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Synthesis of Some New Chromeno[2,3-b]pyridine and [1,2,4]Triazolo[1,5-a]quinoline Nucleoside Analogues with Expected Biological Activity

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Abstract: Direct preparation of 2-amino-5,6,7,8-tetrahydro-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-*4H*-chromene-3-carbonitrile (**2**) and 1,2-diamino-1,4,5,6,7,8-hexahydro-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-3-quinolinecarbonitrile (**11**) which were utilized as starting products for the synthesis of *S*-nucleoside analogues of kinds **10**, **15** and C-nucleoside analogues of types **12**, **13** is presented in the current study. The antibacterial and antifungal activities of these new compounds were evaluated. The structures of the new products were confirmed on the basis of elemental and spectral analysis results.

Keywords: Chromeno[2,3-*b*]pyridines, [1,2,4]triazolo[1,5-*a*]quinolines, L-rhamnopyranosyl bromide, antimicrobial activity.

INTRODUCTION

Recently, chromene derivatives have attracted much attention, as they exhibited a wide range of biological activities, such as antifungal, antibacterial [1-5], antioxidative [6], antileishmanial [7], antitumor [8], hypotensive [9], antiproliferation [10], local anaesthetic [11], antiallergenic [12, 13], central nervous system (CNS) activities and effects [14], as well as efficacious in the treatment of Alzheimer's disease [15] and schizophrenia disorder [16]. On this basis, it was of great importance to prepare fused chromene derivatives which have platelet antiaggregating, local anaesthetic [17-19] and antihistaminic activities [20]. Recently, the current interest in 5,6,7,8-tetrahydro-4H-chromene derivatives bearing nitrile functionality, especially 2-amino-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitriles, has emerged for their potential application in the treatment of human neurodegenerative disorders [21]. A large number of nucleoside analogues showed different biological activities. Most importantly they could exhibit antitumor [22] and antiviral activities [23] which encouraged us to prepare the corresponding chromene S-nucleoside analogues. On the other hand, quinoline derivatives possess diverse pharmacological activities, including antimicrobial [24], antimalarial [25], antiviral [26], antitumor [27], immunomodulatory [28], caspase-3 inhibiting [29], antileishmanial [30], local anesthetic [31], antiarrhythmic [32] and antiinflammatory activities [33]. Here we report, the synthesis of the novel 1,2-diamino-1,4,5,6,7,8-hexahydro-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-3-quinolinecarbonitrile (11) which was allowed to react with D-glucose and L-rhamnose to form C-nucleosides.

Furthermore, the synthesis [34, 35] of C-nucleosides and their acyclic [36,37] analogues also received much attention due to their documented biological activities [38]. Sugar moieties linking to these structures would enhance their penetration into cells, and therefore contribute to their activities.

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RESULTS AND DISCUSSION

(4-Methoxybenzylidene)malononitrile **1** was reacted with 5,5-dimethylcyclohexane-1,3-dione in refluxing ethanol containing catalytic piperidine to give a yellow solid of 2-amino-5,6,7,8-tetrahydro-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-4H-chromene-3-carbonitrile **2** [39,40] (Scheme **1**).

Refluxing of the compound **2** with ethyl acetoacetate in the presence of pyridine gives the corresponding cyclized product 3-acetyl-4-amino-8,9-dihydro-5-(4-methoxyphenyl)-8,8-dimethyl-1H-chromeno[2,3-b]pyridine-2,6-dione **3**. Similarly, compound 2 with ethyl cyanoacetate in hot ethanol containing catalytic triethylamine gives 4-amino-2,5,6,7,8,9-hexahydro-5-(4-methoxyphenyl)-8,8-dimethyl-2,6-dioxo-1H-chromeno[2,3-*b*]pyridine-3-carbonitrile **4** (Scheme **1**).

Compound **4** was allowed to react with ethyl chloroacetate in DMF in the presence of catalytic amount of potassium carbonate to yield the corresponding compound 5 by electrophilic attack. Compound **5** was reacted with hydrazine hydrate in ethanol giving hydrazide **6**. The IR spectrum of the latter compound revealed the appearance of three absorption bands at 3420, 3220, and 3159 cm^{-1} due to NH_2 and NH functions and the mass spectrum showed a peak corresponding to molecular ion at m/z = 463 (M^+). Subsequently, treatment of hydrazide derivative **6** with D-glucose in refluxing ethanol and glacial acetic acid yields the corresponding hydrazone **7**. Its structure was established on the basis of the appearance of NH absorption band at 3154 cm^{-1} and a carbonyl group at 1684 cm^{-1} in the IR spectrum, whereas ^1H NMR spectrum revealed the presence of a signal due to CH=N at 7.43 ppm.

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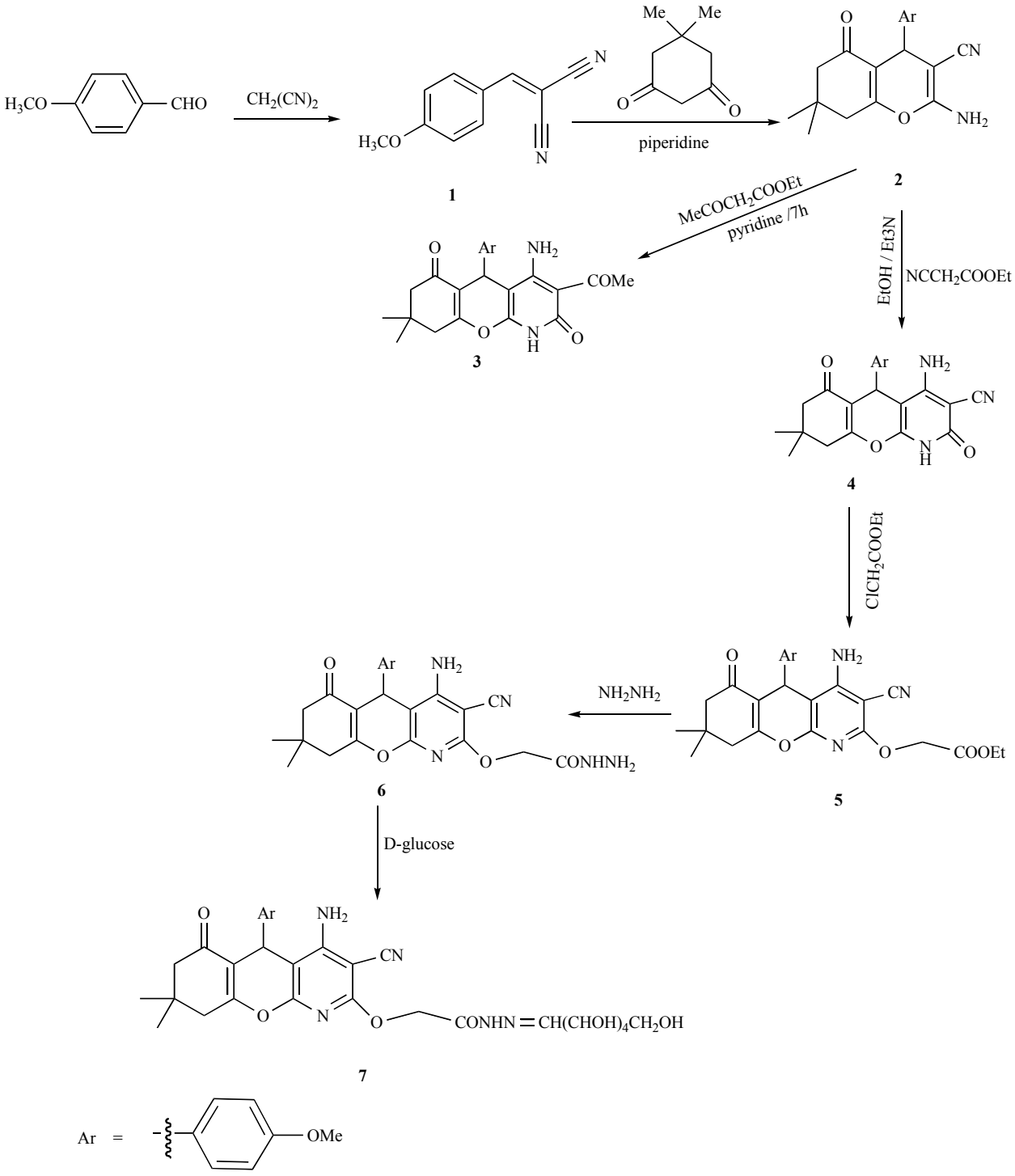
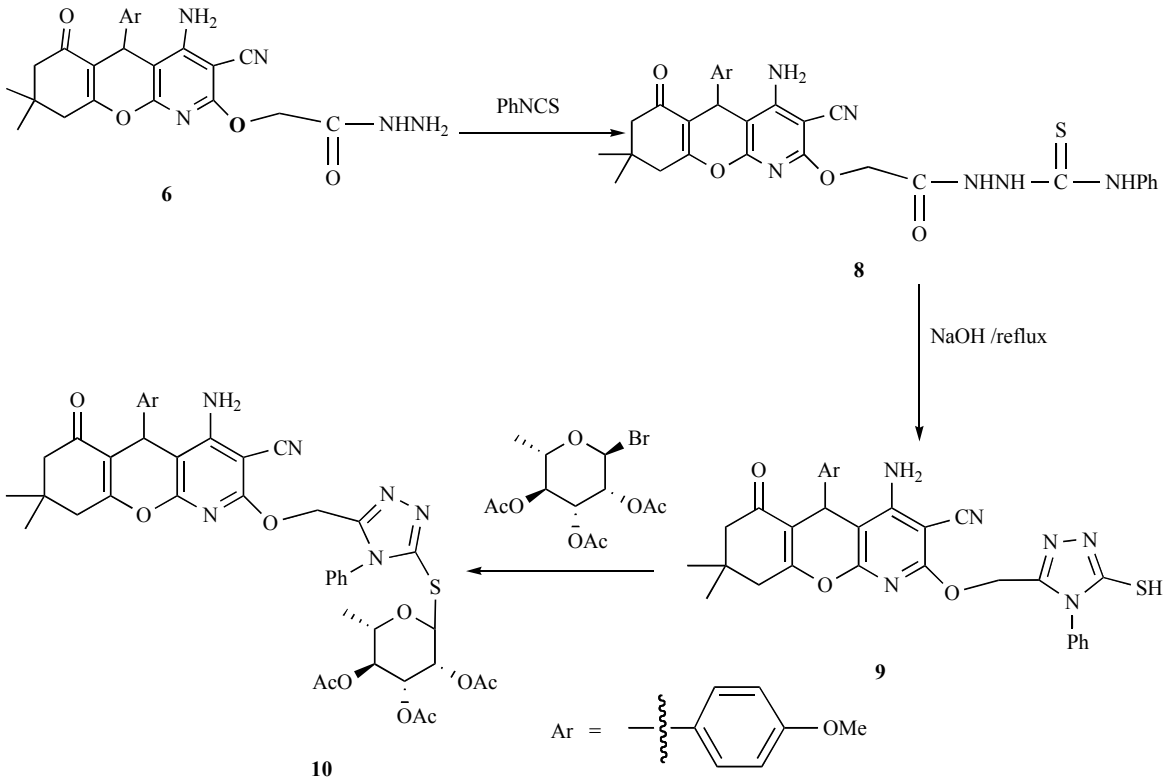


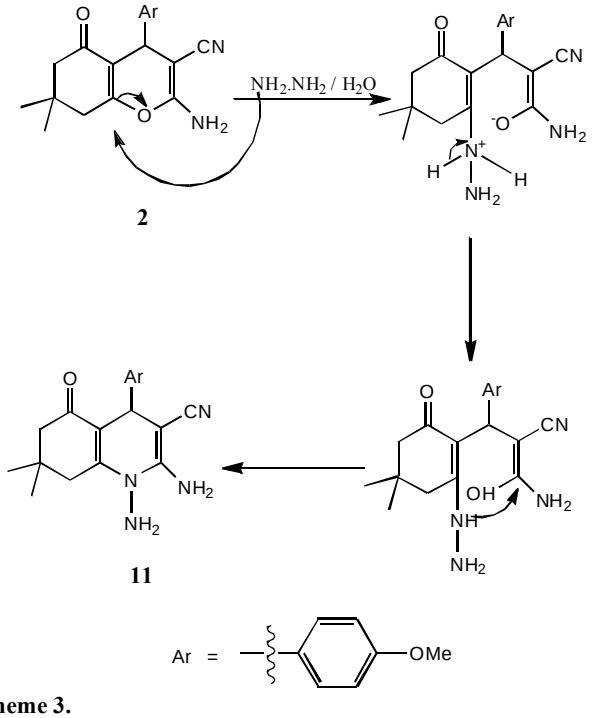
Scheme 1.

Reaction of 2-((4-amino-3-cyano-6,7,8,9-tetrahydro-5-(4-methoxyphenyl)-8,8-dimethyl-6-oxo-5*H*-chromeno[2,3-*b*] pyridin-2-yl)oxy)acetohydrazide **6** with phenyl isothiocyanate in absolute ethanol at reflux produced the corresponding hydrazinecarbothioamide **8** in a good yield. The structure of **8** was confirmed by the IR spectral data, which displayed characteristic absorption bands in the region 3420-3154 cm^{-1} for NH and NH_2, 1694 cm^{-1} for CO and 1348-1335 cm^{-1} corresponding to CS vibrations. The synthesis of compound **9** was achieved by the cyclization of **8** in the presence of sodium hydroxide. When compound **9** was subjected to coupling with 2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl bromide in the presence of potassium hydroxide using ethanol as the solvent, compound **10** was afforded in 66-70% yield (Scheme **2**).

Compound **2** reacted with hydrazine hydrate in the presence of pyridine through the ring opening of chromene. The reaction is presumed to occur *via* nucleophilic attack of the ring, then cyclization to form 1,2-diaminoquinoline



Scheme 2.



Scheme 3.

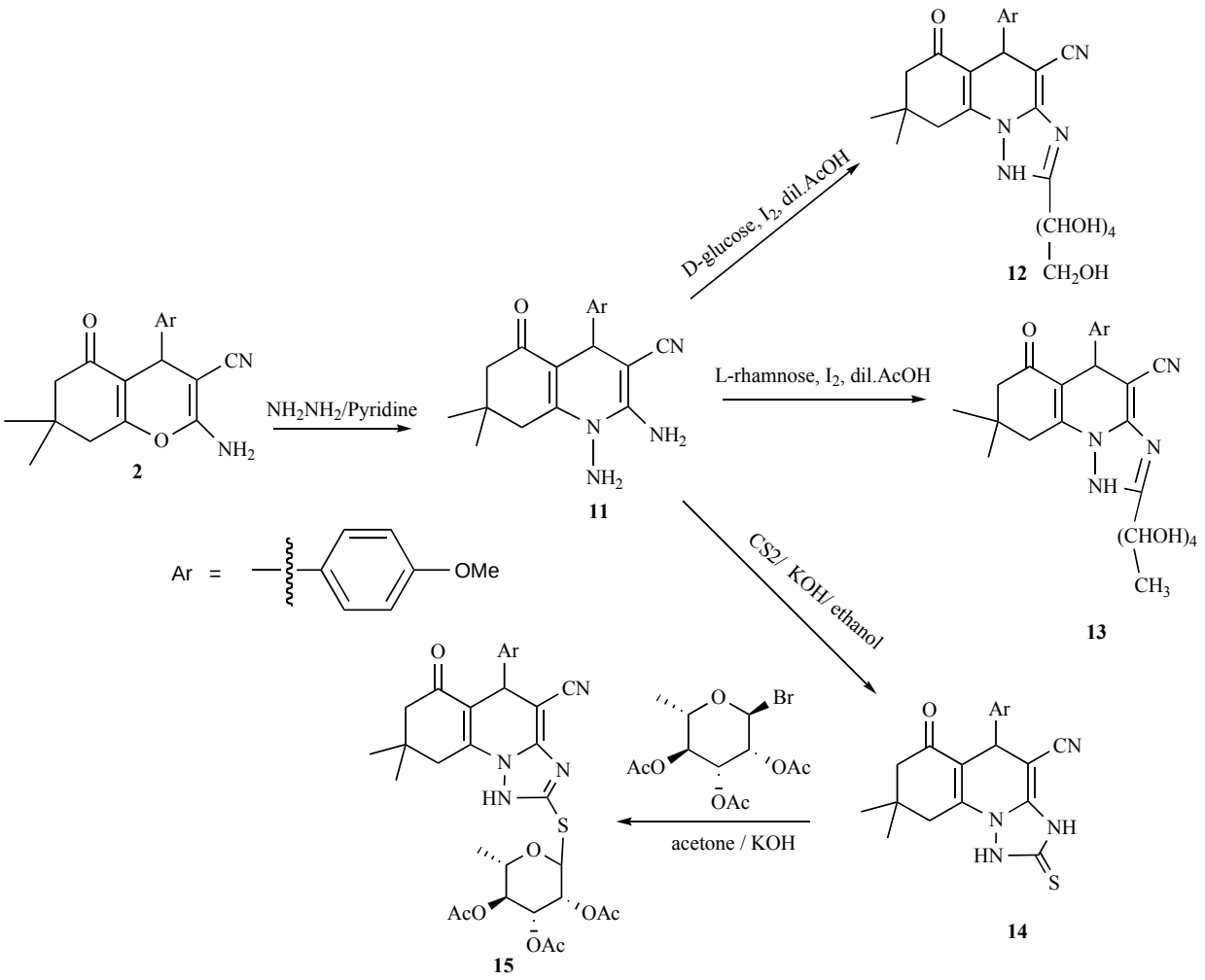
derivative **11**. The suggested mechanism for the formation of compound **11** is outlined in Scheme **3**.

It was very interesting to study the condensation reaction of **11** with D-glucose and L-rhamnose in the presence of methanolic iodine and diluted acetic acid at room temperature under stirring for 22 h, which afforded compounds **12** and **13** (Scheme **4**). The IR spectrum of **12** showed absorption bands at 3363 cm^{-1} due to OH groups, 3126 cm^{-1} due to NH group, 3105 cm^{-1} due to CH aromatic bonds, 2920 cm^{-1} due to CH aliphatic bonds, 2023 cm^{-1} due to CN group.

The IR spectrum of **13** showed absorption bands at 3400 cm^{-1} due to OH groups, 3232 cm^{-1} due to NH group, 2925 cm^{-1} due to CH aliphatic bonds, 2225 cm^{-1} due to CN group.

Compound **11** underwent cyclization with carbon disulfide giving the corresponding triazolo[1,5-a]quinoline derivative **14**. The heterocyclic compound **14** was reacted with 2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl bromide in the presence of potassium hydroxide in acetone and was stirred at room temperature for 17 h to give the corresponding S-glycosylated nucleoside **15** in good yield (Scheme **4**).

Antimicrobial Activity: Some new synthesized compounds were tested for their antibacterial activities using two bacterial strains, namely Staphylococcus aureus which is Gram (+) bacterium and Esherichia coli which is Gram (–) bacterium. In addition, the antifungal activity was also tested using Aspergillus flavus and Candida albicans. The tested compounds were dissolved in DMSO to get 30 mg/mL concentration and the disc diffusion method [41] was used. The inhibition zone was measured in mm at the end of an incubation period of 48 h at 37 °C, and using an inhibition zone diameter in mm/mg sample as criterion for the antimicrobial activity. DMSO showed no inhibition zones. The bactericide chloramphenicol (10 μg/mL) was used as reference for the potency evaluation of the tested compounds under the same conditions. Flucanazole (25 μg/mL) was used as standard antifungal (positive control) while DMSO was used as negative control. The results are depicted in Table **1**. The tested products **7**, **10**, **12**, and **15** exhibited antimicrobial effect. Products 3 and 4 had moderate activity against both Gram (+) and Gram (-) bacteria.



Scheme 4.

Table 1. Screening for antimicrobial activity of the tested compounds.

Inhibition zone diameter(mm/mg of sample)				
Fungus		**Bacterium**		
C. albicans	***A. flavus***	***S. aureus (G+)***	***E. coli (G−)***	**Sample**
11	9	8	10	**3**
11	7	12	10	**4**
16	11	6	17	**7**
6	5	7	12	**10**
10	6	13	10	**12**
16	10	8	8	**13**
12	13	12	11	**15**
-	-	21	21	Chloramphenicol
10	19	-	-	Fluconazole

EXPERIMENTAL SECTION

General Procedures. Melting points were determined on Electrothermal IA 9,100 series digital melting point apparatus in capillaries and are uncorrected. IR spectra were obtained in the solid state as potassium bromide discs using a Perkin-Elmer model 1430 spectrometer. ^{1}H NMR spectra

were recorded on a Varian/Gemini 200 MHz spectrometer in DMSO-d_6 as a solvent and TMS as an internal standard (chemical shifts in δ, ppm). Mass spectra were measured on an instrument VG-7035 at 70 or 15 eV. Elemental analyses were performed at the Microanalytical Centre, Cairo University, and Giza, Egypt.

3-Acetyl-4-amino-8,9-dihydro-5-(4-methoxyphenyl)-8,8-dimethyl-*1H*-chromeno[2,3-*b*]pyridine-2,6-dione (3)

A mixture of **2** (1 mmol) and ethyl acetoacetate (1 mmol) in 50 mL of pyridine was refluxed for 7 h, then the reaction mixture was poured onto ice water and neutralized with hydrochloric acid, filtered, and recrystallized from ethanol to give compound **3.** Yield: 56%, mp 168-170 °C**.** IR (KBr): 3414, 3124 (NH, NH_2), 1681 (C=O), 1215 (C–O) cm^{-1}. ^1H NMR: δ 10.21 (s, 1H, NH), 7.14 (d, 2H, H-Ar), 6.80 (d, 2H, H-Ar), 5.60 (s, 2H, NH_2), 4.30 (s, 1H, CH), 3.76 (s, 3H, OCH_3), 2.13 (s, 3H, CH_3), 2.45 (s, 2H, CH_2), 1.83 (s, 2H, CH_2), 1.10 (s, 3H, CH_3), 1.02 (s, 3H, CH_3). MS: M^+ 408 ($C_{23}H_{24}N_2O_6$). Anal. calcd. for $C_{23}H_{24}N_2O_6$: C, 67.73; H, 5.92; N, 6.86. Found: C, 67.46; H, 5.83; N, 6.32.

4-Amino-2,5,6,7,8,9-hexahydro-5-(4-methoxyphenyl)-8,8-dimethyl-2,6-dioxo-*1H*-chromeno[2,3-*b*]pyridine-3-carbonitrile (4)

To a solution of **2** (1 mmol) in absolute ethanol (30 mL) and triethylamine (5 mL), ethyl cyanoacetate (1 mmol) was added and the reaction mixture was refluxed for 7 h, then left to cool at room temperature, poured onto cold water and neutralized with diluted hydrochloric acid to complete precipitation. The solid obtained was filtered off, washed with water, dried well, and recrystallized from methanol to give compound **4**. Yield: 53-60%, mp 187-189 °C. IR: 3420, 3154 (NH, NH_2), 2187 (CN), 1684 (C=O) cm^{-1}. ^1H NMR: δ 9.12 (s, 1H, NH), 7.23 (d, 2H, H-Ar), 6.80 (d, 2H, H-Ar), 6.30 (s, 2H, NH_2), 4.74 (s, 1H, CH), 3.43 (s, 3H, OCH_3), 2.11 (s, 2H, CH_2), 1.86 (s, 2H, CH_2), 1.13 (s, 3H, CH_3), 1.04 (s, 3H, CH_3). MS m/z = 391 (M+). Anal. calcd. for $C_{22}H_{21}N_3O_4$: C, 67.51; H, 5.41; N, 10.74. Found:C, 64.46; H, 5.93; N, 10.12.

Ethyl 2-((4-amino-3-cyano-6,7,8,9-tetrahydro-5-(4-methoxyphenyl)-8,8-dimethyl-6-oxo-*5H*-chromeno[2,3-*b*] pyridin-2-yl)oxy)acetate (5)

A solution of **4** (1 mmol) in 250 mL of dry DMF was heated at 80–85 °C with ethyl chloroacetate (1 mmol) in an oil bath in the presence of anhydrous potassium carbonate (0.11 mmol). The reaction mixture was cooled and poured onto ice water. A pale yellow crystalline solid was separated, filtered, washed thoroughly first with cold water and then with cold ethanol, recrystallized from 95% ethanol. Yield 70%, mp 273-275 °C. IR: 3433, 3135 (NH_2), 2213 (CN), 1712 (C=O), 1664. ^1H NMR: δ 7.13 (d, 2H, H-Ar), 6.88 (d, 2H, H-Ar), 5.30 (s, 2H, NH_2), 4.93 (s, 2H, CH_2), 4.34 (s, 1H, CH), 3.93 (q, 2H, OCH_2), 3.23 (s, 3H, OCH_3), 2.23 (s, 2H, CH_2), 1.79 (s, 2H, CH_2), 1.24 (t, 3H, CH_3), 1.12 (s, 3H, CH_3), 1.04 (s, 3H, CH_3). MS m/z = 477 (M+) Anal. calcd. for $C_{26}H_{27}N_3O_6$: C, 65.40; H, 5.70; N, 8.80. Found: C, 65.44; H, 5.68; N, 8.76.

2-((4-Amino-3-cyano-6,7,8,9-tetrahydro-5-(4-methoxyphenyl)-8,8-dimethyl-6-oxo-*5H*-chromeno[2,3-*b*]pyridin-2-yl)oxy)acetohydrazide (6)

The reaction of **5** (1 mmol) with hydrazine hydrate (10 mL) in ethanol (30 mL) was heated under reflux for 4 h. The reaction mixture was allowed to cool at room temperature and poured onto water (100 mL). The solid formed was collected by filtration, dried, and crystallized from ethanol to give compound **6** as yellow powder in 83% yield, mp 243-245 °C. IR: 3420, 3220, 3159 (NH, NH, NH_2), 2187(CN), 1685, 1664 (C=O) cm^{-1}. ^1H NMR: 8.22 (d, 2H, H-Ar), 8.05 (br s, 1H, NH, D_2O exchangeable), 7.32 (d, 2H, H-Ar), 6.79 (br s, 2H, NH_2, D_2O exchangeable), 3.94 (s, 1H, CH), 3.55 (br s, 2H, NH_2, D_2O exchangeable), 3.23 (s, 3H, OCH_3), 2.10 (s, 2H, CH_2), 2.03 (s, 2H, CH_2), 1.96 (s, 2H, CH_2), 1.12 (s, 3H, CH_3), 1.04 (s, 3H, CH_3). MS m/z = 463 (M+). Anal. calcd for $C_{24}H_{25}N_5O_5$:C, 62.19; H, 5.44; N, 15.11. Found: C, 62.23; H, 5.41; N, 15.31.

2-((4-Amino-3-cyano-6,7,8,9-tetrahydro-5-(4-methoxyphenyl)-8,8-dimethyl-6-oxo-*5H*-chromeno[2,3-*b*]pyridin-2-yl)oxy)-*N*'-((*2S,3R,4R,5R*)-2,3,4,5,6-pentahydroxyhexylidene)acetohydrazide (7)

A mixture of compound **6** (1 mmol), D-glucose (1 mmol), ethanol (30 mL), and a catalytic amount of glacial acetic acid (3 drops) was heated at 80 °C for 2 h. The formed precipitate was filtered off, dried, and recrystallized from ethanol to give compound 7. Yield: 43%, mp 205-207 °C. IR: 3420, 3154 (NH, NH_2), 2187(CN), 1684 (C=O) cm^{-1}. ^1H NMR: δ 8.58 (s, 1H, NH), 7.43 (m, 1H, N=CH), 7.23 (d, 2H, H-Ar), 6.80 (d, 2H, H-Ar), 5.2-5.5 and 3.7-3.9 (two m, 8H, H-2`-5`, H_2-6`, OCH_2), 5.2-4.3 (m, 5 x OH, D_2O exchangeable), 4.99 (s, 2H, NH_2), 4.74 (s, 1H, CH), 3.43 (s, 3H, OCH_3), 2.11 (s, 2H, CH_2), 1.86 (s, 2H, CH_2), 1.13 (s, 3H, CH_3), 1.04 (s, 3H, CH_3). Anal. calcd. for $C_{30}H_{35}N_5O_{10}$: C, 57.59; H, 5.64; N, 11.19. Found. C, 57.96; H, 6.03; N, 11.21.

2-(2-((4-Amino-3-cyano-6,7,8,9-tetrahydro-5-(4-methoxyphenyl)-8,8-dimethyl-6-oxo-*5H*-chromeno[2,3-*b*]pyridin-2-yl)oxy)acetyl)-*N*-phenylhydrazinecarbothioamide (8)

A mixture of **6** (1 mmol) and phenyl isothiocyanate (1 mmol) in 50 mL of DMF containing a catalytic amount of triethylamine (4 drops) was refluxed for 5 h and then left to cool at room temperature. The reaction mixture was poured into cold water for complete precipitation, and then the solid was filtered off, washed with water, dried well and recrystallized from aqueous methanol to give compound 8. Yield: 62%, mp 263-265 °C. IR: 3420, 3154 (NH, NH_2), 2187 (CN), 1694 (C=O), 1356 (C=S) cm^{-1}. ^1H NMR: δ 11.59 (br s, 1H, NH), 10.40 (br s, 1H, NH), 8.12 (s, 1H, NH), 7.23 (d, 2H, H-Ar), 7.1-7.0 (m, 5H, PhNH), 6.80 (d, 2H, H-Ar), 6.21 (s, 2H, NH_2), 4.74 (s, 1H, CH), 4.22 (s, 2H, OCH_2), 3.43 (s, 3H, OCH_3), 2.11 (s, 2H, CH_2), 1.86 (s, 2H, CH_2), 1.13 (s, 3H, CH_3), 1.04 (s, 3H, CH_3). MS m/z = 598 (M+). Anal. calcd. for $C_{31}H_{30}N_6O_5S$: C, 62.19; H, 5.05; N, 14.04; S, 5.36. Found: C, 62.34; H, 5.13; N, 14.12; S, 5.66.

4-Amino-6,7,8,9-tetrahydro-2-((5-mercapto-4-phenyl-*4H*-1,2,4-triazol-3-yl)methoxy)-5-(4-methoxyphenyl)-8,8-dimethyl-6-oxo-5H-chromeno[2,3-*b*]pyridine-3-carbonitrile (9)

A mixture of **8** (1 mmol) in ethanolic NaOH (100 mL, 5%) was heated under reflux for 4 h. The reaction mixture was left to cool to room temperature, then poured into ice cold water (50 mL) and neutralized with dilute hydrochloric acid; the separated material was filtered off and recrystallized from ethanol to give compound 9. MS m/z = 580 (M+). Anal. calcd. for $C_{31}H_{28}N_6O_4S$: C, 64.12; H, 4.86; N, 14.47; S, 5.52. Found: C, 64.36; H, 4.69; N, 14.32; S, 5.40.

(*3R,4R,5S,6S*)-2-((5-(((4-Amino-3-cyano-6,7,8,9-tetrahydro-5-(4-methoxyphenyl)-8,8-dimethyl-6-oxo-*5H*-chromeno[2,3-*b*]pyridin-2-yl)oxy)methyl)-4-phenyl-4H-1,2,4-triazol-3-yl)thio)-3,4,5,6-tetrahydro-6-methyl-*2H*-pyran-3,4,5-triyl triacetate (10)

Compound **9** (2 mmol) was dissolved in a solution of KOH (2 mmol) in ethanol (25 mL). After stirring of the mixture at room temperature for 30 min, 2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl bromide (2 mmol) was added. The reaction mixture was stirred at room temperature for 48 h. The mixture was concentrated and washed with water. The crude product was purified by flash column chromatography. Yield: 66-70%, mp 210-212 ^oC. IR: 3436, 3144 (NH_2), 2187 (CN), 1684 (C=O) cm^{-1}. ^1H NMR: δ 7.7-7.3 (m, 5H, PhNH), 7.23 (d, 2H, H-Ar), 6.80 (d, 2H, H-Ar), 6.30 (s, 2H, NH_2), 5.09 (d, 1H, H-1`), 4.74 (s, 1H, CH), 4.36 (2H, $OCH_2$), 3.87 (dd, 1H, H-4`), 3.68 (dd, 1H, H-5`), 3.6-3.4 (m, 2H, H-2`,3`), 3.43 (s, 3H, OCH_3), 2.30 (s, 3H, H_3-6'), 2.11 (s, 2H, CH_2), 2.11, 2.05, and 1.99 (three s, 9H, 3 x CH_3CO), 1.86 (s, 2H, CH_2), 1.13 (s, 3H, CH_3), 1.04 (s, 3H, CH_3). MS m/z = 852 (M+). Anal. calcd. for $C_{43}H_{44}N_6O_{11}S$: C, 60.55; H, 5.20; N, 9.85; S, 3.76. Found: C, 60.36; H, 5.49; N, 9.20; S, 3.32.

1,2-Diamino-1,4,5,6,7,8-hexahydro-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxoquinoline-3-carbonitrile (11)

A mixture of **2** (1 mmol) and hydrazine hydrate (10 mL) in pyridine (30 mL) was heated under reflux for 4 h. The reaction mixture was allowed to cool at room temperature, poured onto water (100 mL), and neutralized with hydrochloric acid. The solid formed was collected by filtration, dried, and crystallized from ethanol, to give compound 11 as brown powder. Yield: 63%, mp 145-147 ^oC. IR: 3410, 3154 (NH_2), 2227 (CN), 1684 (C=O) cm^{-1}. ^1H NMR: δ 7.07 (d, 2H, H-Ar), 6.83 (d, 2H, H-Ar), 6.21 (s, 2H, NH_2), 3.30 (s, 3H, OCH_3), 3.24 (s, 1H, CH), 2.32 (s, 2H, NH_2), 2.11 (s, 2H, CH_2), 1.86 (s, 2H, CH_2), 1.13 (s, 3H, CH_3), 1.04 (s, 3H, CH_3).

1,5,6,7,8,9-Hexahydro-2-((*1S,2R,3R,4R*)-1,2,3,4,5-pentahydroxypentyl)-5-(4-methoxyphenyl)-8,8-dimethyl-6-oxo-[1,2,4]triazolo[1,5-a]quinoline-4-carbonitrile (12)

Compound **11** (1 mmol) and D-glucose (1 mmol) were dissolved in a solution of iodine (1 mmol) in acetic acid (5 mL) at room temperature until the D-glucose was completely consumed as indicated by the TLC. The reaction mixture was quenched by addition of $Na_2S_2O_3$ (2 mL of saturated aqueous solution), and the mixture was concentrated under reduced pressure to give crude product which was washed successively with water and methanol, then recrystallized from ethanol to give **12** as yellow powder, 68% yield, mp 212-214 °C. IR: 3432, 3363 (OH), 3126 (NH), 3105, 2920, 2023 (CN), 1687 (CO) cm^{-1}. ^1H NMR: δ 10.12 (s, 1H, NH), 7.07 (d, 2H, H-Ar), 6.83 (d, 2H, H-Ar), 5.49 (m, 1H, H-2`), 4.74 (s, 1H, CH), 4.41 (m, 1H, H-3`), 4.30 (m, 2H, H_2-5`), 3.78 (m, 1H, H-4`), 3.59 (m, 5H, 5 x OH, D_2O exchangeable), 3.43 (s, 3H, OCH_3), 2.31 (s, 2H, CH_2), 1.89 (s, 2H, CH_2), 1.13 (s, 3H, CH_3), 1.04 (s, 3H, CH_3).

1,5,6,7,8,9-Hexahydro-2-((*S,S,S,S*)-1,2,3,4-tetrahydroxypentyl)-5-(4-methoxyphenyl)-8,8-dimethyl-6-oxo-[1,2,4]triazolo[1,5-*a*]quinoline-4-carbonitrile (13)

It was prepared by the same conditions used for the compound **12**. The product was crystallized from methanol to give **13** as yellow powder. Yield: 78%, mp 203-205 °C. IR: 3400 (OH), 3232 (NH), 2925, 2225 (CN), 1684 (C=O) cm^{-1}. MS m/z = 482 (M+). Anal. calcd. for $C_{25}H_{30}N_4O_6$: C, 62.23; H, 6.27; N, 11.61. Found: C, 62.69; H, 6.12; N, 11.39.

1,2,3,5,6,7,8,9-Octahydro-5-(4-methoxyphenyl)-8,8-dimethyl-6-oxo-2-thioxo-[1,2,4]triazolo[1,5-a]quinoline-4-carbonitrile (14)

A mixture of **11** (1 mmol) and carbon disulfide (1 mmol) in ethanolic potassium hydroxide (1 mmol) was refluxed for 5 h, after cooling the reaction mixture was poured onto ice. The solid obtained was filtered, washed with water, and crystallized from DMF to give compound **14** as yellow crystals, yield 75%, mp 233-235 ^oC. IR: 3431, 3254 (NH), 2157 (CN), 1689 (C=O), 1346 (C=S) cm^{-1}. ^1H NMR: δ 9.80 and 10.03 (two br s, 2H, 2NH), 7.22 (d, 2H, H-Ar), 6.83 (d, 2H, H-Ar), 4.74 (s, 1H, CH), 3.32 (s, 3H, OCH_3), 2.41 (s, 2H, CH_2), 1.89 (s, 2H, CH_2), 1.13 (s, 3H, CH_3), 1.04 (s, 3H, CH_3). MS m/z = 380 (M+). Anal. calcd. for $C_{20}H_{20}N_4O_2S$: C, 63.14; H, 5.30; N, 14.73; S, 8.43. Found: C, 63.54; H, 5.13; N, 14.42; S, 8.66.

(*3R,4R,5S,6S*)-2-((4-Cyano-1,5,6,7,8,9-hexahydro-5-(4-methoxyphenyl)-8,8-dimethyl-6-oxo-[1,2,4]triazolo[1,5-a]quinolin-2-yl)thio)-3,4,5,6-tetrahydro-6-methyl-2H-pyran-3,4,5-triyl triacetate (15)

To a solution of **14** (1 mmol) in aqueous potassium hydroxide (0.73 g in 10 mL of distilled water), a solution of 2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl bromide (1 mmol) in acetone (40 mL) was added. The reaction mixture was stirred at room temperature for 24 h (under TLC control). The solvent was evaporated under reduced pressure and the crude product was filtered off and washed with distilled water to remove KBr formed. The product was dried, and crystallized from hexane. Yield: 60%, mp 179-181 ^oC. IR: 3419, 3132 (NH), 2187 (CN), 1684 (C=O) cm^{-1}. ^1H NMR: δ 9.12 (s, 1H, NH), 7.12 (d, 2H, H-Ar), 6.79 (d, 2H, H-Ar), 5.09 (d, 1H, H-1`), 4.34 (s, 1H, CH), 3.87 (dd, 1H, H-4`), 3.68 (dd, 1H, H-5`), 3.6-3.4 (m, 2H, H-2`,3`), 3.53 (s, 3H, OCH_3), 2.71 (s, 2H, CH_2), 2.11, 2.13, and 2.16 (three s, 9H, 3 x CH_3CO), 1.86 (s, 2H, CH_2), 1.15 (s, 3H, CH_3), 1.04 (s, 3H,

CH_3), 1.02 (s, 3H, CH_3). MS m/z = 652 (M+). Anal. calcd. for $C_{32}H_{36}N_4O_9S$: C, 58.88; H, 5.56; N, 8.58; S, 4.91. Found: C, 58.91; H, 5.53; N, 8.51; S, 4.88.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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Declared none.

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's web site along with the published article.

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