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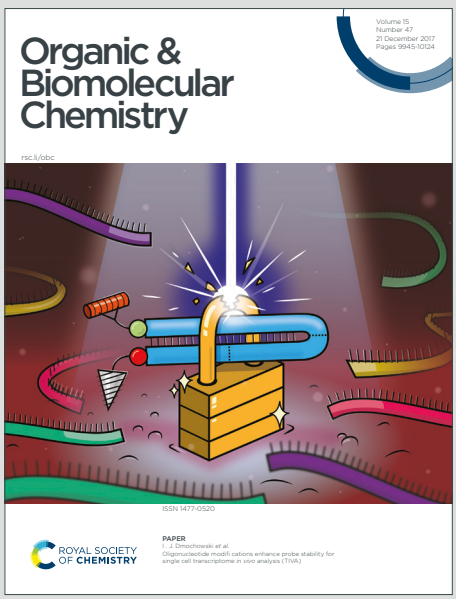

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PAPER

pseudo-Multicomponent 1,3-dipolar cycloaddition involving a metal-free generation of unactivated azomethine ylides

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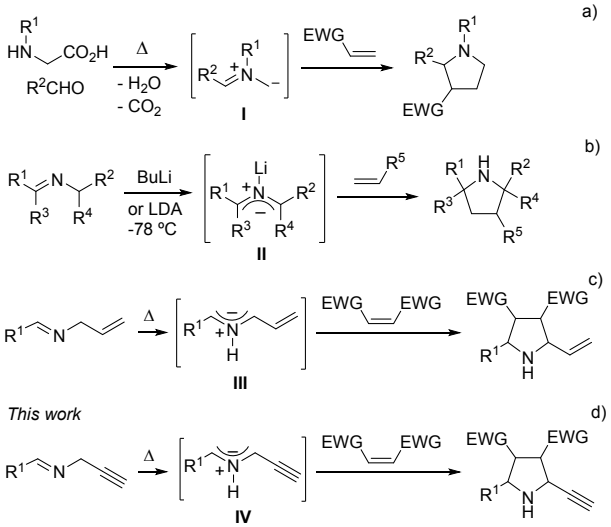
The *pseudo*-multicomponent reaction between propargyl amine, an aldehyde and an electron-deficient alkene is described. The C-H activation takes place thermally and allows to obtain cicloadducts in very good yields and high diastereoselectivities. The relative configuration is determined by X-Ray diffraction analysis of the chiral molecule, obtained as single diastereosiomer, using a chiral maleimide. A brief study of the stability of the possible ylides involved in the process is also mentioned, confirming the high diastereoselectivity observed. The high functional group density of these cycloadducts permits the synthesis of complex heterocycles. After allylation or propargylation of the pyrrolidine nitrogen atom, RCM-DA cycloaddition or a cyclotrimerization with an alkyne are studied, respectively. In this last example, the resulting tetracyclic structures possess potential interest as drugs for the treatment of cystic fibrosis.

Introduction

The C–H bond activation avoiding metals constitutes one of the most important sustainability challenges in organic synthesis.[1] The relevance of the processes bypassing the introduction of activating-directing auxiliary groups, ensuring a total atom economy, is even higher. Cycloadditions, for example, offer a complete atom economy, and, in particular, 1,3-dipolar cycloadditions (1,3-DCs)[2,3] involving azomethine ylides are thermally generated in the presence of activating groups. Thus, *N*-alkyl α-amino acids and aldehydes thermally react to generate the corresponding nonstabilized iminium-type dipole **I** after decarboxylation (Scheme 1a).[2] On the other side, the lack of the reactivity of imines requires strong bases at very low temperatures to afford dipoles, (lithium azaallyl anions) **II** (Scheme 1b), which react with dipolarophiles.[4] Employing a different strategy, our group developed a successful thermal activation of Schiff base derivatives to generate non-stabilized azomethine ylides **III** by promotion of a thermal 1,2-prototropy shift (Scheme 1c). Maleimides and bis(phenylsulfonyl)ethylene (BPSE) were appropriate dipolarophiles whose cycloadducts were key intermediates for the diastereoselective synthesis of a tricyclic thrombin inhibitor.[5]

In this work, we continue with the same strategy, but now replacing the allyl by a propargyl group (Scheme 1d). The risk of suffering thermal isomerization to the corresponding allene,[6] in the presence of basic imines, is fortunately circumvented to afford the desired ethynyl-substituted pyrrolidines, which are key structures to build complex heterocyclic scaffolds.



Scheme 1 Generation of unactivated azomethine ylides.

Results and Discussion

The unactivated propargilic system **1a** was allowed to react with *N*-methylmaleimide (NMM, as bench reaction) under identical sequence (Table 1) that the previously described for the allylic imines shown in Scheme 1c.[5] This, propargylic imine **1a** was tested in a pressure tube at 150, 130 and 100 °C using different reaction times (Table 1, entries 1-5). The complete conversions observed at 150 and 130 °C between 24-18 h revealed the presence of the allene derived from the basic thermal isomerization of the terminal alkyne group (10% approximately, Table 1, entries 1-3). This cumulene was detected in smaller proportions in the reaction performed at 130 °C for 8 h (Table

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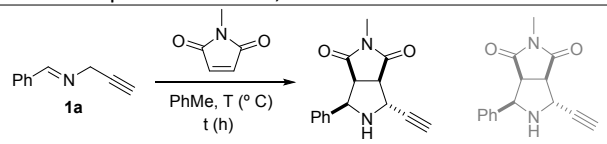
1, entry 4) and it was not present in the crude mixture at 100 °C (Table 1, entry 5). An extraordinary feature of this transformation at 130 ° C *vs* the cycloaddition underwent by the benzylidene allyl amine (run at 150 °C)[5] was the very high diastereoselectivity observed in the crude reaction mixture (>95:5, Table 1, entries 2 and 3 *vs* 71:29 detected in the reaction with allylamine). Fortunately, the undesired allene byproduct was not observed when the reaction was tested in the *pseudo*-multicomponent mode, that means, adding benzaldehyde, the propargylamine and, after 30 min the NMM, heating the resulting reaction mixture in a pressure tube at 130 °C (Table 1, entries 6 and 7). The reaction time of 18 h was necessary because lower reaction times furnished lower conversions (Table 1, entry 8). The employment of water or 1,4-dioxane did not improve the results achieved using toluene as solvent (Table 1, entries 9 and 10).

Table 1 Optimization of 1,3-DC between **1a** and NMM.[a]

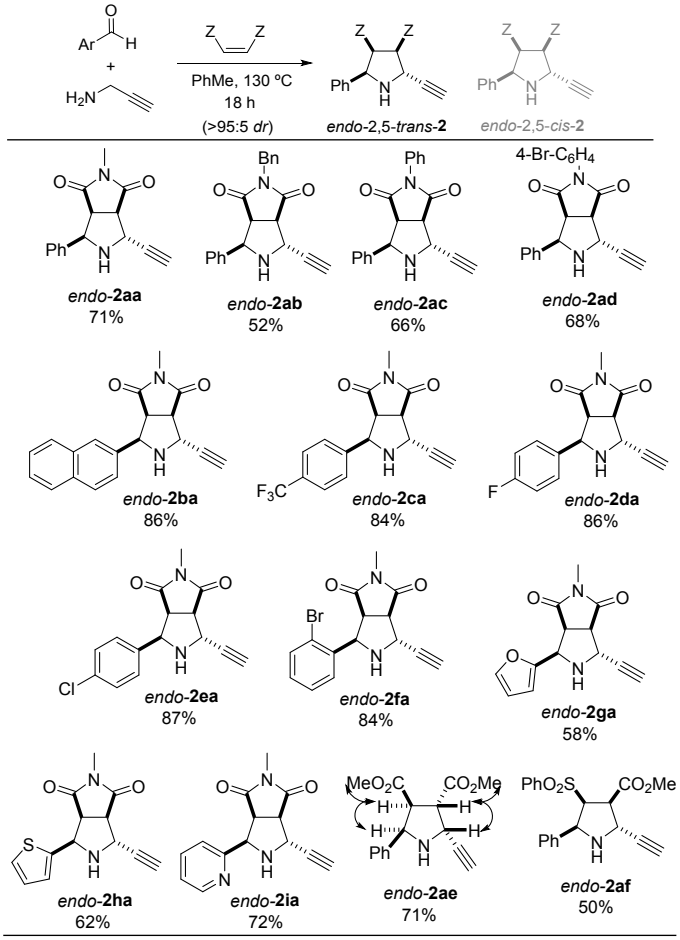


Entry	T (°C)	t (h)	Conv (%)[a]	*dr*[a]
1	150	24	100	65:35[b]
2	130	24	100	>95:5[b]
3	130	18	100	>95:5[b]
4	130	8	58	>95:5[b]
5	100	24	24	>95:5
6[c]	130	24	100	>95:5
7[c]	130	18	100	>95:5
8[c]	130	8	50	>95:5
9[c,d]	130	18	34	---- [b]
10[c,e]	130	18	43	----[b]

[a] Determined by ^{1}H NMR of the crude mixture. [b] Impurified crude reaction material by ^{1}H NMR. [c] *pseudo*-Multicomponent version. [d] Reaction performed in water. [e] Reaction performed in 1,4-dioxane.

Using the best reaction conditions (Table 1, entry 7), the effect of the structures of each component was next evaluated (Table 2). *N*-Alkyl and *N*-arylmalemides afforded the corresponding cycloadducts *endo*-**2** in good yields. Aromatic aldehydes bearing electron-donating or electron-withdrawing groups gave very good results as well. Specially interesting resulted the high chemical yield obtained from halogenated benzaldehydes. Cycloadducts with heretoaromatic substituents bonded at 5-position were also prepared in good yields. Other dipolarophiles, different to maleimides, as dimethyl fumarate and methyl β-(phenylsulfonyl)acrylate afforded the corresponding cycloadducts **2ae** and **2af** in good yields, respectively. In all these examples the high diasteresoelectivity (>95:5) was calculated by ^{1}H NMR spectra of the crude residue, obtaining exclusively the pure major diasteroisomer after flash chromatography (silica-gel). β-(phenylsulfonyl)acrylate These experiments confirmed the high chemoselectivity found when β-(phenylsulfonyl)acrylate was empoyed. In the ^{1}H NMR crude mixture some decomposition material was observed together with compound **2af** and any other cycloadduct was isolated after flash chromatograpy. So, the chemoselesctivity for **2af** can be estimated in >95:5.

Table 2 Scope of 1,3-DC between **1** and dipolarophiles.[a]



The relative configuration of all racemic compounds *endo*-**2**, as well as the absolute configuration of the resulting molecule *endo*-**2ag**[7] obtained after the incorporation of the *N*-[(*R*)-1-phenylethyl]maleimide as dipolarophile under the optimized reaction conditions, was determined by X-Ray diffraction analysis (Figure 1).[8] The isolated chemical yield of the enantiomerically enriched compound *endo*-**2ag** was 67%, and the diastereomeric ratio was very high (>95:5), despite of the high operational temperature used.

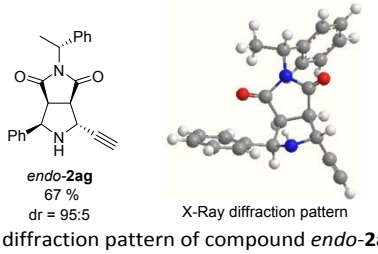


Figure 1 X-Ray diffraction pattern of compound *endo*-**2ag**.

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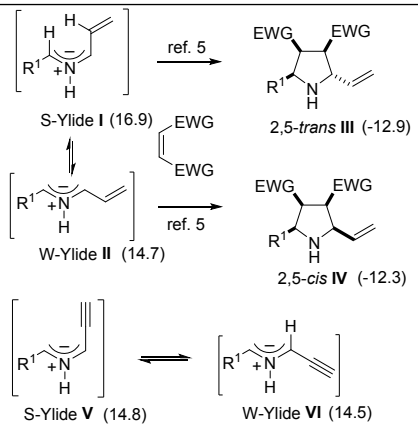
Analysing DFT calculations of the activation process using allylimines (Scheme 1, eq. c)[5] it was justified the lower diastereoselectivity because the S-ylide **I** was the preferred (kinetic intermediate), although the W-ylide **II** was the most stable. In fact, S-ylide **I** afforded the most stable *trans*-heterocycle **III** (Scheme 2).[5] The formation of the preferred S-ylide **IV** is much more stable than S-ylide **I** by steric reasons due to the lineal triple bond character. As well, the energies between S-ylide **V** and W-Ylide **VI** remained closer to each other allowing a better 2,5-*trans* diastereoselectivity experimentally demonstrated in this work. According to the chemoselectivity observed in cycloadduct **2af** we can propose that the negative charge of the ylide **V** remains closer to the propargylic moiety. [9]



Scheme 2 Relative stability of intermediate azomethine ylides. In brackets relative energies in kcal·mol^{-1}.

The high functional group density of these polysubstituted pyrrolidines *endo*-**2** allowed the construction of more complex fused heterocycles. For this purpose, the preparation of the *N*-propargyl pyrrolidine **3** was carried out previously to the cyclotrimerization step. Thus, *endo*-**2** compounds were treated with propargyl bromide (5 equiv) in refluxing acetonitrile for two days using potassium carbonate as base. The intermediate diyne compounds were isolated in good yields (Scheme 3). These *N*-propargylpyrrolidines **3** were allowed to undergo a metal-promoted cyclotrimerization. As in the previous publication of our group involving chiral propargylamides, the cyclotrimerization using $CpCo(CO)_2$ failed.[10] But, fortunately, Wilkinson's catalyst proved to be appropriate to run the reaction satisfactorily.[11] The reaction of a 0.1 M solution of diynes in toluene, with 10 equivalents of the corresponding hexyne, in the presence of 5 mol% of $Rh(PPh_3)_3Cl$, at 100 °C for 19 h, afforded tetracyclic heterocycles **4** in low to modest yields (Scheme 3). In general, yields of the reactions carried out in the presence of 2-butyne-1,4-diol or dimethyl acetylene-dicarboxylate were higher than the transformations employing 3-hexyne.

The large number of examples reported in this section obeys to the importance of the condensed polycyclic skeleton A-B-C-D. Although only one patented example contained this A-B-C-D arrangement, these structures incorporate the A-B-C scaffold (**Σ**) which is crucial in the preparation of pharmaceuticals for the treatment of cystic fibrosis (CF),[12] consisting in a genetic multiorgan disease (Scheme 3). F508del is the most common mutation causing defective formation and function of CFTR.[13]

In other different study, the *N*-allylation of products **2** was achieved with allyl bromide (5 equiv) in refluxing acetonitrile for 24 h using potassium carbonate as base. Enynes **5** were isolated in very high yields and immediately submitted to ring-closing metathesis using Grubbs' II catalyst (20 mol%) under refluxing dichloromethane for 24 h.[14] Tricyclic dienes **6** were isolated in excellent yields and with high purity from the crude reaction mixture (Scheme 3). Next, the [4+2] cycloaddition took place in the presence of NPM, at room temperature for 24 h giving the desired pentacyclic scaffolds **7** in almost quantitative yields (91-94%) (Scheme 2). These new compounds are not registered in data bases but they can be also considered as potential active pharmaceuticals for the treatment of the CF.

The relative configuration of molecules **4** and **7** was assigned after analysis of NOESY experiments (see SI). In the case of compounds **7**, this arrangement corresponded to the most favourable **TS-1** where the NPM approached through the *endo*-front face (according to structure shown in Scheme 3) rather than the *endo*-back position (see SI). The H_a of **7**, as well as the precursor **6**, remained in *trans*-arrangement with R^1, which justified that no epimerization occurred at this stereogenic centre during the metathesis reaction. This fact, and the no epimerization of similar substrates during the Rh-catalyzed cyclotrimerization reported in the literature,[11,14] ensures the relative configuration of **4** and **6** too.

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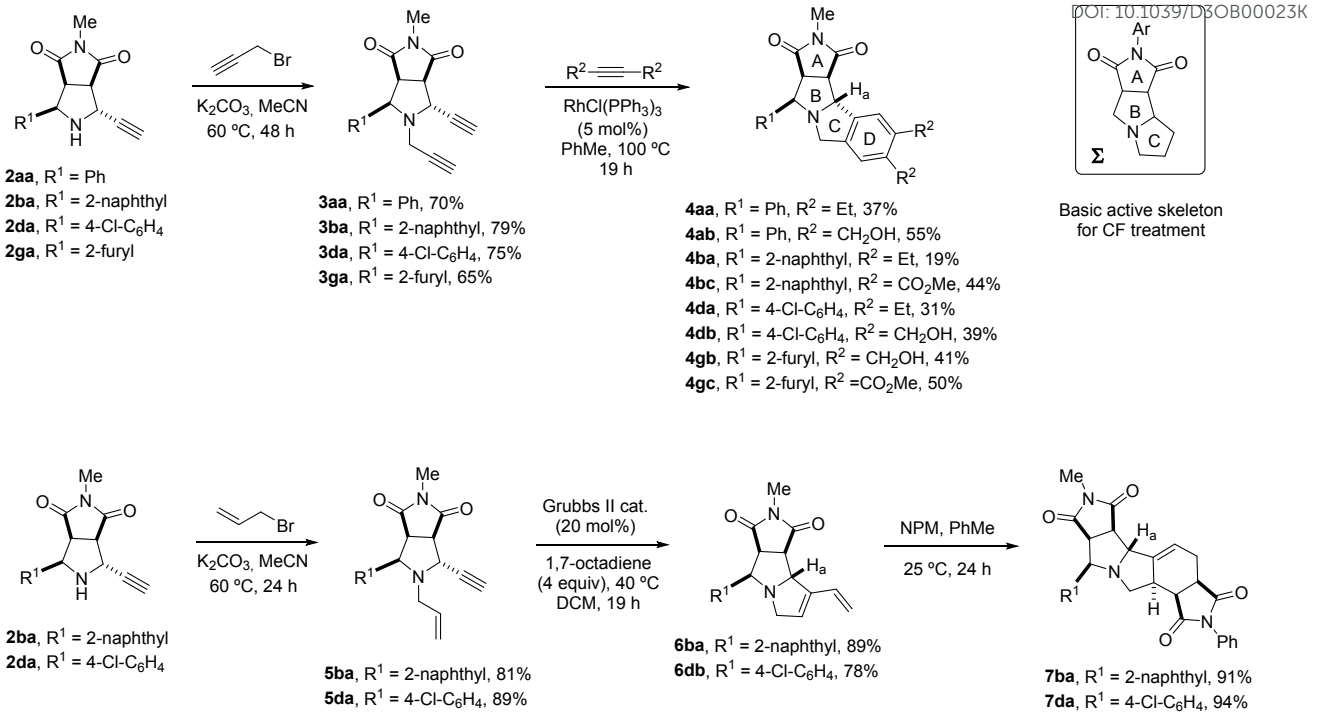

Scheme 3 Synthesis of polyfused heterocycles **4** and **7** involving RCM together with cyclotrimerizations and Diels-Alder reactions.

Conclusions

The thermal activation of *N*-propargyl imines took place avoiding undesired allene isomerization in a *pseudo*-multicomponent process in good to excellent yields. The reaction represented an almost total atom economy and constituted an advance in sustainability in this area avoiding difficult operational transformations. The stereochemical outcome followed the pattern of the allylated systems reported previously, that means, 2,5-*trans* and 3,4,5-*cis* arrangements. The control of the diastereoselectivity is excellent (>95:5) and also the stereochemistry of **2ag** induced by the chiral information attached to the nitrogen atom of the maleimide is almost complete (>95:5). These details obeyed to the high stability of the corresponding fleeting S-ylide. In three very simple steps very complex fused heterocyclic entities were achieved. This process acquires an additional dimension because the cyclotrimerization derivatives are considered active candidates for the treatment of the cystic fibrosis. This family of tetracyclic compounds as well as the corresponding pentacyclic systems obtained by a sequential RCM-DA cycloaddition are currently tested as herbicides and in the control of plant growth.

Experimental Section

1. General

All commercially available reagents and solvents were used without further purification, only aldehydes were also distilled prior to use. Analytical TLC was performed on Schleicher & Schuell F1400/LS 254 silica gel plates, and the spots were visualised under UV light (λ = 254 nm). Flash chromatography was carried out on hand packed columns of Merck silica gel 60 (0.040-0.063 mm). Melting points were determined with a Reichert Thermovar hot plate apparatus and are uncorrected. Optical rotations were measured on a Perkin Elmer 341 polarimeter with a thermally jacketted 5 cm cell at approximately 25˚C and concentrations (*c*) are given in g/100 mL. The structurally most important peaks of the IR spectra (recorded using a Nicolet 510 P-FT) are listed and wavenumbers are given in cm^{-1}. NMR 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 $^{13}C\{1H\}$ NMR, using $CDCl_3$ as the solvent and TMS as internal standard (0.00 ppm) unless otherwise stated. The following abbreviations are used to describe peak patterns where appropriate: s = singlet, d = doublet, t = triplet q = quartet, m = multiplet or unresolved and br s = broad signal. All coupling constants (*J*) are given in Hz and chemical shifts in ppm. $^{13}C\{1H\}$ NMR spectra were referenced to $CDCl_3$ at 77.16 ppm. 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.

2. Preparation of compounds 2

In a pressure tube propargylamine (64 µL, 1 mmol) and the aldehyde (1 mmol) were added in toluene (1.5 mL). The solution was stirred 1 hour at room temperature and later, a solution of the corresponding dipolarophile (1 mmol) in toluene (1.5 mL) was added. The resulting mixture was stirred 130 C for 18 h. The solvent was evaporated, and the residue was purified by flash

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chromatography (flash silica-gel) eluting with *n*-hexane:ethyl acetate mixtures affording pure compounds **2**.

4-Ethynyl-2-methyl-6-phenyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (**2aa**):
Pale yellow prisms (180 mg, 71% yield), mp 161-162 °C (*n*-hexane:EtOAc). IR (neat) ν_{max}: 1693, 1386, 1328, 1285, 1093, 993, 894, 745cm^{-1}. ^{1}H NMR (300 MHz) δ: 2.42 (br s, 1H, NH), 2.45 (d, J = 2.2 Hz, 1H, C≡CH), 2.87 (s, 3H, CH_3), 3.37 (dd, *J* = 7.6, 0.9 Hz, 1H, CH≡CCHCHC=O), 3.43 (dd, *J* = 8.2, 7.6 Hz, 1H, PhCHCH), 4.60 (dd, *J* = 2.2, 1.0 Hz, 1H, NCHC≡), 4.89 (d, *J* = 8.2 Hz, 1H, PhCH), 7.28-7.37 (m, 5H, ArH). ^{13}C NMR (75 MHz) δ: 25.1 (CH3), 48.4, 50.3 (2xCHC=O), 52.1 (NCHC≡), 62.7 (PhCH), 72.9 (C≡CH), 83.3 (C≡CH), 127.3, 128.3, 128.5, 137.3 (ArC), 175.2, 176.9 (2xC=O). LRMS(EI) *m/z* : 254 (M+, 22%), 253 (14), 168 (11), 151 (19), 144 (16), 143 (100), 142 (45), 116 (22), 115 (42), 104 (11). HRMS (ESI) calcd. for $C_{15}H_{14}N_2O_2$: 254.1055; found: 254.1046.

2-Benzyl-4-ethynyl-6-phenyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (**2ab**):
Pale yellow prisms (171 mg, 52% yield); mp 148-153 ºC (*n*-hexane:EtOAc). IR (neat) υ_{max}: 3327, 3265, 1696, 1169, 738, 696, 670, 622, 527 cm^{-1}. ^{1}H NMR (400 MHz) δ: 7.37–7.30 (m, 5H, Ar*H*), 7.29 – 7.18 (m, 3H, Ar*H*), 7.16 – 7.09 (m, 2H, Ar*H*), 4.89 (d, *J* = 7.6 Hz, 1H, NC*H*Ph), 4.65 (d, *J* = 2.3 Hz, 1H, NC*H*C≡C*H*), 4.61 – 4.47 (m, 2H, NCH_2Ph), 3.47 – 3.32 (m, 2H, 2xNCHCHCO), 2.44 (d, *J* = 2.2 Hz, 1H, C≡C*H*), 2.00 (s, 1H, NH). ^{13}C NMR (101 MHz) δ 176.7 (CO), 174.8 (CO), 137.1 (Ar*C*), 135.8 (Ar*C*), 129.2 (Ar*C*H), 128.6 (Ar*C*H), 128.4 (Ar*C*H), 128.2 (Ar*C*H), 128.0 (Ar*C*H), 127.5 (Ar*C*H), 83.4 (*C*≡CH*)*, 72.8 (C≡*C*H), 62.9 (N*C*HPh), 52.3 (*C*HCO), 50.5 (*C*HCO), 48.3 (N*C*HC≡C*H*), 42.8 (CH_2). LRMS (EI) *m/z* 330 (M^+, 17%), 115 (24), 116 (12), 142 (24), 143 (100), 144 (12). HRMS (ESI) calcd. for $C_{21}H_{18}N_2O_2$: 330.1386; found: 330.1388.

4-Ethynyl-2,6-diphenyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (**2ac**):
Colourless needles (209 mg, 66% yield); mp 155-161 ºC (*n*-hexane:EtOAc). IR (neat) υ_{max}: 3334, 1702, 1391, 1179, 733, 689, 615 cm^{-1}. ^{1}H NMR (300 MHz) δ: 7.46 – 7.27 (m, 8H, Ar*H*), 7.23 – 7.07 (m, 2H, Ar*H*), 5.01 (d, *J* = 7.6 Hz, 1H, NC*H*Ph), 4.75 (d, *J* = 2.2 Hz, 1H, NC*H*C≡C*H*), 3.65 – 3.48 (m, 2H, 2xNCHC*H*CO), 2.47 (d, *J* = 2.2 Hz, 1H, C≡C*H*). ^{13}C NMR (101 MHz) δ: 176.0 (CO), 174.2 (CO), 137.3 (Ar*C*), 131.8 (Ar*C*), 129.2 (Ar*C*H), 128.6 (Ar*C*H), 128.6 (Ar*C*H), 127.4 (Ar*C*H), 126.2 (Ar*C*H), 83.1 (*C*≡CH*)*, 73.2 (C≡*C*H*)*, 63.1 (N*C*HPh), 52.4 (*C*HCO), 50.7 (*C*HCO), 48.3 (N*C*HC≡C*H*). LRMS (EI) *m/z*: 316 (M^+, 15%), 115 (25), 116 (12), 142 (26), 143 (100), 144 (12). HRMS (ESI) calcd. for $C_{20}H_{16}N_2O_2$: 316.1200; found 316.1202.

2-(4-Bromophenyl)-4-ethynyl-6-phenyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (**2ad**): Pale yellow plates (268 mg, 68% yield); mp 153-156,5 ºC (*n*-hexane:EtOAc). IR (neat) υ_{max}: 3341, 3277, 1702, 1491, 1384, 1075, 816, 743, 620, 523 cm^{-1}. ^{1}H NMR (300 MHz) δ: 7.63 – 7.48 (m, 2H, Ar*H*), 7.43 – 7.29 (m, 5H, Ar*H*), 7.12 – 7.01 (m, 2H, Ar*H*), 5.01 (d, *J* = 7.7 Hz, 1H, NC*H*Ph), 4.73 (d, *J* = 2.1 Hz, 1H, NC*H*C≡C*H*), 3.73 – 3.46 (m, 2H, 2xNCHC*H*CO), 2.47 (d, *J* = 2.2 Hz, 1H, 1H, C≡C*H*). 2.14 (s, 1H, N*H*). ^{13}C NMR (101 MHz) δ: 175.7 (CO), 173.9 (CO), 137.3 (Ar*C*), 132.4 (Ar*C*H), 130.0 (Ar*C*), 128.6 (Ar*C*H), 127.7 (Ar*C*H), 127.4 (Ar*C*H), 122.4 (Ar*C*), 83.0 (*C*≡CH*)*,73.2 (C≡*C*H*)*, 63.1 (N*C*HPh), 52.4 (*C*HCO), 50.8 (*C*HCO), 48.3 (N*C*HC≡C*H*). LRMS (EI) *m/z*: 394 (M^+, 6%), 115 (19), 142 (20), 143 (100), 144 (12). HRMS (ESI) calcd. for $C_{20}H_{15}BrN_2O_2$: 394.0317; found: 394.0295.

4-Ethynyl-2-methyl-6-(naphth-2-yl)tetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (**2ba**): Colourless prisms (261 mg, 86% yield); mp 182-186 ºC (*n*-hexane:EtOAc). IR (neat) υ_{max}: 3227, 1682, 1698, 1437, 1280, 725 cm^{-1}. ^{1}H NMR (300 MHz) δ: 7.93 – 7.65 (m, 4H Ar*H*), 7.52 – 7.36 (m, 3H Ar*H*), 5.07 (d, *J* = 8.5 Hz, 1H, NC*H*-Ar)), 4.68 (d, *J* = 2.2 Hz, 1H, NC*H*C≡C*H*), 3.54 (t, *J* = 8.1 Hz, 1H, NCHC*H*CO), 3.43 (d, *J* = 7.6 Hz, 1H, NCHC*H*CO), 2.88 (s, 3H, CH_3), 2.46 (d, *J* = 2.1 Hz, 1H, C≡C*H*). ^{13}C NMR (101 MHz) δ: 176.9 (CO), 175.2 (CO), 134.7 (Ar*C*), 133.4 (Ar*C*), 133.4 (Ar*C*), 128.1 (Ar*C*H), 128.1 (Ar*C*H), 128.0 (Ar*C*H), 126.3 (Ar*C*H), 126.2 (Ar*C*H), 126. 0 (Ar*C*H), 125.5 (Ar*C*H), 83.1 (*C*≡CH*)*, 73.2 (C≡*C*H*)*, 62.9 (N*C*HAr), 52.3 (*C*HCO), 50.4 (*C*HCO), 48.4 (N*C*HC≡C*H*), 25.2 (CH_3). LRMS (EI) *m/z*: 304 (M^+, 27%), 139 (10), 151 (11), 154 (11), 165 (37), 166 (13) 191 (10), 192 (71), 193 (100), 194 (15). HRMS (ESI) calcd. for $C_{19}H_{16}N_2O_2$: 304.1212; found: 304.1203.

4-Ethynyl-2-methyl-6-[4-(trifluoromethyl)phenyl)]tetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (**2ca**): Pale yellow plates (270 mg, 84% yield); mp 150-154 ºC (*n*-hexane:EtOAc). IR (neat) υ_{max}: 3249, 1694, 1324, 1122, 1065, 704 cm^{-1}. ^{1}H NMR (400 MHz) δ: 7.59 (d, *J* = 8.1 Hz, 2H, Ar*H*), 7.43 (d, *J* = 8.4 Hz, 2H, Ar*H*), 4.94 (d, *J* = 8.4 Hz, 1H, NC*H*Ar), 4.62 (d, *J* = 2.2 Hz, 1H, NC*H*C≡C*H*), 3.48 (t, *J* = 8.0 Hz, 1H, NCHC*H*CO), 3.41 (d, *J* = 7.6 Hz, 1H, NCHC*H*CO), 2.89 (s, 3H, CH_3), 2.45 (d, *J* = 2.2 Hz, 1H, C≡C*H*), 2.09 (s, 1H, NH). ^{13}C NMR (75 MHz) δ: 176.7 (CO), 174.9 (CO), 141.6 (ArC), 130.5 (q, *J* = 32.4 Hz, *C*-CF_3), 127.8 (Ar*C*H), 125.5 (q, *J* = 3.7 Hz, Ar*C*H), 124.2 (q, *J* = 272.2 Hz, CF_3), 83.1 (*C*≡CH), 73.2 (C≡*C*H), 62.3 (N*C*HAr), 52.1 (*C*HCO), 50.5 (*C*HCO), 48.4 (N*C*HC≡C*H*), 25.2 (CH_3). ^{19}F NMR (282 MHz) δ: -62.47. LRMS (EI) *m/z*: 322 (M^+, 15%), 43 (21), 115 (22), 151 (17), 172 (11), 210 (21) 211 (21), 211 (100), 212 (14). HRMS (ESI) calcd. for $C_{16}H_{13}F_3N_2O_2$: 322.0929; found 322.0926.

4-Ethynyl-6-(4-fluorophenyl)-2-methyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (**2da**): Pale yellow plates (234 mg, 86% yield); mp 145-149 ºC (*n*-hexane:EtOAc). IR (neat) υ_{max}: 3319, 3270, 1689, 1288 1088, 821, 580 cm^{-1}. ^{1}H NMR (400 MHz) δ: 7.34 – 7.20 (m, 2H, Ar*H*), 7.07 – 6.95 (m, 2H, Ar*H*), 4.87 (d, *J* = 7.9 Hz, 1H, NC*H*Ar), 4.59 (d, *J* = 2.2 Hz, 1H, NC*H*C≡C*H*), 3.45 – 3.26 (m, 2H, 2x NCHC*H*CO), 2.88 (s, 3H, CH_3), 2.44 (d, *J* = 2.2 Hz, 1H, C≡C*H*), 2.04 (s, 1H, NH). ^{13}C NMR (101 MHz) δ: 176.9 (CO), 175.2 (CO), 162.58 (d, *J* = 246.3 Hz, *C*F), 133.15 (d, *J* = 3.1 Hz, Ar*C*), 128.9 (d, *J* = 8.1 Hz, Ar*C*H), 115.4 (d, *J* = 21.4 Hz, Ar*C*H), 83.2 (*C*≡CH), 73.0 (C≡*C*H), 62.1 (N*C*HAr), 52.1 (*C*HCO), 50.3 (*C*HCO), 48.4 (N*C*HC≡C*H*), 25.1 (CH_3). ^{19}F NMR (282 MHz) δ: -75.74, -113.79. LRMS (EI) *m/z*: 272 (M^+, 12%), 122 (11), 133(40), 134 (22), 151 (13), 160 (18), 161 (100), 162 (12). HRMS (ESI) calcd. for $C_{15}H_{13}FN_2O_2$: 272.0961; found: 272.0961 m/z.

4-(4-Chlorophenyl)-6-ethynyl-2-methyltetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (**2ea**): Pale yellow prisms (250 mg, 87% yield); mp 188-197 ºC (*n*-hexane:EtOAc). IR (neat) υ_{max}: 3280, 1685, 1279, 1069, 823 cm^{-1}. ^{1}H NMR (300 MHz) δ: 7.49 – 6.93 (m, 4H, Ar*H*), 4.87 (d, *J* = 7.9 Hz, 1H, NC*H*-Ar), 4.61 (d, *J* = 2.2 Hz, 1H, NC*H*C≡C*H*), 3.54 – 3.29 (m, 2H, 2x NCHC*H*CO), 2.89 (s, 3H, CH_3), 2.46 (d, *J* = 2.2 Hz, 1H, C≡C*H*). ^{13}C NMR (101 MHz) δ: 176.8 (CO), 175.1 (CO), 135.9 (Ar*C*), 134.0 (Ar*C*), 128.7 (Ar*C*H), 128.6 (Ar*C*H), 83.1 (*C*≡CH), 73.1 (C≡*C*H), 62.1 (N*C*HAr), 52.1 (*C*HCO), 50.3 (*C*HCO), 48.3 (N*C*HC≡C*H*), 25.1 (CH_3). LRMS (EI)

m/z: 288 (M^+, 8%), 41 (22), 115 (42), 149 (33), 151 (27), 152 (20), 176 (100), 177 (66), 178 (68), 179 (26), 217 (31). HRMS (ESI) calcd. for $C_{15}H_{13}ClN_2O_2$: 288,0644; found: 288,0650.

4-(2-Bromophenyl)-6-ethynyl-2-methyltetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (**2fa**): Colourless prisms (373 mg, 84% yield); mp 160-165 ºC (*n*-hexane:EtOAc). IR (neat) υ_{max}: 3270, 1692, 1433, 1284, 748, 653 cm^{-1}. ^1H NMR (300 MHz) δ: 7.66 – 7.52 (m, 1H, Ar*H*), 7.42 – 7.31 (m, 1H, Ar*H*), 7.30 – 7.08 (m, 2H, Ar*H*), 5.14 (d, *J* = 8.4 Hz, 1H, NC*H*-Ar), 4.61 (d, *J* = 1.9 Hz, 1H, NC*H*C≡C*H*), 3.79 (t, *J* = 8.0 Hz, 1H, NCHC*H*CO), 3.40 (d, *J* = 7.7 Hz, 1H, NCHC*H*CO), 2.82 (s, 3H, CH_3), 2.47 (d, *J* = 2.2 Hz, 1H, C≡C*H*). ^{13}C NMR (101 MHz) δ: 176.9 (CO), 174.8 (CO), 137.0 (Ar*C*), 132.6 (Ar*C*H), 129.5 (Ar*C*H), 127.7 (Ar*C*H), 127.5 (Ar*C*H), 124.1 (CBr), 83.0 (*C*≡CH), 73.3 (C≡*CH)*, 61.8 (N*C*HAr), 51.7 (*C*HCO), 50.1 (*C*HCO), 45.6 (N*C*HC≡C*H*), 25.0 (CH_3). LRMS (EI) *m/z*: 332 (M^+, 9%), 115 (75), 141 (23), 142 (61), 151 (45), 221 (100), 222 (22), 223 (96), 253 (27). HRMS (ESI) calcd. for: $C_{15}H_{13}BrN_2O_2$ -Br: 253.0977; found: 253.0973.

4-Ethynyl-6-(furan-2-yl)-2-methyltetrahydropyrrolo[3,4-c]pyrrole-1,3(2*H*,3a*H*)-dione (**2ga**): Colourless prisms (141 mg, 58% yield); mp 152-158 ºC (*n*-hexane:EtOAc). IR (neat) υ_{max}: 3232, 1691, 1381, 1286, 734, 701, 648, 532 cm^{-1}. ^1H NMR (400 MHz) δ: 7.40 (dd, *J* = 1.9, 0.9 Hz, 1H, O-C*H*), 6.34 (dd, *J* = 3.3, 1.8 Hz, 1H. O-CHC*H*), 6.27 (dt, *J* = 3.2, 0.8 Hz, 1H. O-CC*H*), 4.93 (d, *J* = 8.4 Hz, 1H, NC*H*-Furyl), 4.56 (dt, *J* = 2.1, 0.7 Hz, 1H, NC*H*C≡C*H*), 3.48 (t, *J* = 8.1 Hz, 1H, NCHC*H*CO), 3.40 (d, *J* = 7.7 Hz, 1H, NCHC*H*CO), 2.94 (s, 3H, CH_3), 2.43 (d, *J* = 2.2 Hz, 1H, C≡C*H*), 2.17 (s, 1H, N*H*). ^{13}C NMR (101 MHz) δ: 176.7 (CO), 175.3 (CO), 150.9 (Furyl*C*), 142.7 (Furyl*C*H), 110.4 (Furyl*C*H), 107.9 (Furyl*C*H), 82.8 (*C*≡CH), 73.1 (C≡*C*H), 57.0 (N*C*HAr), 52.3 (*C*HCO), 50.3 (*C*HCO), 47.2 (N*C*HC≡C*H*), 25.3 (CH_3). LRMS (EI) *m/z*: 244 (M^+, 17%), 78 (17), 104 (41), 105 (12), 133 (100), 134 (11). HRMS (ESI) calcd. for $C_{13}H_{12}N_2O_3$: 244.0848; found: 244.0838.

4-Ethynyl-2-methyl-6-(thiophen-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2*H*,3a*H*)-dione (**2ha**): Pale yellow prisms (161 mg, 62% yield); mp 168-170 ºC (*n*-hexane:EtOAc). IR (neat) υ_{max}: 3317, 3254, 1691, 3590, 1088, 693, 518 cm^{-1}. ^1H NMR (400 MHz) δ: 7.23 (dd, *J* = 5.1, 1.2 Hz, 1H, S-C*H*), 7.12 – 7.05 (m, 1H, S-CC*H*), 7.01 (dd, *J* = 5.1, 3.5 Hz, 1H, S-CHC*H*), 5.20 (d, *J* = 8.5 Hz, 1H, NC*H*-Thienyl), 4.57 (d, *J* = 2.2 Hz, 1H, NC*H*C≡C*H*), 3.42 (t, *J* = 8.0 Hz, 1H, NCHC*H*CO), 3.36 (d, *J* = 7.5 Hz, 1H, NCHC*H*CO), 2.90 (s, 3H, CH_3), 2.43 (d, *J* = 2.2 Hz, 1H, C≡C*H*), 2.36 (s, 1H, NH). ^{13}C NMR (101 MHz) δ: 176.7 (CO), 175.0 (CO), 141.7 (Thienyl*C*), 127.2 (Thienyl*C*H), 125.4 (Thienyl*C*H), 125.2 (Thienyl*C*H), 82.9 (*C*≡CH), 73.1 (C≡*C*H), 58.6 (N*C*HAr), 52.2 (*C*HCO), 50.2 (*C*HCO), 48.5 (N*C*HC≡C*H*), 25.2 (CH_3). LRMS (EI) *m/z*: 260 (M^+, 16.18%), 121(18), 122(30), 148(18), 149(100), 150(12), 151(21). HRMS (ESI) calcd. for $C_{13}H_{12}N_2O_2S$: 260.0619; found: 260.0606.

4-Ethynyl-2-methyl-6-(pyridin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2*H*,3a*H*)-dione (**2ia**): Colourless plates (183 mg, 72% yield); mp 140-144 ºC (*n*-hexane:EtOAc). IR (neat) υ_{max}: 3299, 3262, 1689, 1434, 1282, 1104, 754, 664 cm^{-1}. ^1H NMR (400 MHz) δ: 8.52 (ddd, *J* = 4.8, 1.8, 1.0 Hz, 1H, pyridyl-*H*), 7.66 (td, *J* = 7.7, 1.8 Hz, 1H, pyridyl-*H*), 7.32 (dt, *J* = 7.9, 1.2 Hz, 1H, pyridyl-*H*), 7.21 (ddd, *J* = 7.5, 4.9, 1.2 Hz, 1H, pyridyl-*H*), 4.97 (d, *J* = 8.5 Hz, 1H, NC*H*-pyridil), 4.66 (dq, *J* = 2.2, 0.7 Hz, 1H, NC*H*C≡C*H*), 3.61 (t, *J* = 8.1 Hz, 1H NCHC*H*CO), 3.47 (dd, *J* = 7.3, 0.8 Hz, 1H NCHC*H*CO), 2.86 (s, 3H, CH_3), 2.42 (d, *J* = 2.3 Hz, 1H, C≡C*H*). ^{13}C NMR (101 MHz) δ: 176.8 (CO), 175.5 (CO), 156.6 (pyridyl*C*), 149.3 (pyridyl*C*H), 136.7 (pyridyl*C*H), 123.3 (pyridyl*C*H), 122.4 (pyridyl*C*H), 83.2 (*C*≡CH), 72.8(C≡*C*H), 64.9 (N-*C*H-pyridyl), 53.5 (*C*HCO), 51.5 (*C*HCO), 49.1 (N*C*HC≡C*H*), 25.2 (CH_3). LRMS (EI) *m/z*: 255 (M^+, 37%), 65 (18), 78 (22), 79 (20), 91 (16), 92 (35), 105 (23), 177 (60), 118 (17), 143 (91), 144 (100), 198 (23), 254 (62). HRMS (ESI) calcd. for $C_{14}H_{13}N_3O_2$: 255.1008; found: 255.0981.

Dimethyl 2-ethynyl-5-phenylpyrrolidine-3,4-dicarboxylate (**2ae**): Pale yellow needles (203 mg, 71% yield); mp 114-118 ºC (*n*-hexane:EtOAc). IR (neat) υ_{max}: 3327, 3245, 1721, 1099, 1165, 1013, 750, 699, 595 cm^{-1}. ^1H NMR (400 MHz) δ: 7.35 – 7.28 (m, 3H, Ar*H*), 7.30 – 7.20 (m, 2H, Ar*H*), 4.95 (d, *J* = 9.1 Hz, 1H, NC*H*Ar), 4.69 – 4.56 (m, 1H, NC*H*C≡C*H*), 3.97 – 3.77 (m, 2H, 2xC*H*CO_2Me), 3.75 (s, 3H, CH_3), 3.12 (s, 3H, CH_3), 2.38 (d, *J* = 2.2 Hz, 1H, C≡C*H*), 1.67 (s, 1H, N*H*). ^{13}C NMR (101 MHz) δ: 172.1 (CO), 170.9 (CO), 139.6 (Ar*C*), 128.1 (Ar*C*H), 127.9 (Ar*C*H), 127.7 (Ar*C*H), 82.3 (*C*≡CH*)*, 73.3 (C≡*C*H*)*, 62.8 (N*C*HAr), 52.4 (CH_3), 51.6 (CH_3), 51.1 (*C*HCO), 50.9 (*C*HCO), 49.9 (N*C*HC≡C*H*). LRMS (EI) *m/z*: 287 (M^+, 1%), 104 (11), 115 (41), 116 (19), 119 (13), 125 (50), 142 (39), 143 (68), 146 (15), 167 (12), 168 (14), 177 (100), 178 (12), 256 (16). HRMS (ESI) calcd. for $C_{16}H_{17}NO_4$: 287.1158; found: 287.1137.

Methyl 2-ethynyl-5-phenyl-4-(phenylsulfonyl)pyrrolidine-3-carboxylate (**2af**): Pale yellow plates (184 mg, 50% yield); mp 155-160 ºC (*n*-hexane:EtOAc). IR (neat) υ_{max}: 2921, 1730, 1306, 1145, 1081, 685, 603, 531 cm^{-1}. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.06 – 7.92 (m, 2H, Ar*H*), 7.80 – 7.65 (m, 1H, Ar*H*), 7.66 – 7.56 (m, 2H, Ar*H*), 7.45 – 7.18 (m, 5H, Ar*H*), 4.86 (dd, *J* = 8.3, 2.3 Hz, 1H, 1H, NC*H*Ar), 4.73 (d, *J* = 4.8 Hz, 1H, NC*H*C≡C*H*), 4.20 (dd, *J* = 8.3, 6.7 Hz, 1H, C*H*SO_2Ph), 3.73 – 3.66 (m, 1H, C*H*CO_2Me), 3.49 (s, 3H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.3 (CO), 136.3 (Ar*C*), 134.3 (Ar*C*), 129.5 (Ar*C*H), 129.4 (Ar*C*H), 129.3 (Ar*C*H), 129.2 (Ar*C*H), 128.7 (Ar*C*H), 128.6 (Ar*C*H), 128.6 (Ar*C*H), 128.1 (Ar*C*H), 127.9 (Ar*C*H), 126.4 (Ar*C*H), 83.8 (*C*≡CH*)*, 75.5 (C≡*C*H*)*, 72.5 (CHS), 65.4 (N*C*HAr), 52.2 (CH_3), 52.2 (*C*HCO), 49.7 (N*C*HC≡C*H*). LRMS (EI) *m/z*: 369 (M^+, 0.22%), 188 (12), 195 (12), 216 (44), 217 (45), 218 (20), 219 (16), 242 (17), 243 (14), 265 (60), 266 (15), 326 (23), 327 (100), 328 (30), 329 (34). HRMS (ESI) calcd. for
$C_{20}H_{19}NO_4S$: 369.1035; found 369.1045.

(3a*R*,4*R*,6*R*,6a*S*)-4-Ethynyl-6-phenyl-2-[(*R*)-1-phenylethyl]tetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (**2ag**): Colourless needles (230 mg, 67% yield); mp 142-146 ºC (*n*-hexane:EtOAc). $[\alpha]_D^{25}$ = –0.21º (*c* 1, CH_2Cl_2). IR (neat) υ_{max}: 3284, 1696, 1359, 1186, 746, 700, 653, 605, 531 cm^{-1}. ^1H NMR (400 MHz) δ: 7.40 – 7.36 (m, 2H, Ar*H*), 7.34 – 7.20 (m, 6H, Ar*H*), 7.18 – 7.10 (m, 1H, Ar*H*), 7.10 – 6.98 (m, 1H. Ar*H*), 5.33 – 5.21 (m, 1H, C*H*-CH_3), 4.89 – 4.78 (m, 1H, NC*H*Ph), 4.60 (dd, *J* = 6.3, 2.2 Hz, 1H, NC*H*C≡C*H*), 3.55 – 2.84 (m, 2H, 2xNCHC*H*CO), 2.39 (d, *J* = 2.1 Hz, 1H, C≡C*H*), 1.96 (dd, broad signal, *J* = 8.2, 3.5 Hz, 1H, N*H*), 1.71 (dd, *J* = 22.3, 7.3 Hz, 3H, CH_3).^{13}C NMR (101 MHz) δ: 176.8 (CO), 174. 9 (CO), 139.8 (Ar*C*), 137.3 (Ar*C*), 128.4 (Ar*C*H), 128.4 (Ar*C*H), 128.3 (Ar*C*H), 128.3 (Ar*C*H), 128.1 (Ar*C*H), 128.0 (Ar*C*H), 127.9 (Ar*C*H), 127.8 (Ar*C*H), 127.5 (Ar*C*H), 127.4 (Ar*C*H), 83.4 (*C*≡CH*)*, 72.8 (C≡*C*H*)*, 62.9 (N*C*HPh), 52.0 (*C*HCO), 51.0 (*C*HCO), 50.5 (*C*HPh), 47.9 (N*C*HC≡C*H*), 16.89 (CH_3). LRMS

(EI) *m/z*: 344 (M^+, 12%), 105 (18), 115 (21), 116 (10), 142 (22), 143 (100), 144 (12). HRMS (ESI) calcd. for $C_{22}H_{20}N_2O_2$: 344.1525; found: 344.1518.

3. Preparation of compounds 3

In a pressure tube with a magnetic bar, containing 3 mL of acetonitrile, was added the corresponding cycloadduct **2** (0.5 mmol), propargyl bromide (80%, 236 µL, 2.5 mmol) and potasium carbonate (139 mg, 1 mmol). The resulting mixture was stirred at 60 ºC for 72 h. Ethyl acetate (10 mL) was added and washed with water (2x10mL), the organic phase was dried with $MgSO_4$ and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography (flash silica-gel) eluting with mixtures of *n*-hexane:ethyl acetate affording pure compounds **3**.

4-Ethynyl-2-methyl-6-phenyl-5-(prop-2-yn-1-yl)tetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (**3aa**): Colourless prisms (103 mg, 70% yield); mp 159,3-163º C (*n*-hexane:EtOAc). IR (neat) υ_{max}: 3290, 3252, 1694, 1100, 694, 645 cm^{-1}. ^1H NMR (400 MHz) δ: 7.39 – 7.29 (m, 3H, Ar*H*), 7.25 – 7.13 (m, 2H, Ar*H*), 4.84 (d, *J* = 2.2 Hz, 1H, NC*H*Ph), 4.08 (d, *J* = 9.0 Hz, 1H, NC*H*C≡C*H*), 3.51 (dd, *J* = 9.0, 7.8 Hz, 1H, NCHC*H*CO), 3.39 (d, *J* = 7.8 Hz, 1H, NCHC*H*CO), 3.24 (dd, *J* = 16.2, 2.6 Hz, 1H, CH_2-C≡CH), 3.11 (dd, *J* = 16.2, 2.5 Hz, 1H, CH_2-C≡CH), 2.94 – 2.85 (m, 3H, CH_3), 2.52 (d, *J* = 2.2 Hz, 1H, C≡C*H*), 2.21 (t, *J* = 2.5 Hz, 1H, CH_2-C≡C*H*). ^{13}C NMR (101 MHz) δ: 176.5 (CO), 175.2 (CO), 135.6 (Ar*C*), 129.1 (Ar*C*H), 128.9 (Ar*C*H), 128.8 (Ar*C*H), 128.3 (Ar*C*H), 79.3 (*C*≡CH*)*, 77.7 (*C*≡CH*)*, 76.4 (C≡*C*H*)*, 72.4(C≡*C*H*)*, 67.4 (N*C*HPh), 54.6 (*C*HCO), 50.5 (*C*HCO), 49.7 (N*C*HC≡C*H*), 38.0 (CH_2) and 25.1 (CH_3). LRMS (EI) *m/z*: 292 (M^+, 43%), 77 (11), 91 (13), 115 (47), 118 (12), 142 (100), 143 (15), 180 (24), 181 (28), 206 (22), 215 (17), 291 (73). HRMS (ESI) calcd. for $C_{18}H_{16}N_2O_2$: 292.1212; found: 292.1178.

4-Ethynyl-2-methyl-6-(naphth-2-yl)-5-(prop-2-yn-1-yl)tetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (**3ba**): Colourless prisms (135 mg, 79% yield); mp 167-182 ºC (*n*-hexane:EtOAc). IR (neat) υ_{max}: 3314, 3270, 1692, 1284, 818, 751, 657 cm^{-1}. ^1H NMR (300 MHz) δ: 7.92 – 7.69 (m, 3H, Ar*H*), 7.63 (s, 1H, Ar*H*), 7.39 (dt, *J* = 6.2, 3.4 Hz, 2H, Ar*H*), 7.27 – 7.09 (m, 1H, Ar*H*), 4.81 (d, *J* = 2.1 Hz, 1H, NC*H*Ph), 4.17 (d, *J* = 9.0 Hz, 1H, NC*H*C≡C*H*), 3.50 (dd, *J* = 9.1, 7.8 Hz, 1H, NCHC*H*CO), 3.35 (d, *J* = 7.8 Hz, 1H, NCHC*H*CO), 3.17 (d, *J* = 16.4 Hz, 1H, CH_2-C≡CH), 3.06 (dd, *J* = 16.1, 2.5 Hz, 1H, CH_2-C≡CH). 2.83 (s, 3H, CH_3), 2.46 (d, *J* = 2.2 Hz, 1H, C≡C*H*), 2.14 (t, *J* = 2.5 Hz, 1H, CH_2-C≡C*H*). ^{13}C NMR (75 MHz) δ: 176.5 (CO), 175.2 (CO), 133.6 (Ar*C*), 133.4 (Ar*C*), 133.1 (Ar*C*), 128.6 (Ar*C*H), 128.0 (Ar*C*H), 127.9 (Ar*C*H), 126.4 (Ar*C*H), 126.3 (Ar*C*H), 79.3 (*C*≡CH), 77.7 (*C*≡CH*)*, 76.4 (C≡*C*H*)*, 72.5 (C≡*C*H), 67.5 (N*C*HPh), 54.6 (*C*HCO), 50.6 (*C*HCO), 49.7 (N*C*HC≡C*H*), 38.1 (CH_2), 25.1 (CH_3). LRMS (EI) *m/z*: 342 (M^+, 27%), 127 (13), 139 (13), 164 (11), 165 (57), 166 (17), 191 (19), 192 (100), 193 (75), 194 (12), 230 (18), 231 (17), 304 (18), 341 (24). HRMS (ESI) calcd. for $C_{22}H_{18}N_2O_2$: 342.1368; found: 342.1358.

4-(4-Chlorophenyl)-6-ethynyl-2-methyl-5-(prop-2-yn-1-yl)tetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (**3da**): Colourless needles (122 mg, 75% yield); mp 143-147ºC (*n*-hexane:EtOAc). IR (neat) υ_{max}: 3254, 1698, 1286, 1099, 1010, 818, 672 cm^{-1}. ^1H NMR (400 MHz) δ: 7.32 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.14 (d, *J* = 8.1 Hz, 2H, Ar*H*), 4.82 (d, *J* = 1.3 Hz, 1H, NC*H*Ph), 4.07 (d, *J* = 9.0 Hz, 1H, NC*H*C≡C*H*), 3.50 (t, *J* = 8.4 Hz, 1H, NCHC*H*CO), 3.40 (d, *J* = 7.8 Hz, 1H, NCHC*H*CO), 3.15 (dd, *J* = 16.2, 2.5 Hz, 2H, CH_2-C≡CH), 2.91 (s, 3H, CH_3), 2.52 (d, *J* = 2.1 Hz, 1H, C≡C*H*), 2.21 (t, *J* = 2.5 Hz, 1H, CH_2-C≡C*H*). ^{13}C NMR (101 MHz) δ: 176.3 (CO), 175.1 (CO), 134.5 (Ar*C*), 134.2 (Ar*C*), 129.20 (Ar*C*H), 79.0 (*C*≡CH*)*, 77.6 (*C*≡CH*)*, 76.54 (C≡*C*H*)*, 72.6 (C≡*C*H*)*, 66.7 (N*C*HPh), 54.6 (*C*HCO), 50.5 (*C*HCO), 49.6 (N*C*HC≡C*H*), 38.05 (CH_2), 25.21 (CH_3). LRMS (EI) *m/z*: 326 (M^+, 32%), 115 (16), 149 (29), 151 (15), 152 (19), 176 (100), 177 (20), 178 (40), 214 (12), 215 (38), 240 (16), 291 (15), 325 (50). HRMS (ESI) calcd. for $C_{18}H_{15}ClN_2O_2$: 326.0822; found: 326.0799.

4-Ethynyl-6-(furan-2-yl)-2-methyl-5-(prop-2-yn-1-yl)tetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (**3ga**): Colourless prisms (92 mg, 65% yield); mp 157-162 ºC (*n*-hexane:EtOAc). IR (neat) υ_{max}: 3286, 3229, 1697, 1283, 1104, 1005, 753, 659, 598 cm^{-1}. ^1H NMR (400 MHz) δ: 7.38 (dd, *J* = 1.9, 0.9 Hz, 1H, Furyl-C*H*), 6.33 (dd, *J* = 3.3, 1.8 Hz, 1H, Furyl-C*H*), 6.29 (dd, *J* = 3.3, 0.9 Hz, 1H, Furyl-C*H*), 4.71 (d, *J* = 2.1 Hz, 1H, NC*H*Ph), 4.17 (d, *J* = 8.9 Hz, 1H, NC*H*C≡C*H*), 3.57 – 3.42 (m, 1H, NCHC*H*CO), 3.36 (d, *J* = 7.9 Hz, 1H, NCHC*H*CO), 3.25 (dd, *J* = 16.1, 2.6 Hz, 1H, CH_2-C≡CH), 3.14 (dd, *J* = 16.1, 2.5 Hz, 1H, CH_2-C≡CH), 2.95 (s, 3H, CH_3), 2.50 (d, *J* = 2.1 Hz, 1H, C≡C*H*), 2.19 (t, *J* = 2.5 Hz, 1H, CH_2-C≡C*H*). ^{13}C NMR (101 MHz) δ: 176.2 (CO), 175.3 (CO), 148.8 (Furyl*C*), 143.3 (Furyl*C*H), 110.5 (Furyl*C*H), 110.0 (Furyl*C*H), 78.8 (*C*≡CH*)*, 77.3 (*C*≡CH*)*, 76.4 (C≡*C*H*)*, 72.7 (C≡*C*H*)*, 60.9 (N*C*HPh), 54.2 (*C*HCO), 50.3 (*C*HCO), 47.7 (N*C*HC≡C*H*), 38.1 (CH_2), 25.35 (CH_3). LRMS (EI) *m/z*: 282 (M^+, 9%), 77 (11), 108 (11), 132 (100), 171 (37), 281 (19). HRMS (ESI) calcd. for $C_{16}H_{14}N_2O_3$: 282.1004; found: 282.0972.

4. Preparation of compouds 4

In a flask with a magnetic bar, containing 3 mL of degassed toluene (using freezing-pump conditions), containing $RhCl(PPh_3)_3$ (24 mg, 0.025 mmol), was added the corresponding diine **3** (0.5 mmol) and the symmetric alkyne (2.5 mmol). The resulting mixture was stirred at 100 ºC for 19 h. The solvent was evaporated, and the residue was purified by flash chromatography (flash silica-gel) eluting with *n*-hexane:ethyl acetate mixtures affording pure compounds **4**.

8,9-Diethyl-2-methyl-4-phenyl-3a,6,10b,10c-tetrahydropyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoindole-1,3(2*H*,4*H*)-dione (**4aa**): Pale pink plates (69 mg, 37% yield); mp 154-160 ºC (*n*-hexane:EtOAc). IR (neat) υ_{max}: 2962, 1698, 1434, 1284, 1060, 746, 699, 647 cm^{-1}. ^1H NMR (400 MHz) δ: 7.44 – 7.31 (m, 5H, Ar*H*), 7.23 (s, 1H, Ar*H*), 7.03 (s, 1H, Ar*H*), 4.94 (s, 1H, NC*H*Ar), 4.04 (d, *J* = 15.4 Hz, 1H, NCH_2), 3.97 (d, *J* = 8.5 Hz, 1H, NC*H*Ph), 3.69 (d, *J* = 15.4 Hz, 1H, NCH_2), 3.64 (dd, *J* = 8.1, 1.5 Hz, 1H, NCHC*H*CO), 3.38 (t, *J* = 8.3 Hz, 1H, NCHC*H*CO), 2.96 (s, 3H, NCH_3), 2.68 (dq, *J* = 15.1, 7.7 Hz, H and 2xCH_2CH_3), 1.27 (t, *J* = 7.6 Hz, 3H, CH_2CH_3), 1.22 (t, *J* = 7.5 Hz, 3H, CH_2CH_3). ^{13}C NMR (101 MHz) δ: 178.3, 175.6, 141.9, 141.6, 139.5, 137.9, 137.8, 128.4, 128.3, 128.1, 124.0, 122.6, 72.3, 69.9, 56.7, 50.8, 49.0, 25.8, 25.7, 25.2, 15.6, 15.5. LRMS (EI) *m/z*: 374 (M^+, 24%), 262 (27), 263 (100), 264 (21). HRMS (ESI) calcd. for $C_{24}H_{26}N_2O_2 - CH_3$: 359.1760; found: 359.1746.

8,9-Bis(hydroxymethyl)-2-methyl-4-phenyl-3a,6,10b,10c-tetrahydropyrrolo [3',4':3,4]pyrrolo[2,1-*a*]isoindole-1,3(2*H*,4*H*)-dione (**4ab**): Pale pink prisms (104 mg, 55% yield); mp 159-162 ºC (*n*-hexane:EtOAc). IR (neat) υ_{max}: 2923, 1692,

1436, 1284, 1017, 698 cm^{-1}. ^1H NMR (300 MHz) δ: 7.43 (s, 1H, Ar*H*), 7.34 (dd, *J* = 5.7, 3.5 Hz, 5H, Ar*H*), 7.24 (s, 1H, Ar*H*), 4.94 (s, 1H, NC*H*Ar), 4.91 – 4.56 (m, 4H, 2xCH_2OH), 4.05 (d, *J* = 15.7 Hz, 1H, NCH_2), 3.89 (d, *J* = 8.5 Hz, 1H NC*H*Ph), 3.72 (d, *J* = 15.8 Hz, 1H, NCH_2), 3.64 (dd, *J* = 8.2, 1.5 Hz, 1H, NCHC*H*CO), 3.35 (m, 1H, NCHC*H*CO), 2.95 (s, 3H, CH_3). ^{13}C NMR (126 MHz) δ: 178.1, 175.3, 142.2, 140.8, 139.7, 139.5, 137.4, 131.1, 129.0, 128.5, 128.3, 128.2, 125.6, 124.3, 72.2, 70.0, 64.2, 64.2, 56.7, 50.6, 48.9, 25.3. LRMS (EI) *m/z*: 378 (M^+, 19%), 43 (74), 44 (100), 45 (18), 55 (23), 57 (34), 69 (20), 77 (37), 83 (21), 91 (23), 247 (32), 249 (28), 263 (33), 265 (34). HRMS (ESI) calcd. for $C_{22}H_{22}N_2O_4$: 378.1584; found 378.1580.

8,9-Diethyl-2-methyl-4-(naphth-2-yl)-3a,6,10b,10c-tetrahydropyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoindole-1,3(2*H*,4*H*)-dione (**4ba**): Pale pink needles (40 mg, 19% yield); mp 183-189 ºC (*n*-hexane:EtOAc). IR (neat) υ_{max}: 2962, 1698, 1284, 1060, 821, 740 cm^{-1}. ^1H NMR (300 MHz) δ: 8.05 – 7.63 (m, 4H, Ar*H*), 7.59 – 7.38 (m, 3H, Ar*H*), 7.03 (s, 1H, Ar*H*), 5.01 (s, 1H, NC*H*Ar), 4.21 – 3.98 (m, 2H, NC*H*Ph and NCH_2), 3.81 – 3.65 (m, 2H, NCHC*H*CO and NCH_2), 3.48 (t, *J* = 8.3 Hz, 1H, NCHC*H*CO), 2.96 (s, 3H, NCH_3), 2.84 – 2.54 (m, 4H, 2xCH_2CH_3), 1.34 – 1.26 (m, 3H, CH_2CH_3), 1.22 (t, *J* = 7.5 Hz, 3H, CH_2CH_3). ^{13}C NMR (101 MHz) δ: 178.3, 175.5, 142.0, 141.7, 139.5, 137.9, 135.4, 133.5, 133.4, 128.1, 128.0, 127.9, 127.1, 126.4, 126.1, 126.0, 124.1, 122.7, 72.4, 70.1, 56.8, 50.7, 49.1, 25.8, 25.7, 25.3, 15.6, 15.5. LRMS (EI) *m/z*: 424 (M^+, 15%), 174 (32), 312 (41), 313 (100), 314 (24). HRMS (ESI) calcd. for $C_{28}H_{28}N_2O_2$: 424.2151; found: 424.2134.

Dimethyl 2-methyl-4-(naphthalen-2-yl)-1,3-dioxo-1,2,3,3a,4,6,10b,10c-octahydropyrrolo [3',4':3,4]pyrrolo[2,1-*a*]isoindole-8,9-dicarboxylate (**4bc**): Pale pink needles (106 mg, 44% yield); mp 135-136 ºC (*n*-hexane:EtOAc). IR (neat) υ_{max}: 2921, 1696, 1431, 1286, 1117, 1072, 726 cm^{-1}. ^1H NMR (300 MHz) δ: 8.02 – 7.70 (m, 5H, Ar*H*), 7.57 (s, 1H, Ar*H*), 7.53 – 7.42 (m, 2H, Ar*H*), 7.39 (dd, *J* = 8.5, 1.7 Hz, 1H, Ar*H*), 5.05 (s, 1H, NC*H*Ar), 4.15 (d, *J* = 16.1 Hz, 1H, NCH_2), 4.00 (d, *J* = 8.5 Hz, 1H, NC*H*Ph), 3.95 (s, 3H, CO_2CH_3), 3.91 (s, 3H, CO_2CH_3), 3.82 (d, *J* = 16.2 Hz, 1H, NCH_2), 3.72 (dd, *J* = 8.2, 1.4 Hz, 1H, NCHC*H*CO), 3.46 (t, *J* = 8.4 Hz, 1H, NCHC*H*CO), 2.97 (s, 3H, NCH_3). ^{13}C NMR (101 MHz) δ: 177.5, 174.9, 168.1, 167.8, 145.3, 144.3, 134.4, 133.5, 133.4, 132.8, 132.1, 128.1, 128.0, 127.2, 126.3, 126.2, 126.2, 124.9, 123.8, 72.1, 70.1, 56.7, 53.0, 52.9, 50.4, 48.7, 25.3. LRMS (EI) *m/z*: 484 (M^+, 2%), 233 (13), 245 (12), 371 (41), 372 (100), 373 (24), 69 (20). HRMS (ESI) calcd. for $C_{28}H_{24}N_2O_6$: 484.1634; found: 484.1618.

4-(4-Chlorophenyl)-8,9-diethyl-2-methyl-3a,6,10b,10c-tetrahydropyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoindole-1,3(2*H*,4*H*)-dione (**4da**): Pale pink plates (63 mg, 31% yield); mp 162-168 ºC (*n*-hexane:EtOAc). IR (neat) υ_{max}: 2919, 1698, 1284, 1058, 1010, 821 cm^{-1}. ^1H NMR (400 MHz) δ: 7.30 (q, *J* = 8.7 Hz, 4H, Ar*H*), 7.22 (s, 1H, Ar*H*), 7.03 (s, 1H, Ar*H*), 4.92 (s, 1H, NC*H*Ar), 4.02 (d, *J* = 15.3 Hz, 1H, NCH_2), 3.93 (d, *J* = 8.4 Hz, 1H, NC*H*Ph), 3.66 – 3.58 (m, 2H, NCHC*H*CO and NCH_2), 3.36 (t, *J* = 8.3 Hz, 1H, NCHC*H*CO), 2.97 (s, 3H, NCH_3), 2.78 – 2.60 (m, 4H, 2xCH_2CH_3), 1.27 (t, *J* = 6.1 Hz, 3H CH_2CH_3), 1.22 (t, *J* = 7.5 Hz, 3H, CH_2CH_3). ^{13}C NMR (101 MHz) δ: 178.1, 175.5, 142.0, 141.7, 139.3, 137.6, 136.4, 133.7, 131.1, 129.6, 129.0, 128.7, 124.1, 122.6, 72.2, 69.2, 61.8, 50.6, 49.0, 25.8, 25.7, 25.2, 15.6, 15.5. LRMS (EI) *m/z*: 408 (M^+, 22%), 269 (24), 297 (100), 298 (28), 299 (33). HRMS (ESI) calcd. for $C_{24}H_{25}ClN_2O_2$: 408.1605; found 408.1591.

4-(4-Chlorophenyl)-8,9-bis(hydroxymethyl)-2-methyl-3a,6,10b,10c-tetrahydropyrrolo [3',4':3,4]pyrrolo[2,1-*a*]isoindole-1,3(2*H*,4*H*)-dione (**4db**): Pink solid (15mg, 39% yield); mp 159-160 ºC (*n*-hexane:EtOAc). IR (neat) υ_{max}: 2921, 1696, 1434, 1284, 1058, 1010, 821 cm^{-1}. ^1H NMR (400 MHz) δ: 7.45 (s, 1H, Ar*H*), 7.34 (d, *J* = 8.2 Hz, 2H, Ar*H*), 7.31 – 7.21 (m, 4H, Ar*H*), 4.94 (s, 1H, NC*H*Ar), 4.91 – 4.66 (m, 4H, 2xCH_2OH), 4.07 (d, *J* = 15.7 Hz, 1H, NCH_2), 3.88 (d, *J* = 8.4 Hz, 1H, NC*H*Ph), 3.78 – 3.56 (m, 2H, NCH_2 and NCHC*H*CO), 3.36 (t, *J* = 8.3 Hz, 1H, NCHC*H*CO), 2.99 (s, 3H, CH_3). ^{13}C NMR (101 MHz) δ: 177.8, 175.1, 141.9, 140.5, 139.6, 139.4, 135.8, 133.8, 129.4, 128.6, 125.5, 124.2, 72.0, 69.1, 64.1, 64.0, 56.4, 50.4, 48.6, 25.2. LRMS (EI) *m/z:* 412 (M^+, 21%), 43 (19), 89 (14), 115 (19), 267 (18), 283 (13), 299 (20), 300 (30), 301 (100), 302 (27), 303 (32). HRMS (ESI) calcd. for $C_{22}H_{21}ClN_2O_4$-H_2ClO: 360.1474; found: 360.1465.

5. Preparation of compounds 5

In a pressure tube with a magnetic bar, containing 3 mL of acetonitrile, was added the corresponding cycloadduct **2** (0.5 mmol), allyl bromide (216 µL, 2.5 mmol) and potasium carbonate (139 mg, 1 mmol). The resulting mixture was stirred at 60 ºC for 72 h. Ethyl acetate (10 mL) was added and washed with water (2x10mL), the organic phase was dried with $MgSO_4$ and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography (flash silica-gel) eluting with mixtures of *n*-hexane:ethyl acetate affording pure compounds **5**.

5-Allyl-4-ethynyl-2-methyl-6-(naphth-2-yl)tetrahydropyrrolo[3,4-*c*]pyrrole-1,3(2*H*,3a*H*)-dione (**5ba**): Colourless prisms (103 mg, 81% yield); mp 182-184 ºC (*n*-hexane:EtOAc). IR (neat) υ_{max}: 3256, 1694, 1434, 1279, 1104, 931, 821, 751, 664 cm^{-1}. ^1H NMR (400 MHz) δ: 7.81 (dtd, *J* = 9.4, 5.8, 5.4, 2.4 Hz, 3H, Ar*H*), 7.72 (s, 1H, Ar*H*), 7.50 – 7.43 (m, 2H, Ar*H*), 7.28 (s, 1H, Ar*H*), 5.86 – 5.68 (m, 1H, C*H*=CH_2), 5.24 (dq, *J* = 17.1, 1.8 Hz, 1H, CH=CH_2), 5.13 (dq, *J* = 9.5, 1.2 Hz, 1H, CH=CH_2), 4.61 (d, *J* = 2.1 Hz, 1H, NC*H*Ph), 4.32 (d, *J* = 9.1 Hz, 1H, NC*H*C≡*C*H), 3.57 (dd, *J* = 9.2, 7.6 Hz, 1H, NCHC*H*CO), 3.41 (d, *J* = 7.7 Hz, 1H, NCHC*H*CO), 3.18 – 2.94 (m, 2H, CH_2CH=CH_2), 2.91 (s, 3H, NCH_3), 2.50 (d, *J* = 2.2 Hz, 1H, C≡C*H*). ^{13}C NMR (101 MHz) δ: 176.9, 175.5, 134.4, 134.2, 133.6, 133.5, 128.5, 128.0, 126.3, 126.2, 117.9, 78.3, 76.0, 67.9, 53.8, 51.1, 51.0, 49.6, 25.1. LRMS (EI) *m/z*: 344 (M^+, 51%), 41 (20), 57 (14), 139 (21), 141 (19), 149 (14), 154 (14), 164 (11), 165 (59), 166 (18), 167 (14), 191 (26), 192 (100), 193 (20), 194 (29), 232 (40), 233 (33), 343(45). HRMS (ESI) calcd. for $C_{22}H_{20}N_2O_2$: 344.1525; found: 344.1506.

5-allyl-4-(4-chlorophenyl)-6-ethynyl-2-methyltetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (**5da**): Pale yellow prisms (146 mg, 89% yield); mp 156-158 ºC (*n*-hexane:EtOAc). IR (neat) υ_{max}: 3250, 1685, 1434, 1380, 1280, 1107, 750 cm^{-1}. ^1H NMR (300 MHz) δ: 7.37 – 7.26 (m, 2H, Ar*H*), 7.13 (d, *J* = 8.1 Hz, 2H, Ar*H*), 5.85 – 5.59 (m, 1H, C*H*=CH_2), 5.26 – 5.16 (m, 1H, CH=CH_2), 5.15 – 5.09 (m, 1H, CH=CH_2), 4.53 (d, *J* = 2.1 Hz, 1H, NC*H*Ph), 4.11 (d, *J* = 9.0 Hz, 1H, NC*H*C≡*C*H), 3.48 (dd, *J* = 9.0, 7.7 Hz, 1H, NCHC*H*CO), 3.37 (d, *J* = 7.8 Hz, 1H, NCHC*H*CO), 3.04 – 2.93 (m, 2H, CH_2CH=CH_2), 2.90 (s, 3H, NCH_3), 2.47 (d, *J* = 2.1 Hz, 1H, C≡C*H*). ^{13}C NMR (75 MHz) δ: 176.7, 175.4, 135.3,

134.2, 134.1, 129.0, 118.1, 78.1, 76.1, 67.1, 53.8, 51.0, 50.8, 49.5, 25.1. LRMS (EI) *m/z*: 328 (M^+, 33%), 41 (22), 115 (18), 125 (14), 149 (31), 151 (18), 152 (20), 176 (100), 178 (50), 217 (36), 327 (36). HRMS (ESI) calcd. for $C_{18}H_{17}ClN_2O_2$: 328.0962; found: 328.0958.

6. Preparation of compounds 6

In a flask with a magnetic bar, containing 3 mL of dichloromethane, was added the corresponding compound **5** (0.5 mmol), 1,7-octadiene (295 µL, 2.0 mmol) and Grubb's II catalyst (84 mg, 0.1 mmol). The resulting mixture was stirred at 40 ºC for 19 h. The solvent was evaporated, and the residue was purified by flash chromatography (flash silica-gel) eluting with 3/1 *n*-hexane:ethyl acetate affording pure compounds **6**.

2-Methyl-4-(naphth-2-yl)-8-vinyl-3a,6,8a,8b-tetrahydropyrrolo[3,4-*a*]pyrrolizine-1,3(2*H*,4*H*)-dione (**6ba**): Pale yellow needles (46 mg, 89% yield); mp 110-115 ºC (*n*-hexane:EtOAc). IR (neat) υ_{max}: 2922, 1694, 1431, 1279, 814, 746 cm^{-1}. ^1H NMR (300 MHz) δ: 7.98 – 7.71 (m, 4H, Ar*H*), 7.55 – 7.39 (m, 3H, Ar*H*), 6.63 (dd, *J* = 17.9, 11.2 Hz, 1H, C*H*=CH_2), 5.93 – 5.61 (m, 2H, C=C*H*CH_2 and CH=CH_2), 5.35 (d, *J* = 11.2 Hz, 1H, CH=CH_2), 5.02 – 4.70 (m, 1H, NC*H*Naph), 4.35 (d, *J* = 8.0 Hz, 1H, NC*H*C), 3.91 – 3.61 (m, 2H, C=CHCH_2), 3.61 – 3.25 (m, 2H, 2x NCHC*H*CO), 2.79 (s, 3H, CH_3). ^{13}C NMR (101 MHz) δ: 178.4, 175.4, 140.9, 135.7, 133.4, 133.2, 130.0, 128.1, 127.9, 127.8, 127.3, 126.7, 126.2, 126.1, 126.0, 117.4, 73.1, 71.5, 59.5, 50.8, 47.8, 25.0. LRMS (EI) *m/z*: 344 (M^+, 51%), 41 (20), 57 (14), 139 (21), 141 (19), 149 (14), 154 (14), 164 (11), 165 (59), 166 (18), 167 (14), 191 (26), 192 (100), 193 (20), 194 (29), 232 (40). HRMS (ESI) calcd. for $C_{22}H_{20}N_2O_2$: 344.1525; found: 344.1506.

4-(4-Chlorophenyl)-2-methyl-8-vinyl-3a,6,8a,8b-tetrahydropyrrolo[3,4-*a*]pyrrolizine-1,3(2*H*,4*H*)-dione (**6db**): Pale yellow plates (128 mg, 78% yield); mp 149-154 ºC (*n*-hexane:EtOAc). IR (neat) υ_{max}: 2921, 1696, 1433, 1288, 1088, 816, 644 cm^{-1}. ^1H NMR (300 MHz) δ: 7.48 – 7.18 (m, 4H, Ar*H*), 6.60 (dd, *J* = 18.0, 11.2 Hz, 1H, C*H*=CH_2), 5.74 (q, *J* = 2.3 Hz, 1H, C=C*H*CH_2), 5.69 (d, *J* = 18.0 Hz, 1H, CH=CH_2), 5.33 (d, *J* = 11.2 Hz, 1H, CH=CH_2), 4.70 (dt, *J* = 146.7, 3.2 Hz, 1H, NC*H*Ar), 4.15 (d, *J* = 7.9 Hz, 1H, NC*H*C), 3.78 – 3.59 (m, 2H, C=CHCH_2), 3.42 (t, *J* = 8.2 Hz, 1H, NCHC*H*CO), 3.32 (dt, *J* = 17.0, 2.5 Hz, 1H, NCHC*H*CO), 2.84 (s, 3H, CH_3). ^{13}C NMR (75 MHz) δ: 178.2, 175.3, 140.8, 136.7, 133.5, 129.8, 129.3, 128.5, 127.1, 117.4, 72.9, 70.6, 59.2, 50.6, 47.5, 24.9. LRMS (EI) *m/z*: 328 (M^+, 43%), 41 (22), 43 (16), 115 (18), 125 (16), 149 (32), 151 (20), 152 (20), 176 (100), 177 (21), 216 (31), 217 (53), 327 (38). HRMS (ESI) calcd. for $C_{18}H_{17}ClN_2O_2$: 328.0979; found: 328.0935.

7. Preparation of compounds 7

In a flask with a magnetic bar, containing 2 mL of toluene, was added the corresponding compound **6** (0.5 mmol), and *N*-phenylmaleimide (87 mg, 0.5 mmol). The resulting mixture was stirred at 25 ºC for 24 h. The solvent was evaporated, and the residue was purified by flash chromatography (flash silica-gel) eluting with 3/1 *n*-hexane:ethyl acetate affording pure compounds **7**.

7-methyl-9-(naphthalen-2-yl)-2-phenyl-3a,5b,5c,8a,9,11,11a,11b-octahydro-1*H*-pyrrolo[3,4-e]pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoindole-1,3,6,8(2*H*,4*H*,7*H*)-tetraone (**7ba**): Colourless plates (235 mg, 91% yield); mp 118-119 ºC (*n*-hexane:EtOAc). IR (neat) υ_{max}: 2917, 1694, 1381, 1179, 1074, 824, 752, 694 cm^{-1}. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.87 – 7.75 (m, 4H, Ar*H*), 77.52 – 7.35 (m, 6H, Ar*H*), 7.23 – 7.16 (m, 2H, Ar*H*), 6.17 – 5.97 (m, 1H, C=C*H*), 4.31 – 4.25 (m, 1H, NC*H*Ar), 4.18 (d, *J* = 8.5 Hz, 1H, NC*H*C), 3.74 (dd, *J* = 13.4, 9.7 Hz, 1H, NCHC*H*CO), 3.52 (t, *J* = 8.2 Hz, 1H, NCHC*H*CO), 3.41 – 3.33 (m, 3H, 2xNCHC*H*CO and CH_2), 3.21 (dd, *J* = 13.4, 7.9 Hz, 1H, CH_2), 3.07 (dd, *J* = 15.5, 7.2 Hz, 2H, CH_2), 2.91 (s, 3H, CH_3), 2.36 – 2.25 (m, 1H, NCH_2CH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.4, 177.8, 176.3, 175.2, 147.6, 134.6, 133.5, 133.4, 131.8, 129.3, 128.9, 128.1, 128.0, 127.1, 126.6, 126.2, 126.2, 126.1, 118.8, 69.3, 68.5, 50.9, 50.0, 49.1, 41.7, 41.4, 37.4, 26.0, 25.3.LRMS (EI) *m/z*: 517 (M^+, 80%). 77 (14), 91 (20), 118 (14), 130 (19), 141 (34), 152 (15), 165 (38), 166 (24), 232 (61), 233 (41), 265 (37), 267 (44), 343 (63), 406 (100), 407 (32). HRMS (ESI) calcd. for $C_{32}H_{27}N_3O_4$: 517.2002; found: 517.1977.

9-(4-Chlorophenyl)-7-methyl-2-phenyl-3a,5b,5c,8a,9,11,11a,11b-octahydro-1*H*-pyrrolo[3,4-e]pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoindole-1,3,6,8(2*H*,4*H*,7*H*)-tetraone (**7da**):

Colourless plates (235 mg, 94% yield); mp 178-185 ºC; IR (neat) υ_{max}: 1694, 1392, 1181, 1170, 979, 827, 694 cm^{-1}. ^1H NMR (400 MHz) δ: 7.49 – 7.42 (m, 2H, Ar*H*), 7.41 – 7.36 (m, 1H, Ar*H*), 7.35 – 7.26 (m, 4H, Ar*H*), 7.22 – 7.16 (m, 2H, Ar*H*), 6.03 (dq, *J* = 5.9, 2.9 Hz, 1H, C=C*H*), 4.22 – 4.19 (m, 1H, NC*H*Ar), 3.98 (d, *J* = 8.3 Hz, 1H, NC*H*C), 3.68 (dd, *J* = 13.2, 9.7 Hz, 1H, NCHC*H*CO), 3.43 – 3.27 (m, 4H, 3xNCHC*H*CO and CH_2), 3.14 – 2.97 (m, 3H, CH_2), 2.91 (s, 3H, CH_3), 2.35 – 2.20 (m, 1H, NCH_2CH). ^{13}C NMR (101 MHz) δ: 178.3, 177.6, 176.2, 175.1, 147.4, 135.7, 134.0, 131.8, 129.5, 129.3, 128.9, 128.7, 126.6, 118.9, 69.2, 67.7, 50.8, 49.8, 49.0, 41.6, 41.4, 37.3, 26.0, 25.2. LRMS (EI) *m/z*: 501 (M^+, 0,4%), 41 (18), 43 (100), 55 (41) 57 (60), 69 (41), 70 (22), 71 (39), 83 (36), 85 (29), 95 (32), 97 (40), 111 (30), 125 (21), 173 (50). HRMS (ESI) calcd. for $C_{28}H_{24}ClN_3O_4$: 501.9670; found 501.9666.

Conflicts of interest

There are no conflicts to declare.

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