Full Paper

Synthesis and Biological Evaluation of New Niphathesine Analogues

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Niphathesine C and related pyridine alkaloids are well known natural products with interesting antimicrobial activities, characterized by a pyridine ring and a lipophilic side chain with a terminal nitrogen-containing functional group. This paper describes the synthesis of analogues of these alkylpyridine alkaloids with variation of the heterocyclic ring and the terminal functional group. Key steps of the syntheses are a Sonogashira reaction of appropriate aryl iodides with undec-10-ynol or undec-10-ynoic acid derivatives. The resulting compounds were tested in an agar diffusion assay against several bacteria and fungi.

Keywords: Agar diffusion assay / Alkylpyridine alkaloids / Sonogashira reaction

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Introduction

Sponges of the family Niphatidae produce a diverse array of alkaloids that are structurally related by having a 3-alkylpyridine moiety with a terminal nitrogen-containing functional group (oxime, hydroxylamine or amino function). Most of these alkaloids show interesting pharmacological properties like cytotoxic, antibiotic and antimycotic activities [1, 2]. Recently, the new 2-alkylpyridine alkaloid class named phormidines with a terminal secondary hydroxyl function was isolated from the marine cyanobacterium *Phormidium sp*. (Figure 1 shows some representative alkaloids and the dates of their first isolation) [8].

Aim of this work was to replace the amino functional group into an alcohol or other nitrogen-containing functional groups and to introduce other aromatic heterocycles.

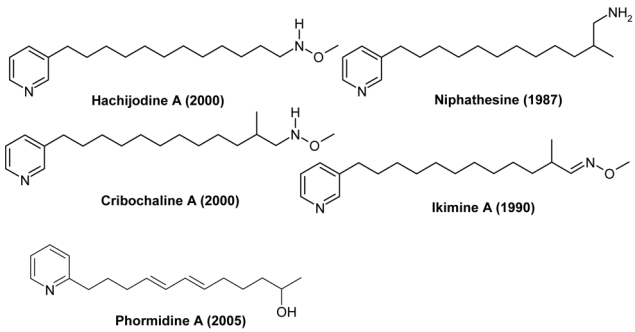

Figure 1. Pyridine alkaloids from marine organisms.

Chemistry

In the first series, the aryl iodide building blocks **1** (R = phenyl-, pyridin-3-yl or indol-5-yl-) were reacted under Sonogashira conditions [6] with undec-10-yn-1-ol to give the resulting alkynols **2**. The triple bonds were hydrogenated under palladium catalysis to give the corresponding arylalkanols **3** (Scheme 1).

In a second series, undec-10-ynoic acid **4** was converted into various amides via the acid chloride with several primary amines like *tert.* butylamine, isopropylamine, benzylamine, 1-phenylethylamine and morpholine. The amides **5** were reacted in a Sonogashira reaction with the aromatic building blocks **1** to give the amides **6**. Exemplarily, the amides **6c** and **6e** were reduced with $LiAlH_4$ to give the corresponding amines **7a** and **7b**. In the course of these reactions, the acetylenic groups were reduced to

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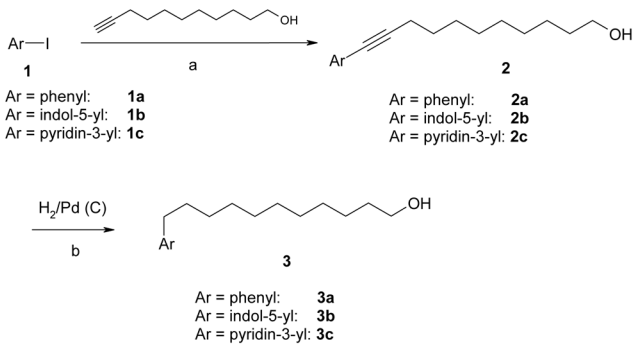
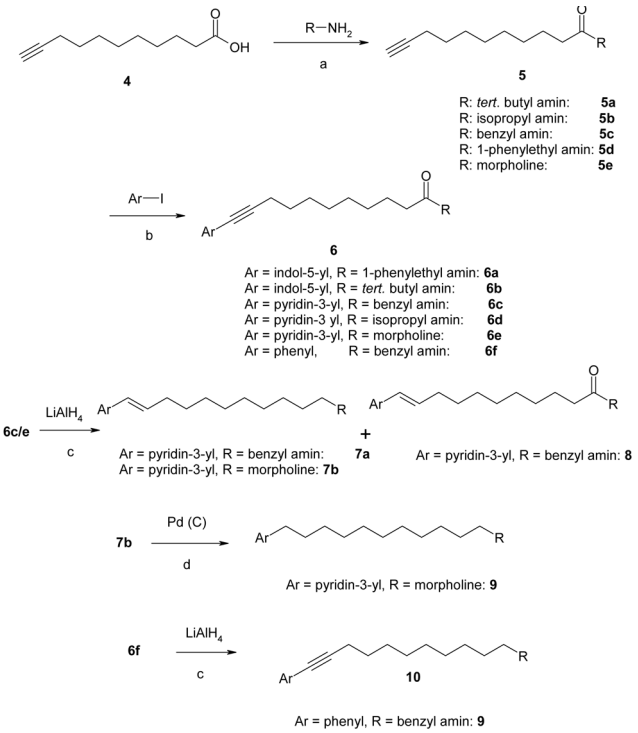


a: CuI, Et_3N, $PdCl_2(PPh_3)_2$; b: MeOH.

Scheme 1. Synthesis route of compounds **1 – 3**.



a: $C_2O_2Cl_2$, toluene; b: CuI, Et_3N, $PdCl_2(PPh_3)_2$; c: $LiAlH_4$, THF; d: methanol.

Scheme 2. Synthesis route of compounds **4 – 9.**

the (*E*)-olefines [9]. The (*E*)-amide **8a** and the corresponding (*Z*)-amine were obtained as by-products in low yields and determined by GLC. In order to avoid these by-products, the crude reaction mixture of **7b** was hydrogenated by Pd (C) to give the amine **9** (Scheme 2)

Reaction of the phenyl derivative **6f** with $LiAlH_4$ led to alkine amine **10** without any reduction of the triple bond.

Results and discussion

The resulting compounds were tested in an agar diffusion assay against several bacteria (*Escherichia coli*, *Staphylococcus equorum*, *Pseudomonas antimicrobia*) and fungi (*Aspergillus niger*, *Candida glabarata*, *Hypopichii burtonii*, *Yarrowia lipolytica*). Tetracycline and clotrimazole served as reference compounds (Table 1). Only compounds with an amine functional group like **7a**, **9** and **10** showed significant antibacterial and antimycotic activities with a wide spectrum.

We are greatly indepted to Martina Stadler for technical support.

Experimental

Chemistry

IR-Spectra: Perkin-Elmer FT-IR Paragon 1000 (Perkin-Elmer, Norwalk, CT, USA); MS: Hewlett Packard MS-Engine (Hewlett-Packard, Palo Alto, CA, USA), electron ionisation (EI) 70 eV, chemical ionisation (CI) with CH_4 (300 eV); NMR (400 MHz): Jeol GSX 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz) (JEOL, Tokyo, Japan); GLC-MS: Shimadzu GC 17 A (Shimadzu, Tokyo, Japan); flash column chromatography (FCC): silica gel 60 (230 – 400 mesh, E. Merck, Darmstadt, Germany).

Compounds **2c** and **3c** were prepared as described in the literature [6] and [7].

11-Phenyl-undec-10-yn-1-ol ***2a***

CuI (100 mg; 0.5 mmol) were dissolved in 50 mL dry EDMA, 1.7 g (11.0 mmol) undec-10-yn-1-ol, 160 mg (0.2 mmol) $PdCl_2(PPh_3)_2$

Table 1. Agar diffusion assay.

	2a	2b	2c	3a	3b	3c	5a	5b	5e	5c	6a	6b	6c	6d	6e	7a	9	10	te	cl
Escherichia coli	6	7	8	0	0	6	0	0	0	0	0	0	0	0	0	18	8	11	39	13
Pseudomonas antimicrobia	0	0	0	0	0	8	6	0	0	0	0	0	0	0	0	12	0	11	35	–
Staphylococcus equorum	7	6	9	0	0	6	0	0	0	0	0	0	0	0	6	15	7	8	12	–
Candida glabarata	8	6	8	0	8	7	0	0	6	0	0	0	0	6	6	15	0	9	nt	11
Aspergillus niger	0	0	7	0	0	6	0	0	0	0	0	0	0	0	0	12	0	0	nt	13
Yarrowia lipolytica	0	7	8	0	0	7	0	0	6	0	0	0	6	6	6	20	7	9	nt	11
Hypopichi burtonii	0	0	10	0	0	nt	0	0	0	0	0	0	0	0	0	18	0	10	nt	11

(50 µg/disc, diameter of inhibition [mm]), te: tetracycline, cl: clotrimazole (25 µg/disc), 0 mm: inactive in test concentration, nt: not tested.

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and 2.04 g (10.0 mmol) 3-iodobenzene were added. The mixture was stirred for 24 h under N_2 atmosphere. The solvent was evaporated and the residue dissolved in 50 mL 5% aqueous $Na_2S_2O_3$ solution, extracted with diethyl ether (3 × 50 mL) and the combined organic layers were dried over Na_2SO_4. The organic solvent was evaporated and the residue purified by FCC (*n*-hexane, ethyl acetate, EDMA; 20 : 3) to give 2.07 g (85%) of **2a**. ^{1}H-NMR ($CDCl_3$) δ (ppm) = 1.33 (m, 8 H, 4 CH_2), 1.45 (m, 2 H, CH_2), 1.58 (m, 4 H, 2 CH_2), 2.40 (t, *J* = 6.4 Hz, 2 H, CH_2), 3.64 (t, *J* = 5.8 Hz, 2 H, CH_2O), 7.26 (m, 3 H, 3 aromat. CH), 7.39 (m, 2 H, 2 aromat. CH). ^{13}C-NMR ($CDCl_3$) δ (ppm) = 19.41 (CH_2), 25.73 (CH_2), 28.75 (CH_2), 28.89 (CH_2), 29.08 (CH_2), 29.38 (CH_2), 29.48 (CH_2), 32.82 (CH_2), 63.08 (CH_2O), 80.60 (quart. C), 90.44 (quart. C), 124.12 (quart. C), 127.46 (aromat. CH), 128.18 (2 aromat. CH), 131.55 (2 aromat. CH). MS (CI): m/z (%) = 245 [M^++1] (10), 227 (46), 171 (50), 157 (100), 117 (98). HR-MS: Calcd.: 244.1827, Found: 244.1813.

11-(1H-Indol-5-yl)-undec-10-yn-1-ol ***2b***

CuI (100 mg; 0.5 mmol) were dissolved in 50 mL dry EDMA, 1.7 g (11.0 mmol) undec-10-yn-1-ol, 160 mg (0.2 mmol) $PdCl_2(PPh_3)_2$ and 2.34 g (10.0 mmol) 5-iodoindole were added. The mixture was stirred for 24 h under N_2 atmosphere. The solvent was evaporated and the residue dissolved in 50 mL 5% aqueous $Na_2S_2O_3$ solution, extracted with diethyl ether (3 × 50 mL) and the combined organic layers were dried over Na_2SO_4. The organic solvent was evaporated and the residue purified by FCC (*n*-hexane, ethyl acetate, EDMA; 5 : 3 : 1) to give 2.26 g (80%) of **2b**. ^{1}H-NMR ($CDCl_3$) δ (ppm) = 1.33 (m, 8 H, 4 CH_2), 1.47 (m, 2 H, CH_2), 1.58 (m, 4 H, 2 CH_2), 2.42 (t, *J* = 6.2 Hz, 2 H, 8-H), 3.63 (t, *J* = 7.6 Hz, 2 H, 1-H), 6.50 (m, 1 H, aromat. CH), 7.24 (m, 3 H, 3 aromat. CH), 7.72 (s, 1 H, aromat. CH), 8.25 (s, 1 H, NH). ^{13}C-NMR ($CDCl_3$) δ (ppm) = 19.47 (CH_2), 25.72 (CH_2), 28.91 (CH_2), 28.95 (CH_2), 29.10 (CH_2), 29.38 (CH_2), 29.49 (CH_2), 32.80 (CH_2), 63.10 (CH_2O), 81.71 (quart. C), 87.54 (quart. C), 102.64 (aromat. CH), 110.91 (aromat. CH), 115.20 (quart. C), 124.26 (aromat. CH), 124.85 (aromat. CH), 125.65 (aromat. CH), 127.72 (quart. C), 135.04 (quart. C). MS (EI): m/z (%) = 283 [M^+] (55), 197 (45), 168 (60), 156 (100). MS (CI): m/z (%) = 284 [M^++1] (90), 156 (70), 130 (100). HR-MS: Calcd.: 283.1936, Found: 283.1900.

11-Phenyl-undecan-1-ol ***3a***

Compound **2a** (500 mg; 2.0 mmol) were dissolved in 50 mL methanol and 100 mg Pd/C (10%) were added. The mixture was stirred under an H_2 atmosphere for 5 h. The catalyst was filtered off and the solvent was evaporated. The residue was purified by FCC (*n*-hexane, ethyl acetate, EDMA; 5 : 1 : 1) to give 470 mg (95%) of **3a**. ^{1}H-NMR ($CDCl_3$) δ (ppm) = 1.27 (m, 14 H, 7 CH_2), 1.58 (m, 4 H, 2 CH_2), 2.60 (t, *J* = 7.8 Hz, 2 H, CH_2), 3.64 (t, *J* = 6.3 Hz, CH_2), 7.22 (m, 5 H, aromat. CH). ^{13}C-NMR ($CDCl_3$) δ (ppm) = 25.74 (CH_2), 29.33 (CH_2), 29.42 (CH_2), 29.50 (CH_2), 29.56 (CH_2), 29.57 (CH_2), 29.59 (CH_2), 31.52 (CH_2), 32.82 (CH_2), 35.99 (CH_2), 63.11 (CH_2O), 125.54 (quart. C), 128.21 (2 aromat. CH), 128.40 (2 aromat. CH). MS (EI): m/z (%) = 248 [M^+] (6), 230 (6), 104 (100), 91 (99). HR-MS: Calcd.: 248.2140, Found: 248.2138.

11-(1H-Indol-5-yl)-undecan-1-ol ***3b***

Compound **3a** (500 mg; 1.76 mmol) were dissolved in 50 mL methanol and 100 mg Pd/C (10%) were added. The mixture was stirred under an H_2 atmosphere for 5 h. The catalyst was filtered off and the solvent was evaporated. The residue was purified by FCC (*n*-hexane, ethyl acetate, EDMA; 5 : 1 : 1) to give 450 mg (89%) of **3b**. ^{1}H-NMR ($CDCl_3$) δ (ppm) = 1.30 (m, 2 H, CH_2), 1.56 (m, 4 H, 2 CH_2), 1.65 (m, 2 H, CH_2), 2.69 (t, *J* = 8.0 Hz, 2 H, CH_2), 3.63 (t, *J* = 6.1 Hz, 2 H, CH_2O), 6.49 (m, 1 H, aromat. CH), 7.03 (dd, *J* = 1.4 Hz, *J* = 8.3 Hz, 1 H, aromat. CH), 7.17 (dd, *J* = 2.7 Hz, *J* = 2.7 Hz, 1 H, aromat. CH), 7.30 (d, *J* = 8.3 Hz, 1 H, aromat. CH), 7.43 (s, 1 H, aromat. CH), 8.10 (s, 1 H, NH). ^{13}C-NMR ($CDCl_3$) δ (ppm) = 25.73 (CH_2), 29.37 (CH_2), 29.42 (2 CH_2), 29.58 (3 CH_2), 32.31 (CH_2), 32.82 (CH_2), 36.07 (CH_2), 63.12 (CH_2O), 102.23 (aromat. CH), 110.63 (aromat. CH), 119.75 (aromat. CH), 123.07 (aromat. CH), 124.16 (aromat. CH), 128.03 (quart. C), 134.28 (quart. C), 134.35 (quart. C). MS (CI): m/z (%) = 288 [M^++1] (100), 130 (42). HR-MS: Calcd.: 287.2249, Found: 287.2268.

Undec-10-ynoic acid isopropylamide ***5a***

Undec-10-ynoic acid (500 mg; 2.7 mmol) were dissolved in 20 mL toluene and 5 mL $C_2O_2Cl_2$ were added. The solution was refluxed for 2 h, then the solvent was evaporated and the residue dissolved in 15 mL toluene. 300 mg (5.0 mmol) isopropyl amine and 5 mL EDMA were added and the mixture was stirred for 2 h. The solvent was evaporated and the residue dissolved in 20 mL 10% aqueous HCl. The suspension was extracted with diethyl ether (3 × 20 mL), the combined organic layers were dried over Na_2SO_4, solvent was evaporated and the residue was purified by FCC (*n*-hexane, ethyl acetate, EDMA; 5 : 2 : 1) to give 512 mg (85%) of **5a**. ^{1}H-NMR ($CDCl_3$) δ (ppm) = 1.13 (d, *J* = 6.7 Hz, 6 H, 2 CH_3), 1.30 (m, 8 H, 4 CH_2), 1.56 (m, 4 H, 2 × CH_2), 1.93 (t, *J* = 2.7 Hz, 1 H, CH), 2.11 (t, *J* =7.4 Hz, 2 H, CH_2), 2.18 (dt, *J* = 2.7 Hz, *J* = 7.0 Hz, 2 H, CH_2), 4.09 (h, *J* = 6.7 Hz, 1 H, CH), 5.19 (s, 1 H, NH). ^{13}C-NMR ($CDCl_3$) δ (ppm) = 18.37 (CH_2), 22.87 (2 × CH_3), 25.74 (CH_2), 28.41 (CH_2), 28.65 (CH_2), 28.91 (CH_2), 29.18 (CH_2), 29.69 (CH_2), 37.03 (CH_2), 41.18 (CH), 77.20 (CH), 84.73 (quart. C), 172.15 (CO). MS (CI): m/z (%) = 224 [M^++1] (100). HR-MS: Calcd.: 223.1936, Found: 223.1980.

Undec-10-ynoic acid tert.–butylamide ***5b***

The compound was prepared as described for **5a** from 600 mg (3.3 mmol) undec-10-ynoic acid and 500 mg (6.8 mmol) *tert.* butyl amine to give 710 mg (91%) of **5b**. ^{1}H-NMR ($CDCl_3$) δ (ppm) = 1.28 (m, 6 H, 3 CH_2), 1.33 (s, 9 H, 3 CH_3), 1.37 (m, 2 H, CH_2), 1.50 (m, 2 H, CH_2), 1.58 (m, 2 H, CH_2), 1.92 (t, *J* = 2.8 Hz, 1 H, CH), 2.08 (t, *J* = 7.9 Hz, 2 H, CH_2), 2.16 (dt, *J* = 2.8 Hz, *J* = 7.5 Hz, 2 H, CH_2), 5.34 (s, 1 H, NH). ^{13}C-NMR ($CDCl_3$) δ (ppm) = 18.34 (CH_2), 25.74 (CH_2), 28.40 (CH_2), 28.65 (CH_2), 28.81 (3 CH_3), 28.90 (CH_2), 29.11 (CH_2), 29.19 (CH_2), 37.64 (CH_2), 51.12 (quart. C), 68.00 (quart. C), 84.66 (CH), 172.64 (CO). MS (CI): m/z (%) = 238 [M^++1] (100). HR-MS: Calcd.: 237.2093, Found: 237.2077.

Undec-10-ynoic acid benzylamide ***5c***

The compound was prepared as described for **5a** from 1.4 g (7.0 mmol) undec-10-ynoic acid and 1.5 g (14.0 mmol) benzyl amine to give 1.69 g (89%) of **5c** as a white solid. ^{1}H-NMR ($CDCl_3$) δ (ppm) = 1.30 (m, 6 H, 3 CH_2), 1.37 (m, 2 H, CH_2), 1.51 (m, 2 H, CH_2), 1.65 (m, 2 H, CH_2), 1.94 (t, *J* = 2.8 Hz, 1 H, 11-H), 2.18 (dt, *J* = 2.8 Hz, *J* = 7.1 Hz, 2 H, 9-H), 2.24 (t, *J* = 7.6 Hz, 2 H, 2-H), 4.45 (d, *J* = 5.6 Hz, 2 H, CH_2), 6.16 (s, 1 H, NH), 7.30 (m, 5 H, 5 aromat. CH). ^{13}C-NMR ($CDCl_3$) δ (ppm) = 17.24 (CH_2), 24.66 (CH_2), 27.29 (CH_2), 25.51 (CH_2), 27.78 (CH_2), 28.03 (CH_2), 28.07 (CH_2), 35.38 (CH_2), 42.60 (CH_2), 68.09 (CH), 84.68 (quart. C), 127.55 (aromat. CH), 127.82 (2 aromat. CH), 128.70 (2 aromat. CH), 138.10 (quart. C), 173.39 (CO). MS (CI): m/z (%) = 272 [M^++1] (100). HR-MS: Calcd.: 271.1936, Found: 271.1982.

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Undec-10-ynoic acid (1-phenylethyl)amide ***5d***

The compound was prepared as described for **5a** from 500 mg (2.7 mmol) undec-10-ynoic acid and 653 mg (5.4 mmol) 1-phenylethyl amine to give 620 mg (80%) of **5d**. ^{1}H-NMR ($CDCl_3$) δ (ppm) = 1.28 (m, 6 H, 3 CH_2), 1.36 (m, 2 H, CH_2), 1.48 (d, *J* = 7.0 Hz, 3 H, CH_3), 1.50 (m, 2 H, CH_2), 1.62 (m, 2 H, CH_2), 1.92 (t, *J* = 2.3 Hz, 1 H, CH), 2.16 (m, 4 H, 2 CH_2), 5.14 (q, *J* = 7.0 Hz, 1 H, CH), 5.69 (s, 1 H, NH). ^{13}C-NMR ($CDCl_3$) δ (ppm) = 18.35 (CH_2), 21.67 (CH_3), 25.68 (CH_2), 28.40 (CH_2), 28.63 (CH_2), 28.90 (CH_2), 29.16 (2 CH_2), 36.83 (CH_2), 48.56 (CH), 68.08 (quart. C), 84.66 (CH), 126.16 (2 aromat. CH), 127.33 (aromat. CH), 128.64 (2 aromat. CH), 143.21 (quart. C), 172.09 (CO). MS (CI): m/z (%) = 286 [M^++1] (100). HR-MS: Calcd.: 285.2093, Found: 285.2054.

1-Morpholin-4-yl-undec-10-yn-1-one ***5e***

The compound was prepared as described for **5a** from 2.15 g (11.7 mmol) undec-10-ynoic acid and 2.03 g (23.4 mmol) morpholine to give 2.94 g (100%) of **5e** as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ (ppm) = 1.32 (m, 8 H, 4 CH_2), 1.52 (tt, *J* = 7.0 Hz, *J* = 7.0 Hz, 2 H, CH_2), 1.63 (m, 2 H, CH_2), 1.94 (dt, *J* = 0.7 Hz, *J* = 2.6 Hz, 1 H, CH), 2.18 (ddt, *J* = 0.6 Hz, *J* = 2.6 Hz, *J* = 7.0 Hz, 2 H, CH_2), 2.31 (t, *J* = 8.1 Hz, 2 H, CH_2), 3.46 (t, *J* = 5.3 Hz, 2 H, CH_2), 3.62 (t, *J* = 5.1 Hz, CH_2), 3.67 (t, *J* = 5.3 Hz, 4 H, 2 CH_2). ^{13}C-NMR ($CDCl_3$) δ (ppm) = 18.38 (CH_2), 25.21 (CH_2), 28.43 (CH_2), 28.67 (CH_2), 28.94 (CH_2), 29.27 (CH_2), 29.40 (CH_2), 33.10 (CH_2), 41.86 (CH_2), 46.04 (CH_2), 66.70 (CH_2), 66.97 (CH_2), 68.11 (CH), 84.73 (quart. C), 171.83 (CO). MS (CI): m/z (%) = 252 [M^++1] (100), 129 (14). HR-MS: Calcd.: 251.1885, Found: 251.1921.

11-(1H-Indol-5-yl)-undec-10-ynoic acid (1-phenylethyl)amide ***6a***

100 mg (0.5 mmol) CuI were dissolved in 50 mL dry EDMA, 1.7 g (11.0 mmol) of **5d**, 160 mg (0.2 mmol) $PdCl_2(PPh_3)_2$ and 2.05 g (10.0 mmol) 5-iodoindole were added. The mixture was stirred for 24 h under N_2 atmosphere. The solvent was evaporated and the residue dissolved in 50 mL of 5% aqueous $Na_2S_2O_3$ solution, extracted with diethyl ether (3 × 50 mL) and the combined organic layers were dried over Na_2SO_4. The organic solvent was evaporated and the residue purified by FCC (*n*-hexane, ethyl acetate, EDMA; 20 : 3 : 1) to give 3.5 g (87%) of **6a**. ^{1}H-NMR ($CDCl_3$) δ (ppm) = 1.32 (m, 8 H, 4 CH_2), 1.47 (d, *J* = 7.7 Hz, 3 H, CH_3), 1.61 (m, 2 H, CH_2), 2.16 (t, *J* = 7.7 Hz, 2 H, CH_2), 2.41 (t, *J* = 7.1 Hz, 2 H, CH_2), 5.14 (m, 1 H, CH), 5.65 (s, 1 H, NH), 6.49 (m, 1 H, aromat. CH), 7.18 (dd, *J* = 2.5 Hz, *J* = 2.5 Hz, 1 H, aromat. CH), 7.22 (dd, *J* = 1.5 Hz, *J* = 8.6 Hz, 1 H, aromat. CH), 7.30 (m, 6 H, 6 aromat. CH), 7.71 (s, 1 H, aromat. CH), 8.37 (s, 1 H, NH). ^{13}C-NMR ($CDCl_3$) δ (ppm) = 19.42 (CH_2), 21.68 (CH_3), 25.71 (CH_2), 28.79 (CH_2), 28.89 (CH_2), 28.96 (CH_2), 29.17 (CH_2), 48.54 (CH), 81.75 (quart. C), 87.44 (quart. C), 102.58 (aromat. CH), 110.92 (aromat. CH), 115.16 (quart. C), 124.23 (aromat. CH), 124.85 (aromat. CH), 125.60 (aromat. CH), 126.15 (2 aromat. CH), 127.31 (aromat. CH), 127.71 (quart. C), 128.64 (aromat. CH), 135.06 (quart. C), 143.27 (quart. C), 172.16 (CO). MS (CI): m/z (%) = 401 [M^++1] (80), 284 (50), 169 (100). HR-MS: Calcd.: 400.2515, Found: 400.2533.

11-(1H-Indol-5-yl)-undec-10-ynoic acid tert. butylamide ***6b***

The compound was prepared as described for **6a** from 500 mg (2.1 mmol) **5b** and 510 mg (2.1 mmol) 5-iodoindole to give 590 mg (80%) of **6b**. ^{1}H-NMR ($CDCl_3$) δ (ppm) = 1.27 (m, 8 H, 4 CH_2), 1.34 (s, 9 H, 3 CH_3), 1.46 (m, 2 H, CH_2), 1.61 (m, 2 H, CH_2), 2.08 (t, *J* = 7.4 Hz, 2 H, CH_2), 2.41 (t, *J* = 7.5 Hz, 2 H, CH_2), 5.22 (s, 1H, NH), 6.50 (m, 1 H, aromat. CH), 7.22 (m, 2 H, 2 aromat. CH), 7.30 (ddd, *J* = 0.6 Hz, *J* = 0.6 Hz, *J* = 8.3 Hz, 1 H, aromat. CH), 7.72 (m, 1 H, aromat. CH), 8.28 (s, 1 H, NH). ^{13}C-NMR ($CDCl_3$) δ (ppm) = 19.47 (CH_2), 25.79 (CH_2), 28.85 (3 CH_3), 28.88 (CH_2), 28.94 (CH_2), 29.04 (CH_2), 29.18 (CH_2), 29.27 (CH_2), 37.77 (CH_2), 51.06 (quart. C), 81.72 (quart. C), 87.49 (quart. C), 102.65 (C-3`), 110.92 (C-7`), 115.21 (quart. C), 124.27 (aromat. CH), 124.99 (aromat. CH), 125.65 (aromat. CH), 127.73 (quart. C), 135.06 (quart. C), 172.58 (CO). MS (CI): m/z (%) = 353 [M^++1] (100), 236 (55), 130 (50). HR-MS: Calcd.: 352.2515, Found: 352.2476.

11-(Pyridin-3-yl)-undec-10-ynoic acid benzylamide ***6c***

The compound was prepared as described for **6a** from 400 mg (2.0 mmol) 3-iodopyridine and 500 mg (1.95 mmol) **5c** to give 476 mg (75%) of **6c**. ^{1}H-NMR ($CDCl_3$) δ (ppm) = 1.33 (m, 6 H, 3 CH_2), 1.44 (m, 2 H, CH_2), 1.61 (m, 2 H, CH_2), 1.66 (m, 2 H, CH_2), 2.22 (t, *J* = 7.9 Hz, 2 H, CH_2), 2.42 (t, *J* = 7.5 Hz, 2 H, CH_2), 4.45 (d, *J* = 5.9 Hz, 2 H, CH_2), 5.83 (s, 1 H, NH), 7.21 (dd, *J* = 5.0 Hz, *J* = 7.9 Hz, 1 H, aromat. CH), 7.28 (m, 3 H, 3 aromat. CH), 7.34 (m, 2 H, 2 aromat. CH), 7.67 (ddd, *J* = 7.7 Hz, *J* = 1.7 Hz, *J* = 1.7 Hz, 1 H, aromat. CH), 8.47 (s, 1 H, aromat. CH), 8.63 (s, 1 H, aromat. CH). ^{13}C-NMR ($CDCl_3$) δ (ppm) = 19.41 (CH_2), 25.73 (CH_2), 28.47 (CH_2), 28.79 (CH_2), 28.93 (CH_2), 29.19 (CH_2), 29.25 (CH_2), 36.78 (CH_2), 43.58 (CH_2), 77.42 (quart. C), 94.09 (quart. C), 126.00 (quart. C), 127.48 (aromat. CH), 127.83 (2 aromat. CH), 128.69 (2 aromat. CH), 138.38 (aromat. CH), 138.43 (quart. C), 147.86 (aromat. CH), 152.33 (aromat. CH), 172.89 (CO).

11-(Pyridin-3-yl)-undec-10-ynoic acid isopropylamide ***6d***

The compound was prepared as described for **6a** from 1.0 g (4.9 mmol) 3-iodopyridine and 510 mg (2.3 mmol) of **5a** to give 460 mg (67%) of **6d** as a brown solid. ^{1}H-NMR ($CDCl_3$) δ (ppm) = 1.14 (d, *J* = 6.8 Hz, 6 H, 2 CH_3), 1.34 (m, 6 H, 3 CH_2), 1.44 (m, 2 H, CH_2), 1.61 (m, 4 H, 2 CH_2), 2.12 (t, *J* = 7.9 Hz, 2 H, CH_2), 2.42 (t, *J* = 7.2 Hz, 2 H, CH_2), 4.08 (h, *J* = 6.8 Hz, 1 H, CH), 5.29 (s, 1 H, NH), 7.21 (dd, *J* = 4.8 Hz, *J* = 7.8 Hz, 1 H, aromat. CH), 7.67 (ddd, *J* = 1.8 Hz, *J* = 1.8 Hz, *J* = 7.8 Hz, 1 H, aromat. CH), 8.48 (d, *J* = 4.3 Hz, 1 H, aromat. CH), 8.63 (s, 1 H, aromat. CH). ^{13}C-NMR ($CDCl_3$) δ (ppm) = 19.39 (CH_2), 22.84 (2 CH_3), 25.75 (CH_2), 28.23 (CH_2), 28.26 (CH_2), 28.56 (CH_2), 28.97 (CH_2), 32.85 (CH_2), 36.78 (CH_2), 40.92 (CH), 77.00 (quart. C), 94.06 (quart. C), 122.87 (aromat. CH), 128.00 (quart. C), 138.37 (aromat. CH), 147.86 (aromat. CH), 152.32 (aromat. CH), 172.10 (CO). MS (EI): m/z (%) = 300 [M^+] (10), 242 (40), 200 (40), 172 (42), 130 (100). HR-MS: Calcd.: 300.2202, Found: 300.2171.

1-Morpholin-4-yl-11-(pyridin-3-yl)-undec-10-yn-1-one ***6e***

The compound was prepared as described for **6a** from 3.27 g (16 mmol) 3 iodopyridine and 2.45 g (9.8 mmol) of **5a** to give 2.38 g (74%) of **6d** as a brown oil. ^{1}H-NMR ($CDCl_3$) δ (ppm) = 1.35 (m, 6 H, 3 CH_2), 1.44 (m, 2 H, CH_2), 1.62 (m, 4 H, 2 CH_2), 2.31 (t, *J* = 7.8 Hz, 2 H, CH_2), 2.42 (t, *J* = 6.8 Hz, 2 H, CH_2), 3.46 (t, *J* = 3.9 Hz, 2 H, CH_2), 3.61 (t, *J* = 4.5 Hz, 2 H, CH_2), 3.66 (t, *J* = 3.9 Hz, 2 H, CH_2), 3.68 (t, *J* = 4.5 Hz, 2 H, CH_2), 7.21 (dd, *J* = 5.0 Hz, *J* = 7.9 Hz, 1 H, aromat. CH), 7.67 (ddd, J = 7.9 Hz, *J* = 1.6 Hz, *J* = 1.6 Hz, 1 H, aromat. CH), 8.48 (dd, *J* = 1.6 Hz, *J* = 5.0 Hz, 1 H, aromat. CH), 8.63 (d, *J* = 1.2 Hz, 1 H, aromat. CH). ^{13}C-NMR ($CDCl_3$) δ (ppm) = 19.40 (CH_2), 25.17 (CH_2), 28.48 (CH_2), 28.76 (CH_2), 28.82 (CH_2), 29.20 (CH_2), 29.27 (CH_2), 33.06 (CH_2), 41.85 (CH_2), 46.02 (CH_2), 66.69 (CH_2), 66.95 (CH_2), 77.00 (quart. C), 94.04 (quart. C), 121.16 (quart. C),

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122.85 (aromat. CH), 138.37 (aromat. CH), 147.89 (aromat. CH), 152.35 (aromat. CH), 171.77 (CO). MS (CI): m/z (%) = 329 [M^++1] (100), 130 (10). HR-MS: Calcd.: 328.2151, Found: 328.2172.

*11-(Phenyl)-undec-10-ynoic acid benzylamide **6f***

The compound was prepared as described for **6a** from 2.0 g (2.0 mmol) iodobenzene and 1.3 g (4.8 mmol) **5c** to give 0.51 g (30%) of **6f**. ^{1}H-NMR ($CDCl_3$) δ (ppm) = 1.33 (m, 8 H, 4 CH_2), 1.44 (m, 2 H, CH_2), 1.59 (m, 2 H, CH_2), 1.66 (m, 2 H, CH_2), 2.21 (t, *J* = 7.4 Hz, 2 H, CH_2), 2.39 (t, *J* = 7.1 Hz, 2 H, CH_2), 4.44 (d, *J* = 5.4 Hz, 2 H, CH_2), 5.72 (s, 1 H, NH), 7.30 (m, 10 H, 10 aromat. CH). ^{13}C-NMR ($CDCl_3$) δ (ppm) = 19.38 (CH_2), 25.73 (CH_2), 28.68 (CH_2), 28.81 (CH_2), 28.97 (CH_2), 29.21 (CH_2), 29.25 (CH_2), 36.80 (CH_2), 43.58 (CH_2), 80.57 (quart. C), 90.40 (quart. C), 124.03 (quart. C), 127.52 (aromat. CH), 127.84 (2 aromat. CH), 128.18 (2 aromat. CH), 128.71 (aromat. CH), 130.25 (2 aromat. CH), 131.54 (2 aromat. CH), 137.46 (quart. C), 172.94 (CO). MS (CI): m/z (%) = 348 [M^++1] (100). HR-MS: Calcd.: 347.2249, Found: 347.2297.

*Benzyl-((E)-11-pyridin-3-yl-undec-10-enyl)-amine **7a***

Compound **6c** (180 mg; 0.6 mmol) of were dissolved in 25 mL dry THF and 180 mg (4.7 mmol) $LiAlH_4$ were added. The suspension was refluxed for 2 h, quenched with 20 mL 10% aqueous NaOH and extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, the solvent was evaporated and the residue was purified by FCC (*n*-hexane, ethyl acetate, EDMA; 2 : 3 : 1) to give 120 mg (60%) of **7** as a colourless oil. ^{1}H-NMR ($CDCl_3$) δ (ppm) = 1.28 (m, H_2, CH_2), 1.46 (m, H_2, CH_2), 2.29 (m, 2 H, CH_2), 2.62 (m, 4 H, CH_2), 3.78 (s, 2 H, CH_2), 5.79 (ddd, *J* = 7.2 Hz, *J* = 7.2 Hz, *J* = 12.0 Hz, 1 H, CH), 6.35 (d, *J* = 12.0 Hz, 1 H, CH), 7.24 (m, 1 H, aromat. CH), 7.32 (m, 5 H, 5 aromat. CH), 7.56 (ddd, *J* = 7.2 Hz, *J* = 1.7 Hz, *J* = 1.7 Hz, 1 H, aromat. CH), 8.45 (dd, *J* = 1.7 Hz, *J* = 4.9 Hz, 1 H, aromat. CH), 8.53 (d, *J* = 1.7 Hz, 1 H, aromat. CH). ^{13}C-NMR ($CDCl_3$) δ (ppm) = 25.80 (CH_2), 27.32 (CH_2), 27.86 (2 CH_2), 27.99 (2 CH_2), 28.57 (2 CH_2), 47.99 (CH_2), 52.58 (CH_2), 123.03 (aromat. CH), 125.11 (aromat. CH), 126.85 (aromat. CH), 128.10 (2 aromat. CH), 128.36 (2 aromat. CH), 133.39 (quart. C), 135.65 (aromat. CH), 140.61 (quart. C), 147.47 (aromat. CH), 149.92 (aromat. CH). MS (CI): m/z (%) = 337 [M^++1] (100), 245 (12). HR-MS: Calcd.: 336.2566, Found: 336.2558.

*4-((E)-11-Pyridin-3-yl-undec-10-enyl)-morpholine **7b***

The compound was prepared as described for **7a** from 500 mg of **6e** and 400 mg $LiAlH_4$ to give 250 mg of **7b**. It was not possible to separate the compound from *trans*- and alkine by-product.

*Benzyl-((E)-11-pyridin-3-yl-undec-10-enoic)–amide **8***

Yield: 30 mg were obtained as by-product by the synthesis of **7**. ^{1}H-NMR ($CDCl_3$) δ (ppm) = 1.28 (m, 8 H, 4 CH_2), 1.43 (m, 2 H, CH_2), 1.63 (m, 2 H, CH_2), 2.23 (m, 4 H, 2 CH_2), 4.43 (d, *J* = 5.5 Hz, 2 H, CH_2O), 5.79 (ddd, *J* = 12.2 Hz, *J* = 8.2 Hz, *J* = 8.2 Hz, 1 H, CH), 5.88 (s, 1H, NH), 6.34 (d, *J* = 12.2 Hz, 1 H, CH), 7.29 (m, 6 H, 6 aromat. CH), 7.55 (m, 1 H, aromat. CH), 8.41 (m, 1 H, aromat. CH), 8.52 (m, 1 H, CH). MS (CI): m/z (%) = 349 [M^++1] (100). HR-MS: Calcd.: 348.2180, Found: 348.2202.

*4-(11-Pyridin-3-yl-undecyl)-morpholine **9***

200 mg (0.6 mmol) of crude **7b** were dissolved in 20 mL methanol and 100 mg Pd/C (10%) were added. The suspension was stirred under H_2 atmosphere for 4 h. The mixture was filtered off and the solvent was evaporated to give 180 mg (84%) of **9** as a brown solid. ^{1}H-NMR ($CDCl_3$) δ (ppm) = 1.25 (m, 16 H, 8 CH_2), 1.49 (m, 4 H, 2 CH_2), 2.32 (m, 4 H, 2 CH_2), 2.60 (t, *J* = 7.2 Hz, 2 H, CH_2), 3.67 (t, *J* = 4.6 Hz, 4 H, 2 CH_2), 7.20 (dd, *J* = 4.9 Hz, *J* = 7.9 Hz, 1 H, aromat. CH), 7.49 (ddd, *J* = 1.9 Hz, *J* = 1.9 Hz, *J* = 7.9 Hz, 1 H, aromat. CH), 8.43 (m, 2 H, 2 aromat. CH). ^{13}C-NMR ($CDCl_3$) δ (ppm) = 25.21 (CH_2), 26.51 (CH_2), 27.51 (CH_2), 28.68 (CH_2), 28.95 (CH_2), 29.14 (CH_2), 29.28 (CH_2), 29.41 (CH_2), 29.56 (CH_2), 29.71 (CH_2), 31.16 (CH_2), 51.58 (CH_2), 53.77 (CH_2), 66.69 (CH_2), 66.95 (CH_2), 121.00 (quart. C), 123.23 (aromat. CH), 135.78 (aromat. CH), 147.18 (aromat. CH), 149.97 (aromat. CH). MS (CI): m/z (%) = 319 [M^++1] (100), 252 (30). HR-MS: Calcd.: 318.2671, Found: 318.2635.

*Benzyl-(11-phenyl-undec-10-ynyl)-amine **10***

Compound **6f** (200 mg; 0.6 mmol) was dissolved in 20 mL THF and 400 mg $LiAlH_4$ were added. The suspension was refluxed for 2 h, quenched with 20 mL 10% aqueous NaOH and extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, the solvent was evaporated and the residue was purified by FCC (*n*-hexane, ethyl acetate, EDMA; 2 : 3 : 1) to give 120 mg (60%) of **10** as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ (ppm) = 1.31 (m, 8 H, 4 CH_2), 1.43 (m, 2 H, CH_2), 1.50 (m, 2 H, CH_2), 1.59 (m, 2 H, CH_2), 2.39 (t, *J* = 8.0 Hz, 2 H, CH_2), 2.62 (m, 2 H, CH_2), 3.78 (s, 2 H, CH_2), 7.29 (m, 10 H, 10 aromat. CH). ^{13}C-NMR ($CDCl_3$) δ (ppm) = 19.41 (CH_2), 27.35 (CH_2), 28.75 (CH_2), 28.91 (CH_2), 29.11 (CH_2), 29.48 (CH_2), 29.53 (CH_2), 30.14 (CH_2), 49.52 (CH_2), 54.04 (CH_2), 80.56 (quart. C), 90.46 (quart. C), 124.10 (quart. C), 126.85 (aromat. CH), 127.45 (aromat. CH), 128.11 (2 aromat. CH), 128.17 (2 aromat. CH), 128.37 (2 aromat. CH), 131.53 (2 aromat. CH), 132.06 (quart. C). MS (CI): m/z (%) = 334 [M^++1] (100). HR-MS: Calcd.: 333.2456, Found: 333.2479.

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