Supporting Information

Exploration of Novel Non-purine Xanthine Oxidase Inhibitors Based on Oxadiazolones by An Integrated Simulation Study

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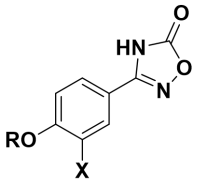
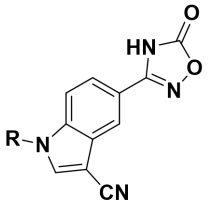
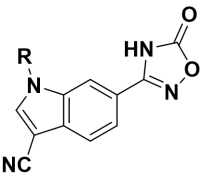
Tab. S1. Chemical structures of the used compounds and their actual and predicted pIC_{50} values.



Compounds 01-21: 1H-tetrazol-1-yl
Compounds 22: H



Compounds 23-43



Compounds 44-47

No.	IC_{50} (μM)	pIC_{50}	R	CoMFA		CoMSIA	
				Predicted pIC_{50}	Residuals	Predicted pIC_{50}	Residuals
01[a]	3.212	5.493	methyl	5.628	0.135	5.436	0.057
02	0.345	6.462	*iso*-propyl	6.477	0.015	6.437	0.025
03[a]	0.514	6.289	*iso*-butyl	6.283	0.006	6.258	0.031
04[b]	0.173	6.762	*iso*-pentyl	6.765	0.003	6.705	0.057
05	0.232	6.635	*iso*-pentenyl	6.624	0.011	6.658	0.023
06[a]	0.245	6.611	propinyl	6.615	0.004	6.594	0.017
07	0.303	6.519	methylene cyclopropane	6.501	0.018	6.564	0.045
08	0.315	6.502	cyclopentyl	6.506	0.004	6.453	0.049
09[b]	0.121	6.917	methylene cyclohexane	6.909	0.008	6.883	0.034
10	0.146	6.836	benzyl	6.819	0.017	6.758	0.078
11	0.208	6.682	*p*-methylbenzyl	6.686	0.004	6.765	0.083
12[a, b]	0.315	6.502	*p*-tert-butylbenzyl	6.434	0.068	6.616	0.114
13	0.160	6.796	*p*-methoxylbenzyl	6.798	0.002	6.833	0.037
14	0.151	6.821	*p*-fluorobenzyl	6.848	0.027	6.794	0.027
15[b]	0.149	6.827	*p*-chlorobenzyl	6.770	0.057	6.775	0.052
16	0.206	6.686	*p*-bromobenzyl	6.722	0.036	6.774	0.088
17[b]	0.157	6.804	*m*-methylbenzyl	6.811	0.007	6.797	0.007
18[a]	0.334	6.476	*m*-methoxylbenzyl	6.493	0.017	6.447	0.029
19	0.233	6.633	*m*-fluorobenzyl	6.651	0.018	6.676	0.043
20	0.185	6.733	*m*-chlorobenzyl	6.695	0.038	6.696	0.037
21	0.215	6.668	*m*-bromobenzyl	6.698	0.030	6.695	0.027

22[a, b]	3.282	5.484	methylene cyclohexane	5.571	0.087	5.406	0.078
23	4.130	5.384	H	5.384	0.000	5.386	0.002
24[a]	5.410	5.267	methyl	5.497	0.230	5.267	0.000
25[a, b]	0.41	6.387	*iso*-propyl	5.987	0.400	5.919	0.468
26[b]	1.09	5.963	*iso*-butyl	5.968	0.005	5.959	0.004
27	1.02	5.991	*iso*-pentyl	5.995	0.004	5.990	0.001
28	1.24	5.907	3-methylbut-2-en-1-yl	5.903	0.004	5.911	0.004
29[a]	0.88	6.056	methylene cyclopropane	5.985	0.071	5.984	0.072
30[a, b]	0.36	6.444	cyclopentyl	6.191	0.253	6.093	0.351
31	2.86	5.544	methylene cyclohexane	5.543	0.001	5.544	0.000
32	1.72	5.764	benzyl	5.724	0.040	5.728	0.036
33	1.71	5.767	*p*-fluorobenzyl	5.697	0.070	5.729	0.038
34	2.40	5.620	*p*-chlorobenzyl	5.708	0.088	5.671	0.051
35	2.07	5.684	*p*-bromobenzyl	5.711	0.027	5.636	0.048
36	1.14	5.943	*p*-methylbenzyl	5.947	0.004	5.931	0.012
37	1.02	5.991	*p*-methoxylbenzyl	5.975	0.016	6.004	0.013
38	1.44	5.842	*p*-tert-butylbenzyl	5.833	0.009	5.828	0.014
39	3.60	5.444	*m*-fluorobenzyl	5.451	0.007	5.546	0.102
40	2.93	5.533	*m*-chlorobenzyl	5.551	0.018	5.540	0.007
41	2.60	5.585	*m*-bromobenzyl	5.558	0.027	5.508	0.077
42[b]	2.16	5.666	*m*-methylbenzyl	5.675	0.009	5.744	0.078
43	1.70	5.770	*m*-methoxylbenzyl	5.778	0.008	5.761	0.009
44	1.80	5.745	*iso*-propyl	5.756	0.011	5.756	0.011
45	6.56	5.183	*iso*-pentyl	5.166	0.017	5.162	0.021
46[a, b]	0.82	6.086	cyclopentyl	6.013	0.073	5.943	0.143
47	1.84	5.735	*p*-methylbenzyl	5.741	0.006	5.749	0.014

[a] The test set compounds used for the 3D-QSAR models.

[b] The compounds used for constructing the pharmacophore models.

Tab. S2. Statistical results of the pharmacophore models constructed by GALAHAD.

Name	SPECIFICITY	N_HITS	FEATS	PARETO	ENERGY	STERICS	HBOND	MOL_QRY
MODEL_001	1.245	11	8	0	4.3	922.6	305.9	84.02
MODEL_002	1.246	11	8	0	5.13	922.5	291.2	97.95
MODEL_003	1.246	11	8	0	21.3	988.6	316.3	91.19
MODEL_004	1.246	11	8	0	21.3	988.6	316.3	91.19
MODEL_005	1.245	11	8	0	3.91	845.3	285.9	91.19
MODEL_006	1.218	11	8	0	6.45	945.5	282.6	97.95
MODEL_007	1.246	11	8	0	4.16	834.8	294.7	91.19
MODEL_008	1.244	11	8	0	9.41	913.9	289.9	98.77
MODEL_009	1.218	11	8	0	4.95	842	290.8	96.55
MODEL_010	1.248	11	8	0	5.48	936	275.2	97.95
MODEL_011	1.247	11	8	0	5.08	877.1	278.2	98.77
MODEL_012	2.202	9	8	0	4.51	833	285.7	94.44
MODEL_013	**4.499**	**10**	**8**	**0**	**4.15**	**882.1**	**288.4**	**54.17**
MODEL_014	1.245	11	8	0	4.77	857.9	280.2	91.19
MODEL_015	1.244	11	8	0	5.04	833.1	277.9	97.95
MODEL_016	2.202	11	8	0	4.31	767.2	280.4	94.44
MODEL_017	3.216	8	9	0	4.99	869.6	277.2	88.15
MODEL_018	2.203	11	8	0	3.9	718.6	262.8	96.55
MODEL_019	1.219	11	8	0	3.44	676.1	249.2	93.3
MODEL_020	3.489	9	8	0	4.59	691	275	95.08

Tab. S3. The ADMET prediction results of the virtual-screened hits (**S01**-**S05**).

Molecule		**S01**	**S02**	**S03**	**S04**	**S05**
pkCSM	Water solubility (log S)	-2.688	-3.016	-3.102	-3.364	-5.47
	Intestinal absorption (%)	76.787	85.867	79.638	78.417	93.816
	Skin permeability (log Kp)	-2.744	-2.728	-2.738	-2.735	-2.684
	P-gp substrate	Yes	No	No	No	Yes
	P-gp I inhibitor	No	No	Yes	Yes	Yes
	P-gp II inhibitor	No	No	No	Yes	Yes
	BBB permeability (log BB)	-1.758	-1.107	-1.216	-1.747	-0.415
	CNS permeability (log PS)	-3.747	-3.062	-3.342	-3.983	-1.712
	CYP2D6 substrate	No	No	No	No	No
	CYP3A4 substrate	No	Yes	Yes	Yes	Yes
	CYP1A2 inhibitior	No	Yes	No	Yes	Yes
	CYP2C19 inhibitior	No	No	Yes	No	Yes
	CYP2C9 inhibitior	No	No	No	No	Yes
	CYP2D6 inhibitior	No	No	No	No	No
	CYP3A4 inhibitior	No	No	No	Yes	No
	AMES toxicity	No	No	No	No	No
SwissADME	MW (g/mol)	333.32	330.29	373.36	396.33	350.374
	Fraction Csp3	0.33	0.19	0.28	0.11	0.20
	RotaTab. bonds	8	7	9	7	4
	H-bond acceptors	8	7	7	9	5
	H-bond donors	1	0	1	0	0
	TPSA ($Å^2$)	98.69	96.70	108.73	117.93	84.48
	GI absorption	High	High	High	High	High
	BBB permeant	No	No	No	No	No
	P-gp substrate	Yes	No	No	No	No
	CYP1A2 inhibitor	No	Yes	No	Yes	Yes
	CYP2C19 inhibitor	No	Yes	Yes	Yes	Yes
	CYP2C9 inhibitor	No	Yes	Yes	No	Yes
	CYP2D6 inhibitor	No	No	No	No	No
	CYP3A4 inhibitor	No	No	Yes	Yes	No
	Lipinski #violations	0	0	0	0	0
	Synthetic accessibility	3.32	3.23	3.44	3.42	3.82

gp: P-glycoprotein; BBB: blood-brain barrier; CNS: central nervous system; CYP: cytochrome P450; MW: molecular weight; TPSA: topological polar surface area; GI: gastrointestinal.

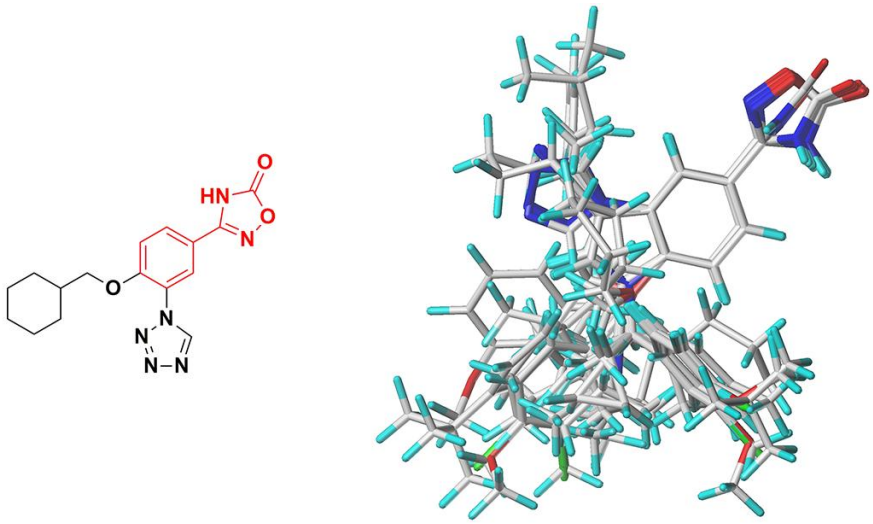


Fig. S1. The molecular alignment for the 3D-QSAR models using compound **09** as a template.

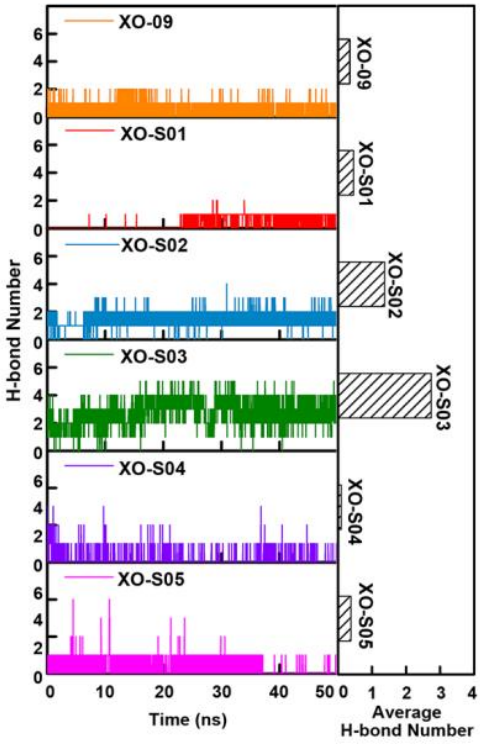


Fig. S2. The H-bond numbers and their average values of complexes XO-**09** (orange), XO-**S01** (red), XO-**S02** (blue), XO-**S03** (olive), XO-**S04** (violet), and XO-**S05** (magenta) during the 50 ns MD simualtions.