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# Synthesis of 3-Thiosemicarbazone and 3-Hydrazone Derivatives of Isatin Nucleosides as Promising Bioactive Compounds

**Omar Abdulateef Mohammed[1,*] Thanaa M. Al-Mouamin[1]**
[1] *Department of Chemistry, College of Science, University of Baghdad, Baghdad, Iraq*

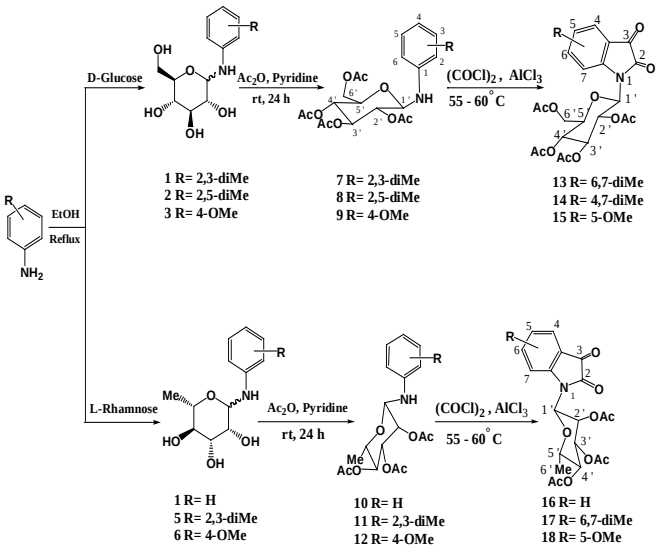
**Abstract**

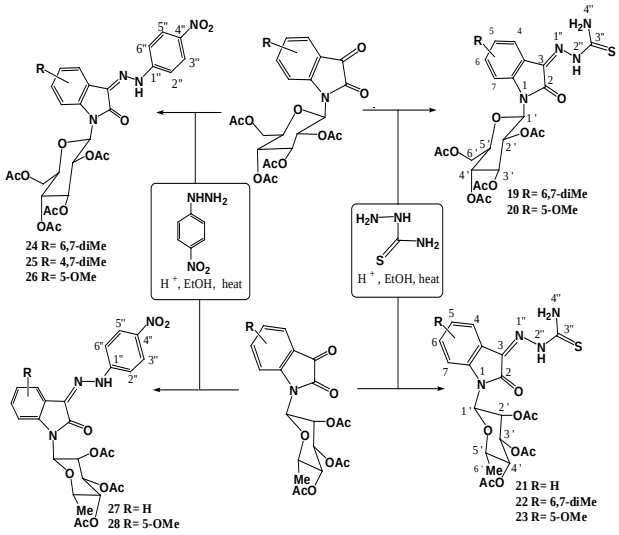
This work describes the synthesis of new nucleoside analogues with substituted isatin as nucleobase, in addition to their 3-thiosemicarbazone and 3-(4-nitrophenyl)hydrazone derivatives. The synthetic route towards isatin nucleosides **13-18** is commenced by the glycosylation of different anilines with D-glucose and with L-rhamnose, and subsequent *O*-acetylation by $Ac_2O$/pyridine to afford the per *O*-acetylated N-arylglycopyranosylamines **7-12**. Intramolecular cyclization of the N-arylglycopyranosylamines **7-12** with oxalyl chloride in the presence of anhydrous $AlCl_3$ furnished the desired isatin nucleosides **13-18**. The new 3-ketimine derivatives **19-28** of isatin nucleosides were simply prepared in high yield and purity. Characterization and structure determination of the synthesized compounds were accomplished by FTIR, $^1$H NMR and $^{13}$C NMR spectroscopy.

**Keywords:** Isatin; Nucleoside analogues; Thiosemicarbazone; Hydrazone.

## 1. INTRODUCTION

Nucleosides and nucleotides are endogenous compounds that are involved in several cellular processes such as DNA and RNA synthesis, cell signaling, enzyme regulation and metabolism. Nucleoside and nucleotide analogues, on the other hand, are synthetic, chemically modified compounds that have been developed to mimic their physiological parents in order to exploit cellular metabolism and subsequently be incorporated into DNA and RNA to inhibit cellular division and viral replication[(1)]. This action is of great value for the treatment of cancer and viral infections in addition to various other indications such as immunomodulation[(2,3)], antiparasite chemotherapy[(4)], epigenetic modulation[(5)] and neuro and cardioprotection[(6)]. Furthermore, nucleoside analogues can interact with and inhibit essential enzymes such as human and viral DNA and RNA polymerases[(7)], kinases[(8,9)], DNA methyltransferases[(7)], PNP[(10)], RNR[(11)] and TS[(7)]. Moreover, nucleoside antibiotics, the naturally occurring nucleoside analogues, are known to possess many biological activities, including anticancer, antiviral, antibacterial, antifungal and antiparasitic activity[(12,13)]. Nevertheless, in spite of the availability of a valuable number of nucleoside analogues that are currently in clinical use, there is a pressing need for the development of newer agents with improved activities and properties to eliminate or suppress the problems of resistance, long-term toxicity, poor oral availability[(1,14,15)], etc.




**Scheme 1: Synthesis of isatin nucleosides 13-18, their 3-thiosemicarbazones 19-23 and 3-(4-nitrophenyl)hydrazones 24-28, with numbering of the atoms for NMR assignment.**

These observations have encouraged us to search for new nucleoside analogues with promising bioactivity to expand the repertoire of available such compounds in chemotherapy study. Isatin and its derivatives have been found to exhibit a wide spectrum of pharmacological properties, and as building block, isatin represents one of the most versatile molecules in the chemical synthesis. For instance, utilizing the electrophilic and nucleophilic character of isatin, several heterocyclic systems have been developed, such as pyrrolidines, quinolines, indoles, β-lactams and oxindoles[(16-18)]. However, the literature reports few studies on the synthesis of isatin nucleosides[(19-22)]. This work, therefore, is aimed to synthesize new isatin nucleosides diversely substituted with electron-releasing groups on aromatic isatin ring as well as their 3-thiosemicarbazone and 3-(4-nitrophenyl)hydrazone derivatives.

## 2. EXPERIMENTAL

### 2. 1. General

Melting points were measured on a Gallenkamp capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Shimadzu FTIR-8400S spectrophotometer, as KBr discs. NMR spectra were performed on a Bruker BioSpin AV 3400 and AV 3500 spectrometer ($^1$H: 400 and 500 MHz, $^{13}$C: 100 and 126 MHz) in $CDCl_3$, DMSO-$d_6$, and $C_6D_6$ as solvents and tetramethylsilane as internal standard, chemical shifts δ in ppm,

the following abbreviations are used: singlet (s), doublet (d), triplet (t), quadruplet (q), doubled doublet (dd), doubled triplet (dt), doubled doubled doublet (ddd), multiplet (m). Thin layer chromatography (TLC) was performed on aluminum plates pre-coated with 0.25 mm layer of silica-gel 60 supplied by Merck and spots were detected with iodine vapor. Column chromatography was carried out with silica-gel 60 (Fluka). All chemicals used were supplied by Merck, Fluka, Sigma-Aldrich, Riedel-De Haen AG. Solvents and liquid reagents were purified and dried in the usual manner before being used.

**2.2. Preparation of N-arylglycosylamines (1-6)** [23]

Two mole equivalents of the aromatic primary amine were added with stirring to a suspension of dry powdered sugar (1 mole equivalent) in absolute ethanol. The resulting mixture was refluxed until all the sugar had dissolved, and the solution was concentrated under vacuum to about one third of its original volume. The remaining solution was treated with ether and allowed to cool with the exclusion of moisture in the refrigerator overnight, whereupon the desired product was deposited as a solid mass. The product was filtered with suction, washed repeatedly with ether to remove the unreacted amine and dried. Recrystallization from absolute ethanol afforded the desired glycosylamine. Reaction time and some physical properties of compounds **1-6** are presented in table 1.

**2.3. Preparation of *O*-acetylated N-arylglycopyranosylamines (7-12)**[24]

Acetic anhydride (4ml) was gradually added with stirring to a cooled solution of N-arylglycosylamine (1g) in dry-freshly redistilled pyridine (4ml), so as the temperature of the reaction did not exceed 0°C. The resulting solution was kept for 24 hours at room temperature with the exclusion of moisture. The reaction mixture was then poured onto a large excess of crushed ice with stirring and kept for several hours. Within this time, the aqueous layer was decanted and a fresh ice-water was added until all of the viscous oil had changed into a hard solid mass. The resulting solid was crushed and collected on a Büchner funnel, washed repeatedly with cold water until the filtrate was neutral and dried. Recrystallization from alcohol-petroleum ether (40-60) afforded the *O*-acetylated glycosylamine. Some physical properties and characteristic IR spectral data are presented in table 2. NMR data and signal assignments of compounds **7-9** are listed in table 3.

**2.4. General procedure for the synthesis of isatin nucleosides (13-18)**

One mole equivalent of the *O*-acetylated N-arylglycopyranosylamine was dissolved in about 7–8 mole equivalents of oxalyl chloride and the solution was left to stir at room temperature, with the exclusion of moisture, for 5 minutes. Anhydrous aluminum chloride (1.2 mole equivalent) was added portion-wise and with stirring to the reaction mixture at 0 °C. Upon completion of the addition, the mixture was slowly heated to 55-60 °C under reflux condenser and $CaCl_2$-drying tube. Heating and stirring were continued until TLC (1:2 hexane/EtOAc) had showed the completion of the reaction. The dark-brown reaction mixture was cooled down to 0 °C and treated with ice water. The resulting mixture was extracted three times with ethyl acetate and the combined organic extracts were washed successively with saturated aqueous sodium bicarbonate solution and water, dried ($Na_2SO_4$), and filtered. The filtrate was evaporated under vacuum and the residue was purified either by column chromatography or recrystallization to yield the desired isatin-N-glycoside.

**1-(2',3',4',6'-Tetra-*O*-acetyl-β-D-glucopyranosyl)-6,7-dimethylindoline-2,3-dione (13):** Starting with the glucoside tetraacetate **7** (2.2 mmole), the reaction was completed after about 3 hours, and the product was isolated as an orange solid in 52% yield. Recrystallization from EtOAc/heptane gave (42%) of **13** as a yellow solid, m.p. 104-106 °C, $R_f$ = 0.83 (hexane/EtOAc, 1:2). FTIR (KBr): 1753 $cm^{-1}$ (νC=O), 1604 $cm^{-1}$ (νC=$C_{aromatic}$), 1230 $cm^{-1}$ (ν O=**C–O**). $^1$H NMR (400 MHz, Chloroform-*d*) δ 7.45 (d, *J* = 7.5 Hz, 1H, H-4), 7.05 (d, *J* = 7.6 Hz, 1H, H-5), 5.87 (d, *J* = 9.9 Hz, 1H, H-1'), 5.54 (t, *J* = 9.8 Hz, 1H, H-2'), 5.32 (t, *J* = 9.2 Hz, 1H, H-3'), 5.26 (t, *J* = 9.6 Hz, 1H, H-4'), 4.31 (dd, *J* = 12.7, 4.6 Hz, 1H, H-6a'), 4.20 (dd, *J* = 12.2, 2.0 Hz, 1H, H-6b'), 4.02 (ddd, *J* = 10.2, 4.7, 2.3 Hz, 1H, H-5'), 2.60, 2.40 (2s, 6H, 2Me), 2.11–2.06 (m, 12H, 4x**CH**$_{3acetate}$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 181.37 (C-3), 170.50, 169.98, 169.58, 169.17 (4x**C**=$O_{acetate}$), 160.75 (C-2), 152.40, 149.60, 147.76, 127.15, 123.55, 118.71 (aromatic), 80.67 (C-1'), 74.79, 73.85, 68.64, 67.50 (C-2',C-3',C-4',C-5'), 61.50 (C-6'), 22.73, 16.47 (2Me), 20.78, 20.67, 20.66, 20.65 (4x**C**H$_{3acetate}$).

**1-(2',3',4',6'-Tetra-*O*-acetyl-β-D-glucopyranosyl)-4,7-dimethylindoline-2,3-dione (14)**: Starting with the glucoside tetraacetate **8** (2.2 mmole), the product was isolated after about 4 hours, and recrystallized from EtOAc/heptane to afford **14** as a yellow solid. Yield; (43%), m.p. 96-98 °C, $R_f$= 0.86 (hexane/EtOAc, 1:2). FTIR (KBr): 1755 $cm^{-1}$ (νC=O), 1585 $cm^{-1}$ (νC=$C_{aromatic}$), 1228 $cm^{-1}$ (ν O=**C–O**).

**1-(2',3',4',6'-Tetra-*O*-acetyl-β-D-glucopyranosyl)-5-methoxyindoline-2,3-dione (15):** Starting with the glucoside tetraacetate **9** (2.2 mmole), the product was isolated after about 4 hours as a dark brown solid in 70% yield. Column chromatography (hexane/EtOAc; 1:2) gave the pure **15** as a brick-red solid. Yield (47%), m.p. 80-82 °C. $R_f$= 0.58 (hexane/EtOAc, 1:2). FTIR (KBr): 1747 $cm^{-1}$ (νC=$O_{acetate}$), 1597 $cm^{-1}$ (νC=$C_{aromatic}$), 1224 $cm^{-1}$ (ν O=**C–O**). $^1$H NMR (400 MHz, Chloroform-*d*) δ 7.21 – 7.16 (m, 2H, H-6, H-7), 7.14 (dd, *J* = 2.3, 1.0 Hz, 1H, H-4), 5.65 (d, *J* = 9.4 Hz, 1H, H-1'), 5.52 (t, *J* = 9.4 Hz, 1H, H-2'), 5.38 (t, *J* = 9.4 Hz, 1H, H-3'), 5.22 (t, *J* = 9.8 Hz, 1H, H-4'), 4.25 (dd, *J* = 12.5, 4.7 Hz, 1H, H-6a'), 4.18 (dd, *J* = 12.5, 2.3 Hz, 1H, H-6b'), 3.93 (ddd, *J* = 10.1, 4.6, 2.3 Hz, 1H, H-5'), 3.80 (s, 3H, O C**H**$_3$), 2.08, 2.07, 2.00, 1.90 (4s, 12H, 4x**CH**$_3$ $_{acetate}$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 182.01 (C-3), 170.48, 169.86, 169.64, 169.58 (4x**C**=O $_{acetate}$), 157.88 (C-2), 156.96, 142.01, 125.58, 118.49, 114.81, 109.28 (aromatic), 79.90 (C-1'), 74.83, 73.06, 67.87, 67.77 (C-2',C-3',C-4',C-5'), 61.77 (C-6'), 56.00 (O**C**H$_3$), 20.80, 20.67, 20.63, 20.39 (4x**C**H$_3$ $_{acetate}$).

**1-(2',3',4'-Tri-*O*-acetyl-β-L-rhamnopyranosyl)indoline-2,3-dione (16):** Starting with the rhamnoside triacetate **10** (2.7 mmole), the product (83%) was isolated, after about 3.5 hours heating. Recrystallization from EtOAc/heptane afforded compound **16** as a yellow solid. Yield (68.4%), m.p. 96-98 °C. $R_f$ = 0.48 (hexane/EtOAc, 1:2) FTIR (KBr): 1743 $cm^{-1}$ (νC=$O_{acetate}$), 1610 $cm^{-1}$ (νC=$C_{aromatic}$), 1218 $cm^{-1}$ (ν O=**C–O**). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.65 (td, *J* = 7.9, 1.3 Hz, 1H, H-4), 7.61 – 7.48 (m, 2H, H-5,H-6), 7.13 (td, *J* = 7.5, 0.8 Hz, 1H, H-7), 6.11 (d, *J* = 1.5 Hz, 1H, H-1'), 5.41 (dd, *J* = 10.2, 3.5 Hz, 1H, H-3'), 5.37 (dd, *J* = 3.5, 1.5 Hz, 1H, H-2'), 5.05 (t, *J* = 9.9 Hz, 1H, H-4'), 4.05 (dd, *J* = 9.8, 6.0 Hz, 1H, H-5'), 2.08, 1.93, 1.75 (3s, 9H, 3xC**H**3 $_{acetate}$), 1.22 (d, *J* = 6.2 Hz, 3H, H-6'). $^{13}$C NMR (101 MHz, DMSO-$D_6$) δ 182.41 (C-3), 170.45, 170.30, 170.26 (3x**C**=$O_{acetate}$), 157.78 (C-2), 149.38, 138.08, 124.69, 123.93, 118.58, 116.11 (aromatic), 80.09 (C-1'), 72.72, 70.54, 70.53, 69.97 (C-2',C-3',C-4',C-5'), 21.12, 21.01, 20.95 (3x**C**H$_{3acetate}$), 17.83 (C-6').

**1-(2',3',4'-Tri-*O*-acetyl-β-L-rhamnopyranosyl)-6,7-dimethylindoline-2,3-dione (17):** Starting with the rhamnoside triacetate **11** (2.5 mmole), the product (73%) was isolated after about 4 hours heating. Recrystallization from EtOAc/heptane gave the pure **17** as a yellow solid. Yield (62%), m.p. 98-100 °C. $R_f$= 0.84 (hexane-EtOAc, 1:2). FTIR (KBr): 1751 $cm^{-1}$ (νC=$O_{acetate}$), 1600 $cm^{-1}$ (νC=$C_{aromatic}$), 1220 $cm^{-1}$ (ν O=**C–O**).

**1-(2',3',4'-Tri-*O*-acetyl-β-L-rhamnopyranosyl)-5-methoxyindoline-2,3-dione (18):** Starting with the rhamnoside triacetate **12** (2.53 mmole), the product was isolated, after about 3.5 hours heating, as a reddish brown solid in 62% yield. Column

chromatography (hexane/EtOAc; 1:2) gave pure **18** as deep red solid. Yield (44%), m.p. 88-90 °C. $R_f$= 0.6 (hexane/EtOAc, 1:2). FTIR (KBr): 1743 $cm^{-1}$ (νC=$O_{acetate}$), 1622, 1595 $cm^{-1}$ (νC=$C_{aromatic}$), 1245, 1220 $cm^{-1}$ (ν O=**C–O**). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.49 (d, *J* = 8.9 Hz, 1H, H-7), 7.24 (dd, *J* = 8.9, 2.9 Hz, 1H, H-6), 7.09 (d, *J* = 2.8 Hz, 1H, H-4), 6.09 (d, *J* = 1.5 Hz, 1H, H-1'), 5.42 (dd, *J* = 10.2, 3.5 Hz, 1H, H-3'), 5.37 (dd, *J* = 3.5, 1.5 Hz, 1H, H-2'), 5.04 (t, *J* = 10.0 Hz, 1H, H-4'), 4.07 (td, *J* = 9.9, 6.3 Hz, 1H, H-5'), 3.76 (s, 3H, OC**H**$_3$), 2.09, 1.93, 1.79 (3s, 9H, 3xC**H**$_{3\ acetate}$), 1.22 (d, *J* = 6.2 Hz, 3H, H-6'). $^{13}$C NMR (101 MHz, DMSO-$D_6$) δ 182.08 (C-3), 169.90, 169.75, 169.45 (3x**C**=O $_{acetate}$), 157.41 (C-2), 155.53, 142.85, 124.00, 118.64, 116.83, 107.90 (aromatic), 79.46 (C-1'), 72.13, 70.08, 70.02, 69.49 (C-2',C-3',C-4',C-5'), 55.78 (O**C**H$_3$), 20.64, 20.59, 20.48 (3x**C**H$_{3\ acetate}$), 17.36 (C-6').

**2.5 Synthesis of 3-thiosemicarbazone and 3-(4-nitrophenyl)hydrazone derivatives of N-glycosyl isatins (19-28): General procedure**

One mole equivalent of the appropriate isatin glycoside in hot absolute ethanol was mixed with a hot solution of 1.2 mole equivalent of the reagent (thiosemicarbazide or 4-nitrophenylhydrazine) in absolute ethanol and the mixture was heated at 85-90 °C for about 2 hours after the addition of 1–2 drops of glacial acetic acid. The thiosemicarbazone was crystallized by the addition of water to the hot reaction mixture, it was then filtered off, washed with hot water and dried. The hydrazone, which crystallized out from the boiling reaction mixture during the course of the reaction, was filtered from the hot reaction mixture, washed with hot ethanol and dried to give the pure product.

**2-[1-(2',3',4',6'-Tetra-*O*-acetyl-β-D-glucopyranosyl)-2-oxo-6,7-dimethyl-2,3-dihydroindol-3-ylidene]hydrazinecarbothioamide (19):** Starting with the isatin glucoside **13** (0.2 mmole) and thiosemicarbazide (0.24 mmole), the thiosemicarbazone **19** was obtained as an orange solid. Yield; (83%), m.p. 144-146 °C. FTIR (KBr): 3180-3445 $cm^{-1}$ (νN**—**H), 1753, 1703 $cm^{-1}$ (νC=O), 1606 $cm^{-1}$ (νC=N, νC=$C_{aromatic}$), 1160 $cm^{-1}$ (νC=S). $^1$H NMR (500 MHz, Chloroform-*d*) δ 12.62 (s, 1H, N**H**), 7.51 (s, 1H, N**H**$_2$), 7.37 (d, *J* = 7.7 Hz, 1H, H-4), 7.03 (d, *J* = 7.6 Hz, 1H, H-5), 6.54 (s, 1H, N**H**$_2$), 5.89 (d, *J* = 9.9 Hz, 1H, H-1'), 5.56 (t, *J* = 9.4 Hz, 1H, H-2'), 5.35 (t, *J* = 9.4 Hz, 1H, H-3'), 5.29 (t, *J* = 9.8 Hz, 1H, H-4'), 4.33 (dd, *J* = 12.5, 4.0 Hz, 1H, H-6a'), 4.21 (dd, *J* = 12.1, 2.3 Hz, 1H, H-6b'), 4.07 – 3.99 (m, 1H, H-5'), 2.61, 2.37 (2s, 6H, 2Me), 2.09, 2.08, 2.00, 1.78 (4s, 12H, 4xC**H**3 $_{acetate}$). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 179.78 (**C**=S), 170.34, 169.81, 169.38, 168.93 (4x**C**=O $_{acetate}$), 162.62 (C-2), 143.76, 140.26, 130.58, 126.40, 122.16, 118.80, 118.09 (C-3, 6C $_{aromatic}$), 79.61 (C-1'), 74.72, 73.82, 68.79, 67.20 (C-2',C-3',C-4',C-5'), 61.35 (C-6'), 21.89, 16.49 (2Me), 20.63, 20.53, 20.50, 20.10 (4x**C**H$_{3\ acetate}$).

**2-[1-(2',3',4',6'-Tetra-*O*-acetyl-β-D-glucopyranosyl)-2-oxo-5-methoxy-2,3-dihydroindol-3-ylidene]hydrazinecarbothioamide (20):** Starting with the isatin glucoside **15** (0.19 mmole) and thiosemicarbazide (0.24 mmole), the thiosemicarbazone **20** was obtained as a beige solid. Yield; (93%), m.p. 224-226 °C. FTIR (KBr): 3168-3447 $cm^{-1}$ (νN**—**H), 1745, 1701 $cm^{-1}$ (νC=O), 1597 $cm^{-1}$ (νC=N, νC=$C_{aromatic}$), 1146 $cm^{-1}$ (νC=S). $^1$H NMR (400 MHz, Chloroform-*d*) δ 12.64 (s, 1H, N**H**), 7.52 (s, 1H, N**H**$_2$), 7.15 (d, *J* = 8.7 Hz, 1H, H-7), 7.11 (d, *J* = 2.6 Hz, 1H, H-4), 6.97 (dd, *J* = 8.7, 2.6 Hz, 1H, H-6), 6.52 (s, 1H, N**H**$_2$), 5.66 (d, *J* = 9.4 Hz, 1H, H-1'), 5.57 (t, *J* = 9.3 Hz, 1H, H-2'), 5.40 (t, *J* = 9.4 Hz, 1H, H-3'), 5.25 (t, *J* = 9.8 Hz, 1H, H-4'), 4.26 (dd, *J* = 12.5, 4.5 Hz, 1H, H-6a'), 4.20 (dd, *J* = 12.5, 2.3 Hz, 1H, H-6b'), 3.95 (ddd, *J* = 10.1, 4.6, 2.2 Hz, 1H, H-5'), 3.83 (s, 3H, OC**H**$_3$), 2.10, 2.08, 2.02, 1.91 (4s, 12H, 4xC**H**$_{3\ acetate}$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 180.23 (**C**=S), 170.70, 170.11, 169.80, 169.58 (4x**C**=O $_{acetate}$), 160.89 (C-2), 156.95, 134.20, 131.18, 120.51, 118.11, 113.75, 106.42 (6C $_{aromatic}$, C-3), 79.46 (C-1'), 74.99, 73.39, 68.12, 68.05 (C-2',C-3',C-4',C-5'), 61.95 (C-6'), 56.11 (O**C**H$_3$), 20.99, 20.86, 20.82, 20.65 (4x**C**H$_{3\ acetate}$).

**2-[1-(2',3',4'-Tri-*O*-acetyl-β-L-rhamnopyranosyl)-2-oxo-2,3-dihydroindol-3-ylidene]hydrazinecarbothioamide (21):** Starting with the isatin rhamnoside **16** (0.24 mmole) and thiosemicarbazide (0.28 mmole), the thiosemicarbazone **21** was obtained as a yellow solid. Yield; (93%), m.p. 162-164 °C. FTIR (KBr): 3184-3500 $cm^{-1}$ (νN**—**H), 1751, 1720, 1697 $cm^{-1}$ (νC=O), 1608 $cm^{-1}$ (νC=N, νC=Caromatic), 1148 $cm^{-1}$ (νC=S). $^1$H NMR (400 MHz, Chloroform-*d*) δ 12.62 (s, 1H, N**H**), 7.54 (dd, *J* = 7.8, 1.5 Hz, 2H, H-4,H-7), 7.51 (s, 1H, N**H**$_2$), 7.35 (td, *J* = 8.0, 1.3 Hz, 1H, H-6), 7.10 (td, *J* = 7.6, 1.0 Hz, 1H, H-5), 6.56 (s, 1H, N**H**$_2$), 5.86 (d, *J* = 1.5 Hz, 1H, H-1'), 5.56 (dd, *J* = 3.2, 1.5 Hz, 1H, H-2'), 5.27 (dd, *J* = 10.2, 3.2 Hz, 1H, H-3'), 5.22 (dd, *J* = 10.2, 9.0 Hz, 1H, H-4'), 3.78 (dq, *J* = 8.9, 6.1 Hz, 1H, H-5'), 2.10, 1.99, 1.83 (3s, 9H, (3xC**H**$_{3\ acetate}$), 1.37 (d, *J* = 6.1 Hz, 3H, H-6'). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 180.10 (**C**=S), 170.15, 169.82, 169.79 (3x**C**=O $_{acetate}$), 159.97 (C-2), 141.60, 131.10, 130.86, 123.61, 120.64, 119.65, 114.89 (C-3, 6C $_{aromatic}$), 80.15 (C-1'), 74.29, 70.54, 70.39, 70.18 (C-2',C-3',C-4',C-5'), 20.92, 20.89, 20.67 (3x**C**H$_{3\ acetate}$), 17.81 (C-6').

**2-[1-(2',3',4'-Tri-*O*-acetyl-β-L-rhamnopyranosyl)-2-oxo-6,7-dimethyl-2,3-dihydroindol-3-ylidene]hydrazinecarbothioamide (22):** Starting with the isatin rhamnoside **17** (0.22 mmole) and thiosemicarbazide (0.27 mmole), the thiosemicarbazone **22** was obtained as yellow-orange solid. Yield; (75%), m.p. 136-140 °C. FTIR (KBr): 3188-3452 $cm^{-1}$ (νN**—**H), 1751, 1689 $cm^{-1}$ (νC=O), 1605 $cm^{-1}$ (νC=N, νC=Caromatic), 1174 $cm^{-1}$ (νC=S). $^1$H NMR (400 MHz, Chloroform-*d*) δ 12.63 (s, 1H, N**H**), 7.49 (s, 1H, N**H**$_2$), 7.36 (d, *J* = 7.6 Hz, 1H, H-4), 6.98 (d, *J* = 7.7 Hz, 1H, H-5), 6.55 (s, 1H, N**H**$_2$), 5.94 (d, *J* = 1.8 Hz, 1H, H-1'), 5.58 (dd, *J* = 3.4, 1.8 Hz, 1H, H-2'), 5.25 (dd, *J* = 10.3, 3.5 Hz, 1H, H-3'), 5.23 – 5.19 (m, 1H, H-4'), 3.79 (dq, *J* = 9.3, 6.3 Hz, 1H, H-5'), 2.55, 2.34 (2s, 6H, 2Me), 2.09, 1.98, 1.89 (3s, 9H, 3xC**H**$_{3\ acetate}$), 1.36 (d, *J* = 6.1 Hz, 3H, H-6'). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 179.95 (**C**=S), 170.06, 169.84, 169.75 (3x**C**=O $_{acetate}$), 162.08 (C-2), 143.35, 141.73, 131.03, 126.15, 123.19, 119.68, 118.16 (C-3,6C $_{\mathbf{aromatic}}$), 81.17 (C-1'), 74.20, 70.77, 70.05, 69.28 (C-2',C-3',C-4',C-5'), 22.34, 17.13 (2Me), 20.91, 20.66, 20.57 (3x**C**H$_{3\ acetate}$), 17.71 (C-6').

**2-[1-(2',3',4'-Tri-*O*-acetyl-β-L-rhamnopyranosyl)-2-oxo-5-methoxy-2,3-dihydroindol-3-ylidene]hydrazinecarbothioamide (23):** Starting with the isatin rhamnoside **18** (0.22 mmole) and thiosemicarbazide (0.27 mmole), the thiosemicarbazone **23** was obtained as an orange solid. Yield; (88%), m.p. 150-154 °C. FTIR (KBr): 3190-3448 $cm^{-1}$ (νN**—**H), 1751, 1695 $cm^{-1}$ (νC=O), 1597 $cm^{-1}$ (νC=N, νC=Caromatic), 1150 $cm^{-1}$ (νC=S). $^1$H NMR (400 MHz, Chloroform-*d*) δ 12.66 (s, 1H, N**H**), 7.51 (s, 1H, N**H**$_2$), 7.42 (d, *J* = 8.9 Hz, 1H, H-7), 7.06 (d, *J* = 2.6 Hz, 1H, H-4), 6.90 (dd, *J* = 8.9, 2.7 Hz, 1H, H-6), 6.51 (s, 1H, N**H**$_2$), 5.82 (d, *J* = 1.5 Hz, 1H, H-1'), 5.55 (dd, *J* = 3.2, 1.5 Hz, 1H, H-2'), 5.26 (dd, *J* = 10.1, 3.3 Hz, 1H, H-3'), 5.20 (dd, *J* = 10.2, 9.1 Hz, 1H, H-4'), 3.82 (s, 3H, OC**H**$_3$), 3.76 (dt, *J* = 9.1, 6.1 Hz, 1H, H-5'), 2.10, 1.99, 1.86 (3s, 9H, 3xC**H**$_{3\ acetate}$), 1.36 (d, *J* = 6.1 Hz, 3H, H-6'). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 180.08 (**C**=S), 170.15, 169.83, 169.80 (3x**C**=O $_{acetate}$), 160.11 (C-2), 156.37, 134.18, 131.15, 129.85, 120.51, 117.71, 115.82 (C-3, 6C $_{\mathbf{aromatic}}$), 80.01 (C-1'), 74.23, 70.56, 70.43, 70.19 (C-2',C-3',C-4',C-5'), 55.96 (O**C**H$_3$), 20.95, 20.92, 20.67 (3x**C**H$_{3\ acetate}$), 17.81 (C-6').

**1-(2',3',4',6'-Tetra-*O*-acetyl-β-D-glucopyranosyl)-6,7-dimethyl-3-[2-(4-nitrophenyl)hydrazono]-2,3-dihydroindol-2-one (24):** Starting with the isatin glucoside **13** (0.2 mmole) and 4-nitrophenylhydrazine (0.24 mmole), the hydrazone **24** was obtained as an orange solid. Yield; (70%), m.p. 273-274 °C. FTIR

(KBr): 3450 $cm^{-1}$ (νN—H), 1751, 1689 $cm^{-1}$ (νC=O), 1602 $cm^{-1}$ (νC=Caromatic), 1566 $cm^{-1}$ (νC=N), 1508, 1330 $cm^{-1}$ ($\nu NO_2$). $^1$H NMR (400 MHz, Chloroform-*d*) δ 12.75 (s, 1H, N**H**), 8.29 – 8.20 (m, 2H, H-3",H-5"), 7.47 (d, *J* = 7.1 Hz, 1H, H-4), 7.43 – 7.36 (m, 2H, H-2",H-6"), 7.06 (d, *J* = 7.6 Hz, 1H, H-5), 5.93 (d, *J* = 10.0 Hz, 1H, H-1'), 5.60 (t, *J* = 9.5 Hz, 1H, H-2'), 5.40 – 5.26 (m, 2H, H-3',H-4'), 4.38 – 4.15 (m, 2H, H-6'), 3.83 (ddd, *J* = 8.6, 4.3, 1.9 Hz, 1H, H-5'), 2.63, 2.38 (2s, 6H, 2Me), 2.10, 2.08, 2.00, 1.75 (4s, 12H, 4xC$\mathbf{H}_{3\ acetate}$).

**1-(2',3',4',6'-Tetra-*O*-acetyl-β-D-glucopyranosyl)-4,7-dimethyl-3-[2-(4-nitrophenyl)hydrazono]-2,3-dihydroindol-2-one (25):** Starting with the isatin glucoside **14** (0.2 mmole) and 4-nitrophenylhydrazine (0.24 mmole), the hydrazone **25** was obtained as a yellow solid. Yield; (86%), m.p. 296 °C. FTIR (KBr): 3455 $cm^{-1}$ (νN—H), 1749, 1687 $cm^{-1}$ (νC=O), 1600 $cm^{-1}$ (νC=Caromatic), 1556 $cm^{-1}$ (νC=N), 1510, 1330 $cm^{-1}$ ($\nu NO_2$). $^1$H NMR (400 MHz, Chloroform-*d*) δ 13.13 (s, 1H, N**H**), 8.31 – 8.22 (m, 2H, H-3",H-5"), 7.39 – 7.30 (m, 2H, H-2",H-6"), 7.01 (d, *J* = 7.9 Hz, 1H, H-6), 6.90 (d, *J* = 7.8 Hz, 1H, H-5), 5.72 (d, *J* = 9.3 Hz, 1H, H-1'), 5.41 (t, *J* = 9.4 Hz, 1H, H-2'), 5.38 – 5.22 (m, 2H, H-3',H-4'), 4.27 (dd, *J* = 12.5, 5.4 Hz, 1H, H-6a'), 4.20 (dd, *J* = 12.5, 2.3 Hz, 1H, H-6b'), 3.85 (ddd, *J* = 8.7, 5.4, 2.3 Hz, 1H, H-5'), 2.61, 2.52 (2s, 6H, 2Me), 2.08, 2.07, 2.05, 1.87 (4s, 12H, 4xC$\mathbf{H}_{3\ acetate}$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 170.73, 170.57, 169.45, 169.31 (4x**C**=O $_{acetate}$), 163.60 (C-2), 147.94, 142.73, 134.39, 133.73, 132.84, 132.26, 131.52, 127.02, 126.21, 126.07, 119.66, 117.33, 113.83 (C-3, 12C $_{\mathbf{aromatic}}$), 79.16 (C-1'), 74.52, 73.94, 68.53, 68.12 (C-2',C-3',C-4',C-5'), 62.26 (C-6'), 21.37, 19.71 (2Me) 20.79, 20.73, 20.43, 20.23 (4x**C**$H_{3\ acetate}$).

**1-(2',3',4',6'-Tetra-O-acetyl-β-D-glucopyranosyl)-5-methoxy-3-[2-(4-nitrophenyl)hydrazono]-2,3-dihydroindol-2-one (26):** Starting with the isatin glucoside **15** (0.19 mmole) and 4-nitrophenylhydrazine (0.23 mmole, the hydrazone **26** was obtained as a reddish brown solid. Yield; (87%), m.p. 277-278 °C. FTIR (KBr): 3450 $cm^{-1}$ (νN—H), 1743, 1687 $cm^{-1}$ (νC=O), 1600 $cm^{-1}$ (νC=Caromatic), 1566 $cm^{-1}$ (νC=N), 1510, 1334 $cm^{-1}$ ($\nu NO_2$). $^1$H NMR (400 MHz, Chloroform-*d*) δ 12.80 (s, 1H, N**H**), 8.27 (d, *J* = 9.2 Hz, 2H, H-3",H-5"), 7.42 (d, *J* = 9.1 Hz, 2H, H-2",H-6"), 7.22 (d, *J* = 2.5 Hz, 1H, H-4), 7.14 (d, *J* = 8.7 Hz, 1H, H-7), 6.92 (dd, *J* = 8.7, 2.6 Hz, 1H, H-6), 5.70 – 5.65 (m, 2H, H-1',H-2'), 5.42 (t, *J* = 9.4 Hz, 1H, H-3'), 5.28 (t, *J* = 9.8 Hz, 1H, H-4'), 4.27 (dd, *J* = 12.5, 4.5 Hz, 1H, H-6a'), 4.21 (dd, *J* = 12.5, 2.4 Hz, 1H, H-6b'), 3.96 (ddd, *J* = 10.0, 4.5, 2.4 Hz, 1H, H-5'), 3.87 (s, 3H, OC$\mathbf{H}_3$), 2.10, 2.09, 2.03, 1.88 (4s, 12H, 4xC$\mathbf{H}_{3\ acetate}$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 170.60, 170.12, 169.62, 169.17 (4x**C**=O $_{acetate}$), 161.89 (C-2), 156.81, 147.57, 143.06, 132.29, 129.93, 126.04, 121.50, 116.32, 114.01, 113.00, 105.28 (C-3, 12C $_{\mathbf{aromatic}}$), 79.34 (C-1'), 74.89, 73.41, 68.06, 67.99 (C-2',C-3',C-4',C-5'), 61.87 (C-6'), 55.98 (O**C**$H_3$), 20.85, 20.73, 20.71, 20.48 (4x**C**$H_{3\ acetate}$).

**1-(2',3',4'-Tri-*O*-acetyl-β-L-rhamnopyranosyl)-3-[2-(4-nitrophenyl)hydrazono]-2,3-dihydroindol-2-one (27):** Starting with the isatin rhamnoside **16** (0.24 mmole) and 4-nitrophenylhydrazine (0.28 mmole), the hydrazone **27** was obtained as yellow-orange solid. Yield; (83%), m.p. 148-150 °C. FTIR (KBr): 3448 $cm^{-1}$ (νN—H), 1751, 1687 $cm^{-1}$ (νC=O), 1604 $cm^{-1}$ (νC=Caromatic), 1568 $cm^{-1}$ (νC=N), 1508, 1334 $cm^{-1}$ ($\nu NO_2$). $^1$H NMR (400 MHz, Chloroform-*d*) δ 12.75 (s, 1H, N**H**), 8.26 (dd, *J* = 9.3, 2.0 Hz, 2H, H-3",H-5"), 7.63 (dd, *J* = 7.6, 1.3 Hz, 1H, H-4), 7.55 (d, *J* = 8.1 Hz, 1H, H-7), 7.40 (d, *J* = 9.1 Hz, 2H, H-2",H-6"), 7.30 (td, *J* = 7.8, 1.3 Hz, 1H, H-6), 7.12 (td, *J* = 7.6, 1.0 Hz, 1H, H-5), 5.89 (d, *J* = 1.6 Hz, 1H, H-1'), 5.59 (dd, *J* = 3.0, 1.5 Hz, 1H, H-2'), 5.33 – 5.20 (m, 2H, H-3',H-4'), 3.79 (dq, *J* = 12.6, 6.3 Hz, 1H, H-5'), 2.11, 2.00, 1.83 (3s, 9H, 3xC$\mathbf{H}_{3\ acetate}$), 1.39 (d, *J* = 6.1 Hz, 3H, H-6'). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 170.10, 169.96, 169.94 (3x**C**=O $_{acetate}$), 160.91 (C-2), 147.70, 142.92, 139.70, 129.78, 129.28, 126.01, 123.40, 120.66, 119.72, 114.52, 113.95 (C-3, 12C $_{\mathbf{aromatic}}$), 80.14 (C-1'), 74.31, 70.69, 70.39, 70.18 (C-2',C-3',C-4',C-5'), 20.92, 20.88, 20.69 (3x**C**$H_3$ $_{acetate}$), 17.83 (C-6').

**1-(2',3',4'-Tri-*O*-acetyl-β-L-rhamnopyranosyl)-5-methoxy-3-[2-(4-nitrophenyl)hydrazono]-2,3-dihydroindol-2-one (28):** Starting with the isatin rhamnoside **18** (0.22 mmole) and 4-nitrophenylhydrazine (0.27 mmole), the hydrazone **28** was obtained a deep orange solid. Yield; (70%), m.p. 282-283 °C. FTIR (KBr): 3450 $cm^{-1}$ (νN—H), 1751, 1683 $cm^{-1}$ (νC=O), 1600 $cm^{-1}$ (νC=Caromatic), 1564 $cm^{-1}$ (νC=N), 1508, 1323 $cm^{-1}$ ($\nu NO_2$). $^1$H NMR (400 MHz, Chloroform-*d*) δ 12.80 (s, 1H, N**H**), 8.26 (d, *J* = 9.2 Hz, 2H, H-3",H-5"), 7.44 (d, *J* = 8.8 Hz, 1H, H-7), 7.41 (d, *J* = 9.2 Hz, 2H, H-2",H-6"), 7.17 (d, *J* = 2.6 Hz, 1H, H-4), 6.86 (dd, *J* = 8.8, 2.7 Hz, 1H, H-6), 5.85 (d, *J* = 1.5 Hz, 1H, H-1'), 5.58 (dd, *J* = 3.0, 1.5 Hz, 1H, H-2'), 5.27 (dd, *J* = 9.7, 3.0 Hz, 1H, H-3'), 5.25 – 5.20 (m, 1H, H-4'), 3.86 (s, 3H, OC$\mathbf{H}_3$), 3.78 (dq, *J* = 9.0, 6.1 Hz, 1H, H-5'), 2.11, 2.00, 1.86 (3s, 9H, 3xC$\mathbf{H}_{3\ acetate}$), 1.38 (d, *J* = 6.1 Hz, 3H, H-6'). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 170.10, 169.96, 169.95 (3x**C**=O $_{\mathbf{acetate}}$), 161.09 (C-2), 156.34, 147.68, 142.96, 133.58, 130.13, 126.02, 121.56, 116.08, 115.45, 113.99, 104.16 (C-3,12C $_{\mathbf{aromatic}}$), 80.02 (C-1'), 74.27, 70.70, 70.43, 70.20 (C-2',C-3',C-4',C-5'), 55.95 (O**C**$H_3$), 20.96, 20.93, 20.70 (3x**C**$H_3$ $_{\mathbf{acetate}}$), 17.85 (C-6').

## 3. RESULTS AND DISCUSSION

The new substituted isatin nucleosides described here were synthesized according to a published procedure[25]. The reaction of free sugar (D-glucose or L-rhamnose) with appropriate primary aromatic amine in refluxing anhydrous ethanol followed by *O*-acetylation in the presence of $Ac_2O$/pyridine furnished the per-*O*-acetylated N-arylglycopyranosylamines **7-12**. The resulting glycosides were subjected to an intramolecular cyclization reaction with oxalyl chloride in the presence of anhydrous $AlCl_3$ to yield the substituted isatin nucleosides **13-18**, scheme 1. The 3-thiosemicarbazones **19-23** and the 3-hydrazones **24-28** were successfully synthesized in good to high yield, according to a published method[26], by heating the ethanolic solution of appropriate isatin nucleoside and the reagent in the presence of catalytic amounts of glacial acetic acid. All synthesized compounds were characterized by FTIR spectroscopy, and the NMR spectroscopy was utilized to characterize and confirm the structure of final 3-ketimine derivatives **19-28** as well as the isatin nucleosides **13,15,16 and 18,** and the starting glycosylamines **7, 8** and **9**. Compound **16** is previously reported[22] and also the starting glycosylamines **1-6** and **9**[27-30].

The method of Hanaoka[23] was followed to prepare the known N-arylglycosylamines **1-6**, and some of their physical properties as well as reaction times are summarized in table 1. FTIR spectra and melting point were used to characterize these derivatives and the results obtained here were in accordance with the previously reported data[27-30]. The FTIR measurements of compounds **1-6** revealed a strong and broad band at (3250-3450) $cm^{-1}$ contributed to the stretching vibration of (O—H) bond of the sugar (which predominately mask the appearance of (N—H) stretching band of the amine). The appearance of two bands at about 1600 and 1440 $cm^{-1}$ for the aromatic (C—C) stretching within the ring, in addition to a frequently strong band around (1505-1530) $cm^{-1}$ attributed to the (N—H) bending of the secondary aromatic amine were good indications for success of the reaction. The spectra also showed strong bands in the region of about 1100-1000 $cm^{-1}$ which assigned for the stretching of (C–O) bond of the pyranose ring and its alcohol groups, in addition to moderate bands between (1240-1360) $cm^{-1}$ attributed to the (O–H) bending and stretching of (C–N) bonds.

**Table 1: Reaction time and some physical properties of the prepared N- arylglycosylamines 1-6.**

| Compound Number | Reaction Time (h) | Molecular Formula | Physical Form | M.p. (°C) | Yield (%) |
|---|---|---|---|---|---|
| 1 | 5 | $C_{14}H_{21}NO_5$ | Off-white solid | 147-150 | 69 |
| 2 | 3.5 | $C_{14}H_{21}NO_5$ | Off-white solid | 93-96 | 58 |
| 3 | 2.5 | $C_{13}H_{19}NO_6$ | Light gray solid | 128-130 | 88 |
| 4 | 5 | $C_{12}H_{17}NO_4$ | Faint yellow solid | 138-140 | 51 |
| 5 | 5 | $C_{14}H_{21}NO_4$ | White solid | 166-168 | 65 |
| 6 | 3.5 | $C_{13}H_{19}NO_5$ | Light gray solid | 130-132 | 75 |

**Table 2: Some physical properties and characteristic IR absorption bands of compounds 7-12.**

| Compound Number | Molecular Formula | Physical Form | M.p. (°C) | Yield (%) | Characteristic IR bands ($cm^{-1}$) | | |
|---|---|---|---|---|---|---|---|
| | | | | | ν(N—H) | ν(C=O) | ν(C=C) aromatic |
| 7 | $C_{22}H_{29}NO_9$ | Off-white solid | 120-124 | 86 | 3431 | 1743 | 1591 |
| 8 | $C_{22}H_{29}NO_9$ | Off-white solid | 112-114 | 84 | 3421 | 1755 | 1618 |
| 9 | $C_{21}H_{27}NO_{10}$ | Beige solid | 128-130 | 72 | 3360 | 1747 | 1437 |
| 10 | $C_{18}H_{23}NO_7$ | Off-white solid | 128-130 | 85 | 3411 | 1751 | 1604 |
| 11 | $C_{20}H_{27}NO_6$ | White solid | 150-152 | 92 | 3431 | 1745 | 1589 |
| 12 | $C_{19}H_{25}NO_7$ | Beige solid | 126-128 | 75 | 3358 | 1745 | 1440 |

**Table 3: 1H-NMR data and signal assignments of compounds 7-9.**

| Compound Number | R | 1H-NMR data and signal assignments |
|---|---|---|
| 7 | 2,3-diMe | $^1$H NMR (400 MHz, Benzene-$d_6$) δ 7.10 (t, *J* = 7.8 Hz, 1H, H-5), 6.76 (d, *J* = 7.5 Hz, 1H, H-4), 6.68 (d, *J* = 8.0 Hz, 1H, H-6), 5.51 (t, *J* = 9.5 Hz, 1H, H-3'), 5.27 (dd, *J* = 10.1, 9.3 Hz, 1H, H-4'), 5.15 (dd, *J* = 9.6, 8.5 Hz, 1H, H-2'), 4.64 – 4.50 (m, 2H, H-1', NH), 4.32 (dd, *J* = 12.2, 5.0 Hz, 1H, H-6a'), 3.95 (dd, *J* = 12.2, 2.3 Hz, 1H, H-6b'), 3.23 (ddd, *J* = 10.1, 4.9, 2.3 Hz, 1H, H-5'), 2.08, 1.85 (2s, 6H, 2xC**H**$_3$), 1.73, 1.72, 1.72, 1.61 (4s, 12H, 4xC**H**$_{3\ acetate}$). |
| 8 | 2,5-diMe | $^1$H NMR (400 MHz, DMSO-$d_6$) δ 6.88 (d, *J* = 7.4 Hz, 1H, H-3), 6.59 (d, *J* = 1.7 Hz, 1H, H-6), 6.49 (dd, *J* = 7.5, 1.6 Hz, 1H, H-4), 5.41 (t, *J* = 9.1 Hz, 1H, H-3'), 5.32 (d, *J* = 9.0 Hz, 1H, H-1'), 5.14 – 5.02 (m, 2H, H-2',NH), 4.90 (t, *J* = 9.5 Hz, 1H, H-4'), 4.19 – 4.11 (m, 2H, H-6a',H-6b'), 4.05 – 3.98 (m, 1H, H-5'), 2.21, 2.01 (2s, 6H, 2xC**H**$_3$), 1.98, 1.97 (2s, 12H, 4xC**H**$_{3\ acetate}$). |
| 9 | 4-OMe | $^1$H NMR (400 MHz, DMSO-$d_6$) δ 6.74 (d, *J* = 9.1 Hz, 2H, H-2,H-6), 6.68 (d, *J* = 9.1 Hz, 2H, H-3,H-5), 6.08 (d, *J* = 10.1 Hz, 1H, H-1'), 5.34 (t, *J* = 9.4 Hz, 1H, H-3'), 5.10 (t, *J* = 9.6 Hz, 1H, H-4'), 4.90 (m, 2H, H-2',NH), 4.16 (dd, *J* = 12.1, 4.9 Hz, 1H, H-6a'), 4.07 (ddd, *J* = 10.1, 5.0, 2.4 Hz, 1H, H-5'), 3.94 (dd, *J* = 12.1, 2.3 Hz, 1H, H-6b'), 3.65 (s, 3H, OC**H**$_3$), 2.00, 1.96, 1.95, 1.95 (4s, 12H, 4xC**H**$_{3\ acetate}$). |

After *O*-acetylation reaction, The FTIR spectra of the products **7-12** (table 2) showed a strong absorption band around (1745-1750) $cm^{-1}$ for the (C=O) stretching vibration of acetate, broad and strong bands at about (1225-1260) $cm^{-1}$ and about (1030-1050) $cm^{-1}$ for (O=**C–O**) and (O=C–**O–C**) stretching respectively and strong band at about 1370 $cm^{-1}$ characteristic for (**CH$_3$**–C=O) bending. Conversely, the absence of (O–H) stretching band at (3450-3250) $cm^{-1}$ and the appearance of a sharp and frequently strong (N–H) stretching band at (3360-3440) $cm^{-1}$, all indicated the success of the protection reaction.

The stereochemistry of some of the prepared per-*O*-acetylated N-arylglycosylamines **7-9** was established by analyzing the $^1$H-NMR data (table 3). The results showed that all vicinal glucosyl protons exhibited large coupling constant within 9-10 Hz which reflects the axial-axial orientation of these protons and hence, confirms the β-configuration at the anomeric carbon (C-1′) as well as the $^4C_1$ pyranose conformation[31].

The cyclization of per-*O*-acetylated N-arylglycosylamines **7-12** with oxalyl chloride/$AlCl_3$ gave, after suitable purification, the isatin nucleosides **13-18** as anomerically pure β-anomers. FTIR spectra revealed absence of both (N—H) stretching and bending bands at the regions of (3360-3440) and (1510-1530) $cm^{-1}$ respectively. $^{13}$C-NMR exhibited two signals at δ 180-182 ppm and at δ 156-160 ppm assigned for isatin ketone and amide carbons ($C_3$ and $C_2$) respectively.

The stereochemistry of the synthesized nucleosides was determined by analyzing the 1H-NMR data. For D-glucosides **13** and **15**, the large coupling constsnt of ca. 9-10 Hz between each couple of vicinal protons confirm both the β-configuration at anomeric carbon and the $^4C_1$ pyranoside conformation. In the case of L-rhamnosides **16** and **18**, the determination of anomeric configuration from $^1$H-NMR is difficult, since the coupling constant observed between H-1' and H-2' ( ~ 1.5 Hz) can be assigned to both the β-anomer ($^3J_{ae}$= 1.5-5.8 Hz) and to the α-anomer ($^3J_{ee}$= 0.6-3.5 Hz), while the differentiation between them is possible only if the observed coupling lies outside the range of overlap of the two sets of values[32]. However, the NMR spectral data obtained for the known **16** were identical with those reported by Langer and coworkers[33], and they have proved the β-configuration of **16** utilizing 2D-NMR and X-ray crystallography. Such agreement between results can therefore be exploited for deducing the configuration of the L-rhamno derivatives **16** and **18** as β-L-rhamnopyranoside. On the other hand, the later derivatives can be proved to exist in the $^1C_4$ conformation, as they comprised three axial arrangements of vicinal hydrogens at C-3', C-4' and C-5' with ($^3J_{aa}$ = 10 Hz) characteristic for the $^1C_4$ conformation of the L-rhamnopyranoside derivatives[34]. The structure and stereochemistry of compounds **14** and **17** were confirmed by the NMR spectra of their 3-hydrazone **25** and 3-thiosemicarbazone **22** respectively (*vide infra*).

The 3-thiosemicarbazones **19-23** and the 3-(4-nitrophenyl)hydrazones **24-28** of isatin nucleosides were obtained in high yield and considerable purity after simple work-up. The FTIR measurements of the thiosemicarbazones showed the absorption of (C=N) stretching as a moderate band near 1620-1640 $cm^{-1}$ either as a separated peak or combined with the aromatic (C=C) stretching band at ca. 1600-1610 $cm^{-1}$ as a shoulder. The stretching of ( C=O ) was absorbed around 1750 $cm^{-1}$ for the acetates and near 1690-1700$cm^{-1}$ for the isatin carbonyl ( C-2 ), and the ( C=S ) stretching was assigned around 1150-1170 $cm^{-1}$ as a moderate band. (N—H) and ($NH_2$) stretching vibration was appeared as a combination of unresolved bands within 3160-3500 $cm^{-1}$ region of the spectra due to the hydrogen bonding. The FTIR spectra of the hydrazones **24-28** showed the (C=N) stretching band at ~1560 $cm^{-1}$ and the (C=C) stretching of aromatic ring at ~1600 $cm^{-1}$. The stretching of amidic carbonyl of isatin moiety absorbed at 1687–1689 $cm^{-1}$ while that of acetate carbonyl absorbed at ~ 1750 $cm^{-1}$. Two bands at about 1330 $cm^{-1}$ and at 1505–1510 $cm^{-1}$ attributed to symmetric and asymmetric stretching of the ($NO_2$) group respectively. The (N—H) stretching vibration represented by a broad band around 3450 $cm^{-1}$.

$^1$H-NMR spectra of the thiosemicarbazones exhibited the (NH) proton as a singlet at δ ~12.6 ppm, while the ($NH_2$) protons represented by two separated broad singlets at δ ~6.5 and at δ ~7.5 ppm, as a result of the hindered rotation about the thioamide group in addition to the hydrogen bonding that both reflect the difference in chemical shifts between the two nonequivalent ($NH_2$) protons[35]. $^{13}$C-NMR revealed the (C=S) carbon at δ ~ 180 ppm in addition to the amidic (C=O) and the (C=N) carbons at δ ~160–162 and δ 131–134 ppm respectively. For the hydrazones, $^1$H-NMR spectra revealed the (NH) proton as singlet at ~12.75–13 ppm, and the $^{13}$C-NMR spectra showed that the ketone carbon signal of the starting isatin at ca. 182 ppm was disappeared in the spectra of the products and substituted with the ketimine (C=N) carbon signal at about 131-134 ppm, while the amidic carbonyl carbon signal of isatin moiety was shifted from ~157 ppm in the starting isatins to about 160-162 ppm in the product.

It has been previously reported that the 3-thiosemicarbazones of isatin that contain a hydrogen atom attached to the N-2" atom can exist in the form of Z-isomer **A** and E-isomer **B** (figure 1), with predominance of the Z-isomer which stabilized by intramolecular hydrogen bonding between N(2")—H and the oxygen of isatin moiety forming a favorable six-membered ring[20,36].

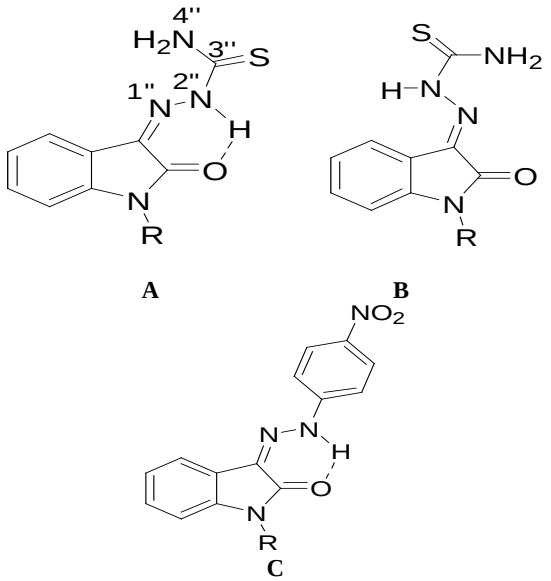



**Figure 1**

The thiosemicarbazones that we obtained evidently also exist primarily in the Z-conformation. Evidence for this is provided by the downfield chemical shifts of the NH proton signals (δ ~ 12.6 ppm). The same low values of chemical shifts are observed for the NH protons in the 1H-NMR spectra of the hydrazones (~12.75–13 ppm), which also provide an evidence for the formation of intramolecular hydrogen bonding-stabilized Z-conformation[37] (i.e.; structure **C** in figure 1). Furthermore, the slight downfield shifts observed in carbon signals for the isatin amide (C-2) from about 157-160 ppm in the starting isatin nucleosides to about 160-163 ppm in their thiosemicarbazones and hydrazones counterparts as well as the lower frequency bands exhibited by the stretching of these amide groups in the IR spectra of the products (1690-1700 $cm^{-1}$), all indicate the contribution of the amide groups in an intramolecular hydrogen bonding and thus the Z-conformation.

The 1H-NMR data for both thiosemicarbazones and hydrazones showed that the *gluco* derivatives exhibited large values of coupling constants between all vicinal hydrogens of the glycon which confirmed the β-configuration at the anomeric C-1' as well as the $^4C_1$ pyranoside conformation. For the *rhamno* derivatives, the $^1C_4$ conformation is confirmed by the large values of coupling constant that observed between vicinal hydrogens on C-3', C-4' and C-5'. The β-configuration, on the other hand, can be deduced based on the agreement of coupling constant values that observed between H-1' and H-2' in starting isatin rhamnosides **16-18** with those in the products **21, 22, 23** and **26, 27, 28**, (i.e.; $^3J_{1',2'}$ =1.5-1.8 Hz) which remain unchanged in all cases.

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