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Synthesis of Bridged Isoflavone Derivatives

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Summary. 7-Chloroalkoxyisoflavones (**10–26**) have been prepared by chemoselective-in the case of 5,7-dihydroxyisoflavones also regioselective-alkylation of hydroxyisoflavones (**3–9**) with α-bromo-ω-chloroalkanes. Compounds **10–26** were allowed to react either with 2′,4′-dihydroxy-3′-*n*-propylacetophenone (**1**) or with 2-ethoxycarbonyl-7-hydroxy-8-*n*-propylchromone (**2**) to afford bridged isoflavone derivatives **27–51** with methylene spacers of various length. Carboxylic acid ethyl esters **43–51** have been saponified to obtain the carboxylic acids **52–60**.

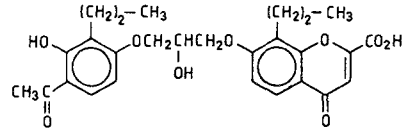
Keywords. 2-Carboxychromone derivatives; 7-Chloroalkoxyisoflavones; 7-Hydroxyisoflavones; ^{1}H NMR spectroscopy.

Darstellung überbrückter Isoflavonderivate

Zusammenfassung. Die chemoselektive und bei den 5,7-Dihydroxyisoflavonen auch regioselektive Alkylierung von Hydroxyisoflavonen **3** bis **9** mit α-Brom-ω-chloralkanen ergibt 7-Chloralkoxyisoflavone **10** bis **26**. Die Umsetzung des 2′,4′-Dihydroxy-3′-*n*-propylacetophenons und 2-Ethoxycarbonyl-7-hydroxy-8-*n*-propylchromons mit den Verbindungen **10** bis **26** liefert die überbrückten Isoflavone **27** bis **51** mit einem Methylen-Spacer verschiedener Länge. Die Verseifung der Ester **43** bis **51** führt zu den Carbonsäuren **52** bis **60**.

Introduction

The slow reacting substance of anaphylaxis (SRS-A) was recognized as early as 1940 [1]. Later, it was detected that SRS-A was comprised of products from the lipoxygenase pathway of the arachidonic acid cascade, the peptidyl leukotrienes [2]. It has also turned out that the leukotrienes are key mediators of various hypersensitivity reactions [3]. A key development of this field was the discovery of the FPL 55712, a relatively selective receptor antagonist for SRS-A. Its poor bioavailability and short half-life were, however, disadvantageous properties to become a widely used medicine. Nevertheless, this compound directed the attention to the synthetic



FPL 55712

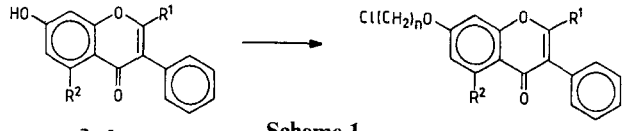
leukotriene receptor antagonists and its structural elements; 2′,4′-dihydroxy-3′-*n*-propylacetophenone and chromone-2-carboxylic acid derivatives became important building blocks of synthetic leukotriene receptor antagosists [4–14]. The acetophenone unit was incorporated into carboxylic acids [5, 6, 9], tetrazol derivatives [7, 8, 14], and benzopyran type compounds [10, 11, 13] as well. In the present paper the syntheses of isoflavone derivatives, as potential leukotriene receptor antagonists, possessing either 2′,4′-dihydroxy-3′-*n*-propylacetophenone or a chromone-2-carboxylic acid unit, are reported.

Results and Discussion

Early studies with synthetic leukotriene receptor antagonists revealed that a chromone moiety may be a beneficial structural unit of these complex molecules. Since 3-phenylchromones (isoflavones) and 2,3-diphenylchromones (2-phenylisoflavones) have not yet been utilized for such purpose, it seemed expedient to synthesize bridged isoflavone derivatives with potential leukotriene receptor antagonist activity.

Hydroxyisoflavones (**3–9**) used as starting materials were synthesized according to known procedures [15, 16, 18–20]. According to literature [21], the length of the spacer between the two major parts of such a molecule may influence its bioactivity. For this reason, we planned to insert methylene spacers of various length into the bridged isoflavone derivatives. In our case, the spacer may be built onto either major part of the planned bridged molecule to obtain an appropriate intermediate for the coupling reaction. After some preliminary experiments, we found it to be useful to build the spacer onto the isoflavone moiety.

Hydroxyisoflavones (**3–9**) were allowed to react with α-bromo-ω-chloroalkanes in boiling acetone solution in the presence of K_2CO_3 to afford 7-chloroalkoxyisoflavones **10–26** (Scheme 1, Table 1). At this temperature, we managed to perform a chemoselective alkylation with the α-bromo-ω-chloroalkanes to obtain 7-chloroalkoxyisoflavones (**10–26**) as useful alkylating agents for the coupling reactions.



3 - 9 **Scheme 1** 10 - 26

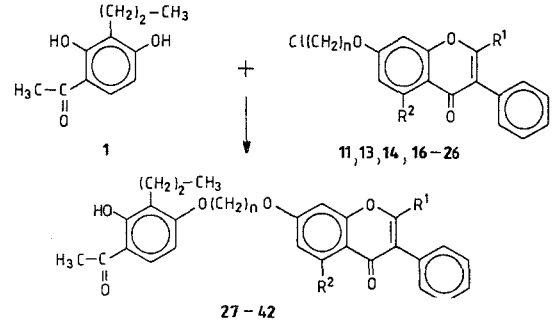
3:	$R^1 = R^2 = H$	**15**:	$R^1 = CH_3$, $R^2 = H$, n = 4
4:	$R^1 = CH_3$, $R^2 = H$	**16**:	$R^1 = CH_3$, $R^2 = OH$, n = 2
5:	$R^1 = CH_3$, $R^2 = OH$	**17**:	$R^1 = CH_3$, $R^2 = OH$, n = 3
6:	$R^1 = CO_2C_2H_5$, $R^2 = H$	**18**:	$R^1 = CH_3$, $R^2 = OH$, n = 4
7:	$R^1 = CO_2C_2H_5$, $R^2 = OH$	**19**:	$R^1 = CO_2C_2H_5$, $R^2 = H$, n = 3
8:	$R^1 = C_6H_5$, $R^2 = H$	**20**:	$R^1 = CO_2C_2H_5$, $R^2 = OH$, n = 3
9:	$R^1 = C_6H_5$, $R^2 = OH$	**21**:	$R^1 = C_6H_5$, $R^2 = H$, n = 2
10:	$R^1 = R^2 = H$, n = 2	**22**:	$R^1 = C_6H_5$, $R^2 = H$, n = 3
11:	$R^1 = R^2 = H$, n = 3	**23**:	$R^1 = C_6H_5$, $R^2 = H$, n = 4
12:	$R^1 = R^2 = H$, n = 4	**24**:	$R^1 = C_6H_5$, $R^2 = OH$, n = 2
13:	$R^1 = CH_3$, $R^2 = H$, n = 2	**25**:	$R^1 = C_6H_5$, $R^2 = OH$, n = 3
14:	$R^1 = CH_3$, $R^2 = H$, n = 3	**26**:	$R^1 = C_6H_5$, $R^2 = OH$, n = 4

Table 1. Physical constants and IR data of compounds **10–26**

Compound	M.p. (°C)	Yield (%)	Molecular formula[a]	$\nu_{C=O}$ (cm^{-1})
10	198–199	60.2	$C_{17}H_{13}ClO_3$	1632
11	147–148	70.6	$C_{18}H_{15}ClO_3$	1634
12	154–155	83.6	$C_{19}H_{17}ClO_3$	1632
13	116–117	72.3	$C_{18}H_{15}ClO_3$	1632
14	126–127	60.9	$C_{19}H_{17}ClO_3$	1632
15	112–113	65.6	$C_{20}H_{19}ClO_3$	1632
16	161–162	51.5	$C_{18}H_{15}ClO_4$	1658
17	149–150	87.2	$C_{19}H_{17}ClO_4$	1660
18	128–129	83.8	$C_{20}H_{19}ClO_4$	1662
19	136–137	71.2	$C_{21}H_{19}ClO_5$	1626
20	84–85	59.2	$C_{21}H_{19}ClO_6$	1664
21	157–158	65.0	$C_{21}H_{17}ClO_3$	1624
22	154–155	58.9	$C_{24}H_{19}ClO_3$	1628
23	144–145	68.3	$C_{25}H_{21}ClO_3$	1630
24	137–138	64.1	$C_{23}H_{17}ClO_4$	1654
25	133–134	81.3	$C_{24}H_{19}ClO_4$	1658
26	132–133	59.3	$C_{25}H_{21}ClO_4$	1662

[a] Elemental analyses (C, H) were in good agreement with calculated values

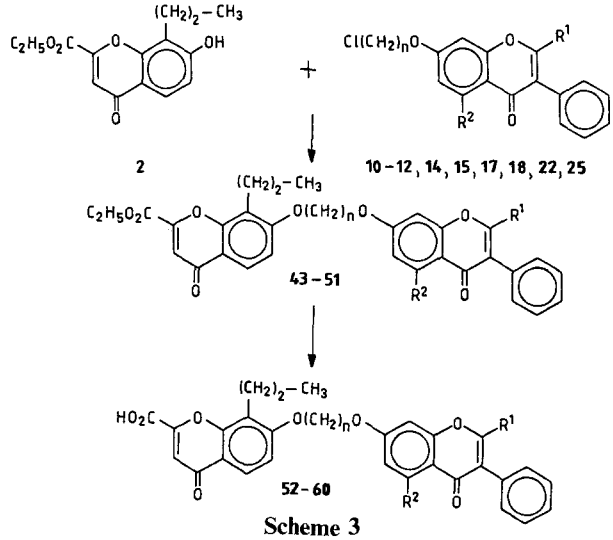
7-Choroalkoxyisoflavones (**10–26**) were allowed to react with 2′,4′-dihydroxy-3′-*n*-propylacetophenone (**1**) [17] in boiling 4-methyl-2-pentanon solution in the presence of KI and K_2CO_3 to yield 7-[ω-(4-acetyl-3-hydroxy-2-*n*-propylphenoxy) alkoxy]-isoflavones **27–40**. Ethyl esters **33** and **34** have been saponified to afford carboxylic acids **41** and **42**.



Scheme 2

27: $R^1 = R^2 = H, n = 3$
28: $R^1 = CH_3, R^2 = H, n = 2$
29: $R^1 = CH_3, R^2 = H, n = 3$
30: $R^1 = CH_3, R^2 = OH, n = 2$
31: $R^1 = CH_3, R^2 = OH, n = 3$
32: $R^1 = CH_3, R^2 = OH, n = 4$
33: $R^1 = CO_2C_2H_5, R^2 = H, n = 3$
34: $R^1 = CO_2C_2H_5, R^2 = OH, n = 3$
35: $R^1 = C_6H_5, R^2 = H, n = 2$
36: $R^1 = C_6H_5, R^2 = H, n = 3$
37: $R^1 = C_6H_5, R^2 = H, n = 4$
38: $R^1 = C_6H_5, R^2 = OH, n = 2$
39: $R^1 = C_6H_5, R^2 = OH, n = 3$
40: $R^1 = C_6H_5, R^2 = OH, n = 4$
41: $R^1 = CO_2H, R^2 = H, n = 3$
42: $R^1 = CO_2H, R^2 = H, n = 3$

Reaction of 7-chloroalkoxyisoflavones **10–26** with 2-ethoxy-carbonyl-7-8-*n*-propylchromone (**2**) [4] under reaction conditions described for the preparation of compounds **27–40** afforded ethyl esters of chromone-2-carboxylic acid related to isoflavones (**43–51**). Ethyl esters **43–51** have been saponified to obtain compounds **52–60** (Scheme 3).



Scheme 3

43, 52: $R^1 = R^2 = H$, n = 2
44, 53: $R^1 = R^2 = H$, n = 3
45, 54: $R^1 = R^2 = H$, n = 4
46, 55: $R^1 = CH_3$, $R^2 = H$, n = 3
47, 56: $R^1 = CH_3$, $R^2 = H$, n = 4
48, 57: $R^1 = CH_3$, $R^2 = OH$, n = 3
49, 58: $R^1 = CH_3$, $R^2 = OH$, n = 4
50, 59: $R^1 = C_6H_5$, $R^2 = H$, n = 3
51, 60: $R^1 = C_6H_5$, $R^2 = OH$, n = 3

Table 2. Physical constants of compounds **27–60**

Compound	M.p. (°C)	Yield (%)	Molecular formula[a]	Compound	M.p. (°C)	Yield (%)	Molecular formula[a]
27	97–99	46.6	$C_{29}H_{28}O_6$	**44**	131–132	63.0	$C_{33}H_{30}O_8$
28	162–163	53.3	$C_{29}H_{28}O_6$	**45**	168–169	59.8	$C_{34}H_{32}O_8$
29	141–142	45.2	$C_{30}H_{30}O_6$	**46**	108–109	55.4	$C_{34}H_{32}O_8$
30	234–235	54.0	$C_{29}H_{28}O_7$	**47**	130–131	65.3	$C_{35}H_{34}O_8$
31	160–161	61.8	$C_{30}H_{30}O_7$	**48**	131–132	45.4	$C_{34}H_{32}O_9$
32	97–98	74.2	$C_{31}H_{32}O_7$	**49**	133–134	40.9	$C_{35}H_{34}O_9$
33	101–102	48.5	$C_{32}H_{32}O_8$	**50**	158–159	62.5	$C_{39}H_{34}O_8$
34	152–154	60.6	$C_{32}H_{32}O_9$	**51**	169–170	61.8	$C_{39}H_{34}O_9$
35	171–172	57.1	$C_{34}H_{30}O_6$	**52**	210–211	75.0	$C_{30}H_{24}O_8$
36	162–163	76.6	$C_{35}H_{32}O_6$	**53**	127–128	84.2	$C_{31}H_{26}O_8$
37	131–132	46.4	$C_{36}H_{34}O_6$	**54**	158–159	81.2	$C_{32}H_{28}O_8$
38	174–175	58.5	$C_{34}H_{30}O_7$	**55**	233–234	85.7	$C_{32}H_{28}O_8$
39	187–188	64.3	$C_{35}H_{32}O_7$	**56**	211–212	84.5	$C_{33}H_{30}O_8$
40	120–121	72.9	$C_{36}H_{34}O_7$	**57**	260–261	70.2	$C_{32}H_{28}O_9$
41	148–149	76.6	$C_{30}H_{28}O_8$	**58**	210–212	85.7	$C_{33}H_{30}O_9$
42	113–114	71.4	$C_{30}H_{28}O_9$	**59**	153–155	73.7	$C_{37}H_{30}O_8$
43	123–124	65.2	$C_{32}H_{28}O_8$	**60**	135–136	83.3	$C_{37}H_{30}O_8$

[a] Elemental analyses (C, H) were in good agreement with calculated values

Table 3. ^{1}H-NMR spectroscopic data of compounds **27–60**

Compound	δ(ppm)
27	0.95 (t, 3H), 1.54 (dd, 2H), 2.36 (dd, 2H), 2.56 (s, 3H), 2.65 (t, 2H), 4.25 (m, 4H), 6.46–8.22 (m, 10 arom. H), 7.94 (s, 1H)
28	0.89 (t, 3H), 1.56 (dd, 2H), 2.31 (s, 3H), 2.60 (s, 3H), 2.65 (t, 2H), 4.48 (m, 4H), 6.50–8.22 (m, 10 arom. H)
29	0.96 (t, 3H), 1.56 (dd, 2H), 2.28 (s, 3H), 2.46 (t, 2H), 2.57 (s, 3H), 2.64 (t, 2H), 4.27 (m, 4H), 6.48–8.14 (m, 10 arom. H)
30	0.91 (t, 3H), 1.54 (dd, 2H), 2.32 (s, 3H), 2.58 (s, 3H), 2.66 (t, 2H), 4.41 (m, 4H), 6.37–7.63 (m, 9 arom. H)
31	0.94 (t, 3H), 1.54 (dd, 2H), 2.27 (s, 3H), 2.34 (t, 2H), 2.55 (s, 3H), 2.66 (t, 2H), 4.27 (m, 4H), 6.36–7.62 (m, 9 arom. H)
32	0.98 (t, 3H), 1.55 (dd, 2H), 2.04 (m, 4H), 2.30 (s, 3H), 2.53 (s, 3H), 2.63 (t, 2H), 4.10 (m, 4H), 6.35–7.62 (m, 9 arom. H)
33	0.98 (t, 6H), 1.54 (dd, 2H), 2.38 (t, 2H), 2.60 (s, 3H), 2.68 (t, 2H), 4.14 (dd, 2H), 4.26 (m, 4H), 6.39–7.65 (m, 10 arom. H)
34	1.00 (t, 6H), 1.56 (dd, 2H), 2.38 (t, 2H), 2.61 (s, 3H), 2.68 (t, 2H), 4.14 (t, 2H), 4.26 (m, 4H), 6.41–7.65 (m, 9 arom. H)
35	0.91 (t, 3H), 1.55 (dd, 2H), 2.58 (s, 3H), 2.66 (t, 2H), 4.43 (m, 4H), 6.51–8.22 (m, 15 arom. H)
36	0.94 (t, 3H), 1.54 (dd, 2H), 2.38 (t, 2H), 2.55 (s, 3H), 2.66 (t, 2H), 4.27 (m, 4H), 6.46–8.22 (m, 15 arom. H)
37	0.96 (s, 3H), 1.56 (dd, 2H), 2.07 (m, 4H), 2.56 (s, 3H), 2.67 (t, 2H), 4.16 (m, 4H), 6.44–8.20 (m, 15 arom. H)
38	0.92 (t, 3H), 1.52 (dd, 2H), 2.57 (s, 3H), 2.66 (t, 2H), 4.41 (m, 4H), 6.42–7.62 (m, 14 arom. H)
39	0.96 (t, 3H), 1.54 (dd, 2H), 2.32 (t, 2H), 2.56 (s, 3H), 2.64 (t, 2H), 4.26 (m, 4H), 6.39–7.62 (m, 10 arom. H)
40	0.96 (t, 3H), 1.56 (dd, 2H), 2.06 (m, 4H), 2.57 (s, 3H), 2.68 (t, 2H), 4.12 (m, 4H), 6.38–7.63 (m, 14 arom. H)
41	0.87 (t, 3H), 1.46 (dd, 2H), 2.28 (t, 2H), 2.61 (s, 3H), 2.67 (t, 2H), 4.28 (m, 4H), 6.78–8.04 (m, 10 arom. H)
42	0.94 (t, 3H), 1.54 (dd, 2H), 2.36 (t, 2H), 2.57 (s, 3H), 2.64 (t, 2H), 4.24 (m, 4H), 6.40–7.58 (m, 9 arom. H)
43	0.94 (t, 3H), 1.43 (t, 3H), 1.68 (dd, 2H), 2.89 (t, 2H), 4.51 (m, 6H), 6.96–8.28 (m, arom. H)
44	0.97 (t, 3H), 1.44 (t, 3H), 1.68 (dd, 2H), 2.42 (t, 2H), 2.92 (t, 2H), 4.35–4.51 (m, 6H), 6.87–8.25 (m, 10 arom. H + 2CH)
45	1.02 (t, 3H), 1.47 (t, 3H), 1.71 (dd, 2H), 2.11 (m, 4H), 2.93 (t, 2H), 4.18 (m, 4H), 4.47 (dd, 2H), 6.98–8.27 (m, 10 arom. H + 2CH)
46	0.98 (t, 3H), 1.42 (t, 3H), 1.67 (dd, 2H), 2.29 (s, 3H), 2.41 (t, 2H), 2.92 (t, 2H), 4.30–4.50 (m, 6H), 6.84–8.16 (m, 10 arom. H + CH)
47	0.98 (t, 3H), 1.48 (t, 3H), 1.69 (dd, 2H), 2.12 (m, 4H), 2.32 (s, 3H), 2.95 (t, 2H), 4.20 (m, 4H), 4.46 (dd, 2H), 6.85–8.19 (m, 10 arom. H + CH)
48	0.98 (t, 3H), 1.44 (t, 3H), 1.67 (dd, 2H), 2.28 (s, 3H), 2.39 (t, 2H), 4.28 (m, 4H), 4.47 (dd, 2H), 6.38–8.07 (m, 9 arom. H + CH)
49	0.99 (t, 3H), 1.48 (t, 3H), 1.68 (dd, 2H), 2.08 (m, 4H), 2.31 (s, 3H), 2.94 (t, 2H), 4.19 (m, 4H), 4.47 (dd, 2H), 6.35–8.10 (m, 9 arom. H + CH)
50	0.98 (t, 3H), 1.46 (t, 3H), 1.68 (dd, 2H), 2.43 (t, 2H), 2.92 (t, 2H), 4.35 (m, 4H), 4.46 (dd, 2H), 6.98–8.23 (m, 15 arom. H + CH)

(*Continued*)

Table 3. (*Continued*)

Compound	δ(ppm)
51	0.98 (t, 3H), 1.44 (t, 3H), 1.66 (dd, 2H), 2.38 (t, 2H), 2.91 (t, 2H), 4.32 (m, 4H), 4.46 (dd, 2H), 6.39–8.08 (m, 14 arom. H + CH)
52	0.89 (t, 3H), 1.63 (dd, 2H), 2.88 (t, 2H), 4.56 (m, 4H), 6.90–8.12 (m, 10 arom. H + 2CH)
53	0.95 (t, 3H), 1.63 (dd, 2H), 2.44 (t, 2H), 2.94 (t, 2H), 4.37 (m, 4H), 6.42–8.20 (m, 10 arom. H + 2CH)
54	0.98 (t, 3H), 1.71 (dd, 2H), 2.09 (m, 4H), 2.95 (t, 2H), 4.21 (m, 4H), 6.47–8.30 (m, 10 arom. H + 2CH)
55	0.90 (t, 3H), 1.60 (dd, 2H), 2.23 (s, 3H), 2.28 (t, 2H), 2.86 (t, 2H), 4.40 (m, 4H), 6.82–7.96 (m, 10 arom. H + CH)
56	0.91 (t, 3H), 1.64 (dd, 2H), 1.99 (m, 4H), 2.25 (s, 3H), 2.81 (t, 2H), 4.22 (m, 4H), 6.82–7.97 (m, 10 arom. H + CH)
57	0.97 (t, 3H), 1.66 (dd, 2H), 2.24 (s, 3H), 2.28 (t, 2H), 2.90 (t, 2H), 4.34 (m, 4H), 6.30–7.98 (m, 9 arom. H + CH)
58	0.98 (t, 3H), 1.68 (dd, 2H), 2.08 (m, 4H), 2.30 (s, 3H), 2.94 (t, 2H), 4.66 (m, 4H), 6.33–8.07 (m, 9 arom. H + CH)
59	0.93 (t, 3H), 1.64 (dd, 2H), 2.41 (t, 2H), 2.92 (t, 2H), 4.33 (m, 4H), 6.96–8.23 (m, 15 arom. H + CH)
60	0.96 (t, 3H), 1.66 (dd, 2H), 2.40 (t, 2H), 2.97 (t, 2H), 4.30 (m, 4H), 6.39–8.10 (m, 14 arom. H + CH)

In summary, bridged isoflavone derivatives with various spacer lengths have been prepared. Some of these molecules possess hydroxy and/or carboxy groups which are considered to be useful for leukotriene receptor antagonist activity.

The structures of all new compounds have been elucidated by microanalysis and IR or ^{1}H NMR spectroscopy. ^{1}H NMR spectroscopic data of the bridged isoflavone derivatives **27–60** are summarized in Table 3.

Experimental

^{1}H-NMR spectra were recorded on a Bruker WP 200 SY spectrometer in $CDCl_3$ (internal standard *TMS*, $\delta = 0.0$ ppm) at room temperature. The IR spectra (KBr discs) were measured with a Perkin-Elmer 16 PC instrument. TLC was performed on Kieselgel 60 F_{254} (Merck) using hexane:acetone (7:3 v/v) or benzene:ethyl acetate:acetic acid (5:4:1 v/v) as eluants. Starting materials **1–9** were synthesized according to known procedures [4, 15–20].

7-Chloroalkoxyisoflavones **10–26**

A mixture of compounds **3–9** (10.0 mmol), α-bromo-ω-chloroalkane (15.0 mmol), K_2CO_3 (5.0 g), and anhydrous acetone (100.0 ml) was refluxed for 5 h, the insoluble material was filtered off, the solvent evaporated *in. vac.*, and the residue crystallized from methanol to afford compounds **10–26** (Scheme 1 and Table 1).

General procedure for the Synthesis of 7-[ω-4-Acetyl-3-hydroxy-2-n-propylphenoxy)alkoxy]-isoflavones **27–40**

A mixture of 2′,4′-dihydroxy-3′-*n*-propylacetophenone [17] (**1**, 5.0 mmol), 7-chloroalkoxyisoflavone **11**, **13**, **14**, **16–26** (5.0 mmol), KI (0.2 g), K_2CO_3 (5.0 g), and anhydrous 4-methyl-2-pentanon (150.0 ml)

was refluxed for 54 h, the insoluble material was filtered off, the solvent evaporated *in. vac.*, and the residue crystallized from methanol to obtain compounds **27–40** (Scheme 2, Tables 2 and 3).

Preparation of compounds **41** *and* **42**

Compound **33** or **34** (0.5 g) was refluxed in a mixture of methanol (50.0 ml) and 2*N* NaOH (2.5 ml) for 10 min, then cooled to room temperature and acidified with dilute hydrochloric acid. The precipitate was filtered off, washed with water, and dried to yield compound **41** or **42** (Scheme 2, Tables 2 and 3).

General procedure for the synthesis of isoflavone derivatives **43–51**

A mixture of 2-ethoxycarbonyl-7-hydroxy-8-*n*-propylchromone [4] (**2**, 5.0 mmol), 7-chloroalkoxy-isoflavone **10–12**, **14**, **15**, **17**, **18**, **22** or **25** (5.0 mmol), KI (0.2 g), K_2CO_3 (10.0 g), and anhydrous 4-methyl-2-pentanon (300.0 ml) was refluxed for 54 h and then worked up as described for compounds **27–40** to afford substances **43–51** (Scheme 3, Tables 2 and 3).

Preparation of carboxylic acids **52–60**

Carboxylic acid ethyl esters **43–51** (1.0 g) were dissolved in a mixture of methanol (50.0 ml) and 2*N* NaOH (4.0 ml) and refluxed for 10 min, then worked up as described for compounds **41** and **42** to obtain substances **52–60** (Scheme 3, Tables 2 and 3).

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