POLYSUBSTITUTED FUSED RING BICYCLIC THIOHYDANTOINS
FROM AMINOCARBO-N-THIOYLPYRROLIDINES DERIVED FROM
AZOMETHINE YLIDE 1,3-DIPOLAR CYCLOADDITIONS

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Abstract – Highly substituted bicyclic thiohydantoins fused to pyrrolidines were prepared from aminocarbo-N-thioylpyrrolidines derived from α-amino acid esters via imine azomethine ylide 1,3-dipolar cycloadditions and subsequent reaction with aroylisothiocyanates. Aminocarbo-N-thioylpyrrolidines efficiently undergo cyclisation in the presence of sodium methoxide to form bicyclic N-substituted thiohydantoins with concomitant cleavage of the N-acyl group in good to excellent yield. And also some interesting both regiospecific and stereospecific rearrangement to the bicyclic fused thiocarbamoil pyrrolidine and bicyclic thiohydantoin were observed.

INTRODUCTION
Thiohydantoins1,2 have found both pharmaceutical and agricultural applications,3 due to their antimicrobial4,5 antiviral,6,7 anti-inflammatory,8 antitumor,8,9 antiandrogenic10 and anticonvulsant11 properties. Further applications include hypolipidemic agents,12 glycosidase,13 glycogen phosphorylase14,15 and fatty acid amide hydrolase inhibitors.16-18 Recently some diaryl thiohydantoin RD162 and MDV3100 have shown activity for treatment of prostate cancer.19 2-Thiohydantoins are also useful intermediates in the synthesis of natural products such as dispacamide,20 leucettamine B,21 polyandrocarpamines A and B22 and aplysinopsins analogues.23 The chemistry of thiohydantoins has been extensively studied.24-38
Pyrrolidines and their derivatives are also an important class of heterocyclic compounds and are present in many bioactive compounds such as lisinopril, ceronapril and meropenem. Grigg et al. have reported a range of thermal and metal catalyzed azomethine ylide 1,3-dipolar cycloaddition cascade reactions furnishing pyrrolidines. This cascade chemistry has provided interalia a series of spirobenzodiazepines related to MK-329, nikkomycin analogues, peptidomimetics, pyrrolidine β-lactam analogues and fused and bridged ring pyrrolidine derivatives.

Thus the combination of pyrrolidines and 2-thiohydantoins into a new fused ring system was attractive. In previous work, we have reported the synthesis, structure determination and antimicrobial activity of novel benzoylaminocarbo-N-thioylpyrrolidines and their metal complexes. In this study, a series of polysubstituted bicyclic thiohydantoins fused to pyrrolidines are reported.

RESULTS AND DISCUSSION
The aroylaminocarbo-N-thioylpyrrolidines 1a,b and 1d-g were prepared from the corresponding pyrrolidines which, in turns were derived from α-amino acid esters via imine-azomethine ylide 1,3-dipolar cycloaddition and aroylisothiocyanates as previously described. The novel aroylaminocarbo-N-thioylpyrrolidine derivatives 1c, 1h-j were similarly prepared, but in the case of 1h it was necessary to reflux for 9 h. Cyclization of aroylaminocarbo-N-thioylpyrrolidines in the presence of sodium methoxide in refluxing dry MeOH for 18-36 h gave the thiohydantoin-pyrrolidine-fused ring systems 2a-j and cleavage of the aroyl group at nitrogen afforded the desired trans- and cis-fused bicyclic thiohydantoins 3a-j (Scheme 1) in 72-93% yield (Table 1). The byproduct methyl benzoate derivatives were also detected and confirmed after flash column chromatography. Compounds 3a-j were obtained as mixture of trans- and cis-isomers assigned according to positions of the functional group at C-5 and C-6. Column chromatography on silica gel and crystallization allowed the separation and isolation of the isomers in most case. Compounds 3a-j were characterized by 1H NMR, 13C NMR, FT-IR, MS and microanalysis. The structural assignment of the trans- and cis-isomers 3a-j is based on the H5 - H6 vicinal coupling constants (J_H-H) and X-ray crystal structures of cis-3a, trans-3a and cis-3j. The vicinal coupling constant for cis-3a is 9.24 Hz and trans-3a is 4.02 Hz. Similarly, the vicinal coupling constant for cis-3c is 8.16 Hz, trans-3c is 5.88 Hz, cis-3h is 8.16 Hz, trans-3h is 6.75 Hz, cis-3i is 6.47 Hz and trans-3i is 3.6 Hz (see experimental). Additionally, the structures of (5R,6S,7aS)-methyl hexahydro-7a-methyl-5-(naphthalen-2-yl)-1-oxo-3-thioxo-1H-pyrrolo[1,2-c]imidazole-6-carboxylate cis-3a, (5R,6R,7aS)-methyl hexahydro-7a-methyl-5-(naphthalen-2-yl)-1-oxo-3-thioxo-1H-pyrrolo[1,2-c]-imidazole-6-carboxylate trans-3a and (5S,6R,7aR)-methyl 7a-benzylhexahydro-1-oxo-5-(pyridin-3-yl)-3-thioxo-1H-pyrrolo[1,2-c]imidazole-6-carboxylate cis-3j were confirmed by X-ray crystal structures (Figures 1-3).
Scheme 1

Table 1. Fused thiohydantoin derivatives

<table>
<thead>
<tr>
<th>Compound</th>
<th>R^1</th>
<th>R^2</th>
<th>R^3</th>
<th>cis:trans (^*)</th>
<th>Yield (%)</th>
</tr>
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<tbody>
<tr>
<td>3a</td>
<td>-Me</td>
<td>-CO_2Me</td>
<td></td>
<td>55:45</td>
<td>85</td>
</tr>
<tr>
<td>3b</td>
<td></td>
<td>-CO_2Me</td>
<td></td>
<td>67:33</td>
<td>78</td>
</tr>
<tr>
<td>3c</td>
<td></td>
<td></td>
<td></td>
<td>80:20</td>
<td>93</td>
</tr>
<tr>
<td>3d</td>
<td></td>
<td>-CO_2Me</td>
<td></td>
<td>54:46</td>
<td>85</td>
</tr>
<tr>
<td>3e</td>
<td></td>
<td>-CO_2Me</td>
<td></td>
<td>50:50</td>
<td>89</td>
</tr>
<tr>
<td>3f</td>
<td></td>
<td>-CO_2Me</td>
<td></td>
<td>67:33</td>
<td>81</td>
</tr>
<tr>
<td>3g</td>
<td></td>
<td>-CO_2Me</td>
<td></td>
<td>75:25</td>
<td>83</td>
</tr>
<tr>
<td>3h</td>
<td></td>
<td></td>
<td></td>
<td>50:50</td>
<td>74</td>
</tr>
<tr>
<td>3i</td>
<td></td>
<td></td>
<td></td>
<td>85:15</td>
<td>72</td>
</tr>
<tr>
<td>3j</td>
<td></td>
<td></td>
<td></td>
<td>75:25</td>
<td>91</td>
</tr>
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</table>

\(^*\) cis:trans stereochemistry was assigned at C-5 and C-6 by vicinal coupling constants \(^3J_{H-H}\) and X-ray crystal structures (Figures 1-3)
Figure 1. An ORTEP drawing of the molecule cis-3a. Displacement ellipsoids are drawn at the 40% probability level.

Figure 2. An ORTEP drawing of the molecule trans-3a. Displacement ellipsoids are drawn at the 40% probability level. For the clarity solvent acetonitrile was not shown in the Figure.

Figure 3. An ORTEP drawing of the molecule cis-3j with two molecules in the asymmetric unit (racemates of the same compound). Displacement ellipsoids are drawn at the 40% probability level.

When the bicyclic aroylaminocarbo-\(N\)-thioylpyrrolidine (5), prepared according to modification of the literature methods,\textsuperscript{56-60} was reacted with sodium methoxide under same reaction conditions (MeOH,
reflux for 36 h) it afforded a mixture of 6 (49%) and 7 (24%) with new functional moieties at C-6 and C-7 (Scheme 2). When the same reaction was carried out at room temperature (MeOH for 36 h), only 7 was obtained in 83% yield. It can be concluded that the reaction is temperature dependent and for confirmation of the reaction mechanism of 7, the bicyclic pyrrolidine (8) was reacted with sodium methoxide in MeOH at reflux for 36 h. This resulted in rearrangement to the bicyclic pyrrolidine (9) in 85% yield (Scheme 3). The rearrangement was both regiospecific and stereospecific (Scheme 3). The driving force for the epimerisation step is to locate the amide and indole groups on the less sterically strained exo-face of the fused ring system (Schemes 4, 5). The structures of 6, 7 and 9 were determined on the basis $^1$H NMR, $^{13}$C NMR, FT-IR, MS and microanalysis. The stereochemistry was unambiguously determined for 6 and 7 by X-ray crystal analysis (Figures 4, 5).

Scheme 2

![Scheme 2](image)

Scheme 3

![Scheme 3](image)
Figure 4. An ORTEP drawing of the molecule 6. Displacement ellipsoids are drawn at the 40% probability level. For the clarity disordered crystal water was not shown in the Figure.

Scheme 4. Mechanism of rearrangement of 5 to 6.
Scheme 5. Mechanism of rearrangement of 5 to 7

In conclusion, an efficient short synthesis of highly substituted bicyclic thiohydantoins fused to pyrrolidines, having further modifiable groups, has been achieved from aminocarbo-N-thiolylypyrrolidines. Some interesting regiospecific and stereospecific rearrangements to the bicyclic pyrrolidines and thiocarbamoil pyrrolidine were also observed. Other chiral versions of these processes and their metal complexes, which can be used as chiral catalysts, are under investigation.

EXPERIMENTAL

IR spectra were recorded on Varian Scimitar Series 1000 FT-IR spectrophotometer, using horizontal ATR. Nuclear magnetic resonance spectra and decoupling experiments were determined at 400 MHz on a Bruker Ultrashield Plus Biospin GmbH and 300 MHz on a Bruker Ultrashield TM spectrometers as specified. Chemical shifts are given in parts per million (δ) downfield from tetramethylsilane as internal standard. Spectra were determined in deuteriochloroform except where otherwise stated. The following abbreviations are used; s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, brd = broad doublet and brs = broad singlet. Flash column chromatography was performed using silica gel 60 (230-400 mesh). Kieselgel columns were packed with silica gel GF254 (Merck 7730). Melting points were determined on Stuart SMP3 hot stage apparatus and are uncorrected. Microanalyses were obtained using a Carlo - Erba Model 1106 instrument. Mass spectra were recorded at Agilent LC/MSD mass spectrometer or Agilent 6460 Triple Quad LC/MS/MS mass spectrometer. The X-ray crystal structure
data were collected on Rigaku R-Axis Rapid-S model X-ray diffractometer.

**General Procedures for the Preparation of Pyrrolidines.** The known pyrrolidine derivatives, dimethyl 2-methyl-5-(naphthalen-2-yl)pyrrolidine-2,4-dicarboxylate,\textsuperscript{61} dimethyl 5-(4-chlorophenyl)-2-phenylpyrrolidine-2,4-dicarboxylate,\textsuperscript{62} dimethyl 2,5-diphenylpyrrolidine-2,4-dicarboxylate,\textsuperscript{56,62,63} dimethyl 5-(naphthalen-2-yl)-2-phenylpyrrolidine-2,4-dicarboxylate,\textsuperscript{64} dimethyl 2-benzyl-5-(4-methoxyphenyl)pyrrolidine-2,4-dicarboxylate,\textsuperscript{61} dimethyl 2-benzyl-5-(4-chlorophenyl)-2-phenylpyrrolidine-2,4-dicarboxylate,\textsuperscript{61} dimethyl 2-benzyl-5-(4-chlorophenyl)-2-phenyl-4-(phenylsulfonyl)pyrrolidine-2-carboxylate,\textsuperscript{59} and methyl 2-benzyl-5-(4-chlorophenyl)-2-phenyl-4-(phenylsulfonyl)pyrrolidine-2-carboxylate,\textsuperscript{59} and 8,\textsuperscript{59} were prepared according to literature methods and an analogues method was used for the phenylsulfonyl adducts and the novel methyl 5-(4-chlorophenyl)-2-phenyl-4-(phenylsulfonyl)pyrrolidine-2-carboxylate, methyl 2-benzyl-4-(methylsulfonyl)-5-phenyl pyrrolidine-2-carboxylate and dimethyl 2-benzyl-5-(pyridin-3-yl)pyrrolidine-2,4-dicarboxylate were similarly prepared as noted below.

**Methyl 5-(4-chlorophenyl)-2-phenyl-4-(phenylsulfonyl)pyrrolidine-2-carboxylate.** Prepared by adaption of literature procedures.\textsuperscript{52} After a reaction time of 26 h and work up the product (0.42 g, 92%) crystallised from Et\textsubscript{2}O:hexane as colourless prisms: mp 146-148 °C. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): $\delta = 7.71-7.09$ (m, 14H, Ar -H), 4.50 (d, 1H, $J = 6.51$ Hz, 5-H), 3.99-3.94 (m, 1H, 4-H), 3.81 (s, 3H, OCH\textsubscript{3}), 3.61 (dd, 1H, $J = 14.64$, 5.19 Hz, 3-H), 2.88 (dd, 1H, $J = 14.64$, 8.01 Hz, 3-H'). \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): $\delta = 173.26$ (C=O), 141.70, 139.03, 134.20, 133.68, 133.02, 129.28 (2 x C), 128.90 (2 x C), 128.67 (2 x C), 128.10 (2 x C), 127.99, 127.65 (2 x C), 126.18 (2 x C), 70.51, 67.37, 62.74, 53.24, 39.39. IR (cm\textsuperscript{-1}): $\nu_{\text{max}}$ 3314, 3071, 3035, 2960, 1727, 1598, 1492, 1446, 1301, 1257, 1208, 1144, 1085, 1010, 816, 729, 691. MS (ES, M+H\textsuperscript{+}): $m/z$ 456.1 (M+H\textsuperscript{+}, 100), 458.1 (M+H\textsuperscript{+}, 45). Anal. Calcd for C\textsubscript{24}H\textsubscript{22}ClNO\textsubscript{4}S: C, 63.20; H, 4.85; N, 3.05; S, 7.05. Found: C, 62.85; H, 4.90; N, 3.15; S, 7.15.

**Methyl 2-benzyl-4-(methylsulfonyl)-5-phenylpyrrolidine-2-carboxylate.** Prepared by adaption of literature procedures.\textsuperscript{52} After a reaction time of 28 h and work up the product (0.28 g, 75%) crystallised from Et\textsubscript{2}O:hexane as colourless prisms: mp 134-136 °C. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): $\delta = 7.47-7.26$ (m, 10H, Ar-H), 4.62 (d, 1H, $J = 6.21$ Hz, 5-H), 3.78 (s, 3H, OCH\textsubscript{3}), 3.57-3.51 (m, 1H, 4-H), 3.16 (d, 1H, $J = 13.2$ Hz, 3-H), 3.05 (d, 1H, $J = 13.17$ Hz, 6-H'), 2.53 (dd, 1H, $J = 15.03$, 8.28 Hz, 3-H'), 2.01 (s, 3H, CH\textsubscript{3}). \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): $\delta = 174.36$ (C=O), 136.15 (2 x C), 130.22 (2 x C), 128.72 (2 x C), 128.59, 128.29 (2 x C), 127.99 (2 x C), 127.15, 68.94, 67.53, 63.43, 52.61, 45.62, 40.33, 35.57. IR (cm\textsuperscript{-1}): $\nu_{\text{max}}$ 3308, 3071, 2964, 1735, 1596, 1495, 1459, 1428, 1301, 1273, 1211, 1132, 1075, 1048, 748, 704. MS (ES, M+H\textsuperscript{+}): $m/z$ 374.1 (M+H\textsuperscript{+}, 100), 376.1 (M+H\textsuperscript{+}, 45). Anal. Calcd for C\textsubscript{20}H\textsubscript{22}ClNO\textsubscript{5}S.0.25H\textsubscript{2}O: C, 63.60; H, 6.20; N, 3.70; S, 8.50. Found: C, 63.75; H, 6.20; N, 3.80; S, 8.55.

**Dimethyl 2-benzyl-5-(pyridin-3-yl)pyrrolidine-2,4-dicarboxylate.** Prepared by adaption of literature procedures.\textsuperscript{52} After a reaction time of 24 h and work up the product (0.33 g, 94%) crystallised from Et\textsubscript{2}O:hexane as colourless prisms: mp 102-104 °C. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): $\delta = 8.52-8.49$ (m, 2H,
Ar-H), 7.73-7.69 (m, 1H, Ar-H), 7.34-7.24 (m, 6H, Ar-H), 4.59 (d, 1H, J = 7.8 Hz, 5-H), 3.79 (s, 3H, OCH₃), 3.30-3.23 (m, 1H, H), 3.24 (s, 3H, OCH₃), 3.17 (d, 1H, J = 13.14 Hz, 6-H), 2.97 (d, 1H, J = 13.14 Hz, 6-H'), 2.78 (dd, 1H, J = 5.94 Hz, 3-H), 2.26 (dd, 1H, J = 13.74 Hz, 3-H'). ¹³C NMR (75 MHz, CDCl₃): δ = 175.47 (C=O), 172.42 (C=O), 148.70, 148.66, 136.57, 135.81, 134.61, 130.06 (2 x C), 128.27 (2 x C), 127.01, 123.24, 70.23, 62.24, 52.38, 51.42, 49.53, 45.65, 38.01. IR (cm⁻¹): ν_max 3358, 3024, 2945, 1738, 1574, 1492, 1433, 1262, 1183, 1098, 1037, 752, 706. MS (ESI, M+H⁺): m/z 355.2 (M+H⁺, 35). Anal. Calcd for C₂₀H₂₂N₂O₄: C, 67.75; H, 6.25; N, 7.90. Found: C, 67.30; H, 6.20; N, 7.90.

General Procedures for the Preparation of Aroylaminocarbonyl-N-thioylpyrrolidines (1a-j, 5). The known aroylaminocarbonyl-N-thioylpyrrolidines (1a, b, e), 60 (1d, g), 56-58 (f) were prepared according to literature procedure from the corresponding pyrrolidines and subsequent reaction with aroylisothiocyanates as previously described. The novel methyl 1-((benzamido)carbonyl-N-thioly)-5-(4-chlorophenyl)-2-phenyl-4-(phenylsulfonyl)pyrrolidine-2-carboxylate (1c), Methyl 2-((1H-indol-3-yl)methyl)-1-((benzamido)carbonyl-N-thioly)-5-phenyl-4-(phenylsulfonyl)pyrrolidine-2-carboxylate (1h), methyl 1-((benzamido)carbonyl-N-thioly)-2-benzyl-4-(methylsulfonyl)-5-phenyl pyrrolidine-2-carboxylate (1i), Dimethyl 1-((benzamido)carbonyl-N-thioly)-2-benzyl-5-(pyridin-3-yl)pyrrolidine-2,4-dicarboxylate (1j) and Ethyl 1-((1H-indol-3-yl)methyl)-2-((benzamido)carbonyl-N-thioly)octahydro-4,6-dioxo-3,5-diphenylpyrrolo[3,4-c]pyrrole-1-carboxylate (5) were similarly prepared. In the case of 1h and 5 the reactions carried out in refluxing acetonitrile for 9 h. Methyl 1-((benzamido)carbonyl-N-thioly)-5-(4-chlorophenyl)-2-phenyl-4-(phenylsulfonyl)pyrrolidine-2-carboxylate (1c). After a reaction time of 8 h and work up the product (0.72 g, 95%) crystallised from Et₂O:hexane as pale yellow prisms as a 1:3 rotamer mixture: mp 163-165 ºC. ¹H NMR (300 MHz, CDCl₃): δ = 7.76 (brs, 1H, NH major rotamer), 7.70-6.99 (m, 38H, Ar-H major and minor rotamers), 7.66 (brs, 1H, NH minor rotamer), 6.02 (d, 1H, J = 8.76 Hz, 5-H major rotamer), 5.98 (d, 1H, J = 8.52 Hz, 5-H minor rotamer), 4.02-3.90 (m, 2H, 4-H major and minor rotamers), 3.87 (s 3H, OCH₃ major rotamer) 3.63 (s 3H, OCH₃ minor rotamer) 3.46 (dd 1H, J = 13.71, 12 Hz, 3-H major rotamer), 3.31 (dd 1H, J = 13.71, 12 Hz, 3-H minor rotamer), 3.18 (dd 1H, J = 12, 5.34, Hz, 3-H' major rotamer). ¹³C NMR (75 MHz, CDCl₃): δ = 187.39 (C=S minor rotamer), 180.03 (C=S major rotamer), 172.63 (C=O minor rotamer), 170.78 (C=O minor rotamer), 169.60 (C=O major rotamer), 164.54 (C=O major rotamer), 137.46, 137.37, 135.13, 134.01, 133.81, 133.49, 133.42, 133.28, 133.12, 133.03, 131.98, 130.58, 129.81, 129.46, 129.14 (3 x C), 129.06 (2 x C), 129.03 (2 x C), 128.93, 128.84 (3 x C), 128.40, 128.32 (3 x C), 128.29 (3 x C), 128.24 (4 x C), 128.21 (4 x C), 128.10, 127.77 (2 x C), 127.44 (2 x C), 127.30, 127.17, 125.06, 78.08, 74.89, 65.97, 64.95, 64.82, 64.47, 53.40, 53.31, 41.70, 41.63. IR (cm⁻¹): ν_max 3218, 3057, 2956, 1720, 1710, 1589, 1526, 1491, 1448, 1293, 1216, 1182, 1141, 740, 706, 686. MS (ESI, M+H⁺): m/z 616.9(M-H⁺, 100), 618.8(M-H⁺, 45). Anal. Calcd for
Methyl 2-((1H-indol-3-yl)methyl)-1-((benzamido)carbonylthioly)-5-phenyl-4-(phenylsulfonyl)pyrrolidine-2-carboxylate (1h). After a reaction time of 9 h and work up the product (0.68 g, 88%) crystallised from Et₂O:hexane as pale yellow prisms as a 1:3 rotamer mixture: mp 158-160 °C. ¹H NMR (300 MHz, CDCl₃): δ = 8.47 (brs, 1H, NH major rotamer), 8.41 (brs, 1H, NH minor rotamer), 8.17-6.79 (m, 42H, Ar-H, NH major and minor rotamers), 5.58 (d, 1H, J = 8.31 Hz, 5-H minor rotamer), 5.50 (d, 1H, J = 8.61 Hz, 5-H major rotamer), 4.65 (d, 1H, J = 15.42 Hz, 6-H major rotamer), 4.23 (d, 1H, J = 15.18 Hz, 6-H minor rotamer), 3.98 (s 3H, OCH₃ major rotamer) 3.84 (s 3H, OCH₃ minor rotamer) 3.65 (d, 1H, J = 15.12 Hz, 6-H' minor rotamer), 3.51 (d, 1H, J = 15.36 Hz, 6-H' major rotamer), 3.13-2.99 (m 4H, 4-H, 3-H major and minor rotamers), 2.29-2.17 (m 2H, 3-H' major and minor rotamers).

¹³C NMR (75 MHz, CDCl₃): δ = 186.26 (C=S minor rotamer), 177.89 (C=S major rotamer), 172.32 (C=O minor rotamer), 171.37 (C=O major rotamer), 164.26 (C=O major rotamer), 138.69, 138.30, 135.62, 134.56, 134.38, 133.61, 133.40, 133.22 (2 x C), 132.93, 132.58 (2 x C), 129.37 (2 x C), 129.31 (3 x C), 129.22 (4 x C), 129.17 (2 x C), 128.76 (2 x C), 128.66 (2 x C), 128.58 (2 x C), 128.27, 127.74 (2 x C), 127.62 (3 x C), 127.49 (2 x C), 127.34 (2 x C), 125.12, 123.71, 122.51, 122.24, 120.84, 120.61, 117.62, 117.53, 111.43, 109.66, 109.18, 75.52, 73.03, 67.40, 66.83, 63.44, 62.33, 53.05 (2 x C), 37.62, 37.12, 26.62, 22.67. IR (cm⁻¹): νmax 3379, 3343, 3060, 3040, 2946, 2844, 1727, 1682, 1599, 1511, 1485, 1447, 1395, 1340, 1303, 1232, 1193, 1147, 742, 697. MS (ESI, M-H⁺): m/z 635.9(M-H⁺, 100). Anal. Calcd for C₃₂H₂₇ClN₂O₅S₂: C, 62.10; H, 4.40; N, 4.50; S, 10.35. Found: C, 62.05; H, 4.45; N, 4.65; S, 10.70.

Methyl 1-((benzamido)carbonylthioly)-2-benzyl-4-(methylsulfonyl)-5-phenylpyrrolidine-2-carboxylate (1i). After a reaction time of 7 h and work up the product (0.55 g, 84%) crystallised from Et₂O:hexane as pale yellow prisms as a 1:2 rotamer mixture: mp 167-169 °C. ¹H NMR (300 MHz, CDCl₃): δ = 8.18 (brs, 1H, NH major rotamer), 8.15-7.12 (m, 30H, Ar-H major and minor rotamers), 7.95 (brs, 1H, NH minor rotamer), 5.43 (d, 1H, J = 8.76 Hz, 5-H minor rotamer), 5.39 (d, 1H, J = 8.73 Hz, 5-H major rotamer), 4.67 (d, 1H, J = 14.46 Hz, 6-H major rotamer), 4.30 (d, 1H, J = 14.13 Hz, 6-H minor rotamer), 3.97 (s 3H, OCH₃ major rotamer) 3.86 (s 3H, OCH₃ minor rotamer) 3.55 (d, 1H, J = 14.13 Hz, 6-H' minor rotamer), 3.43 (d, 1H, J = 14.46 Hz, 6-H' major rotamer), 2.93 (m 2H, 4-H major and minor rotamers), 2.78-2.62 (m 4H, 3-H, 3-H' major and minor rotamers), 2.04 (s 3H, CH₃ major rotamer) 1.90 (s 3H, CH₃ minor rotamer). ¹³C NMR (75 MHz, CDCl₃): δ = 186.84 (C=S major rotamer), 178.17 (C=S minor rotamer), 172.71 (C=O major rotamer), 172.61 (C=O major rotamer), 171.35 (C=O minor rotamer), 163.95 (C=O minor rotamer), 135.96, 135.91, 134.58, 133.98, 133.74, 133.11, 132.92 (2 x C), 132.60, 130.63 (2 x C), 130.01 (2 x C), 129.70, 129.56 (2 x C), 129.37 (3 x C), 129.25 (2 x C), 129.14 (2 x C), 129.05 (2 x C), 128.65 (2 x C), 128.60 (2 x C), 128.54, 128.32, 128.28 (2 x C), 128.17, 127.59 (2 x C), 74.77, 72.04, 66.39, 55.83, 63.55, 63.12, 53.32, 53.23, 41.53, 39.31, 38.48, 37.04, 36.84, 36.11. IR (cm⁻¹):
ν_{max} 3341, 3060, 3027, 2957, 2919, 1728, 1683, 1602, 1564, 1493, 1451, 1353, 1248, 1156, 1126, 1086, 734, 701. MS (ESI, M-H\(^{-}\)): m/z 534.9(M-H\(^{-}\), 100). Anal. Calcd for C\(_{28}\)H\(_{28}\)N\(_{2}\)O\(_{5}\)S\(_{2}\): C, 62.65; H, 5.25; N, 5.20; S, 11.95. Found: C, 62.35; H, 5.35; N, 5.20; S, 12.25.

**Dimethyl 1-((benzamido)carbo-N-thioly)-2-benzyl-5-(pyridin-3-yl)pyrrolidine-2,4-dicarboxylate (1j).** After a reaction time of 7 h and work up the product (0.53 g, 84%) crystallised from Et\(_2\)O:hexane as pale yellow prisms as a 1:3 rotamer mixture: mp 177-179 °C. \(^1\)H NMR (300 MHz, CDCl\(_3\)): δ = 8.66 (brs, 1H, NH major rotamer), 8.50-8.46 (m, 2H, Ar-H major and minor rotamers), 8.40 (brs, 1H, NH minor rotamer), 8.17-7.21 (m, 26H, Ar-H major and minor rotamers), 5.51 (d, 1H, J = 9.57 Hz, 5-H minor rotamer), 5.31 (d, 1H, J = 6.12 Hz, 5-H major rotamer), 4.53 (d, 1H, J = 14.04 Hz, 6-H minor rotamer), 4.22 (d, 1H, J = 13.5 Hz, 6-H major rotamer), 3.95 (s 3H, OCH\(_3\) minor rotamer) 3.84 (s 3H, OCH\(_3\) major rotamer) 3.48 (d, 1H, J = 14.07 Hz, 6-H' major rotamer), 3.40 (d, 1H, J = 14.58 Hz, 6-H' minor rotamer), 3.19 (s 6H, OCH\(_3\) major and minor rotamers), 3.14-2.97 (m 2H, 4-H major and minor rotamers), 2.46-2.37 (m 2H, 3-H, 3-H' major rotamer), 2.36 -2.28 (m 2H, 3-H, 3-H' minor rotamer). \(^1\)C NMR (100 MHz, CDCl\(_3\)): δ = 173.37 (C=S major rotamer), 171.90 (C=S minor rotamer), 169.43 (4 x C=O major and minor rotamers), 169.19 (2 x C=O major and minor rotamers), 150.29, 149.44, 148.96, 148.41, 136.24, 135.99, 135.34, 134.87, 133.66, 133.31, 133.10, 133.07, 132.43, 132.00, 130.92, 130.10 (3 x C), 129.25 (3 x C), 129.03 (3 x C), 128.75, 128.61 (3 x C), 127.82 (2 x C), 127.66, 127.40, 123.57, 123.04, 73.22, 66.03, 65.62, 53.28, 53.05, 51.82 (2 x C), 51.72, 46.68, 45.23, 41.50, 36.71 (2 x C), 35.80. IR (cm\(^{-1}\)): ν_{max} 3161, 2950, 1750, 1675, 1587, 1520, 1436, 1406, 1367, 1280, 1238, 1192, 1101, 741, 706. MS (ESI, M-H\(^{-}\)): m/z 515.9 (M-H\(^{-}\), 100). Anal. Calcd for C\(_{28}\)H\(_{27}\)N\(_{3}\)O\(_{5}\)S\(_{2}\).0.5 H\(_2\)O: C, 63.80; H, 5.30; N, 8.10; S, 6.20. Found: C, 63.85; H, 5.30; N, 7.85; S, 6.05.

**Ethyl 1-((1H-indol-3-yl)methyl)-2-((benzamido)carbo-N-thioly)octahydro-4,6-dioxo-3,5-diphenylpyrrol[3,4-c]pyrrole-1-carboxylate (5).** After a reaction time of 9 h and work up the product (0.69 g, 86%) crystallised from Et\(_2\)O:hexane as pale yellow prisms as a 1:2 rotamer mixture: mp 151-154 °C. \(^1\)H NMR (300 MHz, CDCl\(_3\)): δ = 8.52 (brs, 1H, NH minor rotamer), 8.43 (brs, 1H, NH major rotamer), 8.25-6.43 (m, 42H, Ar-H, NH major and minor rotamers), 5.70 (d, 1H, J = 11.34 Hz, 3-H minor rotamer), 5.63 (d, 1H, J = 11.07 Hz, 3-H major rotamer), 4.55-4.26 (m, 6H, CH\(_2\)CH\(_3\), 3a-H major and minor rotamers), 4.07-3.82 (m, 4H, 7-H, 7-H' major and minor rotamers), 2.88 (dd, 1H, J = 10.56, 10.26 Hz, 6a-H minor izomer), 2.61 (dd, 1H, J = 11.07, 9.90 Hz 6a-H major rotomer), 1.58-1.28 (m, 6H, CH\(_2\)CH\(_3\) major and minor rotamers). \(^1\)C NMR (100 MHz, CDCl\(_3\)): δ = 187.16 (C=S major rotamer), 178.47 (C=S minor rotamer), 172.95 (C=O major rotamer), 172.75 (C=O minor rotamer), 172.44 (C=O major rotamer), 172.10 (C=O major rotamer), 171.95 (C=O major rotamer), 169.58 (C=O major rotamer), 167.68 (C=O minor rotamer), 163.99 (C=O minor rotamer), 136.48, 136.09, 135.90, 135.87, 133.76, 133.10, 132.99, 130.86, 130.48, 129.19 (3 x C), 128.97 (4 x C), 128.91 (4 x C), 128.66 (6 x C), 128.46, 128.31 (2 x C), 127.85, 127.52 (3 x C), 125.90 (4 x C), 125.87 (4 x C), 124.28, 122.83, 122.46, 120.66, 120.41, 118.03,
General Procedures for the Preparation of Thiohydantoins (3a-j). To a stirred solution of aroylaminocarbo-N-thiolylypyrrolidines (1 mmol) in dry MeOH (30 mL) was added a solution of sodium methoxide (0.057 g, 1.05 mmol) in dry MeOH (20 mL) over 5 min. and the mixture stirred at reflux temperature for 18-36 h. After completion of the reaction, the solvent was evaporated under reduced pressure, quenched with saturated aqueous ammonium chloride and extracted with CH$_2$Cl$_2$. The combined organic layers were dried (MgSO$_4$), filtered, evaporated under reduced pressure and the mixture was purified by column chromatography (Et$_2$O:hexane) to afford bicyclic thiohydantoins 3 as a mixture of trans- and cis-isomers together with benzoate byproduct.

Methyl hexahydro-7a-methyl-5-(naphthalen-2-yl)-1-oxo-3-thioxo-1H-pyrrolo[1,2-c]imidazole-6-carboxylate (3a). After completion of the reaction (20 h), the product were obtained as a 55/45 mixture of cis- and trans-isomers which were seperated by column chromatography (Et$_2$O:hexane, 1:3) to afford the products (0.30 g, 85%) as colourless prisms.

(5R,6S,7aS)-Methyl hexahydro-7a-methyl-5-(naphthalen-2-yl)-1-oxo-3-thioxo-1H-pyrrolo[1,2-c]imidazole-6-carboxylate (cis-3a). The product crystallized from Et$_2$O as colourless prisms; mp 271-273 ºC (decomp.). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 8.03 (brs, 1H, NH), 7.83-7.76 (m, 4H, Ar -H), 7.57-7.46 (m, 2H, Ar-H), 7.09 (brs, 1H, Ar-H), 5.52 (d, 1H, J = 9.24 Hz, 5-H), 4.15-4.05 (m, 1H, 6-H), 3.12 (s, 3H, OCH$_3$), 2.92 (dd, 1H, J = 12.99, 12.96 Hz, 7-H), 2.19 (dd, 1H, J = 12.96, 6.27 Hz, 7-H'), 1.74 (s, 3H, CH$_3$). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$= 180.90 (C=S), 177.44 (C=O), 169.94 (C=O), 133.28, 132.86 (2 x C), 128.40, 127.84 (2 x C), 127.36, 126.49 (3 x C), 72.52, 63.62, 51.58 (2 x C), 31.12, 25.10. IR (cm$^{-1}$): $\nu_{\text{max}}$ 3098, 2945, 1750, 1731, 1703, 1602, 1508, 1471, 1365, 1222, 1198, 753, 728, 683. MS (ESI, M-H$^+$): m/z 353.0 (M-H$^+$, 100). Anal. Calcd for C$_{19}$H$_{18}$N$_2$O$_3$S.0.25H$_2$O: C, 63.60; H, 5.00; N, 7.80; S, 8.90. Found: C, 63.80; H, 5.15; N, 7.95; S, 9.15.

(5R,6R,7aS)-Methyl hexahydro-7a-methyl-5-(naphthalen-2-yl)-1-oxo-3-thioxo-1H-pyrrolo[1,2-c]imidazole-6-carboxylate (trans-3a). The product crystallized from Et$_2$O:acetonitrile as colourless prisms; mp 216-218 ºC. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 8.21 (brs, 1H, NH), 7.88-7.77 (m, 4H, Ar-H), 7.55-7.48 (m, 2H, Ar-H), 7.22 (brs, 1H, Ar-H), 5.66 (d, 1H, J = 4.02 Hz, 5-H), 3.81 (s, 3H, OCH$_3$), 3.55-3.49 (m, 1H, 6-H), 2.74 (dd, 1H, J = 13.44, 10.38 Hz, 7-H), 2.54 (dd, 1H, J = 13.41, 2.07 Hz, 7-H'), 1.65 (s, 3H, CH$_3$). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 177.54 (C=S), 175.37 (C=O), 172.90 (C=O), 133.90, 133.14, 133.09, 128.68, 128.12 (2 x C), 127.78 (2 x C), 126.58, 126.56, 73.66, 64.48, 55.11, 53.02, 33.59, 23.87. IR (cm$^{-1}$): $\nu_{\text{max}}$ 3056, 2983, 1751, 1729, 1602, 1502, 1414, 1351, 1214, 1193, 746, 653. MS (ESI, 2102 2102
M-H^+): m/z 352.9 (M-H^+, 100). Anal. Calcd for C_{19}H_{18}N_{2}O_{3}S: C, 64.40; H, 5.10; N, 7.90; S, 9.05. Found: C, 64.00; H, 5.10; N, 7.80; S, 9.35.

**Methyl 5-(4-chlorophenyl)hexahydro-1-oxo-7a-phenyl-3-thioxo-1H-pyrrolo[1,2-c]imidazole-6-carboxylate (3b).** After completion of the reaction (28 h), the product were obtained as a 67/33 mixture of cis- and trans-isomers and separated by column chromatography (Et_2O:hexane, 1:3). The product (0.31 g, 78%) was as an amorphous colourless solid.

**cis-Methyl 5-(4-chlorophenyl)hexahydro-1-oxo-7a-phenyl-3-thioxo-1H-pyrrolo[1,2-c]imidazole-6-carboxylate (3b).**

1H NMR (300 MHz, CDCl_3): δ = 8.14 (brs, 1H, NH), 7.61-7.08 (m, 9H, Ar-H), 5.42 (d, 1H, J = 9.24 Hz, 5-H), 3.68-3.58 (m, 1H, 6-H), 3.27 (s, 3H, OCH_3), 3.05 (dd, 1H, J = 12.9, 12.93 Hz, 7-H), 2.59 (dd, 1H, J = 12.72, 7-H').

IR (cm^{-1}): ν_{max} 3213, 2973, 2902, 1727, 1597, 1491, 1468, 1363, 1209, 1151, 724, 698. MS (ESI, M-H^+): m/z 398.8 (M-H^+, 100), 400.9(M-H^+, 40). Anal. Calcd for C_{20}H_{17}N_{2}O_{3}SCl: C, 59.90; H, 4.25; N, 7.00; S, 8.00. Found: C, 59.60; H, 4.30; N, 6.95; S, 8.20.

**trans-Methyl 5-(4-chlorophenyl)hexahydro-1-oxo-7a-phenyl-3-thioxo-1H-pyrrolo[1,2-c]imidazole-6-carboxylate (cis-3b).**

The product was an amorphous colourless solid; mp 192-194 ºC.

1H NMR (300 MHz, CDCl_3): δ = 8.15 (brs, 1H, NH), 7.60-7.18 (m, 9H, Ar-H), 5.77 (d, 1H, J = 2.07 Hz, 5-H), 3.27-3.21 (m, 1H, 6-H), 3.21 (s, 3H, OCH_3), 3.27-3.11 (m, 1H, 7-H), 2.91 (dd, 1H, J = 13.05, 8.55 Hz, 7-H').

IR (cm^{-1}): ν_{max} 3266, 3069, 2937, 1743, 1597, 1459, 1354, 1254, 1196, 745, 698. MS (ESI, M-H^+): m/z 398.9 (M-H^+, 100), 400.9(M-H^+, 40). Anal. Calcd for C_{20}H_{17}N_{2}O_{3}SCl: C, 59.90; H, 4.25; N, 7.00; S, 8.00. Found: C, 59.60; H, 4.35; N, 6.95; S, 8.20.

**5-(4-Chlorophenyl)hexahydro-7a-phenyl-6-(phenylsulfonyl)-3-thioxopyrrolo[1,2-c]imidazol-1-one (3c).** After completion of the reaction (36 h), the product were obtained as a mixture of cis- and trans-isomers in 80/20 ration and isolated by column chromatography (Et_2O:hexane, 1:3). The product (0.45 g, 93%) was as an amorphous colourless solid.

**cis-5-(4-Chlorophenyl)hexahydro-7a-phenyl-6-(phenylsulfonyl)-3-thioxopyrrolo[1,2-c]imidazol-1-one (3c).**

1H NMR (300 MHz, CDCl_3): δ = 8.37 (brs, 1H, NH), 7.74-6.94 (m, 14H, Ar-H), 5.50 (d, 1H, J = 8.16 Hz, 5-H), 4.27-4.18 (m, 1H, 6-H), 3.06 (dd, 1H, J = 13.14, 12.09 Hz, 7-H), 2.81 (dd, 1H, J = 11.91, 5.25 Hz, 7-H').

IR (cm^{-1}): ν_{max} 3202, 3062, 2922, 1751, 1592, 1491, 1443, 1368, 1215, 1137, 750, 701, 698.
688. MS (ESI, M-H\(^+\)): \(m/z\) 480.8 (M-H\(^+\), 100), 482.8 (M-H\(^+\), 40).

\((5S,6R,7aR)-5-(4-Chlorophenyl)hexahydro-7a-phenyl-6-(phenylsulfonyl)-3-thioxopyrrolo[1,2-c]-imidazol-1-one \textit{(trans-3c)}\). Obtained as an amorphous colourless solid; mp 168-170 °C. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 8.29\) (brs, 1H, NH), 7.61-6.88 (m, 14H, Ar-H), 5.25 (d, 1H, \(J = 5.88\) Hz, 5-H), 4.19-4.12 (m, 1H, 6-H), 3.26-3.08 (m, 2H, 7-H ve 7-H').

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 178.48\) (C=S), 173.13 (C=O), 137.14, 136.53, 134.93, 134.39, 129.47 (3 x C), 129.32 (3 x C), 128.81 (2 x C), 128.54 (3 x C), 125.09 (2 x C), 77.75, 73.81, 63.68, 33.42. IR (cm\(^{-1}\)): \(\nu_{\text{max}}\) 3221, 3060, 2957, 1720, 1592, 1491, 1448, 1293, 1218, 1184, 737, 687. MS (ESI, M-H\(^+\)): \(m/z\) 480.8 (M-H\(^+\), 100), 482.8 (M-H\(^+\), 35).

Anal. Calcd for C\(_{24}\)H\(_{19}\)ClN\(_2\)O\(_3\)S\(_2\): C, 59.70; H, 3.95; N, 5.80; S, 13.30. Found: C, 59.75; H, 4.15; N, 6.65; S, 13.15.

Methyl hexahydro-1-oxo-5,7a-diphenyl-3-thioxo-1\(H\)-pyrrolo[1,2-c]imidazole-6-carboxylate \textit{(3d)}.

After completion of the reaction (24 h), the product were obtained as a 54/46 mixture of cis- and trans-isomers and isolated by column chromatography (Et\(_2\)O:hexane, 1:2). The product (0.31 g, 85%) was as an amorphous colourless solid.

\((5R,6S,7aR)-Methyl \textit{hexahydro-1-oxo-5,7a-diphenyl-3-thioxo-1\(H\)-pyrrolo[1,2-c]imidazole-6-carboxylate \textit{(cis-3d)}\). The product crystallized from Et\(_2\)O as colourless prisms; mp 199-201 °C. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 8.23\) (brs, 1H, NH), 7.62-7.32 (m, 8H, Ar-H), 7.15 (brs, 2H, Ar-H), 5.44 (d, 1H, \(J = 9.18\) Hz, 5-H), 3.68-3.58 (m, 1H, 6-H), 3.22 (s, 3H, OCH\(_3\)), 3.10 (dd, 1H, \(J = 12.93, 12.84\) Hz, 7-H), 2.58 (dd, 1H, \(J = 12.66, 5.76\) Hz, 7-H'). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 179.22\) (C=S), 173.06 (C=O), 168.96 (C=O), 137.43, 133.66, 129.36 (3 x C), 128.69, 128.24 (3 x C), 124.94 (3 x C), 77.59, 63.85, 51.73, 51.29, 34.14. IR (cm\(^{-1}\)): \(\nu_{\text{max}}\) 3190, 3072, 2937, 1722, 1600, 1468, 1444, 1378, 1229, 1198, 725, 697. MS (ES, M+H\(^+\)): m/z 367.3 (M+H\(^+\), 100). Anal. Calcd for C\(_{20}\)H\(_{18}\)N\(_2\)O\(_3\)S: C, 65.55; H, 4.95; N, 7.65; S, 8.75. Found: C, 65.90; H, 5.00; N, 7.70; S, 9.05.

(5R,6R,7aR)-Methyl \textit{hexahydro-1-oxo-5,7a-diphenyl-3-thioxo-1\(H\)-pyrrolo[1,2-c]imidazole-6-carboxylate \textit{(trans-3d)}\). Crystallisation gave trans-isomer together with trace cis-isomer as an amorphous colourless solid; mp 189-191 °C. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 7.97\) (brs, 1H, NH), 7.63-7.25 (m, 10H, Ar-H), 5.80 (d, 1H, \(J = 1.92\) Hz, 5-H), 3.75-3.59 (m, 1H, 6-H), 3.28 (brd, 1H, \(J = 9.06\) Hz, 7-H), 3.21 (s, 3H, OCH\(_3\)), 2.96 (dd, 1H, \(J = 12.99, 8.46\) Hz, 7-H'). \(^{13}\)C NMR (CDCl\(_3\)) (75 MHz): \(\delta = 178.71\) (C=S), 171.05 (C=O), 168.96 (C=O), 137.38, 136.21, 129.35 (2 x C), 129.22, 128.90 (3 x C), 128.40, 125.62 (3 x C), 78.50, 63.85, 55.59, 52.30, 34.94. IR (cm\(^{-1}\)): \(\nu_{\text{max}}\) 3213, 2950, 1725, 1599, 1478, 1444, 1383, 1248, 1210, 723, 696. MS (ES, M+H\(^+\)): m/z 367.2 (M+H\(^+\), 100). Anal. Calcd for C\(_{20}\)H\(_{18}\)N\(_2\)O\(_3\)S: C, 65.55; H, 4.95; N, 7.65; S, 8.75. Found: C, 65.25; H, 5.05; N, 7.55; S, 8.85.

Methyl \textit{hexahydro-5-(naphthalen-2-yl)-1-oxo-7a-phenyl-3-thioxo-1\(H\)-pyrrolo[1,2-c]imidazole-6-carboxylate \textit{(3e)}\). After completion of the reaction (21 h), the product were obtained as a 50/50 mixture of cis- and trans-isomers and isolated by column chromatography (Et\(_2\)O:hexane, 1:2) which afforded the
(5R,6S,7aR)-Methyl hexahydro-5-(naphthalen-2-yl)-1-oxo-7a-phenyl-3-thioxo-1H-pyrrolo[1,2-c]-imidazole-6-carboxylate (cis-3e). The product crystallized from Et₂O as colourless prisms; mp 139-141 ºC (decomp.). ¹H NMR (300 MHz, CDCl₃): δ = 7.93 (brs, 1H, NH), 7.85-7.81 (m, 4H, Ar-H), 7.66-7.62 (m, 3H, Ar-H), 7.56-7.43 (m, 5H, Ar-H), 5.63 (d, 1H, J = 9.21 Hz, 5-H), 3.79-3.66 (m, 1H, 6-H), 3.22 (dd, 1H, J = 12.93, 12.84 Hz, 7-H'), 3.10 (s, 3H, OCH₃), 2.64 (dd, 1H, J = 12.66, 5.76 Hz, 7-H'). ¹³C NMR (75 MHz, DMSO-d₆): δ = 181.04 (C=S), 174.74 (C=O), 169.26 (C=O), 138.51, 132.96, 132.91, 132.76, 129.61, 129.37, 128.46, 127.89, 126.60, 125.35 (3 x C), 124.09, 128.42, 127.95 (2 x C), 125.68 (3 x C), 77.37, 63.07, 51.68, 51.65, 33.28. IR (cm⁻¹): νmax 3200, 3056, 2954, 1746, 1701, 1599, 1461, 1439, 1362, 1208, 1140, 721, 697. MS (ESI, M-H⁺): m/z 414.9 (M-H⁺, 100). Anal. Calcd for C₂₄H₂₀N₂O₃S.0.5H₂O: C, 67.75; H, 4.95; N, 6.60; S, 7.55. Found: C, 68.25; H, 4.90; N, 6.60; S, 7.50.

(5R,6S,7aR)-Methyl hexahydro-5-(naphthalen-2-yl)-1-oxo-7a-phenyl-3-thioxo-1H-pyrrolo[1,2-c]-imidazole-6-carboxylate (trans-3e). Crystallisation gave trans-isomer together with trace cis-isomer as an amorphous colourless solid; mp 236 -238 ºC (decomp.). ¹H NMR (300 MHz, acetone-d₆): 10.50 (brs, 1H, NH), 8.03-7.35 (m, 12H, Ar-H), 5.87 (d, 1H, J = 2.13 Hz, 5-H), 3.77-3.68 (m, 1H, 6-H), 3.32-3.12 (m, 2H, 7-H, 7-H'), 3.22 (s, 3H, OCH₃). ¹³C NMR (75 MHz, DMSO-d₆): δ = 181.04 (C=S), 174.75 (C=O), 169.26 (C=O), 137.45, 135.77, 133.23, 133.02 (2 x C), 129.60, 129.26 (3 x C), 129.20, 128.42, 127.95 (2 x C), 125.68 (3 x C), 78.26, 64.02, 55.49, 52.38, 34.44. IR (cm⁻¹): νmax 3198, 3054, 2945, 1757, 1723, 1598, 1508, 1461, 1364, 1208, 1153, 723, 695. MS (ESI, M-H⁺): m/z 414.9 (M-H⁺, 100). Anal. Calcd for C₂₂H₂₀N₂O₄S: C, 67.75; H, 4.95; N, 6.60; S, 7.55. Found: C, 67.80; H, 4.85; N, 6.60; S, 7.55.

Methyl 7a-benzyl-hexahydro-5-(4-methoxyphenyl)-1-oxo-3-thioxo-1H-pyrrolo[1,2-c]-imidazole-6-carboxylate (3f). After completion of the reaction (18 h), the product were obtained as a 67/33 mixture of cis- and trans-isomers and isolated by column chromatography (Et₂O:hexane, 1:2) which afforded the product (0.33 g, 81%) as an amorphous colourless solid. ¹H NMR (300 MHz, CDCl₃): δ = 7.82 (brs, 1H, NH), 7.37-6.79 (m, 9H, Ar-H), 5.27 (d, 1H, J = 9.33 Hz, 5-H), 3.78 (s, 3H, OCH₃), 3.78-3.65 (m, 1H, 6-H), 3.25 (s, 3H, OCH₃), 3.24 (d, 1H, J = 13.50 Hz, 8-H) 3.15 (d, 1H, J = 13.47 Hz, 8-H'), 2.88 (dd, 1H, J = 13.05, 13.02 Hz, 7-H), 2.26 (dd, 1H, J = 13.17, 6.57 Hz, 7-H'). ¹³C NMR (75 MHz, CDCl₃): δ = 179.60 (C=S), 174.49 (C=O), 169.33 (C=O), 159.48, 133.20, 129.89, 128.80 (3 x C), 128.10 (2 x C), 126.26, 113.41 (3 x C), 76.61, 64.27, 55.13, 51.84, 51.51, 44.45, 30.84. IR (cm⁻¹): νmax 3137, 3038, 2938, 2838, 1737, 1612, 1514, 1454, 1351, 1240, 1197, 742, 700. MS (ESI, M-H⁺): m/z 409.0 (M-H⁺, 100). Anal. Calcd for C₂₂H₂₀N₂O₄S: C, 64.35; H, 5.40; N, 6.80; S, 7.80. Found: C, 64.30; H, 5.40; N, 6.85; S, 8.05.

(5R,6S,7aR)-Methyl 7a-benzyl-hexahydro-5-(4-methoxyphenyl)-1-oxo-3-thioxo-1H-pyrrolo[1,2-c]-imidazole-6-carboxylate (cis-3f). The product crystallized from Et₂O as colourless prisms; mp 191-193 ºC. ¹H NMR (300 MHz, CDCl₃): δ = 7.82 (brs, 1H, NH), 7.37-6.79 (m, 9H, Ar-H), 5.27 (d, 1H, J = 9.33 Hz, 5-H), 3.78 (s, 3H, OCH₃), 3.73-3.65 (m, 1H, 6-H), 3.25 (s, 3H, OCH₃), 3.24 (d, 1H, J = 13.50 Hz, 8-H) 3.15 (d, 1H, J = 13.47 Hz, 8-H') 2.88 (dd, 1H, J = 13.05, 13.02 Hz, 7-H), 2.26 (dd, 1H, J = 13.17, 6.57 Hz, 7-H'). ¹³C NMR (75 MHz, CDCl₃): δ = 179.60 (C=S), 174.49 (C=O), 169.33 (C=O), 159.48, 133.20, 129.89, 128.80 (3 x C), 128.10 (2 x C), 126.26, 113.41 (3 x C), 76.61, 64.27, 55.13, 51.84, 51.51, 44.45, 30.84. IR (cm⁻¹): νmax 3137, 3038, 2938, 2838, 1737, 1612, 1514, 1454, 1351, 1240, 1197, 742, 700. MS (ESI, M-H⁺): m/z 409.0 (M-H⁺, 100). Anal. Calcd for C₂₂H₂₀N₂O₄S: C, 64.35; H, 5.40; N, 6.80; S, 7.80. Found: C, 64.30; H, 5.40; N, 6.85; S, 8.05.
imidazole-6-carboxylate (trans-3f). Crystallisation gave trans-isomer together with trace cis-isomer as an amorphous colourless solid; mp 129-131 °C. 1H NMR (300 MHz, CDCl3): δ = 7.75 (brs, 1H, NH), 7.39-6.78 (m, 9H, Ar-H), 5.50 (d, 1H, J = 4.53 Hz, 5-H), 3.81 (s, 3H, OCH3), 3.53-3.47 (m, 1H, 6-H), 3.26-3.13 (m, 2H, 8-H, 8-H'), 3.15 (s, 3H, OCH3), 2.76 (dd, 1H, J = 10.5 Hz, 7-H), 2.58 (dd, 1H, J = 13.59 Hz, 7-H'). 13C NMR (75 MHz, CDCl3): δ = 180.32 (C=S), 175.28 (C=O), 173.00 (C=O), 158.95, 133.75, 130.14, 129.21, 128.31, 128.02, 127.45, 127.29, 112.97 (3 x C), 76.92, 64.01, 54.90, 54.68, 42.54, 33.05. IR (cm⁻¹): νmax 3158, 3046, 2943, 2840, 1736, 1612, 1514, 1454, 1347, 1227, 1198, 747, 699. MS (ESI, M-H⁺): m/z 409.0 (M-H⁺, 100). Anal. Calcd for C22H22N2O4S: C, 64.35; H, 5.40; N, 6.80; S, 7.80. Found: C, 64.70; H, 5.80; N, 6.40; S, 7.30.

Methyl 7a-benzyl-hexahydro-1-oxo-5-phenyl-3-thioxo-1H-pyrrolo[1,2-c]imidazole-6-carboxylate (3g). After completion of the reaction (24 h), the product were obtained as a 75/25 mixture of cis- and trans-isomers and seperated by column chromatography (Et2O:hexane, 1:2) which afforded the product (0.315 g, 83%) as an amorphous colourless solid.

(5R,6S,7aR)-Methyl 7a-benzyl-hexahydro-1-oxo-5-phenyl-3-thioxo-1H-pyrrolo[1,2-c]imidazole-6-carboxylate (cis-3g). The product crystallized from Et2O as colourless prisms; mp 202-204 °C. 1H NMR (300 MHz, CDCl3): δ= 8.03 (brs, 1H, NH), 7.3-7.02 (m, 10H, Ar-H), 5.30 (d, 1H, J = 9.36 Hz, 5-H), 3.77-3.67 (m, 1H, 6-H), 3.26 (d, 1H, J = 13.5 Hz, 8-H), 3.20 (s, 3H, OCH3), 3.17 (d, 1H, J = 13.59 Hz, 8-H'), 2.91 (dd, 1H, J = 13.11, 13, 02 Hz, 7-H), 2.27 (dd, 1H, J = 13.23, 6.57 Hz, 7-H'). 13C NMR (75 MHz, CDCl3): δ = 179.70 (C=S), 174.62 (C=O), 169.25 (C=O), 134.15, 133.22, 128.82 (3 x C), 128.54, 128.10 (3 x C), 77.13, 64.68, 51.77, 51.56, 44.51, 30.83. IR (cm⁻¹): νmax 3156, 3045, 2948, 1738, 1599, 1454, 1227, 1197, 737, 697. MS (ESI, M-H⁺): m/z 378.9 (M-H⁺, 100). Anal. Calcd for C21H20N2O3S.0.25H2O: C, 65.55; H, 5.35; N, 7.30; S, 8.30. Found: C, 65.80; H, 5.30; N, 7.20; S, 8.35.

(5R,6R,7aR)-Methyl 7a-benzyl-hexahydro-1-oxo-5-phenyl-3-thioxo-1H-pyrrolo[1,2-c]imidazole-6-carboxylate (trans-3g). Crystallisation gave trans-isomer together with trace cis-isomer as an amorphous colourless solid; mp 183-185 °C. 1H NMR (300 MHz, CDCl3): δ = 7.90 (brs, 1H, NH), 7.39-7.01 (m, 10H, Ar-H), 5.50 (d, 1H, J = 9.36 Hz, 5-H), 3.77-3.67 (m, 1H, 6-H), 3.26 (d, 1H, J = 13.5 Hz, 8-H), 3.20 (s, 3H, OCH3), 3.17 (d, 1H, J = 13.59 Hz, 8-H'), 2.27 (dd, 1H, J = 13.11, 13.02 Hz, 7-H), 2.27 (dd, 1H, J = 13.11, 13.02 Hz, 7-H'). 13C NMR (75 MHz, CDCl3): δ = 179.70 (C=S), 174.62 (C=O), 169.25 (C=O), 134.15, 133.22, 128.82 (3 x C), 128.54, 128.10 (3 x C), 77.13, 64.68, 51.77, 51.56, 44.51, 30.83. IR (cm⁻¹): νmax 3156, 3045, 2948, 1738, 1599, 1454, 1227, 1197, 737, 697. MS (ESI, M-H⁺): m/z 378.9 (M-H⁺, 100). Anal. Calcd for C21H20N2O3S.0.25H2O: C, 65.55; H, 5.35; N, 7.30; S, 8.30. Found: C, 65.80; H, 5.30; N, 7.20; S, 8.35.

7a-((1H-Indol-3-yl)methyl)hexahydro-5-phenyl-6-(phenylsulfonyl)-3-thioxopyrrolo[1,2-c]imidazol-1-one (3h). After completion of the reaction (24 h), the product were obtained as a 50/50 mixture of cis- and trans-isomers and seperated by column chromatography (Et2O:hexane, 1:3) which afforded the
product (0.37 g, 74%) as an amorphous colourless solid.

(5S,6S,7aS)-7a-(((1H-Indol-3-yl)methyl)hexahydro-5-phenyl-6-(phenylsulfonyl)-3-thioxopyrrolo[1,2-c]imidazol-1-one (cis-3h). The product crystallized from Et₂O as colourless prisms; mp: 259-262 °C (decomp). ¹H NMR (300 MHz, acetone-d₆): δ = 10.40 (brs, 1H, NH), 10.27 (brs, 1H, NH), 7.78-7.77 (m, H, Ar-H), 7.60-7.51 (m, 3H, Ar-H), 7.43-7.40 (m, 3H, Ar-H), 7.25-7.10 (m, 5H, Ar-H), 7.02-6.97 (m, 3H, Ar-H), 5.30 (d, 1H, J = 14.43 Hz, 8-H'), 2.95-2.82 (m, 1H, 7-H'), 2.43 (dd, 1H, J = 12.21 Hz, 5.88 Hz, 7-H').

¹³C NMR (100 MHz, DMSO-d₆): δ = 179.46 (C=S), 175.79 (C=O), 137.25, 135.66, 134.28, 133.89, 129.41 (3 x C), 128.43 (3 x C), 127.92, 127.49, 127.28 (2 x C), 124.95, 120.82, 118.54, 118.36, 111.23, 106.51, 75.61, 71.63, 63.24, 32.15, 30.24. IR (cm⁻¹): νmax 3402, 3389, 3062, 2955, 1922, 1727, 1582, 1448, 1358, 1210, 1146, 725, 689. MS (ESI, M+H⁺): m/z 502.3 (M+H⁺, 100).

(5S,6R,7aS)-7a-(((1H-Indol-3-yl)methyl)hexahydro-5-phenyl-6-(phenylsulfonyl)-3-thioxopyrrolo[1,2-c]imidazol-1-one (trans-3h). Crystallisation gave trans-isomer together with trace cis-isomer as an amorphous colourless solid; mp 228-230 °C (decomp.). ¹H NMR (300 MHz, acetone-d₆): δ = 10.19 (brs, 1H, NH), 9.91 (brs, 1H, NH), 7.90-6.97 (m, 15H, Ar-H), 5.37 (d, 1H, J = 6.75 Hz, 5-H), 4.70-4.63 (m, 1H, 6-H), 3.52-3.37 (m, 2H, 8-H, 8-H'), 3.14-2.76 (m, 2H, 7-H, 7-H').

¹³C NMR (100 MHz, DMSO-d₆): δ = 181.26 (C=S), 175.74 (C=O), 138.44, 135.71, 133.93, 132.51, 129.25 (3 x C), 129.15 (3 x C), 129.15 (3 x C), 127.92, 127.49, 127.28, 124.95, 120.82, 118.54, 118.36, 111.23, 106.51, 75.61, 71.63, 63.24, 32.15, 30.24. IR (cm⁻¹): νmax 3358, 3280, 3062, 2933, 1753, 1584, 1450, 1374, 1206, 1143, 730, 691. MS (ESI, M+H⁺): m/z 502.3 (M+H⁺, 100). Anal. Calcd for C₂₇H₂₃N₃O₃S₂.0.5H₂O: C, 63.45; H, 4.70; N, 8.20; S, 12.55. Found: C, 63.10; H, 4.70; N, 8.00; S, 12.30.

7a-Benzylhexahydro-6-(methylsulfonyl)-5-phenyl-3-thioxopyrrolo[1,2-c]imidazol-1-one (3i). After completion of the reaction (21 h), the product were obtained as a 85/15 mixture of cis- and trans-isomers and separated by column chromatography (Et₂O:hexane, 1:3) which afforded the product (0.29 g, 72%) as an amorphous colourless solid.

(5S,6S,7aS)-7a-Benzylhexahydro-6-(methylsulfonyl)-5-phenyl-3-thioxopyrrolo[1,2-c]imidazol-1-one (cis-3i). The product crystallized from Et₂O as colourless prisms; mp 228-230 °C (decomp.). ¹H NMR (300 MHz, acetone-d₆): δ = 10.19 (brs, 1H, NH), 7.90-6.97 (m, 15H, Ar-H), 5.37 (d, 1H, J = 6.75 Hz, 5-H), 4.70-4.63 (m, 1H, 6-H), 3.52-3.37 (m, 2H, 8-H, 8-H'), 3.14-2.76 (m, 2H, 7-H, 7-H').

¹³C NMR (100 MHz, DMSO-d₆): δ = 181.26 (C=S), 175.74 (C=O), 138.44, 135.71, 133.93, 132.51, 129.25 (3 x C), 127.92, 127.49, 127.28, 124.95, 120.82, 118.54, 118.36, 111.23, 106.51, 75.61, 71.63, 63.24, 32.15, 30.24. IR (cm⁻¹): νmax 3358, 3280, 3062, 2933, 1753, 1584, 1450, 1374, 1206, 1143, 730, 691. MS (ESI, M+H⁺): m/z 502.3 (M+H⁺, 100). Anal. Calcd for C₂₀H₂₀N₂O₃S: C, 60.00; H, 5.05; N, 7.00; S, 16.00. Found: C, 59.65; H, 5.15; N, 6.85; S, 16.20.
trans-3i). Crystallisation gave trans-isomer together with trace cis-isomer as an amorphous colourless solid; mp 162-164 °C. ¹H NMR (300 MHz, CDCl₃): δ = 7.95 (brs, 1H, NH), 7.44-7.13 (m, 10H, Ar-H), 5.44 (d, 1H, J = 3.6 Hz, 5-H), 3.98-3.85 (m, 1H, 6-H), 3.31 (d, 1H, J = 13.53 Hz, 8-H), 3.22 (d, 1H, J = 13.38 Hz, 8-H'), 2.59 (dd, 1H, J = 12.48 Hz, 7-H'), 2.94-2.80 (m, 1H, 7-H), 2.59 (d, 1H, J = 6.82 Hz, 7-H'), 2.02 (s, 3H, SCH₃). ¹³C NMR (75 MHz, CDCl₃): δ = 180.26 (C=S), 174.11 (C=O), 132.69, 131.71, 129.96 (3 x C), 129.52, 129.96, 129.04 (3 x C), 128.61, 128.48, 75.70, 68.30, 63.83, 45.16, 39.18, 30.27. IR (cm⁻¹): νmax 3239, 3063, 3030, 2951, 2924, 1742, 1601 1452, 1384, 1240, 1200, 730, 698. MS (ESI, M-H⁺): m/z 401.1 (M+H⁺, 70). Anal. Calcd for C₂₀H₂₀N₂O₃S: C, 60.00; H, 5.05; N, 7.00; S, 16.00. Found: C, 60.05; H, 5.25; N, 6.65; S, 15.90.

Methyl 7a-benzylhexahydro-1-oxo-5-(pyridin-3-yl)-3-thioxo-1H-pyrrolo[1,2-c]imidazole-6-carboxylate (3j). After completion of the reaction (18 h), the product were obtained as a 75/25 mixture of cis- and trans-isomers and seperated by column chromatography (Et₂O:hexane, 1:3) which afforded the product (0.35 g, 91%) as an amorphous colourless solid.

(Z)-3j). The product crystallized from Et₂O as colourless prisms; mp 236-238 °C (decomp). ¹H NMR (300 MHz, DMSO-d₆): δ = 11.45 (brs, 1H, NH), 8.39 (dd, 1H, J = 1.44 Hz, 1.44 Hz, Ar-H), 8.27 (brs, 1H, Ar-H), 7.29-7.14 (m, 7H, Ar-H), 5.26 (d, 1H, J = 9.36 Hz, 5-H), 3.81-3.71 (m, 1H, 6-H), 3.13 (s, 3H, OCH₃), 2.98 (brs, 2H, 8-H, 8-H') 2.69 (dd, 1H, J = 13.2, 12.9 Hz, 7-H'), 2.19 (dd, 1H, J = 13.2, 6.57 Hz, 7-H'). ¹³C NMR (75 MHz, DMSO-d₆): δ = 181.12 (C=S), 175.63 (C=O), 169.78 (C=O), 148.87, 134.42, 131.30, 130.40 (3 x C), 128.40 (3 x C), 127.56, 123.10, 76.70, 61.29, 31.17, 31.17. IR (cm⁻¹): νmax 3143, 3044, 2939, 1736, 1580, 1458, 1349, 1204, 1176, 737, 698. MS (ESI, M-H⁺): m/z 379.9 (M-H⁺, 100). Anal. Calcd for C₂₀H₁₉N₃O₃S: C, 62.95; H, 5.00; N, 11.00; S, 8.40. Found: C, 62.90; H, 5.10; N, 10.80; S, 8.25.

(5R,6S,7aR)-Methyl 7a-benzylhexahydro-1-oxo-5-(pyridin-3-yl)-3-thioxo-1H-pyrrolo[1,2-c]-imidazole-6-carboxylate (trans-3j). Crystallisation gave trans-isomer together with trace cis-isomer as an amorphous colourless solid; mp 216-218 °C (decomp). ¹H NMR (400 MHz, DMSO-d₆): δ = 11.27 (brs, 1H, NH), 8.59 (brd, 1H, J = 1.96 Hz, Ar-H), 8.46 (dd, 1H, J = 1.56, 1.52 Hz, Ar-H), 7.27-7.17 (m, 7H, Ar-H), 5.37 (d, 1H, J = 6 Hz, 5-H), 3.81-3.68 (m, 1H, 6-H), 3.69 (s, 3H, OCH₃), 3.39 (d, 1H, J = 4.05 Hz, 8-H), 3.37 (d, 1H, J = 4.05 Hz, 8-H'), 2.91 (dd, 1H, J = 13.16, 11 Hz, 7-H'), 2.35 (dd, 1H, J = 13.2, 3.24 Hz, 7-H'). ¹³C NMR (100 MHz, DMSO-d₆): δ = 179.64 (C=S), 174.95 (C=O), 172.57 (C=O), 148.54, 133.92, 131.91, 129.73 (3 x C), 127.91 (3 x C), 127.13, 122.87, 76.61, 60.64, 53.33, 52.46, 41.68, 32.59. IR (cm⁻¹): νmax 3030, 2950, 1735, 1598, 1443, 1359, 1204, 1180, 741, 702. MS (ESI, M-H⁺): m/z 379.9 (M-H⁺, 100).

Synthesis of compounds 6 and 7. To a stirred solution of aroylaminocarbo-N-thioylpyrrolidines (0.65 g,
1 mmol) in dry MeOH (30 mL) was added a solution of sodium methoxide (0.057 g, 1.05 mmol) in dry MeOH (20 mL) over 5 min. and the mixture stirred at reflux temperature for 36 h. After completion of the reaction, the solvent was evaporated under reduced pressure, quenched with saturated aqueous ammonium chloride and extracted with CH₂Cl₂. The combined organic layers were dried (MgSO₄), filtered, evaporated under reduced pressure and the mixture was purified by column chromatography (Et₂O:hexane, 1:3) to afford bicyclic compounds 6 (0.26 g, 49%) and 7 (0.13 g, 24%). When the same reaction was carried out at room temperature for 36 h, only compound 7 (0.445 g, 83%) was obtained.

\(\text{(5R,6S,7S,7aS)-Methyl} \ 7\text{-}((1H\text{-indol-3-yl)methyl})\text{hexahydro-1-oxo-5-phenyl-3-thioxo-1H-pyrrolo[1,2-c]imidazole-6-carboxylate} \ (6).\) The product crystallized from Et₂O as colourless prisms; mp 202-205 ºC (decomp.). \(^1\)H NMR (300 MHz, CDCl₃): \(\delta = 8.97 \text{ (brs, 1H, NH)}, 8.20 \text{ (brs, 1H, NH)}, 7.75 -6.93 \text{ (m, 16H, NH, Ar-H)}, 5.40 \text{ (d, 1H, J = 9.63 Hz, 5-H)}, 4.42 \text{ (dd, 1H, J = 11.94, 9.66 Hz, 6-H)}, 4.19 \text{ (d, 1H, J = 11.97 Hz, 7-H)}, 3.60 \text{ (d, 1H, J = 14.58 Hz, 8-H)}, 3.38 \text{ (d, 1H, J = 14.61 Hz, 8-H')}, 3.25 \text{ (s, 3H, OCH₃}). \) \(^{13}\)C NMR (75 MHz, CDCl₃): \(\delta = 178.32 \text{ (C=S)}, 176.52 \text{ (C=O)}, 168.61 \text{ (C=O)}, 164.42 \text{ (C=O)}, 137.67, 135.83, 133.25, 129.22 \text{ (3 x C)}, 128.77, 128.17, 127.15 \text{ (2 x C)}, 124.82, 124.71, 122.53, 120.31, 119.87 \text{ (3 x C)}, 118.29, 111.37, 106.09, 75.34, 63.03, 53.43, 52.04, 48.02, 30.46. IR (cm\(^{-1}\)): \(\nu_{\text{max}} = 3404, 3327, 3198, 3130, 2951, 2924, 1746, 1719, 1684, 1598, 1455, 1368, 1210, 1172, 745, 697. \) MS (ESI, M+H\(^+\)): \(m/z = 539.4 \text{ (M+H}^+\text{, 100).} \) Anal. Calcd for C\(_{30}\)H\(_{26}\)N\(_4\)O\(_4\)S: C, 66.90; H, 4.85; N, 10.40; S, 5.95. Found: C, 66.80; H, 5.10; N, 10.05; S, 5.85.

\(\text{(2S,3S,3aS,6aR)-Methyl} \ 6a\text{-}((1H\text{-indol-3-yl)methyl})\text{octahydro-4,6-dioxo-2,5-diphenyl-1-thiocarbamoylpyrrolo[3,4-b]pyrrole-3-carboxylate} \ (7).\) The product crystallized from Et₂O as colourless prisms; mp 234-236 ºC (decomp.). \(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \(\delta = 11.11 \text{ (brs, 1H, NH)}, 10.61 \text{ (brs, 1H, NH)}, 7.70 -7.05 \text{ (m, 15H, Ar-H)}, 5.28 \text{ (d, 1H, J = 7.80 Hz, 2-H)}, 3.94 \text{ (dd, 1H, J = 7.76, 4.16 Hz, 3-H)}, 3.81 \text{ (d, 1H, J = 4.16 Hz, 3a-H)}, 3.68 \text{ (s, 3H, OCH₃)}, 3.53 \text{ (d, 1H, J = 14.72 Hz, 7-H)}, 3.48 \text{ (d, 1H, J = 14.76 Hz, 7-H')}. \) \(^{13}\)C NMR (100 MHz, DMSO-d\(_6\)): \(\delta = 178.30 \text{ (C=S)}, 174.19 \text{ (C=O)}, 171.36 \text{ (C=O)}, 138.36, 135.74, 135.07, 128.75 \text{ (3 x C)}, 128.08, 127.56 \text{ (2 x C), 127.40, 125.35, 123.94, 120.97, 119.75 \text{ (3 x C)}, 118.67, 118.22, 111.32, 105.79, 79.35, 63.93, 58.98, 52.52, 52.17, 32.68. IR (cm\(^{-1}\)): \(\nu_{\text{max}} = 3323, 3208, 3062, 2964, 1759, 1706, 1667, 1596, 1539, 1445, 1394, 1210, 1187, 745, 730, 690. \) MS (ESI, M+H\(^+\)): \(m/z = 539.4 \text{ (M+H}^+\text{, 100).} \)

Synthesis of \(\text{(2S,3S,3aS,6aR)-Methyl} \ 6a\text{-}((1H-indol-3-yl)methyl)octahydro-4,6-dioxo-2,5-diphenyl-1-thiocarbamoylpyrrolo[3,4-b]pyrrole-3-carboxylate} \ (9). \) To a stirred solution of bicyclic pyrrolidine 8 (0.48 g, 1 mmol) in dry MeOH (30 mL) was added a solution of sodium methoxide (0.057 g, 1.05 mmol) in dry MeOH (20 mL) over 5 min. and the mixture stirred and heated at reflux temperature for 36 h. After completion of the reaction, the solvent was evaporated under reduced pressure, quenched with saturated aqueous ammonium chloride and extracted with CH₂Cl₂. The combined organic layers were dried (MgSO₄),
filtered, evaporated under reduced pressure and the mixture was purified by column chromatography (Et₂O:hexane, 1:3) to afford 9. The product (0.41g, 85%) crystallised from Et₂O:hexane as colourless prisms; mp 122-124 ºC. ¹H NMR (400 MHz, CDCl₃): δ = 8.30 (brs, 1H, NH), 7.87 (d, 1H, J = 7.68, Ar-H), 7.57-7.15 (m, 12H, Ar -H), 6.47 (m, 2H, Ar-H), 5.00 (d, 1H, J = 3.64 Hz, 2-H), 3.84 (d, 1H, J = 2.84 Hz, 3a-H), 3.81 (s, 3H, OCH₃), 3.78 (d, 1H, J = 13.87 Hz, 7 -H), 3.72 (t, 1H, 3-H), 3.47 (d, 1H, J = 13.87 Hz, 7-H'). ¹³C NMR (100 MHz, CDCl₃): δ = 178.99 (C=O), 175.73 (C=O), 173.21 (C=O), 140.24, 136.00, 131.41, 128.86 (2 x C), 128.83 (2 x C), 128.60, 127.84, 127.52, 126.34 (2 x C), 126.09 (2 x C), 124.20, 122.50, 120.14, 119.05, 111.28, 109.14, 71.92, 66.14, 54.26, 52.74, 51.30, 30.36. IR (cm⁻¹): νmax 3386, 3351, 3058, 3035, 2953, 2921, 1705, 1596, 1493, 1454, 1380, 1194, 1175, 1128, 1095, 1010, 737, 693. MS (ESI, M-H⁺): m/z 478.0 (M-H⁺, 100).

**Crystallography**

For the crystal structure determination, a single-crystal of the compounds *cis*-3a, *trans*-3a, *cis*-3j, 6 and 7 were used for data collection on a four-circle Rigaku R-AXIS RAPID-S diffractometer (equipped with a two-dimensional area IP detector). The graphite-monochromatized Mo-Kα radiation (λ = 0.71073 Å) and oscillation scans technique with Δω = 5° for one image were used for data collection. The lattice parameters were determined by the least-squares methods on the basis of all reflections with F²>2σ(F²). Integration of the intensities, correction for Lorentz and polarization effects and cell refinement was performed using CrystalClear (Rigaku/MSC Inc., 2005) software. The structures were solved by direct methods using SHELXS-97 and refined by a full-matrix least-squares procedure using the program SHELXL-97. Hydrogen positions were found from difference Fourier maps and geometric calculations and refined using a riding model. The final difference Fourier maps showed no peaks of chemical significance. Crystallographic data for the compounds have been deposited at the Cambridge Crystallographic Data Centre. Copies of the information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

**Crystal data for compound cis-3a.** Compound *cis*-3a was crystallized by slow evaporation from an Et₂O solution at room temperature. C₁₉H₁₈N₂O₃S, crystal system, space group: monoclinic, P2₁/c; (no:14); unit cell dimensions: a = 10.3012(10), b = 14.5412(8), c = 12.5644(11)Å, α = 90, β = 110.029(4), γ = 90°; volume: 1768.2(3) Å³; Z=4; calculated density: 1.331 g/cm³; absorption coefficient: 0.203 mm⁻¹; F(000): 744; θ-range for data collection 2.1–26.4°; refinement method: full-matrix least-square on F²; data/parameters: 2244/227; goodness-of-fit on F²: 1.062; final R indices [I>2σ(I)]: R₁ = 0.070, wR₂ = 0.191; R indices (all data): R₁ = 0.105, wR₂ = 0.220; largest diff. peak and hole: 0.434 and -0.314 e Å⁻³; CCDC : 818055.
Crystal data for compound trans-3a. Compound trans-3a was crystallized by slow evaporation from an Et₂O-MeCN solution at room temperature. C₁₉H₁₈N₂O₃S.MeCN, crystal system, space group: monoclinic, P2₁/c; (no:14); unit cell dimensions: a = 18.6497(7), b = 5.6334(3), c = 20.7534(8)Å, α = 90, β = 112.105(4), γ = 90º; volume: 2020.12(16) Å³; Z = 4; calculated density: 1.30 g/cm³; absorption coefficient: 0.187 mm⁻¹; F(000): 832; 0-range for data collection 2.4–26.4º; refinement method: full-matrix least-square on F²; data/parameters: 2389/257; goodness-of-fit on F²: 1.033; final R indices [I>2σ(I)]: R₁ = 0.066, wR₂ = 0.140; R indices (all data): R₁ = 0.121, wR₂ = 0.162; largest diff. peak and hole: 0.214 and -0.195 e Å⁻³; CCDC: 818642.

Crystal data for compound cis-3j. Compound cis-3j was crystallized by slow evaporation from an Et₂O solution at room temperature. C₂₀H₁₉N₃O₃S, crystal system, space group: monoclinic, P2₁/a; (no:14); unit cell dimensions: a = 19.7407(5), b = 8.0998(2), c = 24.4643(6)Å, α = 90, β = 108.394(7), γ = 90º; volume: 3711.88(16) Å³; Z = 8; calculated density: 1.365 g/cm³; absorption coefficient: 0.200 mm⁻¹; F(000): 1600; 0-range for data collection 2.1–26.6º; refinement method: full-matrix least-square on F²; data/parameters: 3698/487; goodness-of-fit on F²: 0.971; final R indices [I>2σ(I)]: R₁ = 0.076, wR₂ = 0.207; R indices (all data): R₁ = 0.148, wR₂ = 0.272; largest diff. peak and hole: 0.317 and -0.297 e Å⁻³; CCDC: 817919.

Crystal data for compound 6. Compound 6 was crystallized by slow evaporation from an Et₂O solution at room temperature. C₃₀H₂₆N₄O₄S.H₂O, crystal system, space group: triclinic, P-1; (no:2); unit cell dimensions: a = 11.1814(4), b = 12.0039(5), c = 13.9183(5)Å, α = 105.98(4), β = 103.04(7), γ = 111.06(8)º; volume: 1562.38(10) Å³; Z = 2; calculated density: 1.183 g/cm³; absorption coefficient: 0.145 mm⁻¹; F(000): 584; 0-range for data collection 2.1–26.4º; refinement method: full-matrix least-square on F²; data/parameters: 3648/358; goodness-of-fit on F²: 1.062; final R indices [I>2σ(I)]: R₁ = 0.081, wR₂ = 0.244; R indices (all data): R₁ = 0.123, wR₂ = 0.292; largest diff. peak and hole: 0.587 and -0.262 e Å⁻³; CCDC: 817634.

Crystal data for compound 7. Compound 7 was crystallized by slow evaporation from an Et₂O solution at room temperature. C₃₀H₂₆N₄O₄S, crystal system, space group: triclinic, P-1; (no:2); unit cell dimensions: a = 11.4619(4), b = 11.5299(5), c = 11.6129(6)Å, α = 69.52(4), β = 71.23(3), γ = 79.68(5)º; volume: 1357.47(11) Å³; Z = 2; calculated density: 1.318 g/cm³; absorption coefficient: 0.162 mm⁻¹; F(000): 564; 0-range for data collection 2.3–26.4º; refinement method: full-matrix least-square on F²; data/parameters: 3196/352; goodness-of-fit on F²: 1.026; final R indices [I>2σ(I)]: R₁ = 0.081, wR₂ = 0.132; R indices (all data): R₁ = 0.115, wR₂ = 0.157; largest diff. peak and hole: 0.191 and -0.189 e Å⁻³; CCDC: 817614.

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