

Peculiarities of Pharmacological Activity of Tetrahydropyridone and Hexahydroquinoline Derivatives in Experiment

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Abstract

Introduction: Due to widespread inflammatory processes, often accompanied by pain and fever syndromes, NSAIDs are now the most prescribed drug group in the world. NSAIDs are characterized by taking a leading position in the number and severity of adverse actions. In recent decades, the efforts of scientists have been aimed at searching for adequate ways to increase the safety profile of NSAIDs.

Materials and methods: In a series of experiments, the main objects of research were derivatives of α -cyanothioacetamide – new tetrahydropyridones under laboratory codes **TD 0364**, **TD 0353**, **TD 0351**, **CV 036**, as well as hexahydroquinolines **CV 125** and **OCO 5184**. One promising area for searching for effective and safe pharmacological agents is some derivatives of α -cyanothioacetamide (CAS Number: 7357-70-2). The trigeminal orofacial pain test and the thermal tail immersion test were used to assess the analgesic effect. Determination of antipyretic activity was carried out on the yeast-fever model. To study an anti-inflammatory activity, the method of subacute non-infectious parotitis was used.

Results and discussion: The results of the experiment made it possible to find among the new samples of tetrahydropyridones and hexahydroquinolines the compounds with analgesic, anti-inflammatory and antipyretic activities, which, in terms of these types of activities in dynamics, surpass the reference (**paracetamol**, **diclofenac sodium**, and **ketorolac**). It is important that these compounds have low acute toxicity.

Conclusion: The consequence of the above is the necessity of further preclinical and clinical studies of samples of α -cyanothioacetamide derivatives in order to create new promising highly effective and safe drugs with analgesic, anti-inflammatory and antipyretic activities.

Keywords

α -cyanothioacetamide derivatives, hexahydroquinolines, pharmacological properties, tetrahydropyridones, analgesic activity, antipyretic activity, anti-inflammatory activity.

Introduction

In modern clinical practice, the problem of pain and the prevalence of pain syndrome, considering various etiological reasons that cause it, are very relevant (Morozova and Yaroshevsky 2013; Parada et al. 2016). After analyzing the current statistical data of the International Association for the Study of Pain (IASP), we can conclude that every fifth person on the planet suffers from moderate or intense chronic pain. According to the literature data, pain accompanies about 90% of the pathologies of the human body. At the same time, 65% of the world's population regularly feel pain, and in 45% of cases, chronic pain syndrome is recorded (Yakhno 2015; Pelletier et al. 2016; Weisheim et al. 2016). Pain is both a fundamental clinical guideline for assessing the effectiveness of treatment, and a factor that largely determines the delayed consequences of various nosologies (Vertkin et al. 2011; Hunter et al. 2013; Sosnov et al. 2016).

In the practice of a dentist, many maxillofacial inflammatory diseases are accompanied by febrile phenomena (Bello 2012; Smith et al. 2016). This is evidenced by the phenomenon of odontogenic sepsis, as a generalized infectious disease, which often comes with purulent-resorptive fever. Pathological processes of purulent-resorptive fever are usually observed in the presence of undrained pus pockets in the focus, a great amount of dead tissue and a high microbial content (Shavalovskaya 2014; Smith et al. 2016).

Currently, the pharmaceutical industry offers a practitioner more than 70 NSAIDs of various chemical structures (Lesnaya 2018). However, the main stumbling block in the treatment of patients with pain syndrome is their very low safety profile (Fanella et al. 2017; Karateev et al. 2018; Lesnaya 2018).

Ranked second in the world in sales volume after antibiotics, NSAIDs lead in the number and severity of adverse effects. The first position among those in terms of frequency of occurrence is taken by erosive and ulcerative lesions of the digestive tract. They are diagnosed by fibrogastroscopy in 60–70% of people taking NSAIDs (Fanella et al. 2017; Lesnaya 2018). Dyspeptic disorders are noted in 30–40% of patients using NSAIDs for the treatment of chronic diseases.

Due to the widespread prevalence of the inflammatory process, often accompanied by pain and febrile syndromes, NSAIDs are currently the most prescribed group of medicines in the world (Karateev 2014). **Ketorolac**, **diclofenac**, **ibuprofen**, **nimesulide** and other highly effective drugs have a wide range of indications (Lesnaya 2018). However, unfortunately, along with high pharmacotherapeutic efficacy for the main indications, it is the use of NSAIDs that a whole spectrum of complications is associated with (ulcerogenicity, hepatotoxicity, hematotoxicity, neurotoxicity, cardiotoxicity, etc.) (Nozadze et al. 2016; Parada et al. 2016; Karateev et al. 2018).

The essence of the above mentioned comes down to the pressing need for the development, research and introduction into practice of new highly effective, safe and

economically affordable analgesic, antipyretic and anti-inflammatory medicines of a new generation.

Some of the derivatives of α -cyanothioacetamide (CAS Number: 7357-70-2) are among the promising directions for the search of effective and safe analgesics with antipyretic and anti-inflammatory activities. α -cyanothioacetamide can be considered as a convenient polyfunctional reagent for obtaining N, S-containing heterocycles. In their structure, they are close to numerous biologically active compounds that served as objects for the creation of antihypertensive, antihistamine, antiparkinsonian, diuretic, and anticancer medicines (Buryi et al. 2018; Dotsenko et al. 2018; Yang et al. 2018; Dotsenko et al. 2019).

Aim: to search among tetrahydropyridones and hexahydroquinolines, α -cyanothioacetamide derivatives, for safe and highly effective potential analgesic, antipyretic and anti-inflammatory medicines.

Materials and methods

Experimental studies were carried out on 327 white outbred sexually mature rats, females and males, weighing 150–250 g in a scientific laboratory, using measuring and auxiliary equipment. Before the experiment, all the laboratory animals had been quarantined for 2 weeks. In continuation of the experiment, the animals were kept in a vivarium under natural lighting conditions, at air temperature 22–24 °C, relative air humidity 40–50%, in plastic cages for 6 individuals, using a standard diet.

The studies were carried out in the autumn-winter period in order to exclude the influence of seasonal rhythms on laboratory rats. The behavior and general condition of the animals were monitored daily. The experiments were carried out in strict accordance with the global principles of manipulating experimental animals, as well as taking into account the provisions of the Order No. 199n of the Ministry of Health of the Russian Federation dated April 1, 2016 (Approval of the Rules of Good Laboratory Practice).

The experimental studies were carried out in accordance with the guidelines for the preclinical study of medicines (*Guidelines for Experimental (Preclinical) Study of New Pharmacological Substances*, Moscow, (2005) and *Guidelines for Conducting Preclinical Studies of Drugs*, Moscow, (2012).

In a series of experiments, the main objects of research were derivatives of α -cyanothioacetamide – new tetrahydropyridones under laboratory codes **TD 0364**, **TD 0353**, **TD 0351**, **CV 036**, as well as hexahydroquinolines **CV 125** and **OCO 5184** (Fig. 1). These compounds had been synthesized on the basis of the Research Chemex Laboratory of Lugansk National University named after Vladimir Dahl (Zhang et al. 2016; Dotsenko et al. 2018; Dotsenko et al. 2019).

The team of organic chemists was headed by Scientific Director of the Laboratory, D. Sc. in Chemistry, Professor Sergey Gennadievich Krivokolysko – Head of the Department of Pharmaceutical Chemistry and Pharmacognosy of Lugansk State Medical University named after St. Luke.

The group of synthetic chemists who developed the samples for the study included Chief engineer of the Laboratory, PhD in Chemistry, Associate Professor of the Department of Pharmaceutical Chemistry and Pharmacognosy of Lugansk State Medical University named after St. Luke Konstantin Aleksandrovich Frolov and Leading researcher of the Laboratory, D.Sc. in Chemistry, Professor of the Department of Organic Chemistry and Technologies of Kuban State University” Viktor Viktorovich Dotsenko.

The study design involved assessing the pharmacological activity (analgesic, antipyretic, anti-inflammatory) of tetrahydropyridones and hexahydroquinolines, derivatives of α -cyanothioacetamide, and assessing the level of safety of their use.

Two experimental models were used to assess the analgesic effect. The trigeminal orofacial pain, which was simulated by subcutaneous injection of 0.1 ml of 5% formalin solution into the vibrissa area in laboratory rats. Within 20 minutes (10, 15 and 20 minutes) after the introduction of the algogen, the number of scratching movements with the front paws of the orofacial area was counted. **Ketorolac** at a dose of 0.1 mg/kg was used as a comparison drug for the reference group of rats. Samples of original pyridine derivatives were injected intragastrically at a dose of 5 mg/kg 1.5 hours before the administration of the algogen used. The second technique, thermal tail immersion, is based on the spinal flexor reflex in response to immersion of the tail in hot water. Pain irritation was simulated by immersing the tail into a vessel with water heated to 50–54 °C, while measuring the latent period of the reaction. Analgesic activity was assessed by an increased tail-flick reaction time.

Determination of the antipyretic activity was carried out on the yeast fever model, which was simulated by subcutaneous injection of 20% baker’s yeast. Rectal temperature was measured with an electronic thermometer before the pyrogen administration and 18 hours after it. After induction of fever, the test substances were administered intragastrically at a dose of 5 mg/kg. The control animals received an equivalent amount of 0.9% sodium chloride solution. **Paracetamol** at a similar dose was used as a reference drug. The antipyretic effect was assessed 2, 4 and 6 hours after the administration of the test substances by the change in the rectal body temperature of the animals.

As an experimental model of subacute non-infectious parotitis, we used a pathological process that develops in animals when 0.2 ml of 1% formalin solution is injected into the region of the right retromandibular fossa – the projection of the right parotid salivary gland.

In order to predict the possible properties of the studied substances, all the studied samples of tetrahydropyridone and hexahydroquinoline derivatives were subjected to a predictive *in silico* analysis for similarity to drugs. Also, the probable targets, the putative biological activity were determined, and the ADMET parameters (Absorption, Distribution, Metabolism, Excretion, Toxicity) were predicted.

Statistical processing of the obtained results was carried out in the Statistica 10.0 data processing environ-

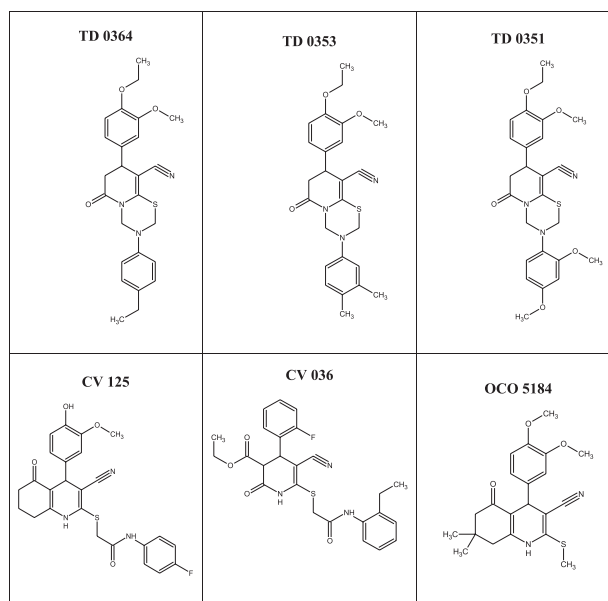


Figure 1. Structural formulas of the studied compounds.

ment. Since the study was carried out on the smallest possible number of laboratory animals, the non-parametric Wilcoxon method of processing the results was used. On the basis of the data obtained (median, quartile, mean values, standard deviation), the reliability of differences between the values of the control and the studied reference and experimental ones was determined.

Results and discussion

The trends to study acute toxicity of newly synthesized chemical compounds with a biological activity have not lost their significance today, being an important aspect of their preclinical study. Evaluation of toxicity with a single dose is an important mandatory part of a preclinical drug safety study. By means of experiments for studying acute toxicity, a toxicity class of compounds of various origins can be determined; doses for studying specific types of toxicity and experiments on chronic toxicity can be predicted as well.

The toxic effect of the studied samples of α -cyanothioacetamide derivatives was judged by the survival rate of the rats in the experimental groups and the general condition of the animals. As it can be seen from the data in Table 1, over a two-week observation period after a single intragastric introduction of the newly synthesized compounds at doses of 50, 300, and 2000 mg/kg, no deaths were registered in the rats at any of the indicated doses in the experimental groups **TD0364**, **TD0353**, **TD0351**, **CV036**, and **CV125**. All the animals of the control and five of these experimental groups were active from the first minutes after intragastric intubation, with good appetite and adequate need for water.

An analysis of the results of toxicological studies carried out in accordance with Interstate Standard GOST 32644-2014 (OECD, Test No. 423: 2001, IDT) on white laboratory rats showed that five investigated derivatives of tetrahydropyridones and hexahydroquinolines with codes **TD 0364**,

Table 1. Data on Toxicity of Tetrahydropyridone and Hexahydroquinoline Derivatives in Acute Experiments on Laboratory Rats (Intragastric)

Group of animals	Dose, mg/kg	Number of animals			Mortality, %
		General	Dead	Survivors	
Control	0	3	0	3	0
TD 0364	50	3	0	3	0
TD 0364	300	3	0	3	0
TD 0364	2000	3	0	3	0
TD 0353	50	3	0	3	0
TD 0353	300	3	0	3	0
TD 0353	2000	3	0	3	0
TD 0351	50	3	0	3	0
TD 0351	300	3	0	3	0
TD 0351	2000	3	0	3	0
CV 125	50	3	0	3	0
CV 125	300	3	0	3	0
CV 125	2000	3	0	3	0
CV 036	50	3	0	3	0
CV 036	300	3	0	3	0
CV 036	2000	3	0	3	0
OC 05184	50	3	0	3	0
OC 05184	300	3	0	3	0
OC 05184	2000	3	3	0	100

TD 0353, TD 0351, CV 036, and CV 125 refer to low-toxic compounds (5th class of toxicity, LD₅₀ ≥ 5000 mg/kg). The compound with laboratory code **OCO 5184** belongs to the 4th class of toxicity, LD₅₀ ≥ 1000 mg/kg (Table 1).

The results of our experiments to study the analgesic activity of 6 selected samples of α -cyanothioacetamide derivatives showed that among them the compounds **CV 125** 2-[[4-(4-hydroxy-3-methoxyphenyl)-5-oxo-3cyano-1,4,5,6,7,8-hexahydroquinolin-2-yl]thio} -N-(4-fluorophenyl) acetamide and **OCO 5184** (7,7-dimethyl-2-methylthio-4-(3,4-dimethoxyphenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile) had the most expressed analgesic activity at a dose of 5 mg/kg. At the same time, their analgesic activity in the tests of trigeminal orofacial pain and thermal tail immersion exceeds that of **ketorolac**. Tetrahydropyridone derivatives with codes **TD 0353** and **TD 0364** exhibited an analgesic activity comparable to the effect of the use of the referent drug (**ketorolac**). The sample with code **TD 0351** had a moderate analgesic activity in the heat tail immersion test (Fig. 2).

Today, there is a clear understanding of the mechanism of action of modern NSAIDs. The pharmacological actions of NSAIDs are achieved by inhibiting the activity of the polyenzyme complex of prostaglandin synthetase, or COX, which includes dioxygenase, isomerase, and other enzymes (Manchikanti et al. 2012; Matveev et al. 2018).

Trivial signs of inflammation include microcirculation disorder and the formation of edema; during the course of an acute inflammatory reaction, mediators and modulators of inflammation (histamine, serotonin, lysosomal enzymes, Pg, kinins, cytokines, etc.) are involved. Intensity, duration of exposure and the nature of the damaging (anti-inflammatory) factor are predetermined by the formation and staging of the release of the above mentioned compounds. It is noted that the transition of the acute phase of inflammation to the chronic (with a superior proliferation

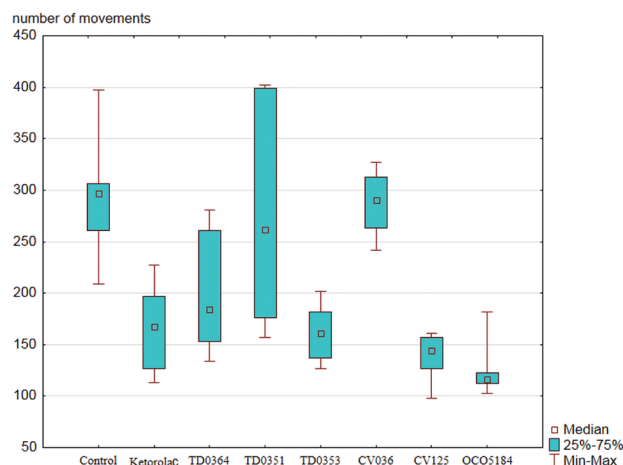


Figure 2. Number of scratching movements of the orofacial area after the introduction of algogen for 20 minutes in rats of the studied groups.

component) is associated with a change in the ratio of the formation of these biogenic substances (Bibik et al. 2018).

The analysis of the results of experimental studies on rats with simulated subacute experimental parotitis showed that among the 6 studied tetrahydropyridones and hexahydroquinolines, derivatives of α -cyanothioacetamide, the compound with the laboratory code **TD 0364** showed the most clearly expressed antiexudative activity. The significantly expressed differences in comparison with the animals in the control group were identified in the experimental groups that had received the samples with codes **TD 0351** and **OCO 5184** for the purpose of pharmacological correction of the inflammatory process.

The results of organometric studies in terms of the length of the parotid salivary gland of rats of different groups show the presence of antiexudative properties in the samples with laboratory codes **TD 0364** and **TD 0353**, which are comparable in effect to the reference drug – **diclofenac sodium**. Their ability to prevent an increase in the thickness of the parotid salivary gland against the background of simulated non-infectious parotitis was also revealed. (Bibik et al. 2018) (Table 2).

Our studies to examine the antipyretic activity of 6 samples of various tetrahydropyridones and hexahydroquinolines, derivatives of α -cyanothioacetamide, showed the presence of the most expressed antipyretic activity in sample **TD 0364** (8-(3-methoxy-4-ethoxyphenyl)-6-oxo-3-(4-ethylphenyl)-3,4,7,8-tetrahydro-2H, 6H-pyrido[2,1-b][1,3,5]thiadiazine-9-carbonitrile – IUPAC), surpassing that of **paracetamol** in duration. It manages to lower the rectal temperature by 1.3 °C during this period. This is its advantage over **paracetamol**, since in rats of the comparison group we noted an increase in temperature at the later stages of yeast fever. Two compounds with laboratory codes **TD 0351** and **OCO 5184** showed an antipyretic activity similar to that of **paracetamol** (Bibik et al. 2019) (Fig. 3).

Thus, in our experimental studies on white outbred rats, in a series of new derivatives of tetrahydropyridones and hexahydroquinolines, derivatives of α -cy-

Table 2. Organometric Parameters of Thickness (mm) of Parotid Salivary Glands in Experimental Parotitis Under Influence of the Studied Samples of Tetrahydropyridones and Hexahydroquinolines, Derivatives of α -cyanothioacetamide (n = 6)

Group of animals	Mean	Median	SD	p-value
Control (left gland)	1.500	1.500	0.540	0.027
Control (right gland)	5.166	5.000	1.600	–
Comparisons (diclofenac) (right gland)	1.500	1.500	0.540	0.027
Experimental TD0364 (right gland)	1.333	1.000	0.520	0.027
Experimental TD0353 (right gland)	1.500	1.000	0.837	0.027
Experimental TD0351 (right gland)	1.666	2.000	0.516	0.027
Experimental OCO5184 (right gland)	1.917	2.000	0.664	0.027
Experimental CV125 (right gland)	1.000	1.000	0.000	0.027
Experimental CV036 (right gland)	1.666	1.750	0.605	0.027

anethioacetamide, some compounds were found with pronounced analgesic, anti-inflammatory and antipyretic properties. The newly synthesized samples were not inferior to **ketorolac**, **diclofenac sodium**, and **acetaminophen** in terms of their analgesic, anti-inflammatory, and antipyretic activities. In addition, their very important advantage is their low acute oral toxicity (Bibik et al. 2019).

Conclusion

The results of the experimental studies made it possible to find among the new samples of tetrahydropyridones and hexahydroquinolines, derivatives of α -cyanothioacetamide, the compounds with analgesic, anti-inflammatory and antipyretic activities, which surpass the reference drugs (**paracetamol**, **diclofenac sodium**, **ketorolac**) by these types of activities in dynamics.

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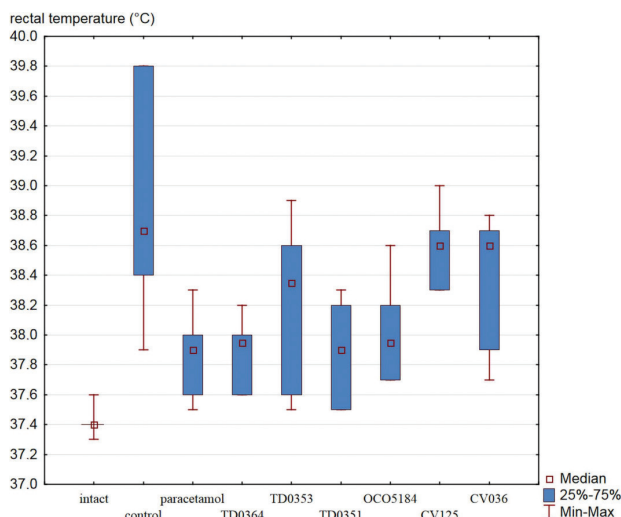


Figure 3. Antipyretic activity of paracetamol and the investigated tetrahydropyridones and hexahydroquinolines 4 hours after their administration against the background of yeast fever.

It is important that these compounds have low acute toxicity. The results of toxicological studies on white laboratory rats showed that the five of the investigated derivatives of tetrahydropyridones and hexahydroquinolines with codes **TD 0364**, **TD 0353**, **TD 0351**, **CV 036**, and **CV 125** belong to low toxicity compounds (5th class of toxicity, LD₅₀ ≥ 5000 mg/kg). The compound with laboratory code **OCO 5184** belongs to the 4th class of toxicity, LD₅₀ ≥ 1000 mg/kg.

The results of the performed predicting in silico analysis prove a high level of gastrointestinal absorption and the possibility of penetration through the BBB, as well as the absence of mutagenic, teratogenic and oncogenic properties of the compounds under study.

The facts that are mentioned make it possible to consider 5 out of 6 new compounds, derivatives of α -cyanothioacetamide with codes **TD 0364**, **TD 0353**, **TD 0351**, **CV 125**, and **OCO 5184**, as promising means for further research in order to obtain effective and safe drugs with analgesic, anti-inflammatory and antipyretic activities.

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