Research paper **P 46**

STRUCTURE-PROPERTY RELATIONSHIP IN STEROIDAL HYDANTOINS: *IN SILICO* EVALUATION OF DRUG-LIKENESS AND ADMET PROFILES

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ABSTRACT

Steroidal hydantoins (HDTs) represent promising scaffolds for the development of biologically active compounds, including potential antitumor agents. In this study, the drug-likeness and ADMET properties of six structurally diverse steroidal HDTs, including mono- and bis-hydantoin derivatives, were evaluated *in silico* using Molinspiration, pkCSM, and ADMETlab 2.0. Most derivatives satisfied the recommended drug-likeness criteria. Mono-HDTs exhibited higher predicted permeability and intestinal absorption, whereas bis-derivatives showed lower clearance, suggesting slower elimination. All compounds demonstrated low predicted risks of mutagenicity and cardiotoxicity. Overall, the obtained results highlight steroidal HDTs, particularly mono-functionalized derivatives, as promising candidates for further synthesis and biological evaluation.

INTRODUCTION

Cancer is the second leading cause of noncommunicable disease-related death worldwide [1], following cardiovascular diseases, highlighting the continuous need for the development of novel antitumor agents. Steroidal scaffolds represent privileged structures in medicinal chemistry due to their favorable membrane permeability and broad potential for structural derivatization, which may yield compounds with enhanced biological activity, including antitumor effects [2]. Numerous biologically active hydantoins have been reported to date [3]; however, steroidal hydantoins (HDTs) remain insufficiently explored. Therefore, the aim of this study was to perform a preliminary *in silico* evaluation of the drug-likeness and ADMET properties of structurally diverse steroidal hydantoins in order to identify promising candidates for future synthesis and biological evaluation.

EXPERIMENTAL

Drug-likeness parameters were assessed using the Molinspiration calculator [4] while ADMET parameters were calculated using the pkCSM and ADMETlab 2.0 software [5–6].

RESULTS AND DISCUSSION

Six steroidal HDTs differing in the C-17 substitution pattern were evaluated *in silico* (Fig. 1), including mono-hydantoin derivatives of androstenedione (A), progesterone (P), testosterone (T), and cholestane (C), as well as bis-hydantoin derivatives of the A and P scaffolds, since only these scaffolds possess two carbonyl groups capable of hydantoin ring formation.

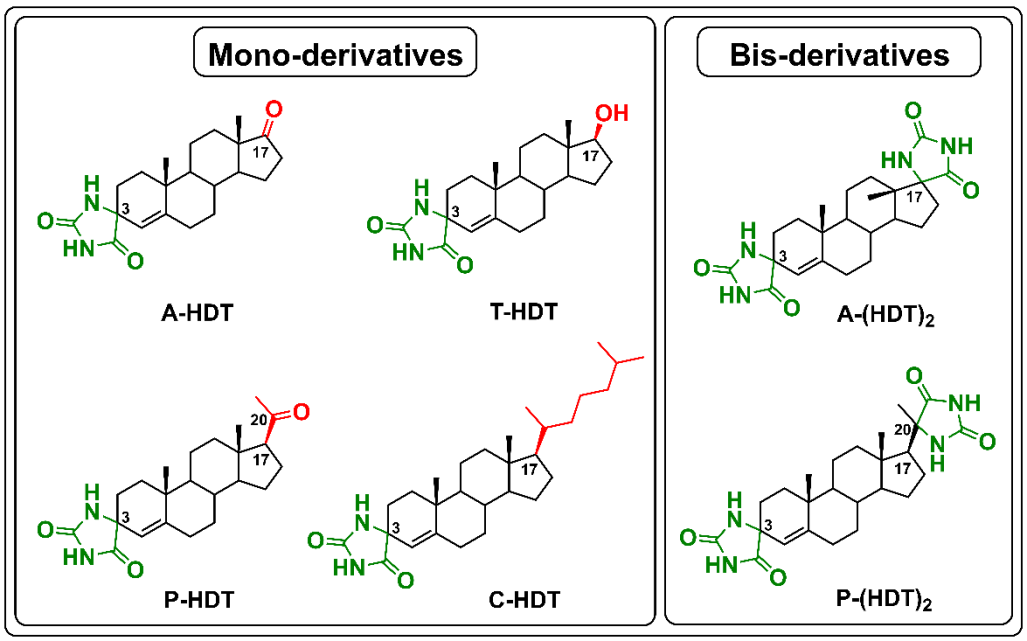


Figure 1. Chemical structures of the evaluated steroidal mono- and bis-hydantoins.

Drug-likeness parameters are presented in Table 1. Except for the highly lipophilic C-HDT (log P ≈ 7), which shows a single Lipinski violation, all analyzed derivatives fall within ranges generally associated with favorable oral bioavailability. Compared to mono-HDTs, bis-derivatives exhibit higher MW, HBA/HBD counts, and TPSA values, suggesting increased hydrogen-bonding capacity and reduced membrane permeability potential.

Table 1. Predicted drug-likeness descriptors of steroidal hydantoins. (Compd. – compound; log P – lipophilicity; MW – molecular weight; HBA/HBD – number of hydrogen bond acceptors/donors; n_{viol} – number of Ro5 violations; TPSA – topological polar surface area (Å²); rotB – number of rotatable bonds; Ref. – recommended reference ranges for drug-likeness)

Compd.	log P	MW	HBA	HBD	n_{viol}	TPSA	rotB
A-HDT	2.56	356	5	2	0	75	0
A-(HDT)$_2$	2.07	427	8	4	0	116	0
P-HDT	3.31	385	5	2	0	75	1
P-(HDT)$_2$	2.82	455	8	4	0	116	1
T-HDT	2.75	358	5	3	0	78	0
C-HDT	6.94	455	4	2	1	58	5
Ref.	≤5	≤500	≤10	≤5	≤1	≤140	≤10

To further evaluate the pharmacokinetic and safety profiles of HDTs, predicted ADMET parameters were analyzed (Tab. 2).

Water solubility (Ws) ranged from 0.05 to 13.6 mg/L, with the lowest value predicted for C-HDT and the highest for T-HDT. Mono-derivatives exhibited higher predicted Caco-2 permeability (>0.9) and intestinal absorption (94–96%) than bis-derivatives (~0.4 and 82%, respectively). Moderate VDss values were predicted for A-HDT and T-HDT, while low Fu values (0.03–0.23) suggested extensive plasma protein binding. BBB permeability indicated moderate brain penetration, reduced for bis-derivatives.

Most compounds were predicted to undergo metabolism via CYP1A2, CYP2C19, CYP2C9, and CYP3A4. Mono-HDTs showed moderate clearance (7.4–14 mL/min/kg), whereas bis-derivatives exhibited lower clearance (1.2–3.1 mL/min/kg), suggesting slower elimination. All compounds demonstrated low predicted risk of hERG inhibition (0.2–2.7%) and AMES mutagenicity (1.4–10.0%), together with similar hepatotoxicity probabilities (~0.3). Overall, mono-derivatives displayed more favorable absorption-related properties than bis-HDTs, whose profiles were mainly influenced by increased molecular size and polarity.

Table 2. Predicted ADMET parameters of steroidal hydantoins. (Compd. – compound; Caco-2 – Caco-2 permeability (logPapp, 10^{-6} cm/s); IA – intestinal absorption (%); VDss – steady-state volume of distribution (log L/kg); Fu – unbound plasma fraction; BBB – blood–brain barrier permeability (logBB); CL – clearance (mL/min/kg); AMES – predicted Ames mutagenicity probability; hERG – predicted hERG inhibition probability)

Compd.	Caco-2	IA	VDss	Fu	BBB	CL	AMES	hERG
A-HDT	0.90	94	0.12	0.17	-0.02	9.6	6.6	0.5
A-(HDT)$_2$	0.45	82	-0.43	0.23	-0.63	1.2	10.0	0.4
P-HDT	1.10	96	-0.20	0.03	-0.01	14.0	1.4	0.6
P-(HDT)$_2$	0.41	82	-0.49	0.14	-0.47	3.1	2.6	0.2
T-HDT	0.94	94	-0.10	0.18	-0.40	9.5	3.0	1.0
C-HDT	1.20	94	-0.19	0.00	-0.32	7.4	2.0	2.7

CONCLUSION

Overall, the analyzed steroidal HDTs exhibited favorable drug-likeness properties, with only the highly lipophilic C-HDT showing a single Lipinski violation. Mono-derivatives displayed more favorable absorption- and clearance-related ADMET properties than bis-derivatives, while all compounds demonstrated low predicted risks of mutagenicity and cardiotoxicity. These findings highlight steroidal hydantoins, particularly mono-functionalized derivatives, as promising candidates for further synthesis and biological evaluation as potential antitumor agents.

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