Potential Antidiabetes/Antiobesity Compounds from the beta-3-adrenergic Receptors Agonists Class (II)

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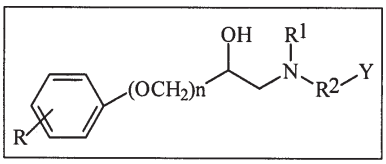
*In this paper we present experimental data regarding the synthesis of seven new aryl-ethanolamines (**5a-i**) by direct reductive amination of ketones (**4a-c**) with amines (**3a-e**) in the presence of sodium triacetoxyborohydride. The new compounds were characterized by IR and NMR (^1H and ^{13}C) spectral data and elemental analysis. The new compounds were tested as antidiabetes / antiobesity agents.*

Keywords: arylethanolamine compounds, ^1H and ^{13}C NMR and FT-IR spectra, antidiabetic/antiobesity activity

Diabetes mellitus (intimately related with obesity) is a chronic disease responsible for glucidic, lipidic and protidic metabolism disturbance which predisposes the patient to cardiovascular diseases and the rise of the mortality risk.

Up to the present, the antidiabetic therapy benefits of several drug types which are different as for their structures and their mechanism of action, such as: hormones (insulin), sulfonylureas, biguanides, thiazolidines, ozes. In the final decade of the last century, experimental pharmacological studies pointed out a new class of beta-3-adrenergic receptors agonists compounds; theses substances reduced the blood glucose level and the body weight of the diabetic animals. [1-17].

The researches carried out in the last years [5-11] resulted in the synthesis and biological testing of a considerable number of new molecules from the beta-3-adrenergic agonist group and showed that all these compounds can be represented by the general formula (**1**).

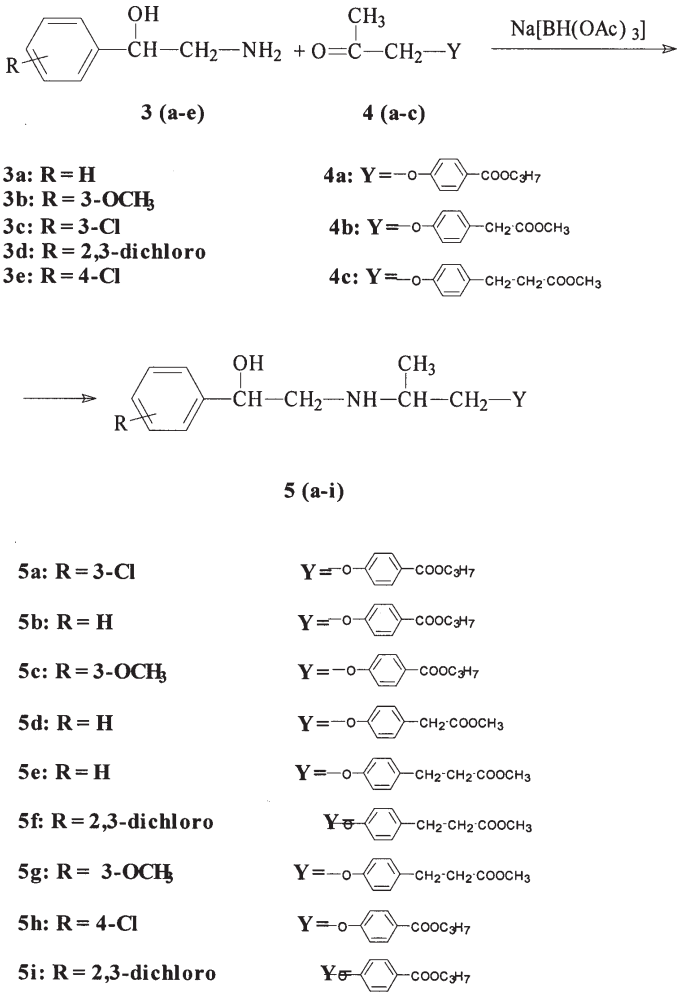


(1)

where:

R = H, 3-Cl
n = 0, 1
R^1 = H
R^2 = -CH(CH_3)-CH_2-; -CH_2-CH_2-O-, etc.
Y = (p)-C_6H_4-O-CH_2-$COOCH_3$; (p)-C_6H_4-$COOCH_3$; (p)-C_6H_4-O-CH_2-CH_2- O-CH_2-CH_3, etc.

In order to extend the series of products having a potential biological activity, this paper is intended to present 9 new compounds (**5a-i**) which were synthesized according to a method concerning the following reactions chain (scheme 1)



Scheme 1

Experimental part

Synthesis and analysis

All melting points were recorded in open capillaries on an OPTIMELT apparatus.

IR Spectra were recorded with a Specord IR75 (Carl-Zeiss) spectrometer în solid state by ATR on a FT-IR BrukerVertex 70 apparatus having a diamond optics..

NMR spectra were recorded at 20^{0}C, on two Varian spectrographs, one of Gemini 300BB type (300 MHz for protons and 75 MHz for carbon) and the other Unity Inova 400 (400 MHz for protons and 100 MHz for carbon), and as solvent we used deuterated chloroform or deuterated

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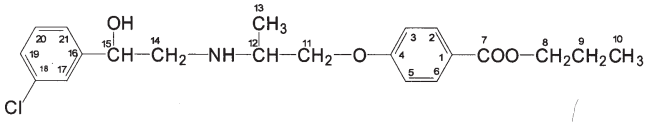
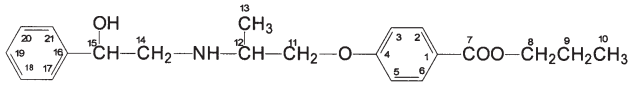
dimethylsulfoxyde having minim 98% deuterium. As an internal standard we used the TMS signal for the proton and carbon spectra (δ = 0 ppm).

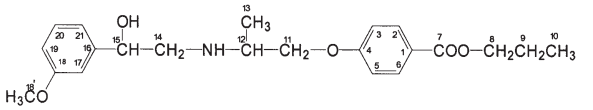
For assigning the chemical shifts of the protons, the notations used are presented in scheme 2.



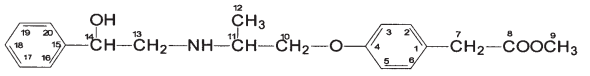
Compound 5a



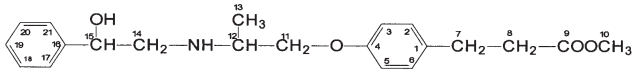
Compound 5b



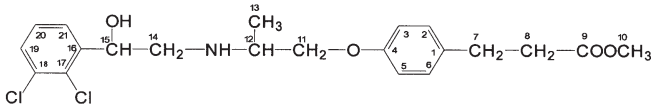
Compound 5c



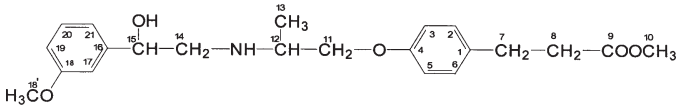
Compound 5d



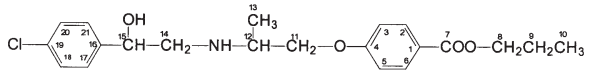
Compound 5e



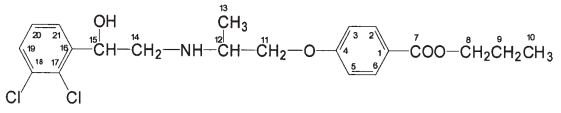
Compound 5f



Compound 5g



Compound 5h



Compound 5i

Scheme 2

The thin layer chromatography analysis (TLC) was effected on Merck $60F_{254}$ silicagel plattes; unidimensional migration, using chloroform : methanol 4 : 1 v/v as eluent. The reading was made by UV light irradiation (λ = 254 nm) and by iodine vapours.

*The synthesis of aryl-ethanolamines (**5a-i**)*

General method

A solution containing 7 mM 1-aryl-2-amino-ethanol (**3a-e) i**n 10 mL 1,2-dichloroethane, is gradually added under stirring onto the complex obtained from 14 mM sodium triacetoxyborohydride, and 20 mL 1,2-dichloroethane; the reaction mixture is stirred 15-20 minutes at 25^{0}C. Then, a solution of 5.6 mM of the ketone (**4a-c**) in 10 mL 1,2-dichloroethane is added in the reaction mixture by dropping during 5 min.; the mixture is stirred for 24 - 40 h at 25-28^{0}C. The reaction mixture is neutralized with 25 mL NaOH 3N solution and the layers are separated. The organic layer is washed with water until neutral, dried and fully concentrated by film evaporation; the product precipitates from the resulted residue by triturating it with suitable solvent, namely ehtylic-ether (compounds **5e, 5g, 5h**), diizopropyl-ether (compounds **5c, 5f, 5i**), *n*-hexane : ethylic-ether in different ratios (compounds **5a**, **5b, 5d**),

*4-{2-[2-(3-Chloro-phenyl)-2-hydroxy-ethylamino]-propoxy}-benzoic acid propyl ester (**5a**)*

White crystals, m.p = 87-89 ^{0}C. Yield: 32%. R_f = 0.75. **$C_{21}H_{26}NO_4Cl$:** %C calculated/found:64,37/62,43; %N calculated/found: 3,57/3,46

^{1}H-NMR(CDCl$_3$, δ ppm, *J* Hz): 7.98(d, 2H, H-2, H-6, 9.0); 6.88(d, 2H, H-3, H-5, 9.0); 7.38÷7.20(m, 4H, H-17, H-19, H-20, H-21); 4.67(dd, 1H, H-15, ^3J(H-^{15}-H^{14A})=3.6, ^3J(H^{15}-H^{14B})=8.6); 4.25(t, 2H, H-8, 6.6); 3.95(dd, 1H, H-11A, sist. AB, ^3J(H^{11A}-H^{12})=4.3, ^2J(H^{11A}-H^{11B})=9.2); 3.86(dd, 1H, H-11B, sist. AB, ^3J(H^{11A}-H^{12})=6.4, ^2J(H^{11A}-H^{11B})9.2); 3.14(m, 1H, H-12); 3.02(dd, 1H, H-14A, sist. AB, ^3J(H^{14A}-H^{15})=3.6, ^2J(H^{14A}-H^{14B})=12.3); 2.69(dd, 1H, H-14B, sist. AB, ^3J(H^{14A}-H^{15})=8.6, ^2J(H^{14A}-H^{14B})=12.3); 1.78(sxt, 2H, H-9, 6.6); 1.20(d, 3H, H-13, 6.4); 1.02(t, 3H, H-10, 6.6).

^{13}C-NMR(CDCl$_3$, δ ppm): 166.39(C-7); 162.39(C-4); 144.76(C-16); 134.41(C-18); 131.59(C-2, C-6); 129.69(CH); 127.64(CH); 126.01(CH); 123.92(CH); 123.32(C-4); 114.10(C-3, C-5); 71.94(C-11); 71.68(C-15); 66.30(C-8); 54.29(C-14); 52.34(C-12); 22.18(C-9); 17.74(C-13); 10.53(C-10).

The signals are 'complicated' on account of the two asymmetric carbon atoms (C-12 and C-15, resp.) which lead to diastereoisomers, in which the chemical shifting of the equivalent protons are no more izochronous, as in the corresponding enantiomers.

The distinction between the two diastereoisomers appears in the text as m or M asterisk behind the chemical shiftings of the unisochronous protons (according to relative proportions among them). When one could not distinguish between the two species, they appear as multiplet.

It was similarly proceeded for the carbon spectra.

FT-IR(ATR in solid, ν cm^{-1}): 3309w; 3129w; 2961m; 2937m; 2893w; 2833m; 1706vs; 1604s; 1582w; 1509m; 1461w; 1434w; 1420m; 1388w; 1274s; 1255vs; 1229s; 1193m; 1162m; 1100m; 1071m; 1050m; 1030m; 943w; 927w; 839w; 785m; 766m; 710m; 687m; 632w.

*4-[2-(2-Hydroxy-2-phenyl-ethylamino)-propoxy]-benzoic acid propyl ester (**5b**)*

White crystals, m.p. = 85-87^{0}C. Yield: 76%. R_f = 0.65.

$C_{21}H_{27}NO_4$:

%C calculated/found: 70.59/68.47;

%N calculated/found: 3.92/3.80.

^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): 7.98(m, 2H, H-2, H-6, 9.0); 7.39÷7.25(m, 5H, H-17÷H-21); 6.89(m, 2H, H-3, H-5, 9.0); 4.69(m, 1H, H-15, 3.6, 9.0); 4.25(t, 2H, H-8, 6.6); 3.94(m, 1H, H-11A, sist. AB); 3.88(m, 1H, H-11B, sist. AB); 3.14(m, 1H, H-12); 3.01(m, 1H, H-14A, sist. AB); 2.76(m, 1H, H-14B, sist. AB); 1.78(sxt, 2H, H-9, 6.6); 1.20(d, 3H, H-13, 6.4); 1.02(t, 3H, H-10, 6.6).

^{13}C-NMR($CDCl_3$, δ ppm): 166.40(C-7); 162.51(C-4); 142.59(C-16^m); 142.43(C-16^M); 131.59(C-2^m, C-6^m); 131.58(C-2^M, C-6^M); 128.44(C-18, C-20); 127.59(C-19); 125.86(C-17^m, C-21^m); 125.83(C-17^M, C-21^M); 123.33(C-1^m); 123.32(C-1^M); 114.16(C-3^m, C-5^m); 114.15(C-3^M, C-5^M); 72.49(C-15); 72.20(C-11^m); 72.09(C-11^M); 66.29(C-8); 54.59(C-14^m); 54.53(C-14^M); 52.35(C-12^m); 52.14(C-12^M); 22.21(C-9); 17.80(C-13^m); 17.61(C-13^M); 10.53(C-10).

FT-IR(ATR in solid, ν cm^{-1}): 3326w; 3304w; 3062w; 3021w; 2967w; 2933w; 2872w; 2823w; 1782s; 1711s; 1604w; 1580w; 1507m; 1451w; 1360w; 1312m; 1277s; 1243vs; 1160s; 1104s; 1061m; 1030m; 964w; 911w; 846m; 770m; 751m; 698m; 652w.

*4-{2-[2-Hydroxy-2-(3-methoxy-phnyl)-ethylamino]-propoxy}-benzoic acid propyl ester (**5c**)*

White crystals, m.p. = 78-80^{0}C. Yield: 42%. R_f = 0.68.

$C_{22}H_{29}NO_5$: %C calculated/found: 68.22 / 66.17.

%N calculated/found: 3.62/3.51

^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): 7.98(d, 2H, H-2, H-6, 8.9); 7.25(t, 1H, H-20, 8.0); 6.90(m, 2H, H-3, H-5, 8.9); 6.81(ddd, 1H, H-19, 1.0, 2.4, 8.0); 6.96÷6.87(m, 2H, H-17, H-21); 4.66(dd, 1H, H-15, 3.6, 9.1); 4.25(t, 2H, H-8, 6.6); 3.94(dd, 1H, H-11A, sist. AB, 4.3, 9.3); 3.88(dd, 1H, H-11B, sist. AB, 6.5, 9.3); 3.80(s, 3H, H-22); 3.14(m, 1H, H-12); 3.01(m, 1H, H-14A, sist. AB); 2.76(m, 1H, H-14B, sist. AB); 1.78(sxt, 2H, H-9, 6.6); 1.20(d, 3H, H-13, 6.4); 1.02(t, 3H, H-10, 6.6).

^{13}C-NMR($CDCl_3$, δ ppm): 166.40(C-7); 162.51(C-4); 159.87(C-18); 144.12(C-16); 131.59(C-2, C-6); 129.45(C-20); 123.33(C-1); 118.16(C-21^m); 118.12(C-21^M); 114.15(C-3, C-5); 113.15(C-19); 111.38(C-17); 72.20(C-11); 72.09(C-15); 66.29(C-8); 55.23(C-22); 54.51(C-14); 52.13(C-12); 22.21(C-9); 17.61(C-13); 10.53(C-10).

FT-IR(ATR in solid, ν cm^{-1}): 3308w; 3075w; 2941m; 2880m; 2833m; 1702vs; 1604s; 1580m; 1510w; 1492w; 1452m; 1435m; 1422w; 1385w; 1335w; 1308w; 1271vs; 1250vs; 1160s; 1098s; 1078s; 1047m; 1022m; 966w; 903w; 845m; 782m; 768m; 696s; 654w; 537w.

*{4-[2-(2-Hydroxy-2-phenyl-ethylamino)-propoxy]-phenyl}-acetic acid methyl ester (**5d**)*

White crystals, m.p. = 70-72^{0}C. Yield: 41%. R_f = 0.73.

$C_{20}H_{25}NO_4$: %C calculated/found: 69.97/67.87

%N calculated/found: 4.08/3.95

^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): 7.39÷7.31(m, 4H, H-17, H-18, H-20, H-21); 7.27(m, 1H, H-19); 7.18^m(d, 2H, H-2, H-6, 8.8); 7.17^M(d, 2H, H-2, H-6, 8.8); 6.84^m(d, 2H, H-3, H-5, 8.8); 6.83^M(d, 2H, H-3, H-5, 8.8); 4.72^M(dd, H-15, ^3J(H^{15}-H^{14A})=3.7, ^3J(H^{15}-H^{14B})=8.8); 4.69^m(dd, H-15, ^3J(H^{15}-H^{14A})=3.7, ^3J(H^{15}-H^{14B})=8.8); 3.68(s, 3H, H-9); 3.56(s, 2H, H-7); 3.89(m, 1H, H-11A, sist. AB); 3.82(dd, 1H, H-11B, sist. AB, ^3J(H^{11B}-H^{12})=6.5, ^2J(H^{11A}-H^{11B})=9.2); 3.12(m, 1H, H-12); 3.03^M(dd, 1H, H-14A, sist. AB, ^3J(H^{14A}-H^{15})=3.7, ^2J(H^{14A}-H^{14B})=12.1); 2.99^m(dd, 1H, H-14A, sist. AB, ^3J(H^{14A}-H^{15})=3.7, ^2J(H^{14A}-H^{14B})=12.1); 2.75^m(dd, 1H, H-14B, sist. AB, ^3J(H^{14B}-H^{15})=5.1, ^2J(H^{14A}-H^{14B})=12.1); 2.75^M(dd, 1H, H-14B, sist. AB, ^3J(H^{14B}-H^{15})=8.8, ^2J(H^{14A}-H^{14B})=12.1); 1.19^M(d, 3H, H-13, 6.4); 1.18^m(d, 3H, H-13, 6.4).

Both signal couples in the AA'BB' system of the aromatic protons are distinguished for simpler and more isolated signals, such as those of the H2-H6 protons. The protons of the phenyl ring are superposed and therefore the signals of the *orto*, *meta* and *para* protons could not be pointed out.

The distinction between the two diastereoisomers appears in the text as m or M asterisk behind the chemical shiftings of the unisochronous protons. When one could not distinguish between the two species, they appear as multiplet. It was similarly proceeded for the carbon spectra.

^{13}C-NMR($CDCl_3$, δ ppm): 172.31(C-8); 157.93(C-4); 142.55^M(C-16); 142.39^m(C-16); 130.33^m(C-2, C-6); 130.32^M(C-2, C-6); 128.41(C-18, C-20); 127.53(C-19); 126.42(C-1); 125.85^m(C-17, C-21); 125.81^M(C-17, C-21); 114.73^M(C-3, C-5); 114.71^m(C-3, C-5); 72.24^M(C-15); 72.02^m(C-15); 71.91^m(C-11); 71.78^M(C-11); 54.49^m(C-14); 54.38^M(C-14); 52.49(C-9); 52.21^m(C-12); 51.99^M(C-12); 40.31(C-7); 17.61^M(C-13); 17.46^m(C-13).

FT-IR(ATR in solid, ν cm^{-1}): 3305w; 3084w; 3035w; 2995m; 2949m; 2927m; 2826m; 1732vs; 1612ws; 1584w; 1511s; 1452m; 1438m; 1241vs; 1157m; 1090m; 1063m; 1035m; 1007m; 925w; 832w; 797w; 757w; 699m; 630w.

*3-{4-[2-(2-Hydroxy-2-phenyl-ethylamino)-propoxy]-phenyl}-propionic acid methyl ester (**5e**)*

White-yellowish crystals, m.p. = 105-107^{0}C. Yield: 85%. R_f = 0.62.

$C_{21}H_{27}NO_4$: %C calculated/found: 72.59/70.41.

%N calculated/found: 3.92/3.80

^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): 7.38÷7.31(m, 4H, H-17, H-18, H-20, H-21); 7.26(m, 1H, H-19);

7.09^M(d, 2H, H-2, H-6, 8.8); 7.08^m(d, 2H, H-2, H-6, 8.8); 6.81^M(d, 2H, H-3, H-5, 8.8); 6.79^m(d, 2H, H-3, H-5, 8.8); 4.69^M(dd, H-15, ^3J(H^{15}-H^{14A})=3.7 Hz, ^3J(H^{15}-H^{14B})=8.8 Hz); 4.67^m(dd, H-15, ^3J(H^{15}-H^{14A})=3.7 Hz, ^3J(H^{15}-H^{14B})=8.8 Hz); 3.66(s, 3H, H-10); 2.89(t, 2H, H-7, 7.7); 2.59(t, 2H, H-8, 7.7); 3.86(m, 1H, H-11A, sist. AB); 3.79(dd, 1H, H-11B, sist. AB, ^3J(H^{11B}-H^{12})=6.5, ^2J(H^{11A}-H^{11B})=9.2); 3.12(m, 1H, H-12); 3.01(m, 1H, H-14A, sist. AB, ^3J(H^{14A}-H^{15})=3.3, ^2J(H^{14A}-H^{14B})=12.1); 2.73(dd, 1H, H-14A, sist. AB, ^3J(H^{14A}-H^{15})=3.3, ^2J(H^{14A}-H^{14B})=12.1); 1.17(d, 3H, H-13, 6.5).

^{13}C-NMR($CDCl_3$, δ ppm): 173.38(C-9); 157.34(C-4); 142.71(C-16^M); 142.50(C-16^m); 132.93 (C-1^M); 132.91(C-1^m); 129.27(C-2, C-6^M); 129.25(C-2, C-6^m); 128.38(C-18, C-20); 127.50(C-19^M); 127.49(C-19^m); 125.85(C-17, C-21^M); 125.82(C-17, C-21^m); 114.66(C-3, C-5^M); 114.63(C-3, C-5^m); 72.34(C-15^M); 71.95(C-15^m); 72.05(C-11^M); 71.95(C-11^m); 54.57(C-14^M); 54.47(C-14^m); 52.42(C-12^M); 52.19(C-12^m); 51.57(C-10); 35.99(C-7); 30.12(C-8); 17.74(C-13^M); 17.57(C-13^m).

FT-IR(ATR in solid, ν cm^{-1}): 3304w; 3064w; 2920w; 2845m; 1731vs; 1608w; 1511m; 1489w; 1446m; 1395w; 1362w; 1299w; 1269m; 1235s; 1197m; 1157s; 1127w; 1098w; 1064w; 1032m; 994w; 957w; 929w; 898w; 825m; 750m; 699m; 631w.

*3-(4-{2-[2-(2,3-Dichloro-phenyl)-2-hydroxy-ethylamino]-propoxy}-phenyl)-propionic acid methyl ester (**5f**)*

White crystals, m.p. = 81-83^{0}C. Yield: 61%. R_f = 0.73.

$C_{21}H_{25}NO_4Cl_2$: %C calculated/found: 59.15/57.38; **%**N calculated/found: 3.28/3.18

^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): 7.55(t, 1H, H-20, 7.5); 7.37(bd, 1H, H-19, 7.5); 7.23(dd, 1H, H-21, 2.9, 7.5); 7.21(dd, 1H, H-21, 2.9, 7.5); 7.10(d, 2H, H-2, H-6, 8.6); 7.09(d, 2H, H-2, H-6, 8.6); 6.82(d, 2H, H-3, H-5, 8.6); 6.79(d, 2H, H-3, H-5, 8.6); 5.08(m, 1H, H-15); 3.89(dd, 1H, H-11A, sist. AB, ^3J(H^{11A}-H^{12})=4.1, ^2J(H^{11A}-H^{11B})=9.2); 3.80 (dd, 1H, H-11B, sist. AB, ^3J(H^{11B}-H^{12})=6.4, ^2J(H^{11A}-H^{11B})=9.2); 3.78(dd, 1H, H-11B, sist. AB, ^3J(H^{11B}-H^{12})=6.4, ^2J(H^{11A}-H^{11B})=9.2); 3.66(s, 3H, H-10); 3.14(m, 2H, H-12, H-14A); 2.89(t, 2H, H-7, 7.7); 2.60(t,

2H, H-8, 7.7); 2.59(m, 1H, H-14B); 1.19(d, 3H, H-13, 6.9); 1.18(d, 3H, H-13, 6.9).

^{13}C-NMR($CDCl_3$, δ ppm): 173.38(C-7); 157.28(C-4); 142.59(C-16); 142.47(C-16); 133.03(C-18); 132.84(C-17); 129.83(C-1); 129.29((C-2, C-6);); 129.16(C-20); 127.50(C-19); 125.42(C-21); 114.65(C-3, C-5); 72.13(C-11); 71.87(C-11); 69.42(C-15); 69.07(C-15); 52.46(C-12); 52.04(C-14); 51.90(C-14); 51.58(C-10); 35.99(C-8); 30.13(C-7); 17.84(C-13); 17.54(C-13).

FT-IR(ATR in solid, ν cm^{-1}): 3317w; 3074m; 2974m; 2942m; 2840m; 2753m; 1736vs; 1612w; 1511m; 1440m; 1372m; 1336w; 1267m; 1234s; 1158vs; 1082m; 1041m; 987w; 871m; 827m; 786m; 739w; 686w; 693w; 560w; 515w.

*3-(4-{2-[2-(3-Methoxy-phenyl)-2-hydroxy-ethylamino]-propoxy}-phenyl)-propionic acid methyl ester (**5g**)*

White crystals, cu m.p. = 87-90^{0}C. Yield: 62%. R_f = 0.81.

$C_{22}H_{29}NO_5$: %C calculated/found: 68.57/66.51;

%N calculated/found: 3.64/3.50

^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): 7.25(t, 1H, H-20, 7.6); 7.10(d, 2H, H-2, H-6, 8.8); 7.09(d, 2H, H-2, H-6, 8.8); 6.95(bd, 1H, H-17, 2.5); 6.93(bd, 1H, H-21, 7.6); 6.81(d, 2H, H-3, H-5, 8.8); 6.80(d, 2H, H-3, H-5, 8.8); 6.79(m, 1H, H-19); 4.68*(dd, H-15, $^3J(H^{15}\text{-}H^{14A})$=3.7 Hz, $^3J(H^{15}\text{-}H^{14B})$=8.8 Hz); 4.65*(dd, H-15, $^3J(H^{15}\text{-}H^{14A})$=3.7 Hz, $^3J(H^{15}\text{-}H^{14B})$=8.8 Hz); 3.88(m, 1H, H-11A, $J(H^{11A}\text{-}H^{11B})$=9.2 Hz); 3.80(s, 3H, H-18'); 3.66(s, 3H, H-10); 3.65 (m, 1H, H-11B, $J(H^{11A}\text{-}H^{11B})$=9.2 Hz); 3.80(s, 3H, H-18'); 3.11(m, 1H, H-12); 3.00(m, 1H, H-14A, sist. AB, $^3J(H^{14A}\text{-}H^{15})$=3.5, $^2J(H^{14A}\text{-}H^{14B})$=12.1); 2.89(t, 2H, H-7, 7.7); 2.73(dd, 1H, H-14A, sist. AB, $^3J(H^{14A}\text{-}H^{15})$=3.5, $^2J(H^{14A}\text{-}H^{14B})$=12.1); 2.59(t, 2H, H-8, 7.7); 1.18*(d, 3H, H-13, 6.5); 1.17*(d, 3H, H-13, 6.5).

Compound **5(g)** is a balanced mixture of the two corresponding diastereoisomers because of the two chiral centers C^{12} and C^{15}.

^{1}H-NMR spectra shows that protons H-2 and H-6 are unisochrone which is mentioned above by the two values of the chemical shiftings. The same case for the vicinal protons H-3 and H-5.

^{13}C-NMR($CDCl_3$, δ ppm): 173.42(C-9); 159.74(C-18); 157.28(C-4); 144.39($C\text{-}16^M$); 144.18($C\text{-}16^m$); 132.89(C-1); 129.40(C-20); 129.26(C-2, C-6); 118.09(C-21); 114.58(C-3, C-5); 113.07(C-19); 111.19(C-17); 72.23(C-15); 71.96($C\text{-}11^M$); 71.87($C\text{-}11^m$); 55.22(C-18'); 54.47($C\text{-}14^M$); 54.36($C\text{-}14^m$); 52.39($C\text{-}12^M$); 52.15($C\text{-}12^m$); 51.61(C-10); 35.99(C-8); 30.10(C-7); 17.74($C\text{-}13^M$); 17.56($C\text{-}13^m$).

FT-IR(ATR in solid, ν cm^{-1}): 3124w; 2996m; 2933m; 2832m; 1732vs; 1597m; 1511m; 1488w; 1434s; 1359w; 1316w; 1296w; 1266s; 1239s; 1193m; 1159s; 1082m; 1065m; 1037s; 992m; 963m; 916m; 864w; 828m; 791m; 740m; 700m; 532w.

*4-{2-[2-(4-Chloro-phenyl)-2-hydroxy-ethylamino]-propoxy}-benzoic acid propyl ester (**5h**)*

White crystals, m.p. = 87-91^{0}C. Yield: 50%. R_f = 0.80.

$C_{21}H_{26}NO_4Cl$: %C calculated/found: 64.36/62.43;

%N calculated/found: 3.57/3.46

^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): 7.98(d, 2H, H-2, H-6, 8.8); 7.29(bs, 4H, H-17, H-18, H-20, H-21); 6.87(d, 2H, H-3, H-5, 8.8); 4.67(dd, H-15, $^3J(H^{15}\text{-}H^{14A})$=3.6 Hz, $^3J(H^{15}\text{-}H^{14B})$=8.8 Hz); 4.25(t, 2H, H-8, 6.9); 3.94(dd, 1H, H-11A, sist. AB, $^3J(H^{11A}\text{-}H^{12})$=4.5, $^2J(H^{11A}\text{-}H^{11B})$=9.2); 3.85(dd, 1H, H-11B, sist. AB, $^3J(H^{11B}\text{-}H^{12})$=6.4, $^2J(H^{11A}\text{-}H^{11B})$=9.2); 3.13(m, 1H, H-12); 3.00(dd, 1H, H-14A, sist. AB, $^3J(H^{14A}\text{-}H^{15})$=3.6, $^2J(H^{14A}\text{-}H^{14B})$=12.1); 2.68(dd, 1H, H-14B, sist. AB, $^3J(H^{14B}\text{-}H^{15})$=8.8, $^2J(H^{14A}\text{-}H^{14B})$=12.1); 1.78(sxt, 2H, H-9, 6.9); 1.19(d, 3H, H-13, 6.4); 1.02(t, 3H, H-10, 6.9).

The ratio between the two couples of diastereoisomers was about 1:10. It was balanced ratios in the other cases.

^{13}C-NMR($CDCl_3$, δ ppm): 166.39(C-9); 162.38(C-4); 141.11(C-16); 133.20(C-19); 131.58(C-2, C-6); 128.55(C-17, C-21); 127.18(C-18, C-20); 123.30(C-1); 114.07(C-3, C-5); 71.93(C-15); 71.69(C-11); 66.30(C-8); 54.39(C-14); 52.32(C-12); 22.18(C-9); 17.69(C-13); 10.54(C-10).

FT-IR(ATR in solid, ν cm^{-1}): 3297w; 3114m; 2957m; 2886m; 2829m; 1709vs; 1604m; 1509m; 1458m; 1393w; 1353w; 1271vs; 1240vs; 1169m; 1104s; 1026m; 950w; 903w; 847w; 822m; 800w; 765m; 693w; 653w; 568w; 507w.

*4-{2-[2-(2,3-Dichloro-phenyl)-2-hydroxy-ethylamino]-propoxy}-benzoic acid propyl ester(**5i**)*

White crystals, m.p. = 86-88^{0}C. Yield: 40%. R_f = 0.80.

$C_{21}H_{26}NO_4Cl_2$: %C calculated/found: 61.97/60.11;

%N calculated/found: 3.29/3.19

H-NMR ($CDCl_3$, δ ppm, *J* Hz, T=303K): 7.97(d, 2H, H-2, H-6, 9.0); 7.54(dd, 1H, H-19, 1.4, 7.9); 7.36(dd, 1H, H-21, 1.4, 7.9); 7.21(t, 1H, H-20, 7.9); 6.86(d, 2H, H-3, H-5, 9.0); 5.10(dd, H-15, $^3J(H^{15}\text{-}H^{14A})$=3.3 Hz, $^3J(H^{15}\text{-}H^{14B})$=8.6 Hz); 4.25(t, 2H, H-8, 7.2); 3.94(dd, 1H, H-11A, sist. AB, $^3J(H^{11A}\text{-}H^{12})$=4.3, $^2J(H^{11A}\text{-}H^{11B})$=9.2); 3.83(dd, 1H, H-11B, sist. AB, $^3J(H^{11B}\text{-}H^{12})$=6.8, $^2J(H^{11A}\text{-}H^{11B})$=9.2); 3.16(dd, 1H, H-14A, sist. AB, $^3J(H^{14A}\text{-}H^{15})$=3.3, $^2J(H^{14A}\text{-}H^{14B})$=12.3); 3.14(m, 1H, H-12); 2.58(dd, 1H, H-14B, sist. AB, $^3J(H^{14B}\text{-}H^{15})$=8.6, $^2J(H^{14A}\text{-}H^{14B})$=12.3); 1.78(sxt, 2H, H-9, 7.2); 1.21(d, 3H, H-13, 6.4); 1.03(t, 3H, H-10, 7.2).

The ratio between the two couples of diastereoisomers was about 1:10.

^{3}C-NMR($CDCl_3$, δ ppm, T=303K): 166.38(C-7); 162.34(C-4); 142.56(C-16); 132.87(C-18); 131.56(C-2, C-6); 129.77(C-17); 129.19(C-19); 127.50(C-20); 125.39(C-21); 123.31(C-1); 114.05(C-3, C-5); 71.92(C-11); 69.50(C-15); 66.28(C-8); 52.27(C-12); 51.98(C-14); 22.18(C-9); 17.70(C-13); 10.53(C-10).

FT-IR(ATR in solid, ν cm^{-1}): 3309w; 3072m; 2967m; 2933m; 2875m; 2848m; 2757m; 1714vs; 1606s; 1510m; 1457w; 1432w; 1415m; 1396w; 1311m; 1271s; 1245vs; 1161s; 1108m; 1084m; 1045m; 1031m; 1008w; 989w; 919w; 890w; 875m; 842m; 784w; 766m; 736w; 717w; 683w; 634w.

Pharmacology

The pharmacological researches have been made in order to investigate the acute toxicity of compounds **5a, 5b, 5c, 5e, 5f, 5g** and **5h** on white male mice, NMRI type. Experimental data demonstrated no mortality or any changes of the motor and sexual behaviour at a dose of 100 mg/kgw. These data agree with other studies which showed a reduced toxicity of the compounds having an aryl-ethanolamine structure [25] and with literature data which specify that compounds having a LD_{50} value of 50-500 mg/kg are considered in the "reduced toxicity" group (Hodge-Sterner scale).

Later pharmacological researches were carried out in order to estimate the effect of these compounds on the basic glucose level at non-diabetic rats (single dose, 100 mg/kg).

Experimental results for the compounds **5a, 5b**, **5g** showed an activity of reducing basic glucose level in comparison with the initial value of every lot as well as the witness lot, statistically significant ($p<0.05$).

Pharmacological screening tests concerning the effect of these compounds (100 mg/kg, p.o) on the glucidic metabolism were carried out on white male rats, Wistar type, to which diabetes has been induced by means of

aloxane (130 mg/kg, i.p.). The comparison of the results has been made with a diabetic witness lot and also with a reference lot which was treated with the selective beta-3-agonist BRL 37344 (25 mg/kg p.o.).

The glucose level and the activity of several enzymes (glucose-6-phosphate-dehydrogenase, glucose-6-phosphatase, hexokinase) have been estimated after repeated administrations (6 days consecutively) of the substances to be tested.

According to our results in diabetic animals, statistically significant ($p<0.05$) decrease was recorded for the activity of glucose 6-phosphate dehydrogenase (G 6PD) and hexokinase while the activity of glucose -6-phosphatse increased ($p>0.05$).

A statistically significant increase in the activity of glucose 6-phosphate dehydrogenase (G 6PD) ($p<0.01$) and hexokinase ($p<0.02$) was recorded after BRL 37344 administration; these results agree with literature data which make mention of an increase in the activity of these enzymes after administering oral antidiabetics to animals with induced diabetes [26, 27]. The same increasing effects in the activity of G 6PD were obtained with the tested substances, as follows: **5a** (maximum stimulating effect on the enzyme activity)**>5f>5e>5c>5h>5g>BRL>5b.**

The enzymatic activity of hexokinase increased for the tested compounds as follows: **5e** (maximum stimulating effect on the enzyme activity) **>5c>5a>BRL>5f>5g.** The compounds **5b** and **5h** did not modify the enzymatic activity of hexokinase, by comparison with the diabetic witness lot.

After BRL 37344 administration, the enzymatic activity of glucose-6-phosphatase had a statistically significant decrease ($p<0.001$) in comparison with the diabetic lot, which is mentioned in the references [28]. After administering the substances to be tested their effect on the enzymatic activity of glucose-6-phosphatase changed, as follows: **5g** (maximum inhibitory effect on the enzyme activity)**>BRL>5b>5f >5a>5c>5e>5h.**

The blood sugar level of the diabetic animals which were treated with the compound **5e** had a 42.3% decrease by comparison with the diabetic witness lot and a 37.68% decrease for the compound **5g.**

By correlating these experimental data about the influencing on the activity of the three enzymes with the effect of the tested compounds on the basic glucose level and on hyperglicemy at the diabetic rat, we come to the conclusion that the compounds **5e** and **5g** have an antidiabetic potential.

Results and discusssions

At present, it does not exist an acceptable treatment for diabetic patients. Thus, the necessity of an improved therapy stimulated the interest for beta-3-adrenergic type receptor agonists from the aryl-ethanolamine group. Therefore , we focused on the synthesis of new compounds (**5a-i**) with the purpose of investigating their physico-chemical properties and testing their biological activity.

The synthesized compounds were obtained by modifying the substituent R on the aromatic ring of the aryl-ethanolamines and of the substituent Y from the side chain of the ketone.

There are two asymmetric carbon atoms in the structure of the compounds (**5a-i**); the new products were isolated and characterized under the form of a mixture of diastereoisomers; their mutual ratio is different at each of the 9 new structures and has been estimated by NMR spectra.

The raw materials required for the synthesis are the arylethanolamines (**3a-e**) and the ketones (**4a-c**); they are known and have been obtained according to the methods presented in the references [13-17].

According to the scheme 1, the main element characterizing this synthesis was the reductive amination of the ketones (**4a-c**) with the ethanolamines (**3a-e**).

In accordance with the literature data for similar products, this can be achieved (depending on the nature of the reducing agent), as follows:

a) in two stages involving the formation of the corresponding Schiff base as an intermediate [7, 14, 19-21] or

b) directly, thus obtaining the corresponding amine in a single phase [22-24].

The second method was used with a mild and selective reducing agent such as sodium triacetoxyborohydride in dichloroethane. The reaction develops in mild conditions and with good yields.

The nine new compounds which were obtained by synthesis have been characterized by melting point, IR and NMR spectra (^{1}H and ^{13}C) and their purity was estimated by TLC and elemental analysis.

The NMR spectra were cleared up for every structure (**5a-i**), the proportion of the two resulted diastereoisomers because of the two asymmetric carbon atoms being specified.

For the purpose of estimating their antidiabetic activity, the new compounds were biologically tested as follows: acute toxicity, the effect on the basic glycemia which was investigated on nondiabetic and diabetic rats, the effect upon the activity of three enzymes, namely, glucose-6-phosphatedehydrogenase, glucose-6-phosphatase and hexokinase.

Conclusions

Nine new compounds (**5a-i**) from the arylethanolamine group were synthesized by direct reductive amination of the ketones (**4a-c**) with the ethanolamines (**3a-d**).

The new compounds belonging to the beta-3-adrenoreceptors agonists group were obtained by synthesis for the purpose of investigating their biological activity as antidiabetic/antiobesity agents and also they were characterized by: elemental analysis, melting points, FT-IR, ^{1}H-NMR and ^{13}C-NMR. spectra.

NMR spectra pointed out the presence of dia-stereoisomers (because of the two asymmetric carbon atoms in the molecule) in various proportions which are specific for every compound (**5a-i**).

The pharmacological screening tests concerning the effect of the new synthesized substances on the glucidic metabolism of nondiabetic and diabetic rats pointed out that the compounds **5e** and **5g** are potential antidiabetic agents.

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