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Diaryl-Substituted (Dihydro)pyrrolo[3,2,1-*hi*]indoles, a Class of Potent COX-2 Inhibitors with Tricyclic Core Structure

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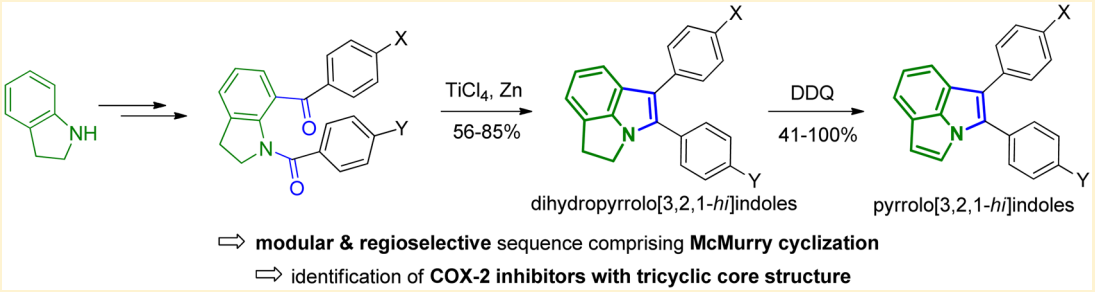
Supporting Information



ABSTRACT: 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 toward dihydropyrrolo[3,2,1-*hi*]indoles and is characterized by good chemical yields and high modularity. From a set of 19 derivatives, 11 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 a fluoro substituent, making them promising candidates for the development of ^{18}F-radiolabeled COX-2 inhibitors for imaging purposes with positron emission tomography (PET).

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 that concurrent inhibition of COX-1 causes unwanted gastrointestinal side effects stimulated the initial search for selective COX-2 inhibitors (COXIBs) in the late 1990s.[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 such as 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 which imaging agents targeting COX-2, e.g., radiolabeled COX-2 inhibitors for positron emission tomography (PET), are highly desirable.[9−12]

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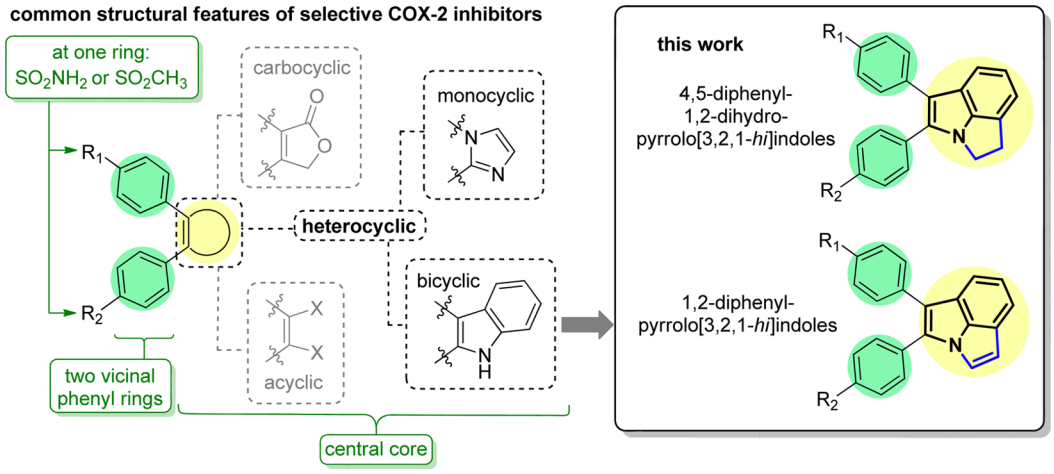


Figure 1. General structure of COX-2 inhibitors and target compounds of this work.

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 have reached the clinic as radiotracers, 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 previously,[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]

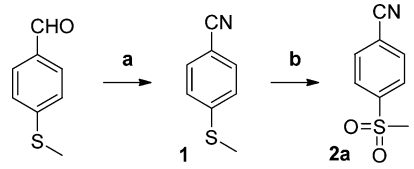
COX-2 inhibitors with a dihydropyrrolo[3,2,1-*hi*]indole and pyrrolo[3,2,1-*hi*]indole core have not been described so far. This prompted us to synthesize a comprehensive set of compounds of this new family and to evaluate their potency as COX inhibitors.

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 approach toward 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 11 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,

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



[a]Reagents and conditions: (a) NH_2OH·HCl, DMSO, 100 °C; (b) MCPBA, DCM, rt.

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 *m*-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.

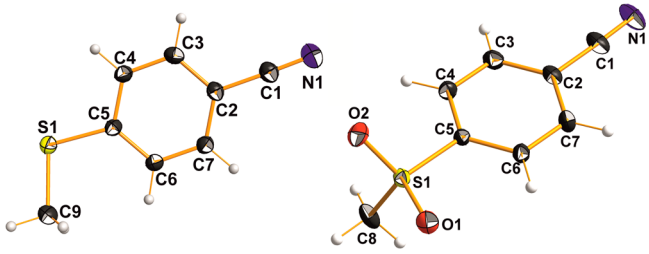


Figure 2. Molecular structure of compounds **1** (left) and **2a** (right) in the crystal (ORTEP plot: displacement thermal ellipsoids are drawn at 50% probability level).

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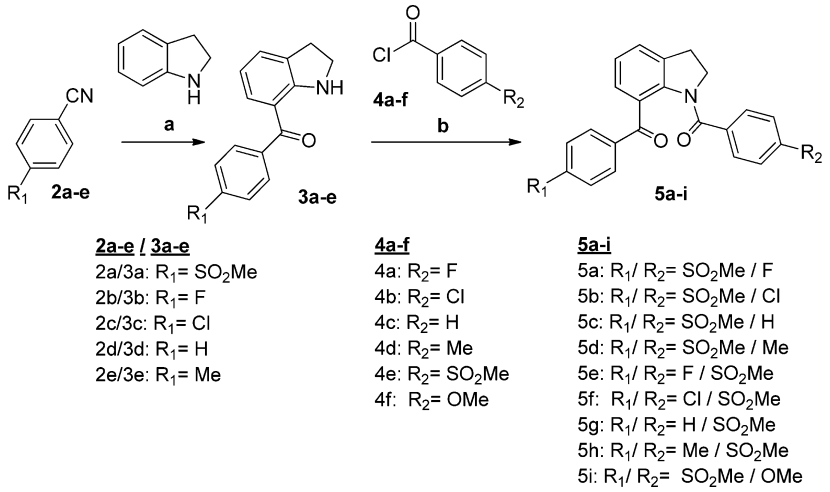
Scheme 2. Modular Synthesis Sequence for *N*-Benzoyl-7-benzoylindolines 5a−i[a]



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

The modular synthesis sequence to form pyrrolo[3,2,1-*hi*]indoles is based on the *N*-benzoyl-substituted 7-benzoylindolines (**5a−i**) as the 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 nitriles (**2b−e**) 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.

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 30 compounds can be obtained that 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] Thus, *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, 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 the 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 toward *N*,7-dibenzoyl-substituted indolines comprising *N*-acylation in the first step 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]

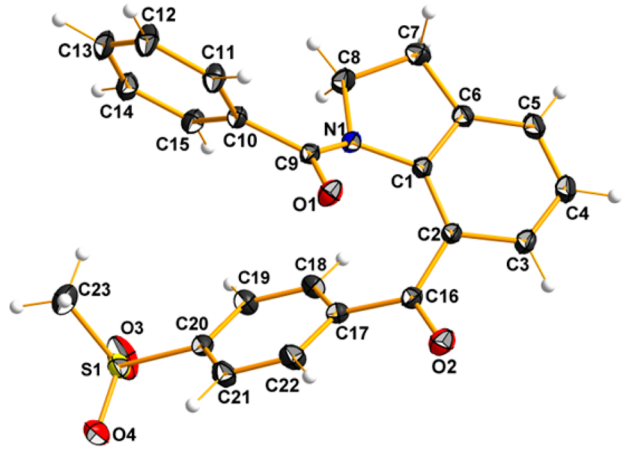


Figure 3. Molecular structure of compound **5c** in the crystal (the figure shows one of two independent molecules in the asymmetric unit; ORTEP plot: displacement thermal ellipsoids are drawn at 50% probability level).

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).

This strategy represents to the best of our knowledge a novel synthetic route toward 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] and 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 general use.

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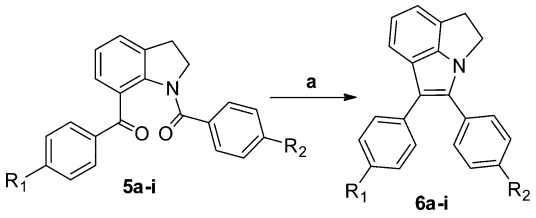
Scheme 3. Synthesis of Dihydropyrrolo[3,2,1-*hi*]indoles 6a–i[a]



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.

Advantageously, with the synthetic route presented by us, differently substituted indolines, nitriles, and benzoyl chlorides may be combined because the BCl_3-mediated Friedel–Crafts acylation yields 7-substituted indolines selectively and the McMurry cyclization has a high compatibility for various functional groups. Hence, our synthetic route gives a highly modular and convenient access to dihydropyrrolo[3,2,1-*hi*]-indoles.

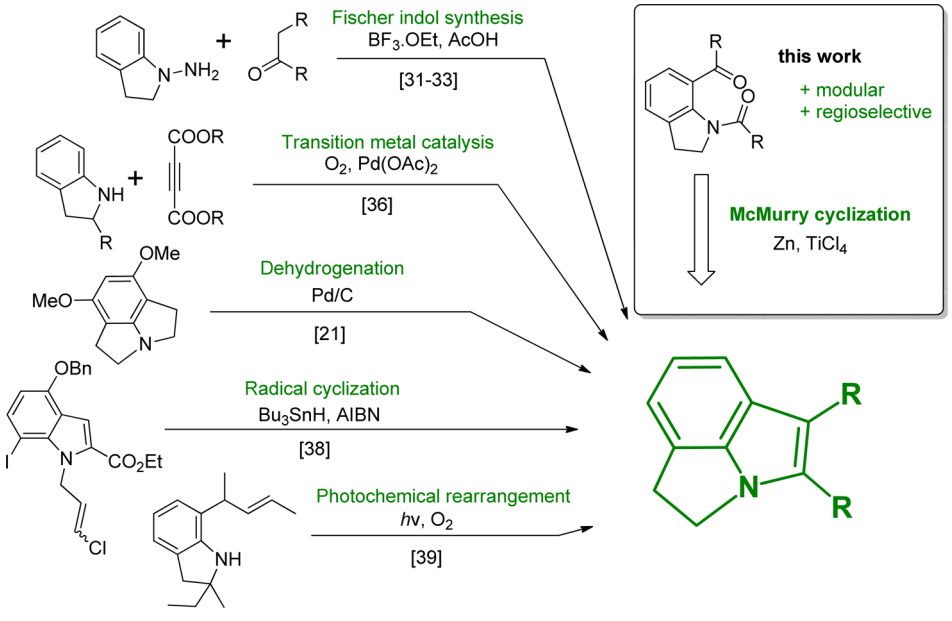
For compounds **6a** and **6e**, X-ray crystal structure analyses were performed that unambiguously confirmed the identity of both regioisomers (Figure 4). Interestingly, the ethylene bridge obviously causes a high ring strain in the 1,2-dihydropyrrolo-[3,2,1-*hi*]indole system, such that the bond between 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.

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.

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 the exception of **8b** for which 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, 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.

COX Inhibitory Activity. From the pool of 19 synthesized dihydropyrrolo[3,2,1-*hi*]indoles **6** and pyrrolo[3,2,1-*hi*]indoles **8**, 11 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

Scheme 4. Synthetic Route toward Dihydropyrrolo[3,2,1-*hi*]indoles Followed in This Work and Examples from the Literature



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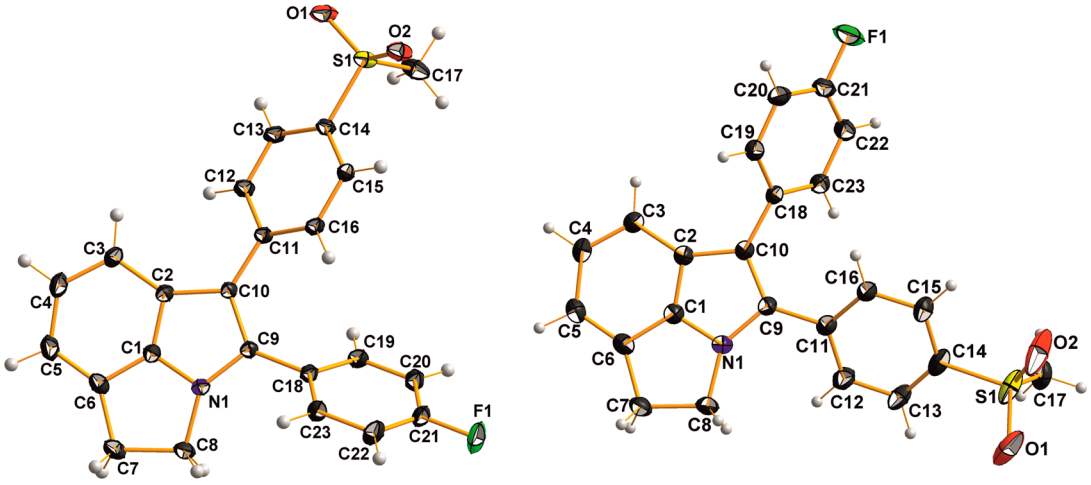
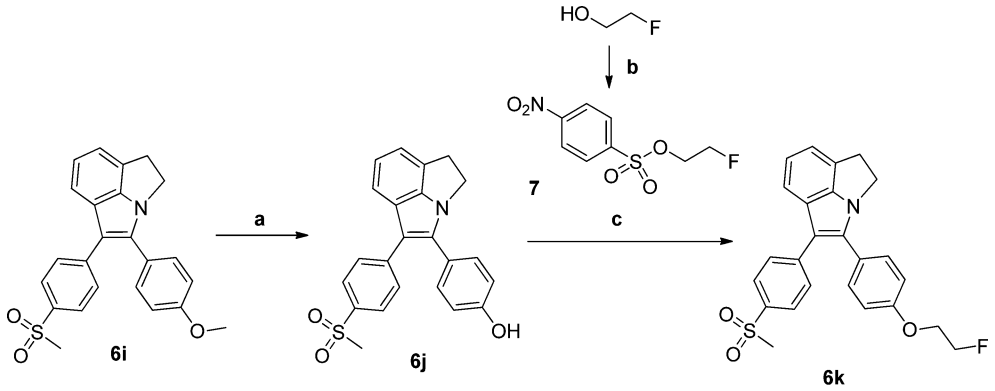


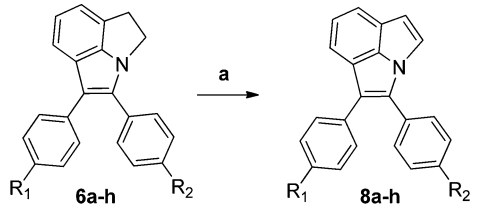
Figure 4. Molecular structure of compound **6a** (left) and **6e** (right) in the crystal (the structure of **6a** shows one of two independent molecules in the asymmetric unit; ORTEP plot: displacement thermal ellipsoids are drawn at 50% probability level).

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



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

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



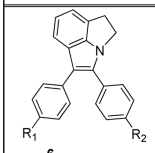
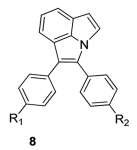
6a-h/ 8a-h
6a/8a: R_1/ R_2= SO_2Me / F **6e/8e**: R_1/ R_2= F / SO_2Me
6b/8b: R_1/ R_2= SO_2Me / Cl **6f/8f**: R_1/ R_2= Cl / SO_2Me
6c/8c: R_1/ R_2= SO_2Me / H **6g/8g**: R_1/ R_2= H / SO_2Me
6d/8d: R_1/ R_2= SO_2Me / Me **6h/8h**: R_1/ R_2= Me / SO_2Me

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

COX 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, MI). The results are shown in Table 1.

At the first view, it became obvious that all tested compounds with the exception of **6a** inhibit COX-2 at 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 of about 2.5 μM.

Table 1. COX Inhibition by Selected Dihydropyrrolo[3,2,1-*hi*]indoles and Pyrrolo[3,2,1-*hi*]indoles[a]

	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

[a]*SI = selectivity index. SI = IC_{50}(COX-1)/IC_{50}(COX-2).

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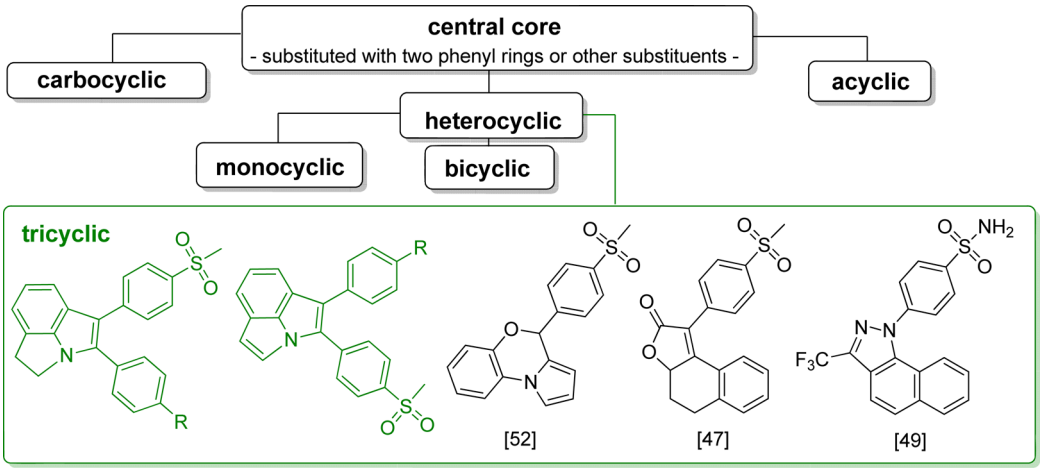

Figure 5. Update of the structural classification of COX-2 inhibitors according to Singh and Mittal[15] with further examples from the literature.

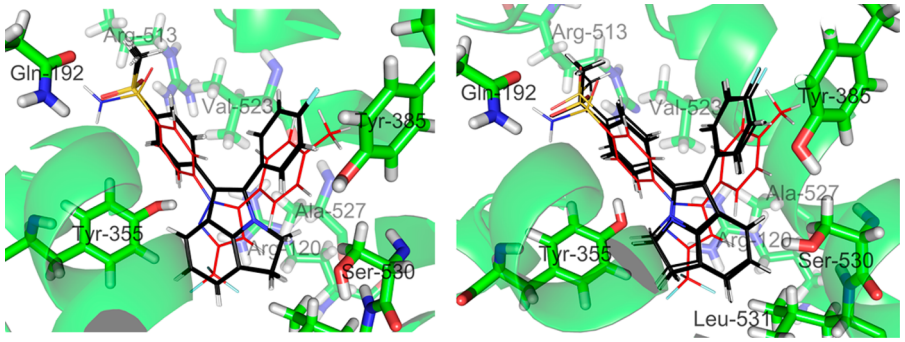

Figure 6. Docking of **6a** (left) and **6e** (right) in the active side of COX-2. The 10 best docking results from 100 runs are shown as superimposed structures (black C atoms) together with the cocrystallized celecoxib molecule (red C atoms) as a reference.

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** led 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 at 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 toward 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 because, to the best of our knowledge, this type of compound has not been described yet as a COX inhibitor in prominent reports and reviews regarding COX.[13−15,43−46] As far as we know, there exist a few reports for COX-2 inhibitors with a tricyclic core but only having none or one phenyl substituent; some of them were designed as conformationally restricted derivatives of monocyclic COXIBs.[47−54] Because the elegant scheme presented by Singh and 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 a tricyclic core.

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]

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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 cocrystallized molecule of celecoxib. Docking studies taking the whole protein as the 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$_{pyrrole}$) = 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$_{pyrrole}$) = 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 to 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, which reflects the ability of both compounds to inhibit COX-2 but is not matching the order of potency observed experimentally.

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, 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 synthetic route represents a novel and versatile access toward 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** besides other intermediates was analyzed by X-ray diffraction analyses. For evaluation of the COX affinity of this compound class, a set of 11 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]fluoro-ethylation 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 tricyclic core structures for the development of inhibitors with high affinity and selectivity toward COX-2. Within this new class of COX-2 inhibitors, 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 Rosenbohm.[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). 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 being measured. 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 a multimode 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 were added 80 μL of DMSO, 100 μL of TWEEN 20, and 9800 μL of 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 performed 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

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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-1H-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) were added, in this order, indoline (449 μL, 4 mmol) in 1.8 mL of 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. Then water (0.25 mL) and 10% HCl (4.5 mL) were 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. Afterward, 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]-1H-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)-1H-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, $^1J_{C,F}$ = 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)-1H-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-1H-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)-1H-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 of $SOCl_2$ and DMF (3 drops). The mixture was heated under reflux (60−70 °C) overnight. A clear solution resulted. $SOCl_2$ and DMF were removed under reduced pressure. Then benzene (1.5 mL) was added three times at room temperature, the mixture was stirred, and the solvent was removed. The resulting colorless solid (mp 130−135 °C, lit.:[66] 132 °C) 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. Then the mixture was preadsorbed 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)). A 212 mg amount of this raw product **3a** was 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). Thus, **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,

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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). A 500 mg amount of this raw product **3a** was 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). Thus, **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). A 250 mg amount of this raw product **3a** was 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). Thus, **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 thus 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 was added the isolated crystal, 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). A 250 mg amount of this raw product **3a** was 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). Thus, **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). Thus, **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). Thus, **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). Thus, **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

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(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). Thus, **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). A 500 mg amount of this raw product **3a** was 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). Thus, **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 preadsorbed 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: λ_{max} (ε) = 293 (20000), 347 (14200); fluorescence: λ_{exc} = 353, λ_{em} = 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: λ_{max} (ε) = 297 (20400), 348 (12600); fluorescence: λ_{exc} = 299, λ_{em} = 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.

*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: λ_{max} (ε) = 294 (19100), 349 (13500); fluorescence: λ_{exc} = 353, λ_{em} = 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: λ_{max} (ε) = 295 (21100), 350 (14300); fluorescence: λ_{exc} = 354, λ_{em} = 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: λ_{max} (ε) = 264 (18100), 330 (13600); fluorescence: λ_{exc} = 337, λ_{em} = 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

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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: λ_{max} (ε) = 266 (17300), 332 (13600); fluorescence: λ_{exc} =340, λ_{em} = 501 nm; ^1H 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 $\{^1H\}$ 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 gray solid (129 mg, 56%); mp 229−231 °C; R_f = 0.47 (petroleum ether/ethyl acetate 33:66); UV/vis: λ_{max} (ε) = 331 (13200); fluorescence: λ_{exc} = 337, λ_{em} = 499 nm; ^1H 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 $\{^1H\}$ 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: λ_{max} (ε) = 332 (13800); fluorescence: λ_{exc} = 340, λ_{em} = 505 nm; ^1H 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 $\{^1H\}$ 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 (first column: petroleum ether/ethyl acetate 80:20 → 0:100, second 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: λ_{max} (ε) = 297 (21500), 351 (13700); fluorescence: λ_{exc} = 359, λ_{em} = 455 nm; ^1H 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 $\{^1H\}$ 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 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 preadsorbed 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: λ_{max} (ε) = 297 (20300), 352 (13100); fluorescence: λ_{exc} = 356, λ_{em} = 454 nm; ^1H 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 $\{^1H\}$ 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 × 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 ^1H NMR) besides an unknown side product. ^1H 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 preadsorption on silica gel, purification was carried out by column chromatography (first column: petroleum ether/ethyl acetate 70:30 → 50:50, then chloroform/methanol 95:5; second 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: λ_{max} (ε) = 297 (20700), 352 (13300); fluorescence: λ_{exc} =354, λ_{em} = 455 nm; ^1H 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 $\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ 33.7, 44.8, 49.7,

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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). Then the organic phase was dried over Na_2SO_4 and filtered, and the mixture was preadsorbed 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: λ_{max} (ε) = 300 (20400), 362sh (4800); fluorescence: λ_{exc} = 306, λ_{em} = 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: λ_{max} (ε) = 301 (19400), 358 (4900); fluorescence: λ_{exc} = 325, λ_{em} = 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: λ_{max} (ε) = 302 (20100), 366sh (4800); fluorescence: λ_{exc} = 307, λ_{em} = 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: λ_{max} (ε) = 304 (21400), 368 (5300); fluorescence: λ_{exc} = 309, λ_{em} = 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: λ_{max} (ε) = 323 (16300), 373 (4300); fluorescence: λ_{exc} =328, λ_{em} =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: λ_{max} (ε) = 324 (17400), 370sh (5200); fluorescence: λ_{exc} = 329, λ_{em} = 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: λ_{max} (ε) = 323 (16200), 376sh (4500); fluorescence: λ_{exc} = 329, λ_{em} = 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 =

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0.45 (petroleum ether/ethyl acetate 50:50); UV/vis: λ_{max} (ε) = 324 (18500), 381 (4900); fluorescence: λ_{exc} = 329, λ_{em} = 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**), and 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) 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 nonlinear logistic regression fitting procedure (sigmoidal dose−response model) with Prism Software.

Molecular Docking. The crystal structure of COX-2 (PDB entry: 3ln1) was chosen because within this crystal structure one molecule of celecoxib was cocrystallized in the COX-2 active side. The PDB file 3ln1 was initially processed using MOE program (Schrödinger LLC, New York, NY, 2012). A total of 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 and 50 Å (for **6a** and **6e**), respectively, in regard to the original position of the cocrystallized celecoxib molecule. Ten 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 sites. One hundred 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, for example, His-75 in PDB file 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.

■ ASSOCIATED CONTENT

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. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00537.

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Notes

The authors declare no competing financial interest.

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