Supporting Information

3-Azatetracyclo[5.2.1.1^{5,8}.0^{1,5}]undecane derivatives: from wild-type inhibitors of the M2 ion channel of influenza A virus to derivatives with potent activity against the V27A mutant

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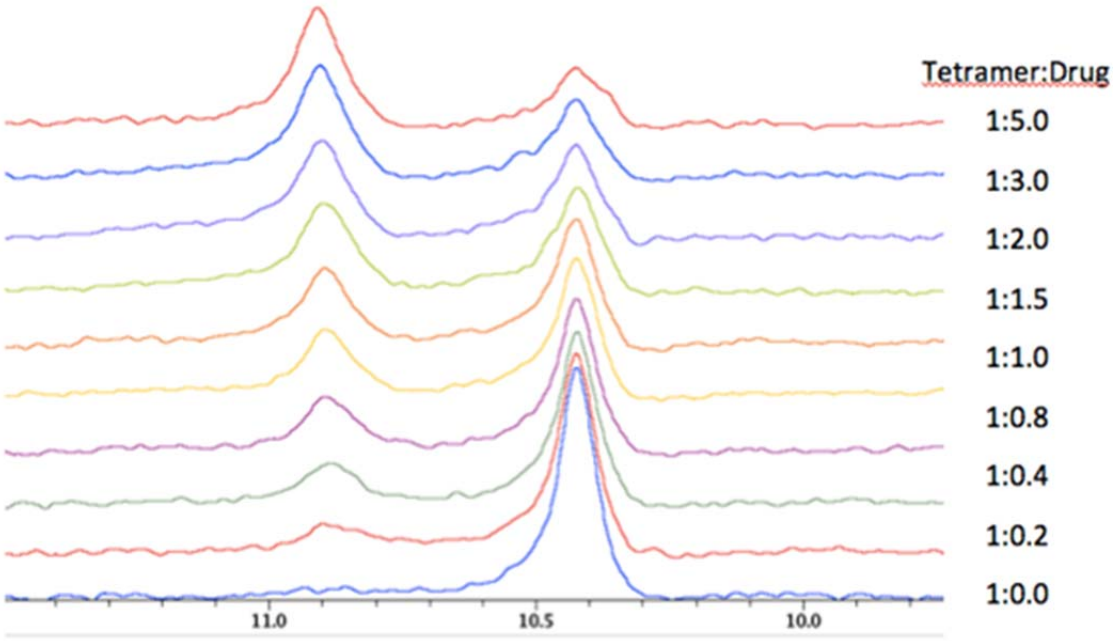

Figure S1. ^{1}H spectra showing chemical shift of W41 $H^{\varepsilon 1}$ as a function of drug concentration. The spectra were recorded for 1.6 mM M2TM in 80 mM DPC, 50mM phosphate buffer pH 7.5 at 313K on a Bruker Avance-I 800 MHz spectrometer. The stepwise titration was performed by addition of high concentration **16d** (250mM).

We used the same approach applied for rimantadine drug binding study on the wt M2.[1]

$$\frac{[\text{Tetra}\bullet\text{Drug}]}{[\text{Tetra}]_T} = \frac{K_D + [\text{Tetra}]_T \times N + [\text{Drug}]_T - \sqrt{\left(K_D + [\text{Tetra}]_T \times N + [\text{Drug}]_T\right)^2 - 4[\text{Tetra}]_T \times N \times [\text{Drug}]_T}}{2[\text{Tetra}]_T \times N}$$

where $[\text{Tetra}]_T$ and $[\text{Drug}]_T$ are the total drugable tetramer and drug concentrations, respectively, N represents the number of drugs per tetrameter, K_D is the dissociation constant. N and K_D were fitted to the fraction of $[\text{Tetra}\bullet\text{Drug}]/ [\text{Drug}]_T$, which was obtained by dividing the peak volume of W41 $H^{\varepsilon 1}$ at certain titration point by the maximum volume during the course of titration. Summary of the fitting is shown in Table S1.

[1] Cady, S. D.; Wang, J.; Wu, Y.; DeGrado, W. F.; Hong, M. *J. Am. Chem. Soc.* **2011**, *133*, 4274-4284.

Table S1. Summary of fitting results

Best-fit Values				
N	1.37 ± 0.28	1[a]	1[a]	1[a]
K_D (μM)	40 ± 24	4[a]	100[a]	400[a]
Goodness of fit R^2	0.963	0.679	0.942	0.369
Absolute sum of squares	0.037	0.333	0.059	0.647

[a]: Values are fixed in the fitting.

***Cis*-1,5-diethylbicyclo[3.3.0]octane-3,7-dione bishydrazone (18c)**. To a solution of known[2] diketone **17c** (15.0 g, 77.2 mmol) in absolute EtOH (225 mL) was added triethylamine (173 mL, 1.25 mmol) and hydrazine monohydrate (39.9 mL, 0.82 mmol). The mixture was heated to reflux for 3 hours. The dark yellow solution obtained was allowed to cool down to room temperature, it was then concentrated to a third of its volume and it was left at 4 ºC overnight. The white precipitate was filtered, washed with cold 96% ethanol and dried under vacuum to give **18c** (*anti* isomer) as white needles (14.95g, 87%), mp 139-140 ºC. IR (KBr) ν 3390, 3372, 3193, 2962, 2939, 2876, 2827, 1636, 1459, 1423, 1338, 1291, 1223, 1056, 826, 791, 675, 591, 513 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.90 [t, J = 7.4 Hz, 6 H, C1(5)-$CH_2C\underline{H}_3$], 1.38 [q, J = 7.4 Hz, 4 H, C1(5)-$C\underline{H}_2CH_3$], 2.11 [dd, J = 18.0 Hz, J' = 0.8 Hz, 2H, 4(8)-H_{endo}], 2.23 [dd, J = 18.0 Hz, J' = 1.6 Hz, 2H, 4(8)-H_{exo}], 2.37 [dd, J = 17.0 Hz, J' = 0.8 Hz, 2H, 2(6)-H_{endo}] , 2.46 [dd, J = 17.0 Hz, J' = 1.6 Hz, 2H, 2(6)-H_{exo}], 4.84 (s, 4 H, 2 NH_2). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 9.8 [CH_3, C1(5)-$CH_2\underline{C}H_3$], 26.0 [CH_2, C1(5)-$\underline{C}H_2CH_3$], 35.2 [CH_2, C4(8)], 42.2 [CH_2, C2(6)], 52.4 [C, C1(5)], 157.7 [C=N, C3(7)]. MS, m/e (%); main ions: 222 ($M^{\cdot+}$, 11), 206 (100), 193 (27), 152 (19), 151 (29), 150 (13), 149 (12), 91 (14).

Mixture of *cis*-1,5-diethyl-3,7-diiodobicyclo[3.3.0]octan-2,7-diene and *cis*-1,5-diethyl-3,7-diiodobicyclo[3.3.0]octan-2,6-diene (*syn*- and *anti*-19c). To a stirred suspension of bis-hydrazone **18c** (1.0 g, 4.5 mmol) in dry diethyl ether (72 mL) under an argon atmosphere, tetramethylguanidine (8.5 ml, 67.5 mmol) was added. The mixture was cooled to −18 ºC and solid iodine (6.88 g, 27.1 mmol) was added in small portions during 1 hour. When the addition was over, the mixture was allowed to warm to room temperature and stirring was continued for 15 hours. The organic layer was washed with $Na_2S_2O_3$ (10% aqueous solution, 5 × 30 ml) and brine (2 × 30 ml). The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure to give an orange solid that was purified by column chromatography (silica gel, *n*-hexane) to give a mixture of ***syn*-** and ***anti*-19c** (876 mg, 47% yield). From some selected fractions, pure ***syn*-19c** was obtained that was fully characterized, mp 63–64 ºC (*n*-hexane); IR (KBr) ν 3446, 2960, 2926, 2874, 1601, 1457, 1430, 1377, 1281, 1148, 1097, 1034, 1015, 964, 893, 853, 805, 790, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 [t, J = 7.2 Hz, 3 H, C1-$CH_2C\underline{H}_3$]*, 0.91 [t, J = 7.6 Hz, 3 H, C5-$CH_2C\underline{H}_3$]*, 1.42 [q, J = 7.2 Hz, 2 H, C1-$C\underline{H}_2CH_3$]*, 1.43 [q, J = 7.2 Hz, 2 H, C5-$C\underline{H}_2CH_3$]*, 2.50 [dd, J = 16.4 Hz, J' = 2 Hz, 2 H, 4(6)-H_{endo}], 2.62 [dd, J = 16.4 Hz, J' = 2 Hz, 2 H, 4(6)-H_{exo}], 6.01 [t, J = 2 Hz, 2 H, 2(8)-H]; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 9.5 [CH_3, C1-$CH_2\underline{C}H_3$]*, 9.9 [CH_3, C5-$CH_2\underline{C}H_3$]*, 25.7 [CH_2, C1-$\underline{C}H_2CH_3$]*, 26.0 [CH_2, C5-$\underline{C}H_2CH_3$]*, 54.8 [CH_2, C4(6)], 58.0 (C, C5), 70.8 (C, C1), 92.5 [C-I, C3(7)], 142.4 [CH, C2(8)]. GC/MS (GC), m/e (%); main ions (*syn* and *anti*): rt (19.5 min): 414 ($M^{\cdot+}$, 15), 287 [$(M\text{-}I)^+$, 56], 160 [$(M\text{-}2I)^{\cdot+}$, 100], 145 [$(C_{11}H_{13})^+$, 31], 131 [$(C_{10}H_{11})^+$, 48], 115 (20), 91 [$(C_7H_7)^+$, 21]; rt (19.6 min): 414 ($M^{\cdot+}$, 15), 385 [$(M\text{-}C_2H_5)^+$, 100], 258 [$(M\text{-}2C_2H_5)^{\cdot+}$, 10], 131 [$(C_{10}H_{11})^+$, 22], 115 (11), 91 [$(C_7H_7)^+$, 21].

Mixture of dimethyl 1,5-diethyl-*cis*-bicyclo[3.3.0]octa-2,7-diene-3,7-dicarboxylate and dimethyl 1,5-diethyl-*cis*-bicyclo[3.3.0]octa-2,6-diene-3,7-dicarboxylate (*syn*- and *anti*-20c). A mixture of **19c** (5.65 g, 13.65 mmol), triphenylphosphine (706 mg, 2.69 mmol), $Pd(OAc)_2$ (316 mg, 1.41 mmol), methanol (175 mL) and triethylamine (11.4 mL, 82.2 mmol) was purged with CO for 10 min and stirred and heated under

[2] Makhseed, S.; McKeown, N. B. Novel spiro-polymers with enhanced solubility. *Chem. Commun.* **1999**, 255-256.

reflux for 22 h under CO (about 1 atm). The black suspension was allowed to cool to room temperature and was evaporated in vacuo to dryness. The residue was taken in dichloromethane (200 mL) and filtered. The orange filtrate was washed with HCl (10% aqueous solution, 3 × 200 mL), $NaHCO_3$ (saturated aqueous solution, 3 × 200 mL) and brine (200 mL). The organic layer was dried (anhydrous Na_2SO_4), filtered and concentrated in vacuo to dryness to give a mixture of *syn*- and *anti*-**20c** as a brown oil. Column chromatography (silica gel, hexanes to ethyl acetate / hexanes mixture 2/8) gave a mixture of *syn*- and *anti*-**20c** (in the approx. ratio of 1:1, ^{1}H NMR or GC/MS) as a yellowish oil (2.36 g, 62% yield). IR (ATR) ν 2964, 2851, 1713, 1634, 1460, 1435, 1381, 1352, 1317, 1239, 1217, 1190, 1159, 1128, 1076, 961, 908, 892, 855, 797, 773, 749, 738, 687, 554 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ *syn*-**20c** 0.93 (t, *J* = 7.4 Hz, 3 H, C1-$CH_2C\underline{H}_3$), 0.97 (t, J = 7.4 Hz, 3 H, C5-$CH_2C\underline{H}_3$), 1.36-1.64 (complex signal, 4 H, C1-$C\underline{H}_2CH_3$ and C5-$C\underline{H}_2CH_3$), 2.45 [dd, *J* = 16.4 Hz, *J'* = 1.8 Hz, 2 H, 4(6)-H_a], 2.58 [dd, *J* = 16.4 Hz, *J'* = 1.8 Hz, 2 H, 4(6)-H_b], 3.70 [s, 6 H, C3(7)-$CO_2\underline{C}H_3$], 6.59 [t, *J* = 1.8 Hz, 2 H, 2(8)-H]; *anti*-**20c** 0.93 [t, *J* = 7.4 Hz, 6 H, C1(5)-$CH_2C\underline{H}_3$], 1.36-1.64 [complex signal, 4 H, C1(5)-$C\underline{H}_2CH_3$], 2.49 [dd, *J* = 16.4 Hz, *J'* = 2.8 Hz, 2 H, 4(8)-H_a], 2.68 [broad d, *J* = 17.2 Hz, 2 H, 4(8)-H_b], 3.71 [2 s, 6 H, C3(7)-$CO_2\underline{C}H_3$], 6.60 [d, *J* = 1.6 Hz, 2 H, 2(6)-H]; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ *syn*-**20c** 9.4 (CH_3, C1-$CH_2\underline{C}H_3$)*, 9.8 (CH_3, C5-$CH_2\underline{C}H_3$)*, 25.5 (CH_2, C1-$\underline{C}H_2CH_3$)*, 26.3 (CH_2, C5-$\underline{C}H_2CH_3$)*, 42.5 [CH_2, C4(6)], 51.5 (CH_3, 2 $CO_2\underline{C}H_3$), 55.6 (C, C5), 68.4 (C, C1), 134.9 [C, C3(7)-*syn*], 150.3 [CH, C2(6)], 165.6 (C, $\underline{C}O_2CH_3$); *anti*-**20c** 9.9 [CH_3, C1(5)-$CH_2\underline{C}H_3$], 27.6 [CH_2, C1(5)-$\underline{C}H_2CH_3$-*anti*], 40.7 [CH_2, C4(8)], 51.4 (CH_3, 2 $CO_2\underline{C}H_3$), 61.2 [C, C1(5)], 132.9 [C, C3(7)], 144.0 [CH, C2(8)], 165.6 (C, $\underline{C}O_2CH_3$). GC/MS, m/e (%); main ions (*syn* and *anti*): rt (19.9 min): 278 ($M^{\cdot+}$, 23), 249 [$(M\text{-}C_2H_5)^+$, 14], 247 (49), 246 [$(M\text{-}CH_3OH)^{\cdot+}$, 100], 219 (27), 218 [$(M\text{-}HCO_2CH_3)^{\cdot+}$, 92], 217 (57), 203 (18), 193 [$(C_{12}H_{17}O)^+$, 91], 189 [$(M\text{-}C_2H_5\text{-}HCO_2CH_3)^+$, 69], 187 (29), 186 (16), 161 (37), 159 [$(C_{12}H_{16})^+$, 87], 157 (25), 145 (20), 133 (20), 131 (32), 130 (22), 129 [$(C_{10}H_{10})^+$, 57], 128 (27), 117 (22), 115 (38), 105 (26), 93 (22), 91 [$(C_7H_7)^+$, 37], 77 (18); rt (20.0 min): 278 ($M^{\cdot+}$, 12), 249 [$(M\text{-}C_2H_5)^+$, 26], 247 (20), 219 (46), 218 [$(M\text{-}HCO_2CH_3)^{\cdot+}$, 100], 217 (27), 189 [$(M\text{-}C_2H_5\text{-}HCO_2CH_3)^+$, 31], 159 [$(C_{12}H_{16})^+$, 49], 129 [$(C_{10}H_{10})^+$, 28], 115 (16), 91 [$(C_7H_7)^+$, 15]. HRMS-ESI+ m/z [*M*+H]$^+$ calcd for $[C_{16}H_{22}O_4+H]^+$: 279.1591, found: 279.1593.

Mixture of *endo,endo*-, *endo,exo*- and *exo,exo*- dimethyl 1,5-diethyl-*cis*-bicyclo[3.3.0]octane-3,7-dicarboxylate (21c). A mixture of **20c** (4.45 g, 15.99 mmol) was dissolved in absolute ethanol (120 mL), Pd on charcoal (1.34 g, 54% water content, ca. 5% Pd, equivalent to 30.9 mg of Pd) was added and the resulting mixture was hydrogenated at 400 psi at room temperature for 7 days. The suspension was filtered, and the solvent was evaporated in vacuo to give a mixture of *endo,endo*-, *endo,exo*- and *exo,exo*- stereoisomers of **21c** (3.47 g, 77% yield) as an oil. IR (ATR) ν 2959, 2878, 1730, 1458, 1434, 1364, 1265, 1192, 1171, 1042, 1027, 930, 830, 761, 668 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ *endo,endo*-**21c** 0.87 [t, *J* = 7.5 Hz, 3 H, C1(5)-$CH_2C\underline{H}_3$], 1.24 [q, *J* = 7.5 Hz, 4 H, C1(5)-$C\underline{H}_2CH_3$], 1.89 [dd, *J* = 13.5 Hz, *J'* = 10.0 Hz, 4 H, 2(4,6,8)-H_a], 1.98 [dd, *J* = 13.5 Hz, *J'* = 8.5 Hz, 4 H, 2(4,6,8)-H_b], 2.88 [m, 2 H, 3(7)-H], 3.67 [s, 6 H, 3(7)-$CO_2C\underline{H}_3$]; *endo,exo*-**21c** and *exo,exo*-**21c** 0.88 [t, *J* = 7.5 Hz, 3 H, C1(5)-$CH_2C\underline{H}_3$], 0.89 [t, *J* = 7.5 Hz, 3 H, C1(5)-$CH_2C\underline{H}_3$], 1.26-1.39 (complex signal, C1(5)-$C\underline{H}_2CH_3$], 1.54 (d, *J* = 12.5 Hz), 1.59 (d, *J* = 11.0 Hz), 1.75 (t, *J* = 12.5 Hz), 1.88 (m) and 2.03 (dd, *J* = 14.5 Hz, *J'* = 7.0 Hz) (CH_2), 2.59 (tt, 1 H, *J* = 14.0 Hz, *J'* = 9.0 Hz), 2.75 (tt, 1 H, J = 14.5 Hz, J' = 9.0 Hz) and 2.87 (m) (CH), 3.66 (s, 6 H, $OC\underline{H}_3$), 3.67 (s, 6 H, $OC\underline{H}_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ *endo,endo*-**21c** 9.9 [CH_3, C1(5)-$CH_2\underline{C}H_3$], 25.8 [CH_2, C1(5)-$\underline{C}H_2CH_3$-*anti*], 38.2 [CH_2, C2(4,6,8)], 51.7 (CH_3, 2

$CO_2\underline{C}H_3$), 57.3 [C, C1(5)], 177.2 (C, $\underline{C}O_2CH_3$); *endo,exo*-**21c** and *exo,exo*-**21c** 10.0 (CH_3), 10.2 (CH_3), 28.0 (CH_2), 30.9 (CH_2), 40.2 (CH), 40.5 (CH_2), 41.5 (CH), 41.9 (CH_2), 42.7 (CH), 43.1 (CH_2), 51.60 (CH_3), 51.62 (CH_3), 55.2 (C), 55.3 (C), 176.1 (C), 176.2 (C), 176.5 (C). GC/MS (GC), m/e (%); main ions (only two peaks were observed): rt (19.6 min): 282 ($M^{\cdot+}$, 2), 251 (37), 250 [$(M\text{-}CH_3OH)^{\cdot+}$, 100], 222 (36), 221 (22), 218 [$(M\text{-}2CH_3OH)^{\cdot+}$, 61], 193 (55), 191 (41), 190 (98), 183 (27), 163 (43), 162 (34), 161 (42), 142 (18), 136 (17), 135 (38), 134 (16), 133 [$(C_{10}H_{14})^+$, 78], 122 (21), 121(39), 110 (18), 107 [$(C_8H_{10})^+$, 53], 105 (30), 93 (39), 91 (33), 79 (34), 77 (18), 59 (18), 55 (24); rt (19.7 min): 282 ($M^{\cdot+}$, 2), 251 (28), 250 [$(M\text{-}CH_3OH)^{\cdot+}$, 73], 222 (48), 221 (38), 218 [$(M\text{-}2CH_3OH)^{\cdot+}$, 56], 193 (47), 191 (31), 190 (28), 181 (16), 163 (66), 162 (26), 161 (47), 158 (98), 149 (21), 142 (32), 136 (24), 135 (38), 133 [$(C_{10}H_{14})^+$, 100], 126 (21), 124 (29), 123 (31), 121 (60), 110 (20), 107 [$(C_8H_{10})^+$, 90], 105 (43), 95 (27), 93 (64), 91 (52), 81 (35), 79 (59), 77 (32), 67 (27), 59 (34), 55 (44). HRMS-ESI+ m/z $[M+H]^+$ calcd for $[C_{16}H_{26}O_4+H]^+$: 283.1904, found: 283.1897.

Dimethyl 3,7-diethyltricyclo[3.3.0.0^{3,7}]octane-1,5-dicarboxylate (22c). A solution of LiHMDS was prepared by reacting a solution of HMDS (3.56 mL, 17.0 mmol) in anhydrous THF (14 mL) with *n*-butyllithium (8.0 mL, 2.0 M in hexanes, 16.0 mmol) at -68ºC under argon for 1 h. Then, a solution of a stereoisomeric mixture of diesters **21c** (2.0 g, 7.08 mmol) in anhydrous THF (14 mL) was added dropwise keeping the temperature at -68ºC. Stirring was continued for 1 h at this temperature and then a solution of iodine (1.80 g, 7.08 mmol) in anhydrous THF (32 mL) was added dropwise. The mixture was maintained 1 h at -68ºC and then allowed to warm to room temperature over 15 h. The mixture was acidified with HCl (10% aqueous solution) until pH 2 (10 mL) and the THF was removed *in vacuo*. The remaining aqueous phase was extracted with diethyl ether (4 × 50 mL) and the combined organic extracts were washed with $Na_2S_2O_3$ (10% aqueous solution, 3 × 100 mL) and brine (2 × 100 mL), dried (Na_2SO_4), filtered and evaporated to dryness under reduced pressure to furnish a dark red oil. Column chromatography of this residue (silica gel, hexanes / ethyl acetate, 9 / 1) gave diester **22c** (930 mg, 47% yield) as an orange oil. IR (ATR) ν 2962, 2891, 1732, 1479, 1459, 1435, 1378, 1325, 1301, 1285, 1219, 1192, 1155, 1132, 1081, 1063, 1042, 1002, 942, 915, 775, 763, 730, 647 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 [t, J = 7.4 Hz, 6 H, C3(7)-$CH_2C\underline{H}_3$], 1.57 [d, J = 7.0 Hz, 4 H, 2(4,6,8)-H_a], 1.59 [q, J = 7.4 H, 4 H, C3(7)-$C\underline{H}_2CH_3$], 2.01 [d, J = 7.0 Hz, 4 H, 2(4,6,8)-H_b], 3.67 [s, 6 H, $CO_2C\underline{H}_3$]; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 10.0 [CH_3, C3(7)-$CH_2\underline{C}H_3$], 22.7 [CH_2, C3(7)-$\underline{C}H_2CH_3$], 51.6 (CH_3, 2 $CO_2\underline{C}H_3$), 52.9 [CH_2, C2(4,6,8)], 53.0 [C, C3(7)], 57.3 [C, C1(5)], 173.6 (C, $\underline{C}O_2CH_3$). GC/MS, m/z (%); main ions: 280 ($M^{\cdot+}$, 1), 249 (41), 248 (25), 220 (100), 191 (67), 189 (28), 181 (72), 180 (25), 179 (44), 161 (87), 160 (27), 149 (88), 133 (20), 131 (37), 121 (60), 119 (30), 105 (38), 93 (31), 91 (49), 77 (21). HRMS-ESI+ m/z $[M+H]^+$ calcd for $[C_{16}H_{24}O_4+H]^+$: 281.1753, found: 281.1750.

3,7-Diethyltricyclo[3.3.0.0^{3,7}]octane-1,5-dicarboxylic acid (12c). A mixture of **22c** (2.32 g, 8.28 mmol) and a solution of KOH (40%) in MeOH (24 mL) was heated under reflux for 3 h. Water (24 mL) was added and heating under reflux was continued for 6 h more. The solution was made acidic with conc. aqueous HCl (25 mL) and concentrated in vacuo. The dark solid was extracted with boiling diethyl ether (6 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated to dryness under reduced pressure to furnish **12c** (1.32 g, 63% yield) as a pale yellow solid, mp 205-206 ºC; IR (KBr) ν 2971, 2930, 2705, 2604, 1702, 1420, 1312, 1235, 1151, 1091, 938, 729 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 [t, J = 7.2 Hz, 6 H, C3(7)-$CH_2C\underline{H}_3$], 1.56-1.64 [complex signal, 8 H, C3(7)-$C\underline{H}_2CH_3$ and 2(4,6,8)-H_a], 2.03 [d, J = 7.6 Hz, 4 H, 2(4,6,8)-H_b], 10.65 (broad s, 2 H, $CO_2\underline{H}$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 10.0

[CH_3, C3(7)-$CH_2\underline{C}H_3$], 22.7 [CH_2, C3(7)-$\underline{C}H_2CH_3$], 52.7 [CH_2, C2(4,6,8)], 53.3 [C, C3(7)], 57.9 [C, C1(5)], 180.1 [C=O, C9(11)]. MS, m/z (%); main ions: 234 [(M-H_2O), 5]$^{\cdot+}$, 206 [(M-HCO_2H)$^{\cdot+}$, 55], 177 (67), 167 (100), 166 (37), 165 (31), 163 (33), 162 (47), 149 (63), 137 (18), 133 (28), 131 (23), 121 (54), 119 (23), 107 (21), 105 (40), 93 (46), 91 (60), 79 (34), 77 (38), 69 (19), 57 (29). HRMS-ESI+ m/z [*M*+H]$^+$ calcd for [$C_{14}H_{20}O_4$+H]$^+$: 253.1434, found: 253.1428.

Tricyclo[4.3.3.0^{1,6}]dodecane-8,11-dione bishydrazone (18d). From known[3] diketone **17d** (37.3 g, 0.19 mol), triethylamine (431 mL, 3.11 mmol) and hydrazine monohydrate (97.4 mL, 2.02 mmol) in absolute EtOH (525 mL) and following the same procedure as reported for **18c**, **18d** was obtained as an orange sticky solid (42.5 g, 99% yield). An analytical sample of **18d** (*anti* isomer) was obtained by crystallization from chloroform, mp 142-143 ºC. IR (KBr) ν 3353, 3195, 2921, 2862, 2841, 1654, 1444, 1420, 1339, 1267, 1225, 1079, 872, 862, 813, 687, 507 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 [broad s, 8 H, 3(4)-H_2 and 2(5)-H_2], 2.15 [dd, J = 18.0 Hz, J' = 1.6 Hz, 2 H, 9(12)-H_a], 2.32 [dd, J = 17.0 Hz, J' = 1.6 Hz, 2 H, 7(10)-H_b], 2.34 [dd, J = 18.0 Hz, J' = 1.8 Hz, 2 H, 9(12)-H_b], 2.47 [broad d, J = 17.2 Hz, 2 H, 7(10)-H_a], 4.85 (broad s, 4 H, NH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.3 (CH_2, C3)*, 21.6 (CH_2, C4)*, 30.4 (CH_2, C2)*, 32.1 (CH_2, C5)*, 37.5 [broad CH_2, C9(12)], 42.5 [broad CH_2, C7(10)], 46.4 (C, C1)*, 47.6 (C, C5)*, 157.5 [C=N, C3(7)]. MS, m/z (%); main ions: 220 (M$^{\cdot+}$, 19), 204 (100), 191 (18), 188 (25), 150 (39), 149 (39), 148 (23), 105 (16), 91 (30), 79 (17). HRMS-ESI+ m/z [*M*+H]$^+$ calcd for [$C_{12}H_{20}N_4$+H]$^+$: 221.1761, found: 221.1756.

Mixture of 8,11-diiodotricyclo[4.3.3.0^{1,6}]dodecan-7,11-diene and 8,11-diiodotricyclo[4.3.3.0^{1,6}]dodecan-7,10-diene (*syn*- and *anti*-19d). From bis-hydrazone **18d** (1.0 g, 4.54 mmol), tetramethylguanidine (8.6 ml, 68.1 mmol) and iodine (9.22 g, 36.3 mmol) in dry diethyl ether (50 mL) and following the same procedure as reported for **19c**, **19d** was obtained as an pink solid (1.07 g, 57% yield). An analytical sample of **19d** (*syn* and *anti* mixture) was obtained by crystallization from *n*-pentane, mp 91-92 ºC. IR (KBr) ν 3404, 3042, 2916, 2843, 1599, 1436, 1270, 1210, 1097, 1074, 989, 856, 790, 739, 594 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ *anti*-**19d** 1.25-1.72 [complex signal, 8 H, 2(5)-H_2 and 3(4)-H_2], 2.51 [dd, J = 16.4 Hz, J' = 1.6 Hz, 2 H, 9(12)-H_a], 2.62 [dd, J = 16.4 Hz, J' = 2.4 Hz, 2 H, 9(12)-H_b], 5.85 [m, 2 H, 7(10)-H]; δ *syn*-**19d** 1.25-1.55 [complex signal, 8 H, 2(5)-H_2 and 3(4)-H_2], 2.54 [m, 4 H, 9(10)-H_2], 5.88 [t, J = 2.0 Hz, 2 H, 7(12)-H]; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ *anti*-**19d** 19.0 [CH_2, C3(4)], 31.0 [CH_2, C2(5)], 52.6 [CH_2, C9(12)], 59.0 [C, C1(6)], 91.1 [C, C8(11)], 148.5 [CH, C7(10)]; δ *syn*-**19d** 19.7 (CH_2, C3)*, 20.8 (CH_2, C4)*, 31.4 (CH_2, C2)*, 31.8 (CH_2, C5)*, 53.2 (C, C1), 55.9 [CH_2, C9(10)], 65.9 (C, C6), 92.6 [C, C8(11)], 143.9 [CH, C7(12)]. GC/MS, m/z (%); main ions (*syn* and *anti*): rt (20.2 min): 412 (M$^{\cdot+}$, 26), 285 [(M-I)$^+$, 40], 158 [(M-2I)$^{\cdot+}$, 100], 157 (51), 143 (24), 130 (34), 129 (48), 128 (28), 117 (27), 116 (22), 115 (49), 102 (23), 91 (40); rt (20.3 min): 412 (M$^{\cdot+}$, 13), 285 [(M-I)$^+$, 84], 158 [(M-2I)$^{\cdot+}$, 100], 143 (17), 130 (26), 129 (35), 128 (23), 117 (18), 115 (34), 102 (11), 91 (23).

Mixture of dimethyl tricyclo[4.3.3.0^{1,6}]dodecan-7,11-diene-8,11-dicarboxylate and dimethyl tricyclo[4.3.3.0^{1,6}]dodecan-7,10-diene-8,11-dicarboxylate (*syn*- and *anti*-20d). From a mixture of **19d** (5.70 g, 13.70 mmol), triphenylphosphine (719 mg, 2.74 mmol), $Pd(OAc)_2$ (308 mg, 1.37 mmol) and triethylamine (11.4 mL, 82.2 mmol) in methanol (180 mL) and following the same procedure as reported for **20c**, **20d** was obtained as a black oil. Column chromatography (silica gel, hexanes to ethyl acetate / hexanes mixture 2/8) gave a mixture of *syn*- and *anti*-**20d** (in the approx. ratio of 1:1, ^{1}H

[3] Weiss U.; Edwards, J. M. A one-step synthesis of ketonic compounds of the pentalane, [3.3.3]- and [4.3.3]propellane series. *Tetrahedron Lett.* **1968**, *47*, 4885-4887.

NMR) as a white solid (2.43 g, 64% yield), mp 71-72 ºC (hexane). IR (KBr) ν 3026, 3001, 2954, 2921, 2899, 2853, 1713, 1627, 1609, 1437, 1352, 1282, 1264, 1244, 1224, 1206, 1194, 1106, 1084, 979, 950, 898, 777, 749, 602, 552 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ *anti*-**20d** 1.20-1.83 [complex signal, 8 H, 2(5)-H_2 and 3(4)-H_2], 2.58 [dd, J = 16.2 Hz, J' = 1.6 Hz, 2 H, 9(12)-H_a], 2.65 [dd, J = 16.4 Hz, J' = 2.8 Hz, 2 H, 9(12)-H_b], 3.70 (s, 6 H, $CO_2C\underline{H}_3$), 6.47 [m, 2 H, 7(10)-H]; δ *syn*-**20d** 1.25-1.60 [complex signal, 8 H, 2(5)-H_2 and 3(4)-H_2], 2.50 [m, 4 H, 9(10)-H_2], 3.71 (s, 6 H, $CO_2C\underline{H}_3$), 6.47 [m, 2 H, 7(12)-H]; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ *anti*-**20d** 19.7 [CH_2, C3(4)], 31.4 [CH_2, C2(5)], 43.6 [CH_2, C9(12)], 51.5 (CH_3, $CO_2\underline{C}H_3$), 56.0 [C, C1(6)], 135.2 [C, C8(11)], 151.9 [CH, C7(10)], 165.9 (C, $\underline{C}O_2CH_3$); δ *syn*-**20d** 20.5 (CH_2, C3)*, 21.0 (CH_2, C4)*, 31.6 (CH_2, C2)*, 32.3 (CH_2, C5), 39.6 [CH_2, C9(10)], 50.7 (C, C1), 51.5 (CH_3, $CO_2\underline{C}H_3$), 63.2 (C, C6), 132.2 [C, C8(11)], 145.5 [CH, C7(12)], 166.0 (C, $\underline{C}O_2CH_3$). MS, m/z (%); main ions: 276 (M^+, 40), 244 (100), 217 (48), 216 (42), 185 (34), 184 (18), 157 (47), 131 (16), 129 (29), 128 (17), 117 (21), 115 (28), 91 (21). HRMS-ESI+ m/z $[M+H]^+$ calcd for $[C_{16}H_{20}O_4+H]^+$: 277.1434, found: 277.1435.

Mixture of *endo,endo*- and *endo,exo*- dimethyl tricyclo[4.3.3.0^{1,6}]dodecan-8,11-dicarboxylate (21d). A mixture of **20d** (5.43 g, 19.7 mmol) was dissolved in absolute ethanol (120 mL), Pd on charcoal (1.09 g, 54% water content, ca. 5% Pd, equivalent to 25.1 mg of Pd) was added and the resulting mixture was hydrogenated at 400 psi at room temperature for 14 days. The suspension was filtered, and the solvent was evaporated in vacuo to give a mixture of *endo,endo*- and *endo,exo*- stereoisomers of **21d** (4.06 g, 74% yield) as a yellow oil. IR (ATR) ν 2924, 2861. 1730, 1700, 1460, 1434, 1364, 1308, 1278, 1192, 1167, 1121, 1020, 930, 890, 830, 761, 722 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20-1.52 [complex signal, 8 H, 2(5)-H_2 and 3(4)-H_2], 1.87-2.02 [complex signal, 8 H, 7(9,10,12)-H_2], 2.93-3.11 [complex signal, 2 H, 8(11)-H], 3.67 (s, 6 H, $CO_2C\underline{H}_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ *endo,exo*-**21d** 20.8 [CH_2, C3(4)], 31.1 [CH_2, C2(5)], 39.6 (CH) and 40.9 (CH) (C8 and C11), 40.1 (CH_2) and 41.1 (CH_2) [C7(9) and C10(12)], 51.69 [C, C1(6)], 51.8 (CH_3, $CO_2\underline{C}H_3$), 177.3 (C, $\underline{C}O_2CH_3$); δ *endo,endo*-**21d** 21.6 [CH_2, C3(4)], 32.3 [CH_2, C2(5)], 40.1 [CH, C8(11)], 40.7 [CH_2, C7(9,10,12)], 50.7 (C, C1), 51.6 [C, C1(6)], 51.72 (CH_3, $CO_2\underline{C}H_3$), 177.3 (C, $\underline{C}O_2CH_3$). GC/MS, m/z (%); main ions: 280 ($M^{\cdot+}$, 2), 248 [$(M-CH_3OH)^{\cdot+}$, 100], 220 [$(M-HCO_2H)^{\cdot+}$, 82], 216 (59), 189 (36), 188 (58), 179 (52), 161 (83), 158 (30), 147 (25), 134 (55), 121 (59), 119 (87), 105 (37), 93 (52), 91 (76), 79 (45), 77 (25). HRMS-ESI+ m/z $[M+H]^+$ calcd for $[C_{16}H_{24}O_4+H]^+$: 281.1747, found: 281.1747.

Dimethyl tetracyclo[6.2.1.1^{3,10}.0^{3,8}]dodecane-1,10-dicarboxylate (22d). From a solution of HMDS (2.50 mL, 11.73 mmol) in anhydrous THF (10 mL), *n*-butyllithium (5.0 mL, 2.0 M in hexanes, 10.0 mmol) a stereoisomeric mixture of diesters **21d** (1.37 g, 4.89 mmol) in anhydrous THF (10 mL) and a solution of iodine (1.24 g, 4.89 mmol) in anhydrous THF (22 mL) and following the same procedure as reported for **22c**, a dark red oil containing **22d** was obtained. Column chromatography of this residue (silica gel, from hexanes to hexanes / ethyl acetate, 87 / 13) gave diester **22d** (771 mg, 57% yield) as a yellow solid, mp 72–73 ºC (hexanes). IR (ATR) ν 3432, 2937, 2856, 1734, 1455, 1436, 1301, 1198, 1176, 1115, 1080, 1031, 930, 799, 758, 566 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.57 [m, 4 H, 5(6)-H_2], 1.65 [m, 4 H, 4(7)-H_2], 1.77 [d, J = 7.2 H, 4 H, 2(9,11,12)-H_a], 1.87 [d, J = 7.2 Hz, 4 H, 2(9,11,12)-H_b], 3.66 [s, 6 H, $CO_2C\underline{H}_3$]; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.8 [CH_2, C5(6)], 25.4 [CH_2, C4(7)], 48.0 [C, C3(8)], 51.6 (CH_3, 2 $CO_2\underline{C}H_3$), 53.9 [CH_2, C2(9,11,12)], 57.5 [C, C1(10)], 173.5 (C, $\underline{C}O_2CH_3$). GC/MS, m/z (%); main ions: 279 [$(M+H)^+$, 13], 247 (32), 246 (51), 237 (31), 219 (25), 205 (17), 203 (19), 196 (13), 188 (18), 179 (53), 177 (30), 164 (55), 159 (37), 147 (63), 133 (16), 131 (25), 119 (100), 117 (29), 115 (19), 105 (25), 91 (64), 79 (21),

77 (21). HRMS-ESI+ m/z $[M+H]^+$ calcd for $[C_{16}H_{22}O_4+H]^+$: 279.1591, found: 279.1588.

Tetracyclo[6.2.1.1^{3,10}.0^{3,8}]dodecane-1,10-dicarboxylic acid (12d). From **22d** (722 mg, 2.59 mmol) and a solution of KOH (40%) in MeOH (7 mL) and following the same procedure as for **12c**, diacid **12d** (520 mg, 80% yield) was obtained as a pale yellow solid, mp 239-240 ºC; IR (ATR) ν 2931, 2859, 2693, 2592, 1696, 1418, 1299, 1236, 1201, 1083, 1038, 885, 714, 600 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58 [m, 4 H, 5(6)-H_2], 1.66 [m, 4 H, 4(7)-H_2], 1.81 [d, J = 7.4 H, 4 H, 2(9,11,12)-H_a], 1.91 [d, J = 7.4 Hz, 4 H, 2(9,11,12)-H_b], 9.88 [very broad s, 2 H, $CO_2\underline{H}$]; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.8 [CH_2, C5(6)], 25.3 [CH_2, C4(7)], 48.3 [C, C3(8)], 53.7 [CH_2, C2(9,11,12)], 58.0 [C, C1(10)], 179.9 (C, $\underline{C}O_2CH_3$). GC/MS, m/z (%); main ions: 250 ($M^{\cdot+}$, 3), 232 [$(M-H_2O)^{\cdot+}$, 48], 204 (37), 165 (78), 164 (28), 160 (30), 159 (36), 150 (67), 147 (53), 146 (26), 145 (26), 131 (44), 119 (89), 117 (53), 115 (28), 105 (30), 93 (17), 92 (20), 91 (100), 79 (33), 77 (40), 65 (20). HRMS-ESI– m/z $[M–H]^-$ calcd for $[C_{14}H_{18}O_4–H]^-$: 249.1132, found: 249.1135.

Elemental analysis data:

Compound	**Molecular Formula**	**Calculated**				**Found**			
		C	H	N	X	C	H	N	X
14a·HCl·0.5H_2O	$C_{12}H_{19}N$·HCl·0.5H_2O	64.70	9.50	6.29	15.91	64.73	9.36	6.68	16.11
15a·HCl·0.2H_2O	$C_{13}H_{21}N$·HCl·0.2H_2O	67.48	9.76	6.05	15.32	67.57	9.57	6.33	15.42
16a·HCl·0.33Et_2O	$C_{13}H_{21}N_3$·HCl·0.33Et_2O	61.37	9.10	14.99	12.65	61.70	9.07	14.62	13.04
14b·HCl·0.35H_2O	$C_{10}H_{15}N$·HCl·0.35H_2O	62.56	8.77	7.30	18.46	62.67	9.08	7.44	18.46
16b·1.75HCl	$C_{11}H_{17}N_3$·1.75HCl	51.80	7.41	16.47	nd	52.03	7.72	16.79	nd
14c·$C_4H_6O_6$·0.25H_2O	$C_{14}H_{23}N$·$C_4H_6O_6$·0.25H_2O	60.06	8.26	3.89	-	60.06	8.51	4.06	-
16c·HCl·0.3H_2O	$C_{15}H_{25}N_3$·HCl·0.3H_2O	62.29	9.27	14.53	12.26	61.90	9.16	14.93	12.31
14d·$C_4H_6O_6$·1CH_3OH	$C_{14}H_{21}N$·$C_4H_6O_6$·1CH_3OH	59.20	8.11	3.63	-	59.41	8.08	3.47	-
16d·HCl·0.25H_2O	$C_{15}H_{25}N_3$·HCl·0.25H_2O	62.92	8.62	14.68	nd	63.04	8.55	14.49	nd
18c	$C_{12}H_{14}N$	64.83	9.97	25.20	-	64.78	10.09	25.11	-
***syn*- and *anti*-19c**	$C_{12}H_{16}I_2$·0.1hexane	35.80	4.15	-	60.05	35.51	3.95	-	60.43
***syn*- and *anti*-19d**	$C_{12}H_{14}I_2$	34.98	3.42	-	61.60	34.87	3.34	-	61.49