Supplementary Materials

Identification of tyrosinase inhibitors and their structure-activity relationships via evolutionary chemical binding similarity and structure-based methods

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Figure S1. The two-dimensional structures of the molecules other than the top seven tyrosinase inhibitors tested in our study.
Figure S2. The precision-recall (PR) curves of the pharmacophore model M10 for its multiple validation sets.
Figure S3. The receiver operating characteristic (ROC) curves of the pharmacophore model M10 for its multiple validation sets.
Figure S4. The new actives other than the two representative chemicals are mapped in the chosen pharmacophore model M10.
**Figure S5.** The tyrosinase sequences related to food products in the PDB ids 1BUG (Sweet potato), 2Y9X (Mushroom), 6ELS (Apple), and 6HQI (Tomato) were aligned with the sequence of human tyrosinase. The conserved residues in their active sites are highlighted in black. Sequence numbers of human tyrosinase are labeled at the right end of the sequence. Green color represents the identical residues that are not located in the active site, and cyan represents the residues that are not in the active site but conserved in many species. The three residues (Glu256, Asn260, and His263) indicated by orange dotted lines are from mushroom tyrosinase that shows interactions with inhibitors in molecular docking (Figure S6). These three residues correspond to Glu345, Asn364, and His367 in human tyrosinase that also exhibits interactions with the inhibitors in molecular docking (Figure 4).
Figure S6. Molecular docking performed for the two representative inhibitors in the mushroom tyrosinase crystal structure (PDB id: 2Y9X). The tyrosinase inhibitors and tyrosinase amino acids are shown as cyan and grey sticks, respectively. The pi-pi interactions and hydrogen bonds are shown as dotted lines. Only the interacting residues are shown for clarity by hiding the Cu ions, and other tyrosinase residues in the surface background of mushroom tyrosinase’s active site.
Table S1. The pharmacophore fit values for all the previous inactives of human tyrosinase given in the table were zero.

| Chemical ID | BindingDB MonomerID |
|-------------|---------------------|
| Molecule    | 50218206            |
| Molecule1   | 50218205            |
| Molecule4   | 50218210            |
| Molecule6   | 85774               |
| Molecule7   | 50031467            |
| Molecule9   | 50242238            |
| Molecule10  | 50139366            |
| Molecule11  | 50139367            |
| Molecule12  | 50139368            |
| Molecule14  | 50139370            |
| Molecule15  | 60953               |
| Molecule24  | 50065387            |
| Molecule25  | 50351096            |
| Molecule26  | 50180259            |
| Molecule27  | 50180261            |
| Molecule28  | 50193668            |
| Molecule29  | 50193669            |
| Molecule30  | 50193670            |
| Molecule32  | 50108046            |
| Molecule33  | 50193673            |
| Molecule34  | 50193672            |
| Molecule35  | 50219502            |
| Molecule36  | 50269344            |
| Molecule37  | 50269342            |
| Molecule  | ID      |
|----------|---------|
| 38       | 50269341|
| 53       | 50067044|
| 55       | 50067028|
| 56       | 50296394|
| 57       | 50264832|
| 58       | 50296395|
| 60       | 50174558|
| 61       | 50176525|
| 62       | 50096003|
| 68       | 50366429|
| 69       | 50287120|
| 70       | 50287121|
| 76       | 50287128|
| 77       | 60928   |
| 78       | 50176696|
| 79       | 50370694|
| 80       | 50176698|
| 81       | 50176699|
| 82       | 50176700|
| 83       | 50176701|
| 84       | 50205806|
| 85       | 50205807|
| 86       | 50205814|
| 87       | 50205815|

Table S1 continued…
Table S2. The PR AUC values of the 40 pharmacophore models are given.

Table S2 continued…

| Model | New actives, previous actives, new inactives, previous inactives and decoys | New actives, new inactives, previous inactives and decoys | New actives and Previous inactives | Previous actives and previous inactives | New actives and previous actives | Training set—new actives and new inactives (1 moderately active SPB03333 is considered positive) | New actives, new inactives, previous inactives and decoys (1 moderately active SPB03333 is considered positive) |
|-------|--------------------------------------------------------------------------------|----------------------------------------------------------|----------------------------------|----------------------------------------|----------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| M1    | 0.39                                                                           | 0.13                                                     | 0.15                             | 0.56                                   | 0.72                             | 0.26                                                                           | 0.95                                                                           |
| M2    | 0.43                                                                           | 0.10                                                     | 0.12                             | 0.42                                   | 0.76                             | 0.15                                                                           | 0.86                                                                           |
| M3    | 0.33                                                                           | 0.60                                                     | 0.65                             | 0.97                                   | 0.58                             | 0.55                                                                           | 0.97                                                                           |
| M4    | 0.36                                                                           | 0.49                                                     | 0.57                             | 1                                      | 0.58                             | 0.43                                                                           | 0.93                                                                           |
| M5    | 0.43                                                                           | 0.39                                                     | 0.43                             | 0.86                                   | 0.75                             | 0.37                                                                           | 0.95                                                                           |
| M6    | 0.37                                                                           | 0.10                                                     | 0.13                             | 0.42                                   | 0.69                             | 0.17                                                                           | 0.91                                                                           |
| M7    | 0.32                                                                           | 0.68                                                     | 0.78                             | 0.97                                   | 0.57                             | 0.79                                                                           | 0.95                                                                           |
| M8    | 0.37                                                                           | 0.48                                                     | 0.54                             | 1                                      | 0.58                             | 0.43                                                                           | 0.92                                                                           |
| M9    | 0.25                                                                           | 0.07                                                     | 0.08                             | 0.30                                   | 0.56                             | 0.25                                                                           | 0.88                                                                           |
| M10   | 0.32                                                                           | 0.75 ( .92 if one moderately active molecule SPB03333 is considered active) | 0.93                             | 1                                      | 0.64                             | 0.88 ( .9 if 1 moderately active SPB03333 is included) | 0.95                                                                           |
| M11   | 0.35                                                                           | 0.75                                                     | 0.84                             | 0.97                                   | 0.58                             | 0.76                                                                           | 0.95                                                                           |
| M12   | 0.43                                                                           | 0.52                                                     | 0.66                             | 0.69                                   | 0.72                             | 0.59                                                                           | 0.88                                                                           |
| M13   | 0.41                                                                           | 0.35                                                     | 0.40                             | 0.74                                   | 0.70                             | 0.38                                                                           | 0.94                                                                           |
| M14   | 0.35                                                                           | 0.11                                                     | 0.13                             | 0.42                                   | 0.72                             | 0.19                                                                           | 0.86                                                                           |
| M15   | 0.36                                                                           | 0.74                                                     | 0.79                             | 0.95                                   | 0.57                             | 0.55                                                                           | 0.97                                                                           |
| M16   | 0.40                                                                           | 0.14                                                     | 0.16                             | 0.53                                   | 0.72                             | 0.26                                                                           | 0.95                                                                           |
| M17   | 0.38                                                                           | 0.20                                                     | 0.21                             | 0.54                                   | 0.70                             | 0.27                                                                           | 0.92                                                                           |
| M18   | 0.45                                                                           | 0.12                                                     | 0.14                             | 0.51                                   | 0.80                             | 0.15                                                                           | 0.87                                                                           |
| M19   | 0.40                                                                           | 0.15                                                     | 0.19                             | 0.45                                   | 0.72                             | 0.19                                                                           | 0.91                                                                           |
| M20   | 0.42                                                                           | 0.20                                                     | 0.22                             | 0.53                                   | 0.70                             | 0.26                                                                           | 0.92                                                                           |
|   | M21 | M22 | M23 | M24 | M25 | M26 | M27 | M28 | M29 | M30 | M31 | M32 | M33 | M34 | M35 | M36 | M37 | M38 | M39 | M40 |
|---|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|   | 0.37| 0.48| 0.43| 0.27| 0.30| 0.22| 0.44| 0.32| 0.43| 0.39| 0.31| 0.28| 0.41| 0.40| 0.39| 0.36| 0.42| 0.36| 0.42| 0.39|
|   | 0.20| 0.49| 0.52| 0.46| 0.23| 0.05| 0.14| 0.76| 0.19| 0.10| 0.63| 0.45| 0.19| 0.02| 0.47| 0.08| 0.04| 0.72| 0.24| 0.39|
|   | 0.21| 0.59| 0.66| 0.54| 0.28| 0.06| 0.18| 0.85| 0.20| 0.12| 0.69| 0.52| 0.20| 0.03| 0.52| 0.09| 0.06| 0.89| 0.25| 0.39|
|   | 0.53| 0.80| 0.69| 0.69| 0.40| 0.38| 0.41| 0.85| 0.55| 0.40| 0.70| 0.97| 0.57| 0.12| 0.75| 0.41| 0.23| 0.97| 0.72| 0.43|
|   | 0.71| 0.81| 0.73| 0.55| 0.57| 0.75| 0.74| 0.58| 0.79| 0.77| 0.56| 0.62| 0.79| 0.62| 0.73| 0.66| 0.57| 0.58| 0.72| 0.86|
|   | 0.26| 0.61| 0.59| 0.44| 0.34| 0.15| 0.18| 0.86| 0.26| 0.15| 0.72| 0.50| 0.50| 0.11| 0.48| 0.14| 0.24| 0.97| 0.56| 0.39|
|   | 0.91| 0.87| 0.90| 0.80| 0.70| 0.70| 0.90| 0.93| 0.95| 0.91| 0.81| 0.91| 0.91| 0.56| 0.88| 0.98| 0.88| 0.94| 0.90| 0.85|
|   | 0.19| 0.64| 0.64| 0.48| 0.22| 0.06| 0.16| 0.85| 0.19| 0.12| 0.72| 0.50| 0.50| 0.03| 0.58| 0.09| 0.05| 0.88| 0.26| 0.44|
|   |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |      |