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Synthesis of new N-substituted isoindoles with an expected anxiolytic and/or β–adrenolytic activity. Derivatives of 4-isobutoxy-4,7-ethano-3a,4,7,7a-tetrahydro-1H-isoindole--1,3,6(2H)trione

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This paper presents the synthesis of a number of new derivatives of 4-isobutoxy-4,7-ethano-3a,4,7,7a-tetrahydro-1H-isoindole-1,3,6(2H)trione with an expected anxiolytic and/or β–adrenolytic activity.

1. INTRODUCTION

Anxiolytics of new generation (buspirone, ipsapirone and tandospirone) display high affinity for the 5-HT_{1A} and D_2 types of the serotonin receptors. These drugs contain 4-aryl(heteroaryl)-1-piperazinealkyl moiety linked with the imide nitrogen, which is believed to give high potency in treatment of anxiety and depression [1].

The currently used β–adrenoreceptor antagonists, like: albuterol, naproxen, bisoprolol, karteolol, contain 3-isopropylamino-2-hydroxypropyl group associated with their antiarrhytmic and hypotensive activity. A number of β–adrenolytic drugs display 5-HT_{1A} affinity, for example pindolol blocks these receptors [2].

Searching for new compounds activating the central serotonin system [3,4] a number of N-(3-(4-aryl-1-piperazinyl)-propyl)-substituted derivatives of 4-isobutoxy-4,7-ethano-3a,4,7,7a-tetrahydro-1H-isoindole-1,3,6(2H)trione were synthesized. Moreover in order to continue our research on new compounds affecting the circulation system [5,6], we decided to synthesize a series of N-1--(2,3-epoxypropyl)-substituted derivatives of that isoindole as well.

The starting material for the synthesis of the desired compounds was 4-isobutoxy-4,7-ethano-3a,4,7,7a-tetrahydro-1H-isoindole-1,3,6(2H)trione **II**,

the product of hydrolysis of 6–acetoxy–4–isobutoxy-4,7-ethano-3a,4,7,7a--tetrahydro-1H-isoindole-1,3(2H)dione **I**. The latter was obtained in Diels--Alder reaction of 3-isobutoxy-2-cyclohexen-1-one with maleimide.

By alkylation of the isoindole **II** with 1-bromo-3-chloropropane, N-(3--bromopropyl) substituted derivative **III** was obtained. Next the compound **III** was condensed with appropriate amines **V-X** (Scheme 1).

As a result of the reaction of the compound **II** with 1-chloro-2,3--epoxypropane, N-(2,3-epoxypropyl) substituted derivative **IV** was produced, condensed then with a series of amines **XI-XVI** (Scheme 1).

The structures of new derivatives of compound **II** were confirmed by ^{1}H NMR spectra and elemental analysis (Table 1).

Tab. 1. Physical and ^{1}H NMR spectra data of compounds [**I-XVI**]

Comp. No	Formula, Molecular weight	Solvent m.p. [ºC]	Yield %	^{1}H NMR δ (ppm) 200/400 MHz, $CDCl_3$
1	**2**	**3**	**4**	**5**
I	$C_{16}H_{21}NO_5$ 307.35	benzene 140-141	40	^{1}H NMR,δ (ppm), 200 MHz, $CDCl_3$ 8.92 (br. s, 1H, NH) 5.79 (s, 1H, C5-H) 3.52 (dd, $J_1=J_2$= 6 Hz, 1H, OCH) 3.22 (dd, $J_1=J_2$=7.4 Hz, 1H, OCH) 3.1 (m, 1H, C7-H) 3.02 (m, 2H, $C3_a$-H, $C7_a$-H) 2.13 (s, 3H, $\underline{CH_3}COO$) 1.99-1.57 (m, 5H, C8-H, C9-H, C$\underline{H}$-$(CH_3)_2$) 0.97 (d, J=3.4 Hz, 3H, CH-$\underline{(CH_3)_2}$) 0.94 (d, J=3.4 Hz, 3H, CH-$\underline{(CH_3)_2}$)
II	$C_{14}H_{19}NO_4$ 265,32	ethanol 164-165.5	75	^{1}H NMR,δ (ppm), 200 MHz, $CDCl_3$ 9.28 (s, 1H, NH) 3.46 (m, 1H, OCH) 3.36 (dd, $J_1=J_2$=1.8 Hz, 1H, $C3_a$-H) 3.24 (m, 2H, OCH, $C7_a$-H) 2.80 (m, 1H, C7-H) 2.46 (m, 2H, C5-H) 2.13-1.68 (m, 5H, C8-H, C9-H, C$\underline{H}$-$(CH_3)_2$) 0.93 (d, J= 6,8 Hz, 6H, CH-$\underline{(CH_3)_2}$)

1	2	3	4	5
III	$C_{17}H_{24}NO_4Br$ 386.30	oil	45	^{1}H NMR,δ (ppm), 200 MHz, $CDCl_3$ 3.63 (m, 2H, OCH, C1'-H) 3.48 (m, 1H, C1'-H) 3.35-3.12 (m, 5H, C3'-H, 0CH, $C3_a$-H, $C7_a$-H) 2.85 (m, 1H, C7-H) 2.52 (dd, $J_1=J_2$=2,2 Hz, 1H, C5-H) 2.22 (dd, $J_1=J_1$=2,6 Hz, 1H, C5-H) 2.15-1.74 (m,7H,C2'-H,C8-H, C9-H, C<u>H</u>-$(CH_3)_2$) 0.97 (d, J=1,6 Hz, 3H, CH-<u>CH_3)</u> 0.94 (d, j= 1,2 Hz, 3H, CH-<u>CH_3)</u>
IV	$C_{17}H_{23}NO_5$ 321.38	oil	85	^{1}H NMR,δ (ppm), 400 MHz, $CDCl_3$ 3,73 (m,2H, C1'-H) 3.48 (m, 1H, OC<u>H</u>) 3.32 (m,1H, $C3_a$-H) 3.19 (m, 1H, OC<u>H</u>) 3.11 (m, 1H, $C7_a$-H) 2.87 (m, 1H, C7-H) 2.75 (m, 1H, C2'-H) 2.62-2.50 (m, 1H, C5-H) 2.38-2.30 (m, 1H, C3'-H) 2.12 (m, 1H, C3'-H) 2.09-1.65 (m, 6H, C5-H,C8-H, C9-H, C<u>H</u>-$(CH_3)_2$) 0.95 (m, 6H, CH-<u>$(CH_3)_2$</u>)
V	$C_{28}H_{39}N_3O_5$ 497.65	oil	40	^{1}H NMR,δ (ppm), 200 MHz, $CDCl_3$ 6.94 (m, 4H, H_{arom}) 3.86 (s, 3H, OCH_3) 3.53 (m, 3H, OCH, C1'-H) 3.26 (dd, $J_1=J_2$=2,4 Hz, 1H, $C3_a$-H) 3.18 (m, 2H, OCH, $C7_a$-H) 3.08 (m, 4H, $(CH_2)_2$-N-Φ) 2.85 (m, 1H, C7-H) 2.61 (m, 5H, C5-H, $(CH_2)_2$-N) 2.39 (m, 2H, C3'-H) 2.25 (dd, $J_1=J_2$=2,4 Hz, 1H, C5-H) 2.10-1.66 (m,7H, C2'-H,C8-H, C9-H,C<u>H</u>-$(CH_3)_2$) 0.97 (d, J=1,6 Hz, 3H, CH-<u>CH_3)</u> 0.95 (d, j= 1,6 Hz, 3H, CH-<u>CH_3)</u>

1	2	3	4	5
VI	$C_{25}H_{35}N_4O_4$ 469.60	octane 120-121	30	^{1}H NMR,δ (ppm), 400 MHz, $CDCl_3$ 8.29 (d, J=4.4 Hz, 2H, Hα pirimidine) 6.46 (dd, $J_1=J_2$= 4.6 Hz, 1H, H_{β} pirimidine) 3.79 (m, 4H, $(CH_2)_2$-N-Φ) 3.55 (t, J= 7.2 Hz, 2H, C1'-H) 3.48 (m, 1H, C7-H) 3.26 (d, J=9,6 Hz, 1H, $C3_a$-H) 3.15 (m, 2H, OCH_2) 2.84 (d, J=2,4 Hz, 1H, $C7_a$-H) 2.47 (m, 6H, C3'-H, $(CH_2)_2$-N-Φ) 2.34 (dd, 2H, $J_1=J_2$= 6,8 Hz, C5-H) 2.09-1.71 (m, 7H, C8-H, C9-H, C2'-H, CH-CH_3) 0.96 (d, J=3,2 Hz, 3H, CH-CH_3) 0.94 (d, J= 3,2 Hz, 3H, CH-CH_3)
VII	$C_{27}H_{36}N_3O_4F$ 503.62	octane 79,5-80,5	30	^{1}H NMR,δ (ppm), 200 MHz, $CDCl_3$ 6.95 (m, 2H, H_{arom}) 6.87 (m, 2H, H_{arom}) 3.56 (m, 2H, OCH, C1'-H) 3.48 (m, 1H, C1'-H) 3.27 (m, 7H, OCH, $C3_a$-H, $C7_a$-H, $(CH_2)_2$-N-Φ) 2.83 (m, 1H, C7-H) 2.67 (m, 4H, $(CH_2)_2$-N) 2.48 (m, 3H, C3'-H, C5-H) 2.24 (dd, $J_1=J_2$=2 Hz, 1H, C5-H) 2.05-1.78 (m,7H, C2'-H,C8-H,C9-H, CH-$(CH_3)_2$) 0.95 (m, 6H, CH-($CH_3)_2$)
VIII	$C_{26}H_{36}N_4O_4$ 468.61	oil	30	^{1}H NMR,δ (ppm), 400 MHz, $CDCl_3$ 8,17 (m, $1H_{arom}$) 7,47 (m, $1H_{arom}$) 6,61 (m, $2H_{arom}$) 3,58-3,47 (m, 7H, C1'-H, C7, $(CH_2)_2$- N-Φ) 3,26 (d, J=8 Hz, 1H, $C3_a$-H) 3,16 (m, 2H, OCH_2) 2,85 (d, J=4 Hz, 1H, $C7_a$-H) 2,47 (m, 6H, C3'-H, $(CH_2)_2$-N) 2,37 (dd, $J_1=J_2$=8 Hz, 1H, C5-H) 2,27 (m, 1H, C5-H) 2,05-1,78 9m, 7H, C8-H, C9-H, C2'-H, CH-$(CH_3)_2$) 0.96 (d, J=3,2 Hz, 3H, CH-CH_3) 0.94 (d, J= 3,2 Hz, 3H, CH-CH_3)

1	2	3	4	5
IX	$C_{27}H_{37}N_3O_4$ 467.62	octane 108-109	30	^{1}H NMR,δ (ppm), 400 MHz, $CDCl_3$ 6.93-6.83 (m, 5H, H_{arom}) 3.56 (t, J=7 Hz, 2H, C1'-H) 3.48 (t, J=7 Hz, 1H, OCH) 3.27 (m, 1H, $C3_a$-H) 3.15 (m, 6H, OCH, $C7_a$-H, $(CH_2)_2$-N-Φ) 2.85 (m, 1H, C7-H) 2.60 (m, 4H, $(CH_2)_2$-N) 2.53-2.38 (m, 3H, C3'-H, C5-H) 2.24 (dd, $J_1=J_2=2,8$ Hz, J_2=... Hz, 1H, C5-H) 2.07-1.75 (m, 7H, C2'-H,C8-H,C9-H,C<u>H</u>-$(CH_3)_2$) 0.96 (d, J=3,2 Hz, 3H, CH-<u>CH_3</u>) 0.94 (d, J= 3,2 Hz, 3H, CH-<u>CH_3</u>)
X	$C_{28}H_{39}N_3O_4$ 481.65	oil	25	^{1}H NMR,δ (ppm), 400 MHz, $CDCl_3$ 7.30 (s, 5H, H_{arom}) 3.52-3.45 (m, 5H,OCH, C1'-H, C3'-H, N-CH_2-Φ) 3.27-3.07 (m, 3H, OCH, C1'-H, C3'-H) 2.82 (d, J=2,8 Hz, 1H, C7-H) 2.5-2.19 (m, 10H, $(CH_2)_2$-N-Φ, C5-H) 2.05-1.84 (m, 4H, $C3_a$-H, $C7_a$-H, C2'-H) 1.78-1.64 (m, 5H, C8-H, C9-H, C<u>H</u>-$(CH_3)_2$) 0.95 (d, J=2,4 Hz, 3H, CH-<u>CH_3</u>) 0.93 (d, J= 2,8 Hz, 3H, CH-<u>CH_3</u>)
XI	$C_{20}H_{32}N_2O_5$ 380.50	oil	35	^{1}H NMR,δ (ppm), 400 MHz, $CDCl_3$ 5.45 (br.s, 2H, O<u>H</u>, N<u>H</u>), 4.28 (m, 1H, C2'-H) 3.61-3.33 (m, 5H, OCH_2, C1'-H, N-C<u>H</u>) 3.15 (t, J=7.2 Hz, 1H, $C3_a$-H) 3.04 (m, 1H, $C7_a$-H) 2.78 (m, 2H, C5-H, C7-H) 2.46-2.22 (m, 2H, C3'-H) 2.10-1.80 (m, 5H, C5-H, C8-H, C9-H) 1.69 (m, 1H, C<u>H</u>-$(CH_3)_2$) 1.40 (m, 6H, N-CH-(C<u>H_3</u>)<u>$_2$</u>) 0.91 (d, J=6 Hz, 6H, CH-(C<u>H_3</u>)<u>$_2$</u>)

1	2	3	4	5
XII	$C_{19}H_{30}N_2O_5$ 366.47	oil	40	^{1}H NMR,δ (ppm), 400 MHz, $CDCl_3$ 3.91-3.80 (m, 1H, C2'-H) 3.62-3.39 (m, 4H, OCH_2, C1'-H) 3.29 (m, 2H, $C3_a$-H, $C7_a$-H) 3.17 (m, 1H, C5-H) 2.84 (m, 1H, C7-H) 2.50-2.18 (m, 10 H, C5-H, C3'-H, -N-$(CH_3)_2$) 2.07-1.66 (m, 5H, C<u>H</u>-$(CH_3)_2$, C7-H, C8-H) 0.93 (m, 6H, CH-(C<u>H</u>$_3)_2$)
XIII	$C_{21}H_{34}N_2O_5$ 394.52	oil	40	^{1}H NMR,δ (ppm), 400 MHz, $CDCl_3$ 3.81-3.71 (m, 1H, C2'-H) 3.61-3.35 (m, 4H, OCH_2, C1'-H) 3.29 (m, 2H, $C3_a$-H, $C7_a$-H) 3.16 (m, 1H, C5-H) 2.83 (m, 1H, C7-H) 2.63-2.39 (m, 7H, C5-H,CH_2-N, 2*N-<u>CH_2</u>CH_3 2.26 (m, 1H, C<u>H</u>-$(CH_3)_2$) 2.08-1.69 (m, 4H, C8-H, C9-H) 0.97 (t, J=8 Hz, 6H, 2* N-CH_2<u>CH_3</u>) 0.93 (d, J=3.2 Hz, 3H, CH-<u>CH_3</u>) 0.91 (d, J=2.8 Hz, 3H, CH-<u>CH_3</u>)
XIV	$C_{21}H_{34}N_2O_5$ 394.52	oil	35	^{1}H NMR,δ (ppm), 400 MHz, $CDCl_3$ 4.27 (m, 1H, C2'-H) 3.41-3.65 (m, 4H, OCH_2, C1'-H) 3.16 (t, J= 7,6 Hz, 1H, $C3_a$-H) 3.07 (m, 1H, $C7_a$) 2.76 (m, 2H, C7-H, C5-H) 2.47-2.23 (m, 2H, C3'-H) 2.11-1.80 (m, 5H, C5-H, C8-H, C9-H) 1.67 (m, 1H, C<u>H</u>-$(CH_3)_2$) 1.45 (s, 9H, C-(<u>CH_3</u>$)_3$) 0.93 (d, J=6 Hz, 6H, CH-(C<u>H</u>$_3)_2$)
XV	$C_{22}H_{34}N_2O_5$ 406.53	oil	30	^{1}H NMR,δ (ppm), 400 MHz, $CDCl_3$ 3.88-3.70 (m, 1H, C2'-H) 3.58-3.26 (m, 4H, OCH_2, C1'-H) 3.28 (m, 1H, $C3_a$-H) 3.16 (m, 2H, C5-H) 2.81 (m, 1H, C7-H) 2.49-3.39 (m, 4H, CH_2 piperidine) 2.27-2.04 (m, 3H, $C7_a$-H, C3'-H) 1.95-1.66 (m, 5H, C<u>H</u>-$(CH_3)_2$, C8-H, C9-H) 1.50-1.38 (m, 6H, 3*CH_2 piperidine) 0.91-0.90 (m, 6H, CH-(C<u>H</u>$_3)_2$)

1	2	3	4	5
XVI	$C_{22}H_{35}N_3O_5$ 421.55	oil	30	^{1}H NMR,δ (ppm), 400 MHz, $CDCl_3$ 3.83-3.93 (m, 1H, C2'-H) 3.64-3.69 (m, 4H, OCH_2, C1'-H) 3.16 (m, 1H, C5-H) 2.85 (m, 2H, $C3_a$, $C7_a$) 2.69 (m, 1H, C7-H) 2.24-2.55 (m,13H, 4*CH_2 piperidine,C3'-H, N-CH_3) 1.73-2.07 (m,6H, C5-H,C<u>H</u>-$(CH_3)_2$, C8-H,C9-H) 0.94 (m, 6H, CH-($C\underline{H_3}$)$_2$)

2. EXPERIMENTAL

Melting points were determined in a capillary Kofler's apparatus and uncorrected. ^{1}H NMR spectra were recorded on a Varian UNITYplus – 200 spectrophotometer and INSTRUM – 400 spectrophotometer. The results of elemental analysis (C, H, N) were within 0.5 % of theoretical values.

6–acetoxy–4–isobutoxy-4,7-ethano-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)dione I

A mixture of 3-isobutoxy-2-cyclohexen-1-one (10 g, 0,059 mol), maleimide (6.92 g, 0.071 mol), isopropenyl acetate (30 ml) and p-toluenosulphonic acid (100 mg) was refluxed for 21 h. The solvent was evaporated. The residue was crystallized from benzene or mixture hexane: ethyl acetate (1:1).

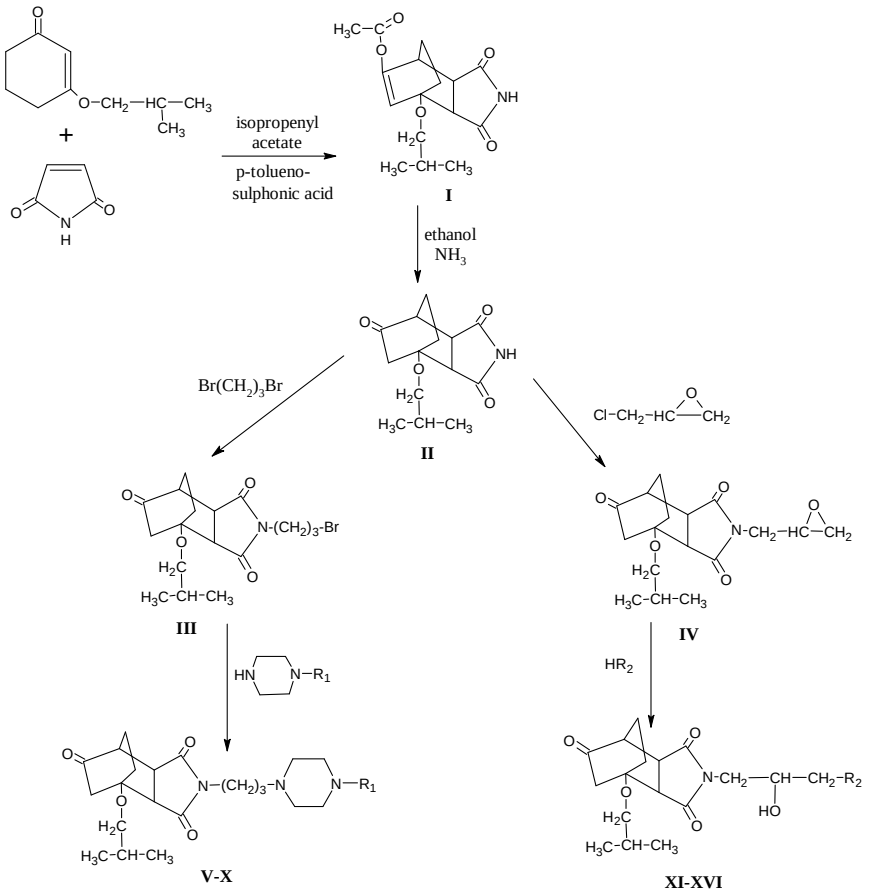
4-isobutoxy-4,7-ethano-3a,4,7,7a-tetrahydro-1H-isoindole-1,3,6(2H)trione II

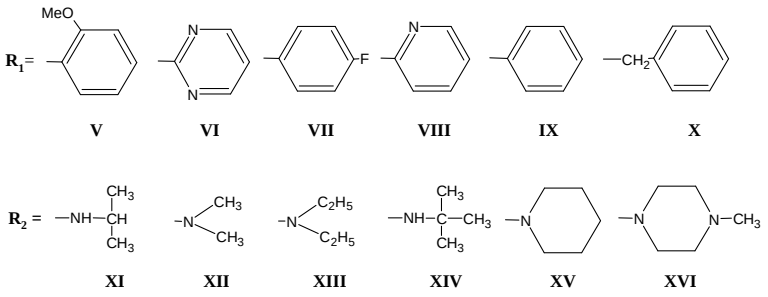
A mixture of compound **I** (10 g, 0.033 mol), anhydrous ethanol (80 ml) and 20 % ammonia solution (15 ml) was refluxed for 1 h. The solvent was evaporated. The residue was crystallized from ethanol.

N-(3-bromopropyl)-4-isobutoxy-4,7-ethano-3a,4,7,7a-tetrahydro-1H-isoindole-1,3,6(2H)trione III

A mixture of isoindole **II** (2 g, 0.0075 mol), dibromopropane (4.57 g, 0.023 mol) and anhydrous K_2CO_3 (2 g, 0.014 mol) in acetone (100 ml) was refluxed for 30 h. The inorganic precipitate was filtered off and the solvent was evaporated. Compound **III** was purified by column chromatography (silica gel, developing system: chloroform: methanol).

Scheme 1.


isopropenyl acetate
p-toluenosulphonic acid
ethanol
NH3
Br(CH2)3Br
I
II
III
IV
V-X
XI-XVI


R1=
V
VI
VII
VIII
IX
X
R2 =
XI
XII
XIII
XIV
XV
XVI

N-(2,3-epoxypropyl)-4-isobutoxy-4,7-ethano-3a,4,7,7a-tetrahydro-1H-isoindole-1,3,6(2H)trione IV

A mixture of isoindole **II** (3 g, 0.0113 mol), 1-chloro-2,3-epoxypropane (28,3 ml) and anhydrous K_2CO_3 (3 g, 0.022 mol) was refluxed for 30 h. The inorganic precipitate was filtered off and the solvent was evaporated. Compound **IV** was purified by column chromatography (silica gel, developing system: chloroform: methanol).

General method of preparing of N-[3-(4-aryl-1-piperazinyl)propyl]-4-isobutoxy-4,7-ethano-3a,4,7,7a-tetrahydro-1H-isoindole-1,3,6(2H)trione derivatives V-X

A mixture of compound **III** (0.5 g, 0.0019 mol), anhydrous K_2CO_3 (0.5 g, 0.0036 mol), KI (0.2 g, 0.0012 mol) and the corresponding N-substituted piperazine (0.0038 mol) was refluxed in 2-butanone (50 ml) for 30-50 h. The inorganic precipitate was filtered off and the solvent was evaporated. Compounds **V-X** were crystallized from appropriate solvent or purified by column chromatography (silica gel, developing system: chloroform: methanol).

General method of preparing of N-(2,3-epoxypropyl)- 4-isobutoxy-4,7--ethano-3a,4,7,7a-tetrahydro-1H-isoindole-1,3,6(2H)trione derivatives XI--XVI

A mixture of compound **IV** (0.5 g, 0.0016 mol), the corresponding N-substituted piperazine (0.0078 mol), methanol (40 ml) and distilled water (1 ml) was refluxed for 30 h. The solvent was evaporated. Compounds **XI-XVI** were purified by column chromatography (silica gel, developing system: chloroform: methanol).

3. REFERENCES

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CURRICULUM VITAE

Anna Wojciechowska was born in Kozienice in 1977. In 1996 she was graduated from secondary school in Radom. The same year she began studies in The Department of Chemistry at Warsaw University. In 2001 she graduated from the University obtaining M.Sc. title. Since 2001 she has worked in The Chair and Department of Medical Chemistry at The Medical University of Warsaw. Fields of her interest are organic synthesis, synthesis of anxiolytic antidepressive and β-adrenolytic compounds.
She is a co-author of 1 publication and 4 posters.