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Synthesis and preliminary anti-inflammatory evaluation of xanthone derivatives

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Abstract: Xanthone derivatives of acetic, propionic and 2-methylpropionic acids were synthesized and assayed for their anti-inflammatory, analgesic and ulcerogenic activities. Compound **8** causes a dose-dependent diminution of paw edema (up to 61%) in the carrageenan model and at the highest tested dose reduces mechanical hyperalgesia in the Randall-Selitto test more effectively than the reference compound (~75% and ~32%, respectively). It shows high *in vitro* metabolic stability (Cl_{int} = 12.5 μL/mg/min, $t_{1/2}$ = 138.6 min) in the rat liver microsomes. None of the studied xanthone derivatives are ulcerogenic. The results of the present study suggest that compound **8** can be of interest in the future for the search for antinociceptive and antiedematous agents devoid of ulcerogenic effect.

Keywords: analgesic; anti-edema; ulcerogenic; xanthones.

Introduction

Xanthone derivatives are desirable templates for drug development. The nature of the substituents on the xanthone tricyclic scaffold can strongly influence biological activity. For example, anticonvulsant activity can be attributed to simple aminoalkyl derivatives [1–4], while entities with a piperazinyl group also exhibit anti-arrhythmic and hypotensive properties [5, 6]. The phenolic hydroxy groups can be important for antifungal [7] and antioxidant [8] activities. More lipophilic prenylated [9] fused xanthones [10] and complex amides of carboxy-substituted xanthones [11] have been investigated as antitumor agents. A few hydroxyxanthone derivatives exhibit potent anti-inflammatory and analgesic properties. Among natural simple xanthone derivatives, 2,8-dihydroxy-1,6-dimethoxyxanthone (**I** in Figure 1) shows significant analgesic properties on the peripheral and central nervous system and anti-inflammatory properties in various *in vivo* models [12]. A synthetic analog of widely studied gambogic acid (**II** in Figure 1) shows a substantial potency in *in vitro* anti-inflammatory assays [13].

The search for anti-inflammatory agents in the group of xanthone derivatives was the subject of our previous study [14]. In a series of xanthonyloxy derivatives of propionic acids, the most active compound **III** (Figure 1) at the highest tested dose exhibits a promising anti-inflammatory activity in the carrageenan-induced edema model, expressing no ulcerogenic liability at the same time. The present study is a further attempt to develop anti-inflammatory compounds in a group of xanthone derivatives of aliphatic acids. For this purpose, new compounds were synthesized and evaluated for the anti-edema and analgesic activities in rat models. Their possible ulcerogenic propensity was checked. The metabolic stability of the most active compound **8** was examined with the use of rat liver microsomes.

Results and discussion

Chemistry

The traditional multistep method was applied to the synthesis of the xanthone core [15, 16]. Starting compound **1** (Scheme 1) was obtained from 2-[(9-oxo-9*H*-xanthen-4-yl) methyl]isothiouronium bromide [17] under hydrolytic alkaline conditions, according to the procedure described by Eckstein and Marona [18]. The detailed preparations of other starting compounds, namely 6-hydroxy-2-methyl-9*H*-xanthen-9-one (**2**), 3-hydroxy-5-methyl-9*H*-xanthen-9-one (**3**) and 3-chloro-5-hydroxy-9*H*-xanthen-9-one (**4**), were

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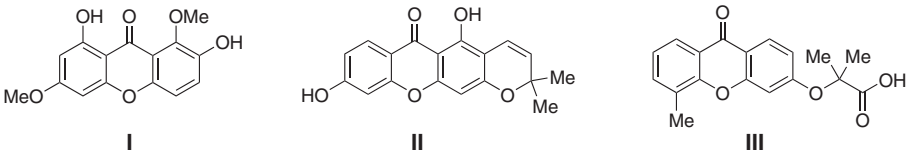
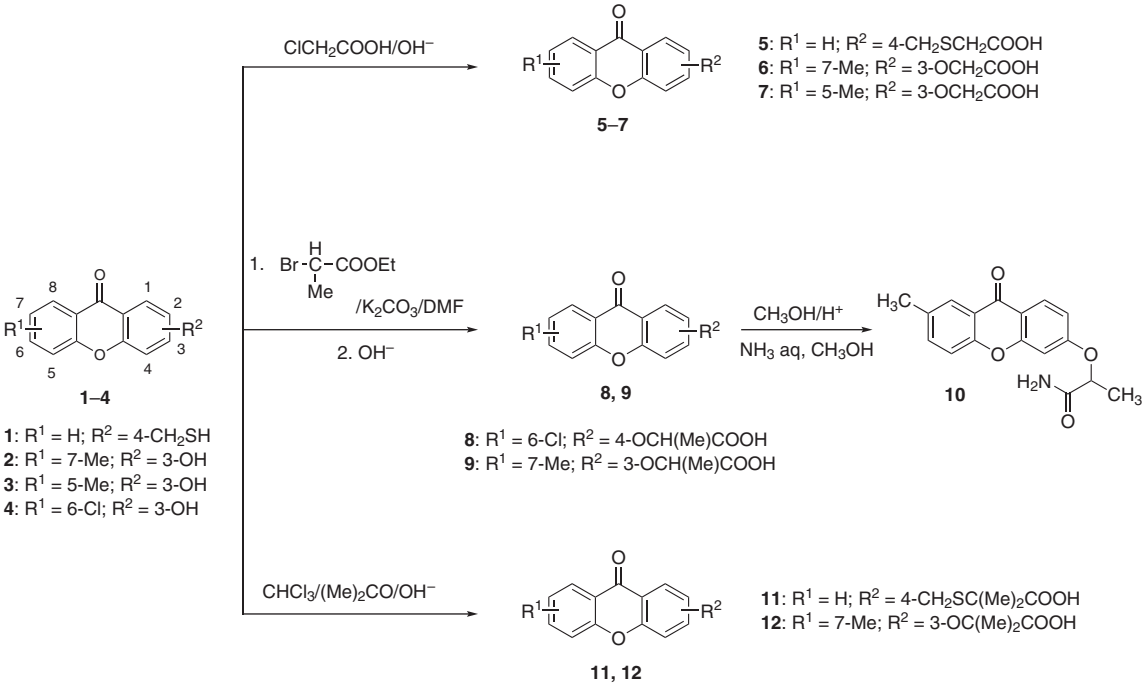


Figure 1 Xanthone derivatives **I–III** exhibiting anti-inflammatory activity.



Scheme 1 Synthesis of compounds **5–12**.

reported elsewhere [19–21]. The target compounds **5–12** were synthesized using methodologies given in Scheme 1. Acetic acid derivatives **5–7** were obtained by the treatment of starting compounds **1–3** with sodium chloroacetate in the presence of NaOH. Esters of propionic acid derivatives were prepared from **2** to **4**, using ethyl 2-bromopropanoate in the presence of K_2CO_3, as described previously [22]. The next step was alkaline hydrolysis of the ethyl esters to yield the acids **8** and **9**. Compound **10** was obtained by the conversion of **9** into its methyl ester, followed by ammonolysis in methanol. 2-Methylpropionic acid derivatives **11** and **12** were obtained from **1** to **2**, respectively, according to the strategy of Link [23]. In this reaction, thiol **1** or phenol **2** was allowed to react under alkaline conditions in a mixed solvent of acetone and chloroform to form **11** and **12**, respectively. All xanthone derivatives (Scheme 1) were obtained with a satisfying yield, and their structures were confirmed by elemental analysis, proton nuclear magnetic resonance (^{1}H NMR) and mass spectrometry (MS).

Pharmacology

The pharmacological activity of compounds **5–12** was investigated using two *in vivo* screening protocols used in the search for potential nonsteroidal anti-inflammatory drugs (NSAIDs). The carrageenan-induced rat paw edema method [24] was applied to check the anti-inflammatory effect. The analgesic activity was studied using the Randall-Selitto test in rats [25], a method that is based on the principle that inflammation increases the sensitivity to pain. In both tests, compounds were given orally at doses of 50, 100 and 200 mg/kg. Ketoprofen (KET) and acetylsalicylic acid (ASA) were used as reference drugs. The results are given in Table 1.

The tested compounds show divergent anti-inflammatory and analgesic activities. In the carrageenan-induced edema test, the most active are derivatives of propionic acid **8** and **12**, exhibiting at the highest tested dose anti-inflammatory activity comparable to that of

Table 1 Anti-inflammatory and analgesic activities of xanthone derivatives and reference compounds in carrageenan rat paw edema and Randall-Sellito tests.

Compound	Dose (mg/kg) *p.o.*	Edema inhibition (%)			Pain inhibition (4 h)
		1 h	2 h	3 h	
5	50	37.60	17.47	10.50	0
	100	12.60	18.47	14.50	15.40
	200	−5.60	−7.00	−5.60	−1.94
6	50	−14.59	−23.07	−13.18	0
	100	−21.45	−14.07	−2.93	25.32
	200	−24.46	−41.53	−20.07	11.39
7	50	0	−4.90	−0.80	0.12
	100	−28.00	−28.70	−10.80	−12.23
	200	4.80	−6.60	−2.40	−3.99
8	50	36.72	36.33	30.26	14.79
	100	39.84	44.64	45.82	55.13
	200	53.41	61.02	51.73	76.92
9	50	0	7.65	0	0
	100	27.53	27.71	0	0
	200	−18.30	29.25	5.36	21.10
10	50	36.00	27.50	39.90	−1.94
	100	12.79	6.70	32.80	−14.28
	200	−0.04	8.25	28.29	−2.90
11	50	−7.70	0	22.30	−17.71
	100	−5.50	17.50	14.80	−2.63
	200	−17.64	7.90	9.40	9.62
12	50	−53.84	−23.30	−36.82	−18.80
	100	23.95	34.59	39.82	23.00
	200	65.42	62.79	56.99	35.45
Acetylsalicylic acid (ASA)	50	43.76	51.72	45.31	−5.94
	100	47.06	54.83	52.59	30.38
	200	54.94	66.30	68.35	31.42
Ketoprofen (KET)	50	66.70	70.72	77.44	28.95
	100	80.00	75.75	80.65	30.96
	200	91.60	75.75	80.65	33.55

ASA. Unfortunately, both compounds are less potent than KET. Interestingly, compound **12** at the lowest tested dose exhibits pro-inflammatory activity that is most noticeable after 1 h. In the peripheral analgesic activity test, compounds **8** and **12** demonstrate the best analgesic effect that is parallel to the results of the carrageenan test. However, only compound **8** exhibits a dose-dependent analgesic activity, reaching a partial analgesia of 55% and 76% at doses of 100 and 200 mg/kg, respectively, which is considerably higher than the effects of both reference drugs (ASA and KET) at the same doses. Non-selective NSAIDs impair the functionality of the gastric mucosa due to their mechanism of action.

The tested compounds were evaluated for the ulcerogenic potential in rats according to the protocol described by Komatsu and co-workers [26]. All compounds do not cause any ulceration at the applied doses in the range of 50 mg/kg–200 mg/kg *p.o.* and some of them evoke only erythema at the highest dose. The most active compounds **8** and **12** do not cause any harmful effect on the rats' stomach mucosa, which is in contrast to the reference drugs KET and ASA. This result is consistent with the outcomes of *in silico* gastric toxicity studies of **12** and KET [27].

Metabolic stability

The metabolic stability of xanthone derivatives has rarely been described. There are a few reports indicating that cytochrome P450 (CYP450) is involved in xanthone metabolism [28, 29]. In this work, compound **8** was selected for studying its metabolic stability in rat liver microsomes. The study was conducted using a procedure described by Kubowicz and co-workers [30]. According to the results, compound **8** demonstrates high metabolic stability *in*

vitro with $t_{1/2} = 138.6$ min and the intrinsic clearance (Cl_{int}) value of 12.5 μL mg^{-1} min^{-1} [31].

Conclusions

Xanthone derivatives of acetic, propionic and 2-methylpropionic acids were synthesized. All compounds were screened for their anti-edema, analgesic and ulcerogenic activities in rat models. Xanthonyloxy derivatives of propionic acid **8** and **12** exhibit a promising anti-inflammatory activity, while only compound **8** substituted with a chlorine atom shows excellent analgesic properties with no irritant activity toward the gastric mucosa. This compound is metabolically stable in a rat microsomal model.

Experimental

All commercial reagents and solvents were at least of 98% purity. Melting points were determined on a Büchi M-560 melting point apparatus and are uncorrected. Reactions were monitored by thin-layer chromatography (TLC) on silica gel plates (Merck, 60, F254) eluting with acetone/toluene (1:3) or toluene/acetone/methanol (5:1:1) and visualizing under ultraviolet (UV) light. NMR spectra were run on a Bruker spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C in dimethyl sulfoxide (DMSO)-d_6 containing tetramethylsilane as an internal standard. A Waters ACQUITY ultra performance liquid chromatography (UPLC) instrument coupled to a Waters triple quadrupole (TQD) mass spectrometer [electrospray ionization (ESI) tandem quadrupole] was used. Elemental analysis was carried out on a Perkin-Elmer 2400 CHN analyzer.

Starting compounds 1–4

The synthesis and properties of 6-hydroxy-2-methyl-9*H*-xanthen-9-one (**2**) [19], 3-hydroxy-5-methyl-9*H*-xanthen-9-one (**3**) [20] and 3-chloro-5-hydroxy-9*H*-xanthen-9-one (**4**) [21] have been published previously. The synthesis of compound **1** followed a published procedure [18] in which 2-[(9-oxo-9*H*-xanthen-4-yl)methyl]isothiouronium bromide [17] (30 mmol) was heated with 150 mL of 10% NaOH solution for 20 min. 4-(Sulfanylmethyl)-9*H*-xanthen-9-one (**1**) precipitated after the addition of 10% HCl solution (160 mL) and was crystallized from ethanol: yield 68%; mp 151–152°C; ESI-MS: *m/z* 242.97 ($C_{14}H_{10}O_2S + H^+$).

Acetic acid derivatives 5–7

A mixture of compound **1–3** (15 mmol), an aqueous solution of NaOH (5%, 16 mL) and an aqueous solution of sodium chloroacetate (5%, 47 mL) was heated under reflux for 1 h, then cooled and acidified with hydrochloric acid (10%). The resultant precipitate of **5–7** was crystallized from ethanol.

Propionic acid derivatives 8–10

A mixture of **2** or **4** (15 mmol), ethyl 2-bromopropanoate (45 mmol) and K_2CO_3 (45 mmol) in dimethylformamide (DMF) (60 mL) was stirred at 70–75°C for 4 h. Then, the mixture was poured into cold water and the resultant precipitate of ethyl ester was filtered off and washed with water. In the next step, the ester was subjected to alkaline hydrolysis in 100 mL solution of 10% NaOH at 70°C. After cooling, the solution was acidified with 15% HCl and the resultant precipitate was filtered off, washed with water, dried and crystallized from ethanol to give pure carboxylic acid **8** or **9**. Compound **9** (20 mmol) was converted into methyl 2-[(7-methyl-9-oxo-9*H*-xanthen-3-yl)oxy]propanoate, yield 76%, mp 139–141°C, by the reaction with methanol (50 mL) in the presence of a catalytic amount of concentrated H_2SO_4. This ester was subjected to ammonolysis in the mixture of methanol (30 mL) and concentrated ammonium hydroxide (60 mL). The resultant amide **10** was crystallized from toluene/hexane (3:1).

2-Methylpropanoic acid derivatives 11 and 12

A mixture of **1** or **2** (20 mmol) and NaOH (100 mmol) in 60 mL of acetone/chloroform (25 mmol) was heated under reflux for 6 h and then concentrated, and the residue was treated with water. After acidification with 10% HCl, the resultant precipitate of **11** or **12** was filtered off and crystallized from ethanol.

{[(9-Oxo-9*H*-xanthen-4-yl)methyl]sulfanyl}acetic acid (5) Yellow crystals; yield 65%; mp 164–166°C; ^{1}H NMR: δ 8.18 (dd, 1H, $J = 8$ Hz, $J = 2$ Hz), 8.1 (dd, 1H, $J = 8$ Hz, $J = 2$ Hz), 7.89 (ddd, 1H, $J = 8$ Hz, $J = 7$ Hz, $J = 2$ Hz), 7.81 (dd, 1H, $J = 7$ Hz, $J = 2$ Hz), 7.70 (dd, 1H, $J = 8$ Hz, $J = 1$ Hz), 7.48 (ddd, 1H, $J = 8$ Hz, $J = 7$ Hz, $J = 1$ Hz), 7.43 (t, 1H, $J = 7$ Hz), 4.16 (s, 2H), 3.24 (s, 2H); ESI-MS: *m/z* 301.03 ($C_{16}H_{12}O_4S + H^+$); purity by LC/MS: 100%. Anal. Calcd for $C_{16}H_{12}O_4S$: C, 63.99; H, 4.03; S, 10.68. Found: C, 64.00; H, 4.05; S, 10.38.

[(2-Methyl-9-oxo-9*H*-xanthen-6-yl)oxy]acetic acid (6) White crystals; yield 70%; mp 244–246°C; ^{1}H NMR: δ 8.08 (d, 1H, $J = 9$ Hz), 7.93 (d, 1H, $J = 2$ Hz), 7.63 (dd, 1H, $J = 9$ Hz, $J = 2$ Hz), 7.50 (d, 1H, $J = 9$ Hz), 7.08 (d, 1H, $J = 2$ Hz), 7.04 (dd, 1H, $J = 9$ Hz, $J = 2$ Hz), 4.88 (s, 2H), 2.41 (s, 3H); ESI-MS: *m/z* 285.04 ($C_{16}H_{12}O_5 + H^+$); purity by LC/MS: 100%. Anal. Calcd for $C_{16}H_{12}O_5$: C, 67.60; H, 4.25. Found: C, 67.63; H, 4.29.

[(5-Methyl-9-oxo-9*H*-xanthen-3-yl)oxy]acetic acid (7) White crystals; yield 61%; mp 208–209°C; ^{1}H NMR: δ 8.07 (d, 1H, $J = 9$ Hz), 7.98 (d, 1H, $J = 8$ Hz), 7.68 (dd, 1H, $J = 7$ Hz, $J = 2$ Hz), 7.32 (t, 1H, $J = 8$ Hz), 7.15 (d, 1H, $J = 2$ Hz), 7.05 (dd, 1H, $J = 9$ Hz, $J = 2$ Hz), 4.91 (s, 2H), 2.50 (s, 3H); ESI-MS: *m/z* 285.06 ($C_{16}H_{12}O_5 + H^+$); purity by LC/MS: 99.2%. Anal. Calcd for $C_{16}H_{12}O_5$: C, 67.60; H, 4.25. Found: C, 67.94; H, 4.27.

2-[(3-Chloro-9-oxo-9*H*-xanthen5-yl)oxy]propanoic acid (8) White crystals; yield 58%; mp 223–225°C; ^{1}H NMR: δ 8.17 (d, 1H, $J = 9$ Hz), 7.88 (d, 1H, $J = 2$ Hz), 7.72 (t, 1H, $J = 9$ Hz), 7.53 (dd, 1H, $J = 9$ Hz, $J = 2$ Hz), 7.36 (m, 2H), 1.63 (d, 3H, $J = 7$ Hz), C<u>H</u>-CH_3 – overlapped with DMSO signal; ^{13}C NMR: δ 175.6, 172.9, 155.9, 147.0, 146.3, 140.2, 128.2, 125.5, 124.6, 122.6, 120.2, 119.2, 118.7, 117.7, 73.4, 18.7; ESI-MS: *m/z* 319.00 ($C_{16}H_{11}ClO_5 + H^+$); purity by LC/MS: 99.04%. Anal. Calcd for $C_{16}H_{11}ClO_5$: C, 60.29; H, 3.48. Found: C, 60.12; H, 3.61.

Carboxylic acid 9 This compound was characterized previously [23].

2-[(2-Methyl-9-oxo-9*H*-xanthen-6-yl)oxy]propanamide (10) White crystals; yield 56%; mp 230–232°C; ^{1}H NMR: δ 8.09 (d, 1H, *J* = 9 Hz), 7.94 (d, 1H, *J* = 1 Hz), 7.65 (dd, 2H, *J* = 9 Hz, *J* = 2 Hz), 7.54 (m, 1H), 7.33 (1H, s), 7.02 (m, 2H), 4.86 (m, 1H), 2.42 (s, 3H), 1.49 (d, 3H, *J* = 7 Hz); ESI-MS: *m/z* 298.06 ($C_{17}H_{15}NO_4 + H^+$): 298.31; purity by LC/MS: 100%. Anal. Calcd for $C_{17}H_{15}NO_4$: C, 68.67; H, 5.08; N, 4.70. Found: C, 68.65; H, 4.87; N, 4.76.

2-Methyl-2-{[(9-oxo-9*H*-xanthen-4-yl)methyl]sulfanyl}propanoic acid (11) Yellow crystals; yield 35%; mp 143–145°C; ^{1}H NMR: *δ* 8.18 (H, 1H, dd, *J* = 8 Hz, *J* = 2 Hz), 8.09 (dd, 1H, *J* = 8 Hz, *J* = 2 Hz), 7.9 (ddd, 1H, *J* = 8 Hz, *J* = 7 Hz, *J* = 2 Hz), 7.83 (dd, 1H, *J* = 7 Hz, *J* = 2 Hz), 7.68 (d, 1H, *J* = 8 Hz, H-5), 7.49 (t, 1H, *J* = 2 Hz), 7.4 (t, 1H, *J* = 8 Hz), 4.2 (s, 2H), 1.49 (s, 6H); ESI-MS: *m/z* 329.03 ($C_{18}H_{16}O_4S + H^+$); purity by LC/MS: 99.00%. Anal. Calcd for $C_{18}H_{16}O_4S$: C, 65.84; H, 4.91; S, 9.76. Found: C, 65.87; H, 4.8; S, 9.85.

Carboxylic acid 12 This compound was characterized previously [23].

Experimental animals

The animals were provided by the Animal Breeding Farm of the Jagiellonian University, Medical College, Faculty of Pharmacy, Krakow. Male albino Wistar rats, weighing between 150 and 250 g, were used. Treatment of laboratory animals was in full accordance with the Polish and European regulations and was approved by the Local Ethics Committees (Decision No 129/2014).

Anti-inflammatory activity by carrageenan-induced rat paw edema method

In order to produce inflammation, 0.1 mL of 1% carrageenan solution in water was injected into the hind paw sub-plantar tissue of rats, according to the previously described method [24, 32, 33]. The development of paw edema was measured and the edema inhibition was calculated as described in the already mentioned references.

Analgesic activity test

The analgesic activity of the tested compounds was measured using the previously described method [25, 32]. Four hours after administration of the compounds, the pain threshold in the hind paw of rat affected by inflammation was measured using an analgesimeter. The mean pain thresholds were calculated for treated and control groups and the percentage change in relation to the control was determined.

Irritant action on the gastric mucosa according to Komatsu

The ulcerogenic effect of the tested compounds was determined using previously described methodologies [26, 32, 33]. Twenty-four hours after the administration of the compounds, the rats were sacrificed. The mucosa of the glandular part of the stomach was inspected using a binocular microscope with a 10-fold magnification. The mucosal lesions were evaluated using the five-point scale: 0 – no lesion, 1 – erythema, 2 – punctiform ulcer, 3 – small ulcer, 4 – large ulcer, 5 – perforation.

In vitro metabolic stability

The metabolic stabilities of selected compounds were measured by incubation with rat liver microsomes using a procedure described previously by Kubowicz and co-workers [30]. The test compound (20 μM final concentration) was preincubated with rat liver microsomes (0.4 mg/mL) in 0.1 M phosphate buffer, pH 7.4, at 37°C followed by the addition of reduced nicotinamide adenine dinucleotide phosphate-regenerating system. After incubation at 37°C for 15, 30 and 60 min, the reactions were terminated and an internal standard was added. All experiments were performed in duplicates. *In vitro* $t_{1/2}$ and Cl_{int} of the studied compounds were determined according to the literature procedure [34].

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