Hetarenocoumarins based on 7-hydroxy-3-(benzothiazol-2-yl)coumarin

Tetyana Shokol, Anastasiya Suprun, Victoriia Moskvina*, Volodymyr Khilya

Department of Chemistry, Taras Shevchenko National University of Kyiv, Volodymyrska Street, 64/13, Kyiv 01601, Ukraine

v.moskvina@gmail.com

Keywords: *7-hydroxy-3-benzothiazolylcoumarin, aminomethylation, formylation, cyclization, hetarenocoumarins.*

The syntheses of angular hetarenocoumarins, namely chromeno[8,7-*e*][1,3]oxazin-2-ones and furo[2,3-*h*]chromen-2-one, have been accomplished starting from 7-hydroxy-3-(benzothiazol-2-yl)-coumarin using aminomethylation and formylation reactions.

Introduction

Coumarins appear naturally in many plants and find wide use in medicine due to their diverse pharmacological activities [1, 2]. They possess excellent photophysical properties such as high quantum yield, strong fluorescence, and high photostability, and therefore are used as dyes for biosensitization and biomarking [3]. 7-Hydroxycoumarin derivatives proved to be popular fluorescent dyes. Heterocyclic substituents in position 3 cause a bathochromic shift of their maximum absorption, which significantly improves the photophysical properties of coumarins.

3-Benzothiazolylcoumarins are actively used as fluorescent probes for rapid detection of H_2S [4], benzenethiols [5], biothiols [6], selenocysteine [7], catecholamine [8], Cu^{2+} [9], for sequential recognition of Ni^{2+} and CN^- [10], hydrazine [11], superoxides [12], palladium [13], and hydrogen peroxide [14]. Many probes were synthesized based on 7-hydroxy-3-benzothiazolylcoumarin, which itself can serve as a laser dye [15].

In addition, the use of 3-benzothiazolylcoumarin derivatives as potential antitumor agents [16] and MEK1 inhibitors has been suggested [17]. 7-Hydroxy-3-benzothiazolylcoumarin was synthesized by the Knoevenagel reaction *via* interaction of 2,4-dihydroxybenzaldehyde with (benzothiazol-2-yl)acetonitrile in ethanol [7, 17, 18] or propanol-2 [19] using piperidine [17-19] or 4% NaOH [3] as a catalyst, followed by hydrolysis with sulfuric [18] or hydrochloric acid [3, 7, 17, 19] or with ethyl 2-benzothiazolyl acetate in pyridine in the presence of aniline as a catalyst [20]. In the second approach, 7-hydroxy-3-benzothiazolylcoumarin was synthesized

from 7-hydroxy-3-cyanocoumarin and 2-aminothiophenol under microwave irradiation in acetic acid or ethanol with a catalytic amount of the HPMo ($H_3PMo_{12}O_3$) [21]. Alkylation and acylation of the hydroxyl group [3, 18], aminomethylation [18, 22, 23], and formylation [23, 24] at position 8 and cyanation at position 4 [17] of 7-hydroxy-3-(benzothiazol-2-yl)coumarin were previously studied.

Experimental part

The reaction progress and identity of obtained compounds were monitored by TLC on Silufol UV-254 plates using $CHCl_3$-MeOH (9:1) system. Melting points were determined using a Kofler-type Leica Galen III micro hot stage microscope. NMR spectra were recorded on Varian Mercury 400 spectrometer (spectrometer frequency for ^{1}H: 400 MHz) using a DMSO residual solvent signal as an internal standard; chemical shifts (δ) are given in ppm. Elemental analyses for C, H, and N were performed using Vario micro cube (Elementar Analysen-systeme GmbH), their results were found to be in good agreement (0.2%) with the calculated values. Mass spectra were recorded on an Agilent 1100 LC / MSD with chemical ionization (SI). *3-(1,3-Benzothiazol-2-yl)-8-dimethylamino-methyl-7-hydroxy-2H-2-chromenone* **2** was synthesized following a published protocol [18].

3-(1,3-Benzothiazol-2-yl)-7-hydroxy-2H-2-chromenone ***1***. 2 Drops of piperidine were added to a solution of 2,4-dihydroxybenzaldehyde (1.38 g, 10 mmol) and (benzothiazole-2)-yl)acetonitrile (1.74 g, 10 mmol) in EtOH (30 mL) and kept for 2 days at room temperature. Then the precipitate was filtered off and refluxed for 5 h in 50 mL of acetic acid. The mixture was cooled and the precipitate was filtered off. Yield 2.6 g, 88 %. Yellow solid, $C_{16}H_9NO_3S$, mp 308°C (AcOH) (lit. [18] 295°C, [19] 305°C). ^{1}H NMR spectrum (400 MHz, DMSO-d_6-CCl_4), δ, ppm (*J*, Hz): 6.79 (1H, d, *J*= 2.0, H-8), 6.66 (1H, dd, $J_{6,5}$= 8.8, $J_{6,8}$= 2.0, H-6), 7.38 (1H, t, *J*= 8.0, H-6′), 7.48 (1H, t, *J*=8.0, H-5′), 7.77 (1H, d, *J*= 8.8, H-5), 7.96 (1H, d, *J*=8.0, H-4′), 8.02 (1H, d, *J*= 8.0, H-7′), 9.09 (1H, s, H-4), 10.84 (1H, s, OH).

General procedure for the preparation of 3-(1,3-benzothiazol-2-yl)-9-R-9,10-dihydro-2H,8H-chromeno[8,7-e][1,3]oxazin-2-ones ***3a-c***. The corresponding benzylamine (0.2 mL, 2 mmol) and 37% formalin (4 mL) were added to 3-(1,3-benzothiazol-2-yl)-7-hydroxy-2*H*-2-chromenone **1** (0.32 g, 1 mmol) in 10 mL of dioxane and refluxed for 3 h (TLC control). The solution was cooled and the resulting precipitate was filtered off and washed with dioxane.

3-(1,3-Benzothiazol-2-yl)-9-benzyl-9,10-dihydro-2H,8H-chromeno[8,7-e][1,3]-oxazin-2-one ***3a***. Yield 0.26 g, 62 %. Yellow solid, $C_{25}H_{18}N_2O_3S$, mp 196-197°C (dioxane). ^{1}H NMR spectrum (400 MHz, DMSO-d_6-CCl_4), δ, ppm (*J*, Hz): 3.90 (2H, s, PhC$\underline{H}_2$), 4.16 (2H, s, 10-CH_2), 4.98 (2H, s, 8-CH_2), 6.84 (1H, d, *J*= 8.8, H-6), 7.26-7.39 (6H, m, H-6′, Ph), 7.47 (1H, t, *J*= 8.0, H-5′), 7.73 (1H, d, *J*=8.8, H-5), 7.96 (1H, d, *J*=8.4, H-4′), 7.99 (1H, d, *J*= 8.4, H-7′), 9.08 (1H, s, H-4). MS (*m/z,* CI): 415 [MH^+-12].

3-(1,3-Benzothiazol-2-yl)-9-(4-methoxybenzyl)-9,10-dihydro-2H,8H-chromeno[8,7-e][1,3]oxazin-2-one ***3b***. Yield 0.34 g, 74 %. Yellow solid, $C_{26}H_{20}N_2O_4S$, mp 203-204°C (dioxane). ^{1}H NMR spectrum (400 MHz, DMSO-d_6-CCl_4), δ, ppm (*J*, Hz): 3.77 (3H, s, CH_3O), 3.81 (2H, s, PhC$\underline{H}_2$), 4.13 (2H, s, 10-CH_2), 4.97 (2H, s, 8-CH_2), 6.85 (3H, d, *J*= 8.4, H-6, H-3′′,5′′), 7.23 (2H, d, *J*= 8.0, H-2′′,6′′), 7.39 (1H, t, *J*= 8.0, H-6′), 7.49 (1H, t, *J*= 8.0, H-5′), 7.77 (1H, d, *J*=8.4, H-5), 7.97 (1H, d, *J*=8.0, H-4′), 8.01 (1H, d, *J*= 8.0, H-7′), 9.11 (1H, s, H-4). MS (*m/z,* CI): 444.9 [MH^+-12].

3-(1,3-Benzothiazol-2-yl)-9-(1-phenylethyl)-9,10-dihydro-2H,8H-chromeno[8,7-e][1,3]oxazin-2-one ***3c***. Yield 0.35 g, 79 %. Yellow solid, $C_{26}H_{20}N_2O_3S$, mp 104-105°C (dioxane). ^{1}H NMR spectrum (400 MHz, DMSO-d_6-CCl_4), δ, ppm (*J*, Hz): 1.45 (3H, d, *J*=7.2, CH_3), 3.91 (1H, k, *J*=7.2, C$\underline{H}$$CH_3$), 3.97 (1H, d, *J*=17.2, 10-CH_α), 4.26 (1H, d, *J*=17.2, 10-CH_β), 4.96 (1H, d, *J*=10.4, 8-CH_α), 5.20 (1H, d, *J*=10.4, 8-CH_β), 6.83 (1H, d, *J*= 8.8, H-6), 7.26-7.33 (5H, m, Ph), 7.38 (1H, t, *J*= 8.0, H-6′), 7.49 (1H, t, *J*= 8.0, H-5′), 7.74 (1H, d, *J*=8.8, H-5), 7.97 (1H, d, *J*=8.0, H-4′), 8.01 (1H, d, *J*= 8.0, H-7′), 9.01 (1H, s, H-4). MS (*m/z,* CI): 429 [MH^+-12].

General procedure for the preparation of 3-(1,3-benzothiazol-2-yl)-7-hydroxy-2-oxo-2H-8-chromenylmethyl-(R)ammonium chlorides ***4a-c***. HCl (0.1 mL) was added to the solution of 3-(1,3-benzothiazol-2-yl)-9-R-9,10-dihydro-2H,8H-chromeno[8,7-e][1,3]oxazin-2-one **3a-c** (0.3 mmol) in dioxane (3 mL) and the reaction mixture was refluxed for 1 h, then it was cooled and the resulted precipitate was filtered off and washed with dioxane.

3-(1,3-Benzothiazol-2-yl)-7-hydroxy-2-oxo-2H-8-chromenylmethy-l(benzyl)ammonium chloride ***4a***. Yield 0.09 g, 67 %. Yellow solid, $C_{24}H_{19}ClN_2O_3S$, mp 268-269°C (dioxane). ^{1}H NMR spectrum (400 MHz, DMSO-d_6-CCl_4), δ, ppm (*J*, Hz): 4.20 (2H, s, PhC$\underline{H}_2$), 4.24 (2H, s, CH_2), 7.23

(1H, d, *J*= 8.4, H-6), 7.36-7.39 (4H, m, H-6′,3′′,4′′,5′′), 7.48 (1H, t, *J*= 7.6, H-5′), 7.62 (2H, d, *J*= 7.2, H-2′′,6′′), 7.85 (1H, d, *J*= 8.4, H-5), 7.96 (1H, d, *J*=7.6, H-4′), 8.02 (1H, d, *J*= 8.4, H-7′), 9.11 (1H, s, H-4), 9.63 (2H, s, NH_2), 12.11 (1H, s, OH). MS (*m/z,* CI): 415 [MH^+-36.5].

3-(1,3-Benzothiazol-2-yl)-7-hydroxy-2-oxo-2H-8-chromenylmethyl(4-methoxybenzyl)ammonium chloride ***4b***. Yield 0.11 g, 78 %. Yellow solid, $C_{25}H_{21}ClN_2O_4S$, mp 263-264°C (dioxane). ^{1}H NMR spectrum (400 MHz, DMSO-d_6-CCl_4), δ, ppm (*J*, Hz): 3.76 (3H, s, CH_3O), 4.13 (2H, s, PhC$\underline{H_2}$), 4.22 (2H, s, CH_2), 6.89 (2H, d, *J*= 8.4, H-3′′,5′′), 7.22 (1H, d, *J*= 8.8, H-6), 7.39 (1H, t, *J*= 8.0, H-6′), 7.47-7.52 (3H, m, H-5′,2′′,6′′), 7.86 (1H, d, *J*= 8.8, H-5), 7.97 (1H, d, *J*=8.0, H-4′), 8.03 (1H, d, *J*= 8.0, H-7′), 9.12 (1H, s, H-4), 9.46 (2H, s, NH_2), 12.08 (2H, s, OH). MS (*m/z,* CI): 445 [M^+-36.5].

3-(1,3-Benzothiazol-2-yl)-7-hydroxy-2-oxo-2H-8-chromenylmethyl(1-phenylethyl)ammonium chloride ***4c***. Yield 0.12 g, 86 %. Yellow solid, $C_{25}H_{21}ClN_2O_3S$, mp 222-223°C (dioxane). ^{1}H NMR spectrum (400 MHz, DMSO-d_6-CCl_4), δ, ppm (*J*, Hz): 1.68 (3H, d, *J*=6.0, CH_3), 3.96 (1H, br s, PhC$\underline{H}$), 4.11 (2H, br s, CH_2), 7.19 (1H, d, *J*= 8, H-6), 7.33-7.39 (4H, m, H-6′,3′′,4′′,5′′), 7.46 (1H, t, *J*= 8.0, H-5′), 7.63 (2H, d, *J*= 7.2, H-2′′,6′′), 7.79 (1H, d, *J*= 8, H-5), 7.94 (1H, d, *J*=8.0, H-4′), 8.02 (1H, d, *J*= 8.0, H-7′), 9.06 (1H, s, H-4), 9.36 (1H, s, NH), 9.89 (1H, s, NH), 1,2.03 (1H, s, OH). MS (*m/z,* CI): 429 [MH^+-36.5].

General procedure for the preparation of 3-(1,3-benzothiazol-2-yl)-8-R-aminomethyl-7-hydroxy-2H-2-chromenones ***5a-c***. A mixture of 3-(1,3-benzothiazol-2-yl)-8-dimethylaminomethyl-7-hydroxy-2*H*-2-chromenone **3** (0.35 g, 1 mmol) and substituted benzylamine (2 mmol) was refluxed in 3 mL of dioxane for 2 h (TLC control). The solution was cooled and the resulting precipitate was filtered off and washed with dioxane.

3-(1,3-Benzothiazol-2-yl)-8-benzyl-aminomethyl-7-hydroxy-2H-2-chromenone ***5a***. Yield 0.20 g, 49 %. Yellow solid, $C_{24}H_{18}N_2O_3S$, mp 242-243°C (dioxane). ^{1}H NMR spectrum (400 MHz, DMSO-d_6-CCl_4), δ, ppm (*J*, Hz): 3.92 (2H, s, PhC$\underline{H_2}$), 4.21 (2H, s, NHC$\underline{H_2}$), 6.61 (1H, d, *J*= 8.4, H-6), 7.29-7.46 (7H, m, H-5′,6′, Ph), 7.56 (1H, d, *J*= 8.4, H-5), 7.90 (1H, d, *J*=8.0, H-4′), 7.96 (1H, d, *J*= 8.0, H-7′), 8.94 (1H, s, H-4), OH and NH exchanged with D_2O). MS (*m/z,* CI): 415 [$MH]^+$.

3-(1,3-Benzothiazol-2-yl)-7-hydroxy-8-(4-methoxybenzylaminomethyl)-2H-2-chromenone ***5b***. Yield 0.22 g, 50 %. Yellow solid, $C_{25}H_{20}N_2O_4S$, mp 257-258°C (dioxane). ^{1}H NMR spectrum (400 MHz, DMSO-d_6-CCl_4), δ, ppm (*J*, Hz): 3.77 (3H, s, CH_3O), 3.91 (2H, s, PhC$\underline{H_2}$), 4.17 (2H, s, NHC$\underline{H_2}$), 6.54 (1H, d, *J*= 8.4, H-6), 6.88 (2H, d, *J*= 8.4, H-3″,5″), 7.29-7.35 (3H, m, H-6′,2″,6″), 7.43 (1H, t, *J*= 8.0, H-5′), 7.53 (1H, d, *J*= 8.4, H-5), 7.89 (1H, d, *J*=8.0, H-4′), 7.96 (1H, d, *J*= 8.0, H-7′), 8.90 (1H, s, H-4), OH and NH exchanged with D_2O). MS (*m/z,* CI): 445 $[MH]^+$.

3-(1,3-Benzothiazol-2-yl)-7-hydroxy-8-(1-phenylethylaminomethyl)-2H-2-chromenone ***5c***. Yield 0.23 g, 54 %. Yellow solid, $C_{25}H_{20}N_2O_3S$, mp 189-190°C (dioxane). ^{1}H NMR spectrum (400 MHz, DMSO-d_6-CCl_4), δ, ppm (*J*, Hz): 1,48 (3H, d, *J*=6.0, CH_3), 3.93-4.07 (3H, m, $CH_3C\underline{H}$, NHC$\underline{H_2}$), 6.61 (1H, d, *J*= 8.4, H-6), 7.6 - 7.46 (7H, m, H-5′,6′, Ph), 7.57 (1H, d, *J*= 8.4, H-5), 7.91 (1H, d, *J*=8.0, H-4′), 7.97 (1H, d, *J*= 8.0, H-7′), 8.94 (1H, s, H-4), OH and NH exchanged with D_2O). MS (*m/z,* CI): 429 $[MH]^+$.

3-(1,3-Benzothiazol-2-yl)-7-hydroxy-2-oxo-2H-8-chromenecarbaldehyde ***6***.

Method A. A solution of 3-(1,3-benzothiazol-2-yl)-7-hydroxy-2*H*-2-chromenone **1** (1.48 g, 5 mmol) and of hexamethylenetetramine (7 g, 50 mmol) in 20 mL of AcOH was heated on a water bath for 6 h. The hot solution was poured into a hot mixture of HCl-H_2O (1:1, 24 mL) and then was diluted with 40 mL of H_2O. After 1 h at room temperature, the precipitate was filtered off and recrystallized from AcOH. Yield 1.39 g, 85 %.

Method B. A solution of 3-(1,3-benzothiazol-2-yl)-8-dimethylaminomethyl-7-hydroxy-2*H*-2-chromenone **3** (0.53 g, 1.5 mmol) and hexamethylenetetramine 0.42 g (3 mmol) in 5 mL of acetic acid was refluxed for 1 h. The hot solution was poured into a hot mixture of HCl-H_2O (1:1, 3 mL) and then was diluted with 15 mL of H_2O. After 1 h at room temperature, the precipitate was filtered off and recrystallized from AcOH. Yield 0.35 g, 73 %. Orange solid, $C_{17}H_9NO_4S$, mp 234-235°C (AcOH). ^{1}H NMR spectrum (400 MHz, DMSO-d_6-CCl_4), δ, ppm (*J*, Hz): 7.02 (1H, d, *J*= 8.8, H-6), 7.36 (1H, t, *J*= 7.6, H-6′), 7.46 (1H, t, *J*=7.6, H-5′), 7.94 (1H, d, *J*=7.6, H-4′), 7.98 (1H, d, *J*= 7.6, H-7′), 8.08 (1H, d, *J*= 8.8, H-5), 9.09 (1H, s, H-4), 10.48 (1H, s, CHO),

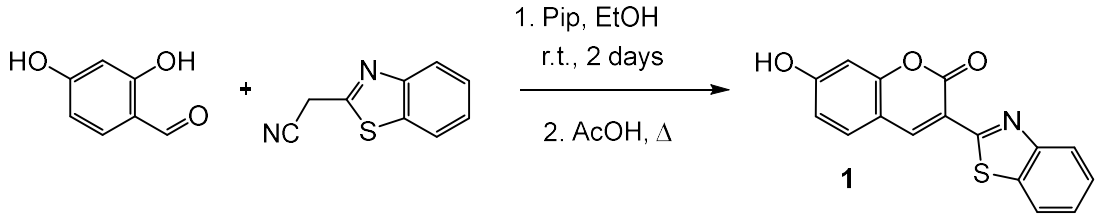
12.19 (1H, s, OH). MS (*m/z,* CI): 324 $[MH]^+$.

3-(1,3-Benzothiazol-2-yl)-8-(4-nitrobenzoyl)-2H-furo[2,3-h]chromen-2-one ***7***. K_2CO_3 (0.14 g, 1 mmol) was added to a solution of 3-(1,3-benzothiazol-2-yl)-7-hydroxy-2-oxo-2*H*-8-chromenecarbaldehyde **6** (0.32 g, 1 mmol) and 4-nitrophenacyl bromide (0.24 g, 1 mmol) in 2 mL of DMF. The reaction mixture was stirred under heating (100°C) for 5 h, then cooled, diluted with H_2O (20 mL), neutralized with HCl. The resulting residue was filtered off and recrystallized from dioxane. Yield 0.15 g, 32 %. Pale yellow solid, $C_{25}H_{12}N_2O_6S$, mp > 300°C (dioxane). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.45 (1H, t, *J*=8.0, H-6′), 7.55 (1H, t, *J*=8.0, H-5′), 7.90 (1H, d, *J*= 8.0, H-5), 8.05 (1H, d, *J*= 8.0, H-6), 8.15 (5H, m, H-4′,7′,9,2″,6″), 8.42 (2H, d, *J*= 7.6, H-3″,5″), 9.38 (1H, s, H-4). MS (*m/z,* CI): 469 $[MH]^+$.

Results and discussion

As part of our ongoing research into the reactivity of 7-hydroxy-3-(benzothiazol-2-yl)coumarin, in this work we explored the construction of hetarenocoumarins based on 7-hydroxy-3-(benzothiazol-2-yl)coumarin and its functional derivatives.

The Knoevenagel methodology [18] was utilized to synthesize 7-hydroxy-3-(benzothiazol-2-yl)coumarin **1**, but the hydrolysis of the reaction mixture was performed in refluxing acetic acid (**Scheme 1**).

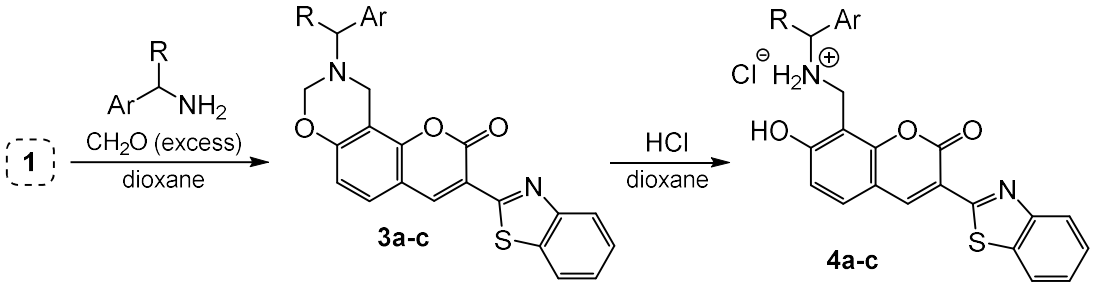


Scheme 1. The synthesis of 7-hydroxy-3-(benzothiazol-2-yl)coumarin

It is known that aminomethylation of 7-hydroxycoumarin **1** with *bis*dimethylaminomethane in dioxane produces 8-dimethylaminomethyl derivative **2** [18].

Aminomethylation of 7-hydroxy-coumarin **1** under classical conditions using benzylamines and an excess of 37% formalin in dioxane led to the annelation of the dihydrooxazine cycle to the coumarin ring and the formation of 3-(1,3-

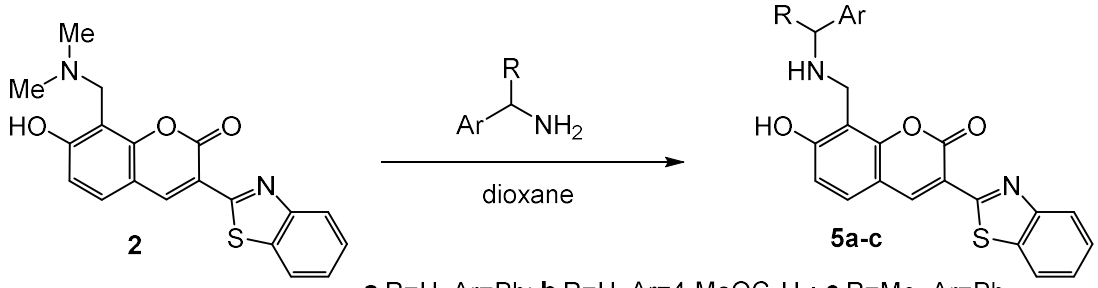
benzothiazol-2-yl)-9-benzyl-9,10-dihydro-2*H*,8*H*-chromeno[8,7-*e*][1,3]oxazin-2-ones **3a-c** (**Scheme 2**). It should be noted that the addition of HCl to the refluxing solution of **3a-c** in dioxane resulted in the opening of the oxazine cycle and the formation of Mannich bases hydrochlorides **4a-c** (**Scheme 2**).



a R=H, Ar=Ph; **b** R=H, Ar=4-MeOC$_6$H$_4$; **c** R=Me, Ar=Ph;

Scheme 2. The synthesis of 3-(1,3-benzothiazol-2-yl)-9-R-9,10-dihydro-2*H*,8*H*-chromeno[8,7-e][1,3]oxazin-2-ones **3a-c** and 3-(1,3-benzothiazol-2-yl)-8-R-aminomethyl-7-hydroxy-2*H*-2-chromenons' hydrochlorides **4a-c**

The corresponding Mannich bases **4a-c** were obtained *via* interaction of 8-dimethylaminomethyl derivative **2** with benzylamines in dioxane at reflux for 2 hours (**Scheme 3**).



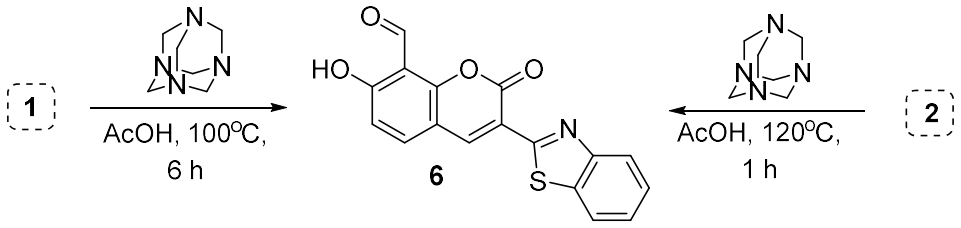
a R=H, Ar=Ph; **b** R=H, Ar=4-MeOC$_6$H$_4$; **c** R=Me, Ar=Ph

Scheme 3. The synthesis of 3-(1,3-benzothiazol-2-yl)-8-R-aminomethyl-7-hydroxy-2H-2-chromenons **5a-c**

The ^{1}H NMR spectra of chromeno[8,7-*e*][1,3]oxazin-2-ones **3a,b** revealed the presence of three two-proton singlets at 3.81-3.90 ppm (Ar$\underline{CH_2}$), 4.13-4.16 ppm (10-CH_2), and 4.97-4.98 ppm (8-CH_2) assigned to the benzyl group and two methylene groups of the dihydrooxazine ring correspondingly, while the ^{1}H NMR spectra

of **4a,b** and **5a,b** showed two two-proton singlets at 4.17-4.24 ppm (8-CH_2) and 3.91-4.20 ppm (CH_2Ar). The signals of dihydrooxazine ring protons in the ^{1}H NMR spectrum of 9-(1-phenylethyl) derivative **3c** are not equivalent due to their proximity to the asymmetric center.

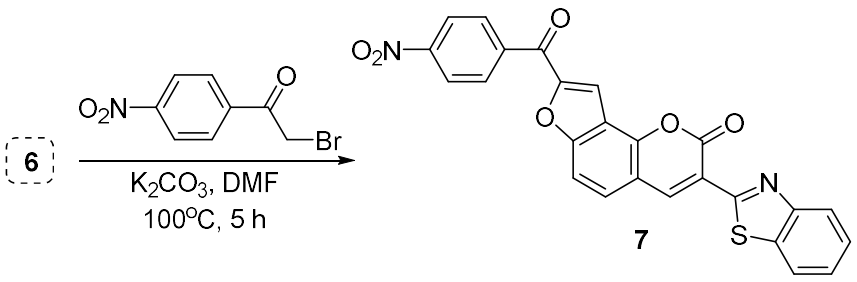
Taking into account that *o*-hydroxy-formyl coumarins are convenient building blocks for the synthesis of condensed coumarins [25, 26], we targeted 3-(1,3-benzothiazol-2-yl-7-hydroxy-2-oxo-2*H*-8-chromenecarbaldehyde **6** as an appropriate substrate for the synthesis of hetarenocoumarins. Previously, 8-formyl derivative **6** was synthesized from 7-hydroxy-3-(benzothiazol-2-yl)coumarin **1** by its interaction with hexamethylenetetramine in trifluoroacetic acid *via* the Duff reaction [23, 24]. Replacing trifluoroacetic acid with acetic acid as a solvent in this reaction allowed us to obtain product **6** in good yield and reduce the above protocol's cost (**Scheme 4**).



Scheme 4. The syntheses of 3-(1,3-benzothiazol-2-yl-7-hydroxy-2 oxo-2*H*-8-chromenecarbaldehyde (**6**)

3-(1,3-Benzothiazol-2-yl)-8-dimethylamino-methyl-7-hydroxy-2*H*-2-chromenone **2** can also be a starting material in the synthesis of 8-formylcoumarin **6** *via* the Duff reaction. Treatment of **2** with hexamethylenetetramine in acetic acid at reflux for 1 h followed by hydrolysis with HCl gave **5** in 73% yield.

7-Hydroxy-8-formylcoumarin **6** was introduced into a reaction with 4-nitro-phenacyl bromide upon heating in dimethylformamide at 100°C in the presence of K_2CO_3. Ring closure proceeded *via* alkylation of the hydroxyl group followed by the condensation of active methylene and carbonyl groups, forming the furan fragment and leading to the formation of 3-(1,3-benzothiazol-2-yl)-8-(4-nitro-benzoyl)-2*H*-furo[2,3-*h*]chromen-2-one **7** (**Scheme 5**). The presence of a singlet at 8.19 ppm for the H-3 proton in the ^{1}H NMR spectrum of this compound is consistent with the formation of a furochromene system.



Scheme 5. The syntheses of furo[2,3-h]coumarin **7**

Conclusions

In conclusion, we have performed the synthesis of angular hetarenocoumarines, namely chromeno[8,7-*e*][1,3]oxazin-2-ones based on 7-hydroxy-3-(benzothiazol-2-yl)coumarin *via* aminomethylation under classical Mannich reaction conditions using an excess of formalin. The furo[2,3-*h*]chromen-2-one system was formed starting from the 8-formyl derivative of 7-hydroxy-3-(benzothiazol-2-yl)coumarin under the Duff reaction conditions with 4-nitrophenacyl bromide. The proposed approaches are simple and effective and will contribute to further unlocking the potential of coumarins.

Acknowledgement

This work has been supported by Ministry of Education and Science of Ukraine: Grant of the Ministry of Education and Science of Ukraine for perspective development of a scientific direction "Mathematical sciences and natural sciences" at Taras Shevchenko National University of Kyiv.

References

[1] Sarker SD, Nahar L. Progress in the Chemistry of Naturally Occurring Coumarins. In: Kinghorn A., Falk H., Gibbons S., Kobayashi J. (eds) Progress in the Chemistry of Organic Natural Products. 2017;106:241-304.

[2] Gouda MA, Salem MA, Helal MH. A Review on Synthesis and Pharmacological Activity of Coumarins and Their Analogs. Curr. Bioactive Compd. 2020;16 (6):818-836.

[3] Chao RY, Ding MF, Chen JY, Lee CC, Lin ST. Preparation and Characterization of Substituted 3-Benzothiazol-2-ylcoumarins J. Chin. Chem. Soc. 2010;57(2):213-221.

[4] Jin X, Wu X, Xie P, Liu S, Wu J, Wang T, Zhou H, Leng X, Chen W. Reaction-based fluorescent probes for rapid detection of hydrogen sulfide: In vivo. Analytical Methods. 2018;10(33):4079–4084.

[5] Lin W, Long L, Tan W. A highly sensitive fluorescent probe for detection of benzenethiols in environmental samples and living cells. Chem. Comm. 2010;46(9):1503–1505.

[6] Zhang Q, Ding S, Zhai Q, Feng G. Highly sensitive and selective detection of biothiols by a new

low dose colorimetric and fluorescent probe. RSC Advances. 2015;5(77):62325–62330.

[7] Zhang H, Li M, Feng W, Feng G. Rapid and selective detection of selenocysteine with a known readily available colorimetric and fluorescent turn-on probe. Dyes and Pigments. 2017;149:475–480.

[8] Tong KY, Zhao J, Tse CW, Wan PK, Rong J, Au-Yeung HY. Selective catecholamine detection in living cells by a copper-mediated oxidative bond cleavage. Chem. Sci. 2019;10(37):8519–8526.

[9] Tan W, Leng T, Lai G, Li Z, Wang K, Shen Y, Wang C. A novel coumarin-based fluorescence enhancement and colorimetric probe for Cu^{2+} via selective hydrolysis reaction. J. Photochemistry and Photobiology A: Chemistry. 2016;324:81–86.

[10] Wang K, Zhao C, Guo S, Lu Y, Shen Y, Wang C. A coumarin-based near-infrared fluorescent probe with a large stokes shift for the sequential recognition of Ni^{2+} and CN^{-}: Performance research and quantum calculation. J. Photochemistry and Photobiology A: Chemistry. 2019;382:111943.

[11] Guo SH, Guo ZQ, Wang CY, Shen Y, Zhu WH. An ultrasensitive fluorescent probe for hydrazine detection and its application in water samples and living cells. Tetrahedron. 2019;75(18):2642–2646.

[12] Yu ZH, Chung CY, Tang FK, Brewer TF, Au-Yeung HY. A modular trigger for the development of selective superoxide probes. Chem. Comm. 2017;53 (72):10042–10045.

[13] Wang K, Lai G, Li Z, Liu M, Shen Y, Wang C. A novel colorimetric and fluorescent probe for the highly selective and sensitive detection of palladium based on Pd(0) mediated reaction. Tetrahedron. 2015;71(41):7874-7878.

[14] Li C, Wang S, Huang Y, Wen Q, Wang L, Kan Y. Photoluminescence properties of a novel cyclometalated iridium(III) complex with coumarin-boronate and its recognition of hydrogen peroxide. Dalton Transactions. 2014;43(14):5595–5602.

[15] Azim SA, Al-Hazmy SM, Ebeid EM, El-Daly SA. A new coumarin laser dye 3-(benzothiazol-2-yl)-7-hydroxycoumarin. Optics and Laser Technology. 2005;37(3):245–249.

[16] Makowska A, Wolf L, Saczewski F, Bednarski PJ, Kornicka A. Synthesis and cytotoxic evaluation of benzoxazole/benzothiazole-2-imino-coumarin hybrids and their coumarin analogues as potential anticancer agents. Pharmazie. 2019;74: 648-657.

[17] Wang C, Xu F, Niu Y, Wu Y, Sun Y, Peng Y, Liang L, Xu P. Synthesis and biological evaluations of 3-benzothiazol-2-yl coumarin derivatives as MEK1 inhibitors. Letters in drug design and discovery. 2013;10(8):727–732.

[18] Khilya OV, Frasinyuk MS, Turov AV, Khilya VP. Chemistry of 3-hetarylcoumarins. 1. 3-(2-benzazolyl)-coumarins. Chem. Heterocycl. Compd. 2001;37(8):1029-1037.

[19] Syzova ZA, Karasyov AA, Lukatskaya LL, Doroshenko AO. Acid-base and spectral properties of 3-(benzothiazolyl-2)cumarins and their imino analogs. Kharkov University Bulletin. Chemical Series. 2016;26(49):26-37.

[20] Wolfbeis OS, Koller E, Hochmuth P. The Unusually Strong Effect of a 4-Cyano Group upon Electronic Spectra and Dissociation Constants of 3-Substituted 7-Hydroxycoumarin. Bull. Chem. Soc. Jpn. 1985;58(2):731-734.

[21] Khoobi M, Ramazani A, Foroumadi AR., Hamadi H, Hojjati Z, Shafiee A. Efficient Microwave-Assisted Synthesis of 3-Benzothiazolo and 3-Benzothiazolino Coumarin Derivatives Catalyzed by Heteropoly Acids. J. Iran. Chem. Soc. 2011;8(4):1036-1042.

[22] Frasinyuk MS, Turov AV, Vinogradova VI., Khilya VP. Aminomethylation of cytisine by 3-hetaryl-7-hydroxycoumarins. Chem. Nat. Compd. 2007;43(2):176–180.

[23] Roubinet B, Renard P-Y, Romieu A. New insights into the water-solubilization of thiol-sensitive fluorogenic probes based on long-wavelength 7-hydroxycoumarin scaffolds. Dyes and Pigments. 2014;110:270-284.

[24] Li J, Li X, Jia J, Chen X, Lv Y, Guo Y, Li J. A ratiometric near-infrared fluorescence strategy based on spiropyran *in situ* switching for tracking dynamic changes of live-cell lysosomal pH. Dyes and Pigments. 2019;166:433-442.

[25] Shokol TV, Moskvina VS, Glebov EK, Khilya VP. Neoflavonoid Angelicin Derivatives. Chem. Nat. Compd. 2019;55(4):716-718.

[26] Moskvina VS, Khilya VP. Synthesis of pyrano[2,3-*f*]chromen-2,8-diones and pyrano[3,2-*g*]chromen-2,8-diones based on *o*-hydroxyformyl(acyl)-neoflavonoids. Chem. Nat. Compd. 2008;44(1):16-23.