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RESEARCH ARTICLE

SYNTHESIS OF THE 2-(TRICHLOROMETHYL)-4(*1H*)-QUINAZOLINONE NUCLEOSIDES

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ABSTRACT

2-(Trichloromethyl)-4-(*1H*)-quinazolinone1. have been ribosylated by coupling with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranose 3 by using the silylation method, afforded mixture *β*-and *α*-anomeric of the benzoylated nucleoside derivatives 4 and 5, respectively. Debenzoylation of each of 4 and 5 by sodium metal in dry methanol to afford the corresponding free nucleosides 6 and 7 respectively. The structures of the newly synthesis compounds have been confirmed on the basis of elemental analyses, IR, ^{1}HNMR, ^{13}CNMR and Mass spectral data.

INTRODUCTION

A large number of quinazolinone compounds have been synthesized and evaluated for their different biological activities.antihypertensive, antineoplastic, antidepressant, antipsychotic activities analgesic, antipsychotic, antiarrhythmic, sedative hypnotics, antibacterial, anti-inflammatory, antifungal, antimalarial, anticonvulsant, anticoccidial, anti-Parkinsonism, cancer and other activities (Mahato *et al*., 2011; Rajput and Mishra, 2012). Quinazolinone nucleosides were first synthesized by Stout and Robins in 1968 as pyrimidine nucleoside analogs (Stout and Robins, 1968) and consequent synthetic studies were contributed by Dunkel and Pfleiderer in the 1990s (Dunkel and Pfleiderer, 1991, 1992 and 1993). However, their biological activities are still relatively less known in literature. In the view of the importance of quinazolino nenucleosides, interest in the synthesis of new of 2-trichloromethyl-4-quinazolinone nucleosides (Break, 2015; Break, 2016; Break *et al*., 2014; Break *et al*., 2013). New nucleosides were expected their biological activity.

MATERIALS 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).

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Thin layer chromatography (TLC) was performed on silica gel sheets F1550 LS 254 of Schleicher and Schull and column chromatography on Merck silica gel 60 (particle size 0.063–0.20. Elemental analyses were obtained on an Elementary 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. ^{1}H NMR and ^{13}C 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.

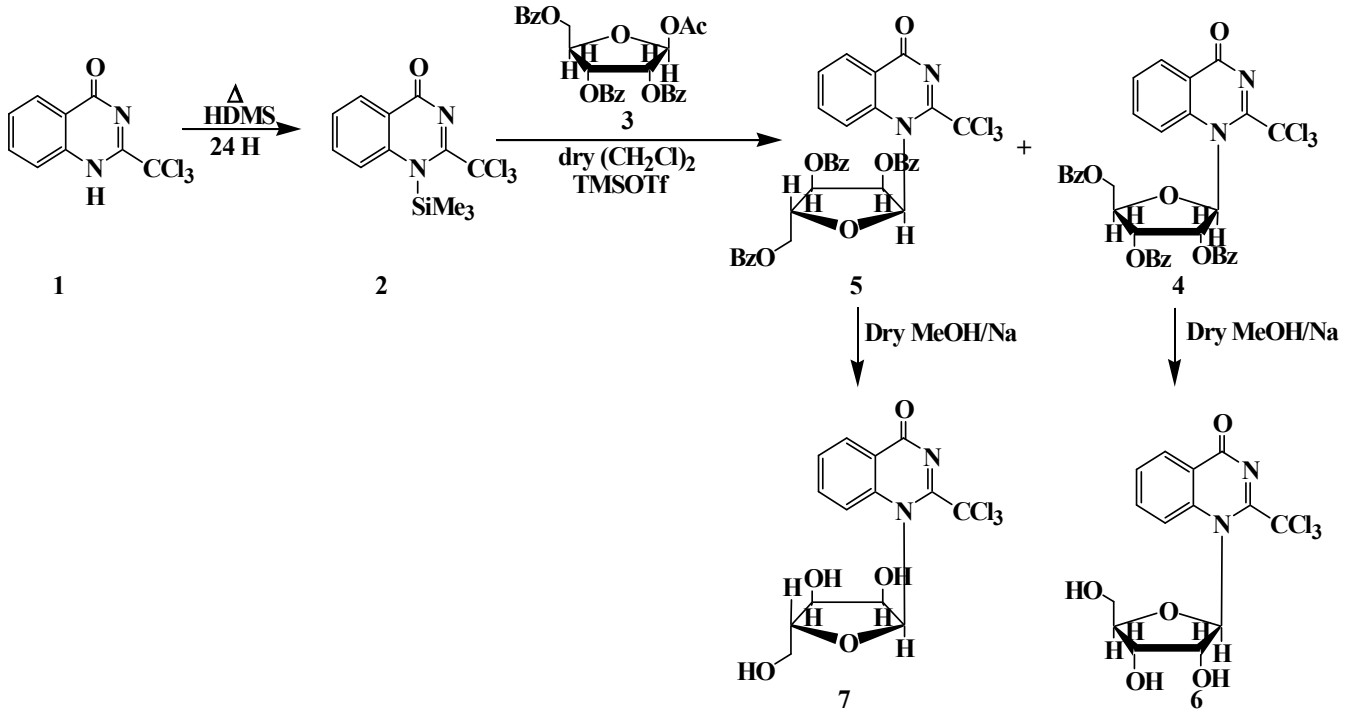
Experimental

2-(trichloromethyl)-(*1H*)-4-quinazolinone

Treatment of anthranilic acid with trichloroacetamidein 1ml of acetic acid was heated at 200^{o}C for2h used Niementowski quinazoline synthesis (Niementowski, 1895). The reaction mixture was cooled and stirred into cold water. The product was filtered and recrystallised from ethanol.

Synthesis of protection nucleoside of 2-(trichloromethyl)-4-quinazolinone 2 by Silyation method

Silyation of 2-(trichloromethyl)-4-(*1H*)-quinazolinone1 (0.013mol, 3.45g) with hexamethyldisilazane (HMDS) (20 ml) was refluxed for 3days with a catalytic a few crystals of



Scheme (1): Synthesis of 2-trichloromethyl 4-quinazolinone Nucleosides

ammonium sulfate under exclusion of moisture. Excess of HMDS was removed in vacuo by co-evaporation with dry 1,2-dichloroethane gave the silyated derivative 2, 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 3 (0.011mol,4 g) was added. The mixture was added dropwise onto a mixture (3.3 ml) of (10 ml trimethylsilyl trifluoromethanesulfonate (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 solvent was removed under vacuum gave an anomeric mixture of β and α-1-(2,3,5-tri-*O*-benzoyl-D-ribofuranosyl)-2-(trichloromethyl)-4-quinazolinone. The protected nucleoside was separated by column chromatography on silica gel with chloroform: hexane (9:1) as eluent to afford a white crystal pure β-anomeric 4 and α-anomeric 5 respectively, in good yields.

β-1-(2,3,5-Tri-*O*-benzoyl-D-ribofuranosyl)-2-(trichloromethyl)-4-quinazolinone 4

Yield (32.89%), w. 2.26 g, m.p. 118 ^{o}C white; ^{1}HNMR (850MHz); (DMSO): δ9.49 (d, 1H, J= 8.5Hz) 9.21-9.16 (dd, 1H, J= 9.35Hz), 8.91(d, 1H, J= 8.5Hz), 8.70(d, 1H, J=9.35), 7.95-7.76(m, 15H), 6.56(d, 1H,J= 7.5Hz)$H_{1`}$, 5.72-5.68(m, 1H)$H_{2`}$, 5.62-5.61(m,1H)$H_{3`}$, 5.40-5.39 (dd,1H)$H_{5`}$, 4.61-4.46(m,1H)$H_{4`}$, ^{13}CNMR (850MHz) (DMSO): δ 168.02, 165.56, 164.89, 146.02, $_{C=O's\ groups}$, 135.24, 133.87, 133.78, 133.55, 133.51, 132.92, 131.28, 130.78, 129.40, 129.40, 129.37, 129.35, 129.31, 129.24, 128.92, 128.89, 128.78, 128.69, 128.62, 128.31, 128.26, 127.64, 127.35,126.15, 121.10$_{Ar\text{-}carbons}$, 94.01 CCl_3, 81.41 $C_{1`}$, 77.63 $C_{2`}$, 75.98 $C_{3`}$, 71.12 $C_{4`}$, 63.04 $C_{5`sugar\ carbons}$. Anal. Calcd. for $C_{35}H_{35}Cl_3N_2O_8$; M.wt. 707.94; C, 59.38; H, 3.56; Cl, 15.02; N, 3.93 (%); Found: C, 59.26; H, 3.89; Cl, 14.8; N,3.95 (%).

α-1-(2,3,5-Tri-*O*-benzoyl-D-ribofuranosyl)-2-(trichloromethyl)-4-quinazolinone 5

Yield (24.74%), w. 1.7 g, m.p. 112^{o}Cwhite; ^{1}HNMR (850MHz); (DMSO): δ9.47(s, 1H) H_{3Amide}, 8.26 (d, 1H, J = 7.5 Hz) H_5, 8.03 (d, 1H, J = 7.2 Hz) H_7, 7.92 (dd, 1H, J = 15.7 Hz) H_6, 7.51-7.25 (m, 15H) $H_{(Ar\text{-}H)}$, 6.48 (d, 1H, J = 4.2Hz) $H_{1`}$, 6.16 (dd, 1H, $J$ = 8.4 Hz) $H_{2`}$, 6.09 (t, 1H, J = 13. 4 Hz)$H_{3`}$, 4.82-4.77 (dd, 1H, $J$= 4.6 Hz) $H_{5`}$, 4.69-4.56 (m, 1H) $H_{4`}$.^{13}CNMR (850MHz) (DMSO): δ 167.40, 165.59, 164.77, 162.18 $_{C=O's\ groups}$, 146.17, 135.78, 133.80, 133.61, 133.55, 133.11, 131.18, 130.78, 129.40, 129.40, 129.37, 129.35, 129.31, 129.24, 128.90, 128.89, 128.78, 128.63, 128.51, 128.25, 127.40, 126.35,126.15,126.15, 123.25 $_{Ar\text{-}carbons}$, 92.69 CCl_3, 82.93 $C_{1`}$, 74.14 $C_{2`}$, 72.21 $C_{3`}$, 70.81 $C_{4`}$, 64.38 $C_{5`sugar\ carbons}$. Anal. Calcd. for $C_{35}H_{35}Cl_3N_2O_8$; M.wt. 707.94; C, 59.38; H, 3.56; Cl, 15.02; N, 3.93 (%); Found: C, 59.71; H, 3.21; Cl, 15.09; N,7.52 (%). Deprotection of 4 and 5. Synthesis of free nucleosides **6** and **7** respectively

General Procedure

The pure anomer of each β 4 and α 5 (0.001 mol for each), dry absolute methanol (20 ml) and sodium metal (0.055 g, 0.001mol) was stirred at room temperature for 2d. 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 ($CHCl_3$: $CH_3COOCH_2CH_3$: Hexane) (6 : 2 : 2) to afford colorless and white crystals of the following Zemplen *et al.*'s method (Zemplen *et al*, 1939) to afford the free nucleosides 6and 7, respectively.

β-1-(2,3,5-Trihydroxy-D-ribofuranosyl)-2-trichloromethyl-4-quinazolinone 6

Yield (83.63%), w. 0.46 g, m.p. <300 ^{o}C white color; IR ν (cm^{-1}) (KBr) 3450, 1714, 1690; ^{1}HNMR (850MHz);

(CD_3OD): δ8.53 (s, 1H), 7.92(d,1H), 7.38-7.36 (t, 1H), 7.33-7.32(t, 1H), 4.86 (d, 1H, J= 7.5 Hz) $H_{1'}$; 3.94-3.93(q,1H) $H_{2'}$, 3.90(d, 1H, J= 5.1 Hz) $H_{3'}$, 3.84 (s, 1H) $OH_{2'}$, 3.77-3.74 (m, 1H) $H_{4'}$, 3.69-3.67 (dd, 1H, J= 4.25 Hz, J= 3.4Hz) $H_{5'}$, 3.64-3.62 (m, 1H) $OH_{3',5'}$.^{13}C NMR CD_3OD, 182.58, 175.59, 169.18, 161.48, 151.71, 139.13, 131.19, 130.23, 128.67$_{Ar\text{-}carbons}$, 94.35 CCl_3, 74.62 $C_{1'}$, 71.04 $C_{2'}$, 66.05 $C_{3'}$, 64.04 $C_{4'}$, 62.53 $C_{5'}$., MS m/z: 395 (M^+, 34%). Anal. Calcd. for $C_{14}H_{13}Cl_3N_2O_5$; M.wt. 395.62; C, 42.50; H, 3.31; Cl, 26.88; N, 7.08 (%); Found: C, 42.73; H, 3.28; Cl, 26.17; N,7.33 (%).

α-1-(2,3,5-Trihydroxy-D-ribofuranosyl)-2-(trichloromethyl)-4-quinazolinone 7

Yield (70.90%), w. 0.39 g, m.p. <300 ^{o}C white color; IR ν (cm^{-1}) (KBr) 3450, 1714, 1690; ^{1}HNMR (850MHz); (CD_3OD): δ8.53 (s, 1H), 7.93-7.92(m, 1H); 7.39-7.37(t, 1H); 7.34-7.32 (t,1H); 4.89(d,1H, J= 4.5 Hz) $H_{1'}$; 3.97-3.94 (d,1H J= 5.95 Hz) $H_{2'}$; 3.86(s,1H) OH; 3.79-3.76 (m,1H) $H_{3'}$; 3.69-3.67 (m, 1H) $H_{4'}$; 3.59-3.48 (m, 1H) $H_{5'}$; 1.88(s,1H) OH. ^{13}C NMR 179.34, 170.47, 151.80, 139.02, 131.28, 130.19, 128.87, 127.49$_{Ar\text{-}carbons}$, 99.87 CCl_3, 74.59 $C_{1'}$, 65.98 $C_{2'}$, 64.79 $C_{3'}$, 63.91 $C_{4'}$, 62.78 $C_{5'sugar\ carbons}$., MS m/z: 395 (M^+, 13%). Anal. Calcd. for $C_{14}H_{13}Cl_3N_2O_5$;M.wt. 395.62; C, 42.50; H, 3.31; Cl, 26.88; N, 7.08 (%); Found: C, 42.01; H, 3.81; Cl, 26.31; N,2.95 (%).

RESULTS AND DISCUSSION

^{1}H NMR spectra of 4 and 5 showed in each case a doublet signals at δ 6.56 (d, 1H, *J*= 7.5Hz) $H_{1'}$for compound 4 and at δ 6.48 (d, 1H, *J* = 4.2 Hz) $H_{1'}$for compound 5assigned to the anomeric proton of the ribose moiety with spin–spin coupling constant ($J_{1',2'}$) equal to 7.5 Hz, which confirms the β-anomeric configuration. While confirms the α-anomeric configuration showed spin–spin coupling constant ($J_{1',2'}$) equal to 4.2 Hz, which confirms the *a*-anomeric configuration for compound 5 (Break , 2016-2015; Break *et al*, 2014; Break *et al*, 2013; Break &Mosselhi, 2012; and Abdullah Hijazi, 1988). The ^{1}H NMR spectra of nucleosides free showed a doublet signals at δ 4.86 (d, 1H, J= 7.5 Hz) $H_{1'}$for compound 6 spin– spin coupling constant ($J_{1',2'}$) equal to 7.5 Hz β-anomeric configuration and at δ 4.89 (d,1H, J= 4.5 Hz) $H_{1'}$for compound 7 assigned to spin–spin coupling constant ($J_{1',2'}$) equal to 4.5 Hz, which confirms the *a*-anomeric configuration. The ^{1}H NMR of compounds 5 and 6 showed the expected base moiety protons in addition to the sugar moiety protons (see the Experimental section). The ^{13}C NMR of nucleoside products revealed the signals are due to the three benzoyl carbonyl groupsand the one signal of carbonyl amide group of each compound, at δ 168.02, 165.56, 164.89 and 146.02 and for compound 4, and δ 167.40, 165.59, 164.77 and 162.18 for compound 5, while showed the one signal of each amide carbons at 148.17, 146.78 for compound 5, and at 147.95C_4, 147.26 C_2 for compound 6, The twenty five signals at 135.24- 121.10and at 146.17- 123.25 Aromatic carbons for compound 4and5 respectively. The eight signals of free nucleosides at 182.58, 175.59, 169.18, 161.48, 151.71, 139.13, 131.19, 130.23, 128.67and at 179.34, 170.47, 151.80, 139.02, 131.28, 130.19, 128.87, 127.49 Aromatic carbons for compound 6 and 7 respectively. The five signals were assigned to C-1', C-2', C-3' , C-4', and C-5' of the sugar moiety, at δ 81.41 $C_{1'}$, 77.63 $C_{2'}$, 75.98 $C_{3'}$, 71.12 $C_{4'}$ and 63.04 $C_{5'}$ for compound 4, at δ82.93 $C_{1'}$, 74.14 $C_{2'}$, 72.21 $C_{3'}$, 70.81 $C_{4'}$ and 64.38 $C_{5'}$ for compound 5, at δ 74.62 $C_{1'}$, 71.04 $C_{2'}$, 66.05 $C_{3'}$, 64.04 $C_{4'}$, 62.53 $C_{5'}$ for compound 6 and at δ 74.59 $C_{1'}$, 65.98 $C_{2'}$, 64.79 $C_{3'}$, 63.91 $C_{4'}$, 62.78 $C_{5'}$ for compound 7. The ^{13}C NMR of CCl_3 group showed at δ 94.01, 92.69, 94.35 and 99.87 of compounds (4, 5, 6 and 7) respectively. The IR spectrum of compounds 4 and 5 showed the stretching vibration frequencies of the carbonyl C=O groups at 1725 cm^{-1}. IR spectra of compounds 6 and 7 showed absorptions around 3450 cm^{-1} for (OH) and 1715 cm^{-1} for (C=O).

Conclusion

Quinazolinone nucleosides are the most important in medicinal chemistry. Ribosylation of 2-trichloromethyl-4-(*1H*)-quinazolinone 1 with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose 3 afforded mixture β-and α-anomeric of the benzoylated nucleoside derivatives 4 and 5, respectively. Debenzoylation of the latter affording the corresponding new free N-nucleosides 6 and 7, respectively. Nucleosides obtained have been identified by their spectral analysis.

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