Supporting Information

Stable and Accurate Atomistic Simulations of Flexible Molecules using Conformationally Generalisable Machine Learned Potentials

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Table S1 Force and energy maximum absolute errors of flexible drug molecule MLPs trained on the rMD17, MD-300K, MD-500K and Meta-300K datasets. Each trained MLP was separately tested on three independent test sets: the reference dataset sub-sample of 1000 structures, as well as torsion scans for rotation about φ and ψ.

molecule	test set	maximum absolute error force (kcal mol^{-1} Å^{-1})				maximum absolute error energy (kcal mol^{-1})			
		rMD17	**MD-300K**	**MD-500K**	**Meta-300K**	**rMD17**	**MD-300K**	**MD-500K**	**Meta-300K**
aspirin	sub-sample	3.04	4.49	9.85	30.94	0.46	0.31	0.88	2.81
	φ-scan	91.18	104.77	15.85	1.11	13.97	9.60	6.06	0.22
	ψ-scan	32.0	7.59	2.62	0.76	3.03	1.43	0.15	0.23
paracetamol	sub-sample	3.17	2.58	4.11	3.50	0.42	0.16	0.28	0.43
	φ-scan	172.50	170.41	137.27	0.92	17.43	31.60	44.59	0.10
	ψ-scan	29.81	0.44	0.55	0.63	4.10	0.05	0.04	0.08
salicylic acid	sub-sample	1.82	1.09	6.20	11.97	0.12	0.06	0.50	1.40
	φ-scan	3763.97	484.94	2.82	1.90	849.23	44.44	0.37	0.55
	ψ-scan	33.28	52.39	10.23	1.42	6.30	8.23	6.20	0.18

Table S2 Aspirin force and energy MAEs for MLPs trained on metadynamics datasets with variable Gaussian heights, *h*.

h **(kcal mol^{-1})**	**force (kcal mol^{-1} Å^{-1})**	**energy (kcal mol^{-1})**
0.06	0.31	0.07
0.12	0.41	0.15
0.18	0.52	0.31
0.24	0.27	0.11

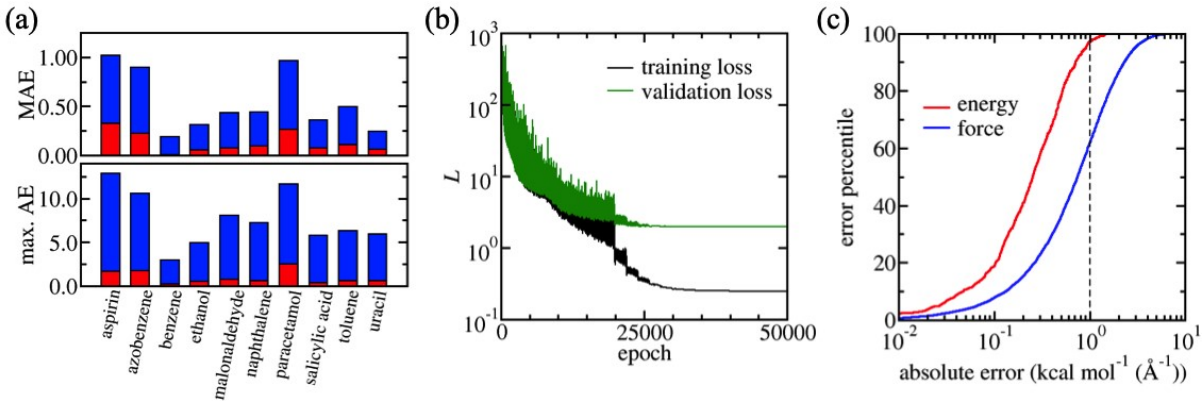

Fig. S1 Performance of PairFE-Net MLPs, trained on 1000 structures from the rMD17 benchmark dataset. (a) Force (kcal mol^{-1} Å^{-1}) and energy (kcal mol^{-1}) test set prediction errors using the rMD17 dataset shown in blue and red, respectively. The top panel shows the MAEs and the bottom panel shows the maximum absolute errors for each 1000 structure test set. (b) Learning curves for the training (black) and validation (green) sets for aspirin. The loss function, *L*, which is minimised during training is defined in Methods. Sudden drops in *L* correspond to a reduction in the learning rate. (c) Force (blue) and energy (red) *S*-curves. The black dashed line marks the threshold for quantum chemical accuracy (1 kcal mol^{-1}).

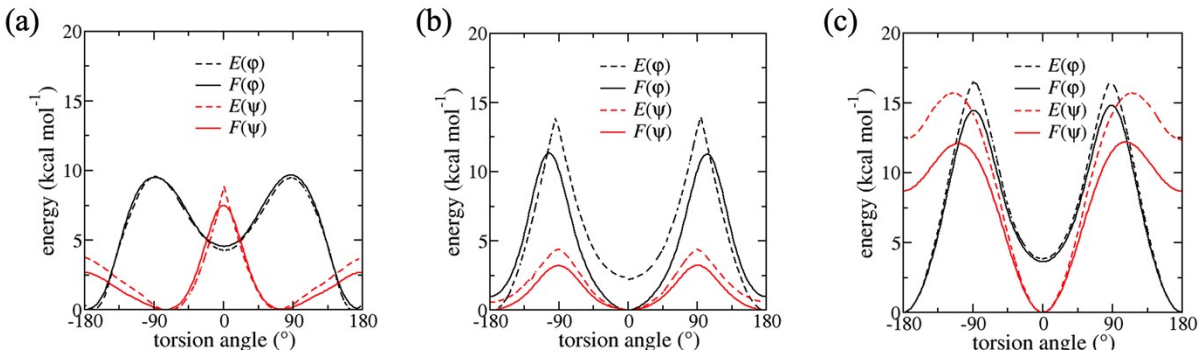

Fig. S2 Torsional potential energy (dashed lines) and free energy profiles (solid lines) for φ (black) and ψ (red) (a) aspirin, (b) paracetamol and (c) salicylic acid, calculated using Meta-300K trained MLPs.

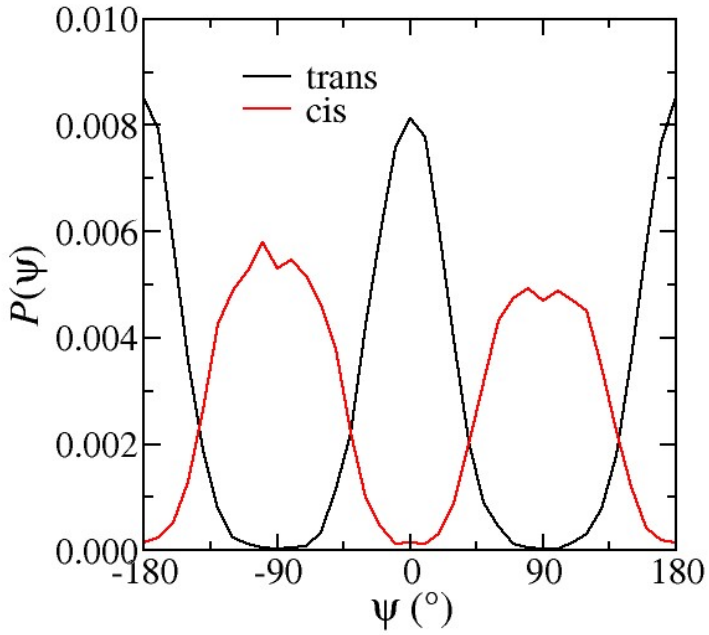

Fig. S3 Probability distribution of torsion angle ψ in paracetamol for the *trans*, φ = 180°, (black) and *cis*, φ = 0°, (red) conformers, highlighting the interdependency of torsional motions. The subtle split in the peak of the *cis* distribution is due to two closely spaced minima in the free energy surface.

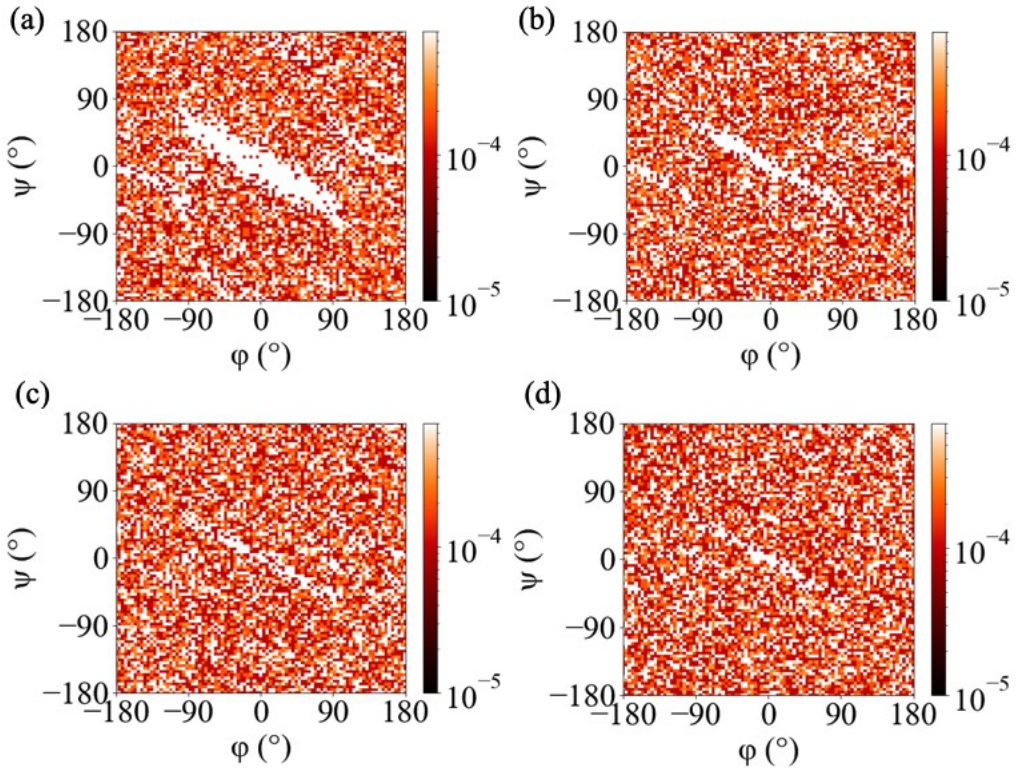

Fig. S4 Relative population density maps for aspirin datasets generated using metadynamics sampling with Gaussian heights, *h*, of (a) 0.06, (b) 0.12, (c) 0.18 and (d) 0.24 kcal mol^{-1} (Meta-300K).

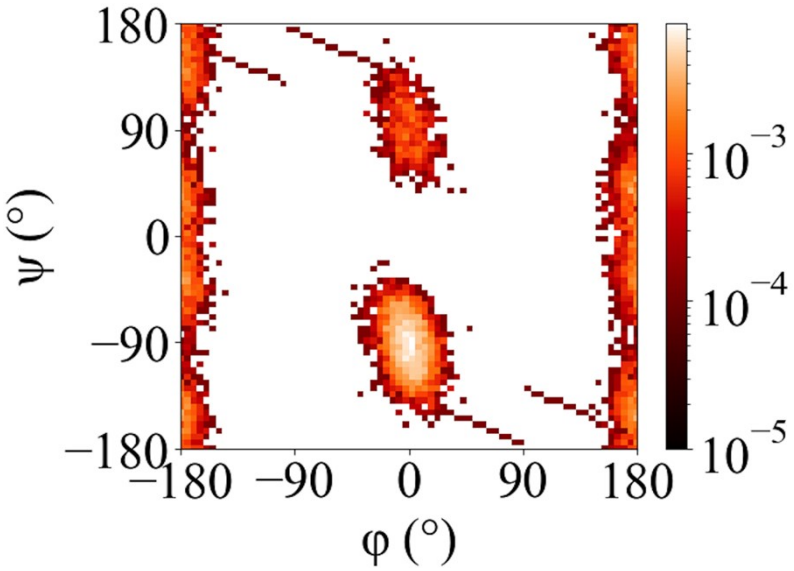

Fig. S5 Relative population density map for a paracetamol dataset constructed from 3928 trans structures, 3928 cis structures and 72 structures from each of the φ– and ψ–scans.

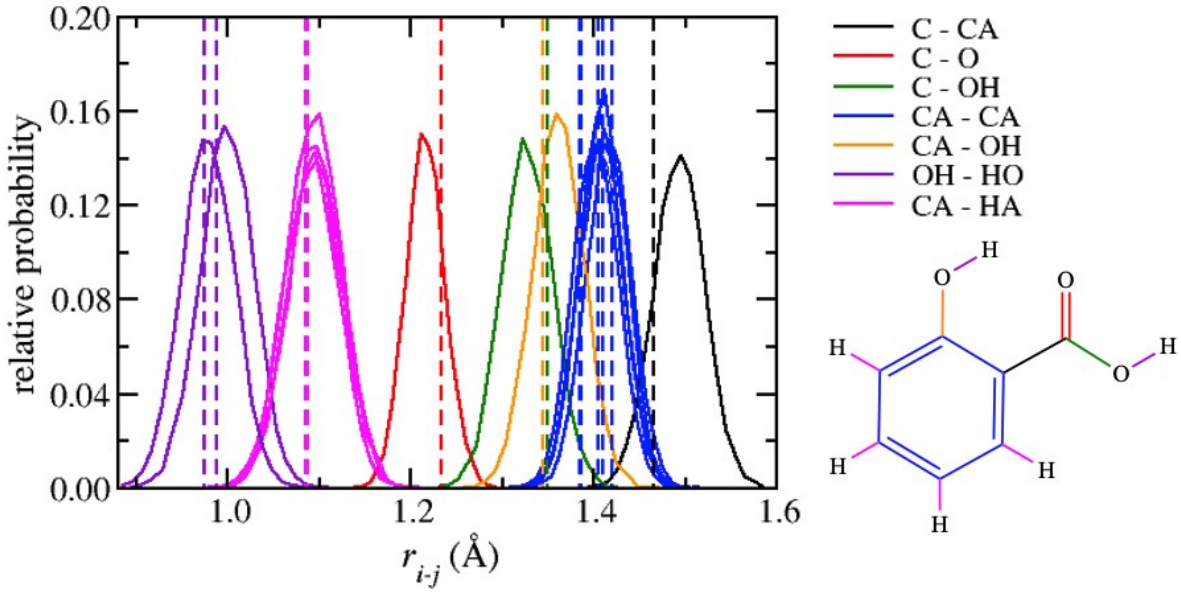

Fig. S6 Comparison of bond distances (r_{ij}) in the MD-300K salicylic dataset (solid lines) and their the DFT optimised values (dashed lines). The colours correspond to different bonds defined by GAFF atom types.

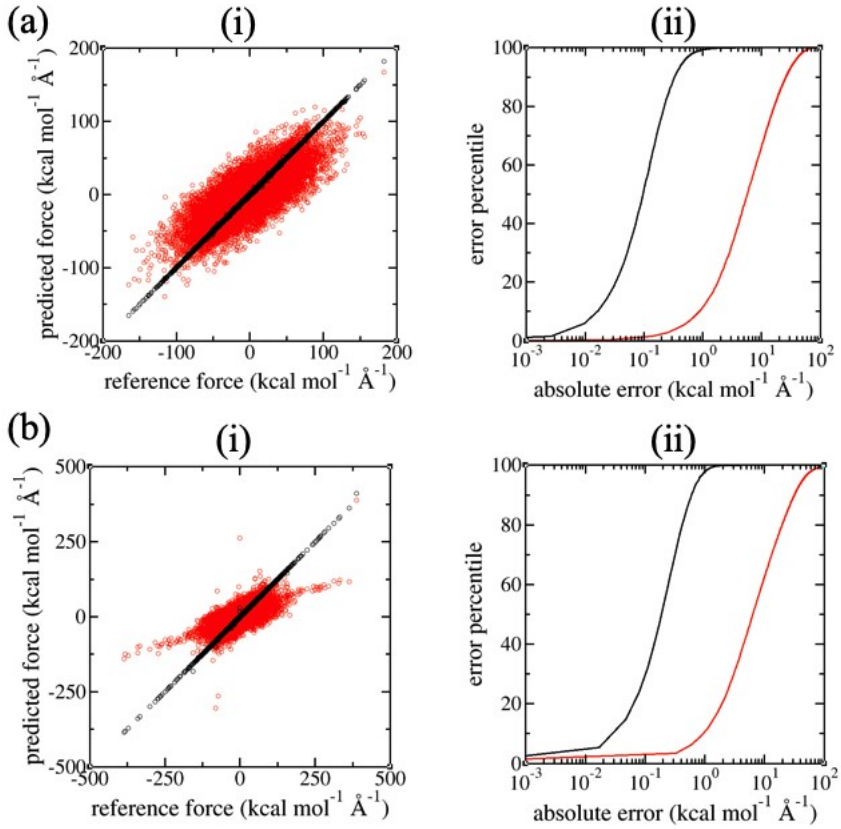

Fig. S7 Comparison of empirical potential (red) and PairFE-Net trained MLP (black) performance for aspirin using the (a) MD-300K dataset and (b) Meta-300K datasets showing (i) force prediction-reference plots and (ii) force *S*-curves.

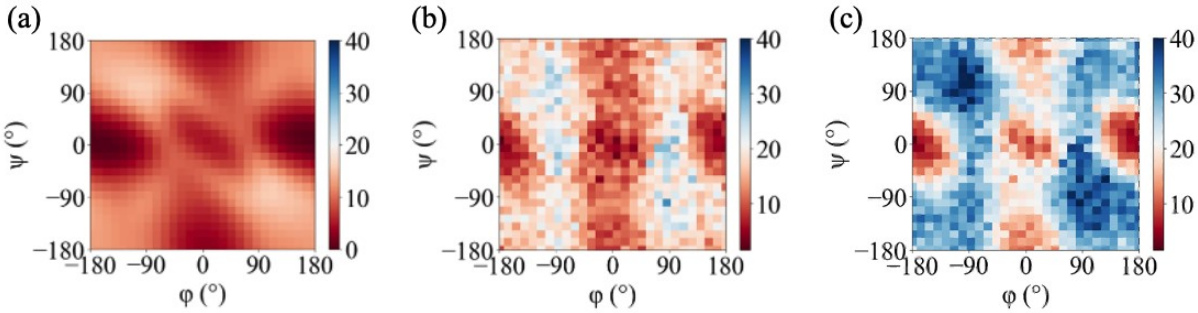

Fig. S8 For salicylic acid, a) $F(\varphi, \psi)$ calculated using GAFF from a well-tempered metadynamics simulation, b) the $\Delta F_{MM \rightarrow QM}$ correction term and c) the corrected free energy surface, $F(\varphi, \psi) + \Delta F_{MM \rightarrow QM}$.