**Table S1.** P-gp residues interacting with each ligand included in the present study, including aminated thioxanthones (ATX 1-8), oxygenated xanthones (OX 1-2 and 4-6), thioxanthones (TX 1-5), and hydroxylated xanthones (X 1-5), all previously reported as P-gp activators. The interactions are detailed for two distinct locations: the drug-binding pocket (DBP) and nucleotide-binding domain 1 (NBD 1). Data were obtained using the BINANA 2.0 software, based on the P-gp structural model from [10].

| Ligands | DBP | NBD1 |
|---|---|---|
| **ATX1** | Hydrogen bonds: SER979, SER733; Hydrophobic contacts: PHE732, PHE983, VAL982, PHE728, ALA729, PHE978, SER979 PHE72, ILE340; T-stacking interactions: PHE732 | Hydrogen bonds: ARG905, THR906; Hydrophobic contacts: SER667, ASP555, SER434, VAL437, ASN903, GLN475, ARG666, ARG659 |
| **ATX2** | Hydrogen bonds: SER979; Hydrophobic contacts: PHE983, MET69, PHE728, ALA729, PHE732, PHE72, PHE978, SER979, VAL982, ILE340, PHE343: T-stacking interactions: PHE732 | Hydrogen bonds: CYS431, SER434; Hydrophobic contacts: ASP555, SER434, ILE585, GLN475, GLU476, ARG666, GLY430, LEU554, VAL437, LEU553 |
| **ATX3** | Hydrogen bonds: SER979; Hydrophobic contacts: PHE983, MET69, PHE728, ALA729, PHE732, PHE978, SER979, VAL982, PHE72, TYR953, ILE340; T-stacking interactions: PHE732 | Hydrogen bonds: ARG659; Hydrophobic contacts: ASP555, SER474, THR906, VAL437, LEU553, LEU554, ILE585, GLY430, ARG659, LYS433 |
| **ATX4** | Hydrophobic contacts: PHE983, PHE728, ALA729, SER979, VAL982, PHE72, TYR953, PHE978, ILE340, PHE343; T-stacking interactions: PHE732 | Hydrogen bonds: ARG659; Hydrophobic contacts: ASP555, SER434, ILE585, SER474, GLU476, GLY430, LEU554, LEU553; Salt bridges: ASP555 |
| **ATX5** | Hydrophobic contacts: VAL982, ALA729, PHE732, PHE983, ILE340, MET949, PHE728, GLN725, LEU339, PHE72, MET69, PHE336; T-stacking interactions: PHE983 | Hydrogen bonds: THR906; Hydrophobic contacts: THR906, ASP555, ILE585, VAL437, LEU553, LEU554, SER667, ASN903, GLY430 |
| **ATX6** | Hydrophobic contacts: VAL982, PHE983, PHE343, ALA729, PHE732, ILE340, LEU339, MET69, GLN725, PHE728, TYR307, TYR310 | Hydrophobic contacts: THR906, ASP555, LEU554, ILE585, VAL437, LEU553, VAL472, GLU476, GLN475, GLY430, HIS587 |
| **ATX7** | Hydrophobic contacts: ALA729, PHE732, PHE983, ILE340, PHE343, PHE728, GLN725, TYR310, PHE759, VAL982, MET69, PHE72, PHE336; T-stacking interactions: PHE983; Cation-π interactions: PHE732 | Hydrogen bonds: ARG659; Hydrophobic contacts: ASP555, SER434, ILE585, ARG666, GLU476, VAL437, VAL473, SER474, LEU553, LEU554, THR906, GLY430; Salt bridges: ASP555 |
| **ATX8** | Hydrophobic contacts: VAL982, PHE732, PHE983, ALA729, ILE340, PHE343, PHE728, PHE759, TYR310, GLN725, SER979, PHE72, TYR953, PHE978; T-stacking interactions: PHE983; Cation-π interactions: PHE732 | Hydrogen bonds: ASN903; Hydrophobic contacts: SER474, ASP555, VAL437, ILE585, LEU553, THR906, GLU476, SER667, ARG666, GLY430; Salt bridges: ASP555 |
| **OX1** | Hydrophobic contacts: ILE836, TYR998, PHE994, ARG832, ILE700, LEU833, ASN704, ALA828; π-π stackings interactions: TYR998 | Hydrophobic contacts: ASP555, SER474, THR906, VAL437, LEU553, LEU554, ILE585, SER667 |
| **OX2** | Hydrophobic contacts: PHE732, PHE983, MET69, PHE72, ALA729, PHE343; T-stacking interactions: PHE343 | Hydrophobic contacts: SER434, SER474, THR906, LEU553, VAL437, LEU554, ASP555, ILE585 |
| **OX4** | Hydrophobic contacts: PHE983, PHE732, VAL982, PHE728, ALA729, PHE72, PHE978, SER979; T-stacking interactions: PHE983, PHE732 | Hydrogen bonds: ARG659, ARG905; Hydrophobic contacts: SER434, ASP555, VAL437, ILE585, LEU553, LEU554, SER474, THR906, GLY430 |

| | | |
|---|---|---|
| **OX5** | Hydrophobic contacts: PHE343, PHE983, SER979, VAL982, MET69, PHE728, ALA729, ILE340; T-stacking interactions: PHE343 | Hydrophobic contacts: SER434, SER474, THR906, LEU553, VAL437, LEU554, ASP555, ILE585, SER667 |
| **OX6** | Hydrophobic contacts: ILE836, TYR998, PHE994, MET701, ILE700, LEU833, ARG832; π-π stackings interactions: TYR998 | Hydrophobic contacts: SER434, THR906, SER474, VAL437, LEU553, LEU554, ASP555, ILE585, SER667 |
| **TX1** | Hydrogen bonds: SER979; Hydrophobic contacts: PHE983, MET69, PHE728, ALA729, PHE732, PHE72, ILE340, PHE343; T-stacking interactions: PHE732 | Hydrogen bonds: ARG659; Hydrophobic contacts: ASP555, SER434, ILE585, SER474, GLU476, GLY430, VAL437, LEU553, LEU554, VAL472, VAL473; Salt bridges: ASP555 |
| **TX2** | Hydrophobic contacts: TYR998, ILE700, LEU883, ASN704, ILE836, ARG832, PHE994; π-π stackings interactions: TYR998 | Hydrophobic contacts: THR906, SER434, ASP555, VAL437, ILE585, LEU553, LEU554, SER474 |
| **TX3** | Hydrogen bonds: TYR310, TYR307, GLN725; Hydrophobic contacts: LEU339, PHE732, SER979, PHE983, ALA729, ILE340, PHE343, PHE728, GLN725, PHE303, VAL982, PHE978, PHE72; π-π stackings interactions: PHE732; T-stacking interactions: PHE343 | Hydrogen bonds: ARG905, GLU476; Hydrophobic contacts: SER434, VAL437, ARG905, THR906, ASP555, ARG659, SER474, GLU476, ARG666, ILE585, LEU554, LEU553 |
| **TX4** | Hydrophobic contacts: VAL982, PHE732, PHE72, LEU339, PHE343, ILE340, PHE983, TYR310, PHE728, PHE759 | Hydrogen bonds: ARG905; Hydrophobic contacts: SER434, GLY430, CYS431, ARG905, THR906, VAL437, ASP555, ILE585, SER474, GLU476; Cation-π interactions: ARG905 |
| **TX5** | Hydrophobic contacts: ALA729, PHE732, PHE983, ILE340, PHE343, PHE728, TYR310, PHE759, SER979, VAL982, PHE72; T-stacking interactions: PHE983; Cation-π interactions: PHE732 | Hydrophobic contacts: ASP555, SER474, THR906, VAL437, VAL472, LEU553, LEU554, ILE585, GLY430, GLU476, SER667; Salt bridges: ASP555 |
| **X1** | Hydrophobic contacts: PHE728, ALA729, PHE983, LEU339, PHE343, ILE340, MET69; T-stacking interactions: PHE343 | Hydrogen bonds: ARG659; Hydrophobic contacts: ASP555, SER434, ILE585, VAL437, LEU553, LEU554, SER474, THR906 |
| **X2** | Hydrophobic contacts: ILE700, MET701, ILE836, TYR998, PHE994; π-π stackings interactions: TYR998 | Hydrogen bonds: ARG659; Hydrophobic contacts: ASP555, ILE585, VAL437, LEU553, VAL472, SER474, THR906 |
| **X3** | Hydrophobic contacts: ILE836, TYR998, PHE994, ILE700, LEU833, ALA828; π-π stackings interactions: TYR998 | Hydrogen bonds: ARG659; Hydrophobic contacts: ASP555, ILE585, VAL437, LEU553, VAL472, SER474, THR906 |
| **X4** | Hydrogen bonds: TYR998; Hydrophobic contacts: ILE700, ILE836, TYR998, ALA828, ARG832, LEU833, ASN704 | Hydrogen bonds: ARG659; Hydrophobic contacts: ASP555, ILE585, VAL437, LEU553, SER474, THR906 |
| **X5** | Hydrophobic contacts: ILE700, LEU833, ASN704, ILE836, TYR998, ALA828, ARG832 | Hydrogen bonds: ARG659; Hydrophobic contacts: SER434, ASP555, ILE585, VAL437, THR906, GLY430 |

## References


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