ABSTRACT

dissertations for the academic degree of Doctor of Philosophy (PhD)
specialty "6D072100 - Chemical technology of organic substances"

DAULETBAKOV ANUAR AMETOVICH

Synthesis, study of ecotoxicity and growth-stimulating ability of ionic derivatives of pharmacologically active substances

Relevance of the research topic. Taking into account the constant growth in the production of chemical products, the development of new and environmentally friendly processes, which can be attributed to "green chemistry", is an urgent problem. Obtaining new substances based on known pharmaceuticals (active pharmaceutical ingredients, API) is an important task of fine organic synthesis. Among these derivatives, ionic compounds and ionic liquids are of particular interest because they are often more bioavailable and have a longer duration of action. An example is a new form of the well-known pharmaceutical preparation lidocaine, developed in the group of Professor Rogers from the University of Alabama, lidocaine docusate, which is easier to digest and has a prolonged action.

This paper discusses various methods of synthesis, physicochemical properties, biological activity of a wide spectrum of action, as well as the practical application of ionic compounds based on trimecaine and diphenhydramine.

Purpose of the study. Synthesis of known and new derivatives of ionic compounds based on trimecaine and diphenhydramine base using classical and alternative methods, study of their structure, ecotoxicity and growth-stimulating activity.

Research objectives:

1. Synthesis of ionic compounds based on trimecaine and diphenhydramine bases under classical conditions;
2. Synthesis of ionic compounds based on trimecaine and diphenhydramine bases using microwave and ultrasonic activation;
3. Study of the ecotoxicity of ionic derivatives of pharmacologically active substances based on trimecaine and diphenhydramine;
4. Study of the growth-stimulating activity of ionic derivatives based on trimecaine and diphenhydramine.

The practical significance of the work lies in the development and expansion of scientific ideas about various functional derivatives of trimecaine and diphenhydramine, methods for their synthesis, structure and properties that can be used in the targeted synthesis of new compounds of this class. Within the framework of this work, substances with growth-stimulating activity were found.

Objects of study: trimecaine, diphenhydramine, *A.fischeri* bacteria and sorghum seeds.

Subject of study: Synthesis of ionic compounds based on trimecaine and diphenhydramine, study of their ecotoxicity and growth-stimulating activity on sorghum seeds.

Scientific novelty:

1. New ionic compounds based on trimecaine and diphenhydramine were synthesized for the first time under classical conditions and using microwave and ultrasonic activation.

2. For the previously known derivatives of trimecaine and diphenhydramine, conditions were selected that provide higher yields of products.

3. The conditions for the synthesis and isolation of these substances using microwave and ultrasonic activation and under classical conditions are optimized, a technological scheme for the production of trimecaine-methyl iodide is proposed.

4. For the first time, the growth-stimulating activity of ionic derivatives of trimecaine and diphenhydramine in relation to sorghum seeds was studied.

5. Ecotoxicity and acute toxicity of ionic derivatives of trimecaine and diphenhydramine were studied.

The main provisions for defense:

1. New ionic compounds based on trimecaine and diphenhydramine with halogen derivatives (CH_2ICN, C_3H_5I, C_3H_3Br, C_2H_5IO, C_3H_7IO, $C_6H_5CH_2Cl$, $C_6H_5C_2H_4I$, $C_6H_5C_3H_6I$, C_4H_9I, C_4H_9I(iso), $C_6H_{13}I$) were synthesized. In all syntheses, ultrasonic and microwave methods have shown higher efficiency compared to the classical method.

2. A technological scheme for the production of 2,4,6-trimethylanilide N-methyl-N,N-diethylaminoacetic acid iodide as a potential biologically active broad-spectrum drug has been developed.

3. Ionic derivatives of trimecaine and diphenhydramine had a better effect on the growth-stimulating activity of sorghum seeds compared to the control (water) and trimecaine and diphenhydramine hydrochlorides.

4. The toxicity of trimecaine compounds in relation to *A. fischeri* strongly depends on the length and size of the alkyl chain, in the case of diphenhydramine, the presence of an additional alkyl chain in the amine increases the toxicity and each of them is about five times more toxic than diphenhydramine HCl.

Based on the results of the dissertation research, the following conclusions were made:

1. New ionic compounds based on trimecaine and diphenhydramine CH_2ICN, C_3H_5I, C_3H_3Br, C_2H_5IO, C_3H_7IO, $C_6H_5CH_2Cl$, $C_6H_5C_2H_4I$, $C_6H_5C_3H_6I$, C_4H_9I, C_4H_9I(iso), $C_6H_{13}I$. were synthesized. For CH_3I, C_2H_5I, C_3H_7I, previously known derivatives of trimecaine and diphenhydramine, the conditions (ultrasound, microwave activation) were selected to provide higher product yields;

2. The conditions for the synthesis and isolation of these substances were optimized using microwave and ultrasonic activation and under classical conditions (thermal activation). Thus, for trimecaine CH_2ICN, the synthesis was carried out under classical conditions (90 min) using microwave (3 min) and ultrasonic (30 min) activation, the yield of the product under classical conditions was 81%, in microwave activation 92% and in ultrasonic activation 73%;

3. A technological scheme has been developed for the production of N-methyl-N,N-diethylaminoacetic acid 2,4,6-trimethylanilide iodide as a potential

broad-spectrum biologically active drug using the AspenHysys program. The material balance and heat balance of the process are calculated;

4. The growth-stimulating activity of ionic derivatives of trimecaine and diphenhydramine was studied. It was shown that in the case of the use of trimecaine CH2ICN in varieties Kiz-9 (2015) and AC-76 (2015), seed germination was 85% and 70%, while in the control variant this figure was only 55 and 15%, respectively;

5. Ecotoxicity and acute toxicity of ionic derivatives of trimecaine and diphenhydramine were studied. The toxicity of trimecaine compounds to *A. fischeri* strongly depends on the length and size of the alkyl chain; in the case of diphenhydramine, the presence of an additional alkyl chain in the amine increases the toxicity (diphenhydramine CH_3I (EC_{50} = 73 mg/l) and diphenhydramine C_2H_5I (EC_{50} = 47 mg/l)), and each is about five times more toxic than diphenhydramine HCl (EC_{50} = 342 mg/l). The ionic compound of diphenhydramine with ICH_2CN is less toxic than diphenhydramine hydrochloride, while the ionic compound of diphenhydramine with $HOCH_2CH_2I$ turned out to be more toxic than diphenhydramine hydrochloride. The most toxic among diphenhydramine derivatives was the ionic compound of diphenhydramine with C_2H_5I. Thus, the ionic compound of diphenhydramine with C_2H_5I is statistically significantly more toxic than lidocaine and trimecaine by 2.15 and 3.49 times, respectively. The results obtained can be applied to the Al-Farabi Kazakh National University, KazNMU named after Asfendiyarov, LLP "Central Laboratory of Biocontrol, certification and preclinical testing", "Kazakh Research Institute of Plant Protection and Quarantine".

Personal contribution of the dissertation student. The results presented in the dissertation were obtained personally by the author with his direct participation in experimental research work and discussions.

Approbation of work and publication. The results of the work performed are reflected in 9 scientific papers, including:

- in 3 articles published in international scientific journals with an impact factor according to the Clarivate Analytics Web of Science information database, or included in the Elsevier Scopus database;
- in 3 articles published in journals without impact factor;
- in 3 abstracts of international, scientific symposiums and conferences.

The structure and scope of the dissertation. The dissertation consists of introduction, literature review, experimental part, results and discussion, conclusion and list of references. The work contains 40 figures, 19 tables and 209 list of references. The total number of pages is 108.