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IN SILICO ANALYSIS OF THE MESOCARB-TYPE MOLECULES INTERACTION WITH THE DOPAMINE TRANSPORTER AS POTENTIAL ANTI-AUTOIMMUNE AGENTS *

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Abstract

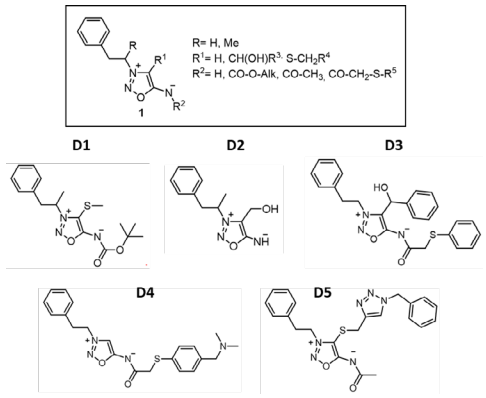
We have designed new mesocarb derivatives with the aim of investigating their binding affinity towards the dopamine transporter (DAT). Induced-fit docking studies into two protein conformational states and corresponding binding affinities revealed substantial binding interactions with DAT surpassing the controls. This finding suggests the efficacy of selected scaffold for further DAT-targeted therapeutics development.

Dopamine Transporter (DAT) inhibitors have emerged as highly promising therapeutic agents in the management of diverse neuro-psychiatric disorders [1]. It is well-established that DAT inhibition plays a crucial role in addressing Parkinson's disease [2] and has been thoroughly investigated for clinical applications in treating several mental health conditions [3–6]. The varied pharmacological effects observed with DAT ligands can be explained by the distinct ways in which different compounds interact with the transporter protein.

Two primary categories of DAT inhibitors have been identified: atypical inhibitors that bind mostly to the inward-facing (*IF*state) conformation of the transporter or induce a conformational change from the metastable state to the occluded state; and cocaine-like compounds that preferentially target the outward-facing (*OF*state) conformation of DAT [7]. The orthosteric site S1/S2 serves as the primary binding region for both natural substrates and various medications [8–10].

Recent studies demonstrated that the dopaminergic system is involved in the regulation of immune responses in various homeostatic and disease conditions inhibiting neuroinflammation [11]. This connection between dopamine and immune regulation opens new avenues for therapeutic development by modulating dopamine levels. Several similar to mesocarb structures were patented for using dopamine reuptake inhibitors and their analogs for treating autommune conditions or preventing autoimmune related pathologic progressions [12]. Taking everything into account, we have designed the set of novel mesocarb-derivatives in order to investigate their ability to bind to DAT, under the premise that structural similarities would result in similar pharmacological activity.

To validate this hypothesis, a series of structurally analogous compounds was synthesized. Compound 1 (the scaffold) exhibits structural homology to mesocarb, with key variations centered around the presence or absence of a methyl group at the α-position of the substituent attached to nitrogen atom N3 within the oxadiazole ring system. The molecular architecture displays the following characteristics: oxadiazole core with defined substituent patterns; position 4 modifications consist of incorporation of proton, thioalkyl, and hydroxymethyl groups; N6 position contains of sydnonymine base salts, acyl groups, and alkoxycarbonyl substituents (see figure). The synthetic approach for generating these derivatives adhered to previously established protocols for sydnone imine modification. These methodologies were specifically tailored to introduce targeted structural variations while preserving the essential framework required for biological activity [13–17].



Initial scaffold (*1*) and designed derivatives (*D1–D5*)

All modeling, protein and ligands preparation, induced-fit docking and MM-GBSA affinity calculation were performed in Schrödinger molecular modeling suite (version 2022-4, version 2024-1) as described previously [18]. *OF*state and *IF*state of DAT were obtained by homology modeling on the templates of PDB 4M48 and PDB 6DZZ, respectively. Induced-fit docking protocol was used with defaults parameters with receptor grid centered at the co-crystalized ligands of both DAT protein states within the S1/S2 binding site.

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The docking results, combined with MM-GBSA ΔG_{bind} calculations for the top-poses (see table), revealed significant insights into the binding behavior of the scaffold derivatives indicating the optimal conformations of ligands within the S1/S2 sites. All compounds D1–D5 demonstrated nearly identical binding affinity to both DAT states, comparable to mesocarb. Notably, compound D3 exhibited significantly enhanced binding to the *OF*state of DAT. The calculated binding affinities of the designed ligands surpassed those of both cocaine and dopamine. These results collectively support the potential of the designed compounds as promising candidates for dopamine transporter-targeted drug development, highlighting the suitability of the chosen scaffold for future therapeutic applications.

Results of induced-fit docking and corresponding MM-GBSA binding affinities of top-poses within both DAT states

Ligand	DAT *OF*state		DAT *IF*state	
	XPscore (kkal/mol)	ΔG_{bind} (kkal/mol)	XPscore (kkal/mol)	ΔG_{bind} (kkal/mol)
Dopamine	−7,3	−43,55	−7,86	−36,97
Cocaine	−9,1	−58,27	−12,1	−67,35
Mesocarb	−12,36	−76,54	−11,83	−71,83
D1	−9,53	−62,85	−9,32	−64,95
D2	−10,65	−55,22	−9,19	−51,6
D3	−13,84	−104,41	−11,11	−79,66
D4	−10,31	−86,28	−12,84	−84,65
D5	−12,09	−75,25	−10,28	−67,81

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