

Synthesis and pharmacological activities of some condensed 4-chloro-2,2-dialkyl chromene-3-carbaldehyde derivatives

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Some new hydrazono **5a,b**, thiosemicarbazono **6a-c**, and oximo chromenes **7a-c** were prepared *via* the reaction of the corresponding β -chlorocarbaldehyde **3** with hydrazine, aromatic hydrazine, thiosemicarbazide and hydroxylamine hydrochloride, respectively. In addition, ether derivatives **8a-h** were prepared from the corresponding aldoximes **7a-c**. The new products were tested for anti-inflammatory and ulcerogenic score activities compared to indomethacin.

Keywords: β -chlorocarbaldehyde, hydrazones, thiosemicarbazones, oxime ethers, anti-inflammatory activity, ulcerogenic activity

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The Vilsmeier-Haack reaction of active methylene compounds led to the formation of β -halo carbaldehydes, which constitute a class of compounds that served as useful intermediates towards construction of different heterocyclic compounds (1). Accordingly, some of β -chlorocarbaldehydes were described to react with phenylhydrazine and 2-mercapto acetic acid and its ethyl ester to give the corresponding pyrazolo and thieno derivatives (2–6). Pawar and Rajput (7) reported the synthesis of 5-anilinothiazolo-[5,4-*d*]isoxazole from 4-chloro-2-anilinothiazol-5-carbaldehyde with hydroxylamine hydrochloride. As it is known, oxime ethers have found many uses in recent years as non-steroidal anti-inflammatory drugs (8), insect growth regulators (9), materials with steroidal effect (10), and as antimicrobial agents (11).

In continuation of our study on hindered β -chlorocarbaldehydes (6), it seemed to be interesting to react some hindered β -chlorocarbaldehydes with some hydrazines, thiosemicarbazide, and hydroxylamine hydrochloride and to evaluate the pharmacological activity of the new products as anti-inflammatory and anti-ulcerogenic agents.

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EXPERIMENTAL

Melting points were determined in open glass capillaries using an Electrothermal IA 9000 SERIES digital melting point apparatus (Electrothermal, UK) and are uncorrected. Microanalyses were performed with all final compounds on an Elementar-Vario EL (Elementar-Vario EL, Germany) (Microanalytical Unit, Central Services Laboratory, National Research Centre, Cairo, Egypt). The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer (Varian, USA). ^1H NMR spectra were run at 300 MHz in CDCl_3 as solvent. Chemical shifts δ are quoted in ppm and were related to that of the solvents. Mass spectra were recorded on a Shimadzu GCMS-QP 1000EX (EI, 70 eV) (Shimadzu, Japan) and Hewlett-Packard (EI, 70 eV) (Hewlett-Packard, USA). IR spectra were obtained with a Bruker-Vector 22 (Bruker Rhein-Stetten, Germany) for neat samples (for liquids) or KBr wafers (for solids).

2,3-Dihydro-2,2-dimethylchromen-4-one (**1a**) (12), 2,3-dihydro spirochromen(2,1')cyclohexane-4-one (**1b**) (13), 2,3-dihydro-2-ethyl-2-methylchromen-4-one (**1c**) (12), 4-chloro-2,2-dimethyl-2H-chromene (**2a**) (14), 4-chloro spiro-2H-chromene(2,1')cyclohexane (**2b**) (15), 4-chloro-2-ethyl-2-methyl-2H-chromene (**2c**) (16), 4-chloro-2,2-dimethyl-2H-chromene-3-carbaldehyde (**3a**) (6), 4-chloro spiro-2H-chromene(2,1')cyclohexane-3-carbaldehyde (**3b**) (6), and 4-chloro-2-ethyl-2-methyl-2H-chromene-3-carbaldehyde (**3c**) (16) were prepared according to the literature.

Syntheses

Reaction of β -chlorocarbaldehyde 3c with hydrazine hydrate. – Hydrazine hydrate (0.10 mL, 2.50 mmol) was added to a solution of β -chloro carbaldehyde (**3c**) (0.60 g, 1.25 mmol) in 99% ethanol (10 mL). The reaction mixture was refluxed for 3 h, the formed solid was filtered and crystallized from ethanol to give the corresponding aldazine RS *N,N'*-bis-[1-(4-chloro-2-ethyl-2-methyl-2H-chromen-3-yl)methylidene]hydrazine (**4**).

Reaction of β -chlorocarbaldehyde 3c with arylhydrazine. – Arylhydrazine (2.5 mmol) was poured into a solution of β -chlorocarbaldehyde (**3c**) (0.6 g, 2.5 mmol) in 99.7% acetic acid (15 mL). The reaction mixture was refluxed for 3 h and then evaporated under reduced pressure. The residue was treated with dichloromethane, then the formed solid was filtered off, which, identified as arylhydrazine, and the filtrate was washed with 5% aqueous NaHCO_3 and water, dried over Na_2SO_4 , and evaporated to dryness. The residue was triturated with EtOH (few mL), the yellow solid was filtered off to give the corresponding hydrazones **5a,b**.

Reaction of β -chlorocarbaldehydes 3a-c with thiosemicarbazide. – A mixture of β -chlorocarbaldehyde (**3a**, **3b** or **3c**) (2 mmol) and thiosemicarbazide (0.18 g, 2 mmol) in 99.7% acetic acid (15 mL) was refluxed for 3 h and then evaporated under reduced pressure. The residue was dissolved in dichloromethane, and the resulting solution was washed with 5% aqueous NaHCO_3 and water. The organic phase was dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by column chromatography on silica gel (Merck 60, particle size 0.06–0.20 mm); chloroform was used as an eluent to afford the corresponding thiosemicarbazones **6a-c**.

Reaction of β -chloro carbaldehydes 3a-c with hydroxylamine hydrochloride. – Hydroxylamine hydrochloride (0.2 g, 3 mmol) was added to a solution of β -chlorocarbaldehyde (**3a**, **3b** or **3c**) (3 mmol) in absolute ethanol (50 mL) containing triethylamine (3 mL). The reaction mixture was refluxed for 5 h, and then the solvent was evaporated under reduced pressure. The residue was dissolved in chloroform and washed with water 3 times. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to afford the corresponding oximes **7a-c** as crude products. The pure oximes **7a-c** were obtained after additional purification by column chromatography on silica gel (Merck 60, particle size 0.06–0.20 mm); petroleum ether 60–80 °C/ether (20:1, V/V) was used as an eluent.

Reaction of 4-chloro-2,2-substituted chromeno-3-aldoximes 7a,b with acyl chlorides or ethyl chloroacetate. – An appropriate acyl chloride (acetyl chloride, chloroacetyl chloride, benzoyl chloride) or ethyl chloroacetate (3 mmol) was added to a solution of 4-chloro-2,2-substituted chromeno-3-aldoxime (**7a** or **7b**) (3 mmol) in dry toluene (20 mL) containing redistilled dry pyridine (0.25 mL, 3 mmol). The reaction mixture was refluxed for 5 h, then cooled and extracted with water; the toluene solution was dried over calcium chloride. The solvent was evaporated under reduced pressure to give the corresponding oxime ethers **8a-h**, respectively.

Pharmacology

Newly synthesized benzopyran derivatives were dissolved in 0.5% carboxymethyl cellulose (CMC) and administered intraperitoneally (*i.p.*), at a dose of 5 mg kg^{-1} body mass.

Wistar albino mice 3 months, 20 g body mass and Sprague Dawley rats (3 months, 100 g body mass) of either sex (National Research Centre, Giza, Egypt) were housed under suitable laboratory conditions (30 °C, RH 55%) throughout the investigation period. Animals were fed standard pellet chow (El-Nasr Chemical Company, Cairo, Egypt) and allowed free access to water.

All animal procedures were performed after approval from the Ethics Committee of the National Research Centre and in accordance with the recommendations for the proper care and use of laboratory animals (NIH publication No. 85-23, revised 1985).

Anti-inflammatory activity. One hundred and eight rats were divided into eighteen groups, each group consisting of six animals. Anti-inflammatory activity of the compounds under investigation was studied in rats using carrageenan. A suspension of the tested compound and of the reference drug indomethacin in aqueous CMC solution (0.5%, *m/V*) was administered orally to rats at a dose level 5 mg kg^{-1} b. m. Control animals were treated with 0.5% CMC only. After 30 min, 0.1 mL of freshly prepared 1.0% carrageenan solution (in sterile 0.9% NaCl) was injected into the subplantar region of the right hind paw according to the method of Hernands-Perez *et al.* (17). The right paw volume was measured using a digital plethysmometer 7150 (Ugo Basile, Italy) directly before and after 1, 2, 3 h intervals after administration of the tested compounds.

Ulcerogenic activity

Seventy-two rats were divided into twelve groups, each group consisting of six animals according to reported procedure (18). Ulcerogenic activity was evaluated after *p.o.* administration of the tested compounds or indomethacin at doses of 10, 50, and 100 mg kg⁻¹ b. m. Control rats received vehicle *per os* (0.5% CMC). Food but not water was removed 24 h before administration of the tested compounds. After 6 h, the rats were sacrificed, the stomach was removed and opened along the greater curvature, washed with distilled water and cleaned gently by dipping in saline. The mucosa damage for each stomach was examined using a stereoscopic microscope (Nikon SMZ 1B stereoscopic microscope, Nikon USA) and compared with indomethacin.

Acute toxicity

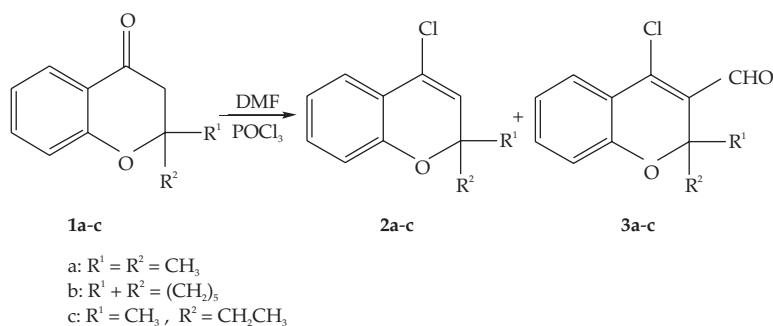
The median lethal doses (LD_{50}) of the most active compounds **6a-c** were determined in mice (19). Groups of male adult mice, each of six animals, were injected *i.p.* with graded doses of each of the test compounds. The percentage of mortality in each group of animals was determined 24 h after injection. Computation of LD_{50} was processed by a graphical method.

RESULTS AND DISCUSSION

Chemistry

The chromanone derivatives **1a-c** were reacted with Vilsmeier reagent (DMF/ $POCl_3$) to give the corresponding 4-chlorochromene derivatives **2a-c** along with 4-chloro (2*H*)chromene-3-carbaldehyde **3a-c** according to Scheme 1.

When *RS*-4-chloro-2-ethyl-2-methyl(2*H*)chromene-3-carbaldehyde (**3c**) was treated with hydrazine hydrate in equimolar ratio 1:1 or in excess of hydrazine hydrate under reflux in ethanol, only the corresponding aldazine derivative **4** (Scheme 2) was separated and characterized by elemental analysis and spectral data (Tables I and II).



Scheme 1

Table I. Physical data and elemental analyses for new compounds

Compd. No.	Solvent for crystallization or chromatography	Physical state/ m.p. (°C)	Yield (%)	Mol. formula (M_r)	Found/calcd. (%)		
					C	H	N
4	EtOH	Red crystals/ 177–178	30	C ₂₆ H ₂₆ Cl ₂ N ₂ O ₂ (469.39)	66.21	5.34	5.79
					66.52	5.58	5.96
5a	PE	Red crystals/ 157–158	5	C ₁₉ H ₁₈ ClN ₃ O ₃ (371.80)	61.21	4.75	11.12
					61.37	4.84	11.30
5b	EtOH	Red crystals/ 182–183	7	C ₁₉ H ₁₇ ClN ₄ O ₅ (416.81)	54.53	3.86	13.09
					54.74	4.07	13.44
6a	Column (CHCl ₃)	Yellow crystals/ 249–250	50	C ₁₃ H ₁₄ ClN ₃ OS (295.77)	52.68	4.70	14.07
					52.78	4.73	14.20
6b	MeOH	Yellow crystals/ 256–257	60	C ₁₆ H ₁₈ ClN ₃ OS (335.83)	57.31	5.21	12.35
					57.21	5.35	12.51
6c	Column (CHCl ₃)	Yellow crystals/ 224–225	46	C ₁₄ H ₁₆ ClN ₃ OS (309.80)	54.18	5.09	13.41
					54.27	5.16	13.56
7a	Column (PE, ether, 20/3, V/V)	Pale green crystals/97–98	89	C ₁₂ H ₁₂ ClNO ₂ (237.67)	60.32	4.85	5.59
					60.63	5.04	5.89
7b	Column (PE, ether, 20/3, V/V)	Pale green crystals/187–188	92	C ₁₅ H ₁₆ ClNO ₂ (277.73)	64.73	5.71	4.86
					64.86	5.76	5.04
7c	Column (PE, ether, 20/1, V/V)	Yellow oil	56	C ₁₃ H ₁₄ ClNO ₂ (251.69)	61.80	5.41	5.38
					62.03	5.56	5.56
8a	Column (PE)	Colorless oil	52	C ₁₄ H ₁₄ ClNO ₃ (279.72)	59.75	4.84	4.75
					60.11	5.00	5.00
8b	PE	Colorless crystals/101–103	60	C ₁₇ H ₁₈ ClNO ₃ (319.78)	63.53	5.47	4.05
					63.84	5.62	4.37
8c	Column (PE)	Colorless oil	48	C ₁₄ H ₁₃ Cl ₂ NO ₃ (314.16)	53.32	3.97	4.27
					53.52	4.13	4.45
8d	PE	Colorless crystals/106–109	55	C ₁₇ H ₁₇ Cl ₂ NO ₃ (354.23)	57.38	4.49	3.73
					57.63	4.79	3.95
8e	Column (PE)	Colorless oil	68	C ₁₉ H ₁₆ ClNO ₃ (341.79)	66.42	4.47	3.86
					66.76	4.68	4.09
8f	PE	Colorless crystals/115–117	80	C ₂₂ H ₂₀ ClNO ₃ (381.85)	69.00	5.15	3.49
					69.19	5.23	3.66
8g	Column (PE)	Colorless oil	38	C ₁₆ H ₁₈ ClNO ₄ (323.77)	59.05	5.34	4.11
					59.35	5.55	4.32
8h	PE	Colorless crystals/97–100	50	C ₁₉ H ₂₂ ClNO ₄ (363.84)	62.80	5.92	3.61
					62.71	6.04	3.84

PE – Petroleum ether (40–60 °C)

Table II. Infrared, ¹H NMR and mass spectra

Compd. No.	IR (ν, cm ⁻¹)	¹ H NMR (δ, ppm)	MS (m/z, %)
4	2959, 2916, 2360, 1591, 1479, 1450, 1256, 753	0.95 (t, J = 7.4 Hz, 6H, 2 CH ₃ CH ₂), 1.74 (s, 6H, 2 CH ₃), 1.89–1.92 (m, 2H, 2 CH ₃ CH _a H _b), 2.24–2.56 (m, 2H, 2 CH ₃ CH _a H _b), 6.85 (d, J = 8.2 Hz, 2H, 2 ArH), 6.97–7.04 (m, 2H, 2 ArH), 7.63–7.64 (m, 2H, 2 ArH), 7.65 (d, J = 7.8 Hz, 2H, 2 ArH), 8.82 (s, 2H, CH=N)	468 (M ⁺ , -1.5), 433 (56), 403 (16), 397 (24), 255 (60), 221 (33), 219 (100), 204 (33), 183 (16), 178 (27)
5a	3450, 1598, 1478, 1312, 1267, 1106, 748	0.90 (t, J = 8.1 Hz, 3H, CH ₃ CH ₂), 1.68 (s, 3H, CH ₃), 1.83–1.91 (m, 2H, CH ₃ CH ₂), 6.86 (d, J = 7.9 Hz, 1H, ArH), 6.98–7.07 (m, 3H, ArH), 7.27–7.32 (m, 1H, ArH), 7.49 (d, J = 6.9 Hz, 1H, ArH), 8.15 (d, J = 9.07 Hz, 2H, ArH), 8.27 (s, 1H, CH=N), 11.52 (s, 1H, NH, exchangeable with D ₂ O)	373 (M ⁺ Cl ³⁷ , 6), 371 (M ⁺ Cl ³⁵ , 22), 342 (54), 306 (100), 260 (24), 204 (23), 178 (14)
5b	3267, 2940, 1596, 1501, 134, 1136, 1091, 760	0.90 (t, J = 8.1 Hz, 3H, CH ₃ CH ₂), 1.68 (s, 3H, CH ₃), 1.83–1.91 (m, 2H, CH ₃ CH ₂), 6.89 (d, J = 8.1 Hz, 1H, ArH), 7.03 (t, J = 7.6 Hz, 1H, ArH), 7.32–7.37 (m, 1H, ArH), 7.54 (d, J = 6.9 Hz, 1H, ArH), 7.77 (d, J = 9.5 Hz, 1H, ArH), 8.43 (dd, J = 9.5, 2.5 Hz, 1H, ArH), 8.85 (s, 1H, ArH), 8.96 (s, 1H, CH=N), 11.85 (s, 1H, NH, exchangeable with D ₂ O)	418 (M ⁺ Cl ³⁷ , 9), 416 (M ⁺ Cl ³⁵ , 27), 387 (100), 351 (97), 204 (44), 178 (22), 170 (23)
6a	3427, 3259, 3153, 2975, 1593, 1529, 1454, 1366, 1289, 1099, 750	1.63 (s, 6H, 2 CH ₃), 6.86 (d, J = 8.1 Hz, 1H, ArH), 7.00–7.05 (m, 1H, ArH), 7.29–7.34 (m, 1H, ArH), 7.44 (s, H, NH, exchangeable with D ₂ O), 7.50 (d, J = 7.8 Hz, 1H, ArH), 8.29 (s, H, NH, exchangeable with D ₂ O), 8.33 (s, 1H, CH=N), 11.52 (s, 1H, NH, exchangeable with D ₂ O)	297 (M ⁺ Cl ³⁷ , 6), 295 (M ⁺ Cl ³⁵ , 21), 219 (16), 204 (100), 185 (54), 115 (13), 60 (31)
6b	3430, 3270, 3152, 2930, 1590, 1528, 1448, 1289, 1244, 1113, 757	1.47–1.69 (m, 8H, 2 CH ₂), 1.82 (d, J = 12.0 Hz, 2H, CH ₂), 6.95 (d, J = 8.1 Hz, 1H, ArH), 7.01–7.06 (m, 1H, ArH), 7.27 (s, H, NH, exchangeable with D ₂ O), 7.31–7.34 (m, 1H, ArH), 7.49 (dd, J = 7.8, 1.5 Hz, 1H, ArH), 8.28 (s, H, NH, exchangeable with D ₂ O), 8.37 (s, 1H, CH=N), 11.53 (s, 1H, NH, exchangeable with D ₂ O)	337 (M ⁺ Cl ³⁷ , 8), 335 (M ⁺ Cl ³⁵ , 24), 259 (53), 216 (100), 203 (20), 197 (27), 115 (15), 60 (47)
6c	3442, 3270, 3150, 2974, 2362, 1592, 1530, 1454, 1372, 1290, 1101, 753	0.85 (t, J = 7.3 Hz, 3H, CH ₃ CH ₂), 1.59 (s, 3H, CH ₃), 1.74–1.83 (m, 1H, CH ₃ CH _a H _b), 2.24–2.33 (m, 1H, CH ₃ CH _a H _b), 6.85 (dd, J = 8.1, 1.2 Hz, 1H, ArH), 7.00–7.04 (m, 1H, ArH), 7.30–7.38 (m, 1H, ArH), 7.40 (s, H, NH, exchangeable with D ₂ O), 7.49 (dd, J = 7.8, 1.5 Hz, 1H, ArH), 8.28 (s, 1H, NH, exchangeable with D ₂ O), 8.37 (s, 1H, CH=N), 11.51 (s, 1H, NH, exchangeable with D ₂ O)	311 (M ⁺ Cl ³⁷ , 5), 309 (M ⁺ Cl ³⁵ , 17), 204 (93), 185 (100), 128 (11), 115 (12), 60 (41)
7a	3282, 1592, 1474, 1296, 1256, 975, 764	1.65 (s, 6H, 2 CH ₃), 6.82 (d, J = 8.1 Hz, 1H, ArH), 6.93–6.98 (m, 1H, ArH), 7.21–7.27 (m, 1H, ArH), 7.45 (s, H, OH, exchangeable with D ₂ O), 7.53 (d, J = 7.6 Hz, 1H, ArH), 8.39 (s, 1H, CH=N)	239 (M ⁺ Cl ³⁷ , 7), 237 (M ⁺ Cl ³⁵ , 27), 222 (100), 204 (25), 186 (36), 180 (28), 178 (16), 115 (20), 77 (22), 63 (29)

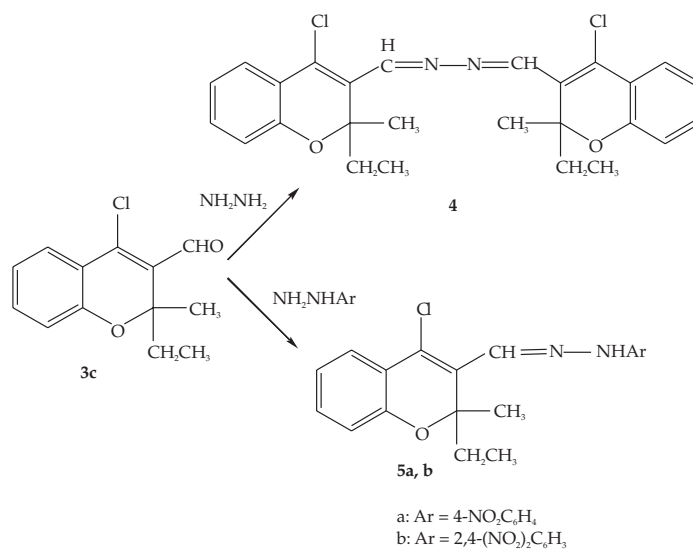
7b	3262, 2928, 1590, 1474, 1445, 1288, 1258, 978, 757	1.23–2.19 (m, 10H, 5 CH ₂), 6.89 (d, <i>J</i> = 7.9 Hz, 1H, ArH), 6.93–6.99 (m, 1H, ArH), 7.22–7.25 (m, 1H, ArH), 7.44 (s, H, OH, exchangeable with D ₂ O), 7.53 (dd, <i>J</i> = 7.6, 1.3 Hz, 1H, ArH), 8.35 (s, 1H, CH=N)	279 (M ⁺ Cl ³⁷ , 5), 277 (M ⁺ Cl ³⁵ , 16), 260 (100), 217 (41), 204 (35), 115 (12), 77 (13), 63 (16)
7c	–	0.83 (t, <i>J</i> = 7.3 Hz, 3H, CH ₃ CH ₂), 1.50 (s, 3H, CH ₃), 1.84–1.89 (m, 1H, CH ₃ CH _a H _b), 2.31–2.36 (m, 1H, CH ₃ CH _a H _b), 6.70 (d, <i>J</i> = 8.1 Hz, 1H, ArH), 6.86–6.99 (m, 1H, ArH), 7.23–7.58 (m, 1H, ArH), 7.41 (d, <i>J</i> = 7.9 Hz, 1H, ArH), 8.31 (s, H, OH, exchangeable with D ₂ O), 8.47 (s, 1H, CH=N)	–
8a	2931, 2925, 1730, 1615, 1474, 1445, 1288, 1258, 978, 757	1.65 (s, 6H, 2 CH ₃), 2.38 (s, 3H, CH ₃), 6.80 (d, <i>J</i> = 8.1 Hz, 1H, ArH), 6.91–6.96 (m, 1H, ArH), 7.21–7.27 (m, 1H, ArH), 7.51 (d, <i>J</i> = 7.6 Hz, 1H, ArH), 8.43 (s, 1H, CH=N)	281 (M ⁺ Cl ³⁷ , 2), 279 (M ⁺ , 8), 221 (32), 219 (100), 206 (7), 204 (25), 186 (36), 180 (28), 178 (16), 115 (20), 77 (22), 63 (29)
8b	2932, 2924, 1729, 1615, 1472, 1443, 1288, 1258, 978, 759	1.20–2.29 (m, 10H, 5 CH ₂), 2.39 (s, 3H, CH ₃), 6.89 (d, <i>J</i> = 8.1 Hz, 1H, ArH), 6.91–6.96 (m, 1H, ArH), 7.21–7.27 (m, 1H, ArH), 7.51 (d, <i>J</i> = 7.6 Hz, 1H, ArH), 8.42 (s, 1H, CH=N)	321 (M ⁺ Cl ³⁷ , 2), 319 (M ⁺ , 10), 261 (33), 259 (100), 233 (23), 231 (80), 206 (21), 204 (65), 186 (26), 180 (27), 178 (26), 115 (25), 77 (23), 63 (30)
8c	2935, 2926, 1730, 1625, 1475, 1439, 1298, 1268, 971, 765	1.65 (s, 6H, 2 CH ₃), 4.46 (s, 2H, CH ₂), 6.80 (d, <i>J</i> = 8.1 Hz, 1H, ArH), 6.92–6.96 (m, 1H, ArH), 7.21–7.27 (m, 1H, ArH), 7.52 (d, <i>J</i> = 7.6 Hz, 1H, ArH), 8.44 (s, 1H, CH=N)	223 (25), 221 (100), 206 (9), 204 (30), 186 (34), 180 (26), 178 (18), 115 (22), 77 (24), 63 (27)
8d	2935, 2924, 1729, 1615, 1473, 1445, 1288, 1258, 976, 759	1.21–2.31 (m, 10H, 5 CH ₂), 4.44 (s, 2H, CH ₂), 6.88 (d, <i>J</i> = 8.1 Hz, 1H, ArH), 6.90–6.95 (m, 1H, ArH), 7.21–7.27 (m, 1H, ArH), 7.50 (d, <i>J</i> = 7.6 Hz, 1H, ArH), 8.42 (s, 1H, CH=N)	261 (29), 259 (100), 233 (21), 231 (78), 206 (23), 204 (65), 186 (26), 180 (27), 178 (26), 115 (25), 77 (23), 63 (30)
8e	2931, 2925, 1735, 1625, 1474, 1445, 1288, 1258, 978, 757	2.40 (s, 6H, 2CH ₃), 6.80 (d, <i>J</i> = 8.1 Hz, 1H, ArH), 6.91–6.96 (m, 1H, ArH), 7.23–7.37 (m, 6H, ArH), 7.51 (d, <i>J</i> = 7.6 Hz, 1H, ArH), 8.45 (s, 1H, CH=N)	343 (M ⁺ Cl ³⁷ , 3), 341 (M ⁺ Cl ³⁵ , 12), 238 (32), 240 (100), 206 (9), 204 (27), 186 (38), 180 (32), 178 (20), 115 (22), 77 (24), 63 (39)
8f	2933, 2925, 1733, 1623, 1474, 1445, 1286, 1254, 976, 759	1.20–2.29 (m, 10H, 5 CH ₂), 6.89 (d, <i>J</i> = 8.1 Hz, 1H, ArH), 6.91–6.96 (m, 1H, ArH), 7.21–7.27 (m, 6H, ArH), 7.51 (d, <i>J</i> = 7.6 Hz, 1H, ArH), 8.43 (s, 1H, CH=N)	383 (M ⁺ Cl ³⁷ , 3), 381 (M ⁺ Cl ³⁵ , 15), 278 (33), 276 (100), 233 (23), 231 (80), 206 (21), 204 (65), 186 (28), 180 (27), 178 (26), 115 (25), 77 (27), 63 (40)

8g	2935, 2925,	0.93 (t, $J = 8.0$ Hz, 3H, CH_2CH_3),	223 (15), 221 (50),
	2926, 2889,	1.65 (s, 6H, 2 CH_3), 4.27 (m, 2H, CH_2CH_3),	206 (31), 204 (100),
	1720, 1615,	4.46 (s, 2H, CH_2), 6.79 (d, $J = 8.1$ Hz, 1H, ArH),	186 (34), 180 (26),
	1475, 1439,	6.91–6.95 (m, 1H, ArH), 7.22–7.27 (m, 1H, ArH),	178 (18), 115 (24), 77
	1294, 1262,	7.52 (d, $J = 7.6$ Hz, 1H, ArH),	(24), 63 (29)
971, 765	8.44 (s, 1H, $\text{CH}=\text{N}$)		
8h	2925, 2926,	0.93 (t, $J = 8.0$ Hz, 3H, CH_2CH_3), 1.21–2.31	261 (17), 259 (55),
	1720, 1615,	(m, 10H, 5 CH_2), 4.25 (m, 2H, CH_2CH_3), 4.44	233 (21), 231 (78),
	1475, 1439,	(s, 2H, CH_2), 6.88 (d, $J = 8.1$ Hz, 1H, ArH),	206 (27), 204 (100),
	1294, 1262,	6.90–6.95 (m, 1H, ArH), 7.21–7.27 (m, 1H, ArH),	186 (26), 180 (27),
	971, 765	7.50 (d, $J = 7.6$ Hz, 1H, ArH), 8.42 (s, 1H, $\text{CH}=\text{N}$)	178 (26), 115 (27), 77
		(23), 63 (32)	

PE – Petroleum ether

The IR spectrum of compound **4** showed C=N absorption at 1591 cm^{-1} , whereas ^1H NMR spectrum of **4** showed the methyldine proton at δ 8.82 ppm. The mass spectrum of **4** showed a prominent ion peak M^+ at m/z 468 (5%).

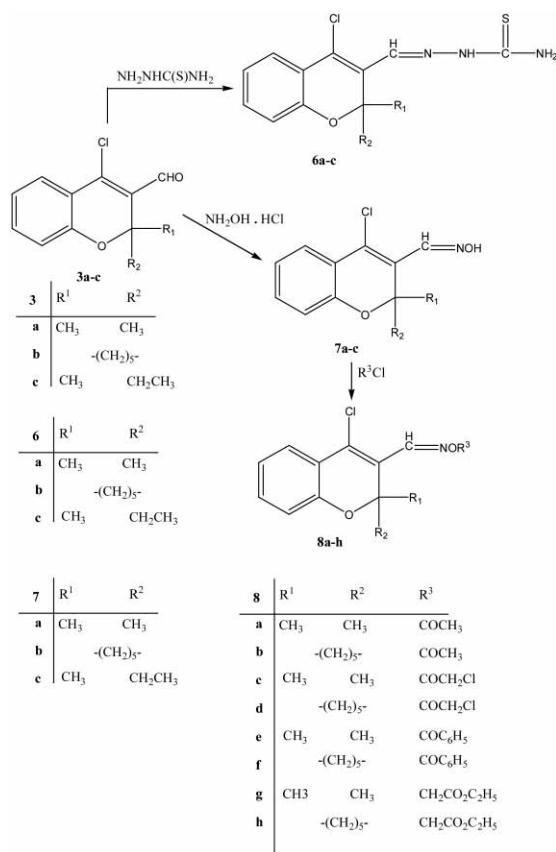
Accordingly, *RS*-4-chloro-2-ethyl-2-methyl(2*H*)chromene-3-carboxaldehyde (**3c**) reacted with 4-nitrophenylhydrazine and 2,4-dinitrophenylhydrazine to produce the corresponding hydrazone derivatives **5a,b** (Scheme 2).



Scheme 2

The elemental analyses and spectral data revealed the required structures. The IR spectra of **5a,b** showed C=N at 1598 and 1596 cm^{-1} , respectively. The ^1H NMR spectra of **5a,b** showed methyldine protons at δ 8.27, 8.96 and NH at δ 11.52, 11.85 ppm (exchangeable with D_2O). The mass spectra of **5a,b** showed prominent ion peaks M^+ at m/z 371 (M^+Cl^{35} , 22%) and 416 (M^+Cl^{35} , 27%), respectively.

Some of the semicarbazones and thiosemicarbazones have been reported as biologically active compounds (20, 21). So, 4-chloro(2*H*)chromene-3-carbaldehydes **3a-c** reacting with thiosemicarbazide in acetic acid under reflux for 3 h afforded the corresponding thiosemicarbazones **6a-c** (Scheme 3). The IR spectra of **6a-c** show NH_2 , NH at 3442–3152, C=N at 1593–1590 cm^{-1} . The ^1H NMR spectra of **6a-c** showed the two protons of NH_2 as magnetically un-equivalent protons, whereas they appeared at 7.27–7.44, 8.28–8.29 ppm (exchangeable with D_2O), methyldine protons at 8.33–8.37 ppm and NH at 11.51–11.53 ppm (exchangeable with D_2O). The mass spectra of **6a-c** showed prominent ion peaks



Scheme 3

Scheme 3

M⁺ at *m/z* 295 (M⁺Cl³⁵, 21%) and 335 (M⁺Cl³⁵, 24%), 309 (M⁺Cl³⁵, 17%), respectively. The thiosemicarbazones **6a-c** were not changed after heating with KOH in ethanol under reflux for 10 h.

Reaction of β-chlorocarbaldehydes **3a-c** with hydroxylamine hydrochloride in absolute ethanol containing triethylamine under reflux for 5 h afforded the corresponding oxime derivatives **7a-c** (Scheme 3). The IR spectra of **7a,b** show OH at 3282, 3262, C=N at 1592, 1590 cm⁻¹. The ¹H NMR spectra of **7a-c** showed OH at 7.45, 7.44, 8.31 ppm (exchangeable with D₂O), respectively, and methylidene protons at 8.39, 8.35, 8.47 ppm, respectively. The mass spectra of **7a,b** showed prominent ion peaks M⁺ at *m/z* 237 (M⁺Cl³⁵, 27%) and 277 (M⁺Cl³⁵, 16%), respectively. However, the oximes **7a,b** reacted with some acyl chlorides, namely, acetyl chloride, chloroacetyl chloride, benzoyl chloride and ethyl chloroacetate in dry toluene in the presence of redistilled dry pyridine to give the corresponding *O*-acyloxime and ethoxy carbamoyl methyl derivatives **8a-h** (Scheme 3). The

Table III. Anti-inflammatory activity of the synthesized compounds

Compd. No.	Edema inhibition (mean ± S.E.M) ^{a,b} (%)		
	1 h	2 h	3 h
Control	15.5 ± 4.3	14.9 ± 4.5	17.2 ± 4.4
4	17.4 ± 4.8	30.0 ± 4.8	36.5 ± 3.4
5a	16.1 ± 5.6	27.8 ± 5.8	34.8 ± 5.6
5b	13.1 ± 5.0	14.7 ± 3.9	31.4 ± 4.9
6a	39.7 ± 1.9	52.6 ± 1.6	59.4 ± 1.9
6b	34.6 ± 2.3	47.6 ± 1.8	54.5 ± 1.6
6c	37.7 ± 1.4	55.6 ± 1.6	62.4 ± 1.9
7a	8.8 ± 7.1	21.7 ± 6.4	28.4 ± 7.1
7b	15.7 ± 5.6	28.6 ± 5.0	35.3 ± 5.6
7c	12.8 ± 6.1	25.7 ± 6.4	32.4 ± 5.6
8a	10.8 ± 7.1	23.8 ± 6.4	30.5 ± 7.1
8b	17.7 ± 5.5	30.5 ± 5.7	37.3 ± 5.5
8c	15.9 ± 2.3	28.8 ± 2.4	35.5 ± 1.2
8d	21.8 ± 4.8	34.8 ± 4.8	41.4 ± 3.4
8e	–	–	–
8f	–	–	–
8g	–	–	–
8h	–	–	–
Indomethacin	42.8 ± 5.7	55.7 ± 6.3	62.0 ± 5.3

(-) – No activity.

^a Dose: 5 mg kg⁻¹ b.m. (*p.o.*).

^b *n* = 6.

analytical and spectroscopic characterization data of compounds **8a-h** given in Tables I and II are in good agreement with the expected structural characteristics.

Anti-inflammatory activity

The results of anti-inflammatory testing are listed in Table III, showing the percent inhibition of edema obtained by the reference drug and tested compounds, respectively. Results show that compounds **4**, **5a,b**, **7a,b,c** and **8a,b,c,d** possess weak anti-inflammatory activity (8–41% of inhibition) in comparison to that of indomethacin (42–62%). Compounds **6a**, **6b** and **6c** showed activity of 35 to 62%, equal to that of indomethacin. The condensation of thiosemicarbazide group with carbaldehyde group in the pyrane ring increased the activity in all cases. Cyclohexyl group at position 2 in the pyrane ring was found to be less active compared to methyl and ethyl groups at position 2 in the pyrane ring (Table III).

Ulcerogenicity and acute toxicity

Compounds **6a-c** were screened for their ulcerogenic activity at dose levels of 10, 50 and 100 mg kg⁻¹ b.m. (Table IV). The Tested Compounds **6a-c** Showed No Ulcerogenic Activity compared to indomethacin, which showed mean ulcerogenic activity of 1.4 to 2.1 mm.

Table IV. Gastric ulceration in rats^a

Compd. No.	Dose (mg kg ⁻¹)		
	10	50	100
Control	0/6	0/6	0/6
6a	0/6 (0)	0/6 (0)	0/6 (0)
6b	0/6 (0)	0/6 (0)	0/6 (0)
6c	0/6 (0)	0/6 (0)	0/6 (0)
Indomethacin	3/6 (1.4 ± 0.2) ^{b,c}	5/6 (1.9 ± 0.2) ^{b,c}	6/6 (2.1 ± 0.2) ^{b,c}

^a Number of rats with lesions bigger than 0.5 mm in length per total number of rats.

^b Mean ulcer lesion ± SEM (mm) (*n* = 6) in parentheses.

^c Significant difference at *p* < 0.05 compared to the control.

Acute toxicity

*LD*₅₀ of compounds **6a-c** was found to be 145, 155 and 165 mg kg⁻¹ (*i.p.*), respectively, whereas, *LD*₅₀ of indomethacin was 50 mg kg⁻¹ (*i.p.*).

CONCLUSIONS

1-[(4-Chloro-2,2-dimethyl-2H-chromen-3-yl)methylene]thiosemicarbazide (**6a**), 1-[(4-chlorospiro-2H-chromen(2,1')cyclohexane-3-yl)methylene]thiosemicarbazide (**6b**) and 1-[(4-chloro-2-ethyl-2-methyl-2H-chromen-3-yl)methylene]thiosemicarbazide (**6c**) were found to be potent anti-inflammatory agents comparable to indomethacin. On the other hand, they show no ulcerative activity and higher LD_{50} values than indomethacin. The thiosemicarbazide group at position 3 of the pyrane ring might be responsible for these activity.

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S A Ž E T A K

Sinteza i farmakološko djelovanje derivata kondenziranih 4-klor-2,2-dialkil kromen-3-karbaldehida

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MOHEY ELLITHEY i MAHMOUD SOLIMAN ARBID

Novi hidrazono- **5a,b**, tiosemikarbazono- **6a-c** i oksimo kromeni **7a-c** sintetizirani su iz odgovarajućeg β -klorkarbaldehida **3** i hidrazina, aromatskog hidrazina, tiosemikarbazona ili hidroksilamin hidroklorida, dok su eterski derivati **8a-h** pripremljeni iz pripadajućih aldoksima **7a-c**. Novi spojevi ispitani su na protuupalno i ulcerogeno djelovanje, a njihovo djelovanje uspoređeno je s djelovanjem indometacina.

Ključne riječi: β -klorkarbaldehid, hidrazoni, tiosemikarbazoni, oksim-eteri, protuupalno, ulcerogeno djelovanje

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