Міжнародний
науково-практичний симпозіум

«100 РОКІВ УСПІХУ ТА ЯКОСТІ»,

присвячений 100-річчю кафедри
фармацевтичної хімії
Національного фармацевтичного
університету

MINISTRY OF HEALTH OF UKRAINE
NATIONAL UNIVERSITY OF PHARMACY
PHARMACEUTICAL CHEMISTRY DEPARTMENT

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ
КАФЕДРА ФАРМАЦЕВТИЧНОЇ ХІМІЇ

100 РОКІВ УСПІХУ ТА ЯКОСТІ

Матеріали міжнародного науково-практичного симпозіуму,
присвяченого 100-річчю кафедри фармацевтичної хімії
Національного фармацевтичного університету

100 YEARS OF SUCCESS AND QUALITY

Materials of the international scientific and practical symposium,
dedicated to the 100th anniversary of pharmaceutical chemistry
department of National University of Pharmacy

18 жовтня 2021 р.
м. Харків

October, 18, 2021
Kharkiv

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УДК 615.1:54 (06)
С 81

Електронне видання мережне

Реєстраційне посвідчення УКРІНТЕІ № 756 від 20.09.2021 р.

100 років успіху та якості : матеріали міжнар. наук.-практ.
С 81 симпозіуму, присвяченого 100-річчю кафедри фармацевтичної хімії Національного фармацевтичного університету (18 жовтня 2021 р., м. Харків) = 100 years of success and quality: materials of the international scientific and practical symposium, dedicated to the 100th anniversary of pharmaceutical chemistry department of National University of Pharmacy (October, 18, 2021, Kharkiv). – Електрон. дані. – Х.: НФаУ, 2021. – 89 с.

Збірка містить матеріали Міжнародного науково-практичного симпозіуму «100 років успіху та якості», присвяченого 100-річчю кафедри фармацевтичної хімії Національного фармацевтичного університету, які згруповано за напрямками, представленими науковцями в ході роботи симпозіуму. Розглянуто теоретичні та практичні аспекти цілеспрямованого конструювання та синтезу біологічно активних сполук; створення на лікарських субстанцій; стандартизації ліків, фармацевтичного аналізу субстанцій, фітопрепаратів та екстемпоральної рецептури.

Для широкого кола наукових і практичних працівників фармації та медицини.

The collection contains materials of the International Scientific and Practical Symposium «100 years of success and quality», dedicated to the 100th anniversary of Pharmaceutical Chemistry Department of National University of Pharmacy, which are grouped by the topics of the scientific reports presented during the symposium. It contains the theoretical and practical aspects of targeted design and synthesis of biologically active compounds, development on medicinal substances, standardization of drugs, pharmaceutical analysis of substances as well as plant drugs and individually prepared formulations.

The book is published for a wide number of scientific and practical workers in pharmacy and medicine.

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DESIGN, SYNTHESIS AND ANTICONVULSANT ACTIVITY OF NEW DIACYLTHIOSEMICARBAZIDES

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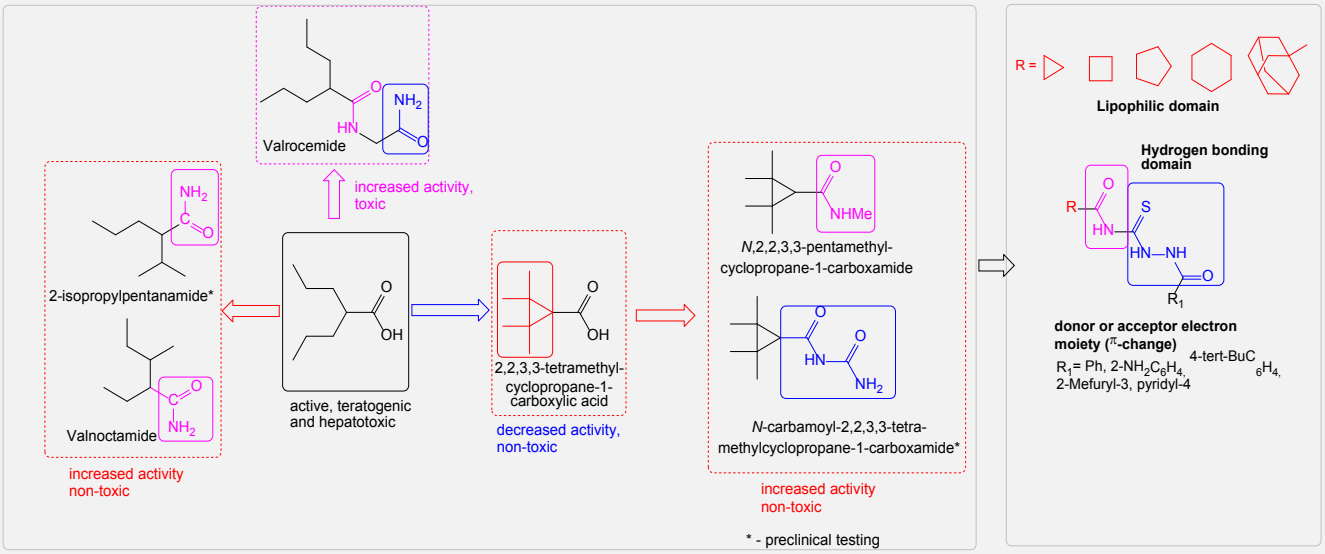
Introduction

The modification products of the carboxyl group of alkyl- and cycloalkylcarboxylic acids (amides, carbamates, semicarbazides, etc.) are one of the promising classes of organic compounds in terms of searching for anticonvulsants [1-3, 7-14]. Firstly, these structural fragments are present in most molecules of both approved for use and experimental anticonvulsant drugs [1, 2]. Secondly, such modification has been studied on valproic acid and is promising, in view of the teratogenicity and hepatotoxicity reduction and a positive epileptogenic effect [3].



The fact that substituted ureas, semicarbazides and their sulfur-containing analogues are actively studied for anticonvulsant activity is an additional confirmation of the prospects of this approach. Their combination with saturated substituents (cyclopropane, cyclocyclohexane, cycloheptane, citral, carvone, camphor) is a favorable factor for the appearance of biological activity [4-6]. It is important, that additional of fragments with lipophilic properties (lipophilic domain) and donor-acceptor properties (π-charge) introduction to the thiosemicarbazide residue (hydrogen bonding domain) is necessary for the interaction with the active receptor center of the corresponding protein target. Therefore, this modification will show the «pharmacophore» (cycloalkyl, amide and acyl-thiosemicarbazide) fragments effect on the anticonvulsant activity manifestation. Virtual screening of studied ligands to the active sites GABAT will allow to determine the compounds for researching an experimental model of pentylenetetrazole seizures.

So, the *aim* of this research is a virtual target-oriented screening, synthesis and study of di-acylthiosemicarbazides for anticonvulsant activity in rats models of pentylenetetrazole seizures with discussion of the «structure-activity» relationship for further directed search for effective drugs.

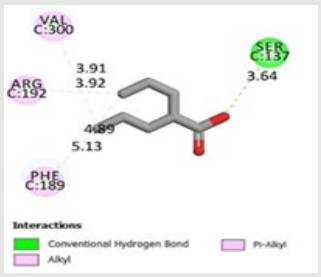
Materials and methods

Reactions of nucleophilic attachment were used for synthesis of target compounds, purity and structure verification were conducted by appropriate physicochemical methods (IR-, 1H NMR-spectroscopy, elemental analysis, LC-MS). In silico studies included usage of such software as AutoDock Vina, AutoDockTools1.5.6, BIOVIADraw 2017R2, Chem3D, HyperChem 7.5, Discovery Studio Visualizer 2017/R2,. SwissADME. Appropriate methods of in vivo (experimental model of «pentylenetetrazole convulsion» in rats) studies were used for screening of biological activity of obtained compounds. Convulsion were modeled by a single subcutaneous administration of pentylenetetrazole at a dose of 80 mg/kg [7]. One hour prior to the administration of the convulsant, the test compounds were administered intragastrically at a dose of 10 mg/kg as an aqueous suspension stabilized with Tween-80. «Depakine» was used as a reference drug, administered similarly at a dose of 150 mg/kg. ANOVA was used for statistical processing of obtained data.

Result and discussion

Molecular docking was used in the first step of our study, as a tool for predicting the affinity of antiepileptic drugs (Valproic acid) and diacylthiosemicarbazides (**2**) to active centers of $GABA_T$-receptors. The results of molecular docking showed, that the planned structural modification of diacylthiosemicarbazides (**2**, Scheme) can be justified. Such, the affinity of compounds **2** was significantly higher for $GABA_T$ receptor inhibitors, than the reference compounds.

This was also confirmed by the visualization of the results of molecular docking for drugs and promising compounds. So, compounds **2.10**, **2.15**, **2.18** and **2.23** have a greater affinity for the $GABA_T$ receptor. For example, compounds **2.15** with an active receptor center there are predicted to be twice as many hydrogen bonds and other types of interactions (hydrophobic, N-alkyl, attractive), then for valproic acid (Fig.). Thus, compound **2.15** forms strong hydrogen bonds between the Nitrogen and Oxygen atoms of the 2-aminobenzoylhydrazide group with THR B: 353 (2.74 Å) and ASN B: 352 (3.27 Å), the hydrogen atom of the amino group in the 2-aminobenzyl moiety with THR B: 353 (2.25 Å). In addition to these interactions, compound **2.15** has additional weak hydrogen bonds of the sulfur atom of the thioamide group with SER A: 137 (4.26 Å), hydrophobic π-alkyl interactions of the cyclopropane moiety with VAL A: 300 (4.89 Å) and PHE A: 189 (5.48 Å) and π-anionic, hydrophobic alkyl and π-π T shaped interactions of the phenyl ring with GLU A: 121 (3.86 Å), with ILE A: 72 (5.16 Å) and PHE B: 351 (4.85) Å). It is important that, compounds **2.10**, **2.18** and **2.23** also interact with similar amino acid residues.



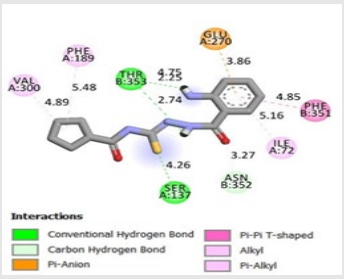
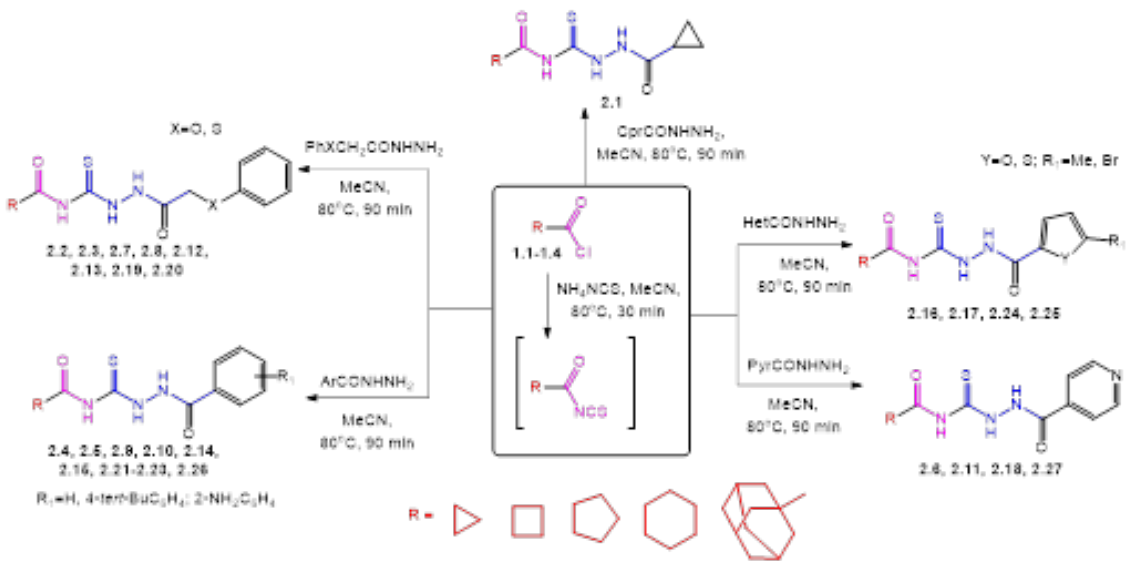


Fig. Visualization of affinity according to the docking. a) Valproic acid with $GABA_T$, b) compound 2.15 with $GABA_T$.

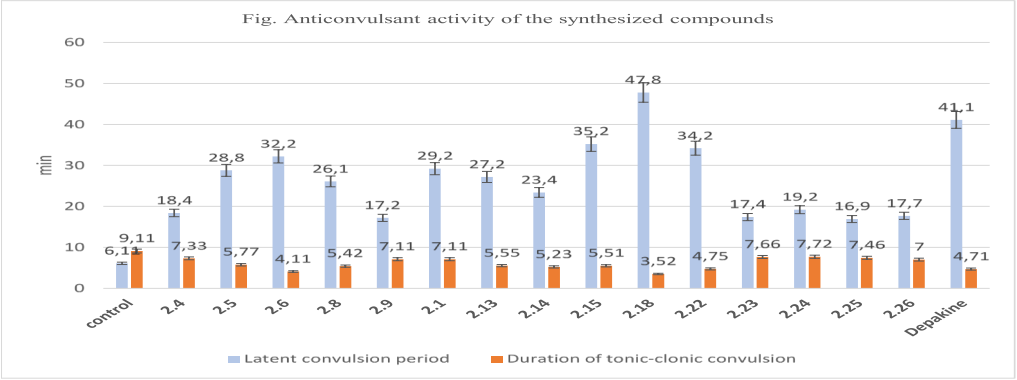
For further implementation of the research design, we have used cycloalkanecarbonyl isothiocyanates, which were obtained by a known synthetic approach. It included the synthesis of cycloalkanecarbonyl chlorides (1.1-1.5) and their subsequent interaction with ammonium isothiocyanate (acetonitrile medium). The latter, without isolation from the reaction medium (in situ method), reacted regioselectively and quite easily with hydrazides of cycloalkyl- (aralkyl-, aryl-, hetaryl-) carboxylic acids (Scheme). This produced individual diacylthiosemicarbazides (2.1-2.27) with satisfactory yields (39-89%).

Scheme



The results of the studies showed that the administration of pentylenetetrazole to experimental animals led to the development of epileptic seizures with the expressed tonic-clonic phase and subsequent 100% mortality. Thus, in the control group, the latency period averaged 6.11 minutes, and the duration of tonic-clonic seizures was 9.11 minutes. Convulsions observed in this group of animals had a expressed tonic-clonic character and recurred periodically. Where as, the introduction of diacylthiosemicarbazides (**2**) to the experimental group of animals led to an increase in the latency period of seizures in 2.77-7.82 times (Fig.). It is important that, compounds **2.6**, **2.15**, **2.22** were close in potency, and compound **2.18** was higher than the reference drugs Depakine.

Fig. Anticonvulsant activity of the synthesized compounds



The test compounds reduced the duration of tonic-clonic seizures by 1.23-5.59 min and prevented animal mortality by 30-60% relative to the control group of animals. Compound **2.18** exceeded Depakine. SAR-analysis showed, that the greatest anticonvulsant activity is characteristic for diacylsemicarbazides, which in their structure contain cyclopropane- (**2.5**, **2.6**) and cyclopentane- (**2.13-2.15, 2.18**) carboxamide fragment. In addition, a significant effect on the activity is characteristic for the hydrazide fragment in the molecule. Thus, compounds with phenylthioacetyl (**2.13**), benzoyl (**2.5**, **2.14**, **2.15**) and isonicotinoyl (**2.6**, **2.18**) moieties in the thiosemicarbazide residue are more active. These functional groups can be considered "critical" pharmacophores for revealing of anticonvulsant activity.

Conclusion

A virtual target-oriented screening, synthesis, and study of diacylthiosemicarbazides for anticonvulsant activity in models of pentylenetetrazole seizures in rats were performed. The structure-activity relationship was discussed for further targeted search for effective drugs. New diacylthiosemicarbazides were synthesized by the *in situ* method, namely by the interaction of cycloalkanecarbonyl chlorides with ammonium isothiocyanate followed by nucleophilic addition of cycloalkyl-(aralkyl, aryl-, hetaryl-)carboxylic acid hydrazides. Biological screening showed that diacylthiosemicarbazides with cyclopropane and cyclopentanecarbamide groups show anticonvulsant activity that exceeds or competes with the reference drug "Depakine". The most active compound **2.18** was identified for further study of anticonvulsant activity in other models.

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ЗМІСТ
CONTENT

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