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ASSESSMENT OF THE EFFECT OF NEW 5-(4-PYRAZOLYL)-1,2,4-TRIAZOLE AND 3-(4- PYRAZOLYL)-1,2,4- TRIAZOLO [3,4-c][1,4]OXAZINE DERIVATIVES ON THE EXCRETORY SYSTEM OF RATS

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Abstract

An important issue of modern nephrology is the treatment of disorders of general hemodynamics and water-electrolytic balance in the body. An elevated sodium level in the blood and intercellular space promotes the increase of osmotic pressure, water retention in the body tissues and formation of edemas [1]. Edemas are found with such diseases as arterial hypertension, chronic heart failure, nephrotic syndrome, fluid retention with obesity, and diabetes insipidus [2]. As a rule a combined pharmacotherapy is used to treat arterial hypertension including angiotensin II receptor blockers and thiazide diuretics [3, 4], which promote reduced reabsorption of sodium ions in the proximal renal tubules and elimination of magnesium and calcium ions, and uric acid [5-8]. The essence of treatment of water-electrolytic balance disorders consists in pharmacological correction of the renal function by means of diuretic means [9]. It should be noted that in addition to pronounced diuretic action diuretic agents demonstrate a number of undesirable effects (hypokalemia, hyperglycemia, protein metabolism disturbances etc.), which limits the sphere of their practical use [10-12]. Therefore, a search of new substances improving excretory renal function is an important issue of the current pharmaceutical science.

The experimental data obtained in the result of the study show that the compounds (IIIa-c) and (IVa-c) by their diuretic action are 14-73% and 36-55% more active respectively than furosemide.

Keywords: *5-(4-pyrazolyl)-1,2,4-triazole, 3-(4-pyrazolyl)-1,2,4-triazolo[3,4-c][1,4]-oxazine, diuretic activity*

Introduction

The treatment of water-electrolytic balance disorders in the body is an important issue of nephrology and consists in pharmacologic correction of the renal function by means of diuretics [13]. At the same time, it should be noted that in addition to pronounced diuretic action diuretic agents demonstrate a number of undesirable effects which limits considerably the sphere of their practical use [10-12]. In modern therapeutic practice furosemide is used, a powerful diuretic of a rapid and short action – (5-aminosulfanyl)-4-chloro-2[(2-furanylmethyl)amino]-benzoic acid, which enhances a selective excretion of sodium ions and decreases heart overload at the expense of dilation of the major vessels. At the same time, in case of a long intake furosemide can cause hyponatremia, susceptibility to blood clot formation, hearing impairment, and deterioration of diabetes mellitus. Therefore, a search of new compounds improving the renal excretory function is a relevant task of pharmacology.

Considering a high pharmacologic activity of a number of derivatives from 1,2,4-triazole [14-16] and pyrazole [17], 1,4-oxazine [18, 19], and the presence of aryl sulfonyl amino fragment in the content of known diuretic agents we have designed new derivatives of 5-(4-pyrazolyl)-1,2,4-triazole and 3-(4-pyrazolyl)-1,2,4-triazolo[3,4-c][1, 4]-oxazine. Its synthetic methodology consists in condensation of the imines 1-phenyl-3-aryl pyrazole-4-carbaldehydes (Ia-f) from ethyl 2-chloro[(4-aminosulfonyl)hydrazino]acetate (II), which is realized in chloroform solution at a room temperature in the presence of thriethylamine, and depending on the character of the substitute R in the imines it stops at the stage of the primary [2+3]-cycloaddition, or it undergoes further annulation of the oxazine cycle. In particular, in case of aldimines (Ia-c) (R=Me, $PhCH_2$) the reaction results in the formation of ethyl 1-[4-(aminosulfonyl)phenyl]-5-(4-pyrazolyl)-4,5-dihydro-1H-1,2,4-triazole-3-carboxylate (IIIa-c) with outcomes of 51-72%. In case of imines (Id-f) (R=CH_2CH_2OH) carboxylates (IIId-f) are only intermediates and undergo secondary cyclization with participation of hydroxyl and ehtoxycarbonyl groups, resulting in 3-(4- pyrazolyl)-1,2,4-triazolo[3,4-c][1,4]- oxazine -8-ions (IVa-c) with outcomes of 47-64%.

The compounds (IIIa-c, IVa-c) are highly melting colorless crystal substances, well soluble in highly polar organic solvents. In the IR-spectra of esters triazole-3-carbonic acid (IIIa-c) carbonyl group is prescribed in the range of 1720-1725 cm-1, and triazolo oxazines (IV a-в) - of 1740 cm-1. For NMR spectra of 1H compounds (III a-c) the singlets of H5 protons with 6.55- 6.60 ppm are significant, and of compounds (IV a-c) - the singlets of H3 protons with 6.80-6.87 ppm. The latter do not possess the signal of the ethoxyl group which in addition to the data of mass-spectra confirms convincingly their structure.

Methods

Learning the effect of the synthesized compounds on the excretory renal function was carried out on outbred albino male rats with the body weight of 100-190 g by means of Berkhin's method [1]. To examine a diuretic action, 6 groups of animals containing 5 animals each were used in the experiment.

While examining diuresis the rats were kept on continuous diet with free access to water. The animals were kept in a room having a temperature 20-22 ° C, and relative humidity of 55-70 % under 12/12 hour light and dark cycle with standard vivarium diet and water was given ad libitum (feeding was stopped 12 hours before blood sampling) [20, 21].

Pharmacological studies have been conducted by the rules and requirements of the "General Principles for the Work on Animals" approved by the I National Congress on Bioethics (Kyiv, Ukraine, 2001, and the Law of Ukraine "On the Protection of Animals from Cruelty" of 26.02.2006 and agreed with the provisions of the European Community Guidelines [22-24].

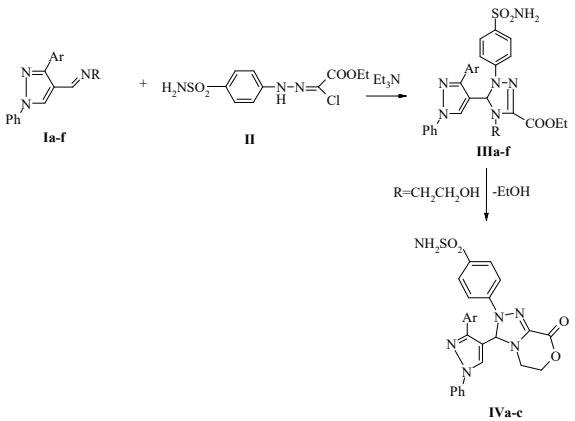
Before the substances were introduced the animals were kept during 2 hours without food and water. Since the substance examined are not completely soluble in water they were introduced into the stomach in the form of water suspension stabilized by starch paste by means of a metallic tube in the dose of 20 mg/kg of the body weight. Water test was simulated by means of introduction of drinking water at a room temperature into the stomach in the volume of 5% out of the body weight of the animals. After that the animals were placed into the exchange cages for 2 hours and diuresis was determined. The amount of urine in ml was measured at intervals of an hour. The volume of urine excreted by the control group of animals which did not receive the compounds examined was considered to be as 100%. Furosemide, a diuretic widely used in therapeutic practice was taken as a test-object.

Results

The experimental data obtained in the result of the study are presented in the (see Table 1) and show that the compounds (IIIa-c) and (IVa-c) by their diuretic action are 14-73% and 36-55% more active respectively than furosemide. Thus, the synthesized compounds may be prototypes to develop new highly effective diuretics.

Discussion

Considering a high pharmacologic activity of a number of 1,2,4-triazole, pyrazole, 1,4-oxazine derivatives, and the presence of aryl sulfonyl amino fragment in the content of known diuretic agents we designed new derivatives of 5-(4-pyrazolyl)-1,2,4-triazole and 3-(4-pyrazolyl)-1,2,4-triazolo[3,4-c][1,4]-oxazine. Its synthetic methodology consists in condensation of the imines 1-phenyl-3-arylpyrazole-4-carbaldehydes (Ia-f) from ethyl 2-chloro[(4-aminosulfonyl)hydrazino]acetate (II), which is realized in chloroform solution at a room temperature in the presence of thriethylamine, and depending on the character of the substitute R in the imines it stops at the stage of the primary [2+3]-cycloaddition, or it undergoes further annulation of the oxazine cycle. In particular, in case of aldimines (Ia-c) (R=Me, PhCH2) the reaction results in the formation of ethyl 1-[4-(aminosulfonyl)phenyl]-5-(4-pyrazolyl)-4,5-dihydro-1H-1,2,4-triazole-3-carboxylate (IIIa-c) with outcomes of 51-72%. In case of imines (Id-f) (R=CH2CH2OH) carboxylates (IIId-f) are only intermediates and undergo secondary cyclization with participation of hydroxyl and ehtoxycarbonyl groups, resulting in 3-(4- pyrazolyl)-1,2,4-triazolo[3,4-c][1,4]- oxazine -8-ions (IVa-c) with outcomes of 47-64%. The compounds (IIIa-c, IVa-c) are highly melting colorless crystal substances, well soluble in highly polar organic solvents. In the IR-spectra of esters triazole-3-carbonic acid (III a-c) carbonyl group is prescribed in the range of 1720-1725 cm-1, and triazolooxazines (IV a-c) - of 1740 cm-1. For NMR spectra of 1H compounds (III a-c) the singlets of H5 protons with 6.55- 6.60 ppm are significant, and of compounds (IV a-c) - the singlets of H3 protons with 6.80-6.87 ppm. The latter do not possess the signal of the ethoxyl group which in addition to the data of mass-spectra confirms convincingly their structure.



R=Me (Ia, IIIa), PhCH2 (Ib, IIIb), CH2CH2OH (Ic, IIIc); Ar= tien-2-yl (Ia, IIIa), 1-benzofuran-2-yl (Ib,f, IIIb,f, IVc), 4-MeC6H4 (Ic, IIIc), 4-FC6H4 (Id, III d, IVd), 4-F2HCOC6H4 (Ie, IIIe, IVb)

Conclusion. The synthesized compounds 5-(4-pyrazolyl)-1,2,4-triazole and 3-(4-pyrazolyl)-1,2,4-triazolo[3,4-c][1,4]oxazine demonstrate diuretic effect and therefore they may be prototypes to develop new highly effective diuretics.

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Table 1. Results of learning diuretic activity of the synthesized compounds (III a-c) and (IVa-c)

Compound	Diuresis		
	(M±m), ml	in % before control	in % before furosemide
IIIa	3.44±0.11**	154	114
IIIb	5.02±0.45**	225	166
IIIc	5.23±0.23***	234	173
IVa	4.67±0.42**	209	155
IVb	4.10±0.48**	184	136
IVc	4.50±0.32**	201	149
control	2.23±0.18	100	74
furosemide	3.02±0.28*	135	100

*,**,***. The results are reliable with $p < 0.05 < 0.01 < 0.001$ respectively in comparison with that of the control.

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