS (FAB): m/z (%) = 446 (31, [M$^+$]). Anal. Calcd. for $C_{20}H_{22}N_4SO_6$: C, 53.80; H, 4.97; N, 12.55. Found: C, 53.85; H, 4.95; N, 12.49.

*4.1.4. General procedure for the synthesis of 2-amino-4-aryl-3,5-dicyano-6-(2′,3′,4′,6′-tetra-O-acetyl-1′-thio-β-D-gluco- or galactopyranosyl) pyridines **8a–f***

Method (*A*): The piperidinium salt of dihydropyridinethiones **3a–e** (0.01 mol) was dissolved in dry acetone (5 ml) and a solution of2,3,4,6-teta-*O*-acetyl-α-D-gluco- or galactopyranosyl bromide **4a**,**b** (4.52g, 0.011 mol) in dry acetone (20 ml) was then added at 30 °C. The reaction mixture was stirred at 30 °C for 18–20 h, the solvent was evaporated under reduced pressure and the residue was solidified with distilled water. The obtained crude solid was filtered off, washed with distilled water and dried. The pure product was extracted from the above solid with petroleum ether (80–100). The petroleum ether part was evaporated under reduced pressure and the solid product was crystallized from benzene to give the thioglycosides **8a–f**.

Method (*B*): A suspension of 1,4-dihdropyridines thioglycosides **5a–c**, **f–h** (0.01 mol) in ethanol were refluxed with stirring for 5 min the resulting products were collected by filtration and crystallized from benzene.

*4.1.4.1. 2-Amino-3,5-dicyano-4-phenyl-6-(2′,3′,4′,6′-tetra-O-acetyl-1′-thio-β-D-glucopyranosyl)pyridines (**8a**).* Yield 3.79 g (65%) (Pale yellow powder): mp 184–185 °C; [α]$_D$ = +24.9 (c 2, $CHCl_3$); IR (KBr) ν_{max} in cm^{-1}: 3230 (NH_2), 2229 (CN), 2215 (CN), 1758 (CO); ^{1}H NMR ($CDCl_3$): δ 1.89–2.11 (4s, 12H, 4CH_3CO), 3.86 (dd, 1H, J = 2.8 Hz, J = 10.5 Hz, H-6′), 4.14 (dd, 1H, J = 3.6 Hz, J = 10.5 Hz, H-6″), 4.28 (m, 1H, H-5′), 5.13 (m, 1H, H-4′), 5.17 (dd, 1H, J = 7.6 Hz, J = 10.8, H-3′), 5.24 (t, 1H, J = 10.2 Hz, H-2′), 5.78 (d, 1H, $J_{1'-2'}$ = 10.2 Hz, H-1′), 6.23 (s, 2H, NH_2), 6.87 (m, 3H, Ar-3H), 7.38 (m, 2H, Ar-2H); ^{13}C NMR ($CDCl_3$): δ 21.54–22.07 (4CH_3CO), 61.25 (C-6′), 67.85 (C-4′), 69.10 (C-3′), 71.90 (C-2′), 75.43 (C-5′), 85.32 (C-1′), 106.36 (C-3), 112.39 (C-5), 121.78 (CN), 121.98 (CN), 126.42–132.80 (Ar-6C), 152.39 (C-4), 157.30 (C-6), 162.08 (C-2), 169.60–170.70 (4C=O); MS (FAB): m/z (%) = 582 (65, [M$^+$]). Anal. Calcd. for $C_{27}H_{26}N_4SO_9$: C, 55.66; H, 4.50; N, 9.62. Found: C, 55.62; H, 4.52; N, 9.59.

*4.1.4.2. 2-Amino-3,5-dicyano-4-(naphthalen-2-yl)-6-(2′,3′,4′,6′-tetra-O-acetyl-1′-thio-β-D-glucopyranosyl)pyridines (**8b**).* Yield 4.43 g (70%) (Pale yellow powder): mp 173–174 °C; [α]$_D$ = +28.4 (c 2, $CHCl_3$); IR (KBr) ν_{max} in cm^{-1}: 3210 (NH_2), 2209 (CN), 2199 (CN), 1748 (CO); ^{1}H NMR ($CDCl_3$): δ 1.88–2.10 (4s, 12H, 4CH_3CO), 3.89 (dd, 1H, J = 3.2 Hz, J = 10.4 Hz, H-6′), 4.12 (dd, 1H, J = 2.8 Hz, J = 10.4 Hz, H-6″), 4.30 (m, 1H, H-5′), 5.12 (m, 1H, H-4′), 5.18 (t, 1H, J = 7.8 Hz, H-3′), 5.22 (dd, 1H, J = 7.8 Hz, J = 10.4 Hz, H-2′), 5.88 (d, 1H, $J_{1'-2'}$ = 10.4 Hz, H-1′), 6.21 (s, 2H, NH_2), 7.43 (m, 2H, Ar-H), 7.48 (d, 1H, J = 8.5 Hz, Ar-H), 7.55 (d, 1H, J = 8.2 Hz, Ar-H), 7.70 (d, 1H, J = 8.2 Hz, Ar-H), 7.78 (s, 1H, Ar-H), 8.20 (d, 1H, J = 8.5 Hz, Ar-H); ^{13}C NMR ($CDCl_3$): δ 20.19–20.97 (4CH_3CO), 62.05 (C-6′), 67.50 (C-4′), 69.80 (C-3′), 71.75 (C-2′), 75.59 (C-5′), 85.12 (C-1′), 106.58 (C-3), 112.30 (C-5), 121.29 (CN), 121.80 (CN), 126.39–132.50 (Ar-10C), 152.12 (C-4), 157.28 (C-6), 161.81 (C-2), 169.20–171.20 (4C=O); MS (FAB): m/z (%) = 632 (80, [M$^+$]). Anal.

Calcd. for $C_{31}H_{28}N_4SO_9$: C, 58.85; H, 4.46; N, 8.86. Found: C, 58.80; H, 4.45; N, 8.85.

*4.1.4.3. 2-Amino-4-(4-bromophenyl)-3,5-dicyano-6-(2′,3′,4′,6′-tetra-O-acetyl-1′-thio-β-D-glucopyranosyl)pyridines (**8c**).* Yield 5.16 g (78%) (Pale yellow powder): mp 230–232 °C; $[\alpha]_D = +23.2$ (c 2, $CHCl_3$); IR (KBr) ν_{max} in cm^{-1}: 3217 (NH_2), 2225 (CN), 2222 (CN), 1752 (CO); ^1H NMR ($CDCl_3$): δ 1.98–2.15 (4S, 12H, $4CH_3CO$), 3.95 (dd, 1H, $J = 3.2$ Hz, $J = 10.8$ Hz, H-6′), 4.12 (dd, 1H, $J = 2.8$ Hz, $J = 10.8$ Hz, H-6″), 4.18 (m, 1H, H-5′), 5.09 (t, 1H, $J = 8.4$ Hz, H-4′), 5.19 (t, 1H, $J = 8.4$ Hz, H-3′), 5.21 (dd, 1H, $J = 8.4$ Hz, $J = 10.4$ Hz, H-2′), 5.98 (d, 1H, $J_{1'-2'} = 10.4$ Hz, H-1′), 6.28 (s, 2H, NH_2), 7.60 (d, 2H, $J = 7.8$ Hz, Ar-2H), 7.98 (d, 2H, $J = 7.8$ Hz, Ar-2H). ^{13}C NMR ($CDCl_3$): δ 20.34–20.67 ($4CH_3CO$), 62.15 (C-6′), 67.90 (C-4′), 69.30 (C-2′), 70.70 (C-2′), 75.53 (C-5′), 76.39 (C-4), 84.05 (C-1′), 106.50 (C-3), 120.20 (CN), 121.90 (CN), 114.30 (C-5), 126.09–132.50 (Ar-6C), 157.20 (C-6), 161.88 (C-2), 169.20–170.80 (4C═O); MS (FAB): *m*/*z* (%) = 661 (49, [M^+]). Anal. Calcd. for $C_{27}H_{25}BrN_4SO_9$: C, 49.02; H, 3.81; N, 8.47. Found: C, 49.07; H, 3.82; N, 8.45.

*4.1.4.4. 2-Amino-3,5-dicyano-4-phenyl-6-(2′,3′,4′,6′-tetra-O-acetyl-1′-thio-β-D-galactopyranosyl)pyridines (**8d**).* Yield 3.96 g (68%) (Pale yellow powder): mp 158–160 °C; $[\alpha]_D = +38.4$ (c 2, $CHCl_3$); IR (KBr) ν_{max} in cm^{-1}: 3268 (NH_2), 2214 (CN), 2200 (CN), 1760 (CO); ^1H NMR ($CDCl_3$): δ 2.13–2.26 (4s, 12H, $4CH_3CO$), 3.83 (dd, 1H, $J = 3.4$ Hz, $J = 11.2$ Hz, H-6′), 4.08 (dd, 1H, $J = 2.8$ Hz, $J = 11.2$ Hz, H-6″), 4.11 (m, 1H, H-5′), 5.12 (m, 1H, H-4′), 5.16 (t, 1H, $J = 8.8$ Hz, H-3′), 5.25 (dd, 1H, $J = 8.8$ Hz, $J = 10.5$, H-2′), 5.89 (d, 1H, $J_{1'-2'} = 10.5$ Hz, H-1′), 6.18 (s, 2H, NH_2), 7.40 (m, 3H, Ar-3H), 7.75 (m, 2H, Ar-2H); ^{13}C NMR ($CDCl_3$): δ 21.14–22.27 ($4CH_3CO$), 62.25 (C-6′), 68.05 (C-4′), 68.50 (C-3′), 70.90 (C-2′), 75.03 (C-5′), 85.32 (C-1′), 107.06 (C-3), 114.49 (C-5), 122.80 (CN), 122.50 (CN), 126.42–132.80 (Ar-6C), 153.09 (C-4), 157.30 (C-6), 162.38 (C-2), 169.60–170.70 (4C═O); MS (FAB): *m*/*z* (%) = 582 (25, [M^+]). Anal. Calcd. for $C_{27}H_{26}N_4SO_9$: C, 55.66; H, 4.50; N, 9.62. Found: C, 55.62; H, 4.50; N, 9.67.

*4.1.4.5. 2-Amino-3,5-dicyano-4-(naphthalen-2-yl)-6-(2′,3′,4′,6′-tetra-O-acetyl-1′-thio-β-D-galactopyranosyl)pyridines (**8e**).* Yield 4.93 g (78%) (Pale yellow powder): mp 236–238 °C; $[\alpha]_D = +40.2$ (c 2, $CHCl_3$); IR (KBr) ν_{max} in cm^{-1}: 3250 (NH_2), 2218 (CN), 2209 (CN), 1757 (CO); ^1H NMR ($CDCl_3$): δ 1.92–2.12 (4s, 12H, $4CH_3CO$), 3.92 (dd, 1H, $J = 2.6$ Hz, $J = 10.8$ Hz, H-6′), 4.14 (dd, 1H, $J = 3.2$ Hz, $J = 10.8$ Hz, H-6″), 4.28 (m, 1H, H-5′), 5.14 (m, 1H, H-4′), 5.18 (t, 1H, $J = 8.4$ Hz, H-3′), 5.20 (dd, 1H, $J = 8.4$ Hz, $J = 10.4$ Hz, H-2′), 5.79 (d, 1H, $J_{1'-2'} = 10.4$ Hz, H-1′), 6.22 (s, 2H, NH_2), 7.21 (m, 1H, Ar-H), 7.35 (d, 1H, $J = 8.5$ Hz, Ar-H), 7.47 (m, 1H, Ar-H), 7.62 (m, 1H, Ar-H), 7.77 (d, 1H, $J = 8.2$ Hz, Ar-H), 7.89 (d, 1H, $J = 8.2$ Hz, Ar-H), 8.24 (d, 1H, $J = 8.5$ Hz, Ar-H); ^{13}C NMR ($CDCl_3$): δ 21.22–22.07 ($4CH_3CO$), 62.05 (C-6′), 67.34 (C-4′), 68.24 (C-3′), 71.75 (C-2′), 75.93 (C-5′), 85.70 (C-1′), 106.58 (C-3), 114.30 (C-5), 121.29 (CN), 121.98 (CN), 126.34–132.93 (Ar-10C), 152.24 (C-4), 157.58 (C-6), 161.81 (C-2), 169.52–171.35 (4C═O); MS (FAB): *m*/*z* (%) = 632 (72, [M^+]). Anal. Calcd. for $C_{31}H_{28}N_4SO_9$: C, 58.85; H, 4.46; N, 8.86. Found: C, 58.86; H, 4.44; N, 8.85.

*4.1.4.6. 2-Amino-3,5-dicyano-4-(4-methoxyphenyl)-6-(2′,3′,4′,6′-tetra-O-acetyl-1′-thio-β-D-galactopyranosyl)pyridines (**8f**).* Yield 4.72 g (77%) (Pale yellow powder): mp 193–194 °C; $[\alpha]_D = +32.9$ (c 2, $CHCl_3$); IR (KBr) ν_{max} in cm^{-1}: 3214 (NH_2), 2211 (CN), 2200 (CN), 1750 (CO); ^1H NMR ($CDCl_3$): δ 1.93–2.17 (4S, 12H, $4CH_3CO$), 3.91 (dd, 1H, $J = 3.2$ Hz, $J = 11.2$ Hz, H-6′), 4.03 (s, 3H, OCH_3), 4.13 (dd, 1H, $J = 3.4$ Hz, $J = 11.2$ Hz, H-6″), 4.28 (m, 1H, H-5′), 5.12 (m, 1H, H-4′), 5.14 (t, 1H, $J = 8.2$ Hz, H-3′), 5.24 (dd, 1H, $J = 8.6$ Hz, $J = 10.4$ Hz, H-2′), 5.91 (d, 1H, $J_{1'-2'} = 10.4$ Hz, H-1′), 6.24 (s, 2H, NH_2), 6.90 (d, 2H, $J = 8.8$ Hz, Ar-2H), 7.30 (d, 2H, $J = 8.8$ Hz, Ar-2H); ^{13}C NMR ($CDCl_3$): δ 20.29–20.69 ($4CH_3CO$), 55.80 (OCH_3), 62.15 (C-6′), 67.90 (C-4′), 68.97 (C-3′), 70.72 (C-2′), 75.53 (C-5′), 85.25 (C-1′), 106.71 (C-3), 121.98 (CN), 122.45 (CN), 114.21 (C-5), 126.69–132.58 (Ar-6C), 153.89 (C-4), 157.20 (C-6), 161.88 (C-2), 169.20–170.85 (4C═O); MS (FAB): *m*/*z* (%) = 612 (26, [M^+]). Anal. Calcd. for $C_{28}H_{28}N_4SO_{10}$: C, 54.90; H, 4.61; N, 9.15. Found: C, 54.86; H, 4.58; N, 9.13.

*4.1.5. General procedure for the synthesis of 4-aryl-2-amino-3,5-dicyano-6-(1′-thio-β-D-glycopyranosyl)pyridines **9a–f***

To a solution of saturated methanolic ammonia (20 ml), glucoside **8a–c** or galactosides **8d–f** (0.01 mol) was added at room temperature. The reaction mixture was stirred at the same temperature for 24 h, and then evaporated under reduced pressure. The residue was treated with distilled water; the formed solid was filtered off, washed with methanol and crystallized from ethanol-DMF (4:1) to give the free glucosides **9a–c** or free galactosides **9d–f**, respectively.

*4.1.5.1. 2-Amino-3,5-dicyano-4-phenyl-6-(1′-thio-β-D-glucopyranosyl)-pyridines (**9a**).* Yield 2.49 g (60%) (Pale yellow powder): mp 233–235 °C; $[\alpha] = +28.0$ (c 1.5, MeOH); IR (KBr) ν_{max} in cm^{-1}: 3331 (OH and NH_2), 2223 (CN), 2218 (CN); ^1H NMR (DMSO-d_6): δ 3.11 (m, 2H, H-6′, H-6″), 3.83 (m, 1H, H-5′), 3.53–3.61 (m, 2H, H-3′, H-4′), 4.14 (dd, 1H, $J = 8.2$ Hz, $J = 9.8$ Hz, H-2′), 4.75 (m, 1H, OH), 4.83 (t, 1H, $J = 4.6$ Hz, OH), 5.12 (m, 1H, OH), 5.22 (t, 1H, $J = 4.8$ Hz, OH), 5.78 (d, 1H, $J_{1'-2'} = 9.8$ Hz, H-1′), 6.23 (bs, 2H, NH_2), 7.58 (m, 3H, Ar-3H), 8.10 (m, 2H, Ar-2H); ^{13}C NMR (DMSO-d_6): δ 62.05 (C-6′), 67.74 (C-4′), 72.85 (C-2′), 73.55 (C-3′), 75.50 (C-5′), 85.22 (C-1′), 106.58 (C-3), 114.30 (C-5), 122.29 (CN), 123.96 (CN), 126.39–132.50 (Ar-6C), 154.39 (C-4), 157.33 (C-6), 161.81 (C-2); MS (FAB): *m*/*z* (%) = 414 (51, [M^+]). Anal. Calcd. for $C_{19}H_{18}N_4SO_5$: C, 55.06; H, 4.38; N, 13.52. Found: C, 55.01; H, 4.35; N, 13.54.

*4.1.5.2. 2-Amino-3,5-dicyano-4-(naphthalen-2-yl)-6-(1′-thio-β-D-gluco-pyranosyl)pyridines (**9b**).* Yield 2.51 g (54%) (Pale yellow powder): mp 218–220 °C; $[\alpha]_D = +36.4$ (c 1.5, MeOH); IR (KBr) ν_{max} in cm^{-1}: 3304 (OH and NH_2), 2226 (CN), 2220 (CN); ^1H NMR (DMSO-d_6): δ 3.28 (m, 2H, H-6′, H-6″), 3.31 (m, 1H, H-5′), 3.51 (m, 1H, H-4′), 3.82 (m, 2H, H-3′, H-2′), 4.76 (m, 1H, OH), 4.87 (t, 1H, $J = 4.6$ Hz, OH), 5.12 (m, 1H, OH), 5.22 (t, 1H, $J = 4.4$ Hz, OH), 5.78 (d, 1H, $J_{1'-2'} = 10.2$ Hz, H-1′), 6.32 (bs, 2H, NH_2), 7.42 (m, 2H, Ar-H), 7.47 (d, 1H, $J = 8.5$ Hz, Ar-H), 7.59 (d, 1H, $J = 8.2$ Hz, Ar-H), 7.71 (d, 1H, $J = 8.2$ Hz, Ar-H), 7.77 (s, 1H, Ar-H), 8.21 (d, 1H, $J = 8.5$ Hz, Ar-H); ^{13}C NMR (DMSO-d_6): δ 62.35 (C-6′), 67.74 (C-4′), 72.65 (C-2′), 73.55 (C-3′), 75.12 (C-5′), 85.20 (C-1′), 106.58 (C-3), 114.24 (C-5); 122.29 (CN), 122.96 (CN), 126.30–133.50 (Ar-10C), 153.80 (C-4); 157.35 (C-6), 161.86 (C-2); MS (FAB): *m*/*z* (%) = 464 (63, [M^+]). Anal. Calcd. for $C_{23}H_{20}N_4SO_5$: C, 59.47; H, 4.34; N, 12.06. Found: C, 59.42; H, 4.35; N, 12.05.

*4.1.5.3. 2-Amino-4-(4-bromophenyl)-3,5-dicyano-6-(1′-thio-β-D-gluco-pyranosyl)pyridines (**9c**).* Yield 2.81 g (57%) (Pale yellow powder): mp 203–205 °C; $[\alpha]_D = +24.6$ (c 1.5, MeOH); IR (KBr) ν_{max} in cm^{-1}: 3311 (OH and NH_2), 2215 (CN), 2200 (CN); ^1H NMR (DMSO-d_6): δ 3.25 (m, 2H, H-6′, H-6″), 3.30 (m, 1H, H-5′), 3.51 (m, 1H, H-4′), 3.96–4.12 (m, 2H, H-3′, H-2′), 4.75 (m, 1H, OH), 5.08 (t, 1H, $J = 4.6$ Hz, OH), 5.18 (m, 1H, OH), 5.58 (t, 1H, $J = 4.4$ Hz, OH), 5.80 (d, 1H, $J_{1'-2'} = 10.2$ Hz, H-1′), 6.33 (bs, 2H, NH_2), 7.30 (d, 2H, $J = 8.5$ Hz, Ar-2H), 7.63 (d, 2H, $J = 8.5$ Hz, Ar-2H); ^{13}C NMR (DMSO-d_6): δ 62.68 (C-6′), 67.89 (C-4′), 71.85 (C-2′), 73.57 (C-3′), 75.52 (C-5′), 85.28 (C-1′), 106.58 (C-3), 115.30 (C-5), 121.88 (CN), 122.22 (CN), 126.39–132.59 (Ar-6C), 154.43 (C-4), 157.30 (C-6), 161.81 (C-2); MS (FAB): *m*/*z* (%) = 493 (39, [M^+]). Anal. Calcd. for $C_{19}H_{17}BrN_4SO_5$: C, 46.26; H, 3.47; N, 11.36. Found: C, 46.29; H, 3.45; N, 11.30.

*4.1.5.4. 2-Amino-3,5-dicyano-4-phenyl-6-(1′-thio-β-D-galactopyranosyl)-pyridines (**9d**).* Yield 2.40 g (58%) (Pale yellow powder): mp 235–236 °C; $[\alpha]_D = +20.2$ (c 1.5, MeOH); IR (KBr) ν_{max} in cm^{-1}: 3279

(OH and NH_2), 2220 (CN), 2213 (CN); ^{1}H NMR (DMSO-d_6): δ 3.22 (m, 2H, H-6′, H-6″), 3.29 (m, 1H, H-5′), 3.50–3.85 (m, 3H, H-4′, H-3′, H-2′), 4.75 (m, 1H, OH), 4.81 (t, 1H, J = 4.6 Hz, OH), 5.17 (m, 1H, OH), 5.27 (t, 1H, J = 4.4 Hz, OH), 5.75 (d, 1H, $J_{1'-2'}$ = 10.2 Hz, H-1′), 6.28 (bs, 2H, NH_2), 6.96 (m, 3H, Ar-3H), 7.29 (m, 2H, Ar-2H). ^{13}C NMR (DMSO-d_6): δ 62.17 (C-6′), 67.70 (C-4′), 70.87 (C-2′), 73.55 (C-3′), 75.55 (C-5′), 85.26 (C-1′), 106.59 (C-3), 114.12 (C-5), 120.29 (CN), 121.96 (CN), 126.99–132.70 (Ar-6C), 152.39 (C-4), 157.83 (C-6), 161.81 (C-2); MS (FAB): m/z (%) = 414 (47, [M^+]). Anal. Calcd. for $C_{19}H_{18}N_4SO_5$: C, 55.06; H, 4.38; N, 13.52. Found: C, 55.01; H, 4.33; N, 13.55.

*4.1.5.5. 2-Amino-3,5-dicyano-4-(naphthalen-2-yl)-6-(1′-thio-β-D-galacto-pyranosyl)pyridines (**9e**).* Yield 3.16 g (68%) (Pale yellow powder): mp 253–255 °C; $[\alpha]_D$ = +32.2 (c 1.5, MeOH); IR (KBr) ν_{max} in cm^{-1}: 3310 (OH and NH_2), 2210 (CN), 2200 (CN); ^{1}H NMR (DMSO-d_6): δ 3.07 (m, 2H, H-6′,6″), 3.28 (m, 1H, H-5′), 3.45 (m, 1H, H-4′), 3.90–4.02 (m, 2H, H-3′, H-2′), 4.72 (m, 1H, OH), 4.86 (t, 1H, J = 4.6 Hz, OH), 5.22 (m, 1H, OH), 5.38 (t, 1H, J = 4.4 Hz, OH), 5.79 (d, 1H, $J_{1'-2'}$ = 9.8 Hz, H-1′), 6.34 (bs, 2H, NH_2), 6.99 (m, 1H, Ar-H), 7.32 (d, 1H, J = 8.5 Hz, Ar-H), 7.38 (m, 1H, Ar-H), 7.52 (m, 1H, Ar-H), 7.55 (d, 1H, J = 8.2 Hz, Ar-H), 7.85 (d, 1H, J = 8.2 Hz, Ar-H), 8.28 (d, 1H, J = 8.5 Hz, Ar-H); ^{13}C NMR (DMSO-d_6): δ 62.05 (C-6′), 67.79 (C-4′), 71.85 (C-2′), 73.05 (C-3′), 75.10 (C-5′), 85.27 (C-1′), 106.58 (C-3), 114.30 (C-5), 122.29 (CN), 122.98 (CN), 127.39–132.80 (Ar-10C), 154.32 (C-4), 157.33 (C-6), 161.81 (C-2); MS (FAB): m/z (%) = 464 (60, [M^+]). Anal. Calcd. for $C_{23}H_{20}N_4SO_5$: C, 59.47; H, 4.34; N, 12.06. Found: C, 59.40; H, 4.31; N, 12.00.

*4.1.5.6. 2-Amino-3,5-dicyano-4-(4-methoxyphenyl)-6-(1′-thio-β-D-galacto-pyranosyl)pyridines (**9f**).* Yield 2.36 g (53%) (Pale yellow powder): mp 143–144 °C; $[\alpha]_D$ = +26.8 (c 1.5, MeOH); IR (KBr) ν_{max} in cm^{-1}:3299 (OH and NH_2), 2208 (CN), 2200 (2CN); ^{1}H NMR (DMSO-d_6): δ 3.14 (m, 2H, H-6′, H-6″), 3.22 (m, 1H, H-5′), 3.46–3.51 (m, 2H, H-4′, H-3′), 3.80 (s, 3H, OCH_3), 4.21 (dd, 1H, J = 8.4 Hz, J = 9.8 Hz, H-2′), 4.74 (m, 1H, OH), 4.82 (t, 1H, J = 4.6 Hz, OH), 5.23 (m, 1H, OH), 5.26 (t, 1H, J = 4.8 Hz, OH), 5.74 (d, 1H, $J_{1'-2'}$ = 9.8 Hz, H-1′), 6.38 (bs, 2H, NH_2), 7.29 (d, 2H, J = 7.8 Hz, Ar-2H), 7.88 (d, 2H, J = 7.8 Hz, Ar-2H). ^{13}C NMR (DMSO-d_6): δ 55.80 (OCH_3), 62.10 (C-6′), 67.90 (C-4′), 72.11 (C-2′), 73.69 (C-3′), 75.03 (C-5′), 85.25 (C-1′), 106.01 (C-3), 115.30 (C-5), 122.98 (CN), 123.43 (CN), 126.69–132.58 (Ar-6C), 154.34 (C-4), 157.20 (C-6), 161.80 (C-2); MS (FAB): m/z (%) = 444 (54, [M^+]). Anal. Calcd. for $C_{20}H_{20}N_4SO_6$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.00; H, 4.50; N, 12.66.

5. Antitumor activity

5.1. Animals

Male Swiss albino mice (body weight 20 ± 2 g). They were kept for a week under environmentally controlled conditions (constant temperature 25–27 °C, with 12 h light/dark cycle) for one week prior to starting the experiments, and they were provided with tap water and commercial diets.

5.2. Cell line

Compounds were tested for their inhibition using human liver carcinoma cell line (HEPG2) and Human cervix carcinoma cell line (HELA). The cells were maintained by intraperitoneal inoculation of 1×10^6 viable cells in mice.

5.3. Ascites tumor model

Animals were divided into groups of 10 animals in each group. All the animals were injected i.p. with 1×10^6 viable (HEPG2) or (HELA) cells. After 24 h of tumor inoculation the prepared compounds were administered i.p. at dose of 10 μg/kg body weight and continued for 10 consecutive days. The group administered with vehicle alone (DMSO) was maintained as control. Cisplatine (2 mg/kg body weight, i.p., for 10 days) was used as the standard reference drug. The mortality rate was noted in each group and the percent increase in life span (ILS) was calculated as described by Ahluwalia et al. [42] and Joy et al. [43].

Table 2
In *vivo* acute toxicity of prepared compounds LD_{50} μg/kg b.w.

Compounds	LD_{50} μg/kg b.w. (HEPG2)	LD_{50} μg/kg b.w. (HELA)
5a	80	75
5c	90	90
5d	85	70
5e	150	160
5f	70	60
5g	65	70
5h	60	65
7a	65	75
7b	110	115
7e	110	95
7g	130	120
7h	60	80
8b	60	60
9c	65	75
8d	65	60
8e	125	135
8f	65	70
9b	130	110
9c	105	120
9e	145	125
9f	115	130

5.4. Assay of acute toxicity

The acute toxicity of the prepared compounds was determined *in vivo* according to Prieur et al. [44] and Ghosh [45]. Briefly, adult Swiss albino mice fasted for 12 h were randomly divided into groups of 10 per group. Each group was separately administrated once with gradually doses of the compounds intraperitoneal (i.p.) in a value of 1 ml/kg body weight. Control animals received the vehicle alone. The fasted mice in both test and control groups were then provided with food and water immediately after the administration. Mortality of the animals was observed up to two week post-treatment. LD_{50} (the median lethal doses) of each extract was determined (the dose resulted in 50% mortality of the animals) (Table 2).

5.5. Statistical analysis

Values are recorded as mean ± SE. The data were analyzed by Student's t-test; differences below the 0.5 level ($P < 0.05$) was considered as statistically significant.

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