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## Synthesis and Investigation of the Pharmacological Activity of Oreoselone Nitrogen-Containing Derivatives

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### Abstract

The bromination of peucedanine using different reagents resulted in the formation of 2-bromoreoselone. *Via* the reaction with the derivatives of piperidine and piperazine we synthesized 2-piperazino and 2-piperidino derivatives of oreoselone. Conditions were determined for the formation of 2-(1,3-dibromopropane-2-ylidene)-2*H*-furo-[3,2-*g*][1]-benzopyran-3,7-dione. The interaction of the latter with tyramine resulted in obtaining bis(diaminophenethyl) derivative of furocoumarin. The amination of the mentioned dibromide with the help of spermine resulted in the formation of a macrocyclic compound containing both furocoumarin and polyamine fragments. The effect of novel oreoselone derivatives on the central nervous system was investigated.

**Key words:** furocoumarins, bromoreoselone, 2-(1,3-dibromopropane-2-ylidene)-2*H*-furo-[3,2-*g*][1]benzopyran-3,7-dione, motion activity, chloral hydrate sleep

### INTRODUCTION

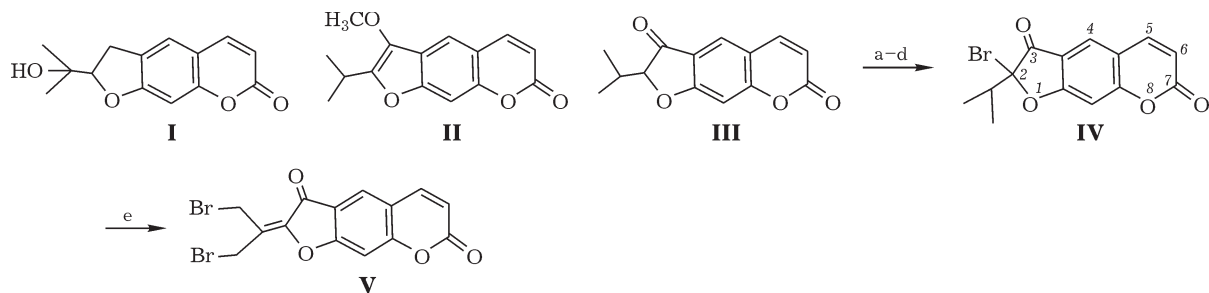
Linear dihydrofurocoumarins represent widespread plant metabolites those exhibit different biological activity [1–3]. So, marmesine **I** is an efficient inhibitor of cAMP synthetase [4] and acetylcholinesterase [5], exhibits cytotoxic properties with respect to tumor cells of KB line [6]. In recent time a question is actively discussed concerning the prospectivity of coumarins for making novel antidepressants due to their specific activity as selective inhibitors of monoaminoxidase (MAO) [7]. Naturally occurring and synthetic 3-amino substituted derivatives of coumarins represent efficient antibiotic, anti-tumor and antiviral agents [8, 9]. 8-Piperazine- and 8-morfolino-7-hydroxycoumarins exhibit a high anti-inflammatory activity [10]. 4-Morfolinocoumarin represents an efficient inhibitor of DNA dependent protein kinase [11].

Thus, the development of the methods for modifying furocoumarins *via* the introduction of nitrogen-containing fragments is of certain interest for medical chemistry. An available source of furocoumarins is presented by *Peu-*

*cedanum morisonii* Bess. widespread in West Siberia whose main metabolite peucedanine **II** can be isolated from the roots of the plant with the yield up to 4 % as calculated for the mass of dry raw material [12]. The authors of [13, 14] described obtaining a number of peucedanine derivatives and oreoselone **III** as the product its hydrolysis *via* the modification of the furan cycle. In this paper, oreoselone synthesis and pharmacological properties of new oreoselone derivatives are presented.

### RESULTS AND DISCUSSION

As a source compound for obtaining nitrogen-containing derivatives we used 2-bromoreoselone **IV** – a single product of peucedanine bromination using bromine in formic acid (yield 98 %), dioxane dibromide in CCl<sub>4</sub> (yield ranging within 94–98 %), *N*-bromosuccinimide in CCl<sub>4</sub> (yield 97–98 %) and pyridine dichlorobromate (PyHBrCl<sub>2</sub>) in methanol (yield 94 %). The further bromination of 2-bromoreoselone **IV** *via* the action of NBS



a) Br<sub>2</sub>-HCOOH; b) NBS-CCl<sub>4</sub>; c) PyHBrCl<sub>2</sub>-MeOH; d) DDB-CCl<sub>4</sub>; e) NBS-[PhC(O)-O]<sub>2</sub>, CCl<sub>4</sub>.

Scheme 1.

(3 equiv.) in the presence of benzoyl peroxide in CCl<sub>4</sub> results in the formation of 2-(1,3-dibromopropane-2-ylidene)-2H-furo-[3,2-g][1]-benzopyran-3,7-dione **V** (yield 73 %) (Scheme 1).

The reaction between 2-bromoreoselone **IV** and alkaloid anabasine **VI** was performed when holding the mixture of the components in chloroform or DMFA, as well as under the conditions of phase-transfer catalysis (the organic phase being ethyl acetate or methylene chloride, the catalyst being TEBAH with catalysis promoted by alcohol [15]). The conditions and composition of the reaction products are presented in Table 1. In all the cases, the main reaction product is presented by 2-isopropyl-2-[(*S*)-2-(pyridine-3-yl)pi peridine-1-yl]-2H-furo-[3,2-*g*]-chromene-3,7-dione **VII**. In addition, we isolated 2-(propane-2-ylidene)-2H-furo-[3,2-*g*]-chromene-3,7-dione **VIII** – the product of detaching HBr from initial bromide **IV**. The interaction between 2-bromoreoselone **IV** and 4-sub-

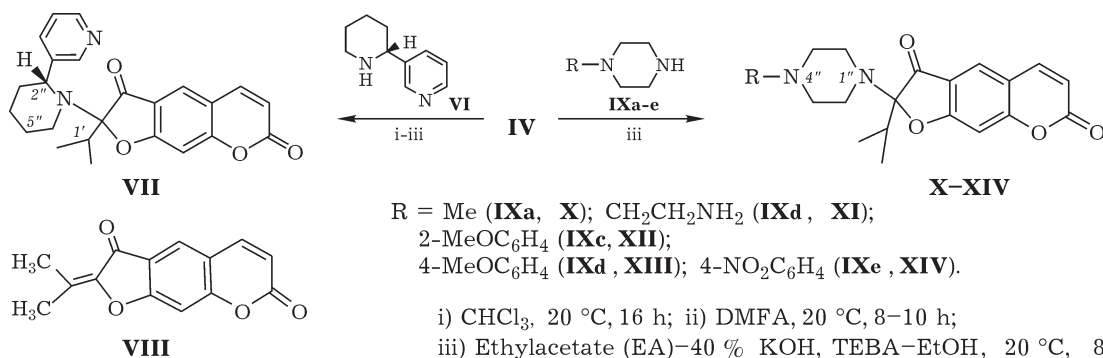
stituted piperazines **IXa–e** occurs with a lower yield of the products corresponding to 2-(4-*R*-piperazine-1-yl)-substituted reoselone derivatives **X–XIV**. Comparing the results of reactions between different piperazines and bromide **IV**, it should be noted that increase in the yield of substitution products is observed in the reaction with *N*-(4-methoxyphenyl)- and *N*-(4-nitrophenyl)piperazines **IXd,e** (Scheme 2).

The reaction of peucedanine dibromo derivative **V** with tyramine performed under boiling components in THF in the presence of sodium hydride. Diamino derivative **XV** was isolated with the yield of 61 % (Scheme 3). Of interest is the synthesis of compounds with polyamine chains or macrocycles, containing coumarin and polyamine fragments [16]. We established that interaction between dibromide of **V** and spermine (2 equiv.) results in the formation of a macrocyclic derivative of furocoumarin **XVI** as the main reaction product. The

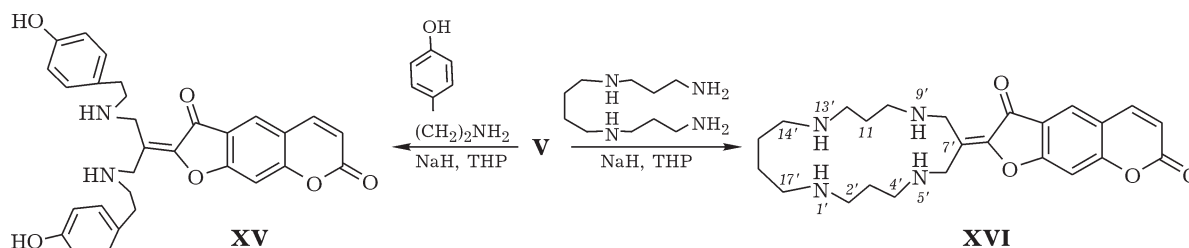
TABLE 1

Conditions and products of 2-bromoreoselone **IV** reaction with anabasine **VI** and substituted piperazines **IXa–e**

Amines	Reaction conditions	Products (Yield, %)	
(–)-Anabasine <b>VI</b>	(i) CHCl <sub>3</sub> , 20 °C, 16 h	<b>VII</b> (64)	<b>VIII</b> (24)
<b>VI</b>	(ii) DMFA, 20 °C, 8–10 h	<b>VII</b> (61)	<b>VIII</b> (25)
<b>VI</b>	(iii) EA-40 % KOH, TEBA-EtOH, 20 °C, 8 h	<b>VII</b> (65)	<b>VIII</b> (27)
<i>N</i> -Methylpiperazine <b>IXa</b>	(i)	<b>X</b> (33)	<b>VIII</b> (41)
<b>IXa</b>	(ii)	<b>X</b> (30)	<b>VIII</b> (57)
<i>N</i> -(2-aminoethyl)piperazine <b>IXb</b>	(ii)	<b>XI</b> (18)	<b>VIII</b> (56)
<b>IXb</b>	(iii)	<b>XI</b> (27)	<b>VIII</b> (58)
1-(2-Methoxyphenyl)piperazine <b>IXc</b>	(iii)	<b>XII</b> (37)	<b>VIII</b> (59)
1-(4-Methoxyphenyl)piperazine <b>IXd</b>	(iii)	<b>XIII</b> (46)	<b>VIII</b> (48)
1-(4-Nitrophenyl)piperazine <b>IXe</b>	(iii)	<b>XIV</b> (48)	<b>VIII</b> (40)



Scheme 2.



Scheme 3.

yield of compound **XVI** after the column chromatography procedure on alumina amounted to 51 %. In addition we isolated compound **VIII** (yield 15 %) (see Scheme 3).

The effect of the compounds synthesized on the central nervous system (CNS) was studied within the framework of the locomotor activity and chloral hydrate sleep model. In the stud-

ies concerning the influence of agents upon the locomotor and emotional behaviour of animals, agents **XIII** and **XIV** appeared the most active (Table 2); against the background of the introduction of those an increase in locomotor activity and a certain decrease of anxiety was observed. The rest agents either demonstrated a low activity in this test, or were inactive.

TABLE 2

Effect of oreoselone amino derivatives on the parameters of locomotor and emotional activity of animals

Compounds	A	B	C	D	E	F	G	H	I
Reference	13.4±1.2	96.8±2.7	279.4±35.5	139.8±17.8	23.3±2.7	9.5±1.3	18.6±2.1	4.3±0.7	4.8±0.8
<b>VII</b>	12.8±1.5	102.3±2.8	319.9±41.1	160.1±20.5	17.8±2.8	6.9±1.7	19.5±4.4	3.8±0.6	4.1±0.9
<b>X</b>	12.1±0.69	104.1±1.1	285.6±19.7	142.8±9.9	15.9±1.1*	9.3±0.5	16.3±1.7	4.0±0.8	5.0±1.2
Reference	15.8±1.0	95.3±2.8	324.1±43.2	162.0±21.6	24.8±2.8	14.9±1.0	30.5±1.5	3.4±0.6	4.5±0.8
<b>XI</b>	12.8±0.9*	101.3±2.5	301.0±21.8	150.4±11.0	18.8±2.5	13.1±1.2	24.8±2.7	3.8±0.8	4.5±0.8
<b>XII</b>	13.0±1.6	103.6±2.2*	285.5±21.5	141.1±12.2	17.1±2.4	12.6±2.1	23.3±5.3	4.6±1.2	5.0±1.3
<b>XIII</b>	10.6±1.6*	107.4±1.8**	283.9±21.7	141.8±10.8	12.6±1.8**	9.8±2.3	15.6±5.0*	5.5±1.4	6.4±1.7
<b>XIV</b>	13.0±1.1	104.0±1.5*	254.5±18.8	127.0±9.6	16.0±1.5*	7.3±1.8	11.6±4.6**	4.6±1.2	6.3±1.5
Reference	12.6±0.9	102.3±2.0	327.5±18.7	163.7±9.3	17.8±2.0	9.9±0.9	16.5±1.8	3.5±0.5	4.1±0.6
<b>XV</b>	10.5±0.9	105.5±1.7	382.0±27.5	191.1±13.7	14.5±1.7	12.0±1.1	21.3±2.7	4.6±0.9	5.6±1.2
<b>XVI</b>	12.4±0.6	99.6±2.6	325.9±29.5	163.1±14.8	20.4±2.6	14.3±1.1*	22.0±2.6	5.0±0.7	5.9±0.8

Note. A – general locomotor activity; B – activity duration, s; C – passed distance, cm; D – motion speed, cm/s; E – still moment, s; F – vertical stand number; G – time spent in stands called on in rack, s; H – number of explored holes; I – duration of exploratory reaction, s.

\**p* < 0.05 compared to reference.

\*\**p* < 0.01 compared to reference.

TABLE 3

Effect of oreoselone amino derivatives on the duration of chloral hydrate sleep, min

Agents	Falling-asleep time	Sleep duration
Reference	3.5±0.2	81.8 ± 10.1
<b>XIII</b>	3.1±0.3	65.5±6.8
<b>XIV</b>	2.6±0.2**	72.1±4.3
Reference	3.4±0.1	102.6±21.8
<b>VII</b>	3.4±0.2	157.0±22.2
<b>XV</b>	3.2±0.3	235.6±1.8***
<b>XVI</b>	3.1±0.1	157.3±28.0

\*\**p* < 0.01 compared to reference.

\*\*\**p* < 0.001 compared to reference.

The chloral hydrate sleep test allows one to evaluate the influence of an agent upon barbiturate hypnotic action. The results of the investigation performed (Table 3) indicate that the greatest activity in this test was demonstrated by agent **XV** that significantly caused a prolonged duration of the sleep. For the other agents the change in the animal sleep duration was at a tendency level. It should be also noted that agent **XIV** caused shortening the latent falling-asleep time, but herewith it did not influence the sleep duration itself.

## EXPERIMENTAL

### Chemistry

The NMR spectra were registered using a Bruker AV-300 spectrometer [with the operation frequency of 300.13 (<sup>1</sup>H) and 75.47 MHz (<sup>13</sup>C)], AM-400 spectrometer [with the operation frequency of 400.13 (<sup>1</sup>H) and 100.78 MHz (<sup>13</sup>C)] and AV-600 [with the operation frequency of 600.30 (<sup>1</sup>H) and 150.96 MHz (<sup>13</sup>C)]. Mass spectra were registered on a DFS high resolution mass spectrometer. The elemental analysis was performed using a Carlo Erba elemental CHN model 1106 analyzer. IR spectra were recorded on a Vector-22 spectrophotometer using KBr tablets. The UV absorption spectra were registered using an HP 8453 UV-Vis spectrometer in ethanol (10<sup>-4</sup> mol/L).

The monitoring of the course of the reaction and of the purity of compounds obtained was performed using the method TLC on Silufol

UV-254 plates with use of the systems such as chloroform/ethanol (3 : 1); benzene/ethyl acetate (1 : 1). The development of the spots was performed in an iodine camera and by means of UV light irradiation. The <sup>13</sup>C NMR spectral data for compounds **V**, **VII**, **X–XIV** are presented in Table 4.

**2-(1,3-Dibromopropane-2-ylidene)-2H-furo-[3,2-g][1]-benzopyran-3,7-dione IV.** To a solution of 1 g (3.1 mmol) of bromoreoselone **III** in 12 mL of CCl<sub>4</sub> was added 1.6 (9.3 mmol) of NBS and 5 mol. % of benzoyl peroxide. The mixture was boiled during 10 h. After cooling 1.18 g of succinimide was filtered (identification basing on m. p.), the remainder was evaporated and processed with ether. We obtained 1.34 g of precipitate, wherefrom using column chromatography on silica gel (chloroform eluent) and recrystallizing the product fraction from ethyl acetate we obtained 0.91 g (73 %) of dibromide **IV**. IR spectrum, ν, cm<sup>-1</sup>: 828, 856, 890, 1138, 1353, 1600, 1620, 1658, 1709, 1744. UV spectrum (CHCl<sub>3</sub>), λ<sub>max</sub>, nm (log ε): 280 (4.25), 309 (4.49), 320 sh (3.45), 364 (3.48). <sup>1</sup>H NMR spectrum (δ, ppm, *J*, Hz): 4.47 (2H, s, CH<sub>2</sub>Br), 4.95 (2H, s, CH<sub>2</sub>Br), 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*<sub>rel</sub>, %): 399 (*M*<sup>+</sup>) (25), 321 (*M*-Br)<sup>+</sup>(40), 240 (*M*-2Br)<sup>+</sup>(100), 211 (100), 188 (10). Found [*M*]: 397.8783. C<sub>14</sub>H<sub>8</sub>Br<sub>2</sub>O<sub>4</sub>. Calculated: C 42.44, H 1.96, Br 39.48. C<sub>14</sub>H<sub>8</sub>Br<sub>2</sub>O<sub>4</sub>. Found, %: C 42.44, H 1.96, Br 39.48. C<sub>14</sub>H<sub>8</sub>Br<sub>2</sub>O<sub>4</sub>. Calculated, %: C 42.04, H 2.02, Br 39.95.

**Interaction between 2-bromoreoselone IV and amines.** (i) To a solution of 5.3 mmol (1.7 g) of 2-bromoreoselone **IV** in 4 mL of chloroform was added under stirring a solution of 10.6 mmol of amine **a** in 4 mL of chloroform. The reaction mixture was held for 16 h at a room temperature. After completing the reaction (TLC monitoring) the reaction mixture was diluted with 10 mL of water, the organic layer was separated, the aqueous layer was extracted by chloroform (3 × 4 mL), the organic layer was dried using MgSO<sub>4</sub> and evaporated. The remainder was dissolved in acetone, the main part of compound **VIII** was filtered under cooling. The mother solution was evaporated, the remainder was chromatographed on alumina (II grade of activity), using chloroform as an eluent. The fraction containing prod-

TABLE 4

Chemical shifts of carbon atoms in  $^{13}\text{C}$  NMR spectra for compounds under investigation ( $\delta$ , ppm)

Atoms	V	VII	X	XI	XII	XIII	XIV
C-2	145.05 s	114.69 s	109.09 s	111.95 s	109.68 s	109.65 s	108.73 s
C-3	181.80 s	197.87 s	197.86 s	197.50 s	197.88 s	197.97 s	197.32 s
C-3a	119.31 s	120.76 s	119.86 s	120.64 s	119.69 s	119.68 s	119.54 s
C-4	125.12 d	124.45 d	124.58 d	124.18 d	124.05 d	124.45 d	124.24 d
C-4a	115.52 s	115.72 s	114.38 s	113.83 s	113.98 s	114.27 s	114.01 s
C-5	143.09 d	143.13 d	143.69 d	143.05 d	143.33 d	143.72 d	143.27 d
C-6	115.48 d	115.39 d	114.77 d	114.04 d	113.98 d	113.81 d	112.71 d
C-7	165.73 s	158.83 s	159.65 s	158.68 s	159.32 s	159.55 s	159.13 s
C-8a	160.51 s	161.13 s	162.06 s	161.11 s	161.43 s	161.74 s	161.64 s
C-9	101.22 d	101.62 d	100.59 s	100.23 s	99.84 s	100.11 s	100.02 s
C-9a	158.88 s	169.60 s	172.97 s	171.70 s	172.61 s	172.81 s	172.49 s
C-1'	126.08 s	31.81 d	31.27 d	31.29 d	31.32 d	31.44 d	29.27 d
C-2'	26.13 t <sup>a</sup>	16.67 q	15.34 q <sup>a</sup>	15.27 q <sup>a</sup>	14.87 q <sup>a</sup>	15.00 q <sup>a</sup>	14.00 q <sup>a</sup>
C-3'	24.58 t <sup>a</sup>	17.52 q	16.94 q <sup>a</sup>	16.06 q <sup>a</sup>	16.43 q <sup>a</sup>	16.53 q <sup>a</sup>	15.02 q <sup>a</sup>
C-2''	–	36.47 d	43.09 t <sup>b</sup>	41.19 t <sup>b</sup>	45.72 t <sup>b</sup>	45.59 t <sup>b</sup>	45.45 t <sup>b</sup>
C-3''	–	29.59 t <sup>a</sup>	54.66 t	54.22 t <sup>c</sup>	50.05 t <sup>c</sup>	50.91 t	50.53 t
C-4''	–	22.59 t	–	–	–	–	–
C-5''	–	29.62 t <sup>a</sup>	54.66 t	56.64 t <sup>c</sup>	51.53 t <sup>c</sup>	50.91 t	50.53 t
C-6''	–	36.47 t	44.48 t <sup>b</sup>	42.18 t <sup>b</sup>	45.92 t <sup>b</sup>	45.90 t <sup>b</sup>	46.91 t <sup>b</sup>

Note. For compound **VII**: 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; **X**: N–CH<sub>3</sub> – 44.78 q; **XI**: N–CH<sub>2</sub> – 59.70 t; CH<sub>2</sub>NH<sub>2</sub> – 36.20 t; **XII**: 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<sub>3</sub> (at C-2) – 55.24 q; **XIII**: Ar–C(1) – 145.50 s; C(2,6) – 118.45 d; C(4) – 154.11 s; C(3,5) – 114.50 d; OCH<sub>3</sub> (at C-4) – 55.59 q; **XIV**: Ar–C(1) – 154.42 s; C(2,6) – 112.72 d; C(4) – 138.69 s; C(3,5) – 125.74 d.

<sup>a,b,c</sup>The values of chemical shift, indicated with the same letter, should be, to all appearance, swapped within one column.

uct was processed the ether. After recrystallization from the corresponding solvent we obtained compounds **VII** and **X**.

(ii) To a solution 3.9 mol of bromoreoselone **IV** in 10 mL DMFA under stirring was added 7.8 mmol of amine, the reaction mixture was stirred during 8–10 h at 25 °C. After completing the reactions was added 10 mL of ammonium chloride saturated solution, the products extracted by methylene chloride (4 × 5 mL) and the solvent was evaporated in vacuum. The Remainder was dried in a Petri dish, treated with hexane, and then the precipitate obtained was recrystallized from acetone. Compound **VIII** was isolated. The mother liquor was evaporated; compounds **VII**, **XXI** were isolated using the technique of column chromatography on aluminium oxide.

(iii) To a mixture of 4 mL 30 % KOH, 20 mL of ethyl acetate and 0.006 mg of TEBAH in

0.5 mL of alcohol under stirring was added 3.1 mmol of bromoreoselone **IV** and 6.2 mmol of corresponding amine. The mixture was stirred during 8 h at a room temperature. The organic layer was separated, the aqueous layer was extracted by methylene chloride (3 × 4 mL) and the solvent was evaporated in vacuum. The remainder was treated by hexane, solid precipitate was recrystallized from acetone; compound **VIII** was isolated. The mother liquor was evaporated; the remainder was either crystallized from ethyl acetate or chromatographed on alumina (chloroform as an eluent). Compound **VII**, **XI**, **XIII** and **XIV** were obtained.

**2-Isopropyl-2-[(S)-2-(pyridine-3-yl)piperidine-1-yl]-2H-furo[3,2-g]chromene-3,7-dione VII**. M. p. 200–201 °C,  $[\alpha]_D^{20}$  –3.2° (s 0.5, chloroform). IR spectrum (KBr,  $\nu$ , cm<sup>-1</sup>): 854, 908, 1100, 1125, 1140, 1353, 1483, 1579, 1627, 1655, 1737, 3230. UV spectrum (EtOH),

$\lambda_{\max}$ , nm (log  $\epsilon$ ): 257 (4.31), 277 (4.19), 299 (4.04), 345 (3.88).  $^1\text{H}$  NMR spectrum ( $\delta$ , ppm,  $J$ , Hz): 1.01, 1.06 (both d, on 3H,  $J = 7.0$ , 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,  $J = 1.2$ ). Found, %: C 69.78, H 6.10, N 7.01.  $\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_4$ . Calculated, %: C 71.27, H 5.98, N 6.93.

**2-Isopropyl-2-(4-methylpiperazine-1-yl)-2H-furo-[3,2-g]chromene-3,7-dione X.** M. p. 214–216 °C. IR spectrum (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ): 826, 859, 909, 1091, 1136, 1350, 1391, 1574, 1624, 1650, 1722, 2975. UV spectrum (EtOH),  $\lambda_{\max}$ , nm (log  $\epsilon$ ): 257 (4.31), 299 (3.99), 313 (3.89), 354 (3.91).  $^1\text{H}$  NMR spectrum ( $\delta$ , ppm,  $J$ , Hz): 0.74, 1.12 (both d, on 3H,  $J = 7.0$ , Me-2',3'), 2.30 (3H, s, N-Me), 2.57 (1H, m, H-1'), 2.52 m (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). Found, %: C 51.08, H 4.51, N 6.27.  $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_4 \cdot \text{CHCl}_3$ . Calculated, %: C 51.67, H 4.95, N 6.03.

**2-[4-(2-Aminoethyl)piperazine-1-yl]-2-isopropyl-2H-furo-[3,2-g]chromene-3,7-dione XI.** M. p. 181–183 °C. IR spectrum (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ): 826, 855, 911, 954, 1102, 1120, 1142, 1292, 1351, 1484, 1574, 1626, 1650, 1732, 2855. UV spectrum (EtOH),  $\lambda_{\max}$ , nm (log  $\epsilon$ ): 256 (4.26), 273 (4.08), 301 (4.06), 349 (3.90).  $^1\text{H}$  NMR spectrum ( $\delta$ , ppm,  $J$ , Hz): 0.80, 1.12 (both d, on 3H,  $J = 7.0$ , Me-2',3'), 1.90 (2H, m,  $\text{NH}_2$ ), 2.45 (2H, m,  $\text{CH}_2$ -N), 2.50 m (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,  $\text{CH}_2$ - $\text{NH}_2$ ), 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). Found, %: C 65.12, H 6.53, N 11.27.  $\text{C}_{20}\text{H}_{25}\text{N}_3\text{O}_4$ . Calculated, %: C 64.67, H 6.78, N 11.31. Found:  $m/z$  371.37.  $\text{C}_{20}\text{H}_{25}\text{N}_3\text{O}_4$ . Calculated: 371.3711.

**2-Isopropyl-2-[4-(2-methoxyphenyl)piperazine-1-yl]-2H-furo[3,2-g]chromene-3,7-dione XII.** M. p. 196–199 °C. IR spectrum (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ): 660, 826, 907, 1010, 1028, 1120, 1145, 1243, 1296, 1310, 1500, 1582, 1625, 1668, 1721, 1746.

UV spectrum (EtOH),  $\lambda_{\max}$ , nm (log  $\epsilon$ ): 208 (4.39), 249 (4.10), 284 (3.81), 308 (3.63), 338 (3.56), 350 sh (3.52).  $^1\text{H}$  NMR spectrum ( $\delta$ , ppm,  $J$ , Hz): 0.78, 1.18 (both d, on 3H,  $J = 7.0$ , Me-2',3'), 2.64 (1H, m, H-1'), 2.84 m (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,  $\text{OCH}_3$ ), 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,  $m/z$  ( $I_{\text{rel}}$ , %): 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  $[M]^+$ .  $\text{C}_{25}\text{H}_{26}\text{N}_2\text{O}_5$ . Calculated:  $M = 434.1836$ . Found, %: C 68.28, H 5.51, N 6.27.  $\text{C}_{25}\text{H}_{26}\text{N}_2\text{O}_5$ . Calculated, %: C 69.11, H 6.03, N 6.45.

**2-Isopropyl-2-[4-(4-methoxyphenyl)piperazine-1-yl]-2H-furo-[3,2-g]chromene-3,7-dione XIII.** M. p. 147–149 °C. IR spectrum (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ): 661, 702, 827, 908, 1010, 1034, 1100, 1145, 1292, 1307, 1349, 1500, 1512, 1624, 1668, 1720, 1746. UV spectrum (EtOH),  $\lambda_{\max}$ , nm (log  $\epsilon$ ): 244 (4.55), 297 (3.87), 347 (3.59).  $^1\text{H}$  NMR spectrum ( $\delta$ , ppm,  $J$ , Hz): 0.74, 1.13 (both d, on 3H,  $J = 7.0$ , Me-2',3'), 2.72 (1H, m, H-1'), 2.76 m (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,  $\text{OCH}_3$ ), 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,  $m/z$  ( $I_{\text{rel}}$ , %): 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  $[M]^+$ .  $\text{C}_{25}\text{H}_{26}\text{N}_2\text{O}_5$ . Calculated:  $M = 434.1836$ . Found, %: N 5.96.  $\text{C}_{25}\text{H}_{26}\text{N}_2\text{O}_5$ . Calculated, %: N 6.45.

**2-Isopropyl-2-[4-(4-nitrophenyl)piperazine-1-yl]-2H-furo-[3,2-g]chromene-3,7-dione XIV.** M. p. 181–185 °C. IR spectrum (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ): 648, 826, 854, 875, 906, 910, 949, 1035, 1092, 1117, 1144, 1246, 1291, 1331, 1340, 1504, 1598, 1625, 1721, 1746. UV spectrum (EtOH),  $\lambda_{\max}$ , nm (log  $\epsilon$ ): 256 (4.02), 301 (3.74), 311 (3.56), 361 (3.87).  $^1\text{H}$  NMR spectrum ( $\delta$ , ppm,  $J$ , Hz): 0.86, 1.20 (both d, on 3H,  $J = 7.0$ , Me-2',3'), 2.42 m (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). Found, %: C 51.28, H 4.25, N 7.29.  $C_{24}H_{23}N_3O_6 \cdot CHCl_3$ . Calculated, %: C 52.77, H 4.22, N 7.34. Found:  $m/z$  449.1583.  $C_{24}H_{23}N_3O_6$ . Calculated: 449.1581.

**2-(1,3-Bis-(4-hydroxyfenethylamino)-propane-2-ylidene)-2H-furo-[3,2-g]chromene-3,7-dione XV.** Sodium hydride 0.084 g in mass (2.5 mmol) was treated by 10 mL of absolute hexane in a flow of argon, then was added 10 mL of absolute THF and 0.274 g (2 mmol) of tyramine. The mixture was held under stirring for 0.5 h at a room temperature. Then was added 0.4 g (1 mmol) of compound **V** and heated up to 60 °C. After 6 h (TLC monitoring) the mixture was cooled, several drops of alcohol was added for the decomposition of sodium hydride, then 20 % HCl solution was added for obtaining neutral pH. The organic layer were separated, the aqueous layer was extracted by ethyl acetate (4 × 5 mL) and by methylene chloride (3 × 5 mL), dried over  $MgSO_4$  and evaporated. The remainder was chromatographed on alumina using as eluents being chloroform and chloroform/ethanol = 50 : 3. After repeated chromatographing, compound **XV** was isolated with the yield of 61 %. M. p. 189–190 °C (from ethyl acetate). IR spectrum (KBr,  $\nu$ ,  $cm^{-1}$ ): 774, 822, 966, 1029, 1113, 1174, 1380, 1467, 1516, 1595, 1700, 2518, 2580, 2868, 2930, 3336. UV spectrum (EtOH),  $\lambda_{max}$ , nm (log  $\epsilon$ ): 201 (4.57), 225 (4.4), 279 (3.89), 335 sh (3.16).  $^1H$  NMR spectrum ( $\delta$ , ppm,  $J$ , Hz): 2.58, 2.96 (both m on 4H, C-1''H2, C-2''H2), 3.21 (4H, t,  $J = 8.8$ , C-2'H2), 6.90 (4H, d,  $J = 7.8$ , H-2,6-Ar), 6.92 (1H, s, H-9), 6.97 (1H, d,  $J = 9.8$ , H-6), 7.01 (4H, d,  $J = 7.8$ , H-3, 5-Ar), 7.54 (1H, d,  $J = 9.8$ , H-5), 7.94 (1H, s, H-4), 12.02 (4H, br.s, OH, NH).  $^{13}C$  NMR spectrum ( $\delta$ , ppm): 36.19, 49.63 (both t, C-1'', C-2''), 44.19 (t, C-2'), 98.01 (d, C-9), 112.80 (d, C-6), 113.49 (s, C-5a), 116.42 (s, C-4a), 116.62 (both d, C-3,5-Ar), 119.96 (s, C-1'), 121.88 (d, C-4), 123.31 (s, C-1-Ar), 130.02 (both d, C-2,6-Ar), 144.15 (s, C-4'), 144.11 (d, C-5), 144.80 (s, C-2), 156.45 (s, C-9a), 156.57 (s, C-4-Ar), 158.85 (s, C-8a), 173.71 (s, C-7), 197.29 (s, C-3). Found, %: N 5.89.  $C_{30}H_{28}N_2O_6$ . Calculated, %: N 5.42.

**2-(1,5,9,13-Tetraazacycloheptadecane-7-ylidene)-2H-furo-[3,2-g]chromene-3,7-dione XVI.** Sodium hydride 0.084 g in mass (2.5 mmol)

was treated by 10 mL of absolute hexane in a flow of argon, then was added 8 mL of absolute THF and 0.404 g (2 mmol) of spermine. The mixture was held under stirring for 0.5 h at a room temperature. Then was added 0.4 g (1 mmol) of compound **IV** and heated up to the solvent boiling point. After 7 h (TLC monitoring) the mixture was cooled, several drops of alcohol were added for decomposing sodium hydride, then 20 % HCl solution was added to obtain a neutral medium pH value. The organic layer was separated; the aqueous layer was extracted by ethyl acetate (4 × 5 mL) and methylene chloride (3 × 5 mL), dried over  $MgSO_4$  and evaporated. The product obtained was consecutively chromatographed on alumina, eluents being chloroform and chloroform/ethanol = 50 : 3. Yield 52 %. M. p. 201–203 °C. IR spectrum (KBr,  $\nu$ ,  $cm^{-1}$ ): 741, 829, 909, 1023, 1138, 1193, 1289, 1350, 1393, 1482, 1624, 1727, 2452, 2592, 2676, 2853, 2934, 2975, 3061, 3437. UV spectrum (EtOH),  $\lambda_{max}$ , nm (log  $\epsilon$ ): 202 (4.83), 223 (4.7), 255 (4.96), 299 (4.73), 348 (4.56).  $^1H$  NMR spectrum ( $\delta$ , ppm,  $J$ , Hz): 1.93 (4H, m, H-15',16'), 2.02 (4H, m, H-3',11'), 2.57 m (4H, m, H-14',17'), 2.70 (4H, m, H-2',12'), 2.72 (4H, s, H-6',8'), 3.50 (4H, m, H-4',10'), 6.24 (1H, d,  $J = 9.8$ , H-6), 6.98 (1H, s, H-9), 7.55 (1H, d,  $J = 9.6$ , H-5), 7.94 (s, 1H, H-4), 8.92 (br.s, 4H, NH).  $^{13}C$  NMR spectrum,  $\delta$ , ppm : 27.54 (t, C-15',16'), 28.59 (t, C-3',11'), 45.88 (t, C-4',10'), 49.13 (t, C-2',12'), 49.84 (t, C-14',17'), 51.31 (t, C-6',8'), 99.65 (d, C-9), 112.77 (d, C-6), 113.46 (s, C-5a), 116.38 (s, C-4a), 123.23 (d, C-4), 126.10 (s, C-7'), 144.16 (d, C-5), 144.76 (s, C-2), 157.33 (s, C-9a), 161.79 (s, C-8a), 171.58 (s, C-7), 192.36 (s, C-3). Found, %: C 54.33, H 6.00, N 10.29.  $C_{24}H_{32}N_4O_4 \cdot CHCl_3$ . Calculated, %: C 53.71, H 5.90, N 10.01.

### Biology

All the studies were performed in white outbred mice 20–25 g in mass. The compounds under investigation were dissolved in water with Tween-80 and entered once intragastrically at a dose of 5 mg/kg (0.2 mL per 10 g of body weight). The testing of pharmacological activity was performed in 1 h after introducing the agent. The animals of the reference group obtained equivalent amounts of the solvent.

The studies of the agent influence on the locomotor and emotional activity of animal was performed using a TruScan system (Coulbourn Instruments, Allentown, USA), into whose centre we placed an animal to register the parameters of vertical and horizontal activity during 2 min. Chloral hydrate sleep was caused by introducing chloral hydrate (350 mg/kg, intraperitoneal introduction), and registered the duration of the lateral position of an animal from the loss and reduction of the flipping reflex [17].

## CONCLUSION

Thus, basing on the primary pharmacological activity screening for oreoselone amino derivatives it was demonstrated that some of compounds described could be of interest for the further investigation as compounds exerting an effect on the central nervous system (CNS). So, agents **XIII** and **XIV** are interesting as CNS stimulants, whereas agent **XV** is promising as a compound making a hypnotic action.

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