Electronic Supplementary Information

# Cross-docking study on InhA inhibitors: a combination of Autodock Vina and PM6-DH2 simulations to retrieve bio-active conformations

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**Table S1** List of the 12 amino acid residues allowed to move during the PM6-DH2 Mopac optimizations

| | | | | | |
|---|---|---|---|---|---|
| M103 | F149 | M155 | Y158 | M161 | T196 |
| M199 | I202 | L207 | I215 | L218 | E219 |

**Table S2** List of the 14 PDB entries used to delineate a common volume occupied by the InhA inhibitors into the binding pocket.

| | | | | | | |
|---|---|---|---|---|---|---|
| 1BVR | 1P44 | 1P45 | 2B35 | 2B37 | 2NSD | 2H7I |
| 2H7L | 2H7M | 2H7N | 2H7P | 3FNE | 3FNG | 3FNH |

**Table S3** Calculated Interaction Energies (kcal/mol) for the first ten Autodock Vina poses of **GEQ**, **d11**, **8PC**, **8PS** and **AYM** docked into the InhA/NADH cavities **1P44**, **1P45**, **2H7M** and **3FNE**. The conserved (or very close to) bioactive conformations are depicted in bold. Shaded lines correspond to calculations performed with the ligands docked in their respective InhA native proteins. *Inverted* pose is relative to a conformation that is inverted compared to the crystal structure of reference. The *out* or *partly out* poses were docked outside the acyl substrate-binding pocket. The computed volume occupied by 14 inhibitors was used to evaluate this “out-of-cavity” notion. The *improper* poses refer to other docked poses whose orientation was far from the awaited result. *Shifted, flipped, folded, displaced* poses are relative to conformations that are oriented in the same way as in the crystal structure of reference, but with some minor changes.

## Docking of GEQ

| | Vina rank | Vina energy | RMSD (Å) | H-bonds with Y158/ribose | Mopac single point ($E_{sp}$) | Mopac optimization ($E_{opt}$) | comparison with the X-ray ligand |
|---|---|---|---|---|---|---|---|
| **1P44** | **1** | **-10.9** | **0.3** | **2** | **-21.1** | **-60.8** | **correct** |
| | 2 | -9.7 | 2 | - | -11.0 | -40.0 | shifted |
| | 3 | -9.7 | 2.3 | - | -14.7 | -57.6 | shifted |
| | 4 | -8.5 | 4.2 | 1 | 2.8 | -21.3 | shifted |
| | 5 | -8.4 | 8.7 | - | -6.9 | -2.7 | inverted |
| | 6 | -8.3 | 7.4 | - | -4.5 | -10.1 | inverted |
| | 7 | -8.2 | 5.4 | - | -5.8 | -23.8 | improper |
| | 8 | -8.1 | 8.5 | - | 10.7 | -6.2 | inverted |
| | 9 | -8.1 | 8.0 | 1 | -10.5 | -9.7 | inverted |
| | 10 | -8 | 8.7 | - | -0.0 | -11.9 | inverted |
| **1P45** | 1 | -9.2 | 8.2 | 2 | 17.4 | -22.1 | inverted |
| | 2 | -8.9 | 7.5 | 2 | 5.9 | -21.0 | inverted |
| | 3 | -8.8 | 5.2 | 1 | 0.0 | -23.6 | shifted |
| | 4 | -8.8 | 9.4 | 2 | 10.4 | -22.8 | inverted |
| | 5 | -8.7 | 3.7 | - | 1.5 | -16.5 | shifted |
| | 6 | -8.6 | 8.9 | 2 | 7.8 | -24.2 | inverted |
| | 7 | -8.5 | 5.0 | - | 10.9 | 1.0 | shifted |
| | 8 | -8.5 | 4.9 | - | 2.7 | -18.9 | improper |
| | 9 | -8.3 | 5.0 | - | 0.1 | 2.8 | improper |
| | **10** | **-7.9** | **2.0** | **2** | **3.9** | **-42.5** | **fluorene flipped** |
| **2H7M** | **1** | **-8.3** | **1.9** | **2** | **-33.4** | **-42.5** | **correct** |
| | 2 | -8.1 | 3.9 | - | 5.1 | -26.0 | shifted |
| | 3 | -8.1 | 3.6 | - | -3.5 | -24.3 | shifted |
| | 4 | -8.1 | 9.0 | 2 | -15.9 | -17.2 | inverted |
| | 5 | -7.7 | 8.7 | 2 | -8.5 | -13.4 | inverted |
| | 6 | -7.4 | 8.5 | - | -6.5 | -6.6 | inverted |
| | 7 | -6.9 | 9.2 | 1 | 0.6 | -11.5 | inverted |
| | 8 | -6.7 | 4.2 | - | -8.4 | -3.2 | shifted |
| | 9 | -6.5 | 5.1 | - | -16.5 | -4.9 | shifted |
| | 10 | -6.5 | 6.4 | - | -15.8 | 2.4 | improper |
| **3FNE** | 1 | -8.8 | 8.5 | - | 0.3 | -23.3 | inverted |
| | 2 | -8.1 | 9.9 | 2 | -8.2 | -26.6 | inverted |
| | **3** | **-7.9** | **3.6** | **1** | **-20.4** | **-25.6** | **shifted** |
| | 4 | -7.7 | 4.7 | 1 | -4.2 | -28.7 | shifted |
| | 5 | -7.3 | 4.2 | - | 1.9 | -23.1 | shifted |
| | 6 | -7.3 | 12.6 | 1 | -3.7 | -4.0 | inverted |
| | 7 | -7.2 | 4.5 | - | -15.4 | -26.2 | shifted |
| | 8 | -7 | 4.5 | - | -6.2 | -19.4 | shifted |
| | 9 | -7 | 5.3 | - | -9.8 | -11.2 | shifted |
| | 10 | -6.2 | 12.1 | 1 | -2.1 | -10.1 | improper |

## Docking of d11

| | Vina rank | Vina energy | RMSD (Å) | H-bonds with Y158/ribose | Mopac single point ($E_{sp}$) | Mopac optimization ($E_{opt}$) | comparison with the X-ray ligand |
|---|---|---|---|---|---|---|---|
| **1P44** | 1 | -7.5 | 5.8 | - | -2.1 | -14.1 | improper |
| | 2 | -7.4 | 5.8 | - | -0.0 | -12.1 | improper |
| | **3** | **-7.3** | **1.1** | **2** | **-2.7** | **-24.9** | **correct** |
| | 4 | -7.1 | 3.8 | 1 | -2.6 | -10.1 | folded |
| | 5 | -7.0 | 6.7 | - | 3.2 | -1.2 | folded |
| | 6 | -7.0 | 7.6 | - | 7.6 | -4.3 | inverted |
| | 7 | -6.7 | 7.2 | - | -0.9 | -8.7 | improper |
| | 8 | -6.7 | 4.8 | - | 1.6 | -12.6 | folded |
| | 9 | -6.7 | 7.0 | - | 7.7 | -5.4 | improper |
| | 10 | -6.6 | 5.2 | - | -1.6 | -11.1 | improper |
| **1P45** | 1 | -7.9 | 7.0 | - | -8.5 | -5.3 | inverted, folded |
| | **2** | **-7.2** | **2.9** | **2** | **-2.3** | **-19.3** | **amide flipped** |
| | 3 | -7.0 | 4.2 | - | 13.1 | -8.4 | folded |
| | 4 | -6.9 | 1.5 | 2 | 1.7 | -11.5 | shifted |
| | 5 | -6.9 | 7.8 | - | 14.2 | -25.1 | inverted |
| | 6 | -6.8 | 2.5 | 1 | 15.0 | -3.6 | folded |
| | 7 | -6.8 | 2.9 | - | 12.0 | -22.8 | folded |
| | 8 | -6.5 | 6.8 | - | 1.6 | -3.3 | improper |
| | 9 | -6.4 | 6.4 | - | 5.0 | -9.5 | improper |
| | 10 | -6.4 | 2.0 | - | 4.7 | -13.5 | shifted |
| **2H7M** | **1** | **-8.3** | **0.4** | **2** | **-15.0** | **-37.5** | **correct** |
| | 2 | -7.2 | 1.5 | 1 | 1.4 | -40.5 | shifted |
| | 3 | -7.1 | 7.9 | - | 15.5 | 5.0 | inverted |
| | 4 | -6.8 | 7.1 | - | 16.5 | 4.6 | improper |
| | 5 | -6.2 | 7.1 | - | 23.8 | 12.6 | folded |
| | 6 | -6.1 | 2.8 | 2 | -11.3 | -23.5 | amide flipped |
| | 7 | -6 | 8.1 | - | 12.7 | 1.7 | improper |
| | 8 | -6.0 | 10.0 | - | 21.0 | 7.9 | partially out |
| | 9 | -6.0 | 9.7 | - | 14.9 | -8.2 | partially out |
| | 10 | -5.9 | 9.9 | - | 22.2 | 8.5 | partially out |
| **3FNE** | 1 | -7.7 | 10.7 | - | 10.2 | -3.6 | out |
| | **2** | **-7.4** | **2.3** | **2** | **-12.2** | **-17.6** | **aryl displaced** |
| | 3 | -7.4 | 9.9 | - | 4.7 | -8.3 | out |
| | 4 | -7.3 | 7.4 | - | 1.8 | -9.2 | inverted |
| | 5 | -7.2 | 13.2 | - | 8.1 | -4.8 | out |
| | 6 | -7.2 | 7.7 | - | 2.1 | -9.6 | inverted |
| | 7 | -7.1 | 11.1 | - | 3.6 | -19.0 | out |
| | 8 | -6.9 | 12.3 | - | 7.4 | -4.0 | out |
| | 9 | -6.9 | 8.5 | - | -1.4 | -13.4 | out |
| | 10 | -6.8 | 9.9 | - | 4.9 | -14.3 | out |

## Docking of 8PC

| | Vina rank | Vina energy | RMSD (Å) | H-bonds with Y158/ribose | Mopac single point ($E_{sp}$) | Mopac optimisation ($E_{opt}$) | comparison with the X-ray ligand |
|---|---|---|---|---|---|---|---|
| **1P44** | 1 | -5.5 | 3.3 | - | -6.6 | 1.0 | shifted |
| | **2** | **-5.4** | **1.6** | **2** | **-16.6** | **-19.1** | **correct** |
| | 3 | -4.9 | 7.8 | - | 10.6 | -12.8 | inverted |
| | 4 | -4.6 | 2.8 | 2 | -3.0 | -24.8 | shifted |
| | 5 | -4.6 | 7.5 | 2 | -7.9 | -23.6 | inverted |
| | 6 | -4.5 | 8.0 | 1 | 3.0 | 6.5 | inverted |
| | 7 | -4.2 | 3.9 | - | -0.8 | -9.5 | shifted |
| | 8 | -4.1 | 6.2 | - | -2.8 | 7.8 | improper |
| | 9 | -3.9 | 6.7 | - | 2.2 | -10.9 | improper |
| | 10 | -3.9 | 7.5 | - | 5.2 | 4.7 | out |
| **1P45** | **1** | **-6.0** | **1.1** | **2** | **-7.8** | **-25.3** | **correct** |
| | 2 | -5.2 | 2.6 | - | 2.4 | -4.1 | shifted |
| | 3 | -5.2 | 2.1 | - | -0.5 | 11.5 | phenol inverted |
| | 4 | -5.0 | 7.6 | - | 8.1 | -0.0 | inverted |
| | 5 | -4.4 | 3.2 | - | -6.0 | -5.7 | shifted |
| | 6 | -4.4 | 7.8 | 2 | 2.9 | -5.7 | inverted |
| | 7 | -4.3 | 3.3 | - | -3.7 | -9.0 | shifted |
| | 8 | -4.3 | 4.2 | - | -2.1 | 5.4 | improper |
| | 9 | -3.7 | 7.6 | - | 2.4 | -17.4 | inverted |
| | 10 | -3.5 | 10.0 | - | 0.8 | -3.6 | out |
| **2H7M** | 1 | -7.6 | 7.7 | 2 | 4.8 | -16.7 | inverted |
| | **2** | **-7.5** | **1.7** | **3** | **-11.2** | **-17.8** | **correct** |
| | 3 | -7.2 | 3.4 | - | 9.2 | -11.3 | shifted |
| | 4 | -6.7 | 3.7 | - | 8.1 | -9.6 | shifted |
| | 5 | -6.4 | 5.9 | - | -3.9 | -18.3 | partly out |
| | 6 | -6.3 | 6.5 | - | 12.8 | -18.8 | partly out |
| | 7 | -6.3 | 8.5 | - | 5.3 | -8.7 | partly out |
| | 8 | -6.1 | 7.4 | - | -2.1 | -17.1 | partly out |
| | 9 | -6.0 | 4.9 | - | 12.6 | -1.6 | improper |
| | 10 | -5.9 | 9.2 | - | 12.4 | -7.5 | out |
| **3FNE** | **1** | **-6.6** | **0.5** | **2** | **-11.5** | **-25.4** | **correct** |
| | 2 | -6.6 | 7.6 | 2 | 1.8 | -21.1 | inverted |
| | 3 | -6.2 | 3.7 | 1 | -7.9 | -19.3 | shifted |
| | 4 | -5.6 | 4.7 | - | 2.9 | -0.6 | shifted |
| | 5 | -5.5 | 4.5 | - | -7.0 | -3.3 | improper |
| | 6 | -5.1 | 10.0 | - | -3.4 | 0.9 | partly out |
| | 7 | -5.0 | 7.5 | 1 | 7.5 | -17.6 | inverted |
| | 8 | -5.0 | 4.8 | - | -2.7 | -4.5 | partly out |
| | 9 | -4.9 | 7.0 | - | -4.4 | -22.3 | partly out |
| | 10 | -4.6 | 7.9 | 1 | 8.4 | -13.4 | inverted |

## Docking of 8PS

| | Vina rank | Vina energy | RMSD (Å) | H-bonds with Y158/ribose | Mopac single point ($E_{sp}$) | Mopac optimisation ($E_{opt}$) | comparison with the X-ray ligand |
|---|---|---|---|---|---|---|---|
| **1P44** | 1 | -3.9 | 8.0 | - | -7.3 | -12.8 | inverted |
| | **2** | **-3.8** | **2.4** | **2** | **-9.3** | **-29.3** | **slightly shifted** |
| | 3 | -3.8 | 4.0 | - | -13.0 | -20.8 | shifted |
| | 4 | -3.7 | 7.1 | - | -13.4 | -15.9 | improper |
| | 5 | -3.5 | 3.6 | - | -8.7 | -19.5 | inverted |
| | 6 | -3.5 | 7.3 | - | -13.7 | -16.5 | improper |
| | 7 | -3.3 | 7.2 | - | -10.4 | -6.5 | improper |
| | 8 | -3.2 | 7.8 | 3 | -1.5 | -15.9 | inverted |
| | 9 | -3.2 | 8.9 | - | -14.1 | -22.0 | improper |
| | 10 | -3 | 8.0 | - | -5.6 | -16.7 | partly out |
| **1P45** | **1** | **-5.2** | **2.9** | **2** | **-30.1** | **-31.3** | **correct** |
| | 2 | -5.1 | 2.8 | 2 | -10.4 | -22.6 | correct |
| | 3 | -4.9 | 8.2 | - | -6.7 | 0.7 | inverted |
| | 4 | -4.8 | 4.1 | - | -11.6 | -11.9 | shifted |
| | 5 | -4.8 | 8.3 | - | -11.6 | -13.7 | inverted |
| | 6 | -4.6 | 7.8 | - | -15.6 | -18.1 | improper |
| | 7 | -4.6 | 3.2 | - | -15.6 | -16.8 | shifted |
| | 8 | -4.6 | 8.2 | - | -14.6 | -13.7 | improper |
| | 9 | -4.4 | 5.5 | - | -15.4 | -9.1 | improper |
| | 10 | -4.0 | 11.4 | - | -12.9 | -9.8 | partly out |
| **2H7M** | **1** | **-5.4** | **2.7** | **2** | **-27.5** | **-34.5** | **correct** |
| | 2 | -5 | 2.5 | 2 | -26.1 | -22.0 | slightly shifted |
| | 3 | -4.8 | 5.4 | - | -5.3 | -14.1 | shifted |
| | 4 | -4.7 | 7.8 | - | -5.5 | -13.4 | inverted |
| | 5 | -4.6 | 3.4 | - | -12.7 | -13.8 | shifted |
| | 6 | -4.6 | 4.0 | - | -15.7 | -11.9 | shifted |
| | 7 | -4.6 | 8.0 | 1 | -10.5 | -16.3 | inverted |
| | 8 | -4.2 | 8.7 | - | -5.9 | -10.8 | partly out |
| | 9 | -3.8 | 4.9 | - | -10.1 | -14.1 | improper |
| | 10 | -3.7 | 6.9 | - | -13.3 | -12.2 | partly out |
| **3FNE** | 1 | -7.2 | 3.7 | - | -20.2 | -24.5 | shifted |
| | **2** | **-7.1** | **2.1** | **3** | **-26.5** | **-45.7** | **correct** |
| | 3 | -6.8 | 5.6 | - | -11.2 | -20.3 | partly out |
| | 4 | -6.8 | 8.6 | - | -10.0 | -22.0 | inverted |
| | 5 | -6.2 | 14.4 | - | 7.2 | -18.9 | out |
| | 6 | -6.1 | 14.0 | - | 3.3 | -9.4 | out |
| | 7 | -6.1 | 8.7 | - | -10.0 | -22.3 | out |
| | 8 | -6.0 | 13.9 | - | 11.4 | -20.5 | out |
| | 9 | -5.8 | 9.5 | - | -11.1 | -24.3 | partly out |
| | 10 | -5.8 | 14.0 | - | 8.9 | -17.9 | out |

## Docking of AYM

| | Vina rank | Vina energy | RMSD (Å) | H-bonds with Y158/ribose | Mopac single point ($E_{sp}$) | Mopac optimisation ($E_{opt}$) | comparison with the X-ray ligand |
|---|---|---|---|---|---|---|---|
| **1P44** | 1 | -7.7 | 4.7 | - | -7.2 | -25.3 | improper |
| | 2 | -7.7 | 8.5 | - | 5.1 | -14.1 | improper |
| | 3 | -7.6 | 4.0 | - | -9.2 | -13.9 | shifted |
| | 4 | -7.4 | 3.9 | - | -4.7 | -17.5 | shifted |
| | 5 | -7.4 | 7.6 | - | -0.6 | -10.0 | inverted |
| | 6 | -7.3 | 3.1 | 1 | -0.6 | -26.9 | shifted |
| | 7 | -7.1 | 7.6 | - | -0.9 | -15.3 | inverted |
| | **8** | **-6.9** | **2.7** | **1** | **-14.6** | **-30.5** | **shifted, indole flipped** |
| | 9 | -6.8 | 3.2 | 2 | 1.3 | -31.9 | shifted, indole flipped |
| | 10 | -6.7 | 4.5 | - | -4.6 | -24.2 | improper |
| **1P45** | 1 | -8.0 | 7.7 | - | 20.2 | -6.9 | inverted |
| | **2** | **-7.7** | **1.0** | **2** | **-7.5** | **-32.2** | **correct** |
| | 3 | -7.3 | 2.6 | - | 7.4 | -36.2 | shifted |
| | 4 | -6.8 | 4.6 | - | 7.1 | 3.5 | partly out |
| | 5 | -6.6 | 8.2 | - | 5.9 | -2.9 | partly out |
| | 6 | -6.5 | 5.9 | - | 14.5 | -0.9 | partly out |
| | 7 | -6.4 | 11.0 | 1 | 22.9 | -8.6 | partly out |
| | 8 | -6.1 | 7.4 | - | 15.7 | -33.6 | inverted |
| | 9 | -6.1 | 4.9 | - | 8.9 | -36.6 | partly out |
| | 10 | -6.1 | 4.0 | - | 2.9 | -14.7 | shifted, indole flipped |
| **2H7M** | **1** | **-7.8** | **1.4** | **2** | **-20.1** | **-38.2** | **correct** |
| | 2 | -7.0 | 4.6 | - | 5.7 | -6.9 | shifted |
| | 3 | -6.7 | 8.2 | - | 13.4 | -16.0 | partly out |
| | 4 | -6.4 | 8.2 | - | 12.9 | -12.8 | partly out |
| | 5 | -6.2 | 10.9 | 1 | 15.2 | -0.3 | partly out |
| | 6 | -6.2 | 8.8 | 1 | 11.9 | -5.9 | partly out |
| | 7 | -6.1 | 8.7 | - | 13.5 | -0.3 | out |
| | 8 | -5.8 | 12.6 | - | 8.8 | -4.1 | out |
| | 9 | -5.6 | 12.0 | - | 3.9 | -10.3 | out |
| | 10 | -5.2 | 7.4 | - | -2.7 | -12.6 | partly out |
| **3FNE** | 1 | -7.4 | 10.7 | - | -6.9 | -14.5 | partly out |
| | 2 | -6.9 | 11.4 | - | 2.0 | -6.9 | partly out |
| | **3** | **-6.9** | **2.4** | **1** | **-18.0** | **-33.0** | **shifted** |
| | 4 | -6.8 | 8.9 | - | 4.1 | -15.4 | partly out |
| | 5 | -6.3 | 11.0 | - | 9.1 | -12.3 | out |
| | 6 | -6.3 | 9.7 | - | -0.9 | -11.9 | partly out |
| | 7 | -6.0 | 11.3 | - | 2.6 | -7.1 | out |
| | 8 | -6.0 | 11.2 | - | 0.5 | -1.9 | out |
| | 9 | -6.0 | 10.8 | - | 7.5 | -12.6 | out |
| | 10 | -6.0 | 8.3 | - | 5.3 | -11.9 | partly out |

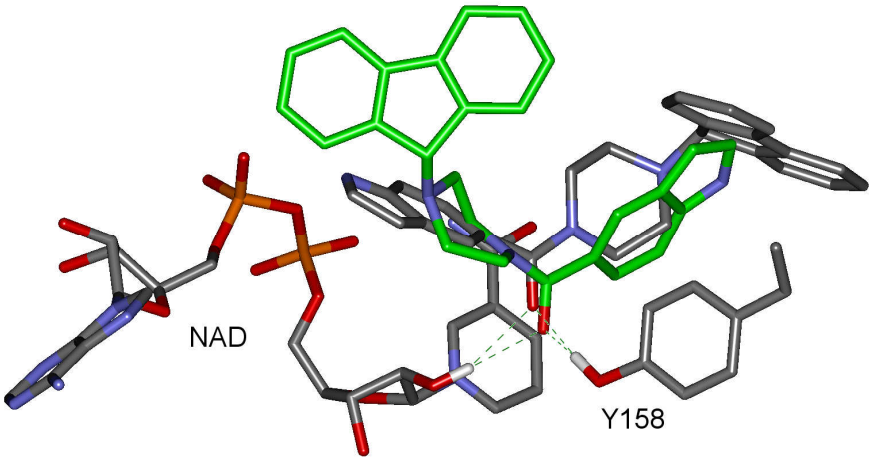


**Fig. S1** Inverted orientation of the first Vina docking model of **GEQ** (in green) into the **1P45** cavity. The X-ray conformation of **GEQ** found in **1P44** (CPK-coloured representation) is displayed for comparison. Dotted green lines represent H-bonds.

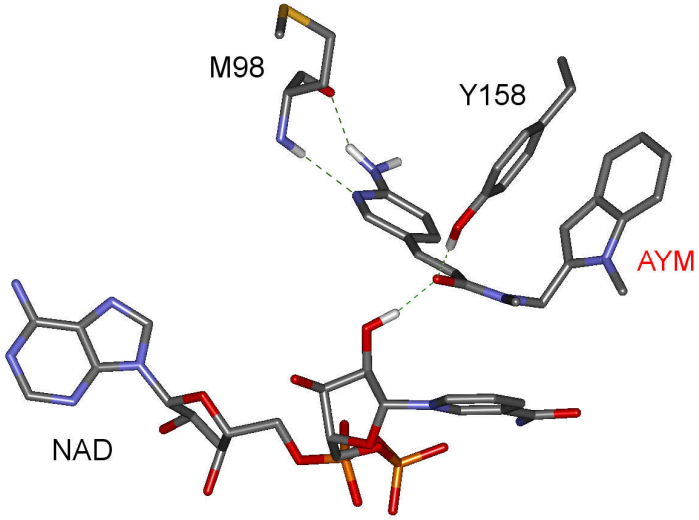


**Fig. S2** The binding mode of the Vina model 1 of **AYM** in the **2H7M** cavity after the PM6-DH2 minimization. Dotted green lines represent H-bonds

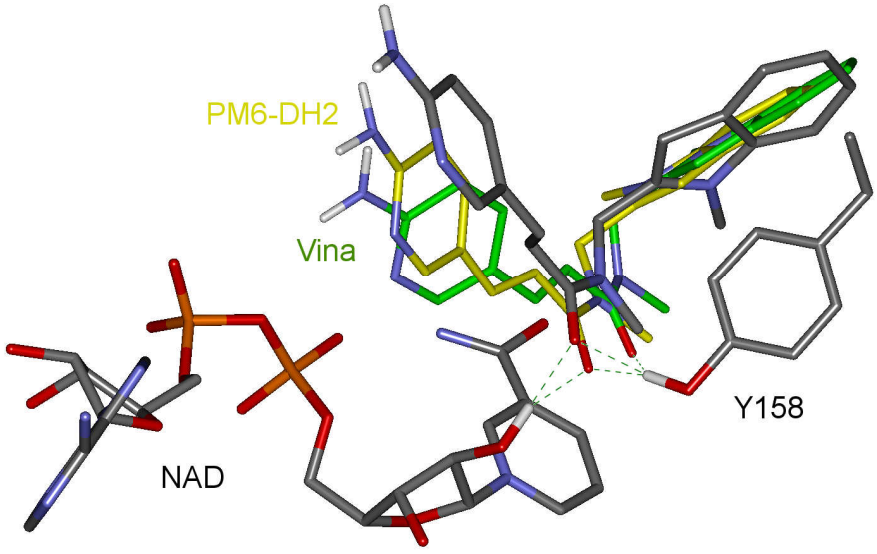


**Fig. S3** Comparison of the third Vina docking model of **AYM** into the **3FNE** cavity, before (in green) and after (in yellow) the Mopac PM6-DH2 optimization. The X-ray conformation of **AYM** (CPK-coloured representation) is displayed for comparison. Dotted green lines represent H-bonds.