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Synthesis of pyrroloazepinones: platinum- and gold-catalyzed cyclization reactions of alkynes

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ABSTRACT

The synthesis of potentially bioactive pyrroloazepinones based on the catalytic intramolecular cyclization of alkyne-substituted 1*H*-pyrrole-2-carboxylic acid amides has been developed. In the presence of either $H_2PtCl_6 \cdot 6H_2O$ at 120 °C or $AuCl_3$ at room temperature pyrrolo[3,2-*c*]azepin-4-ones are formed.

1. Introduction

Pyrroloazepinones represent an important structural motif frequently found in a variety of bioactive compounds, such as Hymenialdisine,[1] Stevensine,[2] Latonduine A,[3] and the Paullones,[4] which have been originally isolated from marine sponges (Fig. 1). So far, pyrroloazepinone derivatives have been identified to inhibit various protein kinases, such as cyclin-dependant kinase (CDK1) or mitogen-activated protein kinase (MEK1).[1,5] These properties offer interesting potential for the development of novel small molecule drugs for cancer, Alzheimer's disease, arthritis, etc.[1–6] Moreover, Hymenialdisine inhibits the production of cytokine resulting in *anti*-inflammatory effects.

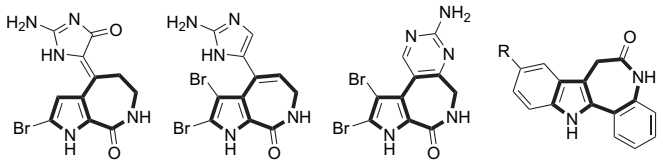

Figure 1. Natural products with a pyrroloazepinone core structure.

Consequently, derivatives are promising candidates for treatment of a range of diseases including Cohn's disease or psoriasis.[6,7] As shown in Figure 1 all compounds related to the Hymenialdisine family share the structural element of a fused bicyclic pyrroloazepinone in common (Fig. 1)[8]

The key step for the synthesis of pyrroloazepinone derivatives is the construction of the bicyclic ring system. In general, cyclization reactions have been used for this purpose. For example, typical electrophilic aromatic substitution reactions using phosphorus pentoxide[9] or trifluoroacetic acid (TFA) are known.[10] More recently, intramolecular Heck reactions were described by Van der Eycken to give benzazepinones and by Joseph et al. for the preparation of Lantoduine derivatives.[11] In addition, Taddei et al. synthesized (pyrroloazepinyl)acetamides by classic Beckmann rearrangement.[12]

In the last decade transition metal-catalyzed cyclizations of aryl-and heteroaryl-substituted alkynes have attracted significant attention. Among these reactions especially intramolecular hydroarylations,[13,14] cycloisomerizations,[15] and cycloadditions[16] offer new and efficient ways for construction of biologically interesting carbo- and heterocycles. Elegant examples include the work of Echavarren et al., who reported the intramolecular cyclization of indoles with alkynes in the presence of gold catalysts to give six- to eight-membered rings.[17] Complementary, England and Padwa developed an $AuCl_3$-catalyzed cycloisomerization of *N*-propargylindole-2-carboxamides.[18]

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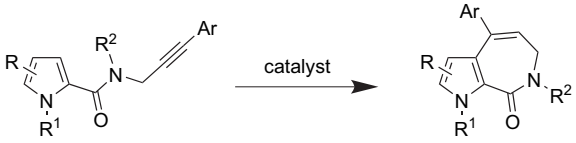
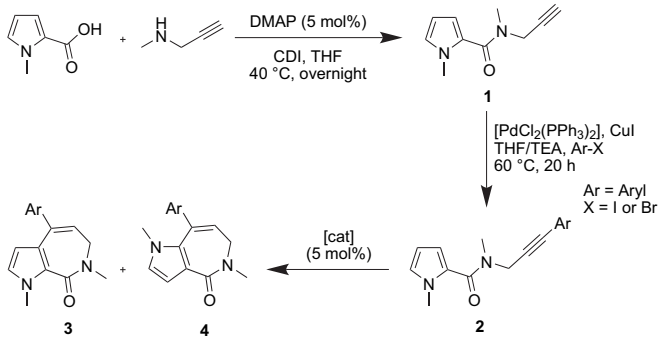
Since some years we are interested in the application of catalytic coupling and amination reactions for the synthesis of novel bioactive compounds.[8,19] In this respect, recently we envisioned the synthesis of pyrroloazepinone derivatives by metal-catalyzed cyclizations of alkyne-substituted pyrrolecarboxamides (Scheme 1). Based on a preliminary communication,[20] here we present a full account of our work on this topic.



Scheme 1. Strategy for the synthesis of pyrroloazepinones from 2-propargylamide-substituted pyrroles.

2. Results and discussion

Our initial investigations aimed at the straightforward synthesis of the pyrrolo[2,3-*c*]azepin-8-one **3** (Scheme 2). Hence, 1-methyl-1*H*-pyrrole-2-carboxylic acid methyl-prop-2-ynyl-amide (**1**) was prepared in 91% yield by addition of *N*-methylpropargylamine to *N*-methyl-1*H*-pyrrole-2-carboxylic acid. Amide formation took place in the presence of 4-(dimethylamino)pyridine (DMAP) and 1,1′-carbonyldiimidazole (CDI) in tetrahydrofurane (THF) at 40 °C over night.[21] Subsequent palladium-catalyzed Sonogashira coupling in the presence of a commercial Pd/Cu-catalyst system with aryl and heteroaryl halides (I, Br) gave different aryl-substituted alkynes **2**.[22] Next, the key step of the sequence, which is the intramolecular cyclization of **2**, was studied in the presence of different metal salts and complexes.

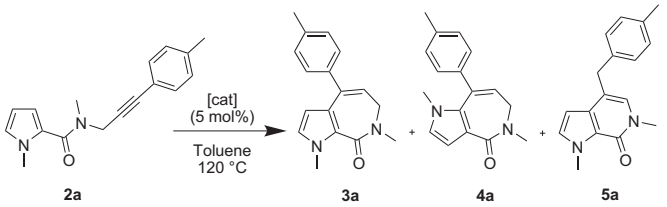


Scheme 2. General synthesis of pyrroloazepinones **3** and **4**.

According to the work of Echavarren et al. the best catalysts for the formation of the seven-membered azepinone derivatives should be Au^{III} complexes. In accordance with previously performed cyclizations, the expected product should have been the pyrrolo[2,3-*c*]azepin-8-one **3** formed by an 7-*endo*-dig process.[17] Surprisingly, we obtained two intramolecular cyclization products: the pyrrolo[2,3-*c*]azepin-8-one **3** and the pyrrolo[3,2-*c*]azepin-4-one **4** as major product (Scheme 2).[20]

In Table 1 the testing of different catalysts for the model reaction of 1-methyl-1*H*-pyrrole-2-carboxylic acid methyl-(3-*p*-tolyl-prop-2-ynyl)-amide (**2a**) is shown. In general, we used 5 mol % of the respective gold, platinum, iron, ruthenium, rhodium, iridium, zinc complexes or *p*-toluenesulfonic acid as classic Broenstedt catalyst. High activity and full conversion are observed in the presence of either $H_2PtCl_6\cdot 6H_2O$, K_2PtCl_6 or $PtCl_2$(COD) (Table 1, entries 4, 5 and 7) as catalyst in toluene at 120 °C. Under these conditions 1,5-dimethyl-8-*p*-tolyl-5,6-dihydro-1*H*-pyrrolo[3,2-*c*]azepin-4-one (**4a**) is obtained in 74–78% yield, while the $AuCl_3$-catalyzed reactions led to the same product in 40% yield. Notably, in these cases only a small amount of the other isomer 1,7-dimethyl-4-*p*-tolyl-6,7-dihydro-1*H*-pyrrolo[2,3-*c*]azepin-8-one (**3a**) is observed (Table 1).

Table 1
Variation of different metal salts for the intramolecular cyclization reaction[a]



Entry	Catalyst	Conv[b] [%]	Yield[b] [%] **3a**	Yield[b] [%] **4a**
1	$AuCl_3$	76	13	40
2	AuCl	41	2	19
3	$AuCl(PPh_3)$	11	0	0
4	$H_2PtCl_6\cdot 6H_2O$	100	7	78
5	K_2PtCl_6	100	5	74
6	$Pt(PPh_3)_4$	88	6	26
7	$PtCl_2$(COD)	100	6	75
8	$Fe(OAc)_2$	19	0	0
9	$FeCl_3$	—	0	0
10	$RuCl_3$	—	0	0
11	$Rh(acac)_3$	8	0	0
12	$IrCl_3$	—	0	0
13	$Zn(OTf)_2$	18	0	0
14	TsOH	89	0	0

[a] Reaction conditions: 5 mol % catalyst, 0.2 mmol compound **2a**, 10 mL toluene, 20 h at 120 °C.
[b] Determined by GC with hexadecane as internal standard.

Apart from Pt and Au, all other catalysts showed no activity for the cyclization process (Table 1, entries 8–14). However, when we used *p*-toluenesulfonic acid (Table 1, entry 14), ^{1}H NMR and GC–MS analysis of the reaction mixture confirmed the formation of the corresponding pyrrolo[2,3-*c*]pyridin-7-one derivative **5a**, which corresponds to the six-membered ring cyclization product. Apparently, this product is formed by an 6-*exo*-dig process.[17,18] In few cases also in the presence of Pt or Au catalysts traces (<1% yield) of this third product were observed.

After the initial catalyst screening, we investigated the influence of different solvents and temperatures on the $H_2PtCl_6\cdot 6H_2O$- and $AuCl_3$-catalyzed cyclization of **2** (Table 2).

The model reaction proceeded in good yield and selectivity (78% or 70% of product **4a**) in the presence of $H_2PtCl_6\cdot 6H_2O$ in toluene at 120 °C (Table 2, entry 1) or $AuCl_3$ in CH_2Cl_2 at room temperature

Table 2
Variation of reaction conditions in the presence of $AuCl_3$ and $H_2PtCl_6\cdot 6H_2O$ catalysts[a]

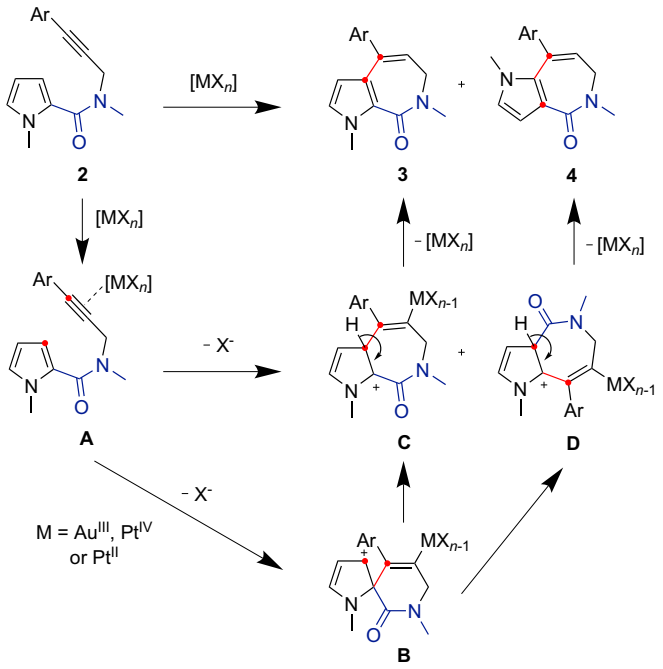
Entry	Catalyst	Solvent	*T* [°C]	Conv.[b] [%]	Yield[b] [%] **3a**	Yield[b] [%] **4a**
1	H_2PtCl_6	Toluene	120	100	7	78
2	H_2PtCl_6	Toluene	60	19	0	3
3	H_2PtCl_6	Toluene	0	0	0	0
4	H_2PtCl_6	Dioxane	120	100	36	60
5	H_2PtCl_6	Dioxane	60	100	35	64
6	H_2PtCl_6	Dioxane	20	21	5	5
7	H_2PtCl_6	CH_2Cl_2	20	9	0	8
8	$AuCl_3$	Toluene	120	76	13	40
9	$AuCl_3$	Dioxane	120	100	31	55
10	$AuCl_3$	Dioxane	60	100	51	48
11	$AuCl_3$	Dioxane	20	29	19	10
12	$AuCl_3$	CH_2Cl_2	20	77	7	70
13	$AuCl_3$	DMF	140	58	6	39
14	$AuCl_3$	DMF	120	41	1	40
15	$AuCl_3$	DMAc	120	69	60	9

[a] Reaction conditions: 5 mol % catalyst, 0.2 mmol compound **2a**, 10 mL solvent, 20 h.
[b] Determined by GC with hexadecane as internal standard.

(Table 2, entry 12). Notably, in both cases only a small amount (7%) of **3a** is observed. It appears that the gold catalyst is more easily deactivated and temperature sensitive compared to the platinum system.

As shown in Table 2, the ratio of **3a** and **4a** depends strongly upon the reaction conditions. For example, the use of $H_2PtCl_6 \cdot 6H_2O$ in 1,4-dioxane at 60 °C gave a ratio of **3a**:**4a** of approximately 1:2 (Table 2, entry 5). Furthermore, in the presence of $AuCl_3$ under the same conditions a 1:1 ratio is obtained (Table 2, entry 10). It is interesting to note that when we used $AuCl_3$ in dimethylacetamide (DMAc) at 120 °C (Table 2, entry 5) **3a** is formed as major product in 60% yield (9% of **4a**).

In Scheme 3 the proposed mechanism of this Au- and Pt-catalyzed cycloisomerization reaction is shown. In agreement with earlier reports in the literature,[13,17,18,23] the pyrrole-substituted alkyne **2** should be activated at the triple bond by coordination to the electrophilic Au^{III}, Pt^{IV} or Pt^{II} catalysts. Then, several modes of cycloisomerization reactions are possible depending on the reaction conditions (Table 2 and Scheme 3). It appears that the pyrrolo-azepinones **3** and **4** are obtained by a 7-*endo*-dig process from **2**.



Scheme 3. Proposed mechanism for the formation of **3** and **4**.

Following the initial activation of the triple bond, cation **C** is formed either directly from intermediate **A** or via cation **B**. Subsequent protonolysis of the carbon–metal bond and deprotonation leads to **3**. On the other hand, the reactive spiro intermediate **B**, already described in literature,[14,17] might form cation **D** by rearrangement, which after deprotonation followed by demetalation provides the seven-membered ring compound **4**.

Structures of the cyclization products **3a** and **4a** have been unambiguously confirmed by 1D and 2D NMR spectroscopy. In the ^1H, ^1H NOESY spectrum of **4a** correlations are found between the aryl protons and the protons of the *N*-methyl group of the pyrrole moiety (Fig. 2). Due to the anisotropic effect of the aryl ring, which is twisted out of the plane of the molecule, the signal of this *N*-methyl group is shifted at about 1 ppm to higher field in the ^1H NMR spectrum, compared to the spectrum of compound **3a**.[20] For compound **3a** a correlation of the aryl protons with the β-pyrrole-proton is observed in the ^1H, ^1H NOESY spectrum. On the other hand in the HMBC spectrum of compound **4a**,

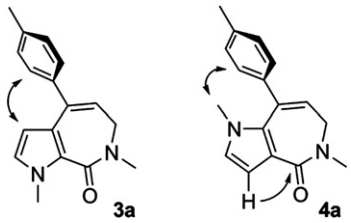


Figure 2. Relevant NOE (double arrows) and HMBC (single arrow) correlations of compounds **3a** and **4a**.

a correlation of the β-pyrrole-proton to the carbonyl group is seen (Fig. 2). In addition, we obtained single crystals of compound **4a** suitable for X-ray structure analysis, which confirmed the given structure (Fig. 3).

Next, we were interested in the scope and limitations of the procedure applying different arylated substrates (Table 3). For this purpose, Sonogashira reactions of *N*-(prop-2-ynyl)-1*H*-pyrrole-2-carboxamides **1a–d** with various aryl halides were performed in presence of $[PdCl_2(PPh_3)_2]$ and CuI.[22] The resulting Sonogashira products **2a–r** were obtained in good yield (up to 90%). Products **2q** and **2r** were formed by Sonogashira reaction follow by protection reaction from compound **2o** (Table 3, entries 17 and 18).[24,25] For the intramolecular cyclization reactions to afford pyrrolo[3,2-*c*]azepin-4-ones **4a–r** we always tested two conditions: 1. $H_2PtCl_6 \cdot 6H_2O$ in toluene at 120 °C and 2. $AuCl_3$ in CH_2Cl_2 at room temperature. As shown in Table 3, in general the first set of conditions in the presence of the platinum catalyst gave superior yields of the corresponding pyrroloazepines in up to 76% (Table 3, entries 1, 4–10, 12, 15, and 18). The cycloisomerization process of substituted alkynes with tolyl, *o*-xylyl, anisyl, chlorophenyl, *p*-acetylphenyl, and naphthyl groups afforded the corresponding products **4a–d**, **4g**, **i** and **4r** (Table 3, entries 1–4, 7, 9, and 18) in good yields. However, trifluoromethylbenzene, cyanobenzene, ethyl benzoate, benzofuran, furan or thiophen substituents (Table 3, entries 5, 6, 8, and 10–12) led to lower yields of the desired coupling products. In addition, we tested heteroaryl-substituted alkynes but no conversion was observed (Table 3, entry 13).

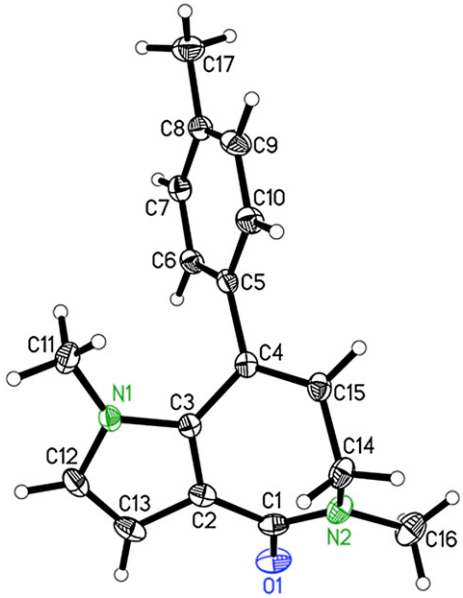
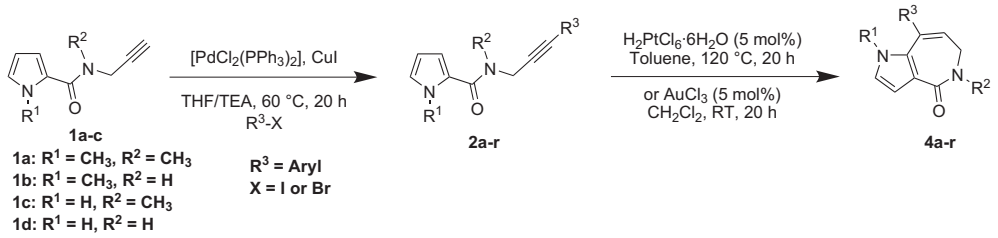


Figure 3. ORTEP view of the molecular structure of 1,5-dimethyl-8-*p*-tolyl-5,6-dihydro-1*H*-pyrrolo[3,2-*c*]azepin-4-one (**4a**). The thermal ellipsoids correspond to 30% probability.

Table 3
Sonogashira and cyclization reactions with various arylated substrates[a]



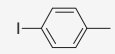
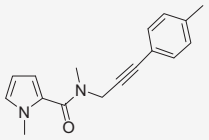
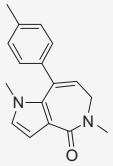
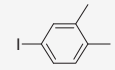
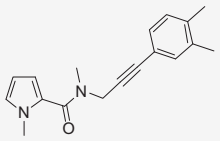
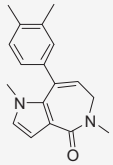
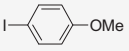
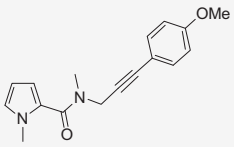
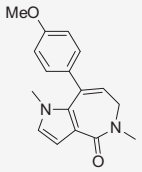
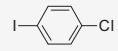
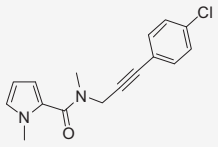
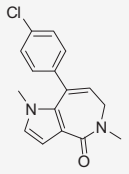
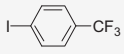
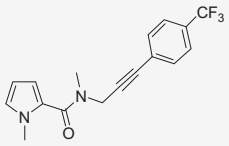
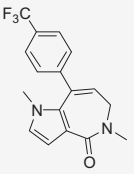
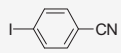
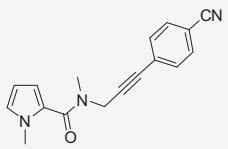
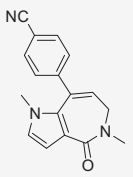
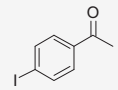
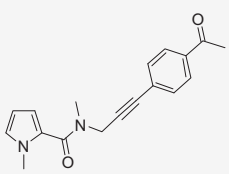
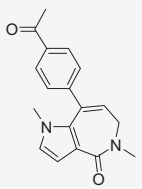
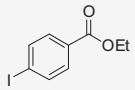
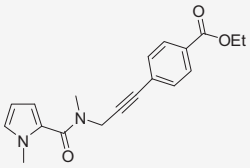
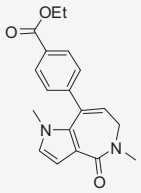
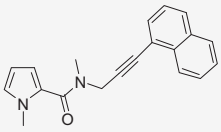
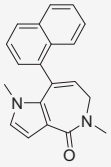
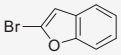
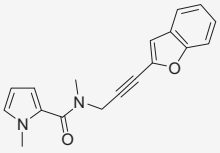
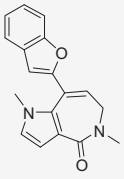
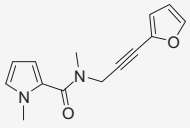
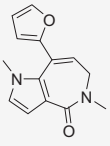
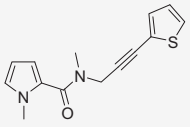
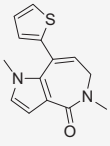
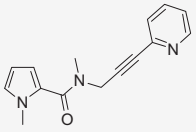
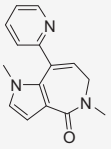
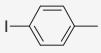
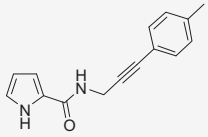
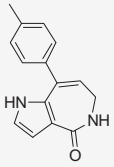
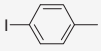
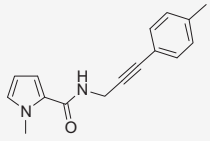
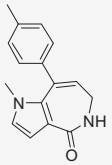
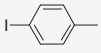
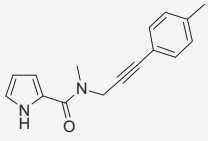
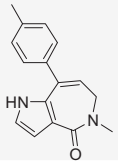
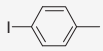
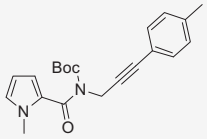
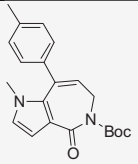
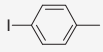
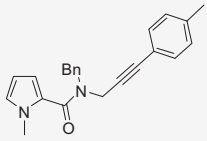
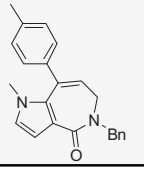
Entry	Substrate	Product **2**		Yield of **2** [%][b]	Product **4**		Yield of **4** [%][b]
1			**2a**	73		**4a**	76 70[c]
2			**2b**	75		**4b**	75
3			**2c**	52		**4c**	68
4			**2d**	82		**4d**	54 <10[c]
5			**2e**	81		**4e**	18 Trace[c]
6			**2f**	77		**4f**	17 Trace[c]
7			**2g**	80		**4g**	58 Trace[c]

Table 3 (*continued*)

Entry	Substrate	Product **2**	Yield of **2** [%][b]	Product **4**	Yield of **4** [%][b]
8		**2h** 	85	**4h** 	30 10[c]
9		**2i** 	72	**4i** 	70 19[c]
10		**2j** 	78	**4j** 	33 Trace[c]
11		**2k** 	42	**4k** 	10
12		**2l** 	65	**4l** 	29 18[c]
13		**2m** 	90	**4m** 	0 0[c]
14		**2n** 	50	**4n** 	0 0[c]
15		**2o** 	66	**4o** 	40 0[c]
16		**2p** 	72	**4p** 	35

(*continued on next page*)

Table 3 (*continued*)

Entry	Substrate	Product **2**		Yield of **2** [%][b]	Product **4**		Yield of **4** [%][b]
17			**2q**	64[d]		**4q**	0 (21% of **4q**) 10[c]
18			**2r**	52[d]		**4r**	68 53[c]

[a] Sonogashira conditions: 2 mol % $[PdCl_2(PPh_3)_2]$, 4 mol % CuI, 1.15 mmol compound **1**, 1.27 mmol aryl halogenide, 8 mL THF/TEA (1:1), 60 °C, 20 h. Cyclization conditions: 5 mol % $H_2PtCl_6 \cdot 6H_2O$, 0.2 mmol compound **2**, 10 mL toluene, 120 °C, 20 h.
[b] Yield of isolated product.
[c] 5 mol % $AuCl_3$, 0.2 mmol compound **2**, 10 mL CH_2Cl_2, rt, 20 h.
[d] Total yield of isolated product after Sonogashira (to give **2o**) and protection reaction.

By comparing the reactivity of *N*,*N*′-dialkyl pyrroles **2a** and **2q**, **r** (Table 3, entries 1, 17, and 18) with *N*-methyl-derivatives **2o**, **p** (Table 3, entries 15 and 16) and **2n** (Table 3, entry 14), it became clear that protection of the nitrogen atoms is beneficial for the cyclization reaction. Notably, in all cases the major product is compound **4** and **3** is obtained only in traces (<5%). Finally non-arylated alkynes have been tested, however under these conditions no cyclization took place.

It should be noted that apart from being mechanistically interesting, this cycloisomerization protocol provides straightforward access of an original β-amino acid scaffold, which is an attractive motif for novel biologically active compounds.

3. Conclusion

In summary, a biologically interesting scaffold can be synthesized in few steps from commercially available starting materials. Au- and Pt-catalyzed cyclization reactions gave a number of pyrrolo[3,2-*c*]azepin-4-one derivatives in good yield. The formation of the products proceeds via a 7-*endo*-dig cyclization process with concomitant rearrangement of the amidocarbonyl group from the 2- to the 3-position of the pyrrole ring. $H_2PtCl_6 \cdot 6H_2O$ is the more general catalyst for the formation of seven-membered pyrrolo[3,2-*c*]azepin-4-one derivatives. Further extensions of this chemistry towards indoles and other heterocycles are currently explored in our laboratory.

4. Experimental section

4.1. General methods

All reactions were carried out under argon atmosphere. Chemicals were purchased from Aldrich, Fluka and Acros and unless otherwise noted were used without further purification. All compounds were characterized by ^1H NMR, ^{13}C NMR, GC–MS, HRMS and IR spectroscopy. ^1H and ^{13}C NMR spectra were recorded on Bruker AV 300 and AV 500 spectrometers with chloroform solutions of the compounds at a temperature of 300 K. The ^1H and ^{13}C NMR chemical shifts are reported relative to the chloroform resonances (δ (^1H)=7.26, δ (^{13}C)=77.0). Due to dynamic effects (restricted rotation in the amide moiety) some signals of compounds **2** appeared in the spectra at room temperature as broadened or were not displayed. IR spectra were recorded on FT-IR ALPHA (Bruker) with Platinum-ATR (Bruker). EI (70 eV) mass spectra were recorded on MAT 95XP (Thermo ELECTRON CORPORATION). GC was performed on Agilent 6890 chromatograph with a 30 m HP5 column. HRMS was performed on MAT 95XP (EI) and Agilent 6210 Time-of-Flight LC/MS (ESI). GC–MS was performed on Agilent 5973 chromatograph Mass Selective Detector. All yields reported in Table 3 refer to isolated yields. The analysis of compounds **1a**, **1b**, **1c**, **2a**, **3a** and **4a** have been already described in earlier publication.[20,21]

4.2. X-ray diffraction

Diffraction Data were collected on a STOE IPDS diffractometer using graphite-monochromated Mo Kα radiation. The structure was solved by direct methods (SHELXS-97)[26] and refined by full-matrix least-squares techniques on F^2 (SHELXL-97)[26]. XP (Bruker AXS) was used for graphical representation. Crystallographic data for the structure in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 730340 [**4a**]. The copy of the data can be obtained free of charge from www.ccdc.cam.ac.uk/data_request/cif or from the Cambrigde Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Crystal data for **4a** $C_{17}H_{18}N_2O$, M_r=266.33, monoclinic, space group $P2_1/c$, a=9.358(2), b=10.587(2), c=14.841(3) Å, β=105.18(3)°, V=1419.0(5) Å^3, Z=4, ρ_{calcd}=1.247 g cm^{-3}, μ=0.078 mm^{-1}, T=200 K, 4994 reflections collected, 2773 independent (R_{int}=0.0325) and 1890 observed reflections [$I>2\sigma(I)$], final R indices [$I>2\sigma(I)$]: R_1=0.0416, wR_2=0.0994, R indices (all data): R_1=0.0700, wR_2=0.1074, 184 refined parameters.

4.3. General procedure for the synthesis of 1-methyl-1*H*-pyrrole-2-carboxylic acid methyl-prop-2-ynyl-amide (1a) and 1-methyl-1*H*-pyrrole-2-carboxylic acid prop-2-ynylamide (1b)

1-Methylpyrrole-2-carboxilic acid (5 g, 40 mmol, 1 equiv), 4-dimethylaminopyridine DMAP (0.24 g, 2 mmol) and 1,1′-carbonyldiimidazole CDI (6.49 g, 40 mmol, 1 equiv) were introduced in 100 mL of tetrahydrofuran (THF). The solution was stirred 90 min at room temperature and *N*-methylpropargylamine (4 mL, 48 mmol, 1.2 equiv) or propargylamine (4.11 mL, 48 mmol, 1.2 equiv) was then added. The brown mixture was stirred overnight at 40 °C (for **1a**) or room temperature (for **1b**). After removal of the solvent in vacuo, the residue was purified by column chromatography (heptane/ethyl acetate 1:1) to give pyrroles **1a** (4.53 g, 91%, yellow oil) or **1b** (6.25 g, 96%, white powder).

4.4. Procedure for the synthesis of 1*H*-pyrrole-2-carboxylic acid methyl-prop-2-ynyl-amide (1c) and 1*H*-pyrrole-2-carboxylic acid prop-2-ynylamide (1d)

N-Methylpropargylamine (0.81 mL, 14.22 mmol, 1.5 equiv) or propargylamine (0.63 mL, 14.22 mmol, 1.5 equiv) was introduced to a solution of 2-trichloroacetylpyrrole (2 g, 9.48 mmol, 1 equiv) in 3 mL of triethylamine (TEA). The reaction mixture was then stirred at 60 °C overnight. After removal of the solvent in vacuo, the residue was purified by column chromatography (heptane/ethyl acetate 1:1) to give pyrroles **1c** as white powder (1.15 g, 75%) or **1d** as light yellow powder (1.06 g, 76%).

4.5. General procedure for Sonogashira reactions

$[PdCl_2(PPh_3)_2]$ (16 mg, 0.023 mmol, 2 mol %) and CuI (9 mg, 0.046 mmol, 4 mol %) were placed in an ACE pressure tube under an argon atmosphere. The aryl halogenide (1.27 mmol, 1.1 equiv) and a solution of *N*,*N*′-dimethyl-*N*-(prop-2-ynyl)-1*H*-pyrrole-2-carboxamide (**1a**) (202.7 mg, 1.15 mmol, 1 equiv) in THF/TEA (1:1, 8 mL) were then added. The pressure tube was sealed and the reaction mixture was heated at 60 °C for 20 h. After removal of the solvent in vacuo, the residue was purified by column chromatography (heptane/ethyl acetate 1:1) to give pyrroles **2a**–**r**.

*4.5.1. 1-Methyl-1H-pyrrole-2-carboxylic acid methyl-(3-p-tolyl-prop-2-ynyl)-amide (**2a**).* Yellow syrup, 73%. ^{1}H NMR (500.13 MHz; $CDCl_3$): δ=7.34 (m, 2H); 7.14 (m, 2H); 6.70 (dd, J=2.5, 1.8 Hz, 1H); 6.61 (br, 1H); 6.09 (dd, J=3.8, 2.5 Hz, 1H); 4.53 (s, 2H, CH_2); 3.80 (s, 3H, NCH_3); 3.23 (br, 3H, $OCNCH_3$); 2.34 (s, 3H, $CH_{3(aryl)}$). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ=163.8 (CO); 138.6 (C); 131.6 (2CH); 129.0 (2CH); 126.7 (CH); 124.8 (C); 119.6 (C); 113.5 (CH); 106.9 (CH); 84.4 (br, *C*≡C); 83.6 (*C*≡C); 40.3 (br, CH_2); 35.9 (NCH_3); 34.8 (br, $OCNCH_3$); 21.4 (CH_3). FT-IR (ATR, cm^{-1}): 3109, 3029, 2921, 1706, 1619, 1532, 1509, 1476, 1444, 1409, 1389, 1243, 1069, 1013, 816, 750, 729, 608. GC–MS (EI, 70 eV): *m*/*z* (%): 266 (22) [M^+], 251 (27), 238 (65), 224 (43), 209 (91), 194 (27), 175 (12), 156 (13), 129 (28), 115 (15), 108 (100), 91 (4), 81 (30), 63 (6), 53 (29), 39 (20). HRMS (EI): calcd for $C_{17}H_{18}ON_2$: 266.14136; found: 266.140787.

*4.5.2. 1-Methyl-1H-pyrrole-2-carboxylic acid [3-(3,4-dimethyl-phenyl)-prop-2-ynyl]-methyl-amide (**2b**).* Yellow syrup, 75%. ^{1}H NMR (500.13 MHz; $CDCl_3$): δ=7.24 (d, J=1.9 Hz, 1H); 7.20 (dd, J=7.7, 1.9 Hz, 1H); 7.07 (d, J=7.7 Hz, 1H); 6.71 (dd, J=2.5, 1.8 Hz, 1H); 6.62 (br, 1H); 6.10 (dd, J=3.8, 2.5 Hz, 1H); 4.54 (s, 2H, CH_2); 3.81 (s, 3H, NCH_3); 3.24 (s, 3H, $OCNCH_3$); 2.26 (s, 3H, $CH_{3(aryl)}$); 2.24 (s, 3H, $CH_{3(aryl)}$). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ=163.7 (CO); 137.3 (C); 136.6 (C); 132.7 (CH); 129.6 (CH); 129.1 (CH); 126.6 (CH); 124.7 (C); 119.8 (C); 113.5 (CH); 106.9 (CH); 84.5 (br, *C*≡C); 83.3 (*C*≡C); 40.6 (br, CH_2); 35.8 (NCH_3); 34.8 (br, $OCNCH_3$); 19.6 (CH_3); 19.5 (CH_3). FT-IR (ATR, cm^{-1}): 3119, 3023, 2920, 1704, 1605, 1534, 1447, 1384, 1254, 1070, 1022, 818, 735, 609. GC–MS (EI, 70 eV): *m*/*z* (%): 280 (28) [M^+], 265 (39), 252 (63), 238 (43), 223 (95), 208 (33), 194 (8), 175 (18), 143 (23), 128 (25), 115 (19), 108 (100), 91 (6), 81 (31), 65 (3), 52 (4), 39 (15). HRMS (ESI, $[M+H]^+$): calcd for $C_{18}H_{21}ON_2$: 281.16484; found: 281.16479.

*4.5.3. 1-Methyl-1H-pyrrole-2-carboxylic acid [3-(4-methoxy-phenyl)-prop-2-ynyl]-methyl-amide (**2c**).* Yellow syrup, 52%. ^{1}H NMR (300.13 MHz; $CDCl_3$): δ=7.39 (m, 2H); 6.84 (m, 2H); 6.71 (dd, J=2.5, 1.8 Hz, 1H); 6.62 (br, 1H); 6.10 (dd, J=3.8, 2.5 Hz, 1H); 4.53 (s, 2H, CH_2); 3.81 (s, 6H, $2CH_3$); 3.24 (s, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=163.7 (C]O); 159.7 ($COCH_3$); 133.2 (2CH); 126.7 (CH); 124.7 (C); 114.7 (C); 114.0 (2CH); 113.6 (CH); 106.9 (CH); 83.0 (br, *C*≡C); 82.8 (*C*≡C); 55.3 (OCH_3); 39.0 (br, CH_2); 35.9 (NCH_3); 34.5 (br, $OCNCH_3$). FT-IR (ATR, cm^{-1}): 3108, 2980, 2957, 2930, 1710, 1605, 1532, 1406, 1389, 1267, 1102, 1069, 1018, 858, 769, 729, 696, 608. GC–MS (EI, 70 eV): *m*/*z* (%): 282 (28) [M^+], 267 (36), 254 (50), 240 (69), 225 (69), 210 (22), 196 (9), 175 (21), 158 (20), 145 (34), 130 (11), 108 (100), 102 (17), 89 (5), 81 (22), 76 (5), 63 (4), 53 (24), 39 (14). HRMS (ESI, $[M+H]^+$): calcd for $C_{17}H_{19}O_2N_2$: 283.1441; found: 283.14411.

*4.5.4. 1-Methyl-1H-pyrrole-2-carboxylic acid [3-(4-chloro-phenyl)-prop-2-ynyl]-methyl-amide (**2d**).* Yellow syrup, 82%. ^{1}H NMR (300.13 MHz; $CDCl_3$): δ=7.38 (m, 2H); 7.30 (m, 2H); 6.72 (dd, J=2.5, 1.8 Hz, 1H); 6.59 (br, 1H); 6.10 (dd, J=3.8, 2.5 Hz, 1H); 4.54 (s, 2H, CH_2); 3.81 (s, 3H, NCH_3); 3.25 (s, 3H, $OCNCH_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=163.7 (CO); 134.5 (C); 133.0 (2CH); 128.7 (2CH); 126.9 (CH); 124.6 (C); 121.1 (C); 113.7 (CH); 107.0 (CH); 85.4 (*C*≡C); 36.0 (NCH_3); not displayed: CH_2, C≡C, $OCNCH_3$. FT-IR (ATR, cm^{-1}): 3104, 2930, 1701, 1618, 1532, 1487, 1390, 1243, 1089, 1069, 1013, 827, 729, 607. GC–MS (EI, 70 eV): *m*/*z* (%): 286 (12) [M^+], 258 (53), 244 (21), 229 (59), 215 (15), 194 (9), 175 (8), 149 (17), 108 (100), 97 (3), 81 (28), 63 (4), 53 (23), 39 (14). HRMS (ESI, $[M+H]^+$): calcd for $C_{16}H_{16}ON_2Cl$: 287.09457; found: 287.09453.

*4.5.5. 1-Methyl-1H-pyrrole-2-carboxylic acid methyl-[3-(4-trifluoromethyl-phenyl)-prop-2-ynyl]-amide (**2e**).* Yellow syrup, 81%. ^{1}H NMR (500.13 MHz; $CDCl_3$): δ=7.58 (m, 4H); 6.73 (dd, J=2.5, 1.8 Hz, 1H); 6.60 (br, 1H); 6.11 (dd, J=3.8, 2.5 Hz, 1H); 4.58 (s, 2H, CH_2); 3.82 (s, 3H, NCH_3); 3.26 (s, 3H, $OCNCH_3$). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ=167.8 (CO); 132.0 (2CH); 130.4 (C); 130.3 (q, $J_{C,F}$=33.0 Hz, *C*–CF_3); 130.0 (C); 127.0 (CH); 126.4 (C); 125.2 (q, $J_{C,F}$=3.9 Hz, 2CH); 124.4 (C); 123.8 (q, $J_{C,F}$=272 Hz, CF_3); 113.7 (CH); 107.0 (CH); 87.0 (*C*≡C); 82.8 (br, *C*≡C); 39.1 (br, CH_2); 36.0 (NCH_3); 35.1 (br, $OCNCH_3$). FT-IR (ATR, cm^{-1}): 3350, 3108, 3041, 3000, 2960, 2920, 1681, 1618, 1600, 1532, 1389, 1323, 1259, 1243, 1066, 837, 750, 728, 592. GC–MS (EI, 70 eV): *m*/*z* (%): 320 (18) [M^+], 301 (6), 292 (66), 278 (14), 263 (81), 249 (13), 211 (5), 194 (5), 183 (16), 175 (6), 147 (6), 133 (8), 118 (3), 108 (100), 94 (23), 81 (27), 53 (21), 39 (12). HRMS (ESI, $[M+H]^+$): calcd for $C_{17}H_{16}ON_2F_3$: 321.12092; found: 321.12107.

*4.5.6. 1-Methyl-1H-pyrrole-2-carboxylic acid [3-(4-cyano-phenyl)-prop-2-ynyl]-methyl-amide (**2f**).* Yellow syrup, 77%. ^{1}H NMR (300.13 MHz; $CDCl_3$): δ=7.61 (m, 2H); 7.53 (m, 2H); 6.73 (dd, J=2.5, 1.8 Hz, 1H); 6.58 (dd, J=3.8, 1.8 Hz, 1H); 6.11 (dd, J=3.8, 2.5 Hz, 1H); 4.58 (s, 2H, CH_2); 3.82 (s, 3H, NCH_3); 3.26 (s, 3H, $OCNCH_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=163.7 (CO); 132.3 (2CH); 132.0 (2CH); 127.5 (C); 127.0 (CH); 124.3 (C); 118.3 (C); 113.7 (CH); 111.8 (C); 107.0 (CH); 89.1 (*C*≡C); 82.6 (br, *C*≡C); 36.0 (NCH_3); not displayed: CH_2, $OCNCH_3$. FT-IR (ATR, cm^{-1}): 3106, 3043, 2922, 2225, 1617, 1603, 1531, 1409, 1389, 1243, 1069, 838, 750, 728, 608, 555. GC–MS (EI, 70 eV): *m*/*z* (%): 277 (19) [M^+], 262 (7), 249 (66), 235 (14), 220 (68), 206 (22), 192 (3), 175 (7), 140 (15), 108 (100), 94 (2), 81 (26), 63 (4), 53 (21), 39 (13). HRMS (ESI, $[M+H]^+$): calcd for $C_{17}H_{16}ON_3$: 278.12879; found: 278.12885.

*4.5.7. 1-Methyl-1H-pyrrole-2-carboxylic acid [3-(4-acetyl-phenyl)-prop-2-ynyl]-methyl-amide (**2g**).* Yellow syrup, 80%. ^{1}H NMR (500.13 MHz; $CDCl_3$): δ=7.92 (m, 2H); 7.53 (m, 2H); 6.72 (dd, J=2.5, 1.9 Hz, 1H); 6.60 (br, 1H); 6.11 (dd, J=3.9, 2.5 Hz, 1H); 4.58 (s, 2H, CH_2); 3.82 (s, 3H, NCH_3); 3.26 (s, 3H, $OCNCH_3$); 2.60 (s, 3H, CH_3CO). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ=197.2 (CH_3CO); 163.7 (CO); 136.4 (C); 131.9 (2CH); 128.2 (2CH); 127.5 (C); 126.9 (CH); 124.5 (C); 113.7 (CH); 107.0 (CH); 87.9 (*C*≡C); 83.5 (br, *C*≡C); 40.0 (br, CH_2); 36.0 (NCH_3); 35.0 (br, $OCNCH_3$); 26.7 (CH_3CO). FT-IR (ATR, cm^{-1}): 3108, 3078, 2931, 1712, 1615, 1533, 1408, 1321, 1244, 1164, 1121, 1105, 1065, 1016, 842, 732, 597. GC–MS (EI, 70 eV): *m*/*z* (%): 294 (20) [M^+], 266 (65), 252 (15), 237 (86), 223 (17), 194 (24), 170 (9), 143 (11), 129 (4),

114 (12), 108 (100), 81 (29), 63 (3), 53 (21), 39 (12). HRMS (ESI, $[M+H]^+$): calcd for $C_{18}H_{19}O_2N_2$: 295.1441; found: 295.14387.

*4.5.8. 4-{3-[Methyl-(1-methyl-1H-pyrrole-2-carbonyl)-amino]-prop-1-ynyl}-benzoic acid ethyl ester (**2h**).* Yellow syrup, 85%. ^{1}H NMR (300.13 MHz; $CDCl_3$): δ=7.99 (m, 2H); 7.50 (m, 2H); 6.72 (d, J=2.5, 1.8 Hz, 1H); 6.60 (br, 1H); 6.11 (dd, J=3.9, 2.5 Hz, 1H); 4.58 (s, 2H, CH_2); 4.38 (q, J=7.1 Hz, 2H, OCH_2); 3.82 (s, 3H, NCH_3); 3.26 (s, 3H, $OCNCH_3$); 1.10 (t, J=7.1 Hz, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=166.0 (CO); 163.7 (CO); 131.6 (2CH); 130.1 (C); 129.4 (2CH); 127.1 (C); 126.9 (CH); 124.5 (C); 113.7 (CH); 107.0 (CH); 87.4 (*C*≡C); 86.0 (br, *C*≡C); 61.1 (OCH_2); 36.0 (NCH_3); 14.3 (CH_3); not displayed: NCH_2, $OCNCH_3$. FT-IR (ATR, cm^{-1}): 3107, 3038, 3001, 2933, 2837, 1705, 1603, 1532, 1508, 1410, 1243, 1171, 1069, 1037, 832, 750, 730, 607, 534. GC–MS (EI, 70 eV): *m*/*z* (%): 324 (26) [M^+], 296 (69), 279 (15), 267 (86), 253 (13), 238 (14), 210 (10), 194 (24), 175 (10), 143 (11), 108 (100), 88 (3), 81 (30), 63 (3), 53 (21), 39 (12). HRMS (ESI, $[M+H]^+$): calcd for $C_{19}H_{21}O_3N_2$: 325.15467; found: 325.15506.

*4.5.9. 1-Methyl-1H-pyrrole-2-carboxylic acid methyl-(3-naphthalen-1-yl-prop-2-ynyl)-amide (**2i**).* Yellow syrup, 72%. ^{1}H NMR (500.13 MHz; $CDCl_3$): δ=8.30 (m, J=8.2 Hz, 1H); 7.85 (m, 2H); 7.69 (dd, J=7.3, 1.2 Hz, 1H); 7.57 (ddd, J=8.2, 7.1, 1.2 Hz, 1H); 7.52 (ddd, J=8.2, 7.1, 1.2 Hz, 1H); 7.43 (dd, J=8.2, 7.1 Hz, 1H); 6.74 (dd, J=2.5 1.8 Hz, 1H); 6.69 (br, 1H); 6.12 (dd, J=3.9, 2.5 Hz, 1H); 4.72 (s, 2H, CH_2); 3.84 (s, 3H, NCH_3); 3.34 (s, 3H, $OCNCH_3$). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ=163.8 (CO); 133.3 (C); 133.1 (C); 130.7 (CH); 128.9 (CH); 128.3 (CH); 126.9 (CH); 126.8 (CH); 126.4 (CH); 126.0 (CH); 125.2 (CH); 124.7 (C); 120.3 (C); 113.7 (CH); 107.0 (CH); 89.3 (*C*≡C); 82.4 (*C*≡C); 40.4 (br, CH_2); 36.0 (NCH_3); 34.8 (br, $OCNCH_3$). FT-IR (ATR, cm^{-1}): 3104, 3055, 2921, 1616, 1531, 1476, 1443, 1409, 1388, 1306, 1242, 1067, 799, 773, 749, 726. GC–MS (EI, 70 eV): *m*/*z* (%): 302 (31) [M^+], 273 (30), 260 (60), 245 (73), 230 (17), 192 (14), 178 (8), 165 (49), 152 (14), 108 (100), 94 (3), 81 (17), 63 (3), 53 (21), 39 (19). HRMS (ESI, $[M+H]^+$): calcd for $C_{20}H_{19}ON_2$: 303.14919; found: 303.14915.

*4.5.10. 1-Methyl-1H-pyrrole-2-carboxylic acid (3-benzofuran-2-yl-prop-2-ynyl)-methyl-amide (**2j**).* Yellow syrup, 78%. ^{1}H NMR (300.13 MHz; $CDCl_3$): δ=7.56 (m, 1H); 7.45 (m, 1H); 7.34 (m, 1H); 7.25 (m, 1H); 6.96 (d, J=0.8 Hz, 1H); 6.73 (dd, J=2.6, 1.8 Hz, 1H); 6.59 (br, 1H); 6.11 (dd, J=3.9, 2.6 Hz, 1H); 4.64 (s, 2H, CH_2); 3.82 (s, 3H, NCH_3); 3.23 (s, 3H, $OCNCH_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=163.8 (C]O); 154.7 (C–O); 138.0 (C–O); 127.4 (C); 127.0 (CH); 125.7 (CH); 124.4 (C); 123.3 (CH); 121.3 (CH); 113.8 (CH); 112.0 (CH); 111.2 (CH); 107.0 (CH); 90.7 (*C*≡C); 74.8 (*C*≡C); 39.8 (br, CH_2); 36.0 (NCH_3); 35.3 (br, $OCNCH_3$). FT-IR (ATR, cm^{-1}): 3103, 3056, 3036, 2921, 1702, 1617, 1531, 1447, 1409, 1387, 1306, 1243, 1068, 748, 730. GC–MS (EI, 70 eV): *m*/*z* (%): 292 (24) [M^+], 277 (21), 263 (25), 250 (26), 235 (100), 220 (14), 184 (9), 169 (6), 155 (20), 144 (7), 126 (8), 108 (81), 94 (5), 80 (15), 63 (4), 53 (21), 39 (12). HRMS (ESI, $[M+H]^+$): calcd for $C_{18}H_{17}O_2N_2$: 293.12845; found: 293.12878.

*4.5.11. 1-Methyl-1H-pyrrole-2-carboxylic acid (3-furan-2-yl-prop-2-ynyl)-methyl-amide (**2k**).* Yellow syrup, 42%. ^{1}H NMR (300.13 MHz; $CDCl_3$): δ=7.38 (m, 1H); 6.71 (dd, J=2.6, 1.7 Hz, 1H); 6.60 (dd, J=3.4, 0.6 Hz, 1H); 6.57 (br, 1H); 6.39 (dd, J=3.4, 1.9 Hz, 1H); 6.10 (dd, J=3.8, 2.6 Hz, 1H); 4.58 (s, 2H, CH_2); 3.82 (s, 3H, NCH_3); 3.23 (s, 3H, $OCNCH_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=163.7 (CO); 143.6 (CH); 136.4 (C); 126.8 (CH); 124.4 (C); 115.5 (CH); 113.7 (CH); 110.8 (CH); 106.9 (CH); 88.8 (*C*≡C); 35.9 (NCH_3); not displayed: CH_2, $OCNCH_3$, *C*≡C. FT-IR (ATR, cm^{-1}): 3110, 2957, 2924, 1701, 1617, 1532, 1480, 1410, 1388, 1244, 1210, 1068, 730, 593. GC–MS (EI, 70 eV): *m*/*z* (%): 242 (12) [M^+], 227 (11), 214 (22), 201 (16), 185 (100), 170 (17), 156 (36), 142 (7), 130 (7), 108 (99), 94 (5), 81 (17), 65 (4), 53 (26), 39 (17). HRMS (EI): calcd for $C_{14}H_{14}O_2N_2$: 242.10498; found: 242.105288.

*4.5.12. 1-Methyl-1H-pyrrole-2-carboxylic acid methyl-(3-thiophen-2-yl-prop-2-ynyl)-amide (**2l**).* Red syrup, 65%. ^{1}H NMR (500.13 MHz; $CDCl_3$): δ=7.25 (dd, J=5.0, 1.2 Hz, 1H); 7.23 (dd, J=3.5, 1.2 Hz, 1H); 6.98 (dd, J=5.0, 3.5 Hz, 1H); 6.71 (dd, J=2.5, 1.9 Hz, 1H); 6.58 (br, 1H); 6.10 (dd, J=3.9, 2.5 Hz, 1H); 4.57 (s, 2H, CH_2); 3.82 (s, 3H, NCH_3); 3.24 (s, 3H, $OCNCH_3$). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ=163.7 (CO); 132.3 (CH); 127.2 (CH); 126.9 (CH); 126.8 (CH); 124.6 (C); 122.5 (C); 113.6 (CH); 106.9 (CH); 88.3 (*C*≡C); 77.5 (br, *C*≡C); 40.3 (br, CH_2); 35.9 (NCH_3); 35.0 (br, $OCNCH_3$). FT-IR (ATR, cm^{-1}): 3102, 2919, 2222, 1615, 1531, 1475, 1443, 1409, 1386, 1306, 1242, 1189, 1066, 847, 725, 700, 606. GC–MS (EI, 70 eV): *m*/*z* (%): 258 (12) [M^+], 243 (15), 230 (20), 216 (38), 201 (99), 187 (14), 168 (12), 148 (5), 135 (3), 121 (22), 108 (100), 94 (5), 81 (20), 63 (5), 53 (25), 39 (16). HRMS (ESI, $[M+H]^+$): calcd for $C_{14}H_{15}ON_2S$: 259.08996; found: 259.09012.

*4.5.13. 1-Methyl-1H-pyrrole-2-carboxylic acid methyl-(3-pyridin-2-yl-prop-2-ynyl)-amide (**2m**).* Orange syrup, 90%. ^{1}H NMR (300.13 MHz; $CDCl_3$): δ=8.58 (ddd, J=4.9, 1.9, 1.0 Hz, 1H); 7.66 (d′t′, J=7.7, 1.9 Hz, 1H); 7.45 (d′t′, J=7.7, 1.1 Hz, 1H); 7.24 (ddd, J=7.7, 4.9, 1.2 Hz, 1H); 6.71 (dd, J=2.6, 1.9 Hz, 1H); 6.59 (br, 1H); 6.09 (dd, J=3.8, 2.6 Hz, 1H); 4.60 (s, 2H, CH_2); 3.80 (s, 3H, NCH_3); 3.26 (s, 3H, $OCNCH_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=163.7 (CO); 150.0 (CH); 142.8 (C); 136.2 (CH); 127.2 (CH); 126.8 (CH); 124.4 (C); 123.1 (CH); 113.7 (CH); 106.9 (CH); 84.5 (*C*≡C); 83.6 (br, *C*≡C); 35.9 (NCH_3); not displayed: CH_2, $OCNCH_3$. FT-IR (ATR, cm^{-1}): 3105, 3078, 3051, 2952, 2921, 2230, 1734, 1617, 1581, 1531, 1461, 1427, 1410, 1387, 1243, 1068, 778, 736, 540. GC–MS (EI, 70 eV): *m*/*z* (%): 253 (18) [M^+], 238 (6), 224 (15), 210 (19), 196 (63), 182 (27), 175 (11), 145 (43), 129 (4), 117 (29), 108 (100), 89 (9), 81 (23), 63 (5), 42 (8), 39 (18). HRMS (ESI, $[M+H]^+$): calcd for $C_{15}H_{16}ON_3$: 254.12879; found: 254.12885.

*4.5.14. 1H-Pyrrole-2-carboxylic acid (3-p-tolyl-prop-2-ynyl)-amide (**2n**).* Light yellow powder, 50%. ^{1}H NMR (300.13 MHz; $CDCl_3$): δ=9.59 (br, 1H, NH); 7.32 (m, 2H); 7.11 (m, 2H); 6.93 (m, 1H); 6.61 (m, 1H); 6.24 (m, 1H); 6.10 (br t, J=5.3 Hz, 1H, OCNH); 4.44 (d, J=5.3 Hz, 2H, CH_2); 2.34 (s, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=160.6 (CO); 138.6 (C); 131.6 (2CH); 129.0 (2CH); 125.4 (C); 121.7 (CH); 119.4 (C); 109.9 (CH); 109.2 (CH); 84.1 (*C*≡C); 83.6 (*C*≡C); 30.1 (CH_2); 21.6 (CH_3). FT-IR (ATR, cm^{-1}): 3357, 3296, 3120, 3079, 3026, 2917, 2858, 1625, 1554, 1523, 1509, 1316, 1125, 816, 741, 526. GC–MS (EI, 70 eV): *m*/*z* (%): 238 (100) [M^+], 223 (7), 209 (59), 194 (14), 180 (13), 167 (4), 144 (86), 130 (27), 115 (25), 102 (7), 94 (54), 91 (8), 77 (8), 66 (26), 51 (6), 39 (18). HRMS (ESI, $[M+H]^+$): calcd for $C_{15}H_{15}ON_2$: 239.11789; found: 239.11768.

*4.5.15. 1-Methyl-1H-pyrrole-2-carboxylic acid (3-p-tolyl-prop-2-ynyl)-amide (**2o**).* Light yellow powder, 66%. ^{1}H NMR (300.13 MHz; $CDCl_3$): δ=7.33 (m, 2H); 7.11 (m, 2H); 6.73 (dd, J=2.6, 1.7 Hz, 1H); 6.60 (dd, J=3.9, 1.7 Hz, 1H); 6.09 (dd, J=3.9, 2.6 Hz, 1H); 6.04 (br, 1H, NH); 4.39 (d, J=5.3 Hz, 2H, CH_2); 3.96 (s, 3H, NCH_3); 2.34 (s, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=161.4 (CO); 138.5 (C); 131.6 (2CH); 129.0 (2CH); 128.2 (CH); 125.1 (C); 119.5 (C); 111.9 (CH); 107.3 (CH); 84.4 (*C*≡C); 83.4 (*C*≡C); 36.7 (NCH_3); 29.8 (CH_2); 21.4 (CH_3). FT-IR (ATR, cm^{-1}): 3324, 3082, 3025, 2920, 2865, 1634, 1542, 1507, 1462, 1409, 1324, 1273, 1259, 1157, 816, 726, 592. GC–MS (EI, 70 eV): *m*/*z* (%): 252 (58) [M^+], 237 (15), 223 (23), 210 (41), 196 (20), 180 (3), 167 (2), 161 (14), 128 (13), 115 (14), 108 (100), 102 (5), 91 (5), 80 (13), 63 (4), 53 (20), 39 (14). HRMS (ESI, $[M+H]^+$): calcd for $C_{16}H_{17}ON_2$: 253.13354; found: 253.13374.

*4.5.16. 1H-Pyrrole-2-carboxylic acid methyl-(3-p-tolyl-prop-2-ynyl)-amide (**2p**).* Light yellow powder, 72%. ^{1}H NMR (300.13 MHz;

$CDCl_3$): δ=9.95 (br, 1H, NH); 7.34 (m, 2H); 7.11 (m, 2H); 6.96 (m, 1H); 6.77 (br, 1H); 6.27 (m, 1H); 4.62 (s, 2H, CH_2); 3.35 (br, 3H, $OCNCH_3$); 2.35 (s, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=162.3 (CO); 138.5 (C); 131.6 (2CH); 129.0 (2CH); 124.5 (C); 121.4 (CH); 119.5 (C); 112.9 (CH); 109.8 (CH); 83.3 (*C*≡C); 21.4 (CH_3); not displayed: CH_2, *C*≡C, $OCNCH_3$. FT-IR (ATR, cm^{-1}): 3247, 3081, 3029, 2917, 2866, 1596, 1487, 1402, 1299, 1135, 1116, 812, 780, 736, 608. GC–MS (EI, 70 eV): *m*/*z* (%): 252 (100) [M^+], 237 (53), 223 (82), 209 (11), 194 (42), 180 (41), 158 (60), 144 (10), 129 (41), 115 (17), 102 (5), 94 (52), 77 (8), 66 (25), 51 (5), 39 (13). HRMS (ESI, [M+H]$^+$): calcd for $C_{16}H_{17}ON_2$: 253.13354; found: 253.1338.

4.6. Procedure for the synthesis of (1-methyl-1*H*-pyrrole-2-carbonyl)-(3-*p*-tolyl-prop-2-ynyl)-carbamic acid *tert*-butyl ester (2q)

To a solution of compound **2o** (200 mg, 0.783 mmol, 1 equiv) and DMAP (32.3 mg, 0.159 mmol) in acetonitrile (20 mL) was added $(Boc)_2O$ (365 μL 1.585 mmol, 2 equiv) under an argon atmosphere. The orange suspension was stirred at room temperature overnight. The reaction mixture was quenched with a saturated solution of aqueous NH_4Cl (50 mL) and extracted with ethyl acetate (2×100 mL). The combined organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue purified by column chromatography (heptane/ethyl acetate 1:1) affording the pyrrole **2q** as yellow oil (271 mg, 97%).

*4.6.1. (1-Methyl-1H-pyrrole-2-carbonyl)-(3-p-tolyl-prop-2-ynyl)-carbamic acid tert-butyl ester (**2q**).* ^1H NMR (300.13 MHz; $CDCl_3$): δ=7.30 (m, 2H); 7.08 (m, 2H); 6.79 (dd, *J*=2.5, 1.7 Hz, 1H); 6.65 (dd, *J*=4.0, 1.7 Hz, 1H); 6.10 (dd, *J*=4.0, 2.5 Hz, 1H); 4.65 (s, 2H, CH_2); 3.86 (s, 3H, NCH_3); 2.32 (s, 3H, CH_3); 1.38 (s, 9H, 3 CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=164.3 (CO); 153.3 (CO); 138.2 (C); 131.7 (2CH); 129.3 (CH); 128.9 (2CH); 127.8 (C); 119.9 (C); 117.7 (CH); 107.9 (CH); 84.1 (C); 82.8 (C); 82.6 (C); 36.0 (CH_3); 35.9 (CH_2); 27.8 (3 CH_3); 21.4 (CH_3). FT-IR (ATR, cm^{-1}): 3029, 2977, 2930, 1722, 1663, 1510, 1410, 1366, 1332, 1220, 1140, 947, 816, 764, 734, 528. HRMS (ESI, [M+Na]$^+$): calcd for $C_{21}H_{24}O_3N_2Na$: 375.16791; found: 375.1679.

4.7. Procedure for the synthesis of 1-methyl-1*H*-pyrrole-2-carboxylic acid benzyl-(3-*p*-tolyl-prop-2-ynyl)-amide (2r)

To a solution of product **2o** (318 mg, 1.26 mmol, 1 equiv) in DMF (30 mL) was added in three times NaH (60% dispersion in mineral oil, 126 mg, 3.15 mmol, 2.5 equiv) at 0 °C under an argon atmosphere. After 1 h, benzylbromide (375 μL, 3.15 mmol, 2.5 equiv) was then added and the yellow suspension was stirred 2 h at room temperature. The reaction mixture was quenched with a saturated solution of aqueous NH_4Cl (50 mL) and extracted with ethyl acetate (2× 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue purified by column chromatography (heptane/ethyl acetate 70:30) affording the pyrrole **2r** as yellow oil (335 mg, 78%).

*4.7.1. 1-Methyl-1H-pyrrole-2-carboxylic acid benzyl-(3-p-tolyl-prop-2-ynyl)-amide (**2r**).* Yellow syrup, 52%. ^1H NMR (300.13 MHz; $CDCl_3$): δ=7.38–7.30 (m, 7H); 7.14 (m, 2H); 6.74 (dd, *J*=2.6, 1.8 Hz, 1H); 6.68 (br, 1H); 6.09 (dd, *J*=3.8, 2.6 Hz, 1H); 4.95 (s, 2H, CH_2); 4.47 (s, 2H, CH_2); 3.86 (s, 3H, NCH_3); 2.37 (s, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=163.9 (CO); 138.5 (C); 136.9 (C); 131.6 (2CH); 129.0 (2CH); 128.7 (2CH); 127.7 (br, 2CH); 127.4 (CH); 127.0 (CH); 124.6 (C); 119.5 (C); 113.1 (CH); 107.0 (CH); 84.4 (br, *C*≡C); 83.7 (*C*≡C); 36.0 (NCH_3); 21.4 (CH_3); not displayed: CH_2, CH_2. FT-IR (ATR, cm^{-1}):3108, 3060, 3028, 2920, 2869, 1621, 1509, 1449, 1418, 1242, 1139, 976, 816, 749, 725, 696, 607, 527. GC–MS (EI, 70 eV): *m*/*z* (%): 342 (10) [M^+], 314 (32), 300 (3), 251 (49), 223 (5), 209 (100), 194 (21), 170 (12), 129 (14), 108 (65), 91 (23), 81 (9), 65 (4), 53 (10), 39 (5). HRMS (ESI, [M+H]$^+$): calcd for $C_{23}H_{23}ON_2$: 343.18049; found: 343.18069.

4.8. General procedure for cyclization reactions

$H_2PtCl_6 \cdot 6H_2O$ or $AuCl_3$ (0.01 mmol, 5 mol %) was placed in an ACE pressure tube under an argon atmosphere. A solution of product **2a**–**r** (0.2 mmol, 1 equiv) in 10 ml of toluene (for [Pt]) or 10 ml of dichloromethane (for [Au]) was then injected into the tube. The pressure tube was sealed and the reaction mixture was heated at 120 °C (for [Pt]) or room temperature (for [Au]) for 20 h. Solvent was removed under reduced pressure and the residue purified by column chromatography (heptane/ethyl acetate) to give pyrrolo[3,2-*c*]azepin-4-ones **4a**–**r**.

*4.8.1. 1,5-Dimethyl-8-p-tolyl-5,6-dihydro-1H-pyrrolo[3,2-c]azepin-4-one (**4a**).* Beige powder, 76%. ^1H NMR (500.13 MHz; $CDCl_3$): δ=7.14 (m, 2H); 7.09 (m, 2H); 6.73 (d, *J*=2.9 Hz, 1H); 6.61 (d, *J*=2.9 Hz, 1H); 6.09 (t, *J*=7.5 Hz, 1H); 3.71 (d, *J*=7.5 Hz, 2H, CH_2); 3.15 (s, 3H, $OCNCH_3$); 3.07 (s, 3H, NCH_3); 2.35 (s, 3H, CH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ=166.0 (CO); 137.9 (C); 137.7 (C); 136.6 (C); 131.6 (C); 129.3 (2CH); 127.4 (2CH); 124.6 (CH); 123.8 (CH); 123.5 (C); 109.6 (CH); 47.5 (CH_2); 36.4 (NCH_3); 35.2 ($OCNCH_3$); 21.1 (CH_3). FT-IR (ATR, cm^{-1}): 3138, 3043, 2995, 2921, 2853, 1609, 1494, 1238, 1066, 838, 811, 730, 702, 521. GC–MS (EI, 70 eV): *m*/*z* (%): 266 (100) [M^+], 251 (14), 237 (48), 224 (29), 210 (29), 194 (11), 175 (20), 165 (4), 152 (9), 115 (5), 91 (3), 77 (3), 63 (3), 51 (2), 42 (11). HRMS (EI): calcd for $C_{17}H_{18}ON_2$: 266.14136; found: 266.141372.

*4.8.2. 8-(3,4-Dimethyl-phenyl)-1,5-dimethyl-5,6-dihydro-1H-pyrrolo[3,2-c]azepin-4-one (**4b**).* Orange powder, 75%. ^1H NMR (300.13 MHz; $CDCl_3$): δ=7.09 (d, *J*=7.7 Hz, 1H); 6.95 (m, 2H); 6.75 (d, *J*=2.9 Hz, 1H); 6.62 (d, *J*=2.9 Hz, 1H); 6.09 (t, *J*=7.4 Hz, 1H); 3.70 (d, *J*=7.4 Hz, 2H, CH_2); 3.15 (s, 3H, $OCNCH_3$); 3.08 (s, 3H, NCH_3); 2.26 (s, 3H, CH_3); 2.23 (s, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=166.0 (CO); 137.9 (C); 137.1 (C); 136.9 (C); 136.6 (C); 131.7 (C); 129.9 (CH); 128.7 (CH); 125.0 (CH); 124.6 (CH); 123.7 (CH); 123.5 (C); 109.6 (CH); 47.5 (CH_2); 36.5 (NCH_3); 35.2 ($OCNCH_3$); 19.7 (CH_3); 19.5 (CH_3). FT-IR (ATR, cm^{-1}): 3114, 3041, 3014, 2919, 2859, 1703, 1598, 1499, 1394, 1241, 827, 810, 729. GC–MS (EI, 70 eV): *m*/*z* (%): 280 (100) [M^+], 264 (2), 251 (44), 238 (23), 224 (38), 208 (9), 194 (10), 180 (5), 175 (21), 165 (6), 152 (5), 132 (6), 115 (3), 96 (3), 77 (3), 63 (2), 51 (1), 42 (8). HRMS (ESI, [M+H]$^+$): calcd for $C_{18}H_{21}ON_2$: 281.16484; found: 281.16507.

*4.8.3. 8-(4-Methoxy-phenyl)-1,5-dimethyl-5,6-dihydro-1H-pyrrolo[3,2-c]azepin-4-one (**4c**).* Brown powder, 68%. ^1H NMR (500.13 MHz; $CDCl_3$): δ=7.14 (m, 2H); 6.87 (m, 2H); 6.74 (d, *J*=2.9 Hz, 1H); 6.62 (d, *J*=2.9 Hz, 1H); 6.05 (t, *J*=7.4 Hz, 1H); 3.80 (s, 3H, OCH_3); 3.70 (d, *J*=7.4 Hz, 2H, CH_2); 3.15 (s, 3H, $OCNCH_3$); 3.08 (s, 3H, NCH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=166.0 (C]O); 159.5 (C–O); 137.4 (C); 132.1 (C); 131.7 (C); 128.7 (2CH); 124.7 (CH); 123.6 (C); 123.1 (CH); 114.1 (2CH); 109.6 (CH); 55.3 (OCH_3); 47.5 (CH_2); 36.4 (NCH_3); 35.3 ($OCNCH_3$). FT-IR (ATR, cm^{-1}): 3118, 3033, 2999, 2951, 2931, 2838, 1611, 1497, 1391, 1237, 1176, 1030, 829, 730, 535. GC–MS (EI, 70 eV): *m*/*z* (%): 282 (100) [M^+], 267 (12), 253 (36), 240 (35), 226 (28), 210 (16), 197 (8), 182 (5), 175 (17), 147 (4), 133 (5), 121 (6), 105 (4), 89 (2), 77 (4), 63 (3), 51 (1), 42 (9). HRMS (ESI, [M+H]$^+$): calcd for $C_{17}H_{19}O_2N_2$: 283.1441; found: 283.14447.

*4.8.4. 8-(4-Chloro-phenyl)-1,5-dimethyl-5,6-dihydro-1H-pyrrolo[3,2-c]azepin-4-one (**4d**).* Beige powder, 54%. ^1H NMR (300.13 MHz; $CDCl_3$): δ=7.32 (m, 2H); 7.15 (m, 2H); 6.75 (d, *J*=2.9 Hz, 1H); 6.63 (d, *J*=2.9 Hz, 1H); 6.12 (t, *J*=7.4 Hz, 1H); 3.72 (d,

J=7.4 Hz, 2H, CH_2); 3.16 (s, 3H, $OCNCH_3$); 3.08 (s, 3H, NCH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=165.9 (CO); 138.0 (C); 136.8 (C); 134.1 (C); 130.9 (C); 129.0 (2CH); 128.9 (2CH); 125.0 (CH); 124.9 (CH); 123.9 (C); 109.9 (CH); 47.5 (CH_2); 36.6 (NCH_3); 35.4 ($OCNCH_3$). FT-IR (ATR, cm^{-1}): 3130, 3095, 3044, 2918, 1615, 1492, 1392, 1237, 1090, 1068, 1012, 830, 818, 764, 730, 703. GC–MS (EI, 70 eV): m/z (%): 286 (100) [M^+], 271 (10), 257 (63), 244 (29), 229 (20), 210 (8), 194 (6), 175 (28), 152 (13), 139 (8), 125 (11), 111 (4), 96 (5), 75 (4), 63 (4), 51 (2), 42 (14). HRMS (ESI, [M+H]$^+$): calcd for $C_{16}H_{16}ON_2Cl$: 287.09457; found: 287.09467.

*4.8.5. 1,5-Dimethyl-8-(4-trifluoromethyl-phenyl)-5,6-dihydro-1H-pyrrolo[3,2-c]azepin-4-one (**4e**).* Beige powder, 18%. ^1H NMR (300.13 MHz; $CDCl_3$): δ=7.62 (m, 2H); 7.35 (m, 2H); 6.78 (d, J=2.9 Hz, 1H); 6.66 (d, J=2.9 Hz, 1H); 6.20 (t, J=7.5 Hz, 1H); 3.76 (d, J=7.5 Hz, 2H, CH_2); 3.17 (s, 3H, $OCNCH_3$); 3.07 (s, 3H, NCH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=165.8 (CO); 143.0 (C); 136.8 (C); 130.7 (C); 130.3 (q, $J_{C,F}$=33.0 Hz, *C*–CF_3); 127.8 (2CH); 126.1 (CH); 125.7 (q, $J_{C,F}$=3.9 Hz, 2CH); 125.1 (CH); 124.1 (q, $J_{C,F}$=274 Hz, CF_3); 123.8 (C); 110.1 (CH); 47.5 (CH_2); 36.6 (NCH_3); 35.5 ($OCNCH_3$). FT-IR (ATR, cm^{-1}): 3108, 2957, 2923, 2854, 1733, 1678, 1599, 1496, 1355, 1263, 1240, 1070, 956, 842, 734, 605, 593. GC–MS (EI, 70 eV): m/z (%): 320 (100) [M^+], 291 (72), 278 (29), 263 (24), 248 (8), 209 (3), 175 (21), 147 (5), 125 (9), 75 (2), 63 (3), 42 (9). HRMS (ESI, [M+H]$^+$): calcd for $C_{17}H_{16}ON_2F$: 321.12092; found: 321.12099.

*4.8.6. 4-(1,5-Dimethyl-4-oxo-1,4,5,6-tetrahydro-pyrrolo[3,2-c]azepin-8-yl)-benzonitrile (**4f**).* Yellow powder, 17%. ^1H NMR (300.13 MHz; $CDCl_3$): δ=7.65 (m, 2H); 7.34 (m, 2H); 6.77 (d, J=2.9 Hz, 1H); 6.67 (d, J=2.9 Hz, 1H); 6.23 (t, J=7.4 Hz, 1H); 3.77 (d, J=7.4 Hz, 2H, CH_2); 3.17 (s, 3H, $OCNCH_3$); 3.07 (s, 3H, NCH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=165.7 (CO); 144.0 (C); 136.4 (C); 132.6 (2CH); 130.1 (C); 128.1 (2CH); 126.8 (CH); 125.2 (CH); 124.2 (C); 118.4 (C); 111.8 (C); 110.1 (CH); 47.4 (CH_2); 36.5 (NCH_3); 35.4 ($OCNCH_3$). FT-IR (ATR, cm^{-1}): 3108, 3035, 2923, 2226, 1731, 1599, 1496, 1393, 1239, 1070, 854, 826, 733, 607, 568, 543. GC–MS (EI, 70 eV): m/z (%): 277 (100) [M^+], 262 (12), 248 (74), 235 (32), 220 (23), 205 (14), 192 (11), 175 (25), 164 (7), 151 (6), 140 (7), 127 (2), 96 (3), 76 (2), 63 (3), 51 (2), 42 (13). HRMS (ESI, [M+H]$^+$): calcd for $C_{17}H_{16}ON_3$: 278.12879; found: 278.12866.

*4.8.7. 8-(4-Acetyl-phenyl)-1,5-dimethyl-5,6-dihydro-1H-pyrrolo[3,2-c]azepin-4-one (**4g**).* Yellow powder, 58%. ^1H NMR (500.13 MHz; $CDCl_3$): δ=7.95 (m, 2H); 7.32 (m, 2H); 6.77 (d, J=2.9 Hz, 1H); 6.66 (d, J=2.9 Hz, 1H); 6.23 (t, J=7.4 Hz, 1H); 3.76 (d, J=7.4 Hz, 2H, CH_2); 3.17 (s, 3H, $OCNCH_3$); 3.07 (s, 3H, NCH_3); 2.61 (s, 3H, $COCH_3$). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ=197.4 (CH_3CO); 165.8 (CO); 144.2 (C); 137.0 (C); 136.6 (C); 130.7 (C); 128.8 (2CH); 127.7 (2CH); 126.1 (CH); 125.0 (CH); 124.0 (C); 110.0 (CH); 47.5 (CH_2); 36.5 (NCH_3); 35.4 ($OCNCH_3$); 26.6 ($COCH_3$). FT-IR (ATR, cm^{-1}): 3110, 3062, 3042, 2994, 2923, 1679, 1600, 1498, 1398, 1356, 1265, 1242, 957, 825, 736, 606. GC–MS (EI, 70 eV): m/z (%): 294 (100) [M^+], 265 (47), 252 (15), 237 (13), 220 (2), 210 (20), 194 (6), 175 (22), 167 (6), 152 (8), 125 (3), 89 (2), 77 (2), 63 (3), 42 (10). HRMS (ESI, [M+H]$^+$): calcd for $C_{18}H_{19}O_2N_2$: 295.1441; found: 295.14414.

*4.8.8. 4-(1,5-Dimethyl-4-oxo-1,4,5,6-tetrahydro-pyrrolo[3,2-c]azepin-8-yl)-benzoic acid ethyl ester (**4h**).* Brown powder, 30%. ^1H NMR (300.13 MHz; $CDCl_3$): δ=8.02 (m, 2H); 7.29 (m, 2H); 6.76 (d, J=2.9 Hz, 1H); 6.65 (d, J=2.9 Hz, 1H); 6.21 (t, J=7.4 Hz, 1H); 4.37 (q, J=7.1 Hz, 2H, OCH_2); 3.75 (d, J=7.4 Hz, 2H, NCH_2); 3.17 (s, 3H, $OCNCH_3$); 3.05 (s, 3H, NCH_3); 1.39 (t, J=7.1 Hz, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=166.1 (CO); 165.8 (CO); 143.9 (C); 137.1 (C); 130.7 (C); 130.1 (C); 130.0 (2CH); 127.5 (2CH); 125.9 (CH); 124.9 (CH); 123.9 (C); 109.9 (CH); 61.1 (OCH_2); 47.4 (NCH_2); 36.5 (NCH_3); 35.4 ($OCNCH_3$); 14.3 (CH_3). FT-IR (ATR, cm^{-1}): 3112, 2957, 2927, 2905, 1710, 1603, 1499, 1269, 1176, 1100, 1019, 775, 732, 709. GC–MS (EI, 70 eV): m/z (%): 324 (100) [M^+], 295 (52), 279 (9), 267 (22), 254 (9), 222 (4), 210 (15), 194 (5), 175 (24), 152 (8), 139 (5), 89 (2), 77 (2), 63 (2), 42 (8). HRMS (ESI, [M+H]$^+$): calcd for $C_{19}H_{21}O_3N_2$: 325.15467; found: 325.15473.

*4.8.9. 1,5-Dimethyl-8-naphthalen-1-yl-5,6-dihydro-1H-pyrrolo[3,2-c]azepin-4-one (**4i**).* Brown powder, 30%. ^1H NMR (300.13 MHz; $CDCl_3$): δ=7.84 (d, J=8.6 Hz, 2H); 7.44 (m, 4H); 7.32 (m, 2H); 6.82 (d, J=2.9 Hz, 1H); 6.50 (d, J=2.9 Hz, 1H); 6.19 (t, J=7.4 Hz, 1H); 3.92 (dd, J=14.3, 7.4 Hz, 1H, CH_2); 3.80 (dd, J=14.3, 7.4 Hz, 1H, CH_2); 3.21 (s, 3H, $OCNCH_3$); 2.72 (s, 3H, NCH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=165.9 (CO); 137.3 (C); 136.5 (C); 133.6 (C); 132.4 (C); 131.3 (C); 128.8 (CH); 128.3 (CH); 127.2 (CH); 126.8 (CH); 126.1 (CH); 126.1 (CH); 125.5 (CH); 124.9 (CH); 124.8 (CH); 122.9 (C); 110.1 (CH); 47.6 (NCH_2); 35.9 (NCH_3); 35.5 ($OCNCH_3$). FT-IR (ATR, cm^{-1}): 3100, 3042, 2922, 2853, 1729, 1610, 1495, 1392, 1241, 1071, 804, 778, 728. GC–MS (EI, 70 eV): m/z (%): 302 (100) [M^+], 287 (9), 273 (25), 260 (15), 244 (13), 230 (8), 217 (7), 202 (8), 189 (9), 175 (14), 161 (9), 141 (4), 128 (3), 101 (3), 77 (1), 63 (1), 42 (7). HRMS (ESI, [M+H]$^+$): calcd for $C_{20}H_{19}ON_2$: 303.14919; found: 303.14917.

*4.8.10. 8-Benzofuran-2-yl-1,5-dimethyl-5,6-dihydro-1H-pyrrolo[3,2-c]azepin-4-one (**4j**).* Beige powder, 33%. ^1H NMR (300.13 MHz; $CDCl_3$): δ=7.56 (m, 2H); 7.54 (m, 2H); 7.27 (m, 3H); 6.78 (d, J=2.9 Hz, 1H); 6.72 (d, J=2.9 Hz, 1H); 6.65 (s, 1H); 6.63 (t, J=7.6 Hz, 1H); 3.78 (d, J=7.6 Hz, 1H, CH_2); 3.37 (s, 3H, $OCNCH_3$); 3.18 (s, 3H, NCH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=165.8 (C]O); 154.7 (CO); 153.8 (CO); 129.4 (C); 128.5 (C); 127.2 (C); 125.6 (CH); 125.2 (CH); 124.9 (CH); 124.0 (C); 123.2 (CH); 121.2 (CH); 111.3 (CH); 110.1 (CH); 105.3 (CH); 47.2 (NCH_2); 36.0 (NCH_3); 35.4 ($OCNCH_3$). FT-IR (ATR, cm^{-1}): 3108, 3052, 3013, 1950, 1922, 1613, 1496, 1450, 1392, 1253, 1240, 975, 861, 821, 731, 613. GC–MS (EI, 70 eV): m/z (%): 292 (100) [M^+], 275 (35), 263 (18), 250 (23), 220 (8), 199 (5), 165 (4), 152 (4), 131 (3), 115 (2), 96 (2), 77 (2), 63 (3), 42 (8). HRMS (ESI, [M+H]$^+$): calcd for $C_{18}H_{17}O_2N_2$: 293.12845; found: 293.12852.

*4.8.11. 8-Furan-2-yl-1,5-dimethyl-5,6-dihydro-1H-pyrrolo[3,2-c]azepin-4-one (**4k**).* Brown powder, <10%. ^1H NMR (500.13 MHz; $CDCl_3$): δ=7.42 (dd, J=1.9, 0.9 Hz, 1H); 6.74 (d, J=2.8 Hz, 1H); 6.68 (d, J=2.8 Hz, 1H); 6.44 (dd, J=3.3, 1.9 Hz, 1H); 6.36 (t, J=7.5 Hz, 1H); 6.32 (dd, J=3.3, 0.9 Hz, 1H); 3.72 (d, J=7.5 Hz, 1H, CH_2); 3.31 (s, 3H, $OCNCH_3$); 3.17 (s, 3H, NCH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ=165.9 (CO); 151.9 (CO); 142.4 (CH); 129.9 (C); 127.2 (C); 125.0 (CH); 123.6 (C); 122.9 (CH); 111.5 (CH); 109.9 (CH); 108.7 (CH); 47.1 (NCH_2); 35.6 (NCH_3); 35.4 ($OCNCH_3$). FT-IR (ATR, cm^{-1}): 3111, 2922, 2852, 1602, 1501, 1461, 1396, 1241, 1095, 1016, 808, 730, 596. GC–MS (EI, 70 eV): m/z (%): 242 (100) [M^+], 227 (3), 213 (96), 200 (20), 185 (44), 170 (19), 156 (8), 144 (16), 130 (7), 115 (11), 103 (4), 89 (6), 77 (6), 63 (6), 51 (6), 42 (17), 32 (6). HRMS (ESI, [M+H]$^+$): calcd for $C_{14}H_{15}O_2N_2$: 243.1128; found: 243.11264.

*4.8.12. 1,5-Dimethyl-8-thiophen-2-yl-5,6-dihydro-1H-pyrrolo[3,2-c]azepin-4-one (**4l**).* Brown powder, 29%. ^1H NMR (500.13 MHz; $CDCl_3$): δ=7.26 (dd, J=5.0, 1.0 Hz, 1H); 7.01 (dd, J=5.0, 3.5 Hz, 1H); 6.86 (dd, J=3.5, 1.0 Hz, 1H); 6.75 (d, J=2.8 Hz, 1H); 6.66 (d, J=2.8 Hz, 1H); 6.23 (t, J=7.3 Hz, 1H); 3.70 (d, J=7.3 Hz, 1H, CH_2); 3.25 (s, 3H, $OCNCH_3$); 3.17 (s, 3H, NCH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ=165.9 (CO); 141.7 (CS); 131.2 (C); 130.7 (C); 127.6 (CH); 126.3 (CH); 125.5 (CH); 125.2 (CH); 124.4 (CH); 123.5 (C); 109.9 (CH); 47.4 (NCH_2); 36.3 (NCH_3); 35.4 ($OCNCH_3$). FT-IR (ATR, cm^{-1}): 3430, 3100, 3068, 2923, 1710, 1608, 1495, 1391, 1239, 1067, 833, 809, 728, 695. GC–MS (EI, 70 eV): m/z (%): 258 (100) [M^+], 243 (7), 229 (28), 216 (28), 202 (28), 186 (10), 173 (7), 161 (4), 147 (5), 133 (3), 115 (5), 97 (3), 77 (3),

63 (3), 42 (10). HRMS (ESI, $[M+H]^+$): calcd for $C_{14}H_{15}ON_2S$: 259.08996; found: 259.08993.

*4.8.13. 1-Methyl-8-p-tolyl-5,6-dihydro-1H-pyrrolo[3,2-c]azepin-4-one (**4o**).* Beige powder, 40%. ^{1}H NMR (300.13 MHz; $CDCl_3$): δ=7.12 (m, 4H); 6.77 (d, J=2.9 Hz, 1H); 6.66 (d, J=2.9 Hz, 1H); 6.34 (t, $J_{NH,CH}$=5.5 Hz, 1H); 6.06 (t, J=7.4 Hz, 1H); 3.59 (dd, J=7.4, 5.5 Hz, 2H, CH_2); 3.09 (s, 3H, NCH_3); 2.36 (s, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=164.1 (CO); 137.9 (C); 137.6 (C); 136.9 (C); 131.0 (C); 129.5 (2CH); 127.4 (2CH); 125.3 (CH); 124.9 (C); 124.9 (CH); 109.5 (CH); 38.8 (CH_2); 36.6 (NCH_3); 21.2 (CH_3). FT-IR (ATR, cm^{-1}): 3246, 3160, 3108, 3023, 2949, 2917, 1631, 1496, 1460, 1439, 1274, 1198, 1087, 928, 816, 733, 519. GC–MS (EI, 70 eV): m/z (%): 252 (100) [M^+], 237 (28), 224 (23), 209 (28), 194 (9), 180 (8), 161 (10), 152 (7), 133 (5), 115 (4), 104 (3), 91 (2), 77 (2), 63 (2), 51 (1), 42 (2). HRMS (ESI, $[M+H]^+$): calcd for $C_{16}H_{17}ON_2$: 253.13354; found: 253.13348.

*4.8.14. 5-Methyl-8-p-tolyl-5,6-dihydro-1H-pyrrolo[3,2-c]azepin-4-one (**4p**).* Brown powder, 35%.^{1}H NMR (500.13 MHz; $CDCl_3$): δ=8.17 (br, 1H, NH); 7.21 (m, 4H); 6.85 ('t', $J_{CH,CH}$=$J_{NH,CH}$=2.8 Hz, 1H); 6.79 ('t', $J_{CH,CH}$=$J_{NH,CH}$=2.8 Hz, 1H); 6.07 (t, J=7.1 Hz, 1H); 3.79 (d, J=7.1 Hz, 2H, CH_2); 3.17 (s, 3H, $OCNCH_3$); 2.38 (s, 3H, CH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ=166.0 (CO); 138.6 (C); 138.2 (C); 135.4 (C); 131.2 (C); 129.6 (2CH); 128.4 (2C H); 122.2 (C); 121.6 (CH); 118.6 (CH); 111.6 (CH); 47.6 (CH_2); 35.5 (NCH_3); 21.2 (CH_3). FT-IR (ATR, cm^{-1}): 3260, 3198, 3046, 3022, 2960, 2921, 2853, 1598, 1491, 1391, 1259, 1081, 1021, 876, 798, 746, 693, 606, 513. GC–MS (EI, 70 eV): m/z (%): 252 (100) [M^+], 237 (10), 223 (34), 210 (27), 196 (15), 180 (9), 167 (11), 161 (8), 152 (7), 139 (4), 115 (4), 96 (3), 77 (2), 63 (2), 51 (1), 42 (4). HRMS (ESI, $[M+H]^+$): calcd for $C_{16}H_{17}ON_2$: 253.13354; found: 253.13353.

*4.8.15. 1-Methyl-4-oxo-8-p-tolyl-4,6-dihydro-1H-pyrrolo[3,2-c]azepine-5-carboxylic acid tert-butyl ester (**4q**).* Brown solid, 10%. ^{1}H NMR (500.13 MHz; $CDCl_3$): δ=7.16 (m, 4H); 6.84 (d, J=2.9 Hz, 1H); 6.63 (d, J=2.9 Hz, 1H); 6.30 (t, J=7.4 Hz, 1H); 4.73, 3.72 (2br s, 2H, CH_2); 3.08 (s, 3H, NCH_3); 2.37 (s, 3H, CH_3); 1.52 (s, 9H, 3 CH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ=164.9 (CO); 152.2 (CO); 138.2 (C); 137.9 (C); 136.5 (C); 132.2 (C); 129.5 (2CH); 127.4 (2CH); 126.7 (CH); 125.0 (CH); 123.1 (C); 111.3 (CH); 82.6 (C); 42.8 (CH_2); 36.9 (NCH_3); 28.1 ($3CH_3$); 21.2 (CH_3). FT-IR (ATR, cm^{-1}): 3138, 3115, 3057, 3033, 2962, 2921, 2851, 1707, 1666, 1329, 1259, 1239, 1152, 1076, 1019, 790, 743, 702. HRMS (ESI, $[M+H]^+$): calcd for $C_{21}H_{25}O_3N_2$: 353.18597; found: 353.18596.

*4.8.16. 5-Benzyl-1-methyl-8-p-tolyl-5,6-dihydro-1H-pyrrolo[3,2-c]azepin-4-one (**4r**).* Brown powder, 68%. ^{1}H NMR (300.13 MHz; $CDCl_3$): δ=7.27 (m, 5H); 7.12 (m, 4H); 6.82 (d, J=2.9 Hz, 1H); 6.65 (d, J=2.9 Hz, 1H); 6.0 (t, J=7.4 Hz, 1H); 4.79 (s, 2H, CH_2); 3.66 (d, J=7.4 Hz, 2H, CH_2); 3.08 (s, 3H, NCH_3); 2.36 (s, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=166.1 (CO); 138.4 (C); 137.9 (C); 137.7 (C); 136.7 (C); 131.7 (C); 129.4 (2C H); 128.5 (2CH); 128.0 (2CH); 127.5 (2CH); 127.2 (CH); 124.7 (CH); 124.5 (CH); 123.2 (C); 110.0 (CH); 50.6 (CH_2); 45.0 (CH_2); 36.6 (NCH_3); 21.2 (CH_3). FT-IR (ATR, cm^{-1}): 3109, 3059, 3027, 2955, 2922, 2855, 1602, 1495, 1452, 1427, 1409, 1244, 1080, 816, 730, 697. GC–MS (EI, 70 eV): m/z (%): 342 (16) [M^+], 251 (20), 238 (100), 224 (23), 209 (11), 194 (8), 181 (5), 165 (3), 152 (6), 129 (3), 115 (3), 91 (15), 77 (3), 63 (4), 42 (3). HRMS (ESI, $[M+H]^+$): calcd for $C_{23}H_{23}ON_2$: 343.18049; found: 343.18066.

*4.8.17. 1,6-Dimethyl-4-(4-methyl-benzyl)-1,6-dihydro-pyrrolo[2,3-c]pyridin-7-one (**5a**).* ^{1}H NMR (500.13 MHz; $CDCl_3$): δ=7.71 (d, J=8.2 Hz, 2H); 7.14 (m, 2H); 6.91 (d, J=2.9 Hz, 1H); 6.59 (s, 1H); 6.14 (d, J=2.9 Hz, 1H); 4.15 (s, 3H, NCH_3); 3.86 (s, 2H, CH_2); 3.55 (s, 3H, $CONCH_3$); 2.33 (s, 3H, CH_3). GC–MS (EI, 70 eV): m/z (%): 366 (100) [M^+], 251 (11), 237 (7), 224 (3), 209 (3), 194 (3), 180 (4), 175 (18), 161 (5), 152 (3), 134 (5), 125 (3), 105 (3), 91 (2), 77 (2), 65 (1), 42 (2). HRMS (ESI, $[M+H]^+$): calcd for $C_{23}H_{23}ON_2$: 267.14919; found: 267.14911.

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