Supporting Information

Discovery of human TyrRS inhibitors by structure-based virtual screening, structural optimization, and bioassays

Shenzhen Huang\textsuperscript{a,†}, Xiang Wang\textsuperscript{b,c,†}, Guifeng Lin\textsuperscript{a}, Jie Cheng\textsuperscript{a}, Xiuli Chen\textsuperscript{a}, Weining Sun\textsuperscript{d}, Rong Xiang\textsuperscript{b}, Yamei Yu\textsuperscript{a}, Linli Li\textsuperscript{d}, and Shengyong Yang\textsuperscript{a,⁎}

\textsuperscript{a} State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University/Collaborative Innovation Center of Biotherapy, Chengdu, Sichuan 610041, China.

\textsuperscript{b} Department of Clinical Medicine, School of Medicine, Nankai University, Tianjin 300071, China.

\textsuperscript{c} Department of Chemistry, Fudan University, Shanghai 200433, China.

\textsuperscript{d} Key Laboratory of Drug Targeting and Drug Delivery System of Ministry of Education, West China School of Pharmacy, Sichuan University, Chengdu, Sichuan 610041, China.

* To whom correspondence should be addressed. Tel.: +86-28-85164063; Fax: +86-28-85164060; E-mail: yangsy@scu.edu.cn

† These authors contributed equally to this work.
Supporting Data

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Chemical materials

All reagents were obtained from standard suppliers and used without further purification. The homogeneity of the compounds was monitored by ascending thin layer chromatography (TLC) on silica gel-G (Merck)-coated aluminum plates, visualized by UV light. NMR spectra were measured on a Bruker AM-400. The $^1$H NMR (400 MHz) chemical shifts were given in ppm relative to the internal reference TMS. The $^{13}$C NMR (100 MHz) chemical shifts were given using CDCl$_3$ and DMSO-$d_6$ as the internal standard. ESI-MS spectral data was recorded on a Finnigan LCQDECA and a Bruker Daltonics Bio TOF mass spectrometer.

Scheme S1 Simple synthetic route for all compounds.

Chemical synthesis experiments section

General procedure for the synthesis of compounds (1-12)

5,7-dihydroxy-6,8-diiodo-2-phenyl-4H-chromen-4-one (1a, 0.25 mmol, 1 equivalent), the derivative of benzenethiol (0.5 mmol, 2 equivalent), Pd$_2$(dba)$_3$ (0.0025 mmol, 0.01 equivalent), X-phos (0.005 mmol, 0.02 equivalent) and Cs$_2$CO$_3$ (0.75 mmol, 3 equivalent) were dissolved in $N$, $N$-dimethylformamide (DMF) under
inert gas and the reaction was stirred overnight at 110 °C. The filter catalysts, ligands and inorganic salts were filtered by celite to obtain black solution. After evaporation of the solvent, the sepia residue was dissolved in dichloromethane was extracted with water. The combined organic layers were dried over MgSO₄ and concentrated, and the residue was purified by column chromatography to give the desired product.

5,7-dihydroxy-6,8-diiodo-2-phenyl-4H-chromen-4-one (1a)

5,7-dihydroxy-2-phenyl-4H-chromen-4-one (5.08 g, 20 mmol) and iodine (5.76 g, 20 mmol) were dissolved in dichloromethane (20 mL) and glacial acetic acid (20 mL). The reaction was stirred 30 min at room temperature and the 2 g of 65 % HNO₃ acid was slowly dripped into the stirred solution using a constant pressure dropping funnel. After 2 h, the reaction was filtered, washed with 10% Na₂S₂O₄ solution, then the mixture of water and cold methanol and diethyl ether, and the solvent was removed in vacuo to afford the intermediate compound 1a as a yellow solid (yield 70.0 %). ¹H NMR (400 MHz, DMSO-d₆) δ 14.50 (s, 1H), 8.04 (dd, J = 8.0, 1.6 Hz, 2H), 7.66-7.58 (m, 3H), 7.28 (s, 1H). ¹³C NMR (101 MHz, DMSO) δ 181.6, 163.8, 162.8, 162.0, 155.6, 130.4, 129.4, 126.8, 105.1, 104.7, 66.9. ESI-MS m/z: 506.04 [M+H]⁺.

6,8-bis((3-bromophenyl)thio)-5,7-dihydroxy-2-phenyl-4H-chromen-4-one (1)

Follow the general method described above (yield 46.0 %). ¹H NMR (400 MHz, CDCl₃) δ 14.26 (s, 1H), 7.81 (d, J = 7.4 Hz, 2H), 7.53 (dt, J = 14.7, 7.1 Hz, 3H), 7.36 (d, J = 14.4 Hz, 2H), 7.33-7.27 (m, 2H), 7.20-7.06 (m, 4H), 6.79 (s, 1H). ESI-MS m/z: 626.59 [M+H]⁺.

6,8-bis((2-bromophenyl)thio)-5,7-dihydroxy-2-phenyl-4H-chromen-4-one (2)
Follow the general method described above (yield 48.1 %). $^1$H NMR (400 MHz, DMSO) $\delta$ 14.28 (s, 1H), 11.29 (s, 1H), 7.90 (s, 2H), 7.56 (d, $J = 41.7$ Hz, 5H), 7.23 (s, 3H), 7.07 (s, 2H), 6.79 (d, $J = 33.6$ Hz, 2H). ESI-MS m/z: 626.60 [M+H]$^+$. 

**5,7-dihydroxy-6,8-bis((2-methoxyphenyl)thio)-2-phenyl-4H-chromen-4-one (3)**

Follow the general method described above (yield 51.9 %). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 14.16 (s, 1H), 10.76 (s, 1H), 7.89 (d, $J = 6.5$ Hz, 2H), 7.62-7.43 (m, 3H), 7.19 (s, 1H), 7.15-6.97 (m, 4H), 6.80 (d, $J = 8.6$ Hz, 2H), 6.70 (d, $J = 6.8$ Hz, 1H), 6.58 (d, $J = 7.1$ Hz, 1H), 3.93 (s, 3H), 3.88 (s, 3H). ESI-MS m/z: 528.84 [M-H]$^-$. 

**5,7-dihydroxy-6,8-bis((3-methoxyphenyl)thio)-2-phenyl-4H-chromen-4-one (4)**

Follow the general method described above (yield 54.2 %). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 14.26 (s, 1H), 11.02 (s, 1H), 7.96 (s, 2H), 7.56 (d, $J = 20.7$ Hz, 3H), 7.19 (d, $J = 14.6$ Hz, 3H), 6.67 (dd, $J = 25.1$, 16.5 Hz, 6H), 3.67 (d, $J = 6.6$ Hz, 6H). $^{13}$C NMR (101 MHz, DMSO) $\delta$ 182.62, 165.57, 163.94, 160.20, 160.11, 159.19, 138.35, 138.24, 132.89, 130.62, 130.41, 129.67, 126.85, 118.61, 118.48, 111.93, 111.89, 111.79, 111.29, 106.00, 101.13, 96.24, 55.56, 55.54. ESI-MS m/z: 528.89 [M-H]$^-$. 

**6,8-bis((4-fluorophenyl)thio)-5,7-dihydroxy-2-phenyl-4H-chromen-4-one (5)**

Follow the general method described above (yield 42.0 %). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 14.18 (s, 1H), 7.82 (dd, $J = 18.6$, 6.3 Hz, 2H), 7.63-7.41 (m, 3H), 7.31 (s, 2H), 7.11 (s, 2H), 6.97 (m, 4H), 6.77 (s, 1H). ESI-MS m/z: 504.89 [M-H]$^-$. 

**5,7-dihydroxy-2-phenyl-6,8-bis(p-tolylthio)-4H-chromen-4-one (6)**

Follow the general method described above (yield 48.1 %). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 14.20 (s, 1H), 10.91 (s, 1H), 7.95 (d, $J = 7.5$ Hz, 2H), 7.64-7.58 (m, 1H),
7.53 (t, J = 7.4 Hz, 2H), 7.19 (s, 1H), 7.09 (s, 4H), 7.03 (d, J = 8.2 Hz, 2H), 2.23 (s, 3H), 2.20 (s, 3H). ESI-MS m/z: 497.89 [M-H].

6,8-bis((3-fluorophenyl)thio)-5,7-dihydroxy-2-phenyl-4H-chromen-4-one (7)

Follow the general method described above (yield 48.0 %). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 14.34 (s, 1H), 11.17 (s, 1H), 7.96 (d, J = 6.6 Hz, 2H), 7.56 (dd, J = 20.0, 6.3 Hz, 3H), 7.30 (d, J = 6.3 Hz, 2H), 7.23 (s, 1H), 6.95 (dd, J = 42.7, 25.2 Hz, 6H).

$^{13}$C NMR (101 MHz, DMSO) $\delta$ 182.7, 177.5, 163.4, 161.8, 161.0, 138.0, 131.1, 130.5, 130.1, 128.3, 127.3, 122.9, 113.6, 109.2, 104.8, 101.3. ESI-MS m/z: 504.85 [M-H].

5,7-dihydroxy-2-phenyl-6,8-bis(o-tolylthio)-4H-chromen-4-one (8)

Follow the general method described above (yield 45.9 %). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 14.14 (s, 1H), 7.91 (s, 1H), 7.72 (d, J = 7.5 Hz, 2H), 7.51 (d, J = 6.9 Hz, 1H), 7.44 (t, J = 7.3 Hz, 2H), 7.19 (t, J = 7.1 Hz, 2H), 7.14-6.93 (m, 4H), 6.86 (d, J = 7.5 Hz, 1H), 6.79 (d, J = 7.6 Hz, 1H), 6.76 (s, 1H), 2.55 (s, 3H), 2.53 (s, 3H). ESI-MS m/z: 497.86 [M-H].

6,8-bis((4-(tert-butyl)phenyl)thio)-5,7-dihydroxy-2-phenyl-4H-chromen-4-one (9)

Follow the general method described above (yield 36.0 %). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 14.13 (s, 1H), 8.09 (s, 1H), 7.79 (d, J = 7.5 Hz, 2H), 7.58 -7.50 (m, 1H), 7.47 (d, J = 7.6 Hz, 2H), 7.28 (m, 3H), 7.25-7.13 (m, 5H), 6.75 (s, 1H), 1.27 (s, 9H), 1.25 (s, 9H). ESI-MS m/z: 581.03 [M-H].

5,7-dihydroxy-2-phenyl-6,8-bis(pyridin-4-ylthio)-4H-chromen-4-one (10)

Follow the general method described above (yield 48.0 %). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 14.35 (s, 1H), 11.94 (s, 1H), 8.27 (s, 4H), 7.87 (d, J = 7.3 Hz, 2H), 7.50
(dd, J = 12.9, 7.1 Hz, 3H), 7.13 (s, 2H), 7.05 (s, 2H), 6.91 (s, 1H). ESI-MS m/z: 410.88 [M-H].

5,7-dihydroxy-6,8-bis((3-hydroxyphenyl)thio)-2-phenyl-4H-chromen-4-one (11)

Follow the general method described above (yield 42.0 %). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 14.19 (s, 1H), 10.96 (s, 1H), 9.34 (s, 1H), 9.31 (s, 1H), 7.90 (d, J = 7.4 Hz, 2H), 7.54 (d, J = 7.3 Hz, 1H), 7.49 (t, J = 7.3 Hz, 2H), 7.01 (dd, J = 16.0, 8.0 Hz, 3H), 6.61 (d, J = 8.0 Hz, 1H), 6.54-6.49 (m, 2H), 6.44 (s, 3H). $^{13}$C NMR (101 MHz, DMSO) δ 182.6, 176.5, 163.1, 161.9, 159.8, 138.7, 132.1, 130.5, 130.1, 129.3, 127.3, 122.8, 112.4, 109.3, 104.5, 101.2. ESI-MS m/z: 500.85 [M-H].

5,7-dihydroxy-6,8-bis((2-hydroxyphenyl)thio)-2-phenyl-4H-chromen-4-one (12)

Follow the general method described above (yield 42.2 %). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 14.13 (s, 1H), 10.36 (s, 3H), 7.99 (d, J = 7.3 Hz, 2H), 7.60 (s, 1H), 7.54 (d, J = 7.6 Hz, 2H), 7.14 (s, 1H), 6.98 (d, J = 6.8 Hz, 2H), 6.90-6.57 (m, 6H). ESI-MS m/z: 500.88 [M-H].

General procedure for the synthesis of compounds (14-22)

Compounds 14-22 were prepared in a manner similar to that described for 1-12.

5,7-dimethoxy-2-phenyl-4H-chromen-4-one (13a)

5,7-dihydroxy-2-phenyl-4H-chromen-4-one (2.54 g, 10 mmol), iodomethane (1.87 mL, 30 mmol) and $\text{K}_2\text{CO}_3$ (4.10 g, 30 mmol) were dissolved in dry DMF under inert gas and the reaction was stirred overnight at room temperature. Dichloromethane (100 mL) and HCl (0.1M, 50 mL) were added into reaction mixture to obtain the organic layers by filtration, and the solvent was removed in vacuo to afford the
intermediate compound 13a as a yellow solid (yield 80 %). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.05 (dd, $J = 7.6$, 1.9 Hz, 2H), 7.57 (dd, $J = 5.8$, 4.8 Hz, 3H), 6.87 (d, $J = 2.2$ Hz, 1H), 6.78 (s, 1H), 6.52 (d, $J = 2.2$ Hz, 1H), 3.91 (s, 3H), 3.84 (s, 3H).

8-iodo-5,7-dimethoxy-2-phenyl-4H-chromen-4-one (13b)

13a (1.41 g, 5 mmol) and NIS (1.35 g, 6 mmol) were dissolved in Trifluoroacetic acid (TFA) and the reaction was stirred overnight at 80 °C. Then, the solid was separated out by adding the superfluous ethyl acetate. After filtration of the solvent, the residue was washed by saturated sodium bicarbonate, water, ethyl alcohol and diethyl ether to obtained the intermediate compound 13b as a white solid (yield 70 %). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.18 (s, 2H), 7.59 (s, 3H), 6.88 (s, 1H), 6.72 (s, 1H), 4.03 (s, 3H), 3.95 (s, 3H).

8-((3-bromophenyl)thio)-7-hydroxy-5-methoxy-2-phenyl-4H-chromen-4-one (14)

Follow the general method described above (yield 30.2 %). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 11.40 (s, 1H), 7.84 (d, $J = 7.1$ Hz, 2H), 7.53-7.43 (m, 3H), 7.29 (dd, $J = 7.2$, 0.9 Hz, 2H), 7.19 (t, $J = 8.1$ Hz, 1H), 7.10 (d, $J = 7.7$ Hz, 1H), 6.82 (s, 1H), 6.65 (s, 1H), 3.89 (s, 3H). ESI-MS m/z: 452.98 [M-H]$^{-}$.

8-((3-fluorophenyl)thio)-7-hydroxy-5-methoxy-2-phenyl-4H-chromen-4-one (15)

Follow the general method described above (yield 28.0 %). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 11.38 (s, 1H), 7.88-7.81 (m, 2H), 7.52-7.42 (m, 3H), 7.28 (s, 1H), 6.97-6.88 (m, 3H), 6.83 (s, 1H), 6.65 (s, 1H), 3.89 (s, 3H). ESI-MS m/z: 392.85 [M-H]$^{-}$.

8-((4-fluorophenyl)thio)-7-hydroxy-5-methoxy-2-phenyl-4H-chromen-4-one (16)

Follow the general method described above (yield 33.1 %). $^1$H NMR (400 MHz,
DMSO-$d_6$ δ 11.21 (s, 1H), 7.99-7.76 (m, 2H), 7.65-7.41 (m, 4H), 7.24 (d, $J = 9.2$ Hz, 2H), 6.93 (d, $J = 9.1$ Hz, 2H), 6.80 (s, 1H), 6.60(s, 1H), 3.83 (s, 3H), 3.64 (s, 3H). ESI-MS m/z: 392.90 [M-H].

7-hydroxy-5-methoxy-8-((3-methoxyphenyl)thio)-2-phenyl-4H-chromen-4-one (17)

Follow the general method described above (yield 43.1 %). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 11.25 (s, 1H), 7.85 (d, $J = 7.4$ Hz, 2H), 7.56-7.41 (m, 3H), 7.15 (t, $J = 8.2$ Hz, 1H), 6.81 (s, 1H), 6.66 (d, $J = 12.9$ Hz, 4H), 3.88 (s, 3H), 3.66 (s, 3H). ESI-MS m/z: 405.02 [M-H].

8-((2-fluorophenyl)thio)-7-hydroxy-5-methoxy-2-phenyl-4H-chromen-4-one (18)

Follow the general method described above (yield 28.9 %). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 11.39 (s, 1H), 7.89-7.79 (m, 2H), 7.48 (dt, $J = 22.0$, 7.1 Hz, 3H), 7.24 (dd, $J = 9.9$, 8.7 Hz, 1H), 7.19-7.09 (m, 1H), 7.07-6.97 (m, 1H), 6.82 (s, 1H), 6.78 (td, $J = 7.9$, 1.5 Hz, 1H), 6.65 (s, 1H), 3.88 (s, 3H). ESI-MS m/z: 405.06 [M-H].

8-((2-bromophenyl)thio)-7-hydroxy-5-methoxy-2-phenyl-4H-chromen-4-one (19)

Follow the general method described above (yield 31.1 %). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 11.43 (s, 1H), 7.84-7.75 (m, 2H), 7.64 (dd, $J = 7.9$, 1.1 Hz, 1H), 7.49 (d, $J = 7.3$ Hz, 1H), 7.42 (t, $J = 7.5$ Hz, 2H), 7.20-7.11 (m, 1H), 7.06-6.97 (m, 1H), 6.82 (s, 1H), 6.67 (s, 1H), 6.63 (dd, $J = 8.0$, 1.4 Hz, 1H), 3.90 (s, 3H). ESI-MS m/z: 452.96 [M-H].

7-hydroxy-5-methoxy-8-((2-methoxyphenyl)thio)-2-phenyl-4H-chromen-4-one (20)

Follow the general method described above (yield 35.0 %). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 11.16 (s, 1H), 7.77 (d, $J = 7.5$ Hz, 2H), 7.49 (t, $J = 7.2$ Hz, 1H), 7.42 (t, $J
= 7.5 Hz, 2H), 7.11-6.99 (m, 2H), 6.79 (s, 1H), 6.76-6.69 (m, 1H), 6.65 (s, 1H), 6.52 (d, J = 7.7 Hz, 1H), 3.94 (s, 3H), 3.88 (s, 3H). ESI-MS m/z: 405.12 [M-H].

7-hydroxy-5-methoxy-8-((4-methoxyphenyl)thio)-2-phenyl-4H-chromen-4-one (21)

Follow the general method described above (yield 38.1 %). ^1H NMR (400 MHz, DMSO-d6) δ 11.19 (s, 1H), 7.97-7.89 (m, 2H), 7.57-7.46 (m, 3H), 7.18-7.10 (m, 2H), 6.83 (d, J = 8.9 Hz, 2H), 6.81 (s, 1H), 6.62 (s, 1H), 3.85 (s, 3H), 3.66 (s, 3H). ESI-MS m/z: 405.03 [M-H].

8-((2-chlorophenyl)thio)-7-hydroxy-5-methoxy-2-phenyl-4H-chromen-4-one (22)

Follow the general method described above (yield 30.0 %). ^1H NMR (400 MHz, DMSO-d6) δ 11.42 (s, 1H), 7.78 (d, J = 7.5 Hz, 2H), 7.53-7.45 (m, 2H), 7.42 (t, J = 7.5 Hz, 2H), 7.17-7.04 (m, 2H), 6.81 (s, 1H), 6.69 – 6.63 (m, 2H), 3.89 (s, 3H). ESI-MS m/z: 409.02 [M-H].

General procedure for the synthesis of compounds (23-31)

14 or 15-22 (0.1 mmol, 1 equivalent) were dissolved in dichloromethane (20 ml). Boron tribromide (5.38mmol, 53.8 equivalents) was added and the reaction was stirred overnight at room temperature and then quenched with cold methanol. After regulation of pH value about 10, the water was added for extraction and washed by saturated salt solution. The combined organic layers were dried over MgSO₄ and concentrated, and the solvent was removed in vacuo to afford the desired product.

8-((3-bromophenyl)thio)-5,7-dihydroxy-2-phenyl-4H-chromen-4-one (23)

Follow the general method described above (yield 68.2 %). ^1H NMR (400 MHz, DMSO-d6) δ 13.11 (s, 1H), 10.47 (s, 1H), 7.91 (d, J = 7.0 Hz, 2H), 7.52 (dd, J = 13.6,
7.4 Hz, 3H), 7.19 (dd, J = 20.1, 12.5 Hz, 3H), 7.13 (d, J = 1.7 Hz, 1H), 6.86 (s, 1H), 6.05 (s, 1H). ESI-MS m/z: 438.92 [M-H].

8-((3-fluorophenyl)thio)-5,7-dihydroxy-2-phenyl-4H-chromen-4-one (24)

Follow the general method described above (yield 65.0 %). ¹H NMR (400 MHz, DMSO-d₆) δ 13.24 (s, 1H), 11.58 (s, 1H), 7.91 (d, J = 7.6 Hz, 2H), 7.62-7.54 (m, 1H), 7.50 (t, J = 7.5 Hz, 2H), 7.29 (dd, J = 14.4, 8.0 Hz, 1H), 7.10 (s, 1H), 7.01-6.88 (m, 3H), 6.48 (s, 1H). ESI-MS m/z: 378.72 [M-H].

8-((4-fluorophenyl)thio)-5,7-dihydroxy-2-phenyl-4H-chromen-4-one (25)

Follow the general method described above (yield 75.1 %). ¹H NMR (400 MHz, DMSO-d₆) δ 13.22 (s, 1H), 11.51 (s, 1H), 7.95 (s, 2H), 7.53 (s, 3H), 7.21 (s, 2H), 7.10 (s, 3H), 6.47 (s, 1H). ESI-MS m/z: 378.78 [M-H].

5,7-dihydroxy-8-((3-hydroxyphenyl)thio)-2-phenyl-4H-chromen-4-one (26)

Follow the general method described above (yield 44.9 %). ¹H NMR (400 MHz, DMSO-d₆) δ 10.21 (s, 1H), 9.38 (s, 1H), 7.91 (d, J = 7.0 Hz, 2H), 7.57-7.44 (m, 3H), 7.20 (s, 1H), 7.01 (s, 1H), 6.83 (s, 1H), 6.57 (d, J = 8.0 Hz, 1H), 6.45 (d, J = 6.9 Hz, 1H), 6.00 (s, 1H). ESI-MS m/z: 376.85 [M-H].

8-((2-fluorophenyl)thio)-5,7-dihydroxy-2-phenyl-4H-chromen-4-one (27)

Follow the general method described above (yield 55.3 %). ¹H NMR (400 MHz, DMSO-d₆) δ 13.23 (s, 1H), 11.66 (s, 1H), 7.92 (d, J = 7.3 Hz, 2H), 7.56 (d, J = 7.2 Hz, 1H), 7.51 (t, J = 7.4 Hz, 2H), 7.23 (d, J = 9.3 Hz, 1H), 7.15 (d, J = 7.1 Hz, 1H), 7.11 (s, 1H), 7.02 (t, J = 7.6 Hz, 1H), 6.86 (dd, J = 7.9, 1.3 Hz, 1H), 6.48 (s, 1H). ESI-MS m/z: 378.98 [M-H].
8-((2-bromophenyl)thio)-5,7-dihydroxy-2-phenyl-4H-chromen-4-one (28)

Follow the general method described above (yield 66.5 %). 1H NMR (400 MHz, DMSO-$_d_6$) $\delta$ 13.22 (s, 1H), 11.64 (s, 1H), 7.91 – 7.83 (m, 2H), 7.64 (dd, $J$ = 7.9, 1.1 Hz, 1H), 7.55 (d, $J$ = 7.3 Hz, 1H), 7.48 (t, $J$ = 7.6 Hz, 2H), 7.21-7.13 (m, 1H), 7.11 (s, 1H), 7.02 (td, $J$ = 7.7, 1.5 Hz, 1H), 6.69 (dd, $J$ = 8.0, 1.4 Hz, 1H), 6.51 (s, 1H). ESI-MS m/z: 438.96 [M-H]$^-$.

5,7-dihydroxy-8-((2-hydroxyphenyl)thio)-2-phenyl-4H-chromen-4-one (29)

Follow the general method described above (yield 34.6 %). 1H NMR (400 MHz, DMSO-$_d_6$) $\delta$ 13.12 (s, 1H), 11.34 (s, 1H), 9.28 (s, 1H), 7.91 (d, $J$ = 7.1 Hz, 2H), 7.64 (dd, $J$ = 7.9, 1.1 Hz, 1H), 7.55 (d, $J$ = 7.3 Hz, 1H), 7.28 (t, $J$ = 7.6 Hz, 2H), 7.11-7.03 (m, 1H), 6.91 (s, 1H), 6.82 (td, $J$ = 7.9, 1.6 Hz, 1H), 6.49 (dd, $J$ = 8.0, 1.5 Hz, 1H), 6.45 (s, 1H). ESI-MS m/z: 376.93 [M-H]$^-$.

5,7-dihydroxy-8-((4-hydroxyphenyl)thio)-2-phenyl-4H-chromen-4-one (30)

Follow the general method described above (yield 42.0 %). 1H NMR (400 MHz, DMSO-$_d_6$) $\delta$ 13.16 (s, 1H), 11.37 (s, 1H), 9.41 (s, 1H), 8.01 (d, $J$ = 7.0 Hz, 2H), 7.61-7.52 (m, 3H), 7.12-7.04 (m, 3H), 6.66 (d, $J$ = 8.6 Hz, 2H), 6.45 (s, 1H). ESI-MS m/z: 376.96 [M-H]$^-$.

8-((2-chlorophenyl)thio)-5,7-dihydroxy-2-phenyl-4H-chromen-4-one (31)

Follow the general method described above (yield 48.0 %). 1H NMR (400 MHz, DMSO-$_d_6$) $\delta$ 13.26 (s, 1H), 11.57 (s, 1H), 10.48 (s, 1H), 7.93-7.79 (m, 2H), 7.50 (dd, $J$ = 14.8, 12.3 Hz, 4H), 7.18-7.00 (m, 2H), 6.85 (s, 1H), 6.67 (d, $J$ = 7.3 Hz, 1H), 6.06 (s, 1H). ESI-MS m/z: 394.83 [M-H]$^-$.
Fig. S1 Activity data against TyrRS of resveratrol and hit compounds selected by virtual screening. (A-D) The Ki values of resveratrol, AK-087/41343686, AH-357/03514064, and SKLB2002, respectively.
**Fig. S2** The molecular docking method was validated. Resveratrol was docked into the TyrRS structure (PDB entry 4D93) according to the described protocol and was found in the same conformation as the Resveratrol ligand (yellow) in the crystal structure.
**Fig. S3** The protein TyrRS peak corresponding to homogenous protein in buffer (20 mM Hepes-Na, pH = 7.5, 50 mM NaCl, 2 mM BME) by gel-filtration (Superdex 200; GE-Healthcare) chromatography.
Fig. S4 The quality of protein purification was validated by SDS–PAGE analysis.
Fig. S5 L-tyrosine $K_m$ from time course data.
Fig. S6 Enzyme Titration from time course data.
Fig. S7 (A) Compound 7 promote TyrRS nuclear localization in HeLa cells. Hela cells were treated with compound 7 (1.1, 3.3, 10, or 30 μM), RSV (1μM), or DMSO for 8 h. Cells cultured in serum-free media for 8 h were under serum starvation. Cytoplasmic fraction and nuclear fraction from cells were subjected to immunoblot assays. (B) Nuclear TyrRS prompted by compound 7 protect cells from DNA damage in HeLa cells. Hela cells were pretreated with compound 7 (30, 10, 3.3, 1.1, or 0.34 μM), RSV (10 μM), or DMSO for 24 h. To induced DNA damage, cells were treated with cisplatin (30 μM) or DMSO at the present of previous compounds or DMSO for 24 h. Then whole cell lysates were subjected to immunoblot assays. Quantification of immunoblots was showed below.
Table S1. The GoldScore and Enzyme Activity against TyrRS of 30 candidate compounds.

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<tr>
<th>NO</th>
<th>IDNUMBER</th>
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<th>GoldScore</th>
<th>IDScore</th>
<th>% Enzyme Activity (relative to DMSO controls)</th>
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<td>Data 1</td>
<td>Data 2</td>
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