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Synthesis of 4-substituted azepino[3,4-*b*]indole-1,5-diones

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Abstract—Mono- or dibromo derivatives **2** and **3** were prepared by an efficient two-step route from 10-methyl-azepino[3,4-*b*]indole-1,5-dione **1**. Elimination reaction on **2** gave access to 4-bromo-10-methyl-2*H*,10*H*-azepino[3,4-*b*]indole-1,5-diones **4**. Finally, 4-substituted 10-methyl-2*H*,10*H*-azepino[3,4-*b*]indole-1,5-diones **6**–**14** were synthesised in good yields from **4** via palladium-mediated cross-coupling reactions.

1. Introduction

Azepino[3,4-*b*]pyrrole scaffold is found in natural products such as hymenialdisine, stevensine or hymenin and displays several biological properties (Fig. 1).[1] Among the related indole derivatives prepared, azepino[3,4-*b*]indole compounds **I** were published as potent myt 1 kinase inhibitors.[2] For our part, we have developed the syntheses of α,β-unsaturated ester **II** and 5-substituted azepino[3,4-*b*]indole-1-ones **III** through palladium-mediated cross-coupling reactions (Fig. 1).[3]

Following a similar synthetic approach based on palladium cross-coupling reactions, we have prepared a new series of 4-substituted azepino[3,4-*b*]indole-1,5-diones **IV** and derivatives with potential biological properties (Fig. 1).[4] To the best of our knowledge, this 4-substituted tricyclic skeleton has not been yet described in the literature. Nevertheless, a closed structure **V** was elaborated, using an other pathway, by Troschutz and Hoffman.[5]

2. Results and discussion

In this paper, we reported our results concerning the reactivity of derivatives **2**–**5** and the synthesis of a new family of compounds with an indole nucleus and different heterocycles or alkenyl chains around a central seven-membered ring. The synthesis of azepino[3,4-*b*]indole-1,5-dione **1** was reported in the literature.[3a–6] Reactivity studies on compound **1** reveal that electrophilic attack in α-position of the ketone in position-5 of the azepino ring was effective.[3a] Thus, dibromo derivative **2a** was prepared in 93% yield from **1a** in the presence of LiHMDS (3 equiv.) in THF at −78°C, followed by addition of dibromine (2 equiv.). The modification of the experimental procedure (LiHMDS (1.8 equiv.) then Br_2 (1 equiv.) afforded compounds **2a** and **3a** in 7 and 88% yield, respectively (Scheme 1).

Compound **2b** was also prepared from **1b** in the presence of 1,2-dibromotetrachloroethane in 90% yield. It should be noted that when LDA was used as base, the corresponding anion was not stable and the α-bromination yield was always low.

Attempts of nucleophilic substitution followed by intramolecular addition-elimination reaction on **2a** and **3a** with diamines such as 1,2-diaminoethane or 1,2-phenylenediamine failed to afford new derivatives with a supplementary fused aza ring between position-4 and -5 of azepino moiety. In all cases, elimination of hydrogen bromide on **2a** or **3a** was observed to give derivatives **4a** or **5a**.

The elimination reaction was optimised by replacement of amines by DBU as base. Thus, treatment of bromo derivatives **2a**,**b** or **3a** with DBU (1 equiv.) in DMF led to **4a**,**b** or **5a** in good yields (93–95%) (Scheme 2). The PMB group of **4a** and **5a** was readily removed by treatment with TFA providing the corresponding azepino derivatives **4a** and **5a** (51 and 68% yield).[7] Boc protection on **4b** was carried out in the presence of Boc_2O and DMAP in acetonitrile to afford **4c** in 61% yield.

Keywords: elimination; cross-coupling reactions; seven-membered ring.
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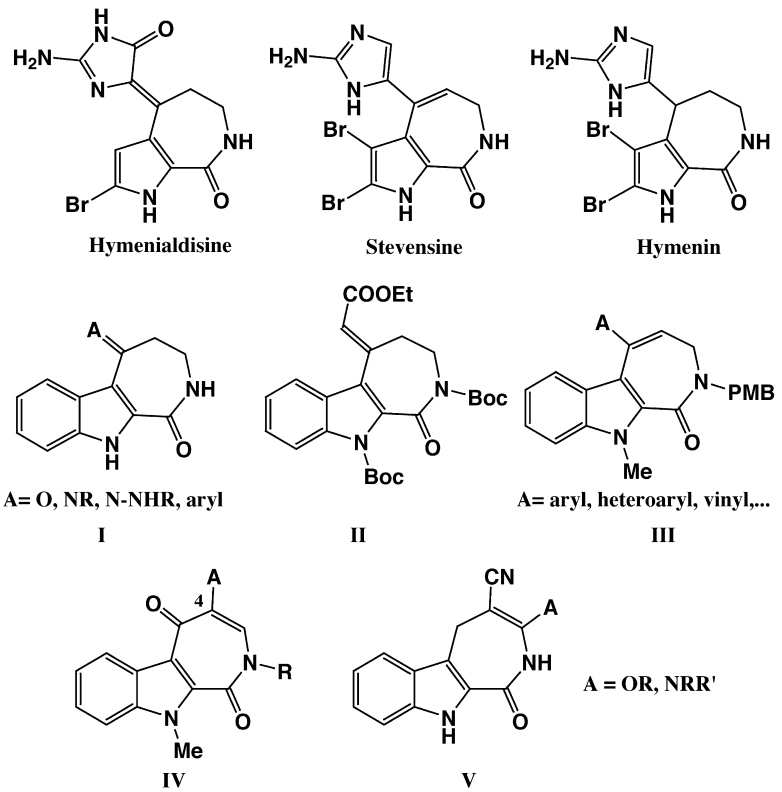
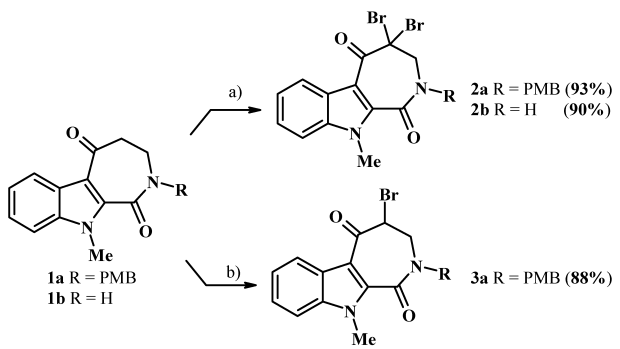


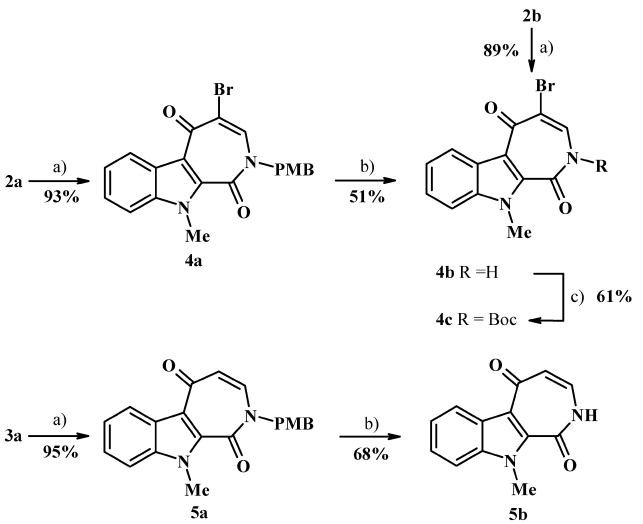
Figure 1.

Suzuki and Stille coupling reactions[8,9] were performed on protected (PMB, Boc) or unprotected α-bromo-α,β-unsaturated ketones **4** to give access to 4-substituted derivatives **6–14**. According to the Suzuki procedure, the desired compounds **6–12** were prepared from commercially available boronic acids (1.5 equiv.), $Pd(PPh_3)_4$ (10% mol) and saturated aqueous hydrogenocarbonate as inorganic base in toluene–ethanol. The phenyl derivatives **6a–c** were prepared from **4a–c**. The best coupling reaction yield was observed from the PMB protected starting material **6a** (84% yield). The compounds **7–12** were prepared from their corresponding boronic acids in 68–97% yield (Scheme 3).

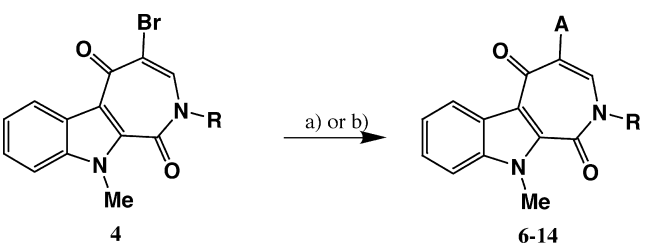
Stille reaction was also investigated. Vinyltributyl- stannane and 1-ethoxyvinyltributylstannane (2 equiv.) were coupled



Scheme 1. (a) (i) LiHMDS (3 equiv.), THF, −78°C, 1 h (ii) Br_2 (2 equiv.), 15 min, −78°C or 1,2-dibromotetrachloroethane (2.5 equiv.), 30 min, −78°C; (b) (i) LiHMDS (1.8 equiv.), THF, −78°C, 1 h (ii) Br_2 (1 equiv.), −78°C, 15 min.



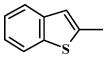
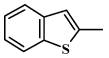
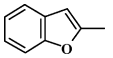
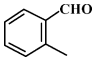
Scheme 2. (a) DBU (1 equiv.), DMF, rt, 30 min; (b) TFA, reflux, 24 h; (c) DMAP, Boc_2O (2 equiv.), CH_3CN, rt, 24 h.



Scheme 3. (a) $Pd(PPh_3)_4$ (10% mol), A–$B(OH)_2$ (1.5 equiv.), toluene–EtOH–aq. sat. $NaHCO_3$, 80°C, 1 h; (b) $Pd(PPh_3)_4$ (10% mol), A-$SnBu_3$ (2 equiv.), DMF, 100°C, 1 h.

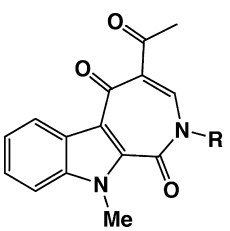
to **4a** to give **13a** and **14a** in 87–95% yield. The compounds **13b** and **14b** were obtained in 28–31% yield from **4c**.

Coupling reaction yields were always better when protected ketone **4a**-**b** were used. The difference of yields observed between both protective groups is explained by Boc hydrolysis of coupling derivatives (**6b**, **10b**) in the reaction medium

Compound	Entry	R	A	Yield (%)[a]
6a	a	PMB		84
6b	a	Boc		66
6c	a	H		44
7	a	PMB		85
8	a	PMB		76
9	a	PMB		82
10a	a	PMB		97
10b	a	Boc		68
11	a	PMB		77
12	a	PMB		96
13a	b	PMB		87
13b	b	H		31
14a	b	PMB		95
14b	b	H		28

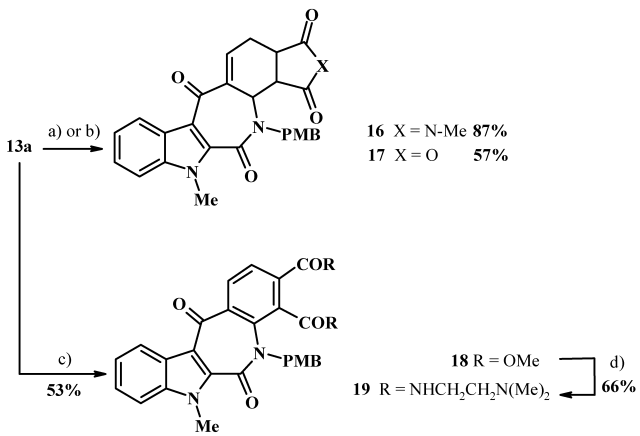
[a] Yield isolated.

Vinylethers **14a**,**b** were hydrolysed in acidic medium (10% HCl, acetone, room temperature, 1 h) to afford the diketo derivatives **15a**,**b** in quantitative yield.



15a R = PMB
15b R = H

The vinyl compound **13a** was engaged in [4+2] cycloaddition reactions with various dienophiles such as dimethyl acetylenedicarboxylate (DMAD), *N*-methyl-maleimide or maleic anhydride to afford unknown tetracyclic compounds **16**–**18** in 53–87% yield. Amide **19** was prepared from **18** in the presence of 2,2-dimethylaminoethylamine in 66% yield (Scheme 4).



Scheme 4. (a) *N*-methylmaleimide (2 equiv.), toluene, sealed tube, 180°C, 1 h; (b) maleic anhydride (2 equiv.), toluene, sealed tube, 180°C, 1 h; (c) DMAD (2 equiv.), toluene, sealed tube, 180°C, 3 h; (d) 2,2-dimethylaminoethylamine, 100°C, 24 h.

3. Conclusion

In summary, we have developed an efficient route to 4-substituted 10-methyl-2*H*,10*H*-azepino[3,4-*b*]indole-1,5-diones **6**–**14** from the corresponding bromides **4** through palladium-catalysed reactions.

4. Experimental

4.1. Chemistry

Melting point were determined using a Büchi SMP-20 melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 K in $CDCl_3$ or DMSO-d_6 on a Bruker Avance DPX 250. The chemical shifts are reported in ppm (δ scale) and all J values are in Hz. The infrared spectra of compounds were recorded on a Perkin–Elmer FTIR PARAGON 1000 PC and values were reported in cm^{-1}. MS spectra (Ion Spray) were performed on a Perkin–Elmer Sciex PI 300. Monitoring of the reactions was performed using silica gel TLC plates (silica Merck 60 F_{254}). Spots were visualised by UV light at 254 and 365 nm. Column chromatography were performed using silica gel 60 (0.063–0.200 mm, Merck). Stannanes and boronic acids were purchased from Lancaster or Sigma-Aldrich companies.

4.1.1. 4,4-Dibromo-2-(4-methoxybenzyl)-10-methyl-3,4-dihydro-2*H*,10*H*-azepino[3,4-*b*]indole-1,5-dione (2a). Under argon, a solution of LiHMDS (3.62 mL, 3.62 mmol, 1 M in THF) was added dropwise to a stirred solution of **1a** (420 mg, 1.21 mmol) in dry THF (20 mL) at −78°C. After 1 h, a solution of bromine (0.12 mL, 2.41 mmol) in THF (10 mL) was slowly added to the mixture. After 15 min, hydrolysis was performed by

addition of aq. sat. NH_4Cl. After extraction with ethyl acetate (50 mL), the combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo. The crude residue was purified by column chromatography on silica gel (petroleum ether–ethyl acetate 7:3) to afford compound **2a** as a yellow solid (560 mg, 93%). Mp 158–160°C (ethyl acetate–petroleum ether); IR (KBr) ν 1651 (CO), 1610 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.82 (s, 3H, CH_3), 4.11 (s, 3H, CH_3), 4.34 (br s, 2H, CH_2), 5.73 (br s, 2H, CH_2), 6.93 (d, 2H, J=8.5 Hz, H_{Ar}), 7.32–7.47 (m, 5H, H_{Ar}), 8.31 (d, 1H, J=7.7 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$, 62.90 MHz) δ 33.2 (CH_3), 51.4 (CH_2), 55.5 (CH_3), 58.3 (CH_2), 67.9 (C), 110.6 (CH), 114.5 (2CH), 114.0 (C), 123.5 (CH), 124.5 (CH), 126.0 (C), 126.5 (CH), 128.0 (C), 130.0 (2CH), 132.9 (C), 139.0 (C), 159.7 (C), 161.6 (CO), 184.0 (CO); MS (IS) *m/z* 527 (^{79}Br, M+Na)$^+$, 529 (^{79}Br+^{81}Br, M+Na)$^+$, 531 (^{81}Br, M+Na)$^+$. Anal. calcd for $C_{21}H_{18}Br_2N_2O_3$: C, 49.83; H, 3.58; N, 5.53. Found: C, 49.58; H, 3.67; N, 5.69.

4.1.2. 4,4-Dibromo-10-methyl-3,4-dihydro-2*H*,10*H*-azepino[3,4-*b*]indole-1,5-dione (2b). Under argon, a solution of LiHMDS (15.8 mL, 15.8 mmol, 1 M in THF) was added dropwise to a stirred solution of **1b** (0.80 g, 3.51 mmol) in dry THF (50 mL) at −78°C. After 1 h, a solution of 1,2-dibromotetrachloroethane (2.85 g, 8.77 mmol) in THF (10 mL) was slowly added to the mixture. After 30 min, hydrolysis was performed by addition of aq. sat. NH_4Cl. After extraction with ethyl acetate (3×50 mL), the combined organic extracts were dried over $MgSO_4$, filtered and evaporated in vacuo. The crude product was recrystallised from ethyl acetate–petroleum ether to afford **2b** (1.21 g, 90%) as a yellow solid. Mp 186–188°C (ethyl acetate–petroleum ether); IR (KBr) ν 3310 (NH), 1670 (CO), 1625 (CO) cm^{-1}; ^1H NMR (DMSO-d_6, 250 MHz) δ 4.03 (s, 3H, CH_3), 4.10 (br s, 2H, CH_2), 7.32–7.51 (m, 2H), 7.74 (d, 1H, J=8.2 Hz), 8.15 (d, 1H, J=8.0 Hz), 9.48 (t, 1H, J=4.2 Hz); ^{13}C NMR (DMSO-d_6, 62.90 MHz) δ 32.7 (CH_3), 52.6 (CH_2), 70.5 (C), 108.9 (C), 111.7 (CH), 122.1 (CH), 124.1 (CH), 125.2 (C), 125.9 (CH), 134.0 (C), 138.4 (C), 161.8 (CO), 184.3 (CO); MS (IS) *m/z* 385 (^{79}Br, M+H)$^+$, 387 (^{79}Br+^{81}Br, M+H)$^+$, 389 (^{81}Br, M+H)$^+$. Anal. calcd for $C_{13}H_{10}Br_2N_2O_2$: C, 40.45; H, 2.61; N, 7.26. Found: C, 40.77; H, 2.44; N, 7.43.

4.1.3. 4-Bromo-2-(4-methoxybenzyl)-10-methyl-3,4-dihydro-2*H*,10*H*-azepino[3,4-*b*]indole-1,5-dione (3a). Under argon, a solution of LiHMDS (0.77 mL, 0.77 mmol, 1 M in THF) was added dropwise under argon to a stirred solution of **1a** (150 mg, 0.43 mmol) in dry THF (20 mL) at −78°C. After 1 h, a solution of bromine (0.02 mL, 0.43 mmol) in THF (1 mL) was slowly added to the mixture. After 15 min, hydrolysis was performed by addition of aq. sat. NH_4Cl. After extraction with ethyl acetate (50 mL), the combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo. The crude residue was purified by column chromatography on silica gel (petroleum ether–EtOAc 7:3) to afford **2a** (15 mg, 7%) and **3a** (160 mg, 88%) as a yellow oil. Compound **3a** was unstable and was used directly in the next step. ^1H NMR ($CDCl_3$, 250 MHz) δ 3.82 (s, 3H, CH_3), 3.95 (m, 2H, CH_2), 4.12 (s, 3H, CH_2), 4.36 (br d, 1H, J=14.0 Hz, CH_2), 4.57 (br t, 1H, J=4.0 Hz, CH), 5.48 (br d, 1H, J=14.0 Hz, CH_2), 6.91 (d, 2H, J=8.5 Hz, H_{Ar}), 7.34–7.47 (m, 5H, H_{Ar}), 8.39 (d, 1H, J=8.0 Hz, H_{Ar}).

4.1.4. 4-Bromo-2-(4-methoxybenzyl)-10-methyl-2*H*,10*H*-azepino[3,4-*b*]indole-1,5-dione (4a). DBU (0.30 mL, 1.96 mmol) was added to a solution of **2a** (1.00 g, 1.96 mmol) in DMF (10 mL). The solution was stirred at room temperature for 30 min followed by addition of 10% HCl solution. After filtration, the residue was washed with water. The solid obtained was partitioned between dichloromethane (30 mL) and water. After extraction, organic layers were dried over $MgSO_4$, filtered and evaporated in vacuo. The crude residue was recrystallised from toluene to afford **4a** (0.81 mg, 93%) as a yellow solid. Mp 178–180°C (toluene); IR (KBr) ν 1640 (CO), 1608 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.80 (s, 3H, CH_3), 4.25 (s, 3H, CH_3), 5.15 (s, 2H, CH_2), 6.91 (d, 2H, J=8.5 Hz, H_{Ar}), 7.26–7.55 (m, 5H, H_{Ar}), 7.82 (s, 1H, H_{Ar}), 8.88 (d, 1H, J=8.3 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$, 62.90 MHz) δ 34.4 (CH_3), 55.4 (CH_3), 56.0 (CH_2), 110.3 (CH), 112.9 (C), 114.5 (2CH), 118.6 (C), 124.1 (CH), 125.2 (C), 125.4 (CH), 126.0 (C), 127.8 (CH), 129.5 (2CH), 130.8 (C), 135.9 (CH), 139.9 (C), 159.7 (C), 159.8 (CO), 175.4 (CO); MS (IS) *m/z* 425 (^{79}Br, M+H)$^+$, 427 (^{81}Br, M+H)$^+$. Anal. calcd for $C_{21}H_{17}BrN_2O_3$: C, 59.31; H, 4.03; N, 6.59. Found: C, 59.55; H, 4.17; N, 6.42.

4.1.5. 4-Bromo-10-methyl-2*H*,10*H*-azepino[3,4-*b*]indole-1,5-dione (4b). *Method 1*: DBU (1.28 mL, 8.42 mmol) was added to a solution of **2b** (1.30 g, 3.37 mmol) in DMF (10 mL). The solution was stirred at room temperature for 30 min followed by addition of 10% HCl solution. After filtration, the residue was washed with water and ether. Compound **4b** was obtained as a yellow solid (920 mg, 89%).

Method 2: Under argon, a solution of **4a** (200 mg, 0.47 mmol) in trifluoroacetic acid (3 mL) was stirred at reflux for 24 h. After cooling, the mixture was poured into ice and neutralised by 10% NaOH solution. After filtration, the crude product was recrystallised once from ethyl acetate–petroleum ether to give **4b** as a yellow solid (73 mg, 51%). Mp 196–198°C (ethyl acetate–petroleum ether); IR (KBr) ν 3260 (NH), 1630 (CO), 1612 (CO) cm^{-1}; ^1H NMR (DMSO-d_6, 250 MHz) δ 4.24 (s, 3H, CH_3), 7.38–7.44 (m, 1H, H_{Ar}), 7.55–7.61 (m, 2H, H_{Ar}), 7.80–7.83 (m, 1H, H_{Ar}), 8.72–8.75 (d, 1H, J=8.2 Hz, H_{Ar}), 11.50 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 62.90 MHz) δ 33.8 (CH_3), 110.6 (C), 111.4 (CH), 118.4 (C), 123.7 (CH), 124.3 (CH), 124.8 (C), 125.5 (C), 127.5 (CH), 133.4 (CH), 139.5 (C), 161.0 (C), 175.2 (CO); MS (IS) *m/z* 305 (^{79}Br, M+H)$^+$, 307 (^{81}Br, M+H)$^+$. Anal. calcd for $C_{13}H_{19}BrN_2O_2$: C, 51.17; H, 2.97; N, 9.18. Found: C, 50.84; H, 3.09; N, 9.29.

4.1.6. 4-Bromo-10-methyl-1,5-dioxo-5,10-dihydro-1*H*-azepino[3,4-*b*]indole-2-carboxylic acid *tert*-butyl ester (4c). Under argon, a solution of **4b** (0.80 g, 2.62 mmol), Boc_2O (1.14 g, 5.24 mmol) and DMAP (32 mg, 0.26 mmol) in acetonitrile (25 mL) was stirred at room temperature for 24 h. The resulting precipitate was filtered and recrystallised once from ethyl acetate–petroleum ether to give the desired compound **4c** as a yellow solid (0.65 g, 61%). Mp

126–128°C (ethyl acetate–petroleum ether); IR (KBr) ν 1773 (CO), 1657 (CO), 1612 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.64 (s, 9H, $3CH_3$), 4.20 (s, 3H, CH_3), 7.40–7.60 (m, 3H, H_{Ar}), 8.01 (s, 1H, H_{Ar}), 8.85 (d, 1H, J=7.9 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$, 62.90 MHz) δ 27.7 ($3CH_3$), 33.7 (CH_3), 87.7 (C), 110.4 (CH), 112.4 (C), 118.5 (C), 124.5 (CH), 125.0 (C), 125.4 (C), 125.5 (CH), 128.2 (CH), 130.1 (CH), 140.0 (C), 151.5 (CO), 159.6 (CO), 175.5 (CO); MS (IS) m/z 405 (^{79}Br, M+H)$^+$, 407 (^{81}Br, M+H)$^+$. Anal. calcd for $C_{18}H_{17}BrN_2O_4$: C, 53.35; H, 4.23; N, 6.91. Found: C, 53.73; H, 4.05; N, 7.03.

4.1.7. 2-(4-Methoxybenzyl)-10-methyl-2*H*,10*H*-azepino-[3,4-*b*]indole-1,5-dione (5a). DBU (0.04 mL, 0.23 mmol) was added to a solution of **3a** (100 mg, 0.23 mmol) in DMF. The solution was stirred at room temperature for 1 h. Hydrolysis was performed by addition of 10% HCl solution. After filtration, the residue was washed with water and ether. The solid obtained was partitioned between dichloromethane (30 mL) and water. After extraction, organic layers were dried over $MgSO_4$, filtered and evaporated in vacuo. Compound **5a** was obtained as a yellow solid (78 mg, 95%). Mp 144–146°C (toluene); IR (KBr) ν 1647 (CO), 1628 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.79 (s, 3H, CH_3), 4.25 (s, 3H, CH_3), 5.12 (s, 2H, CH_2), 5.98 (d, 1H, J=11.0 Hz, =CH), 6.85–6.90 (m, 3H, H_{Ar}), 7.27–7.53 (m, 5H, H_{Ar}), 8.86 (d, 1H, J=8.1 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$, 62.90 MHz) δ 34.5 (CH_3), 55.3 (CH_3), 55.4 (CH_2), 110.3 (CH), 114.4 (2CH), 114.6 (CH), 121.5 (C), 123.8 (CH), 125.0 (C), 125.4 (CH), 127.5 (CH), 128.4 (C), 129.3 (2CH), 129.8 (C), 134.9 (CH), 140.0 (C), 159.6 (C), 161.1 (CO), 182.6 (CO); MS (IS) m/z 347 (M+H)$^+$. Anal. calcd for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09. Found: C, 72.57; H, 5.07; N, 7.92.

4.1.8. 10-methyl-2*H*,10*H*-azepino[3,4-*b*]indole-1,5-dione (5b). Under argon, a solution of **5a** (300 mg, 0.86 mmol) in trifluoroacetic acid (5 mL) was stirred at reflux for 15 h. After cooling, the mixture was poured into ice and neutralised by 10% NaOH solution. After filtration, the crude product was recrystallised once from ethyl acetate–petroleum ether to give **5b** as a white solid (132 mg, 68%). Mp 130–132°C (ethyl acetate–petroleum ether); IR (KBr) ν 3320 (NH), 1650 (CO), 1618 (CO) cm^{-1}; ^1H NMR (DMSO-d_6, 250 MHz) δ 4.24 (s, 2H, CH_3), 5.84 (d, 1H, J=10.0 Hz, =CH), 6.81 (t, 1H, J=10.0 Hz, =CH), 7.37 (t, 1H, J=7.3 Hz, H_{Ar}), 7.55 (t, 1H, J=7.4 Hz, H_{Ar}), 7.79 (d, 1H, J=7.8 Hz, H_{Ar}), 8.74 (d, 1H, J=8.1 Hz, H_{Ar}), 11.18 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 62.90 MHz) δ 33.7 (CH_3), 111.2 (CH), 112.4 (CH), 121.0 (C), 123.2 (CH), 124.4 (CH), 124.6 (C), 127.1 (CH), 131.1 (C), 132.1 (CH), 139.9 (C), 161.1 (CO), 182.3 (CO); MS (IS) m/z 227 (M+H)$^+$. Anal. calcd for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38. Found: C, 69.35; H, 4.60; N, 12.47.

4.2. General procedure for the Suzuki reaction with 4(a–c)

To a stirred solution of compound **4** (1.31 mmol) in dry toluene (5 mL) was added freshly prepared *tetrakis*-(triphenylphosphine)palladium (0.014 mmol). The solution was stirred at room temperature for 15 min. Boronic acid (1.97 mmol) diluted in absolute ethanol (2 mL) was then added, following immediately by saturated aqueous $NaHCO_3$ (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 (2×5 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by column chromatography on silica gel (dichloromethane) to give the desired compound.

4.2.1. 2-(4-Methoxybenzyl)-10-methyl-4-phenyl-2*H*,10*H*-azepino[3,4-*b*]indole-1,5-dione (6a). Yield: 84%. Mp 164–166°C (ethyl acetate–petroleum ether); IR (KBr) ν 1641 (CO), 1606 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.78 (s, 3H, CH_3), 4.25 (s, 3H, CH_3), 5.16 (s, 2H, CH_2), 6.87 (d, 2H, J=8.6 Hz, H_{Ar}), 7.18 (s, 1H, =CH), 7.24–7.48 (m, 8H, H_{Ar}), 7.48–7.50 (m, 2H, H_{Ar}), 8.84 (d, 1H, J=8.3 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$, 62.90 MHz) δ 34.1 (CH_3), 55.4 (CH_3), 55.8 (CH_2), 110.2 (CH), 114.4 (2CH), 122.4 (C), 123.7 (CH), 125.4 (CH), 125.5 (C), 127.3 (C), 127.5 (CH), 127.6 (CH), 128.3 (2CH), 128.4 (C), 129.3 (2CH), 130.0 (2CH), 131.2 (C), 135.9 (CH), 138.6 (C), 139.9 (C), 159.5 (C), 160.3 (CO), 181.5 (CO); MS (IS) m/z 423 (M+H)$^+$. Anal. calcd for $C_{27}H_{22}N_2O_3$: C, 76.76; H, 5.25; N, 6.63. Found: C, 77.01; H, 5.11; N, 6.52.

4.2.2. 10-Methyl-1,5-dioxo-4-phenyl-5,10-dihydro-1*H*-azepino[3,4-*b*]indole-2-carboxylic acid *tert*-butyl ester (6b). Yield: 66%. Mp 174–176°C (ethyl acetate–petroleum ether); IR (KBr) ν 1758 (CO), 1668 (CO), 1614 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.63 (s, 9H, CH_3), 4.26 (s, 3H, CH_3), 7.34 (s, 1H, =CH), 7.36–7.57 (m, 8H, H_{Ar}), 8.83 (d, 1H, J=8.2 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$, 62.90 MHz) δ 27.7 ($3CH_3$), 33.6 (CH_3), 87.0 (C), 110.3 (CH), 122.0 (C), 124.0 (CH), 125.5 (CH), 125.6 (C), 126.6 (C), 127.7 (CH), 127.8 (CH), 128.3 (2CH), 129.7 (CH), 130.0 (2CH), 130.8 (C), 137.8 (C), 139.9 (C), 152.6 (CO), 160.0 (CO), 181.6 (CO); MS (IS) m/z 403 (M+H)$^+$. Anal. calcd for $C_{24}H_{22}N_2O_4$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.30; H, 5.69; N, 6.83.

4.2.3. 10-Methyl-4-phenyl-2*H*,10*H*-azepino[3,4-*b*]-indole-1,5-dione (6c). Yield: 44%. Mp 139–141°C (ethyl acetate–petroleum ether); IR (KBr) ν 3365 (NH), 1652 (CO), 1618 (CO) cm^{-1}; ^1H NMR (DMSO-d_6, 250 MHz) δ 4.25 (s, 3H, CH_3), 7.25–7.48 (m, 3H, =CH+H_{Ar}), 7.85–7.92 (m, 6H, H_{Ar}), 8.77 (d, 1H, J=8.1 Hz, H_{Ar}), 11.48 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 62.90 MHz) δ 33.9 (CH_3), 110.1 (CH), 122.8 (C), 123.8 (CH), 124.1 (CH), 124.5 (CH), 125.0 (C), 126.5 (C), 127.7 (CH), 128.3 (2CH), 128.8 (2CH), 129.6 (CH), 130.2 (C), 138.6 (C), 139.8 (C), 161.2 (CO), 182.7 (CO); MS (IS) m/z 303 (M+H)$^+$. Anal. calcd for $C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67; N, 9.27. Found: C, 75.72; H, 4.84; N, 9.45.

4.2.4. 2-(4-Methoxybenzyl)-10-methyl-4-thiophen-2-yl-2*H*,10*H*-azepino[3,4-*b*]indole-1,5-dione (7). Yield: 85%. Mp 168–169°C (ethyl acetate–petroleum ether); IR (KBr) ν 1642 (CO), 1594 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.80 (s, 3H, CH_3), 4.28 (s, 3H, CH_3), 5.22 (s, 2H, CH_2), 6.90 (d, 2H, J=8.5 Hz, H_{Ar}), 7.00–7.11 (m, 2H, H_{Ar}), 7.31 (s, 1H, =CH), 7.35–7.42 (m, 4H, H_{Ar}), 7.52–7.54 (m, 2H, H_{Ar}), 8.87 (d, 1H, J=8.2 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$, 62.90 MHz) δ 34.1 (CH_3), 55.4 (CH_3), 56.1

(CH_2), 110.2 (CH), 114.5 (2CH), 120.2 (C), 121.7 (C), 123.7 (CH), 125.0 (CH), 125.2 (CH), 125.3 (C), 126.1 (CH), 127.2 (CH), 127.5 (CH), 128.3 (C), 129.5 (2CH), 130.9 (C), 134.5 (CH), 139.2 (C), 139.8 (C), 159.6 (C), 159.9 (CO), 180.3 (CO); MS (IS) *m/z* 429 $(M+H)^+$. Anal. calcd for $C_{25}H_{20}N_2O_3S$: C, 70.07; H, 4.70; N, 6.54. Found: C, 69.84; H, 4.85; N, 6.63.

4.2.5. 4-Furan-2-yl-2-(4-methoxybenzyl)-10-methyl-2*H*,10*H*-azepino[3,4-*b*]indole-1,5-dione (8). Yield: 76%. Mp 127–129°C (ethyl acetate–petroleum ether); IR (KBr) ν 1642 (CO), 1622 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.77 (s, 3H, CH_3), 4.20 (s, 3H, CH_3), 5.21 (s, 2H, CH_2), 6.48–6.50 (m, 1H, H_{Ar}), 6.86–6.89 (m, 2H, H_{Ar}), 7.24–7.50 (m, 7H, =CH+H_{Ar}), 7.82 (s, 1H, =CH), 8.86 (d, 1H, J=8.2 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$, 62.90 MHz) δ 34.0 (CH_3), 55.4 (CH_3), 56.6 (CH_2), 110.2 (CH), 110.8 (CH), 112.1 (CH), 114.4 (2CH), 116.9 (C), 122.2 (C), 123.6 (CH), 125.3 (CH), 125.5 (C), 127.5 (CH), 128.4 (C), 129.4 (2CH), 130.7 (C), 133.6 (CH), 139.8 (C), 141.0 (C), 149.3 (C), 159.6 (C), 159.9 (CO), 179.8 (CO); MS (IS) *m/z* 413 $(M+H)^+$. Anal. calcd for $C_{25}H_{20}N_2O_4$: C, 72.80; H, 4.89; N, 6.79. Found: C, 72.54; H, 4.70; N, 6.67.

4.2.6. 2-(4-Methoxybenzyl)-10-methyl-4-thiophen-3-yl-2*H*,10*H*-azepino[3,4-*b*]indole-1,5-dione (9). Yield: 82%. Mp 171–172°C (ethyl acetate–petroleum ether); IR (KBr) ν 1650 (CO), 1645 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.80 (s, 3H, CH_3), 4.29 (s, 3H, CH_3), 5.20 (s, 2H, CH_2), 6.90 (d, 2H, J=8.8 Hz, H_{Ar}), 7.30–7.41 (m, 7H, =CH+H_{Ar}), 7.52–7.54 (m, 2H, H_{Ar}), 8.85 (d, 1H, J=8.2 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$, 62.90 MHz) δ 34.1 (CH_3), 55.4 (CH_3), 55.7 (CH_2), 110.2 (CH), 114.5 (2CH), 122.1 (C), 122.2 (C), 123.6 (CH), 123.7 (CH), 125.0 (CH), 125.2 (CH), 125.4 (C), 127.4 (CH), 128.4 (C), 129.1 (CH), 129.4 (2CH), 131.0 (C), 135.1 (CH), 138.5 (C), 139.9 (C), 159.6 (C), 160.1 (CO), 181.3 (CO); MS (IS) *m/z* 429 $(M+H)^+$. Anal. calcd for $C_{25}H_{20}N_2O_3S$: C, 70.07; H, 4.70; N, 6.54. Found: C, 70.36; H, 4.89; N, 6.38.

4.2.7. 4-Benzo[*b*]thiophen-2-yl-2-(4-methoxybenzyl)-10-methyl-2*H*,10*H*-azepino[3,4-*b*]indole-1,5-dione (10a). Yield: 97%. Mp 175–176°C (ethyl acetate–petroleum ether); IR (KBr) ν 1642 (CO), 1591 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.77 (s, 3H, CH_3), 4.18 (s, 3H, CH_3), 5.16 (s, 2H, CH_2), 6.90 (d, 2H, J=8.7 Hz, H_{Ar}), 7.24–7.53 (m, 8H, =CH+H_{Ar}), 7.53 (s, 1H, H_{Ar}), 7.66–7.82 (m, 2H, H_{Ar}), 8.84 (d, 1H, J=8.2 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$, 62.90 MHz) δ 34.1 (CH_3), 55.4 (CH_3), 56.1 (CH_2), 110.2 (CH), 114.5 (2CH), 121.7 (C), 121.9 (CH), 122.1 (CH), 122.4 (C), 123.4 (CH), 123.8 (CH), 124.2 (CH), 125.2 (CH), 125.2 (CH), 125.4 (C), 127.5 (CH), 128.2 (C), 129.6 (2CH), 130.8 (C), 135.7 (CH), 139.2 (C), 139.8 (C), 140.2 (C), 140.9 (C), 159.7 (C), 159.9 (CO), 180.3 (CO); MS (IS) *m/z* 479 $(M+H)^+$. Anal. calcd for $C_{29}H_{22}N_2O_3S$: C, 72.78; H, 4.63; N, 5.85. Found: C, 73.05; H, 4.76; N, 5.70.

4.2.8. 4-Benzo[*b*]thiophen-2-yl-10-methyl-1,5-dioxo-5,10-dihydro-1*H*-azepino[3,4-*b*]indole-2-carboxylic acid *tert*-butyl ester (10b). Yield: 68%. Mp 166–168°C (ethyl acetate–petroleum ether); IR (KBr) ν 1730 (CO), 1640 (CO), 1622 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.65 (s, 9H, CH_3), 4.24 (s, 3H, CH_3), 7.30–7.45 (m, 4H, H_{Ar}), 7.53 (s, 1H, =CH), 7.54–7.56 (m, 1H, H_{Ar}), 7.78 (s, 1H, H_{Ar}), 7.79–7.86 (m, 2H, H_{Ar}), 8.87 (d, 1H, J=8.2 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$, 62.90 MHz) δ 27.7 ($3CH_3$), 33.7 (CH_3), 87.4 (C), 110.4 (CH), 120.3 (C), 121.7 (C), 122.0 (CH), 122.8 (CH), 123.6 (CH), 124.3 (CH), 124.4 (CH), 125.2 (C), 125.5 (CH), 125.6 (CH), 128.0 (CH), 129.3 (CH), 130.1 (C), 139.1 (C), 139.3 (C), 140.1 (C), 141.2 (C), 152.4 (CO), 159.8 (CO), 180.8 (CO); MS (IS) *m/z* 459 $(M+H)^+$. Anal. calcd for $C_{26}H_{22}N_2O_4S$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.37; H, 4.67; N, 5.93.

4.2.9. 4-Benzofuran-2-yl-2-(4-methoxybenzyl)-10-methyl-2*H*,10*H*-azepino[3,4-*b*]indole-1,5-dione (11). Yield: 77%. Mp 199–201°C (ethyl acetate–petroleum ether); IR (KBr) ν 1642 (CO), 1621 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.79 (s, 3H, CH_3), 4.27 (s, 3H, CH_3), 5.31 (s, 2H, CH_2), 6.91 (d, 2H, J=8.8 Hz, H_{Ar}), 7.20–7.30 (m, 3H, H_{Ar}+=CH), 7.39–7.45 (m, 3H, H_{Ar}), 7.53–7.61 (m, 3H, H_{Ar}), 7.75 (s, 1H, H_{Ar}), 8.15 (s, 1H, H_{Ar}), 8.83 (d, 1H, J=8.2 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$, 62.90 MHz) δ 34.1 (CH_3), 55.4 (CH_3), 56.9 (CH_2), 107.5 (CH), 110.3 (CH), 110.6 (CH), 114.5 (2CH), 114.6 (C), 116.2 (C), 121.4 (CH), 122.4 (C), 123.0 (CH), 123.9 (CH), 124.4 (CH), 125.4 (CH), 125.5 (C), 127.6 (CH), 128.3 (C), 129.5 (2CH), 130.0 (C), 130.7 (C), 135.1 (CH), 140.0 (C), 153.6 (C), 159.7 (C), 160.0 (CO), 179.9 (CO); MS (IS) *m/z* 463 $(M+H)^+$. Anal. calcd for $C_{29}H_{22}N_2O_4$: C, 75.31; H, 4.79; N, 6.06. Found: C, 75.01; H, 4.92; N, 6.23.

4.2.10. 2-[2-(4-Methoxybenzyl)-10-methyl-1,5-dioxo-1,2,5,10-tetrahydroazepino[3,4-*b*]indol-4-yl]benzaldehyde (12). Yield: 96%. Mp 224–226°C (ethyl acetate–petroleum ether); IR (KBr) ν 1699 (CO), 1636 (CO), 1585 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.79 (s, 3H, CH_3), 4.30 (s, 3H, CH_3), 5.21 (br s, 2H, CH_2), 6.89 (d, 2H, J=8.8 Hz, H_{Ar}), 7.18 (s, 1H, =CH), 7.21–7.38 (m, 4H, H_{Ar}), 7.48–7.63 (m, 4H, H_{Ar}), 7.98 (d, 1H, J=7.6 Hz, H_{Ar}), 8.76 (d, 1H, J=8.2 Hz, H_{Ar}), 9.92 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 62.90 MHz) δ 34.3 (CH_3), 55.5 (CH_3), 55.9 (CH_2), 110.3 (CH), 114.5 (C), 114.6 (2CH), 121.8 (C), 124.0 (CH), 124.7 (C), 125.5 (CH), 127.8 (CH), 128.2 (C), 128.6 (CH), 129.0 (CH), 129.3 (2CH), 129.4 (C), 131.7 (CH), 134.0 (CH), 135.5 (C), 136.0 (CH), 140.1 (C), 140.7 (C), 159.7 (C), 160.4 (CO), 181.4 (CO), 191.6 (CO); MS (IS) *m/z* 451 $(M+H)^+$. Anal. calcd for $C_{28}H_{22}N_2O_4$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.39; H, 5.06; N, 6.41.

4.3. General procedure for the Stille reaction with 4(a-b)

To a suspension of freshly prepared *tetrakis*-(triphenylphosphine)palladium (0.02 mmol) in dry DMF (5 mL) was added, under argon, a solution of **4** (0.23 mmol) and stannane (tributylvinylstannane for **13a**-**13b**, tributyl(1-ethoxyvinyl)stannane for **14a**-**14b**) (0.46 mmol) in dry DMF (2 mL). The solution was stirred at 100°C for 1 h. The solvent was then evaporated in vacuo and the crude residue was purified by column chromatography (dichloromethane for **13a**-**13b** and dichloromethane–triethylamine 98:2 for **14a**-**14b**) to afford the desired products.

4.3.1. 2-(4-Methoxybenzyl)-10-methyl-4-vinyl-2-yl-2*H*,10*H*-azepino[3,4-*b*]indole-1,5-dione (13a). Yield:

87%. Mp 108–110°C (ethyl acetate–petroleum ether); IR (KBr) ν 1644 (CO), 1613 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.77 (s, 3H, CH_3), 4.19 (s, 3H, CH_3), 5.15 (s, 2H, CH_2), 5.19 (dd, 1H, J=1.2, 10.5 Hz, =CH_2), 5.43 (dd, 1H, J=1.2, 17.5 Hz, =CH_2), 6.87 (d, 2H, J=8.5 Hz, H_{Ar}), 6.98 (dd, 1H, J=10.5, 17.5 Hz, =CH), 7.23–7.49 (m, 6H, =CH+H_{Ar}), 8.79 (d, 1H, J=7.9 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$, 62.90 MHz) δ 34.1 (CH_3), 55.4 (CH_3), 55.8 (CH_2), 110.2 (CH), 114.3 (CH_2), 114.4 (2CH), 121.8 (C), 123.7 (CH), 123.9 (C), 125.2 (CH), 125.3 (C), 127.4 (CH), 128.4 (C), 129.4 (2CH), 131.2 (C), 133.2 (CH), 134.2 (CH), 139.8 (C), 159.6 (C), 160.2 (CO), 181.4 (CO); MS (IS) m/z 373 $(M+H)^+$. Anal. calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52. Found: C, 73.83; H, 5.60; N, 7.68.

4.3.2. 10-Methyl-4-vinyl-2*H*,10*H*-azepino[3,4-*b*]-indole-1,5-dione (13b). Yield: 31%. Mp 135–137°C (ethyl acetate–petroleum ether); IR (KBr) ν 3260 (NH), 1654 (CO), 1623 (CO) cm^{-1}; ^1H NMR (DMSO-d_6, 250 MHz) δ 4.29 (s, 3H, CH_3), 5.26 (dd, 1H, J=1.4, 10.4 Hz, =CH_2), 5.69 (dd, 1H, J=1.4, 16.8 Hz, =CH_2), 6.90 (dd, 1H, J=10.4, 16.8 Hz, =CH), 7.52–7.64 (m, 4H, =CH+H_{Ar}), 8.77 (d, 1H, J=8.1 Hz, H_{Ar}), 11.34 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 62.90 MHz) δ 33.9 (CH_3), 110.5 (CH), 114.8 (CH_2), 121.8 (C), 123.1 (CH), 123.2 (CH), 124.5 (C), 127.0 (CH), 127.3 (C), 130.8 (C), 132.0 (CH), 133.1 (CH), 139.5 (C), 161.0 (CO), 178.2 (CO); MS (IS) m/z 253 $(M+H)^+$. Anal. calcd for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.67; H, 4.62; N, 11.25.

4.3.3. 2-(4-Methoxybenzyl)-10-methyl-4-(1-ethoxyvinyl)-2-yl-2*H*,10*H*-azepino[3,4-*b*]indole-1,5-dione (14a). Yield: 95%. Mp 154–156°C (ethyl acetate–petroleum ether); IR (KBr) ν 1644 (CO), 1613 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.34 (t, 3H, J=6.9 Hz, CH_3), 3.79 (s, 3H, CH_3), 3.88 (q, 2H, J=6.9 Hz, CH_2), 4.21 (s, 3H, CH_3), 4.36 (d, 1H, J=2.1 Hz, =CH_2), 4.54 (d, 1H, J=2.1 Hz, =CH_2), 5.13 (s, 2H, CH_2), 6.88 (d, 2H, J=7.2 Hz, H_{Ar}), 7.29–7.47 (m, 6H, =CH+H_{Ar}), 8.81 (d, 1H, J=8.1 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$, 62.90 MHz) δ 14.7 (CH_3), 34.0 (CH_3), 55.4 (CH_3), 55.7 (CH_2), 63.7 (CH_2), 87.5 (CH_2), 110.2 (CH), 114.4 (2CH), 122.7 (C), 123.6 (CH), 123.7 (C), 125.3 (CH), 125.5 (C), 127.4 (CH), 128.4 (C), 129.5 (2CH), 130.9 (C), 135.7 (CH), 139.8 (C), 158.5 (C), 159.6 (C), 160.5 (CO), 181.1 (CO); MS (IS) m/z 439 $(M+Na)^+$. Anal. calcd for $C_{25}H_{24}N_2O_4$: C, 72.10; H, 5.81; N, 6.73. Found: C, 71.72; H, 5.67; N, 6.59.

4.3.4. 4-(1-Ethoxyvinyl)-10-methyl-2*H*,10*H*-azepino-[3,4-*b*]-1,5-dione (14b). Yield: 28%. Mp 181–183°C (ethyl acetate–petroleum ether); IR (KBr) ν 3266 (NH), 1677 (CO), 1642 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.37 (t, 3H, J=6.9 Hz, CH_3), 3.92 (q, 2H, J=6.9 Hz, CH_2), 4.29 (s, 3H, CH_3), 4.41 (d, 1H, J=1.8 Hz, =CH_2), 4.68 (d, 1H, J=1.8 Hz, =H_2), 7.16 (d, 1H, J=4.5 Hz, H_{Ar}), 7.36–7.58 (m, 3H, =CH+H_{Ar}), 8.69 (br s, 1H, NH), 8.91 (d, 1H, J=7.9 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$, 62.90 MHz) δ 14.5 (CH_3), 54.7 (CH_3), 62.4 (CH_2), 86.9 (CH_2), 110.3 (CH), 122.1 (C), 123.2 (C), 124.0 (CH), 125.2 (CH), 126.9 (CH), 125.5 (C), 130.1 (C), 136.0 (CH), 140.8 (C), 159.1 (C), 160.9 (CO), 181.2 (CO); MS (IS) m/z 297 $(M+H)^+$. Anal. calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 68.60; H, 5.60; N, 9.53.

4.3.5. 2-(4-Methoxybenzyl)-10-methyl-4-acetyl-2-yl-2*H*,10*H*-azepino[3,4-*b*]indole-1,5-dione (15a). A solution of **14a** (200 mg, 0.48 mmol) in acetone/10% HCl (14 mL, 5/2) was stirred at room temperature for 1 h. After evaporation, the residue was partitioned between dichloromethane (10 mL) and water. After extraction, organic layers were dried over $MgSO_4$, filtered and evaporated in vacuo. Compound **15a** was obtained as a yellow solid (177 mg, 95%). Mp 159–160°C (ethyl acetate–petroleum ether); IR (KBr) ν 1680 (CO), 1664 (CO), 1610 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.66 (s, 3H, CH_3), 3.79 (s, 3H, CH_3), 4.17 (s, 3H, CH_3), 5.16 (s, 2H, CH_2), 6.87 (d, 2H, J=8.5 Hz, H_{Ar}), 7.31–7.50 (m, 5H, =CH+H_{Ar}), 8.01 (s, 1H, H_{Ar}), 8.74 (d, 1H, J=8.1 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$, 62.90 MHz) δ 31.2 (CH_3), 34.0 (CH_3), 55.3 (CH_3), 56.8 (CH_2), 110.3 (CH), 114.4 (2CH), 123.2 (C), 123.8 (CH), 124.1 (C), 124.9 (CH), 125.0 (C), 127.8 (CH), 128.4 (C), 129.6 (2CH), 130.1 (C), 139.9 (C), 142.1 (CH), 159.7 (C), 160.4 (CO), 181.2 (CO), 199.3 (CO); MS (IS) m/z 411 $(M+Na)^+$. Anal. calcd for $C_{23}H_{20}N_2O_4$: C, 71.12; H, 5.19; N, 7.21. Found: C, 71.43; H, 5.10; N, 7.05.

4.3.6. 10-Methyl-4-acetyl-2-yl-2*H*,10*H*-azepino[3,4-*b*]-indole-1,5-dione (15b). Yield 96%. Mp 118–120°C (ethyl acetate–petroleum ether); IR (KBr) ν 3243 (NH), 1680 (CO), 1664 (CO), 1610 (CO) cm^{-1}; ^1H NMR (DMSO-d_6, 250 MHz) δ 2.48 (s, 3H, CH_3), 4.19 (s, 3H, CH_3), 7.34–7.43 (m, 2H, =CH+H_{Ar}), 7.52–7.58 (m, 1H, H_{Ar}), 7.76–7.79 (m, 1H, H_{Ar}), 8.67 (d, 1H, J=8.3 Hz, H_{Ar}), 11.63 (br s, NH); ^{13}C NMR (DMSO-d_6, 62.90 MHz) δ 30.8 (CH_3), 33.5 (CH_3), 111.4 (CH), 122.3 (C), 123.2 (C), 123.5 (CH), 124.3 (CH), 124.8 (C), 127.4 (CH), 129.5 (C), 137.8 (CH), 139.4 (C), 160.4 (CO), 181.0 (CO), 199.0 (CO); MS (IS) m/z 269 $(M+H)^+$. Anal. calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 67.41; H, 4.40; N, 10.57.

4.4. General procedure for the Diels–Alder reaction with 13a

To a solution of **13a** (0.27 mmol) in toluene (3 mL) was added dienophile (0.54 mmol). The mixture was stirred in a sealed tube at 180°C for 3 h (DMAD) or 1 h (*N*-methylmaleimide and maleic anhydride). The solvent was then evaporated in vacuo and the crude residue was purified by column chromatography (ethyl acetate/ petroleum ether 7:3 for **16**, ethyl acetate–petroleum ether 6:4 for **17** and ethyl acetate–petroleum ether 4:6 for **18**) to give the desired compound.

4.4.1. *N*-Methyl-7-(4-methoxybenzyl)-5-methyl-6,12-dioxo-5,6,7,7a,8,9,10,12-octahydrobenzo[2,3]azepino[6,5-*b*]indole-8,9-dicarboximide (16). Yield: 87%. Mp 139–141°C (ethyl acetate–petroleum ether); IR (KBr) ν 1702 (CO), 1636 (CO), 1610 (CO) cm^{-1}; ^1H NMR (DMSO-d_6, 80°C, 250 MHz) δ 2.11 (s, 3H, CH_3), 2.29–2.38 (m, 1H, CH_2), 2.69–2.78 (m, 1H, CH_2), 3.27–3.35 (m, 1H, CH), 3.43–3.49 (m, 1H, CH), 3.74 (s, 3H, CH_3), 4.07 (s, 3H, CH_3), 4.59 (d, 1H, J=15.3 Hz, CH_2), 4.74 (m, 1H, CH), 5.15 (d, 1H, J=15.3 Hz, CH_2), 6.59 (m, 1H, =CH), 6.89 (d, 2H, J=8.5 Hz, H_{Ar}), 7.22–7.42 (m, 4H, H_{Ar}), 7.62 (d, 1H, J=8.5 Hz, H_{Ar}), 7.95 (d, 1H, J=7.9 Hz, H_{Ar}); ^{13}C NMR (DMSO-d_6, 80°C, 62.90 MHz) δ 23.1 (CH_3), 23.2 (CH_2), 31.9 (CH_3), 39.7 (CH), 42.5 (CH), 50.3 (CH_2), 54.8 (CH_3),

56.6 (CH), 110.2 (CH), 113.7 (2CH), 114.5 (C), 121.1 (CH), 122.3 (CH), 122.9 (C), 124.9 (CH), 128.4 (2CH), 129.0 (C), 132.8 (C), 134.1 (CH), 135.0 (C), 137.8 (C), 158.4 (C), 161.8 (CO), 176.0 (CO), 177.4 (CO), 183.5 (CO); MS (IS) m/z 484 $(M+H)^+$. Anal. calcd for $C_{28}H_{25}N_3O_5$: C, 69.55; H, 5.21; N, 8.69. Found: C, 69.73; H, 5.06; N, 8.81.

4.4.2. 7-(4-Methoxybenzyl)-5-methyl-6,12-dioxo-5,6,7,7a,8,9,10,12-octahydrobenzo[2,3]azepino[6,5-*b*]-indole-8,9-dicarboxylic anhydride (17). Yield: 57%; IR (film) ν 1716 (CO), 1642 (CO), 1612 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.16 (br s, 1H, CH_2), 2.90 (br s, 1H, CH_2), 3.28–3.43 (m, 2H, CH), 3.79 (s, 3H, CH_3), 4.12 (s, 3H, CH_3), 4.44 (br s, 1H, CH_2), 4.96 (m, 2H, CH+CH_2), 6.78 (m, 1H, =CH), 6.88 (d, 2H, J=8.5 Hz, H_{Ar}), 7.28–7.44 (m, 5H, H_{Ar}), 8.16 (d, 1H, J=8.1 Hz, H_{Ar}); ^{13}C NMR (DMSO-d_6, 80°C, 62.90 MHz) δ 23.5 (CH_2), 32.0 (CH_3), 36.4 (CH), 44.0 (CH), 50.4 (CH_2), 54.8 (CH_3), 55.1 (CH), 110.5 (CH), 113.8 (2CH), 114.7 (C), 121.3 (CH), 122.6 (CH), 123.0 (C), 125.1 (CH), 128.4 (2CH), 128.8 (C), 132.8 (C), 134.8 (CH), 135.4 (C), 138.0 (C), 158.5 (C), 161.5 (CO), 171.4 (CO), 173.1 (CO), 182.7 (CO); MS (IS) m/z 471 $(M+H)^+$. Anal. calcd for $C_{27}H_{22}N_2O_6$: C, 68.93; H, 4.71; N, 5.95. Found: C, 68.59; H, 4.87; N, 6.12.

4.4.3. 7-(4-Methoxybenzyl)-5-methyl-6,12-dioxo-5,6,7,12-tetrahydrobenzo[2,3]azepino[6,5-*b*]indole-8,9-dicarboxylic acid dimethyl ester (18). Yield: 53%. Mp 199–201°C (toluene); IR (KBr) ν 1722 (CO), 1708 (CO), 1652 (CO), 1618 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.68 (s, 3H, CH_3), 3.93 (s, 3H, CH_3), 4.06 (s, 3H, CH_3), 4.08 (s, 3H, CH_3), 4.42 (d, 1H, J=14.0 Hz, NCH_2), 5.58 (d, 1H, J=14.0 Hz, NCH_2), 6.69 (d, 2H, J=8.6 Hz, H_{Ar}), 6.99 (d, 2H, J=8.6 Hz, H_{Ar}), 7.28–7.41 (m, 3H, H_{Ar}), 7.83–7.93 (m, 2H, H_{Ar}), 8.16 (d, 1H, J=7.9 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$, 62.90 MHz) δ 32.8 (CH_3), 53.2 (CH_3), 53.7 (CH_3), 55.0 (CH_2), 55.3 (CH_3), 110.5 (CH), 114.1 (2CH), 122.4 (CH), 122.6 (C), 123.9 (C), 124.0 (CH), 124.2 (C), 126.6 (CH), 128.1 (CH), 128.2 (C), 129.5 (2CH), 129.5 (CH), 132.5 (C), 132.8 (C), 139.0 (C), 143.7 (C), 159.3 (C), 159.7 (C), 162.2 (CO), 165.7 (CO), 167.5 (CO), 185.0 (CO); MS (IS) m/z 513 $(M+H)^+$. Anal. calcd for $C_{29}H_{24}N_2O_7$: C, 67.96; H, 4.72; N, 5.47. Found: C, 68.29; H, 4.88; N, 5.63.

4.4.4. 7-(4-Methoxybenzyl)-5-methyl-6,12-dioxo-5,6,7,12-tetrahydrobenzo[2,3]azepino[6,5-*b*]indole-8,9-dicarboxylic acid dimethyl ester (19). A solution of **16** (30 mg, 0.06 mmol) in 2,2-dimethylaminoethylamine (3 mL) was stirred at reflux for 24 h. After evaporation, the crude residue was purified by column chromatography on silica gel (dichloromethane–methanol 9:1) to afford compound **17** as a yellow oil (24 mg, 66%); IR (film) ν 3295 (NH), 1660 (CO), 1640 (CO), 1622 (CO), 1602 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.26 (s, 6H, CH_3), 2.30 (s, 6H, CH_3), 2.49 (t, 2H, J=6.5 Hz, CH_2), 2.59 (t, 2H, J=6.5 Hz, CH_2), 3.43–3.47 (m, 2H, CH_2), 3.68 (s, 3H, CH_3), 3.72–3.81 (m, 2H, CH_2), 3.98 (s, 3H, CH_3), 4.37 (br s, 2H, CH_2), 6.67 (d, 2H, J=8.0 Hz, H_{Ar}), 7.03 (d, 1H, J=7.5 Hz, H_{Ar}), 7.10–7.19 (m, 3H, H_{Ar}), 7.29–7.61 (m, 3H, H_{Ar}), 7.56 (d, 1H, J=7.5 Hz, H_{Ar}), 8.24 (br s, 1H, NH), 8.37 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 62.90 MHz) δ 32.3 (CH_3), 35.9 (CH_2), 37.6 (CH_2), 45.3 ($2CH_3$), 45.6 ($2CH_3$), 50.5 (CH_2), 55.2 (CH_3), 57.3 (CH_2), 57.7 (CH_2), 110.7 (CH), 114.1 (2CH), 122.1 (C), 122.3 (CH), 123.0 (CH), 123.6 (C), 124.4 (C), 124.5 (CH), 129.3 (2CH), 130.2 (CH), 130.4 (C), 130.9 (CH), 135.7 (C), 137.0 (C), 138.7 (C), 145.6 (C), 159.1 (C), 161.0 (C), 161.7 (CO), 169.7 (CO), 170.0 (CO), 191.3 (CO); MS (IS) m/z 625 $(M+H)^+$. Anal. calcd for $C_{35}H_{40}N_6O_5$: C, 67.29; H, 6.45; N, 13.45. Found: C, 67.60; H, 6.61; N, 13.63.

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