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Prediction of the biological activity of a compound depending on its NH-acidity

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Abstract: *Acetamides are building blocks for the synthesis of compounds containing pharmacophores in their structure, manifesting a diverse range of biological activity. The drugs based on these substances possess antidiabetic effect and inhibit blood coagulation. Some of them act as chemosensitizers (i.e., cancer cell inhibitors). However, the full potential of these compounds remains to be fully accomplished. In a previous study, we synthesised acetamides with the RCONHCH (R´) CCl_3 general formula (where R = CH_3, CH_2Cl; R´ = C_6H_5, $C_6H_4CH_3$, $C_6H_4OCH_3$, C_6H_4OH) and studied their acid-base behaviour. The NH-acidity of the studied acetamides is controlled by the polar effects of substituents. In this paper, the potential biological activity of the previously obtained acetamides is calculated, and the dependence of their biological potential on the NH-acidity values is elucidated. Prediction of biological activity was carried out using the PASS software. An analysis of the types of biological activity occurring in all compounds allowed us to determine a linear dependence between the probability of biological potential and the value of dissociation constant.*

Keywords: *acetamides, NH-acidity, dissociation constants, half neutralisation potential, potentiometric titration, PASS*

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Установление зависимости потенциала биологической активности от NH-кислотности соединения

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Резюме: *Ацетамиды являются строительным материалом для синтеза соединений, содержащих в своей структуре фармакофорные группы, которые проявляют различную биологическую активность. Созданные на их основе препараты обладают противодиабетическим действием, являются ингибиторами фактора свертывания крови, некоторые действуют как хемо-сенсибилизаторы (т.е. блокаторы раковых клеток). Однако в полной мере возможности этих соединений не раскрыты. Ранее нами были синтезированы ацетамиды с общей формулой RCONHCH(R´)CCl_3 (где R = CH_3, CH_2Cl; R´ = C_6H_5, $C_6H_4CH_3$, $C_6H_4OCH_3$, C_6H_4OH) и изучено их кислотно-основное поведение. Показано, что NH-кислотность исследованных ацетамидов контролируется полярным эффектом заместителей. Целью настоящей работы являлся расчет потенциальной биологической активности полученных ранее ацетамидов и установление зависимости биологического потенциала от величины NH-кислотности этих соединений. Прогноз биологической активности осуществлен с использованием компьютерной программы PASS. В результате отбора активностей, встречающихся во всех соединениях, установлена линейная зависимость вероятности наличия биологической активности от величины константы диссоциации соединения.*

Ключевые слова: *ацетамиды, NH-кислотность, константы диссоциации, потенциал полунейтрализации, потенциометрическое титрование, PASS*

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INTRODUCTION

Acetamids are one of the most important compound classes from the chemical point of view. They are a building material for creating compounds which contains several pharmacophore groups in their structure. Such compounds, of course, have a biological activity. Acetamids are a part of drugs with diabetic inhibitor[1], coagulation factor inhibitor [1] and some of them are blockers for the cancer cells [2, 3]. Acetamids exhibit anticonvulsant [4], antiviral [5], analgesic [6] and insecticides [7] activities.

The possibilities of these compounds are not fully understood. Acetamids with general structure $RCONHCH(R')CCl_3$ ($R = CH_3$, CH_2Cl; $R' = C_6H_5$, $C_6H_4CH_3$, $C_6H_4OCH_3$, C_6H_4OH) had been studied by us before. The polar effect of substituents controls NH-acidic of the studied compounds [8].

The main idea of this project is to establish the NH acidic potential dependence and biological activity. Our work consists of two stages. We use the PASS online program for the previously obtained acetameds [9] and compare with NH value biological potential [8].

EXPERIMENTAL PART

We used the PASS (Prediction of Activity Spectra for Substances) on-line program criteria biological activity assessment. It is a useful tool to make a quick forecasting of diverse biological activity [10, 11]. PASS is a software product designed as a tool for evaluating the general biological potential of an organic drug-like molecule. This program predicts a lot of types of biological activities based on the organic compounds structure [12, 13].

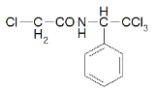
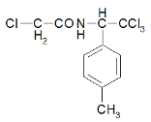
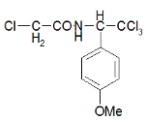
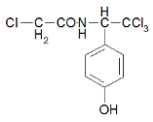
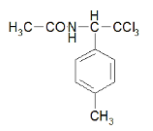
RESULTS AND DISCUSSION

The dissociation constant acetamids pK_A (NH-acidity) has been determined the potentiometric method on «Expert-001» [14–18] as well as biological activity factors (Pa) substances. Table contains the results of the biological activity evaluation acetamids.

Table depicts dissociation constant acetamids due to different (R) substituents of substances. However, substituents equidistant from the –CONH– active center and this fact affects the constant compounds **I–IV** dissociation. The acidity span (pK_A) of these compounds varies slightly (from 12 to 14 units). The main contribution to the – NH group proton mobility and the acidity of these compounds made by the presence of chlorine near the active center. Therefore, these compounds acidity increases to 12 units in comparison with the previously described compounds [19]. In compound **V**, there

Relationship between biological activity (Pa) and NH-acidity (pKA) of acetamides

Взаимосвязь биологической активности (Pa) и NH-кислотности (pK_A) ацетамидов

The forms of biological activities	Pa				
	I  ***pK_A*** (12.03)	**II**  ***pK_A*** (12.33)	**III**  ***pK_A*** (12.68)	**IV**  ***pK_A*** (12.86)	**V**  ***pK_A*** (14.06)
1. Phobic disorders treatment	0.767	0.660	0.598	0.573	0.772
2. Chloride peroxidase inhibitor	0.585	0.525	0.398	0.394	0.553
3. Fusarinine-C ornithinesterase inhibitor	0.580	0.487	0.475	0.473	0.634
4. Complement factor D inhibitor	0.577	0.483	0.474	0.415	0.600
5. Enteropepti-dase inhibitor	0.558	0.462	0.459	0.428	0.391
6. Hematopoietic inhibitor	0.541	0.486	0.445	0.395	0.512
7. Angiogenesis inhibitor	0.426	0.393	0.386	0.327	–
8. Transglutaminase 2 inhibitor	0.343	0.303	0.291	0.276	–

[1]Машковский М.Д. Лекарственные средства: пособие для врачей. 16-е изд., перераб., испр. и доп. М.: Новая волна. 2012. 1216 с.

is a donor methyl group near the active center that reduces proton mobility with nitrogen, so the acid strength of this compound is significantly reduced (pK_A=14.08).

We chose only those activities which are found in all compounds and analyzed them.

Table presents linear relation biological activity and NH-acidic for the first acetamides. The probability biological activity increases with growing coefficient acidity of the compounds. In case of the (**V**) last compound the probability of the 1–4 species biological activities dramatically increases. Meanwhile, 7 and 8 species show zero biological activity. The NH-acidity compound decrease can be explained by the inverse relationship. According to the list of references [12], there are nootropic properties which contain chlorine compound. There have not been any nootropic activities found despite the presence of three or four chlorine atoms in research compounds.

CONCLUSION

Acetamids **I–V** biological activity theoretical prediction was made. NH value biological potential line dependence on compound dissociation constant value has been set.

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