Supplementary Material (ESI) for Organic and Biomolecular Chemistry

Electronic Supplementary Information (ESI)

Multipolar Interactions in the D-Pocket of Thrombin: Large Differences between Tricyclic Imide and Lactam Inhibitors†

Eliane Schweizer,[a] Anja Hoffmann-Röder,[b] Jacob A. Olsen,[a] Paul Seiler,[a] Ulrike Obst-Sander,[c] Björn Wagner,[c] Manfred Kansy,[c] David W. Banner*[c] and François Diederich*[a]

[a] *Laboratorium für Organische Chemie, ETH-Zürich, Hönggerberg HCI, CH-8093 Zürich, Switzerland. Fax +41 44 6321109; Tel. +41 44 6322992; E-mail: diederich@org.chem.ethz.ch*

[b] *Institut für Organische Chemie, Johannes Gutenberg-Universität, Duesbergweg 10-14, D-55128 Mainz, Germany.*

[c] *Pharma Division, Präklinische Forschung, F. Hoffmann-La Roche AG, CH-4070 Basel, Switzerland.*

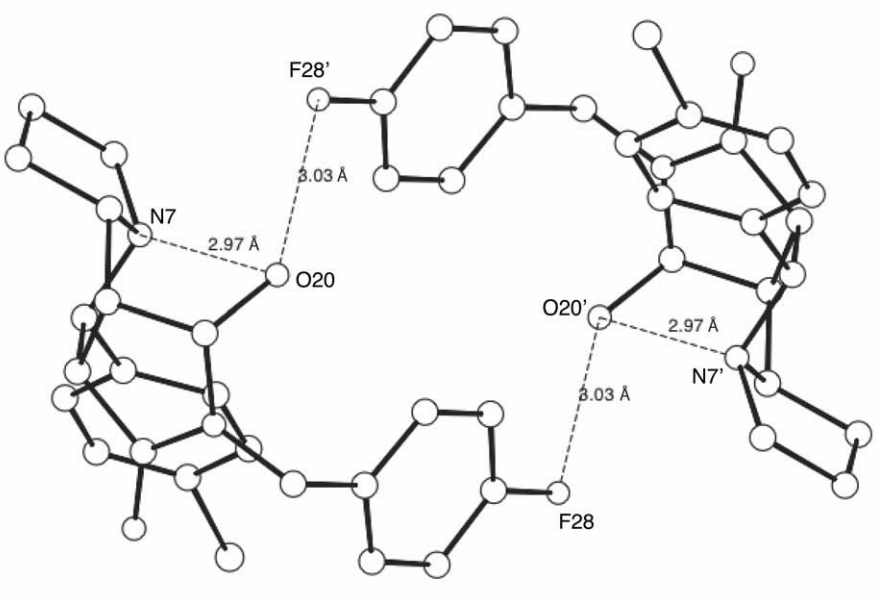

Figure 1 ESI. Crystal packing of (±)-**29**, showing short intermolecular F···O and intramolecular O···N distances.

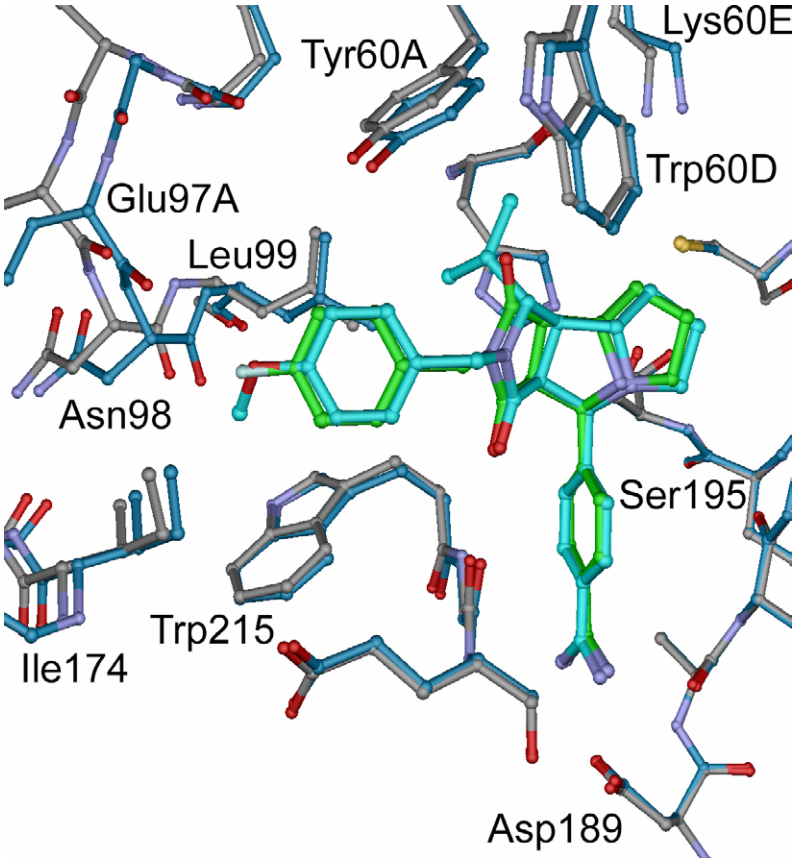

Figure 2 ESI. Overlay of the co-crystal structures of (±)-**1** (PDB-Code: 1OYT, J. Olsen et al., *Angew. Chem. Int. Ed.*, 2003, **42**, 2507-2511) and (±)-**13** (PDB-Code: 2CF9). While the protein residues lining the S1-pocket and the catalytic centre are perfectly superimposable, a slight shift of the amino acids of the D-pocket is observed upon insertion of an isopropyl group in the P-pocket. Color code: C-skeleton of (±)-**1**: *green*, C-skeleton of (±)-**13**: *cyan*, C-skeleton of the protein in complex with (±)-**1**: *blue*, C-skeleton of the protein in complex with (±)-**13**: *grey*, O-atoms: *red*, N-atoms: *blue*, S-atom: *yellow*.

Synthesis ESI

1-(4-Methoxybenzyl)pyrrole-2,5-dione (14)[8a]

General procedure A, starting from 4-methoxybenzylamine (25.0 g, 182 mmol), maleic anhydride (17.9 g, 182 mmol), DMF (0.14 cm^3), oxalyl chloride (17.2 cm^3, 200 mmol) and Et_3N (38.4 cm^3, 237 mmol) in CH_2Cl_2 (500 cm^3), gave **14** as a yellowish powder (23.8 g, 60%); mp 103–105 °C (lit.,[8a] 100.5–102 °C); ν_{max}/cm^{-1} (neat) 3097, 2948, 2840, 1733, 1698, 1610, 1513, 1470, 1438, 1406, 1385, 1348, 1339, 1303, 1292, 1244, 1176, 1147, 1106, 1040; δ_H(300 MHz; $CDCl_3$) 3.76 (3 H), 4.60 (2 H, s), 6.67 (2 H, s), 6.82, 7.27 (4 H, AA'BB', *J* 8.7); δ_C(75 MHz; $CDCl_3$) 41.1, 55.5, 114.2, 128.7, 130.1, 134.4, 159.4, 170.7; MALDI-HR-MS calcd for $C_{12}H_{11}NNaO_3^+$ ([*M*+Na]$^+$): 240.0631; found: 240.0627.

1-Pyridin-4-ylmethylpyrrole-2,5-dione (15)[8b]

To a soln. of maleic anhydride (2.5 g, 25.5 mmol) in dry CH_2Cl_2 (50 cm^3) under Ar, 4-pyridylmethylamine (2.76 g, 25.5 mmol) was added dropwise and the mixture stirred for 2 h at 25 °C, before the solvent was removed in vacuo. The residue was dissolved in CH_3CN (80 cm^3) and Et_3N (7.1 cm^3, 51 mmol) and Me_3SiCl (3.2 cm^3, 25.5 mmol) were added. The mixture was stirred for 1 h at 80 °C, allowed to reach 25 °C, filtered through a plug of SiO_2 and concentrated in vacuo to give coulorless crystals of **15** (2.11 g, 44%); mp 128–130 °C; ν_{max}/cm^{-1} (neat) 3109, 2946, 1694, 1601, 1435, 1408, 1386, 1362, 1345, 1310, 1245, 1135, 1032; δ_H(300 MHz; $CDCl_3$) 4.62 (2 H, s), 6.73 (2 H, s), 7.15, 8.50 (4 H, AA'BB', *J* 6.0); δ_C(75 MHz; $CDCl_3$) 40.1, 122.6, 134.2, 144.5, 150.1, 170.0; MALDI-HR-MS calcd for $C_{10}H_9N_2O_2^+$ ([*M*+H]$^+$): 189.0659; found: 189.0659.

1-(4-Bromobenzyl)pyrrole-2,5-dione (23)[12]

General procedure A, starting from 4-bromobenzylamine (2.2 g, 11.8 mmol), maleic anhydride (1.2 g, 11.8 mmol), DMF (0.01 cm^3), oxalyl chloride (1.1 cm^3, 13.0 mmol) and Et_3N (2.5 cm^3, 17.7 mmol) in CH_2Cl_2 (40 cm^3), gave **23** as a yellowish solid (2.6 g, 82%); mp 75–78 °C; ν_{max}/cm^{-1} (neat) 3107, 1705, 1585, 1488, 1434, 1403, 1383, 1322, 1152, 1074, 1008; δ_H(300 MHz; $CDCl_3$) 4.58 (2 H, s), 6.68 (2 H, s), 7.18, 7.38 (4 H, AA'BB', *J* 8.4); δ_C(75 MHz; $CDCl_3$) 40.6, 122.2, 130.1, 131.8, 134.1, 135.0, 170.1; EI-HR-MS calcd for $C_{11}H_8BrNO_2^+$ (M^+): 264.9733; found: 264.9735.

1-(4-Chlorobenzyl)-pyrrole-2,5-dione (37)

General procedure A, starting from 4-chlorobenzylamine (5.0 g, 35 mmol), maleic anhydride (3.4 g, 35 mmol), DMF (0.02 cm^3), oxalyl chloride (3.4 cm^3, 39 mmol) and Et_3N (7.3 cm^3, 53 mmol) in CH_2Cl_2 (80 cm^3), gave **37** as a yellowish solid (6.4 g, 82%); mp 79–81 °C; ν_{max}/cm^{-1} (neat) 3101, 1698, 1491, 1438, 1404, 1390, 1363, 1325, 1154, 1088, 1015; δ_H(300 MHz; $CDCl_3$) 4.61 (2 H, s), 6.69 (2 H, s), 7.26–7.30 (4 H, m); δ_C(75 MHz; $CDCl_3$) 40.7, 128.7, 128.8, 129.7, 130.2, 134.1, 170.0; EI-HR-MS calcd for $C_{11}H_8ClNO_2^+$ (M^+): 221.0239; found: 221.0241.