Synthesis and Antimicrobial Activity of New *N*-[4-(4-Hydroxy-2-oxo-2*H*-chromen-3-yl)thiazol-2-yl]benzenesulfonamides

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New *N*-[4-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)thiazol-2-yl]benzenesulfonamides were synthesized and their antimicrobial activity was tested in relation to some bacteria and fungi. Through the reaction of bromination with phenyltrimethylammonium tribromide, 3-acetyl-4-hydroxy-2*H*-chromen-2-one yields 3-bromoacetyl-4-hydroxy-2*H*-chromen-2-one which through reaction with thiourea gives 3-(2-aminothiazol-4-yl)-4-hydroxy-2*H*-chromen-2-one (*III*) in the form of a bromide salt. Compound *III* was the starting substrate in condensation reactions with corresponding arenesulfonyl chlorides yielding the required derivatives. Chemical structure of the obtained compounds was confirmed by elemental and structural analysis (IR, ^{1}H and ^{13}C NMR). Also, the disk diffusion method was used to test the inhibitory activity of four of the new sulfonamides in relation to twelve microorganisms.

Derivatives of 2-aminothiazoles are important pharmacological compounds and precursors in syntheses of medicines [1] such as the antibiotic sulfathiazole and the antihelminthic thiabedazole. Moreover, recent research indicates that they are also inhibitors of enzymes such as kinurenine 3-hydroxylase [2]. On the other hand, derivatives of 4-hydroxy-2*H*-chromen-2-one are known as anticoagulants and antitumour compounds [3—5].

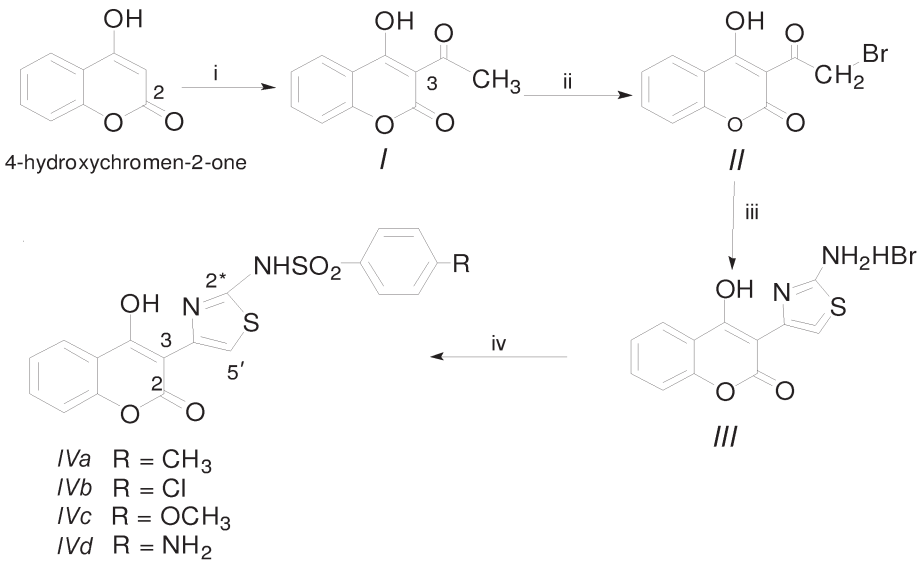
Aminothiazoles are obtained by means of the Hanzch reaction [6—8]. Further functionalization of the starting aminothiazole derivatives involves formation of 3-bromoacetyl-4-hydroxy-2*H*-chromen-2-one (*II*) as a suitable synthon for reaction with thiourea to obtain 3-(2-aminothiazol-4-yl)-4-hydroxy-2*H*-chromen-2-one (*III*) (Scheme 1). In the next phase, reaction of *III* with corresponding arenesulfonyl chlorides yields *N*-[4-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)thiazol-2-yl]-4R-benzenesulfonamide derivatives *IV*.

Compound *II* is useful in synthesis of substituted heterocyclic 2*H*-chromen-2-ones. However, its attainment through reaction with molecular bromine is hindered by pronounced sensitivity of the 2*H*-chromen-2-one ring to reactions of electrophilic substitution [9, 10]. Under the indicated conditions, for example, 4-acetyltropolone ring gave substitution products at the tropolone ring as a main product [11]. However, when 3-acetyl-4-hydroxy-2*H*-chromen-2-one (*I*), obtained by means of acetylation (by the method [12—14]) of 4-hydroxy-2*H*-chromen-2-one with acetic acid in the presence of phosphorous oxychloride,

is treated with phenyltrimethylammonium tribromide [15, 16] in tetrahydrofuran, *II* is obtained in the form of yellow crystals (m.p. = 144—146 °C). Structure of this compound was determined on the basis of spectral data and elemental analysis. Three characteristic absorptions were observed in the IR spectrum: at 3185 cm^{-1} (OH), 1725 cm^{-1} (bromoacetyl, C═O), and 1685 cm^{-1} (2*H*-chromen-2-one, C═O). The ^{1}H NMR spectrum shows a singlet peak at δ = 4.28 (2H) for CH_2, the signals at δ = 7.31—7.67 (4H) for aromatic ring protons, and a singlet peak at δ = 15.7 for OH group.

Compound *II* with thiourea in refluxing ethanol for a period of 30 min gives *III* in the form of a bromide salt. Spicular yellow crystals of compound *III* (m.p. = 255—257 °C) are obtained in a yield of 60 % by crystallization from a mixture of ethanol and 10 % sodium carbonate. The structure of compound *III* was determined on the basis of spectral data and elemental analysis. Three characteristic absorptions were observed in the IR spectrum: at 3381 cm^{-1} (OH), 3122 cm^{-1} (NH), and 1693 cm^{-1} (C═O). In the ^{1}H NMR spectrum one isolated singlet was observed at δ = 7.21 for thiazole H-5′.

A mixture of *III* in the bromide form and the corresponding arenesulfonyl chloride [17] in pyridine was stirred overnight (12 h, r.t.). Following the completed reaction, the red reaction solution was neutralized with 1 M-HCl and filtered. A yellowish-orange crystalline dust (compounds *IVa*—*IVd*) was obtained as a result. The chemical structure of these compounds was determined on the basis of spectral data and elemental analysis.



i) Phosphorous oxychloride, acetic acid, reflux 30 min, ii) phenyltrimethylammonium tribromide, THF, 25 °C, 15 min, iii) $(NH_2)_2CS$, ethanol, reflux 30 min, iv) $ArSO_2Cl$, pyridine, 25 °C, 12 h.

Scheme 1

Table 1. The Inhibition Effect of Compounds *IVa*—*IVd* against Fungi and Bacteria

Microorganism	Inhibition by compounds/%			
	IVa	*IVb*	*IVc*	*IVd*
Fungus *Aspergillus niger*	45	36	42	44
Fungus *Doratomyces stemonitis*	39	31	35	36
Fungus *Trichoderma harzianum*	37	29	29	34
Fungus *Penicillium verrucosum*	48	43	43	46
Yeast *Candida albicans*	59	56	47	61
G^+ *Bacillus mycoides*	69	63	67	68
G^- *Pseudomonas glicinea*	59	49	51	61
G^- *Pseudomonas phaseolicola*	69	57	55	71
G^- *Pseudomonas fluorescens*	75	70	64	77
G^- *Escherichia coli*	76	75	65	79
G^- *Pseudomonas aeruginosa*	49	46	49	56
G^+ *Staphylococcus aureus*	83	76	76	79

Table 1 presents in summary form results of disk diffusion testing [18] of the antimicrobial activity of compounds *IVa*—*IVd* in relation to some bacteria and fungi. The level of inhibition of some bacteria and fungi in the presence of *N*-[4-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)thiazol-2-yl]-benzenesulfonamide derivatives (compounds *IVa*—*IVd*) was tested in the work. At the concentration of the tested compounds of 25 mg for bacteria and 100 mg for fungi, the microorganisms growth was reduced from 40 % to 80 %, and from 30 % to 60 %, respectively.

EXPERIMENTAL

The strains, *Penicillium verrucosum, Doratomyces stemonitis*, *Trichoderma harzianum*, *Aspergillus niger* (fungi) and *Bacillus mycoides, Pseudomonas glicinea, Pseudomonas phaseolicola,* and *Pseudomonas fluorescens* (bacteria) are from the collection of microorganisms of the Faculty of Science, Department of Biology, University of Kragujevac.

Melting points were recorded on a Kofler hot-stage apparatus. Microanalysis of carbon, hydrogen, and nitrogen was carried out with an Erba 1106 microanalyzer. The IR spectra were run on a Perkin—Elmer grating spectrophotometers, Model 137 and Model 197. The NMR spectra were recorded on a Varian FT 80 A and 200"Gemini spectrometers, in $CDCl_3$ and DMSO-d_6, using TMS as the internal standard. Chemical shifts are given in δ; abbreviations: s – singlet, d – doublet, t – triplet, q – quartet, m – multiplet, and br – broadened. Abbreviations used: $PhTAPBr_3$ - phenyltrimethylammonium tribromide, DMSO – dimethyl sulfoxide-d_6.

3-Acetyl-4-hydroxy-2*H*-chromen-2-one (*I*)

To a solution of 4-hydroxychromen-2-one (3 g; 18.6 mmol) in acetic acid (16 cm^3) phosphorous oxychloride (5.6 cm^3) was added. The mixture was heated at reflux for 30 min. After cooling, the precipitate was collected and recrystallized from ethanol to give white needles in a yield of 2.7 g (90 %); m.p. = 134—136 °C. IR spectrum (KBr), $\tilde{\nu}_{max}/cm^{-1}$: 3185, 2950, 1705, 1700, 1610, 1560, 1460, 1310, 1130, 950, 840, 820, 770. ^{1}H NMR spectrum (200 MHz, $CDCl_3$), δ: 2.43 (s, 3H, CH_3), 7.35 (ddd, 1H, C-6—H, $^3J_{6,5}$ = 7.8 Hz, $^4J_{6,8}$ = 1.2 Hz), $^3J_{6,7}$ = 7.4 Hz), 7.42 (dd, 1H, C-8—H, $^3J_{7,8}$ = 8.35 Hz, $^4J_{6,8}$ = 1.2 Hz, 7.42 (ddd, 1H, C-7—H, $^3J_{7,8}$ = 8.35 Hz, $^3J_{7,6}$ = 7.4 Hz, $^4J_{7,5}$ = 1.6 Hz), 7.69 (dd, 1H, C-5—H, $^3J_{5,6}$ = 7.8 Hz, $^4J_{5,7}$ = 1.6 Hz), 15.7 (OH). ^{13}C NMR spectrum (50 MHz, $CDCl_3$), δ: 28.33 (CH_3), 160.10 (CO), 177.32 (C-4), 116.91 (C-8), 159.65 (C-2), 154.10 (C-9), 136.85 (C-7), 116.09 (C-5), 124.82 (C-6), 114.41 (C-10), 101.91 (C-3). Mass spectrum, *m/z* (I_r/%): 204 (100), 189 (74), 161 (43), 120 (17), 119 (31), 92 (56), 78 (33), 43 (28). For $C_{11}H_8O_4$ (M_r = 204.0423) w_i(calc.): 64.71 % C, 3.95 % H; w_i(found): 64.92 % C, 3.68 % H.

3-Bromoacetyl-4-hydroxy-2*H*-chromen-2-one (*II*)

To a solution of *I* (2.0 g; 9.8 mmol) in tetrahydrofuran (b.p. = 60 °C, 40 cm^3) phenyltrimethylammonium tribromide (3.68 g; 9.8 mmol) was added in a period of 15 min, at room temperature (25 °C). A precipitate was deposited from the solution, and the colour of the solution changed into pale yellow. After stirring for 20 min and standing for 30 min, cold water (100 cm^3) was added to the reaction mixture. The precipitate was collected, washed with water and recrystallized from ethanol to afford light yellow needles in a yield of 2.51 g (90 %); m.p. = 144—146 °C. IR spectrum (KBr), $\tilde{\nu}_{max}/cm^{-1}$: 3185, 1725, 1685, 1560, 1437, 1200, 1032, 945, 842, 822, 771. ^{1}H NMR spectrum (200 MHz, $CDCl_3$), δ: 4.28 (s, 2H, CH_2), 7.31 (ddd, 1H, C-6—H, $^3J_{6,5}$ = 7.38 Hz, $^4J_{6,8}$ = 1.16 Hz, $^3J_{6,7}$ = 7.32 Hz), 7.39 (dd, 1H, C-8—H, $^3J_{7,8}$ = 8.35 Hz, $^4J_{6,8}$ = 1.16 Hz), 7.42 (ddd, H, C-7—H), $^3J_{7,8}$ = 8.35 Hz, $^3J_{7,6}$ = 7.37 Hz, $^4J_{7,5}$ = 1.63 Hz), 7.69 (dd, 1H, C-5—H, $^3J_{5,6}$ = 7.89 Hz, $^4J_{5,7}$ = 1.63 Hz), 15.7 (OH). ^{13}C NMR spectrum (50 MHz, $CDCl_3$), δ: 33.41 (CH_2), 183.50 (CO), 185.32 (C-4), 115.91 (C-8), 158.65 (C-2), 153.00 (C-9), 134.85 (C-7), 125.09 (C-5), 124.82 (C-6), 119.41 (C-10), 100.91 (C-3). For $C_{11}H_7O_4Br$ (M_r = 281.9528) w_i(calc.): 46.67 % C; 2.49 % H; w_i(found): 46.92 % C, 2.38 % H.

3-(2-Ammoniothiazol-4-yl)-4-hydroxy-2*H*-chromen-2-one Bromide (*III*)

To a solution of *II* (1 g; 3.5 mmol) in absolute ethanol (60 cm^3) thiourea (0.270 g; 3.5 mmol) was added. The mixture was heated at reflux for 30 min. After cooling, the precipitate was collected and recrystallized from ethanol—10 % sodium hydroxide to give yellow needles in a yield of 0.71 g (60 %); m.p. = 255—257 °C. IR spectrum (KBr), $\tilde{\nu}_{max}/cm^{-1}$: 3433, 3381, 3241, 3122, 1698, 1609, 1524, 1405, 1328, 1294, 1165, 1072, 950.^{1}H NMR spectrum (200 MHz, $CDCl_3$), δ: 7.29—7.37 (m, 2H, C-6—H, C-8—H, $^4J_{6,8}$ = 1.16 Hz, $^3J_{6,5}$ = 7.90 Hz, $^3J_{6,7}$ = 7.35 Hz, $^3J_{8,7}$ = 8.35 Hz), 7.21 (s, 1H, C′-5—H), 7.44 (ddd, 1H, C-7—H, $^3J_{6,7}$ = 7.35 Hz,$^4J_{7,5}$ = 1.63 Hz, $^3J_{8,7}$ = 8.35 Hz), 8.58 (bs, 1H, NH_2), 15.87 (s, 1H, OH). ^{13}C NMR (50 MHz, DMSO-d_6), δ: 165.42 (C′-2), 140.67 (C′-4), 108.56 (C′-5), 154.28 (C-2), 93.86 (C-3), 163.09 (C-4), 123.76 (C-5), 124.06 (C-6), 132.11 (C-7), 116.34 (C-8), 120.23 (C-10), 152.05 (C-9). For $C_{12}H_9BrN_2O_3S$ (M_r = 260.2685, recrystallized from ethanol—10 % sodium carbonate) w_i(calc.): 55.37 % C, 3.10 % H, 10.76 % N; w_i(found): 55.12 % C, 2.98 % H, 10.38 % N.

N-[4-(4-Hydroxy-2-oxo-2*H*-chromen-3-yl)-thiazol-2-yl]-4-R-benzenesulfonamides *IVa—IVd*

A mixture of *III* (5.1 g; 15 mmol) and arenesulfonyl chloride (17 mmol) in pyridine (5 cm^3) was stirred overnight (12 h) at room temperature (25 °C). The red solution was poured into 1 M-HCl (50 cm^3). The yellowish precipitate was collected, redissolved in a mixture of ethanol (20 cm^3) and 2 M-NaOH (20 cm^3) and treated with activated charcoal – Norite. Filtration and neutralizing of the filtrate with concentrated HCl yielded the product as a yellow-orange powder, which was recrystallized from EtOH—water mixture.

N-[4-(4-Hydroxy-2-oxo-2H-chromen-3-yl)thiazol-2-yl]-4-methylbenzenesulfonamide (IVa), 2.6 g (43 %) of a yellow-orange powder from 30 % EtOH; m.p. > 260 °C. IR spectrum (KBr), $\tilde{\nu}_{max}/cm^{-1}$: 3381, 3340, 3165, 3220, 3080, 3060, 1360, 1345, 1170, 1689, 1560, 1490, 1150, 1070, 840. ^{1}H NMR spectrum (200 MHz, $CDCl_3$), δ: 2.32 (s, 3H, CH_3), 7.41—7.71 (m, 4H, C-5—H, C-6—H, C-7—H, C-8—H), 8.22 (s, 1H, C-5′—H), 7.32 (d, 2H, C-2—H, C-6—H, ^3J = 8.53 Hz, H_{arom}), 7.61 (d, 2H, C-3—H, C-5—H, ^3J = 8.53 Hz, H_{arom}), 8.95 (bs, 1H, NH), 10.90 (s, 1H, OH). ^{13}C NMR (50 MHz, DMSO-d_6), δ: 154.28 (C-2), 90.54 (C-3), 163.09 (C-4), 125.79 (C-5), 125.1 (C-6), 129.92 (C-7), 118.95 (C-8), 151.71 (C-9), 127.6 (C-10), 165.4 (C-2′), 107.76 (C-5′), 141.47 (C-4′), 21.50 (CH_3), 144.17 (Ar, C-1), 130.57 (Ar, C-2), 126.99 (Ar, C-3), 138.78 (Ar, C-4), 126.99 (Ar, C-5), 130.57 (Ar, C-6). For $C_{19}H_{14}N_2O_5S_2$ w_i(calc.): 39.87 % C, 3.01 % H, 9.33 % N; w_i(found): 40.12 % C, 2.92 % H, 9.28 % N.

4-Chloro-N-[4-(4-hydroxy-2-oxo-2H-chromen-3-yl)-thiazol-2-yl]benzenesulfonamide (IVb), 0.57 g (41 %) of an orange powder from 50 % EtOH, m.p. ≈ 259—260 °C. IR spectrum (KBr), $\tilde{\nu}_{max}/cm^{-1}$: 3361, 3355,

3145, 3215, 1350, 1325, 1695, 815 cm^{-1}. ^1H NMR spectrum (200 MHz, $CDCl_3$), δ: 7.29—7.71 (m, 4H, C-5—H, C-6—H, C-7—H, C-8—H), 8.31 (s, 1H, C-5′—H), 7.44 (d, 2H, C-3—H, C-5—H, ^3J = 8.35 Hz, H_{arom}), 7.79 (d, 2H, C-2—H, C-6—H, ^3J = 8.35 Hz, H_{arom}), 8.90 (bs, 1H, NH), 11.5 (s, 1H, OH). For $C_{18}H_{11}ClN_2O_5S_2$ w_i(calc.): 49.71 % C, 2.55 % H, 6.44 % N; w_i(found): 49.34 % C, 2.42 % H, 6.28 % N.

N-[4-(4-Hydroxy-2-oxo-2H-chromen-3-yl)thiazol-2-yl]-4-methoxybenzenesulfonamide (IVc), 0.31 g (37 %) of a yellow-orange powder from 30 % EtOH, m.p. = 242—244 °C. IR spectrum (KBr), $\tilde{\nu}_{max}/cm^{-1}$: 3351, 3137, 3212, 1346, 1335, 1690, 1205, 1055. ^1H NMR spectrum (200 MHz, DMSO-d_6), δ: 7.3—7.7 (m, 4H, C-5—H, C-6—H, C-7—H, C-8—H), 7.48 (d, 2H, C-3—H, C-5—H, ^3J = 9.1 Hz, H_{arom}), 7.98 (d, 2H, C-2—H, C-6—H, ^3J = 9.1 Hz, H_{arom}), 8.28 (s, H, C-5′—H), 8.65 (bs, 1H, NH), 10.89 (s, 1H, OH). For $C_{19}H_{14}N_2O_6S_2$ w_i(calc.): 53.01 % C, 3.28 % H, 6.51 % N; w_i(found): 52.68 % C, 3.34 % H, 6.39 % N.

4-Amino-N-[4-(4-hydroxy-2-oxo-2H-chromen-3-yl)-thiazol-2-yl]benzenesulfonamide (IVd), 0.46 g (55 %) of an orange powder from 50 % EtOH, m.p. > 260 °C. IR spectrum (KBr), $\tilde{\nu}_{max}/cm^{-1}$: 3451, 3345, 3130, 2950, 1678, 1344, 1339. ^1H NMR spectrum (200 MHz, DMSO-d_6), δ: 7.35—7.75 (m, 4H, C-5—H, C-6—H, C-7—H, C-8—H), 6.78 (d, 2H, C-3—H, C-5—H, ^3J = 9.1 Hz, H_{arom}), 7.8 (d, 2H, C-2—H, C-6—H, ^3J = 9.1 Hz, H_{arom}), 8.19 (s, 1H, C-5′—H), 7.05 (bs, 2H, NH_2), 8.75 (bs, 1H, NH), 10.85 (s, 1H, OH). For $C_{18}H_{13}N_3O_5S_2$ w_i(calc.): 52.04 % C, 3.15 % H, 10.11 % N; w_i(found): 51.94 % C, 3.08 % H, 9.99 % N.

Antimicrobial Assays

The disk diffusion method was used for screening of antifungal (100 mg/disk) and antibacterial activity (25 mg/disk) of the derivatives. The plates were inoculated with the desired microorganisms before placing compound-impregnated paper disks on them. Nystatin and penicillin (for antifungal testing) and gentamycin (for antibacterial testing) were used as positive controls.

Staphylococcus aureus, Escherichia coli, and *Pseudomonas aeruginosa* were grown on ANTIBIOTIC MEDIUM 1 (Difco Laboratories). *Penicillium verrucosum, Doratomyces stemonitis, Trichoderma harzianum*, *Aspergillus niger, Candida albicans* (fungi) and *Bacillus mycoides*, *Pseudomonas glicinea*, *Pseudomonas phaseolicola, Pseudomonas fluorescens* (bacteria) were grown on TRIPTON SOYA AGAR (Torlak – Beograd). Disks ANTIBIOTICA TEST BLATTCHEN (Dasel, Germany) were immersed in ethanol solution of compounds *IVa—IVd*, then put on the antibiotic medium sown with microorganisms and kept at 37 °C, except for *Candida albicans* which was kept at 25 °C. After 18 h the activities were determined on a FISHER-LILLY ANTIBIOTIC ZONE READER, by measuring the diameter of biological activity zone round the disks.

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