Synthesis new of nucleoside of 1,3-bis-(2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl)-8-(trifluoromethyl)-2-methyl-4-quinazolinone

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Abstract

Fluorinated nucleosides very important in 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.** Ribosylation of compound **4** with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranose **5** by using the silylation method, afforded the benzoylated nucleoside derivative **6**. Debenzoylation the protected nucleoside **6** by reaction with sodium metal in dry methanol to afford 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 quinazolinone are a large class of biologically active compounds that exhibited broad spectrum of biological activities such as anti-HIV, anticancer, antifungal, antibacterial, antimutagenic, anticoccidial, anticonvulsant, anti-inflammatory, antidepressant, antimalarial, antioxidant, antileukemic, and antileishmanial activities and otheractivities. (Asif M., 2014, Alafeefy A. M., 2011 and Abbas S. E etal. 2013). The most interesting method for the synthesis of new nucleoside containing the quinazolinone moiety.

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, from Sigma Aldrich. Thin layer chromatography (TLC) was performed on silica gel sheets F1550 LS 254 of Schleicher & Schull 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 NMR spectrometer (King Abdel Azeez University), IR spectra were recorded on KBr discs on Fourier Transform infrared and Pie Unicom SP 300 Infrared Spectrophotometers at Taif University. Mass spectra were recorded on a GC MS-QP 2000 EX at King Abdel-Aziz University, Saudi Arabia**.**

3. Experimental:

Synthesis of 2-methyl-8-(trifluoromethyl)benzo[2,3-d] 4-oxazinone (2):

Compound **2** was prepared by refluxing 2-amino-3-(trifluoromethyl) benzoic acid **1** (3g, 0.015 mol) with an acetic anhydride for 1 h. The residue was evaporated and washed several times with petroleum ether, 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 an ammonia, refluxing for 6 h, cooling, treating with a few drops of acetic acid. Yield, 2.3g (92%); m.p. 232-236°C; ^{1}HNMR $CDCl_3$: δ 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 $CDCl_3$: δ 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 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** (0.01mol) 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) of dry 1,2-dichloroethane, 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranose **5** (2.1g, 0.004 mol), and trimethylsilyltrifluoromethanesulfonate (6 ml) as catalyst. After the solution had been stirred for 3 weeks (TLC) at room temperature, it washed with a saturated solution of aqueous sodium bicarbonate (3×20 ml), water (3× 20 ml) and dried over anhydrous sodium sulfate. The pure product was separated by silica gel column chromatography with chloroform and ester (90:2), was obtained as a yellow solid. Yield 0.1083 g, (2.88%); m.p. 110 °C; ^{1}HNMR $CDCl_3$: δ 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*= 5.1Hz)$H_{3'}$; 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;1.25-1.24(dm, 3H, $^{7}J_{H\text{-}F}$=6.8Hz)CH_3; ^{13}CNMR $CDCl_3$: δ 166.50, (166.20d, $J_{C\text{-}F}$=12.78Hz), 166.07, (165.60d, $J_{C\text{-}F}$=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 $C_{2'}$ $J_{C\text{-}F}$=14.91 Hz), 78.33, 76.15, (74.91d, $J_{C\text{-}F}$=72.42 Hz), 74.57, 72.33, (71.90dt $J_{C\text{-}F}$= 31.95C3'), (65.17d, $J_{C\text{-}F}$=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.

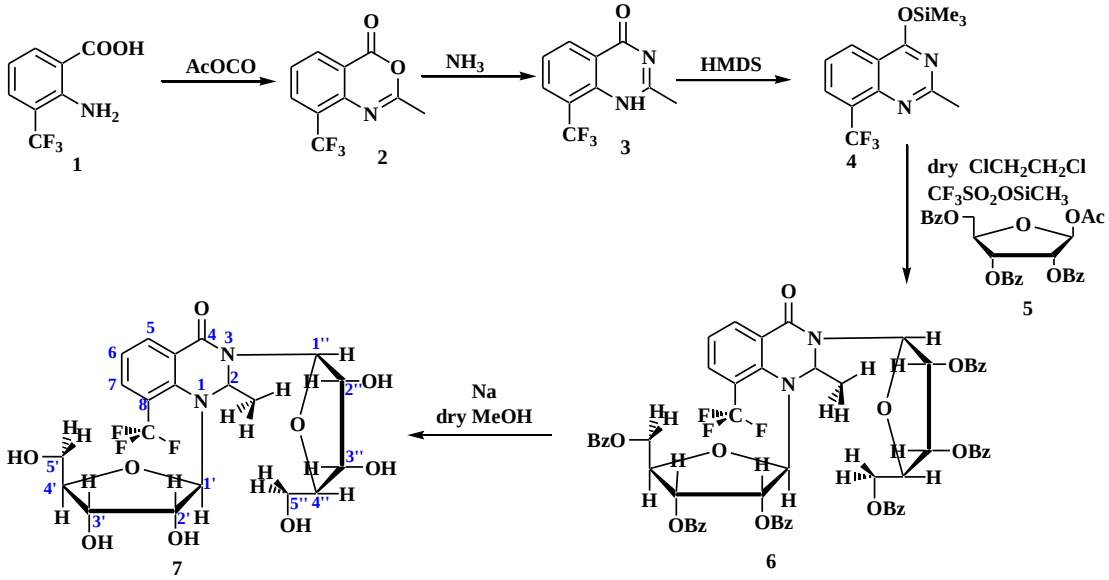
Deprotection of 1,3-bis-(2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl)-8-(trifluoromethyl)-2-methyl-4-quinazolinone: Synthesis of 2-methyl-1,3-bis-(*β*-D-ribofuranosyl)-8-(trifluoromethyl)-4-quinazolinone 7.

The protected nucleoside (0.2mmol) **6**, absolute methanol (20 ml) and sodium metal (0.013g, 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 afford yellow crystals of free nucleoside **7**.
Yield 0.0569g, (92.97%); m.p 224 °C; ^{1}HNMR CD_3OD: δ 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:δ . 180.24, 170.41 (d, $^{3}J_{C\text{-}F}$=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, $^{2}J_{C\text{-}F}$=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 bases of their spectral data (^{1}H & ^{13}C NMR and Mass) (see the Experimental section)(Scheme 1). The structure of compound **3** was confirmed by ^{1}H NMR, consisting of a broad, highly deshielded, singlet proton signal resonating at δ 11.75, which is characteristic of the quinazolinone proton (NH), and protons signals the aromatic

region for H5, H7 and H6 at δ 8.48, 8.09 and 7.52 , respectively. And singlet proton signal at δ 2.63 of CH_3. ^{13}C NMR, consisting of one signal of carbonyl group at δ 163.30 ,eight carbon signals of the aromatic region at δ 154.18, 147.15, 132.94, 130.38, 125.33, 124.10, 122.82, 121.54 and CH_3 group at δ 22.59. MASS: M^+ = 229.05(100%).



Scheme(1) :Synthesis of nucleoside 8-trifluoro methyl-2-methyl-4-quinazolinone

^1H NMR spectra of compound **6** showed in the case is complex spectra showed the protons signals the aromatic region of benzoyl groups and quinazolinone moiety at δ 8.08-7.26. For the observation of CF_3 groups coupling constants protons of the ribose moiety an atom on N1, (suggests this could be a cancellation of through-space and through-bond couplings). While protons ribose moiety on N3 decoupling not effect by ^{19}F. The proton two glycoside bonds on N1and N3 a doublet signals at δ 6.69 (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 confirms the β-anomeric configuration. (Break,2017; Break et al, 2014; Break et al, 2013; Break & Mosselhi, 2012).

The ^{13}C NMR of nucleoside products revealed the signals are due to the seven Lines of carbon carbonyl groups at δ 166.50, (166.20d, $J_{C\text{-}F}$=12.78Hz) $C_{2'}$, 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 showed the signals at δ 133.67-98.85 for aromatic carbons for compound **6,** the signals CH, CH_3 at δ 63.73 and 22.71, respectively.

Deprotection of the benzoyl group of protection nucleoside by Na in dry MeOH formed free nucleoside **7**. ^1H NMR confirmed successful benzoyl groups to the absence of the proton signals, while the proton quinazolinone signals (H_5, H_6 and H_7), and the proton two glycoside bonds proton a doublet signals were assigned to $C_{1'}$ and $C_{1''}$ at δ 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 can appear in 1D carbon-13 spectra showed 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 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 sugar moity on N1 of through-space.
The ten signals of carbon were assigned to two of the sugar moieties, (see the Experimental section). The ^{13}C NMR of CF_3 group showed at δ121.54**,** 104.87 and108.52of compounds **3**, **6** and **7** respectively (Break, 2016 and Break,2015). Mass: M^+ 493.01, 173.04(100%).

5. Conclusion

Quinazolinone nucleosides are scientific importance in many biologically active compounds. So synthesis and characterization of 8-triflulorомethyl-2-methylquinazolin-(*1H*)-4-one **3**. Ribosylation of compound **4** with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranose **5** afforded *β*-anomeric of the benzoylated nucleoside derivatives **6**. Debenzoylation of the latter affording the corresponding new free N-nucleosides **7**. Compounds obtained have been identified by their spectral analysis.

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