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Original article

Synthesis of new dipyrrolo- and furopyrrolopyrazinones related to tripentones and their biological evaluation as potential kinases (CDKs1–5, GSK-3) inhibitors

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Abstract

We herein describe the synthesis of novel dipyrrolo- and furopyrrolopyrazinones related to highly cytotoxic tripentones and to their oximes. The synthetic pathway involved in particular a Curtius rearrangement and a subsequent cyclisation into the title pyrazinones. The biological evaluation towards various cyclin-dependent kinases (CDKs1–5, GSK-3) highlighted a weak inhibitory activity for the oximes whose SAR was studied by a molecular modeling study.

Keywords: Tripentone; Dipyrrolopyrazinone; Furopyrrolopyrazinone; Curtius rearrangement; Cyclin-dependent kinase; CDK; GSK-3

1. Introduction

During the course of our work concerning the synthesis of novel heterocyclic systems with therapeutic interest, we have identified an original series of arylthieno pyrrolizinones **1** named by us as ''tripentones''. Some members of this new family including compound MR22388 exhibit an in vitro cytotoxic activity in the submicromolar range (Fig. 1) [1].

This activity was associated not only to an anti-tubulin effect [2] but also to a weak cyclin-dependent kinase inhibitory activity [3]. In order to establish the requirements of this family for this anti-kinase activity, novel pharmacomodulations were realized. The first one consisted of the bio-isosteric replacement of the sulphur atom of series **1** by a nitrogen or an oxygen, leading to the new pyrrolo- and furopyrrolizinone families **2** and **3**, the syntheses of which were recently described [2,4]. Then, supported by novel docking studies [3], we were interested in investigating the novel modulations of the structure. In order to assess which part of the molecule was linked to the ATP-binding site of the kinase, one of them aimed at increasing the number of potential hydrogen bond donor–acceptor sequence in the tripentones.

We wish herein to describe some of this work leading to the new dipyrrolo **4** and furopyrrolo **5** pyrazinone series. Their access and the evaluation of the potential cyclin-dependent kinase inhibitory activity of all new derivatives **2–5** were reported.

2. Chemistry

The synthesis of the tripentone system in the pyrrolo and furo series was achieved according to the procedure developed for thienopyrrolizinones **1** [1]. This synthesis started from arylacetonitriles **6** via the corresponding *ortho*-aminoesters **7**, **8** and pyrrolyl esters **9**, **10**, respectively (Scheme 1). The access to the pyrazinone systems was considered through two pathways

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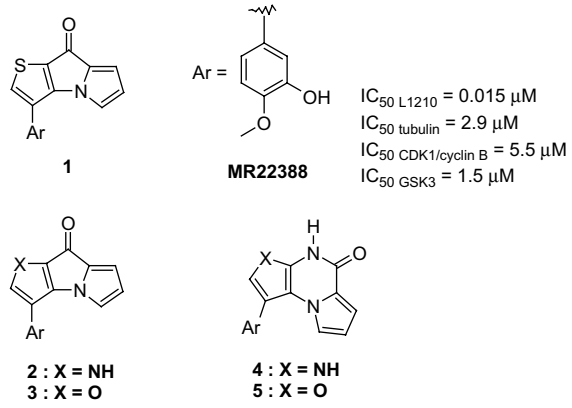
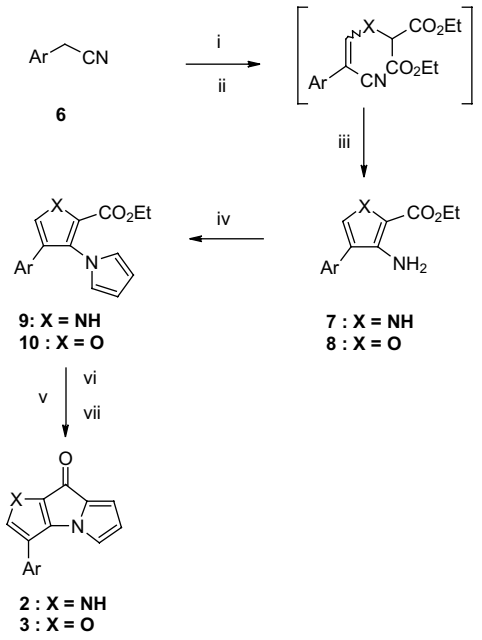


Fig. 1. General structure of tripentones and arylpyrazinones.

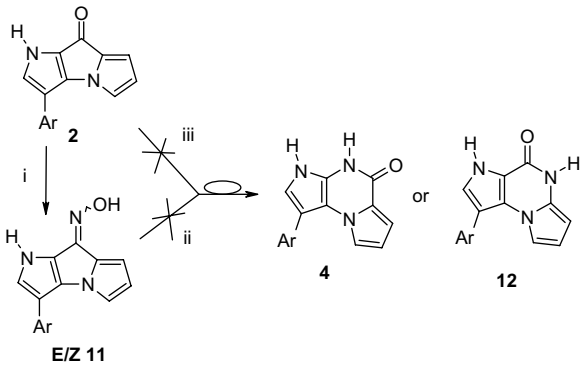
involving either a Schmidt–Beckmann enlargement of the tripentone ring (Scheme 2) or an Eloy–Deryckere cyclisation [5] following a Curtius rearrangement (Scheme 3).

The Beckmann strategy implies the synthesis of oximes **11** which were realized starting from the pyrrolo-pyrrolizinones **2** (Scheme 2) with hydroxylamine hydrochloride in refluxing pyridine. The reaction led to a mixture of the *E* and *Z* forms in a 55/45 ratio. Unfortunately, all attempts aiming at realizing a Beckmann rearrangement [6] by treating **11** with PCl_5 or H_2SO_4 have failed. The starting material was recovered unchanged without traces of the expected dipyrrolopyrazinones **4** neither of their pyrimidinone isomers **12**, whose occurrence appears theoretically possible taking into account the existence of the *E* and *Z* forms of **11**.

In a similar manner, the tripentones **2** did not lead to the Schmidt [7] rearrangement since they were degraded by treatment with NaN_3 in refluxing TFA.

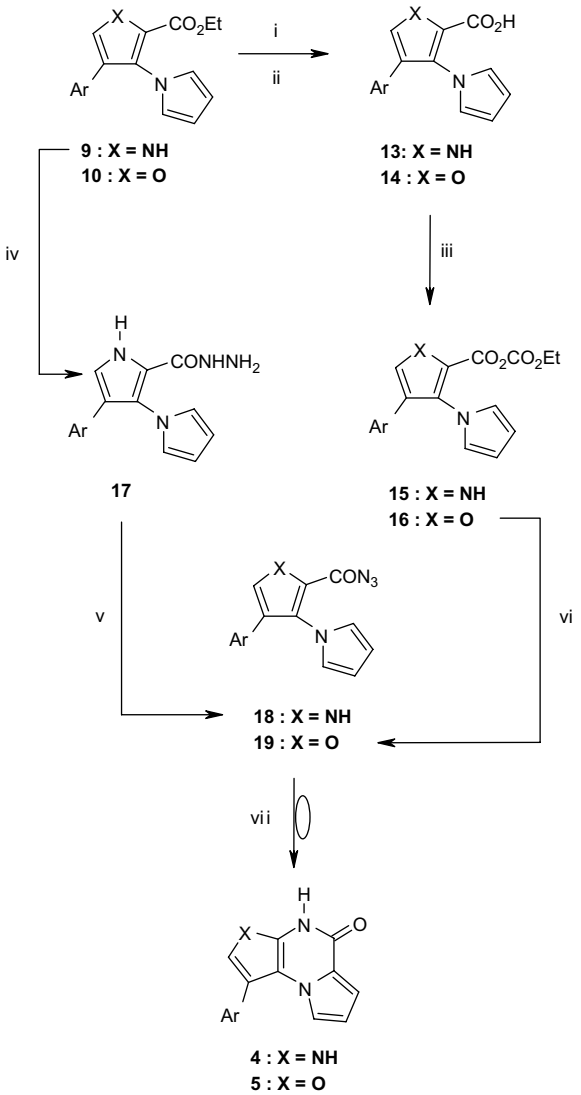


Scheme 1. Reagents: (i) HCO_2Et, NaH, THF; (ii) diethylaminomalonate–HCl, Et_3N, MeOH for **7** or diethylchloromalonate, DMF for **8**; (iii) EtONa, EtOH for **7** or DBN, EtOH for **8**; (iv) 2,5-dimethoxyTHF, 4-chloro-pyridine–HCl, dioxane; (v) pyrrolidine; (vi) $POCl_3$; (vii) 10% aq NaOH.



Scheme 2. Reagents: (i) NH_2OH–HCl, pyridine; (ii) PCl_5 or H_2SO_4; (iii) NaN_3, TFA.

Facing this problem the second strategy was applied, starting from the dipyrrolyl esters **9** and the furylpyrrolyl esters **10** (Scheme 3). In order to convert the ethyl carboxylate group into an azide one, a saponification was first achieved in an



Scheme 3. Reagents: (i) NaOH, acetone, H_2O; (ii) HCl, H_2O; (iii) $ClCO_2Et$, Et_3N, acetone; (iv) N_2H_4–H_2O, EtOH; (v) $NaNO_2$, AcOH, H_2O; (vi) NaN_3, H_2O; (vii) *ortho*-dichlorobenzene.

alkaline medium, leading to the carboxylic acids **13** and **14**. The following step consisted in a treatment with ethyl chloroformate in acetone and TEA in order to synthesize the corresponding mixed anhydrides according to the Weinstock procedure [8].

Under those conditions the furyl series afforded compounds **16**. In the pyrrolyl one, the acids **13** did not lead selectively to **15** but to a mixture of products resulting from a competition between the carboxylic acid group and the free pyrrolic NH. This difficulty was circumvented through the formation of hydrazides **17**, obtained from esters **9** under treatment with hydrazine hydrate in EtOH according to Curtius procedure [9]. The latter were easily converted into the azide derivatives **18** by use of $NaNO_2$ in acetic acid. The mixed anhydrides **16** afforded the furane analogues **19** under treatment with NaN_3 in water with good yields. In all cases, the Curtius rearrangement took place in *ortho*-dichlorobenzene at 180 °C, cyclising in a one-pot step the isocyanate intermediates into the title dipyrrolo- and furopyrrolopyrazinones **4a**,**g** and **5b**–**g**.

3. Biology

Dipyrrolopyrazinones **4a**,**g** and furopyrrolopyrazinones **5b**–**g** were evaluated against two protein kinases CDK5 and GSK-3β. All assays were run in the presence of ATP and the appropriate protein substrates [10]. IC_{50} values were determined from dose–response curves and are provided in Table 1.

The latter were compared to the results obtained with selected tripentones **1h**,**i**, **2a**,**g**–**i**, **3g** (Table 2) and intermediate oximes **11h**,**i** which were further evaluated against CDK1/cyclin B (Table 3).

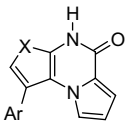
None of our novel pyrazinone compounds **4**,**5** in either the pyrrole or the furane series showed any interesting activity against the different protein kinases. These results confirmed some of our docking pose established for compound **1i** (Fig. 2) and the crucial role of the *p*-MeO-*m*-OH-phenyl substituent not only for the binding to the ATP-binding site of GSK-3, and more precisely to the Asp133-Tyr134-Val135 sequence, but also for the binding in the CDKs active site.

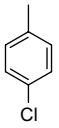
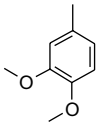
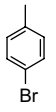
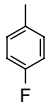
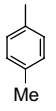
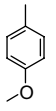
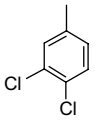
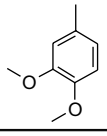
The novel evaluation of the tripentones in the pyrrole **2** and furane **3** series and the weaker activity found for compound **2i** (Table 2) confirmed the crucial influence of the aromatic substituent. This result highlighted a novel important hydrophobic interaction (Fig. 3) between the tripentone and the alkyl chain of Lys85. A similar influence could also be noticed for CDKs1–5 inhibition.

The modulation of the upper part of the tripentones seems to be of great influence on the activity of the tripentones against the selected kinases. Indeed, a novel interesting activity was found for some of our intermediates in this program, the pyrrole oximes **11h** and **11i** (Table 3). Indeed the *E*/*Z* mixture of those compounds showed interesting micromolar values against all range of tested kinases, and for the first time micromolar activities are found with a benzylated phenol **11h** against CDKs1–5 and GSK-3.

This novel activity is supported by a docking study detailed in the next part and it points out the crucial role of the hydrophobic interaction with the Lys85 of the binding site of GSK-3.

Table 1
IC_{50} (μM) for **4a**,**g**, **5b**–**g** against CDK5, GSK-3

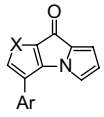


Compound	X	Ar	CDK5	GSK-3
4a	NH		>50	>50
4g	NH		>50	>50
5b	O		>50	>50
5c	O		>50	>50
5d	O		>50	>50
5e	O		>50	>50
5f	O		>50	>50
5g	O		>50	>50

4. Molecular modeling

Previous docking studies, in the GSK-3β binding site, showed that compound **1i** adopted one major orientation

Table 2
IC_{50} (μM) for **1h**,**i**, **2a**,**g**–**i**, **3g** against CDK1, CDK5, GSK-3



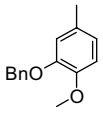
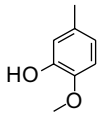
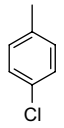
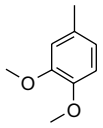
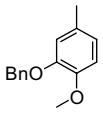
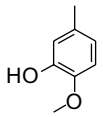
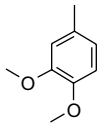
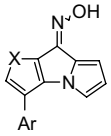
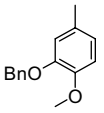
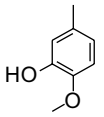
Compound	X	Ar	CDK1	CDK5	GSK-3
1h	S		>50	ND	>50
1i	S		5.5	ND	1.5
2a	NH		>50	>50	>50
2g	NH		ND	>50	>50
2h	NH		>50	>50	>50
2i	NH		22	30	11
3g	O		>50	>50	>50

Table 3
IC_{50} (μM) for **11h**,**i** against CDK1, CDK5, GSK-3



Compound	X	Ar	CDK1	CDK5	GSK-3
11h	NH		9	14	17
11i	NH		3.8	3.2	5.5

[3,11] where 2-methoxyphenol fragment forms hydrogen bonds with the backbone of the sequence Asp133-Tyr134-Val135 (Fig. 2). The oxygen of the carbonyl group forms electrostatic interactions with the amino group of Lys85. We also observed a close contact between the aromatic sulphur and the alkyl chain of Lys85 through a hydrophobic interaction.

The replacement of the sulphur atom by an NH group (**2i**) led to a straight modification of the polarity of the ligand in this last hydrophobic site. A variation of position of **2i** vs **1i** (Fig. 3) was observed with particularly two electrostatic interactions, one involving the NH group (Asp133 for the active site), and the second involving *p*-MeO-*m*-OH-phenyl group (Arg 141 for the active site).

The substitution of carbonyl vs oxime (compound **11i**) led to an increase in the affinity value (see Tables 2 and 3). In the case of *Z* configuration for **11i**, the NH group is involved in an intramolecular hydrogen bond with the oxime group. So, the docking position was observed to be close to **1i** with hydrogen bonds implying the 2-methoxyphenol fragment (Val135/Tyr134) and the oxime function (Lys85) on one side, and hydrophobic interactions between the pyrrole group and the hydrophobic site (Fig. 4a) on the other. In the case of *E* configuration for **11i**, without the intramolecular hydrogen bond, the docking position was like **2i** with notable hydrogen bonds between the NH group and the carbonyl group of Asp133 (Fig. 4b).

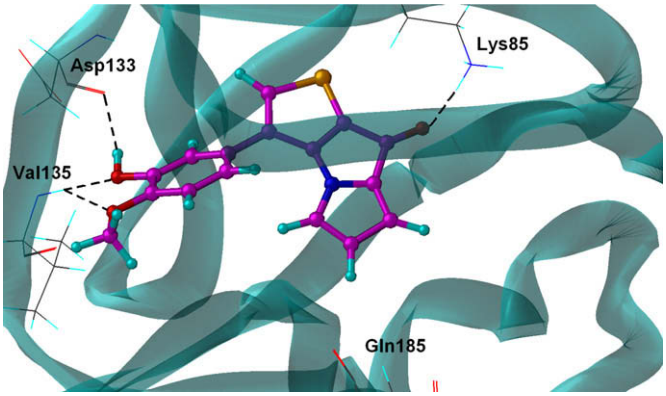


Fig. 2. View of compound **1i** docked in the GSK-3 binding site. Compound **1i** is displayed as ball-and-sticks. The GSK-3 secondary structure is displayed as smooth Cα chain in cyan. For clarity only four residues of the active site are shown (Lys85, Asp133, Val135 and Gln185). Hydrogen bonds are represented with dashed lines.

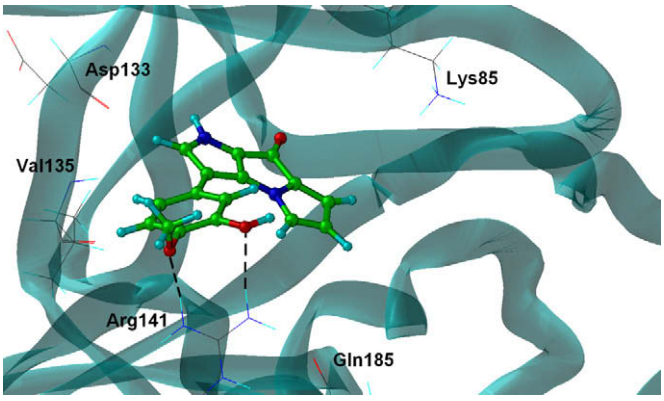


Fig. 3. View of compound **2i** in the GSK-3 binding site after docking. Hydrogen bonds are represented with dashed lines.

5. Conclusion

In conclusion, this work was conducted to synthesize two new heterocyclic families, the dipyrrolo- **4** and furopyrrolopyrazinones **5**. But this work gave us the opportunity to describe more precisely the binding of our tripentones with some kinases. Finally these analyses allowed us to identify a novel interesting series of tripentones including an oxime function. According to these interesting results the synthesis of novel oximes on various tripentones' scaffold will be achieved in the future.

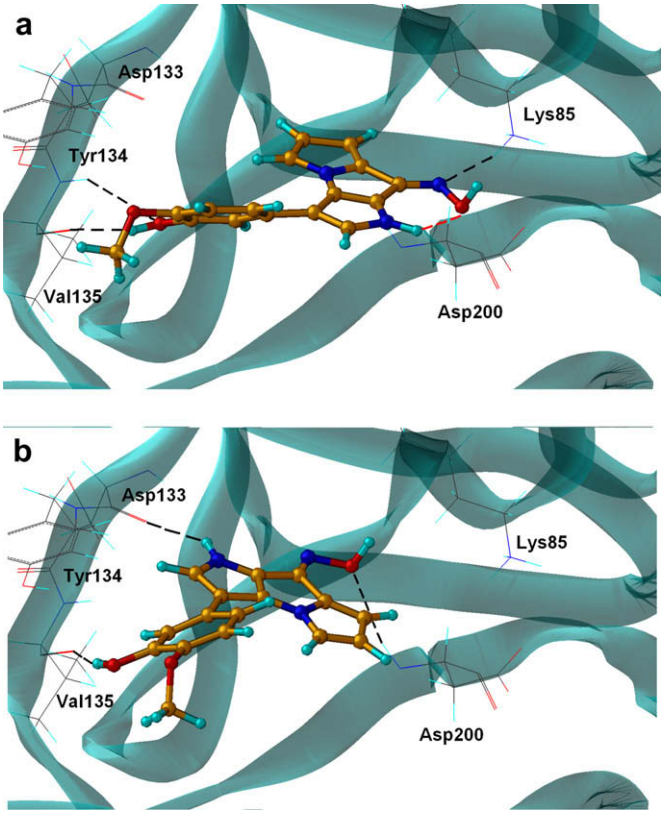


Fig. 4. Docking poses of compound **11i** in the binding site of GSK-3 with a representation of *Z* (a) and *E* (b) isomers. Hydrogen bonds are represented with dashed lines.

6. Experimental protocols

6.1. General

Melting points were determined on a Kofler block and are uncorrected. ^{1}H and ^{13}C NMR spectra were measured on a JEOL JNM-LA 400 spectrometer. Chemical shifts are reported in δ (ppm). Column chromatography was performed on Merck silica gel 60, 0.063–0.200 mm, 70–230 mesh. Precoated silica gel plates (Polygram SIL G/UV254, 0.25 mm) were used for TLC analysis. All products and reagents were purchased from Acros, Belgium.

6.2. Procedure for synthesis of oximes

6.2.1. (E/Z:55/45) 8-[3-(4-Chlorophenyl)pyrrolo [2,3-b]pyrrolizin-8(1H)-one]oxime (*11a*)

Hydroxylamine hydrochloride (0.034 g, 0.491 mmol) was added to a solution of tripentone **2a** (0.06 g, 0.223 mmol) in pyridine (10 mL). The reaction mixture was refluxed for 5 h and then evaporated to dryness. The residue was dissolved in EtOAc (100 mL) and the solution was washed with water (2×100 mL) then with brine (100 mL), dried ($MgSO_4$) and evaporated to give a mixture of *E*/*Z* forms of **11a** as red solid (0.06 g, 99%). Mp 117 °C. IR (KBr): $\nu = 3321$ (NH and OH), 2920, 2847, 1633, 1522, 1383, 1091, 702 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 10.4$ and 9.9 (br s, 1H, NH), 8.7 and 8.1 (br s, 1H, OH), 7.30 (m, 8H, H_{arom}), 6.96 (s, 2H, $2H_2$), 6.83 and 6.78 (d, 1H, $^{3}J_{H5H6} = 2.7$ Hz, H_5), 6.72 and 6.43 (d, 1H, $^{3}J_{H6H7} = 3.4$ Hz, H_7), 6.11 and 6.10 (dd, 1H, $^{3}J_{H5H6} = 2.7$ Hz, $^{3}J_{H6H7} = 3.4$ Hz, H_6). ^{13}C NMR (100 MHz, $CDCl_3$): δ (*E* form) = 141.3, 133.3, 132.1, 129.03, 128.0, 127.9, 120.8, 120.2, 116.5, 114.1, 111.1, 110.6, 106.2. MS (EI^+) *m*/*z*: 283.4 (M, 27), 267.4 (20), 149.2 (20), 84.5 (100).

6.2.2. (E/Z:55/45) 8-[3-(3-Benzyloxy-4-methoxyphenyl) pyrrolo[2,3-b]pyrrolizin-8(1H)-one]oxime (*11h*)

This compound was obtained from **2h** as described for **11a** as orange solid in 99% yield. Mp 116 °C. IR (KBr): $\nu = 3288$ (OH), 3101 (NH), 2929, 2826, 1713, 1516, 1456, 1256, 1132, 1014, 937, 755, 696 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 11.7$ and 11.5 (br s, 1H, NH), 11.5 and 11.4 (br s, 1H, OH), 7.45 (m, 10H, H_{arom}), 7.15 (m, 6H, H_{arom}), 7.07 and 7.04 (d, 1H, $^{3}J_{H2NH} = 2.9$ Hz, H_2), 6.89 and 6.87 (d, 1H, $^{3}J_{H5H6} = 2.7$ Hz, H_5), 6.58 and 6.37 (d, 1H, $^{3}J_{H6H7} = 3.4$ Hz, H_7), 6.08 and 6.05 (dd, 1H, $^{3}J_{H5H6} = 2.7$ Hz, $^{3}J_{H6H7} = 3.4$ Hz, H_6), 5.26 (s, 4H, 2 CH_2Ph), 3.87 (s, 6H, $2OCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ (*E* form) = 150.0, 148.0, 147.8, 139.9, 139.2, 138.9, 137.2, 128.5, 127.8, 127.5, 125.8, 120.1, 119.0, 116.3, 112.8, 112.0, 111.9, 110.8, 105.1, 69.7, 55.7. MS (EI^+) *m*/*z*: 385.1 (M, 15), 294.1 (10), 192.1 (20), 91.0 (100).

6.2.3. (E/Z:55/45) 8-[3-(3-Hydroxy-4-methoxyphenyl) pyrrolo[2,3-b]pyrrolizin-8(1H)-one]oxime (*11i*)

This compound was obtained from **2i** as described for **11a** as red solid in 84% yield. Mp 138 °C. IR (KBr): $\nu = 3288$ (OH), 3101 (NH), 2929, 2826, 1713, 1516, 1456, 1256,

1132, 1014, 937, 755, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 11.7$ and 11.5 (br s, 1H, NH), 11.5 and 11.4 (br s, 1H, OH), 7.45 (m, 10H, H_{arom}), 7.15 (m, 6H, H_{arom}), 7.07 and 7.04 (d, 1H, $^3J_{H2NH} = 2.9$ Hz, H_2), 6.89 and 6.87 (d, 1H, $^3J_{H5H6} = 2.7$ Hz, H_5), 6.58 and 6.37 (d, 1H, $^3J_{H6H7} = 3.4$ Hz, H_7), 6.08 and 6.05 (dd, 1H, $^3J_{H5H6} = 2.7$ Hz, $^3J_{H6H7} = 3.4$ Hz, H_6), 5.26 (s, 4H, 2 CH_2Ph), 3.87 (s, 6H, $2OCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ (*E* form) = 149.9, 148.0, 147.8, 139.9, 139.2, 138.9, 137.2, 128.5, 127.8, 127.5, 125.8, 120.0, 119.0, 116.3, 112.8, 112.0, 111.9, 110.8, 105.1, 69.7, 55.7. MS (EI^+) *m/z*: 385.1 (M, 15), 294.1 (10), 192.1 (20), 91.0 (100).

6.3. Saponification procedure

6.3.1. 4′-(4-Chlorophenyl)-1′H-1,3′-bipyrrole-2′-carboxylic acid (**13a**)

A solution of NaOH (0.8 g, 0.02 mol) in water (30 mL) was added dropwise to a solution of ester **9a** (3.1 g, 0.1 mol) in acetone (30 mL). The reaction mixture was heated at 80 °C for 3 h and the acetone was then evaporated under reduced pressure. The aqueous solution was extracted with ether (2 × 50 mL), acidified until pH = 1 with an 1 N aqueous HCl solution and finally extracted with EtOAc (2 × 100 mL). The organic layer was washed with brine (100 mL), dried ($MgSO_4$) and evaporated to give **13a** as beige solid (2.86 g, 100%). Mp 264 °C. IR (KBr): $\nu = 3342$ (NH), 2530–2900 (OH), 1751 (CO), 1676, 1649, 1579, 1446, 1291, 1084, 843, 730 cm^{-1}. ^1H NMR (400 MHz, DMSO): $\delta = 12.5$ (br s, 1H, OH), 12.2 (br s, 1H, NH), 7.18 (d, 2H, $^3J_{H2'H3'} = 8.4$ Hz, $H_{2'}$ and $H_{6'}$), 7.10 (d, 1H, $^3J_{H5NH} = 3.3$ Hz, H_5), 6.83 (d, 2H, $^3J_{H3'H2'} = 8.4$ Hz, $H_{3'}$ and $H_{5'}$), 6.68 (m, 2H, $H_{\alpha pyrrole}$), 6.24 (m, 2H, $H_{\beta pyrrole}$). ^{13}C NMR (100 MHz, DMSO): $\delta = 160.7$, 131.8, 130.6, 128.3, 127.5, 126.8, 122.8, 120.5, 120.0, 118.1, 108.5. MS (EI^+) *m/z*: 286.0 (M, 12), 241.0 (M − COOH, 100), 206.0 (M − COOH − Cl, 76).

6.3.2. 4′-(3,4-Dimethoxyphenyl)-1′H-1,3′-bipyrrole -2′-carboxylic acid (**13g**)

This compound was obtained from **9g** as described for **13a** as beige solid in 100% yield. Mp 230 °C. IR (KBr): $\nu = 3341$ (NH), 2300–3100 (OH), 1667 (CO), 1573, 1482, 1438, 1250, 1123, 719 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 10.4$ (br s, 1H, OH), 7.09 (d, 1H, $^3J_{H5NH} = 3.4$ Hz, H_5), 6.77 (d, 1H, $^3J_{H5'H6'} = 8.2$ Hz, $H_{5'}$), 6.72 (m, 2H, $H_{\alpha pyrrole}$), 6.71 (dd, 1H, $^4J_{H2'H6'} = 1.9$ Hz, $^3J_{H5'H6'} = 8.2$ Hz, $H_{6'}$), 6.22 (m, 2H, $H_{\beta pyrrole}$), 6.21 (d, 1H, $^4J_{H2'H6'} = 1.9$ Hz, $H_{2'}$), 3.84 (s, 3H, OCH_3), 3.61 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 161.5$, 148.8, 147.6, 127.5, 125.7, 123.0, 122.8, 118.6, 118.5, 117.9, 111.2, 109.6, 108.7, 55.8, 55.5. MS (EI^+) *m/z*: 312.2 (M, 60), 268.2 (M^+ − COOH, 100).

6.3.3. 4-(4-Bromophenyl)-3-(1H-pyrrol-1-yl)-2-furoic acid (**14b**)

This compound was obtained from **10b** as described for **13a** [using EtOH (50 mL) instead of acetone] as brown solid in 81% yield. Mp 215 °C. IR (KBr): $\nu = 3100–2500$ (OH), 1699 (CO), 1515, 1461, 1340, 1251, 1179, 1026, 809 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.77$ (s, 1H, H_5), 7.42 (d, 2H, $^3J_{H2'H3'} = 8.3$ Hz, $H_{2'}$ and $H_{6'}$), 6.81 (d, 2H, $^3J_{H3'H2'} = 8.3$ Hz, $H_{3'}$ and $H_{5'}$), 6.67 (m, 2H, $H_{\alpha pyrrole}$), 6.28 (m, 2H, $H_{\beta pyrrole}$). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 161.7$, 143.6, 139.1, 134.1, 132.6, 128.7, 127.3, 126.5, 123.1, 120.3, 109.9. MS (EI^+) *m/z*: 333.1 (100), 331.1 (95), 288 (65).

6.3.4. 4-(4-Fluorophenyl)-3-(1H-pyrrol-1-yl)-2-furoic acid (**14c**)

This compound was obtained from **10c** as described for **14b** as brown solid in 85% yield. Mp 208 °C. IR (KBr): $\nu = 3100–2500$ (OH), 1684 (CO), 1603, 1479, 1262, 1162, 934, 829 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.74$ (s, 1H, H_5), 7.00 (m, 2H, $H_{5'}$ and $H_{6'}$), 6.94 (m, 2H, $H_{2'}$ and $H_{3'}$), 6.67 (m, 2H, $H_{\alpha pyrrole}$), 6.28 (m, 2H, $H_{\beta pyrrole}$). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 165.7$, 161.7, 159.6, 141.8, 132.2, 130.5, 128.6, 124.8, 120.3, 116.9, 116.5, 115.6, 110.7. MS (EI^+) *m/z*: 271.1 (M, 30), 227.1 ($M^+ - CO_2H$, 67).

6.3.5. 4-(4-Methylphenyl)-3-(1H-pyrrol-1-yl)-2-furoic acid (**14d**)

This compound was obtained from **10d** as described for **14b** as brown solid in 90% yield. Mp 189 °C. IR (KBr): $\nu = 3100–2500$ (OH), 1688 (CO), 1609, 1484, 1444, 1267, 1179, 1026, 809 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.74$ (s, 1H, H_5), 7.10 (d, 2H, $^3J_{H2'H3'} = 8.1$ Hz, $H_{2'}$ and $H_{6'}$), 6.85 (d, 2H, $^3J_{H3'H2'} = 8.1$ Hz, $H_{3'}$ and $H_{5'}$), 6.69 (m, 2H, $H_{\alpha pyrrole}$), 6.27 (m, 2H, $H_{\beta pyrrole}$), 3.32 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 161.7$, 142.6, 136.3, 134.1, 128.5, 126.3, 122.4, 120.7, 117.6, 114.2, 109.9, 25.2. MS (EI^+) *m/z*: 267.2 (M, 60), 222.2 (M − CO_2H, 17).

6.3.6. 4-(4-Methoxyphenyl)-3-(1H-pyrrol-1-yl)-2-furoic acid (**14e**)

This compound was obtained from **10e** as described for **14b** as brown solid in 80% yield. Mp 200 °C. IR (KBr): $\nu = 3100–2500$ (OH), 1736 (CO), 1681, 1604, 1484, 1247, 1178, 931, 730 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.72$ (s, 1H, H_5), 6.89 (d, 2H, $^3J_{H2'H3'} = 8.1$ Hz, $H_{2'}$ and $H_{6'}$), 6.82 (d, 2H, $^3J_{H3'H2'} = 8.1$ Hz, $H_{3'}$ and $H_{5'}$), 6.71 (m, 2H, $H_{\alpha pyrrole}$), 6.28 (m, 2H, $H_{\beta pyrrole}$), 3.79 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 161.7$, 159.6, 142.6, 136.3, 134.1, 128.5, 126.3, 122.4, 120.7, 114.2, 109.9, 55.2. MS (EI^+) *m/z*: 284.1 (M^+, 10), 283.1 (M, 80), 238.1 (38).

6.3.7. 4-(3,4-Dichlorophenyl)-3-(1H-pyrrol-1-yl)-2-furoic acid (**14f**)

This compound was obtained from **10f** as described for **14b** as brown solid in 76% yield. Mp 232 °C. IR (KBr): $\nu = 3100–2500$ (OH), 1689 (CO), 1615, 1472, 1362, 1251, 1193, 907, 816 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.76$ (s, 1H, H_5), 7.38 (d, 1H, $^3J_{H5'H6'} = 8.3$ Hz, $H_{5'}$), 7.17 (d, 1H, $^4J_{H2'H6'} = 1.7$ Hz, $H_{2'}$), 6.75 (dd, 1H, $^3J_{H6'H5'} = 8.3$ Hz, $^4J_{H6'H2'} = 1.7$ Hz, $H_{6'}$), 6.67 (m, 2H, $H_{\alpha pyrrole}$), 6.28 (m, 2H, $H_{\beta pyrrole}$). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 161.7$, 143.0,

137.2, 135.6, 133.8, 132.7, 130.3, 129.9, 128.4, 120.2, 117.2, 115.1, 110.7. MS (EI^+) *m/z*: 322.1 (M, 63), 320.1 (100).

6.3.8. 4-(3,4-Dimethoxyphenyl)-3-(1H-pyrrol-1-yl)-2-furoic acid (**14g**)

This compound was obtained from **10g** as described for **14b** as brown solid in 83% yield. Mp 184 °C. IR (KBr): $\nu = 3100-2600$ (OH), 1689 (CO), 1515, 1472, 1340, 1251, 1179, 1026, 809 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.71$ (s, 1H, H_5), 6.80 (dd, 1H, $^3J_{H6'H5'} = 8.1$ Hz, $^4J_{H6'H2'} = 1.8$ Hz, $H_{6'}$), 6.74 (m, 3H, $H_{5'}$ and $H_{\alpha pyrrole}$), 6.28 (m, 2H, $H_{\beta pyrrole}$), 6.24 (d, $^4J_{H2'H6'} = 1.8$ Hz, $H_{2'}$), 3.86 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 158.7$, 149.1, 141.5, 135.3, 134.8, 133.2, 129.0, 128.5, 122.1, 119.3, 111.1, 109.6, 55.7, 55.5. MS (EI^+) *m/z*: 314.2 (M^+, 18), 313.2 (M, 100), 268.0 ($M - CO_2H$, 15).

6.4. Procedure for synthesis of hydrazides

6.4.1. 4′-(4-Chlorophenyl)-1′H-1,3′-bipyrrole-2′-carbohydrazide (**17a**)

Hydrazine hydrate (1.63 mL, 0.0333 mol) was added to a solution of ester **9a** (1 g, 0.0033 mol) in EtOH (20 mL). The reaction mixture was refluxed for 12 h and then cooled in an ice bath. The precipitate was filtered, washed with EtOH and dried to give **17a** as white solid (0.81 g, 81%). Mp 242 °C. IR (KBr): $\nu = 3329$, 3269 and 3211 (NH and NH_2), 1609 (CO), 1506, 1481, 1375, 1078, 833, 745 cm^{-1}. ^1H NMR (400 MHz, DMSO): $\delta = 7.39$ (s, 1H, H_5), 7.22 (d, 2H, $^3J_{H2'H3'} = 7.2$ Hz, $H_{2'}$ and $H_{6'}$), 6.91 (d, 2H, $^3J_{H3'H2'} = 7.2$ Hz, $H_{3'}$ and $H_{5'}$), 6.83 (m, 2H, $H_{\alpha pyrrole}$), 6.7 (br s, 1H, NH), 6.31 (m, 2H, $H_{\beta pyrrole}$), 4.33 (br s, 2H, NH_2). ^{13}C NMR (100 MHz, DMSO): $\delta = 160.1$, 146.1, 136.5, 131.2, 131.0, 128.01, 126.6, 122.6, 122.0, 117.9, 110.4. MS (EI^+) *m/z*: 300.1 (M, 27), 284.1 (40), 269.0 ($M - NHNH_2$, 100).

6.4.2. 4′-(3,4-Dimethoxyphenyl)-1′H-1,3′-bipyrrole-2′-carbohydrazide (**17g**)

This compound was obtained from **9g** as described for **17a** as white solid in 61% yield. Mp 167 °C. IR (KBr): $\nu = 3397$, 3325 and 3210 (NH and NH_2), 1627 (CO), 1505, 1381, 1255, 1160, 1123, 1024, 740 cm^{-1}. ^1H NMR (400 MHz, DMSO): $\delta = 7.30$ (s, 1H, H_5), 6.66 (m, 5H, $H_{2'}$, $H_{5'}$, $H_{6'}$ and $H_{\alpha pyrrole}$), 6.32 (m, 2H, $H_{\beta pyrrole}$), 4.3 (br s, 2H, NH_2), 3.66 (s, 3H, OCH_3), 3.52 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, DMSO): $\delta = 161.1$, 149.1, 148.0, 131.1, 129.0, 125.2, 123.4, 122.7, 120.4, 118.5, 117.4, 111.5, 109.1, 56.0, 55.8. MS (EI^+) *m/z*: 326.2 (M, 15), 301.1 (30), 273.1 (18), 209.0 (100).

6.5. Procedure for synthesis of azido derivatives

6.5.1. 4′-(4-Chlorophenyl)-1′H-1,3′-bipyrrole-2′-carbonyl azide (**18a**)

A solution of sodium nitrite (0.275 g, 0.004 mol) in water (5 mL) was added to an ice cooled solution of the hydrazide **17a** (0.8 g, 0.0027 mol) in acetic acid (15 mL). The reaction mixture was stirred at 0 °C for 15 min and then for 3 h at room temperature. Once cooled a precipitate was formed, filtered, washed with water and dried to give **18a** as white solid (0.64 g, 77%). Mp 174 °C. IR (KBr): $\nu = 3378$ (NH), 2144 (N_3), 1665 (CO), 1577, 1415, 1378, 1187, 914, 844, 735 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.6$ (br s, 1H, NH), 7.21 (d, 1H, $^3J_{H5NH} = 3.1$ Hz, H_5), 7.20 (d, 2H, $^3J_{H2'H3'} = 8.5$ Hz, $H_{2'}$ and $H_{6'}$), 6.82 (d, 2H, $^3J_{H3'H2'} = 8.5$ Hz, $H_{3'}$ and $H_{5'}$), 6.66 (m, 2H, $H_{\alpha pyrrole}$), 6.30 (m, 2H, $H_{\beta pyrrole}$). MS (EI^+) *m/z*: 311.1 (M, 19), 281.0 ($M - N_2$, 100), 267.1 ($M - N_3$, 10), 254.0 (37).

6.5.2. 4′-(3,4-Dimethoxyphenyl)-1′H-1,3′-bipyrrole-2′-carbonyl azide (**18g**)

This compound was obtained from **10g** as described for **18a** as beige solid in 83% yield. Mp 170 °C. IR (KBr): $\nu = 3322$ (NH), 2133 (N_3), 1657 (CO), 1561, 1365, 1245, 1206, 1144, 731 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.4$ (br s, 1H, NH), 7.21 (d, 1H, $^3J_{H5NH} = 3.1$ Hz, H_5), 6.78 (d, 1H, $^3J_{H5'H6'} = 8.1$ Hz, $H_{5'}$), 6.72 (dd, 1H, $^4J_{H6'H2'} = 1.7$ Hz, $^3J_{H6'H5'} = 8.1$ Hz, $H_{6'}$), 6.70 (m, 2H, $H_{\alpha pyrrole}$), 6.31 (m, 2H, $H_{\beta pyrrole}$), 6.17 (d, 1H, $^4J_{H2'H6'} = 1.7$ Hz, $H_{2'}$), 3.85 (s, 3H, OCH_3), 3.61 (s, 3H, OCH_3). MS (EI^+) *m/z*: 309.1 ($M - N_2$, 87), 295.1 ($M - N_3$, 47), 252.0 (100).

6.5.3. 4-(4-Bromophenyl)-3-(1H-pyrrol-1-yl)-2-furoyl azide (**19b**)

To an ice cooled solution of the acid **14b** (1.53 g, 0.0046 mol) in acetone (40 mL) were successively added every 15 min TEA (0.7 mL, 0.005 mol), ethyl chloroformate (0.5 mL, 0.005 mol) and a solution of sodium azide (0.33 g, 0.005 mol) in water (2 mL). The reaction mixture was stirred at room temperature for 2 h, filtered and poured into water (100 mL). The resulting precipitate was dissolved in ethyl acetate (100 mL) and the organic layer was washed with water (2×50 mL), dried ($MgSO_4$) and evaporated to give **19b** as brown solid (1.47 g, 90%). Mp 124 °C. IR (KBr): $\nu = 2143$ (N_3), 1684 (CO), 1611, 1592, 1475, 1239, 1179, 1064, 845 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.75$ (s, 1H, H_5), 7.42 (d, 2H, $^3J_{H2'H3'} = 8.3$ Hz, $H_{2'}$ and $H_{6'}$), 6.81 (d, 2H, $^3J_{H3'H2'} = 8.3$ Hz, $H_{3'}$ and $H_{5'}$), 6.67 (m, 2H, $H_{\alpha pyrrole}$), 6.31 (m, 2H, $H_{\beta pyrrole}$). MS (EI^+) *m/z*: 358.1 (47), 356.1 (50), 277.1 (65).

6.5.4. 4-(4-Fluorophenyl)-3-(1H-pyrrol-1-yl)-2-furoyl azide (**19c**)

This compound was obtained from **14c** as described for **19b** as brown solid in 82% yield. Mp 128 °C. IR (KBr): $\nu = 2140$ (N_3), 1675 (CO), 1607, 1476, 1242, 1178, 1030, 843 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.76$ (s, 1H, H_5), 7.01 (m, 2H, $H_{5'}$ and $H_{6'}$), 6.95 (m, 2H, $H_{2'}$ and $H_{3'}$), 6.68 (m, 2H, $H_{\alpha pyrrole}$), 6.28 (m, 2H, $H_{\beta pyrrole}$). MS (EI^+) *m/z*: 268.1 ($M - N_2$, 68), 254.1 ($M - N_3$), 226.1 (100).

6.5.5. 4-(4-Methylphenyl)-3-(1H-pyrrol-1-yl)-2-furoyl azide (**19d**)

This compound was obtained from **14d** as described for **19b** as brown solid in 80% yield. Mp 110 °C. IR (KBr):

$\nu = 2139$ (N_3), 1672 (CO), 1606, 1505, 1476, 1343, 1259, 1179, 1033, 841 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.71$ (s, 1H, H_5), 6.90 (d, 2H, $^3J_{H2'H3'} = 8.1$ Hz, $H_{2'}$ and $H_{6'}$), 6.75 (d, 2H, $^3J_{H3'H2'} = 8.1$ Hz, $H_{3'}$ and $H_{5'}$), 6.68 (m, 2H, $H_{\alpha pyrrole}$), 6.37 (m, 2H, $H_{\beta pyrrole}$), 2.32 (s, 3H, CH_3). MS (EI^+) *m/z*: 264.1 ($M - N_2$, 45), 250.1 ($M - N_3$, 11), 222.2 (86).

6.5.6. 4-(4-Methoxyphenyl)-3-(1H-pyrrol-1-yl)-2-furoyl azide (**19e**)

This compound was obtained from **14e** as described for **19b** as brown solid in 90% yield. Mp 115 °C. IR (KBr): $\nu = 2147$ (N_3), 1685 (CO), 1616, 1472, 1251, 1179, 1036, 849 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.71$ (s, 1H, H_5), 6.86 (d, 2H, $^3J_{H2'H3'} = 8.5$ Hz, $H_{2'}$ and $H_{6'}$), 6.72 (d, 2H, $^3J_{H3'H2'} = 8.1$ Hz, $H_{3'}$ and $H_{5'}$), 6.68 (m, 2H, $H_{\alpha pyrrole}$), 6.28 (m, 2H, $H_{\beta pyrrole}$), 3.79 (s, 3H, CH_3). MS (EI^+) *m/z*: 308.2 (M, 45), 268.1 (100), 254.1 (10).

6.5.7. 4-(3,4-Dichlorophenyl)-3-(1H-pyrrol-1-yl)-2-furoyl azide (**19f**)

This compound was obtained from **14f** as described for **19b** as brown solid in 76% yield. Mp 122 °C. IR (KBr): $\nu = 2142$ (N_3), 1668 (CO), 1611, 1463, 1373, 1186, 1030, 732 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.76$ (s, 1H, H_5), 7.37 (d, 1H, $^3J_{H5'H6'} = 8.3$ Hz, $H_{5'}$), 7.17 (d, 1H, $^4J_{H2'H6'} = 1.7$ Hz, $H_{2'}$), 6.75 (dd, 1H, $^3J_{H6'H5'} = 8.3$ Hz, $^4J_{H6'H2'} = 1.7$ Hz, $H_{6'}$), 6.68 (m, 2H, $H_{\alpha pyrrole}$), 6.28 (m, 2H, $H_{\beta pyrrole}$). MS (EI^+) *m/z*: 319 ($M - N_2$, 100), 304 (33).

6.5.8. 4-(3,4-Dimethoxyphenyl)-3-(1H-pyrrol-1-yl)-2-furoyl azide (**19g**)

This compound was obtained from **14g** as described for **19b** as beige solid in 85% yield. Mp 150 °C. IR (KBr): $\nu = 2145$ (N_3), 1670 (CO), 1612, 1515, 1462, 1342, 1245, 1183, 1023, 847 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.73$ (s, 1H, H_5), 6.80 (dd, 1H, $^3J_{H6'H5'} = 8.2$ Hz, $^4J_{H6'H2'} = 1.8$ Hz, $H_{6'}$), 6.78 (m, 3H, $H_{5'}$ and $H_{\alpha pyrrole}$), 6.29 (m, 2H, $H_{\beta pyrrole}$), 6.19 (d, $^4J_{H2'H6'} = 1.8$ Hz, $H_{2'}$), 3.84 (s, 3H, OCH_3), 3.61 (s, 3H, OCH_3). MS (EI^+) *m/z*: 338.0 (M, 46), 310.0 ($M - N_2$, 100), 296.0 ($M - N_3$, 32).

6.6. Typical Curtius rearrangement procedure

6.6.1. 1-(4-Chlorophenyl)-3,4-dihydro-5H-dipyrrolo [1,2-a:2′,3′-e]pyrazin-5-one (**4a**)

To a boiling solution of *ortho*-dichlorobenzene (5 mL) was added portion-wise the acyl azide **18a** (0.8 g, 0.0067 mol). The reaction mixture was refluxed for 30 min. The precipitate that appeared by cooling the solution at 0 °C was filtered and purified by silica gel chromatography, and eluted by dichloromethane/methanol (9/1) to furnish **4a** as brown solid (0.45 g, 82%). Mp > 260 °C. IR (KBr): $\nu = 3315$ and 3239 (NH), 1664 (CO), 1590, 1397, 1351, 1090, 833, 721, 666 cm^{-1}. ^1H NMR (400 MHz, DMSO): $\delta = 11.5$ (br s, 1H, NH), 11.1 (br s, 1H, NH), 7.11 (s, 1H, H_2), 7.48 (m, 4H, H_{arom}), 6.90 (d, 1H, $^3J_{H7H8} = 2.4$ Hz, H_8), 6.62 (d, 1H, $^3J_{H6H7} = 2.4$ Hz, H_6), 6.41 (dd, 1H, $^3J_{H7H8} = {}^3J_{H6H7} = 2.4$ Hz, H_7). ^{13}C NMR (100 MHz, DMSO): $\delta = 154.50$, 132.95, 131.46, 130.76, 128.56, 122.75, 122.22, 116.47, 111.73, 111.37, 110.55, 109.61, 104.54. MS (EI^+) *m/z*: 283.0 (M, 12), 243.1 (17), 172.0 (42).

6.6.2. 1-(3,4-Dimethoxyphenyl)-3,4-dihydro-5H-dipyrrolo [1,2-a:2′,3′-e]pyrazin-5-one (**4g**)

This compound was obtained from **14g** as described for **4b** as brown solid in 46% yield. Mp > 260 °C. IR (KBr): $\nu = 3362$ and 3140 (NH), 1616 (CO), 1517, 1358, 1254, 1136, 1028, 733 cm^{-1}. ^1H NMR (400 MHz, DMSO): $\delta = 11.6$ (br s, 1H, NH), 11.1 (br s, 1H, NH), 7.26 (s, 1H, H_2), 7.10 (d, 1H, $^3J_{H5'H6'} = 8.2$ Hz, $H_{5'}$), 7.07 (d, 1H, $^4J_{H2'H6'} = 1.2$ Hz, $H_{2'}$), 7.03 (dd, 1H, $^4J_{H6'H2'} = 1.2$ Hz, $^3J_{H6'H5'} = 8.2$ Hz, $H_{6'}$), 6.94 (d, 1H, $^3J_{H7H8} = 2.4$ Hz, H_8), 6.61 (d, 1H, $^3J_{H6H7} = 2.4$ Hz, H_6), 6.47 (dd, 1H, $^3J_{H7H8} = {}^3J_{H6H7} = 2.4$ Hz, H_7), 3.85 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, DMSO): $\delta = 154.51$, 148.57, 147.87, 126.46, 123.10, 122.70, 121.31, 116.40, 114.04, 113.12, 112.55, 111.91, 111.08, 110.33, 109.40, 55.54, 55.47. MS (EI^+) *m/z*: 309.2 (M, 15), 256.1 (20), 213.1 (15).

6.6.3. 1-(4-Bromophenyl)furo[2,3-e]pyrrolo[1,2-a] pyrazin-5(4H)-one (**5b**)

To a boiling solution of *ortho*-dichlorobenzene (7 mL) was added portion-wise the acyl azide **19b** (2 g, 0.0056 mol). The reaction mixture was refluxed for 2 min. Ether (100 mL) was then added to the cooled solution at 0 °C. The precipitate that appeared was filtered to furnish **5b** as brown solid (1.2 g, 65%). Mp > 260 °C. IR (KBr): $\nu = 3415$ (NH), 1662 (CO), 1571, 1385, 1275, 1082, 840 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 10.21$ (br s, 1H, NH), 7.75 (m, 3H, H_2, $H_{2'}$ and $H_{6'}$), 7.54 (d, 2H, $^3J_{H3'H2'} = 8.1$ Hz, $H_{3'}$ and $H_{5'}$), 7.14 (d, 1H, $^3J_{H7H8} = 2.4$ Hz, 1H, H_8), 6.99 (d, 1H, $^3J_{H6H7} = 2.4$ Hz, H_6), 6.53 (dd, 1H, $^3J_{H7H8} = {}^3J_{H7H6} = 2.4$ Hz, H_7). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 154.0$, 134.1, 132.8, 132.0, 131.1, 128.8, 121.9, 118.2, 117.2, 113.5, 112.8, 111.9, 110.1. MS (EI^+) *m/z*: 330 (98), 328 (100), 274 (25), 264 (10).

6.6.4. 1-(4-Fluorophenyl)furo[2,3-e]pyrrolo[1,2-a] pyrazin-5(4H)-one (**5c**)

This compound was obtained from **19c** as described for **5b** as brown solid in 60% yield. Mp > 260 °C. IR (KBr): $\nu = 3416$ (NH), 1659 (CO), 1582, 1390, 1272, 1087, 837 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 10.11$ (br s, 1H, NH), 7.85 (s, 1H, H_2), 7.77 (m, 2H, $H_{2'}$ and $H_{6'}$), 7.58 (d, 1H, $^3J_{H7H8} = 2.4$ Hz, 1H, H_8), 7.12 (m, 2H, $H_{3'}$ and $H_{5'}$), 7.00 (d, 1H, $^3J_{H6H7} = 2.4$ Hz, H_6), 6.55 (dd, 1H, $^3J_{H7H8} = {}^3J_{H7H6} = 2.4$ Hz, H_7). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 160.9$, 156.3, 153.9, 147.6, 133.9, 131.1, 130.1, 125.9, 118.1, 116.8, 115.8, 112.6, 111.8. MS (EI^+) *m/z*: 268.1 (M, 26), 225 (17), 172 (100).

6.6.5. 1-(4-Methylphenyl)furo[2,3-e]pyrrolo[1,2-a] pyrazin-5(4H)-one (**5d**)

This compound was obtained from **19d** as described for **5b** as brown solid in 70% yield. Mp > 260 °C. IR (KBr):

$\nu = 3420$ (NH), 1652 (CO), 1525, 1358, 1256, 1137, 1029, 837 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 10.34$ (br s, 1H, NH), 8.81 (s, 1H, H_2), 7.30 (d, 2H, $^3J_{H2'H3'} = 8.7$ Hz, $H_{2'}$ and $H_{6'}$), 7.13 (d, 2H, $^3J_{H3'H2'} = 8.7$ Hz, $H_{3'}$ and $H_{5'}$), 7.26 (d, 1H, $^3J_{H7H8} = 2.7$ Hz, 1H, H_8), 6.98 (d, 1H, $^3J_{H6H7} = 2.7$ Hz, H_6), 6.51 (dd, 1H, $^3J_{H7H8} = {}^3J_{H7H6} = 2.7$ Hz, H_7), 2.37 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 155.9$, 140.3, 133.9, 131.0, 130.7, 129.6, 128.3, 126.6, 122.7, 120.0, 118.5, 113.7, 112.2, 21.3. MS (EI^+) *m/z*: 264.1 (M, 93), 249.1 (11), 221 (32).

6.6.6. 1-(4-Methoxyphenyl)furo[2,3-e]pyrrolo [1,2-a]pyrazin-5(4H)-one (**5e**)

This compound was obtained from **19e** as described for **5b** as brown solid in 70% yield. Mp > 260 °C. IR (KBr): $\nu = 3416$ (NH), 1642 (CO), 1534, 1361, 1252, 1138, 1028, 833 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 12.44$ (br s, 1H, NH), 7.59 (s, 1H, H_2), 7.48 (d, 2H, $^3J_{H2'H3'} = 8.2$ Hz, $H_{2'}$ and $H_{6'}$), 7.13 (d, 1H, $^3J_{H7H8} = 2.4$ Hz, 1H, H_8), 7.09 (d, 2H, $^3J_{H3'H2'} = 8.7$ Hz, $H_{3'}$ and $H_{5'}$), 6.97 (d, 1H, $^3J_{H6H7} = 2.4$ Hz, H_6), 6.51 (dd, 1H, $^3J_{H7H8} = {}^3J_{H7H6} = 2.4$ Hz, H_7), 3.81 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 159.8$, 154.3, 133.9, 131.0, 130.7, 129.2, 122.1, 121.9, 119.2, 117.3, 115.5, 114.8, 112.1, 55.6. MS (EI^+) *m/z*: 279.8 (M, 73), 250.1 (8), 208.8 (17).

6.6.7. 1-(3,4-Dichlorophenyl)furo[2,3-e]pyrrolo [1,2-a]pyrazin-5(4H)-one (**5f**)

This compound was obtained from **19f** as described for **5b** as brown solid in 62% yield. Mp > 260 °C. IR (KBr): $\nu = 3315$ (NH), 1664 (CO), 1590, 1397, 1351, 1090, 833 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 11.12$ (br s, 1H, NH), 7.62 (s, 1H, H_2), 7.48 (d, 1H, $^4J_{H5'H6'} = 8.2$ Hz, $H_{5'}$), 7.01 (d, 1H, $^4J_{H2'H6'} = 1.8$ Hz, 1H, $H_{2'}$), 6.90 (dd, 1H, $^3J_{H6'H5'} = 8.2$ Hz, $^4J_{H6'H2'} = 1.8$ Hz, $H_{6'}$), 6.78 (d, 1H, $^3J_{H7H8} = 2.4$ Hz, H_8), 6.62 (d, 1H, $^3J_{H6H7} = 2.4$ Hz, H_6), 6.41 (dd, 1H, $^3J_{H7H8} = {}^3J_{H7H6} = 2.4$ Hz, H_7). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 154.0$, 132.9, 134.6, 134.5, 131.7, 131.2, 131.0, 130.7, 130.4, 129.2, 128.8, 125.3, 117.1, 112.0, 103.8. MS (EI^+) *m/z*: 318 (M^-, 100), 265.1 (8), 221.1 (17).

6.6.8. 1-(3,4-Dichlorophenyl)furo[2,3-e]pyrrolo [1,2-a]pyrazin-5(4H)-one (**5g**)

This compound was obtained from **19g** as described for **5b** as brown solid in 67% yield. Mp > 260 °C. IR (KBr): $\nu = 3362$ (NH), 1617 (CO), 1517, 1358, 1255, 1136, 1028, 847 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 10.32$ (br s, 1H, NH), 8.42 (s, 1H, H_2), 7.20 (d, 1H, $^4J_{H5'H6'} = 8.2$ Hz, $H_{5'}$), 6.98 (d, 1H, $^4J_{H2'H6'} = 1.2$ Hz, 1H, $H_{2'}$), 6.88 (dd, 1H, $^3J_{H6'H5'} = 8.2$ Hz, $^4J_{H6'H2'} = 1.2$ Hz, $H_{6'}$), 6.76 (d, 1H, $^3J_{H7H8} = 2.4$ Hz, H_8), 6.54 (d, 1H, $^3J_{H6H7} = 2.4$ Hz, H_6), 6.24 (dd, 1H, $^3J_{H7H8} = {}^3J_{H7H6} = 2.4$ Hz, H_7), 3.94 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 155.5$, 148.5, 147.8, 126.4, 123.1, 122.7, 121.3, 116.4, 114.0, 113.1, 112.5, 111.9, 111.0, 110.3, 109.4, 55.6, 55.4. MS (EI^+) *m/z*: 310.2 (M, 46), 257.1 (20), 214.1 (32).

6.7. Biology

Kinase activities were assayed according to the methodology developed by the Cell Cycle Group of the Station Biologique, CNRS, Roscoff, France [10].

6.8. Molecular modeling

Energy minimizations were performed using the Tripos force field [12] with a distance dependent dielectric and the Powell conjugate gradient algorithm (convergence criterion of 0.05 kcal/mol). Partial atomic charges were calculated by the Gasteiger–Huckel method.

For the docking studies, the co-crystal structure, GSK-3β – indirubin-3′-monoxime, was used (PDB ID: 1Q41, resolution 2.1 Å) [13]. After removal of the ligand and water molecules, Gold software [14] was employed to generate a set of docked conformations for each ligand. The genetic algorithm associated with Gold was applied with the following values: 100 for the population size, 1.1 for the selection pressure, 5 for the number of subpopulations (island model), 100 000 for the maximum number of genetic applications and 2 for the size of the niche used to increase the population diversity. Crossover and mutation were applied with equal probability (95/95 for the values) and migration was applied 5% of the time.

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