# Access to Paullone Analogues by Intramolecular *Heck* Reaction

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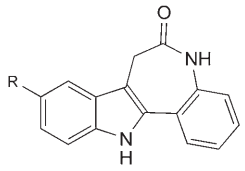
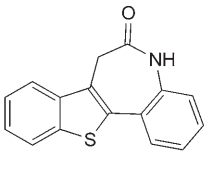
The syntheses of paullone (**1a**) and three paullone derivatives, including a sulfur analogue (**2a**), a tricyclic derivative (**2b**), and a ring-enlarged variant (**2c**), are described, Pd-catalyzed intramolecular *Heck* reaction being the key step. The kinase-inhibitory properties of the novel paullone analogues were investigated.

**Introduction.** – Paullone (**1a**), alsterpaullone (**1b**), and kenpaullone (**1c**), a series of indolo[3,2-*d*][1]benzazepines, have been described as potent cyclin-dependent kinase and glycogen-synthase kinase inhibitors [1a–d]. Thus, the synthesis of paullone and analogues thereof has raised huge interest over the last decade [2a–c]. Several synthetic strategies have been already reported to access the paullone system. The first synthetic pathway involved a construction of the fused 1*H*-indole moiety by a *Fischer* indolization of benzazepinone [3]. Thiophene analogues of kenpaullone (**1c**) were synthesized according to a similar approach [4]. Strategies starting from an indole precursor and using Pd-catalyzed coupling were reported by *Baudoin* and co-workers (*Suzuki–Miyaura* reaction) [5], by *Bremner* and *Sengpracha* (*Heck* reaction) [6], and by *Mérour* and co-workers (*Stille* reaction) [7].

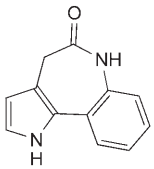
Recently, we have reported a straightforward and easy synthesis of the same skeleton based on an intramolecular *Heck* reaction [8]. Since our preliminary results,



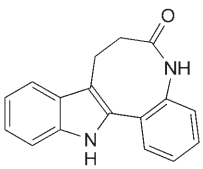

Paullone **1a** R = H
Alsterpaullone **1b** R = $NO_2$
Kenpaullone **1c** R = Br




**2a**




**2b**

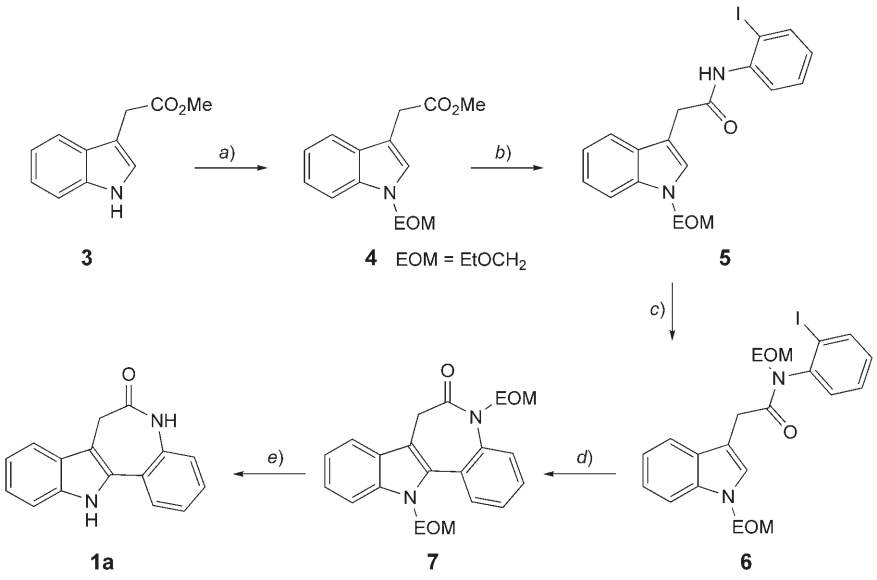



**2c**

two research teams have used the same approach to prepare paullones and its derivatives [9][10]. In the present paper, we wish to apply our methodology to the synthesis of paullone (**1a**) and some derivatives thereof, including the sulfur analogue **2a**, the tricyclic variant **2b**, and the ring-enlarged compound **2c**.

**Results and Discussion.** – 1. *Synthesis.* First, we have envisaged a synthetic strategy allowing the access to fully deprotected analogues (*Scheme 1*). Thus, commercially available 1*H*-indole-3-acetic acid was first esterified, and the so-formed ester **3** [11] was protected under classical conditions with an easily removable, electron-donating ethoxymethyl (EOM) group, providing compound **4** in 69% yield over two steps. This moderate yield could be due to the acidity of the benzylic $CH_2$ moiety, leading to the formation of undesired by-products. Compound **4** was then condensed with a large excess of 2-iodoaniline in the presence of $Me_3Al$ (EDCI coupling failed in our hands) to afford the amide **5** in 98% yield. Protection of the amide N-atom with another EOM group was effected by exposure to NaH and $EtOCH_2Cl$, which afforded the fully protected derivative **6** in 69% yield to be used as precursor for the intramolecular *Heck* reaction. As reported in our first paper [8], this cyclization is highly effective in the presence of $[Pd(OAc)_2]$ (10 mol-%), $Ph_3P$ (20 mol-%), and $Ag_2CO_3$ (2 equiv.) in anhydrous DMF at a substrate concentration of *ca.* 50 mM. When this method was applied, compound **6** was converted within only 30 min at 100° to the doubly EOM-protected paullone **7** in an excellent yield of 92%. Finally, deprotection of **7** was carried

*Scheme 1*

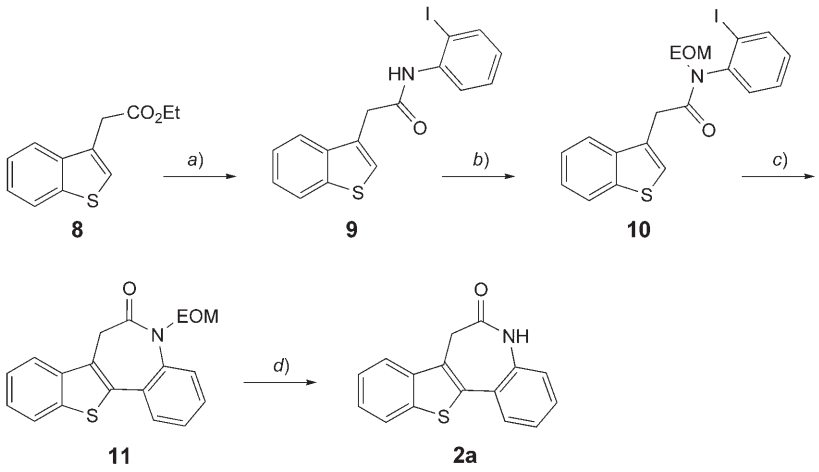



*a*) 1. NaH, THF; 2. $EtOCH_2Cl$, 0° → r.t., 18 h; 69%. *b*) 2-Iodoaniline, $Me_3Al$, $CH_2Cl_2$, −15° → r.t., 18 h; 98%. *c*) 1. NaH, THF; 2. $EtOCH_2Cl$, 0° → r.t., 2 h; 69%. *d*) $[Pd(OAc)_2]$ (10 mol-%), $Ph_3P$ (20 mol-%), $Ag_2CO_3$, DMF, 100°, 30 min; 92%. *e*) 1N aq. HCl, 1,4-dioxane, 80°, 1 h; 37%.

out under acidic conditions, which furnished paullone proper (**1a**) in 37% yield. (Note that the use of $BCl_3$ in $CH_2Cl_2$ at $-78°$ [12] leads to the degradation of **7**).

These results prompted us to investigate the synthesis of paullone bioisosteres by substituting the indole nucleus by a benzo[*b*]thiophene or by a simple pyrrole ring. Following the same pathway as described above, commercially available benzo[*b*]-thiophene-3-acetic acid was converted into the Me ester **8** in near-quantitative yield (*Scheme 2*). Amide coupling and subsequent EOM protection of the amide N-atom afforded, *via* **9**, the amide **10** in 62% overall yield. The following cyclization proved to be incomplete when 10% of $[Pd(OAc)_2]$ was used at 100° (65% conversion, based on $^1$H-NMR analysis). However, the use of 5% of catalyst at 140° gave rise to the desired cyclized product **11** in a fair 70% yield (with 16% of starting material being recovered). The yield could be further improved to 87%, when 10% of the Pd catalyst was used. Finally, deprotection of the EOM group in an acidic medium afforded the target sulfur analogue **2a** in 57% yield.

*Scheme 2*

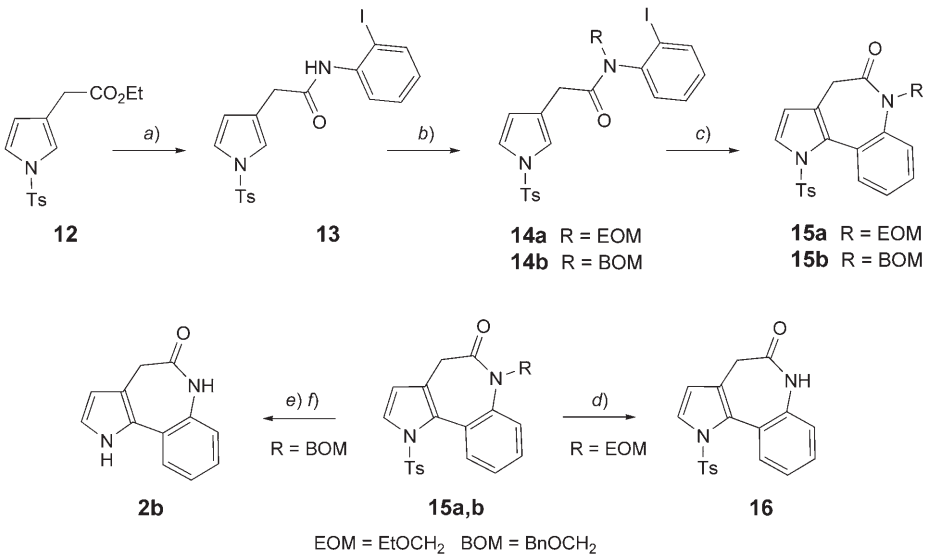



*a*) 2-Iodoaniline, $Me_3Al$, $CH_2Cl_2$, $-15° \rightarrow$ r.t., 18 h; 82%. *b*) 1. NaH, THF; 2. $EtOCH_2Cl$, $0° \rightarrow$ r.t., 2 h; 75%. *c*) $[Pd(OAc)_2]$ (10 mol-%), $Ph_3P$ (20 mol-%), $Ag_2CO_3$, DMF, 140°, 30 min; 87%. *d*) 1N aq. HCl, 1,4-dioxane, 80°, 1 h; 57%.

Application of the previously described methodology to ethyl {1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrol-3-yl}acetate (**12**), prepared according to a procedure reported by *Lemaire* and co-workers [13], provided an easy access to the precursor of the pyrrole analogue (*Scheme 3*). Recent studies suggested the strong influence of the electron density of the olefine during the Pd-catalyzed arylation of nitrogen heterocycles [14]. Indeed, the intramolecular *Heck* coupling failed when the indole nitrogen was protected with a tosyl (Ts) group. Thus, the pyrrole system, characterized by a higher electron density at C(2), should provide the expected cyclized product despite the presence of an electron-withdrawing group at *N*(1). Thus, condensation between 2-iodoaniline and **12** afforded the amide **13** in 98% yield, which was further reacted to afford either the EOM-protected derivative **14a** or the (benzyloxy)methyl (BOM)-

protected analogue **14b** in yields of 98 and 86%, respectively[1]). Both compounds were individually submitted to the intramolecular *Heck* cyclization, providing **15a** and **15b** in excellent yields (86 and 87%, resp.). The reaction ran to completion in less than 30 min, and no trace of a *C*(4)-arylated product was detected. In the $^1$H-NMR spectra of **15a** and **15b**, two characteristic *doublet*s ($J = 3.4$ Hz) were observed for H–C(4) and H–C(5) of the pyrrole moiety, which confirmed the regioselectivity of the reaction, pointing out the pivotal role of electron-rich heterocycles. Finally, removal of the EOM group of **15a** under mild acidic conditions afforded the mono-deprotected paullone analogue **16** in only 42% yield. Fortunately, the BOM group of **15b** could be successfully cleaved by exposure to *Pearlman*'s catalyst under classical hydrogenolysis conditions, and the remaining Ts group was removed in basic medium to afford the fully deprotected pyrrole analogue **2b** in 72% yield over both steps.

*Scheme 3*




*a*) 2-Iodoaniline, $Me_3Al$, $CH_2Cl_2$, $-15° \rightarrow$ r.t., 18 h; 98%. *b*) 1. NaH, THF; 2. $EtOCH_2Cl$ or $BnOCH_2Cl$, $0° \rightarrow$ r.t., 2 h; 98% (**14a**), 86% (**14b**). *c*) [$Pd(OAc)_2$] (10 mol-%), $Ph_3P$ (20 mol-%), $Ag_2CO_3$, DMF, 100°, 30 min; 86% (**15a**), 87% (**15b**). *d*) 1N aq. HCl, 1,4-dioxane, 80°, 1 h; 42%. *e*) [$Pd(OH)_2$], $H_2$ (1 atm), EtOH/THF, r.t., 2 h. *f*) 1N aq. NaOH, 1,4-dioxane, 80°, 1 h; 72% (two steps).

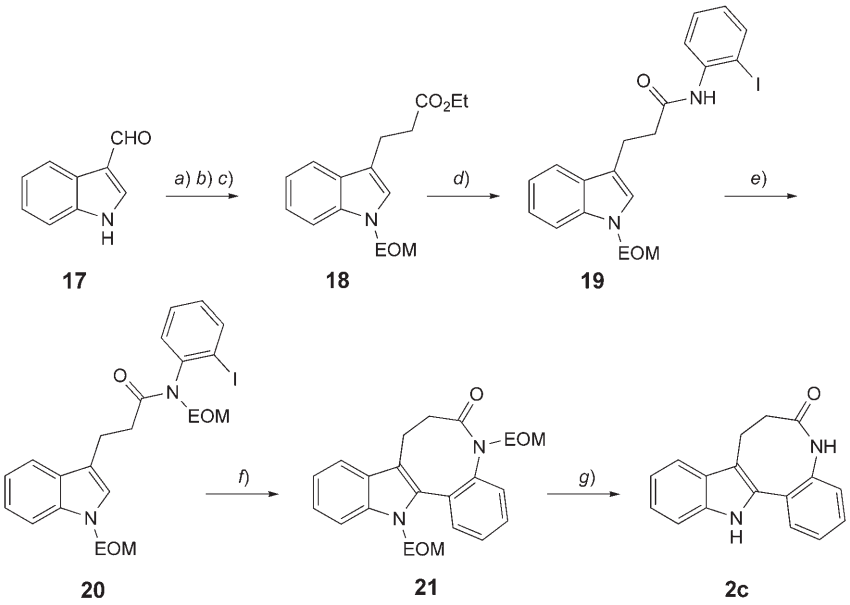
The synthesis of the ring-enlarged compound **2c** started from 1*H*-indole-3-carbaldehyde (**17**)[2]), as shown in *Scheme 4*. Compound **17** was converted into the ester **18** *via* a three-step reaction sequence: *a*) protection of the indole N-atom, *b*) *Wittig* olefination with the appropriate phosphorane, and *c*) hydrogenation of the resulting $\alpha,\beta$-unsaturated ester. Condensation of **18** with 2-iodoaniline afforded **19**,

[1]) The higher yields obtained with the pyrrole nucleus might be explained by a lower stabilization of the carbanion leading to undesired *C*-alkylated by-products.

[2]) Protection of methyl 1*H*-indole-3-propanoate proved to be tedious.

which was EOM-protected to provide the *Heck* precursor **20** in an overall yield of 48% (five steps). As observed for the sulfur analogue, it was necessary to work at a temperature of 140° to effect complete cyclization, which afforded the expected product **21** in 82% yield. Unfortunately, deprotection of **21** failed under acidic conditions. So, the desired product could only be observed by $^1$H-NMR analysis due to the low quantity isolated.

*Scheme 4*




*a*) 1. NaH, THF; 2. $EtOCH_2Cl$, 0° → r.t., 2 h. *b*) $Ph_3P{=}CHCO_2Et$, toluene, reflux, 18 h; 83% (two steps). *c*) 10% Pd/C, $H_2$ (20 atm), MeOH/THF, r.t., 3 h; 99%. *d*) 2-Iodoaniline, $Me_3Al$, $CH_2Cl_2$, −15° → r.t., 18 h; 92%. *e*) 1. NaH, THF; 2. $EtOCH_2Cl$, 0° → r.t., 2 h; 63%. *f*) $[Pd(OAc)_2]$ (10 mol-%), $Ph_3P$ (20 mol-%), $Ag_2CO_3$, DMF, 140°, 30 min; 82%. *g*) 1N aq. HCl, 1,4-dioxane, 80°, 1 h; traces only.

2. *Kinase Activity.* We tested the inhibitory properties of **2a** and **2b** towards CDK1/cyclin B, CDK5/p25, and GSK-3 kinases. Both compounds showed no or only low inhibition activities against these target kinases. The following $IC_{50}$ values were determined for CDK1, CDK5, and GSK-3, resp: **2a**: $IC_{50} > 100$ μM (all three kinases); **2b**: $IC_{50} = 25$, 58, and 40 μM, resp. For comparison, the corresponding $IC_{50}$ values for paullone (**1a**) are 7, 0.62, and 10.1 μM, resp. [1b].

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## Experimental Part

*General.* All commercially available reagents (*Fluka*, *Aldrich*) were used as received. Solvents were dried by standard methods. Petroleum ether (PE) for chromatography had a b.p. range of 40–60°. Thin-layer chromatography (TLC): *Merck 60F$_{254}$* silica gel on Al plates; visualization under UV light. Column

chromatography (CC) and flash chromatography (FC): *Merck* silica gel *60* (40–63 μm). All reactions requiring anh. conditions were conducted in a flame-dried apparatus. Melting points (m.p.) were determined on a *Büchi* capillary apparatus, and are uncorrected. IR Spectra: *Perkin-Elmer-681* spectrophotometer; in $cm^{-1}$. $^1H$- and $^{13}C$-NMR Spectra: *Bruker Avance-300* spectrometer; $\delta$ in ppm, $J$ in Hz. Mass spectra: *Perkin-Elmer SCIEX-API* apparatus; in $m/z$. Elemental analyses: *Thermoquest Flash-1112* elemental analyzer.

*Methyl [1-(Ethoxymethyl)-1*H*-indol-3-yl]acetate* (**4**). At 0° and under $N_2$ atmosphere, 4-(dimethylamino)pyridine (DMAP; 403 mg, 3.3 mmol) was added to a soln. of 1*H*-indole-3-acetic acid (526 mg, 3.0 mmol) in anh. $CH_2Cl_2$ (30 ml). After stirring at 0° for 20 min, anh. MeOH (182 μl, 4.5 mmol) was added dropwise, followed by portionwise addition of EDCI[3]) (634 mg, 3.3 mmol). The mixture was warmed to r.t., and then stirred overnight. Hydrolysis was performed by addition of 1N aq. HCl (15 ml) and $H_2O$ (15 ml). The layers were separated, and the aq. phase was extracted with $CH_2Cl_2$ (3 × 30 ml). The combined org. extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by FC ($SiO_2$; PE/AcOEt 8:2) to afford *methyl 1*H*-indol-3-ylacetate* **3** (562 mg, 99%) as a colorless oil.

To a soln. of **3** (3.0 mmol) in anh. THF (15 ml) was added, at 0° under $N_2$ atmosphere, NaH (60% dispersion in mineral oil; 154 mg, 3.86 mmol). After stirring at 0° for 30 min, $EtOCH_2Cl$ (555 μl, 5.94 mmol) was added dropwise. The soln. was warmed to r.t., and stirred overnight. The mixture was hydrolyzed with 1N aq. HCl (5 ml) and $H_2O$ (10 ml), and extracted with $CH_2Cl_2$ (3 × 20 ml). The combined org. extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by FC ($SiO_2$; PE/AcOEt 9:1) to afford **4** (509 mg, 69%). Colorless oil. IR (NaCl): 2975, 2950, 2900, 1740, 1465, 1355, 1090, 745, 535. $^1H$-NMR (300 MHz, $CDCl_3$): 1.15 (*t*, $J$ = 7.0, Me); 3.43 (*q*, $J$ = 7.0, $CH_2$); 3.71 (*s*, Me); 3.77 (*s*, $CH_2$); 5.47 (*s*, $CH_2$); 7.17 (*t*, $J$ = 7.5, H–C(5)); 7.18 (*s*, H–C(2)); 7.25 (*t*, $J$ = 7.5, H–C(6)); 7.48 (*d*, $J$ = 7.9, H–C(7)); 7.60 (*d*, $J$ = 7.5, H–C(4)). $^{13}C$-NMR (75 MHz, $CDCl_3$): 14.8 (Me); 30.9 ($CH_2$); 51.9 (Me); 63.8 ($CH_2$); 75.8 ($CH_2$); 108.2 (C); 110.0 (CH); 119.0 (CH); 120.0 (CH); 122.3 (CH); 126.8 (CH); 128.3 (C); 136.5 (C); 172.2 (C=O). ESI-MS: 248 ($[M+H]^+$). Anal. calc. for $C_{14}H_{17}NO_3$: C 68.00, H 6.93, N 5.66; found: C 68.27, H 7.11, N 5.80.

*2-[1-(Ethoxymethyl)-1*H*-indol-3-yl]*-N-*(2-iodophenyl)acetamide* (**5**). Under $N_2$ atmosphere at −15°, $Me_3Al$ (2M soln. in toluene; 7.5 ml, 15.0 mmol) was added to anh. $CH_2Cl_2$ (15 ml). A soln. of 2-iodoaniline (2.63 g, 12.0 mmol) in anh. $CH_2Cl_2$ (10 ml) was added dropwise at −15°, and the mixture was stirred for 1 h at this temp. The mixture was then slowly warmed to 0° over 1 h, and a soln. of **4** (0.74 g, 3.0 mmol) in anh. $CH_2Cl_2$ (10 ml) was added dropwise. The mixture was stirred overnight at r.t., and then carefully quenched with 1N aq. HCl (10 ml) at 0°. After addition of more 1N aq HCl (20 ml), the layers were separated, and the aq. phase was extracted with $CH_2Cl_2$ (3 × 30 ml). The combined org. extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by FC ($SiO_2$; PE/AcOEt 85:15) to give **5** (1.23 g, 98%). Solid. M.p. 81–83° (MeOH). IR (KBr): 3240, 2970, 1665, 1520, 1460, 1435, 1090, 740. $^1H$-NMR (300 MHz, $CDCl_3$): 1.17 (*t*, $J$ = 7.0, Me); 3.49 (*q*, $J$ = 7.0, $CH_2$); 3.93 (*s*, $CH_2$); 5.53 (*s*, $CH_2$); 6.75 (*t*, $J$ = 7.6, 1 arom. H); 7.20 (*t*, $J$ = 7.5, 1 arom. H); 7.28–7.33 (*m*, 3 arom. H); 7.52 (*d*, $J$ = 8.3, 1 arom. H); 7.59–7.64 (*m*, 2 arom. H); 7.81 (*s*, NH); 8.30 (*dd*, $J$ = 1.3, 8.3, 1 arom. H). $^{13}C$-NMR (75 MHz, $(D_6)$DMSO): 14.8 (Me); 32.8 ($CH_2$); 63.1($CH_2$); 75.0 ($CH_2$); 94.7 (C); 108.8 (C); 110.2 (CH); 119.1 (CH); 119.5 (CH); 121.8 (CH); 125.9 (CH); 127.1 (CH); 128.0 (CH); 128.2 (C); 128.6 (CH); 136.3 (C); 138.9 (CH); 139.3 (C); 169.4 (C=O). ESI-MS: 435 ($[M+H]^+$). Anal. calc. for $C_{19}H_{19}IN_2O_2$: C 52.55, H 4.41, N 6.45; found: C 52.05, H 4.13, N 6.48.

N-*(Ethoxymethyl)-2-[1-(ethoxymethyl)-1*H*-indol-3-yl]*-N-*(2-iodophenyl)acetamide* (**6**). At 0° and under $N_2$ atmosphere, NaH (60% dispersion in oil; 26 mg, 0.65 mmol) was added to a stirred soln. of **5** (217 mg, 0.5 mmol) in anh. THF (5 ml). The mixture was stirred for 30 min at 0°, then $EtOCH_2Cl$ (70 μl, 0.75 mmol) was added dropwise. The mixture was warmed to r.t., and stirred for 2 h. After addition of 1N aq. HCl (10 ml), the aq. layer was extracted with $CH_2Cl_2$ (3 × 20 ml). The combined org. extracts were dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The crude residue was purified by FC ($SiO_2$; PE/AcOEt 85:15) to afford **6** (170 mg, 69%). Oil. IR (NaCl): 3055, 2975, 2925, 2880, 1670, 1470, 1375, 1090, 1015, 740. $^1H$-NMR (300 MHz, $CDCl_3$): 1.13 (*t*, $J$ = 7.0, Me); 1.18 (*t*, $J$ = 7.0, Me); 3.40 (*q*, $J$ = 7.0, $CH_2$);

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[3]) 1-Ethyl-3-[3-(dimethylamino)propyl]-*N*′-ethylcarbodiimide hydrochloride.

3.47, 3.54 (2*d*, *J* = 8.0, $CH_2$); 3.62–3.73 (*m*, $CH_2$); 4.46 (*d*, *J* = 10.5, 1 H of $CH_2$); 5.42 (*s*, $CH_2$); 5.69 (*d*, *J* = 10.5, 1 H of $CH_2$); 6.97 (*s*, H–C(2)); 7.05–7.22 (*m*, 4 arom. H); 7.33–7.38 (*m*, 2 arom. H); 7.43 (*d*, *J* = 8.1, 1 arom. H); 7.97 (*dd*, *J* = 1.3, 7.9, 1 arom. H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 14.9 (Me); 15.2 (Me); 31.8 ($CH_2$); 63.9 ($CH_2$); 64.9 ($CH_2$); 75.9 ($CH_2$); 76.9 ($CH_2$); 100.8 (C); 108.7 (C); 109.9 (CH); 119.2 (CH); 119.9 (CH); 122.2 (CH); 127.2 (CH); 128.6 (C); 129.5 (CH); 130.1 (CH); 131.3 (CH); 136.5 (C); 140.1 (CH); 143.5 (C); 171.8 (C=O). ESI-MS: 493 ($[M+H]^+$). Anal. calc. for $C_{22}H_{25}IN_2O_3$: C 53.67, H 5.12, N 5.69; found: C 53.99, H 5.22, N 5.86.

*5,12-Bis(ethoxymethyl)-7,12-dihydroindolo[3,2-*d*][1]benzazepin-6(5*H*)-one* (**7**). Under $N_2$ atmosphere, a suspension of **6** (246 mg, 0.5 mmol), $[Pd(OAc)_2]$ (11.2 mg, 0.05 mmol), $Ph_3P$ (26.2 mg, 0.1 mmol), and $Ag_2CO_3$ (276 mg, 1.0 mmol) in anh. DMF (10 ml) was vigorously stirred at 100° for 30 min. After cooling, the solvent was removed under reduced pressure, the residue was taken up in $CH_2Cl_2$, and filtered over *Celite*, eluting with $CH_2Cl_2$. The eluate was evaporated *in vacuo*, and the crude product was purified by FC ($SiO_2$; PE/AcOEt 9:1) to provide **7** (167 mg, 92%). Solid. M.p. 102–103° (PE/AcOEt). IR (KBr): 2980, 1680, 1460, 1365, 1340, 1085, 730. $^1$H-NMR (300 MHz, $CDCl_3$): 1.16 (*t*, *J* = 7.0, Me); 1.25 (*t*, *J* = 7.0, Me); 3.11 (*d*, *J* = 13.6, $CH_2$); 3.41–3.51 (*m*, 1 H of $CH_2$); 3.56–3.70 (*m*, 3 H of $CH_2$); 3.96 (*d*, *J* = 13.6, 1 H of $CH_2$); 4.73 (*d*, *J* = 10.0, 1 H of $CH_2$); 5.39 (*d*, *J* = 10.0, 1 H of $CH_2$); 5.57 (*s*, $CH_2$); 7.21–7.48 (*m*, 4 arom. H); 7.54 (*d*, *J* = 8.3, 1 arom. H); 7.73 (*d*, *J* = 7.9, 1 arom. H); 7.88 (*d*, *J* = 7.9, 1 arom. H); 7.95 (*d*, *J* = 7.6, 1 arom. H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 15.2 (Me); 15.3 ($CH_2$); 32.6 ($CH_2$); 64.3 ($CH_2$); 64.6 ($CH_2$); 73.9 ($CH_2$); 78.9 ($CH_2$); 110.3 (CH); 112.9 (C); 118.9 (CH); 121.0 (CH); 123.5 (CH); 124.8 (CH); 125.3 (C); 126.0 (CH); 126.2 (C); 128.6 (CH); 129.0 (CH); 134.2 (C); 139.2 (C); 140.8 (C); 172.7 (C=O). ESI-MS: 365 ($[M+H]^+$). Anal. calc. for $C_{22}H_{24}N_2O_3$: C 72.51, H 6.64, N 7.69; found: C 72.23, H 6.49, N 7.58.

*7,12-Dihydroindolo[3,2-*d*][1]benzazepin-6(5*H*)-one* (**1a**). A soln. of **7** (30 mg, 0.08 mmol) and 1N aq. HCl (0.75 ml) in 1,4-dioxane (2.25 ml) was stirred at 80° for 1 h. After cooling to r.t., $H_2O$ (10 ml) was added, and the aq. layer was extracted with $CH_2Cl_2$ (3 × 10 ml). The combined org. extracts were dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The crude residue was purified by FC ($SiO_2$; $CH_2Cl_2$/MeOH 99:1) to give **1a** (7.5 mg, 37%). Solid. M.p. > 250°. The $^1$H-NMR data (300 MHz, ($D_6$)DMSO) were identical to those described previously [7].

*Methyl 1-Benzothiophene-3-acetate* (**8**). At 0° and under $N_2$ atmosphere, DMAP (763 mg, 6.24 mmol) was added to a soln. of 1-benzothiophene-3-acetic acid (1.00 g, 5.20 mmol) in anh. $CH_2Cl_2$ (55 ml). After stirring at 0° for 20 min, anh. MeOH (316 µl, 7.80 mmol) was added dropwise, followed by EDCI[3]) (1.20 g, 6.24 mmol). The mixture was warmed to r.t., and stirred overnight. After hydrolysis with 1N aq. HCl (15 ml) and $H_2O$ (15 ml), the layers were separated, and the aq. phase was extracted with $CH_2Cl_2$ (3 × 30 ml). The combined org. extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The oily residue was purified by FC ($SiO_2$; PE/AcOEt 9:1) to give **8** (1.04 g, 97%). Colorless oil. IR (NaCl): 3070, 1735, 1460, 1430, 1260, 1160, 1020, 760, 730. $^1$H-NMR (300 MHz, $CDCl_3$): 3.72 (*s*, Me); 3.89 (*s*, $CH_2$); 7.34–7.44 (*m*, 3 arom. H); 7.77 (*dd*, *J* = 1.7, 7.0, 1 arom. H); 7.87 (*dd*, *J* = 1.7, 7.0, 1 arom. H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 34.4 ($CH_2$); 52.3 (Me); 121.9 (CH); 123.0 (CH); 124.3 (CH); 124.5 (CH); 124.7 (CH); 128.3 (C); 138.6 (C); 140.3 (C); 171.2 (C=O). ESI-MS: 207 ($[M+H]^+$). Anal. calc. for $C_{11}H_{10}O_2S$: C 64.05, H 4.89, S 15.55; found: C 64.38, H 5.02, S 15.67.

*2-(1-Benzothien-3-yl)-*N*-(2-iodophenyl)acetamide* (**9**). Prepared, in analogy to **5**, in 82% yield from **8** after FC ($SiO_2$; PE/AcOEt 9:1). Solid. M.p. 163–164° ($CH_2Cl_2$). IR (KBr): 3305, 3055, 1670, 1575, 1520, 1435, 1285, 1180, 1015, 780, 740, 725. $^1$H-NMR (300 MHz, $CDCl_3$): 4.05 (*s*, $CH_2$); 6.77 (*dd*, *J* = 7.4, 7.7, 1 arom. H); 7.26–7.32 (*m*, 1 arom. H); 7.40–7.46 (*m*, 2 arom. H); 7.53 (*s*, H–C(2)); 7.60–7.63 (*m*, 2 arom. H); 7.79–7.97 (*m*, 2 arom. H); 8.27 (*d*, *J* = 8.1, 1 arom. H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 38.1 ($CH_2$); 89.1 (C); 121.3 (CH); 122.1 (CH); 123.1 (CH); 124.9 (CH); 125.2 (CH); 126.0 (CH); 126.6 (CH); 128.9 (C); 129.3 (CH); 138.0 (C); 138.5 (C); 138.8 (CH); 140.9 (C); 168.3 (C=O). ESI-MS: 394 ($[M+H]^+$). Anal. calc. for $C_{16}H_{12}INOS$: C 48.87, H 3.08, N 3.56, S 8.15; found: C 48.77, H 3.02, N 3.78, S 7.98.

*2-(1-Benzothiophen-3-yl)-*N*-(ethoxymethyl)-*N*-(2-iodophenyl)acetamide* (**10**). Prepared, in analogy to **6**, in 75% yield from **9** after FC ($SiO_2$; PE/AcOEt 9:1). Oil. IR (KBr): 2970, 2930, 2865, 1680, 1470, 1375, 1235, 1070, 1015, 935, 780, 750, 725. $^1$H-NMR (300 MHz, $CDCl_3$): 1.20 (*t*, *J* = 7.1, Me); 3.63–3.71 (*m*, 2 $CH_2$); 4.47, 5.70 (*d*, *J* = 10.5, $CH_2$); 7.04 (*s*, 1 arom. H); 7.05–7.17 (*m*, 2 arom. H); 7.30–7.36 (*m*, 3 arom. H); 7.59–7.62 (*m*, 1 arom. H); 7.80–7.83 (*m*, 1 arom. H); 7.96 (*dd*, *J* = 1.3, 7.9, 1 arom. H).

$^{13}$C-NMR (75 MHz, $CDCl_3$): 15.2 (Me); 35.4 ($CH_2$); 65.0 ($CH_2$); 77.0 ($CH_2$); 100.7 (C); 122.0 (CH); 122.8 (CH); 124.1 (CH); 124.3 (CH); 124.6 (CH); 128.8 (C); 129.6 (CH); 130.3 (CH); 131.3 (CH); 138.8 (C); 140.1 (C); 140.2 (CH); 143.2 (C); 170.6 (C=O). ESI-MS: 452 ($[M+H]^+$). Anal. calc. for $C_{19}H_{18}INO_2S$: C 50.56, H 4.02, N 3.10, S 7.10; found: C 50.24, H 3.98, N 3.01, S 7.00.

*5-(Ethoxymethyl)-5,7-dihydro-6*H*-[1]benzothieno[3,2-*d*][1]benzazepin-6-one* (**11**). Prepared, in analogy to **7**, in 87% yield from **10** after FC ($SiO_2$; PE/AcOEt 8:2). Solid. M.p. 118–119° (AcOEt/PE). IR (KBr): 3055, 2970, 2920, 2865, 1670, 1485, 1445, 1375, 1295, 1095, 1070, 940, 910, 770, 750, 730. $^1$H-NMR (300 MHz, $CDCl_3$): 1.19 (*t*, *J* = 6.8, Me); 3.24 (*m*, 1 H of $CH_2$); 3.52 (*m*, 1 H of $CH_2$); 3.66 (*m*, 1 H of $CH_2$); 4.10 (*m*, 1 H of $CH_2$); 4.79 (*m*, 1 H of $CH_2$); 5.44 (*m*, 1 H of $CH_2$); 7.33–7.48 (*m*, 4 arom. H); 7.64 (*d*, *J* = 7.5, 1 arom. H); 7.86–7.92 (*m*, 3 arom. H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 15.4 (Me); 34.8 ($CH_2$); 64.8 ($CH_2$); 78.9 ($CH_2$); 122.0 (CH); 122.8 (CH); 124.2 (CH); 124.9 (CH); 125.3 (CH); 126.2 (CH); 128.3 (C); 129.1 (C); 129.2 (CH); 129.7 (CH); 136.0 (C); 138.3 (C); 140.3 (C); 140.5 (C); 170.1 (C=O). ESI-MS: 324 ($[M+H]^+$). Anal. calc. for $C_{19}H_{17}NO_2S$: C 70.56, H 5.30, N 4.33, S 9.91; found: C 70.05, H 5.11, N 4.41, S 9.77.

*5,7-Dihydro-6*H*-[1]benzothieno[3,2-*d*]benzazepin-6-one* (**2a**). Prepared, in analogy to **1a**, in 57% yield from **11**. Solid. M.p. >250° ($H_2O$/1,4-dioxane). IR (KBr): 3460, 3185, 3060, 2970, 2915, 1680, 1485, 1385, 720, 725. $^1$H-NMR (300 MHz, ($D_6$)DMSO): 3.63 (*s*, $CH_2$); 7.27–7.30 (*m*, 2 arom. H); 7.44–7.52 (*m*, 3 arom. H); 7.65 (*d*, *J* = 7.7, 1 arom. H); 8.00 (*d*, *J* = 7.9, 1 arom. H); 8.06 (*d*, *J* = 7.7, 1 arom. H); 10.4 (br. *s*, NH). $^{13}$C-NMR (75 MHz, ($D_6$)DMSO): 33.7 ($CH_2$); 121.8 (CH); 122.4 (CH); 122.9 (CH); 124.3 (CH); 124.6 (C); 124.9 (CH); 125.2 (CH); 127.3 (C); 129.1 (CH); 129.2 (CH); 135.7 (C); 136.1 (C); 138.3 (C); 139.4 (C); 170.1 (C=O). ESI-MS: 266 ($[M+H]^+$). Anal. calc. for $C_{16}H_{11}NOS$: C 72.43, H 4.18, N 5.28, S 12.08; found: C 72.35, H 4.05, N 5.33, S 11.92.

N-*(2-Iodophenyl)-2-{1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrol-3-yl}acetamide* (**13**). Prepared, in analogy to **5**, from **12** [13] in 98% yield after FC ($SiO_2$; PE/AcOEt 7:3). Solid. M.p. 146–147° (MeOH). IR (KBr): 3340, 1695, 1585, 1525, 1370, 1170, 1065. $^1$H-NMR (300 MHz, $CDCl_3$): 2.43 (*s*, Me); 3.58 (*s*, $CH_2$); 6.32 (*dd*, *J* = 1.7, 3.0, 1 H); 6.78 (*t*, *J* = 7.7, 1 arom. H); 7.23–7.33 (*m*, 5 H); 7.57 (*s*, NH); 7.64 (*dd*, *J* = 1.3, 7.9, 1 arom. H); 7.82 (*d*, *J* = 8.3, 2 arom. H); 8.25 (*d*, *J* = 8.1, 1 arom. H). $^{13}$C-NMR (75 MHz, ($D_6$)DMSO): 21.0 (Me); 34.1 ($CH_2$); 95.4 (C); 115.3 (CH); 118.9 (CH); 121.0 (CH); 122.6 (C); 126.6 (CH); 126.8 (2 CH); 127.4 (CH); 128.6 (CH); 130.3 (2 CH); 135.3 (C); 138.8 (CH); 139.2 (C); 145.3 (C); 168.7 (C=O). ESI-MS: 481 ($[M+H]^+$). Anal. calc. for $C_{19}H_{17}IN_2O_3S$: C 47.51, H 3.57, N 5.83, S 6.68; found: C 47.66, H 3.39, N 5.88, S 6.65.

N-*(Ethoxymethyl)*-N-*(2-iodophenyl)-2-{1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrol-3-yl}acetamide* (**14a**). Prepared, in analogy to **6**, from **13** in 98% yield after FC ($SiO_2$; PE/AcOEt 8:2). Solid. M.p. 102–103° ($Et_2O$). IR (KBr): 2980, 1675, 1470, 1365, 1230, 1170, 1095. $^1$H-NMR (300 MHz, $CDCl_3$): 1.18 (*t*, *J* = 7.0, Me); 2.39 (*s*, Me); 3.09, 3.17 (*d*, *J* = 16.0, $CH_2$); 3.56–3.71 (*m*, $CH_2$); 4.39, 5.63 (*d*, *J* = 10.4, $CH_2$); 6.15 (*dd*, *J* = 1.5, 3.0, 1 H); 6.83 (br. *s*, 1 H); 7.05–7.07 (*m*, 1 H); 7.11 (*d*, *J* = 7.4, 2 arom. H); 7.26–7.28 (*m*, 2 H arom. H); 7.34 (*t*, *J* = 7.6, 1 arom. H); 7.71 (*d*, *J* = 8.3, 2 arom. H); 7.92 (*d*, *J* = 7.7, 1 arom. H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 15.2 (Me); 21.7 (Me); 33.4 ($CH_2$); 64.9 ($CH_2$); 76.8 ($CH_2$); 100.7 (C); 115.1 (CH); 119.1 (CH); 120.9 (CH); 121.6 (C); 127.0 (2 CH); 129.6 (CH); 130.0 (2 CH); 130.3 (CH); 131.2 (CH); 136.2 (C); 140.1 (CH); 143.2 (C); 145.0 (C); 171.2 (C=O). ESI-MS: 539 ($[M+H]^+$). Anal. calc. for $C_{22}H_{23}IN_2O_4S$: C 49.08, H 4.31, N 5.20, S 5.96; found: C 49.48, H 4.22, N 5.32, S 5.87.

N-*[(Benzyloxy)methyl]*-N-*(2-iodophenyl)-2-{1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrol-3-yl}acetamide* (**14b**). Prepared, in analogy to **6**, from **13** and $BnOCH_2Cl$ in 86% yield after FC ($SiO_2$; PE/AcOEt 9:1). Colorless oil. IR (NaCl): 3140, 3060, 2930, 1675, 1470, 1370, 1170, 1100, 1060, 675, 585, 540. $^1$H-NMR (300 MHz, $CDCl_3$): 2.38 (*s*, Me); 3.12, 3.20 (2*d*, *J* = 16.0, $CH_2$); 4.47 (*d*, *J* = 10.4, 1 H of $CH_2$); 4.62–4.71 (*m*, $CH_2$); 5.73 (*d*, *J* = 10.4, 1 H of $CH_2$); 6.17–6.18 (*m*, 1 H); 6.85 (br. *s*, 1 H); 7.06–7.08 (*m*, 1 H); 7.11 (*d*, *J* = 7.5, 2 arom. H); 7.23–7.38 (*m*, 8 arom. H); 7.71 (*d*, *J* = 8.7, 2 arom. H); 7.92 (*d*, *J* = 7.1, 1 arom. H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 21.5 (Me); 33.2 ($CH_2$); 71.2 ($CH_2$); 76.6 ($CH_2$); 100.5 (C); 114.9 (CH); 118.9 (CH); 120.7 (CH); 121.4 (C); 126.8 (2 CH); 127.5 (2 CH); 127.6 (CH); 128.3 (2 CH); 129.4 (CH); 129.8 (2 CH); 130.2 (CH); 131.1 (CH); 136.0 (C); 137.8 (C); 139.9 (CH); 142.9 (C); 143.2 (C); 144.9 (C); 171.1 (C=O). ESI-MS: 601 ($[M+H^+]$). Anal. calc. for $C_{27}H_{25}IN_2O_4S$: C 54.01, H 4.20, N 4.67; found: C 53.88, H 4.30, N 4.59.

*6-(Ethoxymethyl)-4,6-dihydro-1-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-*d*][1]benzazepin-5(1*H*)-one* (**15a**). Prepared, in analogy to **7**, from **14a** in 86% yield after FC ($SiO_2$; PE/AcOEt 85:15). Solid. M.p. 111–112° (PE/AcOEt). IR (KBr): 3125, 2980, 2930, 1690, 1375, 1310, 1175, 1115, 1075, 770, 695, 585, 545. $^1$H-NMR (300 MHz, $CDCl_3$): 1.25 (*t*, *J* = 7.0, Me); 2.32 (*s*, Me); 2.85 (*d*, *J* = 13.6, 1 H of $CH_2$); 3.39 (*d*, *J* = 13.6, 1 H of $CH_2$); 3.51–3.62 (*m*, 1 H of $CH_2$); 3.67–3.78 (*m*, 1 H of $CH_2$); 3.97, 5.10 (2*d*, *J* = 9.7, $CH_2$); 6.31 (*d*, *J* = 3.4, 1 H); 7.04 (*d*, *J* = 8.3, 2 arom. H); 7.18 (*d*, *J* = 8.3, 2 arom. H); 7.31–7.41 (*m*, 2 arom. H); 7.44 (*d*, *J* = 3.4, 1 H); 7.72–7.75 (*m*, 1 arom. H); 7.85–7.88 (*m*, 1 arom. H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 15.4 (Me); 21.7 (Me); 35.1 ($CH_2$); 64.9 ($CH_2$); 78.5 ($CH_2$); 113.4 (CH); 123.8 (CH); 124.4 (C); 125.3 (CH); 126.7 (CH); 127.2 (CH); 127.5 (C); 128.7 (CH); 129.2 (C); 129.4 (CH); 131.5 (CH); 135.3 (C); 140.0 (C); 145.0 (C); 172.9 (C=O). ESI-MS: 411 ($[M+H]^+$). Anal. calc. for $C_{22}H_{22}N_2O_4S$: C 64.37, H 5.40, N 6.82, S 7.81; found: C 64.36, H 5.14, N 6.82, S 7.72.

*6-[(Benzyloxy)methyl]-4,6-dihydro-1-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-*d*][1]benzazepin-5(1*H*)-one* (**15b**). Prepared, in analogy to **7**, from **14b** in 87% yield after FC ($SiO_2$; PE/AcOEt 85:15). Solid. M.p. 95–96° (PE/AcOEt). IR (KBr): 3125, 3055, 3030, 2935, 1685, 1450, 1375, 1175, 1065, 775, 700, 585, 545. $^1$H-NMR (300 MHz, $CDCl_3$): 2.22 (*s*, Me); 2.88, 3.41 (*d*, *J* = 13.6, 1 H of $CH_2$); 4.08 (*d*, *J* = 9.8, 1 H of $CH_2$); 4.59 (*d*, *J* = 12.0, 1 H of $CH_2$); 4.74 (*d*, *J* = 12.0, 1 H of $CH_2$); 5.13 (*d*, *J* = 9.8, 1 H of $CH_2$); 6.32 (*d*, *J* = 3.4, 1 H); 6.97 (*d*, *J* = 8.3, 2 arom. H); 7.16 (*d*, *J* = 8.3, 2 arom. H); 7.29–7.40 (*m*, 7 arom. H); 7.44 (*d*, *J* = 3.4, 1 H); 7.73–7.76 (*m*, 1 arom. H); 7.86–7.89 (*m*, 1 arom. H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 21.6 (Me); 35.1 ($CH_2$); 71.7 ($CH_2$); 78.5 ($CH_2$); 113.4 (CH); 123.8 (CH); 124.4 (C); 125.3 (CH); 126.7 (2 CH); 127.2 (CH); 127.4 (C); 127.9 (2 CH); 128.6 (2 CH); 128.8 (CH); 129.2 (C); 129.4 (2 CH); 131.5 (CH); 135.2 (C); 138.0 (C); 139.9 (C); 145.1 (C); 173.1 (C=O). ESI-MS: 473 ($[M+H]^+$). Anal. calc. for $C_{27}H_{24}N_2O_4S$: C 68.63, H 5.12, N 5.93, S 6.79; found: C 68.59, H 5.18, N 5.72, S 6.40.

*4,6-Dihydro-1-[(4-methylphenyl)sulfonyl]pyrrolo[3,2-*d*][1]benzazepin-5(1*H*)-one* (**16**). Prepared, in analogy to **1a**, from **15a** in 42% yield after FC ($SiO_2$; PE/AcOEt 1:1). Solid. M.p. 177–179 (MeOH). IR (KBr): 3445, 3210, 3100, 2985, 1670, 1370, 1180, 1160, 760, 585. $^1$H-NMR (300 MHz, $CDCl_3$): 2.31 (*s*, Me); 2.88–2.96 (*m*, 1 H of $CH_2$); 3.28–3.36 (*m*, 1 H of $CH_2$); 6.28 (*d*, *J* = 3.2, 1 H); 6.99 (*dd*, *J* = 1.2, 7.8, 1 arom. H); 7.04 (*d*, *J* = 8.3, 2 arom. H); 7.14–7.17 (*m*, NH and 2 arom. H); 7.29–7.39 (*m*, 2 arom. H); 7.45 (*d*, *J* = 3.2, 1 H); 7.93 (*dd*, *J* = 1.6, 7.8, 1 arom. H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 21.1 (Me); 34.0 ($CH_2$); 114.8 (CH); 121.7 (C); 122.0 (CH); 122.5 (C); 126.2 (2 CH); 127.2 (C); 127.5 (CH); 128.3 (CH); 129.3 (C); 129.7 (2 CH); 131.0 (CH); 134.1 (C); 135.6 (C); 145.2 (C); 172.8 (C=O). ESI-MS: 353 ($[M+H]^+$). Anal. calc. for $C_{19}H_{16}N_2O_3S$: C 64.76, H 4.58, N 7.95; found: C 65.11, H 4.65, N 8.04.

*4,6-Dihydropyrrolo[3,2-*d*][1]benzazepin-5(1*H*)-one* (**2b**). A soln. of **15b** (47 mg, 0.1 mmol) and $[Pd(OH)_2]$ (50% (*w*/*w*); 23 mg) in EtOH/THF 4:1 (5 ml) was stirred under $H_2$ (1 bar) for 2 h at r.t. After filtration over *Celite* and evaporation of the solvent, the crude residue was dissolved in 1,4-dioxane (4 ml), and then treated with 1N aq. NaOH soln. (1 ml). The mixture was stirred at 80° for 1 h, cooled to r.t., and treated with $H_2O$ (10 ml). The aq. layer was extracted with AcOEt (3 × 10 ml), the combined org. extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by FC ($SiO_2$; $CH_2Cl_2$/MeOH 98:2) to afford **2b** (14.3 mg, 72%). Colorless solid. M.p. > 210° (MeOH). IR (KBr): 3445, 3210, 3085, 3040, 1641, 1565, 1410, 1145, 755, 730. $^1$H-NMR (300 MHz, ($D_6$)DMSO): 3.18 (*s*, $CH_2$); 6.06 (*t*, *J* = 2.5, 1 H); 6.93 (*t*, *J* = 2.5, 1 H); 7.13–7.23 (*m*, 3 arom. H); 7.52 (*d*, *J* = 7.5, 1 arom. H); 9.86 (*s*, NH); 11.33 (*s*, NH). $^{13}$C-NMR (75 MHz, ($D_6$)DMSO): 34.6 ($CH_2$); 108.1 (CH); 115.7 (C); 120.3 (CH); 122.0 (CH); 123.4 (CH); 123.5 (C); 125.6 (CH); 125.8 (C); 126.1 (CH); 133.9 (C); 171.7 (C=O). ESI-MS: 199 ($[M+H]^+$). Anal. calc. for $C_{12}H_{10}N_2O$: C 72.71, H 5.08, N 14.13; found: C 72.99, H 4.88, N 13.91.

*Methyl 3-[1-(Ethoxymethyl)-1*H*-indol-3-yl]propanoate* (**18**). This compound was prepared by the following three-step sequence. *a*) At 0° and under $N_2$ atmosphere, NaH (60% dispersion in mineral oil; 390 mg, 9.69 mmol) was added portionwise to a soln. of 1*H*-indole-3-carbaldehyde (**17**; 1.08 g, 7.45 mmol) in anh. THF (35 ml). After 30 min at 0°, $EtOCH_2Cl$ (1.05 ml, 11.2 mmol) was added dropwise, and the final soln. was stirred for 2 h at r.t. After addition of $H_2O$ (15 ml), the mixture was extracted with $CH_2Cl_2$ (3 × 30 ml), the combined org. extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by FC ($SiO_2$; PE/AcOEt 8:2) to afford *1-(ethoxymethyl)-1*H*-indole-3-carbaldehyde* (1.39 g, 92%). Colorless solid. M.p. 79–80° ($Et_2O$). IR (KBr): 3115, 2975, 2880, 2830, 1650, 1530, 1470, 1375, 1245, 1095, 1030, 840, 785, 670. $^1$H-NMR (300 MHz, $CDCl_3$): 1.18 (*t*, *J* = 7.0, Me); 3.48

($q$, $J$ = 7.0, $CH_2$); 5.56 ($s$, $CH_2$); 7.33–7.38 ($m$, H–C(5), H–C(6)); 7.53 ($dd$, $J$ = 2.5, 6.0, H–C(4)); 7.80 ($s$, H–C(2)); 8.31 ($dd$, $J$ = 2.5, 6.0, H–C(7)); 10.1 ($s$, CHO). $^{13}$C-NMR (75 MHz, $CDCl_3$): 14.9 (Me); 64.7 ($CH_2$); 76.9 ($CH_2$); 110.8 (CH); 119.0 (C); 122.2 (CH); 123.4 (CH); 124.6 (CH); 125.6 (C); 137.3 (C); 138.3 (CH); 185.0 (CHO). ESI-MS: 204 ($[M+H]^+$). Anal. calc. for $C_{12}H_{13}NO_2$: C 70.92, H 6.45, N 6.89; found: C 70.79, H 6.33, N 6.99.

*b*) A soln. of *1-(ethoxymethyl)-1*H-*indole-3-carbaldehyde* (1.07 g, 5.28 mmol) and [(ethoxycarbonyl)methylidene]triphenylphosphorane ($EtOC(O)C(H)=PPh_3$; 3.68 g, 10.57 mmol) in anh. toluene (50 ml) was heated under reflux overnight. The mixture was poured into $H_2O$ (30 ml) and extracted with AcOEt (3 × 30 ml). The combined org. extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude compound was purified by FC ($SiO_2$; PE/AcOEt 8:2) to provide *methyl (2*E*)-3-[1-(ethoxymethyl)-1*H-*indol-3-yl]prop-2-enoate* (1.3 g, 90%). Colorless solid. M.p. 87–88° (PE/AcOEt). IR (KBr): 3105, 2975, 2895, 1705, 1635, 1535, 1470, 1370, 1300, 1195, 835, 740, 620. $^1$H-NMR (300 MHz, $CDCl_3$): 1.16 ($t$, $J$ = 7.2, Me); 1.35 ($t$, $J$ = 7.2, Me); 3.44 ($q$, $J$ = 7.2, $CH_2$); 4.27 ($q$, $J$ = 7.2, $CH_2$); 5.50 ($s$, $CH_2$); 6.46 ($d$, $J$ = 15.8, HC=); 7.27–7.35 ($m$, 3 arom. H); 7.45 ($s$, H–C(2)); 7.53 ($d$, $J$ = 7.5, H–C(4)); 7.88 ($d$, $J$ = 15.8, HC=); 7.94 ($d$, $J$ = 6.4, H–C(7)). $^{13}$C-NMR (75 MHz, $CDCl_3$): 14.5 (Me); 14.9 (Me); 60.2 ($CH_2$); 64.3 ($CH_2$); 76.3 ($CH_2$); 110.8 (CH); 113.3 (C); 114.0 (CH); 120.7 (CH); 121.9 (CH); 123.5 (CH); 126.6 (C); 132.0 (CH); 137.5 (C); 137.7 (CH); 168.1 (C=O). ESI-MS: 274 ($[M+H]^+$). Anal. calc. for $C_{16}H_{19}NO_3$: C 70.31, H 7.01, N 5.12; found: C 70.33, H 6.95, N 5.17.

*c*) A soln. of *methyl (2*E*)-3-[1-(ethoxymethyl)-1*H-*indol-3-yl]prop-2-enoate* (1.21 g, 4.44 mmol) in MeOH/THF 6:1 (70 ml) was stirred with a cat. amount of 10% Pd/C (120 mg) in a stainless-steel reactor under $H_2$ (20 atm) for 3 h at r.t. After filtration over *Celite* and solvent removal, the crude product was purified by FC ($SiO_2$; PE/AcOEt 8:2) to afford **18** (1.21 g, 99%). Oil. IR (NaCl): 2975, 1735, 1465, 1370, 1160, 1090, 740. $^1$H-NMR (300 MHz, $CDCl_3$): 1.14 ($t$, $J$ = 7.0, Me); 1.24 ($t$, $J$ = 7.1, Me); 2.71 ($t$, $J$ = 7.5, $CH_2$); 3.09 ($t$, $J$ = 7.5, $CH_2$); 3.40 ($q$, $J$ = 7.0, $CH_2$); 4.13 ($q$, $J$ = 7.1, $CH_2$); 5.45 ($s$, $CH_2$); 7.00 ($s$, H–C(2)); 7.15 ($dd$, $J$ = 7.3, 8.0, H–C(5)); 7.24 ($dd$, $J$ = 7.3, 7.9, H–C(6)); 7.46 ($d$, $J$ = 8.0, H–C(4)); 7.59 ($d$, $J$ = 7.9, H–C(7)). $^{13}$C-NMR (75 MHz, $CDCl_3$): 14.2 (Me); 14.8 (Me); 20.5 ($CH_2$); 34.8 ($CH_2$); 60.3 ($CH_2$); 63.7 ($CH_2$); 75.7 ($CH_2$); 109.8 (CH); 114.9 (C); 118.9 (CH); 119.7 (CH); 122.2 (CH); 125.3 (CH); 128.4 (C); 136.7 (C); 173.2 (C=O). ESI-MS: 276 ($[M+H]^+$). Anal. calc. for $C_{16}H_{21}NO_3$: C 69.79, H 7.69, N 5.09; found: C 70.08, H 7.53, N 5.17.

*3-[1-(Ethoxymethyl)-1*H-*indol-3-yl]-*N-*(2-iodophenyl)propanamide* (**19**). Prepared, in analogy to **5**, from **18** in 92% yield after FC ($SiO_2$; PE/AcOEt 8:2). Solid. M.p. 114.5–115.5° (PE/AcOEt). IR (KBr): 3275, 2970, 2910, 1655, 1575, 1525, 1465, 1435, 1355, 1325, 1285, 1200, 1095, 1015, 755, 730. $^1$H-NMR (300 MHz, $CDCl_3$): 1.07 ($t$, $J$ = 7.0, Me); 2.84 ($t$, $J$ = 7.4, $CH_2$); 3.23 ($t$, $J$ = 7.4, $CH_2$); 3.34 ($q$, $J$ = 7.0, $CH_2$); 5.43 ($s$, $CH_2$); 6.81 ($t$, $J$ = 7.5, 1 arom. H); 7.05 ($s$, H–C(2)); 7.14–7.35 ($m$, 3 arom. H); 7.47 ($d$, $J$ = 8.2, 1 arom. H); 7.64 ($d$, $J$ = 7.8, 1 arom. H); 7.71 ($d$, $J$ = 7.9, 1 arom. H); 8.22 ($d$, $J$ = 7.9, 1 arom. H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 14.9 (Me); 21.2 ($CH_2$); 38.4 ($CH_2$); 63.9 ($CH_2$); 75.8 ($CH_2$); 89.9 (C); 110.2 (CH); 114.3 (C); 118.9 (CH); 119.9 (CH); 122.1 (CH); 122.4 (CH); 125.8 (CH); 125.9 (CH); 128.3 (CH); 129.2 (CH); 137.0 (C); 138.2 (C); 138.8 (CH); 170.9 (C=O). ESI-MS: 449 ($[M+H]^+$). Anal. calc. for $C_{20}H_{21}IN_2O_2$: C 53.58, H 4.72, N 6.25; found: C 53.40, H 4.57, N 6.18.

N-*(Ethoxymethyl)-3-[1-(ethoxymethyl)-1*H-*indol-3-yl]-*N-*(2-iodophenyl)propanamide* (**20**). Prepared, in analogy to **6**, from **19** in 63% yield after FC ($SiO_2$; PE/AcOEt 8:2). Oil. IR (NaCl): 3055, 2975, 2925, 2885, 1665, 1580, 1470, 1380, 1230, 1090, 1015, 740. $^1$H-NMR (300 MHz, $CDCl_3$): 1.13 ($t$, $J$ = 7.1, Me); 1.20 ($t$, $J$ = 7.1, Me); 2.37 ($t$, $J$ = 7.4, $CH_2$); 3.08 ($t$, $J$ = 7.4, $CH_2$); 3.40 ($q$, $J$ = 7.1, $CH_2$); 3.64 ($q$, $J$ = 7.1, $CH_2$); 4.41 ($d$, $J$ = 10.4, 1 H of $CH_2$); 5.40 ($s$, $CH_2$); 5.69 ($d$, $J$ = 10.4, 1 H of $CH_2$); 6.91 ($s$, 1 arom. H); 7.01–7.09 ($m$, 3 arom. H); 7.18–7.31 ($m$, 2 arom. H); 7.36–7.44 ($m$, 2 arom. H); 7.90 ($d$, $J$ = 7.9, 1 arom. H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 14.9 (Me); 15.2 (Me); 20.7 ($CH_2$); 35.5 ($CH_2$); 63.8 ($CH_2$); 64.6 ($CH_2$); 75.7 ($CH_2$); 76.5 ($CH_2$); 100.5 (C); 109.8 (CH); 115.1 (C); 119.0 (CH); 119.6 (CH); 122.1 (CH); 125.5 (CH); 128.4 (C); 129.5 (CH); 130.0 (CH); 130.9 (CH); 136.7 (C); 139.9 (CH); 143.3 (C); 173.3 (C=O). ESI-MS: 507 ($[M+H]^+$). Anal. calc. for $C_{23}H_{27}IN_2O_3$: C 54.55, H 5.37, N 5.53; found: C 54.79, H 5.21, N 5.70.

*5,13-Bis(ethoxymethyl)-5,7,8,13-tetrahydro-6*H-*indolo[3,2-*e*][1]benzazocin-6-one* (**21**). Prepared, in analogy to **7**, from **20** in 82% yield after FC ($SiO_2$; PE/AcOEt 8:2). Solid. M.p. 158–159° (PE/AcOEt). IR (KBr): 3035, 2970, 2880, 1660, 1495, 1465, 1400, 1170, 1090, 1060, 745. $^1$H-NMR (300 MHz, $CDCl_3$):

0.86 ($t$, $J = 7.0$, Me); 1.15 ($t$, $J = 7.0$, Me); 2.40 – 2.47 ($m$, 1 H of $CH_2$); 2.84 – 2.95 ($m$, $CH_2$); 3.03 – 3.10 ($m$, 1 H of $CH_2$); 3.29 – 3.54 ($m$, 2 $CH_2$); 5.04 ($s$, $CH_2$); 5.13, 5.26 ($d$, $J = 10.5$, $CH_2$); 7.15 – 7.26 ($m$, 1 arom. H); 7.43 – 7.62 ($m$, 7 arom. H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 15.0 (Me); 15.2 (Me); 22.4 ($CH_2$); 31.8 ($CH_2$); 63.9 ($CH_2$); 64.4 ($CH_2$); 73.1 ($CH_2$); 76.8 ($CH_2$); 109.7 (CH); 114.1 (C); 119.0 (CH); 120.5 (CH); 123.3 (CH); 127.2 (CH); 127.5 (CH); 128.3 (C); 129.9 (CH); 130.9 (C); 132.4 (C); 132.7 (CH); 137.7 (C); 141.8 (C); 174.5 (C=O). ESI-MS: 379 ($[M + H]^+$). Anal. calc. for $C_{23}H_{26}N_2O_3$: C 72.99, H 6.92, N 7.40; found: C 73.30, H 7.12, N 7.55.

## REFERENCES


[1] a) L. Meijer, M. Leost, O. Lozach, S. Schmitt, C. Kunick, *Handbook Exper. Pharmacol.* **2005**, *167*, 47; b) M. Leost, C. Schultz, A. Link, Y.-Z. Wu, J. Biernat, E.-M. Mandelkow, J. A. Bibb, G. L. Snyder, P. Greengard, D. W. Zaharevitz, R. Gussio, A. M. R. Senderowicz, E. A. Sausville, C. Kunick, L. Meijer, *Eur. J. Biochem.* **2000**, *267*, 5983; c) D. W. Zaharevitz, R. Gussio, M. Leost, A. M. Senderowicz, T. Lahusen, C. Kunick, L. Meijer, E. A. Sausville, *Cancer Res.* **1999**, *59*, 2566; d) T. Lahusen, A. De Siervi, C. Kunick, A. M. Senderowicz, *Mol. Carcinog.* **2003**, *36*, 183.

[2] a) C. Kunick, C. Schultz, T. Lemcke, D. W. Zaharevitz, R. Gussio, R. K. Jalluri, E. A. Sausville, M. Leost, L. Meijer, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 567; b) K. Wieking, M. Knockaert, M. Leost, D. W. Zaharevitz, L. Meijer, C. Kunick, *Arch. Pharm. Pharm. Med. Chem.* **2002**, *7*, 311; c) C. Kunick, K. Lauenroth, M. Leost, L. Meijer, T. Lemcke, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 413.

[3] C. Schultz, A. Link, M. Leost, D. W. Zaharevitz, R. Gussio, E. A. Sausville, L. Meijer, C. Kunick, *J. Med. Chem.* **1999**, *42*, 2909.

[4] L. Brault, E. Migianu, A. Néguesque, E. Battaglia, D. Bagrel, G. Kirsch, *Eur. J. Med. Chem.* **2005**, *40*, 757.

[5] O. Baudoin, M. Cesario, D. Guénard, F. Guéritte, *J. Org. Chem.* **2002**, *67*, 1199.

[6] J. B. Bremner, W. Sengpracha, *Tetrahedron* **2005**, *61*, 5489.

[7] N. Henry, J. Blu, V. Bénéteau, J.-Y. Mérour, *Synthesis* **2006**, 3895.

[8] L. Joucla, A. Putey, B. Joseph, *Tetrahedron Lett.* **2005**, *46*, 8177.

[9] E. M. Beccalli, G. Broggini, M. Martinelli, G. Paladino, E. Rossi, *Synthesis* **2006**, 2404.

[10] J. G. Avila-Zarraga, A. Lujan-Montelongo, A. Covarrubias-Zuniga, M. Romero-Ortega, *Tetrahedron Lett.* **2006**, *47*, 7987.

[11] M. Petrini, R. Ballini, E. Marcantoni, G. Rossini, *Synth. Commun.* **1988**, *18*, 847.

[12] A. L. Bowie Jr., C. C. Hughes, D. Trauner, *Org. Lett.* **2005**, *7*, 5207.

[13] A. Ho-Hoang, F. Fache, G. Boiteux, M. Lemaire, *Synth. Met.* **1994**, *62*, 277.

[14] B. B. Toure, B. S. Lane, D. Sames, *Org. Lett.* **2006**, *8*, 1979; B. S. Lane, D. Sames, *Org. Lett.* **2004**, *6*, 2897.


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