Synthesis and Characterization of New 8-trifluoromethyl Quinazolin-2,4-(3H)-Dione Nucleosides

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Abstract
Synthesis of 8-trifluoromethyl quinazolin-2,4-(1H,3H)-dione 2, which have been ribosylated by coupling with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose 4 by using the silylation method, afforded mixture β-and α-anomeric of the benzoylated nucleoside derivatives 5 and 6, respectively. Debenzoylation of each of 5 and 6 by sodium metal in dry methanol to afford the corresponding free nucleosides 7 and 8 respectively. The structures of the newly synthesis compounds have been confirmed on the basis of elemental analyses, IR, 1H NMR, 13C NMR and Mass spectral data.

Keywords: 1-O-Acetyl-2,3,5-trihydroxy-β-D-ribofuranose, Nucleosides, Quinazolin-2,4-(1H,3H)-dione, Trifluoromethyl

1. Introduction
Quinazolinone is a heterocyclic compound that occupies a distinct and place in the field of medicinal chemistry. Many of them were showed antimicrobial, anti-inflammatory, anticonvulsant, analgesic and anticancer agents (Safinaz E. Abbas et al, 2013; A. Kumar et al, 2011; K.M. Amin et al, 2010; M.M. Aly, 2010; A. Kumar, 2003; S.T. Al-Rashood, 2006 and N. Mulakayala, 2012).

Quinazoline nucleosides were first synthesized by Stout and Robins in 1968 as pyrimidine nucleoside analogs (Stout M. G and Robins R. K., 1968) and consequent synthetic studies were contributed by Dunkel and Pfeiderer in the 1990s. (Dunkel M and Pfeiderer W, 1991, 1992 and1993). More recently, several quinazoline-2,4-dione nucleosides have been incorporated into oligonucleotides as pyrimidine nucleoside substitutes to study the binding affinity and base pairing selectivity(Michel J et al, 1997; Diwan A. R., 1969; T. C. Chien, 2005; F. E. M. El-Baih, 2004; Tun-Cheng CHIEN, 2004).

Many familiar drugs and pharmacological studies contain trifluoromethyl groups. Quinazoline-2,4-diones bearing a trifluoromethyl group derivatives were an inhibitor of human immunodeficiency virus-1 reverse transcriptase, antagonists at ionotropic glutamate receptors (Hao Chen et al, 2003; Vittoria Colotta, 2012) and anticancer compound trifluoromethyl-substituted pyrazole N-nucleoside(Ayman M. Saleh et al, 2016).

In this review, quinazolin-2,4-(3H)-dione nucleosides containing trifluoromethyl group were designed as part of our continuing interest in the synthesis of new nucleosides as expected their biological activity.

2. Material and Methods
Melting points were measured on Gallenkamp melting point apparatus (UK) and are uncorrected. The purity of the compounds was checked by thin layer chromatography (TLC). 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. Elemental analyses were obtained on an Elementar Vario EL 1150C analyzer. IR spectra were recorded on KBr discs on Fourier Transform infrared and Pie Unicom SP 300 Infrared Spectrophotometers at Taif University. 1H NMR and 13C NMR spectra were obtained on a Varian (850 MHz) EM 390 USA instrument at King Abdel-Aziz University by using TMS as the internal reference. Mass spectra were recorded on a JEOL-JMS-AX500 at King Abdel-Aziz University, Saudi Arabia.

3. Experimental
8-trifluoromethyl quinazolin-2,4-(1H,3H)-dione 2
2-Amino-3-trifluoromethyl benzoic acid 1 (Aldrich; 0.019mol, 4g) was added drops of acetic acid in (100 ml) water,
the solution of KNCO (0.049mol, 4g) was dropped to the mixture was stirred in an ice bath at 1h. The reaction mixture was added sodium hydroxide (10 g) and overnight at room temperature and then filtered. The precipitate was neutralized with dilute sulfuric acid (1:1) and washed (3×20 ml) water. The column purified by column chromatography on silica gel with (Ethylacetate: Acetone 9:1) to afford white crystals.

Yield (63.23%), w. 6.1g. m.p. <300°C white ; ν (cm⁻¹) (KBr) 3400, 3075,1740, 1640; ¹H NMR (850MHz); (DMSO-D₂): 11.62 (s, 1H) NH-1, 11.20 (s,1H) NH-3, 8.22 (s, 1H) H₅, 7.79 (d, 1H, J = 7.5 Hz) H₃, 7.18 (d, 1H, J = 7.5 Hz) H₆. ¹³C NMR (850MHz): δ 167.27, 154.77, 133.08, 130.82,128.39, 125.71, 124.15, 123.09, 109.80; MS m/z: 230 (M⁺, 45%). Anal. Calcd. for C₉H₅F₃N₂O₇: M.wt: 230.14; C,46.97; H,2.19; F,24.77; N, 12.17 (%); Found: C, 46.26; H, 2.89; F,24.01; N,11.05 (%).

**Synthesis of protection nucleoside of 8-trifluoromethyl quinazolin-2,4-(1H,3H)-dione 2**

**General Procedure**

Silylation of 8-trifluoromethyl quinazolin-2,4-(1H,3H)-dione 2 (0.021 mol) with hexamethyldisilazane (HMDS) (20 ml) was refluxed for 3days with a catalytic a few crystals of ammonium sulfate under exclusion of moisture. Excess of HMDS was removed in vacuo by co-evaporation with dry dichloroethane gave the silylated derivative 3, using the Vorbruggen's silylation method (Vorbruggen et al., 1981). The residue was dissolved in 20 ml of dry 1,2-dichloroethane and then 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose 4 (10.8 g, 0.021 mol) was added. The mixture was added dropwise onto a mixture (4.5ml) of (10 ml trimethylsilyl trifluoromethane sulfonate (TMSOTf) in dry 1,2-dichloroethane (50 ml)). The mixture was stirred at room temperature for 24 h, and then washed with a saturated solution of aqueous sodium bicarbonate (3 × 50 ml), washed with water (3 × 50 ml), and dried over anhydrous sodium sulfate. the organic phase was extracted with CH₂Cl₂, dried over MgSO₄ and evaporated. The solvent was removed under vacuum gave an anomeric mixture of β and α-1-(2,3,5-tri-O-benzoyl-D-ribofuranosyl)-8-trifluoromethylquinazolin-2,4-(3H)-dione. The protected nucleoside was separated by column chromatography on silica gel with dichloromethane: acetone (9:1) as eluent to afford a white crystal pure β-anomeric 5 and α-anomeric 6 respectively, in good yields.

β-1-(2,3,5-Tri-O-benzoyl-D-ribofuranosyl)-8-trifluoromethyl quinazolin-2,4-(3H)-dione 5

Yield (52.12%), w. 2.7 g, m.p. 119°C white; IR ν (cm⁻¹) (KBr) 3042, 1725, 1680; ¹H NMR (850MHz); (CDCl₃): δ 9.47(s, 1H) H₃Amido, 8.26 (d, 1H, J = 7.5 Hz) H₂, 8.03 (d, 1H, J = 7.2 Hz) H₃, 7.92 (dd, 1H, J = 15.7 Hz) H₆, 7.51-7.25 (m, 15H) H₃Ar-H, 6.48 (d, 1H, J = 7.5 Hz) H₁ , 6.16 (dd, 1H, J = 8.4 Hz) H₂, 6.09 (t, 1H, J = 13, 4 Hz) H₃, 4.82-4.77 (dd, 1H, J = 4.6 Hz) H₆, 4.69-4.56 (m, 1H) H₃. ¹³C NMR (850MHz) (CDCl₃): δ 166.30, 165.46, 164.87,165.53(C₂O₅ groups), 148.17(C₆, 146.78 C₅, 133.61-128.33(C₆), 119.11 CF₃, 88.02 C₁, 79.47 C₅, 73.93 C₇, 70.98 C₄, 63.82 C₅-sugar carbons. Anal. Calcd. for C₂₉H₂₅F₅N₃O₇: M.wt: 764.58; C,62.32; H,3.74; F,8.45; N, 4.15 (%); Found: C, 62.26; H, 3.89; F,8.21; N,3.95 (%).

α-1-(2,3,5-Tri-O-benzoyl-D-ribofuranosyl)-8-trifluoromethyl quinazolin-2,4-(3H)-dione 6

Yield (47.87%), w. 2.48 g, m.p. 105-107°C white color; IR ν (cm⁻¹) (KBr) 3020, 1725, 1685; ¹H NMR (850MHz) (CDCl₃): δ 9.16 (s, 1H) H₃Amido, 8.06 (d, 1H, J = 7.4 Hz) H₂, 7.98 (d, 1H, J = 7.2 Hz) H₃, 7.89 (d, 1H, J = 7.4 Hz) H₆, 7.55-7.25 (m, 15H) H₃Ar-H, 6.73 (d, 1H, J = 2.2 Hz) H₁, 6.14 (dd, 1H, J = 8.8 Hz) H₂, 6.03-5.89 (m, 1H) H₃, 4.81-4.57 (m, 1H ) H₃, 3.73 (m, 1H) H₃. ¹³C NMR (850MHz): δ 166.46,165.82, 165.40(C₂O₅ groups), 147.95(C₁), 147.26(C₂), 13.73-12.80(Aromatic carbons), 118.01 CF₃, 87.46 C₁, 79.37 C₂,73.90 C₃, 71.89 C₄, 63.83 C₅, (CH₂Cl : CH₂COOCH₂CH₃) (9:1). Anal. Calcd. for C₂₉H₂₅F₅N₃O₇: M.wt: 764.58; C,62.32; H,3.74; F,8.45; N, 4.15 (%); Found: C, 62.15; H, 3.45; F,8.91; N,4.09 (%).

Deprotection of 5 and 6. Synthesis of free nucleosides 7 and 8 respectively

**General Procedure**

The pure anomer of each β and α (0.001 mol for each), dry absolute methanol (20 ml) and sodium metal (0.055 g, 0.001mol) was stirred at room temperature for 48h. The solvent was evaporated under vacuum to give a colorless solid, which was dissolved in hot water and neutralized with few drops acetic acid. Purification of each compound by TLC chromatographic on silica gel with chloroform: ethyl acetate (9: 1) to afford colorless and white crystals of the following Zemplen et al.’s method (Zemplen et al, 1939) to afford the free nucleosides 7 and 8, respectively.

β-1-(2,3,5-Trihydroxy-D-ribofuranosyl)-8-trifluoromethyl quinazolin-2,4-(3H)-dione 7

Yield (81.67%), w. 0.307g. m.p. 185°C white color; IR ν (cm⁻¹) (KBr) 3450, 3032, 1715, 1685; ¹H NMR (800MHz)(DMSO-D₂): δ 11.59 (s, 1H) H₃Amido, 8.06 (d, 1H, J = 5.5 Hz) H₂, 7.80-7.79 (d, 1H, J = 8.7 Hz) H₃, 7.77-7.76 (d, 1H, J = 5.2 Hz) H₁, 6.17 (d, 1H, J = 7.5 Hz) H₂, 5.27 (s, 1H) H₃, 5.07 (m, 1H) H₂, 4.45 (t, 1H) H₃, 4.13 (s, 1H) H₃, 3.80-3.76 (m, 1H) H₂OH, 3.66-3.61 (m, 1H) H₃OH, 3.58-3.41 (m, 1H) H₂OH. ¹³C NMR: 155.07 C₁, 153.63 C₂, 139.6, 137.59, 133.73, 129.92, 128.86, 120.00 , 118.96 CF₃, 89.89 C₁, 85.31 C₂, 69.41 C₃, 69.29 C₄, 61.63 C₅.
α-1-(2,3,5-Trihydroxy-D-ribofuranosyl)-8-trifluoromethyl quinazolin-2,4-(3H)-dione

Yield (94.73%), w. 0.41 g, m.p. 220°C white color; IR ν (cm⁻¹) (KBr) 3480, 1725, 1714, 1690; C=O groups at 1725 cm⁻¹. IR spectra of compound 8 showed absorptions around 3450 cm⁻¹ for (OH) and 1715 cm⁻¹ for (C=O). The structures of the products 2-8 were established and confirmed on the bases of their elemental analyses and spectral data (IR, ¹H and ¹³C NMR) (see the Experimental section)(Scheme 1). Thus, their ¹H NMR spectra of compound 2 showed doublet signals at assigned to the aromatic protons of H-5 H-6 and H-7 and two a singlet signal of amide NH-3 and NH-1.

The ¹³C NMR of nucleosides products revealed the signals are due to the three benzoyl carbonyl groups at and for compound 5, and 166.46, 165.82 and 165.40 for compound 6, while showed the two signals of amide carbons at 148.17, 146.78 for compound 5, and at 147.95C₂, 147.26 C₂ for compound 6. The twenty one signals at 133.61-128.40 Aromatic carbons for compound 5 and 6 respectively.

The three signals were assigned to C-1’, C-2’, C-3’, C-4’, and C-5 of the sugar moiety, at δ 88.02 C₁’, 79.47 C₂’, 73.93 C₃, 70.98 C₄ and 63.82 C₅ for compound 5, at δ 87.46 C₁’, 79.37 C₂’, 73.90 C₃, 71.69 C₄, 63.83 C₅ for compound 6, at δ 89.81C₁’, 85.31C₂’, 69.41C₃, 69.29C₄, 61.63C₅ for compound 7 and at δ 89.91 C₁’, 85.32C₂’, 69.42 C₃, 69.29 C₄, 61.63 C₅ for compound 8.

The ¹³C NMR of CF₃ group showed at δ 119.11, 118.01, 118.96 and 118.82 of compounds (5, 6, 7 and 8) respectively Break and Break. The IR spectrum of compounds 5 and 6 showed the stretching vibration frequencies of the carbonyl C=O groups at 1725 cm⁻¹. IR spectra of compounds 7 and 8 showed absorptions around 3450 cm⁻¹ for (OH) and 1715 cm⁻¹ for (C=O).

5. Conclusion

Quinazoline nucleosides are scientific importance in many biologically active compounds. So synthesis and characterization of 8-trifluoromethyl quinazolin-2,4-(3H)-dione 2. Ribosylation of compound 3 with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose 4 afforded mixture β- and α-anomeric of the benzoylated nucleoside derivatives 5 and 6, respectively. Debenzoylation of the latter affording the corresponding new free N-nucleosides 7 and 8, respectively. Nucleosides obtained have been identified by their spectral analysis.
References


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