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Synthesis and Reactivity of Azepino[3,4-*b*]indol-5-yl Trifluoromethanesulfonate

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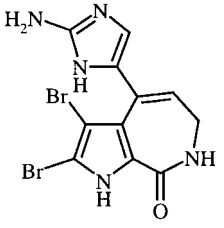
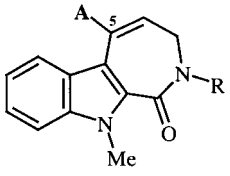
Abstract—A convenient method for the synthesis of 5-substituted azepino[3,4-*b*]indol-1-ones **18**–**27** is described. This synthesis was based on palladium mediated cross-coupling reactions of the key intermediate azepino[3,4-*b*]indol-5-yl trifluoromethanesulfonates **3**, obtained from the corresponding azepino[3,4-*b*]indole-1,5-dione **4**.

A growing collection of marine natural compounds have been reported in recent years as active leads for new drug development[1] or tools for cell biology.[2] A number of cyclic guanidine compounds containing a pyrrole ring, biogenetically derivable from oroïdin, have been extracted from marine organisms and display a large number of biological properties.[3,4] Our attention has been focused on Odiline or Stevensine **1** characterised by a pyrroloazepine skeleton, 6,7-dihydro-1*H*-pyrrolo[2,3-*c*]azepin-8-one, connected to a cyclic guanidine. The name Odiline was given by Potier,[5] but Albizati and Faulkner[6] in a simultaneous and independent study, assigned the name Stevensine. This natural product has been the target of total synthesis efforts.[7–10]



Odiline or Stevensine 1



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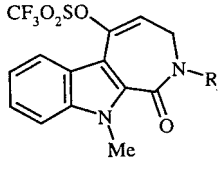
Our interest in indolic chemistry[11] arose out of our desire to prepare a diverse set of 5-substituted azepino indoles **2** which can be potential building blocks. The synthetic approach was based on palladium mediated cross-coupling reactions (Stille or Suzuki reaction) of the key triflate **3**, prepared from the azepino[3,4-*b*]indole-1,5-dione **4**.



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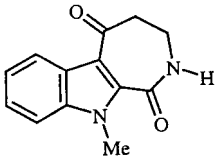

4

The synthesis of compound **4** has been already described.[12,13] Our synthesis is slightly modified and is outlined in Scheme 1. Amidification of the commercially available indole-2-carboxylic acid **5** with β-alanine ethyl ester hydrochloride in the presence of DMAP and EDCI gave **6** in 95% yield. For information, the same reaction on a large scale with **5** (35 mmol) afforded exclusively the 2-indolecarboxylic anhydride **7**. To avoid the intramolecular cyclisation on the indolic nitrogen atom, we decided to protect it with a methyl group. Thus, reaction of compound **6** with iodomethane resulted in a regioselective methylation in good yield of the indolic nitrogen atom to give **8**.[14] Saponification of **8** with lithium hydroxide gave the acid **9** in 96% yield. Final PPA/P_2O_5 cyclisation provided azepino[3,4-*b*]indole-1,5-dione **4** in 86% yield.

The reactivity of the ketone **4** has been thoroughly investigated.

Keywords: indole; palladium; catalysis.

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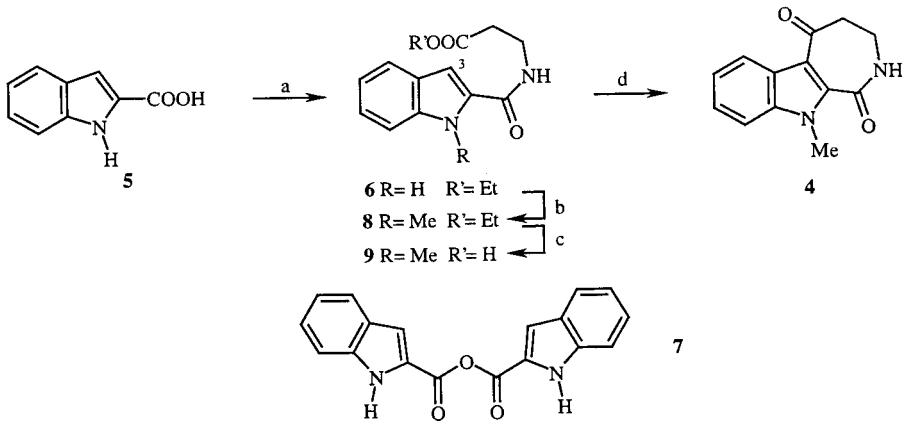


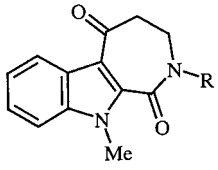
Scheme 1. (a) $H_2NCH_2CH_2COOEt{\cdot}HCl$, DMAP, EDCI, CH_2Cl_2, rt, 20 h, 95%; (b) MeI, K_2CO_3, MeCN reflux, 24 h, 90%; (c) LiOH, EtOH, rt, 18 h, 96%; (d) PPA, P_2O_5, 110°C, 1 h, 86%.

The Wittig reaction of **4** with (carbethoxymethylene)triphenylphosphorane or Horner–Wadsworth–Emmons reaction with triethylphosphonoacetate failed. The low reactivity of the keto group led us to view the functionalisation of the position-5 via palladium-catalysed reactions. The preparation of triflate from **4** was first undergone. Therefore, treatment of the lactam **4** with trifluoromethanesulfonic anhydride in the presence of sodium carbonate in dichloromethane led exclusively to the formation of the *O*,*N*-ditriflate **10** in 70% yield. This structure was supported by IR, ^1H and ^{13}C NMR spectra.[15] If the same reaction was carried out with trifluoromethanesulfonic anhydride in the presence of *N*,*N*-dimethylformamide/dichloromethane (in order to increase the solubility of **4**) the formyl compound **11** was obtained in 52% yield (Scheme 2).

Unfortunately, compound **10** engaged in Stille reaction afforded erratic results, so it was necessary to protect the nitrogen atom of lactam **4** to solve the problem. In the pyrrole series, protection of the lactam by acetyl or tosyl group gave unsatisfactory results.[16] In our hands, according to standard procedures, protection of the amide group of **4** was performed to give the desired compounds **12** (Table 1).

Acetylation in the presence of acetic anhydride gave mainly the compound **12a** (85% yield) with the *O*,*N*-diacetylated derivative **13a** in 13% yield. Similarly reaction of **4** with Boc_2O (1 equiv.) gave the compound **12b** (40% yield) and the *O*,*N*-diBoc **13b** (20% yield). Attempts with 2 equiv. of Boc_2O led to the compound **13b** in 66% yield. *N*-Methylation or *N*-benzylation reaction must be carefully controlled in order to prevent α-alkylation. Reaction of **4** with sodium hydride and iodomethane in *N*,*N*-dimethylformamide at room temperature afforded the desired *N*-methyl derivative **12c** (60% yield), the dimethyl derivative **14** (12% yield) and the trimethyl derivative **15** (3% yield). *N*-Benzylation of **4** afforded **12d** in 72% yield. The two last derivatives **12e** and **12f** were obtained, respectively, in 78 and 90% yield.

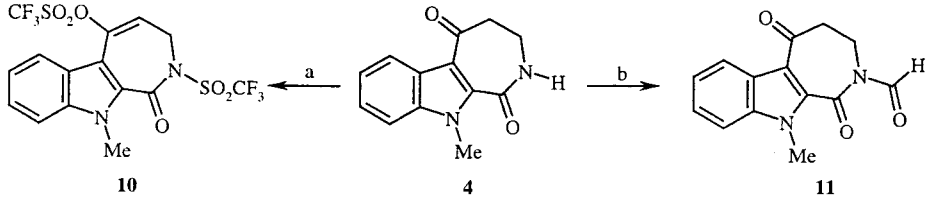
Table 1.



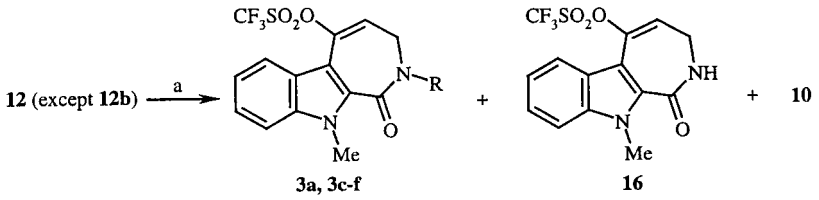
12

Product	R	Conditions	Yield (%)
12a	Ac	Ac_2O, pyridine reflux, 2 h	85
12b	Boc	Boc_2O (1 equiv.), DMAP, MeCN, 24 h	40
12c	Me	MeI, NaH, DMF, 0°C, 15 min	60
12d	Bn	BnCl, NaH, DMF, 0°C, 30 min	72
12e	PMB	PMBCl, NaH, DMF, 0°C, 40 min	78
12f	SO_2Ph	$PhSO_2Cl$, NaH, DMF, 0°C, 1 h	90

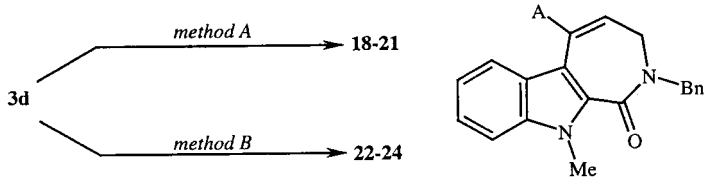
Triflates **3** were easily obtained in fair to good yields, by reaction of **12** with trifluoromethanesulfonic anhydride in the presence of sodium carbonate in dichloromethane. Other experimental approaches were unproductive (LDA/triflimide, −78°C, Hunig base/triflimide, NaH/trifluoromethanesulfonic anhydride). It should be noted that for **12a** and **12e**, three compounds were isolated: the expected triflate **3a** (21% yield) and **3e** (53% yield), the monotriflate **16** with the free NH (30% yield from **12a** and 20% yield from **12e**) and the ditriflate **10** (respectively 13% yield from **12a** and 23% yield from **12e**) (Scheme 3).



Scheme 2. (a) Na_2CO_3, Tf_2O (1.5 equiv.), CH_2Cl_2, rt, 24 h, 70%; (b) Na_2CO_3, Tf_2O (3 equiv.), DMF/CH_2Cl_2, rt, 24 h, 52%.

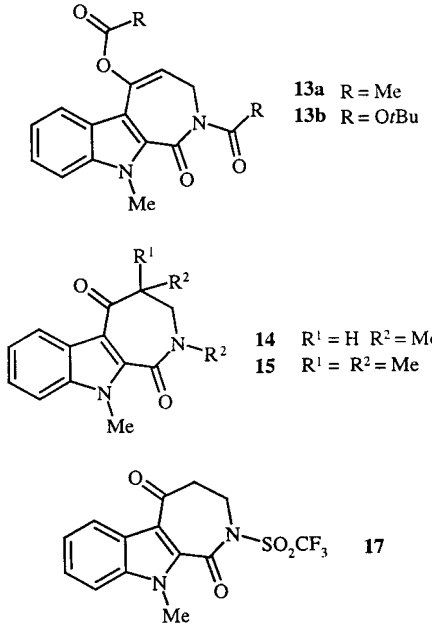


Scheme 3. (a) Na_2CO_3, Tf_2O (1.5 equiv.), CH_2Cl_2, rt, 24 h, **3a** R=Ac, 21%, **3c** R=Me, 90%, **3d** R=Bn, 95%, **3e** R=PMB, 53%, **3f** R=SO_2Ph, 95%.



Scheme 4. *Method A:* $Pd(PPh_3)_4$, A-Sn(R)$_3$, LiCl, DMF, 100°C, 2 h; *Method B:* $Pd(PPh_3)_4$, A-B(OH)$_2$, $NaHCO_3$, EtOH/toluene, 80°C, 2 h.

Reaction on the nitrogen atom was exclusively observed if compound **12b** was treated with trifluoromethanesulfonic anhydride; the monotriflate **17** was obtained in 82% yield.



Among the different monotriflates synthesised, we examined the reactivity of **3d** expecting an easy deprotection of the lactam nitrogen atom. Reactions of **3e**, **3f** and the unprotected triflate **16** were also investigated. A range of palladium mediated cross-coupling reactions with **3d** were carried out in order to introduce various heterocyclic appendages (Scheme 4).

Compounds **18**–**21** were prepared according to Stille reaction by using commercially available stannanes and freshly prepared tetrakis(triphenylphosphine)palladium reagent in *N*,*N*-dimethylformamide (Table 2).[17] Three arylboronic acids were also coupled to **3d** under Suzuki conditions.[18] Compounds **22**–**24** were obtained in good yields (Table 2). Reaction between **3e** and 2-thiophenylboronic acid afforded compound **25** in 86% yield. Stille reaction between triflate **3f** and tetramethylstannane gave the derivative **26** (76% yield). Under similar conditions, the unprotected triflate **16** and tributyl(2-thiophenyl)stannane gave the compound **27** (71% yield). Compound **27** was evaluated for growth inhibitory property, measured as IC_{50} value, against the murine leukemia L1210 cell line. Weak in vitro cytotoxicity was observed (IC_{50} L1210>10 μM).

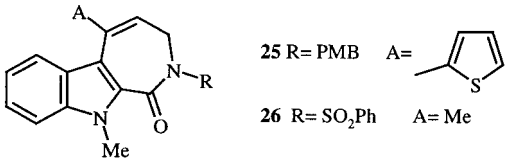
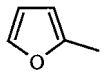
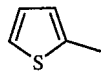
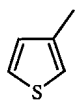
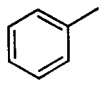
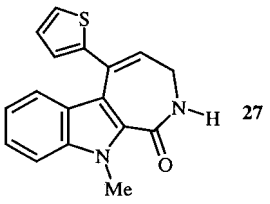


Table 2.

Product	A	Yield (%)
18		90
19	Me	99
20		92
21		74
22		90
23		99
24		86



Attempts to debenzylate compound **19** were till now unproductive (BCl_3, Na/NH_3, etc.). The introduction of the cyclic guanidine moiety, found in the Stevensine structure, is underway using another synthetic approach.

In summary, we have described an easy and versatile synthesis of 5-substituted azepino[3,4-*b*]indol-1-ones **18**–**27** from triflates **3d**, **3e**, **3f** and **16**. These latter compounds were found to be versatile intermediates for palladium mediated cross-coupling reactions.

Experimental

Melting points were determined using a Büchi capillary instrument and are uncorrected. The infrared spectra of the compounds were recorded on a Perkin–Elmer FTIR paragon 1000 spectrometer. The NMR spectra were recorded at 300 K in $CDCl_3$ on a Bruker Avance DPX 250. The chemical shifts are expressed in parts per million relative to tetramethylsilane (TMS). The mass spectra were recorded on Perkin–Elmer SCIEX API 300 using ionspray methodology. Thin-layer chromatography (TLC) was run on precoated silica gel plates (Merck $60F_{254}$) and the spots visualised using an ultraviolet lamp. Flash chromatography was carried out on column using flash silica gel 60 Merck (40–63 μm) as the stationary phase. All the reactions requiring anhydrous conditions were conducted in a flame-dried apparatus. Stannanes and boronic acids were purchased from Lancaster or Sigma–Aldrich.

2-Acetyl-10-methyl-1-oxo-1,2,3,10-tetrahydroazepino-[3,4-*b*]indol-5-yl trifluoromethanesulfonate (3a). To a suspension of compound **12a** (330 mg, 1.3 mmol) and sodium carbonate (198 mg, 1.86 mmol) in dry dichloromethane (5 mL), was added trifluoromethanesulfonic anhydride (271 μL, 1.9 mmol) in dry dichloromethane (8 mL). The mixture was stirred for 24 h at room temperature, then water was added and the mixture was extracted. The organic layer was dried over $MgSO_4$ and evaporated in vacuo. The crude residue was purified by column chromatography (eluent: petroleum ether–ethyl acetate 6:4) to afford **16** (140 mg, 30%), **3a** (105 mg, 21%) and the ditriflate **10** (83 mg, 13%). Mp 161–162°C (ethyl acetate–petroleum ether); IR (KBr) ν 1700 (CO), 1672 (CO), 1422 (OSO_2), 1209 (OSO_2) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.61 (s, 3H, CH_3), 4.15 (s, 3H, CH_3), 4.20–4.50 (m, 2H, CH_2), 6.37 (t, 1H, J=7.5 Hz, CH), 7.33–7.40 (m, 1H, H_{Ar}), 7.51–7.55 (m, 2H, H_{Ar}), 8.04 (d, 1H, J=8.0 Hz, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 27.2 (CH_3), 32.9 (CH_3), 39.4 (CH_2), 110.8 (CH), 112.7 (C), 116.7 (CH), 118.9 (q, J=315 Hz, CF_3), 122.6 (C), 122.6 (CH), 122.9 (CH), 127.1 (CH), 131.2 (C), 139.3 (C), 149.0 (C), 162.1 (CO), 172.2 (CO); Anal. Calcd for $C_{16}H_{13}F_3N_2O_5S$: C, 47.76; H, 3.26; N, 6.96. Found: C, 48.05; H, 3.39; N, 6.80; MS m/z 403 $(M+1)^+$.

2,10-Dimethyl-1-oxo-1,2,3,10-tetrahydroazepino[3,4-*b*]-indol-5-yl trifluoromethanesulfonate (3c). According to the procedure for the synthesis of **3a**, compound **3c** was prepared in 90% yield; mp 112–113°C (ethyl acetate–petroleum ether); IR (KBr) ν 1623 (CO), 1425 (OSO_2), 1200 (OSO_2) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.28 (s, 3H, CH_3), 3.84 (d, 2H, J=7.3 Hz, CH_2), 4.12 (s, 3H, CH_3), 6.18 (t, 1H, J=7.3 Hz, CH), 7.31–7.35 (m, 1H, H_{Ar}), 7.47–7.49 (m, 2H, H_{Ar}), 7.98 (d, 1H, J=8.2 Hz, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 32.3 (CH_3), 35.2 (CH_3), 46.1 (CH_2), 110.3 (C), 110.5 (CH), 113.2 (CH), 118.4 (q, J=315 Hz, CF_3), 121.7 (CH), 122,1 (CH), 122.6 (C), 125.6 (CH), 133.4 (C), 138.2 (C), 149.3 (C), 160.8 (CO). Anal. Calcd for $C_{15}H_{13}F_3N_2O_4S$: C, 48.13; H, 3.50; N, 7.48. Found: C, 48.49; H, 3.69; N, 7.31. MS m/z 375 $(M+1)^+$.

2-Benzyl-10-methyl-1-oxo-1,2,3,10-tetrahydroazepino-[3,4-*b*]indol-5-yl trifluoromethanesulfonate (3d). According to the procedure for the synthesis of **3a**, compound **3d** was prepared in 95% yield; mp 117–118°C (ethyl acetate–petroleum ether); IR (KBr) ν 1631 (CO), 1422 (OSO_2), 1207 (OSO_2) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.76 (d, 2H, J=7.5 Hz, CH_2), 4.12 (s, 3H, CH_3), 4.70–4.90 (m, 2H, CH_2), 5.79 (t, 1H, J=7.5 Hz, CH), 7.18–7.46 (m, 8H, H_{Ar}), 7.92–7.95 (m, 1H, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 32.4 (CH_3), 43.8 (CH_2), 51.0 (CH_2), 110.5 (CH), 114.3 (CH), 121.9 (CH), 122.1 (CH), 122.6 (C), 124.4 (q, J=300 Hz, CF_3), 125.7 (CH), 128.1 (CH), 128.2 (2CH), 128.8 (2CH), 132.3 (C), 132.7 (C), 137.3 (C), 138.3 (C), 148.9 (C), 160.9 (CO); Anal. Calcd for $C_{21}H_{17}F_3N_2O_4S$: C, 56.00; H, 3.80; N, 6.22. Found: C, 56.37; H, 3.68; N, 3.91; MS m/z 451 $(M+1)^+$.

2-(4-Methoxybenzyl)-10-methyl-1-oxo-1,2,3,10-tetrahydroazepino[3,4-*b*]indol-5-yl trifluoromethanesulfonate (3e). According to the procedure for the synthesis of **3a**, compound **3e** was prepared in 53% yield. The compounds **10** and **16** were also obtained, respectively, in 23 and 20% yield (chromatography eluent: petroleum ether–ethyl acetate 1:1). Mp 125–126°C (ethyl acetate–petroleum ether); IR (KBr) ν 1634 (CO), 1413 (OSO_2), 1240 (OSO_2) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.79 (d, 2H, J=7.5 Hz, CH_2), 3.85 (s, 3H, CH_3), 4.16 (s, 3H, CH_3), 4.70–4.80 (m, 2H, CH_2), 5.82 (t, 1H, J=7.5 Hz, CH), 6.92–6.96 (m, 2H, H_{Ar}), 7.30–7.36 (m, 3H, H_{Ar}), 7.48–7.50 (m, 2H, H_{Ar}), 7.98 (d, 1H, J=8.2 Hz, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 32.4 (CH_3), 43.6 (CH_2), 50.3 (CH_2), 55.3 (CH_3), 110.4 (CH), 110.5 (C), 114.2 (2CH), 114.5 (CH), 118.5 (q, J=315 Hz, CF_3), 121.9 (CH), 122.1 (CH), 122.6 (C), 125.6 (CH), 129.5 (2CH), 129.5 (C), 132.8 (C), 138.2 (C), 148.8 (C), 159.3 (C), 160.8 (CO); Anal. Calcd for $C_{22}H_{19}F_3N_2O_5S$: C, 55.00; H, 3.99; N, 5.83. Found: C, 54.67; H, 4.14 N, 5.93; MS m/z 481 $(M+1)^+$.

10-Methyl-1-oxo-2-phenylsulfonyl-1,2,3,10-tetrahydro-azepino[3,4-*b*]indol-5-yl trifluoromethanesulfonate (3f). According to the procedure for the synthesis of **3a**, compound **3f** was prepared in 95% yield; mp 119–120°C (ethyl acetate–petroleum ether); IR (KBr) ν 1668 (CO), 1640 (CO), 1409 (OSO_2), 1218 (OSO_2), 1172 (NSO_2)

cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.99 (s, 3H, CH_3), 4.20–4.70 (m, 2H, CH_2), 6.43 (t, 1H, J=7.5 Hz, CH), 7.26–7.58 (m, 6H, H_{Ar}), 7.93–8.01 (m, 3H, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 32.6 (CH_3), 41.7 (CH_2), 110.7 (CH), 112.2 (C), 115.4 (CH), 118.5 (q, J=330 Hz, CF_3), 122.4 (C), 122.5 (CH), 123.0 (CH), 127.1 (CH), 129.0 (CH), 129.0 (3 CH), 130.2 (C), 134.2 (CH), 137.9 (C), 139.0 (C), 149.6(C), 159.6 (CO); Anal. Calcd for $C_{20}H_{15}F_3N_2O_6S_2$: C, 48.00; H, 3.02; N, 5.60. Found: C, 48.39; H, 2.86; N, 5.75; MS m/z 501 $(M+1)^+$.

10-Methyl-1,2,3,4,5,10-hexahydroazepino[3,4-*b*]indole-1,5-dione (4). In a dry balloon, phosphorus pentoxide (1.30 g) and polyphosphoric acid (9.80 g) were stirred at 110°C until complete dissolution of phosphorus pentoxide. Acid **9** (1.80 g, 7.3 mmol) was added and the final mixture was stirred at 110°C for 1 h. After cooling, the mixture was poured into ice, slowly neutralised by saturated sodium hydrogenocarbonate. Dichloromethane (200 mL) was added and the mixture was stirred overnight. After extraction, the aqueous layer was twice extracted with dichloromethane. The organic phase was dried over $MgSO_4$ and evaporated in vacuo to give a brownish solid that was recrystallised from ethyl acetate–petroleum ether to give a yellow solid **4** (1.43 g, 86%); mp 201–202°C (ethyl acetate–petroleum ether, 208°C lit.[12]); IR (KBr) ν 3208 (NH), 1661 (CO), 1640 (CO) cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.74–2.79 (m, 2H, CH_2), 3.36–3.40 (m, 2H, CH_2), 3.99 (s, 3H, CH_3), 7.22–7.44 (m, 2H, H_{Ar}), 7.63 (d, 1H, J=8.0 Hz, H_{Ar}), 8.27 (d, 1H, J=8.0 Hz, H_{Ar}), 8.78 (broad t, 1H, J=4.5 Hz, NH); ^{13}C NMR (62.90 MHz, DMSO-d_6) δ 32.4 (CH_3), 36.7 (CH_2), 45.0 (CH_2), 111.0 (CH), 114.8 (C), 122.7 (CH), 123.2 (CH), 124.6 (C), 125.1 (CH), 134.7 (C), 138.0 (C), 162.4 (CO), 195.7 (CO); Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.07; H, 5.44; N, 12.39; MS m/z 229 $(M+1)^+$.

Ethyl 3-[(1*H*-2-indolylcarbonyl)amino]propanoate (6). To a solution of β-alanine ethylester hydrochloride (1.57 g, 10.2 mmol) and DMAP (1.87 g, 15.3 mmol) in dry dichloromethane (20 mL) at 0°C was added a solution of indole-2-carboxylic acid **5** (1.50 g, 9.3 mmol) in dry dichloromethane (20 mL) then EDCI (1.96 g, 10.2 mmol) in dry dichloromethane (20 mL). The final mixture was stirred at 0°C for 4 h, then at room temperature for 20 h. After evaporation of the solvent, the solid obtained was suspended in water and filtered. The solid was partitioned between ethyl acetate (50 mL) and 10% hydrochloric acid (50 mL) and extracted. The organic phase was dried over $MgSO_4$ and evaporated to afford **6** (2.30 g, 95%) as white crystals; mp 159–160°C (ether); IR (KBr) ν 3377 (NH), 3350 (NH), 1718 (CO), 1624 (CO) cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.18 (t, 3H, J=7.0 Hz, CH_3), 2.60 (t, 2H, J=6.7 Hz, CH_2), 3.52 (dd, 2H, J=5.2, 6.7 Hz, CH_2), 4.08 (q, 2H, J=7.0 Hz, CH_2), 7.06 (t, 1H, J=7.5 Hz, H_{Ar}), 7.08 (s, 1H, H_3), 7.17 (t, 1H, J=7.5 Hz, H_{Ar}), 7.42 (d, 1H, J=7.5 Hz, H_{Ar}), 7.60 (d, 1H, J=7.5 Hz, H_{Ar}), 8.53 (t, 1H, J=5.2 Hz, NH), 11.56 (broad s, 1H, NH); ^{13}C NMR (62.90 MHz, DMSO-d_6) δ 14.5 (CH_3), 34.3 (CH_2), 35.5 (CH_2), 60.4 (CH_2), 102.9 (CH), 112.7 (CH), 120.1 (CH), 122.0 (CH), 123.3 (CH), 127.4 (C), 132.0 (C), 136.8 (C), 161.6 (CO), 171.7 (CO); Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.25; H, 6.33; N, 10.89; MS m/z 261 $(M+1)^+$.

1*H*-2-Indolecarboxylic anhydride (7). Compound **7** was obtained in 95% yield by upscaling the synthesis of **6** (35 mmol); mp 207–208°C (dichloromethane); IR (KBr) ν 3363 (NH), 3310 (NH), 1770 (CO), 1694 (CO) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.16 (t, 2H, J=8.0 Hz, H_{Ar}), 7.33 (t, 2H, J=8.0 Hz, H_{Ar}), 7.46 (s, 2H, H_3), 7.54 (d, 2H, J=8.0 Hz, H_{Ar}), 7.69 (d, 2H, J=8.0 Hz, H_{Ar}), 11.59 (broad s, 2H, NH); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 111.1 (CH), 112.3 (CH), 120.2 (CH), 122.0 (CH), 125.1 (CH), 125.5 (C), 126.3 (C), 138.2 (C), 156.5 (CO); Anal. Calcd for $C_{18}H_{12}N_2O_3$: C, 71.05; H, 3.97; N, 9.21. Found: C, 71.36; H, 4.09; N, 9.35; MS m/z 305 $(M+1)^+$.

Ethyl 3-{[(1-methyl)-1*H*-2-indolylcarbonyl]amino}propanoate (8). A solution of amide **6** (5.01 g, 19.2 mmol), K_2CO_3 (10.63 g, 77.0 mmol) and iodomethane (2.9 mL, 46.5 mmol) in acetonitrile (150 mL) was stirred at reflux for 24 h. The cooled mixture was filtered and the filtrate was evaporated in vacuo. The crude residue was purified by column chromatography (eluent: petroleum ether–ethyl acetate 9:1) to afford **8** (4.74 g, 90%) as a white solid; mp 75–76°C (ethyl acetate–petroleum ether); IR (KBr) ν 3375–3150 (NH), 1740 (CO), 1629 (CO) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.28 (t, 3H, J=7.2 Hz, CH_3), 2.65 (t, 2H, J=6.0 Hz, CH_2), 3.73 (dd, 2H, J=5.0, 6.0 Hz, CH_2), 4.05 (s, 3H, CH_3), 4.15 (q, 2H, J=7.2 Hz, CH_2), 6.83 (s, 1H, H_3), 6.90 (t, 1H, J=5.0 Hz, NH), 7.10–7.17 (m, 1H, H_{Ar}), 7.39–7.41 (m, 2H, H_{Ar}), 7.63 (d, 1H, J=8.0 Hz, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 14.2 (CH_3), 31.5 (CH_3), 34.0 (CH_2), 34.9 (CH_2), 60.8 (CH_2), 103.9 (CH), 110.1 (CH), 120.4 (CH), 121.8 (CH), 124.0 (CH), 126.0 (C), 131.9 (C), 139.0 (C). 162.5 (CO), 172.7 (CO); Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.90; H, 6.47; N, 10.12; MS m/z 275 $(M+1)^+$.

3-[(1-Methyl-1*H*-2-indolylcarbonyl)amino]propanoic acid (9). A solution of ester **8** (4.2 g, 15.31 mmol) and LiOH (1.29 g, 30.72 mmol) in ethanol (140 mL) was stirred at room temperature for 18 h. After cooling, the solvent was evaporated in vacuo. The residue was dissolved in water and the acidification of the medium led to a white precipitate which was filtered and washed with ethanol to provide **9** (3.62 g, 96%); mp 161°C (ethanol, 160°C lit.[12]); IR (KBr) ν 3392 (NH), 3200–2100 (OH), 1728 (CO), 1700 (CO) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.63 (t, 2H, J=6.2 Hz, CH_2), 3.69 (dd, 2H, J=5.0, 6.2 Hz, CH_2), 4.04 (s, 3H, CH_3), 6.87 (s, 1H, H_3), 7.12–7.36 (m, 3H, H_{Ar}), 7.22 (broad t, 1H, J=5.0 Hz, NH), 7.61 (d, 1H, J=8.0 Hz, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 31.2 (CH_3), 33.6 (CH_2), 34.7 (CH_2), 103.7 (CH), 109.7 (CH), 120.0 (CH), 121.4 (CH), 123.6 (CH), 125.7 (C), 131.7 (C), 138.6 (C), 162.2 (CO), 174.3 (CO); Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.12; H, 5.83; N, 11.51; MS m/z 247 $(M+1)^+$.

10-Methyl-1-oxo-2-{[(trifluoromethyl)sulfonyl]oxy}-1,2,3,10-tetrahydroazepino[3,4-*b*]indol-5-yl trifluoromethanesulfonate (10). Compound **10** was obtained in 70% yield according to the method described for the preparation of triflates **3** (chromatography eluent: petroleum ether–ethyl

acetate 4:6); mp 177–178°C (ethyl acetate–petroleum ether); IR (KBr) ν 1702 (CO) cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 4.03 (s, 3H, CH_3), 4.50 (broad d, 2H, J=7.5 Hz, CH_2), 6.67 (t, 1H, J=7.5 Hz, CH), 7.34–7.40 (m, 1H, H_{Ar}), 7.53–7.59 (m, 1H, H_{Ar}), 7.78 (d, 1H, J=8.0 Hz, H_{Ar}), 7.88 (d, 1H, J=8.0 Hz, H_{Ar}); ^{13}C NMR (62.90 MHz, DMSO-d_6) δ 33.3 (CH_3), 44.7 (CH_2), 112.5 (CH), 112.5 (C), 119.0 (CH), 121.1 (q, J=300 Hz, CF_3), 122.0 (CH), 123.5 (CH), 125.9 (C), 127.8 (CH), 129.1 (C), 139.5 (C), 148.5 (C), 159.6 (CO); Anal. Calcd for $C_{15}H_{10}F_6N_2O_6S_2$: C, 36.59; H, 2.05; N, 5.69. Found: C, 36.20; H, 2.24; N, 5.88; MS m/z 493 $(M+1)^+$.

2-Formyl-10-methyl-1,2,3,4,5,10-hexahydroazepino[3,4-*b*]-indole-1,5-dione (11). To a suspension of compound **4** (347 mg, 1.52 mmol) and potassium carbonate (480 mg, 4.52 mmol) in dry dichloromethane–DMF (7 mL, 6:1 v/v) was added a solution of trifluoromethanesulfonic anhydride (0.76 mL, 4.52 mmol) in dry dichloromethane (6 mL). The final mixture was stirred at room temperature for 24 h. The mixture was hydrolysed with water and extracted. The aqueous phase was extracted with dichloromethane twice. The organic phase was dried over $MgSO_4$ and evaporated in vacuo. The crude residue was triturated with toluene which led to the crystallisation of the desired compound **11** (202 mg, 52%) as a yellow solid; mp 213–214°C (toluene); IR (KBr) ν 1702 (CO), 1677 (CO), 1639 (CO) cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 2.86–2.91 (m, 2H, CH_2), 4.02–4.11 (m, 2H, CH_2), 4.08 (s, 3H, CH_3), 7.37 (t, 1H, J=8.0 Hz, H_{Ar}), 7.50 (t, 1H, J=8.0 Hz, H_{Ar}), 7.76 (d, 1H, J=8.0 Hz, H_{Ar}), 8.29 (d, 1H, J=8.0 Hz, H_{Ar}), 9.44 (s, 1H, CHO); ^{13}C NMR (62.90 MHz, DMSO-d_6) δ 33.0 (CH_3), 42.5 (CH_2), 43.1 (CH_2), 111.5 (CH), 116.4 (C), 123.2 (CH), 123.9 (CH), 124.4 (C), 126.4 (CH), 132.4 (C), 139.0 (C), 162.3 (CO), 163.5 (CO), 195.5 (CO); Anal. Calcd for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.37; H, 4.88; N, 11.12; MS m/z 257 $(M+1)^+$.

2-Acetyl-10-methyl-1,2,3,4,5,10-hexahydroazepino[3,4-*b*]-indole-1,5-dione (12a). To a solution of **4** (500 mg, 2.19 mmol) in acetic anhydride (25 mL) stirred at 100°C, was added pyridine (360 μL, 4.38 mmol) and the final mixture was stirred at 140°C for 2 h. After cooling and evaporation of the solvents, the crude residue was partitioned between water and dichloromethane and extracted. The organic layer was washed with water twice, dried over $MgSO_4$ and evaporated in vacuo. The crude residue was purified by column chromatography (eluent: petroleum ether–ethyl acetate 4:6) to give successively **12a** (503 mg, 85%) and **13a** (89 mg, 13%). Mp 185–186°C (ethyl acetate–petroleum ether); IR (KBr) ν 1707 (CO), 1677 (CO), 1641 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.63 (s, 3H, CH_3), 2.89–2.93 (m, 2H, CH_2), 4.07 (s, 3H, CH_3), 4.31–4.35 (m, 2H, CH_2), 7.33–7.47 (m, 3H, H_{Ar}), 8.35–8.38 (m, 1H, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 26.3 (CH_3), 31.9 (CH_3), 38.6 (CH_2), 42.3 (CH_2), 109.2 (CH), 116.0 (C), 122.9 (CH), 123.1 (CH), 123.7 (C), 125.6 (CH), 131.4 (C), 138.2 (C), 162.2 (CO), 171.2 (CO), 194.6 (CO); Anal. Calcd for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.30; H, 5.38; N, 10.43; MS m/z 271 $(M+1)^+$.

***tert*-Butyl 10-methyl-1,5-dioxo-1,2,3,4,5,10-hexahydroazepino[3,4-*b*]indole-2-carboxylate (12b).** A solution of **4** (200 mg, 0.88 mmol), di-*tert*-butyl dicarbonate (384 mg, 1.76 mmol) and a catalytic amount of DMAP in acetonitrile (5 mL) was stirred at room temperature for 24 h. After evaporation, the crude residue was purified by column chromatography (eluent: petroleum ether–ethyl acetate 6:2) to give **12b** (115 mg, 40%), compound **13b** (75 mg, 20%) and starting material **4** (80 mg, 40%). Mp133–134°C (ethyl acetate–petroleum ether); IR (KBr) ν 1729 (CO), 1677 (CO), 1643 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.58 (s, 9H, $(CH_3)_3$), 2.94–2.96 (m, 2H, CH_2), 4.06 (s, 3H, CH_3), 4.17–4.21 (m, 2H, CH_2), 7.32–7.42 (m, 3H, H_{Ar}), 8.32 (d, 1H, J=8.0 Hz, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 28.4 ($3CH_3$), 33.1 (CH_3), 42.4 (CH_2), 43.7 (CH_2), 84.3 (C), 110.3 (CH), 116.8 (C), 123.8 (CH), 124.0 (CH), 124.9 (C), 126.6 (CH), 133.9 (C), 139.1 (C), 151.8 (CO), 161.4 (CO), 195.7 (CO); Anal. Calcd for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.14; N, 8.53. Found: C, 66.17; H, 6.01; N, 8.65; MS m/z 329 $(M+1)^+$.

2,10-Dimethyl-1,2,3,4,5,10-hexahydroazepino[3,4-*b*]indole-1,5-dione (12c). To a solution of **4** (300 mg, 1.31 mmol) in dry DMF (5 mL) at 0°C, NaH (62 mg, 1.55 mmol, 60% oil dispersion) was added portionwise and the mixture was stirred for 1 h at room temperature. Iodomethane (90 μL, 1.57 mmol) was added and the final mixture was stirred for 15 min. The mixture was diluted with water (10 mL), and extracted with ethyl acetate (2×10 mL). The organic phase was dried over $MgSO_4$ and evaporated. The crude residue was purified by column chromatography (eluent: petroleum ether–ethyl acetate 1:1) to give **12c** (190 mg, 60%), **14** (40 mg, 12%) and **15** (10 mg, 3%). Mp 168–169°C (ethyl acetate–petroleum ether); IR (KBr) ν 1645 (CO), 1642 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.95–2.99 (m, 2H, CH_2), 3.33 (s, 3H, CH_3), 3.81–3.85 (m, 2H, CH_2), 4.10 (s, 3H, CH_3), 7.39–7.48 (m, 3H, H_{Ar}), 8.43–8.47 (m, 1H, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 32.6 (CH_3), 35.2 (CH_3), 43.0 (CH_2), 46.7 (CH_2), 110.1 (CH), 115.4 (C), 123.5 (CH), 123.7 (CH), 125.0 (C), 125.8 (CH), 134.6 (C), 138.4 (C), 161.4 (CO), 195.4 (CO); Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.75; H, 5.99; N, 11.40; MS m/z 243 $(M+1)^+$.

2-Benzyl-10-methyl-1,2,3,4,5,10-hexahydroazepino[3,4-*b*]-indole-1,5-dione (12d). According to the procedure for the synthesis of **12c**, compound **12d** was prepared in 72% yield using benzyl chloride (chromatography eluent: petroleum ether–ethyl acetate 4:6). Mp 127–128°C (ethyl acetate–petroleum ether); IR (KBr) ν 1649 (CO), 1637 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.70–2.75 (m, 2H, CH_2), 3.69–3.73 (m, 2H, CH_2), 4.10 (s, 3H, CH_3), 4.87 (s, 2H, CH_2), 7.31–7.44 (m, 8H, H_{Ar}), 8.37–8.41 (m, 1H, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 32.8 (CH_3), 43.5 (CH_2), 44.2 (CH_2), 50.8 (CH_2), 110.1 (CH), 115.5 (C), 123.5 (CH), 123.7 (CH), 125.0 (C), 125.6 (CH), 125.9 (C), 128.0 (CH), 128.3 (2CH), 129.0 (2CH), 131.7 (C), 138.6 (C), 162.2 (CO), 174.3 (CO); Anal. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.74; H, 5.86; N, 8.63; MS m/z 319 $(M+1)^+$.

2-(4-Methoxybenzyl)-10-methyl-1,2,3,4,5,10-hexahydroazepino[3,4-*b*]indole-1,5-dione (12e). According to the procedure for the synthesis of **12c**, compound **12e** was prepared in 78% yield using 4-methoxybenzyl chloride

(chromatography eluent: petroleum ether–ethyl acetate 1:1); mp 136–137°C (ethyl acetate–petroleum ether); IR (KBr) ν 1650 (CO), 1632 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.69–2.74 (m, 2H, CH_2), 3.71–3.75 (m, 2H, CH_2), 3.84 (s, 3H, CH_3), 4.11 (s, 3H, CH_3), 4.82 (s, 2H, CH_2), 6.90–6.93 (m, 2H, H_{Ar}), 7.29–7.45 (m, 6H, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 33.3 (CH_3), 44.1 (CH_2), 44.5 (CH_2), 50.7 (CH_2), 55.8 (CH_3), 110.0 (CH), 114.2 (2CH), 115.3 (C), 123.4 (CH), 123.5 (CH), 124.9 (C), 125.4 (CH), 128.8 (C), 129.6 (2CH), 134.5 (C), 138.4 (C), 159.2 (C), 161.3 (CO), 195.4 (CO); Anal. Calcd for $C_{21}H_{20}N_2O_2$: C, 72.40; H, 5.79; N, 8.04. Found: C, 72.06; H, 5.96; N, 8.20; MS m/z 349 $(M+1)^+$.

10-Methyl-2-phenylsulfonyl-1,2,3,4,5,10-hexahydroazepino[3,4-*b*]indole-1,5-dione (12f). According to the procedure for the synthesis of **12c**, compound **12f** was prepared in 90% yield using benzenesulfonyl chloride (chromatography eluent: petroleum ether–ethyl acetate 8:2); mp 187–188°C (ethyl acetate–petroleum ether); IR (KBr) ν 1672 (CO), 1646 (CO) 1354, 1165 (NSO_2) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.07–3.11 (m, 2H, CH_2), 3.93 (s, 3H, CH_3), 4.40–4.44 (m, 2H, CH_2), 7.31–7.39 (m, 3H, H_{Ar}), 7.56–7.65 (m, 3H, H_{Ar}), 8.10 (d, 2H, J=8.0 Hz, H_{Ar}), 8.34 (d, 1H, J=8.0 Hz, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 32.9 (CH_3), 42.3 (CH_2), 44.5 (CH_2), 110.4 (CH), 117.2 (C), 124.0 (CH), 124.4 (CH), 124.8 (C), 126.8 (CH), 128.8 (2CH), 129.1 (2CH), 131.2 (C), 134.3 (CH), 138.7 (C), 139.1 (C), 160.9 (CO), 194.4 (CO); Anal. Calcd for $C_{19}H_{16}N_2O_4S$: C, 61.94; H, 4.38; N, 7.60. Found: C, 61.63; H, 4.27; N, 7.89; MS m/z 369 $(M+1)^+$.

2-Acetyl-10-methyl-1-oxo-1,2,3,10-tetrahydroazepino-[3,4-*b*]indol-5-yl acetate (13a). Yield: 13%; gum; IR (film) ν 1707 (CO), 1652 (CO), 1641 (CO); ^1H NMR (250 MHz, $CDCl_3$) δ 2.29 (s, 3H, CH_3), 3.03 (s, 3H, CH_3), 4.06 (s, 3H, CH_3), 4.13–4.53 (m, 2H, CH_2), 6.05 (t, 1H, J=7.3 Hz, CH), 7.18–7.26 (m, 1H, H_{Ar}), 7.41–7.43 (m, 2H, H_{Ar}), 7.85 (d, 1H, J=8.0 Hz, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 22.1 (CH_3), 28.3 (CH_3), 33.7 (CH_3), 40.3 (CH_2), 111.6 (CH), 115.4 (CH), 116.6 (C), 122.9 (CH), 123.2 (CH), 123.8 (C), 127.4 (CH), 131.8 (C), 140.4 (C), 150.0 (C), 163.7 (CO), 169.5 (CO), 173.1 (CO); Anal. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.16; N, 8.97. Found: C, 65.69; H, 5.28; N, 8.80; MS m/z 313 $(M+1)^+$.

***tert*-Butyl 5-[(*tert*-butoxycarbonyl)oxy]-10-methyl-1-oxo-1,2,3,10-tetrahydroazepino[3,4-*b*]indole-2-carboxylate (13b).** Yield: 20%; mp 123–124°C (ethyl acetate–petroleum ether); IR (KBr) ν 1758 (CO), 1704 (CO), 1689 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.41 (s, 9H, $(CH_3)_3$), 1.55 (s, 9H, $(CH_3)_3$), 4.03 (s, 3H, CH_3), 4.14–4.24 (m, 2H, CH_2), 6.08 (t, 1H, J=7.3 Hz, CH), 7.16–7.22 (m, 1H, H_{Ar}), 7.35–7.37 (m, 2H, H_{Ar}), 7.93 (d, 1H, J=8.5 Hz, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 27.4 ($3CH_3$), 27.9 ($3CH_3$), 32.5 (CH_3), 41.7 (CH_2), 83.2 (C), 83.6 (C), 110.2 (CH), 112.6 (CH), 114.7 (C), 121.5 (CH), 122.2 (CH), 122.5 (C), 125.9 (CH), 130.9 (C), 138.8 (C), 149.6 (C), 150.6 (CO), 151.2 (CO), 160.8 (CO); Anal. Calcd for $C_{23}H_{28}N_2O_4$: C, 69.68; H, 7.12; N, 7.07. Found: C, 70.03; H, 7.28; N, 6.89; MS m/z 397 $(M+1)^+$.

2,4,10-Trimethyl-1,2,3,4,5,10-hexahydroazepino[3,4-*b*]-indole-1,5-dione (14). Yield: 12%; mp 146–147°C (ethyl acetate–petroleum ether); IR (KBr) ν broad 1638 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.35 (d, 3H, J= 7.8 Hz, CH_3), 2.88–2.95 (m, 1H, CH), 3.36 (s, 3H, CH_3), 3.76–3.81 (m, 2H, CH_2), 4.10 (s, 3H, CH_3), 7.36–7.47 (m, 3H, H_{Ar}), 8.42–8.46 (m, 1H, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 16.2 (CH_3), 34.1 (CH_3), 37.9 (CH_3), 48.4 (CH), 54.2 (CH_2), 111.5 (CH); 116.7 (C), 125.0 (2CH), 126.7 (C), 126.9 (CH), 135.5 (C), 139.9 (C), 162.9 (CO), 199.8 (CO); Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 69.91; H, 6.45; N, 11.12; MS m/z 257 $(M+1)^+$.

2,4,4,10-Tetramethyl-1,2,3,4,5,10-hexahydroazepino-[3,4-*b*]indole-1,5-dione (15). Yield: 3%; mp 105–106°C (ethyl acetate–petroleum ether); IR (KBr) ν 1642 broad (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.33 (s, 6H, $(CH_3)_2$), 3.34 (s, 3H, CH_3), 3.58–3.78 (m, 2H, CH_2), 4.12 (s, 3H, CH_3), 7.36–7.47 (m, 3H, H_{Ar}), 8.37–8.40 (m, 1H, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 23.3 ($2CH_3$), 32.6 (CH_3), 37.4 (CH_3), 49.5 (C), 58.4 (CH_2), 110.2 (CH), 115.4 (C), 123.5 (2CH), 125.5 (CH), 125.9 (C), 133.6 (C), 138.5 (C), 161.6 (CO), 200.7 (CO); Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.43; H, 6.60; N, 10.42; MS m/z 271 $(M+1)^+$.

10-Methyl-1-oxo-1,2,3,10-tetrahydroazepino[3,4-*b*]indol-5-yl trifluoromethanesulfonate (16). Yield: 20–30%; mp 202–203°C (ethyl acetate–petroleum ether); IR (KBr) ν 3212 (NH), 1640 (CO), 1407 (OSO_2), 1209 (OSO_2) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.65 (dd (d if D_2O exchange), 2H, J=6.0, 7.5 Hz, CH_2), 4.11 (s, 3H, CH_3), 6.08 (t, 1H, J=7.5 Hz, CH), 7.24–7.33 (m, 4H, NH+H_{Ar}), 7.96–7.99 (m, 1H, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 32.3 (CH_3), 37.2 (CH_2), 110.5 (CH), 111.4 (C), 114.7 (CH), 118.4 (q, J=320 Hz, CF_3), 122.1 (CH), 122.3 (CH), 122.8 (C), 125.9 (CH), 131.4 (C), 138.5 (C), 148.9 (C), 163.4 (CO); Anal. Calcd for $C_{14}H_{11}F_3N_2O_4S$: C, 46.67; H, 3.08; N, 7.77. Found: C, 46.98; H, 2.94; N, 7.92; MS m/z 361 $(M+1)^+$.

10-Methyl-2-(trifluoromethylsulfonyl)-1,2,3,4,5,10-hexahydroazepino[3,4-*b*]indole-1,5-dione (17). According to the procedure for the synthesis of **3a**, compound **17** was prepared from **12b** in 82% yield; mp 192–193°C (ethyl acetate–petroleum ether); IR (KBr) ν 1684 (CO), 1653 (CO), 1407 (NSO_2), 1215 (NSO_2) cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 3.14 (t, 2H, J=5.3 Hz, CH_2), 4.08 (s, 3H, CH_3), 4.33 (t, 2H, J=5.3 Hz, CH_2), 7.40 (t, 1H, J=8.0 Hz, H_{Ar}), 7.54 (t, 1H, J=8.0 Hz, H_{Ar}), 7.79 (d, 1H, J=8.0 Hz, H_{Ar}), 8.26 (d, 1H, J=8.0 Hz, H_{Ar}); ^{13}C NMR (62.90 MHz, DMSO-d_6) δ 33.0 (CH_3), 44.1 (CH_2), 45.2 (CH_2), 111.5 (CH), 117.2 (C), 123.1 (CH), 124.0 (C), 124.1 (CH), 124.4 (q, J=290 Hz, CF_3), 126.9 (CH), 130.1 (C), 139.1 (C), 160.4 (CO), 194.1 (CO); Anal. Calcd for $C_{14}H_{11}F_3N_2O_4S$: C, 46.67; H, 3.08; N, 7.77. Found: C, 46.32; H, 3.15; N, 7.89; MS m/z 361 $(M+1)^+$.

General procedure for the Stille reaction with 3d (method A)

To a suspension of freshly prepared tetrakis(triphenylphosphine)palladium (15 mg, 0.013 mmol) and LiCl (26 mg, 0.61 mmol) in dry DMF was added a solution of **3d**

(100 mg, 0.22 mmol) and stannane (tributylvinylstannane for **18**, tetramethylstannane for **19**, tributyl(1-ethoxyvinyl)-stannane for **20** or tributyl-2-furanylstannane for **21**, 0.33 mmol) in dry DMF under argon. The solution was stirred at 100°C for 2 h. The solvent was then removed in vacuo and the crude residue was purified by column chromatography (eluent: toluene for **18** and **20**, toluene–ethyl acetate 1:1 for **19** and petroleum ether–ethyl acetate 6:4 for **21**) to give the desired compounds.

2-Benzyl-10-methyl-5-vinyl-1,2,3,10-tetrahydroazepino-[3,4-*b*]indol-1-one (18). Yield: 90%; mp 153–154°C (methanol); IR (KBr) ν 1622 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.65 (d, 2H, J=7.0 Hz, CH_2), 4.08 (s, 3H, CH_3), 4.80–4.90 (m, 2H, CH_2), 5.29 (dd, 1H, J= 1.3, 10.5 Hz, =CH_2), 5.48 (dd, 1H, J=1.3, 17.5 Hz, =CH_2), 5.94 (t, 1H, J=7.0 Hz, CH), 6.07 (dd, 1H, J= 10.5, 17.5 Hz, CH), 7.14–7.20 (m, 1H, H_{Ar}), 7.31–7.47 (m, 7H, H_{Ar}), 7.84 (d, 1H, J=8.0 Hz, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 32.1 (CH_3), 45.0 (CH_2), 50.5 (CH_2), 110.1 (CH), 116.1 (C), 117.8 (CH_2), 120.1 (CH), 122.7 (CH), 123.0 (CH), 124.5 (C), 124.6 (CH), 127.6 (CH), 128.1 (2CH), 128.7 (2CH), 132.6 (C), 136.2 (CH), 137.9 (C), 138.4 (C), 139.2 (C), 162.4 (CO); Anal. Calcd for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.14; N, 8.53. Found: C, 80.77; H, 6.00; N, 8.69; MS m/z 329 $(M+1)^+$.

2-Benzyl-5,10-dimethyl-1,2,3,10-tetrahydroazepino[3,4-*b*]-indol-1-one (19). Yield: 99%; gum; IR (film) ν 1623 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.42 (s, 3H, CH_3), 3.62 (d, 2H, J=7.0 Hz, CH_2), 4.11 (s, 3H, CH_3), 4.84 (s, 2H, CH_2), 5.71 (t, 1H, J=7.0 Hz, CH), 7.17–7.27 (m, 1H, H_{Ar}), 7.31–7.44 (m, 7H, H_{Ar}), 7.90 (d, 1H, J=8.2 Hz, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 21.8 (CH_3), 32.1 (CH_3), 45.0 (CH_2), 50.4 (CH_2), 110.1 (CH), 119.3 (C), 120.3 (CH), 120.9 (CH), 122.4 (CH), 124.4 (CH), 124.5 (C), 127.4 (CH), 128.0 (2CH), 128.6 (2CH), 132.0 (C), 136.7 (C), 138.0 (C), 138.6 (C), 162.0 (CO); Anal. Calcd for $C_{21}H_{20}N_2O$: C, 79.72; H, 6.37; N, 8.85. Found: C, 79.38; H, 6.53; N, 8.98; MS m/z 317 $(M+1)^+$.

2-Benzyl-10-methyl-5-(1-ethoxyvinyl)-1,2,3,10-tetrahydro-azepino[3,4-*b*]indol-1-one (20). Yield: 92%; mp 129–130°C (methanol); IR (KBr) ν 1628 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.33 (t, 3H, J=7.0 Hz, CH_3), 3.71 (d, 2H, J=7.0 Hz, CH_2), 3.94 (q, 2H, J=7.0 Hz, CH_2), 4.15 (s, 3H, CH_3), 4.36 (d, 1H, J=2.0 Hz, =CH_2), 4.45 (d, 1H, J= 2.0 Hz, =CH_2), 4.75–5.06 (m, 2H, CH_2), 6.34 (t, 1H, J= 7.0 Hz, CH), 7.17–7.21 (m, 1H, H_{Ar}), 7.36–7.48 (m, 7H, H_{Ar}), 7.81 (d, 1H, J=8.0 Hz, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 14.5 (CH_3), 32.1 (CH_3), 44.9 (CH_2), 50.4 (CH_2), 63.5 (CH_2), 87.1 (CH_2), 110.0 (CH), 115.8 (C), 120.1 (CH), 122.6 (CH), 122.8 (CH), 124.5 (CH), 124.6 (C), 127.6 (CH), 128.1 (2CH), 128.7 (2CH), 133.0 (C), 137.8 (C), 137.9 (C), 138.3 (C), 159.6 (C), 162.4 (CO); Anal. Calcd for $C_{24}H_{24}N_2O_2$: C, 77.39; H, 6.49; N, 7.52. Found: C, 77.68; H, 6.57; N, 7.70; MS m/z 373 $(M+1)^+$.

2-Benzyl-10-methyl-5-(2-furanyl)-1,2,3,10-tetrahydroaze-pino[3,4-*b*]indol-1-one (21). Yield: 74%; mp 110–111°C (methanol); IR (KBr) ν 1627 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.76 (t, 2H, J=7.3 Hz, CH_2), 4.14 (s, 3H, CH_3), 4.76–4.94 (m, 2H, CH_2), 6.33 (t, 1H, J=7.3 Hz, CH), 6.40–6.42 (m, 1H, H_{Ar}), 6.46–6.48 (m, 1H, H_{Ar}), 7.09–7.13 (m, 1H, H_{Ar}), 7.19–7.22 (m, 1H, H_{Ar}), 7.29–7.46 (m, 8H, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 32.0 (CH_3), 44.7 (CH_2), 50.3 (CH_2), 109.6 (CH), 110.0 (CH), 111.2 (CH), 115.2 (C), 120.2 (CH), 120.4 (CH), 122.5 (CH), 124.3 (C), 124.5 (CH), 127.6 (CH), 128.0 (2CH), 128.7 (2CH), 130.7 (C), 133.2 (C), 137.7 (C), 138.2 (C), 142.1 (CH), 152.7 (C), 162.3 (CO); Anal. Calcd for $C_{24}H_{20}N_2O_2$: C, 78.24; H, 5.47; N, 7.60. Found: C, 78.52; H, 5.61; N, 7.48; MS m/z 369 $(M+1)^+$.

General procedure for the Suzuki reaction with 3d (method B)

To a stirred solution of **3d** (100 mg, 0.22 mmol) in dry toluene (5 mL) was added freshly prepared tetrakis(triphenylphosphine)palladium (15 mg, 0.013 mmol). The solution was stirred for 30 min at room temperature. Boronic acid (2- or 3-thiophenylboronic acid for **22** or **23** and phenylboronic acid for **24**, 0.33 mmol) diluted in absolute ethanol (2 mL) was then added, followed immediately by saturated aqueous hydrogenocarbonate (2 mL). The heterogeneous solution was stirred at 80°C for 1 h. Brine solution was then added, the two layers were separated and the aqueous phase was extracted with dichloromethane (3×5 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo. The crude residue was purified by column chromatography (eluent: toluene–ethyl acetate 9:1) to give the desired compound.

2-Benzyl-10-methyl-5-(2-thienyl)-1,2,3,10-tetrahydroaze-pino[3,4-*b*]indol-1-one (22). Yield: 90%; mp 139–140°C (methanol); IR (KBr) ν 1625 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.74 (d, 2H, J=7.0 Hz, CH_2), 4.15 (s, 3H, CH_3), 4.65–5.15 (m, 2H, CH_2), 6.13 (t, 1H, J= 7.0 Hz, CH), 6.99–7.04 (m, 3H, H_{Ar}), 7.20–7.36 (m, 9H, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 32.1 (CH_3), 44.9 (CH_2), 50.4 (CH_2), 110.0 (CH), 116.7 (C), 120.1 (CH), 122.0 (CH), 122.7 (CH), 124.4 (C), 124.5 (CH), 125.1 (CH), 127.1 (CH), 127.3 (CH), 127.6 (CH), 128.0 (2CH), 128.7 (2CH), 133.0 (C), 134.8 (C), 137.6 (C), 138.3 (C), 142.7 (C), 162.3 (CO); Anal. Calcd for $C_{24}H_{20}N_2OS$: C, 74.97; H, 5.24; N, 7.29. Found: C, 75.33; H, 5.18; N, 7.47; MS m/z 385 $(M+1)^+$.

2-Benzyl-10-methyl-5-(3-thienyl)-1,2,3,10-tetrahydroaze-pino[3,4-*b*]indol-1-one (23). Yield: 99%; mp 97–98°C (methanol); IR (KBr) ν 1625 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.73 (t, 2H, J=6.9 Hz, CH_2), 4.13 (s, 3H, CH_3), 4.57–5.09 (m, 2H, CH_2), 6.07 (t, 1H, J=6.9 Hz, CH), 6.87–7.05 (m, 3H, H_{Ar}), 7.18–7.43 (m, 9H, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 32.1 (CH_3), 44.9 (CH_2), 50.4 (CH_2), 109.9 (CH), 117.2 (C), 119.7 (C), 120.1 (CH), 121.2 (CH), 122.6 (CH), 123.2 (CH), 124.5 (CH), 125.3 (CH), 126.0 (C), 126.3 (CH), 127.5 (CH), 128.0 (2CH), 128.7 (2CH), 136.3 (C), 137.7 (C), 138.4 (C), 141.4 (C), 162.3 (CO); Anal. Calcd for $C_{24}H_{20}N_2OS$: C, 74.97; H, 5.24; N, 7.29; Found: C, 75.23; H, 5.12; N, 7.15; MS m/z 385 $(M+1)^+$.

2-Benzyl-10-methyl-5-phenyl-1,2,3,10-tetrahydroazepino-[3,4-*b*]indol-1-one (24). Yield: 86%; mp 173–174°C (methanol); IR (KBr) ν 1622 (CO) cm^{-1}; ^1H NMR

(250 MHz, $CDCl_3$) δ 3.75 (t, 2H, J=7.5 Hz, CH_2), 4,13 (s, 3H, CH_3), 4.81–4.90 (m, 2H, CH_2), 6.69 (t, 1H, J=7.5 Hz, CH), 6.65–6.69 (m, 1H, H_{Ar}), 6.85–6.88 (m, 1H, H_{Ar}), 7.22–7.42 (m, 12H, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 32.1 (CH_3), 45.1 (CH_2), 50.4 (CH_2), 109.9 (CH), 117.2 (C), 120.0 (CH), 122.0 (CH), 122.7 (CH), 124.4 (CH), 124.5 (C), 127.5 (CH), 127.9 (CH), 128.0 (2CH), 128.3 (2CH), 128.5 (2CH), 128.7 (2CH), 133.2 (C), 137.7 (C), 138.4 (C), 140.3 (C), 142.0 (C), 162,3 (CO); Anal. Calcd for $C_{26}H_{22}N_2O$: C, 82.51; H, 5.86; N, 7.40. Found: C, 82.17; H, 5.96; N, 7.57; MS m/z 379 $(M+1)^+$.

2-(4-Methoxybenzyl)-10-methyl-5-(2-thienyl)-1,2,3,10-tetrahydroazepino[3,4-*b*]indol-1-one (25). According to *method B*, compound **25** was prepared from **3e** and 2-thiophenylboronic acid in 86% yield (chromatography eluent: dichloromethane–ethyl acetate 9:1). Mp 111–112°C (methanol); IR (KBr) ν 1627 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.75 (d, 2H, J=7.0 Hz, CH_2), 3.84 (s, 3H, CH_3), 4.18 (s, 3H, CH_3), 4.65–5.00 (m, 2H, CH_2), 6.15 (t, 1H, J=7.0 Hz, CH), 6.90–6.94 (m, 2H, H_{Ar}), 7.02–7.07 (m, 4H, H_{Ar}), 7.31–7.46 (m, 5H, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$,) δ 32.0 (CH_3), 44.6 (CH_2), 49.7 (CH_2), 55.2 (CH_3), 110.0 (CH), 114.0 (2CH), 116.6 (C), 120.0 (CH), 122.1 (CH), 122.6 (CH), 124.4 (CH), 125.0 (CH), 125.8 (C), 127.0 (CH), 127.3 (CH), 129.4 (2CH), 129.7 (C), 133.1 (C), 134.6 (C), 138.2 (C), 142.7 (C), 159.0 (C), 162.1 (CO); Anal. Calcd for $C_{25}H_{22}N_2O_2S$: C, 72.44; H, 5.35; N, 6.76. Found: C, 72.17; H, 5.20; N, 6.92; MS m/z 415 $(M+1)^+$.

5,10-Dimethyl-2-phenylsulfonyl-1,2,3,10-tetrahydroazepino[3,4-*b*]indol-1-one (26). To a suspension of freshly prepared tetrakis(triphenylphosphine)palladium (17 mg, 0.015 mmol) and LiCl (28 mg, 0.67 mmol) in dry DMF was added a solution of **3f** (120 mg, 0.24 mmol) and tetramethylstannane (45 μL, 0.36 mmol) in dry DMF. The solution was stirred under argon at 100°C for 2 h. The solvent was then removed in vacuo and the crude residue was purified by column chromatography (eluent: toluene–ethyl acetate 1:1) to give **26** (67 mg, 76%) as solid; mp 141–142°C (methanol); IR (KBr) ν 1676 (CO), 1354 (NSO_2), 1167 (NSO_2) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.45 (s, 3H, CH_3), 3.91 (s, 3H, CH_3), 4.60–5.15 (broad s, 2H, CH_2), 6.17 (t, 1H, J=7.0 Hz, CH), 7.13–7.21 (m, 1H, H_{Ar}), 7.35–7.39 (m, 2H, H_{Ar}), 7.46–7.57 (m, 3H, H_{Ar}), 7.88 (d, 1H, J=8.5 Hz, H_{Ar}), 7.98–8.04 (m, 2H, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 22.1 (CH_3), 32.2 (CH_3), 43.3 (CH_2), 110.4 (CH), 121.0 (CH), 121.1 (C), 121.7 (CH), 122.9 (CH), 124.0 (C), 125.8 (CH), 128.6 (2CH), 128.7 (2CH), 129.5 (C), 133.5 (CH), 138.0 (C), 139.0 (C), 139.2 (C), 161.0 (CO); Anal. Calcd for $C_{20}H_{18}N_2O_3S$: C, 65.56; H, 4.95; N, 7.64. Found: C, 65.89; H, 5.11; N, 7.43; MS m/z 367 $(M+1)^+$.

10-Methyl-5-(2-thienyl)-1,2,3,10-tetrahydroazepino[3,4-*b*]-indol-1-one (27). According to the procedure for the synthesis of **26**, compound **27** was prepared from **16** and tributyl(2-thiophenyl)stannane in 71% yield (chromatography eluent: petroleum ether–ethyl acetate 8:2). Mp 194–195°C (ethanol); IR (KBr) ν 3168 (NH), 1648 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.61 (dd (d if D_2O exchange), 2H, J=6.0, 7.5 Hz, CH_2), 4.12 (s, 3H, CH_3), 6.27 (t, 1H, J=7.5 Hz, CH), 6.94–7.03 (m, 5H, NH+H_{Ar}), 7.25–7.41 (m, 3H, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 32.1 (CH_3), 38.8 (CH_2), 110.2 (CH), 117.6 (C), 120.3 (CH), 123.0 (CH), 123.1 (CH), 124.7 (C), 124.9 (CH), 125.2 (CH), 127.1 (CH), 127.4 (CH), 131.7 (C), 134.7 (C), 138.6 (C), 143.1 (C), 164.6 (CO); Anal. Calcd for $C_{17}H_{14}N_2OS$: C, 69.36; H, 4.79; N, 9.52. Found: C, 69.72; H, 4.58; N, 9.65; MS m/z 295 $(M+1)^+$.

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