Query-guided Protein-Protein Interaction Inhibitor Discovery

Supporting information
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1. Supplementary figures and tables

Figure S1. Detailed summary of steps in workflow (shown in Figure 1 of the manuscript) used to identify inhibitors with a query guided approach (numbers are specific to p53/hDM2, with similar approach used for GKAP/SHANK 1 PDZ): Following hot-spot identification and query generation, a virtual library of small molecules is shape-matched against the query, and promising compounds docked against the target protein. Candidate inhibitors are then subjected to experimental screening and characterisation, enabling selection of hits for: (i) clustering, near neighbour expansion and further screening with reiteration of shape-matching/docking, % inhibition as necessary or (ii) further development/optimization. Clustering was based on Daylight Fingerprint and Tanimoto Similarity. Near neighbours were selected using Tanimoto Similarity from the larger (scored and unscored) AstraZeneca screening database.
Figure S2. (A) Binding of hDM2 17-125 to p53_{15-31}Flu (40 mM Phosphate, 200 mM NaCl, 0.02 mg/ml BSA, pH 7.4, Plate Reader II) monitored by fluorescence anisotropy, after 4 hours of incubation at room temperature; (B) Competition fluorescence anisotropy binding assay (40 mM Phosphate, 200 mM NaCl, 0.02mg/ml BSA, pH 7.4, Plate Reader II) to monitor the replacement of 25 nM p53_{15-31}Flu by Nutlin-3 in the presence of 150nM hDM2, after 4 hours of incubation at room temperature (bottom). Data was analysed using Origin.
Figure S3. Percentage inhibition of compounds from the hydrocarbon query at 10 and 100μM, compared to Nutlin-3 determined after 4 and 24 hours of incubation (150nM hDM2, 25nM p5315-31Flu, 40mM phosphate, pH 7.4, 200mM NaCl and 0.02 mg/ml BSA, Plate Reader I). Data was analysed in Excel and plotted in Origin.
Figure S4. Percentage inhibition of compounds from the peptide query at 10 and 100 μM, compared to Nutlin-3 determined after 4 and 24 hours of incubation (150nM hDM2, 25nM p5315-31 Flu, 40mM phosphate, pH 7.4, 200mM NaCl and 0.02 mg/ml BSA, Plate Reader I). Data was analysed in Excel and plotted in Origin.
Figure S5. Percentage inhibition of random compounds at 10 and 100μM, compared to Nutlin-3 determined after 4 and 24 hours of incubation (150nM hDM2, 25nM p53Δ5-31Flu, 40mM phosphate, pH 7.4, 200mM NaCl and 0.02 mg/ml BSA, Plate Reader I). Data was analysed in Excel and plotted in Origin.
Of the one hundred randomly selected compounds selected for analyses a number inhibited the p53/hDM2 interaction (Fig. S5); hit-rates for the randomly selected compounds were comparable to those for the hydrocarbon and amide queries (Fig. S3-42). However, whilst a number were active at 100 μM, a greater proportion exhibited significantly reduced activity at 10 μM. Team discussions accounting for frequenter hitter status, synthetic accessibility concluded these would be undesirable for further development (not shown) and they were pursued no further.

**Figure S6.** Fluorescence anisotropy competition assays to determine IC50 values for selected compounds (150nM hDM2, 25nM p5315-31Flu, 40mM phosphate, pH 7.4, 200mM NaCl and 0.02 mg/ml BSA, Plate Reader I). The data was analysed using Origin, the curves are grouped based on the clusters.
**Figure S7.** Chemical shift perturbation of hDM2 17-125 upon binding to Nutlin-3 (top) and A-1 (bottom) compounds. For NMR titrations (750 MHz, 100mM phosphate, pH 7.4, 2.5% glycerol, 1mM DTT) increasing amount of compound was titrated into 50μM hDM2. The NMR data was analysed using Sparky.
**Figure S8.** Chemical shift perturbation of hDM2 17-125 upon binding to B-1 (top) and C-1 (bottom) compounds. For NMR titrations (750 MHz, 100mM phosphate, pH 7.4, 2.5% glycerol, 1mM DTT), increasing amount of compound was titrated into 50μM hDM2. The NMR data was analysed using Sparky.
Figure S9. Chemical shift perturbation upon binding to selected compounds mapped on the structure of hDM2 17-125. For NMR titrations (750 MHz, 100mM phosphate, pH 7.4, 2.5% glycerol, 1mM DTT), increasing amount of compound was titrated into 50μM hDM2. CSP was determined at 1:2 protein:compound ratio. The NMR data was analysed using Sparky, the heatmaps were generated in PyMol.
Figure S10. Fluorescence anisotropy competition assays to show the selectivity of selected compounds from clusters A and C (A) compound 11b (B) in the presence of 200nM MCL-1 and 50nM FITC-Ahx-NOXA-B, (25mM Tris, pH 7.5, 150 NaCl, 10mg/ml BSA and 0.01% Triton-X, Plate Reader II). The data was analysed using Origin.
Figure S11. Fluorescence anisotropy competition assay of variant Ac-Glu-Ala-Gln-Thr-Arg-Phe peptide (L6F) and wild-type GKAP (FITC-Ahx-GKAP 50 nM, SHANK1-PDZ 1 µM, pH 7.4, 20mM Tris, 150mM NaCl, 0.01% Triton-X-100 buffer, Plate Reader I);
Supplementary Table S1

<table>
<thead>
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<th>L6F-GKAP/Shank</th>
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Data collection and refinement statistics
Figure S12. Percentage inhibition of compounds from the F-GKAP query at 30 and 300 μM, compared to acetylated GKAP determined after 4 and 24 hours of incubation (FITC-Ahx-GKAP 50 nM, SHANK1-PDZ 1 μM, pH 7.4, 20 mM Tris, 150 mM NaCl, 0.01% Triton-X-100 buffer, Plate Reader). Data was analysed in Excel and plotted in Origin.
Figure S13. Chemical shift perturbation of SHANK-1 PDZ 656-762 upon binding to Z-1. For NMR titrations (750 MHz, 5 mM Tris, 100 mM NaCl, pH 7.4), increasing amount of compound was titrated into 50μM protein. The NMR data was analysed using Sparky.

Figure S14. Fluorescence anisotropy competition assay for compound Z-2 (FITC-GKAP 50 nM, SHANK1-PDZ 1 μM, pH 7.4, 20mM Tris, 150mM NaCl, 0.01% Triton-X-100 buffer, Plate Reader I);
Figure S15. Fluorescence anisotropy competition assays to determine the IC\textsubscript{50} values of selected compounds from SAR (150nM hDM2 and p53\textsubscript{15-31}Flu, 40mM phosphate, pH 7.4, 200mM NaCl and 0.02 mg/ml BSA, Plate Reader II). The data was analysed using Origin.
**Supplementary Table S2.** Summary of IC\textsubscript{50} values for fluorescence anisotropy SAR competition assays

<table>
<thead>
<tr>
<th>compound</th>
<th>IC\textsubscript{50} (µM)</th>
<th>compound</th>
<th>IC\textsubscript{50} (mM)</th>
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<tr>
<td>A1</td>
<td>7.9 ± 0.9</td>
<td>(rac)-syn 10</td>
<td>21 ± 14</td>
</tr>
<tr>
<td>7a*</td>
<td>1.2 ± 1*</td>
<td>(rac)-anti 10</td>
<td>3.1 ± 0.4</td>
</tr>
<tr>
<td>7b*</td>
<td>13 ± 2*</td>
<td>(-)-anti 10</td>
<td>4.6 ± 0.6</td>
</tr>
<tr>
<td>7c*</td>
<td>5 ± 2*</td>
<td>(+)-anti 10</td>
<td>2.9 ± 0.4</td>
</tr>
<tr>
<td>7d</td>
<td>&gt;200</td>
<td>11a</td>
<td>1.7 ± 0.2</td>
</tr>
<tr>
<td>8a</td>
<td>10 ± 2</td>
<td>11b</td>
<td>2.9 ± 0.2</td>
</tr>
<tr>
<td>8b</td>
<td>18 ± 11</td>
<td>11c</td>
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<tr>
<td>8c</td>
<td>86 ± 29</td>
<td>11d</td>
<td>12 ± 9</td>
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<tr>
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<td>11e</td>
<td>14 ± 2</td>
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<td>9b</td>
<td>&gt;200</td>
<td>11f</td>
<td>25 ± 4</td>
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<tr>
<td>9c</td>
<td>n.d.</td>
<td>11g</td>
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<tr>
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*a lower anisotropy was observed in these assays, which we attribute to solubility causing assay interference.*
**Figure S16.** Representative chemical shift perturbation of hDM2 17-125 observed upon binding to second series of ligands. For NMR titrations (750 MHz, 100mM phosphate, pH 7.4, 2.5% glycerol, 1mM DTT), increasing amount of compound was titrated into 50μM hDM2. The NMR data was analysed using Sparky. Top spectra 11b – similar data were used to produce the chemical shift mapping diagrams for anti-10, 11a, 11b, 12 and 13 shown in Fig. 4d). Bottom spectra 7a – here a number of resonances were lost upon titration which is consistent with slow exchange and tight binding (top shift map shows the regions where resonances disappear in pink with bottom map showing all affected regions)
2. Further Discussion of molecular dynamics simulations

The pipeline process that selected A1 matched the 3R stereoisomer to the query. The pose matches the pyridyl group (P) to the F23 (green) site, the indole group (I) to the W21 (magenta) site and the thiophene (T) to the L19 (cyan) site which we can abbreviate to [PIT] (see movie R-A1 and Fig. S16a). The best docked pose of 3S-A1 swaps the position of the thiophene and indole groups and remains in this pose [ITP] throughout (see movie S-A1-I and Fig. S16b). A second, less favourable, 3S-A1 docked pose was chosen [PIT] and simulated. After 45 ns a large change occurs where the pyridyl group joins the thiophene group at the F23 site, giving non-canonical binding with an empty F23 site, indole in the W21 site and both other groups in the L19 site (see S-A1-II and Fig. S16c). Plots of ligand RMSD with time over these trajectories also show that the S-A1 stereoisomer is more mobile and less tightly associated with the protein than R-A1. We interpret these results to indicate the R stereoisomer both fits the design remit and binds more tightly than S-A1.
Figure S17. Molecular dynamics data for A1/hDM2 interaction (200 ns) for R-A1 (a), for S-A1 pose I (b) and for S-A1 pose II (c); plots for the root mean square deviation for the core and tail of the ligand (i) with respect to the initial structure and (ii) with respect to the average structure, (iii) plots of the relative fluctuations per residue over the trajectories. $\Delta$-RMSF = RMSF_{complex} - RMSF_{apo}. Y ordinates are RMSD (nm) X ordinates are residue number. Left-
hand column: RMSD versus structure at t = 0 ns; right-hand column: RMSD versus average coordinates over trajectory. Bars above zero indicate more flexibility of these residues in the complex than in the apo. Likewise, bars below zero indicate a loss of mobility of these residues in the complex compared with the apo. The RMSF of the ligand in each complex is also shown.

Development of A1 focussed on introducing substituents to reduce the conformational flexibility of the molecule. Firstly a methyl group was added to the 2 position to increase steric congestion adjacent to the CO-Cα bond giving a four stereoisomers. Each of these was simulated for 200 ns and the RMSD to the initial and average coordinates recorded (see movies and Fig. S17). The starting poses were based on the A1 simulations with the 3R pair docked [PIT] and the 3S pair [ITP]. Both 2R,3R-10 and 2S,3R-10 remain close to the initial and average positions in the binding site (Fig. S18, and movies RR-10 and SR-10) and induce moderate dampening of fluctuations for residues around the recognition site (Fig. S18 RMSF per residue plots). For both 2R,3S- and 2S,3S-10 the thiophene remains bound to the W21 site (Fig. S20 and movies RS-10 and SS-10). Even with non-canonical binding, 2S,3S-10 is mobile in its binding site, with high values evident in the RMSD plots and shows little perturbation of the protein dynamics beyond an increase in fluctuations around the C-terminus (see RMSF per residue). For 2R,3S in the RMSD and RMSF plots its behaviour is similar to the 3R stereoisomers.

In terms of the correlation with experiment, it is worth reiterating that these simulations were based on the original docked poses of R-A1 and S-A1 and that alternative binding poses for each of the four diasteromers of 10 might be accessible or the ligands may adopt a combination of binding poses. For the more potent anti pair (2R,3R-10 and 2S,3S-10), the simulations indicate that introduction of the 3-methyl group indeed restricts the conformational dynamics of the pyridyl group as intended – the small difference in potency (2.9 μM vs 4.6 μM) may arise from a difference in preferred binding pose, the reduced dynamics of 2R,3R-10 in comparison to 2S,3S-10 or a combination of both. syn-10 was shown to be less potent that anti-10 and we did not separate the enantiomers (2S,3R-10 and 2R,3S-10), thus a more guarded interpretation of the simulations for this pair is warranted. However, similar qualitative conclusions may be drawn i.e. the difference in protein affinity for different poses may be subtle and introduction of a 3-methyl group restricts the conformational dynamics of the ligand.
**Figure S18.** Molecular dynamics data for anti-10/hDM2 interaction (200 ns) for 2R,3R-10 (a) and 2S,3S-10 (b); plots for the root mean square deviation for the core and tail of the ligand (i) with respect to the initial structure and (ii) with respect to the average structure, (iii) plots of the relative fluctuations per residue over the trajectories. \( \Delta \text{RMSF} = \text{RMSF}_{\text{complex}} - \text{RMSF}_{\text{apo}} \). Y ordinates are RMSD (nm) X ordinates are residue number. Left-hand column: RMSD versus structure at \( t = 0 \) ns; right-hand column: RMSD versus average coordinates over trajectory. Bars above zero indicate more flexibility of these residues in the complex than in the apo. Likewise, bars below zero indicate a loss of mobility of these residues in the complex compared with the apo. The RMSF of the ligand in each complex is also shown.
Figure S19. Molecular dynamics data for syn-10/hDM2 interaction (200 ns) for 2S,3R-10 (a) and 2R,3S-10 (b); plots for the root mean square deviation for the core and tail of the ligand (i) with respect to the initial structure and (ii) with respect to the average structure, (iii) plots of the relative fluctuations per residue over the trajectories. Δ-RMSF = RMSF\textsubscript{complex} - RMSF\textsubscript{apo}. Y ordinates are RMSD (nm) X ordinates are residue number. Left-hand column: RMSD versus structure at t = 0 ns; right-hand column: RMSD versus average coordinates over trajectory. Bars above zero indicate more flexibility of these residues in the complex than the in the apo. Likewise, bars below zero indicate a loss of mobility of these residues in the complex compared with the apo. The RMSF of the ligand in each complex is also shown.

A similar observation was made for 7a. Only one stereoisomer of 7a (cyclopropyl in the pyridyl group) could be built based on the preferred pose of R-A1 (3R,X,Y)-7a. Simulation of this complex shows notably low mobility of the ligand (see movie 7a and Fig. S19)
Figure S20. Molecular dynamics data for 7a/hDM2 interaction (200 ns); plots for the root mean square deviation for the core and tail of the ligand (i) with respect to the initial structure and (ii) with respect to the average structure, (iii) plots of the relative fluctuations per residue over the trajectories. $\Delta$-RMSF = RMSF$_{\text{complex}}$ - RMSF$_{\text{apo}}$. Y ordinates are RMSD (nm) X ordinates are residue number. Left-hand column: RMSD versus structure at $t = 0$ ns; right-hand column: RMSD versus average coordinates over trajectory. Bars above zero indicate more flexibility of these residues in the complex than the in the apo. Likewise, bars below zero indicate a loss of mobility of these residues in the complex compared with the apo. The RMSF of the ligand in each complex is also shown.

The final rigidification strategy was to introduce substituents at the indole C2 such as in compound 11b (CO$_2$H at the indole 2 position). The $R$ stereoisomer of 11b is less mobile than the $S$ isomer and shows low RMSD versus the average structure (see movies R-11b and S-11b and Fig. S20). After 115 ns in the trajectory of 11b there is a small rearrangement in the pose that corresponds to a change in the interaction between hDM2 and the carboxyl group. Freezing of residues around the binding site is most evident in the $\Delta$-RMSF plot of 11b over 120-200 ns.
Figure S21. Molecular dynamics data for 11b/hDM2 interaction (200 ns) for R-11b (a) and S-11b (b); plots for the root mean square deviation for the core and tail of the ligand (i) with respect to the initial structure and (ii) with respect to the average structure, (iii) plots of the relative fluctuations per residue over the trajectories. Δ-RMSF = RMSF_{complex} - RMSF_{apo}. Y ordinates are RMSD (nm) X ordinates are residue number. Left-hand column: RMSD versus structure at t = 0 ns; right-hand column: RMSD versus average coordinates over trajectory. Bars above zero indicate more flexibility of these residues in the complex than in the apo.
Likewise, bars below zero indicate a loss of mobility of these residues in the complex compared with the apo. The RMSF of the ligand in each complex is also shown.
3. Determination of the relative configuration of diastereomers

The coupling constant between protons $H_2$ and $H_3$ is $^3J = 11.0$ Hz for syn-10 and anti-10 isomers and $^3J = 11.5$ Hz for syn-49 and anti-49 isomers. Following the Karplus approximation, in which $^3J = 8-15$ Hz for vicinal trans protons, we used the Newman projection along the C2-C3 bond to determine the relative syn/anti configuration by $^1H-^1H$ NOE correlation signals.

**syn-3-(5-Chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-2-methyl-N-[2-(pyridin-2-yl)ethyl]propenamide (syn-10)**

![Chemical structure and NOE correlation experiment](image)

**Figure S22.** Resolution of the relative configuration of syn-10. Top: chemical structure highlighting relevant protons and Newman projection. Bottom: extract of the $^1H-^1H$ NOESY correlation experiment.
**anti-3-(5-Chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-2-methyl-N-[2-(pyridin-2-yl)ethyl]propenamide (anti-10)**

**Figure S23.** Resolution of the relative configuration of anti-10. Top: chemical structure highlighting relevant protons and Newman projection. Bottom: extract of the $^1$H-$^1$H NOESY correlation experiment.
4. Chiral separation of enantiomers (+)-anti-10 and (−)-anti-10

Figure S24. Method and conditions for the chiral separation of enantiomers (+)-anti-10 and (−)-anti-10.
Figure S25. Analytical chromatogram of enantiomer (+)-anti-10.
Figure S26. Analytical chromatogram of enantiomer (—)-anti-10.
5. Supplementary methods

5.1. Biophysical methods

5.1.1. Screening of AZ compounds

Screening of AZ compounds – hDM2

Both for the initial round and for the near neighbours, compound screening was carried out using a competition fluorescence anisotropy assay. 25nM p5315-31Flu bound to 150nM hDM2 was competed against 10 or 100µM compound in assay buffer containing 40mM phosphate (pH 7.5), 200mM NaCl, 0.02mg/ml Bovine Serum Albumin and 1% DMSO. Results were collected using a Perkin-Elmer Envision 2103 Multilabel Reader using a D505fp dichroic mirror, 480(104) nm excitation filter (band width 30 nm), and 535(208-S) and 535(209-P) nm emission filters (band width 40 nm) after 0, 1, 4 and 24 hours of incubation at room temperature (Plate Reader I) or Tecan Spark plate reader using a 485 nm excitation filter (band width 20 nm), and 535 (S) and 535 (P) nm emission filters (band width 25 nm) after 0, 1, 4 and 24 hours of incubation at room temperature (Plate Reader II). Wells containing only hDM2 in assay buffer were used as a blank and Nutlin 3 was used as positive control. Assays were carried out as triplicates.

Fluorescence anisotropy data was processed as described previously. The data from both the P (perpendicular intensity) and S (parallel intensity) channels, resulting from this measurement was corrected by subtracting the corresponding control wells, and used to calculate the intensity and anisotropy for each well following Equations 1 and 2. The average anisotropy (across all replicates) and the standard deviation of these values were then calculated and fit to a sigmoidal logistic model using Origin to determine the maximum ($r_{max}$) and minimum ($r_{min}$) anisotropies. These were used to calculate the fraction ligand bound (Lb) (Equation S3). The fraction ligand bound was multiplied by the [FL] and fit to the model shown in Equation S4 to determine a $K_d$:

\[
I = (2PG)+S \quad \text{Equation 1}
\]

\[
r = (S-PG) \quad \text{Equation 2}
\]

\[
L_b = (r-r_{min})/(r_{max}-r)+r_{min} \quad \text{Equation 3}
\]

\[
y = \{(k+x+[FL])-\sqrt{(k+x+[FL]^2-4x[FL])}/2 \quad \text{Equation 4}
\]
\[ r = \text{anisotropy}, I = \text{total intensity}, P = \text{perpendicular intensity}, S = \text{parallel intensity}, L_b = \text{fraction ligand bound}, \lambda = I_{\text{bound}}/I_{\text{unbound}} = 1, [FL] = \text{concentration of fluorescent ligand}, k = K_d, y = L_b \times \text{Flu-trimer and } x = [\text{added titrant}], G \text{ is an instrument gain factor.} \]

Percentage inhibition values were then calculated using Nutlin 3 as positive control for both 10 and 100\(\mu\)M compound concentrations.

\[
\% \text{ inhibition} = \frac{DMSO \text{ control anisotropy} - \text{sample anisotropy}}{DMSO \text{ control anisotropy} - \text{nutlin 3 anisotropy}} \times 100
\]

The determined values were plotted as a column graph for visualisation, the 4h time point was used to select compounds for further testing.

**Screening of AZ compounds – SHANK1 PDZ**

The screening of compounds was carried out similarly as described for \(h\)DM2 using 50nM FITC labelled GKAP bound to 1\(\mu\)M SHANK1-PDZ, in TRIS buffer (20 mM TRIS, 50 mM NaCl, pH 7.4, 3% DMSO).

Compounds were screened at 30 and 300\(\mu\)M concentration, unlabelled GKAP peptide was used as a positive control.

5.1.2. \(IC_{50}\) determination – fluorescence anisotropy competition assays

Selected compounds both for \(h\)MD2/p53, MCL-1/NOXA-B and SHANK/GKAP were tested in competition assays as previously described.\(^1,2\)

5.1.3. NMR spectroscopy

All NMR experiments were carried out using Bruker Avance NMR spectrometers operating at 750, MHz \(^1\)H frequency. Temperature was maintained at 298 K. Data were processed using Topspin and analysed in NMRFAM-Sparky.\(^5,6\)

NMR titrations for \(h\)DM2 were performed in 100mM Na\(_2\)HPO\(_4\), 2.5% glycerol, 1mM DTT pH 7.4 buffer by recording \(^1\)H-\(^{15}\)N SOFAST NMR spectra of protein-small
molecule complexes. A 50 µM sample of hDM2(17-125) was titrated with various compounds at 0, 0.5, 1, 2, 4 or 0, 0.25, 0.5, 0.75, 1, 1.5, 2 compound:protein ratios. NMR titrations for SHANK1 PDZ were performed in 5 mM TRIS, 100 mM NaCl, pH 7.4.

5.1.4. Crystallography

SHANK1-PDZ was incubated with L6F-GKAP at 1:2 protein:ligand molar ratio in 25 mM Tris, 150 mM NaCl pH 7.5 buffer having 10.5 mg/ml final protein concentration. Conditions were screened using sitting-drop vapor-diffusion method using JCSG Core suites (Quiagen) with mixing 1:1 drops (0.2 µl) at 20 °C. Initial hit conditions were further optimized by screening HEPES pH 7 – 8.25 in 0.25 pH steps and PEG 400 concentration from 25-40% in 5% steps, crystals grew within 3-8 days. Crystals were frozen in liquid nitrogen without addition of any further cryoprotectant and sent to Diamond Lightsource (DLS) for data collection. Data was collected at 100K. Data were processed with the xia2\textsuperscript{7} bundle using XDS\textsuperscript{8} for integration and Pointless,\textsuperscript{9} Aimless\textsuperscript{10} for scaling and merging. Phasing was performed by molecular replacement using Phaser\textsuperscript{11} and using Chain A from PDB ID: 1Q3O as a search model. Refinement was done using REFMAC\textsuperscript{12} and model building in COOT\textsuperscript{13} using the CCP4i2\textsuperscript{14} software package. TLS refinement was done in PHENIX\textsuperscript{15} and structures were analysed by Molprobity.\textsuperscript{16}

5.1.5. Protein expression and purification

hDM2 17-125 was expressed and purified as described previously.\textsuperscript{1} MCL-1 (172-327) was expressed and purified as described previously.\textsuperscript{2} Shank 1 PDZ domain (656-762) was expressed and purified as described previously.\textsuperscript{2} \textsuperscript{15}N labelled samples were prepared following the same protocols as above, with the expression being carried out in M9 minimal media supplemented with \textsuperscript{15}N NH\textsubscript{4}Cl.

5.1.6. Isothermal titration calorimetry experiments

ITC experiments of SHANK with GKAP was carried out as previously described.\textsuperscript{2}
5.2. Computational methods

**Scaffold preparation** Hot residues at the interface of a given protein-protein complex were predicted using the *in silico* alanine scanning web application BAlaS. A set of neighbouring hotspot residues were selected by inspection from the protein partner to be mimicked by the small molecule. We developed a Python application, scaffoldSearch.py, to facilitate the subsequent steps of the search process. ScaffoldSearch.py is run in one of four modes: ‘query’, ‘search’, ‘dock’, ‘results’ or ‘full’ meaning run all four modes in order. Query mode takes a list of residues and generates the query structure for the next step. Search mode takes the query structure and a database of small molecules and passes this to ROCS (OpenEye) for similarity searching. Dock mode takes the best hits from ‘search’ and passes these to BUDE for (re)docking (this code can be readily modified to use other virtual screening or docking tools). Results mode compiles the results into human-friendly format.

This code is available on GitHub [https://github.com/richardbsessions](https://github.com/richardbsessions).

**Structure similarity searching, protein docking and scoring** In this work a modified workflow was used to identify hits as follows. A query protein with a defined receptor binding surface was uploaded into VIDA (https://www.eyesopen.com/vida) along with the relevant peptide query. A virtual library of ~42 million conformers representing the AstraZeneca screening collection was shape-matched using FastRocs. The sum of the ShapeTanimoto and ColorTanimoto scoring functions (TanimotoCombo) was used as the primary filter to select 1000 top scoring hits. The hits were then docked rigidly into the receptor surface using OEDocking (also in VIDA). A significant number of compounds had flipped through ~180 degree during docking and these were removed by applying a script which calculated RMS difference of initial pose to docked pose. High RMS difference compounds were removed. A large number of fragment like hits were observed to be well-scoring two-pocket binders. A handful (<20) were retained, but most were discounted so as to maximise the number of three-pocket binders selected for further profiling. Tanimoto clustering was performed and representative cluster members were selected plus a small number of structurally distinct singletons. Once the *in silico* hit list had been reduced to 100 potential hits per query, a random set of 100 compounds was selection from the AZ screening collection, aiming to explore similar logD, rotatable bond and...
molecular weight space to the selected compounds. A comparison of binned rotatable bonds and calculated logD are shown as two examples:
All compounds from the three sets (the Hydrocarbon query – ‘Original’; the peptidic query – ‘Peptide’; compounds hitting both queries – ‘Both’) were checked for frequent hitter behaviour against the control set of compounds. Frequent hitters are identified by virtue of a highly negative logBSF score. Anything more negative than -5 is regarded as questionable.\(^{27}\) In the figure below, anything not blue is a frequent-hitter as was removed from consideration for IC\(_{50}\) follow-up.

The percent inhibition data at 100 \(\mu\text{M}\) on the 200 compounds from the ‘Original’ and ‘Peptide’ sets was reclustered at Tanimoto 0.7 level of similarity; some clusters were manually combined due to highly similar substructures/embedded scaffolds:
Following clustering, the larger AZ screening collection was mined for near neighbours and the selected hits (43) augmented with NNs (257) for the IC_{50} round of testing.

### 5.3. Molecular Dynamics Methods

The protein-ligand complexes selected for simulation were all treated the same way. The protein was parameterised with the amber99SB-ildn forcefield\(^{28}\) and the small molecules with GAFF.\(^{29}\) All simulations were performed using GROMACS 2019.3.\(^{30}\) using the following general protocol. Hydrogen atoms were added consistent with pH 7. The protein-ligand complex was placed in a cubic box 3 nm larger than the longest dimension of the protein and filled with TIP3P water containing 0.15 M sodium chloride ions to give a charge-neutral system overall. After 10000 steps of steepest descent minimisation, molecular dynamics was initiated with random velocities while restraining the protein backbone to its original position with a force constant of 1000 kJ/nm for 0.2 ns. Simulations were developed for a further 200 ns without the backbone position restraints under periodic boundary conditions. The Particle Mesh Ewald’s method was used for long range electrostatic interactions while short range Coulombic and van de Waals energies were truncated at 1.4 nm. The temperature
was maintained at 300 K using the v-rescale method and the pressure at 1 bar with the Parrinello-Rahman barostat and a 2 fs time step for the leapfrog integrator. Bond constraints were implemented with the LINCS method and SETTLE used for waters. Trajectories were processed and analysed with the GROMACS tools and visualised with VMD 1.9.3 and PyMol 1.8.x. Movies were created using Chimera 1.14 and plots made with gnuplot 5.2.2.

5.4. Synthetic methods
Reactions were carried out in clean and dried glassware under normal atmosphere unless otherwise stated. Solvents and reagents were purchased from Sigma-Aldrich or Fisher and used without further purification unless otherwise stated. Anhydrous dimethyl formamide was obtained from Sigma Aldrich equipped with Sure/Seal™ caps. For reactions under non-anhydrous conditions, the solvents used were HPLC quality and provided by Sigma Aldrich or Fisher. Water in aqueous solutions and used for work up/quenching was deionised. Mixtures of solvents are quoted as ratios and correspond to a volume: volume ratio. Analytical thin layer chromatography was performed on Merck Kieselgel 60 F254 0.25 mm pre-coated aluminium plates. Product spots were visualised under UV light ($\lambda_{\text{max}} = 254$ nm) and/or stains on heating such as phosphomolybdic acid, potassium permanganate and ninhydrin. Purification by flash chromatography was mainly carried out using automated purification by Isolera One (Biotage®) using silica column cartridges from RediSepRf®, Claricep® and Phenomenex®. Alternative non-automated flash chromatography purification was carried out using Merck Kieselgel 60 silica gel 60 (0.043 – 0.063 mm VWR) using pressure by means of head bellows. Nuclear magnetic resonance spectra were obtained at 298 K, unless otherwise stated, using a Bruker AV500 spectrometer operating at 11.4 T (500 MHz for $^1$H and 125 MHz for $^{13}$C) or a Bruker AV3 HD-400 spectrometer (400 MHz for $^1$H and 100 MHz for $^{13}$C) as stated and references to the solvent peak. Infra-red spectra were obtained using a Perkin-Elmer FTIR spectrometer where absorption maxima ($\nu_{\text{max}}$) are quoted in wavenumbers (cm$^{-1}$) and only structurally relevant absorptions have been included. High Resolution Mass Spectra (HRMS) were recorded on a Bruker Daltonics micro TOF using electrospray ionisation (ESI). Liquid Chromatography and Mass Spectrometry (LC-MS) was performed using an Agilent Technologies 1200 series LC and a Bruker HCT ultra ion-trap MS. The
assignment of the $^1$H and $^{13}$C nuclei to their corresponding NMR signals was done according to their IUPAC nomenclature unless otherwise indicated. When mixtures of diastereomers have been characterised, $^1$H and $^{13}$C signals have been described as ‘maj’ or ‘min’ according to the major or minor isomer, respectively. Integration of the $^1$H signal from major and minor isomers associated to the same structural proton has been normalised to sum to the unity. Chiral separation of enantiomers was performed by supercritical fluid chromatography in Sepiatec 100 preparative instrument using Phenomenex® C1 columns (30 x 250 mm, 5 micron). Method conditions employed a back-pressure regulator at 120 bar, 40 °C of temperature and a UV $\nu_{\text{max}} = 210$ nm. The collected fractions were dried down into vials using Genevac Rocket.

5.1. Peptides
The p53 tracer $p53_{15-31}^{\text{Flu}}$ (Ac-SQETFSDLWKLLPENNVC(Flu)-NH$_2$), where Flu is a N-(5-Fluoresceinyl)maleimide adduct, was purchased from Peptide Protein Research Ltd. As in prior studies.3, 4, 33, 34 wt GKAP (Ac-EAQTRL-CO$_2$H) and FITC-Ahx-GKAP (FITC-Ahx-EAQTRL-CO$_2$H, where FITC is fluoresceine isothiourea) were prepared previously2 whilst L6F GPAK (Ac-EAQTRF-CO$_2$H) was prepared using methods as described in this prior report.2

5.2. General synthetic procedures
For methodologies that have been described once, individual procedures are described at their corresponding experimental description.

5.2.1. Procedure A: multicomponent reactions
A1: Multicomponent reaction with C2-H indole derivatives
To a solution of the indole (1.1 eq.) and $p$-toluenesulfinic acid (2.0 eq.) in dichloromethane (5 mL/mmol), the aldehyde (1 eq.) was added and the reaction mixture stirred at room temperature for 1 to 20 h. The mixture was partitioned between dichloromethane/saturated aqueous sodium hydrogen carbonate solution (the added volume of hydrogen carbonate solution was equal to the total reaction volume). The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo.
A2: Multicomponent reaction with C2-substituted indole derivatives
To a solution of the indole (1.1 eq.), p-toluenesulfonic acid (4 to 5 eq.) and p-toluenesulfonic acid monohydrate (1 eq.) in tetrahydrofuran (5 mL/mmol), 5-chloro-2-thiophenecarboxaldehyde (1 eq.) was added and the reaction mixture stirred at 80 °C for 16 to 30 h. The mixture was partitioned between ethyl acetate/saturated aqueous sodium hydrogen carbonate solution (the added volume of hydrogen carbonate solution is equal to the total reaction volume). The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo.
In the case of C2-CO₂H, the reaction mixture was concentrated in vacuo and the crude material purified by column chromatography (silica) without previous work-up.

5.2.2. Procedure B: methyl carboxylate ester formation
B1: Methyl carboxylate ester formation with C2-H indole derivatives
To a solution of the indole (1 eq.) and silyl enol ether (3 to 5 eq.) in dichloromethane (5 to 20 mL/mmol) at 0 °C, trifluoromethanesulfonic acid (5 to 40%) was added and the reaction mixture stirred at room temperature for 3 to 16 h. The mixture was partitioned between dichloromethane/saturated aqueous sodium hydrogen carbonate solution (the added volume of hydrogen carbonate solution is equal to the total reaction volume). The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo.

B2: Methyl carboxylate ester formation with C2-substituted indole derivatives
To a solution of the indole (1 eq.) and [(1-methoxy-1-propenyl)oxy]trimethylsilane or tert-butyl[(1-methoxyvinyl)oxy]dimethylsilane (4 to 10 eq.) in tetrahydrofuran (10 to 20 mL/mmol) at room temperature, trifluoromethanesulfonic acid (40%) was added and the reaction mixture stirred at 60 °C for 16 h. The mixture was partitioned between ethyl acetate/saturated aqueous sodium hydrogen carbonate solution (the added volume of hydrogen carbonate solution is equal to the total reaction volume). The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo.
In the case of C2-CO₂H, the reaction mixture was concentrated in vacuo and the crude material purified by column chromatography (silica) without previous work-up.
5.2.3. Procedure C: ester hydrolysis

To a solution of the ester (1 eq.) in methanol (4 to 20 mL/mmol, 1:1 with tetrahydrofuran where specified), an aqueous solution of sodium hydroxide (3 to 13 eq., 0.5 to 2.5 M) was added and the reaction mixture was stirred at room temperature (unless otherwise specified) for 1 to 72 h. The mixture was cooled down to room temperature, diluted down with saturated brine (the added volume of brine is equal to the total reaction volume) and then cooled down to 0°C. The mixture was acidified to pH 1 using 6 N hydrogen chloride solution. The aqueous layer was extracted with ethyl acetate or dichloromethane (3 x same volume as the previous mixture of organic solvents and brine), the combined organic layers dried over magnesium sulfate, filtered and concentrated \emph{in vacuo} to afford carboxylic acids.

5.2.4. Procedure D: bromination of the C2-H position of an indole

To a solution of the ester (1 eq.) in tetrahydrofuran:chloroform (10 to 20 mL/mmol, 1:1) at 0 °C, pyridinium tribromide (1.1 eq.) was added and the reaction mixture was stirred at room temperature for 2 h. The mixture was quenched with saturated aqueous sodium thiosulfate solution (the added volume of sodium thiosulfate solution is equal to the total reaction volume) and extracted with dichloromethane (3 x same volume as the previous mixture of organic solvents and sodium thiosulfate solution). The combined organic layers were dried over magnesium sulfate, filtered and concentrated \emph{in vacuo}.

5.2.5. Procedure E: amide bond formation

E1: T3P® mediated amide formation

To a solution of the carboxylic acid (1.0 eq), the amine (1 to 3 eq.) and pyridine (3.0 eq.) in ethyl acetate (3 mL/mmol), 1-propanephosphonionic anhydride solution (2.0 eq., 50% wt) was added and the resulting mixture stirred at room temperature for 16 h. The mixture was washed with saturated aqueous sodium carbonate solution (3 x same volume as the previous mixture of organic solvents and sodium thiosulfate solution) and saturated brine (1 x same volume as the sodium carbonate solution), dried over sodium sulfate and concentrated \emph{in vacuo}. 
E2: HCTU mediated amide formation
To a solution of the carboxylic acid (1 eq.), DIPEA (3 eq.) and 2-(2-aminoethyl)pyridine (1.1 to 3 eq.) in dimethylformamide (3 to 10 mL/mmol) at 0°C or room temperature, HCTU (1.1 to 3 eq.) was added and the reaction mixture was stirred at room temperature for 16 h. The mixture was diluted down with ethyl acetate (the added volume of ethyl acetate is equal to the total reaction volume) and washed with saturated aqueous sodium hydrogen carbonate solution (3 x same volume as the added ethyl acetate) and saturated brine (1 x same volume as the added ethyl acetate). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*.

E3: Acyl chloride mediated amide formation
To a suspension of the carboxylic acid (1 eq.) in dichloromethane (50 mL/mmol) at 0°C, Ghosez’s reagent (2 to 6 eq.) was added dropwise while stirring. The reaction mixture was stirred at room temperature until complete consumption of the starting material. The resulting solution was subsequently added to a second solution of the amine (1.2 eq.) and triethylamine (1.2 eq.) in dichloromethane (3 mL/mmol) at 0°C. The reaction mixture was stirred at room temperature for 16 h. The mixture was diluted down with ethyl acetate (the added volume of ethyl acetate is equal to the total reaction volume) and washed with saturated aqueous sodium hydrogen carbonate solution (3 x same volume as the added ethyl acetate) and saturated brine (1 x same volume as the added ethyl acetate). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*.

5.2.6. Procedure F: aza-Diels-Alder cycloaddition
Aniline derivative (2.5 to 3 mmol) was dissolved in dry acetonitrile (2 mL) and ethyl 2-oxoacetate (1.1 eq., 50% solution in toluene) was added. The mixture was stirred for 30 min under nitrogen atmosphere at room temperature. Then, cyclopentadiene (1.5 eq.) and cooper (II) or ytterbium (III) trifluoromethansulfonate (5%) were added. The mixture was stirred at room temperature until consumption of the aniline. The mixture was diluted with ethyl acetate (10 mL) and the combined organic phases were washed with saturated aqueous sodium hydrogen carbonate solution (2 x 15 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. 

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5.3. Synthetic schemes

Compounds were synthesized in general using one of four synthetic routes (Fig 4a, Scheme S1-S3). In the subsequent section (5. Synthesis and characterization), for completeness, data are reported for all compounds prepared in the study, a number of which had poor solubility and were not screened.

Scheme S1. Synthetic approach to prepare C2-H indole analogues. Example of synthetic route to analogues syn-10, anti-10 and 12.
Scheme S2. Synthetic approach to prepare C2-bromo indole analogues. Example of synthetic route to analogue 11a.

Scheme S3. Synthetic approach to prepare aromatic and aliphatic C2-amide indole analogues. Example of synthetic route to analogues 11i. Intermediates without numbering are commercially available or previously reported.
6. Synthesis and characterisation

Ethyl (3aS,4R,9bR)-8-sulfamoyl-3H,3aH,4H,5H,9bH-cyclopenta[c]quinoline-4-carboxylate 16

According to general procedure F, 4-aminobenzene-1-sulfonamide (0.50 g, 2.9 mmol), ethyl 2-oxoacetate 50% toluene solution (0.64 mL, 3.2 mmol), cyclopentadiene (0.36 mL, 4.4 mmol) and ytterbium (III) trifluoromethansulfonate (90 mg, 0.15 mmol) in acetonitrile (4 mL) at RT gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 → 40:60 of ethyl acetate:hexane) afforded ester 16 as a pink solid (526 mg, 56%). δH (500 MHz, chloroform-d) 7.56 (1H, dd, J2.2 and 1.0, 9-H), 7.51 (1H, app ddd, J8.5, 2.2 and 0.6, 7-H), 6.66 (1H, d, J 8.5, 6-H), 5.81–5.76 (1H, m, 2-H), 5.71–5.65 (1H, m, 1-H), 4.74–4.70 (1H, m, NH), 4.67 (2H, s, NH2), 4.39–4.28 (1H, m, ethyl 1-Hα), 4.31–4.19 (1H, m, ethyl 1-Hβ), 4.17 (1H, app dd, J3.6 and 1.0, 4-H), 4.13–4.05 (1H, m, 9b-H), 3.40–3.31 (1H, m, 3a-H), 2.46–2.37 (1H, m, 3-Hα), 2.37–2.29 (1H, m, 3-Hβ) and 1.33 (3H, t, J 7.1, ethyl 2-H3). δC (125 MHz, chloroform-d) 171.2, 147.8, 133.6, 130.7, 127.7, 125.5, 125.4, 115.2, 61.7, 55.4, 45.7, 40.6, 32.4 and 14.3. HRMS m/z calculated for C13H14N2NaO4S (M+Na)+: 345.0885; Found: 345.0879.

(3aS,4R,9bR)-8-Sulfamoyl-3H,3aH,4H,5H,9bH-cyclopenta[c]quinoline-4-carboxylic acid (Z-1)

According to general procedure C, ethyl ester 16 (50 mg, 0.16 mmol) and sodium hydroxide solution (2 mL, 0.5 M) in methanol (5 mL) at RT afforded acid Z-1 as white solid (41 mg, 90%). δH (500 MHz, deuterium oxide) 7.40 – 7.34 (1H, m, 9-H), 7.27 (1H, dd, J 8.4 and 2.2, 7-H), 6.64 (1H, d, J 8.4, 6-H), 5.72 – 5.66 (1H, m, 1-H), 5.62 – 5.56 (1H, m, 2-H), 4.03 – 3.94 (1H, m, 4-H), 3.77 – 3.70 (1H, m, 9b-H), 3.14 – 3.06
(1 H, m, 3a-H) and 2.24 – 2.13 (2 H, m, 3-H2). HRMS m/z calculated for C_{13}H_{14}N_{2}NaO_{4}S (M+Na)^{+}: 317.0572; Found: 317.0564.

9-Nitro-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-4,6-dicarboxylic Acid Z-2

![Chemical Structure](image)

Was synthesized as previously described – characterization matched literature values^{35}

5-Chloro-3-[(5-chlorothiophen-2-yl)(4-methylbenzenesulfonyl)methyl]-1H-indole

![Chemical Structure](image)

According to general procedure A1, 5-chloroindole (1.0 g, 6.5 mmol), 5-chloro-2-thiophenecarboxaldehyde (0.63 mL, 5.9 mmol) and p-toluenesulfonic acid (2.0 g, 13 mmol) in dichloromethane (30 mL) gave the crude product. The product was precipitated in cold diethyl ether (30 mL), filtered, washed with diethyl ether (3 x 10 mL) and dried in vacuo to afford indole 17 as a light red solid (1.8 g, 66%); δ_H (400 MHz, DMSO-d$_6$) 11.56 (1 H, d, J 2.8, NH), 7.71 (1 H, d, J 2.0, 4-H), 7.65 (1 H, d, J 2.8, 2-H), 7.58 (2 H, d, J 8.1, benzenesulfonyl 2- and 6-H), 7.38 (1 H, d, J 8.7, 7-H), 7.29 (2 H, d, J 8.1, benzenesulfonyl 3- and 5-H), 7.08 (1 H, dd, J 8.7 and 2.0, 6-H), 7.03–6.98 (2 H, m, thiophenyl 3- and 4-H), 6.66 (1 H, s, CHS) and 2.33 (3H, s, benzenesulfonyl 4-methyl). δ_C (100 MHz, DMSO-d$_6$) 144.8, 135.4, 135.0, 134.4, 130.1, 129.8 (x2), 129.6, 129.1 (x2), 128.3, 128.2, 127.0, 124.5, 122.1, 118.8, 113.7, 106.3, 62.8 and 21.5. HRMS m/z calculated for C_{13}H_{8}Cl_{2}NS (M-SO$_2$Tol)$^{+}$: 279.9749; Found: 279.9662. IR (film): 3384, 1436, 1287, 1135.
Methyl 3-(5-chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)propanoate

According to general procedure B1, indole 17 (600 mg, 1.4 mmol), tert-butyl((1-methoxyvinyl)oxy)dimethylsilane (0.98 mL, 4.5 mmol) and trifluoromethanesulfonic acid (6.0 µL, 0.07) in dichloromethane (15 mL) gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 → 20:80 of ethyl acetate:hexane) afforded ester 18 as a colourless oil (400 mg, 76%); δ_H (400 MHz, chloroform-d) 8.11 (1 H, s, NH), 7.45 (1 H, d, J 1.9, indolyl 4-H), 7.27 (1 H, d, J 8.1, indolyl 7-H), 7.17–7.10 (2 H, m, indolyl 2- and 6-H), 6.70 (1 H, d, J 3.8, thiophenyl 4-H), 6.68 (1 H, dd, J 3.8 and 0.9, thiophenyl 3-H), 4.91 (1 H, app. t, J 7.7, 3-H), 3.64 (3 H, s, methyl), 3.12 (1 H, dd, J 14.3 and 6.4, 2-H_A) and 3.06 (1 H, dd, J 14.3 and 6.7, 2-H_B). δ_C (100 MHz, chloroform-d) 171.8, 146.5, 134.9, 128.3, 127.3, 125.8, 125.7, 123.7, 123.0, 122.9, 118.8, 117.6, 112.5, 52.0, 41.7 and 34.8. HRMS m/z calculated for C_{16}H_{13}Cl_{2}NNaO_{2}S (M+Na)^+: 375.9942; Found: 375.9734.

3-(5-Chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)propanoic acid

According to general procedure C, ester 18 (580 mg, 1.6 mmol) and sodium hydroxide solution (6 mL, 1.3 M) in methanol (6 mL) afforded acid 19 as a light brown oil (539 mg, 96%); δ_H (400 MHz, chloroform-d) 8.11 (1 H, s, NH), 7.44 (1 H, d, J 1.9, indolyl 4-H), 7.27 (1 H, d, J 8.7, indolyl 7-H), 7.17–7.12 (2 H, m, indolyl 2- and 6-H), 6.72–6.68 (2 H, m, thiophenyl 3- and 4-H), 4.89 (1 H, app. t, J 7.6, 3-H), 3.15 (1 H, dd, J 15.8 and 7.2, 2-H_A) and 3.09 (1 H, dd, J 15.8 and 7.6, 2-H_B). δ_C (125 MHz, chloroform-d) 176.4, 146.4, 135.0, 128.6, 127.4, 126.0, 125.9, 123.9, 123.2, 123.0, 118.9, 117.4, 112.6, 41.5 and 34.7. HRMS m/z calculated for C_{15}H_{10}Cl_{2}NO_{2}S (M-H)^-: 337.9815; Found: 337.9830. IR (film): 3271 (broad), 1720.
3-(5-Chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-N-[2-(pyridin-2-yl)ethyl] propanamide A1

According to general procedure E1, carboxylic acid 19 (100 mg, 0.30 mmol), 2-(2-pyridyl)ethylamine (0.11 mL, 0.90 mmol), pyridine (0.10 mL, 1.2 mmol) and T3P (0.35 mL, 0.6 mmol) in ethyl acetate (3 mL) gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 → 20:80 of ethyl acetate:hexane) afforded amide A1 as a colourless oil which solidified on standing (51 mg, 40%); δ_H (500 MHz, DMSO-d_6) 1.17 (1 H, d, J 2.6, NH_indole), 8.47 (1 H, ddd, J 4.9, 1.9 and 0.9, pyridinyl 6-H), 8.02 (1 H, t, J 5.7, NH_amide), 7.62 (1 H, td, J 7.7 and 1.9, pyridinyl 4-H), 7.39 (1 H, d, J 2.1, indolyl 4-H), 7.37 (1 H, d, J 8.6, indolyl 7-H), 7.35 (1 H, d, J 2.6, indolyl 2-H), 7.19 (1 H, ddd, J 7.7, 4.9 and 1.2, pyridinyl 5-H), 7.06 (1 H, dd, J 8.6 and 2.1, indolyl 6-H), 7.06–7.04 (1 H, m, pyridinyl 3-H), 6.88 (1 H, d, J 3.8, thiophenyl 4-H), 6.79 (1 H, dd, J 3.8 and 0.9, thiophenyl 3-H), 4.86 (1 H, app. t, J 7.7, 3-H), 3.41–3.33 (2 H, m, pyridinylethyl 1-H_2), 2.90–2.79 (2 H, m, 2-H_2) and 2.74 (2 H, t, J 7.2, pyridinylethyl 2-H_2). δ_C (125 MHz, DMSO-d_6) 169.7, 159.0, 149.0, 148.8, 136.3, 134.9, 127.1, 126.2, 125.5, 124.1, 123.6, 123.2, 123.0, 121.4, 121.2, 117.9, 116.4, 113.2, 42.3, 38.4, 37.3 and 34.3. HRMS m/z calculated for C_{22}H_{19}Cl_{2}N_{3}NaOS (M+Na)^{+}: 466.0518; Found: 466.0512. IR (film): 3340, 1629.

3-(5-Chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-N-(2-phenylethyl) propanamide 7b

By general procedure E1, carboxylic acid 19 (50 mg, 0.15 mmol), 2-phenylethylamine (60 µL, 0.48 mmol), pyridine (50 µL, 0.6 mmol) and T3P (175 µL, 0.3 mmol) in ethyl acetate (0.10 mL) gave the crude product. Purification by column chromatography (silica, Eluent: gradient 0:100 → 20:80 of ethyl acetate:hexane) afforded amide 7b as a light brown oil which solidified on standing (23 mg, 36%); δ_H (400 MHz, chloroform-d) 8.51 – 8.33 (1 H, m, NH_indole), 7.42 (1 H, d, J 2.0, indolyl 4-H), 7.36–7.15 (4 H, m, indolyl 7-H and phenyl 3-, 4- and 5-H), 7.14 (1 H, dd, J 8.6 and 2.0, indolyl 6-H), 7.05
(1 H, d, J 2.5, indoly 2-H), 6.93 (2 H, m, phenyl 2- and 6-H), 6.69 (1 H, d, J 3.8, thiophenyl 4-H), 6.64 (1 H, d, J 3.8, thiophenyl 3-H), 5.53–5.34 (1 H, m, NHamide), 4.91 (1 H, t, J 7.5, 3-H), 3.47–3.34 (2 H, m, pyridinylethyl 1-H), 2.95–2.76 (2 H, m, 2-H) and 2.68–2.49 (2 H, m, pyridinylethyl 2-H). δC (100 MHz, chloroform-d) 170.7, 146.7, 138.7, 135.1, 128.9, 128.77, 128.75, 128.2, 127.1, 126.6, 125.8, 125.6, 123.8, 123.5, 122.9, 119.0, 117.1, 112.7, 43.9, 40.7, 35.60 and 35.57. HRMS m/z calculated for C23H20Cl2N2NaO2S (M+Na)+: 465.0566; Found: 465.0562. IR (film): 3416, 3275, 1644.

**N-Benzyl-3-(5-chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)propenamide 7c**

According to general procedure E2, carboxylic acid 19 (20 mg, 0.38 mmol), 1-phenylmethanamine (20 µL, 0.18 mmol), DIPEA (35 µL, 0.18 mmol) and HCTU (50 mg, 0.12 mmol) in dimethylformamide (2 mL) at RT gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 → 50:50 of ethyl acetate:hexane) afforded amide 7c as a white solid (25 mg, 96%). δH (500 MHz, chloroform-d) 8.25 (1 H, s, NHindole), 7.44 (1 H, d, J 2.0, indolyl 4-H), 7.31–7.25 (1 H, m, indolyl 7-H), 7.24–7.20 (3 H, benzyl 4-H, 5-H and 6-H), 7.14 (1 H, dd, J 8.6 and 2.0, indolyl 6-H), 7.04 (1 H, d, J 2.5, indolyl 2-H), 6.95–6.90 (2 H, m, benzyl 3-H and 7-H), 6.70 (1 H, d, J 3.8, thiophenyl 4-H), 6.66 (1 H, dd, J 3.8 and 1.0, thiophenyl 3-H), 5.71–5.62 (1 H, m, NHamide), 4.94 (1 H, tt, J 7.7 and 0.9, 3-H), 4.32 (2 H, d, J 5.8, benzyl 1-H), 3.00 (1 H, dd, J 13.9 and 7.7, 2-Hα) and 2.93 (1 H, dd, J 13.9 and 7.7, 2-Hα). δC (125 MHz, chloroform-d) 170.4, 146.6, 137.9, 135.1, 128.7 (x2), 128.3, 127.6 (x3), 127.1, 125.9, 125.7, 124.0, 123.5, 123.0, 118.9, 117.1, 112.6, 44.1, 43.6 and 35.7. HRMS m/z calculated for C22H19Cl2N2O2S (M+H)+: 429.0595; Found: 429.0582.
3-(5-Chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-N-(2-methoxyethyl) propanamide 7d

According to general procedure E1, carboxylic acid 19 (50 mg, 0.15 mmol), 2-methoxyethylamine (14 µL, 0.16 mmol), pyridine (50 µL, 0.6 mmol) and T3P (175 µL, 0.3 mmol) in ethyl acetate (0.10 mL) gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 → 20:80 of ethyl acetate:hexane) afforded amide 7d as a light brown oil which solidified on standing (53 mg, 90%); δH (400 MHz, chloroform-d) 8.71–8.60 (1 H, m, NH indole), 7.43 (1 H, d, J 2.0, indolyl 4-H), 7.23 (1 H, d, J 8.6, indolyl 7-H), 7.10 (1 H, dd, J 8.6 and 2.0, indolyl 6-H), 7.04 (1 H, d, J 2.6, indolyl 2-H), 6.68 (1 H, d, J 3.8, thiophenyl 4-H), 6.64 (1 H, dd, J 3.8 and 1.0, thiophenyl 3-H), 5.95–5.86 (1 H, m, NHamide), 4.92 (1 H, app. t, J 7.5, 3-H), 3.42–3.23 (4 H, m, methoxyethyl 1- and 2-Hδ), 3.22 (3 H, s, methoxy), 2.95 (1 H, dd, J 14.1 and 7.3, 2-Hα) and 2.88 (1 H, dd, J 14.1 and 7.9, 2-Hβ). δC (125 MHz, chloroform-d) 170.7, 146.8, 135.0, 128.2, 127.2, 125.8, 125.5, 123.8, 123.3, 122.8, 118.9, 117.3, 112.6, 71.1, 58.8, 44.0, 39.3 and 35.5. HRMS m/z calculated for C18H18Cl2N2O2S (M+Na)+: 419.0358; Found: 419.0356. IR (film): 3420, 3286, 1645.

6-Chloro-3-[[5-chlorothiophen-2-yl](4-methylbenzenesulfonyl)methyl]-1H-indole

By general procedure A1, 6-chloroindole (0.94 g, 6.2 mmol), 5-chloro-2-thiophenecarboxaldehyde (0.60 mL, 5.6 mmol) and p-toluenesulfinic acid (2.0 g, 13 mmol) in dichloromethane (30 mL) gave the crude product. The product was precipitated in cold diethyl ether (30 mL), filtered, washed with diethyl ether (3 x 10 mL) and dried in vacuo to afford indole 20 as a light pink solid (1.3 g, 49%); δH (400 MHz, DMSO-d6) 11.46 (1 H, d, J 2.8, NH), 7.70 (1 H, d, J 8.6, 4-H), 7.61–7.54 (3 H, m, 2-H and benzenesulfonyl 2- and 6-H), 7.40 (1 H, d, J 1.9, 7-H), 7.28 (2 H, app. d, J 8.0, benzenesulfonyl 3- and 5-H), 7.04–6.96 (3 H, m, 5-H, thiophenyl 3- and 4-H), 6.63
(1 H, s, CHS) and 2.31 (3 H, s, benzenesulfonyl 4-methyl). δC (125 MHz, DMSO-d$_6$) 144.4, 134.9, 134.5, 133.9, 129.6, 129.3 (x2), 129.2, 128.6 (x2), 127.80, 127.75, 126.5, 124.0, 121.6, 118.3, 113.2, 105.8, 62.3 and 21.0. HRMS m/z calculated for C$_{13}$H$_8$Cl$_2$NS (M-SO$_2$Tol)$^+$: 279.9749; Found: 279.9658. IR (film): 3387, 1437, 1283, 1143, 1135.

Methyl 3-(6-chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)propanoate

According to general procedure B1, indole 20 (1.0 g, 2.3 mmol), tert-butyl((1-methoxyvinyl)oxy)dimethylsilane (1.7 mL, 7.8 mmol) and trifluoromethanesulfonic acid (11.0 µL, 0.12 mmol) in dichloromethane (25 mL) gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 → 20:80 of ethyl acetate:hexane) afforded ester 21 as a light yellow oil (0.41 g, 51%); δH (400 MHz, chloroform-d) 8.10 (1 H, app. s, NH), 7.38 (1 H, d, J 8.5, indolyl 4-H), 7.34 (1 H, d, J 1.8, indolyl 7-H), 7.09 (1 H, d, J 2.4, indolyl 2-H), 7.05 (1 H, dd, J 8.5 and 1.8, indolyl 5-H), 6.69 (1 H, d, J 3.8, thiophenyl 4-H), 6.67 (1 H, dd, J 3.8 and 0.9, thiophenyl 3-H), 4.93 (1 H, app. t, J 7.7, 3-H), 3.64 (3 H, s, methyl) and 3.17–3.01 (2 H, m, 2-H$_2$). δC (100 MHz, chloroform-d) 171.8, 146.5, 134.9, 128.3, 127.3, 125.8, 125.7, 123.7, 123.0, 122.9, 118.8, 117.6, 112.5, 52.0, 41.7 and 34.8. HRMS m/z calculated for C$_{16}$H$_{13}$Cl$_2$NNaO$_2$S (M+Na)$^+$: 375.9942; Found: 375.9932.

3-(6-Chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)propanoic acid

According to general procedure C, ester 21 (43 mg, 0.12 mmol) and sodium hydroxide solution (1 mL, 0.5 M) in methanol:tetrahydrofuran (2 mL) afforded acid 22 as a brown solid (40 mg, 99%). δH (500 MHz, methanol-d$_4$) 7.49–7.43 (1 H, m, indolyl 4-H), 7.31 (1 H, dd, J 2.0 and 0.8, indolyl 7-H), 7.08–7.03 (1 H, m, indolyl 2-H), 6.98 (1 H, ddd, J 8.6, 2.0 and 0.8, indolyl 5-H), 6.72–6.64 (2 H, m, thiophenyl 3- and 4-H), 5.23–5.16 (1
H, m, 3-H), 3.34 (1 H, dd, J 15.7 and 7.9, 2-HA) and 3.06 (1 H, dd, J 15.7 and 7.5, 2-HB). δc (125 MHz, methanol-d4) 174.9, 148.4, 137.6, 134.0, 129.9, 129.8, 127.0, 126.7, 126.6, 124.3, 121.8, 121.0, 112.1, 40.9 and 36.2. HRMS m/z calculated for C15H10Cl2NO2S (M-H): 337.9815; Found: 337.9419.

3-(6-Chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-N-[2-(pyridin-2-yl)ethyl] propanamide 8a

According to general procedure E1, carboxylic acid 22 (50 mg, 0.15 mmol), 2-(2-pyridyl)ethylamine (20 µL, 0.16 mmol), pyridine (50 µL, 0.6 mmol) and T3P (175 µL, 0.3 mmol) in ethyl acetate (0.10 mL) gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 → 20:80 of ethyl acetate:hexane) afforded amide 8a as a colourless solid (32 mg, 49%); δH (500 MHz, DMSO-d6) 11.30 (1 H, app. s, NHindole), 8.47 (1 H, dd, J 5.0 and 1.8, pyridinyl 6-H), 8.17 (1 H, br s, NHamide), 7.63 (1 H, td, J 7.6 and 1.8, pyridinyl 4-H), 7.41 (1 H, d, J 1.9, indolyl 7-H), 7.38 (1 H, d, J 8.5, indolyl 4-H), 7.33 (1 H, d, J 2.4, indolyl 2-H), 7.19 (1 H, dd, J 7.6 and 5.0, pyridinyl 5-H), 7.08 (1 H, d, J 7.6, pyridinyl 3-H), 6.95 (1 H, dd, J 8.5 and 1.9, indolyl 5-H), 6.86 (1 H, d, J 3.8, thiophenyl 4-H), 6.77 (1 H, d, J 3.8, thiophenyl 3-H), 4.87 (1 H, app. t, J 7.7, 3-H), 3.44–3.28 (2 H, m, pyridinylethyl 1-H2), 2.92–2.80 (2 H, m, 2-H2) and 2.75 (2 H, t, J 7.2, pyridinylethyl 2-H2). δc (125 MHz, DMSO-d6) 169.8, 159.0, 149.0, 148.9, 136.8, 136.3, 126.1, 125.9, 125.5, 124.8, 123.6, 123.3, 123.0, 121.4, 120.0, 118.8, 116.7, 111.2, 42.4, 38.4, 37.3 and 34.3. HRMS m/z calculated for C22H19Cl2N3NaOS (M+Na)+: 466.0518; Found: 466.0512. IR (film): 3340, 1630.

3-(6-Chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-N-(2-phenylethyl) propanamide 8b

According to general procedure E1, carboxylic acid 22 (50 mg, 0.15 mmol), 2-phenylethylamine (20 µL, 0.16 mmol), pyridine (50 µL, 0.6 mmol) and T3P (175 µL,
0.3 mmol) in ethyl acetate (0.10 mL) gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 → 20:80 of ethyl acetate:hexane) afforded amide 8b as a light purple oil which solidified on standing (62 mg, 95%); \( \delta_H \) (400 MHz, chloroform-d) 8.60 (1 H, s, NH\_indole), 7.38 (2 H, m, indolyl 4- and 7-H), 7.34–7.20 (3 H, m, phenyl 3-, 4- and 5-H), 7.08–7.03 (2 H, m, indolyl 2- and 5-H), 7.01–6.94 (2 H, m, phenyl 2- and 6-H), 6.73 (1 H, d, J 3.8, thiophenyl 4-H), 6.68 (1 H, d, J 3.8, thiophenyl 3-H), 5.50 (1 H, t, J 6.3, NH\_amide), 4.97 (1 H, t, J 7.5, 3-H), 3.45 (2 H, q, J 6.3, pyridinylethyl 1-H\(_2\)), 2.94 (1 H, dd, J 14.0 and 7.5, 2-H\(_A\)), 2.86 (1 H, dd, J 14.0 and 7.5, 2-H\(_B\)) and 2.63 (2 H, m, pyridinylethyl 2-H\(_2\)). \( \delta_C \) (100 MHz, chloroform-d) 170.7, 146.9, 138.7, 137.1, 128.84, 128.80, 128.75, 128.7, 128.4, 128.2, 126.6, 125.8, 124.7, 123.8, 122.6, 120.5, 120.4, 117.5, 111.5, 44.0, 40.7, 35.61 and 35.57. HRMS \( m/z \) calculated for \( C_{23}H_{20}Cl_2N_2\text{NaO}_2\text{S} \) (M+Na\(^+\)): 465.0566; Found: 465.0560. IR (film): 3387, 3279, 1631.

3-(6-Chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-N-(2-methoxyethyl) propanamidine 8c

According to general procedure E1, carboxylic acid 22 (50 mg, 0.15 mmol), 2-methoxyethylamine (20 µL, 0.23 mmol), pyridine (50 µL, 0.6 mmol) and T3P (175 µL, 0.3 mmol) in ethyl acetate (0.10 mL) gave the crude product. Purification by column chromatography (silica, Eluent: gradient 0:100 → 20:80 of ethyl acetate:hexane) afforded amide 8c as a light purple oil which solidified on standing (61 mg, 99%); \( \delta_H \) (400 MHz, chloroform-d) 8.60 (1 H, app. s, NH\_indole), 7.35 (1 H, d, J 8.5, indolyl 4-H), 7.32 (1 H, d, J 1.9, indolyl 7-H), 7.03 (1 H, d, J 2.4, indolyl 2-H), 7.01 (1 H, dd, J 8.5 and 1.9, indolyl 5-H), 6.68 (1 H, d, J 3.7, thiophenyl 4-H), 6.66–6.63 (1 H, m, thiophenyl 3-H), 5.96–5.85 (1 H, m, NH\_amide), 4.93 (1 H, app. t, J 7.6, 3-H), 3.40–3.19 (4 H, m, methoxyethyl 1- and 2-H\(_2\)), 3.22 (3 H, s, methoxy), 2.96 (1 H, dd, J 14.0 and 7.4, 2-H\(_A\)) and 2.88 (1 H, dd, J 14.0 and 7.9, 2-H\(_B\)). \( \delta_C \) (100 MHz, chloroform-d) 170.9, 146.9, 137.1, 128.4, 128.1, 125.7, 124.8, 123.8, 122.5, 120.5, 120.3, 117.6, 111.5, 71.0, 58.7, 44.0, 39.4 and 35.5. HRMS \( m/z \) calculated for \( C_{18}H_{18}Cl_2N_2\text{NaO}_2\text{S} \) (M+Na\(^+\)): 419.0358; Found: 419.0355. IR (film): 3283, 1644;
5-Chloro-3-[(4-methylbenzenesulfonyl)(phenyl)methyl]-1H-indole

According to general procedure A1, 5-chloroindole (1.0 g, 6.6 mmol), benzaldehyde (0.61 mL, 6.0 mmol) and p-toluenesulfinic acid (2.0 g, 13 mmol) in dichloromethane (30 mL) gave the crude product. The product was precipitated in cold diethyl ether (30 mL), filtered, washed with diethyl ether (3 x 10 mL) and dried *in vacuo* to afford indole 23 as a light pink solid (1.3 g, 48%); δ_H (400 MHz, DMSO-d_6) 11.46 (1 H, d, J 2.7, NH), 7.73 (1 H, d, J 2.7, 2-H), 7.68 (1 H, d, J 2.0, 4-H), 7.59–7.56 (2 H, m, phenyl 2- and 6-H), 7.56–7.52 (2 H, m, benzenesulfonyl 2- and 6-H), 7.32 (1 H, d, J 8.7, 7-H), 7.32–7.22 (3 H, m, phenyl 3-, 4- and 5-H), 7.21 (2 H, app. d, J 8.1, benzenesulfonyl 3- and 5-H), 7.02 (1 H, dd, J 8.7 and 2.0, 6-H), 6.24 (1 H, s, CHS) and 2.26 (3 H, s, benzenesulfonyl 4-methyl). δ_C (100 MHz, DMSO-d_6) 143.9, 135.6, 133.9, 133.8, 130.1 (x2), 129.1 (x2), 128.5 (x2), 128.2 (x3), 128.1, 127.2, 123.8, 121.4, 118.0, 113.0, 106.5, 66.0 and 21.0. HRMS m/z calculated for C_{22}H_{22}Cl_2N_2S (M+NH_4)^+: 413.1080; Found: 413.1085. IR (film): 3356, 1453, 1282, 1138.

Methyl 3-(5-chloro-1H-indol-3-yl)-3-phenylpropanoate

According to general procedure B1, indole 23 (0.50 g, 1.2 mmol), tert-butyl((1-methoxyvinyl)oxy)dimethylsilane (0.80 mL, 3.7 mmol) and trifluoromethanesulfonic acid (6.0 µL, 0.07 mmol) in dichloromethane (15 mL) gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 → 20:80 of ethyl acetate:hexane) afforded ester 24 as a light orange solid (0.32 g, 80%); δ_H (400 MHz, chloroform-d) 8.08 (1 H, app. s, NH), 7.37 (1 H, d, J 1.9, indolyl 4-H), 7.32–7.27 (4 H, m, phenyl 2-, 3-, 5- and 6-H), 7.24–7.16 (2 H, m, indolyl 7-H and phenyl 4-H), 7.10 (1 H, dd, J 8.6 and 1.9, indolyl 6-H), 7.07 (1 H, d, J 2.5, indolyl 2-H), 4.75 (1 H, app. t, J 7.9, 3-H), 3.60 (3 H, s, methyl), 3.13 (1 H, dd, J 15.2 and 8.0, 2-H\textsubscript{A}) and 3.02 (1 H, dd, J 15.2 and 7.8, 2-H\textsubscript{B}). δ_C (100 MHz, chloroform-d) 172.5, 143.3, 135.0, 128.7 (x3), 123.8, 121.4, 118.0, 113.0, 106.5, 66.0 and 21.0. HRMS m/z calculated for C_{22}H_{22}Cl_2N_2O_2S (M+H)^+: 413.1080; Found: 413.1085. IR (film): 3356, 1453, 1282, 1138.
127.7 (x2), 126.8, 125.4, 122.7, 122.6, 119.1, 118.7, 112.2, 51.9, 41.4 and 39.2. HRMS m/z calculated for C_{18}H_{16}ClNNaO_{2} (M+Na)^{+}: 336.0762; Found: 336.0756.

3-(5-Chloro-1H-indol-3-yl)-3-phenylpropanoic acid

According to general procedure C, ester 24 (100 mg, 0.3 mmol) and sodium hydroxide solution (3 mL, 1.3 M) in methanol (2 mL) afforded acid 25 as a light yellow oil which solidified upon standing (95 mg, 99%); δ\text{H} (400 MHz, methanol-d_{4}) 7.34 – 7.19 (7 H, m, indolyl 2-, 4- and 7-H and phenyl 2-, 3-, 5- and 6-H), 7.19–7.13 (1 H, m, phenyl 4-H), 7.00 (1 H, dd, J 8.6 and 2.1, indolyl 6-H), 4.67 (1 H, app. t, J 7.9, 3-H), 3.11 (1 H, dd, J 15.3 and 7.8, 2-H\textsubscript{A}) and 2.97 (1 H, dd, J 15.2 and 7.9, 2-H\textsubscript{B}). δ\text{C} (100 MHz, DMSO-d_{6}) 172.8, 144.5, 134.8, 128.2 (x2), 127.6 (x2), 127.4, 126.1, 123.7, 122.9, 120.9, 117.8, 117.4, 112.9, 54.9 and 38.4. HRMS m/z calculated for C_{17}H_{14}ClNNaO_{2} (M+Na)^{+}: 322.0611; Found: 322.0682.

3-(5-Chloro-1H-indol-3-yl)-3-phenyl-N-[2-(pyridin-2-yl)ethyl]propanamide 9a

According to general procedure E1, carboxylic acid 25 (50 mg, 0.17 mmol), 2-(2-pyridyl)ethylamine (110 µL, 0.90 mmol), pyridine (50 µL, 0.6 mmol) and T3P (175 µL, 0.3 mmol) in ethyl acetate (3 mL) gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 \rightarrow 20:80 of ethyl acetate:hexane) afforded amide 9a as a colourless oil which solidified on standing (39 mg, 59%); δ\text{H} (500 MHz, chloroform-d) 8.52 – 8.45 (1 H, m, pyridinyl 6-H), 8.37 (1 H, s, NH\text{indole}), 7.58 (1 H, td, J 7.7 and 1.9, pyridinyl 4-H), 7.39 (1 H, d, J 2.0, indolyl 4-H), 7.36–7.18 (6 H, m, indolyl 7-H and phenyl 2- to 6-H), 7.20–7.15 (1 H, m, pyridinyl 5-H), 7.15–7.11 (2 H, m, indolyl 2- and 6-H), 6.98 (1 H, d, J 7.7, pyridinyl 3-H), 6.41 (1 H, t, J 6.1, NH\text{amide}), 4.77 (1 H, app. t, J 7.8, 3-H), 3.60 (2 H, q, J 6.1, pyridinylethyl 1-H\textsubscript{2}), 3.05 (1 H, dd, J 14.1 and 8.0, 2-H\textsubscript{A}), 2.90 (1 H, dd, J 14.1 and 7.6, 2-H\textsubscript{B}) and 2.80 (2 H, t, J
According to general procedure E1, carboxylic acid 25 (50 mg, 0.15 mmol), 2-phenylethylamine (20 µL, 0.16 mmol), pyridine (50 µL, 0.6 mmol) and T3P (175 µL, 0.3 mmol) in ethyl acetate (0.10 mL) gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 → 20:80 of ethyl acetate:hexane) afforded amide 9b as a light purple oil which solidified on standing (47 mg, 70%); δH (400 MHz, chloroform-d) 8.73 (1 H, app. s, NHindole), 7.40 (1 H, d, J 2.0, indolyl 4-H), 7.37–6.93 (11 H, m, indolyl 7-H, phenyl 2- to 6-H and ethylphenyl 2- to 6-H), 7.14 (1 H, dd, J 8.6 and 2.0, indolyl 6-H), 7.04 (1 H, d, J 2.5, indolyl 2-H), 5.52 (1 H, t, J 5.9, NHamide), 4.77 (1 H, app. t, J 7.7, 3-H), 3.52–3.32 (2 H, m, phenylethyl 1-H2), 3.00 (1 H, dd, J 14.1 and 7.6, 2-HA), 2.83 (1 H, dd, J 14.1 and 7.8, 2-HB) and 2.66–2.53 (2 H, m, phenylethyl 2-H2). δC (125 MHz, chloroform-d) 171.2, 143.5, 139.0, 135.1, 128.80 (x2), 128.76 (x2), 128.71 (x2), 127.8 (x3), 126.8, 126.5, 125.4, 123.0, 122.7, 119.3, 118.6, 112.3, 43.8, 40.6, 39.7 and 35.7. HRMS m/z calculated for C25H24ClN2O (M+H)+: 403.1578; Found: 403.1589. IR (film): 3420, 3276, 1645.

**N-Benzyl-3-(5-chloro-1H-indol-3-yl)-3-phenylpropanamide 9c**

According to general procedure E1, carboxylic acid 25 (50 mg, 0.15 mmol), benzylamine (20 µL, 0.18 mmol), pyridine (50 µL, 0.6 mmol) and T3P (175 µL, 0.3 mmol) in ethyl acetate (0.10 mL) gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 → 20:80 of ethyl acetate:hexane)
afforded amide 9c as a colourless oil (49 mg, 69%); δH (400 MHz, chloroform-d) 8.66 (1 H, app. s, NHindole), 7.38 (1 H, d, J 2.0, indolyl 4-H), 7.32–6.79 (11 H, m, indolyl 7-H, phenyl 2- to 6-H and benzyl 3 to 7-H), 7.08 (1 H, dd, J 8.6 and 2.0, indolyl 6-H), 6.95 (1 H, d, J 2.5, indolyl 2-H), 5.90 (1 H, app. t, J 5.8, NHamide), 4.75 (1 H, app. t, J 7.8, 3-H), 4.31 (1 H, dd, J 15.0 and 5.9, benzyl 1-HA), 4.24 (1 H, dd, J 15.0 and 5.6, benzyl 1-HB), 3.03 (1 H, dd, J 13.9 and 7.6, 2-HA) and 2.87 (1 H, dd, J 13.9 and 8.0, 2-HB). δC (100 MHz, chloroform-d) 171.5, 143.3, 137.8, 135.0, 128.7 (x2), 128.5 (x2), 127.6, 127.31, 127.27, 126.7, 125.0, 123.2, 122.4, 118.8, 117.9, 112.4, 104.2, 43.6, 43.4 and 39.7. HRMS m/z calculated for C24H21ClN2NaO (M+Na)+: 411.1235; Found: 411.1232. IR (film): 3268, 1641.

3-(5-Chloro-1H-indol-3-yl)-N-(2-methoxyethyl)-3-phenylpropanamide 9d

According to general procedure E1, carboxylic acid 25 (50 mg, 0.15 mmol), 2-methoxyethylamine (20 µL, 0.23 mmol), pyridine (50 µL, 0.6 mmol) and T3P (175 µL, 0.3 mmol) in ethyl acetate (0.10 mL) gave the crude product. Purification by column chromatography (silica, Eluent: gradient 0:100 → 20:80 of ethyl acetate:hexane) afforded amide 9d as a colourless oil which solidified on standing (40 mg, 67%); δH (400 MHz, chloroform-d) 8.65 (1 H, app. s, NHindole), 7.36 (1 H, d, J 2.0, indolyl 4-H), 7.27 (4 H, m, phenyl 2-, 3-, 5- and 6-H), 7.22–7.16 (2 H, m, indolyl 7-H and phenyl 4-H), 7.07 (1 H, dd, J 8.6 and 2.0, indolyl 6-H), 7.00 (1 H, d, J 2.4, indolyl 2-H), 5.78 (1 H, t, J 5.6, NHamide), 4.72 (1 H, app. t, J 7.7, 3-H), 3.37–3.25 (2 H, m, methoxyethyl 1-H2), 3.27–3.11 (2 H, m, methoxyethyl 2-H2), 3.19 (3 H, s, methoxy), 2.99 (1 H, dd, J 14.0 and 7.4, 2-HA) and 2.83 (1 H, dd, J 14.0 and 8.0, 2-HB). δC (125 MHz, chloroform-d) 171.3, 143.5, 135.1, 128.7 (x2), 127.84, 127.79 (x2), 126.8, 125.4, 122.9, 122.7, 119.2, 118.8, 112.2, 71.2, 58.7, 43.8, 39.7 and 39.2. HRMS m/z calculated for C20H21ClN2NaO2S (M+Na)+: C20H21ClN2NaO2 379.1184; Found: 379.1183. IR (film): 3323, 1617.
Methyl 3-(2-bromo-6-chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)propanoate

According to general procedure D, ester 21 (870 mg, 2.46 mmol) and pyridinium tribromide (960 mg, 2.70 mmol) in tetrahydrofuran:chloroform (20 mL) gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 → 20:80 of ethyl acetate:hexane) afforded ester 26 as a yellow oil which solidified on standing (823 mg, 77%); Rf = 0.17 (9:1 hexane:ethyl acetate); δH (500 MHz, chloroform-d) 8.16 (1 H, s, NH), 7.36 (1 H, dt, J 8.6 and 0.6, indolyl 4-H), 7.28 (1 H, dd, J 1.9 and 0.6, indolyl 7-H), 7.05 (1 H, dd, J 8.6 and 1.9, indolyl 5-H), 6.69 (1 H, d, J 3.8, thiophenyl 4-H), 6.64 (1 H, dd, J 3.8 and 1.3, thiophenyl 3-H), 4.94 (1 H, ddd, J 8.4, 7.2 and 1.3, 3-H), 3.63 (3 H, s, methyl), 3.30 (1 H, dd, J 15.7 and 7.2, 2-HA) and 3.16 (1 H, dd, J 15.7 and 8.4, 2-HB). δC (125 MHz, chloroform-d) 171.6, 145.1, 136.7, 128.9, 128.5, 125.7, 124.6, 123.4, 121.3, 119.8, 115.8, 110.9, 109.4, 52.1, 39.5 and 35.0. HRMS m/z calculated for C16H12BrCl2NaO2S (M+Na)+: 453.9047; Found: 453.9031.

tert-Butyl 2-bromo-6-chloro-3-[1-(5-chlorothiophen-2-yl)-3-methoxy-3-oxopropyl]-indole-1-carboxylate

To a solution of 26 (810 mg, 1.87 mmol) and triethylamine (0.80 mL, 5.6 mmol) in dichloromethane (10mL) at 0 °C, di-tert-butyl dicarbonate (817 mg, 3.74 mmol) and DMAP (23 mg, 0.19 mmol) were subsequently added and the reaction mixture was stirred at room temperature for 1.5 h. Saturated aqueous sodium hydrogen carbonate solution (10 mL) was added and the organic layer extracted with dichloromethane (2 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. Purification by column chromatography (silica, eluent: gradient 0:100 → 10:90 of ethyl acetate:hexane) afforded indole 27 as a yellow oil (997 mg, quantitative yield). Rf = 0.54 (8:2 hexane:ethylacetate); δH (500 MHz,
chloroform-d) 8.15 (1 H, d, J 1.9, 7-H), 7.29 (1 H, d, J 8.5, 4-H), 7.15 (1 H, dd, J 8.5 and 1.9, 5-H), 6.70 (1 H, d, J 3.8, thiophenyl 4-H), 6.65 (1 H, dd, J 3.8 and 1.4, thiophenyl 3-H), 5.10 (1 H, app. td, J 7.7 and 1.4, oxopropyl 1-H), 3.65 (3 H, s, methoxy), 3.30 (1 H, dd, J 15.8 and 7.4, oxopropyl 2-HA), 3.12 (1 H, dd, J 15.8 and 7.9, oxopropyl 2-HB) and 1.70 (9 H, s, tert-butyl). δC (125 MHz, chloroform-d) 171.3, 148.7, 143.8, 137.3, 130.9, 128.8, 125.8, 125.4, 123.68, 123.66, 122.3, 119.8, 116.0, 110.7, 86.2, 52.2, 38.6, 35.5 and 28.3 (x3).

HRMS m/z calculated for C21H20BrCl2NNaO4S (M+Na)+: 553.9571; Found: 553.9556.

3-(2-Bromo-6-chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)propanoic acid

According to general procedure C, ester 26 (100 mg, 0.23 mmol) and sodium hydroxide solution (0.5 mL, 1.4 M) in methanol:tetrahydrofuran (2 mL) afforded acid 28 as white solid (96 mg, quantitative yield). δH (500 MHz, chloroform-d) 8.13 (1 H, s, NH), 7.36 (1 H, d, J 8.6, indolyl 4-H), 7.29 (1 H, d, J 1.8, indolyl 7-H), 7.06 (1 H, dd, J 8.6 and 1.8, indolyl 5-H), 6.70 (1 H, d, J 3.8, thiophenyl 4-H), 6.66 (1 H, dd, J 3.8 and 1.0, thiophenyl 3-H), 4.92 (1 H, m, 3-H), 3.33 (1 H, dd, J 16.1 and 7.4, 2-HA) and 3.19 (1 H, dd, J 16.1 and 8.0, 2-HB). δC (125 MHz, chloroform-d) 174.8, 144.8, 136.6, 128.9, 128.6, 125.7, 124.6, 123.4, 121.4, 119.8, 115.6, 110.9, 109.4, 39.0 and 34.8. HRMS m/z calculated for C15H10Cl2NO2S (M-Br)+: 337.9809; Found: 337.9799.

3-(2-Bromo-6-chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-N-[2-(pyridin-2-yl)ethyl]propanamide 11a

According to general procedure E2, carboxylic acid 28 (402 mg, 0.96 mmol), 2-(2-pyridyl)ethylamine (163 µL, 1.36 mmol), DIPEA (0.50 mL, 2.7 mmol) and HCTU (414 mg, 1.0 mmol) in dimethylformamide (3 mL) at RT gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 → 100:0 of ethyl
acetate:hexane) afforded amide 11a as a white solid (484 mg, 91%); δH (500 MHz, chloroform-d) 8.39–8.31 (2 H, m, pyridinyl 6-H and NHindole), 7.55 (1 H, td, J 7.7 and 1.8, pyridinyl 4-H), 7.33 (1 H, d, J 8.5, indolyl 4-H), 7.17 (1 H, d, J 1.8, indolyl 7-H), 7.12 (1 H, ddd, J 7.7, 4.9 and 1.1, pyridinyl 5-H), 7.00 (1 H, dd, J 8.5 and 1.8, indolyl 5-H), 6.97–6.91 (1 H, m, pyridinyl 3-H), 6.66 (1 H, d, J 3.8, thiophenyl 4-H), 6.62–6.55 (1 H, m, thiophenyl 3-H), 6.44–6.35 (1 H, m, NHamide), 4.96 (1 H, ddd, J 9.1, 6.4 and 1.3, 3-H), 3.64–3.54 (1 H, m, pyridinylethyl-1-HA), 3.53–3.44 (1 H, m, pyridinylethyl-1-HB), 3.10 (1 H, dd, J 13.9 and 6.4, 2-HA), 2.97 (1 H, dd, J 13.9 and 9.1, 2-HB), 2.81 (1 H, ddd, J 15.1, 7.0 and 4.8, pyridinylethyl-2-HA) and 2.64 (1 H, ddd, J 15.1, 8.0 and 5.0, pyridinylethyl-2-HB). δC (125 MHz, chloroform-d) 170.0, 159.4, 149.1, 145.6, 136.7 (x2), 128.7, 128.2, 125.7, 124.6, 123.43, 123.41, 121.6, 121.2, 119.8, 115.8, 110.9, 109.8, 42.1, 38.5, 36.6 and 35.7. HRMS m/z calculated for C22H19BrCl2N3O5S (M+H)+: 521.9809; Found:: 521.9823.

Methyl 3-(5-chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-2,2-dimethyl propanoate

According to general procedure B2, indole 17 (200 mg, 0.46 mmol), [(1-methoxy-2-methyl-1-propenyl)oxy](trimethyl)silane (0.47 mL, 2.3 mmol) and trifluoromethanesulfonic acid (16 µL, 0.18 mmol) in dichloromethane (5 mL) gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 → 20:80 of ethyl acetate:hexane) afforded ester 29 as an off-white solid (158 mg, 88%); Rf = 0.17 (9:1 hexane:ethyl acetate); δH (500 MHz, chloroform-d) 8.16 (1 H, s, NH), 7.56–7.49 (1 H, m, indolyl 4-H), 7.31 (1 H, d, J 2.3, indolyl 7-H), 7.28–7.24 (1 H, m, indolyl 2-H), 7.13 (1 H, dd, J 8.6 and 2.3, indolyl 6-H), 6.73–6.67 (2 H, m, thiophenyl 3- and 4-H), 4.90 (1 H, s, 3-H), 3.57 (3 H, s, methyl), 1.36 (3 H, s, 2-methylA) and 1.28 (3 H, s, 2-methylB). δC (125 MHz, chloroform-d) 177.6, 143.7, 133.8, 129.0, 128.4, 126.0, 125.8, 125.4, 123.9, 122.9, 118.7, 115.2, 112.2, 52.1, 47.5, 45.5, 23.8 and 23.7. HRMS m/z calculated for C18H17Cl2NNaO2S (M+Na)+: 404.0255; Found: 404.0247.
3-(5-Chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-2,2-dimethylpropanoic acid

According to general procedure C, ester 29 (150 mg, 0.41 mmol) and sodium hydroxide solution (1.5 mL, 2.5 M) in methanol:tetrahydrofuran (2 mL) at 60 °C afforded acid 30 as white solid (166 mg, 95%). δ_H (500 MHz, chloroform-d) 8.15 (1 H, app. s, NH), 7.52 (1 H, d, J 2.0, indolyl 4-H), 7.31 (1 H, d, J 2.5, indolyl 2-H), 7.26 (1 H, d, J 8.6, indolyl 7-H), 7.14 (1 H, dd, J 8.6 and 2.0, indolyl 6-H), 6.73 (1 H, d, J 3.8, thiophenyl 3-H), 6.69 (1 H, d, J 3.8, thiophenyl 4-H), 4.89 (1 H, s, 3-H), 1.38 (3 H, s, 2-MeA) and 1.30 (3 H, s, 2-MeB). δ_C (125 MHz, chloroform-d) 182.0, 143.5, 133.8, 129.0, 128.5, 126.3, 125.8, 125.5, 123.9, 122.9, 118.7, 115.1, 112.3, 47.3, 45.3, 23.9 and 23.5. HRMS m/z calculated for C_{17}H_{15}Cl_{2}NNaO_{2}S (M+Na)^+: 390.0098; Found: 390.0091.

3-(5-Chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-2,2-dimethyl-N-[2-(pyridin-2-yl)ethyl]propanamide 12

According to general procedure E2, carboxylic acid 30 (140 mg, 0.38 mmol), 2-(2-pyridyl)ethylamine (69 µL, 0.57 mmol), DIPEA (0.20 mL, 1.1 mmol) and HCTU (173 mg, 0.42 mmol) in dimethylformamide (2 mL) at RT gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 → 100:0 of ethyl acetate:hexane) afforded 129 mg of impure material. The material was precipitated in diethyl ether/hexane (2 mL, 1:1), filtered and washed with diethyl ether (2 x 2 mL) to afford amide 12 as a white solid (116 mg, 64%). R_{f} = 0.18 (ethyl acetate); δ_H (500 MHz, chloroform-d) 8.48 – 8.41 (1 H, m, pyridinyl 6-H), 8.23 (1 H, app. s, NH_{indole}), 7.60–7.52 (2 H, m, pyridinyl 4-H and indolyl 4-H), 7.31 (1 H, d, J 2.5, indolyl 2-H), 7.21 (1 H, d, J 8.6, indolyl 7-H), 7.13 (1 H, ddd, J 7.7, 5.0 and 1.1, pyridinyl 5-H), 7.10 (1 H, dd, J 8.6 and 2.0, indolyl 6-H), 7.03–6.96 (2 H, m, pyridinyl 3-H and NH_{amide}), 6.68 (1 H, dd, J 3.8 and 0.8, thiophenyl 3-H), 6.61 (1 H, d, J 3.8, thiophenyl 4-H), 4.91 (1 H, s, 3-H), 3.59–3.50 (2 H, m, pyridinylethyl 1-H), 2.83–2.69 (2 H, m, pyridinylethyl 2-H).
1.31 (3 H, s, 2-methyl\textsubscript{A}) and 1.21 (3 H, s, 2-methyl\textsubscript{B}). δ\textsubscript{C} (125 MHz, chloroform-d) 176.7, 159.9, 149.1, 144.2, 136.8, 133.8, 129.2, 128.0, 126.1, 125.7, 125.3, 124.2, 123.6, 122.7, 121.7, 119.0, 115.3, 112.1, 47.2, 46.0, 38.9, 36.3, 24.6 and 23.3. HRMS m/z calculated for C\textsubscript{24}H\textsubscript{24}Cl\textsubscript{2}N\textsubscript{3}OS (M+H): 472.1017; Found: 472.1020.

**syn- and anti-Methyl 3-(5-chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-2-methylpropanoate**

![Chemical structure](image)

According to general procedure B2, indole 17 (200 mg, 0.46 mmol), ([1-methoxy-1-propenyl]oxy)(trimethyl)silane (0.42 mL, 2.3 mmol) and trifluoromethanesulfonic acid (16 µL, 0.18 mmol) in dichloromethane (5 mL) gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 → 20:80 of ethyl acetate:hexane) afforded ester 31 as a colourless oil (161 mg, 91%); R\textsubscript{f} = 0.20 (8:2 hexane:ethyl acetate); approximately a 7:3 mixture of diastereomers. δ\textsubscript{H} (500 MHz, chloroform-	extsubscript{d}) 8.14 (0.7 H, s, NH\textsuperscript{maj}), 8.06 (0.3 H, s, NH\textsuperscript{min}), 7.54 (0.7 H, d, J 2.0, indolyl 4-H\textsuperscript{maj}), 7.49 (0.3 H, d, J 2.0, indolyl 4-H\textsuperscript{min}), 7.28 (0.7 H, d, J 8.6, indolyl 7-H\textsuperscript{maj}), 7.24 (0.3 H, d, J 8.6, indolyl 7-H\textsuperscript{min}), 7.22–7.10 (2 H, m, indolyl 2-\textsuperscript{maj/min} and 6-H\textsuperscript{maj/min}), 6.77–6.66 (2 H, m, thiophenyl 3-\textsuperscript{maj/min} and 4-H\textsuperscript{maj/min}), 4.64–4.58 (1 H, m, 3-H\textsuperscript{maj/min}), 3.64 (2.1 H, s, methyl\textsuperscript{maj}), 3.52 (0.9 H, s, methyl\textsuperscript{min}), 3.28 (0.7 H, dq, J 10.4 and 7.0, 2-H\textsuperscript{maj}), 3.16 (0.3 H, dq, J 10.9 and 7.0, 2-H\textsuperscript{min}), 1.24 (0.9 H, d, J 7.0, 2-methyl\textsuperscript{min}) and 1.16 (2.1 H, d, J 7.0, 2-methyl\textsuperscript{maj}). δ\textsubscript{C} (125 MHz, chloroform-d) 175.9 (maj), 175.7 (min), 146.2 (maj), 145.3 (min), 134.8 (maj), 134.6 (min), 128.3 (min), 127.7 (maj), 125.8 (min), 125.7 (min), 125.6 (x2 maj), 124.9 (min), 123.8 (maj), 123.6 (maj), 123.0 (maj/min), 122.2 (min), 118.83 (x2 maj), 118.76 (min), 117.8 (min), 116.0 (maj/min), 112.5 (maj), 112.3 (min), 52.04 (maj), 52.00 (min), 46.1 (maj), 45.9 (min), 41.6 (maj), 41.5 (min), 16.74 (min) and 16.69 (maj). HRMS m/z calculated for C\textsubscript{17}H\textsubscript{15}Cl\textsubscript{2}NNaO\textsubscript{2}S (M+Na): 390.0098; Found: 390.0092.
**syn- and anti-3-(5-Chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-2-methylpropanoic acid**

According to general procedure C, ester 31 (154 mg, 0.42 mmol) and sodium hydroxide solution (5 mL, 0.5 M) in methanol (10 mL) at 60 °C afforded acid 32 as white solid (161 mg, 98%); approximately a 7:3 mixture of diastereomers. δ\(\text{H}\) (500 MHz, chloroform-\(d\)) 8.14 (0.7 H, s, NH\text{maj}), 8.06 (0.3 H, s, NH\text{min}), 7.53 (0.7 H, d, J 2.0, indolyl 4-H\text{maj}), 7.48 (0.3 H, d, J 2.0, indolyl 4-H\text{min}), 7.31–7.22 (1 H, m, indolyl 7-H\text{maj/min}), 7.26–7.10 (2 H, m, indolyl 2-\text{maj/min} and 6-H\text{maj/min}), 6.79–6.76 (0.3 H, m, thiophenyl 3-H\text{min}), 6.73 (0.7 H, dd, J 3.8 and 0.9, thiophenyl 3-H\text{maj}), 6.71 (0.3 H, d, J 3.7, thiophenyl 4-H\text{min}), 6.66 (0.7 H, d, J 3.8, thiophenyl 4-H\text{maj}), 4.62 (0.7 H, app. d, J 10.1, 3-H\text{maj}), 4.58 (0.3 H, d, J 10.4, 3-H\text{min}), 3.29 (0.7 H, dq, J 10.1 and 7.0, 2-H\text{maj}), 3.16 (0.3 H, dq, J 10.4 and 7.0, 2-H\text{min}), 1.27 (0.9 H, d, J 7.0, 2-methyl\text{min}) and 1.19 (2.1 H, d, J 7.0, 2-methyl\text{maj}). δ\(\text{C}\) (125 MHz, chloroform-\(d\)) 180.2 (maj), 180.1 (min), 145.9 (maj), 144.9 (min), 134.74 (maj), 134.65 (min), 128.8 (min), 128.4 (maj), 127.73 (min), 127.68 (maj), 125.8 (min), 125.7 (x2 maj), 125.1 (min), 123.9 (x2 maj), 123.7 (min), 123.10 (min), 123.07 (maj), 122.2 (min), 118.8 (maj), 118.7 (min), 117.6 (min), 115.8 (maj), 112.5 (maj), 112.3 (min), 45.7 (maj), 45.4 (min), 41.3 (min), 41.2 (maj), 16.8 (min) and 16.6 (maj). HRMS \(m/z\) calculated for C\text{16}H\text{13}Cl\text{2}NNaO\text{2}S (M+Na)^+: 375.9942; Found: 375.9935.

**syn- and anti-3-(5-Chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-2-methyl-N-[2-(pyridin-2-yl)ethyl]propanamide 10**

According to general procedure E2, carboxylic acid 32 (157 mg, 0.44 mmol), 2-(2-pyridyl)ethylamine (78 µL, 0.66 mmol), DIPEA (0.24 mL, 1.3 mmol) and HCTU (200 mg, 0.48 mmol) in dimethylformamide (2 mL) at RT gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 \(\rightarrow\) 100:0 of ethyl acetate:hexane) afforded two products as colourless materials. Diastereomers syn-10 and anti-10 were isolated in a 7:3 ratio, respectively.
Fraction one was precipitated in diethyl ether/hexane (2 mL, 1:1), filtered and washed with diethyl ether (2 x 2 mL) to afford amide syn-10 as a white solid (97 mg, 69%). Rf = 0.26 (ethyl acetate); δH (500 MHz, DMSO-d6) 11.19 (1 H, d, J 2.5, NHindole), 8.50 (1 H, ddd, J 4.9, 1.9 and 0.9, pyridinyl 6-H), 8.07 (1 H, t, J 5.7, NHamide), 7.68 (1 H, td, J 7.6 and 1.9, pyridinyl 4-H), 7.57 (1 H, d, J 2.0, indolyl 4-H), 7.41 (1 H, d, J 2.5, indolyl 2-H), 7.37 (1 H, d, J 8.6, indolyl 7-H), 7.21 (1 H, ddd, J 7.6, 4.9 and 1.2, pyridinyl 5-H), 7.17–7.12 (1 H, m, pyridinyl 3-H), 7.07 (1 H, dd, J 8.6 and 2.0, indolyl 6-H), 6.82 (1 H, d, J 3.8, thiophenyl 4-H), 6.76 (1 H, dd, J 3.8 and 0.9, thiophenyl 3-H), 4.49 (1 H, app. d, J 11.1, 3-H), 3.47–3.31 (2 H, m, pyridinylethyl 1-H2), 3.28–3.18 (1 H, m, 2-H), 2.83–2.68 (2 H, m, pyridinylethyl 2-H2) and 0.84 (3 H, d, J 6.8, 2-methyl). δC (125 MHz, DMSO-d6) 174.7, 159.0, 149.1, 147.8, 136.4, 135.1, 126.8, 125.8, 125.5, 123.7, 123.2, 123.0, 121.5, 121.1, 118.0, 115.0, 113.3, 44.3, 41.0, 38.2, 37.3 and 17.6. HRMS m/z calculated for C23H22Cl2N3OS (M+H)+: 458.0861; Found: 458.0848.

Fraction two was precipitated in diethyl ether/hexane (2 mL, 1:1), filtered and washed with diethyl ether (2 x 2 mL) to afford amide anti-10 as a white solid (41 mg, 68%). Rf = 0.13 (ethyl acetate); δH (500 MHz, DMSO-d6) 11.10 (1 H, d, J 2.5, NHindole), 8.45 (1 H, ddd, J 4.9, 1.9 and 0.9, pyridinyl 6-H), 8.03 (1 H, t, J 5.7, NHamide), 7.61 (1 H, td, J 7.6 and 1.9, pyridinyl 4-H), 7.51 (1 H, app. d, J 2.1, indolyl 4-H), 7.40 (1 H, d, J 2.5, indolyl 2-H), 7.32 (1 H, dd, J 8.6 and 0.6, indolyl 7-H), 7.18 (1 H, ddd, J 7.6, 4.9 and 1.2, pyridinyl 5-H), 7.07–6.97 (3 H, m, pyridinyl 3-H, indolyl 6-H and thiophenyl 3-H), 6.88 (1 H, d, J 3.7, thiophenyl 4-H), 4.57 (1 H, d, J 11.0, 3-H), 3.25 (2 H, td, J 7.2 and 5.7, pyridinylethyl 1-H2), 3.00 (1 H, dq, J 11.0 and 6.8, 2-H), 2.61 (2 H, t, J 7.2, pyridinylethyl 2-H2) and 0.97 (3 H, d, J 6.8, 2-methyl). δC (125 MHz, DMSO-d6) 174.1, 158.9, 149.0, 148.1, 136.3, 134.4, 127.6, 126.1 (x2), 125.2, 123.13, 123.10, 123.0, 121.4, 121.1, 117.8, 116.9, 112.9, 45.1, 40.5, 38.2, 37.3 and 17.5. HRMS m/z calculated for C23H22Cl2N3OS (M+H)+: 458.0861; Found: 458.0851.

From a racemic mixture of anti-10 (27 mg), enantiomers (+)-anti-10 (6.5 mg, >99.0 %ee) and (−)-anti-10 (1.0 mg, >99.0 %ee) were isolated using the following supercritical fluid chromatography conditions:
Mobile phase: A= 70% scCO2, B= 30% MeOH + 0.1% NH3
Flow rate: 90 ml/min

The collected fractions were analysed using the following conditions:
Column: Phenomenex C1, 3 x 150 mm, 3 micron
Mobile phase: A = 60% scCO$_2$, B = 20% MeOH 0.1% NH$_3$
Gradient 0-1 min 5%B, 1-5 min 5-50%B, 5-10 min 50%B
Flow rate: 2.0 ml/min

Right and left optical rotations have been arbitrarily assigned.

**Methyl 3-(2-bromo-5-chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)propanoate**

![Methyl 3-(2-bromo-5-chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)propanoate](image)

According to general procedure D, ester 18 (850 mg, 2.40 mmol) and pyridinium tribromide (945 mg, 2.64 mmol) in tetrahydrofuran:chloroform (20 mL) gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 → 20:80 of ethyl acetate:hexane) afforded ester 33 as a yellow oil which solidified on standing (729 mg, 70%); $\delta$H (500 MHz, chloroform-d) 8.15 (1 H, s, NH), 7.42 (1 H, d, J 1.9, indolyl 4-H), 7.20 (1 H, d, J 8.7, indolyl 7-H), 7.13 (1 H, dd, J 8.7 and 1.9, indolyl 6-H), 6.71 (1 H, d, J 3.8, thiophenyl 4-H), 6.65 (1 H, dd, J 3.8 and 1.3, thiophenyl 3-H), 4.97–4.90 (1 H, m, 2-H$_A$) and 3.16 (1 H, dd, J 15.8 and 8.2, 2-H$_B$). $\delta$C (125 MHz, chloroform-d) 171.6, 145.0, 134.7, 128.5, 127.0, 126.4, 125.8, 123.4, 123.2, 118.4, 115.5, 111.9, 110.3, 52.1, 39.3 and 35.0. HRMS m/z calculated for C$_{16}$H$_{12}$BrCl$_2$NNaO$_2$S (M+Na)$^+$: 453.9047; Found: 453.9033.

**3-(2-Bromo-5-chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)propanoic acid**

![3-(2-Bromo-5-chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)propanoic acid](image)

According to general procedure C, ester 33 (740 mg, 1.71 mmol) and sodium hydroxide solution (10 mL, 1.4 M) in methanol:tetrahydrofuran (13 mL) afforded acid 34 as white solid (717 mg, quantitative yield). $\delta$H (500 MHz, methanol-d$_4$) 7.39 (1 H, dd, J 2.0 and 0.6, indolyl 4-H), 7.26 (1 H, app. d, J 8.6, indolyl 7-H), 7.07 (1 H, dd, J 8.7 and 2.0, indolyl 6-H), 6.79–6.71 (2 H, m, thiophenyl 3- and 4-H), 4.92 (1 H, ddd, J 8.2, 7.4 and 1.2, 3-H), 3.36–3.27 (1 H, m, 2-H$_A$) and 3.11 (1 H, dd, J 15.6 and 8.2, 2-H$_B$). $\delta$C (125 MHz, methanol-d$_4$) 174.7, 147.6, 136.5, 128.9, 128.1, 126.8, 126.5,
124.4, 123.1, 118.8, 115.6, 113.2, 111.9, 40.2 and 36.2. HRMS m/z calculated for C_{15}H_{10}Cl_{2}NO_{2}S (M-Br)^+: 337.9809; Found: 337.9799.

3-(2-Bromo-5-chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-N-[2-(pyridin-2-yl)ethyl]propanamide 11d

According to general procedure E2, carboxylic acid 34 (717 mg, 1.71 mmol), 2-(2-pyridyl)ethylamine (313 µL, 2.57 mmol), DIPEA (0.90 mL, 5.1 mmol) and HCTU (793 mg, 1.89 mmol) in dimethylformamide (5 mL) at RT gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 → 100:0 of ethyl acetate:hexane) afforded a colourless material. The material was precipitated in diethyl ether/hexane (2 mL, 1:1), filtered and washed with diethyl ether (2 x 2 mL) to afford amide 11d as a white solid (713 mg, 78%). δH (500 MHz, chloroform-d) 8.46 (1 H, s, NH_{indole}), 8.42–8.37 (1 H, m, pyridinyl 6-H), 7.54 (1 H, td, J 7.7 and 1.9, pyridinyl 4-H), 7.40 (1 H, d, J 2.0, indolyl 4-H), 7.16–7.07 (2 H, m, pyridinyl 5-H and indolyl 7-H), 7.07 (1 H, dd, J 8.6 and 2.0, indolyl 6-H), 6.99–6.94 (1 H, m, pyridinyl 3-H), 6.67 (1 H, d, J 3.8, thiophenyl 4-H), 6.60 (1 H, dd, J 3.8 and 1.3, thiophenyl 3-H), 6.42 (1 H, t, J 5.8, NH_{amide}), 4.96 (1 H, ddd, J 8.9, 6.6 and 1.3, 3-H), 3.63–3.54 (1 H, m, pyridinylethyl 1-H_A), 3.54–3.45 (1 H, m, pyridinylethyl 1-H_B), 3.11 (1 H, dd, J 14.1 and 6.6, 2-H_A), 2.97 (1 H, dd, J 14.1 and 8.9, 2-H_B), 2.86–2.81 (1 H, m, pyridinylethyl 2-H_A) and 2.71–2.63 (1 H, m, pyridinylethyl 2-H_B). δC (125 MHz, chloroform-d) 170.0, 159.5, 149.2, 145.5, 136.7, 134.8, 128.2, 127.0, 126.2, 125.8, 123.4 (x2), 123.0, 121.7, 118.3, 115.4, 112.0, 110.7, 42.0, 38.6, 36.7 and 35.6. HRMS m/z calculated for C_{22}H_{19}BrCl_{2}N_{3}OS (M+H)^+: 523.9789; Found: 523.9800.
**N-Benzyl-5-chloro-3-[(5-chlorothiophene-2-yl)(4-methylbenzenesulfonyl) methyl]-1H-indole-2-carboxamide**

According to general procedure A2, N-benzyl-5-chloro-1H-indole-2-carboxamide (190 mg, 0.67 mmol), 5-chloro-2-thiophenecarboxaldehyde (65 µL, 0.61 mmol), p-toluenesulfonic acid (334 mg, 2.1 mmol) and p-toluenesulfonic acid monohydrate (120 mg, 0.62 mmol) in tetrahydrofuran (7 mL) gave the crude product. The product was precipitated in cold diethyl ether (10 mL), filtered, washed with diethyl ether (2 x 2 mL) and dried *in vacuo* to afford indole 35 as a light pink solid (98 mg, 28%). δ_H (500 MHz, DMSO-\text{d}_6) 11.92 (1 H, s, NH_{indole}), 8.72 (1 H, app. t, J 5.7, NH_{carboxamide}), 7.91 (1 H, d, J 2.0, indolyl 4-H), 7.60 (1 H, d, J 1.1, CHS), 7.50 (1 H, d, J 8.8, indolyl 7-H), 7.43–7.34 (4 H, m, benzenesulfonyl 2- and 6-H and benzyl 4- and 6-H), 7.33–7.27 (4 H, m, indolyl 6-H and benzyl 3-, 5- and 7-H), 7.24 (2 H, app. d, J 8.1, benzenesulfonyl 3- and 5-H), 7.04 (1 H, d, J 3.9, thiophenyl 4-H), 6.87 (1 H, dd, J 3.9 and 1.1, thiophenyl 3-H), 4.45 (1 H, dd, J 14.9 and 5.9, benzyl 1-H_A), 4.38 (1 H, dd, J 14.9 and 5.7, benzyl 1-H_B) and 2.32 (3 H, s, benzenesulfonyl 4-methyl). δ_C (125 MHz, DMSO-\text{d}_6) 160.6, 144.8, 138.5, 134.2, 133.9, 133.1, 131.1, 129.5 (x2), 129.3, 129.2, 128.4 (x2), 128.1 (x2), 127.7 (x2), 127.1, 126.6, 125.8, 124.9, 124.5, 121.9, 114.3, 109.4, 62.8, 42.5 and 21.1. HRMS m/z calculated for C_{21}H_{15}Cl_{2}N_{2}O_{5} (M-SO_2Tol)^+: 413.0282; Found: 413.0276.

**Methyl 3-[(2-benzylcarbamoyl)-5-chloro-1H-indol-3-yl]-3-(5-chlorothiophen-2-yl) propanoate**

According to general procedure B2, indole 35 (95 mg, 0.17 mmol), tert-butyl((1-methoxyvinyl)oxy)dimethylsilane (182 µL, 0.83 mmol) and trifluoromethanesulfonic acid (6.0 µL, 0.07 mmol) in tetrahydrofuran (3 mL) gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 → 50:50 of ethyl acetate:hexane) afforded ester 36 as a white solid (18 mg, 22%). R_f = 0.5 (6:4
hexane:ethyl acetate); δH (400 MHz, chloroform-d) 9.34 (1 H, s, NHindole), 8.74–8.57 (1 H, m, NHcarbamoyl), 7.41–7.32 (5 H, m, indolyl 4-H and benzyl 3-, 4-, 6- and 7-H), 7.31–7.27 (2 H, m, indolyl 7-H and benzyl 5-H), 7.17 (1 H, dd, J 8.8 and 1.9, indolyl 6-H), 6.65 (1 H, d, J 3.9, thiophenyl 4-H), 6.45 (1 H, dd, J 3.9 and 1.5, thiophenyl 3-H), 5.23–5.14 (1 H, m, 3-H), 4.74 (1 H, dd, J 14.9 and 5.7, benzyl 1-HA), 4.67 (1 H, dd, J 14.9 and 5.7, benzyl 1-HB), 3.57 (3 H, s, methyl), 3.44 (1 H, dd, J 16.9 and 11.4, 2-HA) and 3.28 (1 H, dd, J 17.0 and 3.8, 2-HB). δC (100 MHz, chloroform-d) 173.7, 160.3, 147.1, 135.4, 132.7, 130.9, 129.8, 128.8 (x2), 127.9 (x2), 127.6 (x2), 125.9 (x2), 125.0 (x2), 123.7, 120.5, 113.5, 52.5, 44.2, 38.9 and 33.9. HRMS m/z calculated for C24H21Cl2N2O3S (M+H)+: 487.0650; Found: 486.9292.

3-[2-(Benzylcarbamoyl)-5-chloro-1H-indol-3-yl]-3-(5-chlorothiophen-2-yl) propanoic acid

According to general procedure C, ester 36 (18 mg, 0.037 mmol) and sodium hydroxide solution (0.6 mL, 0.3 M) in methanol:tetrahydrofuran (1.4 mL) afforded acid 37 as white solid (18 mg, quantitative yield). δH (500 MHz, methanol-d4) 7.44 (1 H, d, J 2.0, indolyl 4-H), 7.42–7.36 (3 H, m, indolyl 7-H and benzyl 3- and 7-H), 7.35–7.30 (2 H, m, benzyl 4- and 6-H), 7.28–7.23 (1 H, m, benzyl 5-H), 7.16 (1 H, dd, J 8.7 and 2.0, indolyl 6-H), 6.75 (1 H, d, J 3.9, thiophenyl 4-H), 6.74 (1 H, dd, J 3.9 and 1.3, thiophenyl 3-H), 5.40 (1 H, ddd, J 9.5, 6.0 and 1.3, 3-H), 4.68–4.58 (2 H, m, benzyl 1-H2), 3.39 (1 H, dd, J 16.4 and 6.0, 2-HA) and 3.38–3.30 (1 H, m, 2-HB). δC (125 MHz, methanol-d4) 175.9, 164.3, 148.0, 139.7, 136.1, 131.4, 129.6 (x2), 129.1, 128.7 (x2), 128.3, 127.9, 126.8, 126.5, 125.3, 124.4, 121.1, 118.4, 114.7, 44.5, 39.8 and 35.0. HRMS m/z calculated for C23H16Cl2N2NaO3S (M+Na)+: 495.0313; Found: 495.0305.
According to general procedure E2, carboxylic acid 37 (18 mg, 0.037 mmol), 2-(2-pyridyl)ethylamine (16 µL, 0.13 mmol), DIPEA (42 µL, 0.24 mmol) and HCTU (25 mg, 0.063 mmol) in dimethylformamide (0.5 mL) at RT gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 → 1:99 of methanol:dichloromethane) afforded indole 11h as a white solid (12.8 mg, 55%). δH (500 MHz, DMSO-d6) 11.70 (1 H, s, NHindole), 9.38 (1 H, t, J 5.9, NHcarboxamide), 8.41 (1 H, ddd, J 4.9, 1.9 and 0.9, pyridinyl 6-H), 8.23 (1 H, t, J 5.7, NHcarboxamide), 7.49 (1 H, td, J 7.6 and 1.9, pyridinyl 4-H), 7.42 (1 H, d, J 8.7, indolyl 7-H), 7.43–7.37 (3 H, m, indolyl 4-H and benzyl 3- and 7-H), 7.33 (2 H, app. dd, J 8.4 and 6.8, benzyl 4- and 6-H), 7.28–7.23 (1 H, m, benzyl 5-H), 7.19 (1 H, dd, J 8.7 and 2.0, indolyl 6-H), 7.15 (1 H, ddd, J 7.6, 4.9 and 1.2, pyridinyl 5-H), 6.90 (1 H, d, J 3.8, thiophenyl 4-H), 6.84 (1 H, app. d, J 7.8, pyridinyl 3-H), 6.77 (1 H, dd, J 3.8 and 1.4, thiophenyl 3-H), 5.43 (1 H, ddd, J 9.4, 6.5 and 1.4, carbamoylethyl 1-H), 4.57 (2 H, d, J 5.9, benzyl 1-H2), 3.41–3.22 (3 H, m, carbamoylethyl 2-HA, pyridinylethyl 1-H2), 3.02 (1 H, dd, J 14.9 and 9.4, carbamoylethyl 2-HB) and 2.67 (2 H, td, J 7.0 and 3.6, pyridinylethyl 2-H2). δC (125 MHz, DMSO-d6) 170.8, 161.5, 158.7, 148.9, 147.4, 139.1, 136.3, 134.3, 130.4, 128.3 (x2), 127.3 (x2), 126.9, 126.3, 126.2, 125.9, 123.8, 123.4, 123.2, 122.9, 121.4, 119.8, 116.4, 114.1, 42.6, 39.2, 38.5, 37.0 and 33.2. HRMS m/z calculated for C30H27Cl2N4O2S (M+H)+: 577.1232; Found: 577.1223.
According to general procedure A2, 5-chloro-1H-indole-2-carboxamide (150 mg, 0.60 mmol), 5-chloro-2-thiophencarboxaldehyde (64 µL, 0.60 mmol), p-toluenesulfinic acid (375 mg, 2.4 mmol) and p-toluenesulfonic acid monohydrate (114 mg, 0.60 mmol) in tetrahydrofuran (5 mL) gave the crude product. The product was precipitated in cold diethyl ether (10 mL), filtered, washed with diethyl ether (2 x 2 mL) and dried in vacuo to afford indole 38 as a light pink solid (152 mg, 46%). \( R_f = 0.38 \) (1:1 hexane:ethyl acetate); \( \delta_H \) (500 MHz, DMSO-\( \text{d}_6 \)) 11.87 (1 H, s, NH indole), 8.20 (1 H, t, \( J = 5.7 \), NHcarboxamide), 7.90 (1 H, d, \( J = 2.0 \), indolyl 4-H), 7.63 (1 H, d, \( J = 1.1 \), CHS), 7.54–7.48 (1 H, m, indolyl 7-H), 7.40–7.33 (2 H, m, benzenesulfonyl 2- and 6-H), 7.30 (1 H, dd, \( J = 8.8 \) and 2.0, indolyl 6-H), 7.29–7.22 (2 H, m, benzenesulfonyl 3- and 5-H), 7.03 (1 H, d, \( J = 3.9 \), thiophenyl 4-H), 6.87 (1 H, dd, \( J = 3.9 \) and 1.1, thiophenyl 3-H), 3.10–3.03 (1 H, m, methylpropyl 1-H\( _A \)), 2.96 (1 H, ddd, \( J = 12.8 \), 6.7 and 5.7, methylpropyl 1-H\( _B \)), 2.32 (3 H, s, benzenesulfonyl 4-methyl), 1.75 (1 H, hept, \( J = 6.7 \), methylpropyl 2-H), 0.87 (3 H, d, \( J = 6.7 \), methylpropyl 3-H\( _A \)) and 0.86 (3 H, d, \( J = 6.7 \), propyl 2-methyl). \( \delta_C \) (125 MHz, DMSO-\( \text{d}_6 \)) 160.6, 144.8, 134.2, 133.8, 133.1, 131.3, 129.5 (x2), 129.3, 129.2, 128.2 (x2), 126.6, 125.9, 124.9, 124.4, 121.9, 114.3, 109.2, 62.7, 46.3, 27.9, 21.1 and 20.2 (x2). HRMS \( m/z \) calculated for C\( _{18} \)H\( _{16} \)Cl\( _2 \)N\( _2 \)NaOS (M-SO\( _2 \)Tol+Na\( ^{+} \))\( : 401.0258 \); Found: 401.0250.

**Methyl 3-{5-chloro-2-[(2-methylpropyl)carbamoyl]1H-indol-3-yl}-3-(5-chlorothiophen-2-yl)propanoate**

According to general procedure B2, 38 (148 mg, 0.28 mmol), tert-butyl((1-methoxyvinyl)oxy)dimethylsilane (610 µL, 2.8 mmol) and trifluoromethanesulfonic acid (10 µL, 0.11 mmol) in tetrahydrofuran (10 mL) gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 → 50:50 of ethyl
acetate:hexane) afforded ester 39 as a yellow oil (50 mg, 40%). Rf = 0.29 (8:2 hexane:ethyl acetate); δH (500 MHz, chloroform-d) 9.83–9.73 (1 H, m, NHindole), 8.41–8.34 (1 H, m, NHcarbamoyl), 7.36 (1 H, d, J 2.0, indolyl 4-H), 7.33 (1 H, d, J 8.7, indolyl 7-H), 7.17 (1 H, dd, J 8.7 and 2.0, indolyl 6-H), 6.67 (1 H, d, J 3.8, thiophenyl 4-H), 6.48 (1 H, dd, J 3.8 and 1.5, thiophenyl 3-H), 5.19 (1 H, ddd, J 11.5, 3.7 and 1.5, 3-H), 3.62 (3 H, s, methyl), 3.50 (1 H, dd, J 17.0 and 11.5, 2-HA), 3.44–3.37 (1 H, m, methylpropyl 1-HA), 3.37–3.28 (2 H, m, methylpropyl 1-HB and 2-HB), 1.99 (1 H, hept, J 6.7, methylpropyl 2-H), 1.02 (3 H, d, J 6.7, methylpropyl 3-H3) and 1.02 (3 H, d, J 6.7, propyl 2-methyl). δC (125 MHz, chloroform-d) 173.8, 162.7, 145.2, 134.3, 131.4, 129.0, 126.7, 125.9, 125.8, 124.7, 123.7, 120.5, 113.9, 113.6, 52.6, 47.8, 39.0, 34.0, 28.6, 20.52 and 20.50. HRMS m/z calculated for C21H23Cl2N2O3S (M+H)+: 453.0807; Found: 453.0796.

3-{5-Chloro-2-[(2-methylpropyl)carbamoyl]-1H-indol-3-yl}-3-(5-chlorothiophen-2-yl)propanoic acid

According to general procedure C, ester 39 (50 mg, 0.11 mmol) and sodium hydroxide solution (1.5 mL, 0.4 M) in methanol:tetrahydrofuran (4 mL) afforded acid 40 as a white solid (54 mg, quantitative yield). δH (500 MHz, methanol-d4) 7.42 (1 H, d, J 2.0, indolyl 4-H), 7.38 (1 H, d, J 8.8, indolyl 7-H), 7.16 (1 H, dd, J 8.8 and 2.0, indolyl 6-H), 6.77 (2 H, app. s, thiophenyl 3- and 4-H), 5.34 (1 H, dd, J 9.9 and 5.5, 3-H), 3.49–3.32 (3 H, m, 2-H2 and methylpropyl 1-HA), 3.24 (1 H, dd, J 13.2 and 6.6, methylpropyl 1-HB), 1.95 (1 H, m, methylpropyl 2-H) and 1.01 (6 H, m, methylpropyl 3-H3 and propyl 2-methyl). δC (125 MHz, methanol-d4) 176.1, 162.7, 145.2, 134.3, 131.4, 129.0, 126.7, 125.9, 125.8, 124.7, 123.7, 120.5, 113.9, 113.6, 52.6, 47.8, 39.0, 34.0, 28.6, 20.52 and 20.50. HRMS m/z calculated for C20H21Cl2N2O3S (M+H)+: 439.0650; Found: 439.0643.
5-Chloro-3-[1-(5-chlorothiophene-2-yl)-2-[[2-pyridin-2-yl]ethyl]carbamoyl]ethyl]-N-(2-methylpropyl)-1H-indole-2-carboxamide 11i

According to general procedure E2, carboxylic acid 40 (50 mg, 0.11 mmol), 2-(2-pyridyl)ethylamine (26 µL, 0.22 mmol), DIPEA (60 µL, 0.33 mmol) and HCTU (60 mg, 0.14 mmol) in dimethylformamide (1 mL) at RT gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 → 3:97 of methanol:dichloromethane) afforded 30 mg of a yellow impure material. The material was precipitated in diethyl ether/hexane (2 mL, 1:1), filtered and washed with diethyl ether (2 x 2 mL) to afford indole 11i as a white solid (20 mg, 32%). δH (500 MHz, DMSO-d6) 11.66 (1 H, s, NH indole), 8.98 (1 H, t, J 5.7, NH carboxamide), 8.39 (1 H, ddd, J 4.9, 1.9 and 0.9, pyridinyl 6-H), 8.25 (1 H, t, J 5.7, NH carbamoyl), 7.45 (1 H, td, J 7.6 and 1.9, pyridinyl 4-H), 7.42 (1 H, d, J 8.7, indolyl 7-H), 7.36 (1 H, d, J 2.0, indolyl 4-H), 7.17 (1 H, dd, J 8.7 and 2.0, indolyl 6-H), 7.13 (1 H, ddd, J 7.6, 4.9 and 1.2, pyridinyl 5-H), 6.90 (1 H, d, J 3.8, thiophenyl 4-H), 6.82–6.75 (2 H, m, pyridinyl 3-H and thiophenyl 3-H), 5.36–5.27 (1 H, m, carbamoylethyl 1-H), 3.39–3.20 (4 H, m, carbamoylethyl 2-HA, pyridinylethyl 1-Hz and methylpropyl 1-HA), 3.19–3.03 (2 H, m, carbamoylethyl 2-Hg and methylpropyl 1-Hg), 1.89 (1 H, hept, J 6.7, methylpropyl 2-H), 0.96 (3 H, d, J 6.7, methylpropyl 3-H) and 0.95 (3 H, d, J 6.7, propyl 2-methyl). δC (125 MHz, DMSO-d6) 170.4, 160.8, 158.2, 148.4, 146.9, 135.6, 133.8, 130.6, 125.8, 125.7, 125.5, 123.1, 122.7 (x2), 122.31, 120.8, 119.2, 114.7, 113.5, 46.0, 38.5, 38.0, 36.5, 32.7, 27.6 and 19.7 (x2). HRMS m/z calculated for C27H29Cl2N4O2S (M+H)+: 543.1389; Found: 543.1403.

**tert-Butyl N-[2-[[5-chloro-1H-indol-2-yl]formamido]ethyl]carbamate**

According to general procedure E2, 5-chloroindole-2-carboxylic acid (500 mg, 2.56 mmol), tert-butyl N-(2-aminoethyl)carbamate (1.2 g, 7.7 mmol), DIPEA (1.4 mL, 7.7 mmol) and HCTU (1.1 g, 2.6 mmol) in dimethylformamide (4 mL) gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 →
100:0 of ethyl acetate:hexane) afforded carbamate 41 as a white solid (178 mg, 20%). δH (500 MHz, methanol-d4) 7.58 (1 H, dd, J 2.1 and 0.7, indolyl 4-H), 7.41 (1 H, dd, J 8.8 and 0.7, indolyl 7-H), 7.17 (1 H, dd, J 8.8 and 2.1, indolyl 6-H), 7.00 (1 H, s, indolyl 3-H), 3.46 (2 H, t, J 6.2, formamidoethyl 1-H2), 3.28 (2 H, t, J 6.2, formamidoethyl 2-H2) and 1.41 (9 H, s, tert-butyl). δC (125 MHz, methanol-d4) 164.0, 158.8, 136.6, 133.8, 129.9, 126.7, 125.2, 121.8, 114.4, 103.7, 80.2, 40.99, 40.95 and 28.7 (x3). HRMS m/z calculated for C16H20ClN3NaO3 (M+H)+: 360.1091; Found: 360.1080.

5-Chloro-3-[(5-chlorothiophene-2-yl)(4-methylbenzenesulfonyl)methyl]-1H-indole-2-carboxylic acid

According to general procedure A2, 5-chloroindole-2-carboxylic acid (300 mg, 1.53 mmol), 5-chloro-2-thiophenecarboxaldehyde (163 µL, 1.53 mmol), p-toluenesulfinic acid (956 mg, 6.12 mmol) and p-toluenesulfonic acid monohydrate (291 mg, 1.53 mmol) in tetrahydrofuran (10 mL) gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 → 2:98 of methanol:dichloromethane) afforded indole 42 as a salmon solid (335 mg, 46%). δH (500 MHz, DMSO-d6) 13.90 (1 H, br s, CO2H), 12.22 (1 H, s, NH), 7.88 (1 H, d, J 2.0, 4-H), 7.47 (1 H, d, J 8.8, 7-H), 7.40–7.34 (2 H, m, benzenesulfonyl 2- and 6-H), 7.36–7.28 (2 H, m, 5-H, CHS), 7.30–7.25 (2 H, m, benzenesulfonyl 3- and 5-H), 7.05 (1 H, d, J 3.9, thiophenyl 4-H), 6.90 (1 H, dd, J 3.9 and 1.1, thiophenyl 3-H) and 2.33 (3 H, s, benzenesulfonyl 4-methyl). δC (125 MHz, DMSO-d6) 162.19, 144.98, 134.41, 133.98, 132.49, 129.52 (x2), 129.48, 128.21 (x2), 126.68 (x2), 125.68 (x2), 125.13, 124.98, 122.14, 114.69, 110.54, 63.25 and 21.07. HRMS m/z calculated for C14H8Cl2NO3S (M-SO2Tol)+: 323.9653; Found: 323.9645.
5-Chloro-3-[1-(5-chlorothiophene-2-yl)-3-methoxy-oxopropyl]-1H-indole-2-carboxylic acid

According to general procedure B2, indole 42 (200 mg, 0.42 mmol), tert-butyl((1-methoxyvinyl)oxy)dimethylsilane (454 µL, 2.08 mmol) and trifluoromethanesulfonic acid (15 µL, 0.17 mmol) in 1,4-dioxane (6 mL) gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 → 4:96 of methanol:dichloromethane) afforded indole 43 as a white solid (130 mg, 74%); δ_H (500 MHz, DMSO-d_6) 13.49 (1 H, br s, CO_2H), 11.87 (1 H, s, NH), 7.64 (1 H, d, J 2.0, 4-H), 7.42 (1 H, d, J 8.8, 7-H), 7.23 (1 H, dd, J 8.8 and 2.0, 6-H), 6.93 (1 H, dd, J 3.9 and 1.1, thiophenyl 3-H), 6.92 (1 H, d, J 3.9, thiophenyl 4-H), 5.76 (1 H, td, J 7.8 and 1.1, oxopropyl 1-H), 3.50 (3 H, s, methoxy), 3.51–3.44 (1 H, m, oxopropyl 2-H_A) and 3.22 (1 H, dd, J 16.0 and 7.8, oxopropyl 2-H_B). δ_C (125 MHz, DMSO-d_6) 171.4, 162.8, 146.7, 134.6, 126.3, 126.2, 126.0, 125.6, 124.7, 124.4, 123.5, 121.3, 120.1, 114.6, 51.5, 38.4 and 32.9. HRMS m/z calculated for C_{17}H_{13}Cl_2NNaO_4S (M+Na)^+: 419.9840; Found: 419.9832.

3-[2-carboxy-1-(5-chlorothiophen-2-yl)ethyl]-5-chloro-1H-indole-2-carboxylic acid

According to general procedure C, indole 43 (40 mg, 0.10 mmol) and sodium hydroxide solution (1.3 mL, 0.4 M) in methanol:tetrahydrofuran (2 mL) afforded indole 44 as yellow material (40 mg, quantitative yield). δ_H (500 MHz, DMSO-d_6) 13.45 (1 H, br s, CO_2H_A), 12.23 (1 H, br s, CO_2H_B), 11.86 (1 H, s, NH), 7.64 (1 H, d, J 2.0, 4-H), 7.42 (1 H, d, J 8.8, 7-H), 7.23 (1 H, dd, J 8.8 and 2.0, 6-H), 6.91 (2 H, app. s, thiophenyl 3- and 4-H), 5.73 (1 H, app. t, J 7.8, ethyl 1-H), 3.38 (1 H, dd, J 16.0 and 8.1, ethyl 2-H_A) and 3.10 (1 H, dd, J 16.0 and 7.5, ethyl 2-H_B). δ_C (125 MHz, DMSO-d_6) 172.3, 162.8, 147.1, 134.6, 126.22, 126.21, 125.8, 125.4, 124.6, 124.2, 123.3, 121.6, 120.1, 114.5, 38.8 and 32.9. HRMS m/z calculated for C_{16}H_{11}Cl_2NNaO_4S (M+na)^+: 405.9676; Found: 405.9684.
5-Chloro-3-[1-(5-chlorothiophen-2-yl)-2-[[2-(pyridin-2-yl)ethyl]carbamoyl]ethyl]-1H-indole-2-carboxylic acid 11b

According to general procedure E2, indole 44 (185 mg, 0.48 mmol), 2-(2-pyridyl)ethylamine (65 µL, 0.53 mmol), DIPEA (0.25 mL, 1.4 mmol) and HCTU (220 mg, 0.53 mmol) in dimethylformamide (4 mL) at 0 °C gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 → 10:90 of methanol:dichloromethane) afforded 110 mg of a brown impure material. The material was precipitated in diethyl ether/hexane (5 mL, 1:1) to afford **indole 11b** as a beige solid (77 mg, 33%). δH (500 MHz, DMSO-d6) 13.39 (1 H, br s, CO2H), 11.76 (1 H, s, NHindole), 8.51 – 8.44 (1 H, m, pyridinyl 6-H), 8.13 (1 H, s, NHcarbamoyl), 7.64 (1 H, td, J 7.6 and 1.9, pyridinyl 4-H), 7.57 (1 H, s, 4-H), 7.42 (1 H, d, J 8.8, 7-H), 7.24 – 7.16 (2 H, m, pyridinyl 5-H and 6-H), 7.11 – 7.06 (1 H, m, pyridinyl 3-H), 6.87 (1 H, d, J 3.8, thiophenyl 4-H), 6.76 (1 H, dd, J 3.8 and 1.3, thiophenyl 3-H), 5.94 – 5.69 (1 H, m, carbamoylethyl 1-H), 3.44 – 3.18 (3 H, m, carbamoylethyl 2-HA and pyridinylethyl 1-H2) and 2.80 – 2.68 (3 H, m, carbamoylethyl 2-He and pyridinylethyl 2-H2). δC (125 MHz, DMSO-d6) 169.8, 163.1, 159.0, 149.0, 147.6, 136.4, 134.5, 126.4, 126.0 (x2), 125.5, 124.2, 123.9, 123.03, 123.01 (x2), 121.4, 120.2, 114.4, 40.2, 38.4, 37.3 and 32.9. HRMS m/z calculated for C23H20Cl2N3O3S (M+H)++: 488.0626; Found: 488.0618.

Methyl 5-chloro-3-[1-(5-chlorothiophen-2-yl)-2-[[2-(pyridin-2-yl)ethyl]carbamoyl]ethyl]-1H-indole-2-carboxylate

To a solution of crude indole 11b (310 mg, 0.81 mmol) in methanol (30 mL), 15 drops of neat sulfuric acid were added and the reaction mixture was stirred at reflux for 40 h. The mixture was cooled down and partitioned between ethyl acetate/saturated aqueous sodium hydrogen carbonate solution (20/30 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. Purification by column chromatography (silica, eluent: gradient 0:100 → 6:94 of
methanol:dichloromethane) afforded indole 45 as a beige solid (150 mg, 46% two steps). δH (500 MHz, chloroform-d) 8.84 (1 H, s, NH\textsubscript{indole}), 8.42 (1 H, ddd, J 4.9, 1.9 and 0.9, pyridinyl 6-H), 7.58–7.51 (2 H, m, pyridinyl 4-H and 4-H), 7.27–7.22 (1 H, m, 7-H), 7.21 (1 H, dd, J 8.8 and 1.9, 6-H), 7.11 (1 H, ddd, J 7.6, 4.9 and 1.1, pyridinyl 5-H), 7.00 – 6.95 (1 H, m, pyridinyl 3-H), 6.67 (1 H, d, J 3.8, thiophenyl 4-H), 6.65 (1 H, ddd, J 3.8 and 1.2, thiophenyl 3-H), 6.52–6.43 (1 H, m, NH\textsubscript{carbamoyl}), 5.77 (1 H, ddd, J 8.3, 7.2 and 1.9, carbamoylethyl 1-H), 3.95 (3 H, s, methyl), 3.61–3.48 (2 H, m, pyridinylethyl 1\textsubscript{H}2), 3.18 (1 H, dd, J 14.3 and 7.2, carbamoylethyl 2-H\textsubscript{A}), 3.02 (1 H, dd, J 14.3 and 8.3, carbamoylethyl 2-H\textsubscript{B}), 2.82 (1 H, ddd, J 14.9, 7.1 and 5.0, pyridinylethyl 2-H\textsubscript{A}) and 2.68 (1 H, ddd, J 14.9, 7.7 and 5.2, pyridinylethyl 2-H\textsubscript{B}). δC (125 MHz, chloroform-d) 170.1, 162.1, 159.5, 149.2, 145.9, 136.6, 134.3, 128.1, 127.1, 126.5, 126.4, 125.7, 124.6, 123.42, 123.41, 123.1, 121.6, 121.2, 113.4, 52.5, 42.5, 38.5, 36.7 and 34.5. HRMS m/z calculated for C\textsubscript{24}H\textsubscript{22}Cl\textsubscript{2}N\textsubscript{3}O\textsubscript{3}S (M+H): 502.0759; Found: 502.0769.

tert-Butyl N-[2-[(5-chloro-3-[1-(5-chlorothiophen-2-yl)]-2-[2-(pyridin-2-yl)ethyl] carbamoyl]ethyl]-1H-indol-2-yl]formamido)ethyl]carbamate 11g

According to general procedure E3, indole 11b (92 mg, 0.19 mmol) and Ghosez’s reagent (50 µL, 0.38 mmol) dichloromethane solution (10 mL) and the N-Boc-ethylenediamine (125 µL, 1.14 mmol) and triethylamine (158 µL, 1.14 mmol) dichloromethane solution (6 mL) at 0°C gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 → 5:95 of methanol:dichloromethane) afforded 44 mg of a colourless impure material. The material was precipitated in dichloromethane:hexane (2 mL, 1:1), filtered and washed with diethyl ether (2 x 2 mL) to afford carbamate 11g as a white solid (34 mg, 28%). δH (500 MHz, chloroform-d) 9.41–9.28 (1 H, m, NH\textsubscript{indole}), 9.17 (1 H, s, NH\textsubscript{formamido}), 8.39–8.30 (1 H, m, pyridinyl 6-H), 7.45 (1 H, td, J 7.7 and 1.9, pyridinyl 4-H), 7.28–7.22 (2 H, m, indolyl 4- and 7-H), 7.12 (1 H, dd, J 8.7 and 2.0, indolyl 6-H), 7.07 (1 H, ddd, J 7.7, 4.9 and 1.1, pyridinyl 5-H), 6.99–6.86 (1 H, m, NH\textsubscript{carbamoyl}), 6.82 (1 H, app. d, J 7.7, pyridinyl 3-H), 6.66 (1 H, d, J 3.8, thiophenyl 4-H), 6.45 (1 H, dd, J 3.8 and 1.5, thiophenyl 3-H), 5.96–5.50
N-(2-Aminoethyl)-5-chloro-3-[1-(5-chlorothiophen-2-yl)-2-[[2-(pyridin-2-yl)ethyl]carbamoyl]ethyl]-1H-indole-2-carboxamide hydrochloride 11f

Cold hydrogen chloride (3N in methanol) was added to carbamate 11g (20 mg, 0.03 mmol) and the reaction mixture was stirred at room temperature for 16 h. The solvent was removed in vacuo and the resulting material was precipitated in dichloromethane:hexane (2 mL, 1:1). The solid was filtered, washed with diethyl ether (1 x 3 mL) and dried in vacuo to afford indole hydrochloride salt 11f as a white solid (18 mg, quantitative yield). $\delta^H$ (500 MHz, DMSO-d$_6$) 11.94 (1 H, s, NHindole), 8.89 (1 H, t, J 5.5, NHcarboxamide), 8.65 (1 H, app. d, J 5.4, pyridinyl 6-H), 8.28 (1 H, app. t, J 5.8, NHcarbamoyl), 8.15–7.97 (4 H, m, pyridinyl 4-H and NH2-HCl), 7.64 (1 H, br s, pyridinyl 5-H), 7.48–7.36 (3 H, m, 4- and 7-H and pyridinyl 3-H), 7.20 (1 H, dd, J 8.6 and 2.1, 6-H), 6.89 (1 H, d, J 3.9, thiophenyl 4-H), 6.77 (1 H, dd, J 3.9 and 1.3, thiophenyl 3-H), 5.53 (1 H, app. td, J 7.9 and 1.3, carbamoylethyl 1-H), 3.64–3.50 (2 H, m, aminoethyl 1-H2), 3.45–3.42 (2 H, m, pyridinylethyl 1-H2), 3.27 (1 H, dd, J 15.0 and 7.9, carbamoylethyl 2-HA), 3.10 – 3.01 (2 H, m, aminoethyl 2-H2), 2.99–2.90 (2 H, m, pyridinylethyl 2-H2) and 2.84 (1 H, dd, J 15.0 and 7.7, carbamoylethyl 2-HB). $\delta^C$ (125 MHz, DMSO-d$_6$) 170.6, 161.9, 159.4, 147.4, 134.1, 129.4 (x2), 126.3, 126.0 (x2), 125.7, 123.8, 123.7 (x2), 123.2 (x2), 119.8, 118.0, 114.0, 39.8, 38.5, 37.8, 36.8, 34.6 and 32.8. HRMS m/z calculated for C$_{25}$H$_{26}$Cl$_2$N$_5$O$_2$S (M+H)$^+$: 530.1184; Found: 530.1185.
Ethyl 3-\{(5-chloro-3-[1-(5-chlorothiophen-2-yl)-2-[2-(pyridin-2-yl)ethyl]carbamoyl]ethyl]-1H-indol-2-yl\}formamido)propanoate 11c

According to general procedure E3, indole 11b (100 mg, 0.20 mmol) and Ghosez’s reagent (166 µL, 1.25 mmol) dichloromethane solution (10 mL) and the ethyl 3-aminopropionate hydrochloride (308 mg, 2.0 mmol) and triethylamine (277 µL, 2.0 mmol) dichloromethane solution (6 mL) at 0°C gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 → 4:96 of methanol:dichloromethane) afforded 44 mg of a colourless impure material. The material was precipitated in dichloromethane:hexane (5 mL, 1:1), filtered and washed with diethyl ether (2 x 2 mL) to afford ester 11c as a white solid (32 mg, 27%). δH (500 MHz, chloroform-d) 9.38–9.22 (2 H, m, NHindole and NHformamido), 8.41 – 8.30 (1 H, m, pyridinyl 6-H), 7.43 (1 H, td, J 7.7 and 1.9, pyridinyl 4-H), 7.33–7.20 (2 H, m, indolyl 4- and 7-H), 7.11 (1 H, dd, J 8.7 and 2.0, indolyl 6-H), 7.06 (1 H, dd, J 7.7 and 5.0, pyridinyl 5-H), 6.77 (1 H, d, J 7.7, pyridinyl 3-H), 6.70 (1 H, app. t, J 5.5, NHcarbamoyl), 6.66 (1 H, d, J 3.8, thiophenyl 4-H), 6.44 (1 H, dd, J 3.8 and 1.5, thiophenyl 3-H), 5.29–5.16 (1 H, m, carbamoylethyl 1-H), 4.20–4.05 (2 H, m, ethyl 1-H2), 3.90–3.80 (1 H, m, 3-HA), 3.81–3.71 (1 H, m, 3-HB), 3.58–3.38 (2 H, m, pyridinylethyl 1-H2), 3.23 (1 H, dd, J 14.7 and 4.0, carbamoylethyl 2-Ha), 3.11 (1 H, dd, J 14.7 and 11.8, carbamoylethyl 2-Hb), 2.84–2.67 (3 H, m, 2-H2 and pyridinylethyl 2-Ha), 2.59 (1 H, ddd, J 14.8, 7.9 and 4.6, pyridinylethyl 2-Hb) and 1.22 (3 H, t, J 7.1, ethyl 2-H3). δC (125 MHz, chloroform-d) 171.9, 171.2, 162.6, 159.1, 149.2, 145.6, 136.6, 134.1, 131.3, 128.5, 126.9, 125.8, 125.6, 124.6, 123.6, 123.3, 121.7, 120.5, 114.3, 113.4, 60.8, 41.3, 38.7, 36.3, 36.1, 34.3, 34.1, 14.3. HRMS m/z calculated for C28H29Cl2N4O4S (M+H)+: 587.1287; Found: 587.1285.
3-{(5-Chloro-3-[1-(5-chlorothiophen-2-yl)-2-[[2-(pyridin-2-yl)ethyl]carbamoyl]ethyl]-1H-indol-2-yl]formamido}propanoic acid 11e

According to general procedure C, ester 11c (21 mg, 0.04 mmol) and sodium hydroxide solution (0.4 mL, 0.3 M) in methanol:tetrahydrofuran (1 mL) gave the crude product. The material was precipitated in diethyl ether (2 mL), filtered and washed with diethyl ether (2 x 2 mL) to afford acid 11e as a white solid (14 mg, 68%). δH (500 MHz, DMSO-d6) 11.79 (1 H, s, NH indole), 8.92 (1 H, t, J 5.4, NH formamido), 8.55 (1 H, app. d, J 5.2, pyridinyl 6-H), 8.29 (1 H, t, J 5.8, NH carbamoyl), 7.85 (1 H, br s, pyridinyl 4-H), 7.47 (1 H, br s, pyridinyl 5-H), 7.43 (1 H, d, J 8.7, indolyl 7-H), 7.40 (1 H, d, J 2.0, indolyl 4-H), 7.35–7.10 (1 H, m, pyridinyl 3-H), 7.19 (1 H, dd, J 8.7 and 2.0, indolyl 6-H), 6.89 (1 H, d, J 3.8, thiophenyl 4-H), 6.76 (1 H, dd, J 3.8 and 1.3, thiophenyl 3-H), 5.47–5.40 (1 H, m, carbamoylethyl 1-H), 3.62–3.51 (1 H, m, 3-HA), 3.53–3.45 (1 H, m, 3-HB), 3.46–3.39 (2 H, m, pyridinylethyl 2-H2), 3.24 (1 H, dd, J 15.2 and 6.8, carbamoylethyl 2-HA), 2.98 (1 H, dd, J 15.2 and 9.0, carbamoylethyl 2-HA), 2.92–2.80 (2 H, m, pyridinylethyl 2-H2) and 2.62–2.51 (2 H, m, 2-H2); CO2H not observed. δC (125 MHz, DMSO-d6) 173.3, 171.3, 165.7, 161.8, 148.0, 134.6 (x2), 130.5 (x2), 126.7, 126.6 (x2), 126.3, 124.2, 123.9, 123.7 (x2), 120.3, 117.2, 114.5, 39.9, 38.5, 35.82, 35.78, 34.1, 33.4. HRMS m/z calculated for C26H25Cl2N4O4S (M+H)+: 559.0974; Found: 559.0980.

syn- and anti-Methyl 3-(5-chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-2-methylpropanoate

According to general procedure B2, indole 20 (100 mg, 0.23 mmol), [(1-methoxy-1-propenyl)oxy](trimethyl)silane (0.17 mL, 0.93 mmol) and trifluoromethanesulfonic acid (8 µL, 0.09 mmol) in dichloromethane (5 mL) gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 → 20:80 of ethyl acetate:hexane) afforded ester 46 as a colourless oil (70 mg, 82%); Rf = 0.22 (8:2 hexane:ethyl acetate); approximately a 7:3 mixture of diastereomers. δH (500 MHz, chloroform-d) 8.13 (0.7 H, app. s, NHmaj), 8.05 (0.3 H, app. s, NHmin), 7.48 (0.7 H, dt,
J 8.5 and 0.8, indolyl 4-H^{maj}), 7.43 (0.3 H, dt, J 8.5 and 0.7, indolyl 4-H^{min}), 7.35 (0.7 H, d, J 1.8, indolyl 7-H^{maj}), 7.31 (0.3 H, d, J 1.8, indolyl 7-H^{min}), 7.17 (0.7 H, dd, J 2.5 and 0.8, indolyl 2-H^{maj}), 7.13 (0.3 H, app. d, J 2.5, indolyl 2-H^{min}), 7.07 (0.7 H, dd, J 8.5 and 1.8, indolyl 5-H^{maj}), 7.04 (0.3 H, dd, J 8.5 and 1.8, indolyl 5-H^{min}), 6.75 (0.3 H, dd, J 3.7 and 0.6, thiophenyl 3-H^{min}), 6.70 (0.3 H, d, J 3.7, thiophenyl 4-H^{min}), 6.68 (0.7 H, dd, J 3.8 and 0.9, thiophenyl 3-H^{maj}), 6.66 (0.7 H, d, J 3.8, thiophenyl 4-H^{maj}), 4.68–4.60 (1 H, m, 3-H^{maj}), 3.64 (2 H, s, methyl^{maj}), 3.52 (1 H, s, methyl^{min}), 3.29 (0.7 H, dq, J 10.2 and 7.0, 2-H^{maj}), 3.18 (0.3 H, dq, J 10.3 and 6.9, 2-H^{min}), 1.24 (1 H, d, J 6.9, 2-methyl^{min}) and 1.16 (2 H, d, J 7.0, 2-methyl^{maj}). δC (125 MHz, chloroform-d) 175.9 (maj), 175.8 (min), 146.3 (maj), 145.3 (min), 136.8 (maj), 136.6 (min), 128.6 (maj), 128.2 (min), 125.62 (min), 125.57 (maj), 125.2 (maj), 124.8 (min), 123.8 (maj/min), 122.9 (maj/min), 121.5 (maj/min), 120.8 (maj), 120.6 (min), 120.3 (min), 120.2 (maj), 118.2 (min), 116.4 (maj), 111.4 (maj), 111.2 (min), 52.1 (maj), 52.0 (min), 46.1 (maj), 45.8 (min), 41.62 (maj), 41.57 (min), 16.74 (min) and 16.66 (maj). HRMS m/z calculated for C_{17}H_{15}Cl_{2}NNaO_{2}S (M+Na)^+: 390.0098; Found: 390.0084.

**syn- and anti-Methyl 3-(2-bromo-5-chloro-1H-indol-3-yl)-3-(5-chloro thiophen-2-yl)-2-methylpropanoate**

According to general procedure D, ester 46 (156 mg, 0.42 mmol) and pyridinium tribromide (148 mg, 0.46 mmol) in tetrahydrofuran:chloroform (10 mL) gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 → 20:80 of ethyl acetate:hexane) afforded ester 47 as a colourless oil (184 mg, 95%); approximately a 7:3 mixture of diastereomers. δH (500 MHz, chloroform-d) 8.23 (0.7 H, s, NH^{maj}), 8.16 (0.3 H, s, NH^{min}), 7.61 (0.3 H, d, J 8.6, indolyl 4-H^{min}), 7.47 (1 H, d, J 8.6, indolyl 4-H^{maj}), 7.28 (0.7 H, d, J 1.9, indolyl 7-H^{maj}), 7.22 (0.3 H, d, J 1.9, indolyl 7-H^{min}), 7.12–7.05 (1 H, m, indolyl 5-H^{maj/min}), 6.81 (0.3 H, dd, J 3.8 and 0.7, thiophenyl 3-H^{min}), 6.73 (0.7 H, dd, J 3.8 and 1.0, thiophenyl 3-H^{maj}), 6.70 (0.3 H, d, J 3.8, thiophenyl 4-H^{min}), 6.65 (0.7 H, d, J 3.8, thiophenyl 4-H^{maj}), 4.67 (0.7 H, dd, J 11.4 and 1.0, 3-H^{maj}), 4.59–4.53 (0.3 H, m, 3-H^{min}), 3.71 (2 H, s, methyl^{maj}), 3.67–3.51 (1 H, m, 2-H^{maj/min}), 3.41 (1 H, s, methyl^{min}), 1.34 (1 H, d, J 6.9, 2-methyl^{min}) and 1.06 (2 H, d, J 7.0, 2-methyl^{maj}). δC (125 MHz, chloroform-d) 176.12 (maj), 175.21 (min), 144.67
(maj), 143.42 (min), 136.78 (maj), 136.57 (min), 128.96 (maj), 128.69 (min), 128.54 (min), 128.41 (maj), 125.62 (min), 125.53 (maj), 124.70 (min), 124.53 (maj), 124.38 (min), 124.28 (min), 124.20 (maj), 124.12 (min), 123.68 (maj), 121.22 (min), 120.19 (min), 119.82 (maj), 115.83 (min), 114.91 (maj), 110.05 (maj), 109.51 (min), 52.25 (maj), 51.86 (min), 44.28 (min), 44.07 (maj), 43.03 (min), 42.02 (maj), 17.33 (min) and 17.04 (maj).

HRMS m/z calculated for C_{17}H_{14}BrCl_{2}NNaO_{2}S (M+Na)^+: 467.9204; Found: 467.9186.

**syn- and anti-3-(2-Bromo-6-chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-2-methylpropanoic acid**

According to general procedure C, ester 47 (161 mg, 0.36 mmol) and sodium hydroxide solution (2 mL, 0.6 M) in methanol:tetrahydrofuran (2 mL) at 60 °C afforded acid 48 as white solid (140 mg, 90%); approximately a 7:3 mixture of diastereomers. δ_H (500 MHz, methanol-d_4) 7.68 (0.3 H, dd, J 8.6 and 0.6, indolyl 4-H^{min}), 7.49 (0.7 H, dd, J 8.6 and 0.6, indolyl 4-H^{maj}), 7.31 (0.7 H, dd, J 1.9 and 0.6, indolyl 7-H^{maj}), 7.25 (0.3 H, dd, J 1.9 and 0.6, indolyl 7-H^{min}), 7.03 (0.3 H, dd, J 8.6 and 1.9, indolyl 5-H^{min}), 7.02 (0.7 H, dd, J 8.6 and 1.9, indolyl 5-H^{maj}), 6.91 (0.3 H, dd, J 3.8 and 0.7, thiophenyl 3-H^{min}), 6.85 (0.7 H, dd, J 3.8 and 1.0, thiophenyl 3-H^{maj}), 6.76 (0.3 H, d, J 3.8, thiophenyl 4-H^{min}), 6.72 (0.7 H, d, J 3.8, thiophenyl 4-H^{maj}), 4.65 (0.7 H, dd, J 11.5 and 1.0, 3-H^{maj}), 4.55 (0.3 H, dd, J 11.4 and 0.7, 3-H^{min}), 3.67–3.56 (0.3 H, m, 2-H^{min}), 3.54 (0.7 H, dq, J 11.5 and 7.0, 2-H^{maj}), 1.30 (1 H, d, J 6.8, 2-methyl^{min}) and 1.02 (2 H, d, J 7.0, 2-methyl^{maj}). δ_C (125 MHz, methanol-d_4) 179.3 (maj), 178.4 (min), 147.1 (maj), 145.7 (min), 138.6 (maj), 138.3 (min), 129.1 (maj), 128.84 (min), 128.79 (min), 128.76 (maj), 126.7 (min), 126.5 (maj), 125.8 (maj), 125.7 (min), 125.6 (min), 124.7 (maj), 121.30 (maj), 121.28 (min), 121.0 (min), 120.6 (maj), 116.1 (min), 115.0 (maj), 111.9 (maj), 111.8 (maj), 111.6 (min), 111.1 (min), 45.3 (min), 45.0 (maj), 44.2 (min), 43.0 (maj), 17.7 (min) and 17.4 (maj). HRMS m/z calculated for C_{16}H_{12}BrCl_{2}NO_{2}S (M+H)^+: 430.9149; Found: 430.9133.
**syn- and anti-3-(2-Bromo-6-chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-2-methyl-N-[2-(pyridin-2-yl)ethyl]propenamide**

According to general procedure E2, carboxylic acid 48 (130 mg, 0.30 mmol), 2-(2-pyridyl)ethylamine (54 µL, 0.45 mmol), DIPEA (160 µL, 0.92 mmol) and HCTU (165 mg, 0.40 mmol) in dimethylformamide (3 mL) at RT gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 → 100:0 of methanol:dichloromethane) afforded two products as colourless materials. Diastereomers **syn-49** and **anti-49** were isolated in a 7:3 ratio, respectively.

Fraction one was precipitated in diethyl ether/hexane (2 mL, 1:1), filtered and washed with diethyl ether (2 x 2 mL) to afford amide **syn-49** as a white solid (90 mg, 80%). Rf = 0.39 (ethyl acetate); δH (500 MHz, DMSO-d6) 12.04 (1 H, s, NHindole), 8.50 (1 H, ddd, J 4.9, 1.9 and 0.9, pyridinyl 6-H), 8.17 (1 H, td, J 5.7, NHamide), 7.69 (1 H, td, J 7.6 and 1.9, pyridinyl 4-H), 7.57 (1 H, d, J 8.6, indolyl 4-H), 7.33 (1 H, d, J 2.0, indolyl 7-H), 7.22 (1 H, ddd, J 7.6, 4.9 and 1.2, pyridinyl 5-H), 7.17 (1 H, app. dt, J 7.6 and 1.2, pyridinyl 3-H), 7.07 (1 H, dd, J 8.6 and 2.0, indolyl 5-H), 6.82 (1 H, d, J 8.6, thiophenyl 4-H), 6.75 (1 H, ddd, J 7.6, 4.9 and 1.2, pyridinyl 5-H), 7.17 (1 H, app. dt, J 7.6 and 1.2, pyridinyl 3-H), 7.07 (1 H, dd, J 8.6 and 2.0, indolyl 5-H), 6.82 (1 H, d, J 3.8, thiophenyl 4-H), 6.75 (1 H, ddd, J 3.8 and 1.0, thiophenyl 3-H), 4.49 (1 H, app. d, J 11.4, 3-H), 3.52 – 3.43 (1 H, m, 2-H), 3.47–3.35 (2 H, m, pyridinylethyl 1-Ha), 2.87–2.72 (2 H, m, pyridinylethyl 2-Ha) and 0.75 (3 H, d, J 6.7, 2-methyl). δC (125 MHz, DMSO-d6) 174.1, 159.0, 149.1, 145.8, 136.8, 136.4 (x2), 126.6, 126.0, 125.5, 123.6, 123.1 (x2), 121.5, 119.8, 119.6, 113.9, 110.8, 42.6, 40.9, 38.2, 37.2 and 17.4. HRMS m/z calculated for C23H21BrClN3OS (M+Na)+: 535.9966; Found: 535.9978.

Fraction two was precipitated in diethyl ether/hexane (2 mL, 1:1), filtered and washed with diethyl ether (2 x 2 mL) to afford amide **anti-49** as a white solid (32 mg, 67%). Rf = 0.19 (ethyl acetate); δH (500 MHz, DMSO-d6) 11.87 (1 H, s, NHindole), 8.39 (1 H, ddd, J 4.8, 1.9 and 0.9, pyridinyl 6-H), 7.78 (1 H, d, J 8.6, indolyl 4-H), 7.75 (1 H, t, J 5.8, NHamide), 7.54 (1 H, td, J 7.7 and 1.9, pyridinyl 4-H), 7.25 (1 H, d, J 2.0, indolyl 7-H), 7.14 (1 H, ddd, J 7.7, 4.8 and 1.2, pyridinyl 5-H), 7.00 (1 H, dd, J 8.6 and 2.0, indolyl 5-H), 6.92 (1 H, d, J 3.8, thiophenyl 3-H), 6.90 (1 H, d, J 3.8, thiophenyl 4-H), 6.78 (1 H, app. dt, J 7.7 and 1.2, pyridinyl 3-H), 4.49 (1 H, d, J 11.5, 3-H), 3.49 – 3.39 (1 H, m, 2-H), 3.22–3.12 (1 H, m, pyridinylethyl 1-Ha), 3.10–3.01 (1 H, m, pyridinylethyl 1-Hb), 2.46–2.36 (1 H, m, pyridinylethyl 2-Ha), 2.33–2.22 (1H, m, pyridinylethyl 2-Hb).
and 1.06 (3 H, d, $J$ 6.6, 2-methyl). $\delta_c$ (125 MHz, DMSO-$d_6$) 173.2, 158.8, 148.9, 145.4, 136.5, 136.2, 126.21, 126.15, 125.8, 124.7, 124.0, 122.7, 121.3, 120.6, 119.5, 114.9, 110.4, 110.3, 43.5, 42.2, 37.9, 37.0 and 17.8. HRMS $m/z$ calculated for C$_{23}$H$_{21}$BrCl$_2$N$_3$OS (M+Na)$^+$: 535.9966; Found: 535.9975.

These compounds were poorly soluble in aqueous buffer and therefore no binding affinity was determined.
Resolution of the relative configuration of syn-49. Top: chemical structure highlighting relevant protons and Newman projection. Bottom: extract of the $^1$H-^1$H NOESY correlation experiment.
anti-3-(2-Bromo-6-chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-2-methyl-N-[2-(pyridin-2-yl)ethyl]propenamide (anti-49)


syn- and anti-3-(6-Chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-2-methylpropanoic acid

According to general procedure C, ester 46 (130 mg, 0.35 mmol) and sodium hydroxide solution (2 mL, 0.5 M) in methanol (5 mL) at 60 °C afforded acid 50 as white solid (128 mg, 99%); approximately a 6:4 mixture of diastereomers. $\delta_H$ (500 MHz, methanol-d$_4$) 10.62 (0.6 H, s, NH$\text{maj}$), 10.53 (0.4 H, s, NH$\text{min}$), 7.46 (0.6 H, d, $J$ 8.5,
indolyl 4-H\textsuperscript{maj}), 7.42 (0.4 H, d, J 8.5, indolyl 4-H\textsuperscript{min}), 7.36 (1 H, d, J 1.9, indolyl 7-H\textsuperscript{maj}), 7.32 (1 H, d, J 1.8, indolyl 7-H\textsuperscript{min}), 7.29–7.26 (1 H, m, indolyl 2-H\textsuperscript{min}), 7.23 (1 H, d, J 2.2, indolyl 2-H\textsuperscript{maj}), 6.97 (1 H, dd, J 8.5 and 1.9, indolyl 5-H\textsuperscript{maj}), 6.94 (1 H, dd, J 8.5 and 1.9, indolyl 5-H\textsuperscript{min}), 6.83 (1 H, dt, J 3.7 and 0.8, thiophenyl 3-H\textsuperscript{min}), 6.79 (1 H, dd, J 3.8 and 0.9, thiophenyl 3-H\textsuperscript{maj}), 6.75–6.72 (1 H, m, thiophenyl 4-H\textsuperscript{min}), 6.71–6.68 (1 H, m, thiophenyl 4-H\textsuperscript{maj}), 4.61 (1 H, d, J 10.5, 3-H\textsuperscript{min}), 4.61 (1 H, d, J 10.4, 3-H\textsuperscript{maj}), 3.31–3.23 (1 H, m, 2-H\textsuperscript{maj}), 3.16 (1 H, dq, J 10.5 and 6.9, 2-H\textsuperscript{min}), 1.21 (1.2 H, d, J 6.9, 2-methyl\textsuperscript{min}) and 1.12 (1.8 H, d, J 6.9, 2-methyl\textsuperscript{maj}). δ\textsubscript{C} (125 MHz, methanol-\textsubscript{d}4) 179.35 (C1\textsuperscript{maj}), 179.20 (C1\textsuperscript{min}), 148.76 (C2\textsuperscript{min}), 147.72 (C2\textsuperscript{maj}), 138.65 (C3\textsuperscript{maj}), 138.49 (C3\textsuperscript{min}), 138.47 (C3\textsuperscript{maj}), 138.31 (C3\textsuperscript{min}), 128.96 (C4\textsuperscript{min}), 128.58 (C4\textsuperscript{maj}), 128.56 (C4\textsuperscript{min}), 128.49 (C4\textsuperscript{maj}), 126.66 (C5\textsuperscript{min}), 126.62 (C6\textsuperscript{maj}), 126.59 (C6\textsuperscript{min}), 126.55 (C5\textsuperscript{maj}), 126.52 (C6\textsuperscript{maj}), 126.49 (C6\textsuperscript{min}), 126.03 (C7\textsuperscript{min}), 125.03 (C8\textsuperscript{maj}), 124.86 (C8\textsuperscript{min}), 124.80 (C7\textsuperscript{maj}), 123.47 (C8\textsuperscript{min}), 123.30 (C8\textsuperscript{min}), 120.81 (C9\textsuperscript{maj}), 120.77 (C9\textsuperscript{min}), 120.51 (C10\textsuperscript{maj}), 120.35 (C10\textsuperscript{min}), 118.48 (C11\textsuperscript{maj}), 118.44 (C11\textsuperscript{min}), 116.49 (C12\textsuperscript{maj}), 116.45 (C12\textsuperscript{min}), 112.33 (C13\textsuperscript{maj}), 112.28 (C13\textsuperscript{maj}), 112.07 (C13\textsuperscript{min}), 112.02 (C13\textsuperscript{min}), 47.15 (C14\textsuperscript{maj}), 46.82 (C14\textsuperscript{min}), 42.70 (C15\textsuperscript{maj}), 42.66 (C15\textsuperscript{min}) and 17.15 (C16). HRMS m/z calculated for C\textsubscript{16}H\textsubscript{13}Cl\textsubscript{2}N\textsubscript{a}O\textsubscript{2}S (M+Na\textsuperscript{+}): 375.9942; Found: 375.9930.

**syn- and anti-3-(6-Chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-2-methyl-1-[3-(pyridin-2-yl)pyrrolidin-1-yl]propan-1-one 13**

According to general procedure E2, acid **50** (65 mg, 0.18 mmol), 2-(pyrrolidin-3-yl)pyridine (41 mg, 0.28 mmol), DIPEA (96 µL, 0.55 mmol) and HCTU (116 mg, 0.28 mmol) in dimethylformamide (3 mL) at RT gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 → 100:0 of ethyl acetate:hexane) afforded amide **13** as a white solid (62 mg, 71%); diastereomeric mixture of rotamers. δ\textsubscript{H} (500 MHz, methanol-\textsubscript{d}4) 8.54 – 8.40 (1 H, m, pyridinyl 6-H), 7.82–7.63 (1 H, m, pyridinyl 4-H), 7.57–7.49 (1 H, m, indolyl 4-H), 7.40–6.66 (7 H, m, indolyl 2-, 5- and 7-H, pyridinyl 3- and 5-H and thiophenyl 3- and 4-H), 4.70–4.56 (1 H, m, 3-H), 4.13–2.96 (6 H, m, 2-H and pyrrolidinyl 2-H\textsubscript{z}, 3-H and 5-H\textsubscript{z}), 2.43–1.63 (2 H, m, pyrrolidinyl 4-H\textsubscript{z}) and 1.23–1.04 (3 H, 2-methyl). δ\textsubscript{C} (125 MHz, methanol-\textsubscript{d}4) δ
176.3 to 175.8 (C1), 162.1 to 161.2 (C2), 150.2 to 149.9 (C3), 149.0 to 148.9 (C4),
147.7 to 147.6 (C5), 138.8 to 138.3 (C6), 128.8 to 128.3 (C7), 126.9 to 122.5 (C8, C9,
C10, C11, C12, C13 and C14), 121.2 to 120.8 (C15), 120.6 to 120.3 (C16), 118.8 to
116.6 (C17), 112.3 to 112.1 (C18), 53.0 to 51.9 (C19), 48.1 to 45.3 (C20, C21 and
C22), 43.3 to 42.9 (C23), 33.4 to 31.4 (C24) and 17.2 to 17.0 (C25). HRMS m/z
calculated for C_{25}H_{24}Cl_{2}N_{3}OS (M+H)^+: 484.1017; Found: 484.1023.

**syn- and anti-(6-Chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-2-methyl-N-[2-
phenylcyclopropyl]propanamide**

![Chemical Structure Image]

According to general procedure E2, acid 50 (65 mg, 0.18 mmol), 2-phenylcyclopropa-
1-amine (37 mg, 0.28 mmol), DIPEA (96 µL, 0.55 mmol) and HCTU (116 mg, 0.28
mmol) in dimethylformamide (3 mL) at RT gave the crude product. Purification by
column chromatography (silica, eluent: gradient 0:100 → 50:50 of ethyl
acetate:hexane) afforded amide 51 as an off-white solid (54 mg, 64%); diastereomeric
mixture. δH (500 MHz, methanol-d4) 7.58–7.49 (1 H, m, indolyl 4-H), 7.38–7.32 (1 H,
m, indolyl 2-H), 7.28–6.76 (6 H, m, indolyl 7-H and phenyl 2-, 3-, 4-, 5- and 6-H), 7.02–
6.97 (1 H, m, indolyl 5-H), 6.90–6.69 (2 H, m, thiophenyl 3- and 4-H), 4.59–4.49 (1 H,
m, 3-H), 3.19–2.98 (1 H, m, 2-H), 2.78–2.49 (1 H, m, cyclopropyl 1-H), 1.93–1.02 (1
H, m, cyclopropyl 2-H), 1.22–1.05 (3 H, m, 2-methyl) and 1.19–0.53 (2 H, m,
cyclopropyl 3-H2). δC (125 MHz, methanol-d4) 179.2 to 178.9 (C1), 148.7 to 148.3 (C2),
142.2 to 142.1 (C3), 138.6 to 138.1 (C4), 129.3 to 125.2 (C5, C6, C7, C8, C9, C10,
C11, C12, C13 and C14), 124.6 to 123.7 (C15), 121.2 to 120.9 (C16), 120.5 to 120.4
(C17), 118.3 to 116.9 (C18), 112.3 and 112.1 (C19), 48.3 to 47.9 (C20), 43.3 to 43.1
(C21), 33.1 to 32.8 (C22), 25.6 to 25.0 (C23), 17.6 to 17.4 (C24) and 16.5 to 15.4
(C25). HRMS m/z calculated for C_{25}H_{22}Cl_{2}N_{2}NaOS (M+Na)^+: 491.0728; Found:
470.0722.

This compound was poorly soluble in aqueous buffer and therefore no binding affinity
was determined.
(3R*)-3-(5-chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-1-[(3R*)-3-(pyridin-2-yl)pyrrolidin-1-yl]propan-1-one and (3R*)-3-(5-chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-1-[(3S*)-3-(pyridin-2-yl)pyrrolidin-1-yl]propan-1-one

According to general procedure E2, the carboxylic acid 19 (65 mg, 0.19 mmol), 2-(pyrrolidin-3-yl)pyridine (54 mg, 0.38 mmol), DIPEA (100 µL, 0.57 mmol) and HCTU (160 mg, 0.38 mmol) in dimethylformamide (3 mL) at RT gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 → 100:0 of ethyl acetate:hexane) afforded amide 52 as a white solid (90 mg, quantitative yield); diastereomeric mixture of rotamers. δH (500 MHz, methanol-d4) 8.53–8.38 (1 H, m, pyridinyl 6-H), 7.79–7.60 (1 H, m, pyridinyl 4-H), 7.41–7.36 (1 H, m, indolyl 4-H), 7.36–7.28 (1 H, m, indolyl 7-H), 7.28–7.24 (2 H, m, indolyl 2-H and pyridinyl 5-H), 7.24–7.03 (2 H, m, indolyl 6-H and pyridinyl 3-H), 6.82–6.68 (2 H, m, thiophenyl 3- and 4-H), 5.00–4.91 (1 H, m, 3-H), 3.90–3.22 (5 H, m, pyrrolidinyl 3-H and 2- and 5-H), 3.21–3.08 (2 H, m, 2-H2) and 2.27–1.83 (2 H, m, pyrrolidinyl 4-H2). δC (125 MHz, methanol-d4) 172.01 (C1), 171.99 (C1), 171.97 (C1), 171.96 (C1), 161.78 (C2), 161.72 (C2), 161.29 (C2), 161.21 (C2), 150.13 (C3), 150.10 (C3), 150.07 (C3), 150.03 (C3), 149.22 (C4), 149.17 (C4), 149.09 (C4), 138.74 (C5), 138.73 (C5), 138.71 (C5), 138.70 (C5), 136.68 (C6), 136.66 (C6), 128.71 (C7), 128.68 (C7), 128.66 (C7), 128.61 (C8), 128.59 (C8), 128.57 (C8), 126.91 (C9), 126.89 (C9), 125.74 (C10), 125.72 (C10), 125.13 (C11), 125.09 (C11), 125.06 (C11), 124.99 (C11), 124.91 (C12), 124.89 (C12), 124.85 (C12), 124.84 (C12), 123.58 (C13), 123.55 (C13), 123.52 (C13), 123.46 (C14), 123.28 (C14), 123.22 (C14), 122.91 (C15), 122.88 (C15), 119.23 (C16), 119.21 (C16), 117.93 (C17), 117.89 (C17), 117.74 (C17), 117.65 (C17), 117.36 (C18), 113.76 (C18), 113.76 (C18), 113.73 (C18), 53.06 (C19), 52.96 (C19), 52.08 (C19), 52.04 (C19), 47.94 (C20), 47.90 (C20), 47.07 (C20), 47.02 (C20), 46.83 (C21), 45.58 (C21), 45.51 (C21), 42.70 (C22), 42.58 (C22), 42.45 (C22), 42.37 (C22), 36.49 (C23), 36.41 (C23), 36.37 (C23), 33.24 (C24), 33.17 (C24), 31.72 (C24) and 31.60 (C24). HRMS m/z calculated for C24H22Cl2N3OS (M+H)+: 470.0861; Found: 470.0875.
This compound was poorly soluble in aqueous buffer and therefore no binding affinity was determined.

3-(5-Chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-N-[2-phenyl cyclopropyl]propanamide 7a

According to general procedure E2, acid 19 (65 mg, 0.19 mmol), 2-phenylcyclopropan-1-amine (45 mg, 0.38 mmol), DIPEA (100 µL, 0.57 mmol) and HCTU (160 mg, 0.38 mmol) in dimethylformamide (3 mL) at RT gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 → 50:50 of ethyl acetate:hexane) afforded amide 7a as an off-white solid (47 mg, 55%); diastereomeric mixture (it seems that 3 main isomers coexist). δH (500 MHz, methanol-d4) 7.41–7.37 (1 H, m, indolyl 4-H), 7.32 (1 H, app. d, J 8.6, indolyl 7-H), 7.23 (1 H, s, indolyl 2-H), 7.24–7.16 (2 H, m, phenyl 3- and 5-H), 7.15–7.10 (1 H, m, phenyl 4-H), 7.08–7.04 (1 H, m, indolyl 6-H), 7.08–6.99 (2 H, m, phenyl 2- and 6-H), 6.80–6.77 (1 H, m, thiophenyl 4-H), 6.77–6.74 (1 H, m, thiophenyl 3-H), 4.92–4.87 (1 H, m, 3-H), 2.97–2.89 (2 H, m, 2-H), 2.76–2.68 (1 H, m, cyclopropyl 1-H), 1.79–1.63 (1 H, m, cyclopropyl 2-H), 1.13–1.06 (1 H, m, cyclopropyl 3-HA) and 0.95–0.90 (1 H, m, cyclopropyl 3-HB). δC (125 MHz, methanol-d4) 174.81 (C1), 174.79 (C1), 149.08 (C2), 149.04 (C2), 142.15 (C3), 142.12 (C3), 136.69 (C4), 136.64 (C4), 129.30 (C5), 129.26 (C6), 128.68 (C7), 128.62 (C7), 128.60 (C7), 127.17 (C8, C9, C10), 126.95 (C11), 126.92 (C11), 126.80 (C12), 126.79 (C12), 125.73 (C13), 125.70 (C13), 124.94 (C14), 124.86 (C14), 124.82 (C15), 124.78 (C15), 122.88 (C16), 119.31 (C17), 119.30 (C17), 117.44 (C18), 113.67 (C19), 44.22 (C20), 44.16 (C20), 36.59 (C21), 36.56 (C21), 33.11 (C22), 33.09 (C22), 25.27 (C23), 25.18 (C23), 15.95 (C24) and 15.89 (C24). HRMS m/z calculated for C24H20Cl2N2NaOS (M+Na)+: 477.0571; Found: 477.0564.
5-chloro-3-[1-(5-chlorothiophen-2-yl)-2-[[2-(pyridin-2-yl)cyclopropyl]carbamoyl]ethyl]-1H-indole-2-carboxylic acid 14

According to general procedure E2, indole 44 (160 mg, 0.41 mmol), 2-phenylcyclopropan-1-amine (54 mg, 0.41 mmol), DIPEA (0.22 mL, 1.2 mmol) and HCTU (169 mg, 0.41 mmol) in dimethylformamide (9 mL) at 0 °C gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 → 5:95 of methanol:dichloromethane) afforded 160 mg of an impure material. Dichloromethane (3 mL) was added to the material and 6-chloro-1-hydroxybenzotriazole from HCTU precipitated. The filtrate was concentrated in vacuo and purification by column chromatography (silica, eluent: gradient 0:100 → 2.5:97.5 of methanol:dichloromethane) afforded amide 14 as a white solid (15 mg, 7%). δ_H (500 MHz, DMSO-d_6) 11.23 (1 H, s, CO_2H), 8.98 – 8.64 (1 H, m, NH_indole), 7.45 – 7.37 (2 H, m, indolyl 4-H and indolyl 7-H), 7.25 – 7.19 (2 H, m, phenyl 2-H and 6-H), 7.15 – 7.10 (1 H, m, phenyl 4-H), 7.10 – 6.99 (3 H, m, indolyl 6-H and phenyl 3-H and 5-H), 6.92 – 6.86 (1 H, m, thiophenyl 4-H), 6.84 – 6.80 (1 H, m, thiophenyl 3-H), 6.20 – 6.11 (1 H, m, carbamoylethyl 1-H), 3.37 – 3.24 (1 H, m, carbamoylethyl 2-H_α), 2.83 – 2.71 (2H, carbamoylethyl 2-H_β and cyclopropyl 1-H), 1.90 – 1.69 (1 H, m, cyclopropyl 2-H), 1.17 – 1.02 (2 H, m, cyclopropyl 3-H_α and 3-H_β). NH_carbamoyl is not observed. δ_C (125 MHz, DMSO-d_6) δ 171.13, 171.05, 148.81, 141.50, 141.42, 133.39, 128.17 (x2), 127.00, 125.90, 125.72, 125.69, 125.51, 125.32, 125.30, 122.87, 122.78, 122.73, 122.03, 119.48, 113.92, 40.67, 40.62, 32.73, 32.46, 32.36, 23.85, 23.70, 15.32, 14.97. HRMS m/z calculated for C_{25}H_{21}Cl_{2}N_{2}O_{3}S (M+H)^+: 499.0650; Found: 499.0646.
According to general procedure E2, indole 44 (20 mg, 0.05 mmol), 2-(pyrrolidin-3-yl)pyridine (11 mg, 0.08 mmol), DIPEA (26 µL, 0.15 mmol) and HCTU (31 mg, 0.08 mmol) in dimethylformamide (2 mL) at 0 ºC gave the crude product. Purification by column chromatography (silica, eluent: gradient 0:100 → 5:95 of methanol:dichloromethane) afforded ketone 15 as a colourless material (11 mg, 33%).

δH (500 MHz, methanol-d4) 8.56–8.20 (2 H, m, pyridinyl 6-HA and 6-HB), 7.86–6.70 (11 H, m, pyridinyl 3-, 4- and 5-HA and pyridinyl 3-, 4- and 5-HB, indolyl 4-, 6- and 7-H and thiophenyl 3- and 4-H), 5.22–5.01 (1 H, m, 3-H), 4.10–3.05 (10 H, m, 2-H2, pyrrolidinyl 2- and 5-H2A and pyrrolidinyl 2- and 5-H2B) and 2.48–1.23 (6 H, m, pyrrolidinyl 3-HA and 4-H2A and pyrrolidinyl 3-HB and 4-H2B). δC (125 MHz, methanol-d4) 171.76, 171.74, 171.72, 171.58, 171.56, 165.22, 165.17, 165.08, 165.03, 165.00, 164.98, 162.14, 162.08, 161.89, 161.74, 161.59, 161.46, 161.42, 161.19, 161.12, 160.80, 150.24, 150.15, 150.13, 150.12, 150.11, 150.00, 149.95, 149.90, 148.00, 147.92, 147.89, 138.76, 138.68, 138.65, 138.63, 138.62, 138.58, 138.53, 135.59, 135.53, 135.46, 132.18, 128.76, 128.71, 128.20, 127.99, 126.80, 126.68, 126.61, 124.92, 124.85, 124.74, 124.65, 124.01, 123.90, 123.73, 123.70, 123.62, 123.58, 123.53, 123.51, 123.43, 123.34, 123.28, 123.05, 122.92, 122.90, 122.64, 120.48, 120.45, 120.41, 120.38, 120.33, 117.52, 117.48, 117.40, 117.32, 117.24, 114.44, 114.37, 114.33, 54.90, 54.85, 54.80, 54.73, 54.12, 53.04, 52.98, 52.95, 52.93, 52.92, 52.24, 52.22, 52.17, 52.12, 52.10, 52.02, 47.89, 47.12, 47.08, 47.06, 47.05, 47.00, 46.98, 46.87, 46.82, 46.79, 46.73, 46.08, 45.56, 45.50, 45.43, 41.12, 41.04, 40.87, 40.76, 40.69, 40.51, 35.62, 35.58, 35.55, 35.47, 35.43, 35.41, 33.39, 33.33, 33.31, 33.18, 33.14, 33.13, 33.06, 33.03, 33.00, 31.96, 31.75, 31.71, 31.66, 31.66, 31.62, 31.61, 31.59, 31.51, 31.45, 31.44, 30.45, 27.55, 27.28.. HRMS m/z calculated for C23H20Cl2N3O3S (M+H)^+: 488.0626; Found: 488.0618.

This compound was poorly soluble in aqueous buffer and therefore no binding affinity was determined.
7. Peptide Characterization data

HPLC and ESI-MS data for wt GKAP peptide
HPLC and ESI-MS data for FITC-Ahx-GKAP peptide
HPLC and ESI-MS data for L6F GKAP peptide
8. Protein Characterization

Characterization of hDM2 (a) deconvoluted mass spectra (b) SDS-PAGE of newly prepared protein after size-exclusion chromatography and (c) CD of purified protein.
9. Small Molecule Spectra

**Ethyl (3aS,4R,9bR)-8-sulfamoyl-3H,3aH,4H,5H,9bH-cyclopenta[c]quinoline-4-carboxylate**
(3aS,4R,9bR)-8-Sulfamoyl-3H,3aH,4H,5H,9bH-cyclopenta[c]quinoline-4-carboxylic acid
5-Chloro-3-[(5-chlorothiophen-2-yl)(4-methylbenzenesulfonyl)methyl]-1H-indole
Methyl 3-(5-chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)propanoate

$\text{Cl} \quad \text{NH} \\
\text{Cl} \quad \text{S} \quad \text{O}$

$\begin{array}{c}
\text{D (m)} \\
\text{E (d)} \\
\text{F (dd)} \\
\text{G (t)} \\
\text{H (s)} \\
\text{J (dd)}
\end{array}$

$\begin{array}{c}
7.14 \\
6.70 \\
6.88 \\
4.91 \\
3.12 \\
3.66
\end{array}$
3-(5-Chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)propanoic acid
3-(5-Chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-N-[2-(pyridin-2-yl)ethyl] propanamide
3-(5-Chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-N-(2-phenylethyl) propanamide
**N-Benzyl-3-(5-chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)propanamide**

![Chemical Structure](image)

**NMR Spectra**

- **1H (ppm)**
  - 7.50
  - 7.44
  - 7.41
  - 7.38
  - 7.35
  - 7.32
  - 7.29
  - 7.26
  - 7.24
  - 7.21
  - 7.18
  - 7.15
  - 7.12
  - 7.09
  - 7.06
  - 7.03
  - 7.00
  - 6.97
  - 6.94
  - 6.91
  - 6.88
  - 6.85
  - 6.82
  - 6.79
  - 6.76
  - 6.73
  - 6.70
  - 6.67
  - 6.64
  - 6.61

- **13C (ppm)**
  - 170.29
  - 168.60
  - 156.74
  - 128.07
  - 125.74
  - 125.62
  - 125.50
  - 122.69
  - 122.67
  - 117.07
  - 112.71

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**Sample**

- Sample 285.10.1.1
- Name: Jengo
- Room: -03.2r
- Sample: SQ.4-I
3-(5-Chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-N-(2-methoxyethyl) propanamide
6-Chloro-3-[(5-chlorothiophen-2-yl)(4-methylbenzenesulfonyl)methyl]-1H-indole
Methyl 3-(6-chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)propanoate

\[ \text{Methyl 3-(6-chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)propanoate} \]
3-(6-Chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)propanoic acid
3-(6-Chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-N-[2-(pyridin-2-yl) ethyl] propanamide
3-(6-Chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-N-(2-phenylethyl) propanamide

Name:  Tom James
Room No.: G53c
Sample:  T9426 6 f1
3-(6-Chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-N-(2-methoxyethyl) propanamide
5-Chloro-3-[(4-methylbenzenesulfonyl)(phenyl)methyl]-1H-indole

\[
\begin{align*}
\text{E (d)} & \quad 7.32 \\
\text{I (m)} & \quad 7.57 \\
\text{B (d)} & \quad 7.68 \\
\text{F (d)} & \quad 11.46 \\
\text{D (d)} & \quad 7.21 \\
\text{D (m)} & \quad 7.54 \\
\text{K (m)} & \quad 7.26 \\
\end{align*}
\]

\[
\begin{align*}
\text{A (d)} & \quad 7.73 \\
\text{C (dd)} & \quad 7.02 \\
\text{H (s)} & \quad 6.24 \\
\text{G (s)} & \quad 2.26 \\
\end{align*}
\]
Methyl 3-(5-chloro-1H-indol-3-yl)-3-phenylpropanoate
3-(5-Chloro-1H-indol-3-yl)-3-phenylpropanoic acid
3-(5-Chloro-1H-indol-3-yl)-3-phenyl-N-[2-(pyridin-2-yl)ethyl]propanamide
3-(5-Chloro-1H-indol-3-yl)-3-phenyl-N-(2-phenylethyl)propanamide

Chemical structure and NMR spectrum
3-(5-Chloro-1H-indol-3-yl)-N-(2-methoxyethyl)-3-phenylpropanamide
Methyl 3-(2-bromo-6-chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)propanoate

The chemical structure and spectra are provided, with detailed peak assignments and chemical shifts.
tert-Butyl 2-bromo-6-chloro-3-[1-(5-chlorothiophen-2-yl)-3-methoxy-3-oxopropyl]-indole-1-carboxylate

Sample: SC021-1
Name: SC021-1
Room No.: G53c
Sample: SC021-1
3-(2-Bromo-6-chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)propanoic acid

Sample: 13048.11.1.11
Name: SC023-1
Room No.: G33c
Sample: SC023-1

1H NMR (500 MHz, CDCl3) δ ppm:
- A (s) 8.13
- B (d) 7.36
- C (d) 7.06
- D (dd) 4.92
- E (d) 3.79
- F (d) 3.19
- G (m) 3.33
- H (dd) 3.33

13C NMR (125 MHz, CDCl3) δ ppm:
- C 174.61
- D 136.61
- E 128.62
- F 128.73
- G 128.45
- H 121.39
- I 119.75
- J 115.94
- K 109.44

Mass spectrum: 389.7
3-(2-Bromo-6-chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-N-[2-(pyridin-2-yl)ethyl]propanamide
Methyl 3-(5-chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-2,2-dimethyl propanoate

Sample: 13318.10.1.1
Name: Sergi Ceis
Room No.: G53c
Sample: SC035-1
3-(5-Chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-2,2-dimethylpropanoic acid
3-(5-Chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-2,2-dimethyl-N-[2-(pyridin-2-yl)ethyl]propanamide

Sample: 13527-10-1.1
Name: Sergi Coats
Room No.: G53c
Sample: SCO43-1
rac-syn- and rac-anti-Methyl 3-(5-chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-2-methylpropanoate
**rac-syn- and rac-anti-3-(5-Chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-2-methylpropanoic acid**

Sample: 13476.10.1.1r
Name: Sergio cell
Room No.: G53c
Sample: SCO42-1

![Chemical Structure Image]

**NMR Spectra**

Sample: 13476.11.1c
Name: Sergio cell
Room No.: G53c
Sample: SCO42-1
rac-syn-3-(5-Chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-2-methyl-N-[2-(pyridin-2-yl)ethyl]propanamide
rac-anti-3-(5-Chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-2-methyl-N-[2-(pyridin-2-yl)ethyl]propanamide

Methyl 3-(2-bromo-5-chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)propanoate
3-(2-Bromo-5-chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)propanoic acid
3-(2-Bromo-5-chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-N-[2-(pyridin-2-yl)ethyl]propanamide
N-Benzyl-5-chloro-3-[(5-chlorothiophene-2-yl)(4-methylbenzenesulfonyl)methyl]-1H-indole-2-carboxamide
Methyl 3-[2-(benzylcarbamoyl)-5-chloro-1H-indol-3-yl]-3-(5-chlorothiophen-2-yl) propanoate
3-[2-(Benzylcarbamoyl)-5-chloro-1H-indol-3-yl]-3-(5-chlorothiophen-2-yl) propanoic acid
**N-Benzyl-5-chloro-3-[1-(5-chlorothiophene-2-yl)-2-[[2-(pyridin-2-yl)ethyl]carbamoyl]ethyl]-1H-indole-2-carboxamide**
5-Chloro-3-[(5-chlorothiophene-2-yl)[4-methylbenzenesulfonyl]methyl]-N-(2-methylpropyl)-1H-indole-2-carboxamide
Methyl 3-[(5-chloro-2-[(2-methylpropyl)carbamoyl]-1H-indol-3-yl]-3-(5-chlorothiophen-2-yl)propanoate
3-{5-Chloro-2-[(2-methylpropyl)carbamoyl]-1H-indol-3-yl}-3-(5-chlorothiophen-2-yl)propanoic acid
5-Chloro-3-[(5-chlorothiophene-2-yl)-2-[(2-pyridin-2-yl)ethyl]carbamoyl]ethyl]-N-(2-methylpropyl)-1H-indole-2-carboxamide
tert-Butyl N-{2-[(5-chloro-1H-indol-2-yl)formamido]ethyl}carbamate
5-Chloro-3-[(5-chlorothiophene-2-yl)(4-methylbenzenesulfonyl)methyl]-1H-indole-2-carboxylic acid
5-Chloro-3-[1-(5-chlorothiophene-2-yl)-3-methoxy-3-oxopropyl]-1H-indole-2-carboxylic acid
3-[2-Carboxy-1-(5-chlorothiophen-2-yl)ethyl]-5-chloro-1H-indole-2-carboxylic acid
5-Chloro-3-[1-(5-chlorothiophen-2-yl)-2-[(2-(pyridin-2-yl)ethyl)carbamoyl]ethyl]-1H-indole-2-carboxylic acid
Methyl 5-chloro-3-[1-(5-chlorothiophen-2-yl)-2-[[2-(pyridin-2-yl)ethyl]carbamoyl]ethyl]-1H-indole-2-carboxylate
**tert-Butyl N-[2-((5-chloro-3-[1-(5-chlorothiophen-2-yl)-2-[[2-(pyridin-2-yl)ethyl]carbamoyl]ethyl]-1H-indol-2-yl)formamido)ethyl]carbamate**
N-(2-Aminoethyl)-5-chloro-3-[1-(5-chlorothiophen-2-yl)-2-[[2-(pyridin-2-yl)ethyl]carbamoyl]ethyl]-1H-indole-2-carboxamide hydrochloride
Ethyl 3-\{(5-chloro-3-[1-(5-chlorothiophen-2-yl)-2-[[2-(pyridin-2-yl)ethyl]carbamoyl]ethyl]-1H-indol-2-yl)formamido\}propanoate
3-((5-Chloro-3-[(5-chlorothiophen-2-yl)-2-[(2-pyridin-2-yl)ethyl]carbamoyl]ethyl]-1H-indol-2-yl)formamido)propanoic acid
rac-syn- and rac-anti-Methyl 3-(5-chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-2-methylpropanoate
**rac-syn- and rac-anti-Methyl 3-(2-bromo-5-chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-2-methyl propanoate**
rac-syn and rac-anti-3-(2-Bromo-6-chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-2-methyl propanoic acid
rac-syn-3-(2-Bromo-6-chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-2-methyl-N-[2-(pyridin-2-yl)ethyl]propanamide
rac-anti-3-(2-Bromo-6-chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-2-methyl-N-[2-(pyridin-2-yl)ethyl]propanamide
**rac-syn**- and **rac-anti**-3-(6-Chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-2-methylpropanoic acid
**rac-syn- and rac-anti-3-(6-Chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-2-methyl-1-[3-(pyridin-2-yl)pyrrolidin-1-yl]propan-1-one**
rac-syn- and rac-anti-3-(6-Chloro-1H-indol-3-yl)-3-(5-chloro thiophen-2-yl)-2-methyl-N-[2-phenylcyclopropyl]propenamide
rac-3-(5-Chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-1-[3-(pyridin-2-yl)pyrrolidin-1-yl]propan-1-one
rac-3-(5-Chloro-1H-indol-3-yl)-3-(5-chlorothiophen-2-yl)-N12-phenyl cyclopropylpropionamide
5-chloro-3-[(5-chlorothiophen-2-yl)-2-[(2-phenylcyclopropyl)carbamoyl]ethyl]-1H-indole-2-carboxylic acid
10. **Bibliography**


