Synthesis of 2-(1,2,4-oxadiazol-5-yl)-2,3-dihydro-4*H*-chromen-4-ones

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Keywords: *flavanone, 2-heteroaryl-4-chromanones, 1,2,4-oxadiazole, fluorine, 1,1'-carbonyldiimidazole (CDI).*

Simple and efficient synthesis of 2-(1,2,4-oxadiazol-5-yl)-2,3-dihydro-4*H*-chromen-4-ones is elaborated. The method relies on CDI-mediated cyclocondensation of substituted 4-oxochromane-2-carboxylic acids and amidoximes. The protocol allows the preparation of 2-oxadiazolylchromanones decorated with two pharmacophores (2,3-dihydro-4*H*-chromen-4-one and 1,2,4-oxadiazole) that are in high demand in drug discovery.

Introduction

Chromones are on demand in the chemical community since their high abundance in natural products and medicines [1, 2]. Compound bearing this core are widely used as fluorescent probes for adenosine triphosphate (ATP) detection [3, 4]. On the other hand, chromanones – saturated derivatives of parent chromones – gained significant interest as synthetic intermediates of flavonoids and as multipurpose tools with a wide range of applications [5, 6]. In particular, chromanones are applied as antianxiety [7], anticancer [8, 9], anti-inflammatory [9], antibacterial [10] and antifungal agents [10 – 14], HIV-1 reverse transcriptase inhibitors [15], and as molecular switch scaffolds [16].

Further expansion of the application field requires introducing more complex substituents, *e.g.*, heterocyclic, into the chromanone molecule for purposes of medicinal chemistry and agrochemistry. Classical approaches towards the synthesis of functionalized flavanones *via* transformations of the corresponding chalcones have many limitations for the synthesis of 2-heteroaryl substituted chromanones [6]. Much effort has been made to find alternative methods for the synthesis of the aforementioned compounds, *i.e.*, the photoredox α-heteroarylation of 2-trifluoroboratochromanones [5] and the enantioselective alkynylation of chromones [17].

Despite the achieved progress in the synthesis of 2-heteroaryl substituted chromanones, no methods for the preparation of

chromanones bearing C(2)-oxadiazole substituent were reported to date. For scientists, 1,2,4-oxadiazoles are particularly interesting because of their presence in various drugs: Pleconaril (antiviral), Fasiplon (anxiolytic), Butalamine (vasodilator), Oxolamine (cough suppressant) [18].

Experimental part

Solvents were purified according to the standard procedures. ^{1}H and ^{13}C NMR spectra were recorded on Mercury 400 Varian (at 400.4 MHz for protons) and Bruker 170 Avance 500 spectrometer (at 499.9 MHz for Protons and 124.9 MHz for Carbon-13). Chemical shifts are reported in ppm downfield from TMS as an internal standard. Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, National Taras Shevchenko University of Kyiv. Compounds **1** were prepared by the same procedures reported in ref [19]. Amidoximes **2** were obtained similar to the published protocol [20].

General procedure for the preparation of 2-(1,2,4-oxadiazol-5-yl)-2,3-dihydro-4H-chromen-4-ones ***3***: 1,1′-carbonyldiimidazole (CDI) (0.18 g, 0,0011 mol) was added to a solution of substituted 4-oxochromane-2-carboxylic acid **1** (0,001 mol) in DMF, and the resulting mixture was stirred for 30 min at ambient temperature. Then corresponding amidoxime **2** (0,0011 mol) was added. The mixture was stirred at 70 °C for 1 h, cooled, and the solvent was evaporated in vacuo. The obtained residue was recrystallized from aqueous ethanol to give product **3** as a beige powder.

2-[3-(dimethylamino)-1,2,4-oxadiazol-5-yl]-6-methyl-2,3-dihydro-4H-chromen-4-one ***(3a).*** Yield 0.194 g, 71 %. Mp 105–106°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.55 (s, 1H), 7.41 (d, J = 8.3 Hz, 1H), 7.02 (d, J = 8.3 Hz, 1H), 6.01 (t, J = 6.3 Hz, 1H), 3.24 – 3.14 (m, 2H), 2.88 (s, 6H), 2.26 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 189.1, 174.2, 169.9, 157.2, 137.3, 131.4, 125.8, 120.3, 117.8, 70.4, 39.3, 37.6 (2C), 19.9. Anal. Calcd. for $C_{14}H_{15}N_3O_3$: C 61.53; H 5.53; N 15.38. Found: C 61.59; H 5.49; N 15.44.

2-[3-(dimethylamino)-1,2,4-oxadiazol-5-yl]-6-fluoro-2,3-dihydro-4H-chromen-4-one ***(3b).*** Yield 0.205 g, 74 %. Mp 127–128°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.52 – 7.45 (m, 2H), 7.21 (dd, J = 8.8, 4.2 Hz, 1H), 6.07 (t, J = 6.5 Hz, 1H), 3.24 (d, J = 6.5 Hz, 2H), 2.88 (s, 6H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 188.5, 173.9, 169.9, 157.0 (d, J_{CF} = 239 Hz), 155.53, 123.9 (d, J_{CF} = 24 Hz), 121.3 (d, J_{CF} = 6 Hz), 120.2 (d, J_{CF} = 8 Hz), 111.1 (d, J_{CF} = 22 Hz), 70.58, 39.04, 37.60 (2C). Anal. Calcd. for $C_{13}H_{12}FN_3O_3$: C 56.32; H 4.36; N 15.16. Found: C 56.29; H 4.42; N 15.21.

2-(3-isopropyl-1,2,4-oxadiazol-5-yl)-6-methyl-2,3-dihydro-4H-chromen-4-one ***(3c).*** Yield 0.187 g, 69 %. Mp 68–70°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.56 (s, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.04 (d, J = 8.4 Hz, 1H), 6.15 (dd, J = 7.7, 5.4 Hz, 1H), 3.29 – 3.17 (m, 2H), 3.13 – 2.97 (m, 1H), 2.26 (s, 3H), 1.22 (d, J = 6.9 Hz, 6H).

^{13}C NMR (125 MHz, DMSO-d_6) δ 188.9, 175.3, 174.7, 157.2, 137.4, 131.5, 125.8, 120.3, 117.8, 70.4, 39.4, 26.1, 20.1, 20.00, 19.9. Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C 66.16; H 5.92; N 10.29. Found: C 66.22; H 5.98; N 10.34.

6-bromo-2-(3-isopropyl-1,2,4-oxadiazol-5-yl)-2,3-dihydro-4H-chromen-4-one ***(3d).*** Yield 0.262 g, 78 %. Mp 110–111°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (s, 1H), 7.77 (d, J = 8.8 Hz, 1H), 7.15 (d, J = 8.8 Hz, 1H), 6.31 – 6.18 (m, 1H), 3.32 – 3.22 (m, 2H), 3.13 – 2.99 (m, 1H), 1.23 (d, J = 6.4 Hz, 6H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 188.2, 174.7, 171.9, 158.1, 137.2, 129.6, 121.9, 118.4, 113.9, 70.6, 39.8, 27.9, 20.7 (2C). Anal. Calcd. for $C_{14}H_{13}BrN_2O_3$: C 49.87; H 3.89; N 8.31. Found: C 49.82; H 3.94; N 8.40.

6-chloro-2-(3-isopropyl-1,2,4-oxadiazol-5-yl)-2,3-dihydro-4H-chromen-4-one ***(3e).*** Yield 0.240 g, 82 %. Mp 109–110°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.71 (s, 1H), 7.65 (d, J = 9.1 Hz, 1H), 7.21 (d, J = 9.1 Hz, 1H), 6.24 (dd, J = 7.5, 4.0 Hz, 1H), 3.32 – 3.21 (m, 2H), 3.13 – 2.98 (m, 1H), 1.22 (d, J = 6.3 Hz, 6H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 188.2, 174.7, 171.9, 158.1, 137.2, 129.6, 121.9, 118.4, 113.9, 70.6, 39.8, 27.9, 20.7 (2C). Anal. Calcd. for $C_{14}H_{13}ClN_2O_3$: C 57.44; H 4.48; N 9.57. Found: C 57.51; H 4.45; N 9.60.

(400 MHz, DMSO-d_6) δ 7.55 (s, 1H), 7.41 (d, J = 8.1 Hz, 1H), 7.03 (d, J = 8.1 Hz, 1H), 6.11 (t, J = 6.0 Hz, 1H), 3.21 (br. d, J = 6.2 Hz, 2H), 2.26 (s, 3H), 2.18 – 2.06 (m, 1H), 1.06 (d, J = 6.2 Hz,

6-fluoro-2-(3-isopropyl-1,2,4-oxadiazol-5-yl)-2,3-dihydro-4H-chromen-4-one ***(3f).*** Yield 0.201 g, 73 %. Mp 83–85°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.61 – 7.41 (m, 2H), 7.22 (dd, J = 8.8, 4.2 Hz, 1H), 6.21 (dd, J = 8.5, 4.8 Hz, 1H), 3.36 – 3.22 (m, 2H), 3.10 – 3.03 (m, 1H), 1.22 (d, J = 6.9 Hz, 6H).). ^{13}C NMR (125 MHz, DMSO-d_6) δ 188.9, 175.4, 175.1, 157.5 (d, J_{CF} = 242 Hz) 156.0, 124.4 (d, J_{CF} = 26 Hz), 121.8 (d, J_{CF} = 8 Hz), 120.7 (d, J_{CF} = 8 Hz), 111.6 (d, J_{CF} = 23 Hz), 70.9, 39.6, 26.5, 20.6, 20.5. Anal. Calcd. for $C_{14}H_{13}FN_2O_3$: C 60.87; H 4.74; N 10.14. Found: C 60.81; H 4.70; N 10.21.

6-chloro-7-fluoro-2-(3-isopropyl-1,2,4-oxadiazol-5-yl)-2,3-dihydro-4H-chromen-4-one ***(3g).*** Yield 0.202 g, 65 %. Mp 128–129°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.88 (d, J = 9.8 Hz, 1H), 7.39 (d, J = 11.5 Hz, 1H), 6.30 – 6.27 (m, 1H), 3.35 – 3.25 (m, 2H), 3.09 – 3.05 (m, 1H), 1.23 (d, J = 8.4 Hz, 6H).). ^{13}C NMR (125 MHz, DMSO-d_6) δ 188.9, 175.4, 175.1, 157.5 (d, J_{CF} = 242 Hz) 156.00, 124.4 (d, J_{CF} = 26 Hz), 121.8 (d, J_{CF} = 8 Hz), 120.7 (d, J_{CF} = 8 Hz), 111.6 (d, J_{CF} = 23 Hz), 70.9, 39.6, 26.5, 20.6, 20.5. Anal. Calcd. for $C_{14}H_{12}ClFN_2O_3$: C 54.12; H 3.89; N 9.02. Found: C 54.17; H 3.87; N 8.98.

2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-6-methyl-2,3-dihydro-4H-chromen-4-one ***(3h).*** Yield 0.205 g, 75 %. Mp 113–114°C. ^{1}H NMR 2H), 0.90 – 0.77 (br. m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 187.1, 174.2, 172.4, 157.6, 131.9, 131.5, 126.4, 121.7, 115.4, 70.4, 39.6, 20.8, 7.9, 6.4 (2C). Anal. Calcd. for $C_{15}H_{14}N_2O_3$:

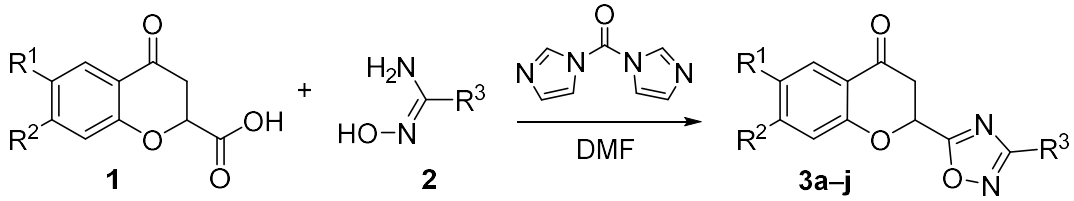
C 66.66; H 5.22; N 10.30. Found: C 66.71; H 5.29; N 10.34.

2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-6-fluoro-2,3-dihydro-4H-chromen-4-one ***(3i).*** Yield 0.219 g, 80 %. Mp 93–95°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82 – 7.75 (m, 2H), 7.14 (d, J = 8.3 Hz, 1H), 6.19 (t, J = 6.6 Hz, 1H), 3.27 (d, J = 6.6 Hz, 2H), 2.19 – 2.08 (m, 1H), 1.06 (d, J = 7.5 Hz, 2H), 0.86 – 0.83 (br. m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 188.4, 174.9, 172.1, 157.0 (d, J_{CF} = 239 Hz), 155.5, 123.9 (d, , J_{CF} = 25 Hz), 121.3 (d, J_{CF} = 6 Hz), 120.2 (d, J_{CF} = 7 Hz), 111.2 (d, J_{CF} = 24 Hz), 70.5, 39.1, 7.7, 6.2 (2C). Anal. Calcd. for $C_{14}H_{11}FN_2O_3$: C 61.31; H 4.04; N 10.21. Found: 61.28; H 4.09; N 10.28.

6-bromo-2-[3-(3-bromo-5-fluorophenyl)-1,2,4-oxadiazol-5-yl]-2,3-dihydro-4H-chromen-4-one ***(3j).*** Yield 0.398 g, 85 %. Mp 171–172°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1H), 7.87 – 7.85 (br. m, 2H), 7.77 (br. d, J = 9.0 Hz, 2H), 7.18 (d, J = 8.9 Hz, 1H), 6.37 (dd, J = 8.1, 5.1 Hz, 1H), 3.42 – 3.38 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 188.3, 176.7, 166.4 (d, J = 3 Hz), 162.7 (d, J = 250 Hz), 158.6, 139.4, 129.5 (d, J = 9 Hz), 128.7, 126.5 (d, J = 1 Hz), 123.5 (d, J = 10 Hz), 122.8 (d, J = 24 Hz), 122.7, 121.2, 114.7, 113.8 (d, J_{CF} = 23 Hz), 70.9, 40.4. Anal. Calcd. for $C_{17}H_9Br_2FN_2O_3$: C 43.62; H 1.94; N 5.98. Found: C 43.68; H 1.99; N 6.01.

Results and discussion

This work is devoted to the preparation of the small library of 2-(1,2,4-oxadiazol-5-yl)-2,3-dihydro-4*H*-chromen-4-ones (**3a–j**) – promising derivatives for medicinal chemistry. For this purpose, CDI (carbonyldiimidazole)-mediated cyclocondensation of substituted 4-oxochromane-2-carboxylic acids **1** and amidoximes **2** was performed (Scheme 1).



3a (71%): R^1 = Me, R^2 = H, R^3 = NMe_2; **3b** (74%): R^1 = F, R^2 = H, R^3 = NMe_2;
3c (69%): R^1 = Me, R^2 = H, R^3 = *i*Pr; **3d** (78%): R^1 = Br, R^2 = H, R^3 = *i*Pr;
3e (82%): R^1 = Cl, R^2 = H, R^3 = *i*Pr; **3f** (73%): R^1 = F, R^2 = H, R^3 = *i*Pr;
3g (65%): R^1 = F, R^2 = Cl, R^3 = *i*Pr; **3h** (75%): R^1 = Me, R^2 = H, R^3 = *cyclo*-Pr;
3i (80%): R^1 = F, R^2 = H, R^3 = *cyclo*-Pr; **3j** (85%): R^1 = Br, R^2 = H, R^3 = 3-Br-5-F-C_6H_3

Scheme 1. Synthesis of 2-(1,2,4-oxadiazol-5-yl)-2,3-dihydro-4*H*-chromen-4-ones

The reaction proceeded smoothly by heating the mixture of starting materials in the presence of CDI in DMF at 70°C for 1 h and gave the target products in 65–85% yield after a simple purification protocol by recrystallization. These mild reaction conditions are suitable for a wide range of substituents at both benzene and 1,2,4-oxadiazole cores. The structures of

compounds obtained were confirmed by ^{1}H NMR and ^{13}C NMR experiments and elementary analysis.

According to the literature data, common methods for the synthesis of 2-hetaryl-2,3-dihydro-4*H*-chromen-4-ones rely on transformations of corresponding carbonyl compounds *via* the chalcone formation. On the other side, the synthetic application of C(2)-substituted carboxylic acids **1** for the construction of the additional heterocyclic core was reported only once [21]. In particular, the known reaction of thiosemicarbazide with dihydrochromenone **1** ($R^1 = R^2 = H$) resulted in the formation of 2-(5-amino-[1,3,4]thiadiazol-2-yl)-4*H*-chromen-4-one that was studied as PTR1 inhibitor and antiparasitic drug candidate [21]. Other examples included the preparation of unsaturated analogs of derivatives **3** – hydroxy-2[3-(4-*tert*-butylphenyl)-1,2,4-oxadiazol-5-yl]chromones, which were synthesized from corresponding acids using the mixed anhydride method. The aforementioned chromones were evaluated as inhibitors of tyrosine kinases, and therefore can be used for cancer treatment, neuroprotection, and protection of skin's stress proteins [22]. These data allow us to anticipate that synthesized compounds **3** will find broad application in medicinal chemistry. Moreover, the introduction of fluorine atoms to chromone derivatives **3** was profitable to improve physico-chemical properties of derivatives with increased metabolic stability and lipophilicity, and diminished idiosyncratic drug toxicity [23].

Conclusions

The general and efficient approach for the synthesis of 2-(1,2,4-oxadiazol-5-yl)-2,3-dihydro-4*H*-chromen-4-ones was reported. The methods relied on cyclocondensation of available 4-oxochromane-2-carboxylic acids and amidoximes in DMF in the presence of CDI as an activating agent. This protocol allowed the combination of two potent pharmacophores (dihydro-4*H*-chromen-4-one and 1,2,4-oxadiazole) and required simple purification steps to give ten representative examples of the title products in good to high yields (65–85%). We anticipate the proposed method and products to be useful in modern medicinal chemistry.

Acknowledgements

This work was supported by the Ministry of Education and Science of Ukraine [grant number 2201290].

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