

SUPPORTING INFORMATION

Discovery of RG7112: a Small-Molecule MDM2 Inhibitor in Clinical Development

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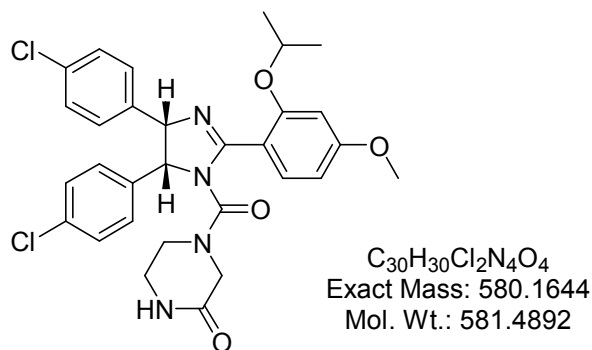
MDM2, p53, RG7112, protein-protein interaction, cancer

General Information

All starting materials were commercially available and used without further purification unless noted otherwise. ¹H NMR and ¹³C NMR spectra were recorded on Varian spectrometer at indicated frequencies. Chemical shifts (δ values) and coupling constants (J values) are given in ppm and hertz, respectively.

Compound 1 (Nutlin-3a)

4-[(4S,5R)-4,5-Bis-(4-chloro-phenyl)-2-(2-isopropoxy-4-methoxy-phenyl)-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one¹

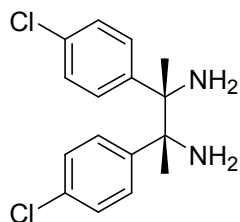


¹H NMR (400 MHz, DMSO-*d*₆) δ 7.93 (br. s, 1H), 7.55 (d, J = 9.04 Hz, 1H), 7.15 (dd, J = 8.53, 14.81 Hz, 4H), 7.06 (d, J = 8.53 Hz, 2H), 6.99 (d, J = 8.53 Hz, 2H), 6.59 - 6.67 (m, 2H), 5.64 - 5.71 (m, 1H), 5.56 - 5.63 (m, 1H), 4.68 - 4.81 (m, 1H), 3.84 (s, 3H), 3.48 - 3.68 (m, 2H), 3.24 - 3.33 (m, 1H), 3.06 - 3.18 (m, 1H), 2.83 (br. s, 2H), 1.21 - 1.31 (m, 6H).

¹³C NMR (100 MHz, DMSO-*d*₆) δ 21.6, 21.7, 38.9, 39.1, 39.3, 39.4, 39.5, 39.7, 39.9, 40.2, 42.1, 48.9, 55.5, 67.8, 69.8, 71.2, 99.4, 104.9, 113.6, 127.4, 127.5, 128.8, 129.7, 131.1, 131.3, 131.9, 136.5, 137.4, 154.6, 156.5, 160.2, 162.3, 165.4.

Compound 3

meso-2,3-bis-(4-chlorophenyl)-2,3-butanediamine²

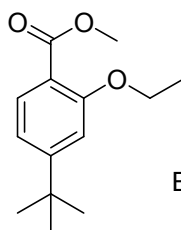


C₁₆H₁₈Cl₂N₂
Exact Mass: 308.0847
Mol. Wt.: 309.2330

¹H NMR (400 MHz, DMSO-*d*₆) δ 1.37 (s, 6H), 1.90 (br. s, 4H), 6.95 - 7.43 (m, 8H).

Compound 4

Methyl 4-*tert*-Butyl-2-ethoxy-benzoate²

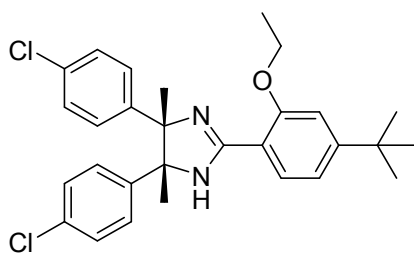


C₁₄H₂₀O₃
Exact Mass: 236.1412
Mol. Wt.: 236.3068

¹H NMR (400 MHz, DMSO-*d*₆) δ 1.30 (s, 9H), 1.33 (t, *J* = 6.90 Hz, 3H), 3.77 (s, 3H), 4.12 (q, *J* = 7.03 Hz, 2H), 6.98 - 7.10 (m, 2H), 7.59 (d, *J* = 8.28 Hz, 1H).

Compound 5

rac-(4*S**,5*R**)-4,5-Bis(4-chlorophenyl)-2-(4-(*tert*-butyl)-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole

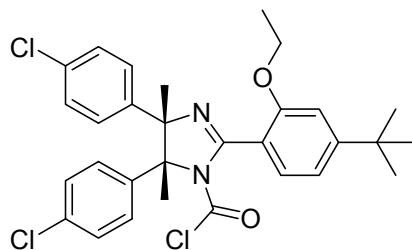


C₂₉H₃₂Cl₂N₂O
Exact Mass: 494.1892
Mol. Wt.: 495.4827

A solution of *meso*-2,3-bis-(4-chlorophenyl)-2,3-butanediamine (2.5 g, 8.08 mmol) in 100 mL of toluene was added to a solution of trimethylaluminum (4 mL, 2M solution in toluene, Aldrich) in 24 mL of toluene at 0 °C. The mixture was stirred 10 min at 0 °C, 20 min at room temperature and then 4-(*tert*-butyl)-2-ethoxy-benzoic acid methyl ester (2.1 g, 8.9 mmol) in 10 mL of toluene was added. The mixture was heated to reflux for 2.5 h then cooled to 0 °C and quenched by drop-wise addition of saturated potassium sodium tartrate solution. The mixture was extracted with ethyl acetate and the ethyl acetate layer washed successively with 10% sodium bicarbonate solution and brine, then dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel, eluting with a 10-50% gradient of ethyl acetate and hexanes provided 710 mg of *rac*-(4*S**,5*R**)-4,5-bis(4-chlorophenyl)-2-(4-(*tert*-butyl)-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole. LR-MS: 495.0 [(M+H)⁺]. ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.35 (s, 9H), 1.39 (t, *J* = 6.90 Hz, 3H), 1.74 (s, 6H), 4.25 (q, *J* = 6.94 Hz, 2H), 7.07 (s, 8H), 7.11 - 7.18 (m, 2H), 7.86 (d, *J* = 8.03 Hz, 1H).

Compound 6

rac-(4*S**,5*R**)-4,5-Bis(4-chlorophenyl)-2-(4-(*tert*-butyl)-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole-1-carbonyl chloride

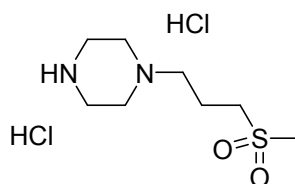


C₃₀H₃₁Cl₃N₂O₂
Exact Mass: 556.1451
Mol. Wt.: 557.9375

To a solution of *rac*-(4*S**,5*R**)-4,5-bis(4-chlorophenyl)-2-(4-(*tert*-butyl)-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole (710 mg, 1.43 mmol) and triethylamine (400 μ L, 2.86 mmol) in 12 mL of dichloromethane at 0 °C was added 1.13 mL of 1.9 M phosgene in toluene solution (Fluka). After stirring for 30 min the mixture was taken up in dichloromethane and washed with water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Purification by chromatography on silica gel, eluting with hexane-ethyl acetate (4:1) provided 689 mg of *rac*-(4*S**,5*R**)-4,5-bis(4-chlorophenyl)-2-(4-(*tert*-butyl)-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-1H-imidazole-1-carbonyl chloride as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 1.43 (s, 9H), 1.51 (br. s, 3H), 1.76 (s, 3H), 2.13 (br. s, 3H), 4.17 - 4.54 (m, 2H), 6.52 - 7.20 (m, 10H), 8.74 (br. s, 1H).

Compound 7

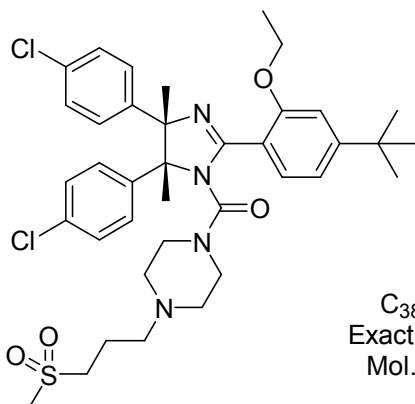
[(Methylsulfonyl)propyl]-piperazine dihydrochloride²



¹H NMR (400 MHz, DMSO-*d*₆) δ 12.07 (br. s, 1H), 9.81 (br. s, 2H), 3.59 - 3.83 (m, 2H), 3.12 - 3.57 (m, 10H), 3.03 (s, 3H), 2.17 (br. s, 2H).

Compound 2g (RG7112)

(4*S*, 5*R*)- 1-[[4-[[4,5-bis(4-chlorophenyl)-2-[4-(*tert*-butyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-1-yl]]-carbonyl]- 4-[3-(methylsulfonyl)propyl]-piperazine



C₃₈H₄₈Cl₂N₄O₄S
Exact Mass: 726.2773
Mol. Wt.: 727.7837

To a solution of *rac*-(4*S**,5*R**)-4,5-bis(4-chlorophenyl)-2-(4-(*tert*-butyl)-2-ethoxy-phenyl)-4,5-dimethyl-4,5-dihydro-1*H*-imidazole-1-carbonyl chloride (50 mg, 0.09 mmol) in 4 mL of dichloromethane at 0 °C were added triethylamine (123 μ L, 0.89 mmol) and 4-[3-(methylsulfonyl)propyl]-piperazine dihydrochloride (26 mg, 0.09 mmol). The mixture was allowed to react for 7 h and then taken up in dichloromethane and washed successively with 10% sodium bicarbonate and water. The dichloromethane phase was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel, eluting with ethyl acetate then 9:1 mixture of ethyl acetate and methanol, provided 61 mg of the title compound as a racemic mixture.

Chiral separation of the enantiomers by supercritical fluid chromatography (Berger Instrument Multi-Gram II, Daicel ChiralPak OD-H 3 x 25 cm, 35°C at 100 bar, eluting with 25% methanol in carbon dioxide) gave 27 mg of the title compound (post peak). HR-MS (ES, *m/z*) calculated for C₃₈H₄₉N₄O₄SCl₂ [(M+H)⁺] 727.2846, observed 727.2846.

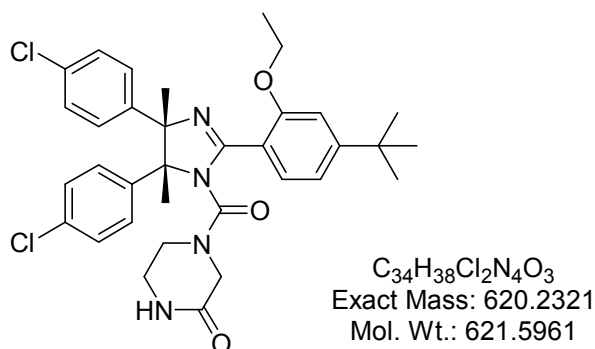
¹H NMR (400 MHz, DMSO-*d*₆) δ 1.36 (t, *J* = 6.90 Hz, 3H), 1.42 (s, 10H), 1.66 (s, 3H), 1.71 - 1.82 (m, 2H), 1.95 (s, 3H), 2.11 - 2.20 (m, 2H), 2.26 (d, *J* = 10.79 Hz, 1H), 2.49 (d, *J* = 10.29 Hz, 1H), 2.85 - 3.12 (m, 9H), 3.21 (d, *J* = 12.30 Hz, 1 H), 3.37 (s, 1H), 3.95 - 4.09 (m, 1H), 4.30 (br. s, 1H), 6.97 - 7.23 (m, 10H), 7.65 (d, *J* = 7.78 Hz, 1H).

¹³C NMR (100 MHz, DMSO-*d*₆) δ 14.2, 19.3, 20.2, 23.8, 31.1, 34.9, 41.7, 44.7, 51.0, 51.2, 51.5, 55.4, 63.6, 75.0, 76.2, 108.4, 117.0, 117.1, 126.4, 127.0, 128.6, 130.4, 130.8, 131.4, 141.2, 141.9, 154.8, 155.7, 156.8, 157.3.

The following compounds were prepared in a manner analogous to the method described for compound **2g**

Compound 2a

4-[(4*S*,5*R*)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-2-one

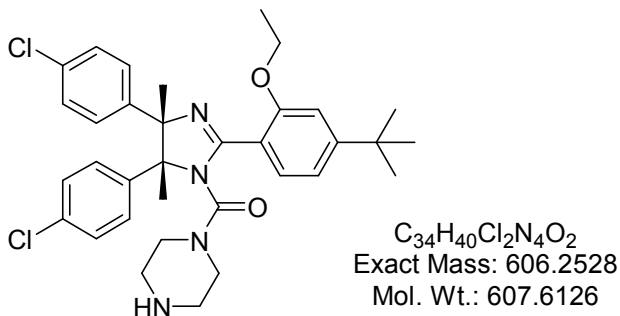


HR-MS (ES, *m/z*) calculated for C₃₄H₃₉N₄O₃Cl₂ [(M+H)⁺] 621.2394, observed 621.2392.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.76 (d, *J* = 9.38 Hz, 1H), 7.59 (d, *J* = 7.88 Hz, 1H), 6.83 - 7.23 (m, 10H), 4.24 (dd, *J* = 8.42, 15.88 Hz, 1H), 3.85 - 4.07 (m, 1H), 3.53 - 3.78 (m, 1H), 2.62 - 3.28 (m, 4H), 1.91 (s, 3H), 1.61 (s, 3H), 1.22 - 1.40 (m, 12H).

Compound 2b

[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone

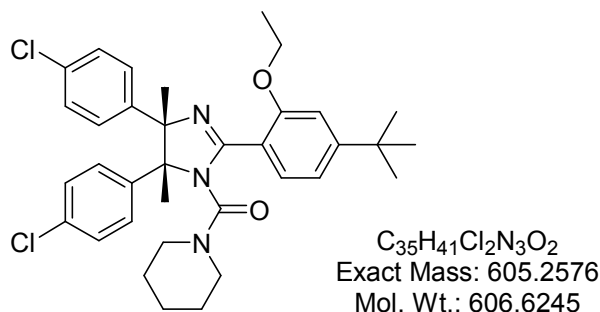


HR-MS (ES, m/z) calculated for $C_{34}H_{41}N_4O_2Cl_2 [(M+H)^+]$ 607.2601, observed 607.2603.

1H NMR (300 MHz, DMSO- d_6) δ 7.55 (d, $J = 8.42$ Hz, 1H), 6.90 - 7.14 (m, 9H), 4.20 (d, $J = 6.59$ Hz, 1H), 3.93 (t, $J = 7.51$ Hz, 1H), 3.49 (s, 2H), 2.88 - 3.01 (m, 1H), 2.75 (br. s, 3H), 2.30 (d, $J = 12.09$ Hz, 1H), 1.99 (br. s, 2H), 1.86 (s, 3H), 1.57 (s, 3H), 1.25 - 1.36 (m, 12H).

Compound 2c

(4S, 5R)- 4-[[4-[[4,5-bis(4-chlorophenyl)-2-[4-(*tert*-butyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-1-yl]carbonyl]-1-piperidine

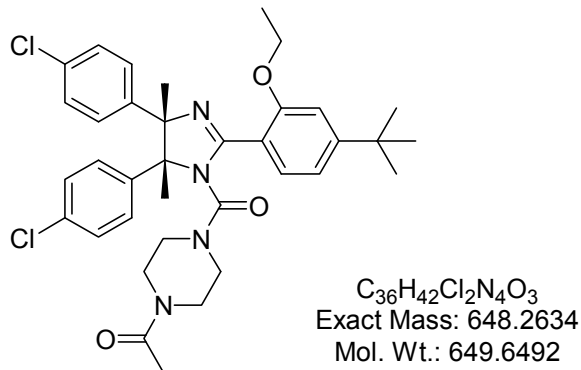


HR-MS (ES, m/z) calculated for $C_{35}H_{42}N_3O_2Cl_2 [(M+H)^+]$ 606.2649, observed 606.2650.

1H NMR (300 MHz, DMSO- d_6) δ 0.02 - 0.22 (m, 1H) 0.84 (br. s, 1H) 1.03 - 1.46 (m, 16H) 1.58 (br. s, 3H) 1.87 (br. s, 3H) 2.68 - 2.96 (m, 4H) 3.12 (br. s, 1 H) 3.95 (br. s, 1H) 4.23 (br. s, 1H) 6.88 - 7.16 (m, 10H) 7.58 (d, $J = 7.85$ Hz, 1H)

Compound 2d

1-{4-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethanone

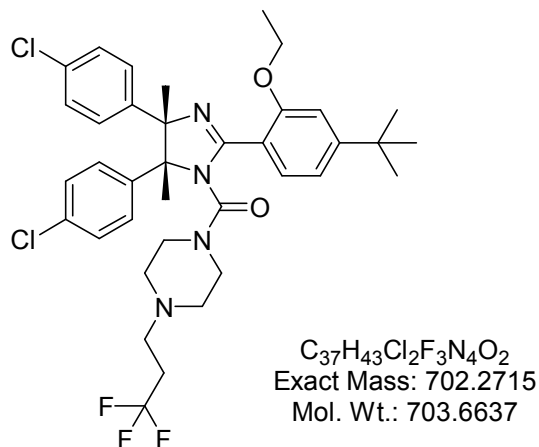


HR-MS (ES, m/z) calculated for $C_{36}H_{43}N_4O_3Cl_2 [(M+H)^+]$ 649.2707, observed 649.2709.

1H NMR (300 MHz, DMSO- d_6) δ 7.60 (d, $J = 8.06$ Hz, 1H), 6.88 - 7.17 (m, 10H), 4.21 (br. s, 1H), 3.98 (br. s, 1H), 3.37 - 3.86 (m, 1H), 3.04 - 3.31 (m, 3H), 2.65 - 2.98 (m, 3H), 1.78 - 1.92 (m, 6H), 1.59 (s, 3H), 1.24 - 1.34 (m, 12H).

Compound 2e

(4S, 5R)- 1-[[4-[[4,5-bis(4-chlorophenyl)-2-[4-(*tert*-butyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-1-yl]]-carbonyl]- 4-[3,3,3-trifluoropropyl]-piperazine

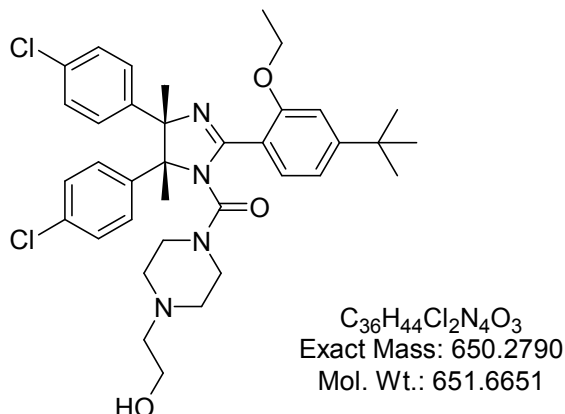


HR-MS (ES, m/z) calculated for $C_{37}H_{44}N_4O_2F_3Cl_2 [(M+H)^+]$ 703.2788, observed 703.2784.

1H NMR (300 MHz, DMSO- d_6) δ 1.16 - 1.47 (m, 14H), 1.57 (s, 3H), 1.86 (s, 3H), 2.24 (d, $J = 8.45$ Hz, 6H), 2.65 - 3.00 (m, 4H), 3.14 (d, $J = 12.98$ Hz, 1H), 3.83 - 4.03 (m, 1H), 4.22 (br. s, 1H), 6.87 - 7.15 (m, 10H), 7.57 (d, $J = 8.45$ Hz, 1H).

Compound 2f

[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazol-1-yl]-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone

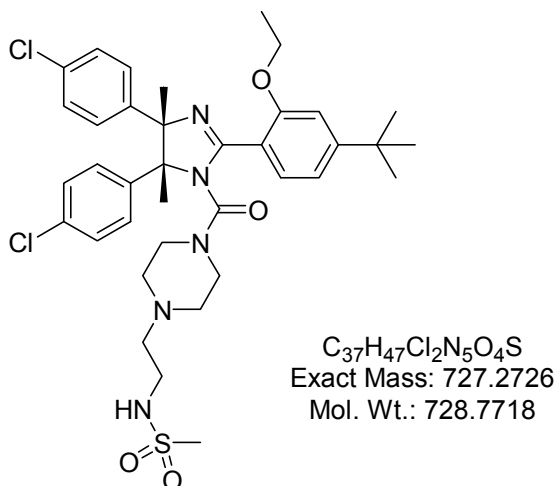


HR-MS (ES, m/z) calculated for C₃₆H₄₅N₄O₃Cl₂ [(M+H)⁺] 651.2863, observed 651.2863.

¹H NMR (300 MHz, DMSO-*d*₆) δ 7.56 (d, J = 8.15 Hz, 1H), 6.86 - 7.15 (m, 10H), 4.33 (t, J = 5.13 Hz, 1H), 4.22 (br. s, 1H), 3.93 (br. s, 1H), 3.11 (d, J = 13.28 Hz, 1H), 2.65 - 2.97 (m, 5H), 2.15 - 2.32 (m, 2H), 2.06 (t, J = 6.19 Hz, 2H), 1.86 (s, 3H), 1.57 (s, 3H), 1.34 (s, 9H), 1.24 - 1.31 (m, 3H)

Compound 2h

N-(2-{4-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethyl)-methanesulfonamide

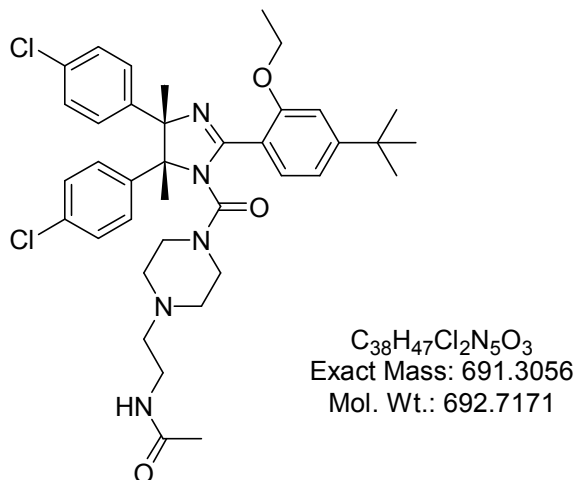


HR-MS (ES, m/z) calculated for C₃₇H₄₈N₅O₄SCl₂ [(M+H)⁺] 728.2799, observed 728.2787.

¹H NMR (300 MHz, DMSO-*d*₆) δ 7.66 (br. s, 1H), 7.57 (d, J = 7.85 Hz, 1H), 6.86 - 7.15 (m, 10H), 4.22 (br. s, 1H), 3.95 (d, J = 7.25 Hz, 1H), 3.10 (br. s, 1H), 2.66 - 3.03 (m, 7H), 2.15 - 2.30 (m, 2H), 1.97 - 2.09 (m, 2H), 1.86 (s, 3H), 1.73 (s, 3H), 1.57 (s, 3H), 1.33 (s, 9H), 1.28 (t, J = 6.94 Hz, 3H).

Compound 2i

N-(2-{4-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-ethyl)-acetamide

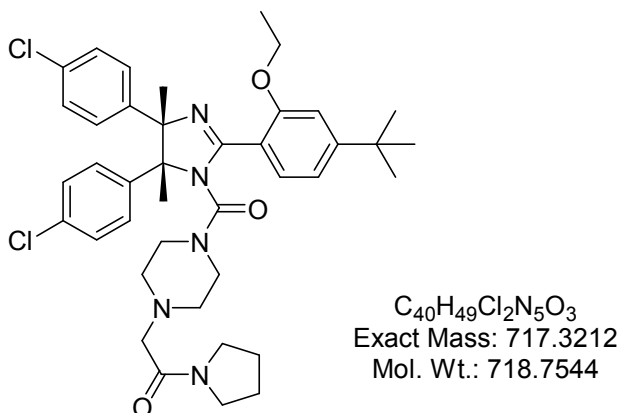


HR-MS (ES, m/z) calculated for $C_{38}H_{48}N_5O_3Cl_2 [(M+H)^+]$ 692.3129, observed 692.3125.

1H NMR (400 MHz, DMSO- d_6) δ 7.66 (br. s, 1H), 7.59 (d, $J = 7.88$ Hz, 1H), 6.88 - 7.21 (m, 9H), 4.24 (br. s, 1H), 3.95 (br. s, 1H), 2.76 - 3.21 (m, 6H), 2.45 (br. s, 2H), 2.33 (s, 1H), 2.21 (d, $J = 9.59$ Hz, 1H), 2.04 (br. s, 2H), 1.88 (s, 3H), 1.75 (s, 3H), 1.59 (s, 3H), 1.35 (s, 9H), 1.30 (t, $J = 7.03$ Hz, 3H).

Compound 2j

2-{4-[(4S,5R)-2-(4-*tert*-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-dimethyl-4,5-dihydro-imidazole-1-carbonyl]-piperazin-1-yl}-1-pyrrolidin-1-yl-ethanone

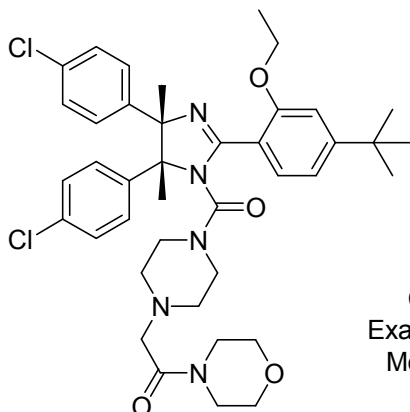


HR-MS (ES, m/z) calculated for $C_{40}H_{50}N_5O_3Cl_2 [(M+H)^+]$ 718.3285, observed 718.3286.

1H NMR (300 MHz, DMSO- d_6) δ 7.57 (d, $J = 8.15$ Hz, 1H), 6.90 - 7.13 (m, 10H), 4.20 (br. s, 1H), 3.95 (br. s, 1H), 3.19 (t, $J = 6.64$ Hz, 2H), 2.66 - 3.14 (m, 6H), 2.17 - 2.33 (m, 2H), 1.87 (br. s, 3H), 1.63 - 1.82 (m, 4H), 1.57 (br. s, 3H), 1.35 (s, 9H), 1.23 - 1.31 (m, 3H).

Compound 2k

(4S, 5R)-4-[[4-[[4,5-Bis(4-chlorophenyl)-2-[4-(tert-butyl)-2-ethoxy-phenyl]-4,5-dimethyl-4,5-dihydro-1H-imidazol-1-yl]carbonyl]-1-piperazinyl]acetyl]-morpholine



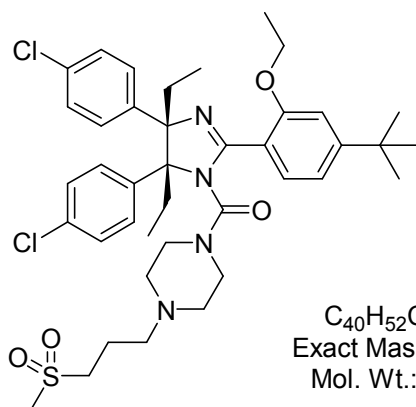
$C_{40}H_{49}Cl_2N_5O_4$
Exact Mass: 733.3162
Mol. Wt.: 734.7538

HR-MS (ES, m/z) calculated for $C_{40}H_{50}N_5O_4Cl_2 [(M+H)^+]$ 734.3235, observed 734.3237.

1H NMR (400 MHz, DMSO- d_6) δ 7.60 (d, $J = 8.53$ Hz, 1H), 6.84 - 7.21 (m, 10H), 4.24 (br. s, 1H), 3.98 (dd, $J = 8.28, 15.81$ Hz, 1H), 3.28 - 3.59 (m, 10H), 3.14 (d, $J = 9.79$ Hz, 1H), 2.78 - 2.99 (m, 5H), 2.38 - 2.48 (m, 1H), 2.22 (d, $J = 10.79$ Hz, 1H), 1.90 (s, 3H), 1.60 (s, 3H), 1.38 (s, 10H), 1.30 (t, $J = 6.90$ Hz, 3H).

Example 2l

[(4S,5R)-2-(4-tert-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4,5-diethyl-4,5-dihydro-imidazol-1-yl]-[4-(3-methanesulfonyl-propyl)-piperazin-1-yl]-methanone



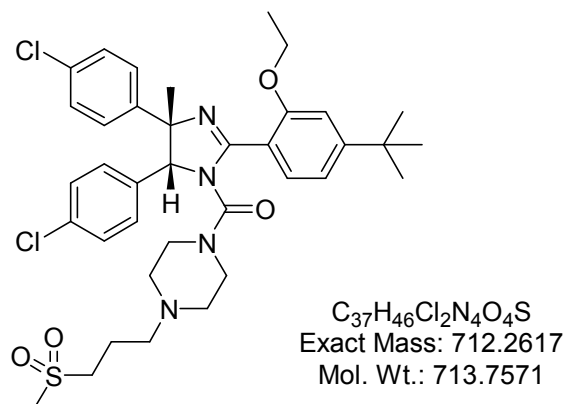
$C_{40}H_{52}Cl_2N_4O_4S$
Exact Mass: 754.3086
Mol. Wt.: 755.8368

HR-MS (ES, m/z) calculated for $C_{40}H_{53}N_4O_4SCL_2 [(M+H)^+]$ 755.3159, observed 755.3157.

1H NMR (400 MHz, DMSO- d_6) δ 7.82 (br. s, 1H), 7.23 - 7.61 (m, 8H), 6.82 - 7.16 (m, 3H), 3.71 - 4.39 (m, 4H), 3.17 (br. s, 3H), 2.97 - 3.07 (m, 3H), 2.93 (s, 3H), 2.73 - 2.89 (m, 1H), 2.11 (d, $J = 15.34$ Hz, 4H), 1.71 (br. s, 5H), 1.35 (s, 11H), 1.28 (br. s, 3H), 1.04 (d, $J = 5.97$ Hz, 2H), 0.86 (br. s, 3H), 0.51 (d, $J = 6.61$ Hz, 3H).

Compound 2m

[(4S,5R)-2-(4-tert-Butyl-2-ethoxy-phenyl)-4,5-bis-(4-chloro-phenyl)-4-methyl-4,5-dihydro-imidazol-1-yl]-piperazin-1-yl-methanone



HR-MS (ES, m/z) calculated for $C_{37}H_{47}N_4O_4SCl_2 [(M+H)^+]$ 713.2690, observed 713.2687.

1H NMR (400 MHz, Methanol- d_4) δ 7.57 (d, $J = 7.87$ Hz, 1H), 7.19 (dd, $J = 1.47, 8.06$ Hz, 1H), 7.04 - 7.16 (m, 7H), 6.86 (d, $J = 7.51$ Hz, 2H), 5.35 (s, 1H), 4.16 (t, $J = 7.05$ Hz, 2H), 3.03 - 3.20 (m, 6H), 2.91 (s, 3H), 2.26 (t, $J = 6.59$ Hz, 2H), 1.98 (br. s, 2H), 1.77 - 1.90 (m, 7H), 1.46 (t, $J = 6.96$ Hz, 3H), 1.39 (s, 9H).

Table 1. Biological data of the active enantiomers of **2a-m**

ID	HTRF IC ₅₀ (μ M)	HCT-116 IC ₅₀ (μ M)	SJSA-1 IC ₅₀ (μ M)	RKO IC ₅₀ (μ M)	MDA- MB-435 IC ₅₀ (μ M)	SW480 IC ₅₀ (μ M)	Ave. wt p53 IC ₅₀ (μ M)	Ave. mut p53 IC ₅₀ (μ M)	Selectivity ^a
2a	0.052	16.4	7.6	23.7	>30	>30	15.9	>30	>1.9
2b	0.030	1.2	0.6	0.5	4.2	2.7	0.8	3.5	4.5
2c	0.209	10.7	7.3	6.8	24.9	23.1	8.3	24.0	2.9
2d	0.023	0.6	0.3	0.5	14.9	17.8	0.5	16.3	35.1
2e	0.022	1.3	2.5	0.4	29.3	5.0	1.4	17.2	11.9
2f	0.026	0.8	0.2	0.3	9.6	12.3	0.4	10.9	26.2
2g	0.018	0.5	0.3	0.4	9.9	16.6	0.4	13.3	33.4
2h	0.046	0.9	0.2	0.3	7.3	9.1	0.5	8.2	18.1
2i	0.033	0.5	0.1	0.3	10.5	11.0	0.3	10.7	35.2
2j	0.014	0.7	0.3	0.5	9.5	14.4	0.5	12.0	23.5
2k	0.018	0.6	0.2	0.6	17.5	14.4	0.5	15.9	34.4
2l	2.163	13.7	>30	12.5	28.2	24.6	13.1	26.4	2.0
2m	0.232	14.4	12.4	>30	>30	>30	13.4	>30	>2.2

^aRatio of average IC₅₀ against mutant p53 cell lines and average IC₅₀ versus wild-type p53 cell lines.

Table S1. Data collection and refinement statistics for compound 1

Data collection	
Space group	C222 ₁
Cell dimensions	
<i>a</i> , <i>b</i> , <i>c</i> (Å)	42.887, 67.657, 67.173
α , β , γ (°)	90.0, 90.0, 90.0
Resolution (Å)	1.91 (1.98-1.91)*
<i>R</i> _{sym} or <i>R</i> _{merge}	0.039 (0.064)
<i>I</i> / σ (<i>I</i>)	46.1 (29.8)
Completeness (%)	95.3 (85.9)
Redundancy	3.8 (2.9)
Refinement	
Resolution (Å)	1.91
No. of reflections	7,488
<i>R</i> _{work} / <i>R</i> _{free}	0.194/0.239
No. of atoms	
Protein	704 [§]
Ligand	40
Water	128
B-factors (Å ²)	
Protein	12.60
Ligand	13.20
Water	25.45
Rms deviations	
Bond lengths (Å)	0.004
Bond angles (°)	1.122

* Values in parentheses are results for the highest resolution shell.

[§] This number includes duplicate atoms for one residue (SER 32) in alternate conformations. There are 698 atoms in the protein.

References

1. Kong, N.; Liu, E. A.; Vu, B. T. "Cis-imidazolines." U.S. Patent 6,734,302. Issued May 11, 2004.
2. Ding, Q.; Graves, B. J.; Kong, N.; Liu, J. J.; Lovey, A. J.; Giacomo, P.; Roberts, J. L.; So, S. S.; Vu, B. T.; Wovkulich, P. M. "4,4,5,5, Tetrasubstituted imidazolines." U.S. Patent 7,851,626. Issued December, 14, 2010.