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Synthesis of novel [(5*H*-tetrazolyl)alkoxy]-substituted chromone and chromanone derivatives†

Tamás Patonay*, Albert Lévai, László Hegedűs, Erzsébet Patonay-Péli

Department of Organic Chemistry, Kossuth Lajos University, H-4010 Debrecen, PO Box 20, Hungary

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Summary — The syntheses of potential leukotriene antagonist 7-[ω-(tetrazol-5-yl)alkoxy]-8-propyl-4*H*-1-benzopyran-4-one and 7-[ω-(tetrazol-5-ylthio)alkoxy]-8-propyl-4*H*-1-benzopyran-4-one derivatives with various substituents and oxidation levels in their benzopyran heteroring and their derivatives containing an extra ω-carboxyalkyl or ω-(tetrazol-5-yl)alkyl chain are described.

alkylation of tetrazole / leukotriene antagonist / 7-hydroxy-8-propylchromonoid / 1-alkylated tetrazole / 1-alkylthioated tetrazole

Résumé — Synthèse de nouvelles [(5*H*-tétrazolyl)alcoxy]chromones et chromanones. La synthèse d'antagonistes de leucotriènes, les 7-[ω-(tétrazol-5-yl)alcoxy]-8-propyl-4*H*-1-benzopyran-4-one et 7-[ω-(tétrazol-5-ylthio)alcoxy]-8-propyl-4*H*-1-benzopyran-4-one avec différents substituants et degrés d'oxydation dans le cycle benzopyrane, et leurs dérivés contenant une chaîne latérale ω-carboxyalkyl ou ω-(tétrazol-5-yl)alkyl, est décrite.

alkylation de tétrazole / antagoniste de leucotriène / chromone / chromanone / tétrazole / alkylthio-tétrazole

Introduction

Leukotrienes (LT), products of arachidonic acid metabolism, belong to the most promising targets of drug developments. LTB_4 has been suggested to play an important role in inflammatory diseases such as psoriasis, rheumatoid arthritis or inflammatory bowel disease while peptidoleukotrienes (pLT's) LTC_4, LTD_4 and LTE_4 (collectively identified as SRS-A previously) are considered major factors in asthma and related allergic symptoms. Therefore, the search for new LT antagonists is of high interest [1]. A well-defined group of pLT antagonists possesses a 3-propylresacetophenone moiety and/or tetrazole unit whereas the 8-propyl-chroman (3,4-dihydro-2*H*-1-benzopyran) or -chromanone (2,3-dihydro-4*H*-1-benzopyran-4-one) skeleton linked to a carboxyl or tetrazole group with a spacer is a frequent building block of LTB_4 antagonists. Some selected structures are shown in figure 1.

To develop new LT antagonists and to collect new data for structure–activity relationships, a systematic synthetic work was planned in our laboratory. The key point of our interest was to determine how the incorporation of the 2′-hydroxy group of the 3-propylresacetophenone unit into a heteroring alters the binding to the receptor. Some literature data supported that the alkylation of the chelated phenolic hydroxy group caused a decrease in the antagonism of LTD_4/LTE_4 but favored the action on LTB_4 receptors [2]. The structures of LTB_4 antagonists SC-41.930 (**6**) [2d, 3] and Ro 25-3562 (**7**) [4] are in agreement with this suggestion but the potent agent LY-255.283 (**5**) and related compounds [5] clearly contradict the theory. Therefore, we decided to synthesize 8-propylchromones (8-propyl-4*H*-benzopyran-4-ones) linked to a tetrazole moiety by an alkoxy chain spacer of 4–6 units. To suppress the possible nucleophilic ring opening of the chromone ring skeleton and to search for the optimum steric fit, the substitution by alkyl, aryl and heteroaryl groups in position 2 as well as the hydrogenation of the chromone double bond was considered. We also wished to study the effect of the incorporation of a sulfur atom into the spacer. This type of modification, mimicking the structure of pLT's, has been found to be useful in the carboxylic acid series [6] but analogous tetrazolylthio derivatives have not been reported. Finally, the preparation of compounds with another tetrazolyl- or carboxyalkyl chain resembling LY-203.647 (**2**) [7] was also among our aims. In this contribution we now wish to report the synthesis and modifications of the compounds outlined above.

† Dedicated to Prof Waldemar Adam on the occasion of his 60th birthday. Part of this work was presented at the 13th International Symposium on Medicinal Chemistry, September 19–23, 1994, Paris, France.

* Correspondence and reprints

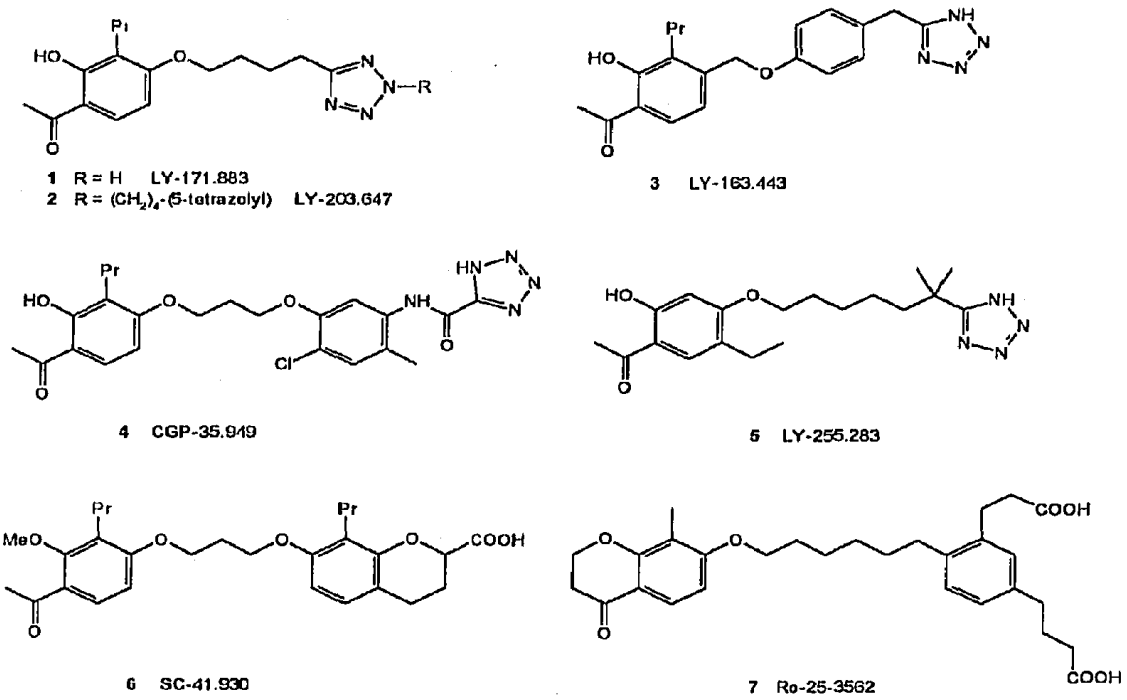


Fig 1

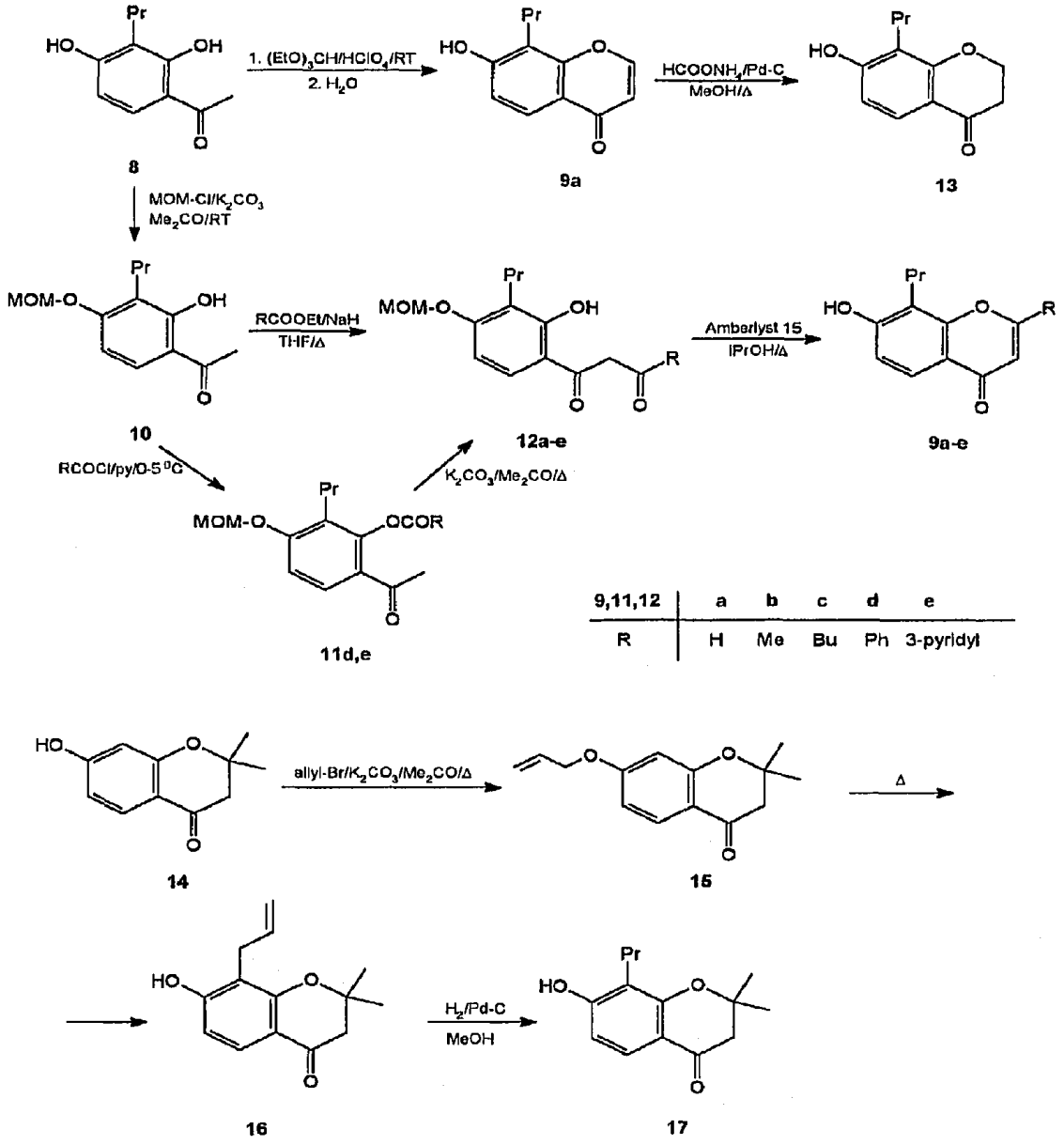
Results and discussion

To achieve our diverse synthetic targets, linear approaches based on a limited number of starting hydroxychromones were chosen. The synthesis of the key intermediates are shown by scheme 1. 2′,4′-Dihydroxy-3′-propylacetophenone **8** [8] was converted to 7-hydroxy-8-propylchromone **9a** by using the procedure of Dorofeenko and Mezheritskii [9]. Other 2-substituted chromones **9b–e** were obtained from acetophenone **8** by our recently developed methodology [10] which exploits the one-pot cyclodehydration and deprotection of 1-[2-hydroxy-4-(methoxymethoxy)phenyl]alkane-1,3-diones **12b–e**. Diones **12b–e** were prepared in moderate yield by either Claisen-condensation of methoxymethylated acetophenone **10** or the classical Baker–Venkataraman approach via (het)aroylated derivatives **11d,e**. Chromone **9a** was also obtained in moderate yield from acetophenone **10** and ethyl formate by the Claisen-condensation route without the isolation of the intermediate dione **12a**. ^{1}H NMR measurements revealed that, in accordance with our earlier observations [10], compounds **12b,c** with alkyl groups at C-3, existing in triple equilibrium, consisted of β-diketone **12**, enol **12′** and the cyclic 2-hydroxychromanone **12″** forms while compounds **12d,e** with aryl moiety at C-3 were found to exist in the enol form exclusively (scheme 2).

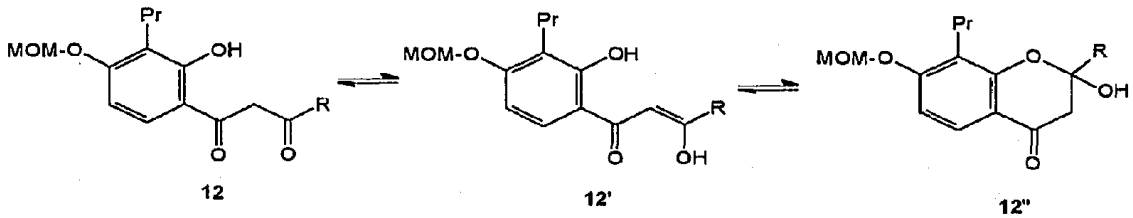
Chemoselective transfer hydrogenation [11] of chromone **9a** using ammonium formate as hydrogen source afforded chromanone **13**. The 2,2-dimethylated derivative **17** was synthesized by allylation of 2,2-dimethyl-7-hydroxychromanone **14** [12] followed by Claisen rearrangement and catalytic hydrogenation.

The syntheses of target compounds with an ω-(tetrazol-5-yl)alkoxy chain **20–24**, **26** are shown in scheme 3. The (tetrazol-5-yl)alkyl units were attached to the chromonoid skeleton by a two-step procedure. Hydroxychromones **9a–e** were alkylated with 4-bromobutanenitrile or 5-chloropentanenitrile in butan-2-one (MEK) or 4-methylpentan-2-one (MIBK) to afford cyanide intermediates **18**, **19** which in turn were easily transformed into the desired tetrazoles **20**, **21** by means of tributyltin azide [13] in excellent yields. The same approach was also applied to the synthesis of 2,2-disubstituted chromanone **26** while 2-unsubstituted chromanones **22**, **23** were easily prepared by transfer hydrogenation of tetrazolylchromones **20a**, **21a**. To study the role of the carbonyl group in the biological activity, oxime derivative **24** was also synthesized by treating chromanone **22** with hydroxylammonium chloride in hot aqueous ethanolic solution.

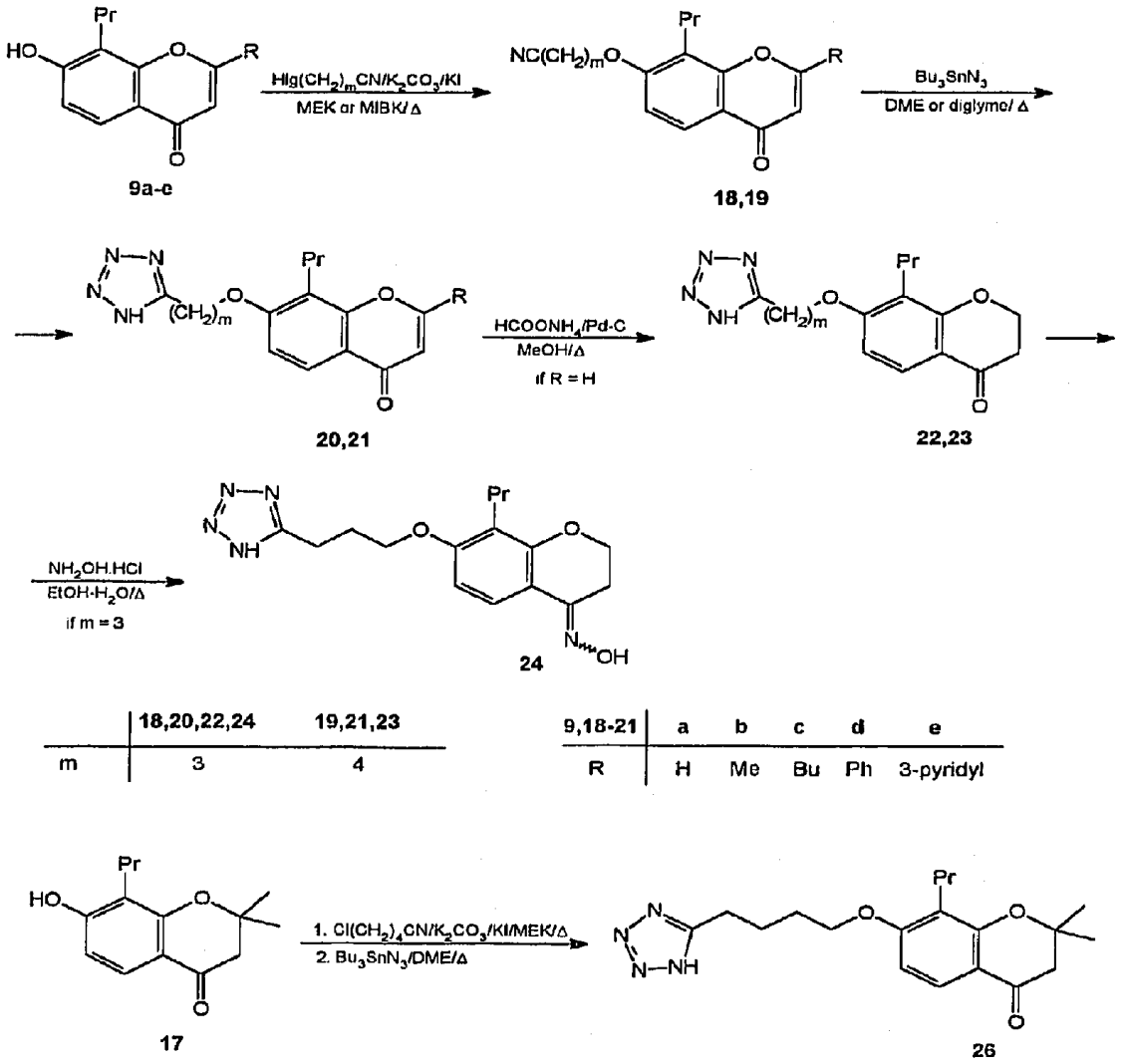
The synthesis of tetrazole derivatives containing a sulfur atom in the spacer is summarized in scheme 4. 7-Hydroxy-8-propylchromone **9a** was alkylated with α-bromo-ω-chloroalkanes of various length. The different reactivity of the halogens allowed the completely chemoselective formation of the corresponding 7-(ω-chloroalkoxy)-8-propylchromones **27–29**, the presence of chlorine was sustained by the characteristic M + 2/M isotope peak pattern in the mass spectrum of compound **28**. Nucleophilic displacement of chlorine atoms in chromones **27–29** by the thiocyanate anion afforded the 7-(ω-thiocyanatoalkoxy)-8-propylchromones **30–32**, exclusively: no formation of any isomeric isothiocyanates was observed. 1,3-Dipolar cycloaddition of tributyltin azide to the carbon–nitrogen triple bond of the thiocyanate group [13] resulted in the tetrazolylthio derivatives **33–35** in good yield. 8-Propyl-



Scheme 1



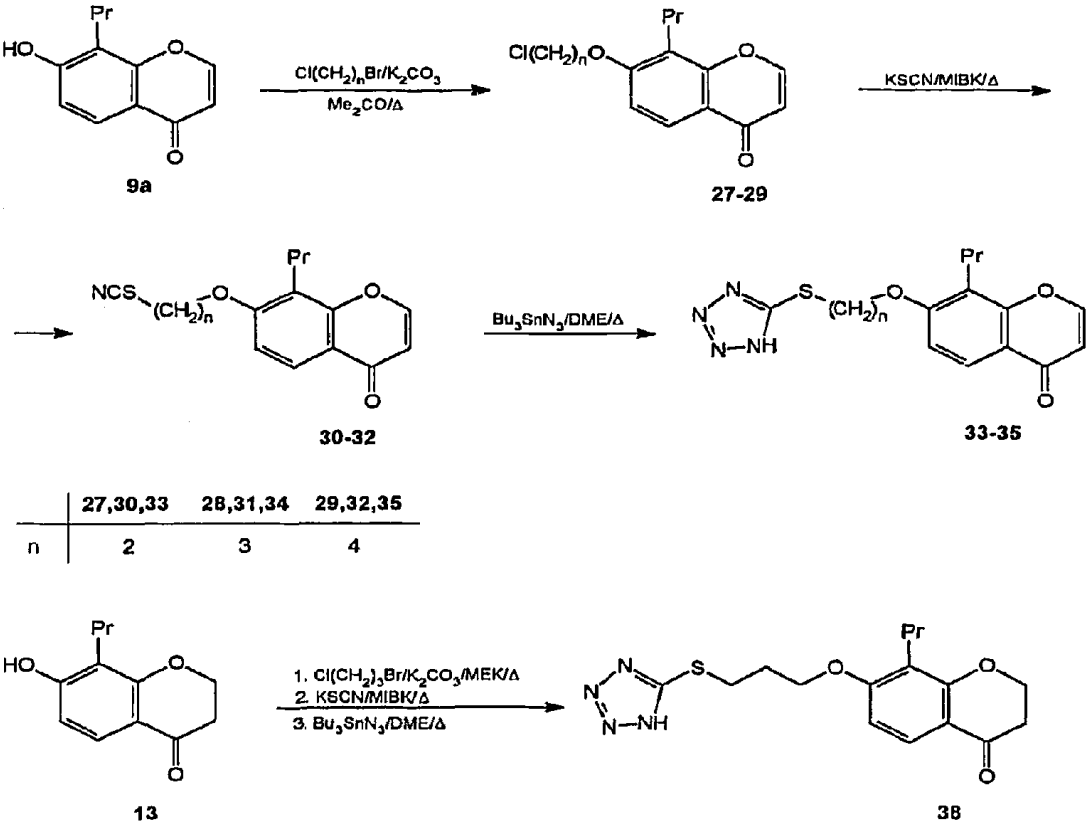
Scheme 2



Scheme 3

7-[3-(tetrazol-5-ylthio)propyl]oxychromanone **38** was obtained from the hydroxychromanone **13** in an analogous three-step procedure to avoid any poisoning of the palladium catalyst during the transfer hydrogenation of chromone **34**.

The preparation of the LY-203.647-like derivatives, which carry an extra alkyl chain functionalized with an acidic group on their tetrazole moiety, is shown in scheme 5. In accordance with the previous reports [14, 15] when the tetrazolate anion generated in situ with sodium hydride from tetrazole **21a** was alkylated with either ethyl ω-chloroalkanoates or 5-chloropentanenitrile, a mixture of 1- (**39**, **40** and **47**) and 2-substituted tetrazoles (**41**, **42** and **48**) was obtained. These regioisomers were separated by column chromatography and distinguished on the basis of their R_f values and their ^{1}H NMR and ^{13}C NMR properties. It is well documented that 1-substituted tetrazoles are more polar than the 2-substituted isomers and, in general, have a higher melting point [15a]. Another characteristic feature is that in 2-alkylated isomers both α-hydrogens and α-carbon of the alkyl chain attached to the tetrazole nitrogen are shifted downfield from that of the 1-isomer [14a, 15]. These differences allowed an unambiguous structure elucidation of regioisomeric alkylated tetrazoles. Moreover, we found that tetrazole carbon of 2-(4-cyanobutyl) isomer **48** showed a considerable downfield shift ($\Delta\delta$ = 12.2 ppm) compared to that of the 1-substituted derivative **47**. Since ^{13}C NMR data presented by Holzer and Jäger [15c] for some regioisomeric tetrazole derivatives showed the same shift phenomenon, this feature may also be useful in the structure elucidation of these derivatives. Surprisingly, no enhancement of methylene signals of 1- and 5-alkyl chains was observed in the NOE difference spectrum of tetrazole **47**, thus, the method suggested by Holzer and Jäger [15c] has less value for discrimination of isomeric tetrazoles with bulkier 1,5-substituents.



Scheme 4

The ratios of 1- and 2-alkylated isomers varied significantly depending on the alkylating fragment. The 1-substituted isomer slightly dominated in the case of ethoxycarbonylmethylation (**39/41** = 1.21) while the 2-substituted isomers were the major products in the case of a longer chain (**40/42** = 0.29, **47/48** = 0.39). The preference of product **39** over **41** could be interpreted in terms of the higher nucleophilicity of the N(1) position [14b] but this difference takes effect only in the reactions with highly reactive alkylating agents such as α-chlorocarbonyl compounds [16]. Upon treatment with less reactive but bulkier alkylating agents the steric hindrance preferring the formation of 2- substituted isomers dominates.

To complete the synthesis of the derivatives with another tetrazolyl- or carboxyalkyl chain attached to the tetrazol unit, the ethyl esters **39–42** were hydrolyzed in alkaline medium to give the free acids **43–46** while cyanobutylated tetrazole **48** was transformed into tetrazol-2-ylbutylated tetrazole **49** by means of tributyltin azide.

In summary, a series of tetrazoles linked to a 2-(un)substituted 7-hydroxy-8-propylchromonoid moiety of various oxidation level by a spacer of various length and/or heteroatom was synthesized. The results of bioactivity studies of the prepared compounds will be reported in a separate paper.

Experimental section

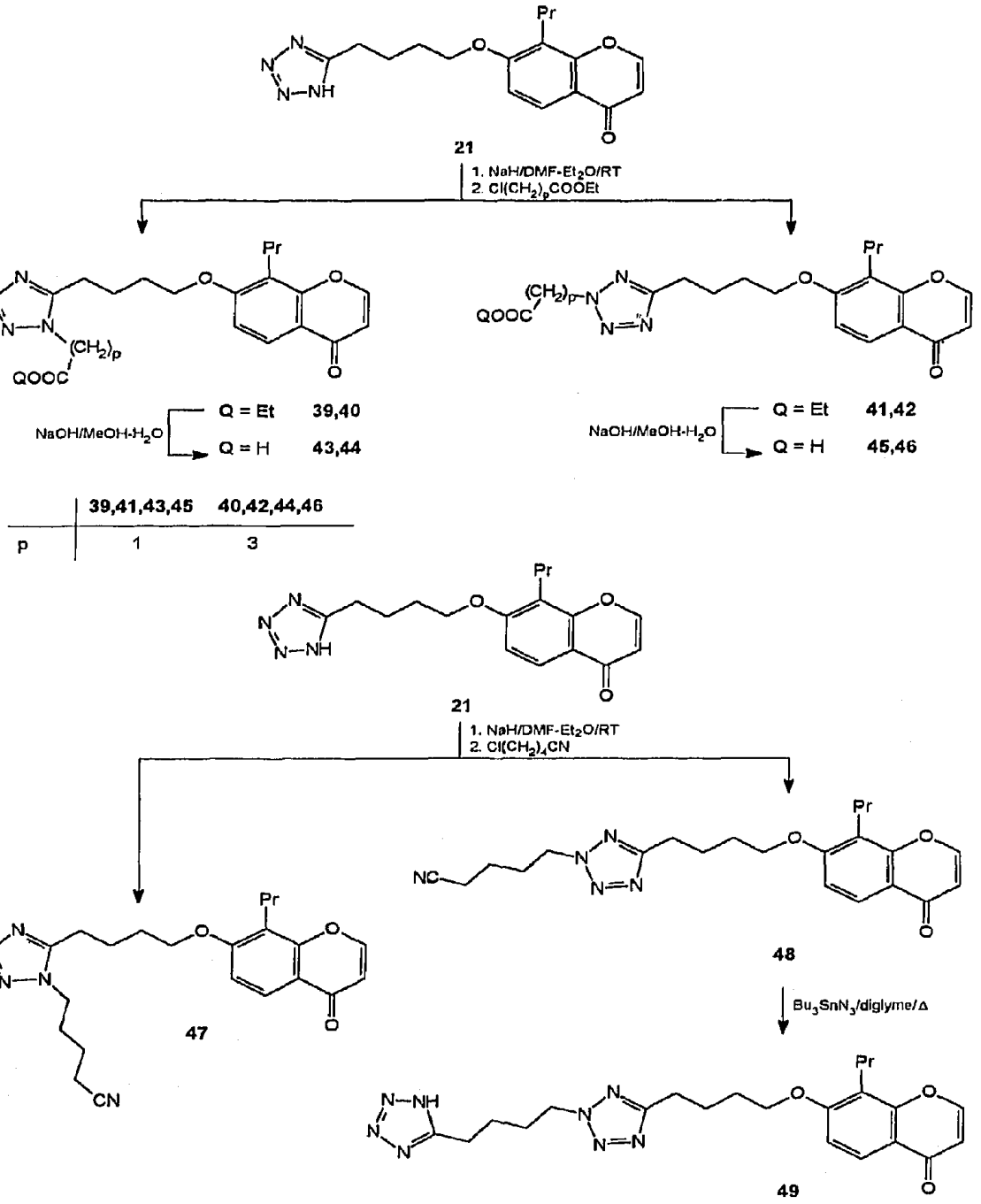
General

Mp's were determined on a Boetius hot-stage apparatus and are uncorrected. IR spectra were recorded with a Perkin-Elmer 16 PC FT-IR instrument in KBr pellet unless otherwise specified. ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were taken with a Bruker WP 200 SY instrument (internal standard TMS, δ = 0 ppm) in $CDCl_3$ solution unless stated otherwise. MS spectra were recorded with a VG 7035 GC-MS-DS system (EI, 70 eV). Elemental analyses were performed in-house on a Carlo Erba EA 1106 analyzer. $MgSO_4$ was used as drying agent, column chromatography was performed on Kieselgel 60 (0.063–0.2 mm) (Reanal). Thin-layer chromatography was performed on Kieselgel 60 F_{254} (Alurolle) (Merck) using toluene/EtOAc (4:1) and hexane/Me_2CO (2:1) mixtures.

• *2′-Hydroxy-4′-(methoxymethoxy)-3′-propylacetophenone* **10**

2′,4′-Dihydroxy-3′-propylacetophenone **8** (15.60 g, 80.32 mmol) was treated with methoxymethyl chloride according to the procedure given in [10]. The crude product was purified by vacuum distillation to yield **10** (15.83 g, 83%). Bp: 152–154 °C/1 mm Hg.

IR (neat): 2 960, 2 870, 2 932, 2 828, 1 630 (C=O), 1 458, 1 416 (CH_2), 1 258, 1 228, 1 204 (C–O–C + C–OH), 1 116, 1 080, 1 032 (C–O–C), 794 cm^{-1}.



Scheme 5

^{1}H NMR: 0.97 (t, J = 7.1 Hz, 3H, CH_2Me), 1.56 (m, 2H, CH_2Me), 2.55 (s, 3H, 2-H), 2.67 (t, J = 7.3 Hz, 2H, CH_2Et), 3.48 (s, 3H, OCH_2OMe), 5.26 (s, 2H, OCH_2OMe), 6.64 (d, J = 8.0 Hz, 1H, 5′-H), 7.57 (d, J = 8.0 Hz, 1H, 6′-H), 12.78 (deuterable s, 1H, OH).

Anal calc for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.44; H, 7.60.

• *2′-Benzoyloxy-4′-(methoxymethoxy)-3′-propylacetophenone* **11d**

Benzoyl chloride (1.2 mL, 10.41 mmol) was added to the cold (−10 °C) solution of 2′-hydroxy-4′-(methoxymethoxy)-3′-propylacetophenone **10** (2.11 g, 8.86 mmol) in absolute pyridine and allowed to stand for 4 days. The mixture was poured onto crushed ice, the crude **11d** was filtered off,

washed with water and recrystallized from methanol to give 2.06 g (68%) pure **11d**. Mp: 85–87 °C.

IR: 2 962, 2 870, 2 932, 1 734 (C=O, ester), 1 670 (C=O, ketone), 1 432, 1 358, 1 264 (C–O–C, ether), 1 208 (C–O–C, ester), 1 114, 1 076 (C–O–C, ether), 1 022 (C–O–C, ester), 816, 706 cm^{-1}.

^1H NMR: 0.90 (t, J = 7.3 Hz, 3H, CH_2Me), 1.56 (m, 2H, CH_2Me), 2.50 (s, 3H, 2-H), 2.59 (t, J = 7.4 Hz, CH_2Et), 3.50 (s, 3H, OCH_2OMe), 5.29 (s, 2H, OCH_2OMe), 7.07 (d, J = 8.8 Hz, 1H, 5′-H), 7.70–7.49 (m, 3H, 3″,4″,5″-H), 7.75 (d, J = 8.8 Hz, 1H, 6′-H), 8.23 (dd, J = 8.2, 1.6 Hz, 2H, 2″,6″-H).

Anal calc for $C_{20}H_{22}O_5$: C, 74.05; H, 6.83. Found: C, 73.87; H, 6.95.

• *4′-(Methoxymethoxy)-3′-propyl-2′-[(3-pyridylcarbonyl)oxy]acetophenone* **11e**

A mixture of nicotinic acid (6.16 g, 50.00 mmol) and thionyl chloride (80 mL) was refluxed for 2 h. The excess thionyl chloride was removed under reduced pressure and a solution of **10** (9.53 g, 40.00 mmol) in absolute pyridine (50 mL) was added to the residue. The mixture was stirred for 18 h and worked up as given for **11d**. Yield: 56%. Mp 81–84 °C (hexane–ethyl acetate).

IR: 2 932, 2 870, 1 740 (C=O, ester), 1 674 (C=O, ketone), 1 278, 1 258 (C–O–C, ether), 1 210 (C–O–C, ester), 1 158, 1 138, 1 112, 1 082 (C–O–C, ether), 1 028, 1 016 (C–O–C, ester), 820, 724 cm^{-1}.

^1H NMR: 0.91 (t, J = 7.2 Hz, 3H, CH_2Me), 1.57 (m, 2H, CH_2Me), 2.51 (s, 3H, 2-H), 2.60 (t, J = 7.4 Hz, 2H, CH_2Et), 3.51 (s, 3H, OCH_2OMe), 5.31 (s, 2H, OCH_2OMe), 7.10 (d, J = 9.7 Hz, 1H, 5′-H), 7.49 (dd, J = 5.0, 8.2 Hz, 1H, 5″-H), 7.78 (d, J = 9.7 Hz, 1H, 6′-H), 8.47 (ddd, J = 8.2, 1.4, 1.2 Hz, 1H, 4″-H), 8.87 (dd, J = 5.0, 1.4 Hz, 1H, 6″-H), 9.16 (d, J = 1.2 Hz, 1H, 2″-H).

Anal calc for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.17; N, 4.08. Found: C, 66.63; H, 5.99; N, 4.27.

Preparation of 1-[2-hydroxy-4-(methoxymethoxy)-3-propylphenyl]-1,3-alkanediones **12**: *general procedures*

■ *Procedure A*

Acetophenone **10** was treated with the ethyl ester of the corresponding carboxylic acid in absolute THF in the presence of sodium hydride according to the procedure given in [10].

■ *Procedure B*

2′-[(Het)aroyloxy]acetophenones **11d,e** was treated with anhydrous K_2CO_3 in hot absolute acetone solution according to the procedure given in [10].

• *1-[2-Hydroxy-4-(methoxymethoxy)-3-propylphenyl]-butane-1,3-dione* **12b**

Procedure A, 1.8 h, purified by crystallization. Yield: 34%. Mp: 72–73.5 °C (hexane–absolute ethanol).

IR: 2 960, 2 926, 2 868, 1 604 (C=O), 1 582 (C=C–OH), 1 494, 1 256 (C–O–C), 1 202 (C–OH), 1 154, 1 132, 1 114, 1 076, 1 034 (C–O–C), 960, 920, 802 cm^{-1}.

^1H NMR: **12b**: 2.30 (s, 3H, 4-H), 4.03 (s, 2H, 2-H), 5.27 (s, 2H, OCH_2OMe), 6.68 (d, J = 9.0 Hz, 1H, 5′-H), 7.50 (d, J = 9.0 Hz, 1H, 6′-H), 12.45 (deuterable s, 1H, 2′-OH). **12b′**: 2.11 (s, 3H, 4-H), 5.26 (s, 2H, OCH_2OMe), 6.07 (s, 1H, 2-H), 6.52 (d, J = 8.5 Hz, 1H, 5′-H), 7.47 (d, J = 8.5 Hz, 1H, 6′-H), 12.58 (deuterable s, 1H, 2′-OH), 13.73 (deuterable s, 1H, 3-OH). **12b″**: 1.76 (s, 3H, 2-Me), 2.89 (s, 2H, 3-H), 6.80 (d, J = 8.9 Hz, 1H, 6-H), 7.77 (s, J = 8.9 Hz, 1H, 5-H). 2-OH signal could not been detected due to the low intensity.

Non-separable signals: 0.98 (t, J = 7.2 Hz, 3H, CH_2Me), 1.57 (m, 2H, CH_2Me), 2.67 (d, J = 7.3 Hz, CH_2Et), 3.49 (s, 3H, OCH_2OMe). Ratio of isomers **12b:12b′:12b″** = 30:62:8 (on the basis of the integrals of 4-H (**12b** and **12b′**) and 2-Me (**12b″**) protons).

Anal calc for $C_{15}H_{20}O_5$ (280.32): C, 64.27; H, 7.19. Found: C, 64.21; H, 6.92.

• *1-[2-Hydroxy-4-(methoxymethoxy)-3-propylphenyl]-heptane-1,3-dione* **12c**

Procedure A, 1.75 h, column chromatography (toluene), yield: 39%. Pale yellow oil.

IR (neat): 2 960, 1 634, 1 622, 1 614 (C=O), 1 574, 1 568 (C=C–OH), 1 492, 1 462, 1 446, 1 434, 1 250 (C–O–C), 1 204 (C–OH), 1 158, 1 132, 1 112, 1 080, 1 028 (C–O–C), 792 cm^{-1}.

^1H NMR: **12c**: 4.01 (s, 2H, 2-H), 6.67 (d, J = 8.6 Hz, 1H, 5′-H), 7.50 (d, J = 8.6 Hz, 1H, 6′-H), 12.48 (deuterable s, 2H, 2′-OH). **12c′**: 6.06 (s, 1H, 2-H), 6.62 (d, J = 9.1 Hz, 1H, 5′-H), 7.47 (d, J = 9.1 Hz, 1H, 6′-H), 12.60 (deuterable s, 1H, 3-OH), 13.70 (deuterable s, 1H, 2′-OH). **12c″**: 2.74 (AB q, J = 13.1 Hz, 2H, 3-H), 6.79 (d, J = 8.9 Hz, 1H, 6-H), 7.76 (d, J = 8.9 Hz, 1H, 5-H). 2-OH signal could not been detected due to the low intensity.

Non-separable signals: 0.87–1.02 (overlapping triplets, 6H, CH_2Me + 7-H), 1.25–1.75 (m, 6H, CH_2Me + 5,6-H), 2.33 (t, J = 7.4 Hz, 2H, CH_2Et), 2.52–2.71 (m, 2H, 4-H), 3.48 (s, 3H, OCH_2OMe), 5.24 (s, 2H, OCH_2OMe). Ratio of isomers **12c:12c′:12c″** = 30:63:7 (on the basis of the integrals of 4-H (**12c** and **12c′**) and 5,6-H (**12c″**) protons).

Anal calc for $C_{18}H_{26}O_5$ (322.41): C, 67.06; H, 8.13. Found: C, 67.23; H, 8.08.

• *1-[2-Hydroxy-4-(methoxymethoxy)-3-propylphenyl]-3-phenylpropane-1,3-dione* **12d**

Procedure A, 2 h. Yield: 36%. Procedure B, 22 h. Yield: 51%. Purified by crystallization. Mp: 76–78 °C (hexane–absolute ethanol).

IR: 2 958, 2 928, 2 866, 1 606 (C=O), 1 652 (C=C–OH), 1 492, 1 298, 1 264, 1 244 (C–O–C), 1 200 (C–OH), 1 114, 1 074, 1 034 (C–O–C), 794, 766 cm^{-1}.

^1H NMR: 0.99 (t, J = 7.2 Hz, 3H, CH_2Me), 1.59 (m, 2H, CH_2Me), 2.70 (t, J = 7.2 Hz, 2H, CH_2Et), 3.50 (s, 3H, OCH_2OMe), 5.28 (s, 2H, OCH_2OMe), 6.69 (d, J = 8.7 Hz, 1H, 5′-H), 6.76 (s, 1H, 2-H), 7.51 (m, 3H, 3″,4″,5″-H), 7.62 (d, J = 8.7 Hz, 1H, 6′-H), 7.92 (dd, J = 7.9, 1.9 Hz), 12.60 (deuterable s, 1H, 2′-OH), 13.16 (deuterable s, 1H, 2-OH). The compound consisted completely of the enol form.

Anal calc for $C_{20}H_{22}O_5$ (342.39): C, 70.16; H, 6.48. Found: C, 70.11; H, 6.12.

• *1-[2-Hydroxy-4-(methoxymethoxy)-3-propylphenyl]-3-(3-pyridyl)propane-1,3-dione* **12e**

Procedure B, 90 h. Purified by crystallization. Yield: 89%. Mp: 123–125 °C (MeOH).

IR: 2 954, 2 926, 2 866, 1 614 (C=O), 1 592, 1 564 (C=C–OH), 1 496, 1 478, 1 454, 1 306, 1 284, 1 246 (C–O–C), 1 200 (C–OH), 1 136, 1 114, 1 072, 1 042, 1 032 (C–O–C), 800 cm^{-1}.

^1H NMR: 0.98 (t, J = 7.3 Hz, 3H, CH_2Me), 1.58 (m, 2H, CH_2CH_2Me), 2.69 (t, J = 7.4 Hz, 2H, CH_2Et), 3.51 (s, 3H, OCH_2OMe), 5.27 (s, 2H, OCH_2OMe), 6.70 (d, J = 9.4 Hz, 1H, 5′-H), 6.77 (s, 1H, 2-H), 7.43 (dd, J = 8.0,

4.7 Hz, 1H, 5″-H), 7.61 (d, J = 9.4 Hz, 1H, 6′-H), 8.19 (ddd, J = 8.0, 1.4, 1.2 Hz, 1H, 4″-H), 8.75 (dd, J = 4.7, 1.4 Hz, 1H, 6″-H), 9.12 (d, J = 1.2 Hz, 1H, 2″-H), 12.47 (deuterable s, 1H, 2′-OH), 13.30 (deuterable s, 1H, 2-OH). The compound consisted completely of the enol form.

Anal calc for $C_{19}H_{21}NO_5$ (343.38): C, 66.46; H, 6.17; N, 4.08. Found: C, 66.31; H, 6.19; N, 4.19.

• *7-Hydroxy-8-propylchromone* **9a**

(a) Perchloric acid (70%, 1.8 mL, 21.0 mmol) was added to the solution of 2′,4′-dihydroxy-3′-propylacetophenone **8** [8] (3.89 g, 20.00 mmol) in triethyl formate (28 mL, 0.241 mol) and allowed to stand at room temperature for 20 h. Diethyl ether (250 mL) was added, the precipitated solid was filtered off and washed with diethyl ether. The dark-reddish salt was dissolved in water (120 mL) and stirred at room temperature for 18 h. The crude product was filtered off and purified by column chromatography (hexane/acetone, 7:3) to give pure **9a** (1.94 g, 47%). Mp 183–185 °C (hexane–acetone).

IR: 1 642 (C=O), 1 627 (C=C), 1 424, 1 390, 1 278, 1 112 (C–O–C), 852, 817 cm^{-1}.

^1H NMR: 1.00 (t, J = 7.2 Hz, 3H, CH_2Me), ~1.60 (br m, 3H, CH_2Me + OH), 2.81 (t, J = 7.3 Hz, 2H, CH_2Et), 6.29 (d, J = 6.5 Hz, 1H, 3-H), 6.90 (d, J = 8.5 Hz, 1H, 6-H), 7.85 (d, J = 6.5 Hz, 1H, 2-H), 7.98 (d, J = 8.5 Hz, 1H, 5-H).

Anal calc for $C_{12}H_{12}O_3$ (204.23): C, 70.57; H, 5.92. Found: C, 70.39; H, 5.99.

(b) A solution of ethyl formate (7.9 mL, 97.79 mmol) and 2′-hydroxy-4′-(methoxymethoxy)-3′-propylacetophenone **10** (9.40 g, 39.45 mmol) in absolute THF (10 mL) was added dropwise in 30 min to the stirred suspension of sodium hydride (60% in mineral oil) (6.31 g, ca 0.158 mol, rinsed with dry hexane prior to use) in absolute hexane (20 mL) under nitrogen. The mixture was refluxed for 3 h, poured into water, neutralized with acetic acid and extracted with diethyl ether (3 × 40 mL). The organic phase was washed with a saturated $NaHCO_3$ solution and water, dried and evaporated. The crude dione **12a** and Amberlyst 15 (2.0 g) was refluxed in propan-2-ol (100 mL) for 3 h, the resin was filtered off and washed with methanol. The solvents were removed in vacuo and the residue was crystallized from the hexane–acetone mixture to afford **9a** (3.82 g, 56%).

• *7-Hydroxy-2-methyl-8-propylchromone* **9b**

A mixture of β-diketone **12b** (2.01 g, 7.17 mmol), Amberlyst 15 (2.45 g) and propan-2-ol (50 mL) was stirred at reflux temperature for 1.8 h, then filtered and the resin was washed with hot methanol (3 × 30 mL). The combined filtrates were evaporated and the residue was crystallized from methanol to afford 1.23 g (79%) chromone **9b** as white crystals. Mp: 199–202 °C.

IR: 3 126 (OH), 2 960, 2 930, 2 870, 1 644 (C=O), 1 620 (C=C), 1 578, 1 436, 1 400, 1 326, 1 302, 1 138, 1 108, 828 cm^{-1}.

^1H NMR (DMSO-d_6): 0.90 (t, J = 7.3 Hz, 3H, CH_2Me), 1.56 (m, 2H, CH_2Me), 2.35 (s, 3H, 2-Me), 2.72 (t, J = 7.3 Hz, 2H, CH_2Et), 6.08 (s, 1H, 3-H), 6.93 (d, J = 8.7 Hz, 1H, 6-H), 7.70 (d, J = 8.7 Hz, 1H, 5-H). The OH signal coalesced with the water content of DMSO.

Anal calc for $C_{13}H_{14}O_3$ (218.25): C, 71.54; H, 6.47. Found: C, 71.42; H, 6.22.

• *2-Butyl-7-hydroxy-8-propylchromone* **9c**

Reaction of β-diketone **12c** (486 mg, 1.51 mmol) as given for **9b** yielded 163 mg (42%) white crystalline **9c**. Mp: 109–112 °C (hexane–absolute ethanol).

IR: 3 122 (OH), 2 960, 2 932, 2 870, 1 638 (C=O), 1 618 (C=C), 1 574, 1 466, 1 436, 1 424, 1 404, 1 318, 1 302, 1 138, 1 110, 836 cm^{-1}.

^1H NMR: 0.96, 1.00 (overlapping triplets, 6H, CH_2Me + 4′-H), 1.45–1.83 (m, 6H, CH_2CH_2Me + 2′,3′-H), 2.67 (t, J = 7.2 Hz, 2H, CH_2Et), 2.87 (t, J = 7.0 Hz, 3H, 1′-H), 6.17 (s, 1H, 3-H), 7.01 (d, J = 8.8 Hz, 1H, 6-H), 7.92 (d, J = 8.8 Hz, 1H, 5-H), 8.48 (deuterable br s, 1H, 7-OH).

Anal calc for $C_{16}H_{20}O_3$ (260.34): C, 74.20; H, 7.74. Found: C, 74.36; H, 7.36.

• *7-Hydroxy-8-propylflavone* **9d**

Reaction of β-diketone **12d** (1.00 g, 2.92 mmol) as given for **9b** yielded 725 mg (89%) white crystalline **9d**. Mp: 227–229 °C (methanol).

IR: 3 090 (OH), 2 958, 2 930, 2 868, 1 628 (C=O), 1 586, 1 440, 1 392, 1 336, 1 300, 1 114, 826, 772, 684 cm^{-1}.

^1H NMR (DMSO-d_6): 1.00 (t, J = 7.2 Hz, 3H, CH_2Me), 1.68 (m, 2H, CH_2Me), 2.90 (t, J = 7.3 Hz, 2H, 8-CH_2Et), 6.90 (s, 1H, 3-H), 6.99 (d, J = 8.6 Hz, 1H, 6-H), 7.61 (m, 3H, 3′,4′,5′-H), 7.75 (d, J = 8.6 Hz, 1H, 5-H), 8.07 (m, 2H, 2′,6′-H). The OH signal coalesced with the water content of DMSO.

Anal calc for $C_{18}H_{16}O_3$ (280.33): C, 77.12; H, 5.75. Found: C, 77.00; H, 5.79.

• *7-Hydroxy-8-propyl-2-(3-pyridyl)chromone* **9e**

Reaction of β-diketone **12d** (1.37 g, 4.00 mmol) as given for **9b** yielded 789 mg (70%) **9e** as pale yellow needles. Mp: 277–278 °C (methanol).

IR: 3 074, 2 958, 2 870, 1 642 (C=O), 1 594, 1 420, 1 384, 1 326, 1 302, 1 204, 1 192, 1 126, 1 110, 814 cm^{-1}.

^1H NMR (DMSO-d_6): 0.98 (t, J = 7.3 Hz, 3H, CH_2Me), 1.66 (m, 2H, CH_2Me), 2.89 (t, J = 7.4 Hz, 2H, CH_2Et), 7.01 (d, J = 9.0 Hz, 1H, 6-H), 7.05 (s, 1H, 3-H), 7.66 (dd, J = 7.8, 5.3 Hz, 1H, 5′-H), 7.79 (d, J = 9.0 Hz, 1H, 5-H), 8.42 (ddd, J = 7.8, 1.9, 1.3 Hz, 1H, 4′-H), 8.78 (dd, J = 5.3, 1.3 Hz, 1H, 6′-H), 9.23 (d, J = 1.9 Hz, 1H, 2′-H), 10.69 (s, 1H, 7-OH).

Anal calc for $C_{17}H_{15}NO_3$ (281.31): C, 72.59; H, 5.37; N, 4.98. Found: C, 72.31; H, 5.30; N, 4.88.

• *7-Hydroxy-8-propylchromanone* **13**

A mixture of 7-hydroxy-8-propylchromone **9a** (3.06 g, 14.98 mmol), ammonium formate (7.64 g, 0.121 mol), 10% Pd/C catalyst (3.62 g) in methanol (200 mL) was stirred at reflux for 2 h. The catalyst was filtered off and washed with methanol. The evaporated filtrate was treated with 5% HCl solution (400 mL) and extracted with $CHCl_3$ (3 × 100 mL). The extract was washed with water, dried and concentrated. The crude product was crystallized from hexane–acetone mixture to afford 2.46 g (80%) chromanone **13**. Mp: 124–126 °C.

IR: 3 136 (OH), 2 956, 2 870, 1 654 (C=O), 1 576, 1 468, 1 440, 1 386, 1 298, 1 280, 1 262, 1 242, 1 216, 1 204 (C–OH), 1 186, 1 160, 1 108, 1 044 (C–O–C), 824 cm^{-1}.

^1H NMR: 0.98 (t, J = 7.3 Hz, 3H, CH_2CH_3), 1.58 (m, 2H; CH_2Me), 2.61 (t, J = 7.4 Hz, 3H, CH_2Et), 2.76 (t, J = 6.6 Hz, 2H, 3-H), 4.52 (t, J = 6.6 Hz, 2H, 2-H), 5.75 (deuterable br s, 1H, 7-OH), 6.50 (t, J = 8.3 Hz, 2H, 6-H), 7.71 (t, J = 8.3 Hz, 2H, 5-H).

Anal calc for $C_{12}H_{14}O_3$ (206.25): C, 69.88; H, 6.84. Found: C, 69.02; H, 6.92.

• *7-Allyloxy-2,2-dimethylchromanone* **15**

A mixture of 2,2-dimethyl-7-hydroxychromanone **14** [12] (9.00 g, 46.82 mmol), allyl bromide (4.20 mL, 49.64 mmol), anh K_2CO_3 (9.39 g, 67.94 mmol) and absolute acetone (40 mL) was stirred at reflux temperature for 6 h, the inorganic salts were filtered off and the filtrate was concentrated in vacuo. Fractionated distillation of the residue afforded **15** (8.29 g, 76%). Bp: 143–145 °C/1 mm Hg.

IR (neat): 3 082, 2 978, 2 932, 2 892, 1 682 (C=O), 1 646 (C=C), 1 610, 1 576, 1 490, 1 440, 1 386, 1 372, 1 284, 1 264, 1 236, 1 214 (C–O–C), 1 184, 1 162, 1 134, 1 122, 1 104, 1 056, 1 004 (C–O–C), 838, 822 cm^{-1}.

^1H NMR: 1.46 (s, 6H, 2Me), 2.68 (s, 2H, 3-H), 4.56 (d, J = 5.2 Hz, 2H, 1′-H), 5.32 (dd, J = 10.4, 1.3 Hz, 1H, 3′-H_{cis}), 5.42 (dd, J = 17.3, 1.3 Hz, 1H, 3′-H_{trans}), 6.05 (m, 1H, 2′-H), 6.39 (d, J = 2.4 Hz, 1H, 8-H), 6.57 (dd, J = 8.7, 2.4 Hz, 1H, 6-H), 7.80 (d, J = 8.7 Hz, 1H, 5-H).

Anal calc for $C_{14}H_{16}O_3$ (232.28): C, 72.39; H, 6.94. Found: C, 72.58; H, 6.76.

• *8-Allyl-2,2-dimethyl-7-hydroxychromanone* **16**

Allyl ether **15** (8.29 g, 35.67 mmol) was heated at 200 °C for 13 h. The solid residue obtained by cooling down to room temperature was triturated with hexane to give 7.89 g (95%) crude **16**, mp: 103–113 °C. Recrystallisation from hexane afforded 4.65 g (55%) pure **16**. Mp: 113–117 °C.

IR: 3 190 (OH), 2 974, 2 932, 2 658 (C=O), 1 640 (C=C), 1 604, 1 584, 1 440, 1 384, 1 372, 1 288, 1 260, 1 242, 1 202 (C–OH), 1 172, 1 108, 1 052, 808, 790 cm^{-1}.

^1H NMR: 1.46 (s, 6H, 2Me), 2.68 (s, 2H, 3-H), 3.44 (d, J = 5.1 Hz, 2H, 1′-H), 5.10, 5.16 (overlapping dd's, 2H, 3′-H), 5.81 (deuterable s, 1H, 7-OH), 5.94 (m, 1H, 2′-H), 6.49 (d, J = 7.9 Hz, 1H, 6-H), 7.72 (d, J = 7.9 Hz, 1H, 5-H).

Anal calc for $C_{14}H_{16}O_3$ (232.28): C, 72.39; H, 6.94. Found: C, 72.26; H, 7.01.

• *2,2-Dimethyl-7-hydroxy-8-propylchromanone* **17**

A solution of chromanone **16** (6.54 g, 28.25 mmol) in methanol (265 mL) was hydrogenated at atmospheric pressure in the presence of 10% Pd/C catalyst (1.09 g) until the consumption of a calculated amount of hydrogen. The catalyst was filtered off, the filtrate was concentrated and the residue was crystallized from hexane to give 5.60 g (85%) white crystalline **17**. Mp: 111–114 °C.

IR: 3 246 br (OH), 2 964, 2 932, 2 868, 1 646 (C=O), 1 600, 1 578, 1 432, 1 386, 1 370, 1 300, 1 260, 1 234, 1 198 (C–OH), 1 176, 1 106, 1 018, 818, 804 cm^{-1}.

^1H NMR: 0.97 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.46 (s, 6H, 2Me), 1.57 (m, 2H, CH_2Me), 2.61 (t, J = 7.3 Hz, 2H, 8-CH_2Et), 2.68 (s, 2H, 3-H), 6.17 (deuterable s, 1H, 7-OH), 6.48 (d, J = 8.5 Hz, 1H, 6-H), 7.68 (d, J = 8.5 Hz, 1H, 5-H).

Anal calc for $C_{14}H_{18}O_3$ (234.30): C, 71.77; H, 7.74. Found: C, 71.66; H, 7.51.

Cyanoalkylation of hydroxychromones **9** *and -chromanone* **17**: *general procedure*

A mixture of hydroxy compound **9**, **17** (10.00 mmol), ω-haloalkyl cyanide (14.22 mmol), anhydrous K_2CO_3 (1.5 g, 10.85 mmol), KI (177 mg, 1.07 mmol) and butan-2-one (MEK) or 4-methylpentan-2-one (MIBK) (45 mL) was stirred at reflux temperature. When the reaction was completed (TLC monitoring), the inorganic salts were filtered off, washed with acetone and the combined filtrates were concentrated in vacuo. The crude product was purified by either recrystallization or column chromatography.

• *7-[(3-Cyanopropyl)oxy]-8-propylchromone* **18a**

From **9a** and 4-bromobutanenitrile in MIBK, 4 h, column chromatography (hexane/acetone: 7:3).

Yield: 65%. Mp: 70.5–73.5 °C (diethyl ether).

IR: 3 072, 2 966, 2 954, 2 940, 2 876, 2 238 (CN), 1 642 (C=O), 1 618 (C=C), 1 594, 1 428, 1 268, 1 256 (C–O–C), 1 112, 1 056 (C–O–C), 818 cm^{-1}.

^1H NMR: 0.98 (t, J = 7.3 Hz, 3H, CH_2Me), 1.60 (m, 2H, 8-CH_2CH_2Me), 2.25 (m, 2H, $OCH_2CH_2CH_2CN$), 2.64 (t, J = 6.8 Hz, 2H, CH_2CN), 2.83 (t, J = 7.4 Hz, 2H, CH_2Et), 4.24 (t, J = 6.0 Hz, 2H, OCH_2), 6.29 (d, J = 5.5 Hz, 1H, 3-H), 6.98 (d, J = 9.2 Hz, 1H, 6-H), 7.86 (d, J = 5.5 Hz, 1H, 2-H), 8.10 (d, J = 9.2 Hz, 1H, 5-H).

Anal calc for $C_{16}H_{17}NO_3$ (271.32): C, 70.83; H, 6.32; N, 5.16. Found: C, 71.02; H, 6.22; N, 5.03.

• *7-[(4-Cyanobutyl)oxy]-8-propylchromone* **19a**

From **9a** and 5-chloropentanenitrile in MEK, column chromatography (toluene/acetone: 4:1). Yield: 91%. Brownish oil.

IR (neat): 3 090, 2 968, 2 942, 2 876, 2 244 (CN), 1 664, 1 649 (C=O), 1 626 (C=C), 1 600, 1 466, 1 432, 1 411, 1 358, 1 320, 1 271, 1 255, 1 232 (C–O–C), 1 112, 1 058 (C–O–C), 844, 808 cm^{-1}.

^1H NMR (DMSO-d_6): 0.93 (t, J = 7.4 Hz, 3H, CH_2Me), 1.56 (m, 2H, CH_2Me), 1.72–1.95 (m, 4H, $OCH_2(CH_2)_2CH_2CN$), 2.63 (t, J = 6.7 Hz, 2H, CH_2CN), 2.78 (t, J = 7.4 Hz, 2H, CH_2Et), 4.19 (t, J = 5.9 Hz, 2H, OCH_2), 6.26 (d, J = 6.3 Hz, 1H, 3-H), 7.21 (d, J = 9.0 Hz, 1H, 6-H), 7.91 (d, J = 9.0 Hz, 1H, 5-H), 8.27 (d, J = 6.3 Hz, 1H, 2-H).

Anal calc for $C_{17}H_{19}NO_3$ (285.34): C, 71.56; H, 6.71; N, 4.91. Found: C, 71.62; H, 6.99; N, 4.77.

• *7-[(4-Cyanobutyl)oxy]-2-methyl-8-propylchromone* **19b**

From **9b** and 5-chloropentanenitrile in MIBK, 14.5 h, column chromatography (toluene/absolute methanol: 10:1). Yield: 95%. Mp: 74–76 °C (hexane).

IR: 2 960, 2 874, 2 246 (CN), 1 654 (C=O), 1 598, 1 430, 1 400, 1 368, 1 266 (C–O–C), 1 206, 1 108, 1 058, 850, 814 cm^{-1}.

^1H NMR: 0.96 (t, J = 7.3 Hz, 3H, CH_2Me), 1.60 (m, 2H, CH_2Me), 1.85–2.10 (m, 4H, $OCH_2(CH_2)_2CH_2CN$), 2.39 (s, 3H, 2-Me), 2.50 (t, J = 7.0 Hz, 2H, CH_2CN), 2.83 (t, J = 7.3 Hz, 2H, CH_2Et), 4.14 (t, J = 5.8 Hz, 2H, OCH_2), 6.11 (s, 1H, 3-H), 6.94 (d, J = 8.8 Hz, 1H, 6-H), 8.03 (d, J = 8.8 Hz, 1H, 5-H).

Anal calc for $C_{18}H_{21}NO_3$ (299.37): C, 72.22; H, 7.07; N, 4.68. Found: C, 71.99; H, 7.15; N, 4.49.

• *2-Butyl-7-[(4-cyanobutyl)oxy]-8-propylchromone* **19c**

From **9c** and 5-chloropentanenitrile in MIBK, 23 h, column chromatography (toluene/absolute methanol: 10:1). Yield: 94%. Yellowish syrup.

IR (neat): 2 958, 2 872, 2 244 (CN), 1 650 (C=O), 1 538, 1 392, 1 268 (C–O–C), 1 210, 1 182, 1 111, 1 080, 1 060, 816 cm^{-1}.

^1H NMR: 0.96 (t, J = 7.1 Hz, 6H, CH_2Me + 4′-H), 1.45–1.80 (m, 6H, CH_2Me +2′,3′-H), 1.89–2.12 (m, 4H, $OCH_2(CH_2)_2CH_2CN$), 2.50 (t, J = 7.1 Hz, 2H, CH_2CN), 2.65 (t, J = 7.0 Hz, 3H, 1′-H), 2.83 (t, J = 7.3 Hz, 2H, 8-CH_2Et), 4.16 (t, J = 5.6 Hz, 2H, OCH_2), 6.12 (s, 1H, 3-H), 6.93 (d, J = 9.0 Hz, 1H, 6-H), 8.03 (d, J = 9.0 Hz, 1H, 5-H).

Anal calc for $C_{21}H_{27}NO_3$ (341.45): C, 73.87; H, 7.97; N, 4.10. Found: C, 73.90; H, 8.11; N, 3.91.

• *7-[(4-Cyanobutyl)oxy]-8-propylflavone* ***19d***

From **9d** and 5-chloropentanenitrile in MIBK, 48 h, purified by recrystallization from ethanol.

Yield: 89%. Mp: 108–110 °C.

IR: 2 960, 2 934, 2 244 (CN), 1 642 (C=O), 1 598, 1 430, 1 382, 1 270 (C–O–C), 1 120, 680 cm^{-1}.

^1H NMR: 1.03 (t, J = 7.3 Hz, 3H, CH_2Me), 1.71 (m, 2H, CH_2Me), 1.88–2.14 (m, 4H, $OCH_2(CH_2)_2CH_2CN$), 2.51 (t, J = 6.8 Hz, 2H, CH_2CN), 2.98 (t, J = 7.3 Hz, 2H, CH_2Et), 4.18 (t, J = 6.0 Hz, 2H, OCH_2), 6.79 (s, 1H, 3-H), 7.00 (d, J = 9.3 Hz, 1H, 6-H), 7.53 (m, 3H, 3′,4′,5′-H), 7.92 (m, 2H, 2′,6′-H), 8.10 (d, J = 9.3 Hz, 1H, 5-H).

Anal calc for $C_{23}H_{23}NO_3$ (361.44): C, 76.43; H, 6.41; N, 3.88. Found: C, 76.27; H, 6.49; N, 3.69.

• *7-[(4-Cyanobutyl)oxy]-8-propyl-2-(3-pyridyl)-chromone* ***19e***

From **9e** and 5-chloropentanenitrile in MIBK, 26 h, purified by recrystallization from hexane–ethyl acetate mixture. Yield: 81%. Mp: 110–112 °C.

IR: 3 080, 2 962, 2 872, 2 240 (CN), 1 650 (C=O), 1 600, 1 432, 1 422, 1 384, 1 272 (C–O–C), 1 124, 810, 700 cm^{-1}.

^1H NMR: 1.02 (t, J = 7.2 Hz, 3H, CH_2Me), 1.70 (m, 2H, CH_2Me), 1.87–2.16 (m, 4H, $OCH_2(CH_2)_2CH_2CN$), 2.50 (t, J = 6.8 Hz, 2H, CH_2CN), 2.96 (t, J = 7.4 Hz, 2H, CH_2Et), 4.19 (t, J = 5.7 Hz, 2H, OCH_2), 6.79 (s, 1H, 3-H), 7.01 (d, J = 9.5 Hz, 1H, 6-H), 7.51 (dd, J = 7.8, 5.1 Hz, 1H, 5′-H), 8.11 (d, J = 9.5 Hz, 1H, 5-H), 8.17 (ddd, J = 7.8, 2.0, 1.4 Hz, 1H, 4′-H), 8.79 (dd, J = 5.1, 1.4 Hz, 1H, 6′-H), 9.20 (d, J = 2.0 Hz, 1H, 2′-H).

Anal calc for $C_{22}H_{22}N_2O_3$ (362.43): C, 72.91; H, 6.12; N, 7.73. Found: C, 72.70; H, 6.01; N, 7.92.

• *7-[(4-Cyanobutyl)oxy]-2,2-dimethyl-8-propyl-chromanone* ***25***

From **17** and 5-chloropentanenitrile in MEK, 46 h, column chromatography (toluene/acetone: 4:1). Yield: 94%. Pale yellow oil.

IR (neat): 2 960, 2 870, 2 246 (CN), 1 682 (C=O), 1 594, 1 430, 1 370, 1 276 (C–O–C), 1 234, 1 200, 1 174, 1 116, 796 cm^{-1}.

^1H NMR: 0.96 (t, J = 7.4 Hz, 3H, CH_2Me), 1.46 (s, 6H, 2Me), 1.52 (m, 2H, CH_2Me), 1.80–2.07 (m, 4H, $OCH_2(CH_2)_2CH_2CN$), 2.49 (t, J = 7.0 Hz, 2H, CH_2CN), 2.62 (t, J = 7.4 Hz, 2H, CH_2Et), 2.67 (s, 2H, 3-H), 4.09 (t, J = 5.8 Hz, 2H, OCH_2), 6.52 (d, J = 9.2 Hz, 1H, 6-H), 7.74 (d, J = 9.2 Hz, 1H, 5-H).

Anal calc for $C_{19}H_{25}NO_3$ (315.42): C, 72.35; H, 7.99; N, 4.44. Found: C, 72.51; H, 8.03; N, 4.19.

Chloroalkylation of hydroxychromone ***9a*** *and hydroxychromanone* ***13****: general procedure*

A mixture of hydroxy compound **9a** or **13** (10.00 mmol), α-bromo-ω-chloroalkane (15.00 mmol), anhydrous K_2CO_3 (5.53 g, 40.00 mmol) and absolute acetone (50 mL) was stirred at reflux. After completion of the reaction (TLC monitoring), the inorganic salts were filtered off, washed with acetone, the filtrate was concentrated in vacuo and the oily residue was submitted to column chromatography.

• *7-[(2-Chloroethyl)oxy]-8-propylchromone* ***27***

From **9a** and 1-bromo-2-chloroethane (2.8 equiv), 72 h, column chromatography (hexane/acetone: 7:3). Yield: 79%. Mp: 63–65 °C (hexane–acetone).

IR: 2 962, 2 934, 2 872, 1 652 (C=O), 1 634 (C=C), 1 590, 1 428, 1 412, 1 288, 1 272 (C–O–C), 1 246, 1 232, 1 118, 846, 810 cm^{-1}.

^1H NMR: 0.97 (t, J = 7.3 Hz, 3H, CH_2Me), 1.59 (m, 2H, CH_2Me), 2.81 (t, J = 7.3 Hz, 2H, CH_2Et), 3.66 (t, J = 6.7 Hz, 2H, CH_2Cl), 4.13 (t, J = 5.9 Hz, 2H, OCH_2), 6.28 (d, J = 5.8 Hz, 1H, 3-H), 6.97 (d, J = 9.1 Hz, 1H, 6-H), 7.84 (d, J = 5.8 Hz, 1H, 2-H), 8.06 (d, J = 9.1 Hz, 1H, 5-H).

Anal calc for $C_{14}H_{15}ClO_3$ (266.73): C, 63.04; H, 5.67. Found: C, 62.87; H, 5.73.

• *7-[(3-Chloropropyl)oxy]-8-propylchromone* ***28***

From **9a** and 1-bromo-3-chloropropane, 15 h, column chromatography (hexane/acetone: 7:3). Yield: 72%. Mp: 74–75.5 °C (hexane–acetone).

IR (CCl_4): 2 962, 2 932, 2 870, 1 648 (C=O), 1 620 (C=C), 1 594, 1 460, 1 428, 1 402, 1 354, 1 318, 1 266 (C–O–C), 1 230, 1 112, 1 056, 844, 812 cm^{-1}.

^1H NMR: 0.98 (t, J = 7.4 Hz, 3H, CH_2Me), 1.61 (m, 2H, CH_2Me), 2.31 (m, 2H, $OCH_2CH_2CH_2Cl$), 2.82 (t, J = 7.4 Hz, 2H, CH_2Et), 3.79 (t, J = 6.9 Hz, 2H, CH_2Cl), 4.26 (t, J = 6.0 Hz, 2H, OCH_2), 6.29 (d, J = 6.0 Hz, 1H, 3-H), 7.01 (d, J = 9.0 Hz, 1H, 6-H), 7.86 (d, J = 6.0 Hz, 1H, 2-H), 8.09 (d, J = 9.0 Hz, 1H, 5-H).

MS: 282 (17%, $M^{+\bullet}$ for ^{37}Cl isotope), 280 (48, $M^{+\bullet}$), 253 (30) + 251 (84), 215 (3), 203 (4.5), 189 (5), 175 (100), 159 (6), 149 (15), 147 (4), 131 (4), 115 (4), 93 (5), 91 (5), 77 (14).

Anal calc for $C_{15}H_{17}ClO_3$ (280.75): C, 64.17; H, 6.10. Found: C, 64.00; H, 5.98.

• *7-[(4-Chlorobutyl)oxy]-8-propylchromone* ***29***

From **9a** and 1-bromo-4-chlorobutane, 10 h, column chromatography (toluene–absolute methanol: 10:1). Yield: 78%. Mp: 73–75 °C (hexane–acetone).

IR: 2 960, 2 934, 2 872, 1 652 (C=O), 1 636 (C=C), 1 592, 1 428, 1 408, 1 398, 1 286, 1 270 (C–O–C), 1 246, 1 230, 1 116, 1 056, 846, 814 cm^{-1}.

^1H NMR: 0.98 (t, J = 7.3 Hz, 3H, CH_2Me), 1.48 (m, 2H, CH_2Me), 2.02 (m, 4H, $OCH_2(CH_2)_2CH_2Cl$), 2.82 (t, J = 7.3 Hz, 2H, CH_2Et), 3.66 (t, J = 6.9 Hz, 2H, CH_2Cl), 4.12 (t, J = 5.7 Hz, 2H, OCH_2), 6.28 (d, J = 5.7 Hz, 1H, 3-H), 6.99 (d, J = 9.0 Hz, 1H, 6-H), 7.85 (d, J = 5.7 Hz, 1H, 2-H), 8.07 (d, J = 9.0 Hz, 1H, 5-H).

Anal calc for $C_{16}H_{19}ClO_3$ (294.78): C, 65.19; H, 6.50. Found: C, 65.23; H, 6.81.

• *7-[(3-Chloropropyl)oxy]-8-propylchromanone* ***36***

From **13** and 1-bromo-3-chloropropane, 12 h, purified by crystallization from hexane–absolute ethanol mixture. Yield: 62%. Mp: 70–72 °C.

IR: 2 964, 2 938, 2 874, 1 674 (C=O), 1 600, 1 434, 1 378, 1 344, 1 268 (C–O–C), 1 112, 794 cm^{-1}.

^1H NMR: 0.94 (t, J = 7.3 Hz, 3H, CH_2Me), 1.51 (m, 2H, CH_2Me), 2.28 (m, 2H, $OCH_2CH_2CH_2Cl$), 2.60 (t, J = 7.3 Hz, 2H, CH_2Et), 2.76 (d, J = 5.9 Hz, 1H, 3-H), 3.76 (t, J = 7.0 Hz, 2H, CH_2Cl), 4.20 (t, J = 5.8 Hz, 2H, OCH_2), 4.51 (d, J = 5.9 Hz, 1H, 2-H), 6.60 (d, J = 9.2 Hz, 1H, 6-H), 7.81 (d, J = 9.2 Hz, 1H, 5-H).

Anal calc for $C_{15}H_{19}ClO_3$ (282.77): C, 63.72; H, 6.77. Found: C, 63.96; H, 6.89.

*Synthesis of thiocyanates **30–32** and **37**: general procedure*

A mixture of chloride **27–29** or **36** (20.00 mmol), KSCN (1.22 g, 12.55 mmol) and MIBK (30 mL) was stirred at reflux. Two additional portions of KSCN (1.22 g, 12.55 mmol each) were added during the reaction period. After completion of the reaction (TLC monitoring), the inorganic salts were filtered off, washed and the filtrate was concentrated under reduced pressure. The oily residue was treated with diethyl ether (50 mL), filtered, the solvent was removed in vacuo and the crude product was purified by column chromatography.

• *8-Propyl-7-[(2-thiocyanatoethyl)oxy]chromone **30***

From **27**, 168 h, column chromatography (hexane/acetone: 7:3). Yield: 82%. Mp: 69–72 °C (hexane–acetone).

IR: 2 962, 2 872, 2 156 (SCN), 1 650 (C=O), 1 594, 1 462, 1 428, 1 354, 1 318, 1 268 (C–O–C), 1 196, 1 140, 1 114, 1 072, 1 046, 848, 810 cm^{-1}.

^1H NMR: 0.98 (t, J = 7.3 Hz, 3H, CH_2Me), 1.61 (m, 2H, CH_2Me), 2.85 (t, J = 7.4 Hz, 2H, CH_2Et), 3.43 (t, J = 7.0 Hz, 2H, CH_2SCN), 4.46 (t, J = 5.7 Hz, 2H, OCH_2), 6.30 (d, J = 6.0 Hz, 1H, 3-H), 6.98 (d, J = 9.1 Hz, 1H, 6-H), 7.89 (d, J = 6.0 Hz, 1H, 2-H), 8.10 (d, J = 9.1 Hz, 1H, 5-H).

Anal calc for $C_{15}H_{15}NO_3S$ (289.36): C, 62.27; H, 5.23; N, 4.84. Found: C, 62.05; H, 5.27; N, 4.65.

• *8-Propyl-7-[(3-thiocyanatopropyl)oxy]chromone **31***

From **28**, 32 h, column chromatography (toluene/ethyl acetate: 4:1. Yield: 69%. Colourless thick oil.

IR (neat): 2 960, 2 932, 2 870, 2 152 (SCN), 1 646 (C=O), 1 618 (C=C), 1 592, 1 462, 1 426, 1 402, 1 354, 1 318, 1 254 (C–O–C), 1 228, 1 110, 1 054, 844, 810 cm^{-1}.

^1H NMR: 0.96 (t, J = 7.3 Hz, 3H, CH_2Me), 1.58 (m, 2H, CH_2Me), 2.40 (m, 2H, $OCH_2CH_2CH_2SCN$), 2.81 (t, J = 7.4 Hz, 2H, CH_2Et), 3.21 (t, J = 7.0 Hz, 2H, CH_2SCN), 4.27 (t, J = 5.6 Hz, 2H, OCH_2), 6.30 (d, J = 6.1 Hz, 1H, 3-H), 6.99 (d, J = 9.0 Hz, 1H, 6-H), 7.86 (d, J = 6.1 Hz, 1H, 2-H), 8.08 (d, J = 9.0 Hz, 1H, 5-H).

Anal calc for $C_{16}H_{17}NO_3S$ (303.38): C, 63.35; H, 5.65; N, 4.62. Found: C, 63.49; H, 5.39; N, 4.55.

• *8-Propyl-7-[(4-thiocyanatobutyl)oxy]chromone **32***

From **29**, 96 h, column chromatography (hexane/acetone: 7:3). Yield: 81%. Mp: 29–30 °C (hexane).

IR: 2 960, 2 870, 2 154 (SCN), 1 650 (C=O), 1 620 (C=C), 1 594, 1 456, 1 428, 1 408, 1 354, 1 316, 1 268 (C–O–C), 1 230, 1 112, 1 058, 810 cm^{-1}.

^1H NMR: 0.98 (t, J = 7.3 Hz, 3H, CH_2Me), 1.60 (m, 2H, CH_2Me), 2.09 (m, 4H, $OCH_2(CH_2)_2CH_2SCN$), 2.82 (t, J = 7.3 Hz, 2H, CH_2Et), 3.09 (t, J = 6.9 Hz, 2H, CH_2SCN), 4.16 (t, J = 5.7 Hz, 2H, OCH_2), 6.29 (d, J = 6.1 Hz, 1H, 3-H), 6.98 (d, J = 9.3 Hz, 1H, 6-H), 7.86 (d, J = 6.1 Hz, 1H, 2-H), 8.07 (d, J = 9.3 Hz, 1H, 5-H).

Anal calc for $C_{17}H_{19}NO_3S$ (317.41): C, 64.33; H, 6.03; N, 6.03. Found: C, 64.17; H, 5.83; N, 4.59.

• *8-Propyl-7-[(3-thiocyanatopropyl)oxy]chromanone **37***

From **38**, 72 h, column chromatography (hexane/acetone: 7:3). Yield: 82%. Colourless oil.

IR (neat): 2 958, 2 870, 2 154 (SCN), 1 682 (C=O), 1 594, 1 468, 1 434, 1 382, 1 344, 1 252 (C–O–C), 1 206, 1 176, 1 120, 1 054, 806, 810 cm^{-1}.

^1H NMR: 0.95 (t, J = 7.2 Hz, 3H, CH_2Me), 1.50 (m, 2H, CH_2Me), 2.36 (m, 2H, $OCH_2CH_2CH_2SCN$), 2.59 (t, J = 7.4 Hz, 2H, CH_2Et), 2.75 (t, J = 6.2 Hz, 2H, 3-H), 3.19 (t, 2H, CH_2SCN), 4.20 (t, 2H, OCH_2), 4.51 (t, J = 6.2 Hz, 2H, 2-H), 6.59 (d, J = 9.0 Hz, 1H, 6-H), 7.80 (d, J = 9.0 Hz, 1H, 5-H).

Anal calc for $C_{16}H_{19}NO_3S$ (305.40): C, 62.93; H, 6.27; N, 4.59. Found: C, 63.11; H, 6.42; N, 4.40.

*Preparation of tetrazoles **20**, **21**, **26**, **33–35** and **38**: general procedure*

A solution of cyanide **18**, **19**, **25** or thiocyanate **30–32**, **37** (6.00 mmol) and tributyltin azide (6.00 g, 18.07 mmol) in 1,2-dimethoxyethane (DME) or diglyme (25 mL, dried over 4 Å molecular sieve) was refluxed. After completion of the reaction (TLC monitoring) the mixture was filtered into a mixture of 4 M HCl solution (100 mL) and toluene (40 mL) and stirred overnight. After separation the aqueous layer was extracted with toluene, the combined organic layers were dried, concentrated and treated with hexane to obtain the crude tetrazole. When the crude product precipitated during the acidic work-up, it was filtered off and washed with water. Crude tetrazoles were recrystallized from the solvent specified below to afford pure products.

• *8-Propyl-7-[(3-tetrazol-5-ylpropyl)oxy]chromone **20a***

From **18a** in diglyme, 2.5 h. Yield: 62%. Mp: 118–122 °C (MEK).

IR: 3 070, 2 962, 1 622 (C=O), 1 596, 1 492, 1 430, 1 276 (C–O–C), 1 116, 1 046 cm^{-1}.

^1H NMR (DMSO-d_6): 0.92 (t, J = 7.2 Hz, 3H, CH_2Me), 1.55 (m, 2H, CH_2Me), 2.24 (m, 2H, $OCH_2CH_2CH_2Tet$), 2.73 (t, J = 7.4 Hz, 2H, CH_2Et), 3.11 (t, J = 6.6 Hz, 2H, CH_2Tet), 4.23 (t, J = 5.6 Hz, 2H, OCH_2), 6.26 (d, J = 6.1 Hz, 1H, 3-H), 7.21 (d, J = 9.3 Hz, 1H, 6-H), 7.90 (d, J = 9.3 Hz, 1H, 5-H), 8.28 (d, J = 6.1 Hz, 1H, 2-H). The tetrazole NH signal coalesced with the water content of DMSO.

Anal calc for $C_{16}H_{18}N_4O_3$ (314.35): C, 61.14; H, 5.77; N, 17.82. Found: C, 61.02; H, 5.93; N, 17.49.

• *8-Propyl-7-[(4-tetrazol-5-ylbutyl)oxy]chromone **21a***

From **19a** in DME, 1 h. Yield: 84%. Mp: 118–122 °C (ethyl acetate).

IR: 2 964, 2 872, 1 640 (C=O), 1 622 (C=C), 1 596, 1 423, 1 286 (C–O–C), 1 113, 813 cm^{-1}.

^1H NMR (DMSO-d_6): 0.89 (t, J = 7.4 Hz, 3H, CH_2Me), 1.54 (m, 2H, CH_2Me), 1.88 (m, 4H, $OCH_2(CH_2)_2CH_2Tet$), 2.77 (t, J = 7.4 Hz, 2H, CH_2Et), 3.00 (t, J = 7.0 Hz, 2H, CH_2Tet), 4.18 (t, J = 5.9 Hz, 2H, OCH_2), 6.26 (d, J = 6.3 Hz, 1H, 3-H), 7.21 (d, J = 9.1 Hz, 1H, 6-H), 7.90 (d, J = 9.1 Hz, 1H, 5-H), 8.27 (d, J = 6.3 Hz, 1H, 2-H).

Anal calc for $C_{17}H_{20}N_4O_3$ (328.37): C, 62.18; H, 6.14; N, 17.06. Found: C, 61.95; H, 6.07; N, 16.87.

• *2-Methyl-8-propyl-7-[(4-tetrazol-5-ylbutyl)oxy]-chromone **21b***

From **19b** in DME, 2 h. Yield: 78%. Mp: 130–132 °C (hexane–absolute ethanol).

IR: 2 960, 2 870, 1 636 (C=O), 1 578, 1 432, 1 404, 1 298, 1 270 (C–O–C), 1 212, 1 122, 1 054 cm^{-1}.

^{1}H NMR: 0.88 (t, J = 7.3 Hz, 3H, CH_2Me), 1.52 (m, 2H, CH_2Me), 1.92, 2.14 (2m, 2 × 2H, $OCH_2(CH_2)_2CH_2$Tet), 2.42 (s, 3H, 2-Me), 2.74 (t, J = 7.3 Hz, 2H, CH_2Et), 3.20 (t, J = 7.2 Hz, J = 6.9 Hz, 2H, CH_2Tet), 4.06 (t, J = 5.7 Hz, 2H, OCH_2), 6.27 (s, 1H, 3-H), 6.78 (d, J = 9.2 Hz, 1H, 6-H), 7.86 (d, J = 9.2 Hz, 1H, 5-H).

Anal calc for $C_{18}H_{22}N_4O_3$ (342.40): C, 63.14; H, 6.48; N, 16.36. Found: C, 62.91; H, 6.66; N, 16.41.

• *2-Butyl-8-propyl-7-[(4-tetrazol-5-ylbutyl)oxy]-chromone* **21c**

From **19c** in diglyme, 1.5 h. Yield: 68%. Mp: 101–103 °C (hexane–absolute ethanol).

IR: 2 956, 2 934, 2 870, 1 628 (C=O), 1 612 (C=C), 1 576, 1 554, 1 430, 1 406, 1 270 (C–O–C), 1 122, 1 028 cm^{-1}.

^{1}H NMR: 0.89 (t, J = 7.2 Hz, 3H, CH_2Me), 0.98 (t, J = 6.8 Hz, 3H, 4′-H), 1.36–1.60 (m, 4H, CH_2Me + 3′-H), 1.73 (m, 2H, 2′-H), 1.92, 2.16 (2m, 2 × 2H, $OCH_2(CH_2)_2CH_2$Tet), 2.67, 2.76 (overlapping triplets, 2 × 2H, CH_2Et + 1′-H), 3.19 (t, J = 6.9 Hz, 2H, CH_2Tet), 4.07 (t, J = 5.7 Hz, 2H, OCH_2), 6.26 (s, 1H, 3-H), 6.73 (d, J = 8.9 Hz, 1H, 6-H), 7.86 (d, J = 8.9 Hz, 1H, 5-H).

Anal calc for $C_{21}H_{28}N_4O_3$ (384.48): C, 65.60; H, 7.34; N, 14.57. Found: C, 65.73; H, 7.17; N, 14.54.

• *8-Propyl-7-[(4-tetrazol-5-ylbutyl)oxy]flavone* **21d**

From **19d** in DME, 4.5 h. Yield: 83%. Mp: 181.5–183 °C (hexane–absolute ethanol).

IR: 2 960, 2 932, 2 870, 1 620 (C=O), 1 586, 1 430, 1 392, 1 268 (C–O–C), 1 208, 1 120, 1 040, 774 cm^{-1}.

^{1}H NMR (DMSO-d_6): 0.92 (t, J = 7.3 Hz, 3H, CH_2Me), 1.62 (m, 2H, CH_2Me), 1.90 (m, 4H, $OCH_2(CH_2)_2CH_2$Tet), 2.86–3.05 (overlapping triplets, 2 × 2H, CH_2Et + CH_2Tet), 4.19 (t, J = 5.7 Hz, 2H, OCH_2), 6.96 (s, 1H, 3-H), 7.22 (d, J = 9.0 Hz, 1H, 6-H), 7.60 (m, 3H, 3′,4′,5′-H), 7.90 (d, J = 9.0 Hz, 1H, 5-H), 8.06 (m, 2H, 2′,6′-H).

Anal calc for $C_{23}H_{24}N_4O_3$ (404.47): C, 68.30; H, 5.98; N, 13.85. Found: C, 68.16; H, 6.17; N, 14.08.

• *8-Propyl-2-(3-pyridyl)-7-[(4-tetrazol-5-ylbutyl)-oxy]chromone* **21e**

From **19e** in diglyme, 1.75 h. Yield: 71%. Mp: 174–175 °C (methanol).

IR: 2 954, 2 870, 1 628 (C=O), 1 590, 1 560, 1 428, 1 386, 1 272 (C–O–C), 1 122, 1 054, 810 cm^{-1}.

^{1}H NMR (DMSO-d_6): 0.93 (t, J = 7.4 Hz, 3H, CH_2Me), 1.63 (m, 2H, CH_2Me), 1.88 (m, 4H, $OCH_2(CH_2)_2CH_2$Tet), 2.73–3.03 (overlapping triplets, 2 × 2H, CH_2Et + CH_2Tet), 4.20 (t, J = 5.8 Hz, 2H, OCH_2), 7.10 (s, 1H, 3-H), 7.24 (d, J = 8.9 Hz, 1H, 6-H), 7.66 (dd, J = 8.1, 4.8 Hz, 1H, 5′-H), 7.93 (d, J = 8.9 Hz, 1H, 5-H), 8.44 (ddd, J = 8.1, 2.0, 1.3 Hz, 1H, 4′-H), 8.79 (dd, J = 4.8, 1.3 Hz, 1H, 6′-H), 9.25 (d, J = 2.0 Hz, 1H, 2′-H).

Anal calc for $C_{22}H_{23}N_5O_3$ (405.46): C, 65.17; H, 5.72; N, 17.27. Found: C, 65.23; H, 5.54; N, 17.41.

• *2,2-Dimethyl-8-propyl-7-[(4-tetrazol-5-ylbutyl)oxy]-chromanone* **26**

From **17** using 4.3 equiv tributyltin azide in DME, 50 h. Yield: 71%. Mp: 97–99 °C (hexane–diisopropyl ether–MEK).

IR: 2 960, 2 872, 1 692 (C=O), 1 600, 1 428, 1 384, 1 324, 1 306, 1 276 (C–O–C), 1 328, 1 228, 1 172, 1 118, 792 cm^{-1}.

^{1}H NMR: 0.89 (t, J = 7.4 Hz, 3H, CH_2Me), 1.43 (s, 6H, 2 × Me), 1.51 (m, 2H, CH_2Me), 1.91, 2.10 (2m, 2 × 2H, $OCH_2(CH_2)_2CH_2$Tet), 2.56 (t, J = 7.4 Hz, 2H, CH_2Et), 2.70 (s, 2H, 3-H), 3.14 (t, J = 6.9 Hz, 2H, CH_2Tet), 4.05 (t, J = 5.9 Hz, 2H, OCH_2), 6.45 (d, J = 9.1 Hz, 1H, 6-H), 7.68 (d, J = 9.1 Hz, 1H, 5-H).

Anal calc for $C_{19}H_{26}N_4O_3$ (358.44): C, 63.67; H, 7.31; N, 15.63. Found: C, 63.79; H, 7.25; N, 15.61.

• *8-Propyl-7-{[2-(tetrazol-5-ylthio)ethyl]oxy}-chromone* **33**

From **30** in DME, 4 h. Yield: 72%. Mp: 171–173 °C (hexane–acetone).

IR: 2 964, 2 934, 2 874, 2 718 (assoc NH), 1 624 (C=O), 1 578, 1 420, 1 268 (C–O–C), 1 234, 1 118, 1 054, 1 034, 818 cm^{-1}.

^{1}H NMR (DMSO-d_6): 0.88 (t, J = 7.1 Hz, 3H, CH_2Me), 1.51 (m, 2H, CH_2Me), 2.69 (t, J = 7.3 Hz, 2H, CH_2Et), 3.77 (t, J = 7.0 Hz, 2H, CH_2STet), 4.48 (t, J = 5.6 Hz, 2H, OCH_2), 6.28 (d, J = 5.9 Hz, 1H, 3-H), 7.24 (d, J = 9.4 Hz, 1H, 6-H), 7.90 (d, J = 9.4 Hz, 1H, 5-H), 8.29 (d, J = 5.9 Hz, 1H, 2-H).

Anal calc for $C_{15}H_{16}N_4O_3S$ (332.38): C, 54.20; H, 4.85; N, 16.86. Found: C, 53.98; H, 4.99; N, 16.66.

• *8-Propyl-7-{[3-(tetrazol-5-ylthio)propyl]oxy}-chromone* **34**

From **31** in DME, 4 h. Yield: 84%. Mp: 134–136 °C (hexane–acetone).

IR: 2 954, 2 932, 2 872, 2 686 (assoc NH), 1 624 (C=O), 1 572, 1 424, 1 278 (C–O–C), 1 256, 1 114, 1 004, 812 cm^{-1}.

^{1}H NMR (DMSO-d_6): 0.91 (t, J = 7.3 Hz, 3H, CH_2Me), 1.56 (m, 2H, CH_2Me), 2.22 (m, 2H, $OCH_2CH_2CH_2$STet), 2.79 (t, J = 7.4 Hz, 2H, CH_2Et), 3.48 (t, J = 6.9 Hz, 2H, CH_2STet), 4.27 (t, J = 5.8 Hz, 2H, OCH_2), 6.27 (d, J = 5.9 Hz, 1H, 3-H), 7.21 (d, J = 9.0 Hz, 1H, 6-H), 7.90 (d, J = 9.0 Hz, 1H, 5-H), 8.28 (d, J = 5.9 Hz, 1H, 2-H).

Anal calc for $C_{16}H_{18}N_4O_3S$ (346.41): C, 55.48; H, 5.24; N, 16.17. Found: C, 55.57; H, 5.11; N, 16.19.

• *8-Propyl-7-{[4-(tetrazol-5-ylthio)butyl]oxy}-chromone* **35**

From **32** in DME, 7 h. Yield: 60%. Mp: 106–109 °C (hexane–acetone).

IR: 3 066, 2 932, 2 870, 2 784, 2 724 (assoc NH), 1 628 (C=O), 1 582, 1 430, 1 416, 1 298, 1 272 (C–O–C), 1 232, 1 114, 1 056, 1 030, 816 cm^{-1}.

^{1}H NMR: 0.92 (t, J = 7.4 Hz, 3H, CH_2Me), 1.55 (m, 2H, CH_2Me), 2.02 (m, 4H, $OCH_2(CH_2)_2CH_2$STet), 2.78 (t, J = 7.4 Hz, 2H, CH_2Et), 3.41 (t, J = 6.9 Hz, 2H, CH_2STet), 4.12 (t, J = 5.9 Hz, 2H, OCH_2), 6.39 (d, J = 5.8 Hz, 1H, 3-H), 6.94 (d, J = 9.2 Hz, 1H, 6-H), 7.91 (d, J = 5.8 Hz, 1H, 2-H), 8.04 (d, J = 9.2 Hz, 1H, 5-H).

Anal calc for $C_{17}H_{20}N_4O_3S$ (360.44): C, 56.65; H, 5.59; N, 15.54. Found: C, 56.91; H, 5.63; N, 15.67.

• *8-Propyl-7-{[3-(tetrazol-5-ylthio)propyl]oxy}-chromanone* **38**

From **37** in DME, 4 h. Yield: 83%. Mp: 112–115 °C (hexane–acetone).

IR: 2 958, 2 928, 2 868, 2 734 (assoc NH), 1 670 (C=O), 1 598, 1 468, 1 434, 1 376, 1 274 (C–O–C), 1 254, 1 206, 1 124, 1 052, 1 036 cm^{-1}.

^{1}H NMR (DMSO-d_6): 0.89 (t, J = 7.1 Hz, 3H, CH_2Me), 1.45 (m, 2H, CH_2Me), 2.18 (m, 2H, $OCH_2CH_2CH_2$STet), 2.56 (t, J = 7.3 Hz, 2H, CH_2Et), 2.70 (t, J = 5.8 Hz, 2H, 3-H), 3.40 (t, J = 7.0 Hz, 2H, CH_2STet), 4.18 (t, J = 5.7 Hz, 2H, OCH_2), 4.51 (t, J = 5.8 Hz, 2H, 2-H),

6.77 (d, J = 9.1 Hz, 1H, 6-H), 7.65 (d, J = 9.1 Hz, 1H, 5-H).

Anal calc for $C_{16}H_{20}N_4O_3S$ (348.43): C, 55.16; H, 5.79; N, 16.08. Found: C, 55.01; H, 5.96; N, 16.09.

• *8-Propyl-7-({4-[2-(4-tetrazol-5-ylbutyl)-2H-tetrazol-5-yl]butyl}oxy)chromone* **49**

From **48** in diglyme, 2.25 h, column chromatography (toluene–ethyl acetate–formic acid, 5:4:1). Yield: 66%. Pale yellow oil.

IR (neat): 2 958, 2 870, 1 626 (C=O), 1 588, 1 428, 1 272 (C–O–C), 1 232, 1 114, 1 056, 812 cm^{-1}.

^1H NMR: 0.92 (t, J = 7.3 Hz, 3H, CH_2Me), 1.57 (m, 2H, CH_2Me), 1.84–2.15 (m, 8H, $OCH_2(CH_2)_2CH_2Tet$ + $NCH_2(CH_2)_2CH_2Tet$), 2.81 (t, J = 7.4 Hz, 2H, CH_2Et), 2.98 (t, J = 6.8 Hz, 2H, CH_2Tet), 3.10 (t, J = 7.0 Hz, 2H, $N(CH_2)_3CH_2Tet$), 4.16 (t, J = 5.7 Hz, 2H, OCH_2), 4.61 (t, J = 6.3 Hz, 2H, NCH_2), 6.39 (d, J = 6.1 Hz, 1H, 3-H), 7.00 (d, J = 9.0 Hz, 1H, 6-H), 7.95 (d, J = 6.1 Hz, 1H, 2-H), 8.03 (d, J = 9.0 Hz, 1H, 5-H).

Anal calc for $C_{22}H_{28}N_8O_3$ (452.52): C, 58.39; H, 6.24; N, 24.76. Found: C, 58.18; H, 6.46; N, 24.53.

• *8-Propyl-7-[(3-tetrazol-5-ylpropyl)oxy]chromanone* **22**

A mixture of chromone **20a** (1.61 g, 5.13 mmol), ammonium formate (2.62 g, 41.60 mmol) and 10% Pd/C catalyst (1.31 g) in methanol (125 mL) was stirred at reflux for 1.5 h, then the catalyst was filtered off and washed. The combined filtrates were concentrated in vacuo and the oily residue was treated with 5% HCl solution. The solidified crude product was washed with water and submitted to column chromatography (toluene–ethyl acetate–formic acid, 20:20:1) to give pure chromanone **22** (920 mg, 57%). Mp: 146–149 °C (hexane–diethyl ether).

IR: 2 956, 2 932, 2 870, 1 656 (C=O), 1 596, 1 436, 1 382, 1 274, 1 266 (C–O–C), 1 124, 1 056 cm^{-1}.

^1H NMR (DMSO-d_6): 0.89 (t, J = 7.2 Hz, 3H, CH_2Me), 1.44 (m, 2H, CH_2Me), 2.20 (m, 2H, $OCH_2CH_2CH_2Tet$), 2.48 (t, J = 7.4 Hz, 2H, CH_2Et), 2.71 (t, J = 6.5 Hz, 2H, 3-H), 3.08 (t, J = 7.0 Hz, 2H, CH_2Tet), 4.13 (t, J = 5.7 Hz, 2H, OCH_2), 4.50 (t, J = 6.5 Hz, 2H, 2-H), 6.76 (d, J = 9.0 Hz, 1H, 6-H), 7.64 (d, J = 9.0 Hz, 1H, 5-H).

Anal calc for $C_{16}H_{20}N_4O_3$ (316.36): C, 60.75; H, 6.37; N, 17.71. Found: C, 60.81; H, 6.11; N, 17.52.

• *8-Propyl-7-[(4-tetrazol-5-ylbutyl)oxy]-chromanone* **23**

From **21a** according to the procedure given for **22**, purified by recrystallization from a diisopropyl ether–MEK mixture. Yield: 73%. Mp: 131–135 °C.

IR: 2 968, 2 943, 2 875, 1 680 (C=O), 1 609, 1 440, 1 275, 1 256 (C–O–C + chromanone skeleton), 1 126 cm^{-1}.

^1H NMR (DMSO-d_6): 0.87 (t, 3H, 8-$(CH_2)_2Me$), 1.46 (m, 2H, 8-CH_2CH_2Me), 2.83 (m, 4H, 7-$OCH_2(CH_2)_2CH_2Tet$), 2.54 (t, 2H, 8-CH_2Et), 2.70 (t, J = 6.3 Hz, 2H, 3-H), 2.98 (t, 2H, CH_2Tet), 4.10 (t, 2H, OCH_2), 4.51 (t, J = 6.3 Hz, 2H, 2-H), 6.75 (d, J = 9.4 Hz, 1H, 6-H), 7.65 (d, J = 9.4 Hz, 1H, 5-H).

Anal calc for $C_{17}H_{22}N_4O_3$ (330.39): C, 61.80; H, 6.71; N, 16.96. Found: C, 61.57; H, 6.95; N, 17.05.

• *4-Hydroxyimino-8-propyl-7-[(3-tetrazol-5-ylpropyl)oxy]chroman* **24**

A mixture of chromanone **22** (538 mg, 1.70 mmol), hydroxylammonium chloride (958 mg, 13.79 mmol), ethanol (14 mL) and water (4 mL) was refluxed for 1.5 h then diluted with water (30 mL). After cooling the precipitated crude product was filtered off and purified by column chromatography (toluene/ethyl acetate/formic acid, 5:4:1) to give 495 mg (56%) of oxime **24**. Mp: 162–166 °C (dec) (hexane–acetone).

IR: 3 384 br (OH), 2 960, 2 870, 1 598, 1 470, 1 434, 1 378, 1 270 (C–O–C), 1 210, 1 122, 1 058 cm^{-1}.

^1H NMR: 0.88 (t, J = 7.3 Hz, 3H, CH_2Me), 1.43 (m, 2H, CH_2Me), 2.19 (m, 2H, $OCH_2CH_2CH_2Tet$), 2.48 (t, J = 7.4 Hz, 2H, CH_2Et), 2.79 (t, J = 6.4 Hz, 2H, 3-H), 3.07 (t, 2H, CH_2Tet), 4.07, 4.17 (overlapping triplets, 2 × 2H, OCH_2 + 2-H), 6.64 (d, J = 8.9 Hz, 1H, 6-H), 7.61 (d, J = 8.9 Hz, 1H, 5-H), 10.95 (s, 1H, OH).

Anal calc for $C_{16}H_{21}N_5O_3$ (331.38): C, 57.99; H, 6.39; N, 21.13. Found: C, 58.11; H, 6.52; N, 20.78.

Alkylation of tetrazole **21**: *general procedure*

To a stirred and cooled (0–5 °C) suspension of 60% NaH in mineral oil (0.65 g, ca 16.25 mmol, rinsed with dry hexane prior to use) and absolute diethyl ether (25 mL), a solution of tetrazole **21** (4.284 g, 13.05 mmol) in absolute DMF (70 mL) was added dropwise in 70 min. The mixture was stirred for 30 min, then a solution of ethyl ω-chloroalkanoate or 5-chloropentanenitrile (18.92 mmol) in absolute DMF (10 mL) was dropped in 30 min and allowed to react at room temperature. When the reaction was completed (TLC monitoring), the mixture was poured into brine (500 mL), extracted with diethyl ether (5 × 100 mL) and dried. The solvents were removed in vacuo and the residue was submitted to column chromatography (benzene/absolute methanol, 20:1).

• *7-({4-[1-(Ethoxycarbonylmethyl)-1H-tetrazol-5-yl]butyl}oxy)-8-propylchromone* **39** *and 7-({4-[2-(ethoxycarbonylmethyl)-2H-tetrazol-5-yl]butyl}oxy)-8-propylchromone* **41**

Using ethyl chloroacetate as alkylating agent, 16 h.

■ ***39***

Yield: 52%. Mp: 85–87 °C (hexane). R_f = 0.13 (benzene/absolute methanol, 20:1).

IR: 2 964, 2 937, 1 749 (C=O, ester), 1 646 (C=O, chromone), 1 619 (C=C), 1 595, 1 428, 1 408, 1 266 (C–O–C), 1 228, 1 113 cm^{-1}.

^1H NMR: 0.94 (t, J = 7.2 Hz, 3H, CH_2Me), 1.29 (t, J = 6.8 Hz, 3H, $COOCH_2Me$), 1.58 (m, 2H, CH_2Me), 1.95–2.17 (m, 4H, $OCH_2(CH_2)_2CH_2Tet$), 2.80 (t, J = 7.3 Hz, 2H, CH_2Et), 2.94 (t, J = 7.0 Hz, 2H, CH_2Tet), 4.15 (t, J = 5.7 Hz, 2H, OCH_2), 4.27 (q, J = 6.8 Hz, 2H, $COOCH_2Me$), 5.18 (s, 2H, NCH_2), 6.24 (d, J = 6.0 Hz, 1H, 3-H), 6.97 (d, J = 9.1 Hz, 1H, 6-H), 7.87 (d, J = 6.0 Hz, 1H, 2-H), 8.02 (d, J = 9.1 Hz, 1H, 5-H).

Anal calc for $C_{21}H_{26}N_4O_5$ (414.47): C, 60.86; H, 6.32; N, 13.52. Found: C, 60.63; H, 6.37; N, 13.44.

■ ***41***

Yield: 43%. Pale yellow oil. R_f = 0.24 (benzene/absolute methanol, 20:1).

IR (neat): 2 960, 1 756 (C=O, ester), 1 651 (C=O, chromone), 1 619 (C=C), 1 595, 1 429, 1 407, 1 351, 1 270 (C–O–C), 1 228, 1 216, 1 113, 1 020, 811 cm^{-1}.

^{1}H NMR: 0.95 (t, J = 7.2 Hz, 3H, CH_2Me), 1.30 (t, J = 6.9 Hz, 3H, $COOCH_2Me$), 1.59 (m, 2H, CH_2Me), 1.87–2.11 (m, 4H, $OCH_2(CH_2)_2CH_2$Tet), 2.80 (t, J = 7.4 Hz, 2H, CH_2Et), 3.07 (t, J = 7.0 Hz, 2H, CH_2Tet), 4.14 (t, J = 5.8 Hz, 2H, OCH_2), 4.28 (q, J = 6.9 Hz, 2H, $COOCH_2$Me), 5.39 (s, 2H, NCH_2), 6.26 (d, J = 6.1 Hz, 1H, 3-H), 6.97 (d, J = 9.1 Hz, 1H, 6-H), 7.86 (d, J = 6.1 Hz, 1H, 2-H), 8.04 (d, J = 9.1 Hz, 1H, 5-H).

Anal calc for $C_{21}H_{26}N_4O_5$ (414.47): C, 60.86; H, 6.32; N, 13.52. Found: C, 60.79; H, 6.18; N, 13.39.

• *7-[(4-{1-[3-(Ethoxycarbonyl)propyl]-1H-tetrazol-5-yl}butyl)oxy]-8-propylchromone* **40** *and 7-[(4-{2-[3-(ethoxycarbonyl)propyl]-2H-tetrazol-5-yl}butyl)oxy]-8-propylchromone* **42**

Using ethyl 4-chlorobutanoate (3.1 equiv) as alkylating agent, 10 days.

■ ***40***

Yield: 19%. Yellow oil. R_f = 0.15 (benzene/absolute methanol, 20:1).

IR (neat): 2 960, 2 935, 2 870, 1 730 (C=O, ester), 1 650 (C=O, chromone), 1 620 (C=C), 1 598, 1 462, 1 426, 1 408, 1 354, 1 320, 1 270 (C–O–C), 1 186, 1 114, 1 058, 812 cm^{-1}.

^{1}H NMR: 0.95 (t, J = 7.1 Hz, 3H, CH_2Me), 1.27 (t, J = 7.0 Hz, 3H, $COOCH_2Me$), 1.58 (m, 2H, CH_2Me), 2.05 (m, 4H, $OCH_2(CH_2)_2CH_2$Tet), 2.22 (m, 2H, $NCH_2CH_2CH_2CO$), 2.43 (t, 2H, CH_2CO), 2.81 (t, J = 7.3 Hz, 2H, CH_2Et), 2.97 (t, J = 5.6 Hz, 2H, $O(CH_2)_3CH_2$Tet), 4.06–4.20 (overlapping triplets, 4H, $OCH_2(CH_2)_3$Tet + $COOCH_2$Me), 4.40 (t, J = 6.8 Hz, 2H, NCH_2), 6.26 (d, J = 5.9 Hz, 1H, 3-H), 6.99 (d, J = 9.0 Hz, 1H, 6-H), 7.86 (d, J = 5.9 Hz, 1H, 2-H), 8.04 (d, J = 9.0 Hz, 1H, 5-H).

Anal calc for $C_{23}H_{30}N_4O_5$ (442.52): C, 62.43; H, 6.83; N, 12.66. Found: C, 62.59; H, 7.03; N, 12.43.

■ ***42***

Yield: 66%. Dark yellow oil. R_f = 0.28 (benzene/absolute methanol: 20:1).

IR (neat): 2 960, 2 936, 1 734 (C=O, ester), 1 654 (C=O, chromone), 1 620 (C=C), 1 594, 1 428, 1 406, 1 270 (C–O–C), 1 186, 1 112 cm^{-1}.

^{1}H NMR: 0.95 (t, J = 7.3 Hz, 3H, CH_2Me), 1.28 (t, J = 6.9 Hz, 3H, $COOCH_2Me$), 1.59 (m, 2H, CH_2Me), 1.98 (m, 4H, $OCH_2(CH_2)_2CH_2$Tet), 2.10 (m, 2H, $NCH_2CH_2CH_2CO$), 2.35 (t, J = 7.1 Hz, 2H, CH_2CO), 2.81 (t, J = 7.4 Hz, 2H, CH_2Et), 3.00 (t, 2H, CH_2Tet), 4.10–4.20 (overlapping triplets, 4H, $OCH_2(CH_2)_3$Tet + $COOCH_2$Me), 4.68 (t, J = 6.6 Hz, 2H, NCH_2), 6.27 (d, J = 6.0 Hz, 1H, 3-H), 6.98 (d, J = 9.2 Hz, 1H, 6-H), 7.86 (d, J = 6.0 Hz, 1H, 2-H), 8.05 (d, J = 9.2 Hz, 1H, 5-H).

Anal calc for $C_{23}H_{30}N_4O_5$ (442.52): C, 62.43; H, 6.83; N, 12.66. Found: C, 62.62; H, 6.70; N, 12.69.

• *7-({4-[1-(4-Cyanobutyl)-1H-tetrazol-5-yl]butyl}oxy)-8-propylchromone* **47** *and 7-({4-[2-(4-cyanobutyl)-2H-tetrazol-5-yl]butyl}oxy)-8-propylchromone* **48**

Using 5-chloropentanenitrile as alkylating agent, 6 days.

■ ***47***

Yield: 17%. Dark yellow oil. R_f = 0.14 (benzene/absolute methanol, 20:1).

IR (neat): 2 960, 2 870, 2 246 (CN), 1 650 (C=O), 1 620 (C=C), 1 594, 1 456, 1 428, 1 408, 1 356, 1 318, 1 270 (C–O–C), 1 114, 1 058, 812 cm^{-1}.

^{1}H NMR: 0.95 (t, J = 7.2 Hz, 3H, CH_2Me), 1.60 (m, 2H, CH_2CH_2Me), 1.70 (m, 2H, $N(CH_2)_2CH_2CH_2CN$), 1.92 (m, 6H, $OCH_2(CH_2)_2CH_2$Tet + $NCH_2CH_2(CH_2)_2CN$), 2.46 (t, J = 6.9 Hz, 2H, CH_2CN), 2.81 (t, J = 7.3 Hz, 2H, CH_2Et), 2.97 (t, J = 7.0 Hz, 2H, CH_2Tet), 4.17 (t, J = 5.7 Hz, 2H, OCH_2), 4.36 (t, J = 6.5 Hz, 2H, NCH_2), 6.25 (d, J = 6.0 Hz, 1H, 3-H), 6.98 (d, J = 8.9 Hz, 1H, 6-H), 7.86 (d, J = 6.0 Hz, 1H, 2-H), 8.04 (d, J = 8.9 Hz, 1H, 5-H).

^{13}C NMR: 14.05 (Me), 16.61 (CH_2CN), 22.24, 22.76, 23.55, 24.80, 28.22, 28.55 (methylenes), 45.81 (NCH_2), 67.71 (OCH_2), 109.53 (C-6), 112.11 (C-3), 118.64, 118.79 (C-4a, C-8 and CN), 124.43 (C-5), 154.28 (tetrazole C), 155.06 (C-2), 155.53 (C-8a), 160.43 (C-7), 177.58 (C-4).

Anal calc for $C_{22}H_{27}N_5O_5$ (409.49): C, 64.53; H, 6.65; N, 17.10. Found: C, 64.41; H, 6.44; N, 16.95.

■ ***48***

Yield: 17%. Yellow oil. R_f = 0.32 (benzene/absolute methanol, 20:1).

IR (neat): 2 960, 2 870, 2 248 (CN), 1 652 (C=O), 1 620 (C=C), 1 594, 1 496, 1 456, 1 428, 1 408, 1 356, 1 318, 1 270 (C–O–C), 1 230, 1 114, 1 058, 812 cm^{-1}.

^{1}H NMR: 0.96 (t, J = 7.3 Hz, 3H, CH_2Me), 1.59 (m, 2H, CH_2Me), 1.71 (m, 2H, $N(CH_2)_2CH_2CH_2CN$), 2.00 (m, 4H, $OCH_2(CH_2)_2CH_2$Tet), 2.19 (m, 2H, $NCH_2CH_2(CH_2)_2CN$), 2.42 (t, J = 6.8 Hz, 2H, CH_2CN), 2.82 (t, J = 7.3 Hz, 2H, CH_2Et), 3.01 (t, J = 6.9 Hz, 2H, CH_2Tet), 4.14 (t, J = 5.8 Hz, 2H, OCH_2), 4.63 (t, J = 6.6 Hz, 2H, NCH_2), 6.28 (d, J = 6.0 Hz, 1H, 3-H), 6.97 (d, J = 9.0 Hz, 1H, 6-H), 7.84 (d, J = 6.0 Hz, 1H, 2-H), 8.06 (d, J = 9.0 Hz, 1H, 5-H).

^{13}C NMR: 14.01 (Me), 16.52 (CH_2CN), 22.25, 24.43, 24.77, 24.93, 27.91, 28.50 (methylenes), 51.60 (NCH_2), 67.93 (OCH_2), 109.52 (C-6), 112.09 (C-3), 118.67, 118.80 (C-4a, C-8 and CN), 124.36 (C-5), 155.01 (C-2), 155.54 (C-8a), 160.61 (C-7), 166.48 (tetrazole C), 177.62 (C-4).

Anal calc for $C_{22}H_{27}N_5O_5$ (409.49): C, 64.53; H, 6.65; N, 17.10. Found: C, 64.33; H, 6.79; N, 17.17.

Hydrolysis of esters ***39–42****: general procedure*

To a hot solution of esters **39–42** (5.66 mmol) in methanol (40 mL), 4% NaOH solution (5.8 mL, 5.80 mmol) was added in one portion and allowed to cool down. After 15 min the mixture was diluted with water (250 mL) and acidified with HCl. The precipitate was filtered off, washed with water and recrystallized to afford pure free acid **43–46**.

• *7-({4-[1-(Carboxymethyl)-1H-tetrazol-5-yl]butyl}oxy)-8-propylchromone* **43**

Yield: 74%. Mp: 174–176 °C (ethanol).

IR: 2 960, 2 937, 2 872, 1 716 (COOH), 1 621 (C=O), 1 562, 1 429, 1 271, 1 227, 1 116 cm^{-1}.

^{1}H NMR (DMSO-d_6): 0.90 (t, J = 7.2 Hz, 3H, CH_2Me), 1.56 (m, 2H, CH_2Me), 1.90 (m, 4H, $OCH_2(CH_2)_2CH_2$Tet), 2.78 (t, J = 7.4 Hz, 2H, CH_2Et), 2.98 (t, J = 6.9 Hz, 2H, CH_2Tet), 4.20 (t, J = 5.8 Hz, 2H, OCH_2), 5.62 (s, 2H, NCH_2), 6.26 (d, J = 6.1 Hz, 1H, 3-H), 7.21 (d, J = 9.0 Hz, 1H, 6-H), 7.90 (d, J = 9.0 Hz, 1H, 5-H), 8.28 (d, J = 6.1 Hz, 1H, 2-H).

Anal calc for $C_{19}H_{22}N_4O_5$ (386.41): C, 59.06; H, 5.74; N, 14.50. Found: C, 58.93; H, 5.81; N, 14.13.

• *7-({4-[2-(Carboxymethyl)-2H-tetrazol-5-yl]butyl}-oxy)-8-propylchromone* ***45***

Yield: 80%. Mp: 185–187 °C (ethanol).

IR: 2 961, 2 934, 2 871, 1 727 (COOH), 1 621 (C=O), 1 569, 1 429, 1 272, 1 231, 1 117 cm^{-1}.

^1H NMR (DMSO-d_6): 0.91 (t, J = 7.3 Hz, 3H, CH_2Me), 1.56 (m, 2H, CH_2Me), 1.92 (m, 4H, $OCH_2(CH_2)_2CH_2Tet$), 2.78 (t, J = 7.3 Hz, 2H, CH_2Et), 2.96 (t, J = 7.0 Hz, 2H, CH_2Tet), 4.20 (t, J = 5.6 Hz, 2H, OCH_2), 5.41 (s, 2H, NCH_2CO), 6.26 (d, J = 6.0 Hz, 1H, 3-H), 7.21 (d, J = 9.0 Hz, 1H, 6-H), 7.90 (d, J = 9.0 Hz, 1H, 5-H), 8.28 (d, J = 6.1 Hz, 1H, 2-H).

Anal calc for $C_{19}H_{22}N_4O_5$ (386.41): C, 59.06; H, 5.74; N, 14.50. Found: C, 59.18; H, 5.55; N, 14.25.

• *7-({4-[1-(3-Carboxypropyl)-1H-tetrazol-5-yl]butyl}-oxy)-8-propylchromone* ***44***

Yield: 62%. Mp: 114–120 °C (dec) (hexane–absolute ethanol).

IR: 2 958, 2 932, 2 872, 1 732 (COOH), 1 620 (C=O), 1 572, 1 416, 1 270 (C–O–C), 1 210, 1 178, 1 114, 1 056, 826 cm^{-1}.

^1H NMR (DMSO-d_6): 0.88 (t, J = 7.2 Hz, 3H, CH_2Me), 1.54 (m, 2H, CH_2Me), 1.90 (m, 4H, $OCH_2(CH_2)_2CH_2Tet$), 2.00 (m, 2H, $NCH_2CH_2CH_2CO$), 2.29 (t, J = 6.8 Hz, 2H, CH_2CO), 2.75 (t, J = 7.4 Hz, 2H, CH_2Et), 2.97 (t, J = 6.6 Hz, 2H, CH_2Tet), 4.19 (t, J = 5.5 Hz, 2H, OCH_2), 4.38 (t, J = 6.8 Hz, 2H, NCH_2), 6.25 (d, J = 5.9 Hz, 1H, 3-H), 7.20 (d, J = 9.0 Hz, 1H, 6-H), 7.89 (d, J = 9.0 Hz, 1H, 5-H), 8.27 (d, J = 5.9 Hz, 1H, 2-H).

Anal calc for $C_{21}H_{26}N_4O_5$ (414.47): C, 60.86; H, 6.32; N, 13.52. Found: C, 60.60; H, 6.14; N, 13.71.

• *7-({4-[2-(3-Carboxypropyl)-2H-tetrazol-5-yl]butyl}-oxy)-8-propylchromone* ***46***

Yield: 66%. Mp: 98–105 °C (dec) (hexane–absolute ethanol).

IR: 2 960, 1 730 (COOH), 1 626 (C=O), 1 578, 1 428, 1 272 (C–O–C), 1 232, 1 116, 816 cm^{-1}.

^1H NMR (DMSO-d_6): 0.98 (t, J = 7.3 Hz, 3H, CH_2Me), 1.52 (m, 2H, CH_2Me), 1.86 (m, 4H, $OCH_2(CH_2)_2CH_2Tet$), 2.10 (m, 2H, $NCH_2CH_2CH_2CO$), 2.27 (t, J = 6.9 Hz, 2H, CH_2CO), 2.75 (t, J = 7.4 Hz, 2H, CH_2Et), 2.93 (t, J = 7.0 Hz, 2H, CH_2Tet), 4.18 (t, J = 5.5 Hz, 2H, OCH_2), 4.64 (t, J = 6.9 Hz, 2H, NCH_2), 6.24 (d, J = 6.0 Hz, 1H, 3-H), 7.20 (d, J = 9.1 Hz, 1H, 6-H), 7.89 (d, J = 9.1 Hz, 1H, 5-H), 8.26 (d, J = 6.0 Hz, 1H, 2-H).

Anal calc for $C_{21}H_{26}N_4O_5$ (414.47): C, 60.86; H, 6.32; N, 13.52. Found: C, 60.81; H, 6.42; N, 13.28.

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References

1 For reviews see:
a) Shaw A, Krell RD, *J Med Chem* (1991) 34, 1235
b) Salman JA, Garland LA, *Progress Drug Res* (1991) 37, 9
c) Sprecher A, Beck A, Garspacher M, Bray MA, *Chimia* (1992) 46, 304
d) Chanarin N, Johnston SL, *Drugs* (1994) 47, 12

2 a) Appleton RA, Bantick JR, Chamberlain TR, Hardern DN, Lee TB, Pratt AD, *J Med Chem* (1977) 20, 371
b) Dillard RB, Carr FP, McCullogh D, Haisch KD, Rinkema LE, Fleisch JH, *J Med Chem* (1987) 30, 911
c) Brown FJ, Bernstein PR, Cronk LA, Dosset DA, Hebbel KC, Maduskie TP, Shapiro HS, Vacek EP, Yee YK, Willard AK, Krell RD, Snyder DW, *J Med Chem* (1989) 32, 807
d) Djuric SW, Collins PW, Jones PH, Shone RL, Tsai BS, Fretland DJ, Butchko GM, Villani-Price D, Keith RH, Zemaitis JM, Metcalf L, Bauer RF, *J Med Chem* (1989) 32, 1145

3 Fretland DJ, Levin S, Tsai BS, Djuric SW, Widomski DL, Zemaitis, JM, Shone RL, Bauer FR, *Agents Actions* (1989) 27, 395

4 Cook CS, Gaginella TS, Fretland DJ, Tsai BS, Djuric SW, Shone RL, *Drugs Future* (1990) 15, 695

5 a) Herron DK, Goodson T, Bollinger NG, Swanson-Bean D, Wright IG, Staten GS, Thompson AR, Froelich LL, Jackson WT, *J Med Chem* (1992) 35, 1818
b) Sofia MJ, Nelson K, Herron DK, Goodson T, Froelich LL, Spaethe SM, Marder P, Roman CR, Fleisch JL, *Bioorg Med Chem Lett* (1995) 5, 1995 and references therein

6 See eg L-649.923: Young RN, Bélanger P, Champion E, De Haven RN, Denis D, Ford-Hutchinson AW, Fontin R, Frenette R, Gauthier JY, Gillard J, Guindon Y, Jones TR, Kakushima M, Masson, P, Maycock A, McFarlane CS, Piechuta H, Pong SS, Rokach J, Williams HWR, Yoakim C, Zamboni R, *J Med Chem* (1986) 29, 1573

7 a) Marshall WS, Sigmund SK, Whitesitt CA, Lifer SL, Roman CR, Rinkema LE, Hahn RA, Fleisch JH, *Agents Actions* (1989) 27, 309
b) Fink MP, Kruithoff KL, Antonsson JB, Wang W, Rothschild HR, *Am J Physiol* (1991) 260, R1007

8 Baker W, Lothian OM, *J Chem Soc* (1925) 628

9 Dorofeenko GN, Mezheritskii VV, *Zh Org Khim* (1968) 4, 1305

10 Patonay T, Molnár D, Murányi Z, *Bull Soc Chim Fr* (1995) 132, 233

11 Wähälä K, Hase T, *Heterocycles* (1989) 28, 183

12 Tímár T, Hosztafi S, Jászberényi JC, Kövér KE, Batta G, *Acta Chim Hung* (1988) 125, 303

13 Patonay T, Lévai A, *Arch Pharm (Weinheim)* (1994) 327, 181

14 For reviews see:
a) Butler RN, In: *Advances in Heterocyclic Chemistry, Vol 21* (Katritzky AR, Boulton AJ, Eds) Academic, New York, 1977, p 323
b) Butler RN, In: *Comprehensive Heterocyclic Chemistry, Vol 5* (Katritzky AR, Rees CW, Eds) Pergamon, Oxford, 1984, p 791
c) Koldobskii GI, Ostrovskii VA, *Usp Khim* (1994) 63, 847

15 a) Spear RJ, *Aust J Chem* (1984) 37, 2453
b) Janda L, Voticky Z, *Chem Papers* (1989) 43, 63
c) Holzer W, Jäger C, *Monatsh Chem* (1992) 123, 1027

16 Einberg F, *J Org Chem* (1970) 35, 3978