

Article

# Exploring the Potential of Oleanolic Acid Dimers—Cytostatic and Antioxidant Activities, Molecular Docking, and ADMETox Profile

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## Supplementary Materials

Table S2. ADMETox parameters for OADs 2a – 2n

	High value (optimal)	Moderate value					Low value				Neutral value				
ADMETox parameters (optimal values)	Compound number														
	1 (OA)	2a	2b	2c	2d	2e	2f	2g	2h	2i	2j	2k	2l	2m	2n
Molecular Weight (100 ~ 600)	456.36	928.75	938.74	952.75	966.77	964.75	964.75	980.78	994.80	1008.81	1022.83	1036.85	1050.86	1064.88	1078.89
Volume	505.75	1025.52	1037.54	1054.83	1072.13	1069.50	1069.49	1089.43	1106.72	1124.02	1141.31	1158.61	1175.91	1193.20	1210.50
Density	0.902	0.906	0.905	0.903	0.902	0.902	0.902	0.900	0.899	0.898	0.896	0.895	0.894	0.892	0.891
NHA (0 ~ 12)	3	6	6	6	6	6	6	6	6	6	6	6	6	6	6
nHD (0 ~ 7)	2	4	2	2	2	2	2	2	2	2	2	2	2	2	2
nRot (0 ~ 11)	1	6	7	8	9	8	8	10	11	12	13	14	15	16	17



Pgp Substrate	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
HIA (< 30%)	0.012	0.581	0.769	0.804	0.806	0.405	0.756	0.782	0.743	0.690	0.643	0.592	0.533	0.472	0.395
F <sub>20%</sub> (< 20%)	0.074	0.992	0.993	0.996	0.997	0.991	0.981	0.999	0.999	0.999	1.000	1.000	1.000	1.000	1.000
F <sub>30%</sub> (< 30%)	0.756	0.968	0.990	0.993	0.995	0.954	0.990	0.996	0.997	0.998	0.998	0.998	0.999	0.999	0.999
PPB (< 90%)	98.13%	97.25%	94.99%	94.31%	93.77%	98.30%	98.16%	93.90%	93.91%	94.05%	94.32%	94.65%	95.01%	95.48%	96.03%
VD (0.04 – 20 L/kg)	0.718	1.194	1.100	1.083	1.094	1.188	1.071	1.100	1.108	1.125	1.146	1.166	1.187	1.211	1.255
BBB Penetration	0.674	0.593	0.367	0.335	0.350	0.713	0.419	0.358	0.366	0.373	0.379	0.39	0.401	0.409	0.415
Fu (> 20%)	3.524%	2.087%	2.070%	1.906%	1.718%	1.666%	2.011%	1.555%	1.418%	1.291%	1.179%	1.074%	0.984%	0.914%	0.850%
CYP1A2 Inhibitor	0.012	0.000	0.002	0.002	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
CYP1A2 Substrate	0.323	0.217	0.209	0.206	0.205	0.206	0.189	0.206	0.208	0.21	0.212	0.213	0.213	0.213	0.212
CYP2C19 Inhibitor	0.028	0.013	0.027	0.028	0.027	0.024	0.024	0.027	0.027	0.027	0.027	0.026	0.026	0.026	0.025
CYP2C19 Substrate	0.916	0.959	0.959	0.958	0.961	0.953	0.941	0.962	0.961	0.959	0.958	0.956	0.954	0.951	0.947
CYP2C9 Inhibitor	0.157	0.033	0.040	0.038	0.034	0.035	0.035	0.031	0.029	0.026	0.024	0.021	0.019	0.017	0.015
CYP2C9 Substrate	0.813	0.033	0.091	0.086	0.105	0.106	0.092	0.124	0.146	0.171	0.202	0.23	0.266	0.302	0.339
CYP2D6 Inhibitor	0.012	0.026	0.009	0.013	0.011	0.023	0.026	0.010	0.008	0.007	0.006	0.005	0.004	0.004	0.003
CYP2D6 Substrate	0.528	0.101	0.113	0.104	0.104	0.443	0.290	0.092	0.083	0.075	0.067	0.060	0.054	0.050	0.046
CYP3A4 Inhibitor	0.172	0.191	0.374	0.352	0.293	0.307	0.281	0.271	0.253	0.238	0.223	0.209	0.196	0.182	0.169
CYP3A4 Substrate	0.208	0.672	0.877	0.872	0.861	0.905	0.871	0.847	0.832	0.816	0.797	0.776	0.753	0.729	0.703
CL (>15 mL/min/kg)	3.094	7.004	10.943	10.569	10.099	9.568	7.953	9.745	9.452	9.148	8.848	8.55	8.262	7.973	7.737
T1/2 (< 3h)	0.023	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
hERG Blockers	0.004	0.063	0.249	0.262	0.313	0.190	0.292	0.329	0.347	0.367	0.387	0.408	0.425	0.432	0.438
H-HT	0.296	0.202	0.199	0.201	0.193	0.207	0.200	0.191	0.189	0.188	0.187	0.186	0.185	0.184	0.182
DILI	0.010	0.001	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003
AMES Toxicity	0.008	0.003	0.010	0.010	0.006	0.017	0.003	0.006	0.005	0.005	0.005	0.005	0.005	0.005	0.005
Rat Oral Acute Toxicity	0.228	0.130	0.198	0.200	0.172	0.208	0.270	0.163	0.154	0.148	0.142	0.135	0.129	0.123	0.117
FDAMDD	0.909	0.962	0.954	0.958	0.957	0.965	0.98	0.957	0.957	0.957	0.957	0.957	0.957	0.957	0.957
Skin Sensitization	0.028	0.018	0.036	0.04	0.043	0.049	0.057	0.048	0.055	0.066	0.079	0.093	0.116	0.145	0.18

Carcinogenicity	0.063	0.02	0.03	0.028	0.025	0.038	0.032	0.023	0.021	0.02	0.018	0.017	0.015	0.014	0.013
Eye Corrosion	0.012	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003
Eye Irritation	0.084	0.011	0.034	0.028	0.025	0.024	0.033	0.026	0.027	0.028	0.029	0.030	0.031	0.032	0.034
Respiratory Toxicity	0.968	0.981	0.874	0.87	0.862	0.746	0.886	0.851	0.839	0.827	0.814	0.796	0.777	0.756	0.735
Bioconcentration Factors	1.944	1.599	1.000	0.893	0.836	0.958	1.152	0.766	0.695	0.622	0.549	0.476	0.403	0.333	0.263
IGC <sub>50</sub>	5.021	6.303	6.306	6.348	6.449	6.403	6.525	6.549	6.648	6.747	6.846	6.945	7.044	7.142	7.241
LC <sub>50</sub> FM	5.937	7.516	7.247	7.28	7.292	7.265	7.759	7.315	7.338	7.36	7.382	7.402	7.388	7.364	7.321
LC <sub>50</sub> DM	6.337	7.516	7.422	7.449	7.474	7.491	7.589	7.469	7.466	7.465	7.466	7.468	7.471	7.473	7.476
NR-AR	0.369	0.011	0.002	0.003	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.001	0.001	0.001	0.001
NR-AR-LBD	0.273	0.984	0.950	0.945	0.946	0.958	0.960	0.942	0.939	0.935	0.932	0.928	0.925	0.921	0.917
NR-AhR	0.001	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
NR-Aromatase	0.759	0.313	0.343	0.329	0.277	0.295	0.320	0.253	0.231	0.210	0.191	0.173	0.156	0.142	0.130
NR-ER	0.412	0.916	0.882	0.825	0.806	0.735	0.727	0.777	0.748	0.727	0.708	0.688	0.673	0.662	0.653
NR-ER-LBD	0.593	0.984	0.986	0.983	0.984	0.978	0.974	0.983	0.982	0.980	0.979	0.977	0.975	0.973	0.970
NR-PPAR gamma	0.965	0.919	0.945	0.940	0.933	0.951	0.948	0.928	0.922	0.915	0.905	0.891	0.876	0.858	0.838
SR-ARE	0.556	0.284	0.390	0.351	0.321	0.397	0.582	0.306	0.290	0.275	0.261	0.247	0.234	0.222	0.211
SR-ATAD5	0.052	0.321	0.665	0.542	0.515	0.658	0.669	0.456	0.403	0.353	0.308	0.266	0.229	0.194	0.163
SR-HSE	0.747	0.173	0.843	0.822	0.808	0.889	0.899	0.799	0.789	0.780	0.770	0.759	0.749	0.736	0.720
SR-MMP	0.971	0.988	0.945	0.935	0.909	0.946	0.968	0.891	0.869	0.841	0.809	0.772	0.728	0.678	0.624
SR-p53	0.271	0.124	0.402	0.293	0.229	0.380	0.426	0.182	0.142	0.115	0.092	0.070	0.050	0.036	0.025
Acute Toxicity Rule (alerts)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Genotoxic Carcinogenicity Rule (alerts)	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0
Non Genotoxic Carcinogenicity Rule (alerts)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Skin SensitizationRule (alerts)	0	1	0	0	0	2	2	0	0	0	0	0	0	0	0
Aquatic Toxicity Rule (alerts)	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1
Non Biodegradable Rule (alerts)	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0

**Legend:** OA – oleanolic acid (reference compound);

For values given in a range 0.000 – 1.000 (unless stated otherwise): 0.000 – 0.300: low probability, 0.301 – 0.699: moderate probability, 0.700 – 1.000: high probability

**Additional Information:** detailed information on individual ADMETox parameters are given in our earlier publication [xxx].

**Physicochemical Properties:** Molecular Weight, Volume, Density, nHA, nHD, nRot, nRing, MaxRing, nHet, fChar, nRig, Flexibility, tPSA, logS, logP, logD.

**Medicinal Chemistry:** QED, SAScore, Fsp3, MCE-18, Npscore, Lipinski Rule, Pfizer Rule, GSK Rule, Golden Triangle, PAINS, ALARM NMR, BMS, Chelator Rule.

**Absorption:** Caco-2 Permeability, MDCK Permeability, Pgp Inhibitor, Pgp Substrate, HIA, F20% , F30%.

**Distribution:** PPB, VD, BBB Penetration, Fu.

**Metabolism:** CYP1A2 Inhibitor, CYP1A2 Substrate, CYP2C19 Inhibitor, CYP2C19 Substrate, CYP2C9 Inhibitor, CYP2C9 Substrate, CYP2D6 Inhibitor, CYP2D6 Substrate, CYP3A4 Inhibitor, CYP3A4 Substrate.

**Excretion:** CL, T1/2.

**Toxicity:** hERG Blockers, H-HT, DILI, AMES Toxicity, Rat Oral Acute Toxicity, FDAMDD, Skin Sensitization, Carcinogenicity, Eye Corrosion, Eye Irritation, Respiratory Toxicity.

**Environmental toxicity:** Bioconcentration Factors, IGC50, LC50FM, LC50DM.

**Tox21 pathway:** NR-AR, NR-AR-LBD, NR-AhR, NR-ER, NR-ER-LBD, NR-PPARgamma, SR-ARE, SR-ATAD5, SR-HSE, SR-MMP.

**Toxicophore Rules:** Acute Toxicity Rule, Genotoxic Carcinogenicity Rule, NonGenotoxic Carcinogenicity Rule, Skin Sensitization Rule, Aquatic Toxicity Rule, NonBiodegradable Rule, SureChEMBL Rule.