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Two versatile routes towards Cerpegin and analogues: applications of a one pot reaction to new analogues of Cerpegin

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ABSTRACT

Simple and efficient routes to the natural alkaloid Cerpegin and new analogues are described herein. In a first approach, we extend the scope of a one pot three steps reaction, which permits the synthesis of new analogues of Cerpegin, substituted in different ways. In a second line of approach, we present an unprecedented synthesis of Cerpegin and analogues where methylfuranones are condensed with dimethylformamide diethylacetal (DMFDEA) to yield enaminolactone esters, which react easily with various primary amines affording Cerpegin and new analogues. We applied this second approach to the synthesis of new bis-Cerpegins and *N*-amino-Cerpegins. Most of the syntheses are performed under environmental friendly conditions.

1. Introduction

Cerpegin **1** is an alkaloid extracted from *Ceropegia juncea* in 1990,[1] which is a plant used in traditional Indian phamacopeia and known for its tranquillising, anti-inflammatory, analgesic and anti-ulcer properties.[2] The skeleton of Cerpegin (Fig. 1) is original and is composed of two fused ring moieties: pyridinone and lactone. The pyridinone ring system and the corresponding derivatives occur abundantly in a wide variety of naturally occurring alkaloids and are also found in synthetic biologically active molecules.[3]

Several syntheses of Cerpegin have been reported in literature.[4–12] Some of them were based on the synthesis of pyridinone ring followed by the synthesis of lactone[4–8] and others were based on lactone modification.[9–12] For instance, most of them were multistep and permitted the synthesis of Cerpegin in poor overall yields (15–34%).[4,6–10] Only three protocols allowed to attain good overall yields: Quéguiner (71%),[5] Villemin (75%),[11] and more recently Avetysian (89%).[12] However, the one-pot protocol described by Quéguiner,[5] required sophisticated reaction conditions (low temperature of −78 °C and use of lithium reagent) and the one reported by Avetysian exhibited several drawbacks (multistep, no easy availability of the reactants, use of hot benzene). In addition, the two methodologies were not versatile enough to permit the synthesis of new Cerpegin analogues **2**,**6**, which can be interesting candidates in the pharmaceutical research.

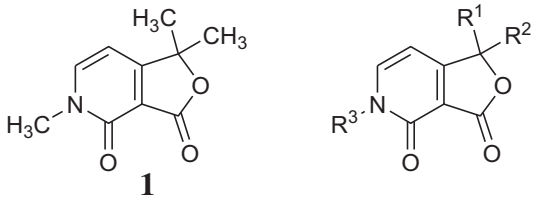

Fig. 1. Cerpegin **1** and analogues of Cerpegin.

In the course of our ongoing research on Cerpegin, we are interested in performing simple, easy and versatile syntheses, which permit the preparation of Cerpegin analogues with high purity and good yields. We report herein two approaches: the first one is based on our previous work,[11] a two or three steps one pot synthesis using 1,3,5-triazine and possibly alkyl halides, affording several Cerpegin derivatives.[13] The second one,[14] which constituted an unprecedented route, permitted the building of the pyridinone ring of the Cerpegin and analogues, via the reaction between an enaminone and several primary amines.

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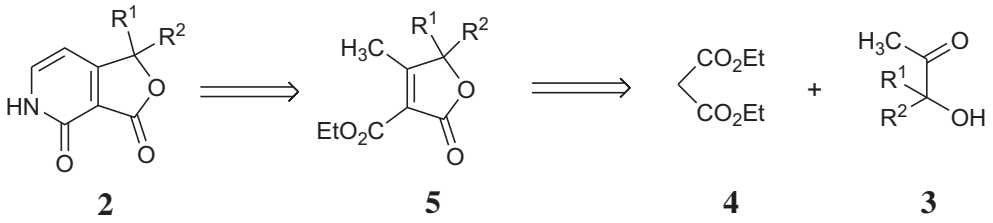
2. Results and discussion

First approach: Initially, we were interested in the synthesis of analogue of Cerpegin, non alkylated on nitrogen **2** (R^3=H). The retrosynthetic pathway for synthesis of such derivatives of Cerpegin is shown in Scheme 1.



Scheme 1. Retrosynthetic scheme of the preparation of *NH*-Cerpegin analogues **2** by the first methodology involving 1,3,5-triazine.

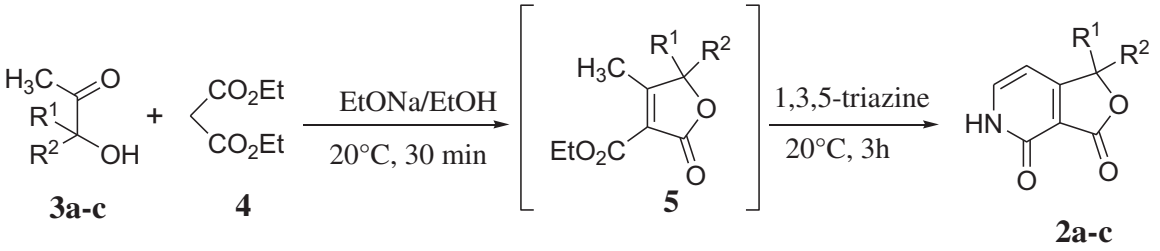
The first step is based on the formation of lactone ring from the reaction of α-hydroxyketone **3a**,**c** with diethyl malonic acid ester **4** in the presence of a base resulting in the formation of 2(5*H*)-furanone **5**. This synthesis involved a base-catalyzed transesterification, followed by a Knoevenagel reaction favoured by the Thorpe–Ingold effect.[15] Precedently,[11] we have shown that Cs_2CO_3 can be employed for the cascade synthesis of Cerpegin, but we have chosen to replace it by EtONa/EtOH because it is less expensive and it improved the reaction yields within shorter reaction times. The butenolide **5** is an allylic analogue of the malonate and can be easily deprotonated at methyl group. The carbanion formed is then condensed with 1,3,5-triazine[16–18] (an aminoformyl equivalent) permitting the formation of the pyridinone ring, affording compounds **2a**–**c** (Scheme 2). The results are reported in the Table 1.

Next, this one pot approach has been extended to the synthesis of Cerpegin **1** and analogues **6a**–**k**, alkylated on nitrogen, by using alkyl halides as described in Scheme 3.

As previously, we performed the synthesis by a one-pot protocol: compared to the first procedure, the alkyl halide was simply added some times after the addition of 1,3,5-triazine and the reaction was allowed to proceed for an additional time at room temperature or under reflux, depending on the nature of the alkyl halide (Scheme 4).

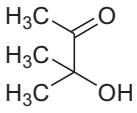
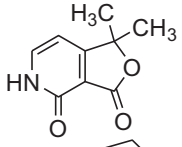
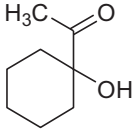
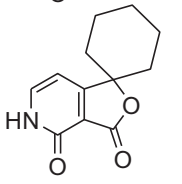
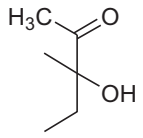
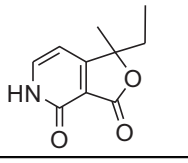
Initially, we have used methyl iodide **7a** permitting the preparation of Cerpegin **1** and analogues **6a**,**b**, which differ from Cerpegin only by the substitution of R^1 and R^2 on the lactone ring (Table 2). Interestingly, the overall yield of Cerpegin **1** was appreciably improved compared to our previous work.[11]

Secondly, other alkyl halides **7b**–**g** as described in Scheme 4, have been used, affording several Cerpegin analogues **6c**–**l**, substituted in various ways. As previously, these analogues are prepared in very good yields (71–98%). The wide range of the alkyl halides used shows the great versatility and the efficiency of this methodology in the preparation of new compounds with pyridinone moiety (Table 3).



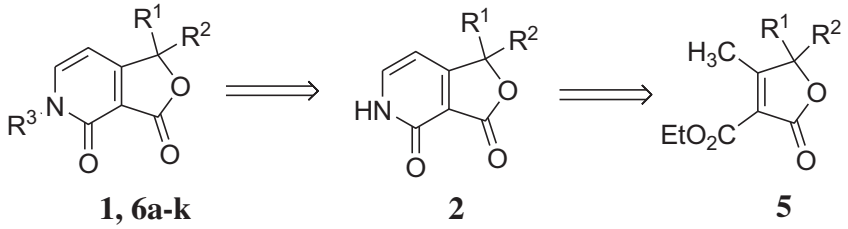
Scheme 2. One pot cascade synthesis of *NH*-Cerpegin analogues **2a**–**c** from hydroxyketones **3a**–**c** (**3a** R^1=R^2=Me; **3b** R^1, R^2=–$(CH_2)_5$–; **3c** R^1=Et, R^2=Me), using 1,3,5-triazine.

Table 1
Synthesis of *NH*-Cerpegin analogues **2a**–**c** in one pot conditions

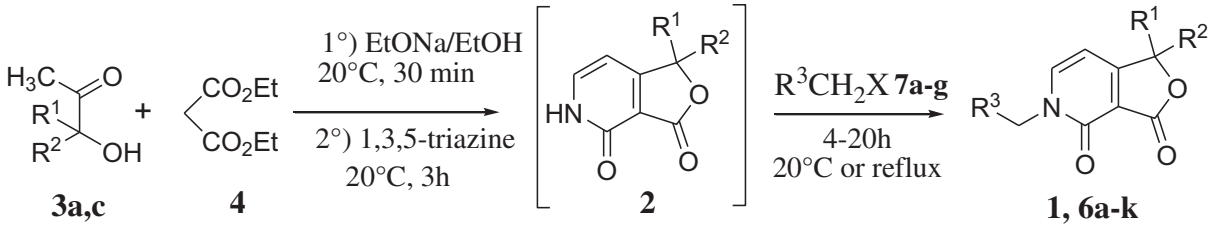
Entry	Hydroxyketone		Product		Yield [%]
1.		**3a**		**2a**	90
2.		**3b**		**2b**	90
3.		**3c**		**2c**	93

Second approach: The second approach for the synthesis of Cerpegin analogues is a multistep one (Scheme 5). The first step is the same as in the first approach. The second step involved the use of enaminone intermediates **8** instead of 1,3,5-triazine and alkyl halide. Indeed, enaminones are attractive intermediates that have been employed in the preparation of various heterocycles.[19,20] In this context, Stanovnik and Svete reported two exhaustive reviews on the synthesis of enaminone derivatives and their use as synthetic intermediates in heterocyclic chemistry and natural products synthesis.[21] Valla et al. have used them for the synthesis of 'terpenoid-like chalcones.[22]

Since the discovery of *N*,*N*-dimethylformamide diethylacetal (DMFDEA), synthesized for the first time by Meerwein,[23] several applications of formamide acetals appeared in literature, in particular as formylating agent for the preparation of enamines.[24] In our present work, DMFDEA is used in the preparation of enaminolactones **8a**–**c**. These compounds are readily obtained by the condensation of the 2(5*H*)-furanone **5a**–**c** with DMFDEA. Surprisingly, a simple mixing of the reactants at room temperature, in the absence of solvent, led to a precipitate corresponding to **8a**–**c** after only 1 h. Thus, new enaminone esters **8a**–**c** are prepared in good yields under solvent-free conditions (Table 4).

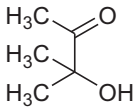
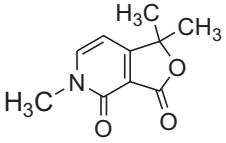
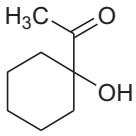
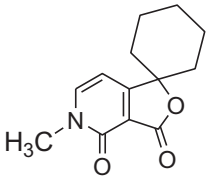
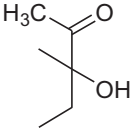
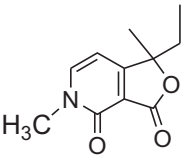


Scheme 3. Retrosynthetic scheme of the preparation of Cerpegin **1** (R^1=R^2=R^3=Me) and *N*-alkyl analogues **6a**–**k** by the first methodology involving 1,3,5-triazine and alkyl halides.



Scheme 4. One pot cascade synthesis of Cerpegin **1** and *N*-alkyl analogues **6** from hydroxyketones **3a**–**c** (**3a** R^1=R^2=Me; **3b** R^1, R^2=–$(CH_2)_5$–; **3c** R^1=Et, R^2=Me), using 1,3,5-triazine and alkyl halide **7a**–**g**.

Table 2
Synthesis of Cerpegin analogues in one pot conditions in the presence of methyl iodide **7a**

Entry	Hydroxyketone	Alkyl halide	Product	Yield [%]
1.	 **3a**	H_3C–I **7a**	 **1**	91
2.	 **3b**	H_3C–I **7a**	 **6a**	84
3.	 **3c**	H_3C–I **7a**	 **6b**	85

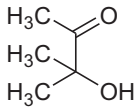
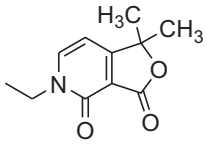
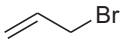
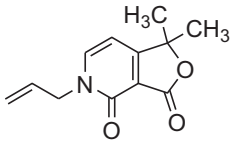
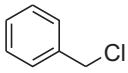
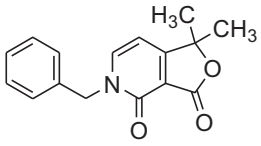
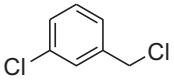
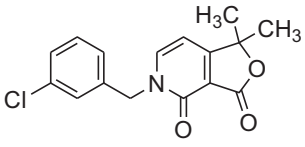
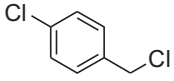
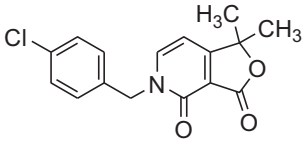
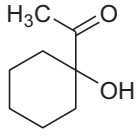
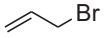
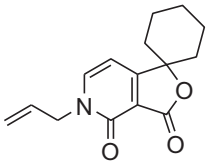
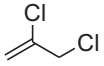
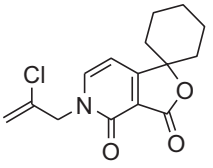
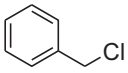
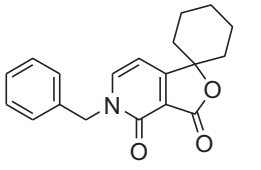
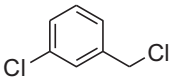
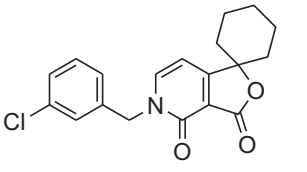
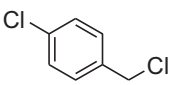
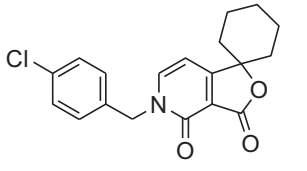
The structure of ethyl 4-(*E*)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carboxylate **8a** is confirmed by X-ray crystallography. The ORTEP diagram is shown in Fig. 2. The X-ray structure of the compound **8a** showed that the molecule is flat and that the double bond of the enamine exhibited a *s*-trans conformation with '*E*' stereochemistry. A weak electrostatic interaction is observed between C7–H7 and O3, the observed distance between O3 and H7 in the structure is smaller than their sum of van der Waals radii minus 0.4 Å. The observed length of the C2–C11 single bond [1.4083(10) Å] is shorter than the theoretical length for a Carom–C bond of 1.46 Å,[25] which indicates the formation of a conjugated-electron system along this bond.

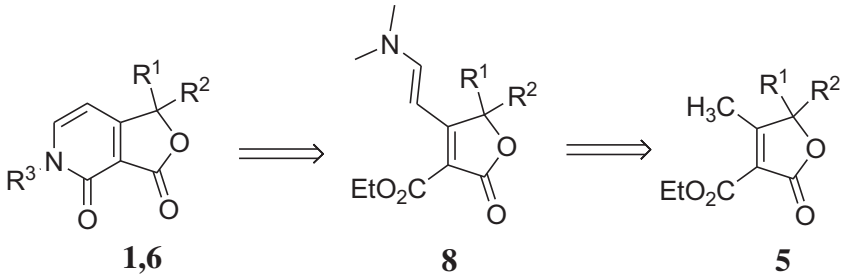
The enaminolactone esters are known to react as 'push–pull' dienes with either nucleophilic or electrophilic reagents, and thus, they can be good candidates for cycloadditions.[21,22] In our case, these enaminolactones are used as electrophilic reagents for the preparation of the Cerpegin and its analogues in the third step.

In fact, Cerpegin is easily prepared by a cyclisation reaction between the ethyl 4-((*E*)-2-(dimethylamino)vinyl)-2,5-dihydro-5,5-dialkyl-2-oxofuran-3-carboxylate **8a** and methylamine as nucleophilic agent under solvent-free conditions. Interestingly, simple heating of the reactants with a heat-gun for a few minutes permitted the preparation of Cerpegin in excellent yield (94%). These reaction conditions are applied to several primary amines providing new analogues of Cerpegin in excellent yields as summarized in Table 5. A wide variety of primary amines (aliphatic, aromatic and heterocyclic as tryptamine **9e** and histamine **9f**) are tested in the aim of investigating the versatility of this methodology and for synthesizing new structures, which could exhibit pronounced biological activities.

Reaction mechanism: The mechanism proposed for this reaction involved the addition of the amine on the double bond of the enaminone **8** accompanied with the departure of dimethylamine $(CH_3)_2NH$, followed by an intramolecular cyclization reaction between the nitrogen of the formed secondary amine **A** and the

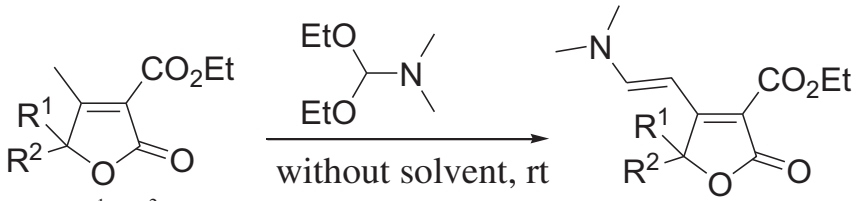
Table 3
Synthesis of Cerpegin analogues in one pot conditions in the presence of alkyl halide **7a**–**g**

Entry	Hydroxyketone	Alkyl halide	Product	Yield [%]
1.	 **3a**	 **7b**	 **6c**	84
2.		 **7c**	 **6d**	87
3.		 **7d**	 **6e**	94
4.		 **7e**	 **6f**	86
5.		 **7f**	 **6g**	98
6.	 **3b**	 **7c**	 **6h**	91
7.		 **7g**	 **6i**	71
8.		 **7d**	 **6j**	84
9.		 **7e**	 **6k**	84
10.		 **7f**	 **6l**	91



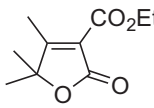
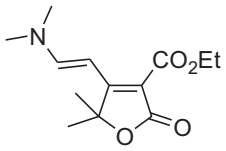
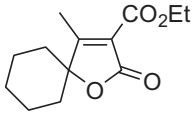
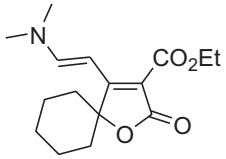
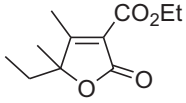
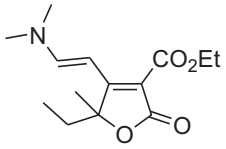
Scheme 5. General retrosynthetic scheme of Cerpegin and analogues by the second approach.

Table 4
Preparation of enaminolactones **8a**–**c** with dimethylformamide diethylacetal (DMFDEA)



5a: $R^1 = R^2 = Me$
5b: $R^1 = R^2 = -(CH_2)_5-$
5c: $R^1 = Me$, $R^2 = Et$

8a: $R^1 = R^2 = Me$
8b: $R^1 = R^2 = -(CH_2)_5-$
8c: $R^1 = Me$, $R^2 = Et$

Entry	Lactone	Enaminolactone	Yield [%]
1.	 **5a**	 **8a**	73
2.	 **5b**	 **8b**	70
3.	 **5c**	 **8c**	62

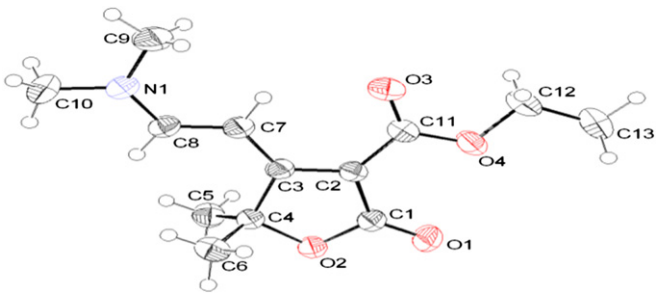


Fig. 2. ORTEP diagram of the X-ray crystal structure of compound **8a** with thermal ellipsoids at 50% probability.

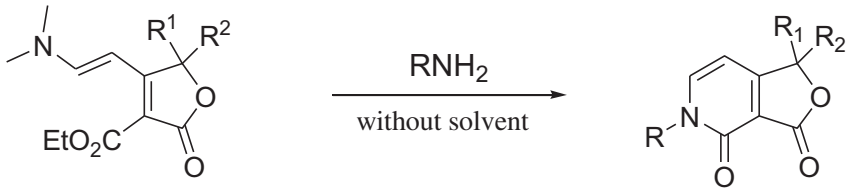
carbonyl of the ester group to give **B**. Finally, the reaction ends up with the elimination of ethanol forming Cerpegin **1** or analogues **6** (Scheme 6).

The structure of the Cerpegin **1** is already described in literature[2a] but we confirm our synthesis by the first example of X-ray crystal structure of a synthetic Cerpegin. The ORTEP diagram is shown in Fig. 3.

The structure is flat; the root mean square deviation (rms) of a least-squares plane through these atoms is about 0.0169 Å.

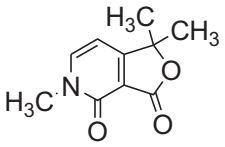
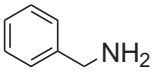
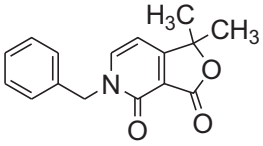
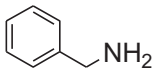
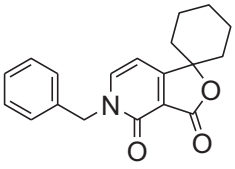
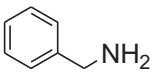
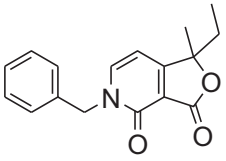
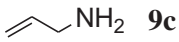
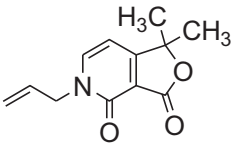
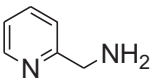
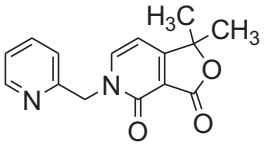
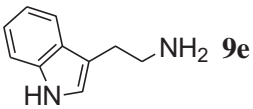
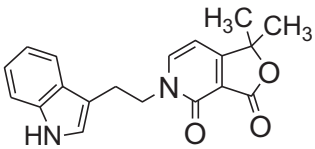
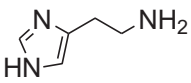
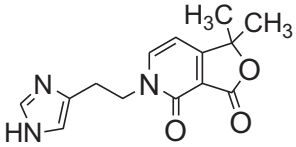
In view of these encouraging results, we have decided to develop this procedure for the preparation of dimers of Cerpegin. For instance, Porthogese has shown that bivalency is often an efficient way for increasing potency of a substance,[26] which could be conferred by bridging two neighbouring recognition sites. In the aim of obtaining new original polycyclic heterocycles, an equivalent of

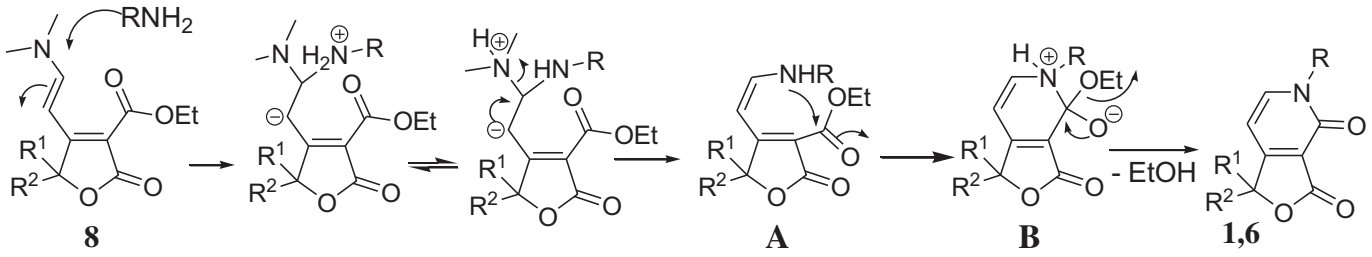
Table 5
Preparation of Cerpegin **1** and derivatives **6** from enaminolactones **8**



8a : $R^1 = R^2 = Me$
8b : $R^1 = R^2 = -(CH_2)_5-$
8c : $R^1 = Me$, $R^2 = Et$

1, 6d,e, j,m-p

Entry	Enaminolactone	RNH_2	Product	Yield [%]
1.	**8a**	 **9a**	 **1**	94
2.	**8a**	 **9b**	 **6e**	89
3.	**8b**	 **9b**	 **6j**	88
4.	**8c**	 **9b**	 **6m**	80
5.	**8a**	 **9c**	 **6d**	91
6.	**8a**	 **9d**	 **6n**	92
7.	**8a**	 **9e**	 **6o**	84
8.	**8a**	 **9f**	 **6p**	87



Scheme 6. Proposed mechanism for the Cerpegin and analogues from enaminolactones **8**.

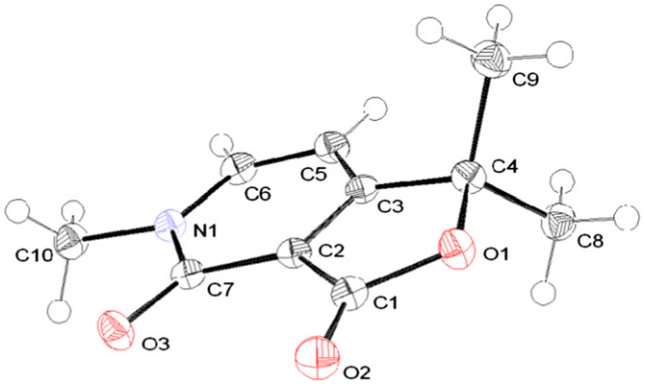


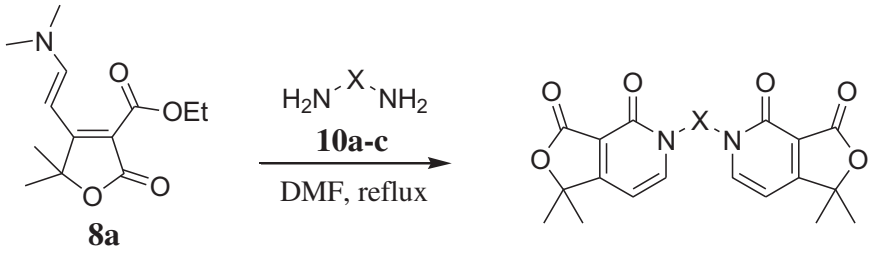
Fig. 3. ORTEP diagram of the X-ray crystal structure of Cerpegin **1** with thermal ellipsoids at 50% probability.

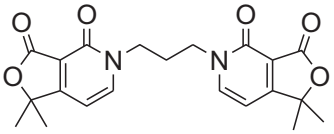
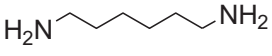
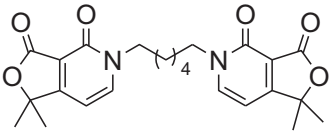
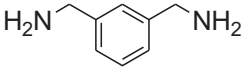
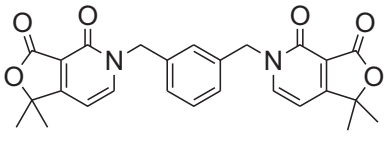
different diamines (**10a**–**c**) is added to 2 equiv of enaminone 4-((*E*)-2-(dimethylamino)vinyl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carboxylate **8a** (Table 6). Contrary to the previous synthesis, where no solvent is used, refluxed DMF is employed in order to render the reaction to completion, because a double addition is necessary resulting in the formation of new original bis-Cerpegins not described in the literature in moderate to good yields according to reaction times (Table 6).

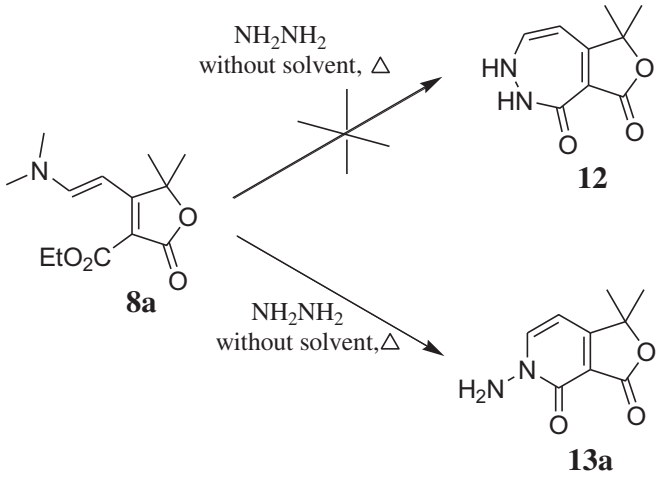
Furthermore, we are interested in synthesizing heterocyclic compounds exhibiting seven-membered rings, such as diazepinones **12**. For this reason, the diamines are replaced with hydrazines: the hydrazine monohydrate and the methylhydrazine (Scheme 7).

Surprisingly, the X-ray structure of the compound (Fig. 4) obtained from the addition of hydrazine on the enaminolactone **8a** was not in accordance with our proposed compound **12**. The X-ray structure did not show a seven-membered cycle, instead,

Table 6
Preparation of bis-Cerpegins from diamines **10a**–**c**



Entry	NH_2–X–NH_2		Product		Yield [%]
1.		**10a**		**11a**	54
2.		**10b**		**11b**	36
3.		**10c**		**11c**	80



Scheme 7. Reaction of enaminolactone **8a** in the presence of hydrazine under solvent-free condition.

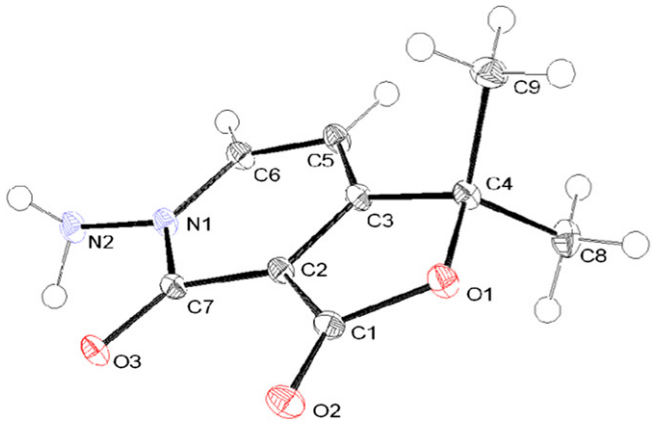


Fig. 4. X-ray of *N*-amino-1,1-dimethylfuro [3,4-*c*] pyridine-3,4(*1H,5H*)-dione **13a**.

a compound **13a** with a six-membered ring and a *N*-amino-pyridinone moiety is formed. Interestingly, the same nitrogen of the hydrazine attacked the enaminolactone in the first step and it is then involved in the cyclization step.

The conformation of compound **13a** is close to the Cerpegin (see Fig. 4), the compound **13a** is also flat (the rms deviation of a least-squares plane through these atoms is about 0.0088 Å). Furthermore, the change of the substituent on N1 affected neither the bond lengths nor bond angles in the cycle. Each hydrogen of the amino group is involved in a hydrogen bond, one with oxygen of the amide function of a separate molecule and one with oxygen of the lactone group of another molecule leading to infinite chain of Cerpegin derivatives along *b* axis (see Fig. 5).

The results about the amino-Cerpegins **13a**–**d** are reported in Table 7.

3. Conclusion

In this work, Cerpegin and many analogues are prepared via two routes in good yields using easily accessible reagents under convenient and environmentally friendly conditions. Firstly, we have extended the scope of a three steps one pot synthesis using 1,3,5-triazine and alkyl halides in order to prepare new *N*-alkyl analogues of Cerpegin. The same reaction without the use of alkyl halide permitted to obtain *NH*-Cerpegin derivatives in excellent yields.

In a second part, we have presented a new unprecedented three steps procedure, which involved the preparation of enaminolactones. This protocol has been applied to the synthesis of *N*-substituted Cerpegins, bis-Cerpegins and *N*-amino-Cerpegins. Except for the synthesis of bis-Cerpegins, all the reactions are performed without solvent, often at room temperature, following the precepts of green chemistry.

4. Experimental section

4.1. General methods

All commercial reagents were purchased from Acros, Aldrich and Sigma and were used as received without further purification. Reaction times were monitored by TLC until no starting material remained. TLC was performed using Silica gel 60 F_{254} precoated aluminium sheets. ^{1}H and ^{13}C NMR spectra are recorded on a Bruker AC 250 or Bruker AC 400 spectrometers. Chemical shifts (δ) are expressed in parts per million [ppm] and are referenced to the internal deuterated solvents with tetramethylsilane as the internal standard. Mass spectra were recorded on a QTOF Micro (Waters) spectrometer with electrospray ionization (ESI, positive mode), lockspray orthophosphoric acid, infusion introduction at 10 μL/min, a source temperature of 80 °C and desolvation temperature of 120 °C.

4.2. General procedure 1: one pot synthesis of the *NH*-Cerpegin 2a–c

In a round-bottomed flask equipped with a condenser, a mixture of α-hydroxyketone **3** (3 mmol), diethyl malonate (480 mg, 3 mmol) and a solution of sodium ethoxide (6 mmol) in ethanol (3.9 mL) was stirred at 20 °C for 30 min; then 1,3,5-triazine (240 mg, 3 mmol) was added and stirred for 3 h. The mixture was then concentrated in vacuum and neutralized with HCl solution (18%). The mixture was extracted by chloroform (3×10 mL). The combined organic layers were dried on $MgSO_4$, filtered and evaporated and the residue was purified on a silica column (EtOH/CH_2Cl_2: 5/95) to afford the corresponding *NH*-Cerpegin **2**.

*4.2.1. 1,1-Dimethylfuro[3,4-c]pyridine-3,4(1H,5H)-dione (**2a**).* The general procedure **1** using 3-hydroxy-3-methylbutan-2-one **3a** (306 mg, 3 mmol) gave **2a** (0.48 g, 90%) as a pale yellow solid, mp 248–249 °C. ^{1}H NMR ($CDCl_3$) δ 8.00 (d, *J*=6.5 Hz, 1H, N–CH=), 6.41 (d, *J*=6.5 Hz, 1H, N–CH=CH), 1.63 (s, 6H, $2CH_3$). ^{13}C NMR ($CDCl_3$) δ 173.3, 167.2, 160.3, 143.5, 112.1, 99.8, 83.4, 25.9. IR ν_{max} (neat/cm^{-1}): 3406, 1758, 1702, 1652, 1606, 1560, 1478. EIMS *m*/*z* (% relative abundance): 180 (M+1, 90), 162 (100), 134 (10). HRMS (ES-QTOF) calcd for $C_9H_{10}NO_3$ M+H 180.0661. Found 180.0665.

*4.2.2. 1,1-Pentamethylenefuro[3,4-c]pyridine-3,4(1H,5H)-dione (**2b**).* The general procedure **1** using 1-(1-hydroxycyclohexyl) ethanone **3b** (426 mg, 3 mmol) gave **2b** (0.59 g, 90%) as a yellow solid, mp 267–269 °C. ^{1}H NMR ($CDCl_3$) δ 7.96 (d, *J*=5.0 Hz, 1H, N–CH=), 6.13 (d, *J*=5.0 Hz, 1H, N–CH=CH), 1.80–1.25 (m, 10H, $5CH_2$). ^{13}C NMR ($CDCl_3$) δ 172.4, 168.4, 163.5, 152.6, 106.8, 100.2, 85.1, 35.2, 24.6, 21.9. IR ν_{max} (neat/cm^{-1}): 2934, 1734, 1680, 1606, 1564, 1516. EIMS *m*/*z* (% relative abundance): 220 (M+1, 85), 202 (100). HRMS (ES-QTOF) calcd for $C_{12}H_{15}NO_3$ M+H 220.0974. Found 220.0966.

*4.2.3. 1-Ethyl-1-methylfuro[3,4-c]pyridine-3,4(1H,5H)-dione (**2c**).* The general procedure **1** using 3-hydroxy-3-methylpentan-2-one **3c** (348 mg, 3 mmol) gave **2c** (0.54 g, 93%) as a yellow solid, mp 215–216 °C. ^{1}H NMR ($CDCl_3$) δ 8.02 (d, *J*=6.4 Hz, 1H, N–CH=), 6.37 (d, *J*=6.4 Hz, 1H, N–CH=CH), 2.04 (dq, *J*=7.3, 14.6 Hz,

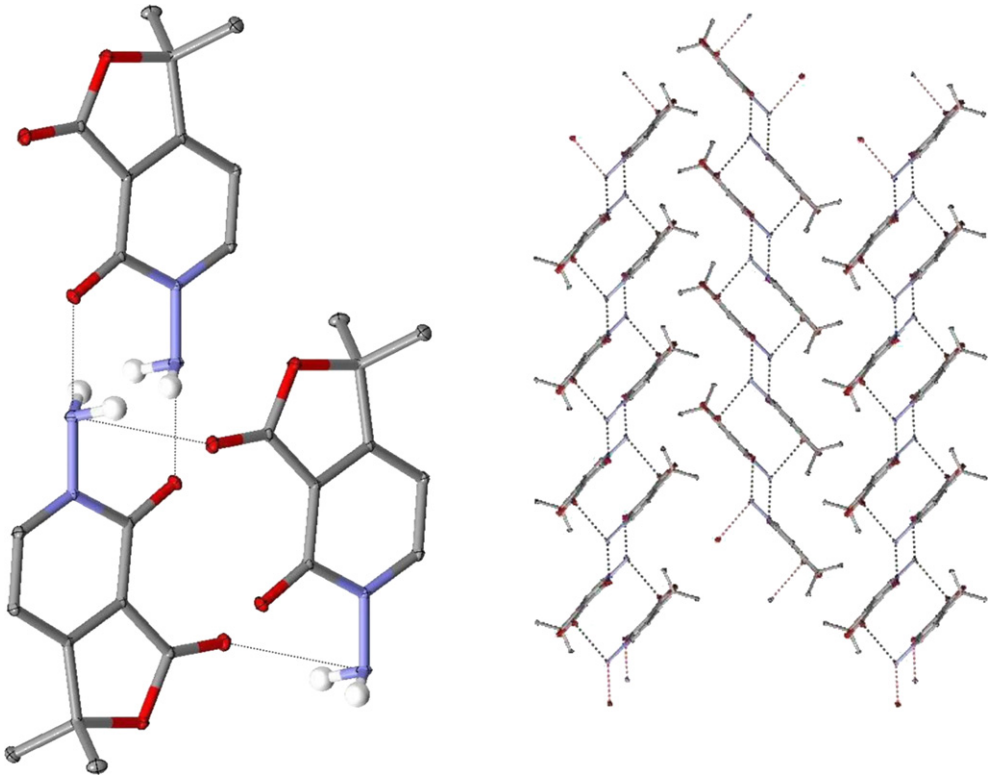
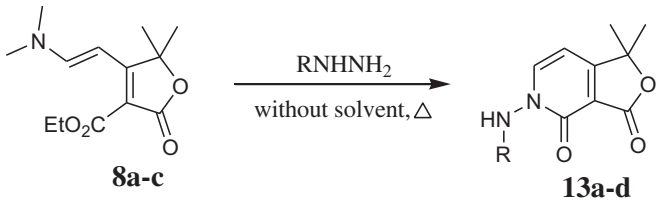
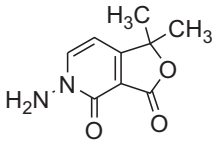
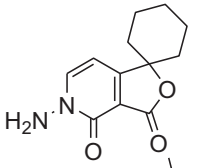
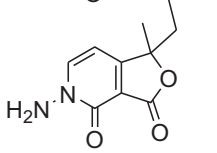
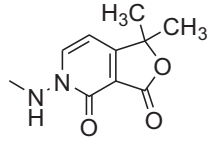


Fig. 5. Infinite chain of Cerpegin derivatives in crystal packing.

Table 7
Synthesis of amino-Cerpegins **13a**–**d** in solvent-free condition



Entry	Enaminolactone	$RNHNH_2$	*N*-Amino-Cerpegin	Yield [%]
1.	**8a**	NH_2NH_2	 **13a**	80
2.	**8b**	NH_2NH_2	 **13b**	71
3.	**8c**	NH_2NH_2	 **13c**	81
4.	**8a**	CH_3NHNH_2	 **13d**	46

$CH_aH_bCH_3$), 1.87 (dq, J=7.3, 14.6 Hz, $CH_aH_bCH_3$)1.60 (s, 3H, CH_3), 0.84 (t, J=7.3 Hz, CH_2CH_3). ^{13}C NMR ($CDCl_3$) δ 172.3, 167.5, 160.4, 143.3, 113.1, 99.9, 86.0, 31.6, 24.4, 7.6. IR ν_{max} (neat/cm^{-1}): 3196, 2974, 2938, 2884, 1751, 1670, 1604, 1556, 1450, 1348, 1210, 1158. EIMS m/z (% relative abundance): 194 (M+1, 60), 176 (100), 148 (30). HRMS (ES-QTOF) calcd for $C_{10}H_{12}NO_3$ M+H 194.0817. Found 194.0820.

4.3. General procedure 2: one pot synthesis of the substituted *N*-alkylCerpegin 1, 6a–l

In a round-bottomed flask equipped with a condenser, a mixture of α-hydroxyketone **3** (3 mmol), diethyl malonate (480 mg, 3 mmol) and a solution of sodium ethoxide (6 mmol) in ethanol (3.9 mL) was stirred at 20 °C for 30 min; then 1,3,5-triazine (240 mg, 3 mmol) was added and stirred for 3 h. After addition of alkyl halide (3 mmol), the reaction was then allowed to proceed under stirring under different conditions proper to every compound. The mixture was then concentrated in vacuum and the residue was extracted by dichloromethane (2×15 mL). The combined organic layers were dried on $MgSO_4$, filtered and evaporated and the residue was crystallised from ethanol–chloroform to afford the corresponding *N*-alkylCerpegin **1**,**6**.

*4.3.1. 1,1,5-Trimethylfuro[3,4-c]pyridine-3,4(1H,5H)-dione or Cerpegin (**1**).* The general procedure **2** using 3-hydroxy-3-methylbutan-2-one **3a** (306 mg, 3 mmol) and methyl iodide (3 mL, 48 mmol) with a third step performed at room temperature during 20 h gave **1** (0.53 g, 91%) as a white solid, mp 267–270 °C. ^{1}H NMR ($CDCl_3$) δ 7.68 (d, J=6.7 Hz, 1H, N–CH=), 6.27 (d, J=6.7 Hz, 1H, N–CH=CH), 3.64 (s, 3H, NCH_3), 1.59 (s, 6H, $2CH_3$). ^{13}C NMR ($CDCl_3$) δ 171.9, 166.9, 157.9, 146.0, 112.2, 98.4, 82.5, 37.8, 26.1. IR ν_{max} (neat/cm^{-1}): 1752, 1720, 1666, 1636, 1598, 1552. EIMS m/z (% relative abundance): 194 (M+H, 81), 176 (100). HRMS (ES-QTOF) calcd for $C_{10}H_{12}NO_3$ M+H 194.0816. Found 194.0817.

*4.3.2. 5-Methyl-1,1-pentamethylenefuro[3,4-c]pyridine-3,4(1H,5H)-dione (**6a**).* The general procedure **2** using 1-(1-hydroxycyclohexyl) ethanone **3b** (426 mg, 3 mmol) and MeI (2.27 g, 16 mmol) with a third step performed at room temperature during 20 h gave **6a** (0.58 g, 84%) as a white solid, mp 247–248 °C. ^{1}H NMR ($CDCl_3$) δ 7.64 (d, J=6.7 Hz, 1H, N–CH=), 6.21 (d, J=6.7 Hz, 1H, NCH=CH), 3.61 (s, 3H, NCH_3), 1.90–1.67 (m, 8H, $4CH_2$), 1.39–1.24 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ 171.8, 167.3, 158.0, 145.8, 112.3, 98.7, 84.2, 37.7, 34.9, 24.6, 21.9. IR ν_{max} (neat/cm^{-1}): 2940, 1748, 1670, 1548. EIMS m/z (% relative abundance): 234 (M+H, 52), 216 (100). HRMS (ES-QTOF) calcd for $C_{13}H_{16}NO_3$ M+H 234.1130. Found 234.1129.

*4.3.3. 1-Ethyl-1,5-dimethylfuro[3,4-c]pyridine-3,4(1H,5H)-dione (**6b**).* The general procedure **2** using 3-hydroxy-3-methylpentan-2-one **3c** (348 mg, 3 mmol) and MeI (3 mL, 48 mmol) with a third step performed at room temperature during 20 h gave **6b** (0.53 g, 85%) as a yellow solid, mp 201–202 °C. ^{1}H NMR ($CDCl_3$) δ 7.65 (d, J=6.5 Hz, 1H, N–CH=), 6.18 (d, J=6.5 Hz, 1H, NCH=CH), 3.63 (s, 3H, NCH_3), 2.00 (dq, J=7.5, 15.0 Hz, $CH_aH_bCH_3$), 1.82 (dq, J=7.5, 15.0 Hz, $CH_aH_bCH_3$),1.56 (s, 3H, CCH_3), 0.81 (t, J=7.5 Hz, 3H, CH_2CH_3). ^{13}C NMR ($CDCl_3$) δ 171.0, 167.3, 158.0, 145.6, 113.6, 98.6, 85.3, 38.0, 32.0, 24.9, 8.0. IR ν_{max} (neat/cm^{-1}): 2966, 2936, 1748, 1670, 1594, 1554, 1456. EIMS m/z (% relative abundance): 207 (M+, 24), 192 (5), 179 (15), 178 (100), 42 (25). HRMS (ES-QTOF) calcd for $C_{11}H_{13}NO_3Na$ M+Na 230.0793. Found 230.0800.

*4.3.4. 5-Ethyl-1,1-dimethylfuro[3,4-c]pyridine-3,4(1H,5H)-dione (**6c**).* The general procedure **2** using 3-hydroxy-3-methyl-2-butanone **3a** (306 mg, 3 mmol) and ethyl iodide (4.67 g, 30 mmol) with a third step performed at 70–80 °C during 3 h gave **6c** (0.52 g, 84%) as an orange solid, mp 125–126 °C. ^{1}H NMR ($CDCl_3$) δ 7.96 (d, J=6.7 Hz, 1H, N–CH=), 6.43 (d, J=6.7 Hz, 1H, N–CH=CH), 4.11 (q, J=6.9 Hz, 2H, CH_2CH_3), 1.59 (s, 6H, $2CH_3$), 1.35 (t, J=6.9 Hz, 3H, CH_3CH_2). ^{13}C NMR ($CDCl_3$) δ 171.3, 167.5, 163.2, 157.4, 145.6, 99.0, 83.0, 44.6, 25.4, 14.4. IR ν_{max} (neat/cm^{-1}): 1754, 1720, 1662, 1552, 1306, 1090, 948. EIMS m/z (% relative abundance): 208 (8), 207 (M+, 76), 203 (49), 192 (50), 188 (63), 163 (100), 43 (56).

*4.3.5. 5-Allyl-1,1-dimethylfuro[3,4-c]pyridine-3,4(1H,5H)-dione (**6d**).* The general procedure **2** using 3-hydroxy-3-methyl-2-butanone **3a** (306 mg, 3 mmol) and H_2C=$CHCH_2Br$ (363 mg, 3 mmol) with a third step performed under reflux during 3 h gave **6d** (0.57 g, 87%) as a yellow solid, mp 174–175 °C. ^{1}H NMR ($CDCl_3$) δ 7.65 (d, J=6.7 Hz, 1H, N–CH=), 6.24 (d, J=6.7 Hz, 1H, N–CH=CH), 6.03–5.87 (m, 1H, CH=CH_2), 5.35–5.25 (2H, m, CH=CH_2), 4.65–4.62 (2H, m, CH_2–CH=CH_2), 1.58 (6H, s, $2CH_3$). ^{13}C NMR ($CDCl_3$) δ 171.7, 166.6, 157.1, 144.5, 131.8, 120.0, 112.5, 98.4, 82.3, 50.9, 25.9. IR ν_{max} (neat/cm^{-1}): 1768, 1660, 1594, 1556, 1428. EIMS m/z (% relative abundance): 220 (M+H, 32), 202 (100), 174 (2). HRMS (ES-QTOF) calcd for $C_{12}H_{14}NO_3$ M+H 220.0974. Found 220.0969.

*4.3.6. 5-Benzyl-1,1-dimethylfuro[3,4-c]pyridine-3,4(1H,5H) dione (**6e**).* The general procedure **2** using 3-hydroxy-3-methyl-2-butanone **3a** (306 mg, 3 mmol) and benzyl chloride $ArCH_2Cl$ (380 mg, 3 mmol) with a third step performed under reflux during 3 h gave **6e** (0.76 g, 94%) as a yellow solid, mp 202–203 °C. ^{1}H NMR ($CDCl_3$) δ 7.63 (d, J=6.8 Hz, 1H, N–CH=), 7.39–7.35 (m, 5H, Harom), 6.19 (d, J=6.8 Hz, 1H, N–CH=CH), 5.20 (s, 2H, CH_2), 1.57 (s, 6H, $2CH_3$). ^{13}C NMR ($CDCl_3$) δ 171.8, 167.0, 157.6, 144.8, 135.7, 129.2, 128.8, 128.6, 112.9, 98.9, 82.6, 52.0, 26.0. IR ν_{max} (neat/cm^{-1}): 1756, 1668, 1548. EIMS m/z (% relative abundance): 270 (M+H, 41), 252 (10), 91 (100). HRMS (ES-QTOF) calcd for $C_{16}H_{16}NO_3$ M+H 270.1130. Found 270.1136.

*4.3.7. 5-(3-Chlorobenzyl)-1,1-dimethylfuro[3,4-c]pyridine-3,4(1H,5H)-dione (**6f**).* The general procedure **2** using 3-hydroxy-3-methyl-2-butanone **3a** (306 mg, 3 mmol) and *m*-Cl–$ArCH_2Cl$ (483 mg, 3 mmol) with a third step performed under reflux during 3 h gave **6f** (0.78 g, 86%) as an orange solid, mp 213–214 °C. ^{1}H NMR ($CDCl_3$) δ 8.00 (d, J=6.8 Hz, 1H, N–CH=), 7.40–7.22 (m, 4H, Harom), 6.48 (d, J=6.8 Hz, 1H, N–CH=CH), 5.30 (s, 2H, CH_2), 1.61 (s, 6H, $2CH_3$). ^{13}C NMR ($CDCl_3$) δ 171.8, 166.4, 157.0, 145.9, 132.9, 132.7, 130.0, 129.4, 129.3, 127.1, 111.4, 98.7, 82.3, 49.5, 25.5. IR ν_{max} (neat/cm^{-1}): 1752, 1670, 1598, 1552. EIMS m/z (% relative abundance): 304 (M+H, 38), 286 (35), 125 (100). HRMS (ES-QTOF) calcd for $C_{16}H_{15}NO_3Cl$ M+H 304.0740. Found 304.0728.

*4.3.8. 5-(4-Chlorobenzyl)-1,1-dimethylfuro[3,4-c]pyridine-3,4(1H,5H)-dione (**6g**).* The general procedure **2** using 3-hydroxy-3-methyl-2-butanone **3a** (306 mg, 3 mmol) and *p*-Cl–$ArCH_2Cl$ (483 mg, 3 mmol) with a third step performed under reflux during 3 h gave **6g** (0.89 g, 98%) as an orange solid, mp 243–244 °C. ^{1}H NMR ($CDCl_3$) δ 8.11 (d, J=6.7 Hz, 1H, N–CH=), 7.40 (d, J=8.5 Hz, 2H, Harom), 7.31 (d, J=8.5 Hz, 2H, Harom), 6.44 (d, J=6.7 Hz, 1H, N–CH=CH), 5.20 (s, 2H, CH_2), 1.59 (s, 6H, $2CH_3$). ^{13}C NMR ($CDCl_3$) δ 171.7, 166.3, 156.9, 145.8, 134.4, 133.4, 129.8, 128.5, 111.4, 98.7, 82.2, 50.9, 25.5. IR ν_{max} (neat/cm^{-1}): 1756, 1668, 1598, 1550. EIMS m/z (% relative abundance): 304 (M+H, 60), 125 (100). HRMS (ES-QTOF) calcd for $C_{16}H_{15}NO_3Cl$ M+H 304.0740. Found 304.0744.

*4.3.9. 5-Allyl-1,1-pentamethylenefuro[3,4-c]pyridine-3,4(1H,5H)-dione (**6h**).* The general procedure **2** using 1-(1-hydroxycyclohexyl) ethanone **3b** (426 mg, 3 mmol) and H_2C=$CHCH_2Br$ (363 mg, 3 mmol) with a third step performed under reflux during 3 h gave **6h** (0.71 g, 91%) as a brown solid, mp 149–151 °C. ^{1}H NMR ($CDCl_3$) δ 7.77 (d, J=6.7 Hz, 1H, N–CH=), 6.35 (d, J=6.7 Hz, 1H, NCH=CH),

6.04–5.91 (m, 1H, CH=CH_2), 5.34–5.30 (m, 2H, CH=CH_2), 4.67 (d, J=6.1 Hz, 2H, NCH_2), 1.90–1.60 (m, 8H, $4CH_2$), 1.45–1.20 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ 171.8, 167.5, 157.6, 144.9, 131.8, 120.0, 112.4, 99.4, 84.6, 51.1, 34.8, 24.5, 21.9. IR ν_{max} (neat/cm^{-1}): 1770, 1700, 1662, 1594, 1552, 1438, 1386, 1148. EIMS m/z (% relative abundance): 259 (M+, 74), 254 (96), 253 (46), 241 (100), 236 (71), 213 (45), 212 (49), 207 (46), 202 (82), 198 (60), 184 (86).

*4.3.10. 5-(2-Chloroprop-1-ene)-1,1-pentamethylenefuro[3,4-c]pyridine-3,4(1H,5H)-dione (**6i**).* The general procedure **2** using 1-(1-hydroxycyclohexyl)ethanone **3b** (426 mg, 3 mmol) and H_2C=$CClCH_2Cl$ (330 mg, 3 mmol) with a third step performed under reflux during 3 h gave **6i** (0.62 g, 71%) as a brown solid, mp 170–171 °C. ^{1}H NMR (DMSO-d_6) δ 8.14 (d, J=6.8 Hz, 1H, N–CH), 6.72 (d, J=6.8 Hz, 1H, NCH–CH), 5.54 (dd, J=2.1, 11.0 Hz, 2H, CCH_2), 4.88 (s, 1H, CH_2CCl), 2.00–1.16 (m, 10H, $5CH_2$). ^{13}C NMR ($CDCl_3$) δ 172.1, 167.1, 157.2, 144.8, 134.7, 118.4, 112.8, 99.1, 84.5, 54.1, 34.8, 24.6, 21.8. IR ν_{max} (neat/cm^{-1}): 2934, 1750, 1673, 1596, 1545. EIMS m/z (% relative abundance): 294 (M+H, 47), 276 (100). HRMS (ES-QTOF) calcd for $C_{15}H_{17}NO_3Cl$ M+H 294.0897. Found 294.0902.

*4.3.11. 5-Benzyl-1,1-pentamethylenefuro[3,4-c]pyridine-3,4(1H,5H)-dione (**6j**).* The general procedure **2** using 1-(1-hydroxycyclohexyl) ethanone **3b** (426 mg, 3 mmol) and $ArCH_2Cl$ (380 mg, 3 mmol) with a third step performed under reflux during 3 h gave **6j** (0.78 g, 84%) as a yellow solid, mp 215–216 °C. ^{1}H NMR ($CDCl_3$) δ 7.59 (1H, d, ^3J=6.8 Hz, =CH–N), 7.37–7.26 (5H, m, Harom), 6.17 (1H, d, ^3J=6.8 Hz, CH=CH–N), 5.18 (2H, s, CH_2Ph), 1.70–1.23 (10H, m, $5CH_2$). ^{13}C NMR (CD_2Cl_2) δ 175.9, 160.8, 151.0, 140.7, 134.5, 132.7, 132.0, 131.9, 114.7, 103.3, 87.6, 55.3, 37.7, 27.9, 25.7. IR ν_{max} (neat/cm^{-1}): 1754, 1664, 1542. EIMS m/z (% relative abundance): 310 (M+H, 19), 292 (100), 91 (33). HRMS (ES-QTOF) calcd for $C_{19}H_{20}NO_3$ M+H 310.1443. Found 310.1452.

*4.3.12. 5-(3-Chlorobenzyl)-1,1-pentamethylenelfuro[3,4-c]pyridine-3,4(1H,5H)-dione (**6k**).* The general procedure **2** using 1-(1-hydroxycyclohexyl)ethanone **3b** (426 mg, 3 mmol) and m-Cl–$ArCH_2Cl$ (483 mg, 3 mmol) with a third step performed under reflux during 3 h gave **6k** (0.86 g, 84%) as a yellow solid, 230–231 °C. ^{1}H NMR (DMSO-d_6) δ 8.24 (d, J=6.8 Hz, 1H, N–CH=), 7.57–7.34 (m, 4H, Harom), 6.76 (d, J=6.8 Hz, 1H, NCH=CH), 5.27 (s, 2H, CH_2), 1.98–1.23 (m, 10H, $5CH_2$). ^{13}C NMR ($CDCl_3$) δ 171.4, 166.6, 157.2, 145.0, 133.1, 132.5, 130.7, 129.5, 129.3, 127.1, 111.8, 98.7, 83.8, 49.3, 34.2, 24.0, 21.4. IR ν_{max} (neat/cm^{-1}): 1749, 1667, 1543. EIMS m/z (% relative abundance): 344 (M+H, 70), 326 (100). HRMS (ES-QTOF) calcd for $C_{19}H_{19}NO_3Cl$ M+H 344.1053. Found 344.1050.

*4.3.13. 5-(4-Chlorobenzyl)-1,1-pentamethylenefuro[3,4-c]pyridine-3,4(1H,5H)-dione (**6l**).* The general procedure **2** using 1-(1-hydroxycyclohexyl)ethanone **3b** (426 mg, 3 mmol) and p-Cl–$ArCH_2Cl$ (483 mg, 3 mmol) with a third step performed under reflux during 3 h gave **6l** (0.93 g, 91%) as a yellow solid, mp 247–248 °C. ^{1}H NMR (DMSO-d_6) δ 8.37 (d, J=6.7 Hz, 1H, N–CH=), 7.48–7.39 (m, 4H, Harom), 6.73 (d, J=6.7 Hz, 1H, NCH=CH), 5.18 (s, 2H, CH_2), 1.98–1.25 (m, 10H, $5CH_2$). ^{13}C NMR ($CDCl_3$) δ 171.8, 167.2, 157.7, 144.8, 134.6, 134.2, 130.2, 129.3, 112.7, 99.5, 84.4, 51.6, 34.8, 24.6, 21.2. IR ν_{max} (neat/cm^{-1}): 2941, 1755, 1664, 1551. EIMS m/z (% relative abundance): 344 (M+H, 93), 326 (100). HRMS (ES-QTOF) calcd for $C_{19}H_{19}NO_3Cl$ M+H 344.1053. Found 344.1055.

4.4. General procedure 3: synthesis of 4-(2-dimethylaminovinyl)-2-oxo-2,5-dihydrofuran-3-ethyl carboxylate (8a–c)

A mixture of ethyl 5,5-dialkyl-4-methyl-2-oxo-2,5-dihydrofuran-3-carboxylate **5a–c** (20 mmol) and DMF acetal (20 mmol) was stirred at room temperature without solvent for 1 or 2 h. A purple colouration more pronounced overtime occurred. The purple solid obtained was washed several times with diethylether and some drops of ethanol. Recrystallisation in absolute ethanol afforded yellow crystals of enaminolactone **8a–c**.

*4.4.1. Ethyl 4-(E)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carboxylate (**8a**).* The general procedure **3** using ethyl 4,5,5-trimethyl-2-oxo-2,5-dihydrofuran-3-carboxylate **5a** (3.96 g, 20 mmol) and DMF acetal (2.94 g, 20 mmol) gave **8a** (3.69 g, 73%) as yellow crystals, mp 159–160 °C. ^{1}H NMR ($CDCl_3$) δ 7.64 (1H, d, ^3J=13.2 Hz, =CH–N), 6.05 (1H, d, ^3J=13.2 Hz, CH=CH–N), 4.32 (2H, q, ^3J=7.0 Hz, CH_2), 3.10 (6H, d large, $N(CH_3)_2$), 1.56 (6H, s, $2CH_3$), 1.37 (3H, t, ^3J=7.0 Hz, CH_2CH_3). ^{13}C NMR ($CDCl_3$) δ 176.8, 169.2, 164.9, 153.4, 100.5, 90.1, 82.2, 60.1, 36.9, 28.1, 14.5. IR ν_{max} (neat/cm^{-1}): 1716, 1681, 1604, 1540, 1188. EIMS m/z (% relative abundance): 254 (M+H, 24), 226 (100), 208 (26). HRMS (ES-QTOF) calcd for $C_{13}H_{19}NO_4Na$ M+Na 276.1212. Found 276.1194.

*4.4.2. Ethyl 4-(E)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-pentamethylene-2-oxofuran-3-carboxylate (**8b**).* The general procedure **3** using ethyl 4-methyl-2,5-dihydro-5,5-pentamethylene-2-oxofuran-3-carboxylate **5b** (4.76 g, 20 mmol) and DMF acetal (2.94 g, 20 mmol) gave **8b** (4.10 g, 70%) as yellow crystals, mp 163–164 °C. ^{1}H NMR ($CDCl_3$) δ 8.00 (1H, d, ^3J=13.2 Hz, =CH–N), 5.81 (1H, d, ^3J=13.2 Hz, CH=CH–N), 4.32 (2H, q, ^3J=7.0 Hz, CH_2), 3.04 (6H, d large, $N(CH_3)_2$), 1.90–1.59 (10H, m, $5CH_2$), 1.37 (3H, t, ^3J=7.0 Hz, CH_2CH_3). ^{13}C NMR ($CDCl_3$) δ 176.4, 169.7, 165.2, 153.9, 100.4, 89.9, 84.4, 60.1, 45.2, 36.7, 24.9, 22.0, 14.5. IR ν_{max} (neat/cm^{-1}): 1720, 1674, 1614, 1540, 1181. EIMS m/z (% relative abundance): 294 (M+H, 36), 266 (100), 248 (17). HRMS (ES-QTOF) calcd for $C_{16}H_{23}NO_4Na$ M+Na 316.1525. Found 316.1506.

*4.4.3. Ethyl 4-(E)-2-(dimethylaminovinyl)-5-ethyl-2,5-dihydro-5-methyl-2-oxofuran-3-carboxylate (**8c**).* The general procedure **3** using ethyl 5-ethyl-2,5-dihydro-4,5-dimethyl-2-oxofuran-3-carboxylate **5c** (4.24 g, 20 mmol) and DMF acetal (2.94 g, 20 mmol) gave **8c** (3.31 g, 62%) as yellow crystals, mp 138–140 °C. ^{1}H NMR ($CDCl_3$) δ 7.64 (1H, d, ^3J=13.0 Hz, =CH–N), 6.08 (1H, d, ^3J=13.0 Hz, CH=CH–N), 4.31 (2H, m, $CO_2CH_2CH_3$), 2,90 (6H, s large, $N(CH_3)_2$), 1.98 (1H, dq J=7.5, 15.0 Hz, $CH_AH_BCH_3$), 1.73 (1H, dq J=7.5, 15.0 Hz, $CH_AH_BCH_3$), 2.06–1.65 (2H, m, CH_2CH_3), 1.52 (3H, s, CCH_3), 1.37 (3H, t, ^3J=7.0 Hz, $CO_2CH_2CH_3$), 0.81 (3H, t, CH_2CH_3). ^{13}C NMR ($CDCl_3$) δ 175.3, 169.7, 164.8, 152.9, 101.7, 90.3, 84.9, 60.0, 36.8, 33.6, 27.1, 14.5, 7.5. IR ν_{max} (neat/cm^{-1}): 1725, 1677, 1605, 1538, 1195. EIMS m/z (% relative abundance): 268 (M+H, 16), 240 (100), 222 (08). HRMS (ES-QTOF) calcd for $C_{14}H_{22}NO_4Na$ M+H 268.1549. Found 268.1559.

4.5. General procedure 4: Cerpegin 1 and analogues 6d,e,j,m–p synthesis via the enaminolactones 8

A mixture of enaminolactone **8** (2 mmol) and primary amine (2 mmol) was heated with a hot gun. After cooling, the solid obtained was washed several times with diethylether. Recrystallisation in absolute ethanol afforded crystals of Cerpegin and analogues.

*4.5.1. 1,1,5-Trimethylfuro[3,4-c]pyridine-3,4(1H,5H)-dione: Cerpegin (**1**).* The general procedure **4** using enaminolactone **8a** (0.50 g, 2 mmol) and methylamine (0.15 g, 3 mmol) gave Cerpegin **1** (0.36 g, 94%) as white crystals, mp 267–269 °C (lit. 268–270 °C).[1b] ^{1}H and ^{13}C NMR, IR and HRMS are conformed to those reported in Section 4.3.1.

*4.5.2. 5-Benzyl-1,1-dimethylfuro[3,4-c]pyridine-3,4(1H,5H)-dione (**6e**).* The general procedure **4** using enaminolactone **8a** (0.50 g, 2 mmol) and benzylamine **9b** (0.21 g, 2 mmol) with a 5 min hot gun

heating gave **6e** (0.48 g, 89%) as a white solid, mp 202–203 °C. ^{1}H and ^{13}C NMR, IR and HRMS are conformed to those reported inSection4.3.6.

*4.5.3. 5-Benzyl-1-cyclohexylfuro[3,4-c]pyridine-3,4(1H,5H)-dione (**6j**).* The general procedure **4** using enaminolactone **8b** (0.58 g, 2 mmol) and benzylamine **9b** (0.21 g, 2 mmol) with a 5 min hot gun heating gave **6j** (0.54 g, 88%) as a white solid, mp 216 °C. ^{1}H and ^{13}C NMR, IR and HRMS are conformed to those reported inSection4.3.11.

*4.5.4. 5-Benzyl-1-ethyl-1-methylfuro[3,4-c]pyridine-3,4(1H,5H)-dione (**6m**).* The general procedure **4** using enaminolactone **8c** (0.53 g, 2 mmol) and benzylamine **9b** (0.21 g, 2 mmol with a 5 min hot gun heating gave **6m** (0.45 g, 80%) as a white solid, mp 165–166 °C. ^{1}H NMR ($CDCl_3$) δ 7.66 (1H, d, ^3J=6.7 Hz, =CH–N), 7.43–7.36 (5H, m, Harom), 6.15 (1H, d, ^3J=6.7 Hz, CH=CH–N), 5.26 (1H, d, J=14.5 Hz, CH_aPh), 5.13 (1H, d, J=14.5 Hz, CH_bPh), 1.98 (1H, dq J=7.5, 15 Hz, CH_aCH_3), 1.81 (1H, dq J=7.5, 15 Hz, CH_bCH_3),1.54 (3H, s, CH_3), 0.81 (3H, t, ^3J=7.5 Hz, CH_2CH_3). ^{13}C NMR ($CDCl_3$) δ 170.6, 167.0, 157.3, 144.3, 135.5, 129.1, 128.7, 128.6, 113.6, 98.7, 85.0, 51.9, 31.6, 24.4, 7.7. IR ν_{max} (neat/cm^{-1}): 1753, 1664, 1547, 1065. EIMS m/z (% relative abundance): 284 (M+H, 67), 266 (100), 91 (73). HRMS (ES-QTOF) calcd for $C_{17}H_{18}NO_3$ M+H 284.1287. Found 284.1298.

*4.5.5. 5-Allyl-1-ethyl-1-methylfuro[3,4-c]pyridine-3,4(1H,5H)-dione (**6d**).* The general procedure **4** using enaminolactone **8a** (0.50 g, 2 mmol) and allylamine **9c** (0.11 g, 2 mmol) with a 2 min hot gun heating gave **6d** (0.40 g, 91%) as a white solid, mp 174–175 °C. ^{1}H and ^{13}C NMR, IR and HRMS are conformed to those reported in Section4.3.5.

*4.5.6. 1,1-Dimethyl-5-((pyridine-2-yl)methyl)furo[3,4-c]pyridine-3,4(1H,5H)-dione (**6n**).* The general procedure **4** using enaminolactone **8a** (0.50 g, 2 mmol) and pyridin-2-ylmethanamine **9d** (0.21 g, 2 mmol) with a 2 min hot gun heating gave **6n** (0.49 g, 92%) as a white solid, mp 175 °C. ^{1}H NMR ($CDCl_3$) δ 8.52–8.51 (1H, m, Hpyr), 8.00 (1H, d, ^3J=6.7 Hz, =CH–N), 7.73–7.66 (1H, m, Hpyr), 7.58–7.55 (1H, m, Hpyr), 7.25–7.21 (1H, m, Hpyr), 6.24 (1H, d, ^3J=6.7 Hz, CH=CH–N), 5.25 (2H, s, CH_2), 1.59 (6H, s, $2CH_3$). ^{13}C NMR ($CDCl_3$) δ 171.8, 157.2, 154.4, 149.5, 145.8, 137.2, 124.3, 123.4, 120.3, 98.4, 82.4, 53.8, 25.9. IR ν_{max} (cm^{-1}): 1746, 1672, 1590, 1546, 1142, 1063. EIMS m/z (% relative abundance): 271 (M+H, 12), 253 (100), 225 (17), 209 (27), 194 (12), 110 (52), 92 (14). HRMS (ES-QTOF) calcd for $C_{15}H_{15}N_2O_3$ M+H 271.1083. Found 271.1087.

*4.5.7. 5-(2-(1H-Indol-3-yl)ethyl)-1,1-dimethylfuro[3,4-c]pyridine-3,4(1H,5H)-dione (**6o**).* The general procedure **4** using enaminolactone **8a** (0.50 g, 2 mmol) and 2-(1*H*-indol-3-yl)ethanamine **9e** (0.32 g, 2 mmol) with 5 min hot gun heating gave **6o** (0.54 g, 84%) as a white solid, mp 245–246 °C. ^{1}H NMR ($CDCl_3$) δ 8.10 (1H, s, NH), 7.59 (1H, d, ^3J=6.5 Hz, CH=CH–N), 7.30–7.09 (4H, m, Harom), 6.99 (1H, s, C=CH–NH), 5.89 (1H, d, ^3J=6.5 Hz, =CH–N), 4.26 (2H, t, ^3J=6.7 Hz, CH_2CH_2–N), 3.28 (2H, t, ^3J=6.7 Hz, CH_2CH_2–N), 1.56 (6H, s, $2CH_3$). ^{13}C NMR ($CDCl_3$) δ 172.3, 166.7, 157.1, 147.4, 136.5, 127.4, 123.6, 121.4, 118.7, 118.5, 111.8, 110.5, 98.6, 82.5, 50.1, 25.8, 24.8. IR ν_{max} (neat/cm^{-1}): 3269, 1760, 1669, 1596, 1552, 1075, 1057. EIMS m/z (% relative abundance): 323 (M+H, 09), 144 (100). HRMS (ES-QTOF) calcd for $C_{19}H_{19}N_2O_3$ M+H 323.1396. Found 323.1404.

*4.5.8. 5-(2-(1H-Imidazol-4-yl)ethyl)-1,1-dimethylfuro[3,4-c]pyridine-3,4(1H,5H)-dione (**6p**).* The general procedure **4** using enaminolactone **8a** (0.50 g, 2 mmol) and 2-(1*H*-imidazol-4-yl)ethanamine **9f** (0.22 g, 2 mmol) with 5 min hot gun heating gave **6p** (0.47 g, 87%) as a white solid, mp 245–246 °C. ^{1}H NMR ($CDCl_3$) δ 12.03 (1H, t, ^3J=2.9 Hz, NH), 7.96 (1H, d, ^3J=5.0 Hz, =CH–N), 7.67 (1H, d, ^3J=2.9 Hz, C=CH–NH), 6.77 (1H, d, ^3J=2.9 Hz, N=CH–NH), 6.58 (1H, d, ^3J=5.0 Hz, CH=CH–N), 4.21 (2H, t, ^3J=6.6 Hz, NCH_2), 2.74 (2H, t, ^3J=6.6 Hz, CH_2CH_2N), 1.55 (6H, s, $2CH_3$). ^{13}C NMR ($CDCl_3$) δ 171.9, 166.3, 156.5, 147.1, 135.5, 135.0, 113.0, 110.1, 98.1, 82.1, 48.8, 26.8, 25.4. IR ν_{max} (neat/cm^{-1}): 3296, 1730, 1668, 1556. EIMS m/z (% relative abundance): 274 (M+H, 12), 256 (100), 212 (17), 180 (27), 95 (100). HRMS (ES-QTOF) calcd for $C_{14}H_{16}N_3O_3$ M+H 274.1192. Found 274.1187.

4.6. General procedure 5: synthesis of bis-Cerpegins 11a–c

Ethyl 4-((*E*)-2-(dimethylamino)vinyl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carboxylate **8a** (2 mmol) and diamine **10** (1 mmol) were stirred in DMF (5 mL). After dissolution, the mixture was refluxed during 3 h. After cooling and evaporation of the solvent, the residue was washed several times with diethylether to give the bis-Cerpegins **11**.

*4.6.1. 1,1-Dimethyl-5-(3-(1,1-dimethyl-3,4-dioxofuro[3,4-c]pyridin-5(1H,3H,4H)-yl)propyl)furo[3,4-c]pyridine-3,4(1H,5H)-dione (**11a**).* The general procedure **5** using ethyl 4-(*E*)-2-(dimethylamino)vinyl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carboxylate **8a** (0.50 g, 2 mmol) and 1,3-propyldiamine **10a** (0.074 g, 1 mmol) gave the compound **11a** (0.21 g, 54%) as a white solid, mp >260 °C. ^{1}H NMR ($CDCl_3$) δ 7.98 (2H, d, ^3J=6.7 Hz, 2CH=CH–N), 6.31 (2H, d, ^3J=6.7 Hz, 2CH=CH–N), 4.11 (4H, t, ^3J=6.2 Hz, $CH_2CH_2CH_2$), 2.32 (2H, t, ^3J=6.2 Hz, $CH_2CH_2CH_2$), 1.60 (12H, s, $4CH_3$). ^{13}C NMR ($CDCl_3$) δ 172.0, 166.9, 147.5, 135.4, 112.2, 99.1, 82.3, 46.8, 30.0, 25.9. IR ν_{max} (neat/cm^{-1}): 1752, 1664, 1594, 1542, 1149, 1082. EIMS m/z (% relative abundance): 399 (M+H, 40), 220 (100). HRMS (ES-QTOF) calcd for $C_{21}H_{23}N_2O_6$ M+H 399.1556. Found 399.1573.

*4.6.2. 1,1-Dimethyl-3,4-dioxofuro[3,4-c]pyridine-5(1H,3H,4H)-hexyl)furo[3,4-c]pyridine-3,4(1H,5H)-dione (**11b**).* The general procedure **5** using ethyl 4-(*E*)-2-(dimethylamino)vinyl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carboxylate **8a** (0.50 g, 2 mmol) and 1,6-hexyldiamine **10b** (0.116 g, 1 mmol) gave the compound **11b** (0.16 g, 36%) as a white solid, mp >260 °C. ^{1}H NMR ($CDCl_3$) δ 8.22 (2H, d, ^3J=6.7 Hz, 2CH=CH–N), 6.68 (2H, d, ^3J=6.7 Hz, 2CH=CH–N), 3.97 (4H, t, ^3J=6.9 Hz, $2CH_2$), 1.67–1.65 (4H, m, $2CH_2$), 1.57 (12H, s, $4CH_3$), 1.41–1.34 (4H, m, $2CH_2$). ^{13}C NMR ($CDCl_3$) δ 172.1, 166.8, 147.5, 135.9, 112.4, 99.2, 85.3, 46.8, 28.00, 26.9, 25.9. IR ν_{max} (neat/cm^{-1}): 1754, 1673, 1594, 1555, 1155, 1112. EIMS m/z (% relative abundance): 463 (M+Na, 100), 441 (M+H, 28), 329 (23), 307 (10). HRMS (ES-QTOF) calcd for $C_{24}H_{29}N_2O_6$ M+H 441.2026. Found 441.2025.

*4.6.3. 1,1-Dimethyl-5-(3-(1,1-dimethyl-3,4-dioxofuro[3,4-c]pyridin-5(1H,3H,4H)-yl)methyl)benzyl)-1,1-dimethylfuro[3,4-c]pyridine-3,4(1H,5H)-dione (**11c**).* The general procedure **5** using ethyl 4-(*E*)-2-(dimethylamino)vinyl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carboxylate **8a** (0.50 g, 2 mmol) and *m*-xylyldiamine **10c** (0.136 g, 1 mmol) gave the compound **11c** (0.37 g, 80%) as a white solid, mp >260 °C. ^{1}H NMR ($CDCl_3$) δ 7.73 (2H, d, ^3J=6.7 Hz, 2CH=CH–N), 7.49 (1H, s, Harom), 7.34 (3H, s, 3Harom), 6.24 (2H, d, ^3J=6.7 Hz, 2CH=CH–N), 5.15 (4H, s, $2CH_2$), 1.57 (12H, s, $4CH_3$). ^{13}C NMR ($CDCl_3$) δ 171.9, 166.8, 157.5, 145.3, 136.4, 128.5–129.6, 112.4, 99.1, 82.6, 52.1, 25.9. IR ν_{max} (neat/cm^{-1}): 1759, 1667, 1603, 1549, 1155. EIMS m/z (% relative abundance): 461 (M+H, 46), 443 (100), 425 (14), 282 (60), 264 (25). HRMS (ES-QTOF) calcd for $C_{26}H_{25}N_2O_6$ M+H 461.1713. Found 461.1707.

4.7. General procedure 6: synthesis of amino-Cerpegins 13a–d

Ethyl 4-((*E*)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-dialkyl-2-oxofuran-3-carboxylate **8** (2 mmol) and hydrazine (3 mmol) were heated with a hot gun during a few minutes. After cooling, the solid obtained was washed several times with diethylether then recrystallised in absolute ethanol to provide amino-Cerpegins **13a–d**.

*4.7.1. N-Amino-1,1-dimethylfuro[3,4-c]pyridine-3,4(1H,5H)-dione (**13a**).* The general procedure **6** using ethyl 4-((*E*)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-dialkyl-2-oxofuran-3-carboxylate **8a** (0.50 g, 2 mmol) and monohydrate hydrazine (0.15 g, 3 mmol) gave the compound **13a** (0.31 g, 80%) as a white solid, mp 245–246 °C. ^{1}H NMR (DMSO-d_6) δ 8.17 (1H, d, ^3J=6.7 Hz, CH=CH–NH), 6.56 (1H, d, ^3J=6.7 Hz, CH=CH–NH), 6.23 (2H, s, NH_2), 1.55 (6H, s, $2CH_3$). ^{13}C NMR (DMSO-d_6) δ 169.6, 166.2, 155.3, 145.0, 109.0, 97.4, 82.3, 25.6. IR ν_{max} (neat/cm^{-1}): 3303, 3203, 1743, 1587, 1639, 1545. EIMS *m*/*z* (% relative abundance): 195 (M+H, 32), 177 (100). HRMS (ES-QTOF) calcd for $C_9H_{11}N_2O_3$ M+H 195.0770. Found 195.0779.

*4.7.2. N-Amino-1-cyclohexylfuro[3,4-c]pyridine-3,4(1H,5H)-dione (**13b**).* The general procedure **6** using ethyl 4-((*E*)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-pentamethylene-2-oxofuran-3-carboxylate **8b** (0.58 g, 2 mmol) and monohydrate hydrazine (0.15 g, 3 mmol) gave the compound **13b** (0.33 g, 71%) as a white solid, mp 238–239 °C. ^{1}H NMR (DMSO-d_6) δ 8.14 (1H, d, ^3J=6.7 Hz, CH=CH–NH), 6.54 (1H, d, ^3J=6.7 Hz, CH=CH–NH), 6.22 (2H, s, NH_2), 1.91–1.32 (10H, m, $5CH_2$). ^{13}C NMR (DMSO-d_6) δ 169.2, 166.3, 155.4, 144.8, 109.1, 97.7, 83.6, 33.9, 23.7, 21.6. IR ν_{max} (neat/cm^{-1}): 3310, 3190, 1748, 1669, 1582, 1545. EIMS *m*/*z* (% relative abundance): 235 (M+H, 19), 217 (100). HRMS (ES-QTOF) calcd for $C_{12}H_{15}N_2O_3$ M+H 235.1083. Found 235.1102.

*4.7.3. N-Amino-1-methyl-1-ethylfuro[3,4-c]pyridine-3,4(1H,5H)-dione (**13c**).* The general procedure **6** using ethyl 4-((*E*)-2-(dimethylaminovinyl)-5-ethyl-2,5-dihydro-5-methyl-2-oxofuran-3-carboxylate **8c** (0.53 g, 2 mmol) and monohydrate hydrazine (0.15 g, 3 mmol) gave the compound **13c** (0.33 g, 81%) as a white solid, mp 206 °C. ^{1}H NMR (DMSO-d_6) δ 8.24 (1H, d, ^3J=6.7 Hz, CH=CH–NH), 6.57 (1H, d, ^3J=6.7 Hz, CH=CH–NH), 6.25 (2H, s, NH_2), 1.91 (2H, m, CH_2CH_3), 1.55 (3H, s, CH_3), 0.69 (3H, t, ^3J=7.3 Hz, CH_2CH_3). ^{13}C NMR (DMSO-d_6) δ 168.27, 166.5, 155.3, 144.9, 110.0, 97.6, 84.9, 30.6, 24.2, 7.4. IR ν_{max} (neat/cm^{-1}): 3303, 3199, 1746, 1664, 1585, 1546. EIMS *m*/*z* (% relative abundance): 209 (M+H, 26), 191 (100), 163 (22). HRMS (ES-QTOF) calcd for $C_{10}H_{13}N_2O_3$ M+H 209.0926. Found 209.0930.

*4.7.4. 1,1-Dimethyl-5-(methylamino)furo[3,4-c]pyridine-3,4(1H,5H)-dione (**13d**).* The general procedure **6** using ethyl 4-((*E*)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carboxylate **8a** (0.50 g, 2 mmol) and methylhydrazine (0.14 g, 3 mmol) gave the compound **13d** (0.19 g, 46%) as a white solid, mp 218 °C. ^{1}H NMR (DMSO-d_6) δ 8.24 (1H, d, ^3J=6.7 Hz, CH=CH–N), 6.78 (1H, q, ^3J=5.7 Hz, NHMe), 6.62 (1H, d, ^3J=6.7 Hz, CH=CH–N), 2.65 (3H, d, ^3J=5.7 Hz, CH_3), 1.52 (6H, s, $2CH_3$). ^{13}C NMR (DMSO-d_6) δ 177.3, 170.7, 155.5, 146.1, 110.2, 98.3, 82.4, 38.5, 25.4. IR ν_{max} (neat/cm^{-1}): 3310, 3190, 1748, 1669, 1582, 1545. EIMS *m*/*z* (% relative abundance): 439 (2M+Na, 20), 231 (59), 209 (100), 191 (58). HRMS (ES-QTOF) calcd for $C_{20}H_{24}N_4O_6Na$ 2M+Na 439.1594. Found 439.1591.

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