Supporting Information

Factor Xa Inhibitors: S1 Binding Interactions of a Series of *N*-{(*3S*)-1-[(*1S*)-1-Methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}sulfonamides*

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*PDB ID codes for **1a**, **1b**, **1d**, **1e** and **1x** complexed with factor Xa are 2cji, 2j95, 2j38, 2j34 and 2j94 respectively.

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Analytical Data for Sulfonamides 1

1a: For $C_{21}H_{24}ClN_3O_5S$. $0.55HCO_2H$, Calcd: C 52.69%, H 5.15%, N 8.55%; found: C 52.63%, H 5.19%, N 8.32%.

1b: For $C_{19}H_{22}ClN_3O_5S_3$. $0.5H_2O$, Calcd: C 44.48%, H 4.52%, N 8.19%; found: C 44.77%, H 4.41%, N 7.89%.

1c: For $C_{19}H_{24}ClN_3O_5S$. $0.6H_2O$, Calcd: C 50.41%, H 5.61%, N 9.28%; found: C 50.50%, H 5.47%, N 8.95%.

1d: For $C_{19}H_{22}ClN_3O_5S_2$. $0.6H_2O$, Calcd: C 47.27%, H 4.84%, N 8.70%; C 47.29%, H 4.68%, N 8.36%.

1e: For $C_{19}H_{22}ClN_3O_5S_2$. $0.5H_2O$, Calcd: C 47.45%, H 4.82%, N 8.74%; found: C 47.59%, H 4.78%, N 8.60%.

1f: For $C_{17}H_{22}ClN_3O_5S_2$, Calcd: C 45.58%, H 4.95%, N 9.38%; found: C 45.33%, H 4.90%, N 9.20%.

1g: For $C_{22}H_{27}N_3O_5S$. $0.9H_2O$, Calcd: C 57.23%, H 6.29%, N 9.10%; found: C 57.12%, H 6.06%, N 8.76%.

1h: For $C_{17}H_{20}ClN_3O_5S_3$. $1.0H_2O$, Calcd: C 41.17%, H 4.47%, N 8.47%; found: C 41.29%, H 4.26%, N 8.39%.

1i: HRMS for $C_{19}H_{23}N_3O_5ClS$, m/z (MH^+) calc. 442.1203; measured 442.1213. LC-MS: t_R 2.70mins, 98% purity; *m/z* (ES) 442/444 MH^+, 440/442 $(M-H)^-$.

1j: For $C_{18}H_{21}ClN_4O_5S_2$. $0.8H_2O$, Calcd: C 44.36%, H 4.67%, N 11.50%; found: C 44.50%, H 4.51%, N 11.15%.

1k: For $C_{18}H_{21}ClN_4O_5S_2$. 0.5Dioxan, Calcd: C 46.46%, H 4.87%, N 10.84%; found: C 46.69%, H 5.04%, N 10.62%.

1l: For $C_{18}H_{21}ClN_4O_5S_2$. $0.3H_2O$, Calcd: C 45.19%, H 4.55%, N 11.71%; found: C 45.39%, H 4.41%, N 11.42%.

1m: For $C_{17}H_{20}ClN_5O_5S_3$. $0.53HCO_2H$, Calcd: C 39.70%, H 4.00%, N 13.20%; found: C 40.09%, H 4.04%, N 12.83%.

1n: HRMS: For $C_{18}H_{21}ClN_4O_5S_3$, m/z (MH^+) calcd. 505.0441; measured: 505.0431. LC-MS: t_R 2.83mins, 95% purity; *m/z* (ES) 505/507 MH^+, 503/505 $(M-H)^-$.

1o: For $C_{19}H_{22}ClN_3O_6S$. $0.5H_2O$, Calcd: C 49.09%, H 4.99%, N 9.04%; found: C 49.22%, H 4.94%, N 8.85%.

1p: For $C_{19}H_{22}ClN_3O_6S$. $0.8H_2O$, Calcd: C 48.52%, H 5.06%, N 8.93%; found: C 48.72%, H 4.74%, N 8.62%.

1q: HRMS: For $C_{18}H_{21}ClN_4O_5S_2$, m/z (MH^+) calcd. 473.0720; measured: 473.0719. LC-MS: t_R 2.98mins, 98% purity; *m*/*z* (ES) 473MH^+.

1r: For $C_{18}H_{21}ClN_4O_5S_2$. 0.6HCO_2H, Calcd: C 44.63%, H 4.47%, N 11.19%; found: C 44.56%, H 4.43%, N 10.93%.

1s: HRMS: For $C_{19}H_{23}ClN_4O_5S$, m/z (MH^+) calcd. 455.1156; measured: 455.1158. LC-MS: t_R 2.95mins, 96% purity; *m*/*z* (ES) 455/457 MH^+, 453/455 $(M-H)^-$.

1t: HRMS: For $C_{19}H_{24}{}^{35}ClN_4O_5S$, m/z ($MH^+$) calc. 455.1156; measured: 455.1160. LC-MS: t_R 2.84mins, 98% purity; *m*/*z* (ES) 455/457 MH^+, 453/455 $(M-H)^-$.

1u: For $C_{19}H_{22}ClN_3O_6S_2$. 0.55HCO_2H, Calcd: C 45.75%, H 4.54%, N 8.19%; found: C 45.66%, H 4.44%, N 7.87%.

1v: For $C_{18}H_{21}ClN_4O_5S_3$. 0.6H_2O, Calcd: C 41.91%, H 4.34%, N 10.86%; found: C 41.99%, H 4.25%, N 10.61%.

1w: For $C_{18}H_{21}ClN_4O_5S_3$. 0.5H_2O, Calcd: C 42.06%, H 4.31%, N 10.90%; found: C 42.35%, H 4.27%, N 10.34%.

1x: For $C_{17}H_{21}ClN_6O_5S_2$. 1.2H_2O, Calcd: C 39.99%, H 4.62%, N 16.46%; found: C 40.09%, H 4.38%, N 16.24%.

1y: For $C_{20}H_{23}ClN_4O_5S_2$. 0.5H_2O, Calcd: C 47.29%, H 4.76%, N 11.03%; found: C 47.32%, H 4.65%, N 10.85%.

Other Spectroscopic and Analytical Data

6-Chloro-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}naphthalene-2-sulfonamide 1a

1a (124mg, 62%) was synthesized from **2** (104mg, 0.43mmol) and 6-chloro-2-naphthalenesulfonyl chloride[13(a)] (1.1 eq., 124mg, 0.475mmol) using **Method A** under General Procedures. ^{1}H-NMR:δ($CDCl_3$) 1.27 (d, 3H, J = 7Hz), 1.70 -2.10 (m, 1H), 2.56-2.65 (m, 1H), 3.24-3.33 (m, 1H), 3.41-3.78 (m, 9H), 3.75 (ddd, 1H, J = 11, 8 and 3Hz), 4.99 (q, 1H, J = 7Hz), 5.36 (bd, 1H, J = 3 Hz), 7.57 (dd, 1H, J = 9 and 2Hz), 7.89-7.95 (m, 4H), 8.45 (s, 1H). LC-MS: t_R 2.98mins; *m*/*z* (ES) 466/468 MH^+, 464/466 $(M-H)^-$. Anal. ($C_{21}H_{24}ClN_3O_5S$. $0.55CH_2O_2$): C, H, N.

5'-Chloro-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}-2,2'-bithiophene-5-sulfonamide 1b

1b (299mg, 54%) as a light brown solid was synthesized from **2** (267mg, 1.11mmol) and 5'-chloro-2,2'-bithiophene-5-sulfonyl chloride[14] (1.05eq., 349mg, 1.17mmol) using **Method A** under General Procedures. ^{1}H-NMR: δ($CDCl_3$) 1.33 (d, 3H, J = 7Hz), 2.03 -2.15 (m, 1H), 2.60-2.68 (m, 1H), 3.31-3.39 (m, 1H), 3.44-3.73 (m, 9H), 3.89 (ddd, 1H, J = 10.5, 8 and 2.5Hz), 5.04 (q, 1H, J = 7Hz), 5.65 (bd, 1H, J = 3 Hz), 6.89 (dd, 1H, J = 4Hz), 7.04-7.05 (m, 2H), 7.55 (d, 1H, J = 4Hz). LC-MS: t_R 3.16mins; *m*/*z* (ES) 504/506 MH^+, 502/504 $(M-H)^-$. Anal. ($C_{19}H_{22}ClN_3O_5S_3$. $0.5H_2O$): C, H, N.

(*E*)-2-(4-Chlorophenyl)-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}ethenesulfonamide 1c

1c (950mg, 52%) as a white powder was synthesized from **2** (1g, 4.14mmol) and (*E*)-2-(4-chlorophenyl)ethenesulfonyl chloride[13(b)] (1.2 eq., 1.178g, 4.97mmol) using **Method A** under General Procedures. ^{1}H-NMR: δ($CDCl_3$) 1.34 (d, 3H, J = 7Hz), 1.99 -2.13 (m, 1H), 2.59-2.68 (m, 1H), 3.30-3.39 (m, 1H), 3.44-3.73 (m, 9H), 3.89 (bt, 1H, J = 10Hz), 5.05 (q, 1H, J = 7Hz), 5.12 (bs, 1H), 6.87 (d, 1H, J = 15.5Hz), 7.39 (d, 1H, J = 8.5Hz), 7.44 (d, 1H, J = 8.5Hz), 7.47 (d, 1H, J = 15.5Hz). LC-MS: t_R 2.87mins; *m*/*z* (ES) 442/444 MH^+, 440/442 $(M-H)^-$. Anal. ($C_{19}H_{24}ClN_3O_5S$. $0.6H_2O$): C, H, N.

5-Chloro-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}-1-benzothiophene-2-sulfonamide 1d

1d (1.8g, 65%) was synthesized from **2** (2.08g, 8.62mmol) and 5-chloro-1-benzothiophene-2-sulfonyl chloride[14] (1.2 eq., 2.75g, 10.3mmol) using **Method A** under General Procedures. ^{1}H-NMR:δ($CDCl_3$) 1.31 (d, 3H, J = 7Hz), 2.04 -2.16 (m, 1H), 2.63-2.72 (m, 1H), 3.30-3.39 (m, 1H), 3.44-3.73 (m, 9H), 3.86-3.94 (m, 1H), 5.01 (q, 1H, J = 7Hz), 5.49 (bs, 1H), 7.47 (dd, 1H, J = 9 and 2Hz), 7.79 (d, 1H, J = 8.5Hz), 7.85-7.90 (m, 2H). LC-MS: t_R 2.87mins; *m*/*z* (ES) 472/474 MH^+, 470/472 $(M-H)^-$. Anal. ($C_{19}H_{22}ClN_3O_5S_2$. $0.6H_2O$): C, H, N.

6-Chloro-N-{(3*S*)-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}-1-benzothiophene-2-sulfonamide 1e

1e (1g, 51%) as a white powder was synthesized from **2** (1g, 4.41 mmol) and 6-chloro-1-benzothiophene-2-sulfonyl chloride[14] (1.2 eq., 1.328g, 4.97mmol) using **Method A** under General Procedures. ^{1}H-NMR: δ($CDCl_3$) 1.31 (d, 3H, J = 7Hz), 2.03 -2.16 (m, 1H), 2.64-2.72 (m, 1H), 3.31-3.39 (m, 1H), 3.44-3.74 (m, 9H), 3.90 (ddd, 1H, J = 10.5, 8 and 2.5Hz), 5.02 (q, 1H, J = 7Hz), 5.49 (bd, 1H, J = 2.5Hz), 7.45

(dd, 1H, J = 8.5 and 2Hz), 7.82 (d, 1H, J = 8.5Hz), 7.86 (bs, 1H), 7.90 (s, 1H). LC-MS: t_R 2.87mins; *m/z* (ES) 472/474 MH^+, 470/472 $(M-H)^-$. Anal. ($C_{19}H_{22}ClN_3O_5S_2$. $0.5H_2O$): C, H, N.

6-Methyl-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-(4-morpholinyl)-2-oxoethyl]-2-oxo-3-pyrrolidinyl}-2-naphthalenesulfonamide 1g

1g (62mg, 84%) as a white foam was synthesized from **2** (39.9mg, 0.165mmol) and 6-methyl-2-naphthalenesulfonyl chloride[13(d)] (42mg, 0.17mmol) using **Method A** under General Procedures. ^{1}H-NMR:δ($CDCl_3$) 1.27 (d, 3H, J = 7Hz), 1.97 -2.10 (m, 1H), 2.56-2.64 (m, 1H), 2.57 (s, 3H), 3.24-3.33 (m, 1H), 3.42-3.76 (m, 10H), 5.00 (q, 1H, J = 7Hz), 5.30-5.53 (bs, 1H), 7.46 (d, 1H, J = 8.5Hz), 7.69 (s, 1H), 7.81-7.92 (m, 3H), 8.42 (s, 1H). LC-MS: t_R 2.79mins; *m/z* (ES) 446 MH^+, 444 $(M-H)^-$. Anal. ($C_{22}H_{27}N_3O_5S.0.9H_2O$): C, H, N.

5-Chloro-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-(4-morpholinyl)-2-oxoethyl]-2-oxo-3-pyrrolidinyl}thieno[3,2-*b*]thiophene-2-sulfonamide 1h

Using **Method A** under General Procedures, **1h** (39.5mg, 20%) was synthesized from **2** (100mg, 0.41mmol) and crude 5-chlorothieno[3,2-*b*]thiophene-2-sulfonyl chloride (226mg, assumed 0.83mmol), prepared from 2-chlorothieno[3,2-b]thiophene [Bugge, A. Electrophilic substitution of thieno[2,3-b]thiophene and thieno[3,2-b]thiophene. Quantitative study. *Chem. Scr.* **1972**, *2(3)*, 137-42.] (150mg, 0.86mmol) using **Method B** under General Procedures. ^{1}H-NMR: δ(d^4-MeOH) 1.44 (d, 3H, J = 7Hz), 1.92-2.05 (m, 1H), 2.46-2.67 (m, 1H), 3.48-3.55 (m, 2H), 3.63-3.86 (m, 8H), 4.37 (dd, 1H, J = 10 and 8.5Hz), 5.18 (q, 1H, J = 7Hz), 7.58 (s, 1H), 8.07 (s, 1H). LC-MS: t_R 2.85mins; *m/z* (ES) 478/480 MH^+, 476/478 $(M-H)^-$. Anal. ($C_{17}H_{20}ClN_3O_5S_3$. $1.0H_2O$): C, H, N.

5-Chloro-N-{(3S)-1-[(1S)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}thieno[3,2-b]pyridine-2-sulfonamide 1j

1j was synthesized from **2** and 5-chlorothieno[3,2-*b*]pyridine-2-sulfonyl chloride[14] using **Method A** under General Procedures. ^{1}H-NMR: δ(d^4-MeOH) 1.25 (d, 3H, J = 7Hz), 1.78-1.91 (m, 1H), 2.36-2.45 (m, 1H), 3.31-3.37 (m, 2H), 3.43-3.68 (m, 8H), 4.31 (dd, 1H, J = 10.5 and 8.5Hz), 4.97 (q, 1H, J = 7Hz), 7.52 (d, 1H, J = 8.6Hz), 8.00 (s, 1H), 8.44 (d, 1H, J = 8.6Hz). LC-MS: t_R 2.56mins; *m/z* (ES) 473/475 MH^+, 471/473 $(M-H)^-$. Anal. ($C_{18}H_{21}ClN_4O_5S_2$. $0.8H_2O$): C, H, N.

5-Chloro-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}thieno[2,3-b]pyridine-2-sulfonamide 1k

1k (66mg, 45%) was synthesized from **2** (75mg, 0.311mmol) and 5-chlorothieno[2,3-*b*]pyridine-2-sulfonyl chloride[15(a)] (100mg, 0.737mmol) using **Method A** under General Procedures. ^{1}H-NMR: δ($CDCl_3$) 1.32 (d, 3H, J = 7Hz), 2.03 -2.17 (m, 1H), 2.63-2.73 (m, 1H), 3.31-3.39 (m, 1H), 3.44-3.75 (m, 9H), 3.93-4.00 (m, 1H), 5.01 (q, 1H, J = 7Hz), 5.57 (d, 1H, J = 3.3Hz), 7.82 (s, 1H), 8.16 (d, 1H, J = 2.3Hz), 8.65 (d, 1H, J = 2.3Hz). LC-MS: t_R 2.64mins; *m/z* (ES) 473/475 MH^+, 471/473 $(M-H)^-$. Anal. ($C_{18}H_{21}ClN_4O_5S_2.0.5C_4H_8O_2$): C, H, N.

6-Chloro-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-(4-morpholinyl)-2-oxoethyl]-2-oxo-3-pyrrolidinyl}thieno[3,2-*b*]pyridine-2-sulfonamide 1l

1l (80mg, 37%) was synthesized from **2** (110mg, 0.46mmol) and 6-chlorothieno[3,2-*b*]pyridine-2-sulfonyl chloride[15(b)] (crude, 177mg) using **Method A** under General

Procedures. ^{1}H-NMR:δ($CDCl_3$) 1.32 (d, 3H, J = 7Hz), 2.04 -2.16 (m, 1H), 2.62-2.72 (m, 1H), 3.30-3.40 (m, 1H), 3.44-3.72 (m, 9H), 3.97 (ddd, 1H, J = 10.5, 8 and 3Hz), 5.02 (q, 1H, J = 7Hz), 5.98 (d, 1H, J = 3Hz), 8.09 (s, 1H), 8.20 (d, 1H, J = 2.3Hz), 8.73 (d, 1H, J = 2.3Hz). LC-MS: t_R 2.59mins; *m*/*z* (ES) 473/475 MH^+, 471/473 $(M-H)^-$. Anal. ($C_{18}H_{21}ClN_4O_5S_2.0.3H_2O$): C, H, N.

5-(5-Chloro-1,3,4-thiadiazol-2-yl)-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}thiophene-2-sulfonamide 1m

1m (9mg, 20%) was synthesized from **2** (22.5mg, 0.09mmol) and 5-(5-chloro-1,3,4-thiadiazol-2-yl)-2-thiophenesulfonyl chloride (78mg, 0.26mmol) using **Method A** under General Procedures. ^{1}H-NMR:δ($CDCl_3$) 1.32 (d, 3H, J = 7Hz), 2.02 -2.18 (m, 1H), 2.62-2.71 (m, 1H), 3.30-3.40 (m, 1H), 3.45-3.73 (m, 9H), 3.93 (dd, 1H, J = 10.5 and 8 Hz), 5.03 (q, 1H, J = 7Hz), 5.62 (bs, 1H), 7.66 (d, 1H, J = 4Hz), 7.81 (d, 1H, J = 4Hz). LC-MS: t_R 2.82mins; *m*/*z* (ES) 506/508 MH^+, 504/506 $(M-H)^-$. Anal. ($C_{17}H_{20}ClN_5O_5S_3.0.53CH_2O_2$): C, H, N.

6-Chloro-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-(4-morpholinyl)-2-oxoethyl]-2-oxo-3-pyrrolidinyl}-1-benzofuran-2-sulfonamide 1o

1o (78mg, 44%) as a white solid was synthesized from **2** (93mg, 0.385mmol) and 6-chloro-1-benzofuran-2-sulfonyl chloride[16] (crude, 116mg) using **Method A** under General Procedures. ^{1}H-NMR: δ($CDCl_3$) 1.32 (d, 3H, J = 7Hz), 2.01 -2.14 (m, 1H), 2.62-2.72 (m, 1H), 3.35 (td, 1H, J = 10 and 6Hz), 3.43-3.74 (m, 9H), 3.98-4.06 (m, 1H), 5.01 (q, 1H, J = 7Hz), 5.74 (bd, 1H, J = 3.5Hz), 7.34 (dd, 1H, J = 8.5 and 2Hz), 7.42 (d, 1H, J = 1Hz), 7.59 (overlapped with part of doublet at 7.60, 1H), 7.60 (d, 1H, J = 8.5Hz). LC-MS: t_R 2.87mins; *m*/*z* (ES) 456/458 MH^+, 454/456 $(M-H)^-$. Anal. ($C_{19}H_{22}ClN_3O_6S.0.5H_2O$), C, H, N.

5-Chloro-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-(4-morpholinyl)-2-oxoethyl]-2-oxo-3-pyrrolidinyl}-1-benzofuran-2-sulfonamide 1p

1p (0.043g) as a white solid was synthesized from **2** (0.077g) and 5-chloro-1-benzofuran-2-sulfonyl chloride[16] (0.043g) using **Method A** under General Procedures. ^{1}H-NMR:δ(d^4-MeOH) 1.25 (d, 3H, J = 7Hz), 1.78-1.91 (m, 1H), 2.34-2.43 (m, 1H), 3.31-3.38 (m, 2H), 3.42-3.68 (m, 8H), 4.28 (dd, 1H, J = 10.6 and 8.6Hz), 4.97 (q, 1H, J = 7Hz), 7.44-7.50 (m, 2H), 7.59 (d, 1H, J = 9Hz), 7.76 (d, 1H, J = 2Hz). LC-MS: t_R 2.73mins; *m*/*z* (ES) 456/458 MH^+, 454/456 $(M-H)^-$. Anal. ($C_{19}H_{22}ClN_3O_6S.0.8H_2O$): C, H, N.

5-Chloro-N-{(3*S*)-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}-1,3-benzothiazole-2-sulfonamide 1r

(3*S*)-3-{[(5-Chloro-1,3-benzothiazol-2-yl)thio]amino}-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]pyrrolidin-2-one (1.56g, 71%) was prepared from **2** (1.19g, 4.95mmol) and 5-chloro-1,3-benzothiazole-2(3*H*)-thione[22] (1g, 4.96mmol) in a similar manner to (3*S*)-3-{[(6-chloro-1,3-benzothiazol-2-yl)thio]amino}-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]pyrrolidin-2-one (the 6-chloro-analogue). ^{1}H-NMR: δ($CDCl_3$) 1.35 (d, 3H, J = 6.8Hz), 2.07 -2.19 (m, 1H), 2.41-2.51 (m, 1H), 3.31-3.46 (m, 2H), 3.49-3.78 (m, 8H), 4.04 (ddd, 1H, J = 11.6, 8.3 and 3.5Hz), 4.81 (d, 1H, J = 3.5Hz), 5.11 (q, 1H, J = 6.8Hz), 7.28 (dd, 1H, J = 8 and 2Hz), 7.70 (d, 1H, J = 8Hz), 7.81 (d, 1H, J = 1.8Hz). LC-MS: t_R 2.88mins;*m*/*z* (ES) 441/443 MH^+, 439/441 $(M-H)^-$.

1r (84mg, 5%) was synthesized from 3(*S*)-3-{[(5-chloro-1,3-benzothiazol-2-yl)thio]amino}-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]pyrrolidin-2-one (1.5g, 3.4mmol) using procedure as described for **1q**. ^{1}H-NMR: δ(d^4-MeOH) 1.25 (d, 3H, J = 7Hz), 1.84-1.96 (m, 1H), 2.40-2.50 (m, 1H), 3.32-3.39 (m, 2H), 3.40-3.68 (m, 8H), 4.43 (dd, 1H, J = 10.4 and 8.6Hz), 4.95 (q, 1H, J = 7Hz), 7.60 (dd, 1H, J = 8.6 and 2Hz), 8.11 (d, 1H, J = 8.6Hz), 8.15 (d, 1H, J = 2Hz). LC-MS: t_R 2.76mins; *m*/*z* (ES) 473/475 MH^+, 471/473 $(M-H)^-$. Anal. ($C_{18}H_{21}ClN_4O_5S_2$. $0.6CH_2O_2$): C, H, N.

6-Chloro-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}-1*H*-indole-2-sulfonamide 1t

t-Butyl 6-chloro-2-[({(3*S*)-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}amino)sulfonyl]-1*H*-indole-1-carboxylate (28.5mg, 12.5%) was synthesized from **2** (100mg, 0.41mmol) and 1,1-dimethylethyl 6-chloro-2-(chlorosulfonyl)-1*H*-indole-1-carboxylate[17] (174mg, 0.50mmol) using **Method A** under General Procedures. ^{1}H-NMR: δ(d^4-MeOH) 1.25 (d, 3H, J = 7Hz), 1.74 (s, 9H), 1.97-2.09 (m, 1H), 2.45-2.54 (m, 1H), 3.32-3.41 (m, 2H), 3.45-3.68 (m, 8H), 4.17 (dd, 1H, J = 10.5 and 8Hz), 4.97 (q, 1H, J = 7Hz), 7.33 (dd, 1H, J = 8 and 2Hz), 7.61 (s, 1H), 7.68 (d, 1H, J = 8Hz), 8.12 (s, 1H). LC-MS: t_R 3.32mins; *m*/*z* (ES) 555/557 MH^+, 553/555 $(M-H)^-$.

1t (14.8mg, 69.5%) was prepared from *t*-butyl 6-chloro-2-[({(3*S*)-1-[(1*S*)-1-methyl-2-morpholin-4-yl-2-oxoethyl]-2-oxopyrrolidin-3-yl}amino)sulfonyl]-1*H*-indole-1-carboxylate (26mg, 0.047mmol) using procedure as described for **1s**. ^{1}H-NMR: δ(d^4-MeOH) 1.27 (d, 3H, J = 7Hz), 1.75-1.87 (m, 1H), 2.29-2.39 (m, 1H), 3.28-3.33 (m, 2H), 3.44-3.68 (m, 8H), 4.24 (dd, 1H, J = 10 and 9Hz), 5.02 (q, 1H, J = 7Hz), 7.05 (s, 1H), 7.10 (dd, 1H, J = 8.6 and 1Hz), 7.46 (s, 1H), 7.61 (d, 1H, J = 8.6Hz). LC-MS: t_R 2.84mins, 98% purity; *m*/*z* (ES) 455/457 MH^+, 453/455 $(M-H)^-$. HRMS: For $C_{19}H_{24}{}^{35}ClN_4O_5S$, m/z ($MH^+$) calc. 455.1156; measured: 455.1160.

6-(5-Chloro-2-thienyl)-*N*-{(3*S*)-1-[(1*S*)-1-methyl-2-(4-morpholinyl)-2-oxoethyl]-2-oxo-3-pyrrolidinyl}-3-pyridinesulfonamide 1y

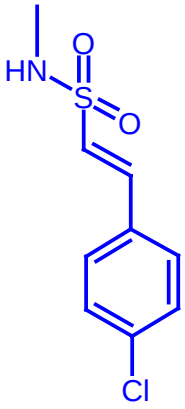
6-(5-Chloro-2-thienyl)-3-pyridinesulfonyl chloride **6y** (crude, 473mg) as an orange gum was prepared from 5-bromo-2-(5-chloro-2-thienyl)pyridine[18] (403mg, 1.47mmol) using **Method B**, except that *t*-BuLi (1.7M in hexanes, 1.05 eq., 0.91mL, 1.54mmol) was used instead of *n*-BuLi, under General Procedures and used without further purification.

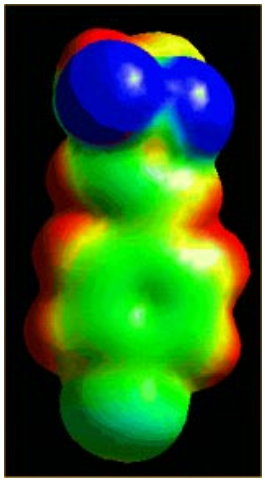
1y (71mg, 33%) as a white solid was synthesized from **2** (104.6mg, 0.434mmol) and 6-(5-chloro-2-thienyl)-3-pyridinesulfonyl chloride **6y** (crude, 153mmol) using **Method A** under General Procedures. ^{1}H-NMR: δ($CDCl_3$) 1.32 (d, 3H, J = 7Hz), 1.97 -2.10 (m, 1H), 2.57-2.67 (m, 1H), 3.33 (td, 1H, J = 10 and 6Hz), 3.43-3.74 (m, 9H), 3.85 (bt, 1H, J = 8.1Hz), 5.00 (q, 1H, J = 7Hz), 5.54 (bs, 1H), 6.98 (d, 1H, J = 4Hz), 7.47 (d, 1H, J = 4Hz), 7.69 (d, 1H, J = 8.6Hz), 8.16 (dd, 1H, J = 8.6 and 2Hz), 8.98 (d, 1H, J = 2Hz). LC-MS: t_R 2.95mins; *m*/*z* (ES) 499/501 MH^+, 497/499 $(M-H)^-$. Anal. ($C_{20}H_{23}ClN_4O_5S_2.0.5H_2O$): C, H, N.

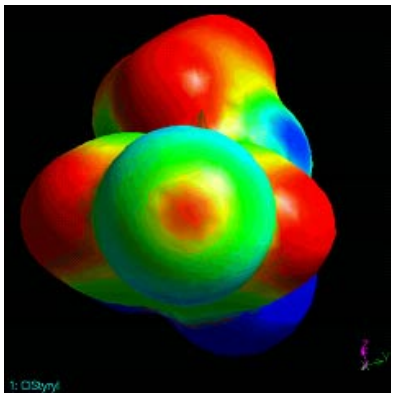
Electrostatic Potential Maps of selected chloro-(hetero)aryl N-methylsulfonamides

Ab initio calculations were carried out on *N*-methyl chloro(hetero)arylsulfonamides, as model systems of a series of arylsulfonamides 1, using Gaussian 94 with HF method, 6-31 G(d) basis set and full geometry optimisation in Cerius[2]. ESPD charges were computed and electrostatic potential (esp) energy range ±20 kcal/mol were mapped onto electron density surfaces. Electrostatic potential maps of selected *N*-methyl chloro(hetero)arylsulfonamides are depicted below (Figure I) and show clearly a slight positive charge at the centre of the chlorine atoms (view B). Similar esp maps were observed with other chloro-(hetero)aryl N-methylsulfonamides.

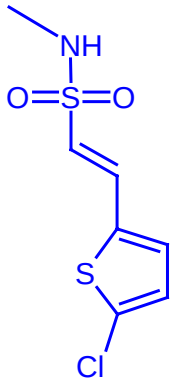
P1 group in 1c:

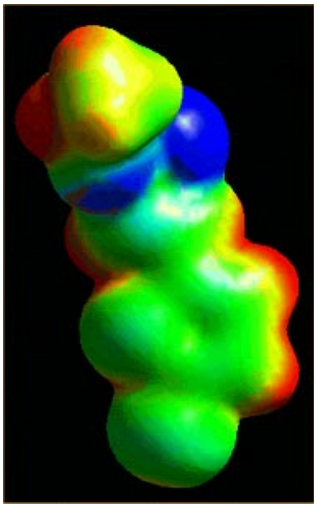


A. 

B. 

P1 group in 1f:



A. 

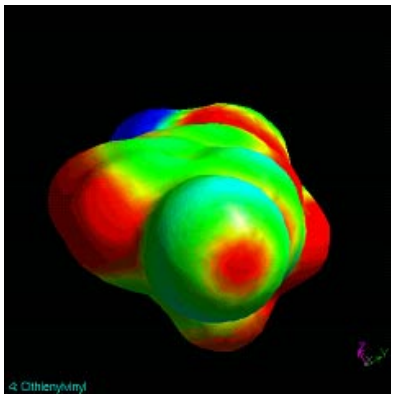
B. 

Figure I: Electrostatic Potential Maps of selected N-methyl sulfonamide P1 groups. A shows esp mapped onto electron densities of the truncated structure viewing from the face of aromatic rings. B shows the slight positive charge at the centre of the chlorine atom.