International Journal of Chemistry; Vol. 9, No. 4; 2017
ISSN 1916-9698 E-ISSN 1916-9701
Published by Canadian Center of Science and Education

Synthesis of 8-Trifluloromethyl-2-Thioquinazolin-(*3H*)-4-One Nucleosides

Laila M. Break

Correspondence: Laila M. Break, Taif University, Al-Haweiah, P.O.Box 888 Zip Code 21974. Taif, Saudi Arabia. E-mail: lailabreek@gmail.com

Received: August 16, 2017 Accepted: October 12, 2017 Online Published: October 17, 2017

doi:10.5539/ijc.v9n4p82 URL: https://doi.org/10.5539/ijc.v9n4p82

Abstract

Synthesis of 8-trifluloromethyl-2-thioquinazolin-(*1H,3H*)-4-one **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 *β*-anomeric of the benzoylated nucleoside derivatives **5**. Debenzoylation of **5** by sodium metal in dry methanol to afford the corresponding free nucleosides **6**. 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.

Keywords: 1-*O*-Acetyl-2,3,5-trihydroxy-*β*-D-ribofuranose, Nucleosides, 2-thioquinazolin-4-one, trifluoromethyl

1. Introduction

Quinazolinone and thioquinazolinone are heterocyclic compounds 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 (AbbasS. E., et al, 2013; Kumar A. et al, 2011; Amin K.M. et al, 2010; Aly M.M., 2010; Al-Rashood S.T., 2006 and Mulakayala N., 2012).

Thioquinazoline derivatives have interesting antimicrobial activity against different species of Gram positive bacteria, Gram negative bacteria and pathogenic Fungi, a possible pharmacophore for antitubercular activity and antiviral activity against TMV (Kottke, K., et al, 1997; Zhihua Wan, 2015).

Quinazolinone and thioquinazolinone 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 Pfleiderer in the 1990s (Hiroshi Takahashi, 1979; Dunkel M and Pfleiderer W, 1991, 1992 and 1993).

Many familiar drugs and pharmacological studies contain trifluoromethyl groups. Quinazoline-2,4-diones and thioquinazolinones 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; Tun-Cheng Chien et al, 2004; Vittoria Colotta, 2012) and anticancer compound trifluoromethyl-substituted pyrazole N-nucleoside (Saleh A. M. et al, 2016).

In this review, 8-trifluloromethyl-2-thioquinazolin-(*3H*)-4-one nucleosides containing trifluloromethyl and thione groups 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 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**.**

3. Experimental

8-triflulorомethyl-2-thioquinazolin-(*1H,3H*)-4-one 2

2-Amino-3-triflulorомethyl benzoic acid **1** (Aldrich; 0.01mol, 2.05g) isothiocyanate KNCS (1.94mol, 0.02g) and triethylamine (1 ml) in absolute ethanol (30 ml) was heated under reflux for 3 h. The reaction mixture was left to cool and the solvent was removed under reduced pressure. The obtained solid was then washed with petroleum ether, dried and crystallized from ethanol. (AlafeefyA. M., 2011; Al-Deeb A. O & Alafeefy A. M., 2008 and Kottke et al., 1977). The compound purified by column chromatography on silica gel with (Chloroform : Ethylacetate 9:1) to afford yellow crystals.

Yield (92.30%), w. 3g, m.p. <193-195 ^{o}C yellow ; ν (cm^{-1}) (KBr) 3300, 3075,1735, 1640; ^{1}HNMR (850MHz); (DMSO-D_6): δ 11.62 (s, 1H) NH-1, 11.31(s,1H) NH-3, 8.62 (d, 1H, J = 7.5 Hz) H_5, 7.89 (d, 1H, J = 7.5 Hz) H_7, 7.03 (d, 1H, J = 7.5 Hz) H_6,. ^{13}CNMR (850MHz): δ 188.2 C=S, 167.27, 154.77, 133.08, 130.82,128.39, 125.71, 124.15, 109.80; MS m/z: 246 (M^+, 36%). Anal. Calcd. for $C_9H_5F_3N_2OS$; M.wt: 246.21; C,43.90; H,2.05; F,23.15; N, 11.38; S,13.02 (%); Found: C, 43.26; H, 2.73; F,23.51; N,11.05; S13.41 (%).

Synthesis of protection nucleoside of 8-triflulorомethyl-2-thioquinazolin-(*1H,3H*)-4-one 2.

General Procedure.

Silyation of 8-triflulorомethyl 2-thioquinazolin-(*1H,3H*)-4-one **2** (0.0121 mol 3g) with hexamethyl-disilazane (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 silyated 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-D-ribofuranose **4** (1 g, 0.00198 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 by CH_2Cl_2, dried over $MgSO_4$ and evaporated. The solvent was removed under vacuum gave an anomeric mixture of β-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-8-triflulorомethylquinazolin-2,4-(*3H*)-thione. The protected nucleoside was separated by column chromatography on silica gel with chloroform: Ethylacetate (9:1) as eluent to afford a white crystal pure β-anomeric **5**, in good yields.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-8-triflulorомethyl-2-thioquinazolin-(*3H*)-4-one 5

Yield (62.50%), w. 2.3 g, m.p. 118^{o}C white; IR ν (cm^{-1}) (KBr) 3342, 1725, 1680; ^{1}HNMR (850MHz); ($CDCl_3$): δ 9.47(s, 1H) H_{3Amide}, 8.36 (d, 1H, J = 7.5 Hz) H_5, 7.93 (d, 1H, J = 7.2 Hz) H_7, 7.92 (dd, 1H, J = 15.7 Hz) H_6, 7.81-7.25 (m, 15H) $H_{(Ar-H)}$, 5.98 (d, 1H, J = 7.5 Hz) $H_{1`}$ , 5.36 (dd, 1H, $J$ = 8.4 Hz) $H_{2`}$, 5.09 (t, 1H, J = 13. 4 Hz) $H_{3`}$, 4.72-4.70 (dd, 1H, $J$ = 4.6 Hz) $H_{5`}$, 4.69-4.36 (m, 1H) $H_{4`}$. $^{13}$CNMR (850MHz) ($CDCl_3$): $\delta$ 189.2 C=S, 167.13,165.71,165.53 and 158.25$_{C=O's\ groups}$, 137.61-124.73 Ar-carbons, 119.32 $CF_3$, 89.52 $C_{1`}$, 76.47 $C_{2`}$,74.93 $C_{3`}$, 71.98 $C_{4`}$, 63.82 $C_{5`\ sugar\ carbons}$. Anal. Calcd. for $C_{35}H_{25}F_3N_2O_8S$; M.wt: 690.64; C,60.87; H,3.65; F,8.25; N, 4.06; S, 4.64 (%); Found: C, 60.26; H, 3.73; F,8.17; N,3.95; S, 4.01 (%).

Deprotection of protection nucleoside to afford the free nucleosides.

General Procedure

The pure anomer of each β **5** and (0.00151 mol, 1.45g), 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 **6**.

1-(2,3,5-Trihydroxy-β-D-ribofuranosyl)-8-triflulorомethyl-2-thioquinazolin-(*3H*)-4-one 6

Yield (63.00%), w. 0.5g. m.p. <300 ^{o}C white color; IR ν (cm^{-1}) (KBr) 3450, 3032, 1715, 1625; ^{1}HNMR (600MHz)(DMSO-D_6): δ 11.59 (s, 1H) H_{3Amide}, 8.06 (d, 1H, J = 5.5 Hz) H_5, 7.80-7.79 (d, 1H, J = 8.7 Hz) H_7, 7.77-7.76 (d, 1H, J = 5.2 Hz) H_6, 5.17 (d, 1H, J = 7.5 Hz) $H_{1`}$, 4.87 (s, 1H) $H_{2`}$, 4.27 (m, 1H) $H_{3`}$, 4.15 (t, 1H) $H_{5`}$, 4.03 (s, 1H) $H_{4`}$, 3.78-3.76 (m, 1H) $H_{2`OH}$, 3.66-3.61 (m, 1H) $H_{3`OH}$, 3.58-3.41 (m, 1H) $H_{3`OH}$. ^{13}C NMR: 190.1 C=S, 165.07 C=O, 153.63 C_2, 139.6, 133.73, 129.92, 128.86, 123.01, 118.96 CF_3, 89.89 $C_{1`}$, 79.31 $C_{2`}$, 76.41 $C_{3`}$, 69.29 $C_{4`}$, 61.63 $C_{5`}$. (Chloroform: Acetone) (9:1); MS m/z: 378 (M^+, 11%). Anal. Calcd. for $C_{14}H_{13}F_3N_2O_5S$; M.wt: 378.32; C,44.45; H,3.45; F,15.07; N, 7.40; S,8.48 (%); Found: C, 44.12; H, 3.75; F,15.51; N,7.10; S, 8.03 (%).

4. Results and Discussion

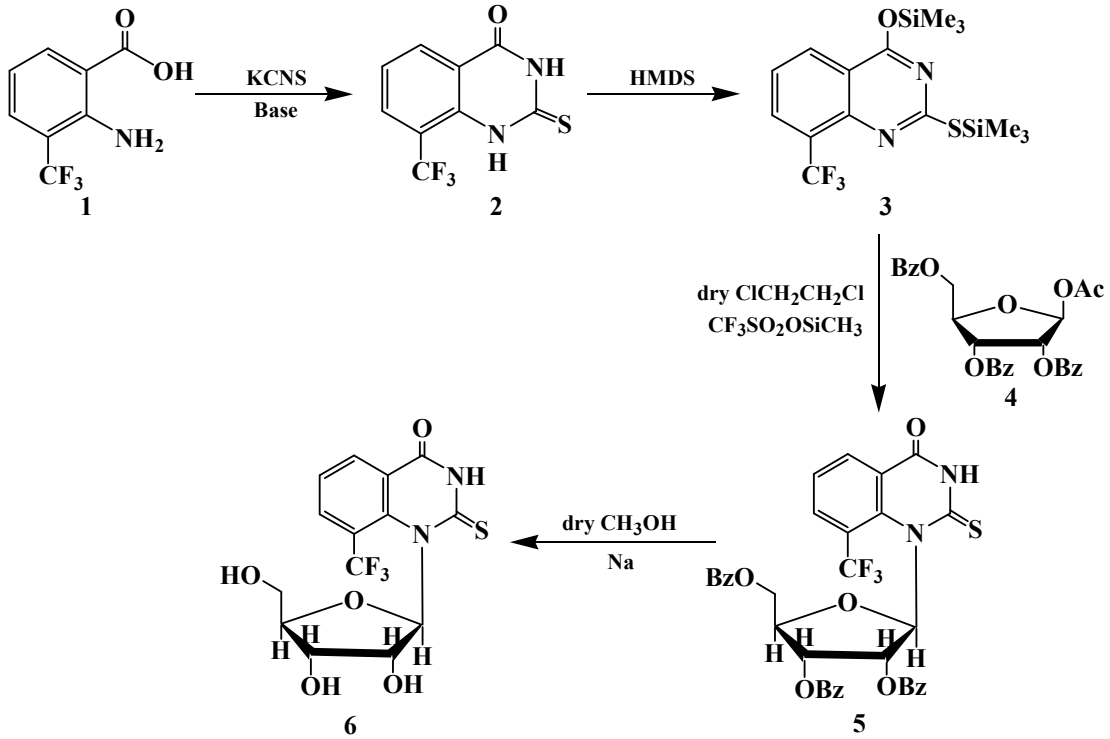
The structures of the products **2-6** were established and confirmed on the bases of their elemental analyses and spectral data (IR, ^{1}H and ^{13}C NMR) (see the Experimental section) (Scheme 1). Thus, their ^{1}H NMR spectra of compound **2** showed doublet signals at assigned to the aromatic protons of H-5 H-6 and H-7 and two a singlet signal of amide NH-3 and NH-1 at d 11.62, and 11.31, respectively.

^{1}H NMR spectra of compound **5** and **6** showed in each case a doublet signals at δ 5.98 (d, 1H, J = 7.5 Hz) $H_{1'}$ for compound **5** and at δ 5.17 (d, 1H, J = 7.5 Hz) $H_{1'}$ for free nucleoside compound **6** assigned 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. (Break,2017; Break et al, 2014; Break et al, 2013; Break & Mosselhi, 2012; Mosselhi & Break, 2011; Break et al, 2010; Chien T.-C. et al, 2005 and Abdullah Hijazi, 1988). 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 four carbonyl groups at 167.13,165.71,165.53 and 158.25$_{C=O's\ groups}$ for compound **5**, while showed the one signal of amide carbons at 165.07 for compound **6**, The twenty one signals at 137.61-124.73 Aromatic carbons for compound **5,** while disappeared the signals of benzoyl carbons for free nucleoside 6.

The five signals were assigned to C-1', C-2', C-3', C-4', and C-5' of the sugar moiety, at δ 89.52 $C_{1'}$, 76.47 $C_{2'}$, 74.93 $C_{3'}$, 71.98 $C_{4'}$ and 63.82 $C_{5'}$ for compound **5,** and at δ 89.89 $C_{1'}$, 79.31 $C_{2'}$, 76.41 $C_{3'}$, 69.29 $C_{4'}$, 61.63 $C_{5'}$ for compound **6**. The ^{13}C NMR of CF_3 group showed at δ119.80, 119.32 and 118.96 of compounds **2**, **5** and **6** respectively (Break, 2016 and Break,2015. ^{13}CNMR shifts of C=S group: those of derivatives **2**, **5**, and **6** lie in the region of 188.2, 189.2 and 190.1 ppm, respectively that of thion groups. (Hanusek J., et al; 2001).

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 **6** showed absorptions around 3450 cm^{-1} for (OH) and 1715 cm^{-1} for (C=O).



Schem (1). 8-trifluloromethyl-2-thioquinazolin-(*3H*)-4-one Nucleosides

5. Conclusion

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

References

Abbas, S. E., Barsoum, F. F., Georgey, H. H., & Mohammed, E. R. (2013). Synthesis and antitumor activity of certain 2,3,6-trisubstituted quinazolin-4(3**H**)-one derivatives, Bulletin of Faculty of Pharmacy, Cairo University, *51*(2), 2273–282. https://doi.org/10.1016/j.bfopcu.2013.08.003

Alafeefy, A. M. (2011). Some new quinazolin-4(3*H*)-one derivatives, synthesis and antitumor activity, *Journal of Saudi Chemical Society, 15*(4), 337-343. https://doi.org/10.1016/j.jscs.2011.06.019

Al-Deeb, A. O., & Alafeefy, A. M. (2008). Synthesis of Some New 3H-quinazolin-4-One Derivatives as Potential Antitubercular Agents, *World Applied Sciences Journal, 5*(1), 94-99. ISSN 1818-4952.

Al-Rashood, S. T., Aboldahab, I. A., Nagi, M. N., Abouzeid, L. A., Abdel-Aziz, A. A. M., Abdelhamide, S. G., … El-Subbagh, H. I. (2006). Synthesis, dihydrofolate reductase inhibition, antitumor testing, and molecular modeling study of some new 4(3**H**)-quinazolinone analogs, *Bioorg. Med. Chem., 14*, 8608–8621. https://doi.org/10.1016/j.bmc.2006.08.030

Aly, M. M., Mohamed, Y. A., El-Bayouki, K. A. M., Basyouni, W. M., & Abbas, S. Y. (2010). Synthesis of some new 4(3**H**)-quinazolinone-2-carboxaldehyde thiosemicarbazones and their metal complexes and a study on their anticonvulsant, analgesic, cytotoxic and antimicrobial activities–Part-1., *Eur. J. Med. Chem., 45*, 3365–3373. https://doi.org/10.1016/j.ejmech.2010.04.020

Amin, K. M., Kamel, M. M., Anwar, M. M., Khedr, M., & Syam, Y. M. (2010). Synthesis, biological evaluation and molecular docking of novel series of spiro [(2**H**,3**H**) quinazoline-2,10-cyclohexan]-4(1**H**)-one derivatives as anti-inflammatory and analgesic agents., *Eur. J. Med. Chem., 45,* 2117–2131. https://doi.org/10.1016/j.ejmech.2009.12.078

Break, L. M. (2015). Synthesis of the Novel 3-Benzotriazole-5-yl difluoromethyl-5-trifluoromethyl benzotriazole Nucleosides. *International Journal of Chemistry, 7*(2), 99. https://doi.org/10.5539/ijc.v7n2p99

Break, L. M. (2016). Synthesis of Some of Fluorinated Benzimidazole Nucleosides. *International Journal of Chemistry. 8*(1), 188. https://doi.org/10.5539/ijc.v8n1p188

Break, L. M. (2017). Synthesis and Characterization of New 8-triflulоromethyl Quinazolin-2,4-(3H)-Dione Nucleosides, *International Journal of Chemistry, 9*(1). https://doi.org/10.5539/ijc.v9n1p73

Break, L. M., & Mosselhi, A. N. M. (2012). Synthesis, structure and Antimicrobial activity of new 3- and 2- arylmethyl and arylacyl-3H [1,2,4] triazino [3,2-b]-quinazoline-2,6 (1H) diones as expect as DNA fluorphores. *Research Journal of Chemical Science, 2*(5), 23-28.

Break, L. M., Mohamed, M., & Abdel-Hafez, S. H. (2014). Synthesis of New Organoselenium Compounds Containing Nucleosides as Antioxidant. *Orient. J. Chem., 30*(4), 1639-1645. https://doi.org/10.13005/ojc/300423

Break, L. M., Mosselhi, M. A., & Elshafai, N. M. (2013). Nucleosides 8 [18]: Ribosylation of Fused Quinazolines—Synthesis of New [1,2,4]Triazolo[5,1-b]- and [1,2,4]Triazino[3,2-b]quinazoline Nucleosides of Fluorescence Interest. *Journal of Chemistry*, Article ID 612756, 11. https://doi.org/10.1155/2013/612756

Break, L. M., Shmiss, N. A. M. M., & Mosselhi, M. A. N. (2010). Synthesis of some news-nucleoside derivatives of 2-thioxo and (2,4-Dithioxo)-5,6,7,8-Tetrahydrobenzo-Thieno[2,3-d]Pyrimi-din-4-(3H) Ones. Phosphorus, *Sulfur and Silicon and the Related Elements, 185*(8), 1615–1622. https://doi.org/10.1080/10426500903147159

Chen, H., Chen, W. Q., Gan, L. S., & Abdul, E. M. (2003). Metabolism of (S)-5,6-DifluoroI-4-Cyclopropylethynyl-4-Trifluorormethyl-3,4-dihydro-2(1H)-Quinazolinone, A non-Nucleoside Reverse Transcriptase Inhibitor, In Human Liver Microsomes. Metabolic Activation and Enzyme Kinetics. *Drug Metabolism and Disposition, 31*(1), 122–132. https://doi.org/10.1124/dmd.31.1.122

Chien, T. C., Chen, C. S., & Chern, J. W. (2005). Nucleosides XIII. Facile synthesis of 4-amino-1-(2-deoxy-β-D-ribofuranosyl)quinazolin-2-one as a 2-deoxycytidine analog for oligonucleotide synthesis. *Journal of the Chinese Chemical Society, 52*(6), 1237–1244. https://doi.org/10.1002/jccs.200500178

Chien, T. C., Chen, C. S., Yu, F. H., & Chern, J. W. (2004). Nucleosides XI.1) Synthesis and Antiviral Evaluation of 5-Alkylthio-5deoxy Quinazolinone Nucleoside Derivatives as S-Adenosyl-Lhomocysteine Analog, *Chem. Pharm. Bull., 52*(12), 1422-1426. https://doi.org/10.1248/cpb.52.1422

Diwan, A. R, Robins, R. K., & Prusoff, W. H. (1969). Antiviral activity of certain substituted purine and pyrimidine nucleosides. *Experientia, 25*, 98-100. PMID: 4304043. https://doi.org/10.1007/BF01903922

Dunkel, M., & Pfleiderer, W. (1991). *Nucleosides Nucleotides, 10*, 799-817.

https://doi.org/10.1080/07328319108046663

Dunkel, M., & Pfleiderer, W. (1992). *Nucleosides Nucleotides, 11*, 787-819. https://doi.org/10.1080/07328319208021742

Dunkel, M., & Pfleiderer, W. (1993). *Nucleosides Nucleotides, 12*, 125-374. https://doi.org/10.1080/07328319308021199

Dunkel, M., & Pfleiderer, W. (1993). Nucleosides. LII. Synthesis and properties of quinazoline-3'-azidonucleosides. *Nucleosides and Nucleotides, 12*(2), 125-137. https://doi.org/10.1080/07328319308021199

El-Baih, F. E. M., Bakari, S. B. A., & Hijazi, A. A. (2004). Synthesis and spectroscopic properties of quinazolinedione derivatives. *Journal of King Abdelaziz University, 16*, 41-53. https://doi.org/10.4197/Sci.16-1.5

Hanusek, J., Hejtmánková, L., Kubicová, L., & Sedlák, M. (2001). Synthesis of Substituted 2-Benzoylaminothiobenzamides and Their Ring Closure to Substituted 2-Phenylquinazoline-4-thiones, *Molecules, 6*, 323-337. https://doi.org/10.3390/60400323

Hijazi, A. A. (1988). Nucleosides, IV Synthesis and Properties of 2-Metylthio-Naphthimidazole-Ribonucleoside. *Nucleosides & nucleotides, 7*(4), 537-547. https://doi.org/10.1080/07328318808075395

Hiroshi, T., Noriyuki, N., & Haruo, O. (1979). A Novel One-Step Synthesis of Thioquinazoline Glycosides and Pyrazolopyrimidine Glycoside Analogs, *27*(5), 1143-1146. https://doi.org/10.1248/cpb.27.1143

Kottke, K., F., Friedrich, D. K., & Kühmstedt, H. (1997). Simplified method for preparing 2-mercapto-3 arylquinazolones. *Pharmazie, 32*(8-9), 540-542.

Kumar, A., Sharma, P., Kumari, P., & Kalal, B. L. (2011). Exploration of antimicrobial and antioxidant potential of newly synthesized 2,3-disubstituted quinazoline-4(3**H**)-ones., *Bioorg. Med. Chem. Lett., 21*, 4353-4357. https://doi.org/10.1016/j.bmcl.2011.05.031

Mosselhi, A. N. M., & Laila M. B. (2011). Nucleosides 79: Synthesis, structure, and biological, activity of new 6-arylidenamino-2-thio- and 2-benzylthiopyrimidine N-nucleosides. *Nucleosides, Nucleotides and Nucleic Acids, 30*, 681-695. https://doi.org/10.1080/15257770.2011.597628

Mulakayala, N., Kandagatla, B., Ismail, R. R. K., Rao, P., Mulakayala, C., Kumar, C. S., … Oruganti, S. (2012). $InCl_3$-catalysed synthesis of 2-aryl quinazolin-4(3**H**)-ones and 5-aryl pyrazolo[4,3-**d**]pyrimidin-7(6**H**)-ones and their evaluation as potential anticancer agents., *Bioorg. Med. Chem. Lett., 22*, 5063-5066. https://doi.org/10.1016/j.bmcl.2012.06.003

Saleh, A. M., Taha, M. O., Aziz, M. A., Al-Qudah, M. A., AbuTayehx, R. F., & Rizvi, S. A. (2016). Novel anticancer compound [trifluoromethyl-substituted pyrazole N-nucleoside] inhibits FLT3 activity to induce differentiation in acute myeloid leukemia cells, *Cancer Letters., 375*(2), 199-208. https://doi.org/10.1016/j.canlet.2016.02.028

Stout, M. G., & Robins, R. K. (1968). The synthesis of some quinazoline nucleosides., *J. Org. Chem., 33*, 1219-1225. https://doi.org/10.1021/jo01267a061

Vittoria, C., Ombretta, L., Daniela, C., Flavia, V., Lucia, S., Chiara, C., …. Stefano, M. (2012). 3-Hydroxy-1*H*-quinazoline-2,4-dione derivatives as new antagonists at ionotropic glutamate receptors: Molecular modeling and pharmacological studies. *European Journal of Medicinal Chemistry, 54*, 470-482. https://doi.org/10.1016/j.ejmech.2012.05.036

Vorbruggen, H, Krolikiewicz, K., & Bennua, B. (1981). *Chem. Ber., 114*, 1234. https://doi.org/10.1002/cber.19811140404

Wan, Z. H., Hu, D. Y., Li, P., Xie, D. D., & Gan, X. H. (2015). Synthesis, Antiviral Bioactivity of Novel 4-Thioquinazoline Derivatives Containing Chalcone Moiety, *Molecules, 20*(7), 11861-11874. https://doi.org/10.3390/molecules200711861

Zemplen, G., Gerecs, A., & Hadacsy, I. (1939). *Ber. Dtsch. Chem. Ges., 69*, 1827. https://doi.org/10.1002/cber.19360690807