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PREDICTION OF PHARMACOTHERAPEUTIC ACTIVITIES OF BIS-CARBAMATES OF THE MEE SERIES

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Abstract

This scientific work is devoted to the study of the biological activities of bis-carbamates of the MEE series for the pharmacology and medicine. Virtual screenings were conducted online by the pass program. As a result of the prediction, many activities were identified with a high percentage of the presence of pharmacotherapeutic activities as inhibitors, agonists and substrates of various cytochromes. The data obtained will help further research on these compounds and their use in pharmaceuticals.

Key words

Bis-carbamate, inhibitor, substrate, agonist, screening, activity, medicine, biological, pharm, therapeutic.

Introduction. Carbamates, or urethanes, are organic compounds derived from carbamic acid (carbonic acid amide). Currently, many studies in the field of carbamates and derivatives of bis-carbamates are awakened not only by theoretical, but also by practical needs. From this point of view, carbamates and derivatives of bis-carbamates are undoubtedly of interest as substances with biological and pharmacological activity [4,5]. The use of these substances in medicine as anti-viral, anti-tumor, anti-inflammatory, anti-arrhythmic and other drugs is of particular interest. This list could be continued, as the geography of application of carbamates, bis-carbamates and polyurethane derivatives is wide. That's why we decided to conduct analyzes with the help of "Computer chemistry" and "Mathematical chemistry" programs, which are currently developing rapidly. In computer chemistry, substances (molecules) are modeled according to molecular graphs, with formal operations on the change of substances (chemical reactions). In chemistry, this approach greatly simplifies the algorithmization of chemical problems, reduces them to typical problems of combinatorics and discrete mathematics, and allows searching for solutions using computer programs [1-3]. As examples of typical tasks of computer chemistry, we can cite the following: search for "structure-activity" relationships; creating sets of chemical structures that meet the specified parameters (composition, presence of functional groups, etc.); listing various chemical reactions between given reagents (called "computational synthesis") and so on [6,9-11]. Computational chemistry methods are often used in combination with methods of quantum chemistry, molecular mechanics, etc. Mathematical statistics methods are widely used to process the results of computational experiments. In some cases, artificial intelligence methods are used to find a solution [13,14]. The authors of this article synthesized bis-carbamates of the MEE series. The mechanism and parameters influencing the reaction have been studied [16,18]. The resulting product was studied

in international chemical databases and classified according to the product range of foreign economic activity of the Republic of Uzbekistan [8]. The aim of this research work was to predict the pharmacological, therapeutic and medicinal activities of compounds of the MEE series by the structure-based in silico "structure-activity" method in the PASS program.

Materials and Methods. Virtual screening of structural formulas based on "Structure-Activity" (SAR) relationship *PASS Online* http://way2drug.com/PassOnline/predict.php computer prediction program to find directions of practical use of new substances. Substances under study: N,N′-hexamethylene bis-[(ortho-cresol)-carbamate] i.e. MEE-1; N,N′-hexamethylene N,N′-dinitroso bis-[(ortho-cresol)-carbamate] i.e. MEE-1a; N,N′-hexamethylene N,N′-disodium bis-[(ortho-cresol)-carbamate] i.e. MEE-1b; N,N′-hexamethylene N,N′-diisopropyl bis-[(ortho-cresol)-carbamate] i.e. MEE-1v; N,N′-hexamethylene N,N′-dichloro bis-[(ortho-cresol)-carbamate] i.e. MEE-1g; N,N′-hexamethylene N,N′-dibenzyl bis-[(ortho-cresol)-carbamate] i.e. MEE-1d.

Results and Discussions. PASS Online predicts over 3500 kinds of biological activity, including pharmacological effects, mechanisms of action, toxic and adverse effects, interaction with metabolic enzymes and transporters, influence on gene expression, etc. To obtain the predicted biological activity profile for your compound, only structural formula is necessary; thus, prediction is possible even for virtual structure designed in computer but not synthesized yet [12,15,17,19]. We have decided to present only those pharmacotherapeutic activities that are most likely to exist (Table 1).

Table 1

Availability of estimated biological activities of synthesized substances for medicine - (Pa >60%)

Substances	Activities	Pa
MEE-1	CYP2H substrate	0,872
	CDP-glycerol glycerophosphotransferase inhibitor	0,855
	Membrane integrity antagonist	0,803
MEE-1a	CYP2F1 substrate	0,759
	CYP2B6 substrate	0,716
MEE-1b	CYP2C12 substrate	0,817
	CYP2J substrate	0,775
	Venombin AB inhibitor	0,773
	Aspulvinone dimethylallyltransferase inhibitor	0,773
	Taurine dehydrogenase inhibitor	0,754
MEE-1v	Taurine dehydrogenase inhibitor	0,807
	Gluconate 2-dehydrogenase (acceptor) inhibitor	0,806
	CYP2C12 substrate	0,787
	Membrane integrity agonist	0,781
	Antidyskinetic	0,761

MEE-1g	CYP2C12 substrate	0,817
	Maleate isomerase inhibitor	0,788
	CYP2J substrate	0,775
	Venombin AB inhibitor	0,773
	Aspulvinone dimethylallyltransferase inhibitor	0,773
MEE-1d	Taurine dehydrogenase inhibitor	0,766
	CYP2J substrate	0,690
	Fibrinolytic	0,674

**Note: Pa - The probability that an activity exists.*

According to predictions of Table 1, compound MEE-1 showed the highest result of CYP2H substrate 0.872 (87%), CDP-glycerol glycerophosphotransferase inhibitor 0.855 (85%) and membrane integrity antagonist 0,803 (80%). All substances of the MEE series showed high activities as substrates of CYP2H, CYP2F1, CYP2B6, CYP2C12, CYP2J and inhibitors of venombin AB, aspulvinone dimethylallyltransferase, taurine dehydrogenase, gluconate 2-dehydrogenase (acceptor) and maleate isomerase. Also, substances MEE-1v and MEE-1d showed antidyskinetic 0,761 (76%) and fibrinolytic 0,674 (67%) activities.

Conclusion. The pharmacokinetic and pharmacotherapeutic parameters of bis-carbamate MEE-1 and its derivatives were predicted, and in silico screening of biological activity for medicine were carried out. Virtual PASS screening revealed that all bis-carbamates can act as CYP2H, CYP2F1, CYP2B6, CYP2C12, CYP2J substrates as well as venombin AB, aspulvinone dimethylallyltransferase, taurine dehydrogenase, gluconate 2-dehydrogenase (acceptor) and maleate isomerase inhibitors. The results show that MEE series bis-carbamates and its derivatives exhibit a wide range of in silico activities and can be used for the synthesis of potential bioactive compounds and used in pharmacology.

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