Article

Finding New Molecular Targets of Familiar Natural Products Using In Silico Target Prediction

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S-1. Pharmacophore models used in this study

Table S 1. Pharmacophore Models used throughout this study.

|  |  |  |  |
| --- | --- | --- | --- |
| Model Name | Software | UniProt entry | Ref. |
| model\_DS4 | DS | 3BHS1\_HUMAN | [1] |
| Model\_1 | LS | 3BHS1\_HUMAN | [1] |
| Model\_2 | LS | 3BHS1\_HUMAN | [1] |
| AChE-1acj-tha-HBA-vers | DS | ACES\_HUMAN | [2] |
| AChE-1acj-tha-xvols | DS | ACES\_HUMAN | [2] |
| AChE-GNT-Hypo1-shape | DS | ACES\_HUMAN | [2] |
| AChE-X015-1 | DS | ACES\_HUMAN | [2] |
| 17b-HSD5-1ry8-rut-1.60-x-1 | DS | AK1C3\_HUMAN | [3] |
| 17b-HSD5-1ry8-rut-1.60-x-1-s | DS | AK1C3\_HUMAN | [3] |
| 17b-HSD5-1s2a-imn-1.70-x-1 | DS | AK1C3\_HUMAN | [3] |
| 17b-HSD5-1s2a-imn-1.70-x-1-s | DS | AK1C3\_HUMAN | [3] |
| 17b-HSD5-1s2c-flf-1.80-x-1 | DS | AK1C3\_HUMAN | [3] |
| 17b-HSD5-1s2c-flf-1.80-x-1-s | DS | AK1C3\_HUMAN | [3] |
| 17b-HSD5-1s2c-flf-1.80-x-2-s | DS | AK1C3\_HUMAN | [3] |
| 17b-HSD5-1zq5-e04-1.30-x-1 | DS | AK1C3\_HUMAN | [3] |
| 17b-HSD5-1zq5-e04-1.30-x-1-s | DS | AK1C3\_HUMAN | [3] |
| 17b-HSD5-1zq5-e04-1.30-x-2-s | DS | AK1C3\_HUMAN | [3] |
| 17b-HSD5-2f38-15m-2.00-x-1-s | DS | AK1C3\_HUMAN | [3] |
| 17b-HSD5-X009-1 | DS | AK1C3\_HUMAN | [3] |
| 17b-HSD5-X009-2 | DS | AK1C3\_HUMAN | [3] |
| FLAPophore6exclu\_LS3-03 | LS | AL5AP\_HUMAN | [4] |
| FLAPophore7exclu\_LS3-03 | LS | AL5AP\_HUMAN | [4] |
| LS3.12-CYP11B1\_2T\_D-1-8 | LS | C11B1\_HUMAN | [5] |
| LS3.12-CYP11B1\_2T\_D-1-8\_refined-Veronika | LS | C11B1\_HUMAN | [5] |
| LS3.12-CYP11B2\_C-1-5 | LS | C11B2\_HUMAN | [5] |
| LS3.12-CYP11B2\_C-1-5-refined-Veronika | LS | C11B2\_HUMAN | [5] |
| CYP17\_3RUK\_LS4\_03\_MA | LS | CP17A\_HUMAN | 1 |
| CYP17\_Abi\_Orteronel\_LS4\_03\_MA | LS | CP17A\_HUMAN | 1 |
| aromatase-X006-1 | DS | CP19A\_HUMAN | [6] |
| aromatase-X006-2 | DS | CP19A\_HUMAN | [6] |
| aromatase-X006-3 | DS | CP19A\_HUMAN | [6] |
| CYP2D6-quant-X012-1 | DS | CP2D6\_HUMAN | [7] |
| CYP2D6-X012-2 | DS | CP2D6\_HUMAN | [7] |
| CYP2D6-X012-3 | DS | CP2D6\_HUMAN | [7] |
| CYP2D6-X012-41 | DS | CP2D6\_HUMAN | [7] |
| CYP2D6-X012-42 | DS | CP2D6\_HUMAN | [7] |
| LS3-03b-17b-HSD2-model6-refined | LS | DHB2\_HUMAN | [8] |
| LS3-03b-17b-HSD2-specific-model-12 | LS | DHB2\_HUMAN | [8] |
| LS3-03b-17b-HSD2-specific-model-6 | LS | DHB2\_HUMAN | [8] |
| LS3-03b-17b-HSD2-specific-model-8 | LS | DHB2\_HUMAN | [8] |
| 17b-HSD3-DS-model-1-X007-1 | DS | DHB3\_HUMAN | [3] |
| 17b-HSD3-DS-model-2-X007-31 | DS | DHB3\_HUMAN | [3] |
| 17b-HSD3-LS3-1-317364-65-1-and-317364-71-9-model-4 | LS | DHB3\_HUMAN | [3] |
| 17b-HSD3-LS3-1-317364-65-1-and-317364-71-9-model-5 | LS | DHB3\_HUMAN | [3] |
| 17b-HSD3-LS3-1-875895-55-9-875895-40-2-model-1 | LS | DHB3\_HUMAN | [3] |
| 17b-HSD3-LS3-1-Benzophenone-1-919118-27-7-model-1 | LS | DHB3\_HUMAN | [3] |
| 17b-HSD3-LS3-1-Harada-2012-19-Fink-18m-model-4 | LS | DHB3\_HUMAN | [3] |
| 17b-HSD3-LS3-1-Harada-2012-19-Fink-18m-model-7 | LS | DHB3\_HUMAN | [3] |
| 17b-HSD4-quercetin-Wetzel-final | DS | DHB4\_HUMAN | [3] |
| 17b-HSD4-Quercetin-Wetzel-HBA-F-model3-2 | DS | DHB4\_HUMAN | [3] |
| 17b-HSD4-Quercetin-Wetzel-HBA-F-model8-1 | DS | DHB4\_HUMAN | [3] |
| 17b-HSD4-Quercetin-Wetzel-model-4-final-LS3-1 | LS | DHB4\_HUMAN | [3] |
| 17b-HSD7-Fiala-DS-shapemodell\_30 | DS | DHB7\_HUMAN | [9] |
| 17b-HSD7-Fiala-DS-shapemodell\_42 | DS | DHB7\_HUMAN | [9] |
| 17b-HSD7-Fiala-DS-shapemodell\_43 | DS | DHB7\_HUMAN | [9] |
| 17b-HSD7-Fiala-DS-shapemodell\_49 | DS | DHB7\_HUMAN | [9] |
| LS4-09-17b-HSD7-Fiala-model2-1 | LS | DHB7\_HUMAN | [9] |
| LS4-09-17b-HSD7-Fiala-model4-1 | LS | DHB7\_HUMAN | [9] |
| 11b-HSD-1-refinedX005-1-HBA-model4new | DS | DHI1\_HUMAN | [10] |
| 11b-HSD1-X005-1-HBA-ohneShape-model4 | DS | DHI1\_HUMAN | [10] |
| 11b-HSD1-X005-1-model1 | DS | DHI1\_HUMAN | [10] |
| 11b-HSD-triterpenes-common-features | DS | DHI1\_HUMAN | [10] |
| 11b-HSD2-refinedX005-2-model2new | DS | DHI2\_HUMAN | [11] |
| 11b-HSD2-X005-2-model2 | DS | DHI2\_HUMAN | [11] |
| LS3-03a-11bHSD2-model3 | LS | DHI2\_HUMAN | [11] |
| LS3-03a11bHSD2-model5 | LS | DHI2\_HUMAN | [11] |
| LS3-03a-refined-11b-HSD2model-model3new | LS | DHI2\_HUMAN | [11] |
| LS3-03a-refined-11bHSD2-model-model5new | LS | DHI2\_HUMAN | [11] |
| ERa-antagonist-LS3-01-model584 | LS | ESR1\_HUMAN | [12] |
| ERa-antagonist-LS3-01-model585 | LS | ESR1\_HUMAN | [12] |
| ERa-antagonist-LS3-01-model586 | LS | ESR1\_HUMAN | [12] |
| ER-agonist-LS3-01-model009 | LS | ESR1\_HUMAN | [12] |
| ER-agonist-LS3-01-model022 | LS | ESR1\_HUMAN | [12] |
| ER-agonist-LS3-01-model030 | LS | ESR1\_HUMAN | [12] |
| ER-agonist-LS3-01-model040 | LS | ESR1\_HUMAN | [12] |
| ER-agonist-LS3-01-model042 | LS | ESR1\_HUMAN | [12] |
| ER-agonist-LS3-01-model047 | LS | ESR1\_HUMAN | [12] |
| ER-agonist-LS3-01-model052 | LS | ESR1\_HUMAN | [12] |
| ER-agonist-LS3-01-model062 | LS | ESR1\_HUMAN | [12] |
| ER-agonist-LS3-01-model069 | LS | ESR1\_HUMAN | [12] |
| ER-agonist-LS3-01-model073 | LS | ESR1\_HUMAN | [12] |
| ER-agonist-LS3-01-model084 | LS | ESR1\_HUMAN | [12] |
| ER-agonist-LS3-01-model087 | LS | ESR1\_HUMAN | [12] |
| ER-agonist-LS3-01-model099 | LS | ESR1\_HUMAN | [12] |
| ER-antagonist-LS3-01-model567 | LS | ESR1\_HUMAN | [12] |
| ER-antagonist-LS3-01-model571 | LS | ESR1\_HUMAN | [12] |
| ER-antagonist-LS3-01-model572 | LS | ESR1\_HUMAN | [12] |
| ER-antagonist-LS3-01-model573 | LS | ESR1\_HUMAN | [12] |
| ER-antagonist-LS3-01-model574 | LS | ESR1\_HUMAN | [12] |
| ER-antagonist-LS3-01-model575 | LS | ESR1\_HUMAN | [12] |
| ER-antagonist-LS3-01-model577 | LS | ESR1\_HUMAN | [12] |
| ER-antagonist-LS3-01-model578 | LS | ESR1\_HUMAN | [12] |
| ER-antagonist-LS3-01-model580 | LS | ESR1\_HUMAN | [12] |
| ER-antagonist-LS3-01-model583 | LS | ESR1\_HUMAN | [12] |
| ER-antagonist-LS3-01-model587 | LS | ESR1\_HUMAN | [12] |
| ERb-agonist-LS3-01-model100 | LS | ESR2\_HUMAN | [12] |
| ERb-agonist-LS3-01-model102 | LS | ESR2\_HUMAN | [12] |
| ERb-agonist-LS3-01-model103 | LS | ESR2\_HUMAN | [12] |
| ERb-agonist-LS3-01-model104 | LS | ESR2\_HUMAN | [12] |
| ERb-antagonist-LS3-01-model567 | LS | ESR2\_HUMAN | [12] |
| ERb-antagonist-LS3-01-model571 | LS | ESR2\_HUMAN | [12] |
| ERb-antagonist-LS3-01-model572 | LS | ESR2\_HUMAN | [12] |
| ERb-antagonist-LS3-01-model573 | LS | ESR2\_HUMAN | [12] |
| ERb-antagonist-LS3-01-model574 | LS | ESR2\_HUMAN | [12] |
| ERb-antagonist-LS3-01-model575 | LS | ESR2\_HUMAN | [12] |
| ERb-antagonist-LS3-01-model577 | LS | ESR2\_HUMAN | [12] |
| ERb-antagonist-LS3-01-model578 | LS | ESR2\_HUMAN | [12] |
| ERb-antagonist-LS3-01-model580 | LS | ESR2\_HUMAN | [12] |
| ERb-antagonist-LS3-01-model583 | LS | ESR2\_HUMAN | [12] |
| ERb-antagonist-LS3-01-model587 | LS | ESR2\_HUMAN | [12] |
| GR-1m2z-dex-2.50-T-1 | DS | GCR\_HUMAN | [13] |
| GR-1nhz-486-2.30-T-1 | DS | GCR\_HUMAN | [13] |
| GR-1nhz-486-2.30-T-2 | DS | GCR\_HUMAN | [13] |
| GR-1nhz-486-2.30-T-3 | DS | GCR\_HUMAN | [13] |
| GR-1nhz-486-2.30-T-4 | DS | GCR\_HUMAN | [13] |
| GR-1nhz-486-2.30-T-5 | DS | GCR\_HUMAN | [13] |
| GR-1p93-dex-2.70-T-1 | DS | GCR\_HUMAN | [13] |
| GR-3bqd-day-2.50-T-1 | DS | GCR\_HUMAN | [13] |
| GR-3bqd-day-2.50-T-2 | DS | GCR\_HUMAN | [13] |
| GR-3cld-gw6-2.84-T-1 | DS | GCR\_HUMAN | [13] |
| GR-3e7c-866-2.15-T-1 | DS | GCR\_HUMAN | [13] |
| GR-T001-1 | DS | GCR\_HUMAN | [13] |
| GR-T001-2 | DS | GCR\_HUMAN | [13] |
| GR-T001-3 | DS | GCR\_HUMAN | [13] |
| GR-T002-1 | DS | GCR\_HUMAN | [13] |
| GR-T002-2 | DS | GCR\_HUMAN | [13] |
| GR-T003-1 | DS | GCR\_HUMAN | [13] |
| GR-T004-1 | DS | GCR\_HUMAN | [13] |
| GR-T005-1 | DS | GCR\_HUMAN | [13] |
| GR-T006-1 | DS | GCR\_HUMAN | [13] |
| GR-T007-1 | DS | GCR\_HUMAN | [13] |
| GR-T008-1 | DS | GCR\_HUMAN | [13] |
| GR-T009-1 | DS | GCR\_HUMAN | [13] |
| GR-T010-1 | DS | GCR\_HUMAN | [13] |
| GR-T011-1 | DS | GCR\_HUMAN | [13] |
| GR-T012-1 | DS | GCR\_HUMAN | [13] |
| GR-T013-1 | DS | GCR\_HUMAN | [13] |
| GR-T014-1 | DS | GCR\_HUMAN | [13] |
| GR-T015-1 | DS | GCR\_HUMAN | [13] |
| GR-T015-2 | DS | GCR\_HUMAN | [13] |
| GR-T016-1 | DS | GCR\_HUMAN | [13] |
| GR-T017-1 | DS | GCR\_HUMAN | [13] |
| sEH-C12\_1\_DS3.5 | DS | HYES\_HUMAN | [14] |
| sEH-C15\_1DS3.5 | DS | HYES\_HUMAN | [14] |
| sEH-1VJ5mod+3ANTmod\_merged(Ref.3ANT)\_LS\_3-02 | LS | HYES\_HUMAN | [14] |
| sEH-1ZD5\_mod5\_LS\_3-02 | LS | HYES\_HUMAN | [14] |
| sEH-3ANT[A]\_modifiziert\_LS\_3-02 | LS | HYES\_HUMAN | [14] |
| sEH-3ANT+3ANTmod\_merged\_LS\_3-02 | LS | HYES\_HUMAN | [14] |
| sEH-3I1Y\_mod2\_LS\_3-02 | LS | HYES\_HUMAN | [14] |
| sEH-3I1Y\_mod4\_LS\_3-02 | LS | HYES\_HUMAN | [14] |
| sEH-3KOO\_mod2\_LS\_3-02 | LS | HYES\_HUMAN | [14] |
| sEH-3KOO\_mod5\_LS\_3-02 | LS | HYES\_HUMAN | [14] |
| sEH-3OTQ\_mod4\_LS\_3-02 | LS | HYES\_HUMAN | [14] |
| sEH-Cl2\_Shared\_mod1\_LS\_3-02 | LS | HYES\_HUMAN | [14] |
| 5-LO-N004-1 | DS | LOX5\_HUMAN | [15] |
| 5-LO-N004-2 | DS | LOX5\_HUMAN | [15] |
| 5-LO-W001-5 | DS | LOX5\_HUMAN | [16] |
| LS4-09-5-LO-bzq\_01v2 | LS | LOX5\_HUMAN | 2 |
| LS4-09-5-LO-bzq\_02v2 | LS | LOX5\_HUMAN | 2 |
| LS4-09-5-LO-bzq\_03v2 | LS | LOX5\_HUMAN | 2 |
| LS4-09-5-LO-bzq-02-02-16-5LOX-benzoquinone\_V2 | LS | LOX5\_HUMAN | 2 |
| LS4-09-5-LO-zlt-20-01-16-zileuton | LS | LOX5\_HUMAN | 2 |
| LS4-09-5-LO-zlt-20-01-16-zIleuton-derivatives | LS | LOX5\_HUMAN | 2 |
| MR-2a3i-c0r-1.95-Z-1 | DS | MCR\_HUMAN | [17] |
| MR-2aa2-as4-1.95-Z-1 | DS | MCR\_HUMAN | [17] |
| MR-2aa2-as4-1.95-Z-2 | DS | MCR\_HUMAN | [17] |
| MR-2aa5-str-2.20-Z-1 | DS | MCR\_HUMAN | [17] |
| MR-2oax-snl-2.29-Z-1 | DS | MCR\_HUMAN | [17] |
| MR-Z001-1 | DS | MCR\_HUMAN | [17] |
| MR-Z001-2 | DS | MCR\_HUMAN | [17] |
| MR-Z002-1 | DS | MCR\_HUMAN | [17] |
| MR-Z002-2 | DS | MCR\_HUMAN | [17] |
| p38-MAPK-1a9u-sb2-800mod1\_h | DS | MK14\_HUMAN | [18] |
| p38-MAPK-1bl6-sb6-800mod1\_h | DS | MK14\_HUMAN | [18] |
| p38-MAPK-1bl7-sb4-800mod1\_ha | DS | MK14\_HUMAN | [18] |
| p38-MAPK-1bmk-sb5-800mod1\_ha | DS | MK14\_HUMAN | [18] |
| p38-MAPK-1ouk+shape | DS | MK14\_HUMAN | [18] |
| p38-MAPK-1w82+shape | DS | MK14\_HUMAN | [18] |
| p38-MAPK-1w83-1wbv+shape | DS | MK14\_HUMAN | [18] |
| p38-MAPK-1wbvneu+shape | DS | MK14\_HUMAN | [18] |
| p38-MAPK-2rg6-3cg2+shape | DS | MK14\_HUMAN | [18] |
| p38-MAPK-3dt1-3ctq+shape | DS | MK14\_HUMAN | [18] |
| NFkB-DNA-site-N003-1 | DS | NFKB1\_HUMAN | 1 |
| LXR-1p8d | DS | NR1H2\_HUMAN | [19] |
| LXR-1pq6 | DS | NR1H2\_HUMAN | [19] |
| LXR-1pqc | DS | NR1H2\_HUMAN | [19] |
| LXR-1uhl | DS | NR1H2\_HUMAN | [19] |
| LXR-1upv | DS | NR1H2\_HUMAN | [19] |
| LXR-1upw | DS | NR1H2\_HUMAN | [19] |
| LXR-2acl | DS | NR1H2\_HUMAN | [19] |
| LXR-3fal | DS | NR1H2\_HUMAN | [19] |
| LXR-3fc6 | DS | NR1H2\_HUMAN | [19] |
| FXR-1osh-fex-1.78-d-1 | DS | NR1H4\_HUMAN | [20] |
| FXR-1osh-fex-1.78-d-1-s | DS | NR1H4\_HUMAN | [20] |
| FXR-1osh-fex-1.78-d-2 | DS | NR1H4\_HUMAN | [20] |
| FXR-1osh-fex-1.78-d-2-s | DS | NR1H4\_HUMAN | [20] |
| FXR-3bej-muf-1.90-x-1 | DS | NR1H4\_HUMAN | [20] |
| FXR-3bej-muf-1.90-x-1-s | DS | NR1H4\_HUMAN | [20] |
| FXR-3bej-muf-1.90-x-2 | DS | NR1H4\_HUMAN | [20] |
| FXR-3bej-muf-1.90-x-2-s | DS | NR1H4\_HUMAN | [20] |
| FXR-3dct-o64-2.50-x-1 | DS | NR1H4\_HUMAN | [20] |
| FXR-3dct-o64-2.50-x-1-s | DS | NR1H4\_HUMAN | [20] |
| FXR-3dct-o64-2.50-x-2 | DS | NR1H4\_HUMAN | [20] |
| FXR-3dct-o64-2.50-x-2-s | DS | NR1H4\_HUMAN | [20] |
| FXR-3fli-33y-2.00-x-1 | DS | NR1H4\_HUMAN | [20] |
| FXR-3fli-33y-2.00-x-1-s | DS | NR1H4\_HUMAN | [20] |
| FXR-X008-1 | DS | NR1H4\_HUMAN | [20] |
| cPLA2alpha-N002-2 | DS | PA2GA\_HUMAN | [21] |
| COX-1-1cqe-flp-3.10-x-1 | DS | PGH1\_HUMAN | [22] |
| COX-1-1pge-isf-3.50-x-2-s | DS | PGH1\_HUMAN | [22] |
| COX-1-2ayl-flp-2.00-x-1 | DS | PGH1\_HUMAN | [22] |
| COX-1-X017-1 | DS | PGH1\_HUMAN | [22] |
| COX-1-1EQH4\_LS3-01 | LS | PGH1\_HUMAN | [23] |
| COX-1-1PGE2\_LS3-01 | LS | PGH1\_HUMAN | [23] |
| COX-1-1PGG2\_LS3-01 | LS | PGH1\_HUMAN | [23] |
| COX-1-2AYL3\_LS3-01 | LS | PGH1\_HUMAN | [23] |
| COX-1-2OYU2\_LS3-01 | LS | PGH1\_HUMAN | [23] |
| COX-2-4cox-imn-2.90-x-2 | DS | PGH2\_HUMAN | [22] |
| COX-2-6cox-s58-2.80-x-1-s | DS | PGH2\_HUMAN | [22] |
| COX-2-3ln11\_LS3-01 | LS | PGH2\_HUMAN | [23] |
| COX-2-3NTB1\_LS3-01 | LS | PGH2\_HUMAN | [23] |
| COX-2-4COX2\_LS3-01 | LS | PGH2\_HUMAN | [23] |
| COX-2-6COX3\_LS3-01 | LS | PGH2\_HUMAN | [23] |
| PPARa-1i7g-az2-2.24-x-1 | DS | PPARA\_HUMAN | [24] |
| PPARa-1i7g-az2-2.24-x-1-s | DS | PPARA\_HUMAN | [24] |
| PPARa-1i7g-az2-2.24-x-2 | DS | PPARA\_HUMAN | [24] |
| PPARa-1k7l-544-2.50-p-1 | DS | PPARA\_HUMAN | [24] |
| PPARa-1k7l-544-2.50-p-1-s | DS | PPARA\_HUMAN | [24] |
| PPARa-1k7l-544-2.50-p-2 | DS | PPARA\_HUMAN | [24] |
| PPARa-1k7l-544-2.50-p-2-s | DS | PPARA\_HUMAN | [24] |
| PPARa-1kkq-471-3.00-x-1 | DS | PPARA\_HUMAN | [24] |
| PPARa-1kkq-471-3.00-x-1-s | DS | PPARA\_HUMAN | [24] |
| PPARa-P007-1 | DS | PPARA\_HUMAN | [24] |
| PPARd-1gwx-433-2.50-p-1 | DS | PPARD\_HUMAN | [24] |
| PPARd-1gwx-433-2.50-p-1-s | DS | PPARD\_HUMAN | [24] |
| PPARd-1y0s-331-2.65-p-1 | DS | PPARD\_HUMAN | [24] |
| PPARd-1y0s-331-2.65-p-1-s | DS | PPARD\_HUMAN | [24] |
| PPARd-1y0s-331-2.65-p-2-s | DS | PPARD\_HUMAN | [24] |
| PPARd-1y0s-331-2.65-p-3 | DS | PPARD\_HUMAN | [24] |
| PPARd-1y0s-331-2.65-p-3-s | DS | PPARD\_HUMAN | [24] |
| PPARd-2awh-vca-2.00-p-1-s | DS | PPARD\_HUMAN | [24] |
| PPARd-2awh-vca-2.00-p-2 | DS | PPARD\_HUMAN | [24] |
| PPARd-2awh-vca-2.00-p-2-s | DS | PPARD\_HUMAN | [24] |
| PPARd-2b50-vca-2.00-p-1-s | DS | PPARD\_HUMAN | [24] |
| PPARd-2b50-vca-2.00-p-2 | DS | PPARD\_HUMAN | [24] |
| PPARd-2b50-vca-2.00-p-2-s | DS | PPARD\_HUMAN | [24] |
| PPARd-2baw-vca-2.30-p-1-s | DS | PPARD\_HUMAN | [24] |
| PPARd-2j14-gni-2.80-p-1-s | DS | PPARD\_HUMAN | [24] |
| PPARd-3gwx-epa-2.40-p-1-s | DS | PPARD\_HUMAN | [24] |
| PPARd-3gwx-epa-2.40-p-2-s | DS | PPARD\_HUMAN | [24] |
| PPARg-1fm6-brl-2.10-p-1 | DS | PPARG\_HUMAN | [24] |
| PPARg-1fm6-brl-2.10-p-1-s | DS | PPARG\_HUMAN | [24] |
| PPARg-1fm9-570-2.10-x-1 | DS | PPARG\_HUMAN | [24] |
| PPARg-1fm9-570-2.10-x-1-s | DS | PPARG\_HUMAN | [24] |
| PPARg-1fm9-570-2.10-x-2 | DS | PPARG\_HUMAN | [24] |
| PPARg-1fm9-570-2.10-x-2-s | DS | PPARG\_HUMAN | [24] |
| PPARg-1i7i-az2-2.35-x-1 | DS | PPARG\_HUMAN | [24] |
| PPARg-1i7i-az2-2.35-x-1-s | DS | PPARG\_HUMAN | [24] |
| PPARg-1k74-544-2.30-p-1-s | DS | PPARG\_HUMAN | [24] |
| PPARg-1knu-ypa-2.50-p-1-s | DS | PPARG\_HUMAN | [24] |
| PPARg-1knu-ypa-2.50-p-2-s | DS | PPARG\_HUMAN | [24] |
| PPARg-1nyx-drf-2.65-p-1 | DS | PPARG\_HUMAN | [24] |
| PPARg-1nyx-drf-2.65-p-1-s | DS | PPARG\_HUMAN | [24] |
| PPARg-1nyx-drf-2.65-p-2-s | DS | PPARG\_HUMAN | [24] |
| PPARg-1wm0-plb-2.90-p-1-s | DS | PPARG\_HUMAN | [24] |
| PPARg-1zeo-c01-2.50-p-1 | DS | PPARG\_HUMAN | [24] |
| PPARg-1zeo-c01-2.50-p-1-s | DS | PPARG\_HUMAN | [24] |
| PPARg-1zgy-brl-1.80-p-1-s | DS | PPARG\_HUMAN | [24] |
| PPARg-2ath-3ea-2.28-p-1-s | DS | PPARG\_HUMAN | [24] |
| PPARg-2f4b-eha-2.07-p-1-s | DS | PPARG\_HUMAN | [24] |
| PPARg-2fvj-ro0-1.99-p-1-s | DS | PPARG\_HUMAN | [24] |
| PPARg-2g0g-sp0-2.54-p-1 | DS | PPARG\_HUMAN | [24] |
| PPARg-2g0g-sp0-2.54-p-1-s | DS | PPARG\_HUMAN | [24] |
| PPARg-2g0h-sp3-2.30-p-1-s | DS | PPARG\_HUMAN | [24] |
| PPARg-2gtk-208-2.10-p-1-s | DS | PPARG\_HUMAN | [24] |
| PPARg-2hfp-nsi-2.00-p-1-s | DS | PPARG\_HUMAN | [24] |
| PPARg-2prg-brl-2.30-p-1 | DS | PPARG\_HUMAN | [24] |
| PPARg-2prg-brl-2.30-p-1-s | DS | PPARG\_HUMAN | [24] |
| PPARg-2q59-240-2.20-p-1-s | DS | PPARG\_HUMAN | [24] |
| PPARg-4prg-072-2.90-p-1-s | DS | PPARG\_HUMAN | [24] |
| PPARg-P002-1 | DS | PPARG\_HUMAN | [24] |
| mPGES-1-Hypo\_62\_01-non-acidic | DS | PTGES\_HUMAN | [25] |
| mPGES-1-X019-1 | DS | PTGES\_HUMAN | [25] |
| mPGES-1-X019-2 | DS | PTGES\_HUMAN | [25] |
| mPGES-1-model-LS3-01 | LS | PTGES\_HUMAN | [25] |
| PTP1b-1bzc-tpi-2.35-d-2 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1bzh-flt-2.10-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1bzj-pic-2.25-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1c83-oai-1.80-d-1-s | DS | PTN1\_HUMAN | [26] |
| PTP1b-1c83-oai-1.80-d-2 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1c83-oai-1.80-d-2-s | DS | PTN1\_HUMAN | [26] |
| PTP1b-1c84-761-2.35-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1c84-761-2.35-d-1-s | DS | PTN1\_HUMAN | [26] |
| PTP1b-1c84-761-2.35-d-2 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1c84-761-2.35-d-2-s | DS | PTN1\_HUMAN | [26] |
| PTP1b-1c84-761-2.35-d-3 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1c84-761-2.35-d-3-s | DS | PTN1\_HUMAN | [26] |
| PTP1b-1c85-oba-2.72-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1c85-oba-2.72-d-1-s | DS | PTN1\_HUMAN | [26] |
| PTP1b-1c86-opa-2.30-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1c86-opa-2.30-d-1-s | DS | PTN1\_HUMAN | [26] |
| PTP1b-1c87-opa-2.10-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1c87-opa-2.10-d-1-s | DS | PTN1\_HUMAN | [26] |
| PTP1b-1c88-ota-1.80-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1ecv-878-1.95-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1ecv-878-1.95-d-1-s | DS | PTN1\_HUMAN | [26] |
| PTP1b-1ecv-878-1.95-d-2 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1ecv-878-1.95-d-2-s | DS | PTN1\_HUMAN | [26] |
| PTP1b-1ecv-878-1.95-d-3 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1ecv-878-1.95-d-3-s | DS | PTN1\_HUMAN | [26] |
| PTP1b-1g7g-inx-2.20-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1gfy-col-2.13-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1gfy-col-2.13-d-1-s | DS | PTN1\_HUMAN | [26] |
| PTP1b-1jf7-tbh-2.20-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1kak-fnp-2.50-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1kak-fnp-2.50-d-2 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1l8g-dbd-2.50-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1nl9-989-2.40-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1nl9-989-2.40-d-1-s | DS | PTN1\_HUMAN | [26] |
| PTP1b-1nny-515-2.40-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1no6-794-2.40-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1no6-794-2.40-d-1-s | DS | PTN1\_HUMAN | [26] |
| PTP1b-1nwl-964-2.40-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1nwl-964-2.40-d-1-s | DS | PTN1\_HUMAN | [26] |
| PTP1b-1nz7-901-2.40-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1ony-588-2.15-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1ony-588-2.15-d-1-s | DS | PTN1\_HUMAN | [26] |
| PTP1b-1onz-968-2.40-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1onz-968-2.40-d-1-s | DS | PTN1\_HUMAN | [26] |
| PTP1b-1ph0-418-2.20-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1ph0-418-2.20-d-2 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1ph0-418-2.20-d-2-s | DS | PTN1\_HUMAN | [26] |
| PTP1b-1pxh-sna-2.15-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1pyn-941-2.20-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1q1m-234-2.60-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1q6j-335-2.20-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1q6j-335-2.20-d-1-s | DS | PTN1\_HUMAN | [26] |
| PTP1b-1q6m-p27-2.20-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1q6m-p27-2.20-d-1-s | DS | PTN1\_HUMAN | [26] |
| PTP1b-1q6n-p90-2.10-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1q6n-p90-2.10-d-1-s | DS | PTN1\_HUMAN | [26] |
| PTP1b-1q6p-213-2.30-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1q6s-214-2.20-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1q6s-214-2.20-d-1-s | DS | PTN1\_HUMAN | [26] |
| PTP1b-1q6t-600-2.30-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-1qxk-429-2.30-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-2bgd-t1d-2.40-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-2cne-dfj-1.80-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-2cne-dfj-1.80-d-1-s | DS | PTN1\_HUMAN | [26] |
| PTP1b-2cne-dfj-1.80-d-2 | DS | PTN1\_HUMAN | [26] |
| PTP1b-2cne-dfj-1.80-d-2-s | DS | PTN1\_HUMAN | [26] |
| PTP1b-2cnf-f32-2.20-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-2cnf-f32-2.20-d-1-s | DS | PTN1\_HUMAN | [26] |
| PTP1b-2cnf-f32-2.20-d-2 | DS | PTN1\_HUMAN | [26] |
| PTP1b-2cnf-f32-2.20-d-2-s | DS | PTN1\_HUMAN | [26] |
| PTP1b-2cng-ize-1.90-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-2cng-ize-1.90-d-1-s | DS | PTN1\_HUMAN | [26] |
| PTP1b-2cnh-izb-1.80-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-2cnh-izb-1.80-d-1-s | DS | PTN1\_HUMAN | [26] |
| PTP1b-2cni-izf-2.00-d-1 | DS | PTN1\_HUMAN | [26] |
| PTP1b-2cni-izf-2.00-d-1-s | DS | PTN1\_HUMAN | [26] |
| PTP2b-1g7f-inz-1.80-d-1 | DS | PTN1\_HUMAN | [26] |
| LS3-03b-1C85-1-model | LS | PTN1\_HUMAN | [26] |
| LS3-03b-1C85-2-model | LS | PTN1\_HUMAN | [26] |
| LS3-03b-1PH0-model | LS | PTN1\_HUMAN | [26] |
| LS3-03b-1PYN-model | LS | PTN1\_HUMAN | [26] |
| LS3-03b-1Q6S-model | LS | PTN1\_HUMAN | [26] |
| LS3-03b-1T49-model | LS | PTN1\_HUMAN | [26] |
| LS3-03b-2CM7-model | LS | PTN1\_HUMAN | [26] |
| LS3-03b-2CNG-model | LS | PTN1\_HUMAN | [26] |
| LS3-03b-2F71-model | LS | PTN1\_HUMAN | [26] |
| LS3-03b-2QBS-model | LS | PTN1\_HUMAN | [26] |
| IKK2-3rzf-xnm-4.00-n-1 | DS | Q6INT1\_XENLA | [27] |
| IKK2-N001-6 | DS | Q6INT1\_XENLA | [27] |
| 5a-red-R003-2 | DS | S5A2\_HUMAN | [28] |
| 5a-red-R003-4 | DS | S5A2\_HUMAN | [28] |
| STS-LS3.12-model10-mostafa-2012a-21-maltais-2009a-55-XVols-binding-site | LS | STS\_HUMAN | [29] |
| STS-LS3.12-model11-lehr-2005a-4f-nussbaumer-2003b-6g | LS | STS\_HUMAN | [29] |
| STS-LS3.12-model12-mostafa-2012a-21-maltais-2009a-55-XVols-binding-site-HBD | LS | STS\_HUMAN | [29] |

1 not published. 2 in preparation.

S-2. Supplementary Figures

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**Figure S 1**. Enrichment of known DHC targets (known DHC biological space) in differently scored predictions for DHC chemical space. (A) Predictions made with stand-alone Ph-DB. (B) Predictions made with SEA, STP, and SP combined, and all four approaches combined with the consensus score of two (C) and three applied (D). Previously known DHC targets are highlighted with green, and targets selected for in vitro evaluation during this study with red overlays.

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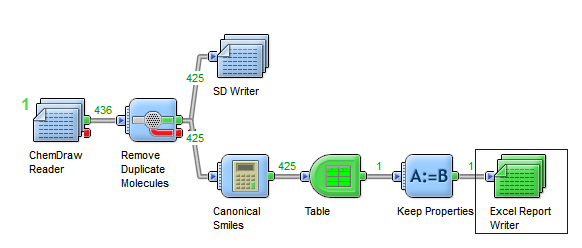
**Figure S 2**. Metrics computed for the isolated and combined target prediction tools.

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**Figure S 3**. Six potential protein targets for DHCs input to STRING, which creates a network of both direct and functional protein-protein interactions [30].

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**Figure S 4**. Results of other protein targets tested in the course of this study due to assay availability shown as bar charts. Compounds **1** – **10** indicated with the respective means (*n* = 3) of percent inhibition at 10 µM (0 – 100%) and standard deviation. Black dashed line again indicates arbitrarily chosen 30% activity cut-off. DMSO was used to measure baseline enzyme activities, on which samples were normalized (not shown) and positive controls (PC) were used as indicated in Materials and Methods.



**Figure S 5**. Pipeline Pilot protocol ‘*chemdraw\_to\_sd\_smiles\_fabian.xml*’ used to convert ChemDraw’s native file format ‘*.cdx*’ to an ‘*.sdf*’-file and a ‘*.csv*’ table with isomeric smiles codes while maintaining issued stereochemistry. Removal of duplicate entries is necessary, since various names of the compounds can be found in literature, and consequently in the hand-drawn library. The protocol is further provided on GitHub (https://github.com/fmayr/DHC\_TargetPrediction).

**Table S 2.** Parameter settings used for the Ligand Profiler protocol used in parallel VS with Discovery Studio.

|  |  |  |
| --- | --- | --- |
| Protocol Settings | Protocol.pr\_xml |  |
|  | Input Ligands | DHC\_full.sdf |
|  | Input LigandProfilerDB Pharmacophores |  |
|  | Input PharmaDB Pharmacophores |  |
| Model Selection | Most Selective |  |
|  | Conformation Generation | BEST |
| Maximum Conformations | 255 |  |
| Discard Existing Conformations | WAHR |  |
| Energy Threshold | 20 |  |
| Ring Fragments File |  |  |
| Save Conformations | FALSCH |  |
|  | Advanced |  |
| Input Type | Ligands |  |
| Input Database | Sample |  |
| Input Database Limit Hits | First N |  |
| Input Database Maximum | 300 |  |
| Input Database Hitlist |  |  |
| Fitting Method | Rigid |  |
| Maximum Omitted Features | 0 |  |
| Minimum Interfeature Distance | 0.00001 |  |
| Scale Fit Values | WAHR |  |
| Prune Empty Fits | WAHR |  |
| Prune Missed Molecules | WAHR |  |
| Keep Input Conformations | FALSCH |  |
| Save Aligned Ligands | FALSCH |  |
| Activity Property |  |  |
| Catalyst Parameter File |  |  |
|  | Parallel Processing | FALSCH |

S-3. File Scheme

**Table S 3.** Files used and produced during this study. Every file is freely available at GitHub (https://github.com/fmayr/DHC\_TargetPrediction). For greater clarity, a file scheme is provided in Supplementary Information S-2 describing all dependencies.

|  |  |  |
| --- | --- | --- |
| File Name | Contains | Subfolder |
| DHC\_full.csv | DHC chemical space as csv-file (name, smiles). | /dataset |
| DHC\_full.sdf | DHC chemical space as 3D-molecule files. | /dataset |
| DHC\_full\_lit\_network.csv | Known DHC biological space and result of bioactivity mining. Ready to be imported to Cytoscape. | /bioactivity%20mining |
| DHC\_full\_online.csv | Result produced by online target prediction servers (SEA, STP, SP) and DHC\_full.csv as input. | /TarPredCrawler |
| DHC\_full\_LS\_mergedhits.csv | Csv-file of hitlists produced by LigandScout models in Ph-DB. | /pharmacophore-based parallel VS |
| DHC\_full\_ligandprofiler.csv | Csv-file of hitlists produced by Discovery Studio model in Ph-DB. | /pharmacophore-based parallel VS |
| DHC\_full\_inhouse.csv | Joined results of LigandScout and Discovery Studio outputs. | /pharmacophore-based parallel VS |
| DHC\_full\_pivoted.csv | Joined results of SEA, STP, SP, and Ph-DB predictions for DHC chemical space. |  |
| DHC\_10\_pivoted.csv | DHC\_full\_pivoted.csv filtered for compounds 1 – 10. |  |
| DHC\_10\_network.csv | DHC\_10\_pivoted.csv joined with DHC\_full\_lit\_network.csv. Network file ready to be imported to Cytoscape. Contains known and predicted compound-target associations. |  |
| Bioactivity\_network\_generator\_SMILES.py | Python script used for literature mining. For installation instruction see README. |  |
| TarPredCrawler.py | Python script used for submitting and collecting results from SEA, STP, and SP. |  |
| DHC\_targetpreidction\_datatreatment.ipynb | Jupyter Notebook containing all data treatment and plotting performed in this study. |  |

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**Figure S 6**. File scheme describing the course of this study. All files are available for download on GitHub (https://github.com/fmayr/DHC\_TargetPrediction), relative paths are written in italics.

S-4. Quality Control of Compounds 1-10



**Figure S 7**. Phloretin (1) CAS: 60-82-2‎



**Figure S 8**. 3-OH-phloretin (2) CAS: 57765-66-9



**Figure S 9**. 2',6'-dihydroxy-4'-methoxy DHC (3) CAS: 35241-55-5



**Figure S 10**. Asebogenin (4) CAS: 35241-54-4



**Figure S 11**. Calomelanen (5) CAS: 520-42-3



**Figure S 12**. Sieboldin (6) CAS: 18777-73-6



**Figure S 13**. Phloridzin (7) CAS: 60-81-1



**Figure S 14**. Trilobatin (8) CAS: 4192-90-9.



**Figure S 15**. Phloretin-2'-xyloglucoside (9) CAS: 145758-09-4.



**Figure S 16**. Neohesperidin DHC (10) CAS: 20702-77-6.

S-5. Positive Controls

**Table S 4**. Positive controls used during this study.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Assay | Name | CAS | Structure | Ref. |
| 3β HSD1 | Trilostane | 13647-35-3 |  | [31,32] |
| 11β HSD1  11β HSD2 | 18β-Glycyrrhetinic acid | 471-53-4 |  | [33] |
| 17β HSD2  17β HSD4 | compound 19 | 1340482-23-6 |  | [34] |
| 17β HSD3 | compound 24 | 873206-61-2 |  | [35] |
| 5-LO | Zileuton | 111406-87-2 |  | [36] |
| aromatase | anastrozole | 120511-73-1 |  | [37] |
| AKR1C3 | compound 2-9 | 745028-76-6 |  | [3] |
| COX-1 | Indomethacin | 53-86-1 |  | [38] |
| CYP17A1 | Abiraterone | 154229-19-3 |  | [31,32] |
| sEH | AUDA | 479413-70-2 |  | [14] |

S-6. Referneces

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