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Diastereoselective Synthesis of Novel Aza-diketopiperazines via a Domino Cyclohydrocarbonylation/Addition Process

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Supporting Information

Table of Contents

General methods

Reagents were obtained from commercial sources and used without any further purification. Thin-layer chromatography was performed on silica gel $60F_{254}$ plates. (Acetylacetonato)dicarbonylrhodium(I) and dry solvents were purchased from Sigma-Aldrich Co. BiPhePhos was prepared as reported previously[1]. All experiments were performed under argon atmosphere except where otherwise noted.
Hydroformylation was performed in a reactor from Equilabo® using 1:1 H_2/CO supplied by Airgas, Inc.
Flash chromatography was performed on silica gel (30 μm) using a Spot II Ultimate apparatus from Armen Instrument or RP-18 (25− 40 μm, Merck) prepacked columns on a PLC 2020 apparatus from Gilson.
^{1}H and ^{13}C NMR spectra were recorded on a Bruker (500 MHz/125 MHz and 400 MHz/100 MHz) spectrometer. Conditions are specified for each spectrum (temperature 25 °C unless specified). Chemical shifts are reported in parts per million (ppm) relative to residual solvent and coupling constants (*J*) are reported in hertz (Hz). Signals are described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), dt (doublet of triplets), ddt (doublet of doublet of triplets), br s (broad singlet), br d (broad doublet), br q (broad quadruplet) and br dd (broad doublet of doublets). Deutered solvents were purchased from Euriso-top®.
HRMS were obtained on an Agilent Technologie 6520 Accurate-Mass Q.Tof LC/MC apparatus using electrospray ionization mode and time-of flight analyzer (ESI-TOF).
Melting points were determined on a Büchi Melting Point B-540 apparatus in open capillary tubes. Specific rotations were measured with a Perkin-Elmer apparatus using a 10 cm cell with a Na 589 nm filter.

[1] Cuny, G. D. & Buchwald, S. L. Practical, high-yield, regioselective, rhodium-catalyzed hydroformylation of functionalized .alpha.-olefins. *J. Am. Chem. Soc.* **115,** 2066–2068 (1993)

General procedures

Reductive amination - General procedure A. In a dry round-bottom flask, triethylamine (10 mmol, 1 equiv) and the aldehyde (11 mmol, 1.1 equiv) were added to a solution of the amino acid methyl ester hydrochloride (10 mmol, 1 equiv) in dry MeOH (10.6 mL). The mixture was stirred for 90 min at room temperature and then cooled to 0 °C. Sodium borohydride (20 mmol, 2 equiv) was added portion wise over 30 min. The reaction was allowed to warm to room temperature over 15 min. Then, the mixture was concentrated under reduced pressure to a slurry. Water was added to the crude and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to a slurry.

Synthesis of 1-allyl or 1-homoallyl-1,2,4-triazine-3,6-diones - General procedure B1. To a solution of BTC (0.335 mmol, 0.335 equiv) in anhydrous THF (6 mL), under argon, was added dropwise (over 5 minutes) a solution of amino acid derivative (1 mmol, 1 equiv) and DIEA (1.1 mmol, 1.1 equiv) in anhydrous tetrahydrofuran (2.5 mL). The mixture was stirred at room temperature for 15 minutes. A solution of *tert*-butyl 2-allylhydrazinecarboxylate or *tert*-butyl 2-(but-3-en-1-yl)hydrazinecarboxylate (1 mmol, 1 equiv) and DIEA (1.1 mmol, 1.1 equiv) in anhydrous THF (1.5 mL) was added dropwise and the mixture was heated at 40 °C overnight. The mixture was evaporated *in vacuo* and a solution of TFA/H_2O (95:5, 1.25 mL) was added. The mixture was stirred at room temperature for 1 h and evaporated under reduced pressure.

Synthesis of 1-allyl or 1-homoallyl-1,2,4-triazine-3,6-diones - General procedure B2. Compounds were prepared as described in General procedure B1, except than the reaction was performed in CH_2Cl_2/THF solvent to ensure the solubility of the mixture.

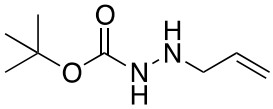
Hydroformylation – General procedure C. A solution of $Rh(CO)_2$acac (0.02 equiv) and Biphephos (0.06 equiv) in anhydrous THF (2 mL), prepared in a Schlenk glassware under an argon atmosphere, was introduced under argon into a stainless steel autoclave containing the substrate (1 equiv) and camphor sulfonic acid (0.5 equiv) in anhydrous THF (8 mL). The reactor was purged three time with H_2/CO (1:1, 5 bar) and filled with H_2/CO (1:1, 5 bar). The reactor was heated to 70 °C and stirred for 16 h. The reactor was then cooled to ambient temperature and vented to ambient pressure. The reaction mixture was evaporated.

Nucleophilic addition of MeOH – General procedure D. The substrate was solubilized in MeOH. Camphorsulfonic acid (0.5 equiv) was added and the resulting mixture was heated under reflux for 16 h. The mixture was then cooled to room temperature, quenched with a saturated aqueous solution of $NaHCO_3$ and concentrated *in vacuo* to a slurry. Water was added to the mixture and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was analyzed by ^{1}H NMR to determine the diastereoselectivity of the reaction.

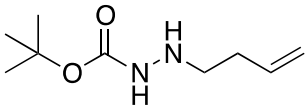
Benzyl deprotection – General procedure E. In a dry round-bottom flask, the substrate was solubilized in dry CH_2Cl_2. A solution of BCl_3 in CH_2Cl_2 (1M, 5 equiv) was added at 0 °C and the reaction was stirred during 10 min. The mixture was carefully quenched with MeOH and a saturated

aqueous solution of $NaHCO_3$ to obtain a neutral pH. The reaction was finally concentrated to a slurry before purification.

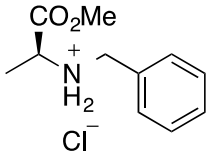
Experimental details and analytical data



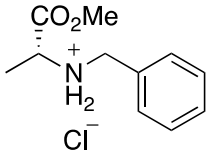
***tert*-butyl 2-allylhydrazinecarboxylate (1a).** To a dry 100 mL flask were added *tert*-butyl hydrazinecarboxylate (4.215 g, 31.89 mmol, 3 equiv), potassium carbonate (1.469 g, 10.63 mmol, 1 equiv) and anhydrous THF/DMF (9:1, 30.7 mL). The suspension was heated to 80 °C. A solution of allyl bromide (920 µL, 10.63 mmol, 1 equiv) dissolved in THF/DMF (9:1, 4 mL) was added over 3 h and the mixture was allowed to stir overnight at 80 °C. Then, the mixture was concentrated *in vacuo* to a slurry and the crude was diluted with water/EtOAc. The aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The crude product was purified on silica gel eluting with 25% EtOAc in n-heptane to yield 1.208 g (7.016 mmol, **66%**) of the title compound as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.22 (br s, 1H), 5.80 (ddt, *J* = 17.1, 10.3, 6.4 Hz, 1H), 5.18 (br dd, *J* = 17.1, 1.8 Hz, 1H), 5.11 (br d, *J* = 10.3 Hz, 1H), 3.71 (br s, 1H), 3.42 (d, *J* = 6.3 Hz, 2H), 1.42 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.9, 134.5, 118.3, 80.6, 54.7, 28.5; $\mathbf{R_f}$: 0.26 (30% EtOAc in n-heptane).



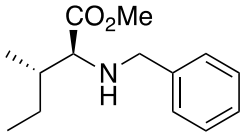
***tert*-butyl 2-(but-3-en-1-yl)hydrazinecarboxylate (1b).** To a dry 250 mL flask were successively added *tert*-butyl hydrazinecarboxylate (9.765 g, 73.89 mmol, 5 equiv) and 4-bromo-1-butene (1.5 mL, 14.78 mmol, 1 equiv) in solution in anhydrous DMF (150 mL). The suspension was heated to 100 °C. The mixture was then concentrated under reduced pressure to a slurry and diluted with water/EtOAc. The aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The crude product was purified on silica gel eluting with 30% EtOAc in n-heptane to yield 2.138 g (11.48 mmol, **78%**) of the title compound as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.16 (br s, 1H), 5.78 (ddt, *J* = 17.2, 10.3, 6.8 Hz, 1H), 5.08 (br dd, *J* = 17.2, 1.8 Hz, 1H), 5.01 (br dd, *J* = 10.3, 1.8 Hz, 1H), 3.94 (br s, 1H), 2.89 (t, *J* = 10.3, 1.8 Hz, 2H), 2.20 (br q, *J* = 7.0 Hz, 2H), 1.43 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.9, 136.1, 116.5, 80.7, 51.1, 32.4, 28.6; $\mathbf{R_f}$: 0.28 (30% EtOAc in n-heptane).



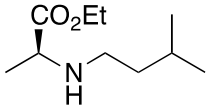
(*S*)-*N*-benzyl-1-methoxy-1-oxopropan-2-aminium chloride (2a). Reductive alkylation was performed following general procedure A. The crude product was purified on silica gel, eluting with 30% EtOAc in n-heptane to obtain a colorless oil containing a mixture of the expected product and benzyl alcohol. The mixture was then solubilized in diethyl ether (60 mL) and allowed to stir at 0 °C. A solution of hydrogen chloride (2M, 40 mL) was slowly added during 20 min. The suspension was filtered, washed with diethyl ether (3 x 20 mL) and dried *in vacuo* to yield the desired product (5.569 g, 24.24 mmol, **72%**) as a white powder. **^{1}H NMR** (400 MHz, MeOD-d_4) δ 7.56-7.45 (m, 5H), 4.26 (s, 2H), 4.19 (q, J = 7.0 Hz, 1H), 3.87 (s, 3H), 1.62 (d, J = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, MeOD-d_4) δ 171.1, 132.4, 131.3, 131.0, 130.5, 56.6, 54.1, 51.2, 15.5; **mp** : 187.0 – 189.0 °C; **R_f** : 0.28 (30% EtOAc in n-heptane).



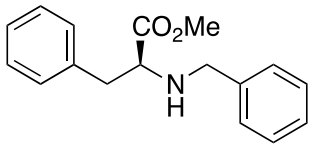
(*R*)-*N*-benzyl-1-methoxy-1-oxopropan-2-aminium chloride (2b). Reductive alkylation was performed following general procedure A. Compound **2b** was isolated as previously described for compound **2a** to yield the desired product (5.048 g, 21.98 mmol, **77%**) as a white powder. **^{1}H NMR** (400 MHz, MeOD-d_4) δ 7.55-7.44 (m, 5H), 4.27 (s, 2H), 4.20 (q, J = 7.0 Hz, 1H), 3.87 (s, 3H), 1.63 (d, J = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, MeOD-d_4) δ 171.1, 132.5, 131.3, 131.0, 130.5, 56.5, 54.0, 51.1, 15.5; **mp** : 185.6 – 187.6 °C; **R_f** : 0.28 (30% EtOAc in n-heptane).



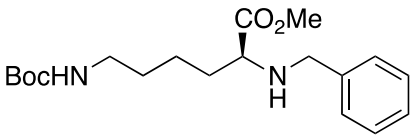
(2*S*,3*S*)-methyl 2-(benzylamino)-3-methylpentanoate (2c). Reductive alkylation was performed following general procedure A. Purification on silica gel eluting with 10% EtOAc in n-heptane afforded (1.570 g, 6.672 mmol, **81%**) of the title compound as a colorless oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.29-7.12 (m, 5H), 3.73 (d, J = 13.1 Hz, 1H), 3.63 (s, 3H), 3.50 (d, J = 13.1 Hz, 1H), 3.02 (d, J = 6.3 Hz, 1H), 1.75 (br s, 1H), 1.65-1.44 (m, 2H), 1.18-1.05 (m, 1H), 0.80 (d, J = 6.9 Hz, 3H), 0.79 (t, J = 7.4 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 175.9, 140.2, 128.5, 127.2, 65.6, 52.7, 51.5, 38.6, 25.7, 15.8, 11.6; **R_f** : 0.35 (10% EtOAc in n-heptane).



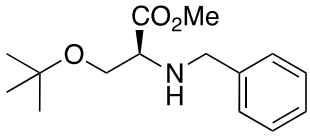
(*S*)-methyl 2-(isopentylamino)propanoate (2d). Reductive alkylation was performed following general procedure A. The residue was purified on silica gel eluting with 10% EtOAc in n-heptane to obtain the desired product (1.310 g, 6.995 mmol, **36%**) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.15 (q, *J* = 7.2 Hz, 2H), 3.29 (q, *J* = 7.0 Hz, 1H), 2.56 (dt, *J* = 11.0, 7.5 Hz, 1H), 2.46 (dt, *J* = 11.0, 7.5 Hz, 1H), 1.64-1.53 (m, 2H), 1.34 (q, *J* = 7.2 Hz, 2H), 1.26 (d, *J* = 7.0 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.85 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.1, 60.8, 57.0, 46.4, 39.5, 26.3, 23.0, 22.6, 19.3, 14.5; $\mathbf{R_f}$: 0.56 (50% EtOAc in n-heptane + 0.1% TEA).



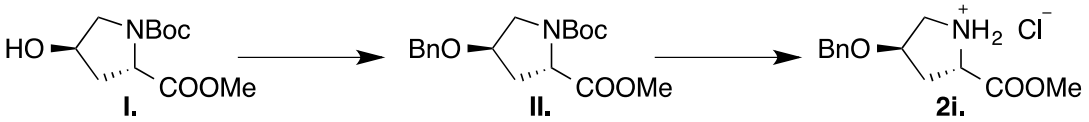
(*S*)-methyl 2-(benzylamino)-3-phenylpropanoate (2e). Reductive alkylation was performed following general procedure A. The residue was purified on silica gel eluting with 10-20% EtOAc in n-heptane to obtain the desired product (1.710 g, 6.348 mmol, **88%**) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34-7.17 (m, 10H), 3.58 (d, *J* = 12.8 Hz, 1H), 3.68 (s, 3H), 3.67 (d, *J* = 12.8 Hz, 1H), 3.58 (t, *J* = 7.0 Hz, 1H), 3.05-2.95 (m, 2H), 1.86 (br s, 1H); **^{13}C NMR** (400 MHz, $CDCl_3$) δ 175.2, 139.6, 137.5, 129.4, 128.6, 128.5, 128.3, 127.2, 126.9, 62.3, 52.2, 51.8, 39.9; $\mathbf{R_f}$: 0.32 (20% EtOAc in n-heptane).



(*S*)-methyl 2-(benzylamino)-6-((*tert*-butoxycarbonyl)amino)hexanoate (2f). Reductive alkylation was performed following general procedure A. Purification on silica gel eluting with 40% EtOAc in n-heptane containing 0.1% of TEA afforded (679 mg, 1.937 mmol, **92%**) of the title compound as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27-7.12 (m, 5H), 4.70 (br s, 1H), 3.71 (d, *J* = 13.0 Hz, 1H), 3.63 (s, 3H), 3.52 (d, *J* = 13.0 Hz, 1H), 3.16 (t, *J* = 6.8 Hz, 1H), 3.05-2.95 (m, 2H), 1.81 (br s, 1H), 1.64-1.16 (m, 15H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 175.8, 156.0, 139.8, 128.3, 128.2, 127.0, 78.9, 60.5, 52.1, 51.6, 40.3, 33.1, 29.8, 28.4, 23.0; $\mathbf{R_f}$: 0.25 (40% EtOAc in n-heptane + 0.1% TEA).



(*S*)-methyl 2-(benzylamino)-3-(*tert*-butoxy)propanoate (2g). Reductive alkylation was performed following general procedure A. The residue was purified on silica gel eluting with 20% EtOAc in n-heptane to obtain the desired product (1.881 g, 7.09 mmol, **75%**) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28-7.12 (m, 5H), 3.83 (d, *J* = 13.3 Hz, 1H), 3.63 (s, 3H), 3.63 (d, *J* = 13.3 Hz, 1H), 3.56-3.46 (m, 2H), 3.36 (t, *J* = 5.0 Hz, 1H), 2.14 (br s, 1H), 1.06 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.9, 140.0, 128.5, 128.4, 127.1, 73.3, 63.3, 61.2, 52.1, 51.8, 27.5; **R_f** : 0.26 (20% EtOAc in n-heptane).

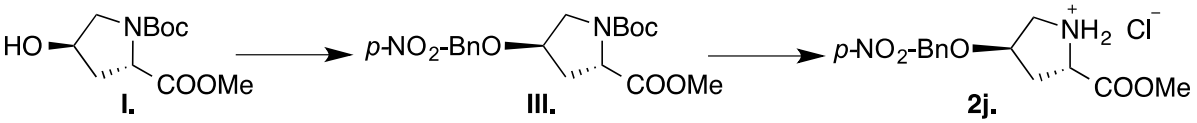


1-(*tert*-butyl) 2-methyl (2*S*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate (I). In a dry round-bottom flask, di-tert-butyl dicarbonate (3.305 g, 15.14 mmol, 1.1 equiv), 4-DMAP (0.505 g, 4.13 mmol, 0.3 equiv) and TEA (2.296 mL, 16.52 mmol, 1.2 equiv) were solubilized in CH_2Cl_2 (58.7 mL). (2*S*,4*R*)-4-hydroxy-2-(methoxycarbonyl)pyrrolidin-1-ium chloride (2.500 g, 13.77 mmol, 1 equiv) was added and the mixture was stirred at room temperature for 16 h. Then, the mixture was concentrated *in vacuo* and water was added on the crude product. The aqueous phase was extracted with EtOAc and the combined organic layers were washed with an aqueous solution of citric acid (5%) and brine, dried over anhydrous sodium sulfate, filtered and concentrated to obtain the desired product as a yellow oil (3.040 g, 12.39 mmol, **90%**). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.50-4.30 (m, 2H), 3.69 (s, 3H), 3.63-3.35 (m, 2H), 2.41 (br s, 1H), 2.33-2.12 (m, 1H), 2.09-1.95 (m, 1H), 1.46-1.32 (m, 9H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 173.3, 172.8, 153.7, 153.0, 79.0, 78.9, 68.5, 67.8, 57.7, 57.4, 54.7, 54.4, 51.8, 51.7, 38.7, 37.9, 28.0, 27.8, **R_f**: 0.22 (50% EtOAc in n-heptane).

1-(*tert*-butyl) 2-methyl (2*S*,4*R*)-4-(benzyloxy)pyrrolidine-1,2-dicarboxylate (II). In a dry 25 mL round-bottom flask, 1-(tert-butyl) 2-methyl (2S,4R)-4-hydroxypyrrolidine-1,2-dicarboxylate (1.500 g, 6.116 mmol, 1 equiv, compound **I**) and benzyl bromide (1.536 g, 12.84 mmol, 2.1 equiv) were solublized in dry DMF (12 mL). Sodium hydride (60 wt-% in mineral oil, 0.294 g, 7.339 mmol, 1.2 equiv) was slowly added and the mixture was stirred for 3 h. Then, the mixture was poured in ice/water and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified on silica gel eluting with 10% EtOAc in n-heptane to obtain the desired product (1.350 g, 4.025 mmol, **66%**) as a colorless oil. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.39-7.26 (m, 5H), 4.55-4.43 (m, 2H), 4.26-4.13 (m, 2H), 3.67 (s, 2H), 3.64 (s, 1H), 3.52-3.41 (m, 2H), 2.44-2.31 (m, 1H), 2.03-1.96 (m, 1H) 1.39 (s, 3 H), 1.33 (s, 6 H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 173.0, 172.6, 153.6, 152.9, 138.2, 138.1, 128.2, 127.5, 127.4, 79.2, 79.1, 76.4, 75.7, 70.0, 69.9, 57.6, 57.3, 51.8, 51.7, 51.5, 35.7, 34.9, 28.0, 27.8, **R_f**: 0.60 (50% EtOAc in n-heptane).

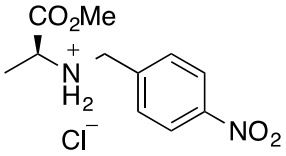
(2*S*,4*R*)-4-(benzyloxy)-2-(methoxycarbonyl)pyrrolidin-1-ium chloride (2i). To 1-(*tert*-butyl) 2-methyl (2*S*,4*R*)-4-(benzyloxy)pyrrolidine-1,2-dicarboxylate (1.289 g, 3.843 mmol, 1 equiv, compound **II**) was added an aqueous solution of HCl 4M in 1,4-dioxane (20.8 mL). The mixture was stirred at room temperature for 1 h and then concentrated under reduced pressure to afford the product (0.959 g, 3.529 mmol, **92%**) as a clear oil which was used in the subsequent step without any further purification. **^{1}H NMR** (500 MHz, DMSO-d_6, 100 °C) δ 10.05 (br s, 2H), 7.48-7.25 (m,

5H), 4.53 (s, 2H), 4.45 (dd, *J* = 10.8, 7.4 Hz, 1H), 4.39-4.33 (m, 1H), 3.78 (s, 3H), 3.50 (dd, *J* = 12.5, 4.9 Hz, 1H), 3.32 (br d, *J* = 12.5 Hz, 1H), 2.46-2.41 (m, 1H), 2.24-2.17 (m, 1H); **^{13}C NMR** (125 MHz, DMSO-d_6) δ 168.7, 137.7, 128.2, 127.8, 127.6, 76.2, 70.0, 57.4, 53.0, 50.3, 33.8; **R_f** : 0.50 (NH_3 7 M in MeOH/CH_2Cl_2, 5/95).



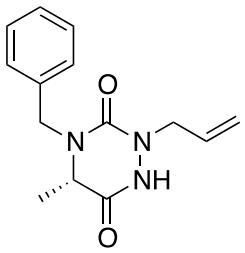
1-(*tert*-butyl) 2-methyl (2*S*,4*R*)-4-((4-nitrobenzyl)oxy)pyrrolidine-1,2-dicarboxylate (III). To a solution of 1-(*tert*-butyl) 2-methyl (2*S*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate (816 mg, 3.327 mmol, 1 equiv, compound **I**) and 4-nitrobenzyl bromide (1.437 g, 6.654 mmol, 2 equiv) in anhydrous CH_2Cl_2 (25 mL) was added, under argon, Ag_2O (2.312 g, 9.981 mmol, 3 equiv) and molecular sieve (4 Å, 1.5 g). The mixture was stirred at room temperature for 16 h. The suspension was filtered through celite, rinsing with CH_2Cl_2 and concentrated. The residue was purified on silica gel eluting with 30-50% EtOAc in n-heptane to afford the desired product as a colorless oil (1.072 g, 2.818 mmol, **85%**). **^{1}H NMR** (500 MHz, DMSO-d_6, 80 °C) δ 8.20 (d, *J* = 8.7 Hz, 2H, AA' of AA'BB'), 7.59 (d, *J* = 8.7 Hz, 2H, BB' of AA'BB'), 4.66 (ABq, ΔδAB = 0.038, J_{AB} = 13.6 Hz, 2H), 4.30-4.19 (m, 2H), 3.72-3.62 (m, 3H), 3.57-3.45 (m, 2H), 3.47-3.35 (m, 1H), 2.10-1.99 (m, 1H), 1.42-1.30 (m, 9H); **^{13}C NMR** (125 MHz, DMSO-d_6, 80 °C) δ 172.7, 172.3, 153.5, 152.7, 146.7, 146.2, 127.9, 123.2, 79.0, 76.9, 76.2, 68.7, 57.5, 57.2, 51.6, 51.3, 35.6, 34.8, 27.8, 27.7; **HRMS (ESI-TOF)** : calcd. for $C_{18}H_{24}N_2O_7Na$ $[M+Na]^+$: 403.14812, found : 403.1478; **R_f** : 0.21 (40% EtOAc in n-heptane); $[\propto]_D^{20} = -37.8\,°(c\ 0.205, CHCl_3)$.

(2*S*,4*R*)-2-(methoxycarbonyl)-4-((4-nitrobenzyl)oxy)pyrrolidin-1-ium chloride (2j). 1-(*tert*-butyl) 2-methyl (2*S*,4*R*)-4-((4-nitrobenzyl)oxy)pyrrolidine-1,2-dicarboxylate (1070 mg, 2.813 mmol, 1 equiv, compound **III**) was dissolved in a solution of HCl in dioxane (10 mL, 4M). The mixture was stirred for 1 h at room temperature and evaporated to afford the desired product as a light yellow solid (890 mg, 2.810 mmol, **100%**). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.80 (br s, 1H), 9.64 (br s, 1H), 8.20 (d, *J* = 8.6 Hz, 2H, AA' of AA'BB'), 7.66 (d, *J* = 8.6 Hz, 2H, BB' of AA'BB'), 4.67 (s, 2H), 4.48 (dd, *J* = 10.8, 7.2 Hz, 1H), 4.41-4.36 (m, 1H), 3.76 (s, 3H), 3.48 (dd, *J* = 12.6, 4.6 Hz, 1H), 3.36 (br d, *J* = 12.6 Hz, 1H), 2.53-2.45 (m, 1H), 2.24-2.13 (m, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 168.6, 146.8, 145.9, 128.3, 123.3, 67.8, 68.7, 57.3, 53.0, 50.1, 33.8; **HRMS (ESI-TOF)** : calcd. for $C_{13}H_{17}N_2O_5$ $[M+H]^+$: 281.11375, found : 281.11369; **R_f** : 0.33 (4% MeOH in CH_2Cl_2 adding 0.2% TEA); **mp** : 182.3 – 184.3 °C; $[\propto]_D^{20} = -17.3\,°(c\ 0.230, MeOH)$

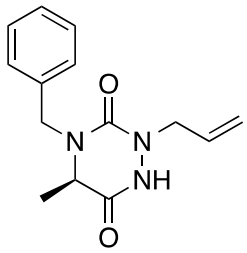


(*S*)-1-methoxy-*N*-(4-nitrobenzyl)-1-oxopropan-2-aminium chloride (2l). Reductive alkylation was performed following General Procedure A. The crude product was purified on silica gel, eluting with 50% EtOAc in n-heptane to obtain a yellow oil containing the product and 4-nitrobenzyl alcohol. The mixture was solubilized in diethyl ether (30 mL) and allowed to stir at 0 °C. A solution of hydrogen chloride (2M, 5 mL) was slowly added during 20 min. The suspension was filtered, washed with diethyl ether (3 x 10 mL) and evaporated to yield the desired product (511 mg, 1.86 mmol, **26%**) as a white powder. **^{1}H NMR** (400 MHz, MeOD-d_4) δ 8.34 (d, *J* = 8.7 Hz, 2H, AA' of AA'BB'), 7.80 (d, *J* = 8.7 Hz, 2H, BB' of AA'BB'), 4.42 (s, 2H), 4.28 (q, *J* = 7.3 Hz, 1H), 3.89 (s,

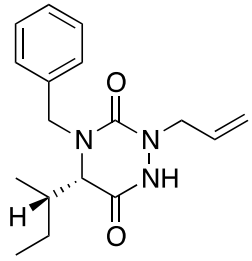
3H), 1.66 (d, *J* = 7.3 Hz); **^{13}C NMR** (100 MHz, MeOD-d_4) δ 171.1, 150.3, 139.5, 132.6, 125.3, 57.0, 54.1, 50.0, 15.5; **R_f** : 0.35 (50% EtOAc in n-heptane); **mp** : 196.9 – 198.9 °C



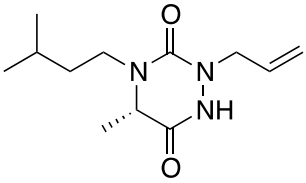
(*S*)-2-allyl-4-benzyl-5-methyl-1,2,4-triazinane-3,6-dione (4a). Synthesis of **4a** was performed following general procedure B2 starting from **2a**. The residue was purified on silica gel eluting with 50-70% EtOAc in n-heptane to obtain the desired product (2.332 g, 8.993 mmol, **70%**) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.50 (br s, 1H), 7.30-7.16 (m, 5H), 5.75 (ddt, *J* = 17.1, 10.2, 6.2 Hz, 1H), 5.23 (br d, *J* = 17.1 Hz, 1H), 5.16 (br d, *J* = 10.2 Hz, 1H), 4.85 (d, *J* = 14.9 Hz, 1H), 4.24 (dd, *J* = 15.7, 6.2 Hz, 1H), 4.05 (d, *J* = 14.2 Hz, 1H), 3.98 (dd, *J* = 15.7, 6.2 Hz, 1H), 3.68 (q, *J* = 7.0 Hz 1H), 1.17 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.4, 153.7, 136.5, 131.3, 128.9, 128.2, 128.0, 120.1, 54.6, 49.9, 48.7, 14.4; **HRMS** (ESI-TOF) : calcd. for $C_{14}H_{18}N_3O_2$ $[M+H]^+$: 260.13990, found : 260.13993; **R_f** : 0.30 (70% EtOAc in n-heptane); $[\propto]_D^{20} = +25.1°$ (c 0.09, $MeOH$).



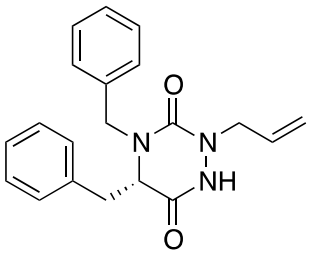
(*R*)-2-allyl-4-benzyl-5-methyl-1,2,4-triazinane-3,6-dione (4b). Synthesis of **4b** was performed following general procedure B2 starting from **2b**. The residue was purified on silica gel eluting with 50-70% EtOAc in n-heptane to obtain the desired product (524 mg, 2.020 mmol, **68%**) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29-7.17 (m, 5H), 6.21 (br s, 1H), 5.77 (ddt, *J* = 17.1, 10.2, 6.2 Hz, 1H), 5.27 (br d, *J* = 17.1 Hz, 1H), 5.23 (br d, *J* = 10.2 Hz, 1H), 4.84 (d, *J* = 15.1 Hz, 1H), 4.17 (dd, *J* = 15.6, 6.3 Hz, 1H), 4.07 (d, *J* = 15.6, 6.3 Hz, 1H), 4.07 (d, *J* = 15.1 Hz, 1H), 3.70 (q, *J* = 7.0 Hz, 1H), 1.19 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.7, 154.0, 136.5, 131.3, 129.1, 128.3, 128.2, 120.8, 54.9, 50.3, 48.9, 14.5; **HRMS** (ESI-TOF) : calcd. for $C_{14}H_{18}N_3O_2$ $[M+H]^+$: 260.13990, found : 260.13973; **R_f** : 0.30 (70% EtOAc in n-heptane; $[\propto]_D^{20} = -26.3°$ (c 0.15, $MeOH$).



(*S*)-2-allyl-4-benzyl-5-((*S*)-*sec*-butyl)-1,2,4-triazinane-3,6-dione (4c). Synthesis of **4c** was performed following general procedure B starting from **2c**. Purification on silica gel eluting with 30-50% EtOAc in n-heptane afforded the title compound as a yellow oil (108 mg, 0.358 mmol, **31%**). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.36 (br s, 1H), 7.30-7.14 (m, 5H), 5.75 (ddt, *J* = 17.1, 10.1, 6.4 Hz, 1H), 5.25 (m, 1H), 5.20 (m, 1H), 5.12 (d, *J* = 15.3 Hz, 1H), 4.13 (dd, *J* = 15.5, 6.0 Hz, 1H), 4.02 (dd, *J* = 15.3, 6.7 Hz, 1H), 3.90 (d, *J* = 15.3 Hz, 1H), 3.56 (d, *J* = 6.1 Hz, 1H), 1.85-1.72 (m, 1H), 1.57-1.44 (m, 1H), 1.27-1.13 (m, 1H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.83 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.4, 153.8, 136.6, 131.5, 129.0, 128.1, 128.0, 120.6, 63.2, 50.4, 50.1, 36.9, 26.5, 15.0, 11.8; **HRMS** (ESI-TOF) : calcd. for $C_{17}H_{24}N_3O_2$ $[M+H]^+$: 302.18685, found : 302.18578; **R_f** : 0.32 (50% EtOAc in n-heptane); $[\propto]_D^{20} = +49.5\,°$ (c 0.24, $MeOH$).

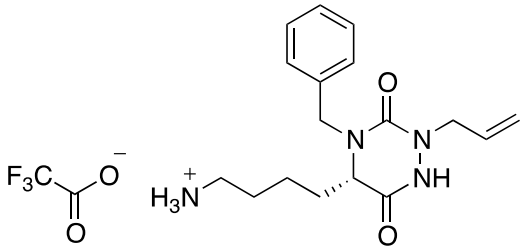


(*S*)-2-allyl-4-isopentyl-5-methyl-1,2,4-triazinane-3,6-dione (4d). Synthesis of **4d** was performed following general procedure B starting from **2d**. Purification on silica gel eluting with 30-60% EtOAc in n-heptane afforded the title compound as a yellow oil (88 mg, 0.366 mmol, **31%**). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.14 (br s, 1H), 5.81 (ddt, *J* = 17.2, 10.2, 6.2 Hz, 1H), 5.30 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.25 (dd, *J* = 10.2, 0.9 Hz, 1H), 4.21 (dd, *J* = 15.6, 6.1 Hz, 1H), 4.04 (dd, *J* = 15.7, 6.3 Hz, 1H), 3.78 (q, *J* = 7.0 Hz, 1H), 3.69 (dt, *J* = 8.0, 1.0 Hz, 1H), 2.94-2.84 (m, 1H), 1.61-1.48 (m, 1H), 1.43-1.37 (m, 2H), 1.32 (d, *J* = 7.0 Hz, 3H), 0.88 (d, *J* = 6.4 Hz, 3H), 0.88 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.7, 153.8, 131.6, 120.2, 55.7, 50.0, 44.0, 37.2, 26.0, 22.8, 22.5, 14.9; **HRMS** (ESI-TOF) : calcd. for $C_{12}H_{22}N_3O_2$ $[M+H]^+$: 240.17120, found : 240.17045; **R_f** : 0.20 (50% EtOAc in n-heptane); $[\propto]_D^{20} = +10.6\,°$ (c 0.16, $MeOH$).

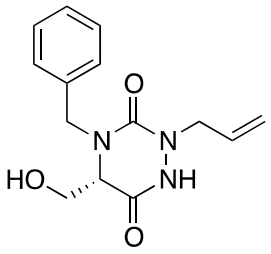


(*S*)-2-allyl-4,5-dibenzyl-1,2,4-triazinane-3,6-dione (4e). Synthesis of **4e** was performed following general procedure B starting from **2e**. Purification on silica gel eluting with 30-50% EtOAc in n-heptane afforded the title compound as a yellow oil (416 mg, 1.242 mmol, **49%**). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.88 (br s, 1H), 7.27-7.15 (m, 6H), 7.12-7.05 (m, 4H), 5.50 (ddt, *J* = 17.1, 10.2, 6.2 Hz, 1H), 5.12-5.02 (m, 2H), 5.02-4.94 (m, 1H), 3.88 (t, *J* = 5.8 Hz, 1H), 3.79 (dd, *J* = 15.7, 6.0 Hz,

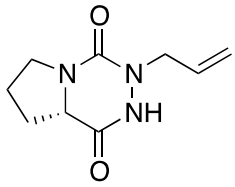
1H), 3.67-3.52 (m, 2H), 2.93 (dd, *J* = 13.7, 5.3 Hz, 1H), 2.85 (dd, *J* = 13.7, 6.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.8, 153.1, 136.2, 135.5, 131.4, 129.7, 128.9, 128.8, 128.2, 128.0, 127.4, 119.9, 60.0, 50.0, 49.2, 35.6; **HRMS** (ESI-TOF) : calcd. for $C_{20}H_{21}N_3O_2Na$ $[M+Na]^+$: 358.15315, found : 358.15264; **R_f** : 0.20 (50% EtOAc in n-heptane); $[\propto]_D^{20}$ =+ 30.1 ° (*c* 0.19, *MeOH*).



(*S*)-4-(2-allyl-4-benzyl-3,6-dioxo-1,2,4-triazinan-5-yl)butan-1-aminium 2,2,2-trifluoroacetate (4f). Synthesis of **4f** was performed following general procedure B starting from **2f**. Purification of the crude on semi-preparative RP-HPLC (5-40% ACN + 0.1 % TFA in water + 0.1% TFA) afforded the title compound as a yellow oil (255 mg, 0.593 mmol, **51%**). **^{1}H NMR** (400 MHz, MeOD-d_4) δ 7.39-7.27 (m, 5H), 5.88 (ddt, *J* = 17.2, 10.3, 6.1 Hz, 1H), 5.32 (br dd, *J* = 17.2, 1.2 Hz, 1H), 5.28 (br dd, *J* = 10.3, 1.2 Hz, 1H), 4.90 (d, *J* = 15.0 Hz, 1H), 4.38-4.30 (m, 1H), 4.23 (d, *J* = 15.0 Hz, 1H), 4.03-3.95 (m, 1H), 3.73 (t, *J* = 7.0 Hz, 1H), 2.86 (t, *J* = 7.6 Hz, 2H), 1.77-1.53 (m, 4H), 1.49-1.35 (m, 2H); **^{13}C NMR** (100 MHz, MeOD-d_4) δ 155.5, 138.4, 133.0, 130.1, 129.2, 129.1, 119.9, 60.3, 50.9, 50.3, 40.5, 30.3, 28.3, 23.4; **HRMS** (ESI-TOF) : calcd. for $C_{17}H_{25}N_4O_2^+$ $[M]^+$: 317.19775, found : 317.19709; **R_f** : 0.20 (10% MeOH in CH_2Cl_2 + 0.2% NEt_3); $[\propto]_D^{20}$ = + 39.4 ° (*c* 0.15, *MeOH*).



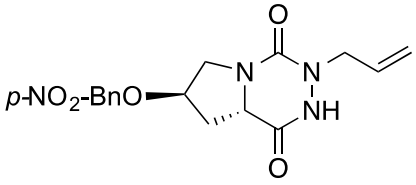
(*S*)-2-allyl-4-benzyl-5-(hydroxymethyl)-1,2,4-triazinane-3,6-dione (4g). Synthesis of **4g** was performed following general procedure B starting from **2g** (except that TFA/H_2O/Et_3SiH, 95:2.5:2.5 was used in place of TFA/H_2O). Purification on silica gel eluting with 5% MeOH in CH_2Cl_2 followed by a purification on flash-chromatography (5-40% ACN + 0.1 % TFA in water + 0.1% TFA) afforded the title compound as a white powder (232 mg, 0.844 mmol, **45%**). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.39 (br s, 1H), 7.33-7.14 (m, 5H), 5.78 (ddt, *J* = 17.1, 10.2, 6.2 Hz, 1H), 5.27 (dd, *J* = 17.3, 1.2 Hz, 1H), 5.20 (br d, *J* = 10.5 Hz, 1H), 5.04 (d, *J* = 15.2 Hz, 1H), 4.20 (dd, *J* = 15.5, 5.8 Hz, 1H), 4.06 (d, *J* = 15.2 Hz, 1H), 4.01 (dd, *J* = 15.5, 5.8 Hz, 1H), 3.78-3.67 (m, 3H), 3.26 (br s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.4, 154.3, 136.2, 131.5, 129.2, 128.3, 128.2, 120.4, 60.6, 60.0, 51.6, 49.0; **mp** : 126.5 – 128.5 °C; **HRMS** (ESI-TOF) : calcd. for $C_{14}H_{18}N_3O_3$ $[M+H]^+$: 276.13482, found : 276.13385; **R_f** : 0.38 (6% MeOH in CH_2Cl_2); $[\propto]_D^{20}$ =+ 36.6 °(*c* 0.19, *MeOH*).



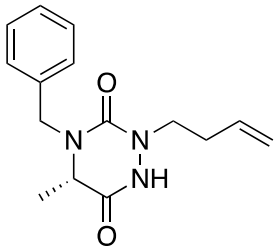
(*S*)-3-allylhexahydropyrrolo[1,2-*d*][1,2,4]triazine-1,4-dione (4h). Synthesis of **4h** was performed following general procedure B2 strating from L-Proline methyl ester hydrochloride. Purification by flash-chromatography (RP-18, 5-40% acetonitrile + 0.1% TFA in water + 0.1% TFA) afforded the title compound as a white solid (134 mg, 0.686 mmol, **38%**). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.69 (br s, 1H), 5.83 (ddt, *J* = 17.2 Hz, 10.2 Hz, 6.2 Hz, 1H), 5.33 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.28 (dd, *J* = 10.2, 1.2 Hz, 1H), 4.14 (dd, *J* = 15.5, 6.6 Hz, 1H), 4.07 (dd, *J* = 15.4, 6.0 Hz, 1H), 3.93 (t, *J* = 7.8 Hz, 1H), 3.53-3.47 (m, 2H), 2.28-2.11 (m, 2H), 2.02-1.85 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.6, 154.4, 131.9, 120.5, 58.0, 49.7, 45.4, 27.1, 23.6; **HRMS** (ESI-TOF) : calcd. for $C_9H_{14}N_3O_2$ $[M+H]^+$: 196.10860, found : 196.10764; **Rf** : 0.35 (4% MeOH in dichloromethane); **mp** : 145.7 – 147.7 °C ; $[\propto]_D^{20} = +\ 25.5\ °\ (c\ 0.12,\ MeOH)$.

(7*R*,8a*S*)-3-allyl-7-(benzyloxy)hexahydropyrrolo[1,2-*d*][1,2,4]triazine-1,4-dione (4i). Synthesis of **4i** was performed following general procedure B2 starting from **2i**. Purification on silica gel eluting with 10% MeOH in CH_2Cl_2 afforded the title compound as a yellow oil (130 mg, 0.431 mmol, **29%**). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.83 (br s, 1H), 7.37-7.25 (m, 5H), 5.82 (ddt, *J* = 17.2, 10.1, 6.3 Hz, 1H), 5.33 (dd, *J* = 17.2, 1.3 Hz, 1H), 5.28 (dd, *J* = 10.1, 1.3 Hz, 1H), 4.51 (ABq, $\Delta\delta_{AB}$ = 0.035, J_{AB} = 11.8 Hz, 2H), 4.26-4.03 (m, 4H), 3.73-3.68 (m, 1H), 3.65-3.59 (m, 1H), 2.47-2.39 (m, 1H), 2.19-2.08 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.7, 154.1, 137.7, 131.8, 128.7, 128.1, 127.9, 120.5, 76.1, 71.2, 56.8, 51.3, 49.7, 34.0; **HRMS** (ESI-TOF) : calcd. for $C_{16}H_{20}N_3O_3$ $[M+H]^+$: 302.15047, found : 302.15043; **R_f** : 0.25 (4% MeOH in CH_2Cl_2); $[\propto]_D^{20} = +\ 5.1\ °\ (c\ 0.08, MeOH)$.

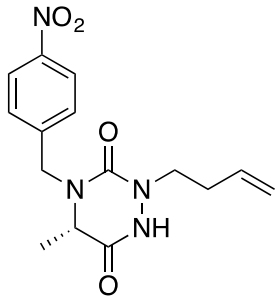
(7*R*,8a*S*)-3-allyl-7-hydroxyhexahydropyrrolo[1,2-*d*][1,2,4]triazine-1,4-dione (IV). Synthesis was performed following general procedure E starting from **4i**. Purification on silica gel eluting with 10% MeOH in CH_2Cl_2 afforded the title compound as a yellow oil (55 mg, 0.259 mmol, **76%**). **^{1}H NMR** (400 MHz, MeOD-d_4) δ 5.86 (ddt, *J* = 17.2, 10.3, 5.8 Hz, 1H), 5.30 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.25 (dd, *J* = 10.2, 1.3 Hz, 1H), 4.49-4.44 (m, 1H), 4.35-4.25 (m, 2H), 3.96-3.88 (m, 1H), 3.68-3.62 (m, 1H), 3.47-3.41 (m, 1H), 2.26-2.08 (m, 2H); **^{13}C NMR** (100 MHz, MeOD-d_4) δ 168.0, 155.8, 133.5, 119.1, 70.0, 57.6, 55.1, 50.3, 37.8; **HRMS** (ESI-TOF) : calcd. for $C_9H_{14}N_3O_3$ $[M+H]^+$: 212.10352, found : 212.10293; **R_f** : 0.32 (10% MeOH in CH_2Cl_2); $[\propto]_D^{20} = +\ 10.8\ °\ (c\ 0.13, MeOH)$.



(7*R*,8a*S*)-3-allyl-7-((4-nitrobenzyl)oxy)hexahydropyrrolo[1,2-*d*][1,2,4]triazine-1,4-dione (4j). Synthesis was performed following General Procedure B2 starting from **2j**. Water was added to the mixture and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified on silica gel eluting with 4% MeOH in CH_2Cl_2 to obtain the desired product (350 mg, 1.011 mmol, **39%**) as a light yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.11 (br s, 1H), 8.11 (d, J = 8.7 Hz, 2H, AA' of AA'BB'), 7.42 (d, J = 8.7 Hz, 2H, BB' of AA'BB'), 5.78 (ddt, J = 17.2, 10.2, 6.1 Hz, 1H), 5.28 (br dd, J = 17.2, 1.5 Hz, 1H), 5.20 (br dd, J = 10.2, 1.4 Hz, 1H), 4.58 (ABq, $\Delta\delta_{AB}$ = 0.021, J_{AB} = 13.1 Hz, 2H), 4.25-4.14 (m, 3H), 3.97 (br dd, J = 15.8, 6.2 Hz, 1H), 3.69 (br d, J = 12.0 Hz, 1H), 3.63 (dd, J = 12.0, 4.6 Hz, 1H), 2.42 (br dd, J = 13.6, 6.5 Hz, 1H), 2.13 (ddd, J = 13.6, 10.4, 4.9 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.3, 153.7, 147.4, 145.2, 131.6, 127.7, 123.7, 119.8, 76.9, 69.7, 56.5, 51.0, 49.3, 33.9; **HRMS (ESI-TOF)** : calcd. for $C_{16}H_{18}N_4O_5Na$ $[M+H]^+$: 369.11749, found : 369.11704; **R_f** : 0.27 (4% MeOH in CH_2Cl_2); $[\propto]_D^{20} = +13.3\,^\circ$ (c 0.33, $MeOH$).



(*S*)-4-benzyl-2-(but-3-en-1-yl)-5-methyl-1,2,4-triazinane-3,6-dione (4k). Synthesis of **4j** was performed following general procedure B starting from **2a**. Purification on silica gel eluting with 2% MeOH in CH_2Cl_2 afforded the title compound as a white solid (456 mg, 1.668 mmol, **77%**). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.42 (br s, 1H), 7.31-7.16 (m, 5H), 5.71 (ddt, J = 17.2, 10.3, 6.9 Hz, 1H), 5.10-5.00 (m, 2H), 4.86 (d, J = 15.1 Hz, 1H), 4.06 (d, J = 15.1 Hz, 1H), 3.84 (dt, J = 14.5, 7.3 Hz, 1H), 3.73 (q, J = 7.0 Hz, 1H), 3.50-3.42 (m, 1H), 2.39-2.32 (m, 2H), 1.21 (d, J = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.0, 153.7, 136.1, 134.4, 129.1, 128.3, 128.2, 118.2, 54.5, 48.9, 46.9, 31.9, 14.4; **HRMS** (ESI-TOF) : calcd. for $C_{15}H_{20}N_3O_2$ $[M+H]^+$: 274.15555, found : 274.15539; **mp** : 58.9 – 60.9 °C; **R_f** : 0.31 (70% EtOAc in n-heptane); $[\propto]_D^{20} = +56.8\,^\circ$($c$ 0.17, $MeOH$).

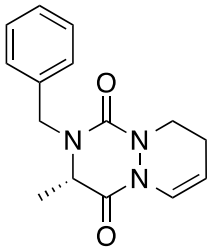


(*S*)-2-(but-3-en-1-yl)-5-methyl-4-(4-nitrobenzyl)-1,2,4-triazinane-3,6-dione (4l). Synthesis was performed following general procedure B2 starting from **2l**. Purification on silica gel eluting with 50-

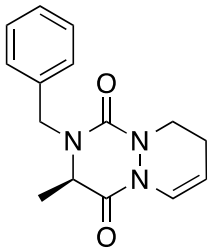
70% EtOAc in n-heptane afforded the title compound as a yellow oil (417 mg, 1.310 mmol, **54%**). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.04 (br s, 1H), 8.18 (d, *J* = 8.5 Hz, 2H, AA' of AA'BB'), 7.44 (d, *J* = 8.5 Hz, 2H, BB' of AA'BB'), 5.77 (ddt, *J* = 17.1, 10.2, 6.8 Hz), 5.11 (br d, *J* = 17.1 Hz, 1H), 5.07 (br d, *J* = 10.2 Hz, 1H), 4.95 (d, *J* = 15.9 Hz, 1H), 4.23 (d, *J* = 15.9 Hz, 1H), 3.92-3.82 (m, 1H), 3.75 (q, *J* = 7.0 Hz, 1H), 3.56-3.45 (m, 1H), 2.45-2.36 (m, 2H), 1.29 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.4, 153.5, 147.9, 144.6, 134.5, 128.8, 124.3, 118.1, 55.7, 48.5, 46.7, 31.9, 14.6; **HRMS (ESI-TOF)** : calcd. for $C_{15}H_{18}N_4O_4Na$ $[M+Na]^+$: 341.12258, found : 341.12227 ; **R_f** : 0.30 (70% EtOAc in n-heptane); $[\propto]_D^{20} = +\ 51.9\ °(c\ 0.26, MeOH)$.

(7*R*)-7-(benzyloxy)-3-(but-3-en-1-yl)hexahydropyrrolo[1,2-d][1,2,4]triazine-1,4-dione (4m). Synthesis was performed following general procedure B starting from **2i**. Purification on silica gel eluting with 4% MeOH in CH_2Cl_2 afforded the title compound as a yellow oil (171 mg, 0.543 mmol, **27%**). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.85 (br s, 1H), 7.31-7.16 (m, 5H), 5.70 (ddt, *J* = 17.2, 10.2, 6.9 Hz, 1H), 5.05 (ddt, *J* = 17.2, 1.6 Hz, 1H), 4.99 (br dd, *J* = 10.2 Hz, 1.6 Hz, 1H), 4.45 (ABq, $\Delta\delta_{AB}$ = 0.035, J_{AB} = 11.8 Hz, 2H), 4.15-4.08 (m, 2H), 3.78 (dt, *J* = 14.4, 6.9 Hz, 1H), 3.66-3.53 (m, 2H), 3.38-3.29 (m, 1H), 2.42-2.26 (m, 3H), 2.10-2.00 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.9, 153.7, 137.7, 134.7, 128.6, 128.0, 127.8, 117.6, 76.0, 71.1, 56.4, 51.2, 46.3, 34.0, 32.0; **HRMS** (ESI-TOF) : calcd. for $C_{17}H_{22}N_3O_3$ $[M+H]^+$: 316.16612, found : 316.16603; **R_f** : 0.25 (4% MeOH in CH_2Cl_2); $[\propto]_D^{20} = -\ 2.8\ °\ (c\ 0.16, MeOH)$.

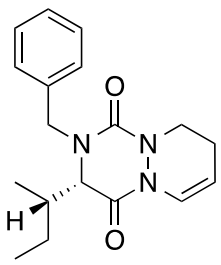
(7*R*,8a*S*)-3-(but-3-en-1-yl)-7-hydroxyhexahydropyrrolo[1,2-*d*][1,2,4]triazine-1,4-dione (V). Synthesis was performed following general procedure D starting from **4m**. Purification on silica gel eluting with 10% MeOH in CH_2Cl_2 afforded the title compound as a yellow oil (88 mg, 0.389 mmol, **71%**). **^{1}H NMR** (400 MHz, MeOD-d_4) δ 5.78 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.12 (dd, *J* = 17.1, 1.6 Hz, 1H), 5.06 (br d, *J* = 10.2 Hz, 1H), 4.46-4.42 (m, 1H), 4.21 (dd, *J* = 10.4, 6.7 Hz, 1H), 3.86 (dt, *J* = 14.5, 7.6 Hz, 1H), 3.63 (dd, *J* = 11.7, 4.8 Hz, 1H), 3.44-3.38 (m, 1H), 3.35-3.26 (m, 1H), 2.41-2.33 (m, 2H), 2.23-2.06 (m, 2H); **^{13}C NMR** (100 MHz, MeOD-d_4) δ 167.9, 155.7, 136.1, 117.8, 70.0, 57.5, 55.0, 47.3, 37.8, 33.0; **HRMS** (ESI-TOF) : calcd. for $C_{10}H_{16}N_3O_3$ $[M+H]^+$: 226.11917, found : 226.11857; **R_f** : 0.32 (10% MeOH in CH_2Cl_2); $[\propto]_D^{20} = -\ 4.0\ °\ (c\ 0.09, acetone)$.



(*S*)-2-benzyl-3-methyl-2,3,8,9-tetrahydropyridazino[1,2-*a*][1,2,4]triazine-1,4-dione (**5a**). Hydroformylation was performed following general procedure C starting from **4a**. Purification on silica gel eluting with 25-50% EtOAc in n-heptane afforded the title compound as a white solide (1.198 g, 4.416 mmol, **81%**). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35-7.23 (m, 5H), 7.07-7.02 (m, 1H), 5.32-5.26 (m, 1H), 4.80 (d, *J* = 15.1 Hz, 1H), 4.56-4.48 (m, 1H), 4.21 (d, *J* = 15.1 Hz, 1H), 3.81 (q, *J* = 7.0 Hz, 1H), 3.20 (ddd, *J* = 13.2, 10.3, 3.9 Hz, 1H), 2.44-2.33 (m, 1H), 2.21-2.11 (m, 1H), 1.17 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.6, 153.8, 136.6, 129.0, 128.4, 128.1, 120.2, 107.4, 54.7, 48.8, 39.9, 22.6, 14.5; **HRMS** (ESI-TOF) : calcd. for $C_{15}H_{18}N_3O_2$ $[M+H]^+$: 272.13990, found : 272.13970; **mp** : 68.1 – 70.1 °C; **R_f** : 0.22 (30% EtOAc in n-heptane); $[\propto]_D^{20} = +37.7\,°$ (c 0.12, $MeOH$).

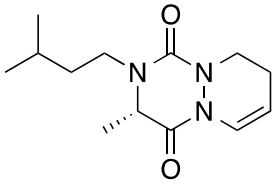


(*R*)-2-benzyl-3-methyl-2,3,8,9-tetrahydropyridazino[1,2-*a*][1,2,4]triazine-1,4-dione (5b). Hydroformylation was performed following general procedure C starting from **4b**. Purification on silica gel eluting with 30% EtOAc in n-heptane afforded the title compound as a white solide (286 mg, 1.054 mmol, **79%**). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34-7.22 (m, 5H), 7.07-7.02 (m, 1H), 5.32-5.26 (m, 1H), 4.80 (d, *J* = 15.1 Hz, 1H), 4.56-4.49 (m, 1H), 4.21 (d, *J* = 15.1 Hz, 1H), 3.81 (q, *J* = 7.0 Hz, 1H), 3.25 (ddd, *J* = 13.2, 10.3, 3.9 Hz, 1H), 2.49-2.37 (m, 1H), 2.25-2.15 (m, 1H), 1.22 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.6, 153.8, 136.6, 129.1, 128.4, 128.1, 120.2, 107.4, 54.7, 48.9, 39.9, 22.7, 14.5; **HRMS** (ESI-TOF) : calcd. for $C_{15}H_{18}N_3O_2$ $[M+H]^+$: 272.13990, found : 272.14006; **R_f** : 0.22 (30% EtOAc in n-heptane); $[\propto]_D^{20} = -35.2\,°$ (c 0.15, $MeOH$).

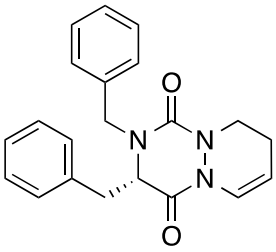


(*S*)-2-benzyl-3-((*S*)-*sec*-butyl)-2,3,8,9-tetrahydropyridazino[1,2-*a*][1,2,4]triazine-1,4-dione (5c). Hydroformylation was performed following general procedure C starting from **4c**. Purification on silica gel eluting with 10-30% EtOAc in n-heptane) afforded the title compound as a yellow oil (80 mg, 0.256 mmol, **81%**). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33-7.17 (m, 5H), 7.10-7.05 (m, 1H), 5.29-5.24 (m, 1H), 5.14 (d, *J* = 15.2 Hz, 1H), 4.63-4.56 (m, 1H), 3.98 (d, *J* = 15.2 Hz, 1H), 3.63 (d, *J* =

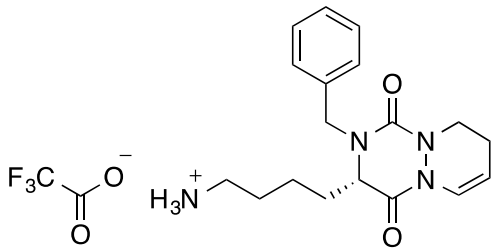
6.2 Hz, 1H), 3.07-2.98 (m, 1H), 2.52-2.41 (m, 1H), 2.17-2.07 (m, 1H), 1.88-1.77 (m, 1H), 1.60-1.49 (m, 1H), 1.28-1.16 (m, 1H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.87 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.6, 153.5, 136.4, 129.1, 128.2, 128.1, 120.2, 107.4, 63.0, 50.1, 40.3, 36.8, 26.4, 22.8, 15.0, 11.7; **HRMS** (ESI-TOF) : calcd. for $C_{18}H_{24}N_3O_2$ $[M+H]^+$: 314.18685, found : 314.18672; **R_f** : 0.28 (30% EtOAc in n-heptane); $[\propto]_D^{20} = +29.9°$ (c 0.20, $MeOH$).



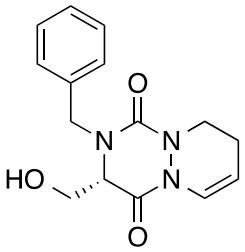
(*S*)-2-isopentyl-3-methyl-2,3,8,9-tetrahydropyridazino[1,2-*a*][1,2,4]triazine-1,4-dione (5d). Hydroformylation was performed following general procedure C starting from **4d**. Purification on silica gel eluting with 20-30% of EtOAc in n-heptane afforded the title compound as a light yellow oil (174 mg, 0.692 mmol, **78%**). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.03 (br d, *J* = 8.5 Hz, 1H), 5.29-5.23 (m, 1H), 4.47-4.40 (m, 1H), 3.84 (q, *J* = 7.0 Hz, 1H), 3.64 (dt, *J* = 14.1 Hz, 8.0 Hz, 1H), 3.24-3.14 (m, 1H), 2.98-2.89 (m, 1H), 2.43-2.32 (m, 1H), 2.20-2.11 (m, 1H), 1.60-1.36 (m, 3H), 1.34 (d, *J* = 7 Hz, 3H), 0.88 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.8, 153.6, 120.2, 107.4, 55.6, 43.9, 39.7, 37.3, 26.1, 22.7, 22.6, 22.6, 14.9; **HRMS** (ESI-TOF) : calcd. for $C_{13}H_{22}N_3O_2$ $[M+H]^+$: 252.17120, found : 252.17064; **R_f** : 0.45 (50% EtOAc in n-heptane); $[\propto]_D^{20} = +51.3°$ (c 0.15, $MeOH$).



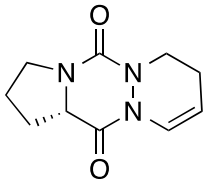
(*S*)-2,3-dibenzyl-2,3,8,9-tetrahydropyridazino[1,2-*a*][1,2,4]triazine-1,4-dione (5e). Hydroformylation was performed following general procedure C starting from **4e**. Purification on silica gel eluting with 30% of EtOAc in n-heptane afforded the title compound as a light yellow oil (277 mg, 0.797 mmol, **77%**). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35-7.17 (m, 8H), 7.15-7.10 (m, 2H), 7.00 (dd, *J* = 8.4, 2.1 Hz, 1H), 5.23-5.17 (m, 1H), 5.08 (d, *J* = 15.0 Hz, 1H), 4.15-4.08 (m, 1H), 4.04 (t, *J* = 5.1 Hz, 1H), 3.90 (d, *J* = 15.0 Hz, 1H), 3.01 (dd, *J* = 14.3, 5.1 Hz, 1H), 2.96 (dd, *J* = 14.3, 5.1 Hz, 1H), 2.34-2.23 (m, 1H), 2.05-1.89 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.7, 152.7, 136.2, 135.3, 129.9, 129.1, 129.0, 128.5, 128.2, 127.6, 119.8, 108.1, 59.5, 49.1, 39.9, 36.1, 22.7; **HRMS** (ESI-TOF) : calcd. for $C_{21}H_{21}N_3O_2Na$ $[M+Na]^+$: 370.15315, found : 370.15279; **R_f** : 0.41 (50% EtOAc in n-heptane); $[\propto]_D^{20} = +68.3°$ (c 0.10, $MeOH$).



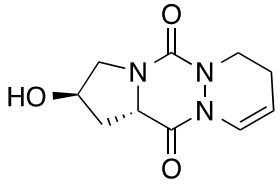
(*S*)-4-(2-benzyl-1,4-dioxo-1,2,3,4,8,9-hexahydropyridazino[1,2-*a*][1,2,4]triazin-3-yl)butan-1-aminium 2,2,2-trifluoroacetate (5f). Hydroformylation was performed following general procedure C starting from **4f**. Purification on semi-preparative RP-HPLC (RP-18, 5-100% ACN + 0.1 % TFA in water + 0.1% TFA) afforded the title compound as a colorless oil (53 mg, 0.121 mmol, **43%**). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 (br s, 3H), 7.32-7.24 (m, 3H), 7.22-7.18 (m, 2H), 6.99 (br dd, *J* = 8.5, 2.5 Hz, 1H), 5.36-5.29 (m, 1H), 4.83 (d, *J* = 15.1 Hz, 1H), 4.53 (dd, *J* = 13.6, 6.3 Hz, 1H), 4.14 (d, *J* = 15.1 Hz, 1H), 3.75-3.69 (m, 1H), 3.16-3.06 (m, 1H), 2.91 (br s, 2H), 2.48-2.36 (m, 1H), 2.23-2.13 (m, 1H), 1.71-1.49 (m, 4H), 1.42-1.28 (m, 2H); **^{13}C NMR** (100 MHz, MeOD-d_4) δ 161.5, 153.6, 136.1, 129.2, 128.4, 128.3, 119.9, 108.4, 58.8, 49.7, 40.3, 39.7, 29.2, 27.2, 22.6, 22.1; **HRMS** (ESI-TOF) : calcd. for $C_{18}H_{25}N_4O_2^+$ $[M]^+$: 329.197751, found : 329.19736; **R_f** : 0.20 (10% MeOH in CH_2Cl_2 + 0.2% TEA); $[\propto]_D^{20} = +30.8°$ (c 0.18, $MeOH$).



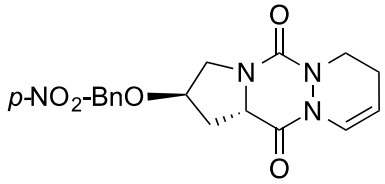
(*S*)-2-benzyl-3-(hydroxymethyl)-2,3,8,9-tetrahydropyridazino[1,2-*a*][1,2,4]triazine-1,4-dione (5g). Hydroformylation was performed following general procedure C starting from **4g**. Purification on silica gel eluting with 70-80% of EtOAc in n-heptane afforded (50 mg, 0.174 mmol, **57%**) of the title compound as a light yellow oil. **^{1}H NMR** (400 MHz, MeOD-d_4) δ 7.39-7.25 (m, 5H), 7.06 (br d, *J* = 8.4 Hz, 1H), 5.42-5.36 (m, 1H), 4.99 (d, *J* = 15.1 Hz, 1H), 4.52-4.45 (m, 1H), 4.21 (d, *J* = 15.1 Hz, 1H), 3.84 (t, *J* = 3.2 Hz, 1H), 3.81-3.70 (m, 2H), 3.18-3.10 (m, 1H), 2.51-2.39 (m, 1H), 2.25-2.16 (m, 1H); **^{13}C NMR** (100 MHz, MeOD-d_4) δ 162.3, 155.6, 138.1, 130.0, 129.2, 129.0, 120.8, 110.2, 62.2, 60.9, 49.9, 43.3, 24.1; **HRMS** (ESI-TOF) : calcd. for $C_{15}H_{17}N_3O_3Na$ $[M+Na]^+$: 310.11676, found : 310.11699; **R_f** : 0.23 (80% EtOAc in n-heptane); $[\propto]_D^{20} = -121.0°$ (c 0.16, $MeOH$).



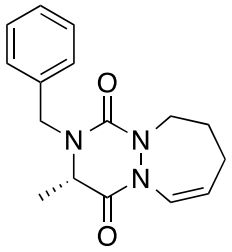
(*S*)-1,2,3,7,8,12a-hexahydro-5*H*,12*H*-pyridazino[1,2-*a*]pyrrolo[1,2-*d*][1,2,4]triazine-5,12-dione (5h). Hydroformylation was performed following general procedure C starting from **4h**. The residue was purified on flash-chromatography (RP-18, 5-50% ACN + 0.1 % TFA in water + 0.1% TFA) and evaporated to obtain the desired product (263 mg, 1.269 mmol, **69%**) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.05 (dd, *J* = 8.4, 2.8 Hz, 1H), 5.28-5.21 (m, 1H), 4.47-4.40 (m, 1H), 3.93 (t, *J* = 7.8 Hz, 1H), 3.57-3.50 (m, 1H), 3.47-3.39 (m, 1H), 3.11-3.03 (m, 1H), 2.42-2.32 (m, 1H), 2.29-2.21 (m, 2H), 2.16-2.06 (m, 1H), 1.99-1.88 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.3, 154.2, 120.6, 106.8, 58.0, 45.0, 39.4, 26.9, 24.0, 22.3; **HRMS** (ESI-TOF) : calcd. for $C_{10}H_{13}N_3O_2Na$ $[M+Na]^+$: 230.09055, found : 230.09037; **R_f** : 0.45 (4% MeOH in CH_2Cl_2); **mp** : 104.5 – 106.5 °C; $[\propto]_D^{20} = -63.4°$ (c 0.17, $MeOH$).



(2*R*,12a*S*)-2-hydroxy-1,2,3,7,8,12a-hexahydro-5*H*,12*H*-pyridazino[1,2-*a*]pyrrolo[1,2-*d*][1,2,4]triazine-5,12-dione (5i). Hydroformylation was performed following general procedure C starting from **4i**. Purification on silica gel eluting with 70-80% of EtOAc in n-heptane afforded (49 mg, 0.220 mmol, **73%**) of the title compound as a white solid. **^{1}H NMR** (400 MHz, MeOD-d_4) δ 7.06 (dd, *J* = 8.4, 2.8 Hz, 1H), 5.38-4.32 (m, 1H), 4.49-4.44 (m, 1H), 4.43-4.36 (m, 1H), 4.32 (dd, *J* = 9.9, 7.0 Hz, 1H), 3.58 (dd, *J* = 11.5, 4.4 Hz, 1H), 3.52-3.46 (m, 1H), 3.24-3.15 (m, 1H), 2.43-2.13 (m, 4H); **^{13}C NMR** (100 MHz, MeOD-d_4) δ 165.2, 155.6, 121.2, 108.5, 70.3, 57.8, 54.5, 40.7, 37.3, 23.2; **HRMS** (ESI-TOF) : calcd. for $C_{10}H_{14}N_3O_3$ $[M+H]^+$: 224.10352, found : 224.10283; **R_f** : 0.21 (5% MeOH in CH_2Cl_2); **mp** : 155.6 – 157.6 °C; $[\propto]_D^{20} = +\ 10.0\ °\ (c\ 0.17, MeOH)$.

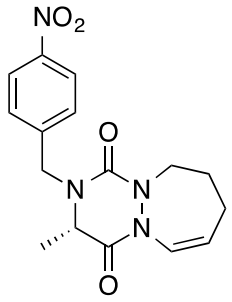


(2*R*,12a*S*)-2-((4-nitrobenzyl)oxy)-1,2,3,7,8,12a-hexahydro-5*H*,12*H*-pyridazino[1,2-*a*]pyrrolo[1,2-*d*][1,2,4]triazine-5,12-dione (5j). Hydroformylation was performed following general procedure C starting from **4j**. Purification on silica gel eluting with 50-70% EtOAc in n-heptane afforded the title compound as a white solid (226 mg, 0.631 mmol, **62%**).**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.6 Hz, 2H, AA' of AA'BB'), 7.46 (d, *J* = 8.6 Hz, 2H, BB' of AA'BB'), 7.06 (br dd, *J* = 8.4, 2.6 Hz, 1H), 5.30-5.25 (m, 1H), 4.62 (ABq, $\Delta\delta_{AB}$ = 0.032, J_{AB} = 12.9 Hz, 2H), 4.51-4.44 (m, 1H), 4.27-4.20 (m, 2H), 3.79 (br d, *J* = 12.1 Hz, 1H), 3.59 (dd, *J* = 12.1, 4.6 Hz, 1H), 3.10 (ddd, *J* = 13.5, 11.1, 3.7 Hz, 1H), 2.54-2.46 (m, 1H), 2.43-2.32 (m, 1H), 2.26 (ddd, *J* = 13.8, 10.3, 4.9 Hz, 1H), 2.18-2.09 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.2, 153.9, 147.7, 145.2, 127.9, 123.9, 120.5, 107.1, 77.4, 69.9, 56.8, 50.6, 39.5, 33.8, 22.3; **HRMS (ESI-TOF)** : calcd. for $C_{17}H_{19}N_4O_5$ $[M+H]^+$: 359.13555, found : 359.13545; **R_f** : 0.32 (70% EtOAc in n-heptane); **mp** : 156.3 – 158.4 °C; $[\propto]_D^{20} = -\ 53.8\ °\ (c\ 0.12, CHCl_3)$.

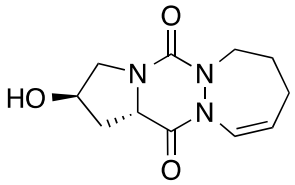


(*S*)-2-benzyl-3-methyl-2,3,9,10-tetrahydro-8*H*-[1,2,4]triazino[1,2-*a*][1,2]diazepine-1,4-dione (5k). Hydroformylation was performed following general procedure C starting from **4k** and using camphorsulfonic acid (0.5 equiv) instead of pyridinium p-toluenesulfonate. Purification on silica gel eluting with 30-50% EtOAc in n-heptane + 0.1% TEA) afforded the title compound as a colorless oil (67 mg, 0.233 mmol, **72%**). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34-7.23 (m, 5H), 6.69 (ddd, *J* = 9.5, 1.7, 1.3 Hz, 1H), 5.18 (ddd, *J* = 9.6, 6.4, 5.6 Hz, 1H), 4.76 (d, *J* = 15.1 Hz, 1H), 4.23 (dt, *J* = 14.2,

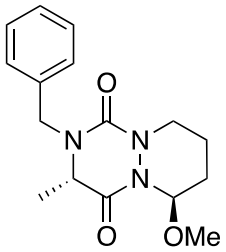
5.3 Hz, 1H), 4.15 (d, *J* = 15.1 Hz, 1H), 3.77 (q, *J* = 7.1 Hz, 1H), 3.49-3.40 (m, 1H), 2.59-2.48 (m, 1H), 2.24-2.02 (m, 2H), 1.91-1.84 (m, 1H), 1.18 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.7, 154.1, 137.7, 131.8, 128.7, 128.1, 127.9, 120.5, 76.1, 71.2, 56.8, 51.3, 49.7, 34.0; **HRMS** (ESI-TOF) : calcd. for $C_{16}H_{20}N_3O_2$ $[M+H]^+$: 286.15555, found : 286.15445; **R_f** : 0.28 (5% MeOH in CH_2Cl_2); **mp** : 110.8 – 112.8 °C; $[\propto]_D^{20} = -45.2\ °(c\ 0.13, MeOH)$.



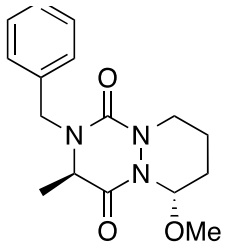
(*S*)-3-methyl-2-(4-nitrobenzyl)-2,3,9,10-tetrahydro-8*H*-[1,2,4]triazino[1,2-*a*][1,2]diazepine-1,4-dione (5l). Hydroformylation was performed following general procedure C starting from **4l**. Purification on silica gel eluting with 50-70% EtOAc in n-heptane afforded the title compound as a white solid (117 mg, 0.354 mmol, **81%**). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.23 (d, *J* = 8.6 Hz, 2H, AA' of AA'BB'), 7.57 (d, *J* = 8.6 Hz, 2H, BB' of AA'BB'), 6.66 (dt, *J* = 9.6, 1.6 Hz, 1H), 5.22 (dt, *J* = 9.5, 5.9 Hz, 1H), 4.75 (d, *J* = 15.8 Hz, 1H), 4.38 (d, *J* = 15.8 Hz, 1H), 4.07 (dt, *J* = 13.8, 5.3 Hz, 1H), 4.03 (q, *J* = 7.0 Hz, 1H), 3.53-3.44 (m, 1H), 2.43-2.31 (m, 1H), 2.23-2.12 (m, 1H), 1.89-1.80 (m, 2H), 1.20 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 165.4, 155.2, 146.8, 145.8, 128.8, 123.7, 123.5, 113.7, 55.4, 48.9, 47.4, 25.4, 24.1, 15.0; **HRMS (ESI-TOF)** : calcd. for $C_{16}H_{19}N_4O_4$ $[M+H]^+$: 331.14063, found : 331.14039; **R_f** : 0.40 (70% EtOAc in n-heptane); **mp** : 152.4 – 154.4 °C; $\propto_D^{20} = -51.1\ °(c\ 0.10, MeOH)$



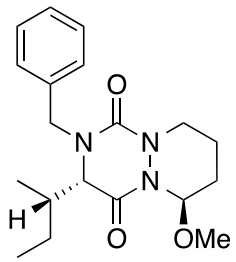
(2*R*,13a*S*)-2-hydroxy-1,2,3,8,9,13a-hexahydro-5*H*,7*H*,13*H*-pyrrolo[1',2':4,5][1,2,4]triazino[1,2-*a*][1,2]diazepine-5,13-dione (5m). Hydroformylation was performed following general procedure C starting from **4m** and using camphorsulfonic acid (0.5 equiv) instead of pyridinium p-toluenesulfonate. Purification on silica gel eluting with 5% MeOH in CH_2Cl_2 followed by a purification on semi-preparative RP-HPLC (5-40% acetonitrile in water) afforded the title compound as a colorless oil (19 mg, 0.078 mmol, **61%**). **^{1}H NMR** (400 MHz, MeOD-d_4) δ 6.69 (br d, *J* = 9.5 Hz, 1H), 5.25 (ddd, *J* = 9.5, 6.7, 5.5 Hz, 1H), 4.49-4.44 (m, 1H), 4.34 (dd, *J* = 10.3, 6.7 Hz, 1H), 4.12 (dt, *J* = 14.3, 5.3 Hz, 1H), 3.60-3.46 (m, 3H), 2.55-2.43 (m, 1H), 2.28-2.10 (m, 3H), 2.10-1.98 (m, 1H), 1.93-1.80 (m, 1H); **^{13}C NMR** (100 MHz, MeOD-d_4) δ 168.2, 157.2, 124.8, 115.2, 70.4, 57.7, 54.5, 49.5, 37.5, 26.6, 25.2; **HRMS** (ESI-TOF) : calcd. for $C_{11}H_{16}N_3O_3$ $[M+H]^+$: 238.11917, found : 238.11804; **R_f** : 0.28 (5% MeOH in CH_2Cl_2); $[\propto]_D^{20} = +91.1\ °\ (c\ 0.09, MeOH)$.



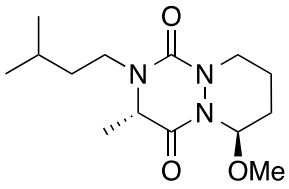
(3*S*,6*R*)-2-benzyl-6-methoxy-3-methylhexahydropyridazino[1,2-*a*][1,2,4]triazine-1,4-dione (6a). Nucleophilic addition of MeOH was performed following general procedure D starting from **5a**. Purification on silica gel eluting with 50-70% EtOAc in n-heptane to afford the title compound as a white solid (279 mg, 0.920 mmol, **86%**).
Hydroformylation was performed following general procedure C starting from **4a** and using MeOH/THF (10 mL, 10:1) instead of THF. Purification on silica gel eluting with 50-70% EtOAc in n-heptane to afford the title compound as a white solid (75 mg, 0.247 mmol, **74%**). **^{1}H NMR** (400 MHz, MeOD-d_4) δ 7.37-7.26 (m, 5H), 5.62-5.59 (m, 1H), 4.85 (d, J = 15.0 Hz, 1H), 4.39-4.32 (m, 1H), 4.13 (d, J = 15.0 Hz, 1H), 3.86 (q, J = 7.0 Hz, 1H), 3.17 (s, 3H), 3.09 (td, J = 12.7, 3.0 Hz, 1H), 2.12-1.97 (m, 2H), 1.78-1.67 (m, 1H), 1.63-1.57 (m, 1H), 1.24 (d, J = 7.0 Hz, 3H); **^{13}C RMN** (100 MHz, MeOD-d_4) δ 169.1, 156.9, 138.5, 130.0, 129.5, 129.2, 81.3, 56.6, 56.5, 48.8, 45.5, 29.1, 19.4, 15.7; **HRMS** (ESI-TOF) : calcd. for $C_{16}H_{21}N_3O_3Na$ $[M+Na]^+$: 326.14806, found : 326.14703; **R_f** : 0.19 (50% EtOAc in n-heptane); **mp** : 99.8 – 101.8 °C; $[\propto]_D^{20} = -2.6\,°\,(c\ 0.07, MeOH)$.



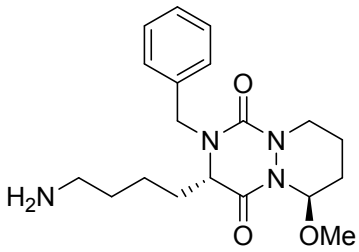
(3*R*,6*S*)-2-benzyl-6-methoxy-3-methylhexahydropyridazino[1,2-*a*][1,2,4]triazine-1,4-dione (**6b**). Nucleophilic addition of MeOH was performed following general procedure D starting from **5b**. Purification on silica gel eluting with 50-70% EtOAc in n-heptane afforded the title compound as a white solid (148 mg, 0.488 mmol, **83%**). **^{1}H NMR** (400 MHz, MeOD-d_4) δ 7.38-7.26 (m, 5H), 5.62-5.59 (m, 1H), 4.85 (d, J = 15.0 Hz, 1H), 4.39-4.32 (m, 1H), 4.13 (d, J = 15.0 Hz, 1H), 3.86 (q, J = 7.0 Hz, 1H), 3.17 (s, 3H), 3.09 (td, J = 12.8, 3.1 Hz, 1H), 2.12-1.97 (m, 2H), 1.78-1.66 (m, 1H), 1.65-1.56 (m, 1H), 1.24 (d, J = 7.0 Hz, 3H); **^{13}C RMN** (100 MHz, MeOD-d_4) δ 169.1, 156.9, 138.5, 130.0, 129.5, 129.2, 81.3, 56.6, 56.5, 48.8, 45.5, 29.1, 19.4, 15.7; **HRMS** (ESI-TOF) : calcd. for $C_{16}H_{21}N_3O_3Na$ $[M+Na]^+$: 326.14806, found : 326.14759; **R_f** : 0.19 (50% EtOAc in n-heptane); **mp** : 97.2 – 99.2 °C; $[\propto]_D^{20} = +2.2\,°\,(c\ 0.20, MeOH)$.



(3*S*,6*R*)-2-benzyl-3-((*S*)-*sec*-butyl)-6-methoxyhexahydropyridazino[1,2-*a*][1,2,4]triazine-1,4-dione (6c). Nucleophilic addition of MeOH was performed following general procedure D starting from **5c**. Purification on silica gel eluting with 20-50% EtOAc in n-heptane afforded the title compound as a colorless oil (123 mg, 0.357 mmol, **65%**). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33-7.22 (m, 5H), 5.66-5.64 (m, 1H), 5.21 (d, *J* = 15.0 Hz, 1H), 4.49-4.42 (m, 1H), 3.85 (d, *J* = 15.0 Hz, 1H), 3.7 (d, *J* = 6.2 Hz, 1H), 3.12 (s, 3H), 2.84 (td, *J* = 12.7, 2.9 Hz, 1H), 2.19-1.96 (m, 2H), 1.80-1.51 (m, 4H), 1.32-1.19 (m, 1H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.2, 154.6, 136.7, 128.9, 128.3, 128.0, 79.4, 63.1, 56.0, 49.8, 44.7, 36.8, 28.5, 26.2, 18.3, 15.1, 11.7; **HRMS** (ESI-TOF) : calcd. for $C_{19}H_{27}N_3O_3Na$ $[M+Na]^+$: 368.19501, found : 368.19495; **R_f** : 0.42 (50% EtOAc in n-heptane); $[\propto]_D^{20} = -1.2\,°\ (c\ 0.26, MeOH)$.

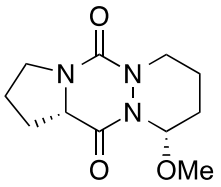


(3*S*,6*R*)-2-isopentyl-6-methoxy-3-methylhexahydropyridazino[1,2-*a*][1,2,4]triazine-1,4-dione (6d). Nucleophilic addition of MeOH was performed following general procedure D starting from **5d**. Purification on silica gel eluting with 20-50% EtOAc in n-heptane afforded the title compound as a colorless oil (119 mg, 0.420 mmol, **74%**). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.64-5.60 (m, 1H), 4.43-4.37 (m, 1H), 3.84-3.70 (m, 2H), 3.21 (s, 3H), 2.91 (td, *J* = 12.6, 3.2 Hz, 1H), 2.81-2.73 (m, 1H), 2.14-1.94 (m, 2H), 1.69-1.47 (m, 3H), 1.42-1.34 (m, 2H), 1.26 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.6, 155.0, 79.4, 56.0, 44.2, 43.5, 37.4, 28.4, 25.9, 22.8, 22.4, 16.5, 16.0; **HRMS** (ESI-TOF) : calcd. for $C_{14}H_{25}N_3O_3Na$ $[M+Na]^+$: 306.17936, found : 306.17876; **R_f** : 0.28 (50% EtOAc in n-heptane); $[\propto]_D^{20} = -3.0\,°\ (c\ 0.19, MeOH)$.

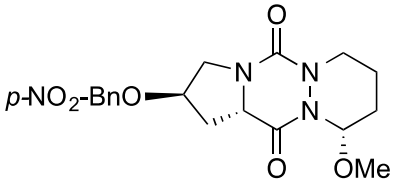


(3*S*,6*R*)-3-(4-aminobutyl)-2-benzyl-6-methoxyhexahydropyridazino[1,2-a][1,2,4]triazine-1,4-dione (6f). Nucleophilic addition of MeOH was performed following general procedure D starting from **5f**. Purification on semi-preparative RP-HPLC (5-40% acetonitrile in water) and freeze-drying followed by a purification on silica gel (10% MeOH in CH_2Cl_2 + 0.5% TEA) afforded the title product (56 mg, 0.154 mmol, **61%**) as a colorless oil. **^{1}H NMR** (400 MHz, MeOD-d_4) δ 7.37-7.26 (m, 5H), 5.62-5.59 (m, 1H), 4.90 (d, *J* = 14.9 Hz, 1H), 4.38-4.29 (m, 1H), 4.13 (d, *J* = 14.9 Hz, 1H),

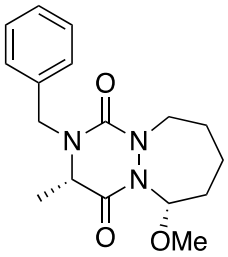
3.82 (dd, *J* = 8.6, 5.8 Hz, 1H), 3.15 (s, 3H), 3.02 (td, *J* = 12.8, 3.0 Hz, 1H), 2.65 (t, *J* = 7.3 Hz, 2H), 2.11-1.96 (m, 2H), 1.76-1.32 (m, 8H); **^{13}C NMR** (100 MHz, MeOD-d_4) δ 168.1, 156.7, 138.5, 130.0, 129.5, 129.2, 81.3, 60.8, 56.7, 50.4, 45.6, 41.9, 32.4, 31.5, 29.1, 23.8, 19.4; **HRMS** (ESI-TOF) : calcd. for $C_{19}H_{29}N_4O_3$ $[M+H]^+$: 360.21614, found : 361.22344; **R_f** : 0.18 (10% MeOH in CH_2Cl_2 + 0.2% NEt_3); $[\propto]_D^{20} = +22.6\,°\,(c\ 0.20, MeOH)$.



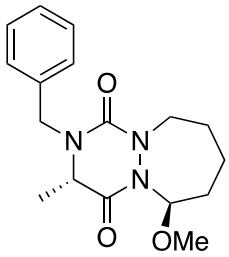
(10*S*,12a*S*)-10-methoxyoctahydropyridazino[1,2-a]pyrrolo[1,2-d][1,2,4]triazine-5,12-dione (6h). Nucleophilic addition of MeOH was performed following general procedure D starting from **5h** except that reaction was stopped after 5h. Purification on semi-preparative RP-HPLC (5-40% acetonitrile in water) and freeze-drying afforded the major diasteroisomer (43 mg, 0.181 mmol, **65%**) as a clear oil. **^{1}H NMR** (400 MHz, MeOD-d_4) δ 5.66-4.62 (m, 1H), 4.28-4.20 (m, 1H), 4.04 (t, *J* = 7.9 Hz, 1H), 3.55-3.36 (m, 2H), 3.19 (s, 3H), 3.09 (td, *J* = 12.8, 3.1 Hz, 1H), 2.32-1.90 (m, 6H), 1.80-1.67 (m, 1H), 1.58-1.49 (m, 1H); **^{13}C NMR** (100 MHz, MeOD-d_4) δ 170.4, 157.1, 81.9, 58.9, 56.8, 45.8, 44.4, 29.2, 28.1, 24.7, 19.3; **HRMS** (ESI-TOF) : calcd. for $C_{11}H_{17}N_3O_3Na$ $[M+Na]^+$: 262.11676, found : 262.11615; **R_f** : 0.47 (4% MeOH in CH_2Cl_2); $[\propto]_D^{20} = +40.7\,°\,(c\ 0.30, MeOH)$.



(2*R*,10*S*,12a*S*)-10-methoxy-2-((4-nitrobenzyl)oxy)octahydro-5*H*,12*H*-pyridazino[1,2-*a*]pyrrolo[1,2-*d*][1,2,4]triazine-5,12-dione (6j). Nucleophilic addition of MeOH was performed following general procedure D starting from **5j** except that reaction was stopped after 5h. Purification on semi-preparative RP-HPLC (5-40% acetonitrile in water) and freeze-drying afforded the major diasteroisomer (146 mg, 0.374 mmol, **59%**) as a white solid. **^{1}H NMR** (400 MHz, MeOD-d_4) δ 8.22 (d, *J* = 8.7 Hz, 2H, AA' of AA'BB'), 7.60 (d, *J* = 8.7 Hz, 2H, BB' of AA'BB'), 5.65 (dd, *J* = 3.1, 2.2 Hz, 1H), 4.71 (s, 2H, AX_2 system), 4.37-4.32 (m, 1H), 4.32-4.22 (m, 2H), 3.72 (dt, *J* = 12.0, 1.4 Hz, 1H), 3.61 (dd, *J* = 12.0, 4.7 Hz, 1H), 3.21 (s, 3H), 3.12 (td, *J* = 12.8, 3.1 Hz, 1H), 2.56-2.48 (m, 1H), 2.19 (ddd, *J* = 13.6, 10.7, 4.8 Hz, 1H), 2.09-1.94 (m, 2H), 1.81-1.68 (m, 1H), 1.60-1.50 (m, 1H); **^{13}C NMR** (100 MHz, MeOD-d_4) δ 170.4, 157.0, 148.9, 147.5, 129.2, 124.6, 81.8, 78.8, 70.7, 57.9, 56.8, 51.7, 44.6, 35.0, 29.2, 19.3; **HRMS (ESI-TOF)** : calcd. for $C_{18}H_{22}N_4O_6Na$ $[M+Na]^+$: 413.14371, found : 413.14386; **R_f** : 0.29 (90% EtOAc in n-heptane); **mp** : 133.0 – 135.0 °C; $[\propto]_D^{20} = +8.9\,°(c\ 0.17, CHCl_3)$.

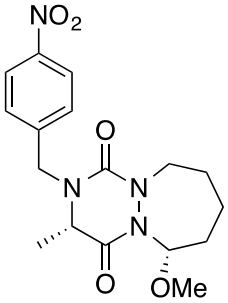


(3S,6S)

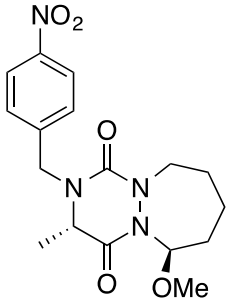


(3S,6R)

(3*S*)-2-benzyl-6-methoxy-3-methylhexahydro-1*H*-[1,2,4]triazino[1,2-a][1,2]diazepine-1,4(6*H*)-dione (**6k**). Nucleophilic addition of MeOH was performed following general procedure D starting from **5k**. Purification on semi-preparative RP-HPLC (5-60% acetonitrile in water) and freeze-*drying* afforded 30 mg (0.093 mmol, **41%**) of the major diasteroisomer and 15 mg (0.048 mmol, **21%**) of the minor product as clear oils. **Major isomer (3*S*,6*S*): ^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34-7.22 (m, 5H), 5.72 (d, *J* = 6.2 Hz, 1H), 4.74 (d, *J* = 15.1 Hz, 1H), 4.21-4.14 (m, 1H), 4.14 (d, *J* = 15.1 Hz, 1H), 3.72 (q, *J* = 7.0 Hz, 1H), 3.39 (s, 3H), 3.30-3.21 (m, 1H), 2.32-2.22 (m, 1H), 1.97-1.74 (m, 3H), 1.66-1.51 (m, 2H), 1.18 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.5, 154.6, 136.9, 129.0, 128.4, 128.0, 85.0, 56.2, 55.3, 48.7, 47.8, 30.8, 28.9, 19.5, 14.1; **HRMS** (ESI-TOF) : calcd. for $C_{17}H_{24}N_3O_3$ $[M+H]^+$: 318.18177, found : 318.18127**;** $\mathbf{R_f}$: 0.36 (40% EtOAc in n-heptane); $[\propto]_D^{20} = +10.1\,°\,(c\ 0.18,\ MeOH)$;. **Minor isomer (3*S*,6*R*): ^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32-7.19 (m, 5H), 5.69-5.65 (m, 1H), 4.86 (d, *J* = 15.1 Hz, 1H), 4.11-4.01 (m, 2H), 3.79 (q, *J* = 7.0 Hz, 1H), 3.64-3.55 (m, 1H), 3.27 (s, 3H), 2.13-2.04 (m, 1H), 2.00-1.90 (m, 1H), 1.83-1.50 (m, 4H), 1.21 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.9, 156.1, 137.1, 129.0, 128.2, 128.0, 86.8, 56.9, 55.3, 49.8, 48.4, 33.0, 26.6, 22.3, 14.0; **HRMS** (ESI-TOF) : calcd. for $C_{17}H_{24}N_3O_3$ $[M+H]^+$: 318.18177, found : 318.18155; $\mathbf{R_f}$: 0.31 (40% EtOAc in n-heptane); $[\propto]_D^{20} = -24.2\,°\,(c\ 0.26,\ MeOH)$.



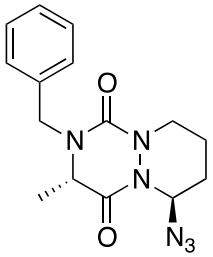
(3S,6S)



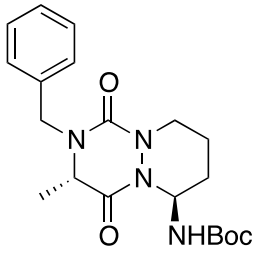
(3S,6R)

(3*S*)-6-methoxy-3-methyl-2-(4-nitrobenzyl)hexahydro-6*H*-[1,2,4]triazino[1,2-*a*][1,2]diazepine-1,4-dione (6l). Nucleophilic addition of MeOH was performed following general procedure D starting from **5l**. Purification on semi-preparative RP-HPLC (5-60% acetonitrile in water) and freeze-drying afforded 43 mg (0.119 mmol, **37%**) of the major diasteroisomer as a white solid and 18 mg (0.058 mmol, **18%**) of the minor product as a colorless oil. **Major isomer (3*S*,6*S*): ^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.6 Hz, 1H, AA' of AA'BB'), 7.42 (d, *J* = 8.6 Hz, 1H, BB' of AA'BB'), 5.74 (d, *J* = 6.2 Hz, 1H), 4.83 (d, *J* = 15.8 Hz), 4.20 (d, *J* = 15.8 Hz, 1H), 4.19-4.12 (m, 1H), 3.72 (q, *J* = 7.0 Hz, 1H), 3.38 (s, 3H), 3.32-3.23 (m, 1H), 2.33-2.23 (m, 1H), 1.99-1.73 (m, 3H), 1.64-1.48 (m, 2H), 1.23 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.0, 154.4, 147.8, 144.8, 128.8, 124.2, 85.0, 56.4, 56.3, 48.4, 47.9, 30.9, 28.8, 19.4, 14.2; **HRMS (ESI-TOF)** : calcd. for $C_{17}H_{23}N_4O_5$ $[M+H]^+$: 363.16685, found : 363.16673; $\mathbf{R_f}$: 0.36 (70% EtOAc in n-heptane); **mp** : 105.2 – 107.2 °C; $\propto_D^{20} = -12.1\,°(c\ 0.08, MeOH)$. **Minor isomer (3*S*,6*R*): ^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 (d, *J* =

8.6 Hz, 2H, AA' of AA'BB'), 7.43 (d, J = 8.6 Hz, 2H, BB' of AA'BB'), 5.70 (dd, J = 4.5, 2.3 Hz, 1H), 4.90 (d, J = 15.9 Hz, 1H), 4.22 (d, J = 15.9 Hz, 1H), 4.13-4.05 (m, 1H), 3.81 (q, J = 7.0 Hz, 1H), 3.57 (ddd, J = 13.5, 11.0, 1.7 Hz, 1H), 3.30 (s, 3H), 2.18-2.09 (m, 1H), 2.00-1.91 (m, 1H), 1.84-1.54 (m, 4H), 1.26 (d, J = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.2, 156.0, 147.7, 145.1, 128.7, 124.2, 86.9, 56.9, 56.1, 49.6, 48.1, 32.8, 26.7, 22.0, 14.0; **HRMS (ESI-TOF)** : calcd. for $C_{17}H_{23}N_4O_5$ $[M+H]^+$: 363.16685, found : 363.16682; **R_f** : 0.27 (70% EtOAc in n-heptane); $\propto_D^{20} = -29.6\ °(c\ 0.15, MeOH)$

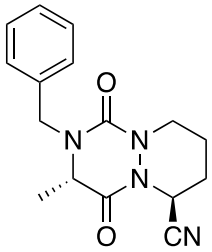


(3*S*,6*R*)-6-azido-2-benzyl-3-methylhexahydropyridazino[1,2-*a*][1,2,4]triazine-1,4-dione (7). To a dry 100 mL round-bottom flask was added **6a** (180 mg, 0.594 mmol, 1 equiv) in anhydrous dichloromethane (3.2 mL). The solution was cooled to 0 °C. $TMSN_3$ (156 µL, 1.188 mmol, 2 equiv) and then $BF_3.OEt_2$ (151 µL, 1.188 mmol, 2 equiv) were added dropwise. The mixture was stirred for 3 h while the temperature was allowed to warm to room temperature. The mixture was then carefully quenched with aqueous solution of $NaHCO_3$ (2%, 50 mL) and stirred for 1 h. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was analyzed by ^{1}H NMR to determine the diastereoselectivity of the reaction. Purification on silica gel (50% EtOAc in n-heptane) afforded the title compound as a white powder (165 mg, 0.525 mmol, **88%**). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34-7.23 (m, 5H), 6.19-6.16 (m, 1H), 4.88 (d, J = 15.0 Hz, 1H), 4.57-4.50 (m, 1H), 4.12 (d, J = 15.0 Hz, 1H), 3.79 (q, J = 7.0 Hz, 1H), 2.97 (td, J = 12.7, 2.8 Hz, 1H), 2.10-1.88 (m, 2H), 1.77-1.61 (m, 2H), 1.20 (d, J = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.6, 154.8, 136.1, 129.1, 128.3, 128.2, 65.6, 54.6, 49.1, 44.1, 27.6, 18.7, 15.5; **HRMS (ESI-TOF)** : calcd. for $C_{15}H_{19}N_6O_2Na$ $[M+Na]^+$: 337.13807, found: 337.13889; **mp** : 110.2 – 112.2 °C; **R_f** : 0.21 (50% EtOAc in n-heptane); $[\propto]_D^{20} = +23.7\ °(c\ 0.20, MeOH)$.

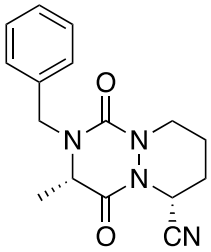


***tert*-butyl ((3*S*,6*S*)-2-benzyl-3-methyl-1,4-dioxooctahydropyridazino[1,2-*a*][1,2,4]triazin-6-yl)carbamate (8).** To a 10 mL round-bottom flask were successively added **7** (30 mg, 0.095 mmol, 1 equiv), di-tert-butyl dicarbonate (102 µL, 0.477 mmol, 5 equiv) and Pd/C (10 wt-%, 9 mg) in EtOAc (10 mL). The reaction was stirred for 24 h under an atmosphere of hydrogene. The suspension was filtered through celite®, washed with EtOAc (20 mL) and concentrated *in vacuo*. The residue was purified on semi-preparative RP-HPLC (5-60% acetonitrile in water) and freeze-dried to obtain a white powder (32 mg, 0.083 mmol, **86%**). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.72 (br s, 1H), 7.33-7.20 (m, 5H), 5.95-5.90 (m, 1H), 4.72 (d, J = 15.4 Hz, 1H), 4.13 (br dd, J = 12.1, 3.2 Hz, 1H), 4.06

(d, J = 15.4 Hz, 1H), 3.69 (q, J = 7.0 Hz, 1H), 2.97 (td, J = 12.8, 3.5 Hz, 1H), 2.23-2.08 (m, 1H), 1.78-1.62 (m, 2H), 1.57-1.47 (m, 1H), 1.37 (s, 9H), 1.15 (d, J = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 164.6, 155.3, 154.2, 137.4, 128.3, 127.4, 127.1, 78.3, 55.9, 54.6, 47.2, 45.3, 28.0, 27.1, 17.8, 16.1; **HRMS (ESI-TOF)** : calcd. for $C_{20}H_{28}N_4O_4Na$ $[M+Na]^+$: 411.20083, found: 411.20055; **R_f** : 0.24 (100% EtOAc); **mp** : 56.8 – 58.8 °C; $[\propto]_D^{20} = +\ 8.8\ °(c\ 0.08, MeOH)$.



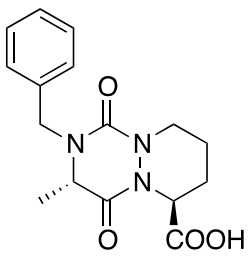
(3S,6S)



(3S,6R)

(3*S*)-2-benzyl-3-methyl-1,4-dioxooctahydropyridazino[1,2-*a*][1,2,4]triazine-6-carbonitrile (9). To a dry 50 mL round-bottom flask was added **6a** (180 mg, 0.594 mmol, 1 equiv) in anhydrous CH_2Cl_2 (5.4 mL). The solution was cooled to 0 °C. TMSCN (220 µL, 1.648 mmol, 2 equiv) and then $BF_3.OEt_2$ (209 µL, 1.648 mmol, 2 equiv) were added dropwise. The mixture was stirred for 3 h and allowed to warm to room temperature. The mixture was carefully quenched with a saturated solution of $NaHCO_3$ (10 mL) and stirred for 1 h. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was analyzed by ^{1}H NMR to determine the diastereoselectivity of the reaction (2.1:1). Purification on silica gel eluting with 30-50% EtOAc in n-heptane afforded a white solid containing the mixture of two diastereoisomeres (226 mg, 0.525 mmol, **92%**). Diastereoisomers were separated by purification on semi-preparative RP-HPLC (5-60% acetonitrile in water) and freeze-drying.

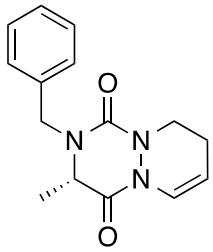
Major isomer (3*S*,6*S*): ^{1}H NMR (400 MHz, MeOD-d_4) δ 7.31-7.18 (m, 5H), 5.55-5.50 (m, 1H), 4.77 (d, J = 15.4 Hz, 1H), 4.40-4.33 (m, 1H), 4.16 (d, J = 15.4 Hz, 1H), 3.78 (q, J = 7.0 Hz, 1H), 3.06-2.97 (m, 1H), 2.15-2.04 (m, 1H), 1.99-1.77 (m, 3H), 1.17 (d, J = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, MeOD-d_4) δ 166.8, 156.0, 138.0, 130.0, 129.1, 117.4, 56.3, 49.9, 45.5, 44.3, 27.2, 21.8, 16.2; **HRMS (ESI-TOF)** : calcd. for $C_{16}H_{18}N_4O_2Na$ $[M+Na]^+$: 321.13275, found: 321.13206; **R_f** : 0.25 (50% EtOAc in n-heptane); **mp** : 131.7 – 133.7 °C; $[\propto]_D^{20} = -129.8\ °(c\ 0.10, MeOH)$. **Minor isomer (3*S*,6*R*): ^{1}H NMR** (400 MHz, MeOD-d_4) δ 7.35-7.21 (m, 5H), 5.59-5.42 (m, 1H), 4.70 (d, J = 16.6 Hz, 1H), 4.59 (d, J = 16.6 Hz, 1H), 4.47-4.38 (m, 1H), 4.15 (q, J = 7.0 Hz, 1H), 3.22-3.12 (m, 1H), 2.22-2.11 (m, 1H), 2.06-1.83 (m, 3H), 1.33 (d, J = 7.0 Hz, 3H); **^{13}C NMR** (400 MHz, MeOD-d_4) δ 168.4, 158.7, 139.4, 129.9, 128.4, 127.9, 117.6, 54.0, 47.5, 45.3, 44.9, 27.2, 21.5, 13.0; **HRMS (ESI-TOF)** : calcd. for $C_{16}H_{18}N_4O_2Na$ $[M+Na]^+$: 321.13275, found: 321.13166; **R_f** : 0.25 (50% EtOAc in n-heptane); **mp** : 67.9 – 69.9 °C; $[\propto]_D^{20} = +\ 123.9\ °(c\ 0.12, MeOH)$.

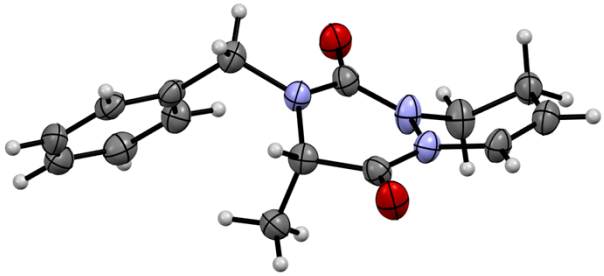


(3*S*,6*S*)-2-benzyl-3-methyl-1,4-dioxooctahydropyridazino[1,2-*a*][1,2,4]triazine-6-carboxylic acid (10). To a 25 mL round-bottom flask was added trans isomer **9** (64 mg, 0.215 mmol, 1 equiv) and an aqueous solution of hydrochloric acid (6 M, 10 mL). The suspension was heated to 100 °C for 6h. After cooling, the reaction was concentrated, purified on semi-preparative RP-HPLC (5-40% acetonitrile + 0.1% TFA in water + 0.1% TFA) and freeze-dried to obtain a white powder (47 mg, 0.149 mmol, **69%**). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.32 (br s, 1H), 7.38-7.22 (m, 5H), 5.02 (br d, *J* = 5.6 Hz, 1H), 4.80 (d, *J* = 15.6 Hz, 1H), 4.28-4.20 (m, 1H), 4.14 (d, *J* = 15.6 Hz, 1H), 3.74 (q, *J* = 6.9 H, 1H), 2.98 (td, *J* = 12.6 Hz, 2.9 Hz, 1H), 2.29-2.20 (m, 1H), 1.83-1.66 (m, 2H), 1.53-1.38 (m, 1H), 1.19 (t, *J* = 6.9 Hz, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ 170.5, 165.0, 153.5, 137.5, 128.4, 127.2, 127.1, 54.4, 52.8, 47.4, 43.5, 24.0, 20.8, 15.8; **HRMS (ESI-TOF)** : calcd. for $C_{16}H_{20}N_3O_4$ $[M+H]^+$: 318.14538, found : 318.14458; **mp** : 198.1 – 200.1 °C; **R_f** : 0.21 (2% MeOH in CH_2Cl_2 + 0.1% AcOH); $[\propto]_D^{20} = -66.7\ °(c\ 0.135, MeOH)$.

Crystallographic data

Structural features of compound **5a**



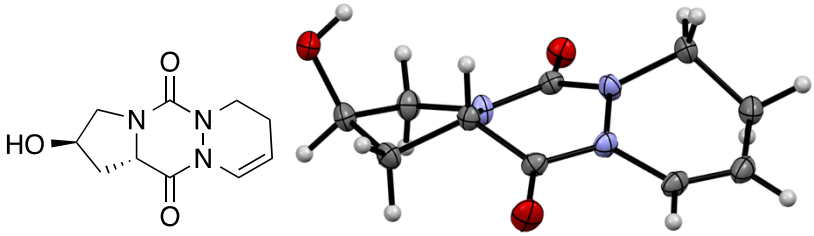


ORTEP diagram of compound **5a**

Table 1. Crystal data and structure refinement for compound **5a**

CDCC number	1001769
Empirical formula	$C_{15}H_{17}N_3O_2$
Formula weight	271.32
Temperature	173(2) K
Wavelength	0.71073 A
Crystal description	Block
Crystal colour	Colorless
Crystal system, space group	Monoclinic, P 21
Unit cell dimensions	a = 7.0231(8) A, alpha = 90 deg. b = 10.3536(6) A, beta = 93.182(4) deg. c = 9.2156(11) A, gamma = 90 deg.
Volume	669.07(12) A^3
Z	2
Calculated density	1.347 g/cm^3
Absorption coefficient, *mu*/mm	0.092 mm^{-1}
F(000)	288
Limiting indices	-5<=h<=9, -10<=k<=13, -11<=l<=11
No. of reflections measured	4161
No. of independent reflections	1605 [R_{int} = 0.1056]
Final R_1 values	0.0876
Final $wR(F^2)$ values	0.1395

Structural features of compound **5i**

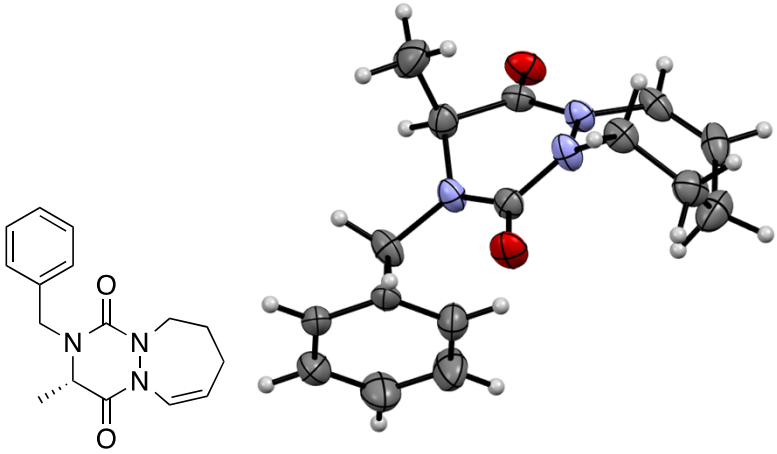


ORTEP diagram of compound **5i**

Table 2. Crystal data and structure refinement for compound **5i**

CDCC number	1001770
Empirical formula	$C_{10}H_{13}N_3O_3$
Formula weight	223.23
Temperature	173(2) K
Wavelength	0.71073 A
Crystal description	Block
Crystal colour	Colorless
Crystal system, space group	Monoclinic, P 21
Unit cell dimensions	a = 7.7486(5) A, alpha = 90 deg. b = 7.2000(5) A, beta = 98.796(2) deg. c = 8.8891(6) A, gamma = 90 deg.
Volume	490.09(6) A^3
Z	2
Calculated density	1.513 g/cm^3
Absorption coefficient	0.114 mm^{-1}
F(000)	236
Limiting indices	-10<=h<=10, -10<=k<=10, -11<=l<=12
No. of reflections measured	4338
No. of independent reflections	2637 [R_{int} = 0.0146]
Final R_1 values	0.0391
Final $wR(F^2)$ values	0.0873

Structural features of compound **5k**

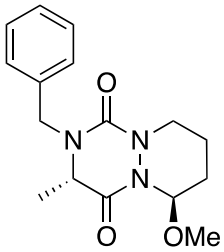


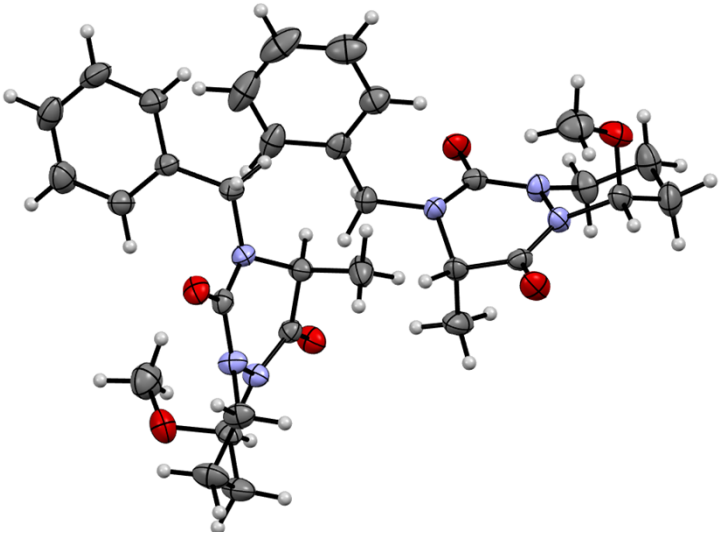
ORTEP diagram of compound **5k**

Table 3. Crystal data and structure refinement for compound **5k**

CDCC number	1001771
Empirical formula	$C_{16}H_{19}N_3O_2$
Formula weight	285.34
Temperature	173(2) K
Wavelength	0.71073 A
Crystal description	Prism
Crystal colour	Colorless
Crystal system, space group	Orthorhombic, P 21 21 21
Unit cell dimensions	a = 7.9124(2) A, alpha = 90 deg. b = 9.5931(3) A, beta = 90 deg. c = 19.4561(6) A, gamma = 90 deg.
Volume	1476.80(7) A^3
Z	4
Calculated density	1.283 g/cm^3
Absorption coefficient	0.087 mm^{-1}
F(000)	608
Limiting indices	-10<=h<=10, -12<=k<=12, -25<=l<=19
No. of reflections measured	11494
No. of independent reflections	1952 [R_{int} = 0.0732]
Final R_1 values	0.0615
Final $wR(F^2)$ values	0.1247

Structural features of compound **6a**



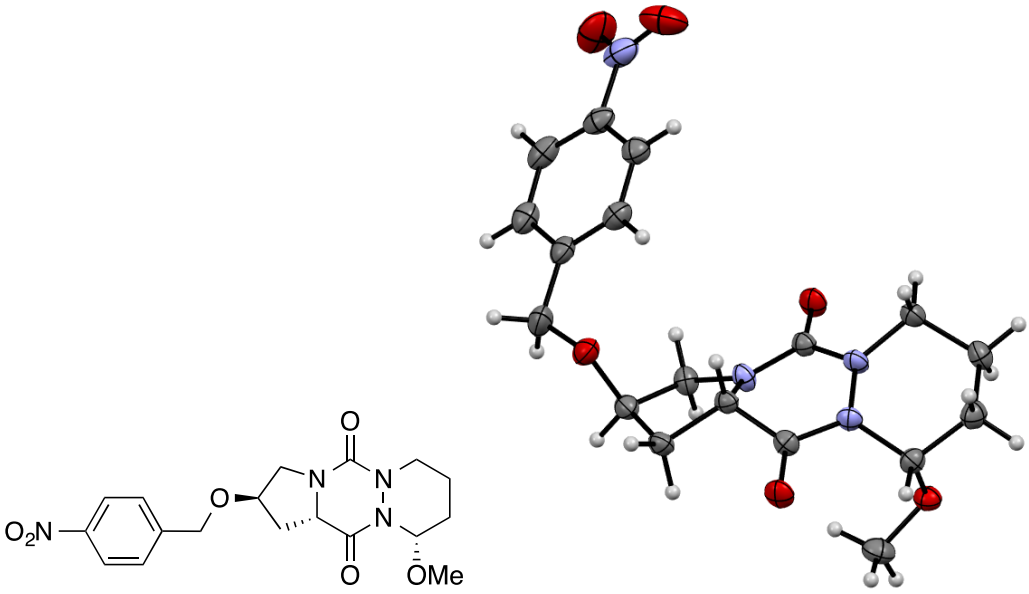


ORTEP diagram of compound **6a**

Table 4. Crystal data and structure refinement for compound **6a**.

CDCC number	1001772
Empirical formula	$C_{16}H_{21}N_3O_3$
Formula weight	303.36
Temperature	173(2) K
Wavelength	0.71073 A
Crystal description	Prism
Crystal colour	Colorless
Crystal system, space group	Monoclinic, C 2
Unit cell dimensions	a = 10.6284(6) A, alpha = 90 deg. b = 11.6932(6) A, beta = 101.369(3) deg. c = 25.7411(15) A, gamma = 90 deg.
Volume	3136.3(3) A^3
Z	8
Calculated density	1.285 g/cm^3
Absorption coefficient	0.735 mm^{-1}
F(000)	1296
Limiting indices	-11<=h<=12, -12<=k<=13, -30<=l<=28
No. of reflections measured	13001
No. of independent reflections	4347 [R_{int} = 0.0274]
Final R_1 values	0.0290
Final $wR(F^2)$ values	0.0770

Structural features of compound **6j**

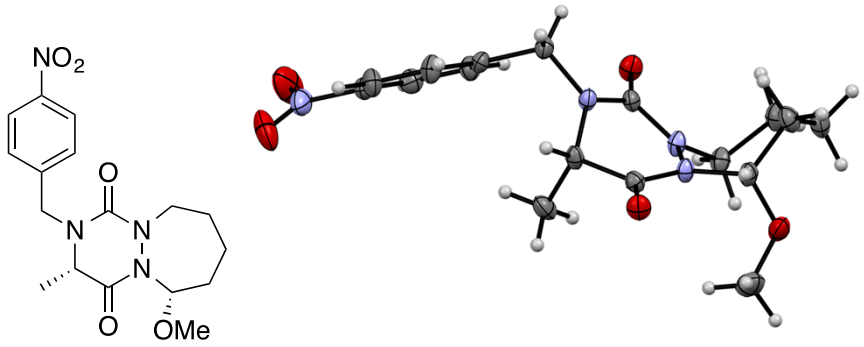


ORTEP diagram of compound **6j**

Table 5. Crystal data and structure refinement for **6j**

CDCC number	1001773
Empirical formula	$C_{18}H_{22}N_4O_6$
Formula weight	390.39
Temperature	173(2) K
Wavelength	0.71073 A
Crystal description	Block
Crystal colour	Colorless
Crystal system, space group	Orthorhombic, P 21 21 21
Unit cell dimensions	a = 7.9428(4) A, alpha = 90 deg. b = 10.4945(4) A, beta = 90 deg. c = 21.4599(5) A, gamma = 90 deg.
Volume	1788.81(12) A^3
Z	4
Calculated density	1.450 g/cm^3
Absorption coefficient	0.110 mm^{-1}
F(000)	824
Limiting indices	-10<=h<=7, -13<=k<=10, -27<=l<=19
No. of reflections measured	8526
No. of independent reflections	4012 [R_{int} = 0.0421]
Final R_1 values	0.0615
Final $wR(F^2)$ values	0.1180

Structural features of compound **6l**

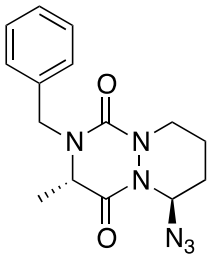


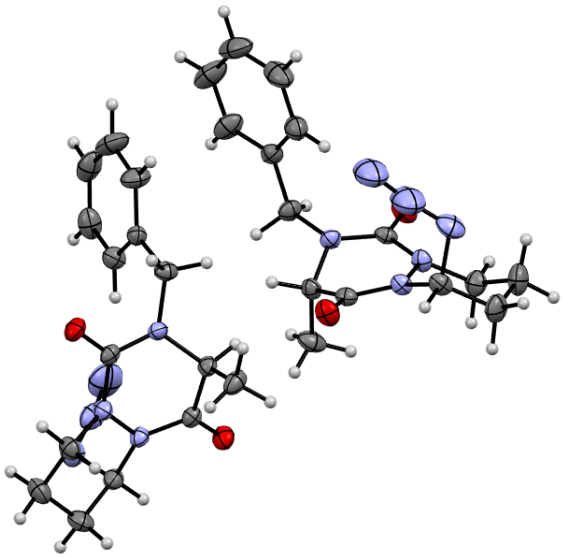
ORTEP diagram of compound **6l** (major isomer)

Table 6. Crystal data and structure refinement for compound **6l** (major isomer).

CDCC number	1001774
Empirical formula	$C_{17}H_{22}N_4O_5$
Formula weight	362.38
Temperature	173(2) K
Wavelength	0.71073 A
Crystal description	Prism
Crystal colour	Colorless
Crystal system, space group	Monoclinic, P 21
Unit cell dimensions	a = 8.3044(4) A, alpha = 90 deg. b = 10.8929(5) A, beta = 90.2690(10) deg. c = 9.6338(5) A, gamma = 90 deg.
Volume	871.45(7) A^3
Z	2
Calculated density	1.381 g/cm^3
Absorption coefficient	0.103 mm^{-1}
F(000)	384
Limiting indices	-10<=h<=11, -12<=k<=14, -13<=l<=13
No. of reflections measured	7024
No. of independent reflections	3903 [R_{int} = 0.0171]
Final R_1 values	0.0395
Final $wR(F^2)$ values	0.0873

Structural features of compound **7**



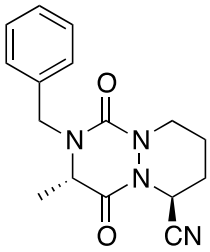


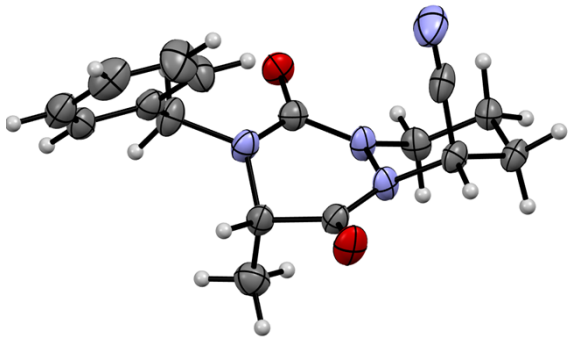
ORTEP diagram of compound **7**

Table 7. Crystal data and structure refinement for compound **7**

CDCC number	1001776
Empirical formula	$C_{15}H_{18}N_6O_2$
Formula weight	314.35
Temperature	173(2) K
Wavelength	0.71073 A
Crystal description	Block
Crystal colour	Colorless
Crystal system, space group	Monoclinic, P 21
Unit cell dimensions	a = 7.9768(4) A, alpha = 90 deg. b = 24.4818(12)A, beta = 97.8230(10). c = 8.0015(4) A, gamma = 90 deg.
Volume	1548.04(13) A^3
Z	4
Calculated density	1.349 g/cm^3
Absorption coefficient	0.095 mm^{-1}
F(000)	664
Limiting indices	-10<=h<=10, -32<=k<=30, -9<=l<=10
No. of reflections measured	11455
No. of independent reflections	3825 [R_{int} = 0.0238]
Final R_1 values	0.0518
Final $wR(F^2)$ values	0.1030

Structural features of compound **9**





ORTEP diagram of compound **9** (major isomer)

Table 8. Crystal data and structure refinement for compound **9** (major isomer)

Empirical formula	$C_{16}H_{18}N_4O_2$
Formula weight	298.34
Temperature	173(2) K
Wavelength	0.71073 A
Crystal description	Block
Crystal colour	Colorless
Crystal system, space group	Orthorhombic, P 21 21 21,
Unit cell dimensions	a = 7.6663(3) A, alpha = 90 deg. b = 13.8258(10) A, beta = 90 deg. c = 14.6694(12) A, gamma = 90 deg.
Volume	1554.85(18) A^3
Z	4
Calculated density	1.274 g/cm^3
Absorption coefficient	0.087 mm^{-1}
F(000)	632
Limiting indices	-9<=h<=7, -17<=k<=11, -16<=l<=18
No. of reflections measured	8305
No. of independent reflections	2022 [R_{int} = 0.0716]
Final R_1 values	0.1066
Final $wR(F^2)$ values	0.1397