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# PREDICTION OF PHARMACOLOGICAL ACTIVITIES OF BIS-CARBAMATE MEE-2 AND ITS DERIVATIVES

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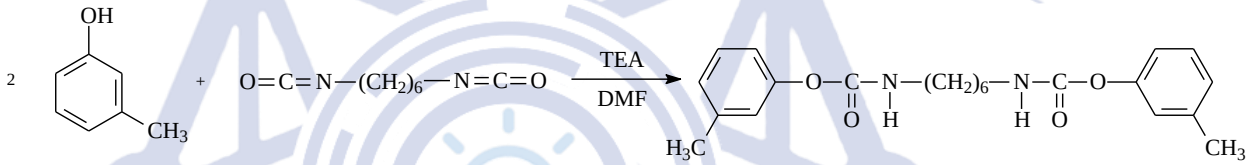
**Abstract.** In this research work, the biological activities of bis-carbamate MEE-2 and its derivatives were studied in the online pass online virtual screening program for the pharmaceutical and medical industries. As a result of screening, many pharmacotherapeutic activities were identified with a high percentage of the presence of various cytochromes as inhibitors, agonists and substrates. The data obtained will help for further research on these compounds and their use in pharmacology.

**Key words:** Bis-carbamate, pass online, screening, agonist, activity, medical, biological, virtual, cytochromes.

**Introduction.** Carbamates, or urethanes, are organic compounds with the general formula R'R"NCOOR 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. Also, representatives of this class of chemical compounds exhibit broad biological activity, due to which they are used as additives and medicines (for example, proserine and carbacholine). 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]. The authors of this article synthesized bis-carbamates of the MEE series [20-23]. For example scheme for the synthesis of bis-carbamate N,N′-hexamethylene bis-[(meta-cresol)-carbamate] i.e. MEE-2:




The mechanism and parameters influencing the reaction have been studied [16,18]. MOL file model of bis-carbamate MEE-2 for Pass online program (fig. 1):

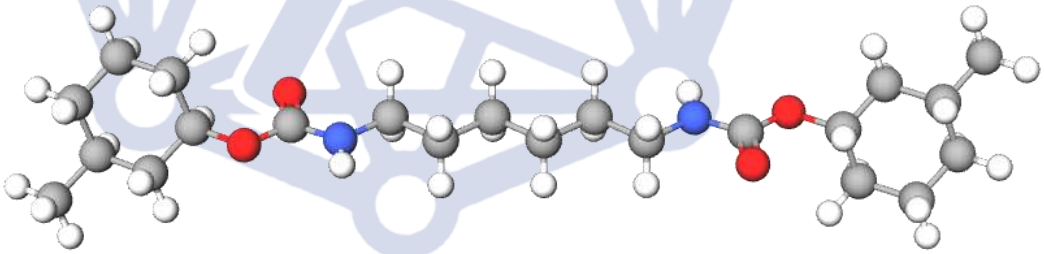


**Figure 1. MolView (model) of bis-carbamate MEE-2**

The resulting product was studied in international chemical databases [8]. We present to you the initial calculations of the bis-carbamate molecule MEE-2 using Pass online program (Table 1):

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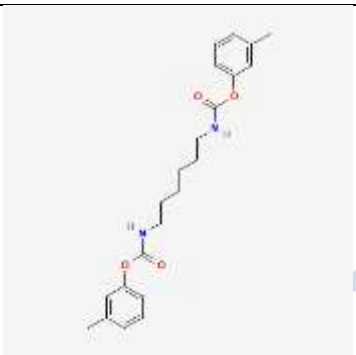
**Table 1**

**Preliminary description of the compound MEE-2**

| | | | |
|---|---|---|---|
|  Compound MEE-2 | Formula | | $C_{22}H_{28}N_2O_4$ |
| | Molecular weight | | 384.4742 u |
| | Hydrogen bond donors | | 2 |
| | Hydrogen bond acceptors | | 4 |
| | Percent composition | | |
| | C | 12.0107 u × 22 | 68.727 % |
| | H | 1.00794 u × 28 | 7.3406 % |
| | N | 14.0067 u × 2 | 7.2863 % |
| | O | 15.9994 u × 4 | 16.646 % |

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.** Synthesis of N,N'-hexamethylene bis-[(m-cresol)-carbamate] i.e. MEE-2: In a three-neck flask equipped with a reflux condenser, a thermometer, and a stirrer, place 7.70 g (0.02 mol) of meta-cresol, add 30 ml of triethylamine (TEA), 60 ml of dimethylformamide (DMF), add drops at a temperature of 40-42 °C with stirring 2.6 ml hexamethylene diisocyanate (HMDI) dissolved in 8 ml DMF. The reaction mixture is stirred for 3 hours at a reaction mixture temperature of 45-48 °C. After the time has passed, the contents of the flask are transferred to a glass and water is added. The deposited precipitate is washed with those. After drying, a colorless powder is obtained with a yield of 9.6 g (93.7% of theoretical). $T_{melt}$ = 201–202°C; $R_f$ = 0.74; $M_M$ = 468.64; Found, %: C – 71.74; H – 8.51; N – 5.98; Calculated, %: C – 71.76; H – 8.60; N – 5.97.

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-[(meta-cresol)-carbamate] i.e. MEE-2; N,N′-hexamethylene N,N′-dinitroso bis-[(meta-cresol)-carbamate] i.e. MEE-2a; N,N′-hexamethylene N,N′-disodium bis-[(meta-cresol)-carbamate] i.e. MEE-2b; N,N′-hexamethylene N,N′-diisopropyl bis-[(meta-cresol)-carbamate] i.e. MEE-2v; N,N′-

hexamethylene N,N′-dichloro bis-[(meta-cresol)-carbamate] i.e. MEE-2g; N,N′-hexamethylene N,N′-dibenzyl bis-[(meta-cresol)-carbamate] i.e. MEE-2d.

**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 2).

**Table 2**

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

| Substances | Activities | Pa |
|---|---|---|
| **MEE-2** | CDP-glycerol glycerophosphotransferase inhibitor | 0,846 |
| | Against eczema | 0,808 |
| **MEE-2a** | CYP2F1 substrate | 0,767 |
| | TP53 expression enhancer | 0,640 |
| **MEE-2b** | CYP2C12 substrate | 0,867 |
| | General anesthesia | 0,734 |
| | Antiseborrheic | 0,743 |
| **MEE-2v** | CYP2C12 substrate | 0,844 |
| | Antidyskinetic | 0,713 |
| | Antihypoxic | 0,667 |
| **MEE-2g** | CYP2C12 substrate | 0,867 |
| | Acaricide | 0,628 |
| | Against infection | 0,615 |
| | Antiseptic | 0,600 |
| **MEE-2d** | Taurine dehydrogenase inhibitor | 0,768 |
| | 1,4-lactonase inhibitor | 0,675 |
| | Fibrinolytic | 0,618 |

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

According to predictions of Table 2, compound MEE-2a showed the highest result of CYP2F1 substrate 0.767 (76%) and TP53 expression enhancer 0.640 (64%), compound MEE-2 showed result CDP-glycerol glycerophosphotransferase inhibitor 0.846 (84%) and against eczema 0,808 (80%). All substances of the MEE series showed high activities as substrates of CYP2F1, CYP2C12. Compound MEE-2d showed inhibitor of taurine dehydrogenase and 1,4-lactonase. Also, substances MEE-2v and MEE-2g showed antidyskinetic 0,713 (71%), antihypoxic 0,667 (66%) and against infection 0,615 (61%), antiseptic 0,600 (60%) activities.

**Conclusion.** The pharmacokinetic and pharmacotherapeutic parameters of bis-carbamate MEE-2 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 CYP2F1, CYP2C12 substrates as well as CDP-glycerol glycerophosphotransferase, taurine dehydrogenase and 1,4-lactonase 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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