Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 1148

www.rsc.org/obc

PAPER

Platinum-catalyzed cyclization reaction of alkynes: synthesis of azepino[3,4-*b*]indol-1-ones†

Marina Gruit, Anahit Pews-Davtyan and Matthias Beller*

Received 15th September 2010, Accepted 26th October 2010
DOI: 10.1039/c0ob00728e

Novel azepino[3,4-*b*]indol-1-ones were synthesized from alkyne-substituted indole-2-carboxamides by catalytic intramolecular cyclization in the presence of $PtCl_2$. The scope and limitations of this straightforward protocol are reported.

Introduction

Pyrrolo-azepinones represent an interesting structural motif found in a variety of bio-active natural products such as hymenialdisine, stevensine, latonduine, and the paullones. In the last decade synthetic hymenialdisine derivatives have emerged as promising therapeutic molecules for the treatment of a range of diseases, including cancer.[1–4] For example, hymenialdisine derivative **B** and paullone derivatives **C** (Fig. 1) have been found to inhibit selectively different kinases and cytokines.[2,3] Recently, structurally related indolobenzazepin-7-ones **D** also showed cytotoxic and anti-tumor properties as inhibitors of tubulin polymerization.[4]

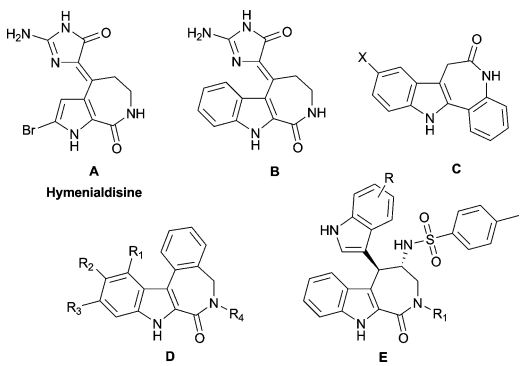
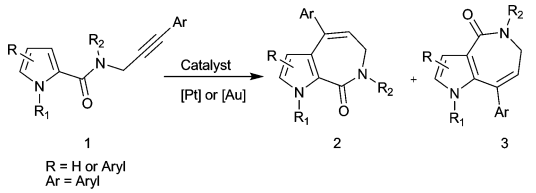


Fig. 1 Hymenialdisine and indoloazepinone derivatives.

Due to their biological properties, the synthesis of indoloazepinones has attracted significant interest in recent years.[5,6] For some time our laboratory has also been involved in the development of novel catalytic methods for the synthesis of potential bio-active hymenialdisine derivatives, *e.g.* **E** (Fig. 1)[7] and indoles.[8] Among the different catalytic methods especially transition-metal-catalyzed cyclizations of aromatic and heteroaromatic compounds with alkynes, in particular, intramolecular gold- or platinum-catalyzed cycloisomerization and hydroarylation,[6,9–11] offer a straightforward preparation of this class of compounds. As an example, recently we reported that the intramolecular cyclization of pyrrole-2-carboxamide alkyne **1** catalyzed by Pt^{II}, Pt^{IV} or Au^{III} complexes gave two pyrroloazepinones **2** and **3** (Scheme 1).[12] In the presence of either $H_2PtCl_6 \cdot H_2O$ at 120 °C or $AuCl_3$ at room temperature new pyrrolo[3,2-*c*]azepin-4-ones **3** were mainly formed in up to 76% yield. Due to the efficiency of this straightforward synthesis we decided to extend this methodology to the preparation of indoloazepinones (R = aryl, Scheme 1). Here, we report for the first time our results in this area.



Scheme 1 Strategy for the synthesis of pyrrolo and indoloazepinones from 2-propargylamide-substituted pyrroles or indoles.

Results and discussion

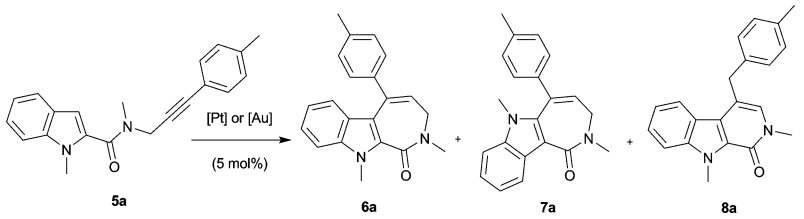
At the start of our investigations, we studied the influence of different solvents and temperatures on platinum- and gold-catalyzed cyclization of the model reaction using 1-methyl-1*H*-indole-2-carboxylic acid methyl-(3-*p*-tolyl-prop-2-ynyl)-amide (**5a**) (Table 1). Compound **5a** was easily formed in two steps from commercially available 1-methylindole-2-carboxylic acid. Amidation with *N*-methylpropargylamine in the presence of 4-(dimethylamino)pyridine (DMAP) and 1,1′-carbonyldiimidazole (CDI) at 40 °C in tetrahydrofuran (THF) gave 1-methyl-1*H*-indole-2-carboxylic acid methyl-prop-2-ynyl-amide (**4a**) in 98% yield. Subsequent Sonogashira reaction (2 mol% $PdCl_2(PPh_3)_2$, 4 mol% CuI, 20 h at 60 °C in triethylamine/THF) using 4-iodotoluene led to **5a** in 62% overall yield.

Among the tested catalysts $H_2PtCl_6 \cdot 6H_2O$, K_2PtCl_6, $PtCl_2$, $AuCl_3$ and AuCl all led to 2,10-dimethyl-5-*p*-tolyl-3,10-dihydro-2*H*-azepino[3,4-*b*]indol-1-one (**6a**) as the main product (Table 1).

Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Albert-Einstein-Str. 29a, D-18059 Rostock, Germany. E-mail: matthias.beller@catalysis.de; Fax: +49 381 1281 51113; Tel: +49 381 1281 113

† Electronic supplementary information (ESI) available: Scans of NMR spectra are available. See DOI: 10.1039/c0ob00728e

Table 1 Catalyst (Pt or Au-salts) and solvent screening reaction for indole synthesis[a]



Entry	Catalyst	Solvent	*T*/°C	Conv[b] [%]	**6a** Yield[b] [%]	**7a** Yield[c] [%]	**8a** Yield[c] [%]
1	$H_2PtCl_6{\cdot}6H_2O$	Toluene	120	100	42	19	4
2	$H_2PtCl_6{\cdot}6H_2O$	Dioxane	60	99	58	< 1	2
3	$H_2PtCl_6{\cdot}6H_2O$	DCM	*RT*	100	97	1	2
4	K_2PtCl_6	Toluene	120	63	30	15	0
5	K_2PtCl_6	Dioxane	60	25	2	< 1	1
6	K_2PtCl_6	DCM	*RT*	0	0	0	0
7	$PtCl_2$	Toluene	140	100	39	27	7
8	$PtCl_2$	Toluene	120	100	35	18	3
9	$PtCl_2$	Dioxane	60	100	80	13	7
10	$PtCl_2$	DCM	*RT*	100	98	1	1
11	$AuCl_3$	Toluene	120	66	24	9	5
12	$AuCl_3$	Dioxane	60	100	93	5	2
13	$AuCl_3$	DCM	*RT*	100	96	1	3
14	AuCl	Toluene	120	97	52	13	6
15	AuCl	Dioxane	60	18	6	0	3
16	AuCl	DCM	*RT*	84	82	1	1
17	$AuCl(PPh_3)$	Toluene	120	12	1	0	0

[a] Reaction conditions: 5 mol% catalyst, 0.2 mmol compound **5a**, 10 mL solvent, 20 h. [b] Determined by GC with hexadecane as internal standard. [c] Ratio determined by ^{1}H NMR.

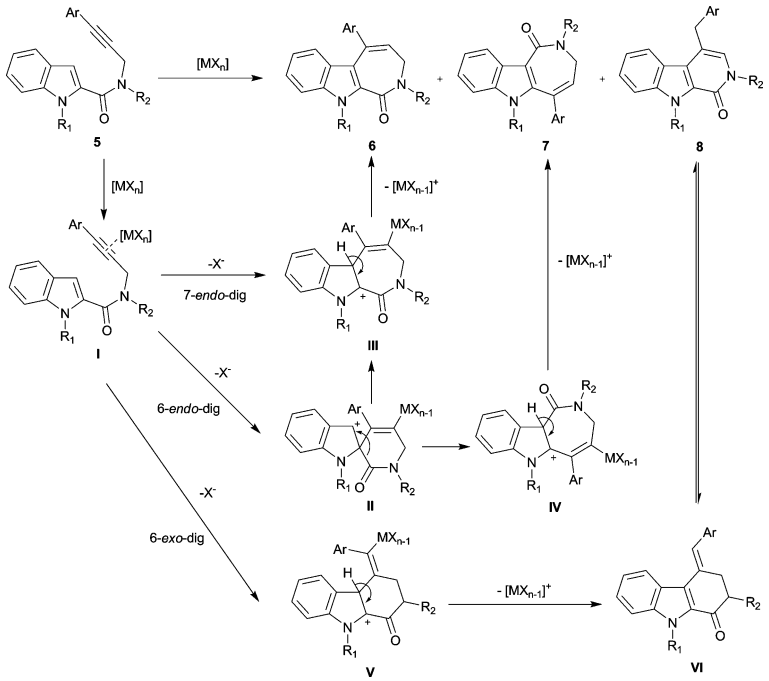
High activity and full conversion are observed in the presence of $H_2PtCl_6{\cdot}6H_2O$, $PtCl_2$ and $AuCl_3$ as catalyst in dichloromethane at room temperature (Table 1, entries 3, 10 and 13). Under these mild conditions the product **6a** is formed in 96–98% yield. On the other hand K_2PtCl_6, AuCl or $AuCl(PPh_3)$ showed no or low activity for the cyclization process (Table 1, entries 5, 6, 15 and 17). As shown in Table 1, in most cases only a small amount of the two other isomers 2,6-dimethyl-5-*p*-tolyl-3,6-dihydro-2*H*-azepino[4,3-*b*]indol-1-one (**7a**) and 2,9-dimethyl-4-(4-methyl-benzyl)-2,9-dihydro-β-carbolin-1-one (**8a**) was observed. It appears that the ratio of **6a** and **7a** depends strongly upon the temperature and solvent. Indeed, we observed that using harsh (Table 1, entries 1, 4, 7, 8 and 14) reaction conditions (120 or 140 °C) promoted the formation of **7a**

Based on previous investigations of related cyclizations,[6,10,11,13] we propose the following mechanism of this Au- or Pt-catalyzed cycloisomerization reaction (Scheme 2). Treatment of the indole-substituted alkyne **5** with a Au^{III}, Pt^{II} or Pt^{IV} catalyst results in an initial activation of the triple bond by the electrophilic metal species (**I**). Then, in principle three modes of cycloisomerization reactions are possible depending on the reaction conditions (Table 1 and Scheme 2). Seven-membered-ring compounds **6** and **7** can be formed by a 7-*endo*-dig cyclization which might require a 6-*endo*-dig process to form the spiro-intermediate **II**, already described in the literature.[6,10] On the other hand, the initial activation of the triple bond (**I**) can also give the cation **V** which might be involved in the formation of β-carbolines **8** by a 6-*exo*-dig cyclization.[11]

On the basis of the catalyst optimization, we choose $PtCl_2$ as catalyst in dichloromethane (Table 1, entry 10) for further studies of the scope and limitations of the cyclization with different arylated substrates (Table 2).

Hence, the Sonogashira coupling of various substituted aryl or heteroaryl iodides and bromides with 1-methyl-1*H*-indole-2-carboxylic acid methyl-prop-2-ynyl-amide (**4a**) was performed to give indole-substituted alkynes **5a–m** in up to 94% isolated yield. Apart from the *N*-methylated derivatives the *N*-benzyl-protected alkyne (**5o**) was also obtained by Sonogashira reaction between *N*-benzylpropargylamine and 4-iodotoluene followed by amidation of benzyl-(3-*p*-tolyl-prop-2-ynyl)-amine with indole-2-carboxylic acid.

As shown in Table 2, the cyclization reaction of compounds **5a–o** in the presence of 5 mol% of $PtCl_2$ in dichloromethane at 50 °C formed three different products **6**, **7** or **8**. Contrary to the model reaction, the reaction temperature needed to be increased to obtain full conversion. In most cases the cycloisomerization formed 4-substituted azepino[3,4-*b*]indol-1-ones **6a–e**, **g**, **i–k**, **m**, **o** as the main products in up to 80% isolated yield (Table 2, entries 1–5, 7, 9–11, 13 and 15). Notably, we observed that the formation of the isomeric 4-substituted β-carbolin-2-one **8** depended on the aryl moieties. More specifically, the presence of an acceptor group on the arylated substrate gave 6-membered-ring products **8d–h** by a 6-*exo*-dig process (Table 2, entries 4–8). Furthermore, it is interesting to note that cyclization of the initial indole alkyne **4a** gave product **8n** in 95% isolated yield.[11] This result clearly showed the importance of the aryl substituent in the cycloisomerization mechanism. We also observed the formation of azepino[4,3-*b*]-indol-1-one isomers **7m** and **7o** when the arylated substrate owned a donor and an acceptor group (Table 2, entry 13). Similar results were obtained in the case of an *N*-benzyl



Scheme 2 General synthesis of azepino[3,4-*b*]indol-1-one **6**, azepino[4,3-*b*]indol-1-one **7** and β-carbolin-2-one **8** derivatives.

protecting group instead of the *N*-methyl substituent (Table 2, entry 15).

Conclusion

In summary, we have prepared a variety of novel azepin[3,4-*b*]indol-1-ones **6** in a straightforward manner. The key step is the platinum-catalyzed 7-*endo*-dig cyclization process which proceeds in good isolated yields under optimized conditions. Contrary to our previous work with pyrrole-substituted alkynes, in general no rearrangement of the amide substituent took place. Nevertheless, the formation of the three different cyclization products **6**, **7** and **8** strongly depends on the catalyst, solvent, temperature, *N*-protecting group and aryl substituents.

Experimental

General information

All reactions were carried out under an argon atmosphere. Chemicals were purchased from Aldrich, Fluka and Acros and unless otherwise noted were used without further purification. All compounds were characterized by ^{1}H NMR, ^{13}C NMR, GC-MS, HRMS and IR spectroscopy. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AV 300 and AV 400 spectrometers with chloroform solutions of the compounds at a temperature of 300 K. The ^{1}H and ^{13}C NMR chemical shifts are reported relative to the chloroform resonances (δ (^{1}H) = 7.26, δ (^{13}C) = 77.0). Due to dynamic effects (restricted rotation in the amide moiety) some signals of compounds **5** 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.

The analyses of compounds **4a** and **8n** have been already described in earlier publication.[11]

General procedure for the synthesis of 1-methyl-1*H*-indole-2-carboxylic acid methyl-prop-2-ynyl-amide (4a)

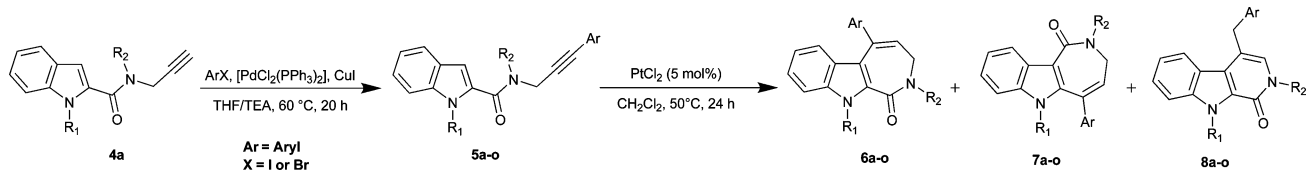
1-Methylindole-2-carboxylic acid (1.5 g, 8.56 mmol, 1 equiv), 4-dimethylaminopyridine (DMAP, 0.105 g, 0.86 mmol) and 1,1′-carbonyldiimidazole (CDI, 1.39 g, 8.56 mmol, 1 equiv) were introduced into 30 mL of tetrahydrofuran (THF). The solution was stirred 90 min at room temperature and *N*-methylpropargylamine (0.87 mL, 10.28 mmol, 1.2 equiv) was then added. The brown mixture was stirred overnight at 40 °C. After removal of the solvent *in vacuo*, the residue was purified by column chromatography (R_f 0.51, solvent heptane–ethyl acetate 1 : 1) to give indole **4a** as a light yellow powder (1.89 g, 98%).

^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.66 (d, J = 8.0 Hz, 1H), 7.35 (m, 1H), 7.32 (ddd, J = 8.3 Hz, J = 6.7 Hz, J = 1.2 Hz, 1H), 7.16 (ddd, J = 8.0 Hz, J = 6.7 Hz, J = 1.3 Hz, 1H), 6.82 (br, 1H), 4.38 (s, 2H, CH_2), 3.86 (s, 3H, NCH_3), 3.25 (s, 3H, $OCNCH_3$), 2.38 (br, 1H, CH≡); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 164.0 (CO), 138.0 (C), 130.9 (C), 126.2 (C), 123.5 (CH), 121.7 (CH), 120.3 (CH), 109.8 (CH), 104.3 (CH), 78.4 (≡CH), 31.2 (NCH_3), not displayed: NCH_2, $OCNCH_3$, C≡CH.

General procedure for Sonogashira reactions

[$PdCl_2(PPh_3)_2$] (16 mg, 0.022 mmol, 2 mol%) and CuI (8.5 mg, 0.044 mmol, 4 mol%) were placed in an ACE pressure tube under

Table 2 Sonogashira and cyclization reactions with various arylated substrates[a]



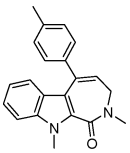
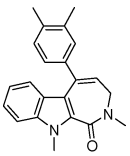
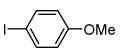
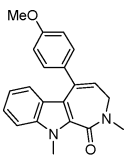
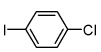
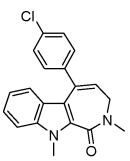
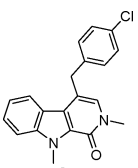
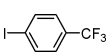
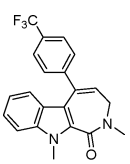
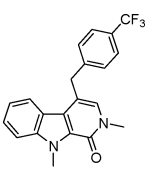
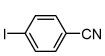
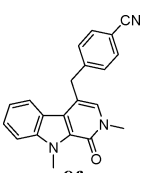
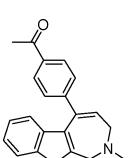
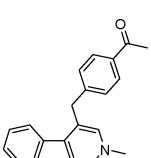
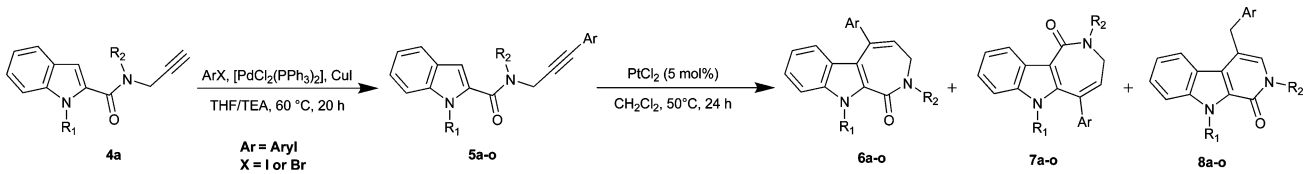
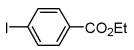
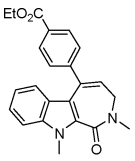
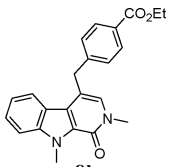
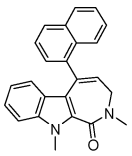
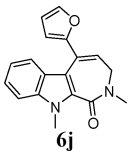
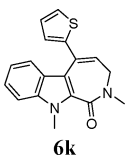
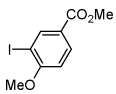
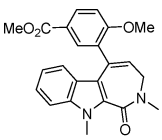
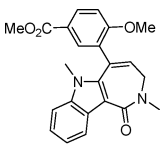
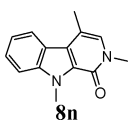
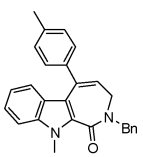
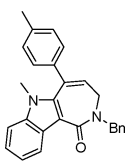
Entry	R_1, R_2	Ar-X	**5** [%][b]	Product **6**	**6** [%][b]	Product/s **7** and/or **8**	**7** and/or **8** [%][b]
1	CH_3,CH_3		**5a**: 62	 **6a**	76	**7a** + **8a**	< 5
2	CH_3,CH_3		**5b**: 60	 **6b**	68	**7b**	< 5
3	CH_3,CH_3		**5c**: 31	 **6c**	78	**8c**	< 5
4	CH_3,CH_3		**5d**: 82	 **6d**	61	 **8d**	12
5	CH_3,CH_3		**5e**: 77	 **6e**	45	 **8e**	29
6	CH_3,CH_3		**5f**: 66	**6f**	< 5	 **8f**	20
7	CH_3,CH_3		**5g**: 85	 **6g**	21	 **8g**	14

Table 2 *(Contd.)*



Entry	R_1, R_2	Ar-X	**5** [%][b]	Product **6**	**6** [%][b]	Product/s **7** and/or **8**	**7** and/or **8** [%][b]
8	CH_3,CH_3		**5h**: 88	 **6h**	25[d]	 **8h**	25[d]
9	CH_3,CH_3		**5i**: 67	 **6i**	80	**8i**	< 5
10	CH_3,CH_3		**5j**: 39	 **6j**	65	**8j**	< 5
11	CH_3,CH_3		**5k**: 65	 **6k**	45	**7k** + **8k**	< 5
12	CH_3,CH_3		**5l**: 94	**6l**	0	**8l**	0
13	CH_3,CH_3		**5m**: 73	 **6m**	60	 **7m**	23
14	CH_3,CH_3	—	—	**6n**	0	 **8n**	95[11]
15	CH_3,Bn		**5o**: 78[c]	 **6o**	77[d]	 **7o**	17[d]

[a] Sonogashira conditions: 2 mol% $[PdCl_2(PPh_3)_2]$, 4 mol% CuI, 1.15 mmol compound **4a**, 1.27 mmol aryl halide, 8 mL THF/TEA (1 : 1), 60 °C, 20 h. Cyclization conditions: 5 mol% $PtCl_2$, 0.2 mmol compound **5**, 10 mL CH_2Cl_2, 50 °C, 24 h. [b] Yield of isolated product. [c] Yield of isolated product after amide formation. [d] Yield determined by ^1H NMR.

an argon atmosphere. The *N*,*N*′-dimethyl-*N*-(prop-2-ynyl)-1*H*-indole-2-carboxamide **4a** (250 mg, 1.10 mmol, 1 equiv) and the aryl halogenide (1.22 mmol, 1.1 equiv) were added and a solution of THF/TEA (1 : 1, 7 mL) was then injected. The pressure tube was sealed and the reaction mixture was heated at 65 °C for 20 h. After removal of the solvent *in vacuo*, the residue was purified by column chromatography (dichloromethane–ethyl acetate or heptane–ethyl acetate) to give indoles **5a–m**.

1-Methyl-1*H*-indole-2-carboxylic acid methyl-(3-*p*-tolyl-prop-2-ynyl)-amide (5a)

Yield: 216 mg, 62%; white powder; purification conditions: CH_2Cl_2–ethyl acetate (90 : 10); ^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.67 (d, J = 7.9 Hz, 1H), 7.35 (m, 4H), 7.17 (m, 3H), 6.88 (br, 1H), 4.59 (s, 2H, CH_2), 3.89 (s, 3H, NCH_3), 3.31 (s, 3H, $OCNCH_3$), 2.38 (s, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 164.1 (CO), 138.8 (C), 138.0 (C), 131.6 (2 CH), 131.3 (C), 129.1 (2 CH), 126.3 (C), 123.5 (CH), 121.7 (CH), 120.2 (CH), 109.8 (CH), 104.2 (C), 83.0 (*C*≡C), 31.2 (NCH_3), 21.5 (CH_3), not displayed: NCH_2, $OCNCH_3$, *C*≡C; FT-IR (ATR, cm^{-1}): 3051, 3024, 2915, 2850, 1609, 1525, 1509, 1465, 1396, 1357, 1231, 1145, 1056, 819, 811, 732, 529; GC-MS (EI, 70 eV): *m*/*z* (%): 316 (13) [M$^+$], 301 (4), 288 (9), 272 (11), 259 (100), 244 (23), 225 (6), 211 (6), 197 (3), 183 (1), 158 (24), 131 (25), 115 (6), 102 (4), 89 (38), 77 (5), 63 (4), 42 (4); HRMS (EI): calcd for $C_{21}H_{20}ON_2$: 316.15701; found: 316.15673.

1-Methyl-1*H*-indole-2-carboxylic acid [3-(3,4-dimethyl-phenyl)-prop-2-ynyl]-methyl-amide (5b)

Yield: 218 mg, 60%; light yellow powder; purification conditions: CH_2Cl_2–ethyl acetate (80 : 20); ^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.65 (d, J = 8.0 Hz, 1H), 7.38 (dd, J = 8.3 Hz, J = 0.8 Hz, 1H), 7.35–7.19 (m, 3H), 7.15 (ddd, J = 8.0 Hz, J = 6.8 Hz, J = 1.2 Hz, 1H), 7.10 (d, J = 7.8 Hz, 1H), 6.88 (br, 1H), 4.58 (s, 2H, CH_2), 3.88 (s, 3H, NCH_3), 3.29 (s, 3H, $OCNCH_3$), 2.28 (s, 3H, CH_3), 2.26 (s, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 164.1 (CO), 138.0 (C), 137.6 (C), 136.7 (C), 132.8 (CH), 131.3 (C), 129.6 (CH), 129.2 (CH), 126.3 (CH), 123.5 (CH), 121.7 (CH), 120.2 (CH), 119.6 (C), 109.8 (CH), 104.2 (C), 82.7 (*C*≡C), 31.2 (NCH_3), 19.7 (CH_3), 19.6 (CH_3), not displayed: NCH_2, $OCNCH_3$, *C*≡C; FT-IR (ATR, cm^{-1}): 3118, 3045, 2917, 2861, 1623, 1518, 1461, 1398, 1340, 1285, 1155, 1063, 803, 732; GC-MS (EI, 70 eV): *m*/*z* (%): 330 (12) [M$^+$], 301 (9), 286 (12), 273 (100), 258 (27), 244 (5), 225 (7), 211 (5), 158 (21), 143 (11), 131 (22), 121 (3), 115 (7), 89 (31), 77 (4), 63 (2), 44 (5), 32 (4); HRMS (ESI, [M+H]$^+$): calcd for $C_{22}H_{23}ON_2$: 331.1805; found: 331.1806.

1-Methyl-1*H*-indole-2-carboxylic acid [3-(4-methoxy-phenyl)-prop-2-ynyl]-methyl-amide (5c)

Yield: 114 mg, 31%; light yellow powder; ^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.65 (d, J = 7.8 Hz, 1H), 7.41 (d, J = 8.8 Hz, 2H), 7.34 (m, 2H), 7.16 (ddd, J = 8.0 Hz, J = 6.8 Hz, J = 1.2 Hz, 1H), 6.87 (br d, J = 8.8 Hz, 3H), 4.58 (br, 2H, CH_2), 3.88 (s, 3H, OCH_3), 3.81 (s, 3H, NCH_3), 3.29 (s, 3H, $OCNCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 164.1 (CO), 159.8 (CO), 138.0 (C), 133.2 (2 CH), 132.1 (C), 131.3 (C), 126.3 (CH), 123.5 (CH), 121.7 (CH), 120.8 (C), 120.2 (CH), 114.0 (2 CH), 109.8 (CH), 104.3 (C), 82.3 (*C*≡C), 55.3 (OCH_3), 31.2 (NCH_3), not displayed: NCH_2, $OCNCH_3$, *C*≡C; FT-IR (ATR, cm^{-1}): 3118, 3055, 3015, 2934, 1729, 1621, 1521, 1507, 1458, 1396, 1281, 1172, 1062, 1028, 833, 733, 664; GC-MS (EI, 70 eV): *m*/*z* (%): 332 (14) [M$^+$], 303 (13), 288 (9), 275 (100), 260 (13), 246 (7), 225 (8), 197 (4), 158 (24), 145 (11), 131 (24), 114 (4), 102 (9), 89 (34), 77 (4), 63 (3), 42 (4); HRMS (EI): calcd for $C_{21}H_{20}O_2N_2$: 332.15193; found: 332.15262.

1-Methyl-1*H*-indole-2-carboxylic acid [3-(4-chloro-phenyl)-prop-2-ynyl]-methyl-amide (5d)

Yield: 304 mg, 82%; light yellow powder; purification conditions: CH_2Cl_2–ethyl acetate (80 : 20); ^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.67 (d, J = 7.7 Hz, 1H), 7.36 (m, 6H), 7.17 (ddd, J = 8.0 Hz, J = 6.8 Hz, J = 1.2 Hz, 1H), 6.85 (br, 1H), 4.60 (s, 2H, CH_2), 3.89 (s, 3H, NCH_3), 3.31 (s, 3H, $OCNCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 164.0 (CO), 138.0 (C), 134.6 (C), 133.0 (2 CH), 131.0 (C), 128.7 (2 CH), 126.2 (CH), 123.5 (CH), 121.6 (CH), 120.2 (CH), 109.8 (CH), 104.3 (C), 84.8 (*C*≡C), 31.2 (NCH_3), not displayed: NCH_2, $OCNCH_3$, *C*≡C; FT-IR (ATR, cm^{-1}): 3053, 2920, 1629, 1520, 1487, 1464, 1397, 1345, 1229, 1089, 1059, 827, 751, 738, 3104, 2930, 1701, 1618, 1532, 1487, 1390, 1243, 1089, 1069, 1013, 827, 729, 607; GC-MS (EI, 70 eV): *m*/*z* (%): 336 (10) [M$^+$], 308 (16), 292 (10), 279 (100), 265 (21), 243 (13), 225 (6), 197 (8), 168 (3), 158 (40), 149 (8), 131 (35), 122 (8), 114 (8), 101 (4), 89 (52), 77 (6), 63 (3), 42 (5); HRMS (ESI, [M+H]$^+$): calcd for $C_{20}H_{18}ON_2Cl$: 337.1102; found: 337.1101.

1-Methyl-1*H*-indole-2-carboxylic acid methyl-[3-(4-trifluoromethyl-phenyl)-prop-2-ynyl]-amide (5e)

Yield: 314 mg, 77%; yellow syrup; purification conditions: heptane–ethyl acetate (80 : 20); ^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.65 (dt, J = 8.0 Hz, J = 0.9 Hz, 1H), 7.59 (dd, J = 8.7 Hz, J = 4.8 Hz, 4H), 7.38 (dd, J = 8.4 Hz, J = 0.9 Hz, 1H), 7.32 (m, 1H), 7.16 (ddd, J = 8.0 Hz, J = 6.8 Hz, J = 1.2 Hz, 1H), 6.82 (br, 1H), 4.63 (s, 2H, CH_2), 3.88 (s, 3H, NCH_3), 3.31 (s, 3H, $OCNCH_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 164.1 (CO), 138.1 (C), 132.0 (2 CH), 131.0 (C), 130.1 (C), 126.3 (CH), 125.6 (C), 125.4 (CH), 125.3 (CH), 123.6 (CH), 122.0 (C), 121.7 (CH), 120.3 (CH), 109.9 (CH), 104.5 (C), 86.4 (*C*≡C), 31.3 (NCH_3), not displayed: NCH_2, $OCNCH_3$, *C*≡C; FT-IR (ATR, cm^{-1}): 3056, 2931, 1630, 1615, 1521, 1465, 1399, 1319, 1164, 1120, 1104, 1063, 1016, 841, 751, 735; GC-MS (EI, 70 eV): *m*/*z* (%): 370 (14) [M$^+$], 342 (20), 326 (9), 313 (100), 299 (21), 244 (2), 225 (4), 211 (6), 183 (6), 158 (26), 131 (6), 133 (24), 116 (4), 89 (35), 77 (3), 63 (3), 42 (3); HRMS (EI): calcd for $C_{21}H_{17}ON_2F_3$: 370.12875; found: 370.12877.

1-Methyl-1*H*-indole-2-carboxylic acid [3-(4-cyano-phenyl)-prop-2-ynyl]-methyl-amide (5f)

Yield: 238 mg, 66%; yellow syrup; purification conditions: heptane–ethyl acetate (60 : 40); ^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.64 (m, 3H), 7.55 (m, 2H), 7.34 (m, 2H), 7.16 (ddd, J = 8.0 Hz, J = 6.8 Hz, J = 1.2 Hz, 1H), 6.81 (br, 1H), 4.64 (s, 2H, CH_2), 3.88 (s, 3H, NCH_3), 3.31 (s, 3H, $OCNCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 164.1 (CO), 138.1 (C), 132.3 (2 CH), 132.1 (2 CH), 130.8 (C), 128.8 (C), 127.2 (C), 126.2 (CH), 123.7 (CH), 121.7 (CH), 120.4 (CH), 118.3 (C), 112.0 (C), 109.9 (CH), 88.4 (*C*≡C), 31.3 (NCH_3), not displayed: NCH_2, $OCNCH_3$, *C*≡C; FT-IR (ATR, cm^{-1}): 3054, 2927, 2226, 1717, 1627, 1603, 1520, 1464, 1396, 1344, 1228, 1058,

838, 750, 735, 555; GC-MS (EI, 70 eV): *m/z* (%): 327 (15) [M^+], 299 (23), 283 (9), 270 (100), 256 (22), 242 (3), 225 (5), 211 (8), 168 (4), 158 (32), 140 (7), 131 (26), 116 (5), 89 (46), 77 (4), 63 (5), 42 (3); HRMS (ESI, [M+Na]$^+$): calcd for $C_{21}H_{17}ON_3Na$: 350.1264; found: 350.1266.

1-Methyl-1*H*-indole-2-carboxylic acid [3-(4-acetyl-phenyl)-prop-2-ynyl]-methyl-amide (5g)

Yield: 322 mg, 85%; yellow syrup; purification conditions: heptane–ethyl acetate (70 : 30); ^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.93 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 7.9 Hz, 1H), 6.55 (d, J = 8.4 Hz, 2H), 7.38 (m, 1H), 7.32 (m, 1H), 7.16 (ddd, J = 8.0 Hz, J = 6.9 Hz, J = 1.2 Hz, 1H), 6.84 (br, 1H), 4.64 (s, 2H, CH_2), 3.88 (s, 3H, NCH_3), 3.32 (s, 3H, $OCNCH_3$), 2.61 (s, 3H, CH_3CO); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 197.3 (CO), 164.1 (CO), 138.1 (C), 136.4 (C), 131.9 (2 CH), 131.0 (C), 128.3 (2 CH), 126.2 (CH), 123.6 (CH), 121.7 (CH), 120.3 (CH), 119.0 (C), 109.9 (CH), 104.5 (C), 87.2 (*C*≡C), 31.3 (NCH_3), 26.6 (*C*H_3CO), not displayed: NCH_2, OCN*C*H_3, *C*≡C; FT-IR (ATR, cm^{-1}): 3109, 3092, 3080, 2936, 1677, 1633, 1600, 1524, 1463, 1397, 1345, 1262, 1240, 1229, 954, 839, 755, 588; GC-MS (EI, 70 eV): *m/z* (%): 344 (16) [M^+], 316 (14), 300 (8), 287 (100), 273 (14), 244 (13), 230 (6), 211 (6), 158 (25), 143 (5), 131 (26), 114 (8), 89 (37), 77 (3), 63 (4), 43 (3); HRMS (ESI, [M+H]$^+$): calcd for $C_{22}H_{21}O_2N_2$: 345.1598; found: 345.1603.

4-{3-[Methyl-(1-methyl-1*H*-indole-2-carbonyl)-amino]-prop-1-ynyl}-benzoic acid ethyl ester (5h)

Yield: 363 mg, 88%; yellow syrup; purification conditions: heptane–ethyl acetate (60 : 40); ^{1}H NMR (300 MHz; $CDCl_3$): δ = 8.02 (d, J = 8.3 Hz, 2H), 7.66 (d, J = 8.0 Hz, 1H), 7.53 (dd, J = 8.3 Hz, J = 1.6 Hz, 2H), 7.34 (m, 2H), 7.16 (ddd, J = 8.0 Hz, J = 6.9 Hz, J = 1.0 Hz, 1H), 6.84 (br, 1H), 4.63 (s, 2H, CH_2), 4.39 (q, J = 7.1 Hz, 2H, OCH_2), 3.88 (s, 3H, NCH_3), 3.32 (s, 3H, $OCNCH_3$), 1.41 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 165.9 (CO), 164.1 (CO), 138.1 (C), 131.7 (2 CH), 131.0 (C), 130.2 (C), 129.5 (2 CH), 126.9 (C), 126.3 (CH), 123.6 (CH), 121.7 (CH), 120.3 (CH), 109.9 (CH), 104.5 (C), 86.7 (*C*≡C), 61.2 (OCH_2), 31.2 (NCH_3), 14.3 (CH_3), not displayed: NCH_2, OCN*C*H_3, *C*≡C; FT-IR (ATR, cm^{-1}): 3107, 3038, 2987, 2966, 2925, 2870, 1707, 1626, 1523, 1464, 1396, 1272, 1154, 1104, 1067, 1018, 851, 766, 737, 693, 524; GC-MS (EI, 70 eV): *m/z* (%): 374 (16) [M^+], 346 (10), 330 (9), 317 (100), 303 (9), 288 (9), 275 (8), 244 (10), 225 (6), 211 (5), 188 (5), 168 (7), 158 (31), 143 (7), 131 (35), 114 (7), 89 (46), 63 (2), 44 (2); HRMS (ESI, [M+Na]$^+$): calcd for $C_{23}H_{22}O_3N_2Na$: 397.1523; found: 397.1526.

1-Methyl-1*H*-indole-2-carboxylic acid methyl-(3-naphthalen-1-yl-prop-2-ynyl)-amide (5i)

Yield: 260 mg, 67%; yellow syrup; purification conditions: heptane–ethyl acetate (70 : 30); ^{1}H NMR (300 MHz; $CDCl_3$): δ = 8.32 (d, J = 8.1 Hz, 1H), 7.88 (m, 2H), 7.69 (m, 2H), 7.57 (m, 2H), 7.41 (m, 3H), 7.17 (ddd, J = 8.0 Hz, J = 6.8 Hz, J = 1.1 Hz, 1H), 6.95 (br, 1H), 4.76 (s, 2H, CH_2), 3.91 (s, 3H, NCH_3), 3.39 (s, 3H, $OCNCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 164.2 (CO), 138.1 (C), 133.3 (C), 133.1 (C), 131.2 (C), 130.8 (CH), 129.1 (CH), 128.4 (CH), 127.8 (C), 126.9 (CH), 126.5 (CH), 126.3 (CH), 125.8 (CH), 125.2 (CH), 123.6 (CH), 121.7 (CH), 120.3 (CH), 109.9 (CH), 104.3 (C), 88.6 (*C*≡C), 31.3 (NCH_3), not displayed: NCH_2, OCN*C*H_3, *C*≡C; FT-IR (ATR, cm^{-1}): 3054, 2921, 1627, 1519, 1463, 1394, 1343, 1228, 1143, 1057, 799, 773, 750, 735, 527; GC-MS (EI, 70 eV): *m/z* (%): 352 (64) [M^+], 323 (24), 308 (23), 295 (100), 281 (35), 267 (4), 252 (5), 225 (7), 211 (8), 194 (4), 178 (9), 165 (33), 158 (44), 154 (13), 147 (7), 139 (11), 131 (40), 116 (6), 89 (60), 77(5), 63 (5), 42 (5); HRMS (ESI, [M+Na]$^+$): calcd for $C_{24}H_{20}ON_2Na$: 375.1468; found: 375.1472.

1-Methyl-1*H*-indole-2-carboxylic acid (3-furan-2-yl-prop-2-ynyl)-methyl-amide (5j)

Yield: 126 mg, 39%; yellow syrup; purification conditions: CH_2Cl_2–ethyl acetate (90 : 10); ^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.65 (d, J = 7.9 Hz, 1H), 7.35 (m, 3H), 7.15 (ddd, J = 8.0 Hz, J = 6.9 Hz, J = 1.0 Hz, 1H), 6.81 (br, 1H), 6.64 (dd, J = 3.4 Hz, J = 0.5 Hz, 1H), 6.41 (dd, J = 3.4 Hz, J = 1.9 Hz, 1H), 4.63 (s, 2H, CH_2), 3.87 (s, 3H, NCH_3), 3.29 (s, 3H, $OCNCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 164.1 (CO), 143.7 (CH), 138.1 (C), 131.0 (C), 126.3 (C), 123.6 (CH), 121.7 (CH), 120.3 (CH), 115.7 (CH), 110.9 (CH), 109.9 (2 CH), 104.4 (C), 88.3 (*C*≡C), 31.2 (NCH_3), not displayed: CH_2, OCN*C*H_3, *C*≡C; FT-IR (ATR, cm^{-1}): 3115, 3055, 2937, 2227, 1733, 1629, 1519, 1464, 1396, 1344, 1240, 1211, 1146, 1058, 736, 592; GC-MS (EI, 70 eV): *m/z* (%): 292 (18) [M^+], 263 (11), 248 (5), 235 (100), 220 (19), 206 (30), 192 (9), 180 (5), 167 (4), 158 (24), 131 (16), 116 (4), 103 (4), 89 (48), 77 (10), 63 (5), 51 (7), 42 (3); HRMS (ESI, [M+H]$^+$): calcd for $C_{18}H_{17}O_2N_2$: 293.1285; found: 293.1286.

1-Methyl-1*H*-indole-2-carboxylic acid methyl-(3-thiophen-2-yl-prop-2-ynyl)-amide (5k)

Yield: 221 mg, 65%; orange syrup; purification conditions: CH_2Cl_2–ethyl acetate (90 : 10); ^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.66 (d, J = 7.9 Hz, 1H), 7.31 (m, 3H), 7.16 (ddd, J = 8.0 Hz, J = 6.9 Hz, J = 1.1 Hz, 1H), 7.00 (dd, J = 5.1 Hz, J = 3.6 Hz, 1H), 6.82 (br, 1H), 4.62 (s, 2H, CH_2), 3.88 (s, 3H, NCH_3), 3.29 (s, 3H, $OCNCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 164.1 (CO), 138.0 (C), 132.5 (CH), 131.1 (C), 127.4 (C), 127.0 (CH), 126.3 (C), 123.5 (2 CH), 121.7 (CH), 120.3 (CH), 109.9 (CH), 87.7 (*C*≡C), 31.2 (NCH_3), not displayed: CH_2, OCN*C*H_3, *C*≡C; FT-IR (ATR, cm^{-1}): 3055, 2926, 2223, 1732, 1627, 1518, 1463, 1396, 1342, 1228, 1189, 1057, 847, 751, 736, 700; GC-MS (EI, 70 eV): *m/z* (%): 308 (22) [M^+], 279 (9), 264 (8), 251 (100), 237 (17), 218 (29), 204 (4), 158 (28), 131 (20), 121 (9), 116 (4), 102 (4), 89 (52), 77 (8), 63 (5), 42 (4); HRMS (ESI, [M+H]$^+$): calcd for $C_{18}H_{175}ON_2S$: 309.1056; found: 309.1062.

1-Methyl-1*H*-indole-2-carboxylic acid methyl-(3-pyridin-2-yl-prop-2-ynyl)-amide (5l)

Yield: 314 mg, 94%; yellow syrup; purification conditions: CH_2Cl_2–ethyl acetate (70 : 30); ^{1}H NMR (300 MHz; $CDCl_3$): δ = 8.61 (br, 1H), 7.70 (dd, J = 7.8 Hz, J = 1.6 Hz, 1H), 7.65 (dt, J = 7.9 Hz, J = 1.0 Hz, 1H), 7.47 (d, J = 7.9 Hz, 1H), 7.32 (m, 3H), 7.15 (ddd, J = 8.0 Hz, J = 6.9 Hz, J = 1.1 Hz, 1H), 6.84 (br, 1H), 4.65 (s, 2H, CH_2), 3.88 (s, 3H, NCH_3), 3.32 (s, 3H, $OCNCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 164.1 (CO), 150.1 (CH), 138.1 (C), 136.3 (CH), 130.9 (C), 127.3 (C), 126.3 (CH), 123.6 (2 CH), 123.3 (C),

121.7 (CH), 120.3 (CH), 109.9 (2 CH), 83.9 (*C*≡C), 31.3 (NCH_3), not displayed: CH_2, OCN*C*H_3, *C*≡C; FT-IR (ATR, cm^{-1}): 3052, 2928, 2236, 1733, 1628, 1580, 1520, 1461, 1427, 1396, 1344, 1229, 1146, 1058, 778, 751, 736; GC-MS (EI, 70 eV): *m*/*z* (%): 303 (100) [M^+], 288 (14), 274 (15), 260 (22), 245 (64), 231 (43), 225 (17), 211 (18), 197 (6), 183 (3), 168 (10), 158 (38), 145 (57), 131 (36), 117 (28), 104 (8), 89 (91), 77 (9), 63 (10), 51 (5), 39 (4); HRMS (EI): calcd for $C_{19}H_{17}ON_3$: 303.13661; found: 303.13605.

4-Methoxy-3-{3-[methyl-(1-methyl-1*H*-indole-2-carbonyl)-amino]-prop-1-ynyl}-benzoic acid methyl ester (5m)

Yield: 314 mg, 73%; light yellow powder; purification conditions: heptane–ethyl acetate (1 : 1); ^{1}H NMR (400 MHz; $CDCl_3$): δ = 8.12 (d, *J* = 2.2 Hz, 1H), 8.02 (dd, *J* = 8.7 Hz, *J* = 2.2 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.38 (dd, *J* = 8.3 Hz, *J* = 0.7 Hz, 1H), 7.31 (ddd, *J* = 8.0 Hz, *J* = 6.9 Hz, *J* = 1.1 Hz, 1H), 7.15 (ddd, *J* = 8.0 Hz, *J* = 6.9 Hz, *J* = 1.0 Hz, 1H), 6.96 (br, 1H), 6.92 (d, *J* = 8.8 Hz, 1H), 4.64 (s, 2H, CH_2), 3.96 (s, 3H, OCH_3), 3.90 (s, 3H, $OCOCH_3$), 3.88 (s, 3H, NCH_3), 3.31 (s, 3H, OCNCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 166.1 (CO), 164.1 (CO), 163.6 (CO), 138.1 (C), 135.2 (CH), 131.9 (CH), 131.2 (C), 126.4 (C), 123.5 (CH), 122.6 (C), 121.7 (CH), 120.2 (CH), 111.8 (C), 110.2 (CH), 109.9 (CH), 104.4 (C), 88.6 (*C*≡C), 56.0 (OCH_3), 52.0 (OCH_3), 31.2 (NCH_3), not displayed: CH_2, OCN*C*H_3, *C*≡C; FT-IR (ATR, cm^{-1}): 3232, 3090, 3018, 2970, 2942, 2838, 1718, 1630, 1604, 1523, 1499, 1460, 1437, 1401, 1291, 1273, 1242, 1220, 1140, 1104, 1061, 1018, 830, 753, 726, 699; GC-MS (EI, 70 eV): *m*/*z* (%): 390 (17) [M^+], 359 (100), 346 (9), 333 (59), 318 (31), 302 (45), 288 (6), 274 (5), 258 (7), 243 (4), 225 (11), 213 (24), 207 (15), 189 (6), 171 (7), 158 (48), 131 (41), 115 (13), 102 (5), 89 (51), 77 (5), 63 (4), 42 (3); HRMS (ESI, $[M+H]^+$): calcd for $C_{23}H_{23}O_4N_2$: 391.1652; found: 391.1659.

Procedure for the synthesis of 1-methyl-1*H*-indole-2-carboxylic acid benzyl-(3-*p*-tolyl-prop-2-ynyl)-amide (5o) and corresponding starting materials

Benzyl-(prop-2-ynyl)-amine. To a stirred solution of benzylamine (10 mL, 91.6 mmol, 6 equiv) was added propargyl bromide (1.64 mL, 15.3 mmol, 1 equiv) dropwise at 0 °C during 30 min. The mixture was stirred overnight at room temperature. The resulting solution was then quenched with water and extracted with Et_2O. The combined organic layer was washed with brine ($NaHCO_3$), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (heptane–ethyl acetate: 60/40) affording the *N*-benzylpropargylamine as colourless liquid (1.654 g, 75%).

Benzyl-(3-*p*-tolyl-prop-2-ynyl)-amine. $[PdCl_2(PPh_3)_2]$ (40.4 mg, 0.058 mmol, 2 mol%) and CuI (21.9 mg, 0.115 mmol, 4 mol%) were placed in an ACE pressure tube under an argon atmosphere. A solution of *N*-benzylpropargylamine (500.9 mg, 3.45 mmol, 1.2 equiv) in THF/TEA (1 : 1, 20 mL) was injected and the 4-iodotoluene (626.8 mg, 2.875 mmol, 1 equiv) was then added. The pressure tube was sealed and the reaction mixture was heated at 65 °C for 20 h. After removal of the solvent *in vacuo*, the residue was purified by column chromatography (heptane–ethyl acetate: 60/40) to give benzyl-(3-*p*-tolyl-prop-2-ynyl)-amine as light brown powder (372 mg, 55%). ^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.42–7.23 (m, 7H), 7.12 (br d, *J* = 7.9 Hz, 2H), 3.95 (s, 2H, CH_2), 3.65 (s, 2H, CH_2), 3.35 (s, 3H, NCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 138.1 (2 C), 131.5 (2 CH), 129.0 (2 CH), 128.4 (4 CH), 127.1 (CH), 120.1 (C), 83.8 (*C*≡C), 52.5 (NCH_2), 31.3 (NCH_3), 21.4 (CH_3), not displayed: CH_2, *C*≡C; FT-IR (ATR, cm^{-1}): 3308, 3028, 2924, 2907, 2864, 2839, 1603, 1507, 1496, 1451, 1323, 1107, 1073, 907, 815, 798, 782, 731, 694, 544; GC-MS (EI, 70 eV): *m*/*z* (%): 234 (100) [M – H], 220 (9), 205 (4), 272 (5), 192 (15), 178 (2), 158 (38), 144 (45), 129 (66), 115 (41), 106 (11), 91 (71), 77 (12), 65 (13), 51(8), 39 (9); HRMS (EI): calcd for $C_{17}H_{16}N_1$: 234.12773; found: 234.12725.

1-Methyl-1*H*-indole-2-carboxylic acid benzyl-(3-*p*-tolyl-prop-2-ynyl)-amide (5o)

To a stirred solution of 1-methyl-1*H*-indole-2-carboxylic acid (294 mg, 1.68 mmol, 2 equiv) in benzene (8.4 mL) was added oxalyl chloride (2 M in CH_2Cl_2, 220 µL, 2.52 mmol, 3 equiv). The resulting solution was stirred at RT for 3 h, after which time the solvent was removed under reduced pressure and then taken up in 3 mL of THF. In a separate schlenk, to a suspension of NaH (60% in oil, 40.3 mg, 1 mmol, 1.2 equiv) in THF (4.2 mL) cooled to 0 °C was added a solution of benzyl-(3-*p*-tolyl-prop-2-ynyl)-amine (197.5 mg, 0.84 mmol, 1 equiv) in THF (2.5 mL). The suspension was allowed to stir at 0 °C for 30 min, after which time, the preformed acid chloride was added. 1.2 mL of THF was used to clean the schlenk with the preformed acid chloride and was added. The resulting yellow suspension was allowed to warm to RT overnight (18 h). The solution was then quenched with water and extracted with ethyl acetate. The combined organic layer was washed with brine (NaCl), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (heptane–ethyl acetate: 70/30) affording the indole **5o** as an orange syrup (258 mg, 78%).[11] ^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.64 (br d, *J* = 7.5 Hz, 1H), 7.44–7.29 (m, 9H), 7.15 (m, 3H), 6.98 (br, 1H), 5.00 (s, 2H, CH_2), 4.49 (s, 2H, CH_2), 3.91 (s, 3H, NCH_3), 2.38 (s, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 138.8 (C), 138.1 (C), 136.6 (C), 131.7 (4 CH), 131.2 (C), 129.1 (4 CH), 128.8 (CH), 127.7 (CH), 126.3 (C), 123.5 (CH), 121.8 (CH), 120.3 (CH), 109.9 (CH), 103.9 (C), 83.2 (*C*≡C), 31.3 (NCH_3), 21.4 (CH_3), not displayed: CO, 2 CH_2, OCN*C*H_3, *C*≡C; FT-IR (ATR, cm^{-1}): 3109, 3082, 3055, 3028, 2919, 1630, 1509, 1464, 1448, 1409, 1344, 1240, 1225, 1170, 994, 815, 734, 699, 527; GC-MS (EI, 70 eV): *m*/*z* (%): 392 (8) [M^+], 364 (6), 301 (8), 272 (5), 259 (100), 244 (18), 230 (2), 170 (3), 158 (25), 131 (16), 117 (5), 102 (3), 89 (27), 77 (3), 65 (2); HRMS (EI): calcd for $C_{27}H_{24}ON_2$: 392.18831; found: 392.18777.

General procedure for cyclization reactions

$PtCl_2$ (0.01 mmol, 5 mol%) was placed in an ACE pressure tube under an argon atmosphere. A solution of product **5a–m**, **o** (0.2 mmol, 1 equiv) in 10 mL of dichloromethane was then injected into the tube. The pressure tube was sealed and the reaction mixture was heated at 50 °C for 24 h. Solvent was removed under reduced pressure and the residue purified by column chromatography to give azepino[3,4-*b*]indol-1-ones **6a–k**, **m**, **o** indolo[4,3-*b*]azepin-1-ones **7a**, **m**, **o** and carbolin-1-ones **8d–h**, **n** (Table 1, and 2).

2,10-Dimethyl-5-*p*-tolyl-3,10-dihydro-2*H*-azepino[3,4-*b*]indol-1-one (6a)

Yield: 48 mg, 76%; white powder; purification conditions: heptane–ethyl acetate (1 : 1); ^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.42 (d, J = 8.4 Hz, 1H), 7.34–7.25 (m, 3H), 7.16 (d, J = 7.8 Hz, 2H), 6.92 (ddd, J = 8.0 Hz, J = 7.0 Hz, J = 1.1 Hz, 1H), 6.76 (dt J = 8.1 Hz, J = 0.9 Hz, 1H), 6.19 (t, J = 7.0 Hz, 1H), 4.11 (s, 3H, NCH_3), 3.81 (br, 2H, CH_2), 3.26 (s, 3H, $OCNCH_3$), 2.41 (s, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 162.2 (CO), 142.0 (C), 138.3 (C), 137.8 (C), 137.3 (C), 133.5 (C), 129.0 (2 CH), 128.3 (2 CH), 124.6 (C), 124.2 (CH), 122.7 (CH), 120.8 (CH), 120.0 (CH), 117.1 (C), 109.8 (CH), 47.5 (CH_2), 34.7 (NCH_3), 31.9 ($OCNCH_3$), 21.2 (CH_3); FT-IR (ATR, cm^{-1}): 3026, 2917, 2853, 1632, 1506, 1466, 1383, 1329, 1226, 1166, 1060, 805, 757, 744, 526; GC-MS (EI, 70 eV): m/z (%): 316 (100) [M$^+$], 301 (13), 287 (33), 274 (7), 259 (52), 244 (7), 225 (21), 202 (5), 197 (12), 158 (8), 121 (6), 115 (4), 89 (2), 77 (1), 63 (1), 42 (4); HRMS (EI): calcd for $C_{21}H_{20}ON_2$: 316.15701; found: 316.15725.

2,6-Dimethyl-5-*p*-tolyl-3,6-dihydro-2*H*-azepino[4,3-*b*]indol-1-one (7a)

White powder, purification conditions: heptane–ethyl acetate (1 : 1); ^{1}H NMR (300 MHz; $CDCl_3$): δ = 8.32 (m, 1H), 7.38–7.22 (m, 3H), 7.16 (m, 4H), 6.42 (t, J = 7.5 Hz, 1H), 3.79 (br, 2H, CH_2), 3.26 (s, 3H, $OCNCH_3$), 3.24 (s, 3H, NCH_3), 2.38 (s, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 165.6 (CO), 138.5 (C), 138.2 (C), 137.8 (C), 137.5 (C), 136.3 (C), 129.6 (2 CH), 127.3 (CH), 127.2 (2 CH), 126.8 (C), 123.7 (CH), 122.4 (CH), 121.4 (CH), 114.4 (C), 109.1 (CH), 47.1 (CH_2), 35.1 (NCH_3), 32.7 ($OCNCH_3$), 21.2 (CH_3); FT-IR (ATR, cm^{-1}): 3052, 3012, 2962, 2913, 2854, 1612, 1463, 1385, 1260 1073, 1016, 855, 810, 795, 749, 738, 705, 522; GC-MS (EI, 70 eV): m/z (%): 316 (100) [M$^+$], 301 (11), 287 (73), 274 (17), 259 (27), 244 (9), 225 (48), 202 (6), 197 (7), 182 (3), 158 (4), 150 (4), 136 (4), 128 (6), 115 (5), 108 (5), 77 (2), 63 (1), 42 (4); HRMS (EI): calcd for $C_{21}H_{20}ON_2$: 316.15701; found: 316.15756.

2,9-Dimethyl-4-(4-methylbenzyl)-2,9-dihydro-β-carbolin-1-one (8a)

Purification conditions: heptane–ethyl acetate (1 : 1); NMR data from inseparable mixture of compounds **7a** and **8a**; ^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.90 (dt, J = 8.1 Hz, J = 0.9 Hz, 1H), 7.46 (dd, J = 4.4 Hz, J = 0.9 Hz, 1H), 7.21–7.07 (m, 5H), 6.64 (s, 1H), 4.38 (s, 3H, NCH_3), 4.29 (br, 2H, CH_2), 3.63 (s, 3H, $OCNCH_3$), 2.32 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 156.2 (CO), 141.0 (C), 136.4 (C), 135.8 (C), 135.8 (C), 129.3 (2 CH), 128.5 (2 CH), 127.6 (CH), 127.0 (C), 126.2 (CH), 124.3 (C), 123.0 (CH), 120.0 (CH), 115.3 (C), 110.0 (CH), 36.6 (NCH_3), 36.1 (CH_2), 31.3 ($OCNCH_3$), 21.0 (CH_3); GC-MS (EI, 70 eV): m/z (%): 316 (100) [M$^+$], 301 (5), 287 (4), 259 (3), 231 (3), 225 (7), 211 (2), 184 (3), 158 (4), 150 (2), 128 (2), 115 (2); HRMS (EI): calcd for $C_{21}H_{20}ON_2$: 316.1570; found: 316.15744.

5-(3,4-Dimethylphenyl)-2,10-dimethyl-3,10-dihydro-2*H*-azepino[3,4-*b*]indol-1-one (6b)

Yield: 45 mg, 68%; light yellow powder; purification conditions: heptane–ethyl acetate (70 : 30); ^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.41 (br d, J = 8.4 Hz, 1H), 7.33–7.25 (m, 1H), 7.16 (br, 1H), 7.10 (m, 2H), 6.95–6.87 (m, 1H), 6.78 (br d, J = 8.1 Hz, 1H), 6.17 (t, J = 7.1 Hz, 1H), 4.10 (s, 3H, NCH_3), 3.80 (br, 2H, CH_2), 3.24 (s, 3H, $OCNCH_3$), 2.31 (s, 3H, CH_3), 2.24 (s, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 162.2 (CO), 142.1 (C), 138.2 (C), 137.8 (C), 136.4 (2 C), 133.4 (C), 129.6 (CH), 129.5 (CH), 125.9 (CH), 124.6 (C), 124.2 (CH), 122.8 (CH), 120.7 (CH), 119.9 (CH), 117.2 (C), 109.8 (CH), 47.5 (CH_2), 34.7 (NCH_3), 31.9 ($OCNCH_3$), 19.7 (CH_3), 19.6 (CH_3); FT-IR (ATR, cm^{-1}): 3503, 3402, 3033, 3018, 2921, 2899, 1614, 1504, 1467, 1386, 1330, 1231, 1081, 828, 757, 744; GC-MS (EI, 70 eV): m/z (%): 330 (100) [M$^+$], 315 (19), 301 (31), 287 (6), 273 (51), 258 (7), 242 (5), 225 (19), 215 (3), 202 (3), 197 (10), 165 (4), 136 (3), 128 (3), 121 (4), 115 (3), 108 (2), 42 (3); HRMS (ESI, [M+H]$^+$): calcd for $C_{22}H_{23}ON_2$: 331.1805; found: 331.1809.

5-(4-Methoxyphenyl)-2,10-dimethyl-3,10-dihydro-2*H*-azepino[3,4-*b*]indol-1-one (6c)

Yield: 52 mg, 78%; white powder; purification conditions: CH_2Cl_2–ethyl acetate (80 : 20); ^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.41 (d, J = 8.3 Hz, 1H), 7.33–7.26 (m, 3H), 6.95–6.84 (m, 3H), 6.76 (dt J = 8.1 Hz, J = 0.8 Hz, 1H), 6.14 (t, J = 7.0 Hz, 1H), 4.01 (s, 3H, NCH_3), 3.85 (s, 3H, OCH_3), 3.75 (br, 2H, CH_2), 3.24 (s, 3H, $OCNCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 162.1 (CO), 159.5 (CO), 141.6 (C), 138.3 (C), 133.5 (C), 132.8 (C), 129.6 (2 CH), 124.6 (C), 124.2 (CH), 122.7 (CH), 120.1 (CH), 119.9 (CH), 117.2 (C), 113.6 (2 CH), 109.9 (CH), 55.3 (OCH_3), 47.5 (CH_2), 34.7 (NCH_3), 31.9 ($OCNCH_3$); FT-IR (ATR, cm^{-1}): 3110, 3035, 2992, 2929, 2835, 1704, 1625, 1506, 1465, 1384, 1280, 1243, 1166, 1033, 839, 810, 740; GC-MS (EI, 70 eV): m/z (%): 332 (100) [M$^+$], 317 (7), 303 (29), 290 (8), 275 (40), 260 (16), 245 (4), 231 (3), 225 (13), 217 (5), 204 (3), 197 (9), 190 (3), 176 (2), 166 (2), 144 (2), 137 (3), 130 (3), 122 (4), 115 (3), 94 (3), 42 (4); HRMS (ESI, [M+H]$^+$): calcd for $C_{21}H_{21}O_2N_2$: 333.1598; found: 333.1599.

5-(4-Chlorophenyl)-2,10-dimethyl-3,10-dihydro-2*H*-azepino[3,4-*b*]indol-1-one (6d)

Yield: 41 mg, 61%; light yellow powder; purification conditions: CH_2Cl_2–ethyl acetate (70 : 30); ^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.42 (d, J = 8.3 Hz, 1H), 7.35–7.27 (m, 5H), 6.93 (ddd, J = 8.0 Hz, J = 7.0 Hz, J = 1.0 Hz, 1H), 6.72 (dt J = 8.2 Hz, J = 0.8 Hz, 1H), 6.19 (t, J = 7.0 Hz, 1H), 4.10 (s, 3H, NCH_3), 3.81 (br, 2H, CH_2), 3.25 (s, 3H, $OCNCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 162.0 (CO), 141.0 (C), 138.6 (C), 138.2 (C), 133.9 (C), 133.6 (C), 129.7 (2 CH), 128.5 (2 CH), 124.4 (CH), 124.2 (C), 122.4 (CH), 121.7 (CH), 120.2 (CH), 116.3 (C), 110.0 (CH), 47.4 (CH_2), 34.8 (NCH_3), 32.0 ($OCNCH_3$); FT-IR (ATR, cm^{-1}): 3045, 2996, 2929, 2906, 1634, 1511, 1467, 1383, 1329, 1226, 1088, 1012, 839, 804, 757, 748, 554; GC-MS (EI, 70 eV): m/z (%): 336 (100) [M$^+$], 307 (33), 294 (8), 279 (55), 264 (4), 258 (4), 244 (5), 225 (28), 214 (5), 197 (17), 168 (5), 128 (3), 114 (4), 101 (3), 42 (5); HRMS (ESI, [M+H]$^+$): calcd for $C_{20}H_{18}ClON_2$: 337.1102; found: 337.1102.

4-(4-Chlorobenzyl)-2,9-dimethyl-2,9-dihydro-β-carbolin-1-one (8d)

Yield: 8 mg, 12%; light yellow powder; purification conditions: CH_2Cl_2–ethyl acetate (70 : 30); ^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.79 (d, J = 8.2 Hz, 1H), 7.47 (d, J = 3.6 Hz, 1H), 7.29–7.24 (m,

2H), 7.22–7.10 (m, 3H), 6.67 (s, 1H), 4.38 (s, 3H, NCH_3), 4.29 (s, 2H, CH_2), 3.65 (s, 3H, $OCNCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 155.9 (CO), 145.8 (C), 141.0 (C), 137.5 (2 C), 131.1 (C), 129.9 (2 CH), 128.8 (2 CH), 127.8 (CH), 126.9 (C), 126.3 (CH), 122.8 (CH), 120.1 (CH), 114.4 (C), 110.1 (CH), 36.7 (NCH_3), 37.9 (CH_2), 31.3 ($OCNCH_3$); FT-IR (ATR, cm^{-1}): 3071, 2923, 2853, 1725, 1652, 1599, 1488, 1477, 1287, 1093, 1014, 814, 790, 731, 587, 533; GC-MS (EI, 70 eV): *m/z* (%): 336 (100) [M^+], 321 (2), 307 (3), 231 (2), 225 (9), 216 (3), 211 (3), 184 (4), 168 (3), 128 (3), 115 (2); HRMS (ESI, $[M+H]^+$): calcd for $C_{20}H_{18}ClON_2$: 337.1102; found: 337.1106.

2,10-Dimethyl-5-(4-trifluoromethylphenyl)-3,10-dihydro-2*H*-azepino[3,4-*b*]indol-1-one (6e)

Yield: 33 mg, 45%; yellow powder; purification conditions: CH_2Cl_2–ethyl acetate (70 : 30); ^1H NMR (300 MHz; $CDCl_3$): δ = 7.61 (d, J = 8.1 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.4 Hz, 1H), 7.31 (ddd, J = 8.1 Hz, J = 7.0 Hz, J = 1.1 Hz, 1H), 6.93 (ddd, J = 8.1 Hz, J = 7.0 Hz, J = 1.0 Hz, 1H), 6.65 (dt J = 8.1 Hz, J = 0.8 Hz, 1H), 6.27 (t, J = 7.0 Hz, 1H), 4.11 (s, 3H, NCH_3), 3.85 (br, 2H, CH_2), 3.26 (s, 3H, $OCNCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 162.0 (CO), 143.7 (C), 141.0 (C), 138.3 (C), 133.7 (C), 128.7 (2 CH), 125.4 (C), 125.3 (CH), 125.3 (CH), 124.5 (CH), 124.1 (C), 122.9 (CH), 122.3 (CH), 120.3 (CH), 116.0 (C), 110.1 (CH), 47.5 (CH_2), 34.9 (NCH_3), 32.0 ($OCNCH_3$), not displayed: *C*-CF_3, CF_3; FT-IR (ATR, cm^{-1}): 3059, 2957, 2929, 2860, 1725, 1622, 1501, 1465, 1324, 1158, 1101, 1068, 1016, 852, 740; GC-MS (EI, 70 eV): *m/z* (%): 370 (100) [M^+], 355 (4), 341 (33), 326 (7), 313 (61), 298 (6), 285 (4), 257 (2), 244 (2), 225 (27), 197 (15), 185 (5), 168 (3), 42 (4); HRMS (ESI, $[M+H]^+$): calcd for $C_{21}H_{18}ON_2F_3$: 371.1366; found: 371.1365.

2,9-Dimethyl-4-(4-trifluoromethyl-benzyl)-2,9-dihydro-β-carbolin-1-one (8e)

Yield: 22 mg, 29%; yellow syrup; purification conditions: CH_2Cl_2–ethyl acetate (70 : 30); ^1H NMR (300 MHz; $CDCl_3$): δ = 7.75 (dt, J = 8.2 Hz, J = 0.9 Hz, 1H), 7.55 (d, J = 8.0 Hz, 2H), 7.47 (m, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.17–7.09 (m, 1H), 6.70 (s, 1H), 4.38 (s, 5H, NCH_3 + CH_2), 3.66 (s, 3H, $OCNCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 156.3 (CO), 143.3 (C), 140.9 (C), 128.8 (2 CH), 128.6 (C), 127.9 (CH), 127.1 (C), 126.3 (CH), 126.0 (C), 125.6 (CH), 125.5 (CH), 123.8 (C), 122.6 (CH), 121.1 (C), 120.2 (CH), 113.7 (C), 110.2 (CH), 36.7 (NCH_3), 36.3 (CH_2), 31.3 ($OCNCH_3$); FT-IR (ATR, cm^{-1}): 3068, 2958, 2927, 2860, 1725, 1655, 1596, 1460, 1322, 1283, 1153, 1111, 1065, 1021, 862, 822, 734; GC-MS (EI, 70 eV): *m/z* (%): 370 (100) [M^+], 351 (4), 285 (2), 225 (8), 211 (3), 184 (4), 175 (2), 150 (2); HRMS (ESI, $[M+H]^+$): calcd for $C_{21}H_{18}ON_2F_3$: 371.1366; found: 371.1367.

4-(2,9-Dimethyl-1-oxo-2,9-dihydro-1*H*-β-carbolin-4-ylmethyl)-benzonitrile (8f)

Yield: 13 mg, 20%; yellow powder; purification conditions: heptane–ethyl acetate (1 : 1); ^1H NMR (400 MHz; $CDCl_3$): δ = 7.66 (d, J = 8.2 Hz, 1H), 7.57 (d, J = 8.2 Hz, 2H), 7.46 (m, 2H), 7.36 (d, J = 8.1 Hz, 2H), 7.15–7.07 (m, 1H), 6.74 (s, 1H), 4.38 (s, 3H, NCH_3), 4.375 (br, 2H, CH_2), 3.67 (s, 3H, $OCNCH_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 156.3 (CO), 144.9 (C), 140.9 (C), 132.5 (2 CH), 129.2 (2 CH), 128.1 (CH), 127.2 (C), 126.4 (CH), 123.6 (C), 122.4 (CH), 121.0 (C), 120.3 (CH), 118.8 (C), 112.9 (C), 110.5 (C), 110.3 (CH), 36.7 (NCH_3), 36.6 (CH_2), 31.3 ($OCNCH_3$); FT-IR (ATR, cm^{-1}): 3059, 2992, 2922, 2853, 2225, 1732, 1648, 1588, 1567, 1457, 1435, 1333, 1293, 1155, 1102, 821, 742, 594, 546; GC-MS (EI, 70 eV): *m/z* (%): 327 (100) [M^+], 298 (3), 241 (2), 225 (7), 211 (2), 184 (3), 164 (5), 140 (2), 128 (2); HRMS (ESI, $[M+H]^+$): calcd for $C_{21}H_{18}ON_3$: 328.1444; found: 328.1444.

5-(4-Acetylphenyl)-2,10-dimethyl-3,10-dihydro-2*H*-azepino[3,4-*b*]indol-1-one (6g). Yield: 15 mg, 21%; yellow powder; purification conditions: heptane–ethyl acetate (70 : 30); ^1H NMR (300 MHz; $CDCl_3$): δ = 7.94 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 1H), 7.30 (ddd, J = 8.2 Hz, J = 7.0 Hz, J = 1.1 Hz, 1H), 6.90 (ddd, J = 8.0 Hz, J = 7.0 Hz, J = 0.9 Hz, 1H), 6.66 (d, J = 8.2 Hz, 1H), 6.29 (t, J = 7.0 Hz, 1H), 4.11 (s, 3H, NCH_3), 3.85 (br, 2H, CH_2), 3.26 (s, 3H, $OCNCH_3$), 2.63 (s, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 197.8 (CO), 162.0 (CO), 144.8 (C), 141.3 (C), 138.3 (C), 136.5 (C), 133.6 (C), 128.7 (2 CH), 128.5 (2 CH), 124.5 (CH), 124.2 (C), 122.9 (CH), 122.3 (CH), 120.2 (CH), 116.0 (C), 110.1 (CH), 47.4 (CH_2), 34.9 (NCH_3), 32.0 ($OCNCH_3$), 26.7 (CH_3); FT-IR (ATR, cm^{-1}): 3050, 2921, 2852, 1678, 1624, 1600, 1503, 1466, 1400, 1378, 1355, 1331, 1262, 1231, 1075, 1060, 847, 806, 739, 594; GC-MS (EI, 70 eV): *m/z* (%): 344 (100) [M^+], 329 (4), 315 (28), 301 (8), 287 (46), 272 (4), 260 (7), 244 (7), 225 (24), 214 (3), 202 (4), 197 (13), 189 (3), 182 (2), 172 (3), 136 (4), 121 (4), 114 (2), 101 (2), 43 (5); HRMS (EI): calcd for $C_{22}H_{20}O_2N_2$: 344.15193; found: 344.1514.

4-(4-Acetylbenzyl)-2,9-dimethyl-2,9-dihydro-β-carbolin-1-one (8g)

Yield: 10 mg, 14%; yellow syrup; purification conditions: heptane–ethyl acetate (70 : 30); ^1H NMR (300 MHz; $CDCl_3$): δ = 7.89 (dt, J = 8.4 Hz, J = 1.9 Hz, 2H), 7.75 (dt, J = 8.1 Hz, J = 0.8 Hz, 1H), 7.47 (d, J = 0.9 Hz, 1H), 7.45 (m, 1H), 7.35 (d, J = 8.4 Hz, 2H), 7.11 (ddd, J = 8.1 Hz, J = 5.0 Hz, J = 3.1 Hz, 1H), 6.71 (s, 1H), 4.38 (s, 5H, CH_2 + NCH_3), 3.66 (s, 3H, $OCNCH_3$), 2.56 (s, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 197.8 (CO), 156.3 (CO), 144.8 (C), 140.9 (C), 135.6 (C), 128.8 (2 CH), 128.7 (2 CH), 127.9 (CH), 127.1 (C), 126.3 (CH), 123.9 (C), 122.7 (CH), 121.1 (C), 120.2 (CH), 113.8 (C), 110.1 (CH), 36.7 (NCH_3), 36.5 (CH_2), 31.3 ($OCNCH_3$), 26.6 (CH_3); FT-IR (ATR, cm^{-1}): 3050, 2921, 2852, 1678, 1649, 1588, 1565, 1472, 1411, 1355, 1333, 1293, 1264, 1102, 957, 823, 739, 600; GC-MS (EI, 70 eV): *m/z* (%): 344 (100) [M^+], 315 (3), 301 (4), 244 (1), 225 (8), 184 (3), 165 (9), 128 (2), 114 (1), 89 (1), 43 (3); HRMS (EI): calcd for $C_{22}H_{20}O_2N_2$: 344.15193; found: 344.15115.

4-(2,10-Dimethyl-1-oxo-1,2,3,10-tetrahydro-azepino[3,4-*b*]indol-5-yl)-benzoic acid ethyl ester (6h)

Yield: 19 mg, 25%; yellow powder; purification conditions: heptane–ethyl acetate (70 : 30); ^1H NMR (300 MHz; $CDCl_3$): δ = 8.03 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 7.41 (d, J = 7.7 Hz, 1H), 7.30 (m, 1H), 6.89 (t, J = 7.5 Hz, 1H), 6.65 (d, J = 8.2 Hz, 1H), 6.28 (t, J = 7.0 Hz, 1H), 4.40 (q, J = 7.1 Hz, 1H), 4.11 (s, 3H, NCH_3), 3.84 (br, 2H, CH_2), 3.26 (s, 3H, $OCNCH_3$), 2.41 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 166.5 (CO), 162.0 (CO), 144.6 (C), 141.4 (C), 138.3 (C), 133.6 (C), 129.9 (C), 129.6 (2 CH), 128.4 (2 CH), 124.4 (CH), 124.2 (C), 122.8 (CH),

122.4 (CH), 120.2 (CH), 116.2 (C), 110.1 (CH), 61.0 ($OCOCH_2$), 47.4 (CH_2), 34.9 (NCH_3), 32.0 ($OCNCH_3$), 14.3 (CH_3); GC-MS (EI, 70 eV): *m/z* (%): 374 (100) [M^+], 345 (22), 329 (5), 317 (5), 301 (11), 289 (8), 273 (2), 260 (6), 242 (5), 225 (26), 214 (3), 202 (5), 197 (11), 187 (3), 136 (4), 128 (2), 121 (3), 115 (2), 42 (2); HRMS (ESI, [M+H]$^+$): calcd for $C_{23}H_{23}O_3N_2$: 375.1703; found: 375.1706.

4-(2,9-Dimethyl-1-oxo-2,9-dihydro-1*H*-β-carbolin-4-ylmethyl)-benzoic acid ethyl ester (8h)

Yield: 19 mg, 25%; yellow syrup; purification conditions: heptane–ethyl acetate (70 : 30); NMR data from inseparable mixture of compounds **8h**:**6h** (9 : 1). ^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.97 (d, J = 8.2 Hz, 2H), 7.76 (d, J = 8.1 Hz, 1H), 7.46 (d, J = 4.1 Hz, 1H), 7.32 (d, J = 8.1 Hz, 2H), 7.11 (m, 1H), 6.68 (s, 1H), 4.38 (s, 5H, CH_2 + NCH_3), 4.35 (q, J = 7.1 Hz, 1H), 3.65 (s, 3H, $OCNCH_3$), 1.34 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 166.5 (CO), 156.3 (CO), 144.4 (C), 140.9 (C), 129.9 (2 CH), 128.8 (C); 128.5 (2 CH), 127.9 (CH), 127.1 (C), 126.3 (CH), 123.9 (C), 122.7 (CH), 121.2 (C), 120.1 (CH), 113.9 (C), 110.1 (CH), 60.9 ($OCOCH_2$), 36.7 (NCH_3), 36.5 (CH_2), 31.3 ($OCNCH_3$), 14.3 (CH_3); GC-MS (EI, 70 eV): *m/z* (%): 374 (100) [M^+], 346 (20), 329 (6), 301 (4), 286 (2), 271 (3), 242 (2), 231 (3), 225 (8), 211 (3), 202 (3), 184 (5), 164 (25), 154 (3), 149 (3), 144 (3), 135 (6), 129 (5), 121 (3), 115 (3), 108 (2); HRMS (ESI, [M+H]$^+$): calcd for $C_{23}H_{23}O_3N_2$: 375.1703; found: 375.1702.

2,10-Dimethyl-5-naphthalen-1-yl-3,10-dihydro-2*H*-azepino[3,4-*b*]indol-1-one (6i)

Yield: 57 mg, 80%; light yellow powder; purification conditions: CH_2Cl_2–ethyl acetate (70 : 30); ^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.88 (m, 2H), 7.78 (br, 1H), 7.51 (d, J = 4.7 Hz, 2H), 7.45–7.21 (m, 3H), 7.17 (ddd, J = 8.1 Hz, J = 7.1 Hz, J = 1.1 Hz, 1H), 6.65 (ddd, J = 8.1 Hz, J = 7.0 Hz, J = 0.9 Hz, 1H), 6.25 (dt, J = 8.2 Hz, J = 0.9 Hz, 1H), 6.24 (t, J = 6.9 Hz, 1H), 4.13 (s, 3H, NCH_3), 3.95 (d, J = 6.3 Hz, 2H, CH_2), 3.31 (s, 3H, $OCNCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 162.1 (CO), 138.6 (C), 138.4 (2 C), 133.5 (C), 131.7 (C), 128.5 (CH), 128.1 (CH), 127.4 (CH), 126.2 (CH), 125.8 (CH), 125.6 (CH), 125.4 (CH), 124.4 (CH), 124.2 (C), 123.8 (CH), 121.7 (CH), 120.2 (CH), 118.7 (C), 109.7 (CH), 47.6 (CH_2), 35.0 (NCH_3), 32.1 ($OCNCH_3$); FT-IR (ATR, cm^{-1}): 3049, 2926, 1733, 1634, 1503, 1456, 1386, 1330, 1232, 1017, 797, 780, 739, 676, 614; GC-MS (EI, 70 eV): *m/z* (%): 352 (100) [M^+], 323 (24), 208 (7), 295 (30), 278 (7), 266 (5), 253 (4), 239 (3), 225 (15), 197 (5), 154 (9), 145 (5), 139 (5), 132 (3), 127 (2); HRMS (ESI, [M+H]$^+$): calcd for $C_{24}H_{21}ON_2$: 353.1648; found: 353.1651.

5-Furan-2-yl-2,10-dimethyl-3,10-dihydro-2*H*-azepino[3,4-*b*]indol-1-one (6j)

Yield: 38 mg, 65%; light orange powder; purification conditions: CH_2Cl_2–ethyl acetate (90 : 10); ^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.43 (m, 2H), 7.39–7.29 (m, 2H), 7.07 (ddd, J = 8.1 Hz, J = 6.8 Hz, J = 1.1 Hz, 1H), 6.51 (t, J = 7.2 Hz, 1H), 6.45 (dd, J = 3.3 Hz, J = 1.9 Hz, 1H), 6.38 (d, J = 3.2 Hz, 1H), 4.08 (s, 3H, NCH_3), 3.81 (br, 2H, CH_2), 3.24 (s, 3H, $OCNCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 162.1 (CO), 152.6 (CO), 142.1 (CH), 138.1 (C), 133.5 (C), 130.9 (C), 124.4 (CH), 124.2 (C), 122.4 (CH), 120.1 (CH), 119.7 (CH), 114.9 (C), 111.3 (CH), 110.0 (CH), 109.7 (CH), 47.2 (CH_2), 34.8 (NCH_3), 31.9 ($OCNCH_3$); FT-IR (ATR, cm^{-1}): 3154, 3116, 3058, 2909, 1620, 1511, 1464, 1385, 1332, 1231, 1212, 1064, 1008, 851, 737, 687; GC-MS (EI, 70 eV): *m/z* (%): 292 (100) [M^+], 277 (3), 263 (47), 248 (8), 235 (79), 220 (13), 206 (11), 191 (7), 180 (4), 165 (5), 152 (4), 139 (2), 117 (4), 110 (2), 102 (2), 42 (4); HRMS (ESI, [M+H]$^+$): calcd for $C_{18}H_{17}O_2N_2$: 293.1285; found: 293.1290.

2,10-Dimethyl-5-thiophen-2-yl-3,10-dihydro-2*H*-azepino[3,4-*b*]indol-1-one (6k)

Yield: 28 mg, 45%; light yellow powder; purification conditions: CH_2Cl_2–ethyl acetate (90 : 10); ^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.42 (dt, J = 8.4 Hz, J = 0.8 Hz, 1H), 7.36-7.27 (m, 2H), 7.09-6.96 (m, 4H), 6.32 (t, J = 7.1 Hz, 1H), 4.09 (s, 3H, NCH_3), 3.80 (br, 2H, CH_2), 3.25 (s, 3H, $OCNCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 162.0 (CO), 142.6 (C), 138.2 (C), 134.9 (C), 133.3 (C), 127.3 (CH), 127.1 (CH), 125.1 (CH), 124.4 (CH), 124.3 (C), 122.6 (CH), 121.4 (CH), 120.1 (CH), 116.5 (C), 110.0 (CH), 47.3 (CH_2), 34.8 (NCH_3), 31.9 ($OCNCH_3$); FT-IR (ATR, cm^{-1}): 3102, 3057, 2927, 2902, 1620, 1503, 1463, 1382, 1331, 1229, 1060, 850, 739, 705, 665, 613; GC-MS (EI, 70 eV): *m/z* (%): 308 (100) [M^+], 279 (32), 266 (8), 251 (59), 236 (7), 225 (9), 218 (3), 209 (2), 204 (3), 197 (8), 190 (3), 165 (2), 154 (4), 139 (2), 42 (3); HRMS (ESI, [M+H]$^+$): calcd for $C_{18}H_{17}ON_2S$: 309.1056; found: 309.1061.

3-(2,10-Dimethyl-1-oxo-1,2,3,10-tetrahydro-azepino[3,4-*b*]indol-5-yl)-4-methoxy-benzoic acid methyl ester (6m)

Yield: 47 mg, 60%; white powder; purification conditions: CH_2Cl_2–ethyl acetate (80 : 20); ^{1}H NMR (300 MHz; $CDCl_3$): δ = 8.09 (dd, J = 8.7 Hz, J = 2.2 Hz, 1H), 8.00 (s, 1H), 7.36 (d, J = 8.3 Hz, 1H), 7.24 (ddd, J = 8.2 Hz, J = 7.0 Hz, J = 1.1 Hz, 1H), 6.91 (d, J = 8.7 Hz, 1H), 6.82 (ddd, J = 8.1 Hz, J = 7.0 Hz, J = 1.0 Hz, 1H), 6.57 (d, J = 8.1 Hz, 1H), 6.19 (t, J = 7.0 Hz, 1H), 4.08 (s, 3H, NCH_3), 3.87 (s, 3H, OCH_3), 3.83 (d, J = 6.9 Hz, 2H, CH_2), 3.53 (s, 3H, $OCOCH_3$), 3.26 (s, 3H, $OCNCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 168.8 (CO), 162.1 (CO), 161.0 (CO), 138.2 (2 C), 132.6 (CH), 131.6 (CH), 129.7 (C), 124.5 (C), 124.2 (CH), 123.5 (CH), 122.5 (2 C), 121.2 (CH), 120.0 (CH), 118.0 (C), 110.6 (CH), 109.8 (CH), 55.7 (OCH_3), 51.9 ($OCOCH_3$), 47.4 (CH_2), 34.9 (NCH_3), 32.0 ($OCNCH_3$); FT-IR (ATR, cm^{-1}): 3052, 2947, 2839, 1713, 1626, 1601, 1500, 1466, 1435, 1303, 1263, 1224, 1132, 1106, 1021, 768, 739, 631; GC-MS (EI, 70 eV): *m/z* (%): 390 (100) [M^+], 375 (5), 361 (15), 345 (4), 333 (19), 318 (7), 302 (3), 287 (2), 274 (4), 258 (3), 244 (2), 230 (3), 225 (20), 216 (3), 202 (2), 197 (7), 189 (2), 179 (5), 165 (3), 158 (3), 151 (7), 144 (2), 136 (2); HRMS (EI): calcd for $C_{23}H_{23}O_4N_2$: 391.1652; found: 391.1656.

3-(2,6-Dimethyl-1-oxo-1,2,3,6-tetrahydro-azepino[4,3-*b*]indol-5-yl)-4-methoxy-benzoic acid methyl ester (7m)

Yield: 18 mg, 23%; white powder; purification conditions: CH_2Cl_2–ethyl acetate (80 : 20); ^{1}H NMR (300 MHz; $CDCl_3$): δ = 8.31 (m, 1H), 8.06 (dd, J = 8.6 Hz, J = 2.2 Hz, 1H), 7.90 (br, 1H), 7.36-7.21 (m, 3H), 6.94 (d, J = 8.7 Hz, 1H), 6.49 (t, J = 7.5 Hz, 1H), 3.87 (s, 3H, NCH_3), 3.81 (d, J = 7.5 Hz, 2H, CH_2), 3.27 (s, 3H, $OCNCH_3$), 3.19 (s, 3H, OCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 166.5 (CO), 165.7 (CO), 160.2 (CO), 138.8 (C), 137.4 (C), 131.8 (CH), 131.7 (CH), 130.7 (C), 128.2 (C), 126.9 (CH), 123.5 (CH), 122.9 (2 C), 122.4 (CH), 121.3 (CH), 119.6 (C), 110.5 (CH), 108.9

(CH), 56.0 (OCH_3), 52.0 ($OCOCH_3$), 47.1 (CH_2), 35.2 (NCH_3), 31.8 ($OCNCH_3$); FT-IR (ATR, cm^{-1}): 2922, 2851, 1712, 1603, 1463, 1435, 1392, 1295, 1264, 1227, 1165, 1129, 1018, 768, 750, 735, 712; GC-MS (EI, 70 eV): *m/z* (%): 390 (100) [M^+], 361 (43), 348 (3), 333 (7), 315 (6), 301 (5), 287 (4), 274 (4), 258 (3), 244 (4), 225 (28), 217 (3), 202 (3), 195 (5), 189 (2), 179 (4), 165 (4), 158 (2), 150 (2), 144 (3), 135 (2), 121 (3), 95 (2), 42 (2); HRMS (EI): calcd for $C_{23}H_{23}O_4N_2$: 391.1652; found: 391.1660.

2,4,9-Trimethyl-2,9-dihydro-β-carbolin-1-one (8n)

Yield: 43 mg, 95%; white powder: purification conditions: ethyl acetate; ^1H NMR (400 MHz; $CDCl_3$): δ = 8.10 (dt, J = 8.1 Hz, J = 1.0 Hz, 1H), 7.54–7.45 (m, 2H), 7.25 (ddd, J = 8.1 Hz, J = 6.5 Hz, J = 1.6 Hz, 1H), 6.80 (d, J = 1.1 Hz, 1H), 4.36 (s, 3H, NCH_3), 3.65 (s, 3H, $OCNCH_3$), 2.57 (d, J = 1.1 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 156.3 (CO), 140.9 (C), 126.8 (C), 126.4 (CH), 126.2 (CH), 124.7 (C), 122.7 (CH), 122.0 (C), 120.0 (CH), 112.2 (C), 110.0 (CH), 36.5 (NCH_3), 31.2 ($OCNCH_3$), 16.9 (CH_3); FT-IR (ATR, cm^{-1}): 3060, 2923, 2890, 2855, 1652, 1596, 1475, 1437, 1333, 1291, 991, 811, 728, 620, 539, 508; GC-MS (EI, 70 eV): *m/z* (%): 226 (100) [M^+], 211 (15), 197 (4), 181 (4), 168 (4), 154 (4), 140 (4), 128 (3), 113 (6); HRMS (ESI, $[M+H]^+$): calcd for $C_{14}H_{15}ON_2$: 227.1179; found: 227.1184.

2-Benzyl-10-methyl-5-*p*-tolyl-3,10-dihydro-2*H*-azepino[3,4-*b*]indol-1-one (6o)

Yield: 61 mg, 77%; white powder; purification conditions: heptane–ethyl acetate (70 : 30); NMR data from inseparable mixture of compounds **6o**:**7o** (5.7 : 1); ^1H NMR (300 MHz; $CDCl_3$): δ = 7.43 (dt, J = 8.6 Hz, J = 0.8 Hz, 1H), 7.40–7.23 (m, 8H), 7.16 (m, 2H), 6.91 (ddd, J = 8.1 Hz, J = 7.0 Hz, J = 1.0 Hz, 1H), 6.75 (dt, J = 8.1 Hz, J = 0.8 Hz, 1H), 6.00 (t, J = 7.0 Hz, 1H), 4.95 (br, 2H, CH_2), 4.15 (s, 3H, NCH_3), 3.77 (d, J = 7.0 Hz, 2H, CH_2), 2.41 (s, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 162.4 (CO), 141.9 (C), 138.4 (C), 137.7 (C), 137.4 (C), 133.2 (C), 129.0 (2 CH), 128.7 (2 CH), 128.4 (2 CH), 128.2 (C), 128.0 (2 CH), 127.5 (CH), 124.6 (C), 124.3 (CH), 122.8 (CH), 121.4 (CH), 120.0 (CH), 117.3 (C), 109.9 (CH), 50.4 (CH_2), 45.1 (CH_2), 32.1 (NCH_3), 21.2 (CH_3); GC-MS (EI, 70 eV): *m/z* (%): 392 (100) [M^+], 377 (5), 301 (41), 288 (26), 274 (14), 259 (56), 242 (5), 230 (6), 216 (3), 202 (5), 189 (2), 168 (2), 115 (2), 91 (15), 65 (2); HRMS (ESI, $[M+H]^+$): calcd for $C_{27}H_{25}ON_2$: 393.1961; found: 393.1971.

Acknowledgements

This work has been supported by the State of Mecklenburg-Western Pomerania, the BMBF (Bundesministerium für Bildung und Forschung) and the Deutsche Forschungsgemeinschaft (Leibniz-price; GRK 1113). We also thank Drs D. Michalik, W. Baumann, C. Fischer, and Mrs S. Buchholz, Mrs S. Schareina, Mrs A. Lehmann, and Mrs K. Mevius (all LIKAT) for their excellent analytical support.

Notes and references

1 R. Martinez, J. G. Avila, M. T. Ramirez, A. Pérez and A. Martinez, *Bioorg. Med. Chem.*, 2006, **14**, 4007.

2 (*a*) J.-G. Parmentier, B. Portevin, R. M. Golsteyn, A. Pierré, J. Hickman, P. Gloanec and G. De Nanteuil, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 841; (*b*) N. Dessalew and P. V. Bharatam, *Biophys. Chem.*, 2007, **128**, 165; (*c*) V. Sharma and J. J. Tepe, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 4319; (*d*) Y. Wan, W. Hur, C. Y. Cho, Y. Liu, F. J. Adrian, O. Lozach, S. Bach, T. Meijer and N. S. Gray, *Chem. Bio.*, 2004, **11**, 247; (*e*) C. Schultz, A. Link, M. Leost, D. W. Zaharevitz, R. Gussio, A. A. Sausville, L. Meijer and C. J. Kunick, *J. Med. Chem.*, 1999, **42**, 2909.

3 V. Sharma, T. A. Lansdell, G. Jin and J. J. Tepe, *J. Med. Chem.*, 2004, **47**, 3700.

4 (*a*) A. Putey, F. Popowycz, Q.-T. Do, P. Bernard, S. K. Talapatra, F. Kozielski, C. M. Galmarini and B. Joseph, *J. Med. Chem.*, 2009, **52**, 5916; (*b*) L. Keller, S. Beaumont, J.-M. Liu, S. Thoret, J. S. Bignon, J. Wdzieczak-Bakala, P. Dauban and R. H. Dodd, *J. Med. Chem.*, 2008, **51**, 3414.

5 (*a*) S. G. Stewart, E. L. Ghisalberti, B. W. Skelton and C. H. Heath, *Org. Biomol. Chem.*, 2010, **8**, 3563; (*b*) R. Cincinelli, S. Dallavalle, L. Merlini, R. Nannei and L. Scaglioni, *Tetrahedron*, 2009, **65**, 3465; (*c*) R. Cincinelli, G. Cassinelli, S. Dallavalle, C. Lanzi, L. Merlini, M. Botta, T. Tuccinardi, A. Martinelli, S. Penco and F. Zumino, *J. Med. Chem.*, 2008, **51**, 7777; (*d*) A. Putey, L. Joucla, L. Picot, T. Besson and B. Joseph, *Tetrahedron*, 2007, **63**, 867; (*e*) N. Henry, Jérôme Blu, V. Bénéteau and J.-Y. Mérour, *Synthesis*, 2006, **22**, 3895; (*f*) J. Perron, B. Joseph and J.-Y. Mérour, *Eur. J. Org. Chem.*, 2004, 4606.

6 (*a*) C. Ferrer, C. H. M. Amijs and A. M. Echavarren, *Chem.–Eur. J.*, 2007, **13**, 1358; (*b*) C. Ferrer and A. M. Echavarren, *Angew. Chem., Int. Ed.*, 2006, **45**, 1105.

7 (*a*) N. Mangu, A. Spannenberg and M. Beller, *Synlett*, 2010, **2**, 211; (*b*) N. Mangu, H. M. Kaiser, A. Kar, A. Spannenberg, M. Beller and M. K. Tse, *Tetrahedron*, 2008, **64**, 7171; (*c*) H. M. Kaiser, I. Zenz, W. F. Lo, A. Spannenberg, K. Schröder, H. Jiao, D. Gördes, M. Beller and M. K. Tse, *J. Org. Chem.*, 2007, **72**, 8847; (*d*) H. M. Kaiser, W. F. Lo, A. M. Riahi, A. Spannenberg, M. Beller and M. K. Tse, *Org. Lett.*, 2006, **8**, 5761.

8 (*a*) A. Pews-Davtyan, A. Tillack, A.-C Schmöle, S. Ortinau, M. J. Frech, A. Rolfs and M. Beller, *Org. Biomol. Chem.*, 2010, **8**, 1149; (*b*) A. Brennfürher, H. Neumann, A. Pews-Davtyan and M. Beller, *Eur. J. Org. Chem.*, 2009, 38; (*c*) K. Alex, A. Tillack, N. Schwarz and M. Beller, *Angew. Chem.*, 2008, **120**, 2337(; *Angew. Chem., Int. Ed.*, 2008, 47, 2304); (*d*) K. Alex, N. Schwarz, V. Khedkar, I. A. Sayyed, A. Tillack, D. Michalik, J. Holenz, J. L. Diaz and M. Beller, *Org. Biomol. Chem.*, 2008, **6**, 1802; (*e*) I. A. Sayyed, K. Alex, A. Tillack, N. Schwarz, D. Michalik and M. Beller, *Eur. J. Org. Chem.*, 2007, 4525.

9 (*a*) G. Verniest, D. B. England, N. De Kimpe and A. Padwa, *Tetrahedron*, 2010, **66**, 1496; (*b*) K. Hirano, Y. Inaba, T. Watanabe, S. Oishi, N. Fujii and H. Ohno, *Adv. Synth. Catal.*, 2010, **352**, 368; (*c*) A. S. K. Hashmi, S. Pankajakshan, M. Rudolph, E. Enns, T. Bander, F. Rominger and W. Frey, *Adv. Synth. Catal.*, 2009, **351**, 2855; (*d*) C. Ferrer, A. Escribano-Cruesta and A. M. Echavarren, *Tetrahedron*, 2009, **65**, 9015.

10 (*a*) Y. Lu, X. Du, X. Jia and Y. Liu, *Adv. Synth. Catal.*, 2009, **351**, 1517; (*b*) C. Ferrer, M. Raducan, C. Nevado, C. K. Claverie and A. M. Echavarren, *Tetrahedron*, 2007, **63**, 6306; (*c*) C. Nevado and A. M. Echavarren, *Chem.–Eur. J.*, 2005, **11**, 3155.

11 (*a*) G. Verniest, D. England, N. De Kimpe and A. Padwa, *Tetrahedron*, 2010, **66**, 1496; (*b*) D. B. England and A. Padwa, *Org. Lett.*, 2008, **10**, 3631.

12 (*a*) M. Gruit, D. Michalik, K. Krüger, A. Spannenberg, A. Tillack, A. Pews-Davtyan and M. Beller, *Tetrahedron*, 2010, **66**, 3341; (*b*) M. Gruit, D. Michalik, A. Tillack and M. Beller, *Angew. Chem., Int. Ed.*, 2009, **48**, 7212.

13 (*a*) J. P. Weyrauch, A. S. K. Hasmi, A. Schuster, T. Hengst, S. Schetter, A. Littmann, M. Rudolph, M. Hamzic, J. Visus, F. Rominger, W. Frey and J. W. Bats, *Chem. Eur. J.*, 2010, **16**, 956; (*b*) A. Martinez, P. Garcia-Garcia, M. A. Fernandez-Rodriguez, F. Rodriguez and R. Sanz, *Angew. Chem., Int. Ed.*, 2010, **49**, 4633; (*c*) A. Fürstner and P. W. Davies, *Angew. Chem., Int. Ed.*, 2007, **46**, 3410; (*d*) V. Mamane, P. Hannen and A. Fürstner, *Chem.–Eur. J.*, 2004, **10**, 4556; (*e*) A. Fürstner and V. Mamane, *J. Org. Chem.*, 2002, **102**, 813.