An Anti-Crystal Engineering Approach to the Preparation of Pharmaceutically Active Ionic Liquids (AILs)

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Supporting Information

Synthesis and characterisation

Pyridostigmine saccharinate, 1·7

A mixture of pyridostigmine bromide (1.67 g, 6.4 mmol) and silver saccharinate (1.86 g, 6.4 mmol) in distilled water (150 cm^3) was stirred for 2 h, protected from light, at room temperature. The reaction mixture was filtered through Celite to remove precipitated AgBr (dichloromethane was added to aid precipitation of the impurity). After treatment with activated carbon, the mixture was filtered through basic alumina to provide a colourless solution. The solvent was removed *in vacuo* at 80 °C to give the product **1·7** as a yellow oil, which crystallised on standing (1.16 g, 51 %). M.p. 94-96 °C

^{1}H NMR (300 MHz; D_2O) δ 2.86 (s, 3H), 2.97 (s, 3H), 4.31 (s, 3H), 7.60 – 7.70 (m, 4H), 7.91 (t, 1H), 8.17 (d, 1H), 8.54 (d, 1H), 8.66 (s, 1H). MS (ESI): ES+ *m/z* 181.8 (pyridostigmine$^+$, 100 %), ES- *m/z* 180.8 (saccharinate$^-$, 100 %).

Benzethonium saccharinate, 2·7

A solution of benzethonium chloride (2.96 g, 6.61 mmol) and sodium saccharinate (1.63 g, 7.93 mmol) in dichloromethane (80 cm^3) was stirred at 25 °C for 24 h. The precipitated NaCl was removed by filtration, followed by repeated washing of the organic phase with small volumes of water until no Cl^- was detected ($AgNO_3$ test). The organic phase was dried ($MgSO_4$) and concentrated under reduced

pressure before drying *in vacuo,* at 70 °C, for 48 h, giving the product **2·7** as a colourless oil (3.18 g, 86 %).

^{1}H NMR (300 MHz; DMSO-d_6) δ 0.62 (s, 9H), 1.24 (s, 6H), 1.63 (s, 2H), 2.97 (s, 6H), 3.51 (s, 2H), 3.79 (s, 2H), 3.96 (s, 2H), 4.07 (s, 2H), 4.55 (s, 2H), 6.80 (s, 2H), 7.21 (s, 2H), 7.53 (s(b)*, 9H). MS (ESI): ES+ *m/z* 412.4 (Benzethonium$^+$, 100 %), ES- *m/z* 181.9 (Saccharinate$^-$, 100 %).

Choline phenytoin, 3.6

Choline chloride (2.54 g, 18.00 mol) and sodium 5,5-diphenylhydantoin (5 g, 18.00 mmol) were mixed in 100 ml dry acetone and NaCl filtered off. The clear solution was stored at *ca* 4 °C for 3 d, whereupon large colourless crystals of the **3.6** formed and were isolated (4.67 g, 73 %). M.p. 215-217 °C

^{1}H NMR (300 MHz; DMSO-d_6): δ 3.12 (s, 9H), 3.44 (m, 2H), 3.86-3.83 (m, 2H), 7.44-7.21 (m, 10H) ppm. MS (ESI): ES+ m/z: 104.0 (Choline$^+$, 100 %), ES- m/z: 251.3 (5,5-diphenylhydantoin $^-$, 100 %).

Propantheline saccharinate, 4·7

A mixture of propantheline bromide (9.72 g, 21.70 mmol) and silver saccharinate (6.29 g, 21.70 mmol) in acetonitrile (150 cm^3) was stirred overnight, protected from light, at room temperature. The reaction mixture was filtered through Celite to remove AgBr. After treatment with activated carbon, the mixture was filtered through basic alumina to provide a colourless solution which was concentrated under reduced pressure giving a yellow oil of **4·7,** which crystallised slowly on standing (10.62 g, 89 %). M.p. 133-135 °C

^{1}H NMR (300 MHz; DMSO-d_6): δ 1.01-1.17 (t, J_1 = 6.0, 12H), 2.66 (s, 3H), 3.43-4.46 (t, J_1 = 4.7, 2H), 3.70-3.79 (m, 2H), 4.35-4.38 (t, J_1 = 4.7, 2H), 5.31 (s, 1H), 7.14-7.22 (m, 4H), 7.35-7.42 (m, 4H), 7.57-7.59 (m, 4H). MS (ESI): ES+ *m/z*: 368.2 (Propantheline$^+$, 100 %), ES- *m/z:* 181.8 (Saccharinate$^-$, 100 %).

Propantheline acesulfamate, 4·8

A mixture of propantheline bromide (3.05 g, 6.80 mmol) and silver acesulfamate (1.84 g, 6.80 mmol) in acetonitrile (150 cm^3) was stirred overnight, protected from light, at room temperature. The reaction

mixture was filtered through Celite to remove AgBr and the solution concentrated under reduced pressure before drying *in vacuo*, at 55 ^{o}C, for 72 h to give the product **4·8** as a colourless oil (3.12 g, 86 %).

^{1}H NMR (300 MHz; DMSO-d_6): δ 1.05-1.18 (t, J_1 = 6.0, 12H), 1.87-1.90 (d, J_1 = 1.0, 3H), 2.66 (s, 3H), 3.43-3.46 (t(b), J_1 = 4.7, 2H), 3.73-3.77 (m, 2H), 4.36-4.39 (t(b), J_1 = 4.7, 2H), 5.24-5.26 (q, J_1 = 1.0, 1H), 5.30 (s, 1H), 7.16-7.22 (m, 4H), 7.40-7.42 (m, 4H). MS (ESI): ES+ *m/z*: 368.1 (Propantheline^{+}, 100 %), ES- *m/z:* 161.7 (Acesulfamate^{-}, 100 %).

Propantheline cyclamate, 4·9

A mixture of propantheline bromide (2.46 g, 5.49 mmol) and silver cyclamate (1.57 g, 5.49 mmol) in acetonitrile (150 cm^{3}) was stirred overnight, protected from light, at room temperature. The reaction mixture was filtered through Celite to remove AgBr and the solution concentrated to leave a clear viscous residue, which was dried *in vacuo* at 55 ^{o}C for 72 h to yield **4·9** as a colourless oil, , which crystallised on standing (2.76 g, 92 %). M.p. 133-137 °C

^{1}H NMR (300 MHz; DMSO-d_6): δ 0.95-1.21 (m, 5H) 1.14-1.19 (t, *J* 6.0), 1.47-1.52 (m, 1H), 1.57-1.64 (m, 2H), 1.85-1.91 (m, 2H), 2.66 (s, 3H), 2.81-2.91 (m, 1H), 3.43-3.47 (t(b), J_1 = 4.7, 2H), 3.73-3.78 (m, 2H), 4.36-4.39 (t(b), J_1 = 4.7, 2H), 5.31 (s, 1H), 7.17-7.22 (m, 4H), 7.35-7.42 (m, 4H). MS (ESI): ES+ *m/z*: 368.1 (Propantheline^{+}, 100 %), ES- *m/z:* 177.8 (Cyclamate^{-}, 100 %).

Propantheline *p*-toluenesulfonate, 4·10

A mixture of propantheline bromide (1.55 g, 5.56 mmol) and silver *p*-toluenesulfonate (2.49 g, 5.56 mmol) in acetonitrile (100 cm^{3}) was stirred overnight, protected from light, at room temperature. The reaction mixture was filtered through Celite to remove AgBr and the solution concentrated to leave a clear viscous residue, which was dried *in vacuo* at 55 ^{o}C for 72 h yielding **4·10** as a colourless oil (2.42 g, 81 %).

^{1}H NMR (300 MHz; DMSO-d_6): δ 1.14-1.18 (t, J_1 = 6.0, 12H), 2.29 (s, 3H), 2.66 (s, 3H), 3.42-3.45 (t(b), J_1 = 4.7, 2H), 3.70-3.79 (m, 2H), 4.36-4.39 (t(b), J_1 = 4.7, 2H), 5.31 (s, 1H), 7.09-7.12 (m, 2H),

7.12-7.22 (m, 4H), 7.39-7.40 (m, 4H), 7.46-7.49 (m, 2H). MS (ESI): ES+ *m/z*: 368.1 (Propantheline$^+$, 100 %), ES- *m/z:* 170.8 (*p*-Toluenesulfonate$^-$, 100 %).

Mepenzolate saccharinate, 5·7

A mixture of mepenzolate bromide (5.80 g, 14.00 mmol) and silver saccharinate (4.0 g, 14.00 mmol) in dry acetonitrile (120 cm^3) was stirred overnight, protected from light, at room temperature. The reaction mixture was filtered through Celite to remove AgBr and the solution concentrated to give a colourless oil, which was dried *in vacuo* at 55 °C for 72 h at which point the product crystallized. The product was successfully recrystallized using acetonitrile (excess and heating), resulting in colourless crystals (4.83 g, 66 %). M.p. 187-189 °C.

^{1}H NMR (300 MHz; DMSO-d_6): δ 1.85-1.69 (m, 4H), 2.81 (s, 3H), 3.08 (s, 3H), 3.32-3.44 (m, 2H), 3.53 (d, J_1 = 13.5 Hz, 1H), 3.42 (d, J_1 = 13.5 Hz, 1H), 5.30 (m, 1H), 6.80 (s, 1H), 7.31-7.40 (m, 10H), 7.58-7.61 (m, 4H) ppm. MS (EI): ES+ m/z: 340.2 (Mepenzolate$^+$, 100%), ES$^-$ m/z 181.8 (Saccharinate$^-$, 100%).

Mepenzolate acesulfamate, 5·8

A mixture of mepenzolate bromide (1.56 g, 3.70 mmol) and silver acesulfamate (1.0 g, 3.70 mmol) in acetonitrile (150 cm^3) was stirred overnight, protected from light, at room temperature. The reaction mixture was filtered through Celite and 0.45 and 0.20 μm membrane filters to remove AgBr. The solvent was evaporated to give a colourless oil, which crystallized within 1 h giving **5·8** as colourless crystals (1.63 g, 88 %). M.p. 135-137 °C

^{1}H NMR (300 MHz; DMSO-d_6): δ 1.68-1.85 (m, 4H), 1.89-1.90 (d, J_1 = 1.0, 3H), 2.82 (s, 3H), 3.08 (s, 3H), 3.33-3.35 (m, 2H), 3.48-3.56 (d.d, J_1 = 13.45, J_2 = 5.02 Hz, 1H), 3.57-3.62 (d.d, J_1 = 13.45, J_2 = 5.02 Hz, 1H), 5.27-5.30 (m, 1H), 5.26-5.27 (q, J_1 = 1.0, 1H), 6.81 (s, 1H), 7.32-7.38 (m, 10H). MS (ESI): ES+ *m/z*: 340.2 (Mepenzolate$^+$, 100 %), ES- *m/z:* 161.9 (Acesulfamate$^-$, 100 %).

Crystallographic ORTEP and packing diagrams

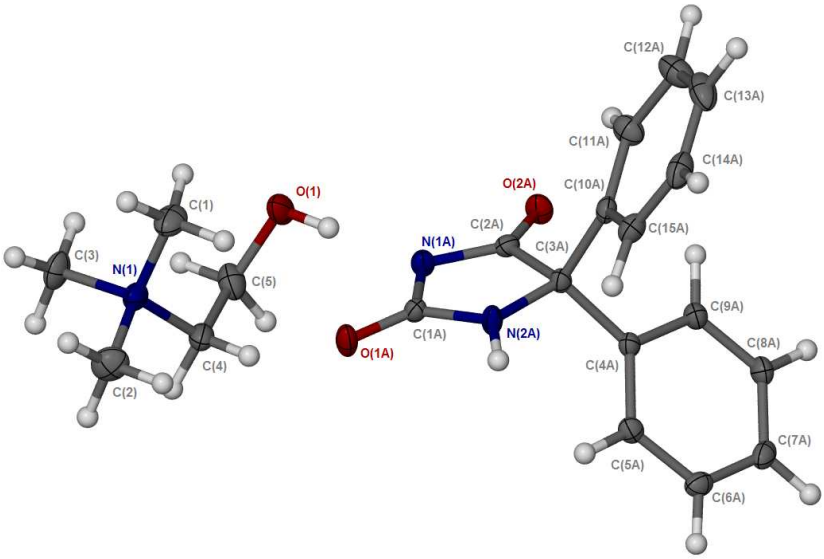

Figure 1a. The asymmetric unit of *choline phenytoin* shown with 50 % thermal ellipsoids, hydrogen atoms as spheres of arbitrary size and numbering scheme.

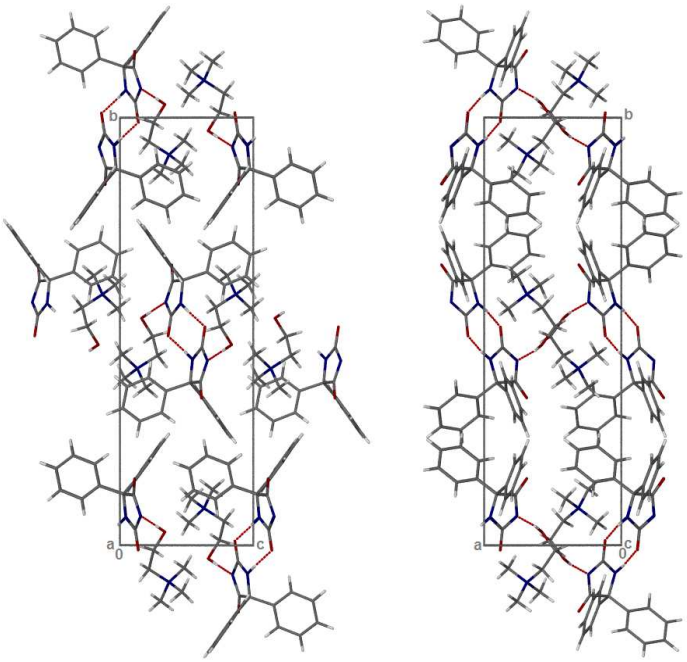

Figure 1b. Stick representation of the unit cell contents of *choline phenytoin* viewed down *b**, hydrogen bonding is indicated by red dashed lines.

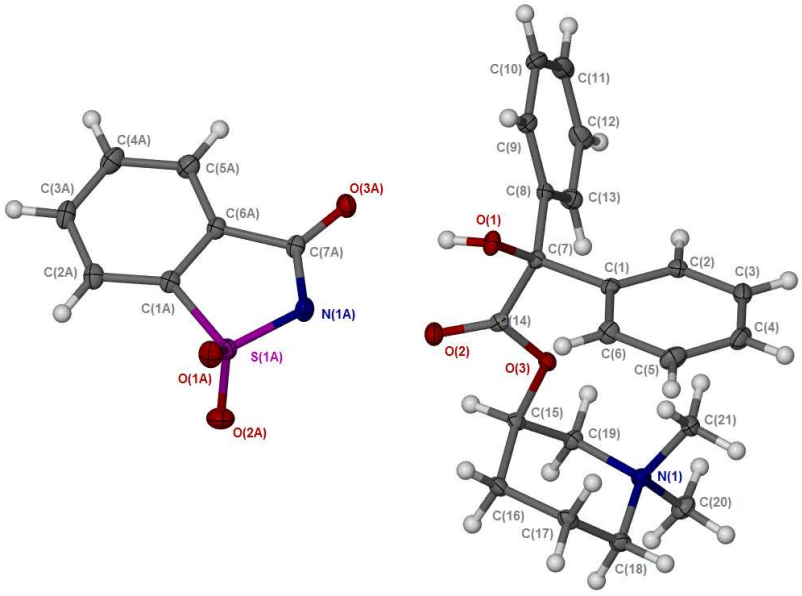

Figure 2a. The asymmetric unit of *mepenzolate saccharinate* shown with 50% thermal ellipsoids, hydrogen atoms as spheres of arbitrary size and numbering scheme.

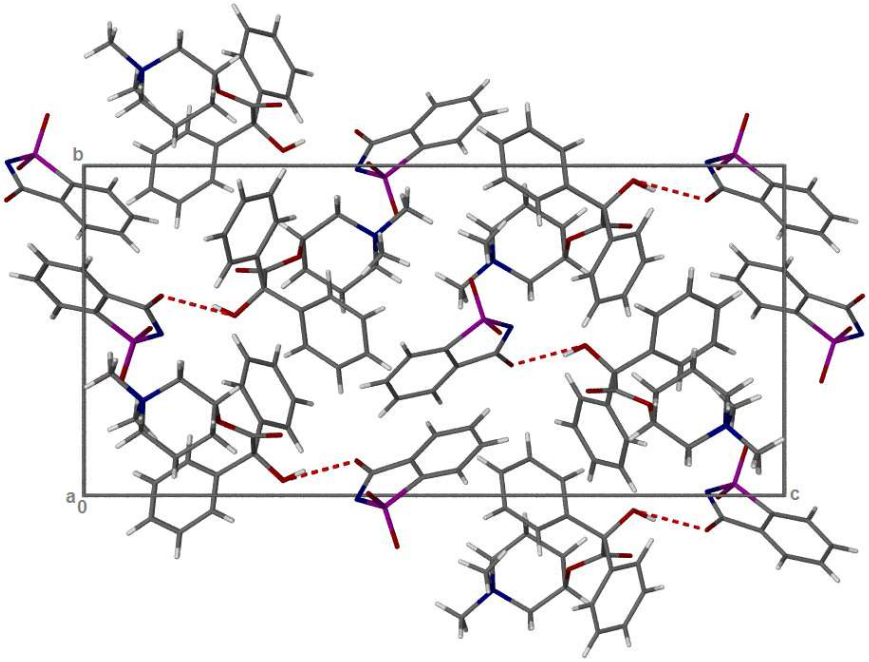

Figure 2b. Packing diagram of *mepenzolate saccharinate* with hydrogen bonding indicated by dashed red lines.

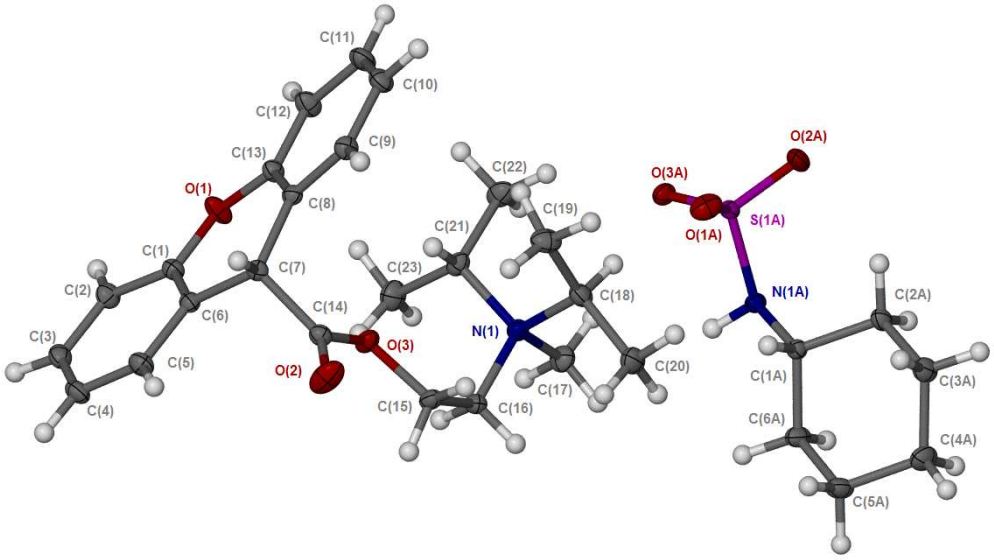

Figure 3a. The asymmetric unit of *propantheline cyclamate* shown with 50 % thermal ellipsoids, hydrogen atoms as spheres of arbitrary size and numbering scheme.

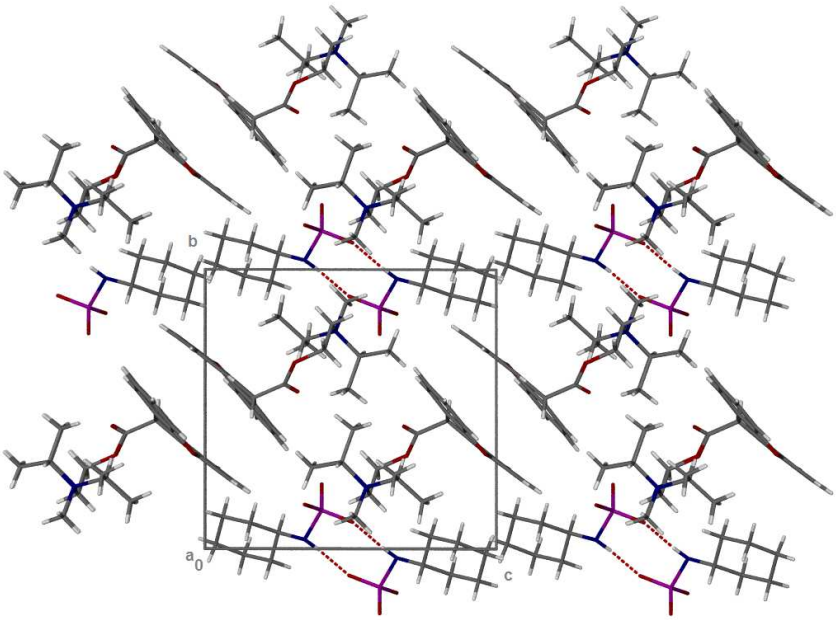

Figure 3b. Packing diagram of *propantheline cyclamate* viewed down the *a*-axis with hydrogen bonding indicated by dashed red lines.

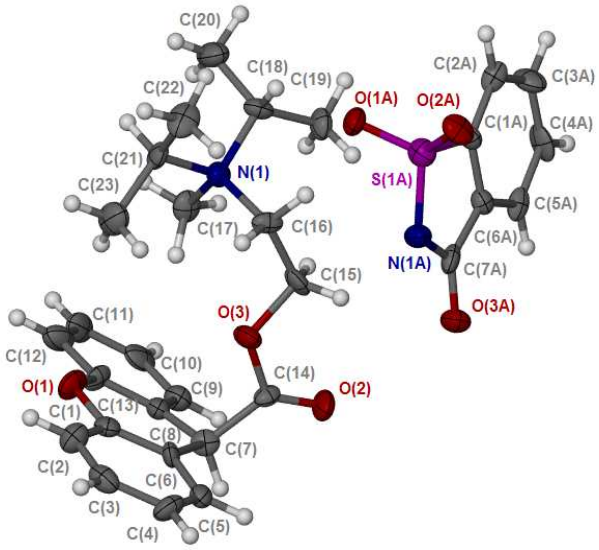

Figure 4a. The asymmetric unit of *propantheline saccharinate* shown with 50 % thermal ellipsoids, hydrogen atoms as spheres of arbitrary size and numbering scheme.

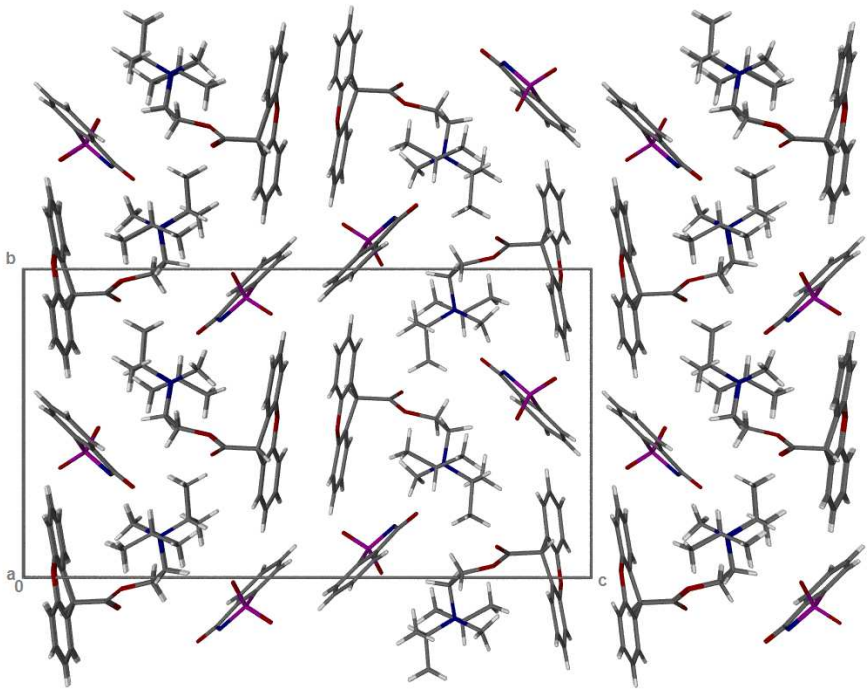

Figure 4b. Packing diagram of *propantheline saccharinate* viewed down the *a*-axis with hydrogen bonding indicated with dashed red lines.