Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry 14 (2006) 8162–8175
Bioorganic & Medicinal Chemistry

Synthesis and biological evaluation of novel pyrrolopyrrolizinones as anticancer agents

C. Rochais,[a] V. Lisowski,[b] P. Dallemagne[a] and S. Rault[a,*]

[a]*Centre d'Etudes et de Recherche sur le Médicament de Normandie, Université de Caen Basse-Normandie, 5, rue Vaubénard, 14032 CAEN Cedex, France*
[b]*Faculté de Pharmacie de Montpellier, 15 avenue Charles Flahault BP 14491, 34093 Montpellier Cedex 5, France*

Received 11 July 2006; revised 25 August 2006; accepted 13 September 2006
Available online 29 September 2006

Abstract—We herein describe the synthesis of novel 3-(het)aryl-pyrrolo[2,3-*b*]pyrrolizin-8(1*H*)-ones starting from commercial (het)aryl-acetonitriles. A more convergent route was also described through the first synthesis of ethyl 3-amino-4-bromo-1*H*-pyrrole-2-carboxylate **17**. The antiproliferative activities of these compounds were tested toward various cell lines and one of them **10k** shows interesting cytotoxic properties, although it was less potent than our lead compound in thiophene series **1k**.

1. Introduction

In the view to identify novel microtubule polymerization inhibitors, we have recently described an unknown heterocyclic family of potent compounds: thienopyrrolizinones (Fig. 1), or 'tripentones'.[1] The first hit in that series **1a**, detected by the National Cancer Institute, exhibits an in vitro cytotoxic activity in submicromolar concentrations in all cell lines tested. Further pharmacomodulations[2] realized on that core have conducted to a new lead **1k** substituted in position 3 by a 4-methoxy-3-hydroxyphenyl group.

Indeed pharmacological evaluations of **1k** over a panel of tumoral cell lines revealed nanomolar activities range. According to results of preliminary flow cytometric studies, tripentones were first supposed to interact with the mitotic spindle.

Tubulin polymerization inhibitory tests were then performed and showed an IC_{50} of 2.9 μM, similar to the reference deoxypodophyllotoxin (2.4 μM).

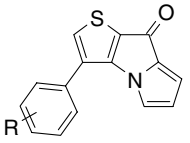
However first in vivo evaluations of **1k** by the NCI[3] were disappointing and pointed out its insufficient bioavailibility due to a lack of solubility in physiological conditions. Aiming to improve the latter, a study has recently been developed in our laboratory to encapsulate the lead in lipidic nanocaps,[4] with encouraging results.

Furthermore in order to specify structural requirements we decided to extend the study toward synthesis of novel tripentones based on other heterocyclic rings such as pyrrole.

2. Chemistry

According to the route elaborated in the thiophene series, *o*-aminoesters appeared as crucial intermediates toward expected tripentones. We have recently developed novel methyl 3-amino-4-(het)aryl-1*H*-pyrrole-2-carboxylates **2a**–**j** in an efficient three step synthesis,[5] derived from Elliot's procedure.[6]

Applying the developed four step sequence to these esters led to the N-unprotected ketones **5a**–**k** (Scheme 1).[7]

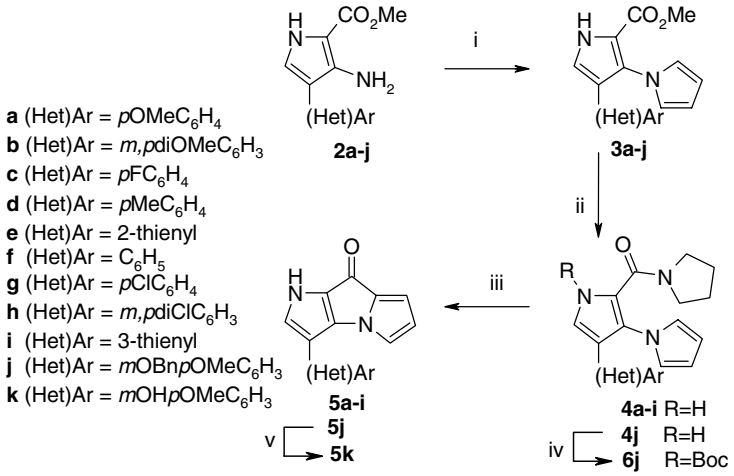


1a R=*p*OMe
1k R=*p*OM*e*mOH

Figure 1.

Keywords: Cyclization; Pyrroles; Fused-ring systems; L1210 murine leukemia cells.
* Corresponding author. Tel.: +33 2 31 93 64 58; fax: +33 2 31 93 11 88; e-mail: sylvain.rault@unicaen.fr

0968-0896/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2006.09.022



Scheme 1. Reagents and conditions: (i) 2,5-dimethoxyTHF, 4-chloropyridine hydrochloride, dioxane, 100 °C, 57–99%; (ii) pyrrolidine, 87 °C, 47–69%; (iii) (a) $POCl_3$, 70 °C; (b) 10% NaOH, 50 °C, 2–32%; (iv) $(Boc)_2O$, TEA, DMAP, CH_2Cl_2, 25 °C, 78%; (v) (a) 33% HBr in AcOH, 25 °C; (b) NaOH 1 N, MeOH, 25 °C, 55%.

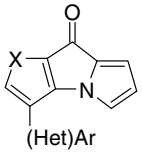
Aminoesters **2a**–**j** were first submitted to a modified[8] Clauson-Kaas procedure[9] (Scheme 1), with 2,5-dimethoxytetrahydrofuran and 4-chloropyridine hydrochloride to afford esters **3a**–**j**. These esters were then submitted to amidification in refluxing pyrrolidine to obtain amides **4a**–**j**. The latter afforded expected tripentones **5a**–**j** through ring closure under Vilsmeier–Haack conditions and alkaline treatment. In a previous study,[7] we showed that the ring closure procedure was improved through N-protection of carboxamides **4j** as Boc-substituted compounds **6j**. The O-deprotection of benzylated **5j** was realized using a 33% hydrobromic acid solution in glacial acetic acid, followed by an alkaline hydrolysis of the acetate intermediate,[7] to obtain the expected compound **4k**.

The antiproliferative properties of this first series of pyrrolo[2,3-*b*]pyrrolizinones **5a**–**k** were then evaluated (see Pharmacological results, Table 1).

According to the benefits of N-protection, we decided to realize novel modulations on that structure through other N-substitution reactions and particularly with the *m*-hydroxy-*p*-methoxyphenyl derivatives **j**, our best series for a biological point of view (Scheme 2). However these alkylation reactions were first optimized in the easily obtained *p*-chlorophenyl series **g**.

Carboxamides **4g**, **j** were then alkylated to afford methyl **7g**, **j**, ethyl **8g**, **j**, and benzyl **9g**, **j** compounds in quantitative yields using sodium hydride as a base. The products **7**–**9g**, **j** were then introduced in the ring closure procedure to afford in good to excellent yields the corresponding tripentones **10g**, **j**, **11g**, **j**, and **12g**, **j**, respectively. We could here notice the important influence of the N-substitution toward the yield enhancement of the ring closure reaction. O-Deprotections of benzylated compounds were then realized as previously described to afford corresponding phenol compounds **10k**–**12k** in good yields.

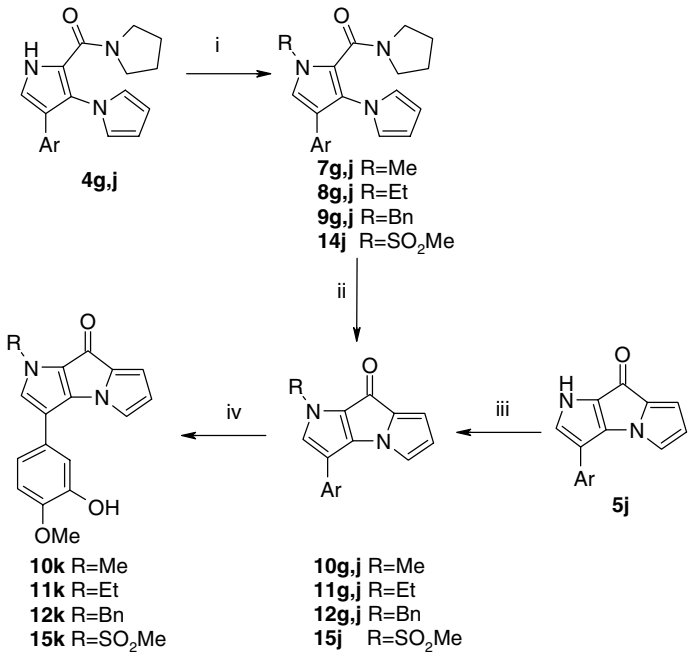
Table 1. Cytotoxicity results for compounds **5a**–**x**



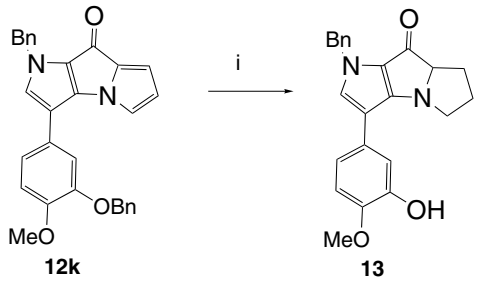
Compound	X	(Het)Ar	IC_{50}, μM L1210	IC_{50}, μM HT29
1a	S	*p*-OMe–C_6H_4	0.19	Not tested
1k	S	(*m*-OH,*p*-OMe)–C_6H_3	0.015	Not tested
5a	NH	*p*-OMe–C_6H_4	64.6	23.2
5b	NH	(*m*–*p*-di-OMe)–C_6H_3	11.8	Not tested
5c	NH	*p*-F–C_6H_4	13.4	26
5d	NH	*p*-Me–C_6H_4	10.9	12.5
5e	NH	2-Thienyl	25.3	26.6
5f	NH	C_6H_5	36.9	26.7
5g	NH	*p*-Cl–C_6H_4	34.3	21.9
5h	NH	*m*,*p*-di-Cl–C_6H_3	12.7	19.9
5i	NH	3-Thienyl	26.7	24
5j	NH	(*m*-OBn,*p*-OMe)–C_6H_3	8.9	13.4
5k	NH	(*m*-OH,*p*-OMe)–C_6H_3	12.2	19.3

In order to realize selective modulations of the phenol moiety, we also managed to obtain a selective N-protected tricycle. Unfortunately, all our attempts to deprotect the *N*-benzyl group failed in the case of compound **12k**. Even if hydrogenation of reduced **12k** conducted to the benzyl compound **13** (Scheme 3).

According to the previous procedure, we decided to test novel selective protecting groups. Mesylated amide **14j** (Scheme 2) was isolated, but the ring closure appeared inefficient in that case. Ketone **15j** was then obtained from the tripentone **5j** and was O-deprotected to afford the attempted compound **15k**. A selection of these N-substituted pyrrolopyrrolizinones was evaluated (see pharmacological results, Table 2) and showed an interesting improvement of activity.

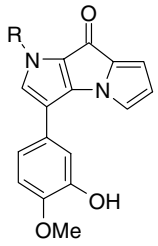


Scheme 2. Reagents and conditions: (i) NaH, RX, DMF, 0–25 °C, 82–95%; (ii) (a) $POCl_3$, 70 °C; (b) 10% NaOH, 50 °C, 60–95%; (iii) NaH, $MeSO_2Cl$, DMF, 0–25 °C, 93%; (iv) (a) 33% HBr in AcOH, 25 °C; (b) NaOH 1 N, MeOH, 25 °C, 40–85%.



Scheme 3. Reagents: (i) H_2, Pd, MeOH, 55%.

Table 2. Growth percentage (%) at 1×10^{-4} mol for compounds **5k**,**10k**,**12k**, and **15k**



Compound	R	MCF7	NCI-H460	SF-268
5k	H	62	81	99
10k	Me	19	6	58
12k	Bn	66	53	98
15k	SO_2Me	65	84	84

In order to introduce more diversity on these structures and to obtain a more convergent route, the synthesis of an halogenated tripentone **16** was then studied (Fig. 2).

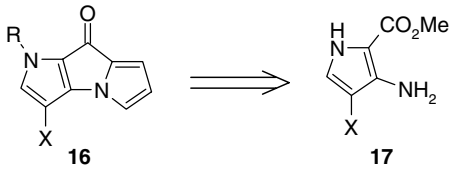
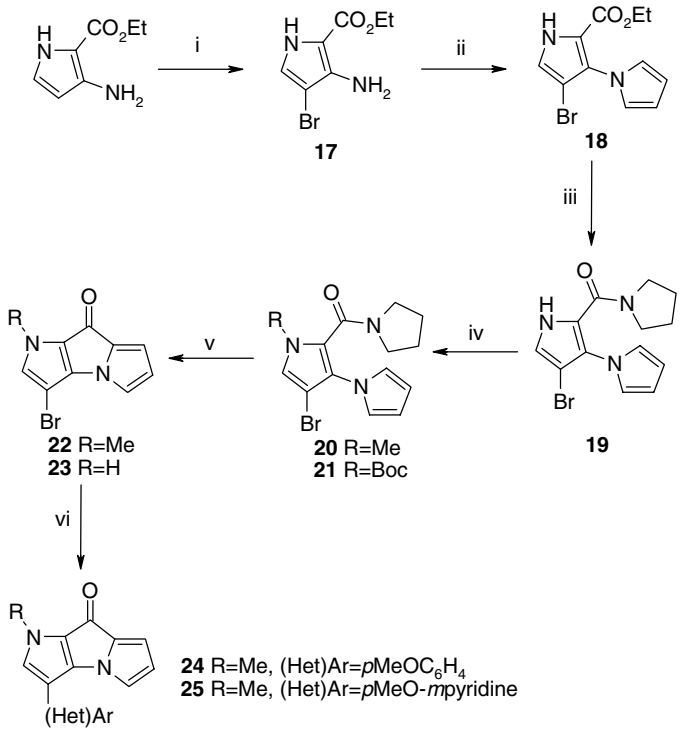


Figure 2.

Indeed, this compound could be modulated through modern cross-coupling reactions. As previously exposed, one of the crucial intermediates toward **16** could be the corresponding methyl 3-amino-4-halogeno-1*H*-pyrrole-2-carboxylate **17** (Fig. 2).

The chemical strategy adopted for the access to **17** was based on halogenation of ethyl 3-aminopyrrole-2-carboxylate, described by Furneaux.[10] Astonishingly best results were obtained without any nitrogen protection either on the amino or the pyrrole moieties, and using *N*-bromosuccinimide as bromination agent (Scheme 4). The resulting pyrrole **17** was then introduced in the exposed sequence to lead to the amide **18**. The latter was then alkylated or protected to conduct after ring closure and alkaline hydrolysis to two novel brominated tripentones **22** and **23**.

Functionalization of our structure was achieved through Suzuki cross-coupling reaction with two various arylboronic acids. Use of *p*-methoxyphenylboronic acid and 2-methoxypyridine-5-boronic acid[11] afforded tripentones **24** and **25** in excellent yield. According to these good results this second route appeared to be really effective and will be developed in the future in order to allow access to novel tripentones.



Scheme 4. Reagents and conditions: (i) NBS, $CHCl_3$, AcOH, 0 °C to rt, 40%; (ii) 2,5-dimethoxyTHF, 4-chloropyridine hydrochloride, dioxane, 100 °C, 99%; (iii) pyrrolidine, 87 °C, 43%; (iv) $(Boc)_2O$, TEA, DMAP, CH_2Cl_2, 25 °C, 99% or NaH, MeI, DMF, 0–25 °C, 99%; (v) (a) $POCl_3$, 70 °C; (b) 10% NaOH, 50 °C, 43–86%; (vi) (Het)ArB$(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, DMF, 110 °C, 87–90%.

3. Pharmacological results

The antiproliferative properties of the first series of unprotected compounds **5a**–**k** were evaluated on the murine leukemia L1210 and on HT29 cell lines and are reported in Table 1.

This first series of compounds appeared less active than the thiophene isomers, with IC_{50} values ranging from 8.9 to 64 μM. Compared now more precisely, the lead series substituted by a 4-methoxy-3-hydroxyphenyl group, compound **1k** appeared 1000 times more potent than its isomer **5k**. The presence of the free NH group instead of the S seems to have a significant harmful effect on biological activities. In order to explore this influence, a selection of the N-substituted compounds was screened by the National Cancer Institute. The protocol developed by the NCI began with a one dose primary anticancer assay on 3 cell lines panel consisting of the MCF7 (breast), NCI-H460 (lung), and SF-268 (central nervous system). Compounds **5k**, **10k**, **12k**, and **15k** were then selected and tested. Results are exposed in Table 2 in percent of growth of the treated cells when compared to the untreated control cells.

Only **10k** (NSC 733670), which reduced the growth of two cell lines to less than 32%, was selected for evaluation in the full panel of 60 cell lines over a 5-log dose range.[12] However, we could point out the strong influence of a small substituent on the growth percentage for our product, since compound **10k** appears much more potent than non-substituted tripentone **5k** or other substituted ones **12k** and **15k**. These first results could also suggest an important steric hindrance on that position.

A selection of the results was reported in comparison with compound **1a** in Table 3 in the form of their GI_{50}.

If **10k** appeared as the much active derivative in the pyrrole series, with a strong enhancement through N-substitution of the tripentone core, this compound remains

Table 3. GI_{50} (μM) of **1** and **10k** on various cell lines

Cell lines Compound	Leukemia MOLT4	NSCL[a] HCC2298	CNS[b] SF295	Ovarian OVCAR-3	Renal A498	Prostate DU145	Breast HS578T
1a	0.04	0.3	0.44	0.04	0.6	0.2	0.05
10k	7.21	2.48	5.22	3.39	2.82	12.5	0.6

[a] Non-small cell lung.
[b] Central nervous system.

less active than the first hit in the thiophene series **1a** with moderate GI_{50} values ranging from 0.6 to 12.5 μM in the selected cell lines.

These results revealed the crucial role of the thiophene ring in the tripentone cytotoxic activities. Any modification on that position in our novel pyrrole series conducts to less active compounds, especially with large N-substituent or loss of this substitution. Moreover the weak activity of **10k** actually did not allow us to realize further studies in an in vivo model or any solubility evaluation. However, the novel synthetic route exposed only in pyrrole series, opens wide opportunities to explore with more diversity the nature of the aromatic substituants.

In conclusion, we have described here the synthesis and the antiproliferative activities of novel pyrrolo[2,3-*b*]pyrrolizinones, which gave crucial information in the development of novel tripentone compounds. Finally a novel and convergent synthesis was reported through Suzuki cross-coupling and will be applied to afford more diversity on these new structures.

4. Experimental

4.1. General

Commercial reagents were used as received without additional purification. Melting points were determined on a Köfler melting point apparatus and are uncorrected. IR spectra were taken with a Perkin-Elmer spectrum BX FT-IR spectrometer. ^{1}H NMR (400 MHz) and ^{13}C (100 MHz) were recorded on a JEOL Lambda 400 Spectrometer. Chemical shifts are expressed in parts per million downfield from TMS as an internal standard. Mass spectrum was recorded on a JEOL JMS GCMate with ionizing potential of 70 eV. Elemental analyses for new compounds were performed at the 'Institut de Recherche en Chimie Organique Fine' (Rouen).

4.2. Clauson-Kaas reaction procedure

4.2.1. Methyl 4′-(4-methoxyphenyl)-1′*H*-1,3′-bipyrrole-2′-carboxylate (3a). A solution of 2,5-dimethoxytetrahydrofuran (0.46 mL, 3.6 mmol) in dioxane (20 mL) was stirred for 15 min with 4-chloropyridine hydrochloride (0.54 g, 3.6 mmol). The aminoester **2a** (0.8 g, 3.25 mmol) was added and the reaction mixture was refluxed for 1.5 h and filtered through a small pad of Celite. The solvent was evaporated to give a brown residue that was dissolved in methylene chloride (100 mL). The solution was washed with an 1 N aqueous hydrochloric acid solution (2× 100 mL), dried ($MgSO_4$), and evaporated to give **3a** as a beige solid (550 mg, 57%) that was crystallized from Et_2O. Mp 110 °C. IR (KBr): ν = 3335(NH), 3100, 2949, 2838, 1697(CO), 1584, 1508, 1438, 1380, 1264, 1081, 721 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.3 (br s, 1H, NH), 7.05 (d, J = 3.2 Hz, 1H, H_5), 6.87 (d, J = 8.7 Hz, 2H, H_{arom}), 6.77 (d, J = 8.7 Hz, 2H, H_{arom}), 6.68 (m, 2H, $H_{\alpha pyrrole}$), 6.26 (m, 2H, $H_{\beta pyrrole}$), 3.76 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.60, 158.51, 127.83, 124.76, 123.48, 122.82, 118.68, 117.05, 114.60, 113.98, 108.74, 55.18, 51.72. MS (EI^+) *m*/*z*: 296,1. Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 69.01; H, 5.42; N, 9.13.

4.2.2. Methyl 4′-(3,4-dimethoxyphenyl)-1′*H*-1,3′-bipyrrole-2′-carboxylate (3b). This compound was obtained from **2b** as described for **3a** as beige solid in 72% yield. Mp 158–161 °C. IR (KBr): ν = 3385(NH), 3123, 3088, 2955, 1704(CO), 1588, 1575, 1437, 1249, 1115, 1013, 728 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.3 (br s, 1H, NH), 7.10 (d, J = 3.3 Hz, 1H, H_5), 6.78 (d, J = 8.3 Hz, 1H, $H_{5'}$), 6.73 (dd, J = 1.8, 8.3 Hz, 1H, $H_{6'}$), 6.69 (m, 2H, $H_{\alpha pyrrole}$), 6.26 (m, 2H, $H_{\beta pyrrole}$), 6.21 (d, J = 1.8 Hz, 1H, $H_{2'}$), 3.84 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.61 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.71, 148.73, 147.62, 127.71, 125.12, 123.19, 122.83, 118.97, 118.44, 117.05, 110.92, 109.33, 108.82, 55.61, 55.44, 51.61. MS (EI^+) *m*/*z*: 326.1. Anal. Calcd for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.41; H, 5.48; N, 8.74.

4.2.3. Methyl 4′-(4-fluorophenyl)-1′*H*-1,3′-bipyrrole-2′-carboxylate (3c). This compound was obtained from **2c** as described for **3a** as beige solid in 90% yield. Mp 172 °C. IR (KBr): ν = 3295, 3139, 3043, 2951, 1671(CO), 1570, 1443, 1383, 1159, 1137, 726 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.3 (br s, 1H, N*H*), 7.07 (d, J = 3.4 Hz, 1H, H_5), 6.90 (m, 4H, H_{arom}), 6.66 (m, 2H, $H_{\alpha pyrrole}$), 6.26 (m, 2H, $H_{\beta pyrrole}$), 3.77 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.85 (d, J = 246 Hz), 160.54, 128.31 (d, J = 7 Hz), 129.29, 128.01, 122.88, 122.76, 118.92, 117.26, 115.45 (d, J = 21 Hz), 108.97, 51.79. MS (EI^+) *m*/*z*: 284.0. Anal. Calcd for $C_{16}H_{17}FN_2O_2$: C, 67.60; H, 4.61; N, 9.85. Found: C, 67.87; H, 4.56; N, 9.53.

4.2.4. Methyl 4′-(4-methylphenyl)-1′*H*-1,3′-bipyrrole-2′-carboxylate (3d). This compound was obtained from **2d** as described for **3a** as beige solid in 78% yield. Mp 128 °C. IR (KBr): ν = 3293, 3133, 2999, 2950, 1672(CO), 1576, 1467, 1413, 1289, 1202, 1079, 721 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.3 (br s, 1H, N*H*), 7.06 (m, 3H, H_{arom} + H_5), 6.84 (d, J = 8.7 Hz, 2H, H_{arom}), 6.68 (m, 2H, $H_{\alpha pyrrole}$), 6.26 (m, 2H, $H_{\beta pyrrole}$), 3.76 (s, 3H, OCH_3), 2.29 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.82, 136.72, 129.55, 129.47, 128.30, 126.76, 123.95, 123.04, 119.21, 117.33, 108.96, 51.95, 21.33. MS (EI^+) *m*/*z*: 280.0. Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 73.13; H, 6.04; N, 10.34.

4.2.5. Methyl 4′-(2-thienyl)-1′*H*-1,3′-bipyrrole-2′-carboxylate (3e). This compound was obtained from **2e** as described for **3a** as brown solid in 92% yield. Mp 130 °C. IR (KBr): ν = 3301, 3116, 3110, 2948, 1734(CO), 1587, 1402, 1441, 1217, 1165, 735, 702 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.3 (br s, 1H, N*H*), 7.13 (m, 2H, H_{thio} + H_5), 6.89 (m, 1H, H_{thio}), 6.71 (m, 2H, $H_{\alpha pyrrole}$), 6.45 (m, 1H, H_{thio}), 6.26 (m, 2H, $H_{\beta pyrrole}$), 3.75 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.55, 133.77, 127.69, 127.58, 123.83, 123.62, 122.90, 118.77, 118.54, 118.27, 103.14, 52.04.

MS (EI^+) *m/z*: 272.0. Anal. Calcd for $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.44; N, 10.29. Found: C, 61.45; H, 4.67; N, 10.45.

4.2.6. Methyl 4′-phenyl-1′*H*-1,3′-bipyrrole-2′-carboxylate (3f). This compound was obtained from **2f** as described for **3a** as beige solid in 96% yield. Mp 168 °C. IR (KBr): ν = 3312, 3125, 2948, 1708(CO), 1585, 1398, 1264, 1162, 1084, 738, 673 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.2 (br s, 1H, N*H*), 7.22 (m, 3H, H_{arom}), 7.10 (d, J = 3.1 Hz, 1H, H_5), 6.96 (m, 2H, H_{arom}), 6.68 (m, 2H, $H_{\alpha pyrrole}$), 6.27 (m, 2H, $H_{\beta pyrrole}$), 3.77 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.66, 132.29, 128.53, 128.16, 126.78, 126.66, 123.68, 122.82, 119.27, 117.19, 108.80, 51.76. MS (EI^+) *m/z*: 266.1. Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.17; H, 5.30; N, 10.52. Found: C, 72.01; H, 5.02; N, 10.43.

4.2.7. Methyl 4′-(4-chlorophenyl)-1′*H*-1,3′-bipyrrole-2′-carboxylate (3g). This compound was obtained from **2g** as described for **3a** as beige solid in 99% yield. Mp 194°C. IR (KBr): ν = 3403, 3155, 3101, 2947, 1710(CO), 1585, 1438, 1377, 1192, 1083, 723, 579 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.3 (br s, 1H, N*H*), 7.19 (d, J = 8.5 Hz, 2H, H_{arom}), 7.05 (d, J = 3.3 Hz, 1H, H_5), 6.84 (d, J = 8.5 Hz, 2H, H_{arom}), 6.66 (m, 2H, $H_{\alpha pyrrole}$), 6.26 (m, 2H, $H_{\beta pyrrole}$), 3.77 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.69, 132.79, 130.94, 128.91, 128.19, 128.06, 122.89, 122.83, 119.25, 117.60, 109.25, 52.02. MS (EI^+) *m/z*: 300.1. Anal. Calcd for $C_{16}H_{13}ClN_2O_2$: C, 63.90; H, 4.36; N, 9.31. Found: C, 64.21; H, 4.56; N, 9.10.

4.2.8. Methyl 4′-(3,4-dichlorophenyl)-1′*H*-1,3′-bipyrrole-2′-carboxylate (3h). This compound was obtained from **2h** as described for **3a** as beige solid in 80% yield. Mp 166 °C. IR (KBr): ν = 3398, 3125, 2946, 1708(CO), 1583, 1439, 1274, 1250, 1058, 1014, 732, 572 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.4 (br s, 1H, NH), 7.16 (d, J = 8.3 Hz, 1H, $H_{5'}$), 7.12 (d, J = 3.3 Hz, 1H, H_5), 7.02 (d, J = 1.8 Hz, 1H, $H_{2'}$), 6.65 (m, 3H, $H_{\alpha pyrrole}$+ $H_{6'}$), 6.29 (m, 2H, $H_{\beta pyrrole}$), 3.77 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.56, 132.63, 132.44, 130.67, 130.60, 130.58, 128.47, 125.84, 122.74, 121.77, 119.28, 117.85, 109.51, 51.94. MS (EI^+) *m/z*: 336.1. Anal. Calcd for $C_{16}H_{12}Cl_2N_2O_2$: C, 57.33; H, 3.61; N, 8.36. Found: C, 57.64; H, 3.60; N, 8.34.

4.2.9. Methyl 4′-(3-thienyl)-1′*H*-1,3′-bipyrrole-2′-carboxylate (3i). This compound was obtained from **2i** as described for **3a** as brown solid in 99% yield. Mp 152 °C. IR (KBr): ν = 3293, 3130, 3098, 2946, 1675(CO), 1443, 1399, 1349, 1196, 1133, 786, 729 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.4 (br s, 1H, N*H*), 7.22 (d, J = 3.3 Hz, 1H, H_5), 7.14 (m, 1H, H_{thio}), 6.80 (m, 1H, H_{thio}), 6.71 (m, 2H, $H_{\alpha pyrrole}$), 6.54 (m, 1H, H_{thio}), 6.32 (m, 2H, $H_{\beta pyrrole}$), 3.74 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.25, 136.97, 133.19, 132.28, 131.48, 125.56, 121.96, 119.73, 118.46, 111.27, 107.24, 51.19. MS (EI^+) *m/z*: 272.0. Anal. Calcd for $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.44; N, 10.29. Found: C, 61.74; H, 4.56; N, 10.24.

4.2.10. Methyl 4′-(3-benzyloxy-4-methoxyphenyl)-1′*H*-1,3′-bipyrrole-2′-carboxylate (3j). This compound was obtained from **2j** as described for **3a** as beige solid in 70% yield. Mp 180 °C. IR (KBr): ν = 3289, 3151, 3036, 2998, 2930, 1671(CO), 1569, 1515, 1474, 1446, 1381, 1247, 1147, 749 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.2 (br s, 1H, NH), 7.34 (m, 5H, H_{arom}), 7.02 (d, J = 2.9 Hz, 1H, H_5), 6.79 (d, J = 8.2 Hz, 1H, $H_{5'}$), 6.70 (m, 3H, $H_{6'} + H_{\alpha pyrrole}$), 6.29 (m, 3H, $H_{\beta pyrrole} + H_{2'}$), 4.85 (s, 2H, CH_2Ph), 3.85 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.57, 148.41, 148.07, 137.15, 128.37, 127.79, 127.66, 127.36, 124.98, 123.38, 122.89, 119.16, 118.50, 117.16, 111.94, 111.70, 108.94, 70.42, 55.92, 51.70. MS (EI^+) *m/z*: 402.2. Anal. Calcd for $C_{24}H_{22}N_2O_4$: C, 71.63; H, 5.51; N, 6.96. Found: C, 72.00; H, 5.48; N, 6.85.

4.2.11. Ethyl 4′-bromo-1′*H*-1,3′-bipyrrole-2′-carboxylate (18). This compound was obtained from **17** as described for **3a** as yellow solid in 99% yield. Mp 112 °C. IR (KBr): ν = 3263, 2963, 2928, 1675(CO), 1417, 1290, 1127, 721 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.3 (br s, 1H, N*H*), 6.98 (d, J = 3.4 Hz, 1H, H_5), 6.80 (m, 2H, $H_{\alpha pyrrole}$), 6.29 (m, 2H, $H_{\beta pyrrole}$), 4.21 (q, J = 7.1 Hz, 2H, OCH_2), 1.19 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.37, 129.68, 122.92, 120.94, 116.88, 108.58, 97.24, 60.98, 14.01. MS (EI^+) *m/z*: 294.2 (M^+), 282.2 (M^-). Anal. Calcd for $C_{11}H_{11}BrN_2O_2$: C, 46.67; H, 3.92; N, 9.89. Found: C, 46.56; H, 4.05; N, 9.87.

4.3. Typical amidification reaction procedure

4.3.1. 4′-(4-Methoxyphenyl)-2′-(pyrrolidin-1-ylcarbonyl)-1′*H*-1,3′-bipyrrole (4a). A solution of **3a** (500 mg, 1.69 mmol) in pyrrolidine (20 mL) was refluxed for 12 h. After the mixture was cooled and evaporated, the yellow oil was dissolved in chloroform (100 mL) and the solution was washed with an 1 N aqueous hydrochloric acid solution (2× 100 mL), dried ($CaCl_2$), and evaporated to give a brown solid. This residue was purified by silica gel chromatography, eluting by cyclohexane/ethyl acetate (1:2) to furnish carboxamide **4a** as a beige solid (300 mg, 53%). Mp 166 °C. IR (KBr): ν = 3219, 2971, 2927, 2869, 1590(CO), 1447, 1243, 1175, 1032, 832, 731 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.9 (br s, 1H, N*H*), 6.97 (d, J = 3.2 Hz, 1H, C*H*N), 6.87 (d, J = 8.7 Hz, 2H, H_{arom}), 6.78 (d, J = 8.7 Hz, 2H, H_{arom}), 6.61 (m, 2H, $H_{\alpha pyrrole}$), 6.19 (m, 2H, $H_{\beta pyrrole}$), 3.77 (s, 1H, OCH_3), 3.56 (m, 2H, $H_{\alpha pyrrolidine}$), 2.52 (m, 2H, $H_{\alpha pyrrolidine}$), 1.77 (m, 2H, $H_{\beta pyrrolidine}$), 1.60 (m, 2H, $H_{\beta pyrrolidine}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.45, 158.18, 128.21, 126.38, 126.08, 125.48, 122.15, 121.23, 117.56, 113.81, 109.48, 55.14, 46.44, 46.14, 24.95, 21.32. MS (EI^+) *m/z*: 335.2. Anal. Calcd for $C_{20}H2_1N_3O_2$: C, 71.62; H, 6.31; N, 12.53. Found: C, 71.54; H, 6.45; N, 12.57.

4.3.2. 4′-(3,4-Dimethoxyphenyl)-2′-(pyrrolidin-1-ylcarbonyl)-1′*H*-1,3′-bipyrrole (4b). This compound was obtained from **3b** as described for **4a** as yellow solid in 69% yield. Mp 150 °C. IR (KBr): ν = 3223, 2973, 2950,

2879, 2839, 1587(CO), 1515, 1484, 1447, 1247, 1221, 1136, 1025, 723 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 10.6 (br s, 1H, N*H*), 7.02 (d, J = 3.1 Hz, 1H, H_5), 6.78 (d, J = 8.2 Hz, 1H, $H_{5'}$), 6.71 (dd, J = 1.8, 8.2 Hz, 1H, $H_{6'}$), 6.63 (m, 2H, $H_{\alpha pyrrole}$), 6.24 (d, J = 1.8 Hz, 1H, $H_{2'}$), 6.20 (m, 2H, $H_{\beta pyrrole}$), 3.84 (s, 3H, OCH_3), 3.60 (s, 5H, $OCH_3 + H_{\alpha pyrrolidine}$), 2.57 (m, 2H, $H_{\alpha pyrrolidine}$), 1.78 (m, 2H, $H_{\beta pyrrolidine}$), 1.61 (m, 2H, $H_{\beta pyrrolidine}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.71, 148.63, 147.42, 126.11, 123.52, 122.19, 120.83, 120.47, 118.95, 117.92, 110.93, 109.92, 109.51, 55.71, 55.34, 46.61, 46.42, 26.03, 23.81. Anal. Calcd for $C_{21}H_{23}N_3O_3$: C, 69.02; H, 6.34; N, 11.50. Found: C, 69.21; H, 6.39; N, 11.48. HRMS (EI^+) *m/z*: 365.17253 (M^+, 71.2, $C_{21}H_{23}N_3O_3$ required 365.17392).

4.3.3. 4′-(4-Fluorophenyl)-2′-(pyrrolidin-1-ylcarbonyl)-1′*H*-1,3′-bipyrrole (4c). This compound was obtained from **3c** as described for **4a** as beige solid in 47% yield. Mp 222 °C. IR (KBr): ν = 3215, 2970, 2880, 1598(CO), 1474, 1212, 837, 729 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 10.03 (br s, 1H, N*H*), 6.99 (d, J = 3.1 Hz, 1H, H_5), 6.90 (m, 4H, H_{arom}), 6.59 (m, 2H, $H_{\alpha pyrrole}$), 6.20 (m, 2H, $H_{\beta pyrrole}$), 3.56 (m, 2H, $H_{\alpha pyrrolidine}$), 2.53 (m, 2H, $H_{\alpha pyrrolidine}$), 1.78 (m, 2H, $H_{\beta pyrrolidine}$), 1.61 (m, 2H, $H_{\beta pyrrolidine}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.33, 160.31 (d, J = 241 Hz), 129.09, 128.63 (d, J = 9 Hz), 128.45, 123.58, 122.08, 120.77, 117.73, 115.28 (d, J = 23 Hz), 109.71, 46.45, 46.32, 26.07, 23.89. MS (EI^+) *m/z*: 323.2. Anal. Calcd for $C_{19}H_{19}FN_3O$: C, 70.57; H, 5.61; N, 12.99. Found: C, 70.62; H, 5.46; N, 13.12.

4.3.4. 4′-(4-Methylphenyl)-2′-(pyrrolidin-1-ylcarbonyl)-1′*H*-1,3′-bipyrrole (4d). This compound was obtained from **3d** as described for **4a** as beige solid in 53% yield. Mp 200 °C. IR (KBr): ν = 3237, 2966, 2877, 1589(CO), 1444, 1384, 1137, 823, 728, 623 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 10.0 (br s, 1H, N*H*), 7.04 (d, J = 7.8 Hz, 2H, H_{arom}), 7.01 (d, J = 3.3 Hz, 1H, H_5), 6.84 (d, J = 7.8 Hz, 2H, H_{arom}), 6.62 (m, 2H, $H_{\alpha pyrrole}$), 6.20 (m, 2H, $H_{\beta pyrrole}$), 3.56 (m, 2H, $H_{\alpha pyrrolidine}$), 2.53 (m, 2H, $H_{\alpha pyrrolidine}$), 2.30 (s, 3H, CH_3), 1.77 (m, 2H, $H_{\beta pyrrolidine}$), 1.60 (m, 2H, $H_{\beta pyrrolidine}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.54, 135.95, 130.11, 129.10, 126.92, 123.66, 122.14, 121.48, 120.65, 117.84, 109.48, 46.44, 46.35, 26.10, 23.92, 21.10. MS (EI^+) *m/z*: 319.1. Anal. Calcd for $C_{20}H2_1N_3O$: C, 75.21; H, 6.63; N, 13.16. Found: C, 75.22; H, 6.53; N, 13.15.

4.3.5. 2′-(Pyrrolidin-1-ylcarbonyl)-4′-thien-2-yl-1′*H*-1,3′-bipyrrole (4e). This compound was obtained from **3e** as described for **4a** as beige solid in 65% yield. Mp 174 °C. IR (KBr): ν = 3202, 2973, 2877, 1587(CO), 1479, 1447, 1432, 842, 735 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 10.2 (br s, 1H, N*H*), 7.09 (m, 2H, $H_{thio} + H_5$), 6.89 (dd, J = 5.1, 3.4 Hz, 1H, $H_{3'}$), 6.64 (m, 2H, $H_{\alpha pyrrole}$), 6.46 (d, J = 3.4 Hz, 1H, H_{thio}), 6.23 (m, 2H, $H_{\beta pyrrole}$), 3.51 (m, 2H, $H_{\alpha pyrrolidine}$), 2.49 (m, 2H, $H_{\alpha pyrrolidine}$), 1.72 (m, 2H, $H_{\beta pyrrolidine}$), 1.58 (m, 2H, $H_{\beta pyrrolidine}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.04, 134.53, 127.55, 123.69, 123.54, 122.78, 122.61, 117.96, 116.33, 109.77, 108.76, 46.77, 46.62, 24.50, 22.86. MS (EI^+) *m/z*: 311.1. Anal. Calcd for $C_{17}H_{17}N_3OS$: C, 65.57; H, 5.50; N, 13.49. Found: C, 65.43; H, 5.85; N, 13.31.

4.3.6. 4′-Phenyl-2′-(pyrrolidin-1-ylcarbonyl)-1′*H*-1,3′-bipyrrole (4f). This compound was obtained from **3f** as described for **4a** as white solid in 47% yield. Mp 184 °C. IR (KBr): ν = 3192, 2970, 2869, 1590(CO), 1438, 1347, 1081, 1067, 910, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 10.2 (br s, 1H, N*H*), 7.21 (m, 3H, H_{arom}), 7.03 (d, J = 3.1 Hz, 1H, H_5), 6.95 (d, J = 7.1 Hz, 2H, H_{arom}), 6.61 (m, 2H, $H_{\alpha pyrrole}$), 6.20 (m, 2H, $H_{\beta pyrrole}$), 3.57 (m, 2H, $H_{\alpha pyrrolidine}$), 2.53 (m, 2H, $H_{\alpha pyrrolidine}$), 1.78 (m, 2H, $H_{\beta pyrrolidine}$), 1.61 (m, 2H, $H_{\beta pyrrolidine}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.72, 133.33, 128.58, 127.26, 126.53, 123.93, 122.32, 121.62, 120.90, 118.31, 109.76, 46.68, 46.67, 26.26, 24.10. MS (EI^+) *m/z*: 305.1. Anal. Calcd for $C_{19}H_{19}N_3O$: C, 74.73; H, 6.27; N, 13.76. Found: C, 75.10; H, 6.23; N, 14.03.

4.3.7. 4′-(4-Chlorophenyl)-2′-(pyrrolidin-1-ylcarbonyl)-1′*H*-1,3′-bipyrrole (4g). This compound was obtained from **3g** as described for **4a** as white solid in 48% yield. Mp 210 °C. IR (KBr): ν = 3214, 2966, 2877, 1589(CO), 1447, 1387, 1137, 1078, 829, 724, 622 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 10.6 (br s, 1H, N*H*), 7.18 (d, J = 8.3 Hz, 2H, H_{arom}), 7.02 (d, J = 3.3 Hz, 1H, H_5), 6.85 (d, J = 7.8 Hz, 2H, H_{arom}), 6.59 (m, 2H, $H_{\alpha pyrrole}$), 6.21 (m, 2H, $H_{\beta pyrrole}$), 3.57 (m, 2H, $H_{\alpha pyrrolidine}$), 2.53 (m, 2H, $H_{\alpha pyrrolidine}$), 1.78 (m, 2H, $H_{\beta pyrrolidine}$), 1.61 (m, 2H, $H_{\beta pyrrolidine}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.36, 132.11, 131.63, 128.56, 128.23, 123.65, 122.01, 120.81, 120.24, 118.18, 109.82, 46.53, 46.35, 26.04, 23.85. MS (EI^+) *m/z*: 339.0. Anal. Calcd for $C_{19}H_{18}ClN_3O$: C, 67.16; H, 5.34; N, 12.37. Found: C, 67.24; H, 5.53; N, 12.45.

4.3.8. 4′-(3,4-Dichlorophenyl)-2′-(pyrrolidin-1-ylcarbonyl)-1′*H*-1,3′-bipyrrole (4h). This compound was obtained from **3h** as described for **4a** as yellow solid in 51% yield. Mp 226 °C. IR (KBr): ν = 3210, 2971, 2869, 1585(CO), 1451, 1134, 759, 722, 627 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 10.7 (br s, 1H, N*H*), 7.25 (d, J = 8.0 Hz, 1H, $H_{5'}$), 7.05 (d, J = 3.3 Hz, 1H, H_5), 7.03 (d, J = 1.9 Hz, 1H, $H_{2'}$), 6.66 (dd, J = 1.9, 8.0 Hz, 1H, $H_{6'}$), 6.58 (m, 2H, $H_{\alpha pyrrole}$), 6.24 (m, 2H, $H_{\beta pyrrole}$), 3.56 (m, 2H, $H_{\alpha pyrrolidine}$), 2.54 (m, 2H, $H_{\alpha pyrrolidine}$), 1.78 (m, 2H, $H_{\beta pyrrolidine}$), 1.62 (m, 2H, $H_{\beta pyrrolidine}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.18, 133.29, 132.47, 130.41, 130.29, 128.78, 126.22, 123.64, 122.13, 121.36, 119.64, 118.23, 110.24, 46.66, 46.65, 26.21, 23.98. MS (EI^+) *m/z*: 375.0. Anal. Calcd for $C_{19}H_{17}Cl_2N_3O$: C, 67.16; H, 5.34; N, 12.37. Found: C, 67.12; H, 5.56; N, 12.42.

4.3.9. 2′-(Pyrrolidin-1-ylcarbonyl)-4′-thien-3-yl-1′*H*-1,3′-bipyrrole (4i). This compound was obtained from **3e** as described for **4i** as beige solid in 68% yield. Mp 201 °C. IR (KBr): ν = 3242, 2971, 2882, 2826, 1588(CO), 1447, 1344, 1188, 1077, 1029, 854, 734 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.6 (br s, 1H, N*H*), 7.21 (m, 1H, H_{thio}), 7.05 (d, J = 3.1 Hz, 1H, H_5), 6.77 (d, J = 5.0 Hz, 1H, $H_{4'}$), 6.66 (m, 2H,

$H_{\alpha pyrrole}$), 6.62 (m, 1H, H_{thio}), 6.24 (m, 2H, $H_{\beta pyrrole}$), 3.55 (m, 2H, $H_{\alpha pyrrolidine}$), 2.56 (m, 2H, $H_{\alpha pyrrolidine}$), 1.81 (m, 2H, $H_{\beta pyrrolidine}$), 1.65 (m, 2H, $H_{\beta pyrrolidine}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.27, 133.01, 126.67, 125.27, 123.56, 122.59, 121.39, 119.58, 118.03, 117.65, 109.84, 46.79, 46.66, 26.32, 22.89. MS (EI^+) *m/z*: 311.1. Anal. Calcd for $C_{17}H_{17}N_3O_2S$: C, 65.57; H, 5.50; N, 13.49. Found: C, 65.78; H, 5.43; N, 13.56.

4.3.10. 4′-(3-Benzyloxy-4-methoxyphenyl)-2′-(pyrrolidin-1-ylcarbonyl)-1′*H*-1,3′-bipyrrole (4j). This compound was obtained from **3j** as described for **4a** as beige solid in 50% yield. Mp 151 °C. IR (KBr): ν = 3190, 2968, 2929, 1587(CO), 1448, 1250, 1111, 1024, 731, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 10.5 (br s, 1H, N*H*), 7.29 (m; 5H, H_{arom}), 6.95 (d, *J* = 3.2 Hz, 1H, H_5), 6.79 (d, *J* = 8.3 Hz, 1H, $H_{5'}$), 6.68 (dd, *J* = 1.7, 8.3 Hz, 1H, $H_{6'}$), 6.62 (m, 2H, $H_{\alpha pyrrole}$), 6.30 (d, *J* = 1.7 Hz, 1H, $H_{2'}$), 6.22 (m, 2H, $H_{\beta pyrrole}$), 4.85 (s, 2H, OCH_2), 3.84 (s, 3H, OCH_3), 3.57 (m, 2H, $H_{\alpha pyrrolidine}$), 2.55 (m, 2H, $H_{\alpha pyrrolidine}$), 1.77 (m, 2H, $H_{\beta pyrrolidine}$), 1.61 (m, 2H, $H_{\beta pyrrolidine}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.37, 148.18, 147.99, 137.04, 128.40, 127.68, 127.38, 125.80, 123.49, 122.38, 121.39, 120.82, 119.56, 117.43, 112.47, 111.74, 109.66, 70.43, 55.97, 46.49, 46.37, 25.30, 21.10. MS (EI^+) *m/z*: 441.0. Anal. Calcd for $C_{26}H_{26}N_3O_3$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.42; H, 6.04; N, 9.86.

4.3.11. 4′-Bromo-2′-(pyrrolidin-1-ylcarbonyl)-1′*H*-1,3′-bipyrrole (19). This compound was obtained from **18** as described for **4a** as white solid in 43% yield. Mp 164 °C. IR (KBr): ν = 3421, 2956, 2924, 1855, 1549(CO), 1451, 1383, 1344, 1261, 1088, 801 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 11.0 (br s, 1H, N*H*), 6.92 (d, *J* = 2.9 Hz, 1H, H_5), 6.79 (m, 2H, $H_{\alpha pyrrole}$), 6.26 (m, 2H, $H_{\beta pyrrole}$), 3.53 (m, 2H, $H_{\alpha pyrrolidine}$), 2.45 (m, 2H, $H_{\alpha pyrrolidine}$), 1.73 (m, 2H, $H_{\beta pyrrolidine}$), 1.64 (m, 2H, $H_{\beta pyrrolidine}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.81, 125.19, 122.12, 120.16, 119.85, 109.63, 94.12, 46.52, 46.38, 26.01, 23;91. MS (EI^+) *m/z*: 309.2 (M^+), 307.2 (M^-). Anal. Calcd for $C_{13}H_{14}BrN_3O$: C, 50.67; H, 4.58; N, 13.63. Found: C, 51.19; H, 4.69; N, 13.07.

4.4. Typical cyclization reaction procedure

4.4.1. 3-(4-Methoxyphenyl)pyrrolo[2,3-*b*]pyrrolizin-8(1*H*)-one (5a). A solution of the carboxamide **4a** (250 mg, 0.75 mmol) in phosphorus oxychloride (20 mL) was stirred at 70 °C for 3 h. After cooling, the reaction mixture was concentrated to give the intermediary iminium salt which was slowly added to a 10% aqueous sodium hydroxide solution (50 mL) and heated at 80 °C for 3 h. After cooling, the resulting suspension was extracted with ethyl acetate (2× 50 mL) and the combined organic layers were washed with water (2× 100 mL) and brine (100 mL), dried ($MgSO_4$), and evaporated to give a dark red solid. This residue was purified by silica gel chromatography, eluting by cyclohexane/ethyl acetate (1:1) to furnish thienopyrrolizinone **5a** as a red solid (30 mg, 10%). Mp 243 °C. IR (KBr): ν = 3091, 2964, 2932, 2834, 1654(CO), 1643, 1434, 1350, 1249, 1153, 1140, 1023, 723 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.8 (br s, 1H, NH), 7.39 (d, *J* = 8.6 Hz, 2H, H_{arom}), 6.97 (d, *J* = 8.6 Hz, 2H, $H_{aromatic}$), 6.98 (d, *J* = 2.9 Hz, 1H, H_2), 6.87 (d, 1H, *J* = 2.3 Hz, 1H, H_5), 6.55 (d, *J* = 3.5 Hz, 1H, H_7), 5.96 (dd, *J* = 2.3, 3.5 Hz, 1H, H_{-6}), 3.85 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.74, 158.93, 158.32, 133.11, 129.12, 127.79, 127.23, 125.27, 116.51, 115.32, 114.73, 113.62, 109.41, 55.24. MS (EI^+) *m/z*: 264.1. Anal. Calcd for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 73.05; H, 4.43; N, 10.45.

4.4.2. 3-(3,4-Dimethoxyphenyl)pyrrolo[2,3-*b*]pyrrolizin-8(1*H*)-one (5b). This compound was obtained from **4b** as described for **5a** as red solid in 30% yield. Mp 190 °C. IR (KBr): ν = 3142, 2965, 2924, 2828, 1655(CO), 1637, 1453, 1349, 1249, 1156, 1129, 1080, 728 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.9 (br s, 1H, NH), 7.04 (dd, *J* = 1.8, 8.2 Hz, 1H, $H_{6'}$), 6.97 (d, *J* = 3.0 Hz, 1H, H_2), 6.88 (d, *J* = 1.8 Hz, 1H, $H_{2'}$), 6.84 (d, 1H, *J* = 8.4 Hz, 1H, $H_{5'}$), 6.81 (d, *J* = 2.2 Hz, 1H, H_5), 6.47 (d, *J* = 3.6 Hz, 1H, H_7), 5.88 (dd, *J* = 2.2, 3.6 Hz, 1H, H_{-6}), 3.84 (s, 6H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.93, 149.33, 148.42, 140.21, 136.22, 126.69, 125.13, 124.87, 121.71, 119.12, 114.63, 113.12, 112.21, 111.71, 110.13, 56.10, 56.04. MS (EI^+) *m/z*: 294.1. Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.37; H, 4.79; N, 9.52. Found: C, 69.41; H, 4.88; N, 9.49.

4.4.3. 3-(4-Fluorophenyl)pyrrolo[2,3-*b*]pyrrolizin-8(1*H*)-one (5c). This compound was obtained from **4c** as described for **5a** as red solid in 30% yield. Mp 252 °C. IR (KBr): ν = 3175, 2990, 2965, 2932, 1663(CO), 1586, 1534, 1522, 1385, 1224, 1150, 826, 720 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 10.3 (br s, 1H, NH), 7.44 (d, *J* = 8.5 Hz, 2H, H_{arom}), 7.13 (d, *J* = 8.5 Hz, 2H, H_{arom}), 6.93 (d, *J* = 2.9 Hz, 1H, H_2), 6.84 (d, 1H, *J* = 2.8 Hz, 1H, H_5), 6.56 (d, *J* = 3.7 Hz, 1H, H_7), 5.97 (dd, *J* = 2.8, 3.7 Hz, 1H, H_6). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.78, 167.89, 161.75 (d, *J* = 246 Hz), 136.13, 128.73, 128.25 (d, *J* = 8 Hz), 125.57, 125.25, 120.78, 115.92 (d, *J* = 21 Hz), 113.26, 111.83, 111.56. HRMS (EI^+) *m/z*: 252.0699 (M^+, 100, $C_{15}H_9N_2OF$ required 252.0699).

4.4.4. 3-(4-Methylphenyl)pyrrolo[2,3-*b*]pyrrolizin-8(1*H*)-one (5d). This compound was obtained from **4d** as described for **5a** as red solid in 23% yield. Mp 255 °C. IR (KBr): ν = 3136, 2924, 2860, 1669(CO), 1517 1322, 1148, 820, 773, 721 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 10.2 (br s, 1H, NH), 7.36 (d, *J* = 7.9 Hz, 2H, H_{arom}), 7.24 (d, *J* = 7.9 Hz, 2H, H_{arom}), 6.96 (d, *J* = 2.9 Hz, 1H, H_2), 6.90 (d, 1H, *J* = 2.3 Hz, 1H, H_5), 6.55 (d, *J* = 3.6 Hz, 1H, H_7), 5.96 (dd, *J* = 2.3, 3.6 Hz, 1H, H_6), 2.39 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.71, 157.90, 137.09, 135.99, 129.70, 129.09, 126.59, 125.67, 121.76, 114.43, 114.39, 113.33, 112.06, 21.34. MS (EI^+) *m/z*: 248.1. Anal. Calcd for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.24; H, 4.56; N, 11.12.

4.4.5. 3-(Thien-2-yl)pyrrolo[2,3-*b*]pyrrolizin-8(1*H*)-one (5e). This compound was obtained from **4e** as described for **5a** as red solid in 28% yield. Mp 243 °C. IR (KBr):

ν = 3125, 3079, 2963, 2928, 1662(CO), 1588, 1535, 1416, 1387, 779, 727, 708 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.9 (br s, 1H, NH), 7.09 (m, 4H, H_{thio} + H_5), 6.99 (d, J = 2.2 Hz, 1H, H_2), 6.55 (d, J = 3.5 Hz, 1H, H_7), 5.96 (dd, J = 2.7, 3.5 Hz, 1H, H_{-6}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.55, 154.82, 138.27, 133.68, 131.83, 127.74, 125.67, 123.99, 122.08, 120.50, 119.67, 114.65, 112.25. MS (EI^+) m/z: 240.0. Anal. Calcd for $C_{13}H_8N_2OS$: C, 64.98; H, 3.36; N, 11.66. Found: C, 65.23; H, 3.32; N, 11.66.

4.4.6. 3-Phenylpyrrolo[2,3-*b*]pyrrolizin-8(1*H*)-one (5f). This compound was obtained from **4f** as described for **5a** as red solid in 5% yield. Mp 243 °C. IR (KBr): ν = 3111, 2978, 2891, 1647(CO), 1533, 1398, 1289, 1100, 762, 732 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.7 (br s, 1H, NH), 7.46 (m, 5H, H_{arom}), 6.98 (d, J = 2.8 Hz, 1H, H_2), 6.91 (d, J = 2.2 Hz, 1H, H_5), 6.55 (d, J = 3.5 Hz, 1H, H_7), 5.97 (dd, J = 2.2, 3.5 Hz, 1H, H_{-6}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.93, 156.33, 135.42, 131.21, 129.22, 128.69, 126.33, 125.71, 125.67, 116.52, 115.33, 114.72, 109.41. MS (EI^+) m/z: 264.0. Anal. Calcd for $C_{15}H_{10}N_2O$: C, 76.91; H, 4.30; N, 11.96. Found: C, 77.23; H, 4.23; N, 11.75.

4.4.7. 3-(4-Chlorophenyl)pyrrolo[2,3-*b*]pyrrolizin-8(1*H*)-one (5g). This compound was obtained from **4g** as described for **5a** as red solid in 16% yield. Mp 255 °C. IR (KBr): ν = 3138, 2963, 2920, 1688(CO), 1573, 1515, 1379, 1092, 820, 713, 580 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.7 (br s, 1H, NH), 7.41 (m, 4H, H_{arom}), 6.93 (d, J = 3.2 Hz, 1H, H_2), 6.84 (dd, J = 0.7, 2.7 Hz, 1H, H_5), 6.55 (dd, J = 0.7, 3.7 Hz, 1H, H_7), 5.97 (dd, J = 2.7, 3.7 Hz, 1H, H_{-6}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.73, 139.65, 136.20, 134.41, 132.72, 131.16, 129.19, 127.93, 125.79, 125.21, 120.96, 113.55, 111.99. MS (EI^+) m/z: 269.9. Anal. Calcd for $C_{15}H_9N_2OCl$: C, 67.05; H, 3.38; N, 10.43. Found: C, 67.03; H, 3.34; N, 10.24.

4.4.8. 3-(3,4-Dichlorophenyl)pyrrolo[2,3-*b*]pyrrolizin-8(1*H*)-one (5h). This compound was obtained from **4h** as described for **5a** as red solid in 14% yield. Mp 260 °C. IR (KBr): ν = 3142, 2978, 2905, 2847, 1674(CO), 1571, 1555, 1371, 1353, 1136, 821, 718 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 10.1 (br s, 1H, NH), 7.56 (d, J = 1.8 Hz, 1H, $H_{2'}$), 7.50 (d, 1H, J = 8.3 Hz, 1H, $H_{5'}$), 7.30 (dd, J = 1.8, 8.3 Hz, 1H, $H_{6'}$), 6.96 (d, J = 2.7 Hz, 1H, H_2), 6.84 (d, J = 2.4 Hz, 1H, H_5), 6.58 (d, J = 3.6 Hz, 1H, H_7), 6.01 (dd, J = 2.4, 3.6 Hz, 1H, H_{-6}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.79, 156.27, 133.78, 131.84, 130.70, 130.63, 129.84, 129.14, 127.78, 125.26, 119.29, 116.56, 115.33, 114.78, 109.44. MS (EI^+) m/z: 304.0. Anal. Calcd for $C_{15}H_8N_2OCl_2$: C, 59.43; H, 2.66; N, 9.24. Found: C, 59.34; H, 2.54; N, 9.34.

4.4.9. 3-(Thien-3-yl)pyrrolo[2,3-*b*]pyrrolizin-8(1*H*)-one (5i). This compound was obtained from **4i** as described for **5a** as red solid in 4% yield. Mp 250 °C. IR (KBr): ν = 3124, 3084, 2967, 2926, 1662(CO), 1536, 1384, 1143, 826, 767, 715, 577 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.8 (br s, 1H, NH), 7.09 (m, 1H, $H_{4'}$), 7.29 (s, 1H, $H_{2'}$), 7.21 (d, J = 4.7 Hz, 1H, $H_{3'}$), 6.95 (d, J = 2.2 Hz, 1H, H_2), 6.90 (d, J = 2.6 Hz, 1H, H_5), 6.55 (d, J = 3.3 Hz, 1H, H_7), 5.96 (dd, J = 2.6, 3.3 Hz, 1H, H_{-6}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.43, 141.24, 137.63, 129.60, 126.88, 126.75, 125.78, 125.21, 121.72, 120.65, 114.59, 112.48, 108.47. MS (EI^+) m/z: 239.9. Anal. Calcd for $C_{13}H_8N_2OS$: C, 64.98; H, 3.36; N, 11.66. Found: C, 65.34; H, 3.32; N, 11.56.

4.4.10. 3-(3-Benzyloxy-4-methoxyphenyl)pyrrolo[2,3-*b*]pyrrolizin-8(1*H*)-one (5j). This compound was obtained from **4j** as described for **5a** in 2% yield, or from **6j** as described for **5a** as red solid in 32% yield. Mp 244 °C. IR (KBr): ν = 3133, 2968, 2931, 2902, 2840, 1670(CO), 1520, 1381, 1257, 1145, 1016, 762, 706 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 12.0 (br s, 1H, NH), 7.40 (m, 5H, H_{arom}), 7.02 (m, 3H, H_{arom}), 6.81 (d, J = 2.7 Hz, 1H, H_2), 6.75 (d, J = 2.1 Hz, 1H, H_5), 6.46 (d, J = 3.4 Hz, 1H, H_7), 5.93 (dd, J = 2.1, 3.4 Hz, 1H, H_{-6}), 5.17 (s, 2H, OCH_2), 3.79 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.42, 148.26, 148.01, 138.41, 137.13, 135.44, 128.48, 127.82, 127.48, 126.36, 124.68, 124.59, 121.22, 119.20, 112.85, 112.79, 112.05, 111.97, 111.87, 69.73, 55.69. MS (EI^+) m/z: 370.1. Anal. Calcd for $C_{23}H_{18}N_2O_3$: C, 74.58; H, 4.90; N, 7.56. Found: C, 74.56; H, 4.87; N, 7.49.

4.4.11. 3-(4-Chlorophenyl)-1-methylpyrrolo[2,3-*b*] pyrrolizin-8(1*H*)-one (10g). This compound was obtained from **7g** as described for **5a** as red solid in 72% yield. Mp 180 °C. IR (KBr): ν = 3109, 2934, 2920, 1660(CO), 1564, 1398, 1359, 1154, 1092, 799, 706 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.32 (d, J = 8.7 Hz, 2H, H_{arom}), 7.29 (d, J = 8.7 Hz, 2H, H_{arom}), 6.75 (d, J = 2.6 Hz, 1H, H_5), 6.57 (s, 1H, H_2), 6.48 (d, J = 3.7 Hz, 1H, H_7), 5.91 (dd, J = 2.6, 3.7 Hz, 1H, H_{-6}), 3.67 (s, 3H, NCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.28, 148.14, 137.85, 132.81, 132.62, 131.45, 130.77, 129.23, 127.77, 120.71, 116.12, 113.69, 112.05, 34.87. MS (EI^+) m/z: 282.3. Anal. Calcd for $C_{16}H_{11}ClN_2O$: C, 67.97; H, 3.92; N, 9.91. Found: C, 67.89; H, 3.57; N, 9.74.

4.4.12. 3-(3-Benzyloxy-4-methoxyphenyl)-1-methylpyrrolo[2,3-*b*]pyrrolizin-8(1*H*)-one (10j). This compound was obtained from **7j** as described for **5a** in 95% yield. Mp 144 °C. IR (KBr): ν = 2963, 2925, 2854, 1682(CO), 1525, 1392, 1257, 1136, 1029, 820, 732 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42 (m, 5H, H_{arom}), 6.98 (dd, J = 1.7, 8.2 Hz, 1H, $H_{6'}$), 6.94 (d, J = 8.2 Hz, 1H, $H_{5'}$), 6.90 (d, J = 1.7 Hz, 1H, $H_{2'}$), 6.53 (s, 1H, H_2), 6.49 (d, J = 3.7 Hz, 1H, H_7), 6.32 (d, J = 2.4 Hz, 1H, H_5), 5.82 (dd, J = 2.4, 3.7 Hz, 1H, H_{-6}), 5.23 (s, 2H, OCH_2), 3.94 (s, 3H, OCH_3), 3.71 (s, 3H, NCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.46, 156.42, 148.98, 147.79, 135.90, 128.76, 128.57, 127.93, 127.85, 127.32, 126.88, 126.85, 120.72, 119.97, 119.67, 115.52, 113.31, 112.25, 111.86, 70.82, 56.12, 34.72. MS (EI^+) m/z: 384.2. Anal. Calcd for $C_{24}H_{20}N_2O_3$: C, 61.75; H, 4.44; N, 10.29. Found: C, 61.64; H, 4.35; N, 10.14.

4.4.13. 3-(4-Chlorophenyl)-1-ethylpyrrolo[2,3-*b*]pyrrolizin-8(1*H*)-one (11g). This compound was obtained from **8g** as described for **5a** as red solid in 66% yield. Mp

158 °C. IR (KBr): ν = 3094, 2973, 2920, 1677(CO), 1659, 1565, 1365, 1089, 829, 795, 723 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.30 (m, 4H, H_{arom}), 6.75 (d, J = 2.4 Hz, 1H, H_5), 6.63 (s, 1H, H_2), 6.47 (d, J = 3.3 Hz, 1H, H_7), 5.91 (dd, J = 2.4, 3.3 Hz, 1H, H_{-6}), 3.95 (q, J = 7.3 Hz, 2H, NCH_2), 1.44 (t, J = 7.3 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.38, 138.98, 136.04, 132.74, 130.87, 129.20, 127.77, 126.41, 120.77, 120.62, 113.59, 112.03, 110.81, 43.77, 15.95. MS (EI^+) m/z: 296.2. Anal. Calcd for $C_{17}H_{13}ClN_2O$: C, 68.81; H, 4.42; N, 9.44. Found: C, 68.80; H, 4.38; N, 9.27.

4.4.14. 3-(3-Benzyloxy-4-methoxyphenyl)-1-ethylpyrrolo[2,3-*b*]pyrrolizin-8(1*H*)-one (11j). This compound was obtained from **8j** as described for **5a** in 66% yield. Mp 136 °C. IR (KBr): ν = 3122, 2931, 2919, 1668(CO), 1506, 1354, 1251, 1220, 1172, 1137, 1023, 726 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42 (m, 5H, H_{arom}), 6.98 (dd, J = 1.8, 8.3 Hz, 1H, $H_{6'}$), 6.94 (d, J = 8.3 Hz, 1H, $H_{5'}$), 6.91 (d, J = 1.8 Hz, 1H, $H_{2'}$), 6.60 (s, 1H, H_2), 6.48 (d, J = 3.6 Hz, 1H, H_7), 6.33 (d, J = 2.5 Hz, 1H, H_5), 5.82 (dd, J = 2.5, 3.6 Hz, 1H, H_{-6}), 5.23 (s, 2H, OCH_2), 3.99 (q, J = 7.3 Hz, 2H, NCH_2), 3.94 (s, 3H, OCH_3), 1.49 (s, J = 7.3 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.93, 149.09, 148.41, 137.03, 136.11, 131.93, 129.77, 128.91, 128.08, 127.05, 126.55, 125.20, 123.61, 120.77, 119.81, 113.36, 112.87, 112.41, 112.00, 70.98, 56.27, 43.77, 16.11. MS (EI^+) m/z: 398.2. Anal. Calcd for $C_{25}H_{22}N_2O_3$: C, 75.36; H, 5.57; N, 7.03. Found: C, 75.24; H, 5.43; N, 7.32.

4.4.15. 1-Benzyl-3-(4-chlorophenyl)pyrrolo[2,3-*b*]pyrrolizin-8(1*H*)-one (12g). This compound was obtained from **9g** as described for **5a** as red solid in 82% yield. Mp 160 °C. IR (KBr): ν = 3061, 3030, 2961, 1666(CO), 1565, 1400, 1361, 1260, 1098, 827, 727 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.28 (m, 9H, H_{arom}), 6.75 (d, J = 2.2 Hz, 1H, H_5), 6.61 (s, 1H, H_2), 6.48 (d, J = 3.6 Hz, 1H, H_7), 5.91 (dd, J = 2.2, 3.6 Hz, 1H, H_{-6}), 5.07 (s, 2H, NCH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.63, 136.03, 135.98, 132.89, 130.73, 129.19, 128.98, 128.66, 128.48, 128.07, 128.11, 127.84, 126.62, 120.79, 113.77, 112.15, 111.83, 51.93. MS (EI^+) m/z: 358.3. Anal. Calcd for $C_{22}H_{15}ClN_2O$: C, 73.45; H, 4.21; N, 7.81. Found: C, 73.41; H, 4.19; N, 7.74.

4.4.16. 1-Benzyl-3-(3-benzyloxy-4-methoxyphenyl) pyrrolo[2,3-*b*]pyrrolizin-8(1*H*)-one (12j). This compound was obtained from **9j** as described for **5a** in 60% yield. Mp 124 °C. IR (KBr): ν = 3104, 3061, 2929, 1671(CO), 1525, 1405, 1249, 729, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35 (m, 10H, H_{arom}), 6.95 (dd, J = 1.7, 8.3 Hz, 1H, $H_{6'}$), 6.91 (d, J = 8.3 Hz, 1H, $H_{5'}$), 6.88 (d, J = 1.7 Hz, 1H, $H_{2'}$), 6.58 (s, 1H, H_2), 6.49 (d, J = 3.7 Hz, 1H, H_7), 6.32 (d, J = 2.4 Hz, 1H, H_5), 5.82 (dd, J = 2.4, 3.7 Hz, 1H, H_{-6}), 5.20 (s, 2H, OCH_2), 5.11 (s, 2H, NCH_2), 3.93 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.68, 149.,07, 148.31, 138.77, 136.90, 136.18, 135.97, 128.93, 128.77, 128.38, 128.09, 127.96, 126.94, 126.67, 124.93, 120.82, 119.77, 119.70, 113.42, 112.87, 112.64, 112.31, 111.97, 70.92, 56.16, 51.83. MS (EI^+) m/z: 460.0. Anal. Calcd for $C_{30}H_{24}N_2O_3$: C, 78.24; H, 5.25; N, 6.08. Found: C, 78.13; H, 5.34; N, 5.94.

4.4.17. 3-Bromo-1-methylpyrrolo[2,3-*b*]pyrrolizin-8(1*H*)-one (23). This compound was obtained from **20** as described for **5a** in 86% yield. Mp 130 °C. IR (KBr): ν = 3117, 2924, 2853, 1683(CO), 1573, 1243, 964, 720 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.88 (dd, J = 0.7, 2.4 Hz, 1H, H_5), 6.54 (dd, J = 0.7, 3.7 Hz, 1H, H_7), 6.51 (s, 1H, H_2), 6.02 (dd, J = 2.4, 3.7 Hz, 1H, H_{-6}), 3.69 (s, 3H, NCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.09, 140.31, 129.49, 120.25, 117.98, 113.99, 112.47, 107.26, 92.14, 34.99. MS (EI^+) m/z: 252.1 (M^+), 250.1 (M^-). Anal. Calcd for $C_{10}H_7BrN_2O$: C, 47.84; H, 2.81; N, 11.16. Found: C, 47.76; H, 2.66; N, 11.10.

4.4.18. 3-Bromopyrrolo[2,3-*b*]pyrrolizin-8(1*H*)-one (23). This compound was obtained from **21** as described for **5a** in 43% yield. Mp 234 °C. IR (KBr): ν = 3121, 2966, 2916, 2855, 1668(CO), 1570, 1525, 1385, 1248, 818, 720 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.7 (br s, 1H, NH), 6.92 (dd, J = 0.9, 2.7 Hz, 1H, H_5), 6.80 (d, J = 2.4 Hz, 1H, H_2), 6.55 (dd, J = 0.9, 3.9 Hz, 1H, H_7), 6.03 (dd, J = 2.7, 3.9 Hz, 1H, H_{-6}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.91, 141.52, 128.45, 121.12, 114.99, 112.82, 112.47, 109.85, 95.44. MS (EI^+) m/z: 238.0 (M^+), 236.0 (M^-). Anal. Calcd for $C_9H_5BrN_2O$: C, 45.60; H, 2.13; N, 11.82. Found: C, 45.59; H, 2.08; N, 11.76.

4.5. O-Debenzylation procedure

4.5.1. 3-(3-Hydroxy-4-methoxyphenyl)pyrrolo[2,3-*b*]-pyrrolizin-8(1*H*)-one (5j). A solution of **5k** (0.25 g, 0.68 mmol) in a 33% solution of hydrobromic acid in glacial acetic acid (15 mL) was stirred at room temperature for 1 h. After cooling, the reaction mixture was diluted with water (50 mL) and the resulting precipitate was extracted with ethyl acetate (3× 20 mL). Then, the organic layers were combined, washed with water (2× 100 mL), dried ($MgSO_4$), and evaporated to give a dark red solid. The residue was diluted in methanol (10 mL) and a molar aqueous solution of NaOH was added (5 mL) before being stirred for 1 h. The reaction mixture was concentrated under vacuum, diluted with water, acidified with 1 M HCl, and extracted with ethyl acetate (2× 100 mL). The organic layers were combined, washed with water (2× 100 mL), dried ($MgSO_4$), and evaporated to give a dark red solid which was purified by silica gel chromatography, eluting by cyclohexane/ethyl acetate (3:2) to furnish thienopyrrolizinone **5j** as a red solid (100 mg, 55%). Mp >260 °C. IR (KBr): ν = 3368, 3172, 2965, 2927, 1658(CO), 1580, 1282, 1261, 1141, 1006, 725 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 10.9 (br s, 1H, NH), 7.04 (d, J = 2.1 Hz, 1H, $H_{2'}$), 6.94 (dd, J = 2.1, 8.3 Hz, 1H, $H_{6'}$), 6.88 (d, J = 8.3 Hz, 1H, $H_{5'}$), 6.87 (s, 1H, H_2), 6.82 (d, J = 3.2 Hz, 1H, H_5), 6.49 (d, J = 3.7 Hz, 1H, H_7), 5.95 (dd, J = 3.2, 3.7 Hz, 1H, H_{-6}), 3.92 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.73, 159.13, 147.18, 147.09, 126.36, 124.97, 124.95, 121.77, 117.54, 113.81, 113.27, 113.22, 112.24, 110.27, 109.82, 55.97. HRMS (EI^+) m/z: 280.08457 (M^+, 78, $C_{16}H_{12}N_2O_3$ required 280.08477).

4.5.2. 3-(3-Hydroxy-4-methoxyphenyl)-1-methylpyrrolo-[2,3-b]pyrrolizin-8(1*H*)-one (10k). This compound was obtained from **10j** as described for **5k** in 41% yield. Mp 160 °C. IR (KBr): ν = 3435, 3123, 2963, 2826, 1635(CO), 1607, 1436, 1401, 1255, 1219, 1027, 709 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00 (d, J = 1.8 Hz, 1H, $H_{2'}$), 6.93 (dd, J = 1.8, 8.3 Hz, 1H, $H_{6'}$), 6.88 (m, 2H, $H_{5'} + H_5$), 6.59 (s, 1H, H_2), 6.53 (dd, J = 0.7, 3.5 Hz, 1H, H_7), 5.96 (dd, J = 2.7, 3.5 Hz, 1H, H_{-6}), 5.7 (br s, 1H, OH), 3.92 (s, 3H, OCH_3), 3.73 (s, 3H, NCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.66, 148.34, 146.07, 129.63, 127.93, 127.44, 125.66, 120.25, 118.33, 114.76, 113.41, 112.91, 112.08, 111.74, 111.08, 56.07, 34.76. MS (EI^+) m/z: 294.0. Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.34; H, 4.54; N, 9.67.

4.5.3. 3-(3-Hydroxy-4-methoxyphenyl)-1-ethylpyrrolo-[2,3-b]pyrrolizin-8(1*H*)-one (11k). This compound was obtained from **11j** as described for **5k** in 85% yield. Mp 154 °C. IR (KBr): ν = 3411, 3115, 2956, 2932, 1579(CO), 1505, 1253, 1024, 804, 723 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.01 (d, J = 1.8 Hz, 1H, $H_{2'}$), 6.94 (dd, J = 1.8, 8.2 Hz, 1H, $H_{6'}$), 6.89 (m, 2H, $H_{5'} + H_5$), 6.67 (s, 1H, H_2), 6.52 (d, J = 3.7 Hz, 1H, H_7), 5.95 (dd, J = 2.8, 3.7 Hz, 1H, H_{-6}), 5.7 (br s, 1H, OH), 4.02 (q, J = 7.3 Hz, 2H, NCH_2), 3.93 (s, 3H, OCH_3), 1.51 (t, J = 7.3 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.75, 146.07, 145.75, 138.94, 130.87, 128.80, 126.43, 125.76, 124.93, 120.84, 118.32, 113.30, 112.91, 111.72, 111.08, 56.06, 43.65, 15.96. MS (EI^+) m/z: 308.1. Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 70.23; H, 5.34; N, 9.05.

4.5.4. 1-Benzyl-3-(3-hydroxy-4-methoxyphenyl)pyrrolo[2,3-*b*]pyrrolizin-8(1*H*)-one (12k). This compound was obtained from **12j** as described for **5k** in 40% yield. Mp 110 °C. IR (KBr): ν = 3402, 2940, 2927, 2840, 1672(CO), 1651, 1506, 1406, 1255, 1175, 701 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (m, 5H, H_{arom}), 6.98 (s, 1H, H_2), 6.90 (m, 2H, $H_{5'} + H_5$), 6.86 (dd, J = 1.5, 8.3 Hz, 1H, $H_{6'}$), 6.64 (d, J = 1.5 Hz, 1H, $H_{2'}$), 6.52 (d, J = 3.9 Hz, 1H, H_7), 5.95 (dd, J = 2.7, 3.9 Hz, 1H, H_{-6}), 5.7 (br s, 1H, OH), 5.13 (s, 2H, NCH_2), 3.91 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.20, 148.68, 147.53, 142.12, 137.46, 136.16, 128.94, 128.38, 128.12, 127.33, 126.67, 121.02, 120.92, 118.37, 113.47, 112.94, 111.82, 111.06, 111.04, 56.08, 51.86. MS (EI^+) m/z: 370.2. Anal. Calcd for $C_{23}H_{18}N_2O_3$: C, 74.58; H, 4.90; N, 7.56. Found: C, 74.53; H, 4.86; N, 7.43.

4.5.5. 3-(3-Hydroxy-4-methoxyphenyl)-1-(methylsulfonyl)pyrrolo[2,3-*b*]pyrrolizin-8(1*H*)-one (15k). This compound was obtained from **15j** as described for **5k** in 42% yield. Mp >260 °C. IR (KBr): ν = 3169, 2924, 2852, 1656(CO), 1579, 1388, 1261, 1140, 1006, 724 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.31 (br s, 1H, OH), 7.27 (s, 1H, H_2), 7.16 (d, J = 2.4 Hz, 1H, H_5), 7.03 (d, J = 8.0 Hz, 1H, $H_{5'}$), 7.01 (d, J = 2.0 Hz, 1H, $H_{2'}$), 6.97 (dd, J = 2.0, 8.0 Hz, 1H, $H_{6'}$), 6.55 (d, J = 3.7 Hz, 1H, H_7), 6.09 (dd, J = 2.4, 3.7 Hz, 1H, H_{-6}), 3.84 (s, 3H, OCH_3), 3.38 (s, 3H, SCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.75, 169.39, 146.90, 146.76, 135.49, 126.03, 124.71, 124.65, 121.44, 117.19, 113.54, 112.97, 112.84, 111.94, 111.87, 55.67, 39.01. MS (EI^+) m/z: 358.3. Anal. Calcd for $C_{17}H_{14}N_2O_5$: C, 56.98; H, 3.94; N, 7.82. Found: C, 56.95; H, 3.85; N, 7.74.

4.5.6. 1-Benzyl-3-(3-hydroxy-4-methoxyphenyl)-5,6,7,7a-tetrahydropyrrolo[2,3-*b*]pyrrolizin-8(1*H*)-one (13). A solution of **12k** (0.15 g, 0.33 mmol) and Pd/C (0.15 equiv) in methanol was degassed and stirred at rt under hydrogen flow for 3 h. The reaction mixture was filtered on Celite and evaporated to give a dark red solid which was purified by silica gel chromatography, eluting by cyclohexane/ethyl acetate (1:2) to furnish tetrahydropyrrolizine **13** as a yellow solid (67 mg, 55%). Mp 98 °C. IR (KBr): ν = 3272, 2936, 2901, 2835, 1651(CO), 1563, 1418, 1257, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (m, 5H, H_{arom}), 7.06 (s, 1H, H_2), 7.05 (d, J = 1.9 Hz, 1H, $H_{2'}$), 6.99 (dd, J = 1.9, 8.3 Hz, 1H, $H_{6'}$), 6.83 (d, J = 8.3 Hz, 1H, $H_{5'}$), 5.6 (br s, 1H, OH), 5.20 (d, J = 14.5 Hz, 1H, NCHPh), 5.07 (d, J = 14.5 Hz, 1H, NCHPh), 4.34 (m, 1H, H_7), 3.89 (s, 3H, OCH_3), 3.32 (m, 1H, H_5), 2.92 (m, 1H, H_5), 1.90 (m, 3H, $H_6 + H_7$). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.47, 146.08, 136.75, 133.04, 129.09, 129.07, 129.00, 128.37, 128.32, 128.27, 128.08, 118.00, 112.48, 111.21, 111.09, 79.05, 56.22, 51.79, 51.26, 29.88, 27.95. MS (EI^+) m/z: 374.1. Anal. Calcd for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.64; H, 5.84; N, 7.32.

4.6. N-Substitution procedure

4.6.1. *tert*-Butyl 4′-(3-benzyloxy-4-methoxyphenyl)-2′-(pyrrolidin-1-ylcarbonyl)-1′*H*-1,3′-bipyrrole carboxylate (6j). To a solution of carboxamide **3j** (4.5 g, 10.2 mmol) in dichloromethane (10 mL) were added 4-dimethylaminopyridine (2.22 g, 18.1 mmol) and triethylamine (2.52 mL, 18.1 mmol). The solution was cooled at 0 °C using an iced-bath and ditertbutyl dicarbonate (2.37 g, 10.9 mmol) was then added. The reaction mixture was stirred at rt for 2 h and poured into dichloromethane (100 mL) and water (100 mL). The organic layer was washed with water (2× 100 mL), dried ($CaCl_2$), and evaporated to give a beige solid which was purified by silica gel chromatography, eluting by cyclohexane:ethyl acetate (1:1) to furnish amide **6j** as a yellow solid (4.33 g, 78%). Mp 90 °C. IR (KBr): ν = 2975, 2927, 2875, 1748, 1641(CO), 1487, 1454, 1368, 1249, 1155, 1126, 1079, 729 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (m, 6H, $H_{arom} + H_5$), 6.80 (d, J = 8.3 Hz, 1H, $H_{5'}$), 6.70 (dd, J = 1.9, 8.3 Hz, 1H, $H_{6'}$), 6.65 (m, 2H, $H_{\alpha pyrrole}$), 6.35 (d, J = 1.9 Hz, 1H, $H_{2'}$), 6.21 (m, 2H, $H_{\beta pyrrole}$), 4.87 (s, 2H, OCH_2), 3.85 (s, 3H, OCH_3), 3.47 (m, 2H, $H_{\alpha pyrrolidine}$), 3.09 (m, 2H, $H_{\alpha pyrrolidine}$), 1.81 (m, 2H, $H_{\beta pyrrolidine}$), 1.68 (m, 2H, $H_{\beta pyrrolidine}$), 1.57 (s, 9H, $(CH_3)_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.32, 148.88, 148.03, 147.88, 137.04, 128.45, 127.76, 127.33, 125.47, 124.22, 123.46, 122.65, 122.03, 119.79, 116.88, 112.64, 111.76, 109.50, 85.17, 70.56, 55.97, 47.54, 45.29, 27.84 ($3CH_3$), 25.48, 24.42. MS (EI^+) m/z: 540.8. Anal. Calcd for $C_{32}H_{35}N_3O_5$: C, 70.96; H, 6.51; N, 7.76. Found: C, 70.87; H, 6.45; N, 7.64.

4.6.2. *tert*-Butyl 4′-bromo-2′-(pyrrolidin-1-ylcarbonyl)-1′*H*-1,3′-bipyrrole carboxylate (21). This compound was obtained from **19** as described for **13** as a white solid in 99% yield. Mp 140 °C. IR (KBr): ν = 3139, 2977, 2974, 1755, 1631(CO), 1359, 1271, 1154, 719 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33 (s, 1H, H_5), 6.85 (m, 2H, $H_{\alpha pyrrole}$), 6.26 (m, 2H, $H_{\beta pyrrole}$), 3.47 (m, 2H, $H_{\alpha pyrrolidine}$), 2.95 (m, 2H, $H_{\alpha pyrrolidine}$), 1.80 (m, 2H, $H_{\beta pyrrolidine}$), 1.69 (m, 2H, $H_{\beta pyrrolidine}$), 1.56 (s, 9H, $(CH_3)_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.93, 159.50, 125.90, 121.59, 120.54, 120.39, 109.62, 97.16, 85.85, 47.27, 45.39, 27.77, 25.43, 24.37. MS (EI^+) *m*/*z*: 409.1 (M^+), 407.1 (M^-). Anal. Calcd for $C_{18}H_{22}BrN_3O_3$: C, 52.95; H, 5.43; N, 10.29. Found: C, 53.04; H, 5.34; N, 10.23.

4.6.3. 4′-(4-Chlorophenyl)-1′-methyl-2′-(pyrrolidin-1-ylcarbonyl)-1′*H*-1,3′-bipyrrole (7g). To a cooled solution of **4g** (350 mg, 1.03 mmol) in dimethylformamide (10 mL) were successively added sodium hydride at 55% in a mineral oil (54 mg, 1.23 mmol) and methyl iodide (77 μL, 1.23 mmol). The reaction mixture was stirred at rt for 1 h, diluted with water (100 mL), and extracted with diethyl ether (2× 100 mL). The combined organic layers were washed with brine (2× 100 mL), dried ($MgSO_4$), and evaporated to furnish amide **7g** as a white solid (310 mg, 85%). Mp 132 °C. IR (KBr): ν = 2949, 2913, 2847, 1608(CO), 1451, 1375, 1261, 1090, 804, 721 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.17 (d, J = 8.3 Hz, 2H, H_{arom}), 6.87 (d, J = 8.3 Hz, 2H, H_{arom}), 6.76 (s, 1H, H_5), 6.54 (m, 2H, $H_{\alpha pyrrole}$), 6.16 (m, 2H, $H_{\beta pyrrole}$), 3.75 (s, 3H, NCH_3), 3.49 (m, 2H, $H_{\alpha pyrrolidine}$), 2.65 (m, 2H, $H_{\alpha pyrrolidine}$), 1.75 (m, 2H, $H_{\beta pyrrolidine}$), 1.55 (m, 2H, $H_{\beta pyrrolidine}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.56, 131.94, 131.50, 128.54, 128.23, 123.52, 122.32, 121.99, 121.51, 117.62, 109.43, 46.88, 45.53, 35.91, 25.67, 23.97. MS (EI^+) *m*/*z*: 353.1. Anal. Calcd for $C_{20}H_{20}ClN_3O$: C, 67.89; H, 5.70; N, 11.87. Found: C, 67.85; H, 5.60; N, 11.84.

4.6.4. 4′-(3-Benzyloxy-4-methoxyphenyl)-1′-methyl-2′-(pyrrolidin-1-ylcarbonyl)-1′*H*-1,3′-bipyrrole (7j). This compound was obtained from **4j** as described for **7g** as pale yellow solid in 95% yield. Mp 170 °C. IR (KBr): ν = 2956, 2926, 2872, 1629(CO), 1584, 1545, 1480, 1387, 1257, 1142, 1024, 739 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.29 (m, 5H, H_{arom}) , 6.79 (d, J = 8.3 Hz, 1H, $H_{5'}$), 6.69 (m, 2H, $H_{6'} + H_5$), 6.58 (m, 2H, $H_{\alpha pyrrole}$), 6.35 (d, J = 1.7 Hz, 1H, $H_{2'}$), 6.19 (m, 2H, $H_{\beta pyrrole}$), 4.86 (s, 2H, OCH_2), 3.85 (s, 3H, OCH_3), 3.75 (s, 3H, NCH_3), 3.51 (m, 2H, $H_{\alpha pyrrolidine}$), 2.69 (m, 2H, $H_{\alpha pyrrolidine}$), 1.76 (m, 2H, $H_{\beta pyrrolidine}$), 1.61 (m, 2H, $H_{\beta pyrrolidine}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.61, 147.83, 145.37, 137.05, 128.26, 127.52, 127.20, 125.58, 123.43, 121.69, 121.47, 119.28, 118.43, 117.44, 112.54, 111.60, 109.17, 70.32, 55.82, 46.85, 45.38, 35.72, 25.59, 23.87. MS (EI^+) *m*/*z*: 455.1. Anal. Calcd for $C_{28}H_{29}N_3O_3$: C, 76.81; H, 6.26; N, 7.90. Found: C, 76.74; H, 6.11; N, 7.99.

4.6.5. 4′-Bromo-1′-methyl-2′-(pyrrolidin-1-ylcarbonyl)-1′*H*-1,3′-bipyrrole (20). This compound was obtained from **19** as described for **7g** as a white solid in 99% yield. Mp 175 °C. IR (KBr): ν = 2954, 2925, 1621(CO), 1448, 1370, 1069, 994, 725 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.78 (m, 2H, $H_{\alpha pyrrole}$), 6.71 (s, 1H, H_5), 6.24 (m, 2H, $H_{\beta pyrrole}$), 3.72 (s, 3H, NCH_3), 3.49 (m, 2H, $H_{\alpha pyrrolidine}$), 2.54 (m, 2H, $H_{\alpha pyrrolidine}$), 1.75 (m, 2H, $H_{\beta pyrrolidine}$), 1.61 (m, 2H, $H_{\beta pyrrolidine}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.73, 125.44, 123.70, 121.52, 121.47, 109.38, 91.05, 46.64, 45.66, 36.15, 25.70, 24.02. MS (EI^+) *m*/*z*: 323.8 (M^+), 321.4 (M^-). Anal. Calcd for $C_{14}H_{16}BrN_3O$: C, 52.19; H, 5.01; N, 13.04. Found: C, 52.45; H, 5.06; N, 13.34.

4.6.6. 4′-(4-Chlorophenyl)-1′-ethyl-2′-(pyrrolidin-1-ylcarbonyl)-1′*H*-1,3′-bipyrrole (8g). To a cooled solution of **4g** (200 mg, 0.59 mmol) in dimethylformamide (5 mL) were successively added sodium hydride at 55% in a mineral oil (31 mg, 0.71 mmol) and ethyl iodide (57 μL, 0.71 mmol). The reaction mixture was stirred at rt for 1 h, diluted with water (100 mL), and extracted with diethyl ether (2× 100 mL). The combined organic layers were washed with brine (2× 100 mL), dried ($MgSO_4$), and evaporated to furnish amide **8g** as a pale yellow solid (180 mg, 82%). Mp 119 °C. IR (KBr): ν = 2990, 2923, 2860, 1620(CO), 1556, 1447, 1384, 1084, 991, 835, 729 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.17 (d, J = 8.5 Hz, 2H, H_{arom}), 6.88 (d, J = 8.5 Hz, 2H, H_{arom}), 6.82 (s, 1H, H_5), 6.54 (m, 2H, $H_{\alpha pyrrole}$), 6.15 (m, 2H, $H_{\beta pyrrole}$), 4.11 (q, J = 7.1 Hz, 2H, NCH_2), 3.49 (m, 2H, $H_{\alpha pyrrolidine}$), 2.65 (m, 2H, $H_{\alpha pyrrolidine}$), 1.75 (m, 2H, $H_{\beta pyrrolidine}$), 1.55 (m, 2H, $H_{\beta pyrrolidine}$), 1,39 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.93, 132.01, 131.78, 128.67, 128.34, 123.39, 121.85, 121.66, 120.12, 117.65, 109.47, 47.09, 45.61, 43.66, 25.77, 24.17, 16.99. MS (EI^+) *m*/*z*: 367.2. Anal. Calcd for $C_{21}H_{22}ClN_3O$: C, 68.56; H, 6.03; N, 11.42. Found: C, 68.47; H, 5.94; N, 11.32.

4.6.7. 4′-(3-Benzyloxy-4-methoxyphenyl)-1-ethyl-2′-(pyrrolidin-1-ylcarbonyl)-1′*H*-1,3′-bipyrrole (8j). This compound was obtained from **4j** as described for **8g** as pale yellow solid in 94% yield. Mp 130 °C. IR (KBr): ν = 2976, 2949, 2929, 1620(CO), 1478, 1453, 1413, 1253, 1221, 1138, 1024, 733 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.29 (m; 5H, H_{arom}), 6.79 (d, J = 8.3 Hz, 1H, $H_{5'}$), 6.66 (s, 1H, H_5), 6.70 (dd, J = 1.8, 8.3 Hz, 1H, $H_{5'}$), 6.59 (m, 2H, $H_{\alpha pyrrole}$), 6.37 (d, J = 1.8 Hz, 1H, $H_{2'}$), 6.19 (m, 2H, $H_{\beta pyrrole}$), 4.86 (s, 2H, OCH_2), 4.11 (q, J = 7.2 Hz, 2H, NCH_2), 3.85 (s, 3H, OCH_3), 3.51 (m, 2H, $H_{\alpha pyrrolidine}$), 2.74 (m, 2H, $H_{\alpha pyrrolidine}$), 1.76 (m, 2H, $H_{\beta pyrrolidine}$), 1.60 (m, 2H, $H_{\beta pyrrolidine}$), 1,40 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.87, 147.89, 147.86, 137.09, 128.27, 127.53, 127.24, 125.77, 123.15, 121.72, 121.34, 119.44, 119.25, 118.34, 112.53, 111.63, 109.10, 70.34, 55.84, 46.95, 45.36, 43.32, 25.58, 23.94, 16.77. MS (EI^+) *m*/*z*: 469.4. Anal. Calcd for $C_{29}H_{31}N_3O_3$: C, 74.18; H, 6.65; N, 8.95. Found: C, 73.95; H, 6.54; N, 8.67.

4.6.8. 4′-(4-Chlorophenyl)-1′-benzyl-2′-(pyrrolidin-1-ylcarbonyl)-1′*H*-1,3′-bipyrrole (9g). To a cooled solution of **4g** (500 mg, 1.47 mmol) in dimethylformamide (10 mL) were successively added sodium hydride at 55% in a mineral oil (77 mg, 1.77 mmol) and benzyl bro-

mide (210 μL, 1.77 mmol). The reaction mixture was stirred at rt for 1 h, diluted with water (100 mL), and extracted with diethyl ether (2× 100 mL). The combined organic layers were washed with brine (2× 100 mL), dried ($MgSO_4$), and evaporated to furnish amide **9g** as a pale yellow solid (550 mg, 86%). Mp 196 °C. IR (KBr): ν = 3046, 2973, 2927, 1619(CO), 1571, 1472, 1455, 1433, 1362, 1091, 1079, 730 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.20 (m, 7H, H_{arom}), 6.91 (d, J = 8.5 Hz, 2H, H_{arom}), 6.90 (s, 1H, H_5), 6.53 (m, 2H, $H_{\alpha pyrrole}$), 6.13 (m, 2H, $H_{\beta pyrrole}$), 5.24 (s, 2H, CH_2Ph), 3.28 (m, 2H, $H_{\alpha pyrrolidine}$), 2.33 (m, 2H, $H_{\alpha pyrrolidine}$), 1.56 (m, 2H, $H_{\beta pyrrolidine}$), 1.27 (m, 2H, $H_{\beta pyrrolidine}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.81, 137.54, 132.11, 131.63, 128.68, 128.62, 128.42, 127.99, 127.76, 123.99, 122.42, 121.59, 121.15, 117.64, 109.47, 52.46, 46.85, 45.29, 25.34, 24.03. MS (EI^+) m/z: 429.4. Anal. Calcd for $C_{26}H_{24}ClN_3O$: C, 72.63; H, 5.63; N, 9.77. Found: C, 72.52; H, 5.49; N, 9.78.

4.6.9. 4′-(3-Benzyloxy-4-methoxyphenyl)-1′-benzyl-2′-(pyrrolidin-1-ylcarbonyl)-1′*H*-1,3′-bipyrrole (9j). This compound was obtained from **4j** as described for **9g** as pale yellow solid in 99% yield. Mp 136 °C. IR (KBr): ν = 3057, 2965, 2930, 1623(CO), 1513, 1465, 1450, 1411, 1250, 1218, 1027, 732 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.30 (m, 10H, H_{arom}), 6.85 (s, 1H, H_5), 6.79 (d, J = 8.3 Hz, 1H, $H_{5'}$), 6.73 (dd, J = 1.9, 8.3 Hz, 1H, $H_{6'}$), 6.59 (m, 2H, $H_{\alpha pyrrole}$), 6.38 (d, J = 1.9 Hz, 1H, $H_{2'}$), 6.18 (m, 2H, $H_{\beta pyrrole}$), 5.23 (s, 2H, NCH_2), 4.86 (s, 2H, OCH_2), 3.82 (s, 3H, OCH_3), 3.29 (m, 2H, $H_{\alpha pyrrolidine}$), 2.39 (m, 2H, $H_{\alpha pyrrolidine}$), 1.60 (m, 2H, $H_{\beta pyrrolidine}$), 1.27 (m, 2H, $H_{\beta pyrrolidine}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.88, 148.14, 148.03, 137.68, 137.22, 128.99, 128.77, 128.53, 128.38, 127.77, 127.63, 127.37, 125.75, 123.88, 121.79, 120.58, 119.51, 118.48, 112.82, 111.83, 109.21, 70.55, 55.99, 52.24, 46.83, 45.17, 25.27, 23.93. MS (EI^+) m/z: 530.8. Anal. Calcd for $C_{34}H_{33}N_3O_3$: C, 76.81; H, 6.26; N, 7.90. Found: C, 76.90; H, 6.45; N, 7.56.

4.6.10. 3-(3-Benzyloxy-4-methoxyphenyl)-1′-(methyl sulfonyl)pyrrolo[2,3-*b*]pyrrolizin-8(1*H*)-one (15j). To a cooled solution of **5j** (150 mg, 0.41 mmol) in dimethylformamide (5 mL) were successively added sodium hydride at 55% in a mineral oil (12 mg, 0.49 mmol) and methylsulfonyl chloride (48 μL, 0.49 mmol). The reaction mixture was stirred at rt for 12 h, diluted with water (100 mL), and extracted with diethyl ether (2× 100 mL). The combined organic layers were washed with brine (2× 100 mL), dried ($MgSO_4$) and evaporated to furnish amide **15j** as a yellow solid (170 mg, 93%). Mp 132 °C. IR (KBr): ν = 2924, 2854, 1681(CO), 1521, 1365, 1250, 1171, 1082, 771, 552 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.34 (m, 5H, H_{arom}), 7.21 (s, 1H, H_2), 7.03 (dd, J = 1.9, 8.3 Hz, 1H, $H_{6'}$), 6.97 (d, J = 8.3 Hz, 1H, $H_{5'}$), 6.91 (d, J = 1.9 Hz, 1H, $H_{2'}$), 6.61 (d, J = 3.7 Hz, 1H, H_7), 6.35 (d, J = 2.7 Hz, 1H, H_5), 5.88 (dd, J = 2.7, 3.7 Hz, 1H, H_{-6}), 5.23 (s, 2H, OCH_2), 3.95 (s, 3H, OCH_3), 3.59 (s, 3H, SCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.44, 150.08, 148.44, 143.55, 136.68, 134.94, 128.83, 128.08, 126.95, 125.99, 123.23, 122.56, 121.94, 120.46, 115.76, 113.36, 113.06, 112.35, 70.93, 56.15, 42.14. MS (EI^+) m/z: 447.9. Anal. Calcd for $C_{24}H_{20}N_2O_5S$: C, 64.27; H, 4.49; N, 6.25. Found: C, 63.34; H, 4.35; N, 6.14.

4.7. Ethyl 3-amino-4-bromo-1*H*-pyrrole-2-carboxylate (17)

To a cooled solution of ethyl 3-amino-1*H*-pyrrole-2-carboxylate (4 g, 26.6 mmol) in a mixture of chloroform (15 mL) and acetic acid (15 mL), was slowly added *N*-bromosuccinimide (4.7 g, 26.6 mmol). The reaction mixture was stirred at rt for 1 h 30, diluted with water (100 mL), and extracted with ethyl acetate (2× 100 mL). The combined organic layers were washed with brine (2× 100 mL), dried ($MgSO_4$), and evaporated to give a yellow oil which was purified by silica gel chromatography, eluting by cyclohexane/ethyl acetate (2:1) to furnish amide **17** as a yellow solid (2.2 g, 40%). Mp 92 °C. IR (KBr): ν = 3402, 3301, 3202, 3131, 2991, 2869, 1674(CO), 1614, 1431, 1133, 769, 589 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.4 (br s, 1H, NH), 6.76 (s, 1H, H_5), 4.3 (m, 4H, NH_2 +OCH_2), 1.35 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.32, 133.82, 129.61, 122.05, 87.78, 60.02, 14.65. MS (EI^+) m/z: 234.2 (M^+), 232.2 (M^-). Anal. Calcd for $C_7H_9BrN_2O_2$: C, 36.07; H, 3.89; N, 12.02. Found: C, 36.32; H, 3.70; N, 12.31.

4.8. Typical Suzuki cross-coupling reaction

4.8.1. 3-(4-Methoxyphenyl)-1-methylpyrrolo[2,3-*b*] pyrrolizin-8(1*H*)-one (24). To a solution of tripentone 22 (30 mg, 0.19 mmol) in DMF (2 mL) under argon were successively added $Pd(PPh_3)_4$ (6×10^{-3} mmol, 5%), 4-methoxyphenylboronic acid (0.3 mmol) and the mixture was heated at 70 °C. Sodium carbonate (1.07 mmol) dissolved in water was then added and the reaction mixture was stirred at 110 °C under argon for 14 h and extracted with ethyl acetate (2× 100 mL). The combined organic layers were washed with brine (2× 100 mL), dried ($MgSO_4$), and evaporated to give a yellow oil which was purified by silica gel chromatography, eluting by cyclohexane/ethyl acetate (3:2) to furnish tripentone 24 as an orange solid (30 mg, 90%). Mp 180 °C. IR (KBr): ν = 3115, 2920, 1714(CO), 1682, 1506, 1395, 1249, 833 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, J = 8.5 Hz, 2H, H_{arom}), 6.95 (d, J = 8.5 Hz, 2H, H_{arom}), 6.85 (d, J = 2.7 Hz, 1H, H_5), 6.60 (s, 1H, H_2), 6.53 (d, J = 3.9 Hz, 1H, H_7), 5.96 (dd, J = 2.7, 3.4 Hz, 1H, H_{-6}), 3.84 (s, 3H, OCH_3), 3.73 (s, 3H, NCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.84, 158.83, 145.34, 131.65, 130.35, 127.85, 124.71, 120.98, 120.72, 114.51, 113.21, 113.77, 111.85, 55.37, 34.74. MS (EI^+) m/z: 278.1. Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.34; H, 5.12; N, 10.14.

4.8.2. 3-(4-Methoxyphenyl)-1-methylpyrrolo[2,3-*b*]pyrrolizin-8(1*H*)-one (25). This compound was obtained from **22** as described for **24** and using 6-methoxypyridin-3-boronic acid as an orange solid in 87% yield. Mp 184 °C. IR (KBr): ν = 3108, 2924, 2852, 1659(CO), 1494, 1392, 1279, 1030, 706 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.27 (d, J = 2.4 Hz, 1H, $H_{2'}$), 7.63 (dd, J = 2.4, 8.5 Hz, 1H, $H_{6'}$), 6.55 (dd, J = 0.8,

2.7 Hz, 1H, H_5), 6.81 (d, $J = 8.5$ Hz, 1H, $H_{5'}$), 6.62 (s, 1H, H_2), 6.54 (dd, $J = 0.8$, 3.6 Hz, 1H, H_7), 5.98 (dd, $J = 2.7$, 3.6 Hz, 1H, H_{-6}), 3.97 (s, 3H, OCH_3), 3.75 (s, 3H, NCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 168.70$, 152.64, 144.59, 137.01, 134.75, 127.69, 121.48, 120.85, 120.62, 119.96, 119.15, 113.66, 112.10, 111.28, 53.61, 34.84. MS (EI^+) *m/z*: 279.2. Anal. Calcd for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.04. Found: C, 68.75; H, 4.43; N, 15.21.

4.9. Pharmacology. Standard proliferation assay

The principle of this assay and its application to anticancer drug screening have been the subject of publications.[13] Adherent cells were trypsinized and seeded in 96-well microplates at the indicated densities, previously determined to maintain control cells in the exponential phase of growth for the duration of the experiment and to obtain a linear relationship between the optical density and the number of viable cells.[14] The plates were incubated with the tested compounds for four doubling times, the maximum duration being 7 days. At the end of this period, an amount of 15 μL of 5 mg/mL 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT, Sigma Chemical Co., St. Louis, MO) was added to each well and the plates were incubated for 4 h at 37 °C. The medium was aspirated, and the formazan was solubilized by 100 μL DMSO. The optical density (OD) was read at 540 nm with a plate reader (Multiskan MCC, Labsystem) connected to a computer. The percentage of growth was calculated for each well: % growth [(OD treated cells)/(OD control cells)] × 100. The percentages of growth of the tri- or hexaplicate were then averaged and plotted as a function of the log of the concentration. The IC_{50} (concentration reducing by 50% of the OD) was calculated by a linear regression performed on the linear zone of the curve.

References and notes

1. Lisowski, V.; Enguehard, C.; Lancelot, J. C.; Caignard, D.-H.; Lambel, S.; Leonce, S.; Pierré, A.; Atassi, G.; Renard, P.; Rault, S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2205.
2. Lisowski, V.; Leonce, S.; Kraus-Berthier, L.; Sopkova-de Oliveira Santos, J.; Pierré, A.; Atassi, G.; Caignard, D.-H.; Renard, P.; Rault, S. *J. Med. Chem.* **2004**, *47*, 1448.
3. Plowman, J.; Dykes, D. J.; Hollingshead, M.; Simpson-Herren, L.; Alley, M. C. In *Anticancer Drug Development Guide: Preclinical Screening, Clinical Trials and Approval*; Teicher, B., Ed.; Humana Press: Totowa, NJ, 1997; pp 101–125.
4. Malzert-Fréon, A.; Vrignaud, S.; Saulnier, P.; Lisowski, V.; Rault, S. *Pharm. Res.* **2006**, *320*, 157.
5. Rochais, C.; Lisowski, V.; Dallemagne, P.; Rault, S. *Tetrahedron* **2004**, *60*, 2267.
6. Elliot, A. J.; Morris, P. E.; Petty, S. L.; William, C. H. *J. Org. Chem.* **1997**, *62*, 8071.
7. Rochais, C.; Lisowski, V.; Dallemagne, P.; Rault, S. *Tetrahedron Lett.* **2004**, *45*, 6353.
8. Cardinaud, I.; Gueffier, A.; Debouzy, J. C.; Milhared, J. C.; Chapat, J. P. *Heterocycles* **1993**, *36*, 2513.
9. Clauson-Kaas, N.; Zdenek, T. *Acta Chem. Scand.* **1952**, *6*, 667.
10. Furneaux, R. H.; Tyler, P. C. *J. Org. Chem.* **1999**, *64*, 8411.
11. Parry, P. R.; Wang, C.; Batsanov, A. S.; Bryce, M. R.; Tarbit, B. *J. Org. Chem.* **2002**, *67*, 7541.
12. Monks, A.; Scudiero, D.; Skekan, P.; Shoemaker, R.; Paull, K.; Viscita, D.; Hose, C.; Langley, J.; Cronise, P.; Vaigro-Wolff, A. *J. Natl. Cancer Inst.* **1991**, *83*, 757.
13. Alley, M. C.; Scudiero, D. A.; Monks, A.; Hursey, M. L.; Czerwinski, M. J.; Fine, D. L.; Abott, B. J.; Mayo, J. G.; Shoemaker, R. H.; Boyd, M. R. *Cancer Res.* **1988**, *48*, 589.
14. Pierre, A.; Krauss-Berthier, L.; Atassi, G.; Cros, S.; Poupon, M. F.; Lavielle, G.; Berlion, M.; Bizzari, J. P. *Cancer Res.* **1991**, *51*, 2312.