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SYNTHESIS AND BIOLOGICAL ACTIVITY OF 4*H*-THIENO[3,2-*c*]CHROMENE DERIVATIVES

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The formyl group of 4H-thieno[3,2-c]chromene-2-carbaldehyde was transformed into the respective nitrile, amide, ester, carboxylic, hydroxamic, or hydroxy group. Electrophilic substitution in 4H-thieno[3,2-c]chromene-2-carbaldehyde was shown to occur at the C-8 atom, while oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in methanol led to 4-methoxy-4H-thieno[3,2-c]chromene-2-carbaldehyde. The latter compound was found to possess high antiulcer activity.

Keywords: 4*H*-thieno[3,2-*c*]chromene, antiulcer activity, electrophilic substitution, oxidation, reduction.

Derivatives of 4*H*-thieno[3,2-*c*]chromene are of interest as biologically active agents. Examples with significant anti-inflammatory [1-4], antiallergic [3, 4], analgesic [1], antiparkinsonian [1], antibacterial [5], antifungal [5, 6], and mucolytic [7-9] activity are known among these compounds. Derivatives of 4*H*-thieno-[3,2-*c*]chromene are used for the treatment of diabetes and hyperlipidaemia [10], cancer [11-14], and symptoms associated with menopause [15], which motivates the synthetic studies and characterization of such compounds.

Previously we have reported simple and convenient methods for the synthesis [16, 17] of 4*H*-thieno-[3,2-*c*]chromene-2-carbaldehydes that are difficult to obtain otherwise [18], based on Pd-catalyzed intramolecular arylation of iodo derivatives of 4-(aryloxy)methylthiophene-2-carbaldehydes. At the same time, the chemical properties of 4*H*-thieno[3,2-*c*]chromene-2-carbaldehyde prepared by these methods remain essentially unknown.

In order to remedy this lack of information, we studied the reactions of 4*H*-thieno[3,2-*c*]chromene-2-carbaldehyde (**1**) at the benzene ring or methylene bridge, performed functional group transformations at the C-2 position, as well as characterized the antiulcer and anti-inflammatory activity of one of the prepared compounds.

Heating compound **1** with hydroxylamine hydrochloride in concentrated formic acid transformed the formyl group into nitrile, but the yield of nitrile **4** did not exceed 35% in this case. A better yield of compound **4** (76%) was obtained by reaction of aldehyde **1** with ammonia and iodine in THF at room

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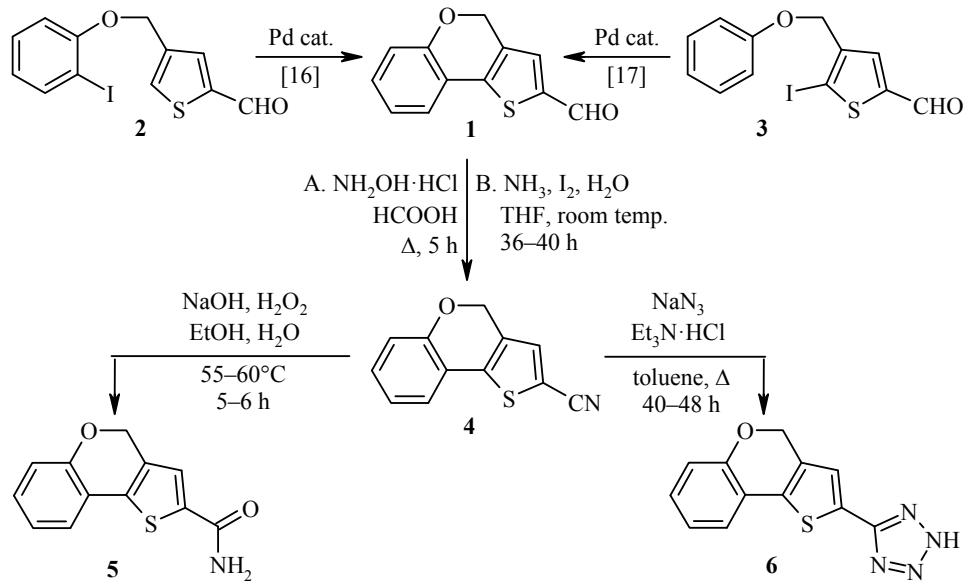
temperature for 36-40 h. Hydrolysis of nitrile **4** in the presence of sodium hydroxide and hydrogen peroxide gave 90% yield of amide **5**, while reaction with hydrazoic acid generated in the reaction medium from sodium azide and triethylammonium chloride in toluene gave 65% yield of the tetrazole **6**.

In order to study the direction of electrophilic substitution in 4*H*-thieno[3,2-*c*]chromene-2-carbaldehyde (**1**), we performed its bromination and iodination. The interaction of compound **1** with bromo-



succinimide (NBS) as well as with iodosuccinimide (NIS) in glacial acetic acid occurred very slowly, but the addition of catalytic amounts of $HClO_4$ to the reaction mixture produced after 4 h the derivatives **7a**,**b** with halogen at the C-8 atom, in 90 and 60% yields, respectively.

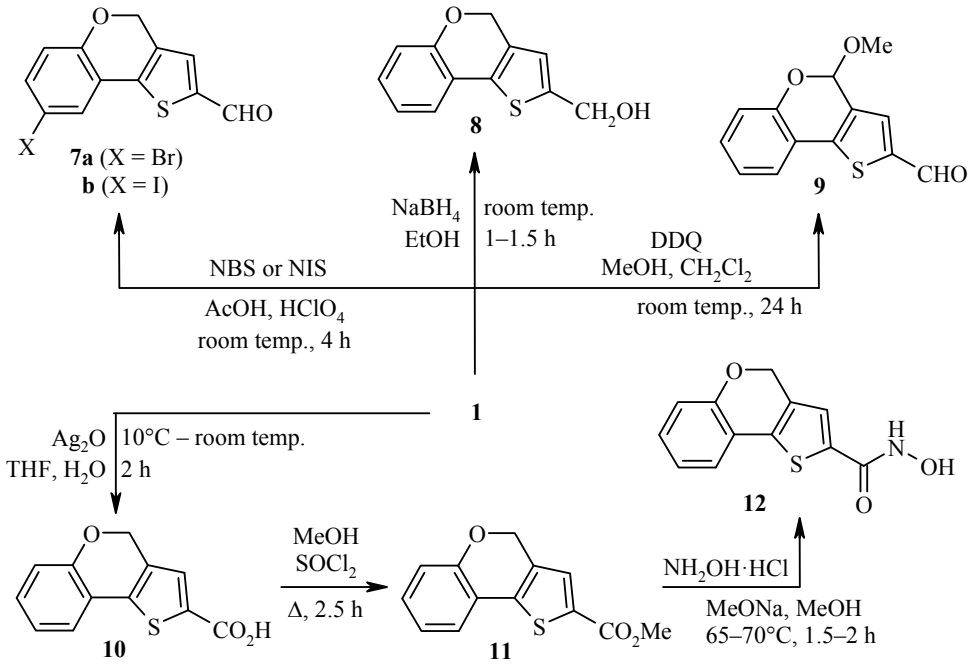


TABLE 1. Physicochemical Characteristics of Compounds **4-12**

Compound	Empirical formula	Found, % / Calculated, %			Mp, °C (solvent)	Yield, %
		C	H	N		
4	$C_{12}H_7NOS$	67.39 / 67.59	3.36 / 3.31	6.71 / 6.57	121-122 (EtOH)	76*
5	$C_{12}H_9NO_2S$	62.15 / 62.32	4.01 / 3.92	6.11 / 6.06	181-183 (EtOH)	90
6	$C_{12}H_8N_4OS$	56.30 / 56.24	3.23 / 3.15	22.01 / 21.86	220-222 (EtOH–EtOAc)	65
7a	$C_{12}H_7BrO_2S$	48.94 / 48.83	2.48 / 2.39	—	207-208 (EtOH)	90
7b	$C_{12}H_7IO_2S$	42.27 / 42.13	2.15 / 2.06	—	197-198 (EtOH)	60
8	$C_{12}H_{10}O_2S$	65.92 / 66.03	4.70 / 4.62	—	Oil (oil [19])	97
9	$C_{13}H_{10}O_3S$	63.25 / 63.40	4.17 / 4.09	—	97-99 (MeOH)	81
10	$C_{12}H_8O_3S$	62.19 / 62.06	3.58 / 3.47	—	210-212 (THF–hexane)	85
11	$C_{13}H_{10}O_3S$	63.29 / 63.40	4.01 / 4.09	—	93-94 (MeOH) (94-96 [19])	95
12	$C_{12}H_9NO_3S$	57.98 / 58.29	3.78 / 3.67	5.81 / 5.66	194-196 (EtOH-H_2O)	97

*Obtained by method B.

Reduction of the formyl group in compound **1** with sodium borohydride in ethanol gave (4*H*-thieno-[3,2-*c*]chromen-2-yl)methanol (**8**) in 97% yield.

Oxidation of the aldehyde **1** with wet silver oxide in THF led to the formation of 4*H*-thieno[3,2-*c*]-chromene-2-carboxylic acid (**10**) in 85% yield, which was then converted to the methyl ester **11** by the action of thionyl chloride in methanol. The yield of compound **11** was 95%.

Oxidation of methylene group in the presence of an aldehyde group presents a challenge. We were able to oxidize the methylene bridge in 4*H*-thieno[3,2-*c*]chromene-2-carbaldehyde (**1**) by using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) [20] in dichloromethane in the presence of methanol and thus obtained 4-methoxy-4*H*-thieno[3,2-*c*]chromene-2-carbaldehyde (**9**) in 81% yield.

The structures of all obtained compounds were confirmed by elemental analysis data (Table 1), IR spectra, ^{1}H and ^{13}C NMR spectra.

The antiulcer and anti-inflammatory activity of the previously unknown thieno[3,2-*c*]chromene derivative **9** was investigated (Table 2).

Table 2 shows that compound **9** at 100 mg/kg dose significantly reduced the development of injury to stomach caused by indometacin, correspondingly decreasing the Paul's index to 0.75 and therefore exhibited high (7.3) antiulcer activity. Since the compound **9** did not show anti-inflammatory activity, data are not presented.

TABLE 2. Antiulcer Activity of 4-Methoxy-4*H*-thieno[3,2-*c*]chromene-2-carbaldehyde (**9**)

Groups	Number of ulcers	Paul's index	Antiulcer activity
I. Control group: indometacin (20 mg/kg *per os*)	33	5.50	—
II. Test group: indometacin (20 mg/kg *per os*) + + compound **9** (100 mg/kg *per os*)	9	0.75	7.3

Thus, we have studied the reactions of 4*H*-thieno[3,2-*c*]chromene-2-carbaldehyde at the formyl group. Halogenation of this compound was used as example to establish that electrophilic substitution occurred at the C-8 position, while reaction with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone resulted in selective oxidation of the methylene fragment and the formation of 4-methoxy-4*H*-thieno[3,2-*c*]chromene-2-carbaldehyde, characterized with high antiulcer activity.

EXPERIMENTAL

IR spectra were recorded on a FT-801 FT-IR spectrometer in KBr pellets. The ^{1}H and ^{13}C NMR spectra were acquired on a Bruker DRX 400 instrument (400 and 100 MHz, respectively) in acetone-d_6 (compounds **5**, **6**), DMSO-d_6 (compounds **10**, **12**), and in $CDCl_3$ (the rest of the compounds), with TMS as internal standard. Mass spectra were recorded on an Agilent 6890N instrument (EI ionization, 70 eV, evaporator temperature 230-250°C). Elemental analysis was performed on a Carlo Erba 1106 CHN-analyzer. Melting points were determined on a Kofler hot bench. The reaction progress and the purity of the obtained compounds were controlled by TLC on Sorbfil UV-254 plates, visualization with iodine vapor or UV light.

4*H*-Thieno[3,2-*c*]chromene-2-carbonitrile (4). A. A mixture of 4*H*-thieno[3,2-*c*]chromene-2-carbaldehyde (**1**) (0.324 g, 1.5 mmol) and $NH_2OH\cdot HCl$ (0.208 g, 3.0 mmol) in conc. HCOOH (3 ml) was refluxed for 5 h. The reaction mixture was poured into ice water and extracted with Et_2O. The combined ether extracts were washed with water, dried over Na_2SO_4, and the solvent was removed by evaporation. The product was purified by flash chromatography on alumina (eluent 1:1 $CHCl_3$–petroleum ether). Yield 0.112 g (35%).

B. Iodine (0.761 g, 3.0 mmol) was added to a mixture of 4*H*-thieno[3,2-*c*]chromene-2-carbaldehyde (**1**) (0.324 g, 1.5 mmol) in 28% aqueous ammonia (9 ml) and THF (7.5 ml) at room temperature. The reaction mixture was stirred for 36-40 h. Then 5% solution of $Na_2S_2O_3$ (12 ml) was added to the reaction mixture, and the aqueous layer was extracted with EtOAc (3×10 ml). The extract was dried over Na_2SO_4, and solvent was removed on a rotary evaporator. The product was purified by flash chromatography on silica gel (0.035-0.070 mm, eluent 1:1 $CHCl_3$–hexane) and recrystallized from MeOH or EtOH. Yield 0.243 g (76%). Light-yellow crystals. IR spectrum, ν, cm^{-1}: 2209 (C≡N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.25 (2H, s, CH_2); 6.95-7.02 (2H, m, H-6,8); 7.23-7.29 (1H, m, H-7); 7.32 (1H, dd, ^3J = 7.6, ^4J = 1.4, H-9); 7.34 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 65.5 (C-4); 107.6 (C-2); 114.3 (C-9a); 117.2 (C-6); 118.6 (CN); 122.5 (C-8); 123.7 (C-9); 131.2 (2C, C-3,3a); 134.1 (C-7); 140.0 (C-9b); 153.0 (C-5a). Mass spectrum, *m*/*z* (I_{rel}, %): 213 $[M]^+$ (57), 212 (100), 140 (10).

4*H*-Thieno[3,2-*c*]chromene-2-carboxamide (5) [9, 21]. A solution of nitrile **4** (0.640 g, 3.0 mmol) and NaOH (0.136 g, 3.4 mmol) in EtOH (23 ml) was stirred at room temperature and treated with 40% solution of H_2O_2 (2×3 ml with interval of 1 h). The reaction mixture was heated at 55-60°C until the reaction was complete (5-6 h). The crystals formed were filtered off, washed with water, dried, and recrystallized from EtOH. Yield 0.624 g (90%). Colorless needles. IR spectrum, ν, cm^{-1}: 3346, 3208 (NH_2), 1650 (C=O, amide I), 1595 (N–C=O, amide II). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.26 (2H, s, CH_2); 6.92 (1H, dd, ^3J = 8.1, ^4J = 1.0, H-6); 7.00 (1H, td, ^3J = 7.5, ^4J = 1.0, H-8); 7.19-7.25 (1H, m, H-7); 7.40 (1H, dd, ^3J = 7.5, ^4J = 1.5, H-9); 7.55 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 66.5 (C-4); 117.7 (C-6); 120.7 (C-9b); 123.1 (C-8); 124.3 (C-9); 126.7 (C-7); 130.9 (C-3); 133.3 (C-9a); 137.4 (C-3a); 139.9 (C-2); 153.7 (C-5a); 163.8 ($CONH_2$).

5-(4*H*-Thieno[3,2-*c*]chromen-2-yl)-2*H*-tetrazole (6). A mixture of 4*H*-thieno[3,2-*c*]chromene-2-carbonitrile (**4**) (0.213 g, 1.0 mmol), $Et_3N\cdot HCl$ (0.206 g, 1.5 mmol), and NaN_3 (0.098 g, 1.5 mmol) in toluene (8 ml) was refluxed for 40-48 h. After cooling, the mixture was extracted with water, the aqueous layer was acidified with concentrated HCl. The precipitate formed was filtered off, dried, and recrystallized from EtOH–EtOAc mixture. Yield 0.166 g (65%). Brown powder. IR spectrum, ν, cm^{-1}: 3487 (NH), 1600 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.12 (1H, br. s, NH); 5.33 (2H, s, CH_2); 6.94 (1H, d, ^3J = 8.1, H-6); 6.98-7.03 (1H, m, H-8); 7.21-7.26 (1H, m, H-7); 7.42 (1H, d, ^3J = 7.6, H-9); 7.66 (1H, s, H-3). ^{13}C NMR spectrum, δ,

ppm: 66.5 (C-4); 117.6 (C-6); 120.2 (C-9b); 122.8 (C-9a); 123.1 (C-8); 124.2 (C-9); 127.0 (C-7); 130.9 (C-3); 131.2 (C-3a); 133.8 (C-2); 136.4 (C-5 tetrazole); 153.6 (C-5a).

8-Halo-4*H*-thieno[3,2-*c*]chromene-2-carbaldehydes 7a,b (General Method). A mixture of 4*H*-thieno-[3,2-*c*]chromene-2-carbaldehyde (**1**) (0.260 g, 1.2 mmol) and *N*-bromo- or *N*-iodosuccinimide (1.3 mmol) in AcOH (3 ml) with added catalytic amount of $HClO_4$ was stirred for 4 h at room temperature. After the reaction was complete, the mixture was poured into water and the precipitate formed was filtered off. The product was purified by flash chromatography on 0.035-0.070 mm silica gel, eluent $CHCl_3$.

8-Bromo-4*H*-thieno[3,2-*c*]chromene-2-carbaldehyde (7a). Yield 0.319 g (90%). Amber colored crystals. IR spectrum, ν, cm^{-1}: 1648 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.28 (2H, s, CH_2); 6.84 (1H, d, ^3J = 8.7, H-6); 7.33 (1H, dd, ^3J = 8.6, ^4J = 2.3, H-7); 7.47-7.51 (2H, m, H-3,9); 9.87 (1H, s, CHO). ^{13}C NMR spectrum, δ, ppm: 65.8 (C-4); 114.5 (C-8); 118.9 (C-6); 120.9 (C-9a); 126.5 (C-7); 132.5 (C-9b); 132.6 (C-3); 133.7 (C-9); 140.6 (C-3a); 142.7 (C-2); 152.1 (C-5a); 182.2 (CHO).

8-Iodo-4*H*-thieno[3,2-*c*]chromene-2-carbaldehyde (7b). Yield 0.246 g (60%). Amber colored crystals. IR spectrum, ν, cm^{-1}: 1650 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.29 (2H, s, CH_2); 6.72 (1H, d, ^3J = 8.5, H-6); 7.48 (1H, s, H-3); 7.51 (1H, dd, ^3J = 8.6, ^4J = 2.1, H-7); 7.66 (1H, d, ^4J = 2.1, H-9); 9.86 (1H, s, CHO). ^{13}C NMR spectrum, δ, ppm: 65.8 (C-4); 84.2 (C-8); 119.3 (C-6); 119.6 (C-9b); 121.4 (C-9a); 132.4 (2C, C-3,9); 139.7 (C-7); 140.4 (C-3a); 142.7 (C-2); 152.9 (C-5a); 182.1 (CHO).

(4*H*-Thieno[3,2-*c*]chromen-2-yl)methanol (8) [19]. A solution of 4*H*-thieno[3,2-*c*]chromene-2-carb-aldehyde (**1**) (0.216 g, 1.0 mmol) in abs. EtOH (5 ml) was treated with $NaBH_4$ (0.038 g, 1.0 mmol). The reaction mixture was stirred at room temperature for 1-1.5 h. After the reaction was complete, H_2O (10 ml) was added and the product was extracted with Et_2O (3×10 ml). The organic extracts were combined, dried over Na_2SO_4, the solvent was removed by evaporation. The product was purified by column chromatography (0.060-0.200 mm silica gel, eluent CH_2Cl_2). Yield 0.212 g (97%). Yellow oil. IR spectrum, ν, cm^{-1}: 3445 (OH). ^{1}H NMR spectrum, δ, ppm: 2.05 (1H, br. s, OH); 4.75-4.81 (2H, m, C$\underline{H_2}$OH); 5.21 (2H, s, 4-CH_2); 6.71 (1H, s, H-3); 6.88-6.96 (2H, m, H-6,8); 7.09-7.16 (1H, m, H-7); 7.22-7.26 (1H, m, H-9). ^{13}C NMR spectrum, δ, ppm: 60.1 (CH_2OH); 66.2 (C-4); 116.6 (C-6); 120.3 (C-9a); 121.9 (C-3); 122.6 (C-8); 122.8 (C-9); 128.7 (C-7); 131.2 (C-9b); 132.5 (C-3a); 143.4 (C-2); 152.0 (C-5a).

4-Methoxy-4*H*-thieno[3,2-*c*]chromene-2-carbaldehyde (9). A solution of 4*H*-thieno[3,2-*c*]chromene-2-carbaldehyde (**1**) (0.099 g, 0.457 mmol) in CH_2Cl_2 (5 ml) was treated with MeOH (0.022 ml, 0.543 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.124 g, 0.548 mmol). After stirring for 24 h at room temperature, the reaction mixture was treated with 5% aqueous $NaHCO_3$ (10 ml) and extracted with CH_2Cl_2 (3×15 ml). The combined organic extracts were washed with saturated NaCl solution and dried over Na_2SO_4. The solvent was evaporated at reduced pressure, the residue was purified by column chromatography (0.035-0.070 mm silica gel, eluent CH_2Cl_2). The product was recrystallized from MeOH. Yield 0.091 g (81%). Colorless crystals. IR spectrum, ν, cm^{-1}: 1663 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.57 (3H, s, OCH_3); 6.16 (1H, s, 4-CH); 7.05-7.10 (1H, m, H-8); 7.12-7.15 (1H, m, H-6); 7.32-7.37 (1H, m, H-7); 7.50-7.54 (1H, dd, ^3J = 7.7, ^4J = 1.6, H-9); 7.67 (1H, s, H-3); 9.88 (1H, s, CHO). ^{13}C NMR spectrum, δ, ppm: 55.5 (OCH_3); 96.4 (C-4); 117.8 (2C, C-6,9a); 122.7 (C-8); 124.2 (C-7); 131.2 (C-9b); 131.3 (C-9); 134.2 (C-3); 142.1 (C-3a); 143.4 (C-2); 150.3 (C-5a); 182.4 (CHO).

4*H*-Thieno[3,2-*c*]chromene-2-carboxylic Acid (10) [21]. A suspension of Ag_2O was prepared from concentrated aqueous solution of $AgNO_3$ (0.493 g, 2.9 mmol) and 5 M aqueous NaOH (1.45 ml), and was added to a stirred solution of aldehyde **1** (0.303 g, 1.4 mmol) in THF (3 ml) at a temperature not exceeding 10°C. The cooling bath was removed, and the reaction mixture was stirred for further 2 h. Then the reaction mixture was filtered through paper filter with suction, the filtrate was diluted with water to 20 ml, and acidified with conc. HCl while cooling. The precipitate was filtered off and recrystallized from THF–hexane mixture. Yield 0.276 g (85%). Light-green powder. IR spectrum, ν, cm^{-1}: 2500-3250 (COOH), 1655 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.26 (2H, s, CH_2); 6.95 (1H, d, ^3J = 8.0, H-6); 6.92-7.04 (1H, m, H-8); 7.20-7.28 (1H, m, H-7); 7.42 (1H, dd, ^3J = 7.5, ^4J = 1.3, H-9); 7.58 (1H, s, H-3); 13.21 (1H, s, COOH). ^{13}C NMR spectrum, δ, ppm: 65.3

(CH_2); 116.8 (C-6); 119.1 (C-9a); 122.3 (C-8); 123.6 (C-9); 130.5 (C-3); 130.7 (C-7); 132.5 (C-9b); 133.0 (C-3a); 137.6 (C-2); 152.5 (C-5a); 162.8 (COOH).

Methyl 4*H*-Thieno[3,2-*c*]chromene-2-carboxylate (11) [19, 21, 22]. A solution of 4*H*-thieno[3,2-*c*]-chromene-2-carboxylic acid (**10**) (0.929 g, 4.0 mmol) in MeOH (6.0 ml) was cooled and treated over 10 min with $SOCl_2$ (0.43 ml, 6.0 mmol). The mixture was refluxed for 2.5 h. The precipitate formed was filtered off and recrystallized from MeOH. Yield 0.936 g (95%). Light-yellow crystals. IR spectrum, ν, cm^{-1}: 1714 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.89 (3H, s, OCH_3); 5.25 (2H, s, CH_2); 6.91-7.01 (2H, m, H-6,8); 7.18-7.24 (1H, m, H-7); 7.34 (1H, dd, ^3J = 7.7, ^4J = 1.5, H-9); 7.51 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 52.2 (OCH_3); 65.8 (C-4); 117.0 (C-6); 119.5 (C-9b); 122.2 (C-8); 123.6 (C-9); 130.2 (C-7); 130.4 (C-3); 131.6 (C-2); 131.7 (C-3a); 139.5 (C-9a); 152.9 (C-5a); 162.6 (C=O).

***N*-Hydroxy-4*H*-thieno[3,2-*c*]chromene-2-carboxamide (12)**. Sodium metal (0.101 g, 4.4 mmol) was dissolved in anhydrous MeOH (3 ml), then solution of $NH_2OH \cdot HCl$ (0.140 g, 2.0 mmol) in anhydrous MeOH (10 ml) was added, and the mixture was stirred for 20 min. The precipitate of NaCl was removed by filtration and washed with anhydrous MeOH (10 ml), then ester **11** (0.492 g, 2.0 mmol) was added to the filtrate. The obtained solution was heated on steam bath at 65-70°C until the reaction was complete (1.5-2 h). Methanol was removed on rotary evaporator, the residue was dissolved in minimum amount of H_2O and acidified with AcOH to pH 4. The precipitate formed was filtered off and recrystallized from a mixture of EtOH–H_2O. Yield 0.480 g (97%). Beige crystals. IR spectrum, ν, cm^{-1}: 3355 (NH), 3250-2500 (OH), 1645 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.24 (2H, s, CH_2); 6.93 (1H, d, ^3J = 8.0, H-6); 6.98 (1H, t, ^3J = 7.5, H-8); 7.15-7.27 (1H, m, H-7); 7.38 (1H, d, ^3J = 7.5, H-9); 7.43 (1H, s, H-3); 9.24 (1H, br. s, NH); 11.32 (1H, br. s, OH). ^{13}C NMR spectrum, δ, ppm: 65.4 (C-4); 116.8 (C-6); 119.3 (C-9b); 122.4 (C-8); 123.5 (C-9); 125.0 (C-7); 130.2 (C-3); 132.4 (C-3a); 132.6 (C-2); 135.0 (C-9a); 152.2 (C-2); 152.5 (C-5a).

Biological Studies. The antiulcer effect was studied on standard model of ulcers experimentally induced by introducing 20 mg/kg of indometacin into stomach. The study was performed on 12 adult male rats of Vistar line with mass of 200-220 g. The study compound was introduced as single dose of 100 mg/kg into the stomach 1 h before the induction of ulcers. The animals were sacrificed 24 h later by decapitation under ether anesthesia.

The antiulcer effect was evaluated according to the following parameters:

1) Reduction in the number of ulcers and area of ulcers in the stomach lining by calculation of Paul's index (product of the average number of ulcers on the number of animals with ulcers, divided by 100);

2) The antiulcer activity (AA), calculated by dividing the Paul's index (PI) of control group with the Paul's index (PI) of test group (AA = PI control/ PI test). [20]. The study compounds were considered effective in cases when AA reached 2 and more units.

The anti-inflammatory effect was determined by the histamine-induced mouse paw edema index. Mice were divided in groups, and the study compound (100 mg/kg) was introduced three times at 1 h intervals. One hour after the first introduction of study compounds all mice were injected with 0.05 ml of 0.1% aqueous histamine solution (as phlogogenic agent) in the subplanar pad area of hind paw. Three hours after the last injection the animals were sacrificed by craniocervical dislocation, the hind paws were removed below ankle and each was weighed. The anti-inflammatory effect was estimated by the reduction in swelling index, compared to control. The swelling index was determined by dividing the mass difference between healthy and inflamed paw with the mass of healthy paw, expressed as percentage [23].

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