Evaluating the pharmacological profile of angular triquinane type hydantoins

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Abstract: The aim of this study is the *in silico* prediction and comprehensive analysis of the pharmacological profile of a mini series of angular triquinane type hydantoin compounds. The ADMET analysis estimates favorable absorption and distribution capabilities. Slow clearance is predicted, so they would have enough time to exhibit their activities. Toxicological assessments predicts the possibility of some toxic effects, so an experimental toxicological evaluation is needed for confirmation. These results could provide a framework for the design, structural optimization and development of novel triquinane hydantoin based therapeutics.

Keywords: hydantoin, triquinane, alkaloid, ADMET

1. Introduction

Hydantoins are a broad class of drug-like compounds with a cyclic ureide structure, mostly known for the wide spectra of biological activities they exhibit and their applications in medicine and industry [1]. The hydantoin molecule, albeit small, contains five derivatization points and is able to for various complex and diverse structures.

The angular triquinane skeleton has been a point of interest in organic synthesis and drug discovery, because its core structure is present is many natural products [2] and these types of structurally diverse compounds exhibit unique biological activities, such as antiholinesterase activity, for example, which could lead to the development of novel antidotes [3].

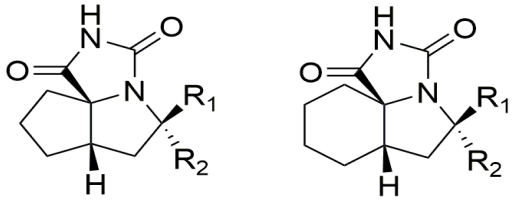

Figure 1. Structure of angular triquinane type hydantoins.

In our previous work, we have reported the synthesis of a series of angularly fused triquinane type hydantoins (Figure 1) [4] and the aim of this study is the evaluation of the pharmacological profile of these compounds through ADMET analysis. Evaluation of how compounds behave in the body is a crucial step in drug discovery, as it not only narrows down further synthetic dilemmas, but also helps in the SAR inspired design and optimization process.

2. Methodlogy

ADMET analysis was performed using the resources from the ADMETlab 3.0 web server [5]. ADMETlab 3.0 was chosen over other ADMET prediction tools because it was shown to be efficient and easily comprehensible.

3. Results and Discussion

ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) analysis is a conventient method for predicting how a potential drug could behave inside the body. Evaluating various physicochemical and pharmacological parameters of synthesized compounds is in important step in determining their potential as a therapeutic agents.

Empirically, compounds with therapeutic applicability have certain physicochemical parameters (molecular weight, volume, density, number of hydrogen bond donors and acceptors, polarity, flexibility, solubility, lipophilicity and more) within a certain range. Physicochemical parameters for the investigated compounds fall within the optimal range suggested by Lipinski, Pfizer and GSK rules, indicating a favorable ADMET profile.

Absorption and distribution are measures of drug intake and their assessment is crucial for evaluating bioavailability of an orally administered drug. Predicted absorption and distribution parameters are given in Table 1. The Caco-2 human colon adenocarcinoma cell line is widely used for modeling gastrointestinal permeability. All compounds have predicted permeability values greater than -5.15 log cm s^{-1}, which is considered optimal. HIA (Human Intestinal Absorption) is another important indicator of drug absorption. All compounds have predicted values lower than 0.3, which indicates high intestinal absorption. Another significant absorption parameter is oral availability. $F_{20\%}$, $F_{30\%}$ and $F_{50\%}$ are probablities of the compounds having a 20%, 30% and 50% oral bioavailability. Values under 0.3 indicate high probability, so all investigated compounds except **2a** have a high probability of having oral bioavailability of around 50%, while **2c** possibly has even higher oral availability.

PPB (Plasma Protein Binding) is a value that estimates what fraction of the compound is reversibly bound to plasma proteins, while Fu represents the unbound fraction of the compound in plasma. Only the unbound fraction of the compound is free to further distribute in tissues and exhibit its pharmacological activity. Values of PPB under 90% are considered optimal, which all of the investigated compounds are predicted to have. All of the compounds except **2c** also have a high unbound fraction (Fu over 20%). VD (Volume Distribution) refers to how investigated compounds are distributed within the body. VD values between 0.04-20 L kg^{-1} are considered optimal

and only **2c** falls in this range. The other compounds are indicated to have poor or sub-optimal distribution.

Table 1. Predicted absorption and distribution criteria of the investigated compounds.

	Absorption					Distribution		
	Caco-2	**HIA**	**$F_{20\%}$**	**$F_{30\%}$**	**$F_{50\%}$**	**PPB**	**VD**	**Fu**
1a	-4.972	0.042	0.038	0.081	0.291	23.557	-0.148	70.626
1b	-4.876	0.038	0.062	0.079	0.236	39.61	-0.224	54.202
2a	-4.898	0.022	0.031	0.073	0.327	35.403	-0.104	60.153
2b	-4.821	0.023	0.048	0.063	0.236	52.931	-0.201	45.015
2c	-4.779	0.045	0.031	0.027	0.16	82.263	0.14	15.721

Metabolism parameters for the investigated compounds are given in Table 2 and refer to the probablity of the compounds to interact with important cytochrome P450 enzymes in the liver as either substrates or inhibitors. All compounds are predicted as non-inhibitors of CYP1A2, while only **1b** and **2b** have a medium probability of being its substrates. Only **2c** is predicted to be an inhibitor of CYP2C9, while none are estimated to be substrates. None of the compounds are estimated to be inhibitors of CYP3A4, while all of them are predicted to be its substrates, with high probability. HLM (Human Liver Microsomal) stability is a measure of a drug's resistance to breakdown by liver enzymes. Values under 0.3 indicate high stability, which all compounds exhibit. The results indicate that all compounds except **2c** could be well metabolized in the body.

All compounds are predicted to have low clearance values, below 5 ml min^{-1} kg^{-1} (Table 2), which means adequate time for the compounds to exhibit their effects. All compounds have short half-lives ($T_{1/2}$), meaning that they would be quickly metabolized.

Table 2. Predicted metabolism and excretion criteria of the investigated compounds.

	Metabolism							Excretion	
	CYP1A2		CYP2C9		CYP3A4		HLM	CL_{plasma}	$T_{1/2}$
	inh.	sub.	inh.	sub.	inh.	sub.			
1a	0.0	0.038	0.29	0.0	0.033	1.0	0.001	2.731	1.481
1b	0.0	0.548	0.002	0.0	0.06	1.0	0.001	3.038	1.615
2a	0.0	0.174	0.137	0.0	0.039	1.0	0.001	2.848	1.335
2b	0.0	0.376	0.002	0.0	0.1	1.0	0.001	3.127	1.451
2c	0.0	0.076	0.777	0.001	0.16	1.0	0.048	4.947	1.085

Toxicological parameters of the investigated compounds are given in Table 3. None of the compounds are predicted to be hERG blockers. All compounds have a moderate probability of being mutagenic and a high probability of being carcinogenic. All compounds except **2c** have a medium probability of exhibiting ototoxicity and a medium probability of exhibiting hematotoxicity.

Table 3. Predicted toxicity criteria of the investigated compounds.

	hERG	AMES	Carcinogenicity	Ototoxicity	Hematotoxicity
1a	0.029	0.527	0.885	0.468	0.704
1b	0.033	0.56	0.851	0.453	0.676
2a	0.024	0.504	0.869	0.436	0.698
2b	0.026	0.538	0.822	0.42	0.67
2c	0.022	0.548	0.853	0.298	0.531

4. Conclusions

ADMET evaluation is a convenient tool for exploring the pharmacological profile of potential therapeutic agents. The results of the analysis indicate that the investigated compounds could be well absorbed and distributed throughout the body. The compounds are estimated to have a slow clearance from the body, which gives them enough time to exhibit their activity, but are metabolized relatively fast, which would mean that more frequent doses would be more optimal. Toxicological assessment reveals a possibility of carcinogenic, ototoxic and hematotoxic effects. Although relying on *in silico* methods alone is unreliable, this analysis reveals a need for further assessment. If experimental metabolic and toxicological evaluations would demonstrate the drawbacks that the ADMET analysis predicted, then further structure optimization would be prudent to possibly ameliorate these effects.

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