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From Bioactive Pyrrolidino[3,4-*c*]pyrrolidines to more Bioactive Pyrrolidino[3,4-*b*]pyrrolidines via Ring-Opening/Ring-Closing Promoted by Sodium Methoxide

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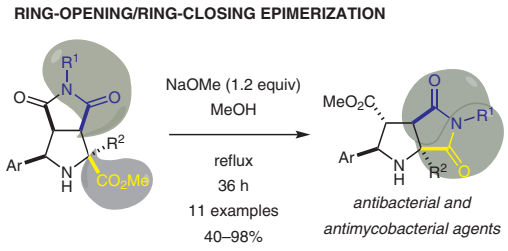

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Abstract The process involving a rearrangement of pyrrolidino[3,4-*c*]pyrrolidine to another pyrrolidino[3,4-*b*]pyrrolidine using sodium methoxide as base is fully studied. The effects of the substituents are analyzed during the ring-opening/ring-closing sequence. Computational studies are also performed to explain the importance of susbstituents and quaternary carbons, especially when the (3-indolyl)methyl is present in the starting material. Finally, all the samples are evaluated as potential candidates for antibacterial and antimycobacterial activities.

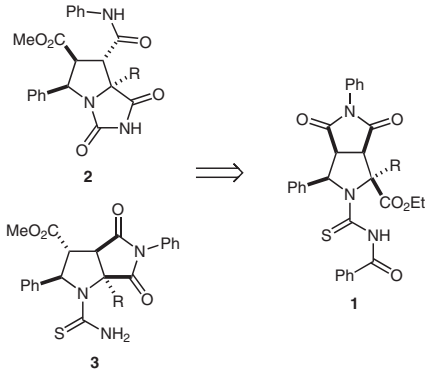
Key words cycloaddition, azomethine ylides, rearrangement, antibacterials, DFT calculations

Introduction

The design of very simple molecular architectures with the broadest biological and medicinal coverage is always pursued, and especially for the long treatment of degenerative illnesses. A clear example is represented by succinimides,[1] whose activities such as CNS depressant, analgesic, antitumor, antispasmodic, bacteriostatic, hypotensive, antibacterial, antifungal, anti-tubercular, etc., have been reported in the literature.[1–3] Succinimides are easily available from succinic acid or succinic anhydride and their derivatives involving ring-opening/ring-closing strategies.[1,4] However, the imido group and the double bond of maleimides offer new substitution patterns. For example, their electrophilic character make them excellent dienophiles in Diels–Alder reactions and dipolarophiles in 1,3-dipolar cycloadditions.[5] In fact, maleimides are frequently used for the optimization of this cycloaddition processes.

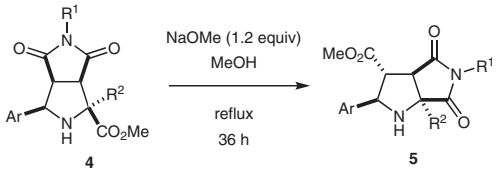
During our investigation on the synthesis of new derivatives with a thiohydantoin framework[6] (similar to **2**) with anti-tuberculosis and antibacterial activities,[7,8] we discovered the formation of unexpected compounds, which resulted from a rearrangement of the succinimide in the presence of sodium methoxide. The result of this rearrangement is a chemical switch in which from one fused succinimide with a tetrahydropyrrolo[3,4-*c*]pyrrole skeleton **1** it was possible to access a new succinimide with tetrahydropyrrolo[3,4-*b*]pyrrole framework **3** (Scheme 1).

In this work, we thoroughly studied the mechanism of the particular rearrangement originated by the methoxide anion, which reacts with molecules **4** to give products **5**



Scheme 1 First evidence of the titled succinimide rearrangement

(Scheme 2).[6] We envisage the possible scope and its utility in synthetic organic chemistry and as antituberculosis and antibacterial agent.[7]



Scheme 2 Succinimide rearrangement studied in this work

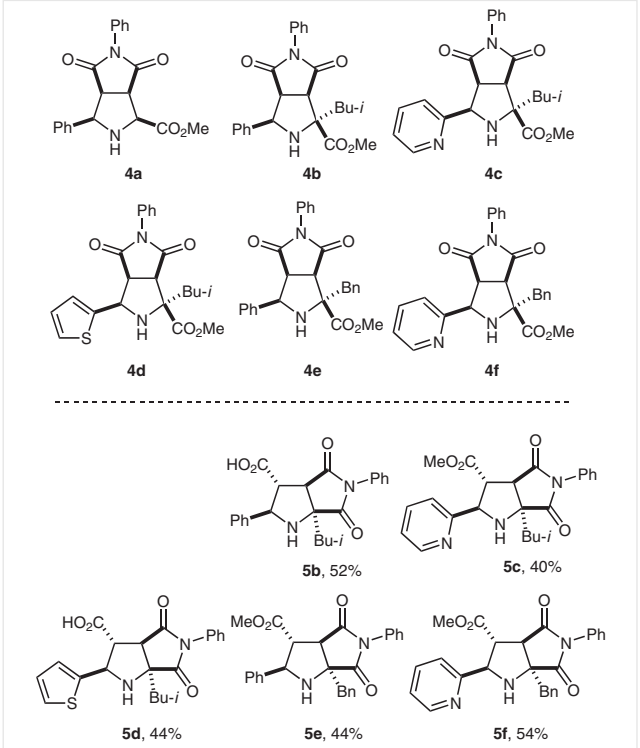


Figure 1 Products **5** of succinimide rearrangement observed in compounds **4a–f**

Results and Discussion

Scope of the Rearrangement and Structural Determination of Compounds 5, 6, and 7

Following the reaction conditions found in the confirmation of the structure of compound **5** (Ar, R^1 = Ph, R^2 = 3-indolyl) in our previous publication,[6] we started with the analysis of the tetrahydropyrrolo[3,4-*c*]pyrrole **4a** obtained from 1,3-dipolar cycloaddition of the corresponding methyl benzylideneaminoglycinate with *N*-methylmaleimide (NMM), (see experimental part). Under general conditions described in Scheme 2, compound **4a** afforded a very complex mixture of unidentified products detected by ^{1}H NMR experiment of the crude reaction mixture.

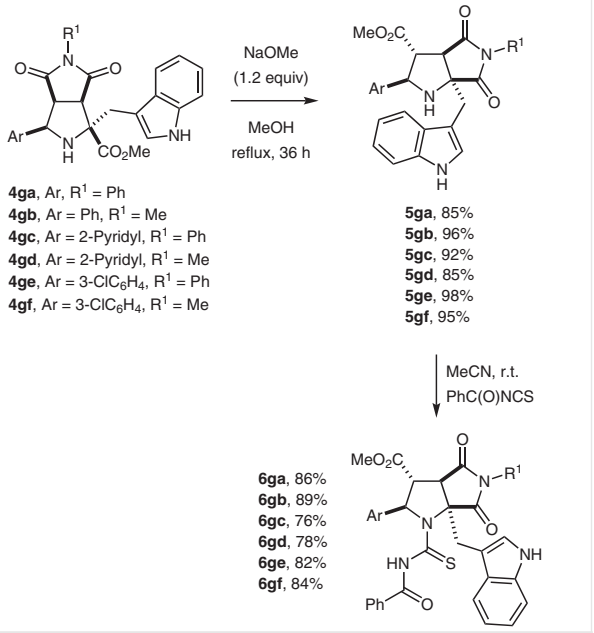
Cycloadducts **4b–f**, obtained from imino esters derived from leucine and phenylalanine were submitted to conditions depicted in Scheme 2, furnishing the corresponding tetrahydropyrrolo[3,4-*b*]pyrroles **5b–f** in moderate yields (up to 54%, Figure 1). Despite purification of all these compounds by deactivated flash silica gel, we observed some decomposition/epimerization during this process. We also discovered that they were not stable under storage for more than one week at –20 °C.

According to our experience,[8] the introduction of an indole ring can be beneficial for increasing the biological effect of the substance.[9] With this aim, cycloadducts **4g**, derived from tryptophan, were prepared (see experimental part) and were allowed to undergo the titled stereospecific rearrangement. Again, the reaction proceeded regio- and stereospecifically to give the corresponding compounds **5g**[10] in very high yields (70–98%) (Scheme 3). These series of molecules **5g** are very stable and could be stored for a long time.

The preparation of *N*-benzoylcarbothioamides **6g** was achieved smoothly by the reaction of **5g** with benzoylisothiocyanate in acetonitrile at room temperature over 24–30 hours (Scheme 3). The incorporation of this unit to the pyrrolidine ring increases the biological potency of the precursor heterocycles.

The relative configuration of all new racemic compounds was stablished according to data acquired using NMR experiments and by single crystal X-ray diffraction analysis for the compound **6gf** (Figure 2).

A larger excess of sodium methoxide in methanol (not anhydrous) furnished the same arrangement (under identical reaction conditions) affording free betaproline amino acid[12] derivative **7gg** (possessing a zwitterionic structure) in almost quantitative yield (Scheme 4). The structure of its



Scheme 3 Synthetic **4g** → **5g** → **6g** sequence involving (3-indolyl)methyl derivatives

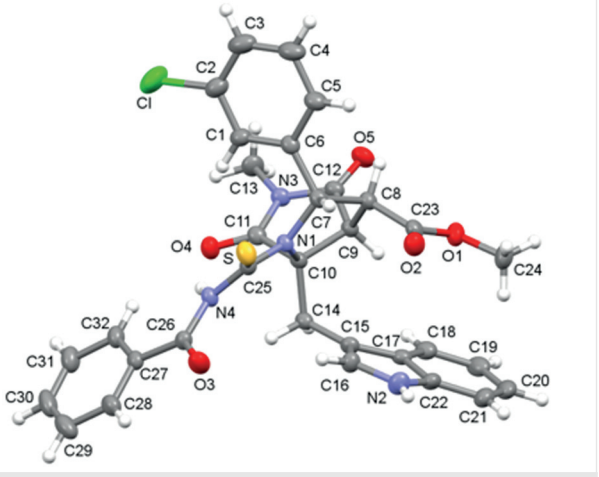


Figure 2 X-Ray diffraction analysis of compound **6gf**. Thermal ellipsoids are drawn at 40% probability level.[11]

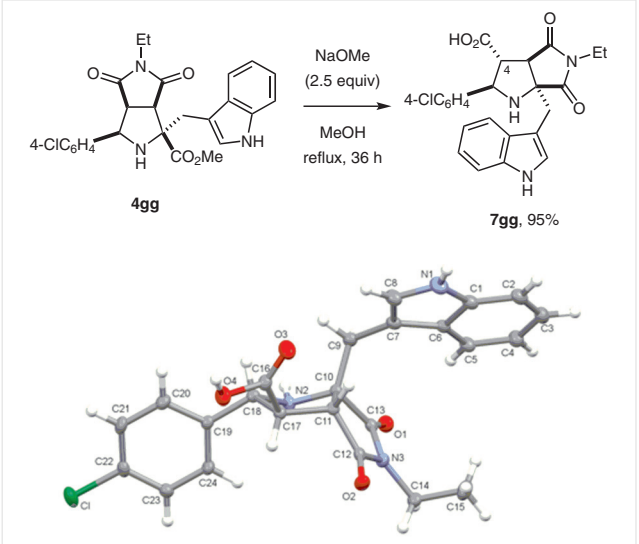
skeleton was also confirmed by X-ray diffraction analysis demonstrating that epimerization occurred only at the carbon atom 4.

Study of the Mechanism by DFT Calculations

At this point we can argue that the presence of a quaternary carbon at 2-position in the prolinate ring of compounds **4** seems to be crucial for the development of the arrangement in basic media. The Thorpe–Ingold effect can justify the scarce reactivity of cycloadduct **4a** and the moderate to excellent yields achieved in substrates **4b–g**. Additionally, the presence of the (3-indolyl)methyl residue at this position accelerated the process and gave an extra stability to the final compounds. We decided to perform computational calculations within the DFT framework in order to better understand the reaction mechanism associated with succinimide **4** rearrangement and its subsequent isomerization to yield compounds **5**. For that, **4ga** was selected as the model compound. In the first part of this study we analyzed all the possible reactions of methoxide anion with **4ga.** This anion can act as a nucleophile, reacting with the C=O bond of the imido groups (**TS1** and **TS1b** in Figure 4). On the other hand, methoxide can also act as a base, therefore the abstraction the protons in the α position of the imido groups of maleimide moiety were also considered (Figure 3).

The main geometrical features of the transition structures associated with these processes and their relative energies are collected in Figure 4.

Our calculations show that the activation energy barriers associated with the methoxide addition are lower than the deprotonation ones. This difference is even smaller considering Gibbs free activation barriers. However, the corresponding enolates formed are high in energy, consequently, their formation is thermodynamically disfavored. Therefore, any possible isomerization of compound **4ga** via direct proton abstraction will not be further considered in this study. In addition, calculations also show that bridged ring formation is also kinetically disfavored (see Supporting Information for further details about other possible computationally analyzed reaction paths). Within these results, we next analyzed the succinimide rearrangement processes leading towards formation of fused rings **5**. The relative and activation energies (and Gibbs free energies) computed are



Scheme 4 Sythesis of betaproline derivative **7gg** and its X-ray diffraction analysis pattern[13]

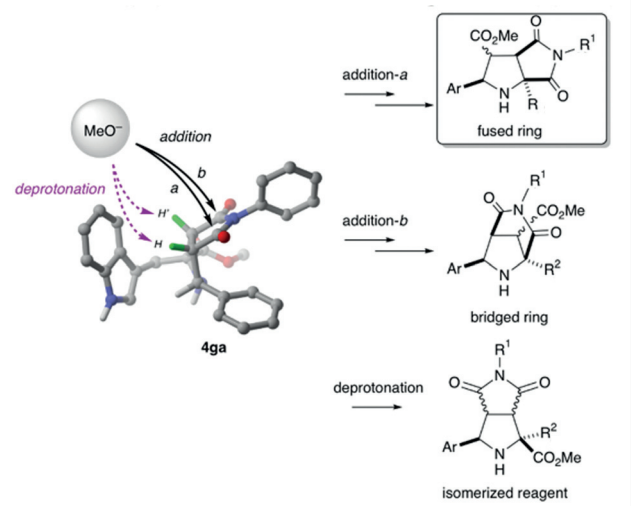


Figure 3 Possible reactions of compound **4ga** with methoxide anion. Acidic hydrogens considered are highlighted in green.

collected in Scheme 5. The main geometrical features of the corresponding transition structures are depicted in Figure 5.

Within the proposed mechanism, formation of the new maleimide ring is the rate-limiting step (**TS3a** has activation barrier ca. 1 kcal mol^{-1} higher than any other step). Moreover, calculations show that formation of **INT4a** is thermodynamically disfavored.

Once formation of **INT4a** via ring-opening ring-closing mechanism was assessed, we next analyzed computationally the subsequent isomerization towards ring-fused **5ag**.

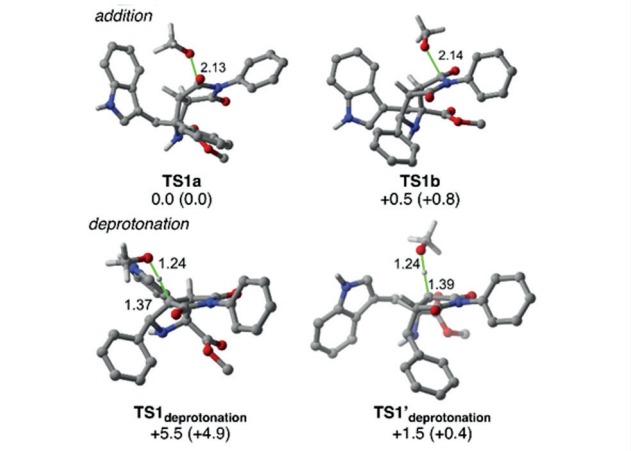


Figure 4 Main geometrical features and relative activation and free Gibbs energies (between brackets) associated with the possible reactions of methoxide anion with computed at B3LYP-D3(PCM)/6-31+G* level at 298.15 K. Distances and energies are in Å and kcal mol^{-1}, respectively. Non-relevant hydrogen atoms are omitted for clarity.

Relative and activation energies (and Gibbs free energies) and main geometrical features of the corresponding transition structures are collected in Scheme 6.

Our calculations indicate that the isomerization of **INT4a** towards **5ga** formation is thermodynamically favored, as reflected by its stability. Geometry inspection revealed that **INT4a** is highly energetic due to the repulsion associated with the eclipsed conformation of methoxycar-

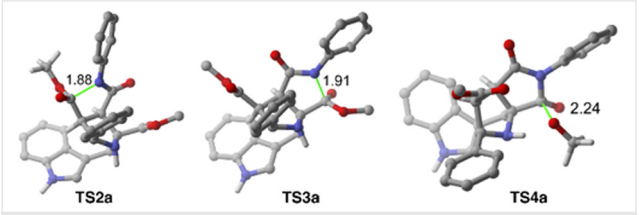
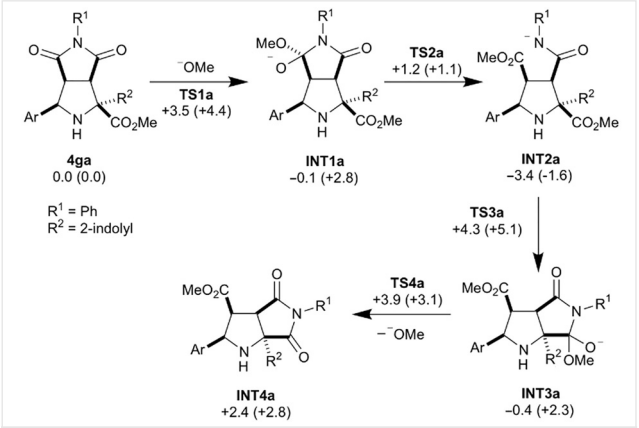
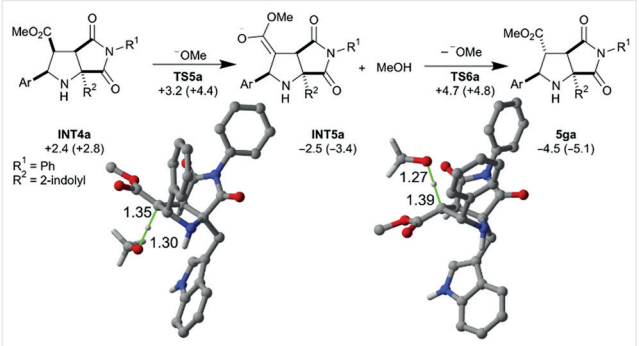


Figure 5 Main geometrical features and relative activation and free Gibbs' energies (between parentheses) associated with **4ga** rearrangement. See caption of Figure 3 for further details



Scheme 5 Activation and relative energies (and Gibbs free energies between parentheses) associated with **4ga** rearrangement with methoxide anion computed at B3LYP-D3/6-31+G(d) level of theory at 298 K. Energies are in kcal mol^{-1}.



Scheme 6 Activation and relative energies (and Gibbs free energies between parentheses) associated with **5ga** formation. See caption of Figure 3 for further details

bonyl and maleimide moieties. That repulsion is dismissed due to the isomerization process, being replaced by a stabilizing π,π-stacking interaction with the 3-indolyl moiety, and a close indole-ester hydrogen bonding, thus making this step the driving force of the reaction (Figure 6). Remarkably, the activation barriers associated with the proposed mechanism are lower than 6 kcal mol^{-1}, compatible with the relatively mild conditions experimentally required (reaction temperature of 65 °C). These stabilizing interactions, which did not exist in compounds **5b–f**, can be the reasons of the epimerization/decomposition of these last molecules.

Antimycobacterial Activity

Antimycobacterial activity of the prepared compounds were tested against *M. tuberculosis* H37Rv strain using Microplate Alamar Blue assay according to literature method[14] measured by means of MIC (minimum inhibitory concentration) values (μg/mL). Ethambutol (EMB) (Sigma E4630) and isoniazid (INH) (Sigma I3377) were used as standard reference drugs. The anti-TB activity against *M. tuberculosis* H37Rv strain showed moderate activity, in the range of 10–80 μg/mL, when compared to isoniazid and ethambutol as known reference drugs (Table 1). Especially the compound **4gf** (possessing Cl on the phenyl ring and Me on the maleimide ring) revealed the highest activities with the MIC values of 10 μg/mL whereas the compounds **4ga**, **4gc**, **4ge**, **6gd**, and **7gg** showed activity in the value range of 20–40 μg/mL and the other compounds showed the lowest activities with the MIC values of 80 μg/mL. In addition, the tested compounds exhibited better anti-TB activity when compared their antibacterial activity as indicated in Table 1. Although the mode of action or biological target of these molecules is unknown at the moment, further work to get more potent derivatives is under investigation.

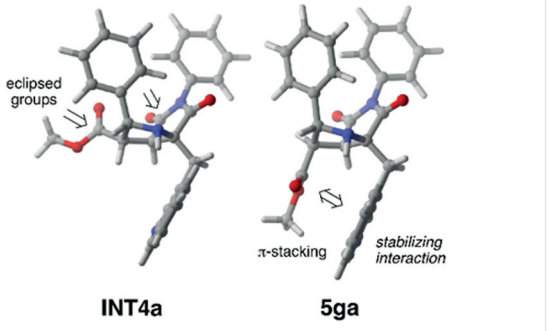


Figure 6 Optimized structures of **INT4a** and **5ga**

Antibacterial Activity

Antibacterial activity of prepared compounds were tested against two Gram (+) bacteria *Staphylococcus aureus* (ATCC 25925), *Bacillus subtilis* (ATCC 6633) and three Gram (–) bacteria *Escherichia coli* (ATCC 25923), *Acinetobacter baumannii* (ATCC 02026), and *Aeromonas hydrophila* (ATCC 95080), which were obtained from the Refik Saydam Hıfzısıhha Institute, Ankara, Turkey. Ampicillin was used as control drug. The MIC values was determined by agar dilution in duplicate as recommended by the Clinical Laborato-

Table 1 The MIC Values (μg/mL) of the Tested Compounds Against the Bacterial and Mycobacterial Strains.

	S. aureus (ATCC 25925)	*E. coli* (ATCC 25923)	*A. baumannii* (ATCC 02026)	*B. subtilis* (ATCC 6633)	*A. hydrophila* (ATCC 95080)	*M. tuberculosis* H37Rv
4ga	250	125	62.5	125	125	20
4gb	125	125	125	125	125	80
4gc	125	125	62.5	125	125	40
4gd	250	125	62.5	125	125	80
4ge	125	125	62.5	125	125	40
4gf	125	125	62.5	62.5	62.5	10
5gd	125	125	62.5	125	62.5	80
6ga	125	125	125	125	125	80
6gb	250	250	125	250	250	80
6gd	250	250	125	250	500	31.25
6ge	125	125	125	125	125	80
6gf	125	250	125	125	125	80
7gg	62.5	125	62.5	125	62.5	40
Ampicillin	31.25	15.62	125	0.9	31.25	
Isoniazid						0.2 and 0.1
Etambuol						5 and 10

ry Standards Institute.[15] To ensure that the solvents had no effect on microbial growth, a control test was performed containing inoculated broth supplemented with DMSO at the same dilutions used for the test compounds and was determined to be inactive.

The tested compounds inhibited the growth of bacteria at MIC values in the range of 62.5–500 μg/mL whereas the control, ampicillin, showed activity against the tested bacteria in a range of 125–0.9 μg/mL as given in Table 1. It is also important to note that the screened compounds were found to show the better activity against *A. baumannii* (ATCC 02026) in the range of 62.5–125 μg/mL whereas the control ampicillin showed activity in MIC values of 125 μg/mL.

Conclusions

The rearrangement of tetrahydropyrrolo[3,4-*c*]pyrrole skeleton to a new tetrahydropyrrolo[3,4-*b*]pyrrole structure could be efficiently controlled in basic media. The presence of quaternary carbons in the starting bicyclic succinimide favored the rearrangement. The presence of the (3-indolyl)methyl group attached to this quaternary carbon is crucial for the stability of the final rearranged succinimides, increasing the biological activity of this family of compounds. Calculated predictions were in agreement with the experimental findings: first, the methoxide anion attacked the carbonyl group rather than promote the deprotonation; second, the spontaneous isomerization afforded a much more stable compound; third, a stabilizing π-stacking interaction between the indole ring and the ester group bonded to the epimerized carbon atom was the driving force of the reaction. Compound **4gf** was the most active compound after the evaluation of all biological tests.

The commercially available reagents for syntheses and analyses were obtained in the analytical grade and used as received. Column chromatography was performed on silica gel 60 (Merck, 230–400 mesh). Melting points were determined with a Reichert Thermovar hot plate apparatus and are uncorrected. Mass spectra were obtained using a Bruker AC-300 or AC-400 and were recorded at 300 or 400 MHz for ^{1}H NMR and 75 or 100 MHz for ^{13}C NMR using $CDCl_3$ and MeOD as a solvent. Chemical shifts are given in parts per million (δ) downfield from TMS. Standard abbreviations are used to indicate spin multiplicities. IR spectra were taken on a PerkinElmer Spectrum One FT-IR spectrometer and on a Nicolet 510 P-FT spectrometer. Low-resolution electron impact (EI) mass spectra were obtained at 70 eV using a Shimadzu QP-5000 by injection or DIP; fragment ions in *m*/*z* are given with relative intensities (%) in parentheses. High-resolution mass spectra (HRMS) were measured on an instrument using a quadrupole time-of-flight mass spectrometer (QTOF) and also through the electron impact mode (EI) at 70 eV using a Finnigan VG Platform or a Finnigan MAT 95S. The compounds are named according to the IUPAC system; names were obtained using MDL Autonom. The known pyrrolidine derivative methyl (1*S*,3*R*)-1-[(1*H*-indol-3-yl)methyl]-4,6-dioxo-3,5-diphenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (**4ga**) and and aminocarbothiol pyrrolidine derivatives methyl (2*S*,3*S*,3a*S*,6a*R*)-6a-[(1*H*-indol-3-yl)methyl]octahydro-4,6-dioxo-2,5-diphenylpyrrolo[3,4-*b*]pyrrole-3-carboxylate (**5ga**) were prepared according to literature protocol.[6,16] Novel bicyclic pyrrolidine derivatives **4gb–gf** were prepared by modification of literature methods.[6,17]

Computational Methods

Theoretical calculations were carried out at the B3LYP-D3/6-31+G(D)[18] level by using the GAUSSIAN 09[19] suite of programs. Activation and relative (Gibbs) energies were computed within the DFT framework[20] at the B3LYP-D3/6-31+G(D) level at 298K in which dispersion corrections are included by means of Grimme's D3 model.[21] Solvent effects were estimated by the polarization continuum model[22] (PCM) method within the self-consistent reaction field (SCRF) approach.[23] All SCRF-PCM calculations were performed using DMSO (ε = 46.826) as model solvent. Merz–Kollman atomic radii cavities (as invoked by the radii = Pauling keyword) were used in reaction steps associated with hydrogen atom migration.

All the stationary points were characterized by harmonic vibrational analysis. Local minima showed positive definite Hessians. Fully optimized transition structures (TSs) showed one and only one imaginary frequency associated with nuclear motion along the chemical transformation under study. Reaction paths were checked by Intrinsic Reaction Coordinate (IRC) calculations. In order to avoid errors associated with 1N solvation state, activation barriers were compute comparing energies of directly connected stationary points.

Pyrrolidines 4a–f; General Procedure

To a suspension of AgOAc in toluene (3 mL) was added a solution of imino ester (1 mmol) and *N*-phenylmaleimide (1 mmol) in toluene (2 mL). To the resulting suspension was added Et_3N (0.05 mmol, 7 μL) and the mixture stirred at r.t. (20–30 °C) for 18–24 h. The crude reaction mixture was filtered through a small Celite pad. The residue was purified by flash chromatography or the solid products were recrystallized from a mixture of *n*-hexane/Et_2O.

Preparation of Indole Derivatives 4ga–gf; General Procedure

To a stirred solution of corresponding imine (1 mmol) in dry toluene (25 mL), dipolarophile (1 mmol) was added. The resulting solution was refluxing for an appropriate time (reaction monitored by TLC). The solvent was evaporated under vacuo and the residue purified by crystallization.

Rearrangement of Pyrrolidines 4b–f to Pyrrole-4,6-diones 5b–f; General Procedure

To a stirred solution of bicyclic pyrrolidine **4b–f** (1 mmol) in anhyd MeOH (10 mL) was added dropwise a solution of NaOMe (1.2 mmol) in anhyd MeOH (10 mL) over 10–15 min, and the mixture stirred and refluxed for 32–36 h. The solvent was evaporated under reduced pressure and quenched with sat. aq NH_4Cl, then extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried ($MgSO_4$) and filtered. The product **5b–f** were purified by flash chromatography using deactivated silica gel (a 5% of Et_3N was added as co-eluent) to improve the yield of the final product.

N-Benzoylcarbothioamides 6ga–gf; General Procedure

To a stirred solution of corresponding pyrrolidines (**5ga–5gf**) (1.2 mmol) in dry acetonitrile (30 mL), benzoyl isothiocyanate (1.3 mmol) was added. The resulting solution was stirred at room temperature for an appropriate time (reaction monitored by TLC). The solvent was evaporated under vacuo and the product was purified by crystallization or by flash chromatography.

Methyl (1*S*,3*R*,3a*S*,6a*R*)-4,6-Dioxo-3,5-diphenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (4a)

After 18 h and workup, the product was isolated by column chromatography (*n*-hexane/EtOAc 8:2) as a white solid; yield: 318 mg (91%); mp 153–155 °C.

All spectra were in agreement with the reported data.

Methyl (1*S*,3*R*,3a*S*,6a*R*)-1-Isobutyl-4,6-dioxo-3,5-diphenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (4b)

After 18 h and workup, the product was isolated by column chromatography (*n*-hexane/EtOAc; 8:2) as a white solid; yield: 321 mg (79%); mp 145–149 °C.

IR (ATR): 1713, 1502, 1375, 1206, 1166, 1140, 854, 702, 692 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 6.5 Hz, 3 H), 1.01 (d, *J* = 6.5 Hz, 3 H), 1.69–1.87 (m, 2 H), 2.01–2.19 (m, 1 H), 2.81 (d, *J* = 7.2 Hz, 1 H, NH), 3.38 (d, *J* = 7.6 Hz, 1 H), 3.76 (dd, *J* = 9.3, 7.6 Hz, 1 H), 3.83 (s, 3 H, OCH_3), 4.72 (dd, *J* = 9.2, 7.1 Hz, 1 H), 7.01–7.10 (m, 2 H, ArH), 7.25–7.48 (m, 8 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.2 (CH_3), 24.4 (CH_3), 24.7 (CH), 43.2 (CH_2), 50.3 (CH), 52.5 (CH_3), 56.4 (CH), 62.3 (CH), 70.5 (C), 126.1, 127.2, 128.5, 128.6, 128.7, 129.1, 131.6, 137.1 (CH_{Ar} and C_{Ar}), 172.8 (C=O), 173.8 (C=O), 174.8 (C=O).

MS (EI): *m*/*z* (%) = 350 ($M^+ - C_4H_9$, 21), 349 (50), 347 (100), 233 (16), 202 (10), 190 (50), 170 (11), 147 (11), 143 (13), 130 (14), 115 (10), 103 (15).

HRMS (DIP): *m*/*z* [M^+] calcd for $C_{24}H_{26}N_2O_4$: 406.1893; found: 406.1905.

Methyl 6a-Isobutyl-4,6-dioxo-2,5-diphenyloctahydropyrrolo[3,4-*b*]pyrrole-3-carboxylate (5b)

After 36 h and workup, the product was isolated by column chromatography (silica gel deactivated with 5% Et_3N; eluent: *n*-hexane/EtOAc 8:2) as a sticky yellow oil; yield: 211 mg (52%).

IR (ATR): 29254, 2922, 1709, 1495, 1378, 1235, 1191, 734, 702, 690, 617, 586 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.98 (d, *J* = 6.5 Hz, 3 H), 1.07 (d, *J* = 6.5 Hz, 3 H), 1.79–1.98 (m, 2 H), 2.10–2.19 (m, 1 H), 3.64 (dd, *J* = 4.7, 3.3 Hz, 1 H), 3.76 (d, *J* = 3.3 Hz, 1 H), 3.79 (s, 3 H, OCH_3), 4.79 (d, *J* = 4.7 Hz, 1 H), 6.80–6.90 (m, 2 H, ArH), 7.23–7.67 (m, 8 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.4 (CH_3), 24.3 (CH_3), 25.6 (CH), 43.2 (CH_2), 51.2 (CH), 52.9 (CH_3), 54.7 (CH), 65.8 (CH), 69.9 (C), 126.4, 128.1, 128.8, 128.9, 129.1, 131.8 (CH_{Ar} and C_{Ar}), 173.1 (C=O), 175.9 (C=O), 178.2 (C=O).

MS (EI): *m*/*z* (%) = 350 ($M^+ - C_4H_9$, 36), 318 (13), 200 (94), 191 (20), 177 (100), 171 (13), 144 (21), 143 (14), 119 (14), 91 (21).

HRMS (DIP): *m*/*z* [M^+] calcd for $C_{24}H_{26}N_2O_4$: 406.1893; found: 406.1868.

Methyl 1-Isobutyl-4,6-dioxo-5-phenyl-3-(pyridin-2-yl)octahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (4c)

After 18 h and workup, the product was isolated by column chromatography (*n*-hexane/EtOAc 6:4) as a white solid; yield: 350 mg (86%); mp 171–175 °C.

IR (ATR): 1705.7, 1387, 1248, 1207, 1151, 1181, 764, 728, 691 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.6 Hz, 3 H), 1.01 (d, *J* = 6.7 Hz, 3 H), 1.69 (dd, *J* = 14.1, 4.7 Hz, 1 H), 1.81–1.97 (m, 1 H), 2.16 (m, 1 H), 3.46 (d, *J* = 7.6 Hz, 1 H), 3.70 (dd, *J* = 9.0, 7.6 Hz, 1 H), 3.86 (s, 3 H, OCH_3), 4.70 (d, *J* = 9.0 Hz, 1 H), 7.02–7.25 (m, 3 H, ArH), 7.30–7.49 (m, 4 H, ArH), 7.68–7.73 (m, 1 H, ArH), 8.34–8.65 (m, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.1 (CH_3), 24.4 (CH_3), 25.0 (CH), 44.3 (CH_2), 51.7 (CH), 52.6 (CH_3), 58.5 (CH), 65.0 (CH), 72.2 (C), 123.7, 123.9, 126.6, 128.7, 129.1, 131.9, 136.9, 149.4, 155.5 (CH_{Ar} and C_{Ar}), 172.33 (C=O), 174.5 (C=O) 174.8 (C=O).

MS (EI): *m*/*z* (%) = 408 (M^+, 12), 407 (47), 351 (14), 350 (24), 349 (23), 348 (100), 177 (10), 175 (41), 171 (17), 145 (18), 131 (13).

HRMS (DIP): *m*/*z* [M^+] calcd for $C_{23}H_{25}N_3O_4$: 407.1845; found: 407.1851.

Methyl 6a-Isobutyl-4,6-dioxo-5-phenyl-2-(pyridin-2-yl)octahydropyrrolo[3,4-*b*]pyrrole-3-carboxylate (5c)

After 37 h and workup, the product was isolated by column chromatography (silica gel deactivated with 5% Et_3N; eluent: *n*-hexane/EtOAc 6:4) as a sticky yellow oil; yield: 157 mg (40%).

IR (ATR): 3321, 2957, 2925, 1709, 1593, 1375, 1191, 1138, 749, 690, 599 cm^{-1}.

^1H NMR (300 MHz, MeOD): δ = 0.94 (d, *J* = 6.5 Hz, 3 H), 1.02 (d, *J* = 6.6 Hz, 3 H), 1.72–1.99 (m, 2 H), 2.02–2.23 (m, 1 H), 3.79–3.83 (m, 1 H), 3.93 (d, *J* = 2.7 Hz, 1 H), 4.93 (d, *J* = 3.3 Hz, 1 H), 6.73–6.94 (m, 2 H, ArH), 7.20–7.43 (m, 4 H, ArH), 7.60 (d, *J* = 7.9 Hz, 1 H, ArH), 7.69–7.74 (m, 1 H, ArH), 8.40–8.46 (m, 1 H, ArH).

^{13}C NMR (75 MHz, MeOD): δ = 24.0 (CH_3), 24.7 (CH_3), 26.5 (CH), 45.4 (CH_2), 53.5 (CH), 57.4 (CH), 68.3 (CH), 71.8 (C), 122.9, 123.8, 127.5, 129.6, 129.9, 133.3, 138.7, 149.8, 162.5 (CH_{Ar} and C_{Ar}), 178.6 (C=O), 178.6 (C=O), 181.0 (C=O).

MS (EI): *m*/*z* (%) = 348 (M – CHO_2, 14), 228 (100), 227 (36), 171 (24), 145 (36), 119 (56), 92 (43), 91 (25), 77 (22), 44 (14).

HRMS (DIP): *m*/*z* [M – CHO_2] calcd for $C_{21}H_{22}N_3O_2$: 348.1692; found: 348.1712.

Methyl 1-Isobutyl-4,6-dioxo-5-phenyl-3-(thiophen-2-yl)octahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (4d)

After 19 h and workup, the product was isolated by column chromatography (*n*-hexane/EtOAc; 6:4) as a pale red solid; yield: 301 mg (73%); mp 139–143 °C.

IR (ATR): 1710, 1501, 1384, 1236, 1208, 1177, 1164, 822, 701, 692 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.4 Hz, 3 H), 1.01 (d, *J* = 6.4 Hz, 3 H), 1.61–1.75 (m, 2 H), 2.03–2.24 (m, 1 H), 3.37 (d, *J* = 7.6 Hz, 1 H), 3.59 (dd, *J* = 9.2, 7.6 Hz, 1 H), 3.85 (s, 3 H, OCH_3), 5.00 (d, *J* = 9.1 Hz, 1 H), 7.01 (dd, *J* = 5.1, 3.6 Hz, 1 H, ArH), 7.11–7.43 (m, 7 H, ArH).

^{13}C NMR (101 MHz $CDCl_3$): δ = 22.1 (CH_3), 24.3 (CH_3), 24.4 (CH), 43.0 (CH_2), 50.1 (CH), 52.4 (CH_3), 55.5 (CH), 57.9 (CH), 70.0 (C), 125.1, 125.4, 126.2, 127.1, 128.5, 129.0, 131.6, 141.1 (CH_{Ar} and C_{Ar}), 172.3 (C=O), 173.3 (C=O), 174.6 (C=O).

MS (EI): *m*/*z* (%) = 369 (M – C_3H_7, 2), 357 (5), 356 (22), 355 (34), 354 (23), 353 (100), 296 (11), 239 (45), 206 (10), 197 (9), 196 (80), 179 (26), 162 (11), 149 (12) 136 (17), 109 (15).

HRMS (DIP): *m*/*z* [M^+] calcd for $C_{22}H_{24}N_2O_4S$: 412.1457; found: 412.1469.

Methyl 6a-Isobutyl-4,6-dioxo-5-phenyl-2-(thiophen-2-yl)octahydropyrrolo[3,4-*b*]pyrrole-3-carboxylate (5d)

After 36 h and workup, the product was isolated by column chromatography (silica gel deactivated with 5% Et_3N; *n*-hexane/EtOAc; 6:4) as a sticky yellow oil; yield: 175 mg (44%).

IR (ATR): 3340, 2956, 2926, 1708, 1378, 1198, 1139, 843, 689, 597 cm^{-1}.

^1H NMR (300 MHz, MeOD): δ = 0.95 (d, *J* = 6.4 Hz, 3 H), 1.04 (d, *J* = 6.4 Hz, 3 H), 1.71–2.00 (m, 2 H), 2.03–2.16 (m, 1 H), 3.66 (dd, *J* = 4.7, 2.2 Hz, 1 H), 3.89 (d, *J* = 2.3 Hz, 1 H), 5.05 (m, 1 H), 6.76–6.69 (m, 2 H, ArH), 6.92 (dd, *J* = 5.1, 3.5 Hz, 1 H, ArH), 6.98 (d, *J* = 3.5 Hz, 1 H, ArH), 7.25–7.43 (m, 4 H, ArH).

^{13}C NMR (75 MHz MeOD): δ = 23.9 (CH_3), 24.7 (CH_3), 26.5 (CH), 44.7 (CH_2), 52.5 (CH), 53.5 (CH), 63.7 (CH), 71.9 (C), 121.0, 125.0, 126.2, 127.8, 128.2, 129.8, 133.3, 150.5 (CH_{Ar} and C_{Ar}), 178.6 (2 × C=O), 181.0 (C=O).

MS (EI): *m*/*z* (%) = 310 (M – $C_4H_8O_2$, 2%), 278 (11), 277 (11), 251 (14), 209 (15), 207 (15), 206 (100), 183 (23), 169 (80), 150 (19), 149 (17).

HRMS (DIP): *m*/*z* [M^+] calcd for $C_{22}H_{24}N_2O_4S$: 412.1457; found: 412.1452.

Methyl 1-Benzyl-4,6-dioxo-3,5-diphenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (4e)

After 18 h and workup, the product was isolated by column chromatography (*n*-hexane/EtOAc 8:2) as a white solid; yield: 356 mg (81%); mp 231–234 °C.

IR (ATR): 1750, 1716, 1493, 1380, 1209, 1178, 1101, 853, 724, 703, 661 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.35 (br s,1 H, NH), 3.11 (d, *J* = 13.5 Hz, 1 H), 3.49 (d, *J* = 13.3 Hz, 1 H), 3.61 (d, *J* = 7.6 Hz, 1 H), 3.70 (dd, *J* = 9.4, 7.6 Hz, 1 H), 3.86 (s, 3 H, OCH_3), 4.96 (d, *J* = 9.4 Hz, 1 H), 6.94–7.05 (m, 2 H, ArH), 7.11–7.18 (m, 2 H, ArH), 7.25–7.41 (m, 9 H, ArH), 7.48–7.57 (m, 2 H, ArH).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 40.4 (CH_2), 49.15 (CH), 52.4 (CH_3), 54.3 (CH), 61.3 (CH), 71.3 (C), 126.1, 127.4, 127.6, 128.5, 128.6, 128.6, 128.9, 129.0, 129.5, 131.4, 134.8, 137.2 (CH_{Ar} and C_{Ar}), 171.5 (C=O), 173.8 (C=O), 174.9 (C=O).

MS (EI): *m*/*z* (%) = 381 (M – $C_2H_3O_2$, 3), 350 (22), 349 (100), 202 (14), 170 (13), 143 (11), 91 (15).

HRMS (DIP): *m*/*z* [M^+] calcd for $C_{27}H_{24}N_2O_4$: 440.1736; found: 440.1755.

Methyl 6a-Benzyl-4,6-dioxo-2,5-diphenyloctahydropyrrolo[3,4-*b*]pyrrole-3-carboxylate (5e)

After 37 h and workup, the product was isolated by column chromatography (silica gel deactivated with 5% Et_3N; eluent: *n*-hexane/EtOAc 8:2); as a sticky yellow oil; yield: 194 mg (44%).

IR (ATR): 2918, 2849, 1711, 1455, 1377, 1259, 1173, 1028, 732, 700, 691, 587 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.16 (d, *J* = 12.8 Hz, 1 H), 3.63 (d, *J* = 12.8 Hz, 1 H), 3.67 (dd, *J* = 4.0, 2.9 Hz, 1 H), 3.77 (d, *J* = 2.9 Hz, 1 H), 3.83 (s, 3 H, OCH_3), 4.88 (d, *J* = 4.0 Hz, 1 H), 6.37–6.60 (m, 2 H, ArH), 7.27–7.36 (m, 11 H, ArH), 7.39–7.45 (m, 2 H, ArH).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 40.7 (CH_2), 50.3 (CH), 53.0 (CH_3), 54.2 (CH), 66.4 (CH), 71.6 (C), 126.4, 126.5, 127.8, 128.2, 128.8, 129.0, 129.1, 130.5, 131.6, 134.9 (CH_{Ar} and C_{Ar}), 173.1 (C=O), 175.3 (C=O), 178.0 (C=O).

MS (EI): *m*/*z* (%) = 349 (M – C_7H_7, 14), 317 (39), 289 (35), 234 (21), 178 (12), 177 (100), 170 (19), 143 (12), 115 (16), 91 (43).

HRMS (DIP): *m*/*z* [M^+] calcd for $C_{27}H_{24}N_2O_4$: 440.1736; found: 440.1697.

Methyl 1-Benzyl-4,6-dioxo-5-phenyl-3-(pyridin-2-yl)octahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (4f)

After 18 h and workup, the product was isolated by column chromatography (*n*-hexane/EtOAc; 6:4) as a white solid; yield: 388 mg (87%); mp 197–200 °C.

IR (ATR): 1710, 1495, 1395, 1212, 1137, 1104, 1090, 859, 767, 729 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.11 (d, *J* = 13.7 Hz, 1 H), 3.42 (d, *J* = 13.7 Hz, 1 H), 3.63–3.77 (m, 2 H), 3.85 (s, 3 H, OCH_3), 4.83 (d, *J* = 8.9 Hz, 1 H), 7.04–7.16 (m, 2 H, ArH), 7.20–7.47 (m, 10 H, ArH), 7.66 (td, *J* = 7.7, 1.8 Hz, 1 H, ArH), 8.53 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1 H, ArH).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 42.0 (CH_2), 51.4 (CH), 52.7 (CH_3), 57.1 (CH), 64.8 (CH), 73.5 (C), 123.6, 123.7, 126.5, 127.3, 128.5, 128.7, 129.1, 130.2, 131.8, 135.8, 136.9, 149.3, 156.0 (CH_{Ar} and C_{Ar}), 171.1 (C=O), 174.3 (C=O), 174.9 (C=O).

MS (EI): *m*/*z* (%) = 382 (M – $C_2H_3O_2$, 0.5%), 351 (21), 350 (100), 193 (4), 177 (17), 171 (23), 145 (23), 143 (4), 117 (6), 116 (5), 91 (13).

HRMS (DIP): *m*/*z* [M^+] calcd for $C_{26}H_{23}N_3O_4$: 441.1689; found: 441.1669.

Methyl 6a-Benzyl-4,6-dioxo-5-phenyl-2-(pyridin-2-yl)octahydropyrrolo[3,4-*b*]pyrrole-3-carboxylate (5f)

After 36 h and workup, the product was isolated by column chromatography (silica gel deactivated with 5% Et_3N; *n*-hexane/EtOAc 6:4) as a sticky yellow oil; yield: 238 mg (54%).

IR (ATR): 2923, 2853, 1709, 1592, 1378, 1178, 1051, 744, 702, 590 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.18 (d, *J* = 12.8 Hz, 1 H), 3.60 (d, *J* = 12.9 Hz, 1 H), 3.87 (s, 3 H, OCH_3), 3.89 (d, *J* = 2.0 Hz, 1 H), 4.11–4.15 (m, 1 H), 5.04 (d, *J* = 2.7 Hz, 1 H), 6.48–6.70 (m, 2 H, ArH), 6.90–7.53 (m, 9 H, ArH), 7.54 (d, *J* = 7.8 Hz, 1 H, ArH), 7.66–7.77 (m, 1 H, ArH), 8.49 (ddd, *J* = 4.9 Hz, 1 H, ArH).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 41.8 (CH_2), 49.9 (CH), 52.5 (CH), 53.19 (CH_3), 67.1 (CH), 72.3 (C), 121.6, 123.1, 126.1, 127.7, 128.6, 128.9, 130.4, 131.5, 135.0, 138.0, 148.7, 159.2 (CH_{Ar} and C_{Ar}), 173.1 (C=O), 175.2 (C=O), 178.3 (C=O).

MS (EI): *m*/*z* (%) = 382 (M^+ – $C_2H_3O_2$, 51), 350 (100), 235 (14), 177 (19), 171 (22), 145 (24), 119 (28), 117 (19), 93 (21), 92(22), 91 (52), 78 (14), 44 (23).

HRMS (DIP): *m*/*z* [M^+] calcd for $C_{26}H_{23}N_3O_4$: 441.1689; found: 441.1698.

Methyl (1*S*,3*R*)-1-[(1*H*-Indol-3-yl)methyl]-5-methyl-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (4gb)

After 26 h and workup, the product crystallized as colorless prisms; yield: 317 mg (76%); mp 232–234 °C (dec.).

IR (ATR): 3358, 2981, 2884, 1776, 1732, 1685, 1440, 1387, 1285, 1200, 1103, 1078, 963, 843, 727, 701, 654 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.36 (d, *J* = 5.02 Hz, 1 H, NH), 2.66 (s, 3 H, NCH_3), 3.34 (d, *J* = 14.50 Hz, 1 H), 3.44 (d, *J* = 14.56 Hz, 1 H), 3.62 (d, *J* = 7.40 Hz, 1 H), 3.69 (s, 3 H, OCH_3), 3.74 (dd, *J* = 9.20, 7.64 Hz, 1 H), 5.00 (dd, *J* = 9.40, 5.16 Hz, 1 H), 7.36–6.96 (m, 9 H, ArH), 7.55 (d, *J* = 7.88 Hz, 1 H, ArH), 10.98 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 24.2, 30.2, 49.0, 51.5, 53.78, 59.7, 70.2, 107.9, 111.4, 118.1, 118.5, 120.9, 124.3, 127.3 (2 C), 127.4, 127.5, 127.9 (2 C), 135.9, 139.1, 171.7 (C=O), 174.9 (C=O), 176.1 (C=O).

MS (ESI, M + H$^+$): *m*/*z* = 418.3 (M + H$^+$, 100%).

HRMS (DIP): *m*/*z* [M$^+$] calcd for $C_{24}H_{23}N_3O_4$: 417.1694; found: 417.1689.

Methyl (1*S*,3*R*)-1-[(1*H*-Indol-3-yl)methyl]-4,6-dioxo-5-phenyl-3-(pyridin-2-yl)octahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (4gc)

After 26 h and workup, the product was crystallized as colorless prisms; yield: 384 mg (80%); mp 231–233 °C (dec.).

IR (ATR): 3381, 3350, 3061, 2959, 2878, 1779, 1707, 1614, 1591, 1489, 1435, 1384, 1323, 1204, 1178, 1101, 739, 686 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.30 (d, *J* = 14.60 Hz, 1 H), 3.47 (d, *J* = 14.68 Hz, 1 H), 3.68 (s, 3 H, OCH_3), 3.79 (d, *J* = 11.24 Hz, 1 H, NH), 3.89 (d, *J* = 7.60 Hz, 1 H), 3.97 (dd, *J* = 9.16, 7.64 Hz, 1 H), 5.16 (dd, *J* = 11.22, 9.26 Hz, 1 H), 7.85–6.97 (m, 13 H, ArH), 8.59–8.57 (m, 1 H, ArH), 10.86 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 31.1, 51.4, 51.8, 57.4, 63.4, 70.0, 109.2, 111.2, 118.2, 120.6, 123.3, 123.9, 124.3, 126.7 (2 C), 128.1, 128.2, 128.8 (2 C), 132.2, 135.6, 136.8, 148.8, 156.4, 171.7 (C=O), 174.4 (C=O), 175.2 (C=O).

MS (ESI, M + H$^+$): *m*/*z* = 481.2 (M + H$^+$, 100%).

HRMS (DIP): *m*/*z* [M$^+$] calcd for $C_{28}H_{24}N_4O_4$: 480.1798; found: 480.1702.

Methyl (1*S*,3*R*)-1-[(1*H*-Indol-3-yl)methyl]-5-methyl-4,6-dioxo-3-(pyridin-2-yl)octahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (4gd)

After 26 h and workup, the product was crystallized as colorless prisms; yield: 313 mg (75%); mp 229–231 °C (dec.).

IR (ATR): 3359, 3300, 2981, 1774, 1735, 1682, 1595, 1443, 1289, 1224, 1095, 995, 727 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.61 (s, 3 H, NCH_3), 3.21 (d, *J* = 14.84 Hz, 1 H), 3.39 (d, *J* = 14.92 Hz, 1 H), 3.55 (d, *J* = 11.12 Hz, 1 H, NH), 3.65 (d, *J* = 7.48 Hz, 1 H), 3.67 (s, 3 H, OCH_3), 3.97 (dd, *J* = 9.14, 7.54 Hz, 1 H), 5.02 (dd, *J* = 11.04, 9.32 Hz, 1 H), 7.78–6.92 (m, 8 H, ArH), 8.49–8.44 (m, 1 H, ArH), 10.82 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 24.3, 30.9, 51.3, 51.8, 57.0, 62.9, 72.6, 109.1, 111.1, 118.2, 188.5, 120.6, 123.0, 123.7, 124.2, 128.0, 135.5, 136.6, 148.7, 156.4, 171.7 (C=O), 175.2 (C=O), 176.0 (C=O).

MS (ESI, M + H$^+$): *m*/*z* = 419.2 (M + H$^+$, 100%).

HRMS (DIP): *m*/*z* [M$^+$] calcd for $C_{23}H_{22}N_4O_4$: 418.1641; found: 418.1642.

Methyl (1*S*,3*R*)-1-[(1*H*-Indol-3-yl)methyl]-3-(3-chlorophenyl)-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (4ge)

After 26 h and workup, the product was crystallized as colorless prisms; yield: 349 mg (68%); mp 273–275 °C (dec.).

IR (ATR): 3335, 2981, 1779, 1708, 1598, 1573, 1433, 1385, 1202, 1181, 1100, 954, 748, 689 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.69 (d, *J* = 4.36 Hz, 1 H, NH), 3.35 (d, *J* = 14.52 Hz, 1 H), 3.50 (d, *J* = 14.56 Hz, 1 H), 3.66 (s, 3 H, OCH_3), 3.83 (dd, *J* = 7.56, 1.60 Hz, 1 H), 3.91 (dd, *J* = 9.48, 7.64 Hz, 1 H), 5.14 (dd, *J* = 9.46, 4.50 Hz, 1 H), 7.58–6.98 (m, 9 H, ArH), 11.02 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 30.3, 48.7, 51.5, 53.7, 59.0, 70.3, 107.6, 111.4, 118.0, 118.5, 121.0, 124.6, 126.4, 126.5 (2 C), 127.1, 127.5 (2 C), 128.2, 128.8 (2 C), 129.8, 132.0, 132.7, 135.9, 142.0, 171.6 (C=O), 174.0 (C=O), 175.3 (C=O).

MS (ESI, M + H$^+$): *m*/*z* (%) = 512.2 (M – H$^+$, 100), 514.2 (M + H$^+$, 35).

HRMS (DIP): *m*/*z* [M$^+$] calcd for $C_{29}H_{24}ClN_3O_4$: 513.1455; found: 513.1442.

Methyl (1*S*,3*R*)-1-[(1*H*-Indol-3-yl)methyl]-3-(3-chlorophenyl)-5-methyl-4,6-dioxooctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (4gf)

After 26 h and workup, the product was crystallized as colorless prisms; yield: 307 mg (68%); mp 251–253 °C (dec.).

IR (ATR): 3339, 3324, 3062, 2949, 2926, 1782, 1704, 1672, 1426, 1290, 1203, 1099, 1081,755, 748 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.66 (s, 3 H, NCH_3), 3.29 (d, *J* = 14.56 Hz, 1 H), 3.45 (d, *J* = 14.60 Hz, 1 H), 3.62 (dd, *J* = 7.40, 1.32 Hz, 1 H), 3.68 (s, 3 H, OCH_3), 3.75 (dd, *J* = 9.30, 7.54 Hz, 1 H), 5.01 (dd, *J* = 9.38, 4.66 Hz, 1 H), 7.54–6.96 (m, 9 H, ArH), 10.99 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 24.2, 30.2, 48.7, 51.5, 53.4, 58.8, 70.1, 107.7, 111.4, 118.0, 118.5, 121.0, 124.5, 126.0, 127.3, 127.4, 127.9, 129.7, 132.5, 135.9, 142.0, 171.5 (C=O), 174.9 (C=O), 176.0 (C=O).

MS (ESI, M + H$^+$): *m*/*z* (%) = 452.2 (M + H$^+$, 100), 454.2 (M + H$^+$, 35).

HRMS (DIP): *m*/*z* [M$^+$] calcd for $C_{24}H_{22}ClN_3O_4$: 451.1299; found: 451.1293.

Methyl (1*S*,3*R*)-1-[(1*H*-Indol-3-yl)methyl]-3-(4-chlorophenyl)-5-ethyl-4,6-dioxooctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (4gg)

After 26 h and workup, the product was crystallized as colorless prisms; yield: 340 mg (73%); mp 237–239 °C (dec.).

IR (ATR): 3339, 2981, 2944, 2840, 1774 (C=O), 1739 (C=O), 1683 (C=O), 744 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.91(t, *J* = 7.16 Hz, 3 H, CH_2CH_3), 2.42 (d, *J* = 3.56 Hz, 1 H), 3.44 (s, 1 H, NH), 3.25–3.13 (m, 2 H and NH), 3.30 (d, *J* = 14.56 Hz, 1 H), 3.43 (d, *J* = 14.6 Hz, 1 H), 3.60 (d, *J* = 7.48 Hz, 1 H, $CHHCH_3$), 3.68 (s, 3 H, OCH_3), 3.72 (d, *J* = 7.6 Hz, 1 H, $CHHCH_3$), 5.02 (dd, *J* = 4.68, 9.4 Hz, 1 H), 7.17–6.96 (m, 3 H, ArH), 7.35–7.33 (m, 5 H, Ar*H*), 7.54 (d, *J* = 7.88 Hz, 1 H, ArH), 11.00 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 138.1, 135.9, 131.8, 129.2 (2 C), 127.7 (2 C), 127.5, 124.4, 120.9, 118.5, 118.0, 111.4, 107.8, 70.2, 58.8, 53.4, 51.5, 48.5, 32.9, 30.2, 12.7, 30.2, 32.9, 48.5, 51.5, 53.4, 58.8, 70.2, 107.8, 111.4, 118.0, 118.5, 120.9, 124.4, 127.5, 127.7 (2C), 129.2 (2C), 131.8, 135.9, 138.1, 171.5 (C=O), 174.6 (C=O), 175.7 (C=O).

MS (ESI, M + H$^+$): *m*/*z* (%) = 466.3 (M$^+$, 100, Cl: 35)/468.3 (M$^+$, 33.3, Cl: 37) [3:1], 467.3 (M + 1, 100, Cl: 35)/469.3 (M + 1, 33.3, Cl: 37) [3:1].

HRMS (DIP): *m*/*z* [M$^+$] calcd for $C_{25}H_{24}ClN_3O_4$: 465.1451; found: 465.1455.

Methyl (2*S*,3*S*,6a*R*)-6a-[(1*H*-Indol-3-yl)methyl]-5-methyl-4,6-dioxo-2-phenyloctahydropyrrolo[3,4-*b*]pyrrole-3-carboxylate (5gb)

After 36 h and workup, the product was isolated and crystallized as colorless prisms; yield: 400 mg (96%); mp 151–153 °C.

IR (ATR): 3355, 3059, 2981, 2889, 1710, 1595, 1495, 1436, 1383, 1195, 1011, 744 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.59 (s, 3 H, NCH_3), 3.12 (dd, J = 6.18, 5.14 Hz, 1 H), 3.22 (d, J = 14.24 Hz, 1 H), 3.42 (d, J = 14.20 Hz, 1 H), 3.50 (d, J = 4.96 Hz, 1 H), 3.54 (s, 3 H, OCH_3), 4.06 (d, J = 5.36 Hz, 1 H, NH), 4.66 (dd, J = 5.90, 5.90 Hz, 1 H), 7.40–7.02 (m, 9 H, ArH), 7.70 (d, J = 7.76 Hz, 1 H, ArH), 11.00 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 24.4, 28.8, 51.1, 52.1, 54.1, 65.3, 70.9, 107.6, 111.5, 118.2, 118.6, 121.0, 121.0, 124.7, 125.2, 126.2, 127.3, 127.4, 125.2, 126.2, 127.3, 127.4, 130.0,132.9, 135.9, 143.9, 171.5 (C=O), 176.1 (C=O), 178.9 (C=O).

MS (ESI, M + H$^+$): m/z = 417.4 (M + H$^+$, 100%).

HRMS (DIP): m/z [M$^+$] calcd for $C_{24}H_{23}N_3O_4$: 417.1694; found: 417.1688.

Methyl (2*S*,3*S*,6a*R*)-6a-[(1*H*-Indol-3-yl)methyl)-4,6-dioxo-5-phenyl-2-(pyridin-2-yl)octahydropyrrolo[3,4-*b*]pyrrole-3-carboxylate (5gc)

After 36 h and workup, the product was crystallized as colorless prisms; yield: 441 mg (92%); mp 219–221 °C (dec.).

IR (ATR): 3352, 3058, 2981, 1712, 1595, 1541, 1436, 1383, 1099, 744 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.39–3.30 (m, 2 H), 3.43 (s, 3 H, OCH_3), 3.67–3.60 (m, 2 H), 4.45 (dd, J = 8.24, 8.20 Hz, 1 H), 7.80–6.94 (m, 13 H, ArH), 8.72 (br d, J = 4.16 Hz, 1 H, ArH), 10.91 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.2, 51.1, 52.3, 66.9, 72.5, 107.5, 111.6, 118.3, 118.7, 121.1, 121.3, 122.5, 124.7, 126.1 (2 C), 127.4, 128.2, 128.6 (2 C), 131.6, 136.0, 136.9, 148.6, 160.2, 172.7 (C=O), 175.1 (C=O), 178.8 (C=O).

MS (ESI, M + H$^+$): m/z = 481.2 (M + H$^+$, 100%).

HRMS (DIP): m/z [M$^+$] calcd for $C_{28}H_{24}N_4O_4$: 480.1798; found: 480.1704.

Methyl (2*S*,3*S*,6a*R*)-6a-[(1*H*-Indol-3-yl)methyl]-5-methyl-4,6-dioxo-2-(pyridin-2-yl)octahydropyrrolo[3,4-*b*]pyrrole-3-carboxylate (5gd)

After 36 h and workup, the product was crystallized as colorless prisms; yield: 355 mg (85%); mp 198–200 °C (dec.).

IR (ATR): 3355, 2981, 2972, 2889, 1975, 1774, 1698, 1520, 1432, 1380, 1251, 1150, 1073, 955, 775, 741 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.33 (s, 3 H, NCH_3), 3.15 (d, J = 14.08 Hz, 1 H), 3.39 (d, J = 14.08 Hz, 1 H), 3.47 (d, J = 2.64 Hz, 1 H), 3.57 (s, 3 H, OCH_3), 3.79 (dd, J = 3.01, 2.76 Hz, 1 H), 4.07 (d, J = 5.36 Hz, 1 H, NH), 4.78 (dd, J = 4.74, 3.34 Hz, 1 H), 7.47–6.99 (m, 6 H, ArH), 7.75–7.67 (m, 2 H, ArH), 8.40–8.38 (m, 1 H, ArH), 10.97 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.9, 148.5, 136.6, 135.8, 127.4, 124.6, 122.3, 121.0, 120.9, 118.6, 118.1, 111.5, 107.6, 72.1, 66.7, 52.2, 51.7, 50.8, 29.5, 24.1, 29.5, 50.8, 51.7, 52.2, 66.7, 72.1, 107.6, 111.5, 118.1, 118.6, 120.9, 121.0, 122.3, 124.6, 127.4, 135.8, 136.6, 148.5, 159.9, 172.5 (C=O), 176.1 (C=O), 179.5 (C=O).

MS (ESI, M + H$^+$): m/z = 419.2 (M + H$^+$, 100%).

HRMS (DIP): m/z [M$^+$] calcd for $C_{23}H_{22}N_4O_4$: 418.1641; found: 418.1649.

Methyl (2*S*,3*S*,6a*R*)-6a-[(1*H*-Indol-3-yl)methyl]-2-(3-chlorophenyl)-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-*b*]pyrrole-3-carboxylate (5ge)

After 36 h and workup, the product was crystallized as colorless prisms; yield: 503 mg (98%); mp 169–171 °C.

IR (ATR): 3315, 3060, 2983, 2950, 1782, 1739, 1703, 1595, 1436, 1392, 1253, 1240, 1164, 981, 747 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.30 (d, J = 14.18 Hz, 1 H), 3.43 (dd, J = 5.42, 4.48 Hz, 1 H), 3.55 (d, J = 14.12 Hz, 1 H), 3.58 (s, 3 H, OCH_3), 3.72 (d, J = 4.44 Hz, 1 H), 4.24 (d, J = 5.48 Hz, 1 H, NH), 4.78 (dd, J = 5.42, 5.42 Hz, 1 H), 7.53–6.64 (m, 13 H, ArH), 7.75 (d, J = 7.80 Hz, 1 H, ArH), 11.08 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 30.5, 52.5, 52.8, 55.9, 66.6, 72.7, 109.3, 112.4, 119.6, 120.0, 122.5, 125.8, 126.0, 127.4, 127.5 (2 C), 128.4, 128.7, 129.1, 129.4 (2 C), 131.0, 133.3, 134.8, 137.5, 145.3, 173.1 (C=O), 176.3 (C=O), 179.1 (C=O).

MS (ESI, M – H$^+$): m/z (%) = 512.2 (M – H$^+$, 100), 514.2 (M + H$^+$, 35).

HRMS (DIP): m/z [M$^+$] calcd for $C_{29}H_{24}ClN_3O_4$: 513.1455; found: 513.1450.

Methyl (2*S*,3*S*,6a*R*)-6a-[(1*H*-Indol-3-yl)methyl]-2-(3-chlorophenyl)-5-methyl-4,6-dioxooctahydropyrrolo[3,4-*b*]pyrrole-3-carboxylate (5gf)

After 26 h and workup, the product was crystallized as colorless prisms; yield: 429 mg (95%); mp 152–154 °C.

IR (ATR): 3344, 3270, 3060, 2982, 2949, 1780, 1737, 1705, 1378, 1288, 1173, 747, 681 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.59 (s, 3 H, NCH_3), 3.13 (dd, J = 6.36, 4.96 Hz, 1 H), 3.22 (d, J = 14.20 Hz, 1 H)), 3.43 (d, J = 14.20 Hz, 1 H), 3.50 (d, J = 4.88 Hz, 1 H), 3.54 (s, 3 H, OCH_3), 4.06 (d, J = 5.28 Hz, 1 H, NH), 4.66 (dd, J = 5.68, 5.68 Hz, 1 H), 7.40–7.02 (m, 8 H, ArH), 7.70 (d, J = 7.76 Hz, 1 H, ArH), 11.00 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 24.1, 28.8, 51.1, 52.1, 54.1, 65.3, 70.9, 107.6, 111.5, 118.2, 118.6, 121.0, 124.7, 125.2, 126.2, 127.3, 127.4, 130.0, 132.9, 135.9, 143.9, 171.5 (C=O), 176.1 (C=O), 178.8 (C=O).

MS (ESI, M + H$^+$): m/z (%) = 452.2 (M + H$^+$, 100), 454.2 (M + H$^+$, 35).

HRMS (DIP): m/z [M$^+$] calcd for $C_{24}H_{22}ClN_3O_4$: 451.1299; found: 451.1301.

Methyl (2*S*,3*S*,3a*S*,6a*R*)-6a-[(1*H*-Indol-3-yl)methyl]-1-(benzoylcarbamothioyl)-4,6-dioxo-2,5-diphenyloctahydropyrrolo[3,4-*b*]pyrrole-3-carboxylate (6ga)

After 24 h and workup, the product was crystallized as pale yellow prisms; 552 mg (86%); mp 150–152 °C.

IR (ATR): 3202, 3060, 2981, 2889, 1787, 1739, 1702, 1537, 1492, 1389, 1252, 1202, 923, 743, 704 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.78 (s, 3 H, OCH_3), 3.46 (dd, J = 1.76, 1.76 Hz, 1 H), 3.91 (br s, 2 H), 4.22 (d, J = 1.44 Hz, 1 H), 6.80 (br s, 1 H), 7.72–7.00 (m, 17 H, ArH), 8.11 (d, J = 7.40 Hz, 2 H, ArH), 11.33 (br s, 1 H, NH), 11.60 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d6): δ = 26.7, 50.1, 51.5, 54.2, 69.2, 74.2, 104.5, 111.4, 118.1, 118.8, 121.1, 125.1 (2 C), 126.2, 126.5 (2 C), 127.3, 127.8, 127.8 (2 C), 128.8 (2 C), 129.0 (2 C), 129.6 (2 C), 129.2, 130.8, 133.0, 133.3, 135.4, 138.5, 165.1 (C=O), 168.7 (C=O), 173.9 (C=O), 176.4 (C=O), 179.7 (C=S).

MS (ESI, M + H$^+$): m/z = 643.2 (M + H$^+$, 100%).

HRMS (DIP): m/z [M$^+$] calcd for $C_{37}H_{30}N_4O_5S$: 642.1937; found: 642.1930.

Methyl (2*S*,3*S*,3a*S*,6a*R*)-6a-[(1*H*-Indol-3-yl)methyl]-1-(benzoylcarbamothioyl)-5-methyl-4,6-dioxo-2-phenyloctahydropyrrolo[3,4-*b*]pyrrole-3-carboxylate (6gb)

After 24 h and workup, the product was crystallized as pale yellow prisms; 516 mg (89%); mp 207–209 °C.

IR (ATR): 3267, 3187, 3060, 3027, 2885, 1786, 1741, 1686, 1546, 1445, 1225, 955, 703 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.75 (s, 3 H, NCH_3), 2.81 (s, 3 H, OCH_3), 3.24 (dd, *J* = 2.16, 2.16 Hz, 1 H), 3.76 (br s, 2 H), 3.97 (d, *J* = 1.84 Hz, 1 H), 6.64 (br s, 1 H), 7.38–6.98 (m, 9 H, ArH), 7.73–7.59 (m, 4 H, Ar-H), 8.12 (d, *J* = 7.24 Hz, 2 H, ArH), 11.25 (br s, 1 H, NH), 11.74 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 25.3, 26.2, 50.0, 51.5, 53.9, 69.2, 74.2, 104.5, 111.4, 118.0, 118.8, 121.1, 124.8 (2 C), 126.0, 127.2, 127.7, 127.8 (2 C), 128.6 (2 C), 129.1 (2 C), 133.1, 133.3, 135.4, 138.7, 164.9 (C=O), 168.7 (C=O), 174.6 (C=O), 178.0 (C=O), 178.8 (C=S).

MS (ESI, M + H^+): *m*/*z* = 580.6 (M + H^+, 100%).

HRMS (DIP): *m*/*z* [M^+] calcd for $C_{32}H_{28}N_4O_5S$: 580.1780; found: 580.1776.

Methyl (2*S*,3*S*,3a*S*,6a*R*)-6a-[(1*H*-Indol-3-yl)methyl)-1-(benzoylcarbamothioyl)-4,6-dioxo-5-phenyl-2-(pyridin-2-yl)octahydropyrrolo[3,4-*b*]pyrrole-3-carboxylate (6gc)

After 30 h and workup, the product was crystallized as pale yellow prisms; 489 mg (76%); mp 170–172 °C.

IR (ATR): 3357, 2981, 1782, 1755, 1738, 1698, 1538, 1255, 1238, 743,706 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.73 (s, 3 H, OCH_3), 3.24 (s, 1 H), 3.84 (d, *J* = 15.12 Hz, 1 H), 3.90 (d, *J* = 15.06 Hz, 1 H), 4.25 (s, 1 H), 6.56 (br s, 1 H), 8.01–7.06 (m, 18 H, ArH), 8.45–8.43 (m, 1 H, ArH), 11.33 (br s, 1 H, NH), 11.92 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 25.8, 46.4, 50.4, 53.4, 69.5, 73.0, 103.4, 110.2, 117.1, 117.6, 120.0, 121.9, 122.8, 124.9, 125.4 (2 C), 126.4 (2 C), 126.6, 128.0 (2 C), 128.1, 128.1 (2 C), 130.2, 131.9, 132.0, 134.2, 135.7, 148.2, 156.8, 163.6 (C=O), 167.5 (C=O), 173.2 (C=O), 176.5 (C=O), 176.6 (C=S).

MS (ESI, M + H^+): *m*/*z* = 644.2 (M + H^+, 100%).

HRMS (DIP): *m*/*z* [M^+] calcd for $C_{36}H_{29}N_5O_5S$: 643.1889; found: 643.1883.

Methyl (2*S*,3*S*,3a*S*,6a*R*)-6a-[(1*H*-Indol-3-yl)methyl)-1-(benzoylcarbamothioyl)-5-methyl-4,6-dioxo-2-(pyridin-2-yl)octahydropyrrolo[3,4-*b*]pyrrole-3-carboxylate (6gd)

After 24 h and workup, the product was crystallized as pale yellow prisms; yield: 453 mg (78%); mp 198–200 °C.

IR (ATR): 3170, 3060, 2961, 1785, 1755, 1738, 1685, 1553, 1449, 1357, 1233, 1007, 748,705 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.65 (s, 3 H, NCH_3), 3.07–3.05 (m, 1 H), 3.07 (s, 3 H, OCH_3), 3.35 (br s, 2 H), 3.99 (d, *J* = 1.36 Hz, 1 H), 6.56 (d, *J* = 1.24 Hz, 1 H), 7.37–7.00 (m, 6 H, ArH), 7.76–7.60 (m, 5 H, ArH), 8.02–8.00 (m, 2 H, ArH), 8.41–8.39 (m, 1 H, ArH), 11.25 (br s, 1 H, NH), 11.99 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 25.5, 26.5, 47.5, 51.5, 54.5, 70.4, 74.1, 104.7, 111.3, 118.0, 118.8, 121.0, 122.9, 123.6, 125.9, 127.6 (2 C), 127.7, 129.1 (2 C), 133.1, 133.2, 135.4, 136.7, 149.4, 157.8, 164.7 (C=O), 168.7 (C=O), 175.3 (C=O), 177.5 (C=O), 178.9 (C=S).

MS (ESI, M + H^+): *m*/*z* = 581.6 (M + H^+, 100%).

HRMS (DIP): *m*/*z* [M^+] calcd for $C_{31}H_{27}N_5O_5S$: 581.1733; found: 581.1727.

Methyl (2*S*,3*S*,3a*S*,6a*R*)-6a-[(1*H*-Indol-3-yl)methyl]-1-(benzoylcarbamothioyl)-2-(3-chlorophenyl)-4,6-dioxo-5-phenyloctahydropyrrolo[3,4-*b*]pyrrole-3-carboxylate (6ge)

After 24 h and workup, the product was crystallized as pale yellow prisms; yield: 554 mg (82%); mp 157–159 °C.

IR (ATR): 3387, 3196, 3051, 2956, 1787, 1704, 1529, 1491, 1348, 1255, 1191, 755, 699 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.76 (s, 3 H, OCH_3), 3.44 (dd, *J* = 2.30, 2.30 Hz, 1 H), 3.91 (br s, 2 H), 4.22 (d, *J* = 1.84 Hz, 1 H), 6.69 (br s, 1 H), 7.71–7.03 (m, 17 H, ArH), 8.09 (d, *J* = 7.24 Hz, 2 H, ArH), 11.31 (br s, 1 H, NH), 11.51 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 26.7, 49.9, 51.6, 54.1, 69.2, 74.7, 104.5, 111.4, 118.1, 118.8, 121.1, 124.0, 125.2, 126.1, 126.4 (2 C), 127.4, 127.8, 127.9 (2 C), 128.9 (2 C), 129.1 (2 C), 129.2, 130.6, 130.9, 132.9, 133.3, 133.5, 135.5, 141.5, 165.4 (C=O), 168.5 (C=O), 173.8 (C=O), 175.5 (C=O), 180.5 (C=S).

MS (ESI, M + H^+): *m*/*z* (%) = 678.2 (M + H^+, 100), 679.2 (M + H^+, 35).

HRMS (DIP): *m*/*z* [M^+] calcd for $C_{37}H_{29}ClN_4O_5S$: 676.1547; found: 676.1544.

Methyl (2*S*,3*S*,3a*S*,6a*R*)-6a-[(1*H*-Indol-3-yl)methyl)-1-(benzoylcarbamothioyl)-2-(3-chlorophenyl)-5-methyl-4,6-dioxooctahydropyrrolo[3,4-*b*]pyrrole-3-carboxylate (6gf)

After 24 h and workup, the product was crystallized as pale yellow prisms; 538 mg (84%); mp 192–194 °C.

IR (ATR): 3384, 3203, 2982, 2951, 1784, 1745, 1693, 1537, 1365, 1352, 1254, 1237, 1213, 752, 693 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.74 (s, 3 H, NCH_3), 2.84 (s, 3 H, OCH_3), 3.26 (dd, *J* = 2.36, 2.36 Hz, 1 H), 3.75 (br s, 2 H), 3.96 (d, *J* = 1.88 Hz, 1 H), 6.53 (br s, 1 H), 7.11–6.95 (m, 4 H, ArH), 7.37–7.23 (m, 4 H, ArH), 7.73–7.56 (m, 4 H, ArH), 8.10 (d, *J* = 7.40 Hz, 2 H, ArH), 11.24 (br s, 1 H, NH), 11.67 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 25.3, 26.3, 49.7, 51.6, 53.8, 69.0, 74.5, 104.5, 111.4, 117.9, 118.8, 121.1, 123.5, 125.2, 125.9, 127.3, 127.6, 127.8 (2 C), 129.0 (2 C), 130.5, 133.1, 133.2, 133.4, 135.4, 141.4, 165.0 (C=O), 168.5 (C=O), 174.5 (C=O), 177.5 (C=O), 179.2 (C=S).

MS (ESI, M + H^+): *m*/*z* (%) = 615.2 (M + H^+, 100), 616.1 (M + H^+, 35).

HRMS (DIP): *m*/*z* [M^+] calcd for $C_{32}H_{27}ClN_4O_5S$: 614.1391; found: 614.1386.

2*R*,3*R*,3a*R*,6a*S*)-6a-[(1*H*-Indol-3-yl)methyl)-2-(4-chlorophenyl)-5-ethyl-4,6-dioxooctahydropyrrolo[3,4-*b*]pyrrole-3-carboxylic Acid (7gg)

To a stirred solution of bicyclic pyrrolidine **4gg** (0.4 g, 0.85mmol) in MeOH (not anhyd, 20 mL) was added dropwise a solution of NaOMe (0.38 g, 2.04 mmol) in anhyd MeOH (10 mL) over 10 min and the mixture was stirred and heated at reflux temperature for 36 h. The solvent was evaporated under reduced pressure, quenched with sat. aq NH_4Cl, and then extracted with CH_2Cl_2 (3 ×). The combined organic solvents were dried ($MgSO_4$) and filtered. The product crystallized from CH_2Cl_2 as a colorless solid; yield: 0.13 g (95%); mp 207–209 °C (dec.).

IR (ATR): 3429, 3304, 3065, 2979, 2934, 2905, 2831, 1770 (C=O), 1724 (C=O), 1675(C=O), 831 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.62 (t, J = 7.16 Hz, 3 H, CH_2CH_3), 2.99 (dd, J = 5.16, 6.46 Hz, 1 H), 3.15–3.04 (m, 2 H, CH_2CH_3), 3.22 (d, J = 13.92 Hz, 1 H), 3.4 (d, J = 14 Hz, 1 H), 3.44 (s, 1 H, NH), 3.49 (d, J = 5 Hz, 1 H), 4.72 (d, J = 6.52 Hz, 1 H), 7.11–6.96 (m, 3 H, ArH), 7.42–7.27 (m, 5 H, ArH), 7.70 (d, J = 7.88 Hz, 1 H, ArH), 10.98 (br s, 1 H, NH), 12.8 (br s, 1 H, OH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 11.8, 29.1, 32.7, 51.1, 54.7, 65.6, 71.0, 107.7, 111.4, 118.3, 118.6, 121.0, 124.4, 127.3, 128.0 (2 C), 128.3 (2 C), 131.8, 135.8, 140.6, 173.0 (C=O), 176.1 (C=O), 178.7 (C=O).

MS (ESI, M + H$^+$): m/z (%) = 452.2 (M$^+$, 100, Cl: 35)/454.2 (M$^+$, 33.3, Cl: 37) [3:1], 453.2 (M + 1, 100, Cl: 35)/455.2 (M + 1, 33.3, Cl: 37) [3:1].

HRMS (DIP): m/z [M$^+$] calcd for $C_{24}H_{22}ClN_3O_4$: 451.1299; found: 451.1289.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611356.

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