Synthesis of Spin Labelled Chromones

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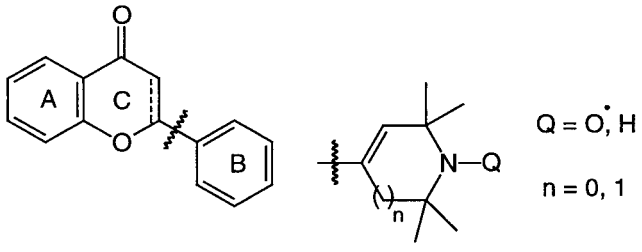
Abstract: Synthesis of spin labelled chromone **4a** is described from paramagnetic acid derivatives **1a**, **1b** by the conventional Baker–Venkataraman procedure. Different hydroxylated paramagnetic chromone derivatives **8**, **9**, **12a**, and **12b** could be obtained by different one-pot reactions and a glycoside of 5-hydroxy-2-(1-oxyl-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-3-yl) chromone radical **14b** was synthesized.

Key words: chromones, free radicals, glycosides, heterocycles, nitroxides

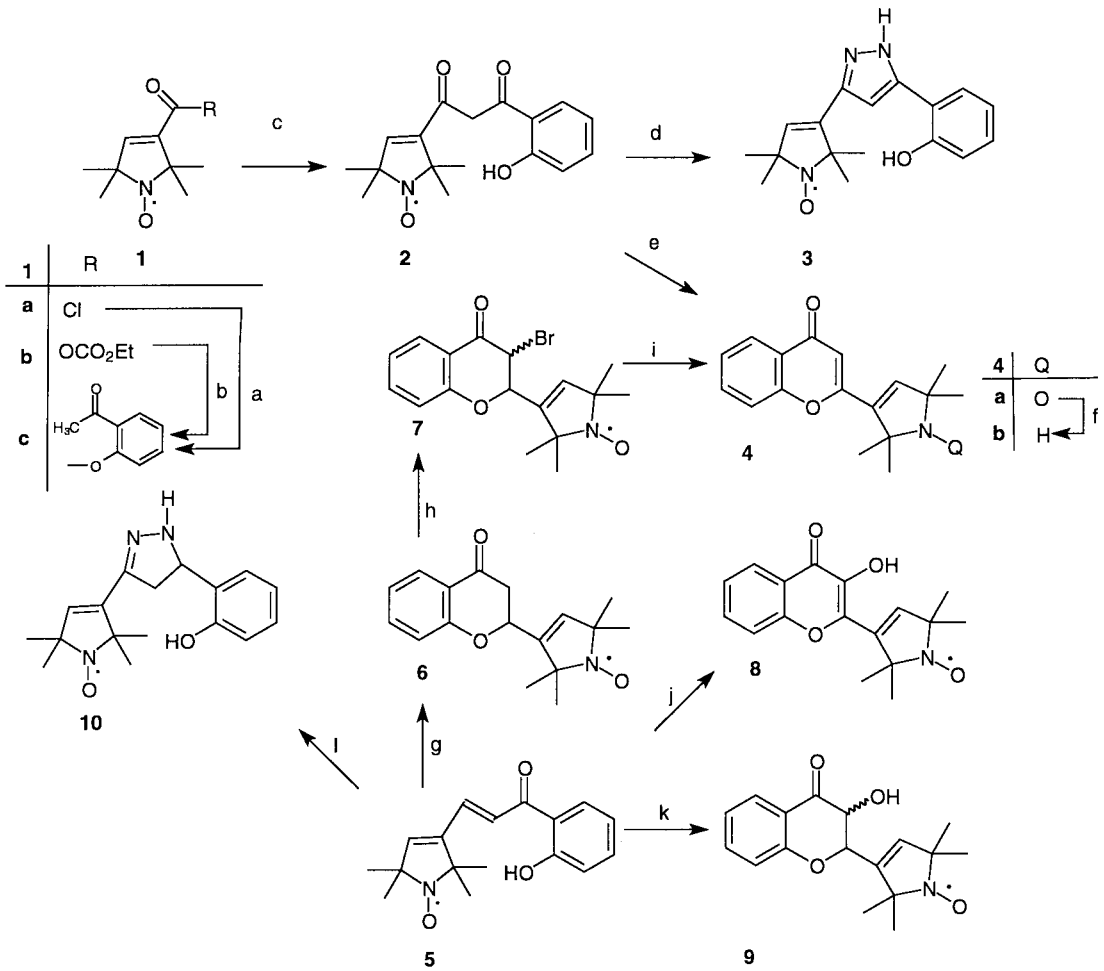
The most widespread chromones are flavones occurring mainly in plants. They have marked a wide range of different physiological effects in animals and human beings,[1] although they play no part in normal metabolism. Recently, much attention has been paid to different flavonoid derivatives as antioxidant compounds, and dietary intake of these natural compounds is thought to be very important for preventing a variety of diseases.[2] The antioxidant activity of flavones has been considered to be via two possible modes of action, radical scavenging and metal chelating.[3] The most effective compounds have an *o*-dihydroxycathecol structural element on the **B** ring.[4] The question of substitution of the **B** ring with another aromatic or heteroaromatic ring had arisen earlier, indole,[5] pyrrole,[6] pyridine, and piperidine[7] derivatives were synthesized. Replacement of the carbocyclic ring **B** with a non-aromatic paramagnetic heterocycle or its diamagnetic amine precursor compound may contribute to increase the antioxidant effect of flavonoids.



Substitution of the **B** ring of flavonoids with a five- or six-membered nitroxide or their amine precursor was therefore an attractive challenge, since these paramagnetic moieties as well as their sterically hindered amine precursors exhibit remarkable antioxidant activity by scavenging reactive oxygen intermediaries.[8] The other aim was to investigate the applicability of the well established synthetic procedures of flavonoid chemistry in the presence of a stable nitroxide free radical.

Compound **1c** was obtained by esterification of 2-hydroxy acetophenone with acid chloride **1a**[9]or with mixed anhydride ester **1b**.[10] Ester **1c** could be rearranged in pyridine with KOH to 1,3-dicarbonyl compound **2**. Reaction of compound **2** with hydrazine gave 5(3)-(2-hydroxyphenyl)-3(5)-(1-oxyl-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-3-yl)-pyrazole (**3**). Compound **2** could be cyclized in acetic acid in the presence of catalytic amount H_2SO_4[11] to 2-(1-oxyl-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-3-yl)chromen-4-one (**4a**), which could be selectively reduced with acetic acid/Fe powder[12] to the diamagnetic derivative **4b** without reduction of chromene moiety. Compound **4a** could also be achieved by another reaction pathway: bromination of chroman-4-one **6**[13] at α-position to carbonyl group with pyrrolidone hydrotribromide[14] (PHT) gave compound **7**, which was dehydrobrominated with DBU to **4a**. Compound **6** was synthesized by acidic cyclization from ketone **5**,[13] which proved to be a key compound for synthesis of 3-hydroxy-chromen-4-one (**8**)[15] and 3-hydroxy-chroman-4-one (**9**) derivatives. Treatment of compound **5** with basic H_2O_2 at 0 °C for 24 hours gave 2-(1-oxyl-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-3-yl)-3-hydroxychromen-4-one (**8**)[5] as the main product, while treatment at room temperature for 3 hours yielded 2-(1-oxyl-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-3-yl)-3-hydroxychroman-4-one (**9**) as the main product.[16] Reaction of compound **5** with hydrazine gave 4,5-dihydro-3-(1-oxyl-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-3-yl)-5-(2-hydroxyphenyl)-1*H*-pyrazole (**10**) (Scheme 1, Table).

Flavonoids occur in the nature mainly as glycosides of their polyhydroxylated derivatives,[17] therefore we also attempted to synthesize such paramagnetic derivatives. Fortunately, a one-pot method described recently[18] was extendable for synthesis of 2-(1-oxyl-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-3-yl)-5-hydroxychromen-4-one (**12a**). Reaction of acid chloride **1a** with 2,6-dihydroxyacetophenone in the presence of 5 equivalents of K_2CO_3 in acetone gave compound **12a**, and **13a** biradical as a by-product. To mimic the shape of flavone, we introduced a six-membered ring instead of five-membered one. However, the acid chloride from **11a**[19] proved to be unstable, therefore the imidazolide **11b**, prepared by Staab's method,[20] was used instead. In this reaction, we obtained 2-(1-oxyl-1,2,5,6-tetrahydro-2,2,6,6-tetramethylpyridin-



Reagents and conditions: a) 2-hydroxyacetophenone (1 equiv), Et_3N (1.1 equiv), CH_2Cl_2, 0 °C to r.t., 1 h, (82%); b) 2-hydroxyacetophenone (1 equiv), NaH (0.1 equiv), THF, 65 °C, 1 h, (58%); c) KOH 1.5 (equiv), pyridine, 50 °C, 30 min., then 10% aq HOAc, (72%); d) $N_2H_4{\cdot}H_2O$ (1.2 equiv), EtOH, 1 h, r.t. (40%); e) $HOAc/H_2SO_4$, 100 °C, 30 min., then $NaHCO_3$, MnO_2 (0.3 equiv), O_2, 5 min., (25%); f) Fe (10 equiv), HOAc, 50 °C, 30 min, then K_2CO_3, (44%); g) Ref. 13.; h) PHT (1.25 equiv), 2-pyrrolidone (1.25 equiv), THF 65 °C, 30 min., (68%); i) DBU (1 equiv), $CHCl_3$, 63 °C, 30 min., (72%); j) NaOH (0.4 equiv), H_2O_2 (4.0 equiv), 0 °C, 24 h, (26%); k) NaOH (0.4 equiv), H_2O_2 (4.0 equiv), r.t. 3 h, (22%); l) $N_2H_4{\cdot}H_2O$ (1.2 equiv), MeOH, 2 h, r.t. (60%)

Scheme 1

4-yl)-5-hydroxychromen-4-one (**12b**) monoradical exclusively, which hints that this one-pot reaction can be carried out not only with acid chlorides but also with imidazolides. Reaction of compound **12a** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide in quinoline in the presence of Ag_2O gave compound **14a** in moderate yield.[21] This compound was hydrolyzed to 2-(1-oxyl-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-3-yl)-5-β-D-glucopyranosyloxychromen-4-one (**14b**) by Zemplen's method[22] (Scheme 2).

In summary, spin labelled chromones and chromanes as well as their 5- or 3-hydroxy derivatives could be synthesized by application of the well-established procedures of flavonoid chemistry. Paramagnetic pyrazole derivative and chromone glycoside were also achieved. Investigation of biological activity of these derivatives is in progress.

Mps were determined with a Boetius micro melting point apparatus and are uncorrected. Elemental analyses (C, H, N, S) were performed on Fisons EA 1110 CHNS elemental analyzer. The IR (Specord 75) spectra were in each case consistent with the assigned structure. Mass spectra were recorded on a VG TRIO-2 instrument in the EI mode (70 eV, direct inlet) or with thermospray technique. Samples were analyzed in the by-pass mode. The sample (10 μL) solution in CH_3OH was introduced via the thermospray interface. The mobile phase was CH_3OH/H_2O (1:1) containing 0.1 M NH_4OAc. The capillary tip temperature was 230 °C, the electrode voltage was 180 V and the source temperature was 210 °C. The ESR spectra were obtained from 10^{-5} M solution ($CHCl_3$), using BRUKER ECS-106 spectrometer. All monoradicals exhibit three equidistant lines with $a_N = 14.7-15.5$ G. Biradical **13a** exhibits quintet lines. ^1H NMR spectra were recorded with Bruker 400 spectrometer at 400 MHz. Chemical shifts are given in ppm, relative to TMS internal standard. To obtain the high resolution NMR spectra of the radicals, they were reduced with an excess of co-dissolved $(PhNH)_2$ additive. Flash column chromatography was performed on Merck Kieselgel 60 (0.040−0.063 mm). Qualitative TLC was carried out

Table Compounds **1c**–**14b** Prepared

Product	Yield (%) Method	Mp (°C)	IR (Nujol) ν (cm^{-1})	MS *m/z* (%)
1c	82 (A) 58 (B)	124–125	1725, 1670 (C=O) 1625, 1590 (C=C)	302 (M^+, 8), 288 (6), 137 (45), 109 (100)
2	72	110–111	1615 (C=O) 1570 (C=C)	302 (M^+, 7), 288 (16), 257 (15), 121 (100)
3	40	228–230	3200 (NH) 1610, 1580, 1540, 1505 (C=C)	298 (M^+, 31), 284 (67), 268 (95), 253 (100)
4a	25 (A) 72 (B)	131–132	1630 (C=O) 1610, 1560 (C=C)	284 (M^+, 27), 270 (45), 254 (53), 121 (100)
4b	44	90– 91	3300 (NH), 1630 (C=O) 605, 1555 (C=C)	269 (M^+, <1), 254 (100), 239 (8), 134 (13)
7	68	140–141	1675 (C=O) 1600, 1575 (C=C)	364/366 (M^+, 11/11), 350/352 (11/11), 147 (40), 121 (100)
8	26	166–167	3240 (OH), 1620 (C=O) 1605, 1555 (C=C)	300 (M^+, 3), 270 (17), 154 (93), 41 (100)
9	22	93– 95	1710 (C=O) 1630, 1600 (C=C)	302 (M^+, 3), 196 (33), 135 (39), 41 (100)
10	60	160–161	3260 (NH) 1610, 1590, 1560 (C=C)	300 (M^+, 3), 286 (8), 270 (10), 161 (100)
11b	78	42– 44	1690 (C=O) 1590 (C=C)	248 (M^+, <1), 184 (10), 168 (35), 68 (100)
12a	15	148–149	1650 (C=O) 1610, 1555 (C=C	300 (M^+, 40), 286 (67), 270 (61), 137 (100)
12b	17	184–185	1645 (C=O) 1600 (C=C)	314 (M^+, 31), 300 (100), 284 (69), 269 (35)
13	8	208–209	1650, 1640 (C=O) 1595 (C=C)	TSP: 467 $(M+H)^+$
14a	36	72– 74	1740, 1640 (C=O) 1600 (C=C)	TSP: 631 $(M+H)^+$
14b	41	125–126	3320 (OH), 1630 (C=O) 1600 (C=C)	TSP: 463 $(M+H)^+$

on commercially prepared plates ($20 \times 20 \times 0.02$ cm) coated with Merck Kieselgel GF_{254}. Compounds **1a**,[9] **1b**,[10] **5**,[13] **6**,[13] **11a**[19] were prepared according to published procedures. The physical and spectral data of all new compounds are listed in the Table.

3-(2′-Acetyl-carboxyphenyl)-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-1-yloxyl Radical (1c)

Method A

To a stirred solution of 2-hydroxyacetophenone (1.36 g, 10.0 mmol) and Et_3N (1.11 g, 11.0 mmol) in CH_2Cl_2 (20 mL) was added compound **1a** (2.02 g, 10.0 mmol) in CH_2Cl_2 (10 mL) dropwise at 0 °C, then the mixture was stirred further for 1 h at r.t. The organic phase was washed with brine (10 mL), separated, dried ($MgSO_4$), filtered, and evaporated. The residue was crystallized from hexane to give compound **1c** as a pale yellow solid (2.47 g, 82%); mp: 124−125 °C; R_f 0.36 (hexane/EtOAc, 2:1).

Method B

To a stirred solution of 2-hydroxyacetophenone (1.36 g, 10.0 mmol) and compound **1b** (2.56 g, 10.0 mmol) in anhyd THF (30 mL) was added NaH (24 mg, 1.0 mmol) and the mixture was further stirred under reflux for 1 h. After cooling, EtOH (0.5 mL) and then Et_2O (20 mL) were added. The organic phase was washed with brine (20 mL), separated, dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography (hexane/Et_2O) to give the title compound **1c** (1.75 g, 58%).

1-(1-Oxyl-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-3-yl)-3-(2′-hydroxyphenyl)-propane-1,3-dione Radical (2)

To a stirred solution of compound **1c** (1.51 g, 5 mmol) in pyridine (10 mL) was added KOH (421 mg, 7.5 mmol) at 50 °C, then the mixture was stirred further for 30 min. The mixture was poured onto crushed ice (30 g) and 10% aqueous HOAc (10 mL) was added, upon which compound **2** crystallized out. After filtration, compound **2** was obtained as a yellow solid (1.10 g, 72%); mp: 110−111°C; R_f 0.50 (hexane/EtOAc, 2:1).

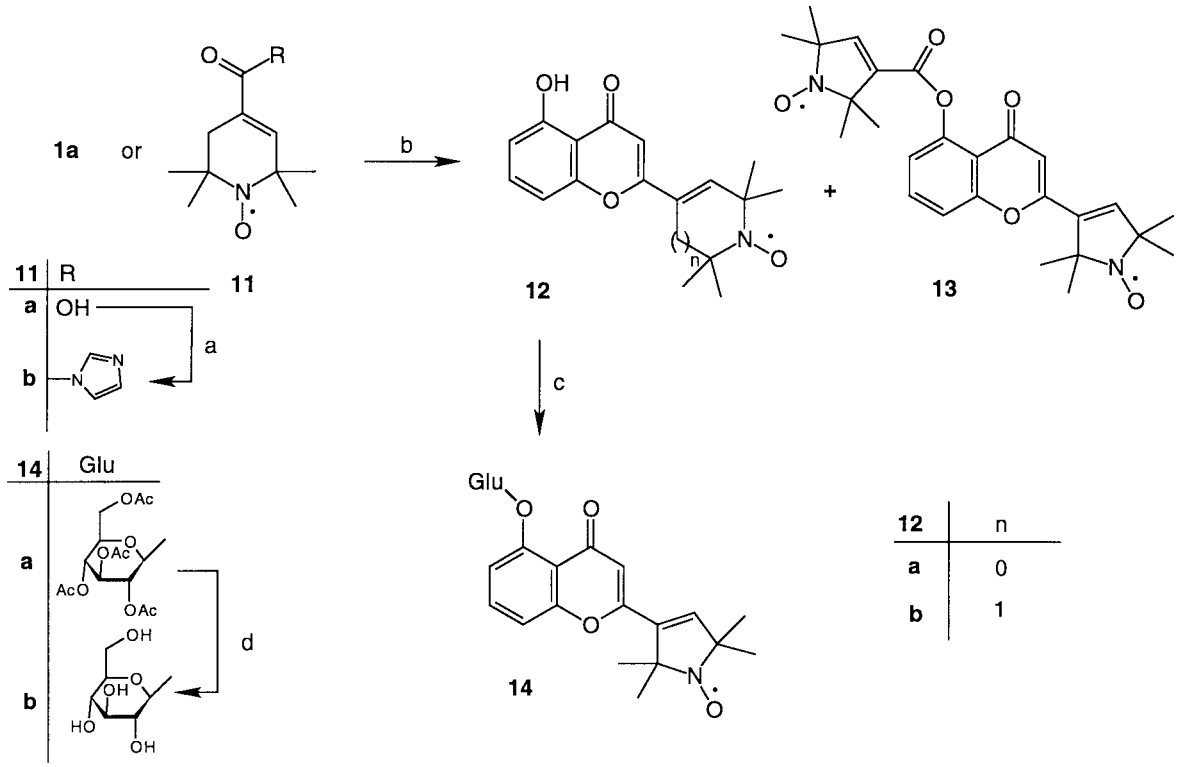
5(3)-(2-Hydroxyphenyl)-3(5)-(1-oxyl-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-3-yl)-pyrazole Radical (3)

To a solution of compound **2** (302 mg, 1 mmol) in EtOH (10 mL) was added hydrazine monohydrate (60 mg, 1.2 mmol) and the mixture was allowed to stand at r.t. After 1 h, brine was added (5 mL), and then extracted with $CHCl_3$ (2×10 mL). The organic phase was separated, dried ($MgSO_4$), and filtered. The residue was purified by flash column chromatography (hexane/Et_2O), to yield compound **3** as a pale yellow solid (119 mg, 40%); mp: 228−230 °C; R_f 0.30 (hexane/EtOAc, 2:1).

2-(1-Oxyl-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-3-yl)-chromen-4-one Radical (4a)

Method A

To a stirred solution of compound **2** (906 mg, 3.0 mmol) in HOAc (10 mL) was added 98% H_2SO_4 (0.15 mL). The mixture was heated at 100 °C for 30 min, then poured onto crushed ice (50 g). The solution was made basic by addition of $NaHCO_3$, and extracted with $CHCl_3$ (3×20 mL). The organic phase was separated and dried



Reagents and conditions: a)1,1′-carbonyldiimidazole (1.1 equiv), THF, 65 °C, 20 min., (78%); b) 2,6-dihydroxyacetophenone (1 equiv), K_2CO_3 (5 equiv), acetone, 56 °C, 24 h, then 1 M aq HCl, MnO_2 (0.1−0.2 equiv), O_2, 5 min., (8−17%); c) **12a**, 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosylbromide (1 equiv), Ag_2O (1 equiv), quinoline, 70 °C, 4 h, (36%); d) NaOMe (0.6 equiv), MeOH, 1 h, r.t., then aq NH_4Cl, (41%).

Scheme 2

($MgSO_4$). Activated MnO_2 (100 mg, 1.15 mmol) was added, O_2 was bubbled through for 5 min., the mixture was filtered, and evaporated. After purification of the residue, compound **4a** was obtained as a yellow solid (220 mg, 25%); mp: 131−132 °C; R_f 0.27 (hexane/EtOAc, 2:1).

Method B

To a stirred solution of **7** (730 mg, 2.0 mmol) in dry $CHCl_3$ (20 mL) was added DBU (304 mg, 2.0 mmol), and the mixture was refluxed for 30 min. The cooled mixture was washed with 5% H_2SO_4 (20 mL) then with H_2O (20 mL), separated, dried ($MgSO_4$), and evaporated. The crude material was purified by flash column chromatography (hexane/Et_2O) to give compound **4a** (409 mg, 72%).

2-(2,5-Dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-3-yl)chromen-4-one (4b)

To a stirred solution of **4a** (284 mg, 1.0 mmol) in HOAc (5 mL) was added Fe powder (560 mg, 10.0 mmol) and the mixture was warmed gently to 50 °C and kept at this temperature for 30 min. The mixture was diluted with H_2O (20 mL), and the solution was decanted from Fe powder. The mixture was basified with K_2CO_3 to pH 8, and extracted with $CHCl_3$ (3 × 20 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography ($CHCl_3$/Et_2O) to give compound **4b** as a white solid (120 mg, 44%); mp: 90−91 °C; R_f 0.33 ($CHCl_3$/MeOH, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (s, 6H), 1.52 (s, 6H), 6.44 (s, 1H), 6.56 (s, 1H), 7.34−7.44 (m, 2H), 7.62−7.68 (m, 1H), 8.14−8.18 (dd, 1H).

3-Bromo-2-(1-oxyl-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-3-yl)chroman-4-one Radical (7)

To a stirred solution of compound **6** (572 mg, 2.0 mmol) in dry THF (20 mL) were added 2-pyrrolidinone (215 mg, 2.5 mmol) and PHT (1.24 g, 2.5 mmol), and the mixture was refluxed for 30 min. The cooled mixture was filtered, the organic phase was washed with H_2O (20 mL), dried ($MgSO_4$), and evaporated to dryness. The residue was purified by flash column chromatography (hexane/Et_2O), to give the title compound **7** as a pale yellow solid (500 mg, 68%); mp: 140−141°C; R_f 0.48 (hexane/EtOAc, 2:1).

3-Hydroxy-2-(1-oxyl-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-3-yl)chromen-4-one Radical (8)

To a stirred solution of compound **5** (1.43 g, 5.0 mmol) in MeOH (10 mL) were added 8% NaOH (1 mL) and 30% aqueous H_2O_2 (2.4 mL) at 0 °C, then the mixture was allowed to stand at 0 °C for 24 h. The MeOH was evaporated in vacuo at 30 °C, and the solution was acidified with 1 M HCl, upon which a gummy solid precipitated. The solid was filtered off and further purified by flash column chromatography (hexane/Et_2O) to afford compound **8** (400 mg, 26%), as a yellow solid; mp: 166−167 °C; R_f 0.40 (hexane/EtOAc, 2:1).

3-Hydroxy-2-(1-oxyl-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-3-yl)chroman-4-on Radical (9)

To a stirred solution of compound **5** (286 mg, 1.0 mmol) in MeOH (5 mL) were added 8% NaOH (0.2 mL) and 30% aqueous H_2O_2 (0.5 mL), then the mixture was stirred at r.t. for 3 h. The MeOH was evaporated in vacuo at 30 °C, the solution was diluted with H_2O (10 mL), acidified with 1 M HCl, and extracted with $CHCl_3$ (2 × 20 mL). The organic phase was separated, dried ($MgSO_4$),

filtered, and evaporated. The residue was purified by flash column chromatography (hexane/EtOAc) then ($CHCl_3$/Et_2O) to yield compound **9** (68 mg, 22%), as a yellow solid; mp: 93−95 °C; R_f 0.59 ($CHCl_3$/MeOH, 4:1).

4,5-Dihydro-3-(1-oxyl-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-3-yl)-5-(2-hydroxyphenyl)-1*H*-pyrazole Radical (10)

To a solution of compound **5** (286 mg, 1.0 mmol) in MeOH (5 mL) and H_2O (5 mL) was added hydrazine monohydrate (60 mg, 1.2 mmol), and the mixture was allowed to stand at r.t. for 2 h. Compound **10** (80 mg, 60%) crystallized out spontaneously as yellow pellets; mp: 160−161 °C; R_f 0.33 (hexane/EtOAc, 2:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.10 (s, 3H), 1.12 (s, 3H), 1.18 (s, 3H), 1.19 (s, 3H) 2.79 (q, 1H), 3.45 (q, 1H), 4.22 (dt, 1H, *J* = 4 Hz), 5.61 (s, 1H).

***N*-(1-oxyl-1,2,5,6-tetrahydro-2,2,6,6-tetramethylpyridin-4-carboxylic Acid)imidazole Radical (11b)**

A solution of acid **11a** (990 mg, 5.0 mmol) and 1,1′-carbonyldiimidazole (891 mg, 5.5 mmol) in anhyd THF (15 mL) was refluxed for 20 min. After cooling, Et_2O (15 mL) was added, and the solution washed with cold sat. $NaHCO_3$ (15 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and evaporated. The residue was crystallized from hexane/Et_2O to give compound **11b** (970 mg, 78%) as an orange solid; mp: 42−44 °C; R_f 0.36 ($CHCl_3$/MeOH, 9:1).

2-(1-Oxyl-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-3-yl)-5-hydroxychromen-4-one Radical (12a) and 2-(1-Oxyl-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-3-yl)-5-[(1-oxyl-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-3-yl)carbonyloxy]chromen-4-one Biradical (13)

To a stirred mixture of compound 2,6-dihydroxyacetophenone (1.52 g, 10.0 mmol) and K_2CO_3 (6.90 g, 50.0 mmol) in dry acetone (40 mL) was added **1a** (2.02 g, 10.0 mmol) dissolved in dry acetone (10 mL) dropwise during 5 min., and the mixture was stirred under reflux for 24 h. After cooling, acetone was evaporated off, the residue was dissolved in H_2O (10 mL), acidified with 1 M HCl, and extracted with $CHCl_3$ (2 × 30 mL). The organic phase was separated and dried ($MgSO_4$). Activated MnO_2 (100 mg, 1.15 mmol) was added, O_2 was bubbled through for 5 min., the mixture was then filtered, and evaporated. After chromatography (hexane/Et_2O followed by hexane/EtOAc), compound **12a (**450 mg, 15%) was obtained from the first band at R_f 0.46 (hexane/EtOAc, 2:1); mp: 148−149 °C. The second band at R_f 0.33 (hexane/EtOAc, 2:1) gave **13** (400 mg, 8%); mp: 208−209 °C.

2-(1-Oxyl-1,2,5,6-tetrahydro-2,2,5,5-tetramethyl-pyridin-4-yl)-5-hydroxychromen-4-one (12b)

A mixture of compound 2,6-dihydroxyacetophenone (760 mg, 5.0 mmol) and K_2CO_3 (138 mg, 1.0 mmol) was stirred for 10 min., then compound **11b** (1.24 g, 5.0 mmol) in dry acetone (10 mL) was added dropwise. The mixture was stirred for 1 h, further K_2CO_3 (3.31 g, 24.0 mmol) was added and the mixture was stirred under reflux for 24 h. After cooling, acetone was evaporated off, the residue was dissolved in H_2O (10 mL), acidified with 1 M HCl, and extracted with $CHCl_3$ (2 × 30 mL). The organic phase was separated and dried ($MgSO_4$). Activated MnO_2 (100 mg, 1.15 mmol) was added, O_2 was bubbled through for 5 min., the mixture was filtered, and evaporated. After chromatography (hexane/Et_2O), compound **12b** (280 mg, 17%) was obtained as an orange solid; mp: 184−185 °C; R_f 0.53 (hexane/EtOAc, 2:1).

2-(1-Oxyl-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-3-yl)-5-(β-D-2,3,4,6-tetra-*O*-acetyl-glucopyranosyloxy)chromen-4-one Radical (14a)

A mixture of compound **12a** (300 mg, 1.0 mmol) and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl-bromide (411 mg, 1.0 mmol) and Ag_2O (232 mg, 1.0 mmol) in quinoline (8 mL) was stirred at 70 °C for 4 h. The mixture was then poured onto a mixture of crushed ice (40 g) and 2 M HCl (40 mL). The solution was extracted with EtOAc (2 × 30 mL), the organic phase was dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography (hexane/EtOAc) then ($CHCl_3$/Et_2O) to give compound **14a** (230 mg, 36%) as a brownish-yellow solid; mp: 72−74 °C; R_f 0.66 ($CHCl_3$/MeOH, 9:1).

2-(1-Oxyl-2,5-dihydro-2,2,5,5-tetramethyl-1*H*-pyrrol-3-yl)-5-(β-D-glucopyranosyloxy) chromen-4-one Radical (14b)

To a solution of compound **14a** (200 mg, 0.31 mmol) in dry MeOH (10 mL) was added freshly-made NaOMe solution [1 mL, Na (100 mg) dissolved in dry MeOH (10 mL)], and the mixture was allowed to stand for 1 h at r.t. The solvent was evaporated off, and the residue was dissolved in sat. NH_4Cl (10 mL). The mixture was evaporated to dryness, the residue was redissolved in MeOH/$CHCl_3$ (1:1, 40 mL), filtered, and evaporated. The residue was purified by flash column chromatography ($CHCl_3$/MeOH) to give the title compound **14b** as a yellow solid 60 mg (41%); mp: 125−126 °C; R_f 0.51 ($CHCl_3$/MeOH, 4:1).

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