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N-arylsulfonyl indolines as ROR γ agonists

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Abstract

The nuclear receptor ROR γ (NR1F3) is a key regulator of inflammatory gene programs involved in T helper 17 (T_H17) cell proliferation. As such, synthetic small molecule repressors (inverse agonists) targeting ROR γ have been extensively studied for their potential as therapeutic agents for various autoimmune diseases. Alternatively, enhancing T_H17 cell proliferation through activation (agonism) of ROR γ may boost an immune response thus offering a potentially new approach in cancer immunotherapy. Here we describe the development of N-arylsulfonyl indolines as ROR γ agonists. Structure-activity studies reveal a critical linker region in these molecules as the major determinant for agonism. Hydrogen/deuterium exchange coupled to mass spectrometry (HDX-MS) analysis of ROR γ -ligand complexes help rationalize the observed results.

Graphical Abstract

Pharmacology switches from inverse agonist to agonist. Immunotherapy is an exciting new approach in oncology. ROR γ agonists have the potential to enhance immune responses through modulation of T_H17 cell proliferation. Starting from an N-arylsulfonamide indoline ROR γ inverse agonist, we were able to identify the key area where small modifications lead to ROR γ agonists. A binding mode hypothesis, supported by HDX-MS analysis, is also proposed.

Keywords

Nuclear receptor; ROR γ agonist; N-arylsulfonyl indoline

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Introduction

The retinoic acid receptor-related orphan receptors (RORs) are members of the NR1F subfamily of nuclear receptors (NRs). This ROR subfamily is composed of three members: ROR α (NR1F1), ROR β (NR1F2) and ROR γ (NR1F3), also known as ROR α –ROR γ . Previous studies have identified sterols and oxysterols as ROR γ modulators, but these putative endogenous ligand(s) remain controversial.^{1–4} Two isoforms of ROR γ are expressed, differing only by their N-terminal sequence, thus containing the same ligand binding domain (LBD) sequence and structure. ROR γ 1 is expressed mainly in liver, kidney, adipose tissue and skeletal muscle⁵, whereas ROR γ 2 also known as ROR γ t for the T cell isoform ROR γ t, is only found in lymphoid organs, like the thymus and immune cells.⁶ In 2006, Littman *et al.* described ROR γ t as a key transcription factor involved in the survival and differentiation of CD4⁺/CD8⁺ double positive cells into T helper 17 (T_H17) cells, a subset of pro-inflammatory T helper cells. These cells are defined by their production of the cytokine Interleukin 17 (IL-17).⁷ Several studies have implicated IL-17's in various autoimmune diseases, such as multiple sclerosis, rheumatoid arthritis, inflammatory bowel diseases and psoriasis.^{8–11} Interestingly, studies have shown the presence of T_H17 cells in tumor microenvironment,^{12,13} although it is unclear whether T_H17 cells are activated or recruited by tumors. T_H17 cells do not express granzyme B or perforin and alone have no direct cytotoxic effect on tumor proliferation,¹³ but tumor progression was observed in IL-17 deficient mice and suppression of tumor growth was noticed in overexpressed IL-17 tumor cells.^{14–17} Therefore, increased IL-17 production could lead to a new therapeutic strategy to boost the immune system in response to cancer.

Given that activation of ROR γ t controls gene programs that enhance immunity, increases IL17 production, and decrease immune suppression,^{18,19} this NR has become a high priority target for numerous pharmaceutical companies over the past decade.^{20–25}

Significant effort to develop small molecules exhibiting selective inverse agonist (repressive) activity against ROR γ for the treatment of autoimmune diseases has ultimately resulted in several clinical candidates.^{26,27} A plethora of diverse chemical scaffolds have been published that bind to the ROR γ oxysterol orthosteric site such as SR2211²⁸, indole **1**²¹, triazole **2**²² and biaryl amide **3**²³ (Figure 1).

More recently, modulators that bind to an allosteric site, distinct from the oxysterol pocket and containing elements of the activation function 2 (AF-2) cleft on ROR γ , like MRL871²⁴ (inverse agonist) and SR0987²⁹ (agonist) have been described.³⁰ The identification of ligands with opposing pharmacology from within the same scaffold is not uncommon.³¹ Minor structural changes to the molecules can perturb receptor interactions altering hydrogen bond networks leading to conformational changes that modulate interactions with coregulatory proteins and or impacting post-translational modifications resulting in distinct pharmacological outcomes. During the development of ROR γ modulators, this has been reported on multiple occasions (Figure 2). Scientists at Genentech discovered that excision of a methylene group (**4a–b**)³² converted an inverse agonist to an agonist. Researchers at Lycera and AstraZeneca published similar findings during optimization of flexible linkers in related scaffolds (**5a**³³ to **5b**,³⁴ and **6a–b**³⁵, respectively).

Our SAR efforts to identify potent ROR γ inverse agonists in an indoline scaffold led to the identification of agonists from within this particular chemotype. The work presented herein is focused on the SAR and optimization of a new class of ROR γ agonists with potential application as adjuvants for cancer immunotherapy.

Results and Discussion

Our initial lead molecule in this series was indoline sulfonamide **7** (Table 1). This was a ROR γ inverse agonist with potent binding affinity that displayed functional repression in a GAL4 luciferase reporter gene assay. Similar to that reported by researchers at AstraZeneca³⁵ (Figure 2), N-methylation of the amide bond (**8**) resulted in a switch in the observed pharmacology and our first ROR γ agonist modulator in this series. Interestingly, the corresponding inverse amides (**9**, **10**), despite being potent binders of ROR γ were functionally inactive, and might perhaps be ‘silent’ binders or neutral antagonists (block agonist activation but are not repressors).

The binding mode of such compounds likely do not facilitate engagement of specific ligand binding pocket (LBP) interactions necessary to alter the receptor conformation which is required to increase or repress the basal activity of the NR. The amines (**11–13**) were weaker in binding than the N-methylamide **8** but N-alkylamine (**12–13**) exhibited better functional output. Ester **14** was a weak ROR γ agonist, as was the inverse ester **15**, unlike its amide counterpart.

Analogs contained ether linkages (**16** and **17**) with both isomers are nearly equipotent. Similar linker variations were examined in indole sulfonamides, which despite potent binding, exhibited significant loss in functional potency. (ie **17** vs **20**). The reasons for this are unclear at the moment, but as stated above, both binding and induction of conformational change is required to alter the transcriptional activity of the receptor. Given that the binding assay is performed on purified receptor LBD, and the reporter gene assay is performed in live cells requiring compounds to be cell penetrant, bind to the native receptor, and alter the basal conformation, it is not surprising to see significant deviations between binding potency and modulation of transcription of the reporter gene. Linkers containing heteroatoms were not required, as the saturated ethyl linkage (**21**) was equipotent to ethers **19** and **20**, however alkene and alkyne (**22** and **23**) were considerably less active.

With a preferred linker identified ($-\text{CH}_2\text{O}-$, **17**) for ROR γ agonism, we looked to optimize the R₁-substituent in the indoline series (Table 2). Compounds were synthesized as described in Scheme 1 starting from 5-hydroxyindole **24**. To investigate the SAR of the ether at the 5-position, the indole was first reduced to the indoline (**25**) in near quantitative yield. Chemoselective sulfonylation of the aniline occurred uneventfully to afford **26**. Finally, installation of the ethers using Mitsunobu chemistry or nucleophilic substitution of BnBr/BnMs derivatives gave final products (Table 2). To investigate the SAR of the sulfonamide portion, the ether was installed first to give **27**. Reduction again under acidic conditions provided **28**, which could then be derivatized with the appropriate sulfonyl chloride (**44–55**, Table 3).

Almost all substitution patterns in the benzyl ethers afforded potent ROR γ agonists (Table 2). From simple 2-substituted analogs (**29**, **30**) to 2,3- (**31**), 2,4- (**32**), 2,5- (**33**), and 2,6-disubstituted analogs (**16**, **17**, **34–37**). The 2,6-disubstituted analogs show a slight potency preference, so this is where we focused much of our effort. There was little SAR here, as all substitutions were acceptable with little change in potency. On occasion, we tested the reversed ether linkage (**17** vs **16**) for activity given similar potencies, and were surprised to see the complete loss of transcriptional activity for **43** vs **40**. Pyridine rings were also incorporated into the benzyl ethers to look for additional hydrogen bonding interactions, but these modifications had little effect on potency (**38–42**). These were, however, helpful substitutions as the corresponding phenyl analogs (**29**, **17**) were difficult to detect by LC/MS analysis as they failed to ionize under conditions used. This compromised their use as *in vivo* tools given they were difficult to detect in plasma samples, however, the pyridine analogs worked well in this regard.

With the optimized aryl ether substitution in place, we investigated the arylsulfonamide portion of the molecule (Scheme 1, Table 3). Unsubstituted or ortho-substituted aryl sulfonamides were not very potent (**44**, **45**). Meta-substitution was highly preferred giving the most potent compounds (**17**, **46–53**) with small 4-substituents (**54**) also tolerated. The nature of the meta substituent seemed to have little impact on binding or functional potency with the exception of the biphenylsulfonamide (**49**) losing some cell-based activity. Pyridine sulfonamides were equally well tolerated (**50–53**) facilitating *in vivo* monitoring and tracking.

Introduction of substituents at the 2- and 3-position of the indoline was also investigated in racemic fashion (Schemes 2–4, Table 4). Each substitution required a separate synthesis. A methyl group could be introduced at the indole 3-position by Vilsmeier-Haak formylation followed by reduction to give **56** (scheme 2). Indole reduction and sulfonylation as described previously afforded the final product **57**.

To introduce a methyl group at C2 of the indoline, nitro-phenol **58** was O-alkylated and then reduced to give aniline **59** (scheme 3). A Gassman protocol was then used to build the indole ring with reductive cleavage of the SMe group to afford **60**.³⁶ Uneventful reduction and sulfonylation provided the final product **61**.

Finally, the 3-trifluoromethyl group was introduced by yet a third protocol (Scheme 4). Reduction and acylation of nitro-bromotoluene **62** gave acetamide **63**. An intramolecular Wittig condensation gave indole **65**. The presence of the CF₃ group reduced the reactivity of indole **65** and required harsher conditions (TFA in presence of NaBH₃CN) to convert the indole to the indoline. The same lack of reactivity was observed during the introduction of the arylsulfonyl chloride requiring pyridine as solvent at 90°C to convert to **66**. The 5-bromoindoline **66** was converted to the corresponding 5-hydroxyindoline **67** by introduction of the pinacolborane followed by an in situ oxidation with H₂O₂. Finally - desired compounds **68–70** were obtained following the general protocol already described.

Inclusion of a methyl group at the 2-position (**61**) or the 3-position (**57**) led to slight drop in binding, but had more pronounced effects on cell-based potency. Compound **57** was nearly

10-fold less potent than **17**, whereas **61** was 2-fold more potent. We also incorporated a more lipophilic group CF₃ at the 2-position of the indole (**68–70**). All analogs exhibited excellent potency in binding as well as in the cell based assay, especially with regards to % activation.

To better understand how the changes in the spacer affected the binding mode of the ligands and their divergent pharmacology, we used differential hydrogen/deuterium exchange (HDX) mass spectrometry (Figure 3). HDX data show a clear difference in structural perturbations between the agonist (**16**) and the inverse agonist (**7**) bound receptor despite similarities in their binding modes. HDX revealed that helix 11 (H11) showed increased protection from solvent exchange (interpreted as stabilization) with both ROR γ t ligands tested, suggesting common sites of interaction within the ligand-binding pocket (LBP) of ROR γ . On the contrary, binding to indoline **16**, but not compound **7**, showed increased stabilization of activation-function 2 (AF2) helix (H12), which forms the docking site for transcriptional coactivators and likely contributes to the agonist activity of indoline **16**. H12 stabilization with agonists but not inverse agonists have been observed in other previously published crystal structures of ROR γ t-LBD in complex with synthetic tertiary sulfonamide derivatives (PDB ID: 4WQP, 4WPF).³² Minor structural change within the sulfonamide scaffold described in Rene et al³² resulted in a switch in pharmacology with the phenyl analog exhibiting strong agonist activity and the corresponding benzyl sulfonamide substituent retaining the inverse agonist profile of the parent scaffold. Structures revealed that the phenyl analog agonist compound (PDB ID: 4WQP) packs against H3 and H11/12 interface and engages with ROR γ LBD residues W317 (H3), H479 (H11) and Y502 (H12) resulting in a stable H12 conformation through a direct hydrogen bond between H479 and Y502 side chains. Whereas the benzyl derivative inverse agonist (PDB ID: 4WPF) dislodges H479 side chain into an orientation that is unfavorable for forming the hydrogen bond with Y502, which destabilized H12 (disordered in the structure) and disrupted co-activator interactions. In the absence of a crystal structure or a docking model, we postulate that our indoline compounds could adopt a similar H12-dependent structural mechanism to exert distinct pharmacological responses. Similar agonist induced H12 protections have been previously observed with other NRs such as PPAR γ ³⁷ and VDR³⁸.

Selected indoline analogs were then evaluated in a potentiation assay of IL-17 in T_H17 cells in the presence of ursolic acid (Table 5). Compound **7** profiled as an inverse agonist suppressing IL-17 secretion. The magnitude of repression was not large, but these experiments were performed in the presence of a fixed concentration of the inverse agonist ursolic acid, thus basal secretion of IL-17 was already repressed. Most agonist compounds showed good correlation between potency in GAL4 with that in the IL-17 assay. One notable exception is sulfonamide **61** which contains a 2-Me-substituted indoline which showed a 10-fold shift in EC₅₀. The shift in potency for **61** is not obvious given the corresponding 3-CF₃ substituted analogs **70** and **68** showed little to no shift between the assays. Compounds induced IL-17 secretion anywhere from 25–61%.

In general, synthesized compounds had poor stability in the presence of mouse liver microsomes (T_{1/2} < 5min). Likely metabolic soft spots are at both benzylic positions in the molecule. Compounds also had high logP values, correlating with high plasma protein

binding (>99%) in mouse. Despite the poor stability, the high PPB allowed for modest plasma exposure at 2 and 4h following 10mg/kg IP injections (Table 6). The most lipophilic analog **70** bearing an additional CF₃-group at the indoline 2-position showed the highest clearance. Metabolite identification studies are on-going to confirm sites of metabolism, so that we can attempt to improve the stability of the compounds. Pyridines were incorporated into analogs to improve ionization potential, and thus allow for tracking drug plasma samples by LC/MS, however these substitutions appeared to do little with regards to lowering lipophilicity. Attempt to incorporate polarity into future analogs is on-going.

Conclusions

Preliminary SAR in a series of indoline sulfonamides led to a series of potent agonists of ROR γ . Optimization of the sulfonamide and aryl ether substitution had minor effects on *in vitro* activity. The linker at the 5-position of the indoline played a major role in the observed pharmacology for specific compounds wherein a potent ROR γ inverse agonist was converted to a ROR γ agonist by converting an amide to an ether. These data correlate with that of others who have observed similar effects in related series. HDX data was able to delineate the structural mechanism for the switch in pharmacology from an inverse agonist **7** to an agonist **16** through increased H12 stabilization, a phenomenon that is observed in other nuclear receptors. Despite poor metabolic stability, compounds have adequate plasma exposure following IP dosing and may be used as tools to interrogate activation of ROR γ in cancer models. Attempts to improve stability and lower lipophilicity are in progress and will be reported in due course.

Experimental Section

The syntheses of all non-commercial available reagents are described in the supporting information.

General Procedure A: Reduction of indole in indoline

To the solution of indole (1 eq.) in AcOH (C: 0.5 mmol) at room temperature was added NaBH₃CN (3 eq.). The reaction was stirred at the same temperature for 2–4h. The completion of the reaction was monitored by HPLC. Upon completion, H₂O was added and the reaction mixture was concentrated to dryness. H₂O was added to the crude residue and the reaction mixture was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaHCO₃, brine and dried over Na₂SO₄. Filtration and removal of the solvent provided the desired product, which was used without further purification or purified by Combiflash silica gel chromatography to give the corresponding products.

General Procedure B: Mitsunobu reaction

To the solution of benzyl alcohol (1eq.) in anhydrous DCM (C: 0.1 mmol/mL) at room temperature were added the selected phenol or hydroxypyridine (1.05 eq.), PPh₃ (1.2 eq.) and DIAD (1.2 eq.). The reaction was stirred at the same temperature for 1–2h. The completion of the reaction was monitored by HPLC. Upon completion, the solvent was

removed and the crude product was purified by preparative HPLC or Combiflash silica gel chromatography to afford the corresponding products.

General Procedure C: Nucleophilic substitution of benzyl bromide by hydroxyindoline

To the solution of hydroxyindoline (1 eq.) in DMF (C: 0.1 mmol) at room temperature were added K_2CO_3 (3 eq.) and the selected benzyl bromide (1.1 eq.). The reaction was stirred at the same temperature for 2–4 h. The completion of the reaction was monitored by HPLC. Upon completion, H_2O was added and the reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4 . Filtration and removal of the solvent provided the crude product, which was purified by Combiflash silica gel chromatography or preparative HPLC to afford the corresponding products.

General Procedure D: Preparation of N-sulfonyl indoline

To the solution of N-H-indoline (1 eq.) in DCM (C: 0.1 mmol/mL) were added Et_3N (3 eq.) and aryl/heteroarylsulfonyl chloride (1.5 eq.). The reaction was stirred at room temperature for 4–12 h. The completion of the reaction was monitored by HPLC. Upon completion, H_2O was added and the reaction mixture was extracted with DCM. The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine and dried over Na_2SO_4 . Filtration and removal of the solvent provided the crude product, which was purified by Combiflash silica gel chromatography or preparative HPLC to afford the corresponding products.

Indolin-6-ol **25**

The title compound was prepared according to General Procedure A from 6-hydroindole **24** (400 mg, 3.00 mmol). The extraction provided 400 mg (99%) of the title compound **25** as a colorless oil which was used without further purification; 1H NMR (400 MHz, MeOD) δ = 6.86 (d, J = 8.3 Hz, 1 H), 6.18 (d, J = 1.8 Hz, 1 H), 6.14 (dd, J = 1.8, 8.3 Hz, 1 H), 3.43 (t, J = 8.2 Hz, 2 H), 2.87 (t, J = 8.2 Hz, 2 H).

1-((3-(trifluoromethyl)phenyl)sulfonyl)indolin-6-ol **26**

To the solution of indolin-6-ol **25** (240 mg, 1.78 mmol) in 15 mL THF at 0 °C were added pyridine (172 μ L, 2.13 mmol) and dropwise solution of 3-(trifluoromethyl)benzenesulfonyl chloride (285 μ L, 1.78 mmol) in 5 mL THF. The reaction mixture was stirred 4 h at 0 °C. The completion of the reaction was monitored by HPLC. Upon completion, aqueous HCl 1N was added and the crude residue was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4 . Filtration and removal of the solvent provided the crude product, which was purified by Combiflash silica gel chromatography (0–30% of EtOAc in hexane), which provided 280 mg (46%) of the title compound **26** as a yellow solid; 1H NMR (400 MHz, $CDCl_3$) δ = 8.08 (s, 1 H), 8.00 - 7.98 (m, 1 H), 7.84 - 7.82 (m, 1 H), 7.67 - 7.56 (m, 1 H), 7.20 (d, J = 2.4 Hz, 1 H), 6.94 (td, J = 0.9, 8.1 Hz, 1 H), 6.51 (dd, J = 2.4, 8.1 Hz, 1 H), 3.95 (t, J = 8.3 Hz, 2 H), 2.84 (t, J = 8.3 Hz, 2 H).

6-((2-chloro-6-fluorobenzyl)oxy)-1-((3-(trifluoromethyl)phenyl)sulfonyl)indoline **17**

The title compound was prepared according to General Procedure B from 1-((3-(trifluoromethyl)phenyl)sulfonyl)indolin-6-ol **26** (40 mg, 0.12 mmol) and (2-chloro-6-

fluorophenyl)methanol (20 mg, 0.12 mmol). The crude product was purified by preparative HPLC (20–100% CH₃CN/MeOH (1:1) in H₂O (0.01% TFA)) which provided after lyophilization 21 mg (31%) of the title compound **17** as a colorless solid; ¹H NMR (400 MHz, CDCl₃) δ = 8.10 (s, 1 H), 7.99 (d, *J* = 7.8 Hz, 1 H), 7.83 (d, *J* = 7.8 Hz, 1 H), 7.66 - 7.57 (m, 1 H), 7.37 (d, *J* = 2.3 Hz, 1 H), 7.36 - 7.25 (m, 2 H), 7.12 - 7.04 (m, 1 H), 7.00 (d, *J* = 8.1 Hz, 1 H), 6.67 (dd, *J* = 2.4, 8.2 Hz, 1 H), 5.20 (d, *J* = 2.0 Hz, 2 H), 3.97 (t, *J* = 8.3 Hz, 2 H), 2.86 (t, *J* = 8.3 Hz, 2 H).

6-(1-(2-chloro-6-fluorophenyl)ethoxy)-1-((3-(trifluoromethyl)phenyl)sulfonyl)indoline **18**

To the solution of 1-((3-(trifluoromethyl)phenyl)sulfonyl)indolin-6-ol **26** (30 mg, 0.09 mmol) in 0.8 mL of DMF at room temperature were added K₂CO₃ (48 mg, 0.35 mmol) and 1-(2-chloro-6-fluorophenyl)ethyl methanesulfonate (44 mg, 0.17 mmol). The reaction was stirred at 60 °C overnight. The completion of the reaction was monitored by HPLC. Upon completion, H₂O was added and the reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na₂SO₄. Filtration and removal of the solvent *in vacuo* provided the crude product, which was purified by preparative HPLC (20–100% CH₃CN/MeOH (1:1) in H₂O (0.01% TFA)) which provided after lyophilization 38 mg (87%) of the title compound **18** as a colorless solid; ¹H NMR (400 MHz, CDCl₃) δ = 8.01 (s, 1 H), 7.79 (d, *J* = 7.0 Hz, 1 H), 7.74 (d, *J* = 7.9 Hz, 1 H), 7.54 - 7.46 (m, 1 H), 7.24 (d, *J* = 2.4 Hz, 1 H), 7.21 - 7.17 (m, 2 H), 7.02 - 6.94 (m, 1 H), 6.89 (d, *J* = 8.3 Hz, 1 H), 6.56 (dd, *J* = 2.3, 8.2 Hz, 1 H), 5.95 - 5.83 (m, 1 H), 3.89 (t, *J* = 8.3 Hz, 2 H), 2.76 (t, *J* = 8.3 Hz, 2 H), 1.79 (d, *J* = 6.8 Hz, 3 H).

6-((2-methoxybenzyl)oxy)-1-((3-(trifluoromethyl)phenyl)sulfonyl)indoline **29**

The title compound was prepared according to General Procedure B from 1-((3-(trifluoromethyl)phenyl)sulfonyl)indolin-6-ol **26** (40 mg, 0.12 mmol) and (2-methoxyphenyl)methanol (17 mg, 0.12 mmol). The crude product was purified by preparative HPLC (20–100% CH₃CN/MeOH (1:1) in H₂O (0.01% TFA)) which provided after lyophilization 28 mg (52%) of the title compound **29** as a colorless solid; ¹H NMR (400 MHz, CDCl₃) δ = 8.09 (s, 1 H), 7.82 - 7.77 (m, 2 H), 7.58 - 7.51 (m, 1 H), 7.49 - 7.46 (m, 1 H), 7.36 - 7.30 (m, 2 H), 7.04 - 6.93 (m, 3 H), 6.66 (dd, *J* = 2.4, 8.2 Hz, 1 H), 5.17 (s, 2 H), 3.98 - 3.90 (m, 5 H), 2.83 (t, *J* = 8.3 Hz, 2 H).

6-((2-(trifluoromethoxy)benzyl)oxy)-1-((3-(trifluoromethyl)phenyl)sulfonyl)indoline **30**

The title compound was prepared according to General Procedure C from 1-((3-(trifluoromethyl)phenyl)sulfonyl)indolin-6-ol **26** (30 mg, 0.09 mmol) and 1-(bromomethyl)-2-(trifluoromethoxy)benzene (33 mg, 0.13 mmol). The crude product was purified by preparative HPLC (20–100% CH₃CN/MeOH (1:1) in H₂O (0.01% TFA)) which provided after lyophilization 13 mg (29%) of the title compound **30** as a colorless solid; ¹H NMR (400 MHz, CDCl₃) δ = 8.08 (s, 1 H), 7.95 - 7.89 (m, 1 H), 7.85 - 7.78 (m, 1 H), 7.65 - 7.55 (m, 2 H), 7.44 - 7.29 (m, 4 H), 7.01 - 6.96 (m, 1 H), 6.62 (dd, *J* = 2.3, 8.2 Hz, 1 H), 5.17 (s, 2 H), 3.96 (t, *J* = 8.4 Hz, 2 H), 2.85 (t, *J* = 8.4 Hz, 2 H).

6-((3-chloro-2-methoxybenzyl)oxy)-1-((3-(trifluoromethyl)phenyl)sulfonyl)indoline 31

The title compound was prepared according to General Procedure C from 1-((3-(trifluoromethyl)phenyl)sulfonyl)indolin-6-ol **26** (25 mg, 0.07 mmol) and 1-(bromomethyl)-3-chloro-2-methoxybenzene (34 mg, 0.15 mmol). The crude product was purified by preparative HPLC (20–100% CH₃CN/MeOH (1:1) in H₂O (0.01% TFA)) which provided after lyophilization 24 mg (66%) of the title compound **31** as a colorless solid; ¹H NMR (400 MHz, CDCl₃) δ = 8.07 (s, 1 H), 7.93 (d, *J* = 8.3 Hz, 1 H), 7.83 (d, *J* = 8.6 Hz, 1 H), 7.59 (t, *J* = 7.8 Hz, 1 H), 7.43 - 7.38 (m, 2 H), 7.34 (d, *J* = 2.3 Hz, 1 H), 7.15 - 7.09 (m, 1 H), 7.00 (d, *J* = 8.1 Hz, 1 H), 6.64 (dd, *J* = 2.3, 8.3 Hz, 1 H), 5.14 (s, 2 H), 4.02 - 3.92 (m, 5 H), 2.86 (t, *J* = 8.3 Hz, 2 H).

6-((4-chloro-2-methoxybenzyl)oxy)-1-((3-(trifluoromethyl)phenyl)sulfonyl)indoline 32

The title compound was prepared according to General Procedure C from 1-((3-(trifluoromethyl)phenyl)sulfonyl)indolin-6-ol **26** (25 mg, 0.07 mmol) and 1-(bromomethyl)-4-chloro-2-methoxybenzene (34 mg, 0.15 mmol). The crude product was purified by preparative HPLC (20–100% CH₃CN/MeOH (1:1) in H₂O (0.01% TFA)) which provided after lyophilization 22 mg (61%) of the title compound **32** as a colorless solid; ¹H NMR (400 MHz, CDCl₃) δ = 8.07 (s, 1 H), 7.81 (d, *J* = 7.9 Hz, 1 H), 7.76 (d, *J* = 8.1 Hz, 1 H), 7.58 - 7.52 (m, 1 H), 7.38 (d, *J* = 7.9 Hz, 1 H), 7.29 (d, *J* = 2.4 Hz, 1 H), 7.00 - 6.94 (m, 2 H), 6.92 (d, *J* = 2.0 Hz, 1 H), 6.62 (dd, *J* = 2.3, 8.2 Hz, 1 H), 5.11 (s, 2 H), 4.02 - 3.86 (m, 5 H), 2.83 (t, *J* = 8.3 Hz, 2 H).

6-((5-chloro-2-methoxybenzyl)oxy)-1-((3-(trifluoromethyl)phenyl)sulfonyl)indoline 33

The title compound was prepared according to General Procedure C from 1-((3-(trifluoromethyl)phenyl)sulfonyl)indolin-6-ol **26** (25 mg, 0.07 mmol) and 2-(bromomethyl)-4-chloro-1-methoxybenzene (34 mg, 0.15 mmol). The crude product was purified by preparative HPLC (20–100% CH₃CN/MeOH (1:1) in H₂O (0.01% TFA)) which provided after lyophilization 23 mg (63%) of the title compound **33** as a colorless solid; ¹H NMR (400 MHz, CDCl₃) δ = 8.08 (s, 1 H), 7.81 (d, *J* = 7.8 Hz, 1 H), 7.73 (d, *J* = 7.8 Hz, 1 H), 7.56 (t, *J* = 7.8 Hz, 1 H), 7.46 (d, *J* = 2.8 Hz, 1 H), 7.30 - 7.24 (m, 2 H), 6.97 (d, *J* = 8.3 Hz, 1 H), 6.86 (d, *J* = 8.8 Hz, 1 H), 6.65 (dd, *J* = 2.4, 8.2 Hz, 1 H), 5.12 (s, 2 H), 3.93 (t, *J* = 8.3 Hz, 2 H), 3.89 (s, 3 H), 2.83 (t, *J* = 8.3 Hz, 2 H).

6-((2,6-dichlorobenzyl)oxy)-1-((3-(trifluoromethyl)phenyl)sulfonyl)indoline 34

The title compound was prepared according to General Procedure B from 1-((3-(trifluoromethyl)phenyl)sulfonyl)indolin-6-ol **26** (40 mg, 0.12 mmol) and (2,6-dichlorophenyl)methanol (22 mg, 0.12 mmol). The crude product was purified by preparative HPLC (20–100% CH₃CN/MeOH (1:1) in H₂O (0.01% TFA)) which provided after lyophilization 30 mg (51%) of the title compound **34** as a colorless solid; ¹H NMR (400 MHz, CDCl₃) δ = 8.11 (s, 1 H), 8.01 (d, *J* = 7.8 Hz, 1 H), 7.83 (d, *J* = 7.1 Hz, 1 H), 7.68 - 7.58 (m, 1 H), 7.42 - 7.37 (m, 3 H), 7.28 (dd, *J* = 7.3, 8.8 Hz, 1 H), 7.02 (d, *J* = 8.3 Hz, 1 H), 6.69 (dd, *J* = 2.4, 8.2 Hz, 1 H), 5.30 (s, 2 H), 3.98 (t, *J* = 8.3 Hz, 2 H), 2.88 (t, *J* = 8.3 Hz, 2 H).

6-((2-bromo-6-methylbenzyl)oxy)-1-((3-(trifluoromethyl)phenyl)sulfonyl)indoline 35

The title compound was prepared according to General Procedure B from 1-((3-(trifluoromethyl)phenyl)sulfonyl)indolin-6-ol **26** (40 mg, 0.12 mmol) and (2-bromo-6-methylphenyl)methanol (22 mg, 0.12 mmol). The crude product was purified by preparative HPLC (20–100% CH₃CN/MeOH (1:1) in H₂O (0.01% TFA)) which provided after lyophilization 32 mg (52%) of the title compound **35** as a colorless solid; ¹H NMR (400 MHz, CDCl₃) δ = 8.10 (s, 1 H), 8.01 (d, *J* = 7.9 Hz, 1 H), 7.83 (d, *J* = 7.9 Hz, 1 H), 7.66 - 7.58 (m, 1 H), 7.50 (d, *J* = 7.9 Hz, 1 H), 7.37 (d, *J* = 2.4 Hz, 1 H), 7.21 (d, *J* = 7.0 Hz, 1 H), 7.14 (t, *J* = 7.8 Hz, 1 H), 7.02 (d, *J* = 8.3 Hz, 1 H), 6.68 (dd, *J* = 2.4, 8.3 Hz, 1 H), 5.23 (s, 2 H), 3.98 (t, *J* = 8.4 Hz, 2 H), 2.88 (t, *J* = 8.4 Hz, 2 H), 2.48 (s, 3 H).

6-((2,6-dimethylbenzyl)oxy)-1-((3-(trifluoromethyl)phenyl)sulfonyl)indoline 36

The title compound was prepared according to General Procedure B from 1-((3-(trifluoromethyl)phenyl)sulfonyl)indolin-6-ol **26** (40 mg, 0.12 mmol) and (2,6-dimethylphenyl)methanol (17 mg, 0.12 mmol). The crude product was purified by preparative HPLC (20–100% CH₃CN/MeOH (1:1) in H₂O (0.01% TFA)) which provided after lyophilization 28 mg (52%) of the title compound **36** as a colorless solid; ¹H NMR (400 MHz, CDCl₃) δ = 8.10 (s, 1 H), 7.98 (d, *J* = 7.8 Hz, 1 H), 7.83 (d, *J* = 8.1 Hz, 1 H), 7.64 - 7.58 (m, 1 H), 7.37 (d, *J* = 2.3 Hz, 1 H), 7.23 - 7.17 (m, 1 H), 7.11 (d, *J* = 7.6 Hz, 2 H), 7.02 (d, *J* = 8.1 Hz, 1 H), 6.67 (dd, *J* = 2.4, 8.2 Hz, 1 H), 5.07 (s, 2 H), 3.98 (t, *J* = 8.3 Hz, 2 H), 2.88 (t, *J* = 8.3 Hz, 2 H), 2.43 (s, 6 H).

6-((2-chloro-6-(trifluoromethyl)benzyl)oxy)-1-((3-(trifluoromethyl)phenyl)sulfonyl)indoline 37

The title compound was prepared according to General Procedure B from 1-((3-(trifluoromethyl)phenyl)sulfonyl)indolin-6-ol **26** (40 mg, 0.12 mmol) and (2-chloro-6-(trifluoromethyl)phenyl)methanol (26 mg, 0.12 mmol). The crude product was purified by preparative HPLC (20–100% CH₃CN/MeOH (1:1) in H₂O (0.01% TFA)) which provided after lyophilization 35 mg (56%) of the title compound **37** as a colorless solid; ¹H NMR (400 MHz, CDCl₃) δ = 8.10 (s, 1 H), 8.01 (d, *J* = 7.8 Hz, 1 H), 7.83 (d, *J* = 7.8 Hz, 1 H), 7.72 - 7.68 (m, 2 H), 7.62 (t, *J* = 7.8 Hz, 1 H), 7.52 - 7.42 (m, 1 H), 7.36 (d, *J* = 2.3 Hz, 1 H), 7.02 (d, *J* = 8.3 Hz, 1 H), 6.66 (dd, *J* = 2.4, 8.2 Hz, 1 H), 5.26 (s, 2 H), 3.98 (t, *J* = 8.5 Hz, 2 H), 2.88 (t, *J* = 8.3 Hz, 2 H).

6-((3-methoxypyridin-2-yl)methoxy)-1-((3-(trifluoromethyl)phenyl)sulfonyl)indoline 38

The title compound was prepared according to General Procedure C from 1-((3-(trifluoromethyl)phenyl)sulfonyl)indolin-6-ol **26** (30 mg, 0.09 mmol) and 2-(bromomethyl)-3-methoxypyridine (26 mg, 0.13 mmol). The crude product was purified by preparative HPLC (20–100% CH₃CN/MeOH (1:1) in H₂O (0.01% TFA)) which provided after lyophilization 43 mg (85%) of the title compound **38** as a colorless solid as TFA salt; ¹H NMR (400 MHz, CDCl₃) δ = 8.52 (d, *J* = 4.4 Hz, 1 H), 8.05 (s, 1 H), 7.88 (d, *J* = 7.9 Hz, 1 H), 7.81 (d, *J* = 7.7 Hz, 1 H), 7.77 - 7.66 (m, 2 H), 7.64 - 7.57 (m, 1 H), 7.29 (d, *J* = 2.4 Hz, 1 H), 7.00 (d, *J* = 8.3 Hz, 1 H), 6.76 (dd, *J* = 2.2, 8.3 Hz, 1 H), 5.38 (s, 2 H), 4.07 (s, 3 H), 3.92 (t, *J* = 8.3 Hz, 2 H), 2.82 (t, *J* = 8.3 Hz, 2 H). MS (ESI⁺) *m/z*: 464.88 [M+H⁺]

6-((2,4-dichloropyridin-3-yl)methoxy)-1-((3-(trifluoromethyl)phenyl)sulfonyl)indoline 39

The title compound was prepared according to General Procedure C from 1-((3-(trifluoromethyl)phenyl)sulfonyl)indolin-6-ol **26** (25 mg, 0.07 mmol) and 3-(bromomethyl)-2,4-dichloropyridine (35 mg, 0.15 mmol). The crude product was purified by preparative HPLC (20–100% CH₃CN/MeOH (1:1) in H₂O (0.01% TFA)) which provided after lyophilization 25 mg (56%) of the title compound **39** as a colorless solid as TFA salt; ¹H NMR (400 MHz, CDCl₃) δ = 8.35 (d, *J* = 5.1 Hz, 1 H), 8.10 (s, 1 H), 8.00 (d, *J* = 8.1 Hz, 1 H), 7.84 (d, *J* = 7.3 Hz, 1 H), 7.66 - 7.60 (m, 1 H), 7.41 (d, *J* = 5.3 Hz, 1 H), 7.36 (d, *J* = 2.3 Hz, 1 H), 7.03 (d, *J* = 8.3 Hz, 1 H), 6.67 (dd, *J* = 2.4, 8.2 Hz, 1 H), 5.29 (s, 2 H), 3.98 (t, *J* = 8.5 Hz, 2 H), 2.88 (t, *J* = 8.5 Hz, 2 H). MS (ESI⁺) *m/z*: 502.79 [M+H⁺]

6-((3,5-dichloropyridin-4-yl)methoxy)-1-((3-(trifluoromethyl)phenyl)sulfonyl)indoline 40

The title compound was prepared according to General Procedure C from 1-((3-(trifluoromethyl)phenyl)sulfonyl)indolin-6-ol **26** (30 mg, 0.09 mmol) and 4-(bromomethyl)-3,5-dichloropyridine (32 mg, 0.13 mmol). The crude product was purified by preparative HPLC (20–100% CH₃CN/MeOH (1:1) in H₂O (0.01% TFA)) which provided after lyophilization 33 mg (61%) of the title compound **40** as a colorless solid as TFA salt; ¹H NMR (400 MHz, CDCl₃) δ = 8.58 (s, 2 H), 8.09 (s, 1 H), 7.99 (d, *J* = 7.8 Hz, 1 H), 7.84 (d, *J* = 7.8 Hz, 1 H), 7.68 - 7.58 (m, 1 H), 7.36 (d, *J* = 2.3 Hz, 1 H), 7.02 (d, *J* = 8.1 Hz, 1 H), 6.66 (dd, *J* = 2.4, 8.2 Hz, 1 H), 5.27 (s, 2 H), 3.97 (t, *J* = 8.3 Hz, 2 H), 2.88 (t, *J* = 8.3 Hz, 2 H). MS (ESI⁺) *m/z*: 502.73 [M+H⁺].

6-((3-chloro-5-fluoropyridin-4-yl)methoxy)-1-((3-(trifluoromethyl)phenyl)sulfonyl)indoline 41

The title compound was prepared according to General Procedure C from 1-((3-(trifluoromethyl)phenyl)sulfonyl)indolin-6-ol **26** (20 mg, 0.06 mmol) and 4-(bromomethyl)-3-chloro-5-fluoropyridine (16 mg, 0.07 mmol). The crude product was purified by preparative HPLC (20–100% CH₃CN/MeOH (1:1) in H₂O (0.01% TFA)) which provided after lyophilization 24 mg (69%) of the title compound **41** as a colorless solid as TFA salt; ¹H NMR (400 MHz, CDCl₃) δ = 8.53 (s, 1 H), 8.47 (s, 1 H), 8.08 (s, 1 H), 7.97 (d, *J* = 7.9 Hz, 1 H), 7.84 (d, *J* = 7.9 Hz, 1 H), 7.66 - 7.57 (m, 1 H), 7.34 (d, *J* = 2.4 Hz, 1 H), 7.01 (d, *J* = 8.3 Hz, 1 H), 6.64 (dd, *J* = 2.4, 8.1 Hz, 1 H), 5.22 (d, *J* = 1.5 Hz, 2 H), 3.97 (t, *J* = 8.3 Hz, 2 H), 2.87 (t, *J* = 8.3 Hz, 2 H). MS (ESI⁺) *m/z*: 486.90 [M+H⁺]

6-((3-chloro-5-(trifluoromethyl)pyridin-4-yl)methoxy)-1-((3-(trifluoromethyl)phenyl)sulfonyl)indoline 42

The title compound was prepared according to General Procedure C from 1-((3-(trifluoromethyl)phenyl)sulfonyl)indolin-6-ol **26** (20 mg, 0.06 mmol) and 4-(bromomethyl)-3-chloro-5-(trifluoromethyl)pyridine (18 mg, 0.07 mmol, obtained by the same synthetic pathway than 4-(bromomethyl)-3-chloro-5-fluoropyridine). The crude product was purified by preparative HPLC (20–100% CH₃CN/MeOH (1:1) in H₂O (0.01% TFA)) which provided after lyophilization 22 mg (65%) of the title compound **42** as a colorless solid as TFA salt; ¹H NMR (400 MHz, CDCl₃) δ = 8.91 (s, 1 H), 8.90 (s, 1 H), 8.08 (s, 1 H), 8.00 (d, *J* = 7.8 Hz, 1 H), 7.84 (d, *J* = 7.8 Hz, 1 H), 7.69 - 7.59 (m, 1 H), 7.33

(d, $J = 2.5$ Hz, 1 H), 7.03 (d, $J = 8.3$ Hz, 1 H), 6.64 (dd, $J = 2.3, 8.3$ Hz, 1 H), 5.24 (s, 2 H), 3.98 (t, $J = 8.3$ Hz, 2 H), 2.89 (t, $J = 8.1$ Hz, 2 H). MS (ESI⁺) m/z : 536.81 [M+H⁺]

6-((2-chloro-6-fluorobenzyl)oxy)-1H-indole **27**

The title compound was prepared according to General Procedure C from 6-hydroxyindole **24** (400 mg, 3.00 mmol) and 2-(bromomethyl)-1-chloro-3-fluorobenzene (738 mg, 3.11 mmol). The crude product was purified by Combiflash silica gel chromatography (0–20% of EtOAc in hexane), which provided 565 mg (68%) of the title compound **27** as a colorless solid; ¹H NMR (400 MHz, CDCl₃) δ = 8.09 (s, 1 H), 7.55 (d, $J = 8.6$ Hz, 1 H), 7.35 - 7.23 (m, 1 H), 7.15 (dd, $J = 2.4, 3.3$ Hz, 1 H), 7.10 - 7.03 (m, 2 H), 6.92 (dd, $J = 2.2, 8.8$ Hz, 1 H), 6.54 - 6.51 (m, 1 H), 5.24 (d, $J = 2.0$ Hz, 2 H). MS (ESI⁺) m/z : 276.07 [M+H⁺]

Synthesis of 6-((2-chloro-6-fluorobenzyl)oxy)indoline **28**

The title compound was prepared according to General Procedure A from 6-((2-chloro-6-fluorobenzyl)oxy)-1H-indole **27** (200 mg, 0.72 mmol). The extraction provided 200 mg (100%) of the title compound **28** as a colorless solid which was used without further purification; ¹H NMR (400 MHz, CDCl₃) δ = 7.33 - 7.17 (m, 3 H), 7.08 - 7.00 (m, 2 H), 6.37 (dd, $J = 2.2, 8.3$ Hz, 1 H), 5.12 (d, $J = 2.0$ Hz, 2 H), 3.58 (t, $J = 8.3$ Hz, 2 H), 2.98 (t, $J = 8.3$ Hz, 2 H). MS (ESI⁺) m/z : 278.11 [M+H⁺]

6-((2-chloro-6-fluorobenzyl)oxy)-1-(phenylsulfonyl)indoline **44**

The title compound was prepared according to General Procedure D from 6-((2-chloro-6-fluorobenzyl)oxy)indoline **28** (20 mg, 0.07 mmol) and benzenesulfonyl chloride (14 μ L, 0.11 mmol). The crude product was purified by preparative HPLC (20–100% CH₃CN/MeOH (1:1) in H₂O (0.01% TFA)) which provided after lyophilization 20 mg (66%) of the title compound **44** as a colorless solid; ¹H NMR (400 MHz, CDCl₃) δ = 7.86 - 7.79 (m, 2 H), 7.60 - 7.54 (m, 1 H), 7.49 - 7.43 (m, 2 H), 7.39 (d, $J = 2.4$ Hz, 1 H), 7.35 - 7.25 (m, 2 H), 7.10 - 7.06 (m, 1 H), 6.99 - 6.96 (m, 1 H), 6.64 (dd, $J = 2.4, 8.1$ Hz, 1 H), 5.20 (d, $J = 1.8$ Hz, 2 H), 3.94 (t, $J = 8.4$ Hz, 2 H), 2.83 (t, $J = 8.4$ Hz, 2 H).

6-((2-chloro-6-fluorobenzyl)oxy)-1-((2-chlorophenyl)sulfonyl)indoline **45**

The title compound was prepared according to General Procedure D from 6-((2-chloro-6-fluorobenzyl)oxy)indoline **28** (20 mg, 0.07 mmol) and 2-chlorobenzenesulfonyl chloride (15 μ L, 0.11 mmol). The crude product was purified by preparative HPLC (20–100% CH₃CN/MeOH (1:1) in H₂O (0.01% TFA)) which provided after lyophilization 18 mg (55%) of the title compound **45** as a colorless solid; ¹H NMR (400 MHz, CDCl₃) δ = 8.21 - 8.10 (m, 1 H), 7.52 - 7.45 (m, 2 H), 7.44 - 7.37 (m, 1 H), 7.33 - 7.23 (m, 2 H), 7.07 - 7.01 (m, 2 H), 6.97 (d, $J = 2.4$ Hz, 1 H), 6.60 (dd, $J = 2.3, 8.2$ Hz, 1 H), 5.09 (d, $J = 2.0$ Hz, 2 H), 4.28 (t, $J = 8.2$ Hz, 2 H), 3.06 (t, $J = 8.2$ Hz, 2 H).

6-((2-chloro-6-fluorobenzyl)oxy)-1-(*m*-tolylsulfonyl)indoline **46**

The title compound was prepared according to General Procedure D from 6-((2-chloro-6-fluorobenzyl)oxy)indoline **28** (20 mg, 0.07 mmol) and *m*-toluenesulfonyl chloride (16 μ L, 0.11 mmol). The crude product was purified by preparative HPLC (20–100% CH₃CN/

MeOH (1:1) in H₂O (0.01% TFA)) which provided after lyophilization 16 mg (51%) of the title compound **46** as a colorless solid; ¹H NMR (400 MHz, CDCl₃) δ = 7.65 (s, 1 H), 7.61 (d, *J* = 7.8 Hz, 1 H), 7.39 (d, *J* = 2.5 Hz, 1 H), 7.37 - 7.26 (m, 4 H), 7.10 - 7.05 (m, 1 H), 6.98 (d, *J* = 8.1 Hz, 1 H), 6.63 (dd, *J* = 2.4, 8.2 Hz, 1 H), 5.20 (d, *J* = 1.8 Hz, 2 H), 3.95 (t, *J* = 8.5 Hz, 2 H), 2.91 - 2.81 (m, 2 H), 2.38 (s, 3 H).

6-((2-chloro-6-fluorobenzyl)oxy)-1-((3-methoxyphenyl)sulfonyl)indoline **47**

The title compound was prepared according to General Procedure D from 6-((2-chloro-6-fluorobenzyl)oxy)indoline **28** (20 mg, 0.07 mmol) and 3-methoxybenzenesulfonyl chloride (15 μL, 0.11 mmol). The crude product was purified by preparative HPLC (20–100% CH₃CN/MeOH (1:1) in H₂O (0.01% TFA)) which provided after lyophilization 17 mg (53%) of the title compound **47** as a colorless solid; ¹H NMR (400 MHz, CDCl₃) δ = 7.42 - 7.38 (m, 2 H), 7.37 (d, *J* = 8.1 Hz, 1 H), 7.32 (dd, *J* = 2.3, 8.2 Hz, 1 H), 7.30 - 7.27 (m, 2 H), 7.10 - 7.08 (m, 1 H), 7.08 - 7.06 (m, 1 H), 6.99 (d, *J* = 8.1 Hz, 1 H), 6.65 (dd, *J* = 2.4, 8.1 Hz, 1 H), 5.19 (d, *J* = 2.0 Hz, 2 H), 3.94 (dd, *J* = 8.0, 8.9 Hz, 2 H), 3.75 (s, 3 H), 2.84 (t, *J* = 8.4 Hz, 2 H).

6-((2-chloro-6-fluorobenzyl)oxy)-1-((3-chlorophenyl)sulfonyl)indoline **48**

The title compound was prepared according to General Procedure D from 6-((2-chloro-6-fluorobenzyl)oxy)indoline **28** (25 mg, 0.09 mmol) and 3-chlorobenzenesulfonyl chloride (19 μL, 0.13 mmol). The crude product was purified by preparative HPLC (20–100% CH₃CN/MeOH (1:1) in H₂O (0.01% TFA)) which provided after lyophilization 35 mg (86%) of the title compound **48** as a colorless solid; ¹H NMR (400 MHz, CDCl₃) δ = 7.83 (t, *J* = 1.9 Hz, 1 H), 7.70 - 7.67 (m, 1 H), 7.56 - 7.52 (m, 1 H), 7.40 (t, *J* = 7.9 Hz, 1 H), 7.37 - 7.35 (m, 1 H), 7.34 - 7.26 (m, 2 H), 7.07 (dt, *J* = 1.5, 8.6 Hz, 1 H), 7.01 (d, *J* = 8.1 Hz, 1 H), 6.66 (dd, *J* = 2.4, 8.1 Hz, 1 H), 5.21 (d, *J* = 2.0 Hz, 2 H), 3.96 (t, *J* = 8.4 Hz, 2 H), 2.88 (t, *J* = 8.3 Hz, 2 H).

1-([1,1'-biphenyl]-3-ylsulfonyl)-6-((2-chloro-6-fluorobenzyl)oxy)indoline **49**

The title compound was prepared according to General Procedure D from 6-((2-chloro-6-fluorobenzyl)oxy)indoline **28** (25 mg, 0.09 mmol) and [1,1'-biphenyl]-3-sulfonyl chloride (34 mg, 0.13 mmol). The crude product was purified by preparative HPLC (20–100% CH₃CN/MeOH (1:1) in H₂O (0.01% TFA)) which provided after lyophilization 28 mg (63%) of the title compound **49** as a colorless solid; ¹H NMR (400 MHz, CDCl₃) δ = 8.03 (t, *J* = 1.8 Hz, 1 H), 7.82 - 7.74 (m, 2 H), 7.58 - 7.36 (m, 7 H), 7.36 - 7.22 (m, 2 H), 7.11 - 7.03 (m, 1 H), 7.00 (d, *J* = 8.1 Hz, 1 H), 6.66 (dd, *J* = 2.4, 8.3 Hz, 1 H), 5.21 (d, *J* = 1.8 Hz, 2 H), 3.99 (t, *J* = 8.3 Hz, 2 H), 2.85 (t, *J* = 8.3 Hz, 2 H).

6-((2-chloro-6-fluorobenzyl)oxy)-1-((6-(trifluoromethyl)pyridin-2-yl)sulfonyl)indoline **50**

The title compound was prepared according to General Procedure D from 6-((2-chloro-6-fluorobenzyl)oxy)indoline **28** (25 mg, 0.09 mmol) and 6-(trifluoromethyl)pyridine-2-sulfonyl chloride (23 mg, 0.13 mmol). The crude product was purified by preparative HPLC (20–100% CH₃CN/MeOH (1:1) in H₂O (0.01% TFA)) which provided after lyophilization 32 mg (59%) of the title compound **50** as a colorless solid as TFA salt; ¹H NMR (400 MHz,

CDCl₃) δ = 8.17 (d, J = 7.9 Hz, 1 H), 8.11 - 8.01 (m, 1 H), 7.80 (dd, J = 1.0, 7.8 Hz, 1 H), 7.34 - 7.22 (m, 2 H), 7.15 (d, J = 2.2 Hz, 1 H), 7.07 - 6.99 (m, 2 H), 6.61 (dd, J = 2.4, 8.1 Hz, 1 H), 5.11 (d, J = 2.0 Hz, 2 H), 4.45 (t, J = 8.3 Hz, 2 H), 3.08 (t, J = 8.3 Hz, 2 H). MS (ESI⁺) m/z : 486.68 [M+H⁺]

6-((2-chloro-6-fluorobenzyl)oxy)-1-((2-(trifluoromethyl)pyridin-4-yl)sulfonyl)indoline 51

The title compound was prepared according to General Procedure D from 6-((2-chloro-6-fluorobenzyl)oxy)indoline **28** (25 mg, 0.09 mmol) and 2-(trifluoromethyl)pyridine-4-sulfonyl chloride (27 mg, 0.11 mmol). The crude product was purified by preparative HPLC (20–100% CH₃CN/MeOH (1:1) in H₂O (0.01% TFA)) which provided after lyophilization 25 mg (46%) of the title compound **51** as a colorless solid as TFA salt; ¹H NMR (400 MHz, CDCl₃) δ = 8.82 (d, J = 4.8 Hz, 1 H), 7.95 (s, 1 H), 7.79 - 7.70 (m, 1 H), 7.29 - 7.21 (m, 3 H), 7.04 - 6.92 (m, 2 H), 6.64 (dd, J = 2.3, 8.2 Hz, 1 H), 5.13 (d, J = 2.0 Hz, 2 H), 3.92 (t, J = 8.3 Hz, 2 H), 2.84 (t, J = 8.3 Hz, 2 H). MS (ESI⁺) m/z : 486.66 [M+H⁺].

6-((2-chloro-6-fluorobenzyl)oxy)-1-((5-(trifluoromethyl)pyridin-3-yl)sulfonyl)indoline 52

The title compound was prepared according to General Procedure D from 6-((2-chloro-6-fluorobenzyl)oxy)indoline **28** (20 mg, 0.07 mmol) and 5-(trifluoromethyl)pyridine-3-sulfonyl chloride (27 mg, 0.11 mmol). The crude product was purified by preparative HPLC (20–100% CH₃CN/MeOH (1:1) in H₂O (0.01% TFA)) which provided after lyophilization 19 mg (44%) of the title compound **52** as a colorless solid as TFA salt; ¹H NMR (400 MHz, CDCl₃) δ = 9.19 (d, J = 2.3 Hz, 1 H), 9.05 (d, J = 1.0 Hz, 1 H), 8.37 - 8.29 (m, 1 H), 7.38 - 7.25 (m, 3 H), 7.10 - 7.05 (m, 1 H), 7.03 (d, J = 8.3 Hz, 1 H), 6.71 (dd, J = 2.3, 8.3 Hz, 1 H), 5.20 (d, J = 2.0 Hz, 2 H), 4.01 (t, J = 8.3 Hz, 2 H), 2.90 (t, J = 8.5 Hz, 2 H). MS (ESI⁺) m/z : 486.77 [M+H⁺]

6-((2-chloro-6-fluorobenzyl)oxy)-1-((4-(trifluoromethyl)pyridin-2-yl)sulfonyl)indoline 53

The title compound was prepared according to General Procedure D from 6-((2-chloro-6-fluorobenzyl)oxy)indoline (20 mg, 0.07 mmol) and 4-(trifluoromethyl)pyridine-2-sulfonyl chloride (21 mg, 0.09 mmol). The crude product was purified by preparative HPLC (20–100% CH₃CN/MeOH (1:1) in H₂O (0.01% TFA)) which provided after lyophilization 20 mg (46%) of the title compound **53** as a colorless solid as TFA salt; ¹H NMR (400 MHz, CDCl₃) δ = 8.83 (d, J = 4.8 Hz, 1 H), 8.22 (s, 1 H), 7.72 - 7.64 (m, 1 H), 7.34 - 7.22 (m, 2 H), 7.19 (d, J = 2.4 Hz, 1 H), 7.08 - 6.99 (m, 2 H), 6.62 (dd, J = 2.3, 8.2 Hz, 1 H), 5.13 (d, J = 2.0 Hz, 2 H), 4.38 (t, J = 8.4 Hz, 2 H), 3.05 (t, J = 8.3 Hz, 2 H). MS (ESI⁺) m/z : 486.60 [M+H⁺].

6-((2-chloro-6-fluorobenzyl)oxy)-1-((4-fluorophenyl)sulfonyl)indoline 54

The title compound was prepared according to General Procedure D from 6-((2-chloro-6-fluorobenzyl)oxy)indoline **28** (20 mg, 0.07 mmol) and 4-fluorobenzenesulfonyl chloride (21 mg, 0.11 mmol). The crude product was purified by preparative HPLC (20–100% CH₃CN/MeOH (1:1) in H₂O (0.01% TFA)) which provided after lyophilization 19 mg (61%) of the title compound **54** as a colorless solid; ¹H NMR (400 MHz, CDCl₃) δ = 7.78 - 7.70 (m, 2

H), 7.30 - 7.20 (m, 3 H), 7.09 - 6.94 (m, 3 H), 6.92 (d, $J = 8.3$ Hz, 1 H), 6.58 (dd, $J = 2.3, 8.2$ Hz, 1 H), 5.12 (d, $J = 2.0$ Hz, 2 H), 3.85 (t, $J = 8.3$ Hz, 2 H), 2.77 (t, $J = 8.3$ Hz, 2 H).

6-((2-chloro-6-fluorobenzyl)oxy)-1-((3,5-dichlorophenyl)sulfonyl)indoline 55

The title compound was prepared according to General Procedure D from 6-((2-chloro-6-fluorobenzyl)oxy)indoline **28** (20 mg, 0.07 mmol) and 3,5-dichlorobenzenesulfonyl chloride (27 mg, 0.11 mmol). The crude product was purified by preparative HPLC (20–100% CH₃CN/MeOH (1:1) in H₂O (0.01% TFA)) which provided after lyophilization 14 mg (40%) of the title compound **55** as a colorless solid; ¹H NMR (400 MHz, CDCl₃) δ = 7.70 (d, $J = 1.8$ Hz, 2 H), 7.54 (t, $J = 1.9$ Hz, 1 H), 7.36 - 7.27 (m, 3 H), 7.11 - 7.02 (m, 2 H), 6.69 (dd, $J = 2.4, 8.3$ Hz, 1 H), 5.21 (d, $J = 2.0$ Hz, 2 H), 3.98 (t, $J = 8.3$ Hz, 2 H), 2.93 (t, $J = 8.4$ Hz, 2 H).

6-((2-chloro-6-fluorobenzyl)oxy)-3-methyl-1H-indole 56

Step 1—To the solution of 6-((2-chloro-6-fluorophenoxy)methyl)-1H-indole **27** (200 mg, 0.72 mmol) in 5 mL of DMF at 0 °C was added POCl₃ (81 μ L, 0.87 mmol). The reaction was stirred at 65 °C for 3h. The completion of the reaction was monitored by HPLC. Upon completion, solvent was removed *in vacuo*, H₂O was added to the crude residue and the reaction mixture was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaHCO₃, brine and dried over Na₂SO₄. Filtration and removal of the solvent provided 210 mg (95%) of 6-((2-chloro-6-fluorobenzyl)oxy)-1H-indole-3-carbaldehyde as a colorless oil, which was used without further purification; ¹H NMR (400 MHz, CDCl₃) δ = 10.01 (s, 1 H), 9.10 (br. s, 1 H), 8.21 (d, $J = 8.6$ Hz, 1 H), 7.77 (d, $J = 3.1$ Hz, 1 H), 7.35 - 7.23 (m, 2 H), 7.09 - 7.02 (m, 3 H), 5.22 (d, $J = 2.0$ Hz, 2 H). MS (ESI⁺) m/z : 304.12 [M+H⁺].

Step 2—To the solution of 6-((2-chloro-6-fluorobenzyl)oxy)-1H-indole-3-carbaldehyde (210 mg, 0.69 mmol) in 4 mL of anhydrous THF was added LiAlH₄ (79 mg, 2.07 mmol). The reaction was stirred at 65 °C for 3h. The completion of the reaction was monitored by HPLC. Upon completion, were added 200 μ L H₂O, 200 μ L NaOH 1M in H₂O and finally 650 μ L H₂O. After 30 min, the solid was removed by filtration. Solvent was removed *in vacuo*, H₂O was added to the crude residue and the reaction mixture was extracted with EtOAc. The combined organic layers were washed with NaOH 1M, brine and dried over Na₂SO₄. Filtration and removal of the solvent provided 150 mg (75%) of the title compound **56** as a colorless solid, which was used without further purification; ¹H NMR (400 MHz, CDCl₃) δ = 7.42 - 7.36 (m, 1 H), 7.24 - 7.15 (m, 2 H), 7.00 - 6.94 (m, 1 H), 6.94 - 6.91 (m, 1 H), 6.86 - 6.77 (m, 2 H), 5.14 (d, $J = 2.0$ Hz, 2 H), 2.2 (d, $J = 1.1$ Hz, 3 H). MS (ESI⁺) m/z : 290.12 [M+H⁺].

6-((2-chloro-6-fluorobenzyl)oxy)-3-methyl-1-((3-(trifluoromethyl)phenyl)sulfonyl)indoline 57

Step1—6-((2-chloro-6-fluorobenzyl)oxy)-3-methylindoline was prepared according to General Procedure A from 6-((2-chloro-6-fluorobenzyl)oxy)-3-methyl-1H-indole **56** (150 mg, 0.52 mmol). The extraction provided 130 mg (85%) of the desired compound as a colorless oil which was used without further purification; ¹H NMR (400 MHz, CDCl₃) δ = 7.34 - 7.23 (m, 2 H), 7.09 - 6.99 (m, 2 H), 6.50 (dd, $J = 2.1, 8.2$ Hz, 1 H), 6.46 - 6.41 (m, 1

H), 5.13 (d, $J = 2.0$ Hz, 2 H), 3.77 (t, $J = 8.8$ Hz, 1 H), 3.40 - 3.30 (m, 1 H), 3.17 (t, $J = 8.7$ Hz, 1 H), 1.32 (d, $J = 6.8$ Hz, 3 H). MS (ESI⁺) m/z : 292.22 [M+H⁺].

Step 2—The title compound **57** was prepared according to General Procedure D from 6-((2-chloro-6-fluorobenzyl)oxy)-3-methylindoline (25 mg, 0.09 mmol) and 3-(trifluoromethyl)benzenesulfonyl chloride (27 μ L, 0.17 mmol). The crude product was purified by preparative HPLC (20–100% CH₃CN/MeOH (1:1) in H₂O (0.01% TFA)) which provided after lyophilization 11 mg (26%) of the title compound **57** as a colorless solid; ¹H NMR (400 MHz, CDCl₃) δ = 8.03 (s, 1 H), 7.93 - 7.89 (m, 1 H), 7.77 - 7.73 (m, 1 H), 7.57 - 7.51 (m, 1 H), 7.28 (d, $J = 2.4$ Hz, 1 H), 7.26 - 7.20 (m, 2 H), 7.03 - 6.97 (m, 1 H), 6.90 (dd, $J = 0.8, 8.2$ Hz, 1 H), 6.61 (dd, $J = 2.3, 8.2$ Hz, 1 H), 5.12 (d, $J = 2.0$ Hz, 2 H), 4.05 (dd, $J = 9.0, 10.5$ Hz, 1 H), 3.39 (dd, $J = 6.8, 10.5$ Hz, 1 H), 3.15 - 3.04 (m, 1 H), 1.01 (d, $J = 6.8$ Hz, 3 H).

3-((2-chloro-6-fluorobenzyl)oxy)aniline **59**

Step 1—To the solution of 3-nitrophenol **58** (1.50 g, 10.78 mmol) in 70 mL of DMF were added K₂CO₃ (4.47 g, 32.35 mmol) and 2-(bromomethyl)-1-chloro-3-fluorobenzene (2.65 g, 11.86 mmol). The reaction was stirred overnight at room temperature. The completion of the reaction was monitored by HPLC. Upon completion, solvent was removed *in vacuo*, H₂O was added to the crude residue and the reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na₂SO₄. Filtration and removal of the solvent provided 1-chloro-3-fluoro-2-((3-nitrophenoxy)methyl)benzene as a colorless solid, which was used without further purification; ¹H NMR (400 MHz, CDCl₃) δ = 7.92 - 7.85 (m, 2 H), 7.50 - 7.42 (m, 1 H), 7.39 - 7.27 (m, 3 H), 7.11 - 7.06 (m, 1 H), 5.27 (d, $J = 1.8$ Hz, 2 H).

Step 2—To the solution of 1-chloro-3-fluoro-2-((3-nitrophenoxy)methyl)benzene in 30 mL of EtOH and 30 mL of H₂O were added NH₄Cl (5.2 g, 97.05 mmol) and Fe (1.81 g, 32.35 mmol). The reaction was stirred at 80 °C for 2h. The completion of the reaction was monitored by HPLC. Upon completion, the reaction mixture was filtered over Celite®. The cake was washed with MeOH and the filtrate was concentrated *in vacuo*. To the crude residue was added H₂O and the reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na₂SO₄. Filtration and removal of the solvent provided 2.66 g (98% yield over 2 steps) of the title compound **59** as a light yellow oil, which was used without further purification; ¹H NMR (400 MHz, CDCl₃) δ = 7.34 - 7.23 (m, 2 H), 7.12 (t, $J = 7.9$ Hz, 1 H), 7.07 - 7.02 (m, 1 H), 6.53 - 6.47 (m, 1 H), 6.45 - 6.38 (m, 2 H), 5.15 (d, $J = 1.8$ Hz, 2 H). MS (ESI⁺) m/z : 252.09 [M+H⁺].

6-((2-chloro-6-fluorobenzyl)oxy)-2-methyl-1H-indole **60**

Step 1—To a vigorously stirred solution of 3-((2-chloro-6-fluorobenzyl)oxy)aniline **59** (1.00 g, 3.97 mmol) in 20 mL of DCM at -78 °C was added dropwise a solution of tert-butyl hypochlorite (447 μ L, 3.97 mmol) in 4 mL of the same solvent. After 10 min, a solution of methylthio-2-propanone (407 μ L, 3.97 mmol) in DCM (4 mL) was added slowly over 10 min. After stirring for another hour at -78 °C, a solution of Et₃N (554 μ L, 3.97 mmol) in 4 mL of DCM was added slowly over 5 min. After an additional 10 min at -78 °C, the cooling

bath was removed and the reaction was allowed to warm to room temperature. A 20 mL portion of H₂O was added under vigorous stirring, and the organic layer was separated, dried over Na₂SO₄, filtered, and concentrated *in vacuo* to give a 2:1 mixture of the desired 6-((2-chloro-6-fluorobenzyl)oxy)-2-methyl-3-(methylthio)-1H-indole and the corresponding 4-benzyloxy isomer as an orange oil. The crude product was used in the next step without further purification. MS (ESI⁺) m/z: 336.12 [M+H⁺].

Step 2—To the solution of the crude product formed in step 1 in 50 mL of ethanol was added 15 mL of Raney-Ni suspended in H₂O. The reaction was stirred at room temperature for 1h. The completion of the reaction was monitored by HPLC. Upon completion, The Raney nickel was removed by filtration through Celite[®] and washed with ethanol. The combined ethanolic solutions were concentrated *in vacuo*. The crude product was purified by Combiflash silica gel chromatography (0–10% EtOAc in hexane) which provided 490 mg (43%) of the title compound **60** as a colorless oil; ¹H NMR (400 MHz, CDCl₃) δ = 7.41 (d, *J* = 8.6 Hz, 1 H), 7.34 - 7.25 (m, 3 H), 7.09 - 7.03 (m, 1 H), 7.00 (s, 1 H), 6.87 (d, *J* = 10.7 Hz, 1 H), 5.23 (d, *J* = 2.0 Hz, 2 H), 2.46 (s, 3 H). MS (ESI⁺) m/z: 290.14 [M+H⁺]

6-((2-chloro-6-fluorobenzyl)oxy)-2-methyl-1-((3-(trifluoromethyl)phenyl)sulfonyl)indoline **61**

Step 1—6-((2-chloro-6-fluorobenzyl)oxy)-2-methylindoline was prepared according to General Procedure A from 6-((2-chloro-6-fluorobenzyl)oxy)-2-methyl-1H-indole **60** (200 mg, 0.69 mmol). The extraction provided 180 mg (89%) of the desired compound as a colorless oil which was used without further purification; ¹H NMR (400 MHz, CDCl₃) δ = 7.34 - 7.21 (m, 2 H), 7.10 - 6.98 (m, 2 H), 6.43 (dd, *J* = 1.8, 8.1 Hz, 1 H), 6.38 (s, 1 H), 5.12 (d, *J* = 2.0 Hz, 2 H), 4.09 - 3.99 (m, 1 H), 3.12 (dd, *J* = 8.4, 15.2 Hz, 1 H), 2.61 (dd, *J* = 7.6, 15.2 Hz, 2 H), 1.32 (d, *J* = 6.1 Hz, 3 H). MS (ESI⁺) m/z: 292.16 [M+H⁺]

Step 2—The title compound was prepared according to General Procedure D from 6-((2-chloro-6-fluorobenzyl)oxy)-2-methylindoline (25 mg, 0.09 mmol) and 3-(trifluoromethyl)benzenesulfonyl chloride (27 μL, 0.17 mmol). The crude product was purified by preparative HPLC (20–100% CH₃CN/MeOH (1:1) in H₂O (0.01% TFA)) which provided after lyophilization 38 mg (89%) of the title compound **61** as a colorless solid; ¹H NMR (400 MHz, CDCl₃) δ = 8.02 (s, 1 H), 7.86 (d, *J* = 7.9 Hz, 1 H), 7.79 (d, *J* = 7.2 Hz, 1 H), 7.58 - 7.52 (m, 1 H), 7.39 (d, *J* = 2.2 Hz, 1 H), 7.36 - 7.27 (m, 2 H), 7.11 - 7.05 (m, 1 H), 6.97 (d, *J* = 8.3 Hz, 1 H), 6.71 (dd, *J* = 2.3, 8.2 Hz, 1 H), 5.21 (d, *J* = 1.8 Hz, 2 H), 4.44 - 4.34 (m, 1 H), 2.84 (dd, *J* = 9.3, 15.7 Hz, 1 H), 2.42 (dd, *J* = 2.7, 15.7 Hz, 1 H), 1.46 (d, *J* = 6.4 Hz, 3 H).

N-(5-bromo-2-methylphenyl)-2,2,2-trifluoroacetamide **63**

Step 1—To the solution of 4-bromo-2-nitrotoluene **62** (8.00 g, 37.03mmol) in 100 mL of ethanol and 100 mL of H₂O were added NH₄Cl (19.8 g, 370.3 mmol) and Fe (14.4 g, 259.2 mmol). The reaction was stirred at 80 °C for 2h. The completion of the reaction was monitored by HPLC. Upon completion, the reaction mixture was filtered over Celite[®]. The cake was washed with MeOH and the filtrate was concentrated *in vacuo*. To the crude residue was added H₂O and the reaction mixture was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaHCO₃, brine and dried over Na₂SO₄.

Filtration and removal of the solvent *in vacuo* provided the 5-bromo-2-methylaniline as a light yellow oil, which was used without further purification; ^1H NMR (400 MHz, CDCl_3) δ = 6.99 - 6.82 (m, 3 H), 4.47 (br. s., 2 H), 2.15 (s, 3 H). MS (ESI⁺) m/z : 184.54 [$\text{M}+\text{H}^+$].

Step 2—To the solution of 5-bromo-2-methylaniline in 200 mL of DCM was added trifluoroacetic anhydride (6.18 mL, 44.43 mmol). The reaction was stirred at room temperature for 1h. The completion of the reaction was monitored by HPLC. Upon completion, removal of volatils *in vacuo* provided 9.30g (89% yield over 2 steps) of the title compound **63** as a light yellow solid, which was used without further purification; ^1H NMR (400 MHz, CDCl_3) δ = 7.99 (s, 1 H), 7.76 (br. s., 1 H), 7.33 (dd, J = 2.0, 8.1 Hz, 1 H), 7.12 (d, J = 8.1 Hz, 1 H), 2.25 (s, 3 H).

(4-bromo-2-(2,2,2-trifluoroacetamido)benzyl)triphenylphosphonium bromide **64**

Step 1—To the solution of N-(5-bromo-2-methylphenyl)-2,2,2-trifluoroacetamide **63** (4.00 g, 14.20 mmol) in 40 mL of DCM/ H_2O : 7/3 was added Br_2 (880 μL , 17.04 mmol). The reaction was stirred at 50 °C, followed by the dropwise addition over 1h of H_2O_2 50wt% in H_2O (965 μL , 14.20 mmol). The reaction was stirred at 50 °C for 4h. The maximum conversion of the starting material was observed after 4h by HPLC. At room temperature, an aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$ was added and the reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4 . Filtration and removal of the solvent *in vacuo* provided a yellow oil as an inseparable mixture of the starting material **63** and the desired compound (4/6), which was used without further purification; ^1H NMR (400 MHz, CDCl_3) δ = 8.36 (br. s., 1 H), 8.15 (d, J = 2.0 Hz, 1 H), 7.41 (dd, J = 2.0, 8.1 Hz, 1 H), 7.25 (d, J = 8.1 Hz, 3 H), 4.46 (s, 2 H).

Step 2—The solution of crude N-(5-bromo-2-(bromomethyl)phenyl)-2,2,2-trifluoroacetamide in 20 mL of toluene was added 145 mg of PPh_3 . The reaction solution was stirred at 90 °C for 1h. The completion of the reaction was monitored by HPLC. Upon completion, the precipitate was filtered and washed with toluene to provide 3.98 g (45% yield over 2 steps) of the title compound **64** as a colorless solid, which was used without further purification; ^1H NMR (400 MHz, DMSO) δ = 10.93 (s, 1 H), 7.90 (t, J = 7.3 Hz, 3 H), 7.77 - 7.72 (m, 7 H), 7.59 - 7.56 (m, 6 H), 7.42 (d, J = 7.7 Hz, 1 H), 6.98 (dd, J = 2.5, 8.4 Hz, 1 H), 5.20 (d, J = 15.3 Hz, 2 H). MS (ESI⁺) m/z : 542.04 [$\text{M}+\text{H}^+$].

6-bromo-2-(trifluoromethyl)-1H-indole **65**

The solution of (4-bromo-2-(2,2,2-trifluoroacetamido)benzyl)triphenylphosphonium bromide **64** (2.00 g, 3.28 mmol) in 12 mL of DMF was stirred at 200 °C for 15min under MW irradiation. The completion of the reaction was monitored by HPLC. Upon completion, solvent was removed, H_2O was added to the crude residue and the reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4 . Filtration and removal of the solvent provided the crude product, which was purified by Combiflash silica gel chromatography (0–10% EtOAc in hexane) to afford 795 mg (94%) of the title compound **65** as a colorless solid; ^1H NMR (400 MHz, CDCl_3) δ = 8.46 (br. s., 1 H), 7.61 (s, 1 H), 7.56 (d, J = 8.6 Hz, 1 H), 7.32 (dd, J = 1.4, 8.6 Hz, 1 H), 6.92 (td, J = 1.4, 2.3 Hz, 1 H).

6-bromo-2-(trifluoromethyl)-1-((3-(trifluoromethyl)phenyl)sulfonyl)indoline 66

Step 1—To the solution of 6-bromo-2-(trifluoromethyl)-1H-indole **65** (500 mg, 1.89 mmol) in 7 mL of TFA at 4 °C was added NaBH₃CN (120 mg, 1.89 mmol). The reaction was stirred at the same temperature for 15 min. The completion of the reaction was monitored by HPLC. Upon completion, H₂O was added and the reaction mixture was concentrated to dryness. H₂O was added to the crude residue and the reaction mixture was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaHCO₃, brine and dried over Na₂SO₄. Filtration and removal of the solvent *in vacuo* provided the crude product, which was purified by Combiflash silica gel chromatography (0–50% EtOAc in hexane) to afford 450 mg (90%) of the desired compound as a colorless oil; ¹H NMR (400 MHz, CDCl₃) δ = 6.96 (d, *J* = 7.8 Hz, 1 H), 6.88 (dd, *J* = 1.8, 7.8 Hz, 1 H), 4.35 (quind, *J* = 6.9, 10.3 Hz, 1 H), 3.29 (dd, *J* = 10.2, 16.5 Hz, 1 H), 3.14 (dd, *J* = 6.8, 16.7 Hz, 1 H).

Step 2—To the solution of 6-bromo-2-(trifluoromethyl)indoline (90 mg, 0.34 mmol) in 0.4 mL of pyridine were added 3-(trifluoromethyl)benzenesulfonyl chloride (108 μL, 0.68 mmol) and DMAP (4 mg, 0.03 mmol). The reaction was stirred overnight at 90 °C. The completion of the reaction was monitored by HPLC. Upon completion, aqueous solution of HCl 1N was added and the mixture was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaHCO₃, brine and dried over Na₂SO₄. Filtration and removal of the solvent *in vacuo* provided the crude product, which was purified by Combiflash silica gel chromatography (0–20% EtOAc in hexane) to afford 120 mg (75%) of the title compound **66** as a colorless solid; ¹H NMR (400 MHz, CDCl₃) δ = 7.87 (s, 1 H), 7.80 - 7.76 (m, 2 H), 7.72 (s, 1 H), 7.58 - 7.51 (m, 1 H), 7.18 (d, *J* = 8.6 Hz, 1 H), 6.90 (d, *J* = 7.9 Hz, 1 H), 4.76 - 4.62 (m, 1 H), 2.88 (dd, *J* = 1.8, 17.3 Hz, 1 H), 2.76 (dd, *J* = 9.8, 17.3 Hz, 1 H).

2-(trifluoromethyl)-1-((3-(trifluoromethyl)phenyl)sulfonyl)indolin-6-ol 67

In a dried MW flask under Ar were introduced 6-bromo-2-(trifluoromethyl)-1-((3-(trifluoromethyl)phenyl)sulfonyl)indoline **66** (120 mg, 0.25 mmol), AcOK (75 mg, 0.76 mmol), bis(pinacolato)diboron (96 mg, 0.38 mmol) and 2.5 mL of anhydrous dioxane. The flask was purged three times with Ar before the addition of Pd(dppf)Cl₂.CH₂Cl₂ (21 mg, 0.03 mmol). The flask was sealed and the reaction mixture was stirred at 80 °C for 6h. The completion of the reaction was monitored by HPLC (mixture 1/1: corresponding boronic ester/boronic acid). The reaction mixture was cooled down to room temperature. To the reaction mixture were added 0.25 mL of H₂O, NaOH (30 mg, 0.76 mmol) and H₂O₂ 50%wt in H₂O (52 μL, 0.76 mmol). The reaction was stirred at room temperature for 1h. The completion of the reaction was monitored by HPLC. Upon completion, aqueous solution of HCl 1N was added and the reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na₂SO₄. Filtration and removal of the solvent provided the crude product, which was purified by Combiflash silica gel chromatography (0–40% EtOAc in hexane) to afford 90 mg (86%) of the title compound **67** as a colorless solid; ¹H NMR (400 MHz, CDCl₃) δ = 7.93 (s, 1 H), 7.88 - 7.81 (m, 2 H), 7.62 - 7.55 (m, 1 H), 7.19 (d, *J* = 2.2 Hz, 1 H), 6.94 (d, *J* = 8.3 Hz, 1 H), 6.63 (dd, *J* = 2.3, 8.2 Hz, 1 H), 4.77 - 4.70 (m, 1 H), 2.94 - 2.87 (m, 1 H), 2.81 - 2.72 (m, 1 H).

6-((2-chloro-6-fluorobenzyl)oxy)-2-(trifluoromethyl)-1-((3-(trifluoromethyl)phenyl)sulfonyl)indoline 68

The title compound was prepared according to General Procedure C from 2-(trifluoromethyl)-1-((3-(trifluoromethyl)phenyl)sulfonyl)indolin-6-ol **67** (20 mg, 0.05 mmol) and 2-(bromomethyl)-1-chloro-3-fluorobenzene (22 mg, 0.10 mmol). The crude product was purified by preparative HPLC (20–100% CH₃CN/MeOH (1:1) in H₂O (0.01% TFA)) which provided after lyophilization 26 mg (97%) of the title compound **68** as a colorless solid; ¹H NMR (400 MHz, CDCl₃) δ = 7.93 (s, 1 H), 7.83 (t, *J* = 6.7 Hz, 2 H), 7.61 - 7.54 (m, 1 H), 7.37 - 7.27 (m, 3 H), 7.12 - 7.04 (m, 1 H), 6.99 (d, *J* = 8.3 Hz, 1 H), 6.76 (dd, *J* = 2.5, 8.3 Hz, 1 H), 5.20 (d, *J* = 1.8 Hz, 2 H), 4.81 - 4.69 (m, 1 H), 2.93 (dd, *J* = 1.9, 16.5 Hz, 1 H), 2.80 (dd, *J* = 9.7, 16.5 Hz, 1 H).

6-((3-chloro-5-fluoropyridin-4-yl)methoxy)-2-(trifluoromethyl)-1-((3-(trifluoromethyl)phenyl)sulfonyl)indoline 69

The title compound was prepared according to General Procedure C from 2-(trifluoromethyl)-1-((3-(trifluoromethyl)phenyl)sulfonyl)indolin-6-ol **67** (20 mg, 0.05 mmol) and 4-(bromomethyl)-3-chloro-5-fluoropyridine (22 mg, 0.10 mmol). The crude product was purified by preparative HPLC (20–100% CH₃CN/MeOH (1:1) in H₂O (0.01% TFA)) which provided after lyophilization 12 mg (37%) of the title compound **69** as a colorless solid, as TFA salt; ¹H NMR (400 MHz, CDCl₃) δ = 8.56 (s, 1 H), 8.49 (s, 1 H), 7.90 (s, 1 H), 7.84 (d, *J* = 8.1 Hz, 2 H), 7.64 - 7.55 (m, 1 H), 7.33 (d, *J* = 2.3 Hz, 1 H), 7.01 (d, *J* = 8.3 Hz, 1 H), 6.75 (dd, *J* = 2.3, 8.3 Hz, 1 H), 5.23 (d, *J* = 1.3 Hz, 2 H), 4.81 - 4.71 (m, 1 H), 2.98 - 2.90 (m, 1 H), 2.87 - 2.76 (m, 1 H). MS (ESI⁺) *m/z*: 554.84 [M+H⁺].

6-((3,5-dichloropyridin-4-yl)methoxy)-2-(trifluoromethyl)-1-((3-(trifluoromethyl)phenyl)sulfonyl)indoline 70

The title compound was prepared according to General Procedure C from 2-(trifluoromethyl)-1-((3-(trifluoromethyl)phenyl)sulfonyl)indolin-6-ol **67** (20 mg, 0.05 mmol) and 4-(bromomethyl)-3,5-dichloropyridine (23 mg, 0.10 mmol). The crude product was purified by preparative HPLC (20–100% CH₃CN/MeOH (1:1) in H₂O (0.01% TFA)) which provided after lyophilization 16 mg (48%) of the title compound **70** as a colorless solid, as TFA salt; ¹H NMR (400 MHz, CDCl₃) δ = 8.60 (s, 2 H), 7.95 - 7.80 (m, 3 H), 7.65 - 7.56 (m, 1 H), 7.34 (d, *J* = 2.5 Hz, 1 H), 7.02 (d, *J* = 8.3 Hz, 1 H), 6.76 (dd, *J* = 2.3, 8.3 Hz, 1 H), 5.29 (s, 2 H), 4.86 - 4.72 (m, 1 H), 2.95 (dd, *J* = 1.8, 16.5 Hz, 1 H), 2.82 (dd, *J* = 9.7, 16.5 Hz, 1 H). MS (ESI⁺) *m/z*: 572.82 [M+H⁺].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Examples of published ROR γ modulators

Figure 2.
Minor structural changes to ROR γ inverse agonists led to ROR γ agonists.

Figure 3. Conformational dynamics probed by HDX of A: ROR γ agonist **16** and B: ROR γ inverse agonist **7**.

Scheme 1. General Synthetic Procedure for indoline^a

^a**Reagents:** a) NaBH_3CN , AcOH, rt, (99%); b) 3- $\text{CF}_3\text{PhSO}_2\text{Cl}$, pyridine, THF, 0°C , (46%); c) ArCH_2OH , PPh_3 , DIAD, DCM, rt, (31–56%) or 2-Cl-6-F- $\text{PhCH}(\text{CH}_3)\text{OMs}$, K_2CO_3 , DMF, 60°C , (87%) or ArCH_2Br , K_2CO_3 , DMF, (29–85%), rt; d) 2-Cl-6-F- PhCH_2Br , K_2CO_3 , DMF, rt, (68%); e) ArSO_2Cl , Et_3N , DCM, rt, (40–86%).

Scheme 2.

Synthesis of N-Arylsulfonamide 3-methylindoline.^a

^a**Reagents.** a) POCl₃, DMF, 65 °C, (95%); b) LiAlH₄, THF, 65 °C, (75%); c) NaBH₃CN, AcOH, rt, (85%); d) 3-CF₃PhSO₂Cl, Et₃N, DCM, rt, (26%).

Scheme 3.

Synthesis of N-Arylsulfonamide 2-methylindoline^a

^a**Reagents:** a) 2-Cl,6-FPhCH₂Br, K₂CO₃, DMF, rt.; b) NH₄Cl, Fe, EtOH/H₂O, 80 °C, (98% from **58**); c) tBuOCl, methyl thio-2-propanone, Et₃N, DCM, −78 °C-rt; then Raney-Ni, EtOH/H₂O, rt, (43%); d) NaBH₃CN, AcOH, rt, (89%); e) 3-CF₃PhSO₂Cl, Et₃N, DCM, rt, (89%).

Scheme 4.

Synthesis of N-Arylsulfonamide 2-trifluoromethylindoline.^a

^a**Reagents:** a) NH_4Cl , Fe, EtOH/ H_2O , 80 °C; b) $(\text{CF}_3\text{CO})_2\text{O}$, DCM, rt, (89% from **62**); c) Br_2 , H_2O_2 50% wt, DCM/ H_2O , 50 °C; d) PPh_3 , toluene, 90 °C, (45% from **63**); e) DMF, 200 °C, MW, (94%); f) NaBH_3CN , TFA, 4 °C (90%); g) 3- $\text{CF}_3\text{PhSO}_2\text{Cl}$, DMAP, pyridine, 90 °C, (75%); h) bis(pinacolato)diboron, AcOK, $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$, dioxane, 80 °C, then NaOH, H_2O_2 50% wt, H_2O , rt, (86%); i) BnBr , K_2CO_3 , DMF, rt, (37–97%).

Table 1

From inverse agonist to agonist

Cmpd	X-Y	A-B	IC ₅₀ SPA ^a (μM)	EC ₅₀ GAL4 ^b (μM)
7		CH ₂ -CH ₂	0.053±0.001	0.05±0.01 (-1) ^{c,d}
8		CH ₂ -CH ₂	0.097±0.01	0.58±0.08 (+2.2) ^d
9		CH ₂ -CH ₂	0.059±0.005	n.a
10		CH ₂ -CH ₂	0.11±0.02	n.a
11		CH ₂ -CH ₂	0.21±0.02	0.40±0.11 (+1.8) ^d
12		CH ₂ -CH ₂	0.18±0.02	0.25±0.04 (+3.8) ^d
13		CH ₂ -CH ₂	0.15±0.02	0.21±0.04 (+3.5) ^d
14		CH ₂ -CH ₂	0.29±0.02	1.1±0.37 (+4.1) ^d

Cmpd	X-Y	A-B	IC ₅₀ SPA ^a (μM)	EC ₅₀ GAL4 ^b (μM)
15		CH ₂ -CH ₂	0.24±0.02	3.9±0.58 (+2.9) ^d
16		CH ₂ -CH ₂	0.22±0.04	0.18±0.03 (+3.2) ^d
17		CH ₂ -CH ₂	0.12±0.01	0.26±0.04 (+3.8) ^d
18		CH ₂ -CH ₂	0.35±0.10	0.75±0.25 (+1.5) ^d
19		CH=CH	0.32±0.02	2.7±0.46 (+3.4) ^d
20		CH=CH	0.35±0.06	1.9±0.42 (+2.8) ^d
21		CH=CH	0.29±0.06	3.4±0.71 (+2.6) ^d
22		CH=CH	55% ^e	n.t.
23		CH=CH	15% ^e	n.t.

^aDisplacement of ³H-T09 from human RORγ LBD;

^bThe EC₅₀s are mean values of at least 3 replicates in presence of ursolic acid (2 μM);

^cThe EC₅₀ was determined without the presence of ursolic acid;

^dmaximum fold change over DMSO;

^e% displacement of ³H-T09 at 10 μM;

n.t.: not tested; n.a.: not active < 30 μM.

Table 2

SAR study of the benzyl ether

Cmpd	R ¹	IC ₅₀ SPA ^a (μM)	EC ₅₀ GAL4 ^b (μM)
29		0.20±0.02	0.62±0.16 (+2.6) ^c
30		0.29±0.03	1.2±0.24 (+3.3) ^c
31		0.44±0.05	1.2±0.24 (+1.9) ^c
32		0.35±0.1	1.5±0.29 (+3.1) ^c
33		0.17±0.01	0.49±0.04 (+3.4) ^c
17		0.12±0.01	0.26±0.04 (+3.8) ^c
16		0.22±0.04	0.18±0.03 (+3.2) ^c

Cmpd	R ¹	IC ₅₀ SPA ^a (μM)	EC ₅₀ GAL4 ^b (μM)
34		0.13±0.01	0.17±0.04 (+3.3) ^c
35		0.16±0.01	0.20±0.04 (+3.1) ^c
36		0.23±0.02	0.29±0.08 (+2.2) ^c
37		0.17±0.02	0.09±0.02 (+3.9) ^c
38		0.085±0.009	0.48±0.13 (+1.3) ^c
39		0.078±0.008	0.16±0.03 (+3.2) ^c
40		0.18±0.02	0.45±0.10 (+2.9) ^c

Cmpd	R ¹	IC ₅₀ SPA ^a (μM)	EC ₅₀ GAL4 ^b (μM)
41		0.23±0.03	0.76±0.12 (+2.1) ^c
42		0.19±0.02	0.60±0.11 (+4.0) ^c
43		n.a	n.a

^aDisplacement of ³H-T09 from human RORγ LBD;

^bThe EC₅₀s are mean values of at least 3 replicates in presence of ursolic acid (2 μM);

^c maximum fold change over DMSO;

n.a.: not active < 30 μM.

Table 3

SAR study of the N-Arylsulfonamide

Cmpd	R ¹	IC ₅₀ SPA ^a (μM)	EC ₅₀ GAL4 ^b (μM)
44		0.80	n.t.
45		75% ^c	n.t.
17		0.12±0.01	0.26±0.04 (+3.8) ^d
46		0.23±0.02	0.50±0.11 (+3.1) ^d
47		0.25±0.03	0.65±0.21 (+3.4) ^d
48		0.37±0.02	2.3±0.41 (+5.4) ^d
49		0.25±0.03	7.8±2.1 (+2.8) ^d
50		0.25±0.03	0.43±0.10 (+1.9) ^d

Cmpd	R ¹	IC ₅₀ SPA ^a (μM)	EC ₅₀ GAL4 ^b (μM)
51		0.23±0.04	1.6±0.41 (+4.6) ^d
52		0.29±0.04	0.47±0.07 (+2.8) ^d
53		0.18±0.04	0.33±0.05 (+3.1) ^d
54		0.50±0.03	n.t.
55		0.34±0.09	0.38±0.10 (+0.5) ^d

^aDisplacement of ³H-T09 from human RORγ LBD;

^bThe EC₅₀s are mean values of at least 3 replicates in presence of ursolic acid (2 μM);

^c% displacement of ³H-T09 at 10 μM;

^d maximum fold change over DMSO;

n.t: not tested.

Table 4

Influence of substituent on the indoline scaffold.

Cmpd	R ¹	R ²	R ³	IC ₅₀ SPA ^a (μM)	EC ₅₀ GAL4 ^b (μM)
17		H	H	0.12±0.01	0.26±0.04 (+3.8) ^c
57		H	CH ₃	0.18±0.01	1.8±0.64 (+4.1) ^c
61		CH ₃	H	0.38±0.02	0.11±0.02 (+4.8) ^c
68		CF ₃	H	0.19±0.02	0.18±0.03 (+6.2) ^c
69		CF ₃	H	0.29±0.03	0.15±0.02 (+5.0) ^c
70		CF ₃	H	0.15±0.01	0.12±0.03 (+5.3) ^c

^a Displacement of ³H-T09 from human RORγ LBD;

^b The EC₅₀s are mean values of at least 3 replicates in presence of ursolic acid (2 μM);

^c maximum fold change over DMSO.

Table 5Activation of IL-17 promoter by full length ROR γ in presence of ursolic acid in HEK293T cells

Cmpd	EC ₅₀ IL-17 Cell (μ M) {%eff.}	Cmpd	EC ₅₀ IL-17 Cell (μ M) {%eff.}
7	1.4 {−10% }	40	0.18 {+ 40% }
12	0.14 {+ 37% }	61	1.13 {+ 61% }
16	0.87 {+ 55% }	68	0.15 {+ 42% }
29	0.11 {+ 25% }	70	0.095 {+ 36% }

Table 6*In vivo* exposures of selected indolines

Cmpd	Plasma 2h (μM) ^a	Plasma 4h (μM) ^a	clogP
7	1.21	0.66	4.5
8	0.73	0.41	4.1
9	0.74	0.36	4.4
12	0.33	0.17	6.7
40	0.89	0.62	4.6
41	0.41	0.21	4.1
43	1.62	0.46	4.6
50	0.29	0.12	4.3
70	0.60	0.16	6.0

^a average range over 3 mice, IP, 10mg/kg, formulation 1mg/mL, vehicle used 10/10/80 DMSO/Tween80/water.