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Synthesis New of Nucleoside of 1,3-bis-(2,3,5-tri-*O*-Benzoyl-*β*-D-Ribofuranosyl)-8-(Trifluoromethyl)-2-Methyl-4-Quinazolinone †

Laila Mohammed Break and Wafa Saad Al-harthi *

Department of Chemistry, Faculty of Science, Taif University, Taif 888, Saudi Arabia; lailabreek@gmail.com

* Correspondence: alwafa2009ww@hotmail.com

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Abstract: Fluorinated nucleosides are very important for increased biological and chemical stability of organ fluorine compounds. Synthesis of (*1H*)-8-triflulorомethyl-2-methyl-4-quinazolinone **3** from 2-amino-3-(trifluoromethyl) benzoic acid **1** was performed**.** Ribosylation of compound **4** with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranose **5** using the silylation method created the benzoylated nucleoside derivative **6**. Debenzoylation of the protected nucleoside **6** via reaction with sodium metal in dry methanol to create the corresponding free nucleoside 1,3-*bis*-(2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl)-8-(trifluoromethyl)-2-methyl-4-quinazolinone **7**. The structures of the newly synthesis compounds have been confirmed on the basis of IR, ^{1}HNMR, ^{13}CNMR, and mass spectral data.

Keywords: 1-*O*-Acetyl-2,3,5-trihydroxy-*β*-D-ribofuranose; nucleosides; 2-Methyl-4-quinazolinone; trifluoromethylquinazolinone

1. Introduction

Quinazolines and quinazolinones are a large class of biologically active compounds that exhibit a broad spectrum of biological activities such as anti-HIV, anticancer, antifungal, antibacterial, antimutagenic, anticoccidial, anticonvulsant, anti-inflammatory, antidepressant, antimalarial, antioxidant, antileukemic, and antileishmanial activities, among others [1–3]. The most interesting method for the synthesis of new nucleoside containing the quinazolinone is will apply the biologically effect.

2. Material and Methods

2-amino-6-(trifluoromethyl)benzoic acid, hexamethyldisilazane (HMDS), l-*O*-acety1–2,3–5-tri-*O*-benzoyl-*β*-D-ribofuranose, and trimethylsilyltrifluorosulfonate **(**TMSOTf) were purchased from Sigma Aldrich. Thin layer chromatography (TLC) was performed on Schleicher & Schull silica gel sheets F1550 LS 254 and column chromatography on Merck silica gel 60 (particle size 0.063–0.20). Melting points were measured on an electrothermal digital melting point apparatus. The ^{1}H and ^{13}C NMR spectra were recorded in deuterochloroform ($CDCl_3$) and deuterated methanol (CD_3OD) at 850 MHz on an NMR spectrometer (King Abdel-Aziz University). IR spectra were recorded on KBr discs using Fourier transform infrared and Pie Unicom SP 300 Infrared Spectrophotometers at Taif University, Taif, Saudi Arabia. Mass spectra were recorded on a GC MS-QP 2000 EX at King Abdel-Aziz University, Jeddah, Saudi Arabia**.**

3. Experimental

Synthesis of 2-Methyl-8-(Trifluoromethyl)benzo[2,3-d] 4-Oxazinone **2**: Compound **2** was prepared via refluxing 2-amino-3-(trifluoromethyl) benzoic acid **1** (3 g, 0.015 mol) with an acetic anhydride for 1 h. The residue was evaporated and washed several times with petroleum ether, then filtered and dried. Yield 2.64 g, (79.04%); m.p. 132 °C.

Synthesis of of 1H-2-Methyl-8-(Trifluoromethyl)-4-Quinazolinone **3:** Compound **3** was prepared by refluxing 2.6 g (0.01 mol) of compound **2** with 10 mL of ammonia, refluxing for 6 h, cooling, and treating with a few drops of acetic acid. Yield, 2.3 g (92%); m.p. 232–236 °C; ^{1}HNMR $CDCl_3$: 11.75 (s, 1H) NH; 8.48 (d, 1H; *J* = 6.8 Hz) H_5; 8.09 (d, 1H; *J* = 7.65 Hz) H_7; 7.52 (t, 1H) H_6; 2.63 (s, 3H) CH_3. ^{13}CNMR $CDCl_3$: 163.30, 154.18, 147.15, 132.94, 130.38, 125.33, 124.10, 122.82, 121.54, 22.59; Mass: M^+ = 229.05(100%), 218.21, 209.05, 155.08, 151.03. Formula. $C_{10}H_7F_3N_2O$; M.wt: 228.17.

Ribosylation of 1H-8-(Trifluoromethyl)-2-Methyl-4-Quinazolinone: Synthesis of 1,3-bis-(2,3,5-tri-O-benzoyl-β-D-Ribofuranosyl)-8-(Trifluoromethyl)-2-Methyl-4-Quinazolinone **6**. 1H-8-(trifluoromethyl)-2-methyl-4-quinazolinone **3** (0.01 mol) and dry hexamethyldisilazane (20 mL) was heated under reflux for 24 h with a catalytic amount of ammonium sulfate. It was evaporated to dryness under anhydrous condition to give the silylated derivative **4**, which was directly added (40 mL) to dry 1,2-dichloroethane, 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose **5** (2.1 g, 0.004 mol), and trimethylsilyltrifluoromethanesulfonate (6 mL) was used as a catalyst. After the solution had been stirred for 3 weeks (TLC) at room temperature, it was washed with a saturated solution of aqueous sodium bicarbonate (3 × 20 mL) and water (3 × 20 mL), and dried over anhydrous sodium sulfate. The pure product was separated using silica gel column chromatography with chloroform and ester (90:2), which produced a yellow solid. Yield 0.1083 g, (2.88%); m.p. 110 °C; ^{1}HNMR $CDCl_3$: 8.08–7.26 (m, 1H) Aromatic protons; 6.69 (d, 1H, *J* = 5.1 Hz) $H_{1''}$, 5.90(t, 1H)$H_{2''}$, 5.80–5.78 (q, 1H) N-CH-N; 5.69–5–63 (ds,1H; *J* = 4.25 Hz) $H_{1'}$; 5.59–5.47 (tt, 1H)$H_{2'}$; 5.35 (d, 1H, *J* = Hz) $H_{3''}$; 5.15–5.09 (d,1H, *J* = 5.1 Hz) $H_{3'}$; 4.80–4.60 (m, 1H) $H_{4''}$; 4.59–4.47 (dd,1H; *J* = 5.1 Hz) $H_{4'}$; 4.49–4.35 (m,1H) $H_{5''}$; 3.81–3.45 (m,1H) $H_{5'}$; sugars protons; 1.25–1.4 (dm, 3H, $^{7}J_{H-F}$ = 6.8 Hz) CH_3; ^{13}CNMR $CDCl_3$: 166.50, (166.20d, J_{C-F} = 12.78 Hz), 166.07, (165.60d, J_{C-F} = 23.43), 165.47, 165.36, 165.24 C=O groups, 133.67, 133.59, 133.53, 133.46, 133.36, 133.24, 133.18, 133.12, 129.88, 129.84, 129.79, 129.76, 129.65, 129.50, 129.19, 129.04, 128.92, 128.84, 128.63, 128.58, 128.51, 128.45, 128.41, 128.35, 128.47, 128.37, 127.28, 107.35, 104.87, 100.49, 95.85, 80.85, (79.68d $C_{2'}$ J_{C-F} = 14.91 Hz), 78.33, 76.15, (74.91d, J_{C-F} = 72.42 Hz), 74.57, 72.33, (71.90dt J_{C-F} = 31.95C3′), (65.17d, J_{C-F} = 6.39 Hz), 64.74, 64.16, 63.73 N-CH-N, 22.71 CH_3. Formula $C_{62}H_{49}F_3N_2O_{15}$; M.wt: 1119.05.

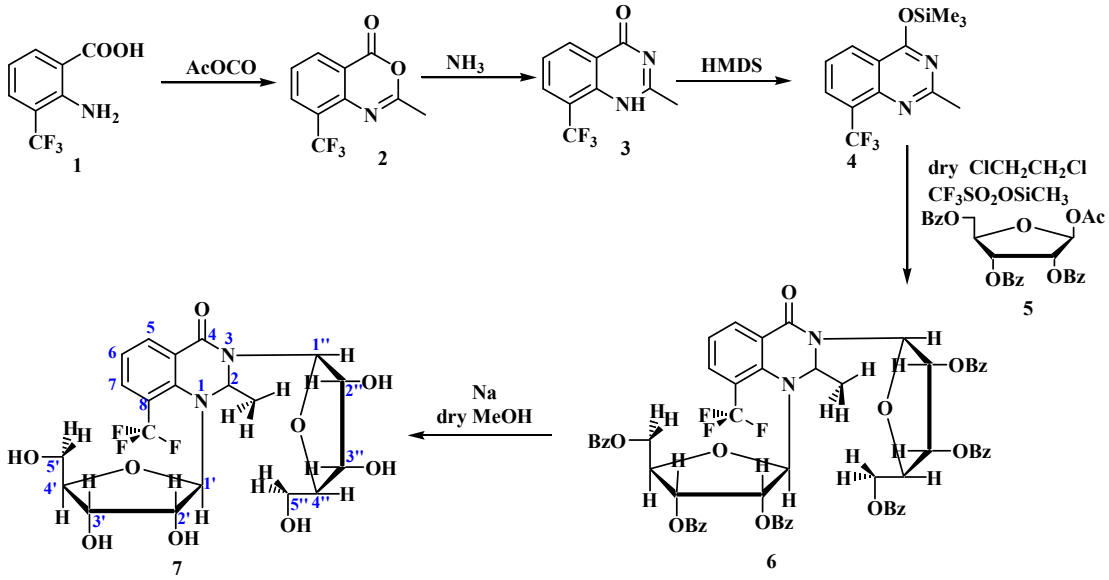
Deprotection of 1,3-bis-(2,3,5-tri-O-Benzoyl-β-D-Ribofuranosyl)-8-(Trifluoromethyl)-2-Methyl-4-Quinazolinone: Synthesis of 2-Methyl-1,3-bis-(β-D-Ribofuranosyl)-8-(Trifluoromethyl)-4-Quinazolinone **7**. The protected nucleoside (0.2mmol) **6**, absolute methanol (20 mL) and sodium metal (0.013 g, 0.5 mmol) was stirred at room temperature for 24 h (TLC). The solvent was evaporated under vacuum and the residue was dissolved in hot water and neutralized with few drops of acetic acid. The precipitate formed was filtered, dried, and crystallized from water to leave yellow crystals of free nucleoside **7**.

Yield 0.0569 g, (92.97%); m.p 224 °C; ^{1}HNMR CD_3OD: 8.53 (s, 1H) H_5; 7.93 (dd, 1H; *J* = 6.8 Hz) H_7; 7.56–7.39–7.32 (tt, 1H) H_6; 5.24 (d, 1H; $^{3}J_{H,H}$ = 4.25 Hz) $H_{1'}$; 5.11–5.08 (dd, 1H) $H_{2'}$; 4.93 (d, 1H; *J* = 4.25 Hz) $H_{1''}$; 4.87 (s,1H) OH, 4.85 (s,1H) OH, 4.77 (d, 1H) OH, 4.14–4.11 (m,1H) $H_{3'}$; 4.06–4.03 (m,1H) $H_{3''}$; 3.94–3.84 (m,1H) $H_{4'}$, 3.78–3.67 (m,1H) $H_{4''}$; 3.65–3.63 (q,1H) CH; 3.55–3.52 (m,1H) $H_{5'}$; 3.48–3.43 (m,1H) $H_{5''}$; 3.40 (s,1H) OH; (m, 1H)sugar protons; 2.34 (t, 1H) OH; 1.95 (s, 1H) OH; 1.88 (t, 1H) OH; 1.81 (s, 1H) OH; 1.27 (d, 1H; $^{3}J_{H\_H}$ = 28.9 Hz)CH_3. ^{13}CNMR CD_3OD: . 180.24, 170.41 (d, $^{3}J_{C-F}$ = 6.39 Hz) C9, 131.26 C_5, 130.24 C_7, 128.70 C_6, 108.52 CF_3, 104.49 C10, 102.94 (d, $^{2}J_{C-F}$ = 29.82 Hz) C_8, 96.08 $C_{1'}$, 84.75 $C_{1''}$, 76.37 (d, $J_{C,F}$ = 14.91 Hz) $C_{2'}$, 74.97 $C_{3''}$, 73.94 $C_{3'}$, 73.15–72.74 (d, $J_{C,F}$ = 87.33 Hz) $C_{4'}$, 72.02–71.13d $C_{4''}$, 70.09 $C_{5''}$, 68.83 C_2, 65.55–64.03 (m) $C_{5'}$, 15.43 CH_3; MS m/z: M^+ 493..01, 479.00, 469.32, 437.18,

413.26, 393.29, 381.29, 360.32, 305.08, 173.04 (100%), 135.00, 104.99. Formula: $C_{20}H_{25}F_3N_2O_9$; M.wt: 494.42.

4. Results and Discussion

The structures of the products **3, 6–7** were established and confirmed on the basis of their spectral data (^{1}H, ^{13}C NMR, and mass spectra) (see the Experimental section) (Scheme 1). The structure of Compound **3** was confirmed using ^{1}H NMR, consisting of a broad, highly deshielded, singlet proton signal resonating at δ11.75, which is characteristic of the quinazolinone proton (NH), and protons signal the aromatic region for H5, H7, and H6 at δ8.48, 8.09, and 7.52, respectively. Furthermore, the singlet proton signal was found at δ2.63 of CH_3. ^{13}C NMR, consisting of one signal of carbonyl group at δ163.30, contained eight carbon signals of the aromatic region at δ154.18, 147.15, 132.94, 130.38, 125.33, 124.10, 122.82, and 121.54 and CH_3 group at δ22.59. Mass: M^+ = 229.05 (100%).



Scheme 1. Synthesis of nucleoside 8-trifluoro methyl-2-methyl-4-quinazolinone.

The ^{1}H NMR spectrum of Compound **6** is a complex spectrum showing the protons signals of the aromatic region of benzoyl groups and quinazolinone moiety at δ8.08–7.26. For the observation of CF_3 groups, coupling constants for protons of the ribose moiety of an atom on N1 suggests this could be a cancellation of through-space and through-bond couplings. Meanwhile the protons' ribose moiety on N3 decoupling was not affected by ^{19}F. The proton's two glycoside bonds on N1 and N3 produced doublet signals at δ6.69 (d, 1H, $^3J_{H\text{-}H}$ = 5.1 Hz) $H_{1''}$ and 5.69–5.63 (d,1H; $^3J_{H\text{-}H}$ = 4.25 Hz) $H_{1'}$ for compound **6**, which confirmed the β-anomeric configuration [4–7].

The ^{13}C NMR spectra of nucleoside products revealed the signals were due to the seven lines of carbon carbonyl groups at 166.50, (166.20d, $J_{C\text{-}F}$ = 12.78 Hz) $C_{2'}$, 166.07, (165.60d, $J_{C\text{-}F}$ = 23.43) $C_{3'}$, 165.47, 165.36, and 165.24 C=O's groups for compound **6**, while showing the signals at 133.67–98.85 for aromatic carbons for compound **6**, and the signals for CH and CH_3 at 63.73 and 22.71, respectively.

Deprotection of the benzoyl group of protection nucleoside by Na in dry MeOH formed free nucleoside **7**. ^{1}H NMR confirmed successful benzoyl groups with the absence of the proton signals, while the proton quinazolinone signals (H_5, H_6, and H_7), and the two proton glycoside bonds produced doublet signals that were assigned to $C_{1'}$ and $C_{1''}$ at 5.24 (d, 1H; J = 4.25 Hz) $H_{1'}$ and 4.93 (d, 1H; J = 4.25 Hz) $H_{1''}$, respectively. ^{13}C NMR fluorine couplings appeared in 1D carbon-13 spectra at 170.41 (d, $^3J_{C\text{-}F}$ = 6.39 Hz) C_9, and 102.94 (d, $^2J_{C\text{-}F}$ = 29.82 Hz) C_8 of the quinazolinon ring. In addition, 76.37 (d, $J_{C,F}$ = 14.91 Hz) $C_{2'}$ and 73.15–72.74 (d, $J_{C,F}$ = 87.33 Hz) $C_{4'}$ of the sugar moiety was found on N1 of the through-space.

The ten signals of carbon were assigned to two of the sugar moieties (see the Experimental section). The ^{13}C NMR of the CF_3 group showed at δ121.54, 104.87 and 108.52 of Compounds **3**, **6**, and **7**, respectively Mass: M^+ 493.01, 173.04 (100%)[8,9].

5. Conclusions

Quinazolinone nucleosides are scientifically important in many biologically active compounds. Therefore, synthesis and characterization of 8-triflulorомethyl-2-methylquinazolin-(*1H*)-4-one **3** was undertaken in this study. Ribosylation of compound **4** with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranose **5** created -anomeric of the benzoylated nucleoside derivative **6**. Debenzoylation of the latter created the corresponding new free N-nucleoside **7**. Compounds obtained were identified using their spectral analysis.

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