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DETERMINATION OF BIOLOGICAL ACTIVITY OF DERIVATIVES

N7-ARYL/BENZYL-3-(8-OXO-7,8-DIHYDRO[1,2,4]TRIAZOLO[4,3-*a*]-PYRAZIN-3-YL)CARBOXYLIC ACIDS

he principal possibility of synthesis f tens of hundreds of thousands of ompounds by combinatorial chemis- y leads to the understanding of the eeds for rational up to synthetic se- ction for most promising compounds accordance with the requirements a specific task. One of the most ef- ctive and efficient way to solve this oblem is a computer prediction of e various properties of chemical mpounds, which at this stage of de- lopment of organic chemistry can e considered as applied tool for ex- riment planning.

ABSTRACT

the help of the PASS program computer prediction ological activity of the virtual library prepared on the nd of the basic structure of [1,2,4]triazolo[4,3-*a*]pyra- was carried out. According to the results libraries of ryl/benzyl-3-(8-oxo-7,8-dihydro[1,2,4]triazolo[4,3-*a*] zine-3yl)carboxylic acids and their amides were gen- ed, and by previously developed techniques the syn- s of a number of substances was conducted to as- their impact on lipid metabolism.

eywords: [1,2,4]triazolo[4,3-*a*]pyrazines, PASS- ction, metabolic syndrome.

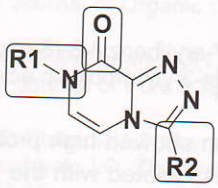
ne of the priority criteria that are appreciated by ing new effective drugs are their selective effect, as well as the absence of not advisable side effects. Search for new high-performance and low-toxic molecules is conducted among natural and synthetic compounds.

To evaluate pharmacological profile of an array of possible derivatives on the basis of [1,2,4]triazolo[4,3-*a*]pyrazine computer system for prediction of biological activity spectrum PASS C&T (Prediction Activity Spectra for Substances: Complex & Training) was used [1,2].

RESULTS AND DISCUSSION

Modern and most efficient chemical technology that solves the problem of synthesis of large arrays of compounds to find molecules leading to the development of new drugs is a combinatorial synthesis.

On the assumption of the analysis of the chemical potential of the 3,7-substituted [1,2,4]triazolo[4,3-*a*]pyrazines [3-5] and using preparativity of developed by us methods for synthesis of their derivatives [6] design of library on the ground of base structure [1,2,4]triazolo[4,3-*a*] pyrazine, which has 3 randomization points, was performed (Figure1).



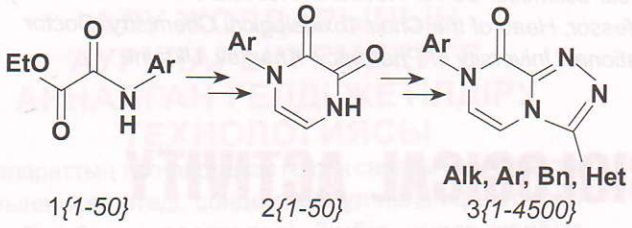
R1 = Ar.
R2 = Alk, Ar, Bn, Het.

Figure1 – Basic structure of [1,2,4]triazolo[4,3-*a*]pyrazine

Previously developed synthetic scheme [7] can be used to generate a large library of structures for virtual screening (Scheme 1).

Among the main requirements for structures for screening should allocate their synthetic accessibility and availability of favorable pharmacological characteristics.

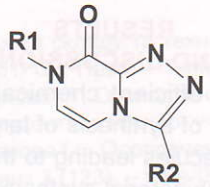
The most important are the minimization of side reactions, to ensure maximum variability of substituents and the ability of the final molecule to conformational isomerism.



Scheme 1

From this perspective, special attention among the structures obtained library attracted derivatives N^7-aryl/benzyl-3-(8-oxo-7,8-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-3-yl)carboxylic acids that contain conformationally mobile carboxylic acid moiety.

Primary array of N^7-aryl/benzyl-3-(8-oxo-7,8-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-3-yl)carboxylic acids, which can be synthesized subsequently, consisted of 170 compounds of the general formula (Figure 2) and 1360 their amides. Among these compounds computer screening by 921 kind of biological activity was carried out, and an assessment of their potential toxicity to determine the most promising molecular target for future research in the synthesis and biological experiment.



R1 = Ph; 3,4-diMePh; 3,5-diMePh; 4-OMePh; 4-OEtPh; 4-BrPh; 4-ClPh; 3-FPh; 4-FPh; 3,4-diFPh; $PhCH_2$; 4-$FPhCH_2$.
R2 = CH_2COOH; $CH(CH_3)COOH$; $(CH_2)_2COOH$; 4-$ClPhCH_2$; $(CH_2)_3COOH$; $CH_2CH(CH_3)CH_2COOH$; $CH_2C(CH_3)_2CH_2COOH$; $CH_2CH(CH_3)CH_2CH(CH_3)COOH$; $(CH_2)_4COOH$; $CH_2CH(CH_3)(CH_2)_2COOH$; $CH_2CH_2CH(CH_3)CH_2COOH$

Figure 2 – General formula of N^7-aryl/benzyl-3-(8-oxo-7,8-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-3-yl)carboxylic acids

All structures of pre-selection showed high probability of pharmacological effects associated with the regulation of lipid metabolism. Thus the probability is hardly changed depending on the substituent in position 7 (aryl/benzyl), as well as the branching of the acid residue. However, taking to account obtained data in planning the synthesis from focused libraries, the focus should be on the basis of dialkylamino N^7-aryl/benzyl-3-(8-oxo-7,8-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-3-yl)carboxylic acids, which contain 4-5 carbon atoms and have branching in the carbon chain.

Conducting of PASS prediction also allows us to formulate recommendations for screening research. In this way, received focused libraries of N^7-aryl/benzyl-3-(8-oxo-7,8-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-3-yl)carboxylic acids and their amides should check for the ability of these substance to effect on the level lipoproteins and receptivity of tissue to glucose, and research their effect on purine metabolism [8-10].

It should also be noted that almost all N^7-benzyl-3-(8-oxo-7,8-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-3-yl)carboxylic acids with a high extent of probability could be regarded as an inhibitor of histamine (Pa > 0.750) release. But according the prediction for 7-aryl derivatives this activity is not typical.

It draw attention the high degree of probability for anti-seborrhoetic activity of compounds in which substituent of acid contains a methyl group in β-position (in the region of 0.790-0.850 Pa).

The computer analysis of investigated derivatives N^7-aryl/benzyl-3-(8-oxo-7,8-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-3-yl)carboxylic acids and their amides allowed to identify the most promising compounds for the synthesis planning and conducting of the biological experiment. Producing of the focused library (75 substances) was conducted on basis of the exploited lab and combinatorial methodics of synthesis. Original N^1-aryl/benzyl-3-hydrazinopyrazin-2(1H)-ones were obtained on basis monoester oxalamic acid [7].

EXPERIMENTAL

Combinatorial synthesis of substances was performed using the device «CombiSyn-012-3000» [11].

N^7-aryl/benzyl-3-(8-oxo-7,8-dihydro[1,2,4]triazolo[4,3-a]pyrazin-3-yl) carboxylic acids (combinatorial technique). A solution of 0.05 mmol of the appropriate *N1*-aryl/benzyl-3-hydrazinopyrazin-2(1H)-one and 0.2 mmol of the appropriate anhydride in 5 ml of anhydrous dimethylformamide, was immersed in each of the five reactors. The reaction mixture was heated for 12 hours. After reactors were cooled, the mixture was diluted with water. At next day the precipitate was filtered, washed twice with 30 ml acetone and dried at 100° C for 20 hours. Yield 50–63%.

N^7-aryl/benzyl-3-(8-oxo-7,8-dihydro[1,2,4]triazolo[4,3-a]pyrazin-3-yl) carboxamides (combinatorial technique). A suspension of 0.005 mmol of the corresponding N^7-aryl/benzyl-3-(8-oxo-7,8-dihydro[1,2,4]triazolo[4,3-*a*]pyrazin-3-yl)carboxylic acid in 3 ml of anhydrous dioxane was charged into each of the reactors 5, heated with stirring to 90° C and added dropwise 0.0055 mmol 1-(1H-imidazol-1-ylcarbonyl)-1H-imidazole (KDI) in 1 ml of anhydrous dioxane. The resulting mixture was refluxed with stirring for 1 hour. Then 0.005 mmol of the appropriate amine was added. The resulting mixture was heated at 90° C for 12 hours. After cooling the mixture was diluted with water and allowed to stand for 2 days to form a precipitate, which was filtered, washed with water and recrystallized from a mixture of dimethylformamide and i-propanol. Yield 74-92%.

ТҮЙІНДЕМЕ

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КАРБОН ҚЫШҚЫЛДАРЫНЫҢ ӨНДІРІСТІК N^7-АРИЛ/БЕНЗИЛ-3-(8-ОКСО-7,8-ДИГИДРО [1,2,4] ТРИАЗОЛО[4,3-*a*]ПИРАЗИН-3-ИЛ) КӨРІНІСІНІҢ БИОЛОГИЯЛЫҚ БЕЛСЕНДІЛІГІН АНЫҚТАУ

SS бағдарламасының көмегімен [1,2,4]триазо-[4,3-*a*]пиразин базалық құрылымының негізінде ынған виртуалды кітапхананың биологиялық бел-ділігінің компьютерлік болжамы жасалды. Нәтиже-де карбон қышқылдары мен олардың амидтерінің -арил/бензил-3-(8-оксо-7,8-дигидро[1,2,4]три-ло[4,3-*a*]пиразин-3-ил) кітапханасы жасақталды не бұрын жетілдірілген әдістер бойынша липид-дің зат алмасуға әсер етуін бағалау үшін бірқатар тардың синтезі жасалды.

Түйін сөздер: 1,2,4]триазоло[4,3-*a*]пиразиндер, SS-болжам, зат алмасу синдромы.

РЕЗЮМЕ

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ОПРЕДЕЛЕНИЕ ПРОФИЛЯ БИОЛОГИЧЕСКОЙ АКТИВНОСТИ ПРОИЗВОДНЫХ N^7-АРИЛ/БЕНЗИЛ-3-(8-ОКСО-7,8-ДИГИДРО [1,2,4] ТРИАЗОЛО[4,3-*a*]ПИРАЗИН-3-ИЛ)КАРБОНОВЫХ КИСЛОТ

С помощью программы PASS проведен компьютерный прогноз биологической активности виртуальной библиотеки, полученной на основе базовой структуры [1,2,4]триазоло[4,3-*a*]пиразина. По результатам сгенерирована библиотека N^7-арил/бензил-3-(8-оксо-7,8-дигидро[1,2,4]триазоло[4,3-*a*]пиразин-3-ил)карбоновых кислот и их амидов и по разработанным ранее методикам осуществлен синтез ряда веществ для оценки их влияния на метаболизм липидов.

Ключевые слова: [1,2,4]триазоло[4,3-*a*]пиразины, PASS-прогноз, метаболический синдром. ■

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