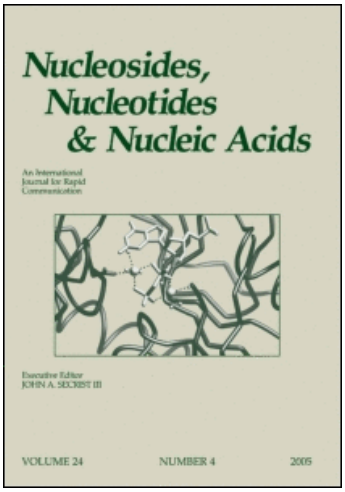

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Synthesis and Anti-HIV Activity of Different Novel Nonclassical Nucleosides

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SYNTHESIS AND ANTI-HIV ACTIVITY OF DIFFERENT NOVEL NONCLASSICAL NUCLEOSIDES

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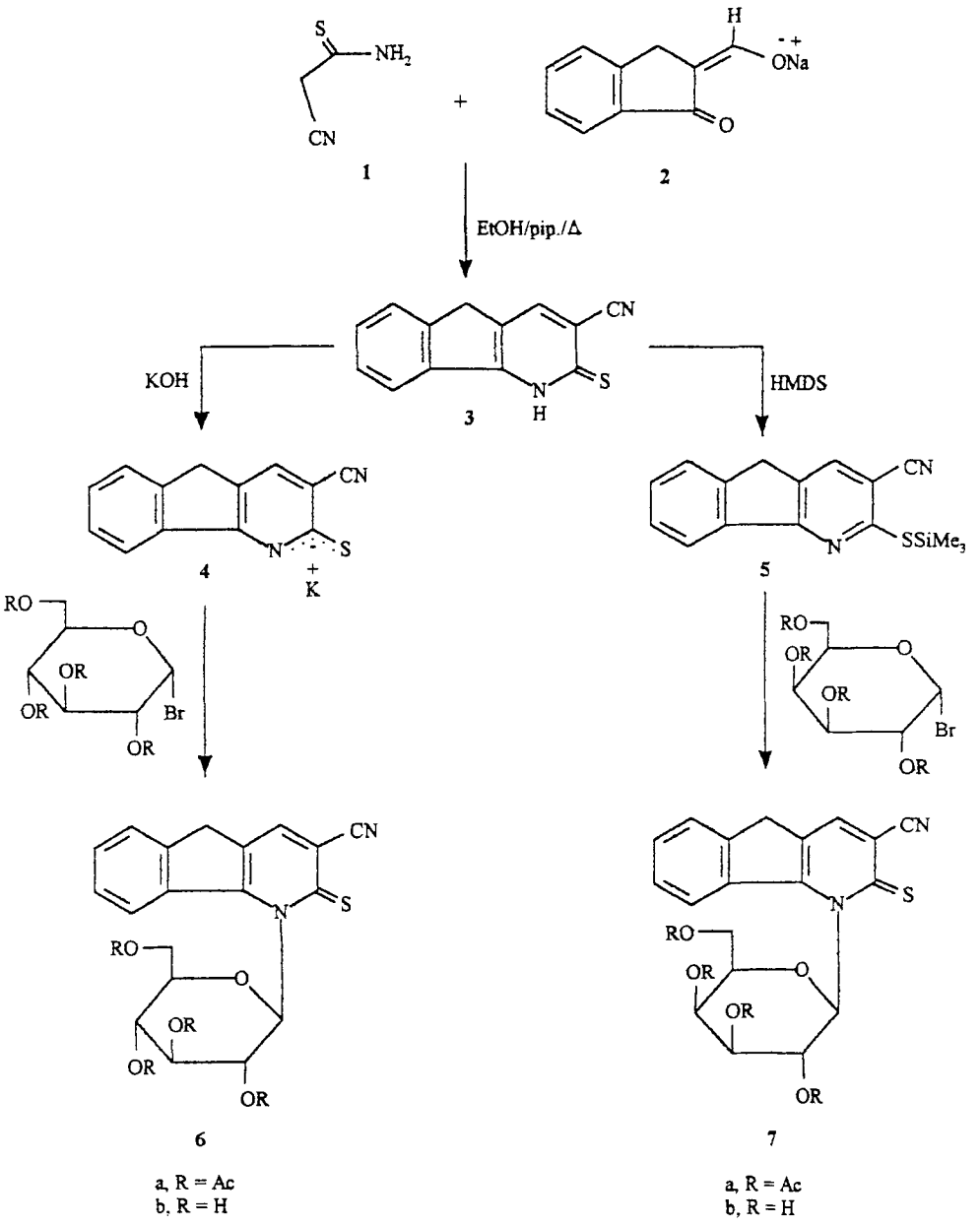
ABSTRACT- A series of different novel nonclassical nucleosides have been synthesised and evaluated for their inhibitory activity against human immunodeficiency virus (HIV) replication in MT-4 cells.

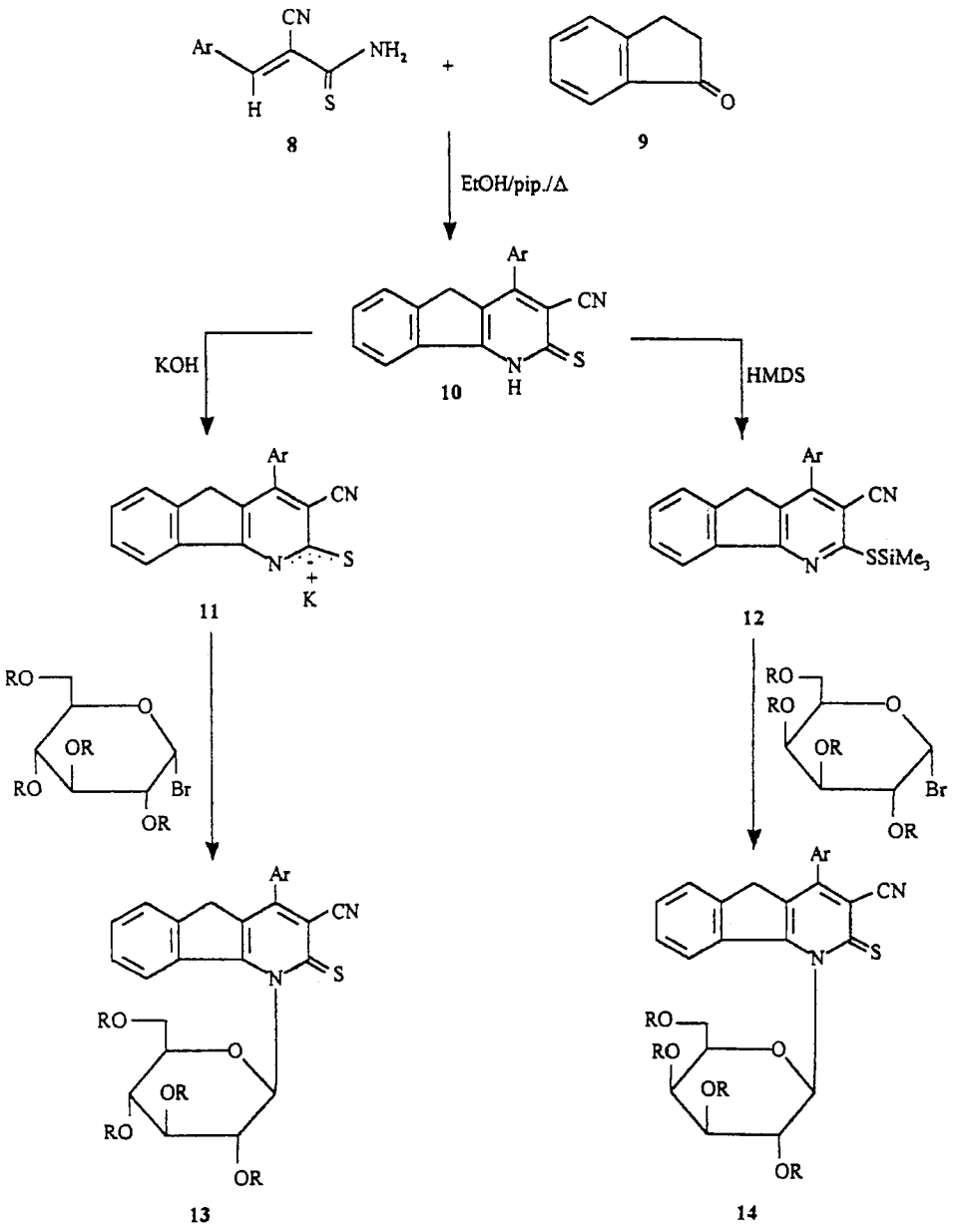
Since the discovery of the human immunodeficiency virus (HIV) as the causative agent of the acquired immunodeficiency syndrome, there has been a high interest in compounds that can block the replication of retroviruses. Considering the importance of the virus-encoded reverse transcriptase in the replication of HIV, this enzyme is an attractive target for the design of new effective chemotherapeutic agents. Since the discovery of the utility of 3 '-azido-3'-deoxythymidine (AZT) and 2',3'-dideoxyinosine (DDI) as antiretroviral agents in spite of their toxic side effects, the synthesis of other drugs has been desirable. Recently, a new class of anti HIV-1 agents has been identified. These compounds like 1-(benzyloxymethy1)-5-ethyl-6-(phenylthio)uracil (EBPU) and 1-[(2-hydroxyethoxy)-methyl]-6-(phenylthio)thymine (HEPT), show a high selectivity for the HIV-1 reverse transcriptase1. Other active related compounds related to HEPT and EBPU, like pyridinethione nucleosides were recently discovered in our laboratories, and all these compounds look promising as anti-HIV agents2-5. As an extension of our work on pyridinethione nucleosides, we report herein a novel synthesis of a new class of indano[1,2-b]pyridinethione nucleosides. The latter compounds will be considered as precursors of modified nucleosides. Also, we have tested these nucleosides against HIV.

Thus, it was found that cyanothioacetamide **1** reacted with the sodium salt of 2-(hydroxymethylene)-1-indanone **2** to give the indano[1,2-b]pyridine-2(1H)-thione **3**. The structure of **3** was established on the basis of its elemental analysis and spectral data as well as its mass

spectrum which showed a molecular ion corresponding to (M^+ 223). 1H-NMR spectroscopy also confirmed this structure for this product. Thus, 1H-NMR spectrum revealed a singlet at 7.77 ppm assigned for pyridine H-4 proton and a broad band at 13.80 ppm assigned to the N(1)-proton. Compound **3** reacted with 2,3,4,6-tetra-O-acetyl-α-D-gluco- and -galacto-pyranosyl bromides in the presence of aqueous potassium hydroxide to give the correspounding N-glucoside **6a** and N-galactoside **7a**, respectively. Although the coupling of **3** with the glycosyl bromides could also give the corresponding thioglycosides, the formation of **6a** and **7a** was proved chemically. Reaction of **3** with hexamethyldisilazane (HMDS) in the presence of ammonium sulfate gave the corresponding 3-cyano-indano[1,2-b]-2-trimethylsilylthiopyridine **5**, which was subsequently treated with peracetylated sugars in the presence of redistilled $SnCl_4$ to afford the corresponding N-glycosyl compounds. All the previous literature reported that Lewis acid-induced coupling reactions of S-silylated heterocyclic bases with peracetylated sugars gave the corresponding N- nucleosides as the sole heterocyclic product6,7. The structures of the reaction products **6a** and **7a** were established and confirmed by their elemental analyses and spectral data (MS, IR, UV, 1H-NMR, 13C-NMR). The analytical data for **6a** revealed a molecular ion corresponding to (M^+ 554). The 1H-NMR spectrum showed the anomeric proton as a doublet at 5.51-5.59 ppm with a spin-spin coupling constant of 8.30 Hz corresponding to a diaxial orientation of H-1' and H-2' protons and indicating the β-configuration, while the other six glucose protons resonated at 4.22-5.51 ppm. The ^{13}C-NMR spectrum of **6a** contained a signal at 93.8 corresponding to the C-1' atom of the β-configuration. Four signals appearing at 67.5, 67.8, 70.1 and 71.1 ppm were assigned to C-6', C-4', C-2', C-3' and C-5', respectively. The UV spectrum of **6a** proved that the reaction had led selectively to the formation of N-glycosyl derivatives and excluded substitution at the sulfur atom. Thus, whereas the S-methyl derivative of **3** showed two maxima at 275 (17.6) and 320 (7.8) nm, its N-glucosyl derivative exhibited three maxima at 268 (18.2), 322 (11.4) and 367 (22.3) nm. After deprotection of compounds **6a** and **7a** with a saturated solution of ammonia in methanol the free nucleosides **6b** and **7b** were obtained in almost quantitative yields, the structures of which were established on the basis of elemental analyses and spectral data. The analytical data for **7b** reveal the molecular ion corresponding to (M^+ 386). The 1H- NMR spectrum showed the anomeric proton as a doublet at 5.67 ($J_{1'2'}$ = 9.70 Hz) ppm indicating the presence of only the β-D-configuration, while the signals of the four hydroxy groups of the glucose moiety are observed at 4.48-5.20 ppm (exchangable by D_2O). The 13C-NMR spectrum of **7b** is characterized by a signal at 83.2 ppm corresponding to the C-1' atom of β-D- glucopyranose. Another five signals at 60.7, 69.7, 71.7, 78.8 and 81.6 ppm were assigned to C-6', C-4', C-2', C-3' and C-5', respectively. The 4-aryl-3-cyano-indano[1,2-b]pyridine-2(1H)-thiones **10** were prepared by the reaction of (arylmethylene)(cyano)thioacetamide **8** with 1-indanone **9** in boiling ethanol containing catalytic



amounts of piperidine. The structure of compounds **10** were established on the basis of their elemental analysis and spectral data (MS, IR, 1H-NMR). The mass spectrum of **10a** was compatible with the molecular formula $C_{19}H_{10}ClN_2S$ (M^+ 334) and The 1H-NMR spectrum had signals at 2.60 (s, CH_2), 7.21-8.02 (m, ArH) and 14.2 (br, NH) ppm. The formation of **10** from **8** and **9** proceeds most likely via addition of the active methylene group of **9** to the double bond of



13, 14	Ar	R	Ar	R
	a, 4-ClC_6H_4	Ac	e, 4-ClC_6H_4	H
	b, 4-$CH_3C_6H_4$	Ac	f, 4-$CH_3C_6H_4$	H
	c, 4-$CH_3OC_6H_4$	Ac	g, 4-$CH_3OC_6H_4$	H
	d, 4-$(CH_3)_2NC_6H_4$	Ac	h, 4-$(CH_3)_2NC_6H_4$	H

Table 1: Comparative potency and selectivity of 3-cyano-1-(2,3,4,6-tetra-O-acetyl-β-D-gluco-and-galactopyranosyl)-indano[1,2-b]pyridine-2(1H)-thiones **13c, 13e** and **14a** as inhibitors of HIV replication in MT-4 cells.

Compd	EC_{50}[a] μM	IC_{50}[b] μM	TI[c] (ratio IC_{50} / EC_{50})
13c	1.79	8.91	4.98
13e	0.166	3.01	18.1
14a	5.56	8.76	1.57

a. Approximate values for 50% effective concentration of MT-4 cells against the cytopathic effect of HIV (EC_{50}).

b. Inhibitory concentration for 50% (IC_{50}).

c. Therapeutic index TI (IC_{50}/EC_{50}).

8 to give intermediate Michael adducts, which then cyclize via water elimination and oxidation under the reaction conditions to yield **10**. Compounds **10** reacted with 2,3,4,6-tetra-O-acetyl-α-D-gluco- and -galacto-pyranosyl bromides in the presence of aqueous potassium hydroxide via an intermediary acyl oxonium ion to afford the corresponding N-glucosides **13a-d** and N-galactosides **14a-d.** The structures of the reaction products **13a-d** and **14a-d** were established and confirmed on the basis of their elemental analyses and spectral data (MS, IR, UV, 1H-NMR, 13C-NMR). When compounds **13a-d** and **14a-d** were treated with methanolic ammonia at 0° C, the free glycoside derivatives **13e-h** and **14e-h** were obtained, the structures of which were established on the basis of elemental analysis and spectral data. The IR spectrum of **13e** showed a band at 3600-3200 cm^{-1} due to the hydroxy groups of the glucose moiety. The 1H-NMR spectrum showed the anomeric proton as a doublet at 5.42 ($J_{1',2'}$ = 9.55 Hz) ppm indicating the presence of only the β-configuration. The other six glucose protons appeared as a multiplet at 3.18-3.70 ppm, while the four hydroxy groups of the glucose moiety resonated at 4.40-5.18 ppm (exchangeable by D_2O).

Antiviral Activity

The anti-HIV activity and cytotoxicity of the indano[1,2-b]pyridine-2(1H)-thione nucleoside derivatives are shown inTable 1. Among the acetylated derivatives, compound **13c** turned out to be the most selective anti-HIV agent, followed by **14a**. The other compounds were virtually devoid of any anti-HIV activity. Among the free glycoside derivatives, the free nucleoside **13e**

proved clearly more active and selective than the corresponding protected derivative. None of the other rest of free sugars showed any selectivity and/or antiviral activity. Since compounds **6**, **7**, **13** and **14** belong to a new class of active nucleosides and also were active against HIV, further investigations are needed in order to determine the mechanism of their action against HIV.

Experimental

All evaporations were carried out under reduced pressure at 40°C. Melting points were uncorrected. Aluminium sheets [silica gel 60 F_{254} (Merck)] were used for TLC; spots were detected by viewing under a short-wavelength UV lamp. IR spectra were obtained (KBr disc) on a Pye Unicam Spectra-1000 spectrophotometer. 1H-NMR and 13C-NMR spectra were measured on Wilmad 270 MHz or Varian 400 MHz spectrometers for solution in (DMSO-d_6 or $CDCl_3$) using SiMe4 as internal standard. Mass spectra were recorded on a Varian MAT 112 spectrometer. Analytical data were obtained from the Microanalytical Data Center at Cairo University.

3-Cyano-indano[1,2-b]pyridine-2(1H)-thione 3.

A solution of 2-(hydroxymethylene)-1-indanone **2** (0.01mol), cyanothioacetamide **1** (0.01mol) and piperidine acetate (0.95 ml) [prepared from glacial acetic acid (0.42 ml), water (1ml) and piperidine (0.72 ml)] in water (5 ml) was refluxed for 10 minutes. Acetic acid (1.5 ml) was added to the hot solution. The precipitated solid was collected by filtration and recrystallized from the appropriate solvent.

3: mp 250 °C, yield 90%. IR (KBr) υ 2220 (CN), 3450-3400 (NH); 1H-NMR (DMSO-d_6) δ 2.32 (s, 2H, CH_2), 7.77 (s, 1H, pyridine H-4), 7.60-8.02 (m, 4H, Ar-H), 13.80 (s, br, 1H, NH); m/z 223 (Found: C, 69.8; H, 3.0; N, 12.3; S, 14.1. $C_{13}H_7N_2S$ calculated C, 70.0; H, 3.1; N, 12.5; S, 14.3%).

4-Aryl-3-cyano-indano[1,2-b]pyridine-2(1H)-thiones 10a-d.

To a mixture of (arylmethylene)(cyano)thioacetamides (0.01 mol) **8a-d** and 1-indanone **9** (0.01 mol) in ethanol (50 ml) was added, piperidine (0.3 ml). The reaction mixture was heated under reflux for 3 hr, and then set aside overnight. The resultant precipitate was filtered off and recrystallized from EtOH/dioxane to yield coloured crystals.

10a: mp 295 °C, yield 93%. IR (KBr) υ 2221 (CN), 3450-3400 (NH); 1H-NMR (DMSO-d_6) δ 2.60 (s, 2H, CH_2), 7.21-8.02 (m, 8H, Ar-H), 14.20 (s, br, 1H, NH); m/z 334 (Found: C, 68.0; H, 2.7; N, 8.6; S, 9.7. $C_{19}H_{10}ClN_2S$ calculated C, 68.2; H, 3.0; N, 8.5; S, 9.5%).

10b: mp 240 °C, yield 85%. IR (KBr) υ 2220 (CN), 3450-3400 (NH); 1H-NMR (DMSO-d_6) δ 2.35 (s, 3H, CH_3), 2.60 (s, 2H, CH_2), 7.40-8.10 (m, 8H, Ar-H), 13.95 (s, br, 1H, NH); m/z 313 (Found: C, 76.8; H, 3.9; N, 9.1; S, 10.0. $C_{20}H_{13}N_2S$ calculated C, 76.6; H, 4.1; N, 8.9; S, 10.2%).

10c: mp 288 °C, yield 85%. IR (KBr) υ 2219 (CN), 3450-3400 (NH); 1H-NMR (DMSO-d_6) δ 2.67 (s, 2H, CH_2), 3.75 (s, 3H, OCH_3), 7.40-8.20 (m, 8H, Ar-H), 14.10 (s, br, 1H, NH); m/z 329 (Found: C, 73.1; H, 3.8; N, 8.7; S, 9.5. $C_{20}H_{13}N_2OS$ calculated C, 72.9; H, 4.0; N, 8.5; S, 9.7%).

10d: mp 310 °C, yield 87%. IR (KBr) υ 2221(CN), 3450-3400 (NH); 1H-NMR (DMSO-d_6) δ 2.60 (s, 2H, CH_2), 2.68 (s, 6H, $2CH_3$), 7.45-8.15(m, 8H, Ar-H), 14.21(s, br, 1H, NH); m/z 342 (Found: C, 73.4; H, 4.4; N, 12.0; S, 9.5. $C_{21}H_{16}N_3S$ calculated C, 73.6; H, 4.6; N, 12.2; S, 9.3%).

3-Cyano-1-(2,3,4,6-tetra-O-acetyl-β-D-gluco- and -galactopyranosyl)-indano[1,2-b]-pyridine-2(1H)-thiones 6a, 7a , 13a-d and 14a-d.

General procedure:

Method A. To a solution of the 3-cyano-indano[1,2-b]pyridine-2(1H)-thione **3** and/or 3-cyano-4-arylindano[1,2-b]pyridine-2(1H)-thiones **10a-d** (0.01 mol) in aqueous potassium hydroxide [0.56 g (0.01 mol) in 6 ml of distilled water], a solution of 2,3,4,6-tetra-O-acetyl-α-D-gluco- or -galacto-pyranosyl bromide (4.52 g, 0.01 mol) in acetone (30 ml) was added. The reaction mixture was stirred at room temperature for 60 min, then evaporated under reduced pressure at 40 °C, and the residue washed with distilled water to remove the formed potassium bromide. The product was dried and recrystallized from ethanol to afford pale yellow crystals.

Method B. The 3-cyano-indano[1,2-b]pyridine-2(1H)-thione **3** and /or 3-cyano-4-aryl-indano-[1,2-b]pyridine-2(1H)-thiones **10a-d** (0.01 mol) were boiled under reflux and anhydrous conditions for 48 hours with hexamethyldisilazane (25 ml) and $(NH_4)_2SO_4$ (0.02 g). The excess hexamethyldisilazane was removed under diminished pressure to provide the silylated bases **5** and **12** as a colourless oils. To a solution of the silylated base in dry MeCN (30 ml), a solution of α-D-glucose- or α-D-galactose pentaacetate (0.01 mol) in dry MeCN (20 ml) was added followed by the addition of $SnCl_4$ (1.6 ml). The reaction mixture was stirred at room temperature until the reaction was completed as indicated by TLC (3 to 6 h). The solution was poured into a saturated $NaHCO_3$ solution and extracted with $CHCl_3$. The organic layers were dried over $MgSO_4$, filtered and concentrated to give the crude nucleosides which were purified by recrystallization from EtOH to afford pale yellow crystals.

6a: mp 220 °C, yield 70%. UV (EtOH), λmax 268 (18.2), 322 (11.4), 367 (22.3) nm; IR (KBr) 2218 (CN), 1745(CO); 1H-NMR (DMSO-d_6) δ 1.99-2.05 (4s, 12H, $4CH_3CO$), 2.32 (s, 2H, CH_2), 3.84 (m, 1H, H-5'), 4.22 (d, 2H, 2H-6'), 5.10-5.51 (m, 3H, H-4', H-3', H-2'), 5.95 (d, 1H, H-1'), 7.30-8.0 (m, 4H, Ar-H), 8.40 (s, 1H, pyridine H-4); m/z 554 (Found: C, 58.6; H, 4.8; N, 5.2; S, 5.8. $C_{27}H_{26}N_2O_9S$ calculated C, 58.4; H, 4.7; N, 5.0; S, 5.7%).

7a: mp 220 °C, yield 70%. IR (KBr) 2219 (CN), 1746(CO); 1H-NMR (DMSO-d_6) δ 1.98-2.05 (4s, 12H, $4CH_3CO$), 2.34 (s, 2H, CH_2), 3.84 (m, 1H, H-5'), 4.22 (d, 2H, 2H-6'), 5.10-5.40 (m,

3H, H-4′, H-3′, H-2′), 5.95 (d, 1H, H-1′), 7.30-8.0 (m, 4H, C_6H_4), 8.40 (s, 1H, pyridine H-4); m/z 554 (Found: C, 58.3; H, 4.6; N, 5.2; S, 5.5. $C_{27}H_{26}N_2O_9S$ calculated C, 58.4; H, 4.7; N, 5.0; S, 5.7%).

13a: mp 196 °C, yield 85%. IR (KBr) 2222 (CN), 1744(CO); 1H-NMR (DMSO-d_6) δ 1.98-2.05 (4s, 12H, $4CH_3CO$), 2.60 (s, 2H, CH_2), 3.90 (m, 1H, H-5′), 4.10 (d, 2H, 2H-6′), 5.11-5.37 (m, 3H, H-4′, H-3′, H-2′), 5.93 (d, 1H, H-1′), 7.35-8.02 (m, 8H, $2C_6H_4$); m/z 664 (Found: C, 59.4; H, 4.5; N, 4.1; S, 4.6. $C_{33}H_{29}ClN_2O_9S$ calculated C, 59.5; H, 4.3; N, 4.2; S, 4.8%).

13b: mp 180 °C, yield 75%. IR (KBr) 2222 (CN), 1745(CO); 1H-NMR (DMSO-d_6) δ 1.99-2.04 (4s, 12H, $4CH_3CO$), 2.05 (s, 3H, CH_3),2.65 (s, 2H, CH_2) 3.90 (m, 1H, H-5′), 4.40 (d, 2H, 2H-6′), 5.61-6.0 (m, 3H, H-4′, H-3′, H-2′), 6.25 (d, $J_{1,2}$ 10.32 Hz, 1H, H-1″), 7.35-8.02 (m, 8H, $2C_6H_4$); m/z 644 (Found: C, 63.0; H, 5.1; N, 4.5; S, 4.7. $C_{34}H_{32}N_2O_9S$ calculated C, 63.2; H, 4.9; N, 4.3; S, 4.9%).

13c: mp 205 °C, yield 86%. IR (KBr) 2210 (CN), 1746(CO); 1H-NMR (DMSO-d_6) δ 1.98-2.02 (4s, 12H, $4CH_3CO$), 2.35 (s, 2H, CH_2), 2.75 (s, 3H, OCH_3) 3.95 (m, 1H, H-5′), 4.08-4.16 (d, 2H, 2H-6′), 5.50 (m, 3H, H-4′, H-3′, H-2′), 6.30 (d, $J_{1,2}$ 10.22 Hz, 1H, H-1″), 7.20-8.0 (m, 8H, $2C_6H_4$); m/z 660 (Found: C, 61.6; H, 4.6; N, 4.0; S, 4.6. $C_{34}H_{32}N_2O_{10}S$ calculated C, 61.6; H, 4.7; N, 4.2; S, 4.8%).

13d: mp 215 °C, yield 78%. IR (KBr) 2222 (CN), 1744(CO); 1H-NMR (DMSO-d_6) δ 1.99-2.04 (4s, 12H, $4CH_3CO$), 2.63 (s, 2H, CH_2), 2.70 (s, 6H, $2CH_3$), 3.90 (m, 1H, H-5′), 4.40 (d, 2H, 2H-6′), 5.61-6.0 (m, 3H, H-4′ H-3′, H-2′), 6.25 (d, $J_{1,2}$ 10.32 Hz, 1H, H-1′), 7.35-8.02 (m, 8H, $2C_6H_4$); m/z 673 (Found: C, 62.1; H, 4.9; N, 6.0; S, 4.5. $C_{35}H_{35}N_3O_9S$ calculated C, 62.4; H, 5.2; N, 6.2; S, 4.7%).

14a: mp 185 °C, yield 75%. IR (KBr) 2210 (CN), 1750(CO); 1H-NMR (DMSO-d_6) δ 1.78-2.02 (4s, 12H, $4CH_3CO$), 2.60 (s, 2H, CH_2), 3.85 (m, 1H, H-5′), 4.60 (d, 2H, 2H-6′), 5.20-5.62 (m, 3H, H-4′, H-3′, H-2′), 6.31 (d, 1H, H-1′), 7.40-8.02 (m, 8H, $2C_6H_4$); m/z 664 (Found: C, 59.4; H, 4.4; N, 4.0; S, 4.9. $C_{33}H_{29}ClN_2O_9S$ calculated C, 59.6; H, 4.3; N, 4.2; S, 4.8%).

14b: mp 173 °C, yield 80%. IR (KBr) 2215 (CN), 1755(CO); 1H-NMR (DMSO-d_6) δ 1.99-2.04 (4s, 12H, $4CH_3CO$), 2.05 (s, 3H, CH_3),2.60 (s, 2H, CH_2) 3.80 (m, 1H, H-5′), 4.42 (d, 2H, 2H-6′), 5.55-6.10 (m, 3H, H-4′, H-3′, H-2′), 6.20 (d, $J_{1,2}$ 10.32 Hz, 1H, H-1′), 7.20-8.10 (m, 8H, $2C_6H_4$); m/z 644 (Found: C, 63.1; H, 5.1; N, 4.5; S, 4.7. $C_{34}H_{32}N_2O_9S$ calculated C, 63.3; H, 4.9; N, 4.3; S, 4.9%).

14c: mp 175 °C, yield 84%. IR (KBr) 2210 (CN), 1752(CO); 1H-NMR (DMSO-d_6) δ 1.99-2.10 (4s, 12H, $4CH_3CO$), 2.30 (s, 2H, CH_2), 3.85(s, 3H, OCH_3), 3.85 (m, 1H, H-5′), 4.60-4.80 (d, 2H, 2H-6′), 5.21-5.80 (m, 3H, H-4′, H-3′, H-2′), 6.35 (d, $J_{1,2}$ 10.12 Hz, 1H, H-1″), 7.10-8.40 (m, 8H, $2C_6H_4$); m/z 660 (Found: C, 61.6; H, 4.6; N, 4.0; S, 4.7. $C_{34}H_{32}N_2O_{10}S$ calculated C, 61.8; H, 4.8; N, 4.2; S, 4.8%).

14d: mp 160 °C, yield 80%. IR (KBr) 2210 (CN), 1751(CO); 1H-NMR (DMSO-d_6) δ 1.82-2.20 (4s,12H, $4CH_3CO$), 2.65 (s, 2H, CH_2), 3.00 (s, 6H, $2CH_3$), 3.85 (m, 1H, H-5'), 4.60 (d, 2H, 2H-6') 5.22-5.85 (m, 3H, H-4', H-3'H-2'), 6.35 (d, $J_{1,2}$ 10.20 Hz, 1H, H-1'), 7.35-8.20 (m, 8H, $2C_6H_4$); m/z 673 (Found: C, 62.6; H, 5.3; N, 6.0; S, 4.5. $C_{35}H_{35}N_3O_9S$ calculated C, 62.4; H, 5.2; N, 6.2; S, 4.7%).

3-Cyano-1-(β-D-gluco- and -galactopyranosyl)-indano- pyridine-2(1H)-thiones 6b, 7b , 13e-h and 14e-h.

General procedure:

Dry gaseous NH_3 was passed through a solution of protected nucleosides **6a, 7a , 13a-d** and **14a-d** (0.5 g) in dry MeOH (25 ml) at 0 °C for about 0.5 h, then the reaction mixture was stirred until judged complete by TLC (4 to 18 h). The resulting reaction mixture was evaporated under reduced pressure at 40 °C giving a solid residue which was crystallized from EtOH to afford pale yellow crystals.

6b: mp 200 °C, yield 70%. IR (KBr) 2218 (CN), 3600-3200 (OH); 1H-NMR (DMSO-d_6) δ 2.65 (s, 2H, CH_2), 3 .15-3.80 (m, 6H, 2H-6', H-5',H-4', H-3' and H-2'), 4.55 (m, 2H,OH-1' and OH-3'), 5.02 (d, J 9.8 Hz, 1H, OH-4'), 5.35 (d, J 10.5 Hz, 1H, OH-6'), 5.65 (d, $J_{1,2}$ 10.55 Hz, 1H, H-1'), 7.27-7.99 (m, 4H, C_6H_4), 8.32 (s, 1H, pyridine H-4); m/z 386 (Found: C, 59.2; H, 4.4; N, 7.0; S, 8.0. $C_{19}H_{18}N_2O_5S$ calculated C, 59.0; H, 4.6; N, 7.2; S, 8.3%).

7b: mp 200°C, yield 70%. IR (KBr) 2218 (CN), 3600-3200 (OH); 1H-NMR (DMSO-d_6) δ 2.74 (s, 2H, CH_2), 3 .23-3.71 (m, 6H, 2H-6', H-5', H-4', H-3'and H-2'), 4.48 (t, 1H, 3'-OH), 5.00 (d, 1H,2'-OH), 5.02 (d, J 10 Hz, 1H, 4'-OH), 5.67 (d, $J_{1',2'}$ = 9.70 Hz, 1H, 1'-OH and 1H, 6'-OH'), 6.92-7.82 (m, 4H, C_6H_4), 8.09 (s, 1H, pyridine H-4); 13C-NMR (DMSO) δ 26.4 (CH_2), 60.7 (C-6'), 69.7 (C-4'), 71.7 (C-2'), 78.8 (C-3'), 81.6 (C-5'), 83.2 (C-1'), 107.0 (C-4), 115 (CN), 122.2-138.2 (aromatic-C), 153.8 (C-5), 157.3 (C-6), 158.4 (C-3) and 163.1 (C=S); m/z 386 (Found: C, 59.3; H, 4.4; N, 7.4; S, 8.1. $C_{19}H_{18}N_2O_5S$ calculated C, 59.0; H, 4.6; N, 7.2; S, 8.3%).

13e: mp 250 °C, yield 70%. IR (KBr) 2219 (CN), 3600-3200 (OH); 1H-NMR (DMSO-d_6) δ 2.75 (m, 4H, $2CH_2$), 3 .18-3.70 (m, 6H, 2H-6', H-5'H-4', H-3'and H-2'), 4.40 (t, 1H, H-4', H-3', H-2'), 5.02 (d, 1H, 2'-OH), 5.18 (d, J 9.8 Hz, 1H, 4'-OH), 5.42 (d, $J_{1',2'}$ = 9.55 Hz, 1H, H-1'and 1H, 6'-OH), 7.02-8.00 (m, 8H, $2C_6H_4$); 13C-NMR (DMSO) δ 28.6 (CH_2), 60.2 (C-6'), 66.6 (C-4'), 71.9 (C-2'), 79.5 (C-3'), 82.3 (C-5'), 85.2 (C-1'), 105.2 (C-3), 116.2 (CN), 127.2-162.3 (Ar-C), 150.2 (C-5), 152.9 (C-6), 156.2 (C-4) and 162.2 (C=S); m/z 497 (Found: C, 60.1; H, 4.0; N, 5.3; S, 6.2. $C_{25}H_{21}ClN_2O_5S$ calculated C, 60.3; H, 4.2; N, 5.6; S, 6.4%).

13f: mp 250 °C, yield 70%. IR (KBr) 2219 (CN), 3600-3200 (OH); m/z 476 (Found: C, 65.3; H, 4.8; N, 5.1; S, 6.5. $C_{26}H_{24}N_2O_5S$ calculated C, 65.5; H, 5.0; N, 5.8; S, 6.7%).

13g: mp 250 °C, yield 70%. IR (KBr) 2219 (CN), 3600-3200 (OH); 1H-NMR (DMSO-d_6) δ 2.62 (m, 4H, $2CH_2$), 3.22-3.80 (m, 6H, 2H-6′, H-5′,H-4′, H-3′and H-2′), 3.92 (s, 3H, OCH_3), 4.58 (m, 2H, 2′-OH and 3′-OH), 4.92 (t, 1H, 4′-OH), 5.36 (t, 1H, 6′-OH), 5.62 (d, $J_{1',2'}$ = 9.72 Hz, 1H, H-1′), 6.92-8.05 (m, 8H, $2C_6H_4$); m/z 492 (Found: C, 63.2; H, 4.6; N, 5.5; S, 6.5. $C_{26}H_{24}N_2O_6S$ calculated C, 63.4; H, 4.8; N, 5.7; S, 6.3%).

13h: mp 250 °C, yield 70%. IR (KBr) 2219 (CN), 3600-3200 (OH); m/z 505 (Found: C, 63.9; H, 5.1; N, 8.1; S, 6.1. $C_{27}H_{27}N_3O_5S$ calculated C, 64.1; H, 5.3; N, 8.3; S, 6.3%).

14e: mp 250 °C, yield 70%. IR (KBr) 2220(CN), 3600-3200 (OH); m/z 497 (Found: C, 60.5; H, 4.4; N, 5.3; S, 6.2. $C_{25}H_{21}ClN_2O_5S$ calculated C, 60.3; H, 4.2; N, 5.6; S, 6.4%).

14f: mp 250 °C, yield 75%. IR (KBr) 2216 (CN), 3600-3200 (OH); 1H-NMR (DMSO-d_6) δ 2.35 (s, 3H, CH_3), 2.65 (s, 2H, CH_2), 3.25-3.82 (m, 6H, 2H-6′, H-5′, H-4′, H-3′and H-2′), 4.22 (t, 2H, 2′-OH and 3′-OH) 4.69 (d,1H,4′-OH), 5.42 (d, 1H, 6′-OH), 5.67 (d, 1H, d, $J_{1',2'}$ =10.30 Hz, H-1′), 7.02-8.09 (m, 8H, $2C_6H_4$); m/z 476 (Found: C, 65.7; H, 4.8; N, 5.10; S, 6.5. $C_{26}H_{24}N_2O_5S$ calculated C, 65.5; H, 5.0; N, 5.8; S, 6.7%).

14g: mp 250 °C, yield 78%. IR (KBr) 2219 (CN), 3600-3200 (OH); m/z 492 (Found: C, 63.6; H, 4.6; N, 5.5; S, 6.5. $C_{19}H_{18}N_2O_5S$ calculated C, 63.4; H, 4.8; N, 5.7; S, 6.6%).

14h: mp 250 °C, yield 70%. IR (KBr) 2219 (CN), 3600-3200 (OH); 1H-NMR (DMSO-d_6) δ 2.51 (s, 2H, CH_2), 2.68 (s, 6H, $2CH_3$), 3.32-3.73 (m, 6H, 2H-6′, H-5′, H-4′, H-3′and H-2′), 4.50 (s, 2H, 2′-OH and 3′-OH) 4.88 (s,1H, 4′-OH), 5.28 (s, 1H, 6′-OH), 5.55 (d, 1H, d, $J_{1',2'}$ =10.09 Hz, H-1′), 7.11-8.10 (m, 8H, $2C_6H_4$); m/z 505 (Found: C, 63.9; H, 5.1; N,8.1; S,6.1. $C_{27}H_{27}N_3O_5S$ calculated C, 64.1; H, 5.3; N, 8.3; S, 6.3%).

Biological Procedure

The compounds **6a-b**, **7a-b**, **13a-h** and **14a-h**, were dissolved in dimethyl sulfoxide then diluted 1:100 in cell culture medium before preparing serial half-log_{10} dilutions. T_4 lymphocytes were added and after a brief interval HIV-1 was added, resulting in 1:20 final dilution of the compound. Uninfected cells with the compound served as a toxicity control, and infected and uninfected cells without the compound served as basic controls. Cultures were incubated at 37°C in a 5% carbon dioxide atmosphere for 6 days. The tetrazolium salt, XTT, was added to all wells, and cultures were incubated to allow formazan color development by viable cells. Individual wells were analyzed spectrophotometrically to quantitate formazan production, and in addition were viewed microscopically for detection of viable cells and confirmation of protective activity. Drug-treated virus-infected cells were compared with drug-treated noninfected cells and with other appropriate controls on the same plate. Data were reviewed in comparison with other tests done at the same time and a determination about activity was made.

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