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THIAZOLE ANALOGS OF ISOFLAVOLIGNANS

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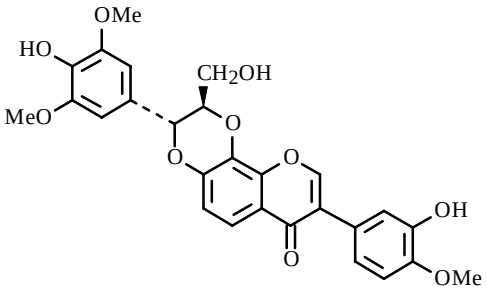
Modified analogs of isoflavolignans are prepared by annelation of dioxole, dioxane, and dioxepan fragments to 3-thiazolyl-7,8-dihydroxychromones.

Key words: thiozole derivatives, 7,8-dihydroxychromones, synthesis.

Natural and synthetic compounds with 1,3-benzodioxole and 1,4-benzodioxane fragments exhibit various types of biological activity and are widely studied [1-6]. Benzodioxane lignoids that are encountered in plants include various phenols, e.g., flavonoids. Xanthocercin A, which has the isoflavolignan structure, was isolated from *Xanthocercis zambesiaca* [7]. Analogs of xanthocercin of simpler structure have also been obtained [8].



Xanthocercin A

We synthesized modified analogs of flavolignans in which benzodioxole, benzodioxane, or benzodioxepan moieties are annelated to the chromone nucleus. The isoflavonoid 3-phenyl is replaced by a thiazole ring. Thiazole derivatives are known as bioactive substrates in life-cycle processes of living organisms.

The key compounds in the synthesis of these compounds were 7,8-dihydroxychromones with various substituents on the second (-H, -CH_3, -CF_3, -COOEt) and third [4-(2-methylthiazolyl) and 2-(4-methylthiazolyl)] positions of the chromen-4-one system. The last compounds were synthesized using a modified Hoesch reaction. Condensation of pyrogallol with the corresponding thiazolylacetonitriles in BF_3 etherate in the presence of dry HCl with subsequent hydrolysis of the resulting imines gave the intermediate α-thiazolyl-2,3,4-trihydroxyacetophenones **1a** [9] and **1b**.

The PMR spectrum in DMSO-D_6 and the bright yellow color of ketone **1b** indicate that this compound, in contrast with the isomeric ketone **1a** [9], has the enol form. A peak of an enol proton is located at weak field and coalesces with the peak for the 2-OH group at 13.8 ppm. The signals of the 3-OH and 4-OH protons also coalesce into one broad peak at 9.6 ppm. The aromatic protons H-5 and H-6 of the phenol ring appear as doublets at 6.4 and 7.0 ppm with spin—spin coupling constant (SSCC) 8.5 Hz. Protons of the methine group and H-5 of the thiazole ring give singlets at 6.4 and 7.1 ppm, respectively.

Many methods for synthesizing isoflavones and their hetero-analogs are based on C-formylation of the methylene group of α-hetaryl-2-hydroxyacetophenones with subsequent cyclization.

Ketone **1b** was heated with triethylorthoformate in pyridine at 70-80°C in the presence of a catalytic amount of piperidine in order to prepare 3-(4-methyl-2-thiazolyl)-7,8-dihydroxychromone **2b**, which is not substituted at the 2-position of the chromone ring.

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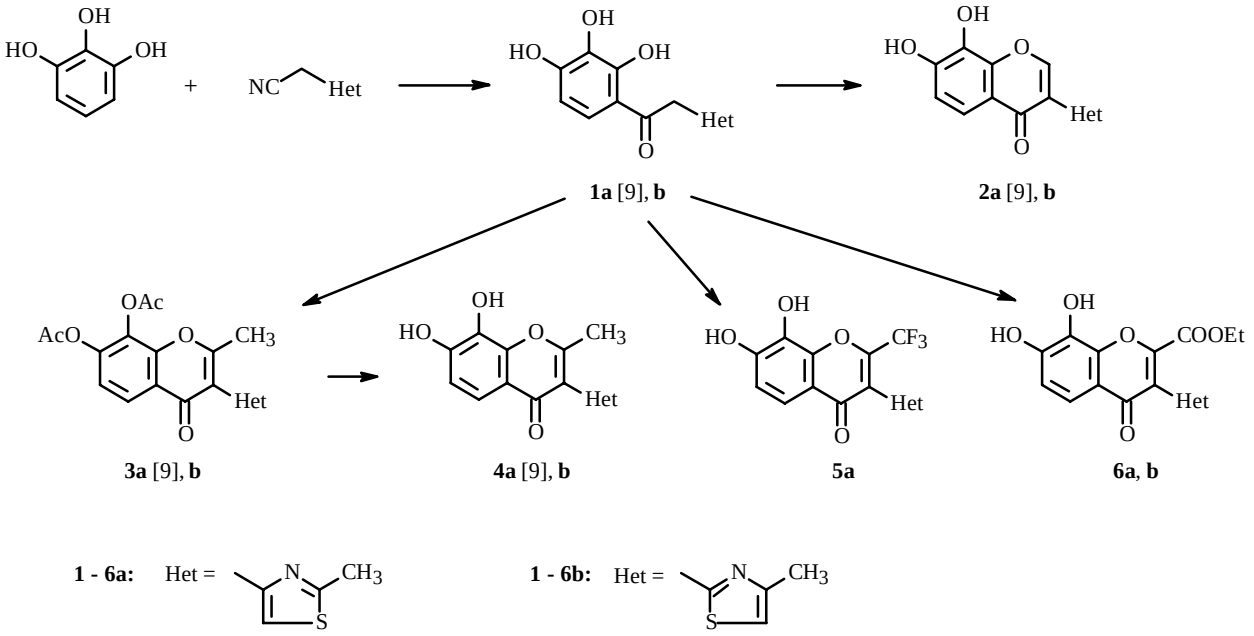


1 - 6a: Het =

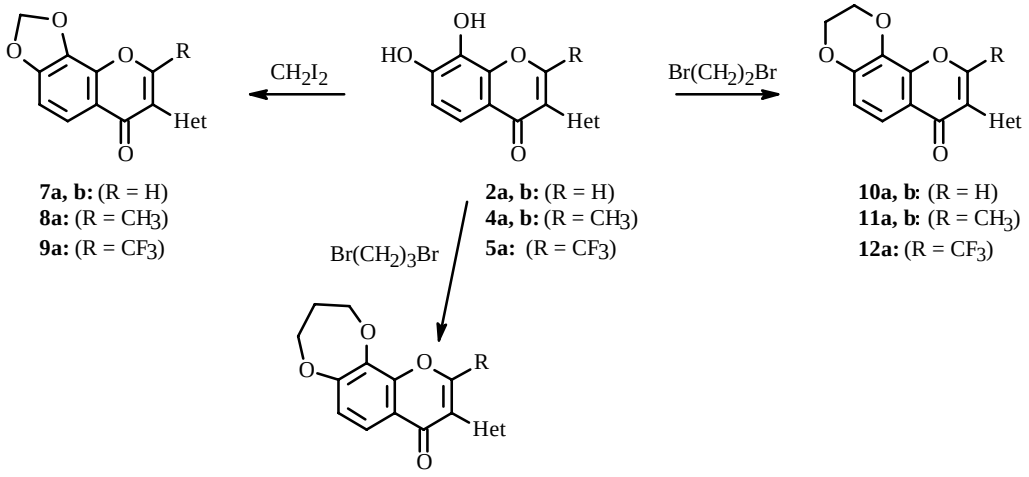
1 - 6b: Het =

In contrast with the synthetic method proposed earlier [9], 3-(2-methyl-4-thiazolyl)-7,8-dihydroxychromone **2a** was prepared in high purity and yield by heating ketone **1a** with BF_3 etherate and PCl_5 in DMF under Vilsmeier conditions [10, 11].

Thiazolylchromones with different substituents in the 2-position of the chromone system were isolated using various acylating agents. Heating **1a** and **b** with acetic anhydride and triethylamine forms 2-methyl-7,8-diacetoxychromones **3a** [9] and **3b**, brief heating of which with 5% alkali in ethanol converts them to the corresponding 2-methyl-7,8-dihydroxychromones **4a** [9] and **4b**.

Chromones **5a** and **6a** and **b** were isolated from the reaction of the corresponding ketones with trifluoroacetic anhydride or ethoxalyl chloride in pyridine in the cold.

Thiazole analogs of isoflavolignans were prepared using the condensation of 7,8-dihydroxychromones with methylene iodide, 1,2-dibromoethane, or 1,3-dibromopropane in DMF in the presence of freshly calcined potash.

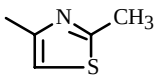


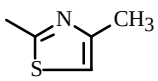
7a, b: (R = H)
8a: (R = CH_3)
9a: (R = CF_3)

2a, b: (R = H)
4a, b: (R = CH_3)
5a: (R = CF_3)

10a, b: (R = H)
11a, b: (R = CH_3)
12a: (R = CF_3)

13a, b: (R =H); **14a:** (R = CH_3); **15a:** (R = CF_3)

a: Het = 

b: Het = 

The synthesized compounds are colorless crystalline substances with high melting points. They are very soluble in most organic solvents and insoluble in water. The melting points of the isoflavolignans decrease with increasing size of the "lignoid" ring.

TABLE 1. Chemical Shifts in PMR Spectra of Isoflavones **2-6** (δ, ppm)*

Compound	Chromone protons					Thiazole protons	
	H-2, Me-2, COOEt-2	H-5, J ≈8.5 Hz	H-6, J ≈8.5 Hz	AcO-7 or HO-7	AcO-8 or HO-8	Me-2 or Me-4	H-5
2a	8.91	7.54	7.01	9.76		2.75	8.28
2b	9.14	7.55	7.03	10.57	9.69	2.43	7.32
3b	2.95	8.18	7.27	2.43	2.36	2.51	7.04
4a	2.69	7.41	6.95	9.79	9.60	2.46	7.62
4b	2.96	7.51	6.98	10.37	9.54	2.46	7.31
5a	-	7.46	7.05	10.78	9.66	2.69	7.60
6a	1.22; 4.33	7.55	7.04	10.50	9.50	2.67	8.13
6b	1.30; 4.41	7.59	7.08	10.64	9.75	2.38	7.42

*PMR spectrum of **3b** measured in $CDCl_3$; remainder, in DMSO-D_6.

TABLE 2. Chemical Shifts in PMR Spectra of Flavolignans **7-15** (δ, ppm)*

Compound	Chromone protons				Thiazole protons	
	H-2 or Me-2, c	H-5, d, J = 8.5 Hz	H-6, d, J = 8.5 Hz	O-$(CH_2)_n$-O	Me-2 or Me-4	H-5
7a	8.92	7.89	6.96	6.20	2.73	8.34
7b	9.11	7.78	7.21	6.33	2.43	7.33
8a	2.51	7.81	6.93	6.20	2.76	7.46
9a	-	7.79	6.99	6.24	2.76	7.29
10a	8.97	7.81	6.94	4.41	2.73	8.36
10b	9.06	7.82	7.00	4.43	2.51	7.40
11a	2.56	7.72	6.91	4.41	2.75	7.57
11b	2.99	7.79	6.96	4.42	2.51	7.28
12a	-	7.70	7.00	4.48	2.76	7.30
13a	8.91	7.82	6.94	4.42; 2.28	2.72	8.34
13b	9.16	7.76	7.13	4.39; 2.29	2.45	7.32
14a	2.48	7.60	7.01	4.34; 2.24	2.70	7.66
15a	-	7.74	7.01	4.44; 2.33	2.73	7.28

*PMR spectra of **7b**, **14a**, and **13b** measured in DMSO-D_6; remainder in $CDCl_3$.

The H-2 proton of the pyrone ring in the PMR spectra of **2-15** (Tables 1 and 2) appears as a narrow singlet at 8.91-9.16 ppm because it is affected by the unshared electron pair on the N atom of the thiazole substituent. The acetyl groups give singlets at 2.36 and 2.43 ppm. The 8-OH and 7-OH absorb in the range 9.50-10.78 ppm. Protons H-5 and H-6 form an AB spin system and appear as doublets with SSCC 8.5 Hz at 7.41-8.18 and 6.91-7.27 ppm.

Signals of the methylenes of the dioxole (6.20-6.33 ppm) and dioxane (4.41-4.48 ppm) rings appear as singlets. Protons of the dioxepan ring give a triplet (4.34-4.44 ppm) and quintet (2.24-2.33 ppm).

Thus, simultaneous alkylation of 7-OH and 8-OH in 3-thiazolylchromones forms new modified isoflavolignans. The structures of the compounds are confirmed by PMR (Tables 1 and 2) and analytical data (Table 3).

TABLE 3. Properties of **1-15**

Compound	Yield, %	mp, °C	Empirical formula	Crystallization solvent
1b	44	>300	$C_{12}H_{11}NO_4S$	EtOH:H_2O
2a [9]	98	247-248	$C_{13}H_9NO_4S$	EtOH:H_2O
2b	85	272	$C_{13}H_9NO_4S$	EtOH
3a [9]	76	138	$C_{18}H_{15}NO_6S$	EtOAc—hexane (1:1)
3b	52	207	$C_{18}H_{15}NO_6S$	EtOAc
4a [9]	79	286-287	$C_{14}H_{11}NO_4S$	EtOH:H_2O
4b	64	252	$C_{14}H_{11}NO_4S$	EtOH
5a	73	267	$C_{14}H_8F_3NO_4S$	EtOH
6a	70	260	$C_{16}H_{13}NO_6S$	i-PrOH
6b	56	198 (decom.)	$C_{16}H_{13}NO_6S$	MeOH
7a	48	262-263	$C_{14}H_9NO_4S$	EtOH
7b	39	256-257	$C_{14}H_9NO_4S$	Dioxane
8a	51	195	$C_{15}H_{11}NO_4S$	EtOH
9a	52	243	$C_{15}H_8F_3NO_4S$	EtOH
10a	68	227	$C_{15}H_{11}NO_4S$	EtOH
10b	56	247	$C_{15}H_{11}NO_4S$	EtOAc
11a	59	192	$C_{16}H_{13}NO_4S$	EtOH
11b	58	220	$C_{16}H_{13}NO_4S$	EtOAc
12a	61	225	$C_{16}H_{10}F_3NO_4S$	EtOH
13a	78	208	$C_{16}H_{13}NO_4S$	Toluene
13b	82	201	$C_{16}H_{13}NO_4S$	EtOH
14a	81	163	$C_{17}H_{15}NO_4S$	Toluene
15a	80	161-162	$C_{17}H_{12}F_3NO_4S$	Cyclohexane

EXPERIMENTAL

The course of the reaction and the purity of the products were monitored by TLC on Silufol UV-254 plates using C_6H_6:C_2H_5OH (9:1) and $CHCl_3$:CH_3OH (9:1). PMR spectra were measured on a SU-Bruker WP-100 instrument in DMSO-D_6 or $CDCl_3$ with TMS internal standard. Elemental analyses of all compounds corresponded to those calculated.

α-(4-Methyl-2-thiazolyl)-2,3,4-trihydroxyacetophenone (1b). A mixture of sublimed pyrogallol (12.6 g, 0.1 mol) and 4-methyl-2-thiazolylacetonitrile hydrobromide (21.9 g, 0.1 mol) in BF_3 etherate (100 mL) was stirred in a stream of dry HCl for 6 h at 30-40°C. The reaction mixture was left for 24 h at room temperature, treated with water (600 mL), boiled for 1 h, and neutralized with NH_3 until the pH was 3. The precipitate was filtered off, washed with water, and crystallized from aqueous ethanol.

3-(4-Methyl-2-thiazolyl)-7,8-dihydroxychromone (2b). A mixture of ketone **1b** (2.65 g, 10 mmol), triethylorthoformate (7 mL, 40 mmol), dry pyridine (7 mL), and piperidine (0.5 mL) was heated at 70-80°C for 4 h on a magnetic stirrer. The precipitate was filtered off, washed with isopropanol, and crystallized from ethanol.

3-(2-Methyl-4-thiazolyl)-7,8-dihydroxychromone (2a). A solution of ketone **1a** (50 mmol) and DMF (75 mL, 100 mmol) was treated with BF_3 etherate (12 mL, 100 mmol) and PCl_5 (60 mmol). The reaction mixture was held for 20 min at 60°C, collecting simultaneously the evolved ether. The reaction mixture was poured into water (400 mL), boiled for 30 min, and cooled. The precipitate was filtered off and crystallized from aqueous ethanol.

2-Methyl-3-thiazolyl-7,8-diacetoxychromones (3a and b). A mixture of the appropriate ketone (**1a** or **b**, 20 mmol), acetic anhydride (13.6 mL, 140 mmol), and triethylamine (21 mL, 100 mmol) was heated at 120-130°C for 5-6 h and poured into cold water (300 mL). The precipitate was repeatedly washed with water on the filter. The crystallization solvents are listed in Table 3.

2-Methyl-3-thiazolyl-7,8-dihydroxychromones (4a and b). A hot solution of chromone (**3a** or **b**, 20 mmol) in ethanol

(60 mL) was treated with NaOH solution (25.9 mL, 5%) and boiled for 3 min. Water (40 mL) was added. The solution was heated and boiled for another 10 min and neutralized with dilute HCl until the pH was 4-5. The precipitate was filtered off. The crystallization solvents are listed in Table 3.

2-Trifluoromethyl- (5a) and 2-Ethoxycarbonyl-3-thiazolyl-7,8-dihydroxychromones (6a and b). A solution of the appropriate ketone (**1a** or **b**, 10 mmol) in absolute pyridine (10-15 mL) cooled to 0°C was treated dropwise with trifluoroacetic anhydride or ethoxalyl chloride (30 mmol), held for 48 h at room temperature, and poured into icewater. The precipitate was filtered off. The crystallization solvents are listed in Table 3.

3-(2-Methyl-4-thiazolyl)-7,8-methylenedioxychromone (7a). A warm solution of chromone **2a** (10 mmol) in absolute DMF (25 mL) was treated with freshly calcined potash (3.45 g, 25 mmol) and methylene iodide (0.9 mL, 11 mmol). The mixture was stirred on a magnetic stirrer, heated at 80-90°C for 1-1.5 h, and poured into cold water (40-50 mL). The precipitate was filtered off and crystallized from ethanol.

Compounds **7b**, **8a**, and **9a** were obtained analogously to **7a** from the corresponding chromones.

2-Methyl-3-(2-methyl-4-thiazolyl)-7,8-ethylenedioxychromone (11a). A warm solution of **4a** (10 mmol) in absolute DMF (25 mL) was treated with freshly calcined potash (3.45 g, 25 mmol) and 1,2-dibromoethane (0.92 mL, 11 mmol), stirred on a magnetic stirrer, heated at 80-90°C for 1.5-2 h, and poured into cold water (40-50 mL). The precipitate was filtered off and crystallized from ethanol.

Compounds **10a**, **10b**, **11b**, and **12a** were obtained analogously to **11a** from chromones **2a**, **2b**, **4b**, and **5a**, respectively.

2-Trifluoromethyl-3-(2-methyl-4-thiazolyl)-7,8-propylendioxychromone (15a). A warm solution of chromone **5a** (10 mmol) in absolute DMF (25 mL) was treated with freshly calcined potash (3.45 g, 25 mmol) and 1,3-dibromopropane (11 mmol), stirred on a magnetic stirrer, heated at 80-90°C for 1-1.5 h, and poured into cold water (40-50 mL). The precipitate was filtered off and crystallized from cyclohexane.

Compounds **13a**, **13b**, and **14a** were obtained analogously to **15a** from chromones **2a**, **2b**, and **4a**, respectively.

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