SUPPORTING INFORMATION

Synthesis and Discovery of *N*-Carbonylpyrrolidine- or *N*-Sulfonylpyrrolidine-containing Uracil Derivatives as Potent Human Deoxyuridine Triphosphatase Inhibitors

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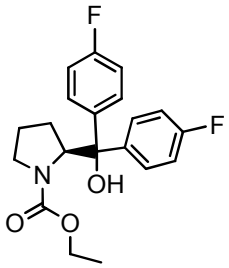
Contents:

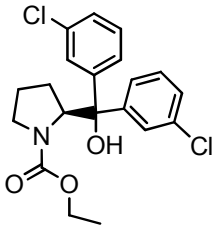
Experimental Section of chemistry

General Methods and Materials. All commercially available starting materials and solvents were reagent grade. Silica gel column chromatography was performed on Merck silica gel 60 (230-400 mesh). ^{1}H NMR spectra were measured at 270 MHz on a JEOL JNM-EX270 or 400 MHz on a JEOL JNM-LA400. ^{13}C NMR spectra were measured 100 MHz on a JEOL JNM-LA400. Chemical shifts were recorded in parts per million (ppm, δ) and were reported relative to the solvent peak or internal tetramethylsilane peak. High-resolution mass spectra (HRMS) were measured with JEOL JMS-700 (FAB) or Waters micromass Q-Tof-2 (TOF). Chemical purities of tested compounds were determined by combustion analysis or HPLC analysis and confirmed ≥95% purity. Combustion analyses (C, H, N) were performed on a Thermo electron Corp. Flash EA 1112 series, and values were within ±0.4% of the theoretical values. Chemical purities of tested compounds **11i** and **11r** were determined by HPLC analysis with SHIMADZU Prominence HPLC system. Optical rotations were measured by HORIBA SEPA-200 polarimeter.Optical rotations were measured by HORIBA SEPA-200 polarimeter. The details of the experimental procedures of Method A-H were described in experimental section of the main manuscript.



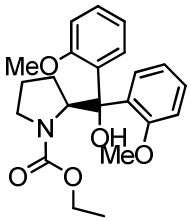
(*S*)-Ethyl 2-(bis(4-fluorophenyl)(hydroxy)methyl)pyrrolidine-1-carboxylate (7b)

Compound **7b** (1.20 g, 66% as a colorless solid) was synthesized from **6a** (1.0 g, 5.0 mmol) and a THF solution of 4-fluorophenylmagnesium bromide (1.0 M, 20 mL, 20 mmol) according to the procedure described for Method A. ^{1}H NMR ($CDCl_3$) δ 0.80-0.90 (1H, m), 1.25 (3H, t, *J* = 6.8 Hz), 1.51-1.54 (1H, m), 1.83-1.90 (1H, m), 2.04-2.14 (1H, m), 2.93-3.00 (1H, m), 3.43 (1H, dd, *J* = 8.0, 18.0 Hz), 4.12-4.16 (2H, m), 4.85 (1H, dd, *J* = 4.0, 8.8 Hz), 6.09 (1H, brs), 6.96-7.03 (4H, m), 7.32-7.37 (4H, m); TOF-HRMS m/z $[M+H]^+$: Calcd. for $C_{20}H_{22}F_2NO_3$, 362.1568; Found, 362.1570



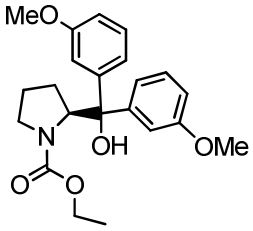
(*S*)-Ethyl 2-(bis(3-chlorophenyl)(hydroxy)methyl)pyrrolidine-1-carboxylate (7c)

Compound **7c** (480 mg, 81%, a colorless solid) was synthesized from **6a** (300 mg, 1.5 mmol) and a THF solution of 3-chlorophenylmagnesium bromide (0.5 M, 9.0 mL, 4.5 mmol) according to the procedure described for Method A. ^{1}H NMR ($CDCl_3$) δ 0.90-1.00 (1H, m), 1.24 (3H, t, *J* = 7.0 Hz), 1.51-1.64 (1H, m), 1.83-1.94 (1H, m), 2.02-2.13 (1H, m), 2.95-3.04 (1H, m), 3.42-3.52 (1H, m), 4.06-4.20 (2H, m), 4.82 (1H, dd, *J* = 4.3, 8.9 Hz), 7.20-7.30 (6H, m), 7.38 (1H, s), 7.43 (1H, s); FAB-HRMS m/z $[M+Na]^+$: Calcd. for $C_{20}H_{21}Cl_2NO_3Na$, 416.0796; Found, 416.0791



(*S*)-Ethyl 2-(hydroxybis(2-methoxyphenyl)methyl)pyrrolidine-1-carboxylate (7d)

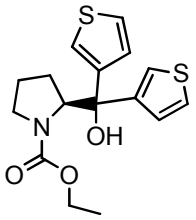
Compound **7d** (1.41 g, 73%, a colorless solid) was synthesized from **6a** (1.0 g, 5.0 mmol) and a THF solution of 2-methoxyphenylmagnesium bromide (1.0 M, 20 mL, 20mmol) according to the procedure described for Method A. ^{1}H NMR ($CDCl_3$) δ 0.94 (3H, brs), 1.72-1.83 (1H, m), 2.10-2.23 (3H, m), 3.42 (2H, brs), 3.45 (6H, s), 3.72-3.83 (2H, m), 4.95 (1H, brs), 5.28 (1H, brs), 6.70 (1H, d, *J* = 7.8 Hz), 6.82 (1H, dd, *J* = 1.1, 8.1 Hz), 6.89 (1H, t, *J* = 7.8 Hz), 6.99 (1H, td, *J* = 1.1, 7.6 Hz), 7.13 (1H, td, *J* = 1.9, 8.1 Hz), 7.16-7.23 (1H, m), 7.54 (1H, d, J = 7.83 Hz), 7.59 (1H, d, *J* = 7.6 Hz); FAB-HRMS m/z $[M+Na]^+$: Calcd. for $C_{22}H_{27}NO_5Na$, 408.1787; Found, 408.1783



(*S*)-Ethyl 2-(hydroxybis(3-methoxyphenyl)methyl)pyrrolidine-1-carboxylate (7e)

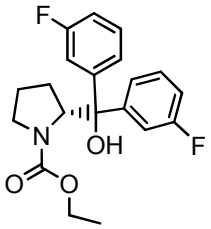
Compound **7e** (1.25 g, 65%, a colorless gum) was synthesized from **6a** (1.0 g, 5.0 mmol) and a THF

solution of 3-methoxyphenylmagnesium bromide (1.0 M, 20 mL, 20mmol) according to the procedure described for Method A. ^{1}H NMR ($CDCl_3$) δ 0.87-1.00 (1H, m), 1.22 (3H, t, J = 6.8 Hz), 1.44-1.56 (1H, m), 1.91-2.15 (2H, m), 2.97-3.06 (1H, m), 3.39-3.51 (1H, m), 3.76 (3H, s), 3.78 (3H, s), 4.04-4.21 (2H, m), 4.87 (1H, dd, J = 3.8, 8.6 Hz), 6.79-6.83 (2H, m), 6.90 (1H, d, J = 8.1 Hz), 6.97-7.00 (2H, m), 7.04-7.05 (1H, m), 7.16-7.23 (2H, m); FAB-HRMS m/z $[M+H]^+$: Calcd. for $C_{22}H_{28}NO_5$, 386.1967; Found, 386.1951



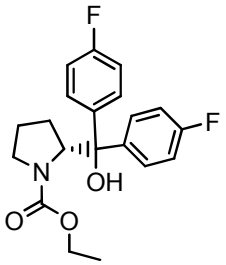
(*S*)-Ethyl 2-(hydroxydithiophen-3-ylmethyl)pyrrolidine-1-carboxylate (7f)

Compound **7f** (1.01 g, 60%, a colorless solid) was synthesized from **6a** (1.0 g, 5.0 mmol) and a THF solution of 3-thienylmagnesium iodide (0.3 M, 67 mL, 20 mmol) according to the procedure described for Method A. ^{1}H NMR ($CDCl_3$) δ 1.09-1.20 (1H, m), 1.25 (3H, t, *J* = 7.0 Hz), 1.51-1.64 (1H, m), 1.85-2.10 (2H, m), 2.92-2.95 (1H, m), 3.44-3.53 (1H, m), 4.12-4.21 (2H, m), 4.73 (1H, dd, *J* = 5.1, 8.6 Hz), 7.08 (1H, dd, *J* = 1.4, 4.6 Hz), 7.15-7.18 (2H, m), 7.21-7.30 (3H, m); FAB-HRMS m/z $[M+Na]^+$: Calcd. for $C_{16}H_{19}NO_3S_2Na$, 360.0704; Found, 360.0689



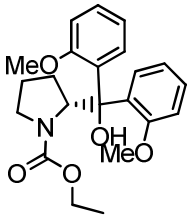
(*R*)-Ethyl 2-(bis(3-fluorophenyl)(hydroxy)methyl)pyrrolidine-1-carboxylate (7g)

Compound **7g** (4.23 g, 78%, a colorless solid) was synthesized from *N*-carboethoxy-D-proline methyl ester **6b** (3.0 g, 15 mmol) and a THF solution of 3-fluorophenylmagnesium bromide (1.0 M, 52 mL, 52 mmol) according to the procedure described for Method A. ^{1}H NMR ($CDCl_3$) δ 0.89-1.00 (1H, m), 1.24 (3H, t, *J* = 7.0 Hz), 1.49-1.63 (1H, m), 1.85-1.97 (1H, m), 2.05-2.13 (1H, m), 2.96-3.06 (1H, m), 3.46 (1H, dt, *J* = 7.8, 10.5 Hz), 4.06-4.22 (2H, m), 4.83 (1H, dd, *J* = 4.1, 8.6 Hz), 6.94-7.03 (2H, m), 7.08-7.33 (6H, m); FAB-HRMS m/z $[M-H]^-$: Calcd. for $C_{20}H_{20}F_2NO_3$, 360.1411; Found, 360.1409



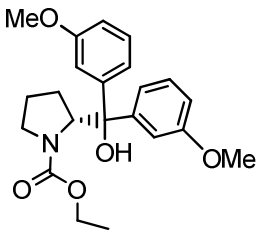
(*R*)-Ethyl 2-(bis(4-fluorophenyl)(hydroxy)methyl)pyrrolidine-1-carboxylate (7h)

Compound **7h** (3.74 g, 69%, a colorless solid) was synthesized from *N*-carboethoxy-D-proline methyl ester **6b** (3.0 g, 15 mmol) and a THF solution of 4-fluorophenylmagnesium bromide (1.0 M, 52 mL, 52 mmol) according to the procedure described for Method A. ^{1}H NMR ($CDCl_3$) δ 0.79-0.90 (1H, m), 1.25 (3H, t, *J* = 7.3 Hz), 1.45-1.57 (1H, m), 1.81-1.92 (1H, m), 2.01-2.16 (1H, m), 2.91-3.00 (1H, m), 3.43 (1H, dd, *J* = 7.8, 18.6 Hz), 4.09-4.22 (2H, m), 4.85 (1H, dd, *J* = 3.8, 8.6 Hz), 6.09 (1H, brs), 6.95-7.05 (4H, m), 7.30-7.37 (4H, m); FAB-HRMS m/z $[M+H]^+$: Calcd. for $C_{20}H_{22}F_2NO_3$, 362.1568; Found, 362.1561



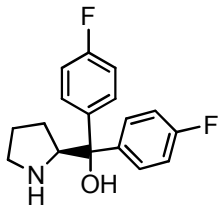
(*R*)-Ethyl 2-(hydroxybis(2-methoxyphenyl)methyl)pyrrolidine-1-carboxylate (7i)

Compound **7i** (4.57 g, 79%, a colorless solid) was synthesized from *N*-carboethoxy-D-proline methyl ester **6b** (3.0 g, 15 mmol) and a THF solution of 2-methoxyphenylmagnesium bromide (1.0 M, 45 mL, 45 mmol) according to the procedure described for Method A. ^{1}H NMR ($CDCl_3$) δ 0.86-1.22 (4H, m), 1.72-1.83 (1H, m), 2.05-2.25 (2H, m), 3.42 (2H, brs), 3.49 (6H, s), 3.70-3.82 (2H, m), 4.95 (1H, brs), 5.29 (1H, brs), 6.70 (1H, d, *J* = 8.1 Hz), 6.82 (1H, d, *J* = 8.4 Hz), 6.89 (1H, t, *J* = 7.6 Hz), 6.99 (1H, td, *J* = 1.1, 7.6 Hz), 7.13 (1H, td, *J* = 1.6, 7.6 Hz), 7.20 (1H, td, *J* = 1.6, 7.8 Hz), 7.54 (1H, d, *J* = 6.8 Hz), 7.60 (1H, d, *J* = 8.1 Hz); FAB-HRMS m/z $[M+H]^+$: Calcd. for $C_{22}H_{28}NO_5$, 386.1967; Found, 386.1968



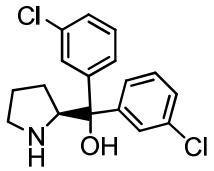
(*R*)-Ethyl 2-(hydroxybis(3-methoxyphenyl)methyl)pyrrolidine-1-carboxylate (7j)

Compound **7j** (925 mg, 80%, a colorless gum) was synthesized from *N*-carboethoxy-D-proline methyl ester **6b** (600 mg, 3.0 mmol) and a THF solution of 3-methoxyphenylmagnesium bromide (1.0 M, 9 mL, 9.0 mmol) according to the procedure described for Method A. ^{1}H NMR ($CDCl_3$) δ 0.89-0.98 (1H, m), 1.22 (3H, t , *J* = 7.0 Hz), 1.44-1.55 (1H, m), 1.91-2.15 (2H, m), 2.97-3.06 (1H, m), 3.39-3.51 (1H, m), 3.76 (3H, s), 3.78 (3H, s), 4.04-4.21 (2H, m), 4.87 (1H, dd, *J* = 4.1, 8.6 Hz), 6.79-6.80 (1H, m), 6.83 (1H, t, *J* = 2.2 Hz), 6.90 (1H, d, *J* = 7.8 Hz), 6.97-7.00 (2H, m), 7.04 (1H, t, *J* = 2.2 Hz), 7.16-7.23 (2H, m); FAB-HRMS m/z $[M+Na]^+$: Calcd. for $C_{22}H_{27}NO_5Na$, 408.1787; Found, 408.1807



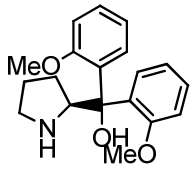
(*S*)-Bis(4-Fluorophenyl)(pyrrolidin-2-yl)methanol (8b)

Potassium hydroxide (1.85 g, 33mmol) was added to a solution of **7b** (1.2 g, 3.3 mmol) in MeOH (10 mL). The mixture was heated to reflux for 12 hr. The mixture was evaporated to give a residue, which was dissolved in water (10 mL), followed by extraction with $CHCl_3$ (20 mL). The organic phase was washed with water (10 mL) and brine (10 mL), dried (K_2CO_3), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (10-20% MeOH in $CHCl_3$) to give **8b** (907 mg, 95% as a colorless solid). ^{1}H NMR ($CDCl_3$) δ 1.49-1.62 (2H, m), 1.64-1.79 (2H, m), 2.93-3.06 (2H, m), 4.17 (1H, t, *J* = 7.6 Hz), 6.93-7.00 (4H, m), 7.40-7.45 (2H, m), 7.47-7.52 (2H, m); TOF-HR MS m/z $[M+H]^+$: Calcd. for $C_{17}H_{18}F_2NO$, 290.1356; Found, 290.1360; $[\alpha]^{25}_D$ = -48.42 (*c* 0.38, MeOH), reference data[1] $[\alpha]^{22}_D$ = -48.5 (*c* 0.32, MeOH)



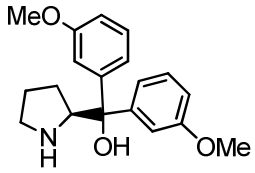
(*S*)-Bis(3-chlorophenyl)(pyrrolidin-2-yl)methanol (8c)

Compound **8c** (370 mg, 94%, a colorless gum) was synthesized from **7c** (480 mg, 1.2 mmol) according to the procedure described for Method B. ^{1}H NMR (DMSO-d_6) δ 1.36-1.43 (2H, m), 1.51-1.58 (2H, m), 2.35 (1H, brs), 2.80 (2H, t, *J* = 1.9 Hz), 4.23 (1H, t, *J* = 7.6 Hz), 5.42 (1H, brs), 7.19-7.44 (6H, m), 7.50-7.59 (2H, m); FAB-HRMS m/z $[M+H]^+$: Calcd. for $C_{17}H_{18}Cl_2NO$, 322.0765; Found, 322.0749



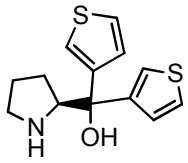
(*S*)-Bis(2-methoxyphenyl)(pyrrolidin-2-yl)methanol (8d)

Compound **8d** (1.07 g, 92%, a colorless solid) was synthesized from **7d** (1.41 g, 3.7 mmol) according to the procedure described for Method B. ^{1}H NMR (DMSO-d_6) δ 1.14-1.26 (1H, m), 1.32-1.42 (1H, m), 1.47-1.61 (2H, m), 2.24 (1H, brs), 2.75-2.92 (2H, m), 3.37 (3H, s), 3.46 (3H, s), 4.50 (1H, t, *J* = 7.6 Hz), 5.14 (1H, brs), 6.77-6.95 (4H, m), 7.10-7.16 (2H, m), 7.58 (1H, dd, *J* = 1.6, 7.6 Hz), 7.71 (1H, dd, *J* = 1.9, 7.8 Hz); FAB-HRMS m/z $[M+H]^+$: Calcd. for $C_{19}H_{24}NO_3$, 314.1756; Found, 314.1766



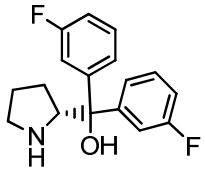
(*S*)-Bis(3-methoxyphenyl)(pyrrolidin-2-yl)methanol (8e)

Compound **8e** (917 mg, 90%, a colorless gum) was synthesized from **7e** (1.25 g, 3.3 mmol) according to the procedure described for Method B. ^{1}H NMR (DMSO-d_6) δ 1.37-1.45 (2H, m), 1.53-1.62 (2H, m), 2.25 (1H, brs), 2.75-2.90 (2H, m), 3.70 (3H, s), 3.71 (3H, s), 4.22 (1H, d, *J* = 7.3 Hz), 5.04 (1H, brs), 6.68-6.73 (2H, m), 7.00-7.04 (2H, m), 7.12-7.20 (4H, m); FAB-HRMS m/z $[M+H]^+$: Calcd. for $C_{19}H_{24}NO_3$, 314.1756; Found, 314.1741



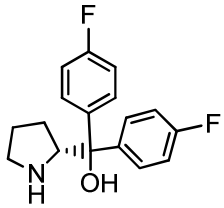
(*S*)-Pyrrolidin-2-yldithiophen-3-ylmethanol (8f)

Compound **8f** (676 mg, 85%, a colorless solid) was synthesized from **7f** (1.01 g, 3.0 mmol) according to the procedure described for Method B. ^{1}H NMR (DMSO-d_6) δ 1.43-1.56 (4H, m), 2.80 (2H, t, *J* = 4.6 Hz), 3.98 (1H, t, *J* = 7.6 Hz), 7.07 (1H, d, *J* = 4.9 Hz), 7.14 (1H, d, *J* = 4.9 Hz), 7.31-7.38 (4H, m); FAB-HRMS m/z $[M+H]^+$: Calcd. for $C_{13}H_{16}NOS_2$, 266.0673; Found, 266.0657



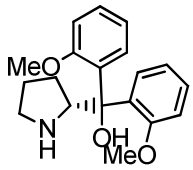
(*R*)-Bis(3-fluorophenyl)(pyrrolidin-2-yl)methanol (8g)

Compound **8g** (721 mg, 90%, a colorless gum) was synthesized from **7g** (1.0 g, 2.77 mmol) according to the procedure described for Method B. ^{1}H NMR (DMSO-d_6) δ 1.36-1.45 (2H, m), 1.53-1.62 (2H, m), 2.38 (1H, brs), 2.75-2.88 (2H, m), 4.26 (1H, t, *J* = 7.6 Hz), 5.34 (1H, brs), 6.94-7.02 (2H, m), 7.28-7.43 (6H, m); FAB-HRMS m/z $[M+H]^+$: Calcd. for $C_{17}H_{18}F_2NO$, 290.1356; Found, 290.1385



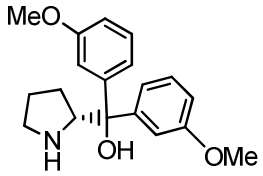
(*R*)-Bis(4-fluorophenyl)(pyrrolidin-2-yl)methanol (8h)

Compound **8h** (721 mg, 92%, a colorless solid) was synthesized from **7h** (1.0 g, 2.77 mmol) according to the procedure described for Method B. ^{1}H NMR (DMSO-d_6) δ 1.38 (2H, q, *J* = 7.6 Hz), 1.55 (2H, quint, *J* = 6.8 Hz), 2.23 (1H, brs), 2.80 (2H, m), 4.18 (1H, t, *J* = 7.6 Hz), 5.22 (1H, brs), 7.02-7.10 (4H, m), 7.41-7.48 (2H, m), 7.52-7.60 (2H, m); FAB-HRMS m/z $[M+H]^+$: Calcd. for $C_{17}H_{18}F_2NO$, 290.1356; Found, 290.1358



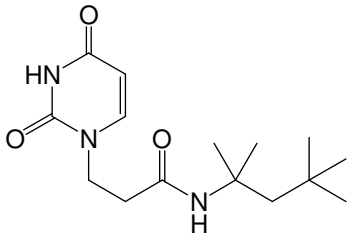
(*R*)-Bis(2-methoxyphenyl)(pyrrolidin-2-yl)methanol (8i)

Compound **8i** (3.2 g, 86%, a colorless solid) was synthesized from **7i** (4.57 g, 11.9 mmol) according to the procedure described for Method B. ^{1}H NMR (DMSO-d_6) δ 1.14-1.26 (1H, m), 1.32-1.45 (1H, m), 1.49-1.59 (2H, m), 2.24 (1H, brs), 2.75-2.92 (2H, m), 3.37 (3H, s), 3.46 (3H, s), 4.50 (1H, t, *J* = 7.8 Hz), 5.13 (1H, brs), 6.77-6.95 (4H, m), 7.13 (2H, tt, *J* = 1.6, 8.9 Hz), 7.58 (1H, dd, *J* = 1.9, 7.8 Hz), 7.70 (1H, dd, *J* = 1.9, 7.8 Hz); FAB-HRMS m/z $[M+H]^+$: Calcd. for $C_{19}H_{24}NO_3$, 314.1756; Found, 314.1780



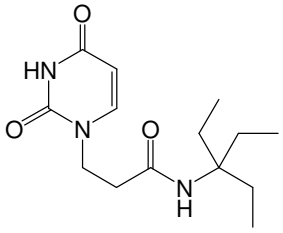
(*R*)-Bis(3-methoxyphenyl)(pyrrolidin-2-yl)methanol (8j)

Compound **8j** (730 mg, 97%, a colorless gum) was synthesized from **7j** (925 mg, 2.40 mmol) according to the procedure described for Method B. ^{1}H NMR (DMSO-d_6) δ 1.41 (2H, q, J = 8.0 Hz), 1.58 (2H, qiunt, J = 8.0 Hz), 2.28 (1H, brs), 2.77-2.88 (2H, m), 3.70 (3H, s), 3.71 (3H, s), 4.22 (1H, t, J = 8.0 Hz), 5.04 (1H, brs), 6.68-6.73 (2H, m), 7.00-7.04 (2H, m), 7.12-7.19 (4H, m); FAB-HRMS m/z $[M+H]^+$: Calcd. for $C_{19}H_{24}NO_3$, 314.1756; Found, 314.1738



3-(2,4-Dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-*N*-(2,4,4-trimethylpentan-2-yl)propanamide (11a)

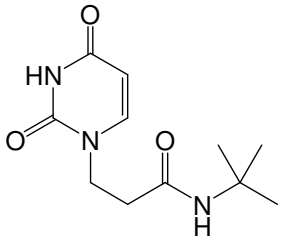
Compound **11a** (48 mg, 81%, a colorless solid) was synthesized from 3-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)propanoic acid **9**[2] (37 mg, 0.20 mmol) and *tert*-octylamine (66 μL, 0.40 mmol) according to the procedure described for Method C. ^{1}H NMR ($CDCl_3$) δ 0.95 (9H, s), 1.36 (6H, s), 1.71 (2H, s), 2.53 (2H, t, J = 5.8 Hz), 4.00 (2H, t, J = 5.6 Hz), 5.29 (1H, brs), 5.62 (1H, dd, J = 2.3, 7.9 Hz), 7.43 (1H, d, J = 7.8 Hz), 8.18 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 29.32, 31.03, 31.21, 34.73, 44.80, 49.49, 53.75, 100.17, 146.57, 150.78, 163.77, 168.72; Anal. Calcd for $C_{15}H_{25}N_3O_3$: C, 60.99; H, 8.53; N, 14.23. Found: C, 61.33; H, 8.65; N, 14.23



3-(2,4-Dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-*N*-(3-ethylpentan-3-yl)propanamide (11b)

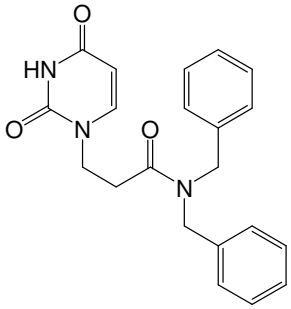
A mixture of **9** (2.39 g, 13 mmol), 3-ethylpentane-3-amine hydrochloride[3] (3.85 g, 26 mmol), EDC·HCl (3.74 g, 19.5 mmol), triethylamine (2.7 mL, 19.5 mmol) and HOBt (2.28 g, 16.9 mmol) in DMF (30 mL) was stirred at room temperature for 3 hr. The reaction mixture was evaporated and the

residue was purified by silica gel column chromatography (1-3% MeOH in $CHCl_3$) to give **11b** (2.8 g, 77% as a colorless solid). ^{1}H NMR ($CDCl_3$) δ 0.72 (9H, t, *J* = 7.3 Hz), 1.63 (6H, q, *J* = 7.6 Hz), 2.60 (2H, t, *J* = 6.2 Hz), 4.02 (2H, t, *J* = 5.9 Hz), 4.99 (1H, brs), 5.62 (1H, d, *J* = 8.1 Hz), 7.40 (1H, d, *J* = 8.1 Hz), 8.80 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 7.27, 25.46, 34.49, 44.86, 58.58, 100.22, 146.346, 150.76, 163.77, 168.67; Anal. Calcd for $C_{14}H_{23}N_3O_3$: C, 59.77; H, 8.24; N, 14.94. Found: C, 60.00; H, 8.36; N, 15.00



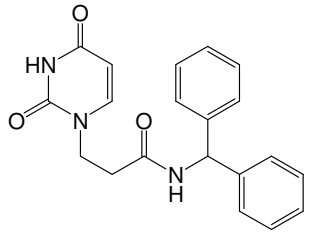
***N*-tert-Butyl-3-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)propanamide (11c)**

Compound **11c** (41 mg, quant., a colorless solid) was synthesized from **9** (27 mg, 0.15 mmol) and *tert*-butylamine (30 μL, 0.30 mmol) according to the procedure described for Method C. ^{1}H NMR ($CDCl_3$) δ 1.32 (9H, s), 2.54 (2H, t, *J* = 5.8 Hz), 4.02 (2H, t, *J* = 5.6 Hz), 5.57 (1H, d, *J* = 7.7 Hz), 6.26 (1H, brs), 7.40 (1H, d, *J* = 7.9 Hz), 7.7 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 28.43, 34.93, 44.82, 50.04, 100.28, 146.22, 150.77, 163.81, 169.00; Anal. Calcd for $C_{11}H_{17}N_3O_3$: C, 55.22; H, 7.16; N, 17.56. Found: C, 55.20; H, 7.25; N, 17.43



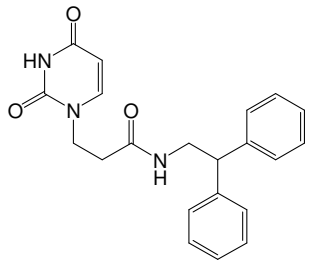
***N,N*-Dibenzyl-3-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)propanamide (11d)**

Compound **11d** (55 mg, 56%, a colorless solid) was synthesized from **9** (50 mg, 0.27 mmol) and dibenzylamine (62 μL, 0.33 mmol) according to the procedure described for Method C. ^{1}H NMR (DMSO-d_6) δ 2.81 (2H, t, *J* = 6.6 Hz), 3.94 (2H, t, *J* = 6.6 Hz), 4.50 (4H, d, *J* = 5.0 Hz), 5.52 (1H, d, *J* = 7.9 Hz), 7.13-7.38 (10H, m), 7.65 (1H, d, *J* = 7.9 Hz), 11.21 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 31.34, 44.73, 48.01, 49.78, 100.41, 126.41, 127.08, 127.31, 127.62, 128.40, 128.70, 136.89, 137.46, 146.44, 150.85, 163.78, 170.53; Anal. Calcd for $C_{21}H_{21}N_3O_3$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.48; H, 5.77; N, 11.55



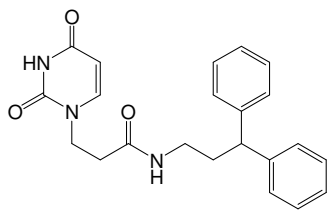
***N*-Benzhydryl-3-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)propanamide (11e)**

Compound **11e** (60 mg, 63%, a colorless solid) was synthesized from **9** (50 mg, 0.27 mmol) and benzhydrylamine (60 μL, 0.35 mmol) according to the procedure described for Method C. ^{1}H NMR (DMSO-d_6) δ 2.61 (2H, t, J = 6.8 Hz), 3.88 (2H, t, J = 6.2 Hz), 5.44 (1H, d, J = 8.1 Hz), 6.11 (1H, d, J = 8.4 Hz), 7.16-7.34 (10H, m), 7.46 (1H, d, J = 7.6 Hz), 8.92 (1H, d, J = 8.6 Hz), 11.24 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 34.05, 44.78, 55.82, 100.44, 126.91, 127.23, 128.29, 142.19, 146.12, 150.76, 163.74, 168.86; Anal. Calcd for $C_{20}H_{19}N_3O_3 \cdot 0.2H_2O$: C, 68.05; H, 5.54; N, 11.90. Found: C, 68.24; H, 5.55; N, 11.92



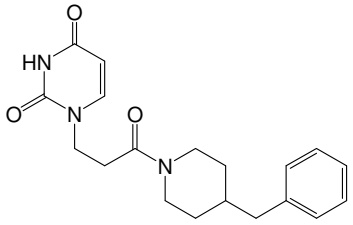
3-(2,4-Dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-*N*-(2,2-diphenylethyl)propanamide (11f)

Compound **11f** (63 mg, 63%, a colorless solid) was synthesized from **9** (50 mg, 0.27 mmol) and 2,2-diphenylethylamine (69 mg, 0.35 mmol) according to the procedure described for Method C. ^{1}H NMR (DMSO-d_6) δ 2.36 (2H, t, J = 6.5 Hz), 3.65-3.70 (2H, m), 3.78 (2H, t, J = 6.8 Hz), 4.13 (1H, t, J = 8.1 Hz), 5.49 (1H, d, J = 7.8 Hz), 7.14-7.30 (10H, m), 7.43 (1H, d, J = 7.8 Hz), 8.05 (1H, t, J = 5.4 Hz), 11.19 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 33.96, 43.23, 44.74, 50.01, 100.45, 126.31, 127.81, 128.39, 142.82, 146.17, 150.72, 163.80, 169.63; Anal. Calcd for $C_{21}H_{21}N_3O_3$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.41; H, 5.72; N, 11.63



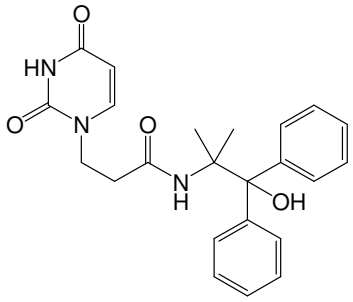
3-(2,4-Dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-*N*-(3,3-diphenylpropyl)propanamide (11g)

Compound **11g** (70 mg, 67%, a colorless solid) was synthesized from **9** (50 mg, 0.27 mmol) and 3,3-diphenylpropylamine (74 mg, 0.35 mmol) according to the procedure described for Method C**.** ^{1}H NMR (DMSO-d_6) δ 2.24 (2H, q, J = 7.6 Hz), 2.48 (2H, t, J = 5.4 Hz), 3.21 (2H, q, J = 6.5 Hz), 3.88-3.99 (3H, m), 5.55 (1H, d, J = 7.8 Hz), 5.72 (1H, t, J = 5.9 Hz), 7.14-7.30 (10H, m), 7.36 (1H, d, J = 7.8 Hz), 9.07 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 34.10, 34.42, 37.29, 44.77, 47.83, 100.37, 126.06, 127.54, 128.38, 144.64, 146.18, 150.76, 163.75, 169.33; Anal. Calcd for $C_{22}H_{23}N_3O_3$: C, 70.01; H, 6.14; N, 11.13. Found: C, 69.82; H, 6.19; N, 11.03



1-(3-(4-Benzylpiperidin-1-yl)-3-oxopropyl)pyrimidine-2,4(*1H,3H*)-dione (11h)

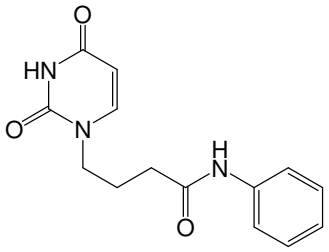
Compound **11h** (55 mg, 60%, a colorless solid) was synthesized from **9** (50 mg, 0.27 mmol) and 4-benzylpiperidine (62 μL, 0.35 mmol) according to the procedure described for Method C**.** ^{1}H NMR ($CDCl_3$) δ 1.04-1.19 (2H, m), 1.68-1.80 (3H, m), 2.46-2.56 (3H, m), 2.75 (2H, t, J = 5.4 Hz), 2.88-2.98 (1H, m), 3.71-3.78 (1H, m), 4.04 (2H, t, J = 5.4 Hz), 4.51-4.56 (1H, m), 5.63 (1H, dd, J = 2.2, 7.8 Hz), 7.11-7.31 (5H, m), 7.59 (1H, d, J = 8.1 Hz), 8.14 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 31.34, 32.00, 37.28, 41.11, 42.06, 44.72, 44.86, 100.39, 125.83, 128.16, 128.99, 140.00, 146.47, 150.90, 163.80, 167.96; Anal. Calcd for $C_{19}H_{23}N_3O_3$: C, 66.84; H, 6.79; N, 12.31. Found: C, 67.01; H, 6.85; N, 12.33



3-(2,4-Dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-*N*-(1-hydroxy-2-methyl-1,1-diphenylpropan-2-yl) propanamide (11i)

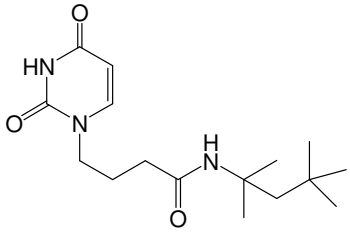
Compound **11i** (53 mg, 30%, a colorless solid) was synthesized from **9** (80 mg, 0.43 mmol) and 2-amino-2-methyl-1,1-diphenylpropan-1-ol[4] (195 mg, 0.80 mmol) according to the procedure described for Method C. ^{1}H NMR (DMSO-d_6) δ 1.27 (6H, s), 2.37 (2H, t, J = 6.5 Hz), 3.61 (2H, t, J

= 6.5 Hz), 5.35 (1H, d, *J* = 7.6 Hz), 7.12 -7.44 (12H, m), 8.43 (1H, s), 11.17 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 34.40, 44.67, 61.43, 81.65, 100.45, 126.42, 126.91, 128.16, 145.84, 150.66, 163.71, 170.99; TOF-HRMS m/z $[M+H]^+$: Calcd. for $C_{23}H_{26}N_3O_4$, 408.1923; Found, 408.1917; Purity: 98.54% (Column: Shim-pack XR-ODS 3 mmID×50 mm, 2.2 μm, Column temperature: 40 °C, Mobile phase: 10 mM Phosphate buffred solution pH 6.5 /Acetonitrile :0 min 90/10, 8 min 20/80, 10 min 20/80, Flow rate : 0.8 mL/min, **11i** was eluted at 5.4 min)



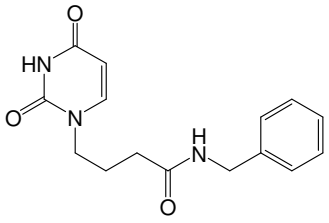
4-(2,4-Dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-*N*-phenylbutanamide (11j)

Compound **11j** (169 mg, 76%, a colorless solid) was synthesized from **10** (161 mg, 0.81 mmol) and aniline (311 mg, 3.24 mmol) according to the procedure described for Method C. ^{1}H NMR (DMSO-d_6) δ 1.84-1.94 (2H, m), 2.32 (2H, t, *J* = 7.6 Hz), 3.71 (2H, t, *J* = 7.0 Hz), 5.54 (1H, d, *J* = 7.6 Hz), 7.01 (1H, t, *J* = 7.6 Hz), 7.27 (2H, t, *J* = 8.4 Hz), 7.55 (2H, d, *J* = 8.1 Hz), 7.63 (1H, d, *J* = 7.8 Hz), 9.88 (1H, brs), 11.20 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 24.37, 33.08, 47.05, 100.94, 119.12, 123.05, 128.65, 139.20, 145.65, 151.02, 163.79, 170.29; Anal. Calcd for $C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.53; N, 15.38. Found: C, 61.31; H, 5.50; N, 15.26



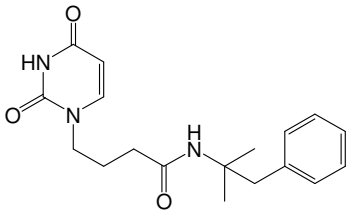
4-(2,4-Dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-*N*-(2,4,4-trimethylpentan-2-yl)butanamide (11k)

Compound **11k** (51 mg, 20%, a colorless solid) was synthesized from **10** (161 mg, 0.81 mmol) and *tert*-octylamine (520 μL, 3.24 mmol) according to the procedure described for Method C. ^{1}H NMR (DMSO-d_6) δ 0.91 (9H, s), 1.25 (6H, s), 1.68 (2H, s), 1.71-1.79 (2H, m), 2.00 (2H, t, *J* = 8.1 Hz), 3.63 (2H, t, *J* = 7.3 Hz), 5.52 (1H, d, *J* = 7.8 Hz), 7.28 (1H, brs), 7.59 (1H, d, *J* = 7.6 Hz), 11.18 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 24.64, 29.27, 31.43, 31.63, 33.41, 47.78, 51.32, 55.31, 102.32, 144.75, 151.16, 163.63, 170.44; Anal. Calcd for $C_{16}H_{27}N_3O_3$: C, 62.11; H, 8.80; N, 13.58. Found: C, 62.15; H, 8.89; N, 13.44



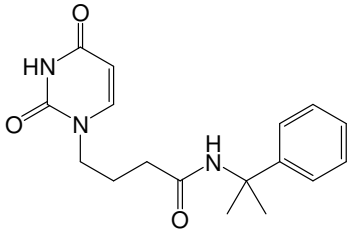
***N*-Benzyl-4-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)butanamide (11l)**

Compound **11l** (92 mg, 39%, a colorless solid) was synthesized from **10** (161 mg, 0.81 mmol) and benzylamine (354 μL, 3.24 mmol) according to the procedure described for Method C. ^{1}H NMR (DMSO-d_6) δ 1.77-1.88 (2H, m), 2.15 (2H, t, J = 7.8 Hz), 3.66 (2H, t, J = 7.0 Hz), 4.24 (2H, d, J = 5.9 Hz), 5.52 (1H, d, J = 7.8 Hz), 7.19-7.34 (5H, m), 7.59 (1H, J = 7.8 Hz), 8.33 (1H, t, J = 5.4 Hz), 11.19 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 24.67, 32.05, 42.03, 47.14, 100.82, 126.69, 127.19, 128.25, 139.50, 145.64, 150.93, 163.72, 171.18; Anal. Calcd for $C_{15}H_{17}N_3O_3$: C, 62.71; H, 5.96; N, 14.63. Found: C, 62.91; H, 6.03; N, 14.42



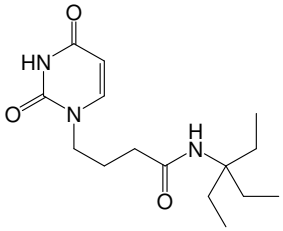
4-(2,4-Dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-*N*-(2-methyl-1-phenylpropan-2-yl)butanamide (11m)

Compound **11m** (155 mg, quant., a colorless solid) was synthesized from **10** (92 mg, 0.46 mmol) and phentermine (148 μL, 0.92 mmol) according to the procedure described for Method C. ^{1}H NMR (DMSO-d_6) δ 1.17 (6H, s), 1.74-1.85 (2H, m), 2.02 (2H, t, J = 8.1 Hz), 2.96 (2H, s), 3.66 (2H, t, J = 6.8 Hz), 5.53 (1H, d, J = 7.8 Hz), 7.06-7.09 (2H, m), 7.15-7.28 (4H, m), 7.60 (1H, d, J = 7.6 Hz), 11.19 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 24.82, 27.36, 33.29, 44.78, 47.78, 54.23, 102.37, 126.43, 128.01, 130.47, 137.95, 144.75, 151.24, 163.78, 171.12; Anal. Calcd for $C_{18}H_{23}N_3O_3$: C, 65.63; H, 7.04; N, 12.76. Found: C, 65.60; H, 7.09; N, 12.56



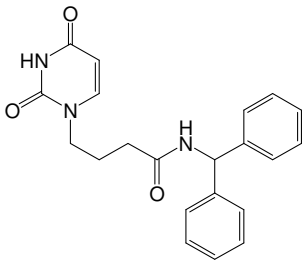
4-(2,4-Dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-*N*-(2-phenylpropan-2-yl)butanamide (11n)

Compound **11n** (152 mg, quant., a colorless solid) was synthesized from **10** (92 mg, 0.46 mmol) and cumylamine (132 μL, 0.92 mmol) according to the procedure described for Method C. ^{1}H NMR (DMSO-d_6) δ 1.51 (6H, s), 1.70-1.81 (2H, m), 2.12 (2H, t, *J* = 7.8 Hz), 3.63 (2H, t, *J* = 6.8 Hz), 5.53 (1H, d, *J* = 7.8 Hz), 7.10-7.31 (5H, m), 7.57 (1H, d, *J* = 7.6 Hz), 8.02 (1H, brs), 11.20 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 24.67, 29.44, 32.58, 47.10, 54.62, 100.86, 124.63, 125.66, 127.84, 145.62, 147.91, 150.95, 163.74, 170.37; Anal. Calcd for $C_{17}H_{21}N_3O_3$: C, 64.74; H, 6.71; N, 13.32. Found: C, 64.56; H, 6.82; N, 13.25



4-(2,4-Dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-*N*-(3-ethylpentan-3-yl)butanamide (11o)

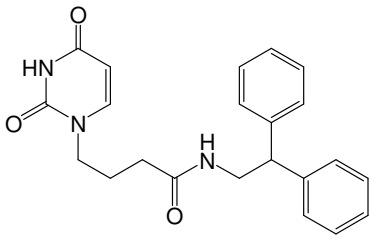
Compound **11o** (12 mg, 24% as a colorless solid) was synthesized from (34 mg, 0.17 mmol) and 3-ethylpentane-3-amine hydrochloride[3] (60 mg, 0.34 mmol) according to the procedure described for the conversion of **9** to **11b**. ^{1}H NMR ($CDCl_3$) δ 0.78 (9H, t, *J* = 7.6 Hz), 1.67 (6H, q, *J* = 7.3 Hz), 1.94-2.04 (2H, m), 2.21 (2H, t, *J* = 6.8 Hz), 3.82 (2H, t, *J* = 7.0 Hz), 5.09 (1H, brs), 5.71 (1H, d, *J* = 7.8 Hz), 7.29(1H, d, *J* = 7.8 Hz), 7.81 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 7.37, 25.14, 25.53, 32.85, 47.22, 58.22, 100.87, 145.65, 150.95, 163.76, 170.62; Anal. Calcd for $C_{15}H_{25}N_3O_3$: C, 60.99; H, 8.53; N, 14.23. Found: C, 61.10; H, 8.59; N, 13.99



***N*-Benzhydryl-4-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)butanamide (11p)**

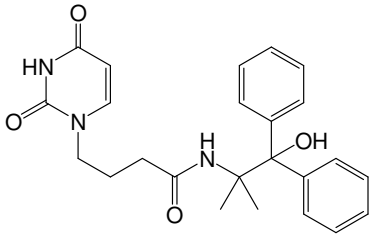
Compound **11p** (51 mg, 70%, a colorless solid) was synthesized from **10** (40 mg, 0.20 mmol) and benzhydrylamine (38 μL, 0.22 mmol) according to the procedure described for Method C**.** ^{1}H NMR (DMSO-d_6) δ 1.77-1.88 (2H, m), 2.23 (2H, t, *J* = 6.9 Hz), 3.67 (2H, t, *J* = 6.9 Hz), 5.51 (1H, dd, *J* = 2.0, 7.9 Hz), 6.11 (1H, d, *J* = 8.6 Hz), 7.20-7.35 (10H, m), 7.58 (1H, d, *J* = 7.9 Hz), 8.78 (1H, d, *J* = 8.6 Hz), 11.22 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 24.68, 32.01, 47.16, 55.84, 100.83, 126.87, 127.23,

128.33, 142.52, 145.61, 150.93, 163.72, 170.56; Anal. Calcd for $C_{21}H_{21}N_3O_3$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.11; H, 5.85; N, 11.87



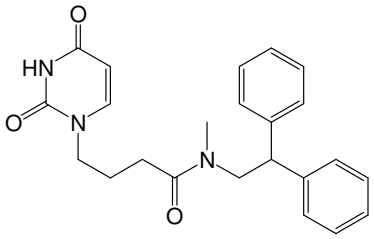
4-(2,4-Dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-*N*-(2,2-diphenylethyl)butanamide (11q)

Compound **11q** (58 mg, 75%, a colorless solid) was synthesized from **10** (40 mg, 0.20 mmol) and 2,2-diphenylethylamine (43 mg, 0.22 mmol) according to the procedure described for Method C**.** ^{1}H NMR (DMSO-d_6) δ 1.63-1.73 (2H, m), 1.97 (2H, t, *J* = 7.3 Hz), 3.51 (2H, t, *J* = 6.8 Hz), 3.68 (2H, t, *J* = 6.6 Hz), 4.19 (1H, t, *J* = 7.8 Hz), 5.48 (1H, dd, *J* = 1.9, 7.6 Hz), 7.14-7.32 (10H, m), 7.40 (1H, d, *J* = 8.1 Hz), 7.93 (1H, t, *J* = 5.7 Hz), 11.20 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 24.54, 31.94, 43.01, 47.06, 50.11, 100.73, 126.30, 127.85, 128.39, 142.86, 145.61, 150.82, 163.70, 171.21; Anal. Calcd for $C_{22}H_{23}N_3O_3 \cdot 0.3H_2O$: C, 69.02; H, 6.21; N, 10.98. Found: C, 69.04; H, 6.10; N, 11.38



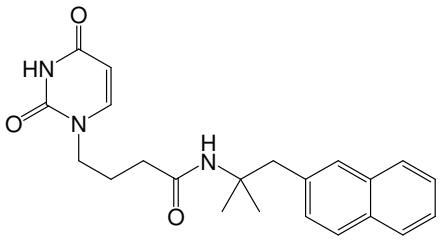
4-(2,4-Dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-*N*-(1-hydroxy-2-methyl-1,1-diphenylpropan-2-yl) butanamide (11r)

Compound **11r** (100 mg, 59%, a colorless solid) was synthesized from **10** (80 mg, 0.40 mmol) and 2-amino-2-methyl-1,1-diphenylpropan-1-ol[4] (195 mg, 0.80 mmol) according to the procedure described for Method C**.** ^{1}H NMR (DMSO-d_6) δ 1.25 (6H, s), 1.46 (2H, t, *J* = 7.3 Hz), 1.93-1.99 (2H, m), 3.28-3.36 (2H, m), 5.52 (1H, d, *J* = 7.8 Hz), 7.13-7.50 (11H, m), 7.66 (1H, s), 8.39 (1H, s), 11.2 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 24.49, 32.30, 46.68, 61.43, 81.66, 100.85, 126.33, 126.95, 128.08, 145.46, 150.80, 163.70, 173.02; TOF-HRMS m/z $[M+H]^+$: Calcd. for $C_{24}H_{28}N_3O_4$, 422.2080; Found, 422.2084; Purity: 95.34% (Column: Shim-pack XR-ODS 3 mmID×50 mm, 2.2 μm, Column temperature: 40 °C, Mobile phase: 10 mM Phosphate buffred solution pH 6.5 /Acetonitrile :0 min 90/10, 8 min 20/80, 10 min 20/80, Flow rate : 0.8 mL/min, **11r** was eluted 5.6 min)



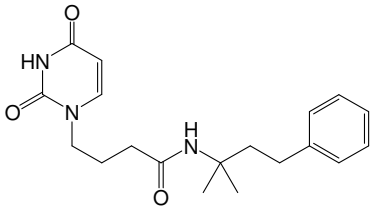
4-(2,4-Dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-*N*-(2,2-diphenylethyl)-*N*-methylbutanamide (11s)

Compound **11s** (80 mg, 50%, a colorless solid) was synthesized from **10** (40 mg, 0.20 mmol) and 2-(methylamino)-1,1-diphenylethanol[5] (91 mg, 0.40 mmol) according to the procedure described for Method C**.** ^{1}H NMR (DMSO-d_6) δ 1.57-1.74 (2H, m), 1.99 (0.8H, t, J = 7.0 Hz), 2.15 (1.2H, t, J = 7.0 Hz), 2.68 (1.8H, s), 2.72 (1.2H, s), 3.50-3.58 (2H, m), 3.94 (2H, d, J = 7.8 Hz), 4.26-4.38 (1H, m), 5.50 (0.6H, d, J = 7.8 Hz), 5.53 (0.4H, d, J = 7.8 Hz), 7.16-7.36 (10H, m), 7.41 (0.6H, d, J = 7.8 Hz), 7.52 (0.4H, d, J = 7.8 Hz), 11.2 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 23.83, 24.12, 28.44, 29.26, 33.32, 35.49, 47.09, 48.58, 49.04, 51.46, 53.87, 100.78, 100.83, 126.38, 126.58, 127.97, 128.08, 128.33, 128.39, 142.20, 142.55, 145.54, 150.86, 163.69, 171.07, 171.16; Anal. Calcd for $C_{23}H_{25}N_3O_3$: C, 70.57; H, 6.44; N, 10.73. Found: C, 70.40; H, 6.56; N, 10.71



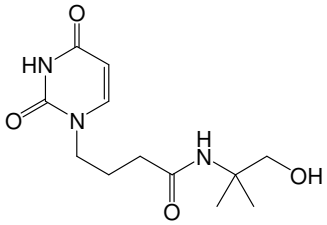
4-(2,4-Dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-*N*-(2-methyl-1-(naphthalen-2-yl)propan-2-yl)butanamide (11t)

Compound **11t** (51 mg, 61%, a colorless solid) was synthesized from **10** (40 mg, 0.20 mmol) and 2-methyl-1-(naphthalen-2-yl)propan-2-amine[6] (48 mg, 0.24 mmol) according to the procedure described for Method C**.** ^{1}H NMR (DMSO-d_6) δ 1.23 (6H, s), 1.82-1.90 (2H, m), 2.02-2.09 (2H, m), 3.15 (2H, s), 3.68 (2H, t, J = 7.0 Hz), 5.55 (1H, dd, J = 2.2, 8.1 Hz), 7.26 (1H, s), 7.30 (1H, s), 7.42-7.49 (2H, m), 7.56 (1H,s), 7.62 (1H, d, J = 7.6 Hz), 7.79-7.88 (3H, m), 11.22 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 24.95, 27.12, 32.94, 43.45, 47.20, 53.20, 100.87, 125.27, 125.84, 126.83, 127.28, 127.33, 128.39, 129.21, 131.65, 132.81, 136.16, 145.65, 150.95, 163.76, 171.30; Anal. Calcd for $C_{22}H_{25}N_3O_3 \cdot 0.3H_2O$: C, 68.66; H, 6.70; N, 10.92. Found: C, 68.75; H, 6.64; N, 11.16



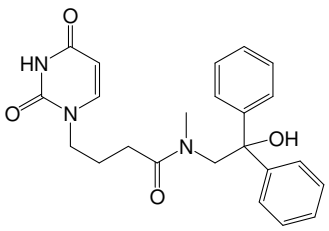
4-(2,4-Dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-*N*-(2-methyl-4-phenylbutan-2-yl)butanamide (11u)

Compound **11u** (53 mg, 70%, a colorless solid) was synthesized from **10** (40 mg, 0.20 mmol) and 1,1-dimethyl-3-phenyl-propylamine hydrochloride[7] (46 mg, 0.23 mmol) according to the procedure described for Method C**.** ^{1}H NMR (DMSO-d_6) δ 1.25 (6H, s), 1.74-1.93 (4H, m), 2.04-2.10 (2H, m), 2.45-2.52 (2H, m), 3.66 (2H, t, *J* = 7.0 Hz), 5.54 (1H, dd, *J* = 1.9, 7.6 Hz), 7.12-7.27 (5H, m), 7.28 (1H, s), 7.61 (1H, d, *J* = 7.6 Hz), 11.22 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 24.99, 27.10, 30.75, 33.21, 41.72, 47.77, 53.93, 102.44, 125.83, 128.38, 128.43, 142.14, 144.74, 151.35, 163.74, 170.86; Anal. Calcd for $C_{19}H_{25}N_3O_3$: C, 66.45; H, 7.34; N, 12.24. Found: C, 66.18; H, 7.49; N, 12.01



4-(2,4-Dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-*N*-(1-hydroxy-2-methylpropan-2-yl)butanamide (11v)

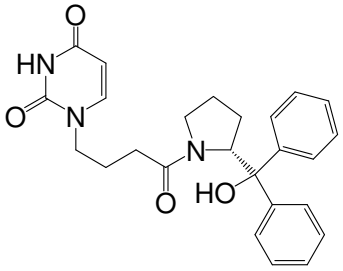
Compound **11v** (102 mg, 83%, a colorless solid) was synthesized from **10** (92 mg, 0.46 mmol) and 2-amino-2-methyl-1-propanol (82 mg, 0.92 mmol) according to the procedure described for Method C. ^{1}H NMR (DMSO-d_6) δ 1.14 (6H, s), 1.70-1.80 (2H, m), 2.04 (2H, t, *J* = 7.6 Hz), 3.36 (2H, d, *J* = 5.7 Hz), 3.63 (2H, t, *J* = 7.0 Hz), 4.78 (1H, t, *J* = 5.9 Hz), 5.52 (1H, d, *J* = 7.8 Hz), 7.23 (1H, brs), 7.58 (1H, d, *J* = 8.1 Hz), 11.2 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 23.68, 24.67, 32.70, 47.12, 54.18, 67.23, 100.83, 145.69, 150.95, 163.75, 171.25; Anal. Calcd for $C_{12}H_{19}N_3O_4$: C, 53.52; H, 7.11; N, 15.60. Found: C, 53.30; H, 7.11; N, 15.36



4-(2,4-Dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-*N*-(2-hydroxy-2,2-diphenylethyl)-*N*-methylbutan

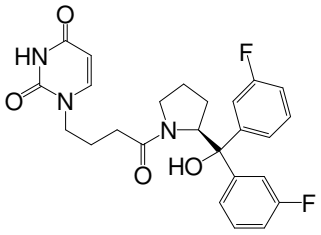
amide (11w)

Compound **11w** (23 mg, 14%, a colorless solid) was synthesized from **10** (80 mg, 0.40 mmol) and 2-(methylamino)-1,1-diphenylethanol[8] (182 mg, 0.80 mmol) according to the procedure described for Method C. ^{1}H NMR ($CDCl_3$) δ 1.95-2.05 (2H, m), 2.29 (2H, t, *J* = 6.2 Hz), 2.52 (3H, s), 3.77 (2H, t, *J* = 7.0 Hz), 4.28 (2H, s), 5.45 (1H, s), 5.67 (1H, d, *J* = 8.1 Hz), 7.21-7.48 (11H, m), 8.54 (1H, brs); ^{13}C NMR (DMSO-d_6) δ 23.84, 24.28, 28.49, 29.22, 36.15, 37.18, 47.03, 47.16, 56.50, 58.64, 77.38, 78.30, 100.82, 126.11, 126.51, 126.83, 127.65, 127.78, 145.56, 145.90, 146.11, 150.84, 150.87, 163.72, 163.75, 172.26, 173.28; Anal. Calcd for $C_{23}H_{25}N_3O_4$: C, 67.80; H, 6.18; N, 10.31. Found: C, 67.65; H, 6.25; N, 10.18



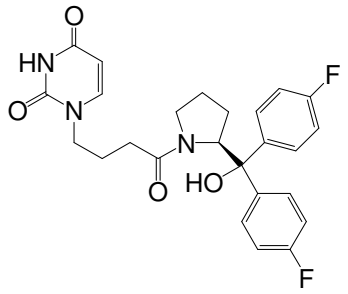
(*R*)-1-(4-(2-(Hydroxydiphenylmethyl)pyrrolidin-1-yl)-4-oxobutyl)pyrimidine-2,4(1*H*,3*H*)-dione (12b)

Compound **12b** (63 mg, 66%, a colorless foam) was synthesized from **10** (40 mg, 0.22 mmol) and (*R*)-(+)-α, α-diphenyl-2-pyrrolidinemethanol (56 mg, 0.22 mmol) according to the procedure described for Method D. ^{1}H NMR ($CDCl_3$) δ 1.01-1.09 (1H, m), 1.55-1.65 (1H, m), 1.91-2.10 (4H, m), 2.19-2.40 (2H, m), 3.02-3.13 (1H, m), 3.35-3.47 (1H, m), 3.51-3.60 (1H, m), 3.66-3.79 (1H, m), 5.13 (1H, dd, *J* = 5.7, 8.4 Hz), 5.69 (1H, dd, *J* = 1.9, 7.8 Hz), 6.69 (1H, s), 7.13 (1H, d, *J* = 7.8 Hz), 7.20-7.43 (10H, m), 8.77 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 23.27, 23.87, 29.80, 31.02, 47.72, 48.75, 67.39, 81.57, 102.13, 127.34, 127.40, 127.57, 127.87, 127.98, 143.52, 145.03, 146.06, 150.82, 163.54, 173.77; Anal. Calcd for $C_{25}H_{27}N_3O_4 \cdot 0.6H_2O$: C, 67.58; H, 6.40; N, 9.46. Found: C, 67.62; H, 6.42; N, 9.23; $[\alpha]^{25}_D$ = 102.46 (*c* 1.05, $CHCl_3$)



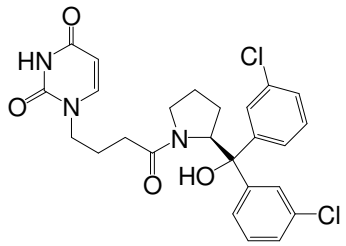
(*S*)-1-(4-(2-(Bis(3-fluorophenyl)(hydroxy)methyl)pyrrolidin-1-yl)-4-oxobutyl)pyrimidine-2,4(1*H*,3*H*)-dione (12c)

Compound **12c** (80 mg, 85%, a colorless solid) was synthesized from **10** (40 mg, 0.22 mmol) and (*S*)-α, α-bis(3-fluorophenyl)-2-pyrrolidinemethanol **8a** (64 mg, 0.22 mmol) according to the procedure described for Method D. ^{1}H NMR ($CDCl_3$) δ 1.08-1.21 (1H, m), 1.57-1.72 (1H, m), 1.88-2.13 (4H, m), 2.21-2.43 (2H, m), 3.06-3.15 (1H, m), 3.39-3.48 (1H, m), 3.54-3.80 (2H, m), 5.03 (1H, dd, *J* = 5.7, 8.6 Hz), 5.71 (1H, dd, *J* = 2.4, 7.8 Hz), 6.93-7.35 (10H, m), 8.77 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 23.35, 23.91, 29.77, 31.10, 47.70, 48.76, 67.42, 80.97, 102.28, 114.40, 114.61, 114.68, 114.90, 114.94, 115.16, 123.02, 123.05, 123.42, 128.99, 129.08, 129.50, 129.58, 144.76, 145.91, 145.97, 148.06, 148.12, 150.78, 161.30, 161.34, 163.36, 163.74, 163.79, 174.09; Anal. Calcd for $C_{25}H_{25}F_2N_3O_4$: C, 63.96; H, 5.37; N, 8.95. Found: C, 63.82; H, 5.20; N, 9.21; $[\alpha]^{25}_D$ = -121.24 (*c* 0.32, $CHCl_3$)



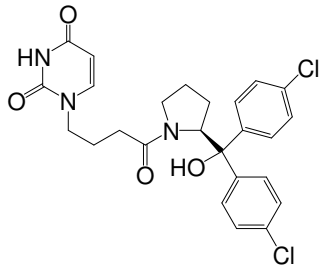
(*S*)-1-(4-(2-(Bis(4-fluorophenyl)(hydroxy)methyl)pyrrolidin-1-yl)-4-oxobutyl)pyrimidine-2,4(1*H*,3*H*)-dione (12d)

Compound **12d** (80 mg, 77%, a colorless solid) was synthesized from **10** (40 mg, 0.22 mmol) and (*S*)-α, α-bis(4-fluorophenyl)-2-pyrrolidinemethanol **8b** (64 mg, 0.22 mmol) according to the procedure described for Method D. ^{1}H NMR ($CDCl_3$) δ 0.95-1.08 (1H, m), 1.57-1.69 (1H, m), 1.84-2.10 (4H, m), 2.23-2.44 (2H, m), 3.00-3.09 (1H, m), 3.36-3.45 (1H, m), 3.61-3.84 (2H, m), 5.08 (1H, dd, J = 4.5, 8.6 Hz), 5.71 (1H, d, *J* = 7.8 Hz), 6.71 (1H, s), 7.00 (4H, t, *J* = 8.9 Hz), 7.20 (1H, d, *J* = 7.8 Hz), 7.31-7.37 (4H, m), 8.71 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 23.25, 23.97, 29.63, 31.12, 47.76, 48.64, 67.06, 80.93, 102.30, 114.40, 114.60, 114.74, 114.94, 129.20, 129.28, 129.49, 129.56, 139.15, 141.89, 141.93, 144.72, 150.84, 160.74, 161.01, 163.19, 163.39, 163.47, 174.14; Anal. Calcd for $C_{25}H_{25}F_2N_3O_4 \cdot 0.3H_2O$: C, 63.23; H, 5.43; N, 8.85. Found: C, 63.42; H, 5.42; N, 8.86; $[\alpha]^{25}_D$ = -105.38 (*c* 0.52, $CHCl_3$)



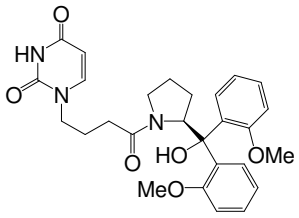
(*S*)-1-(4-(2-(Bis(3-chlorophenyl)(hydroxy)methyl)pyrrolidin-1-yl)-4-oxobutyl)pyrimidine-2,4(1*H*,3*H*)-dione (12e)

Compound **12e** (137 mg, 68%, a colorless foam) was synthesized from **10** (79 mg, 0.4 mmol) and (*S*)- α, α-bis(3-chlorophenyl)-2-pyrrolidinemethanol **8c** (190 mg, 0.68 mmol) according to the procedure described for Method D. ^{1}H NMR ($CDCl_3$) δ 1.12-1.26 (1H, m), 1.60-1.70 (1H, m), 1.85-2.10 (4H, m), 2.22-2.42 (2H, m), 3.06 (1H, m), 3.40-3.60 (2H, m), 3.68-3.83 (1H, m), 4.99-5.04 (1H, m), 5.71 (1H, d, *J* = 7.8 Hz), 6.94 (1H, s), 7.16-7.32 (7H, m), 7.37 (1H, d, *J* = 1.1 Hz), 7.49 (1H, s), 8.31 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 23.39, 23.94, 29.85, 31.16, 47.69, 48.81, 67.45, 81.00, 102.30, 125.72, 125.92, 127.71, 127.80, 127.98, 128.91, 129.39, 134.01, 134.13, 144.80, 145.21, 147.41, 150.84, 163.47, 174.05; Anal. Calcd for $C_{25}H_{25}Cl_2N_3O_4$: C, 59.77; H, 5.02; N, 8.36. Found: C, 59.64; H, 4.91; N, 8.17; $[\alpha]^{25}_D$ = -103.96 (*c* 1.06, $CHCl_3$)



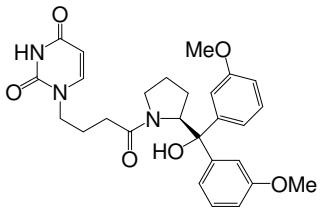
(*S*)-1-(4-(2-(Bis(4-chlorophenyl)(hydroxy)methyl)pyrrolidin-1-yl)-4-oxobutyl)pyrimidine-2,4(1*H*,3*H*)-dione (12f)

Compound **12f** (74 mg, 74%, a colorless foam) was synthesized from **10** (40 mg, 0.22 mmol) and (*S*)-α, α-bis(4-Chlorophenyl)-2-pyrrolidinemethanol[1] (71 mg, 0.22 mmol) according to the procedure described for Method D. ^{1}H NMR ($CDCl_3$) δ 1.02-1.15 (1H, m), 1.59-1.66 (1H, m), 1.87-2.06 (4H, m), 2.28-2.37 (2H, m), 3.06-3.09 (1H, m), 3.40-3.46 (1H, m), 3.57-3.80 (2H, m), 5.05 (1H, dd, *J* = 5.1, 8.6 Hz), 5.71 (1H, d, *J* = 7.8 Hz), 6.77 (1H, brs), 7.16 (1H, d, *J* = 7.8 Hz), 7.28-7.35 (8H, m), 8.46 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 23.34, 23.94, 29.65, 31.14, 47.73, 48.69, 67.05, 80.91, 102.34, 127.84, 128.21, 128.91, 129.24, 133.41, 133.62, 141.82, 144.26, 144.67, 150.88, 163.48, 174.12; Anal. Calcd for $C_{25}H_{25}Cl_2N_3O_4$: C, 59.77; H, 5.02; N, 8.36. Found: C, 59.48; H, 5.05; N, 8.44; $[\alpha]^{25}_D$ = -119.22 (*c* 1.05, $CHCl_3$)



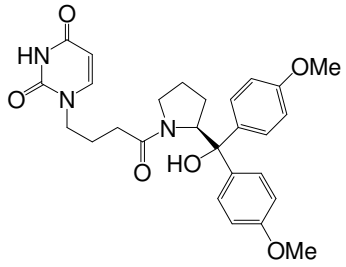
(*S*)-1-(4-(2-(Hydroxybis(2-methoxyphenyl)methyl)pyrrolidin-1-yl)-4-oxobutyl)pyrimidine-2,4(1*H*,3*H*)-dione (12g)

Compound **12g** (83 mg, 84%, a colorless foam) was synthesized from **10** (40 mg, 0.22 mmol) and (*S*)- α, α-bis(2-methoxyphenyl-2-pyrrolidinemethanol **8d** (81 mg, 0.26 mmol) according to the procedure described for Method D. ^{1}H NMR (DMSO-d_6) δ 0.80-2.32 (8H, m), 3.24-3.83 (10H, m), 5.10-5.20 (1H, m), 5.51-5.60 (2H, m), 6.71-7.61 (9H, m), 11.2 (1H, brs); Anal. Calcd for $C_{27}H_{31}N_3O_6 \cdot 0.7H_2O$: C, 64.07; H, 6.45; N, 8.30. Found: C, 64.12; H, 6.22; N, 8.68; $[\alpha]^{25}_D$ = 100.00 (*c* 0.33, $CHCl_3$)



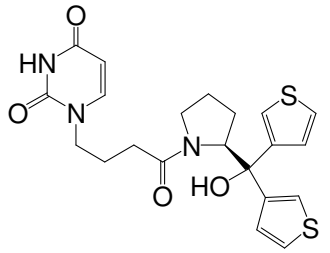
(*S*)-1-(4-(2-(Hydroxybis(3-methoxyphenyl)methyl)pyrrolidin-1-yl)-4-oxobutyl)pyrimidine-2,4(1*H*,3*H*)-dione (12h)

Compound **12h** (85 mg, 86%, a colorless foam) was synthesized from **10** (40 mg, 0.22 mmol) and (*S*)-α, α-bis(3-methoxyphenyl)-2-pyrrolidinemethanol **8e** (81 mg, 0.26 mmol) according to the procedure described for Method D. ^{1}H NMR ($CDCl_3$) δ 1.15-1.26 (1H, m), 1.56-1.67 (1H, m), 1.89-2.04 (4H, m), 2.24-2.40 (2H, m), 3.09-3.18 (1H, m), 3.38-3.56 (2H, m), 3.63-3.73 (1H, m), 3.76 (6H, s), 5.04 (1H, t, *J* = 8.1 Hz), 5.69 (1H, dd, *J* = 2.4, 7.8 Hz), 6.78-7.08 (7H, m), 7.13 (1H, d, *J* = 7.8 Hz), 7.18-7.27 (2H, m), 8.84 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 23.41, 23.85, 29.99, 31.04, 47.69, 48.91, 55.25, 55.27, 67.87, 81.37, 102.07, 112.08, 112.54, 113.83, 114.44, 119.89, 120.25, 128.34, 128.85, 145.05, 145.16, 147.46, 150.74, 159.21, 159.28, 163.43, 173.65; Anal. Calcd for $C_{27}H_{31}N_3O_6 \cdot 0.5H_2O$: C, 64.53; H, 6.42; N, 8.36. Found: C, 64.48; H, 6.43; N, 8.08; $[\alpha]^{25}_D$ = -77.19 (*c* 1.14, $CHCl_3$)



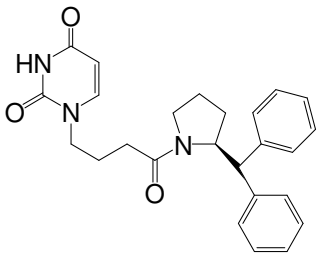
(*S*)-1-(4-(2-(Hydroxybis(4-methoxyphenyl)methyl)pyrrolidin-1-yl)-4-oxobutyl)pyrimidine-2,4(1*H*,3*H*)-dione (12i)

Compound **12i** (70 mg, 71%, a colorless foam) was synthesized from **10** (40 mg, 0.22 mmol) and (*S*)-α,α-bis(4-methoxyphenyl)-2-pyrrolidinemethanol[1] (81 mg, 0.26 mmol) according to the procedure described for Method D. ^{1}H NMR ($CDCl_3$) δ 0.98-1.08 (1H, m), 1.54-1.63 (1H, m), 1.91-2.08 (4H, m), 2.27-2.39 (2H, m), 3.00-3.09 (1H, m), 3.34-3.43 (1H, m), 3.53-3.84 (2H, m), 3.80 (6H, s), 5.09 (1H, q, 4.9 Hz), 5.69 (1H, d, *J* = 7.8 Hz), 6.49 (1H, s), 6.81-6.87 (4H, m), 7.17 (1H, d, *J* = 7.6 Hz), 7.24-7.31 (4H, m), 8.36 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 23.28, 23.91, 29.67, 31.02, 47.78, 48.67, 55.25, 67.17, 81.07, 102.12, 112.85, 113.23, 128.72, 129.01, 135.72, 138.67, 144.99, 150.78, 158.63, 158.85, 163.44, 173.76; Anal. Calcd for $C_{27}H_{31}N_3O_6 \cdot 0.2H_2O$: C, 65.23; H, 6.37; N, 8.45. Found: C, 65.16; H, 6.33; N, 8.42; $[\alpha]^{25}_D$ = -115.98 (*c* 0.50, $CHCl_3$)



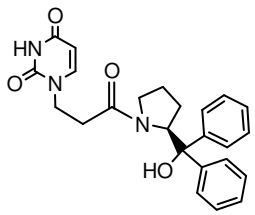
(*S*)-1-(4-(2-(Hydroxydithiophen-3-ylmethyl)pyrrolidin-1-yl)-4-oxobutyl)pyrimidine-2,4(1*H*,3*H*)-dione (12j)

Compound **12j** (40 mg, 45%, a colorless foam) was synthesized from **10** (40 mg, 0.22 mmol) and (*S*)-α, α-bis(3-thienyl)-2-pyrrolidinemethanol **8f** (66 mg, 0.25 mmol) according to the procedure described for Method D. ^{1}H NMR ($CDCl_3$) δ 1.33-1.70 (2H, m), 1.90-2.05 (4H, m), 2.18-2.39 (2H, m), 2.98-3.08 (1H, m), 3.39-3.48 (1H, m), 3.63-3.79 (2H, m), 4.93 (1H, t, *J*= 8.1 Hz), 5.70 (1H, d, *J* = 7.8 Hz), 7.08-7.31 (7H, m), 8.25 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 23.60, 23.98, 29.40, 31.12, 47.75, 48.84, 67.84, 78.96, 102.23, 121.97, 122.82, 124.97, 125.63, 127.17, 127.40, 144.76, 144.90, 146.81, 150.86, 163.54, 173.72; Anal. Calcd for $C_{21}H_{23}N_3O_4S_2$: C, 56.61; H, 5.20; N, 9.43. Found: C,56.43; H, 5.25; N, 9.35; $[\alpha]^{25}_D$ = -87.02 (*c* 1.08, $CHCl_3$)



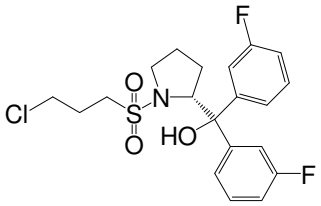
(*S*)-1-(4-(2-Benzhydrylpyrrolidin-1-yl)-4-oxobutyl)pyrimidine-2,4(1*H*,3*H*)-dione (12k)

Compound **12k** (80 mg, 96%, a colorless foam) was synthesized from **10** (40 mg, 0.22 mmol) and (*S*)-2-(diphenylmethyl)pyrrolidine (48 mg, 0.20 mmol) according to the procedure described for Method D. ^{1}H NMR (DMSO-d_6) δ 0.87-1.25 (0.4H, m), 1.50-1.96 (6.6H, m), 2.15-2.23 (1H, m), 3.09-3.66 (4H, m), 4.00 (0.5H, d, *J* = 11 Hz), 4.44 (0.5H, d, *J* = 5.9 Hz), 4.63-4.65 (0.5H, m), 4.83-4.85 (0.5H, m), 5.52 (1H, d, *J* = 8.1 Hz), 7.11-7.45 (11H, m), 11.2 (1H, brs); Anal. Calcd for $C_{25}H_{27}N_3O_3 \cdot 0.2H_2O$: C, 71.30; H, 6.56; N, 9.98. Found: C, 71.27; H, 6.53; N, 10.03; $[\alpha]^{25}_D = 36.00$ (*c* 0.55, $CHCl_3$)



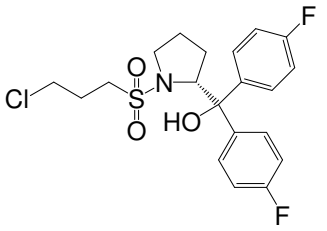
(*S*)-1-(3-(2-(Hydroxydiphenylmethyl)pyrrolidin-1-yl)-3-oxopropyl)pyrimidine-2,4(1*H*,3*H*)-dion e (12l)

Compound **12l** (59 mg, 64%, a colorless foam) was synthesized from **9** (41 mg, 0.22 mmol) and (*S*)-(-)-α, α-diphenyl-2-pyrrolidinemethanol (56 mg, 0.22 mmol) according to the procedure described for Method D. ^{1}H NMR ($CDCl_3$) δ 1.12-1.26 (1H, m), 1.60-1.70 (1H, m), 1.85-2.10 (4H, m), 2.22-2.42 (2H, m), 3.06 (1H, m), 3.40-3.60 (2H, m), 3.68-3.83 (1H, m), 4.99-5.04 (1H, m), 5.71 (1H, d, *J* = 7.8 Hz), 6.94 (1H, s), 7.16-7.32 (7H, m), 7.37 (1H, d, *J* = 1.1 Hz), 7.49 (1H, s), 8.31 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 23.17, 29.58, 33.56, 45.36, 48.57, 67.34, 81.64, 101.47, 127.37, 127.45, 127.54, 127.57, 127.76, 127.97, 143.21, 146.01, 146.65, 150.96, 163.66, 172.28; Anal. Calcd for $C_{24}H_{25}N_3O_4 \cdot 0.5H_2O$: C, 67.27; H, 6.12; N, 9.81. Found: C, 67.36; H, 6.19; N, 9.46; $[\alpha]^{25}_D = -152.44$ (*c* 0.45, $CHCl_3$)



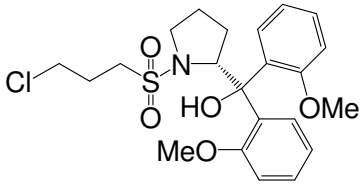
(*R*)-(1-(3-Chloropropylsulfonyl)pyrrolidin-2-yl)bis(3-fluorophenyl)methanol (13a)

Compound **13a** (1.80 g, 84%, a colorless solid) was synthesized from (*R*)-α, α-bis(3-fluorophenyl)-2-pyrrolidinemethanol **8g** (1.53 g, 5.3 mmol) according to the procedure described for Method E. ^{1}H NMR ($CDCl_3$) δ 1.41-1.49 (1H, m), 1.70-1.80 (1H, m), 1.84-1.95 (1H, m), 2.07-2.23 (3H, m), 2.71-2.85 (2H, m), 3.01 (1H, dt, *J* = 7.6, 11.1 Hz), 3.25 (1H, s), 3.53-3.58 (2H, m), 3.65-3.73 (1H, m), 5.17 (1H, dd, *J* = 4.3, 8.9 Hz), 6.94-7.02 (2H, m), 7.16-7.36 (6H, m); FAB-HRMS m/z $[M-H]^-$: Calcd. for $C_{20}H_{21}ClF_2NO_3S$, 428.0899; Found, 428.0879



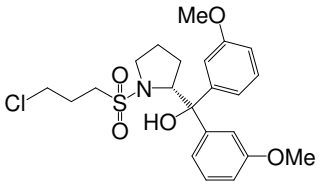
(*R*)-(1-(3-Chloropropylsulfonyl)pyrrolidin-2-yl)bis(4-fluorophenyl)methanol (13b)

Compound **13b** (1.83 g, 80%, a colorless solid) was synthesized from (*R*)-α, α-bis(4-fluorophenyl)-2-pyrrolidinemethanol **8h** (1.53 g, 5.3 mmol) according to the procedure described for Method E. ^{1}H NMR ($CDCl_3$) δ 1.23-1.38 (1H, m), 1.64-1.80 (1H, m), 1.83-1.94 (1H, m), 2.11-2.27 (3H, m), 2.85-2.97 (3H, m), 3.30 (1H, brs), 3.52-3.68 (3H, m), 5.14 (1H, dd, *J* = 3.8, 8.9 Hz), 6.96-7.06 (4H, m), 7.34-7.49 (4H, m); FAB-HRMS m/z $[M-H]^-$: Calcd. for $C_{20}H_{21}ClF_2NO_3S$, 428.0899; Found, 428.0879



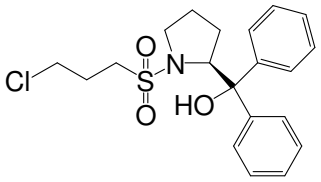
(*R*)-(1-(3-Chloropropylsulfonyl)pyrrolidin-2-yl)bis(2-methoxyphenyl)methanol (13c)

Compound **13c** (2.10 g, 73%, a colorless solid) was synthesized from (*R*)-α, α-bis(2-methoxyphenyl)-2-pyrrolidinemethanol **8i** (2.0 g, 6.4 mmol) according to the procedure described for Method E. ^{1}H NMR ($CDCl_3$) δ 1.75-1.93 (4H, m), 1.95-2.12 (2H, m), 2.21 (2H, dt, *J* = 4.6, 8.4 Hz), 3.32-3.42 (3H, m), 3.56 (6H, s), 3.76 (1H, m), 5.10 (1H, d, *J* = 2.2 Hz), 5.80 (1H, td, *J* = 2.2, 6.8 Hz), 6.72-6.81 (2H, m), 6.97 (2H, qd, *J* = 1.4, 7.3 Hz), 7.16-7.24 (2H, m), 7.52 (1H, dd, *J* = 1.6, 7.8 Hz), 7.77 (1H, dd, *J* = 1.6, 7.8 Hz); FAB-HRMS m/z $[M+Na]^+$: Calcd. for $C_{22}H_{28}ClNO_5SNa$, 476.1274; Found, 476.1283



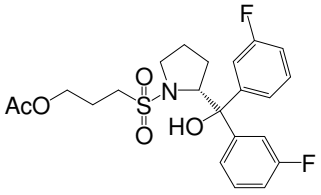
(*R*)-(1-(3-Chloropropylsulfonyl)pyrrolidin-2-yl)bis(3-methoxyphenyl)methanol (13d)

Compound **13d** (679 mg, 88%, a colorless solid) was synthesized from (*R*)- α, α-bis(3-methoxyphenyl)-2-pyrrolidinemethanol **8j** (540 mg, 1.7 mmol) according to the procedure described for Method E. ^{1}H NMR ($CDCl_3$) δ 1.20-1.36 (1H, m), 1.49-1.57 (1H, m), 1.90-1.96 (1H, m), 2.03-2.09 (2H, m), 2.15-2.23 (1H, m), 2.48-2.56 (1H, m), 2.63-2.70 (1H, m), 3.00-3.14 (1H, m), 3.49 (2H, td, *J* = 4.0, 6.4 Hz), 3.73-3.78 (1H, m), 3.78 (3H, s), 3.79 (3H, s), 5.26 (1H, dd, *J* = 4.0, 8.8 Hz), 6.77-6.87 (2H, m), 7.00 (1H, dd, *J* = 0.8, 8.0 Hz), 7.04 (1H, t, *J* = 1.6 Hz), 7.09-7.11 (2H, m), 7.20-7.20 (2H, m); FAB-HRMS m/z $[M+Na]^+$: Calcd. for $C_{22}H_{28}ClNO_5SNa$, 476.1274; Found, 476.1268



(*S*)-(1-(3-Chloropropylsulfonyl)pyrrolidin-2-yl)diphenylmethanol (13f)

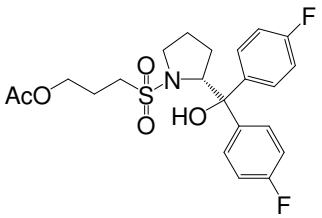
Compound **13f** (1.3 g, 84%, a colorless solid) was synthesized from (*S*)-(-)- α, α-diphenyl -2-pyrrolidinemethanol **8l** (1.0 g, 3.95 mmol) according to the procedure described for Method E. ^{1}H NMR ($CDCl_3$) δ 1.38-1.44 (1H, m), 1.65-1.77 (1H, m), 1.88-2.00 (1H, m), 2.04-2.24 (3H, m), 2.56-2.69 (2H, m), 2.94-3.03 (1H, m), 3.02 (1H, s), 3.48-3.54 (2H, m), 3.66-3.75 (1H, m), 5.28 (1H, dd, *J* = 4.1, 8.9 Hz), 7.22-7.36 (6H, m), 7.41-7.46 (2H, m), 7.50-7.54 (2H, m); FAB-HRMS m/z $[M-H]^-$: Calcd. for $C_{20}H_{23}ClNO_3S$, 392.1087; Found, 392.1067



(*R*)-3-(2-(Bis(3-fluorophenyl)(hydroxy)methyl)pyrrolidin-1-ylsulfonyl)propyl acetate (14a)

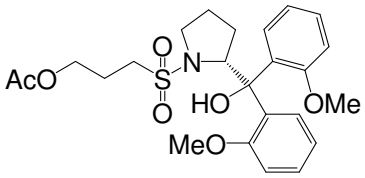
Compound **14a** (666 mg, 63%, a colorless solid) was synthesized from **13a** (1.0 g, 2.33 mmol) according to the procedure described for Method F. ^{1}H NMR ($CDCl_3$) δ 1.43-1.50 (1H, m), 1.69-1.79 (1H, m), 1.83-2.09 (3H, m), 2.07 (3H, s), 2.12-2.22 (1H, m), 2.54-2.74 (2H, m), 3.00 (1H,

dt, *J* = 7.3, 10.8 Hz), 3.26 (1H, s), 3.66-3.74 (1H, m), 4.04 (2H, t, *J* = 6.2 Hz), 5.20 (1H, dd, *J* = 4.1, 8.9 Hz), 6.94-7.01 (2H, m), 7.16-7.21 (2H, m), 7.25-7.36 (4H, m); FAB-HRMS m/z $[M-H]^-$: Calcd. for $C_{22}H_{24}F_2NO_5S$, 452.1343; Found, 452.1351



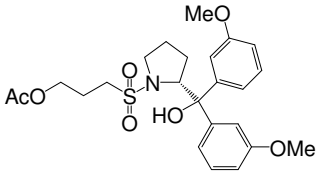
(*R*)-3-(2-(Bis(4-fluorophenyl)(hydroxy)methyl)pyrrolidin-1-ylsulfonyl)propyl acetate (14b)

Compound **14b** (738 mg, 70%, a colorless solid) was synthesized from **13b** (1.0 g, 2.33 mmol) according to the procedure described for Method F. ^1H NMR ($CDCl_3$) δ 1.29-1.40 (1H, m), 1.64-1.80 (1H, m), 1.82-1.93 (1H, m), 1.96-2.06 (2H, m), 2.08 (3H, s), 2.11-2.25 (1H, m), 2.63-2.97 (3H, m), 3.27 (1H, s), 3.60-3.69 (1H, m), 4.08 (2H, t, *J* = 6.2 Hz), 5.17 (1H, dd, *J* = 4.1, 8.9 Hz), 6.97-7.06 (4H, m), 7.34-7.40 (2H, m), 7.43-7.49 (2H, m); FAB-HRMS m/z $[M-H]^-$: Calcd. for $C_{22}H_{24}F_2NO_5S$, 452.1343; Found, 452.1373



(*R*)-3-(2-(Hydroxybis(2-methoxyphenyl)methyl)pyrrolidin-1-ylsulfonyl)propyl acetate (14c)

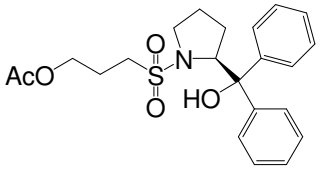
Compound **14c** (715 mg, 68%, a colorless solid) was synthesized from **13c** (1.0 g, 2.2 mmol) according to the procedure described for Method F. ^1H NMR ($CDCl_3$) δ 1.63-1.89 (4H, m), 1.98-2.10 (2H, m), 2.04 (3H, s), 2,17-2.25 (2H, m), 3.32-3.42 (1H, m), 3.56 (6H, s), 3.73-3.94 (3H, m), 5.09 (1H, brs), 5.81 (1H, brt, *J* = 5.4 Hz), 6.73 (1H, d, *J* = 8.1 Hz), 6.80 (1H, d, *J* = 8.4 Hz), 6.97 (2H, q, *J* = 7.6 Hz), 7.20 (2H, brt, *J* = 7.3 Hz), 7.53 (1H, dd, *J* = 1.6, 7.8 Hz), 7.78 (1H, dd, *J* = 1.9, 7.8 Hz); FAB-HRMS m/z $[M+Na]^+$: Calcd. for $C_{24}H_{31}NO_7SNa$, 500.1719; Found, 500.1723



(*R*)-3-(2-(Hydroxybis(3-methoxyphenyl)methyl)pyrrolidin-1-ylsulfonyl)propyl acetate (14d)

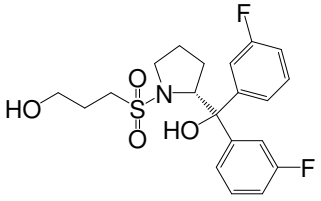
Compound **14d** (442 mg, 70%, a colorless gum) was synthesized from **13d** (600 mg, 1.32 mmol) according to the procedure described for Method F. ^1H NMR ($CDCl_3$) δ 1.52-1.59 (1H, m),

1.69-1.73 (1H, m), 1.89-1.97 (3H, m), 2.06 (3H, s), 2.12-2.18 (1H, m), 2.34-2.41 (1H, m), 2.54-2.60 (1H, m), 3.01-3.08 (1H, m), 3.78 (6H, s), 3.78 (1H, s), 3.78 (1H, s), 3.98 (2H, td, *J* = 1.2, 6.4 Hz), 5.28 (1H, dd, *J* = 3.6, 8.8 Hz), 6.77-6.79 (2H, m), 7.00 (1H, dd, *J* = 1.2, 8.0 Hz), 7.05 (1H, t, *J* = 2.0 Hz), 7.11-7.13 (2H, m), 7.20-7.26 (2H, m); FAB-HRMS m/z $[M+Na]^+$: Calcd. for $C_{24}H_{31}NO_7SNa$, 500.1719; Found, 500.1739



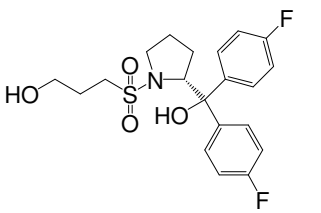
(*S*)-3-(2-(Hydroxydiphenylmethyl)pyrrolidin-1-ylsulfonyl)propyl acetate (14f)

Compound **14f** (710 mg, 67%, a colorless solid) was synthesized from **13f** (1.0 g, 2.54 mmol) according to the procedure described for Method F. ^{1}H NMR (DMSO-d_6) δ 1.63 (4H, quint, *J* = 7.3 Hz), 1.76-1.84 (2H, m), 2.00 (3H, s), 2.04-2.15 (1H, m), 2.29-2.40 (1H, m), 3.17-3.27 (1H, m), 3.57-3.64 (1H, m), 3.82 (2H, t, *J* = 6.8 Hz), 5.21 (1H, brd, *J* = 5.9 Hz), 5.65 (1H, brs), 7.10-7.32 (6H, m), 7.45-7.52 (4H, m); FAB-HRMS m/z $[M-H]^-$: Calcd. for $C_{22}H_{26}NO_5S$, 416.1532; Found, 416.1532



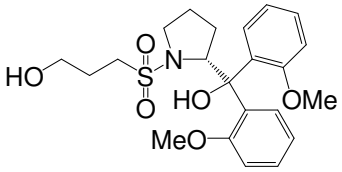
(*R*)-3-(2-(bis(3-fluorophenyl)(hydroxy)methyl)pyrrolidin-1-ylsulfonyl)propan-1-ol (15a)

Compound **15a** (416 mg, 92%, a colorless solid) was synthesized from **14a** (500 mg, 1.10 mmol) according to the procedure described for Method G. ^{1}H NMR ($CDCl_3$) δ 1.35-1.49 (1H, m), 1.67-1.77 (2H, m), 1.82-1.96 (3H, m), 2.10-2.24 (1H, m), 2.68 (1H, quint, *J* = 7.3 Hz), 2.81 (1H, quint, *J* = 7.3 Hz), 3.00 (1H, dt, *J* = 7.3, 11.1 Hz), 3.63 (1H, s), 3.63-3.74 (3H, m), 5.17 (1H, dd, *J* = 4.3, 8.9 Hz), 6.93-7.02 (2H, m), 7.18-7.36 (6H, m); FAB-HRMS m/z $[M-H]^-$: Calcd. for $C_{20}H_{22}F_2NO_4S$, 410.1238; Found, 410.1218



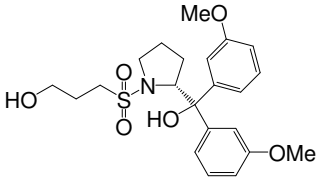
(*R*)-3-(2-(Bis(4-fluorophenyl)(hydroxy)methyl)pyrrolidin-1-ylsulfonyl)propan-1-ol (15b)

Compound **15b** (416 mg, 92%, a colorless solid) was synthesized from **14b** (500 mg, 1.10 mmol) according to the procedure described for Method G. ^{1}H NMR ($CDCl_3$) δ 1.20-1.35 (1H, m), 1.65-1.74 (2H, m), 1.81-2.00 (3H, m), 2.17-2.19 (1H, m), 2.74-2.96 (3H, m), 3.59-3.76 (3H, m), 3.62 (1H, s), 5.12 (1H, dd, *J* = 4.1, 8.9 Hz), 6.95-7.05 (4H, m), 7.34-7.40 (2H, m), 7.43-7.49 (2H, m); FAB-HRMS m/z $[M-H]^-$: Calcd. for $C_{20}H_{22}F_2NO_4S$, 410.1238; Found, 410.1259



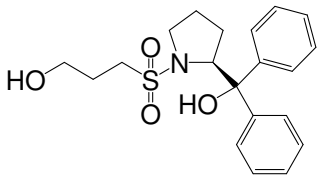
(*R*)-3-(2-(Hydroxybis(2-methoxyphenyl)methyl)pyrrolidin-1-ylsulfonyl)propan-1-ol (15c)

Compound **15c** (438 mg, 96%, a colorless foam) was synthesized from **14c** (500 mg, 1.05 mmol) according to the procedure described for Method G. ^{1}H NMR ($CDCl_3$) δ 1.56-1.71 (2H, m), 1.79-1.92 (2H, m), 1.98-2.05 (2H, m), 2.17-2.25 (2H, m), 3.32-3.45 (1H, m), 3.50 (2H, t, *J* = 6.2 Hz), 3.56 (6H, s), 3.72-3.80 (1H, m), 5.10 (1H, d, *J* = 1.9 Hz), 5.81 (1H, brt, *J* = 5.7 Hz), 6.74 (1H, d, *J* = 8.1 Hz), 6.80 (1H, d, *J* = 8.1 Hz), 6.97 (2H, q, *J* = 7.6 Hz), 7.20 (2H, brt, *J* = 8.1 Hz), 7.53 (1H, brd, *J* = 7.3 Hz), 7.79 (1H, brd, *J* = 7.3); FAB-HRMS m/z $[M+Na]^+$: Calcd. for $C_{22}H_{29}NO_6SNa$, 458.1613; Found, 458.1624



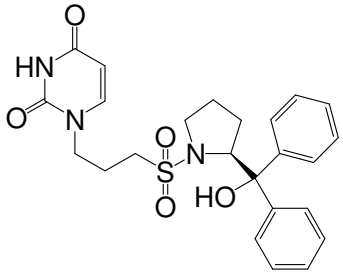
(*R*)-3-(2-(Hydroxybis(3-methoxyphenyl)methyl)pyrrolidin-1-ylsulfonyl)propan-1-ol (15d)

Compound **15d** (361 mg, 99%, a colorless gum) was synthesized from **14d** (400 mg, 0.84 mmol) according to the procedure described for Method G. ^{1}H NMR ($CDCl_3$) δ 1.44-1.52 (1H, m), 1.67-1.74 (2H, m), 1.85-1.95 (3H, m), 2.14-2.19 (1H, m), 2.53-2.60 (1H, m), 2.66-2.70 (1H, m), 2.99-3.02 (1H, m), 3.24 (1H, s), 3.60-3.66 (2H, m), 3.71-3.76 (1H, m), 3.79 (6H, m), 5.25 (1H, dd, *J* = 4.0, 8.8 Hz), 6.77-6.79 (2H, m), 6.98 (1H, d, *J* = 5.4 Hz), 7.09 (1H, t, *J* = 2.0 Hz), 7.11-7.13 (2H, m), 7.19-7.26 (2H, m); FAB-HRMS m/z $[M-H]^-$: Calcd. for $C_{22}H_{28}NO_6S$, 434.1637; Found, 434.1653



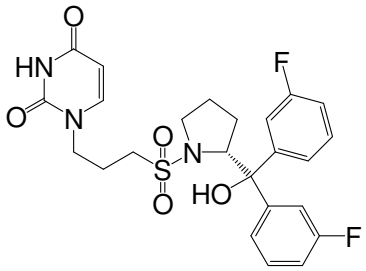
(*S*)-3-(2-(Hydroxydiphenylmethyl)pyrrolidin-1-ylsulfonyl)propan-1-ol (15f)

Compound **15f** (428 mg, 95%, a colorless solid) was synthesized from **14f** (500 mg, 1.20 mmol) according to the procedure described for Method G. ^{1}H NMR ($CDCl_3$) δ 1.34-1.45 (1H, m), 1.62-1.78 (1H, m), 1.83-1.98 (3H, m), 2.12-2.26 (1H, m), 2.57 (1H, quint, *J* = 6.8 Hz), 2.69 (1H, quint, *J* = 7.3 Hz), 2.98 (1H, dt, *J* = 7.6, 10.5 Hz), 3.28 (1H, s), 3.61-3.75 (3H, m), 5.27 (1H, dd, *J* = 3.8, 8.6 Hz), 7.22-7.36 (6H, m), 7.43-7.46 (2H, m), 7.52-7.55 (2H, m); FAB-HRMS m/z $[M-H]^-$: Calcd. for $C_{20}H_{24}NO_4S$, 374.1426; Found, 374.1396



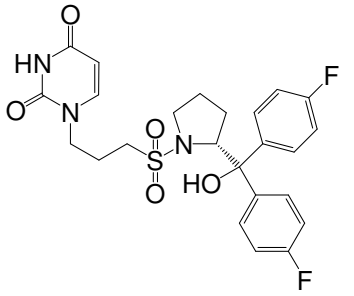
(*S*)-1-(3-(2-(Hydroxydiphenylmethyl)pyrrolidin-1-ylsulfonyl)propyl)pyrimidine-2,4(1*H*,3*H*)-dione (16b)

Compound **16b** (317 mg, 63%, a colorless foam) was synthesized from **15f** (400 mg, 1.07 mmol) according to the procedure described for Method H. ^{1}H NMR ($CDCl_3$) δ 1.47-1.54 (1H, m), 1.69-1.76 (1H, m), 1.90-2.04 (3H, m), 2.14-2.24 (1H, m), 2.32-2.39 (1H, m), 2.46-2.53 (1H, m), 2.98 (1H, s), 3.00-3.06 (1H, m), 3.70-3.76 (3H, m), 5.30-5.33 (1H, dd, *J* = 4.0, 9.2 Hz), 5.70 (1H, dd, *J* = 2.0, 7.6 Hz), 7.18 (1H, d, *J* = 7.6 Hz), 7.22-7.34 (6H, m), 7.42-7.44 (2H, m), 7.52-7.55 (2H, m), 8.38 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 22.99, 26.00, 29.10, 47.24, 49.51, 50.64, 67.16, 81.16, 102.52, 126.67, 126.99, 127.34, 127.36, 128.15, 128.19, 144.12, 144.60, 145.76, 150.80, 163.47; Anal. Calcd for $C_{24}H_{27}N_3O_5S \cdot 0.3H_2O$: C, 60.69; H, 5.86; N, 8.85. Found: C, 60.69; H, 5.79; N, 8.93; $[\alpha]^{25}_D = 13.17$ (*c* 0.41, $CHCl_3$)



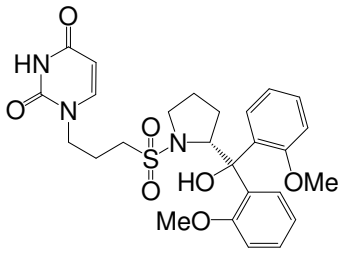
(*R*)-1-(3-(2-(Bis(3-fluorophenyl)(hydroxy)methyl)pyrrolidin-1-ylsulfonyl)propyl)pyrimidine-2,4(1*H*,3*H*)-dione (16c)

Compound **16c** (270 mg, 55%, a colorless foam) was synthesized from **15a** (400 mg, 0.97 mmol) according to the procedure described for Method H. ^{1}H NMR ($CDCl_3$) δ 1.53-1.58 (1H, m), 1.72-1.91 (2H, m), 2.02-2.17 (3H, m), 2.48-2.66 (2H, m), 3.03-3.10 (1H, m), 3.34 (1H, s), 3.67-3.79 (3H, m), 5.22 (1H, dd, *J* = 3.8, 8.6 Hz), 5.73 (1H, d, *J* = 7.8 Hz), 6.93-7.00 (2H, m), 7.17-7.33 (7H, m), 8.66 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 23.00, 26.01, 29.08, 47.30, 49.61, 50.84, 66.74, 80.53, 102.76, 113.85, 114.08, 114.14, 114.32, 114.37, 114.53, 114.58, 122.23, 122.26, 122.77, 122.79, 129.69, 129.73, 129.78, 129.81, 144.46, 146.25, 146.32, 147.91, 147.97, 151.09, 161.31, 161.47, 163.48, 163.76, 163.92; Anal. Calcd for $C_{24}H_{25}F_2N_3O_5S{\cdot}0.3H_2O$: C, 56.42; H, 5.05; N, 8.22. Found: C, 56.51; H, 4.88; N, 8.35; $[\alpha]^{25}_D$ = -1.98 (*c* 0.60, $CHCl_3$)



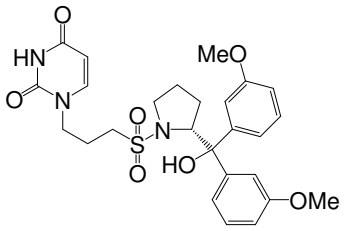
(*R*)-1-(3-(2-(Bis(4-fluorophenyl)(hydroxy)methyl)pyrrolidin-1-ylsulfonyl)propyl)pyrimidine-2,4(1*H*,3*H*)-dione (16d)

Compound **16d** (299 mg, 61%, a colorless solid) was synthesized from **15b** (400 mg, 0.97 mmol) according to the procedure described for Method H. ^{1}H NMR (DMSO-d_6) δ 1.71-1.79 (5H, m), 2.00-2.09 (1H, m), 2.43-2.72 (2H, m), 3.20-3.27 (1H, m), 3.51-3.70 (3H, m), 5.06 (1H, d, *J* = 6.5 Hz), 5.56 (1H, d, *J* = 7.8 Hz), 5.78 (1H, brs), 6.98-7.12 (4H, m), 7.38-7.57 (5H, m), 11.0 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 22.98, 25.73, 29.19, 47.34, 49.19, 50.50, 66.94, 80.32, 102.69, 114.92, 115.13, 128.66, 128.74, 128.90, 128.99, 139.47, 141.33, 141.36, 144.44, 150.86, 160.73, 160.83, 163.19, 163.23, 163,29; Anal. Calcd for $C_{24}H_{25}F_2N_3O_5S$: C, 57.02; H, 4.98; N, 8.31. Found: C, 57.11; H, 4.86; N, 8.31; $[\alpha]^{25}_D$ = 14.20 (*c* 0.38, $CHCl_3$)



(*R*)-1-(3-(2-(Hydroxybis(2-methoxyphenyl)methyl)pyrrolidin-1-ylsulfonyl)propyl)pyrimidine-2,4(1*H*,3*H*)-dione (16e)

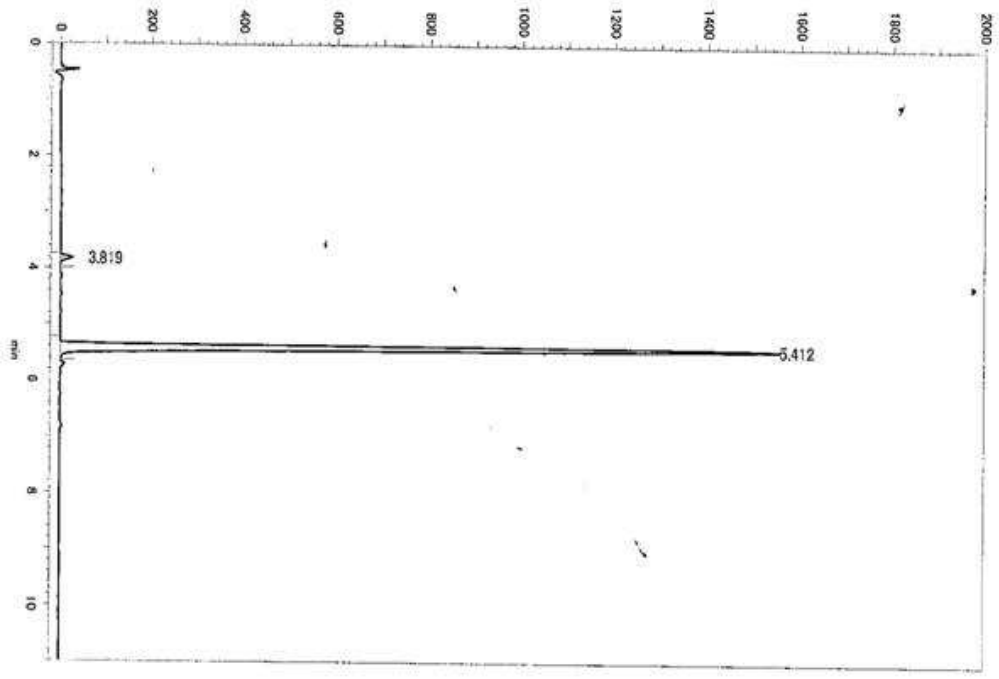
Compound **16e** (345 mg, 71%, a colorless solid) was synthesized from **15c** (400 mg, 0.91 mmol) according to the procedure described for Method H. ^{1}H NMR (DMSO-d_6) δ 1.57-1.68 (2H, m), 1.85-1.96 (2H, m), 2.82-2.88 (2H, m), 2.93-2.99 (2H, m), 3.33-3.37 (2H, m), 3.70-3.80 (8H, m), 5.54 (1H, d, *J* = 7.8 Hz), 5.60 (1H, s), 6.75-6.78 (2H, m), 6.84-6.90 (2H, m), 7.01-7.08 (3H, m), 7.23-7.29 (2H, m), 7.59 (1H, d, *J* = 7.8 Hz), 11.24 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 23.30, 24.24, 39.02, 42.84, 47.11, 48.93, 51.24, 55.60, 102.45, 110.74, 120.67, 126.10, 128.62, 129.79, 144.75, 150.78, 157.14, 163.34; Anal. Calcd for $C_{26}H_{31}N_3O_7S$: C, 58.96; H, 5.90; N, 7.93. Found: C, 58.96; H, 5.82; N, 7.86; $[\alpha]^{25}_D$ = 0.39 (*c* 1.01, $CHCl_3$)



(*R*)-1-(3-(2-(Hydroxybis(3-methoxyphenyl)methyl)pyrrolidin-1-ylsulfonyl)propyl)pyrimidine-2,4(1*H*,3*H*)-dione (16f)

Compound **16f** (89 mg, 73%, a colorless foam) was synthesized from **15d** (100 mg, 0.23 mmol) according to the procedure described for Method H. ^{1}H NMR ($CDCl_3$) δ 1.55-1.62 (1H, m), 1.70-1.78 (1H, m), 1.92-2.02 (3H, m), 2.15-2.19 (1H, m), 2.30-2.37 (1H, m), 2.45-2.52 (1H, m), 2.90 (1H, s), 3.04-3.10 (1H, m), 3.65-3.75 (3H, m), 3.78 (3H, s), 3.79 (3H, s), 5.28-5.31 (1H, m), 5.69-5.71 (1H, dd, *J* = 2.4, 8.0 Hz), 6.77-6.79 (2H, m), 6.99 (1H, d, *J* = 8.0 Hz), 7.04 (1H, t, *J* = 2.0 Hz), 7.11-7.13 (2H, m), 7.18-7.26 (3H, m), 8.12 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 23.04, 26.15, 29.15, 47.21, 49.70, 50.84, 55.27, 55.34, 67.14, 81.06, 102.49, 112.13, 112.61, 113.04, 118.89, 119.20, 129.17, 129.22, 144.52, 145.69, 147.33, 150.58, 159.39, 159.49, 163.06; Anal. Calcd for $C_{26}H_{31}N_3O_7S{\cdot}0.2H_2O$: C, 58.57; H, 5.94; N, 7.88. Found: C, 58.49; H, 6.06; N, 7.65; $[\alpha]^{25}_D$ = -26.22 (*c* 0.45, $CHCl_3$)

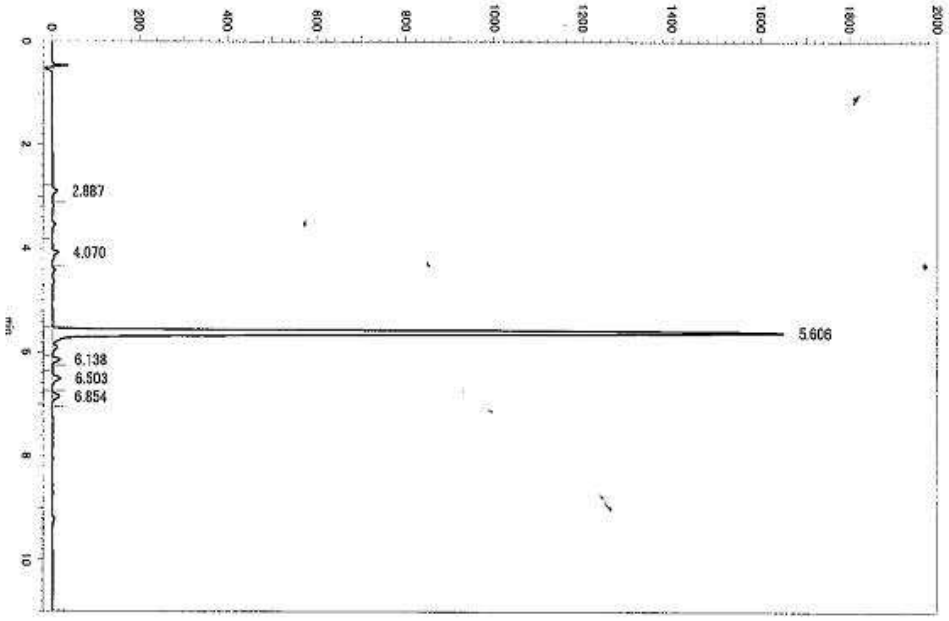
HPLC analysis chart of 11i



Peak number	Retention time	Area	Area%
1	3.819	117982	1.46
2	5.412	7942060	98.54
Total		8060043	100.00

Column: Shim-pack XR-ODS 3 mmID X 50mm, 2.2um
Column Temp. : 40
Mobile phase : 10mM PB)pH6.5) /Acetonitrile 0 min : [90:10] 8min : [20:80] 10min : [20:80]
Flow rate : 0.8 mL/min

HPLC analysis chart of 11r

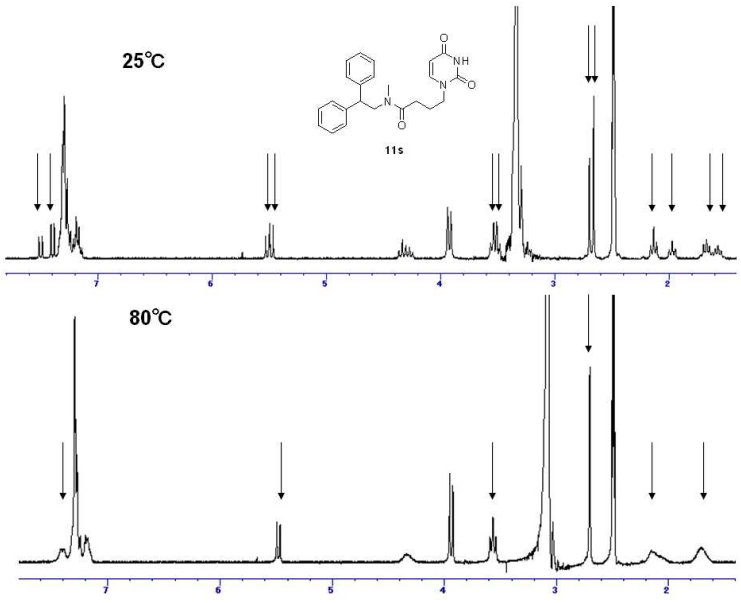


Peak number	Retention time	Area	Area%
1	2.887	60149	0.65
2	4.070	87299	0.94
3	5.606	8842679	95.34
4	6.138	77735	0.84
5	6.503	108347	1.17
6	6.854	99073	1.07
Total		9275281	100.00

Column: Shim-pack XR-ODS 3 mmID X 50mm, 2.2um
Column Temp. : 40
Mobile phase : 10mM PB)pH6.5) /Acetonitrile 0 min : [90:10] 8min : [20:80] 10min : [20:80]
Flow rate : 0.8 mL/min

^{1}H-NMR spectrum of 11s in DMSO-d_6 at 25 °C and 80 °C.

Figure S1 ^{1}H-NMR spectrum of **11s** in DMSO-d_6 at 25 °C and 80 °C. Arrows represents exchanged ^{1}H peaks between 25 °C and 80 °C



The ^{1}H-NMR spectrum of **11s** in DMSO-d_6 revealed that **11s** exists as mixture of two conformational isomers at 25 °C, and undergoes interconversion between the two conformers at 80 °C.

Cloning, expression and purification of recombinant human dUTPase

The cDNA of human dUTPase was subcloned into the expression vector pET19b. The construct was then transformed into E. coli BL21(DE3) cells (Novagen) in Luria broth at 37°C. Protein expression was induced with 0.01mM isopropyl-β-D-thiogalactopyranoside (IPTG) at an optical density of 0.6 at 595 nm. The cell pellet was resuspended in ice-cold lysis buffer containing 50 mM Tris–HCl pH 7.5, 150 mM NaCl and 1 mM dithiothreitol (DTT). After sonication, the disrupted debris was removed by centrifugation. The supernatant was applied to Ni-NTA affinity gels and the 6×His-Tag was removed by digestion with enterokinase in 50 mM Tris–HCl pH 7.5, 150 mM NaCl, 1 mM DTT for 12 hours. The protein solutions used for crystallization were gelfiltrated in a buffer containing 50 mM Tris–HCl pH 7.5, 50 mM NaCl, and 1 mM DTT, on a preparative grade Superdex75 column (GE Healthcare Life Sciences).

Statistics for X-ray data processing and structure refinement for complex dUTPase:compound 16a (PDB code: 3ARA)

Table S1 Statistics for X-ray data processing and structure refinement (PDB code: 3ARA)

Crystal data	
$P2_12_12_1$ cell dimensions (Å)	a = 81.89, b = 83.26, c = 89.66
Resolution range (Å)	100.00 - 1.70 (1.76 - 1.70)
No. observed reflections	344252
No. unique reflections	66325
Completeness of data (%)	97.5 (99.5)
R_{sym} [a]	0.048 (0.210)
I/σI	11.6 (2.6)
Refinement statistics	
Rcryst (%) [b]	21.5
Rfree (%) [c]	24.0
Rmsd. bonds (Å) [d]	0.029
Rmsd. angles (°) [d]	2.256
Nonhydrogen atoms	3410
Water molecules	387
Average B-factor (Å^2)	23.16

[a] $R_{sym} = \Sigma\Sigma_j |I_j - \langle I \rangle| / \Sigma \langle I \rangle$, where I_j is the recorded intensity of the jth reflection and ‹I› is the average intensity over multiple recordings.

[b] $R_{cryst} = \Sigma_h ||F_o(h) - F_c(h)|| / \Sigma_h |F(h)|$, where $F_c(h)$ and $F_c(h)$ are observed and calculated structure factors.

[c] R_{free} values are calculated for a randomly selected 5% of the data.

[d] Root mean square deviation from ideal/target geometries.

Crystallization and Data Collection

The protein solution prepared for co-crystallization contained 20 mg/ml dUTPase, 0.1mM Uracil derivative and 10 mM $MgCl_2$. Crystallization experiments were carried out by the hanging-drop vapor diffusion method. Crystals were obtained at 25 °C from the reservoir solution consisting of 15%~20% PEG 4000, 50mM Tris–HCl pH 7.5, 15% (v/v) glycerol and 50mM $MgCl_2$. Data sets were collected from a cryo-cooled (100 K) crystal at Pharmaceutical Industry Beamline BL32B2 of Spring-8 Synchrotron in Harima, Japan, using a RAXIS V (Rigaku Corporation) imaging plate (IP) area detector. The data, extending to 1.7 Å , were integrated and scaled by using the CrystalClear software package (Rigaku Corporation)(Table 1).

Structure determination and refinement

The structure of the dUTPase:compound **16a** complex was solved by molecular replacement using the program AMoRe[9] from the CCP4 suite.[10] The search model was based upon human dUTPase structure (PDB ID code: 1Q5U).[11] The structure of the dUTPase:compound **16a** complex was refined using REFMAC5.[12] Manual rebuilding of the models and electron density map interpretation were carried out using Turbo-Frodo.[13] The final model has *R* values of R_{cryst} = 21.5% R_{free} = 24.0%. A summary of statistics from the data collection and refinement is given in Table 1.

Docking study of 16b on the X-ray structure of human dUTPase and 16a

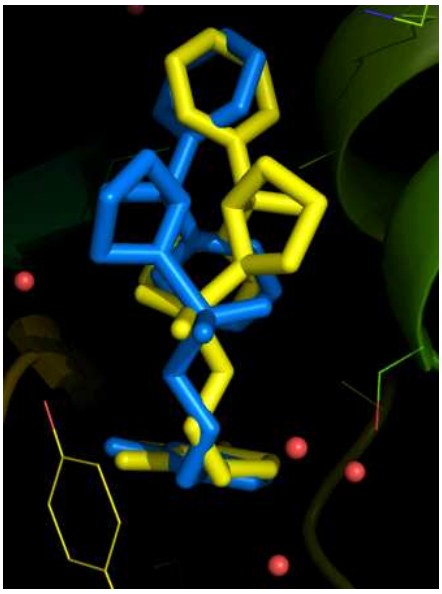


Figure S2 X ray structure of **16a** (blue stick) and Docking model of **16b** (yellow stick) binding in the catalytic site of dUTPase

We build binding model of **16b** in the active site of human dUTPase on the basis of the X-ray diffraction data of **16a**, on the premise that stacking interaction between uracil ring and phenyl ring are essential for dUTPase inhibition activity. First, possible conformations of free **16b** were generated exhaustively with OMEGA.[14] Next, best aligned conformation of **16b** to the binding conformation of **16a**, which was extracted from the X-ray structure, was selected with ROCS.[15] For the alignment, two pharmacophores, which are uracil ring and terminal phenyl ring, were used as constraints. Finally, best aligned conformation of **16b** was superposed to the active site of X-ray structure of **16a** and the energy minimization was performed in the active site to afford the binding model of **16b**. Contrary to human dUTPase inhibition activity data, the contact surface area of **16b** with human dUTPase was proved to be larger than that of **16a** which meant **16b** had more potent

inhibition activity (**16a**: 565.5Å^2, **16b**: 590.9Å^2). This results obviously indicated difficulty to explain the difference of the inhibition activity by the factor of contact surface area.

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