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Synthesis of 5-(3-amino-2-hydroxypropoxy)-2,3-diphenyl--1,2,4-triazol derivatives

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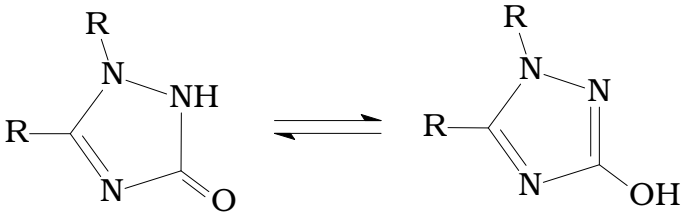
This paper presents the preparation of a number of new derivatives of 2,3-diphenyl-1,2,4-triazol-5-ol with an expected β-adrenolytic activity.

1. INTRODUCTION

1,2,4-Triazolin-5-one derivatives can exist in two tautomeric forms.



In earlier papers studying properties of these derivatives, some nucleophilic substitution reactions were carried out to obtain O- or N- derivatives [1,-5].

In the case of 4-phenyl-1,2,4-triazolin-5-one and 3,4-diphenyl-1,2,4--triazolin-5-one in the nucleophilic substitution reaction a lot of new compounds with potential pharmacological action were obtained, e.g. N^1-aminomethyl derivatives and N^1-aminoalkanol derivatives of soothing effect on the central nervous system [2, 3]. This paper is a continuation of investigations on nucleophilic substitution of pharmacophoric group into the 1,2,4-triazolin-5--one system introduced 3-aminopropyl group characteristic for compound possessing analgesic [6, 7], hypotensive, antiarrhytmic [8, 9] actions.

2,3-diphenyl-1,2,4-triazol-5-ol obtained in the reaction of phenyl hydrazine and benzoyl isocyanate, were used as initial compounds [10]. The reaction of 2,3-diphenyl-1,2,4-triazol-5-ol with 1-chloro-2,3-epoxypropane in the presence

of anhydrous K_2CO_3 was carried out at room temperature. In order to react the alcoholic hydroxyl group with the oxirane system, an excess of 1-chloro-2,3--epoxypropane was used [11].

The characteristic absorption band about 1700–1715 cm^{-1} for C=O group was not observed in the IR spectrum of the compound **I**. The data show the compound **I** occurs in the 1,2,4-triazol-5-ol form. Then the compound I was converted with appropriate amines into corresponding aminoalkanol derivatives of 1,2,4-triazole [**IIa,b –VIIa,b**]. Scheme 1. The reactions were performed by heating the reactants in methanol in the presence of small quantities of water.

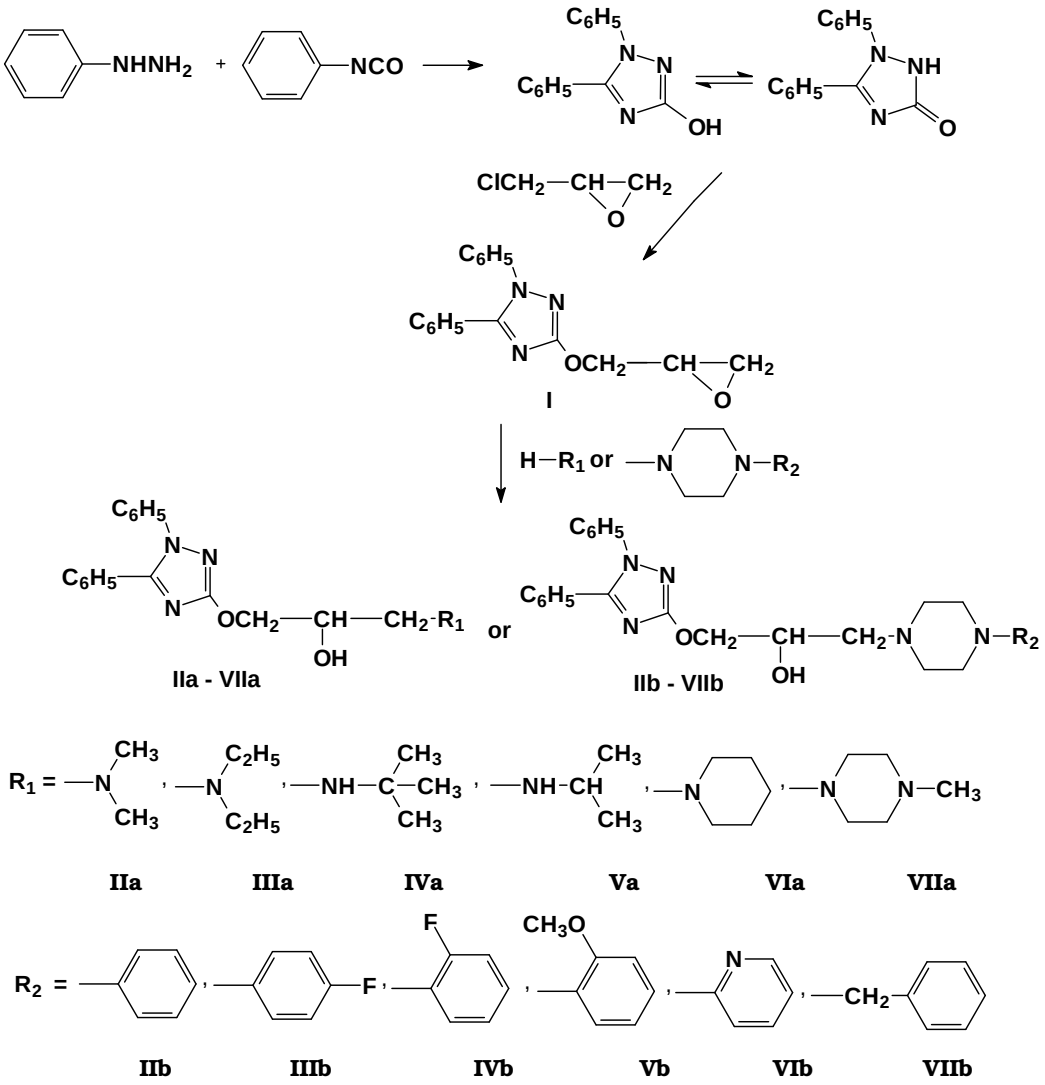
The structure of all new compounds was confirmed by elemental analysis as well as by the ^1H NMR spectra. Physical and analytical properties for compounds **[I and IIa,b - VIIa,b**] are summarized in Table 1.

2. EXPERIMENTAL

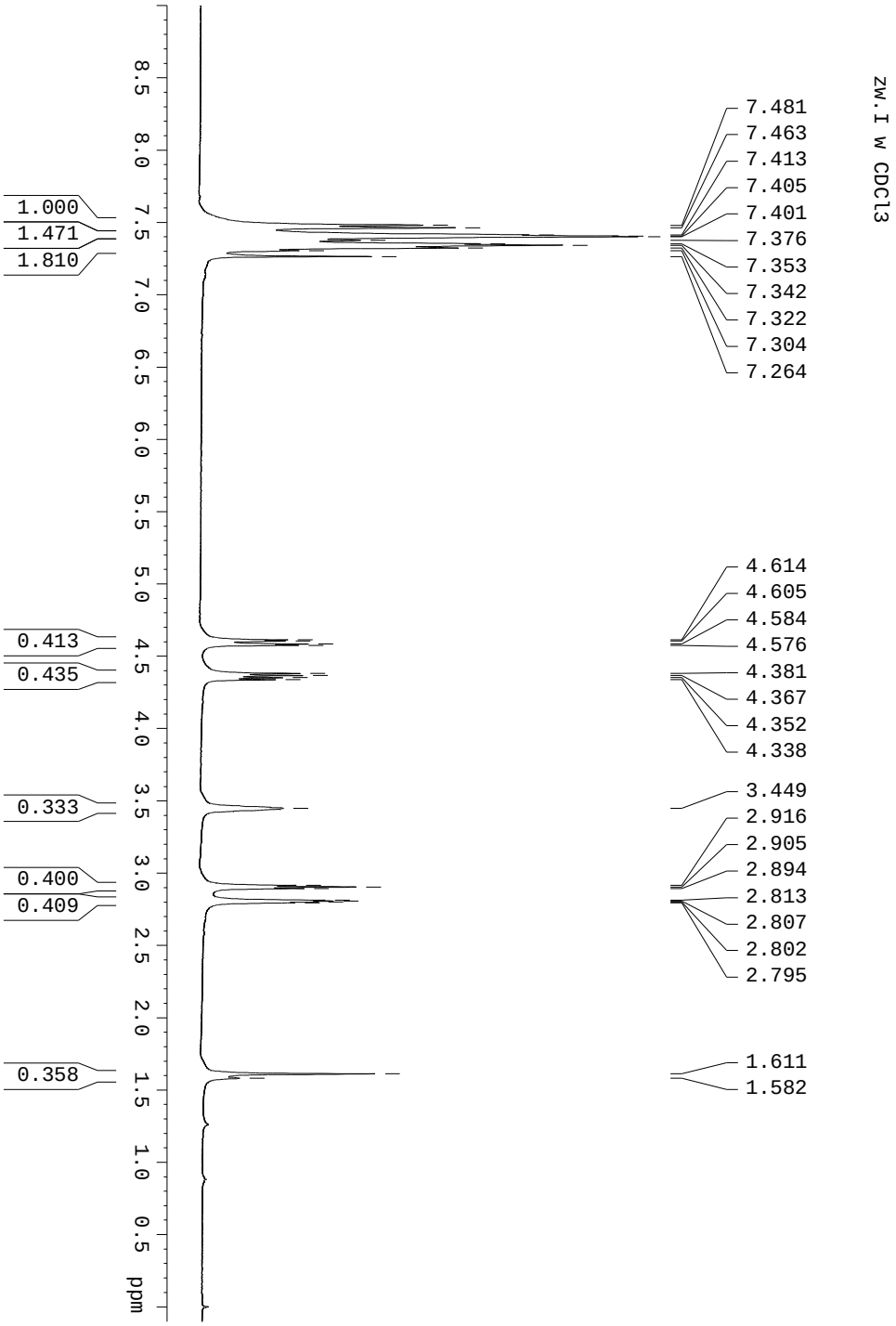
Melting points were determined in a capillary Kofler's apparatus and are uncorrected. The ^1H NMR spectra were recorded in Warsaw Medical University, Pharmacy Department on a Brucer AVANCE DMX400 spectrometer, operating at 400.13 MHz for ^1H or in the Department of Chemistry, Warsaw University on a Varian UNITYplus-200 spectrometer, operating at 199.97 MHz for ^1H. The chemical shift values, expressed in ppm, were references downfield to TMS at ambient temperature. The IR spectra were recorded in KBr a Perkin Elmer FT 1725X spectrophotometer. Microanalysis was performed at the Microanalysis Laboratory of Warsaw Technical University and all values were within ± 0.4% of the calculated compositions. Column flash chromatography and TLC were performed on silica gel 60 (Merck) using chloroform/methanol (19:1) mixture or chloroform as eluent.

5-(2,3-epoxypropoxy)-2,3-diphenyl-1,2,4-triazol [i]

A mixture of 2,3-diphenyl-1,2,4-triazol-5-ol (0.015 mol), 1-chloro-2,3--epoxypropane (40 cm^3) and anhydrous K_2CO_3 (4.5g, 0.033 mol) was left at room temperature for 48 h. The inorganic precipitate was filtered off, the solvent was evaporated. The oily residue was extracted several times with boiling heptane. The crude product precipitated on cooling. Then the mixture was filtered and purified by flash chromatography (a developing system: chloroform).


NHNH2
NCO
C6H5
OH
NH
O
ClCH2—CH—CH2
OCH2—CH—CH2
I
H—R1 or
N—R2
OCH2—CH—CH2-R1
OH
IIa - VIIa
or
OCH2—CH—CH2-N
IIb - VIIb
R1 =
CH3
C2H5
NH—C—CH3
NH—CH
CH3O
R2 =
CH2
IIa
IIIa
IVa
Va
VIa
VIIa
IIb
IIIb
IVb
Vb
VIb
VIIb

Scheme 1.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7.481
7.463
7.413
7.405
7.401
7.376
7.353
7.342
7.322
7.304
7.264
4.614
4.605
4.584
4.576
4.381
4.367
4.352
4.338
3.449
2.916
2.905
2.894
2.813
2.807
2.802
2.795
1.611
1.582
1.000
1.471
1.810
0.413
0.435
0.333
0.400
0.409
0.358
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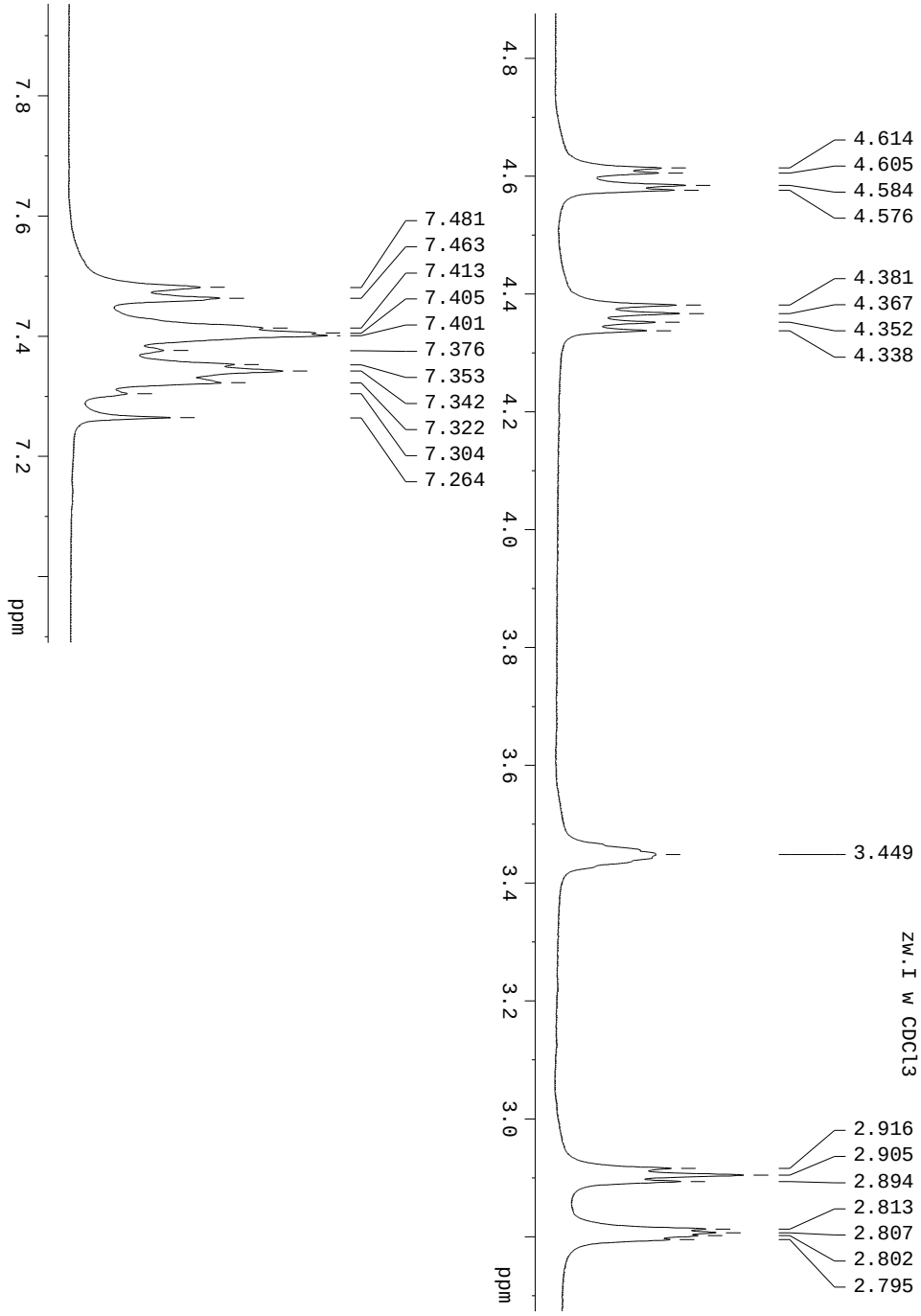
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ppm
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4.381
4.367
4.352
4.338
3.449
2.916
2.905
2.894
2.813
2.807
2.802
2.795
zw.I w CDCl3
ppm

Tab. 1. Physicochemical and spectral properties of compounds: [I, IIa,b – VIIa, b]

Comp. no.	Formula, molecular mass	M.p. [^{0}C]	Yield [%]	Analyses (calcul./found)			^{1}H NMR ($CDCl_3$) δ (ppm)
				C%	H%	N%	
I	$C_{17}H_{15}N_3O_2$ 293.1	108-110	74	69.64 70.0	5.11 5.1	14.33 14.5	7.30-7.48 (m, 10H, arom.) 4.6 (dd, 1H, CH_2, J = 5.3 Hz); 4.36 (dd, 1H, CH_2, J= 6.6Hz); 3.44 (m, 1H, CH); 2.9 (dd, 1H, CH_2, J = 4Hz); 2.8 (dd, 1H, CH_2, J = 2.66Hz)
IIa	$C_{19}H_{22}N_4O_2$ 338.40	139	68	67.44 67.75	6.55 6.48	16.56 17.02	7.29-7.48 (m, 10H, arom.); 4.35-4.46 (qq, 2H, CH_2-O); 4.09-4.1 (m, 1H, CH-O); 2.4-2.63 (m, 2H, CH_2-N); 2.32 (s, 6H, CH_3)
IIIa	$C_{21}H_{26}N_4O_2$ 366.45	78	65	68.83 68.73	7.15 7.2	15.29 15.03	7.29-7.48 (m, 10H, arom.); 4.4 (d, 2H, CH_2, J=8Hz); 4.07 (m, 1H, CH-O); 2,56-2.71 (m, 6H, CH_2); 1.06 (t, 6H, CH_3, J=7.2Hz)
IVa	$C_{21}H_{26}N_4O_2$ 366.45	161-2	70	68.82 68.88	7.15 7.15	15.29 15.28	7.3-7.47 (m, 10H, arom.); 4.41 (d, 2H, CH_2-O, J=5.2Hz); 4.12-4.13 (m, 1H, CH-O); 2.78-2.94(m, 2H, CH_2-N); 1.68 (s, 9H, CH_3)
Va	$C_{20}H_{24}N_4O_2$ 352,4	127-8	60	68.16 67.95	6.86 6.91	15.9 15.76	7.3-7.47 (m, 10H, arom); 4.36-4.43 (m, 2H, CH_2); 4.07-4.12 (m, 1H, CH-O); 2.74-2.9 (m, 2H, CH-N); 1.07 (d, 6H, CH_3, J=6.4Hz)
VIa	$C_{22}H_{26}N_4O_2$ 378.46	123-124	80	69.81 70.06	6.92 6.84	14.81 14.71	7.37-7.47 (m, 10H, arom.); 4.96 (s, 1H, OH); 3.99-4.16 (m, 2H, CH_2); 4.49-4.36 (m, 2H, CH_2); 2.28-2.46 (m, 6H, $(CH_2)_2$ piper, CH_2); 1.23-1.57 (m, 6H $(CH_2)_3$ piper., CH_2)
VIIa	$C_{22}H_{27}N_5O_2$ 393.51	99-100	76	67.15 67.12	6.91 6.62	17.80 17.62	7.29-7.47 (m, 10H, arom.); 4.35-4.43 (dq, 2H, CH_2); 4.12-4.17 (m, 1H, CH-O); 3.6 (s, 1H, OH); 2.46-2.7 (m, 10H, CH_2); 2.29 (s, 3H, CH_3)

	Formula, molecular mass	M.p. [^{0}C]	Yield [%]	Analyses (calcul./found)			^{1}H NMR ($CDCl_3$) δ (ppm)
				C%	H%	N%	
IIb	$C_{27}H_{29}N_5O_2$ 455.54	181-182	92	71.18 71.02	6.42 6.31	15.38 15.34	7.29-7.48 (m, 10H, arom.); 6.86-6.94 (m, 5H, arom.); 4.45 (s, 2H, CH_2); 4.29 (s, 1H, CH-O); 3.28 (s, 4H, CH_2); 2.91 (s, 2H, CH_2-N); 2.77-2.78 (m, 4H, $(CH_2)_2$-N)
IIIb	$C_{27}H_{28}FN_5O_2$ 473.54	130	74	68.48 68.56	5.96 5.82	14.79 14.79	7.26-7.48(m, 10H, arom.); 6.86-6.96 (m, 4H, arom.); 4.38-4.49 (m, 2H, CH_2); 4.18-4.22 (m, 1H, CH-O); 3.59 (s, 1H, OH); 3.14 (s, 4H, $(CH_2)_2$-N); 2.71-2.74 (m, 2H, CH_2-N); 2.61-2.69 (m, 4H, $(CH_2)_2$-N)
IVb	$C_{27}H_{28}FN_5O_2$ 473.54	170-1	80	68.48 68.20	5.95 5.88	14.79 14.54	7.35-7.48 (m, 10H, arom.); 6.93-7.04 (m, 4H, arom.); 4.4 (m, 2H, CH_2); 4.19-4.2 (m, 1H, CH-O); 3.13 (s, 4H, $(CH_2)_2$-N); 2.85-2.86 (m, 2H, CH_2-N); 2.62-2.69 (m, 4H, $(CH_2)_2$-N)
Vb	$C_{28}H_{31}N_5O_3$ 485.57	127-8	73	69.25 69.28	6.44 6.41	14.42 14.39	7.26-7.48 (m, 10H, arom.); 6.86-6.94 (m, 4H, arom.); 4.39-4.48 (m, 2H, CH_2); 4.2 (s, 1H, CH-O); 3.87 (s, 3H, CH_3-O); 3.12 (s, 4H, $(CH_2)_2$-N); 2.88 (s, 2H, CH_2-N); 2.7 (s, 4H, $(CH_2)_2$-N)
VIb	$C_{26}H_{28}N_6O_2$ 456.52	173-4	88	68.40 68.39	6.17 5.97	18.4 18.26	8.17 (dd, 1H, H_α pyr, J_1=0.5Hz, J_2=0.45Hz); 7.47 (m, 1H, Hγ pyr.); 6.63 (m, 2H, H_β pyr.); 4.52-4.36 (m, 2H, CH_2); 4.26-4.15 (m, 1H, CH-O); 3.56 (t, 4H, $(CH_2)_2$-N, J=4.5Hz); 2.83-2.56 (m, 6H, $(CH_2)_2$-N, CH_2)
VIIb	$C_{28}H_{31}N_5O_2$ 469.57	140	55	71.61 71.87	6.65 6.64	14.92 14.76	7.26-7.47 (m, 15H, arom.); 4.35-4.45 (m, 2H, CH_2); 4.13-4.15 (m, 1H, CH-O); 3.51 (s, 2H, CH_2); 2.5-2.69 (m, 10H, $(CH_2)_2$-N, CH_2)

IR [cm^{-1}] KBr:
I - 3063 (CH arom.); 2944, 1411, 777 (CH alif.); 1378, 1178, 864 (C-O-C); 1599 (C=N)

General procedure of preparing 5-(3-amino-2-hydroxypropoxy)-2,3--diphenyl-1,2,4-triazol (iia – viia) and 5-[3-(4-aryl-1-piperazynyl)-2--hydroxypropoxy)]-2,3-diphenyl-1,2,4-triazol (iib – viib)

A mixture of the compound **II** (0.003 mol) and the corresponding amine (0.015 mol), was refluxed in a mixture of methanol and water (39 : 1 V/V) (40 cm^3). The reaction was monitored by TLC. When the reaction was complete, the mixture was filtered and the solvent evaporated. The residue was crystallized from heptane (**IIb – VIIb**) or purified by flash chromatography (developing system: chloroform/methanol 9:1) (**IIa – VIIa**).

3. REFERENCES

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CURRICULA VITAE

Professor Jerzy Kossakowski was born in 1943. He studied at Warsaw University. In 1967 he obtained M.Sc. title, and started to work as scientific assistant in the Chair and Department of General Chemistry, the Medical University in Warsaw.
In 1975 he presented the thesis “Synthesis of new derivatives of isovisnagine and khellin with expected pharmacological activity” and obtained the Ph.D. in pharmacy. Synthesis in the field of new derivatives of coumarins, benzofurans and benzopirans resulted in many papers and habilitation “Searching for new compounds affecting the circulation system – in the group of derivatives of furobenzopiranone, benzofuran and benzopiranone” presented in 1989. In April 1993 was appointed to an Assistant Professor post of the Ist Faculty of Medicine, the Medical University of Warsaw.

Scientific activity of Professor comprises investigation of relationship between pharmacological activity and chemical structure of anxiolytic, antidepressants and β-blockers. Professor's scientific output consists of 65 papers, 7 patents and 90 communications.
Professor Kossakowski is a member of the Polish Pharmaceutical Society.

Marta Struga was born in Dwikozy in 1971. She studied Chemistry (1990–1995) at Maria Curie-Skłodowska University in Lublin and graduated in 1995 receiving M.Sc. Then she started to work as scientific assistant in Chair and Department of Organic Chemistry, Faculty of Pharmacy of Medical University in Lublin. In 2001 she presented the thesis "Synthesis of 1,2,4-triazole derivatives in the nucleophilic substitution reactions" and obtained the Ph.D. in pharmacy.
In 2001 she started to work as a lecturer in Chair and Department of Medical Chemistry, the Medical University in Warsaw. Fields of interest: organic synthesis, synthesis of anxiolytic, antidepressive and β-adrenolytic compounds. During the time she was a co-author of 5 publications and 15 posters.