HETEROCYCLES, Vol. 83, No. 9, 2011, pp. 2091 - 2114. © The Japan Institute of Heterocyclic Chemistry
Received, 7th June, 2011, Accepted, 15th July, 2011, Published online, 22nd July, 2011
DOI: 10.3987/COM-11-12276

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

Yahya Nural,[a] H. Ali Döndaş,[a,b]* Ronald Grigg,[c] and Ertan Şahin[d]

[a] Department of Chemistry, Faculty of Pharmacy, Mersin University, 33160, Mersin, Turkey

[b] Advanced Technology Education, Research and Application Centre, 33342, Mersin, Turkey

[c] MIDAS Centre, School of Chemistry, Leeds University, Leeds LS2 9JT, UK

[d] Department of Chemistry, Faculty of Science, Atatürk University, 25240, Erzurum, Turkey

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

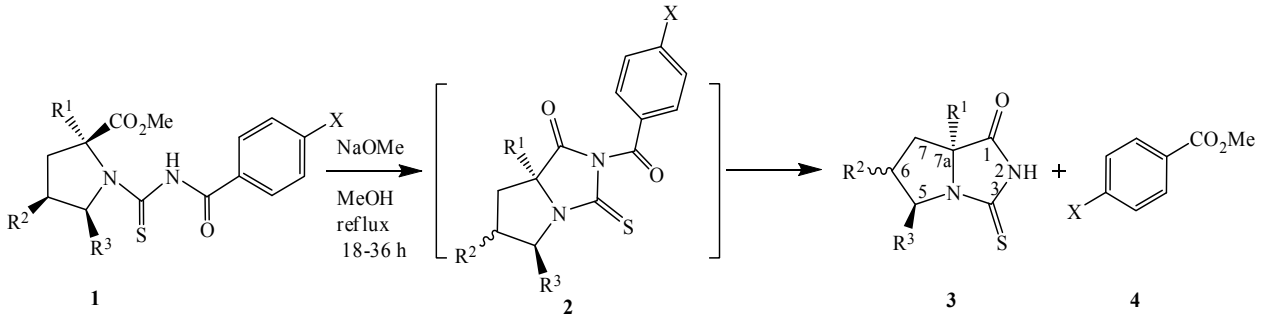
Thiohydantoins[1,2] have found both pharmaceutical and agricultural applications,[3] due to their antimicrobial[4,5] antiviral,[6,7] anti-inflammatory,[8] antitumor,[8,9] antiandrogenic[10] and anticonvulsant[11] properties. Further applications include hypolipidemic agents,[12] glycosidase,[13] glycogen phosphorylase[14,15] 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 B[22] 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,[39] ceronapril[40,41] and meropenem.[42] Grigg *et al* have reported a range of thermal and metal catalyzed azomethine ylide 1,3-dipolar cycloaddition cascade reactions furnishing pyrrolidines.[43-48] This cascade chemistry has provided interalia a series of spirobenzodiazepines related to MK-329,[47] nikkomycin analogues,[49] peptidomimetics,[45] pyrrolidine ß-lactam analogues[50] and fused and bridged ring pyrrolidine derivatives.[50-55]

Thus the combination of pyrrolidines and 2-thiohydantoins into a new fused ring system was attractive. In previous work,[56-58] 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.[56-59] 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 **4** 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 ^{1}H NMR, ^{13}C 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 ($^{3}J_{H\text{-}H}$) 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-1*H*-pyrrolo[1,2-*c*]imidazole-6-carboxylate ***cis*-3a**, (*5R,6R,7aS*)-methyl hexahydro-7a-methyl-5-(naphthalen-2-yl)-1-oxo-3-thioxo-1*H*-pyrrolo[1,2-*c*]-imidazole-6-carboxylate ***trans*-3a** and (*5S,6R,7aR*)-methyl 7a-benzyl-hexahydro-1-oxo-5-(pyridin-3-yl)-3-thioxo-1*H*-pyrrolo[1,2-c]imidazole-6-carboxylate ***cis*-3j** were confirmed by X-ray crystal structures (**Figures 1-3**).



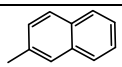
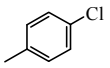
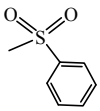
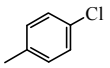
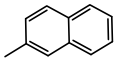
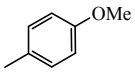
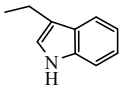
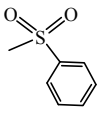
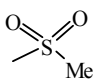
1 2 3 4

1a. R^1= Me, R^2= CO_2Me, R^3= 2-naphthyl, X= H
1b. R^1= Ph, R^2= CO_2Me, R^3= 4-chlorophenyl, X= OMe
1c. R^1= Ph, R^2=phenylsulfonyl, R^3= 4-chlorophenyl, X= H
1d. R_1= Ph, R^2=CO_2Me, R^3= Ph, X= H
1e. R^1= Ph, R^2= CO_2Me, R^3= 2-naphthyl, X= H
1f. R^1= $PhCH_2$, R^2= CO_2Me, R^3= 4-methoxyphenyl, X= H
1g. R^1= $PhCH_2$, R^2 = CO_2Me, R^3= Ph, X= H
1h. R^1= (1H-indol-3-yl)CH_2, R^2= phenylsulfonyl, R^3= Ph, X= H
1i. R^1 = $PhCH_2$, R^2= methylsulfonyl, R^3= Ph, X= H
1j. R^1= $PhCH_2$, R^2=CO_2Me, R^3= pyridin-3-yl, X= H

3a. R^1= Me, R^2= CO_2Me, R^3= 2-naphthyl
3b. R^1= Ph, R^2= CO_2Me, R^3= 4-chlorophenyl
3c. R^1= Ph, R^2=phenylsulfonyl, R^3= 4-chlorophenyl
3d. R_1= Ph, R^2=CO_2Me, R^3= Ph
3e. R^1= Ph, R^2= CO_2Me, R^3= 2-naphthyl
3f. R^1= $PhCH_2$, R^2= CO_2Me, R^3= 4-methoxyphenyl
3g. R^1= $PhCH_2$, R^2 = CO_2Me, R^3= Ph
3h. R^1= (1H-indol-3-yl)CH_2, R^2= phenylsulfonyl, R^3= Ph
3i. R^1 = $PhCH_2$, R^2= methylsulfonyl, R^3= Ph
3j. R^1= $PhCH_2$, R^2=CO_2Me, R^3= pyridin-3-yl

Scheme 1

Table 1. Fused thiohydantoin derivatives

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

***cis**:**trans** stereochemistry was asigned at C-5 and C-6 by vicinal coupling constants $^3J_{H\text{-}H}$ and X-ray crystal structures (**Figures 1-3**)

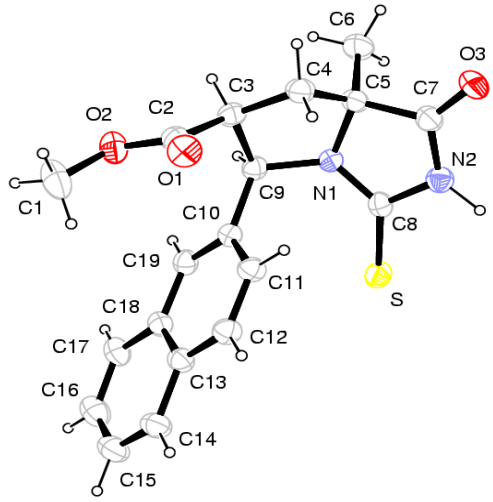


Figure 1. An ORTEP drawing of the molecule ***cis*-3a.** Displacement ellipsoids are drawn at the 40% probability level

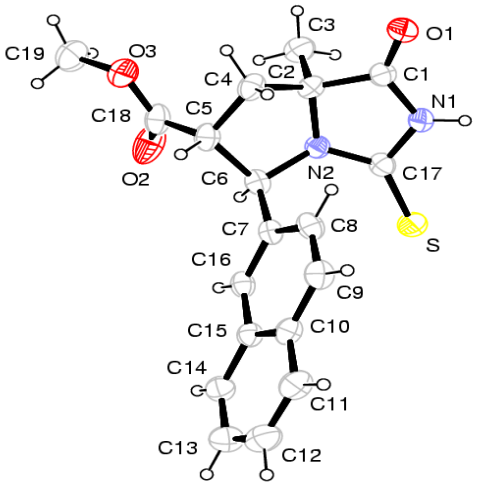


Figure 2. An ORTEP drawing of the molecule ***trans*-3a.** Displacement ellipsoids are drawn at the 40% probability level. For the clarity solvent acetonitrile was not shown in the Figure

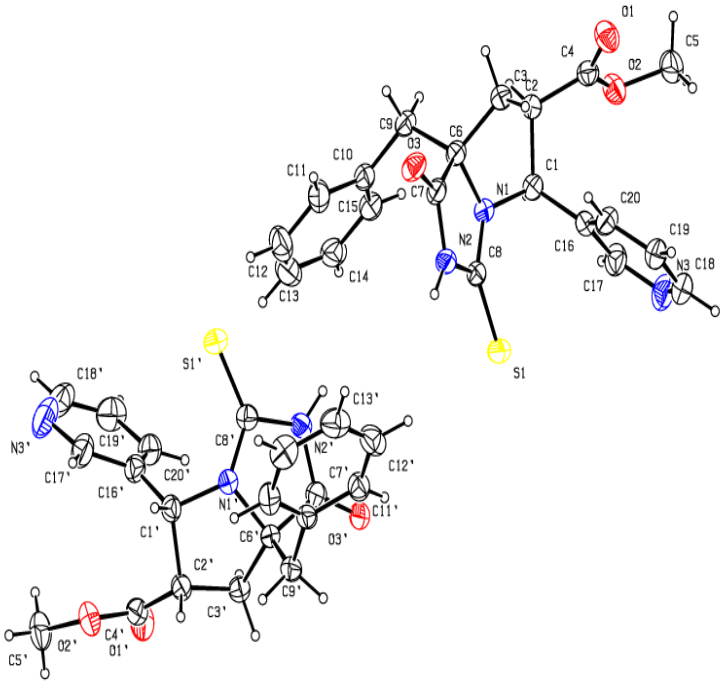
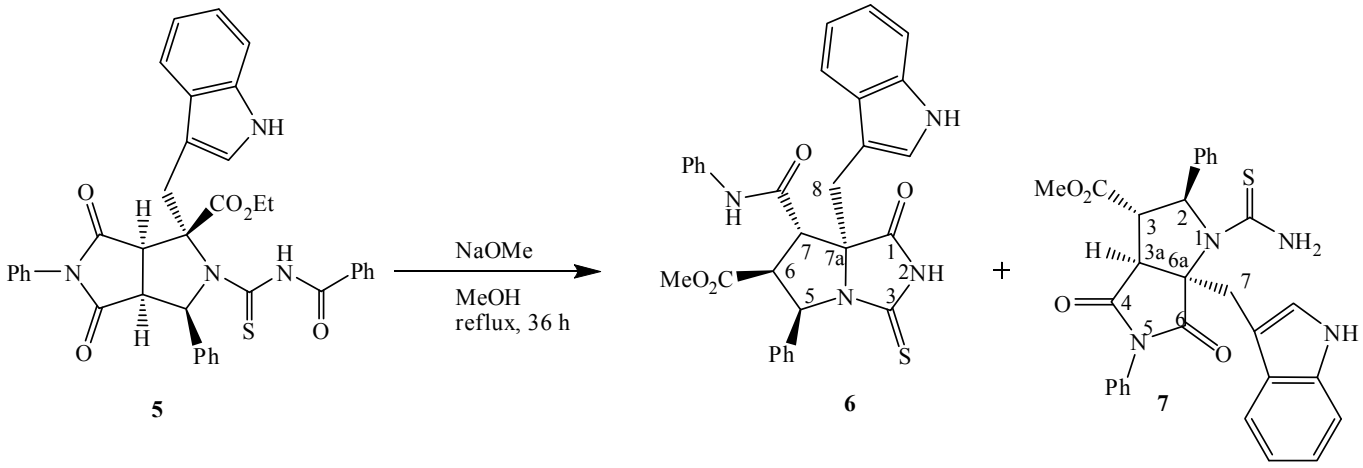


Figure 3. An ORTEP drawing of the molecule ***cis*-3j** with two molecules in the asymmetric unit (racemates of the same compound). Displacement ellipsoids are drawn at the 40% probability level

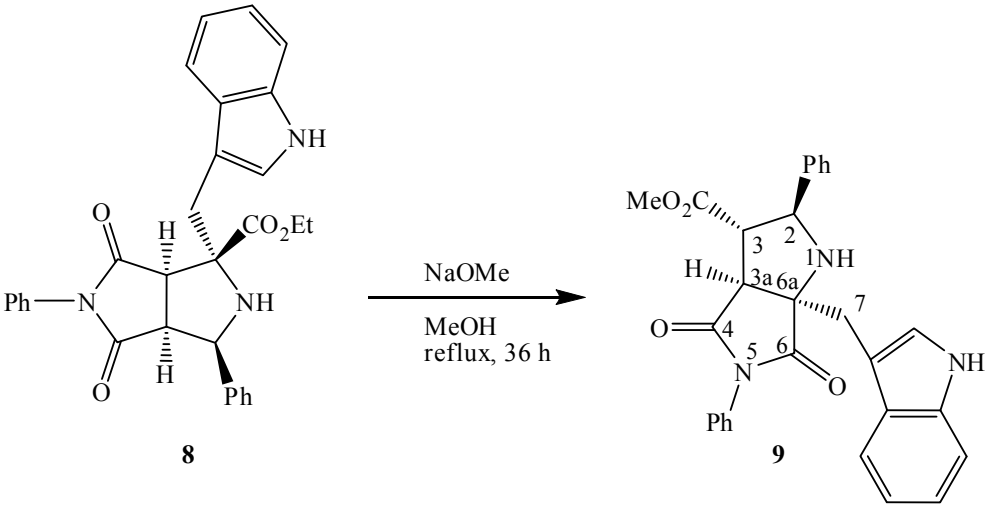
When the bicyclic aroylaminocarbo-*N*-thioylpyrrolidine (**5**), prepared according to modification of the literature methods,[56-60] was reacted with sodium methoxide under same reaction conditions (MeOH,

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**).



5 **6** **7**

Scheme 2



8 **9**

Scheme 3

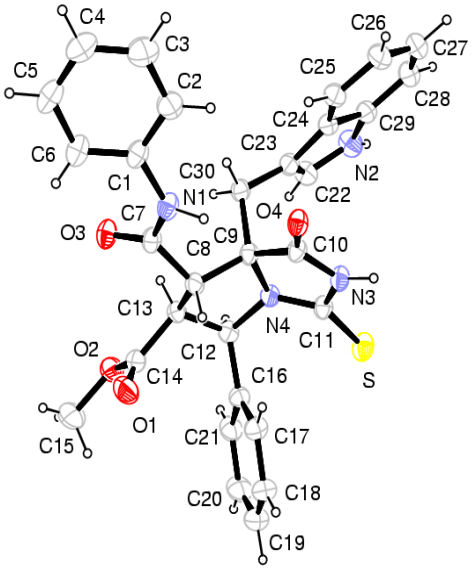


Figure 4. An ORTEP drawing of the molecule **6.** Displacement ellipsoids are drawn at the 40% probability level. For the clarity disordered crystal water was not shown in the Figure

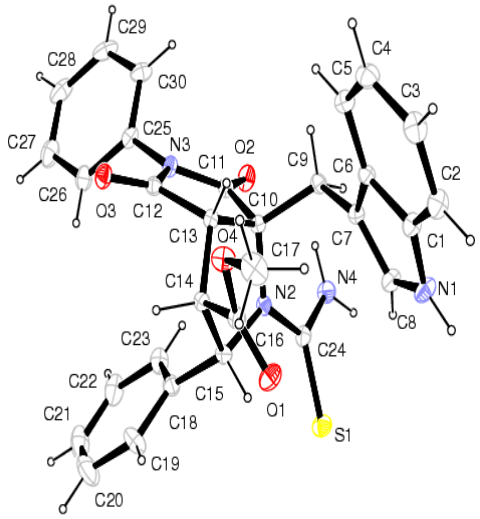
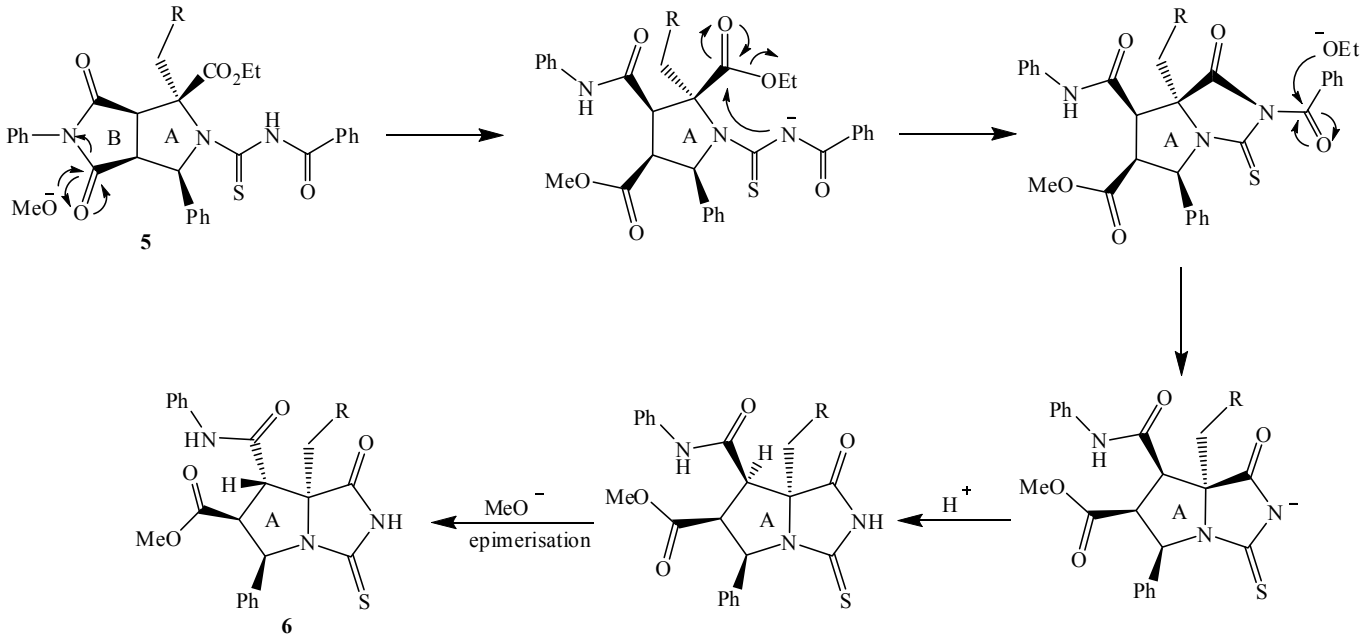
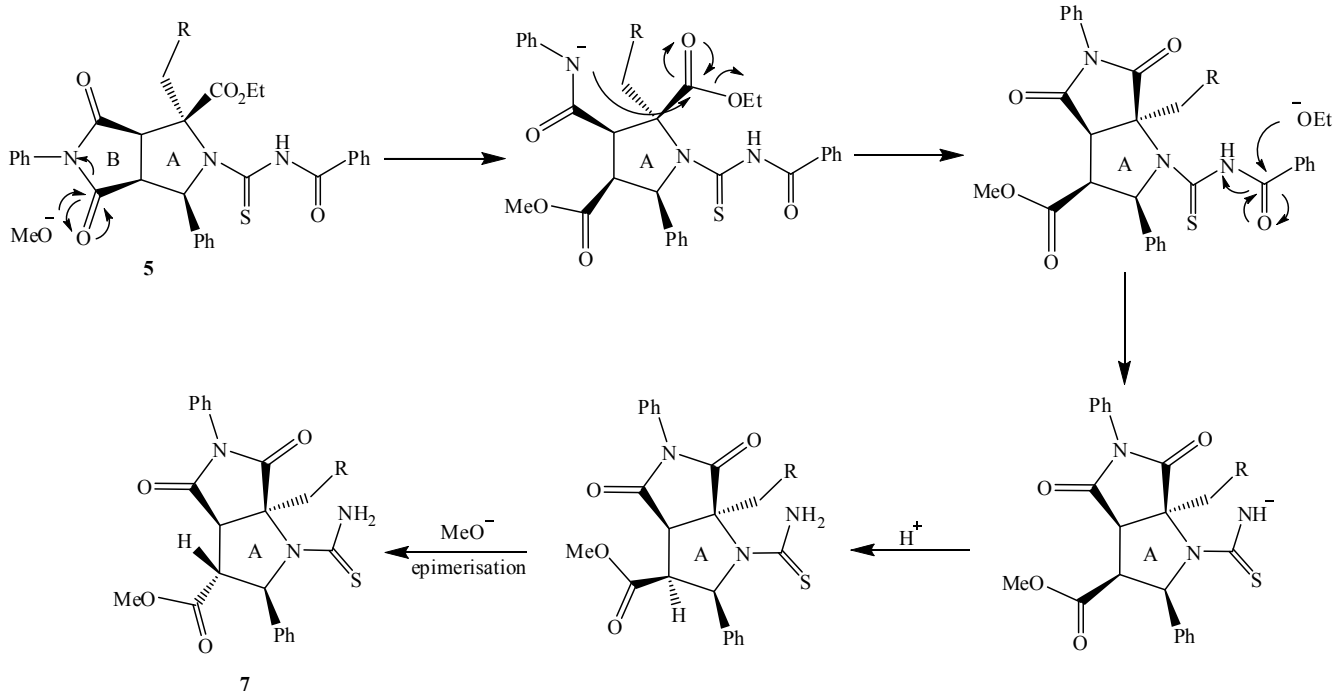


Figure 5. An ORTEP drawing of the molecule **7.** Displacement ellipsoids are drawn at the 30% probability level



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 modificable groups, has been achieved from aminocarbo-*N*-thioylpyrrolidines. 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,[61] dimethyl 5-(4-chlorophenyl)-2-phenyl-pyrrolidine-2,4-dicarboxylate,[62] dimethyl 2,5-diphenylpyrrolidine-2,4-dicarboxylate,[56,62,63] dimethyl 5-(naphthalen-2-yl)-2-phenylpyrrolidine-2,4-dicarboxylate,[64] dimethyl 2-benzyl-5-(4-methoxyphenyl)-pyrrolidine-2,4-dicarboxylate,[61] dimethyl 2-benzyl-5-phenylpyrrolidine-2,4-dicarboxylate,[56] and methyl 2-((1*H*-indol-3-yl)methyl)-5-phenyl-4-(phenylsulfonyl)pyrrolidine-2-carboxylate[59] and **8**,[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.[52] After a reaction time of 26 h and work up the product (0.42 g, 92%) crystallised from Et_2O:hexane as colourless prisms: mp 146-148 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 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_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'). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 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^{-1}): ν_{max} 3314, 3071, 3035, 2960, 1727, 1598, 1492, 1446, 1301, 1257, 1208, 1144, 1085, 1010, 816, 729, 691. MS (ES, $M+H^+$): *m/z* 456.1 ($M+H^+$, 100), 458.1 ($M+H^+$, 45). Anal. Calcd for $C_{24}H_{22}ClNO_4S$: 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.[52] After a reaction time of 28 h and work up the product (0.28 g, 75%) crystallised from Et_2O:hexane as colourless prisms: mp 134-136 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47-7.26 (m, 10H, Ar-H), 4.62 (d, 1H, J = 6.21 Hz, 5-H), 3.78 (s, 3H, OCH_3), 3.57-3.51 (m, 1H, 4-H), 3.19 (dd, 1H, J = 15.03, 4.56 Hz, 3-H), 3.16 (d, 1H, J = 13.2 Hz, 6-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_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 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^{-1}): ν_{max} 3308, 3017, 2964, 1735, 1596, 1495, 1459, 1428, 1301, 1273, 1211, 1132, 1075, 1048, 748, 704. MS (ES, $M+H^+$): *m/z* 374.1($M+H^+$, 100). Anal. Calcd for $C_{20}H_{23}NO_4S.0.25H_2O$: 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.[52] After a reaction time of 24 h and work up the product (0.33 g, 94%) crystallised from Et_2O:hexane as colourless prisms: mp 102-104 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 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, OCH_3), 3.30-3.23 (m, 1H, 4-H), 3.24 (s, 3H, OCH_3), 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 = 13.74, 5.94 Hz, 3-H), 2.26 (dd, 1H, J = 13.74, 7.56 Hz, 3-H'). ^{13}C NMR (75 MHz, $CDCl_3$): 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 (ES, $M+H^+$): *m/z* 355.2 ($M+H^+$, 35). Anal. Calcd for $C_{20}H_{22}N_2O_4$: 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 Aroylaminocarbo-*N*-thioylpyrrolidines (1a-j, 5). The known aroylaminocarbo-*N*-thioylpyrrolidines (**1a**,**b,e**),[60] (**1d,g**),[56-58] (**f**)[58] were prepared according to literature procedure from the corresponding pyrrolidines and subsequent reaction with aroylisothiocyanates as previously described. The novel methyl 1-((benzamido)carbo-*N*-thioly)-5-(4-chlorophenyl)-2-phenyl-4-(phenylsulfonyl)pyrrolidine-2-carboxylate (**1c**), Methyl 2-((1*H*-indol-3-yl)-methyl)-1-((benzamido)carbo-*N*-thioly)-5-phenyl-4-(phenylsulfonyl)pyrrolidine-2-car-boxylate (**1h**), methyl 1-((benzamido)carbo-*N*-thioly)-2-benzyl-4-(methylsulfonyl)-5-phenyl pyrrolidine- 2-carboxylate (**1i**), Dimethyl 1-((benzamido)carbo-*N*-thioly)-2-benzyl-5-(pyridin-3-yl)pyrrolidine-2,4-dicarboxylate (**1j**) and Ethyl 1-((1*H*-indol-3-yl)methyl)-2-((benzamido)carbo-*N*-thioly)octahydro-4,6-dioxo-3,5-diphenyl-pyrrolo[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)carbo-*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 Et_2O:hexane as pale yellow prisms as a 1:3 rotamer mixture: mp 163-165 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): 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, OCH_3 major rotamer) 3.63 (s 3H, OCH_3 minor rotamer) 3.46 (dd 1H, J = 13.71, 12 Hz, 3-H major rotamer), 3.31 (dd 1H, J = 13.71, 11.58, Hz 3-H minor rotamer), 2.95 (dd 1H, J = 15.15 Hz, 8.37 Hz, 3-H' minor rotamer), 2.68 (dt 1H, J = 12, 5.34, Hz, 3-H' major rotamer). ^{13}C NMR (75 MHz, $CDCl_3$): 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

$C_{32}H_{27}ClN_2O_5S_2$: 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 2-((1*H*-indol-3-yl)methyl)-1-((benzamido)carbo-*N*-thioly)-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 Et_2O:hexane as pale yellow prisms as a 1:3 rotamer mixture: mp 158-160 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): 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, OCH_3 major rotamer) 3.84 (s 3H, OCH_3 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). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.26 (C=S minor rotamer), 177.89 (C=S major rotamer), 172.82 (C=O minor 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), 129.05 (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}): ν_{max} 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 $C_{35}H_{31}N_3O_5S_2$: C, 65.90; H, 4.90; N, 6.60; S, 10.05. Found: C, 65.60; H, 5.10; N, 6.45; S, 9.95.

Methyl 1-((benzamido)carbo-*N*-thioly)-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 Et_2O:hexane as pale yellow prisms as a 1:2 rotamer mixture: mp 167-169 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): 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, OCH_3 major rotamer) 3.86 (s 3H, OCH_3 minor rotamer) 3.55 (d, 1H, J = 14.13 Hz, 6H' 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, CH_3 major rotamer) 1.90 (s 3H, CH_3 minor rotamer). ^{13}C NMR (75 MHz, $CDCl_3$): 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, 1374, 1353, 1248, 1156, 1126, 1086, 734, 701. MS (ESI, M-H^+): m/z 534.9(M-H^+, 100). Anal. Calcd for $C_{28}H_{28}N_2O_5S_2$: 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_2O:hexane as pale yellow prisms as a 1:3 rotamer mixture: mp 177-179 ºC. ^{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). ^{13}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 $C_{28}H_{27}N_3O_5S_2.0.5\ H_2O$: 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-((1*H*-indol-3-yl)methyl)-2-((benzamido)carbo-*N*-thioly)octahydro-4,6-dioxo-3,5-diphenyl-pyrrol[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_2O:hexane as pale yellow prisms as a 1:2 rotamer mixture: mp 151-154 ºC. ^{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, $\underline{CH_2}CH_3$, 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, $CH_2\underline{CH_3}$ major and minor rotamers). ^{13}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 minor 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, 132.90, 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,

117.94, 111.91, 111.80, 108.93, 108.41, 76.07, 69.58, 69.04, 62.49, 54.42, 52.83, 49.45, 48.01, 33.04, 31.61, 22.71, 22.67, 14.15, 13.97. IR (cm^{-1}): ν_{max} 3383, 3063, 2922, 2852, 1736, 1711, 1596, 1562, 1494, 1451, 1368, 1241, 1197, 1168, 740, 711, 693. MS (ESI, M-H^+): *m/z* 654.9 (M-H^+, 100). Anal. Calcd for $C_{38}H_{32}N_4O_5S$: C, 69.50; H, 4.90; N, 8.55; S,4.90. Found: C, 69.95; H, 5.15; N, 8.60; S, 4.55.

General Procedures for the Preparation of Thiohydantoins (3a-j). To a stirred solution of aroylaminocarbo-*N*-thioylpyrrolidines (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_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, evaporated under reduced pressure and the mixture was purified by column chromatography (Et_2O: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-1*H*-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_2O: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-1*H*-pyrrolo[1,2-*c*]-imidazole-6-carboxylate (*cis*-3a). The product crystallized from Et_2O as colourless prisms; mp 271-273 ºC (decomp.). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ= 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}): ν_{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 $C_{19}H_{18}N_2O_3S.0.25H_2O$: 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-1*H*-pyrrolo[1,2-*c*]-imidazole-6-carboxylate (*trans*-3a). The product crystallized from Et_2O:acetonitrile as colourless prisms; mp 216-218 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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}): ν_{max} 3056, 2803, 1751, 1729, 1602, 1502, 1414, 1351, 1214, 1193, 746, 653. MS (ESI,

M-H$^+$): *m/z* 352.9 (M-H$^+$, 100). Anal. Calcd for $C_{19}H_{18}N_2O_3S$: 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-1*H*-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 seperated by column chromatography (Et_2O:hexane, 1:3). The product (0.31 g, 78%) was as an amorphous colourless solid.

(*5R,6S,7aR*)-Methyl 5-(4-chlorophenyl)hexahydro-1-oxo-7a-phenyl-3-thioxo-1*H*-pyrrolo[1,2-*c*]-imidazole-6-carboxylate (*cis*-3b). The product crystallized from Et_2O as colourless prisms; mp 243-245 ºC (decomp.). ^{1}H 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, 5.82 Hz, 7-H'). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.98 (C=S), 172.77 (C=O), 168.77 (C=O), 137.20, 134.59, 132.24, 129.41 (3 x C), 128.53 (3 x C), 124.88 (3 x C), 77.51, 63.13, 51.90, 51.18, 34.22. 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 $C_{20}H_{17}N_2O_3SCl$: 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.

(*5R,6R,7aR*)-Methyl 5-(4-chlorophenyl)hexahydro-1-oxo-7a-phenyl-3-thioxo-1*H*-pyrrolo[1,2-*c*]-imidazole-6-carboxylate (*trans*-3b). The product was an amorphous colourless solid; mp 192-194 ºC. ^{1}H 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'). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.49 (C=S), 172.80 (C=O), 170.82 (C=O), 135.9, 135.76, 134.27, 129.41, 129.31, 129.11 (2 x C), 128.95 (2 x C), 128.52, 125.56 (2 x C), 78.41, 63.36, 55.46, 52.39, 35.00. 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 $C_{20}H_{17}N_2O_3SCl$: C, 59.90; H, 4.25; N, 7.00; S, 8.00. Found: C, 60.05; H, 4.35; N, 7.05; 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.

(5*S*,6*S*,7*aR*)-5-(4-Chlorophenyl)hexahydro-7a-phenyl-6-(phenylsulfonyl)-3-thioxopyrrolo[1,2-*c*]-imidazol-1-one (*cis*-3c). The product crystallized from Et_2O as colourless prisms; mp 219-221 ºC (decomp.). ^{1}H 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'). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.82 (C=S), 172.49 (C=O), 137.17, 136.52, 135.22, 133.98, 129.87, 129.63 (3 x C), 129.44, 129.15 (3 x C), 128.35, 128.22 (3 x C), 124.85 (2 x C), 76.33, 68.69, 62.70, 34.57. IR (cm^{-1}): ν_{max} 3202, 3062, 2922, 1751, 1592, 1491, 1443, 1368, 1215, 1137, 750,

688. MS (ESI, M-H^+): *m/z* 480.8 (M-H^+, 100), 482.8(M-H^+, 40).

(5*S*,6*R*,7a*R*)-5-(4-Chlorophenyl)hexahydro-7a-phenyl-6-(phenylsulfonyl)-3-thioxopyrrolo[1,2-*c*]-imidazol-1-one (*trans*-3c). Obtained as an amorphous colourless solid; mp 168-170 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 178.48 (C=S), 173.13 (C=O), 137.14, 136.53, 134.93, 134.39, 132.55, 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}): ν_{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 $C_{24}H_{19}ClN_2O_3S_2$: 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 (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_2O:hexane, 1:2). The product (0.31 g, 85%) was as an amorphous colourless solid.

(5*R*,6*S*,7a*R*)-Methyl hexahydro-1-oxo-5,7a-diphenyl-3-thioxo-1*H*-pyrrolo[1,2-*c*]imidazole-6-carboxylate (*cis*-3d). The product crystallized from Et_2O as colourless prisms; mp 199-201 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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}): ν_{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 $C_{20}H_{18}N_2O_3S$: 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.

(5*R*,6*R*,7a*R*)-Methyl hexahydro-1-oxo-5,7a-diphenyl-3-thioxo-1*H*-pyrrolo[1,2-*c*]imidazole-6-carboxylate (*trans*-3d). Crystallisation gave *trans*-isomer together with trace *cis*-isomer as an amorphous colourless solid; mp 189-191 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 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): δ = 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}): ν_{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 $C_{20}H_{18}N_2O_3S$: 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 hexahydro-5-(naphthalen-2-yl)-1-oxo-7a-phenyl-3-thioxo-1*H*-pyrrolo[1,2-*c*]imidazole-6-carboxylate (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_2O:hexane, 1:2) which afforded the

product (0.37 g, 89%) as an amorphous colourless solid.

(5*R*,6*S*,7a*R*)-Methyl hexahydro-5-(naphthalen-2-yl)-1-oxo-7a-phenyl-3-thioxo-1*H*-pyrrolo[1,2-*c*]-imidazole-6-carboxylate (*cis*-3e). The product crystallized from Et_2O as colourless prisms; mp 139-141 ºC (decomp.). ^{1}H NMR (300 MHz, $CDCl_3$): 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, OCH_3), 2.64 (dd, 1H, J = 12.66, 5.76 Hz, 7-H'). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 181.04 (C=S), 174.74 (C=O), 169.26 (C=O), 138.51, 132.96, 132.91, 132.76, 129.61 (3 x C), 129.37, 128.46, 127.89, 127.48, 126.60, 126.53, 125.35 (3 x C), 77.37, 63.07, 51.68, 51.65, 33.28. IR (cm^{-1}): ν_{max} 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 $C_{24}H_{20}N_2O_3S.0.5H_2O$: 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.

(5*R*,6*R*,7a*R*)-Methyl hexahydro-5-(naphthalen-2-yl)-1-oxo-7a-phenyl-3-thioxo-1*H*-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.). ^{1}H NMR (300 MHz, acetone-d_6): 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, OCH_3). ^{13}C NMR (75 MHz, DMSO-d_6): 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}): ν_{max} 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 $C_{24}H_{20}N_2O_3S.0.5H_2O$: 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-1*H*-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 (Et_2O:hexane, 1:2) which afforded the product (0.33 g, 81%) as an amorphous colourless solid.

(5*R*,6*S*,7a*R*)-Methyl 7a-benzyl-hexahydro-5-(4-methoxyphenyl)-1-oxo-3-thioxo-1*H*-pyrrolo[1,2-*c*]-imidazole-6-carboxylate (*cis*-3f). The product crystallized from Et_2O as colourless prisms; mp 191-193 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): 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, OCH_3), 3.73-3.65 (m, 1H, 6-H), 3.25 (s, 3H, OCH_3), 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'). ^{13}C NMR (75 MHz, $CDCl_3$): 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}): ν_{max} 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 $C_{22}H_{22}N_2O_4S$: 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.

**(5*R*,6*S*,7a*R*)-Methyl 7a-benzyl-hexahydro-5-(4-methoxyphenyl)-1-oxo-3-thioxo-1*H*-pyrrolo[1,2-*c*]-

imidazole-6-carboxylate (*trans*-3f). Crystallisation gave *trans*-isomer together with trace *cis*-isomer as an amorphous colourless solid; mp 129-131 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): 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, OCH_3), 3.53-3.47 (m, 1H, 6-H), 3.26-3.13 (m, 2H, 8-H, 8-H') 3.15 (s, 3H, OCH_3), 2.76 (dd, 1H, J = 13.59, 10.5 Hz, 7-H), 2.58 (dd, 1H, J = 13.59 Hz, 2.67 Hz, 7-H'). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.32 (C=S), 175.28 (C=O), 173.00 (C=O), 158.95, 133.75, 130.14, 130.00, 129.21, 128.31, 128.02, 127.45, 127.29, 112.97 (3 x C), 76.92, 64.01, 54.90, 54.68, 52.68, 42.54, 33.05. IR (cm^{-1}): ν_{max} 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 $C_{22}H_{22}N_2O_4S$: 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-1*H*-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 (Et_2O:hexane, 1:2) which afforded the product (0.315 g, 83%) as an amorphous colourless solid.

(5*R*,6*S*,7a*R*)-Methyl 7a-benzyl-hexahydro-1-oxo-5-phenyl-3-thioxo-1*H*-pyrrolo[1,2-*c*]imidazole-6-carboxylate (*cis*-3g). The product crystallized from Et_2O as colourless prisms; mp 202-204 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): 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'). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.70 (C=S), 174.62 (C=O), 169.25 (C=O), 134.15, 133.22, 129.91 (3 x C), 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}): ν_{max} 3156, 3045, 2948, 1738, 1599, 1454, 1349, 1227, 1197, 737, 697. MS (ESI, M-H$^+$): *m/z* 378.9 (M-H$^+$, 100). Anal. Calcd for $C_{21}H_{20}N_2O_3S.0.25H_2O$: 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.

(5*R*,6*R*,7a*R*)-Methyl 7a-benzyl-hexahydro-1-oxo-5-phenyl-3-thioxo-1*H*-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 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90 (brs, 1H, NH), 7.39-7.01 (m, 10H, Ar-H), 5.58 (d, 1H, J = 3.99 Hz, 5-H), 3.83 (s, 3H, OCH_3), 3.54-3.49 (m, 1H, 6-H), 3.27-3.10 (m, 2H, 8-H, 8-H'), 2.77 (dd, 1H, J = 13.59 Hz, 10.35 Hz, 7-H), 2.62 (dd, 1H, J = 13.59 Hz, 2.19 Hz, 7-H'). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.34 (C=S), 174.22 (C=O), 173.03 (C=O), 136.72, 132.99, 128.91 (3 x C), 128.78 (2 x C), 128.57 (2 x C), 127.92 (3 x C), 77.92, 64.64, 55.07, 53.07, 42.99, 33.24. IR (cm^{-1}): ν_{max} 3238, 3035, 2954, 2924, 1728, 1616, 1452, 1351, 1204,1176, 736, 697. MS (ESI, M-H$^+$): *m/z* 378.9 (M-H$^+$, 100). Anal. Calcd for $C_{21}H_{20}N_2O_3S.0.25H_2O$: C, 65.55; H, 5.35; N, 7.30; S, 8.30. Found: C, 65.50; H, 5.20; N, 7.25; S, 8.55.

7a-((1*H*-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 (Et_2O:hexane, 1:3) which afforded the

product (0.37 g, 74%) as an amorphous colourless solid.

(5*S*,6*S*,7a*S*)-7a-((1*H*-Indol-3-yl)methyl)hexahydro-5-phenyl-6-(phenylsulfonyl)-3-thioxopyrrolo-[1,2-*c*]imidazol-1-one (*cis*-3h). The product crystallized from Et_2O as colourless prisms; mp: 259-262 ºC (decomp). ^{1}H NMR (300 MHz, acetone-d_6): 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 = 8.16 Hz, 5-H), 4.61-4.52 (m, 1H, 6-H), 3.46 (d, 1H, J = 14.31 Hz, 8-H), 3.40 (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'). ^{13}C NMR (100 MHz, DMSO-d_6): 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}): ν_{max} 3402, 3389, 3062, 2955, 1922, 1727, 1582, 1448, 1358, 1210, 1146, 725, 689. MS (ESI, M+H$^+$): *m/z* 502.3 (M+H$^+$, 100).

(5*S*,6*R*,7a*S*)-7a-((1*H*-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 ºC (decomp.). ^{1}H NMR (300 MHz, acetone-d_6): 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'). ^{13}C NMR (100 MHz, DMSO-d_6): δ= 181.26 (C=S), 175.74 (C=O), 138.44, 135.71, 133.93, 132.51, 129.25 (3 x C) 127.93 (3 x C), 127.76 (3 x C), 127.16 (2 x C), 125.38, 120.87, 118.68, 118.34, 106.37, 74.87, 64.04, 63.28, 33.90, 30.01. IR (cm^{-1}): ν_{max} 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 $C_{27}H_{23}N_3O_3S_2.0.5H_20$: 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 seperated by column chromatography (Et_2O:hexane, 1:3) which afforded the product (0.29 g, 72%) as an amorphous colourless solid.

(5*S*,6*S*,7a*S*)-7a-Benzylhexahydro-6-(methylsulfonyl)-5-phenyl-3-thioxopyrrolo[1,2-*c*]imidazol-1-one (*cis*-3i). The product crystallized from Et_2O as colourless prisms; mp 151-153 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44-7.14 (m, 11H, Ar-H and N-H), 5.44 (d, 1H, J = 6.47 Hz, 5-H), 4.19-4.12 (m, 1H, 6-H), 3.74 (d, 1H, J = 13.83 Hz, 8-H), 3.24 (d, 1H, J = 13.83 Hz, 8-H'), 2.94-2.80 (m, 2H, 7-H ve 7H'), 2.75 (s, 3H, SCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.51 (C=S), 173.60 (C=O), 133.70, 133.03, 129.88 (3 x C), 129.75, 129.15 (2 x C), 128.60 (3 x C), 127.92 76.97, 72.39, 64.43, 42.64, 41.27, 30.45. IR (cm^{-1}): ν_{max} 3239, 3022, 2955, 2924, 2866, 1742, 1603, 1452, 1378, 1240, 1200, 734, 697. MS (ESI, M-H$^+$): *m/z* 398.9 (M-H$^+$, 100). Anal. Calcd for $C_{20}H_{20}N_2O_3S$: 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.

(5*S*,6*R*,7a*S*)-7a-Benzylhexahydro-6-(methylsulfonyl)-5-phenyl-3-thioxopyrrolo[1,2-*c*]imidazol-1-one

(*trans*-3i). Crystallisation gave *trans*-isomer together with trace *cis*-isomer as an amorphous colourless solid; mp 162-164 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): 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') 2.94-2.80 (m, 1H, 7-H), 2.59 (dd, 1H, J = 12.48 Hz, 5.82 Hz, 7-H'), 2.02 (s, 3H, SCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 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}): ν_{max} 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 $C_{20}H_{20}N_2O_3S$: 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-1*H*-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 (Et_2O:hexane, 1:3) which afforded the product (0.35 g, 91%) as an amorphous colourless solid.

(5*R*,6*S*,7a*R*)-Methyl 7a-benzyl-hexahydro-1-oxo-5-(pyridin-3-yl)-3-thioxo-1*H*-pyrrolo[1,2-*c*]-imidazole-6-carboxylate (*Z*-3j). The product crystallized from Et_2O as colourless prisms; mp 236-238 ºC (decomp). ^{1}H NMR (300 MHz, DMSO-d_6): 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, OCH_3), 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'). ^{13}C NMR (75 MHz, DMSO-d_6): 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, 51.71, 51.35, 43.16, 31.17. IR (cm^{-1}): ν_{max} 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 $C_{20}H_{19}N_3O_3S$: 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.

(5*R*,6*R*,7a*R*)-Methyl 7a-benzylhexahydro-1-oxo-5-(pyridin-3-yl)-3-thioxo-1*H*-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 ºC (decomp). ^{1}H NMR (400 MHz, DMSO-d_6): 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), 5.45 (d, 1H, J = 6 Hz, 5-H), 3.81-3.68 (m, 1H, 6-H), 3.69 (s, 3H, OCH_3), 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'). ^{13}C NMR (100 MHz, DMSO-d_6): 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}): ν_{max} 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 CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, evaporated under reduced pressure and the mixture was purified by column chromatography (Et_2O: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.

(5*R*,6*S*,7*S*,7a*S*)-Methyl 7-(phenylcarbamoyl)-7a-((1*H*-indol-3-yl)methyl)hexahydro-1-oxo-5-phenyl-3-thioxo-1*H*-pyrrolo[1,2-*c*]imidazole-6-carboxylate (6). The product crystallized from Et_2O as colourless prisms; mp 202-205 ºC (decomp.). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.97 (brs, 1H, NH), 8.20 (brs, 1H, NH), 7.75-6.93 (m, 16H, NH, Ar-H), 5.40 (d, 1H, J = 9.63 Hz, 5-H), 4.42 (dd, 1H, J = 11.94, 9.66 Hz, 6-H), 4.19 (d, 1H, J = 11.97 Hz, 7-H), 3.60 (d, 1H, J = 14.58 Hz, 8-H), 3.38 (d, 1H, J = 14.61 Hz, 8-H'), 3.25(s, 3H, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.32 (C=S), 176.52 (C=O), 168.61 (C=O), 164.42 (C=O), 137.67, 135.83, 133.25, 129.22 (3 x C), 128.77, 128.17, 127.15 (2 x C), 124.82, 124.71, 122.53, 120.31, 119.87 (3 x C), 118.29, 111.37, 106.09, 75.34, 63.03, 53.43, 52.04, 48.02, 30.46. IR (cm^{-1}): ν_{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 (M+H$^+$, 100). Anal. Calcd for $C_{30}H_{26}N_4O_4S$: 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.

(2*S*,3*S*,3a*S*,6a*R*)-Methyl 6a-((1*H*-indol-3-yl)methyl)octahydro-4,6-dioxo-2,5-diphenyl-1-thiocarbamoylpyrrolo[3,4-*b*]pyrrole-3-carboxylate (7). The product crystallized from Et_2O as colourless prisms; mp 234-236 ºC (decomp.). ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ = 11.11 (brs, 1H, NH), 11.10 (brs, 1H, NH), 10.61 (brs, 1H, NH), 7.70-7.05 (m, 15H, Ar-H), 5.28 (d, 1H, J = 7.80 Hz, 2-H), 3.94 (dd, 1H, J = 7.76, 4.16 Hz, 3-H), 3.81 (d, 1H, J = 4.16 Hz, 3a-H), 3.68 (s, 3H, OCH_3), 3.53(d, 1H, J = 14.72 Hz, 7-H), 3.48 (d, 1H, J = 14.76 Hz, 7-H'). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ = 178.30 (C=S), 174.19 (C=O), 171.36 (C=O), 169.59 (C=O), 138.36, 135.74, 135.07, 128.75 (3 x C), 128.08, 127.56 (2 x C), 127.40, 125.35, 123.94, 120.97, 119.75 (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}): ν_{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 (M+H$^+$, 100).

Synthesis of (2*S*,3*S*,3a*S*,6a*R*)-Methyl 6a-((1*H*-indol-3-yl)methyl)octahydro-4,6-dioxo-2,5-diphenyl-pyrrolo[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 CH_2Cl_2. The combined organic layers were dried ($MgSO_4$),

filtered, evaporated under reduced pressure and the mixture was purified by column chromatography (Et_2O:hexane, 1:3) to afford **9.** The product (0.41g, 85%) crystallised from Et_2O:hexane as colourless prisms; mp 122-124 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): 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, OCH_3), 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'). ^{13}C NMR (100 MHz, $CDCl_3$): 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}): ν_{max} 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).

Crystallograpy

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-K_α 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 $F^2>2\sigma(F^2)$. Integration of the intensities, correction for Lorentz and polarization effects and cell refinement was performed using CrystalClear (Rigaku/MSC Inc., 2005) software.[65] The structures were solved by direct methods using SHELXS-97[66] and refined by a full-matrix least-squares procedure using the program SHELXL-97.[66] 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 Et_2O solution at room temperature. $C_{19}H_{18}N_2O_3S$, crystal system, space group: monoclinic, $P2_1/c$; (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 = 90º; volume: 1768.2(3) $Å^3$; Z=4; calculated density: 1.331 g/cm^3; absorption coefficient: 0.203 mm^{-1}; F(000): 744; θ-range for data collection 2.1–26.4º; refinement method: full-matrix least-square on F^2; data/parameters: 2244/227; goodness-of-fit on F^2: 1.062; final R indices [$I>2\sigma(I)$]: R_1 = 0.070, wR_2 = 0.191; R indices (all data): R_1 = 0.105, wR_2 = 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 Et_2O-MeCN solution at room temperature. $C_{19}H_{18}N_2O_3S.MeCN$, crystal system, space group: monoclinic, $P2_1/c$; (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) $Å^3$; Z = 4; calculated density: 1.30 g/cm^3; absorption coefficient: 0.187 mm^{-1}; F(000): 832; θ-range for data collection 2.4–26.4º; refinement method: full-matrix least-square on F^2; data/parameters: 2389/257; goodness-of-fit on F^2: 1.033; final R indices [I>2σ(I)]: R_1 = 0.066, wR_2 = 0.140; R indices (all data): R_1 = 0.121, wR_2 = 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 Et_2O solution at room temperature. $C_{20}H_{19}N_3O_3S$, crystal system, space group: monoclinic, $P2_1/a$; (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) $Å^3$; Z = 8; calculated density: 1.365 g/cm^3; absorption coefficient: 0.200 mm^{-1}; F(000): 1600; θ-range for data collection 2.1–26.6º; refinement method: full-matrix least-square on F^2; data/parameters: 3698/487; goodness-of-fit on F^2: 0.971; final R indices [I>2σ(I)]: R_1 = 0.076, wR_2 = 0.207; R indices (all data): R_1 = 0.148, wR_2 = 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 Et_2O solution at room temperature. $C_{30}H_{26}N_4O_4S{\cdot}H_2O$, 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) $Å^3$; Z = 2; calculated density: 1.183 g/cm^3; absorption coefficient: 0.145 mm^{-1}; F(000): 584; θ-range for data collection 2.1–26.4º; refinement method: full-matrix least-square on F^2; data/parameters: 3648/358; goodness-of-fit on F^2: 1.062; final R indices [I>2σ(I)]: R_1 = 0.081, wR_2 = 0.244; R indices (all data): R_1 = 0.123, wR_2 = 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 Et_2O solution at room temperature. $C_{30}H_{26}N_4O_4S$, 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) $Å^3$; Z = 2; calculated density: 1.318 g/cm^3; absorption coefficient: 0.162 mm^{-1}; F(000): 564; θ-range for data collection 2.3–26.4º; refinement method: full-matrix least-square on F^2; data/parameters: 3196/352; goodness-of-fit on F^2: 1.026; final R indices [I>2σ(I)]: R_1 = 0.062, wR_2 = 0.132; R indices (all data): R_1 = 0.115, wR_2 = 0.157; largest diff. peak and hole: 0.191 and -0.189 e $Å^{-3}$; CCDC: 817614.

ACKNOWLEDGEMENTS

This work is a part of Yahya Nural PhD thesis and we thank to Mersin University (project grant

BAP-SBE AKB (YN) 2009-3 DR for Yahya Nural) for financial support.

REFERENCES

1. Z. D. Wang, S. O. Sheikh, and Y. Zhang, *Molecules*, 2006, **11**, 739.
2. J. Thanusu, V. Kanagarajan, and M. Gopalakrishnan, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 713.
3. S. Cao, L. Zhu, C. Zhao, X. Tang, H. Sun, X. Feng, and X. Qian, *Monatsh. Chem.*, 2008, **139**, 923.
4. J. Marton, J. Enisz, S. Hosztafi, and T. Timar, *J. Agric. Food Chem.*, 1993, **41**, 148.
5. K. M. Thakar, D. J. Paghdar, P. T. Chovatia, and H. Joshi, *J. Serb. Chem. Soc.*, 2005, **70**, 807.
6. A. A. El-Barbary, A. I. Khodair, E. B. Pedersen, and C. Nielsen, *J. Med. Chem.*, 1994, **37**, 73.
7. A. I. Khodair, A. A. El-Barbary, Y. A. Abbas, and D. R. Imam, *Phosphorus Sulfur and Silicon*, 2001, **170**, 261.
8. M. Blanc, M. Cussac, A. Boucherle, and G. Leclerc, *Eur. J. Med. Chem.*, 1992, **27**, 267.
9. A. M. Al-Obaid, H. I. El-Subbagh, A. I. Khodair, and M. M. A. Elmazar, *Anti-Cancer Drugs*, 1996, **7**, 873.
10. K. Tachibana, I. Imaoka, T. Shiraishi, H. Yoshino, M. Nakamura, M. Ohta, H. Kawata, K. Taniguchi, N. Ishikura, T. Tsunenari, H. Saito, M. Nagamuta, T. Nakagawa, K. Takanashi, E. Onuma, and H. Sato, *Chem. Pharm. Bull.*, 2008, **56**, 1555.
11. A. Le Tiran, J. P. Stables, and H. Kohn, *Bioorg. Med. Chem.*, 2001, **9**, 2693.
12. J. C. Elwood, A. D. Richert, and W. W. Westerfeld, *Biochemical Pharmacology*, 1972, **21**, 1127.
13. M. Aguilar-Moncaya, C. O. Mellet, J. M. G. Fernandez, and M. I. Garcia-Moreno, *J. Org. Chem.*, 2009, **74**, 3595.
14. E. Ösz, L. Somsak, L. Szilagyi, L. Kovacs, T. Docsa, B. Toth, and P. Gergely, *Bioorg. Med. Chem. Lett*., 1999, **9**, 1385.
15. T. Kurz and K. A. Widyan, *Tetrahedron Lett.*, 2004, **45**, 7049.
16. G. G. Muccioli, N. Fazio, G. K. E. Scriba, W. Poppitz, F. Cannata, and J. H. Poupaert, *J. Med. Chem.*, 2006, **49**, 417.
17. G. G. Muccioli, J. Wouters, C. Charlier, G. K. E. Scriba, T. Pizza, P. Di Pace, P. De Martino, W. Poppitz, J. H. Poupaert, and D. M. Lambert, *J. Med. Chem.*, 2006, **49**, 872.
18. E. Gallienne, G. G. Muccioli, D. M. Lambert, and M. Shipman, *Tetrahedron Lett.*, 2008, **49**, 6495.
19. C. Tran, S. Ouk, N. J. Clegg, Y. Chen, P. A. Watson, V. Arora, J. Wongvipat, P. M. Smith-Jones, D. Yoo, A. Kwon, T. Wasielewska, D. Welsbie, C. D. Chen, C. S. Higano, T. M. Beer, D. T. Hung, H. I. Scher, M. E. Jung, and C. L. Sawyers, *Science*, 2009, **324**, 787.
20. T. Lindel and H. Hoffmann, *Tetrahedron Lett*., 1997, **38**, 8935.
21. N. Roue and J. Bergman, *Tetrahedron*, 1999, **55**, 14729.
22. R. A. Davis, W. Aalbersberg, S. Meo, R. M. Da Rocha, and C. M. Ireland, *Tetrahedron*, 2002, **58**,

3263.
23. R. Jakse, S. Recnik, J. Svete, A. Golobic, L. Golic, and B. Stanovnik, *Tetrahedron*, 2001, **57**, 8395.
24. M. M. Sim and A. Ganesan, *J. Org. Chem.*, 1997, **62**, 3230.
25. Y. Dürüst and F. Nohut, *Synt. Commun.*, 1999, **29**, 1997.
26. J. Schmeyers and G. Kaupp, *Tetrahedron,* 2002, **58**, 7241.
27. M. Solymar, M. Palko, T. Martinek, and F. Fülöp, *Monatsh. Chem.*, 2002, **133**, 1423.
28. G. G. Muccioli, J. H. Poupaert, J. Wouters, B. Norberg, W. Poppitz, G. K. E. Scriba, and D. M. Lambert, *Tetrahedron*, 2003, **59**, 1301.
29. M. Marinov, S. Minchev, N. Stoyanov, G. Ivanova, M. Spassova, and V. Enchev, *Croat. Chem. Acta,* 2005, **78**, 9.
30. Y. Chu, V. Lynch, and B. L. Iverson, *Tetrahedron,* 2006, **62**, 5536.
31. J. Fuentes, B. A. B. Salameh, M. A. Pradera, F. J. F. De Cordoba, and C. Gasch, *Tetrahedron*, 2006, **62**, 97.
32. F. Gao, G. Zhang, S. Zhang, Y. Cheng, Z. Shi, Y. Li, and J. Gao, *Tetrahedron*, 2007, **63**, 3973.
33. S. Bouzroura, L. Hammal, B. Nedjar-Kolli, F. Balegroune, M. Hamadene, and S. Poulain, *Synth. Commun.*, 2007, **38**, 448.
34. D. Blanco-Ania, P. H. H. Hermkens, L. A. J. M. Sliedregt, H. W. Scheere, and F. P. J. T. Rutjes, *J. Comb. Chem.*, 2009, **11**, 527.
35. D. Blanco-Ania, P. H. H. Hermkens, L. A. J. M. Sliedregt, H. W. Scheere, and F. P. J. T. Rutjes, *J. Comb. Chem*., 2009, **11**, 547.
36. B. Singh, G. S. M. Sundaram, N. C. Misra, and H. Ila, *Tetrahedron Lett.*, 2009, **50**, 366.
37. E. Ware, *Chem. Rev.*, 1950, **46**, 403.
38. A. I. Khodair, E. S. H. El Ashry, and N. A. L. Al-Masoudi, *Monatsh. Chem*., 2004, **135**, 1061.
39. R. Natesh, S. L. Schwager, E. D. Sturrock, and K. R. Acharya, *Nature*, 2003, **421**, 551.
40. B. Z. Chen and F. A. O. Msendelsohn, *Neuropharmacology*, 1992, **31**, 929.
41. P. L. Nicklin, W. J. Irwin, P. Timmins, and R. A. Morrison, *Int. J. of Pharm.*, 1996, **140**, 175.
42. D. B. Kastrinsky and C. E. Barry III, *Tetrahedron Lett.*, 2010, **51**, 197.
43. R. Grigg, *Chem. Soc. Rev.*, 1987, **16**, 89.
44. H. A. Dondas and R. Grigg, unpublished results.
45. H. A. Dondas, R. Grigg, and C. Kilner, *Tetrahedron*, 2003, **59**, 8481.
46. D. A. Barr, R. Grigg, N. H. Q. Gunarate, J. Kemp, P. McMeekin, and V. Sridharan, *Tetrahedron*, 1988, **44**, 557.
47. H. A. Dondas, R. Grigg, and M. Thornton-Pett, *Tetrahedron*, 1996, **52**, 13455.
48. H. A. Dondas, Y. Durust, R. Grigg, M. J. Slater, and M. A. B. Sarker, *Tetrahedron*, 2005, **61**, 10667.
49. H. A. Dondas, C. W. G. Fiswick, R. Grigg, and C. Kilner, *Tetrahedron*, 2004, **60**, 3473.

50. R. Grigg, M. Thornton-Pett, J. Xu, and L. H. Xu, *Tetrahedron*, 1999, **55**, 13841.
51. H. A. Dondas, R. Grigg, W. S. MacLachlan, D. T. MacPerson, J. Markandu, V. Sridharan, and S. Suganthan, *Tetrahedron Lett*., 2000, **41**, 967.
52. H. A. Dondas, J. Duraisingham, R. Grigg, W. S. MacLaclan, D. T. MacPherson, M. Thornton-Pett, V. Sridharan, and S. Suganthan, *Tetrahedron*, 2000, **56**, 4063.
53. H. A. Dondas, C. W. G. Fishwick, X. Gai, R. Grigg, C. Kilner, N. Dumrongchai, B. Kongkathip, N. Kongkathip, C. Polysuk, and V. Sridharan, *Angew. Chem. Int. Ed.*, 2005, **44**, 7570.
54. R. Grigg, H. Q. N. Gunaratne, and V. Sridharan, *Tetrahedron*, 1987, **43**, 5887.
55. J. Casas, R. Grigg, C. Najera, and J. M. Sansano, *Eur. J. Org. Chem*., 2001, **10**, 1971.
56. H. A. Dondas and O. Altınbas, *Heterocycl. Commun*., 2004, **10**, 167.
57. H. A. Dondas, Y. Nural, N. Duran, and C. Kilner, *Turk. J. Chem.*, 2006, **30**, 573.
58. Y. Nural, R. Kilincarslan, H. A. Dondas, B. Cetinkaya, M. S. Serin, R. Grigg, T. Ince, and C. Kilner, *Polyhedron*, 2009, **28**, 2847.
59. Y. Nural, MSc Thesis, Mersin University, Mersin, 2006.
60. T. Ince, MSc Thesis, Mersin University, Mersin, 2009.
61. R. Grigg, D. M. Cooper, S. Holloway, S. McDonald, E. Millington, and M. A. B. Sarker, *Tetrahedron*, 2005, **61**, 8677.
62. R. Grigg, J. Kemp, and J. Tangthongkum, *J. Chem. Soc., Chem. Commun.*, 1980, **14**, 648.
63. R. Grigg, H. Q. N. Gunaratne, and V. J. McNaghten, *J. Chem. Soc., Perkin Trans. 1*, 1983, 185.
64. D. A. Barr, M. J. Dorrity, R. Grigg, S. Hargreaves, J. F. Malone, J. Montgomery, J. Redpath, P. Stevenson, and M. Thornton-Pett, *Tetrahedron*, 1995, **51**, 273.
65. Rigaku/MSC, Inc., 9009 new Trails Drive, The Woodlands, TX 77381 Rigaku/MSC, Inc., 9009 new Trails Drive, The Woodlands, TX 77381.
66. G. M. Sheldrick, *SHELXS97* and *SHELXL97*, University of Göttingen, Germany, 1997.