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A serendipitous conversion of enaminolactone nitriles with primary amines: a new synthesis of substituted 2-aminopyridine derivatives

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ABSTRACT

In the course of our studies on Cerpegin analogues synthesis, a serendipitous reactivity of enaminolactone nitrile has been observed. Instead of expecting iminocerpegins, we have gained new class of substituted 2-aminopyridines. The methodology has been applied on a wide range of primary amines, as aliphatic, aromatic, heteroaromatic and also, diamines, hydrazines and chiral amines.

1. Introduction

The fascinating chemistry of enaminones and their derivatives has attracted the attention of numerous researchers due to their potential properties in the synthesis of heterocyclic compounds.[1,2] They are known to react as diene 'push–pull' with nucleophilic or electrophilic reagents and they can be good candidates for cycloadditions.

Since the discovery of *N*,*N*-dimethylformamide diethylacetal (DMFDEA), synthesized for the first time by Meerwein,[3] several applications of formamide acetals were appeared in literature, in particular as formylating agent for the preparation of enamines using usually active methylene ketones.[4–6]

Recently, in a previous work, we have reported the successful synthesis of Cerpegin and derivatives **1**.[7] The Cerpegin is an alkaloid extracted from *Ceropegia juncea* in 1990,[8] which is a plant used in traditional Indian pharmacopeia and well-known for its tranquillizing, anti-inflammatory, analgesic, and antiulcer properties.[9] The Cerpegin and derivatives **1** synthesis was based on two steps: initially, the reaction began with the condensation of butenolide ester **2** and DMFDEA at room temperature under solvent free conditions providing enaminolactone ester **3** with good yields. In a second time, the reaction between enaminolactones **3** and various primary amines were easily performed without solvent under thermal heating leading to Cerpegin and derivatives.[7]

In this context and in continuation of our work, we were interested to develop efficient and easy methods for the preparation of new biologically active heterocyclic compounds, in particular new Cerpegin analogues, starting from another class of furanones, the butenolide nitriles.

2. Results and discussion

The synthesis of new analogues of Cerpegin begins by the preparation of butenolide nitriles **4**. These latter were easily obtained, in cascade reaction, from α-hydroxyketones **5** and ethyl cyanoacetate in the presence of base like EtONa/EtOH,[7,10,11] K_2CO_3,[12,13] or $CsCO_3$.[14] We have shown that these bases could be favourably substituted by Al_2O_3/KF[15,16] as basic support, less expensive and easy to prepare and to handle. The reaction was carried out in solvent free conditions for 3 h and gave good yields (80–89%) (Table 1).

In connection with our previous work shown in Scheme 1, and in the aim of obtaining new analogues of Cerpegin like iminocerpegin **7**, we have decided to perform the reaction of butenolide nitriles **4** with DMFDEA in order to obtain corresponding

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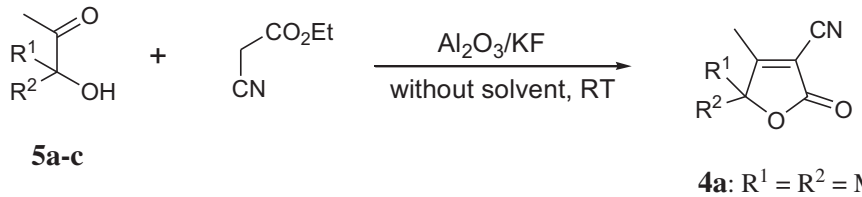
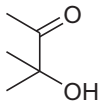
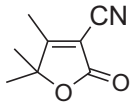
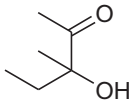
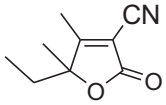
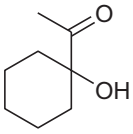
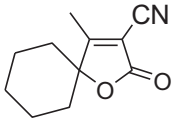
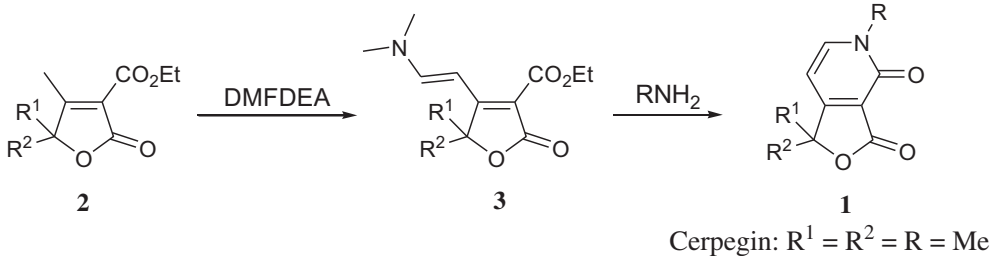
Table 1
Preparation of butenolide nitrile **4a**–**c**



5a-c

4a: $R^1 = R^2 = Me$
4b: $R^1 = Me$, $R^2 = Et$
4c: $R^1 = R^2 = -(CH_2)_5-$

Entry	Hydroxyketone	Butenolide	Yield [%]
1	 **5a**	 **4a**	89
2	 **5b**	 **4b**	80
3	 **5c**	 **4c**	86

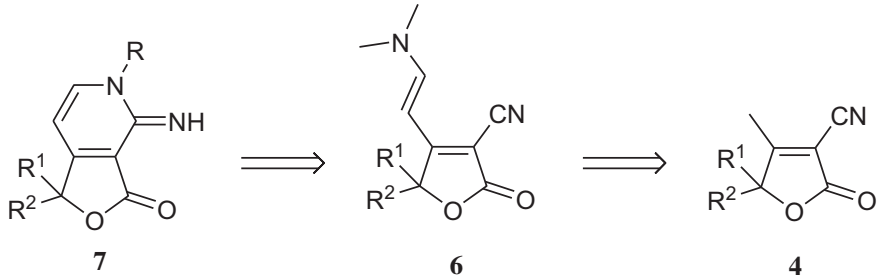


Scheme 1. Synthesis of Cerpegin and derivatives.

enaminolactone nitriles **6**. These latter were expecting to be convert in iminocerpegins **7** when treated with various primary amines (Scheme 2).

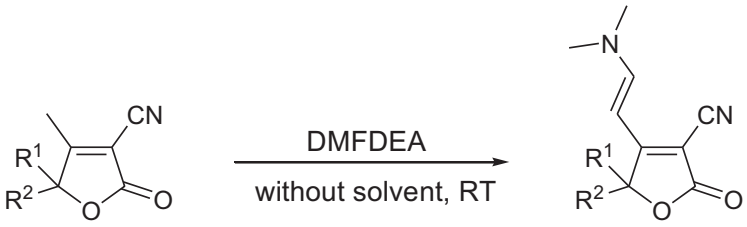
The enaminobutenolide nitriles **6a**–**c** were obtained by condensation of 4-methyl-5,5-dialkyl-2-oxo-2,5-dihydrofuran-3-carbonitriles **4a**–**c** with dimethylformamide diethylacetal DMFDEA in stoichiometric amounts. The reactions were performed without solvent and at room temperature during 1 h. The reactions afforded good yields of **6a**–**c** (66–81%). The results obtained for the preparation of enaminobutenolide nitriles **6a**–**c** are reported in Table 2.

The values of the coupling constants (12.6, 13.0 Hz) in ^{1}H NMR showed the '*E*' configuration of the double bond. Also, the X-ray single-crystal diffraction analysis of 4-(2-(dimethylaminovinyl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carbonitrile) **6a** confirmed



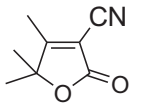
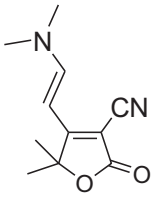
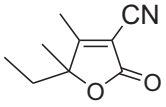
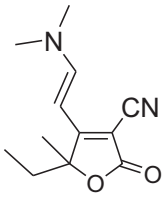
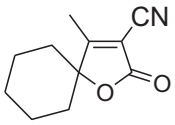
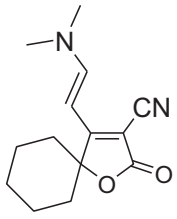
Scheme 2. Retrosynthetic scheme of preparation of iminocerpegin and derivatives.

Table 2
Preparation of enaminobutenolide nitriles **6a**–**c** with DMFDEA under free solvent conditions



4a: $R^1 = R^2 = Me$
4b: $R^1 = Me$, $R^2 = Et$
4c: $R^1 = R^2 = -(CH_2)_5-$

6a: $R^1 = R^2 = Me$
6b: $R^1 = Me$, $R^2 = Et$
6c: $R^1 = R^2 = -(CH_2)_5-$

Entry	Butenolide	Enaminobutenolide	Yield [%]
1	 **4a**	 **6a**	81
2	 **4b**	 **6b**	66
3	 **4c**	 **6c**	73

the configuration *E* for the double bond and moreover showed the conformation '*s-cis*' for the two carbon–carbon double bonds (Fig. 1a and b).

The diagram of the X-ray crystal showed that the substructure of $(CH_3)_2NCH{=}CH{-}C{=}C{-}CN$ is plane involving the push–pull diene is conjugated. This effect was already found with the corresponding ester derivative.[7] The crystal packing of **6a** shows two weak intermolecular C–H···X (N and O) hydrogen-bonds. The first one occurs between N1 and H6 to form infinite columns of molecules along *a* axis. Hydrogen-bond between O2 and H7 reinforces the crystal structure in the *b* axis direction.

After the formation of enaminolactone **6a**–**c**, the next step was the subsequent ring-closure to the iminocerpegin **7**. The condensation of enaminolactone nitriles with various primary amines was carried out in stoichiometric amounts in solvent free conditions and with thermal heating expecting the synthesis of iminocerpegins **7** (Scheme 2).

Surprisingly, the X-ray diffraction analysis of the product obtained by reaction between enaminolactone nitrile **6a** and tryptamine **8d** showed the formation of a 2-aminopyridine structure **9d** (Scheme 3 and Fig. 2) rather than the expected structure of iminocerpegin **7** (Fig. 2).

The crystal packing of **9d** displays one intramolecular N–H···O hydrogen-bond between O2 and H2 and one intermolecular N–H···..N hydrogen-bond (N3–H3···N1) leading to infinite helices of aminopyridine along the **b** axis.

Furthermore, HMBC experiments of compound **9d** have confirmed a correlation between the amine proton (NH) with a methylene carbon (CH_2) in the structure of aminopyridine, which is not possible with a structure of iminocerpegin.

Similarly, all the compounds prepared **9a**–**h** from primary amines were characterized by ^1H and ^{13}C NMR spectroscopy and they showed similar results. So, the synthesis of 2-aminopyridines instead of iminocerpegins seems to be general (Scheme 4).

These results could constitute a convenient and effective synthesis of new 2-aminopyridines **9**, which belong to a very important class of heterocyclic compounds.

The class of 2-aminopyridine presents a wide range of applications that are receiving considerable attention in the literature. This functional group, because of its chelating abilities, is commonly used as ligands in inorganic and organometallic chemistry. Additionally, aminopyridines have been shown to be biologically active molecules, they constitute an important class of heterocyclic compounds founding in numerous natural and pharmaceutical

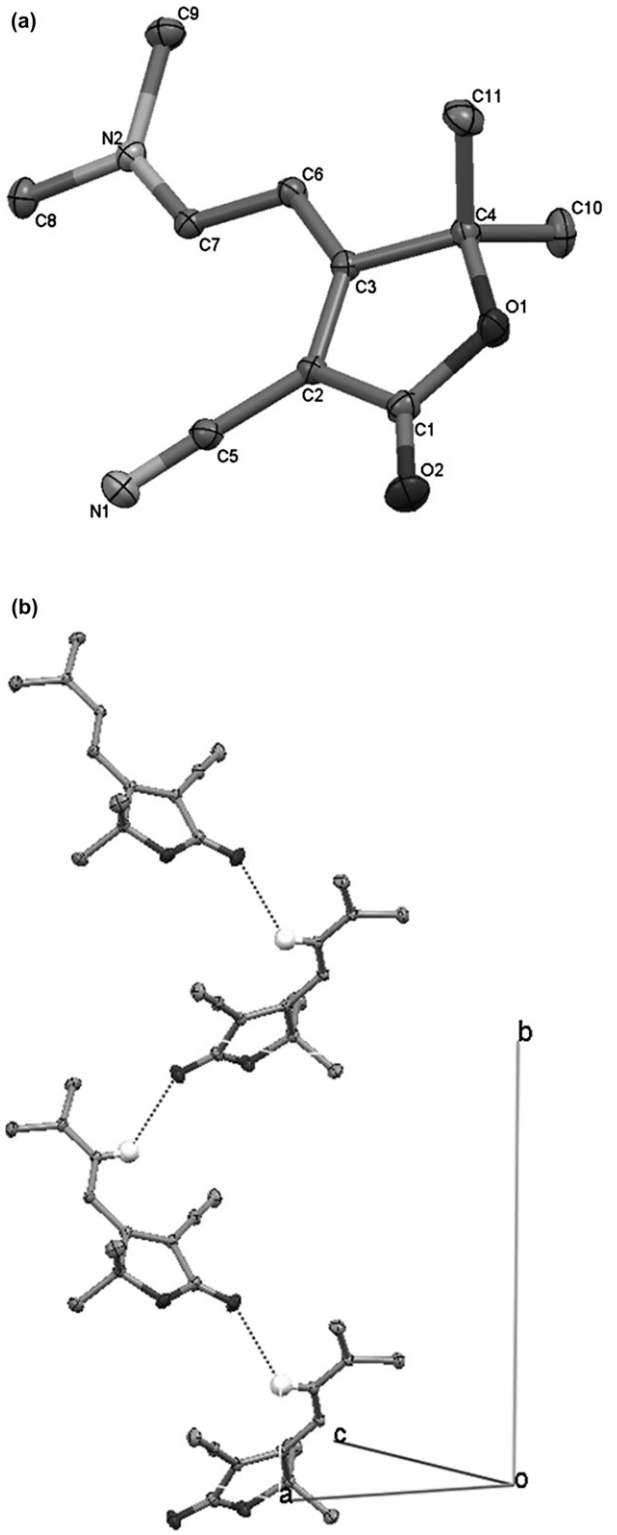


Fig. 1. a. Diagram of the X-ray crystal structure of compound **6a**. b. The crystal packing of **6a**.

products that exhibit remarkable biological activities. For all these reasons, 2-aminopyridines are valuable synthetic targets.

Today a number of synthetic routes have been reported for the synthesis of 2-aminopyridines derivatives.[17–24] Yet, a versatile route for the synthesis of *N*-substituted 2-aminopyridines using amines as nucleophilic agents under mild conditions is highly desirable.

In this work, 2-aminopyridines **9a**–**h** were prepared from a wide variety of primary amines as aliphatic, aromatic, and heterocyclic amines like tryptamine **8d** and histamine **8e** (Table 3). These two latter were tested in the aim of gaining new structures, which could exhibit pronounced biological activities.

Pleasingly, all the primary amines tested gave excellent yields (75–95%) of the desired products under the conditions described previously. The results in Table 3 show that this protocol can be applied to a variety of substrates, thus demonstrating the wide scope of this methodology.

Based on these results above, a possible mechanism for the formation of 2-aminopyridine was depicted in Scheme 5. Firstly, intermediate **A** was formed via an initial addition reaction between primary amines and the nitrile group of the enaminolactone **6**.

A then underwent an intramolecular cyclization reaction between the nitrogen group of imine anion and the double bond of the enamine accompanied by the departure of dimethylamine $(CH_3)_2NH$. **B** was transformed in 2-substituted aminopyridines **9** after an aromatization step, which constitutes probably the driving force of the reaction (Scheme 5).

The addition of primary amine can take on the carbon 2 (addition 1,2) or 4 (addition 1,4) or 6 (addition 1,6) on the system aminodienenitrile of **6**. All these additions are reversible (addition of Michael on carbon 4 or carbon 6), however only the addition on the nitrile group of the carbon 2 is followed by an intramolecular ring formation. Moreover, in order to justify our mechanism, we have done some computation. The amine is a hard nucleophile, so we have used the chelpg obtained by DFT to determinate the more electrophilic carbon. The carbon 2 of the nitrile (0.437) seems more electrophilic than the carbon 4 (0.103) and the carbon 6 (0.050).

In view of the success of this approach, diamines were tested in the aim of obtaining new original polycyclic compounds, bis(2-aminopyridines). These dimer compounds were obtained by condensation of 1 equiv of diamines **10a**–**f** with 2 equiv of enaminolactone nitrile **6a**,**b**. The mixture was refluxed in DMF during 6 h. After removing of the solvent and purification by column chromatography, we afforded the new original bis-(2-aminopyridines) **11a**–**g** in moderate to good yields (Table 4).

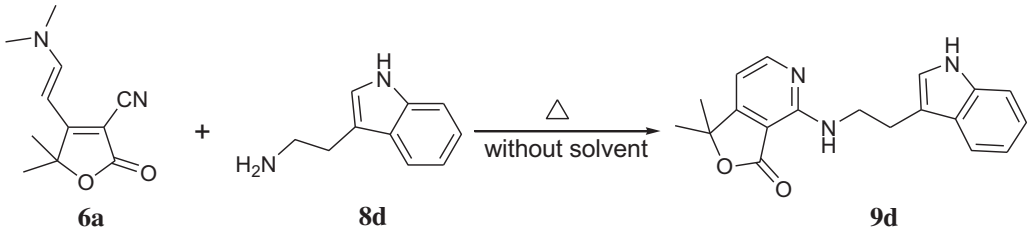
All the structures obtained present at least four cycles, many suitable locating nitrogen and oxygen atoms, allowing them to be very good chelating candidates.

Next, we have decided to study the extension of this method with hydrazines **12a**,**b**. In a similar manner to the formation of 2-aminopyridine, the enaminolactone nitriles **6a**,**b** were reacted with methylhydrazine **12a** and hydrazine **12b** under solvent free conditions for giving new heterocyclic compounds containing in their structure three atoms of nitrogen, named 2-hydrazinopyridines **13a**–**c** in excellent yields (81–95%) as summarized in Table 5.

The structure of the 4-(2-methylhydrazinyl)-1,1-dimethylfuro [3,4-*c*]pyridin-3(1*H*)-one **13a** was confirmed by X-ray crystallography. The ORTEP diagram is shown in Fig. 3a.

The crystal packing of **13a** is governed by two intramolecular hydrogen-bonds: one between O2 and H2 to form a six-membered ring and one between N1 and H3 to give a five-membered ring. The structure also displays two N–H···H intermolecular H-bonds. In fact, N3 acts as hydrogen-bond acceptor to H2 but as well as hydrogen-bond donor, through H3, to N1 from another molecule to give infinite columns along *c* axis.

Finally, all those important results have encouraged us for the synthesis of new chiral substituted 2-aminopyridines. For this reason, we thought of adding enantiopure chiral amines **14a**–**i** in the same manner with enaminolactone nitrile **6a**. The reaction was refluxed in DMF for 6 h. The purification by column



Scheme 3. Synthesis of 2-aminopyridine **9d**.

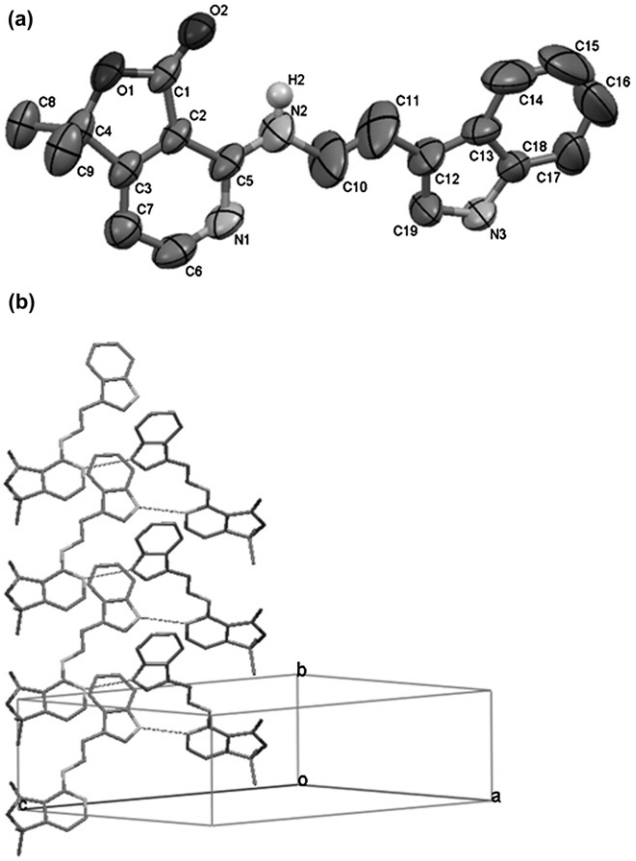


Fig. 2. a. Diagram of the X-ray crystal structure of compound **9d**. b. The crystal packing of **9d**.

chromatography afforded new chiral 2-aminopyridines **15a**–**i** in good yields (52–85%) (Table 6).

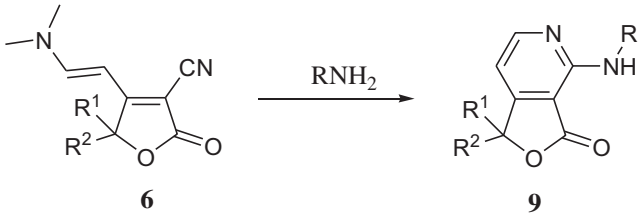
We have used commercially enantiopure primary amines to prepare chiral 2-aminopyridines **15a**–**i**. As shown in Table 6, all the products are optically active. The values of optical rotations of phenylethylamine **15a** and **15b** are very interesting because they are similar with opposite signs, explaining that they are enantiomers from each other. This allowed us to deduce that the operating conditions are not racemating.

We also have tested an aminoacid, L-phenylalanine **14i** as chiral amine in the aim of gaining new 2-(aminoacids)pyridines. Surprisingly, the product of the reaction was decarboxylated affording an achiral compound **15i**, restringing seemingly the interest of reaction.

However, this example permits us to confirm our proposed mechanism in Scheme 6: the observed decarboxylation step involved the formation of an imino bond of the phenylalanine, which can be shown in the intermediate **C** (Scheme 6).

The structures of the 4-(2-methylhydrazinyl)-1,1-dimethylfuro[3,4-*c*]pyridin-3(1*H*)-one **15a** and **15f** were confirmed by X-ray crystallography. The ORTEP diagrams are shown in Figs. 4 and 5.

From these results, we can conclude that using enantiopure amines can serve to produce chiral auxiliaries or chiral ligands useful in asymmetric synthesis.



Scheme 4. Synthesis of 2-aminopyridines derivatives.

3. Conclusion

In summary, we have successfully developed a novel and efficient approach for the synthesis of new original heterocyclic compounds of substituted 2-aminopyridines via the treatment of enaminolactone nitriles with a wide variety of amines (primary amines, diamines, alkylhydrazines, and chiral amines), under very mild conditions. This method provides high yields of products with high selectivity affording a useful and attractive strategy for the preparation of chelating and biologically active 2-substituted aminopyridines from available building blocks. To the best of our knowledge there are no reports in literature for the synthesis of these types of heterocyclic compounds.

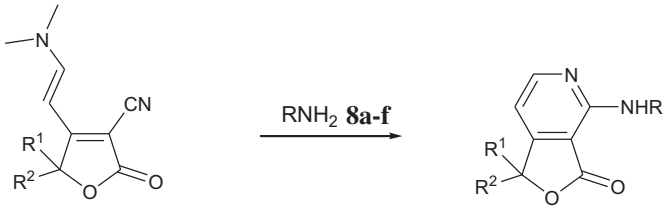
4. Experimental section

4.1. General information

Melting points were recorded on a Kofler apparatus and were uncorrected. IR spectra were obtained with solids or neat liquids with a Fourier transform Perkin–Elmer Spectrum One with ATR accessory. Only significant absorptions are listed. NMR spectra were recorded at 250 MHz for ^{1}H NMR and 62.9 MHz for ^{13}C NMR with a 'Bruker AC 250' spectroctrometer in 250 MHz, $CDCl_3$ and DMSO-d_6; δ-values are in parts per million relative to tetramethylsilane as an internal standard. Mass spectra were recorded on a QTOF Micro (Waters), ionization electrospray positive (ESI), lockspray PEG, infusion introduction (5 mL/min), source temperature 80 °C, desolvatation temperature 120 °C. Al_2O_3/KF was prepared through a protocol described by Villemin.[25]

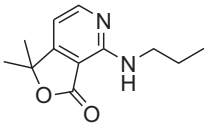
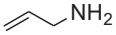
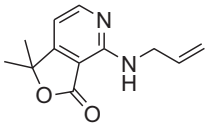
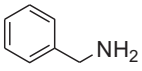
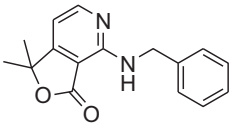
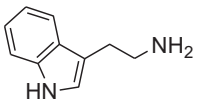
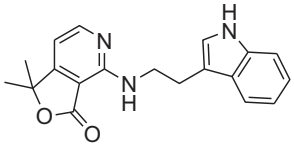
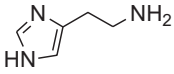
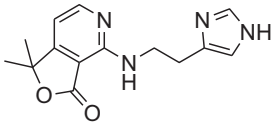
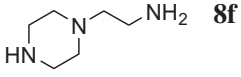
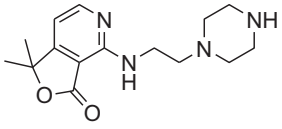
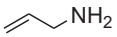
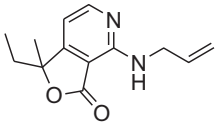
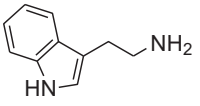
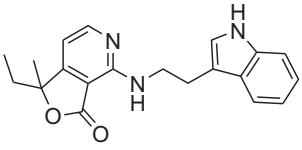
Computational details: full geometry optimization for **6a** and computation of chelpg have been performed at the B3LYP/6-31G(d) level of theory, which is the implemented in Gaussian 03 Rev02 package of programs.

Table 3
Preparation of substituted 2-aminopyridines **9a**–**h** by reaction of enaminobutenolide nitriles **6a**,**b** and primary amines **8a**–**f** under free solvent conditions



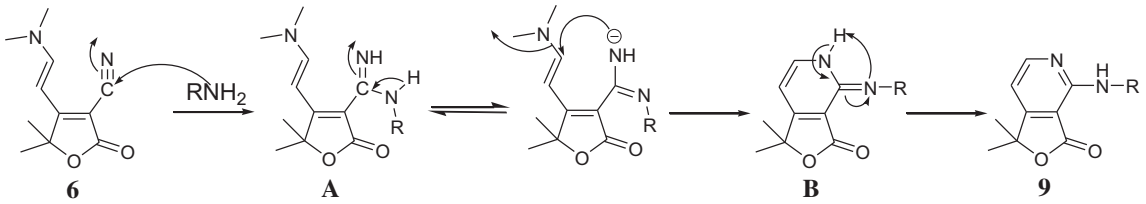
6a: $R^1 = R^2 = Me$
6b: $R^1 = Me$, $R^2 = Et$

9a-h

Entry	Enaminolactone	RNH_2	Product	Yield [%]
1	**6a**	**8a**	 **9a**	95
2	**6a**	 **8b**	 **9b**	86
3	**6a**	 **8c**	 **9c**	87
4	**6a**	 **8d**	 **9d**	92
5	**6a**	 **8e**	 **9e**	94
6	**6a**	 **8f**	 **9f**	75
7	**6b**	 **8b**	 **9g**	86
8	**6b**	 **8d**	 **9h**	87

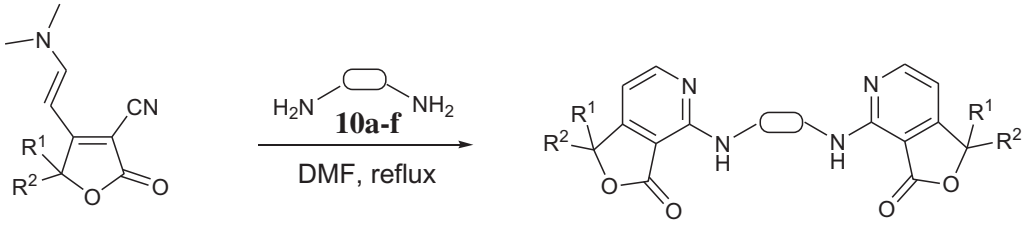
4.2. Synthesis of substituted 2-aminopyridines

*4.2.1. General procedure **1** for the synthesis of butenolide nitriles **4a**–**c**.* A mixture of α-hydroxyketone **5a**–**c** (20 mmol) and ethyl cyanoacetate (2.26 g, 20 mmol) was adsorbed on KF-alumina (3 g) and then stirred at room temperature without solvent for 3 h. The mixture was extracted with diethylether (3×20 mL). The combined organic layers were subsequently washed with water, dried on



Scheme 5. Plausible mechanism for the synthesis of 2-substituted aminopyridines **9**.

Table 4
Preparation of bis-aminopyridines **11a**–**g** from diamines **10a**–**f**



6a-b **11a-g**

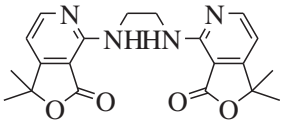
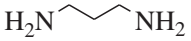
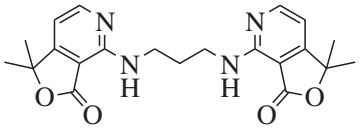
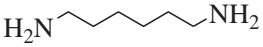
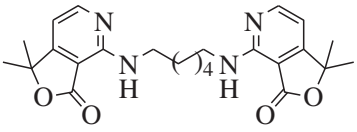
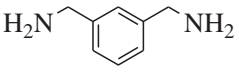
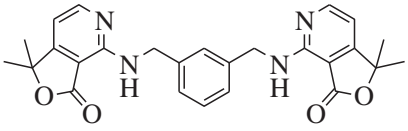
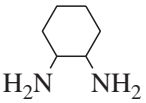
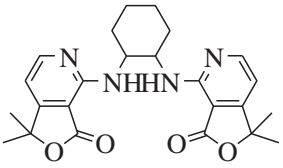
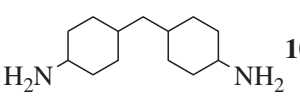
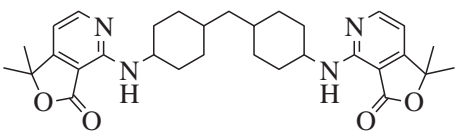
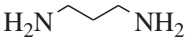
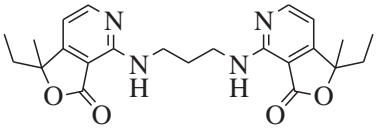
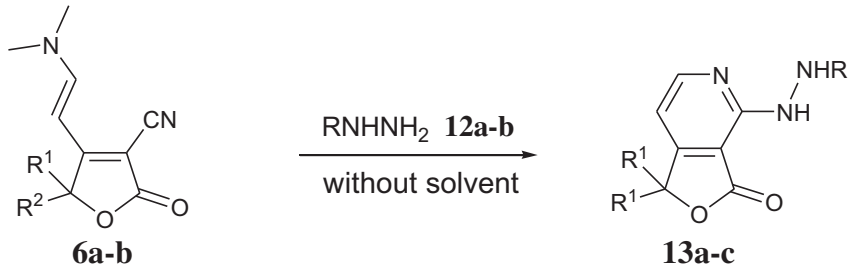
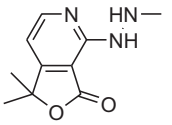
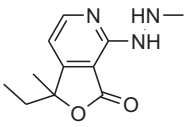
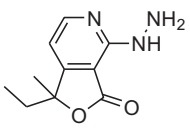
Entry		H_2N—◯—NH_2		Product		Yield [%]
1	**6a**		**10a**		**11a**	83
2	**6a**		**10b**		**11b**	36
3	**6a**		**10c**		**11c**	83
4	**6a**		**10d**		**11d**	82
5	**6a**		**10e**		**11e**	52
6	**6a**		**10f**		**11f**	35
7	**6b**		**10b**		**11g**	85

Table 5
Synthesis of 2-hydrazinopyridines **13a–c**



6a-b **13a-c**

Entry	Enaminolactone	$RNHNH_2$		*N*-Aminopyridine		Yield [%]
1	**6a**	CH_3NHNH_2	**12a**		**13a**	81
2	**6b**	CH_3NHNH_2	**12a**		**13b**	95
3	**6b**	NH_2NH_2	**12b**		**13c**	90

$MgSO_4$, and concentrated to obtain 2,5-dihydro-4,5,5-trimethyl-2-oxofuran-3-carbonitrile **4a–c**.

*4.2.1.1. 2,5-Dihydro-4,5,5-trimethyl-2-oxofuran-3-carbonitrile **4a**.* The general procedure **1** using (2.04 g, 20 mmol) of 3-hydroxy-3-methylbutan-2-one **5a** gave (2.70 g, 89%) of **4a** as white solid, mp 60–61 °C. IR ν_{max} (cm^{-1}): 2239, 1763, 1651. ^1H NMR ($CDCl_3$) δ 2.32 (3H, s, CH_3), 1.54 (6H, s, 2× CH_3). ^{13}C NMR ($CDCl_3$) δ 184.8, 165.5, 110.7, 104.6, 88.4, 24.4, 13.9.

*4.2.1.2. 2,5-Dihydro-4-ethyl-5,5-trimethyl-2-oxofuran-3-carbonitrile **4b**.* The general procedure **1** using (2.32 g, 20 mmol) of 3-hydroxy-3-methylpentan-2-one **5b**, gave (2.65, 80%) of **4b** as viscous liquid, bp 129 °C/5 mtorr. IR ν_{max} (cm^{-1}): 2239, 1764, 1650. ^1H NMR ($CDCl_3$) δ 2.29 (3H, s, C=C–CH_3), 2.07–1.71 (2H, m, CH_2), 1.53 (3H, s, CCH_3), 0.83 (3H, t, ^3J=7.5 Hz, CH_2CH_3). ^{13}C NMR ($CDCl_3$) δ 184.3, 165.7, 110.6, 105.0, 90.9, 30.2, 22.9, 14.2, 7.1.

*4.2.1.3. 2,5-Dihydro-4-methyl-5,5-pentamethylene-2-oxofuran-3-carbonitrile **4c**.* The general procedure **1** using (2.84 g; 20 mmol) of 1-(1-hydroxy-cyclohexyl)ethanone **5c**, gave (3.30 g, 86%) of **4c** as white solid, mp 119–120 °C. IR ν_{max} (cm^{-1}): 2236, 1764, 1650. ^1H NMR ($CDCl_3$): δ 2.28 (3H, s, CH_3), 1.34–1.22 (10H, m, 5× CH_2). ^{13}C NMR ($CDCl_3$) δ 184.4, 165.6, 110.6, 104.6, 89.9, 33.1, 24.1, 21.4, 14.0.

*4.2.2. General procedure **2** for the synthesis of 4-(E)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-dialkyl-2-oxofuran-3-carbonitrile **6a–c**.* DMFDEA (0.73 g, 5 mmol) was added to the 4-methyl-5,5-dialkyl-2-oxo-2,5-dihydrofuran-3-carbonitrile **4a–c** (5 mmol). The mixture was stirred at room temperature without solvent during 1 h. Ethyl acetate (20 mL) was added to the crude reaction mixture. The organic layer was washed with water, brine and dried on $MgSO_4$. The solvent was removed under vacuum providing a yellow solid of enaminolactone nitriles **6a–c**.

*4.2.2.1. 4-(E)-2-(Dimethylaminovinyl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carbonitrile **6a**.* The general procedure **2** using (0.76 g, 5 mmol) of 2,5-dihydro-4,5,5-dimethyl-2-oxofuran-3-carbonitrile **4a**, gave (0.84 g, 81%) of **6a** as yellow solid, mp 170–172 °C. IR ν_{max} (neat/cm^{-1}): 2208, 1721, 1624, 1556, 1205. ^1H NMR ($CDCl_3$) δ 8.08 (1H, d, ^3J=12.6 Hz, CH=CH–N), 4.76 (1H, d, ^3J=12.6 Hz, CH=CH–N), 3.26 (3H, s, NCH_3), 3.01 (3H, s, NCH_3), 1.48 (6H, s, 2× CH_3). ^{13}C NMR ($CDCl_3$) δ 177.8, 169.3, 154.0, 116.4, 104.9, 86.7, 85.6, 46.2, 37.1, 26.5. MS *m*/*z* (% relative abundance): 207 (M+H, 30), 189 (68), 164 (100), 134 (95). HRMS (ES-QTOF) calcd for $C_{11}H_{14}N_2O_2Na$ M+Na 229.0953. Found 229.0953.

*4.2.2.2. 4-(E)-2-(Dimethylaminovinyl)-5-ethyl-2,5-dihydro-5-methyl-2-oxofuran-3-carbonitrile **6b**.* The general procedure **2** using (106 mg, 5 mmol) of 5-ethyl-2,5-dihydro-4,5-dimethyl-2-oxofuran-3-carbonitrile **4b**, gave (73 mg, 66%) of **6b** as yellow solid, mp 97–98 °C. IR ν_{max} (neat/cm^{-1}): 2202, 1716, 1622, 1556, 1199. ^1H NMR ($CDCl_3$) δ 8.09 (1H, d, ^3J=12.5 Hz, CH=CH–N), 4.75 (1H, d, ^3J=13.0 Hz, CH=CH–N), 3.26 (3H, s, NCH_3), 3.00 (3H, s, NCH_3), 1.94–1.65 (2H, m, CH_2), 1.63 (3H, s, CCH_3), 0.81 (3H, t, ^3J=7.2 Hz, CH_2CH_3). ^{13}C NMR ($CDCl_3$) δ 176.6, 169.6, 153.8, 116.3, 88.2, 86.6, 46.1, 37.1, 32.0, 25.4, 7.3. MS *m*/*z* (% relative abundance): 221 (M+H, 50), 203 (45), 191 (95), 175 (66), 148 (100). HRMS (ES-QTOF) calcd for $C_{12}H_{16}N_2O_2Na$ M+Na 243.1109. Found 243.1115.

*4.2.2.3. 4-(E)-2-(Dimethylaminovinyl)-2,5-dihydro-5,5-pentamethylene-2-oxofuran-3-carbonitrile **6c**.* The general procedure **2** using (95 mg, 5 mmol) of 4-methyl-2,5-dihydro-4,5-dimethyl-5,5-pentamethylene-2-oxofuran-3-carbonitrile **4c**, gave (90 mg, 73%) of **6c** as yellow solid, mp 182–183 °C. IR ν_{max} (neat/cm^{-1}): 2202,

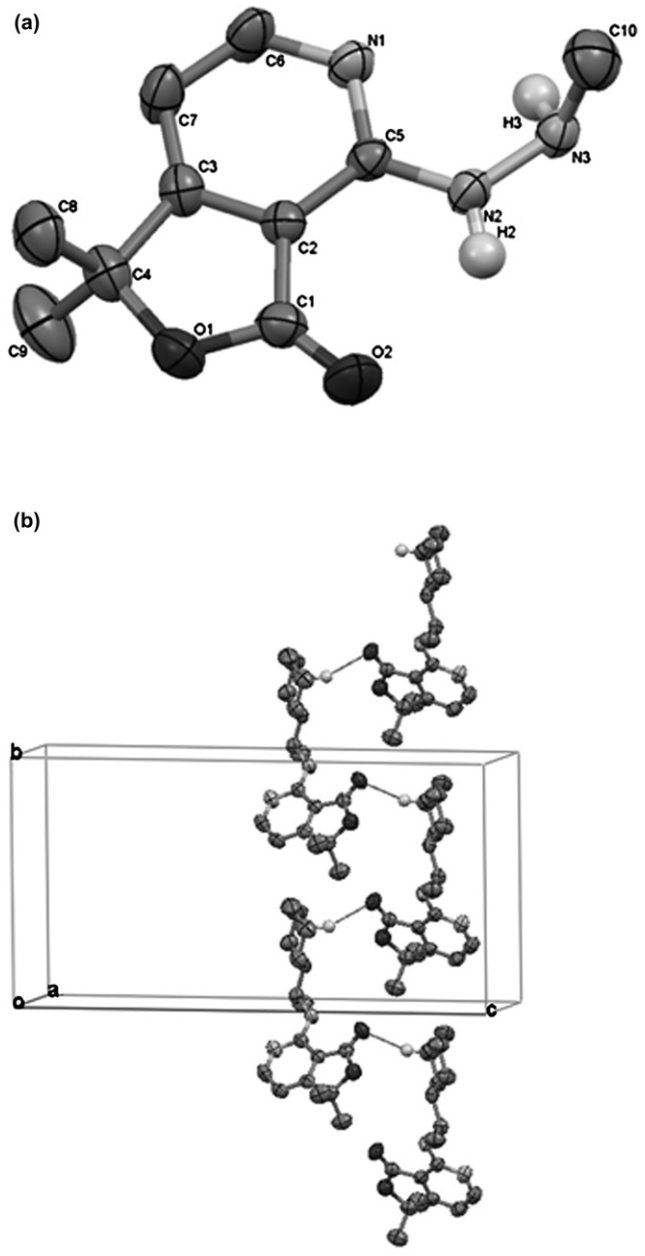


Fig. 3. a. ORTEP diagram of the X-ray crystal structure of compound **13a**. b. The crystal packing of **13a**.

1716, 1614, 1532, 1210. ^{1}H NMR ($CDCl_3$) δ 8.17 (1H, d, ^3J=12.7 Hz, CH=CH–N), 4.72 (1H, d, ^3J=13.0 Hz, CH=CH–N), 3.25 (3H, s, NCH_3), 3.00 (3H, s, NCH_3), 1.81–1.21 (10H, m, 5× CH_2). ^{13}C NMR ($CDCl_3$) δ 177.6, 169.7, 154.1, 116.7, 104.0, 87.5, 87.0, 46.2, 37.1, 35.1, 24.6, 21.8. MS *m*/*z* (% relative abundance): 247 (M+H, 100), 229 (80), 203 (50), 174 (59). HRMS (ES-QTOF) calcd for $C_{14}H_{18}N_2O_2Na$ M+Na 269.1266. Found 269.1259.

4.2.3. Synthesis of 2-aminopyridine derivatives

*4.2.3.1. General procedure **3** for the synthesis of 2-aminopyridines **9a**–**h**.* A mixture of 4-(*E*)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-dialkyl-2-oxofuran-3-carbonitrile **6a**,**b** (1.45 mmol) and primary amine **8a**–**h** (1.45 mmol) was heated until homogenization and the heating was continued for 5 min. The crude product obtained was washed several time with diethylether and purified by column chromatography (silica gel, ethyl acetate/cyclohexane (70:30)) to give 2-aminopyridines derivatives **9a**–**h**.

*4.2.3.1.1. 1,1-Dimethyl-4-(propylamino)furo[3,4-c]pyridin-3(1H)-one **9a**.* The general procedure **3** using (300 mg, 1.45 mmol) of 4-(*E*)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carbonitrile **6a** and (86 mg, 1.45 mmol) of propylamine **8a** gave (303 mg, 95%) of **9a** as viscous oil. IR ν_{max} (neat/cm^{-1}): 3392, 1730, 1616, 1590, 1524. ^{1}H NMR ($CDCl_3$) δ 8.15 (1H, d, ^3J=5.2 Hz, CH=C*H*–N), 6.42 (1H, s large, N*H*), 6.39 (1H, d, ^3J=5.2 Hz, C*H*=CH–N), 3.39 (2H, td, ^3J=5.8 Hz, ^3J=7.1 Hz, $CH_2CH_2CH_3$), 1.57 (2H, sextuplet, ^3J=7.3 Hz, CH_2CH_3), 1.48 (6H, s, 2× CH_3), 0.87 (3H, t, ^3J=7.3 Hz, CH_2CH_3). ^{13}C NMR ($CDCl_3$) δ 170.4, 165.6, 156.4, 154.5, 103.6, 102.7, 85.2, 42.3, 26.4, 22.8, 11.4. EIMS *m*/*z* (% relative abundance): 221 (M+H, 67), 203 (100), 185 (52), 179 (58), 161 (89). HRMS (ES-QTOF) calcd for $C_{15}H_{18}NO_3$ $C_{12}H_{17}N_2O_2$ M+H 221.1290. Found 221.1294.

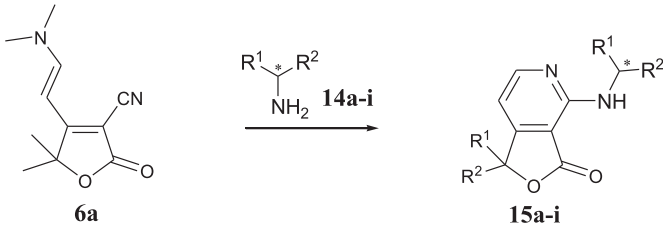
*4.2.3.1.2. 4-(Allylamino)-1,1-dimethylfuro[3,4-c]pyridin-3(1H)-one **9b**.* The general procedure **3** using (300 mg, 1.45 mmol) of 4-(*E*)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carbonitrile **6a** and (83 mg, 1.45 mmol) of allylamine **8b** gave (272 mg, 86%) of **9b** as yellow solid, mp 82–84 °C. IR ν_{max} (neat/cm^{-1}): 3396, 1732, 1617, 1592, 1524. ^{1}H NMR ($CDCl_3$) δ 8.26 (1H, d, ^3J=5.2 Hz, CH=C*H*–N), 6.42 (1H, s large, N*H*), 6.40 (1H, d, ^3J=5.1 Hz, C*H*=CH–N), 5.96 (1H, ddt, $^3J_{trans}$=17.2 Hz, $^3J_{cis}$=10.3 Hz, ^3J=5.4 Hz, C*H*=CH_aH_b), 5.26 (1H, dq, $^3J_{trans}$=17.2 Hz, ^4J=^2J=1.6 Hz, CH=C*H*$_a$H$_b$), 5.14 (1H, dq, $^3J_{cis}$=10.3 Hz, ^4J=^2J=1.6 Hz, CH=CH$_a$*H*$_b$), 4.19 (2H, tt, ^3J=5.4 Hz, ^4J=1.6 Hz, CH_2CH=CH_2), 1.59 (6H, s, 2× CH_3). ^{13}C NMR ($CDCl_3$) δ 170.3, 165.7, 156.1, 154.5, 134.3, 116.2, 104.0, 102.9, 85.6, 42.8, 26.5. EIMS *m*/*z* (% relative abundance): 219 (M+H, 75), 201 (100), 173 (24). HRMS (ES-QTOF) calcd for $C_{12}H_{15}N_2O_2$ M+H 219.1134. Found 219.1126. Anal. Calcd for $C_{12}H_{15}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.12; H, 6.78; N, 12.98%.

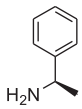
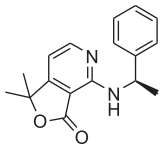
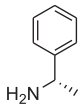
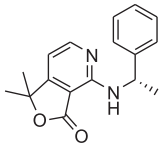
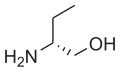
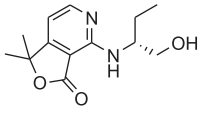
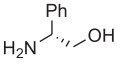
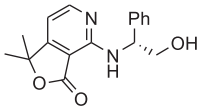
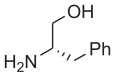
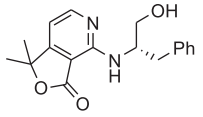
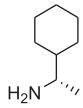
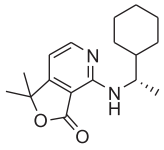
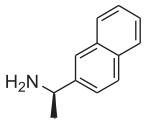
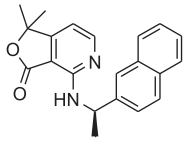
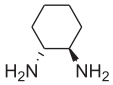
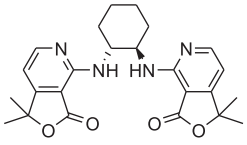
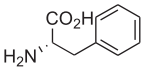
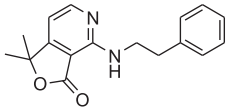
*4.2.3.1.3. 4-(Benzylamino)-1,1-dimethylfuro[3,4-c]pyridin-3(1H)-one **9c**.* The general procedure **3** using (300 mg, 1.45 mmol) of 4-(*E*)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carbonitrile **6a** and (155 mg, 1.45 mmol) of benzylamine **8c** gave (338 mg, 87%) of **9c** as yellow solid, mp 183–184 °C. IR ν_{max} (neat/cm^{-1}): 3414, 1733, 1619, 1591, 1523. ^{1}H NMR ($CDCl_3$) δ 8.30 (1H, d, ^3J=5.2 Hz, CH=C*H*–N), 7.39–7.28 (5H, m, *H*arom), 6.83 (1H, s large, N*H*), 6.53 (1H, d, ^3J=5.2 Hz, C*H*=CH–N), 4.78 (2H, d, ^3J=5.9 Hz, CH_2Ph), 1.61 (6H, s, 2× CH_3). ^{13}C NMR ($CDCl_3$) δ 170.3, 165.6, 156.1, 154.5, 139.1, 128.9, 127.2, 126.6, 104.0, 103.0, 85.4, 44.2, 26.9. EIMS *m*/*z* (% relative abundance): 269 (M+H, 33), 191 (12), 173 (10), 91 (100). HRMS (ES-QTOF) calcd for $C_{16}H_{17}N_2O_2$ M+H 269.1290. Found 269.1292. Anal. Calcd for $C_{16}H_{17}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 69.57; H, 6.15; N, 10.38%.

*4.2.3.1.4. 4-(2-(1H-Indol-3-yl)ethylamino)-1,1-dimethylfuro[3,4-c]pyridin-3(1H)-one **9d**.* The general procedure **3** using (300 mg, 1.45 mmol) of 4-(*E*)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carbonitrile **6a** and (232 mg, 1.45 mmol) of tryptamine **8d** gave (428 mg, 92%) of **9d** as white solid, mp 161–163 °C. IR ν_{max} (neat/cm^{-1}): 3392, 3163, 1738, 1620, 1587, 1520. ^{1}H NMR ($CDCl_3$) δ 8.30 (1H, d, ^3J=5.1 Hz, CH=C*H*–N), 8.17 (1H, s large, N*H*indol), 7.64 (1H, d, ^3J=7.7 Hz, *CH*NH), 7.38–7.11 (4H, m, Harom), 6.63 (1H, t, ^3J=4.6 Hz, N*H*CH_2), 6.48 (1H, d, ^3J=5.1 Hz, C*H*=CH–N), 3.87 (2H, td, ^3J=4.6 Hz, ^3J=6.9 Hz, NHCH_2CH_2), 3.13 (2H, t, ^3J=6.9 Hz, $NHCH_2CH_2$), 1.58 (6H, s, 2× CH_3). ^{13}C NMR ($CDCl_3$) δ 170.4, 165.6, 156.3, 154.5, 136.5, 127.3, 122.2, 122.1, 119.34, 118.8, 113.0, 111.2, 103.7, 102.9, 85.3, 40.8, 26.4, 25.3. EIMS *m*/*z* (% relative abundance): 322 (M+H, 42), 144 (100). HRMS (ES-QTOF) calcd for $C_{19}H_{20}N_3O_2$ M+H 322.1556. Found 322.1566. Anal. Calcd for $C_{19}H_{20}N_3O_2$: C, 71.01; H, 5.96; N, 13.08. Found: C, 70.71; H, 6.28; N, 12.99%.

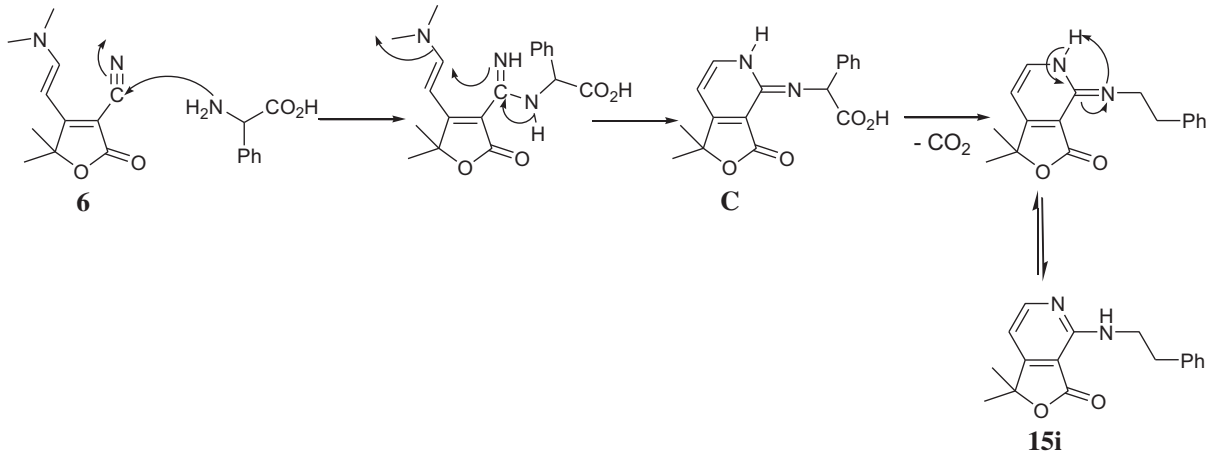
*4.2.3.1.5. 4-(2-(1H-Imidazol-4-yl)ethylamino)-1,1-dimethylfuro[3,4-c]pyridin-3(1H)-one **9e**.* The general procedure **3** using (300 mg, 1.45 mmol) of 4-(*E*)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carbonitrile **6a** and (161 mg, 1.45 mmol)

Table 6
Preparation of chiral substituted 2-aminopyridines **15a–i**



Entry	RR′CHNH$_2$		Product		Yield [%]	$[\alpha]_D^{20}$ (c 1, $CHCl_3$)
1.		**14a**		**15a**	75	−111.0
2.		**14b**		**15b**	75	+112.4
3.		**14c**		**15c**	76	+31.3
4.		**14d**		**15d**	75	+48.6
5.		**14e**		**15e**	71	−98.3
6.		**14f**		**15f**	85	+80.0
7.		**14g**		**15g**	83	−244.7
8.		**14h**		**15h**	52	−230.6
9.		**14i**		**15i**	52	—

of histamine **8e** gave (370 mg, 94%) of **9e** as yellow solid, mp 150 °C. IR ν_{max} (neat/cm^{-1}): 3395, 3120, 1735, 1671, 1620, 1592, 1527. ^{1}H NMR ($CDCl_3$) δ 8.27 (1H, d, ^3J=5.2 Hz, CH=C*H*–N), 7.58 (1H, s, NH–C*H*=N), 6.88 (1H, s, C=C*H*–NH), 6.72 (1H, s large, N*H*), 6.49 (1H, d, ^3J=5.2 Hz, C*H*=CH–N), 3.84 (2H, td, ^3J=6.2 Hz, ^3J=6.7 Hz, NHCH_2CH_2), 2.96 (2H, t, ^3J=6.7 Hz, NCH_2CH_2), 1.58 (6H, s, 2× CH_3). ^{13}C NMR ($CDCl_3$) δ 170.4, 165.7, 156.2, 154.4, 135.3, 135.0, 116.6, 103.9, 103.0, 85.4, 40.4, 27.3, 26.4. EIMS m/z (% relative abundance): 273



Scheme 6. Plausible mechanism of preparation of compound **15i**.

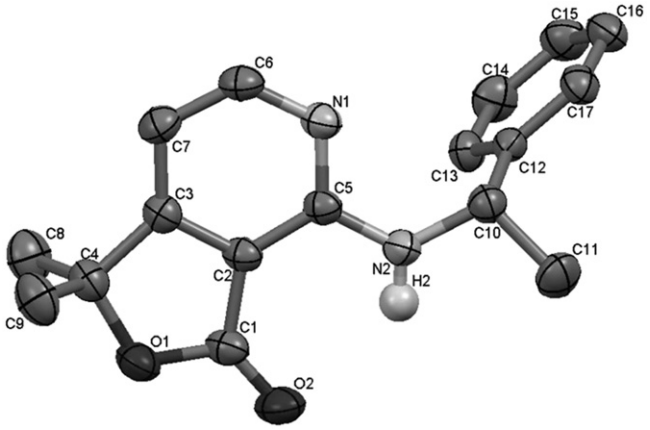


Fig. 4. ORTEP diagram of the X-ray crystal structure of compound **15a** with thermal ellipsoids at 50% probability.

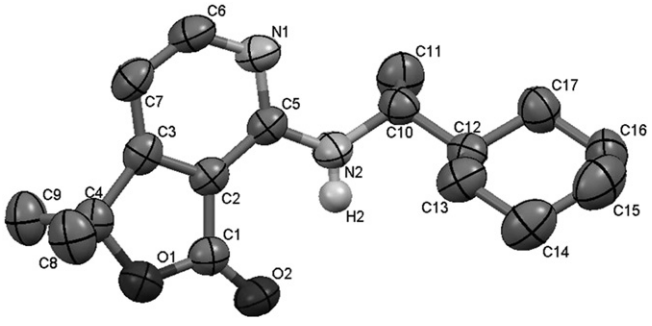


Fig. 5. ORTEP diagram of the X-ray crystal structure of compound **15f** with thermal ellipsoids at 50% probability.

(M+H, 55), 191 (14), 179 (56), 95 (100). HRMS (ES-QTOF) calcd for $C_{14}H_{17}N_4O_2$ M+H 273.1352. Found 273.1364.

4.2.3.1.6. 4-(2-(Piperazin-1-yl)ethylamino)-1,1-dimethylfuro[3,4-c]pyridine-3(1H)-one ***9f***. The general procedure **3** using (300 mg, 1.45 mmol) of 4-(*E*)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carbonitrile **6a** and (187 mg, 1.45 mmol) of 2-(piperazin-1-yl)ethanamine **8f** gave (315 mg, 75%) of **9f** as viscous oil. IR ν_{max} (neat/cm^{-1}): 3394, 3340, 1736, 1671, 1618, 1589, 1523. ^{1}H NMR ($CDCl_3$) δ 8.22 (1H, d, ^3J=5.1 Hz, CH=C*H*–N), 6.90 (1H, s large, N*H*), 6.44 (1H, d, ^3J=5.1 Hz, C*H*=CH–N), 3.60 (2H, td, ^3J=5.5 Hz, ^3J=6.3 Hz, NHCH_2CH$_2$), 2.88 (4H, t, ^3J=4.7 Hz, CH_2NHCH_2), 2.58 (2H, t, ^3J=6.3 Hz, NHCH$_2$CH_2), 2.34 (4H, s large, CH_2NCH_2), 2.17 (1H, s large, CH$_2$N*H*CH$_2$), 1.55 (6H, s, 2× CH_3). ^{13}C NMR ($CDCl_3$) δ 170.2, 165.7, 156.2, 154.4, 103.6, 103.0, 85.1, 57.9, 54.3, 46.1, 37.2, 26.5. EIMS *m*/*z* (% relative abundance): 291 (M+H, 57), 205 (100). HRMS (ES-QTOF) calcd for $C_{15}H_{23}N_4O_2$ M+H 291.1821. Found 291.1818.

4.2.3.1.7. 4-(Allylamino)-1-ethyl-1-methylfuro[3,4-c]pyridin-3(1H)-one ***9g***. The general procedure **3** using (319 mg, 1.45 mmol) of 4-(*E*)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carbonitrile **6b** and (86 mg, 1.45 mmol) of allylamine **8b** gave (289 mg, 86%) of **9g** as viscous oil. IR ν_{max} (neat/cm^{-1}): 3395, 1731, 1616, 1590, 1522. ^{1}H NMR ($CDCl_3$) δ 8.23 (1H, d, ^3J=5.1 Hz, CH=C*H*–N), 6.55 (1H, s large, N*H*), 6.44 (1H, d, ^3J=5.1 Hz, C*H*=CH–N), 5.94 (1H, ddt, $^3J_{trans}$=17.1 Hz, $^3J_{cis}$=10.3 Hz, ^3J=5.4 Hz, C*H*=CH$_a$H$_b$), 5.23 (1H, dq, $^3J_{trans}$=17.1 Hz, ^4J=^2J=1.3 Hz, CH=C*H*$_a$H$_b$), 5.12 (1H, dq, $^3J_{cis}$=10.3 Hz, ^4J=^2J=1.3 Hz, CH=CH$_a$*H*$_b$), 4.18–4.14 (2H, m, CH_2CH=CH$_2$), 1.88 (H$_A$, H$_B$ ABq, J_{AB}=14.4 Hz, J_{ABq}=7.3 Hz, C*HH*CH$_3$), 1.53 (3H, s, CH_3), 0.75 (3H, t, ^3J=7.3 Hz, CH$_2$CH_3). ^{13}C NMR ($CDCl_3$) δ 170.6, 164.5, 156.1, 154.4, 134.4, 116.2, 104.4, 103.8, 88.1, 42.8, 32.1, 24.9, 7.8. EIMS *m*/*z* (% relative abundance): 233 (M+H, 94), 215 (100), 200 (12), 197 (23), 187 (24). HRMS (ES-QTOF) calcd for $C_{13}H_{17}N_2O_2$ M+H 233.1290. Found 233.1294.

4.2.3.1.8. 4-(2-(1H-Indol-3-yl)ethylamino)-1-ethyl-1-methylfuro[3,4-c]pyridin-3(1H)-one ***9h***. The general procedure **3** using (319 mg, 1.45 mmol) of 4-(*E*)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carbonitrile **6b** and (161 mg, 1.45 mmol) of tryptamine **8d** gave (422 mg, 87%) of **9h** as yellow solid. Mp 150 °C. IR ν_{max} (neat/cm^{-1}): 3392, 1738, 1620, 1587, 1520. ^{1}H NMR ($CDCl_3$) δ 8.29 (1H, d, ^3J=5.1 Hz, CH=C*H*–N), 8.14 (1H, s large, N*H*indol), 7.65 (1H, d, ^3J=7.6 Hz, C=C*H*–NH), 7.38–7.09 (4H, m, Harom), 6.63 (1H, s large, N*H*), 6.44 (1H, d, ^3J=5.1 Hz, C*H*=CH–N), 3.87 (2H, q, J_{NHCH_2} = $J_{CH_2CH_2}$=6.8 Hz, NHCH_2CH$_2$), 3.13 (2H, t, ^3J=6.8 Hz, NCH$_2$CH_2), 1.91 (H$_A$, H$_B$ ABq, J_{AB}=14.4 Hz, J_{ABq}=7.4 Hz, C*HH*CH$_3$), 1.56 (3H, s, CH_3), 0.79 (3H, t, ^3J=7.4 Hz, CH$_2$CH_3). ^{13}C NMR ($CDCl_3$) δ 170.7, 164.4, 156.3, 154.4, 136.5, 127.3, 122.2, 122.1, 119.3, 118.8, 113.0, 111.2, 103.9, 103.8, 87.9, 40.8, 32.1, 25.3, 24.9, 7.8. EIMS *m*/*z* (% relative abundance): 336 (M+H, 34), 144 (100). HRMS (ES-QTOF) calcd for $C_{20}H_{22}N_3O_2$ M+H 336.1712. Found 336.1703.

4.2.3.2. General procedure ***4*** *for the synthesis of bis(2-aminopyridines)* ***11a–g***. To a solution of 4-(2-dimethylaminovinyl)-5,5-dimethyl-2-oxo-2,5-dihydrofuran-3-carbonitrile **6a**,**b** (2.90 mmol) dissolved in DMF was added diamine **10a–h** (1.45 mmol). The

mixture was refluxed for 3 h. The solvent was evaporated and the residue obtained was purified by column chromatography (silica gel, ethyl acetate (100)) to give bis(2-aminopyridines) **11a**–**g**.

*4.2.3.2.1. 4-(2-(1,3-Dihydro-1,1-dimethyl-3-oxofuro[3,4-c]pyridin-4-ylamino)ethylamino)-1,1-dimethylfuro[3,4-c]pyridin-3(1H)-one **11a**.* The general procedure **4** using (600 mg, 2.90 mmol) of 4-(*E*)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carbonitrile **6a** and (87 mg, 1.45 mmol) of ethane-1,2-diamine **10a** gave (460 mg, 83%) of **11a** as white solid, mp 225–227 °C. IR ν_{max} (neat/cm^{-1}): 3426, 1723, 1615, 1593, 1516. ^{1}H NMR ($CDCl_3$) δ 8.35 (2H, d, ^3J=5.1 Hz, 2× CH=C*H*–N), 7.13 (2H, s large, 2× N*H*), 6.52 (2H, d, ^3J=5.1 Hz, 2× C*H*=CH–N), 3.85 (4H, m, 2× CH_2), 1.59 (12H, s, 4× CH_3). ^{13}C NMR ($CDCl_3$) δ 170.1, 165.7, 156.4, 154.6, 104.1, 103.1, 85.2, 41.3, 26.5. EIMS *m*/*z* (% relative abundance): 383 (M+H, 83), 205 (100). HRMS (ES-QTOF) calcd for $C_{20}H_{23}N_4O_4$ M+H 383.1719. Found 383.1721.

*4.2.3.2.2. 4-(3-(1,3-Dihydro-1,1-dimethyl-3-oxofuro[3,4-c]pyridin-4-ylamino)propylamino)-1,1-dimethylfuro[3,4-c]pyridin-3(1H)-one **11b**.* The general procedure **4** using (600 mg, 2.90 mmol) of 4-(*E*)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carbonitrile **6a** and (107 mg, 1.45 mmol) of propan-1,3-diamine **10b** gave (488 mg, 85%) of **11b** as white solid, mp 138–140 °C. IR ν_{max} (neat/cm^{-1}): 3395, 1733, 1616, 1591, 1527. ^{1}H NMR ($CDCl_3$) δ 8.39 (2H, d, ^3J=5.1 Hz, 2× CH=C*H*–N), 7.07 (2H, s large, 2× N*H*), 6.48 (2H, d, ^3J=5.1 Hz, 2× C*H*=CH–N), 3.68 (4H, q, $^3J_{CH_2NH} = {}^3J_{CH_2CH_2}$=6.3 Hz, $CH_2CH_2CH_2$), 1.92 (2H, m, $CH_2CH_2CH_2$), 1.60 (12H, s, 4× CH_3). ^{13}C NMR ($CDCl_3$) δ 170.4, 165.8, 156.6, 154.8, 103.7, 102.8, 85.2, 37.3, 30.1, 26.5. EIMS *m*/*z* (% relative abundance): 397 (M+H, 53), 219 (100). HRMS (ES-QTOF) calcd for $C_{21}H_{25}N_4O_4$ M+H 397.1876. Found 397.1864.

*4.2.3.2.3. 4-(6-(1,3-Dihydro-1,1-dimethyl-3-oxofuro[3,4-c]pyridin-4-ylamino)hexylamino)-1,1-dimethylfuro[3,4-c]pyridin-3(1H)-one **11c**.* The general procedure **4** using (600 mg, 2.90 mmol) of 4-(*E*)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carbonitrile **6a** and (168 mg, 1.45 mmol) of hexane-1,6-diamine **10c** gave (527 mg, 83%) of **11c** as white solid, mp 130–132 °C. IR ν_{max} (neat/cm^{-1}): 3396, 1732, 1619, 1591, 1526. ^{1}H NMR ($CDCl_3$) δ 8.25 (2H, d, ^3J=5.1 Hz, 2× CH=C*H*–N), 6.48 (2H, s large, 2× N*H*), 6.46 (2H, d, ^3J=5.1 Hz, 2× C*H*=CH–N), 3.52 (4H, q, $^3J_{CH_2NH} = {}^3J_{CH_2CH_2}$=6.8 Hz, 2× $NHCH_2$), 1.68–1.60 (4H, m, 2× CH_2), 1.57 (12H, s, 4× CH_3), 1.47–1.42 (4H, m, 2× CH_2). ^{13}C NMR ($CDCl_3$) δ 170.5, 165.6, 156.4, 154.5, 103.6, 102.7, 85.3, 40.5, 29.5, 26.7, 26.4. EIMS *m*/*z* (% relative abundance): 439 (M+H, 100), 421 (29), 395 (16), 261 (59), 243 (14), 191 (28). HRMS (ES-QTOF) calcd for $C_{24}H_{31}N_4O_4$ M+H 439.2345. Found 439.2326.

*4.2.3.2.4. 4-((3-((1,3-Dihydro-1,1-dimethyl-3-oxofuro[3,4-c]pyridin-4-ylamino) methyl)phenyl)methylamino)-1,1-dimethylfuro[3,4-c]pyridin-3(1H)-one **11d**.* The general procedure **4** using (600 mg, 2.90 mmol) of 4-(*E*)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carbonitrile **6a** and (197 mg, 1.45 mmol) of (3-(aminomethyl)phenyl)methanamine **10d** gave (544 mg, 82%) of **11d** as yellow solid, mp 156–157 °C. IR ν_{max} (neat/cm^{-1}): 3395, 1734, 1618, 1592, 1525. ^{1}H NMR ($CDCl_3$) δ 8.29 (2H, d, ^3J=5.1 Hz, 2× CH=C*H*–N), 7.37–7.29 (4H, m, *H*arom), 6.83 (2H, s large, 2× N*H*), 6.53 (2H, d, ^3J=5.1 Hz, 2× C*H*=CH–N), 4.76 (4H, d, ^3J=6.0 Hz, 2× $NHCH_2$), 1.61 (12H, s, 4× CH_3). ^{13}C NMR ($CDCl_3$) δ 170.3, 165.6, 156.1, 154.5, 139.1, 128.9, 126.9, 126.6, 104.2, 103.0, 85.4, 44.2, 26.5. EIMS *m*/*z* (% relative abundance): 459 (M+H, 14), 281 (100). HRMS (ES-QTOF) calcd for $C_{26}H_{27}N_4O_4$ M+H 459.2032. Found 459.2009.

*4.2.3.2.5. 4-((trans)-2-(1,3-Dihydro-1,1-dimethyl-3-oxofuran[3,4-c]pyridin-4-yl-amino)cyclohexylamino)-1,1-dimethylfuro[3,4-c]pyridin-3(1H)-one **11e**.* The general procedure **4** using (600 mg, 2.90 mmol) of 4-(*E*)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carbonitrile **6a** and (165 mg, 1.45 mmol) of cyclohexane-1,2-diamine **10e** gave (345 mg, 52%) of **11e** as yellow solid, mp 205–206 °C. IR ν_{max} (neat/cm^{-1}): 3380, 1732, 1615, 1592, 1520. ^{1}H NMR ($CDCl_3$) δ 8.26 (2H, d, ^3J=5.1 Hz, 2× CH=C*H*–N), 6.82 (2H, d, ^3J=6.6 Hz, 2× N*H*), 6.38 (2H, d, ^3J=5.1 Hz, 2× C*H*=CH–N), 4.24 (2H, s large, 2× C*H*), 2.20 (2H, s large, 2× C*H*), 1.82 (2H, s large, 2× C*H*), 1.52 (12H, s, 4× CH_3), 1.46 (4H, s large, 4× C*H*). ^{13}C NMR ($CDCl_3$) δ 169.8, 165.4, 156.2, 154.6, 103.5, 102.3, 84.7, 54.7, 32.6, 26.5, 26.4, 24.9. EIMS *m*/*z* (% relative abundance): 437 (M+H, 80), 259 (100). HRMS (ES-QTOF) calcd for $C_{24}H_{29}N_4O_4$ M+H 437.2189. Found 437.2188.

*4.2.3.2.6. 4-(4-((4-(1,3-Dihydro-1,1-dimethyl-3-oxofuro[3,4-c]pyridin-4-ylamino) cyclohexyl)methyl)cyclohexylamino)-1,1-dimethylfuro[3,4-c]pyridin-3(1H)-one **11f**.* The general procedure **4** using (600 mg, 2.90 mmol) of 4-(*E*)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carbonitrile **6a** and (305 mg, 1.45 mmol) of 4-((4-aminocyclohexyl)methyl)cyclohexanamine **10f** gave (270 mg, 35%) of **11f** as white solid, mp 236 °C. IR ν_{max} (neat/cm^{-1}): 3386, 1734, 1619, 1592, 1522. ^{1}H NMR ($CDCl_3$) δ 8.26 (2H, d, ^3J=5.1 Hz, 2× CH=C*H*–N), 6.45 (2H, d, ^3J=5.1 Hz, 2× C*H*=CH–N), 6.36 (2H, d, ^3J=8.1 Hz, 2× N*H*), 4.06–3.96 (2H, m, 2× C*H*NH), 2.13–1.65 (10H, m, 4× CH_2, 2× C*H*), 1.59 (12H, s, 4× CH_3), 1.35–1.04 (10H, m, 5× CH_2). ^{13}C NMR ($CDCl_3$) δ 170.4, 165.7, 155.8, 154.6, 103.3, 102.5, 85.1, 49.6, 44.4, 33.9, 33.2, 32.2, 26.5. EIMS *m*/*z* (% relative abundance): 533 (M+H, 100), 355 (70), 179 (84). HRMS (ES-QTOF) calcd for $C_{20}H_{23}N_4O_4$ M+H 533.3128. Found 533.3108.

*4.2.3.2.7. 4-(3-(1-Ethyl-1,3-dihydro-1-methyl-3-oxofuro[3,4-c]pyridin-4-ylamino) propylamino)-1-ethyl-1-methylfuro[3,4-c]pyridin-3(1H)-one **11g**.* The general procedure **4** using (638 mg, 2.90 mmol) of 4-(*E*)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carbonitrile **6b** and (107 mg, 1.45 mmol) of propane-1,2-diamine **10b** gave (523 mg, 85%) of **11g** as white solid, mp 127–128 °C; IR ν_{max} (neat/cm^{-1}): 3396, 1733, 1616, 1590, 1527. ^{1}H NMR ($CDCl_3$) δ 8.37 (2H, d, ^3J=5.1 Hz, 2× CH=C*H*–N), 7.07 (2H, t, ^3J=6.0 Hz, 2× N*H*), 6.44 (2H, d, ^3J=5.1 Hz, 2× C*H*=CH–N), 3.68 (4H, q, $J_{NHCH_2} = J_{CH_2CH_2}$=6.1 Hz, $CH_2CH_2CH_2$), 2.03–1.75 (6H, m, 2× CH_2CH_3, $CH_2CH_2CH_2$), 1.55 (6H, s, 2× CH_3), 0.78 (3H, t, ^3J=7.3 Hz, 2× CH_2CH_3). ^{13}C NMR ($CDCl_3$) δ 170.7, 164.6, 156.6, 154.7, 104.0, 103.7, 87.9, 37.3, 32.1, 30.1, 24.9, 7.8. EIMS *m*/*z* (% relative abundance): 425 (M+H, 43), 233 (100). HRMS (ES-QTOF) calcd for $C_{23}H_{29}N_4O_4$ M+H 425.2189. Found 425.2168.

*4.2.3.3. General procedure **5** for the synthesis of 2-hydrazinopyridines **13a**–**c**.* A mixture of 4-(*E*)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-dialkyl-2-oxofuran-3-carbonitrile **6a**,**b** (1.45 mmol) and excess of hydrazine **12a**,**b** (2 mmol) was heated until homogenization and the heating was continued for 5 min. The crude product obtained was washed several times with diethylether and purified by column chromatography (silica gel, ethyl acetate/cyclohexane (70:30)) to give 2-hydrazinopyridines **13a**–**c**.

*4.2.3.3.1. 4-(2-Methylhydrazinyl)-1,1-dimethylfuro[3,4-c]pyridin-3(1H)-one **13a**.* The general procedure **5** using (300 mg, 1.45 mmol) of 4-(*E*)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carbonitrile **6a** and (92 mg, 2 mmol) of methylhydrazine **12a** gave (243 mg, 81%) of **13a** as white solid, mp 150–152 °C. IR ν_{max} (neat/cm^{-1}): 3232, 1740, 1607, 1587. ^{1}H NMR ($CDCl_3$) δ 8.29 (1H, d, ^3J=5.2 Hz, CH=C*H*–N), 7.70 (1H, s large, N*H*), 6.55 (1H, d, ^3J=5.2 Hz, C*H*=CH–N), 2.74 (1H, s, $NHCH_3$), 1.59 (6H, s, 2× CH_3). ^{13}C NMR ($CDCl_3$) δ 170.0, 166.3, 156.7, 154.8, 105.2, 103.1, 86.1, 39.6, 26.8. EIMS *m*/*z* (% relative abundance): 208 (M+H, 45), 190 (16), 178 (48), 163 (100), 148 (26). HRMS (ES-QTOF) calcd for $C_{10}H_{14}N_3O_2$ M+H 208.1086. Found 208.1078.

*4.2.3.3.2. 4-(2-Methylhydrazinyl)-1-ethyl-1-methylfuro[3,4-c]pyridin-3(1H)-one **13b**.* The general procedure **5** using (318 mg, 1.45 mmol) of 4-(*E*)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carbonitrile **6b** and (92 mg, 2 mmol) of methylhydrazine **12a** gave (304 mg, 95%) of **13b** as white solid, 120–122 °C. IR ν_{max} (neat/cm^{-1}): 3394, 3304, 1732, 1610, 1586, 1515. ^{1}H NMR ($CDCl_3$) δ 8.24 (1H, d, ^3J=5.1 Hz, CH=C*H*–N), 6.57 (1H, d,

^3J=5.1 Hz, C*H*=CH–N), 5.82 (1H, s large, N*H*), 1.94 (H_A, H_B, ABq, J_{AB}=14.5 Hz, J_{ABq}=7.4 Hz, C*HH*CH$_3$), 1.60 (1H, s large, NHC*H*$_3$), 1.59 (3H, s, C*H*$_3$), 0.80 (3H, t, ^3J=7.4 Hz, CH$_2$C*H*$_3$). ^{13}C NMR ($CDCl_3$) δ 169.9, 164.8, 156.3, 154.3, 105.2, 103.6, 88.5, 39.3, 32.1, 24.8, 7.8. EIMS *m*/*z* (% relative abundance): 222 (M+H, 76), 204 (57), 186 (34), 174 (68), 163 (100), 162 (61), 158 (23), 147 (22), 143 (42). HRMS (ES-QTOF) calcd for $C_{11}H_{16}N_3O_2$ M+H 222.1243. Found 222.1236.

4.2.3.3.3. 1-Ethyl-4-hydrazinyl-1-methylfuro[3,4-c]pyridin-3(1H)-one ***13c***. The general procedure **5** using (318 mg, 1.45 mmol) of 4-(*E*)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carbonitrile **6b** and (64 mg, 2 mmol) of hydrazine **12b** gave (270 mg, 90%) of **13c** as white solid, mp 190–192 °C. IR ν_{max} (neat/cm^{-1}): 3281, 3149, 1723, 1651, 1542. ^{1}H NMR ($CDCl_3$) δ 7.64 (1H, d, ^3J=6.9 Hz, CH=C*H*–N), 5.68 (1H, d, ^3J=6.9 Hz, C*H*=CH–N), 4.99 (1H, s large, N*H*$_2$), 1.84 (H_A, H_B, ABq, J_{AB}=14.4 Hz, J_{ABq}=7.3 Hz, C*HH*CH$_3$), 1.65 (1H, s large, N*H*), 1.53 (3H, s, C*H*$_3$), 0.82 (3H, t, ^3J=7.3 Hz, CH$_2$C*H*$_3$). ^{13}C NMR ($CDCl_3$) δ 169.9, 164.8, 156.3, 154.3, 105.2, 103.6, 85.6, 31.4, 24.2, 7.7. EIMS *m*/*z* (% relative abundance): 208 (M+H, 100), 190 (94), 179 (50), 173 (30), 163 (54). HRMS (ES-QTOF) calcd for $C_{10}H_{14}N_3O_2$ M+H 208.1086. Found 208.1093.

4.2.3.4. General procedure ***6*** *for the synthesis of chiral 2-aminopyridines* ***15a–i***. To a solution of 4-(2-dimethylaminovinyl)-5,5-dimethyl-2-oxo-2,5-dihydrofuran-3-carbonitrile **6a** (300 mg, 1.45 mmol) dissolved in DMF was added chiral amine **14a–i** (1.45 mmol). The mixture was refluxed for 3 h. The solvent was evaporated and the residue obtained was purified by column chromatography (silica gel, ethyl acetate/cyclohexane (70:30)) to give chiral 2-aminopyridines **15a–i**.

4.2.3.4.1. 4-((R)-1-Phenylethylamino)-1,1-dimethylfuro[3,4-c]pyridin-3(1H)-one ***15a***. The general procedure **6** using (300 mg, 1.45 mmol) of 4-(*E*)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carbonitrile **6a** and (175 mg, 1.45 mmol) of (*R*)-1-phenyl-ethanamine **14a** gave (307 mg, 75%) of **15a** as white solid, mp 112–113 °C; $[\alpha]_D^{20}$ −111.0 (*c* 1, $CHCl_3$). IR ν_{max} (neat/cm^{-1}): 3393, 1734, 1618, 1591, 1519. ^{1}H NMR ($CDCl_3$) δ 8.24 (1H, d, ^3J=5.1 Hz, CH=C*H*–N), 7.43–7.21 (5H, m, *H*arom), 6.81 (1H, d, ^3J=7.6 Hz, N*H*), 6.48 (1H, d, ^3J=5.1 Hz, C*H*=CH–N), 5.46 (1H, quint, $^3J_{CHNH}$=7.5 Hz, $^3J_{CHCH_3}$=7.0 Hz, C*H*NH), 1.61 (3H, d, ^3J=7.0 Hz, CHCH$_3$), 1.58 (6H, s, 2× CH$_3$). ^{13}C NMR ($CDCl_3$) δ 170.2, 165.6, 155.6, 154.6, 143.9, 128.6, 127.13, 126.1, 103.9, 102.8, 85.3, 49.6, 26.4, 22.9. EIMS *m*/*z* (% relative abundance): 283 (M+H, 82), 179 (100), 105 (15). HRMS (ES-QTOF) calcd for $C_{17}H_{19}N_2O_2$ M+H 283.1447. Found 283.1443.

4.2.3.4.2. 4-((S)-1-Phenylethylamino)-1,1-dimethylfuro[3,4-c]pyridin-3(1H)-one ***15b***. The general procedure 6 using (300 mg, 1.45 mmol) of 4-(*E*)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carbonitrile **6a** and (175 mg, 1.45 mmol) of (*S*)-1-phenyl-ethanamine **14b** gave (307 mg, 75%) of **15b** as white solid, mp 110–111 °C; $[\alpha]_D^{20}$ +112.4 (*c* 1, $CHCl_3$). IR, ^{1}H and ^{13}C NMR spectra and masse spectroscopy are similar to the described in precedent Section 4.2.3.4.2.

4.2.3.4.3. 4-((R)-1-Hydroxybutan-2-ylamino)-1,1-dimethylfuro[3,4-c]pyridin-3(1H)-one ***15c***. The general procedure **6** using (300 mg, 1.45 mmol) of 4-(*E*)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carbonitrile **6a** and (129 mg, 1.45 mmol) of (*R*)-2-aminobutanol **14c** gave (275 mg, 76%) of **15c** as viscous oil, $[\alpha]_D^{20}$ +31.3 (*c* 1, $CHCl_3$). IR ν_{max} (neat/cm^{-1}): 3460, 3380, 1730, 1615, 1588, 1520. ^{1}H NMR ($CDCl_3$) δ 8.18 (1H, d, ^3J=5.2 Hz, CH=C*H*–N), 6.58 (1H, d, ^3J=6.1 Hz, N*H*), 6.51 (1H, d, ^3J=5.2 Hz, C*H*=CH–N), 4.36 (1H, s large, O*H*), 4.05 (1H, m, C*H*NH), 3.72 (2H, ABd, $J_{Ha'Hb'}$=11.0 Hz, $J_{Ha'CH}$=6.9 Hz, $J_{Hb'CH}$=2.9 Hz, C$H_{a'}H_{b'}$OH), 1.70 (2H, m, CH_2CH$_3$), 1.62 (3H, s, CH$_3$), 1.59 (3H, s, C*H*$_3$), 1.02 (3H, t, ^3J=7.4 Hz, CH$_2$C*H*$_3$). ^{13}C NMR ($CDCl_3$) δ 170.5, 166.5, 157.1, 154.2, 104.7, 102.8, 85.7, 67.5, 56.2, 26.8, 25.0, 11.1. EIMS *m*/*z* (% relative abundance): 251 (M+H, 40), 233 (27), 215 (22), 179 (100), 161 (43). HRMS (ES-QTOF) calcd for $C_{13}H_{19}N_2O_3$ M+H 251.1396. Found 251.1398.

4.2.3.4.4. 4-((R)-2-Hydroxy-1-phenylethylamino)-1,1-dimethylfuro[3,4-c]pyridin-3(1H)-one ***15d***. The general procedure **6** using (300 mg, 1.45 mmol) of 4-(*E*)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carbonitrile **6a** and (199 mg, 1.45 mmol) of (*R*)-2-amino-2-phenylethanol **14d** gave (324 mg, 75%) of **15d** as white solid, mp 109–110 °C, $[\alpha]_D^{20}$ +48.6 (*c* 1, $CHCl_3$). IR ν_{max} (neat/cm^{-1}): 3480, 3382, 1734, 1617, 1592, 1519. ^{1}H NMR ($CDCl_3$) δ 8.22 (1H, d, ^3J=5.2 Hz, CH=C*H*–N), 7.42–7.30 (5H, m, *H*arom), 7.08 (1H, s large, N*H*), 6.56 (1H, d, ^3J=5.2 Hz, C*H*=CH–N), 5.37 (1H, dt, ^3J=5.9 Hz, NHC*H*), 3.98 (2H, d, ^3J=5.4 Hz, CH_2OH), 3.76 (1H, s large, O*H*), 1.62 (3H, s, C*H*$_3$), 1.59 (3H, s, C*H*$_3$). ^{13}C NMR ($CDCl_3$) δ 170.0, 165.9, 156.2, 153.9, 139.3, 129.0, 128.0, 126.7, 104.7, 103.6, 85.5, 60.4, 57.7, 26.4. EIMS *m*/*z* (% relative abundance): 299 (M+H, 66), 179 (100). HRMS (ES-QTOF) calcd for $C_{17}H_{19}N_2O_3$ M+H 299.1396. Found 299.1383.

4.2.3.4.5. 4-((S)-1-Hydroxy-3-phenylpropan-2-ylamino)-1,1-dimethylfuro[3,4-c]pyridin-3(1H)-one ***15e***. The general procedure **6** using (300 mg, 1.45 mmol) of 4-(*E*)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carbonitrile **6a** and (219 mg, 1.45 mmol) of (*S*)-2-amino-3-phenylpropanol **14e** gave (321 mg, 71%) of **15e** as viscous oil, $[\alpha]_D^{20}$ −98.3 (*c* 1, $CHCl_3$). IR ν_{max} (neat/cm^{-1}): 3425 (OH); 3378, 1731, 1615, 1590, 1518. ^{1}H NMR ($CDCl_3$) δ 8.16 (1H, d, ^3J=5.2 Hz, CH=C*H*–N), 7.28–7.16 (5H, m, *H*arom), 6.69 (1H, d, ^3J=6.5 Hz, N*H*), 6.49 (1H, d, ^3J=5.2 Hz, C*H*=CH–N), 4.38 (1H, m, C*H*NH), 4.18 (1H, s large, O*H*), 3.74 (2H, ABd, $J_{Ha'Hb'}$=11.1 Hz, $J_{Ha'CH}$=6.4 Hz, $J_{Hb'CH}$=2.9 Hz, C$H_{a'}H_{b'}$OH), 2.95 (2H, ABd, J_{HaHb}=13.7 Hz, J_{HaCH}=7.7 Hz, J_{HbCH}=6.7 Hz, CH_aH_bPh), 1.55 (6H, s, 2× C*H*$_3$). ^{13}C NMR ($CDCl_3$) δ 169.9, 165.9, 156.3, 153.7, 137.7, 129.3, 128.6, 126.7, 154.6, 104.4, 103.5, 85.4, 65.9, 55.3, 37.7, 26.4. EIMS *m*/*z* (% relative abundance): 313 (M+H, 33), 295 (40), 179 (100), 161 (28), 133 (07), 117 (20), 91 (35). HRMS (ES-QTOF) calcd for $C_{18}H_{21}N_2O_3$ M+H 313.1552. Found 313.1563.

4.2.3.4.6. 4-((S)-1-Cyclohexylethylamino)-1,1-dimethylfuro[3,4-c]pyridin-3(1H)-one ***15f***. The general procedure **6** using (300 mg, 1.45 mmol) of 4-(*E*)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carbonitrile **6a** and (184 mg, 1.45 mmol) of (*S*)-1-cyclohexylethanamine **14f** gave (355 mg, 85%) of **15f** as white solid, mp 78–79 °C, $[\alpha]_D^{20}$ +80.0 (*c* 1, $CHCl_3$). IR ν_{max} (neat/cm^{-1}): 3385, 1731, 1618, 1589, 1521. ^{1}H NMR ($CDCl_3$) δ 8.23 (1H, d, ^3J=5.1 Hz, CH=C*H*–N), 6.44 (1H, s large, N*H*), 6.42 (1H, d, ^3J=5.1 Hz, C*H*=CH–N), 4.16 (1H, m, C*H*NH), 1.85–1.61 (6H, m, 3× CH_2), 1.58 (3H, s, CH$_3$), 1.56 (3H, s, CH$_3$), 1.45 (1H, m, C*H*(CH$_2$)$_5$), 1.18 (3H, d, ^3J=6.6 Hz, CHC*H*$_3$), 1.26–1.03 (4H, m, 2× C*H*$_2$). ^{13}C NMR ($CDCl_3$) δ 170.6, 165.7, 156.3, 154.6, 103.2, 102.4, 85.1, 50.2, 43.2, 29.3, 29.0, 26.4, 26.2, 17.9. EIMS *m*/*z* (% relative abundance): 289 (M+H, 78), 179 (100), 161 (14). HRMS (ES-QTOF) calcd for $C_{17}H_{25}N_2O_2$ M+H 289.1916. Found 289.1911.

4.2.3.4.7. 4-((R)-1-(Naphthalen-3-yl)ethylamino)-1,1-dimethylfuro[3,4-c]pyridin-3-(1H)-one ***15g***. The general procedure **6** using (300 mg, 1.45 mmol) of 4-(*E*)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carbonitrile **6a** and (248 mg, 1.45 mmol) of (*R*)-1-(naphtalen-2-yl)ethanamine **14g** gave (400 mg, 83%) of **15g** as white solid, mp 162–164 °C, $[\alpha]_D^{20}$ −244.7 (*c* 1, $CHCl_3$). IR ν_{max} (neat/cm^{-1}): 3390, 1732, 1615, 1592, 1514. ^{1}H NMR ($CDCl_3$) δ 8.26 (1H, d, ^3J=5.1 Hz, CH=C*H*–N), 8.21–7.37 (7H, m, *H*arom), 6.87 (1H, d, ^3J=7.9 Hz, N*H*), 6.49 (1H, d, ^3J=5.1 Hz, C*H*=CH–N), 6.31 (1H, dq, ^3J=7.3 Hz, ^3J=6.8 Hz, C*H*NH), 1.76 (3H, d, ^3J=6.8 Hz, CHC*H*$_3$), 1.61 (3H, s, C*H*$_3$), 1.58 (3H, s, C*H*$_3$). ^{13}C NMR ($CDCl_3$) δ 170.4, 165.6, 155.3, 154.7, 139.4–122.3, 104.0, 102.8, 85.3, 45.6, 26.4, 22.0. EIMS *m*/*z* (% relative abundance): 333 (M+H, 88), 205 (42), 179 (100), 155 (88). HRMS (ES-QTOF) calcd for $C_{21}H_{20}N_2O_2$ M+H 333.1603. Found 333.1596.

4.2.3.4.8. 4-((1R,2R)-2-(1,3-Dihydro-1,1-dimethyl-3-oxofuran[3,4-c]pyridin-4-ylamino)cyclohexylamino)-1,1-dimethylfuro[3,4-c]pyridin-3(1H)-one ***15h***. The general procedure **6** using (600 mg, 2.90 mmol) of 4-(*E*)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-

dimethyl-2-oxofuran-3-carbonitrile **6a** and (165 mg, 1.45 mmol) of (1*R*,2*R*)-cyclohexane-1,2-diamine **14h** gave (329 mg, 52%) of **15h** as yellow solid, mp 105–106 °C, $[\alpha]_D^{20}$ −230.6 (*c* 1, $CHCl_3$). IR ν_{max} (neat/cm^{-1}): 3367, 1732, 1614, 1591, 1519. ^{1}H NMR ($CDCl_3$) δ 8.26 (2H, d, ^3J=5.1 Hz, 2× CH=C*H*–N), 6.82 (2H, d, ^3J=6.4 Hz, 2× N*H*), 6.37 (2H, d, ^3J=5.1 Hz, 2× C*H*=CH–N), 4.24 (2H, s large, 2× CH), 2.19 (2H, s large, 2× CH), 1.82 (2H, s large, 2× CH), 1.52 (6H, s, 2× CH_3), 1.48 (6H, s, 2× CH_3), 1.46 (4H, s large, 4× CH). ^{13}C NMR ($CDCl_3$) δ 169.8, 165.4, 156.2, 154.6, 103.5, 102.3, 84.7, 54.7, 32.6, 26.5, 24.9. EIMS *m*/*z* (% relative abundance): 437 (M+H, 83), 259 (100), 179 (10). HRMS (ES-QTOF) calcd for $C_{24}H_{29}N_4O_4$ M+H 437.2189. Found 437.2173.

4.2.3.4.9. 4-(Ethylamino)-1,1-dimethylfuro[3,4-c]pyridin-3(1H)-one ***15i****.* The general procedure **6** using (300 mg, 1.45 mmol) of 4-(*E*)-2-(dimethylaminovinyl)-2,5-dihydro-5,5-dimethyl-2-oxofuran-3-carbonitrile **6a** and (239 mg, 1.45 mmol) of L-phenylalanine **14i** gave (242 mg, 81%) of **15i** as viscous oil, IR ν_{max} (neat/cm^{-1}): 3675, 3391, 1732, 1617, 1591, 1523. ^{1}H NMR ($CDCl_3$) δ 8.29 (H, d, ^3J=5.2 Hz, CH=C*H*–N), 7.34–7.19 (5H, m, *H*arom), 6.58 (H, s large, N*H*), 6.49 (H, d, ^3J=5.2 Hz, C*H*=CH–N), 3.79 (2H, q, $J_{NHCH_2} = J_{CH_2CH_2}$=7.0 Hz, NHC$H_2$), 2.96 (2H, t, ^3J=7.0 Hz, NHCH$_2$CH_2), 1.59 (6H, s, 2× CH_3). ^{13}C NMR ($CDCl_3$) δ 170.3, 165.6, 156.2, 154.5, 139.0, 128.8, 128.6, 126.5, 103.8, 102.9, 85.3, 42.0, 35.9, 26.4. EIMS *m*/*z* (% relative abundance): 283 (M+H, 100), 105 (88).

Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2012.10.108.

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