28-29 September 2023,
Kragujevac, Serbia

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2nd International Conference on Chemo and Bioinformatics
ICCBIKG_2023

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BOOK OF PROCEEDINGS

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Sponsored by

2nd International Conference on Chemo and BioInformatics, Kragujevac, September 28-29, 2023, Serbia.

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Publisher:

Institute for Information Technologies, University of Kragujevac, Serbia, Jovana Cvijića bb, 2023

Press:

„Grafo Ink“, Kragujevac

Impression:

120 copies

CIP - Каталогизација у публикацији - Народна библиотека Србије, Београд

54:004(048)(0.034.2)
57+61]:004(082)(0.034.2)

INTERNATIONAL Conference on Chemo and BioInformatics (2 ; 2023 ;
Kragujevac) Book of Proceedings [Elektronski izvor] / 2nd International Conference on
Chemo and BioInformatics, ICCBIKG 2023, September 28-29, 2023 Kragujevac,
Serbia ; [editors Zoran Marković, Nenad Filipović]. - Kragujevac : University,
Institute for Information Technologies, 2023 (Kragujevac : Grafo Ink). - 1 USB
fleš memorija ; 1 x 2 x 6 cm

Sistemski zahtevi: Nisu navedeni. - Nasl. sa naslovne strane dokumenta. - Tiraž
120. - Bibliografija uz svaki rad.

ISBN 978-86-82172-02-4

a) Хемија -- Информациона технологија -- Зборници b) Биомедицина --
Информациона технологија -- Зборници

COBISS.SR-ID 125908489

In silico Drug-Likeness, Pharmacokinetic and other ADME properties of 2-(aminomethyl)cyclopropane-1,1-dicarboxylic acid

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DOI: 10.46793/ICCBI23.455K

Abstract: Herein we present the results of *in silico* determination of Drug-Likeness, Pharmacokinetic and other ADME properties of 2-(aminomethyl)cyclopropane-1,1-dicarboxylic acid as an example constrained γ-amino dicarboxylic acid. The results of *in silico* screening of drug-likeness, pharmacokinetic and other ADME (absorption, distribution, metabolism and elimination) properties of 2-(aminomethyl)cyclopropane-1,1-dicarboxylic acid have revealed that this compound is not able to cross the blood-brain barrier, but it shows good solubility and gastrointestinal absorption. The possible target screening has indicated the family C G protein-coupled receptors as the most probable physiological targets. More specifically, the 2-(aminomethyl)cyclopropane-1,1-dicarboxylic acid has the highest structural similarity with the known compounds that act on metabotropic glutamate receptor, excitatory amino acid transporter and betaine transporter. Taking all the above into consideration, it can be concluded that our investigated compound could be considered as a candidate molecule for further structural transformations that could enable better pharmacological performance and physiochemical properties.

Keywords: amino acids; ADMET; pharmacology

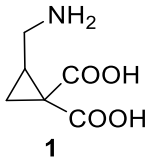
1. Introduction

Taking into consideration that drug discovery can be time-consuming and very expensive process, the application of different predictors for the determination of a potential drug's in vivo studies and properties necessary for the administration under physiological conditions, is today a recognizable concept for successful drug design and synthesis. ADME properties (absorption, distribution, metabolism and elimination) are excellent predictors of the potential drug's success. Numerous different *in silico* ADME tools have been developed, all based solely on the use of chemical structures [1-3]. Herein we present the results obtained by

the application of SwissADME tool for the evaluation of pharmacokinetics, drug-likeness and other ADME properties of 2-(aminomethyl)cyclopropane-1,1-dicarboxylic acid as an example of sterically constrained amino acids.

2. Results and Discussions

2-(Aminomethyl)cyclopropane-1,1-dicarboxylic acid 1 (Figure 1) as an example of the unnatural amino acids, previously synthetized by us [4], as an example of sterically constrained gamma amino acids. Taking into consideration that our previous work was directed to the resolution of the synthetic pathway for approaching this compound and that compound has never been screened for pharmacological potential, herein we present the results of it *in silico* determination of Drug-Likeness, Pharmacokinetic and other ADME properties. For this purpose, the SwissADME online tool [3] was used to evaluate pharmacokinetics, drug-likeness and other ADME properties and the obtained data are presented in Table 1. According to the data given in Table 1 it can be noticed that the compound has good water solubility and high gastrointestinal absorption, but no possibility to cross the blood-brain barrier.



1

Figure 1. 2-(Aminomethyl)cyclopropane-1,1-dicarboxylic acid.

Table 1. Predicted Drug-Likeness, Pharmacokinetic and other ADME properties calculated by SwissADME web tool for 2-(aminomethyl)cyclopropane-1,1-dicarboxylic acid .

Substrate: 2-(aminomethyl)cyclopropane-1,1-dicarboxylic acid			
Physicochemical Properties		**Pharmacokinetics**	
Formula	$C_5H_9NO_4$	GI absorption	High
Molecular weight	159.14 g/mol	BBB permeant	No
Fraction Csp3	0.67	P-gp substrate	No
Num. rotatable bonds	3	CYP1A2 inhibitor	No
Num. H-bond acceptor	5	CYP2C19 inhibitor	No
Num. H-bond donors	3	CYP2C9 inhibitor	No
Molar Refractivity	34.83	CYP2D6 inhibitor	No
TPSA [a)]	100.62 Å²	CYP3A4 inhibitor	No
		Log Kp (skin permeation)	-9.75 cm/s
Lipophilicity		**Drug-Likeness**	
Log Po/w (iLOGP)	0.32	Lipinski	Yes; 0 violation
Log Po/w (XLOGP3)	-3.49	Ghose	No; 3 violations [c)]
Log Po/w (WLOGP)	-0.88	Veber	Yes
Log Po/w (MLOGP)	-0.98	Egan	Yes
Log Po/w (SILICOS-IT)	-0.088	Muegge	No; 2 violations [d)]
Log Po/w [b)]	-1.18	Bioavailability Score	0.56
Water Solubility		**Medicinal Chemistry**	
Log S (ESOL)	1.57	PAINS	0 alert
Solubility	5.91e+03 mg/mL ; 3.72e+01 mol/L	Brenk	1 alert: β-keto anhydride
Class	**Highly soluble**	Leadlikeness	No; 1 violation [e)]
Log S (Ali)	1.96	Synthetic accessibility	1.79
Solubility	1.44e+04 mg/mL ; 9.06e+01 mol/L		
Class	**Highly soluble**		
Log S (SILICOS-IT)	0.75		
Solubility	3.95e+02 mg/mL ; 5.62e+00 mol/L		
Class	**Soluble**		

a) topological polar surfes area; b) average of all 5 predictions; c) MW<160,WLOGP<-0.4, MR<40
d) MW<200, XLOGP3<-2 e) molecular weight <250

The possible intracellular targets of 2-(aminomethyl)cyclopropane-1,1-dicarboxylic acid are given in Figure 2. As it can be seen, our compound has appeared to act on family C G protein-

coupled receptors. C G protein-coupled receptors are transmembrane proteins of the mammalian genome that became pharmaceutically interesting due to the fact that they represent targets of the many approved drugs. More specifically, the 2-(aminomethyl)cyclopropane-1,1-dicarboxylic acid has the highest structural similarity with the known compounds that act on metabotropic glutamate receptor, excitatory amino acid transporter and betaine transporter.

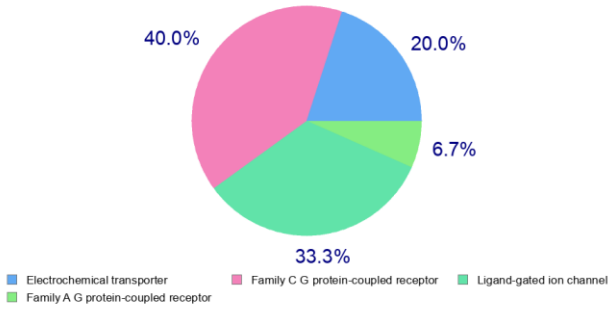


Figure 2. Target prediction of 2-(aminomethyl)cyclopropane-1,1-dicarboxylic acid.

3. *In silico* Drug-Likeness, Pharmacokinetic and other ADME properties study

The physicochemical, ADME, and drug-likeness parameters were computed using the SwissADME online program [3]. This software was used to calculate basic physicochemical properties including topological polar surface area (TPSA) and molecular refractivity. Lipophilicity was estimated through iLOGP, XLOGP3, WLOGP, MLOGP, and SILICOS-IT models from which an average value of all five predictions log Po/w was determined. The solubility (log S) was calculated by three different models: ESOL, Ali, and SILICOS-IT. Drug-likeness evaluation was based on Lipinski, Ghose, Veber, Egan and Muegge rules of 5. The Abbot Bioavailability scores were computed to predict the probability of a compound having at least 10% oral bioavailability by relying on total charge, TPSA, and violation of the Lipinski's filter. From pharmacokinetic properties gastrointestinal (GI) absorption, blood-brain barrier (BBB) permeation, inhibition of the cytochrome P450 system, permeability glycoprotein (P-gp) substrate and the skin permeation coefficient (kp) were calculated. Also, tested compounds are screened through PAINS and Brenk filters and Lead likeness potential and synthetic accessibility are calculated.

4. Conclusions

The results of *in silico* screening of drug-likeness, pharmacokinetic and other ADME properties of 2-(aminomethyl)cyclopropane-1,1-dicarboxylic acid have revealed that this compound is not able to cross the blood-brain barrier, but it shows good solubility and gastrointestinal absorption. The possible target screening has indicated the family C G

protein-coupled receptors as the most probable physiological targets. Taking all the above into consideration, it can be concluded that our investigated compound could be considered as a candidate molecule for further structural transformations that could enable better pharmacological performance and physiochemical properties.

Acknowledgment

This research is funded by the Ministry of Education and Ministry of Science, Technological Development and Innovation, Republic of Serbia, Grants: (Agreement No. 451-03-47/2023-01/ 200122 and 451-03-47/2023-01/200378).

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