

# Supplementary Data B

*(Supporting data for EDDA calculations)*

## **Quantum Mechanics-Driven Structure-Activity Relationship Study of PEX5-PEX14 Protein-Protein Interaction Inhibitors Based On a Dibenzo[*b,e*]azepin-6(6*H*)-one Scaffold**

Michał Nowacki <sup>a,\*</sup>, Filipe Menezes <sup>b,\*</sup>, Emilia Pykacz <sup>a,c,d</sup>, Mateusz Popiołek <sup>a</sup>, Valeria Napolitano <sup>b,†</sup>, Chethan K. Krishna <sup>e</sup>, Vishal C. Kalel <sup>e</sup>, Ralf Erdmann <sup>e</sup>, Tony Fröhlich <sup>b</sup>, Oliver Plettenburg <sup>c,d</sup>, Michael Sattler <sup>b,f</sup>, Grzegorz M. Popowicz <sup>b,f,\*</sup>, Maciej Dawidowski <sup>a,\*</sup>

<sup>a</sup> Department of Drug Technology and Pharmaceutical Biotechnology Medical University of Warsaw, Banacha 1, 02-097 Warszawa, Poland.

<sup>b</sup> Institute of Structural Biology, Molecular Targets and Therapeutics Center, Helmholtz Munich, Ingolstädter Landstrasse 1, 85764 Neuherberg, Germany.

<sup>c</sup> Institute of Medicinal Chemistry, Molecular Targets and Therapeutics Center, Helmholtz Munich, Ingolstädter Landstrasse 1, 85764 Neuherberg, Germany.

<sup>d</sup> Center of Biomolecular Drug Research (BMWZ), Institute of Organic Chemistry, Leibniz Universität Hannover, Schneiderberg 1b, 30167 Hannover, Germany.

<sup>e</sup> Institute of Biochemistry and Pathobiochemistry, Department of Systems Biochemistry, Faculty of Medicine, Ruhr-University Bochum, 44780 Bochum, Germany.

<sup>f</sup> Bavarian NMR Center, Department of Bioscience, TUM School of Natural Sciences, Technical University of Munich, Lichtenbergstrasse 4, 85747 Garching, Germany.

---

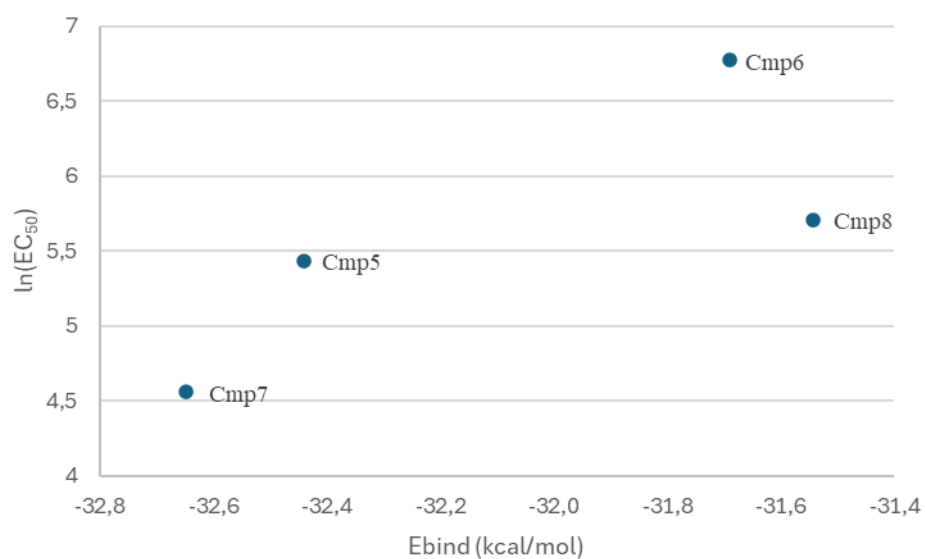
\* Corresponding authors: [michal.nowacki@wum.edu.pl](mailto:michal.nowacki@wum.edu.pl) (M. Nowacki), [filipe.menezes@helmholtz-munich.de](mailto:filipe.menezes@helmholtz-munich.de) (F. Menezes), [grzegorz.popowicz@helmholtz-munich.de](mailto:grzegorz.popowicz@helmholtz-munich.de) (G.M. Popowicz), [maciej.dawidowski@wum.edu.pl](mailto:maciej.dawidowski@wum.edu.pl) (M. Dawidowski, lead contact)

† Current affiliation: Institute of Biostructures and Bioimaging, National Research Council (CNR), Via Pietro Castellino, 111, 80131 Napoli, Italy.

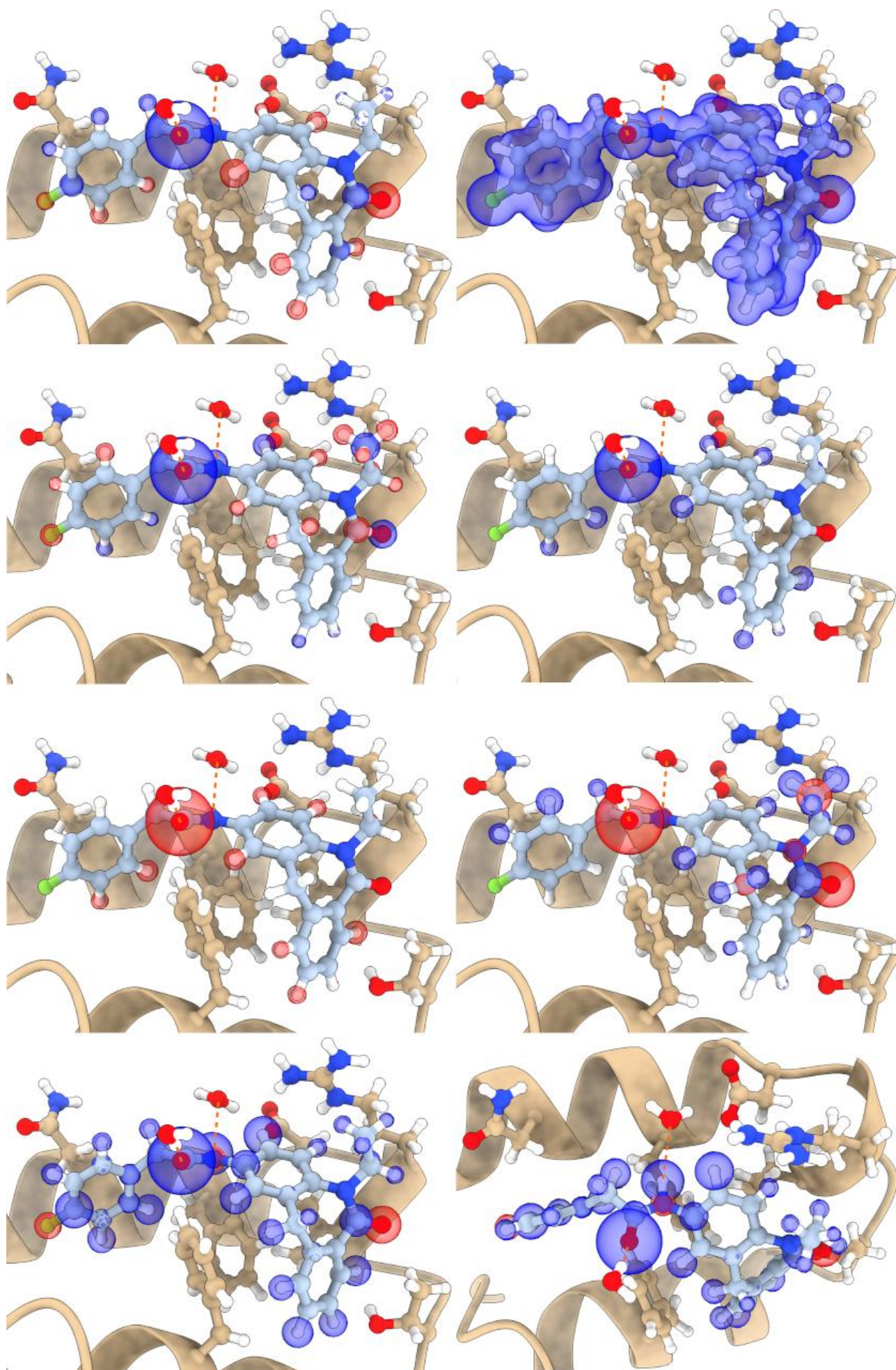
## S1. Supporting data for EDDAs of compounds 5-8

**Table S1.** Energy Decomposition Analysis data for compounds **5-8**. All values are given in kcal/mol.

Compound	5	6	7	8
ES	-23.22	-24.62	-22.39	-21.93
POL	-58.10	-59.47	-58.95	-57.60
CT	-0.58	-0.63	-0.72	-0.69
REP	65.04	66.12	66.80	65.05
DISP	-37.76	-36.81	-37.64	-37.06
SOLV	22.18	23.72	20.26	20.68
INT	-32.44	-31.69	-32.65	-31.54

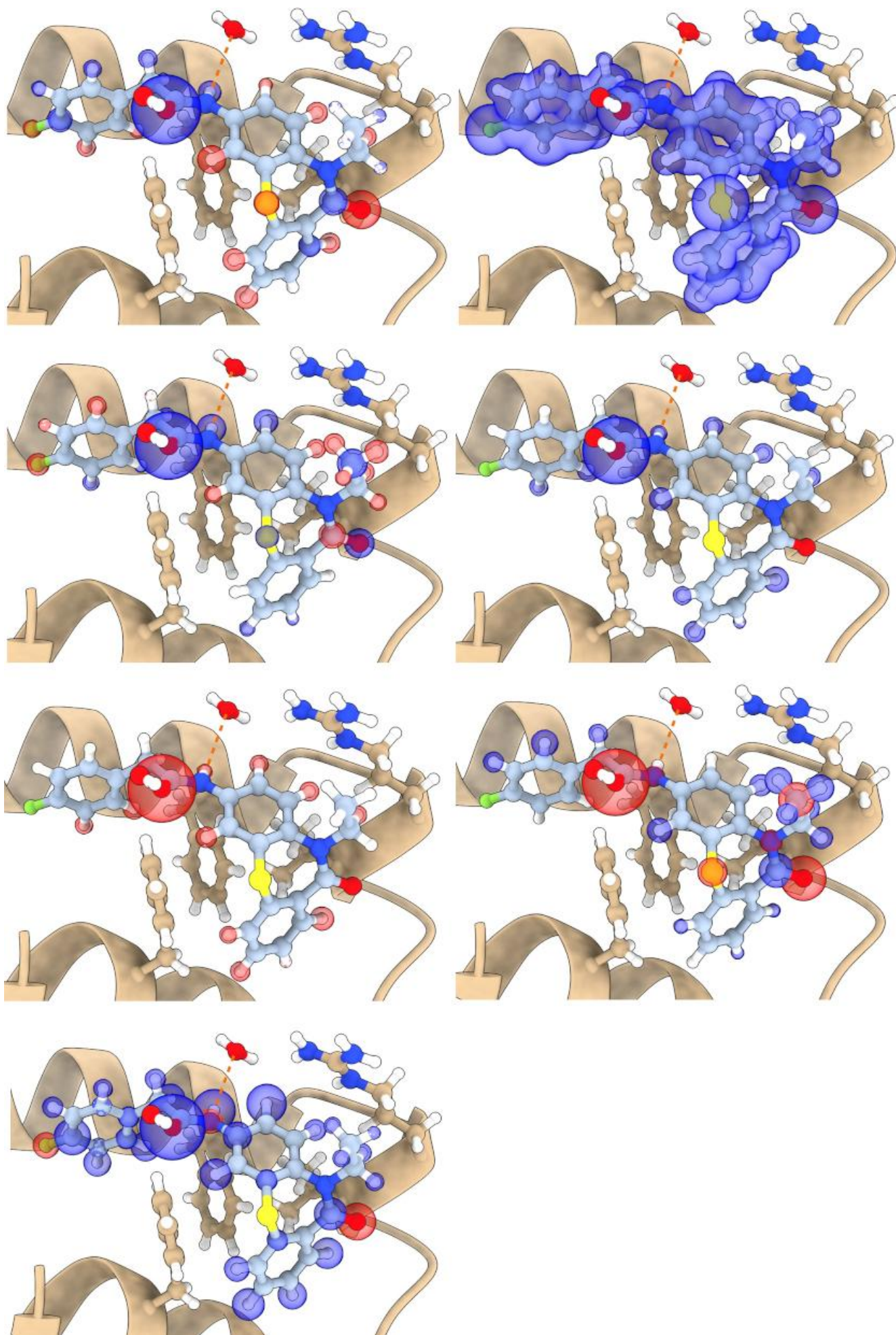


**Figure S1A.** Correlation between experimental EC<sub>50</sub> values for PEX5-PEX14 PPI inhibition and EDDA-derived binding energies for compounds **5-7**. The calculated  $R^2 = 0.61$  indicates an overall acceptable correlation.



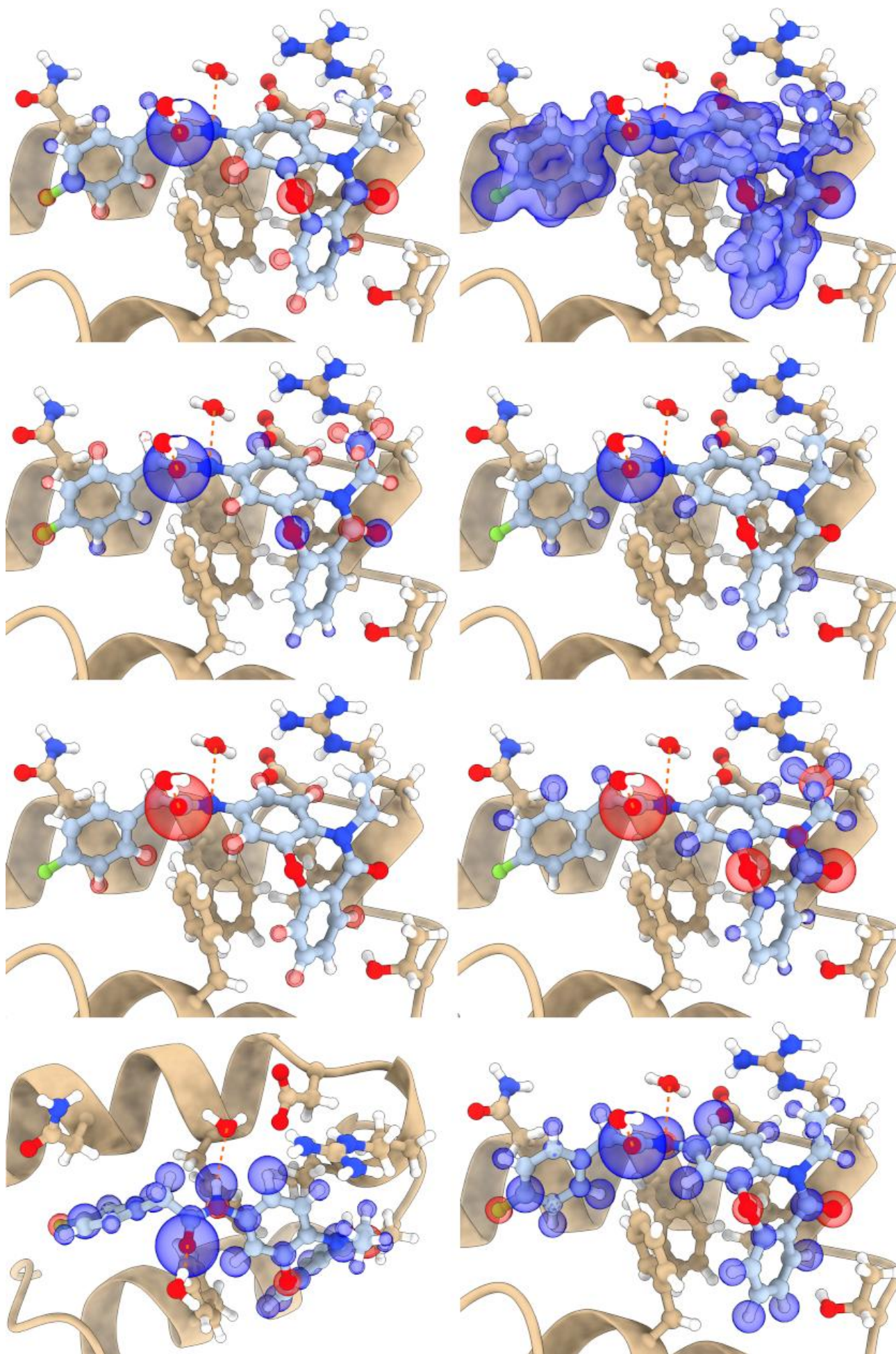
**Figure S1B.** All Energy Decomposition Analysis maps for compound 7. By order of presentation, the figure shows charge transfer (CT), dispersion (DISP), electrostatics (ES), polarization (POL), electronic density repulsion (REP), solvation (SOLV) and the total interaction (INT) maps in two orientations.





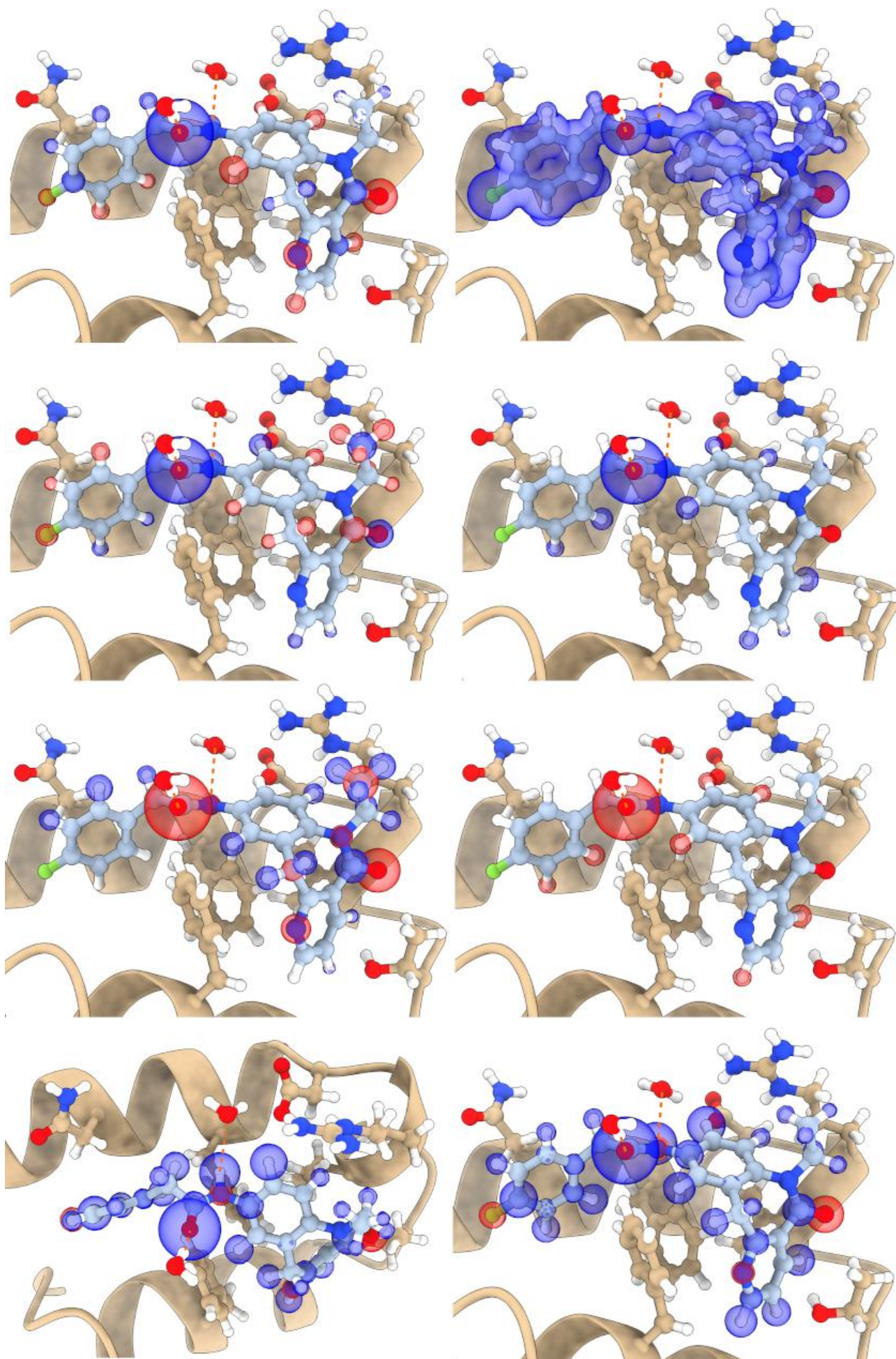
**Figure S1C.** All Energy Decomposition Analysis maps for compound **5**. By order of presentation, the figure shows charge transfer (CT), dispersion (DISP), electrostatics (ES), polarization (POL), electronic density repulsion (REP), solvation (SOLV) and the total interaction (INT) maps.





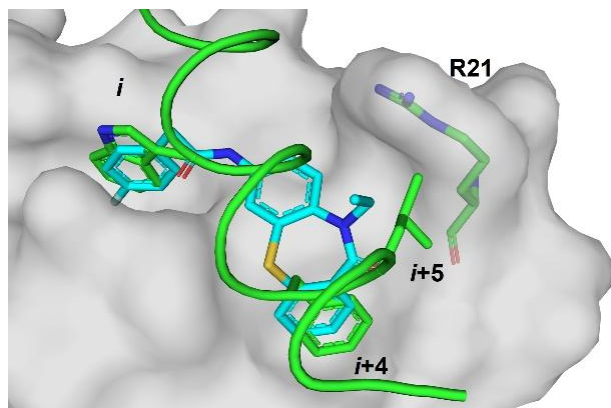
**Figure S1D.** All Energy Decomposition Analysis maps for compound **6**. By order of presentation, the figure shows charge transfer (CT), dispersion (DISP), electrostatics (ES), polarization (POL), electronic density repulsion (REP), solvation (SOLV) and the total interaction (INT) maps in two orientations.



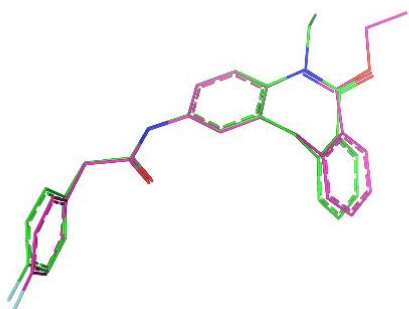


**Figure S1E.** All Energy Decomposition Analysis maps for compound **8**. By order of presentation, the figure shows charge transfer (CT), dispersion (DISP), electrostatics (ES), polarization (POL), electronic density repulsion (REP), solvation (SOLV) and the total interaction (INT) maps in two orientations.

## S2. Supporting data for SAR analysis of compounds 9-13



**Figure S2A.** Overlay of the co-crystal structure of compound **5** with *Tc*PEX14 NTD (PDB accession code: 7QRC) with the model of PEX WxxxFL fragment (derived from the NMR structure of its complex with *Hs*PEX14 NTD, PDB accession code: 2W84). The L (*i*+5) side chain of PEX5 interacts with the aliphatic portion of R22 of *Tc*PEX14 NTD. This interaction is mimicked by the *N*-alkyl residues of the tricyclic PEX5-PEX14 PPI

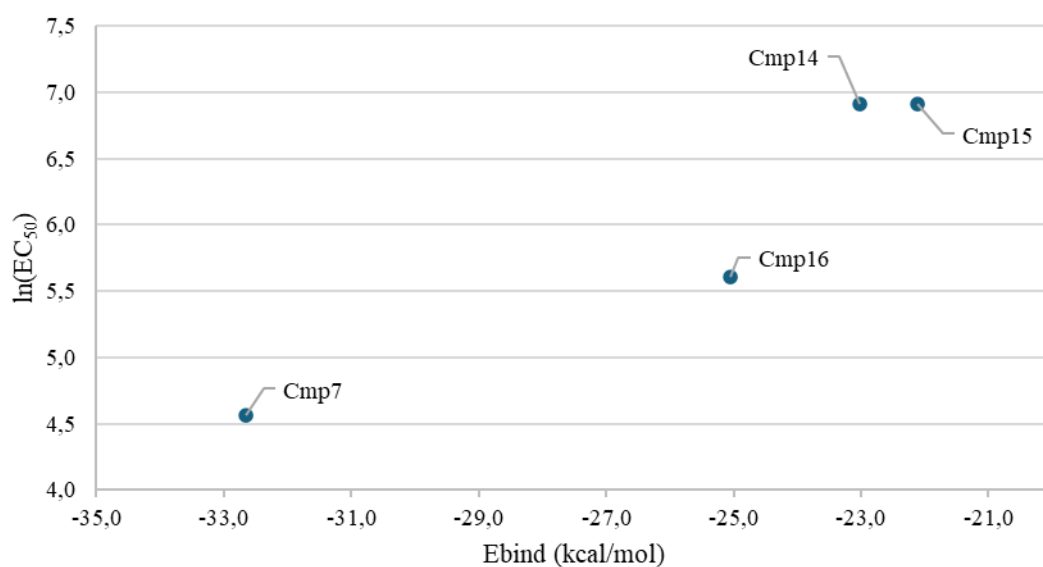


**Figure S2B.** Overlay of the QM-optimized structures of compounds **7** (green) and **13** (magenta). No significant differences are observed between the conformations of the respective tricyclic systems.

### S3. Supporting data for EDDAs for compounds 14-16

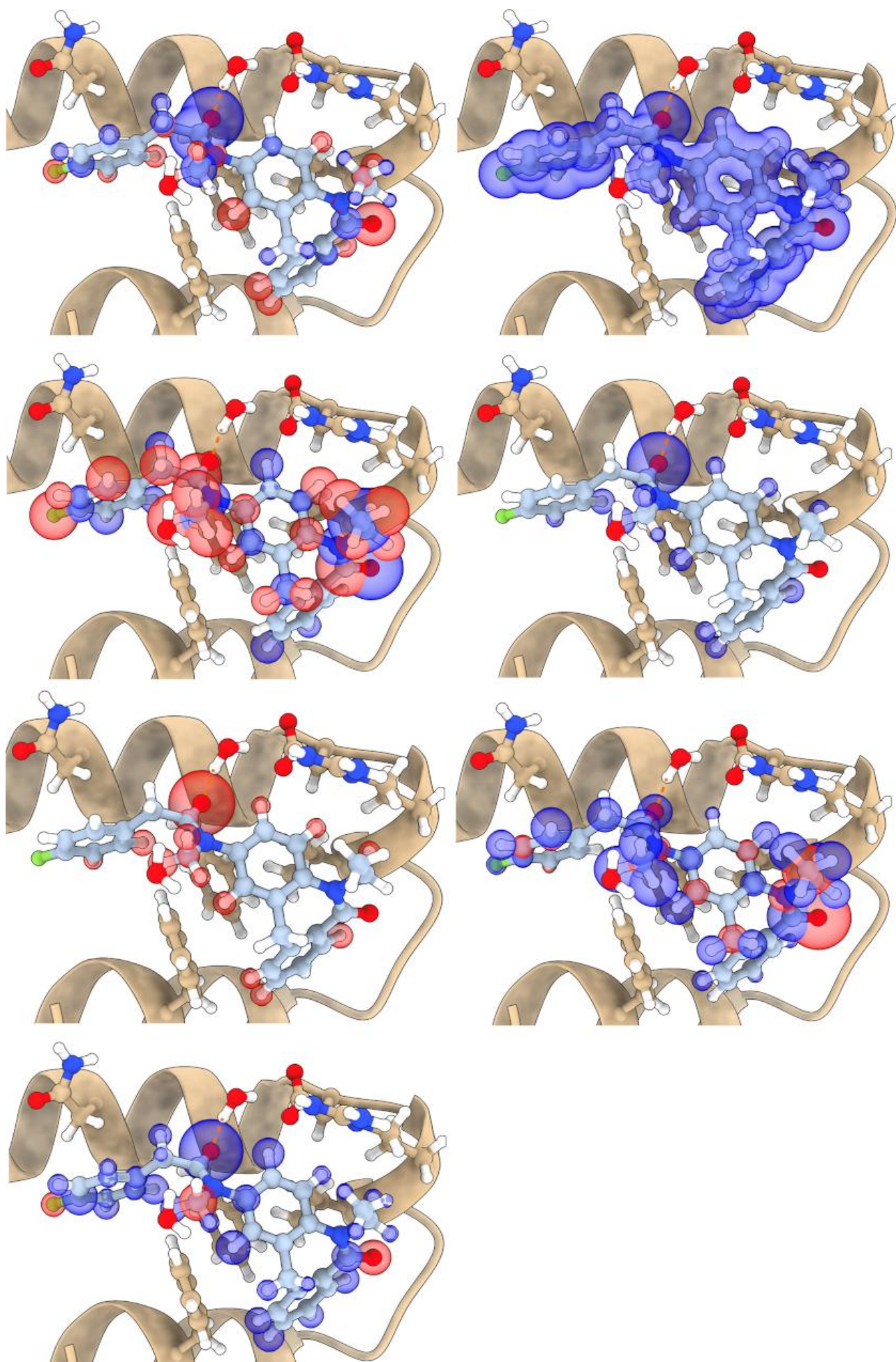
**Table S3.** Energy Decomposition Analysis data for compounds **14**, **15**, and **16**. All values are given in kcal/mol.

Compound	14	15	16
ES	12.24	3.97	2.83
POL	-57.92	-39.70	-79.10
CT	0.41	0.08	-0.35
EXC	0.00	0.00	0.00
REP	79.12	47.95	96.30
DISP	-39.40	-39.41	-40.53
SOLV	-17.46	4.99	-4.20
INT	-23.02	-22.12	-25.06



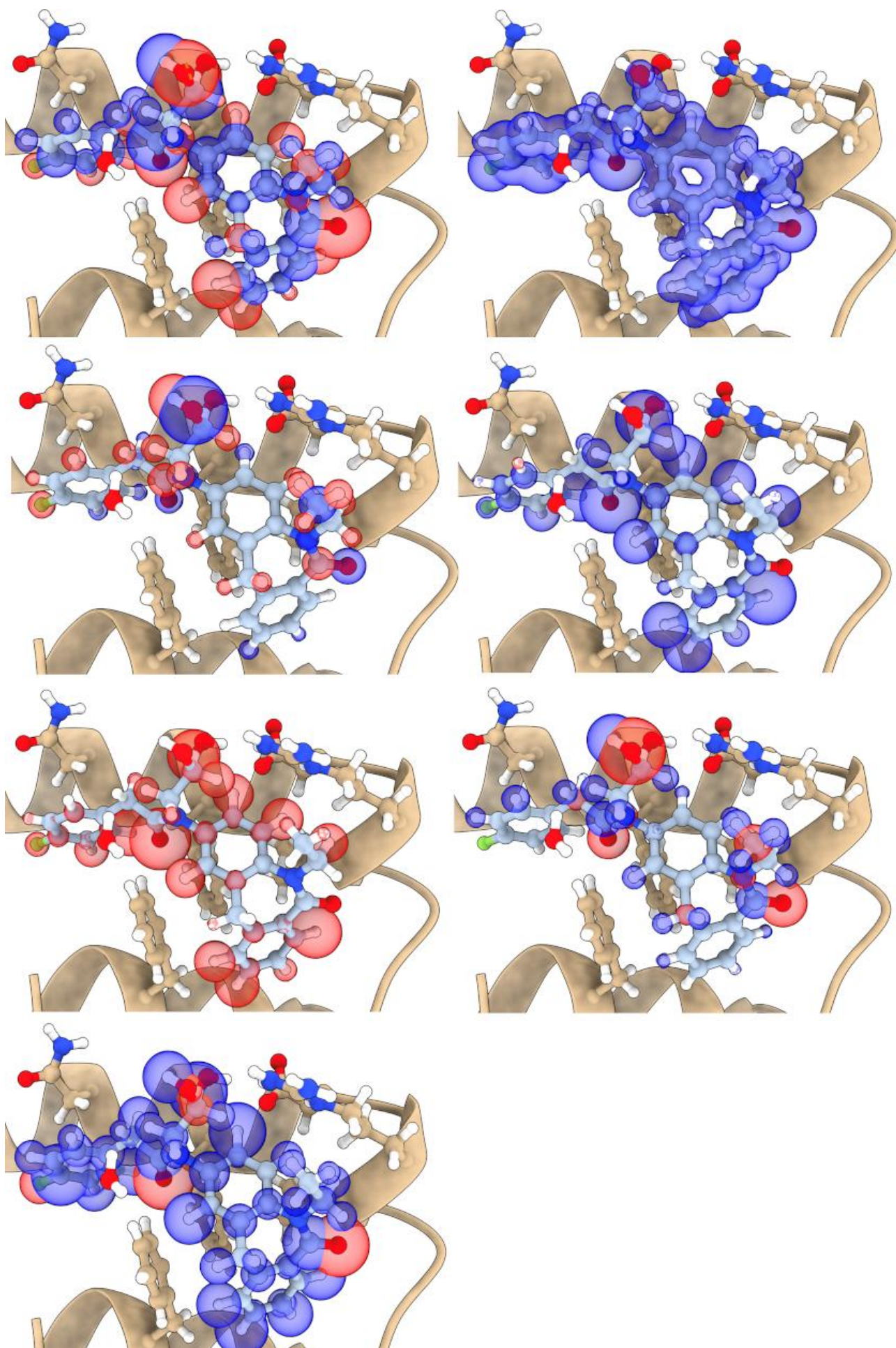
**Figure S3A.** Correlation between experimental EC<sub>50</sub> values for PEX5-PEX14 PPI inhibition and EDDA-derived binding energies for compounds **14-16**. The calculated  $R^2 = 0.90$  indicates an overall good correlation.





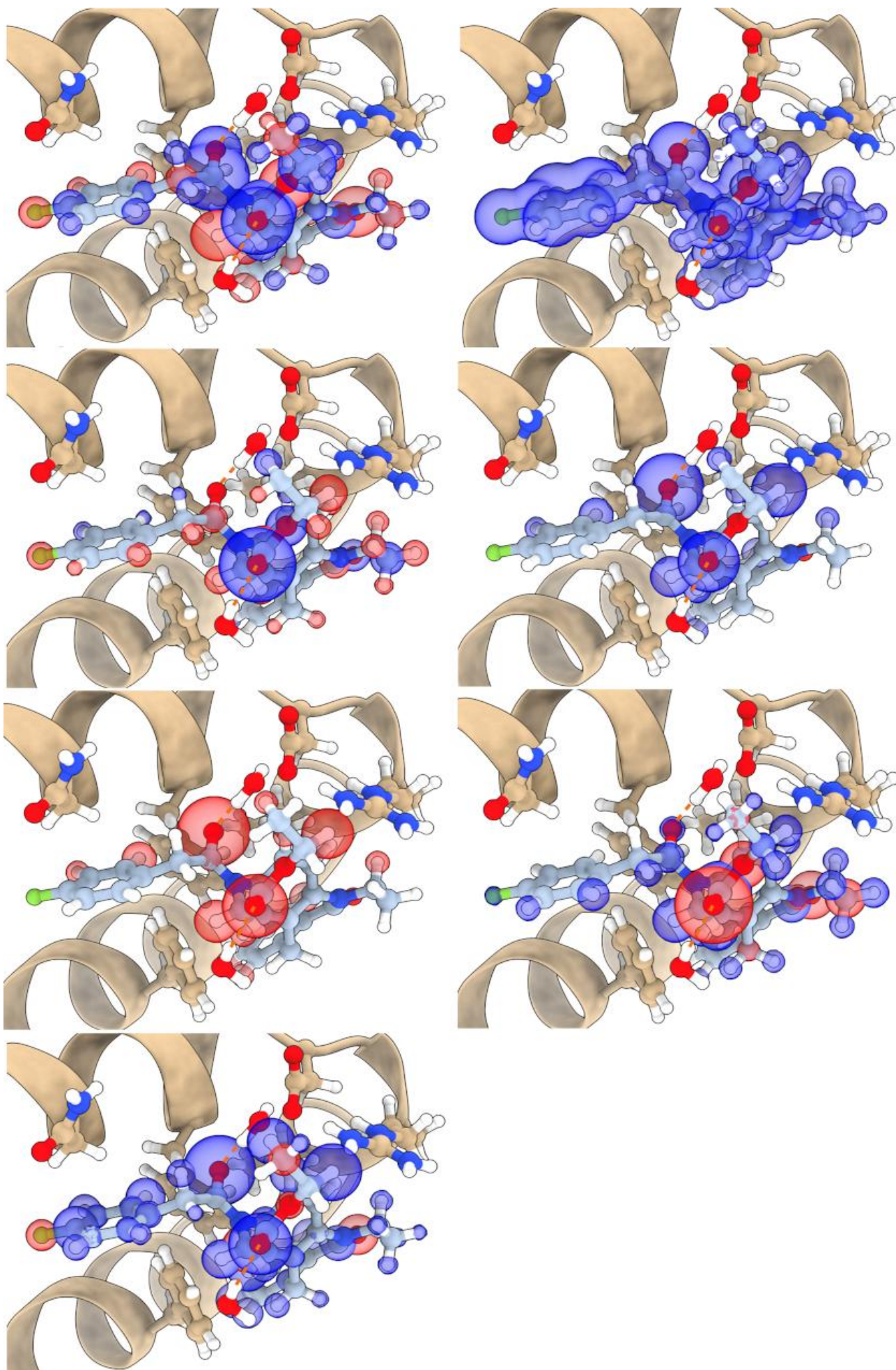
**Figure S3B.** All Energy Decomposition Analysis maps for compound **14**. By order of presentation, the figure shows charge transfer (CT), dispersion (DISP), electrostatics (ES), polarization (POL), electronic density repulsion (REP), solvation (SOLV) and the total interaction (INT) maps.





**Figure S3C.** All Energy Decomposition Analysis maps for compound **15**. By order of presentation, the figure shows charge transfer (CT), dispersion (DISP), electrostatics (ES), polarization (POL), electronic density repulsion (REP), solvation (SOLV) and the total interaction (INT) maps.



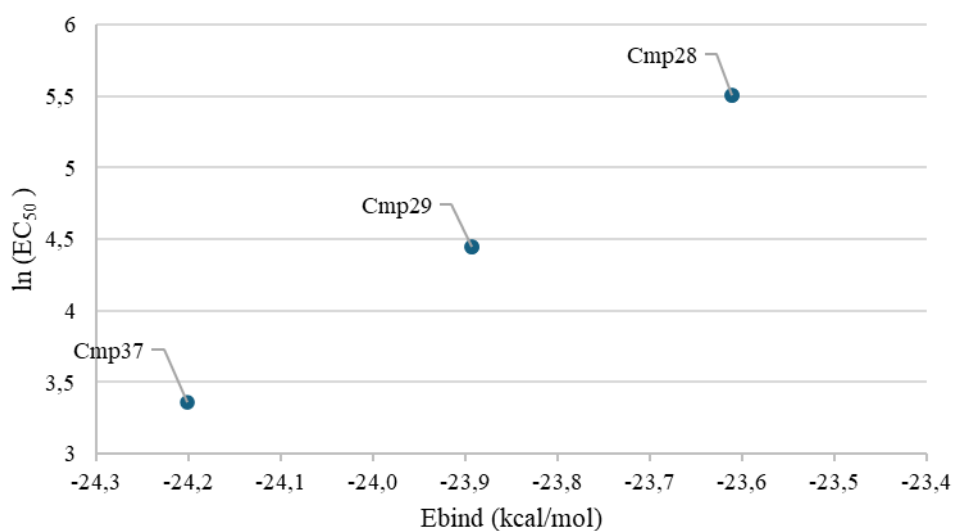


**Figure S3D.** All Energy Decomposition Analysis maps for compound **16**. By order of presentation, the figure shows charge transfer (CT), dispersion (DISP), electrostatics (ES), polarization (POL), electronic density repulsion (REP), solvation (SOLV) and the total interaction (INT) maps.

#### S4. Supporting data for EDDAs for compounds 28, 29 and 37

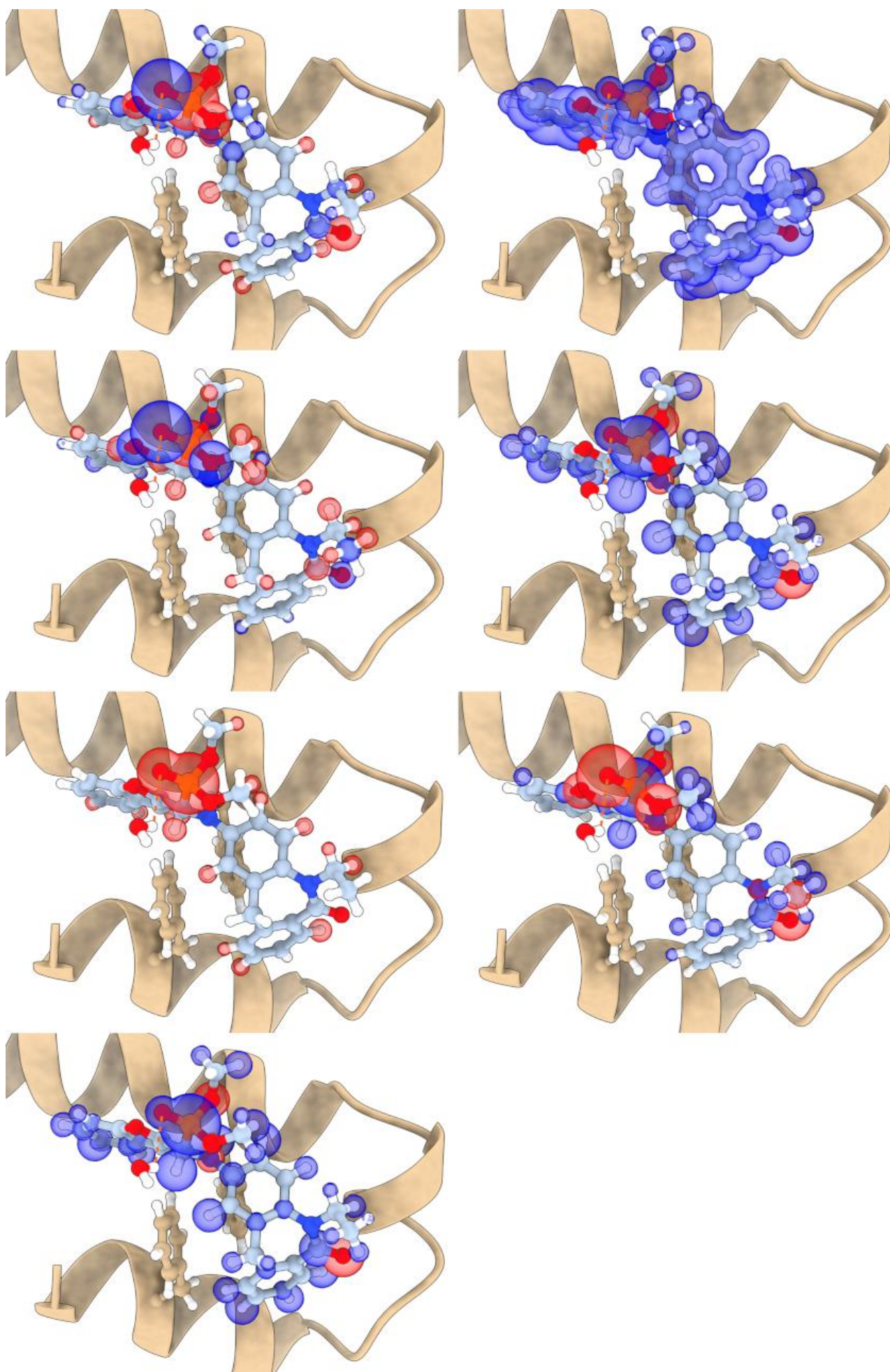
**Table S4.** Energy Decomposition Analysis data for compounds **28**, **29** and **37**. All values are given in kcal/mol.

Compound	28	29	37
ES	-14,62	-8,56	-12,52
POL	-82,59	-81,04	-73,97
CT	-0,40	-0,46	-0,80
REP	90,38	91,00	84,57
DISP	-41,19	-41,78	-41,28
SOLV	24,79	16,95	19,76
INT	-23,61	-23,89	-24,25



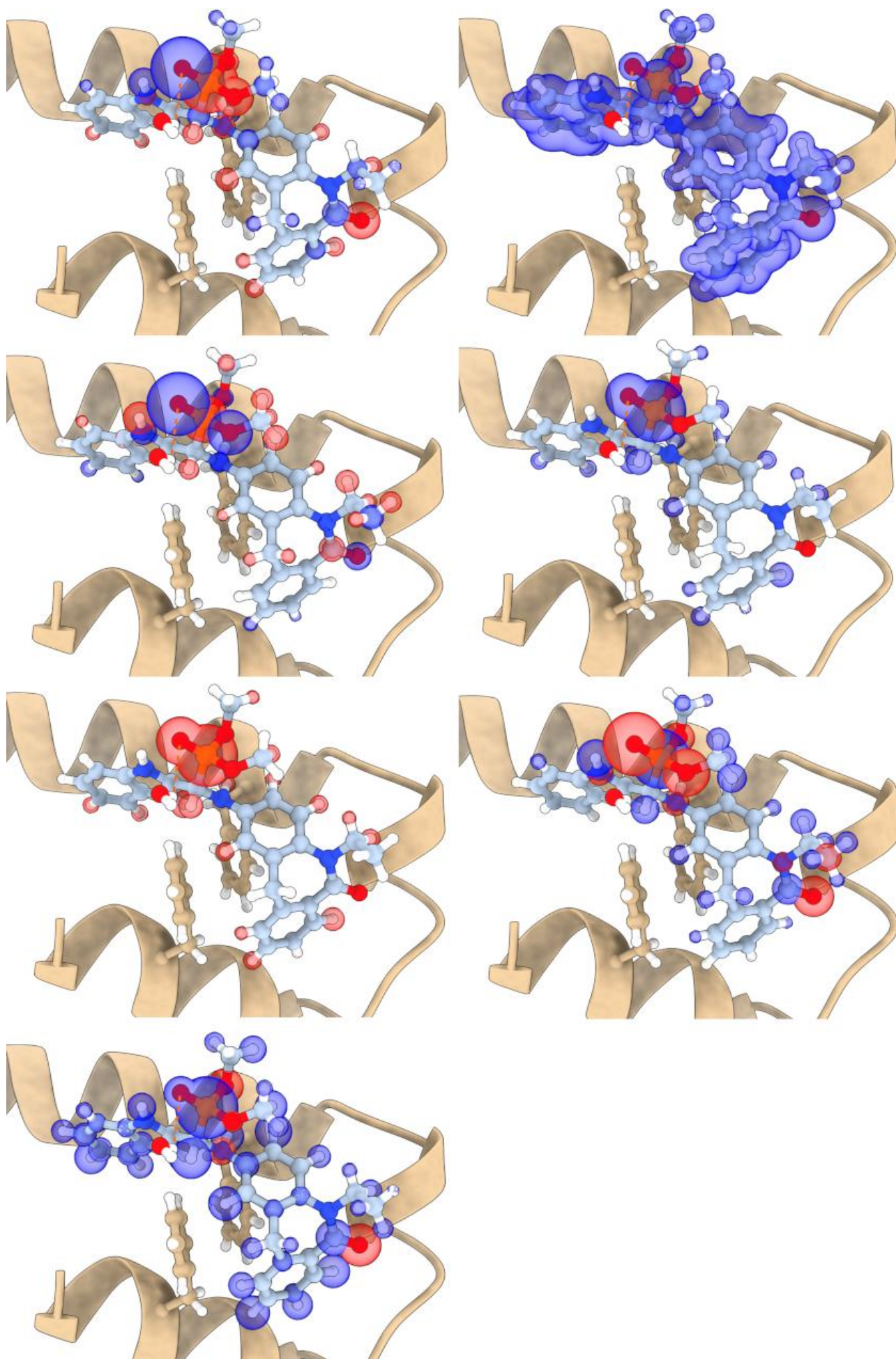
**Figure S4A.** Correlation between experimental EC<sub>50</sub> values for PEX5-PEX14 PPI inhibition and EDDA-derived binding energies for compounds **28**, **29**, and **37**. The calculated  $R^2 = 1.00$  indicates an excellent correlation.





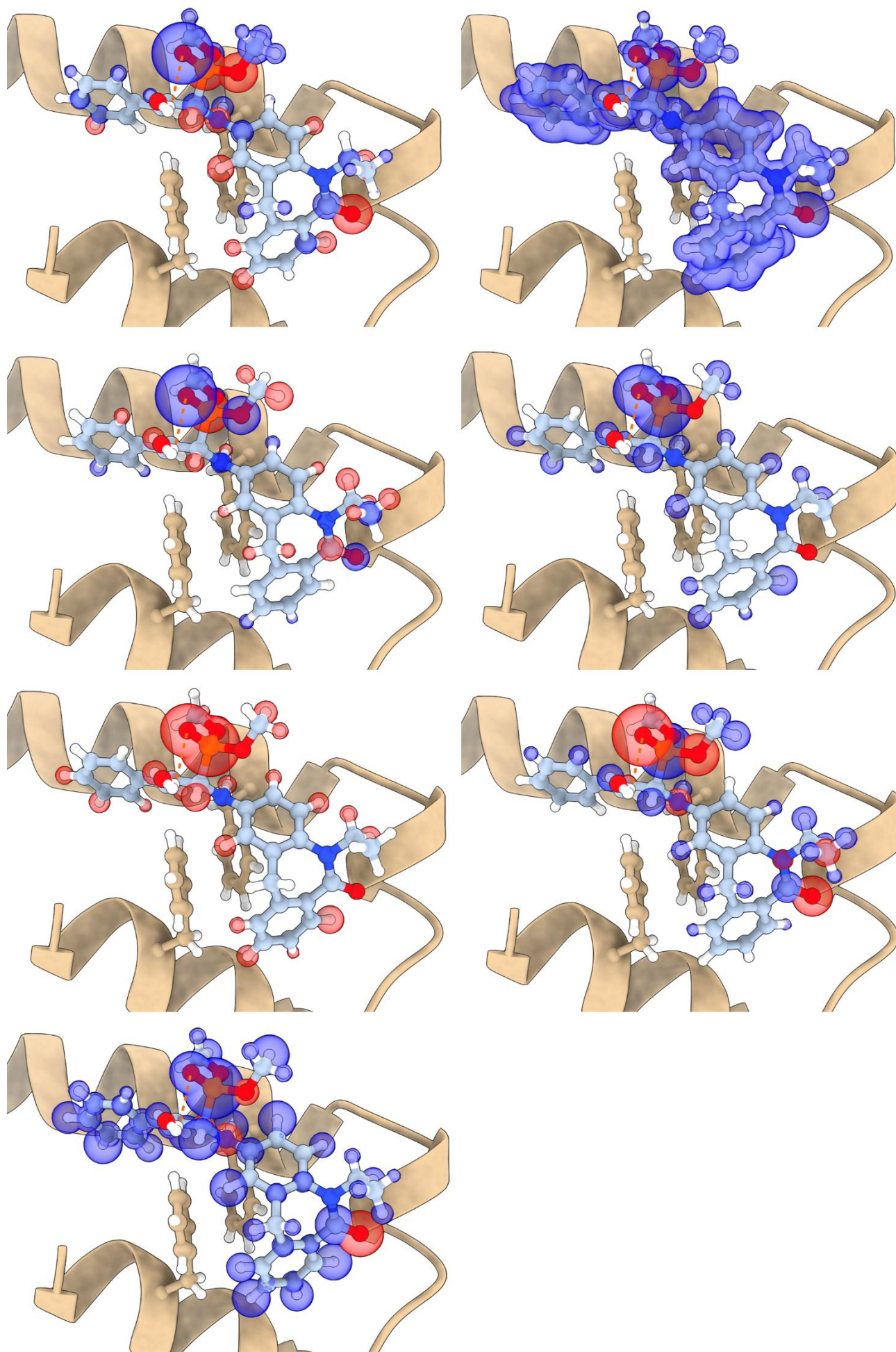
**Figure S4B.** All Energy Decomposition Analysis maps for compound **28**. By order of presentation, the figure shows charge transfer (CT), dispersion (DISP), electrostatics (ES), polarization (POL), electronic density repulsion (REP), solvation (SOLV) and the total interaction (INT) maps.



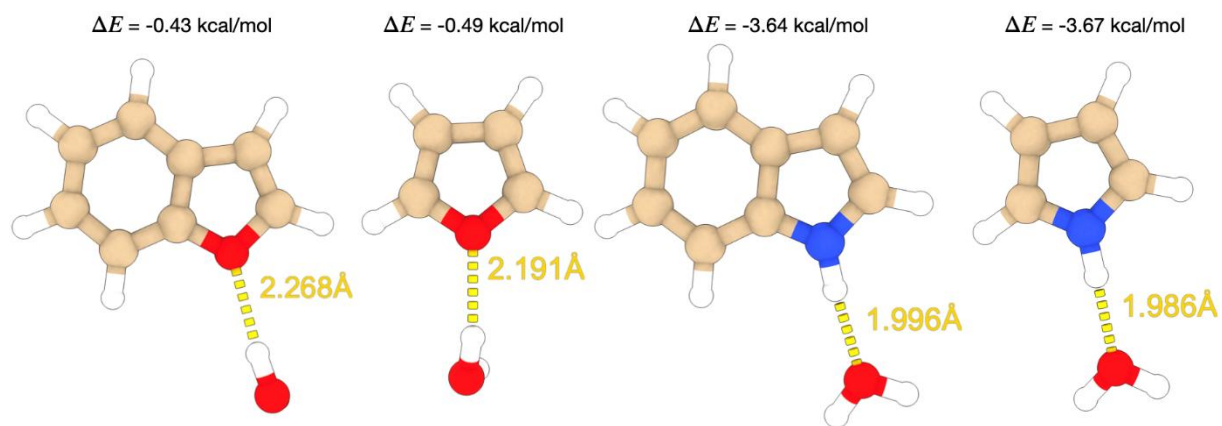


**Figure S4C.** All Energy Decomposition Analysis maps for compound **29**. By order of presentation, the figure shows charge transfer (CT), dispersion (DISP), electrostatics (ES), polarization (POL), electronic density repulsion (REP), solvation (SOLV) and the total interaction (INT) maps.

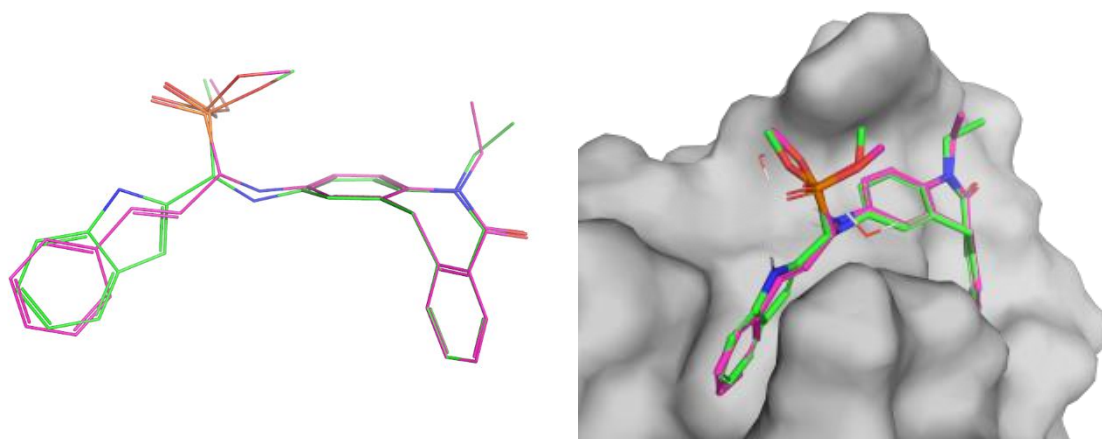




**Figure S4D.** All Energy Decomposition Analysis maps for compound **37**. By order of presentation, the figure shows charge transfer (CT), dispersion (DISP), electrostatics (ES), polarization (POL), electronic density repulsion (REP), solvation (SOLV) and the total interaction (INT) maps.



**Figure S4E.** Evaluation of the interaction energy between heteroaromatics and water molecules. Indole and pyrrole NH hydrogen atom offers stronger interactions with water than the benzoxazole or furan oxygen.



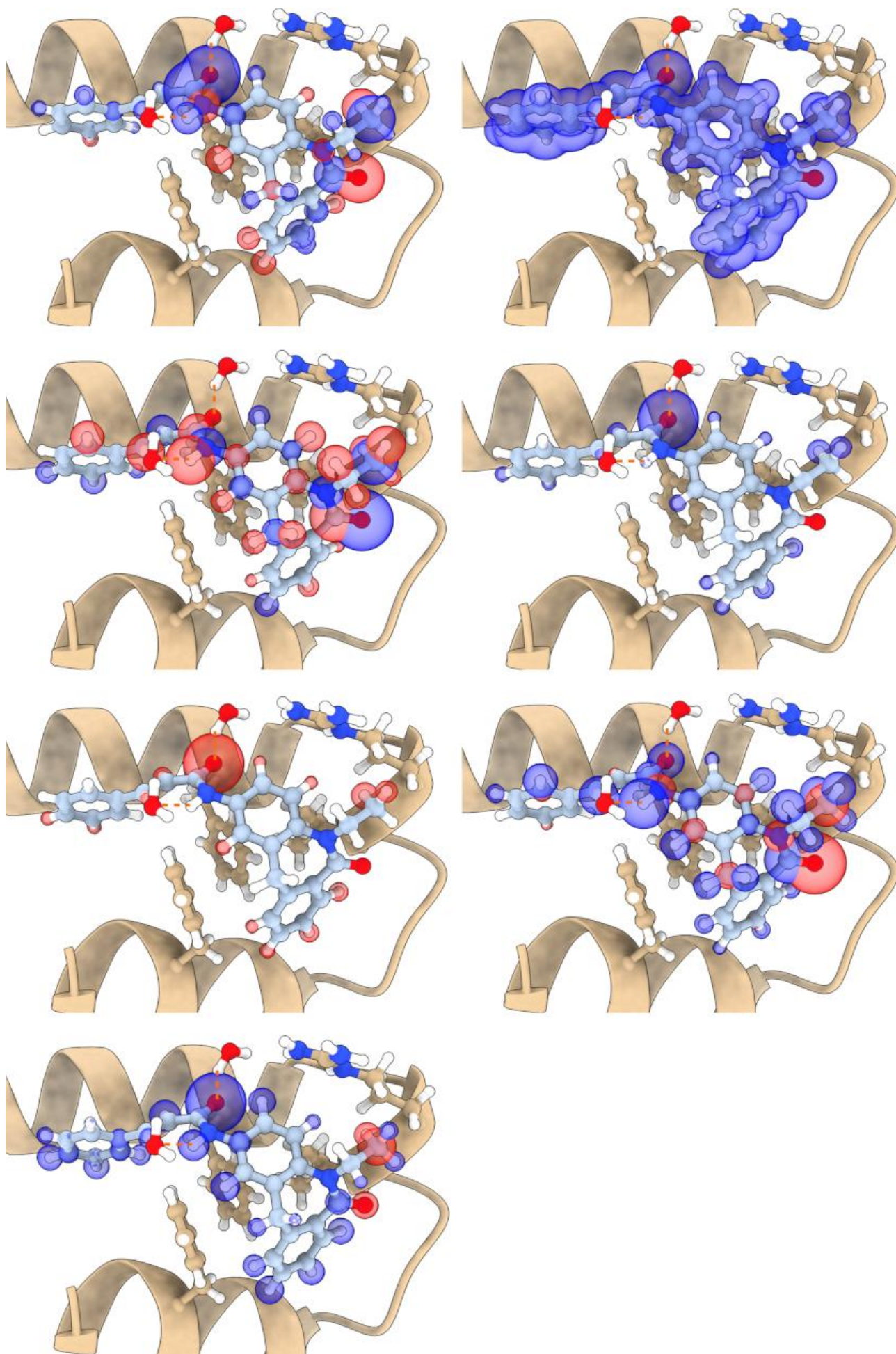
**Figure S4F.** Overlay of the structures of compounds **29** (green) and **37** (magenta).



## S5. Supporting data for EDDAs for compound 43

**Table S5.** Energy Decomposition Analysis data for compound 43.

Compound	43
ES	5.72
POL	-88.25
CT	1.34
REP	112.20
DISP	-40.24
SOLV	-10.91
INT	-20.15



**Figure S5.** All Energy Decomposition Analysis maps for compound **43**. By order of presentation, the figure shows charge transfer (CT), dispersion (DISP), electrostatics (ES), polarization (POL), electronic density repulsion (REP), solvation (SOLV) and the total interaction (INT) maps.