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PLANT COUMARINS. 4.* SYNTHESIS OF *N*-CONTAINING DERIVATIVES OF OREOSELONE

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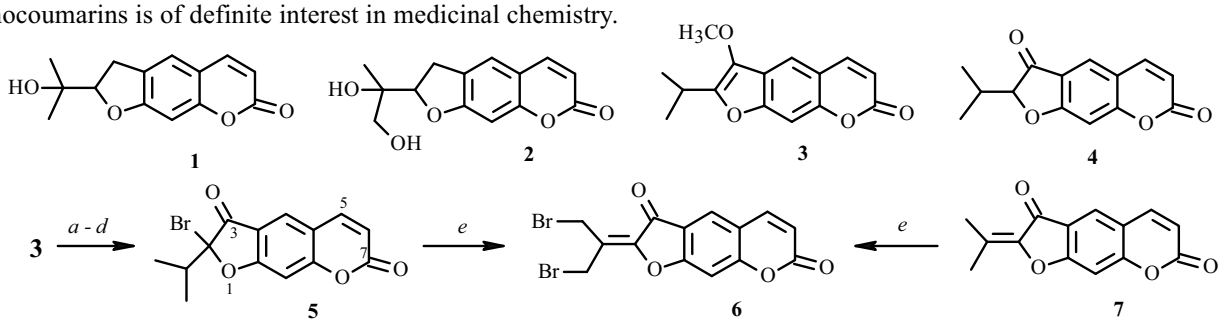
Bromination of peucedanin by various reagents was studied. Conditions for forming 2-(1,3-dibromopropan-2-ylidene)-2H-furo[3,2-g][1]benzopyran-3,7-dione were found. Several 2-aminofuranocoumarins were synthesized by reaction of 2-bromoreoselone with derivatives of pyrrolidine, piperidine, and piperazine. The new compounds were interesting as potential biologically active compounds.

Key words: furanocoumarins, bromoreoselone, 2-(1-methylethylidene)-7*H*-furo[3,2-*g*][1]benzopyran-3,7-dione.

Linear dihydrofuranocoumarins are widely distributed plant metabolites with pronounced biological activity [2-4]. Thus, marmesin (**1**) is an effective c-AMP synthetase [5] and acetylcholinesterase [6] inhibitor. Propanediol (**2**) is used as an antidote to snake venom [7]. The potential of coumarins for creating new antioxidants has recently been actively discussed owing to their specific activity as selective MAO inhibitors [8]. Thus, the development of methods for modifying furanocoumarins is of definite interest in medicinal chemistry.



a. Br_2-HCOOH; *b.* NBS-CCl_4; *c.* $PyHBrCl_2$–MeOH; *d.* DDB-CCl_4; *e.* NBS-$(PhCO\text{-})_2O$, CCl_4

Scheme 1

An accessible source of furanocoumarins is *Peucedanum morisonii* Bess., which is widely distributed in western Siberia. Its main metabolite peucedanin (**3**) can be isolated from roots of the plant in yields up to 4% of the dry raw material mass [9]. The preparation of several derivatives of peucedanin and its hydrolysis product oreoselone (**4**) through modification of the furan ring has been reported [10, 11]. Herein we describe the synthesis of new oreoselone derivatives.

The starting material for the transformations was 2-bromoreoselone (**5**), which was formed by bromination of **3** with Br_2 in $CHCl_3$, as previously reported [10]. We found that **5** was also the only product from bromination of peucedanin by Br_2 in formic acid (98% yield), by dioxanedibromide in CCl_4 (94-98% yield), by *N*-bromosuccinimide in CCl_4 (97-98% yield), and by pyridine dichlorobromate ($PyHBrCl_2$) in CH_3OH (94% yield).

Subsequent bromination of **5** by NBS (3 equiv.) in the presence of benzoyl peroxide in CCl_4 formed 2-(1,3-dibromopropan-2-ylidene)-2*H*-furo[3,2-*g*][1]benzopyran-3,7-dione (**6**) (73% yield). Obviously benzoyl peroxide enhances dehydrobromination of 2-bromoreoselone and subsequent allylic bromination. This was confirmed by the fact that **6** was formed by bromination of known 2-(1-methylethylidene)-7*H*-furo[3,2-*g*][1]benzopyran-3,7-dione (**7**) under these conditions [10, 12] (51% yield).

*For Part 2, see [1].

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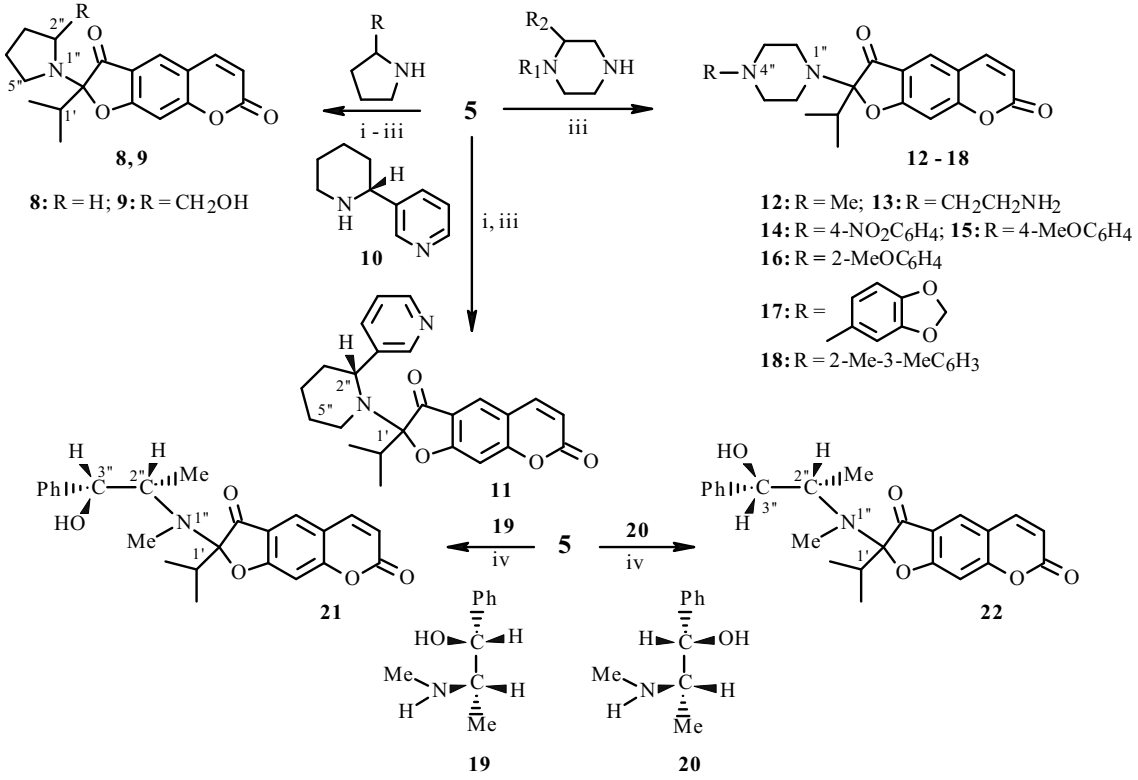
N-containing derivatives of coumarins are known to exhibit a broad spectrum of biological activity [4]. Thus, 8-piperazino-7-hydroxycoumarins exhibit high anti-inflammatory activity [13]. We studied the behavior of **5** upon reaction with various amines. The reaction of **5** with pyrrolidine and (*S*)-prolinol was carried out by mixing the components in $CHCl_3$ or DMF and under phase-transfer catalysis conditions (organic phase EtOAc or CH_2Cl_2; catalyst TEBAC with catalysis promoter alcohol [14]). In all instances products of nucleophilic substitution of Br, compounds **8** and **9** (34-42% yield), and **7**, the product of HBr elimination from starting **5**, were isolated. Table 1 gives the conditions and composition of reaction products. It can be seen that performing the reaction of pyrrolidine with **5** in DMF increases the yield of the substitution product 2-isopropyl-2-(pyrrolidin-1-yl)-2*H*-furo[3,2-*g*]chromen-3,7-dione (**8**). The reaction of the alkaloid anabasine (**10**) with **5** gave high yields of the pure substitution product 2-isopropyl-2-[(*S*)-2-(pyridin-3-yl)piperidin-1-yl]-2*H*-furo[3,2-*g*]chromen-3,7-dione (**11**) (61-65%). Reaction of **5** with 4-substituted piperazines gave low yields of 2-isopropyl-2-(4-*R*-piperazin-1-yl)-2*H*-furo[3,2-*g*]chromen-3,7-diones **12-18** (18-48%). The reaction of *N*-(2-aminoethyl)-piperazine with **5** was used as an example to show that performing the reaction under phase-transfer catalysis conditions increased the yield of substitution product **13**. A comparison of the reactions of various piperazines with **5** found that the yields of substitution products were greatest for the reaction of **5** bromide with *N*-(4-methoxyphenyl)- and *N*-(4-nitrophenylpiperazines. The reaction of **5** with alkaloids (-)-ephedrine (**19**) and (+)-pseudoephedrine (**20**) was carried out under phase-transfer catalysis conditions using EtOAc and CH_2Cl_2 as the organic phase. Using the latter could increase the yields of **21** and **22**.



i. $CHCl_3$, 20°C, 16 h; ii. DMFA, 20°C, 8 – 10 h; iii. EtOAc – 40% KOH, TEBAC–EtOH, 20°C, 8 h; iv. CH_2Cl_2 – 40% KOH, TEBAC– EtOH, 20°C, 8 h

Scheme 2

The compositions and structures of 2-substituted oreoselone derivatives **6**, **8**, **9**, **11**-**18**, **21**, and **22** were confirmed by elemental analyses and mass, IR, UV, and NMR spectra. Both dibromide **6** and products from reactions with amines **8**, **9**, **11**-**18**, **21**, and **22** had UV spectra characteristic of furanocoumarins. For example, the spectrum of **6** had absorption bands with maxima at 280, 309, 320 (sh), and 364 nm. UV spectra of amino-derivatives **8**, **9**, **11**-**18**, **21**, and **22** had four absorption bands, the maxima of which, for example for **22**, were located at 266, 274, 303, and 356 nm. PMR and ^{13}C NMR spectra of the products agreed fully with their structures and contained one set of resonances characteristic of the furanocoumarin backbone and the corresponding substituent. Compounds **9**, **11**, **21**, and **22** were formed as pure diastereoisomers. The principal differences in PMR spectra of (1*R*,2*S*)- and (1*S*,2*S*)-2-{[(1-hydroxy-1-phenylpropan-2-yl](methyl)amino}-2-isopropyl-2*H*-furo[3,2-*g*]chromen-3,7-diones **21** and **22** were the chemical shifts and SSCCs of side-chain protons H-2″ and H-3″.

TABLE 1. Conditions and Products from Reaction of 2-Bromoreoselone (**5**) with Amines

Amine	Reaction conditions	Yield, %	
Pyrrolidine	$CHCl_3$, 20°C, 16 h (i)	**8** (38)	**7** (51)
Pyrrolidine	DMF, 20°C, 8–10 h (ii)	**8** (42)	**7** (49)
Pyrrolidine	EA-40% KOH, TEBAC–EtOH, 20°C, 8 h (iii)	**8** (34)	**7** (50)
S-Prolinol	(i)	**9** (36)	**7** (51)
S-Prolinol	(iii)	**9** (36)	**7** (52)
(–)-Anabasine (**10**)	(i)	**11** (64)	**7** (24)
(**10**)	(ii)	**11** (61)	**7** (25)
(**10**)	(iii)	**11** (65)	**7** (27)
N-Methylpiperazine	(i)	**12** (33)	**7** (41)
N-Methylpiperazine	(ii)	**12** (30)	**7** (57)
N-(2-Aminoethyl)-piperazine	(ii)	**13** (18)	**7** (56)
N-(2-Aminoethyl)-piperazine	(iii)	**13** (27)	**7** (58)
1-(3,4-Methylenedioxy)piperazine	(iii)	**14** (34)	**7** (54)
1-(4-Nitrophenyl)piperazine	(iii)	**15** (48)	**7** (40)
1-(4-Methoxyphenyl)piperazine	(iii)	**16** (46)	**7** (48)
1-(2-Methoxyphenyl)piperazine	(iii)	**17** (37)	**7** (59)
1-(2,3-Dimethylphenyl)piperazine	(iii)	**18** (34)	**7** (60)
(–)-Ephedrine (**19**)	CH_2Cl_2–40% KOH, TEBAC–EtOH, 20°C, 8 h (iv)	**21** (41)	**7** (48)
(+)-Pseudoephedrine (**20**)	(iv)	**22** (40)	**7** (50)

TABLE 2. Chemical Shifts in ^{13}C NMR Spectra of **6**, **8**, **9**, and **11**–**14** (δ, ppm)

C atom	**6**	**8**	**9**	**11**	**12**	**13**	**14**
2	145.05 s	111.86 s	111.93 s	114.69 s	109.09 s	111.95 s	108.73 s
3	181.80 s	198.21 s	197.55 s	197.87 s	197.86 s	197.50 s	197.32 s
3a	119.31 s	120.47 s	118.10 s	120.76 s	119.86 s	120.64 s	119.54 s
4	125.12 d	124.35 d	123.90 d	124.45 d	124.58 d	124.18 d	124.24 d
4a	115.52 s	113.28 s	114.11 s	115.72 s	114.38 s	113.83 s	114.01 s
5	143.09 d	143.41 d	142.98 d	143.13 d	143.69 d	143.05 d	143.27 d
6	115.48 d	114.60 d	114.01 d	115.39 d	114.77 d	114.04 d	112.71 d
7	165.73 s	159.30 s	158.75 s	158.83 s	159.65 s	158.68 s	159.13 s
8a	160.51 s	161.67 s	161.09 s	161.13 s	162.06 s	161.11 s	161.64 s
9	101.22 d	100.55 d	99.85 d	101.62 d	100.59 s	100.23 s	100.02 s
9a	158.88 s	169.64 s	171.39 s	169.60 s	172.97 s	171.70 s	172.49 s
1′	126.08 s	34.70 d	33.63 d	31.81 d	31.27 d	31.29 d	29.27 d
2′	26.13 t[a]	15.63 q[a]	15.24 q[a]	16.67 q	15.34 q[a]	15.27 q[a]	14.00 q[a]
3′	24.58 t[a]	15.90 q[a]	14.47 q[a]	17.52 q	16.94 q[a]	16.06 q[a]	15.02 q[a]
2″	–	45.58 t[b]	59.32 d	36.47 d	43.09 t[b]	41.19 t[b]	45.45 t[b]
3″	–	24.24 t[c]	29.03 t	29.59 t[a]	54.66 t	54.22 t[c]	50.53 t
4″	–	25.91 t[c]	22.27 t	22.59 t	–	–	–
5″	–	46.71 t[b]	45.09 t	29.62 t[a]	54.66 t	56.64 t[c]	50.53 t
6″	–	–	62.95 t	36.47 t	44.48 t[b]	42.18 t[b]	46.91 t[b]

For **21**, these protons were situated at weaker field and had SSCC corresponding to *cis* protons [δ 2.90 (H-2″) and 4.97 ppm (H-3″), ^3J = 3.0 Hz] as compared with their position in the spectrum of **22** [δ 2.57 (H-2″) and 4.14 (H-3″)]. The SSCC between these protons in **22** (^3J = 9.2 Hz) corresponded with their *trans* position. It was also interesting that the chemical shifts of methyl protons of the isopropyl substituent in **20** and **21** were significantly different (Δδ 0.41 ppm). This difference in the PMR spectra of **12**-**18** was Δδ 0.32-0.40 ppm; in those of **8** and **9**, Δδ 0.17-0.19 ppm.

TABLE 2a. Chemical Shifts in ^{13}C NMR Spectra of **15**–**18**, **21**, and **22** (δ, ppm)

C atom	**15**	**16**	**17**	**18**	**21**	**22**
2	109.65 s	109.68 s	109.87 s	109.38 s	114.99 s	115.47 s
3	197.97 s	197.88 s	198.00 s	197.78 s	196.67 s	197.48 s
3a	119.68 s	119.69 s	119.81 s	119.07 s	120.54 s	116.54 s
4	124.45 d	124.05 d	123.77 d	125.84 d	125.27 d	126.81 d
4a	114.27 s	113.98 s	113.36 s	114.68 s	115.19 s	116.16 s
5	143.72 d	143.33 d	143.53 d	143.64 d	143.91 d	143.93 d
6	113.81 d	113.98 d	113.70 d	115.43 d	114.28 d	116.16 d
7	159.55 s	159.32 s	159.51 s	160.78 s	159.31 s	158.73 s
8a	161.74 s	161.43 s	161.57 s	162.25 s	160.09 s	161.93 s
9	100.11 s	99.84 s	100.82 s	100.43 s	100.20 s	101.19 s
9a	172.81 s	172.61 s	172.77 s	171.49 s	166.09 s	170.39 s
1′	31.44 d	31.32 d	31.50 d	29.60 d	30.52 d	32.86 d
2′	15.00 q[a]	14.87 q[a]	15.01 q[a]	15.45 q[a]	17.17 q[a]	17.47 q[a]
3′	16.53 q[a]	16.43 q[a]	16.60 q[a]	15.84 q[a]	19.28 q[a]	18.34 q[a]
2″	45.59 t[b]	45.72 t[b]	45.71 t	44.72 t	73.14 d	78.03 d
3″	50.91 t	50.05 t[c]	52.47 t	51.43 t	60.26 d	61.83 d
4″	–	–	–	–	–	–
5″	50.91 t	51.53 t[c]	52.47 t	51.43 t	–	–
6″	45.90 t[b]	45.92 t[b]	45.71 t	44.72 t	–	–

[a,b,c,d]Chemical shifts denoted by the same letters may be switched within one column.

*For **11**: Ar(Py)-C(2), 143.60 s; C(3), 143.67 d; C(4), 143.13 d; C(5), 125.99 d; C(6), 161.27 d; **12**: N–CH_3, 44.78 q; **13**: N–CH_2, 59.70 t; CH_2NH_2, 36.20 t; **14**: Ar–C(1), 154.42 s; C(2,6), 112.72 d; C(4), 138.69 s; C(3,5), 125.74 d; **15**: Ar–C(1), 145.50 s; C(2,6), 118.45 d; C(4), 154.11 s; C(3,5), 114.50 d; OCH_3 (on C-4), 55.59 q; **16**: Ar–C(1), 160.63 s; C(2), 140.69 s; C(3), 117.94 d; C(4), 122.95 d; C(5), 120.84 d, C(6), 123.51 d; CH_3 (on C-2), 55.24 q; **17**: Ar–C(1), 146.62 s; C(2), 100.42 d; C(3), 147.59 s; C(4), 143.50 s; C(5), 114.14 d; C(6), 107.80 d; (–O–CH_2–O), 110.05 t; **18**: Ar–C(1), 150.39 s; C(2), 119.07 s; C(3), 138.16 s; C(4), 118.48 d; C(5), 125.98 d; C(6), 114.44 d; CH_3 (on C-2) 13.71 q; CH_3 (on C-3), 20.54 q; **21**: Ar–C(1), 139.51 s; C(2,6), 125.37 d; C(3,5), 128.14 d; C(4), 127.45 d; CH_3 (on C″), 14.48 q; **22**: Ar–C(1), 142.10 s; C(2,6), 127.80 d; C(3,5), 129.15 d; C(4), 118.48 d; CH_3 (on C-2″), 14.71 q.

EXPERIMENTAL

NMR spectra were recorded on Bruker AV-300 [operating frequency 300.13 (^1H) and 75.47 MHz (^{13}C)], AM-400 [operating frequency 400.13 (^1H) and 100.78 MHz (^{13}C)], and DRX-500 [operating frequency 500.13 (^1H) and 125.76 MHz (^{13}C)] instruments. The multiplicity of resonances in ^{13}C NMR spectra were determined by standard methods of recording spectra in JMOD and with off-resonance proton decoupling. Mass spectra were obtained in a DFS high-resolution mass spectrometer. Specific rotations were measured on a Polar 3005 polarimeter at room (20-23°C) temperature. Elemental analyses were performed on a Carlo Erba Model 1106 CHN-analyzer. IR spectra in KBr disks were recorded on a Vector-22 instrument. UV absorption spectra in ethanol (c 10^{-4} M) were recorded on a HP 8453 UV—Vis spectrometer.

The course of reactions and purity of products were monitored by TLC on Silufol UV-254 plates with elution by $CHCl_3$:C_2H_5OH (3:1), benzene, and benzene—EtOAc (1:1). Spots were detected in an iodine chamber and by using UV light.

Pyridinium dichlorobromate was prepared by the literature method [15]. Alkaloids used in the reactions were isolated from plant material: (-)-anabasine [(2*S*)-3-(2-piperidinyl)-pyridine] (**10**), mp 104-105°C (2 Torr), lit. [16] n_D^{20} 1.5430, $[\alpha]_{578}^{23}$ −62° (c 5, C_6H_6)] from the aerial part of *Anabasis aphylla* L. by the literature method [17]; (-)-ephedrine (**19**) [(1*R*,2*S*)-2-methylamino-1-phenylpropan-1-ol], mp 38-39°C (hexane), lit. [18] mp 38-39°C (petroleum ether), from the hydrochloride {mp 216-217°C (EtOH), $[\alpha]_{578}^{20}$ −36° (c 2, H_2O), lit. [18] mp 216-217°C (EtOH), $[\alpha]_{589}$ −34.4° (c 1.5, H_2O)}. The latter was prepared from ephedrine contained in the non-woody upper part of *Ephedra equisetina* Bunge by the literature method [19].

(+)-Pseudoephedrine (**20**) [(1*S*,2*S*)-2-methylamino-1-phenylpropan-1-ol] {mp 118-119°C (distilled at 100°C/12 Torr after crystallization from C_6H_6), $[\alpha]_{578}^{20}$ +53° (*c* 3, EtOH), lit. [18] mp 118-119°C (purified as above), $[\alpha]_{589}$ +55.5° (*c* 8.1, EtOH)} was isolated as the hydrochloride from ephedra without preliminary purification.

Tables 2 and 2a list the ^{13}C NMR spectra of **6**, **8**, **9**, **11**-**18**, **21**, and **22**.

2-(1,3-Dibromopropan-2-ylidene)-2*H*-furo[3,2-*g*][1]benzopyran-3,7-dione (6). Method A. A solution of bromoreoselone (**5**, 1 g, 3.1 mmol) in CCl_4 (12 mL) was treated with NBS (1.6 g, 9.3 mmol) and benzoyl peroxide (5 mol%). The mixture was refluxed for 10 h, cooled, and filtered to remove succinimide (1.18 g, identified by mp). The filtrate was evaporated and treated with ether to afford a precipitate (1.34 g) from which column chromatography over silica gel ($CHCl_3$ eluent) and recrystallization of the product fraction from EtOAc afforded dibromide **6** (0.91 g, 73%).

Method B. A solution of **7** (0.5 g, 2.05 mmol) in CCl_4 (12 mL) was treated with NBS (0.73 g, 4.1 mmol) and benzoyl peroxide (5 mol %). The mixture was refluxed for 10 h. Succinimide (0.4 g, identified by mp) was filtered off after the reaction was finished. The mother liquor was evaporated and treated with ether to afford a precipitate (0.61 g) from which column chromatography over silica gel ($CHCl_3$ eluent) and recrystallization of the product fraction from EtOAc afforded dibromide **6** (0.41 g, 51%), mp 189°C. IR spectrum (ν, cm^{-1}): 828, 856, 890, 1138, 1353, 1600, 1620, 1658, 1709, 1744. UV spectrum ($CHCl_3$, λ_{max}, nm, log ε): 280 (4.25), 309 (4.49), 320 sh (3.45), 364 (3.48).

PMR spectrum (δ, ppm, J/Hz): 4.47 (2H, s, CH_2Br), 4.95 (2H, s, CH_2Br), 6.42 (1H, d, J = 9.6, H-6), 7.15 (1H, s, H-9), 7.74 (1H, d, J = 9.6, H-5), 7.91 (1H, s, H-4).

Mass spectrum (*m*/*z*, I_{rel}, %): 399 (25) $[M]^+$, 321 (40) $[M - Br]^+$, 240 (100) $[M - 2Br]^+$, 211 (100), 188 (10). Found [M] 397.8783. $C_{14}H_8Br_2O_4$. Calcd 397.8784. $C_{14}H_8Br_2O_4$.

Reaction of 2-Bromoreoselone with Amines. i: a solution of **5** (5.3 mmol, 1.7 g) in $CHCl_3$ (4 mL) was stirred, treated with a solution of the amine (10.6 mmol) in $CHCl_3$ (4 mL), and held at room temperature for 16 h. When the reaction was finished (TLC monitoring), the reaction mixture was diluted with water (10 mL). The organic layer was separated. The aqueous layer was extracted with $CHCl_3$ (3 × 4 mL). The organic layer was dried over $MgSO_4$ and evaporated. The solid was dissolved in acetone and cooled. The majority of **7** was filtered off. The mother liquor was evaporated. The solid was chromatographed over aluminum oxide (activity level II) with elution by $CHCl_3$. The product fraction was treated with ether. Recrystallization from the appropriate solvent afforded **8**, **9**, **11**, and **12**.

ii: a solution of **5** (3.9 mol) in DMF (10 mL) was stirred, treated with amine (7.8 mmol), and stirred for 8-10 h at 25°C. When the reaction was finished, saturated NH_4Cl solution (10 mL) was added. Products were extracted by CH_2Cl_2 (4 × 5 mL). Solvent was evaporated in vacuo. The solid was dried in a Petri dish and treated with hexane. The resulting precipitate was recrystallized from acetone to afford **7**. The mother liquor was evaporated. Compounds **8** and **11**-**13** were isolated by column chromatography over aluminum oxide.

iii: a mixture of KOH (4 mL, 30%), EtOAc (20 mL), and TEBAC (0.006 mg) in alcohol (0.5 mL) was stirred, treated with **5** (3.1 mmol) and amine (6.2 mmol), and stirred for 8 h at room temperature. The organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 4 mL). Solvent was evaporated in vacuo. The solid was treated with hexane and recrystallized from acetone to afford **7**. The mother liquor was evaporated. The solid was crystallized from EtOAc or chromatographed over aluminum oxide ($CHCl_3$ eluent) to afford **8**, **9**, **11**, and **13**-**18**.

iv: a mixture of KOH (4 mL, 30%), EtOAc (20 mL), and TEBAC (0.006 mg) in alcohol (0.5 mL) was stirred, treated with **5** (3.1 mmol) and amine (6.2 mmol), and stirred for 8 h at room temperature. The organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 4 mL). Solvent was evaporated in vacuo. The solid was treated with hexane and recrystallized from acetone to isolate **7**. The mother liquor was evaporated. The solid was chromatographed twice over aluminum oxide ($CHCl_3$ eluent). The product fraction was crystallized from EtOAc to afford **21** and **22**.

2-Isopropyl-2-(pyrrolidin-1-yl)-2*H*-furo[3,2-*g*]chromen-3,7-dione (8). Mp 158-161°C (EtOAc). IR spectrum (KBr, ν, cm^{-1}): 908, 1096, 1142, 1170, 1298, 1343, 1622, 1708, 1724. UV spectrum (EtOH, λ_{max}, nm, log ε): 257 (3.94), 278 (3.88), 314 (3.72), 337 (3.67).

PMR spectrum (δ, ppm, J/Hz): 0.84, 1.02 (both d, 3H each, J = 7.0, Me-2′,3′), 1.56, 1.75 (both m, 4H, H-3″,4″), 1.87-2.10 (2H, m, H-2″,5″), 2.70-2.90 (2H, m, H-2″,5″), 3.17 m (1H, m, H-1′), 6.33 (1H, d, J = 9.6, H-6), 6.94 (1H, s, H-9), 7.67 (1H, d, J = 9.6, H-5), 7.76 (s, 1H, H-4). $C_{18}H_{19}NO_4$.

2-[(*R*)-(2-Hydroxymethyl)pyrrolidin-1-yl]-2-isopropyl-2*H*-furo[3,2-*g*]chromen-3,7-dione (9). Mp 212-215°C (ether), $[\alpha]_D^{20}$ −7.6° (*c* 1.0, $CHCl_3$:EtOH, 1:1). IR spectrum (KBr, ν, cm^{-1}): 826, 856, 1140, 1351, 1451, 1624, 1731, 2929, 3007, 3330. UV spectrum (EtOH, λ_{max}, nm, log ε): 257 (4.04), 273 (3.84), 301 (3.80), 350 (3.65).

PMR spectrum (δ, ppm, J/Hz): 0.83, 1.02 (both d, 3H each, J = 7.0, Me-2′,3′), 1.52-1.67 (2H, m, H-3″,4″), 1.78-2.10 (4H, m, H-3″,4″,5″,5″), 2.32 (1H, m, H-1′), 3.32-3.60 (3H, m, H-2″,6″,6″), 4.16 (1H, m, OH), 6.32 (1H, d, J = 9.6, H-6), 6.95 (1H, s, H-9), 7.67 (1H, d, J = 9.6, H-5), 7.76 (s, 1H, H-4). $C_{19}H_{21}NO_5 \times CHCl_3$.

2-Isopropyl-2-[(*S*)-2-(pyridin-3-yl)piperidin-1-yl]-2*H*-furo[3,2-*g*]chromen-3,7-dione (11). Mp 200-201°C, $[\alpha]_D^{20}$ −3.2° (*c* 0.5, $CHCl_3$). IR spectrum (KBr, ν, cm^{-1}): 854, 908, 1100, 1125, 1140, 1353, 1483, 1579, 1627, 1655, 1737, 3230. UV spectrum (EtOH, λ_{max}, nm, log ε): 257 (4.31), 277 (4.19), 299 (4.04), 345 (3.88).

PMR spectrum (δ, ppm, J/Hz): 1.01, 1.06 (both d, 3H each, J = 7.0, Me-2′,3′), 1.42-1.55 (m, 2H, H-5″), 1.70-1.84 (m, 3H, 2H, H-4″ and 1H, H-3″), 1.98 (m, 1H, H-3″), 2.37 (1H, m, H-1″), 2.83 (m, 1H, H-6″), 3.21 (m, 1H, H-6″), 3.88 (m, 1H, H-2″), 6.27 (1H, d, J = 9.6, H-6), 6.85 (1H, s, H-9), 7.22 [t, 1H, H(5)-Py, J = 7.6, 7.5], 7.64 (1H, d, J = 9.6, H-5), 7.69 (s, 1H, H-4), 7.84 [d, 1H, H(4)-Py, J = 7.5], 8.42 [d, 1H, H(6)-Py, J = 7.6], 8.56 [d, 1H, H(2)-Py, J = 1.2]. $C_{24}H_{24}N_2O_4$.

2-Isopropyl-2-(4-methylpiperazin-1-yl)-2*H*-furo[3,2-*g*]chromen-3,7-dione (12). Mp 214-216°C. IR spectrum (KBr, ν, cm^{-1}): 825, 859, 909, 1091, 1136, 1350, 1391, 1574, 1624, 1650, 1722, 2975. UV spectrum (EtOH, λ_{max}, nm, log ε): 257 (4.31), 299 (3.99), 313 (3.89), 354 (3.91).

PMR spectrum (δ, ppm, J/Hz): 0.74, 1.12 (both d, 3H each, J = 7.0, Me-2′,3′), 2.30 (3H, s, N–Me), 2.57 (1H, m, H-1′), 2.52 (2H, m, H-2″,6″), 2.60-2.88 (4H, m, H-2″,3″,5″,6″), 3.27 (2H, m, H-3″,5″), 6.30 (1H, d, J = 9.6, H-6), 6.88 (1H, s, H-9), 7.66 (1H, d, J = 9.6, H-5), 7.73 (s, 1H, H-4). $C_{19}H_{22}N_2O_4 \times CHCl_3$.

2-[4-(2-Aminoethyl)piperazin-1-yl]-2-isopropyl-2*H*-furo[3,2-*g*]chromen-3,7-dione (13). Mp 181-183°C. IR spectrum (KBr, ν, cm^{-1}): 826, 855, 911, 954, 1102, 1120, 1142, 1292, 1351, 1484, 1574, 1626, 1650, 1732, 2855. UV spectrum (EtOH, λ_{max}, nm, log ε): 256 (4.26), 273 (4.08), 301 (4.06), 349 (3.90).

PMR spectrum (δ, ppm, J/Hz): 0.80, 1.12 (both d, 3H each, J = 7.0, Me-2′,3′), 1.90 (2H, m, NH_2), 2.45 (2H, m, CH_2–N), 2.50 (2H, m, H-2″,6″), 2.57 (1H, m, H-1′), 2.60-2.88 (4H, m, H-2″,3″,5″,6″), 3.31 (2H, m, H-3″,5″), 3.44 (2H, m, CH_2–NH_2), 6.29 (1H, d, J = 9.6, H-6), 6.91 (1H, s, H-9), 7.68 (1H, d, J = 9.6, H-5), 7.74 (s, 1H, H-4). $C_{20}H_{25}N_3O_4$. Found: *m*/*z* 371.37. $C_{20}H_{25}N_3O_4$. Calcd 371.3711.

2-Isopropyl-2-[4-(4-nitrophenyl)piperazin-1-yl]-2*H*-furo[3,2-*g*]chromen-3,7-dione (14). Mp 181-185°C. IR spectrum (KBr, ν, cm^{-1}): 648, 826, 854, 875, 906, 910, 949, 1035, 1092, 1117, 1144, 1246, 1291, 1331, 1340, 1504, 1598, 1625, 1721, 1746. UV spectrum (EtOH, λ_{max}, nm, log ε): 256 (4.02), 301 (3.74), 311 (3.56), 361 (3.87).

PMR spectrum (δ, ppm, J/Hz): 0.86, 1.20 (both d, 3H each, J = 7.0, Me-2′,3′), 2.42 (2H, m, H-2″,6″), 2.60 (1H, m, H-1′), 2.78 (2H, m, H-2″,6″), 2.98 (2H, m, H-3″,5″), 3.42 (2H, m, H-3″,5″), 6.34 (1H, d, J = 9.6, H-6), 6.76 (2H, d, J = 8.6, H-2,6-Ar), 6.91 (1H, s, H-9), 7.67 (1H, d, J = 9.6, H-5), 7.74 (1H, s, H-4), 8.10 (2H, d, J = 8.6, H-3,5-Ar). $C_{24}H_{23}N_3O_6 \times CHCl_3$. Found *m*/*z* 449.1583. $C_{24}H_{23}N_3O_6$. Calcd 449.1581.

2-Isopropyl-2-[4-(4-methoxyphenyl)piperazin-1-yl]-2*H*-furo[3,2-*g*]chromen-3,7-dione (15). Mp 147-149°C. IR spectrum (KBr, ν, cm^{-1}): 661, 702, 827, 908, 1010, 1034, 1100, 1145, 1292, 1307, 1349, 1500, 1512, 1624, 1668, 1720, 1746. UV spectrum (EtOH, λ_{max}, nm, log ε): 244 (4.55), 297 (3.87), 347 (3.59).

PMR spectrum (δ, ppm, J/Hz): 0.74, 1.13 (both d, 3H each, J = 7.0, Me-2′,3′), 2.72 (1H, m, H-1′), 2.76 (2H, m, H-2″,6″), 2.85 (2H, m, H-2″,6″), 3.06 (2H, m, H-3″,5″), 3.42 (2H, m, H-3″,5″), 3.69 (3H, s, OCH_3), 6.25 (1H, d, J = 9.6, H-6), 6.74 (2H, d, J = 8.6, H-2,6-Ar), 6.77 (1H, s, H-9), 6.84 (2H, d, J = 8.6, H-3,5-Ar), 7.63 (1H, d, J = 9.6, H-5), 8.01 (1H, s, H-4).

Mass spectrum (*m*/*z*, I_{rel}, %): 435.2 (11), 434.2 (37), 392 (5), 391 (17), 243 (5), 242 (18), 192 (32), 191 (18), 190 (16), 150 (100). Found *m*/*z* 434.1829 $[M]^+$. $C_{25}H_{26}N_2O_5$. Calcd MW = 434.1836. $C_{25}H_{26}N_2O_5$.

2-Isopropyl-2-[4-(2-methoxyphenyl)piperazin-1-yl]-2*H*-furo[3,2-*g*]chromen-3,7-dione (16). Mp 196-199°C. IR spectrum (KBr, ν, cm^{-1}): 660, 826, 907, 1010, 1028, 1120, 1145, 1243, 1296, 1310, 1500, 1582, 1625, 1668, 1721, 1746. UV spectrum (EtOH, λ_{max}, nm, log ε): 208 (4.39), 249 (4.10), 284 (3.81), 308 (3.63), 338 (3.56), 350 sh (3.52).

PMR spectrum (δ, ppm, J/Hz): 0.78, 1.18 (both d, 3H each, J = 7.0, Me-2′,3′), 2.64 (1H, m, H-1′), 2.84 (2H, m, H-2″,6″), 2.95-3.11 (4H, m, H-2″,3″,5″,6″), 3.53, 3.73 (2H, m, H-3″,5″), 3.73 (3H, s, OCH_3), 6.31 (1H, d, J = 9.6, H-6), 6.82 (2H, m, H-4,6-Ar), 6.89 (1H, s, H-9), 6.90 (1H, ddd, J = 8.2, 8.0, 1.8, H-5-Ar), 7.02 (1H, t, J = 8.6, H-3-Ar), 7.67 (1H, d, J = 9.6, H-5), 7.75 (1H, s, H-4).

Mass spectrum (*m*/*z*, I_{rel}, %): 435.1 (20), 434.1 (65), 391 (58), 341 (41), 242 (13), 220 (38), 192 (43), 191 (58), 190 (37), 162 (91), 150 (100). Found *m*/*z* 434.1846 $[M]^+$. $C_{25}H_{26}N_2O_5$. Calcd MW = 434.1836. $C_{25}H_{26}N_2O_5$.

2-[4-(Benzo[*d*][1,3]dioxol-5-yl)piperazin-1-yl]-2-isopropyl-2*H*-furo[3,2-*g*]chromen-3,7-dione (17). Mp 126-128°C. IR spectrum (KBr, ν, cm^{-1}): 824, 846, 863, 906, 1036, 1100, 1144, 1192, 1350, 1395, 1572, 1623, 1654, 1699, 1727, 3075.

PMR spectrum (δ, ppm, J/Hz): 0.74, 1.12 (both d, 3H each, J = 7.0, Me-2′,3′), 2.30 (3H, s, N–Me), 2.48 (1H, m, H-1′), 2.64 (4H, m, H-2″,6″), 2.83 (2H, m, H-3″,5″), 3.30 (2H, m, H-3″,5″), 5.90 (2H, m, O–CH_2–O), 6.27 (1H, d, J = 9.8, H-6), 6.34 (1H, d, J = 7.8, H-6-Ar), 6.69 (1H, s, H-2-Ar), 6.86 (1H, d, J = 7.8, H-5-Ar), 7.07 (1H, s, H-9), 7.64 (1H, d, J = 9.6, H-5), 7.72 (s, 1H, H-4). $C_{25}H_{24}N_2O_6$.

2-(4-(2,3-Dimethylphenyl)piperazin-1-yl)-2-isopropyl-2*H*-furo[3,2-*g*][1]benzopyran-3,7-dione (18). Mp 166-168°C. IR spectrum (KBr, ν, cm^{-1}): 661, 702, 827, 908, 1010, 1034, 1100, 1145, 1292, 1307, 1349, 1500, 1512, 1624, 1668, 1720, 1746. UV spectrum (EtOH, λ_{max}, nm, log ε): 241 (4.01), 266 (4.08), 274 (4.18), 303 (4.27), 356 (3.59).

PMR spectrum (δ, ppm, J/Hz): 0.88, 1.26 (both d, 3H each, J = 7.0, Me-2′,3′), 2.10 (3H, s, CH_3), 2.16 (3H, s, CH_3), 2.45 (1H, m, H-1′), 2.90 (4H, m, H-2″,6″), 3.08 (2H, m, H-3″,5″), 3.16 (2H, m, H-3″,5″), 6.32 (1H, d, J = 9.6, H-6), 6.78 (1H, d, J = 8.2, H-6-Ar), 6.81 (1H, s, H-9), 6.86 (1H, d, J = 8.0, H-2-Ar), 6.97 (1H, t, J = 8.2, 8.0, H-5-Ar), 7.72 (1H, d, J = 9.6, H-5), 7.98 (1H, s, H-4). $C_{26}H_{28}N_2O_4$.

2-{[(1*R*,2*S*)-1-Hydroxy-1-phenylpropan-2-yl](methyl)amino}-2-isopropyl-2*H*-furo[3,2-*g*]chromen-3,7-dione (21). Mp 210-211°C, $[\alpha]_D^{20}$ –27° (*c* 1.0, EtOH, 1:1). UV spectrum (EtOH, λ_{max}, nm, log ε): 231 (3.71), 271 (4.16), 301 (4.28), 357 (3.55).

PMR spectrum (δ, ppm, J/Hz): 0.82 (3H, d, J = 7.0, Me on C-2″), 0.91, 1.31 (both d, 3H each, J = 7.0, Me-2′,3′), 2.40 (3H, s, CH_3), 2.41 (1H, m, H-1′), 2.90 (1H, m, H-2″), 4.97 (1H, d, J = 3.0, H-3″), 5.22 (1H, m, OH), 6.33 (1H, d, J = 9.6, H-6), 6.97 (1H, s, H-9), 7.15 (2H, m, H-Ar), 7.28 (3H, m, H-Ar), 7.68 (1H, d, J = 9.6, H-5), 7.87 (1H, s, H-4). $C_{24}H_{25}NO_5$.

2-{[(1*S*,2*S*)-1-Hydroxy-1-phenylpropan-2-yl](methyl)amino}-2-isopropyl-2*H*-furo[3,2-*g*]chromen-3,7-dione (22). Mp 223-224°C, $[\alpha]_D^{20}$ +12.4° (*c* 0.5, EtOH, 1:1). IR spectrum (KBr, ν, cm^{-1}): 661, 702, 827, 908, 1010, 1034, 1100, 1145, 1292, 1307, 1349, 1500, 1512, 1624, 1668, 1720, 1746. UV spectrum (EtOH, λ_{max}, nm, log ε): 266 (4.18), 274 (4.29), 303 (4.40), 356 (3.71).

PMR spectrum (δ, ppm, J/Hz): 0.86 (3H, d, J = 7.0, Me on C-2″), 0.90, 1.30 (both d, 3H each, J = 7.0, Me-2′,3′), 2.33 (3H, s, CH_3), 2.48 (1H, m, H-1′), 2.57 (1H, m, H-2″), 3.57 (1H, m, OH), 4.14 (1H, d, J = 9.2, H-3″), 6.31 (1H, d, J = 9.6, H-6), 6.97 (1H, s, H-9), 7.19 (2H, m, H-Ar), 7.25 (3H, m, H-Ar), 7.66 (1H, d, J = 9.6, H-5), 7.86 (1H, s, H-4). $C_{24}H_{25}NO_5$.

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