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Synthesis of a New Series of Chromones Based on Formylthiazoles

Abstract

A preparative approach to thiazole-containing chromone derivatives has been developed by modifying the corresponding aldehydes with their further transformation into propenone derivatives, and finally introducing them into the Algar-Flynn-Oyamada reaction. Several methods for obtaining propenones have been analyzed, and the most effective and practically convenient one has been found. The thiazole-containing analogs of chromones obtained have a great potential as probes for a wide range of studies.

Keywords: thiazole; chromone; heterocycle; complex formation

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Синтез нового ряду хромонів на основі формілтіазолів

Анотація

Розроблено препаративний підхід до тіазолвмісних похідних хромону шляхом модифікації відповідних альдегідів та наступним одержанням на їх основі похідних пропенонів, які було застосовано в реакції Альгара-Флінна-Оямади. Проаналізовано декілька методів одержання пропенонів та виявлено найбільш ефективний та практично зручний. Отримані тіазолвмісні аналоги хромонів мають великий потенціал як зонди для широкого спектра досліджень.

Ключові слова: тіазол; хромон; гетероцикл; комплексоутворення

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Supporting information: Copies of ^1H and ^{13}C NMR spectra of the synthesized compounds.

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■ Introduction

Various flavonols are currently widely used primarily due to their luminescent properties and sensitivity to various parameters of media [1, 2]. They can be used both as detectors for some cations [3, 4] and anions [5], as well as for individual neutral compounds [6, 7]. They are also useful in studying the properties of the medium [8–11] and biochemical studies [12–14], some of them are also used as probes to study drug delivery to the required places in “containers” [15].

However, the potential for application of flavonols is much wider. And their properties are

currently being studied [16–18]; the results of these studies may further expand the scope of flavonols.

Therefore, although the methods for the synthesis of many flavonols and other chromones have been known for a long time [19, 20], researching new ways for obtaining chromones remains an important issue. Their heterocyclic analogs are especially interesting in this regard since they create several additional centers for forming complexes, as well as due to the heterocyclic substituent effect on the electronic transition.

Developments in the field of heterocyclic analogs of flavonols – the synthesis of hetarylchromones – are particularly interesting and relevant

as they are promising complexing agents. Moreover, hetarylchromones may have interesting spectral properties due to the effect of the heterocyclic fragment on the electronic structure of molecules.

In this work, we present a synthetic approach that allows synthesizing a new series of thiazole-containing chromones.

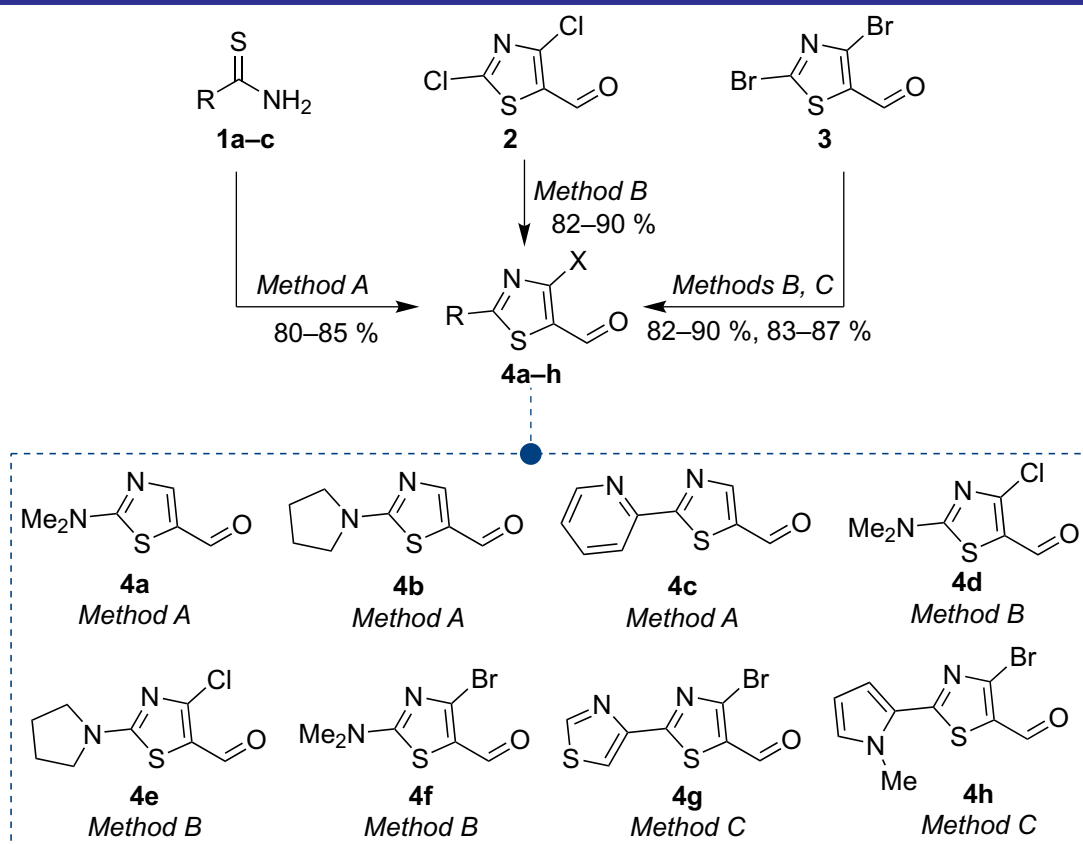
Results and discussion

Chromones were planned to be obtained by the Algar-Flynn-Oyamada reaction, starting from the corresponding analogs of chalcones. The latter were prepared by the Claisen condensation of the corresponding aldehydes with 2-hydroxyacetophenone. Thus, initially 5-formylthiazoles **4a–c** with dimethylamino, 1-pyrrolidinyl and 2-pyridinyl substituents in position 2 of thiazole were obtained (Scheme 1). For this purpose, the interaction of the corresponding thioureas **1a–c** with 2-chloromalondialdehyde was used. In addition, to study the effect of the halogen on the electronic structure revealed in the absorption and luminescence spectra in position 4, the corresponding 4-bromo- and 4-chloro-5-formylthiazoles **4d–f** were obtained [21, 22]. Finally, to study

the impact of a *bis*-heterocyclic system, we synthesized compounds **4g,h** using 2,4-dibromo-5-formylthiazole as a starting compound, according to our previously developed method [23], followed by the removal of the dioxolane protection [24]. Detailed conditions for the synthesis of each of the compounds studied are given below.

At the next stage, by the condensation of formylthiazoles **4** with 2-hydroxyacetophenone (**7**) the corresponding hetarylpropenones **5** were obtained (Scheme 2). To prepare the propenones, several methods were tested. The first was the interaction of the starting compounds under the alkaline catalysis (KOH) in methanol and did not lead to the target products. Then we investigated a method using sodium hydride in the DMF medium, and another one with NaOMe in DMF. Both methods made it possible to obtain the desired products with satisfactory yields. Among these two methods, the option with NaOMe was chosen as preferable since it was more convenient as it did not require additional purification of the products from mineral oil impurities.

Then according to the Algar-Flynn-Oyamada method [19, 25], the corresponding hetarylchromones **6** were synthesized. Solutions of potassium



Conditions: A: chlormalondialdehyde, HOAc, NaOAc, 100 °C, 3 hours; B: R_2NH $\text{CH}_3\text{CN}/\text{H}_2\text{O}$, 10 °C, 30 min; C: 1) ethylene glycol, TosOH, toluene, 115 °C, 24 hours, 2) R_3SnBu_3 , DMF, CuI, Pd G3 AmPhos, 100 °C, 24 hours, 3) oxalic acid, SiO_2 , CH_2Cl_2 , 20 °C, 48 hours

Scheme 1. The synthesis of 5-formylthiazoles

hydroxide and 30% hydrogen peroxide were added to a solution of the corresponding chalcone analog in methanol. At first, a precipitate of epoxy derivatives was formed, and it was dissolved over time. Due to the amphoteric nature of the products, neutralization was carried out with the calculated amount of acetic acid.

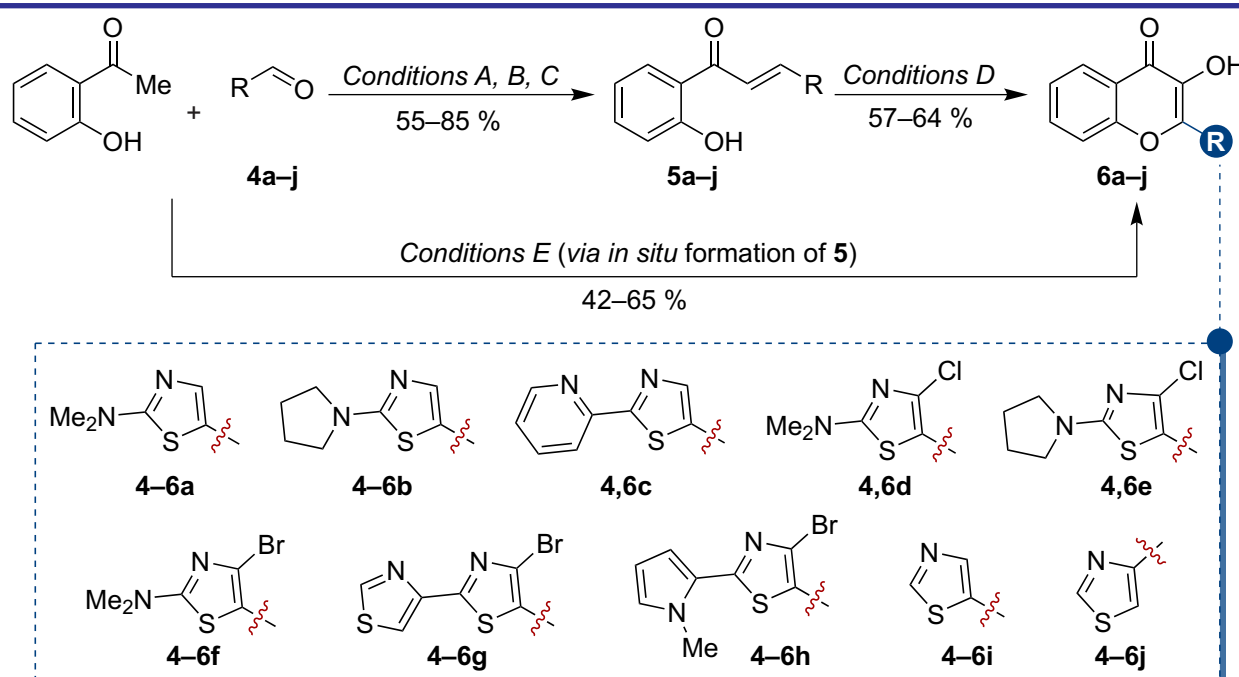
One should mention that for some derivatives the preparation of the intermediate chalcone analogs had some difficulties (compounds **5c–e**). In these cases, upon neutralization with acetic acid, a resinous substance was formed. It was a mixture of the target chalcone analog and other unidentified condensation products. It was not possible to separate the required chalcone from by-products, and their isolation was considered inappropriate. In order to reach our purpose of obtaining compounds **6c–e**, we proposed an alternative synthetic approach. It included the formation of unsaturated ketones *in situ* and the effect of the reaction medium to an oxidizing agent (hydrogen peroxide) in the alkaline medium (**Scheme 2, Method E**). Moreover, it was found that the yield of products **6** using the one-pot approach was only slightly lower as compared to the two-stage sequence with the isolation of intermediate chalcones. Thus, the one-pot yield of the final heterarylchromones **6a,f,i** differed from the stepwise one obtained by the stepwise transformation by 4–7%.

Conclusions

The synthetic approach to thiazole-containing chromones with amino, halogen and heterocyclic substituents has been developed. The method can be easily used to extend the series of related heterocyclic chromones. It has been shown that a direct one-pot transformation from thiazole-5-carbaldehyde to chromone is advantageous comparing to a two-step transformation with the isolation of the intermediate chalcone analogs.

Experimental part

All chemicals, unless otherwise stated, were obtained from Enamine Ltd. and used without further purification. Products **4a–f** were synthesized as described in [22, 26], substances **4i,j** were received from commercial sources. All solvents were purified by standard methods. All procedures were carried out at 1 atm. with no precautions taken to exclude ambient moisture. Melting points of all the compounds synthesized were determined with a Gallenkamp melting point apparatus in open capillary tubes. ¹H NMR spectra were recorded on a Varian MR-400 spectrometer (400 MHz) with TMS as an internal standard. ¹³C NMR spectra were recorded on a Bruker Avance DRX 500 (126 MHz) spectrometer with TMS as an internal standard. HPLC-MS spectra were recorded



Conditions: A: DMF, NaOMe, 20 °C 2 hours; B: MeOH, KOH, 20 °C, 2 hours; C: DMF, NaH, 0 °C 2 hours; D: 1) MeOH, KOH, 20 °C, 10 min, 2) H₂O₂ (30% aqueous), 20 °C, 3 hours; E: 1) MeOH, KOH, 10 hours, 2) KOH, H₂O₂ (30% aqueous), 65 °C, 1 hour

Scheme 2. The synthesis of thiazole-containing chromones

using the chromatography/mass-spectrometric system consisting of a high-performance liquid chromatograph Agilent 1100 LC MSD SL instrument equipped with a diode-matrix and mass-selective detector "Agilent LC/MSD SL". The parameters of the chromatography-mass analysis were the column – SUPELCO Ascentis Express C18, 2.7 μm 4.6 mm \times 15 cm. According to the HPLC-MS data, all the compounds synthesized had purity > 95%. The elemental analysis was performed in the Institute of Organic Chemistry of the NASU. Absorption spectra were measured on a Hitachi U3210 spectrophotometer, fluorescence spectra were measured on a Hitachi 850 spectrofluorimeter in a concentration of the compounds studied of 10^{-5} – 10^{-6} mol/l in acetonitrile and a thickness of the absorbing layer of 1 cm.

The general procedure for the synthesis of compounds 4g,h (Method C)

First two stages (dioxolane protection and the Stille reaction) were performed as described in our previous work [23].

A solution (1 mmol) of the corresponding dioxolane-protected aldehyde in 20 mL of CH_2Cl_2 and 0.25 mL of a 5% aqueous solution of oxalic acid were added to 5 g of SiO_2 and stirred for 24 h. Then the mixture was filtered through a layer of Na_2SO_4 , and the solvent was removed on a rotary evaporator.

4-Bromo-[2,4'-bithiazole]-5-carbaldehyde (4g)

A yellow solid. Yield – 83%. Anal. Calcd for $\text{C}_7\text{H}_3\text{BrN}_2\text{OS}_2$, %: C 30.56, H 1.10, N 10.18, S 23.30. Found, %: C 30.52, H 1.12, N 10.15, S 23.32. ^1H NMR (400 MHz, Chloroform-*d*), δ , ppm: 8.24 (1H, d, $J = 2.0$ Hz, S-CH=N-C=CH), 8.88 (1H, d, $J = 2.1$ Hz, S-CH=N), 10.01 (1H, s, CHO). Mass spectrum, m/z (I_{rel} , %): $[\text{M}+\text{H}]^+$ 274 (100), 276 (98).

4-Bromo-2-(1-methyl-1H-pyrrol-2-yl)thiazole-5-carbaldehyde (4h)

A yellow solid. Yield – 87%. Anal. Calcd for $\text{C}_8\text{H}_6\text{BrN}_3\text{OS}$, %: C 35.31, H 2.22, N 15.44, S 11.78. Found, %: C 35.33, H 2.24, N 15.42, S 11.77. ^1H NMR (400 MHz, Chloroform-*d*), δ , ppm: 4.02 (3H, s, CH_3), 6.19 (1H, dd, $J = 4.1, 2.5$ Hz, N-CH=CH-CH), 6.83 (1H, s, N-CH=CH-CH), 6.89 (1H, dd, $J = 4.1, 1.7$ Hz, N-CH=CH-CH), 9.91 (1H, s, CHO). ^{13}C NMR (101 MHz, Chloroform-*d*), δ , ppm: 37.44, 98.42, 109.86, 116.53, 125.49, 128.67, 130.26, 135.28, 182.61. Mass spectrum, m/z (I_{rel} , %): $[\text{M}+\text{H}]^+$ 270 (100), 272 (98).

The general procedure for the synthesis of compounds 5a,b,f–i (Conditions C)

2-Hydroxyacetophenone (1 mmol) and the corresponding aldehyde (1 mmol) were dissolved in

15 mL of DMF. Sodium methoxide (3 mmol) was added, and the reaction mixture was stirred for 2 h. Water (30 mL) was added to the solution, and then it was neutralized with acetic acid (3 mmol). The precipitate formed was filtered and washed with water.

(E)-3-(2-(Dimethylamino)thiazol-5-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one (5a)

A yellow solid. Yield – 84%. M. p. 178 $^\circ\text{C}$. Anal. Calcd for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_2\text{S}$, %: C 61.29, H 5.14, N 10.21, S 11.69. Found, %: C 61.32, H 5.11, N 10.19, S 11.69. ^1H NMR (400 MHz, DMSO-*d*₆), δ , ppm: 3.11 (6H, s, 2CH_3), 6.89 (2H, dd, $J = 7.7, 6.1$ Hz, C(OH)=CH-CH=CH-CH), 7.09 (1H, d, $J = 14.7$ Hz, C(O)-CH=CH), 7.46 (1H, t, $J = 7.8$ Hz, C(OH)=CH-CH=CH-CH), 7.79 (1H, s, S-C=N-CH=C), 7.92 (1H, d, $J = 14.7$ Hz, C(O)-CH=CH), 8.04 (1H, d, $J = 8.4$ Hz, C(OH)=CH-CH=CH-CH), 12.87 (1H, s, OH). ^{13}C NMR (151 MHz, DMSO-*d*₆), δ , ppm: 39.99, 115.48, 118.12, 119.43, 120.90, 124.39, 130.63, 136.16, 137.40, 151.84, 162.38, 173.32, 192.68. Mass spectrum, m/z (I_{rel} , %): $[\text{M}+\text{H}]^+$ 274 (100).

(E)-1-(2-Hydroxyphenyl)-3-(2-(pyrrolidin-1-yl)thiazol-5-yl)prop-2-en-1-one (5b)

A yellow solid. Yield – 75%. M. p. 210 $^\circ\text{C}$. Anal. Calcd for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_2\text{S}$, %: C 63.98, H 5.37, N 9.33, S 10.67. Found, %: C 63.94, H 5.33, N 9.35, S 10.70. ^1H NMR (400 MHz, DMSO-*d*₆), δ , ppm: 2.03 (4H, s, N-CH₂-CH₂-), 3.50 (4H, s, N-CH₂-CH₂-), 6.95 (2H, s, C(OH)=CH-CH=CH-CH), 7.15 (1H, d, $J = 14.7$ Hz, C(O)-CH=CH), 7.52 (1H, s, C(OH)=CH-CH=CH-CH), 7.87 (1H, s, C(OH)=CH-CH=CH-CH), 8.00 (1H, d, $J = 14.7$ Hz, C(O)-CH=CH), 8.11 (1H, s, S-C=N-CH=C), 12.97 (1H, s, OH). ^{13}C NMR (151 MHz, DMSO-*d*₆), δ , ppm: 25.19, 51.11, 118.18, 120.04, 121.15, 124.17, 129.29, 130.49, 135.38, 136.18, 140.66, 151.96, 162.18, 193.42. Mass spectrum, m/z (I_{rel} , %): $[\text{M}+\text{H}]^+$ 300 (100).

(E)-3-(4-Bromo-2-(dimethylamino)thiazol-5-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one (5f)

A yellow solid. Yield – 70%. M. p. 190 $^\circ\text{C}$. Anal. Calcd for $\text{C}_{14}\text{H}_{13}\text{BrN}_2\text{O}_2\text{S}$, %: C 47.60, H 3.71, N 7.93, S 9.08. Found, %: C 46.58, H 3.72, N 7.97, S 9.06. ^1H NMR (400 MHz, DMSO-*d*₆), δ , ppm: 3.15 (6H, s, 2CH_3), 6.94 (2H, dd, $J = 8.5, 7.3$ Hz, C(OH)=CH-CH=CH-CH), 7.21 (1H, d, $J = 14.7$ Hz, C(O)-CH=CH), 7.47–7.57 (1H, m, C(OH)=CH-CH=CH-CH), 7.78 (1H, d, $J = 14.7$ Hz, C(O)-CH=CH), 8.05–8.13 (1H, m, C(OH)=CH-CH=CH-CH), 12.68 (1H, s, OH). ^{13}C NMR (151 MHz, DMSO-*d*₆), δ , ppm: 39.09, 118.18, 120.06, 121.16, 123.86, 126.64, 127.72, 130.32, 134.84, 135.33, 162.51, 167.04,

192.90. Mass spectrum, m/z (I_{rel} , %): $[M+H]^+$ 351 (100), 353(97).

(E)-3-(4-Bromo-[2,4'-bithiazol]-5-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one (**5g**)

A yellow solid. Yield – 55%. M. p. 172 °C. Anal. Calcd for $C_{15}H_9BrN_2O_2S_2$, %: C 45.81, H 2.31, N 7.12, S 16.30. Found, %: C 45.79, H 2.33, N 7.10, S 8.17. 1H NMR (500 MHz, Chloroform-*d*), δ , ppm: 6.93 (1H, d, $J = 15.3$ Hz, C(O)-CH=CH), 7.00 (1H, d, $J = 8.4$ Hz, C(OH)=CH-CH=CH-CH), 7.44–7.53 (2H, m, C(OH)=CH-CH=CH-CH), 7.81 (1H, d, $J = 8.1$ Hz, C(OH)=CH-CH=CH-CH), 7.99 (1H, d, $J = 15.3$ Hz, C(O)-CH=CH), 8.18 (1H, s, N-CH=CH-CH), 8.87 (1H, s, S-CH=N), 12.65 (1H, s, OH). ^{13}C NMR (126 MHz, Chloroform-*d*), δ , ppm: 118.21, 118.54, 119.19, 122.49, 128.94, 130.47, 132.67, 133.43, 136.25, 148.28, 153.61, 162.08, 163.15, 170.62, 191.80. Mass spectrum, m/z (I_{rel} , %): $[M+H]^+$ 392 (100), 394 (98).

(E)-3-(4-Bromo-2-(1-methyl-1H-pyrrol-2-yl)thiazol-5-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one (**5h**)

A yellow solid. Yield – 65%. M. p. 195 °C. Anal. Calcd for $C_{17}H_{13}BrN_2O_2S_2$, %: C 52.45, H 3.37, N 7.20, S 8.24. Found, %: C 52.49, H 3.33, N 7.18, S 8.21. 1H NMR (400 MHz, DMSO-*d*₆), δ , ppm: 3.79 (3H, s, CH₃), 6.04 (1H, dd, $J = 4.1, 2.6$ Hz, N-CH=CH-CH), 6.72 (1H, dd, $J = 4.1, 1.7$ Hz, N-CH=CH-CH), 6.82 (2H, t, $J = 8.2$ Hz, C(OH)=CH-CH=CH-CH), 7.00 (1H, d, $J = 2.2$ Hz, N-CH=CH-CH), 7.36–7.41 (1H, m, C(OH)=CH-CH=CH-CH), 7.46 (1H, d, $J = 15.2$ Hz, C(O)-CH=CH), 7.62 (1H, d, $J = 15.2$ Hz, C(O)-CH=CH), 7.90–7.98 (1H, m, C(OH)=CH-CH=CH-CH), 12.04 (1H, s, OH). ^{13}C NMR (126 MHz, DMSO-*d*₆), δ , ppm: 36.68, 109.44, 115.25, 117.66, 119.23, 120.97, 124.15, 124.77, 126.54, 130.42, 130.68, 132.20, 132.60, 136.22, 143.03, 161.67, 191.72. Mass spectrum, m/z (I_{rel} , %): $[M+H]^+$ 388 (100), 390 (98).

(E)-1-(2-Hydroxyphenyl)-3-(thiazol-5-yl)prop-2-en-1-one (**5i**)

A yellow solid. Yield – 81%. M. p. 111 °C. Anal. Calcd for $C_{12}H_9NO_2S$, %: C 62.32, H 3.92, N 6.06, S 13.86. Found, %: C 62.35, H 3.97, N 6.00, S 13.89. 1H NMR (400 MHz, DMSO-*d*₆), δ , ppm: 6.99 (2H, t, $J = 7.6$ Hz, C(OH)=CH-CH=CH-CH), 7.55 (1H, t, $J = 7.2$ Hz, C(OH)=CH-CH=CH-CH), 8.12 (1H, d, $J = 7.6$ Hz, C(OH)=CH-CH=CH-CH), 8.07 (1H, d, $J = 15.3$ Hz, C(O)-CH=CH), 7.74 (1H, d, $J = 15.3$ Hz, C(O)-CH=CH), 8.44 (1H, s, S-CH=N-CH=C), 9.26 (1H, s, S-CH=N), 12.22 (1H, s, OH). ^{13}C NMR (126 MHz, DMSO-*d*₆), δ , ppm: 117.64, 119.21, 120.94, 124.16, 130.76, 133.88, 135.17, 136.20, 148.27, 157.50, 161.33, 192.43. Mass spectrum, m/z (I_{rel} , %): $[M+H]^+$ 232 (100).

(E)-1-(2-Hydroxyphenyl)-3-(thiazol-4-yl)prop-2-en-1-one (**5j**)

A yellow solid. Yield – 85%. M. p. 110–112 °C. Anal. Calcd for $C_{12}H_9NO_2S$, %: C 62.32, H 3.92, N 6.06, S 13.86. Found, %: C 62.29, H 3.95, N 6.03, S 13.89. 1H NMR (400 MHz, DMSO-*d*₆), δ , ppm: 6.99 (2H, t, $J = 8.0$ Hz, C(OH)=CH-CH=CH-CH), 7.48–7.63 (1H, m, C(OH)=CH-CH=CH-CH), 7.84 (1H, d, $J = 15.2$ Hz, C(O)-CH=CH), 7.98 (1H, d, $J = 2.8$ Hz, C(OH)=CH-CH=CH-CH), 8.01 (1H, d, $J = 15.2$ Hz, C(O)-CH=CH), 8.32 (1H, d, $J = 1.8$ Hz, S-CH=N-C=CH), 9.23 (1H, d, $J = 1.8$ Hz, S-CH=N), 12.16 (1H, s, OH). ^{13}C NMR (126 MHz, DMSO-*d*₆), δ , ppm: 118.21, 119.86, 121.88, 124.02, 125.63, 130.96, 136.56, 136.89, 152.66, 156.31, 161.65, 193.87. Mass spectrum, m/z (I_{rel} , %): $[M+H]^+$ 232 (100).

The general procedure for the synthesis of compounds 6a,b,e,f-i (Conditions D)

The corresponding propenone (1 mmol) was dissolved in methanol, then while stirring potassium hydroxide (3 mmol) was added to the solution. After 10 min of stirring 30% aqueous hydrogen peroxide (3 mmol) was added, and the reaction mixture was stirred for 3 more h. Then mixture was neutralized with acetic acid (3 mmol), and the formed precipitate was filtered and washed with methanol.

The one-pot procedure for the synthesis of compounds 6a,c,d,e,f,i (Conditions E)

2-Hydroxyacetophenone (1 mmol) and the corresponding aldehyde (1 mmol) were dissolved in methanol (10 mL), a catalytic amount of potassium hydroxide was added, and the reaction mixture was stirred for 10 h. Then potassium hydroxide (2 mmol) and 2 mL of a 30% aqueous hydrogen peroxide was added. The resulting mixture was refluxed for 1 h, cooled and neutralized with hydrochloric acid (2 mmol). The precipitate formed was filtered off and washed with methanol and water.

2-(2-(Dimethylamino)thiazol-5-yl)-3-hydroxy-4H-chromen-4-one (**6a**)

A yellow solid. Yield – 60% (48% for the Method H). M. p. 255 °C (decomp.). Anal. Calcd for $C_{14}H_{12}N_2O_3S$, %: C 58.32, H 4.20, N 9.72, S 11.12. Found, %: C 58.30, H 4.24, N 9.76, S 11.10. 1H NMR (400 MHz, DMSO-*d*₆), δ , ppm: 2.00 (6H, s, 2×CH₃), 6.93 (2H, s, C(-O)=CH-CH=CH-CH), 7.21 (1H, s, C(-O)=CH-CH=CH-CH), 7.49 (1H, s, S-CH=N-CH=C), 8.07 (1H, s, C(-O)=CH-CH=CH-CH). ^{13}C NMR (126 MHz, DMSO-*d*₆), δ , ppm: 39.44, 114.75, 117.75, 121.97, 124.35, 124.62, 133.00, 134.67, 143.61, 153.92, 170.71, 173.27. Mass

spectrum, m/z (I_{rel} , %): $[M+H]^+$ 288 (100). $\lambda_{a\ max}$ (nm) = 400, $\lambda_{f\ max}$ (nm) = 580.

3-Hydroxy-2-(2-(pyrrolidin-1-yl)thiazol-5-yl)-4H-chromen-4-one (6b)

A yellow solid. Yield – 63%. M. p. 261 °C decomp. Anal. Calcd for $C_{16}H_{14}N_2O_3S$, %: C 61.13, H 4.49, N 8.91, S 10.20. Found, %: C 61.15, H 4.45, N 8.94, S 10.25. 1H NMR (400 MHz, DMSO- d_6), δ , ppm: 2.01 (4H, s, N-CH₂-CH₂-), 3.46 (4H, s, N-CH₂-CH₂-), 7.41 (1H, s, C(-O)=CH-CH=CH-CH), 7.61 (1H, s, C(-O)=CH-CH=CH-CH), 7.71 (C(-O)=CH-CH=CH-CH), 8.01 (1H, s, S-CH=N-CH=C), 8.05 (1H, s, C(-O)=CH-CH=CH-CH). ^{13}C NMR (126 MHz, DMSO- d_6), δ , ppm: 25.66, 49.88, 114.66, 118.27, 122.53, 124.86, 125.13, 133.49, 135.06, 143.71, 144.30, 154.44, 170.15, 171.14. Mass spectrum, m/z (I_{rel} , %): $[M+H]^+$ 314 (100). $\lambda_{a\ max}$ (nm) = 405, $\lambda_{f\ max}$ (nm) = 580.

3-Hydroxy-2-(2-(pyridin-2-yl)thiazol-5-yl)-4-chromen-4-one (6c) (Method H)

A yellow solid. Yield – 46%. M. p. 255 °C (decomp.). Anal. Calcd for $C_{17}H_{10}N_2O_3S$, %: C 63.35, H 3.13, N 8.69, S 9.95. Found, %: C 63.32, H 3.14, N 8.65, S 9.93. 1H NMR (500 MHz, DMSO- d_6), δ , ppm: 7.48 (1H, t, J = 7.6 Hz, N-CH=CH-CH=CH), 7.51–7.59 (1H, m, C(-O)=CH-CH=CH-CH), 7.76 (1H, d, J = 8.5 Hz, C(-O)=CH-CH=CH-CH), 7.82 (1H, t, J = 7.8 Hz, C(-O)=CH-CH=CH-CH), 8.00 (1H, t, J = 7.8 Hz, N-CH=CH-CH=CH), 8.11 (1H, d, J = 8.0 Hz, N-CH=CH-CH=CH), 8.20 (1H, d, J = 7.8 Hz, C(-O)=CH-CH=CH-CH), 8.67 (1H, d, J = 5.7 Hz, N-CH=CH-CH=CH), 8.69 (1H, s, CH(Thz)), 10.72 (1H, s, OH). ^{13}C NMR (126 MHz, DMSO- d_6), δ , ppm: 117.55, 120.97, 122.57, 123.00, 124.25, 124.87, 125.62, 125.72, 134.38, 134.89, 137.30, 140.97, 142.55, 145.39, 149.69, 152.65, 162.61, 175.35. Mass spectrum, m/z (I_{rel} , %): $[M+H]^+$ 322 (100). $\lambda_{a\ max}$ (nm) = 380, $\lambda_{f\ max}$ (nm) = 570.

2-(4-Chloro-2-(dimethylamino)thiazol-5-yl)-3-hydroxy-4H-chromen-4-one (6d) (Method H)

A yellow solid. Yield – 43%. M. p. 254 °C (decomp.). Anal. Calcd for $C_{14}H_{11}ClN_2O_3S$, %: C 52.10, H 3.44, N 8.68, S 9.93. Found, %: C 52.13, H 3.42, N 8.65, S 9.97. 1H NMR (400 MHz, DMSO- d_6), δ , ppm: 3.08 (6H, d, J = 6.2 Hz, 2CH₃), 7.43 (1H, t, J = 7.8 Hz, C(-O)=CH-CH=CH-CH), 7.60 (1H, d, J = 8.5 Hz, C(-O)=CH-CH=CH-CH), 7.74 (1H, t, J = 6.9 Hz, C(-O)=CH-CH=CH-CH), 8.06 (1H, d, J = 8.0 Hz, C(-O)=CH-CH=CH-CH). ^{13}C NMR (126 MHz, DMSO- d_6), δ , ppm: 39.30, 105.34, 117.78, 121.91, 124.53, 124.63, 133.35, 135.91, 137.26, 141.53, 153.91, 169.53, 171.11. Mass spectrum, m/z (I_{rel} , %): $[M+H]^+$ 322 (100), 324(33). $\lambda_{a\ max}$ (nm) = 390, $\lambda_{f\ max}$ (nm) = 580.

2-(4-Chloro-2-(pyrrolidin-1-yl)thiazol-5-yl)-3-hydroxy-4H-chromen-4-one (6e) (Method H)

A yellow solid. Yield – 65%. M. p. 255 °C (decomp.). Anal. Calcd for $C_{16}H_{13}ClN_2O_3S$, %: C 55.10, H 3.76, N 8.03, S 9.19. Found, %: C 55.11, H 3.80, N 8.01, S 9.24. 1H NMR (400 MHz, DMSO- d_6), δ , ppm: 1.99 (4H, s, N-CH₂-CH₂-), 3.40 (4H, s, N-CH₂-CH₂-), 7.38 (1H, s, C(-O)=CH-CH=CH-CH), 7.57 (1H, s, C(-O)=CH-CH=CH-CH), 7.68 (1H, s, C(-O)=CH-CH=CH-CH), 8.04 (1H, s, C(-O)=CH-CH=CH-CH). ^{13}C NMR (126 MHz, DMSO- d_6), δ , ppm: 25.17, 49.65, 115.08, 117.77, 122.59, 124.33, 124.96, 134.49, 134.86, 136.78, 143.68, 153.85, 162.33, 175.27. Mass spectrum, m/z (I_{rel} , %): $[M+H]^+$ 348 (100), 350(33). $\lambda_{a\ max}$ (nm) = 395, $\lambda_{f\ max}$ (nm) = 585.

2-(4-Bromo-2-(dimethylamino)thiazol-5-yl)-3-hydroxy-4H-chromen-4-one (6f)

A yellow solid. Yield – 64% (42% for the Method H). M. p. 259 °C (decomp.). Anal. Calcd for $C_{14}H_{11}BrN_2O_3S$, %: C 45.79, H 3.02, N 7.63, S 8.73. Found, %: C 45.81, H 2.98, N 7.67, S 8.75. 1H NMR (500 MHz, DMSO- d_6), δ , ppm: 3.09 (6H, s, 2CH₃), 7.44 (1H, t, J = 7.4 Hz, C(-O)=CH-CH=CH-CH), 7.61 (1H, d, J = 8.5 Hz, C(-O)=CH-CH=CH-CH), 7.75 (1H, t, J = 6.9 Hz, C(-O)=CH-CH=CH-CH), 8.07 (1H, d, J = 8.1 Hz, C(-O)=CH-CH=CH-CH), 10.11 (1H, s, OH). ^{13}C NMR (126 MHz, DMSO- d_6), δ , ppm: 39.29, 107.62, 117.71, 121.93, 124.57, 124.68, 125.28, 133.42, 136.27, 153.93, 170.65, 171.28. Mass spectrum, m/z (I_{rel} , %): $[M+H]^+$ 366 (100), 368(97). $\lambda_{a\ max}$ (nm) = 395, $\lambda_{f\ max}$ (nm) = 585.

2-(4-Bromo-2-(thiazol-4-yl)thiazol-5-yl)-3-hydroxy-4H-chromen-4-one (6g)

A yellow solid. Yield – 57%. M. p. 265 °C (decomp.). Anal. Calcd for $C_{15}H_7BrN_2O_3S_2$, %: C 44.24, H 1.73, N 6.88, S 15.74. Found, %: C 44.26, H 1.78, N 6.82, S 15.70. 1H NMR (500 MHz, DMSO- d_6), δ , ppm: 6.73–6.57 (2H, m, C(-O)=CH-CH=CH-CH), 7.16 (1H, t, J = 7.6 Hz, C(-O)=CH-CH=CH-CH), 7.45 (1H, s, S-CH=N-C=CH), 7.70 (1H, d, J = 7.7 Hz, C(-O)=CH-CH=CH-CH), 9.25 (1H, s, S-CH=N). Mass spectrum, m/z (I_{rel} , %): $[M+H]^+$ 407 (100), 409(98).

2-(4-Bromo-2-(1-methyl-1H-pyrrol-2-yl)thiazol-5-yl)-3-hydroxy-4H-chromen-4-one (6h)

A yellow solid. Yield – 60%. M. p. 265 °C (decomp.). Anal. Calcd for $C_{17}H_{11}BrN_2O_3S$, %: C 50.64, H 2.75, N 6.95, S 7.95. Found, %: C 50.68, H 2.79, N 6.90, S 7.97. 1H NMR (400 MHz, Chloroform- d), δ , ppm: 4.04 (3H, s, CH₃), 6.18 (1H, s, N-CH=CH-CH), 6.80 (2H, d, J = 3.3 Hz, N-CH=CH-CH), 7.22–7.38 (1H, m, C(-O)=CH-CH=CH-CH), 7.62 (1H, d, J = 8.8 Hz, C(-O)=CH-CH=CH-CH), 7.71 (1H, d,

$J = 7.7$ Hz, C(-O)=CH-CH=CH-CH), 8.23 (1H, d, $J = 7.9$ Hz, C(-O)=CH-CH=CH-CH). ^{13}C NMR (126 MHz, DMSO- d_6), δ , ppm: 34.22, 108.02, 112.15, 117.71, 121.98, 122.62, 124.36, 124.88, 125.67, 126.03, 134.46, 134.86, 142.86, 153.29, 153.48, 175.10. Mass spectrum, m/z (I_{rel} , %): $[\text{M}+\text{H}]^+$ 402 (100), 404(98). $\lambda_{a\max}$ (nm) = 400, $\lambda_{f\max}$ (nm) = 600.

3-Hydroxy-2-(thiazol-5-yl)-4H-chromen-4-one (6i)

A white solid. Yield – 64% (49% for the Method H). M. p. 230 °C (decomp.). Anal. Calcd for $\text{C}_{12}\text{H}_7\text{NO}_3\text{S}$, %: C 58.77, H 2.88, N 5.71, S 13.07. Found, %: C 58.73, H 2.91, N 5.74, S 13.09. ^1H NMR (400 MHz, DMSO- d_6), δ , ppm: 7.47 (1H, t, $J = 7.5$ Hz, C(-O)=CH-CH=CH-CH), 7.74 (1H, d, $J = 8.6$ Hz, C(-O)=CH-CH=CH-CH), 7.81 (1H, t, $J = 7.7$ Hz, C(-O)=CH-CH=CH-CH), 8.11 (1H, d, $J = 8.0$ Hz, C(-O)=CH-CH=CH-CH), 8.67 (1H, s, S-CH=N-CH=C), 9.33 (1H, s, S-CH=N). ^{13}C NMR (126 MHz, DMSO- d_6), δ , ppm: 118.20, 121.79,

124.66, 124.84, 127.77, 133.85, 137.46, 141.45, 143.20, 154.25, 157.63, 172.08. Mass spectrum, m/z (I_{rel} , %): $[\text{M}+\text{H}]^+$ 245 (100). $\lambda_{a\max}$ (nm) = 350, $\lambda_{f\max}$ (nm) = 535.

3-Hydroxy-2-thiazol-4-yl-chromen-4-one (6j)

A white solid. Yield (62%), mp. 229-232 °C. Anal. Calcd for $\text{C}_{12}\text{H}_7\text{NO}_3\text{S}$, %: C 58.77, H 2.88, N 5.71, S 13.07. Found, %: C 58.74, H 2.91, N 5.75, S 13.09. ^1H NMR (400 MHz, DMSO- d_6), δ , ppm: 7.48 (t, $J = 7.3$ Hz, 1H, C(-O)=CH-CH=CH-CH), 7.72 (dd, $J = 8.5, 4.2$ Hz, 1H, C(-O)=CH-CH=CH-CH), 7.77–7.88 (m, 1H, C(-O)=CH-CH=CH-CH), 8.13 (dd, $J = 8.4, 4.2$ Hz, 1H, C(-O)=CH-CH=CH-CH), 8.56 (dd, $J = 4.3, 2.0$ Hz, 1H, S-CH=N-C=CH), 9.35 (dd, $J = 4.3, 2.0$ Hz, 1H, S-CH=N). ^{13}C NMR (126 MHz, DMSO- d_6), δ , ppm: 118.31, 121.88, 122.95, 124.51, 124.85, 133.75, 138.99, 141.54, 146.29, 154.27, 155.01, 172.45. Mass spectrum, m/z (I_{rel} , %): $[\text{M}+\text{H}]^+$ 246 (100). $\lambda_{a\max}$ (nm) = 340, $\lambda_{f\max}$ (nm) = 515.

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