МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ

ТЕРНОПІЛЬСЬКИЙ НАЦІОНАЛЬНИЙ МЕДИЧНИЙ УНІВЕРСИТЕТ

ІМЕНІ І. Я. ГОРБАЧЕВСЬКОГО

НАУКОВО-ТЕХНІЧНИЙ ПРОГРЕС І ОПТИМІЗАЦІЯ ТЕХНОЛОГІЧНИХ ПРОЦЕСІВ СТВОРЕННЯ ЛІКАРСЬКИХ ПРЕПАРАТІВ

МАТЕРІАЛИ IX НАУКОВО-ПРАКТИЧНОЇ КОНФЕРЕНЦІЇ З МІЖНАРОДНОЮ УЧАСТЮ

22-23 вересня 2022 року

Тернопіль

ТНМУ

«Укрмедкнига»

2022

УДК 615.1

Науково-технічний прогрес і оптимізація технологічних процесів створення лікарських препаратів: матеріали IX наук.-практ. конф. з міжнар. участю (22 – 23 вересня 2022 р.). – Тернопіль : ТНМУ, 2022. – 245 с.

Усі матеріали збірника подаються в авторській редакції. Відповідальність за представлені результати досліджень несуть автори тез.

The structure of the obtained compounds was determined by ^{1}H NMR spectroscopy, IR spectrophotometry, and elemental analysis. The identity was confirmed by chromato-mass spectrometry. Preliminary prediction of acute toxicity parameters and biological activity parameters was performed using the GUSAR Online® and PASS Online® services, respectively.

In order to justify the further choice of the direction of subsequent research, docking studies were conducted. The choice of the biomisheni model was determined by the nature of pharmacophore fragments in the structure of synthesized compounds and literature data. Thus, for the purpose of qualitative and quantitative assessment of the interaction process with the active center of the enzyme, models of cyclooxygenase-1, cyclooxygenase-2, 5-lipoxygenase, lanosterol-14α-demethylase and receptor tyrosine kinase were selected. The identified targets were loaded from the PDB bank. The studies were compared with data obtained for diclofenac, celecoxib, fluconazole, and crizotinib. The study was conducted in stages and included: ligand preparation (MarvinSketch 6.3.0, Hyper Chem 8, AutoDockTools-1.5.6); enzyme preparation (Discovery Studio 4.0, AutoDockTools-1.5.6); docking (Vina, Discovery Studio 4.0).

Results. A number of synthetic derivatives of 9-R-3-(methylthio)pyrazolo[1,5-*d*][1,2,4]triazolo[3,4-*f*][1,2,4]triazine have been developed, for which acute toxicity and possible types of biological activity are predicted *in silico*, which makes it possible to identify a priority research area in the future. Thanks to the results of molecular docking, further investigation of antifungal activity is the most promising.

Conclusions. 12 compounds in a number of derivatives of 9-R-3-(methylthio)pyrazolo[1,5-*d*][1,2,4]triazolo[3,4-*f*][1,2,4]triazine were synthesized, for which spectral characteristics were studied, some physico-chemical constants were established, and the structure was proved. Previously, using *in silico* modeling, it is assumed that the obtained substances belong to the class of low-toxic ones. The prospects for searching among the synthesized structures of substances with antifungal activity are established

USE OF IN VITRO METHODOLOGY AND SEARCH OF ANTIOXIDANTS AMONG S-PTERIDIN DERIVATIVES

N.V. Groma[1], I.S. Nosulenko[2], G.G. Berest[2], V.M. Shvets[2], S.I. Kovalenko[2]
[1]Zaporizhzhia National University, Ukraine
[2]Zaporizhzhia State Medical University, Ukraine
groma.natalia@ukr.net

Introduction. Stress is one of the most common etiological factors of various diseases (pathologies of the central nervous system, lungs, cardiovascular system, diseases, etc.) [1-3]. The realization of the damaging effect of stress is associated with the stimulation of free radical processes in cells. Free radical oxidation is an important and multifaceted biochemical process of transformation of lipids, nucleic acids, proteins, etc. under the influence of free radicals, and lipid peroxidation (LPO) is one of its consequences [4-6]. Due to this, a promising direction in the development of effective approaches to the treatment and prevention of diseases caused by the etiological factor, which is stress, is the search for compounds with pronounced antioxidant activity [7]. Considering the above, a group of new pteridines, which are biologically active compounds of natural (luminophores, folic acid, etc.) and synthetic origin [8], was chosen as the object of research.

The aim of the work. The aim of the work is the search and selection of effective antioxidants in a number of new substituted pteridines for further research on various experimental pathologies.

Materials and methods. We used the activity\toxicity prediction (GUSAR) [9] to select compounds for antioxidant activity studies. Studies of antiradical (APA) and antioxidant (AOA) activity were carried out by in vitro methods on the following models: a model based on inhibition

of 2,2-diphenyl-1-picrylhydrazyl (DPPH) and on a model of AAPH-induced oxidation of linolenic acid.

The results. It was established that among the studied pteridin-2,4(1*H*,3*H*)-diones and 2-thioxo-2,3-dihydropteridin-4(1*H*)-ones, the highest ARA is characteristic of thio-containing derivatives. Thio-containing derivatives bind the DPPH radical up to 28-99% at concentrations of 10^{-3} and 10^{-4} M. These compounds were also active in the model of AAPN-induced oxidation of linolenic acid. Thus, they inhibit the oxidation of linolenic acid by 32-96% in the specified concentrations. Analysis of the «structure-activity» relationship showed that the key «pharmacophore» in the molecule is undoubtedly the mercapto group in position 2 of the pteridine heterocycle. Additional introduction of carboxyl substituents in position 6 and oxo group in position 7 leads to a significant increase in activity. Interestingly, alkylation of sulfur at position 6 of pteridine with halogen acids preserves ARA and AOA and, importantly, improves the pharmacotechnological characteristics of the studied compounds (solubility). In our opinion, high ARA and AOA of 2-thioxo-2,3-dihydropteridin-4(1*H*)-ones are associated with the presence of a mercapto group in their molecules, which is characterized by redox properties and the ability to bind. free radicals.

Conclusions. The results of the research allowed to identify a number of promising 2-thioxo-2,3-dihydropteridin-4(1*H*)-ones, which in vitro models (scavenging of DPPH and inhibition of AAPN-induced oxidation of linolenic acid) compete with or exceed the activity of reference drugs « Ascorbic acid» and «Trolox», respectively. These results served as the basis for further studies of «leader compounds» on antioxidant activity in experimental in vivo models and study of their mechanisms of action.

References

1.Pham-Huy LA, He H, Pham-Huy C. Free radicals, antioxidants in disease and health. *Int J Biomed Sci* 2008, №4, P.89-96.

2.Li, S., Tan, H.-Y., Wang, N., Zhang, Z.-J., Lao, L., Wong, C.-W., & Feng, Y. (2015). The Role of Oxidative Stress and Antioxidants in Liver Diseases. *International Journal of Molecular Sciences*, №16(11), 26087–26124. doi:10.3390/ijms161125942]

3.Bernabeu-Wittel, M., Gómez-Díaz, R., González-Molina, Á., Vidal-Serrano, S., Díez-Manglano, J., Salgado, F. (2020). Oxidative Stress, Telomere Shortening, and Apoptosis Associated to Sarcopenia and Frailty in Patients with Multimorbidity. *Journal of Clinical Medicine*, № 9(8), P.2669. doi:10.3390/jcm9082669].

4. Davydov VV, Shvets VN. Lipid peroxidation in the heart of adult and old rats during immobilization stress. *Exp Gerontol* 2001; №36:1155-60.

5.Yousefi-Manesh, H., Shirooie, S., Partoazar, A., Nikoui, V., Estakhri, M. R. A., & Bakhtiarian, A. (2019). Hepatoprotective effects of phosphatidylserine liposomes on carbon tetrachloride-induced hepatotoxicity in rats. *Journal of Cellular Biochemistry*. doi:10.1002/jcb.28464

6. McIntyre TM, Hazen SL. Lipid oxidation and cardiovascular disease: Introduction to a review series. *Circ Res* 2010, №107:1167-9.

7. Oettl K., Reibnegger G. (2002). Pteridine Derivatives as Modulators of Oxidative Stress. *Current Drug Metabolism*, №3(2), 203-207. http://dx.doi.org/10.2174/1389200024605127.

8. E. Ayling, M. Gopal Nair, Charles M. Baugh. Chemistry and biology of pteridines and folates P. 805 March 21-26, 1993, in Orange Beach, Alabama»-T.p. verso. DOI 10.1007/978-1-4615-2960

9. Stefanov O.V., editor. Preclinical study of drugs (methodical recommendation). *[Preclinical studies of medical conditions (methodological recommendations)]* Kyiv: Avitsena; 2001. Ukrainian