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**STUDY OF ANALEPTIC ACTIVITY OF  
TETRAHYDROPYRIDO [2,1-b] [1,3,5] THIADIAZINE  
DERIVATIVES**

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**Abstract**

**Introduction:** Our goal is to conduct an investigation of the analeptic activity of the tetrahydropyrido [2,1-b] [1, 3, 5] thiadiazine derivative group.

**Materials and Methods:** Biological studies were carried out on 78 white pedigreed mature sexually transmitted rats of both sexes weighing 230-270 g in the autumn-winter period. The test substances were administered intragastrically at a dose of 5 mg/kg 1 hour prior to the induction of anesthesia. Animals of the control group received thiopental sodium at a dose of 70 mg/kg. As the reference preparation, sodium caffeine-benzoate was used intraperitoneally at a dose of 10 mg/kg.

**Results and Discussion:** In the group of experimental animals that received intragastric substance 1 1 hour before thiopental anesthesia, a six-fold prolongation of the period of injection into anesthesia was found, the duration of anesthesia was comparable to that of the control. However, after 16 hours, 33.3% of the rats died, the rest of the animals were sharply inhibited. The original substance with laboratory cipher 2 significantly increases the time of introduction into anesthesia, has a pronounced analeptic activity, superior to that of caffeine.

**Conclusion:** Thus, the conducted studies on the presence of 10 new biologically active compounds based on tetrahydropyrido [2,1-b] [1, 3, 5] thiadiazine derivatives in the spectrum of pharmacological activity showed the presence of the most pronounced analeptic and antinarcotic activity in compounds with laboratory ciphers 3, 6, 7 and 10. Compound 2, which is 6-oxo-8- {4 - [(2-chlorobenzyl) oxy] phenyl} -3- (2-ethoxyphenyl) -3,4,7,8-tetrahydro -2H, 6H-pyrido [2,1-b] [1, 3, 5] thiadiazine-9-carbonitrile, the analeptic effect is significantly superior to that of caffeine-benzoate that of sodium.

**Keywords:** analeptic activity, derivatives of tetrahydropyrido[2,1-b][1,3,5]thiadiazine, thiopental sodium, caffeine-sodium benzoate.

## Introduction

The steady interest of various groups of researchers in the 1,3,5-thiadiazine derivatives is due primarily to their biological activity and high demand in agriculture and medicine. The spectrum of practically important properties of the most studied representatives of this group of compounds is very wide and includes antifibrinolytic, antituberculous, fungicidal, bactericidal, anthelmintic, antitumor, anticancer, hyperglycemic and other types of activity. General questions of the chemistry and application of 1,3,5-thiadiazines are considered in a number of fundamental reviews [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11]. It's necessary to note that the practical aspects of the use of condensed 1,3,5-thiadiazine derivatives have been studied to a much lesser extent up to the present.

Recently, we have shown that tetrahydropyrido [2,1-b] [1, 3, 5] thiadiazines can act as effective inhibitors of the replication of tick-borne flaviviruses, while in vivo in mice they exhibit low total toxicity [12]; studies with pronounced analgesic activity significantly exceeding that of analgin have been observed [13], studies of their anti-inflammatory and antipyretic activity have been carried out.

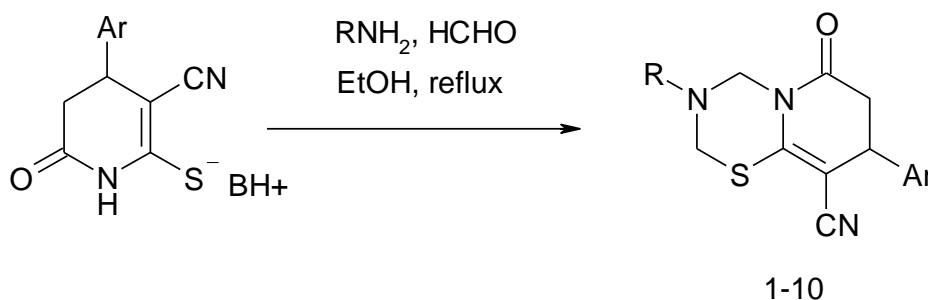
In this connection, screening studies to identify the analeptic activity of

tetrahydropyrido [2,1-b] [1, 3, 5] thiadiazine derivatives are of particular interest. On the one hand, analeptics are antagonists of narcotic substances, they are used for respiratory depression due to carbon monoxide poisoning and have a pronounced awakening effect in narcosis [14, 15]. On the other hand, the respiratory analeptic caffeine is a part of numerous combined paracetamol-containing medicines with antipyretic and anti-inflammatory activity. This increases mental and physical performance, stimulates mental activity, motor activity, shortens the reaction time, temporarily reduces fatigue and drowsiness in patients.

Our goal is to conduct an investigation of the analeptic activity of the tetrahydropyrido [2,1-b] [1, 3, 5] thiadiazine derivative group.

## Materials and Methods

For the studies, (8R / 8S) -3-R-8-aryl-6-oxo-3,4,7,8-tetrahydro-2H, 6H-pyrido [2,1-b] [1, 3, 5] thiadiazine-9-carbonitriles (1-10) synthesized by us from the noncatalyzed Mannich reaction of substituted tetrahydropyridine-2-thiolates of N-methylmorpholinium with primary amines and excess formaldehyde [16, 17]:



where, B = N-methylmorpholine; 1 – Ar = 3-MeO-4-EtOC6H3, R = 4-FC6H4; 2 – 4- (2-ClC6H4CH2O) C6H4, 2 – EtOC6H4; 3 – 4-MeOC6H4, cyclohexyl; 4 – 2-MeOC6H4, 3-Cl-4-MeC6H3; 5 – 2,4,5- (MeO) 3C6H2, 2-furfuryl; 6 – 3,4- (MeO) 2C6H3, 2-Me-3-Cl-C6H3; 7 – 3,4,5- (MeO) 3C6H2, benzyl; 8 – 3-MeO-4-EtOC6H3, 4-ClC6H4; 9 – 3-MeO-4-EtOC6H3, 2-FC6H4; 10 – 2-MeOC6H4, 2-EtC6H4.

Biological studies were carried out on 78 white pedigreed mature sexually transmitted rats of both sexes weighing 230-270 g in the autumn-winter period in the certified morphological laboratory of the State Institution "Lugansk State Medical University" (certificate No. PБ105 / 2008 from 30.12.2011).

Animals throughout the study period were kept in vivarium conditions on a standard diet of no more than six individuals in a cage in accordance with the rules for working with laboratory animals. The conditions of keeping animals and manipulations conducted with them met the requirements contained in the guidelines for ethical review of biomedical

research [18]. Before the beginning of the experiment, all animals were carefully examined, their weight, age, motor activity and condition of the wool cover were taken into account. The rats were divided into intact, control (sodium thiopental), a comparison group (sodium caffeine-benzoate) and 10 experimental groups by the number of original tetrahydropyrido [2,1-b] [1,3,5] thiadiazine studied.

In the experiment, the number of animals (6 in the group), the minimum number of animals acceptable for statistical processing and obtaining reliable results, and the minimum number of experimental groups, that is, for achieving the goal and solving the research problems, were used. total number of animals. Determination of analeptic activity was carried out on the model of "thiopental anesthesia" [19]. The test substances were administered intragastrically at a dose of 5 mg / kg 1 hour prior to the induction of anesthesia. Animals of the control group received thiopental sodium at a dose of 70 mg/kg. As the reference preparation, sodium caffeine-benzoate was used intraperitoneally at a dose of 10 mg/kg. The analeptic effect was assessed by the time of onset of narcosis, its duration and the behavior of the animals of the experimental groups for the next 2 days.

The primary data obtained during the experimental part of the study showed the normality of the distribution in the samples studied. Samples were evaluated as continuous, sufficient in the variability of the trait. To determine the reliability of the differences, the t-test was used [20].

### Results and Discussion

Screening studies of analeptic activity among tetrahydropyrido [2,1-b] [1, 3, 5] thiadiazine derivatives have shown differences in the time of onset of narcosis, qualitative characteristics of anesthesia-duration, depth, and in the features of the postnarcotic period (Table). The rats of the control group after 20 minutes of deep anesthesia, which occurred in the 6-7 minute, are active. Intraperitoneal administration of the drug for comparing caffeine-sodium benzoate for 1 hour of rats injection into anesthesia resulted in a more than

triple lengthening of the injection time into anesthesia, and a shortening of 25% of the time spent in anesthesia.

An analysis of the results of the experimental study showed that the test samples of the tetrahydropyrido [2,1-b] [1, 3, 5] thiadiazine derivatives can be divided into three groups by analeptic properties. Thus, rats of experimental groups receiving compounds 3, 6, 7 and 10 for 1 hour of injection into anesthesia were characterized by the fact that the stages of anesthesia had not occurred. No animal from these experimental groups took a lateral posture. However, 10 minutes after the administration of sodium thiopental, insignificant lethargy was noted in the rats, which disappeared for 20 minutes. All rats of these groups are alive, active, showing an interest in food. Such a reaction may indicate a strong analeptic effect. Considering the chemical structure of sodium thiopental and its mechanism of action, the ability of the test samples of tetrahydropyrido [2,1-b] [1, 3, 5] thiadiazine derivatives to block barbituric sites of GABA-benzodiazepine, the barbituric receptor complex, is likely to be seen. In addition, there may be a presence in the spectrum of their pharmacological effects of naloxone-like activity, which may serve as a prerequisite for further research in this vein.

In the group of laboratory animals receiving substance 9 prior to administration to thiopental anesthesia, the following features were found: after administration of the drug, rats are aggressive and excited. Time of occurrence in anesthesia 4 minutes. During the first hour of observation, 50% of the animals died. After 16 hours, 16.6% of the animals did not get out of anesthesia, and 33.3% of the animals are extremely inhibited, do not resist, do not escape from the tray. Taking into account, the obtained results of earlier experimental studies on the extremely low toxicity of all the test samples [8], such a picture may indicate a potentiation of the action of sodium thiopental and / or the formation of toxic products for the respiratory and vasomotor center of the interaction of sodium thiopental with the substances or their metabolites.

Table

**The indices of the determination of analeptic activity in tetrahydropyrido [2,1-b] [1, 3, 5] thiadiazine derivatives**

Group	Time of introduction in anesthesia, min	Duration of anesthesia, min	Characteristics of the clinical picture
Control (sodium thiopental)	6	20	
Comparison group (sodium caffeine-benzoate)	20	15	
1	2	20	Sharp slowing
2	55	15	Active
3	0	0	Animals did not enter anesthesia
4	6	20	Active
5	2	2	Death 50% within 1 hour
6	0	0	Animals did not enter anesthesia
7	0	0	Animals did not enter anesthesia
8	2	15	Active
9	4	960	Death 50% within 1 hour
10	0	0	Animals did not enter anesthesia

Substance 5, administered to the experimental animal 1 hour before the experimental modeling of non-anional anesthesia at a dose of 5 mg / kg, promoted acceleration of 3-fold occurrence in anesthesia. At the same time during the first hour, 50% of the rats of this group died, and the remaining 50% died for another 1.5 hours.

In the group of experimental animals that received intragastric substance 1 1 hour before thiopental anesthesia, a six-fold prolongation of the period of injection into anesthesia was found, the duration of anesthesia was comparable to that of the control. However, after 16 hours, 33.3% of the rats died, the rest of the animals were sharply inhibited.

Comparing the parameters of injection and the duration of anesthesia in rats that previously received substance 8 with those in the rats of the control group, anesthesia appears 3 times faster, and in duration is slightly shorter. In the experimental group with substance 4, indices

comparable to those in the control group of animals were recorded.

The original substance with laboratory cipher 2 significantly increases the time of introduction into anesthesia, has a pronounced analeptic activity, superior to that of caffeine. Attention is drawn to the triple extension of the period of introduction into anesthesia of animals of this experimental group. At the same time, animals are not inhibited, active, show interest in food.

**Conclusion**

Thus, the conducted studies on the presence of 10 new biologically active compounds based on tetrahydropyrido [2,1-b] [1,3,5] thiadiazine derivatives in the spectrum of pharmacological activity showed the presence of the most pronounced analeptic and antinarcotic activity in compounds with laboratory ciphers 3, 6, 7 and 10. Compound 2, which is 6-oxo-8- {4 – [(2-chlorobenzyl) oxy] phenyl} -3-(2-ethoxyphenyl) -3,4,7,8-

tetrahydro -2H, 6H-pyrido [2,1-b] [1,3,5] thiadiazine-9-carbonitrile, the analeptic effect is significantly superior to that of caffeine-benzoate that of sodium.

### Conflicts of Interest

The authors have no conflict of interest to declare.

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