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PAPER

An efficient approach to dispacamide A and its derivatives†

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Dispacamide A and new analogs of this marine alkaloid were prepared in seven steps with an overall yield ranging from 12 to 33%. The key step of the strategy was a stereocontrolled Knoevenagel condensation under microwave dielectric heating in the last step. In this condensation, the 2-aminoimidazolin-4-one hydrochloride partners **10a–c** were synthesized in three steps with good overall yields (33–79%) *via* the ring closure of *N*-guanidino acetic acids **9a–c** and the aldehydes **5a**,**b** as the two others building-blocks, in 3 steps with 60–66% overall yields. The six synthetic products have been obtained with a *Z* geometry about their exocyclic bond on the basis of $^{13}C/^{1}H$ long-range coupling constants using a gHSQMBC experiment.

Introduction

In recent decades, the exploration of marine natural products has been a fascinating subject of intensive researches for organic chemists, biochemists and biologists. In this context, marine sponges are undoubtedly an immense reservoir of unique, biologically active natural products to be explored. In many natural products, the 2-aminoimidazolin-4-one moiety is present and represents an attractive scaffold in the search for new drug development[1] or tools for cell biology.

Among the marine sponge alkaloids, (*Z*)-hymenialdisine[2] and debromohymenialdisine[2] (Fig. 1) were identified as inhibitors of various protein kinases.[3] (+)-Dihydrohymenialdisine[4] isolated from the New Caledonian sponge *Cymbastela cantharella* showed moderate inhibition of Polo-Like-Kinase 1 (PLK-1). Recently in our group, we reported the patented synthesis of leucettines,[5] a family of kinase inhibitors (CLKs and DYRKs) derived from the alkaloid leucettamine B, isolated in 1993 from the sponge *Leucetta hæckel* (Alcarea class) of the Argulpelu Reef in Palau[6] and initially synthesized by the Bergman's group.[7] Polyandrocarpamine A,[8] an alkaloid from a Fijian ascidian, displays selective cytotoxicity towards the SF 268 cell line (central nervous system) with a GI_{50} value of 65 μM.[9] In the marine sponge of the genus *Agelas*, dispacamides[10] A and B showed antagonist effect of a non-competitive type toward histamine receptors[11] in tests on guinea pig ileum. For the dispacamide D alkaloid, it presented moderate antiplasmodial activity[1] against *Plasmodium falciparum* (IC_{50} > 20 μM). Due to the interest of the 2-aminoimidazolin-4-one scaffold in many marine alkaloid structures associated with

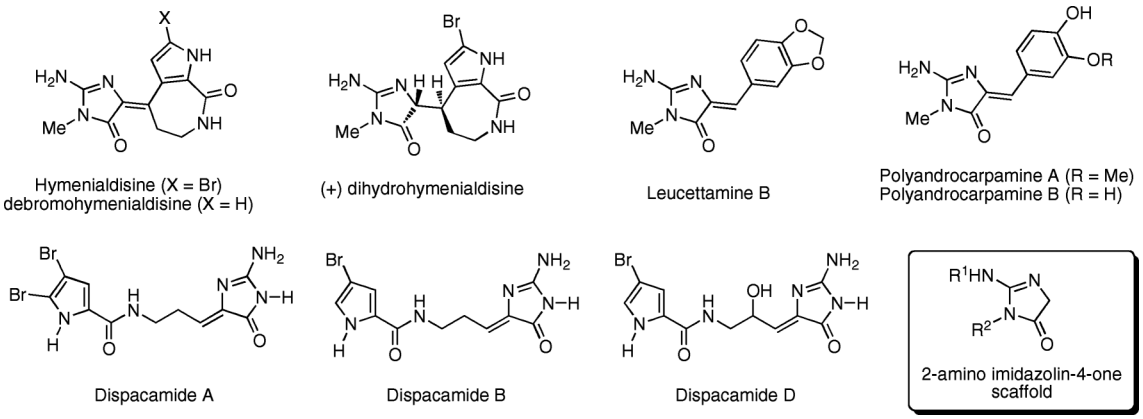

Fig. 1 Selected alkaloids from marine sponges with 2-aminoimidazolin-4-one scaffold.

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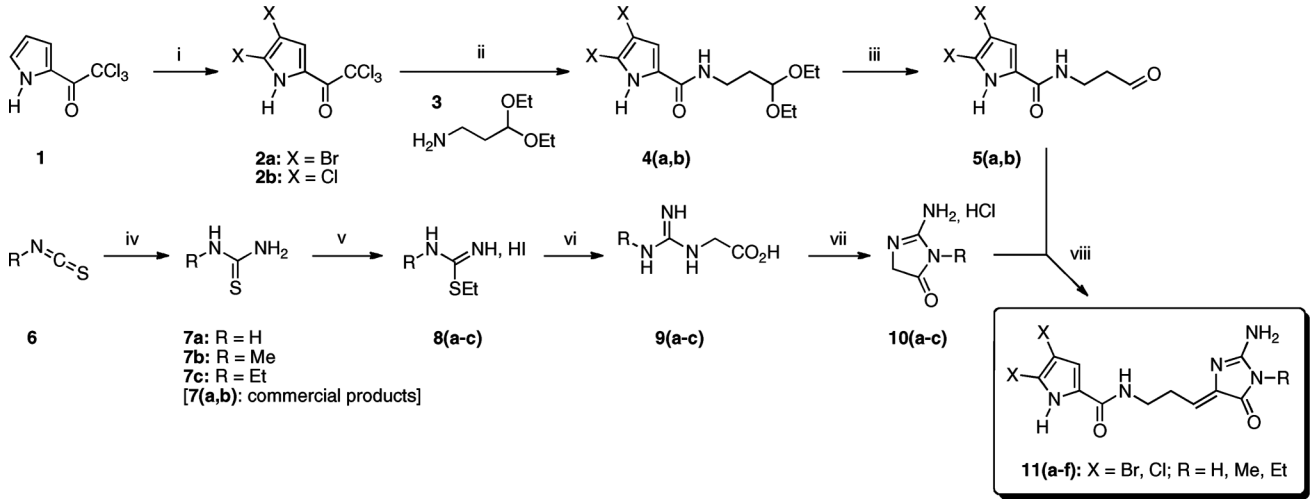


Scheme 1 *Reagent and reaction conditions*: (i) Br_2, $CHCl_3$, 0 °C, 20 h. or SO_2Cl_2, $CHCl_3$, 25 °C, 20 h. (ii) method A: **3** (1 eq.), MeCN, 23–29 h; method B: **3** (1 eq.), μω, 70 °C, 30 min. (iii) method A: Me_2CO, HCl 1 M, 8 h then sat. $NaHCO_3$; method B: *p*-$MeC_6H_5SO_3H$ (0.5 eq.), Me_2CO/H_2O (1 : 1), 50 °C, 6 h.; method C: *p*-$MeC_6H_5SO_3H$ (0.5 eq.), Me_2CO/H_2O (1 : 1), μω, 90 °C, 15 min. (iv) EtNCS **6**, EtOH, sol. 7 M NH_3/MeOH, 60 °C, 2.5 h. (v) EtI, abs. EtOH, 60 °C, 3.5 h. (vi) glycine, aq. NaOH, 25 °C, 22 h. (vii) HCl 6 M, 120 °C, 22 h. (viii) **10** (1.1 eq.), AcONa (1 eq.), AcOH (6.6 eq.), 120 °C, μω, 20 min or **10** (1.1 eq.), piperidine (1.1 eq.), EtOH, 60 °C, μω, 30 min.

potential biological activities, we have attempted to develop a novel strategy that can afford not only natural dispacamide A but also new analogs.

Considering the synthetic steps to construct the characteristic 2-aminoimidazolin-4-one moiety of these marine alkaloids, the total syntheses of dispacamide A reported thus far can be roughly divided in three categories. The first one involved the electrophilic activation of C═S bond on thiohydantoin nucleus through an oxidation of the sulphur ether using *tert*-butylhydroperoxide (TBHP) and aqueous ammonia.[12] In the second, oxidation of *N*-Boc protected 2-aminoimidazole with tetra-n-butyl ammonium tribromide or bromine in a solution of dimethylsulfoxyde afforded the 2-amino-Δ^1-imidazolin-4-one derivative in moderate yields.[13] And the third one was a cyclization strategy, which is based on the use of the potential explosive *N*-acylated α-azido-ω-aminovalerate intermediate.[14] In these approaches, the construction of the 2-aminoimidazolin-4-one moiety is usually attempted at the later synthetic stages. In this context, our aim in this study was to develop a convenient, robust and high yielding reaction protocol for the preparation of new derivatives of dispacamide A.

The planned retrosynthesis of dispacamide A derivatives is based around the key aldol condensation between a *N*-(4,5-dihalogenopyrrol-2-yl)carbamoyl aldehyde and the 2-aminoimidazolin-4-one (Fig. 2). The 2-aminoimidazolin-4-one partner can be built from *N*-alkyl guanidino acetic acid, which is available from glycine and monosubstituted thiourea. This convergent route was envisaged to be highly amenable to the design of analogues for eventual screening as kinase inhibitors.

Results and discussion

The overall strategy for the target dispacamide A derivatives is outlined in Scheme 1. Our first task was to accomplish a reliable synthesis of aliphatic aldehyde **5** bearing a (4,5-dihalogenopyrrol-2-yl)carbamoyl fragment. Starting from 2-trichloroacetyl pyrrole[15] **1**, a regioselective bromination was conducted in solution by slow addition of bromine[16] (2 equiv.). After 20 h, thin layer chromatography indicated consumption of the starting material **1** and a single pure product **2a** was obtained in 70% yield after concentration of the solvent and recrystallization from a mixture of ethanol/water (1 : 1 v/v). The dichloro derivative **2b** was then targeted by reacting the 2-trichloro acetyl pyrrole **1** with two equivalents of sulfuryl chloride[17] to give the C-4, C-5 dichloro compound **2b** in good yield (90%). With multigram quantities of 4,5-dihalogenopyrroles **2a**,**b**, their conversion into the desired protected aldehydes **4a**,**b** was investigated.

Two experimental protocols were examined for the preparation of the *N*-(4,5-dibromopyrrol-2-yl)carbamoyl acetal **4a** (details of the two methods are presented in the experimental section). In the first (method A), the 2-trichloroacetyl-(4,5-dibromopyrrole)

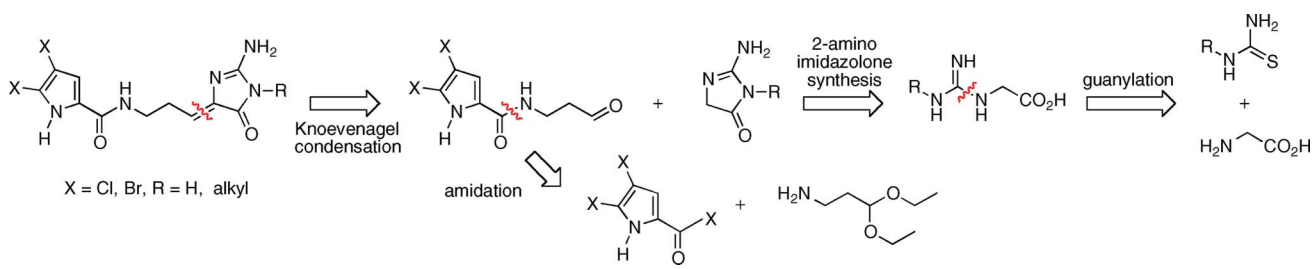


Fig. 2 Retrosynthetic strategy towards new dispacamide A derivatives.

Table 1 Results for the preparation of aldehydes **5a**,**b** from precursors **2a**,**b** and **4a**,**b**

Product	X	Yield[a] (%)	Overall yield[b] (%)
2a	Br	70	—
2b	Cl	90	—
4a	Br	88[c]	—
4b	Cl	75	—
5a	Br	98[d]	60
5b	Cl	98[e]	66

[a] Isolated yield. [b] Overall yield calculated from **2**. [c] Yield obtained with method A at room temperature (method B: 87% yield under μω). [d] Yield obtained with methods B or C (method A: 93% yield under reflux). [e] Yield obtained with method B (method C: 95% yield under μω).

2a was coupled[18] with commercial 3,3-diethoxy-1-aminopropane **3** in acetonitrile at room temperature. After 23 h, the desired insoluble *N*-(4,5-dibromopyrrol-2-yl)carbamoyl acetal **4a** was easily collected by filtration in 88% yield (Table 1). For the second method (B), we thus decided to examine the preparation of compound **4a** under microwave (μω) because microwave-assisted organic synthesis[19] (MAOS) has been demonstrated to dramatically reduce reaction times and affect product ratios and yields. Reaction optimization for the synthesis of **4a** consisted of varying the reaction temperature, the power and the ratio of **2a** and **3** under microwave. The experiments revealed that the optimal reaction conditions were obtained after 30 min with a stoichiometric mixture of **2a** and **3** in a closed reactor to produce product **4a** in 87% yield under microwave irradiation at 70 °C. In the same manner, the *N*-(4,5-dichloropyrrol-2-yl)carbamoyl acetal **4b** was directly prepared according to the method (A) in 75% yield after purification by preparative chromatography (Combi Flash R_f apparatus from Serlabo Technologies, France) on silica gel using a stepwise gradient from 0 to 50% of CH_2Cl_2/AcOEt as mobile phase.

The transformation of the acetal moiety of compounds **4a**,**b** into the corresponding *N*-(4,5-dihalogenopyrrol-2-yl)carbamoyl aldehydes **5a**,**b** was carried out under different acidic conditions. All the common methods are based on acidic hydrolysis conditions: AcOH in water,[20] $HCl_{aq.}$ in dioxane[21] or in a mixture of acetone/THF,[22] or *p*TsOH in acetone/water.[23] This implies that specific tedious synthetic protocol has to be devised for each new compound.[24] From Table 2, it can be observed that the optimal reaction conditions for the *N*-(4,5-dibromopyrrol-2-yl)carbamoyl aldehyde **5a** were obtained with a solution of 1 M HCl in acetone at 50 °C after a reaction time of 8 h (entry 5: 93% yield for method A) or, with *p*TsOH (0.5 equiv.) in a solution of acetone/water at 55 °C after 6 h (entry 6: 98% yield for method B), or under microwave irradiation with *p*TsOH (0.5 equiv.) in a closed reactor at 90 °C after a short reaction time of 15 min to produce the desired dibromoaldehyde **5a** also in good yield (entry 7: 93% yield for method C). The versatility of these protocols for deprotection were also demonstrated for the preparation of *N*-(4,5-dichloropyrrol-2-yl)carbamoyl aldehyde **5b**. Compound **4b** was deprotected at 50 °C albeit requiring 14 h of reaction time in oil bath, to give the desired aldehyde **5b** in nearly quantitative yield (98%) according to method B and under microwave irradiation using the same reaction conditions of method C (90 °C, 15 min), **5b** was obtained with an isolated yield of 95%. The structure of the *N*-(4,5-dihalogenopyrrol-2-yl)carbamoyl aldehyde **5a**,**b** was ascertained by high resolution mass-spectrometry, proton and carbon NMR confirming that the compound is the expected aldehyde.

Next, the second part of the synthesis concerns the construction of the 2-aminoimidazolin-4-one moiety. Attention was turned towards the choice of an appropriate approach for the preparation of the 2-aminoimidazolin-4-one partner **10**. Synthetic approaches described in the literature involve: (i) the sulphur/nitrogen displacement of the SMe group of an imidazolin-4-one structure with aqueous ammonia using an oxidative procedure[7] (*tert*-butylhydroperoxide was used in this method), or (ii) reaction of glycine with *S*-ethylisothiouronium halide to produce the corresponding glycoamidine,[25] or (iii) the cleavage of the 1-5-bond of 2-oxazolin-5-one by appropriate primary amines[26] and its applications is important in the synthesis of dehydropeptides. In order to find a straightforward synthesis of the 2-aminoimidazolin-4-one partner, it was pertinent to evaluate the accessibility of this scaffold *via* the ring closure of *N*-substituted guanidine acetic acid **9a–c** for introduction of diversity in position N-3 of **10**.

Starting from commercial thiourea **7a** (R = H), *N*-methyl thiourea **7b** (R = Me) and *N*-ethyl thiourea **7c** (R = Et, readily available by addition[27] of a commercial methanolic solution of 7 M ammonia on ethyl isothiocyanate **6**, yield = 98%), they underwent facile *S*-alkylation[28] with iodoethane in absolute ethanol to give the respective *N*-alkyl-*S*-ethylisothiouronium iodides **8a–c** in quantitative yield after evaporation of the solvent (Table 3). Access to the N′-alkyl guanidino acetic acids **9a–c** in step 6, could be accomplished by reaction of the *N*-alkyl-*S*-ethylisothiouronium iodides **8a–c** with glycine in aqueous sodium hydroxide. After a reaction time ranging from 1 h at 0 °C for **9a** to 22 h at room temperature for **9b**,**c**, the desired unsoluble compounds **9a–c** were obtained in good to high yields (69–98%) after simple filtration.

Table 2 Results of reaction conditions evaluated for the preparation of aldehyde **5a** from **4a** by deprotection

Entry	Solvent	Acid	Reaction *T*/°C	Reaction time (h)	Yield[a] of **5a** (%)
1	H_2O (6 equiv.)	AcOH (7 eq.)	25	26	~50[b]
2	H_2O (6 equiv.)	AcOH (7 eq.)	40	23	~40[b]
3	Dioxane	HCl 0.6M	25	23	0
4	Me_2CO	HCl 37%	60	22	—[c]
5	Me_2CO	HCl 1M	50	8	93
6	Me_2CO/H_2O (1 : 1)	*p*TsOH[d]	55	6	98
7	Me_2CO/H_2O (1 : 1)	*p*TsOH	90	15 min[e]	93

[a] Isolated yield. [b] Calculated from ^{1}H NMR spectra of the crude reaction mixture (DMSO-d6, 300 MHz). [c] Decomposition. [d] *p*TsOH: *p*-$MeC_6H_4SO_3H$, monohydrate (0.5 eq.). [e] Reaction realized in a tube (sealed with a snap cap) under microwave irradiation (μω) in the Explorer® 24 CEM reactor.

Table 3 Results for the preparation of 2-aminoimidazol-4-one hydrochloride **10a–c** and precursors **7a–c**, **8a–c**, **9a–c**

Product	R	Yield[a] (%)	Overall yield[c] (%)
7a	H	—[b]	—
7b	Me	—[b]	—
7c	Et	98	—
8a	H	98	—
8b	Me	98	—
8c	Et	98	—
9a	H	69	68
9b	Me	98	96
9c	Et	98	96
10a	H	49	33
10b	Me	76	73
10c	Et	82	79

[a] Isolated yield. [b] Commercial product. [c] Overall yield calculated from **8**.

Finally treatment of the guanidino acetic acid **9a** with a solution of 6 M HCl at 120 °C during 22 h afforded the expected 2-aminoimidazolin-4-one **10a** in moderate yield (49%). It is worth noting that creatinine hydrochloride **10a** could be prepared under microwave irradiation[9] in short reaction time (30 min at 160 °C) but in lower yield (37%). In order to explore the question of generality, two further 2-aminoimidazolin-4-ones hydrochlorides **10b**,**c** were synthesized in good yields according to the experimental protocol used for **10a**; the compounds **10b** and **10c** were obtained with an isolated yield of 76 and 82% respectively.

With the desired *N*-(4,5-dihalogenopyrrol-2-yl)carbamoyl aldehydes **5a**,**b** and 2-aminoimidazolin-4-ones **10a–c** in hand, we wish to examine the Knoevenagel reaction under microwave dielectric heating as the last step in the synthesis of the dispacamide A derivatives. In literature, condensation of an aryl aldehyde to 2-aminoimidazolin-4-one **10a** or creatinine hydrochloride required the presence of a base such as AcONa in acetic acid,[7] eventually under microwave,[9] or without base in ethylene glycol[25] at 130 °C. On the basis of these studies, we thus decided to examine several experimental reaction conditions under microwave. As can be seen from inspection of the experiments presented in Table 4 for the preparation of dispacamide **11a**, the best result was encountered in a AcONa/AcOH media (entry 5) under microwave conditions of 120 °C during 20 min using a glass tube sealed with a snap cap. The spectral data of **11a** (^{1}H and ^{13}C NMR) were similar to those of dispacamide A isolated from Caribbean *Agelas* sponge.[10] Application of these experimental conditions using AcONa/AcOH as media with microwave dielectric heating for thermal activation (with appropriate reaction time and temperature/power) to *N*-(4,5-dichloropyrrol-2-yl)carbamoyl aldehyde **5b** (and also **5a**) with the other 2-aminoimidazolin-4-one hydrochlorides **10b**,**c** led to the expected new dispacamide derivatives **11b–f** in yield ranging from 25 to 69% (Table 5).

The structural identification of these new compounds **11b–f** was based on the ^{1}H and ^{13}C assignments and was performed extensive 1D and 2D NMR spectroscopy. The geometry of the exocyclic double bond of these new dispacamide derivatives **11b–f** recorded in DMSO-d_6 was determined on the basis of ^{13}C/^{1}H long-range coupling constants, which were measured by a gHSQMBC experiment[29] and was attributed as being *Z* by the shielding effect of the carbonyl C-4 on the olefinic proton =CH (δ_{CH} = 5.43–5.63 ppm).

Conclusion

In this paper, we have successfully synthesized dispacamide A **11a** and five new derivatives **11b–f** stereoselectively in good overall yields ranging from 12 to 33%. The key step of this sequential solution-phase organic synthesis is the Knoevenagel condensation under microwave dielectric heating in the last step (25–69%) from the *N*-(4,5-dihalogenopyrrol-2-yl)carbamoyl aldehydes **5a**,**b** (60–66% overall yields for **5**) and the 2-aminoimoidazolin-4-one hydrochloride partners **10a–c** (33–79% overall yields for **10**). This useful approach may be used as an alternative route to provide new dispacamide A derivatives and may be complementary to the previous methods described in the literature. Although a limited number of new derivatives are presented here, it is obvious that a much larger diversity could be achieved for a structure–activity relationship study. This work is on going in our laboratory.

Experimental

Melting points were determined on a Kofler melting point apparatus and were uncorrected. Thin-layer chromatography (TLC) was accomplished on 0.2-mm precoated plates of silica gel 60 F-254 (Merck). Visualization was made with ultraviolet light (254 and 365 nm) or with a fluorescence indicator. ^{1}H NMR spectra were recorded on BRUKER AC 300 P (300 MHz) spectrometer, ^{13}C NMR spectra on BRUKER AC 300 P (75 MHz) spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. Data are given in the following order: δ value, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), number of protons,

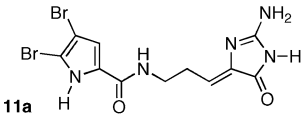
Table 4 Results of reaction conditions evaluated for the preparation of dispacamide A **11a** from aldehyde **5a** under microwave irradiation

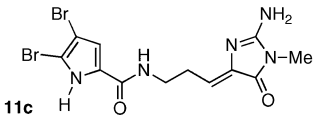
			Reaction conditions under microwave			
Entry	Base	Solvent	*T*/°C	Time (min)	Power (W)	Yield[a] (%) or remark
1	piperidine	EtOH	60	30	60[b]	mixture of products
2	AcONa	AcOH	160	20	200[c]	decomposition
3	AcONa	AcOH	140	20	200[c]	decomposition
4	AcONa	AcOH	140	20	60[c]	mixture of products
5	AcONa	AcOH	120	20	100[d]	61

[a] Isolated yield. [b] Reaction realized in open tube under microwave irradiation (μω) in the Explorer® 24 CEM reactor. [c] Reaction realized in a tube (sealed with a snap cap) under microwave irradiation (μω) in the Explorer® 24 CEM reactor. [d] Reaction realized in an open glass tube under microwave irradiation (μω) in the Monowave® 300 Anton Paar reactor.

Table 5 Results for the preparation of dispacamide A **11a** and derivatives **11(b–f)**

Product	X	R	Reaction condition under microwave			Yield of **11**[a] (%)	Overall yield[b] (%)
			T/°C	Reaction time (min)	Power (W)		
11a[c]	Br	H	120	20	100	61	12
11b[c]	Cl	H	120	20	100	54	12
11c[d]	Br	Me	60	30	60	68	30
11d[d]	Cl	Me	60	30	60	69	33
11e[d]	Br	Et	60	30	60	25	12
11f[d]	Cl	Et	60	30	60	34	18


11a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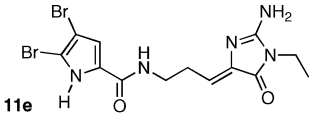
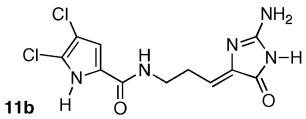
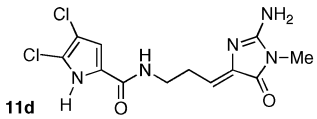
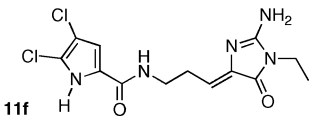

11e


11b


11d


11f

[a] Isolated yield. [b] Overall yield calculated from **5** and **10**. [c] Reaction realized in a tube (sealed with a snap cap) in the Monowave® 300 Anton Paar reactor. [d] Reaction realized in a tube (sealed with a snap cap) under microwave irradiation (μω) in the Explorer® 24 CEM reactor.

coupling constants *J* is given in Hz. The mass spectra (HRMS) were taken respectively on a MS/MS ZABSpec Tof Micromass (EBE TOF geometry) at an ionizing potential of 8 eV and on a VARIAN MAT 311 at an ionizing potential of 70 eV in the "Centre Régional de Mesures Physiques de l'Ouest" (CRMPO, Rennes). Reactions under microwave irradiations were realized in the Explorer® 24 CEM microwave reactor (CEM France) and also in the Anton Paar Monowave 300® microwave reactor (Anton Paar France) using borosilicate glass vials of 10 ml equipped with snap caps (at the end of the irradiation, cooling reaction was realized by compressed air). The microwave instrument consists of a continuous focused microwave power output from 0 to 300 W for the Explorer® 24 CEM apparatus and from 0 to 800 W for the Anton Paar Monowave 300® apparatus. All the experiments were performed using stirring option. The target temperature was reached with a ramp of 2 min and the chosen microwave power stay constant to hold the mixture at this temperature. The reaction temperature is monitored using calibrated infrared sensor and the reaction time included the ramp period. The microwave irradiation parameters (power and temperature) were monitored by the ChemDriver software package for the Explorer® 24 CEM apparatus and by the Monowave software package for the Anton Paar Monowave 300® reactor. Preparative chromatographies were realized on a Combi Flash R_f 200 psi (Serlabo Technologies France) using pre-packed column of silica gel 60 F 254 Merck equipped with a DAD UV/Vis 200–360 nm detector. Elemental analyses were performed on a Flash Microanalyzer EA1112 CHNS/O Thermo Electron in the "Centre Régional de Mesures Physiques de l'Ouest" (CRMPO, Rennes). Solvents were evaporated with a BUCHI rotary evaporator. All reagents and solvents were purchased from Acros, Aldrich Chimie, and Fluka France and were used without further purification.

2,2,2-Trichloro-1-(4,5-dibromo-1*H*-pyrrol-2-yl)ethanone (2a)

In a 250 ml two-necked round-bottomed flask provided with a magnetic stirrer and condenser, 2,2,2-trichloro-1-(1*H*-pyrrol-2-yl)ethanone **1** (2 g, 9.41 mmol) was dispersed in chloroform (80 ml) at 0 °C under a stream of argon. To this mixture, bromine Br_2 (0.96 ml, 18.83 mmol) was added dropwise during 30 min. The reaction was monitored by thin layer chromatography on silica plates using cyclohexane/AcOEt (4 : 1) as eluent (**2a**: R_f 0.58). The reaction mixture was stirred at room temperature over period of 20 h. After elimination of the solvent in a rotary evaporator under reduced pressure, the crude residue was submitted to purification by recrystallization in a mixture of ethanol/water (1 : 1). The desired product **2a** was obtained as a pure white powder in 70% yield (2.439 g) Mp = 151–153 °C. ^{1}H NMR (DMSO-d_6) δ: 7.38 (s, 1H, H-3); 13.73 (br s, 1H, H-1). ^{13}C NMR (DMSO-d_6) δ: 94.02 (CCl_3); 100.82 (C-3); 114.54 (C-4); 122.39 (C-5); 123.23 (C-2); 170.88 (C=O). HRMS *m*/*z*: 389.7463 found (calculated for $C_6H_2NO^{79}Br_2Na$ $[M+Na]^{+\bullet}$ requires 389.7466).

2,2,2-Trichloro-1-(4,5-dichloro-1*H*-pyrrol-2-yl)-ethanone (2b)

In a 25 ml two-necked round-bottomed flask provided with a magnetic stirrer and condenser, 2,2,2-trichloro-1-(1*H*-pyrrol-2-yl)-ethanone **1** (1 g, 4.71 mmol) was solubilized in chloroform (13 ml) at room temperature under a stream of argon. To this solution, sulfuryl chloride SO_2Cl_2 (0.8 ml, 9.88 mmol, 2.1 equiv.) was added dropwise during 10 min. The reaction was monitored by thin layer chromatography on silica plates using cyclohexane/AcOEt (4 : 1) as eluent (**2b**: R_f 0.63). After 26 h of vigorous magnetic stirring, the yellowish reaction mixture was washed with a solution of saturated sodium hydrogen carbonate $NaHCO_3$. The whole mixture was transferred to a separating funnel; after separating and extraction with methylene chloride (2 × 20 ml), the combined organic phases were dried over $MgSO_4$, filtered and the solvent of the filtrate was eliminated *in vacuo*. The crude residue was submitted to purification by column chromatography on silica gel 60F 254 Merck with cyclohexane/AcOEt (7 : 3) as eluent. Pooling and evaporation of the solvent under vacuum afforded the expected product **2b** in 90% yield (1.19 g) as yellowish needles. Mp = 140–142 °C. ^{1}H NMR (DMSO-d_6) δ: 7.40 (s, 1H, H-3); 13.83

(br s, 1H; H-1). ^{13}C NMR (DMSO-d$_6$) δ: 94.13 (*C*Cl$_3$); 110.77 (C-3); 119.58 (C-4); 119.85 (C-5); 123.53 (C-2); 171.11 (C═O).

4,5-Dibromo-1*H*-pyrrole-2-carboxylic acid (3,3-diethoxypropyl)-amide (4a)

Method A: To a solution of 2,2,2-trichloro-1-(4,5-dibromo-1*H*-pyrrol-2-yl)-ethanone **2a** (1.21 g, 3.27 mmol) in dry acetonitrile (5 ml) was added portion wise 3,3-diethoxy-1-aminopropane **3** (0.53 ml, 3.27 mmol, 1 equiv.) at room temperature. After vigorous stirring over a period of 23 h (monitoring by thin layer chromatography on silica plates with a mixture of cyclohexane/AcOEt (4 : 1) as eluent, **4a**: R_f 0.52), the desired insoluble compound **4a** was collected by filtration and was dried under high vacuum (10^{-2} Torr) at 25 °C for 1 h. The white product **4a** (1.14 g, 88% yield) was further used without purification.

Method B: A solution of 2,2,2-trichloro-1-(4,5-dibromo-1*H*-pyrrol-2-yl)-ethanone **2a** (1 g, 2.7 mmol) and 3,3-diethoxy-1-aminopropanone **3** (0.44 ml, 2.7 mmol) in 10 ml of MeCN was placed in a borosilicate glass vial (10 ml) and sealed with a snap cap. The glass tube was then introduced into an Explorer® 24 CEM microwave cavity (P = 300 W). The stirred mixture was irradiated at 70 °C (with a power of 50 Watt) for 30 min. After microwave dielectric heating, the crude reaction mixture was allowed to cool down at room temperature and was stored in a refrigerator (4 °C) during 12 h. The crystallized compound **4a** was collected by filtration and was dried under high vacuum (10^{-2} Torr) at 25 °C for 1 h. The product **4a** (0.944 g, 87% yield) was further used without purification.

Mp = 139–141 °C. ^{1}H NMR (DMSO-d$_6$) δ: 1.10 (t, 6H, J = 7.0 Hz, 2xCH_3); 1.70 (q, 2H, J = 6.5 Hz, CH_2); 3.21 (q, 2H, J = 6.5 Hz, CH_2); 3.41 (m, 2H, H-2); 3.56 (m, 2H, CH_2); 4.51 (t, 1H, J = 5.5 Hz, CH); 6.76 (s, 1H, H-3′); 8.09 (t, 1H, J = 5.5 Hz, H-1′, NH Ar); 12.66 (br s, 1H, NH). ^{13}C NMR (DMSO-d$_6$) δ: 15.22-15.28 (2x*C*H3); 32.83–35.66 (4xCH_2); 96.29 (*C*H); 100.59 (C-3′, Ar); 106.04 (C-4′, Ar); 112.19 (C-5′, Ar); 129.42 (C-2′, Ar); 159.94 (C═O). HRMS m/z: 418.9579 found (calculated for $C_{12}H_{18}N_2O_3{}^{79}Br_2Na$ $[M+Na]^{+\bullet}$ requires 418.9582).

4,5-Dichloro-1*H*-pyrrole-2-carboxylic acid (3,3-diethoxypropyl)-amide (4b)

To a solution of 2,2,2-trichloro-1-(4,5-dichloro-1*H*-pyrrol-2-yl)-ethanone **2b** (0.5 g, 1.78 mmol) in dry acetonitrile (3 ml) was added portion-wise 3,3-diethoxy-1-aminopropane **3** (0.29 ml, 1.78 mmol, 1 equiv.) at room temperature. After vigorous stirring over a period of 29 h (monitoring by thin layer chromatography on silica plates with a mixture of CH_2Cl_2/AcOEt (4 : 1) as eluent, **4b**: R_f 0.51), the solvent was eliminated in a rotary evaporator under reduced pressure. The crude residue was submitted to purification by preparative chromatography (Combi Flash R_f 200 psi apparatus) on pre-packed column of silica gel 60F 254 Merck using a stepwise gradient of CH_2Cl_2/AcOEt (0–50%). Pooling and evaporation of the solvent *in vacuo* gave the expected compound **4b** in 75% yield as yellowish needles. Mp = 134–136 °C. ^{1}H NMR (DMSO-d$_6$) δ: 1.11 (m, 6H, 2xCH_3); 1.73 (m, 2H, CH_2); 3.22 (m, 2H, CH_2); 3.43 (m, 2H, CH_2); 3.56 (m, 2H, CH_2); 4.53 (m, 1H, CH); 6.85 (s, 1H, H-3, Ar); 8.10 (br s; 1H, NH Ar); 12.70 (br, 1H, NH). ^{13}C NMR (DMSO-d$_6$) δ: 15.23 (2xCH_3); 33.40 (CH_2); 34.74 (CH_2); 60.64 (2xCH_2); 10.42 (*C*H); 107.82 (C-4, Ar); 109.36 (C-5, Ar); 114.61 (C-3, Ar); 124.91 (C-2, Ar); 158.88 (C═O).

4,5-Dibromo-1*H*-pyrrole-2-carboxylic acid (3-oxo-propyl)-amide (5a)

Method A: To a solution of 4,5-dibromo-1*H*-pyrrole-2-carboxylic acid (3,3-diethoxypropyl)-amide **4a** (730 mg, 1.84 mmol) in acetone (12 ml) was added dropwise a solution 1 M chlorhydric acid (0.56 ml) over a period of 10 min. The reaction mixture was vigorously stirred at 50 °C during 8 h (the reaction was monitored by thin layer chromatography on silica plates using a mixture of CH_2Cl_2/AcOEt (4 : 1) as eluent, **5a**: R_f 0.21). The reaction mixture was concentrated in a rotary evaporator under reduced pressure and to the yellowish crude residue was added 20 ml of methylene chloride. The organic phase was washed with a solution of saturated sodium hydrogen carbonate (2 × 3 ml) and was dried over $MgSO_4$. After filtration, the solvent of the filtrate was eliminated *in vacuo* and the crude residue was dried under high vacuum (10^{-2} Torr) at 25 °C for 1 h. The desired product **5a** was obtained as whitish powder in 93% yield (554 mg).

Method B: In a 10 ml two-necked round-bottomed flask provided with a magnetic stirrer and condenser, a mixture of 4,5-dibromo-1*H*-pyrrole-2-carboxylic acid (3,3-diethoxypropyl)-amide **4a** (200 mg, 0.5 mmol) and commercial *para*-toluene sulfonic acid monohydrate (48 mg, 0.25 mmol, 0.5 equiv.) in 3 ml of a solution of acetone/water (1 : 1) was heated at 50 °C during 6 h in a thermostatted oil bath. After cooling down to room temperature, the mixture was extracted with methylene chloride (3 × 5 ml). The combined organic phases were dried over $MgSO_4$, filtered and the volatile solvents were eliminated in a rotary evaporator under reduced pressure. The crude residue was dried under high vacuum (10^{-2} Torr) at 25 °C for 1 h. The desired product **5a** was obtained as a white powder in 98% yield (212 mg).

Method C: A solution of 4,5-dibromo-1*H*-pyrrole-2-carboxylic acid (3,3-diethoxypropyl)-amide **4a** (100 g, 0.25 mmol) and commercial *para*-toluene sulfonic acid monohydrate (24 mg, 0.125 mmol, 0.5 equiv.) in 2 ml of acetone/water (1 : 1) was placed in a borosilicate glass vial (10 ml) and sealed with a snap cap. The glass tube was then introduced into an Explorer® 24 CEM microwave cavity (P = 300 W). The stirred mixture was irradiated at 90 °C (with a power of 40 Watt) for 15 min. After microwave dielectric heating, the crude reaction mixture was allowed to cool down at room temperature and was extracted with methylene chloride (3 × 3 ml). The combined organic phases were dried over $MgSO_4$, filtered and the volatile solvents were eliminated in a rotary evaporator under reduced pressure. The crude residue was dried under high vacuum (10^{-2} Torr) at 25 °C for 1 h and gave 81 mg of the desired product **5a** as a white powder in 98% yield.

Mp = 139–141 °C. ^{1}H NMR (DMSO-d$_6$) δ: 1.10 (t, 6H, J = 7.0 Hz, 2xCH_3); 1.70 (q, 2H, J = 6.5 Hz, CH_2); 3.21 (q, 2H, J = 6.5 Hz, CH_2); 3.41 (m, 2H, H-2); 3.56 (m, 2H, H-1); 4.51 (t, 1H, J = 5.5 Hz, H-3); 6.76 (s, 1H, H-3′, Ar); 8.09 (t, 1H, J = 5.5 Hz, NH); 12.66 (br s, 1H, NH, Ar). ^{13}C NMR (DMSO-d$_6$) δ: 15.22–15.28 (2x*C*H3); 32.83–35.66 (4xCH_2); 96.29 (C-3, *C*H); 100.59 (C-3, Ar); 106.04 (C-4, Ar); 112.19 (C-5, Ar); 129.42 (C-2); 159.94 (*C*═O).

HRMS *m/z*: 344.8860 found (calculated for $C_8H_8N_2O_2{}^{79}Br_2Na$ $[M+Na]^{+\bullet}$ requires 344.8851).

4,5-Dichloro-1*H*-pyrrole-2-carboxylic acid (3-oxo-propyl)-amide (5b)

Method B: In a 100 ml two-necked round-bottomed flask provided with a magnetic stirrer and condenser, a mixture of 4,5-dichloro-1*H*-pyrrole-2-carboxylic acid (3,3-diethoxypropyl)-amide **4b** (2.11g, 6.8 mmol) and commercial *para*-toluene sulfonic acid monohydrate (649 mg, 3.4 mmol, 0.5 equiv.) in 42 ml of a solution of acetone/water (1 : 1) was heated at 50 °C during 14 h in a thermostatted oil bath. After cooling down to room temperature, the mixture was extracted with methylene chloride (3 × 100 ml). The combined organic phases were dried over $MgSO_4$, filtered and the volatile solvents were eliminated in a rotary evaporator under reduced pressure. The crude residue was dried under high vacuum (10^{-2} Torr) at 25 °C for 1 h. The desired product **5a** was obtained as a yellow powder in 98% yield (1.59 g).

Method C: A suspension of 4,5-dibromo-1*H*-pyrrole-2-carboxylic acid (3,3-diethoxypropyl)-amide **4a** (100 mg, 0.32 mmol) and commercial *para*-toluene sulfonic acid monohydrate (31 mg, 0.16 mmol, 0.5 equiv.) in 2 ml of a solution of acetone/water (1 : 1) was placed in a borosilicate glass vial (10 ml) and sealed with a snap cap. The glass tube was then introduced into an Explorer® 24 CEM microwave cavity (*P* = 300 W). The stirred mixture was irradiated at 90 °C (with a power of 40 W) for 15 min. After microwave dielectric heating, the yellowish crude reaction mixture was allowed to cool down at room temperature and was extracted with methylene chloride (3 × 6 ml). The combined organic phases were dried over $MgSO_4$, filtered and the volatile solvents were eliminated in a rotary evaporator under reduced pressure. The crude residue was dried under high vacuum (10^{-2} Torr) at 25 °C for 1 h and gave 72 mg of the desired product **5b** as a white powder in 95% yield.

Mp = 150–152 °C. ^{1}H NMR (DMSO-d_6) δ: 2.63 (dt, *J* = 1.7, 6.6 Hz, 2H, H-2); 3.47 (m, 2H, H-1); 6.84 (s, 1H, H-3); 8.24 (t, *J* = 5.6 Hz, 1H, NH); 9.66 (s, 1H, H-3, Ar); 12.73 (br s, 1H, NH, Ar). ^{13}C NMR (DMSO-d_6) δ: 32.63 (CH_2); 43.22 (CH_2); 107.88 (C-4′, Ar); 109.60 (C-3′, Ar); 114.83 (C-5, Ar); 124.63 (C-2, Ar); 158.98 (C=O); 202.14 (CHO). HRMS *m/z*: 256.9865 found (calculated for $C_8H_8N_2O_2{}^{35}Cl_2Na$ $[M+Na]^{+\bullet}$ requires 256.9861).

N-Ethylthiourea (7c)

In a 10 ml two-necked round-bottomed flask provided with a magnetic stirrer and condenser, ethyl isothiocyanate **6c** (644 mg, 7.4 mmol) was dissolved in absolute ethanol (7 ml). To this solution was added in one portion 2.64 ml of commercial solution of 7 M ammonia in methanol (18.5 mmol, 2.5 equiv.). After heating at 60 °C under vigorous magnetic stirring during 2.5 h, the reaction mixture was concentrated in a rotary evaporator under reduced pressure. The crude residue was dried under high vacuum (10^{-2} Torr) at 25 °C for 30 min and gave the desired *N*-ethyl thiourea **7c** as a white needles in 98% yield. Mp = 121–123 °C. ^{1}H NMR (DMSO-d_6) δ: 1.03 (t, *J* = 7.1 Hz, 3H, CH_3); 3.33 (m, H, CH_2). ^{13}C NMR (DMSO-d_6) δ: 14.44 (CH_3); 37.53 (CH_2); 182.82 (C=S). HRMS *m/z*: 127.0307 found (calculated for $C_3H_8N_2S$ $[M+Na]^{+\bullet}$ requires 127.0306).

Standard procedure for the preparation of 2-ethylisothiourea hydroiodide (8a–c)

In a 10 ml two-necked round-bottomed flask provided with a magnetic stirrer and condenser, 13.1 mmol of thiourea **7** were dissolved in 3 ml of absolute ethanol. Commercial iodoethane (1.26 ml, 15.8 mmol, 1.2 equiv.) was added in one portion in the thiourea solution. After heating at 60 °C during 3.5 h, the reaction mixture was concentrated by rotary evaporation under reduced pressure. The desired 2-ethyl isothiourea hydroiodide **8** was obtained as mobile yellowish oil and was further used without purification.

2-Ethyl-isothiourea hydroiodide (8a). Yellowish oil. Yield = 98%. ^{1}H NMR (DMSO-d_6) δ: 1.24 (t, *J* = 7.1 Hz, 3H, CH_3); 3.15 (q, *J* = 7.1 Hz, 2H, CH_2); 8.91 (br s, 4H, 2xNH_2). ^{13}C NMR (acetone-d_6) δ: 13.60 (CH_3); 25.80 (CH_2); 172.30 (C=NH_2^+). HRMS *m/z*: 105.0487 found (calculated for $C_3H_9N_2S$ $[C]^{+\bullet}$ requires 105.0487).

2-Ethyl-1-methyl-isothiourea hydroiodide (8b). Yellowish oil. Yield = 98%. ^{1}H NMR (DMSO-d_6) δ: 1.23 (t, *J* = 7.3 Hz, 3H, CH_3); 2.88 (s, 3H, NCH_3); 3.17 (q, *J* = 7.3 Hz, CH_2); 9.15 (br s, 3H, NH_2+NH). ^{13}C NMR (acetone-d_6) δ: 13.60 (CH_3); 26.40 (CH_2); 30.90 (C_1); 167.7 (C=NH_2^+). HRMS *m/z*: 119.0612 found (calculated for $C_4H_{11}N_2S$ $[C]^{+\bullet}$ requires 119.0643).

2-Ethyl-1-ethyl-isothiourea hydroiodide (8c). Yellowish oil. Yield = 98%. ^{1}H NMR (DMSO-d_6) δ: 1.11 (t, *J* = 7.2 Hz, 3H, NCH_2CH_3); 1.23 (t, *J* = 7.3 Hz, 3H, SCH_2CH_3); 3.18 (q, *J* = 7.3 Hz, 2H, NCH_2); 3.32 (m, 2H, SCH_2). ^{13}C NMR (acetone-d_6) δ: 13.13 (CH_3); 14.14 (CH_3); 25.38 (SCH_2); 38.62 (NCH_2); 165.26 (C=NH_2^+). HRMS *m/z*: 133.0800 found (calculated for $C_3H_{13}N_2S$ $[C]^{+\bullet}$ requires 133.07795).

Guanidino acetic acid (9a)

In a 10 ml two-necked round-bottomed flask provided with a magnetic stirrer and condenser was placed 2-ethylisothiourea hydroiodide **8a** (1 g, 4.3 mmol) in a solution of 2 M sodium hydroxide (2.8 ml). To this mixture was added dropwise a solution of glycine (356 mg, 4.7 mmol, 1.1 equiv.) in 1 ml of hot deionized water (80 °C) during 15 min. After cooling down to room temperature, the reaction mixture was stirred vigorously at 0 °C over a period of 1 h, after which 1 ml of diethyl ether was added in one portion. Then, the resulting mixture was stirred slowly at 0 °C during 22 h and white needles appeared in the suspension. The reaction mixture was half-concentrated *in vacuo* and the desired insoluble compound **9a** was collected by filtration, and then washed successively with cooled deionized water (0.25 ml), absolute ethanol (2 × 1.5 ml) and diethyl ether (2 × 1.5 ml). The guanidino acetic acid **9a** was dried under high vacuum (10^{-2} Torr) at 25 °C for 1 h. The product **9a** was obtained as white needles in 69% yield (346 mg). Mp > 250 °C. ^{1}H NMR (D_2O) δ: 3.73 (s, 2H, CH_2). ^{13}C NMR (D_2O) δ: 44.6 (CH_2); 175.1 (C=O).

(*N*′-Methylguanidino)acetic acid (9b)

In a 50 ml two-necked round-bottomed flask provided with a magnetic stirrer and condenser was dissolved commercial glycine (1.51 g, 20.2 mmol) in a solution of 4 M sodium hydroxide

(5 ml). To this mixture was added at 0 °C a solution of 2-ethyl-1-methylisothiourea hydroiodide **8b** (5.46 g, 22.2 mmol, 1.1 equiv.) in deionized water (3 ml) during 15 min. The reaction mixture was stirred at room temperature over a period of 19 h, after which 9 ml of diethyl ether was added in two portions at 0 °C. The resulting suspension was stirred slowly at 0 °C during 16 h and white needles appeared. The reaction mixture was concentrated *in vacuo* and the desired insoluble compound **9b** was collected by filtration, then triturated and washed with 3 ml of acetone. The (*N′*-methylguanidino)acetic acid **9b** was dried under high vacuum (10^{-2} Torr) at 25 °C for 1 h. The product **9b** was obtained as white needles in 98% yield (2.7 g). Mp > 250 °C. ^{1}H NMR (D_2O) δ: 2.74 (s, 3H, CH_3); 3.68 (s, 2H, CH_2). ^{13}C NMR (D_2O) δ: 27.3 (CH_3); 44.5 (CH_2); 175.3 (C═O). HRMS *m/z*: 113.0587 found (calculated for $C_4H_7N_3O$ [M-H_2O]$^{+\bullet}$ requires 113.0589).

(*N′*-Ethylguanidino)acetic acid (9c)

In a 50 ml two-necked round-bottomed flask provided with a magnetic stirrer and condenser was dissolved commercial glycine (1.57 g, 20.9 mmol) in a solution of 4 M sodium hydroxide (5.2 ml). To this mixture was added at 0 °C a solution of 2-ethyl-1-ethylisothiourea hydroiodide **8c** (5.97 g, 22.95 mmol, 1.1 equiv.) in deionized water (3 ml) during 15 min. The yellowish reaction mixture was stirred vigorously at room temperature over a period of 22 h, after which 9 ml of diethyl ether was added in two portions at 0 °C. The resulting suspension was stirred slowly at 0 °C during 20 h and white needles appeared. The reaction mixture was concentrated *in vacuo* and the desired insoluble compound **9c** was collected by filtration, then triturated and washed with 10 ml of dry acetone. The (*N′*-ethylguanidino)acetic acid **9c** was dried under high vacuum (10^{-2} Torr) at 25 °C for 1 h. The product **9c** was obtained as needles in quantitative yield and was rapidly stored under nitrogen at 4 °C. Mp > 250 °C. ^{1}H NMR (DMSO-d_6) δ: 1.06 (m, 3H, CH_3); 3.08 (m, 2H, CH_2); 3.40 (s, 2H, CH_2).

Standard procedure for the preparation of 2-aminoimidazol-4-one 10a–c

In a 25 ml round-bottomed flask provided with a magnetic stirrer and condenser, a suspension of guanidine-acetic acid **9** (2.95 mmol) in 9 ml of a solution of 6 M chlorhydric acid was stirred at 120 °C during 22 h. The reaction mixture was concentrated *in vacuo* and was dried under high vacuum (10^{-2} Torr) at 25 °C for 1 h. In the crude residue, was added successively 9 ml of hot absolute ethanol and 6 ml of diethyl ether. The reaction mixture was cooled at 0 °C and white needles appeared. The resulting suspension was stirred slowly at 0 °C over a period of 6 h and the desired insoluble product **10** was collected by filtration. The compound **10** was dried under high vacuum (10^{-2} Torr) at 25 °C for 1 h and was further used without purification.

2-Amino-3,5-dihydro-imidazol-4-one hydrochloride (10a). White needles. Yield = 49%. Mp = 199–201 °C. ^{1}H NMR (D_2O) δ: 4.18 (s, 2H, CH_2). ^{13}C NMR (D_2O) δ: 48.5 (CH_2); 174.9 (C═O). HRMS *m/z*: 99.0427 found (calculated for $C_3H_5N_3O$ [M-HCl]$^{+\bullet}$ requires 99.0433).

2-Amino-3-methyl-3,5-dihydro-imidazol-4-one hydrochloride (10b). Beige needles. Yield = 76%. Mp > 250 °C. ^{1}H NMR (D_2O) δ: 3.08 (s, 3H, CH_3); 4.17 (s, 2H, CH_2). ^{13}C NMR (D_2O) δ: 25.6 (CH_3); 47.6 (CH_2); 173.2 (C═O). HRMS *m/z*: 114.0667 found (calculated for $C_4H_8N_3O$ [M – H]$^{+\bullet}$ requires 114.06674).

2-Amino-3-ethyl-3,5-dihydro-imidazol-4-one hydrochloride (10c). Beige needles. Yield = 82%. Mp = 240–242 °C. ^{1}H NMR (DMSO-d_6) δ: 1.09 (t, *J* = 7.1 Hz, 3H, CH_3); 3.63 (q, *J* = 7.1 Hz, 2H, CH_2); 4.15 (s, 2H, NCH_2C═O); 9.43 (br s, 3H, NH_3). ^{13}C NMR (DMSO-d_6) δ: 12.87 (CH_3); 34.29 (CH_2); 47.41 (NCH_2C═O); 158.23 (C═N, C-2); 171.23 (C═O). HRMS *m/z*: 128.0823 found (calculated for $C_5H_{10}N_3O$ [M – H]$^{+\bullet}$ requires 128.08239).

Standard procedure for the preparation of dispacamide A 11a and the derivative 11b under microwave irradiation

In a 10 ml glass tube were placed successively aldehyde **5a**,**b** (0.46 mmol), 2-amino-imidazol-4-one hydrochloride **10a** (69 mg, 0.51 mmol, 1.1 equiv.), commercial sodium acetate (38 mg, 0.46 mmol) and glacial acetic acid (0.18 ml, 3.05 mmol, 6.6 equiv.). The glass tube was sealed with a snap cap and placed in the Anton Paar Monowave 300® microwave cavity (*P* = 800 W). The stirred mixture was irradiated at 120 °C (with a power of 100 W) for 20 min. After microwave dielectric heating, the crude reaction mixture was allowed to cool down at room temperature and deionized water (2 ml) was added in the tube, then the reaction mixture in the glass tube was submitted to ultrasound in a Branson 1510 apparatus at 25 °C during 1 h. The desired insoluble product **11** was collected by filtration and was washed with cooled water (2 × 2 ml). The compound **11a**,**b** was dried under high vacuum (10^{-2} Torr) at 25 °C for 2 h and was stored at 4 °C.

(5*Z*)-4,5-Dibromo-1*H*-pyrrole-2-carboxylic acid [3-(2-amino-4-oxo-1,5-dihydro-imidazol-5-ylidene)propyl]amide or Dispacamide A (11a). White powder. Mp ~ 210 °C (decomposition). Yield = 61%. ^{1}H NMR (methanol-d_4) δ: 2.53 (q, *J* = 7.1 Hz, 2H, CH_2); 3.45 (m, 2H, CH_2); 5.77 (t, *J* = 7.9 Hz, 1H, CH═); 6.80 (s, 1H, H-3″, Ar); 6.81 (m, 1H, NH); 8.27 (br s, 1H, NH); 12.72 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 27.18 (CH_2); 37.79 (CH_2); 97.77 (C-4′, Ar); 104.41 (CH═); 112.54 (CH, C-3′, Ar); 128.12 (C-2′, Ar); 128.12 (C-5′, Ar); 136.11 (C-4, C═); 158.82 (C═O); 168.30 (C-2, C═N); 172.04 (C═O). HRMS *m/z*: 425.9179 found (calculated for $C_{11}H_{11}N_5O_2{}^{79}Br_2Na$ [M+Na]$^{+\bullet}$ requires 425.9177). Anal. Calc. for $C_{11}H_{11}N_5O_2Br_2$: C, 32.62; H, 2.74; N, 17.29. Found for C, 32.71; H, 2.82; N, 17.11.

(5*Z*) 4,5-Dichloro-1*H*-pyrrole-2-carboxylic acid [3-(2-amino-4-oxo-1,5-dihydro-imidazol-5-ylidene)propyl]amide (11b). Brown-orange powder. Mp ~ 200 °C (decomposition). Yield = 54%. ^{1}H NMR (DMSO-d_6) δ: 2.53 (q, *J* = 7.1 Hz, 2H, CH_2); 3.45 (m, 2H, CH_2); 5.43 (t, *J* = 7.5 Hz, 1H, CH═); 6.86 (s, 1H, H-3″, Ar); 8.27 (br s, 1H, NH); 12.72 (br s, 1H, NH).

^{13}C NMR (DMSO-d_6) δ: 27.19 (CH_2); 37.97 (CH_2); 107.87 (C-4′, Ar); 108.49 (CH═); 109.59 (CH, C-3′, Ar); 114.68 (C-2′, Ar); 123.29 (C-5′, Ar); 124.85 (C-4, C═); 158.92 (C═O), 168.30 (C-2, C═N); 172.04 (C═O). HRMS *m/z*: 338.0189 found (calculated for $C_{11}H_{11}N_5O_2{}^{35}Cl_2Na$ [M+Na]$^{+\bullet}$ requires 338.0188). Anal. Calc. for $C_{11}H_{11}N_5O_2Cl_2$: C, 41.79; H, 3.51; N, 22.15. Found for C, 41.82; H, 3.62; N, 22.05.

Standard procedure for the preparation of dispacamide derivatives 11c,d under microwave irradiation

In a 10 ml glass tube were placed successively aldehyde **5a**,**b** (0.67 mmol), 2-amino-3-methyl-imidazol-4-one hydrochloride **10b** (100 mg, 0.67 mmol), dry piperidine (63 mg, 0.74 mmol, 1.1 equiv.) and absolute ethanol (6.5 ml). The open glass tube was placed in the Explorer® 24 CEM microwave cavity ($P = 300$ W). The stirred mixture was irradiated at 60 °C (with a power of 60 W) for 30 min. After microwave dielectric heating, the crude reaction mixture was allowed to cool down at room temperature. The desired insoluble product **11** was collected by filtration and was washed with cooled water (2 × 2 ml). The compound **11c**,**d** was dried under high vacuum (10^{-2} Torr) at 25 °C for 2 h and was stored at 4 °C.

(5*Z*) 4,5-Dibromo-1*H*-pyrrole-2-carboxylic acid [3-(2-amino-1-methyl-4-oxo-1,5-dihydro-imidazol-5-ylidene)propyl]amide (11c). Yellow powder. Mp > 250 °C. Yield = 68%. ^{1}H NMR (DMSO-d_6) δ: 2.49 (m, 2H, CH_2); 2.96 (s, 3H, NCH_3); 3.29 (m, 2H, CH_2); 5.63 (t, J = 7.4 Hz, 1H, CH═); 6.88 (s, 1H, H-3, Ar); 7.20 (br s, 2H, NH_2); 8.24 (br s, 1H, NHCO); 12.38 (br s, 1H, NH, Ar). ^{13}C NMR (DMSO-d_6) δ: 25.41 (*C*H_3); 27.20 (*C*H_2); 38.11 (*C*H_2); 97.73 (C-4′, Ar); 104.39 (C-5′, Ar); 112.42 (*C*H, Ar); 114.30 (*C*H═); 128.18 (C-2′, Ar); 142.50 (C-4); 158.12 (*C*═O); 158.78 (*C*═O); 168.06 (C-2, *C*═N). HRMS *m*/*z*: 417.9507 found (calculated for $C_{12}H_{14}N_5O_2{}^{79}Br_2$ [M+H]$^{+\bullet}$ requires 417.9514). Anal. Calc. for $C_{12}H_{13}N_5O_2Br_2$: C, 34.39; H, 3.13; N, 16.71. Found for C, 34.43; H, 3.21; N, 16.04.

(5*Z*) 4,5-Dichloro-1*H*-pyrrole-2-carboxylic acid [3-(2-amino-1-methyl-4-oxo-1,5-dihydro-imidazol-5-ylidene)-propyl]-amide (11d). Yellow powder. Mp > 250 °C. Yield = 69%. ^{1}H NMR (DMSO-d_6) δ: 2.45 (m, 2H, CH_2); 2.96 (s, 3H, CH_3); 3.41 (m, 2H, CH_2); 5.63 (t, J = 7.5 Hz, 1H, CH═); 6.86 (s, 1H, H-3, Ar); 7.19 (br s, 2H, NH_2); 8.27 (br s, 1H, NHCO). 12.31 (br s, 1H, NH, Ar). ^{13}C NMR (DMSO-d_6) δ: 25.42 (*C*H_3); 27.20 (CH_2); 38.11 (*C*H_2); 107.81 (C-4′, Ar); 109.57 (CH═); 114.25 (C-5′, Ar); 114.68 (C-3′, Ar); 124.97 (C-2, Ar); 142.47 (C-4); 158.15 (*C*═O); 158.93 (*C*═O); 168.06 (C-2, *C*═N). HRMS *m*/*z*: 330.0522 found (calculated for $C_{12}H_{14}N_5O_2{}^{35}Cl_2$ [M+H]$^{+\bullet}$ requires 330.0525). Anal. Calc. for $C_{12}H_{13}N_5O_2Cl_2$: C, 43.65; H, 3.97; N, 21.21. Found for C, 43.71; H, 4.09; N, 20.94.

Standard procedure for the preparation of dispacamide derivatives 11e,f under microwave irradiation

In a 10 ml glass tube were placed successively aldehyde **5(b**,**c)** (0.93 mmol), 2-amino-3-ethyl-imidazol-4-one hydrochloride **10c** (152 mg, 0.93 mmol, 1 equiv.), dry piperidine (86 mg, 1.02 mmol, 1.1 equiv.) and absolute ethanol (6 ml). The open glass tube was placed in the Explorer® 24 CEM microwave cavity ($P = 300$ W). The stirred mixture was irradiated at 60 °C (with a power of 60 W) for 30 min. After microwave dielectric heating, the crude reaction mixture was allowed to cool down at room temperature and the desired insoluble product **11e**,**f**, was collected by filtration and was dried under high vacuum (10^{-2} Torr) at 25 °C for 1 h. For **11e** this compound was dissolved in hot absolute ethanol (4 ml) and to this solution was added at 0 °C dry diethyl ether (4 ml). The insoluble product **11e** was submitted to filtration (109 mg, 25% yield) and was dried under high vacuum (10^{-2} Torr) at 25 °C for 0.5 h. For **11f**, this compound was also dissolved in hot absolute ethanol (4 ml) and the resulting suspension was submitted to ultrasound in a Branson 1510 apparatus at 25 °C during 1 h. The desired insoluble product **11f** was collected by filtration (108 mg, 34% yield) and was dried under high vacuum (10^{-2} Torr) at 25 °C for 1 h. The products **11(e**,**f)** were stored at 4 °C.

(5*Z*) 4,5-Dibromo-1*H*-pyrrole-2-carboxylic acid [3-(2-amino-1-ethyl-4-oxo-1,5-dihydro-imidazol-5-ylidene)propyl]amide (11e). Yellow powder. Mp > 250 °C. Yield = 25%. ^{1}H NMR (DMSO-d_6) δ: 1.03 (m, 3H, CH_3); 2.48 (m, 2H, CH_2); 3.30 (m, 4H, CH_2); 3.51 (q, J = 7.2 Hz, 2H, CH_2); 5.61 (t, J = 7.2 Hz, 1H, CH═); 6.88 (s, 1H, H-3′, Ar); 7.26 (br s, 2H, NH_2); 8.30 (br s, 1H, NHCO); 11.92 (br s, 1H, H-1′, Ar). ^{13}C NMR (DMSO-d_6) δ: 13.90 (*C*H_3); 27.19 (*C*H_2); 33.39 (*C*H_2); 38.07 (*C*H_2); 97.52 (C-5′, Ar); 104.56 (C-4′, Ar); 112.52 (C-3′, Ar); 114.24 (*C*H═); 128.39 (C-2′, Ar); 142.63 (C-4); 157.48 (C-2, *C*═N); 158.91 (*C*═O); 167.91 (*C*═O). HRMS *m*/*z*: 431.9668 found (calculated for $C_{13}H_{16}N_5O_2{}^{79}Br_2$ [M+H]$^{+\bullet}$ requires 431.9671). Anal. Calc. for $C_{13}H_{15}N_5O_2Br_2$: C, 36.05; H, 3.49; N, 16.17. Found for C, 36.11; H, 3.51; N, 16.02.

(5*Z*) 4,5-Dichloro-1*H*-pyrrole-2-carboxylic acid [3-(2-amino-1-ethyl-4-oxo-1,5-dihydro-imidazol-5-ylidene)propyl]amide (11f). Yellow powder. Mp > 250 °C. Yield = 34%. ^{1}H NMR (DMSO-d_6) δ: 1.04 (t, J = 6.9 Hz, 3H, CH_3); 2.47 (m, 2H, CH_2); 3.29 (m, 2H, CH_2); 3.35 (m, 2H, CH_2); 3.53 (m, 2H, CH_2); 5.62 (t, J = 7.4 Hz, 1H, CH═); 6.87 (s, 1H, H-3′, Ar); 7.32 (br s, 2H, NH_2); 8.35 (br s, 1H, NH); 12.51 (br, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 13.90 (*C*H_3); 27.19 (*C*H_2); 33.39 (*C*H_2); 38.07 (*C*H_2); 55.96 (C-4, Ar); 97.52 (C-5′, Ar); 104.56 (C-4′, Ar); 112.52 (C-3′, Ar); 114.24 (CH═); 128.39 (C-24, Ar); 157.48 (C═N); 158.91 (C═O); 167.91 (C═O). HRMS *m*/*z*: 344.0678 found (calculated for $C_{13}H_{16}N_5O_2{}^{35}Cl_2$ [M+H]$^{+\bullet}$ requires 344.0681). Anal. Calc. for $C_{13}H_{15}N_5O_2Cl_2$: C, 45.36; H, 4.39; N, 20.35. Found for C, 45.47; H, 4.43; N, 20.02.

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