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Synthesis of new tetracyclic paullone derivatives as potential CDK inhibitors

Abstract: Synthetic efforts towards new tetracyclic heterocycles bearing the pyrrolo[2′,3′:5,6]azepino[4,3-*b*]indol-4(11*H*)-one core are described. Synthesized tetracyclic compounds are the first analogs, structurally related to protein kinase inhibitors paullones which incorporate an azepinone, an indole and a pyrrole ring. The synthetic approach involves palladium mediated intramolecular Heck coupling as a key step.

Keywords: azepinone; Heck coupling; kinase tetracyclic core; paullones.

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Introduction

Protein kinases are key components of many important signaling pathways related to vital biological processes (Mannig et al., 2002). Overexpression or hyperactivation of kinases has been implicated in pathological disorders such as cancer, inflammation, neurodegenerative and metabolic disorders. Over the past decade, a considerable amount of research has been conducted on the discovery of novel small molecules with selective kinase inhibitory activities for the targeted and personalized treatment of these diseases (Jänne et al., 2009; Zhang et al., 2009). Among other kinases, cyclin-dependent kinases (CDKs) play a pivotal role in cell cycle and transcription regulation (Malumbres, 2011). Deregulation of CDK activity or/and alterations of the expression of cyclins is a common pathological aberration which occurs in different tumor types (Malumbres and Barbacid, 2005, 2009; Musgrove et al., 2011). Small heterocycles of diverse chemical origin have been confirmed as either broad range or selective CDK inhibitors (Cicenas and Valius, 2011). The vast majority of them act as ATP competitors, targeting the ATP binding site through the formation of hydrogen bonds and hydrophobic interactions.

Paullones (**1**, **2** in Figure 1) (Tolle and Kunick, 2011), a family of synthetic benzazepinone derivatives, were initially identified as CDK inhibitors (Schultz et al., 1999; Zaharevitz et al., 1999), but soon their interesting biological activities against other kinases such as GSK-3β (Leost et al., 2000) or molecular targets were revealed. Structurally, paullone basic scaffold is a fused tetracyclic ring system which incorporates seven-membered lactam, indole and benzene moieties. As confirmed from crystal structures of alsterpaullone (**2**) with GSK-3β (Bertrand et al., 2003) and estimated from related molecular modeling studies (Zaharevitz et al., 1999; Gussio et al., 2000), the endocylic amide moiety comprises a unique structural feature of these compounds which is implicated in crucial interactions with amino acid residues of the ATP binding site and substantially contributes to their bioactivity.

It should be noted that the azepinone framework occurs as part of the structure of many bioactive heterocycles. For instance, the marine natural product hymenialdisine (**3**) has been shown to exhibit potent CDK, GSK-3, checkpoint kinase (Chk) 1 and 2 inhibitory activity (Nguyen and Tepe, 2009), whereas hymenialdisine indoloazepinone derivative **4** is a potent cytokine (Sharma et al., 2004) and Chk1, 2 inhibitor (Sharma and Tepe, 2004). Various azepino[3,4-*b*]indole derivatives **5** have shown interesting kinase inhibitory activities (Wan et al., 2004), whereas azepino[3,4-*b*]indole-1,5-diones either substituted in the 4-position (**6**) or fused with carbocyles (**7a–c**) have been arising as promising bioactive scaffolds (Perron et al., 2003, 2004). Marine natural products Latonduines A (**8**) and B (**9**) (Linington et al., 2003) bear a pyrrolo[2,3-*c*]azepinone core fused with a pyrimidine ring. Structurally related heteroazepinones **10** show cytotoxic activities (Putey et al., 2007). Finally, C5-alkylated indolobenzazepinones **11** and modified analogs show interesting tubulin polymerization inhibitory activity (Keller et al., 2008; Putey et al., 2009).

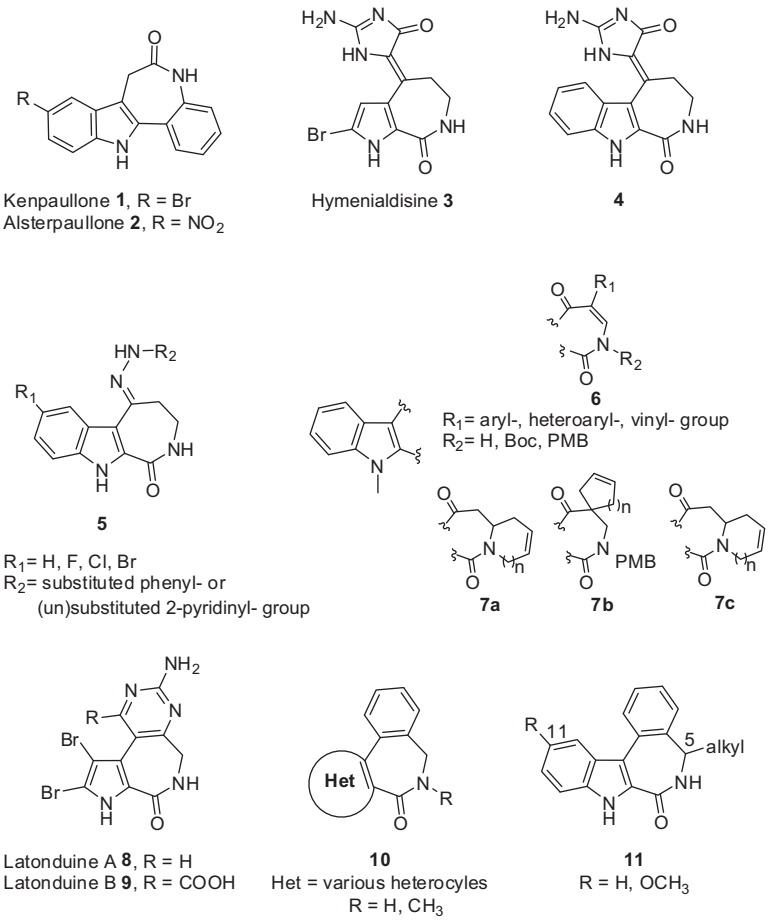

Figure 1 Structures of natural and synthetic bioactive azepinone derivatives.

Additionally, a diverse library of paullone derivatives is available and has been extensively studied for their bioactivity. Aside from the insertion of various moieties at distinct positions of the parent paullone scaffold, modifications of the benzazepinone or/and indole part have been introduced (Tolle and Kunick, 2011). Precisely, synthesis of fused tetracyclic paullone derivatives which incorporate a pyridine or a thiophene instead of the benzene ring and/or an aza-indole or an imidazo[1,2-*a*]pyridine instead of the indole ring has been achieved (Tolle and Kunick, 2011).

Although access to the paullone basic core has been achieved via a variety of synthetic approaches (Kunick, 1992; Baudoin et al., 2002; Bremner et al., 2005; Joucla et al., 2005; Avila-Zarraga et al., 2006; Henry et al., 2006; Soto et al., 2012), fused tetracyclic paullone derivatives which involve a pyrrole, an indole and a seven membered lactam ring have not yet appeared in the literature, suggesting a potential synthetic target with unexplored bioactivity. Moreover, considering that such derivatives might be proved valuable tools for further elucidation of structure-activity relations and as part of our ongoing efforts in the field of CDK inhibitors (Fousteris et al., 2008), we designed and synthesized a number of derivatives which bear the new tetracyclic core pyrrolo[2′,3′:5,6]azepino[4,3-*b*]indol-4(11*H*)-one **12** which is depicted in Figure 2. Apart from the maintenance of requisite structural features, such as the azepinone and indole moiety, which ensure efficient protein kinase inhibition, the introduction of the functionalized pyrrole ring to the fused tetracyclic core was not only considered a synthetic challenge but also it might give rise to the development of a new generation of paullones with potential bioactivity.

Herein, we describe our synthetic efforts towards the construction of this new tetracyclic core which involves the application of an intramolecular Heck coupling reaction as the key step.

Results and discussion

A retrosynthetic plan towards the new tetracyclic core **12** is presented in Scheme 1. The seven membered lactam

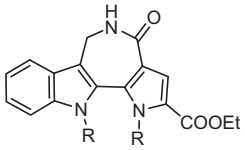

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Figure 2 New tetracyclic paullone derivatives.

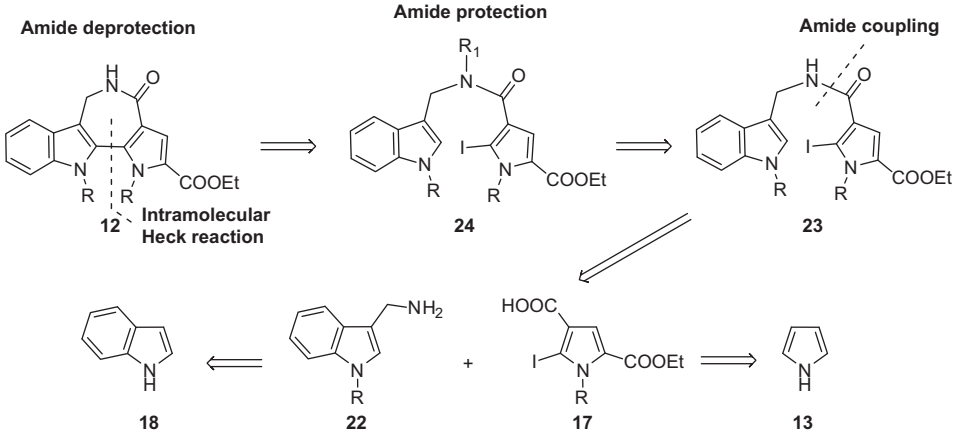
ring would be assembled via Pd-catalyzed intramolecular Heck coupling of the functionalized *N*-protected amides **24**. The latter would be prepared by *N*-protection of the amide conjugates **23**. Intermediates **23** could be obtained by amide coupling of appropriate *N*-protected pyrrole **17** and indole precursors **22**, which would be derived via substitution of the corresponding basic heterocyclic cores **13** and **18**, respectively.

Starting from pyrrole **13** and the following well-established three-step procedure (trichloroacetylation, ethanolysis, formylation), the known pyrrole-3-carboxaldehyde **14** (Bailey et al., 1971; Garrido et al., 1988) was obtained (Scheme 2). Subsequently, iodination of the intermediate **14** using I_2/HIO_3 followed by chromatographic separation of the regioisomeric products afforded the desired iodinated isomer **15** (Farnier and Fournari, 1973) in moderate yield. This compound was *N*-protected using either ethoxymethyl chloride (EOM-Cl), 2-(trimethylsilyl)ethoxymethyl chloride (SEM-Cl) or benzyloxymethyl chloride (BOM-Cl) in the presence of NaH to the corresponding aldehydes **16a–c**. The selection of these specific alkyl halides was based on previous observations which denoted that *N*-electron-donating protective groups promoted the intramolecular palladium mediated cyclization of related indolo- and pyrrolo-amide conjugates (Joucla et al., 2005). The pyrrole-4-carboxylic acids **17a–c** were obtained upon treatment of **16a–c** with $KMnO_4$ in good yields.

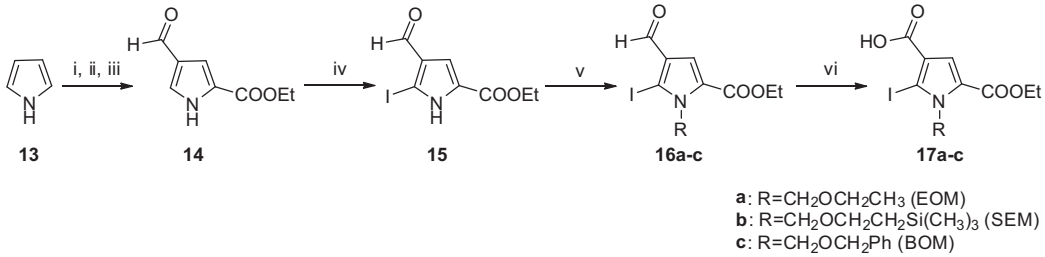
The synthesis of the indole precursors started from indole **18** which was formylated under Vilsmeier-Haack conditions giving the known indole-3-carboxaldehyde **19** (Xu and Fan, 2011) (Scheme 3). *N*-Indole protection with the aforementioned alkyl halides provided the intermediates **20a–c**. Oxidation of the aldehydes **20a–c** led to a mixture of *Z* and *E* oximes **21a–c** which upon reduction with $NiCl_2{\cdot}6H_2O/NaBH_4$ afforded the *N*-protected indol-3-ylmethylamines **22a–c**.

Amide coupling of the pyrrole-4-carboxylic acids **17a–c** with the corresponding indole-3-methylamines **22a–c** in the presence of *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (EDCI) and 4-(dimethylamino)pyridine (DMAP) furnished the amide conjugates **23a–c** in good yields (Scheme 4). Subsequently, *N*-amide protection was achieved upon treatment with Boc anhydride (Boc_2O) in the presence of DMAP in acetonitrile affording the functionalized intermediates **24a–c** which were subjected to palladium mediated intramolecular Heck reaction.

Initially, the investigation of Heck coupling conditions was performed using amide **24a** as substrate. The results of these trial experiments are presented in Table 1. Particularly, Heck cyclization of **24a** was explored using Ph_3P as the ligand, $Pd(AcO)_2$ as the catalyst and Ag_2CO_3 as the base in anhydrous DMF, based on the results of previous studies which had indicated the effectiveness of this combination of reagents in the synthesis of structurally related polycyclic heterocycles (Mouaddib et al., 2000; Joucla et al., 2005). Unfortunately, changing the amounts of the reagents (ligand, catalyst, base) or performing the reaction under various conditions (temperature, time) resulted either in recovery of deiodinated uncyclized amide (Table 1, entries 1–4) or decomposition of the starting material (entry 5). Nevertheless, using 0.2 equiv. of PPh_3, 0.1 equiv. of $Pd(AcO)_2$, 4 equiv. of Ag_2CO_3 and increasing the reaction



Scheme 1 Retrosynthetic analysis of the new tetracyclic core **12**.



Scheme 2 Reagents and conditions: (i) (Bailey et al., 1971) (1) Cl_3CCOCl, $(C_2H_5)_2O$, rt, 1 h (2) K_2CO_3, H_2O, 79%; (ii) (Bailey et al., 1971) Na/C_2H_5OH, rt, 0.5 h, 91%; (iii) (Garrido et al., 1988) $Cl_2CCH_2OCH_3$, $AlCl_3$, CH_2Cl_2/CH_3NO_2, -20°C, 18 h, 80%; (iv) (Farnier and Fournari, 1973) I_2, HIO_3, H_2SO_4, $CH_3COOH/H_2O/CCl_4$, 5 h, 80°C, 33%; (v) RCl, NaH, DMF, rt, 2 h, R = EOM, 95%; R = SEM, 94%; R = BOM, 70%; (vi) $KMnO_4$, acetone/H_2O, rt, 5.5 h, R = EOM, 80%; R = SEM, 50%; R = BOM, 80%.

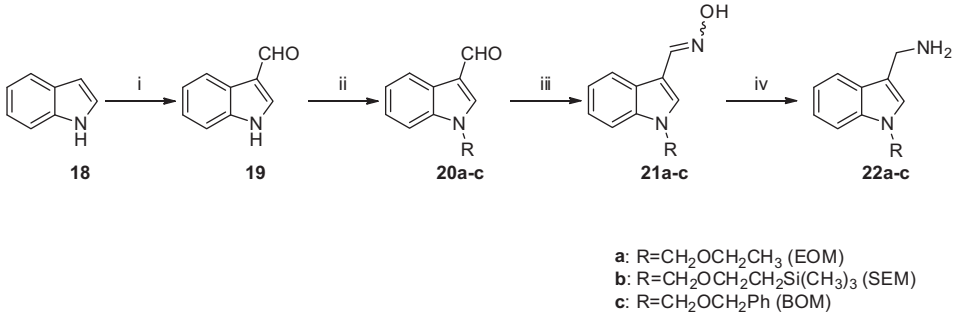
temperature almost to reflux, the tetracyclic compound **25a** was obtained in only 0.5 h and in a moderate yield of 32% (entry 6). With this result in hand, the cyclization of substrates **24b,c** was attempted under similar conditions. The tetracyclic derivatives **25b,c** were obtained in slightly improved yields of 41% and 40%, respectively.

Subsequently, cleavage of the *N*-Boc protecting group from compounds **25a–c** under acidic conditions afforded the new tetracyclic derivatives **12a–c** which bear the requisite *NH*-free azepinone framework (Scheme 5).

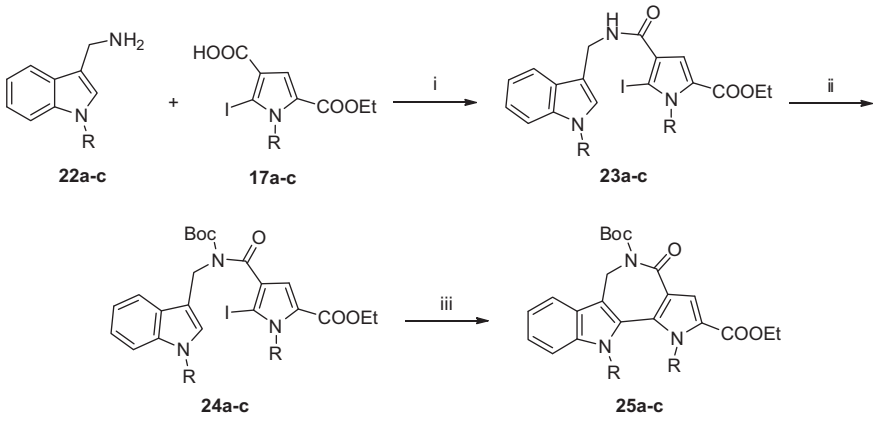
Next, we focused our efforts on the removal of the *N*-indole and *N*-pyrrole protecting groups aiming at the generation of the fully unprotected tetracyclic core **26** (Scheme 5). The results of representative trials are summarized in Table 2. Various acidic conditions were applied for cleavage of the EOM protecting group from **12a** using excess of HCl either in CH_3OH or in 1,4-dioxane under the indicated time and temperature (Table 2, entries 1–7), but all these attempts resulted in decomposition of the starting material. Moreover, milder conditions were tried using $BF_3{\cdot}OEt_2$ and benzyltrimethylammonium hydroxide (Triton B) in CH_2Cl_2 following a two-step procedure (entry 8), but also decomposition of **12a** was detected. Similarly, removal of the SEM protecting group from **12b** was attempted using either HCl in CH_3OH (entries 9–13) or $BF_3{\cdot}OEt_2$ and Triton B in CH_2Cl_2 (entry 14). Despite extensive trials, none of them succeeded to the complete removal of both SEM groups from pyrrole and indole nitrogen atom. These attempts led to an inseparable mixture of partially cleaved products according to ^{1}H NMR analysis. Additionally, treating **12b** under basic conditions with excess of tetrabutylammonium fluoride (TBAF) and ethylenediamine (entry 15) unfortunately led to the same result. Lastly, BOM deprotection of **12c** was tried under hydrogenolysis conditions using $Pd(OH)_2$ as catalyst (entry 16). Although cleavage of the benzyl ether was effected, treatment of the partially cleaved intermediate with 1 N NaOH in 1,4-dioxane did not result in the generation of fully unprotected compound **26**, which was confirmed by ^{1}H NMR analysis.

Conclusions

The synthetic endeavors towards the construction of the new tetracyclic core pyrrolo[2′,3′:5,6]azepino[4,3-b]indol-4(11*H*)-one **12** are described. This new core incorporates as a privileged structural feature an azepinone framework,



Scheme 3 Reagents and conditions: (i) (Xu and Fan, 2011) $POCl_3$, DMF, 35°C, 1 h, then 20% aq. NaOH, reflux, 6 h, 96%; (ii) RCl, NaH, DMF, rt, 2 h, R = EOM, 89%; R = SEM, 98%; R = BOM, 98%; (iii) $H_2NOH{\cdot}HCl$, Na_2CO_3, C_2H_5OH/H_2O, reflux, 2–5.5 h, R = EOM, 95%; R = SEM, 89%, R = BOM, 96%; (iv) $NiCl_2.6H_2O$, $NaBH_4$, MeOH, rt, 10 min, R = EOM, 100%; R = SEM, 60%; R = BOM, 93%.



Scheme 4 Reagents and conditions: (i) EDCI·HCl, DMAP, CH_2Cl_2, 0°C, 4 h, then rt 19 h, R = EOM, 80%; R = SEM, 70%; R = BOM, 62%; (ii) Boc_2O, DMAP, CH_3CN, 21 h, rt, R = EOM, 63%; R = SEM, 63%, R = BOM, 62%; (iii) $Pd(OAc)_2$, PPh_3, Ag_2CO_3, DMF, 0.5 h, 135°C, R = EOM, 32%; R = SEM, 41%; R = BOM, 40%.

which also exists in the structure of many protein kinase inhibitors such as paullones, hymenialdisine and structurally related bioactive compounds.

Our synthetic approach involves the amide coupling of appropriate substituted *N*-protected pyrrole **17a–c** and indole **22a–c** precursors and the subsequent *N*-Boc protection of the amide conjugates **23a–c**. The fully protected amides **24a–c** were inserted in intramolecular palladium mediated Heck coupling reaction. After optimization of the experimental conditions, Heck coupling proceeded effectively affording the tetracylic derivatives **25a–c** in moderate yields. Boc deprotection provided access to the *N*-amide free derivatives **12a–c** which can be considered as the first paullone analogs which incorporate the biologically important seven membered lactam, an indole moiety and a 2-ethoxycarbonylpyrrole function. The latter could comprise an entry point of further functionalization and possible access to a diverse library of compounds. Extensive efforts to remove EOM, SEM and BOM protecting groups from tetracyclic derivatives **12a–c** under various cleavage conditions unfortunately did not lead to fully unprotected skeleton **26**.

Biological evaluation of the new derivatives **12a–c** as potential protein kinase inhibitors is in progress and the results will be published in due course.

Entry	SM (equiv.)	PPh3 (equiv.)	Pd(AcO)2 (equiv.)	Ag2CO3 (equiv.)	t (h)	T (°C)	25[a] (%)
1	1	0.1	0.05	2	21	100	[a]
2	1	0.1	0.05	2	4	100	[a]
3	1	0.1	0.05	2	2	110	[a]
4	1	0.2	0.1	4	1	100	[a]
5	1	0.4	0.2	2	4	100	[b]
6	1	0.2	0.1	4	0.5	135	32

Table 1 Heck coupling of compound **24a**.
[a]Deiodinated **24a** was recovered.
[b]Decomposition of **24a** was detected.

Experimental section

General

Anhydrous solvents were obtained according to literature procedures. Melting points were determined on a Kallenkamp melting point apparatus in capillary tubes and are uncorrected. The IR spectra were recorded on a FT-IR Jasco spectrophotometer. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded using a Brucker DPX 400 MHz spectrometer. Chemical shifts are relative to $CHCl_3$ (7.26 ppm) or DMSO (2.50 ppm) and the following abbreviations are used: broad (br), singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m). Liquid chromatography-mass spectrometry (LC-MS) was carried out on a Waters Micromas 2696 instrument running in positive ion electrospray mode, employing a Lichrospher RP-8 column (5 μm; 4 × 150 mm) and a gradient elution from 30% to 100% acetonitrile in water within 30 min (flow rate 1 mL/min). Thin layer chromatography (TLC) was carried out on Merck precoated silica gel plates (Kieselgel 60 F_{254}). Visualization was achieved by exposure to iodide vapors or/and under UV light (254 and 365 nm). Column chromatography was performed using silica gel (Merck, 70–230 mesh).

Compounds **14** (Bailey et al., 1971; Garrido et al., 1988), **15** (Farnier and Fournari, 1973) and **19** (Xu and Fan, 2011) were prepared according to methods reported in the literature.

General procedure for the synthesis of the *N*-protected pyrrole 16a–c and indole 20a–c intermediates

To an ice-cooled solution of ethyl 4-formyl-5-iodo-1*H*-pyrrole-2-carboxylate (**15**, 100 mg, 0.34 mmol) in dry DMF (1 mL), sodium hydride (60% dispersion in mineral oil, 15.3 mg, 0.51 mmol) was added under argon atmosphere. The cooling bath was removed and the mixture was allowed to warm to room temperature and stirred for 1 h. The corresponding chloride (0.17 mmol) was added dropwise and the mixture was stirred for 2 h at room temperature. Then, the mixture was quenched with water and extracted twice with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The crude residue was purified by silica gel flash column chromatography (0–20% EtOAc in *n*-hexane) to afford the corresponding *N*-protected pyrrole **16a–c** and indole **20a–c** derivatives.

In a similar way, the reaction of indole-3-carboxaldehyde (**19**) instead of compound **15** under otherwise identical conditions yielded indole derivatives **20a–c**.

Ethyl 1-ethoxymethyl-4-formyl-5-iodo-1*H*-pyrrole-2-carboxylate (16a) Yield 95%; white powder; mp 77–80°C; ^{1}H NMR ($CDCl_3$): δ 1.19 (t, *J* = 7.0 Hz, 1H), 1.35 (t, *J* = 7.1 Hz, 3H), 3.57 (q, *J* = 7.0 Hz, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 5.92 (s, 2H), 7.49 (s, 1H), 9.71 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 187.0, 159.8, 128.6, 127.2, 118.9, 91.3, 76.8, 64.3, 60.9, 14.9, 14.2; MS: m/z 374.22 $[M+Na]^+$.

Ethyl 4-formyl-5-iodo-1-[2-(trimethylsilyl)ethoxymethyl]-1*H*-pyrrole-2-carboxylate (16b) Yield 94%; oil; ^{1}H NMR ($CDCl_3$): δ -0.05 (s, 9H), 0.88–0.92 (m, 2H), 1.33 (t, *J* = 7.1 Hz, 3H), 3.57–3.62 (m, 2H), 4.29 (q, *J* = 7.1 Hz, 2H), 5.89 (s, 2H), 7.47 (s, 1H), 9.69 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 187.0, 159.8, 128.6, 127.1, 118.9, 91.4, 76.5, 66.4, 60.9, 17.8, 14.2, -1.5 (3C); MS: m/z 446.02 $[M+Na]^+$.

Ethyl 1-(benzyloxymethyl)-5-iodo-4-formyl-pyrrole-2-carboxylate (16c) Yield 70%; oil; ^{1}H NMR ($CDCl_3$) δ 1.36 (t, J = 7.1 Hz, 3H), 4.32 (q, J = 7.1 Hz, 2H), 4.62 (s, 2H), 6.01 (s, 2H), 7.25–7.36 (m, 5H), 7.46 (s, 1H), 9.71 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 186.9, 159.8, 136.9, 128.5, 128.4 (2C), 127.9, 127.5 (2C), 127.3, 118.9, 91.4, 76.7, 70.8, 61.0, 14.2; MS: m/z 436.21 $[M+Na]^+$.

1-(Ethoxymethyl)-3-formyl-1*H*-indole (20a) Yield 89%; white powder; mp 154–157°C; ^{1}H NMR ($CDCl_3$): δ 1.18 (t, *J* = 7.0 Hz, 3H), 3.49 (q, *J* = 7.0 Hz, 2H), 5.56 (s, 2H), 7.32–7.39 (m, 2H), 7.54 (dd, *J* = 6.4, 2.3 Hz, 1H), 7.80 (s, 1H), 8.31 (dd, *J* = 6.3, 2.7 Hz, 1H), 10.06 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 184.8, 138.2, 137.1, 125.4, 124.4, 123.2, 122.0, 118.8, 110.6, 76.7, 64.5, 14.7; MS: m/z 204.05 $[M+H]^+$.

3-Formyl-1-[2-(trimethylsilyl)ethoxymethyl]-1*H*-indole (20b) Yield 98%; oil; ^{1}H NMR ($CDCl_3$): δ -0.08 (s, 9H), 0.87–0.93 (m, 2H), 3.49 (t, *J* = 8.5 Hz, 2H), 5.50 (s, 2H), 7.28–7.36 (m, 2H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.77 (s, 1H), 8.28 (d, *J* = 8.1 Hz, 1H), 10.00 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 184.8, 138.1, 137.2, 125.5, 124.3, 123.2, 122.0, 118.8, 110.6, 76.4, 66.5, 17.6, -1.5 (3C); MS: m/z 298.28 $[M+Na]^+$.

1-(Benzyloxymethyl)-3-formyl-1*H*-indole (20c) Yield 98%; white powder; mp 53–56°C; ^{1}H NMR ($CDCl_3$): δ 4.48 (s, 2H), 5.59 (s, 2H), 7.26–7.39 (m, 7H), 7.53 (ddd, *J* = 4.5, 2.2, 0.7 Hz, 1H), 7.76 (s, 1H), 8.33 (ddd, *J* = 3.8, 2.4, 0.7 Hz, 1H), 10.06 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 184.9, 138.2, 137.1, 136.1, 128.5 (2C), 128.21, 127.8 (2C), 125.5, 124.5, 123.4, 122.0, 119.0, 110.7, 75.6, 70.2; MS: m/z 288.26 $[M+Na]^+$.

General procedure for the synthesis of pyrrole-4-carboxylic acids 17a–c

To a solution of the appropriate pyrrole-4-carboxaldehyde **16a–c** (0.29 mmol) in acetone (25 mL), a solution of potassium permanganate (90.6 mg, 0.57 mmol) in acetone/water (1:1) (10 mL) was added dropwise at room temperature. The mixture was stirred at the same temperature for 5.5 h. Then, a solution of sodium hydrogen sulfate 10% in 1 N HCl (100 mL) was added. The mixture was concentrated under reduced pressure to remove the acetone, and the aqueous phase was extracted three times with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the corresponding *N*-protected pyrrole-4-carboxylic acids **17a–c**.

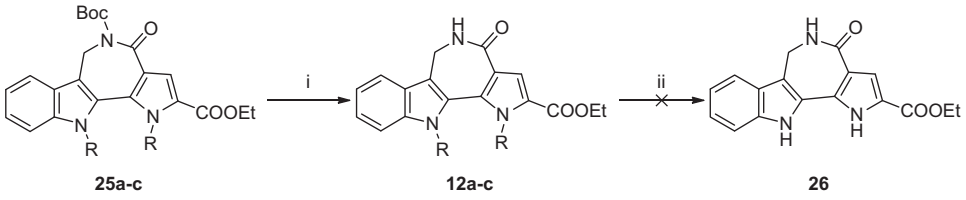
5-Ethoxycarbonyl-1-ethoxymethyl-2-iodo-1*H*-pyrrole-3-carboxylic acid (17a) Yield 80%; white powder; mp 186–189°C; ^{1}H NMR ($CDCl_3$): δ 1.18 (t, *J* = 7.0 Hz, 3H), 1.36 (t, *J* = 7.1 Hz, 3H), 3.57 (q, *J* = 7.0 Hz, 2H), 4.32 (q, *J* = 7.1 Hz, 2H), 5.94 (s, 2H), 7.61 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 167.6, 159.7, 127.6, 121.8, 119.4, 89.2, 77.2, 64.2, 60.8, 15.00, 14.2; MS: m/z 390.22 $[M+Na]^+$.

5-Ethoxycarbonyl-2-iodo-1-[2-(trimethylsilyl)ethoxymethyl]-1*H*-pyrrole-3-carboxylic acid (17b) Yield 50%; white powder; mp 119°C; ^{1}H NMR (DMSO-d_6): δ -0.07 (s, 9H), 0.79–0.84 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 3.50–3.56 (m, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 5.79 (s, 2H), 7.33 (s, 1H), 12.55 (br s, 1H); ^{13}C NMR (DMSO-d_6): δ 163.5, 159.1, 126.2, 120.5, 120.2, 92.7, 76.5, 65.3, 60.3, 17.2, 14.0, -1.4 (3 C); MS: m/z 462.08 $[M+Na]^+$.

1-Benzyloxymethyl-5-ethoxycarbonyl-2-iodo-1*H*-pyrrole-3-carboxylic acid (17c) Yield 80%; white powder; mp 114–117°C; ^{1}H NMR ($CDCl_3$): δ 1.32 (t, *J* = 6.6 Hz, 3H), 4.26 (q, *J* = 7.1 Hz, 2H), 4.57 (s, 2H), 5.99 (s, 2H), 7.18–7.66 (m, 5H), 8.08 (d, *J* = 6.9 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 162.2, 159.8, 137.1, 130.2, 128.5, 128.4 (2C), 127.9, 127.6 (2C), 122.0, 89.4, 77.3, 70.8, 60.9, 14.3; MS: m/z 452.19 $[M+Na]^+$.

General synthesis of indole-3-carboxaldehyde oximes 21a–c

To a solution of the appropriate indole-3-carboxaldehyde **20a–c** (1.49 mmol) in ethanol (3 mL), a solution of hydroxylamine hydrochloride (162 mg, 2.33 mmol) and sodium carbonate (113 mg, 1.07 mmol) in water (1.5 mL) was added dropwise. The mixture was heated for



Scheme 5 Reagents and conditions: (i) CF_3COOH, CH_2Cl_2, rt, 1 h, R = EOM, 66%; R = SEM, 45%; R = BOM, 30%; (ii) See Table 2.

2–5 h. Then, the ethanol was removed under reduced pressure and the residue was extracted three times with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (70% EtOAc in *n*-hexane) to afford the corresponding indole-3-carboxaldehyde oximes **21a–c**.

(*E*, *Z*)-1-(Ethoxymethyl)-1*H*-indole-3-carboxaldehyde oxime (21a) Yield 95%; white powder; mp 90–91°C; mixture of isomers, 48:42; ^{1}H NMR ($CDCl_3$): δ 1.03–1.07 (m, 6H), 3.35–3.48 (m, 4H), 5.57 (s, 2H, minor), 5.64 (s, 2H, major), 7.17 (dd, *J* = 15.3, 7.8 Hz, 2H), 7.25 (t, *J* = 7.5 Hz, 2H), 7.60 (t, *J* = 7.2 Hz, 2H), 7.75 (s, 1H, minor), 7.81 (s, 1H, major), 7.90 (d, *J* = 7.8 Hz, 1H, major), 8.00 (d, *J* = 7.8 Hz, 1H, minor), 8.26 (s, 1H, minor), 8.37 (s, 1H, major), 10.64 (s, 1H, minor), 11.37 (s, 1H, major);^{13}C NMR ($CDCl_3$): δ 145.6, 137.2, 135.4, 134.2, 130.3, 125.7, 123.5, 123.1, 122.1, 121.7, 121.5, 118.3, 110.6, 110.2, 110.1, 76.6, 76.2, 64.2, 64.2, 14.8, 14.8; MS: m/z 241.21 $[M+Na]^+$.

(*E*, *Z*)-1-[2-(Trimethylsilyl)ethoxymethyl]-1*H*-indole-3-carboxaldehyde oxime (21b) Yield 89%; white powder; mp 89–91°C; mixture of isomers, 50:50; ^{1}H NMR ($CDCl_3$): δ -0.12 (s, 18H), 1.13–1.23 (m, 4H), 3.39–3.48 (m, 4H), 5.42 (s, 2H), 5.48 (s, 2H), 7.15–7.21 (m, 2H), 7.21–7.28 (m, 2H), 7.33 (s, 1H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.49 (d, *J* = 8.2 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 2H), 8.01–8.05 (m, 1H), 8.28–8.31 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 145.58, 139.4, 137.2, 135.4, 134.4, 130.3, 127.7, 125.7, 123.5, 123.0, 122.0, 121.6, 121.4, 118.3, 110.6, 110.2, 110.0, 106.2, 76.2, 75.8, 66.2, 66.1, 17.7, 17.6, -1.4, -1.5; MS: m/z 313.33 $[M+Na]^+$.

(*E*, *Z*)-1-Benzyloxymethyl-3-formyl-1*H*-indole-3-carboxaldehyde oxime (21c) Yield 96%; oil; mixture of isomers, 49:41; ^{1}H NMR ($CDCl_3$): δ 4.43 (s, 2H, minor), 4.45 (s, 2H, major), 5.54 (s, 2H, minor), 5.61 (s, 2H, major), 7.26–7.39 (m, 16H), 7.48–7.52 (m, 1H, minor), 7.57 (dd, *J* = 7.1, 1.3 Hz, 1H,major), 7.78–7.82 (m, 1H, major), 8.10–8.15 (m, 1H, major), 8.35 (s, 2H); ^{13}C NMR ($CDCl_3$): δ 145.5, 137.1, 136.5, 136.5, 135.3, 134.3, 130.3, 128.5 (2C), 128.45 (2C), 128.04, 127.98, 127.93 (2C), 127.89 (2C), 125.74, 123.56, 123.1, 122.0, 121.8, 121.5, 118.3, 110.6, 110.3, 110.2, 75.5, 75.1, 69.9, 69.8; MS: m/z 281.45 $[M+H]^+$, 303.49 $[M+Na]^+$.

General procedure for the synthesis of indol-3-ylmethylamines 22a–c

To a solution of $NiCl_2{\cdot}6H_2O$ (381 mg, 1.6 mmol) and $NaBH_4$ (61 mg, 1.6 mmol) in methanol (25 mL), a solution of the appropriate

Entry	R	Reagents (equiv.)	Solvent	t (h)	T (°C)	Notes
1	EOM	HCl 1.25 N (10)	CH3OH	1	50	a
2	EOM	HCl 1.25 N (10)	CH3OH	1	80	a
3	EOM	HCl 1.25 N (10)	CH3OH	3	80	a
4	EOM	HCl 1.25 N (15)	CH3OH	2	80	a
5	EOM	HCl 1.25 N (20)	CH3OH	2	80	a
6	EOM	HCl 1 N (1)	1,4-Dioxane	2	80	a
7	EOM	HCl 6 N (10)	1,4-Dioxane	5	80	a
8	EOM	BF3·OEt2 (5)Triton B (0.5)	CH2Cl2	22	0 to rt60	a
9	SEM	HCl 1.25 N (5)	CH3OH	1.6	60	b
10	SEM	HCl 1.25 N (12)	CH3OH	7.5	90	a
11	SEM	HCl 6 N (1)	CH3OH	2	rt	b
12	SEM	HCl 6 N (2)	CH3OH	2	50	b
13	SEM	HCl 12 N (5)	CH3OH	2	90	b
14	SEM	BF3·OEt2 (5)Triton B (0.5)	CH2Cl2	22	0 to rt60	b
15	SEM	TBAF (5)Ethylenediamine (46)	CH2Cl2	6	80	b
16	BOM	H2 (1 atm)Pd(OH)2NaOH (1 N)	THF/C2H5OH1,4-dioxane	2	rt	b

Table 2 Cleavage of *N*-pyrrole and *N*-indole protecting groups from compounds **12a–c**.
[a]Decomposition of **12a** was detected.
[b]Partial cleavage of either SEM or BOM protecting group from **12b** or **12c**, respectively, according to ^{1}H NMR analysis.

indole-3-carboxaldehyde oxime **21a–c** (1.6 mmol) was added followed by the addition of $NaBH_4$ (330 mg, 8.72 mmol). The mixture was stirred for 10 min after which time a black precipitate was filtered off. The filtrate was concentrated under reduced pressure, water was added, the pH was adjusted to 11 with aqueous NH_3 (25%) and the mixture was extracted three times with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford indol-3-ylmethyl amines **22a–c**. In the case of derivative **22b**, the crude residue was purified by silica gel flash column chromatography eluting with 0–4% CH_3OH in CH_2Cl_2.

1-(Ethoxymethyl)-1*H*-indol-3-ylmethylamine (22a) Yield 100%; white powder; mp 126–129°C; ^{1}H NMR ($CDCl_3$/drops of CD_3OD): δ 1.24 (t, *J* = 7.0 Hz, 3H), 3.53 (q, *J* = 7.0 Hz, 2H), 4.12 (s, 2H), 5.57 (s, 2H), 7.23–7.29 (m, 1H), 7.35 (t, *J* = 7.7 Hz, 1H), 7.45 (s, 1H), 7.58 (d, *J* = 8.2 Hz, 1H), 7.71 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 136.9, 127.6, 125.2, 122.3, 119.9, 118.9, 110.0, 75.8, 63.8, 37.4, 14.8; MS: m/z 187.73 $[M\text{-}NH_2]^+$.

1-[2-(Trimethylsilyl)ethoxymethyl]-1*H*-indol-3-ylmethylamine (22b) Yield 60%; oil; ^{1}H NMR ($CDCl_3$/drops of CD_3OD): δ -0.09 (s, 9H), 0.80–0.89 (m, 2H), 3.49 (t, *J* = 7.9 Hz, 2H), 3.99 (s, 2H), 5.50 (s, 2H), 7.03–7.33 (m, 3H), 7.48 (d, *J* = 6.9 Hz, 1H), 7.62 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 136.75, 127.52, 126.81, 122.5, 120.2, 118.9, 112.6, 110.1, 75.4, 65.8, 34.9, 17.6, -1.5 (3C); MS: m/z 260.48 $[M\text{-}NH_2]^+$.

1-(Benzyloxymethyl)-1*H*-indol-3-ylmethyl amine (22c) Yield 93%; white powder; mp 109°C; ^{1}H NMR ($CDCl_3$): δ 4.07 (s, 2H), 4.42 (s, 2H), 5.51 (s, 2H), 7.13 (s, 1H), 7.15–7.20 (m, 1C), 7.24–7.36 (m, 6H), 7.46 (d, *J* = 8.2 Hz, 1H), 7.65 (d, *J* = 7.9 Hz, 1H); MS: m/z 250.31 $[M\text{-}NH_2]^+$.

General procedure for the synthesis of amide conjugates 23a–c

To an ice-cooled solution of the appropriate pyrrole-carboxylic acid **17a–c** (1.33 mmol) and indole-3-ylmethylamine **22a–c** (1.49 mmol) in dry dichloromethane (20 mL), DMAP (166 mg, 1.36 mmol) and EDCI·HCl (287 mg, 1.49 mmol) was added under argon atmosphere and the mixture was stirred at 0°C for 4 h and then at room temperature for an additional 19 h. Water was added, the mixture was acidified (pH 4) with 1 N HCl solution and extracted three times with dichloromethane. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (50% EtOAc in *n*-hexane) to afford the amide **23a–c**.

Ethyl 1-ethoxymethyl-4-{[(1-(ethoxymethyl)-1*H*-indol-3-yl) methyl]carbamoyl}-5-iodo-1*H*-pyrrole-2-carboxylate (23a) Yield 80%; white powder; mp 132–134°C; ^{1}H NMR ($CDCl_3$): δ 1.14–1.18 (m, 6H), 1.32 (t, *J* = 7.1 Hz, 3H), 3.46 (q, *J* = 7.0 Hz, 2H), 3.53 (q, *J* = 7.0 Hz, 2H), 4.27 (q, *J* = 7.1 Hz, 2H), 4.78 (d, *J* = 5.1 Hz, 2H), 5.48 (s, 2H), 5.89 (s, 2H), 6.19 (br s, 1H), 7.20 (dd, *J* = 14.1, 6.3 Hz, 2H), 7.24–7.32 (m, 2H), 7.50 (d, *J* = 8.2 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 162.7, 159.7, 136.8, 127.7, 127.1, 127.1, 123.8, 122.7, 120.4, 119.2, 118.7, 112.5, 110.1, 84.2, 76.9, 75.9, 64.0, 64.0, 60.7, 35.1, 14.9, 14.8, 14.2; MS: m/z 575.95 $[M+Na]^+$.

Ethyl 1-[2-(trimethylsilyl)ethoxymethyl]-4-{[(1-[2-(trimethylsilyl) ethoxymethyl]-1*H*-indol-3-yl)methyl]carbamoyl}-5-iodo-1*H*-pyrrole-2-carboxylate (23b) Yield 70%; oil; ^{1}H NMR ($CDCl_3$): δ -0.10 (s, 9H), -0.09 (s, 9H), 0.82–0.88 (m, 4H), 1.27 (t, *J* = 7.1 Hz, 3H), 3.42–3.48 (m, 2H), 3.49–3.56 (m, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 4.73 (d, *J* = 5.0 Hz, 2H), 5.41 (s, 2H), 5.83 (s, 2H), 6.17 (t, *J* = 4.9 Hz, 1H), 7.14 (dt, *J* = 8.0, 7.6, 0.9 Hz, 1H), 7.17 (s, 1H), 7.21–7.26 (m, 2H), 7.45 (d, *J* = 8.2 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 162.60, 159.63, 136.75, 127.6, 127.0, 126.9, 123.5, 122.5, 120.2, 119.1, 118.7, 112.3, 110.1, 84.3, 76.5, 75.4, 65.9, 65.8, 60.5, 35.0, 17.7, 17.6, 14.2, -1.5 (3C), -1.5 (3C); MS: m/z 334.42 $[M+2H+Na]^+$, 719.92 $[M+Na]^+$, 736.11 $[M+K]^+$.

Ethyl 1-Benzyloxymethyl-4-{[(1-(benzyloxymethyl)-1*H*-indol-3-yl) methyl]carbamoyl}-5-iodo-1*H*-pyrrole-2-carboxylate (23c) Yield 62%; oil; ^{1}H NMR ($CDCl_3$): δ 1.28 (t, *J* = 7.1 Hz, 3H), 4.24 (q, *J* = 7.1 Hz, 2H), 4.40–4.41 (m, 3H), 4.55 (s, 1H), 4.77 (dd, *J* = 11.9, 5.2 Hz, 2H), 5.46 (d, *J* = 4.1 Hz, 3H), 5.93 (s, 1H), 6.37 (t, *J* = 5.1 Hz, 1H), 7.15–7.18 (m, 2H), 7.21–7.31 (m, 10H), 7.32 (s, 1H), 7.45 (d, *J* = 8.1 Hz, 1H), 7.68 (t, *J* = 7.0 Hz, 1H), 7.76 (d, *J* = 7.1 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 162.6, 159.7, 137.2, 136.9, 136.9, 128.5 (2C), 128.5 (2C), 128.3, 128.0, 127.8 (2C), 127.8, 127.6 (2C), 127.0, 126.9, 122.8, 122.8, 120.5, 119.3, 118.8, 112.8, 110.3, 84.3, 77.2, 75.0, 70.1, 69.9, 60.7, 35.1, 14.3; MS: m/z 334.48 $[M+2H+Na]^+$, 700.21 $[M+Na]^+$, 716.02 $[M+K]^+$.

General procedure for the synthesis of *N*-protected amides 24a–c

To a solution of the appropriate amide **23a–c** (0.95 mmol) in acetonitrile (15 mL), $(Boc)_2O$ (0.40 mL, 3.08 mmol) and DMAP (11.57 mg, 0.095 mmol) were added and the mixture was stirred for 21 h at room temperature under argon atmosphere. Then it was quenched with water and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (10–50% EtOAc in *n*-hexane) to afford the corresponding *N*-protected amide **24a–c**.

Ethyl 1-ethoxymethyl-4-{*tert*-butoxycarbonyl[(1-ethoxymethyl-1*H*-indol-3-yl)methyl] carbamoyl}-5-iodo-1*H*-pyrrole-2-carboxylate (24a) Yield 63%; oil; ^{1}H NMR ($CDCl_3$): δ 1.09–1.16 (m, 6H), 1.26 (s, 9H), 1.29 (t, *J* = 7.2 Hz, 3H), 3.38 (q, *J* = 7.0 Hz, 2H), 3.53 (t, *J* = 7.1 Hz, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 5.13 (s, 2H), 5.45 (s, 2H), 5.83 (s, 2H), 7.06 (s, 1H), 7.15–7.20 (m, 1H), 7.20–7.25 (m, 1H), 7.31 (s, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 167.5, 159.7, 153.2, 136.3, 129.0, 128.2, 127.8, 126.2, 122.1, 120.1, 120.1, 119.9, 112.2, 109.8, 84.4, 82.8, 76.8, 75.9, 64.0, 63.8, 60.5, 40.0, 27.6 (3C), 14.9, 14.8, 14.2; MS: m/z 676.21 $[M+Na]^+$.

Ethyl 1-[2-(trimethylsilyl)ethoxymethyl]-4-{*tert*-butoxycarbonyl-[(1-[2-(trimethylsilyl) ethoxymethyl]-1*H*-indol-3-yl)methyl]carbamoyl}-5-iodo-1*H*-pyrrole-2-carboxylate (24b) Yield 63%; oil; ^{1}H NMR ($CDCl_3$): δ -0.08 (s, 9H), -0.04 (s, 9H), 0.83–0.92 (m, 4H), 1.26 (s, 9H), 1.29 (t, *J* = 7.1 Hz, 3H), 3.41–3.47 (m, 2H), 3.54–3.60 (m, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 5.13 (s, 2H), 5.43 (s, 2H), 5.81 (s, 2H), 7.05 (s, 1H), 7.15–7.20 (m, 1H), 7.20–7.25 (m, 1H), 7.31 (s, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 167.5, 159.7, 153.2, 136.3, 129.0, 128.2, 127.6, 126.2, 122.1, 120.0, 120.0, 119.9, 112.1, 109.8, 84.5, 82.8, 76.5, 75.6, 66.1, 65.7, 60.5, 38.7, 27.6 (3C), 17.8, 17.7, 14.2, -1.4 (3C), -1.5 (3C); MS: m/z 820.00 $[M+Na]^+$, 835.93 $[M+K]^+$.

Ethyl 1-benzyloxymethyl-4-{*tert*-butoxycarbonyl[(1-(benzyloxymethyl)-1*H*-indol-3-yl)methyl]carbamoyl}-5-iodo-1*H*-pyrrole-2-carboxylate (24c) Yield 62%; oil; ^{1}H NMR ($CDCl_3$): δ 1.28 (t, *J* = 6.1 Hz, 3H), 1.25 (s, 9H), 4.24 (q, *J* = 7.1 Hz, 2H), 4.78 (s, 2H), 4.84 (s, 2H), 5.15 (s, 2H), 5.49 (s, 2H), 5.61 (s, 2H), 7.07 (s, 1H), 7.34–7.46 (m, 13H), 7.51 (d, *J* = 3.8 Hz, 1H), 7.94 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 165.95, 159.7, 153.2, 136.9, 136.9, 136.3, 129.0, 128.4 (2C), 128.4 (2C), 128.2, 127.9, 127.9, 127.9 (2C), 127.8 (2C), 127.7, 126.3, 122.2, 120.2, 120.1, 120.0, 112.4, 109.9, 88.9, 82.9, 74.9, 72.0, 70.5, 70.4, 60.6, 40.0, 27.6 (3C), 14.2; MS: m/z 799.91 $[M+Na]^+$, 816.03 $[M+K]^+$.

General procedure for the synthesis of tetracylic derivatives 25a–c

To a solution of the appropriate *N*-protected amide **24a–c** (230 μmol) in anhydrous DMF (5 mL), Ph_3P (12.11 mg, 46.2 μmol), $Pd(AcO)_2$ (5.15 mg, 23.0 μmol) and Ag_2CO_3 (253 mg, 918 μmol) was added and the mixture was stirred for 0.5 h at 135°C under argon atmosphere. Then it was diluted with water and extracted three times with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (0–20% EtOAc in *n*-hexane) to afford the corresponding tetracylic derivative **25a–c**.

5-*tert*-Butyl 2-ethyl 1,11-bis(ethoxymethyl)-4-oxo-6,11-dihydro-1*H*-pyrrolo[2′,3′:5,6] azepino[4,3-*b*]indole-2,5(4*H*)-dicarboxylate (25a) Yield 32%; oil; ^{1}H NMR ($CDCl_3$): δ 0.96 (t, *J* = 7.0 Hz, 3H), 1.15 (t, *J* = 7.0 Hz, 3H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.49 (s, 9H), 3.10 (dq, *J* = 7.0, 1.3 Hz, 2H), 3.43 (q, *J* = 7.0 Hz, 2H), 4.11 (d, *J* = 15.4 Hz, 1H), 4.32–4.43 (m, 2H), 5.36 (d, *J* = 10.2 Hz, 1H), 5.50 (d, *J* = 10.2 Hz, 1H), 5.61 (d, *J* = 10.5 Hz, 1H), 5.64 (d, *J* = 5.0 Hz, 1H), 6.18 (d, *J* = 9.9 Hz, 1H), 7.27–7.32 (m, 1H), 7.35–7.40 (m, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.74 (s, 1H), 7.80 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 164.1, 160.5, 151.5, 139.6, 131.6, 129.5, 126.3, 125.8, 124.5, 122.8, 121.9, 121.8, 119.6, 118.7, 111.6, 83.1, 76.9, 75.8, 64.4, 64.3, 60.8, 39.6, 28.1 (3C), 14.8, 14.7, 14.3; MS: m/z 548.24 $[M+Na]^+$, 564.17 $[M+K]^+$.

5-*tert*-Butyl 2-ethyl 1,11-bis[2-(trimethylsilyl)ethoxymethyl]-4-oxo-6,11-dihydro-1*H*-pyrrolo[2′,3′:5,6] azepino[4,3-*b*]indole-2,5(4*H*)-dicarboxylate (25b) Yield 41%; oil; ^{1}H NMR (CD_3OD): δ -0.22 (s, 9H), -0.21 (s, 9H), 0.50–0.76 (m, 4H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.50 (s, 9H), 3.02–3.14 (m, 2H), 3.15–3.27 (m, 2H), 4.16 (d, *J* = 15.6 Hz, 1H), 4.37 (dq, *J* = 7.1, 1.1 Hz, 2H), 5.44 (d, *J* = 11.1 Hz, 1H), 5.58–5.65 (m, 2H), 5.78 (d, *J* = 11.1 Hz, 1H), 6.29 (d, *J* = 10.2 Hz, 1H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.36–7.41 (m, 1H), 7.64 (s, 1H), 7.67 (d, *J* = 8.3 Hz, 1H), 7.81 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 164.1, 160.5, 151.5, 139.5, 131.7, 129.6, 126.3, 125.8, 124.4, 122.9, 121.8, 121.7, 119.5, 118.5, 111.6, 83.1, 76.6, 75.6, 66.2, 66.1, 60.8, 39.5, 28.1 (3C), 17.8, 17.3, -1.5 (3C), -1.7 (3C); MS: m/z 692.15 $[M+Na]^+$, 708.90 $[M+K]^+$.

5-*tert*-Butyl 2-ethyl 1,11-bis(benzyloxymethyl)-4-oxo-6,11-dihydro-1*H*-pyrrolo[2′,3′:5,6] azepino[4,3-*b*]indole-2,5(4*H*)-dicarboxylate (25c) Yield 40%; oil; ^{1}H NMR (CD_3OD): δ ^{1}H NMR ($CDCl_3$): δ 1.40 (t, *J* = 7.1 Hz, 3H), 1.49 (s, 9H), 4.20 (d, *J* = 4.8 Hz, 1H), 4.22 (d, *J* = 4.9 Hz, 1H), 4.29–4.40 (m, 2H), 5.33 (d, *J* = 10.3 Hz, 1H), 5.47 (d, *J* = 10.3 Hz, 1H), 5.63 (d, *J* = 9.5 Hz, 1H), 6.14 (d, *J* = 10.0 Hz, 1H), 6.85 (d, *J* = 7.3 Hz, 2H), 7.02 (t, *J* = 7.5 Hz, 2H), 7.06–7.11 (m, 2H), 7.27–7.39 (m, 5H), 7.46 (d, *J* = 7.9 Hz, 1H), 7.75 (s, 1H), 7.82 (d, *J* = 7.1 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 164.1, 160.5, 151.5, 139.5, 136.4, 136.1, 131.5, 129.7, 128.5 (2C), 128.2 (2C), 127.9, 127.8, 127.72 (2C), 127.6 (2C), 126.5, 126.4, 125.8, 124.5, 122.9, 122.0, 119.6, 119.2, 111.8, 83.1, 75.8, 74.8, 70.7, 70.4, 60.8, 39.5, 28.1 (3C), 14.3; MS: m/z 672.18 $[M+Na]^+$, 688.18 $[M+K]^+$.

General procedure for the synthesis of tetracylic derivatives 12a–c

To a solution of the appropriate *N*-Boc protected amide **25a–c** (0.11 mmol) in dry DCM (4 mL), a solution of trifluoroacetic acid (0.91 mmol) in dry DCM (1 mL) was added and the mixture was stirred at room temperature for 1 h under argon atmosphere. Then it was poured to ice-aqueous NH_3 solution (25%). The aqueous phase was washed three times with DCM and the combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (20% EtOAc in *n*-hexane) to afford the tetracylic derivative **12a–c.**

Ethyl 1,11-bis(ethoxymethyl)-4-oxo-4,5,6,11-tetrahydro-1*H*-pyrrolo[2′,3′:5,6]azepino [4,3-*b*]indole-2-carboxylate (12a) Yield 66%; white powder; mp 194–197°C; ^{1}H NMR ($CDCl_3$): δ 0.97 (t, *J* = 7.0 Hz, 3H), 1.11 (t, *J* = 7.0 Hz, 3H), 1.40 (t, *J* = 7.1 Hz, 3H), 3.14 (q, *J* = 7.0 Hz, 2H), 3.31 (q, *J* = 7.0 Hz, 2H), 4.19 (dd, *J* = 15.3, 3.0 Hz, 1H), 4.29–4.44 (m, 2H), 4.49 (dd, *J* = 15.2, 6.7 Hz, 1H), 5.34 (d, *J* = 10.4 Hz, 1H), 5.52 (d, *J* = 10.4 Hz, 1H), 5.61 (d, *J* = 9.8 Hz, 1H), 6.23 (d, *J* = 9.8 Hz, 1H), 6.97 (br s, 1H), 7.29 (t, *J* = 7.1 Hz, 1H), 7.37 (t, *J* = 7.7 Hz, 1H), 7.56 (d, *J* = 8.2 Hz, 1H), 7.65–7.67 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 167.3, 160.6, 139.5, 132.0, 129.4, 125.8, 125.7, 124.2, 121.7, 121.4, 120.5, 118.7, 118.6, 111.8, 76.8, 75.5, 64.4, 64.2, 60.7, 35.9, 14.8, 14.7, 14.3; MS: m/z 426.31 $[M+H]^+$, 448.29 $[M+Na]^+$, 464.22 $[M+K]^+$.

Ethyl 1,11-bis[2-(trimethylsilyl)ethoxymethyl]-4-oxo-4,5,6,11-tetrahydro-1*H*-pyrrolo [2′,3′:5,6]azepino[4,3-*b*]indole-2-carboxylate (12b) Yield 45%; oil; ^{1}H NMR ($CDCl_3$): δ -0.20 (s, 9H), -0.10 (s, 9H), 0.55–0.73 (m, 2H), 0.79–0.98 (m, 2H), 1.39 (t, *J* = 7.1 Hz, 3H), 3.13 (t, *J* = 8.2 Hz, 2H), 3.33 (t, *J* = 8.2 Hz, 2H), 4.17 (d, *J* = 17.6 Hz, 1H), 4.30–4.48 (m, 3H), 5.31 (d, *J* = 10.1 Hz, 1H), 5.51 (d, *J* = 10.4 Hz, 1H), 5.59 (d, *J* = 10.0 Hz, 1H), 6.26 (d, *J* = 9.8 Hz, 1H), 6.38 (br s, 1H), 7.25–7.32 (m, 1H), 7.36 (t, *J* = 7.2 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.64–7.70 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 167.2, 160.6, 139.5, 132.1, 129.6, 126.0, 125.8, 124.2, 121.8, 121.6, 120.5, 118.7, 118.6, 111.9, 8.19, 7.13, 7.2 (2C), 60.7, 35.9, 17.8, 17.4, 14.3, -1.54 (3C), -1.6 (3C); MS: m/z 570.03 $[M+H]^+$, 591.88 $[M+Na]^+$, 608.07 $[M+K]^+$.

Ethyl 1,11-bis(benzyloxymethyl)-4-oxo-4,5,6,11-tetrahydro-1*H*-pyrrolo[2′,3′:5,6]azepino [4,3-b]indole-2-carboxylate (12c) Yield 30%; oil; ^{1}H NMR ($CDCl_3$): δ 1.40 (t, *J* = 7.1 Hz, 3H), 4.15 (d, *J* = 9.4 Hz, 1H), 4.21 (d, *J* = 3.6 Hz, 1H), 4.29–4.47 (m, 2H), 5.31 (d, *J* = 10.5 Hz, 1H), 5.49 (d, *J* = 10.5 Hz, 1H), 5.56 (d, *J* = 9.9 Hz, 1H), 6.16 (d, *J* = 10.0 Hz, 1H), 6.51 (br s, 1H), 6.87 (d, *J* = 7.2 Hz, 2H), 7.01–7.06 (m, 4H), 7.21–7.26 (m, 3H), 7.27–7.39 (m, 3H), 7.47 (d, *J* = 8.1 Hz, 1H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.70 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 167.1, 160.5, 139.5, 136.5, 136.2, 131.8, 129.7, 128.5 (2C), 128.2 (2C), 128.0, 127.8, 127.7 (2C), 127.7 (2C), 126.1, 125.8, 124.2, 121.8, 121.7, 121.0, 119.2, 118.7, 112.0, 75.7, 74.5, 70.6, 70.4, 60.7, 35.8, 14.3; MS: m/z 550.13 $[M+H]^+$, 572.11 $[M+Na]^+$, 588.10 $[M+K]^+$.

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