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Synthesis of new cycloalkenyliden-pyrroles by domino reaction

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Dedicated to Professor Branko Stanovnik on the occasion of his 70th birthday

ABSTRACT

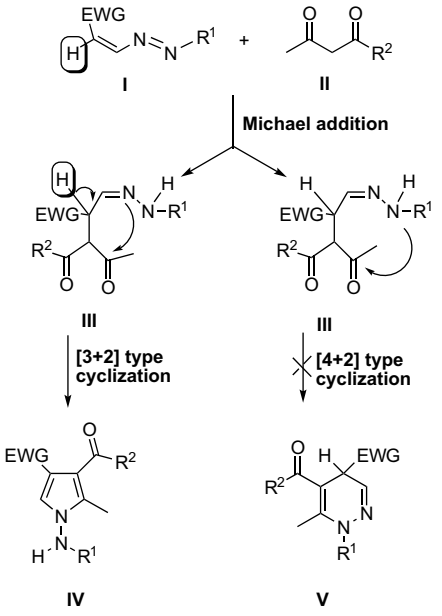
Easily accessible cycloalkenyl-1-diazenes and β-dicarbonyl compounds are converted in one-pot into previously unknown functionalized fused cycloalkenyliden-pyrroles of different sizes. The domino reaction proceeds through a base-catalyzed conjugate addition/cyclization/elimination sequence.

1. Introduction

Recently, 1,2-diaza-1,3-butadienes have been intensively studied by several authors and they have been demonstrated to be interesting products and powerful intermediates in organic synthesis.[1] In our investigations, these compounds have manifested the aptitude to furnish polyfunctionalized five-,[2] six-[3] and seven-membered[4] heterocycles containing nitrogen, sulfur and phosphorus.

In the course of our activity in this field, we have detected that the reaction between 1,2-diaza-1,3-butadienes **I** and β-dicarbonyl compounds containing activated methylene groups **II** always generates pyrrole derivatives **IV** rather than dihydropyridazines **V**, as erroneously reported by previous authors (Scheme 1).[5] This behaviour is a consequence of initial 1,4-Michael-type addition that leads to α-substituted hydrazone intermediates **III**, and subsequent internal ring closure. In particular, when the nucleophilic reagent bears a ketonic function in the α-position with respect to the attacking carbon atom, the ring annulation occurs via a [3+2] instead of a [4+2] cyclization process.[6] This ring closure is promoted in the intermediates **III** by the presence of an acidic hydrogen originally placed in position 4 of the azo-ene system **I** (Scheme 1).

In an attempt to promote the [4+2] cyclization, we have previously investigated the reactions of cyclopentenyl- and cyclohexenyl-1-diazenes, which lack the above-mentioned hydrogen, with β-ketoamide derivatives. Surprisingly, we synthesized tetrahydro-1*H*-indoles from cyclohexenyl-1-diazenes by means of an 'uncommon' [3+2] cyclization and no formation of dihydropyridazines was observed.[7]



Scheme 1.

Herein, we report full details of these studies. With regard to our preliminary communication, the scope considerably extends the applicability of this protocol, involving cycloheptenyl- or

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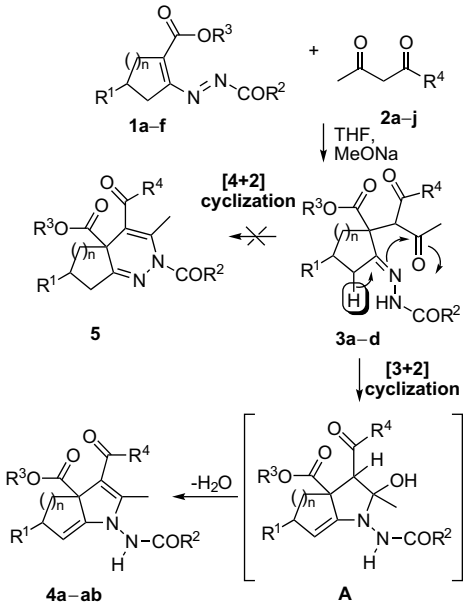
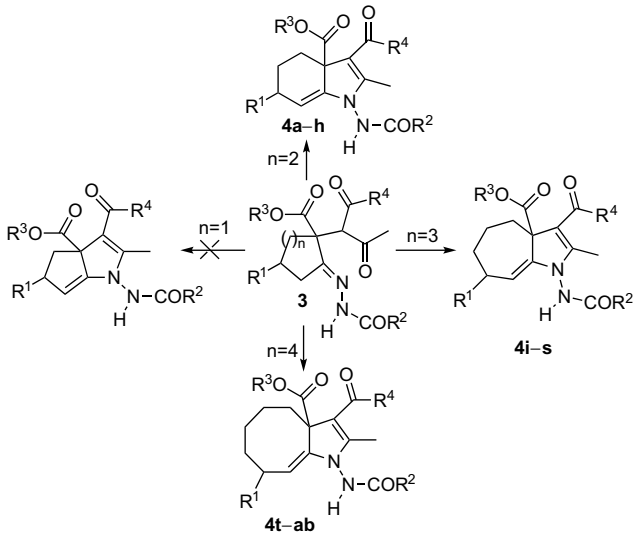


Scheme 2.



Scheme 3.

cyclooctenyl-1-diazenes and different β-dicarbonyl compounds such as 2,4-pentandione, β-ketoesters and β-ketoamides.[7] The here reported 2-cycloalkenylpyrrole derivatives of different sizes are unknown and not readily available by other methods, have potential usefulness in medicinal[8] and technological fields.[9] Moreover, the flexibility in the introduction of different groups in these systems confers an interesting contribution to this work, making them suitable as intermediates for more complex compounds.

2. Results and discussion

Cycloalkenyl-1-diazenes **1a–f** of different sizes were easily prepared starting from the corresponding cycloketone derivatives as previously reported.[7,10] The fast reaction of **1a–f** with β-dicarbonyl compounds **2a–j** confirms their good electrophilic character (Scheme 2). However, we have observed some differences in the final products obtained, depending on the ring-sizes of the starting cycloalkenyl-1-diazenes **1** (Scheme 3). In fact, the reaction of cyclopentenyl-1-diazenes **1a**,**b** (n=1) with β-ketoamides **2a**,**b** or ketoester **2d** in tetrahydrofuran at room temperature in the presence of catalytic sodium methoxide led to the exclusive formation of the hydrazonic derivatives **3a–c** in good yields (Scheme 2, Table 1). The reaction takes place by means of conjugated addition (Michael-type) of the nucleophiles **2** to the terminal carbon atom of the 1,2-diaza-1,3-diene system. All attempts to convert **3a–c** into the corresponding cyclopentenyliden-pyrroles **4** failed either by means of heat or under basic or acid conditions.

Under the same conditions for the synthesis of **3a–c**, the reaction between cyclohexenyl-1-diazenes **1c**,**d** (n=2) and **2a–e** revealed the presence of two major products by TLC analysis. However, it was possible to isolate by flash chromatography only the most non-polar ones that were identified as 3-substituted tetrahydro-1*H*-indoles **4a–i**. Only in the case of the reaction between **1d** and **2a** we have isolated a small amount of the more polar ethyl 3-[2-(aminocarbonyl)hydrazono]-1-[1-(anilinocarbonyl)-2-oxopropyl]-1-cyclohexanecarboxylate **3d**. In the other cases, hydrazones **3** were converted into the corresponding tetrahydro-1*H*-indoles **4a–i** during the chromatographic processes (Scheme 2, Table 1). The ring closure process that transforms the hydrazones **3** into the corresponding tetrahydro-1*H*-indoles **4a–i** happens by means of an uncommon [3+2] cyclization. Usually, in the reaction that involves 1,2-diaza-1,3-butadienes **I** and β-dicarbonyl derivatives **II** (Scheme 1), the [3+2] annulation starts by deprotonation of a hydrogen activated by two electron withdrawing substituents (i.e., carbonyl groups) yielding aromatic pyrrole derivatives.[6] In this case, the regioselective conjugate nucleophilic attack of the hydrazonic nitrogen at the ketonic function is promoted by the loss of a hydrogen in the α-position to only one hydrazone moiety. This occurrence produces the hexahydro-1*H*-2-indolol intermediate **A** that spontaneously furnishes the final tetrahydro-1*H*-indoles **4a–i** by elimination of a water molecule. It is noteworthy that although the final products **4** are not stabilized by aromaticity, no [4+2] ring closure occurred and pyridazine derivatives **5** were not found (Scheme 2). The X-ray diffraction study of **4f** confirms unequivocally the structure assigned to these compounds (Fig. 1).[11]

The ^{1}H NMR and ^{13}C NMR spectroscopic analysis of **4f**,**g**,**i** revealed that these compounds were obtained exclusively as a sole couple of enantiomers that corresponds to racemic forms *R*,*R*/*S*,*S* as evinced by X-ray of **4f**. Compound **4h** was isolated as a mixture of *R*,*R*/*S*,*S* and *R*,*S*/*S*,*R* forms in 80:20 ratio.

Then, we have extended our investigations employing cycloheptenyl-1-diazene **1e** (n=3) or cyclooctenyl-1-diazene **1f** (n=4) as starting materials. They easily reacted with β-dicarbonyl compounds **2a–j** in tetrahydrofuran at room temperature in the presence of catalytic sodium methoxide. At the disappearance of the typical red colour of the 1,2-diaza-1,3-dienes, a TLC analysis of the crude mixture showed the presence of only one product that was isolated and identified as 2-methyl-1,3a,4,5,6,7-hexahydro cyclohepta[*b*]pyrroles **4j–s** (n=3) or 2-methyl-3a,4,5,6,7,8-hexahydro-1*H*-cycloocta[*b*]pyrroles **4t–ab** (n=4), respectively (Scheme 3, Table 1). In these cases, no hydrazone intermediate was observed in the reaction mixture. The ring strain due to the presence of the carbon–carbon double bonds in the fused bicyclic ring systems of **4** can explain these experimental results (Scheme 3, Table 1). In particular, due to an increment in the dimension of the cycloalkyl portion, a lower ring strain results. Thus, in the case of cycloheptenyl-1-diazene **1e** (n=3) or cyclooctenyl-1-diazene **1f** (n=4) only cycloalkenyliden-pyrroles **4j–s** and **4t–ab** were produced,

Table 1
Yields and reaction times of α-substituted hydrazones **3a–c** and cycloalkenyliden-pyrroles **4a–ab**

1	*n*	R^1	R^2	R^3	2	R^4	3	Yield[a] %	Time (h)	4	Yield[a] %	Time (h)
1a	1	H	O*t*-Bu	Et	**2a**	NHPh	**3a**	79	0.5			
1b	1	H	NH_2	Et	**2b**	NHC_6H_4-4-OMe	**3b**	84	0.5			
1b	1	H	NH_2	Et	**2d**	OMe	**3c**	68	0.5			
1c	2	H	NH_2	Et	**2a**	NHPh				**4a**	63	3.5
1c	2	H	NH_2	Et	**2b**	NHC_6H_4-4-OMe				**4b**	59	5.0
1c	2	H	NH_2	Et	**2c**	NHC_6H_4-4-Cl				**4c**	62	3.0
1c	2	H	NH_2	Et	**2d**	OMe				**4d**	51	4.0
1c	2	H	NH_2	Et	**2e**	OEt				**4e**	54	4.5
1d	2	Me	NH_2	Et	**2a**	NHPh	**3d**	7	3.5	**4f**	61	3.5
1d	2	Me	NH_2	Et	**2b**	NHC_6H_4-4-OMe				**4g**	57	3.0
1d	2	Me	NH_2	Et	**2c**	NHC_6H_4-4-Cl				**4h**	66	3.5
1d	2	Me	NH_2	Et	**2d**	OMe				**4i**	58	4.5
1e	3	H	NH_2	Me	**2a**	NHPh				**4j**	68	1.0
1e	3	H	NH_2	Me	**2b**	NHC_6H_4-4-OMe				**4k**	71	1.0
1e	3	H	NH_2	Me	**2c**	NHC_6H_4-4-Cl				**4l**	83	1.5
1e	3	H	NH_2	Me	**2d**	OMe				**4m**	74	0.5
1e	3	H	NH_2	Me	**2e**	OEt				**4n**	51	1.0
1e	3	H	NH_2	Me	**2f**	O*i*-Pr				**4o**	76	2.0
1e	3	H	NH_2	Me	**2g**	O*t*-Bu				**4p**	63	1.0
1e	3	H	NH_2	Me	**2h**	OAllyl				**4q**	56	1.5
1e	3	H	NH_2	Me	**2i**	OBn				**4r**	59	2.0
1e	3	H	NH_2	Me	**2j**	Me				**4s**	81	2.0
1f	4	H	NH_2	Et	**2a**	NHPh				**4t**	63	1.5
1f	4	H	NH_2	Et	**2b**	NHC_6H_4-4-OMe				**4u**	71	1.5
1f	4	H	NH_2	Et	**2c**	NHC_6H_4-4-Cl				**4v**	65	2.5
1f	4	H	NH_2	Et	**2d**	OMe				**4w**	86	2.0
1f	4	H	NH_2	Et	**2e**	OEt				**4x**	95	1.5
1f	4	H	NH_2	Et	**2f**	O*i*-Pr				**4y**	64	1.5
1f	4	H	NH_2	Et	**2g**	O*t*-Bu				**4z**	73	1.5
1f	4	H	NH_2	Et	**2h**	OAllyl				**4aa**	78	2.0
1f	4	H	NH_2	Et	**2i**	OBn				**4ab**	92	1.0

[a] Yield of pure isolated products **3a–d** and **4a–ab** based on starting 1,2-diaza-1,3-dienes **1a–f**.

while cyclohexenyl-1-diazenes (*n*=2) furnish a mixture of tetrahydro-1*H*-indoles **4a–i** and hydrazones **3**. Only in the case of cyclopentenyl-1-diazenes (*n*=1) hydrazones **3a–c** were formed exclusively (Scheme 3, Table 1).

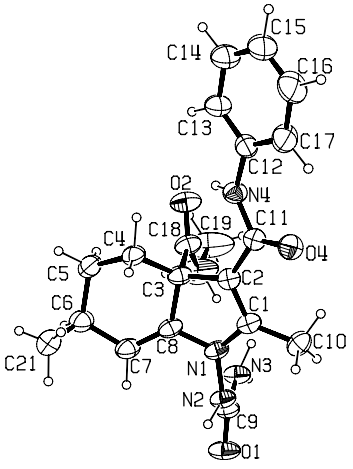


Figure 1. A view of the asymmetric unit of **4f**, showing the labelling of the non-hydrogen atoms.

3. Conclusion

In conclusion, this paper describes the convenient regioselective synthesis of functionalized fused cycloalkenyliden-pyrroles of different sizes through base-catalyzed one-pot conjugate addition/cyclization/elimination reactions of β-dicarbonyl derivatives with cycloalkenyl-1-diazenes. The advantage of this type of synthesis is the accessibility of the starting materials and the simplicity of the experimental procedures. It is noteworthy that the 1-amino cycloalkenyliden-pyrroles are not easily available from other methods and they represent new classes of polyheterocycles of interest as targets in organic,[12] biological,[13] medicinal[14] and agricultural chemistry.[15]

4. Experimental

4.1. General

Methyl, ethyl, *iso*-propyl, *tert*-butyl, allyl, benzyl acetoacetates, acetoacetanilide, 4′-methoxyacetanilide, 4′-chloroacetoacetanilide, 2,4-pentandione, sodium methoxide were commercial materials and were used without further purification. Solvents were purchased and used without further purification with the exception of THF, which was distilled over sodium hydroxide. Melting points were determined on open capillary tubes. FTIR spectra were obtained as Nujol mulls. Mass spectra (EI) were made at an ionizing voltage of 70 eV. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100.32 MHz, respectively. All NMR spectra were recorded in $CDCl_3$ or in DMSO-d_6, as specified below. Chemical shifts (δ_H) are reported in parts per million (ppm), relative to TMS as internal standard. All coupling constants (*J*) values are given in hertz. Chemical shifts (δ_C) are reported in parts per million (ppm), relative to $CDCl_3$ or DMSO-d_6 as internal standard in a broad band decoupled mode; the multiplicities were obtained using 135° and 90° DEPT experiments to aid in assignment (CH_3=methyl, CH_2=methylene, CH=methine, C=quaternary). The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m,

multiplet; br, broad. All the NH and NH_2 exchanged with D_2O. Precoated silica gel plates 0.25 mm were employed for analytical thin layer chromatography and silica gel 35–70 μ for column chromatography.

4.1.1. General procedure for the synthesis of α-substituted hydrazones **3a–d** and cycloalkenyliden-pyrroles **4a–ab**

To a magnetically stirred solution of β-dicarbonyl compounds **2a–j** (1.0 mmol) and cycloalkenyl-1-diazenes **1a–f** (1.0 mmol) in tetrahydrofuran (30 mL) catalytic sodium methoxide (0.1 equiv) was added. The reaction was allowed to stand at room temperature until the disappearance of the reagents (TLC analysis, 0.5–5 h) and then the solvent was evaporated under reduced pressure. Starting from cyclopentenyl-1-diazenes **1a**,**b**, only α-substituted cyclopentanone hydrazones **3a–c** were obtained by crystallization from ethyl acetate–light petroleum ether (40–60 °C). Instead, in the case of cyclohexenyl-1-diazenes **1c**,**d**, the TLC check revealed the formation of two major products. The crudes were chromatographed on silica column (elution mixtures: ethyl acetate–cyclohexane). Only in the case of the reaction between **1d** and **2a**, ethyl 3-[2-(aminocarbonyl)hydrazono]-1-[1-(anilinocarbonyl)-2-oxopropyl]-1-cyclohexanecarboxylate **3d** was isolated together with the corresponding tetrahydro-1*H*-indole **4f**. In the other cases, the chromatographic processes furnished only tetrahydro-1*H*-indoles **4a–e**,**g–i**. Compounds **3d** and **4a–i** were crystallized from ethyl acetate–light petroleum ether (40–60 °C). Starting from cycloheptenyl-1-diazene **1e** or from cyclooctenyl-1-diazene **1f** only 2-methyl-1,3a,4,5,6,7-hexahydrocyclohepta[*b*]pyrroles **4j–s** (n=3) or 2-methyl-3a,4,5,6,7,8-hexahydro-1*H*-cycloocta[*b*]pyrroles **4t–ab** were formed. Products **4j–s** and **4t–ab** were purified by silica gel flash chromatography (elution mixtures: ethyl acetate–cyclohexane) and were crystallized from diethyl ether–cyclohexane.

4.1.2. tert-Butyl 2-(2-[(ethyloxy)carbonyl]-2-{2-oxo-1-[(phenylamino)carbonyl]propyl}cyclopentyliden)-1-hydrazinecarboxylate **3a**

Yield 352 mg, 79%, white powder, mp 116–118 °C; IR (Nujol): ν_{max}=3307, 3243, 1776, 1704 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.16 (t, 3H, ^3J=7.2 Hz), 1.25 (s, 9H), 1.61–1.69 (m, 1H), 1.71–1.86 (m, 1H), 2.00–2.31 (m, 3H), 2.26 (s, 3H), 2.80–2.89 (m, 1H), 4.04–4.18 (m, 2H), 4.68 (br s, 1H), 7.06 (t, 1H, ^3J=7.2 Hz), 7.20 (t, 2H, ^3J=8.0 Hz), 7.58–7.67 (m, 2H), 7.70 (br s, 1H), 9.17 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.8 (CH_3), 13.9 (CH_3), 19.6 (CH_3), 21.0 (CH_2), 21.6 (CH_2), 26.7 (CH_2), 26.8 (CH_2), 28.0 (CH_3), 28.1 (CH_3), 32.8 (CH_2), 33.7 (CH_2), 57.9 (CH), 61.3 (CH_2), 61.6 (CH_2), 65.0 (C), 119.8 (CH), 124.2 (CH), 128.6 (CH), 138.0 (C), 152.7 (C), 159.9 (C), 166.0 (C), 168.9 (C), 171.2 (C), 171.8 (C), 201.9 (C); MS: m/z (%)=445 (M^+, 1), 368 (12), 314 (14), 295 (12), 249 (18), 214 (93), 168 (43), 124 (100). Anal. Calcd for $C_{23}H_{31}N_3O_6$: C, 62.01; H, 7.01; N, 9.43. Found: C, 62.12; H, 7.06; N, 9.42.

4.1.3. Ethyl 2-[2-(aminocarbonyl)hydrazono]-1-[1-({[4-(methoxy)phenyl]amino}carbonyl)-2-oxopropyl]-1-cyclopentanecarboxylate **3b**

Yield 351 mg, 84%, white powder; mp 142–143 °C; IR (Nujol): ν_{max}=3374, 3258, 1762, 1735 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.12 (t, 3H, ^3J=7.2 Hz), 1.70–1.82 (m, 1H), 2.00–2.21 (m, 2H), 2.17 (s, 3H), 2.35–2.50 (m, 2H), 2.63–2.72 (m, 1H), 3.69 (s, 3H), 3.96–4.11 (m, 2H), 4.79 (s, 1H), 6.53 (br s, 2H), 6.85 (d, 2H, ^3J=7.2 Hz), 7.37 (d, 2H, ^3J=7.2 Hz), 9.01 (s, 1H), 10.03 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.6 (CH_3), 22.9 (CH_3), 28.3 (CH_2), 29.4 (CH_2), 31.4 (CH_2), 55.9 (CH_3), 57.7 (CH), 61.5 (CH_2), 64.2 (C), 114.5 (CH), 121.8 (CH), 132.2 (C), 155.6 (C), 156.4 (C), 157.7 (C), 166.0 (C), 173.0 (C), 203.0 (C); MS: m/z (%)=418 (M^+, 2), 372 (2), 344 (100), 329 (14), 298 (10), 270 (27), 228 (48), 179 (24), 137 (40), 123 (93). Anal. Calcd for $C_{20}H_{26}N_4O_6$: C, 57.41; H, 6.26; N, 13.39. Found: C, 57.55; H, 6.29; N, 13.44.

4.1.4. Ethyl 2-[2-(aminocarbonyl)hydrazono]-1-{1-[(methyloxy)-carbonyl]-2-oxopropyl}-1-cyclopentanecarboxylate **3c**

Yield 222 mg, 68%, white powder; mp 136–138 °C; IR (Nujol): ν_{max}=3320, 3232, 1781, 1701 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.13 (t, 3H, ^3J=7.2 Hz), 1.79–1.93 (m, 2H), 2.04–2.23 (m, 3H), 2.27 (s, 3H), 2.33–2.41 (m, 1H), 3.61–3.64 (m, 3H), 3.98–4.08 (m, 2H), 4.81 and 4.92 (2s, 1H), 6.23 and 6.34 (2br s, 2H), 9.13 and 9.16 (2s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.4 (CH_3), 22.9 (CH_3), 28.3 (CH_2), 31.6 (CH_2), 32.5 (CH_2), 52.9 (CH_3), 57.8 (CH), 61.6 (CH_2), 62.2 (C), 155.5 (C), 156.4 (C), 157.6 (C), 169.1 (C), 169.8 (C), 172.5 (C), 172.7 (C), 203.5 (C), 203.6 (C); MS: m/z (%)=327 (M^+, 1), 282 (17), 253 (100), 223 (61), 193 (17), 139 (61), 123 (78). Anal. Calcd for $C_{14}H_{21}N_3O_6$: C, 51.37; H, 6.47; N, 12.84. Found: C, 51.45; H, 6.39; N, 12.87.

4.1.5. Ethyl 2-[2-(aminocarbonyl)hydrazono]-1-(anilinocarbonyl)-2-oxopropyl]-4-methyl-1-cyclohexanecarboxylate **3d**

Yield 29 mg, 7%, white powder; mp 132–134 °C; IR (Nujol): ν_{max}=3482, 3310, 3207, 1720, 1684 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, 3H, ^3J=6.4 Hz), 1.04–1.08 (m, 1H), 1.16 (t, 3H, ^3J=7.2 Hz), 1.27–1.31 (m, 1H), 1.73–1.76 (m, 2H), 1.96–2.07 (m, 1H), 2.09 (s, 3H), 2.60–2.64 (m, 1H), 3.33–3.39 (m, 1H), 4.06 (q, 2H, ^3J=7.2 Hz), 4.36 (s, 1H), 5.91 and 6.12 (2br s, 2H), 7.07 (t, 1H, ^3J=7.2 Hz), 7.30 (t, 2H, ^3J=7.6 Hz), 7.53 (d, 2H, ^3J=8.0 Hz), 9.47 (s, 1H), 10.24 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5 (CH_3), 15.9 (CH_3), 21.1 (CH_2), 29.5 (CH_3), 30.3 (CH), 32.1 (CH_2), 56.9 (CH_2), 61.2 (CH), 62.0 (CH_2), 65.6 (C), 120.1 (CH), 124.4 (CH), 129.5 (CH), 139.2 (C), 149.9 (C), 157.8 (C), 167.4 (C), 172.2 (C), 203.8 (C); MS: m/z (%)=416 (M^+, 1), 398 (8), 355 (7), 342 (13), 325 (100). Anal. Calcd for $C_{21}H_{28}N_4O_5$: C, 60.56; H, 6.78; N, 13.45. Found: C, 60.51; H, 6.83; N, 13.52.

4.1.6. Ethyl 1-[(aminocarbonyl)amino]-3-(anilinocarbonyl)-2-methyl-3a,4,5,6-tetrahydro-1H-3a-indolecarboxylate **4a**

Yield 242 mg, 63%, white powder; mp 189–191 °C; IR (Nujol): ν_{max}=3431, 3327, 3187, 1739, 1724 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.11–1.15 (m, 3H), 1.36–1.48 (m, 3H), 1.63–1.79 (m, 1H), 1.98–2.13 (m, 1H), 2.11 (s, 3H), 2.67–2.71 (m, 1H), 4.10–4.21 (m, 2H), 4.88–4.90 (m, 1H), 6.02 (br s, 2H), 7.02 (t, 1H, ^3J=8.0 Hz), 7.28 (m, 2H), 7.56 (d, 2H, ^3J=8.0 Hz), 8.41 and 8.54 (2br s, 1H), 8.99 and 9.08 (2br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.6 (CH_3), 13.8 (CH_3), 18.7 (CH_2), 21.4 (CH_2), 28.4 (CH_2), 52.8 (C), 61.7 (CH_2), 96.2 (CH), 106.7 (C), 119.2 (CH), 122.9 (CH), 128.7 (CH), 139.2 (C), 144.1 (C), 155.7 (C), 158.6 (C), 162.5 (C), 172.8 (C); MS: m/z (%)=384 (M^+, 7), 325 (1), 311 (100), 264 (6), 192 (5). Anal. Calcd for $C_{20}H_{24}N_4O_4$: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.44; H, 6.31; N, 14.71.

4.1.7. Ethyl 1-[(aminocarbonyl)amino]-3-[(4-methoxyanilino)-carbonyl]-2-methyl-3a,4,5,6-tetrahydro-1H-3a-indole-carboxylate **4b**

Yield 244 mg, 59%, white powder; mp 167–170 °C; IR (Nujol): ν_{max}=3426, 3346, 3259, 1784, 1742 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.13–1.16 (m, 3H), 1.39–1.52 (m, 2H), 1.65–1.79 (m, 2H), 1.91–2.12 (m, 1H), 2.10 (s, 3H), 2.66–2.69 (m, 1H), 3.71 (s, 3H), 4.10–4.19 (m, 2H), 4.72–4.88 (m, 1H), 5.99 (br s, 2H), 6.86 (d, 2H, ^3J=9.2 Hz), 7.47 (d, 2H, ^3J=9.2 Hz), 8.36 and 8.50 (2br s, 1H), 8.83 and 8.92 (2br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.5 (CH_3), 13.7 (CH_3), 18.7 (CH_2), 21.4 (CH_2), 28.3 (CH_2), 52.8 (C), 55.1 (CH_3), 61.5 (CH_2), 96.0 (CH), 106.9 (C), 113.8 (CH), 120.7 (CH), 132.2 (C), 144.2 (C), 154.9 (C), 155.0 (C), 158.5 (C), 162.2 (C), 172.7 (C); MS: m/z (%)=414 (M^+, 11), 356 (3), 341 (100), 324 (6), 298 (6), 282 (7), 264 (18). Anal. Calcd for $C_{21}H_{26}N_4O_5$: C, 60.86; H, 6.32; N, 13.52. Found: C, 60.84; H, 6.28; N, 13.61.

4.1.8. Ethyl 1-[(aminocarbonyl)amino]-3-[(4-chloroanilino)carbonyl]-2-methyl-3a,4,5,6-tetrahydro-1H-3a-indolecarboxylate ***4c***

Yield 259 mg, 62%, white powder; mp 178–180 °C; IR (Nujol): ν_{max}=3412, 3385, 3231, 1745, 1723 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.11–1.15 (m, 3H), 1.36–1.54 (m, 2H), 1.62–1.79 (m, 2H), 1.91–2.08 (m, 1H), 2.10 (s, 3H), 2.66–2.69 (m, 1H), 4.08–4.17 (m, 2H), 4.77–4.89 (m, 1H), 6.01 (br s, 2H), 7.33 (d, 2H, ^3J=8.4 Hz), 7.60 (d, 2H, ^3J=8.4 Hz), 8.42 and 8.55 (2br s, 1H), 9.12 and 9.23 (2br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.6 (CH_3), 13.7 (CH_3), 16.6 (CH_2), 21.4 (CH_2), 28.3 (CH_2), 52.8 (C), 61.6 (CH_2), 96.3 (CH), 106.7 (C), 120.7 (CH), 126.4 (C), 128.5 (CH), 138.2 (C), 144.0 (C), 155.4 (C), 158.5 (C), 162.7 (C), 172.6 (C); MS: *m*/*z* (%)=420 (M^++2, 2), 418 (M^+, 7), 390 (12), 388 (38), 374 (21), 372 (56), 346 (32), 344 (100), 218 (26), 202 (67). Anal. Calcd for $C_{20}H_{23}ClN_4O_4$: C, 57.35; H, 5.53; N, 13.38. Found: C, 57.34; H, 5.32; N, 13.51.

4.1.9. 3a-Ethyl 3-methyl 1-[(aminocarbonyl)amino]-2-methyl-3a,4,5,6-tetrahydro-1H-3-3a-indoledicarboxylate ***4d***

Yield 165 mg, 51%, white powder; mp 173–176 °C; IR (Nujol): ν_{max}=3423, 3362, 3158, 1748, 1693 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.13–1.28 (m, 3H), 1.34–1.68 (m, 3H), 1.87–2.19 (m, 2H), 2.28 (s, 3H), 2.69–2.75 (m, 1H), 3.69 (s, 3H), 4.14–4.28 (m, 2H), 5.06–5.12 (m, 1H), 5.27 and 6.13 (2br s, 2H), 7.52 and 9.00 (2br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.5 (CH_3), 14.0 (CH_3), 20.4 (CH_2), 23.7 (CH_2), 29.6 (CH_2), 50.5 (CH_3), 52.7 (C), 61.5 (CH_2), 94.9 (CH), 98.3 (C), 143.7 (C), 148.7 (C), 159.9 (C), 165.2 (C), 172.6 (C); MS: *m*/*z* (%)=323 (M^+, 7), 294 (16), 278 (83), 249 (100), 235 (26), 191 (33), 132 (52). Anal. Calcd for $C_{15}H_{21}N_3O_5$: C, 55.72; H, 6.55; N, 13.00. Found: C, 55.64; H, 6.42; N, 13.08.

4.1.10. Diethyl 1-[(aminocarbonyl)amino]-2-methyl-3a,4,5,6-tetrahydro-1H-3a-indoledicarboxylate ***4e***

Yield 182 mg, 54%, white powder; mp 154–156 °C; IR (Nujol): ν_{max}=3410, 3342, 3218, 1782, 1737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.14–1.34 (m, 6H), 1.39–1.58 (m, 3H), 1.87–2.04 (m, 2H), 2.23 (s, 3H), 2.69–2.77 (m, 1H), 4.11–4.25 (m, 4H), 5.01–5.08 (m, 1H), 5.42 and 6.20 (2br s, 2H), 7.05 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5 (CH_3), 14.1 (CH_3), 14.3 (CH_3), 19.0 (CH_2), 26.7 (CH_2), 29.3 (CH_2), 56.2 (C), 61.3 (CH_2), 62.6 (CH_2), 98.3 (CH), 105.0 (C), 143.9 (C), 150.4 (C), 159.5 (C), 164.8 (C), 172.7 (C); MS: *m*/*z* (%)=337 (M^+, 19), 308 (4), 292 (70), 264 (100), 235 (29), 219 (21), 190 (100), 175 (56), 132 (63). Anal. Calcd for $C_{16}H_{23}N_3O_5$: C, 56.96; H, 6.87; N, 12.46. Found: C, 56.91; H, 6.95; N, 12.39.

4.1.11. Ethyl 1-[(aminocarbonyl)amino]-3-(anilinocarbonyl)-2,6-dimethyl-3a,4,5,6-tetrahydro-1H-3a-indolecarboxylate ***4f***

Yield 243 mg, 61%, white powder; mp 201–203 °C; IR (Nujol): ν_{max}=3465, 3353, 3196, 1719, 1709, 1647 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (d, 3H, ^3J=6.0 Hz), 1.13 (t, 3H, ^3J=7.2 Hz), 1.36–1.43 (m, 1H), 1.51 (dt, 1H, ^2J=12.8 Hz, ^3J=4.0 Hz), 1.66–1.74 (m, 1H), 2.11 (s, 3H), 2.21–2.33 (m, 1H), 2.52–2.58 (m, 1H), 4.14 (q, 2H, ^3J=7.2 Hz), 4.80 (d, 1H, ^3J=3.6 Hz), 6.07 (br s, 2H), 7.02 (t, 1H, ^3J=7.2 Hz), 7.29 (t, 2H, ^3J=8.4 Hz), 7.56 (dd, 2H, ^3J=8.4 Hz, ^4J=0.8 Hz), 8.41 and 8.58 (2br s, 1H), 8.91 and 9.09 (2br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5 (CH_3), 13.7 (CH_3), 22.2 (CH_2), 24.8 (CH_3), 25.9 (CH_2), 26.1 (CH), 53.1 (C), 61.6 (CH_2), 102.4 (CH), 106.9 (C), 119.0 (CH), 122.9 (CH), 128.7 (CH), 139.1 (C), 143.7 (C), 155.5 (C), 158.4 (C), 162.5 (C), 172.5 (C); MS: *m*/*z* (%)=398 (M^+, 7), 340 (5), 325 (100). Anal. Calcd for $C_{21}H_{26}N_4O_4$: C, 63.30; H, 6.58; N, 14.06. Found: C, 63.21; H, 6.63; N, 14.01.

4.1.12. Ethyl 1-[(aminocarbonyl)amino]-3-[(4-methoxyanilino)carbonyl]-2,6-dimethyl-3a,4,5,6-tetrahydro-1H-3a-indolecarboxylate ***4g***

Yield 244 mg, 57%, white powder; mp 158–160 °C; IR (Nujol): ν_{max}=3395, 3364, 3218, 1773, 1721 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.95 (d, 3H, ^3J=7.6 Hz), 1.14 (t, 3H, ^3J=7.2 Hz), 1.21–1.39 (m, 1H), 1.43–1.51 (m, 1H), 1.62–1.76 (m, 1H), 2.08 (s, 3H), 2.23–2.37 (m, 1H), 2.49–2.55 (m, 1H), 3.69 (s, 3H), 4.07–4.15 (m, 2H), 4.77 (d, 1H, ^3J=3.2 Hz), 5.99 (br s, 2H), 6.84 (d, 2H, ^3J=8.8 Hz), 7.45 (d, 2H, ^3J=8.8 Hz), 8.57 (br s, 1H), 8.90 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.5 (CH_3), 13.7 (CH_3), 22.3 (CH_3), 22.6 (CH_2), 24.7 (CH_2), 25.9 (CH_2), 26.3 (CH), 53.4 (C), 55.1 (CH_3), 61.5 (CH_2), 102.2 (CH), 107.1 (C), 113.8 (CH), 120.6 (CH), 132.3 (C), 143.8 (C), 154.9 (C), 158.5 (C), 162.2 (C), 172.5 (C); MS: *m*/*z* (%)=428 (M^+, 12), 369 (1), 355 (100), 278 (21), 206 (29), 146 (33). Anal. Calcd for $C_{22}H_{28}N_4O_5$: C, 61.67; H, 6.59; N, 13.08. Found: C, 61.81; H, 6.48; N, 13.11.

4.1.13. Ethyl 1-[(aminocarbonyl)amino]-3-[(4-chloroanilino)-carbonyl]-2,6-dimethyl-3a,4,5,6-tetrahydro-1H-3a-indolecarboxylate ***4h***

Yield 285 mg, 66%, white powder; mp 183–184 °C; IR (Nujol): ν_{max}=3465, 3376, 3265, 1758, 1737 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.95 (d, 3H, ^3J=6.8 Hz), 1.09–1.15 (m, 3H), 1.35–1.39 (m, 1H), 1.44–1.53 (m, 1H), 1.66–1.74 (m, 1H), 2.09 (s, 3H), 2.28–2.36 (m, 1H), 2.48–2.56 (m, 1H), 4.05–4.17 (m, 2H), 4.62 (d, 0.2H, ^3J=3.2 Hz), 4.79 (d, 0.8H, ^3J=3.2 Hz), 5.99 (br s, 2H), 7.31 (d, 2H, ^3J=8.8 Hz), 7.59 (d, 2H, ^3J=8.8 Hz), 8.41 and 8.54 (2br s, 1H), 9.08 and 9.21 (2br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.6 (CH_3), 13.7 (CH_3), 13.9 (CH_3), 22.3 (CH_3), 22.5 (CH_2), 24.7 (CH_2), 25.9 (CH_2), 26.1 (CH_2), 26.2 (CH), 53.1 (C), 61.1 (CH_2), 61.6 (CH_2), 102.5 (CH), 106.9 (C), 120.6 (CH), 120.7 (CH), 126.4 (C), 128.5 (CH), 138.1 (C), 138.4 (C), 143.6 (C), 155.5 (C), 158.4 (C), 162.7 (C), 172.4 (C); MS: *m*/*z* (%)=434 (M^++2, 2), 432 (M^+, 9), 361 (35), 359 (100), 264 (96), 219 (26), 189 (36). Anal. Calcd for $C_{21}H_{25}ClN_4O_4$: C, 58.26; H, 5.82; N, 12.94. Found: C, 58.24; H, 5.69; N, 13.01.

4.1.14. 3a-Ethyl 3-methyl 1-[(aminocarbonyl)amino]-2,6-dimethyl-3a,4,5,6-tetrahydro-1H-3-3a-indoledicarboxylate ***4i***

Yield 195 mg, 58%, white powder; mp 177–178 °C; IR (Nujol): ν_{max}=3295, 3232, 1776, 1727 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 0.98 (d, 3H, ^3J=6.8 Hz), 1.19 (t, 3H, ^3J=7.2 Hz), 1.21–1.35 (m, 2H), 1.42–1.57 (m, 1H), 1.74–1.98 (m, 1H), 2.26 (s, 3H), 2.73–2.85 (m, 1H), 3.66 (s, 3H), 4.12 (q, 2H, ^3J=7.2 Hz), 4.93 (d, 1H, ^3J=3.2 Hz), 6.14 (br s, 2H), 7.45 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.7 (CH_3), 14.3 (CH_3), 22.6 (CH), 24.5 (CH_2), 26.8 (CH_2), 27.1 (CH_2), 50.8 (CH_3), 53.2 (C), 61.6 (CH_2), 104.7 (CH), 105.0 (C), 143.7 (C), 158.4 (C), 160.1 (C), 165.4 (C), 172.5 (C); MS: *m*/*z* (%)=337 (M^+, 6), 306 (1), 278 (10), 264 (100), 247 (30), 232 (13), 205 (17), 189 (20), 172 (38). Anal. Calcd for $C_{16}H_{23}N_3O_5$: C, 56.96; H, 6.87; N, 12.46. Found: C, 56.91; H, 6.94; N, 12.41.

4.1.15. Methyl 1-[(aminocarbonyl)amino]-3-(anilinocarbonyl)-2-methyl-1,3a,4,5,6,7-hexahydrocyclohepta[b]pyrrole-3a-dicarboxylate ***4j***

Yield 261 mg, 68%, pale-pink powder; mp 189–191 °C; IR (Nujol): ν_{max}=3379, 3316, 3128, 1783, 1745 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.24–1.31 (m, 1H), 1.40–1.47 (m, 1H), 1.61–1.67 (m, 1H), 1.88–2.01 (m, 4H), 2.06 (s, 3H), 2.38–2.52 (m, 1H), 3.68 (s, 3H), 4.91–5.05 (m, 1H), 6.06 (br s, 2H), 6.89–7.01 (m, 1H), 7.26 (d, 2H, ^3J=8.0 Hz), 7.53 (d, 2H, ^3J=8.0 Hz), 8.44 and 8.50 (2br s, 1H), 9.12 and 9.32 (2br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.5 (CH_3), 25.4 (CH_2), 28.5 (CH_2), 28.7 (CH_2), 32.6 (CH_2), 53.2 (CH_3), 58.9 (C), 100.8 (CH), 105.1 (C), 119.9 (CH), 123.3 (CH), 129.3 (CH), 140.1 (C), 140.2 (C), 148.1 (C), 158.8 (C), 163.3 (C), 173.0 (C); MS: *m*/*z* (%)=384 (M^+, 14), 369 (5), 325 (78), 206 (36), 119 (100). Anal. Calcd for $C_{20}H_{24}N_4O_4$: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.44; H, 6.21; N, 14.71.

4.1.16. Methyl 1-[(aminocarbonyl)amino]-3-[(4-methoxy-anilino)carbonyl]-2-methyl-1,3a,4,5,6,7-hexahydro-cyclohepta[b]pyrrole-3a-dicarboxylate ***4k***

Yield 294 mg, 71%, white powder; mp 202–204 °C; IR (Nujol): ν_{max}=3440, 3364, 3303, 1784, 1762 cm^{-1}; ^1H NMR (400 MHz,

DMSO-d_6) δ 1.07–1.33 (m, 2H), 1.41–1.73 (m, 2H), 1.89–2.20 (m, 4H), 2.02 (s, 3H), 3.69 (s, 3H), 3.71 (s, 3H), 4.91–5.06 (m, 1H), 6.04 (br s, 2H), 6.84 (d, 2H, ^3J=8.8 Hz), 7.45 (d, 2H, ^3J=8.8 Hz), 8.42 and 8.48 (2br s, 1H), 8.98 and 9.19 (2br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.7 (CH_3), 24.6 (CH_2), 24.9 (CH_2), 28.0 (CH_2), 31.8 (CH_2), 52.4 (CH_3), 55.1 (CH_3), 58.2 (C), 99.9 (CH), 104.5 (C), 113.7 (CH), 120.6 (CH), 132.4 (C), 132.6 (C), 147.4 (C), 154.9 (C), 158.2 (C), 162.3 (C), 172.3 (C); MS: *m*/*z* (%)=414 (M^+, 7), 382 (2), 357 (39), 323 (7), 234 (16), 123 (100). Anal. Calcd for $C_{21}H_{26}N_4O_5$: C, 60.86; H, 6.32; N, 13.52. Found: C, 60.74; H, 6.24; N, 13.70.

4.1.17. Methyl 1-[(aminocarbonyl)amino]-3-[(4-chloroanilino)-carbonyl]-2-methyl-1,3a,4,5,6,7-hexahydrocyclohepta[b]pyrrole-3a-dicarboxylate **4l**

Yield 347 mg, 83%, pale-yellow powder; mp 178–180 °C; IR (Nujol): ν_{max}=3378, 3326, 3241, 1790, 1686 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.18–1.71 (m, 3H), 1.83–2.16 (m, 4H), 2.05 (s, 3H), 2.45–2.52 (m, 1H), 3.67 (s, 3H), 4.98–5.06 (m, 1H), 6.02 (br s, 2H), 7.29 (d, 2H, ^3J=8.8 Hz), 7.57 (d, 2H, ^3J=8.8 Hz), 8.43 and 8.48 (2br s, 1H), 9.23 and 9.42 (2br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.8 (CH_3), 24.6 (CH_2), 27.8 (CH_2), 28.0 (CH_2), 31.8 (CH_2), 52.4 (CH_3), 58.1 (C), 100.3 (CH), 104.4 (C), 120.6 (CH), 126.2 (C), 128.4 (CH), 138.3 (C), 138.5 (C), 147.2 (C), 158.1 (C), 162.6 (C), 172.3 (C); MS: *m*/*z* (%)=420 (M^++2, 6), 418 (M^+, 20), 405 (2), 403 (5), 361 (26), 359 (80), 265 (17), 234 (44), 206 (100). Anal. Calcd for $C_{20}H_{23}ClN_4O_4$: C, 57.35; H, 5.53; N, 13.38. Found: C, 57.44; H, 5.51; N, 13.31.

4.1.18. Dimethyl 1-[(aminocarbonyl)amino]-2-methyl-1,3a,4,5,6,7-hexahydrocyclohepta[b]pyrrole-3,3a-dicarboxylate **4m**

Yield 239 mg, 74%, beige powder; mp 139–142 °C; IR (Nujol): ν_{max}=3378, 3312, 3186, 1756, 1711 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19–1.39 (m, 2H), 1.58–1.91 (m, 2H), 2.01–2.30 (m, 3H), 2.18 (s, 3H), 2.69–2.81 (m, 1H), 3.58 (s, 3H), 3.65 (s, 3H), 5.14–5.29 (m, 1H), 5.83 (br s, 2H), 8.19 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6 (CH_3), 25.1 (CH_2), 27.7 (CH_2), 29.7 (CH_2), 30.1 (CH_2), 50.3 (CH_3), 52.2 (CH_3), 57.4 (C), 102.5 (CH), 102.9 (C), 146.3 (C), 157.5 (C), 159.7 (C), 164.6 (C), 172.3 (C); MS: *m*/*z* (%)=323 (M^+, 9), 308 (1), 264 (100), 205 (14), 150 (30). Anal. Calcd for $C_{15}H_{21}N_3O_5$: C, 55.72; H, 6.55; N, 13.00. Found: C, 55.84; H, 6.49; N, 13.03.

4.1.19. 3-Ethyl 3a-methyl 1-[(aminocarbonyl)amino]-2-methyl-1,3a,4,5,6,7-hexahydrocyclohepta[b]pyrrole-3,3a-dicarboxylate **4n**

Yield 172 mg, 51%, white powder; mp 149–152 °C; IR (Nujol): ν_{max}=3426, 3387, 3265, 1801, 1739 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15–1.23 (m, 3H), 1.24–1.54 (m, 2H), 1.60–1.74 (m, 2H), 1.80–2.14 (m, 3H), 2.19 (s, 3H), 2.73–2.77 (m, 1H), 3.67 (s, 3H), 4.01–4.06 (m, 2H), 5.16–5.20 (m, 1H), 5.85 (br s, 2H), 8.15 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6 (CH_3), 13.7 (CH_3), 24.5 (CH_2), 25.1 (CH_2), 27.8 (CH_3), 30.1 (CH_2), 52.1 (CH_3), 57.5 (C), 59.1 (CH_2), 102.4 (CH), 103.3 (C), 146.3 (C), 157.3 (C), 159.8 (C), 164.2 (C), 172.6 (C); MS: *m*/*z* (%)=337 (M^+, 9), 293 (4), 278 (100), 232 (13), 205 (24), 191 (26). Anal. Calcd for $C_{16}H_{23}N_3O_5$: C, 56.96; H, 6.87; N, 12.46. Found: C, 57.05; H, 6.99; N, 12.34.

4.1.20. 3a-Methyl 3-iso-propyl 1-[(aminocarbonyl)amino]-2-methyl-1,3a,4,5,6,7-hexahydrocyclohepta[b]pyrrole-3,3a-dicarboxylate **4o**

Yield 267 mg, 76%, white powder; mp 133–136 °C; IR (Nujol): ν_{max}=3249, 3218, 3056, 1784, 1738 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (d, 3H, ^3J=6.4 Hz), 1.21 (d, 3H, ^3J=6.4 Hz), 1.24–1.35 (m, 2H), 1.61–1.79 (m, 2H), 1.83–2.18 (m, 3H), 2.21 (s, 3H), 2.74–2.81 (m, 1H), 3.74 (s, 3H), 4.99 (q, 1H, ^3J=6.4 Hz), 5.18–5.24 (m, 1H), 5.71 and 5.93 (2br s, 2H), 7.98 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6 (CH_3), 21.8 (CH_3), 21.9 (CH_3), 25.2 (CH_2), 27.9 (CH_2), 28.1 (CH_2), 30.2 (CH_2), 52.2 (CH_3), 57.7 (C), 66.5 (CH), 102.5 (CH), 104.0 (C), 146.5 (C), 157.1 (C), 159.8 (C), 163.8 (C), 172.9 (C); MS: *m*/*z* (%)=351 (M^+, 10), 308 (2), 292 (100), 264 (8), 250 (17), 234 (15), 206 (30). Anal. Calcd for $C_{17}H_{25}N_3O_5$: C, 58.11; H, 7.17; N, 11.96. Found: C, 57.98; H, 7.21; N, 12.01.

4.1.21. 3-(tert-Butyl) 3a-methyl 1-[(aminocarbonyl)amino]-2-methyl-1,3a,4,5,6,7-hexahydrocyclohepta[b]pyrrole-3,3a-dicarboxylate **4p**

Yield 230 mg, 63%, white powder; mp 125–129 °C; IR (Nujol): ν_{max}=3386, 3253, 3167, 1735, 1697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (s, 9H), 1.54–1.67 (m, 2H), 1.80–1.91 (m, 2H), 1.93–2.11 (m, 2H), 2.13–2.21 (m, 1H), 2.19 (s, 3H), 2.69–2.74 (m, 1H), 3.67 (s, 3H), 5.14 and 5.16 (2d, 1H, ^3J=4.8 Hz), 5.85 (br s, 2H), 8.05 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5 (CH_3), 25.0 (CH_2), 27.8 (CH_2), 27.9 (CH_2), 28.2 (CH_3), 30.3 (CH_2), 52.1 (CH_3), 57.6 (C), 79.6 (C), 102.0 (CH), 105.0 (C), 146.5 (C), 156.3 (C), 160.0 (C), 163.6 (C), 172.6 (C); MS: *m*/*z* (%)=365 (M^+, 11), 306 (58), 292 (2), 264 (7), 250 (100), 233 (9), 206 (28), 189 (17), 146 (24). Anal. Calcd for $C_{18}H_{27}N_3O_5$: C, 59.16; H, 7.45; N, 11.50. Found: C, 59.11; H, 7.48; N, 11.65.

4.1.22. 3-Allyl 3a-methyl 1-[(aminocarbonyl)amino]-2-methyl-1,3a,4,5,6,7-hexahydrocyclohepta[b]pyrrole-3,3a-dicarboxylate **4q**

Yield 195 mg, 56%, pale-yellow powder; mp 68–71 °C; IR (Nujol): ν_{max}=3413, 3317, 3105, 1769, 1719 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30–1.44 (m, 2H), 1.65–1.70 (m, 2H), 1.85–2.15 (m, 3H), 2.23 (s, 3H), 2.79–2.83 (m, 1H), 3.70 (s, 3H), 4.50–4.61 (m, 2H), 5.14–5.30 (m, 3H), 5.63 and 5.88 (2br s, 2H), 5.83–5.93 (m, 1H), 8.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8 (CH_3), 25.3 (CH_2), 27.8 (CH_2), 28.1 (CH_2), 30.2 (CH_2), 52.3 (CH_3), 57.6 (C), 64.1 (CH_2), 102.8 (CH), 103.2 (C), 117.3 (CH_2), 132.6 (CH), 146.4 (C), 157.9 (C), 159.7 (C), 163.9 (C), 172.7 (C); MS: *m*/*z* (%)=349 (M^+, 11), 306 (4), 292 (19), 290 (100), 264 (7), 249 (14), 232 (16), 205 (30). Anal. Calcd for $C_{17}H_{23}N_3O_5$: C, 58.44; H, 6.64; N, 12.03. Found: C, 58.55; H, 6.66; N, 11.92.

4.1.23. 3-Benzyl 3a-methyl 1-[(aminocarbonyl)amino]-2-methyl-1,3a,4,5,6,7-hexahydrocyclohepta[b]pyrrole-3,3a-dicarboxylate **4r**

Yield 235 mg, 59%, pale-yellow powder; mp 136–138 °C; IR (Nujol): ν_{max}=3402, 3315, 3174, 1819, 1745 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20–1.42 (m, 2H), 1.55–1.68 (m, 2H), 2.05–2.21 (m, 3H), 2.19 (s, 3H), 2.70–2.84 (m, 1H), 3.56 (s, 3H), 5.01 (d, 1H, ^2J=12.4 Hz), 5.13 (d, 1H, ^2J=12.4 Hz), 5.15–5.20 (m, 1H), 5.42 and 5.91 (2br s, 2H), 6.85–7.58 (m, 5H), 7.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8 (CH_3), 25.3 (CH_2), 27.8 (CH_2), 28.1 (CH_2), 30.3 (CH_2), 52.2 (CH_3), 57.6 (C), 65.1 (CH_2), 102.8 (CH), 103.2 (C), 127.8 (CH), 128.4 (CH), 128.8 (CH), 136.4 (C), 146.4 (C), 158.0 (C), 159.5 (C), 163.9 (C), 172.7 (C); MS: *m*/*z* (%)=399 (M^+, 7), 340 (100), 249 (28), 193 (28). Anal. Calcd for $C_{21}H_{25}N_3O_5$: C, 63.15; H, 6.31; N, 10.52. Found: C, 63.09; H, 6.39; N, 10.47.

4.1.24. Methyl 3-acetyl-1-[(aminocarbonyl)amino]-2-methyl-1,3a,4,5,6,7-hexahydrocyclohepta[b]pyrrole-3a-carboxylate **4s**

Yield 249 mg, 81%, pale-yellow powder; mp 189–191 °C; IR (Nujol): ν_{max}=3389, 3306, 3268, 1756, 1713 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.06–1.46 (m, 3H), 1.58–1.84 (m, 2H), 1.91–2.06 (m, 1H), 2.12 (s, 3H), 2.16 (s, 3H), 2.28–2.49 (m, 1H), 2.61–2.74 (m, 1H), 3.57 (s, 3H), 4.96–5.11 (m, 1H), 5.75 and 6.14 (2br s, 2H), 8.59 and 8.66 (2br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.4 (CH_3), 12.6 (CH_3), 23.5 (CH_2), 24.2 (CH_2), 27.5 (CH_2), 29.7 (CH_2), 51.6 (CH_3), 56.2 (C), 101.2 (CH), 114.4 (C), 146.9 (C), 156.7 (C), 157.5 (C), 170.8 (C), 189.0 (C); MS: *m*/*z* (%)=307 (M^+, 6), 276 (45), 248 (100), 203 (43), 161 (49). Anal. Calcd for $C_{15}H_{21}N_3O_4$: C, 58.62; H, 6.89; N, 13.67. Found: C, 58.51; H, 7.00; N, 13.65.

4.1.25. Ethyl 1-[(aminocarbonyl)amino]-3-(anilinocarbonyl)-2-methyl-3a,4,5,6,7,8-hexahydro-1H-cycloocta[b]pyrrole-3a-dicarboxylate **4t**

Yield 260 mg, 63%, white powder; mp 139–141 °C; IR (Nujol): ν_{max}=3354, 3278, 3127, 1784, 1728 cm^{-1}; ^{1}H NMR (400 MHz,

DMSO-d_6) δ 0.98–1.19 (m, 2H), 1.13 (t, 3H, ^3J=7.2 Hz), 1.23–1.51 (m, 3H), 1.61–1.94 (m, 3H), 1.98–2.11 (m, 2H), 2.05 (s, 3H), 3.98–4.19 (m, 2H), 4.59–4.77 (m, 1H), 6.08 (br s, 2H), 6.94–7.01 (m, 1H), 7.24–7.31 (m, 2H), 7.54 (t, 2H, ^3J=7.2 Hz), 8.43 and 8.70 (2br s, 1H), 8.90 and 9.31 (2br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.9 (CH_3), 13.9 (CH_3), 21.8 (CH_2), 22.8 (CH_2), 24.9 (CH_2), 29.5 (CH_2), 37.4 (CH_2), 56.3 (CH_2), 60.6 (C), 96.3 (CH), 108.5 (C), 119.3 (CH), 122.7 (CH), 128.4 (CH), 139.5 (C), 146.2 (C), 150.2 (C), 158.0 (C), 162.7 (C), 172.3 (C); MS: *m*/*z* (%)=412 (M^+, 23), 383 (26), 367 (100), 339 (65), 319 (100), 291 (31), 247 (39), 203 (48). Anal. Calcd for $C_{22}H_{28}N_4O_4$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.14; H, 6.81; N, 13.50.

4.1.26. Ethyl 1-[(aminocarbonyl)amino]-3-[(4-methoxyanilino)-carbonyl]-2-methyl-3a,4,5,6,7,8-hexahydro-1H-cycloocta[b]pyrrole-3a-dicarboxylate **4u**

Yield 314 mg, 71%, white powder; mp 173–176 °C; IR (Nujol): ν_{max}=3425, 3352, 3263, 1792, 1710 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.11–1.19 (m, 3H), 1.13 (t, 3H, ^3J=7.2 Hz), 1.27–1.78 (m, 4H), 1.95–2.19 (m, 3H), 2.08 (s, 3H), 3.70 (s, 3H), 4.01–4.15 (m, 2H), 4.58–4.79 (m, 1H), 6.06 (br s, 2H), 6.83 (d, 2H, ^3J=6.8 Hz), 7.45 (d, 2H, ^3J=6.8 Hz), 8.40 and 8.63 (2br s, 1H), 8.76 and 9.21 (2br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.9 (CH_3), 13.9 (CH_3), 21.9 (CH_2), 22.4 (CH_2), 24.9 (CH_2), 28.9 (CH_2), 37.4 (CH_2), 55.1 (CH_3), 56.3 (CH_3), 60.6 (C), 96.2 (CH), 108.3 (C), 113.6 (CH), 120.9 (CH), 132.5 (C), 132.7 (C), 146.4 (C), 154.9 (C), 157.2 (C), 162.4 (C), 172.3 (C); MS: *m*/*z* (%)=442 (M^+, 5), 397 (71), 369 (100), 335 (61), 319 (16), 292 (8), 262 (82), 219 (45), 174 (27). Anal. Calcd for $C_{23}H_{30}N_4O_5$: C, 62.43; H, 6.85; N, 12.66. Found: C, 64.34; H, 6.81; N, 12.70.

4.1.27. Ethyl 1-[(aminocarbonyl)amino]-3-[(4-chloroanilino) carbonyl]-2-methyl-3a,4,5,6,7-hexahydro-1H-cycloocta[b]pyrrole-3a-dicarboxylate **4v**

Yield 290 mg, 65%, white powder; mp 156–158 °C; IR (Nujol): ν_{max}=3289, 3216, 3164, 1745, 1723 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.01–1.20 (m, 2H), 1.13 (t, 3H, ^3J=7.2 Hz), 1.28–1.49 (m, 4H), 1.55–1.76 (m, 2H), 1.86–2.15 (m, 2H), 2.08 (s, 3H), 3.99–4.18 (m, 2H), 4.59–4.81 (m, 1H), 6.07 (br s, 2H), 7.29 (d, 2H, ^3J=8.8 Hz), 7.58 (d, 2H, ^3J=8.8 Hz), 8.45 and 8.71 (2br s, 1H), 9.08 and 9.43 (2br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.0 (CH_3), 13.9 (CH_3), 21.8 (CH_2), 22.8 (CH_2), 24.7 (CH_2), 28.9 (CH_2), 37.4 (CH_2), 56.3 (CH_2), 60.2 (C), 96.5 (CH), 108.5 (C), 120.7 (CH), 125.9 (C), 128.3 (CH), 138.6 (C), 146.2 (C), 150.3 (C), 158.0 (C), 162.8 (C), 172.1 (C); MS: *m*/*z* (%)=448 (M^++2, 3), 446 (M^+, 8), 421 (15), 419 (42), 377 (35), 375 (100), 322 (73), 293 (36), 249 (43), 205 (17). Anal. Calcd for $C_{22}H_{27}N_4O_4$: C, 59.12; H, 6.09; N, 12.54. Found: C, 59.14; H, 6.21; N, 12.50.

4.1.28. 3a-Ethyl 3-methyl 1-[(aminocarbonyl)amino]-2-methyl-3a,4,5,6,7,8-hexahydro-1H-cycloocta[b]pyrrole-3,3a-dicarboxylate **4w**

Yield 302 mg, 86%, beige powder; mp 149–151 °C; IR (Nujol): ν_{max}=3347, 3318, 3216, 1768, 1752 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02–1.26 (m, 2H), 1.17 (t, 3H, ^3J=7.2 Hz), 1.30–1.47 (m, 2H), 1.65–2.00 (m, 5H), 2.21 (s, 3H), 2.58–2.71 (m, 1H), 3.58 (s, 3H), 4.02–4.17 (m, 2H), 4.72–4.95 (m, 1H), 5.41 and 5.78 (2br s, 2H), 8.12 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5 (CH_3), 13.8 (CH_3), 22.1 (CH_2), 22.7 (CH_2), 24.9 (CH_2), 28.6 (CH_2), 37.5 (CH_2), 50.4 (CH_3), 55.8 (C), 60.9 (CH_2), 100.3 (CH), 106.6 (C), 144.3 (C), 155.7 (C), 159.5 (C), 164.6 (C), 172.3 (C); MS: *m*/*z* (%)=351 (M^+, 3), 322 (1), 278 (24), 246 (9), 203 (3), 149 (100). Anal. Calcd for $C_{17}H_{25}N_3O_5$: C, 58.11; H, 7.17; N, 11.96. Found: C, 58.04; H, 7.21; N, 12.01.

4.1.29. Diethyl 1-[(aminocarbonyl)amino]-2-methyl-3a,4,5,6,7,8-hexahydro-1H-cycloocta[b]pyrrole-3,3a-dicarboxylate **4x**

Yield 347 mg, 95%, pale-yellow powder; mp 152–154 °C; IR (Nujol): ν_{max}=3427, 3372, 3117, 1742, 1688 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12–1.37 (m, 8H), 1.39–1.55 (m, 2H), 1.62–1.83 (m, 2H), 1.96–2.14 (m, 3H), 2.25 (s, 3H), 2.63–2.81 (m, 1H), 3.99–4.24 (m, 4H), 4.78–5.01 (m, 1H), 5.51 (s, 2H), 7.82 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5 (CH_3), 13.9 (CH_3), 14.2 (CH_3), 22.1 (CH_2), 22.8 (CH_2), 25.1 (CH_2), 28.6 (CH_2), 36.9 (CH_2), 56.0 (C), 61.0 (CH_2), 61.2 (CH_2), 100.5 (CH), 107.1 (C), 144.5 (C), 155.4 (C), 159.3 (C), 164.3 (C), 172.5 (C); MS: *m*/*z* (%)=365 (M^+, 8), 336 (1), 320 (5), 292 (100), 246 (36), 203 (12). Anal. Calcd for $C_{18}H_{27}N_3O_5$: C, 59.16; H, 7.45; N, 11.50. Found: C, 59.19; H, 7.43; N, 11.39.

4.1.30. 3a-Ethyl 3-iso-propyl 1-[(aminocarbonyl)amino]-2-methyl-3a,4,5,6,7,8-hexahydro-1H-cycloocta[b]pyrrole-3,3a-dicarboxylate **4y**

Yield 242 mg, 64%, pale-yellow powder; mp 136–138 °C; IR (Nujol): ν_{max}=3256, 3157, 3086, 1812, 1789 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11–1.48 (m, 9H), 1.16–1.27 (m, 3H), 1.40–1.52 (m, 2H), 1.58–1.85 (m, 3H), 1.92–2.05 (m, 2H), 2.14 (s, 3H), 4.00–4.10 (m, 2H), 4.61–4.71 (m, 1H), 4.74–4.89 (m, 1H), 6.14 (br s, 2H), 8.45 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5 (CH_3), 13.9 (CH_3), 20.7 (CH_3), 21.8 (CH_2), 23.1 (CH_2), 24.9 (CH_2), 26.3 (CH_2), 29.6 (CH_2), 55.2 (C), 59.9 (CH_2), 65.2 (CH), 97.7 (CH), 104.1 (C), 146.0 (C), 156.7 (C), 157.5 (C), 163.2 (C), 171.6 (C); MS: *m*/*z* (%)=379 (M^+, 16), 350 (11), 336 (21), 320 (45), 320 (65), 292 (100), 247 (38), 219 (64), 175 (69). Anal. Calcd for $C_{19}H_{29}N_3O_5$: C, 60.14; H, 7.70; N, 11.07. Found: C, 60.03; H, 7.63; N, 10.96.

4.1.31. 3-(tert-Butyl) 3a-ethyl 1-[(aminocarbonyl)amino]-2-methyl-3a,4,5,6,7,8-hexahydro-1H-cycloocta[b]pyrrole-3,3a-dicarboxylate **4z**

Yield 287 mg, 73%, beige powder; mp 110–112 °C; IR (Nujol): ν_{max}=3417, 3354, 3156, 1784, 1743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03–1.54 (m, 4H), 1.21 (t, 3H, ^3J=7.2 Hz), 1.43 (s, 9H), 1.53–2.06 (m, 5H), 2.23 (s, 3H), 2.67–2.76 (m, 1H), 4.15 (q, 2H, ^3J=7.2 Hz), 4.93 (t, 1H, ^3J=8.2 Hz), 5.49 (br s, 2H), 7.67 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4 (CH_3), 14.1 (CH_3), 22.1 (CH_2), 22.9 (CH_2), 25.2 (CH_2), 28.3 (CH_3), 28.7 (CH_2), 37.0 (CH_2), 56.0 (C), 61.0 (CH_2), 80.0 (C), 100.2 (CH), 108.5 (C), 144.5 (C), 154.4 (C), 159.4 (C), 163.7 (C), 172.1 (C); MS: *m*/*z* (%)=393 (M^+, 12), 336 (3), 320 (100), 264 (100), 247 (10), 220 (89). Anal. Calcd for $C_{20}H_{31}N_3O_5$: C, 61.05; H, 7.94; N, 10.68. Found: C, 60.99; H, 7.88; N, 10.81.

4.1.32. 3-Allyl 3a-ethyl 1-[(aminocarbonyl)amino]-2-methyl-3a,4,5,6,7,8-hexahydro-1H-cycloocta[b]pyrrole-3,3a-dicarboxylate **4aa**

Yield 294 mg, 78%, pale-yellow powder; mp 149–153 °C; IR (Nujol): ν_{max}=3386, 3265, 3218, 1793, 1742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (t, 3H, ^3J=7.2 Hz), 1.33–1.51 (m, 2H), 1.67–2.02 (m, 2H), 2.04–2.17 (m, 5H), 2.26 (s, 3H), 2.73–2.86 (m, 1H), 4.12 (q, 2H, ^3J=7.2 Hz), 4.51–4.57 (m, 1H), 4.79–4.96 (m, 2H), 5.12–5.27 (m, 2H), 5.81–5.92 (m, 1H), 6.02 and 6.13 (2br s, 2H), 7.92 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6 (CH_3), 13.9 (CH_3), 22.8 (CH_2), 25.1 (CH_2), 28.7 (CH_2), 30.2 (CH_2), 37.0 (CH_2), 56.0 (C), 61.2 (CH_2), 64.2 (CH_2), 100.7 (CH), 101.6 (C), 117.5 (CH_2), 132.5 (CH), 146.1 (C), 156.3 (C), 158.2 (C), 162.9 (C), 170.9 (C); MS: *m*/*z* (%)=377 (M^+, 14), 336 (23), 320 (58), 304 (67), 292 (79), 247 (100), 219 (38), 175 (28). Anal. Calcd for $C_{19}H_{27}N_3O_5$: C, 60.46; H, 7.21; N, 11.13. Found: C, 60.52; H, 7.34; N, 11.21.

4.1.33. 3-Benzyl 3a-ethyl 1-[(aminocarbonyl)amino]-2-methyl-3a,4,5,6,7,8-hexahydro-1H-cycloocta[b]pyrrole-3,3a-dicarboxylate **4ab**

Yield 393 mg, 92%, yellow powder; mp 142–147 °C; IR (Nujol): ν_{max}=3422, 3276, 3179, 1786, 1740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96–1.13 (m, 3H), 1.18–1.46 (m, 4H), 1.67–2.01 (m, 5H), 2.22 (s, 3H), 2.70–2.82 (m, 1H), 3.98 (q, 2H, ^3J=7.2 Hz), 4.79–4.99 (m, 1H), 5.02 (d, 1H, ^2J=8.4 Hz), 5.09 (d, 1H, ^2J=8.4 Hz), 5.30 (br s, 2H), 7.07–7.39 (m, 5H), 7.41 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.7 (CH_3),

13.9 (CH_3), 22.2 (CH_2), 22.9 (CH_2), 25.1 (CH_2), 28.6 (CH_3), 37.0 (CH_2), 56.1 (C), 61.3 (CH_2), 65.3 (CH_2), 100.7 (CH), 106.9 (C), 127.9 (CH), 128.1 (CH), 128.4 (CH), 136.4 (C), 144.5 (C), 156.1 (C), 158.9 (C), 164.1 (C), 172.6 (C); MS: m/z (%)=427 (M^+, 11), 398 (1), 354 (100), 310 (13). Anal. Calcd for $C_{23}H_{29}N_3O_5$: C, 64.62; H, 6.84; N, 9.83. Found: C, 64.69; H, 6.97; N, 9.71.

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