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Short communication

Synthesis and anti-inflammatory activity of *N*-(aza)arylcarboxamides derived from Trolox®

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Abstract – A series of 6-(aza)arylmethoxychroman-2-carboxamides **22–38**, derived from Trolox® or 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid, was prepared using two strategies, i.e. phenol blockade was carried out before or after amidification. These compounds were evaluated against peripheral inflammation by a carrageenin-induced foot-pad edema test. A permanent blockade of the phenol function by arylmethoxy groupings, in particular by the quinolylmethoxy moiety, was generally detrimental to activity; only the 6-benzyloxy and quinolylmethoxy derivatives **22** and **31** exhibited significant inhibition (58.3 and 97.1%) after oral administration of 0.4 mmol kg^{-1}. Among their 6-acetoxy or 6-hydroxy precursors **12–21**, evaluated at 0.4 and 0.1 mmol kg^{-1}, the *N*-(4-pyridyl) chromancarboxamides **15** and **20** exerted the highest inhibitory activity. Their ID_{50} were 14.7 ± 5.5 mg kg^{-1} and 14.7 ± 4.5 mg kg^{-1}, respectively. © Elsevier, Paris

Trolox® (derivatives of) / 6-quinolylmethoxy-2,5,7,8-tetramethylchroman-2-carboxamides / 4-aminopyridine (amide derivative) / anti-inflammatory activity

1. Introduction

Vitamin E or tocopherol is a potent antioxidant which acts as a free radical chain breaker. The generation of reactive oxygen species is involved in the pathophysiology of various disease processes including inflammation, ischaemia, reperfusion injury, neoplasia and ageing. Moreover, it has been shown that tocopherol reduces rat platelet phospholipase A2 (PLA2) activity [1] and exhibits substantial 5-lipoxygenase (5-LO) inhibitory activity [2], providing a beneficial effect against inflammation and platelet aggregation. Scott et al. [3] have determined that the side chain is not necessary for activity and that 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (Trolox®) is more active than tocopherol as an antioxidant.

5-LO is one of the major enzymes involved in the arachidonic acid cascade, leading to the formation of leukotrienes which are implicated in the pathology of various diseases such as asthma, rheumatoid arthritis, inflammatory bowel disease, psoriasis, stroke and coronary reperfusion injury [4]. Pharmacological and clinical results suggest that a blockade of the leukotriene cascade could be of therapeutic benefit in the treatment of inflammatory diseases [5–7]. Extensive efforts to develop 5-LO inhibitors have led notably to the incorporation of an aralkoxy and especially (2-quinolyl)methoxy moieties into different anti-inflammatory templates. However, the prototypes of these leukotriene biosynthesis inhibitors, REV 5901 [8, 9] and WY-47,288 [10], lack the arylalkanoic acid chain present in most of them, e.g. WY-50,295 tromethamine [8], BAY-X-1005 [9], A-81834 [10] and MK-0591 [9] (see *figure 1*).

We have previously described the synthesis of *N*-phenylcarboxamides of Trolox®, which act as leucotriene B_4 (LTB_4) biosynthesis inhibitors at subnanomolar concentrations [11]. The presence of a phenolic group in these compounds led us to seek access to the corresponding aralkyl ethers. Simultaneous pharmaco-

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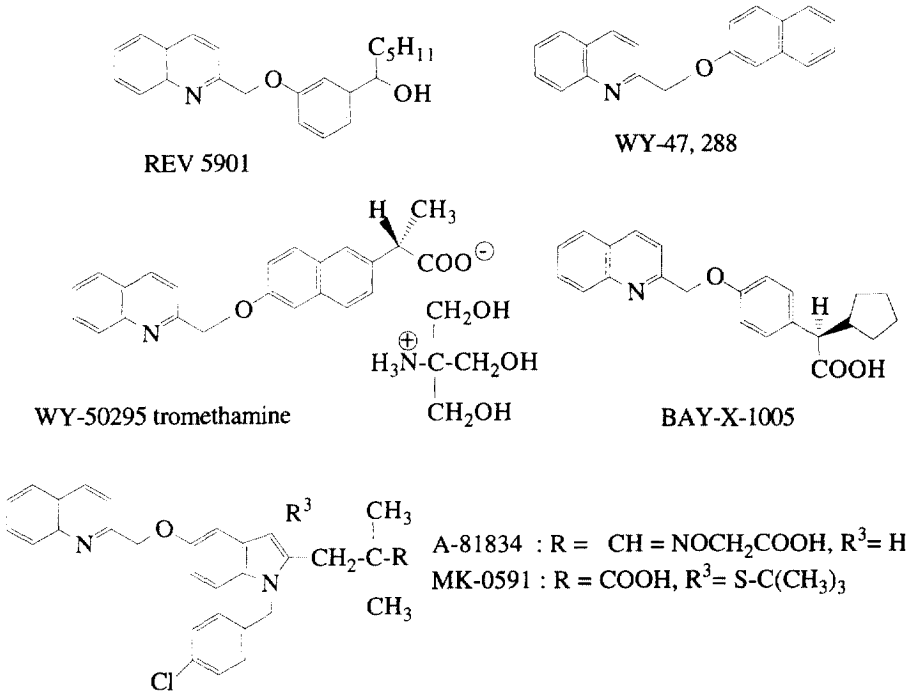


Figure 1.

modulation at the level of the amidic function was carried out by replacing the phenyl moiety with pyridyl or *N*-arylpiperazinyl fragments. These compounds were evaluated for their oral anti-inflammatory activity by determining their inhibitory effect in rat-paw edema. The pharmacological results indicated that 6-aryl(heteroaryl)methoxy substituted carboxamides I were inactive or moderately active. Conversely, two N(4-pyridyl)carboxamides (V) with a 6-hydroxy (**20**) or 6-acetoxy (**15**) substituent were found to display potent inhibitory effects.

2. Chemistry

The two synthetic routes to targeting 6-(aza)aralkylchroman-2-carboxamides I are outlined in *figure 2*. After metallation of the phenolic group of ester **2** by NaH, aralkylation was better achieved in DMF than in DMSO: 61% instead of 35% for **6** (method B). It was possible to increase the yield to 80% by using K_2CO_3/acetone in the presence of a catalytic amount of Cs_2CO_3 (method C): compounds **6** and **7**. After alkaline hydrolysis, acids III: **8–11** were activated via acid chloride (method E), imidazolide [12] (method F), or acyloxypyridinium salt [13] (method G), affording amides I: **22**, **23**, **25**, **27**, **29** and **35** in yields ranging from 65 to 99%. With method G, a marked increase in yield (from 46 to 81% for **25**) was observed in the presence of two equivalents of the condensed amine.

In an alternate sequence, amides I were obtained directly from Trolox **1** by method F (compound **17**), or after acetylation of the phenolic group to **3** by method F, or by formation of a mixed anhydride using phenyl dichlorophosphate [14] (method I), leading to compounds IV. Alkaline hydrolysis of IV gave 6-hydroxychroman-2-carboxamides V which were converted into the corresponding (aza)aralkyl ethers by the previously described methods B and C or by method K using Cs_2CO_3 in refluxing CH_3CN. Compounds I: **24**, **26**, **28**, **30–34**, **36–38** were obtained in this manner with good overall yields The physicochemical characteristics of the newly synthesized compounds are reported in *tables I–V*.

3. Pharmacology

6-Benzyloxy and (chloro)quinolylmethoxy-*N*-substituted-chroman-2-carboxamides **22–26** and **27–38** derived from Trolox® were tested on carrageenin-induced rat paw edema by the oral route using two doses, 0.4 and 0.1 mmol kg^{-1} (*table VI*). Among the

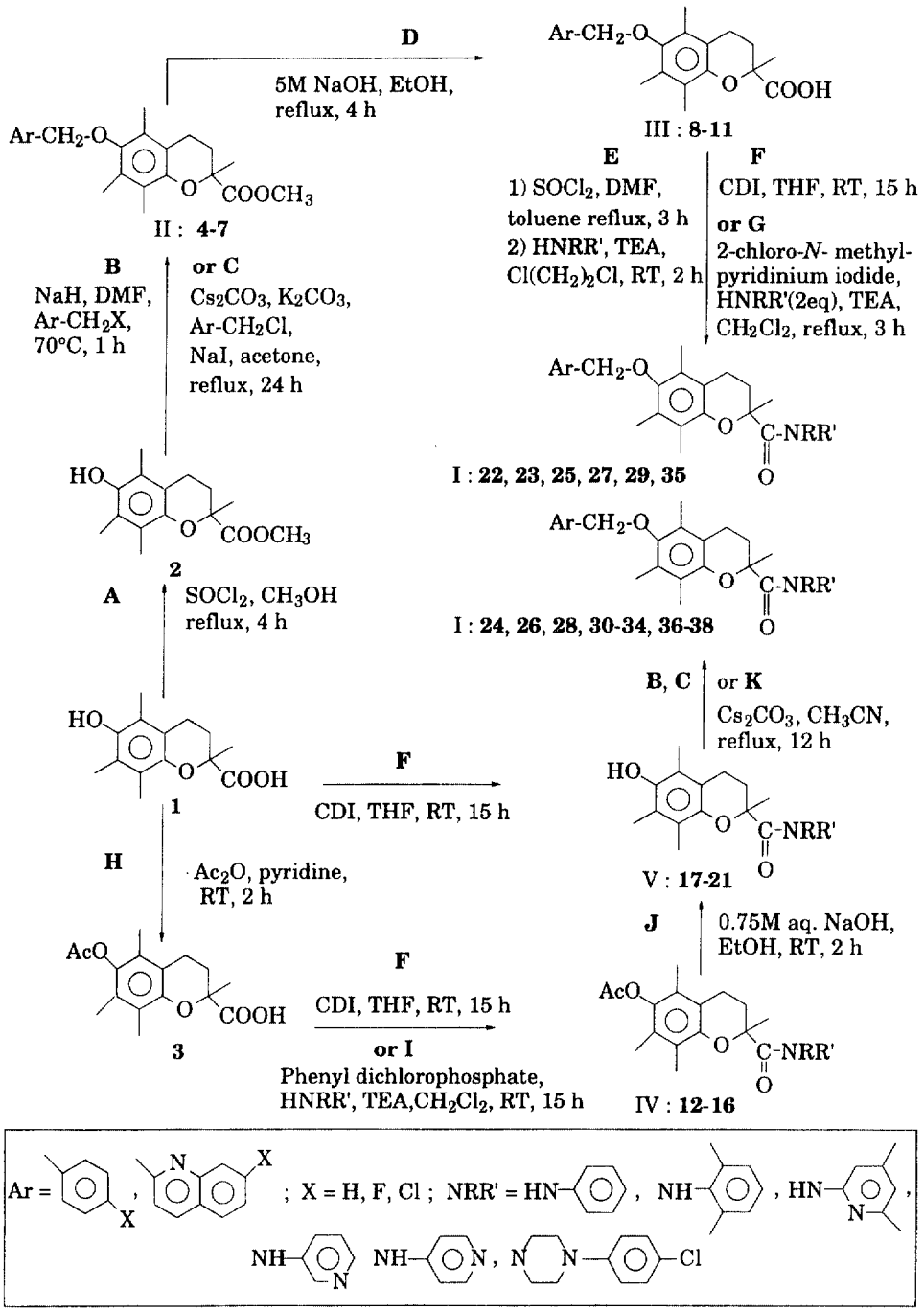
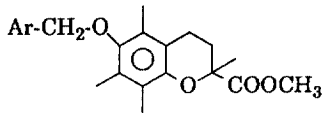


Figure 2.

six 6-benzyloxy derivatives, only benzyloxycarboxamide **22** exhibited significant inhibition (58.3%) at 0.4 mmol kg^{-1}. In the 6-(chloro)quinolylmethoxy subseries, the three *N*-(2-, 3- and 4-pyridyl)-6-quinolylmethoxychroman-2-carboxamides **29**, **30** and **31** induced 26.3, 35.6 and 97.1% inhibition, respectively, at the same dose. The higher potency of **31**, tested at 0.1 mmol kg^{-1}, prompted us to investigate the activity of 3- and 4-pyridyl precursors incorporating a labile ester or a free hydroxyl group, at 0.4 and 0.1 mmol

Table I. Physical properties of methyl 6-(aza)arylmethoxychroman-2-carboxylates II.



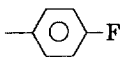
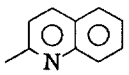
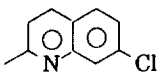
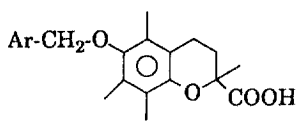
Compound	Ar	Molecular formula M_r	Method Yield (%)	Mp (°C) Diisopr. ether
4		$C_{22}H_{26}O_4$ 354.45	B: 76	75
5		$C_{22}H_{25}FO_4$ 372.44	B: 85	76
6		$C_{14}H_{27}NO_4$ 405.50	B: 61 C: 77	oil
7		$C_{25}H_{26}ClNO_4$ 439.94	C: 80	115

Table II. Physical properties of 6-(aza)arylmethoxychroman-2-carboxylic acids III.



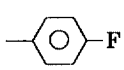
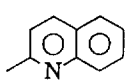
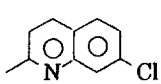
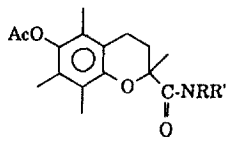
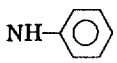
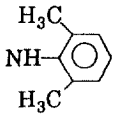
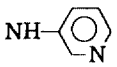
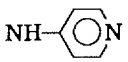
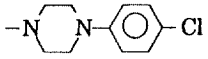
Compound	Ar	Molecular formula M_r	Method D Yield (%)	Mp (°C) Diisopr. ether
8		$C_{21}H_{24}O_4$ 340.42	82	145
9		$C_{21}H_{23}FO_4$ 358.41	81	146
10		$C_{14}H_{25}NO_4$ 391.47	85	168
11		$C_{24}H_{24}ClNO$ 425.92	80	> 250

Table III. Physical properties of *N*-substituted-6-acetoxychroman-2-carboxamides IV.



Compound	NRR'	Molecular formula M_r	Method Yield (%)	Mp (°C) Diisopr. ether
12		$C_{22}H_{25}NO_4$ 367.42	I: 66	97
13		$C_{24}H_{29}NO_4$ 395.50	F: 62 I: 43	131
14		$C_{11}H_{24}N_2O_4$ 368.44	I: 77	157–159
15		$C_{21}H_{24}N_2O_4$ 368.44	I: 87	165
16		$C_{26}H_{31}ClN_2O_4$ 435.55	F: 70 I: 63	142–143

kg^{-1}. In the **3**-pyridyl subseries, only acetate **14** elicited moderate activity (40% inhibition) at 0.4 mmol kg^{-1}, whereas phenol **19** was inactive. Conversely, in the 4-pyridyl subseries, phenol **20** and the corresponding acetate **15** exerted a potent inhibitory effect at 0.4 and 0.1 mmol kg^{-1}, which was still significant at 0.05 mmol kg^{-1}. Their ID_{50}, under the same experimental conditions, were 14.7 ± 5.5 mg kg^{-1} and 14.7 ± 4.5 mg kg^{-1}, respectively. Their equipotence may have resulted from the easy bioconversion of ester (**15**) into phenol (**20**).

Since the lack of anti-edema activity of 6-quinolylmetoxychromancarboxamides could have been related to their poor oral bioavailability, we are currently testing them in the TPA-induced mouse ear-swelling model. We have recently demonstrated that analogous *N*-pyridinylaryl(alkyl)carboxamides [17] are topically active on single and multiple phorbol ester models considered to be relevant models of skin inflammatory diseases such as psoriasis (J.M. Robert, manuscript in preparation).

4. Experimental protocols

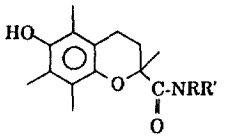
4.1. Chemistry

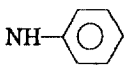
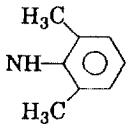
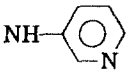
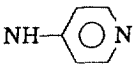
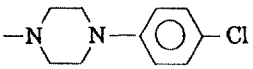
Melting points, as determined on a Tottoli-Büchi apparatus, are uncorrected. The structures of the described products were confirmed by IR, ^{1}H-NMR and microanalytical data. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer. The compounds were prepared as KBr pellets or as a film on NaCl plates. ^{1}H-NMR spectra were recorded on a Bruker AC 250 spectrometer (250 MHz), using $CDCl_3$ and DMSO-d_6 as solvents. Chemical shifts (δ) are reported in parts per million (ppm). Microanalyses performed on a Perkin Elmer CHN 240 apparatus indicated that the symbols of the elements were within ± 0.4% of theoretical values. Analytical TLC was performed on precoated silica gel aluminium plates (0.2 mm, GF 254, Merck). Spots were located by UV illumination. Silica gel 60 (Merck; 70–230 mesh) was used for column chromatography.

4.1.1. Method A: Methyl 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylate 2

Thionyl chloride (11 mL, 150 mmol) was added dropwise to stirred dry methanol (111 mL, 274 mmol) cooled at 0 °C. Trolox (20 g, 79.58 mmol) was added portionwise. The solu-

Table IV. Physical properties of *N*-substituted-6-hydroxychroman-2-carboxamides V.



Compound	NRR'	Molecular formula M_r	Method Yield (%)	Mp (°C) Diisopr. ether
17		$C_{20}H_{23}NO_3$ 325.41	F: 76 J: 86	93
18		$C_{22}H_{27}NO_3$ 353.46	J: 97	154
19		$C_{19}H_{22}N_2O_3$ 326.40	J: 95	149–151
20		$C_{19}H_{22}N_2O_3$ 326.40	J: 96	220
21		$C_{24}H_{29}ClN_2O_3$ 428.96	J: 93	143

tion was refluxed under stirring for 4 h and cooled to room temperature. The formed precipitate was collected by filtration, washed with methanol and recrystallized from diisopropyl ether.

Yield: 99.7%; m.p.: 135 °C (diisopr. ether); IR (KBr) cm^{-1}: 3527 (νOH); 1745 (νC=O); 1250 (νC–O–C_{as} ester and ether); 1193 (νC–O–C_s ester); 1090 (νC–O–C_s ether); ^{1}H-NMR ($CDCl_3$) δ ppm: 1.61 (s, 3H, 2-CH_3); 1.87 (m, 1H, H^3); 2.07 (s, 3H, CH_3); 2.17 (s, 3H, CH_3), 2.19 (s, 3H, CH_3); 2.50 (m, 3H, $H^{3'}$, H^4, $H^{4'}$); 3.68 (s, 3H, OCH_3); 4.29 (s, 1H, OH). Anal. $C_{15}H_{20}O_4$ (C, H).

4.1.2. Method B: Methyl 6-benzyloxy-2,5,7,8-tetramethylchroman-2-carboxylate ***4***

Sodium hydride (60% dispersion oil, 0.70 g, 17.70 mmol), washed with dry toluene, was added portionwise to a suspension of **2** (4 g, 15.15 mmol) in dry DMF (200 mL). After stirring for 20 min at room temperature, benzyl bromide (1.91 mL, 16.10 mmol) was added dropwise. The mixture was strirred at 70 °C for 1 h, then cooled to room temperature. The excess of NaH was removed by dropwise addition of water (10 mL). The mixture was then evaporated in vacuo to a small volume, poured onto ice and extracted with CH_2Cl_2. The combined extracts were washed with water, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (CH_2Cl_2) to give 4.06 g of pure product.

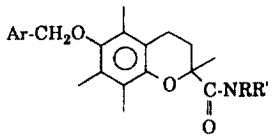
Yield: 76%, m.p.: 75 °C (diisopr. ether); IR (KBr) cm^{-1}: 1745 (νC=O); 1250 (νC–O–C_{as} ester and ether); 1195 (νC–O–C_s ester), 1085 (νC–O–C_s ether); ^{1}H-NMR ($CDCl_3$) δ ppm: 1.63 (s, 3H, 2-CH_3); 1.89 (m, 1H, H^3); 2.14 (s, 3H, CH_3); 2.19 (s, 3H, CH_3); 2.24 (s, 3H, CH_3); 2.54 (m, 3H, $H^{3'}$, H^4, $H^{4'}$); 3.70 (s, 3H, OCH_3); 4.70 (s, 2H, CH_2O); 7.34–7.52 (m, $5H_{ar}$). Anal. $C_{20}H_{26}O_4$ (C, H).

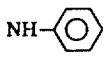
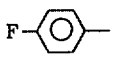
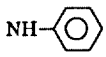
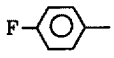
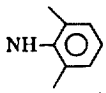
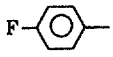
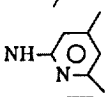
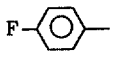
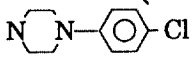
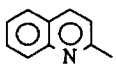
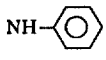
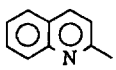
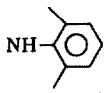
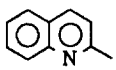
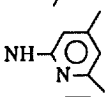
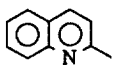
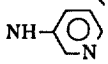
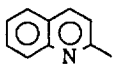
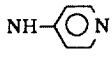
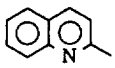
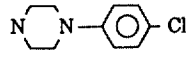
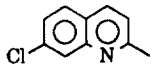
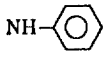
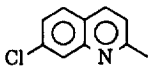
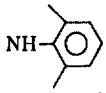
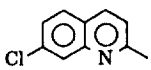
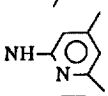
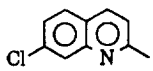
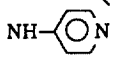
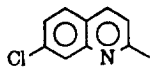
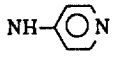
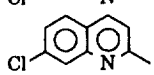
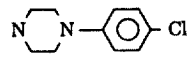
4.1.3. Method C: Methyl 6-[(7-chloro-2-quinolyl)methoxy]-2,5,7,8-tetramethylchroman-2-carboxylate ***7***

A mixture of **2** (1.55 g, 5.85 mmol), 2-bromomethyl-7-chloroquinoline (1.43 g, 5.7 mmol), potassium carbonate (0.89 g, 6.50 mmol), cesium carbonate (0.37 g, 1.15 mmol) and sodium iodide (0.18 g, 1.30 mmol) in dry acetone (20 mL) was refluxed for 24 h. The suspension was then cooled to room temperature, poured onto water and extracted with EtOAc. The combined extracts were washed with 1 M aqueous NaOH, with brine and dried (Na_2SO_4). Evaporation of solvent, followed by flash chromatography (CH_2Cl_2), afforded **7** as a white solid.

Yield: 80%, m.p.: 115 °C (diisopr. ether); IR (KBr) cm^{-1}: 1747 (νC=O); 1615 (νC=N); 1256 (νC–O–C_{as} ester and ether); 1194 (νC–O–C_s ester); 1090 (νC–O–C_s ether); ^{1}H-NMR ($CDCl_3$) δ ppm: 1.63 (s, 3H, 2-CH_3); 1.90 (m, 1H, H^3); 2.15 (s, 3H, CH_3); 2.20 (s, 3H, CH_3); 2.25 (s, 3H, CH_3); 2.55 (m, 3H, $H^{3'}$, H^4, $H^{4'}$); 3.70 (s, 3H, OCH_3); 4.99 (s, 2H, CH_2O); 7.5 (dd, 1H, H^6q, J = 8.7 Hz, J' = 1.9 Hz); 7.79 (d, 1H, H^5q, J = 8.7 Hz); 7.91 (d, 1H, H^3q, J = 8.5 Hz); 8.08 (d, 1H, H^8q, J = 1.9 Hz); 8.23 (d, 1H, H^4q, J = 8.5 Hz). Anal. $C_{25}H_{26}NO_4Cl$ (C, H, N).

Table V. Physical properties of *N*-(aza)aryl-6-(aza)arylmethoxychroman-2-carboxamides I.



Compound	Ar	NRR"	Molecular formula M_r	Method Yield (%)	Mp (°C) solvent
22			$C_{27}H_{29}NO_3$ 415.54	E: 75 F: 91	oil
23			$C_{27}H_{28}FNO_3$ 433.53	E: 60 F: 79	oil
24			$C_{29}H_{32}FNO_3$ 461.58	B: 76	153[b]
25			$C_{28}H_{31}FN_2O_3$ 462.57	G: 81	114[b]
26			$C_{31}H_{34}FClN_2O_3$ 537.08	B: 80	oil
27			$C_{30}H_{30}N_2O_3$ 466.59	E: 82 F: 99	oil
28			$C_{32}H_{34}N_2O_3$ 494.64	B: 55	185[b]
29			$C_{31}H_{33}N_3O_3$ 495.63	G: 79	152[b]
30			$C_{29}H_{29}N_3O_3$ 467.57	K: 75	203–205[b]
31			$C_{29}H_{29}N_3O_3$ 467.57	K: 80	108[a]
32			$C_{34}H_{36}ClN_3O_3$ 570.14	B: 64 C: 48	75[a]
33			$C_{30}H_{29}ClN_2O_3$ 487.02	C: 67	105–107[a]
34			$C_{32}H_{33}ClN_2O_3$ 529.08	C: 72	104–106[a]
35			$C_{31}H_{32}ClN_3O_3$ 530.07	G: 72	80[a]
36			$C_{29}H_{28}ClN_3O_3$ 502.01	K: 76	126[a]
37			$C_{29}H_{28}ClN_3O_3$ 502.01	K: 77	115[a]
38			$C_{34}H_{35}Cl_2N_3O_3$ 604.58	C: 94	138–140[a]

Crystallization solvent: [a]diisopropyl ether; [b]petroleum ether.

Table VI. Anti-inflammatory activity of *N*-(aza)arylchroman-2-carboxamides.

Compound	Carrageenin-induced rat-paw edema inhibition%, after oral administration of the test compound at (mmol kg^{-1})		
	0.4	0.1	0.05
14	40.0 ± 10.9	NA[a]	
15	82.5 ± 6.5	83.1 ± 3.5	75.5 ± 3.5
19	NA	NA	
20	96.1 ± 3.9	80.2 ± 6.3	64.1 ± 4.4
22	58.3 ± 6.2	19.1 ± 4.6	
23	38.6 ± 4.3	NA	
25	NA	NA	
29	26.3 ± 10.6	NA	
30	35.6 ± 6.2	NA	
31	97.1 ± 2.9	24.7 ± 5.8	
35	NA	NA	
36	NA	NA	
37	NA	NA	
Indomethacin, at 10 mg kg^{-1} (0.28 mmol kg^{-1})	53.6 ± 2.1		

[a]NA: no activity; **14**: 34.5 ± 5.8 at 0.2 mmol kg^{-1}.

4.1.4. Method D: 6-Benzyloxy-2,5,7,8-tetramethylchroman-2-carboxylic acid ***8***

A mixture of **4** (1.43 g, 4.05 mmol), ethanol (100 mL) and 5 M aqueous NaOH (6.3 mL, 31.5 mmol) was heated at 90 °C under stirring for 4 h. The solvent was evaporated in vacuo, and water (40 mL) was added to the residue. The aqueous layer was acidified with 1 M aqueous HCl, and the precipitate was then filtered off, washed with cold water and dried in vacuo over P_2O_5, to give 1.13 g of pure product.

Yield: 82%, m.p.: 145 °C (diisopr. ether); IR (KBr) cm^{-1}: 3200–2500 (νOH); 1720 (νC=O); 1250 (νC–O–C_{ar}); 1085 (νC–O–C_s); ^{1}H-NMR ($CDCl_3$) δ ppm: 1.63 (s, 3H, 2-CH_3); 1.94 (m, 1H, H^3); 2.16 (s, 3H, CH_3); 2.18 (s, 3H, CH_3); 2.24 (s, 3H, CH_3); 2.41 (m, 1H, $H^{3'}$); 2.66 (m, 2H, H^4, $H^{4'}$); 4.70 (s, 2H, CH_2O); 7.35–7.50 (m, $5H_{ar}$). Anal. $C_{21}H_{24}O_4$ (C, H).

4.1.5. Method E: N-Phenyl-6-benzyloxy-2,5,7,8-tetramethylchroman-2-carboxamide ***12***

Thionyl chloride (0.27 mL, 3.72 mmol) and three drops of DMF were added to a solution of **8** (0.85 g, 2.5 mmol) in dry toluene (10 mL). The mixture was refluxed for 3 h and cooled to room temperature. Solvent and excess thionyl chloride were evaporated in vacuo. The acid chloride was dissolved in 1,2-dichloroethane (7 mL) and added dropwise to a solution of aniline (0.23 mL, 2.5 mmol) and triethylamine (1.04 mL, 7.5 mmol) in 1,2-dichloroethane (5 mL). After stirring at room temperature for 2 h, the solvent was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 and washed first with 10% aqueous $NaHCO_3$ and then with water. The organic layer, when dried (Na_2SO_4) and evaporated, gave an oily residue which was purified by column chromatography (CH_2Cl_2/EtOH, 95: 5), yielding 0.75 g of **12** as a yellow oil.

Yield: 75%; IR (KBr) cm^{-1}: 3400 (νNH); 1690 (νC=O); 1520 (δNH); 1250 (comb. NH/CN); ^{1}H-NMR ($CDCl_3$) δ ppm: 1.54 (s, 3H, 2-CH_3); 1.93 (m, 1H, H, H^3); 2.07 (s, 3H, CH_3); 2.18 (s, 3H, CH_3); 2.19 (s, 3H, CH_3); 2.35 (m, 1H, $H^{3'}$); 2.57 (m, 2H, H^4, $H^{4'}$); 4.26 (s, 2H, CH_2O); 7.01 (m, $1H_{ar}$); 7.23–7.35 (m, 5H, $PhCH_2O$); 7.38–7.44 (m, $4H_{ar}$); 8.26 (broad s, 1H, NH). Anal. $C_{27}H_{29}NO_3$ (C, H, N).

4.1.6. Method F: N-Phenyl-6-benzyloxy-2,5,7,8-tetramethylchroman-2-carboxamide ***12***

N,N'-Carbonyldiimidazole (0.57 g, 3.55 mmol) was added portionwise to a solution of **8** (0.85 g, 2.50 mmol) in dry THF. After stirring for 1 h at room temperature, aniline (0.35 mL, 3.80 mmol) was added, and the resulting mixture was stirred at room temperature overnight. The solvent was evaporated in vacuo, and the residue was dissolved in CH_2Cl_2, washed with water, dried (Na_2SO_4) and purified by column chromatography (CH_2Cl_2) to give **12** as a yellow oil.

Yield: 91%; IR, ^{1}H-NMR: See *Method E*.

4.1.7. Method G: N-(4,6-Dimethyl-2-pyridyl)-6-parafluorobenzyloxy-2,5,7,8-tetramethylchroman-2-carboxamide ***25***

A solution of **9** (1 g, 2.8 mmol), 6-amino-2,4-lutidine (0.68 g, 5.6 mmol), triethylamine (0.21 mL, 1.51 mmol) and 2-chloro-1-methylpyridinium iodide (0.86 g, 3.36 mmol) in dry CH_2Cl_2 (20 mL) was refluxed for 2.5 h. The solvent was evaporated, and the residue was purified by column chromatography (CH_2Cl_2/EtOH, 97.5: 2.5) to give 1.05 g of **25**.

Yield: 81%, m.p.: 114 °C (petroleum ether); IR (KBr) cm^{-1}: 3405 (νNH); 1680 (νC=O); 1520 (δNH); 1215 (νC–O–C); 1250 (comb NH/CN); ^{1}H-NMR ($CDCl_3$) δ ppm: 1.61 (s, 3H, 2-CH_3); 1.99 (m, 1H, H^3); 2.14 (s, 3H, CH_3); 2.18 (s, 3H, CH_3); 2.21 (s, 3H, CH_3); 2.32 (s, 3H, CH_{3pyr}); 2.40 (s, 3H, CH_{3pyr}); 2.44 (m, 1H, $H^{3'}$); 2.66 (m, 2H, H^4, $H^{4'}$); 4.66 (s, 2H, CH_2O); 6.74 (s, 1H, $H^5{}_{pyr}$); 7.01 (m, $1H_{ar}$); 7.07 (dd, 2H, $H^3{}_{ar}$, $H^5{}_{ar}$, J_{HH} = J_{HF} = 8.7 Hz); 7.44 (dd, 2H, $H^3{}_{ar}$, $H^6{}_{ar}$, J_{HH} = 8.7 Hz, J_{HF} = 5.5 Hz); 7.9 (s, 1H, $H^3{}_{pyr}$); 8.80 (broad s, 1H, NH); Anal. $C_{28}H_{31}N_2O_3$ (C, H, N).

4.1.8. Method H: 6-Acetoxy-2,5,7,8-tetramethylchroman-2-carboxylic acid ***3***

This acetate **3** was prepared by acetylation of Trolox® with acetic anhydride in pyridine according to [3].

Yield: 94%, m.p.: 139–141 °C (diisopr. ether) lit. [3]: 140 °C; Anal. $C_{16}H_{20}O_5$ (C, H).

4.1.9. Method I: N-(4-Pyridyl)-6-acetoxy-2,5,7,8-tetramethylchroman-2-carboxamide ***15***

A suspension of **3** (2 g, 6.85 mmol), triethylamine (2.85 mL, 20.52 mmol) and 4-aminopyridine (0.66 g, 6.85 mmol) in dry CH_2Cl_2 (17 mL) was cooled to 0 °C. Phenyl dichlorophosphate (1.02 mL, 6.85 mmol) was then added dropwise. The mixture was stirred at room temperature overnight and washed twice with water and once with 5% aqueous $NaHCO_3$. The organic layer was then dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (CH_2Cl_2/EtOH, 97.5:2.5) to give 2.6 g of **15** as a translucent oil which was recrystallized from diisopropyl ether as a white solid.

Yield: 87.3%, m.p.: 165 °C (diisopr. ether); IR (KBr) cm^{-1}: 3326 (νNH); 1757 (νC=O ester); 1680 (νC=O amide); 1528 (δNH); 1253 (comb NH/CN); ^{1}H-NMR ($CDCl_3$) δ ppm: 1.56 (s, 3H, 2-CH_3); 1.90 (m, 1H, H^3); 1.95 (s, 3H, CH_3); 2.04 (s, 3H, CH_3); 2.22 (s, 3H, CH_3); 2.29 (s, 3H, CH_3); 2.37 (m, 1H, $H^{3'}$); 2.61 (m, 2H, H^4, $H^{4'}$); 7.43 (d, 2H, H^3_{pyr}, H^5_{pyr}, J = 5 Hz); 8.44 (d, 2H, H^2_{pyr}, H^6_{pyr}, J = 5 Hz); 8.58 (broad s, 1H, NH); Anal. $C_{21}H_{24}N_2O_4$ (C, H, N).

4.1.10. Method J: N-(2,6-Dimethylphenyl)-6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxamide ***18***

The acetate **13** (4 g, 10.10 mmol) in EtOH (50 mL) was stirred in 2 M aqueous NaOH (31 mL) under N_2 at room temperature for 2 h. Water was then added, and the mixture was acidified using aqueous 1 M CH_3COOH. The product was extracted with CH_2Cl_2, and the organic layer was washed with water, dried (Na_2SO_4) and evaporated. The solid residue was recrystallized from diisopropyl ether to afford 3.5 g of a beige powder.

Yield: 97%, m.p.: 154 °C (diisopr. ether); IR (KBr) cm^{-1}: 3420 (νOH); 3300 (νNH); 1662 (νC=O); 1521 (δNH); 1120 (comb NH/CN); ^{1}H-NMR ($CDCl_3$) δ ppm: 1.70 (s, 3H, 2-CH_3); 1.93 (m, 1H, H^3); 2.00 (s, 6H, 2 CH_{3ar}); 2.11 (s, 3H, CH_3); 2.19 (s, 3H, CH_3); 2.24 (s, 3H, CH_3); 2.53 (m, 1H, $H^{3'}$); 2.68 (m, 2H, H^4, $H^{4'}$); 4.39 (s, 1H, OH); 7.01–7.11 (m, 3H, H_{ar}); 7.69 (s, 1H, NH); Anal. $C_{22}H_{27}NO_3$ (C, H, N).

4.1.11. Method K: N-(4-Pyridyl)-6-[(2-quinolyl)methoxy]-2,5,7,8-tetramethylchroman-2-carboxamide ***31***

A mixture of **20** (1 g, 3.06 mmol), 2-chloromethylquinoline (1.09 g, 6.13 mmol) and cesium carbonate (1.22 g, 3.75 mmol) in dry acetonitrile (21 mL) was refluxed for 12 h. Water was then added, and the product was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and evaporated. The residue was purified twice by column chromatography: first by CH_2Cl_2/EtOH, 97.5:2.5 and then by AcOEt, to give 1.15 g of a brown solid.

Yield: 80%, m.p.: 108 °C (diisopr. ether); IR (KBr) cm^{-1}: 3325 (νNH); 1675 (νC=O); 1510 (δNH); 1605 (νC=N); 1250 (νC–O–C and comb NH/CN); ^{1}H-NMR ($CDCl_3$) δ ppm: 1.63 (s, 3H, 2-CH_3); 2.06 (m, 1H, H^3); 2.20 (s, 3H, CH_3); 2.29 (s, 6H, 2 CH_3); 2.41 (m, 1H, $H^{3'}$); 2.67 (m, 2H, H^4, $H^{4'}$); 5.02 (s, 2H, CH_2O); 7.46 (d, 2H, H^3_{pyr}, H^5_{pyr}, J = 6.2 Hz); 7.56 (dd, 1H, H^{6}q, J = J' = 8.5 Hz); 7.73 (dd, 1H, H^{7}q, J = J' = 8.5 Hz); 7.86 (d, 1H, H^{5}q, J = 8.5 Hz); 7.89 (d, 1H, H^{3}q, J = 8.3 Hz); 8.07 (d, 1H, H^{8}q, J = 8.5 Hz); 8.26 (d, 1H, H^{4}q, J = 8.3 Hz); 8.49 (broad s, 1H, NH); 8.59 (d, 2H, H^2_{pyr}, H^6_{pyr}, J = 6.2 Hz); Anal. $C_{29}H_{30}N_2O_3$ (C, H, N).

4.1.12. Method L: 2-Bromomethyl-7-chloroquinoline ***40***

2-Bromomethyl-7-chloroquinoline was prepared by bromination of 7-chloroquinaldine with NBS in the presence of benzoyl peroxide in refluxing benzene according to [15].

Yield: 41%; m.p.: 110 °C (hexane), lit. [16]: 112 °C; IR (KBr) cm^{-1}: 1609, 1591 (νC=C, νC=N); 614 (νC–Br); ^{1}H-NMR ($CDCl_3$) δ ppm: 4.7 (s, 2H, CH_2); 7.48 (d, 1H, H^3, J = 8.5 Hz); 7.67 (d, 1H, H^5, J = 8.7 Hz); 7.76 (dd, 1H, H^6, J = 8.7 Hz, J' = 2.5 Hz); 7.99 (d, 1H, H^8, J = 2.5 Hz); 8.06 (d, 1H, H^4, J = 8.5 Hz).

4.2. Pharmacology

Anti-inflammatory activity against carrageenin-induced rat-paw edema was assayed in adult male Wistar CF rats weighing 180–220 g according to the method of Winter et al. [16], with slight modification. The drugs were orally administered 1 h before injection of 0.05 mL of a 1% suspension of carrageenin in saline into subcutaneous tissues of one hind paw. The other hind paw was injected with 0.05 mL of a saline solution. Rats were fasted 24 h before the experiment, and water (1.5 mL/100 g body weight) was orally administered twice (20 h and 4 h) before injections. The volumes of both hind paws of control and treated animals were measured with a plethysmograph 3 h after injection. Rats were kept in the same experimental conditions.

The percentage of inhibition of the inflammatory reaction was determined for each animal by comparison with controls and calculated by the formula $I(\%) = 100 \times (1 - dt/dc)$ where dt is the difference in paw volume in the drug-treated group and dc the difference in paw volume in the control group. Data are expressed as mean ± SE.

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