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Supporting Information

A multiscale screening strategy for identification of novel xanthine oxidase inhibitors based on the pharmacological features of febuxostat analogues

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Table S1 Predicted ADMET properties of virtual-screened hits and febuxostat by pkCSM and SwissADME.

Properties	N1	N2	N3	N4	N5	N6	Febuxostat
Absorption							
Water solubility (log mol/L)	-2.829	-4.754	-3.744	-4.463	-3.469	-4.335	-3.019
Caco2 permeability (log Papp in 10^{-6} cm/s)	0.247	1.4	0.656	1.261	0.607	0.244	1.031
Intestinal absorption (human) (% Absorbed)	63.307	91.589	87.33	91.359	64.954	90.963	93.929
Skin Permeability (log Kp)	-2.735	-2.761	-2.817	-2.745	-2.734	-2.735	-2.734
P-glycoprotein substrate	Yes	No	Yes	No	Yes	Yes	Yes
P-glycoprotein I inhibitor	No	Yes	Yes	Yes	No	Yes	No
P-glycoprotein II inhibitor	No	Yes	No	Yes	No	Yes	No
Distribution							
VDss (human) (log L/kg)	-1.045	-0.275	-0.54	-0.565	-0.838	-0.55	-1.209
Fraction unbound (human)	0.326	0.083	0.007	0.1	0.105	0	0.285
BBB permeability (log BB)	-0.713	-0.661	-1.423	-1.384	-1.105	-1.069	-0.629
CNS permeability (log PS)	-3.15	-2.503	-3.762	-3.384	-3.573	-2.414	-2.146
Metabolism							
CYP2D6 substrate	No	No	No	No	No	No	No
CYP3A4 substrate	No	Yes	Yes	Yes	No	Yes	No
CYP1A2 inhibitor	No	Yes	No	No	No	No	No
CYP2C19 inhibitor	No	Yes	No	Yes	No	Yes	No
CYP2C9 inhibitor	No	Yes	Yes	Yes	No	Yes	No
CYP2D6 inhibitor	No	No	No	No	No	No	No
CYP3A4 inhibitor	No	Yes	Yes	Yes	No	Yes	No
Excretion							
Total Clearance (log ml/min/kg)	0.568	0.244	0.626	0.537	0.514	0.71	0.313
Renal OCT2 substrate	No	No	No	No	No	No	No

Toxicity							
AMES toxicity	No	No	No	No	No	No	No
Max. tolerated dose (human)	1.414	0.722	-0.229	0.637	0.418	0.246	0.598
hERG I inhibitor	No	No	No	No	No	No	No
hERG II inhibitor	No	Yes	No	No	No	Yes	No
Oral Rat Acute Toxicity (LD_{50})	2.201	2.195	2.627	2.734	2.812	2.207	2.649
Oral Rat Chronic Toxicity (LOAEL)	1.894	1.373	1.177	1.179	1.98	1.823	1.323
Hepatotoxicity	Yes	Yes	Yes	Yes	Yes	Yes	No
Skin Sensitisation	No	No	No	No	No	No	No
T. Pyriformis toxicity (log ug/L)	0.285	0.408	0.309	0.309	0.285	0.287	0.327
Minnow toxicity (log mM)	2.174	-2.005	1.342	-1.205	1.53	-1.737	-0.491
Synthetic accessibility	2.61	2.96	3.85	3.73	3.49	3.82	3.12

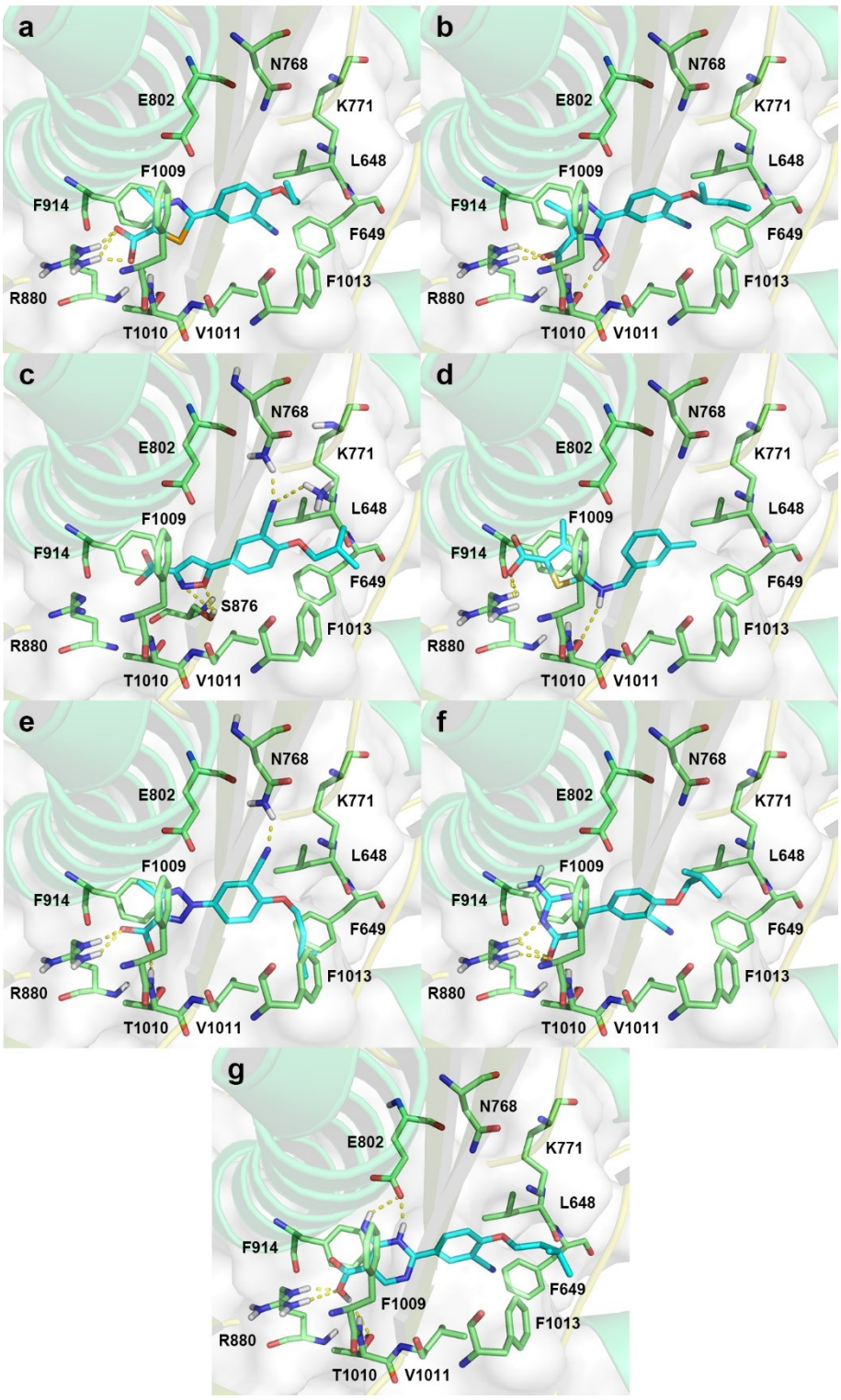


Fig. S1 Docking results of febuxostat analogues **4-10** (a-g) with 1N5X. The protein, binding pocket, ligands, important residues, and H-bonds were shown as cartoon, surface, bule sticks, green sticks, and yellow dashes, respectively.

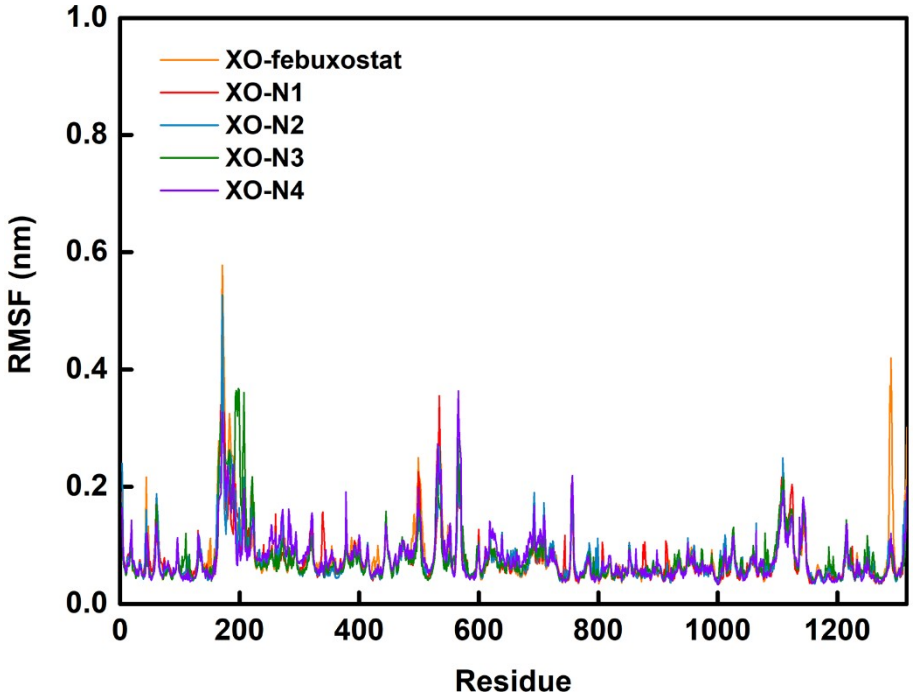
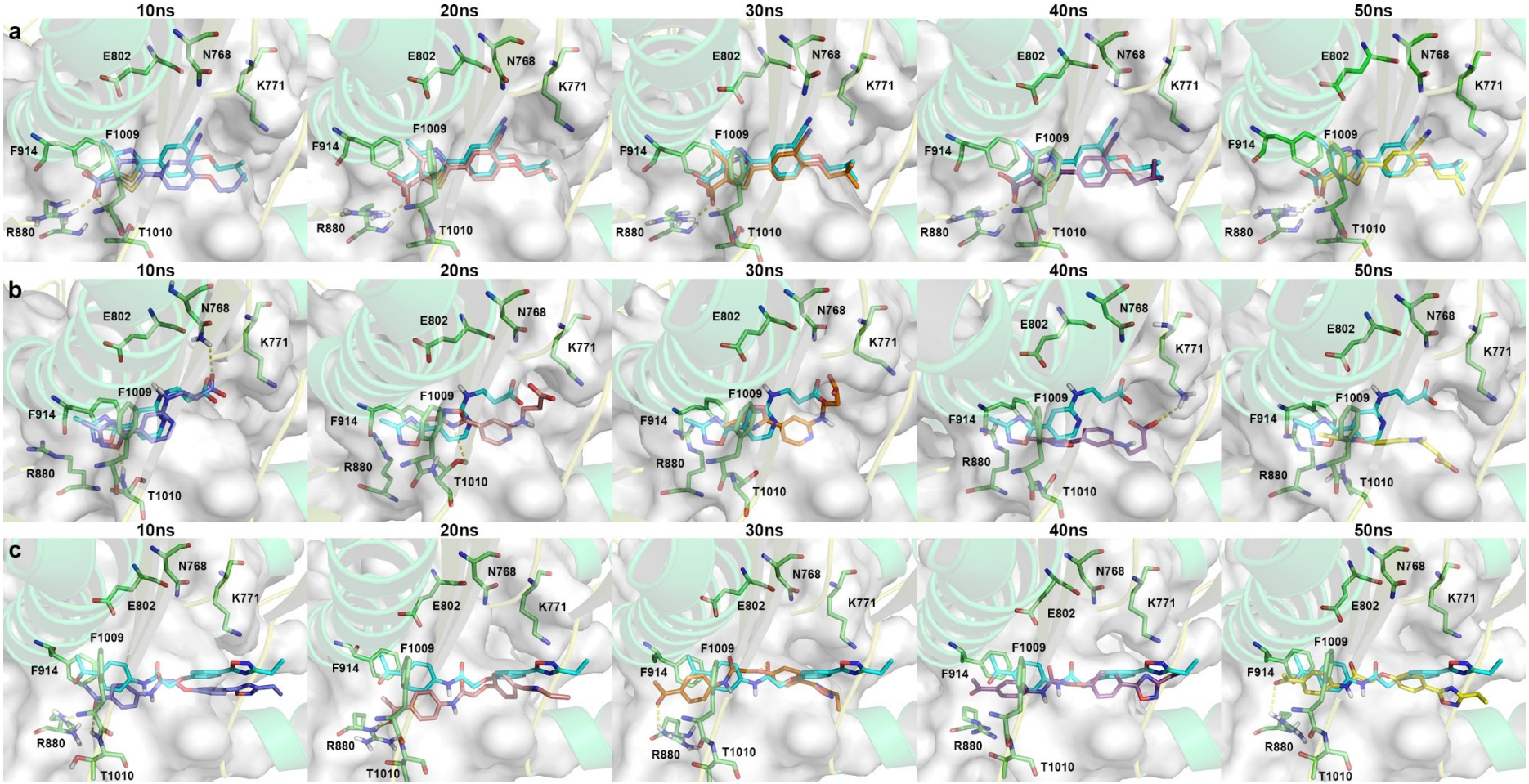


Fig. S2 RMSF plots of complexes XO-febuxostat (orange), XO-**N1** (red), XO-**N2** (blue), XO-**N3** (olive), and XO-**N4** (violet) during MD simulations.


a
10ns
20ns
30ns
40ns
50ns
E802
N768
K771
F1009
F914
R880
T1010
b
10ns
20ns
30ns
40ns
50ns
E802
N768
K771
F1009
F914
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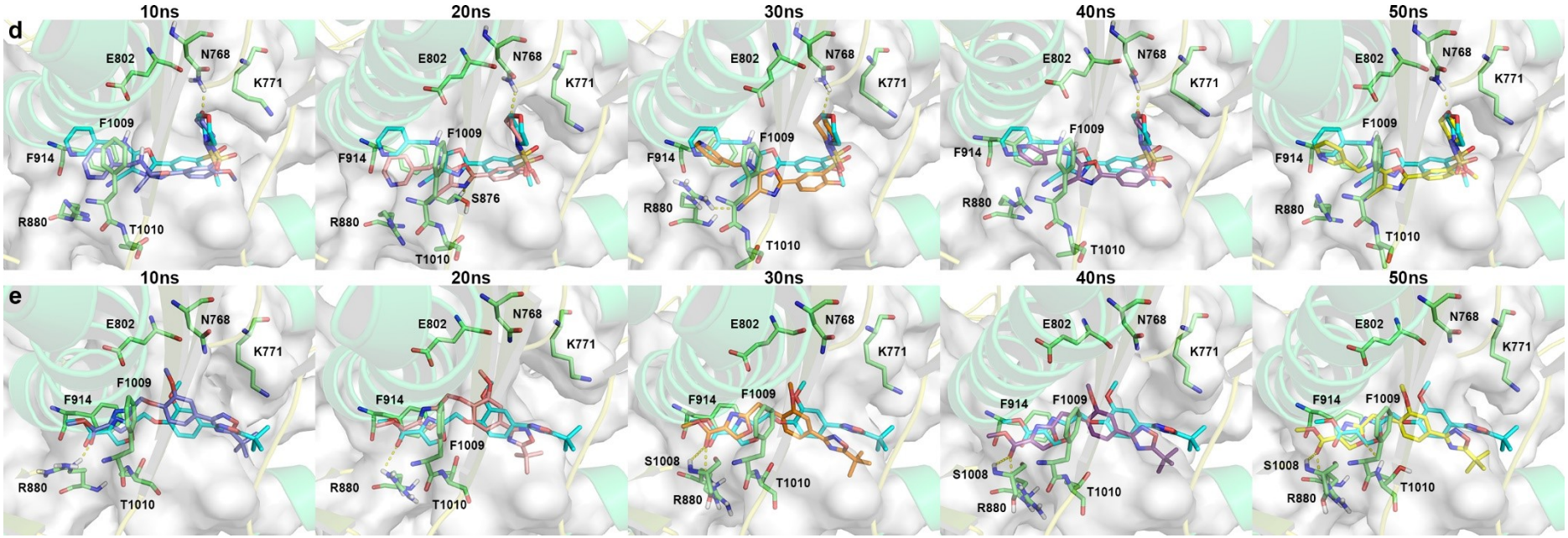

Fig. S3 3D plots of febuxostat (a), **N1** (b), **N2** (c), **N3** (d) and **N4** (e) with XO at 10, 20, 30, 40, and 50 ns during MD simulations. The protein, binding pocket, H-bonds, and important residues were shown as cartoon, surface, yellow dashes, and green sticks, and the different conformations at 0, 10, 20, 30, 40 and 50 ns were shown as blue, violet, pink, orange, purple, and yellow sticks, respectively.