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Short communication

Synthesis and pharmacological activity of 2-oxo-(2*H*) 1-benzopyran-3-carboxamide derivatives

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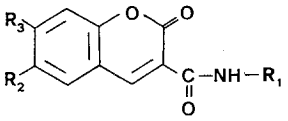
Summary — Continuing our research on the synthesis and biological activity of heterocyclic compounds synthesized by carbon suboxide, we prepared and screened some 2-oxo (2*H*) 1-benzopyran-3-carboxamide derivatives. The results of pharmacological assays are reported and discussed.

2-oxo-(2*H*) 1-benzopyran-3-carboxamide derivatives / diuretic activity / analgesic activity / myorelaxant activity

Introduction

Though coumarin derivatives are oxygenated heterocycles of known anticoagulant activity [1], a preliminary test revealed that some of these substances, which had been previously synthesized [2], showed an unexpected diuretic activity (unpublished results).

Continuing the study on this type of structure we varied the nature and position of the substituents in order to assess the pharmacological characteristics of the coumarin derivatives.

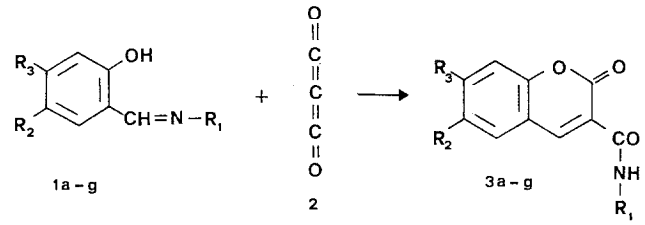


a: $R_1 = C_6H_5$; $R_2 = H$; $R_3 = H$
b: $R_1 = p\text{-}CH_3\text{-}C_6H_4$; $R_2 = H$; $R_3 = H$
c: $R_1 = p\text{-}OCH_3\text{-}C_6H_4$; $R_2 = H$; $R_3 = H$
d: $R_1 = C_6H_5$; $R_2 = H$; $R_3 = CH_3$
e: $R_1 = C_6H_5$; $R_2 = CH_3$; $R_3 = H$
f: $R_1 = p\text{-}CF_3\text{-}C_6H_4$; $R_2 = H$; $R_3 = H$
g: $R_1 = -CH_2\text{-}C_6H_5$; $R_2 = H$; $R_3 = H$

Chemistry

The *N*-substituted 2-oxo-(2*H*) 1-benzopyran-3-carboxamide derivatives (**3a–g**) were synthesized by reacting equimolecular amounts of the azomethines (**1a–g**) with carbon suboxide **2**.

The reaction is reported in scheme 1. The IR and ^{1}H-NMR data were in agreement with the literature



Scheme 1.

data [2] for compounds **3a–c** and with the assigned structures for compounds **3d–g** (table I).

Pharmacological results and discussion

The tested compounds exhibit an interesting diuretic activity. In fact, as shown in table II the compounds **3c**, **3d** and **3f** showed good activity, compound **3f** being the best. The test conducted to evaluate ulcerogenic effects indicated that mice treated with a dose of 50 mg/kg/po did not show any gastric lesions 6 h after the administration.

The compounds showed good analgesic activity in the acetic acid writhing test. Only compound **3f** showed lower activity than indomethacin, while the other compounds exhibited higher analgesic activity. It is interesting to note that these compounds show

Table I. Analytical and spectroscopic data of 2*H*, 1-benzopyran-3-carboxamide-2-oxo derivatives **3a–g**.

Comp	*Yield (%)*	*mp (°C)*	*Formula*	*IR (cm^{-1})*	*^{1}H-NMR ($CDCl_3$) (δ) ppm*	*Lit*
3a	68	245	$C_{16}H_{11}NO_3$	3280(NH) 1720(CO) 1660(CO)	10.18(s, 1H, NH D_2O exch) 8.95(s, 1H, CH=), 7.75–7.19 (m, 9H, arom)	[2]
3b	75	235	$C_{17}H_{13}NO_3$	3280(NH) 1715(CO) 1660(CO)	10.19(s, 1H, NH D_2O exch) 8.94(s, 1H, CH=), 7.76–7.15 (m, 8H, arom), 2.28(s, 3H, CH_3)	[2]
3c	70	215	$C_{17}H_{13}NO_4$	3290(NH) 1720(CO) 1660(CO)	10.18(s, 1H, NH D_2O exch) 8.94(s, 1H, CH=), 7.76–6.63 (m, 8H, arom), 3.75(s, 3H, OCH_3)	[2]
3d	59	230	$C_{17}H_{13}NO_3$	3230(NH) 1710(CO) 1650(CO)	10.62 (s, 1H, NH D_2O exch) 8.70(s, 1H, CH=), 7.72–7.10 (m, 8H, arom), 2.27(s, 3H, CH_3)	
3e	73	176	$C_{17}H_{13}NO_3$	3200(NH) 1705(CO) 1660(CO)	10.80(s, 1H, NH D_2O exch) 8.89(s, 1H, CH=), 7.68–7.06 (m, 8H, arom), 2.38(s, 3H, CH_3)	
3f	48	291	$C_{17}H_{10}F_3NO_3$	3250(NH) 1720(CO) 1650(CO)	10.45(s, 1H, NH D_2O exch) 8.98(s, 1H, CH=), 7.72–6.90 (m, 8H, arom)	
3g	83	146	$C_{17}H_{13}NO_3$	3320(NH) 1720(CO) 1660(CO)	10.18(s, 1H, NH D_2O exch) 8.89(s, 1H, CH=), 7.78–7.16 (m, 9H, arom), 4.63(d, 2H, CH_2-C_6H_5)	

Table II. Diuretic activity.

Compd	*Dose (mg/kg)*	*Urine excretion (ml/24 h)*
Control	–	4 ± 0.7
3a	50	8 ± 0.4
3b	50	8 ± 0.63
3c	50	14 ± 1.13
3d	50	11 ± 1.20
3e	50	3 ± 0.28
3f	50	15 ± 0.84
3g	50	6 ± 0.88
HCTZ[a]	10	9 ± 0.7

[a]Hydrochlorothiazide. Experiments were performed on groups of 6 mice.

activity in the same writhing test where also the non steroidal anti-inflammatory drugs are active, and do not produce any gastric lesions (table III).

All compounds screened increased the performance in the rotarod test and only compound **3c** at a dose of 50 mg/kg decreased the persistence time on the rotary axis (table IV).

In conclusion, the tested compounds showed different types of activities, the most important being analgesic activity. Moreover, some compounds whose activity was similar to hydrochlorothiazide showed diuretic activity.

Experimental protocols

Chemistry

All melting points were obtained on a Kofler apparatus and are uncorrected. The IR spectra were recorded on a Perkin–Elmer 1310 spectrophotometer using KBr mulls. The ^{1}H-NMR spectra were recorded on a Varian Unit 300 using tetramethylsilane as internal standard. Elemental analyses were carried out on a Carlo–Erba 1016 Elemental Analyzer. Reagent-grade commercially available reagents and solvents were used. Literature

Table III. Analgesic activity.

Compd	*Dose (mg/kg)*	*No of contractions (20 min obs)*	*Inhibition (%)*
Control	–	45 ± 4	
3a	5	22 ± 2	50.3*
	50	23 ± 5	49*
3b	5	22 ± 3	50*
	50	19 ± 5	57*
3c	5	9 ± 5	80*
	50	17 ± 6	61*
3d	5	20 ± 2	55*
	50	40 ± 3	11*
3e	5	18 ± 4	60*
	50	23 ± 5	49*
3f	5	25 ± 3	45*
	50	19 ± 5	58*
3g	5	13 ± 3	72*
	50	10 ± 4	77*
INDO[a]	5	22 ± 4	50.3*

[a]Indomethacin; *significant at $P < 0.05$; experiments were performed on groups of 6 mice.

procedures were followed in the preparation of carbon suboxide [3] and azomethines [4, 5].

*General procedure for the synthesis of 2-oxo-(2H) 1-benzopyran-3-carboxamide derivatives **3a–g***

Carbon suboxide **2** (16 mM) was added over 1 h at –70 °C to a stirred solution of **1a–g** (16 mM) in anhydrous diethyl ether (250 ml). At completion the mixture was stirred at 0°C for 5 h and kept at room temperature for 48 h under stirring. The precipitate was filtered and crystallized from ethanol to give **3 a–g** as needle-shaped yellow crystals. The analytical and spectroscopic data for compounds **3a–g** are reported in table I.

Pharmacology

Diuretic activity

Experiments were performed on male Swiss mice (20–25 g bw), randomly divided into groups of 6, after 16 h of fasting with free access to water.

The reference drug (hydrochlorothiazide) and the drugs under trial were administered only once by gavage at 50 mg/kg in 5 ml/kg of 10% gum arabic at T_0. The control group received saline only. The animals were kept in single metabolic cages for urine collection for the 24 h following drug administration.

Means and standard errors were also calculated and the difference between means was tested for significance according to the Student's *t*-test.

Analgesic activity

The acetic acid writhing test was used. Groups of 6 mice were injected intraperitoneally with 0.05% acetic acid solution (0.5 ml/mice) 1 h after the administration of the test compounds (5–50 mg/kg). The writhing movements of each

Table IV. Myorelaxant activity.

Compd	*Dose (mg/kg)*	*Time of permanence*[a]			
		30	*Var%*	*60*	*Var%*
Control	–	200 ± 6	–	227 ± 111	–
3a	5	212 ± 10	+ 6	218 ± 9	+ 9
	50	220 ± 15	+ 10	292 ± 12	+46*
3b	5	230 ± 8	+ 15	364 ± 10	+ 82*
	50	297 ± 12	+ 48	563 ± 7	+ 181*
3c	5	260 ± 9	+ 30	286 ± 9	+ 43*
	50	122 ± 7	– 36	102 ± 12	– 49*
3d	5	206 ± 11	+ 3	218 ± 11	+ 9
	50	298 ± 15	+ 49	328 ± 9	+ 64*
3e	5	186 ± 12	– 7	238 ± 10	+ 19
	50	226 ± 13	+ 13	254 ± 9	+ 27
3f	5	228 ± 9	+ 14	252 ± 15	+ 26
	50	268 ± 11	+ 34	324 ± 13	+ 62*
3g	5	178 ± 11	– 11	160 ± 15	– 20
	50	266 ± 15	+ 33	256 ± 11	+ 28
AMPH[b]	1	395 ± 15	+ 97.5	624 ± 18	+ 174

[a]Persistence time on the rotary axis in s ± SE at 2 different times of treatment and variance; % in comparison to control; [b]amphetamine sulfate; *significant at $P < 0.05$; experiments were performed on groups of 6 mice.

animal were counted for 20 min (from the 5th to the 25th min after injection of irritant). The analgesic effect of the test compounds was expressed as protection percentage compared to the control group.

Ulcerogenic activity
The experiments were performed in rats according to Domenjoz [6]. The compounds were administered orally (50 mg/kg) to groups of 4 mice, fasting for 24 h, and after 2 h the treatment was repeated. Six h after the first dose, the animals were killed by ether inhalation, their stomachs removed and examined with a dissecting microscope. The severity of mucosal damage (ulcerogenic index) was rated by means of scores from 0–4. The following arbitrary scale was used for the evaluation of the ulcers: 0 = no lesion; 1 = haemorrhagic suffusion; 2 = from 1–5 erosions; 3 = from 6–10 erosions; 4 = 1 wide erosion (> 1 mm) or many small erosions.

Myorelaxant activity
Myorelaxant activity was evaluated using the rotarod test in mice treated orally with the drugs under trial. The mice were placed on the rotary axis 90 and 120 min after drug administration.

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