# Physicochemical and pharmacological properties of fused bicyclic hydantoins

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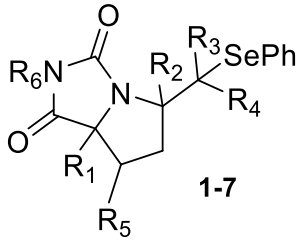
**Abstract**: The aim of this study is the *in silico* prediction and analysis of the physicochemical and pharmacological profile of a series of fused bicyclic hydantoin derivatives. The analysis estimates a favorable ADMET profile, high gastrointestinal absorbion and distribution capabilities. All compounds could be well metabolized in the body, with low to moderate clearance. With few exceptions, toxicological assessments do not predicts a possibility of toxic effects.

**Keywords**: hydantoins, fused bicyclic heterocycles, unnatural amino acids, ADMET

## 1. Introduction

Hydantoins are an ubiquitous structural core found in various biologically active compounds, which exhibit diverse activities, such as anticolvulsant, antitumor, anticancer, antiarrythmic, herbicidal, and others [1]. The observed activities usually do not arise from the hydantoin nucleus itself but from the different substituents that have been attached to it. In particular, spirohydantoins and fused bicyclic hydantoin derivatives have recently attracted much attention in drug discovery. Moreover, substituted hydantoins are important building blocks for the synthesis of non-natural amino acids used to create peptidomimetic, synthetic molecules designed to mimic therapeutic peptides [2].




**1**) $R_1$= Me; $R_2$, $R_3$, $R_4$, $R_5$, $R_6$= H
**2**) $R_1$, $R_3$, $R_4$= Me; $R_2$, $R_5$, $R_6$= H
**3**) $R_1$, $R_2$= Me; $R_3$, $R_4$, $R_5$, $R_6$= H
**4**) $R_1$, $R_2$= Me; $R_3$, $R_4$, $R_6$= H; $R_5$= COOEt
**5**) $R_1$= Me; $R_2$, $R_3$, $R_4$, $R_6$= H; $R_5$= COOEt
**6**) $R_1$, $R_3$, $R_4$, $R_6$= Me; $R_2$, $R_5$= H
**7**) $R_1$, $R_3$, $R_4$= Me; $R_2$, $R_5$= H; $R_6$= $CH_2Ph$

**Figure 1**. Structure of fused bicyclic hydantoins.

In our previous work, we have reported the synthesis of a series of angularly fused bicyclic hydantoins, using selenocyclization as a key step (Figure 1) [3]. The aim of this study is the evaluation of the physicochemical properties and pharmacological profile of

seven selected compounds through ADMET analysis. Evaluation of how compounds behave in the body is a crutial step in drug design and discovery.

## 2. Methodology

ADMET analysis was performed using the resources from the ADMETlab 3.0 web server [4]. ADMETlab 3.0 was chosen over other ADMET prediction tools because it was shown to be efficient and easily comprehensible.

## 3. Results and Discussion

The Lipinski and Veber rules provide criteria for assessing the drugability of compounds. According to Lipinski's rule, a compound should have a molecular weight (MW) of less than 500 g/mol, an octanol/water partition coefficient (logP) of less than 5, no more than 5 hydrogen bond donors (nHD), and 10 hydrogen bond acceptors (nHA). Veber's rule considers the optimal number rotatable bonds (nRot) to be less than 10, and the total polar surface area (TPSA) should not exceed 140 $Å^2$. Evaluated physicochemical properties of the hydantoin derivatives **1**-**7** are presented in Table 1. All tested compounds exhibit good lipophilicity, enabling them to traverse the lipid bilayer of the cell membrane. All of them met Lipinski's and Veber's rules, indicating a favorable ADMET profile.

**Table 1.** Physicochemical properties of the investigated compounds.

| | MW [g/mol] | nHA | nHD | nRot | TPSA | logP | logS |
|---|---|---|---|---|---|---|---|
| **1** | 324.04 | 4.0 | 1.0 | 3.0 | 49.41 | 2.712 | -3.383 |
| **2** | 352.07 | 4.0 | 1.0 | 3.0 | 49.41 | 3.147 | -4.074 |
| **3** | 338.05 | 4.0 | 1.0 | 3.0 | 49.41 | 3.253 | -3.982 |
| **4** | 410.07 | 6.0 | 1.0 | 6.0 | 75.71 | 3.27 | -3.840 |
| **5** | 396.06 | 6.0 | 1.0 | 6.0 | 75.71 | 3.082 | -3.583 |
| **6** | 366.08 | 4.0 | 0.0 | 3.0 | 40.62 | 3.326 | -3.968 |
| **7** | 442.12 | 4.0 | 0.0 | 5.0 | 40.62 | 4.298 | -4.631 |

Upon oral administration, the drug is primarily absorbed in the gastrointestinal (GI) tract and enters the bloodstream, where it may cross the blood-brain barrier by passive diffusion. All derivatives have good estimated solubility in water and high GI absorption. Predicted absorption and distribution parameters are given in Table 2. Four compounds (**2**, **5**-**7**) have predicted Caco-2 permeability values greater than -5.15 log cm/s, which is considered optimal. All compounds have predicted values of Human Intestinal Absorbtion (HIA) lower than 0.3, which indicates high absorption. Another significant absorption parameter is oral availability. F20%, F30% and F50% are probablilities of the compounds having a 20%, 30% and 50% oral bioavailability. Values under 0.3 indicate high probability. All investigated derivatives, except **5**, have a high probability of having oral bioavailability of around 50% or higher. 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 compounds **1** and **4** are predicted to have. VD (Volume Distribution) refers to how investigated compounds are distributed within the body. VD values between 0.04-20 L/kg are considered optimal and only **6** falls in this range. Compounds **1**, **2**, **4** and **5** are predicted to penetrate the BBB, suggesting potential central nervous system activity.

**Table 2.** Predicted absorbtion and distribution criteria of the investigated compounds.

| | Absorption | | | | | | Distribution | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Caco-2** | **HIA** | **$F_{20\%}$** | **$F_{30\%}$** | **$F_{50\%}$** | **PPB** | **BBB** | **VD** | **Fu** |
| **1** | -5.285 | 0.033 | 0.001 | 0.034 | 0.077 | 82.559 | 0.634 | -0.316 | 14.997 |
| **2** | -4.886 | 0.003 | 0.002 | 0.007 | 0.083 | 96.477 | 0.516 | -0.134 | 2.69 |
| **3** | -5.239 | 0.005 | 0.004 | 0.008 | 0.04 | 94.387 | 0.837 | -0.248 | 4.267 |
| **4** | -5.321 | 0.002 | 0.002 | 0.013 | 0.027 | 82.972 | 0.268 | -0.202 | 17.303 |
| **5** | -4.71 | 0.005 | 0.03 | 0.062 | 0.504 | 92.284 | 0.925 | -0.328 | 5.157 |
| **6** | -4.71 | 0.004 | 0.005 | 0.048 | 0.037 | 93.936 | 0.985 | 0.348 | 3.937 |
| **7** | -4.741 | 0.0 | 0.0 | 0.0 | 0.0 | 98.304 | 0.907 | -0.017 | 1.164 |

Metabolism parameters for the tested compounds are given in Table 3 and refer to the probablility 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, CYP2C9 and CYP3A4. Compounds **1**, **2**, **6** and **7** have probability of being CYP1A2 substrates, while all of them are predicted to be CYP3A4 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 could be well metabolized in the body. All compounds have low to moderate predicted clearance, but a short half-life.

**Table 3.** 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.** | | | |
| **1** | 0.0 | 0.756 | 0.008 | 0.131 | 0.003 | 0.998 | 0.105 | 2.559 | 1.187 |
| **2** | 0.0 | 0.932 | 0.0 | 0.005 | 0.004 | 1.0 | 0.061 | 3.487 | 0.956 |
| **3** | 0.0 | 0.62 | 0.004 | 0.451 | 0.006 | 0.999 | 0.165 | 3.641 | 0.651 |
| **4** | 0.0 | 0.05 | 0.004 | 0.006 | 0.016 | 1.0 | 0.248 | 3.286 | 0.784 |
| **5** | 0.0 | 0.107 | 0.096 | 0.002 | 0.003 | 0.999 | 0.269 | 2.848 | 0.986 |
| **6** | 0.0 | 0.999 | 0.181 | 0.088 | 0.006 | 1.0 | 0.02 | 8.729 | 1.255 |
| **7** | 0.298 | 0.998 | 0.88 | 0.0 | 0.405 | 1.0 | 0.013 | 5.132 | 0.68 |

Toxicological parameters of the investigated compounds are given in Table 4. None of the compounds are predicted to be toxic, except compound **1** which has a high probability of exhibiting carcinogenicity, and compounds **1** and **5** which have probability of exhibiting ototoxicity.

**Table 4.** Predicted toxicity criteria of the investigated compounds.

| | hERG | AMES | Carcinogenicity | Human hepatotoxicity | Drug Induced nephrotoxicity | Ototoxicity | Hematotoxicity |
|---|---|---|---|---|---|---|---|
| **1** | 0.287 | 0.04 | 0.999 | 0.036 | 0.091 | 0.555 | 0.028 |
| **2** | 0.066 | 0.05 | 0.127 | 0.017 | 0.025 | 0.165 | 0.012 |
| **3** | 0.164 | 0.119 | 0.338 | 0.052 | 0.248 | 0.21 | 0.07 |
| **4** | 0.156 | 0.054 | 0.333 | 0.022 | 0.155 | 0.183 | 0.021 |
| **5** | 0.286 | 0.021 | 0.3 | 0.017 | 0.035 | 0.512 | 0.007 |
| **6** | 0.074 | 0.186 | 0.347 | 0.018 | 0.048 | 0.17 | 0.033 |
| **7** | 0.192 | 0.138 | 0.246 | 0.02 | 0.028 | 0.126 | 0.023 |

## 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 and ototoxic effects for just a few derivatives. Although relying on *in silico* methods alone is unreliable, this analysis reveals a need for further experimental assessment.

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