Synthesis of 3-(2-*N*,*N*-diethylaminoethoxy)indoles as potential 5-HT$_6$ receptor ligands

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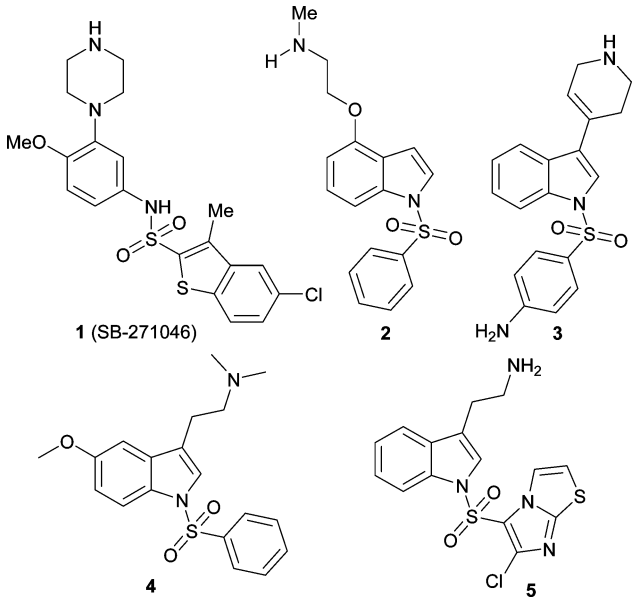
The synthesis of new pharmaceutically interesting 3-(2-*N,N*-diethylaminoethoxy)indole derivatives is described. Starting from 3-silyloxy-2-methylindoles, deprotection and *in situ* aminoalkylation provided 3-(2-*N,N*-diethylaminoethoxy)indoles in good yield. Further sulfonylation of these novel indoles gave access to potential 5-HT$_6$ receptor ligands.

Introduction

The 5-hydroxytryptamine$_6$ (5-HT$_6$) receptor is one of the latest subtypes of the mammalian serotonin receptor family to have been identified.[1] The high affinity of a wide range of antipsychotics for the receptor, coupled with its almost exclusive distribution in the brain, prompted much interest into the potential role of the 5-HT$_6$ as a target for central nervous system (CNS)-mediated diseases such as schizophrenia, Alzheimer's disease (cognitive function), anxiety, and obesity.[2] A variety of 5-HT$_6$ selective agents have been reported, however, there is still a need for more selective and active compounds.[3]

For example, in 1998 Bromidge and co-workers presented SB-271046 (**1**) as one of the first 5-HT$_6$ selective antagonists which entered into clinical trials (Phase I, not continued).[4] As shown in Scheme 1 SB-271046 is a 2-benzo-thiophene-sulfonamide derivative, which is substituted with a 4-methoxy-3-piperazinyl-phenyl group. Recently, this basic unit was replaced by a 4-(2-aminoethoxy)indole derivative **2** in 2005 by Zhou and co-workers.[5] Comparing the latest reported 5-HT$_6$ receptor ligands, it is evident that the majority of active compounds are indole derivatives, especially with a tryptamine scaffold.[6] Some typical examples are shown in Scheme 1.

Due to their importance as one of the most represented building blocks in natural bioactive products and known marketed drugs, there is a continuing interest in the development of catalytic methods for the synthesis of indoles.[7] For us especially, domino sequences whereby a reactive intermediate is generated from easily available substrates with the aid of a catalyst were of interest. Apart from domino hydroformylation–Fischer indole reactions,[8] alkyne-hydroamination–Fischer indole sequences were studied.[9] Most recently, we demonstrated that commercially available aryl-hydrazines and alkynes yielded a variety of potentially bio-active functionalized tryptamine and trypthophol derivatives, as well as 3-silyloxy-2-methylindoles in the presence of either Zn(OTf)$_2$ or ZnCl$_2$.[10]



Scheme 1 SB-271046 (**1**) and N-sulfonylindole derivatives **2–5** as 5-HT$_6$ receptor ligands.

Herein, we describe for the first time the synthesis of 3-(2-*N,N*-diethylaminoethoxy)-2-methylindoles. Deprotection and sulfonylation gave a novel class of biarylsulfonylindoles as 5-HT$_6$ receptor ligands.

Results and discussion

Based on the recently developed synthesis of 3-silyloxy-2-methylindoles **8**, we thought it should be possible to prepare 3-alkoxylated indoles. So far, this class of compounds has scarcely been investigated.[11] Of special interest to us was amino-functionalized alkoxy chains because of their resemblance to natural tryptamines.

Initially, seven electron-rich indole derivatives were synthesized in good yields *via* titanium-catalyzed hydroamination (Ti(NEt$_2$)$_4$–2,6-di-*tert*-butyl-4-methylphenol) of the silyl-protected propargylic alcohol (Scheme 2).[9a] Due to the exclusive Markovnikov hydroamination, only the 2,3-disubstituted indoles were obtained.[12] Next, the desired 3-(2-*N,N*-diethylaminoethoxy)indoles **9** were

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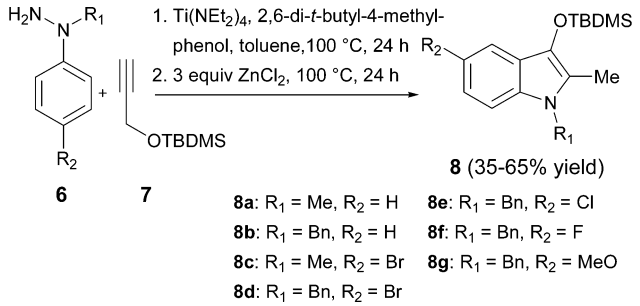
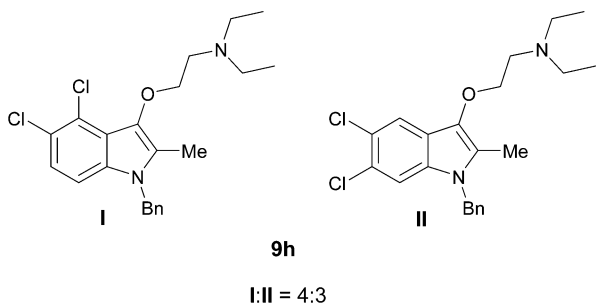


Scheme 2 Ti-catalyzed synthesis of electron-rich 3-silyloxy-2-methylindoles (**8**).

prepared by treating the appropriate 3-silyloxy-2-methylindole **8a–g** with 2-*N,N*-diethylaminoethyl chloride.

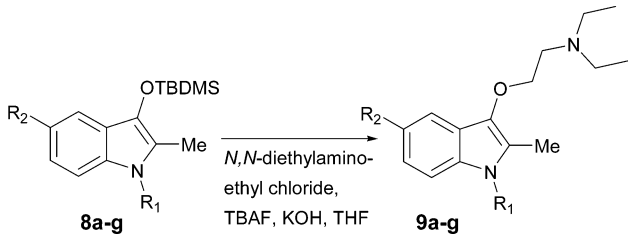
After some optimization, it turned out that a mixture of potassium hydroxide and tetra-*n*-butylammonium fluoride (TBAF) in tetrahydrofuran gave the best results for the *in situ* desilylation reaction. The resulting 3-hydroxyindoles were not stable and had to be directly alkylated. Under these conditions, the new indole derivatives **9a–g** were obtained in good to moderate yields (30–70%) (Table 1). In general, the *N*-methyl-protected indoles gave higher yields compared to the *N*-benzyl-protected indoles. However, in agreement with previous results on the synthesis of substituted tryptophols,[9c] the Fischer indole synthesis of 3,4-dichlorophenylhydrazine with **7** gave a mixture of two regioisomers of the corresponding 3-silyloxy-2-methylindole **8h**. This purified indole was used without particular analytical investigations for the synthesis of 3-(2-*N,N*-diethylaminoethoxy)indole (**9h**). Due to the presence of two isomers in the case of **8h**, we also observed the formation of compound **9h** as a mixture of two isomers (Scheme 3).

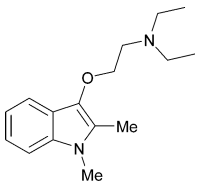
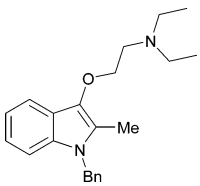
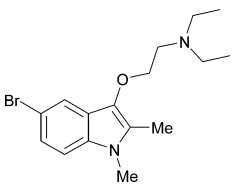
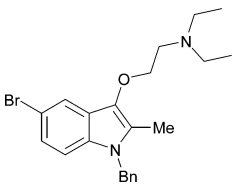
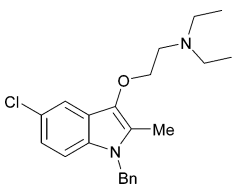
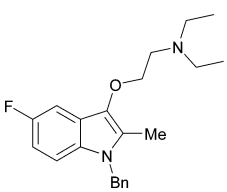
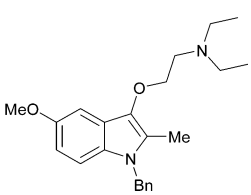


Scheme 3 Regioisomers **I** and **II** of the dichlorosubstituted derivative **9h**.

Then, we turned our attention to the deprotection of the benzyl group of the indole system. The different debenzylation methods were tested with compound **9b**, which was the most readily available product. Initially, reductive debenzylation in the presence of palladium on carbon was tried.[13] Despite variation of the solvent and hydrogen pressure or adding acetic acid, we did not obtain the free indole. The use of aluminium trichloride in benzene presents another well established method for *N*-debenzylation.[14] But neither applying aluminium trichloride nor using the known system of potassium *tert*-butoxide in dimethylsulfoxide and oxygen,[15] were effective in the *N*-debenzylation of **9b**. Apparently, the steric hindrance of an additional substituent in the 2-position makes the debenzylation of these electron-rich indoles difficult. Finally, the use of sodium in excess in liquid ammonia

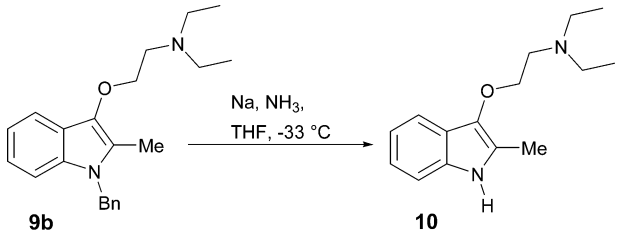
Table 1 Synthesis of 3-(2-*N,N*-diethylaminoethoxy)indoles [a]



Entry	Indole		Yield (%) [b]
1		**9a**	70
2		**9b**	60
3		**9c**	65
4		**9d**	30
5		**9e**	65
6		**9f**	50
7		**9g**	46

[a] Reaction conditions: 3-silyloxy-2-methylindole (1.0 equiv), 2-*N,N*-diethylaminoethyl chloride (1.1 equiv), KOH (1.1 equiv), TBAF (2.0 equiv), THF, 50 °C. [b] Isolated yield.

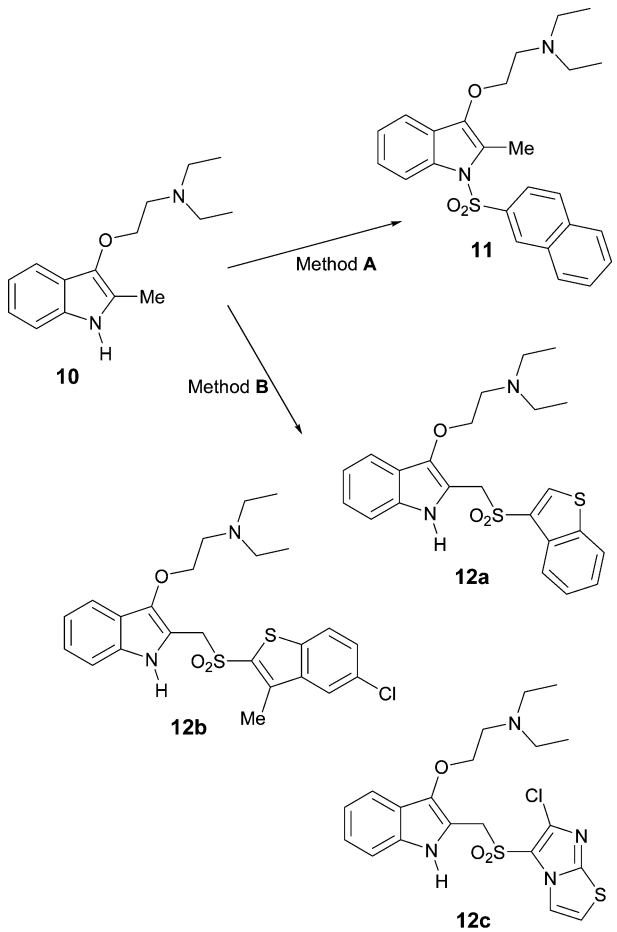
at −33 °C afforded the *N*-deprotected indole in high yield (95%) (Scheme 4).[16] Although this method worked well on most of the indoles, unfortunately, it was not usable for debenzylation of the 5-chlorinated 3-(2-*N,N*-diethylaminoethoxy)indole **9e**.



Scheme 4 Deprotection of the *N*-benzyl-3-(2-*N,N*-diethylaminoethoxy)-indole (**9b**).

Connected with this, not only debenzylation occurred, but also reductive dehalogenation at the 5-position of the indole. After successful debenzylation, different sulfonylation protocols were investigated applying 3-(2-*N,N*-diethylaminoethoxy)indole **10** as a substrate. Here, phase transfer sulfonylations with 2-naphthalenesulfonyl chloride (50% solution of sodium hydroxide, benzene, tetra-*n*-butylammonium hydrogen sulfate)[17] as well as typical nucleophilic substitution conditions (potassium hydroxide in ethanol) did not result in any desired product.[18] However, reaction of **10** with sodium hydride[19] and subsequent treatment with 2-naphthalenesulfonyl chloride gave *N*-naphthalenesulfonylindole **11** in 24% yield (Scheme 5). To our delight this product showed significant activity in initial binding studies towards the $5HT_6$-receptor.

Using the latter sulfonylation protocol, we tried to synthesize additional biarylsulfonylindoles of heteroaromatic sulfonic acids such as benzo[*b*]thiophen-3-ylsulfonyl chloride, 5-chloro-3-methylbenzo[*b*]thiophen-2-ylsulfonyl chloride and 6-chloroimidazo[2,1-*b*]thiazol-5-ylsulfonyl chloride. Unfortunately, the use of the less reactive arylsulfonic chlorides was not successful in the sulfonylation reaction of the free indole. Interestingly, by applying *n*-butyllithium[20] as a base in these reactions, we observed deprotonation at the methyl group in the 2-position of the indole, which is then subsequently sulfonylated. Based on this observation, we also synthesized the 2-(benzo[*b*]thiophen-3-ylsulfonyl)methyl-3-(2-*N*,*N*-diethylaminoethoxy)indole **12a** in 23% yield. In addition, we prepared the 2-(5-chloro-3-methylbenzo[*b*]thiophen-2-ylsulfonyl)methyl-3-(2-*N*,*N*-diethylaminoethoxy)indole **12b** and the 2-(6-chloroimidazo[2,1-*b*]thiazol-5-ylsulfonyl)methyl-3-(2-*N*,*N*-diethylaminoethoxy)indole **12c** both in similar yield (20%) (Scheme 5). The reaction of **10** with 2-naphthalenesulfonyl chloride in the presence of *n*-butyllithium gave the *N*-sulfonylated product **11** in 14% yield. The appropriate 2-methyl sulfonylated product was found only in traces. Because of the instability of the biarylsulfonylindoles **11** and **12**, the corresponding oxalates were prepared.



Scheme 5 Sulfonylation of the free 3-(2-*N,N*-diethylaminoethoxy)indole **10** with biarylsulfonyl chlorides in the presence of sodium hydride (method **A**) or *n*-butyllithium (method **B**).

Conclusions

To summarize, a variety of 3-(2-*N,N*-diethylaminoethoxy)indole derivatives were synthesized. By subsequent deprotection of the indole and sulfonylation with biarylsulfonyl chlorides, two novel classes of potential $5\text{-}HT_6$ receptor ligands could be prepared. Besides the desired 2-naphthalenesulfonylindole **11**, an unexpected sulfonylation of the 2-methyl group of the indole system created further interesting biarylsulfonylindoles **12a–c**.

Experimental

All reactions were carried out under an argon atmosphere. Chemicals were purchased from Aldrich, Fluka and Acros and unless otherwise noted were used without further purification. The compounds were characterized by ^{1}H NMR, ^{13}C NMR, MS and HRMS. ^{1}H NMR spectra (300.13 MHz and 500.13 MHz) and ^{13}C NMR spectra (75.5 MHz and 125.8 MHz) were recorded on Bruker spectrometers Avance 300 and Avance 500 in $CDCl_3$ and DMSO-d_6. The calibration of spectra was carried out on solvent signals ($CDCl_3$: δ (^{1}H) = 7.25, δ (^{13}C) = 77.0; DMSO-d_6: δ (^{1}H) = 2.50, δ (^{13}C) = 39.7). EI mass spectra were recorded on an MAT 95XP spectrometer (Thermo ELECTRON CORPORATION). GC was performed on a Hewlett Packard HP 6890 chromatograph with a 30 m HP5 column.

The preparation of compounds **8a–g** is described in the literature.[9a] The derivative **8h** was prepared by this method as well, but after purification by column chromatography, the product

mixture was used for the synthesis of compound **9h** without particular analytical investigations.

General procedure for the reaction of the 3-silyloxy-2-methylindoles with 2-*N,N*-diethylaminoethyl chloride to give the 3-(2-*N,N*-diethylaminoethoxy)indoles (9a–h)

To powdered potassium hydroxide (1.50 mmol) in a round bottom flask under an argon atmosphere, 15 mL dry THF and TBAF (2.75 mL of 1 M solution in THF, 2.75 mmol) were added. After the addition of the appropriate 3-silyloxy-2-methylindole (1.37 mmol) and *N,N*-diethylaminoethyl chloride (1.50 mmol), the mixture was stirred at 50 °C overnight. When the mixture had cooled to room temperature, H_2O (15 mL) was added. Then the separated aqueous layer was extracted with $CHCl_3$ (3 × 20 mL). The organic layers were dried (Na_2SO_4) and the solvents were evaporated *in vacuo.* The residue was chromatographed on a silica gel column (eluent: $CHCl_3$–10% MeOH) to give the 3-(2-*N,N*-diethylaminoethoxy)indole derivatives as brown oils.

1,2-Dimethyl-3-(2-*N,N*-diethylaminoethoxy)indole (9a). Yield: 70%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.57$ (d, 1H, $J = 8.0$ Hz), 7.22 (d, 1H, $J = 8.2$ Hz), 7.13 (ddd, 1H, $J = 1.2$ Hz, $J = 6.9$ Hz, $J = 8.2$ Hz), 7.05 (ddd, 1H, $J = 1.2$ Hz, $J = 6.9$ Hz, $J = 8.0$ Hz), 4.16 (t, 2H, $J = 6.3$ Hz), 3.57 (s, 3H), 2.94 (t, 2H, $J = 6.3$ Hz), 2.72 (q, 4H, $J = 7.2$ Hz), 2.35 (s, 3H), 1.11 (t, 6H, $J = 7.2$ Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 134.5$, 133.6, 124.7, 120.6, 120.5, 118.4, 116.7, 108.5, 72.1, 52.4, 47.3, 29.1, 11.2, 8.7 ppm. MS (EI, 70 eV): *m/z* (relative intensity): 260 (10) [M$^+$], 160 (24), 145 (4), 117 (7), 100 (100), 86 (56), 77 (5), 72 (27), 57 (9), 45 (36). HRMS (CI, M + H$^+$): calcd. for $C_{16}H_{24}N_2O$: 261.1967; found: 261.1952.

1-Benzyl-2-methyl-3-(2-*N,N*-diethylaminoethoxy)indole (9b). Yield: 60%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.62$–7.59 (m, 1H), 7.25–7.15 (m, 4H), 7.09–7.02 (m, 2H), 6.93–6.90 (m, 2H), 5.23 (s, 2H), 4.17 (t, 2H, $J = 6.4$ Hz), 2.90 (t, 2H, $J = 6.4$ Hz), 2.65 (q, 4H, $J = 7.2$ Hz), 2.28 (s, 3H), 1.06 (t, 6H, $J = 7.2$ Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 137.9$, 135.1, 133.7, 128.6, 127.1, 125.8, 124.6, 121.1, 120.9, 118.8, 117.0, 109.0, 72.6, 52.6, 47.5, 46.3, 11.7, 8.8 ppm. MS (EI, 70 eV): *m/z* (relative intensity): 336 (6) [M$^+$], 279 (2), 237 (7), 221 (4), 208 (2), 195 (58), 180 (6), 165 (9), 117 (5), 100 (100), 91 (36), 86 (12), 71 (5), 57 (7), 43 (16). HRMS (EI): calcd. for $C_{22}H_{28}N_2O$: 336.2196; found: 336.2193.

5-Bromo-1,2-dimethyl-3-(2-*N,N*-diethylaminoethoxy)indole (9c). Yield: 65%. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.67$ (d, 1H, $J = 1.9$ Hz), 7.17 (dd, 1H, $J = 8.5$ Hz, $J = 1.9$ Hz), 7.07 (d, 1H, $J = 8.5$ Hz), 4.09 (t, 2H, $J = 6.3$ Hz), 3.57 (s, 3H), 2.89 (t, 2H, $J = 6.3$ Hz), 2.68 (q, 4H, $J = 7.3$ Hz), 2.33 (s, 3H), 1.09 (t, 6H, $J = 7.3$ Hz) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 134.2$, 132.5, 126.3, 123.4, 122.5, 119.5, 112.0, 110.1, 73.0, 52.8, 47.5, 29.5, 11.7, 8.9 ppm. MS (EI, 70 eV): *m/z* (relative intensity): 339 (3), 338 (2) [M$^+$], 266 (4), 239 (10), 159 (2), 130 (4), 100 (100) 86 (36), 72 (13), 56 (5), 44 (11). HRMS (EI): calcd. for $C_{16}H_{23}BrN_2O$: 338.0988; found: 338.0976.

1-Benzyl-5-bromo-2-methyl-3-(2-*N,N*-diethylaminoethoxy)indole (9d). Yield: 30%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.72$ (br s, 1H), 7.25–7.16 (m, 3H), 7.13 (d, 1H, $J = 8.4$ Hz), 7.02 (d, 1H, $J = 8.4$ Hz), 6.88 (d, 2H, $J = 7.4$ Hz), 5.22 (s, 2H), 4.12 (t, 2H, $J = 6.2$ Hz), 2.88 (t, 2H, $J = 6.2$ Hz), 2.67 (q, 4H, $J = 7.3$ Hz), 2.28 (s, 3H), 1.08 (t, 6H, $J = 7.3$ Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 137.5$, 134.6, 132.4, 128.8, 127.4, 126.3, 125.8, 123.8, 122.8, 119.6, 112.3, 110.7, 72.9, 52.7, 47.5, 46.6, 11.7, 9.0 ppm. MS (EI, 70 eV): *m/z* (relative intensity): 415 (6), 414 (2) [M$^+$], 149 (5), 101 (11), 100 (100), 91 (68), 86 (33), 44 (12). HRMS (EI): calcd. for $C_{22}H_{27}BrN_2O$: 414.1301; found: 414.1298.

1-Benzyl-5-chloro-2-methyl-3-(2-*N,N*-diethylaminoethoxy)indole (9e). Yield: 65%. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.57$ (d, 1H, $J = 2.0$ Hz), 7.26–7.21 (m, 3H), 7.07 (d, 1H, $J = 8.5$ Hz), 7.01 (dd, 1H, $J = 2.0$ Hz, $J = 8.5$ Hz), 6.89 (m, 2H), 5.21 (s, 2H), 4.13 (t, 2H, $J = 6.3$ Hz), 2.88 (t, 2H, $J = 6.3$ Hz), 2.67 (q, 4H, $J = 7.3$ Hz), 2.28 (s, 3H), 1.07 (t, 6H, $J = 7.3$ Hz) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 137.5$, 134.8, 132.2, 128.6, 127.3, 126.4, 125.8, 124.1, 122.2, 121.2, 116.6, 110.2, 73.0, 52.7, 47.5, 46.5, 11.7, 9.0 ppm. MS (EI, 70 eV): *m/z* (relative intensity): 370 (2) [M$^+$], 271 (7), 237 (2), 207 (3), 179 (3), 151 (7), 110 (3), 100 (100), 91 (78), 86 (40), 72 (15), 56 (9), 44 (16). HRMS (EI): calcd. for $C_{22}H_{27}ClN_2O$: 370.1805; found: 370.1807.

1-Benzyl-5-fluoro-2-methyl-3-(2-*N,N*-diethylaminoethoxy)indole (9f). Yield: 50%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.30$–7.21 (m, 4H), 7.09 (dd, 1H, $J = 9.0$ Hz, $J = 4.0$ Hz), 6.92 (m, 2H), 6.83 (dt, 1H, $J = 9.0$ Hz, $J = 2.5$ Hz), 5.24 (s, 2H), 4.27 (t, 2H, $J = 6.0$ Hz), 3.10 (t, 2H, $J = 6.0$ Hz), 2.91 (q, 4H, $J = 7.2$ Hz), 2.31 (s, 3H), 1.22 (t, 6H, $J = 7.2$ Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 157.5$ (d, $J = 234$ Hz), 137.5, 134.8 (d, $J = 4.5$ Hz), 130.2, 128.7, 127.3, 126.9, 125.7, 120.9 (d, $J = 9.7$ Hz), 109.9 (d, $J = 9.7$ Hz), 109.2 (d, $J = 26.0$ Hz), 101.8 (d, $J = 24.5$ Hz), 71.4, 51.2, 47.5, 46.6, 10.7, 9.2 ppm. MS (EI, 70 eV): *m/z* (relative intensity): 354 (2) [M$^+$], 255 (3), 135 (6), 101 (9), 100 (100), 91 (50), 86 (23), 43 (17). HRMS (EI): calcd. for $C_{22}H_{27}FN_2O$: 354.2102, found: 354.2109.

1-Benzyl-5-methoxy-2-methyl-3-(2-*N,N*-diethylaminoethoxy)-indole (9g). Yield: 46%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.27$–7.19 (m, 3H), 7.06 (d, 1H, $J = 8.8$ Hz), 7.02 (d, 1H, $J = 2.5$ Hz), 6.92 (m, 2H), 6.73 (dd, 1H, $J = 8.8$ Hz, $J = 2.5$ Hz), 5.20 (s, 2H), 4.31 (t, 2H, $J = 6.0$ Hz), 3.85 (s, 3H), 3.13 (t, 2H, $J = 6.0$ Hz), 3.00–2.90 (m, 4H), 2.27 (s, 3H), 1.24 (t, 6H, $J = 7.2$ Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 153.7$, 137.8, 134.6, 129.0, 128.6, 127.2, 125.8, 125.5, 120.9, 110.9, 110.0, 98.9, 70.9, 55.9, 52.1, 47.5, 46.4, 10.5, 9.0 ppm. MS (EI, 70 eV): *m/z* (relative intensity): 366 (20) [M$^+$], 267 (26), 266 (14), 265 (20), 251 (11), 176 (9), 147 (16), 106 (19), 101 (45), 100 (100), 92 (14), 91 (92), 86 (67), 72 (29), 57 (12), 56 (15), 44 (32). HRMS (EI): calcd. for $C_{23}H_{30}N_2O_2$: 366.2302; found: 366.2308.

1-Benzyl-4,5-dichloro-2-methyl-3-(2-*N,N*-diethylaminoethoxy)-indole (I)/1-benzyl-5,6-dichloro-2-methyl-3-(2-*N,N*-diethylamino-ethoxy)indole (II) (9h). Yield: 30%. **(I)** ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.28$–7.20 (m, 3H), 7.08 (d, 1H, $J = 8.8$ Hz), 6.96 (d, 1H, $J = 8.8$ Hz), 6.88–6.85 (m, 2H), 5.20 (s, 2H), 4.09 (t, 2H, $J = 6.3$ Hz), 2.85 (t, 2H, $J = 6.3$ Hz), 2.64 (q, 4H, $J = 7.2$ Hz), 2.29 (s, 3H), 1.05 (t, 6H, $J = 7.2$ Hz) ppm.^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 136.9$, 134.8, 133.1, 128.9, 128.4, 127.6, 125.7, 123.7, 122.4, 121.5, 120.1, 108.6, 73.1, 52.3, 47.6, 46.7, 11.7, 9.0 ppm. **(II)** ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.28$–7.20 (m, 3H), 7.66 (s, 1H), 7.22 (s, 1H), 6.88–6.85 (m, 2H), 5.16 (s, 2H), 4.06 (t, 2H, $J = 6.6$ Hz), 2.95 (t, 2H, $J = 6.6$ Hz), 2.67 (q, 4H, $J = 7.2$ Hz), 2.25 (s, 3H), 1.07 (t, 6H, $J = 7.2$ Hz) ppm. ^{13}C NMR (126 MHz,

$CDCl_3$) δ = 137.0, 134.7, 132.6, 128.9, 127.6, 127.0, 125.7, 124.9, 123.0, 121.0, 118.1, 110.7, 74.9, 52.8, 47.6, 46.7, 11.6, 8.9 ppm. MS (CI, M + H^+): *m/z* (relative intensity): 405. HRMS (CI, M − H^+) calcd. for $C_{22}H_{26}Cl_2N_2O$: 403.1338; found: 403.1334.

2-Methyl-3-(2-*N,N*-diethylaminoethoxy)indole (10). To a deep blue solution of Na (684 mg, 29.7 mmol) in NH_3 (*ca.* 20 mL) at −78 °C, a solution of compound **9b** (1.0 g, 2.97 mmol) in dry THF (10 mL) was added dropwise. The mixture was stirred at −33 °C for 2 h, quenched with NH_4Cl at −78 °C, allowed to warm to room temperature, and concentrated. The residue was diluted with H_2O and extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvents were removed *in vacuo* to give a yellow oil in 95% yield (700 mg, 2.84 mmol). The crude material was used for the next reaction.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (br s, 1H, NH), 7.54 (m, 1H), 7.09 (m, 1H), 7.11–7.01 (m, 2H), 4.14 (t, 2H, J = 6.6 Hz), 2.89 (t, 2H, J = 6.6 Hz), 2.66 (q, 4H, J = 7.2 Hz), 2.33 (s, 3H), 1.07 (t, 6H, J = 7.2 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.1, 132.7, 122.5, 121.9, 120.9, 118.9, 116.9, 110.6, 72.3, 52.6, 47.5, 11.6, 10.2 ppm. MS (EI, 70 eV): *m/z* (relative intensity): 246 (1) [M^+], 160 (1), 146 (11), 117 (5), 100 (100), 86 (40), 72 (11), 56 (7), 44 (18). HRMS (EI): calcd. for $C_{15}H_{22}N_2O$: 246.1987; found: 246.2006.

1-(*N*-Naphthalene-2-ylsulfonyl)-2-methyl-3-(2-*N,N*-diethylaminoethoxy)indole (11). The above mentioned crude **10** (700 mg, 2.84 mmol) in dry THF (8 mL) was added dropwise to NaH (682 mg, 28.4 mmol, 65% content in a mineral oil suspension that was washed with dry *n*-hexane three times before use) suspended in dry THF (10 mL) at room temperature under argon, and then the mixture was stirred for 10 min. A dry THF (3 mL) solution of 2-naphthalenesulfonylchloride (1.9 g, 8.5 mmol) was added to the mixture, and the resulting solution was stirred at 50 °C for 2 h. The reaction was quenched by adding aq. Na_2CO_3 (20 mL) and the mixture was extracted with $CHCl_3$ (3 × 20 mL). After drying with Na_2SO_4, removal of the solvent and chromatography of the crude material with $CHCl_3$–10% MeOH gave compound **11** as brown oil in 24% yield (300 mg, 0.69 mmol).

^{1}H NMR (300 MHz, DMSO), **11** (**oxalate**): δ = 9.53 (br, 2H), 8.70 (d, 1H, J = 2.2 Hz), 8.22 (d, 1H, J = 8.2 Hz), 8.18 (d, 1H, J = 8.5 Hz), 8.04 (d, 1H, J = 8.8 Hz), 7.99 (d, 1H, J = 8.2 Hz), 7.75–7.66 (m, 2H), 7.65 (dd, 1H, J = 8.8 Hz, J = 2.0 Hz), 7.59 (d, 1H, J = 7.9 Hz), 7.35 (m, 1H), 7.26 (t, 1H, J = 7.6 Hz), 4.28 (t, 2H, J = 5.4 Hz), 3.38 (t, 2H, J = 5.4 Hz), 3.13 (q, 4H, J = 7.3 Hz), 2.60 (s, 3H), 1.17 (t, 6H, J = 7.3 Hz) ppm. ^{13}C NMR (75 MHz, DMSO), **11** (**oxalate**): δ = 164.4, 140.3, 134.9, 134.4, 133.8, 131.6, 130.2, 129.9, 129.8, 128.3, 128.2, 128.0, 124.9 (2), 124.1, 124.0, 120.9, 117.9, 114.7, 68.5, 50.9, 47.0, 11.4, 8.9 ppm. MS (EI, 70 eV): *m/z* (relative intensity): 436 (1) [M^+], 160 (1), 146 (11), 117 (5), 100 (100), 86 (40), 72 (11), 56 (7), 44 (18), 29 (6). HRMS (EI): calcd. for $C_{25}H_{28}N_2O_3S$: 436.1815; found: 436.1808.

General procedure for the formation of the oxalate

The product oil was diluted in a small amount of dry ethanol. After addition of oxalic acid in excess (1.1 equiv), the solution was stored in a fridge. The formed precipitate was isolated. The yield after the formation of the oxalate from the product oil for compound **11** constituted 55%.

General procedure for the sulfonylation with *n*-butyl lithium

n-Butyl lithium (1.6 M in hexane, 1.33 mL, 2.1 mmol) was added to a solution of the free indole **10** (2.03 mmol) in anhydrous THF (5 mL) at −78 °C during 20 min. After complete addition, the mixture was stirred at −78 °C for 10 min, and was thereafter allowed to reach room temperature over 1 h. After cooling to −78 °C, a solution of sulfonyl chloride (2.3 mmol) in anhydrous THF (3 mL) was added over 20 min at −78 °C. The resulting mixture was allowed to slowly reach room temperature over 3 days, was thereafter poured into water (20 mL) containing brine (5 mL), and extracted with $CHCl_3$ (3 × 30 mL). The combined organic extracts were washed with water (50 mL) and dried over $MgSO_4$. After removal of the solvents *in vacuo*, the desired product was isolated by column chromatography in $CHCl_3$–MeOH as brown oil. This isolated oil was used for the preparation of the oxalate.

2-(Benzo[*b*]thiophen-3-ylsulfonyl)methyl-3-(2-*N,N*-diethylaminoethoxy)indole (12a) (oxalate). Yield: 23% free indole, 70% oxalate (from product oil). ^{1}H NMR (300 MHz, DMSO): δ = 11.02 (s, 1H), 9.82 (br, 2H), 8.55 (s, 1H), 8.17 (ddd, 1H, J = 8.0 Hz, J = 1.3 Hz, J = 0.8 Hz), 8.05 (ddd, 1H, J = 8.0 Hz, J = 1.3 Hz, J = 0.8 Hz), 7.55–7.42 (m, 3H), 7.35 (dt, 1H, J = 8.0 Hz, J = 1.0 Hz), 7.11 (ddd, 1H, J = 8.0 Hz, J = 7.0 Hz, J = 1.0 Hz), 6.98 (ddd, 1H, J = 8.0 Hz, J = 7.0 Hz, J = 1.0 Hz), 4.88 (s, 2H), 4.04 (t, 2H, J = 5.3 Hz), 3.11–3.04 (m, 6H), 1.16 (t, 6H, J = 7.2 Hz) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 164.7, 140.2, 139.4, 137.4, 134.1, 134.0, 132.5, 125.8, 123.7, 122.8, 122.5, 119.3, 119.0, 117.8, 113.0, 112.2, 68.3, 52.8, 50.7, 47.0, 8.9 ppm. MS (EI, 70 eV): *m/z* (relative intensity): 442 (28) [M^+ − oxalic acid], 245 (30), 181 (30), 145 (69), 134 (83), 100 (78), 86 (100), 72 (58), 64 (17), 56 (44), 44 (90). HRMS (EI): calcd. for $C_{23}H_{26}N_2O_3S_2$: 442.1379; found: 442.1384.

2-(5-Chloro-3-methylbenzo[*b*]thiophen-2-ylsulfonyl)-methyl-3-(2-*N,N*-diethylaminoethoxy)indole (12b) (oxalate)

Yield: 20% free indole, 46% oxalate (from product oil). ^{1}H NMR (300 MHz, DMSO): δ = 11.00 (s, 1H), 8.14 (d, 1H, J = 8.7 Hz), 8.09 (d, 1H, J = 2.1 Hz), 7.64 (dd, 1H, J = 8.7 Hz, J = 2.1 Hz), 7.58 (d, 1H, J = 8.0 Hz), 7.35 (d, 1H, J = 8.0 Hz), 7.13 (ddd, 1H, J = 8.0 Hz, J = 7.0 Hz, J = 1.2 Hz), 7.00 (ddd, 1H, J = 8.0 Hz, J = 7.0 Hz, J = 1.1 Hz), 4.94 (s, 2H), 4.18 (t, 2H, J = 5.1 Hz), 3.27 (t, 2H, J = 5.1 Hz), 3.08 (q, 4H, J = 7.2 Hz), 2.38 (s, 3H), 1.15 (t, 6H, J = 7.2 Hz) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 164.4, 140.8, 140.0, 138.5, 137.7, 135.6, 134.0, 130.8, 128.3, 125.2, 124.1, 122.7, 119.3, 119.1, 117.9, 112.8, 68.6, 53.9, 51.0, 47.1, 11.9, 9.0 ppm. MS (EI, 70 eV): *m/z* (relative intensity): 490 (1) [M^+ − oxalic acid], 422 (2), 244 (6), 214 (4), 181 (100), 147 (29), 100 (63), 86 (20), 72 (10), 64 (16), 56 (16), 44 (9). HRMS (EI): calcd. for $C_{24}H_{27}ClN_2O_3S_2$: 490.1146; found: 490.1140.

2-(6-Chloroimidazo[2,1-*b*]thiazol-5-ylsulfonyl)methyl-3-(2-*N,N*-diethylaminoethoxy)indole (12c) (oxalate). Yield: 20% free indole, 64% oxalate (from product oil). ^{1}H NMR (300 MHz, DMSO): δ = 10.90 (s, 1H), 7.55 (d, 1H, J = 8.0 Hz), 7.47 (d, 1H, J = 4.5 Hz), 7.39 (d, 1H, J = 4.5 Hz), 7.30 (d, 1H, J = 8.0 Hz),

7.11 (ddd, 1H, $J = 8.0$ Hz, $J = 7.0$ Hz, $J = 1.0$ Hz), 6.99 (ddd, 1H, $J = 8.0$ Hz, $J = 7.0$ Hz, $J = 1.0$ Hz), 4.92 (s, 2H), 4.24 (t, 2H, $J = 5.3$ Hz), 3.34 (t, 2H, $J = 5.3$ Hz), 3.17 (q, 4H, $J = 7.2$ Hz), 1.22 (t, 6H, $J = 7.2$ Hz) ppm. ^{13}C NMR (75 MHz, DMSO): $\delta =$ 164.4, 151.1, 138.9, 137.8, 134.0, 122.7, 119.9, 119.3, 119.1, 117.8, 116.9, 116.9, 112.4, 112.2, 68.6, 53.5, 51.1, 47.2, 9.1 ppm. MS (CI, M + H$^+$, 70 eV): m/z (relative intensity): 467 (7) [M$^+$ − oxalic acid], 445 (8), 403 (67), 245 (39), 159 (40), 100 (100), 86 (15), 72 (10). HRMS (CI, M + H$^+$): calcd. for $C_{20}H_{23}ClN_4O_3S_2$: 467.0973; found: 467.0963.

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