Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Spl Issue [5] 2022 : 693-696

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

ORIGINAL ARTICLE **OPEN ACCESS**

In Silico ADME Prediction of Drug Likeness and Pharmacokinetics Properties of Rhodamine Molecules

Stephen Kumar Celestina*[1],Rajendran Kumar[2], Kaveri Sundaram[2], Senthilraja[1], M. Narayanan[1], and Puja Rai[3]
1. Dhanalakshmi Srinivasan college of Arts and science for women, perambalur-621212, Tamilnadu, India
2. Karpagam Academy of Higher Education, Coimbatore-641021, Tamilnadu, India
3.Sr. Lecturer, Babu Banarasi Das University, Lucknow, U.P., INDIA)
Email-celestinachem@gmail.com

ABSTRACT
The development of drug involves the action of absorption, distribution, metabolism, excretion raising earlier in the discovery progress of drug. Various experimental and computational methods have been developed to obtain ADME properties in an economical manner in terms of time and cost. As in vitro and in vivo experimental data on ADME have accumulated, the accuracy of in silico models in ADME increases and thus, many in silico models are now widely used in drug discovery. Because of the demands from drug discovery researchers, the development of in silico models in ADME has become more active. Here, the four different rhodanine were predicted by Swiss ADME to determine the pharmacokinetic properties. The pharmacokinetic properties of the molecule must be achievable at the earliest which ultimately pays to the success or failure of the compound. In silico ADME have been developed as an extra tool to support medicinal chemists to design and optimization.All the compounds were found to have good pharmacokinetic and drug likeness properties.
Keywords: ADME, rhodanine, pharmacokinetics, druglikeness properties.

Received 22.10.2022 Revised 20.11.2022 Accepted 16.12.2022

INTRODUCTION

The biochemical behaviour, pharmacokinetics and safety are the combination of a successful drug. In addition to this, high selectivity and potency, absorption, distribution, metabolism, excretion and toxicity (ADMET) properties plays a significant role in drug development [1-3]. An ideal drug must be taken in to the body, distributed to various organs and tissues, then metabolized, that does not instantly remove its activity, eliminated in a proper way and confirmed the drug by non-toxicity [4]. Around 40% of drug failures are mainly caused by ADMET problems. Despite the fact the preclinical study of ADMET have led to decreases the amount of drug failures caused by pharmacokinetics. The nonoptimal ADMET can end up with late-stage failures, it is responsible for a large unproductive investment of time and money [5]. In silico models are used to improve the ADMET prediction and are contributing to drug optimization [6]. Usually, the ADMET properties measurement for a drug was generally scheduled and it can be determined after its potency of a particular target [7].

Unfortunately, undesirable effects were also often detected in this stage, and therefore a new molecular design need to be conducted or the undesirable compounds can be excluded at the earlier stage of discovery and development of drugs [8,9]. In past years, the many studies based on insilico concerning ADMET parameters. Meanwhile, the researchers developed a variety of webtools and it is used in the application of drug discovery [10-12].Rhodanine are an important class of compounds which showed a wide range of biological activity such as antifungal, antitumor, antiviral, anticancer and antidiabetic activity [13-17]. Swiss ADME is a far reaching and a new website run by the Swiss institute of bioinformatics. In present study, we aimed to evaluate the chemical profiles of rhodanine derivatives shows in **Fig.1.,**was already reported [17-19]and the biological activity was predicted using computational analysis.

MATERIALS AND METHODS

Experimental method

In the present study, we predicted the pharmacological properties and drug likeness like toxicity and mutagenicity using the Swiss ADME tool [18]. The ADMET properties were determined using

pharmacokinetics parameters. The lipophilicity and hydrophilicity were predicted by using XLOGP3, WLOGP, MLOGP, SILICOSIT and iLOGP. The lipophilicity character of a compound was evaluated by the models are iLOGP, WLOGP, SILICOS-IT, XLOGP3, MLOGP. iLOGP is a physics-based technique to analyse the solvation in n-octanol and water. WLOGP is an atomistical process that is applied to a fragmental system. SILICOS-IT is a hybrid system that depend on 7 topological and 27 fragments descriptors. XLOGP3, atomistic approach with knowledge-based library and corrective aspects. MLOGP, topological method, is based on linear relationship. Water solubility was predicted using ESOL and Ali *et al* method [19]. The fragmental technique is used to calculate the topological polar surface area (TPSA). It was calculated using sulphur and phosphorus atoms. Drug likeness properties were predicted using more filters namely Lipinski, Ghose [20], Egan [21], Veber[22], Muegge. The Bioavailability score was implemented without changes from Martin [23] and it is similar but seeks to predict the probability of a compound to have at least 10% oral bioavailability in rat or measurable Caco-2 permeability

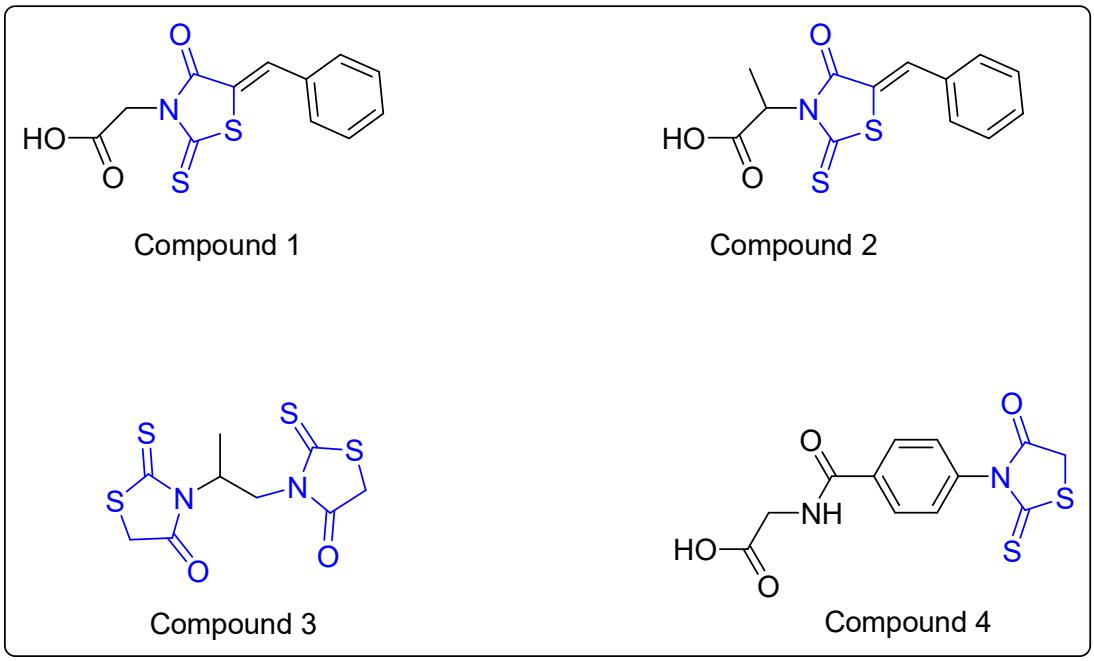

Fig.1 Structure of four different rhodanine for ADME properties

RESULT AND DISCUSSIONS

The discovery and development of drug is the most important and difficult step which is carrying out pharmacokinetics and drug metabolism. The different rhodanine compounds are evaluated for ADME properties using Swiss ADME Tools. Lipinski rule of 5 was used to predict rapidly the drug likeliness of the compounds as reported in **Table 1**.The physicochemical properties include molecular weight, molecular formula, No. of heavy atoms, No. of rotatable bonds, No. of aromatic heavy atoms, No. of hydrogen bond donor, No. of hydrogen bond acceptor, TPSA and molar refractivity. The physicochemical properties show in Table. The PSA is figured by a technique known as (TPSA) topological polar surface area and polar atoms phosphorus and sulphur. All the compounds revealed that the molecular weight less than 500 Da, which is important for the drug likeness of the small molecules. The molecular weight of four different rhodanine compounds ranges from 279.33-310.35.

Table1 Physicochemical properties rhodanine

Compounds	Molecular mass	No. of rotatable bonds	H-Bond donor	H-Bond acceptor	Molar Refractivity (m^3/mol)	TPSA Å^2
1	279.33	3	1	3	77.81	115.00
2	293.36	3	1	3	82.62	115.00
3	306.45	3	0	2	85.93	115.40
4	310.35	5	2	4	81.43	144.10

Lipophilicity (log P) of compounds takes place in a significant position in the membrane transport of the compounds thereby determining the drug's action. So, it is advisable to have the Log P value within the optimal range to improve the compound's quality and likelihood of its success in therapeutics. If the

lipophilicity is too low, a drug will exhibit a poor ADMET property. All compounds the Log P values were below 5. The values are depicted in **Table2.**

Table2 Lipophilicity characteristics of rhodanine

Compounds	iLOGP	WLOGP	XLOGP3	MLOGP	SILICOS-IT
1	1.81	1.48	2.57	0.89	2.84
2	2.11	1.87	2.97	1.16	3.04
3	2.09	0.33	1.91	0.14	3.54
4	1.30	0.48	1.28	0.19	1.94

Water solubility is similar to lipophilicity, the method of multiple predictive and the results are showed in **Table 3**. It is one of important factors determining oral bioavailability. In Most of the compounds were soluble and remaining are moderately soluble. The solubility is strongly influenced by the solvent used and the ambient pressure and temperature.

Table3 water solubility characteristics of rhodanine

Compounds	LOG S(ESOL)	class	LOG S (ALI)	Class	LOG S (SILICOS-IT)	Class
1	-3.24	soluble	-4.63	Moderately soluble	-2.46	soluble
2	-3.57	soluble	-5.05	Moderately soluble	-2.49	soluble
3	-2.75	soluble	-4.80	Moderately soluble	-1.22	soluble
4	-2.46	soluble	-3.91	soluble	-2.42	soluble

The gastrointestinal absorption is the process, of passing the drug into the blood stream. It affects the drug bioavailability and determines how rapidly and how far of the drug reaches the place of action.The compound **1** and **2** had high values of GI absorption which is directly proportional to the Blood-brain barrier. In BBB, no compounds can pass through the barrier proposed that all the compounds were safe to be developed the drug. This shows all the compounds was predicted to have good absorbtion. There is no single compound has a tendency to act as P-gp substrate. The pharmacokinetics parameters and bioavailabilty of the rhodanine shows in **Table 4.**

Table4 Pharmacokinetics parameters of rhodanine

Compounds	GI absorption	BBB permeant	P-gp substrate
1	High	No	No
2	High	No	No
3	Low	No	No
4	Low	No	No

A drug absorbed in time requirement and well distributed into the system for its active metabolism and action is said to be a good drug. In drug likeness properties shows in **Table 5,** the all the compounds were obeying the Lipinski's rule and Ghose with no violation. In compound **1** and **2**showed that all the filters did not have any violation. In compound 3 ,the structures that show one violation of the veber, Egan and Muegge filters must be excluded from further preclinical processes.In compound 4, the veber and Egan filters show one violation.

Table5 Bioavailability of rhodanine

Compounds	Lipinski	Ghose	veber	Egan	Muegge	Bio availability score
1	Yes	Yes	Yes	Yes	Yes	0.56
2	Yes	Yes	Yes	Yes	Yes	0.56
3	Yes	Yes	No	No	No	0.55
4	Yes	Yes	No	No	Yes	0.56

CONCLUSION

Drug designing and development process, the pharmacokinetics and physicochemical properties evaluation the primary task. In the present work, we evaluated 4 different rhodanine compounds with *In Silico* screening process based on ADME properties. Furthermore, it can be oblique that the most of the compound have good physicochemical properties with some other ADMET properties. Hence, we can now say that these designed compounds possess a good pharmacokinetic property.

ACKNOWLEDGEMENT
The authors acknowledge Chancellor Shri A.Srinivasan , Dhanalakshmi Srinivasan Group of Institutions, for the financial support of this work .

CONFLICT OF INTEREST
The authors declare that they have no conflict of interest.

REFERENCES
1. Cumming, J. G., Davis, A. M., Muresan, S.,Haeberlein, M.,&Chen, H. (2013).Chemical predictive modelling to improve compound quality.Nat. Rev. Drug Discov., **12:**948–962.
2. Hou, T.,&Wang, J. (2008). Structure – ADME relationship: still a long way to go?.DrugMetab. Toxicol., **4:** 759–770.
3. Gupta, P. K. (2018).Illustrated Toxicology.Elsevier, 67−106.
4. Hodgson,J. (2001).ADMET—turning chemicals into drugs. Nat. Biotechnol.,**19:** 722–726.
5. Bocci, G.,Carosati, E., Vayer, P., Arrault,A.,Lozano, S.,&Cruciani, G. (2017).ADME-Space: a new tool for medicinal chemists to explore ADME properties.Sci. Rep.,**7:**6359.
6. Wang, Y., Xing, J., Xu, Y., Zhou, N., Peng, J., Xiong, Z., Liu, X., Luo, X., Luo, C., Chen, K., Zheng, M.,& Jiang, H. (2015). Q. Rev. Biophys., 48: 488–515.
7. Selick, HE., Beresford, AP.,&Tarbit MH. (2002).The emerging importance of predictive ADME simulation in drug discovery.Drug Discov., Today, **7**: 109–116**.**
8. Kennedy, T. (1997). Managing the drug discovery/development interface.Drug Discov. Today**., 2**: 436–444.
9. Kola,I. &Landis, J. (2004).Can the pharmaceutical industry reduce attrition rates?.Nat. Rev. Drug Discov.,**3**:711–715.
10. Dong,J., Wang, N. N., Yao,Z. J., Zhang, L., Cheng,Y., Ouyang, D., Lu,A. P. &Cao, D. S. (2018).ADMETlab: a platform for systematic ADMET evaluation based on a comprehensively collected ADMET database. J Cheminform, **10:**29.
11. Lagorce,D.,Bouslama,L., Becot, J., Miteva,M. A. &Villoutreix, B. O. (2017). FAF-Drugs4: free ADME-tox filtering computations for chemical biology and early stages drug discovery. Bioinformatics.,**33:**3658–3660.
12. Yang, H.,Lou, C., Sun, L., Li, J., Cai, Y., Wang,Z.,&Tang,Y. (2019). admetSAR 2.0: web-service for prediction and optimization of chemical ADMET propertiesBioinformatics., **35**:1067–1069.
13. Celestina, S. K., Sundaram, K.,& Ravi,S. (2015).Synthesis of 5-benzylidine rhodanines and their cytotoxicity on hela cell lines.Research Journal of Pharmaceutical, Biological and Chemical Sciences,**6(5)**: 1695-1700.
14. Sortino, M., Delgado, P., Jua´ rez, S., Quiroga, J., Aboni´a, R., Insuasty, B., Nogueras, M., Rodero, L., Garibotto, F M., Enriz, R D.,&Zacchino, S A. (2007). Bioorg. Med. Chem.,**15**: 484.
15. Tomasic, T., Zidar, N., Mueller-Premru, M.,Kikelj, D.,&Masic, L. (2010).Synthesis and antibacterial activity of 5-ylidenethiazolidin-4-ones and 5-benzylidene-4,6-pyrimidinediones. Eur. J. Med. Chem.,**45:** 1667.
16. Sim, MM., Ng, S. B., Buss, A. D., Crasta, S. C., Goh, K. L.,&Lee, S. K. (2002). Benzylidene Rhodanines as Novel Inhibitors of UDP-*N*-Acetylmuramate/L-Alanine Ligase.Bioorg. Med. Chem. Lett**., 12**: 697.
17. Celestina, S. K., Sundaram, K.,&Ravi, S. (2020). *In vitro* studies of potent aldose reductase inhibitors: Synthesis, characterization, biological evaluation and docking analysis of rhodanine-3-hippuric acid derivatives. Bioorganic Chemistry,**97:** 103640.
18. Harshitharaj, PK., Kumar, R.,&Ravi, S. (2016).Synthesis, cytotoxic activity and molecular docking study of Bis-Rhodanine derivative. Journal of chemical and pharmaceutical science, **9**: 2478-2482.
19. Kumar, R., celestina, S. K.,&Sundarm, K. (2018).Molecular docking studies of 3-A-carboxy ethyl rhodanine and 3-A-carboxy methyl rhodanine against T315i BCR-ABL and HPV 16.Journal of pharmaceutical science and Research,**10:** 2069-2073.
20. Lohidashan, K., Rajan, M., Ganesh, A., Paul, M. &Jerin, J. (2018). Pass and Swiss ADME collaborated in silico docking approach to the synthesis of certain pyrazoline spacer compounds for dihydrofolate reductase inhibition and antimalarial activity.Bangladesh J. *Pharmacol.*, **13:**23.
21. Ali, J., Camilleri, P., Brown, M. B., Hutt A.J., &Kirton, S.B. (2012).Revisiting the general solubility equation: in silico prediction of aqueous solubility incorporating the effect of topographical polar surface area. J. Chem. Inf. Model., **52:**420.
22. Ghose, A.K.,ViswanadhanV. N.,&Wendoloski, J.J. (1999).A knowledge-based approach in designing combinatorial or medicinal chemistry libraries for drug discovery.J. Comb. Chem.,**1:**55.
23. Egan, W. J., Zlokarnik,G., &Grootenhuis, P.D. (2004). *In silico* prediction of drug safety: despite progress there is abundant room for improvement. Drug Discov. Today. Technol., **1**:381.
24. Veber, D. F., Johnson, S. R., Cheng, H.Y., Smith, B.R., Ward K.W.,& Kopple, K.D. (2002).Molecular Properties That Influence the Oral Bioavailability of Drug Candidates.J. Med. Chem., **45:**2615.
25. Martin, Y.C.(2005). A Bioavailability Score. J Med. Chem., **48:** 3164.

CITATION OF THIS ARTICLE
Stephen Kumar Celestina, Rajendran Kumar, Kaveri Sundaram, Senthilraja, M. Narayanan. and Puja Rai: In silico ADME Prediction of Drug Likeness and Pharmacokinetics Properties of Rhodamine Molecules. Bull. Env.Pharmacol. Life Sci., Spl Issue [5]: 2022: 693-696.