Research Article

Chemical Modification of Tetrahydroisoquinolines and their Cytotoxic Activity

Ekaterina O. Terenteva[a*], Zaynat S. Khashimova[b], Elena A. Tsay[a], Sherzod N. Zhurakulov[a], Abdusalom Sh. Saidov[c], Valentina I. Vinogradova[a], Shakhnoz S. Azimova[a]

[a]*Institute of the Chemistry of Plant Substances, Uzbek Academy of Sciences, M. Ulugbek str. 77, 100170 Tashkent, Uzbekistan;*

[b]*Institute of the Bioorganic Chemistry, Uzbek Academy of Sciences, M. Ulugbek str. 83, 100125 Tashkent, Uzbekistan;*

[c]*Samarkand State University, Str. University Boulevard, 15, 140104 Samarkand, Uzbekistan.*

Received: 2 May 2017 Revised: 18 May 2017 Accepted: 25 May 2017

Abstract

Objective: The wide variety of potent biological activities of natural and synthetic isoquinoline alkaloids encouraged us to develop novel cytotoxic isoquinoline compounds. A variety of differently functionalized 1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines were synthesized. **Materials and methods:** We employed classic intramolecular Bischler-Napieralski cyclodehydration to generate the isoquinoline core. All the structures were characterized by nuclear magnetic resonance and mass spectrometry. The cytotoxic activities against three human cancer cell lines and primary culture of healthy hepatocyte cells were evaluated for all the synthesized compounds and structure-activity relationships were established by MTT asay. **Results:** It was shown that 8a has demonstrated selective cytotoxicity against breast adenocarcinoma (IC50: 43.3 μM), 4d, 3f against laryngeal adenocarcinoma (IC50: 18.0 and 2.3 μM respectively) with the absence of toxicity to healthy cells. Bis compounds exhibit greater cytotoxic effect than mono-series compounds. Among bis samples 8f showed the greatest cytotoxic properties with an IC50 value of 3.1-4.0 μM. The all conjugate compounds completely lacked cytotoxicity toward cancer cell lines in this study. 10 b,d demonstrated proliferative activity. **Conclusions:** Thus, the most promising compounds for further study in vitro and in vivo methods are dibasic compound 8d, 8e. Later these substances can be offered as a basis for drugs with anti-tumor properties.

Keywords: 1,2,3,4-tetrahydroisoquinoline derivatives, Bischler-Napieralski cyclization, cancer cells, cytotoxicity

Introduction

Isoquinoline alkaloids have a special place among the many nitrogen-containing heterocyclic compounds. This is one of the largest groups of alkaloids. Natural isoquinolines and their numerous derivatives have high activity and they are the subject of attention of medical chemistry (Abe et al, 2005; Galán et al, 2013; Seo et al, 2008). This line of organic chemistry at the present time is one of the leading trends.

The transformation of natural metabolites and the synthesis of the compounds containing natural pharmacophore groups are used as an additional source of natural drugs.

The subject of our research is directed synthesis of individual representatives of isoquinolines various groups and study of their cytotoxic activity. Using of available homoveratrilamine as the parent compound made it possible to synthesize various ranks of isoquinoline derivatives.

**Address for Corresponding Author:*
Ekaterina O. Terenteva
Institute of the Chemistry of Plant Substances, Uzbek Academy of Sciences, M. Ulugbek str. 77, 100170 Tashkent, Uzbekistan
E-mail: genlab_icps@yahoo.com (E.O. Terenteva)

Materials and methods

IR spectra were recorded from KBr pellets on a System 2000 FTIR instrument (Perkin-Elmer); mass spectra, on a Kratos M90; NMR spectra, on Varian Unity-400+ spectrometer ($CDCl_3$ or MeOH-d_4 Py, DMSO-d_6 solvents, HMDS internal standard). Melting points of all synthesized compounds were measured on a Boetius microstage.

General Method for Preparing Substituted Tetrahydroisoquinolines

A solution of 3,4-dimethoxyphenylethylamine (**1**, 5.05 g, 0.028 mol) in C_6H_6 (30 mL) was treated with substituted aldehydes (**2a-f**, 0.028 mol) and refluxed with a Dean–Stark trap until water separation was complete (1–2 h). The solvent was distilled off. The resulting imine was treated

with CF_3CO_2H (10 mL), heated on a water bath for ~2 h, cooled, and made basic with NH_4OH to pH 9–10. The amine was extracted exhaustively with $CHCl_3$. The crude product was purified by preparing the hydrochloride or by column chromatography over silica gel using $CHCl_3$: MeOH (100:1, 100:10). The resulting product was crystallized from Me_2CO.

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline (3a), $C_{11}H_{15}O_2N$.

Prepared from **1** (5.05 g, 0.028 mol) and formalin (**2a**, 3 mL, 0.01 mol). Yield 4.84 g (90%), mp of hydrochloride 263–266°C (Me_2CO).

^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm): 1.99(1H, br. s, NH), 2.65(2H, t, J = 5.9, H-4), 3.05(2H, t, J = 5.9, H-3), 3.77(3H, s, 7-OCH_3), 3.78(3H, s, 6-OCH_3), 3.88(2H, s, H-1), 6.45(1H, s, H-8), 6.51(1H, s, H-5).

1-Phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (3b), $C_{17}H_{19}O_2N$.

Prepared from **1** (1.81 g, 0.01 mol) and benzaldehyde (**2b**, 1.06 g, 0.01 mol). Yield 2.17 g (81%), mp 118–121°C (Me_2CO), mp 102–103°C (Me_2CO).

^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 2.68 (1H, m, H-4), 2.85 (2H, m, H-3, 4), 3.25 (1H, m, H-3), 3.42* (3H, s, 7-OCH_3), 3.67* (3H, s, 6-OCH_3), 4.85 (1H, s, H-1), 6.14 (1H, s, H-8), 6.67 (1H, s, H-5), 7.20 (5H, m, Ar-H).

1-(3′,4′-Dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (3c), $C_{19}H_{23}O_4N$.

Prepared from **1** (1.81 g, 0.01 mol) and veratrylaldehyde (**2c**, 1.66 g, 0.01 mol). Yield 2.38 g (72%), mp 72–74°C (Me_2CO).

^{1}H NMR spectrum (DMSO-d_6, δ, ppm): 2.65 and 2.80 (3H, 2m, 2H-4, H-3), 3.24 (1H, m, H-4), 3.44* (3H, s, 7-OCH_3), 3.62* (3H, s, 3′-OCH_3), 3.66* (6H, s, 6, 4′-OCH_3), 4.78 (1H, s, H-1), 6.18 (1H, s, H-8), 6.77 (1H, s, H-5), 6.62, 6.68, 6.82 (each 1H, br.d, H-2′, 5′, 6′).

1-(3′,4′-Methylenedioxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (3d). $C_{18}H_{19}O_4N$.

Prepared from **1** (1.66 g, 0.009 mol) and 3,4-methylenedioxybenzaldehyde (**2d**, 1.37 g, 0.009 mol). Yield 2.06 g (72%), mp of hydrochloride 254-257 °C (Me_2CO).

^{1}H NMR spectrum (DMSO-d_6, δ, ppm): 2.5–3.0 (4H, m, H-3, 4), 3.45* (3H, s, 7-OCH_3), 3.66* (3H, s, 6-OCH_3), 4.86 (1H, s, H-1), 5.92* (2H, s, 3′-OCH_2O-4′), 6.17 (1H, s, H-8), 6.62–6.87 (4H, m, H-5, Ar-H).

1-(6′-Bromo-3′,4′-methylenedioxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (3e). $C_{18}H_{18}O_4NBr$.

Prepared from **1** (2.54 g, 0.014 mol) and 6-bromo-3,4-methylenedioxybenzaldehyde (**2e**, 3.21 g, 0.014 mol). Yield 4.95 g (90%), mp 201–203°C (Me_2CO).

Mass spectrum (70 eV) *m/z* (I_{rel},%): 393/391 (M^+, 100, Br-79/81), 379/377 (24, Br-79/81), 363/361 (14, Br-79/81), 193 (22), 192 (65).

^{1}H NMR (DMSO-d_6, δ, ppm): 2.98 and 3.05 (2H, m, H-4), 3.31 and 3.43 (2H, m, H-3), 3.53* (3H, s, 7-OCH_3), 3.73* (3H, s, 6-OCH_3), 5.78 (1H, s, H-1), 6.07* (2H, s, 3′-OCH_2O-4′), 6.15 (1H, s, H-8), 6.65 (1H, s, H-5), 6.82 (1H, s, H-2′), 7.30 (1H, s, H-5′).

1-(6′-Chloro-3′,4′-methylenedioxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (3f). $C_{18}H_{18}O_4NCl$.

Prepared from **1** (2.2 g, 0.012 mol) and 6-chloro-3,4-methylenedioxybenzaldehyde (**2f**, 2.24 g, 0.012 mol). Yield 1.79 g (42%), mp 107–108°C (Me_2CO).

^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.8–2.85 (2H, ddd, J = 16.4, 6.2, 5.5, H-4), 3.03–3.11 (2H, dt, J = 12.1, 6.2, 6.2, H-3), 3.71* (3H, s, 7-OCH_3), 3.88* (3H, s, 6-OCH_3), 5.48 (1H, s, H-1), 5.92* (1H, d, J = 0.4, 3′-OCH_2O-4′), 5.93* (1H, d, J = 0.4, 3′-OCH_2O-4′), 6.27 (1H, s, H-8), 6.44 (1H, s, H-5), 6.63 (1H, s, H-2′), 6.88 (1H, s, H-5′).

General Method for Preparing Alkaloids 4c, 4d.

A solution of 1-(3′,4′-dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (1.0 g, 0.003 mol) in MeOH (20 mL) was treated with formalin (0.08 mL, 0.003 mol, 27%), refluxed for 1.5 h (TLC monitoring), cooled in ice, and reduced by $NaBH_4$ (1 g). The solvent was distilled off. The solid was dissolved in H_2O (10 mL) and extracted exhaustively with $CHCl_3$. The crude product was purified by producing the hydrochloride or by chromatography over SiO_2 using $CHCl_3$: MeOH (100:1 100:10). The product was crystallized from Me_2CO or MeOH.

1-(3′, 4′-Dimethoxyphenyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (4c, cryptostylin II**).** $C_{20}H_{22}O_4N$.

Prepared from 1-(3′,4′-dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**3c**, 1.0 g, 0.003 mol) and formalin (0.08 mL, 0.003 mol, 27%). Yield 0.84 g (81%), mp of hydrochloride 206–209°C (Me_2CO).

NMR spectral data corresponded to those for cryptostylin II.

1-(3′, 4′-Methylenedioxyphenyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (4d, cryptostylin I**).** $C_{19}H_{21}O_4N$.

Prepared from 1-(3′,4′-methylenedioxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**3d**, 0.7 g, 0.002 mol) and formalin (0.06 mL, 0.002 mol, 27%). Yield 0.47 g

(64%), mp 115–117°C (MeOH).

NMR spectral data corresponded to those for cryptostylin I (Zhurakulov et al, 2013).

General Method for Preparation of Hydroxyethyl Derivatives of 1-(Aryl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 5 c-f.

A solution of 1-aryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**3 c-f**, 0.0015 mol) in EtOH (30 mL) was treated with ethylenechlorohydrin (0.0045 mol) and K_2CO_3 (0.0045 mol) and refluxed for 4–6 h (TLC monitoring). The mixture was worked up analogously as described above.

1-(3′,4′-Dimethoxyphenyl)-2β-hydroxyethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (5c). $C_{21}H_{27}NO_5$.

Prepared as the hydrochloride from **3c** (0.5 g, 0.0015 mol) and ethylenechlorohydrin (0.3 mL 0.0045 mol). Yield 0.35 g (62%), mp of hydrochloride 201–203°C (Me_2CO).

Prepared as the hydrochloride from **3c** (1.98 g, 0.006 mol), ethylenechlorohydrin (1.1 mL, 0.016 mol), and KOH (0.68 g, 0.012 mol). Yield 2.04 g (91%).

IR spectrum (KBr, $\nu_{max,}cm^{-1}$): 3265 (OH), 2944, 2585, 1609 (C=C), 1523 (Ar–H), 1466 (CH_2), 1264, 1241 (C–O) 1162 (C–N).

^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.63 (1H, m, H-9), 2.71 (3H, m, H-4, 9), 3.11 and 3.34 (each 1H, m, H-3), 3.57 (1H, s, 7-OCH_3), 3.55 and 3.70 (each 1H, m, H-10), 3.77* (3H, s, 3′-OCH_3), 3.80* (3H, s, 6-OCH_3), 3.81* (3H, s, 4′-OCH_3), 4.69 (1H, s, H-1), 6.17 (1I, s, H-8), 6.57 (1H, s, H-5), 6.72 (1H, dd, J = 2, 8, H-6′), 6.75 (1H, d, J = 8, H-5′), 6.84 (1H, br. signal, H-2′).

1-(3′,4′-Methylenedioxyphenyl)-2-hydroxyethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (5d). $C_{20}H_{23}NO_5$.

Prepared as the hydrochloride from **3d** (1.5 g, 0.005 mol), ethylenechlorohydrin (0.9 mL, 0.013 mol), and K_2CO_3 (0.8 g, 0.006 mol). Yield 1.34 g (78%), mp of hydrochloride 149–152°C (Me_2CO).

^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.56 (1H, dt, J = 4.4, 4.4, 12.9, H_e-9), 2.67 (1H, ddd, J = 4.6, 9.0, 12.0, H_a-3), 2.77 (1H, ddd, J = 5.4, 9.0, 16.0, H_e-4), 2.90 (1H, ddd, J = 4.4, 8.3, 12.9, H_a-9), 2.96 (1H, dt, J = 5.3, 5.3, 16.0, H_a-4), 3.19 (1H, dt, J = 5.5, 5.5, 12.0, H_e-3), 3.48 (1H, ddd, J = 4.4, 9.4, 11.1, H_e-10), 3.58 (3H, s, 7-OCH_3), 3.64 (1H, ddd, J = 4.4, 8.3, 11.1, H_a-10), 3.78 (3H, s, 6-OCH_3), 4.57 (1H, s, H-1), 5.85, 5.86 (each 1H, d, J = 1.5, 3′-OCH_2O-4′), 6.17 (1H, s, H-8), 6.55 (1H, s, H-5), 6.63 (1H, s, H-6′), 6.67 (1H, s, H-5′), 6.67 (1H, s, H-2′).

1-(6′-Bromo-3′,4′-methylenedioxyphenyl)-2β-hydroxyethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (5e). $C_{20}H_{22}BrNO_5$.

Prepared from **3e** (1.5 g, 0.004 mol), ethylenechlorohydrin (0.78 mL, 0.012 mol), and K_2CO_3 (0.8 g, 0.006 mol). Yield 1.17 g (77%), mp 143–144°C (MeOH).

IR spectrum (KBr, $\nu_{max,}cm^{-1}$): 3425 (OH), 1610 (C=C), 1515 (Ar–H), 1476 (CH_2), 1251, 1225 (C–O), 1131 (C–N), 1040 (C–Br), 939, 928 (O–CH_2–O), 859, 804.

^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.47 (1H, dt, J = 3.5, 3.5, 12.7, H_e-9), 2.58 (1H, ddd, J = 4.0, 9.5, 12.0, H_a-3), 2.69 (1H, dt, J = 4.6, 4.2, 16.0, H_e-4), 2.76 (1H, ddd, J = 4.8, 9.8, 12.8, H_a-9), 2.92 (1H, ddd, J = 4.6, 9.5, 15.5, H_a-4), 3.16 (1H, dt, J = 4.5, 4.5, 11.8, H_e-3), 3.39 (1H, ddd, J = 3.6, 4.8, 11.0, H_e-10), 3.61 (3H, s, 7-OCH_3), 3.64 (1H, ddd, J = 3.5, 9.8, 11.0, H_a-10), 3.79 (3H, s, 6-OCH_3), 4.99 (1H, s, H-1), 5.86 (2H, s, 3′-OCH_2O-4′), 6.16 (1H, s, H-8), 6.50 (1H, s, H-2′), 6.54 (1H, s, H-5), 6.95 (1H, s, H-5′).

1-(6′-Chloro-3′,4′-methylenedioxyphenyl)-2β-hydroxyethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (5f). $C_{20}H_{22}ClNO_5$.

Prepared from **3f** (1.5 g, 0.004 mol), ethylenechlorohydrin (0.9 mL, 0.013 mol), and K_2CO_3 (0.8 g, 0.006 mol). Yield 1.46 g (87%), mp 157–159°C (MeOH).

IR spectrum (KBr, $\nu_{max,}cm^{-1}$): 3503 (OH), 1613 (C=C), 1505 (Ar–H), 1474 (CH_2), 1248, 1225 (C–O), 1128 (C–N), 1033 (C–Cl), 929 (O–CH_2–O), 877, 859.

IR spectrum in vaseline oil ($\nu_{max,}cm^{-1}$): 3501 (OH free), 3159 (intramolecular H-bond), 1611 (C=C), 1499 (Ar–H), 1306, 1222 (C–O), 1127 (C–N), 1032 (C–Cl), 928 (O–CH_2–O).

^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.49 (1H, dt, J = 3.7, 13.0, H_e-9), 2.58 (1H, ddd, J = 4.1, 9.3, 12,1, H_a-3), 2.70 (1H, dt, J = 4.1, 5.1, 15.7, H_e-4), 2.73 (1H, ddd, J = 4.9, 9.6, 13.0, H_a-9), 2.89 (1H, ddd, J = 5.1, 9.3, 15.7, H_a-4), 3.15 (1H, dt, J = 5.1, 5.1, 12.1, H_e-3), 3.41 (1H, ddd, J = 3.7, 4.9, 11.1, H_e-10), 3.61 (3H, s, 7-OCH_3), 3.63 (1H, ddd, J = 3.7, 9.6, 11.1, H_a-10), 3.79 (3H, s, 6-OCH_3), 5.02 (1H, s, H-1), 5.86 (2H, s, 3′-OCH_2O-4′), 6.14 (1H, s, H-8), 6.47 (1H, s, H-2′), 6.54 (1H, s, H-5), 6.78 (1H, s, H-5′).

***N*-(3, 4-Dimethoxy-β-phenethyl)heptanamide (7a).** $C_{17}H_{27}NO_3$.

A mixture of homoveratrylamine (**1**, 1.84 g, 0.01 mol) and heptanoic acid (**6a**, acid 7:0, 1.32 g, 0.01 mol). in MeOH (5 mL) underwent spontaneous heating. The mixture was heated on an oil bath for 2 h at 178°C, treated with $CHCl_3$ (100 mL), and washed with HCl solution (3%), NaOH solution (2%), and H_2O until neutral. The $CHCl_3$ was evaporated. The residue was crystallized from Me_2CO or hexane. The resulting crystals were filtered off. Yield 84% (2.47 g), mp 55–57°C (hexane).

IR spectrum (KBr, $\nu_{max,}$ cm^{-1}): 3310 (NH), 2933 (Ar-CH), 1645 (N-C=O).

^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.81 (3H, t, J = 7.3, CH_3), 1.21 (6H, br. s, $3CH_2$), 1.52 (2H, m, H-2′), 2.05 (2H, t, J = 7.3, H-1′), 2.70 (2H, t, J = 7, H*α*), 3.43 (2H, q, J = 7, H*β*), 3.795 (3H, s, OCH_3), 3.801 (3H, s, OCH_3), 5.45 (1H, m, NH), 6.65 (1H, H-2), 6.67 (1H, H-6), 6.74 (1H, H-5).

1-Hexyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (8a). $C_{17}H_{27}NO_2$.

A mixture amide **7a** (1 g, 3.4 mmol) anhydrous benzene (30 mL), and $POCl_3$ (0.7 mL) was refluxed for 1 h. The course of the reaction was monitored by TLC. The benzene and $POCl_3$ were distilled off. The residue was dissolved in MeOH (30 mL) and treated in portions at 0–5°C with $NaBH_4$ (0.02 mol). The MeOH was distilled off. The residue was dissolved in H_2O and extracted with $CHCl_3$. The $CHCl_3$ was removed. Isoquinoline **8a** were crystallized from Me_2CO. Yield 74% (0.7 g), mp of hydrochloride 188–191°C (Me_2CO).

IR spectrum (KBr, $\nu_{max,}$ cm^{-1}): 3450, 2930, 1611, 1519, 1450, 1264.

^{1}H NMR spectrum (400 MHz, CD_3OD, δ, ppm, J/Hz): 0.86 (3H, m, J = 6, CH_3), 1.30 (6H, d, J = 6, $3CH_2$), 1.38 and 1.44 (each 1H, m, CH_2), 1.84 and 2.05 (each 1H, m, H-1′), 2.96 (2H, m, H-4), 3.47 (2H, q, J = 6, H-3), 3.76 (6H, s, $2OCH_3$), 4,40 (1H, m, H-1), 6.74 (2H, s, H-5, 8).

General Method for Preparing Diamides 7b–h.

A mixture of homoveratrylamine (**1**, 0.02 mol) and dibasic acid (0.01 mol) was dissolved in MeOH (10 mL). The mixture underwent self-heating. The MeOH was distilled off. The resulting salt was heated on an oil bath for 1–2 h at 175–178°C, dissolved in $CHCl_3$ (100 mL), and washed with HCl solution (3%), NaOH solution (2%), and H_2O until neutral. The $CHCl_3$ was distilled off. The solid was crystallized from Me_2CO. The resulting crystals were filtered off.

***N*,*N*-(3,4-Dimethoxy-β-phenethyl)-adipoyl diamide (7b)**, $C_{26}H_{36}N_2O_6$, was prepared from **1** (4.6 g, 0.03 mol) and adipic acid (1.95 g, 0.013 mol). Yield 77% (4.64 g), mp 173–175°C (Me_2CO).

IR spectrum (KBr, $\nu_{max,}$ cm^{-1}): 3313 (NH), 1634 (CO). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.54 (4H, m, H-3, 4), 2.07 (4H, m, H-2, 5), 2.69 (4H, t, J = 6.95, H-*α*), 3.42 (4H, q, J = 7.14, H-*β*), 3.791 (6H, s, OCH_3), 3.797 (6H, s, OCH_3), 5.66 (2H, t, J = 5.6, NH), 6.65 (2H, d, J = 1.9, H-2), 6.66 (2H, dd, J = 8.7, 1.9, H-6), 6.74 (2H, d, J = 8.7, H-5).

***N*,*N*-(3,4-Dimethoxy-β-phenylethyl)-pimeloyl diamide (7c)**, $C_{27}H_{38}N_2O_6$, was prepared from **1** (1.87 g, 0.01 mol) and pimelic acid (0.9 g, 0.005 mol). Yield 62.4% (1.56 g), mp 138–141°C (Me_2CO).

IR spectrum (KBr, $\nu_{max,}$ cm^{-1}): 3307 (NH), 1643 (CO). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.20 (2H, m, H-4), 1.52 (4H, m, H-3′, 5′), 2.04 (4H, t, J = 7.5, H-2′, 6′), 2.70 (4H, t, J = 7.0, H-*α*), 3.43 (4H, q, J = 7.0, H-*β*), 3.793 (6H, s, OCH_3), 3.796 (6H, s, OCH_3), 5.51 (2H, br.t, J = 5.6, NH), 6.65 (2H, d, J = 2, H-2), 6.66 (2H, dd, J = 2, 8.8, H-6), 6.74 (2H, d, J = 8.8, H-5).

***N*,*N*-(3,4-Dimethoxy-β-phenethyl)-azelaoyl diamide (7d)**, $C_{29}H_{42}N_2O_6$, was prepared from **1** (1.58 g, 0.009 mol) and azelaic acid (0.9 g, 0.005 mol). Yield 66% (1.48 g), mp 141–145°C (Me_2CO).

IR spectrum (KBr, $\nu_{max,}$ cm^{-1}): 3306 (NH), 1642 (CO). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.20 (6H, s, H-4′, 5′, 6′), 1.51 (4H, t, J = 6.7, H-3′, 7′), 2.04 (4H, t, J = 7.5, H-2′, 8′), 2.69 (4H, t, J = 6.96, H-*α*), 3.43 (4H, q, J = 6.4, H-*β*), 3.79 (12H, s, OCH_3), 5.52 (2H, t, NH), 6.65 (2H, s, H-2), 6.64 (2H, d, J = 2, 8.5, H-6), 6.74 (2H, d, J = 8.5, H-5).

***N*,*N*-(3,4-Dimethoxy-β-phenethyl)-sebacoyl diamide (7e)**, $C_{30}H_{44}N_2O_6$, was prepared from **1** (1.59 g, 0.009 mol) and sebacic acid (0.98 g, 0.004 mol). Yield 65% (1.5 g), mp 152–156°C (Me_2CO). IR spectrum (KBr, $\nu_{max,}$ cm^{-1}): 3310 (NH), 1639 (CO). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.182 (8H, s, H-4′, 5′, 6′, 7′), 1.503 (4H, t, J = 6.9, H-3′, 8′), 2.04 (4H, t, J = 7.4, H-2′, 9′), 2.68 (4H, t, J = 6.9, H-*α*), 3.41 (4H, q, J = 6.8, H-*β*), 3.78 (12H, s, OCH_3), 5.59 (2H, t, J = 5.5, NH), 6.64 (2H, s, H-2), 6.65 (2H, d, J = 8.5, H-6), 6.73 (2H, d, J = 8.5, H-5).

***N*,*N′*-*bis*(3,4-Dimethoxy-β-phenethyl)-brassyloyl diamide (7f),** $C_{33}H_{50}N_2O_6$, was prepared from **1 (**0.8 g, 4.4 mmol) and brassylic acid (0.58 g, 2.4 mmol). Yield 91% (1.15 g), mp 160-162°C (Me_2CO). IR spectrum (film, *ν*, $см^{-1}$): 3304 (NH), 2919, 2850 (Ar-C), 1639 (N –C=O), 1547, 1519, 1470 (C=C). Спектр ЯМР ^{1}H (400 PMR spectrum (400 MHz, CD_3OD, δ, ppm, J/Hz): 0.63 (2H, m, H-7′); 1.22 (10H, br. s, H-4′,5′,6′,8′,9′,10′); 1.50 (4H, t, J=7, H-3′,11′); 2.07 (4H, t, J=7.6, H-2′,12′); 2.67 (4H, t, J=7, H-α); 3.32 (4H, kv, J=7, H-β); 3.73 (6H, s, OCH_3); 3.76 (6H, s, OCH_3); 6.68 (2H, dd, J=2, 8, H-6); 6.76 (2H, d, J=2, H-2); 6.79 (2H, d, J=8, H-5).

***N*^{1},*N*^{13}-*bis*(3,4-Methylenedioxy-β-phenethyl)-brassyloyl diamide (7g),** $C_{31}H_{42}N_2O_6$. was prepared from **1 (**0.9 g, 5.4 mmol) and brassylic acid (0.6 g 2.4 mmol). Yield 69% (0.9g), mp. 172-174° C (Me_2CO). IR spectrum (film, *ν*, $см^{-1}$): 3430, 3305 (NH), 2922, 2849 (Ar-C), 1637 (N -C=O), 1543, 1503, 1491 (C=C). ^{1}H NMR spectrum (400 MHz, CD_3OD, δ, ppm, J/Hz): 1.18 (14H, br. s, H-4″,5″,6″,7″,8″,9″,10″); 1.51 (4H, t, J=7.4, H-3″,11″); 2.04 (4H, t, J=7.8, H-2″,12″); 2.65 (4H, t, J=6.8, H-α); 3.39 (4H, kv,

J=6.7, H-β); 5.37 (2H, br. s, NH); 5.86 (4H, s, OCH_2O); 6.55 (2H, dd, J=1.5, 7.8, H-6, 6′); 6.61 (2H, d, J=1.5, H-2, 2′); 6.67 (2H, d, J=7.8, H-5,5′).

***N,N-bis*(3,4-Dimethoxy-β-phenethyl)isophtalamide (7h),** $C_{28}H_{32}N_2O_6$. ***Method A*.** A mixture of homoveratrylamine (**1**, 3.06 g, 0.017 mol) and isophthalic acid (1.5 g, 0.009 mol) dissolved in MeOH (5 mL) was heated on an oil bath at 170–180°C for 2–5 h, dissolved in $CHCl_3$ (100 mL), and washed with HCl solution (3%), NaOH solution (2%), and H_2O until neutral. The $CHCl_3$ was distilled off. Yield 29% (1.2 g), mp 132–134°C (Me_2CO).

***Method B*.** A mixture of homoveratrylamine (2.1 g, 0.011 mol) $CHCl_3$ (30 mL), and NaOH solution (30 mL, 10%) was treated dropwise over 1 h with a solution of and isophthalic acid chloride (1.2 g, 0.006 mol). in C_6H_6 (10 mL) at 5°C. The resulting precipitate (**7h**) was separated and crystallized from Me_2CO The resulting crystals were filtered off. Yield 82% (2.33 g).

IR spectrum (KBr, $\nu_{max,}$ cm^{-1}): 3316 (NH), 2938 (Ar-C), 1671, 1634 (N-C=O), 1542, 1516 (Ar-H). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.82 (4H, t, J = 7, Hα, α′), 3.64 (4H, q, J = 7, Hβ, β′), 3.78 (6H, s, 3, 3′-OCH_3), 3.80 (6H, s, 4, 4′-OCH_3,), 6.18 (2H, m, NH), 6.68 (2H, d, J = 2, H-2, 2′), 6.69 (2H, dd, J = 2, 8, H-6, 6′), 6.76 (2H, d, J = 8, H-5, 5′), 7.40 (1H, t, J = 7.7, H-5′′), 7.75 (2H, dd, J = 2, 8, H-6′′, 4′′), 8.01 (1H, t, J = 2, H-2′′).

General Method for Preparing *bis*-Tetrahydroisoquinolines 8b–g. A mixture of dibasic acid amide (0.006 mol), anhydrous benzene (30 mL), and $POCl_3$ (0.05 mol) was refluxed for 2 h. The course of the reaction was monitored by TLC. Benzene and $POCl_3$ were distilled off. The residue was dissolved in MeOH (30 mL). The resulting solution was cooled to 0–5°C and treated in portions with $NaBH_4$ (0.02 mol). The MeOH was distilled off. The residue was dissolved in H_2O and extracted with $CHCl_3$. The $CHCl_3$ was removed. The solid was crystallized from Me_2CO.

1,4-*bis*(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)butane (8b), $C_{26}H_{36}N_2O_4$, was prepared from **7b** (3 g, 0.006 mol) and $POCl_3$ (7 mL). Yield 76% (2.09 g), mp 112–116°C (Me_2CO). IR spectrum (KBr, $\nu_{max,}$ cm^{-1}): 3340 (NH), 1610, 1519, 1464. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.38–1.52 (4H, m, H-3′, 4′), 1.65–1.78 (4H, m, H-2′, 5′), 2.60 (2H, m, H-4), 2.66 (2H, m, H-4), 2.89 (2H, m, H-3), 3.15 (2H, m, H-3), 3.776 (6H, s, OCH_3), 3.780 (6H, s, OCH_3), 3.82 (2H, m, H-1), 6.50* (2H, s, H-8), 6.54* (2H, s, H-5).

1,5-*bis*(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)pentane (8c), $C_{27}H_{38}N_2O_4$, was prepared from **7c** (0.5 g, 0.001 mol) and $POCl_3$ (1.5 mL). Yield 80% (0.39 g), mp of dihydrochloride 220–224°C (Me_2CO). IR spectrum (KBr, $\nu_{max,}$ cm^{-1}): 3423 (NH), 1613, 1519, 1460. PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.35–1.50 (6H, 2m, H-3′, 4′, 5′), 1.65–1.75 (4H, m, H-2′, 5′), 2.60 (2H, m, H-4), 2.68 (2H, m, H-4), 2.90 (2H, m, H-3), 3.16 (2H, m, H-3), 3.770 (6H, s, OCH_3), 3.774 (6H, s, OCH_3), 3.86 (2H, m, H-1), 6.49* (2H, s, H-8), 6.53* (2H, s, H-5).

1,7-*bis*-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)heptane (8d), $C_{29}H_{42}N_2O_4$, was prepared from **7d** (0.5 g, 0.001 mol) and $POCl_3$ (1.5 mL). Yield 67.4% (0.31 g), mp of dihydrochloride 163–166°C (Me_2CO). IR spectrum (KBr, $\nu_{max,}$ cm^{-1}): 3429 (NH), 1613, 1519, 1464. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.3–1.5 (10H, 2m, H-3′, 4′, 5′, 6′, 7′), 1.65–1.85 (4H, m, H-2′, 8′), 2.65 (2H, m, H-4), 2.80 (2H, m, H-4), 2.95 (2H, m, H-3), 3.25 (2H, m, H-3), 3.78 (6H, s, OCH_3), 3.77 (6H, s, OCH_3), 3.98 (2H, m, H-1), 4.67 (2H, s, NH), 6.50* (2H, s, H-8), 6.53* (2H, s, H-5).

1,8-*bis*(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)octane (8e), $C_{30}H_{44}N_2O_4$, was prepared from **7e** (0.5 g, 0.001 mol) and $POCl_3$ (1.5 mL). Yield 70% (0.33 g), mp of dihydrochloride 240–244°C (Me_2CO). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.10–1.24 (12H, m, H-3′, 4′, 5′, 6′, 7′, 8′), 1.6–1.8 (4H, m, H-2′, 9′), 2.55–2.75 (4H, m, H-4), 2.90 (2H, m, H-3), 3.15 (2H, m, H-3), 3.776 (6H, s, OCH_3), 3.783 (6H, s, OCH_3), 3.8–3.9 (2H, m, H-1), 6.50* (2H, s, H-8), 6.54* (2H, s, H-5).

1,11-*bis*(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)undecan (8f) $C_{30}H_{44}N_2O_4$ was prepared from **7f** (0.5 g, 0.88 mmol) and $POCl_3$ (1.5 mL). Yield 87 % (0.41 g), R_f 0.44, mp 208-211°C (Me_2CO). IR spectrum (KBr, $\nu_{max,}$ cm^{-1}): 3456, 2929, 2854, 2786, 1613, 1519, 1463. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.25-1.37 (14H, m, H-4′,5′,6′,7′,8′,9′,10′); 1.46 (4H, m, H-3′,11′); 1.88 (4H, m, H-2′,12′); 2.86-3.05 (4H, m, H-4); 3.25, 3.48 (each 2H, m, H-3); 3.79 (12H, s, OCH_3); 4.33 (2H, t, J=6, H-1); 6.57*(2H, s, H-8); 6.59*(2H, s, H-5).

1,11-*bis*-(6,7-Methylenedioxy-1,2,3,4-tetrahydroisoquinolin-1-yl)undecan (8g), $C_{31}H_{42}N_2O_4$. was prepared from **7g** (0.6 g, 1.1 mmol) and $POCl_3$ (1.5 mL). Yield 97 % (0.548), mp 115-117°C (Me_2CO), IR spectrum (KBr, $\nu_{max,}$ cm^{-1}): 3431, 3314, 2923, 2851, 1507, 1481. PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.20 (18H, br. s, H-3″,4″,5″,6″,7″,8″,9″,10″,11″); 1.60-1.69 (4H, m, H-2″, 12″); 2.61 (4H, ttt, J=2.3, 5.2, 6.7, 8.6, H-4); 2.86 (2H, dt, J=5.6, 6.4, H-3); 3.12(2H, dt, J=5.4, 6.4, H-3′); 3.78 (2H, dt, J=1.9, 8.9, H-1,1′); 5.81 (2H, s, OCH_2O); 6.47*(2H, s, H-8,8′); 6.54*(2H, s, H-5,5′).

1,3-*bis*-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)benzene (8h), $C_{28}H_{32}N_2O_4$. A mixture of diamide **7h** (1.2 g, 2.4 mmol), anhydrous **7i** C_6H_6 (30 mL), and $POCl_3$ (7.4 mL) was refluxed for 3 h. The course of the reaction was monitoredby TLC. The C_6H_6 and $POCl_3$ were distilled

off. The residue was dissolved in MeOH (60 mL), cooled to 0–5°C, and treated in portions with $NaBH_4$ (0.05 mol). The MeOH was distilled off. The residue was dissolved in H_2O and extracted with$CHCl_3$. The $CHCl_3$ was removed. The residue was crystallized from Me_2CO. Yield 71% (0.8 g), mp of hydrochloride 230–233°C (Me_2CO). IR spectrum (KBr, ν, cm^{-1}): 3376 (NH), 2952 (Ar-C), 1613 (Ar-H), 1519 (Ar-H), 1460 (Ar-H). ^{1}H NMR spectrum (400 MHz, CD_3OD, 50°C, δ, ppm, J/Hz): 3.05 (2H, m, H-4). 3.19* (2H, m, H-4′), 3.37 (4H, m, H-3), 3.58* (3H, s, 6-OCH_3), 3.59* (3H, s, 6′-OCH_3), 3.79** (6H, s, 7-OCH_3), 3.81** (6H, s, 7′-OCH_3), 5.68 (2H, s, H-1), 6.32 (2H, s, H-8), 6.81 (2H, s, H-5), 7.36–7.38 (2H, d, J = 7.4, H-4″, 6″), 7.45 (1H, s, H-2″), 7.51 (1H, t, J = 7.4, H-5″).

Reaction of amines with DHQ (9). General Method. A solution of amine (0.667 mmol) in *i*-PrOH (5 mL) was stirred, treated drop wise over 10 min with a solution of DHQ (0.2 g, 0.667 mmol) in *i*-PrOH (5 mL), held at 20–25°C for 0.5 h, and treated drop wise with formalin solution (30%, 0.06 mL, 0.667 mmol, d = 1.092). A precipitate began to form immediately. The mixture was left for 12 h. The course of the reaction was monitored by TLC. The precipitate was filtered off and rinsed with *i*-PrOH, hexane–Et_2O (1:1), $CHCl_3$–Et_2O (1:1), and $CHCl_3$. The precipitates polymerized in benzene and dioxane. Equimolar amounts of DHQ (0.2 g, 0.667 mmol) and formalin solution (30%, 0.06 mL, 0.667 mmol) were used in the reactions described below.

2-[(3,4-dimetoxyphenethylino)-methyl]-2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychroman-4-one (10a).

3,4-dimetoxyphenylethylamine (**1a**, 0.16 g, 0.88 mmol) afforded DHQ **9,** (0.27 g, 0.88 mmol). Yield 0.33 g (75%), mp >360°C (*i*-PrOH). IR spectrum (KBr, ν, $см^{-1}$): 3431 (OH), 1645, 1636 (C=O), 1517, 1456 (C=C), 1265 (C-O).

2-[(3,4-Methylenedioxyphenethylino)-methyl]-2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychroman-4-one (10b).

3,4-methylenedioxyphenylethylamine (**1b**, 0.15 g, 0.9 mmol) afforded DHQ **9,** (0.27 g, 0.9 mmol). Yield 0.30 g (68%), mp 360°C (*i*-PrOH). IR spectrum (KBr, ν_{max}, $см^{-1}$): 3409 (OH), 1645 (C=O), 1503, 1489, 1446 (C=C), 1364, 1283, 1249 (C-O).

^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): a) DHQ fragment: 3.89 (2H, s, N-CH_2), 4.27 (1H, d, J=11.5, H-3), 4.92 (1H, d, J=11.1, H-2), 5.38 (1H, s, H-8), 6.82 (3H, s, H-5′, 6′, H-2′), b) 3,4-methylenedioxyphenylethylamine fragment: 2.69 (1H, m, H_a-7′′), 2.80 (1H, m, H_a-8′′), 2.90 (1H, m, H_e-7′′), 2.96 (1H, m, H_e-8′′), 5.96 (2H, s, 3′′-OCH_2O-4′′), 6.69 (3H, s, Ar-H); ^{13}C NMR spectrum; (δ, ppm): a) DHQ fragment: 47.65 (CH_2–N), 71.29 (C-3), 82.59 (C-2), 95.79 (C-8), 99.97 (C-6), 100.89 (C-8a), 115.15 (C-2'), 115.29 (C-5'), 119.29 (C-6'), 128.91 (C-1'), 145.03 (C-3'), 145.65 (C-4'), 161.64 (C-4a), 161.81 (C-5), 178.05 (C-7), 193.02 (C-4); b) 3,4-methylenedioxyphenylethylamine fragment: 25.57 (C-7′′), 32.10 (C-8′′) 108.42 (10-OCH_2O), 109.15 (C-2′′), 121.79 (C-5′′), 131.57 (C-6′′), 145.69 (C-1′′), 147.42 (C-3′′), 147.45 (C-4′′).

2-(Dihydroxyphenyl)-3,5,7-trihydroxy-6-[(1-hydroxy-1phenylpropan-2-il-aminomethyl)methyl]-chroman-4-one (10c).

Psevdoephydryne (**1c**, 0.11 g, 0.66 mmol) afforded DHQ **9,** (0.20 g, 0.66 mmol). Yield 0.16 g (52%), mp 133-137°C (*i*-PrOH).

IR spectrum (KBr, ν_{max}, $см^{-1}$): 3430 (OH), 1643 (C=O), 1456 (C=C), 1365, 1282 (C-O). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): a) DHQ fragment: 3.60 (2H, s, N-CH_2), 4.48 (1H, d, J=11.0, H-3), 4.96 (1H, d, J=10.7, H-2), 5.76 (1H, br. s, 7-OH or 7′′-OH), 5.85 (1H, br. s, H-8), 6.17 (1H, s, H-2′), 6.68 (1H, s, H-5′), 7.22 (1H, s, 6′), 8.97, 9.03 (each 1H, br. s, 3′, 4′-OH), 12.34 (1H, br. s, 5-OH); b) Psevdoephydryne fragment: 1.91 (1H, s. H-8′′), 2.50 (3H, s, N-CH_3), 3.49 (3H, s, CH_3-8′′), 4.94 (1H, d, J=11.1, H-7′′), 7.73 (5H, m, Ar-H).

2-(Dihydroxyphenyl)-6-[1-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2(1*H*)-yl)methyl]-3,5,7-trihydroxychroman-4-one (10d).

6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**3a**, 0.13 g, 0.67 mmol) afforded DHQ **9** (0.2 g, 0.67 mmol). Yield 0.32 г (91 %), mp 187-190 °C (*i*-PrOH). IR spectrum (KBr, ν_{max}, $см^{-1}$): 3418 (OH), 1640 (C=O), 1519, 1452 (C=C), 1262 (C–O). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): a) DHQ fragment: 3.72 (2H, resonance overlapped, N-CH_2), 4.42 (1H, d, J=11.0, H-3), 4.90 (1H, d, J=11.0, H-2), 5.74 (1H, s, H-8), 6.69 (2H, s, H-5′, 6′), 6.82 (1H, s, H-2′); b) 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline fragment: 2.73 (2H, m, H-4), 2.83 (2H, m, H-3), 3.63 (3H, s, 7-OCH_3), 3.65 (3H, s, 6-OCH_3), 3.80 (2H, s, H-1), 6.62 (1H, s, H-8), 6.65 (1H, s, H-5); ^{13}C NMR spectrum; (δ, ppm): a) DHQ fragment: 48.66 (CH_2–N), 71.92 (C-3), 83.39 (C-2), 96.21 (C-8), 99.51 (C-6), 100.21 (C-4a), 115.55 (C-2'), 115.80 (C-5'), 119.81 (C-6'), 128.64 (C-1'), 145.38 (C-3'), 146.18 (C-4'), 160.99 (C-8a), 162.10 (C-5), 171.54 (C-7), 197.40 (C-4); b) 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline fragment: 20.06 (C-4), 24.55 (C-1), 42.78 (C-3), 55.11 (6-OCH_3), 55.14 (7-OCH_3), 111.56 (C-8), 115.40 (C-5), 124.50 (C-8a), 127.85 (C-4a), 145.76 (C-6), 146.89 (C-7).

2-(Dihydroxyphenyl)-)6-[1-(6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinolin-2(1*H*)-yl)methyl]-3,5,7-trihydroxychroman-4-one (10e).

Salsolidyn (**3b**, 0.25 g, 1.2 mmol) afforded DHQ **9** (0.367 g, 1.2 mmol). Yield 0.49 г (78 %), mp 198-201 °C (*i*-PrOH).

IR spectrum (KBr, ν_{max}, см$^{-1}$): 3418 (OH), 1639 (C=O), 1519, 1446 (C=C), 1281 (C-O). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): a) DHQ fragment: 3.89 (2H, s, N-CH_2), 4.41 (1H, d, J=11.0, H-3), 4.90 (1H, d, J=11.0, H-2), 5.69 (1H, s, H-8), 6.68 (2H, s, H-5′, 6′), 6.81 (1H, s, H-2′), 8.95 (each 1H, br. s, 3′, 4′-OH); б) salsolidyn fragment: 1.32 (3H, d, J=6.6, 1-CH_3), 2.58 (1H, m, H_a-4), 2.83 (2H, m, H_e-4, H_a-3), 3.11 (2H, m, H_e-3, H-1), 3.65 (3H, s, 7-OCH_3), 3.66 (3H, s, 6-OCH_3), 6.65 (1H, s, H-8), 6.66 (1H, s, H-5).

2-(3,4-Dihydroxyphenyl)-6-{[1-(3,4-dimethoxyphenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl]methyl}-3,5,7-trihydroxychroman-4-one (10f).

1-(3′,4′-dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**3c**, 0.2 g, 0.67 mmol) afforded DHQ (**3e**, 0.2 g, 0.67 mmol). Yield 0.35 g (84%), mp 174–178°C (*i*-PrOH). IR spectrum (KBr, ν_{max}, cm^{-1}): 3434 (OH), 1641 (C=O), 1516, 1462, 1449 (C=C), 1261 (C–O). ^{1}H NMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): a) DHQ fragment: 3.70 (2H, resonance overlapped, N–CH_2), 4.48 (1H, dd, J = 3.6, 11.0, H-3), 4.95 (1H, t, J = 10.9, H-2), 5.82 (1H, s, H-8), 6.74 (2H, s, H-5′, 6′), 6.87 (1H, s, H-2′), 8.98 (2H, br.s, 3′, 4′-OH), 12.36 (1H, br.s, 5-OH); b) 1-(3′,4′-dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline fragment: 2.68 (1H, m, H_a-3), 2.85 (2H, m, H-4), 3.03 (1H, m, H_e-3), 3.51 (3H, s, 7-OCH_3), 3.69 (3H, s, 6-OCH_3), 3.74 (3H, s, 3′-OCH_3), 3.75 (1H, s, 4′-OCH_3), 4.47 (1H, d, J = 1.9, H-1), 6.28 (1H, s, H-8), 6.67 (2H, dd, J = 1.8, 8.2, H-6′), 6.77 (1H, s, H-5), 6.80 (1H, d, J = 1.8, H-2′), 6.91 (1H, d, J = 8.2, H-5′); ^{13}C NMR spectrum (δ, ppm): a) DHQ fragment: 48.36 (CH_2–N), 71.78 (C-3), 83.24 (C-2), 95.44 (C-8), 100.11, 101.18 (C-4a, 6), 115.35 (C-2′), 115.58 (C-5′), 119.59 (C-6′), 128.24 (C-1′), 145.17 (C-3′), 146.00 (C-4′), 160.84 (C-8a), 161.72 (C-5), 168.60 (C-7), 197.95 (C-4); b) 1-(3′,4′-dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline fragment: 21.44 (C-4), 45.07 (C-3), 55.65 (6-OCH_3), 55.67 (7-OCH_3), 55.67 (3′-OCH_3), 55.79 (4′-OCH_3), 65.96 (C-1), 111.56 (C-8), 111.67 (C-5), 112.12 (C-6′), 113.27 (C-5′), 122.26 (C-2′), 125.99 (C-1′), 127.97 (C-8a), 133.88 (C-4a), 147.37 (C-6), 148.02 (C-7), 148.54 (C-3′), 148.78 (C-4′).

2-(3,4-Dihydroxyphenyl)-6-{[1-(3,4-methylenedioxyphenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl]methyl}-3,5,7-trihydroxychroman-4-one (10g).

1-(3,4-Methylenedioxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**3d**, 0.21 g, 0.67 mmol) afforded DHQ (**9,** 0.20 g, 0.67 mmol. Yield 0.34 g (83%), mp 176–180°C (*i*-PrOH). IR spectrum (KBr, ν_{max}, cm^{-1}): 3204 (OH), 1639 (C=O), 1516, 1488 (C=C), 1252 (C-O). ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): a) DHQ fragment: 3.67 (1H, dd, J = 3.3, 14.3, N–CH_2), 3.79 (1H, d, J = 14.3, N–CH_2), 4.49 (1H, dd, J = 3.9, 11.1, H-3), 4.96 (1H, dd, J = 7.8, 11.1, H-2), 5.83 (1H, s, H-8), 6.74 (2H, s, H-5′, 6′), 6.87 (1H, s, H-2′), 9.00 (2H, br.s, 3′, 4′-OH), 12.33 (1H, br.s, 5-OH); b) 1-(3′4′-methylenedioxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline fragment: 2.65 (1H, m, H_a-3), 2.82 (2H, m, H-4), 2.99 (1H, m, H_e-3), 3.52 (3H, s, 7-OCH_3), 3.74 (3H, s, 6-OCH_3), 4.77 (1H, s, H-1), 6.01 (2H, d, J = 3.4, 3′-OCH_2O-4′), 6.27 (1H, s, H-8), 6.68 (1H, s, H-2′), 6.69 (1H, d, J = 6.4, H-6′), 6.76 (1H, s, H-5), 6.88 (1H, d, J = 8.5, H-5′); ^{13}C NMR spectrum (δ, ppm): a) DHQ fragment: 47.87 (CH_2–N), 71.51 (C-3), 82.99 (C-2), 95.20 (C-8), 99.93, 101.09 (C-4a, 6), 115.09 (C-2′), 115.33 (C-5′), 119.37 (C-6′), 127.69 (C-1′), 144.92 (C-3′), 145.76 (C-4′), 160.67 (C-8a), 161.48 (C-5), 168.08 (C-7), 197.83 (C-4); b) 1-(3′4′-methylenedioxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline fragment: 25.49 (C-4), 44.53 (C-3), 55.40 (6-OCH_3), 55.48 (7-OCH_3), 65.60 (C-1), 101.09 (C-7′), 107.78 (C-5′), 109.36 (C-2′), 111.37 (C-8), 111.64 (C-5), 123.28 (C-6′), 125.80 (C-1′), 127.99 (C-8a), 135.32 (C-4a), 146.68 (C-6), 147.12 (C-7), 147.31 (C-3′), 147.74 (C-4′).

Cell culture

Normal rat hepatocyte cells and three human cancer cell lines cervical carcinoma cells (HeLa, collection of Russian Academy of Science), laryngeal adenocarcinoma cells (HEp-2, ATCC: CCL-23) and breast carcinoma cells (HBL-100, ATCC: HTB-124) were used for cytotoxicity screening of the 1,2,3,4–tetrahydroisoquinoline derivatives. The verified cell lines were purchased from the Bank of Cell Cultures in the Institute of Cytology of Russian Federation. The primary culture of hepatocytes was obtained from the liver of rats as adult animals (Tseomashko et al, 2015). Cell lines were cultured in advanced DMEM and RPMI-1640 (SIGMA, USA) supplemented with 10% inactivated FBS (SIGMA, USA) and 2 mM L-glutamine and 1% antibiotic-antimycotic solution, and grown at 37°C in a humidified atmosphere of 5% CO_2 in air. To subculture the cells were detached with Versen solution.

MTT assay

The MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] colorimetric assay developed by (Mosmann T., 1983) was used to screen for cytotoxic activity of the 1,2,3,4–tetrahydroisoquinoline derivatives.

The all substances were dissolved in DMSO. Briefly, the cells were seeded in 96-well plates at a density from $2x10^3$ to $5x10^3$ cells per well. Following 24-h incubation and attachment, the cells were treated with substances concentrations 1 - 100 µg/ml for 24 h. Following incubation with MTT solution (5 mg/mL) for 3.5 h, cells were lysed with DMSO. The absorbance was measured after 30 min

using the «EnSpire 2600» microplate reader (Perkin Elmer, USA) at a wavelength of 620 nm. Intact cells with solvent in the culture medium served as the control. The effect was compared with antineoplastic drug «Ciplatin» (Fresenius Kabi, India) with cis-diamminedichloroplatinum as active ingredient and bioflavonoid dihydroquercetin (DHQ).

Cell viability was determined by the ratio of viable cells exposed to the test substance to the amount of living cells in the control. The results are generated from three independent experiments; each experiment was performed in triplicate.

Statistical analysis

Statistical processing and graphing were performed using the program «Origin 5». Results were considered significant at $p \leq 0.05$.

Results

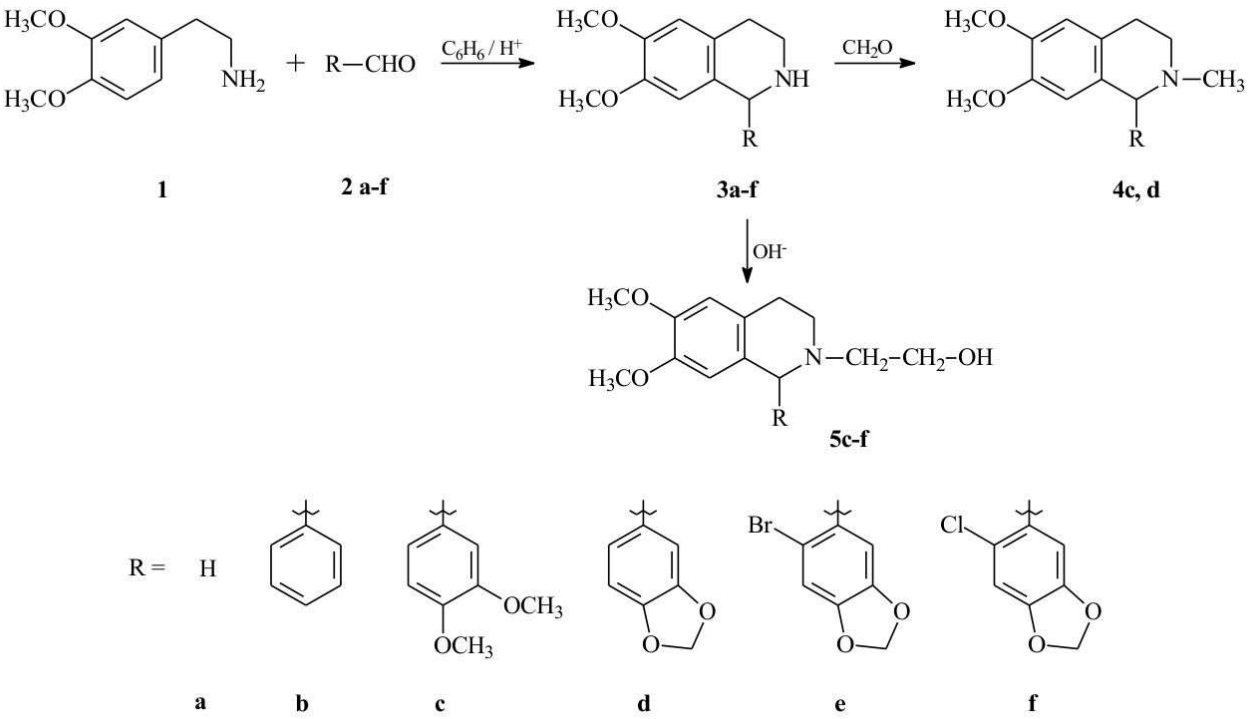
At first this is to obtain natural alkaloids analogues such as cryptostylines and salsolidine (**3a-f**, **4c,d and 8a**); at the second is alkylation at N atom (**5c-f**); at the third is synthesis of biomolecular compounds 1,4-*bis*(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)alkanes and 1,2,3,4-tetrahydroisoquinolin-2(1*H*)-yl)methyl]-3,5,7-trihydroxychroman-4-ones (**8b-h** and **10 d-g**).

For isoquinolines **3a-f** Pictet-Spengler reaction has been used by (Zhurakulov et al, 2013). Target isoquinolines **3a-f** were synthesized after interaction of amine **1** with aldehydes **2a-f** through a Schiff base and following their cyclization by the action SF_3COOH. Target isoquinolines methylation by Craig resulted alkaloids cryptostyline I and II (**4c**,**d**). Hydroxyethyl ariltetrahydroisoquinoline derivatives **5c-f** were obtained by condensation **3c-f** with ethylenechlorohydrine. (Zhurakulov et al, 2014) (Scheme 1). The KOH use instead of K_2CO_3 in the final stage resulted in increase in output a **5c** from 62% to 91%.

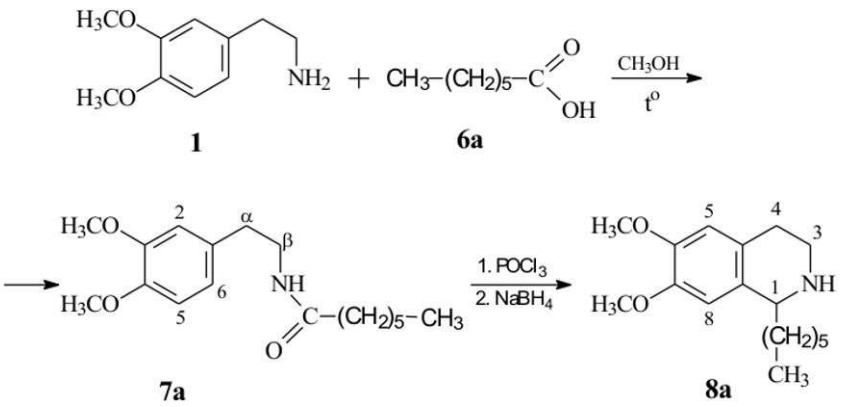
Derivatization 8a-h

Simple synthetic scheme was used for the synthesis of **8a-h** target products: preparation of amides from ghomoveratrilamine (**1**) and the corresponding acids– **6a** (7:0 heptanoic acid), **6b-h** dicarboxylic acids (adipic, sebacic, tridecanoic, brassylic and izoftaleic acids) and their subsequent Bischler-Napieralski cyclization to 3.4-dihydroisoquinolines (Scheme 2).

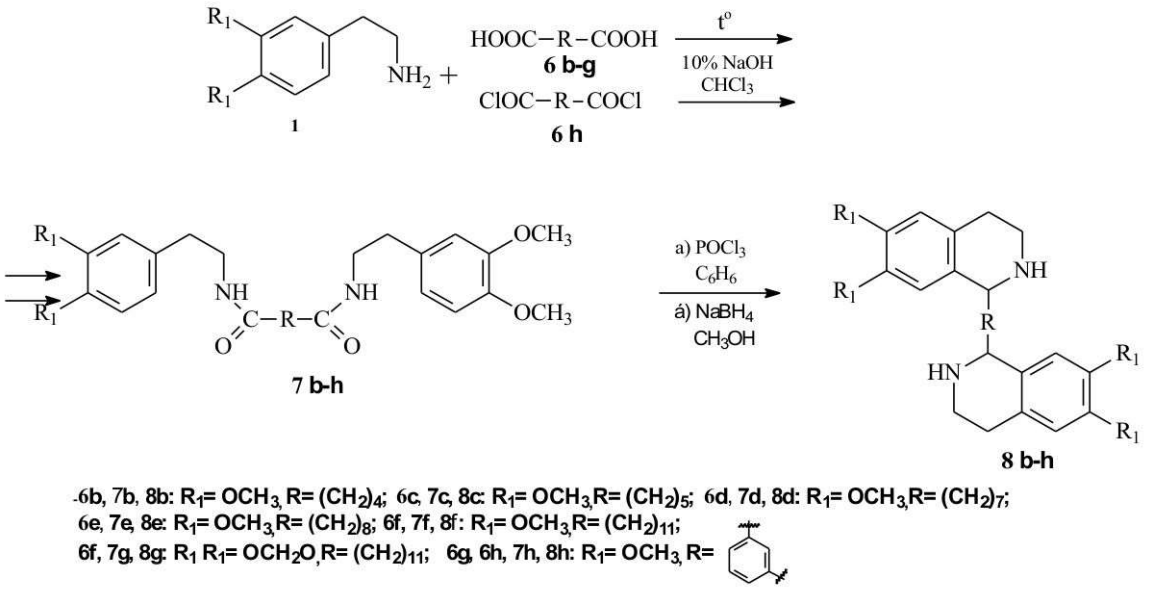
Using the obtained salt of the corresponding acid and amine **1** instead of a substances mixture in the first step yielded high yield of **7a-g** amides. **7a-g** amides are almost easy by heating the salt to 178ºS for 2 hours. In the second step $POCl_3$ as a condensing agent was used. **a-h** target isoquinolines by reduction 3,4-dihydroisoquinolines with $NaBH_4$ were prepared. Isophthalic acid (**6g**) gave **7h** amide in 29% yield. Interaction of amine **1** with isophthalic acid **6h** chloroanhydride proved more effective method (Method B). Thereby **7h** amide was isolated with 82% yield (Scheme 3).



Scheme 1. The obtaining of hydroxyethyl ariltetrahydroisoquinoline derivatives **5c-f** by condensation **3c-f** with ethylenechlorohydrine.



Scheme 2 The synthesis of amides from ghomoveratrilamine (**1**) with the corresponding acids **6a-h** and their subsequent Bischler-Napieralski cyclization to 3.4-dihydroisoquinolines



6b, 7b, 8b: R_1= OCH_3, R= $(CH_2)_4$; 6c, 7c, 8c: R_1= OCH_3,R= $(CH_2)_5$; 6d, 7d, 8d: R_1= OCH_3,R= $(CH_2)_7$;
6e, 7e, 8e: R_1= OCH_3,R= $(CH_2)_8$; 6f, 7f, 8f: R_1= OCH_3,R= $(CH_2)_{11}$;
6f, 7g, 8g: R_1 R_1= OCH_2O,R= $(CH_2)_{11}$; 6g, 6h, 7h, 8h: R_1= OCH_3, R=

Scheme 3 The synthesis of **8b-h** target products

The structure of the synthesized compounds was confirmed by IR and H1 NMR spectroscopy. PMR spectra of **7a-h** compounds contain proton signals of all structural fragments. Proton signal H-1 in **8a-h** NMR spectra appeared at 4.40, 3.82 - 3.98, 4.33, 3.78 and 5.68 ppm, respectively.

Conjugates dihydroquercetin receiption

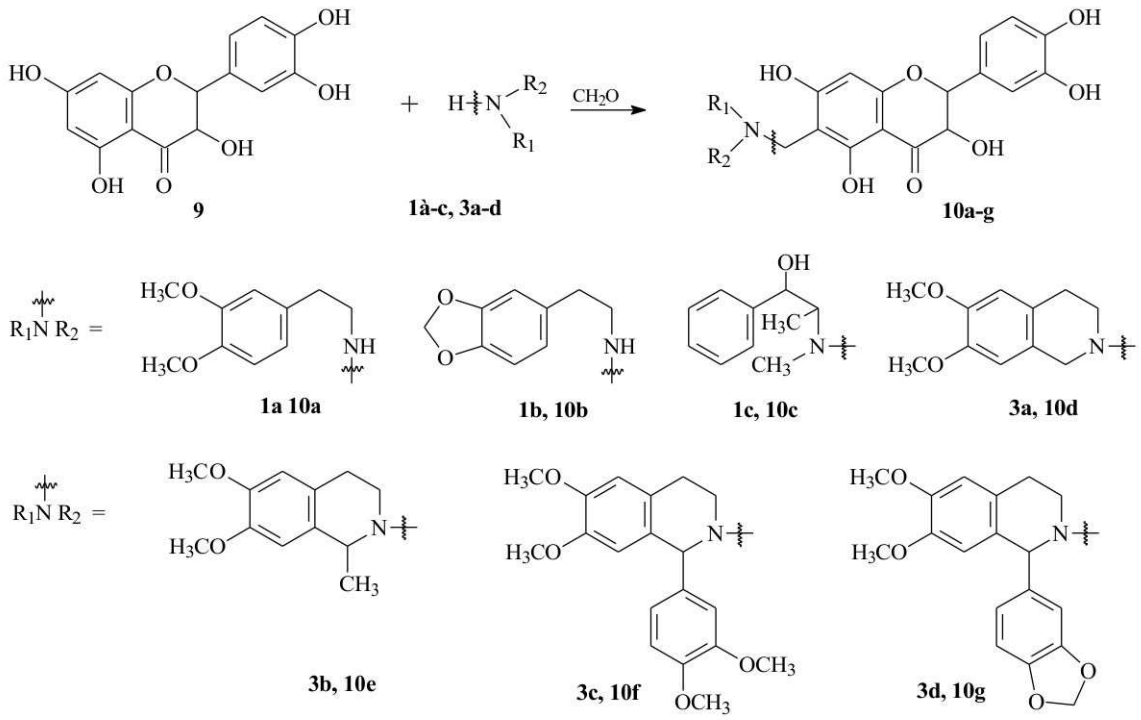
Flavonoids like alkaloids from a practical point of view are of particular interest as medicine drugs. One bioflavonoid dihydroquercetin (DHQ) has powerful antioxidant, hepatoprotective, anti-tumor, immunomodulatory properties (Babkin et al, 2011; Nifant'ev et al, 2013). Unfortunately, flavonoids are not produced by the human body and have low solubility in water. These properties determine the interest of chemists from leading research centers to modificate quercetin and dihydroquercetin.

We obtained conjugates dihydroquercetine (9) from the primary **1**,**1a** and secondary **1b**, **3a**, **3c**, **3d** amines. Reactions were carried out in isopropyl alcohol at room temperature (25-30 °C) applying the ratio of DHA / amine / formaldehyde = 1: 1: 1. Wherein **10a-g** monosubstituted products were synthesized (Scheme 4).

The structure of the synthesized compounds was confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy.

Cytotoxic activity

The literature suggests a wide range of physiological activity of 1,2,3,4-tetrahydroisoquinoline derivatives. So, substances were found to exhibit properties of central nervous system depressants (Ott at all, 1968) and NMDA receptor blockers (Wanner at al, 1998). A biological activity of 1,2,3,4-tetrahydroisoquinoline grounds includes antitumor properties (Debono at al, 2014; Mihoubi at al, 2015; Patil at al, 2014; Uesawa at al, 2011).



Scheme 4 The obtaining of conjugates dihydroquercetine (9) from the primary **1**,**1a** and secondary **1b**, **3a**, **3c**, **3d** amines and **10a-g** monosubstituted products

Table 1. Cytotoxic activity of tetrahydroisoquinoline derivatives (alive cells, %)

Substance, μg/ml	HeLa		HEp-2		HBL-100		hepatocytes	
	10	**1**	**10**	**1**	**10**	**1**	**10**	**1**
3a	86,5±2,6	90,0±1,4	**57,5±0,8**	93,1±3,4	75,0±1,3	83,5±2,2	83,9±3,9	112,8±1,7
3b	**55,9±1,5**	**64,2±0,3**	87,8±2,9	90,7±4,3	73,5±2,0	77,5±1,9	125,1±4,7	119,4±5,0
3c	81,6±1,3	100,5±0,8	86,5±1,7	92,3±1,1	62,7±2,5	88,7±3,0	100,4±2,7	100,6±2,9
3d	73,5±1,6	77,2±2,5	62,6±0,7	62,9±2,5	68,7±0,9	69,9±1,6	68,6±3,0	99,5±0,9
3e	**56,1±0,6**	**58,4±1,1**	63,0±1,7	66,4±2,0	89,7±2,3	90,9±3,6	69,8±1,7	99,7±4,2
3f	**54,2±1,1**	89,2±1,7	**43,8±0,9**	**47,6±2,2**	98,6±2,4	97,8±1,6	91,4±4,1	100,3±1,6
4c	100,2±0,9	100,5±0,1	90,4±1,0	94,7±3,3	94,3±2,1	100,0±1,2	100,0±0,0	100,2±4,1
4d	64,9±2,7	70,4±0,9	**33,1±0,5**	69,8±1,8	75,0±2,8	81,7±2,4	**72,9±1,6**	81,8±2,7
5c	94,1±2,5	94,3±1,9	84,0±3,1	88,1±0,8	90,3±4,4	97,1±0,9	100,1±1,5	100,0±4,0
5d	85,3±2,7	94,1±2,0	79,1±0,6	84,0±1,8	82,1±0,0	100,2±0,9	100,3±0,3	100,5±4,7
5e	89,5±0,9	100,7±0,4	89,6±1,4	97,6±2,0	91,5±1,4	96,8±1,8	100,4±1,7	100,7±3,1
5f	96,0±2,9	100,2±3,2	97,3±3,7	100,1±4,5	98,4±2,8	100,0±4,0	100,0±3,9	100,4±2,8
8a	90,8±4,1	94,0±3,9	**59,1±2,9**	78,3±3,0	**55,2±1,7**	**56,3±1,6**	**90,3±4,1**	**94,4±3,0**
cisplatin	30,0±1,4	48,1±1,7	48,9±1,6	79,2±2,7	24,4±1,2	51,2±2,3	27,8±0,9	86,3±4,0

In the present study, we investigated the cytotoxic activity of three types of substances: monobasic tetrahydroisoquinoline derivatives, dibasic tetrahydroisoquinolines and synthetic complexes of alkaloids, amides and their derivatives with a natural bioflavonoid dihydroquercetin (DHQ). Monohydric tetrahydroisoquinoline data presented in Table 1.

Several monobasic tetrahydroisoquinolines have different effects of cell growth suppression at concentration of 10 μg/ml. Thus, a sample **4d** showed the most selective cytotoxic activity among the derivatives, which suppressed growth of larynx cell on 66.9%, while its toxicity to normal cells was only 26.1% compared with the control.

Compounds **3a**, **3b**, **3e**, **3f** and **8a** were less active, where the cell growth inhibition ranged from 56.2 to 40.9%. It is interesting to note that with regard **8a** was only active to breast adenocarcinoma - at doses of 1 and 10 μg/ml of cell

Table 2. Cytotoxic activity of bis-tetrahydroisoquinoline derivatives (alive cells, %)

Substance,	HeLa cells		HEp-2 cells		HBL-100 cells		hepatocytes	
μg/ml	10	1	10	1	10	1	10	1
8b	90,5±3,8	100,0±4,1	85,9±2,3	93,3±4,0	92,2±2,8	97,8±4,0	83,1±1,5	96,2±3,7
8c	96,2±0,9	100,0±0,0	89,2±0,7	91,4±1,4	96,1±1,6	98,9±2,7	85,2±0,5	99,3±0,8
8d	**6,3±0,1**	**55,2±0,9**	67,8±1,5	85,2±2,2	22,3±1,0	66,7±1,8	87,4±2,0	99,3±3,1
8e	**15,1±0,6**	96,4±3,5	**15,0±0,4**	91,1±2,8	**2,1±0,0**	**27,2±0,9**	**30,5±0,4**	**89,8±0,6**
8f	**0,0±0.0**	91,2±2,8	**0,1±0,0**	76,0±1,3	**0,0±0,0**	90,3±1,3	**22,1±1,0**	90,1±3,4
8g	**0,0±0.0**	95,1±3,8	**2,1±0,1**	78,9±2,5	**5,1±0,2**	92,1±3,0	**30,2±1,1**	91,1±3,0
8h	83,9±1,8	90,6±2,6	**37,4±0,8**	**67,7±1,7**	**38,4±0,8**	**42,4±0,6**	**60,1±1,4**	**79,2±1,5**
cisplatin	30,0±1,4	48,1±1,7	48,9±1,6	79,2±2,7	24,4±1,2	51,2±2,3	27,8±0,9	86,3±4,0

Table 3. Cytotoxic activity of synthetic products of alkaloid with DHQ (alive cells, %)

Substance, μg/ml	HeLa		HEp-2		HBL-100		hepatocytes	
	10	1	10	1	10	1	10	1
10a	100,3±3,4	89,0±2,2	83,5±2,4	84,5±1,9	99,1±3,2	87,4±1,9	122,9±6,0	125,7±4,9
10b	99,4±3,1	92,0±3,0	**184,1±6,4**	**148,7±5,1**	**126,3±6,9**	**110,1±7,0**	**143,5±3,8**	**130,5±6,0**
10c	81,2±5,2	82,0±4,9	105,1±7,4	99,1±5,2	96,8±5,2	85,1±1,2	110,4±3,7	104,2±5,0
10d	90,0±3,8	87,0±5,2	**149,2±9,1**	**146,1±7,3**	106,7±2,5	102,0±1,8	**131,1±4,6**	**116,9±4,8**
10e	103,1±1,6	100,0±2,3	81,3±3,1	78,7±2,0	100,±2,8	99,3±2,4	**119,1±3,8**	**108,5±4,2**
10f	98,0±4,9	87,5±3,6	103,5±3,7	93,4±4,2	107,2±4,8	90,0±2,8	115,6±4,3	120,7±5,6
10g	**120,0±6,1**	105,0±3,5	83,0±2,9	82,2±3,6	100,5±3,1	97,6±1,9	**128,0±5,0**	**116,0±5,0**
DHQ	106,3±7,1	100,5±5,8	112,4±6,2	101,2±4,6	109,1±5,0	106,0±3,3	**157,3±4,0**	**119,8±5,1**
Cisplatin	30,4±1,4	48,0±2,9	49,3±3,5	89,3±4,0	24,5±0,5	51,2±0,9	27,8±0,9	86,3±4,0

Table 4. IC_{50} value (μM)

Substance, μM	HeLa	HEp-2	HBL-100	hepatocytes
4d	152.9	18.0	214.1	210.6
3f	43.2	2.3	230.5	240.1
8a	288.8	54.2	43.3	252.7
8d	4.1	83.0	1.0	1.65
8f	3.1	3.5	4.0	10.9
8g	5.2	5.5	6.2	12.6
8h	173.9	10.9	1.1	43.5

growth inhibition was 44.8 and 43.7% respectively with the absence of toxicity to hepatocytes.

Cytotoxic activity of dibasic tetrahydroisoquinolines presented in Table 2.

Bis compounds exhibit greater cytotoxic effect than mono-series compounds. There was a tendency for activity growth of dibasic compounds for continuous cell cultures with increasing length of the hydrocarbon chain between the two isoquinoline molecules: the longer hydrocarbons chain, the derivative more active inhibits cell growth. The sample **8f** showed the greatest cytotoxic activity among bis-substances: at a concentration of 10 μg/ml the sample has caused the 100% death of cell cultures.

The sample **8d** showed highly selective inhibitory activity against cervical adenocarcinoma (93.7%). Another substance **8h** containing the benzene ring between two isoquinoline molecules exhibits mild cytotoxic effect against HEp-2 and HBL-100 (62-63% inhibition of cell growth at 10 μg/ml).

Cytotoxic activity of synthetic complexes of alkaloids and derivatives with DHQ is presented in Table 3.

The all compounds completely lacked cytotoxicity toward cancer cell lines in this study. Some of them have shown pronounced proliferation (table 3). Sample **10b** demonstrated the most proliferative activity on HEp-2 cells:

184.1 and 148.7 % at 10 and 1 µg/ml, respectively. **10d** had similar proliferative effects on laryngeal adenocarcinoma cells: 149.2 and 146.1% cell growth compared with the control.

It is interesting to note that the DHQ reference drug showed a pronounced proliferation only in healthy liver cells.

Compounds showing cytotoxic activity were further tested at additional concentrations to calculate the IC_{50} values (table 4).

Discussion

In studying the relationship between the structure of the investigated compounds and their ability to inhibit the growth of cancer cells was detected following: in a series of 1-ariltetrahydroisoquinoline absence of ring C (sample **3a**) shows a weak activity of the compound, and the presence of the benzene ring slightly increases its cytotoxicity. Dimethoxy- and methylenedioxy- groups in ring A at the tetrahydroisoquinoline molecule in this concentration range are functionally significant, because the inhibitory effect is manifested in different ways (**3c, 3d**).

N-alkylation of these compounds leads to a double effect: the presence of the methylenedioxy group (**4d**) shows the manifestation of the selectivity of the molecule, which is enhanced with the introduction of halogens. At the same time isoquinoline with a dimethoxy group (samples **4c**, **5c**) loses its cytotoxic properties completely. Halogen nature is essential for cytotoxicity: inhibitory effect of the substance is manifested more in the presence of Cl atom than of Br (**3e**, **3f**). Hexyl group in tetrahydroisoquinoline (**8a**) maintains the high activity of the substance.

With regard to the bis-tetrahydroisoquinolines, the introduction into their structure of the second molecule greatly enhances the cytotoxic effect of substance. Methylene chain length between molecules is important.

Possibly, a long chain between the isoquinoline molecules helps substance to cling specific receptors of cancer cells. It leads to the suppression of their growth. Because of which healthy cells less susceptible to the influence of the cytotoxic derivatives than transformed. A similar effect is described in the scientific literature. For example, substances derived from plants of the family Cruciferaceae, have the ability to "stick" to faulty proteins located on the surface of cancer cells and cause their death by apoptosis. It is noteworthy that the normal cells are resistant to these compounds, since their surface is not defective proteins specific to tumor cells (Cavell et al, 2011; Wang et al, 2008).

Synthetic complexes of tetrahydroisoquinoline alkaloid derivatives with DHQ demonstrated another interesting result. Complex compounds are interest to researchers to broaden their spectrum of activity and reduce the toxicity.

In this paper, we studied the cytotoxic activity of synthetic derivatives containing the 1-ariltetrahydroisoquinoline (**3c**, **3d**), their amines and alkaloids salsolidyn, homoveratril, pseudoephedrine. All individual compounds have little overwhelming effect. DHQ provided with weak proliferative effect on cancer cells cultures and the average - to normal.

Substances **10f**, salsolidin, pseudoephedrine and **10a** in conjunction with DHQ were totally inactive against all cell cultures. Complexes containing the remaining compounds, started to show proliferative properties such as on the individual cell lines (**10d**, **10g**), and almost all cultures (**10b**). Probably, a similar effect of the samples is connected with the manifestation of the DHQ activity and the weakening of the alkaloid action.

Thus, the most promising compounds for further study in vitro and in vivo methods are dibasic compound **8d**, **8e**. Later these substances can be offered as a basis for drugs with anti-tumor properties.

Acknowledgement

This work is done according to the fundamental research FA-F6-T198 of Academy of Sciences of Uzbekistan with funding from the state of Uzbekistan.

References

Abe K, Saitoh T, Horiguchi Y, Utsunomiya I, Taguchi K, 2005. Synthesis and neurotoxicity of tetrahydroisoquinoline derivatives for studying Parkinson's disease. Biological and Pharmaceutical Bulletin, 28: 1355-1362.

Babkin VA, Ostroukhova NN, and Trofimova NN, 2011. Larch Biomass: From Chemical Composition to Innovative Products [in Russian], Novosibirsk Izdatelstvo Sibirskoe otdelenie Rossiyskoy Akademii Nauk, 236.

Cavell BE, Syed Alwi SS, Donlevy A, Packham G, 2011. Anti-angiogenic effects of dietary isothiocyanates: mechanisms of action and implications for human health. Biochemical Pharmacology, 81(3):327-336.

Debono AJ, Mistry SJ, Xie J, Muthiah D, Phillips J, Ventura S, Callaghan R, Pouton CW, Capuano B, Scammells PJ, 2014. The synthesis and biological evaluation of multifunctionalised derivatives of noscapine as cytotoxic agents. ChemMedChem, 9(2):399-410.

Galán A, Moreno L, Párraga J, Serrano Á, Sanz MJ., Cortes D, Cabedo N, 2014. Novel isoquinoline derivatives as antimicrobial agents. Bioorganic & Medicinal Chemistry, 21(11):3221-3230.

Mihoubi M, Micale N, Scala A, Jarraya RM, Bouaziz A,

Schirmeister T, Risitano F, Piperno A, Grassi G, 2015. Synthesis of C3/C1-Substituted Tetrahydroisoquinolines. Molecules, 20(8):14902-14914.

Mosmann T, 1983. Rapid colorimetric assay for cellular growth and survival: Application to proliferation and cytotoxicity assays. Journal of Immunological Methods, 65:55–63.

Nifant'ev EE, Mosyurov SE, Kukhareva TS, Vasyanina LK, 2013. N,N′-diethyl-1,3-propanediamine in the dihydroquercetin aminomethylation reaction. Doklady Akademii Nauk, 451(4): 404–407.

Ott H, Hardtmann GE, Denzer M, Frey A J, Gogerty JH, Leslie GH, Trapold JH, 1968. Tetrahydroisoquino[2,1-d][1,4]benzodiazepines. Synthesis and neuropharmacological activity. Journal of Medicinal Chemistry, 11:777.

Patil R, Hosni-Ahmed A, Jones TS, Patil SA, Asres LB, Wang X, Yates RC, Geisert EE, Miller DD, 2014. Synthesis and in vitro evaluation of novel 1,2,3,4-tetrahydroisoquinoline derivatives as potent antiglioma agents. Anti-Cancer Agents in Medicinal Chemistry, 14(3):473-482.

Pingaew R, Mandi P, Nantasenamat C, Prachayasittikul S, Ruchirawat S, Prachayasittikul V, 2014. Design, synthesis and molecular docking studies of novel N-benzenesulfonyl-1,2,3,4-tetrahydroisoquinoline-based triazoles with potential anticancer activity. European Journal of Medicinal Chemistry, 81:192-203.

Seo JW, Srisook E, Son HJ, Hwang O, Cha YN, Chi DY, 2008. Synthesis of tetrahydroisoquinoline derivatives that inhibit NO production in activated BV-2 microglial cells. European Journal of Medicinal Chemistry, 43: 1160-1170.

Tseomashko NE, Tsay EA, Azimova ShS, 2015. Obtaining of the primary hepatocytes culture for *in vitro* research [in Russian]. Uzbek Biological Journal, 2: 40-42.

Uesawa Y, Mohri K, Kawase M, Ishihara M, Sakagami H, 2011. Quantitative structure-activity relationship (QSAR) analysis of tumor-specificity of 1,2,3,4-tetrahydroisoquinoline derivatives. AnticancerResearch, 31(12):4231-4238.

Wang KR, Zhang BZ, Zhang W, Yan JX, Li J, Wang R, 2008. Antitumor effects, cell selectivity and structure-activity relationship of a novel antimicrobial peptide polybia-MPI. Peptides, 29(6): 963-968.

Wanner KT, Beer H, Höfner G, Ludwig M, 1998. Asymmetric Synthesis and Enantioselectivity of Binding of 1-Aryl-1,2,3,4-Tetrahydroisoquinolines at the PCP Site of the NMDA-Receptor Complex. European Journal of Organic Chemistry, 2019-2029.

Zhurakulov ShN, Levkovich MG, Vinogradova VI, 2014. Synthesis of Hydroxyethyl Perivatives of 1-aryltetrahydroisoquinoline alkaloids. Chemistry of Natural Compounds, 49: 1095-1098.

Zhurakulov ShN, Vinogradova VI, Levkovich MG, 2013. Synthesis of 1-aryltetrahydroisoquinoline alkaloids and their analogs. Chemistry of Natural Compounds, 49: 70-74.