Supporting information

Molecular docking based on virtual screening, molecular dynamics, and Atoms in Molecules studies to identify the potential human epidermal receptor 2 intracellular domain inhibitors

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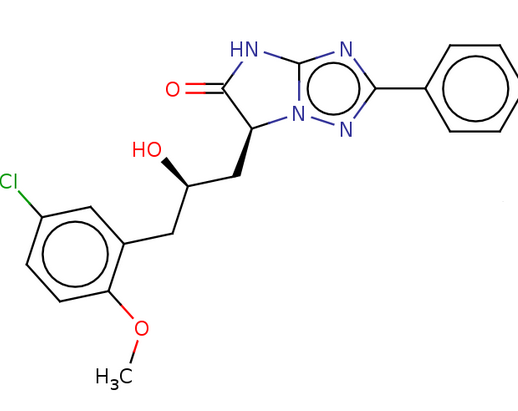
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**Table S1:** The obtained results for toxicity of compounds A -F

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Number of ligand | ZINC database code | Ligand-Protein | E(kcal/mol) | TOX | MolDock Score |  |
| A(COM 1) | ZINC01398025 |  | -14.02 | 495mg/kg | -121.619 |  |
| B | ZINC72240630 |  | -11.31 | 500mg/kg | -97.357 |  |
| C | ZINC32097318 |  | -11.14 | 125mg/Kg | -95.119 |  |
| D | ZINC49467748 |  | -10.25 | 1000mg/kg | *-84.028* |  |
| E | ZINC40781039 |  | -9.93 | 1600mg/kg | -83.703 |  |
| F | template | pyrrolo[3,2-d]  pyrimidine analogue [[33](#_ENREF_33)] | -10.27 | template |  |  |

# Table S2: Details of physico-chemical property filters available in FAF-*Drugs*

|  | [Rule of 3](http://fafdrugs2.mti.univ-paris-diderot.fr/downloads/filters/faf2.param.ro3) | [Rule of 5](http://fafdrugs2.mti.univ-paris-diderot.fr/downloads/filters/faf2.param.ro5) | [Drug-Like Soft 1](http://fafdrugs2.mti.univ-paris-diderot.fr/downloads/filters/faf2.param.drug) | [Lead-Like Soft 2](http://fafdrugs2.mti.univ-paris-diderot.fr/downloads/filters/faf2.param.lead) | [R.E.O.S](http://fafdrugs2.mti.univ-paris-diderot.fr/downloads/filters/faf2.param.reos) | [ZINC](http://fafdrugs2.mti.univ-paris-diderot.fr/downloads/filters/faf2.param.zinc) | [CNS](http://fafdrugs2.mti.univ-paris-diderot.fr/downloads/filters/faf2.param.cns) | [Respiratory](http://fafdrugs2.mti.univ-paris-diderot.fr/downloads/filters/faf2.param.respiratory) |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| [MW](http://fafdrugs2.mti.univ-paris-diderot.fr/descriptors.html#MW) | ≤ 300 | (≤ 500) | 100 - 600 | 150 - 400 | 200 - 500 | 60 - 600 | 135 - 582 | 240 - 520 |
| [logP](http://fafdrugs2.mti.univ-paris-diderot.fr/descriptors.html#logP) | -3 to 3 | (≤ 5) | -3 to 6 | -3 to 4 | -5 to 5 | -4 to 6 | -0.2 to 6.1 | -2 to 4.7 |
| [HBA](http://fafdrugs2.mti.univ-paris-diderot.fr/descriptors.html#MW) | ≤ 3 | (≤ 10) | ≤ 12 | ≤ 7 | ≤ 10 | ≤ 11 | ≤ 5 | - |
| [HBD](http://fafdrugs2.mti.univ-paris-diderot.fr/descriptors.html#logP) | ≤ 3 | (≤ 5) | ≤ 7 | ≤ 4 | ≤ 5 | ≤ 6 | ≤ 3 | - |
| [HBonds](http://fafdrugs2.mti.univ-paris-diderot.fr/descriptors.html#HBonds) | - | - | - | - | - | - | - | 6 - 12 |
| [tPSA](http://fafdrugs2.mti.univ-paris-diderot.fr/descriptors.html#tPSA) | ≤ 60 | - | ≤ 180 | ≤ 160 | ≤ 150 | ≤ 150 | 3 - 118 | 51 - 135 |
| [Rotatable Bonds](http://fafdrugs2.mti.univ-paris-diderot.fr/descriptors.html#RotatableBonds) | ≤ 3 | - | ≤ 11 | ≤ 9 | ≤ 8 | ≤ 12 | - | 3 - 8 |
| [Rigid Bonds](http://fafdrugs2.mti.univ-paris-diderot.fr/descriptors.html#RigidBonds) | - | - | ≤ 30 | ≤ 30 |  | ≤ 50 |  |  |
| [Rings](http://fafdrugs2.mti.univ-paris-diderot.fr/descriptors.html#n_SystemRing) | - | - | ≤ 6 | ≤ 4 | - | ≤ 7 | - | 1 - 5 |
| [MaxSizeSystemRing](http://fafdrugs2.mti.univ-paris-diderot.fr/descriptors.html#MaxSizeSystemRing) | - | - | ≤ 18 | ≤ 18 | - | ≤ 12 | - | - |
| [Carbons](http://fafdrugs2.mti.univ-paris-diderot.fr/descriptors.html#n_carbon) | - | - | 3 - 35 | 3 - 35 | - | ≥ 3 | - | - |
| [HeteroAtoms](http://fafdrugs2.mti.univ-paris-diderot.fr/descriptors.html#n_hetero) | - | - | 1 - 15 | 1 - 15 | - | ≥ 0 | - | - |
| [H/C Ratio](http://fafdrugs2.mti.univ-paris-diderot.fr/descriptors.html#ratioH_C) | - | - | 0.1 to 1.1 | 0.1 to 1.1 |  | ≤ 2.0 | - | - |
| [Charges](http://fafdrugs2.mti.univ-paris-diderot.fr/descriptors.html#NumCharges) | - | - | ≤ 4 | ≤ 4 | - | ≤ 4 | - | - |
| [TotalCharge](http://fafdrugs2.mti.univ-paris-diderot.fr/descriptors.html#TotalCharge) | - | - | -4 to 4 | -4 to 4 | -4 to 4 | -4 to 4 | - | - |
| [RO5 Violations](http://fafdrugs2.mti.univ-paris-diderot.fr/descriptors.html#n_LipinskiViolations) | - | 2 | - | - | - | - | - | - |
| [StereoCenters](http://fafdrugs2.mti.univ-paris-diderot.fr/descriptors.html#StereoCenters) | - | - | - | ≤ 2 | - | - | - | - |
| [References](http://fafdrugs2.mti.univ-paris-diderot.fr/references.html) | 13 | [1](http://fafdrugs2.mti.univ-paris-diderot.fr/references.html#[13]) | [1,](http://fafdrugs2.mti.univ-paris-diderot.fr/references.html#[13])[2,](http://fafdrugs2.mti.univ-paris-diderot.fr/references.html#[19])[3,](http://fafdrugs2.mti.univ-paris-diderot.fr/references.html#[24])[4,](http://fafdrugs2.mti.univ-paris-diderot.fr/references.html#[30])8 | [4,](http://fafdrugs2.mti.univ-paris-diderot.fr/references.html#[30])[5,](http://fafdrugs2.mti.univ-paris-diderot.fr/references.html#[32])[6,](http://fafdrugs2.mti.univ-paris-diderot.fr/references.html#[47])7 | [9](http://fafdrugs2.mti.univ-paris-diderot.fr/references.html#[34]) | [10](http://fafdrugs2.mti.univ-paris-diderot.fr/references.html#[24]) | 11 | 12 |



**Figure S1**: Structure 2D of ligand A

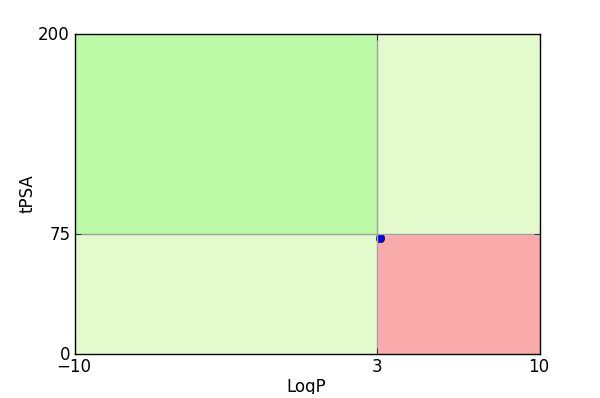
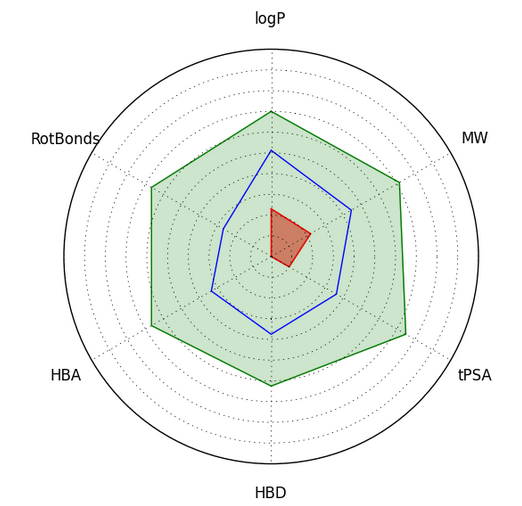
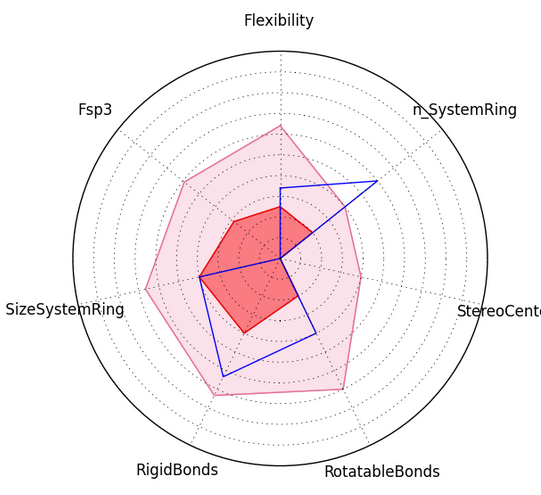


Figure S2: compounds located in the red square are likely to cause toxicity and experimental promiscuity PhysChem Filter Positioning of ligand A

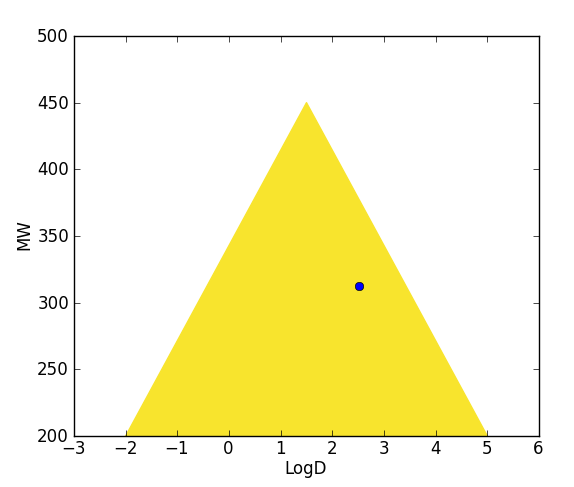
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**Figure S3:** Compound values (blue line) should fall within the drug-like filter area. (Light blue)

### Compound Complexity of ligand A



**Figure S4**: Compound values (blue line) superimposed on an oral library min and max ranges (pink and red) of ligand A

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**Figure** S**5:** Compounds located in the yellow triangle are likely to have an optimal permeability (low clearance) and a good metabolic stabilityfor ligand A

**Table S3**: Oral toxicity prediction results for input compond A

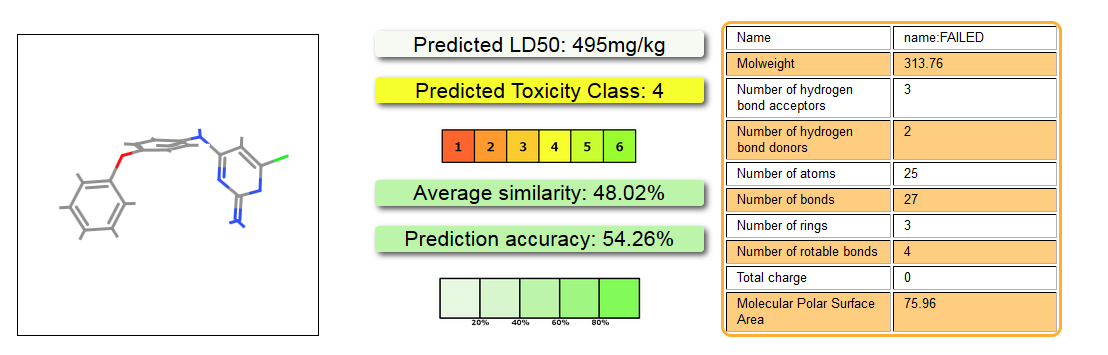
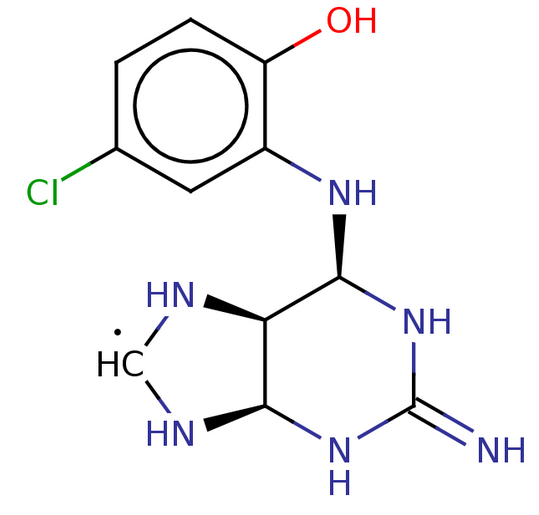
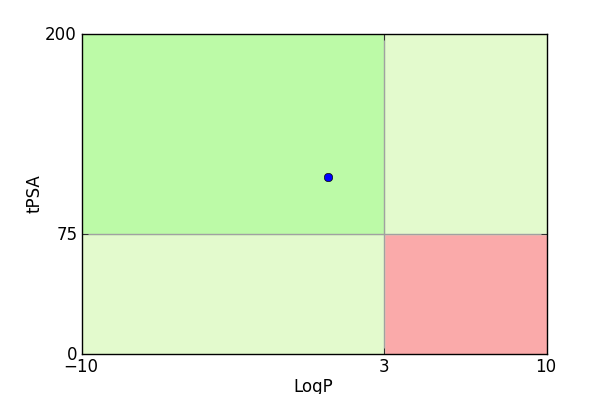


Table S4: FAF-*Drugs* rule for ligand A

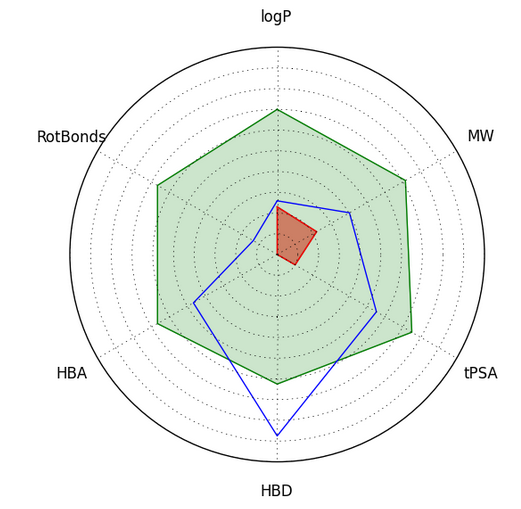
|  |  |
| --- | --- |
| D | ZIN\_1\_1 |
| smiles | Clc1cc(Nc2ccc(Oc3ccccc3)  cc2)nc(=N)[nH]1 |
| MW | 313.75 |
| logP | 3.12 |
| logD | 2.51 |
| logSw | -3.86 |
| tPSA | 72.63 |
| RotatableBonds | 4 |
| RigidBonds | 19 |
| Flexibility | 0.17 |
| HBD | 3 |
| HBA | 5 |
| HBD\_HBA | 8 |
| n\_SystemRing | 3 |
| MaxSizeSystemRing | 6 |
| NumCharges | 1 |
| TotalCharge | 1 |
| n\_HeavyAtoms | 22 |
| n\_carbon | 16 |
| n\_hetero | 6 |
| ratioH\_C | 0.38 |
| n\_LipinskiViolations | 0 |
| Solubility | 6580.90 |
| SolubilityForecastIndex | Reduced Solubility |
| VeberRule | Good |
| EganRule | Good |
| TrafficLights | 1 |
| 4\_400 | good |
| 3\_75 | bad |
| Phospholipidosis | NonInducer |
| Fsp3 | 0.00 |
| StereoCenters | 0 |
| PPI\_Friendly | Yes |
| State | Intermediate |
| iFilter | drug |
| Lilly | PASS |



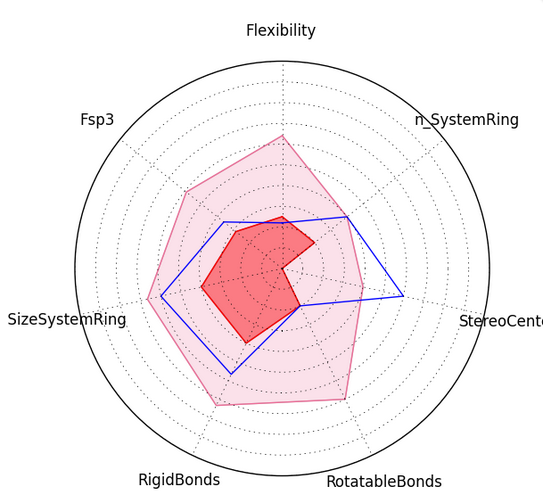
**Figure S6**: Structure 2D of ligand B



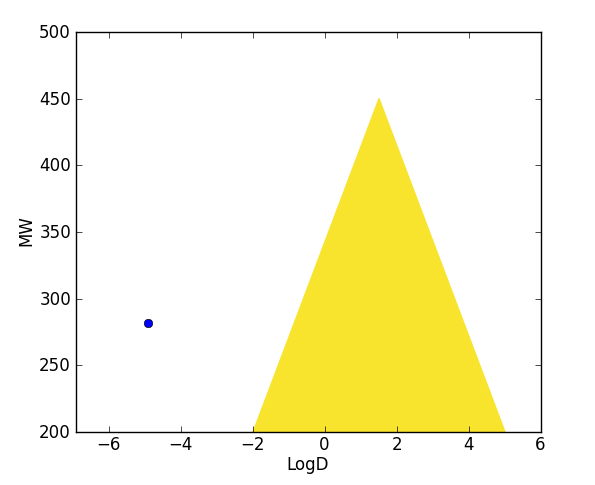
**Figure S7**: compounds located in the red square are likely to cause toxicity and experimental promiscuity of ligand B

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**Figure S8:** Compound values (blue line) should fall within the drug-like filter area. (Light blue)of ligand B



**Figure S9**: Compound values (blue line) superimposed on an oral library min and max ranges (pink and red) of ligand B



**Figure S10**: Compounds located in the yellow triangle are likely to have an optimal permeability (low clearance) and a good metabolic stability

**Table S5**: Oral toxicity prediction results for input compond B

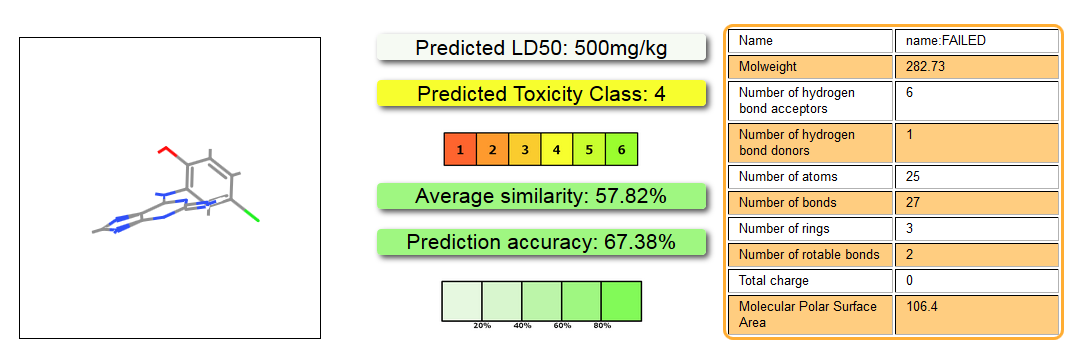
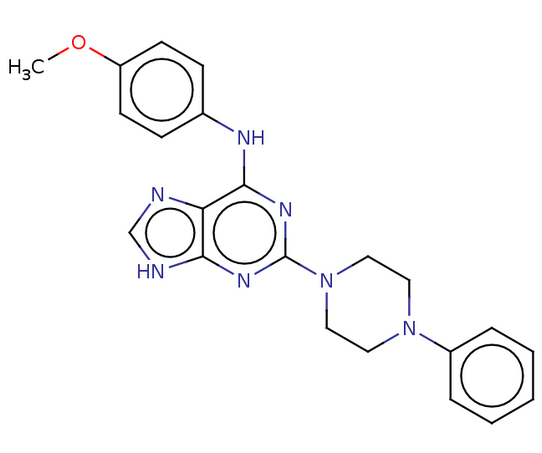
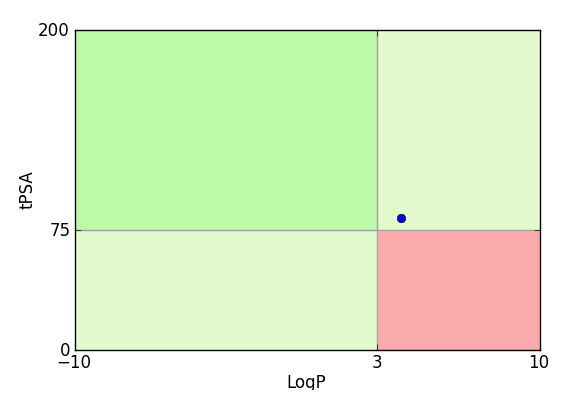


Table S6: FAF-*Drugs* rule for ligand B

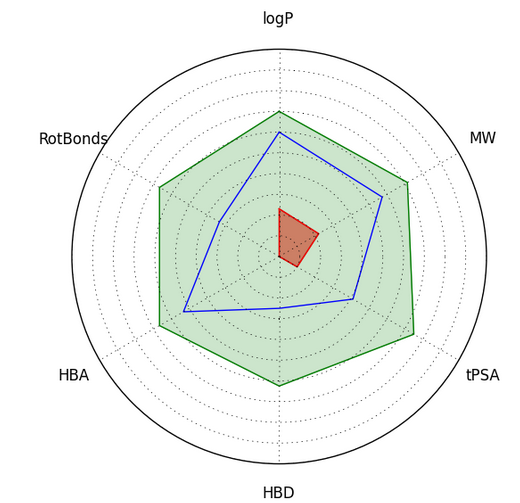
|  |  |
| --- | --- |
|  | ZIN\_1\_1 |
| smiles | Oc1ccc(Cl)cc1N[C@H]1NC(=N)N[C@H]  2N[CH]N[C@@H]12 |
| MW | 281.72 |
| logP | 0.59 |
| logD | -4.92 |
| logSw | -1.96 |
| tPSA | 110.55 |
| RotatableBonds | 2 |
| RigidBonds | 17 |
| Flexibility | 0.11 |
| HBD | 7 |
| HBA | 7 |
| HBD\_HBA | 14 |
| n\_SystemRing | 2 |
| MaxSizeSystemRing | 9 |
| NumCharges | 2 |
| TotalCharge | 2 |
| n\_HeavyAtoms | 19 |
| n\_carbon | 11 |
| n\_hetero | 8 |
| ratioH\_C | 0.73 |
| n\_LipinskiViolations | 1 |
| Solubility | 39646.41 |
| SolubilityForecastIndex | Good Solubility |
| VeberRule | Good |
| EganRule | Good |
| TrafficLights | 0 |
| 4\_400 | good |
| 3\_75 | good |
| Phospholipidosis | NonInducer |
| Fsp3 | 0.36 |
| StereoCenters | 3 |
| PPI\_Friendly | No |
| State | Rejected |
| iFilter | drug |
| Lilly | Lilly\_TP1 abnormal\_valenc |



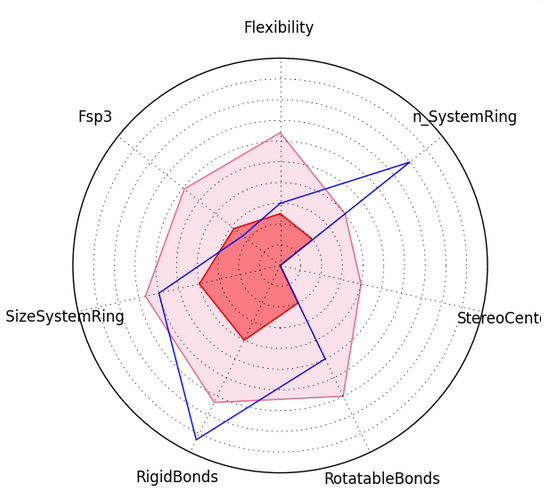
**Figure s11** Structure 2D of ligand C



**Figure S12**: compounds located in the red square are likely to cause toxicity and experimental promiscuity of ligand C

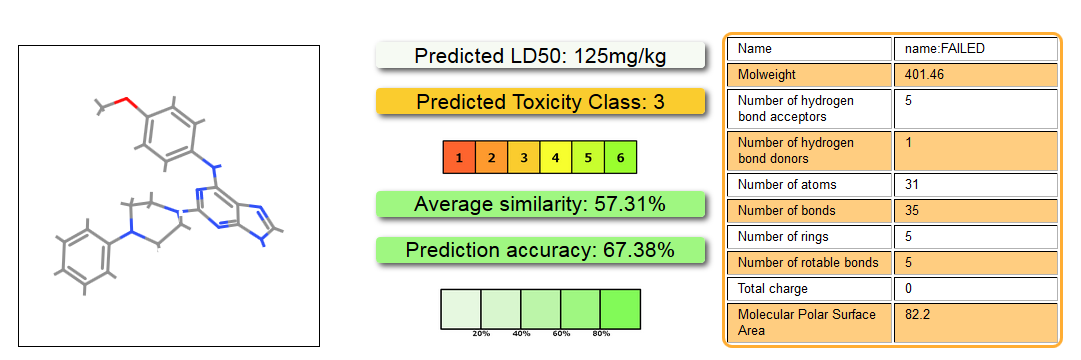


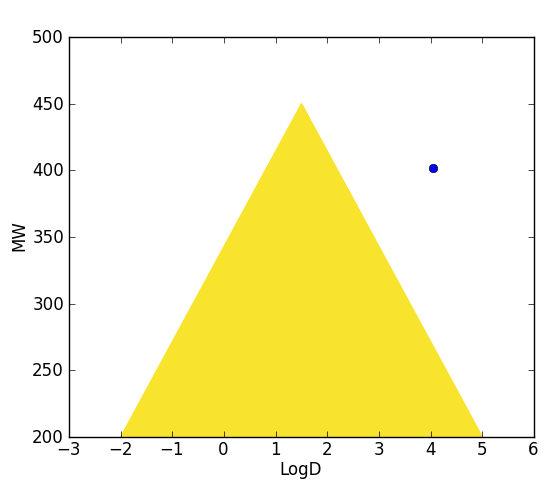
**Figure S13:** Compound values (blue line) should fall within the drug-like filter area. (Light blue)of ligand C



**FigureS 14**: Compound values (blue line) superimposed on an oral library min and max ranges (pink and red) of ligand C

**Table 7**: Oral toxicity prediction results for input compond C

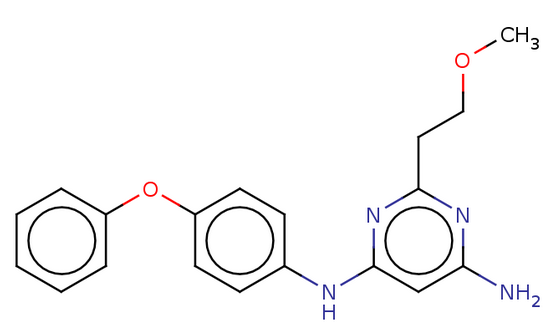




**Figure 15**: Compounds located in the yellow triangle are likely to have an optimal permeability (low clearance) and a good metabolic stability

**Table s7**: FAF-*Drugs* rule for ligand C

|  |  |
| --- | --- |
| D | ZIN\_1\_1 |
| smiles | COc1ccc(Nc2nc(nc3[nH]cnc23)N2CCN(CC2)c2ccccc2)cc1 |
| MW | 401.46 |
| logP | 4.00 |
| logD | 4.05 |
| logSw | -4.81 |
| tPSA | 82.20 |
| RotatableBonds | 5 |
| RigidBonds | 28 |
| Flexibility | 0.15 |
| HBD | 2 |
| HBA | 8 |
| HBD\_HBA | 10 |
| n\_SystemRing | 4 |
| MaxSizeSystemRing | 9 |
| NumCharges | 0 |
| TotalCharge | 0 |
| n\_HeavyAtoms | 30 |
| n\_carbon | 22 |
| n\_hetero | 8 |
| ratioH\_C | 0.36 |
| n\_LipinskiViolations | 0 |
| Solubility | 3263.60 |
| SolubilityForecastIndex | Reduced Solubility |
| VeberRule | Good |
| EganRule | Good |
| TrafficLights | 2 |
| 4\_400 | bad |
| 3\_75 | warning |
| Phospholipidosis | Inducer |
| Fsp3 | 0.23 |
| StereoCenters | 0 |
| PPI\_Friendly | Yes |
| State  iFilter  Lilly | Accepted  Drug  PASS |



**Figure s16**: Structure 2D of ligand D

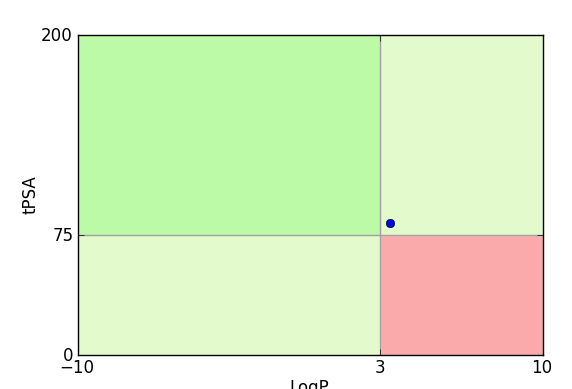
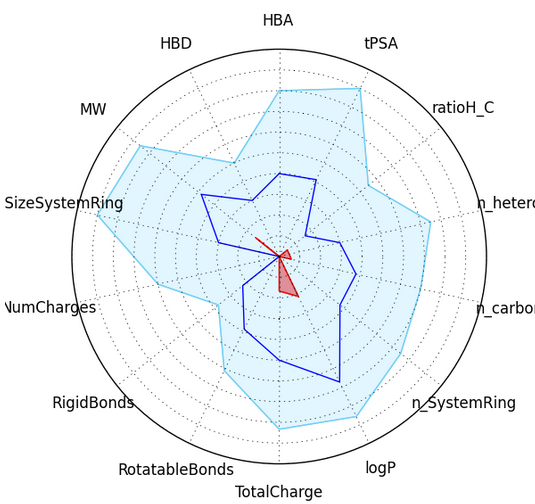
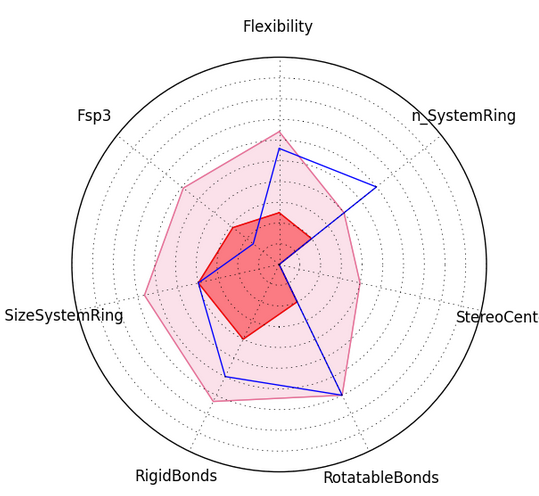


Figure s17: compounds located in the red square are likely to cause toxicity and experimental promiscuity of ligand D

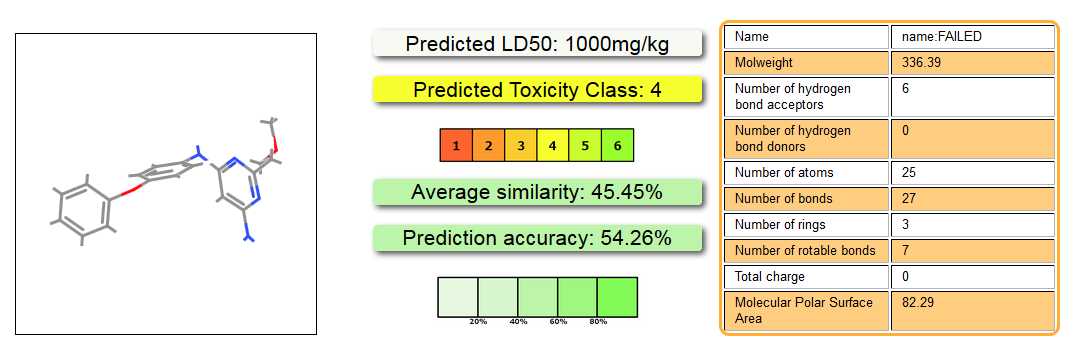


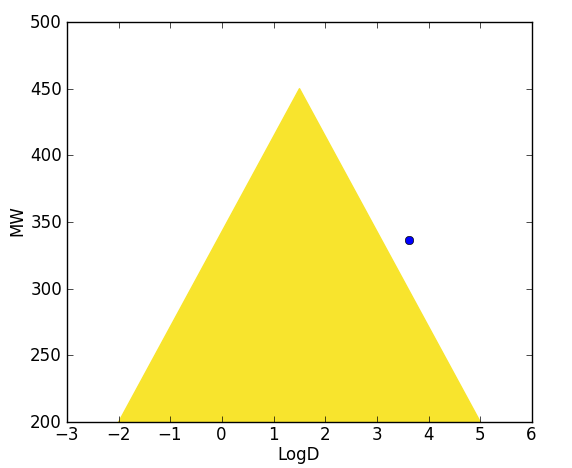
**Figures 18:** Compound values (blue line) should fall within the drug-like filter area. (Light blue)of ligand D



**Figure s19**: Compound values (blue line) superimposed on an oral library min and max ranges (pink and red) of ligand D

**Table s8**: Oral toxicity prediction results for input compond D

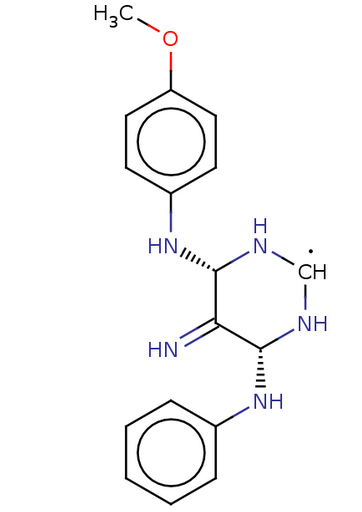




**Figure s20:** Compounds located in the yellow triangle are likely to have an optimal permeability (low clearance) and a good metabolic stability for ligand D

**Table s9:** FAF-*Drugs* rule for ligand D

|  |  |
| --- | --- |
| ID | ZIN\_1\_1 |
| smiles | COCCc1nc(N)cc(Nc2ccc  (Oc3ccccc3)cc2)n1 |
| MW | 336.39 |
| logP | 3.41 |
| logD | 3.62 |
| logSw | -3.91 |
| tPSA | 82.29 |
| RotatableBonds | 7 |
| RigidBonds | 18 |
| Flexibility | 0.28 |
| HBD | 3 |
| HBA | 6 |
| HBD\_HBA | 9 |
| n\_SystemRing | 3 |
| MaxSizeSystemRing | 6 |
| NumCharges | 0 |
| TotalCharge | 0 |
| n\_HeavyAtoms | 25 |
| n\_carbon | 19 |
| n\_hetero | 6 |
| ratioH\_C | 0.32 |
| n\_LipinskiViolations | 0 |
| Solubility | 6755.52 |
| SolubilityForecastIndex | Reduced Solubility |
| VeberRule | Good |
| EganRule | Good |
| TrafficLights | 1 |
| 4\_400 | good |
| 3\_75 | warning |
| Phospholipidosis | NonInducer |
| Fsp3 | 0.16 |
| StereoCenters | 0 |
| PPI\_Friendly | Yes |
| State | Accepted |
| iFilter | drug |
| Lilly | PASS |



**Figure s21**: Structure 2D of ligand E

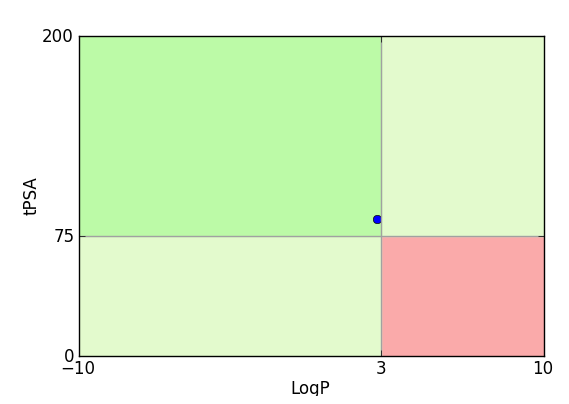
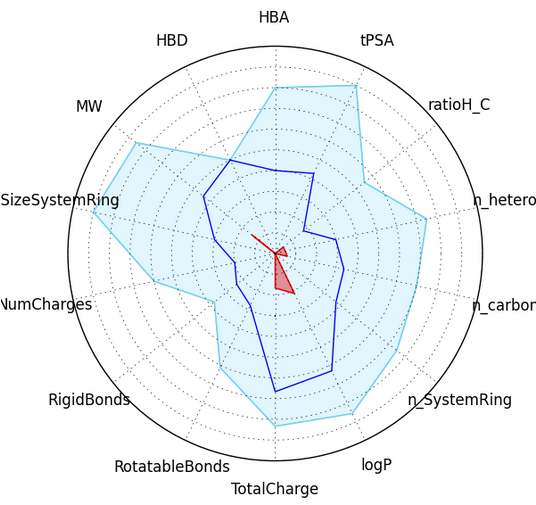
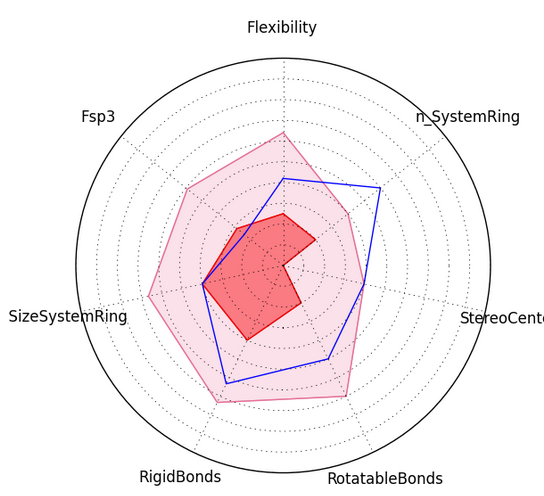


Figure s22:compounds located in the red square are likely to cause toxicity and experimental promiscuity of ligand E

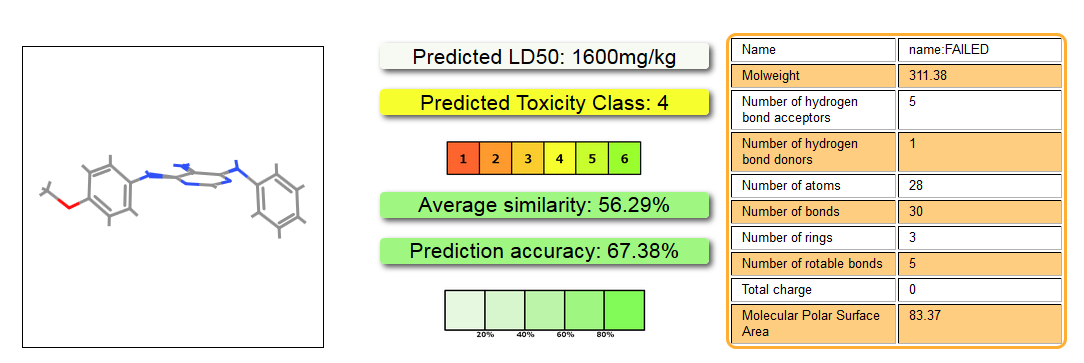


**Figure s23:** Compound values (blue line) should fall within the drug-like filter area. (Light blue)of ligand E



**Figure s24:** Compound values (blue line) superimposed on an oral library min and max ranges (pink and red) of ligand E

**Table s10** Oral toxicity prediction results for input compond E



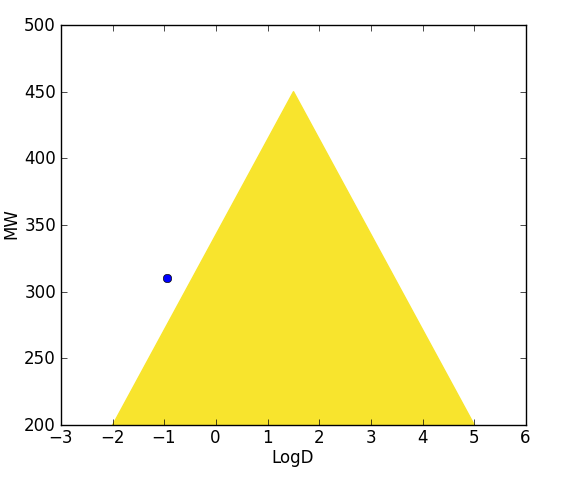
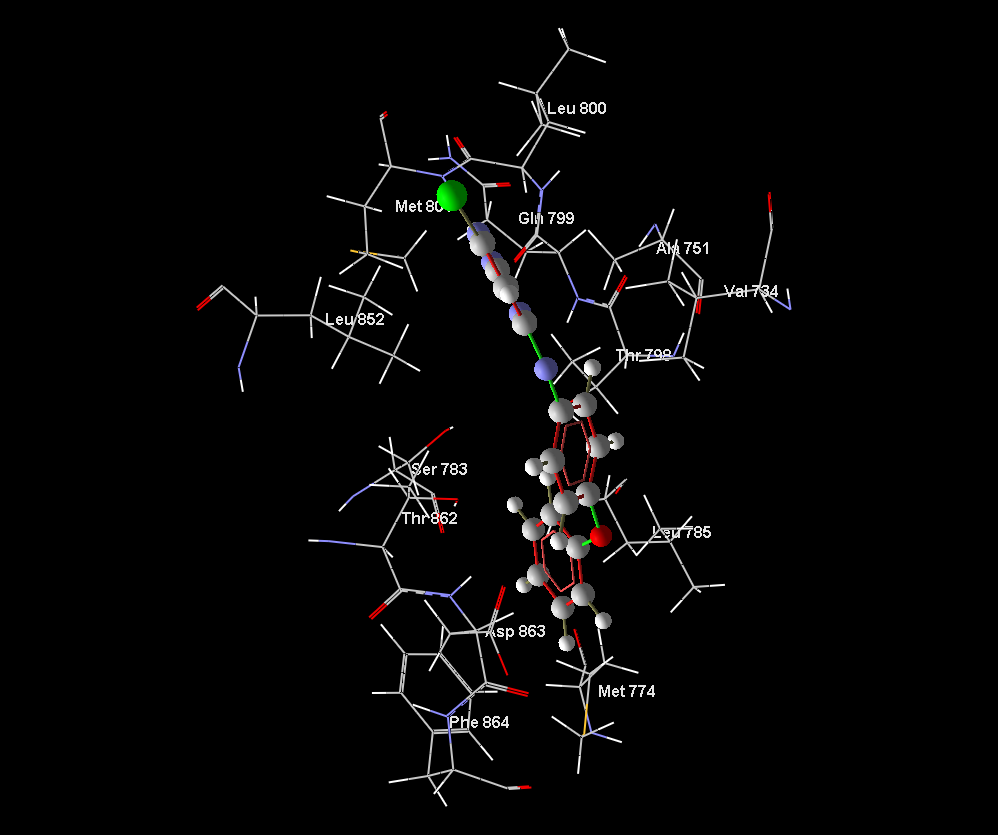


Figure s25: Compounds located in the yellow triangle are likely to have an optimal permeability (low clearance) and a good metabolic stability for ligand E

**Table s11** FAF-*Drugs* rule for ligand E

|  |  |
| --- | --- |
| ID | ZIN\_1\_1 |
| smiles | COc1ccc(N[C@@H]2N[CH]N[  C@H](Nc3ccccc3)C2=N)cc1 |
| MW | 310.37 |
| logP | 2.80 |
| logD | -0.94 |
| logSw | -3.40 |
| tPSA | 85.78 |
| RotatableBonds | 5 |
| RigidBonds | 19 |
| Flexibility | 0.21 |
| HBD | 5 |
| HBA | 6 |
| HBD\_HBA | 11 |
| n\_SystemRing | 3 |
| MaxSizeSystemRing | 6 |
| NumCharges | 1 |
| TotalCharge | 1 |
| n\_HeavyAtoms | 23 |
| n\_carbon | 17 |
| n\_hetero | 6 |
| ratioH\_C | 0.35 |
| n\_LipinskiViolations | 0 |
| Solubility | 10308.29 |
| SolubilityForecastIndex | Good Solubility |
| VeberRule | Good |
| EganRule | Good |
| TrafficLights | 0 |
| 4\_400 | good |
| 3\_75 | good |
| Phospholipidosis | NonInducer |
| Fsp3 | 0.24 |
| StereoCenters | 2 |
| PPI\_Friendly | No |
| State | Rejected |
| iFilter | drug |
| Lilly | Lilly\_TP1 abnormal\_valence |



**Figure s26**: Amino acid residues located at active site of the COM 1

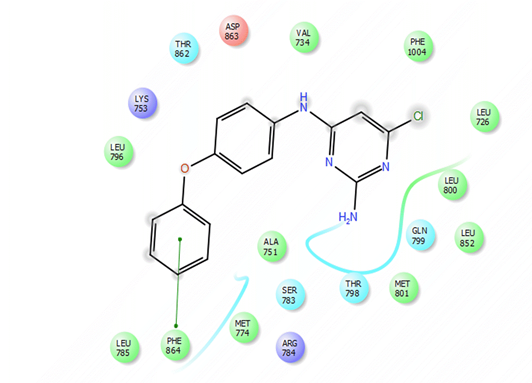
Supplementary validation of docking calculation of COM1

Schematic and tables below representations of the binding interactions between compound 1 and HER2 TK active site.

Regarding Ala751, Arg784, Asp863, Gln 798, Gly804, Ile752, Leu726, Leu785, Le796, , Leu800 , Leu852, Lys753, Met774, Met801, Phe864, Phe1004, Ser783, Thr798, Val 734, the biggest cavity that was found by mvd overlapped with the active sight predicted by auto dock vina. As such, these cavities were taken as the active sight in the models.

Also, the cavity with geometric position (X=12.03, Y=0.27, Z=29.73A) which was found by MVD in the predicted model, was confirmed by Autodock vina as substrate binding site.

Of course, two residue have very low energy traces and reported only by Molegro virtual docker (Gly804, Ile752).



**Figure s27** Docking results of **COM1** that show residue and molecule contribution on the active site which obtained by Autodock Vina

**Table s12** Atom energies of **COM 1** obtained Molegro virtual docker

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ID | Name | Total | EPair | EIntra |
| 0 | C | -7.70775 | -8.8016 | 1.09385 |
| 1 | C | -6.17677 | -7.22384 | 1.04706 |
| 2 | C | -4.13518 | -5.07563 | 0.940444 |
| 3 | C | -2.62669 | -4.43449 | 1.8078 |
| 4 | C | -3.85609 | -5.97868 | 2.12258 |
| 5 | C | -7.9269 | -8.68292 | 0.756022 |
| 8 | O | -5.49717 | -4.23475 | -1.26242 |
| 9 | C | -2.77336 | -4.56174 | 1.78838 |
| 10 | C | -3.97299 | -5.10345 | 1.13046 |
| 11 | C | -4.61006 | -4.77063 | 0.160566 |
| 12 | C | -2.59994 | -4.35097 | 1.75103 |
| 13 | C | -4.35325 | -5.96912 | 1.61588 |
| 14 | C | -6.13292 | -6.40894 | 0.276022 |
| 17 | N | -4.60112 | -3.06241 | -1.53872 |
| 18 | C | -1.64979 | -3.18978 | 1.53999 |
| 19 | C | -1.8463 | -2.93382 | 1.08752 |
| 20 | C | -3.84786 | -5.05968 | 1.21181 |
| 21 | N | -5.41938 | -6.69352 | 1.27413 |
| 22 | C | -5.45609 | -6.41323 | 0.957142 |
| 23 | N | -0.45043 | -3.52049 | 3.07006 |
| 24 | N | -9.8694 | -8.74855 | -1.12085 |
| 27 | CL | -7.27333 | -6.40072 | -0.872607 |
| 0 | C | -7.70775 | -8.8016 | 1.09385 |
| 1 | C | -6.17677 | -7.22384 | 1.04706 |
| 2 | C | -4.13518 | -5.07563 | 0.940444 |
| 3 | C | -2.62669 | -4.43449 | 1.8078 |

**Table s13** Docking results of **COM1** that show residue and molecule contribution on the active site which obtained by Molegro virtual docker

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Target | Residue | ID | E total | EPair |
| COM 1 | Ala | 751 | -8.42788 | -8.42788 |
| COM 1 | Arg | 784 | -2.55212 | -2.55212 |
| COM 1 | Asp | 863 | -10.4445 | -10.4445 |
| COM 1 | Gln | 798 | -2.92751 | -2.92751 |
| COM 1 | Gly | 804 | -1.09468 | -1.09468 |
| COM 1 | Ile | 752 | -1.22436 | -1.22436 |
| COM 1 | Leu | 726 | -1.34089 | -1.34089 |
| COM 1 | Leu | 785 | -9.74985 | -9.74985 |
| COM 1 | Leu | 796 | -5.34151 | -5.34151 |
| COM 1 | Leu | 800 | -6.76172 | -6.76172 |
| COM 1 | Leu | 852 | -10.4453 | -10.4453 |
| COM 1 | Lys | 753 | -10.9037 | -10.9037 |
| COM 1 | Met | 774 | -1.5502 | -1.5502 |
| COM 1 | Met | 801 | -7.89442 | -7.89442 |
| COM 1 | Phe | 864 | -5.66617 | -5.66617 |
| COM 1 | Phe | 1004 | -1.34357 | -1.34357 |
| COM 1 | Ser | 783 | -5.59438 | -5.59438 |
| COM 1 | Thr | 798 | -9.69431 | -9.69431 |
| COM 1 | Thr | 862 | -10.4476 | -10.4476 |
| COM 1 | Val | 734 | -4.39876 | -4.39876 |

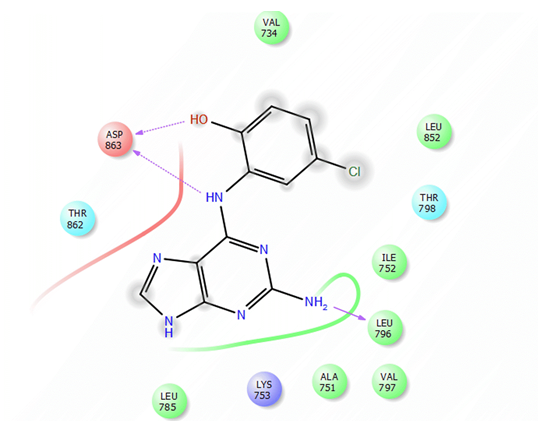
Supplementary validation of docking calculation of COM 2

Schematic and tables below representations of the binding interactions between compound 2 and HER2 TK active site.

Regarding Ala751, Asp863, Ile752, Leu726, Leu785, Leu796, Leu800 , Leu852, Lys753, Phe864, Thr798, Thr862, Val 734, Val797 the biggest cavity that was found by MVD overlapped with the active sight predicted by auto dock vina. As such, these cavities were taken as the active sight in the models.

Also, the cavity with geometric position (X=12.03, Y=0.27, Z=29.73A) which was found by MVD in the predicted model, was confirmed by Autodock vina as substrate binding site.

Of course, three residue have very low energies are reported only by Molegro virtual docker (Leu726, Leu800, Phe864).



**Figure s28** Docking results of **COM2** that show residue and molecule contribution on the active site which obtained by Autodock Vina

**Table s14** Atom energies of **COM 2** obtained Molegro virtual docker

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ID | Name | Total | E Pair | E Intra |
| 0 | C | -1.69616 | -2.57246 | 0.876301 |
| 1 | C | -1.85633 | -2.68421 | 0.827883 |
| 2 | C | -3.56037 | -4.23547 | 0.675099 |
| 3 | C | -2.6166 | -4.3407 | 1.72409 |
| 4 | C | -1.42803 | -3.57142 | 2.14339 |
| 5 | C | -2.34294 | -2.99007 | 0.647139 |
| 6 | CL | -4.59395 | -3.69426 | -0.899688 |
| 8 | N | -5.0708 | -5.67543 | 0.604637 |
| 9 | C | -3.18722 | -4.27431 | 1.08709 |
| 10 | C | -4.07747 | -4.94319 | 0.865724 |
| 11 | C | -3.57867 | -4.79537 | 1.2167 |
| 12 | N | -4.00134 | -3.07672 | -0.924617 |
| 14 | C | -6.32235 | -5.33837 | -0.983974 |
| 15 | N | -7.47716 | -7.11491 | -0.362249 |
| 17 | N | -5.49213 | -6.37952 | 0.887387 |
| 18 | C | -8.43169 | -8.87139 | 0.439696 |
| 19 | N | -2.04088 | -4.59041 | 2.54952 |
| 20 | N | -12.3158 | -11.0069 | -1.3089 |
| 24 | O | -6.8556 | -7.20164 | 0.346041 |

**Table s15** Docking results of **COM2** that show residue and molecule contribution on the active site which obtained by Molegro virtual docker

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Target | Residue | ID | E Total | EPair |
| COM 2 | Ala | 751 | -5.54884 | -5.54884 |
| COM 2 | Asp | 863 | -17.4698 | -17.4698 |
| COM 2 | Ile | 752 | -2.29892 | -2.29892 |
| COM 2 | Leu | 726 | -0.42001 | -0.42001 |
| COM 2 | Leu | 785 | -3.43031 | -3.43031 |
| COM 2 | Leu | 796 | -12.9129 | -12.9129 |
| COM 2 | Leu | 800 | -0.331085 | -0.331085 |
| COM 2 | Leu | 852 | -5.38666 | -5.38666 |
| COM 2 | Lys | 753 | -16.6065 | -16.6065 |
| COM 2 | Phe | 864 | -0.811626 | -0.811626 |
| COM 2 | Thr | 798 | -7.36196 | -7.36196 |
| COM 2 | Thr | 862 | -11.7125 | -11.7125 |
| COM 2 | Val | 734 | -6.52737 | -6.52737 |
| COM 2 | Val | 797 | -2.93235 | -2.93235 |

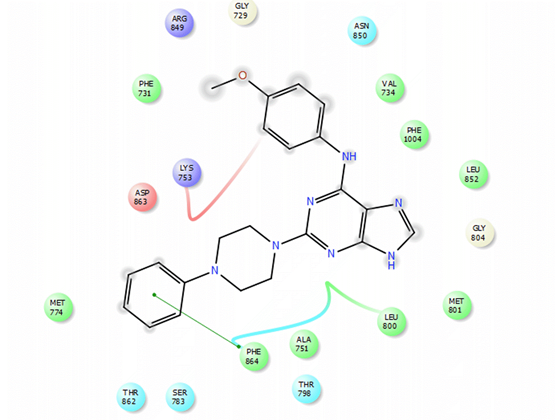
Supplementary validation of docking calculation of COM 3

Schematic and tables below representations of the binding interactions between compound 3 and HER2 TK active site.

Regarding Ala751, Asp863,Arg849, Asn850,Leu726, Leu785, Leu796, Leu800 , Leu852, Lys753, Met774, Met801, Phe864, Phe1004, Phe731, Cys 805, Ser783, Thr798, Thr862, Val 734, the biggest cavity that was found by MVD overlapped with the active sight predicted by auto dock vina. As such, these cavities were taken as the active sight in the models.

Also, the cavity with geometric position (X=12.03, Y=0.27, Z=29.73A) which was found by MVD in the predicted model, was confirmed by Autodock vina as substrate binding site.

Of course, three residue have very low energies are reported only by the molecular (Leu726, Leu785, Leu796, Cys 805).



**Figure s29** Docking results of COM3 that show residue and molecule contribution on the active site which obtained by Autodock Vina

**Table s16** Atom energies of **COM 3** obtained Molegro virtual docker

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ID | Name | Total | EPair | EIntra |
| 0 | C | -4.54747 | -5.30902 | 0.761547 |
| 1 | O | -3.89035 | -3.23116 | -0.659192 |
| 2 | C | -1.91412 | -2.87553 | 0.961409 |
| 3 | C | -1.74866 | -3.7485 | 1.99984 |
| 4 | C | -1.30473 | -3.00952 | 1.70478 |
| 5 | C | -0.125552 | -1.70538 | 1.57983 |
| 6 | C | -1.4801 | -1.87605 | 0.395944 |
| 7 | C | -1.66372 | -2.47089 | 0.807165 |
| 10 | N | -3.14665 | -1.85728 | -1.28937 |
| 11 | C | -1.59687 | -2.4134 | 0.816536 |
| 12 | C | -1.96647 | -2.67326 | 0.706792 |
| 13 | C | -2.36889 | -3.10029 | 0.731396 |
| 14 | N | -6.23331 | -5.21549 | -1.01781 |
| 16 | C | -7.04691 | -6.07258 | -0.974338 |
| 17 | N | -4.20416 | -3.84231 | -0.361844 |
| 19 | N | -1.6397 | -3.11804 | 1.47834 |
| 20 | C | -3.74478 | -3.47978 | -0.265003 |
| 21 | N | 1.25789 | -2.71807 | 3.97596 |
| 22 | N | -4.19644 | -3.55833 | -0.638115 |
| 23 | C | -4.02536 | -4.73179 | 0.706431 |
| 24 | C | -3.78281 | -5.20055 | 1.41774 |
| 25 | N | -4.43799 | -4.59293 | 0.154936 |
| 26 | C | -2.91394 | -4.09349 | 1.17955 |
| 27 | C | -3.75213 | -5.3665 | 1.61437 |
| 32 | C | -3.78192 | -4.68324 | 0.901323 |
| 33 | C | -2.87084 | -4.95976 | 2.08892 |
| 34 | C | -7.12281 | -8.11541 | 0.992594 |
| 35 | C | -5.97946 | -7.09648 | 1.11702 |
| 36 | C | -3.97584 | -4.98495 | 1.00911 |
| 37 | C | -2.7079 | -4.73686 | 2.02896 |

**Table s17** Docking results of **COM3** that show residue and molecule contribution on the active site which obtained by Molegro virtual docker

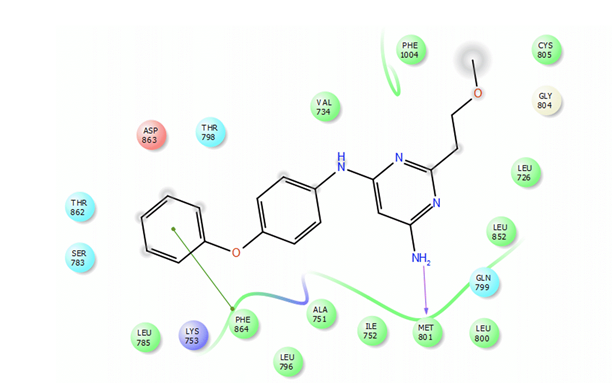
|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ID | Name | Total | E Pair | E Intra |
| COM 3 | Ala | 751 | -5.67636 | -5.67636 |
| COM 3 | Arg | 849 | -2.01074 | -2.01074 |
| COM 3 | Asn | 850 | -3.40317 | -3.40317 |
| COM 3 | Asp | 863 | -19.8467 | -19.8467 |
| COM 3 | Cys | 805 | -0.308596 | -0.308596 |
| COM 3 | Gly | 729 | -2.0012 | -2.0012 |
| COM 3 | Gly | 804 | -1.83709 | -1.83709 |
| COM 3 | Leu | 726 | -2.12913 | -2.12913 |
| COM 3 | Leu | 785 | -5.35537 | -5.35537 |
| COM 3 | Leu | 796 | -1.8838 | -1.8838 |
| COM 3 | Leu | 800 | -1.88423 | -1.88423 |
| COM 3 | Leu | 852 | -10.6847 | -10.6847 |
| COM 3 | Lys | 753 | -10.9908 | -10.9908 |
| COM 3 | Met | 774 | -1.46989 | -1.46989 |
| COM 3 | Met | 801 | -2.03794 | -2.03794 |
| COM 3 | Phe | 731 | -1.68469 | -1.68469 |
| COM 3 | Phe | 864 | -7.59365 | -7.59365 |
| COM 3 | Phe | 1004 | -1.35615 | -1.35615 |
| COM 3 | Ser | 783 | -3.52494 | -3.52494 |
| COM 3 | Thr | 798 | -5.16625 | -5.16625 |
| COM 3 | Thr | 862 | -11.5294 | -11.5294 |
| COM 3 | Val | 734 | -11.4722 | -11.4722 |

Supplementary validation of docking calculation of COM 4

Schematic and tables below representations of the binding interactions between compound 4 and HER2 TK active site.

Regarding Ala751, Asp863,Leu726, Leu785, Leu796, Gln799, Gly804, Leu800 , Leu852, Leu 726, Leu 785, Leu 796, Lys753, Met774, Met801, Phe864, Phe1004, Cys 805, Ile752, Ser783, Thr798, Thr862, Val 734, the biggest cavity that was found by MVD overlapped with the active sight predicted by auto dock vina. As such, these cavities were taken as the active sight in the models.

Also, the cavity with geometric position (X=12.03, Y=0.27, Z=29.73A) which was found by MVD in the predicted model, was confirmed by Autodock vina as substrate binding site.



**Figure s30** Docking results of **COM4** that show residue and molecule contribution on the active site which obtained by Autodock Vina

**Table s18** Atom energies of **COM 4** obtained Molegro virtual docker

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ID | Name | ETotal | EPair | EIntra |
| 0 | C | -3.37583 | -3.47108 | 0.0952481 |
| 1 | O | -6.45661 | -5.77957 | -0.677043 |
| 2 | C | -4.94518 | -4.58431 | -0.36087 |
| 3 | C | -5.38579 | -4.96955 | -0.416239 |
| 4 | C | -2.63917 | -3.55936 | 0.920189 |
| 5 | N | -4.13962 | -5.38394 | 1.24431 |
| 6 | C | -4.91806 | -5.50237 | 0.584311 |
| 7 | C | -1.21773 | -3.45472 | 2.23699 |
| 8 | C | -1.96651 | -3.00103 | 1.03452 |
| 9 | N | -2.12575 | -2.84554 | 0.719783 |
| 10 | N | -4.54209 | -2.92542 | -1.61668 |
| 11 | C | -3.27776 | -4.85566 | 1.5779 |
| 12 | C | -5.73329 | -6.79612 | 1.06283 |
| 13 | C | -7.53192 | -7.73751 | 0.205595 |
| 14 | C | -3.76194 | -5.05786 | 1.29592 |
| 15 | C | -2.60628 | -4.54622 | 1.93994 |
| 16 | C | -4.50746 | -4.54874 | 0.0412753 |
| 19 | O | -6.40075 | -5.13861 | -1.26214 |
| 20 | C | -1.91089 | -4.38203 | 2.47113 |
| 21 | C | -4.2979 | -5.86472 | 1.56682 |
| 22 | C | -6.72724 | -7.58313 | 0.855889 |
| 23 | C | -5.2425 | -6.31797 | 1.07546 |
| 24 | C | -2.77047 | -3.6701 | 0.899631 |
| 25 | C | -2.91515 | -4.15659 | 1.24144 |
| 35 | N | -8.30426 | -7.12844 | -1.17582 |

**Table s19** Docking results of **COM4** that show residue and molecule contribution on the active site which obtained by Molegro virtual docker

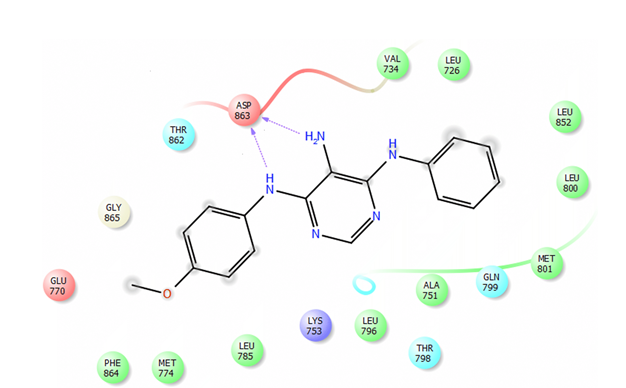
|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Target | Residue | ID | Total | EPair |
| COM 4 | Ala | 751 | -8.71394 | -8.71394 |
| COM 4 | Asp | 863 | -8.598 | -8.598 |
| COM 4 | Cys | 805 | -4.85484 | -4.85484 |
| COM 4 | Gln | 799 | -0.934878 | -0.934878 |
| COM 4 | Gly | 804 | -5.01648 | -5.01648 |
| COM 4 | Ile | 752 | -2.74404 | -2.74404 |
| COM 4 | Leu | 726 | -3.30803 | -3.30803 |
| COM 4 | Leu | 785 | -4.41473 | -4.41473 |
| COM 4 | Leu | 796 | -8.43301 | -8.43301 |
| COM 4 | Leu | 800 | -4.7358 | -4.7358 |
| COM 4 | Leu | 852 | -11.1539 | -11.1539 |
| COM 4 | Lys | 753 | -12.9086 | -12.9086 |
| COM 4 | Met | 774 | -0.754163 | -0.754163 |
| COM 4 | Met | 801 | -4.59579 | -4.59579 |
| COM 4 | Phe | 864 | -7.54508 | -7.54508 |
| COM 4 | Phe | 1004 | -5.59331 | -5.59331 |
| COM 4 | Ser | 783 | -2.12274 | -2.12274 |
| COM 4 | Thr | 798 | -7.13067 | -7.13067 |
| COM 4 | Thr | 862 | -8.69573 | -8.69573 |
| COM 4 | Val | 734 | -6.77797 | -6.77797 |

Supplementary validation of docking calculation of COM 5

Schematic and tables below representations of the binding interactions between compound 5 and HER2 TK active site.

Regarding Ala751, Ala771,Gln770, Asp 863,Leu726, Leu785, Leu796, Gly804, Leu800 , Leu852, Leu 726, Leu 785, Leu 796, Lys753, Met774, Met801, Phe864, Phe1004, Cys 805, Ile752, Ser783, Thr798, Thr862, Val 734, the biggest cavity that was found by MVD overlapped with the active sight predicted by auto dock vina. As such, these cavities were taken as the active sight in the models.

Also, the cavity with geometric position (X=12.03, Y=0.27, Z=29.73A) which was found by MVD in the predicted model, was confirmed by Autodock vina as substrate binding site.



**Figure s31** Docking results of **COM5** that show residue and molecule contribution on the active site which obtained by Autodock Vina

**Table s20** Atom energies of **COM 5** obtained Molegro virtual docker

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ID | Name | ETotal | EPair | EIntra |
| 0 | C | -5.86791 | -6.64667 | 0.778757 |
| 1 | O | -6.73076 | -6.07152 | -0.659239 |
| 2 | C | -3.46618 | -4.53195 | 1.06577 |
| 3 | C | -4.2739 | -4.96976 | 0.695861 |
| 4 | C | -2.76787 | -4.70391 | 1.93604 |
| 5 | C | -3.85524 | -5.62049 | 1.76525 |
| 6 | C | -4.97958 | -5.40714 | 0.427554 |
| 7 | C | -0.673861 | -3.20829 | 2.53443 |
| 10 | N | -6.62941 | -6.87033 | 0.240921 |
| 11 | C | -3.09786 | -4.40155 | 1.30369 |
| 12 | C | -3.78821 | -4.48788 | 0.699668 |
| 13 | C | -2.74296 | -4.45508 | 1.71212 |
| 14 | N | -3.17432 | -5.0051 | 1.83078 |
| 15 | C | -7.07602 | -7.40496 | 0.328944 |
| 16 | N | -1.55065 | -4.14696 | 2.59631 |
| 18 | N | -2.56696 | -2.94998 | 0.383022 |
| 19 | C | -1.49652 | -3.09023 | 1.59372 |
| 20 | C | -1.66782 | -3.91718 | 2.24936 |
| 21 | C | -5.94779 | -6.7548 | 0.807007 |
| 22 | C | -6.13706 | -7.27376 | 1.1367 |
| 23 | C | -3.71077 | -4.81321 | 1.10244 |
| 24 | C | -2.27447 | -3.0626 | 0.788131 |
| 31 | N | -4.79292 | -6.46077 | 1.66785 |

**Table s21** Docking results of **COM5** that show residue and molecule contribution on the active site which obtained by Molegro virtual docker

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Target | Residue | ID | Total | EPair |
| COM 5 | Ala | 751 | -8.11429 | -8.11429 |
| COM 5 | Ala | 771 | -0.896555 | -0.896555 |
| COM 5 | Asp | 863 | -21.7285 | -21.7285 |
| COM 5 | Gln | 799 | -0.821274 | -0.821274 |
| COM 5 | Glu | 770 | -2.57672 | -2.57672 |
| COM 5 | Gly | 804 | -1.03638 | -1.03638 |
| COM 5 | Gly | 865 | -1.0998 | -1.0998 |
| COM 5 | Ile | 752 | -2.26943 | -2.26943 |
| COM 5 | Leu | 726 | -1.42356 | -1.42356 |
| COM 5 | Leu | 785 | -3.06573 | -3.06573 |
| COM 5 | Leu | 796 | -7.72296 | -7.72296 |
| COM 5 | Leu | 800 | -4.1139 | -4.1139 |
| COM 5 | Leu | 852 | -8.79387 | -8.79387 |
| COM 5 | Lys | 753 | -15.2976 | -15.2976 |
| COM 5 | Met | 774 | -2.22886 | -2.22886 |
| COM 5 | Met | 801 | -5.34838 | -5.34838 |
| COM 5 | Phe | 864 | -5.86445 | -5.86445 |
| COM 5 | Phe | 1004 | -0.975051 | -0.975051 |
| COM 5 | Thr | 798 | -4.08336 | -4.08336 |
| COM 5 | Thr | 862 | -8.26044 | -8.26044 |
| COM 5 | Val | 734 | -6.07539 | -6.07539 |