Article

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Title

Diaryl-substituted (dihydro)pyrrolo[3,2,1-*hi*]indoles, a class of potent COX-2 inhibitors with tricyclic core structure

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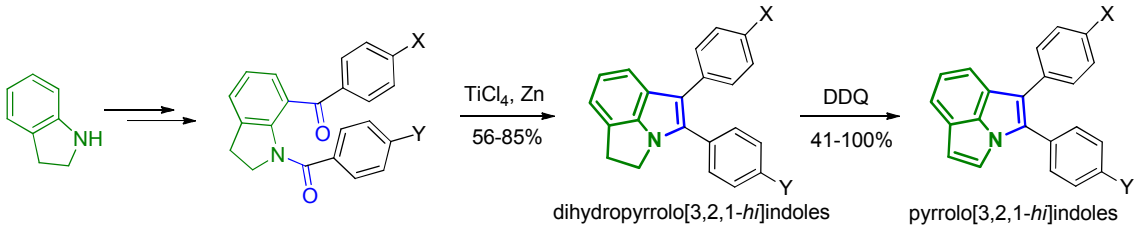
Abstract



⇨ **modular & regioselective** sequence comprising **McMurry cyclization**

⇨ identification of **COX-2 inhibitors with tricyclic core structure**

A new compound class of diaryl-substituted heterocycles with tricyclic dihydropyrrolo[3,2,1-*hi*]indole and pyrrolo[3,2,1-*hi*]indole core structures has been designed and was synthesized by a modular sequence of Friedel-Crafts acylation, amide formation, and McMurry cyclization. This synthesis route represents a novel and versatile access towards dihydropyrrolo[3,2,1-*hi*]indoles and is characterized by good chemical yields and high modularity. From a set of nineteen derivatives, eleven candidates were selected for determination of their COX inhibition potency and were found to be selective inhibitors with high affinity to COX-2 (IC_{50} ranging from 20 – 2500 nM and negligible inhibition of COX-1). The binding mode of the novel inhibitors in the active side of COX-2 was calculated *in silico* using the protein-ligand docking program GOLD by application of the molecular structures of two compounds derived from X-ray crystallography. Two novel compounds with high affinity to COX-2 (**6k** = 70 nM, **8e** = 60 nM) have got a fluoro-substituent making them to promising candidates for the development of ^{18}F-radiolabeled COX-2 inhibitors for imaging purposes with positron emission tomography (PET).

Key words

pyrrolo[3,2,1-*hi*]indoles, selective COX-2 inhibitors, McMurry cyclization, GOLD, docking studies, radiotracer

Introduction

The enzyme cyclooxygenase-2 (COX-2 or prostaglandin H synthase-2, PGHS-2) mediates the rate-limiting step in the biosynthesis of prostanoids, a class of autocrine and paracrine acting lipid-mediators responsible for the regulation of physiological as well as pathophysiological processes.[1, 2] COX-2 is involved in the pathogenesis of acute and chronic inflammatory diseases and its expression is inducible by proinflammatory and proliferative stimuli. The fact that inhibition of COX-2 exerts anti-inflammatory, analgesic and antipyretic actions but concurrent inhibition of COX-1 causes unwanted gastrointestinal side effects stimulated the initial search for selective COX-2 inhibitors (COXIBs) in the late 1990's.[3] Meanwhile, COX-2 overexpression was also identified in a variety of cancer entities implicating the possibility to prevent and treat these diseases with COXIBs, e.g., in combination with chemotherapy and/ or radiation therapy.[4-6] Due to this and the fact that the long-term use of COXIBs like celecoxib and etoricoxib is limited because of adverse cardiovascular effects, the search for novel compounds with improved pharmacological profile is an ongoing challenge in medicinal and pharmaceutical chemistry.[7, 8] COX-2 is considered as a biological marker in a number of diseases for that imaging agents targeting COX-2, e.g., radiolabeled COX-2 inhibitors for positron emission tomography (PET), are highly desirable.[9-12]

In general, most of the synthetic COXIBs can be assigned to the class of diaryl substituted heterocycles bearing a methylsulfonyl or aminosulfonyl group at one of the phenyl rings.[13, 14] Within this class, the inhibitors can possess a monocyclic and bicyclic core structure (figure 1).[15] While for example celecoxib has a pyrazole (monocyclic) core, some diaryl-substituted indoles represent potent inhibitors of COX-2 with a bicyclic core.[16, 17] In the search for radiolabeled COX-2 inhibitors a variety of compounds had been evaluated but none of them has been transferred as radiotracer into the clinic showing the need for further efforts in this field.[9-12] In our previous work to develop a ^{18}F-labeled COX-2 inhibitor based on the 2,3-diaryl-1*H*-indole scaffold[18] we recognized QSAR studies postulating for 2,3-diarylindoles a positive influence on the inhibitory potency by an increase in the van der Waals volume of the inhibitor.[19] In this regard we hypothesized that novel potent leads for COX-2 inhibitors would be accessible by bridging the indole heterocycle between N1 and C7 using formally an ethylene and ethenyl moiety (figure 1). The resulting heterocycle, the pyrrolo[3,2,1-*hi*]indole, is an aromatic, tricyclic 6,5,5-membered system containing one nitrogen atom. Although the synthesis of some pyrrolo[3,2,1-*hi*]indoles has been described before[20, 21], for this compound class no pharmacological effects have been reported yet. In contrast, the 1,2-dihydropyrrolo[3,2,1-*hi*]indole heterocycle can be found in some pharmacologically interesting molecules, as CB_2-receptor antagonists and inhibitors of c-Met expression.[22-24]

COX-2 inhibitors with a dihydropyrrolo[3,2,1-*hi*]indole and pyrrolo[3,2,1-*hi*]indole core have not been described so far. This prompted us to synthesize a comprehensive set of compounds of this new family and to evaluate their potency as COX inhibitors.

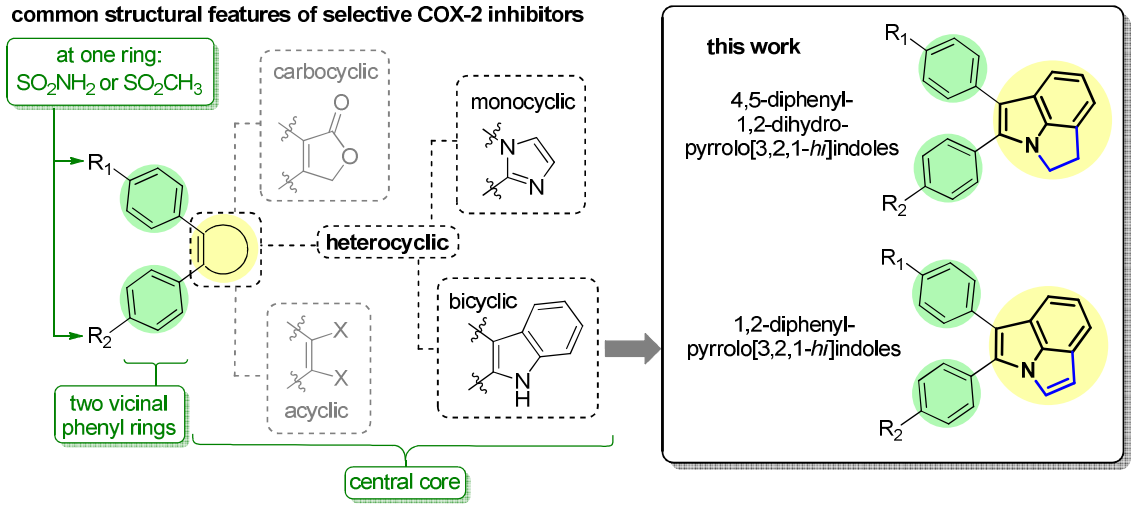


Figure 1. General structure of COX-2 inhibitors and target compounds of this work

Here we describe the synthesis of diaryl-substituted dihydropyrrolo[3,2,1-*hi*]indoles starting from indoline and para-substituted benzonitriles via Friedel-Crafts acylation and McMurry cyclization and their conversion to the respective pyrrolo[3,2,1-*hi*]indoles by dehydrogenation. This represents a novel route towards 1,2-dihydropyrrolo[3,2,1-*hi*]indoles that is characterized by modularity, regioselectivity and a straightforward synthetic route. COX-1/COX-2 inhibition activity of eleven candidates was determined where compounds of both classes turned out to be highly potent and selective COX-2 inhibitors. These findings were supported *in silico* by protein-ligand docking studies with GOLD.

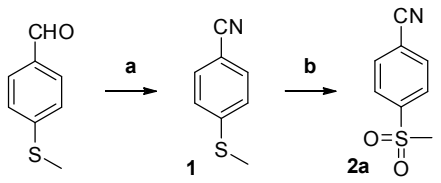
Results and Discussion

Chemical Synthesis

Primarily, 4-(methylsulfonyl)benzonitrile **2a**, one of the starting materials for the main synthesis sequence, was synthesized in two steps starting from 4-(methylthio)benzaldehyde (scheme 1). In brief, 4-(methylthio)benzaldehyde was allowed to react with hydroxylamine hydrochloride in DMSO to afford the 4-(methylthio)benzonitrile **1** in 84% yield *via* aldehyde oxime formation and spontaneous dehydratization at a temperature of 100°C as described by Chill and Mebane for other nitriles.[25] The oxidation with *meta*-chloroperbenzoic acid formed **2a** in a yield of 77%. X-ray structure analysis unambiguously confirmed the molecular

structure of compounds **1** and **2a** (figure 2). For details of the X-ray structure analyses, the reader is referred to the supporting information.

Scheme 1. Synthesis of 4-(methylsulfonyl)benzonitrile (2a)[a]



[a]Reagents and conditions: (a) $NH_2OH \cdot HCl$, DMSO, 100°C; (b) MCPBA, DCM, r.t.

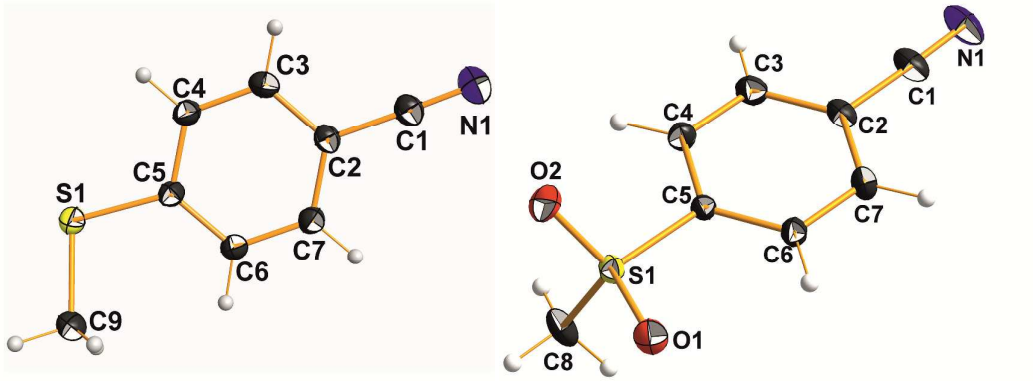
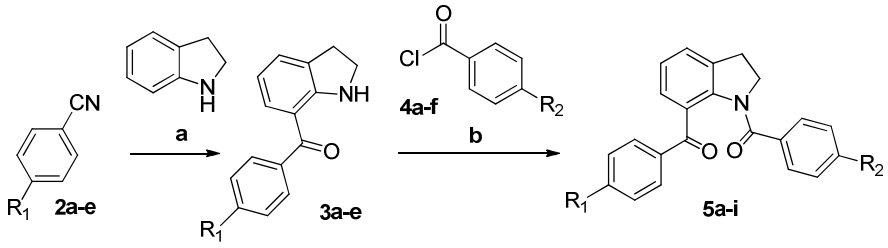


Figure 2. Molecular structure of compounds 1 (left) and 2a (right) in the crystal (ORTEP plot: displacement thermal ellipsoids are drawn at 50% probability level)

The modular synthesis sequence to form pyrrolo[3,2,1-*hi*]indoles is based on the *N*-benzoyl-substituted 7-benzoyl-indolines (**5a-i**) as main building block. The synthetic route starting from *para*-substituted benzonitriles **2a-e** is outlined in scheme 2. The first step in this sequence is the selective benzoylation of indoline in 7-position that was achieved starting from the benzonitriles **2a-e** by a BCl_3-mediated Friedel-Crafts reaction.[26] The reaction with the fluoro-, chloro-, methyl- or unsubstituted (**2b-e**) nitriles afforded the desired 7-benzoylindolines **3b-e** in 78-98% yield and high purity according to TLC, HPLC and NMR analysis. In contrast, the reaction of indoline with the methylsulfonyl-substituted benzonitrile **2a** under the same conditions gave the 7-[4-(methylsulfonyl)benzoyl]-1*H*-indoline **3a** not in a pure form and ^{1}H-NMR analysis indicated the presence of 11-35% (m/m) **2a** in the mixture. Despite all efforts we were unable to purify **3a** by column chromatography; hence the crude product was used for the following step.

Scheme 2. Modular synthesis sequence for *N*-benzoyl-7-benzoylindolines 5a-i[a]



2a-e / 3a-e

2a/3a: R_1= SO_2Me
2b/3b: R_1= F
2c/3c: R_1= Cl
2d/3d: R_1= H
2e/3e: R_1= Me

4a-f

4a: R_2= F
4b: R_2= Cl
4c: R_2= H
4d: R_2= Me
4e: R_2= SO_2Me
4f: R_2= OMe

5a-i

5a: R_1/ R_2= SO_2Me / F
5b: R_1/ R_2= SO_2Me / Cl
5c: R_1/ R_2= SO_2Me / H
5d: R_1/ R_2= SO_2Me / Me
5e: R_1/ R_2= F / SO_2Me
5f: R_1/ R_2= Cl / SO_2Me
5g: R_1/ R_2= H / SO_2Me
5h: R_1/ R_2= Me / SO_2Me
5i: R_1/ R_2= SO_2Me / OMe

[a]Reagents and conditions: (a) i: BCl_3, $AlCl_3$, toluene, reflux, ii: 2 M HCl, reflux; (b) NEt_3, THF, r.t.

Then, the 7-benzoyl-substituted indolines **3a-e** were converted by *N*-acylation with the *para*-substituted benzoyl chlorides **4a-f** to the corresponding *N*,7-dibenzoyl-substituted indolines **5a-i**. By combination of the five 7-benzoyl-indolines **3a-e** and the six benzoyl chlorides **4a-f**, a potential library of thirty compounds can be obtained what demonstrates nicely the modularity of the experimental setup. However, we focused on compounds containing a methylsulfonyl group at one of the aromatic rings because this structural motif is important for the selective binding to COX-2.[15] By that, *N*-acylation of the crude methylsufonyl-substituted 7-benzoylindoline **3a** afforded the building blocks **5a-d** and **5i** in 41-57% yield starting from indoline. Analogously, the compounds **5e-h** were prepared in 56-66% yield starting from the 7-benzoylindolines **3b-e** and 4-(methylsulfonyl)benzoic acid chloride **4e** which was synthesized from the corresponding acid using $SOCl_2$. The successful substitution in 7-position of the indoline was unambiguously confirmed by X-ray crystal structure analysis of **5c** as a representative (figure 3). Of note, an alternative modular synthetic route towards *N*,7-dibenzoyl-substituted indolines comprising *N*-acylation in the first followed by Pd-catalyzed 7-acylation in the second step has been presented recently by Kim *et al.* which could be useful if this route fails.[27]

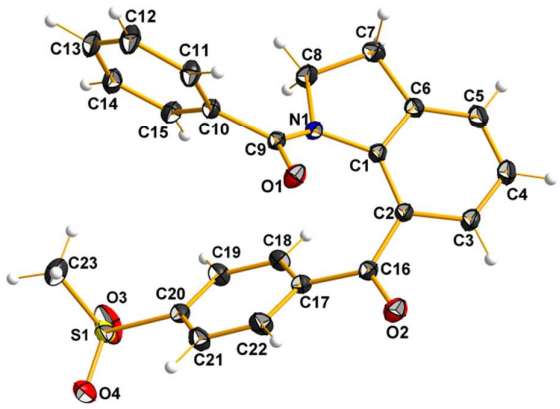
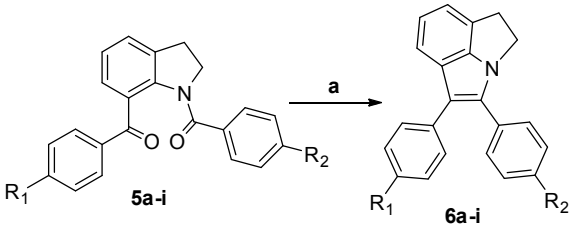


Figure 3. Molecular structure of compound 5c in the crystal (the figure shows one of the two independent molecules in the asymmetric; ORTEP plot: displacement thermal ellipsoids are drawn at 50% probability level).

To build the 6,5,5-membered heterocyclic core of the dihydropyrrolo[3,2,1-*hi*]indoles, McMurry cyclization was conducted using the "Instant-method".[28-30] Briefly, each *N*,7-dibenzoyl-substituted indoline **5a-i** was allowed to react with $TiCl_4$ and Zn in THF under reflux affording the dihydropyrrolo[3,2,1-*hi*]indoles **6a-i** in yields of 56-85% (scheme 3).

Scheme 3. Synthesis of dihydropyrrolo[3,2,1-*hi*]indoles 6a-i[a]



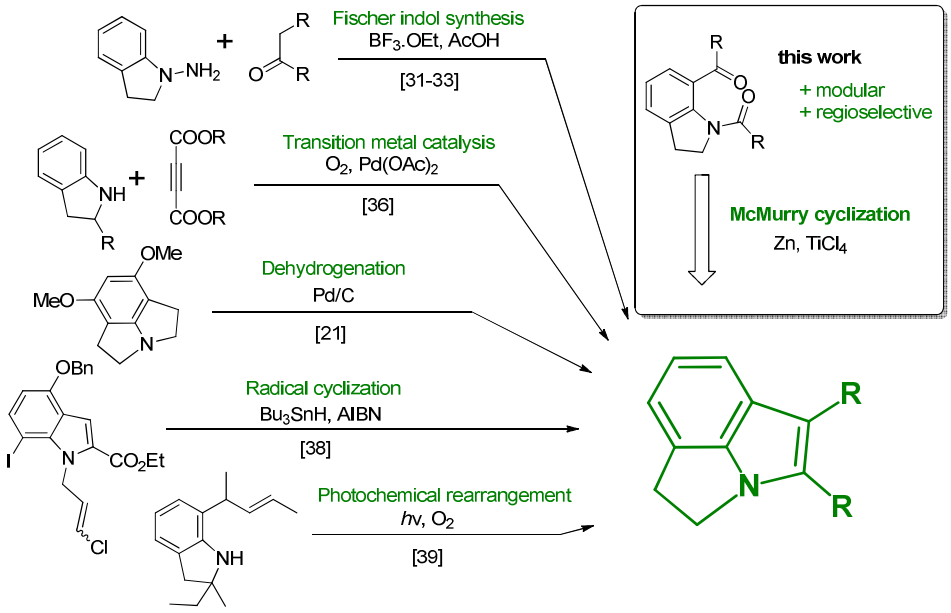
5a-i/ 6a-i
5a/**6a**: R_1/ R_2= SO_2Me / F **5f**/**6f**: R_1/ R_2= Cl / SO_2Me
5b/**6b**: R_1/ R_2= SO_2Me / Cl **5g**/**6g**: R_1/ R_2= H / SO_2Me
5c/**6c**: R_1/ R_2= SO_2Me / H **5h**/**6h**: R_1/ R_2= Me / SO_2Me
5d/**6d**: R_1/ R_2= SO_2Me / Me **5i**/**6i**: R_1/ R_2= SO_2Me / OMe
5e/**6e**: R_1/ R_2= F / SO_2Me

[a]Reagents and conditions: (a) $TiCl_4$, Zn, THF, 70°C.

This strategy represents to the best of our knowledge a novel synthetic route towards dihydropyrrolo[3,2,1-*hi*]indoles. In the past, the synthesis of dihydropyrrolo[3,2,1-*hi*]indoles has been generally described by Fischer indole synthesis.[31-33] Although this reaction is useful due to its regioselectivity, the low modularity and, in some cases, the laborious access to appropriate starting materials may be disadvantageous for its utilization, especially for the library synthesized in this work. Another access to dihydropyrrolo[3,2,1-*hi*]indoles is the

synthesis by transition metal catalyzed methods[34-37], dehydrogenation[21], radical cyclization[38], as well as photochemical rearrangements[39] (scheme 4). However, steric restrictions for the starting materials, low regioselectivity or the need for special catalysts make these approaches unsuitable for a general use. Advantageously, with the synthetic route presented by us differently substituted indolines, nitriles as well as benzoyl chlorides may be combined because the BCl_3-mediated Friedel-Crafts acylation is yielding 7-substituted indolines selectively and the McMurry cyclization has a high compatibility for different functional groups. Hence, our synthetic route gives a highly modular and convenient access to dihydropyrrolo[3,2,1-*hi*]indoles.

Scheme 4. Synthetic route towards dihydropyrrolo[3,2,1-*hi*]indoles followed in this work and examples from the literature



For compounds **6a** and **6e**, X-ray crystal structure analyses were performed what unambiguously confirmed the identity of both regioisomers (figure 4). Interestingly, the ethylene bridge obviously causes a high ring strain in the 1,2-dihydropyrrolo[3,2,1-*hi*]indole system, such that the bond between the carbon atoms C1 and C2 (accordingly C7 and C8 in the numbering in figure 4) is stretched. Although the ethylene bridge is not part of the aromatic system, the dihydropyrrolo[3,2,1-*hi*]indole system is almost planar. In both compounds, the methylsulfonyl-substituted phenyl ring is less twisted out of the plane of the dihydropyrrolo[3,2,1-*hi*]indole moiety than the fluoro-substituted phenyl ring. This indicates the preferred interaction of the electron-deficient methylsulfonyl-substituted phenyl ring with the indole-like π-system of the electron-rich dihydropyrrolo[3,2,1-*hi*]indole compared to the fluoro-substituted phenyl ring.

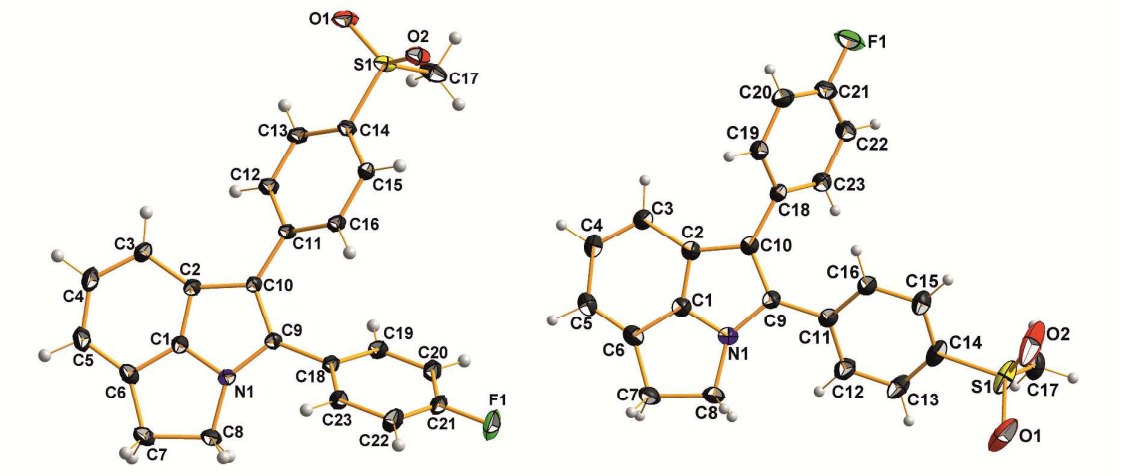
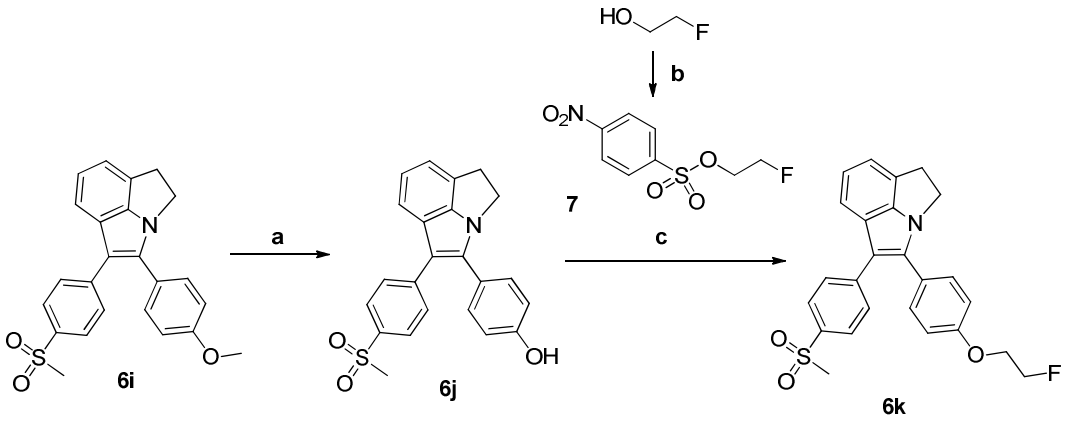


Figure 4. Molecular structure of compound 6a (left) and 6e (right) in the crystal (the figure of 6a shows one of the two independent molecules in the asymmetric unit; ORTEP plot: displacement thermal ellipsoids are drawn at 50% probability level)

With the aim to synthesize an appropriate precursor for PET radiotracer development, that means in this case a compound suitable for [^{18}F]fluoroethylation, additionally a hydroxyl derivative was prepared (scheme 5). Therefore, **6i** was demethylated using BBr_3 in DCM to give the 4-hydroxyphenyl-substituted dihydropyrrolo[3,2,1-*hi*]indole **6j** in 91% yield. Then, 2-fluoroethyl-4-nitrobenzenesulfonate **7**, prepared by the reaction of 4-nitrobenzenesulfonyl chloride and 2-fluoroethanol in THF with $KOSiMe_3$, was allowed to react with **6j** in THF using KO^{t}Bu as a base. This gave the 2-fluoroethoxy-substituted dihydropyrrolo[3,2,1-*hi*]indole **6k** in 55% yield, a compound that can serve as reference for the radiosynthesis of the corresponding ^{18}F-radiolabeled PET-tracer.

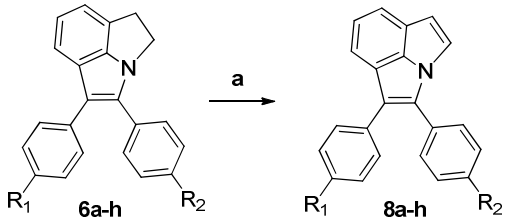
Scheme 5. Synthesis of dihydropyrrolo[3,2,1-*hi*]indole 6k[a]



[a]Reagents and conditions: (a) BBr_3, DCM, r.t.; (b) 4-nitrobenzenesulfonyl chloride, $KOSiMe_3$, THF, 0°C; (c) KO^{t}Bu, THF, 70°C.

Finally, from the 1,2-dihydropyrrolo[3,2,1-*hi*]indoles **6a-h** the corresponding pyrrolo[3,2,1-*hi*]indoles **8a-h** were generated by dehydrogenation using DDQ in benzene (scheme 6). With exception of **8b** for that the yield was only moderate (41%), all other pyrrolo[3,2,1-*hi*]indoles were formed in high yields of 75-100%. Noteworthy, according to the structural similarity of starting materials and products the column chromatographic purification required eluents with high retention on silica gel (R_f of 0.1-0.2). Only few synthetic approaches for the synthesis of pyrrolo[3,2,1-*hi*]indoles have been reported which are i.e. intramolecular Aldol-cyclization[20, 21], dehydrogenation of 1,2-dihydro- and 1,2,4,5-tetrahydropyrrolo[3,2,1-*hi*]indoles by Pd/C[21, 40] and a polyphosphoric acid catalyzed reaction[41]. In this context, dehydrogenation by DDQ in benzene represents a suitable system for the synthesis of this highly strained ring system as well.

Scheme 6. Synthesis of pyrrolo[3,2,1-*hi*]indoles 8a-h[a]



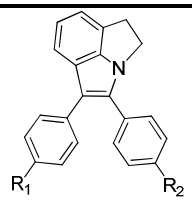
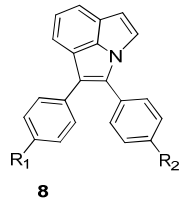
6a-h/ 8a-h
6a/8a: R_1/ R_2= SO_2Me / F **6e/8e**: R_1/ R_2= F / SO_2Me
6b/8b: R_1/ R_2= SO_2Me / Cl **6f/8f**: R_1/ R_2= Cl / SO_2Me
6c/8c: R_1/ R_2= SO_2Me / H **6g/8g**: R_1/ R_2= H / SO_2Me
6d/8d: R_1/ R_2= SO_2Me / Me **6h/8h**: R_1/ R_2= Me / SO_2Me

[a]Reagents and conditions: (a) DDQ, benzene, 100°C.

COX inhibitory activity

From the pool of nineteen synthesized dihydropyrrolo[3,2,1-*hi*]indoles **6** and pyrrolo[3,2,1-*hi*]indoles **8**, eleven candidates were selected for determination of the COX inhibition potency in order to find suitable candidates for labeling with fluorine-18 or carbon-11 and, on the other hand, to get deeper insights into structure activity relationships. The COX inhibition potency of the selected dihydropyrrolo[3,2,1-*hi*]indoles and pyrrolo[3,2,1-*hi*]indoles as well as celecoxib as a reference was determined *in vitro* using a commercial COX assay ("COX Fluorescent Inhibitor Screening Assay Kit", Item No. 700100, Cayman Chemical, Ann Arbor, USA). The results are shown in table 1.

Table 1. COX-inhibitory selected dihydropyrrolo[3,2,1-*hi*]indoles and pyrrolo[3,2,1-*hi*]indoles

	No. (R^1 / R^2)	IC_{50} (COX-1) [μM]	IC_{50} (COX-2) [μM]	SI*
 **6**	**6a** (SO_2CH_3 / F)	>100	2.50	> 40
	6c (SO_2CH_3 / H)	>100	0.40	> 250
	6e (F / SO_2CH_3)	>100	0.15	> 666
	6h (CH_3 / SO_2CH_3)	>100	0.10	> 1000
	6k (SO_2CH_3 / OEtF)	>100	0.07	> 1428
 **8**	**8a** (SO_2CH_3 / F)	>100	0.60	> 166
	8b (SO_2CH_3 / Cl)	>100	0.05	> 2000
	8c (SO_2CH_3 / H)	>100	0.20	> 500
	8d (SO_2CH_3 / CH_3)	>100	0.02	> 5000
	8e (F / SO_2CH_3)	>100	0.04	> 2500
	8h (CH_3 / SO_2CH_3)	>100	0.50	> 200
	Celecoxib	115	0.06	1917

*SI… Selectivity index, SI = IC_{50} (COX-1) / IC_{50} (COX-2)

At the first view it became obvious that all tested compounds with exception of **6a** inhibit COX-2 in the nanomolar level and, noteworthy, do not substantially inhibit COX-1 at all. This demonstrates that the compound class of dihydropyrrolo- and pyrrolo[3,2,1-*hi*]indoles are COX inhibitors with exceptional selectivity for COX-2, with four compounds (**6k**, **8b**, **8d** and **8e**) showing a selectivity index comparable with that of celecoxib. Within the evaluated series, the fluoro-substituted dihydropyrrolo[3,2,1-*hi*]indole **6a** shows the weakest COX-2 inhibition potency with an IC_{50} for COX-2 about 2.5 μM. Compounds **6c**, **6e**, **6h**, **8a**, **8c** and **8h** were identified as selective COX-2 inhibitors with an IC_{50} ranging in the 0.5 - 0.1 μM level whereas compounds **6k**, **8b**, **8d** and **8e** turned out to inhibit COX-2 with an IC_{50} between 20 and 70 nM. By a direct comparison, the pyrrolo[3,2,1-*hi*]indoles are more potent than their analogous dihydropyrrolo[3,2,1-*hi*]indole derivatives. In three of four pairs the affinity to COX-2 was improved by a magnitude of ten comparing the dihydro-compound with the oxidized

species (**6a** *vs.* **8a**, **6c** *vs.* **8c**, **6e** *vs.* **8e**). This indicates not only a steric but also electronic influence resulting from the extended π-system. However, for one pair the dihydropyrrolo[3,2,1-*hi*]indole is slightly more potent (**6h** *vs.* **8h**). It is obvious that bulkier substituents cause higher inhibition potency because a replacement of a fluoro- by a chloro atom results in an improvement by factor 10 (**8a** *vs.* **8b**). A similar effect was observed by substitution of hydrogen by a methyl group (**8c** *vs.* **8d**). Regarding the regioisomers there are no clear tendencies to conclude; in the case of dihydropyrrolo[3,2,1-*hi*]indoles **6a** and **6e** the inhibition potency was increased by shifting the methylsulfonyl substituent from the 4-phenyl ring to the 5-phenyl ring. The same tendency was found by shifting the methylsulfonyl group in the corresponding pyrrolo[3,2,1-*hi*]indoles **8a** and **8e**. In contrast**,** the analogous displacement within the pair **8d** and **8h** leads to a decrease of affinity for COX-2.

Recently, we investigated the COX inhibition potency of a number of fluoro- and methoxy-substituted 2,3-diaryl-1*H*-indole derivatives and found with the same assay 5-42% inhibition of COX-2 in the 0.1 μM level indicating IC_{50}-values in the upper nanomolar or even micromolar range.[42] By a direct comparison of the indole derivatives with the dihydropyrrolo[3,2,1-*hi*]indoles as well as the pyrrolo[3,2,1-*hi*]indoles, the last two demonstrate a noteworthy higher affinity as well as increased selectivity towards COX-2. Hence, the enlargement of the bicyclic indole core by either an ethenyl or an ethylene bridge has a positive impact on the COX-2 inhibition potency. This is in agreement with previous QSAR studies for 2,3-diaryl-1*H*-indoles postulating a positive impact on COX inhibition potency by increasing the van der Waals volume of the indole core.[19]

Thus, we have identified a class of vicinal substituted diarylheterocycles with a tricyclic core that act as potent COX-2 inhibitors. This is much more surprising since, to the best of our knowledge, this type of compounds has not been described yet as COX inhibitors at all in prominent reports and reviews regarding COX.[13-15, 43-46] As much as we know, there exist a few reports for COX-2 inhibitors with tricyclic core but only having none or one phenyl substituent, some of them were designed as conformational restricted derivatives of monocyclic COXIBs.[47-54] Since the elegant scheme presented by Singh & Mittal[15] to classify COX-2 inhibitors lacks this class of inhibitors, herewith we present an updated scheme (figure 5) with the aim to stimulate synthetic approaches for the synthesis of novel COX-2 inhibitors with tricyclic core.

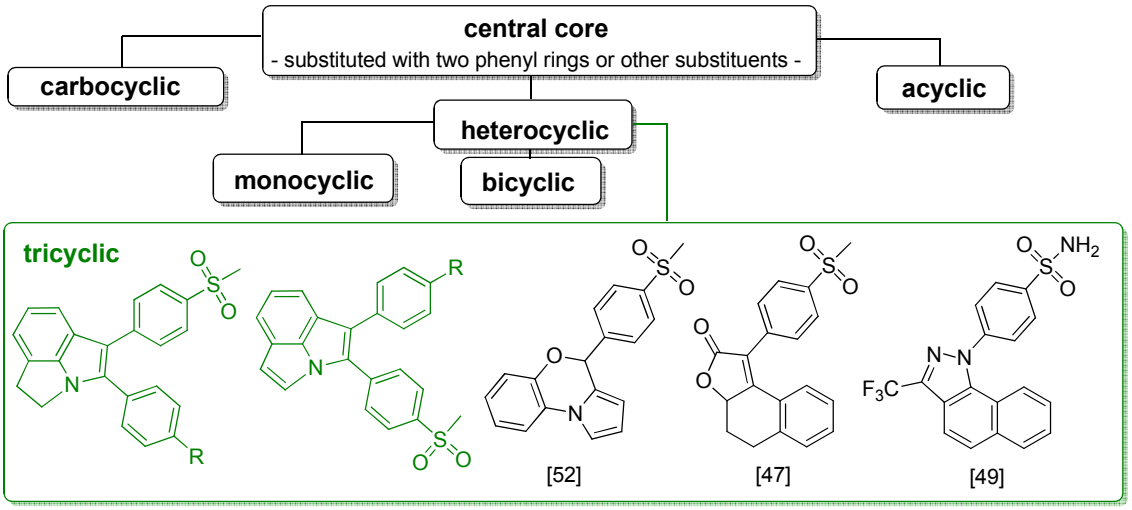


Figure 5. Update of the structural classification of COX-2 inhibitors according to Singh & Mittal[15] with further examples from the literature

Molecular docking studies

As mentioned above, the diaryl-substituted (dihydro)pyrrolo[3,2,1-*hi*]indoles **6** and **8** represent potent inhibitors of COX-2. We performed *in silico* studies using the protein ligand docking program GOLD [55] using the elucidated molecular structure of **6a** and **6e** to get information about the binding mode of the novel inhibitors in the active side of COX-2. For this, the crystal structure of COX-2 (PDB-entry 3LN1, numbering based on ovine COX-1[56]) was prepared for docking using MOE. The center of the active side was defined at the position of the co-crystallized molecule of celecoxib. Docking studies taking the whole protein as docking side (n = 10, r = 50 Å) revealed that the most preferred docking position is located within the active side of the enzyme. When docking in the active side of COX-2 (n = 100, r = 10 Å) was performed as shown in figure 6, the proposed binding mode of **6a** and **6e** was found to be very similar to that of celecoxib. That is consistent with the ability of both compounds to inhibit COX-2 with high affinity. The methylsulfonyl-substituted phenyl ring of **6a** sticks into the side pocket of COX-2 and forms hydrogen bonds to Arg-513 (**6a**: d(N-*H*···*O*) = 1.926 Å, **6e**: d(N-*H*···*O*) = 1.997 Å) and His-90 (**6a**: d(N-*H*···*O*) = 2.243 Å, **6e**: d(N-*H*···*O*) = 2.321 Å) as well as C-H···π-interactions between the phenyl ring and Ser-353 as well as Val-523 (**6a**: d = 2.702-2.790 Å, **6e**: d = 2.699-2.773 Å,). The fluoro-substituted phenyl ring interacts by donor-acceptor interactions (**6a**: d(C_{indole}-*H*···*F*) = 1.561 Å, **6e**: d(C_{indole}-*H*···*F*) = 1.538 Å) with Trp-387. In **6a**, the indole-moiety of the central dihydropyrrolo[3,2,1-*hi*]indole-core interacts by C-H···π-interactions to Val-349 (D(*C*-H···*Centroid*$_{phenyl}$) = 3.219 Å) and Ala-527 (D(*C*-H···*Centroid*$_{pyrrol}$) = 3.919 Å) as well as weak hydrogen bonds with Ser-530 (**6a**: d(C-*H*···*O*) = 2.737 Å). In **6e**, the indole-moiety of the central dihydropyrrolo[3,2,1-*hi*]indole-core interacts by C-H···π-interactions also with Val-349

(D(*C*-H···*Centroid*$_{phenyl}$) = 3.345 Å) and Ala-527 (D(*C*-H···*Centroid*$_{pyrrol}$) = 3.432 Å). Furthermore, **6e** forms weak hydrogen bonds with Tyr-355 (**6a**: d(C-H···O) = 2.725 Å). Of note, the GOLD score, a dimensionless value giving a guide how good the docking pose is, was determined to be 107.2 for **6a**, 105.5 for **6e**, and 97.5 for docking of celecoxib what reflects the ability of both compounds to inhibit COX-2 but is not matching the order of potency observed experimentally.

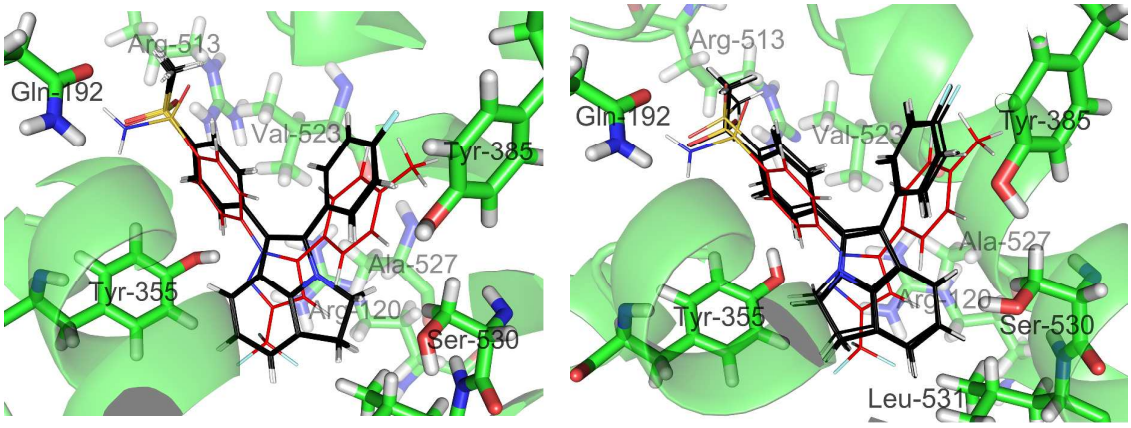


Figure 6. Docking of 6a (left) and 6e (right) in the active side of COX-2. The ten best docking results from 100 runs are shown as superimposed structures (black C-atoms) together with the co-crystallized celecoxib molecule (red C-atoms) as a reference.

Identification of candidates for radiotracer development

Several highly potent COX-2 inhibitors were identified within the (dihydro)pyrrolo[3,2,1-*hi*]indole series, among them compound **8d** as the most potent one having an IC_{50} for COX-2 of 20 nM. Thus, **8d** represents a promising candidate for radiolabeling with carbon-11 by introduction of a ^{11}C-methylsulfonyl group, e.g. starting from the respective sulfinate precursor as described by de Vries *et al.*[57] **8e** shows high COX-2 inhibition potency with an IC_{50}(COX-2) of 40 nM and is hence a suitable compound for the development of a fluorine-18 labeled radiotracer via McMurry cyclization as described by us.[18] Furthermore, **6k** represents a promising candidate for labeling with fluorine-18 by means of [^{18}F]fluoroethylation starting from the corresponding hydroxyl-precursor.

Summary and Conclusion

A set of diaryl-substituted heterocycles with the tricyclic dihydropyrrolo[3,2,1-*hi*]indole and pyrrolo[3,2,1-*hi*]indole ring core was successfully synthesized by a sequence of Friedel-Crafts acylation, amide formation, McMurry cyclization, and dehydrogenation. This synthesis route represents a novel and versatile access towards dihydropyrrolo[3,2,1-*hi*]indoles and is characterized by good chemical yields and high modularity. The molecular structure of the substituted dihydropyrrolo[3,2,1-*hi*]indoles **6a** and **6e** beside other intermediates was

analyzed by X-ray diffraction analyses. For evaluation of the COX affinity of this compound class, a set of eleven compounds was selected and subjected to a COX-inhibition assay. Within this series the dihydropyrrolo[3,2,1-*hi*]indole **6k**, and the pyrrolo[3,2,1-*hi*]indoles **8d** and **8e** were identified as COX-2 inhibitors having an affinity similar or higher than celecoxib. In regard to PET radiotracer development, the methyl-substituted compound **8d** with an IC_{50}(COX-2) of 20 nM is the most potent inhibitor of both classes and a promising candidate for radiolabeling with carbon-11. The fluoroethoxy-substituted compounds **6k** and the fluoro-substituted derivative **8e** were identified as worthy candidates for ^{18}F-radiotracer development, particularly accessible by either [^{18}F]fluoroethylation or ^{18}F-fluorination with subsequent McMurry cyclization.

In summary, the dihydropyrrolo[3,2,1-*hi*]indoles and pyrrolo[3,2,1-*hi*]indoles were found to be suitable as tricyclic core structures for the development of inhibitors with high affinity and selectivity towards COX-2. Within this new class of COX-2 inhibitors with tricyclic core, three compounds, **6k**, **8d**, and **8e,** were identified to have a considerable potential for the development of radiolabeled COX-2 inhibitors for functional imaging of COX-2 activity by PET.

Experimental Section

All commercial reagents and solvents were used without further purification unless otherwise specified. Flash chromatography was conducted using Silica Gel (mesh size 40-63 μm). DCVC indicates the use of "Dry Column Vacuum Chromatography" as reported by Pedersen and Rosenbaum.[58] Thin-layer chromatography (TLC) was performed on silica gel F-254 aluminum plates. Visualization was carried out using UV (254 nm/366 nm). Analytical HPLC analysis were carried out with a C18 column (250 × 4.6 mm, 5 μm) using an isocratic eluent (acetonitrile/ water+0.1% TFA 70/30) by a gradient pump with a flow rate of 1 mL/min. The products were monitored by an UV detector at 254 nm. Purity of all compounds exceeded 95% as determined by analytical HPLC analysis unless otherwise stated. Low resolution mass spectra were obtained using ASAP ionization (Atmospheric Solids Analysis Probe^{TM}). High resolution mass spectra were obtained on a Q-TOF MS using electrospray ionization. Elemental analyses were performed using an Elemental Analyzer. Melting points were determined on a melting points apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a 400 MHz spectrometer. NMR spectra were referenced to the residual solvent shifts for ^{1}H and ^{13}C, and to $CFCl_3$ for ^{19}F spectra as internal standard. δ-Values are given in ppm. For compounds **3a** and **6j**, isotope effects on ^{13}C-NMR chemical

shifts[59] were observed in acetone-d_6 which were caused by hydrogen/deuterium exchange while measurement. The signals with deuterium isotope shifts are indicated and the range from minimal to maximal value is given.

Spectroscopic and fluorescent properties were determined using an multi-mode microplate reader. The samples were dissolved in an appropriate amount of DMSO to give a 10 mM stock solution. To 20 µL of this stock solution was added 80 µL DMSO, 100 µL TWEEN 20 and 9800 µL PBS to yield a 20 µM test solution for the measurement of the extinction coefficient. Using 1 cm quartz vessels, the extinction coefficients at λ > 280 nm were determined from the absorption spectra. The extinction coefficients are given in ε/dm^3 mol^{-1} cm^{-1} at the specified wavelength in nm. The fluorescence excitation and emission spectra were determined using a 100 µM solution of the test compound in a solution of 1% DMSO and 1% TWEEN 20 in PBS. In both experiments, baseline correction was done using a solution of 1% DMSO and 1% TWEEN 20 in PBS.

Chemical Synthesis

4-(Methylthio)benzonitrile (1). 4-(Methylthio)benzaldehyde (8.57 mL, 10 g, 65 mmol) was added at room temperature to a solution of hydroxylamine hydrochloride (8.41 g, 0.121 mol) in anhydrous DMSO (130 mL). The mixture was heated at 100°C for 1 h. After cooling to room temperature, the mixture was poured into water (300 mL) and the resulting precipitate was separated by filtration and washed with a small amount of water. After drying the solid in vacuum, **1** was obtained as pale beige solid (8.19 g, 84%). mp 60-62°C (Lit. [60]: 62-63°C); R_f = 0.62 (petroleum ether/ ethyl acetate 50:50); ^{1}H NMR (acetone-d_6, 400 MHz): δ 2.57 (s, 3H), 7.42 (d, ^3J = 8.7 Hz, 2H), 7.66 (d, ^3J = 8.7 Hz, 2H); ^{13}C {^{1}H} NMR (acetone-d_6, 101 MHz): δ 14.5, 108.4, 119.4, 126.5, 133.1, 147.2. Crystals suitable for X-ray analysis were obtained by slow evaporation of a solution of **1** in DCM layered with petroleum ether.

4-(Methylsulfonyl)benzonitrile (2a). The synthesis was performed as described by Creary *et al.*[60] Instead of separation in water and ether, a mixture of water (150 mL) and ethyl acetate (200 mL) was used. Instead of crystallization from hexane/ether, the crude product was purified by column chromatography (DCVC, petroleum ether/ ethyl acetate 100:0→85:15→50:50→0:100). Starting from **1** (8.18 g, 55 mmol) and 77% *m*-chloroperbenzoic acid (27.85 g, 124 mmol), **2a** was obtained as colorless, crystalline solid (7.62 g, 77%). mp 144-146°C (Lit. [60]: 142-143°C); R_f = 0.32 (petroleum ether/ ethyl acetate 50:50); ^{1}H NMR (acetone-d_6, 400 MHz,): δ 3.23 (s, 3H); 8.10 (d, ^3J = 8.7 Hz, 2H), 8.17 (d, ^3J = 8.7 Hz, 2H); ^{13}C {^{1}H} NMR (acetone-d_6,101 MHz): δ 43.9, 117.8, 118.1, 129.1, 134.2,

146.1. Crystals suitable for X-ray analysis were obtained by slow evaporation of a solution of **2a** in DCM layered with petroleum ether.

General Procedure A for the synthesis of 7-benzoyl-1*H*-indolines (3a-e). The synthesis followed the procedure described by Lo *et al.*[26] and Walsh *et al.*[61] Under nitrogen atmosphere, to a solution of a 1 M BCl_3 solution in toluene (4.4 mL. 4.4 mmol) was added in this order indoline (449 µL, 4 mmol) in 1.8 mL toluene, the appropriate nitrile (as given below) and anhydrous $AlCl_3$ (608 mg, 4.4 mmol). The mixture was heated to reflux for 12-18 h. After that, water (0.25 mL) and 10% HCl (4.5 mL) was added at a temperature of 0°C and the mixture was heated to reflux for 2 h. The mixture was cooled to 0°C and the resulting precipitate was filtered off by vacuum filtration. Afterwards, the solid was suspended in 2.5% NaOH (10 mL) and stirred for 1 h at room temperature. Filtration and drying in vacuo yields the desired product.

7-[4-(Methylsulfonyl)benzoyl]-1*H*-indoline (3a). By following general procedure A, a yellow solid resulted that contains 65-89% (w/w) of **3a** in a mixture beside **2a**. The crude product was used for the next step (see general procedure C for synthesis of **5a-d** and **5i**). R_f = 0.28 (petroleum ether/ ethyl acetate 50:50); ^{1}H NMR (acetone-d_6, 400 MHz): δ 3.10 (t, ^3J = 8.6 Hz, 2H), 3.20 (s, 3H), 3.83 (td, ^3J = 8.6 Hz, ^3J = 3.4 Hz, 2H), 6.47 (t, ^3J = 7.1 Hz, ^3J = 8.1 Hz, 1H, H), 7.04 (s, 1H), 7.11 (d, ^3J = 8.2 Hz, 1H), 7.22 (d, ^3J = 6.9 Hz, ^4J = 1.1 Hz, 1H), 7.82 (d, ^3J = 8.3 Hz, 2H), 8.05-8.12[#] (m, ^3J = 8.3 Hz, 2H), further signals of 4-(methylsulfonyl)benzonitrile (**2a**) in the spectra: 3.23 (s, 3H), 8.05-8.12[#] (m, ^3J = 8.4 Hz, 2H), 8.17 (d, ^3J = 8.4 Hz, 1H),[#] signal overlay from **2a** and **3a**; ^{13}C {^{1}H} NMR (acetone-d_6, 101 MHz): δ 28.4, 44.2, 47.4*, 114.7*, 115.8*, 128.1, 129.8, 129.9, 130.8, 132.9, 143.7, 145.5, 156.4*, 195.6, further signals of 4-(methylsulfonyl)benzonitrile (**2a**) in the spectra: 43.9, 117.8, 118.1, 129.1, 134.2, 146.1, *deuterium isotope shifts were observed in the range of 30 and 110 ppb.

7-(4-Fluorobenzoyl)-1*H*-indoline (3b). Starting from 4-fluorobenzonitrile (**2b**) (729 mg, 6.0 mmol) and indoline (449 µL, 477 mg, 4.0 mmol), **3b** was obtained by following general procedure A as a yellow solid (842 mg, 87%). mp 135-137°C (Lit. [62]: 131-133°C); R_f = 0.63 (petroleum ether/ ethyl acetate 50:50); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.11 (t, ^3J = 8.6 Hz, 2H), 3.80 (t, ^3J = 8.6 Hz, 2H), 6.49 (t, ^3J = 7.8 Hz, ^3J = 7.3 Hz, 1H), 7.03 (br. s., 1H), 7.14 (t, $^3J_{H,H}$ = $^3J_{H,F}$ = 8.7 Hz, 2H), 7.18 (d, ^3J = 6.8 Hz, 1H), 7.23 (d, ^3J = 8.2 Hz, 1H), 7.68 (dd, ^3J = 8.7 Hz, $^4J_{H,F}$ = 5.5 Hz, 1H); ^{13}C {^{1}H} NMR ($CDCl_3$, 101 MHz): δ 28.3, 46.9, 114.9, 115.3, 115.3 (d, $^2J_{C,F}$ = 22 Hz), 128.8, 130.5, 131.4 (d, $^3J_{C,F}$ = 9 Hz), 131.7, 136.0 (d, $^4J_{C,F}$ = 3 Hz),

155.6, 164.5 (d, $^{1}J_{C,F}$ = 251 Hz), 196.0; ^{19}F NMR ($CDCl_3$, 376 MHz): δ -114.0; MS (ASAP$^+$): *m/z* (%) = 242 (100) $[M+H]^+$, 241 (72) $[M]^+$.

7-(4-Chlorobenzoyl)-1*H*-indoline (3c). Starting from 4-chlorobenzonitrile (**2c**) (826 mg, 6.0 mmol) and indoline (449 µL, 477 mg, 4.0 mmol), **3c** was obtained by following general procedure A as a yellow solid (1008 mg, 98%). mp 110-113°C (Lit. [62]: 109-111°C); R_f = 0.64 (petroleum ether/ ethyl acetate 50:50); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.11 (t, ^3J = 8.5 Hz, 2H), 3.81 (t, ^3J = 8.6 Hz, 2H), 6.49 (dd, ^3J = 8.1 Hz, ^3J = 7.0 Hz, 1H), 7.07 (br. s., 1H), 7.17-7.23 (m, ^3J = 8.3 Hz, ^3J = 7.1 Hz, ^4J = 0.8 Hz, 2H), 7.43 (d, ^3J = 8.5 Hz, 2H), 7.60 (d, ^3J = 8.5 Hz, 2H); ^{13}C {^{1}H} NMR ($CDCl_3$, 101 MHz): δ 28.2, 46.9, 114.7, 115.3, 128.5, 128.9, 130.4, 130.4, 131.8, 137.1, 138.2, 155.7, 196.0; MS (ASAP$^+$): *m/z* (%) = 260 (32) [M+H, ^{37}Cl]$^+$, 259 (32), 258 (100) [M+H, ^{35}Cl]$^+$, 257 (52) [M, ^{35}Cl]$^+$.

7-Benzoyl-1*H*-indoline (3d). Starting from benzonitrile (**2d**) (619 µL, 619 mg, 6.0 mmol) and indoline (449 µL, 477 mg, 4.0 mmol), **3d** was obtained by following general procedure A as a yellow solid (746 mg, 84%). mp 122-124°C (Lit. [63]: 124-125°C); R_f = 0.63 (petroleum ether/ ethyl acetate 50:50); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.11 (t, ^3J = 8.5 Hz, 2H), 3.81 (t, ^3J = 8.6 Hz, 2H), 6.49 (dd, ^3J = 8.1 Hz, ^3J = 7.0 Hz, 1H), 7.10 (br. s., 1H), 7.18 (d, ^3J = 6.9 Hz, 1H), 7.27 (d, ^3J = 8.0 Hz, 1H), 7.43–7.54 (m, 3H), 7.65 (dd, ^3J = 8.0 Hz, ^4J = 1.3 Hz, 2H); ^{13}C {^{1}H} NMR ($CDCl_3$, 101 MHz): δ 28.2, 46.9, 115.0, 115.2, 128.2, 128.7, 128.9, 130.8, 130.9, 131.6, 139.9, 155.6, 197.5; MS (ASAP$^+$): *m/z* (%) = 224 (100) $[M+H]^+$, 223 (83) $[M]^+$.

7-(4-Methylbenzoyl)-1*H*-indoline (3e). Starting from 4-tolunitrile (**2e**) (706 mg, 6.0 mmol) and indoline (449 µL, 477 mg, 4.0 mmol), **3e** was obtained by following general procedure A as a yellow solid (744 mg, 78%). mp 102-104°C; R_f = 0.67 (petroleum ether/ ethyl acetate 50:50); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.43 (s, 3H), 3.10 (t, ^3J = 8.6 Hz, 2H), 3.79 (t, ^3J = 8.6 Hz, 2H), 6.49 (dd, ^3J = 8.0 Hz, ^3J = 7.1 Hz, 1H), 7.02 (br. s., 1H), 7.18 (d, ^3J = 6.9 Hz, 1H), 7.26 (d, ^3J = 8.0 Hz, 2H), 7.29 (d, ^3J = 8.2 Hz, 1H), 7.57 (d, ^3J = 8.1 Hz, 2H); ^{13}C {^{1}H} NMR ($CDCl_3$, 101 MHz): δ = 21.7, 28.3, 46.9, 115.2, 115.3, 128.5, 128.9, 129.2, 130.8, 131.5, 137.1, 141.4, 155.5, 197.3; MS (ASAP$^+$): *m/z* (%) = 238 (100) $[M+H]^+$, 237 (62) $[M]^+$; HRMS (ESI$^+$) *m/z* calcd for $C_{16}H_{15}NONa$ [M + Na^+] 260.10458, found 260.10480.

Procedure B for the synthesis of 4-(Methylsulfonyl)benzoyl chloride (4e). The synthesis followed the procedure described by Guo *et al.*[64] modified by the removal of $SOCl_2$ according to Gubert *et al.*[65] Under nitrogen atmosphere, 4-(methylsulfonyl)benzoic acid (269 mg, 1.34 mmol) was added to 1.13 mL $SOCl_2$ and DMF (3 drops). The mixture was heated under reflux (60-70°C) over night. A clear solution resulted. $SOCl_2$ and DMF were removed under

reduced pressure. Then three times, benzene (1.5 mL) was added at room temperature, the mixture was stirred and the solvent was removed. The resulting colorless solid (mp 130-135°C, Lit: [66]) was used without further purification for the synthesis of **5e-h**.

General procedure C for the synthesis of *N*-benzoyl-7-(benzoyl)indolines (5a-i). Under nitrogen atmosphere, the corresponding acid chloride (0.87 mmol) in anhydrous THF (1.0 mL) was added to a solution of the 7-benzoylindoline (0.87 mmol) and NEt_3 (138 µL, 101 mg, 1.00 mmol) in anhydrous THF (1.8 mL). The reaction mixture was stirred for 2 h at room temperature. After that, the mixture was pre-adsorbed on silica gel and purification was carried out by column chromatography as given below.

***N*-(4-Fluorobenzoyl)-7-[4-(methylsulfonyl)benzoyl]indoline (5a).** The crude starting material 7-[4-(methylsulfonyl)benzoyl]-1*H*-indoline (**3a**) (232 mg) was synthesized by following general procedure A starting from indoline (126 µL, 133 mg, 1.12 mmol) and **2a** (245 mg, 1.35 mmol)). 212 mg of this raw product of **3a** were allowed to react with 4-fluorobenzoyl chloride (**4a**) (84.3 µL, 113.1 mg, 0.71 mmol) following general procedure C. Purification was carried out by column chromatography (DCVC, petroleum ether/ ethyl acetate 100:0→0:100, then chloroform/ methanol 90:10). By that, **5a** was obtained as a pale yellow solid (202 mg, 47% starting from indoline). mp 245-248°C; R_f = 0.14 (petroleum ether/ ethyl acetate 50:50); R_f = 0.59 (chloroform/ methanol 95:5); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.04 (s, 3H), 3.17 (t, ^3J = 7.9 Hz, 2H), 4.14 (t, ^3J = 7.9 Hz, 2H), 7.05 (t, $^3J_{H,H}$ = $^3J_{H,F}$ = 8.6 Hz, 2H), 7.21 (t, ^3J = 7.5 Hz, 1H), 7.28 (d, ^3J = 7.6 Hz, 1H), 7.42–7.48 (m, ^3J = 8.8 Hz, $^4J_{H,F}$ = 5.2 Hz, 3H), 7.99 (d, ^3J = 8.5 Hz, 2H), 8.07 (d, ^3J = 8.5 Hz, 2H); ^{13}C {^{1}H} NMR ($CDCl_3$, 101 MHz): δ 29.7, 44.5, 52.9, 115.8 (d, $^2J_{C,F}$ = 22 Hz), 125.0, 127.4, 127.4, 127.9, 128.1, 130.3 (d, $^3J_{C,F}$ = 9 Hz), 130.9, 131.4 (d, $^4J_{C,F}$ = 3 Hz), 134.6, 140.2, 141.8, 143.5, 164.5 (d, $^1J_{C,F}$ = 253 Hz), 168.8, 192.9; ^{19}F NMR ($CDCl_3$, 376 MHz): δ -107.9; MS (ESI^+): *m/z* (%) = 424 (100%) $[M+H]^+$; HRMS (ESI^+) *m/z* calcd for $C_{23}H_{18}FNO_4SNa$ $[M + Na^+]$ 446.08328, found 446.08301.

***N*-(4-Chlorobenzoyl)-[4-(methylsulfonyl)benzoyl]indoline (5b).** The crude starting material 7-[4-(methylsulfonyl)benzoyl]-1*H*-indoline (**3a**) (2884 mg) was synthesized by following general procedure A starting from indoline (1038 µL, 1.10 g, 9.24 mmol) and **2a** (2.00 g, 11.04 mmol). 500 mg of this raw product of **3a** were allowed to react with 4-chlorobenzoyl chloride (**4b**) (211 µL, 290 mg, 1.66 mmol) following general procedure C. Purification was carried out by column chromatography (DCVC, petroleum ether/ ethyl acetate 50:50→0:100, then chloroform/ methanol 100:1). By that, **5b** was obtained as a pale yellow solid (345 mg, 49% starting from indoline). mp 272-274°C; R_f = 0.21 (petroleum ether/

ethyl acetate 50:50); R_f = 0.60 (chloroform/ methanol 95:5); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.04 (s, 3H), 3.17 (t, ^3J = 7.9 Hz, 2H), 4.12 (t, ^3J = 7.9 Hz, 2H), 7.21 (t, ^3J = 7.6 Hz, ^3J = 7.4 Hz, 1H), 7.27 (d, ^3J = 7.7 Hz, 1H), 7.34 (d, ^3J = 8.6 Hz, 2H), 7.38 (d, ^3J = 8.4 Hz, 2H), 7.45 (d, ^3J = 7.3 Hz, 1H), 7.99 (d, ^3J = 8.3 Hz, 2H), 8.06 (d, ^3J = 8.2 Hz, 2H); ^{13}C {^{1}H} NMR ($CDCl_3$, 101 MHz): δ 29.6, 44.5, 52.8, 125.1, 127.4, 127.5, 127.9, 128.1, 128.9, 129.3, 130.9, 133.7, 134.7, 137.7, 140.0, 141.8, 143.5, 168.7, 192.8; MS (ESI$^+$): *m/z* (%) = 462 (84) [M+Na, ^{35}Cl]$^+$, 440 (40) [M+H, ^{35}Cl]$^+$, 139 (100) [ClC_6H_4CO, ^{35}Cl]$^+$; HRMS (ESI$^+$) *m*/*z* calcd for $C_{23}H_{18}ClNO_4SNa$ [M + Na$^+$, ^{35}Cl] 462.05373, found 462.05348.

***N*-Benzoyl-7-[4-(methylsulfonyl)benzoyl]indoline (5c).** The crude starting material 7-[4-(methylsulfonyl)benzoyl]-1*H*-indoline (**3a**) (1028 mg) was synthesized by following general procedure A starting from indoline (504 µL, 534 mg, 4.48 mmol) and **2a** (974 mg, 5.37 mmol). 250 mg of this raw product of **3a** were allowed to react with benzoyl chloride (**4c**) (96 µL, 117 mg, 0.83 mmol) following general procedure C. Purification was carried out by column chromatography (DCVC, petroleum ether/ ethyl acetate 90:10→50:50, then chloroform/ methanol 90:10). By that, **5c** was obtained as a pale yellow solid (180 mg, 41% starting from indoline). mp 235-237°C; R_f = 0.11 (petroleum ether/ ethyl acetate 50:50); R_f = 0.54 (chloroform/ methanol 95:5); ^{1}H NMR (acetone-d_6, 400 MHz): δ 3.10 (s, 3H), 3.19 (t, ^3J = 7.9 Hz, 3H), 4.14 (t, ^3J = 7.9 Hz, 2H), 7.27–7.33 (m, 3H), 7.37 (t, ^3J = 7.6 Hz, 2H), 7.40–7.48 (m, 2H), 7.56 (dd, ^3J = 7.4 Hz, ^4J = 1.2 Hz, 1H), 7.96 (d, ^3J = 8.8 Hz, 2H), 8.00 (d, ^3J = 8.6 Hz, 2H); ^{13}C {^{1}H} NMR (acetone-d_6, 101 MHz): δ 30.0*, 44.2, 53.3, 125.8, 127.9, 128.1, 128.4, 128.5, 128.7, 129.1, 130.8, 131.8, 135.9, 136.6, 141.2, 142.9, 144.7, 169.9, 192.4, *signal overlay with the residual solvent peak; MS (ESI$^+$): *m/z* (%) = 406 (100) [M+H]$^+$; Anal. Calcd for $C_{23}H_{19}NO_4S$: C, 68.13; H, 4.72; N, 3.45; S, 7.91. Found: C, 68.45; H, 4.76; N, 3.48; S, 7.74. Crystals suitable for X-ray analysis were obtained by the following procedure. A solution of **5c** in DCM was slowly evaporated to dryness and, by that, crystals were formed which were unsuitable for X-ray analysis. One well-formed crystal was separated and washed with a small amount of DCM. The rest was dissolved in DCM. To this solution the isolated crystal was added and by slow evaporation of the solvent suitable crystals for X-ray analysis were obtained.

***N*-(4-Methylbenzoyl)-7-[4-(methylsulfonyl)benzoyl]indoline (5d).** The crude starting material 7-[4-(methylsulfonyl)benzoyl]-1*H*-indoline (**3a**) (234 mg) was synthesized by following general procedure A starting from indoline (126 µL, 133 mg, 1.12 mmol) and **2a** (245 mg, 1,35 mmol). 250 mg of this raw product of **3a** were allowed to react with 4-methylbenzoyl chloride (**4d**) (98.7 µL, 115 mg, 0.75 mmol) following general procedure C. Purification was carried out by column chromatography (DCVC, petroleum ether/ ethyl

acetate 100:0→50:50, then chloroform/ methanol 90:10). By that, **5d** was obtained as a pale yellow solid (255 mg, 57% starting from indoline). mp 255-257°C; R_f = 0.25 (petroleum ether/ ethyl acetate 50:50); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.34 (s, 3H), 3.01 (s, 3H), 3.14 (t, ^3J = 7.9 Hz, 2H), 4.13 (t, ^3J = 8.0 Hz, 2H), 7.14 (d, ^3J = 8.0 Hz, 2H), 7.20 (t, ^3J = 7.6 Hz, 1H), 7.32–7.27 (m, ^3J = 8.1 Hz, ^3J = 7.6 Hz, ^4J = 1.1 Hz, 3H), 7.43 (dd, ^3J = 7.4 Hz, ^4J = 1.1 Hz, 1H), 7.97 (d, ^3J = 8.5 Hz, 2H), 8.05 (d, ^3J = 8.5 Hz, 2H); ^{13}C {^{1}H} NMR ($CDCl_3$, 101 MHz): δ 21.6, 29.6, 44.5, 52.9, 124.9, 127.3, 127.5, 127.8, 127.9*, 129.2, 130.8, 132.3, 134.6, 140.3, 141.9, 142.0, 143.3, 169.9, 192.7, *two carbon atoms with identical chemical shift; MS (ESI$^+$): *m/z* (%) = 442 (50) $[M+Na]^+$, 420 (16) $[M+H]^+$, 118 (100); Anal. Calcd for $C_{24}H_{21}NO_4S$: C, 68.72; H, 5.05; N, 3.34; S, 7.64. Found: C, 68.62; H, 5.04; N, 3.35; S, 7.44.

7-(4-Fluorobenzoyl)-*N*-[4-(methylsulfonyl)benzoyl]indoline (5e). The starting material 4-(methylsulfonyl)benzoyl chloride (**4e**) was synthesized by following general procedure B starting from 4-(methylsulfonyl)benzoic acid (312 mg, 1.56 mmol). **3b** (400 mg, 1.66 mmol) and **4e** were allowed to react in anhydrous THF (in total 7 mL) following general procedure C. Purification was carried out by column chromatography (DCVC, petroleum ether/ ethyl acetate 50:50→33:66, then chloroform/ methanol 100:0→100:1). By that, **5e** was obtained as a pale yellow solid (366 mg, 56%). mp 267-268°C; R_f = 0.21 (petroleum ether/ ethyl acetate 33:66); R_f = 0.52 (chloroform/ methanol 95:5); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.04 (s, 3H), 3.18 (t, ^3J = 7.9 Hz, 2H), 4.10 (t, ^2J = 7.9 Hz, 2H), 7.11 (t, $^3J_{H,H}$ = $^3J_{H,F}$ = 8.6 Hz, 2H), 7.22 (t, ^3J = 7.6 Hz, 1H), 7.31 (d, ^3J = 7.4 Hz, 1H), 7.43 (dd, ^3J = 7.4 Hz, ^4J = 0.8 Hz, 1H), 7.66 (d, ^3J = 8.3 Hz, 2H), 7.92 (dd, ^3J = 8.7 Hz, $^4J_{H,F}$ = 5.9 Hz, 2H), 7.95 (d, ^3J = 8.3 Hz, 2H); ^{13}C {^{1}H} NMR ($CDCl_3$, 101 MHz): δ 29.7, 44.5, 52.6, 115.5 (d, $^2J_{C,F}$ = 22 Hz), 125.3, 127.4, 127.8*, 128.9*, 132.7 (d, $^3J_{C,F}$ = 9 Hz), 133.5 (d, $^4J_{C,F}$ = 3 Hz), 134.6, 139.7, 140.8, 142.8, 165.6 (d, $^1J_{C,F}$ = 254 Hz), 167.5,192.9, *two carbon atoms with identical chemical shift; ^{19}F NMR ($CDCl_3$, 376 MHz): δ -106.5; MS (ASAP$^+$): *m/z* (%) = 423 (100) $[M]^+$; HRMS (ESI$^+$) *m*/*z* calcd for $C_{23}H_{18}FNO_4SNa$ $[M + Na^+]$ 446.08328, found 446.08376.

7-(4-Chlorobenzoyl)-*N*-[4-(methylsulfonyl)benzoyl]indoline (5f). The starting material 4-(methylsulfonyl)benzoyl chloride (**4e**) was synthesized by following general procedure B starting from 4-(methylsulfonyl)benzoic acid (311 mg, 1.55 mmol). **3c** (400 mg, 1.55 mmol) and **4e** were allowed to react in anhydrous THF (in total 8 mL) following general procedure C. Purification was carried out by column chromatography (DCVC, petroleum ether/ ethyl acetate 50:50→33:66, then chloroform/ methanol 100:0→100:1). By that, **5f** was obtained as a pale yellow solid (413 mg, 61%). mp 267-269°C; R_f = 0.23 (petroleum ether/ ethyl acetate 33:66); R_f = 0.56 (chloroform/ methanol 95:5); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.04 (s, 3H), 3.18 (t, ^3J = 7.8 Hz, 2H), 4.09 (t, ^3J = 7.9 Hz, 2H), 7.22 (t, ^3J = 7.5 Hz, 1H), 7.30 (d,

^3J = 7.5 Hz, 1H), 7.40 (d, ^3J = 8.5 Hz, 2H), 7.43 (d, ^3J = 7.4 Hz, 1H), 7.64 (d, ^3J = 8.3 Hz, 2H), 7.83 (d, ^3J = 8.4 Hz, 2H), 7.95 (d, ^3J = 8.2 Hz, 2H); ^{13}C {^{1}H} NMR ($CDCl_3$, 101 MHz): δ 29.7, 44.5, 52.5, 125.3, 127.5, 127.7, 127.8, 128.6, 128.7, 128.9, 131.5, 134.6, 135.5, 139.1, 139.6, 140.8, 142.8, 167.5, 193.1; MS (ASAP$^+$): *m/z* (%) = 442 (27) [M+H, ^{37}Cl]$^+$, 441 (55) [M, ^{37}Cl]$^+$, 440 (67) [M+H, ^{35}Cl]$^+$, 439 (100) [M, ^{35}Cl]$^+$; HRMS (ESI$^+$) *m*/*z* calcd for $C_{23}H_{18}ClNO_4SNa$ [M + Na$^+$, ^{35}Cl] 462.05373, found 462.05421.

7-Benzoyl-*N*-[4-(methylsulfonyl)benzoyl]indoline (5g). The starting material 4-(methylsulfonyl)benzoyl chloride (**4e**) was synthesized by following general procedure B starting from 4-(methylsulfonyl)benzoic acid (269 mg, 1.34 mmol). **3d** (300 mg, 1.34 mmol) and **4e** were allowed to react in anhydrous THF (in total 7 mL) following general procedure C. Purification was carried out by column chromatography (DCVC, petroleum ether/ ethyl acetate 50:50→0:100, then chloroform/ methanol 97.5:2.5). By that, **5g** was obtained as a pale yellow solid (343 mg, 63%). mp 254-255°C; R_f = 0.22 (petroleum ether/ ethyl acetate 33:66); R_f = 0.48 (chloroform/ methanol 95:5); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.02 (s, 3H), 3.17 (t, ^3J = 7.8 Hz, 2H), 4.06 (t, ^2J = 7.8 Hz, 2H), 7.22 (t, ^3J = 7.6 Hz, 1H), 7.36 (d, ^3J = 7.6 Hz, 1H), 7.39–7.45 (m, 3H), 7.52 (t, ^3J = 7.4 Hz, 1H), 7.59 (d, ^3J = 8.4 Hz, 2H), 7.86 (d, ^3J = 7.5 Hz, 2H), 7.92 (d, ^3J = 8.2 Hz, 2H); ^{13}C {^{1}H} NMR ($CDCl_3$, 101 MHz): δ 29.6, 44.5, 52.5, 125.3, 127.4, 127.7, 128.1, 128.3, 128.9, 129.1, 130.1, 132.7, 134.5, 137.1, 139.8, 140.9, 142.6, 167.5, 194.3; MS (ASAP$^+$): *m/z* (%) = 406 (38) [M+H]$^+$, 405 (100) [M]$^+$; HRMS (ESI$^+$) *m*/*z* calcd for $C_{23}H_{19}NO_4SNa$ [M + Na$^+$] 428.09270, found 428.09306.

7-(4-Methylbenzoyl)-*N*-[4-(methylsulfonyl)benzoyl]indoline (5h). The starting material 4-(methylsulfonyl)benzoyl chloride (**4e**) was synthesized by following general procedure B starting from 4-(methylsulfonyl)benzoic acid (253 mg, 1.26 mmol). **3e** (300 mg, 1.26 mmol) and **4e** were allowed to react in anhydrous THF (in total 7 mL) following general procedure C. Purification was carried out by column chromatography (DCVC, petroleum ether/ ethyl acetate 50:50→33:66, then chloroform/ methanol 100:0→100:1). By that, **5h** was obtained as a pale yellow solid (349 mg, 66%). mp 296°C; R_f = 0.21 (petroleum ether/ ethyl acetate 33:66); R_f = 0.49 (chloroform/ methanol 95:5); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.40 (s, 3H), 3.02 (s, 3H), 3.17 (t, ^3J = 7.8 Hz, 2H), 4.09 (t, ^3J = 7.8 Hz, 2H), 7.18–7.25 (m, 3H), 7.32 (d, ^3J = 7.4 Hz, 1H), 7.41 (d, ^3J = 7.4 Hz, 1H), 7.64 (d, ^2J = 8.2 Hz, 2H), 7.77 (d, ^3J = 7.3 Hz, 2H), 7.92 (d, ^3J = 8.0 Hz, 2H); ^{13}C {^{1}H} NMR ($CDCl_3$, 101 MHz): δ 21.8, 29.7, 44.5, 52.5, 125.1, 127.2, 127.7*, 128.1, 129.0, 129.0, 130.3*, 131.2, 134.6, 141.0, 142.6, 143.6, 167.4, 194.2, *two carbon atoms with identical chemical shift; MS (ASAP$^+$): *m/z* (%) = 419 (100) [M+H]$^+$, 236 (47) [M-$CH_3SO_2C_6H_4CO$]$^+$; HRMS (ESI$^+$) *m*/*z* calcd for $C_{24}H_{21}NO_4SNa$ [M + Na$^+$] 442.10835, found 442.10902.

7-[4-(Methylsulfonyl)benzoyl]-*N*-(4-methoxybenzoyl)indoline (5i). The crude starting material 7-[4-(methylsulfonyl)benzoyl]-1*H*-indoline (**3a**) (1028 mg) was synthesized by following general procedure A starting from indoline (504 µL, 534 mg, 4.48 mmol) and **2a** (974 mg, 5.37 mmol). 500 mg of this raw product of **3a** were allowed to react with 4-methoxybenzoyl chloride (**4f**) (282 mg, 1.66 mmol) following general procedure C. Purification was carried out by column chromatography (DCVC, petroleum ether/ ethyl acetate 80:20→50:50, then chloroform/ methanol 90:10). By that, **5i** was obtained as a pale yellow solid (506 mg, 54% starting from indoline). mp 237-240°C; R_f = 0.09 (petroleum ether/ ethyl acetate 50:50); R_f = 0.50 (chloroform/ methanol 95:5); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.02 (s, 3H), 3.15 (t, ^3J = 7.9 Hz, 2H), 3.81 (s, 3H), 4.16 (t, ^3J = 8.0 Hz, 2H), 6.84 (d, ^3J = 8.9 Hz, 2H), 7.19 (t, ^3J = 7.6 Hz, ^3J = 7.5 Hz, 1H), 7.29 (dd, ^3J = 7.7 Hz, ^4J = 1.1 Hz, 1H), 7.39 (d, ^3J = 8.9 Hz, 2H), 7.43 (dd, ^3J = 7.4 Hz, ^4J = 1.1 Hz, 1H), 7.96 (d, ^3J = 8.6 Hz, 2H), 8.04 (d, ^3J = 8.6 Hz, 2H); ^{13}C {^{1}H} NMR ($CDCl_3$, 101 MHz): δ 29.7, 44.5, 53.1, 55.6, 113.8, 124.8, 127.3*, 127.5, 127.8*, 130.0, 130.8, 134.6, 140.6, 142.0, 143.3, 162.2, 169.7, 192.8, *two carbon atoms with identical chemical shift; MS (ESI$^+$): *m/z* (%) = 474 (50) $[M+K]^+$, 458 (24) $[M+Na]^+$, 135 (48) $[CH_3OC_6H_4CO]^+$, 118 (100); Anal. Calcd for $C_{24}H_{21}NO_5S$: C, 66.19; H, 4.86; N, 3.22; S, 7.36. Found: C, 65.65; H, 4.88; N, 3.37; S, 7.72.

General procedure D for the synthesis of 4,5-diphenyl-1,2-dihydropyrrolo[3,2,1-*hi*]indoles (6a-i). Under nitrogen atmosphere, $TiCl_4$ (146.2 µL, 253 mg, 1.33 mmol) was added to a suspension of the *N*-benzoyl-7-(benzoyl)indoline (0.62 mmol) **5a-i**, respectively, and Zn (163 mg, 2.5 mmol) in anhydrous THF (5.5 mL). The mixture was heated for 1.5-2 h at 70°C under slight reflux. After cooling to room temperature, the mixture was pre-adsorbed on silica gel and purification was carried out by column chromatography as given below.

4-(4-Fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1,2-dihydropyrrolo[3,2,1-*hi*]indole (6a). Purification was carried out by column chromatography (petroleum ether/ ethyl acetate 66:33→50:50). Starting from **5a** (202 mg, 0.48 mmol), **6a** was obtained following general procedure D as colorless crystals (112 mg, 60%). mp 201-203°C; R_f = 0.49 (petroleum ether/ ethyl acetate 50:50); UV/vis: λmax (ε) = 293 (20000), 347 (14200); Fluorescence: λexc = 353, λem = 452 nm; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.09 (s, 3H), 3.83 (t, ^3J = 7.0 Hz, 2H), 4.55 (t, ^3J = 7.0 Hz, 2H) , 7.03 (d, ^3J = 6.8 Hz, 1H), 7.08-7.16 (m, $^3J_{H,H}$ = $^3J_{H,F}$ = 8.6 Hz, ^3J = 7.3 Hz, 3H), 7.39 (dd, ^3J = 8.5 Hz, $^4J_{H,F}$ = 5.3 Hz, 2H), 7.48 (d, ^3J = 7.9 Hz, 1H), 7.58 (d, ^3J = 8.3 Hz, 2H), 7.84 (d, ^3J = 8.3 Hz, 2H); ^{13}C {^{1}H} NMR ($CDCl_3$, 101 MHz): δ 33.7, 44.7, 49.7, 115.6, 116.4 (d, $^2J_{C,F}$ = 21 Hz), 116.5, 116.9, 119.6, 123.5, 125.1, 127.7, 128.1 (d, $^4J_{C,F}$ = 3 Hz), 129.2, 131.1 (d, $^4J_{C,F}$ = 8 Hz), 135.6, 136.8. 142.7, 147.9, 162.8 (d,

$^1J_{C,F}$ = 249 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz): δ -112.9; MS (ASAP$^+$): *m/z* (%) = 392 (91) [M+H]$^+$, 391 (100) [M]$^+$, 149 (48); Anal. Calcd for $C_{23}H_{18}FNO_2S$: C, 70.57; H, 4.63; N, 3.58; S, 8.19. Found: C, 70.97; H, 4.79; N, 3.53; S, 7.88. Crystals suitable for X-ray analysis were obtained by slow evaporation of a solution of **5a** in DCM layered with petroleum ether.

4-(4-Chlorophenyl)-5-[4-(methylsulfonyl)phenyl]-1,2-dihydropyrrolo[3,2,1-*hi*]indole (6b). Purification was carried out by column chromatography (petroleum ether/ ethyl acetate 70:30→60:40). Starting from **5b** (280 mg, 0.63 mmol), **6b** was obtained following general procedure D as colorless crystals (186 mg, 72%). mp 224-227°C; R_f = 0.53 (petroleum ether/ ethyl acetate 50:50); UV/vis: λmax (ε) = 297 (20400), 348 (12600); Fluorescence: λexc = 299, λem = 476 nm; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.09 (s, 3H), 3.84 (t, ^3J = 6.9 Hz, 2H), 4.56 (t, ^3J = 7.0 Hz, 2H), 7.03 (d, ^3J = 6.7 Hz, 1H), 7.13 (t, ^3J = 7.7 Hz, ^3J = 7.0 Hz, 1H), 7.34 (d, ^3J = 8.6 Hz, 2H), 7.38 (d, ^3J = 8.6 Hz, 1H), 7.47 (d, ^3J = 7.9 Hz, 1H), 7.58 (d, ^3J = 8.4 Hz, 2H), 7.85 (d, ^3J = 8.4 Hz, 2H); ^{13}C {^{1}H} NMR ($CDCl_3$, 101 MHz) 33.7, 44.7, 49.9, 116.0, 116.7, 116.9, 119.6, 123.6, 125.2, 127.8, 129.4, 129.5, 130.5*, 134.5, 135.3, 137.0, 142.5, 148.0, *two carbon atoms with identical chemical shift; MS (ASAP$^+$): *m/z* (%) = 410 (32) [M+H, ^{37}Cl]$^+$, 409 (52) [M, ^{37}Cl]$^+$, 408 (93) [M+H, ^{35}Cl]$^+$, 407 (100) [M, ^{35}Cl]$^+$; Anal. Calcd for $C_{23}H_{18}ClNO_2S$: C, 67.72; H, 4.45; N, 3.43; S, 7.86. Found: C, 68.13; H, 4.72; N, 3.34; S, 7.39.

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5-(4-(Methylsulfonyl)phenyl)-4-phenyl-1,2-dihydropyrrolo[3,2,1-*hi*]indole (6c). Purification was carried out by column chromatography (petroleum ether/ ethyl acetate 66:33→33:66). Starting from **5c** (100 mg, 0.25 mmol), **6c** was obtained following general procedure D as colorless crystals (79 mg, 85%). mp 199-202°C; R_f = 0.46 (petroleum ether/ ethyl acetate 50:50); UV/vis: λmax (ε) = 294 (19100), 349 (13500); Fluorescence: λexc = 353, λem = 452 nm; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.08 (s, 3H), 3.83 (t, ^3J = 7.0 Hz, 2H), 4.58 (t, ^3J = 7.0 Hz, 2H), 7.02 (d, ^3J = 6.7 Hz, 1H), 7.13 (t, ^3J = 7.8 Hz, ^3J = 6.9 Hz, 1H), 7.37-7.43 (m, 5H), 7.49 (d, ^3J = 7.8 Hz, 1H), 7.60 (d, ^3J = 8.6 Hz, 2H), 7.83 (d, ^3J = 8.6 Hz, 2H); ^{13}C {^{1}H} NMR ($CDCl_3$, 101 MHz): δ 33.6, 44.7, 49.8, 115.5, 116.4, 116.9, 119.6, 123.4, 125.2, 127.7, 128.4, 129.1, 129.3, 129.3, 132.0, 136.6, 136.7, 142.9, 147.9; MS (ASAP$^+$): *m/z* (%) = 374 (100) [M+H]$^+$, 373 (56) [M]$^+$; Anal. Calcd for $C_{23}H_{19}NO_2S$: C, 73.97; H, 5.13; N, 3.75; S, 8.59. Found: C, 74.34; H, 5.29; N, 3.72; S, 8.22.

4-(4-Methylphenyl)-5-[4-(methylsulfonyl)phenyl]-1,2-dihydropyrrolo[3,2,1-*hi*]indole (6d).

Purification was carried out by column chromatography (petroleum ether/ ethyl acetate 100:0→33:66). Starting from **5d** (200 mg, 0.48 mmol), **6d** was obtained following general procedure D as a pale yellow solid (150 mg, 81%). mp 194-197°C; R_f = 0.52 (petroleum ether/ ethyl acetate 50:50); UV/vis: λmax (ε) = 295 (21100), 350 (14300); Fluorescence: λexc = 354, λem = 454 nm; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.41 (s, 3H), 3.08 (s, 3H), 3.82 (t, ^3J = 7.0 Hz, 2H), 4.56 (t, ^3J = 7.0 Hz, 2H), 7.01 (d, ^3J = 6.8 Hz, 1H), 7.12 (t, ^3J = 7.9 Hz, ^3J = 6.8 Hz, 1H), 7.21 (d, ^3J = 8.1 Hz, 2H), 7.30 (d, ^3J = 8.1 Hz, 2H), 7.48 (d, ^3J = 7.9 Hz, 1H), 7.60 (d, ^3J = 8.7 Hz, 2H), 7.83 (d, ^3J = 8.6 Hz, 2H); ^{13}C {^{1}H} NMR ($CDCl_3$, 101 MHz): δ 21.5, 33.7, 44.8, 49.7, 115.2, 116.3, 116.8, 119.7, 123.4, 125.1, 127.6, 129.1, 129.2, 129.2, 129.9, 136.5, 137.0, 138.5, 143.1, 147.8; MS (ASAP$^+$): *m/z* (%) = 388 (68) $[M+H]^+$, 387 (100) $[M]^+$; Anal. Calcd for $C_{24}H_{21}NO_2S$: C, 74.39; H, 5.46; N, 3.61; S, 8.27. Found: C, 74.74; H, 5.56; N, 3.63; S, 8.04.

5-(4-Fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-1,2-dihydropyrrolo[3,2,1-*hi*]indole (6e). Purification was carried out by column chromatography (petroleum ether/ ethyl acetate 70:30→60:40). Starting from **5e** (250 mg, 0.59 mmol), **6e** was obtained following general procedure D as a beige solid (165 mg, 71%). mp 218-219°C; R_f = 0.48 (petroleum ether/ ethyl acetate 33:66); UV/vis: λmax (ε) = 264 (18100), 330 (13600); Fluorescence: λexc = 337, λem = 501 nm; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.10 (s, 3H), 3.84 (t, ^3J = 7.0 Hz, 2H), 4.59 (t, ^3J = 7.0 Hz, 2H), 6.99–7.14 (m, 4H), 7.36 (dd, ^3J = 8.6 Hz, $^4J_{H,F}$ = 5.5 Hz, 1H), 7.41 (d, ^3J = 7.9 Hz, 1H), 7.58 (d, ^3J = 8.4 Hz, 1H), 7.89 (d, ^3J = 8.4 Hz, 1H); ^{13}C {^{1}H} NMR ($CDCl_3$, 101 MHz): δ 33.7, 44.6, 50.6, 115.9 (d, $^2J_{C,F}$ = 21 Hz), 116.9, 117.3, 119.1, 120.2, 123.2, 125.1, 127.9, 129.5, 130.9 (d, $^3J_{C,F}$ = 8 Hz), 131.7 (d, $^4J_{C,F}$ = 3 Hz), 133.0, 138.4, 139.0, 148.8, 161.7 (d, $^1J_{C,F}$ = 246 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz): δ -116.4; MS (ASAP$^+$): *m/z* (%) = 392 (55) $[M+H]^+$, 391 (100) $[M]^+$; HRMS (ESI$^+$) *m/z* calcd for $C_{23}H_{18}FNO_2SNa$ $[M + Na^+]$ 414.09345, found 414.09386. Crystals suitable for X-ray analysis were obtained by slow evaporation of a solution of **6e** in chloroform layered with petroleum ether.

5-(4-Chlorophenyl)-4-[4-(methylsulfonyl)phenyl]-1,2-dihydropyrrolo[3,2,1-*hi*]indole (6f). Purification was carried out by column chromatography (petroleum ether/ ethyl acetate 70:30→60:40). Starting from **5f** (250 mg, 0.57 mmol), **6f** was obtained following general procedure D as a colorless solid (177 mg, 76%). mp 205-207°C; R_f = 0.47 (petroleum ether/ ethyl acetate 33:66); UV/vis: λmax (ε) = 266 (17300), 332 (13600); Fluorescence: λexc = 340, λem = 501 nm; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.11 (s, 3H), 3.84 (t, ^3J = 7.0 Hz, 2H), 4.59 (t, ^3J = 7.0 Hz, 2H), 7.03 (d, ^3J = 6.7 Hz, 1H), 7.10 (dd, ^3J = 7.5 Hz, ^3J = 7.1 Hz, 1H), 7.29–7.36 (m, 4H), 7.42 (d, ^3J = 7.9 Hz, 1H), 7.59 (d, ^3J = 8.4 Hz, 2H), 7.91 (d, ^3J = 8.4 Hz, 2H); ^{13}C {^{1}H} NMR ($CDCl_3$, 101 MHz): δ 33.7, 44.6, 50.5, 117.0, 117.3, 118.8, 120.0, 123.4, 125.1,

127.9, 129.1, 129.6, 130.6, 132.2, 133.1, 134.3, 138.2, 139.2, 148.7; MS (ASAP$^+$): *m/z* (%) = 410 (63), 408 (100) [M+H, ^{35}Cl]$^+$, 407 (90) [M, ^{35}Cl]$^+$, 391 (78); HRMS (ESI$^+$) *m*/*z* calcd for $C_{23}H_{19}ClNO_2S$ [M + H$^+$, ^{35}Cl] 408.08195, found 408.08167.

4-(4-(Methylsulfonyl)phenyl)-5-phenyl-1,2-dihydropyrrolo[3,2,1-*hi*]indole (6g). Purification was carried out by column chromatography (petroleum ether/ ethyl acetate 70:30→50:50). Product containing fractions were combined and solvent was removed under reduced pressure. The resulting solid was dissolved in DCM (10 mL) and petroleum ether (15 mL) was added to the solution. A precipitate resulted which was isolated by filtration. Starting from **5g** (250 mg, 0.62 mmol), **6g** was obtained following general procedure D as a pale grey solid (129 mg, 56%). mp 229-231°C; R_f = 0.47 (petroleum ether/ ethyl acetate 33:66); UV/vis: λmax (ε) = 331 (13200); Fluorescence: λexc = 337, λem = 499 nm; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.10 (s, 3H), 3.83 (t, ^3J = 7.0 Hz, 2H), 4.59 (t, ^3J = 7.0 Hz, 2H), 7.02 (d, ^3J = 7.0 Hz, 1H), 7.09 (dd, ^3J = 7.9 Hz, ^3J = 6.8 Hz, 1H), 7.27 (t, ^3J = 7.2 Hz, 1H), 7.36 (t, ^3J = 7.8 Hz, ^3J = 7.3 Hz, 2H), 7.42 (dd, ^3J = 8.1 Hz, ^4J = 1.1 Hz, 2H), 7.46 (d, ^3J = 7.8 Hz, 1H), 7.60 (d, ^3J = 8.5 Hz, 2H), 7.88 (d, ^3J = 8.5 Hz, 2H); ^{13}C {^{1}H} NMR ($CDCl_3$, 101 MHz): δ 33.7, 44.6, 50.5, 116.8, 117.6, 120.3*,123.1, 125.0, 126.4, 127.8, 128.9, 129.4, 129.5, 133.0, 135.7, 138.6, 138.8, 148.9, *two carbon atoms with identical chemical shift; MS (ASAP$^+$): *m/z* (%) = 374 (100) [M+H]$^+$; HRMS (ESI$^+$) *m*/*z* calcd for $C_{23}H_{19}NO_2SNa$ [M + Na$^+$] 396.10287, found 396.10298.

5-(4-Methylphenyl)-4-[4-(methylsulfonyl)phenyl]-1,2-dihydropyrrolo[3,2,1-*hi*]indole (6h). Purification was carried out by column chromatography (petroleum ether/ ethyl acetate 70:30→60:40). Starting from **5h** (250 mg, 0.60 mmol), **6h** was obtained following general procedure D as a yellow solid (141 mg, 61%). mp 192-194°C; R_f = 0.49 (petroleum ether/ ethyl acetate 33:66); UV/vis: λmax (ε) = 332 (13800); Fluorescence: λexc = 340, λem = 505 nm; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.39 (s, 3H), 3.10 (s, 3H), 3.83 (t, ^3J = 7.0 Hz, 2H), 4.58 (t, ^3J = 7.0 Hz, 2H), 7.01 (d, ^3J = 6.6 Hz, 1H), 7.08 (dd, ^3J = 8.0 Hz, ^3J = 6.7 Hz, 1H), 7.17 (d, ^3J = 7.9 Hz, 2H), 7.31 (d, ^3J = 8.1 Hz, 2H), 7.44 (d, ^3J = 7.8 Hz, 1H), 7.60 (d, ^3J = 8.6 Hz, 2H), 7.88 (d, ^3J = 8.5 Hz, 2H); ^{13}C {^{1}H} NMR ($CDCl_3$, 101 MHz): δ 21.4, 33.7, 44.6, 50.6, 116.7, 117.6, 120.3, 120.4, 123.0, 125.0, 127.8, 129.3, 129.5, 129.7, 132.7, 132.9, 136.1, 138.7*, 148.9, *two carbon atoms with identical chemical shift; MS (ASAP$^+$): *m/z* (%) = 388 (81) [M+H]$^+$, 387 (100) [M]$^+$; Anal. Calcd for $C_{24}H_{21}NO_2S$: C, 74.39; H, 5.46; N, 3.61; S, 8.27. Found: C, 74.13; H, 5.59; N, 3.55; S, 7.79.

4-(4-Methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-1,2-dihydropyrrolo[3,2,1-*hi*]indole (6i). Purification was carried out by column chromatography (1. column: petroleum ether/

ethyl acetate 80:20→0:100, 2nd column: chloroform). Starting from **5i** (450 mg, 1.03 mmol), **6i** was obtained following general procedure D as a pale yellow solid (317 mg, 76%). mp 213-216°C; R_f = 0.43 (petroleum ether/ ethyl acetate 50:50); R_f = 0.65 (chloroform/ methanol 95:5); UV/vis: λmax (ε) = 297 (21500), 351 (13700); Fluorescence: λexc = 359, λem = 455 nm; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.08 (s, 3H), 3.82 (t, ^3J = 7.0 Hz, 2H), 3.86 (s, 3H), 4.55 (t, ^3J = 7.0 Hz, 2H), 6.94 (d, ^3J = 8.8 Hz, 2H), 7.00 (d, ^3J = 6.8 Hz, 1H), 7.11 (dd, ^3J = 7.8 Hz, ^3J = 6.9 Hz, 1H), 7.34 (d, ^3J = 8.8 Hz, 2H), 7.48 (d, ^3J = 7.9 Hz, 1H), 7.60 (d, ^3J = 8.6 Hz, 2H), 7.83 (d, ^3J = 8.6 Hz, 2H); ^{13}C {^{1}H} NMR ($CDCl_3$, 101 MHz): δ 33.7, 44.8, 49.6, 55.5, 114.7, 114.9, 116.2, 116.7, 119.7, 123.3, 124.3, 125.0, 127.7, 129.2, 130.6, 136.4, 136.8, 143.2, 147.8, 159.8; MS (ESI$^+$): *m/z* (%) = 404 (100) $[M+H]^+$; Anal. Calcd for $C_{24}H_{21}NO_3S$: C, 71.44; H, 5.25; N, 3.47; S, 7.95. Found: C, C, 71.48; H, 5.45; N, 3.40; S, 7.49.

4-(4-Hydroxyphenyl)-5-[4-(methylsulfonyl)phenyl]-1,2-dihydropyrrolo[3,2,1-*hi*]indole (6j). Under nitrogen atmosphere, 1 M BBr_3 in DCM (2.1 mL, 2.1 mmol) was added to a solution of **6i** (222 mg, 0.55 mmol) in anhydrous DCM (10 mL) at -5°C. The solution was stirred for 3 h and allowed to warm up slowly to room temperature. Additionally, 1 M BBr_3 in DCM (2.0 mL, 2.0 mmol) was added and the mixture was stirred at room temperature for 18 h. Then, the mixture was pre-adsorbed on silica-gel and purified by column chromatography (chloroform/ methanol 98:2→97.5:2.5). This gave **6j** as pale brown solid (195 mg, 91%). mp 209-215°C; R_f = 0.24 (petroleum ether/ ethyl acetate 50:50); R_f = 0.24 (chloroform/ methanol 95:5); UV/vis: λmax (ε) = 297 (20300), 352 (13100); Fluorescence: λexc = 356, λem = 454 nm; ^{1}H NMR (acetone-d_6, 400 MHz): δ 3.11 (s, 3H), 3.79 (t, ^3J = 7.0 Hz, 2H), 4.60 (t, ^3J = 7.0 Hz, 2H), 6.92 (d, ^3J = 8.7 Hz, 2H), 6.95 (d, ^3J = 6.9 Hz, 1H), 7.05 (dd, ^3J = 7.8 Hz, ^3J = 6.9 Hz, 1H), 7.36 (d, ^3J = 8.6 Hz, 2H), 7.46 (d, ^3J = 7.9 Hz, 1H), 7.64 (d, ^3J = 8.4 Hz, 2H), 7.84 (d, ^3J = 8.4 Hz, 2H), 8.70 (s, 1H); ^{13}C {^{1}H} NMR (acetone-d_6, 101 MHz): δ 33.9, 44.5, 50.1, 114.8, 116.6, 116.8*, 117.1, 120.4, 123.8, 124.0, 126.2, 128.3, 129.5, 131.5, 137.7, 138.1, 143.7, 148.4, 158.6*, *deuterium isotope shifts were observed in the range of 89 and 91 ppb; MS (ASAP$^+$): *m/z* (%) = 389 (100) $[M]^+$; HRMS (ESI$^+$) *m*/*z* calcd for $C_{23}H_{19}NO_3SNa$ $[M + Na^+]$ 412.09779, found 412.09834..

4-[4-(2-Fluoroethoxy)phenyl]-5-[4-(methylsulfonyl)phenyl]-1,2-dihydropyrrolo[3,2,1-*hi*]indole (6k). Under nitrogen atmosphere, 4-nitrobenzenesulfonyl chloride (940 mg, 4.24 mmol) in anhydrous THF (6 mL) was added to a solution of 2-fluoroethanol (197 µL, 218 mg, 3.4 mmol) in anhydrous THF (4 mL) at 0°C. The mixture was stirred at this temperature and potassium trimethylsilanolate (2.17 g, 16.95 mmol) was added in portions over a period of 30 min. After stirring for additional 2 h at 0°C, the mixture was poured over ice-cold water (100 mL) and extracted with DCM (3 x 50 mL). The organic phase was

washed with brine (50 mL), dried over Na_2SO_4 and filtered. The filtrate was reduced to dryness under reduced pressure and purified by column chromatography (petroleum ether/ ethyl acetate 80:20→60:40). A solid (608 mg) was obtained that contained 2-fluoroethyl-4-nitrobenzenesulfonate **7** in an amount-of-substance fraction of ca. 80% (calculated from ^{1}H-NMR) beside an unknown side product. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.41 (dt, $^3J_{H,F}$ = 27.3 Hz, ^3J = 3,9 Hz, 2H), 4.80 (dt, $^2J_{H,F}$ = 47.0 Hz, ^3J = 3.9 Hz, 2H), 8.13 (d, ^3J = 8.9 Hz, 2H), 8.41 (d, ^3J = 8.9 Hz, 2H), further signals of the unknown side product with an intensity of 20% in the spectra: 4.32 (dt, $^3J_{H,F}$ = 27.4 Hz, ^3J = 4.0 Hz, 2H), 4.61 (dt, $^2J_{H,F}$ = 47.3 Hz, ^3J = 4.0 Hz, 2H), 7.00 (d, ^3J = 8.9 Hz, 2H), 8.22 (d, ^3J = 8.9 Hz, 2H).

Under nitrogen atmosphere, crude 2-fluoroethyl-4-nitrobenzenesulfonate **7** (122 mg) was added to a solution of **6j** (75 mg, 0.19 mmol) and potassium *tert*-butoxide (25.3 mg, 0.25 mmol) in anhydrous THF (3.15 mL). Then, the mixture was heated for 20 h at 70°C. After cooling the mixture to room temperature and pre-adsorption on silica-gel, purification was carried out by column chromatography (1. column: petroleum ether/ ethyl acetate 70:30→50:50, then chloroform/ methanol 95:5; 2nd column: (using a Merck Lichrolut Si SPE cartridge) chloroform/ methanol 100:0→98:2). This gave **6k** as a pale yellow solid (46 mg, 55%). mp 203-206°C (polymorphism at 176°C); R_f = 0.35 (petroleum ether/ ethyl acetate 50:50); R_f = 0.64 (chloroform/ methanol 95:5); UV/vis: λmax (ε) = 297 (20700), 352 (13300); Fluorescence: λexc = 354, λem = 455 nm; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.08 (s, 3H), 3.82 (t, ^3J = 7.0 Hz, 2H), 4.27 (dt, $^3J_{H,F}$ = 27.7 Hz, ^3J = 4.1 Hz, 2H), 4.55 (t, ^3J = 7.0 Hz, 2H), 4.79 (dt, $^2J_{H,F}$ = 47.4 Hz, ^3J = 4.1 Hz, 2H), 6.96 (d, ^3J = 8.8 Hz, 2H), 7.01 (d, ^3J = 6.8 Hz, 1H), 7.12 (dd, ^3J = 7.8 Hz, ^3J = 6.9 Hz, 1H), 7.34 (d, ^3J = 8.7 Hz, 2H), 7.48 (d, ^3J = 7.9 Hz, 1H), 7.60 (d, ^3J = 8.5 Hz, 2H), 7.83 (d, ^3J = 8.5 Hz, 2H); ^{13}C {^{1}H} NMR ($CDCl_3$, 101 MHz): δ 33.7, 44.8, 49.7, 67.3 (d, $^2J_{C,F}$ = 20 Hz), 82.0 (d, $^1J_{C,F}$ = 172 Hz), 115.0, 115.3, 116.3, 116.8, 119.7, 123.4, 124.9, 125.0, 127.7, 129.2, 130.7, 136.5, 136.6, 143.1, 147.8, 158.6; ^{19}F NMR ($CDCl_3$, 376 MHz): δ -224.3; MS (ASAP$^+$): *m/z* (%) = 437 (32), 436 (100) $[M+H]^+$, 435 (510) $[M]^+$; HRMS (ESI$^+$) *m*/*z* calcd for $C_{25}H_{22}FNO_3SNa$ $[M + Na^+]$ 458.11966, found 458.12011.

General procedure E for the synthesis of 1,2-diphenylpyrrolo[3,2,1-*hi*]indoles (8a-h).

Under nitrogen atmosphere, a solution of the corresponding 4,5-diphenyl-1,2-dihydropyrrolo[3,2,1-*hi*]indole **6a-h** (0.165 mmol) and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ, 130.8 mg, 0.576 mmol) in anhydrous benzene (9.3 mL) was heated under reflux for 6 h. After cooling to room temperature, ethyl acetate (19 mL) was added and the solution was transferred to a separatory funnel. The organic phase was washed with saturated Na_2SO_4 (19 mL), saturated $NaHCO_3$ (19 mL) and brine (9 mL). After that, the organic phase was over Na_2SO_4, filtered, and the mixture was pre-adsorbed on silica-gel.

The purification was performed by column chromatography as given below. The raw and final product should be stored cool and in the dark.

2-(4-Fluorophenyl)-1-[4-(methylsulfonyl)phenyl]pyrrolo[3,2,1-*hi*]indole (8a). Purification was carried out by column chromatography (petroleum ether/ ethyl acetate 80:20→70:30). Starting from **6a** (61.1 mg, 0.156 mmol) and DDQ (247.1 mg, 1.097 mmol), **8a** was obtained following general procedure E as a yellow-green solid (49.0 mg, 81%). mp 205-208°C; R_f = 0.53 (petroleum ether/ ethyl acetate 50:50); UV/vis: λmax (ε) = 300 (20400), 362sh (4800); Fluorescence: λexc = 306, λem = 487 nm; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.12 (s, 3H), 6.91 (d, ^3J = 3.2 Hz, 1H), 7.17 (t, $^3J_{H,H}$ = $^3J_{H,F}$ = 8.6 Hz, 2H), 7.50 (d, ^3J = 3.1 Hz, 1H), 7.52–7.56 (m, ^3J = 8.6 Hz, $^4J_{H,F}$ = 5.4 Hz, ^3J = 7.4 Hz, 3H), 7.70 (d, ^3J = 8.6 Hz, 2H), 7.75–7.79 (m, ^3J = 7.4 Hz, ^3J = 7.3 Hz, 2H), 7.93 (d, ^3J = 8.5 Hz, 2H); ^{13}C {^{1}H} NMR ($CDCl_3$, 101 MHz): δ 44.7, 111.8, 116.7 (d, $^2J_{C,F}$ = 22 Hz), 119.7, 120.7, 121.2, 122.0, 122.5, 124.3, 125.0, 127.0 (d, $^4J_{C,F}$ = 4 Hz), 128.0, 130.0, 131.6 (d, $^3J_{C,F}$ = 8 Hz), 135.3, 137.1, 138.2, 141.2, 163.2 (d, $^1J_{C,F}$ = 251 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz): δ -111.6; MS (ASAP$^+$): *m/z* (%) = 389 (100) [M]$^+$; HRMS (ESI$^+$) *m*/*z* calcd for $C_{23}H_{16}FNO_2SNa$ [M + Na^+] 412.07780, found 412.07759.

2-(4-Chlorophenyl)-1-[4-(methylsulfonyl)phenyl]pyrrolo[3,2,1-*hi*]indole (8b). Purification was carried out by column chromatography (petroleum ether/ ethyl acetate 70:30). Starting from **6b** (67.1 mg, 0.164 mmol), **8b** was obtained following general procedure E as a yellow solid (27.6 mg, 41%). mp 224-227°C; R_f = 0.54 (petroleum ether/ ethyl acetate 50:50); UV/vis: λmax (ε) = 301 (19400), 358 (4900); Fluorescence: λexc = 325, λem = 489 nm; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.12 (s, 3H), 6.92 (d, ^3J = 3.2 Hz, 1H), 7.44 (d, ^3J = 8.7 Hz, 2H), 7.49 (d, ^3J = 8.7 Hz, 2H), 7.51 (d, ^3J = 3.2 Hz, 1H), 7.54 (t, ^3J = 7.4 Hz, 1H), 7.70 (d, ^3J = 8.6 Hz, 2H), 7.75–7.79 (m, ^3J = 7.4 Hz, ^3J = 7.3 Hz, 2H), 7.94 (d, ^3J = 8.5 Hz, 2H); ^{13}C {^{1}H} NMR ($CDCl_3$, 101 MHz): δ 44.7, 111.8, 119.7, 121.0, 121.4, 122.0, 122.6, 124.4, 125.0, 128.0, 129.4, 129.8, 130.1, 130.9, 135.1, 135.4, 137.2, 138.4, 141.0; MS (ASAP$^+$): *m/z* (%) = 407 (47), 406 (53), 405 (100) [M, ^{35}Cl]$^+$; HRMS (ESI$^+$) *m*/*z* calcd for $C_{23}H_{20}ClN_2O_2S$ [M + NH_4^+, ^{35}Cl] 423.09340, found 423.09280.

1-[4-(Methylsulfonyl)phenyl]-2-phenylpyrrolo[3,2,1-*hi*]indole (8c). Purification was carried out by column chromatography (petroleum ether/ ethyl acetate 70:30→60:40). Starting from **6c** (61.5 mg, 0.165 mmol), **8c** was obtained following general procedure E as a pale yellow solid (51.4 mg, 84%). mp 161-164°C; R_f = 0.48 (petroleum ether/ ethyl acetate 50:50); UV/vis: λmax (ε) = 302 (20100), 366sh (4800); Fluorescence: λexc = 307, λem = 489

nm; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.11 (s, 3H), 6.91 (d, ^3J = 3.1 Hz, 1H), 7.44-7.49 (m, 3H), 7.53-7.58 (m, 4H), 7.72 (d, ^3J = 8.6 Hz, 2H), 7.77 (t, ^3J = 7.8 Hz, ^3J = 7.6 Hz, 2H), 7.91 (d, ^3J = 8.6 Hz, 2H); ^{13}C {^{1}H} NMR ($CDCl_3$, 101 MHz): δ 44.7, 111.6, 119.6, 120.6, 121.1, 122.1, 122.5, 124.6, 124.9, 127.9, 129.2, 129.4, 129.7, 130.0, 130.9, 136.5, 137.1, 138.1, 141.4; MS (ASAP$^+$): *m/z* (%) = 372 (62) [M+H]$^+$, 371 (100) [M]$^+$; HRMS (ESI$^+$) *m*/*z* calcd for $C_{23}H_{17}NO_2SNa$ [M + Na$^+$] 394.08722, found 394.08748.

2-(4-Methylphenyl)-1-[4-(methylsulfonyl)phenyl]pyrrolo[3,2,1-*hi*]indole (8d).
Purification was carried out by column chromatography (petroleum ether/ ethyl acetate 70:30). Starting from **6d** (69.9 mg, 0.180 mmol), **8d** was obtained following general procedure E as a pale yellow solid (52.1 mg, 75%). mp 180-183°C; R_f = 0.54 (petroleum ether/ ethyl acetate 50:50); UV/vis: λmax (ε) = 304 (21400), 368 (5300); Fluorescence: λexc = 309, λem = 489 nm; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.44 (s, 3H), 3.11 (s, 3H), 6.89 (d, ^3J = 3.1 Hz, 1H), 7.27 (d, ^3J = 8.2 Hz, 2H), 7.45 (d, ^3J = 8.1 Hz, 2H), 7.50–7.55 (m, ^3J = 3.1 Hz, ^3J = 7.4 Hz, 2H), 7.72 (d, ^3J = 8.6 Hz, 2H), 7.75 (d, ^3J = 7.3 Hz, 1H), 7.77 (d, ^3J = 7.4 Hz, 1H), 7.91 (d, ^3J = 8.5 Hz, 2H); ^{13}C {^{1}H} NMR ($CDCl_3$, 101 MHz): δ 21.6, 44.7, 111.5, 119.5, 120.1, 120.9, 122.2, 122.4, 124.6, 124.8, 127.8, 127.9, 129.6, 130.0, 130.1, 136.7, 137.1, 137.9, 139.4, 141.6; MS (ASAP$^+$): *m/z* (%) = 386 (67) [M+H]$^+$, 385 (100) [M]$^+$; Anal. Calcd for $C_{24}H_{19}NO_2S$: C, 74.78; H, 4.97; N, 3.63; S, 8.32. Found: C, 74.51; H, 5.17; N, 3.54; S, 7.90.

1-(4-Fluorophenyl)-2-[4-(methylsulfonyl)phenyl]pyrrolo[3,2,1-*hi*]indole (8e). Purification was carried out by column chromatography (petroleum ether/ ethyl acetate 70:30→50:50). Starting from **6e** (70.0 mg, 0.179 mmol), **8e** was obtained following general procedure E as a pale yellow solid (69.7 mg, 100%). mp 245°C; R_f = 0.44 (petroleum ether/ ethyl acetate 50:50); UV/vis: λmax (ε) = 323 (16300), 373 (4300); Fluorescence: λexc = 328, λem = 496 nm; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.13 (s, 3H), 6.92 (d, ^3J = 3.1 Hz, 1H), 7.12 (t, $^3J_{H,H}$ = $^3J_{H,F}$ = 8.7 Hz, 2H), 7.47 (dd, ^3J = 8.8 Hz, $^4J_{H,F}$ = 5.4 Hz, 2H), 7.53 (t, ^3J = 7.4 Hz, 1H), 7.56 (d, ^3J = 3.1 Hz, 1H), 7.72–7.76 (m, ^3J = 8.6 Hz, 3H), 7.79 (d, ^3J = 7.3 Hz, 1H), 7.98 (d, ^3J = 8.6 Hz, 2H); ^{13}C {^{1}H} NMR ($CDCl_3$, 101 MHz): δ 44.6, 111.3, 116.2 (d, $^2J_{C,F}$ = 22 Hz), 120.1, 121.7, 122.5, 122.6, 124.2, 124.6, 124.9, 128.2, 130.1, 130.3 (d, $^4J_{C,F}$ = 3 Hz), 131.3 (d, $^3J_{C,F}$ = 8 Hz), 132.6, 137.2, 137.5, 139.9, 162.3 (d, $^1J_{C,F}$ = 248 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz): δ -114.8; MS (ASAP$^+$): *m/z* (%) = 390 (93) [M+H]$^+$, 389 (100) [M]$^+$; HRMS (ESI$^+$) *m*/*z* calcd for $C_{23}H_{16}FNO_2SNa$ [M + Na$^+$] 412.07780, found 412.07761.

1-(4-Chlorophenyl)-2-[4-(methylsulfonyl)phenyl]pyrrolo[3,2,1-*hi*]indole (8f). Purification was carried out by column chromatography (petroleum ether/ ethyl acetate 70:30). Starting from **6f** (70 mg, 0.17 mmol), **8f** was obtained following general procedure E as a beige-pale brown solid (62 mg, 89%). mp 235-236°C; R_f = 0.44 (petroleum ether/ ethyl acetate 50:50); UV/vis: λmax (ε) = 324 (17400), 370sh (5200); Fluorescence: λexc = 329, λem = 499 nm; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.14 (s, 3H), 6.92 (d, ^3J = 2.9 Hz, 1H), 7.39 (d, ^3J = 8.4 Hz, 2H), 7.44 (d, ^3J = 8.4 Hz, 2H), 7.49–7.56 (m, ^3J = 7.4 Hz, 2H), 7.72–7.77 (m, ^3J = 8.3 Hz, 3H), 7.79 (d, ^3J = 7.3 Hz, 1H), 7.99 (d, ^3J = 8.2 Hz, 2H); ^{13}C {^{1}H} NMR ($CDCl_3$, 101 MHz): δ 44.6, 111.5, 120.1, 121.7, 122.4, 122.6, 123.9, 124.6, 125.0, 128.2, 129.4, 130.1, 130.9, 132.7, 132.8, 133.4, 137.1, 137.5, 140.1; MS (ASAP$^+$): *m/z* (%) = 408 (23) [M+H, ^{37}Cl]$^+$, 407 (58) [M, ^{37}Cl]$^+$, 406 (48) [M+H, ^{35}Cl]$^+$, 405 (100) [M, ^{35}Cl]$^+$, 149 (39); HRMS (ESI$^+$) *m*/*z* calcd for $C_{23}H_{16}ClNO_2SNa$ [M + Na$^+$, ^{35}C]l 428.04824, found 428.04846.

2-[4-(Methylsulfonyl)phenyl]-1-phenylpyrrolo[3,2,1-*hi*]indole (8g). Purification was carried out by column chromatography (petroleum ether/ ethyl acetate 70:30→50:50). Starting from **6g** (70.0 mg, 0.187 mmol), **8g** was obtained following general procedure E as a pale yellow solid (61.3 mg, 88%). mp 253-254°C; R_f = 0.43 (petroleum ether/ ethyl acetate 50:50); UV/vis: λmax (ε) = 323 (16200), 376sh (4500); Fluorescence: λexc = 329, λem = 490 nm; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.13 (s, 3H), 6.92 (d, ^3J = 3.1 Hz, 1H), 7.35 (t, ^3J = 7.2 Hz, 1H), 7.42 (t, ^3J = 7.7 Hz, ^3J = 7.0 Hz, 2H), 7.49–7.55 (m, ^3J = 7.5 Hz, ^3J = 7.2 Hz, 3H), 7.56 (d, ^3J = 3.1 Hz, 1H), 7.73–7.81 (m, ^3J = 7.2 Hz, 4H), 7.97 (d, ^3J = 8.3 Hz, 2H); ^{13}C {^{1}H} NMR ($CDCl_3$, 101 MHz): δ 44.6, 111.2, 120.3, 121.5, 122.5, 122.8, 124.6, 124.8, 125.3, 127.5, 128.1, 129.1, 129.7, 130.1, 132.6, 134.3, 137.4, 137.6, 139.8; MS (ASAP$^+$): *m/z* (%) = 371 (100) [M]$^+$; HRMS (ESI$^+$) *m*/*z* calcd for $C_{23}H_{17}NO_2SNa$ [M + Na$^+$] 394.08722, found 394.08721.

1-(4-Methylphenyl)-2-[4-(methylsulfonyl)phenyl]pyrrolo[3,2,1-*hi*]indole (8h). Purification was carried out by column chromatography (petroleum ether/ ethyl acetate 70:30→50:50). Starting from **6h** (70.0 mg, 0.181 mmol), **8h** was obtained following general procedure E as a yellow solid (64.6 mg, 93%). mp 221-222°C; R_f = 0.45 (petroleum ether/ ethyl acetate 50:50); UV/vis: λmax (ε) = 324 (18500), 381 (4900); Fluorescence: λexc = 329, λem = 499 nm; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.42 (s, 3H), 3.13 (s, 3H), 6.90 (d, ^3J = 3.1 Hz, 1H), 7.22 (d, ^3J = 7.9 Hz, 2H), 7.40 (d, ^3J = 8.0 Hz, 2H), 7.51 (t, ^3J = 7.4 Hz, 1H), 7.55 (d, ^3J = 3.1 Hz, 1H), 7.74–7.80 (m, ^3J = 8,5 Hz, ^3J = 7.3 Hz, ^3J = 7.2 Hz, 4H), 7.96 (d, ^3J = 8.5 Hz, 2H); ^{13}C {^{1}H} NMR ($CDCl_3$, 101 MHz): δ 21.4, 44.6, 111.0, 120.3, 121.5, 122.5, 122.9, 124.6, 124.8, 125.4, 128.0, 129.6, 129.9, 130.0, 131.3, 132.3, 137.3, 137.6, 137.6, 139.6; MS (ASAP$^+$): *m/z*

(%) = 386 (69) $[M+H]^+$, 385 (100) $[M]^+$; Anal. Calcd for $C_{24}H_{19}NO_2S$: C, 74.78; H, 4.97; N, 3.63; S, 8.32. Found: C, 74.94; H, 5.31; N, 3.53; S, 7.88

X-ray Crystallography. The crystallographic data were collected using CCD detector based X-ray diffractometers, with Mo-Kα radiation (λ=0.71073 Å). The structures were solved using SHELXS-97 and refined against F^2 on all data by full-matrix least squares with SHELXL-97 [67]. All non-hydrogen atoms were refined anisotropically; all hydrogen atoms bonded to carbon atoms were placed on geometrically calculated positions and refined using a riding model. Full crystallographic data for compounds **1**, **2a**, **5c**, **6a**, and **6e** were deposited with the Cambridge Crystallographic Data Center as supplementary publication nos. CCDC-992983 (compound **1**), CCDC-963608 (compound **2a**, CCDC-963606 (compound **5c**), CCDC-963607 (compound **6a**), CCDC-963611 (compound **6e**). Copies can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44(0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

COX inhibition assay. The COX inhibition activity against ovine COX-1 and human COX-2 was determined using the fluorescence based COX assay "COX Fluorescent Inhibitor Screening Assay Kit" (catalog number 700100; Cayman Chemical, Ann Arbor, MI, USA) according to the manufacturer's instructions. All compounds were assayed in a concentration range of 0.1 nM to 100 µM and every concentration was assayed in duplicate. Celecoxib was used as internal control and gave reliable results (intra-assay variance < 2.6%). IC_{50} values were estimated using a non-linear logistic regression fitting procedure (sigmoidal dose response model) with Prism Software.

Molecular docking. The crystal structure of COX-2 (PDB-entry: pdb-3ln1) was chosen because within this crystal structure one molecule of celecoxib was co-crystallized in the COX-2 active side. The PDB-file pdb-3ln1 was initially processed using MOE program (Schrödinger LLC, New York, NY (USA), 2012). 4503 hydrogen atoms were added, H_2O-16 was extracted from the COX-2 active side and the other water molecules were deleted. The ligand (celecoxib) was extracted as a reference. For docking experiments with **6a** and **6e**, the molecular structure of **6a** and **6e** derived from X-ray single crystal structure analysis was used. Docking studies were performed using GOLD Suite v. 5.2.1[55] with ChemPLP as fitness function and the "automatic"-option for genetic algorithm search option. The binding site was defined as all atoms within a distance of 10 Å and 50 Å (for **6a** and **6e**), respectively, in regard to the original position of the co-crystallized celecoxib molecule. 10 independent genetic algorithm search runs were performed for docking of **6a** and **6e** within a 50 Å binding site to get information about other preferred binding site. 100 independent genetic algorithm

search runs were performed for docking of the reference celecoxib, **6a** and **6e** within a 10 Å binding side to get information about the preferred binding mode of the inhibitors. In both, discussions and figures, the numbering is based on ovine COX-1.[56] Hence, e.g. His-75 in PDB-file pdb-3ln1 is mentioned as His-90 in this work. Accordingly, the numbering of the following residues was adjusted as follows: Arg-106 →(=mentioned as) Arg-120; Gln-178 → Gln192; Val-335 → Val-349; Ser-339 → Ser-353; Tyr-341 → Tyr-355; Trp-373 → Trp-387; Arg-499 → Arg-513; Val-509 → Val-523; Ala-513 → Ala-527; Ser-516 → Ser-530.

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Supporting Information.

Details of the X-ray structure analyses of compounds **1**, **2a**, **5c**, **6a**, and **6e**; Copies of ^{1}H-and ^{13}C-NMR. This material is available free of charge via the Internet at http://pubs.acs.org.

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