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DIRECT MODIFICATION OF QUERCETIN BY 6-NITROAZOLO[1,5-*a*]PYRIMIDINES

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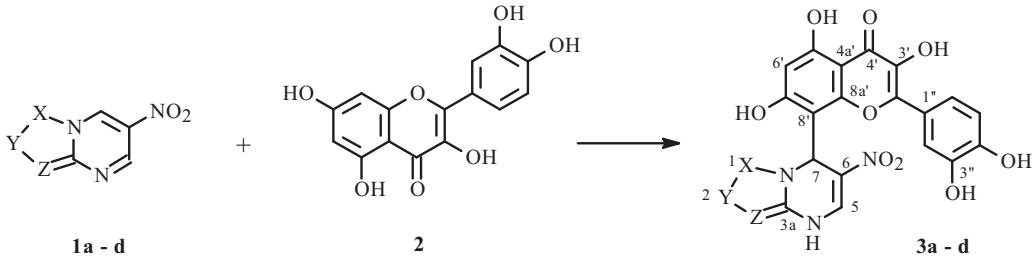
Quercetin is the most well-known flavonoid and is widely distributed in the plant world. It possesses a broad spectrum of biological activity including anti-allergic, antiulcer, cardiovascular, and antipyretic [1]. Furthermore, quercetin itself and its derivatives are effective against HIV [2], SARS [3], HCV [4], and several other dangerous viruses because flavonoids inhibit key enzymatic systems [5–7]. Recently, the number of publications on its transformation has increased sharply. According to Reaxys, 870 compounds based on quercetin were synthesized from 1888 to the present. About 361 articles were published. The number of new compounds since 2002 is 749 (described in 202 publications). However, the types of reactions that have been used are exceedingly limited and represented mainly by acylation [6, 8–10], alkylation [7], glycosylation [11], and aminoalkylation [8] despite the significant volume of work on quercetin transformations. Also, the introduction of nitrogen heterocycles, i.e., structural analogs of natural purines, is a highly acclaimed method for increasing the biological activity of natural compounds. This broad class of compounds also comprises 1,2,4-triazolo[1,5-*a*]pyrimidines, which exhibit high antiviral activity [12–14]. Herein we report the addition to quercetin of 6-nitroazolo[1,5-*a*]pyrimidines as structural analogs of natural purines.

We showed previously [15] that 6-nitroazolo[1,5-*a*]pyrimidines activated by a nitro group react with resorcinol and phloroglucinol to give products from stable addition at the heterocycle 7-position.

We found during the work that quercetin (**2**) reacted with 6-nitroazolo[1,5-*a*]pyrimidines **1a**–**d** in refluxing AcOH–EtOH (1:1) in 4 h to form stable adducts (course of reaction monitored by TLC using $CHCl_3$–MeOH, 9:1) as racemates. The two-center phloroglucinol moiety in **2** creates the possibility of forming two regioisomeric products at C-6′ and C-8′.



1a - d **2** **3a - d**

a: X = N, Y = CH; **b:** X = C-CO_2Et, Y = CH
c: X = C-CN, Y = CH; **d:** X = N, Y = C-S-CH_2CN

^{1}H–^{13}C HMBC correlation spectra of the product from the reaction of 6-nitro-1,2,4-triazolo[1,5-*a*]pyrimidine (**1a**) with quercetin established the position of the azolo[1,5-*a*]pyrimidine fragment on the quercetin system. The hydroxyl H atom bonded to C-5′ (δ 12.75 ppm [16, 17]) had common cross peaks with the four C atoms C-4′, C-4a′, C-5′, and C-6′ [16, 17], with which the quercetin aromatic proton also coupled.

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However, C-7 did not couple with a hydroxyl H atom on C-6′. This was possible only if the aromatic proton occupied the C-6′ position. Therefore, the azolopyrimidine fragment was bonded to quercetin C-8′. Chemical shifts of quercetin CH and OH protons were assigned based on the literature [16, 17].

Thus, quercetin was modified for the first time by natural purine isosteres.

2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-8-(6-nitro-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidin-7-yl)-4*H*-chromen-4-one (3a). Yield 49%, mp > 300°C (dec). ^{1}H NMR spectrum (spectrometer Avance DRX-400, 400 MHz, DMSO-d_6, δ, ppm, J/Hz): 6.10 (1H, s, H-6′), 6.85 (1H, d, J = 8.4, H-5″), 7.38 (1H, s, H-7), 7.70–7.68 (1H, dd, J_1 = 8.4, J_2 = 2.4, H-6″), 7.76 (1H, s, H-2), 7.80 (1H, d, J = 2.4, H-2″), 8.51 (1H, s, H-5), 9.33 (1H, br.s, 3″-OH), 9.54 (1H, br.s, 4″-OH), 9.63 (1H, br.s, 3′-OH), 11.09 (1H, br.s, 7′-OH), 12.00 (1H, br.s, NH), 12.71 (1H, br.s, 5′-OH). ^{13}C NMR spectrum (100 MHz, DMSO-d_6, δ, ppm): 176.12 (C-4′), 162.59 (C-7′), 160.60 (C-5′), 153.26 (C-8a′), 150.56 (C-2), 147.95 (C-2′), 147.37 (C-4″), 147.15 (C-3a), 145.19 (C-3″), 137.16 (C-5), 135.83 (C-3′), 122.31 (C-6), 122.10 (C-1″), 120.38 (C-6″), 115.86 (C-5″), 115.17 (C-2″), 102.63 (C-8′), 102.39 (C-4a′), 98.11 (C-6′), 50.20 (C-7).

2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-8-(3-ethoxycarbonyl-6-nitro-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-7-yl)-4*H*-chromen-4-one (3b). Yield 48%, mp 239–241°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.30 (3H, t, J = 7.0, CH_3), 4.28 (2H, q, J = 7.0, CH_2), 6.07 (1H, s, H-6′), 6.90 (1H, d, J = 8.5, H-5″), 7.36 (1H, s, H-7), 7.70–7.68 (1H, dd, J = 8.5, 2.0, H-6″), 7.74 (1H, s, H-2), 7.80 (1H, d, J = 2.0, H-2″), 8.21 (1H, s, H-5), 9.33 (1H, br.s, 3″-OH), 9.53 (1H, br.s, 4″-OH), 9.62 (1H, br.s, 3′-OH), 10.92 (1H, br.s, 7′-OH), 11.10 (1H, br.s, NH), 12.71 (1H, br.s, 5′-OH).

2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-8-(3-cyano-6-nitro-4,7-dihydropyrazolo[1,5-*a*]pyrimidin-7-yl)-4*H*-chromen-4-one (3c). Yield 40%, mp > 300°C (dec). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 6.10 (1H, s, H-6′), 6.90 (1H, d, J = 8.4, H-5″), 7.36 (1H, s, H-7), 7.70–7.67 (1H, dd, J = 8.4, 2.0, H-6″), 7.80 (1H, d, J = 2.0, H-2″), 7.93 (1H, s, H-2), 8.45 (1H, s, H-5), 9.33 (1H, br.s, 3″-OH), 9.55 (1H, br.s, 4″-OH), 9.63 (1H, br.s, 3′-OH), 11.14 (1H, br.s, 7′-OH), 12.39 (1H, br.s, NH), 12.72 (1H, br.s, 5′-OH).

2-(3,4-Dihydroxyphenyl)-3,5,7-trihydroxy-8-(2-cyanomethylthio-6-nitro-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidin-7-yl)-4*H*-chromen-4-one (3d). Yield 39%, mp 273–274°C (dec). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 4.13 (2H, s, CH_2), 6.12 (1H, s, H-6′), 6.91 (1H, d, J = 8.8, H-5″), 7.37 (1H, s, H-7), 7.70–7.67 (1H, dd, J = 8.8, 2.0, H-6″), 7.81 (1H, d, J = 2.0, H-2″), 8.51 (1H, s, H-5), 9.32 (1H, br.s, 3″-OH), 9.56 (1H, br.s, 4″-OH), 9.64 (1H, br.s, 3′-OH), 11.20 (1H, br.s, 7′-OH), 12.17 (1H, br.s, NH), 12.73 (1H, br.s, 5′-OH).

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