DOI: 10.21276/sjmps.2017.3.2.6

Saudi Journal of Medical and Pharmaceutical Sciences **ISSN 2413-4929 (Print)**
Scholars Middle East Publishers **ISSN 2413-4910 (Online)**
Dubai, United Arab Emirates
Website: http://scholarsmepub.com/

Original Research Article

Research of Diuretic Action of 5-Substituted Derivatives of 1,3,4-Thiadiazole

Igor V. Sych[1], Andrii V. Berezniakov[2]*, Lina O. Perekhoda[1], Svitlana G. Taran[1], Vitaliy D. Yaremenko[1]
[1]Department of Medicinal Chemistry, National University of Pharmacy, Kharkiv, Ukraine
[2]Department of Clinical Pharmacology, National University of Pharmacy, Kharkiv, Ukraine

***Corresponding Author:**
Andrii V. Berezniakov
Email: natalibereznyakova@gmail.com

Abstract: Search and creation new biologically active compounds which exhibit diuretic action is an current task of the modern Medical Chemistry. In order to identify diuretic activity a series of 5-substituted of 1,3,4-thiadiazole have been investigated. As index of urinary intensity the amount of urine was considered allocated by animals for 2 hours in terms of 100 g of body weight. In determining the diuretic action, a hydrochlorothiazide was selected as a comparative preparation. Screening research which have been conducted together with the study of the effect on the excretory renal function showed that the synthesized compounds exhibit diuretic activity, competing with the comparison standard. The comparative analysis of the biological action of 5-substituted of 1,3,4-thiadiazole and the preparation "Hydrochlorothiazide" showed that the most active among these compounds are derivatives with code 1.1 and 2.2, which significantly exceed the diuretic effect of the reference medicine. The prospectivity and feasibility of further targeted synthesis of this class of substances has shown to create more effective and safe medicines with diuretic action.
Keywords: Substance, 1,3,4-Thiadiazole, Diuretic action

INTRODUCTION

Currently, a large number of people have problems with the cardiovascular system associated with the influence of various factors, whereas this leads to complications such as heart and kidney failure, the main symptoms of which is fluid retention in the body and the formation of edema. In order to correct disorders of kidney activity and to establish a functional balance the diuretics medicines are applied. The basis of the modern arsenal of the most effective of these compounds is presented by the compounds of heterocyclic structure containing sulfamide fragment in their structure [1].

The heterocyclic compounds with presented core of 1,3,4-thiadiazole are the most important class of compounds for development of new drugs, since they exhibit a very wide range of biological activity [1-3]. Data analysis of the latest literature has shown that, recently, huge work is being conducted to search among the class's compounds the five-membered heterocycles – 1,3,4-thiadiazole derivatives.

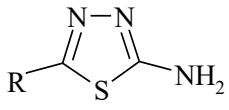
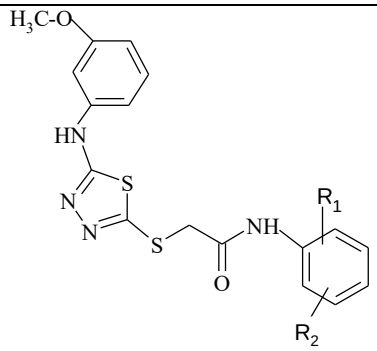
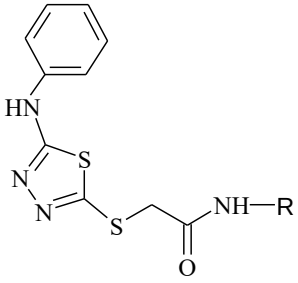
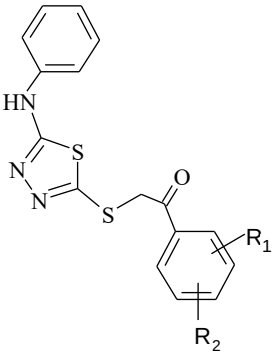
Based on the mentioned above, an important and key issue of the modern medical and pharmaceutical science is a synthesis of new, more effective and less toxic biologically active compounds to regulate filtration and reabsorbable function of kidney.

The aim of this work is to study the diuretic activity of new derivatives of 1,3,4-thiadiazole and their comparative characteristics with the famous medicine with diuretic action "Hydrochlorothiazide" which relates to compounds of heterocyclic series, as well as mentioned compounds.

MATERIALS AND METHODS

An influence of 5-substituted of 1,3,4-thiadiazole derivatives on urinary kidney function have been studied by the method of Berkhin Ye. B. ten compounds have been selected (Table. 1) to the research and synthesized at the Department of Medical Chemistry of the National University of Pharmacy [4, 5].

Table 1: Chemical structure of 5-substituted derivatives of 1,3,4-thiadiazole

 **1.1 R = CH_3,** **1.2 R = C_2H_5,** **1.3 R = SC_2H_5,**	 **2.1 R_1 = 2-COO-CH_2-CH_3,** **R_2 = H;** **2.2 NHR = naphthyl;** **2.3 R_1 = 2-CH_3,** **R_2 = 4-CH_3**	 **3.1 R = 3,6 -$OCH_3C_6H_4$;** **3.2 R = Bn**	 **4.1 R_1 = H,** **R_2 = H;** **4.2 R_1 = H,** **R_2 = 4-OPh**

Experimental studies of the compounds **1.1-4.1** in terms of the diuretic activity was performed on 55 white nonlinear male rats with 160-220 g of body weight. The animals were divided into 11 experimental groups of 5 animals in each one. The rats, in accordance with current regulations, passed acclimatization for 7 days in an experimental room [6]. The animals care complied with existing rules on devices, equipment and maintenance at a vivarium. The animals received a standard diet in accordance with the applicable regulations. Indoor air temperature was 21-24 ° C, humidity not more than 60-65% [7].

The animals were treated according to the "General ethical principles of animal experiments" [8], that agrees to the items of the European Convention for the Protection of vertebrate animals used with experimental and other scientific purposes (Strasbourg, 1986, with amendments as of 1998).

Within the study of pharmacological action the compounds **1.1-4.2** were administered once intragastrically directly before urine collecting in an equimolar dose to the effective one of hydrochlorothiazide 40 mg/kg. Prior the substances were suspended with distilled water and injected at the rate of 10 ml/kg, then the experimental animals were placed in "exchange cages". The group of intact control was injected with the solvent - distilled water in the appropriate volume. On the stage of screening research of new substances with potential diuretic activity the study was conducted of the urine volume in intact animals for two hours without additional water stress [9].

The diuretic effect of examined substances was evaluated in terms of the ability to alter urine in the experimental group in comparison with the group of intact control, and was calculated in terms of 100 g of body weight; the calculation was performed by the formula:

$$V_{relative} = \frac{V_{urine}}{m_{animal\ body}} \times 100 \quad (1),$$

where $V_{relative}$ – relative urine volume, ml/100g;
V_{urine} – urine volume secreted by each animal for a period of time, ml;
$m_{animal\ body}$ – mass of animal body, g.

In order to evaluate the results of research, the methods of mathematical statistics were applied. To compare samples which are subjects to the normal distribution, the disperse analysis (ANOVA) and the Newman-Keuls method were applied. The analysis of reliability of differences between samples which are to be normally distributed was performed by the Kruskal-Wallis method and the Mann-Whitney criterion [10, 11].

RESULTS AND DISCUSSION

Having analyzed the results of screening research of the diuretic activity of new synthetic substances in a dosage of 40 mg/kg, which presented in the Table 2, we can conclude that not all of them display efficiency and increase dieresis in animals.

Table 2: Diuretic action of substances while single administration intragastrically to the intact rats, n=5

Groups of animals	Diuresis (ml/100g of body weight)		
	1 hour	2 hours	In total
1.1	0,52±0,09**	0,32±0,06*	0,84±0,11**
1.2	0,33±0,06	0,19±0,11	0,52±0,14
1.3	0,24±0,06	0,26±0,05	0,50±0,08
2.1	0,19±0,06	0,12±0,07	0,31±0,08
2.2	0,53±0,05**	0,30±0,03**	0,83±0,08**
2.3	0,41±0,06*	0,32±0,09*	0,73±0,14*
3.1	0,43±0,08	0,14±0,02	0,57±0,07*
3.2	0,31±0,07	0,08±0,01	0,39±0,07
4.1	0,27±0,02	0,16±0,03	0,43±0,05
4.2	0,37±0,05*	0,27±0,06*	0,64±0,10*
Intact control	0,32±0,06	0,15±0,03	0,46±0,08
Hydroclorthiazide	0,48±0,02	0,32±0,05	0,80±0,07

* - probable distinctions regarding to the group of control pathology (the Newman-Keuls criterion, p≤0,05);
** - probable distinctions regarding to the group of comparative preparation (the Newman-Keuls criterion, p≤0,05).

As indicator of the intensity of urine excretion the urine volume served, which was extracted by animals for two hours. In the intact control animals for the first hour of pharmacological screening 0.32 ml / 100 g of urine have been collected. Within the further trials, the dieresis decreased twice. However, to provide with any general conclusion for the whole group of the examined compounds which clearly describes correlation between a chemical structure and ability to influence the urinary kidney function is not possible. Nevertheless, in smaller homological rows the certain patterns are being still visible. Thus, for example, in a row of 5-substituted **1.1→1.2→1.3** with increasing alkyl moiety and the introduction of sulphur atom an ability to the diuresis inhibition dramatically increases. The similar pattern is observed when amidated **(3.1→3.2)** and **(4.2→4.1)** derivatives. The special attention from the all analyzed substances must be paid to the only two compounds - **1.1** and **2.2**, which have shown the diuretic action at a level of hydrochlorothiazide that requires the necessity their more detailed pharmacological study. In reference to the compound with the code **2.2**, the diuretic action has been ascertained as at the first, as at the second hour of the research. In estimation the total volume of urine for two hours of the experiment the dieresis increase 1.8 times was recorded in comparison to the control, and was exceeded the comparative medicine. The quite high level of the diuretic action of the compound with the code **1.1** should also be noted which showed almost the same activity, but due to the bigger discrepancy between the results in animals of this group and bigger error in the group, statistically significant differences have been established only within the analysis of the total quantity for two hours.

CONCLUSION

The screening tests of the series of 5-substituted 1,3,4-thiadiazole derivatives have been conducted for the existence of diuretic activity. Comparative analysis of the biological action of 5-substituted 1,3,4-thiadiazole derivatives and the comparative medicine hydrochlorothiazide has found that among the most active compounds analyzed are the following: 1.1 and 2.2, which significantly exceed the reference drug in terms of diuretic action. Taking into consideration the chemical structure of the synthesized new derivatives of 1,3,4-thiadiazole, it has proved that this series of compounds are promising for further research.

REFERENCES

1. Ukrainets, I. V., & Bereznyakova, N. L. (2012). Heterocyclic diuretics. *Chem. of Heterocycl. Comp, 1*, 155-165.
2. Mullick, P., Khan, S. A., Verma, S., & Alam, O. (2011). Synthesis, biological evaluation and molecular docking studies of 1,3,4-thiadiazole derivatives containing 1,4-benzodioxan as potential antitumor agents. *Bull. of the Korean Chem. Society*, *32*(3), 1011-1016.
3. Zhao, J., Xuan, L., Zhao, H., Cheng, J., Fu, X., Li, S., ... & Chen, B. (2014). Synthesis and antitumor activities of 1, 3, 4-thiadiazole derivatives possessing benzisoselenazolone scaffold. *Chemical Research in Chinese Universities*, *30*(5), 764-769.
4. Sych, I. V., Perekhoda, L. O., Yeromina, H. O., Grinevych, L. O., & Kobzar, N. P. (2016). Synthesis and physicochemical properties of new derivatives of 5-R-phenilamino-2-mercapto-1,3,4-thiadiazole. *Journ. of Pharm. 2016*, 24-28.
5. Sych, I. V., Perekhoda, L. O., & Ieromina, Z. G. (2015). Synthesis, physicochemical properties and prediction of biological activity of new derivatives of 2-R1-N-(5-R-1,3,4-thiadiazol-2-yl) benzolsulfonamidiv. *Annals of Mechn. Inst, 2015*, 4.
6. Kozhemyakin, Y., Khromov, A., Filonenko, M., & Sayretdinova, T. (2002). Scientific and practical advice on keeping laboratory animals and work with him. *Kyiv: House "Avicenna*, *156*.

7. Zapadnyuk, M. P., Zapadnyuk, V. I., & Zaharyya, E. A. (1983). Laboratory equipment animals. Using experimentally. Kiev: Higher School.
8. Aleksandrov, A., Ishchuk, T., Skopenko, O., & Konopelniuk, V. (2016). Amino acids level in rats upon long-term administration of progesterone. *Bulletin of Taras Shevchenko National University of Kyiv. Series: Problems of Physiological Functions Regulation*, *21*(2), 75-78.
9. Stefanov, V. O. (2001). Preclinical studies of medicines. Kyiv: 2001.
10. Lapach, S. N., Chubenko, A. V., & Babich, P. N. (2001). Statistical methods in biomedical research using Excel, 2001.
11. Basic methods of statistical processing of the results of pharmacological experiments. (2000). Proc.: Manual on experimental (preclinical) study of new pharmacological substances. *M.: Remedium*, 349-354.