Supplementary materials for

Identification of broad-spectrum MMP inhibitors by virtual screening

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Table S1. Canonical SMILES and PAINS-REMOVER (https://www.cbligand.org/PAINS/) results for the 20 compounds selected for *in vitro* validation.

Molecule ID	Canonical SMILES	Classified as a PAINS by PAINS-REMOVER
1	CC(OC(=O)c1c(C)oc2c1cc(cc2)NS(=O)(=O)c1ccc(cc1)Br)C	No
2	CN(/N=N/c1ccc(cc1)S(=O)(=O)/N=C(/CCC(=O)[O-])\[O-])C	Yes
3	Brc1ccc(cc1)/C=C/C(=O)c1cc(Br)ccc(=O)c1O	No
4	O=C(Nc1ccc(cc1)S(=O)(=O)NCCc1ccccc1)CCC(=O)O	No
5	Ic1ccc(cc1)S(=O)(=O)Nc1ccccc1C(=O)O	No
6	O=C(Nc1scc(c1C(=O)O)c1ccc(cc1)Br)/C=C/c1ccco1	No
7	O=C(c1ccccc(=O)c1O)/C=C/c1cccc(c1)Oc1ccccc1	No
8	Cc1cc(O)c(c(=O)o1)/C(=N/NS(=O)(=O)c1ccccc1)/C	No
9	OC(=O)CCCCCNS(=O)(=O)c1ccc2c(c1)oc(=O)n2C	No
10	O=C(Nc1ccc(cc1)S(=O)(=O)Nc1noc(c1)C)COc1ccc(cc1)Br	No
11	O=C(NS(=O)(=O)c1ccc(cc1)C)OCc1ccccc1F	No
12	COc1ccc(cc1)C(=O)Nc1ccc(cc1)S(=O)(=O)Nc1ncccn1	No
13	Oc1ccc(cc1/C=N/c1ccc(cc1)c1ccccc1)[N+](=O)O	No
14	CC(=O)Nc1ccc(cc1)S(=O)(=O)Nc1ccc(cc1)C(=O)OC(C)C	No
15	BrCCc1ccc(cc1)c1cs/c(=N\c2cccc(c2)C(=O)O)/o1	No
16	O=C(Nc1cccc(c1)NC(=O)CCC(=O)O)CCc1ccccc1	No
17	COc1ccc(cc1)c1nnc(n1c1ccc(cc1)S(=O)(=O)N)S	No
18	OC(=O)c1ccccc1C(=O)Nc1ccc(cc1)S(=O)(=O)Nc1c(C)cccc1C	No
19	OC(=O)CCc1ccc(n1NC(=S)N)c1ccc(cc1)Br	No
20	O=C(Nc1ccc(cc1)Oc1ccc(cc1)Br)CCCC(=O)O	No

Figure S1. Best docking poses for hit compounds **7**, **8** and **15** at the Zn²⁺ binding site of MMP-8, MMP-9, MMP-12 and MMP-13. Docked poses for **15**/MMP-8, **7**/MMP-12 and **8**/MMP-13 pairs are not shown because these compounds/target pairs were not predicted to be possible by the virtual screening workflows.
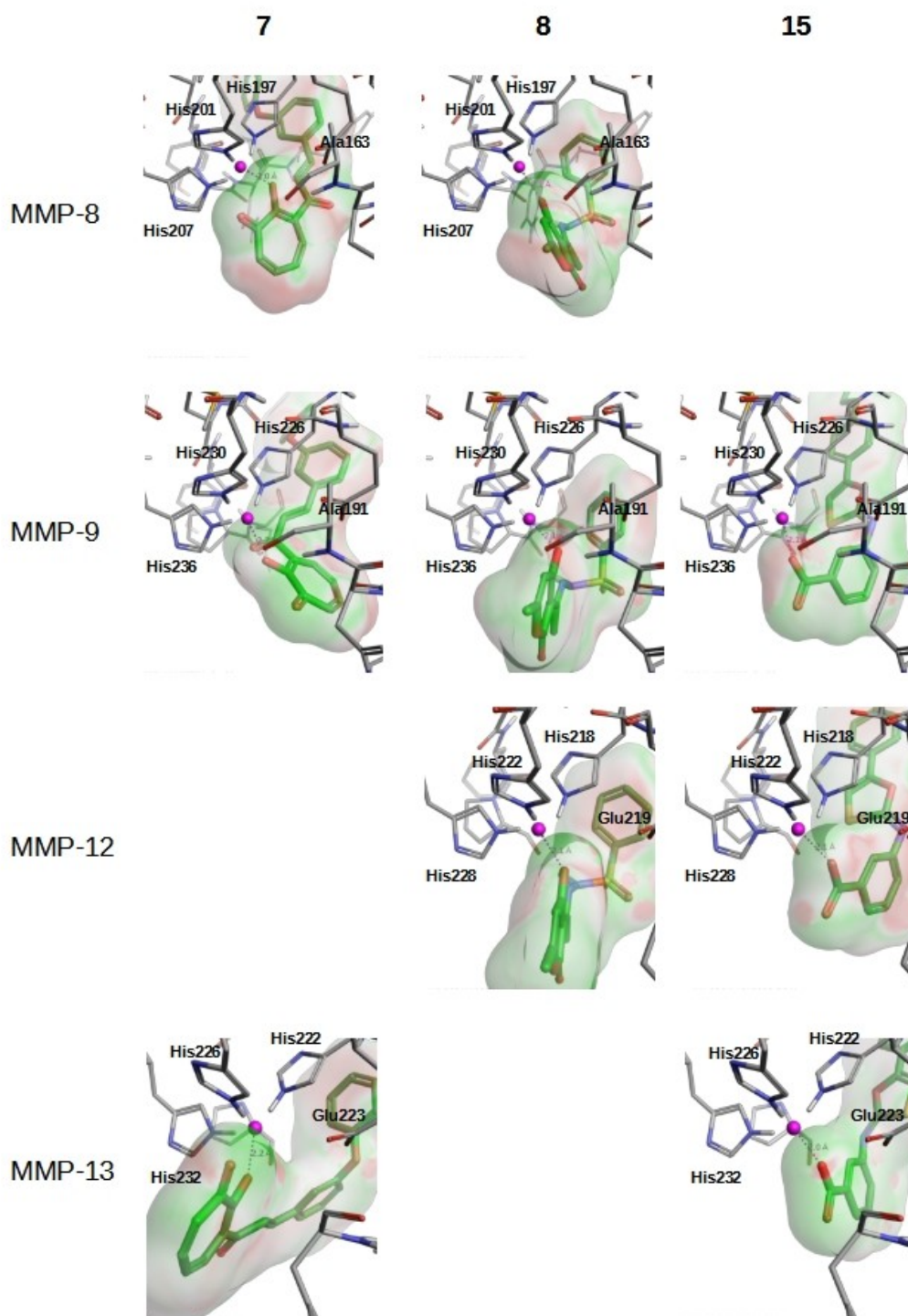
Figure S2. Best docking poses for natural compounds **5186914** and **8177094** at the Zn²⁺ binding site of MMP-8, MMP-9, MMP-12 and MMP-13.
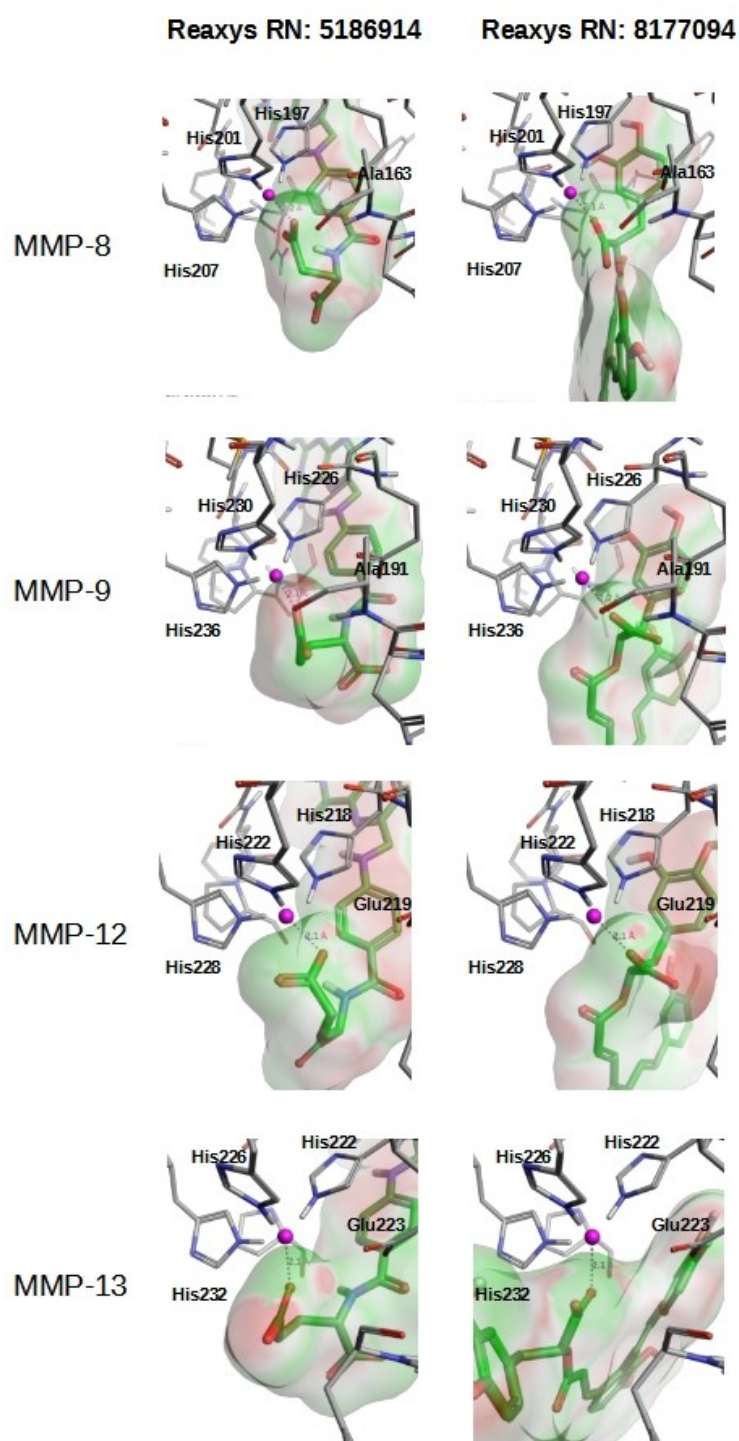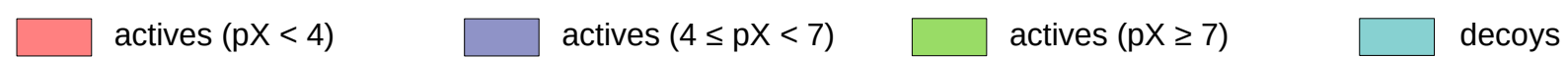
Figure S3. Histogram representations of the highest electrostatic Tanimoto (*i.e.* EON_ET_pb) values obtained when comparing the validation set to each query. Panels A, B, C and D show the validations for each of the queries for MMP-8, -9, -12 and -13, respectively. For each query, two histograms are shown: one corresponding to the actives and one corresponding to the decoys. In the actives histogram, actives with a pX lower than 4 are in red, actives with a pX between 4 and 7 are in blue, and actives with a pX higher than 7 are in green. In the decoys histogram, decoys are in cyan.

MMP-8

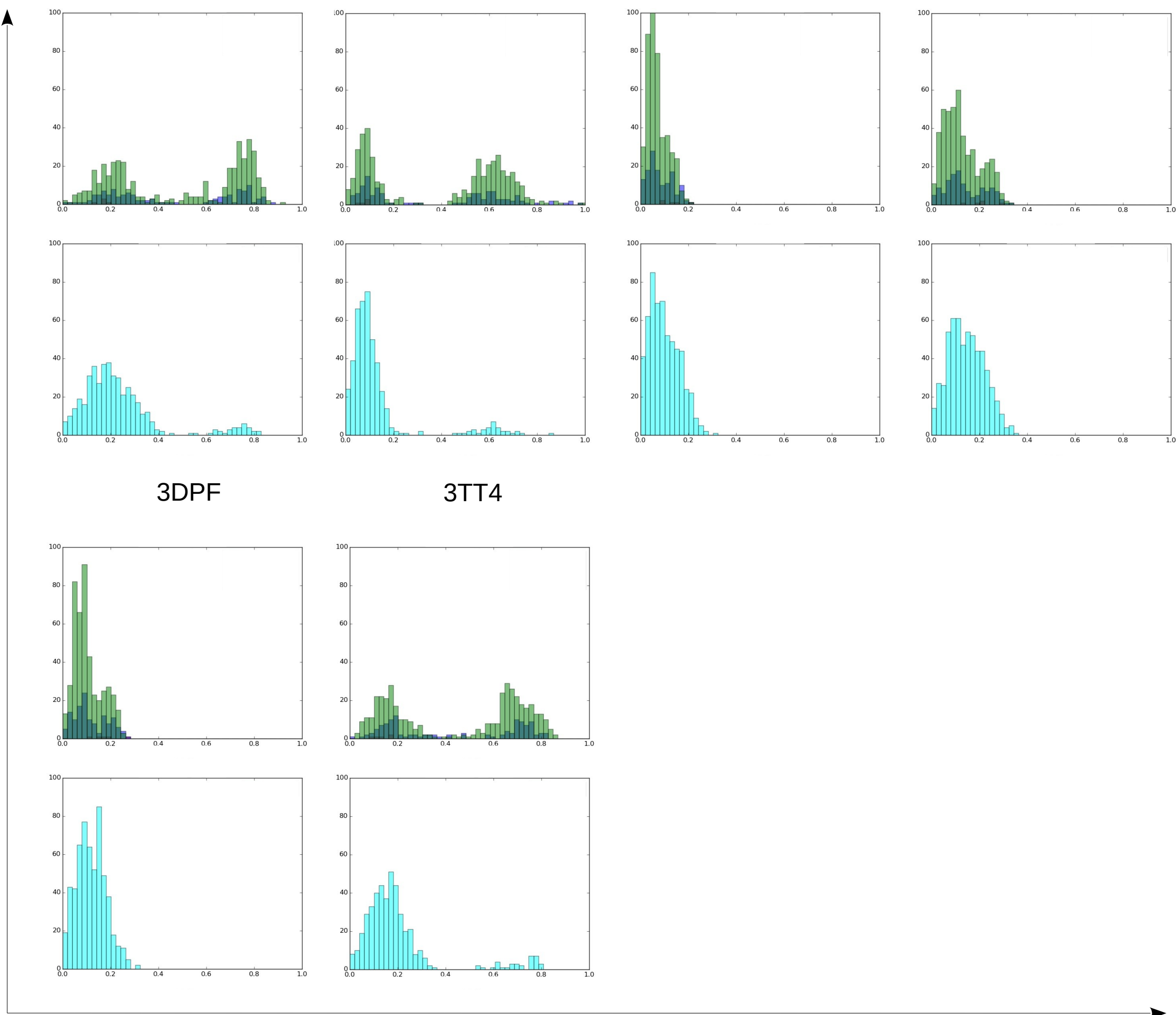actives (pX < 4)   actives (4 ≤ pX < 7)   actives (pX ≥ 7)   decoys

A

1BZS   1ZVX   3DNG   3DPE

3DPF   3TT4

Number of compounds

EON_ET_pb

B

MMP-9
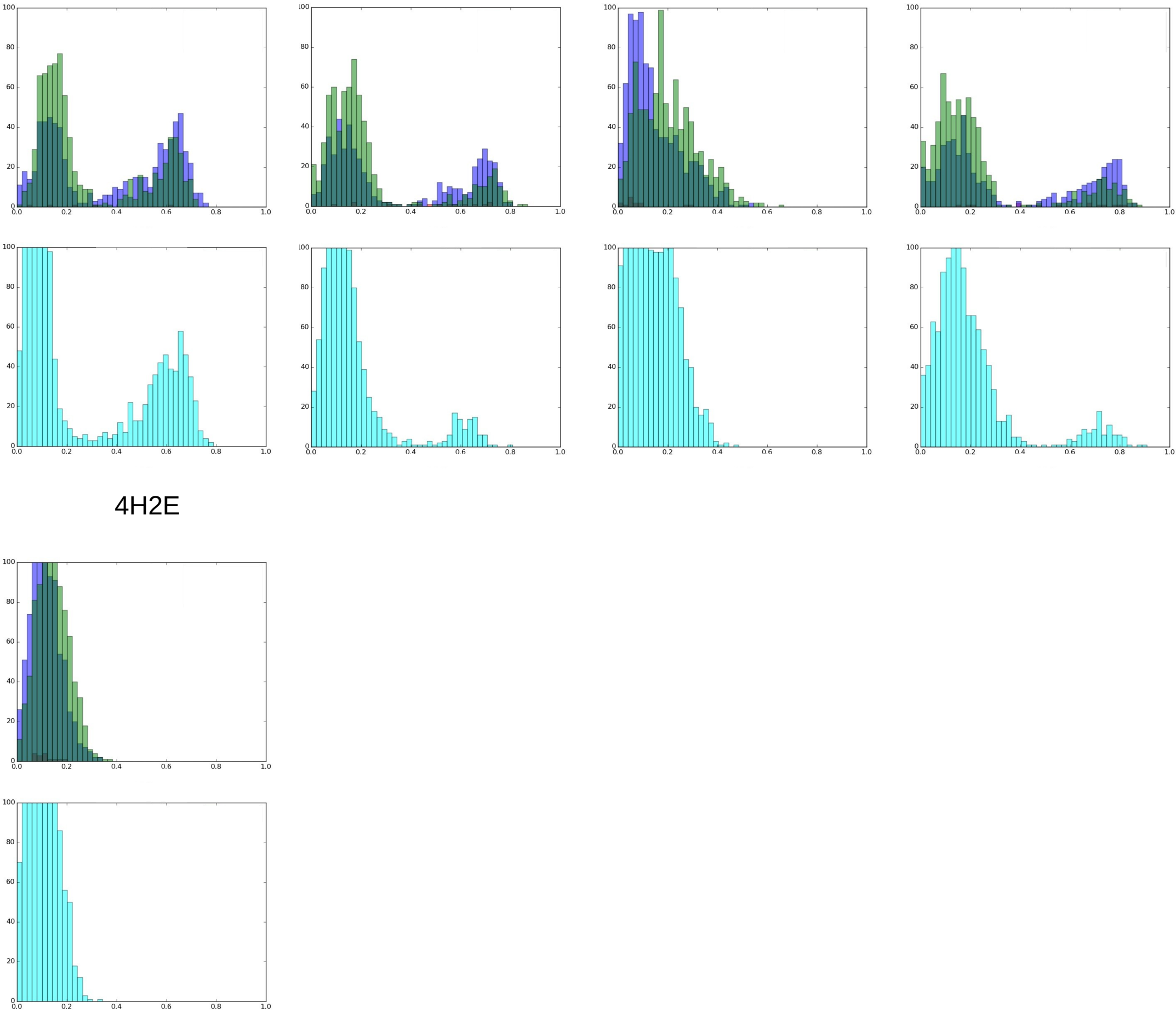

2OVX   2OVZ   2OW1   2OW2

4H2E

Number of compounds

EON_ET_pb

C

MMP-12

Number of compounds

EON_ET_pb

D

MMP-13

Number of compounds

EON_ET_pb