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Article

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Indole based weapons to fight antibiotic resistance: a structure-activity relationship study

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TITLE RUNNING HEAD: Fight MRSA antibiotic resistance

ABSTRACT

Antibiotic resistance represents a worldwide concern, especially regarding the outbreak of methicillin-resistant *Staphylococcus aureus*, a common cause for serious skin and soft tissues infections. A major contributor to *Staphylococcus aureus* antibiotic resistance is the NorA efflux pump, which is able to extrude selected antibacterial drugs and biocides from the membrane, lowering their effective concentrations. Thus, the inhibition of NorA represents a promising and challenging strategy that would allow recycling of substrate antimicrobial agents. Among NorA inhibitors, the indole scaffold proved particularly effective and suitable for further optimization. In this study, some unexplored modifications on the indole scaffold are proposed. In particular, for the first time, substitutions at the C5 and N1 positions have been designed to give 48 compounds, which were synthesized and tested against *norA*-overexpressing *S. aureus*. Among them, 4 compounds have NorA IC_{50} values lower than

5.0 μM proving to be good efflux pump inhibitors (EPI) candidates. In addition, preliminary data on their ADME (absorption, distribution, metabolism, and excretion) profile is reported.

INTRODUCTION

Antibiotic resistance represents a worldwide threat. According to a new report issued by the Centers for Disease Control and Prevention[1] each year more than two million people in the United States get infections that are resistant to antibiotics and at least 23,000 people die as a result. In particular, methicillin resistant *S. aureus* (MRSA) is a major community-acquired as well as nosocomial pathogen causing skin and soft tissues infections, respiratory disease and more serious illness like pneumonia, endocarditis and sepsis.[2]

The most important factor in antibiotic multi-drug resistance (MDR) is the irresponsible use of antibiotics. Since Fleming's revolutionary discovery of penicillin G in 1928, a great effort has been lavished on the development of novel antibiotic classes (e.g. sulfonamides, quinolones, oxazolidinones)[3] but with time their utility became compromised by the emergence of resistant bacteria. This led the medical community to ask for urgent development of novel drugs to fight resistant strains.

Bacterial resistance can rise through three main mechanisms: drug target modification, drug inactivation or export by membrane-based efflux proteins. While the fight against drug target modification or drug inactivation entails developing new classes of antibiotics with novel mechanisms of action, the inhibition of efflux pump systems represents a valid option for both its innovative character and the intrinsic advantage of recycling antimicrobial agents that are efflux pump substrates. Efflux pumps are transport proteins involved in the extrusion of toxic substrates (including antibiotics) from within cells into the external environment.[4] The genes expressing many pump proteins are present in both antibiotic susceptible and resistant bacteria.[5] Whether resistance is related to increased pump

gene expression or an amino acid substitution, which improves the efficiency of the pump protein, the end result is a reduced concentration of the antimicrobial drug at its active site. In particular, the *S. aureus* NorA efflux pump, which belongs to the major facilitator superfamily (MFS) of transport proteins, can contribute to quinolone-based drug resistance[6] by removal of these drugs thus lowering their effective concentrations.[7,8]

Increased interest has been devoted towards molecules able to inhibit the NorA efflux pump, whose action is considered an important factor for selected drug and biocide resistance. The major obstacle in designing specific inhibitors of the NorA pump is that the three dimensional structure of the protein is not yet known. Some molecules are well-known inhibitors of NorA, such as reserpine, which is frequently used as reference compound in inhibition studies. Unfortunately, although reserpine is an approved drug for other targets, it cannot be used for NorA inhibition because of its neurotoxic effect at the required concentrations.[9] In the past, a number of NorA inhibitors belonging to different chemical classes have been developed including flavones and flavonolignans,[10] hydroxyquinoline derivates,[11] piperines,[12] pyridines and phenylpiperidine,[13,14] chalcones and alkenamides.[15-17] Their activities are mainly evaluated in terms of ethidium bromide (EtBr) efflux inhibition, or for their capacity of restoring the antibacterial activity of an antibiotic such as ciprofloxacin (CPX).

The indole moiety has been shown to be promising with respect to the EPI activity of a compound. The compound 5-nitro-2-phenyl-(*1H*)-indole (**1**), known as INF55,[9] is one of the first identified indole-based inhibitors of NorA and is capable of producing a 4-fold increase in the susceptibility of *S. aureus* to ciprofloxacin at a concentration of 1.5 μg/mL (Figure 1). Since the discovery of **1**, a number of indole-based analogues were synthesized and tested for EPI activity and the most potent of these are illustrated in Figure 1 (**2**-**6**).[18-20] Structural modifications were introduced at the C2, C3 and C5 positions; in particular, in the first discovered compounds, an electron withdrawing group was always preserved (a nitro group in **1, 3-4** or a cyano group in **2**).[18,19] In addition, an aromatic moiety with

various substituents was preserved in all active compounds (**1-5**). More recently, indoles bearing halogen atoms in the C5 position and a peculiar nitrone moiety in the C3 position have been evaluated for their good EPI properties (compounds **6a-c**, Figure 1).[20] However, to the best of our knowledge the NH group in the indole scaffold has yet to be derivatized.

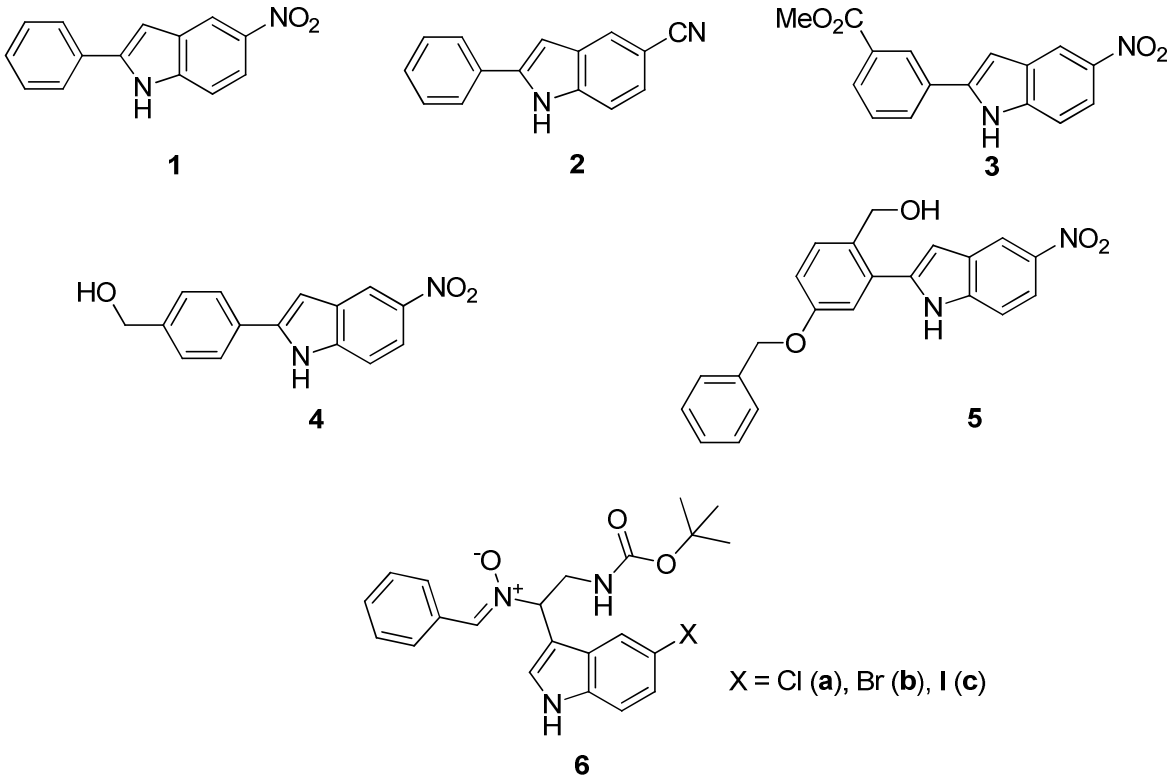


Figure 1. Structures of indole-based compounds discovered to date that target NorA.

In this study, we report on a novel series of compounds bearing an indole scaffold in which modifications were performed at the N1, C3, and C5 positions of the indole nucleus. *Staphylococcus aureus* strains SA-1199 (wild type) and SA-1199B (overexpressing *norA*) were used to evaluate the inhibition effect.[21] As a result, twenty novel EPIs with various scaffolds inhibited EtBr efflux by more than 90%. Among them, four compounds exhibited an IC_{50} lower than 5.0 μM. Our results show that

tuning of the molecular features can result in pure NorA inhibitors that lack any significant antimicrobial effect.

METHODOLOGY

Inhibitor Design

Inhibitor design for the NorA efflux pump is a challenging issue due to the lack of a crystal structure of the target. However, a "ligand-based" approach can be performed utilizing known inhibitors as templates. *N*-substituted indoles were designed by inspecting compounds in Figure 1. Our strategy was to remove the phenyl group at the C2 position and to synthesize an *N*-substituted indole that could possibly mimic the C2-phenyl hydrophobic interaction. Toward this end, the *N*-benzyl moiety was designed; indeed, the *N*-benzyl indole and the 2-phenyl indole were superimposed using the FLAP software[22] to compare them in size, shape and hydrophobic interactions. The latter ones were evaluated by comparing the GRID molecular interaction fields[23] generated by the DRY probe (see Materials and Methods). Based on this simulation the two compounds share similar hydrophobic interactions as well as size and shape, as shown in Figure 2.

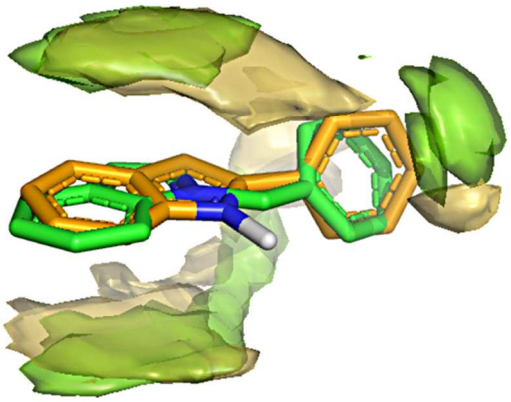


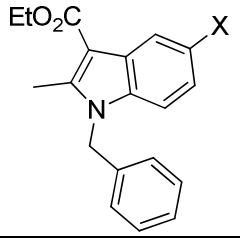
Figure 2. Overlay of 2-phenylindole (in yellow sticks) and *N*-benzylindole (green sticks), obtained using the FLAP software.[22] GRID[23] hydrophobic molecular interaction fields are shown in yellow and green color, respectively.

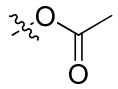
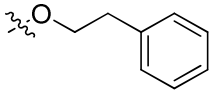
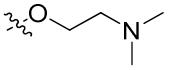
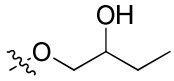
From Figure 1 we also noticed that the presence of an electron-withdrawing group (EWG) such as NO_2, CN, and halogen atoms in the C5 position was highly conserved. As such, we elected to maintain the nitro moiety at this position. In addition, the most recent series of indole derivatives (**6**) reported by Hequet et al.[20] suggested that the presence of a polar substituent in the C3 position might be important for an inhibitory effect. Thus, an ester group was placed at C3 of the indole scaffold. Based on these considerations, compound **7** in Table 1 was the first designed compound. Finally, aiming at examining substituents other than EWGs, we also explored substitutions at the C5 position. Consequently, compounds **8**-**13** were designed (Table 1). Trifluoromethylated compound **8** still bears an EWG group at C5, but differs from NO_2- and CN- moieties by its greater hydrophobicity. In Compound **9**, a hydroxyl group was positioned at C5. This compound was also the starting material for further functionalizations. Indeed, reaction with acetyl chloride gave the acetyl derivative **10**, and the reaction with phenethyl bromide gave the correspondent phenethyl ether **11**. Finally, the reaction with 2-chloro-*N,N*-dimethylethylamine or 1,2-epoxybutane allowed the synthesis of the amino ether and the hydroxyl ether **12** and **13**, respectively.

In particular, with respect to structures in Figure 1, selected modifications allowed to include a weak acid group (compounds **9** and **13**) and a basic center (compound **12**), also varying the number of H-bond donor (HBD) and H-bond acceptor (HBA) atoms in the series. Of course, both the protonation state and the number and disposition of HBD and HBA groups might have an impact on the interaction with the target. The logP values for all compounds are in the range between 4 and 5, and the most lipophilic compounds are trifluoromethyl **8** and phenethyl derivative **11**. The presence at physiological pH of protonated species should be also taken in consideration: for example, according to the pK_a

values predicted by Moka[24,25] (Table 1), for **12** the protonated form is 93% abundant, while for **9** the neutral form prevails over the deprotonated one (99%).

Table 1. Designed NorA inhibitors bearing modification at the *C5* position.



Comp.	X	LogP[a]	pK_a[b]	% EtBr efflux inhibition @50 µM[c]	MIC (µg/ml)[d]	IC_{50} (µM)[e]
7	NO_2	4.43	–	9.1	ND[f]	ND
8	CF_3	5.43	–	36.6	ND	ND
9	OH	4.07	9.43 (a)	1.0	>100	ND
10		4.41	–	20.4	ND	ND
11		6.42	–	4.7	>100	ND
12		4.51	8.63 (b)	98.2	>100	22.5
13		4.88	15.58 (a)	71.1	>100	ND

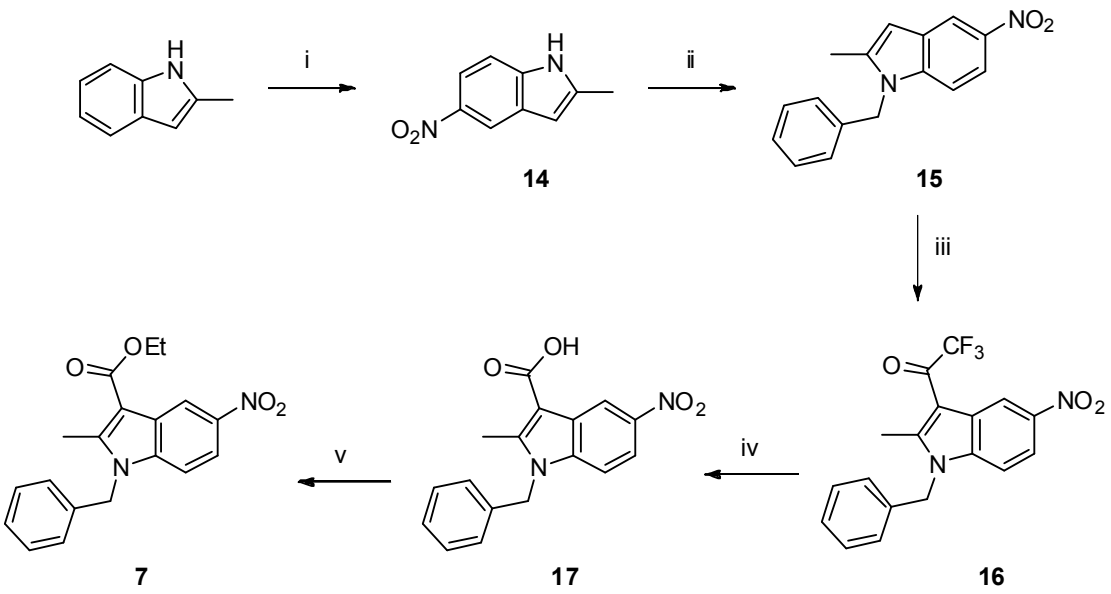
Biological data were generated employing SA-1199B, which overexpresses *norA*; a) predicted by Volsurf;[26] b) predicted by Moka;[24,25] c) % of ethidium bromide (EtBr) efflux inhibition with compound at a concentration of 50 µM; d) intrinsic antimicrobial activity of test compounds; e) IC_{50} (inhibitor concentration producing a 50% reduction in EtBr efflux) calculated from dose-response experiments. See Biology section for details; f) ND, not determined.

Chemistry

The studied compounds were obtained through a number of diverse approaches, summarized in Schemes 1−4.

2-Methyl-5-nitroindole **14**, prepared by direct nitration of 2-methylindole,[27] was benzylated at the nitrogen to obtain the *N*-benzylindole **15** (Scheme 1). Trifluoroacetylation with TFAA[28] gave the 3-trifluoroacetylated indole **16** which was hydrolyzed to the corresponding acid **17** with 20% aqueous NaOH. The acyl chloride obtained by refluxing the acid **17** in thionyl chloride was then transformed to the corresponding ethyl ester **7** by treatment with ethanol.

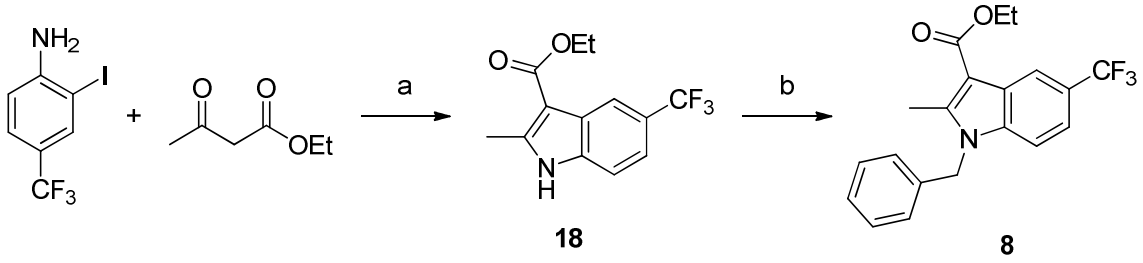
Scheme 1[a]



[a]Reagents and conditions: (i) HNO_3, H_2SO_4, 0 °C; (ii) NaH, BnBr, DMF; (iii) TFAA, DMF; (iv) NaOH aq. 20%, 70 °C; (v) *1*. $SOCl_2$ reflux; *2*. EtOH, r.t.

The 5-trifluoromethylindole **18** was prepared one-pot from 2-iodo-4-trifluoromethylaniline and ethyl acetoacetate, according to the Suzuki's protocol (Scheme 2).[29] The resulting ester **18** was then alkylated at *N*-1 position by simply treatment with sodium hydride and benzyl bromide in DMF.

Scheme 2[a]

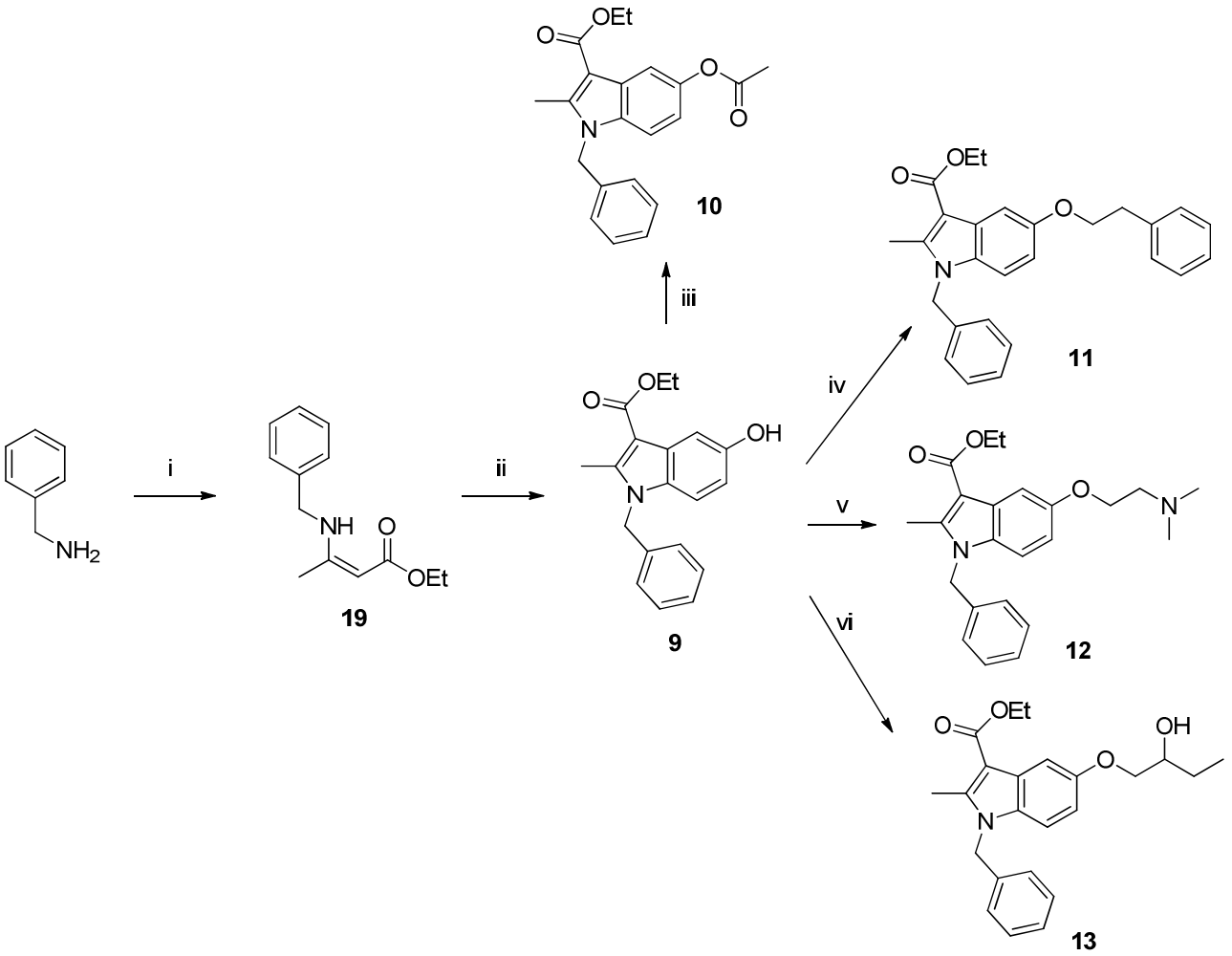


[a] Reagents and conditions: (a) NaH, CuI, DMF;[29] (b) NaH, BnBr, DMF.

The hydroxyindole **9** was the common precursor of the target indole derivatives **11-13**. The substituted 5-hydroxyindole **9** was synthesized according to a modified Nenitzescu reaction by refluxing 1,4-p-benzoquinone, zinc chloride, and aminocrotonate **19** in dichloromethane.[30] **19** was prepared from condensation of ethyl acetoacetate and benzylamine (Scheme 3).

Thus, the reaction of **9** with acetyl chloride in acetone in the presence of pyridine gave ester **10**; in addition, reaction of **9** with 2-phenethylbromide in DMF at 50 °C, in the presence of K_2CO_3, gave phenethoxyindole **11**. The amino derivative **12** was obtained from **9** by nucleophilic substitution on 2-chloro-*N,N*-dimethylamine hydrochloride in the presence of K_2CO_3; eventually, it gave the hydroxyl ether **13** in 70 % yield by reaction with 1,2-epoxybutane in DMF (Scheme 3).

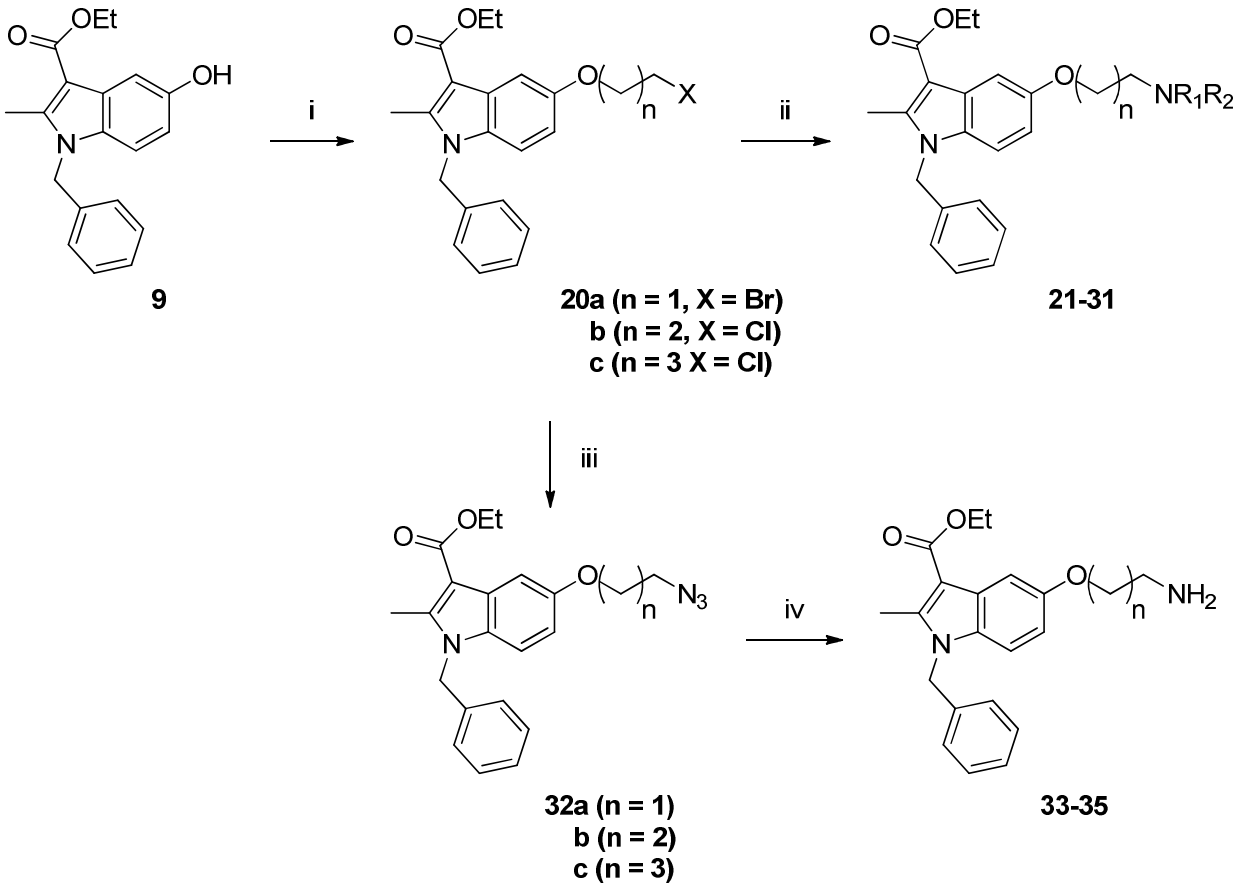
Scheme 3[a]



[a]Reagents and conditions: (i) Ethyl acetoacetate, *p*-TsOH, benzene reflux; (ii) *p*-benzoquinone, $ZnCl_2$, CH_2Cl_2 reflux;[30] (iii) acethyl chloride, pyridine 45 °C; (iv) 2-phenylethylbromide, K_2CO_3, DMF 50 °C; (v) 2-chloro-*N,N*-dimethylamine, K_2CO_3, ethanol/toluene 1:1, reflux; (vi) 1-butene oxide, NaH, DMF, 100 °C.

O-alkylation of 5-hydroxyindole **9** afforded halo intermediates **20a-c**, which were converted into the secondary or tertiary amino compounds **21-31** (for further details see Experimental section); the halo intermediates **20a-c** were also used to prepare the azides **32a-c**, which were converted by triphenylphosphine in THF/water mixture into the final primary amines **33-35** (Scheme 4).

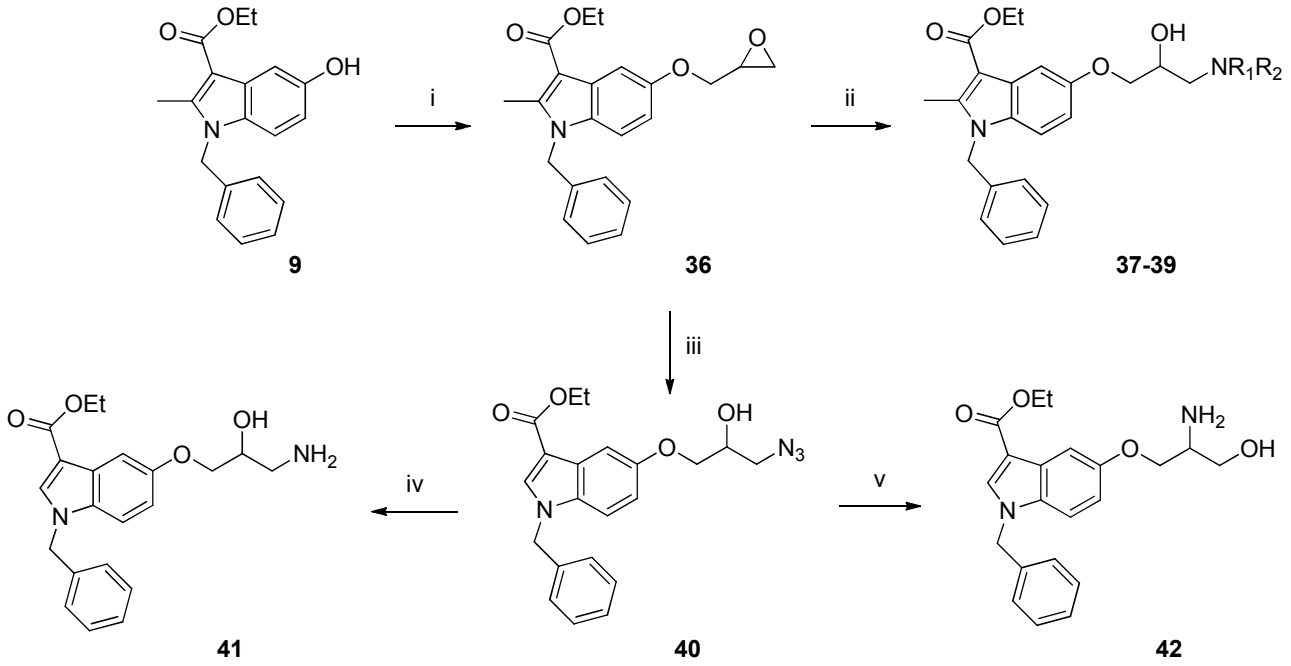
Scheme 4[a]



[a]Reagents and conditions: (i) suitable dibromo- or bromochloro-alkane, K_2CO_3, ethanol reflux;[31] (ii) *1.* NaI, acetonitrile reflux; *2.* R_1R_2NH, K_2CO_3, reflux;[31] (iii) NaN_3, DMF 80 °C;[32] (iv) PPh_3, THF/H_2O r.t;[33]

O-alkylation of the hydroxyindole **9** with epibromohydrin afforded the epoxide **36**, which was converted into the desired amino alcohols **37-39** by reaction with the proper aliphatic secondary amines. In particular, primary amino alcohols **41-42** were obtained passing through the azido intermediate **40** which gave amino alcohol **41** by reduction with tin chloride or its regioisomer **42** using triphenylphosphine in tetrahydrofuran/water mixture (Scheme 5).

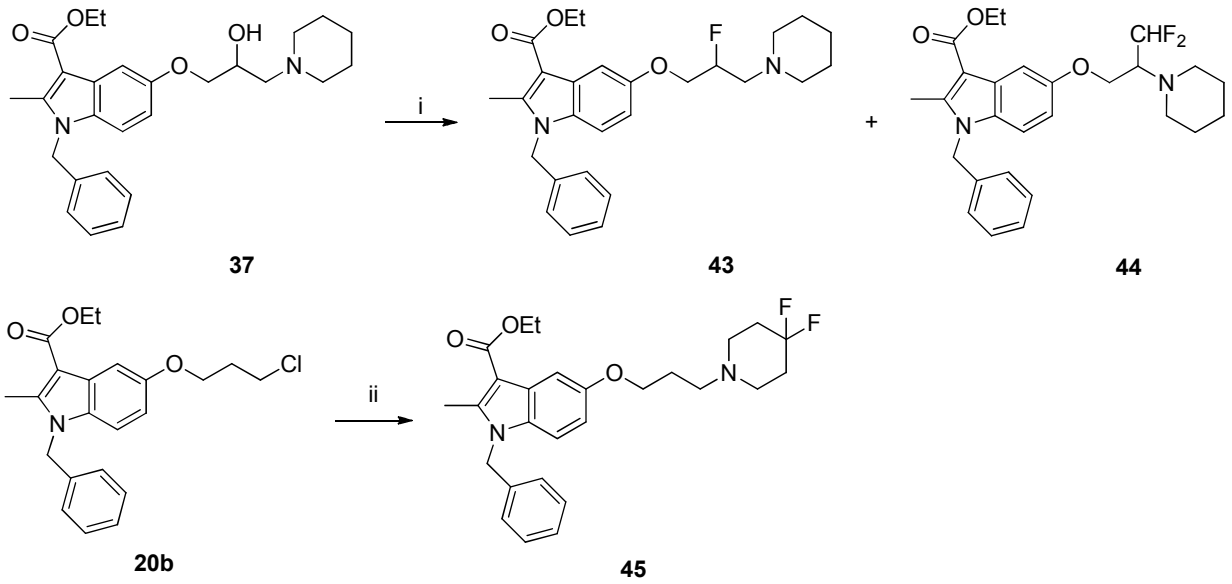
Scheme 5[a]



[a]Reagents and conditions: (i) epibromohydrin, K_2CO_3, acetone reflux;[34] (ii) $LiClO_4$, R_1R_2NH, acetonitrile reflux;[35] (iii) NaN_3, $LiClO_4$, acetonitrile reflux; [36,37] (iv) $SnCl_2 \cdot 2\ H_2O$, MeOH, r.t;[38] (v) PPh_3, THF/H_2O r.t.[33]

Three fluorinated compounds were also investigated (Scheme 6); in particular, upon exposure to DAST, hydroxyl compound **37** was converted into two regioisomers **43**-**44**. In addition, the NaI mediated reaction of chloro derivative **20b** gave difluorinated compound **45** after treatment with 4,4-difluoropiperidine in the presence of K_2CO_3 as a base.

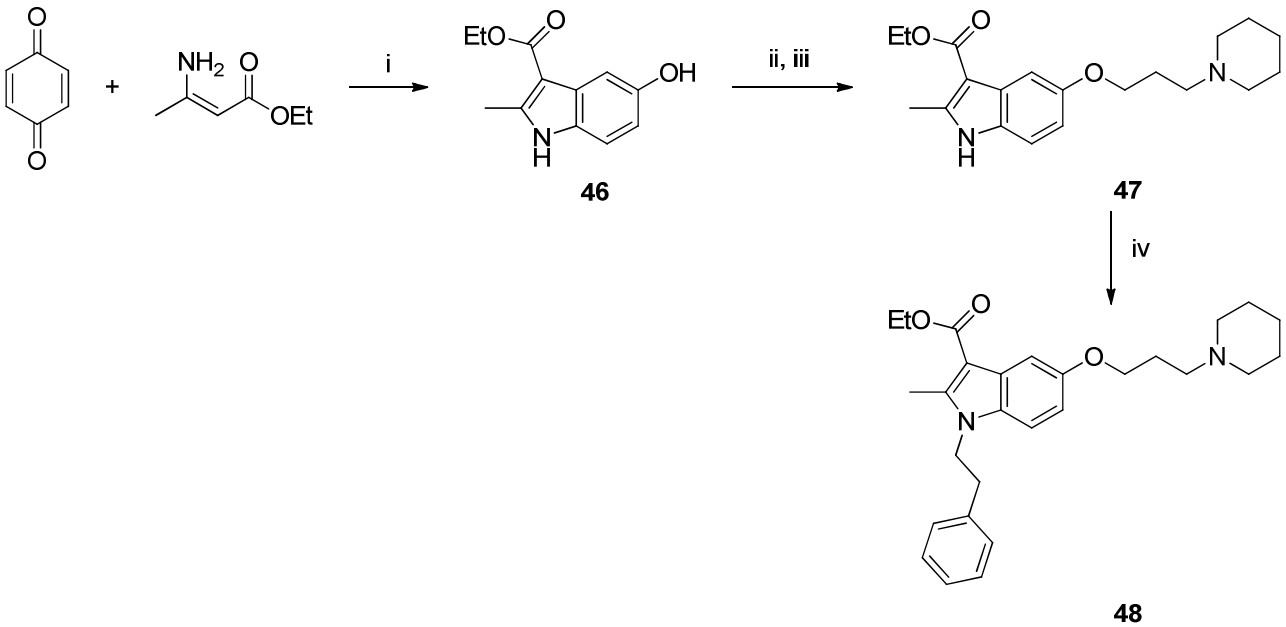
Scheme 6[a]



[a]Reagents and conditions: (i) DAST, DCM, 0 °C; (ii) *1.* NaI, acetonitrile reflux; *2.* 4,4-difluoropiperidine hydrochloride, K_2CO_3, reflux.

Ethyl 5-hydroxy-2-methyl-1*H*-indole-3-carboxylate **46** was obtained according to Nenitzescu's method [39] and further converted into final amine **47** (Scheme 7). From the (*1H)*-indole **47**, a phenethyl derivative **48** was obtained by treatment with phenethyl bromide in the presence of NaH.

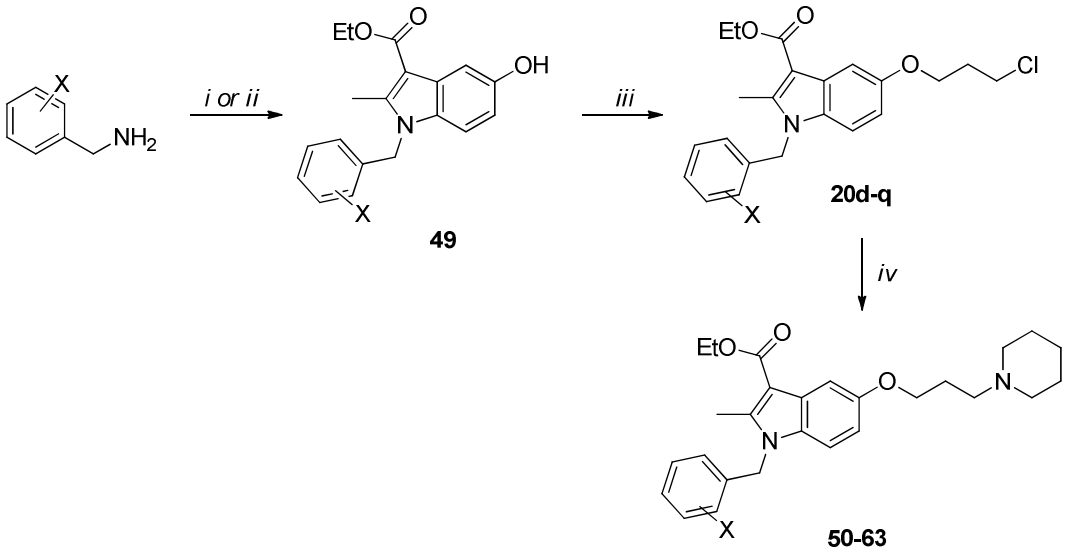
Scheme 7[a]



[a]Reagents and conditions: (i) AcOH, r.t.;[39] (ii) 3-chloro-1-bromopropane, K_2CO_3, ethanol reflux;[31] (iii) *1*. NaI, acetonitrile reflux; *2*. piperidine, K_2CO_3, reflux.[31] (iv) NaH, phenethyl bromide, DMF, 50 ºC.

Finally, different substituted benzylindoles **49** were synthesized by CAN[40] induced cyclization or by triethylamine catalysis[41] (Scheme 8). Intermediates **49** were converted, similarly to hydroxyindole **9**, to final compounds **50-63**. Nitro derivatives were obtained by a different route or triethylamine[41]

Scheme 8[a]

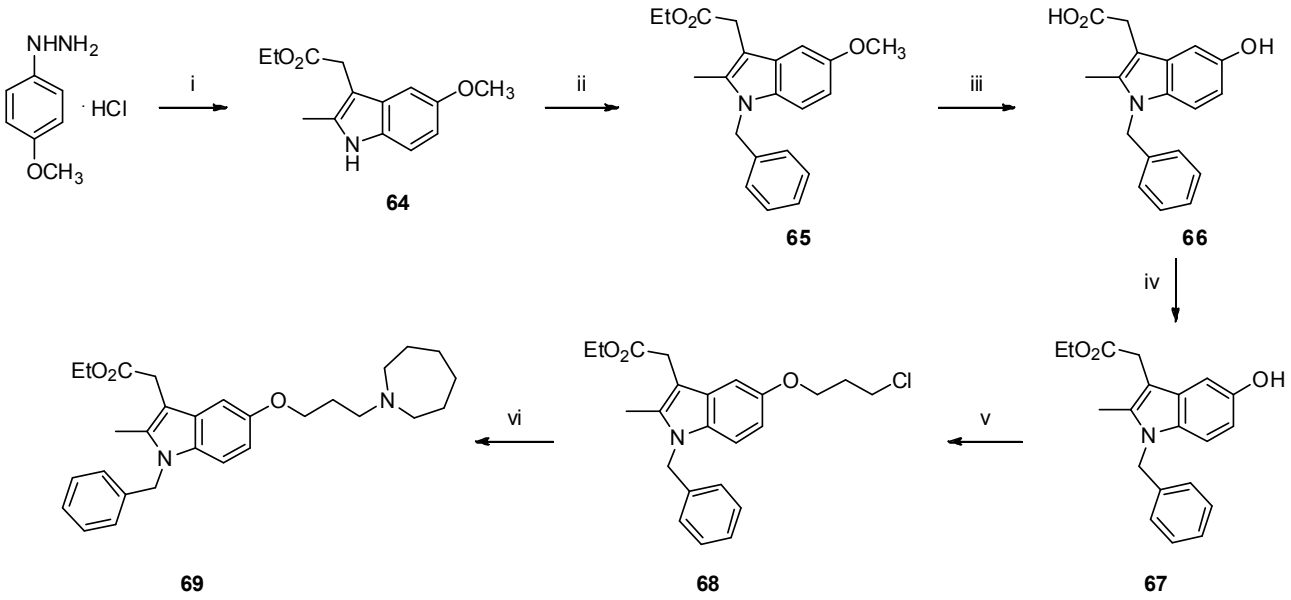


[a]Reagents and conditions: (i) *p*-benzoquinone, ethyl acetoacetate, CAN, EtOH, r.t.;[40] (ii) *1*. ethyl acetoacetate, Et_3N, r.t. *2*. *p*-benzoquinone, CH_3NO_2, r.t.;[41] (iii) 3-chloro-1-bromopropane, K_2CO_3, ethanol, reflux;[31] (iv) *1*. NaI, acetonitrile reflux; *2*. piperidine, K_2CO_3, reflux.[31]

The strategy adopted for the synthesis of the aminoether **69** is illustrated below (Scheme 9). The Fisher condensation of *p*-methoxyphenylhydrazine with ethyl levulinate in acetic acid gave the ethyl indolacetate **64** which was transformed into the corresponding *N*-benzyl derivative **65** by reaction with NaH and benzyl bromide. Treatment of the ester **65** with BBr_3 in dichloromethane at -78 °C afforded

the hydroxyacid **66** which was converted in the hydroxyester **67** by ethanolysis of corresponding acyl chloride. Treatment of the ester **67** with 3-chloro-1-bromopropane in refluxing acetone, in the presence of K_2CO_3 gave the chloro derivative **68** which, in turn, was converted into the target aminoether **69** as previously reported.

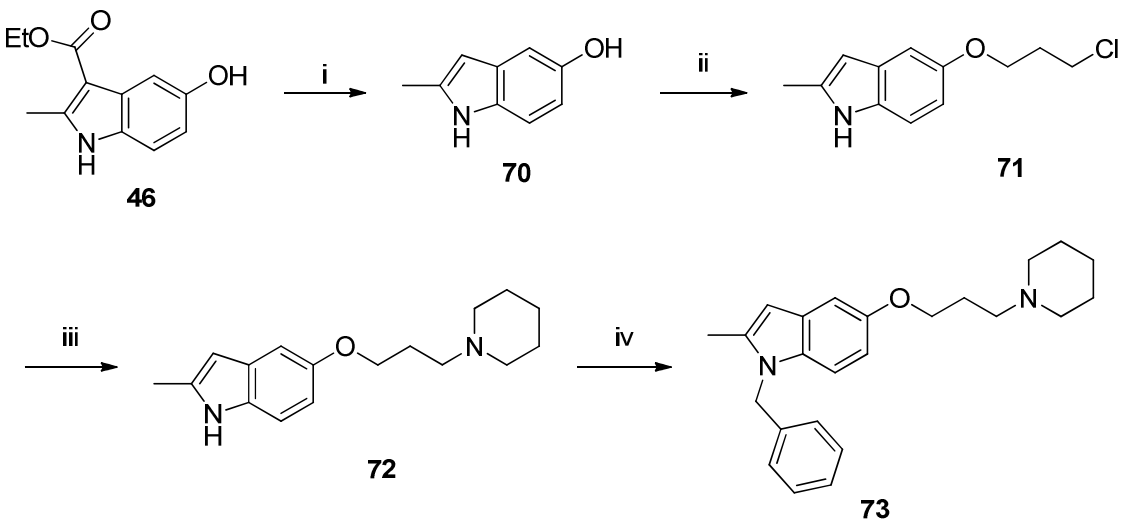
Scheme 9[a]



[a]Reagents and conditions: (i) ethyl levulinate, AcONa, AcOH, reflux; (ii) NaH, BnBr DMF; (iii) BBr_3, DCM, -78 °C; (iv) *1*. $SOCl_2$; *2*. EtOH; (v) 3-chloro-1-bromopropane, K_2CO_3, ethanol, reflux;[31] (vi) *1*. NaI, acetonitrile reflux; *2*. piperidine, K_2CO_3, reflux.[31]

Aminoether **73**, was obtained by decarboxylation of **46** and further converted into final amine **72** (Scheme 10). From this 1*H*-indole, the benzyl derivative **73** was obtained by treatment with benzyl bromide in the presence of NaH.

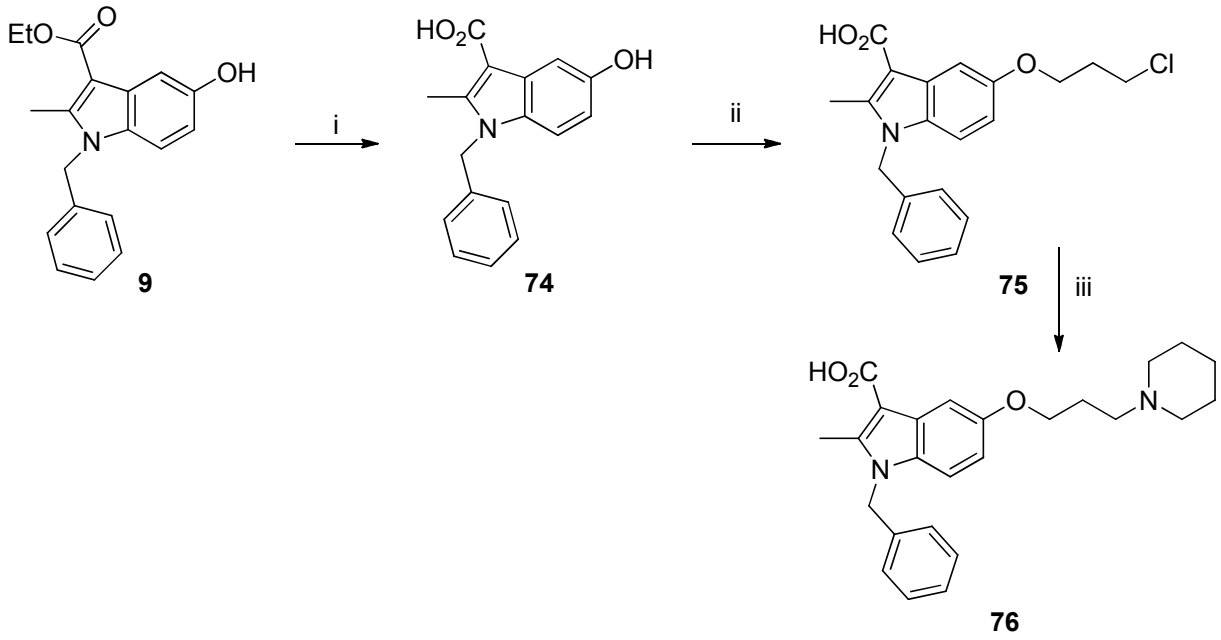
Scheme 10[a]



[a]Reagents and conditions: (i) 2N HCl, reflux;[39] (ii) 3-chloro-1-bromopropane, K_2CO_3, ethanol, reflux;[31] (iii) *1*. NaI, acetonitrile reflux; *2*. piperidine, K_2CO_3, reflux.[31] (iv) NaH, BnBr DMF.

Finally, indole-3-carboxylic acid **76** was obtained by hydrolysis of **9** and further converted into final amine **76** (Scheme 11).

Scheme 11[a]



[a]Reagents and conditions: (i) *1*. 2N NaOH, tetrahydrofurane, reflux; *2*. 2N HCl;[42] (ii) 3-chloro-1-bromopropane, K_2CO_3, ethanol, reflux;[31] (iii) *1*. NaI, acetonitrile reflux; *2*. piperidine, K_2CO_3, reflux.[31]

Biology

Ethidium bromide efflux inhibition

All 48 synthesized compounds were evaluated for their ability to inhibit efflux of ethidium bromide, (EtBr) by SA-1199B. This strain overexpresses *norA*, resulting in an avid efflux phenotype.[43] EtBr was used because it is an excellent NorA substrate and has convenient fluorescent properties that allow qualitative monitoring of its intracellular concentration. The efflux inhibition assay employed a real-time fluorometric approach essentially as described previously.[44] SA-1199B was grown overnight in cation-supplemented Mueller-Hinton broth (SMHB, BD Biosciences, Sparks, MD) and then was diluted 25-fold into fresh SMHB. Cultures were incubated at 35 °C with shaking until an optical density at 600 nm (OD600) of 0.7–0.8 was achieved. Cells were then pelleted and re-suspended at OD600 = 0.8 in 0.5 mL aliquots of SMHB containing EtBr plus carbonyl cyanide m-chlorophenylhydrazone to "load" cells with EtBr (final concentrations, 25 and 100 μM, respectively).

Following gentle agitation for 20 min at room temperature, cells were pelleted and stored on ice. Pellets were warmed at room temperature for 5 min and then re-suspended in 1 mL of fresh SMHB and 200 µL aliquots were immediately transferred into the wells of opaque 96-well flat-bottom plates (Corning Inc., Corning, NY) containing or lacking a 50 µM concentration of each test compound. Fluorescence was monitored continuously using a BioTek FLx800 microplate reader (BioTek Instruments Inc., Winooski, VT) at excitation and emission wavelengths of 485 nm and 645 nm, respectively, for 5 min. Experiments were performed in triplicate with two technical replicates per biological replicate.

Efflux activity of SA-1199B was expressed as percent fluorescence decrease over a 5-min time course. Inhibition of this efflux by test compounds was determined using the equation [efflux in the absence]-[efflux in the presence of test compound]/[efflux in absence of test compound] × 100, giving the percent efflux inhibition observed. If a 50 µM concentration of test compound achieved at least 80% efflux inhibition, a series of concentrations were tested to quantify potency by determining the 50% inhibitory concentration (IC_{50}). IC_{50} determinations also were performed for selected compounds having less than 80% efflux inhibition.

Intrinsic antimicrobial activity

In addition to IC_{50} determinations, compounds with at least 80% efflux inhibition were evaluated for intrinsic antimicrobial activity. This was accomplished by determining minimal inhibitory concentrations (MIC) employing a microdilution method according to Clinical and Laboratory Standards Institute (CLSI) guidelines.[45] The antimicrobial activity of selected compounds having less than 80% efflux inhibition were also determined. Compounds having an MIC value greater than 100 µg/ml were considered antimicrobially inactive. In these instances, efflux inhibitory activity was considered to be unrelated to any direct antimicrobial effect on the test strain.

Lead optimization

Based on data in Table 1 (to be discussed in detail subsequently), the most promising EPIs were the dimethylamino ether **12** and the hydroxylether **13**, inhibiting EtBr efflux by 98.2 and 71.1 %, respectively, at the 50 μM screening concentration. Indeed, the EWG group in the C5 position appears non-essential to preserve the inhibitory effect, and the target seems to be able to accommodate larger compounds with respect to data previously reported in the literature.[18,19]

Thus, we decided to perform additional structural modifications involving both basic and acid functionalities. In particular, we decided to synthesize and test a novel series of compounds with a two-, three or four-carbon atom linker carrying different amino groups. A series of compounds having the hydroxylic group together with different amines was also explored and, finally, a compound presenting the amine and hydroxylic group in inverted positions was synthesized (Figures 3 and 4).

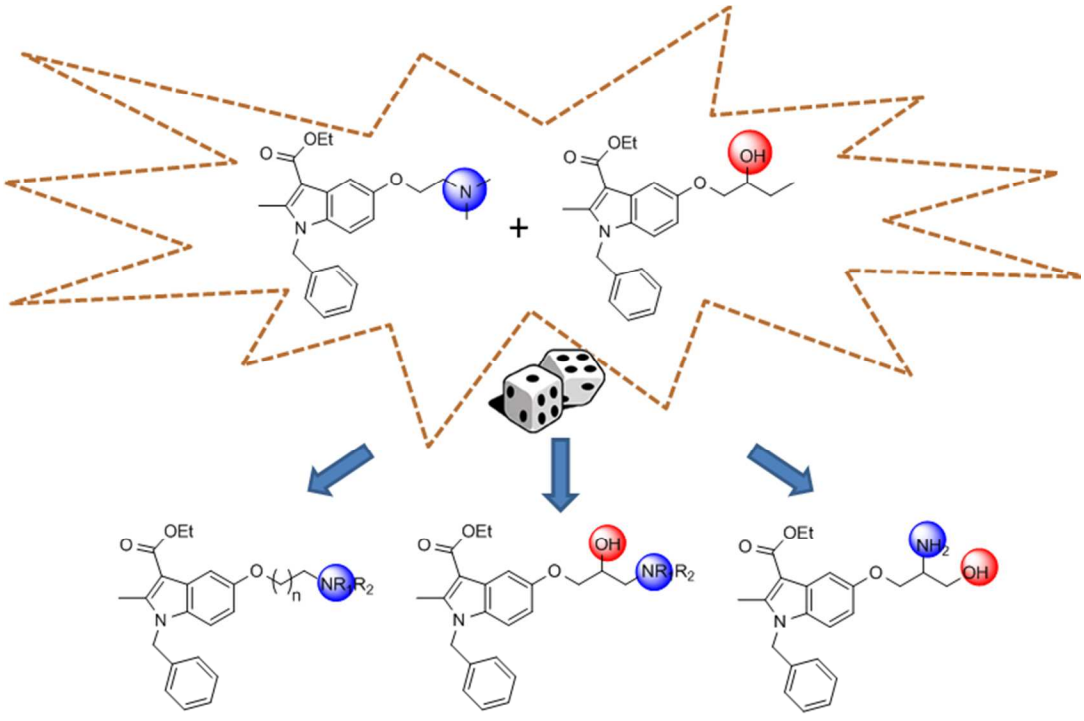


Figure 3. Scheme of the modulation of the indole-based compounds reported in this study. Blue spheres represent basic centers, while red spheres represent weak acid centers.

Subsequently, different spacers (two-, three- and four carbons) were used to evaluate the appropriated distance between the aromatic portion and the basic functionality. As well as the length of the chain, the different terminal amines were investigated; the aim was to determine the effect of a primary amine compared to the tertiary one. Furthermore five- or six-membered rings were used, and additional hydrogen bond donors (HBD) or acceptors (HBA) were introduced (e.g. using morpholine or piperazine instead of piperidine). As a refinement three fluorinated derivatives, together with indoles bearing different benzyl groups or substituted at C3, were synthesized and investigated (Figure 4).

Even though the mentioned compounds differ for slight modifications in the NMe_2 replacement, the basic pK_a values of the novel amine groups (see Table 2) fall in a broad range from 4.12 (**28**) to 10.35 (**35**). For example, a morpholinic moiety (compounds **22**, **27**, and **39**) has a notable effect on the pK_a value when compared with a piperidine group (derivatives **21**, **25**, and **37**). In addition, a piperazine moiety might be important to modulate the interaction with the targeted protein due to the possible protonation of both nitrogen atoms. Similarly, the LogP (see Table 2) is also heavily affected by the proposed modifications, ranging from 2.85 (**41**) to 6.45 (**26**). In general, the greater the spacer and the ring size, the higher the liphophilicity. The presence of fluorinated rings or chains also have an impact on the basicity of the amino group, with compound **45** being one of the less basic in our series.

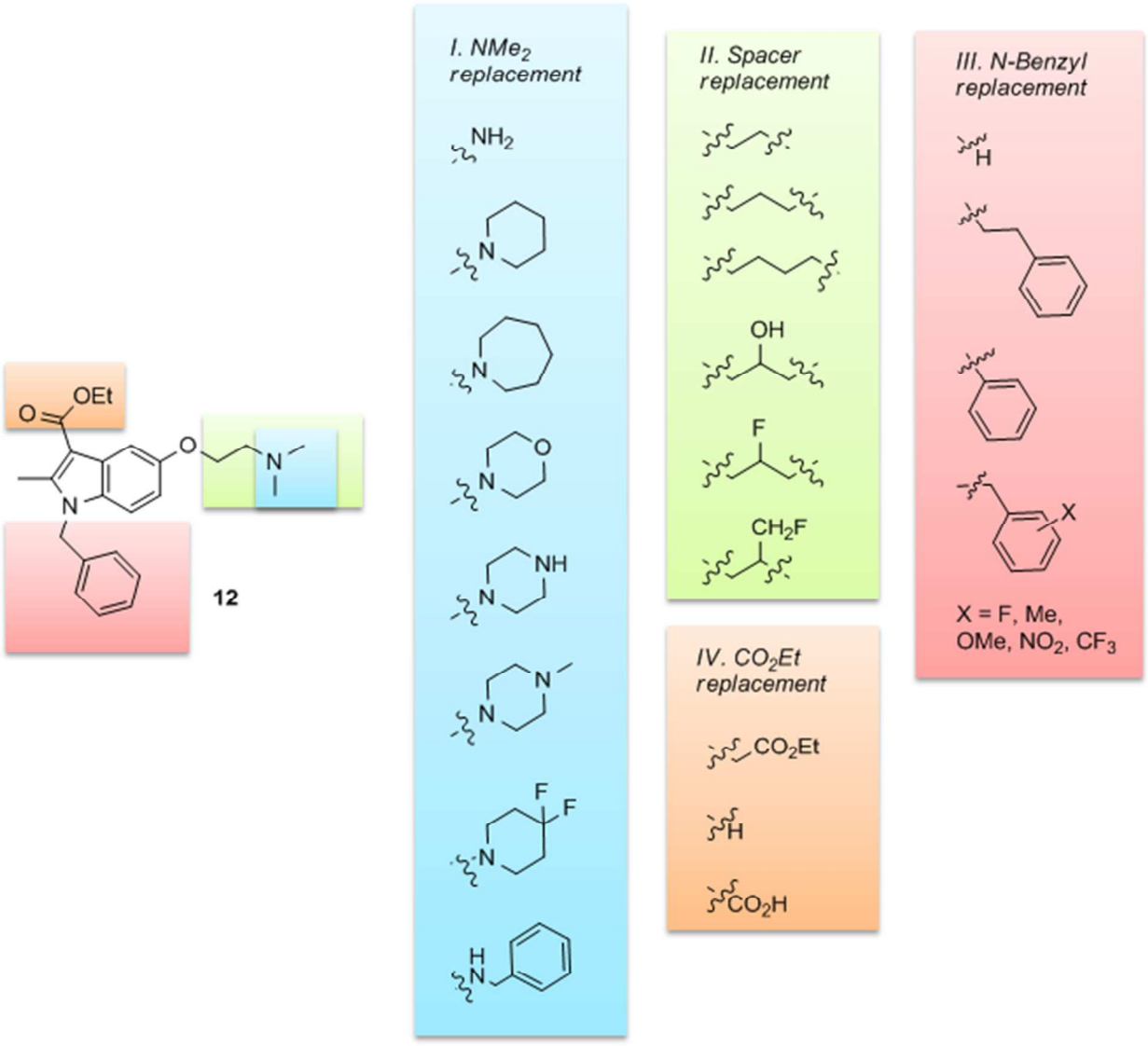
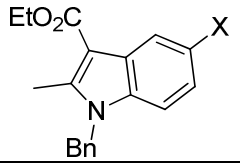


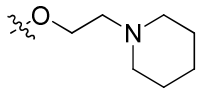
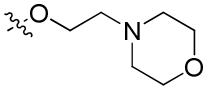
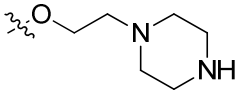
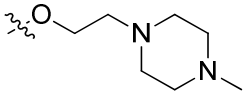
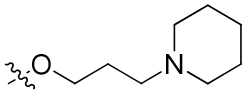
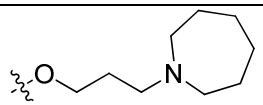
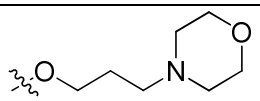
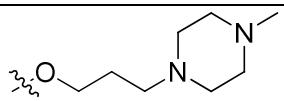
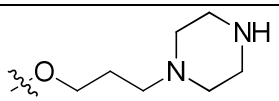
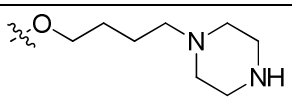
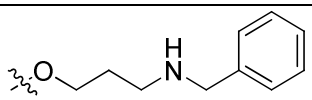
Figure 4. Detailed structural modification of lead compound **12** involving the replacement of the terminal dimethylamine moiety (block I), ethyl linker (block II), benzyl group (block III), and ethyl carboxylate (block IV).

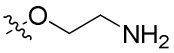
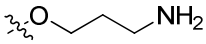
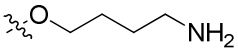
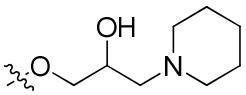
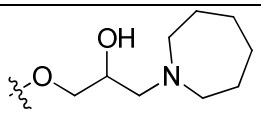
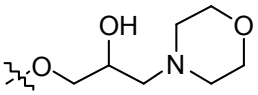
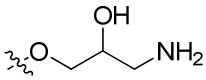
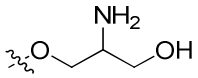
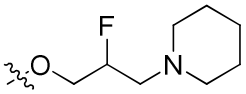
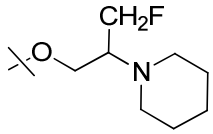
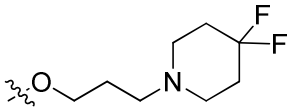
RESULTS AND DISCUSSION

All new indole-based compounds were evaluated using EtBr efflux inhibition assays and MIC determinations. These data are provided in Tables 2 and 3.

Table 2. Side chain effect on inhibition of EtBr efflux in *S. aureus* 1199B



Comp.	X	LogP[a]	pK_a[b]	% EtBr efflux inhibition @50 µM	MIC (µg/ml)	IC_{50} (µM)
21		5.54	8.82	100	>100	11.6
22		4.11	6.83	90.9	>100	16.8
23		3.79	4.64; 9.51	99.2	>100	15.5
24		4.34	4.14; 8.71	99.7	>100	10.1
25		6.03	9.59	98.5	>100	6.0
26		6.45	9.49	77.4	>100	ND[c]
27		4.60	7.60	98.6	>100	10.6
28		4.83	4.12; 8.69	100	>100	11.9
29		4.28	5.23; 9.80	100	100	12.5
30		4.77	5.23; 9.80	71.9	>100	ND
31		5.98	8.81	45.4	ND	ND

33		3.49	9.07	67.7	ND	ND
34		3.98	10.13	100	>100	12.5
35		4.47	10.35	93.7	100	6.7
37		4.90	14.46*; 8.91	99.3	>100	5.8
38		5.32	14.46*; 8.80	92.8	100	6.8
39		3.47	14.46*; 6.92	99	>100	17.0
41		2.85	13.74*; 9.34	100.0	>100	17.1
42		2.96	13.81*; 8.31	100	>100	10.4
43		5.41	7.91	96.7	>100	5.1
44		5.32	7.29	38.5	>100	ND
45		6.09	5.50	25.9	ND	ND

a) predicted by Volsurf; [26] b) predicted by Moka;[24,25] c) ND, not determined; *relative to the acidity of OH group.

Looking at the activities shown in Table 1 and 2, it appears that while the hydroxylic group is not essential the terminal amine moiety is fundamental for activity retention. Thus, all other compounds having a different terminal amino group (for example **37**-**39** and **41**), containing or lacking the hydroxyl group in C2' position (**26**-**29**, **34**), and having a shorter (2 carbon atoms, **12**, **21**-**24**) or longer spacer (4 carbon atoms, **30** and **35**) resulted very strong inhibitors (% inhibition > 89 %). Among the

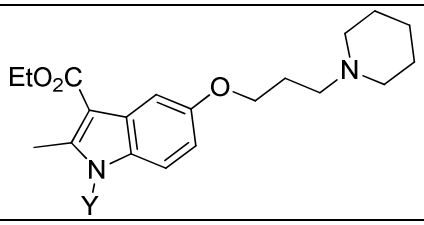
different acyclic (dimethylamine **12**, or amino **33-35**, and **41-42**) and cyclic amines examined, such as morpholine (**22**, **27**, **39**), azepane (**26** and **38**), and piperazines (**23-24** and **28-29**), the best results were achieved with the piperidine-containing compounds (**25** and **37**), showing IC_{50} values of 6 and 5.8 μM, respectively. In particular, comparing compounds **13** (Table 1), **34** and **41** (Table 2) is possible to notice that the lacking of the amino group produced an inhibition activity decrease from 100% (compound **41**) to 71.1% (compound **13**); while the lacking of the hydroxyl group in compound **34** respect to compound **41** did not affect at all the inhibition ability that is 100%.

Concerning the length of the spacer, three and four carbon atoms seems to positively affect the inhibitory activity. For example, between the two piperidine containing compounds **25** and **21** the first (containing the three carbon atom chain) exhibits a 2-fold IC_{50} increase with respect to **21** (containing a two carbons linker). Moreover, trying to increase hydrophobicity by using a benzylamine (such as in compound **31**) was detrimental for EtBr efflux inhibition activity.

In addition, inspection of the three fluorinated analogues of the most active **25** (pKa = 9.60 predicted by Moka)[24,25] revealed that introduction of two fluorine atoms in 4-position of the piperidine ring (compound **45**, pK_a = 5.54 predicted by Moka)[24,25] were detrimental for the inhibitory effect. On the contrary, the presence of one fluorine in the C2' position of the spacer gave the most active compound **43** (pK_a = 7.92 predicted by Moka,[24,25] IC_{50} = 5.1 μM). Finally, the fluoromethyl compound **44**, which is a regioisomer of compound **43** (pK_a = 7.28 predicted by Moka,[24,25] resulted in a weak inhibitor. The inhibition behavior correlated well with the pK_a value in that the greater the pK_a, the higher the possibility for the protonated compound to bind the target. However, comparison between the regioisomers **43** and **44**, having similar pK_a values but bearing a different spacer length, suggests that the interaction with the NorA cavity is sensitive to the distances between the indole scaffold and the basic center.

The importance of *N*-benzyl moiety in the piperidine-containing derivative **25** was also explored (see Table 3). The replacement performed slightly affected the predicted LogP values (in the range of 4.51 − 6.97). A benzyl replacement with a phenethyl moiety (**48**) produced a 2-fold activity decrease based on IC_{50} values, while the substitution with a hydrogen resulted in a compound with much reduced activity indicating that benzyl is more advisable. An attempt to make the analogue of **25** by replacing the benzyl group with a phenyl ring was made. However, the compound instability prevented further investigations. Different benzyl-substituted compounds were synthesized and tested by the insertion of a methyl group in the *ortho*, *meta* and *para* positions (**50-52**). These changes resulted in less active compounds in terms of the 50 μM screening concentration, but all were antimicrobially active. This effect might be attributable to an increased hydrophobicity rather than an increased steric hindrance. Indeed, methoxy- (**53-55**) and nitro-substituted (**61-63**) compounds maintained good EPI without any appreciable antimicrobial activity. Noteworthy, fluoro derivatives **56-58** turned out to be very good candidates (IC_{50} values of 4.8−8.7 μM), while their trifluoromethyl counterpart **59-60** showed a twofold increase in IC_{50} values.

Table 3. Benzyl effect on EtBr efflux inhibition



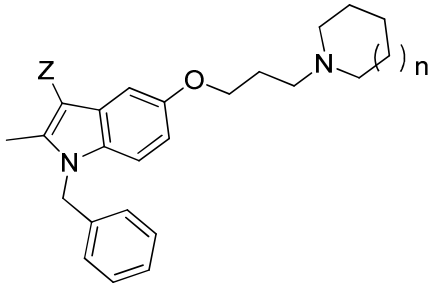
Comp.	Y	LogP[a]	% EtBr efflux inhibition @50 μM	MIC (μg/ml)	IC_{50} (μM)
25	benzyl	6.03	98.5	>100	6
47	H	4.51	34.2	ND[b]	ND
48	phenethyl	6.39	99.3	>100	13.7

50	*o*-methylbenzyl	6.41	54	25	4.8
51	*m*-methylbenzyl	6.49	70.9	50	6.1
52	*p*-methylbenzyl	6.47	58.3	25	6.7
53	*o*-methoxylbenzyl	5.89	87.9	> 100	5
54	*m*-methoxylbenzyl	6.11	77.1	> 100	7.3
55	*p*-methoxylbenzyl	6.09	77.7	> 100	7.1
56	*o*-fluorobenzyl	6.10	89	> 100	4.8
57	*m*-fluorobenzyl	6.23	89.7	> 100	6.1
58	*p*-fluorobenzyl	6.22	91.1	> 100	8.7
59	*m*-trifluoromethylbenzyl	6.97	12.9	> 100	14.2
60	*p*-trifluoromethylbenzyl	6.96	77.7	> 100	14.1
61	*o*-nitrobenzyl	5.87	91.8	> 100	6.3
62	*m*-nitrobenzyl	5.97	85.1	> 100	4.4
63	*p*-nitrobenzyl	5.55	89.9	> 100	6.5

a) predicted by Volsurf; [26] b) ND, not determined.

Finally, we investigated the effect of modification at the C3 position of the most potent indole **25**. In particular, a further investigation on the role of the ester group by varying the substituent at C3 (**69**) or completely removing it (**73**). Eventually, an acidic moiety (**76**) was explored (pK_a = 2.65 predicted by Moka).[24,25]

Table 4. Effect of substitution in C3 position on EtBr efflux inhibition in *S. aureus* 1199-B



Comp.	Z	n	LogP[a]	pK_a[b]	% EtBr efflux inhibition @50 µM	MIC (µg/ml)	IC_{50} (µM)
25	CO_2Et	1	6.03	9.59	98.5	>100	6
69	CH_2CO_2Et	2	6.31	9.49	98.4	100	6.1
73	H	1	5.55	9.59	95.6	0.63	6.6
76	COOH	1	5.25	2.65 (a); 9.59	0	ND[c]	ND

a) predicted by Moka;[24,25] b) predicted by Volsurf; [26] ND, not determined.

Data in Table 4 show that removing the ester function at C3 (**73**) does not affect the % inhibition and IC_{50} values compared to **25** but does strongly increase antimicrobial activity. This antimicrobial activity could contribute to the low IC_{50} value observed, unrelated to any pump inhibitory effect that may be present. Indeed, further studies would be necessary to discriminate between EPI and intrinsic antimicrobial activity, as previously reported for Totarol.[46] Similarly, the substitution of the ethyl ester group with a methylene-ethyl ester function did not alter the inhibition properties (**69**), showing that the position C3 is not critical for interaction with the NorA pump cavity.

On the contrary, a carboxylic acid in the C3 position had a detrimental effect with a complete loss of inhibition (**76**). This data are noteworthy, because the ester functionality usually undergoes hydrolysis to some extent in a biological environment. Thus, although many drugs possess ester groups to improve ADME properties,[47] a valuable test in our study could be the total removal of the ester function making

compound **73** a good candidate for further development although its intrinsic antimicrobial activity may pose problems to separate the antimicrobial from the EPI activities.

Preliminary pharmacokinetic studies

Finally, preliminary ADME studies (see Table 5) were carried out for the best compounds **23**, **25**, **29**, **34**, **43**, **53**, **61**, and **73** in order to experimentally evaluate their metabolic stability (*in vitro* assays with HLM) and water solubility (by ^{1}H NMR experiments in D_2O solution using TSP as internal standard).[48] In addition, permeability in CaCo2 cells has been evaluated *in silico* (Table 5).

Table 5. ADME study on best compounds.

	pK_a	Solubility (mM)[a]	% substrate after 30 min (HLM)[b]	Metabolites analysis[b]	CaCo2 Permeability[c]
23	4.64; 9.51	0.19	72	M-90 (*N*-dealkylation); M-28 (*O*-dealkylation)	0.81
25	9.59	0.023	76	M-90 (*N*-dealkylation); M-28 (*O*-dealkylation)	1.28
29	5.23; 9.80	0.02	82	M-90 (*N*-dealkylation); M-28 (*O*-dealkylation)	0.82
34	10.13	0.017	87	M-90 (*N*-dealkylation); M-28 (*O*-dealkylation)	0.46
43	7.91	0.020	52	M-90 (*N*-dealkylation), M-68 (*N*-dealkylation)	1.36
53	9.59	0.025	66	M-120 (*N*-dealkylation); M-14 (*O*-demethylation)	1.21
61	9.59	0.014	89	stable	1.00
73	9.59	0.070	100	stable	1.53

a) evaluated by ^{1}H-NMR in D_2O solution (containing 0.4% of DMSO-d_6) at 25 °C;[48] b) see experimental section for further details; c) predicted by Volsurf (the value +1 is assigned to permeable compounds, with Papp. $\geq 8 \times 10^{-6}$ cm s^{-1}).[26]

All tested indoles exhibit a medium to high metabolic stability. While compound **23**, **25**, **29**, **34**, **43**, and **53** underwent *N*-dealkylation (loss of the benzyl group), nitrobenzylindole **61** was quite stable with no metabolite detected. This finding suggests that the presence of an electron-withdrawing group (such a nitro group) enhances the compound metabolic stability. On the contrary, the presence of electron-donor group (i.e. **53**) induced a slight metabolic stability drop, also due to the presence of a further metabolic reaction by direct involvement of the methoxy group. To be noted that **25** is fully protonated under physiologic conditions. The different behavior shown by fluorinated compound **43** with respect to its analogue **25** has been rationalized with the aid of MetaSite,[49] a software predicting the Site of Metabolism (SoM) of a compound with different CYP450 using reactivity and molecular interaction fields information. According to MetaSite,[49] as reported in Figure 5a the charged piperazinyl group of **25** is linked to Glu183 thus the ester group and the benzyl group (the two experimental sites of oxidation) are in close proximity of the heme. The *O*-dealkylation is faster while the benzylic oxidation leading to *N*-dealkylation is slower, but both contribute to the parent disappearance. A fluorine atom β to the amino group (**43**, Figure 5b), makes the pK_a of the piperazinyl group drop significantly leading to a majority of neutral form. The CYP recognition is now different, and the main recognition anchorage is produced by the benzyl group (that was the less reactive in molecule **25**). This binding mode makes the exposure of the piperazinyl group towards the heme more favourable, leading to a fast oxidation. The molecular stability decreases and the main metabolite of **43** becomes the M-68 (*N*-dealkylation twice in the ring).

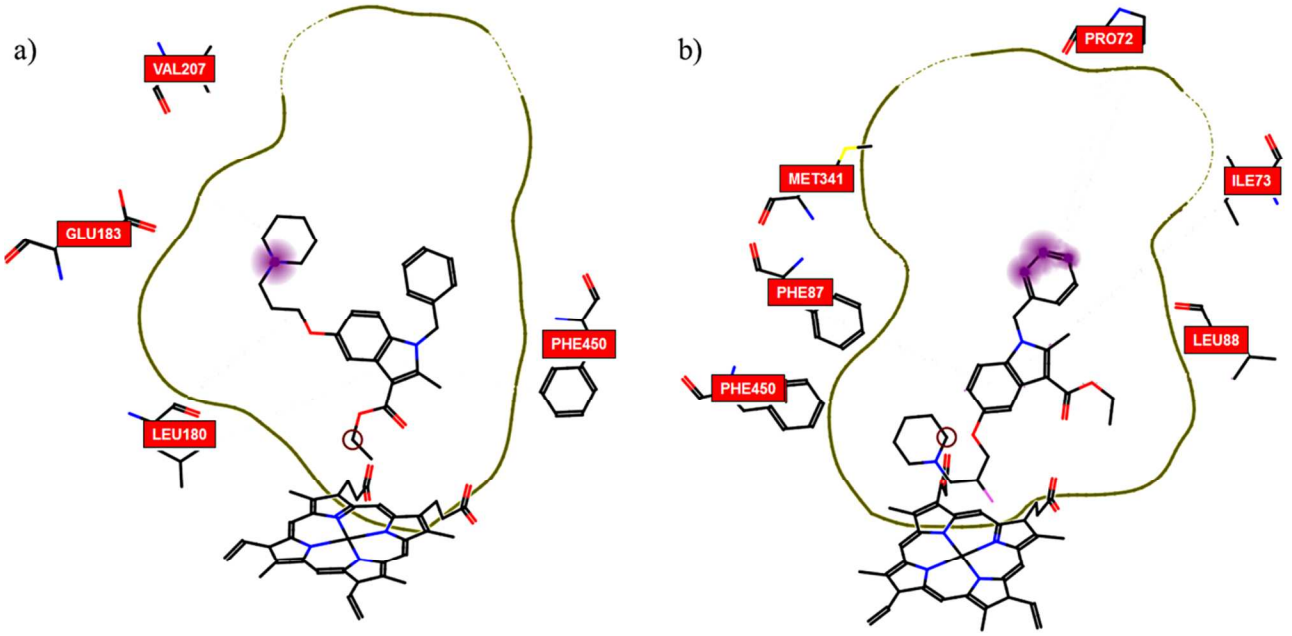


Figure 5. Experimental sites of metabolism for two similar compounds (**25** and **43**, respectively), and the score contribution -violet circles in (a) and (b). The SoM (Sites of Metabolism) are reported with open circles. The CYP amino acids, which contribute the most to the CYP-recognition determining the SoM, are highlighted.

Compound **73**, lacking the ester substituent in C3 position, was highly stable. This suggests that a good balance between activity and metabolic stability can be obtained with a proper decoration at the C3 position.

Ciprofloxacin Synergistic Activity Results

In order to evaluate the effectiveness of NorA efflux pump inhibitors in restoring original antibacterial activity of ciprofloxacin (CPX), further studies were performed on three of the best compounds from Table 5 (IC_{50} lower than 16 μM, Table 2), according to compound availability. Thus, compounds **23**, **29** and **34** were tested in MIC determination of CPX against both SA-1199 (wild type of *S. aureus* strain) and SA-1199B (over-expressing *norA* and carrying an A116E GrlA mutation) as described

elsewhere.[21] As shown in Figure 6, compounds **23**, **29** and **34** had a similar synergistic effect, indeed they all were able to increase CPX activity 4-fold at 3.13 µg/mL and 8-fold at 12.5 µg/mL. The lack of any significant activity of all tested compounds against the parent strain (SA-1199) verifies that the resistance reversal effect seen in SA-1199B is inhibition of NorA-mediated CPX efflux.

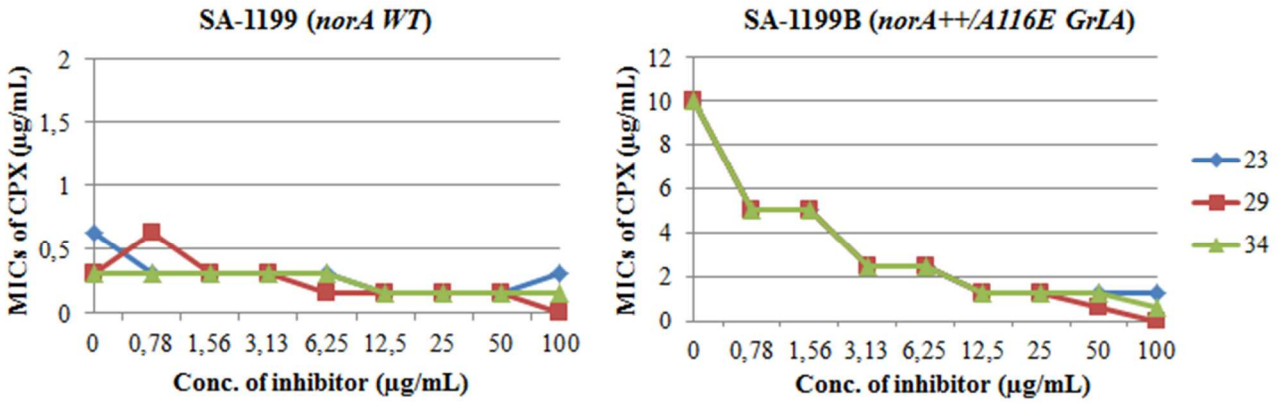


Figure 6. Effect of compounds **23** (A), **29** (B), and **34** (C) on the MIC of ciprofloxacin against *S. aureus* SA-1199 and SA-1199B.

CONCLUSION

Increasing drug resistance among bacteria is a major cause for concern. *S. aureus* is among these problem bacteria and is one of the most studied due to the large number of people with infections caused by it every year. Some *S. aureus* strains also demonstrate multidrug resistance (MDR), translated into inefficacy of "last line" drugs such as vancomycin or linezolid. A major contributing factor to drug and biocide resistance in *S. aureus* is the overexpression of genes encoding the NorA and related efflux pumps. Thus, NorA is an attractive target in medicinal chemistry because a molecule able to inhibit its functions might restore the activities of substrate antibiotics such as fluoroquinolones. To date, no NorA EPI has been approved for clinical use. This study resulted in the identification of a novel class of highly active NorA inhibitors based on the indole scaffold and some necessary requisites

for activity retention have been highlighted. We found that appropriate substitution of the indole C5 position results in a potent EPI; in particular, the presence of a propoxyl chain carrying terminal cyclic amino groups seems essential to permit NorA pump inhibition at low μM concentrations. Moreover, the presence of the *N*-benzyl moiety not only preserves inhibition but also can contribute to modulate the biological effect(s) and ADME properties depending on its substituents. Finally, we presented preliminary CPX synergistic activity assays proving that compounds presented in this work were effective in restoring antibiotic activity in a resistant *S. aureus* strain. Based on the data presented herein, additional novel analogues will be necessary to further investigate the potency of this series. For instance, in order to discern the role of charged or uncharged hydrogen bond donors some analogues with replacement of the terminal amino group in the chain with a non-chargeable group (like an amide), should be investigated.

While the alkoxyl chain is definitely able to ensure high inhibition, further exploration of the C-3 position should be performed to investigate its role with respect to intrinsic antimicrobial activity.

EXPERIMENTAL SECTION

Chemistry

Instrument and materials. Starting materials were purchased from Aldrich-Fluka and Apollo Scientific Ltd. All commercial reagents were used without further purification. Air and moisture sensitive compounds were stored in Schlenk tubes or Schlenk burettes and handled under an inert atmosphere using appropriate glassware. If not specified otherwise, ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded with a Bruker AVANCE III 400 MHz. Chemical shifts (δ) are reported in parts per million (ppm), and peak multiplicity are reported as s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), hept (heptet), m (multiplet), or br s (broad singlet). Solubility was determined by ^{1}H NMR experiments

in D_2O solution at 25 °C using 3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid sodium salt (TSP) as internal standard according to literature procedure.[48] HRMS spectra were registered on Agilent Technologies 6540 UHD Accurate Mass Q-TOF LC/MS, HPLC 1290 Infinity. Purities of the final compounds were ≥98% pure and were determined by UHPLC: column, Phenomenex AERIS Peptide 1.2 mm × 1000 mm (1.7 μm); flow rate, 0.8 mL/min; acquisition time, 20 min; DAD 190-650 nm; oven temperature, 45 °C; gradient of acetonitrile in water containing 0.1% of formic acid (0-100% in 20 minutes).

Ethyl 1-benzyl-2-methyl-5-nitroindole-3-carboxylate (7). 1-benzyl-2-methyl-5-nitroindole-3-carboxylate **17** (400 mg, 1.18 mmol) in thionyl chloride (4 ml) was refluxed 4 h, then volatile materials were evaporated and toluene (10 mL) was added. The mixture were evaporated again. Then absolute ethanol (8 mL) was added and the mixture was made reacted for 12 h. After solvent evaporation under reduced pressure, flash chromatography of the solid residue on Silica Gel gave a white solid exhibiting the following spectroscopic properties: mp 147 – 149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (d, J = 2.3 Hz, 1H), 8.10 (dd, J = 9.0, 2.3 Hz, 1H), 7.35 – 7.27 (m, 4H), 7.04 – 6.89 (m, 2H), 5.42 (s, 2H), 4.47 (q, J = 7.1 Hz, 2H), 2.78 (s, 3H), 1.51 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 148.2, 143.3, 139.1, 135.1, 129.1 (2C), 128.1, 126.1, 125.7 (2C), 118.6, 118.0, 109.5, 106.7, 60.1, 47.0, 14.5, 12.0; HRMS: calcd for $C_{19}H_{18}N_2O_4$ 339.1345 ($M+H^+$), found 339.1347 ($M+H^+$).

Ethyl 1-benzyl-2-methyl-5-(trifluoromethyl)-indole-3-carboxylate (8). Ethyl 2-methyl-5-(trifluoromethyl)-1*H*-indole-3-carboxylate (**18**) (150 mg, 0.55 mmol) was added at r.t. to a suspension of sodium hydride (60% dispersion in mineral oil, washed for 3 times by petroleum ether, 24.0 mg) in DMF. After 40 minutes benzyl bromide (95 mg) were added and the mixture was made to react at r.t. 14 h and then poured into iced water, extracted with chloroform (15 x 3 mL) and washed with warm water (3 x 15 mL). The organic solution was dried with sodium sulfate anhydrous and evaporated under reduced pressure. The solid residue was purified by column chromatography on silica gel (ethyl

acetate-petroleum ether 1:9) to obtain a white solid (196 mg, yield 98%) exhibiting the following spectroscopic properties: mp 115 – 116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 1.8 Hz, 1H), 7.50 – 7.37 (m, 1H), 7.37 – 7.19 (m, 4H), 6.96 (dd, *J* = 7.5, 2.1 Hz, 2H), 5.39 (s, 2H), 4.44 (q, *J* = 7.1 Hz, 2H), 2.76 (s, 3H), 1.47 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 146.8, 137.7, 135.7, 129.1 (2C), 127.94, 126.2, 125,5 (q, *J* = 152.3 Hz), 125.8 (2C), 124.2 (q, ^{2}J = 31.8 Hz), 119.4 (q, *J* = 4.2 Hz), 119.2 (q, *J* = 3.3 Hz), 109.8, 105.6, 59.9, 46.8, 14.5, 12.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ – 61.04 (s, 3F); HRMS: calcd for $C_{20}H_{18}F_3NO_2$ 362.1368 ($M+H^+$), found 362.1376 ($M+H^+$).

Ethyl 1-benzyl-2-methyl-5-phenethoxyindole-3-carboxylate (9).[30] Anhydrous $ZnCl_2$ (10% mol) was added to a stirred suspension of *p*-benzoquinone (1.08 g, 10 mmol) in 30 ml of dry DCM. After having heated at reflux, a solution of crotonamine **19** (2.2 g, 10 mmol) in dry DCM (20 ml) was added in 5 minutes and stirred at reflux for further 45 minutes. The mixture was cooled to r.t. and poured at 4 °C for 3 h to allow the product precipitation. The solid was filtered and washed with DCM and acetone to give a pink solid (2.5 g, yield 81%). NMR spectrum was in accordance to that described in the literature.[30]

Ethyl 5-acetoxy-1-benzyl-2-methyl-1*H*-indole-3-carboxylate (10). Acetic anhydride (0.50 ml, 5.2 mmol) was added to a stirred solution of hydroxyindole **9** (160 mg, 0.52 mmol) in dry pyridine (3 mL) and the mixture was refluxed overnight. The reaction was diluted with water, extracted with DCM (x3) and then washed with HCl 2N and brine. Column chromatography on Silica gel of the crude (eluent PE/EA 9:1) afforded a white solid (yield 55%) which was characterized as follows. mp 110 – 111 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 2.3 Hz, 1H), 7.36-7.27 (m, 3H), 7.22 (d, *J* = 8.7 Hz, 1H), 7.04-6.97 (m, 2H), 6.93 (dd, *J* = 8.7, 2.3 Hz, 2H), 5.34 (s, 2H), 4.43 (q, *J* = 7.1 Hz, 2H), 2.75 (s, 3H), 2.36 (s, 3H), 1.47 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 170.3, 165.8, 146.0, 136.0, 134.2, 129.0 (2C), 127.8, 127.2, 125.9 (2C), 122.2, 116.3, 115.9, 114.0, 110.0, 102.7, 59.6, 46.7, 21.3, 14.7, 12.0; HRMS: calcd for $C_{21}H_{21}NO_4$ 352.1549 ($M+H^+$), found 352.1547 ($M+H^+$).

Ethyl 1-benzyl-2-methyl-5-phenethoxyindole-3-carboxylate (11). A stirred mixture of hydroxyindole **9** (618 mg, 2.00 mmol), 2-phenylethylbromide (1.73 g, 1.23 mL, 9.00 mmol), K_2CO_3 (1.3 g, 9.5 mmol) in DMF (1.5 mL) was heated at the reflux temperature for 48 h. In the meantime three portions of both 2-phenylethylbromide (0.20 g each portion) and K_2CO_3 (150 mg, each portion) were further added. The volatile materials were evaporated at reduced pressure, the residue was taken up in ethyl acetate and washed with water. After the solvent evaporation chromatography of the crude product on silica gel (15:85 ethyl acetate-petroleum ether) afforded 0.55 g (66%) of a white solid, having the following properties: mp 102 – 103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 2.5 Hz, 1H), 7.31 (d, *J* = 4.4 Hz, 4H), 7.28 – 7.18 (m, 4H), 7.08 (d, *J* = 8.8 Hz, 1H), 6.94 (ddd, *J* = 7.1, 2.2, 0.8 Hz, 2H), 6.81 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.27 (s, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 4.26 (t, *J* = 7.1 Hz, 2H), 3.13 (t, *J* = 7.1 Hz, 2H), 2.68 (s, 3H), 1.43 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 154.9, 145.2, 138.6, 136.4, 131.5, 129.1 (2C), 129.0 (2C), 128.5 (2C), 127.7, 127.6, 126.4, 125.9 (2C), 112.5, 110.3, 104.9, 104.3, 69.3, 59.5, 46.6, 36.0, 14.7, 12.1; HRMS: calcd for $C_{27}H_{27}NO_3$ 414.2069 ($M+H^+$), found 414.2067 ($M+H^+$).

Ethyl 1-benzyl-5-(2-(dimethylamino)ethoxy)-2-methyl-1*H*-indole-3-carboxylate (12). A mixture of hydroxyindole **9** (0.500 g, 1.62 mmol), 2-chloro-*N,N*-dimethylethanamine hydrochloride (0.256 g, 1.78 mmol), and K_2CO_3 (0.600 g, 4.3 mmol) in ethanol (8 mL) and toluene (5 mL) was refluxed for 48 h. After being cooled at r.t., the mixture was diluted with EA and washed with water. Concentration and chromatography on SiO_2 (eluent EA and then EA/MeOH/Et_3N 7:2:1) gave the expected product as a pale yellow solid (0.321 g, 52% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 2.5 Hz, 1H), 7.34 – 7.20 (m, 3H), 7.12 (d, *J* = 8.9 Hz, 1H), 7.01 – 6.93 (m, 2H), 6.86 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.32 (s, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.18 (t, *J* = 5.7 Hz, 2H), 2.81 (t, *J* = 5.7 Hz, 2H), 2.70 (s, 3H), 2.39 (s, 6H), 1.45 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 154.8, 145.1, 136.3, 131.4, 128.8 (2C),

127.6, 127.4, 125.8 (2C), 112.5, 110.1, 104.7, 104.3, 66.2, 59.3, 58.3, 46.6, 45.7 (2C), 14.6, 12.0; HRMS: calcd. for $C_{23}H_{28}N_2O_3$ 381.2178 ($M+H^+$), found 381.2175 ($M+H^+$).

Ethyl 1-benzyl-5-(2-hydroxypropoxy)-2-methylindole-3-carboxylate (13). Hydroxyindole **9** (600 mg, 1.94 mmol, 1.0 eq) was added to a suspension of NaH (60% dispersion in mineral oil, 86 mg, 2.13 mmol, 1.2 eq) in DMF (6 mL) under nitrogen atmosphere while stirring After hydrogen evolution ceased, 1-butene oxide (153 mg, 2.13 mmol, 1.2 eq). was added and the mixture was made to react 12 h at 25 °C while stirring before it was heated at 100 °C and kept 24 h at this temperature. After cooling, the mixture was diluted with diethyl ether and the resulting organic solution was washed with brine. After the solvent evaporation, chromatography of the residue on silica gel (eluent, 20:80 ethyl acetate-petroleum ether mixture) allowed to recover the pure product (250 mg, 70% yield) as a white solid. Mp 90-93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 2.5 Hz, 1H), 7.33 – 7.20 (m, 3H), 7.11 (d, J = 10.8 Hz, 1H), 7.01 – 6.90 (m, 2H), 6.83 (dd, J = 8.8, 2.5 Hz, 1H), 5.30 (s, 2H), 4.41 (q, J = 7.1 Hz, 2H), 4.18 – 3.78 (m, 3H), 2.69 (s, 3H), 2.50 – 2.34 (m, 1H), 1.64 (p, J = 7.3 Hz, 2H), 1.45 (t, J = 7.1 Hz, 3H), 1.04 (t, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 154.8, 145.3, 136.3, 131.6, 129.0 (2C), 127.7, 127.6, 125.9 (2C), 112.4, 110.3, 105.0, 104.4, 72.6, 71.6, 59.5, 46.7, 26.2, 14.7, 12.1, 10.0; GCMS (ESI) *m/z*: 381 (M^+); HRMS: calcd for $C_{23}H_{27}NO_4$ 382.2018 ($M+H^+$), found 382.2022 ($M+H^+$).

2-Methyl-5-nitro-1*H*-indole (14).[50] To an ice-cold solution of 2-methyl-1*H*-indole (4 g, 0.03 mol) in sulfuric acid (25 mL) was added, dropwise, a solution of $NaNO_3$ (2.7 g) in sulfuric acid (25 mL). After the addition was completed, the reaction mixture was poured in ice and the obtained yellow solid was filtered off, washed with water, and then let air-dry (4.8 g, yield 90%). Mp. 174-176 °C; ^{1}H NMR δ (200 MHz, $CDCl_3$) 8.48 (d, J = 2.0 Hz, 1H), 8.41 (bs, 1H), 8.04– 8.01 (d, J = Hz, 1H), 7.36 – 7.26 (m, 1H), 6.42 – 6.39 (m, 1H), 2.51 (s, 3H).

1-Benzyl-2-methyl-5-nitroindole (15). The 5-nitroindole **14** (1.00 g, 5.68 mmol, 1.0 eq) was added to a stirred suspension of NaH (60% dispersion in mineral oil, 0.25 g, 6.2 mmol, 1.1 eq) in DMF (2 mL)

under a nitrogen atmosphere. After 40 minutes benzyl bromide (0.7 mL, 6.2 mmol, 1.1 eq) was added dropwise and the mixture was allowed to react overnight. The mixture was poured in water and the resulting precipitated was filtered off, washed with water and dried. The white solid (1.4 g, 92%) was characterized as follows. Mp. 157-159 °C; ^{1}H NMR (400 MHz, methanol-d_4) δ 8.49 (d, J = 2.2 Hz, 1H), 8.01 (dd, J = 9.0, 2.2 Hz, 1H), 7.35 – 7.25 (m, 3H), 7.20 (d, J = 9.1 Hz, 1H), 6.96 (d, J = 7.5 Hz, 2H), 6.51 (s, 1H), 5.35 (s, 2H), 2.41 (d, J = 1.1 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 141.6, 140.4, 140.0, 136.5, 129.0 (2C), 127.7, 127.3, 125.8 (2C), 116.8, 116.6, 108.9, 102.9, 46.9, 12.9; HRMS: calcd for $C_{16}H_{14}N_2O_2$ 267.1134 ($M+H^+$), found 267.1132 ($M+H^+$).

1-Benzyl-2-methyl-5-nitro-3-(trifluoroacethyl)indole (16).[28] Trifluoroacetic anhydride (1.05 mL) was added drop-wise to a solution of 1-benzyl-2-methyl-5-nitroindole (**15**) (1.00 g, 3.76 mmol) in DMF (10 mL) and the reaction mixture was made react for 22 h at 25 °C before the solvent was evaporated. The crude product was re-crystallized from diethyl ether to obtain a light pink solid (1.3 g, yield 96%) exhibiting the following spectroscopic characteristics. Mp 170 – 174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (d, J = 2.1 Hz, 1H), 8.17 (dd, J = 9.1, 2.2 Hz, 1H), 7.40 (d, J = 9.1 Hz, 1H), 7.34 (dd, J = 6.2, 1.5 Hz, 3H), 7.04 – 6.95 (m, 2H), 5.49 (s, 2H), 2.80 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5 (q, J = 36.9 Hz), 152.6, 144.3, 139.4, 134.0, 129.4 (2C), 128.5, 125.7 (2C), 124.8, 119.0, 117.8 (q, J = 4.3 Hz), 116.6 (q, J = 289.4 Hz), 110.4, 109.5, 47.4, 13.3; ^{19}F NMR (376 MHz,) δ – 74.73 (s, 3F).

1-Benzyl-2-methyl-5-nitroindole-3-carboxylate (17). 1-Benzyl-2-methyl-5-nitro-3-(trifluoroacethyl)indole **16** (1.30 g, 3.51 mmol) was added to a NaOH solution (20% in water, 20 mL) and the mixture was made to react at 60 °C for 48 h. The resulting suspension was filtered off and washed with 5 N NaOH and water. After acidification of the *aqueous* solution by hydrochloric acid, a yellow solid was collected, washed with water and dried (520 mg, yield 48%). Mp 258-260 °C; ^{1}H NMR (400 MHz, DMSO-*d*6) δ 12.63 (s, 1H), 8.90 (d, J = 2.4 Hz, 1H), 8.05 (dd, J = 9.1, 2.4 Hz, 1H),

7.74 (d, *J* = 9.1 Hz, 1H), 7.45 – 7.12 (m, 3H), 7.15 – 6.79 (m, 2H), 5.62 (s, 2H), 2.71 (s, 3H); ^{13}C NMR (101 MHz, DMSO-*d*6) δ 166.1, 149.2, 142.8, 139.6, 136.9, 129.3 (2C), 128.0, 126.6 (2C), 126.4, 117.8, 117.5, 111.5, 106.4, 46.8, 12.3; HRMS: calcd for $C_{17}H_{14}N_2O_4$ 311.1032 ($M+H^+$), found 311.1036 ($M+H^+$).

Ethyl 2-methyl-5-(trifluoromethyl)-1*H*-indole-3-carboxylate (18). Ethyl acetoacetate (650 mg, 5.10 mmol) was added dropwise at r.t. to a suspension of sodium hydride (60% dispersion in mineral oil, washed for 3 times by petroleum ether, 270 mg) in DMF (3 mL). Copper iodide (969 mg, 5.10 mmol) was added in one portion while stirring and, after 10 minute, aniline (1.0 g, 3.38 mmol) was successively added. The mixture was made to react for 14 h at 130 °C before it was poured into iced water, extracted with chloroform, washed with warm water. The organic solution was dried with sodium sulfate. After solvent evaporation under reduced pressure, the solid residue was purified by column chromatography on silica gel (diethyl ether-petroleum ether 75:25) to obtain a dark oil (150 mg, yield 16%) exhibiting the following spectroscopic properties. ^{1}H NMR δ (200 MHz, $CDCl_3$) 8.43 (bs, 1H), 8.41 (s, 1H), 7.45 – 7.33 (m, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 2.79 (s, 3H), 1.47 (t, *J* = 7.1 Hz, 3H); HRMS: calcd for $C_{13}H_{12}F_3NO_2$ 272.0898 ($M+H^+$), found 272.0900.

Ethyl 3-(benzylamino)but-2-enoate (19). Ethyl acetoacetate (10.0 g, 0.077 mol), *N*-benzylamine (8.23 g, 0.077 mol), and *p*-toluenesufonic acid monohydrated (0.366 g, 1.9 mmol) were refluxed in toluene for 2 h in a Dean-Stark apparatus. The solvent was evaporated and the residue taken-up with diethyl ether, washed with saturated aqueous $NaHCO_3$ and concentred to afford the titled compound as a yellow oil (16.75 g, yield 99%). ^{1}H NMR (101 MHz, $CDCl_3$) δ 8.88 (bs, 1H), 7.37 – 7.20 (m, 5H), 4.54 (s, 1H), 4.41 (d, *J* = 6.3 Hz, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 1.90 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H).

Ethyl 1-benzyl-5-(2-bromoethoxy)-2-methylindole-3-carboxylate (20a).[31] 1,2-dibromoethane (2.50 mL, 29.1 mmol) was added to a stirred mixture of 5-hydroxyindole **9** (3.0 g, 9.7 mmol) and K_2CO_3 (1.3 g, 9.7 mmol) in ethanol (16 mL) and the reaction was refluxed overnight. The cooled mixture was

diluted with water and extracted with ethyl acetate. The organic solution was dried with sodium sulfate anhydrous and evaporated under reduced pressure. The solid residue was purified by column chromatography on Silica gel (dichloromethane) to obtain 1.5 g (yield 37%) of a white solid exhibiting the following spectroscopic properties: mp 148 – 150 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.33 – 7.23 (m, 3H), 7.11 (dd, *J* = 8.8, 1.0 Hz, 1H), 6.9 – 6.8 (m, 2H), 6.83 (dd, *J* = 8.9, 2.5 Hz, 1H), 5.30 (s, 2H), 4.41 – 4.33 (m, 4H), 3.65 (t, *J* = 6.3 Hz, 2H), 2.68 (s, 3H), 1.41 (t, *J* = 9.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 154.0, 145.4, 136.2, 131.8, 128.9 (2C), 127.6, 127.5, 125.8 (2C), 112.7, 110.3, 105.4, 104.4, 68.7, 59.4, 46.6, 29.5, 14.6, 12.0; HRMS: calcd for $C_{21}H_{22}{}^{79}BrNO_3$ 417.3162 ($M+H^+$), found 417.3161 ($M+H^+$).

Ethyl 1-benzyl-5-(3-chloropropoxy)-2-methylindole-3-carboxylate (20b). According to the procedure described for bromo **20a**, but using 1,3-chlorobromopropane instead, it was obtained 2.3 g (yield 56%) of a white solid exhibiting the following spectroscopic properties: mp 95 – 97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 2.5 Hz, 1H), 7.37 – 7.22 (m, 3H), 7.12 (d, *J* = 8.8 Hz, 1H), 7.04 – 6.90 (m, 2H), 6.82 (dd, *J* = 8.9, 2.5 Hz, 1H), 5.32 (s, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 4.19 (t, *J* = 5.8 Hz, 2H), 3.64 (t, *J* = 6.5 Hz, 2H), 2.71 (s, 3H), 2.35 (p, *J* = 6.2 Hz, 2H), 1.47 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 154.7, 145.2, 136.3, 131.5, 128.9 (2C), 127.6, 127.5, 125.8 (2C), 112.3, 110.2, 104.9, 104.3, 65.9, 59.4, 46.6, 32.6, 30.2, 14.6, 12.0; HRMS: calcd for $C_{22}H_{24}{}^{35}ClNO_3$ 385.1445 ($M+H^+$), found 385.1445 ($M+H^+$).

Ethyl 1-benzyl-5-(4-chlorobutoxy)-2-methylindole-3-carboxylate (20c). According to the procedure described for bromo **20a**, but using 1,4-chlorobromopropane instead, it was obtained 2.1 g (yield 81%) of a white solid exhibiting the following spectroscopic properties: mp 97 – 98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 2.5 Hz, 1H), 7.35 – 7.23 (m, 3H), 7.14 (d, *J* = 8.8 Hz, 1H), 7.04 – 6.96 (m, 2H), 6.83 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.34 (s, 2H), 4.44 (q, *J* = 7.1 Hz, 2H), 4.11 (t, *J* = 5.7 Hz, 2H), 3.66 (t, *J* = 6.2 Hz, 2H), 2.73 (s, 3H), 2.13 – 1.93 (m, 4H), 1.48 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$)

δ 166.2, 155.0, 145.3, 136.5, 131.5, 129.0 (2C), 127.7, 127.7, 126.0 (2C), 112.5, 110.3, 104.7, 104.4, 67.6, 59.5, 46.7, 45.0, 29.6, 27.0, 14.8, 12.2; HRMS: calcd for $C_{23}H_{26}{}^{35}ClNO_3$ 400.1679 ($M+H^+$), found 400.1681 ($M+H^+$).

Ethyl 1-(2-methylbenzyl)-5-(3-chloropropoxy)-2-methylindole-3-carboxylate (20d). According to the procedure described for bromo **20a**, but using 1,3-chlorobromopropane and hydroxyindole **49a** instead, the titled product was obtained as brown solid (170 mg, yield 92%). Mp 88 – 89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 2.5 Hz, 1H), 7.22 (d, *J* = 7.7 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 8.9 Hz, 1H), 6.98 (t, *J* = 7.9 Hz, 1H), 6.80 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.22 (d, *J* = 8.0 Hz, 1H), 5.25 (s, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 4.20 (t, *J* = 5.8 Hz, 2H), 3.78 (t, *J* = 6.4 Hz, 2H), 2.66 (s, 3H), 2.44 (s, 3H), 2.27 (p, *J* = 6.1 Hz, 2H), 1.47 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 154.9, 145.5, 134.5, 134.3, 131.6, 130.4, 127.7, 127.5, 126.8, 124.8, 112.5, 110.3, 105.0, 104.5, 65.0, 59.6, 44.7, 41.9, 32.6, 19.3, 14.8, 12.0. HRMS: calcd. for $C_{23}H_{26}NO_3$ 400.1679 ($M+H^+$), found 400.1674 ($M+H^+$).

Ethyl 1-(3-methylbenzyl)-5-(3-chloropropoxy)-2-methylindole-3-carboxylate (20e). The titled product was obtained from indole **49b** according to the procedure for intermediate **20b** as a white solid (239 mg, yield 97%). Mp 78 – 80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 2.5 Hz, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 8.9 Hz, 1H), 7.05 (d, *J* = 7.6 Hz, 1H), 6.85 – 6.79 (m, 2H), 6.75 (d, *J* = 7.6 Hz, 1H), 5.28 (s, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.20 (t, *J* = 5.8 Hz, 2H), 3.78 (t, *J* = 6.4 Hz, 2H), 2.71 (s, 3H), 2.28 (s, 3H), 2.27 (p, *J* = 6.3 Hz, 2H), 1.46 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 154.9, 145.5, 138.9, 136.4, 131.7, 129.0, 128.6, 127.7, 126.6, 123.1, 112.4, 110.4, 105.0, 104.4, 65.1, 59.6, 46.8, 41.9, 32.6, 21.6, 14.8, 12.3; HRMS: calcd. for $C_{23}H_{26}{}^{35}ClNO_3$ 400.1679 ($M+H^+$), found 400.1686 ($M+H^+$).

Ethyl 1-(4-methylbenzyl)-5-(3-chloropropoxy)-2-methylindole-3-carboxylate (20f). The titled product was obtained from indole **49c** according to the procedure for intermediate **20b** as a white solid

(243 mg, yield 98%). Mp 115 – 116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 2.5 Hz, 1H), 7.09 (dd, *J* = 16.1, 8.3 Hz, 3H), 6.85 (d, *J* = 7.9 Hz, 2H), 6.81 (dd, *J* = 8.9, 2.5 Hz, 1H), 5.27 (s, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.19 (t, *J* = 5.8 Hz, 2H), 3.77 (t, *J* = 6.4 Hz, 2H), 2.70 (s, 3H), 2.29 (s, 3H), 2.25 (p, *J* = 6.2 Hz, 2H), 1.46 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 154.8, 145.4, 137.5, 133.4, 131.7, 129.7 (2C), 127.7, 126.0 (2C), 112.4, 110.4, 105.0, 104.4, 65.1, 59.6, 46.6, 41.9, 32.6, 21.2, 14.8, 12.2; HRMS: calcd. for $C_{23}H_{26}{}^{35}ClNO_3$ 400.1679 ($M+H^+$), found 400.1683 ($M+H^+$).

Ethyl 1-(2-methoxybenzyl)-5-(3-chloropropoxy)-2-methylindole-3-carboxylate (20g). The titled product was obtained from indole **49d** according to the procedure for intermediate **20b** as a white solid (196 mg, yield 80%). Mp 104 – 105 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 2.5 Hz, 1H), 7.25 – 7.18 (m, 1H), 7.09 (d, *J* = 8.9 Hz, 1H), 6.91 (dd, *J* = 8.3, 1.0 Hz, 1H), 6.79 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.73 (td, *J* = 7.5, 1.0 Hz, 1H), 6.30 (dd, *J* = 7.5, 1.6 Hz, 1H), 5.30 (s, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 4.20 (t, *J* = 5.8 Hz, 2H), 3.92 (s, 3H), 3.78 (t, *J* = 6.4 Hz, 2H), 2.68 (s, 3H), 2.27 (p, *J* = 6.2 Hz, 2H), 1.46 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 156.3, 154.7, 145.7, 131.6, 128.5, 127.5, 126.2, 124.4, 120.8, 112.2, 110.4, 109.9, 104.8, 104.1, 64.9, 59.4, 55.3, 42.0, 41.8, 32.5, 14.7, 11.9; HRMS: calcd. for $C_{23}H_{26}{}^{35}ClNO_4$ 416.1629 ($M+H^+$), found 416.1628 ($M+H^+$).

Ethyl 1-(3-methoxybenzyl)-5-(3-chloropropoxy)-2-methylindole-3-carboxylate (20h). The titled product was obtained from indole **49e** according to the procedure for intermediate **20b** as a white solid (240 mg, yield 98%). Mp 65 – 66 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 2.5 Hz, 1H), 7.17 (t, *J* = 8.1 Hz, 1H), 7.10 (d, *J* = 8.8 Hz, 1H), 6.80 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.76 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.56 – 6.46 (m, 2H), 5.25 (s, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.18 (t, *J* = 5.8 Hz, 2H), 3.77 (t, *J* = 6.4 Hz, 2H), 3.70 (s, 3H), 2.69 (s, 3H), 2.26 (p, *J* = 6.3 Hz, 2H), 1.45 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 160.2, 154.8, 145.3, 138.1, 131.6, 130.1, 127.7, 118.2, 112.6, 112.4, 112.1, 110.3, 105.0, 104.4, 65.0, 59.5, 55.3, 46.6, 41.9, 32.6, 14.7, 12.2; HRMS: calcd. for $C_{23}H_{26}{}^{35}ClNO_4$ 416.1629 ($M+H^+$), found 416.1623 ($M+H^+$).

Ethyl 1-(4-methoxybenzyl)-5-(3-chloropropoxy)-2-methylindole-3-carboxylate (20i). The titled product was obtained from indole **49f** according to the procedure for intermediate **20b** as a white solid (242 mg, yield 98%). Mp 105 – 106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 2.5 Hz, 1H), 7.13 (d, *J* = 8.8 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 2H), 6.85 – 6.76 (m, 3H), 5.26 (s, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.19 (t, *J* = 5.8 Hz, 2H), 3.78 (t, *J* = 6.6 Hz, 2H), 3.75 (s, 3H), 2.71 (s, 3H), 2.27 (p, *J* = 6.2 Hz, 2H), 1.46 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 159.0, 154.7, 145.2, 131.5, 128.3, 127.6, 127.2 (2C), 114.3 (2C), 112.3, 110.3, 104.9, 104.3, 64.9, 59.4, 55.3, 46.2, 41.8, 32.5, 14.7, 12.1; HRMS: calcd. for $C_{23}H_{26}{}^{35}ClNO_4$ 416.1629 ($M+H^+$), found 416.1628 ($M+H^+$).

Ethyl 1-(2-fluorobenzyl)-5-(3-chloropropoxy)-2-methylindole-3-carboxylate (20j). The titled product was obtained from indole **49g** according to the procedure for intermediate **20b** as a yellow solid (163 mg, yield 88%). Mp 94 – 95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 2.5 Hz, 1H), 7.25 – 7.20 (m, 1H), 7.16 – 7.06 (m, 2H), 6.99 – 6.90 (m, 1H), 6.83 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.54 – 6.43 (m, 1H), 5.37 (s, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 4.20 (t, *J* = 5.8 Hz, 2H), 3.78 (t, *J* = 6.4 Hz, 2H), 2.71 (s, 3H), 2.27 (p, *J* = 6.1 Hz, 2H), 1.46 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 160.0 (d, *J* = 245.9 Hz), 155.0, 145.3, 131.5, 129.5 (d, *J* = 8.0 Hz), 127.7, 127.5 (d, *J* = 3.8 Hz), 124.8 (d, *J* = 3.6 Hz), 123.6 (d, *J* = 14.3 Hz), 115.5 (d, *J* = 20.8 Hz), 112.6, 110.2, 105.1, 104.7, 65.1, 59.6, 41.9, 40.7, 32.6, 14.8, 12.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -118.43 – -118.61 (m); HRMS: calcd. for $C_{22}H_{23}{}^{35}ClFNO_3$ 404.1429 ($M+H^+$), found 404.1429 ($M+H^+$).

Ethyl 1-(3-fluorobenzyl)-5-(3-chloropropoxy)-2-methylindole-3-carboxylate (20k). The titled product was obtained from indole **49h** according to the procedure for intermediate **20b** as a brown solid (264 mg, yield 99%). Mp 104 – 105 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 2.5 Hz, 1H), 7.34 – 7.23 (m, 1H), 7.11 (d, *J* = 8.9 Hz, 1H), 6.97 (td, *J* = 8.4, 2.6 Hz, 1H), 6.85 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.77 (d, *J* = 7.9 Hz, 1H), 6.68 (d, *J* = 9.6 Hz, 1H), 5.34 (s, 2H), 4.44 (q, *J* = 7.1 Hz, 2H), 4.22 (t, *J* = 5.8 Hz, 2H), 3.80 (t, *J* = 6.4 Hz, 2H), 2.73 (s, 3H), 2.30 (p, *J* = 6.2 Hz, 2H), 1.49 (t, *J* = 7.1 Hz, 3H); ^{13}C

NMR (101 MHz, $CDCl_3$) δ 166.2, 164.6, 155.0, 145.1, 139.1 (d, *J* = 7.0 Hz), 131.5, 130.7 (d, *J* = 8.3 Hz), 127.7, 121.6 (d, *J* = 3.0 Hz), 114.8 (d, *J* = 21.2 Hz), 113.1 (d, *J* = 22.3 Hz), 112.6, 110.2, 105.1, 104.8, 65.1, 59.7, 46.3, 41.9, 32.6, 14.8, 12.2; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -111.92 (td, *J* = 9.0, 5.7 Hz); HRMS: calcd. for $C_{22}H_{23}{}^{35}ClFNO_3$ 404.1429 ($M+H^+$), found 404.1428 ($M+H^+$).

Ethyl 1-(4-fluorobenzyl)-5-(3-chloropropoxy)-2-methylindole-3-carboxylate (20l). The titled product was obtained from indole **49i** according to the procedure for intermediate **20b** as a brown solid (239 mg, yield 95%). Mp 110 – 111 °C;^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 2.2 Hz, 1H), 7.14 – 7.05 (m, 1H), 7.02 – 6.90 (m, 4H), 6.82 (dt, *J* = 8.7, 2.2 Hz, 1H), 5.29 (s, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.20 (t, *J* = 6.0 Hz, 2H), 3.78 (t, *J* = 6.0 Hz, 2H), 2.70 (s, 3H), 2.27 (p, *J* = 6.9 Hz, 2H), 1.46 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 162.2 (d, *J* = 246.4 Hz), 154.8, 145.0, 132.1 (d, *J* = 3.2 Hz), 131.4, 127.8, 127.5 (d, *J* = 8.1 Hz, 2C), 115.9 (d, *J* = 21.7 Hz, 2C), 112.5, 110.1, 105.0, 104.5, 64.9, 59.5, 46.0, 41.7, 32.5, 14.7, 12.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.51 – -114.65 (m); HRMS: calcd. for $C_{22}H_{23}{}^{35}ClFNO_3$ 404.1429 ($M+H^+$), found 404.1426 ($M+H^+$).

Ethyl 1-(3-trifluoromethylbenzyl)-5-(3-chloropropoxy)-2-methylindole-3-carboxylate (20m). The titled product was obtained from indole **49j** according to the procedure for intermediate **20b** as a brown solid (195 mg, yield 81%). Mp 127 – 128 °C;^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 2.5 Hz, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.43 – 7.33 (m, 2H), 7.07 (dd, *J* = 8.9, 0.5 Hz, 1H), 6.98 (d, *J* = 8.1 Hz, 1H), 6.83 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.37 (s, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 4.20 (t, *J* = 5.8 Hz, 2H), 3.78 (t, *J* = 6.4 Hz, 2H), 2.70 (s, 3H), 2.27 (p, *J* = 6.1 Hz, 2H), 1.47 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 155.0, 145.0, 137.6, 131.49 (q, *J* = 32.7 Hz), 131.4, 129.8, 129.2, 127.8, 124.8 (q, *J* = 3.7 Hz), 124.7 (q, *J* = 271.7 Hz), 122.92 (q, *J* = 3.8 Hz), 112.7, 110.1, 105.2, 104.9, 65.1, 59.7, 46.4, 41.9, 32.6, 14.8, 12.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.67; HRMS: calcd. for $C_{23}H_{23}{}^{35}ClF_3NO_3$ 454.1397 ($M+H^+$), found 454.1392 ($M+H^+$).

Ethyl 1-(4-trifluoromethylbenzyl)-5-(3-chloropropoxy)-2-methylindole-3-carboxylate (20n). The titled product was obtained from indole **49k** according to the procedure for intermediate **20b** as a orange solid (323 mg, yield 88%). Mp 97 – 98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 2.5 Hz, 1H), 7.54 (d, *J* = 8.1 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 3H), 6.83 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.38 (s, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 4.20 (t, *J* = 5.8 Hz, 2H), 3.78 (t, *J* = 6.4 Hz, 2H), 2.70 (s, 3H), 2.27 (p, *J* = 6.1 Hz, 2H), 1.47 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 155.1, 145.0, 140.6, 131.4, 130.2 (q, *J* = 33.2 Hz), 127.8, 126.3 (2C), 126.1 (q, *J* = 3.8 Hz, 2C), 123.93 (q, *J* = 272.1 Hz), 112.7, 110.1, 105.2, 104.9, 65.1, 59.7, 46.4, 41.9, 32.6, 14.8, 12.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.65; HRMS: calcd. for $C_{23}H_{23}{}^{35}ClF_3NO_3$ 454.1397 ($M+H^+$), found 454.1395 ($M+H^+$).

Ethyl 1-(2-nitrobenzyl)-5-(3-chloropropoxy)-2-methylindole-3-carboxylate (20o). The titled product was obtained from indole **49l** according to the procedure for intermediate **20b** as a yellow solid (205 mg, yield 85%). Mp 117 – 118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.74 (d, *J* = 2.5 Hz, 1H), 7.50 – 7.37 (m, 2H), 7.01 (d, *J* = 8.9 Hz, 1H), 6.82 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.31 (d, *J* = 8.1 Hz, 1H), 5.74 (s, 2H), 4.44 (q, *J* = 7.1 Hz, 2H), 4.20 (t, *J* = 5.8 Hz, 2H), 3.78 (t, *J* = 6.4 Hz, 2H), 2.66 (s, 2H), 2.27 (p, *J* = 6.1 Hz, 2H), 1.48 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 155.2, 147.1, 145.1, 134.8, 132.9, 131.3, 128.8, 127.8, 127.4, 125.7, 112.9, 110.1, 105.2, 100.1, 65.0, 59.8, 44.7, 41.9, 32.6, 14.8, 12.0; HRMS: calcd. for $C_{22}H_{23}{}^{35}ClN_2O_5$ 431.1374 ($M+H^+$), found 431.1371 ($M+H^+$).

Ethyl 1-(3-nitrobenzyl)-5-(3-chloropropoxy)-2-methylindole-3-carboxylate (20p). The titled product was obtained from indole **49m** according to the procedure for intermediate **20b** as a orange solid (304 mg, yield 83%). Mp 118 – 119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.98 (t, *J* = 1.9 Hz, 1H), 7.72 (d, *J* = 2.5 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 1H), 7.14 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.06 (dd, *J* = 8.9, 0.5 Hz, 1H), 6.83 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.42 (s, 2H), 4.43 (q, *J* = 7.1 Hz, 2H), 4.20 (t, *J* = 5.8 Hz, 2H), 3.78 (t, *J* = 6.4 Hz, 2H), 2.72 (s, 3H), 2.27 (p, *J* = 6.1 Hz, 2H), 1.47 (t, *J* =

7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 155.1, 148.8, 144.7, 138.8, 131.9, 131.2, 130.3, 127.8, 123.0, 121.2, 112.9, 109.9, 105.3, 105.2, 65.1, 59.8, 46.1, 41.8, 32.6, 14.8, 12.2; HRMS: calcd. for $C_{22}H_{23}{}^{35}ClN_2O_5$ 431.1374 ($M+H^+$), found 431.1378 ($M+H^+$).

Ethyl 1-(4-nitrobenzyl)-5-(3-chloropropoxy)-2-methylindole-3-carboxylate (20q). The titled product was obtained from indole **49n** according to the procedure for intermediate **20b** as a white solid (304 mg, yield 83%). Mp 161 – 162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.7 Hz, 2H), 7.72 (d, *J* = 2.5 Hz, 1H), 7.10 (d, *J* = 7.7 Hz, 2H), 7.03 (d, *J* = 8.8 Hz, 1H), 6.83 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.41 (s, 2H), 4.43 (q, *J* = 7.1 Hz, 2H), 4.20 (t, *J* = 5.8 Hz, 2H), 3.78 (t, *J* = 6.4 Hz, 2H), 2.69 (s, 3H), 2.27 (p, *J* = 6.1 Hz, 2H), 1.47 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 155.2, 147.7, 144.7, 143.8, 131.2, 127.8, 126.8 (2C), 124.4 (2C), 112.9, 109.9, 105.3, 105.2, 65.1, 59.8, 46.3, 41.8, 32.6, 14.8, 12.1; HRMS: calcd. for $C_{22}H_{23}{}^{35}ClN_2O_5$ 431.1374 ($M+H^+$), found 431.1377 ($M+H^+$).

General procedure for amines 21-31 and 50-63.[31]

A mixture of suitable halo intermediate **20** (0.7 mmol) and NaI (210.0 mg, 1.4 mmol) in CH_3CN (3 mL) was heated to reflux for 30 min and then cooled to r.t. The desired amine (2.1 mmol) and anhydrous K_2CO_3 (387 mg, 2.81 mmol) were added and the mixture was heated for 1 h, following by *tlc* (ethyl acetate/petroleum ether, 3:7 mixture) the disappearance of starting material. The cooled mixture was diluted with water and extracted with ethyl acetate three times. The reunited organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with dichloromethane/methanol 9:1 plus 1% triethylamine.

.**Ethyl 1-benzyl-2-methyl-5-(2-(piperidin-1-yl)ethoxy)-1*H*-indole-3-carboxylate (21).** According to the general procedure described above, from bromo derivative **20a** (100 mg, 0.24 mmol) and piperidine (61 mg, 0.72 mmol) the titled compound was obtained as a white solid (97 mg, yield 96%). Mp 99 –

100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 2.5 Hz, 1H), 7.23 – 7.10 (m, 3H), 7.01 (d, *J* = 8.9 Hz, 1H), 6.90 – 6.83 (m, 2H), 6.73 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.22 (s, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 4.09 (t, *J* = 6.1 Hz, 2H), 2.72 (t, *J* = 6.1 Hz, 2H), 2.60 (s, 3H), 2.43 (m, 4H), 1.52 (p, *J* = 5.6 Hz, 4H), 1.35 (t, *J* = 7.1 Hz, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 154.9, 145.2, 136.4, 131.4, 128.9 (2C), 127.6, 127.5, 125.9 (2C), 112.5, 110.2, 104.9, 104.4, 66.5, 59.4, 58.2, 55.0 (2C), 46.6, 26.0 (2C), 24.3, 14.7, 12.1; HRMS: calcd for $C_{26}H_{32}N_2O_3$ 421.2491 ($M+H^+$), found 421.2488 ($M+H^+$).

Ethyl 1-benzyl-2-methyl-5-(2-morpholinoethoxy)-1*H*-indole-3-carboxylate (22). According to the general procedure described above, from bromo derivative **20a** (100 mg, 0.24 mmol) and morpholine (63 mg, 0.72 mmol) the titled compound was obtained as a white solid (106 mg, yield 99%). Mp 103 – 104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 2.5 Hz, 1H), 7.24 – 7.13 (m, 3H), 7.03 (d, *J* = 8.8 Hz, 1H), 6.92 – 6.85 (m, 2H), 6.75 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.24 (s, 2H), 4.33 (q, *J* = 7.1 Hz, 2H), 4.12 (t, *J* = 5.7 Hz, 2H), 3.73 – 3.59 (m, 4H), 2.76 (t, *J* = 5.7 Hz, 2H), 2.62 (s, 3H), 2.57 – 2.47 (m, 4H), 1.37 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 154.8, 145.2, 136.4, 131.5, 128.9 (2C), 127.7, 127.6, 125.9 (2C), 112.6, 110.2, 104.8, 104.4, 67.0 (2C), 66.3, 59.4, 57.9, 54.1 (2C), 46.7, 14.7, 12.1; HRMS: calcd for $C_{25}H_{31}N_2O_4$ 423.2284 ($M+H^+$), found 423.2282 ($M+H^+$).

Ethyl 1-benzyl-2-methyl-5-(2-(piperazin-1-yl)ethoxy)-1*H*-indole-3-carboxylate (23). The titled product was obtained from bromo intermediate **20a** and piperazines according to the general procedure described below in 74% yield. Mp 89 – 91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.22 – 7.14 (m, 3H), 7.03 (d, J = 8.9 Hz, 1H), 6.90 – 6.85 (m, 2H), 6.75 (dd, J = 8.8, 2.5 Hz, 1H), 5.24 (s, 2H), 4.33 (q, J = 7.1 Hz, 2H), 4.13 (t, *J* = 7.7 Hz, 2H), 2.89 – 2.87 (m, 4H), 2.78 (t, *J* = 6.5 Hz, 2H), 2.62 (s, 3H), 2.53 (bs, 4H), 2.29 – 2.01 (bs, 1H), 1.38 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 154.8, 145.2, 136.4, 131.5, 128.9 (2C), 127.7, 127.6, 125.9 (2C), 112.6, 110.2, 104.9, 104.4, 66.4, 59.4, 57.9, 54.5, 46.7, 45.8, 14.7, 12.1; HRMS: calcd for $C_{25}H_{31}N_3O_3$ 422.2444 ($M+H^+$), found 422.2441 ($M+H^+$).

Ethyl 1-benzyl-2-methyl-5-(2-(4-methylpiperazin-1-yl)ethoxy)-1*H*-indole-3-carboxylate (24). According to literature procedures,[51] to a solution of piperazine derivative **23** (200 mg, 0.47 mmol) and benzotriazole (56 mg, 0.47 mmol) in CH_3OH/H_2O (9:1, 10 ml) was added formaldehyde (37% aqueous solution, 0.94 mmol). The mixture was stirred at room temperature for 6 h. The solution was concentrated and the residue purified by flash chromatography on silica gel (eluent DCM/MeOH/Et_3N 97:2:1) to give 163 mg of ethyl 5-(2-(4-((1*H*-benzo[d][1,2,3]triazol-1-yl)methyl)piperazin-1-yl)ethoxy)-1-benzyl-2-methyl-1H-indole-3-carboxylate (yield 64%). Mp 92 – 93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.4 Hz, 1H), 7.59 – 7.49 (m, 2H), 7.40 (ddd, *J* = 8.2, 6.9, 1.0 Hz, 1H), 7.33 – 7.25 (m, 1H), 7.22 – 7.12 (m, 3H), 7.00 (d, *J* = 8.8 Hz, 1H), 6.86 (dd, *J* = 7.6, 1.8 Hz, 2H), 6.70 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.38 (s, 2H), 5.21 (s, 2H), 4.30 (q, *J* = 7.1 Hz, 2H), 4.04 (t, *J* = 5.7 Hz, 2H), 2.72 (t, *J* = 5.6 Hz, 2H), 2.69 – 2.62 (m, 2H), 2.60 (s, 3H), 2.59 – 2.48 (m, 6H), 1.34 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 154.8, 146.0, 145.3, 144.3, 136.4, 134.0, 131.6, 129.0 (2C), 127.7, 127.6, 126.0 (2C), 123.9, 120.0, 112.6, 110.3, 110.1, 104.9, 104.4, 69.3, 66.5, 59.5, 57.3, 53.4 (2C), 50.3 (2C), 46.7, 14.8, 12.2.

A solution of the previously obtained benzotriazolyl derivative (163 mg, 0.29 mmol) and $NaBH_4$ (22 mg, 0.58 mmol) was refluxed in dry THF (3 ml) overnight. After removal of the solvent in vacuum, the residue was diluted with EtOAc. The mixture was washed with 1 N NaOH, and brine and dried over Na_2SO_4 and evaporation of the solvent in vacuum, the residue was purified by flash chromatography on silica gel (eluent DCM/MeOH/Et_3N 89:10:1) to give the titled compound (**24**) as a white solid (70 mg, yield 55%). Mp 92 – 93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 2.4 Hz, 1H), 7.24 – 7.13 (m, 3H), 7.03 (d, *J* = 8.9 Hz, 1H), 6.88 (dd, *J* = 7.8, 1.8 Hz, 2H), 6.75 (dd, *J* = 8.9, 2.5 Hz, 1H), 5.23 (s, 2H), 4.33 (q, *J* = 7.1 Hz, 2H), 4.12 (t, *J* = 5.8 Hz, 2H), 2.78 (t, *J* = 5.8 Hz, 2H), 2.62 (s, 3H), 2.60 – 2.33 (m, 8H), 2.23 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 155.0, 145.3, 136.5, 131.6, 129.0 (2C), 127.7, 127.6, 126.0 (2C), 112.7, 110.3, 105.0, 104.4, 66.6, 59.5, 57.5, 55.2

(2C), 53.6 (2C), 46.7, 46.1, 14.8, 12.2; HRMS: calcd for $C_{26}H_{33}N_3O_3$ 436.2600 ($M+H^+$), found 436.2596 ($M+H^+$).

Ethyl 1-benzyl-2-methyl-5-(3-(piperidin-1-yl)propoxy)-1*H*-indole-3-carboxylate (25). The titled product was obtained from chloro intermediate **20b** and piperidine as a white solid (143 mg, yield 85%). Mp 110 – 111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 2.4 Hz, 1H), 7.34 – 7.23 (m, 3H), 7.12 (d, *J* = 8.8 Hz, 1H), 6.98 (dd, *J* = 7.8, 1.7 Hz, 2H), 6.84 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.34 (s, 2H), 4.43 (q, *J* = 7.1 Hz, 2H), 4.10 (t, *J* = 6.4 Hz, 2H), 2.72 (s, 3H), 2.54 (t, *J* = 7.3 Hz, 2H), 2.45 (bs, 4H), 2.04 (p, *J* = 7.3 Hz, 2H), 1.62 (p, *J* = 5.6 Hz, 4H), 1.48 (t, *J* = 7.1 Hz, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 155.2, 145.2, 136.5, 131.4, 129.0 (2C), 127.7, 127.6, 126.0 (2C), 112.5, 110.2, 104.9, 104.4, 67.2, 59.5, 56.3, 54.7 (2C), 46.7, 27.1, 26.1 (2C), 24.5, 14.7, 12.2; HRMS: calcd for $C_{27}H_{34}N_2O_3$ 435.2648 ($M+H^+$), found 435.2644 ($M+H^+$).

Ethyl 5-(3-(azepan-1-yl)propoxy)-1-benzyl-2-methyl-(*1H)*-indole-3-carboxylate (26). The titled product was obtained from chloro intermediate **20b** and azepane as a white solid (308 mg, yield 98%). Mp 96 −97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.45 (m, 1H), 7.43 – 7.31 (m, 1H), 7.31 – 7.18 (m, 3H), 7.05 – 6.93 (m, 2H), 6.83 – 6.72 (m, 1H), 5.46 (s, 2H), 4.27 (q, J = 7.1 Hz, 2H), 4.00 (t, J = 6.5 Hz, 2H), 2.65 (s, 3H), 2.63 – 2.51 (m, 6H), 1.85 (p, J = 6.7 Hz, 2H), 1.63 – 1.44 (m, 8H), 1.34 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 155.0, 145.7, 137.7, 131.5, 129.2 (2C), 127.8, 127.4, 126.6 (2C), 112.3, 111.6, 104.5, 103.5, 66.63, 59.4, 55.3 (3C), 54.6, 46.4, 28.3, 27.7, 27.0 (2C), 14.9, 12.3; HRMS: calcd for $C_{28}H_{36}N_2O_3$ 449.2804 ($M+H^+$), found 449.2806 ($M+H^+$).

Ethyl 1-benzyl-2-methyl-5-(3-morpholinopropoxy)-1*H*-indole-3-carboxylate (27). The titled product was obtained from chloro intermediate **20b** and morpholine as a white solid (149 mg, yield 87%). Mp 109 – 110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 2.5 Hz, 1H), 7.39 – 7.21 (m, 3H), 7.13 (d, *J* = 8.8 Hz, 1H), 7.01 – 6.94 (m, 2H), 6.84 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.34 (s, 2H), 4.43 (q, *J* = 7.1 Hz, 2H), 4.13 (t, *J* = 6.3 Hz, 2H), 3.75 (t, *J* = 4.6 Hz, 4H), 2.72 (s, 3H), 2.58 (t, *J* = 7.2 Hz, 2H),

2.54 – 2.45 (m, 4H), 2.03 (p, *J* = 6.8 Hz, 2H), 1.48 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 155.2, 145.2, 136.5, 131.5, 129.0 (2C), 127.8, 127.7, 126.0 (2C), 112.5, 110.3, 104.8, 104.4, 67.2 (2C), 66.8, 59.5, 55.9, 53.9 (2C), 46.8, 26.8, 14.8, 12.2; HRMS: calcd for $C_{26}H_{32}N_2O_3$ 437.2440 ($M+H^+$), found 437.2437 ($M+H^+$).

Ethyl 1-benzyl-2-methyl-5-(3-(4-methylpiperazin-1-yl)propoxy)-1*H*-indole-3-carboxylate (28). According to the procedure used for **24**, ethyl 5-(3-(4-((1*H*-benzo[d][1,2,3]triazol-1-yl)methyl)piperazin-1-yl)propoxy)-1-benzyl-2-methyl-1H-indole-3-carboxylate intermediate was obtained from piperazines derivative **29** as a white solid (104 mg, yield 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dt, *J* = 8.4, 1.0 Hz, 1H), 7.59 – 7.52 (m, 2H), 7.42 (ddd, *J* = 8.2, 6.9, 1.0 Hz, 1H), 7.34 – 7.25 (m, 1H), 7.24 – 7.13 (m, 3H), 7.01 (d, *J* = 8.8 Hz, 1H), 6.88 (dd, *J* = 7.7, 1.8 Hz, 2H), 6.70 (dd, *J* = 8.9, 2.5 Hz, 1H), 5.40 (s, 2H), 5.23 (s, 2H), 4.30 (q, *J* = 7.0 Hz, 2H), 3.95 (t, *J* = 6.3 Hz, 2H), 2.67 – 2.62 (m, 2H), 2.62 (s, 3H), 2.44 (t, *J* = 7.4 Hz, 6H), 1.85 (p, *J* = 6.5 Hz, 2H), 1.54 (bs, 2H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 155.1, 146.1, 145.2, 136.5, 134.1, 131.5, 129.1 (2C), 127.8, 127.7, 127.6, 126.0 (2C), 124.0, 120.1, 112.5, 110.3, 110.1, 104.9, 104.4, 69.3, 66.8, 59.5, 55.3, 53.1 (2C), 50.4 (2C), 46.8, 27.1, 14.7, 12.2; HRMS: calcd for $C_{27}H_{35}N_3O_3$ 450.2757 ($M+H^+$), found 450.2752 ($M+H^+$). Later, the titled compound was obtained from the above benzotriazole derivative as a white solid (72 mg, yield 55%). Mp 102 – 103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 2.5 Hz, 1H), 7.24 – 7.13 (m, 3H), 7.02 (d, *J* = 8.9 Hz, 1H), 6.92 – 6.84 (m, 2H), 6.73 (dd, *J* = 8.9, 2.5 Hz, 1H), 5.23 (s, 2H), 4.33 (q, *J* = 7.1 Hz, 2H), 4.01 (t, *J* = 6.3 Hz, 2H), 2.62 (s, 3H), 2.56 – 2.31 (m, 10H), 2.22 (s, 3H), 1.93 (p, *J* = 6.4 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 155.2, 145.2, 136.5, 131.5, 129.0 (2C), 127.7, 127.7, 126.0 (2C), 112.5, 110.3, 104.8, 104.4, 67.0, 59.5, 55.4, 55.2 (2C), 53.3 (2C), 46.7, 46.1, 27.1, 14.8, 12.2.

Ethyl 1-benzyl-2-methyl-5-(3-(piperazin-1-yl)propoxy)-(*1H)*-indole-3-carboxylate (29). The titled product was obtained from chloro intermediate **20b** and piperazines as a white solid (300 mg, yield

98%). Mp 183 – 184 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.22 – 7.13 (m, 3H), 7.03 (d, *J* = 8.1 Hz, 1H), 6.91 – 6.82 (m, 2H), 6.78 – 6.72 (m, 1H), 5.24 (s, 2H), 4.33 (q, *J* = 7.1 Hz, 2H), 4.02 (t, *J* = 6.3 Hz, 2H), 2.88 – 2.82 (m, 4H), 2.62 (s, 3H), 2.47 (t, *J* = 7.5 Hz, 2H), 2.45 – 2.37 (m, 4H), 2.14 (bs, 1H), 1.93 (p, *J* = 6.3 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 155.0, 145.0, 136.3, 131.3, 128.9 (2C), 127.6, 127.5, 125.8 (2C), 112.4, 110.1, 104.7, 104.3, 66.8, 59.3, 55.9, 54.4 (2C), 46.6, 45.9 (2C), 26.7, 14.6, 12.0; HRMS: calcd for $C_{26}H_{33}N_3O_3$ 436.2600 ($M+H^+$), found 436.2603 ($M+H^+$).

Ethyl 1-benzyl-2-methyl-5-(4-(piperazin-1-yl)butoxy)-1*H*-indole-3-carboxylate (30). The titled product was obtained from chloro intermediate **20c** and piperazines as a white solid (72 mg, yield 43%). Mp 129 – 130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 2.5 Hz, 1H), 7.25 – 7.13 (m, 3H), 7.03 (d, *J* = 8.8 Hz, 1H), 6.93 – 6.86 (m, 2H), 6.73 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.24 (s, 2H), 4.33 (q, *J* = 7.1 Hz, 2H), 3.98 (t, *J* = 6.3 Hz, 2H), 2.84 (t, *J* = 4.9 Hz, 4H), 2.62 (s, 3H), 2.45 – 2.28 (m, 6H), 2.21 (bs, 1H, NH), 1.76 (p, *J* = 6.0 Hz, 2H), 1.62 (p, *J* = 5.8 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 155.1, 145.1, 136.4, 131.3, 128.9 (2C), 127.6, 127.6, 125.9 (2C), 112.4, 110.2, 104.6, 104.3, 68.2, 59.4, 58.9, 54.4 (2C), 46.6, 46.0 (2C), 27.5, 23.3, 14.7, 12.1; HRMS: calcd for $C_{27}H_{35}N_3O_3$ 450.2757 ($M+H^+$), found 450.2754 ($M+H^+$).

Ethyl 1-benzyl-5-(3-(benzylamino)propoxy)-2-methyl-1*H*-indole-3-carboxylate (31). The titled compound was obtained according to the general procedure from chloro intermediate **20b** and benzylamine as a white solid (45 mg, yield 77%). Mp 59 – 60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 2.5 Hz, 1H), 7.29 – 7.12 (m, 8H), 7.02 (d, *J* = 8.9 Hz, 1H), 6.91 – 6.85 (m, 2H), 6.72 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.22 (s, 2H), 4.32 (q, *J* = 7.1 Hz, 2H), 4.05 (t, *J* = 6.1 Hz, 2H), 3.74 (s, 2H), 2.78 (t, *J* = 6.9 Hz, 2H), 2.61 (s, 3H), 1.95 (p, *J* = 6.5 Hz, 2H), 1.58 (bs, 1H, NH), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 155.0, 145.2, 140.4, 136.4, 131.4, 128.9 (2C), 128.4 (2C), 128.1

(2C), 127.6, 127.6, 126.9, 125.9 (2C), 112.4, 110.2, 104.7, 104.3, 67.0, 59.4, 54.1, 46.6 (2C), 29.9, 14.7, 12.1; HRMS: calcd for $C_{29}H_{32}N_2O_3$ 457.2491 ($M+H^+$), found 457.2487 ($M+H^+$).

Ethyl 5-(2-azidoethoxy)-1-benzyl-2-methyl-(*1H)*-indole-3-carboxylate (32a).[32] Sodium azide (390 mg, 6.00 mmol, 2.5 eq) was added to a solution of bromo intermediate **20a** (1.0 g, 2.4 mmol) in DMF (17 mL) and the reaction was stirred at 85 °C for 2 h under nitrogen atmosphere. After cooling at rt the mixture was diluted with water and extracted with diethyl ether. The organic solution was dried over sodium sulfate anhydrous and evaporated under reduced pressure to afford the titled compounds (**32a**) as a pale yellow solid residue (900 mg, yield 99%) was used in the following reaction without any further purification. Mp 88-91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.25 – 7.20 (m, 3H), 7.08 – 7.02 (m, 1H), 6.98 – 6.90 (m, 2H), 6.89 – 6.80 (m, 1H), 5.21 (s, 2H), 4.39 (q, *J* = 7.0 Hz, 2H), 4.19 (t, *J* = 6.2 Hz, 2H), 3.56 (t, *J* = 6.2 Hz, 2H), 2.65 (s, 3H), 1.43 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 154.2, 145.3, 136.3, 131.7, 128.9 (2C), 127.8, 127.6, 125.8 (2C), 112.4, 110.3, 104.9, 104.3, 67.7, 59.4, 50.2, 46.5, 14.6, 11.7; HRMS: calcd for $C_{21}H_{22}N_4O_3$ 379.1770 ($M+H^+$), found 379.1774 ($M+H^+$).

Ethyl 5-(3-azidopropoxy)-1-benzyl-2-methyl-(*1H)*-indole-3-carboxylate (32b).[32] Following the same procedure described for compound **32a** but starting from chloro intermediate **20b** instead, ethyl 5-(3-azidopropoxy)-1-benzyl-2-methyl-(*1H)*-indole-3-carboxylate was obtained as a white solid (mp 79-81 °C, 846 mg, yield 93%) exhibiting the following spectroscopic properties: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 2.2 Hz, 1H), 7.40 – 7.20 (m, 3H), 7.12 (d, *J* = 8.8 Hz, 1H), 6.98 – 6.85 (m, 2H), 6.79 (dd, *J* = 8.8, 2.3 Hz, 1H), 5.32 (s, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 4.11 (t, *J* = 5.9 Hz, 2H), 3.51 (t, *J* = 5.9 Hz, 2H), 2.67 (s, 3H), 2.06 (p, *J* = 5.9 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 154.6, 145.1, 136.5, 131.6, 128.9 (2C), 127.7, 127.4, 126.0 (2C), 112.4, 110.3, 104.9, 104.5, 65.8, 59.3, 50.3, 46.7, 32.7, 14.4, 12.1; HRMS: calcd for $C_{22}H_{24}N_4O_3$ 393.1927 ($M+H^+$), found 393.1929 ($M+H^+$).

Ethyl 5-(4-azidobutoxy)-1-benzyl-2-methyl-(*1H*)-indole-3-carboxylate (32c).[32] Following the same procedure described for compound **32a** but starting from chloro intermediate **20c** instead, the titled compound was obtained as a white solid (mp 80-81 °C, 237 mg, yield 77%) exhibiting the following spectroscopic properties: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 2.5 Hz, 1H), 7.21 – 7.10 (m, 3H), 7.02 (d, *J* = 8.9 Hz, 1H), 6.87 (d, *J* = 7.0 Hz, 2H), 6.72 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.22 (s, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.98 (t, *J* = 5.9 Hz, 2H), 3.28 (t, *J* = 6.7 Hz, 2H), 2.61 (s, 3H), 1.86 – 1.69 (m, 4H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 154.9, 145.2, 136.4, 131.4, 128.9 (2C), 127.7, 127.6, 125.9 (2C), 112.4, 110.3, 104.6, 104.3, 67.7, 59.4, 51.3, 46.7, 26.7, 25.9, 14.7, 12.1; HRMS: calcd for $C_{23}H_{26}N_4O_3$ 407.2083 ($M+H^+$), found 407.2080 ($M+H^+$).

Ethyl 5-(2-aminoethoxy)-1-benzyl-2-methyl-(*1H*)-indole-3-carboxylate (33).[33] A mixture of ethyl 5-(3-azidoethoxy)-1-benzyl-2-methyl-(*1H*)-indole-3-carboxylate (0.83 mg, 2.2 mmol, 1.0 eq) and triphenylphosphine (0.87 g, 3.3 mmol, 1.1 eq) in THF (44 mL) and H_2O (4 mL) was stirred for 12 h. The mixture was concentrated and purified by flash column chromatography eluting with dichloromethane/methanol/triethylamine 98.9:1:0.1mixture to give a white solid (648 mg, yield 83%). Mp 116 – 117 °C; ^{1}H NMR (400 MHz, MeOD) δ 7.62 (s, 1H), 7.27 – 7.20 (m, 4H), 6.98 – 7.89 (m, 2H), 6.88 – 6.80 (m, 1H), 5.38 (s, 2H), 4.35 (q, *J* = 9.5 Hz, 2H), 4.03 (t, *J* = 5.3 Hz, 2H), 3.01 (t, *J* = 5.2 Hz, 2H), 2.63 (s, 3H), 1.38 (t, *J* = 9.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 154.2, 145.5, 136.5, 131.8, 128.9 (2C), 127.8, 127.5, 125.9 (2C), 112.5, 110.5, 104.6, 104.3, 67.8, 59.5, 46.4, 39.6, 14.0, 11.2; HRMS: calcd for $C_{21}H_{24}N_2O_3$ 353.1865 ($M+H^+$), found 353.1866 ($M+H^+$).

Ethyl 5-(3-aminopropoxy)-1-benzyl-2-methyl-(*1H*)-indole-3-carboxylate (34).[33] Further reduction of the azido intermediate **32c** (0.70 g, 1.78 mmol) with PPh_3/water afforded the amine **34** (0.566 g, yield 87%) as a white solid exhibiting the following spectroscopic properties. Mp 85 – 86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.34 – 7.24 (m, 4H), 7.14 (d, *J* = 8.8 Hz, 1H), 7.01 – 6.97 (m, 2H), 6.84 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.32 (s, 2H), 4.42 (q, *J* = 7.2 Hz, 2H), 4.16 (t, *J* = 6.0 Hz, 2H), 3.01 (t, t,

J = 6.0 Hz, 2H), 2.71 (s, 3H), 2.32 (bs, 2H), 2.00 (p, *J* = 6.0 Hz, 2H), 1.49 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 154.9, 145.2, 136.4, 131.5, 128.9 (2C), 127.7, 127.6, 125.9 (2C), 112.4, 110.2, 104.6, 104.3, 66.4, 59.4, 46.7, 39.3, 32.4, 14.4, 12.1; HRMS: calcd for $C_{22}H_{26}N_2O_3$ 367.2022 ($M+H^+$), found 367.2024 ($M+H^+$).

Ethyl 5-(4-aminobutoxy)-1-benzyl-2-methyl-(*1H*)-indole-3-carboxylate (35).[33] Further reduction of the azido intermediate **32c** (0.70 g, 1.8 mmol) with PPh_3/water afforded the amine **35** (187 mg, yield 84%) as a white solid exhibiting the following spectroscopic properties. Mp 80 – 82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 2.5 Hz, 1H), 7.23 – 7.12 (m, 3H), 7.01 (d, *J* = 8.8 Hz, 1H), 6.91 – 6.84 (m, 2H), 6.73 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.21 (s, 2H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.98 (t, *J* = 6.4 Hz, 2H), 2.70 (t, *J* = 7.1 Hz, 2H), 2.61 (s, 3H), 1.77 (p, *J* = 6.3 Hz, 2H), 1.56 (p, *J* = 7.4 Hz, 2H), 1.49 (bs, 2H, NH_2), 1.37 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 155.1, 145.1, 136.4, 131.4, 128.9 (2C), 127.7, 127.6, 125.9 (2C), 112.5, 110.2, 104.7, 104.3, 68.3, 59.4, 46.7, 42.0, 30.5, 26.9, 14.7, 12.1; HRMS: calcd for $C_{23}H_{28}N_2O_3$ 381.2178 ($M+H^+$), found 381.2176 ($M+H^+$).

Ethyl 1-benzyl-5-(2-oxiranylmethoxy)-2-methylindole-3-carboxylate (36). Epibromohydrin (0.7 mL, 1.1 g, 8.6 mmol) was added to a suspension of hydroxyindole **9** (6,5 mmol) and potassium carbonate (1.2 g, 8.6 mmol) in acetone (30 mL) and the mixture was refluxed for 48 h. After cooling, all the volatile materials were evaporated under reduced pressure and the residue was taken-up with ethyl acetate (100 mL). The organic phase was washed with a saturated aqueous sodium bicarbonate solution (2 x 30 mL) and water (2 x 30 mL) and dried with sodium sulfate anhydrous. After the solvent was evaporated under reduced pressure, the crude product was purified by chromatography on silica using ethyl acetate-petroleum ether 3:7 mixture as the eluent.

Epoxide **57** was obtained in 91% yield as a white solid. Mp 102 – 104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 2.5 Hz, 1H), 7.23 (d, *J* = 7.3 Hz, 3H), 7.09 (d, *J* = 8.9 Hz, 1H), 6.92 (d, *J* = 7.4 Hz, 2H), 6.82 (dd, *J* = 8.9, 2.5 Hz, 1H), 5.29 (s, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 4.25 (dd, *J* = 11, 3.3 Hz, 1H), 4.01

(dd, *J* = 11, 5.6 Hz, 1H), 3.40 – 3.33 (m, 1H), 2.88 (t, *J* = 4.6 Hz, 1H), 2.75 (dd, *J* = 5.0, 2.6 Hz, 1H), 2.67 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 155.0, 145.7, 136.7, 132.1, 129.3 (2C), 128.1, 127.9, 126.3 (2C), 112.9, 110.7, 105.4, 104.8, 69.9, 59.9, 47.8, 47.1, 45.3, 15.1, 12.5; HRMS: calcd for $C_{22}H_{23}NO_4$ 366.1700 ($M+H^+$), found 366.1701 ($M+H^+$).

Ethyl 1-benzyl-5-(2-hydroxy-3-(piperidin-1-yl)propoxy)-2-methyl-1*H*-indole-3-carboxylate (37). Lithium perchlorate (88 mg, 0.83 mmol) was added to a stirred solution of epoxide **36** (200 mg, 0.55 mmol) in acetonitrile (1 mL) until complete solution of the salt. Piperidine (71 mg, 0.83 mmol) was added and the mixture was kept 3 h at the reflux temperature. After the solvent evaporation at reduced pressure, chromatography of the residue on silica gel (eluent DCM/MeOH 9:1) afforded 226 mg of the titled product as a white solid (yield 91%), which was characterized as follows. Mp 133 – 134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 2.2 Hz, 1H), 7.35 – 7.18 (m, 3H), 7.12 (d, *J* = 8.9 Hz, 1H), 7.01 – 6.93 (m, 2H), 6.88 (dt, *J* = 8.7, 2.2 Hz, 1H), 5.29 (s, 2H), 4.43 (q, *J* = 7.1 Hz, 2H), 4.23 – 3.97 (m, 3H), 3.67 (bs, 1H), 2.70 (s, 3H), 2.68 – 2.59 (m, 2H), 2.58 – 2.48 (m, 2H), 2.48 – 2.32 (m, 2H), 1.72 – 1.55 (m, 4H), 1.49 (t, *J* = 7.1 Hz, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 155.0, 145.2, 136.4, 131.5, 128.9 (2C), 127.6, 127.5, 125.9 (2C), 112.4, 110.2, 104.9, 104.3, 71.2, 65.6, 61.3, 59.4, 54.8 (2C), 46.6, 26.1 (2C), 24.3, 14.7, 12.1; HRMS: calcd for $C_{22}H_{24}N_4O_4$: 409.1876 ($M+H^+$), found 409.1877 ($M+H^+$).

Ethyl 5-(3-(azepan-1-yl)-2-hydroxypropoxy)-1-benzyl-2-methyl-1*H*-indole-3-carboxylate (38). Following the procedure for compound **37** but using azepane, the titled compound was obtained as a white solid (yield 96%). Mp 175 – 176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 2.4 Hz, 1H), 7.31-7.24 (m, 3H), 7.14 (d, *J* = 8.8 Hz, 1H), 6.99 (d, *J* = 7.2 Hz, 2H), 6.89 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.34 (s, 2H), 4.43 (q, *J* = 7.2 Hz, 2H), 4.11-4.04 (m, 3H), 2.90-2-78 (m, 5H), 2,76 (s, 3H), 2.69-2.61 (m, 1H), 1.73-1.60 (m, 8H), 1.48 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 155.0, 145.2, 136.4, 131.5, 128.9 (2C), 127.6, 127.5, 125.9 (2C), 112.4, 110.2, 104.9, 104.3, 71.0, 66.1, 60.5,

59.4, 55.9 (2C), 46.6, 28.2 (2C), 26.9 (2C), 14.7, 12.1, HRMS: calcd for $C_{28}H_{36}N_2O_4$ 464.2675 ($M+H^+$), found 464.2682 ($M+H^+$).

Ethyl 1-benzyl-5-(2-hydroxy-3-morpholinopropoxy)-2-methyl-1*H*-indole-3-carboxylate (39). Following the procedure for compound **37** but using morpholine, the titled compound was obtained as a white solid (yield 92%). Mp 168 – 169 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 2.4 Hz, 1H), 7.32-7.27 (m, 3H), 7.13 (d, *J* = 8.8 Hz, 1H), 6.98 (d, *J* = 7.2 Hz, 2H), 6.87 (dd, , *J* = 8.8, 2.8 Hz, 1H), 5.33 (s, 2H), 4.43 (q, *J* = 7.2 Hz, 2H), 4.21-4.11 (m, 1H), 4.10-4.06 (m, 2H), 3.80-3.71 (m, 4H), 2.72 (s, 3H), 2.72-2.49 (m, 6H), 1.48 (t, *J* = 7.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1 , 154.8 , 145.3 , 136.4 , 131.6 , 128.9 (2C), 127.8 , 127.6 , 125.9 , 125.6 (2C), 112.4 , 110.3 , 104.9 , 104.4 , 70.9 , 67.0 (2C), 65.7 , 61.2 , 59.4 , 53.8 , 46.7 , 14.7 , 12.1; HRMS: calcd for $C_{26}H_{32}N_2O_5$ 452.2311 ($M+H^+$), found 452.2317 ($M+H^+$).

Ethyl 5-(3-azido-2-hydroxypropoxy)-1-benzyl-2-methyl-1*H*-indole-3-carboxylate (40).[36] Lithium perchlorate (439 mg, 3.00 mmol, 1.5 eq) was added to a stirred solution of epoxide **35** (730 mg, 2.00 mmol, 1.0 eq) in acetonitrile (2 mL) until complete solution of the salt. Sodium azide (195 mg, 3 mmol, 1.5 eq) was added and the mixture was kept 24 h at the reflux temperature. After the solvent evaporation at reduced pressure, chromatography of the residue on silica gel (eluent EA/PE 3:7) afforded 637 mg of ethyl 5-(3-azido-2-hydroxypropoxy)-1-benzyl-2-methyl-1*H*-indole-3-carboxylate as a white solid (yield 78%), which was characterized as follows. Mp 98 – 100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 2.6 Hz, 1H), 7.49 – 7.21 (m, 3H), 7.13 (d, *J* = 8.7 Hz, 1H), 7.06 – 6.89 (m, 2H), 6.83 (dd, *J* = 8.7, 2.5 Hz, 1H), 5.33 (s, 2H), 4.41 (q, *J* = 6.9 Hz, 2H), 4.18 – 4.02 (m, 3H), 3.73 – 3.46 (m, 2H), 2.71 (d, *J* = 3.8 Hz, 3H), 1.66 (s, 1H), 1.46 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 154.2, 145.4, 136.2, 131.7, 128.9 (2C), 127.6, 127.5, 125.8 (2C), 112.1, 110.3, 105.0, 104.3, 69.6, 69.4, 59.5, 53.4, 46.6, 14.6, 12.1; HRMS: calcd for $C_{22}H_{24}N_4O_4$: 409.1876 ($M+H^+$), found 409.1877 ($M+H^+$).

Ethyl 5-(3-amino-2-hydroxypropoxy)-1-benzyl-2-methyl-1*H*-indole-3-carboxylate (41).[38] A solution of $SnCl_2 \cdot 2\ H_2O$ (110 mg, 0.5 mmol) in methanol (0.5 mL) was added to a stirred solution of azide **40** (70 mg, 0.17 mmol) in methanol (0.5 mL) and the mixture was made to react at 25 °C for 4 days before it was dropped in water. Solid $NaHCO_3$ was added (50mg) and the mixture was filtered and the aqueous phase was extracted with dichloromethane. After the solvent evaporation at reduced pressure, the crude product was purified by flash chromatography on silica gel (eluent 8:2 ethyl acetate-methanol) to obtain 59 mg (91% yield) of pure product as a white solid. Mp 147 – 149 °C; ^{1}H NMR (400 MHz, methanol-d_4) δ 7.65 (d, J = 2.5 Hz, 1H), 7.30 – 7.14 (m, 4H), 7.00 – 6.92 (m, 2H), 6.86 (dd, J = 8.9, 2.5 Hz, 1H), 5.39 (s, 2H), 4.36 (q, J = 7.1 Hz, 2H), 4.29 – 4.17 (m, 1H), 4.15 – 3.99 (m, 2H), 3.27 (dd, J = 13, 3.4 Hz, 1H), 3.08 (dd, J = 12.9, 9.0 Hz, 1H), 2.65 (s, 3H), 1.43 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, methanol-d_4) δ 166.3, 154.4, 145.6, 136.8, 131.8, 128.4 (2C), 127.4, 127.1, 125.6 (2C), 111.6, 110.4, 104.5, 103.4, 70.1, 66.0, 59.2, 45.9, 42.1, 13.5, 10.9; HRMS: calcd for $C_{22}H_{26}N_2O_4$ 383.1971 ($M+H^+$), found 383.1974 ($M+H^+$).

Ethyl 5-(2-amino-3-hydroxypropoxy)-1-benzyl-2-methyl-1*H*-indole-3-carboxylate (42).[33] The titled compound was obtained according to reduction procedure described for amino intermediate **33** but starting from hydroxylazide **40** as a white solid (255 mg, yield 92%); Mp 139 – 142 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.54 (d, J = 2.5 Hz, 1H), 7.40 (d, J = 8.9 Hz, 1H), 7.35 – 7.21 (m, 3H), 7.01 (d, J = 6.7 Hz, 2H), 6.82 (dd, J = 8.9, 2.5 Hz, 1H), 5.49 (s, 2H), 4.30 (q, J = 7.1 Hz, 2H), 3.93 (qd, J = 9.7, 5.4 Hz, 2H), 3.83 (q, J = 5.7 Hz, 1H), 2.80 (dd, J = 12.8, 4.4 Hz, 1H), 2.67 (s, 4H), 2.51 (p, J = 1.8 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.4, 154.9, 145.7, 137.6, 131.6, 129.2, 127.8, 127.4, 126.6, 112.1, 111.6, 104.7, 103.6, 71.0, 70.0, 59.4, 46.4, 44.8, 14.9, 12.3; HRMS: calcd for $C_{22}H_{26}N_2O_4$ 383.1971 ($M+H^+$), found 383.1969 ($M+H^+$).

Ethyl 1-benzyl-5-(2-fluoro-3-(piperidin-1-yl)propoxy)-2-methyl-1H-indole-3-carboxylate (43) and ethyl 1-benzyl-5-(3-fluoro-2-(piperidin-1-yl)propoxy)-2-methyl-1*H*-indole-3-carboxylate (44). To

a stirred solution of hydroxyl compound **37** (100 mg, 0.22 mmol) in dry DCM (1.5 ml) DAST (43.5 mg, 0.27 mmol) was added at 0 °C. After being stirred at r.t. for 3h, the reaction was dropped in iced $NaHCO_3$ sat. solution. The mixture was extracted with DCM 3 times, the organic phases collected and evaporated. Chromatography of the residue on silica gel (eluent DCM/MeOH/Et_3N 97:2:1) allowed to separate the two products. Major product **44** (47 mg, R_f = 0.4): mp 68 – 69 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 2.5 Hz, 1H), 7.25 – 7.13 (m, 3H), 7.04 (d, *J* = 8.9 Hz, 1H), 6.89 (d, *J* = 7.3 Hz, 2H), 6.75 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.24 (s, 2H), 4.73 (d, *J* = 5.3 Hz, 1H), 4.61 (d, *J* = 5.3 Hz, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 4.20 – 4.06 (m, 2H), 3.06 (pd, *J* = 22.6, 5.1 Hz, 1H), 2.75 – 2.54 (m, 7H), 1.52 (p, *J* = 5.5 Hz, 4H), 1.38 (t, *J* = 7.1 Hz, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 154.8, 145.3, 136.5, 131.7, 129.1 (2C), 127.8, 127.7, 126.0 (2C), 112.5, 110.3, 105.0, 104.5, 82.2 (d, *J* = 170.6 Hz), 65.5 (d, *J* = 7.2 Hz), 63.8 (d, *J* = 18.3 Hz), 59.6, 51.7 (2C), 46.8, 26.7, 24.7 (2C), 14.8, 12.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ 23.04 (td, *J* = 47.5, 23.4 Hz). HRMS: calcd for $C_{27}H_{33}N_2O_3$ 453.2553 ($M+H^+$), found 453.2550 ($M+H^+$). Minor product **43** (31 mg, Rf = 0.3): mp 99 – 101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 2.5 Hz, 1H), 7.31 – 7.22 (m, 3H), 7.11 (d, *J* = 8.8 Hz, 1H), 6.95 (dd, *J* = 7.6, 1.8 Hz, 2H), 6.86 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.31 (s, 2H), 5.13 – 4.92 (m, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.24 (dd, *J* = 4.6, 2.0 Hz, 1H), 4.21 – 4.15 (m, 1H), 2.84 – 2.60 (m, 5H), 2.50 (t, *J* = 5.3 Hz, 4H), 1.59 (p, *J* = 5.6 Hz, 4H), 1.46 (t, *J* = 7.1 Hz, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 154.7, 145.4, 136.4, 131.8, 129.0 (2C), 127.8, 127.6, 126.0 (2C), 112.6, 110.4, 105.1, 104.5, 90.5 (d, *J* = 173.3 Hz), 69.6 (d, *J* = 23.4 Hz), 60.1 (d, *J* = 21.6 Hz), 59.6, 55.4 (2C), 46.8, 26.1 (2C), 24.2, 14.8, 12.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -186.57 – -187.06 (m); HRMS: calcd for $C_{27}H_{33}N_2O_3$ 453.2553 ($M+H^+$), found 453.2551 ($M+H^+$).

Ethyl 1-benzyl-5-(3-(4,4-difluoropiperidin-1-yl)propoxy)-2-methyl-1*H*-indole-3-carboxylate (45). The titled compound was obtained as a white solid (10 mg, yield 20%) by the same procedure described for compounds **25-38**, but using 4,4-difluoropiperidine hydrochloride as amine and 8.0 eq of

K_2CO_3 (instead of 4.0). Mp 95 – 96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.38 – 7.25 (m, 3H), 7.13 (d, *J* = 8.6 Hz, 1H), 7.03 – 6.89 (m, 2H), 7.910 – 6.78 (m, 1H), 5.34 (s, 2H), 4.43 (q, *J* = 7.3 Hz, 2H), 4.13 (bt, *J* = 5.9 Hz, 2H), 2.7 (s, 3H), 2.69 – 2.54 (m, 6H), 2.11– 1.96 (m, 6H), 1.48 (t, *J* = 7.3 Hz, 3H;^{13}C NMR (101 MHz, $CDCl_3$) δ 166.16, 155.05, 145.11, 136.40, 131.42, 128.94 (2C), 127.66, 127.64, 125.90 (2C), 122.17 (t, *J* = 242 Hz), 112.42, 110.22, 104.71, 104.32, 66.63, 59.43, 54.42, 50.11 (t, *J* = 5.3 Hz, 2C), 46.67, 34.04 (t, *J* = 22 Hz, 2C), 27.33, 14.66, 12.12; ^{19}F NMR (376 MHz, $CDCl_3$) δ –96.7 (s, 2F); HRMS: calcd for $C_{27}H_{32}N_2O_3$ 471.2459 ($M+H^+$), found 471.2456 ($M+H^+$).

Ethyl 5-hydroxy-2-methyl-1*H*-indole-3-carboxylate (46) Over a mixture of 1,4-benzoquinone (757 mg, 7 mmol, 1.4 eq) in AcOH (10 mL) at 10-15 ºC was added dropwise ethyl 3-aminocrotonate (0.63 mL, 5 mmol, 1 eq), and the reaction was stirred for 6 hours. The mixture was then concentrated and partitioned between water (20 mL) and ethyl acetate (20 mL), extracted with ethyl acetate (3 x 20 mL), dried under Na_2SO_4, filtered and concentrated. The crude material was purified through flash column chromatography (3:1 petroleum ether: ethyl acetate) to give **46** as a yellowish solid (yield 68%). NMR spectrum was in accordance to that described in the literature.[39]

Ethyl 2-methyl-5-(3-(piperidin-1-yl)propoxy)-1*H*-indole-3-carboxylate (47). 1-Bromo, 3-chloropropane (0.38 mL, 3.8 mmol, 6 eq) was added to a stirred mixture of 5-hydroxyindole **46** (219 mg, 1 mmol, 1 eq) and K_2CO_3 (828 mg, 6 mmol, 6 eq) in ethanol (3 mL) and the reaction was refluxed for 3 hours. The cooled mixture was diluted with water and extracted with ethyl acetate. The organic solution was dried with sodium sulfate anhydrous and evaporated under reduced pressure. The solid residue was solved in dichloromethane (5 mL) and filtered through a small path of silica gel, rinsing with dichloromethane and evaporated, to obtain the chloro intermediate, which was directly solved in CH_3CN (5 mL), then NaI (300 mg, 2 mmol, 2.0 eq) was added and the reaction mixture was heated to reflux for 30 min. After cooled to r.t. piperidine (0.30 mL, 3 mmol, 3.0 eq), anhydrous K_2CO_3 (553 mg, 4 mmol, 4.0 eq) were added and the mixture was heated for 1 h, following by *tlc* (ethyl

acetate/petroleum ether, 3:7 mixture) the disappearance of starting material. The cooled mixture was diluted with water and extracted with ethyl acetate three times. The reunited organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on Silica gel, eluting with dichloromethane/methanol 9:1 plus 1% triethylamine to afford **47** as a yellowish solid (yield 60%). Mp 115 – 118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (m, 1H), 7.14(d, *J* = 8.8 Hz, 1H), 6.81 (m, 1H), 4.40 (q, *J* = 7.2 Hz, 2H), 4.06 (t, *J* = 6.4 Hz, 2H), 2.71 (s, 3H), 2.56-2.41 (m, 6H), 2.061-1.98 (m, 2H), 1.65-1.58 (m, 4H), 1.51-1.43 (m, 2H), 1.44 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 154.7, 144.3, 144.3, 129.5, 128.2, 112.4, 111.2, 104.5, 67.0, 59.4, 56.2, 54.6 (2C), 26.8, 25.8 (2C), 24.4, 14.6, 14.4. HRMS: calcd for $C_{20}H_{28}N_2O_3$ 345.2100 ($M+H^+$), found 345.2106 ($M+H^+$).

Ethyl 2-methyl-1-phenethyl-5-(3-(piperidin-1-yl)propoxy)-1*H*-indole-3-carboxylate (48). Ethyl 2-methyl-5-(3-(piperidin-1-yl)propoxy)-1H-indole-3-carboxylate **47** (138 mg, 0.4 mmol, 1 eq) was added at r.t. to a suspension of sodium hydride (60% dispersion in mineral oil, 19 mg, 0.48 mmol, 1.2 eq) in DMF. After 40 minutes 2-phenethyl bromide (60 µL, 0.44 mmol, 1.1 eq) was added and the mixture was made to react at r.t for 16 h and then poured into iced water, extracted with ethyl acetate (15 x 3 mL) and washed with water (3 x 15 mL). The organic solution was dried with sodium sulfate anhydrous and evaporated under reduced pressure. The solid residue was purified by column chromatography on silica gel (dichloromethane: methanol 95:5) to afford **48** as a white solid (yield 24%). Mp 115 – 116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (m, 1H), 7.31-7.26 (m, 3H), 7.21 (d, *J* = 8.8 Hz, 1H), 7.42 (dd, *J* = 7.4, 2.0 Hz, 2H), 6.84 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.40 (q, *J* = 7.2 Hz, 2H), 4.32 (t, *J* = 7.2 Hz, 2H), 4.17 (t, *J* = 5.6 Hz, 2H), 3.04 (t, *J* = 7.2 Hz, 2H), 2.56-2.41 (m, 6H), 2.47 (s, 3H), 2.061-1.98 (m, 2H), 1.65-1.58 (m, 4H), 1.51-1.43 (m, 2H), 1.46 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 154.3, 145.4, 137.8, 130.9, 128.8 (3C), 127.7, 127.0 (2C), 111.6, 110.0,

105.1, 103.8, 65.8, 59.4 (2C), 55.8, 53.7, 50.9, 36.0, 29.7, 22.5 (2C), 14.7, 11.7. HRMS: calcd for $C_{28}H_{36}N_2O_3$ 448.2726 ($M+H^+$), found 448.2731 ($M+H^+$).

General procedure A to afford *N*-benzyl indoles 49a-k.[40]

To a stirred mixture of benzyl amines (10 mmol) and ethyl acetoacetate (10 mmol) in ethanol (20 mL) was added CAN (5 mol%) and stirring was continued for 30 min at room temperature. 1,4-*p*-Benzoquinone (10 mmol) was then added and the mixture was refluxed for further 3h. Dichloromethane (70 mL) was added to the mixture and the resulting solution was washed with water (15 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude reaction mixture was purified by silica gel column chromatography using PE/EA 9:1. When required, more pure compounds where obtained upon trituration with DEE.

General procedure B to afford *N*-benzyl indoles 49l-n.[41]

Ethyl acetoacetate (1.20 ml, 1.24 g, 9.5 mmol), was added to a stirred mixture of 4-nitrobenzylamine hydrochloride (1.79 g, 9.5 mmol) and triethylamine (1.32 ml, 0.96 g, 9.5 mmol) at room temperature. After the initial exothermic reaction had subsided (~1 h), the mixture was diluted with ether (40 ml) and after a further 30 min the resulting solution was washed with water (20 ml). The ether layer was dried ($MgSO_4$) and concentrated in vacuum. The resulting crude ethyl 3-(4-nitrobenzylamino)but-2-enoate (2.4 g, 9.5 mmol) was added to a solution of *p*-benzoquinone (1.0 g, 9.5 mmol) in nitromethane (10 ml) and allowed to stand at room temperature for 18 h. The solvent was removed under a stream of nitrogen and the residue recrystallized from ethyl acetate to give the title compound as a yellow powder (0.95 g, yield 28%).

Ethyl 1-(2-methylbenzyl)-2-methyl-5-hydroxyindole-3-carboxylate (49a). The titled compound was obtained from 3-methylbenzylamine according to the general procedure A as pink solid (207 mg, yield 7%). Mp 230 – 231 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 2.5 Hz, 1H), 7.22 (d, J = 7.4 Hz, 1H), 7.15 (t, J = 7.4 Hz, 1H), 7.04 – 6.93 (m, 2H), 6.73 (dd, J = 8.7, 2.5 Hz, 1H), 6.23 (d, J = 7.8 Hz,

1H), 5.24 (s, 2H), 4.97 (s, 1H, OH), 4.42 (q, J = 7.1 Hz, 2H), 2.66 (s, 3H), 2.44 (s, 3H), 1.46 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.1, 152.8, 145.2, 135.2, 134.9, 130.4, 130.1, 127.2, 126.9, 126.1, 123.7, 111.6, 110.7, 105.6, 102.7, 58.8, 44.0, 18.7, 14.5, 11.6; HRMS: calcd. for $C_{20}H_{21}NO_3$ 324.1600 ($M+H^+$), found 324.1605 ($M+H^+$).

Ethyl 1-(3-methylbenzyl)-2-methyl-5-hydroxyindole-3-carboxylate (49b). The titled compound was obtained from 3-methylbenzylamine according to the general procedure A as orange solid (732 mg, yield 21%). Mp 176 – 177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 2.3 Hz, 1H), 7.16 (t, J = 7.7 Hz, 1H), 7.12 – 7.01 (m, 2H), 6.83 – 6.68 (m, 3H), 5.27 (s, 2H), 5.17 (s, 1H, OH), 4.40 (q, J = 7.2 Hz, 2H), 2.70 (s, 3H), 2.27 (s, 3H), 1.44 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 151.5, 145.6, 138.7, 136.3, 131.6, 128.8, 128.4, 127.8, 126.5, 123.0, 111.5, 110.3, 106.4, 103.9, 59.6, 46.7, 21.4, 14.7, 12.1; HRMS: calcd. for $C_{20}H_{21}NO_3$ 324.1600 ($M+H^+$), found 324.1605 ($M+H^+$).

Ethyl 1-(4-methylbenzyl)-2-methyl-5-hydroxyindole-3-carboxylate (49c). The titled compound was obtained from 4-methylbenzylamine according to the general procedure A as greenish solid (400 mg, yield 18%). Mp 177 – 178 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 2.5 Hz, 1H), 7.08 (dd, J = 8.2, 3.3 Hz, 3H), 6.86 (d, J = 7.6 Hz, 2H), 6.75 (d, J = 8.2 Hz, 1H), 5.27 (s, 2H), 5.15 (s, 1H), 4.40 (q, J = 7.2 Hz, 2H), 2.69 (s, 3H), 2.30 (s, 3H), 1.44 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 151.4, 145.6, 137.4, 133.3, 131.5, 129.6 (2C), 127.8, 125.8 (2C), 111.5, 110.3, 106.4, 103.9, 59.6, 46.5, 21.0, 14.7, 12.1; HRMS: calcd. for $C_{20}H_{21}NO_3$ 324.1600 ($M+H^+$), found 324.1605 ($M+H^+$).

Ethyl 1-(2-methoxybenzyl)-2-methyl-5-hydroxyindole-3-carboxylate (49d). The titled compound was obtained from 2-methoxbenzylamine according to the general procedure A as greenish solid (400 mg, yield 12%). Mp 203 – 204 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.22 (t, J = 7.9 Hz, 1H), 7.06 (d, J = 8.8 Hz, 1H), 6.91 (d, J = 8.2 Hz, 1H), 6.80 – 6.68 (m, 2H), 6.31 (d, J = 7.6 Hz, 1H), 5.29 (s, 2H), 5.12 (s, 1H, OH), 4.41 (q, J = 7.2 Hz, 2H), 3.92 (s, 3H), 2.68 (s, 3H), 1.45 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 156.3, 151.4, 146.0, 131.6, 128.5, 127.8, 126.2, 124.4, 120.8,

111.4, 110.4, 109.9, 106.4, 103.8, 59.5, 55.3, 42.0, 14.7, 12.0; HRMS: calcd. for $C_{20}H_{21}NO_4$ 340.1549 ($M+H^+$), found 340.1550 ($M+H^+$).

Ethyl 1-(3-methoxybenzyl)-2-methyl-5-hydroxyindole-3-carboxylate (49e). The titled compound was obtained from 3-methoxbenzylamine according to the general procedure A as greenish solid (242 mg, yield 98%). Mp 171 – 172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 2.5 Hz, 1H), 7.19 (t, *J* = 7.9 Hz, 1H), 7.08 (d, *J* = 8.7 Hz, 1H), 6.76 (td, *J* = 8.6, 2.3 Hz, 2H), 6.60 – 6.47 (m, 2H), 5.28 (s, 2H), 5.22 (s, 1H, OH), 4.40 (q, *J* = 7.1 Hz, 2H), 3.72 (s, 3H), 2.70 (s, 3H), 1.44 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 160.2, 151.6, 145.7, 138.1, 131.6, 130.2, 127.9, 118.3, 112.7, 112.1, 111.7, 110.4, 106.6, 104.2, 59.7, 55.3, 46.7, 14.8, 12.2; HRMS: calcd. for $C_{20}H_{21}NO_4$ 340.1549 ($M+H^+$), found 340.1545 ($M+H^+$).

Ethyl 1-(4-methoxybenzyl)-2-methyl-5-hydroxyindole-3-carboxylate (49f). The titled compound was obtained from 4-methoxbenzylamine according to the general procedure A as greenish solid (498 mg, yield 15%). Mp 163 – 164 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 2.3 Hz, 1H), 7.13 – 7.04 (m, 1H), 6.90 (d, *J* = 8.0 Hz, 2H), 6.84 – 6.71 (m, 3H), 5.30 (s, 1H), 5.24 (s, 2H), 4.39 (q, *J* = 7.2 Hz, 2H), 3.75 (s, 3H), 2.70 (s, 3H), 1.43 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 159.0, 151.5, 145.5, 131.5, 128.3, 127.8, 127.2 (2C), 114.3 (2C), 111.5, 110.3, 106.4, 103.9, 59.6, 55.3, 46.2, 14.6, 12.2; HRMS: calcd. for $C_{20}H_{22}NO_4$ 340.1549 ($M+H^+$), found 340.1547 ($M+H^+$).

Ethyl 1-(2-fluorobenzyl)-2-methyl-5-hydroxyindole-3-carboxylate (49g). The titled compound was obtained from 2-fluorobenzylamine according to the general procedure A as yellow solid (292 mg, yield 11%). Mp 176 – 177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 2.5 Hz, 1H), 7.25 – 7.18 (m, 2H), 7.10 (dd, *J* = 11.0, 8.3 Hz, 2H), 6.95 (t, *J* = 7.9 Hz, 1H), 6.77 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.49 (t, *J* = 7.4 Hz, 1H), 5.36 (s, 2H), 5.26 (s, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 2.70 (s, 3H), 1.45 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 161.2, 158.8, 151.8, 145.7, 131.5, 129.5 (d, *J* = 8.0 Hz), 128.0, 127.5 (d, *J* = 3.8 Hz), 124.8 (d, *J* = 3.6 Hz), 123.6 (d, *J* = 14.4 Hz), 115.5 (d, *J* = 20.8 Hz), 111.8,

110.2, 106.7, 104.4, 59.8, 40.7, 14.8, 12.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -118.44 – -118.61 (m); HRMS: calcd. for $C_{19}H_{18}NO_3$ 328.1349 ($M+H^+$), found 328.1345 ($M+H^+$).

Ethyl 1-(3-fluorobenzyl)-2-methyl-5-hydroxyindole-3-carboxylate (49h). The titled compound was obtained from 3-fluorobenzylamine according to the general procedure A as yellow solid (147 mg, yield 6%). Mp 187 – 188 °C; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.65 (d, *J* = 2.5 Hz, 1H), 7.29 – 7.19 (m, 1H), 7.06 (d, *J* = 8.5 Hz, 1H), 6.95 (t, *J* = 8.5 Hz, 1H), 6.76 (t, *J* = 7.8 Hz, 2H), 6.66 (d, *J* = 9.4 Hz, 1H), 5.30 (s, 2H), 5.04 (s, 1H, OH), 4.41 (q, *J* = 7.2 Hz, 2H), 2.70 (s, 3H), 1.45 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.1, 162.3 (d, *J* = 244.2 Hz), 152.9, 144.9, 140.3 (d, *J* = 7.1 Hz), 130.8 (d, *J* = 8.3 Hz), 130.2, 127.2, 122.1, 114.15 (d, *J* = 20.9 Hz), 113.05 (d, *J* = 22.0 Hz), 111.7, 110.7, 105.6, 102.8, 58.8, 45.4, 14.5, 11.8; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -111.86 – -111.97 (m); HRMS: calcd. for $C_{19}H_{18}NO_3$ 328.1349 ($M+H^+$), found 328.1341 ($M+H^+$).

Ethyl 1-(4-fluorobenzyl)-2-methyl-5-hydroxyindole-3-carboxylate (49i). The titled compound was obtained from 4-fluorobenzylamine according to the general procedure A as yellow solid (485 mg, yield 15%). Mp 197 – 198 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 2.8 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 1H), 7.01 – 6.86 (m, 4H), 6.77 (d, *J* = 8.7 Hz, 1H), 5.53 (s, 1H, OH), 5.27 (s, 2H), 4.40 (q, *J* = 7.3 Hz, 2H), 2.68 (s, 3H), 1.44 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 162.2 (d, *J* = 246.6 Hz), 151.6, 145.3, 132.0 (d, *J* = 3.2 Hz), 131.3, 127.8, 127.6 (d, *J* = 8.2 Hz, 2C), 115.9 (d, *J* = 21.6 Hz, 2C), 111.7, 110.2, 106.5, 104.2, 59.7, 46.0, 14.6, 12.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.48 – -114.68; HRMS: calcd. for $C_{19}H_{18}NO_3$ 328.1349 ($M+H^+$), found 328.1349 ($M+H^+$).

Ethyl 1-(3-trifluoromethylbenzyl)-2-methyl-5-hydroxyindole-3-carboxylate (49j). The titled compound was obtained from 3-trifluoromethylbenzylamine according to the general procedure A as yellow solid (508 mg, yield 24%). Mp 190 – 191 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 2.5 Hz, 1H), 7.53 (d, *J* = 8.1 Hz, 1H), 7.38 (t, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.7 Hz, 1H), 6.99 (d, *J* = 8.1 Hz, 1H), 6.77 (dd, *J* = 8.7, 2.5 Hz, 1H), 5.36 (s, 2H), 5.06 (s, 1H, OH), 4.41 (q, *J* = 7.1 Hz, 2H), 2.70 (s,

3H), 1.46 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 151.7, 145.4, 137.6, 131.5 (q, J = 33 Hz), 131.4, 129.8, 129.2, 128.0, 124.8 (q, J = 3.8 Hz), 123.9 (q, J = 272 Hz), 122.9 (t, J = 3.9 Hz), 111.9, 110.1, 106.8, 104.6, 59.8, 46.4, 14.8, 12.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.68; HRMS: calcd. for $C_{20}H_{18}F_3NO_3$ 378.1317 ($M+H^+$), found 378.1311 ($M+H^+$).

Ethyl 1-(4-trifluoromethylbenzyl)-2-methyl-5-hydroxyindole-3-carboxylate (49k). The titled compound was obtained from 4-trifluoromethylbenzylamine according to the general procedure A as yellow solid (418 mg, yield 19%). Mp 193 – 194 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.65 (m, 1H), 7.54 (d, J = 8.2 Hz, 2H), 7.11 – 6.99 (m, 3H), 6.77 (dd, J = 8.7, 2.5 Hz, 1H), 5.36 (s, 2H), 5.31 (s, 1H, OH), 4.41 (q, J = 7.1 Hz, 2H), 2.68 (s, 3H), 1.45 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 151.8, 145.3, 140.5, 131.4, 130.2 (q, J = 33 Hz), 128.0, 126.3 (2C), 126.1 (q, J = 3.8 Hz, 2C), 124.0 (q, J = 272 Hz), 111.9, 110.1, 106.8, 104.6, 59.9, 46.4, 14.7, 12.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.66; HRMS: calcd. for $C_{20}H_{18}F_3NO_3$ 378.1317 ($M+H^+$), found 378.1313 ($M+H^+$).

Ethyl 1-(2-nitrobenzyl)-2-methyl-5-hydroxyindole-3-carboxylate (49l). The titled compound was obtained from 2-nitrobenzylamine according to the general procedure B as yellow solid (570 mg, yield 17%). Mp 187 – 188 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.01 (s, 1H, OH), 8.23 (dd, J = 7.6, 1.9 Hz, 1H), 7.56 (tt, J = 7.7, 6.0 Hz, 2H), 7.44 (d, J = 2.4 Hz, 1H), 7.24 (d, J = 8.8 Hz, 1H), 6.60 (dd, J = 8.7, 2.4 Hz, 1H), 6.17 (dd, J = 6.9, 2.0 Hz, 1H), 5.82 (s, 2H), 4.30 (q, J = 7.1 Hz, 2H), 2.60 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.0, 153.0, 147.0, 145.2, 134.6, 133.0, 130.1, 128.6, 127.2, 126.5, 125.4, 111.8, 110.8, 105.6, 103.2, 58.9, 44.0, 14.5, 11.5; HRMS: calcd. for $C_{19}H_{18}N_2O_5$ 355.1294 ($M+H^+$), found 355.1290 ($M+H^+$).

Ethyl 1-(3-nitrobenzyl)-2-methyl-5-hydroxyindole-3-carboxylate (49m). The titled compound was obtained from 3-nitrobenzylamine according to the general procedure B as yellow solid (387 mg, yield 21%). Mp 223 – 224 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.02 (s, 1H, OH), 8.13 (dd, J = 8.3, 1.7 Hz, 1H), 7.96 – 7.89 (m, 1H), 7.61 (t, J = 8.0 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H),

7.29 (d, J = 8.8 Hz, 1H), 6.65 (dd, J = 8.7, 2.4 Hz, 1H), 5.63 (s, 2H), 4.29 (q, J = 7.1 Hz, 2H), 2.66 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.0, 152.9, 148.0, 144.9, 139.7, 132.7, 130.4, 130.1, 127.2, 122.3, 120.9, 111.8, 110.7, 105.6, 103.0, 58.9, 45.1, 14.5, 11.8; HRMS: calcd. for $C_{19}H_{18}N_2O_5$ 355.1294 ($M+H^+$), found 355.1292 ($M+H^+$).

Ethyl 1-(4-nitrobenzyl)-2-methyl-5-hydroxyindole-3-carboxylate (49n). The titled compound was obtained from 4-nitrobenzylamine according to the general procedure B as yellow solid (950 mg, yield 28%). Mp 218–219 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.01 (s, 1H, OH), 8.19 (d, J = 8.5 Hz, 2H), 7.42 (d, J = 2.4 Hz, 1H), 7.23 (dd, J = 11.1, 8.6 Hz, 3H), 6.64 (dd, J = 8.7, 2.4 Hz, 1H), 5.63 (s, 2H), 4.29 (q, J = 7.1 Hz, 2H), 2.64 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.0, 152.9, 146.7, 145.2, 144.9, 130.1, 127.3 (2C), 127.2, 123.9 (2C), 111.8, 110.6, 105.6, 103.0, 58.9, 45.4, 14.5, 11.7; HRMS: calcd. for $C_{19}H_{18}N_2O_5$ 355.1294 ($M+H^+$), found 355.1291 ($M+H^+$).

Ethyl 1-(2-methylbenzyl)-2-methyl-5-(3-(piperidin-1-yl)propoxy)-1*H*-indole-3-carboxylate (50). The titled product was obtained from chloro intermediate **20d** according to the general procedure as a yellow solid (70 mg, yield 64%). Mp 98 – 99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 2.5 Hz, 1H), 7.20 (d, J = 4.5 Hz, 1H), 7.14 (t, J = 7.4 Hz, 1H), 7.05 – 6.93 (m, 2H), 6.79 (dd, J = 8.8, 2.5 Hz, 1H), 6.21 (d, J = 7.7 Hz, 1H), 5.21 (s, 2H), 4.42 (q, J = 7.1 Hz, 2H), 4.08 (t, J = 6.3 Hz, 2H), 2.64 (s, 3H), 2.59 – 2.49 (m, 2H), 2.43 (bs, 5H), 2.07 – 1.98 (m, 2H), 1.61 (dq, J = 11.2, 5.3 Hz, 4H), 1.47 (t, J = 7.1 Hz, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 155.2, 145.4, 134.5, 134.3, 131.5, 130.4, 127.7, 127.5, 126.7, 124.8, 112.5, 110.2, 104.9, 104.4, 67.2, 59.5, 54.7 (2C), 44.7, 27.1, 26.0 (2C), 24.5, 19.2, 14.8, 12.0; HRMS: calcd. for $C_{28}H_{36}N_2O_3$ 449.2804 ($M+H^+$), found 449.2809 ($M+H^+$).

Ethyl 1-(3-methylbenzyl)-2-methyl-5-(3-(piperidin-1-yl)propoxy)-1*H*-indole-3-carboxylate (51). The titled product was obtained from chloro intermediate **20e** according to the general procedure as a yellow solid (77 mg, yield 68%). Mp 84 – 87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 2.5 Hz, 1H), 7.14 (t, J = 7.6 Hz, 1H), 7.09 (d, J = 8.8 Hz, 1H), 7.04 (d, J = 7.6 Hz, 1H), 6.81 (dd, J = 8.9, 2.5

Hz, 1H), 6.78 (bs, 1H), 6.73 (d, *J* = 7.6 Hz, 1H), 5.25 (s, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.08 (t, *J* = 6.3 Hz, 2H), 2.69 (s, 3H), 2.57 – 2.49 (m, 2H), 2.44 (bs, 4H), 2.26 (s, 3H), 2.13 – 1.95 (m, 2H), 1.61 (p, *J* = 5.6 Hz, 4H), 1.46 (t, *J* = 7.1 Hz, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 155.1, 145.2, 138.7, 136.4, 131.5, 128.9, 128.5, 127.6, 126.5, 123.0, 112.4, 110.3, 104.8, 104.2, 67.1, 59.5, 56.3, 54.7 (2C), 46.7, 27.0, 25.9 (2C), 24.4, 21.5; HRMS: calcd. for $C_{28}H_{36}N_2O_3$ 449.2804 ($M+H^+$), found 449.2802 ($M+H^+$).

Ethyl 1-(4-methylbenzyl)-2-methyl-5-(3-(piperidin-1-yl)propoxy)-1*H*-indole-3-carboxylate (52). The titled product was obtained from chloro intermediate **20f** according to the general procedure as a yellow solid (98 mg, yield 88%). Mp 101 – 102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 2.5 Hz, 1H), 7.12 – 7.02 (m, 3H), 6.84 (d, *J* = 8.1 Hz, 2H), 6.80 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.25 (s, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.08 (t, *J* = 6.3 Hz, 2H), 2.69 (s, 3H), 2.58 – 2.47 (m, 2H), 2.44 (bs, 4H), 2.29 (s, 3H), 2.09 – 1.92 (m, 2H), 1.60 (p, *J* = 5.6 Hz, 4H), 1.45 (t, *J* = 7.1 Hz, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 155.1, 145.2, 137.4, 133.4, 131.5, 129.6 (2C), 127.6, 125.9 (2C), 112.4, 110.3, 104.8, 104.3, 67.2, 59.5, 56.3, 54.7 (2C), 46.5, 27.1, 26.0 (2C), 24.5, 21.1, 14.7, 12.2; HRMS: calcd. for $C_{28}H_{36}N_2O_3$ 449.2804 ($M+H^+$), found 449.2808 ($M+H^+$).

Ethyl 1-(2-methoxybenzyl)-2-methyl-5-(3-(piperidin-1-yl)propoxy)-1*H*-indole-3-carboxylate (53). The titled product was obtained from chloro intermediate **20g** according to the general procedure as a yellow solid (100 mg, yield 90%). Mp 120 – 121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 2.5 Hz, 1H), 7.26 – 7.17 (m, 1H), 7.08 (d, *J* = 8.8 Hz, 1H), 6.90 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.82 – 6.68 (m, 2H), 6.29 (dd, *J* = 7.6, 1.6 Hz, 1H), 5.29 (s, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.09 (t, *J* = 6.2 Hz, 2H), 3.92 (s, 3H), 2.67 (s, 3H), 2.64 – 2.58 (m, 2H), 2.54 – 2.50 (m, 4H), 2.14 – 2.01 (m, 2H), 1.66 (p, *J* = 5.6 Hz, 4H), 1.46 (t, *J* = 7.1 Hz, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 156.4, 155.0, 145.7, 131.6, 128.6, 127.6, 126.3, 124.6, 120.9, 112.3, 110.4, 110.0, 104.8, 104.2, 67.0, 59.5, 56.3, 55.4, 54.6 (2C), 42.1, 26.7, 25.6 (2C), 24.3, 14.8, 12.0; HRMS: calcd. for $C_{28}H_{36}N_2O_4$ 465.2753 ($M+H^+$), found 465.2750 ($M+H^+$).

Ethyl 1-(3-methoxybenzyl)-2-methyl-5-(3-(piperidin-1-yl)propoxy)-1*H*-indole-3-carboxylate (54). The titled product was obtained from chloro intermediate **20h** according to the general procedure as a white solid (61 mg, yield 55%). Mp 61 – 64 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 2.5 Hz, 1H), 7.18 (t, *J* = 7.9 Hz, 1H), 7.10 (d, *J* = 8.9 Hz, 1H), 6.84 – 6.73 (m, 2H), 6.56 – 6.49 (m, 2H), 5.27 (s, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.09 (t, *J* = 6.2 Hz, 2H), 3.71 (s, 3H), 2.70 (s, 3H), 2.68 – 2.50 (m, 6H), 2.16 – 2.05 (m, 2H), 1.70 (p, *J* = 5.6 Hz, 4H), 1.53 – 1.41 (m, 2H), 1.45 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 160.1, 155.0, 145.3, 138.1, 131.5, 130.1, 127.6, 118.2, 112.6, 112.4, 112.1, 110.2, 104.9, 104.4, 66.9, 59.5, 56.2, 55.3, 54.5 (2C), 46.6, 26.5, 25.4 (2C), 24.1, 14.8, 12.2; HRMS: calcd. for $C_{28}H_{36}N_2O_4$ 465.2753 ($M+H^+$), found 465.2750 ($M+H^+$).

Ethyl 1-(4-methoxybenzyl)-2-methyl-5-(3-(piperidin-1-yl)propoxy)-1*H*-indole-3-carboxylate (55). The titled product was obtained from chloro intermediate **20i** according to the general procedure as a white solid (100 mg, yield 90%). Mp 111 – 112 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 2.5 Hz, 1H), 7.12 (d, *J* = 8.8 Hz, 1H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.84 – 6.73 (m, 3H), 5.25 (s, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.08 (t, *J* = 6.3 Hz, 2H), 3.75 (s, 3H), 2.70 (s, 3H), 2.60 – 2.49 (m, 2H), 2.44 (bs, 4H), 2.02 (p, *J* = 6.5 Hz, 2H), 1.61 (p, *J* = 5.7 Hz, 4H), 1.45 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 159.2, 155.2, 145.2, 131.5, 128.5, 127.7, 127.3 (2C), 114.4 (2C), 112.5, 110.3, 104.9, 104.3, 67.2, 59.5, 56.4, 55.4, 54.8 (2C), 46.3, 27.1, 26.0 (2C), 24.5, 14.8, 12.2; HRMS: calcd. for $C_{28}H_{36}N_2O_4$ 465.2753 ($M+H^+$), found 465.2750 ($M+H^+$).

Ethyl 1-(2-fluorobenzyl)-2-methyl-5-(3-(piperidin-1-yl)propoxy)-1*H*-indole-3-carboxylate (56). The titled product was obtained from chloro intermediate **20j** according to the general procedure as a yellow solid (40 mg, yield 36%). Mp 99 – 100 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 2.5 Hz, 1H), 7.32 – 7.20 (m, 1H), 7.17 – 7.07 (m, 2H), 6.96 (t, *J* = 7.5 Hz, 1H), 6.85 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.50 (t, *J* = 7.7 Hz, 1H), 5.37 (s, 2H), 4.43 (q, *J* = 7.1 Hz, 2H), 4.10 (t, *J* = 6.4 Hz, 2H), 2.72 (s, 3H), 2.53 (t, *J* = 7.4 Hz, 2H), 2.44 (bs, 4H), 2.04 (p, *J* = 6.5 Hz, 2H), 1.62 (p, *J* = 5.6 Hz, 4H), 1.47 (t, *J* =

7.4 Hz, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 159.8 (d, *J* = 246.0 Hz), 155.2, 145.1, 131.2, 129.3 (d, *J* = 8.0 Hz), 127.6, 127.4 (d, *J* = 3.8 Hz), 124.6 (d, *J* = 3.6 Hz), 123.5 (d, *J* = 14.3 Hz), 115.4 (d, *J* = 20.8 Hz), 112.6, 110.0, 104.8, 104.5, 67.1, 59.5, 56.2, 54.7 (2C), 40.6, 27.0, 26.0 (2C), 24.5, 14.6, 11.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -118.48 – -118.59 (m); HRMS: calcd. for $C_{27}H_{33}FN_2O_3$ 453.2553 ($M+H^+$), found 453.2550 ($M+H^+$).

Ethyl 1-(3-fluorobenzyl)-2-methyl-5-(3-(piperidin-1-yl)propoxy)-1*H*-indole-3-carboxylate (57). The titled product was obtained from chloro intermediate **20k** according to the general procedure as a white solid (36 mg, yield 32%). Mp 109 – 110 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 2.5 Hz, 1H), 7.23 (dd, *J* = 6.1, 2.2 Hz, 1H), 7.07 (d, *J* = 8.8 Hz, 1H), 6.93 (td, *J* = 8.5, 2.6 Hz, 1H), 6.82 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.73 (d, *J* = 7.7 Hz, 1H), 6.65 (d, *J* = 8.7 Hz, 1H), 5.28 (s, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.08 (t, *J* = 6.4 Hz, 2H), 2.69 (s, 3H), 2.51 (t, *J* = 7.8 Hz, 2H), 2.42 (bs, 4H), 2.01 (p, *J* = 7.2 Hz, 2H), 1.60 (p, *J* = 5.6 Hz, 4H), 1.46 (t, *J* = 7.1 Hz, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 163.3 (d, *J* = 247.4 Hz), 155.3, 144.9, 139.2 (d, *J* = 6.9 Hz), 131.3, 130.6 (d, *J* = 8.3 Hz), 127.7, 121.5 (d, *J* = 2.9 Hz), 114.8 (d, *J* = 21.1 Hz), 113.1 (d, *J* = 22.3 Hz), 112.7, 110.1, 105.0, 104.7, 67.3, 59.6, 56.3, 54.8 (2C), 46.2, 27.1, 26.1 (2C), 24.6, 14.7, 12.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.95 (td, *J* = 9.1, 5.9 Hz); HRMS: calcd. for $C_{27}H_{33}FN_2O_3$ 453.2553 ($M+H^+$), found 453.2550 ($M+H^+$).

Ethyl 1-(4-fluorobenzyl)-2-methyl-5-(3-(piperidin-1-yl)propoxy)-1*H*-indole-3-carboxylate (58). The titled product was obtained from chloro intermediate **20l** according to the general procedure as a orange solid (64 mg, yield 93%). Mp 122 – 123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 2.5 Hz, 1H), 7.07 (d, *J* = 8.8 Hz, 1H), 7.00 – 6.88 (m, 4H), 6.81 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.26 (s, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.07 (t, *J* = 6.3 Hz, 2H), 2.68 (s, 3H), 2.60 – 2.53 (m, 2H), 2.47 (bs, 4H), 2.12 – 1.97 (m, 2H), 1.62 (p, *J* = 5.6 Hz, 4H), 1.45 (t, *J* = 7.1 Hz, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 162.2 (d, *J* = 246.3 Hz), 155.2, 145.0, 132.2 (d, *J* = 3.2 Hz), 131.3, 127.8, 127.6 (d, *J* = 8.2 Hz, 2C), 116.0 (d, *J* = 21.7 Hz, 2C), 112.6, 110.1, 104.9, 104.6, 67.1, 59.6, 56.3, 54.7 (2C), 46.1, 26.9, 25.8 (2C), 24.4,

14.7, 12.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.53 – -114.71 (m); HRMS: calcd. for $C_{27}H_{33}FN_2O_3$ 453.2553 ($M+H^+$), found 453.2550 ($M+H^+$).

Ethyl 1-(3-trifluoromethylbenzyl)-2-methyl-5-(3-(piperidin-1-yl)propoxy)-1*H*-indole-3-carboxylate (59). The titled product was obtained from chloro intermediate **20m** according to the general procedure as a white solid (76 mg, yield 68%). Mp 146 – 147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 2.5 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.43 – 7.34 (m, 2H), 7.06 (d, *J* = 8.8 Hz, 1H), 6.98 (d, *J* = 7.8 Hz, 1H), 6.83 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.36 (s, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 4.09 (t, *J* = 6.3 Hz, 2H), 2.70 (s, 3H), 2.53 (t, *J* = 7.5 Hz, 2H), 2.44 (bs, 5H), 2.03 (p, *J* = 7.4 Hz, 2H), 1.61 (p, *J* = 5.6 Hz, 5H), 1.46 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 155.4, 144.8, 137.7, 131.4 (q, *J* = 30.8 Hz), 131.3, 129.8, 129.2, 127.7, 124.8 (q, *J* = 3.7 Hz), 124.7 (q, *J* = 273.3 Hz), 122.9 (q, *J* = 3.7 Hz), 112.8, 110.0, 105.1, 104.9, 67.2, 59.7, 56.3, 54.8 (2C), 46.4, 27.1, 26.0 (2C), 24.5, 14.8, 12.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.7; HRMS: calcd. for $C_{28}H_{33}F_3N_2O_3$ 503.2522 ($M+H^+$), found 503.2522 ($M+H^+$).

Ethyl 1-(4-trifluoromethylbenzyl)-2-methyl-5-(3-(piperidin-1-yl)propoxy)-1*H*-indole-3-carboxylate (60). The titled product was obtained from chloro intermediate **20n** according to the general procedure as a white solid (90 mg, yield 82%). Mp 148 – 149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 2.5 Hz, 1H), 7.53 (d, *J* = 8.1 Hz, 2H), 7.05 (dd, *J* = 8.5, 3.7 Hz, 3H), 6.82 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.37 (s, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.08 (t, *J* = 6.3 Hz, 2H), 2.69 (s, 3H), 2.53 (t, *J* = 7.5 Hz, 2H), 2.43 (bs, 4H), 2.02 (p, *J* = 6.5 Hz, 2H), 1.61 (p, *J* = 5.6 Hz, 4H), 1.46 (t, *J* = 7.1 Hz, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 155.4, 144.8, 140.6, 131.2, 130.0 (q, *J* = 32.8 Hz), 127.7, 126.3 (2C), 126.1 (q, *J* = 3.8 Hz, 2C), 124.0 (q, *J* = 274.3 Hz), 112.8, 110.0, 105.1, 104.9, 67.3, 59.7, 56.3, 54.8 (2C), 46.3, 27.1, 26.0 (2C), 24.5, 14.8, 12.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.6; HRMS: calcd. for $C_{28}H_{33}F_3N_2O_3$ 503.2522 ($M+H^+$), found 503.2525 ($M+H^+$).

Ethyl 1-(2-nitrobenzyl)-2-methyl-5-(3-(piperidin-1-yl)propoxy)-1*H*-indole-3-carboxylate (61). The titled product was obtained from chloro intermediate **20o** according to the general procedure as a orange solid (130 mg, yield 69%). Mp 123 – 124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.72 (d, *J* = 2.5 Hz, 1H), 7.50 – 7.34 (m, 2H), 6.99 (d, *J* = 8.8 Hz, 1H), 6.81 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.31 (dd, *J* = 7.4, 1.4 Hz, 1H), 5.72 (s, 2H), 4.43 (q, *J* = 7.1 Hz, 2H), 4.09 (t, *J* = 6.4 Hz, 2H), 2.65 (s, 3H), 2.51 (t, *J* = 7.4 Hz, 2H), 2.42 (bs, 4H), 2.02 (p, *J* = 7.5 Hz, 2H), 1.60 (p, *J* = 5.6 Hz, 4H), 1.52 – 1.38 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 155.5, 147.1, 144.9, 134.7, 133.0, 131.1, 128.7, 127.7, 127.4, 125.7, 112.9, 110.0, 105.1, 105.0, 67.2, 59.7, 56.3, 54.8 (2C), 44.6, 27.1, 26.1 (2C), 24.6, 14.7, 11.9; HRMS: calcd. for $C_{27}H_{33}N_3O_5$ 480.2498 ($M+H^+$), found 480.2499 ($M+H^+$).

Ethyl 1-(3-nitrobenzyl)-2-methyl-5-(3-(piperidin-1-yl)propoxy)-1*H*-indole-3-carboxylate (62). The titled product was obtained from chloro intermediate **20p** according to the general procedure as an orange solid (141 mg, yield 53%). Mp 102 – 104 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.4 Hz, 1H), 7.97 (q, *J* = 2.0 Hz, 1H), 7.70 (d, *J* = 2.5 Hz, 1H), 7.43 (td, *J* = 8.0, 1.4 Hz, 1H), 7.13 (d, *J* = 7.7 Hz, 1H), 7.04 (d, *J* = 8.8 Hz, 1H), 6.83 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.39 (s, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.08 (t, *J* = 6.3 Hz, 2H), 2.70 (s, 3H), 2.52 (t, *J* = 8.2 Hz, 2H), 2.42 (bs, 4H), 2.02 (p, *J* = 7.0 Hz, 2H), 1.60 (p, *J* = 5.5 Hz, 4H), 1.52 – 1.37 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 155.4, 148.7, 144.5, 138.8, 131.9, 131.0, 130.2, 127.8, 122.9, 121.1, 112.9, 109.8, 105.1, 105.1, 67.2, 59.7, 56.3, 54.7 (2C), 46.0, 27.1, 26.1 (2C), 24.5, 14.7, 12.1; HRMS: calcd. for $C_{27}H_{33}N_3O_5$ 480.2498 ($M+H^+$), found 480.2499 ($M+H^+$).

Ethyl 1-(4-nitrobenzyl)-2-methyl-5-(3-(piperidin-1-yl)propoxy)-1*H*-indole-3-carboxylate (63). The titled product was obtained from chloro intermediate **20q** according to the general procedure as a yellow solid (82 mg, yield 69%). Mp 107 – 108 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.07 (m, 2H), 7.70 (d, *J* = 2.4 Hz, 1H), 7.09 (d, *J* = 9.0 Hz, 2H), 7.01 (d, *J* = 8.9 Hz, 1H), 6.82 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.38 (s, 2H), 4.42 (q, *J* = 7.2 Hz, 2H), 4.08 (t, *J* = 6.4 Hz, 2H), 2.67 (s, 3H), 2.52 (t, *J* = 7.7 Hz,

2H), 2.42 (bs, 4H), 2.02 (p, *J* = 7.7 Hz, 2H), 1.60 (p, *J* = 5.6 Hz, 4H), 1.47 (t, *J* = 7.1 Hz, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 155.4, 147.6, 144.5, 143.9, 131.0, 127.7, 126.8 (2C), 124.3 (2C), 112.9, 109.8, 105.1, 105.1, 67.2, 59.7, 56.2, 54.7 (2C), 46.1, 27.1, 26.0 (2C), 24.5, 14.7, 12.0; HRMS: calcd. for $C_{27}H_{33}N_3O_5$ 480.2498 ($M+H^+$), found 480.2499 ($M+H^+$).

Ethyl 2-(5-methoxy-2-methyl-1*H*-indol-3-yl)acetate (64).[52] A stirred mixture of 4-methoxyphenylhydrazine hydrochloride (6 g, 34.4 mmol, 1.0 eq), ethyl levulinate (4.96 g, 34.4 mmol, 1.0 eq), and sodium acetate (2.81 g, 34.4 mmol) in glacial acetic acid (46 mL) was heated at reflux for 3 h. The reaction mixture was concentrated to dryness. The residue was dissolved in ethanol (30 mL), treated with 4 M HCl in 1,4-dioxane (18 mL), and heated at a gentle reflux for 15 h. The mixture was concentrated to remove the volatiles, and the residue was taken up with EtOAc, washed with water, aqueous K_2CO_3, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated. Chromatography of the residue (1:1 EtOAc/hexane, silica gel) afforded the title compound as a pink solid (6.8 g, yield 80%). Mp 83 – 88 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.07 (dd, *J* = 8.6, 1.0 Hz, 1H), 7.04 – 7.01 (m, 1H), 6.77 (dd, *J* = 8.7, 2.4 Hz, 1H), 4.15 (q, *J* = 7.5, 7.0 Hz, 2H), 3.87 (s, 3H), 3.66 (s, 2H), 2.31 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 154.0, 133.6, 130.2, 128.8, 111.0, 110.8, 104.2, 100.4, 60.6, 55.8, 30.5, 14.2, 11.6; HRMS: calcd. for $C_{14}H_{17}NO_3$ 248.1287 ($M+H^+$), found 248.1287 ($M+H^+$).

Ethyl 2-(5-methoxy-2-methyl-1benzyl-indol-3-yl)acetate (65). To a stirred suspension of NaH (60 % dispersion in mineral oil) (233.0 mg, 9,7 mmol, 1.1 eq) in dry DMF (10 ml), a solution of indole **64** (2.0 g, 8.1 mmol, 1.0 eq) in dry DMF (10 ml) was added at r.t. dropwise. The stirring was continued for 40 minutes, then benzyl bromide (1.06 ml, 8.9 mmol, 1.05 eq) was added and the mixture was made to react overnight. The mixture was dropped in a water:ice 50/50 mixture, the solid filtered off and washed with water. After drying, was triturated with petroleum ether to afford 2.55 g (yield 92%) of a white solid that was characterized as follows. Mp 64 – 65 °C; ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.39 – 7.18 (m, 3H), 7.11 – 7.03 (m, 2H), 7.01 – 6.89 (m, 2 H), 6.76 (dd, *J* = 8.7, 2.5 Hz, 1H), 5.28 (s, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 3H), 3.70 (s, 2H), 2.33 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 154.1, 137.8, 134.9, 131.5, 128.7 (2C), 128.1, 127.2, 125.8 (2C), 110.8, 109.7, 104.2, 100.4, 60.6, 55.9, 46.7, 30.8, 14.2, 10.4; HRMS: calcd. for $C_{21}H_{23}NO_3$ 338.1756 ($M+H^+$), found 338.1751 ($M+H^+$).

2-(1-Benzyl-5-hydroxy-2-methyl-1*H*-indol-3-yl)acetic acid (66). Boron tribromide (1 M solution in dichloromethane, 15.2 ml, 15.2 mmol) was added dropwise at -78 °C under nitrogen to a stirred solution of methyl ether intermediate **64** (1.69 g, 5.00 mmol, 1.0 eq) in dichloromethane (20 ml). The mixture was made to react 4 h at r.t., then was quenched with ice, diluted with water and the resulting solid was filtered off, washed with water and dried. A white solid was isolated and used in the following reaction without any further purification (1.20 g, yield 82 %). Mp 218 °C dec; ^{1}H NMR (400 MHz, DMSO-*d*6) δ 12.05 (s, 1H), 8.62 (bs, 1H), 7.32 – 7.16 (m, 3H), 7.11 (d, *J* = 8.6 Hz, 1H), 7.02 – 6.91 (m, 2H), 6.77 (d, *J* = 2.3 Hz, 1H), 6.51 (dd, *J* = 8.7, 2.3 Hz, 1H), 5.29 (s, 2H), 3.51 (s, 2H), 2.24 (s, 3H); ^{13}C NMR (101 MHz, DMSO-*d*6) δ 173.5, 151.1, 139.1, 134.8, 130.9, 128.9 (2C), 128.7, 127.4, 126.5 (2C), 110.7, 110.1, 104.3, 102.7, 46.2, 30.7, 10.5; HRMS: calcd. for $C_{18}H_{17}NO_3$ 296.1287 ($M+H^+$), found 296.1288 ($M+H^+$).

Ethyl 2-(1-benzyl-5-hydroxy-2-methyl-1*H*-indol-3-yl)acetate (67). Thionyl chloride (16 ml) was added to carboxylic acid intermediate **65** (1.0 g, 3.38 mmol) and the mixture was refluxed 3 h. The volatile materials were evaporated, toluene was added and the solution was evaporated again. The solid was dissolved in 20 ml of ethanol abs. and stirred at r.t. overnight. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (eluent ethylacetate/petroleum ether 3:7) to give 646 mg (yield 59%) of a white solid. Mp 180 – 181 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (bs, 1H), 7.41 – 7.14 (m, 3H), 7.14 – 7.01 (m, 2H), 6.95 (dd, *J* = 7.7, 1.8 Hz, 2H), 6.76 (dd, *J* = 8.7, 2.5 Hz, 1H), 5.28 (s, 2H), 4.14 (q, *J* = 7.2 Hz, 2H),

3.71 (s, 2H), 2.33 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 154.1, 137.8, 134.9, 131.5, 128.7 (2C), 128.1, 127.2, 125.8 (2C), 110.8, 109.7, 104.2, 100.4, 60.6, 46.7, 30.8, 14.2, 10.4; HRMS: calcd. for $C_{20}H_{21}NO_3$ 324.1600 ($M+H^+$), found 324.1601 ($M+H^+$).

Ethyl 2-(1-benzyl-5-(3-chloropropoxy)-2-methyl-1*H*-indol-3-yl)acetate (68). The title product was obtained according to the general procedure for intermediate **20b** starting from compound **67** as pale yellow solid (150 mg, yield 60%). Mp 102 – 105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.16 (m, 3H), 7.10 – 7.03 (m, 2H), 6.93 (d, J = 7.2 Hz, 2H), 6.75 (d, J = 8.8 Hz, 1H), 5.25 (s, 2H), 4.22 – 4.06 (m, 4H), 3.76 (t, J = 6.5 Hz, 2H), 3.69 (s, 2H), 2.31 (s, 3H), 2.24 (p, J = 6.3 Hz, 2H), 1.23 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 153.2, 137.9, 135.1, 131.8, 128.8 (2C), 128.2, 127.3, 125.9 (2C), 111.3, 109.8, 104.4, 101.8, 65.2, 60.7, 46.7, 41.9, 32.6, 30.9, 14.3, 10.5. HRMS: calcd. for $C_{23}H_{27}{}^{35}ClNO_3$ 400.1679 ($M+H^+$), found 400.1679 ($M+H^+$).

Ethyl 2-(5-(3-(azepan-1-yl)propoxy)-1-benzyl-2-methyl-1*H*-indol-3-yl)acetate (69). The titled compound was obtained according to the general procedure as a yellow solid (47 mg, yield 53%); Mp 180 – 182 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.18 (m, 3H), 7.10 – 7.03 (m, 2H), 6.94 (d, J = 7.3 Hz, 2H), 6.75 (d, J = 8.9 Hz, 1H), 5.26 (s, 2H), 4.12 (q, J = 7.1 Hz, 2H), 4.05 (t, J = 6.4 Hz, 2H), 3.69 (s, 2H), 2.78 – 2.64 (m, 6H), 2.31 (s, 3H), 2.00 (p, J = 6.7 Hz, 2H), 1.73 – 1.55 (m, 8H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 153.5, 138.0, 135.0, 131.6, 128.7 (2C), 128.2, 127.2, 125.9 (2C), 111.3, 109.7, 104.3, 101.7, 67.2, 60.6, 55.5 (2C), 55.0, 46.7, 30.9 (2C), 27.7, 27.5, 27.0 (2C), 14.3, 10.5; HRMS: calcd. for $C_{29}H_{38}N_2O_3$ 463.2961 ($M+H^+$), found 463.2964 ($M+H^+$).

2-Methyl-1*H*-indol-5-ol (70). Ethyl 5-hydroxy-2-methyl-1*H*-indole-3-carboxylate **46** (219 mg, 1 mmol) was suspended in a mixture of EtOH (0.5 mL) and 5N HCl (2.5 mL) and it was refluxed for 3 hours. The ethanol was removed under vacuum and the mixture was cooled and neutralized with 5N NaOH to pH 7 below 15 ºC. The crude product was extracted with ethyl acetate, washed with water, dried under Na_2SO_4, filtrated and concentrated. If necessary, the crude material was purified through

flash column chromatography (petroleum ether: ethyl acetate 4:1) to give **70** as a yellow solid (yield 78%). NMR spectrum was in accordance to that described in the literature.[39]

5-(3-Chloropropoxy)-2-methyl-1*H*-indole (71). The titled product was obtained from hydroxyindole **70** following the general procedure described previously for the compound **20b** in 20% yield. Mp 71 – 72 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.8 Hz, 1H), 7.04 (s, 1H), 6.79 (d, *J* = 8.8 Hz, 1H), 6.17 (s, 1H, 4.17 (t, *J* = 5.6 Hz, 2H), 3.80 (t, *J* = 6.4 Hz, 2H), 2.44 (s, 3H), 2.29 – 2.22 (m, 2H).

2-Methyl-5-(3-(piperidin-1-yl)propoxy)-1*H*-indole (72). The titled product was obtained from chloro derivative **71** following the general procedure described previously for the compound **21-31** in 57% yield. Mp 110 – 111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.8 Hz, 1H), 7.02 (s, 1H), 6.77 (d, *J* = 8.8 Hz, 1H), 6.15 (s, 1H), 4.05 (t, *J* = 6.8 Hz, 2H), 2.55 (t, *J* = 7.2 Hz, 2H), 2.49 – 2.43 (m, 2H), 2.44 (s, 3H), 2.09 – 1.99 (m, 2H), 1.67 – 1.44 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.9, 134.6, 120.9, 111.2, 103.2 (2C), 100.3, 67.3, 56.2, 54.5 (2C), 29.7 (2C), 25.5, 24.3, 13.8.

1-Benzyl-2-methyl-5-(3-(piperidin-1-yl)propoxy)-1*H*-indole (73). 2-Methyl-5-(3-(piperidin-1-yl)propoxy)-1*H*-indole **72** (156 mg, 0.5 mmol, 1 eq) was added at r.t. to a suspension of sodium hydride (60% dispersion in mineral oil, 24 mg, 0.6 mmol, 1.2 eq) in DMF. After 40 minutes benzyl bromide (65 µL, 0.55 mmol, 1.1 eq) was added and the mixture was made to react for 16 h at r.t and then poured into iced water, extracted with ethyl acetate (3 x 15 mL) and washed with water (3 x 15 mL). The organic solution was dried with sodium sulfate and evaporated under reduced pressure. The solid residue was purified by column chromatography on silica gel (dichloromethane: methanol 95:5) to afford **73** as a white solid (yield 28%). Mp 87 – 88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.21 (m, 3H), 7.09 – -7.04 (m, 2H), 6.96 (d, *J* = 7.2 Hz, 2H), 6.74 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.26 (s, 1H), 5.28 (s, 2H), 4.09 (t, *J* = 6.0 Hz, 2H), 2.91 – 2.76 (m, 6H), 2.37 (s, 3H), 2.34 – 2.20 (m, 2H), 1.95 – 1.86 (m, 4H), 1.61 – 1.56 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.0, 154.3, 137.5, 128.5, 128.7

(2C), 128.5, 127.3, 125.9 (2C), 125.8, 110.7, 109.8, 103.2, 100.2, 66.4, 55.9, 53.9 (2C), 46.6, 25.3, 24.0 (2C), 23.1, 13.0. HRMS: calcd for $C_{24}H_{30}N_2O$ 362.2358 ($M+H^+$), found 362.2351 ($M+H^+$).

1-Benzyl-5-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid (74). Ethyl 1-benzyl-5-hydroxy-2-methyl-1H-indole-3-carboxylate **9** (306 mg, 1 mmol) was suspended in 2N NaOH (5 mL) and refluxed for 2 hours. After cooling to 0 ºC, the pH was adjusted to pH= 2 using 2N HCl. The aqueous layer was extracted with ethyl acetate (3 x 15 mL) and the combined organic phases were washed with brine, dried with sodium sulfate and evaporated under reduced pressure. The solid residue was purified by column chromatography on silica gel (dichloromethane/methanol 9:1) to afford **74** as a purple solid (yield 78%). Mp 158 – 159 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.90 (s, 1H), 7.43 (d, *J* = 2.4 Hz, 1H), 7.31 – 7.23 (m, 4H), 7.01 (d, *J* = 7.2 Hz, 2H), 6.61 (d, *J* = 8.4 Hz, 1H), 5.43 (s, 2H), 2.64 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 153.2, 138.9, 139.1, 129.2 (2C), 127.5, 126.7 (2C), 116.0, 111.8, 111.1, 106.1, 46.4, 12.2.

1-Benzyl-5-(3-chloropropoxy)-2-methyl-1*H*-indole-3-carboxylic acid (75). The titled product was obtained from hydroxyl derivative **74** following the procedure described previously for compound **20b** as a brown solid (11 mg, yield 10%); Mp 151 – 154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 2.4 Hz, 1H), 7.29 – 2.23 (m, 2H), 7.13 – 7.10 (m, 1H), 6.94 (d, *J* = 7.2 Hz, 2H), 6.82 – 6.79 (m, 2H), 5.31 (s, 2H), 4.17 (t, *J* = 6.4 Hz, 2H), 4.04 (t, *J* = 5.6 Hz, 2H), 2.68 (s, 3H), 2.24-2.15 (m, 2H).

1-Benzyl-2-methyl-5-(3-(piperidin-1-yl)propoxy)-1*H*-indole-3-carboxylic acid (76). The titled product was obtained from carboxylic acid **74** following the general procedure described previously for the compound **21-33** in 90% yield. Mp 110 – 112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.73 (m, 1H), 7.31 – 7.26 (m, 3H), 7.14 – 6.99 (m, 3H), 6.85 (d, *J* = 8.4 Hz, 1H), 5.37 (s, 2H), 4.22 (t, *J* = 5.6 Hz, 2H), 3.80 (t, *J* = 6.4 Hz, 2H), 2.75 (s, 3H), 2.76 – 2.71 (m, 2H), 2.37 – 2.27 (m, 4H), 2.03 – 1.98 (m, 2H), 1.47 – 1.25 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.1, 146.7, 136.1, 131.6, 129.0 (2C),

128.9, 127.8, 127.7, 125.9 (2C), 112.7, 110.4, 104.9, 65.0, 53.5, 46.8, 41.8 (2C), 32.6, 31.0, 29.7 (2C), 12.3. HRMS: calcd for $C_{25}H_{30}N_2O_3$ 406.2256 ($M+H^+$), found 406.2251 ($M+H^+$).

Metabolism

Substrates were incubated with human liver microsomes (HLM, 0.5 mg protein/ml) (BD Biosciences) according to the manufacturer's recommendations with minor modifications. Briefly, substrates at 10 µM final concentration were incubated in a shaking water bath for 5 minutes at 37 °C in 100 mM potassium phosphate buffer (pH 7.4) in a total volume of 250 µl. The reactions were initiated by addition of 1 mM NADPH. After incubation for 0 and 30 minutes, 250 µl of cold acetonitrile (containing 0.6 mM labetalol as internal standard) was added to terminate the reaction. Proteins were precipitated by centrifugation at 12000 g for 5 min at 4 °C, and aliquots of supernatants were analyzed by HPLC-MS/MS. The LC/MS analyses were run on a Agilent 6540 UHD accurate mass Q-TOF LC/MSMS system (Agilent Technologies, Palo Alto, CA) governed by Agilent MassHunter software (B.05.00 version). The system consists of a binary pump, autosampler, thermostatic column compartment, DAD detector, source, and Q-TOF spectrometer. Chromatographic separation of the metabolites (Agilent 1290 UHPLC system) was performed with Aeris Peptide 1.7 JXB-C18, 100 x 2.1 mm (Phenomenex USA) at a constant temperature of 40 °C. The mobile phases consisted of A: H_2O/0.1% formic acid and B: acetonitrile/0.1% formic acid at the flow of 0.3 mL/min with the following gradient: Time 0 min, B 0%; Time 10 min, B 100%. The DAD Detector stored all the acquired spectra in the 10-640 nm range (2 nm spectrum step). The ion source was an Agilent Dual JetStream operating under positive ionization mode (4000 V), with nitrogen the desolvating gas (320 °C, 10 L/min, 35 psig). The fragmentor was set to 110 V, the skimmer to 65 V, and the octrapole RF to 750 V. The spectrometric data were collected in All Ion mode in the 100-1000 mass range, with 3 scans/sec at Collision Energy of 0, 30, 40 V. The TOF operated at 2 GHz.

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Author Contributions

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Abbreviations: CPX, ciprofloxacin; S. aureus, Staphylococcus aureus; MIC, minimum inhibitory concentration; FLAP, fingerprints for ligands and proteins; MDR, multiple drug resistance; MRSA, methicillin-resistant Staphylococcus aureus; EPI, efflux pump inhibitor; EtBr, ethidium bromide; HBD, hydrogen Bond donor; HBA, hydrogen Bond acceptor; EWG, electron withdrawing group; ADME, adsorption disposition metabolism excretion; HLM, human liver microsoms; TFAA, trifluoroacetic anhydride; DMF, *N,N*-dimethylformamide; THF, tetrahydrofuran; TSP, 3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid sodium salt; DAST, diethylaminosulfur trifluoride; CAN, cerium ammonium nitrate; SMHB, cation-supplemented Mueller-Hinton broth; CLSI, Clinical and Laboratory Standards Institute.

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