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STUDYING THE BIOLOGICAL ACTIVITY OF ISOMERIC N-(TOLYL)-α-PICOLINAMIDES IN THE PASS ONLINE PROGRAM

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Abstract

The biological activity of the isomers of toluidine and N-(tolyl)-α-picolinamides synthesized on the basis of picolinic acid was studied in the PASS online program (https://www.way2drug.com/PassOnline/index.php). Indicators of the biological activity of isomeric amides in relation to certain diseases, adverse and toxic effects on the body, negative effects of drugs on the cardiovascular and hepatobiliary systems, cytotoxic effects on cancer cells and human breast cancer cell lines were obtained. The results are summarized in a table. Judging by the tables above, the biological activity of isomeric N-(tolyl)-α-picolinamides showed very similar results compared to each other

Keywords: *PASS online program, N-(tolyl)-α-picolinamide, Pa and Pi values, toxicity, cancer cells, prognosis*

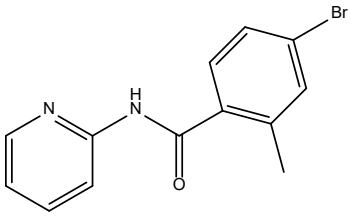
Introduction

Today, the development of new, more effective and safe drugs is one of the priorities of organic chemistry, and in the production of such drugs PASS, GUSAR and Pharma Expert programs are used, which make it possible to accurately predict various types of biological activity based on structural formulas of compounds of different chemical classes. On the basis of these programs, the initial approximate primary biological properties of organic compounds are revealed and used in the practical study of biological properties of substances. This helps save time and money.

One of the most important properties of chemical compounds is their biological activity, the presence of which allows or prevents the practical application of a chemical compound in medicine, cosmetics, food industry, agricultural chemistry and other fields (Barenboim G.M., Malenkov A.G., 1986). By using the PASS (Prediction of Activity Spectra for Substances) program, the pharmacotherapeutic effect, biochemical mechanisms of action, toxic and adverse effects, interaction

characteristics with antitargets, drug metabolism for a given compound can be determined. It is possible to estimate the properties associated with the transporter proteins, the parameters of the interaction and the changes in the expression of certain genes. The GUSAR program allows prediction of acute toxicity in mice and rats with four types of administration, interactions with antitargets, and certain characteristics of ecotoxicology. PharmaExpert software is designed to analyze the results of PASS and GUSAR predictions, to see the relationships between different activities and to search for chemical compounds with the required bio-logical activity profiles (Druzhilovskiy D.S., Rudik A.V., Filimonov D.A., Gloriozova T.A., Lagunin A.A., Dmitriev A.V., Poroikov V.V., 2017). As part of the collaborative work of the Institute of Chemical and Energy Technology Problems (Siberian branch of the Russian Academy of Sciences) and the Novosibirsk Institute of Organic Chemistry (Siberian branch of the Russian Academy of Sciences), the biological activity spectra of a number of compounds in the hexaazaisowurtzitane structure (the biological activity spectrum of a chemical compound is the spectrum of various biological properties of this compound a set of different types of biological activity reflecting the results of interaction with objects (URL: https://www.way2drug.com/passonline/index.php) predicted and the results of in vivo analysis reviewed by scientists of the Siberian Department of the Russian Academy of Sciences of the compounds studied in the PASS program confirmed the predicted activity (Tolstikova T.G., Morozova E.A., Sysolyatin S.V., Kalashnikov A.I., Zhukova Yu.I., Surmachev V.N., 2010). The biological activity spectra of the hexaazaizawurtzitan structure according to PASS Online program analyzes predicted nootropic and analgesic activity with high probability (Pa = 0.881–0.956) and their subsequent pharmacological in vivo analysis confirmed only analgesic activity for these compounds and studies two patents were obtained as a result (RF Patent No. 2558148; Byul. Izobret. [Invention Bulletin], 2015, 21; RF Patent No. 2565766; Byul. Izobret. [Invention Bulletin], 2015, 29).

Amide functionalities attract much attention in current chemical and industrial research, not only because of their wide biological and pharmacological activity, but also because they are versatile reagents for the synthesis of various useful molecules. A review of the literature shows that more than 50% of known drugs contain amide units. Among bioactive compounds, N-hetero-aryl amides are widely distributed as an important class of medicinal compounds. Recently, pyridyl benzamide derivative (1) has been reported as Trypanosoma brucei inhibitors (Ferrins L., Gazdik M., Rahmani R., Varghese S., Sykes M.L., Jones A.J., Avery V.M., White K.L., Ryan E., Charman S.A., Kaiser M., Bergström C.A.S. and Baell J.B., 2014), tubulin (2) polymerization inhibitor – tumor growth reduction (Colley H.E., Muthana M., Danson S.J., Jackson L.V., Brett M.L., Harrison J., Coole S.F., Mason D.P., Jennings L.R., Wong M., Tulasi V., Norman D., Lockey P.M., Williams L., Dossetter A.G., Griffen E.J. and Thompson M.J. 2015), thiazolyl amides (3) as protein methyltransferase selective inhibitors (Gao C., Margolis B.J., Strelow J.M., Vidler L.R. and Mader M.M., 2016).



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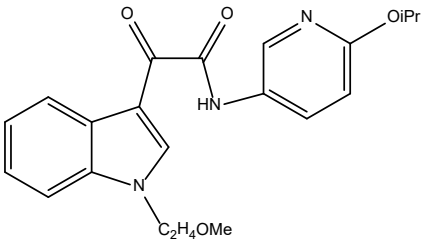

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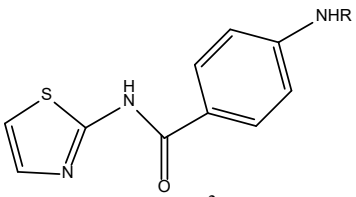

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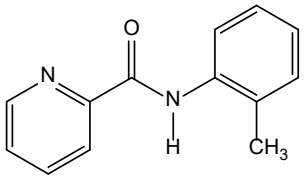
Research methodology

In this article, N-(tolyl)-α-picolinamides were synthesized from toluidine isomers and picolinic acid, and how the position of the methyl ($-CH_3$) group in the benzene ring in the N (tolyl)-α-picolinamide molecule affects the biological activities of amides PASS online (https://www.way2drug.com/PassOnline/

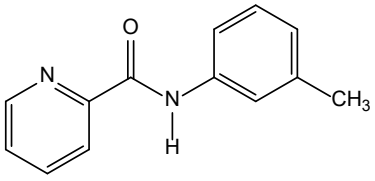
index.php) was studied using the program. The PASS online program is a software product designed as a tool to assess the overall biological potential of an organic drug-like molecule. The PASS program provides simultaneous prediction of many types of biological activity based on the structure of organic compounds. Thus, PASS can be used for chemical synthesis of virtual molecules and evaluation of biological activity profiles prior to biological testing. PASS results are expressed as Pa (probability of active compound) and Pi (probability of inactive compound). If Pa > 0.7 according to the results of PASS, the possibility of finding the activity experimentally is high. 0.5 < Pa < 0.7 indicates moderate therapeutic potential. Pa < 0.5 indicates weak pharmaceutical activity and the activity is less likely to be found experimentally (URL: https://www.way2drug.com/passonline/index.php; Abe Kawsar S.M., Hosen Mohammed A., Tasneem Sultana Chowdhury, Kazi Masud Rana, Yuki Fujii, Yasuhiro Ozeki, 2021).

Results and discussion

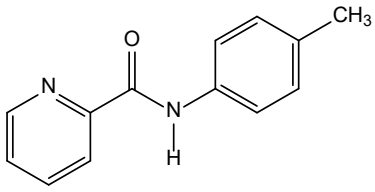
Three isomeric amides are formed from the reaction of toluidine isomers and picolinic acid.



N-(o-tolyl)-α-picolinamide



N-(m-tolyl)-α-picolinamide



N-(p-tolyl)-α-picolinamide

In the PASS online program, indicators of biological activity of isomeric N-(tolyl)-α-picolinamides against some diseases, adverse and toxic effects on the body, adverse drug effects on the cardiovascular and hepatobiliary systems, cancer cell lines the cytotoxic effect of chemical compounds and the cytotoxicity of the substance against human breast cancer cell lines were obtained and the obtained results were compared in the form of a table. The results show that the biological activities of amides synthesized from picolinic acid and toluidine isomers are close to each other.

The N-(tolyl)-α-picolinamide isomers obtained using the program are mainly 5-hydroxytryptamine release inhibitor, amine dehydrogenase inhibitor, membrane integrity agonist, mucosa protector, platelet-derived growth factor receptor kinase inhibitor, taurine dehydrogenase inhibitor, urethanease inhibitor, indications of biological activity against some diseases such as an insulin inhibitor (https://www.way2drug.com/passonline). The Pa value of the obtained results shows a close value in isomeric amides (Table 1).

Table 1. *Predicted biological activities of N-(tolyl)-α-picolinamides against some diseases using PASS online program*

Biological activity	Molecules					
	N-(o-tolyl)-α-picolinamide		N-(m-tolyl)-α-picolinamide		N-(p-tolyl)-α-picolinamide	
	Pa	Pi	Pa	Pi	Pa	Pi
5-Hydroxytryptamine release inhibitor	0.776	0.004	0.791	0.004	0.788	0.004
Amine dehydrogenase inhibitor	0.718	0.007	0.663	0.010	0.718	0.007
Membrane integrity agonist	0.661	0.062	0.690	0.057	0.762	0.044
Mucous membrane protector	0.684	0.064	0.777	0.025	0.769	0.028

Biological activity	Molecules					
	N-(o-tolyl)-α-picolinamide		N-(m-tolyl)-α-picolinamide		N-(p-tolyl)-α-picolinamide	
	Pa	Pi	Pa	Pi	Pa	Pi
Platelet-derived growth factor receptor kinase inhibitor	0.768	0.005	0.794	0.004	0.777	0.004
Taurine dehydrogenase inhibitor	0.781	0.016	0.745	0.023	0.781	0.016
Urethanease inhibitor	0.707	0.008	0.556	0.021	0.618	0.015
Insulin inhibitor	0.583	0.028	0.698	0.009	0.686	0.010

On the basis of the PASS online program, along with the results of the activity of chemical compounds against certain diseases, it is possible to obtain estimates about the adverse and toxic effects of the chemical compound on the body, and preliminary information about the negative and toxic effects of the studied compound (https://www.way2drug.com/passonline) (Table 2). Estimated results are sometimes based on clinical manifestations observed in a few or even a single patient.

Table 2. *Adverse and toxic effects of N-(tolyl)-α-picolinamides studied in the PASS online program*

Biological activity	Molecules					
	N-(o-tolyl)-α-picolinamide		N-(m-tolyl)-α-picolinamide		N-(p-tolyl)-α-picolinamide	
	Pa	Pi	Pa	Pi	Pa	Pi
Crampy syndrome	0.888	0.006	0.840	0.021	0.858	0.014
Hematemesis	0.813	0.012	0.779	0.016	0.813	0.012
Stomach ulcer, aphth	0.735	0.034	0.757	0.028	0.787	0.021
Bleeding from the gastrointestinal tract	0.750	0.014	0.719	0.020	0.750	0.014
Neutrophil dermatosis (Sweet's syndrome)	0.653	0.068	0.685	0.056	0.723	0.044

The results of predicting the adverse effects of drugs based on N-(tolyl)-α-picolinamides on the cardiovascular and hepatobiliary systems (https://www.way2drug.com/adverpred/) Pa value for isomeric amides range from 0.600 to 0.413 showed activity in (Table 3).

Table 3. *Results of predicting adverse effects of drugs based on N-(tolyl)-α-picolinamides on cardiovascular and hepatobiliary systems*

Biological activity	Molecules					
	N-(o-tolyl)-α-picolinamide		N-(m-tolyl)-α-picolinamide		N-(p-tolyl)-α-picolinamide	
	Pa	Pi	Pa	Pi	Pa	Pi
Myocardial infarction	0.562	0.034	0.600	0.028	0.599	0.028
Heart failure	0.538	0.040	0.553	0.034	0.556	0.033
Arrhythmia	0.537	0.080	0.413	0.175	0.432	0.162
Hepatotoxicity	0.428	0.238	0.619	0.134	0.570	0.160

Simultaneous quantitative and qualitative predictions of IC_{50} and IG_{50} values were obtained for each isomeric amide to predict the cytotoxic effects of chemical compounds on cancer cell lines and drug-like compound cytotoxicity against nine breast cancer cell lines (https://www.way2drug.com/Cell-line/). Cytotoxic effects of isomeric amides on cancer cell lines Pa and Pi values are 0.533 and 0.027 for N-(o-tolyl)-α-picolinamide. 0.525 and 0.031 for N-(m-tolyl)-α-picolinamide and N-(β-tolyl)-α-picolinamides. The obtained results are presented in tables 4 and 5.

Table 4. *Cytotoxic effects of N-(tolyl)-α-picolinamides on cancer cell lines*

Pa	Pi	Cell line	Cell-line Full name	Tissue	Tumor type
0.533 – – 0.525	0.027 – –0.031	Kasumi 1	Childhood acute myeloid leukemia with maturation	Haematopoietic and lymphoid tissue	Leukemia

Table 5. *Cytotoxic effects of N-(tolyl)-α-picolinamides against breast cancer cell lines*

Breast cancer cell name	Classification				Quantitative			
	IC_{50}		GI_{50}		pIC_{50}		pGI_{50}	
	Value	AD	Value	AD	Value	AD	Value	AD
N-(o-tolyl)-α – picolinamide								
Bcap37	inactive	+						
BT-20	inactive	+	active	+			5.5762	+
Hs-578T	inactive	+	inactive	+				
MCF7			inactive	+	4.7098	+	4.9716	+
MCF7-DOX	active	+			5.7560	+		
MCF7R	inactive	+			4.5544	+		
MX-1	inactive	+			6.3299	+		
T47D	inactive	+	active	+	5.3721	+	5.8061	+
ZR-75–1	inactive	+	inactive	+	5.6109	+	4.7132	+
N-(m-tolyl)-α – picolinamide								
Bcap37	inactive	+						
BT-20	inactive	+	active	+			5.5155	+
Hs-578T	inactive	+	inactive	+				
MCF7			inactive	+	4.7823	+	4.9231	+
MCF7-DOX	active	+			5.6372	+		
MCF7R	inactive	+			4.4986	+		
MX-1	inactive	+			6.4528	+		
T47D	inactive	+	active	+	5.2233	+	5.6010	+
ZR-75–1	inactive	+	inactive	+	5.5816	+	4.7709	+
N-(p-tolyl)-α – picolinamide								
Bcap37	inactive	+						
BT-20	inactive	+	active	+			5.5144	+
Hs-578T	inactive	+	inactive	+				
MCF7			inactive	+	4.7705	+	4.7912	+
MCF7-DOX	active	+			5.4059	+		
MCF7R	inactive	+			4.5290	+		
MX-1	inactive	+			6.3985	+		
T47D	inactive	+	active	+	5.3755	+	5.4059	+
ZR-75–1	inactive	+	inactive	+	5.5704	+	4.7616	+
Bcap37	inactive	+						

Conclusion

Based on the given tables, the biological activities of N-(tolyl)-α picolinamides showed very close results when compared to each other. The position of the methyl ($-CH_3$) group in the benzene ring of the N-(tolyl)-α-picolinamide molecule does not affect the biological activity of the molecule, and the biological activity is similar regardless of the position of the methyl group in the ring. The results obtained in the PASS online program serve as a basis for studying the biological activity of substances in practice.

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