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Iodine(III)-Mediated Selective Intermolecular C−H Amination for the Chemical Diversification of Tryptamines

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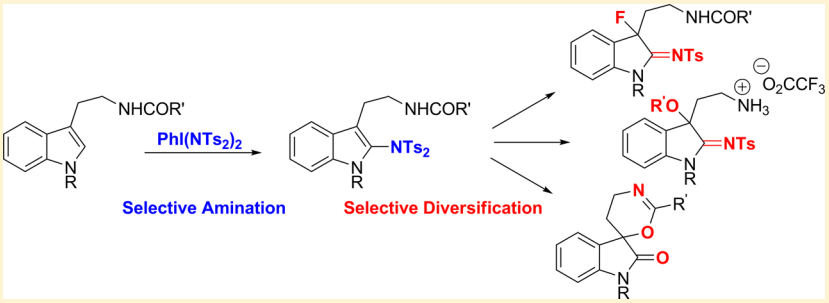
Supporting Information



ABSTRACT: Defined hypervalent iodine reagents of the general structure $PhI[N(SO_2R)(SO_2R')]_2$ promote the selective direct C−H-amination of the indole core of various tryptamines. Starting from a general C2-amination strategy, subsequent transformations enable a variety of site-selective functionalizations, which proceed with noteworthy high chemoselectivity and provide an overall access to structurally diversified products.

INTRODUCTION

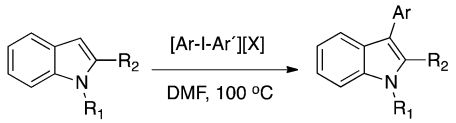
Hypervalent iodine(III) reagents have emerged as versatile tools in modern organic oxidation, where they have contributed to the realization of new chemical transformations.[1,2] The ability of hypervalent iodine(III) reagents to expand synthetic possibilities and their benign reactivity without requirement for metal promoters have stirred particular interest from fields such as pharmaceutical and medicinal chemistry. In these cases, it is preferred that transformations to supply suitable molecules for biological studies do not lead to potential contamination by metal traces.

We have recently been interested in the application of iodine(III) compounds as reagents or catalysts for the synthesis of indoles.[3] Within the quest for new oxidative functionalization of indoles, hypervalent iodine reagents have also been employed with certain success in recent years. In particular, (diacetoxy)iodosobenzene $[PhI(OAc)_2]$ has enabled interesting transformations, such as the direct C3-oxygenation[4] and *trans*-diacetoxylation[5] of N-protected indoles, respectively. Application of alternative hypervalent iodine(III) reagents should provide access to complementary substitution at the indole core. Within this concept, Ackermann disclosed the direct C3-arylation of indoles with diaryliodonium salts (Scheme 1, eq 1).[6]

We recently became interested in the application of hypervalent iodine(III) reagents such as $PhI(NTs_2)_2$[7] with preformed iodine−nitrogen bonds as uniquely active promoters for the selective amination of hydrocarbon molecules.[8,9] This chemistry can either be carried out with preformed reagents or through their in situ generation and greatly surpasses the chemistry of related reagents bearing nitrogen groups, such as phthalimide and saccharin,[10] which require the presence of metal promoters for amination reactions. It has resulted in the development of direct amination reactions, such as allylic,[11,12] acetylenylic,[13] allenylic,[14] and aromatic[3a,7,15] amination reactions, and the diamination of alkenes[16] and butadienes.[17,18] These reagents also enable the position-selective 3-amination of indoles under metal-free conditions (eq 2).[3a] A related process

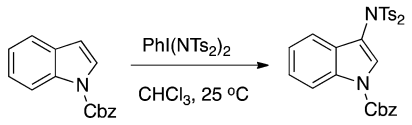
Scheme 1. Iodine(III) Reagents for the Selective 3-Functionalization of Indoles

Iodine-Mediated Direct 3-Arylation of Indoles:



(1)

Iodine-Mediated Direct 3-Amination of Indoles:



(2)

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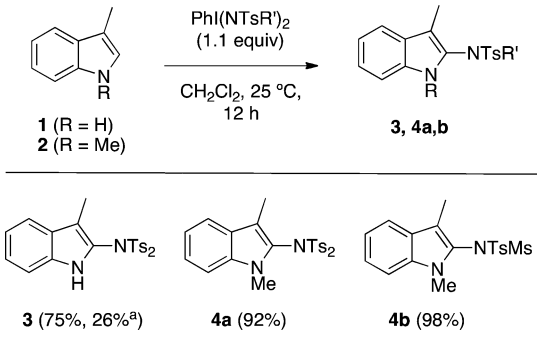
was reported using *N*-fluorobis(benzenesulfonyl)imide as aminating agent.[19] Amination of indoles should be considered a particularly interesting topic given the inherent biological diversification that arises from amine incorporation into the aromatic indole core. Consequently, investigation of protocols for additional selective C−N bond formation is highly desirable. We herein report our general results on this topic and demonstrate that the conceived products can be selectively further diversified into higher-functionalized molecules.

RESULTS AND DISCUSSION

For indoles with a substituted 3-position, as demonstrated by the introduction of a methyl substituent, the amination reaction with $PhI(NTs_2)_2$ takes place selectively at the 2-position (Table 1).

Table 1. Selective 2-Amination of 3-Methylindoles 1 and 2[a]



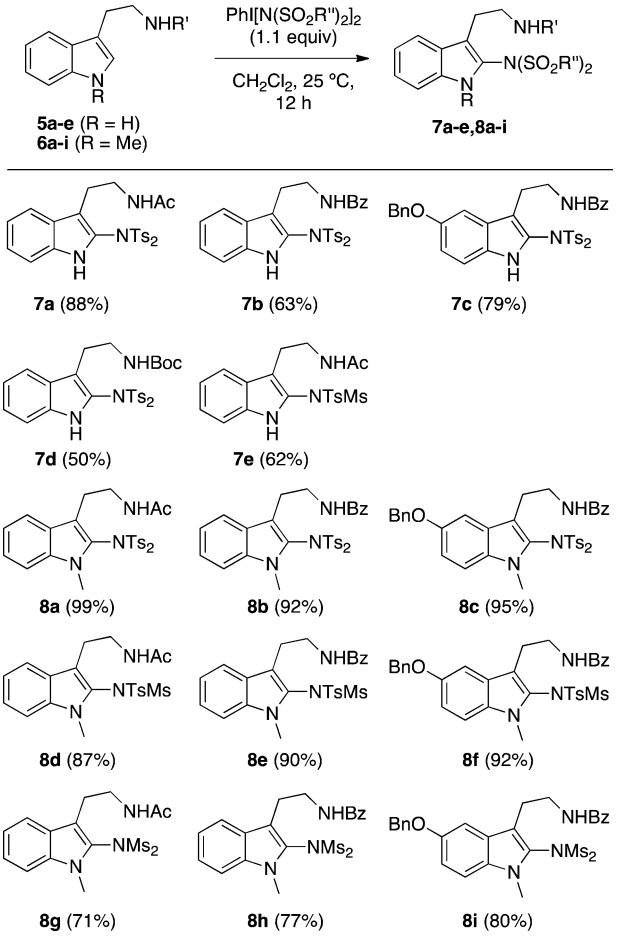
[a]Reaction with $PhI(OAc)_2$/2 $HNTs_2$.

The reaction was explored for free 3-methylindole **1** and its *N*-methylated derivative **2**, both of which underwent 2-bistosylimidation to the corresponding products **3** and **4a** in good yields. Changing the bissulfonimide group in the hypervalent iodine reagent to mesyltosylimide led to formation of **4b** in excellent yield. As demonstrated for **3** as substrate, a reagent combination of (diacetoxy)iodosobenzene and bistosylimide for in situ formation of $PhI(NTs_2)_2$ gives inferior results, which is due to the high reactivity of the indole core. It also appears that N-protected indoles give higher yields, possibly due to the nonproductive reactivity of the N−H bond in **1**, while **2** reacts with complete selectivity. The successful formation of **3** and **4a,b** adds to recent work on iodine-mediated 2-amination of indoles[19−23] and to a recent nonrelated 2-selective amination at the free indole core by Togo and co-workers, who employed our $PhI(OAc)_2$/$HNTs_2$ reagent combination.[15]

Aiming for a higher functional derivatization, we turned attention to tryptamines as the starting point for structural diversification by amination with hypervalent iodine reagents. In the field of tryptamine alkaloids, the hexahydropyrroloindole derivatives derived from intramolecular 2-amination represent common entities that constitute a fascinating class of natural products.[24] Tryptamine and derivatives thereof have therefore been of interest for the exploration of oxidative transformations. Interestingly, the parent oxidant (diacetoxy)iodosobenzene is known to enable aminooxygenation of *N*-acetyltryptamine to form the corresponding 2-acetoxylated fused pyrrolidine products.[25] In another reaction, we had reported a single example that, unlike this reagent, $PhI(NTs_2)_2$ does not provide the corresponding diamination reaction but rather provides access to the corresponding 2-aminated tryptamine product.[7]

Efficient reactions for intermolecular 2-aminations of tryptamines are apparently rare, since they require over-riding the intramolecular cyclization event. We therefore investigated the scope of such a transformation and discovered that the reaction is of general applicability. As outlined in Table 2 for 14

Table 2. Intermolecular 2-Amination of Tryptamines: Scope



examples, differently substituted tryptamines, either free (**5a−e**) or methylated (**6a−i**) at the aromatic nitrogen, underwent clean 2-amination with complete selectivity in favor of the intermolecular pathway. Transferred nitrogen groups include bistosylimide, bismesylimide, and mesyltosylimide alike and the reaction follows the feature from Table 1 that N-protected tryptamines (71−99% isolated yield) give higher yields that the one with a free N−H group (50−88% isolated yield).

The formed 2-aminated tryptamine derivatives should represent interesting starting points for additional amination/cyclization under electrophilic conditions.[24] Such a process appeared of interest and was briefly addressed experimentally. At the outset, electrophilic iodonium generated from established IPy_2BF_4[26] was investigated. Despite experimental variation, the desired iodoamination was never accomplished. Obviously, the size of the bissulfonylimido group at the 2-position of the substrate exercises significant steric shielding of both faces of the C2−C3 double bond of the indole, thus preventing electrophilic activation, even with an iodonium of enhanced electrophilicity. Instead, position-selective iodination

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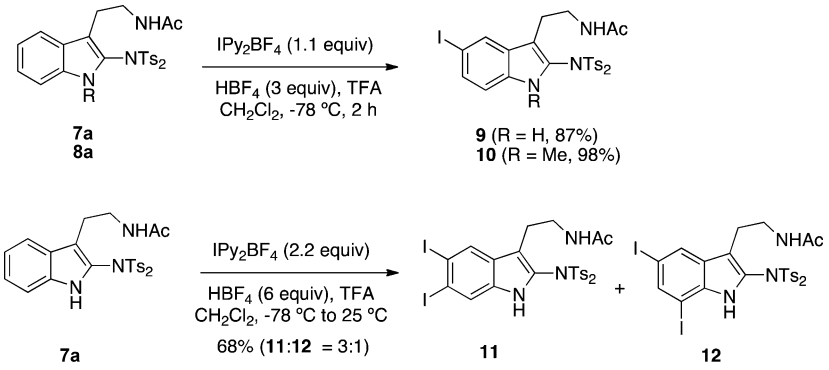
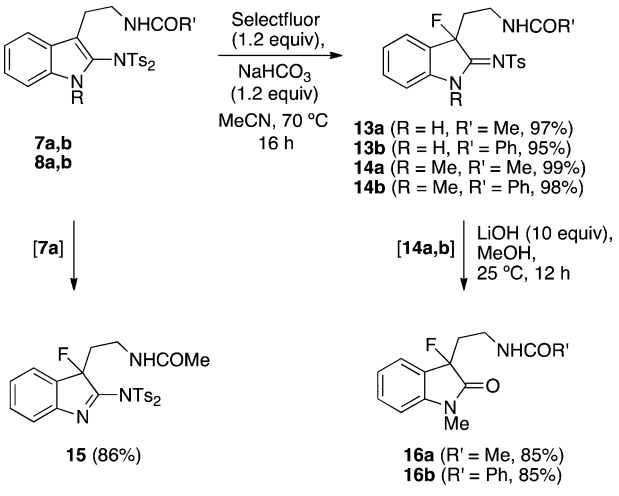
Scheme 2. Iodination of 2-Aminated Tryptamines 7a and 8a



of the arene core was observed, as demonstrated for the reactions of **7a** and **8a**, yielding **9** and **10** in very good to quantitative yield, respectively (Scheme 2).[27] By forcing the reaction with higher amounts of reagent, additional arene iodination took place at the 6- and 7-position of **7a**, respectively.[27] Particularly, the latter is an interesting outcome, since functionalization at the 7-position of the indole is usually complicated.[28] Other common iodonium precursors, such as *N*-iodosuccinimide, or hypervalent iodine reagents, such as bis(trifluoroacetoxy)iodosobenzene,[10a,b] led to no conversion.

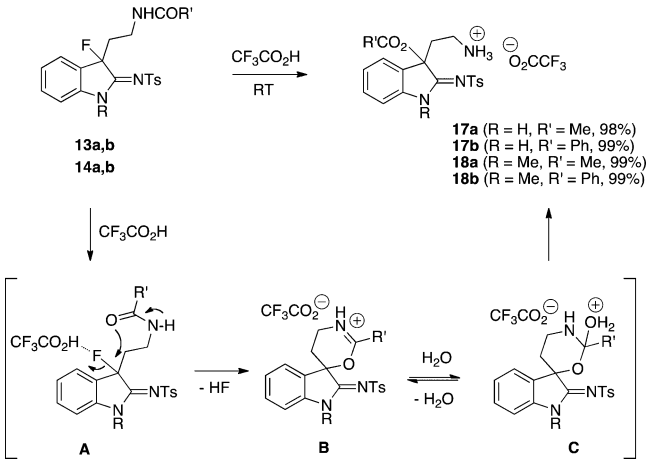
In order to investigate a smaller electrophile, attention was turned to electrophilic fluorination. To this end, a recent report by Gouvernor and co-workers on fluoroamination of tryptamines using Selectfluor set the basis to investigate a possible cyclization.[29a] Although the reported requirement for cinchona alkaloids shut down any reactivity for the present cases, exposing compounds **7a,b** and **8a,b**, respectively, to the presence of Selectfluor and base resulted in clean fluorination.[29] However, despite several attempts, no accompanying cyclization could be accomplished, but rather, detosylation resulted in an imino group at C2 to produce the so far unknown amidine products **13a,b** and **14a,b** (Scheme 3). Under these conditions, products **13a,b** and **14a,b** were obtained in almost quantitative yields. These transformations were considered to involve an initial participation of the lone pair of the nitrogen of the indole core. This assumption could be confirmed when the reaction of **7a** was conducted for a shorter period of time, which led to the isolation of compound **15** as the major product in 86% yield. Exposure of **15** to an additional period of heating in acetonitrile led to unprecedented detosylation and formation of **13a** as the only product.

Scheme 3. Chemical Transformation of Compounds 7a,b and 8a,b upon Electrophilic Fluorination



The treatment of **14a,b** with lithium hydroxide in methanol provided conditions for a clean hydrolysis of their tosylimido groups, leading to their conversion into the corresponding new oxindole derivatives **16a,b**. Again, this transformation is completely selective and the two compounds are isolated as the only products in 85% yield each. When fluorinated compounds **13a,b** and **14a,b** were exposed to acidic conditions with neat trifluoroacetic acid (TFA), clean defluorination was observed (Scheme 4).

Scheme 4. Chemical Transformation of Compounds 13a,b and 14a,b



These conditions led to nucleophilic substitution by the *N*-acetyl and *N*-benzoyl groups from the ethylenylamine side chain at the benzylic position. Upon exposure to moisture during crystallization, they converted in quantitative yields into the benzylic esters **17a,b** and **18a,b**, respectively, bearing an ammonium trifluoroacetate group in the side chain.[16] This overall transformation initiates from **A** upon activation of the benzylic fluoride in the presence of TFA as a strong acid, thereby greatly enhancing its leaving group quality. Subsequently, intermediate **B** forms via intramolecular nucleophilic substitution followed by reversible addition of water to **C**, from which an intramolecular proton shift affords the products. Note that in the presence of basic conditions, compounds **13a,b** and **14a,b** retain the benzylic fluoride moiety. Exposure of products

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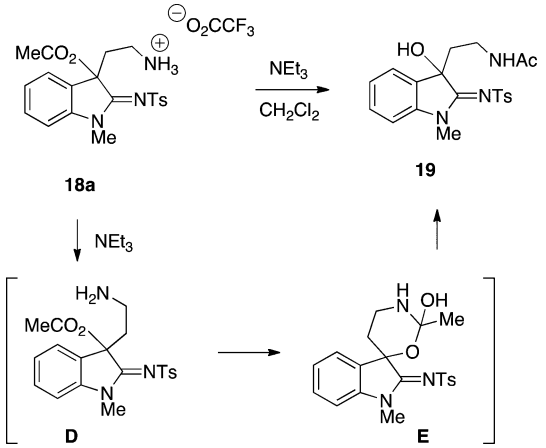
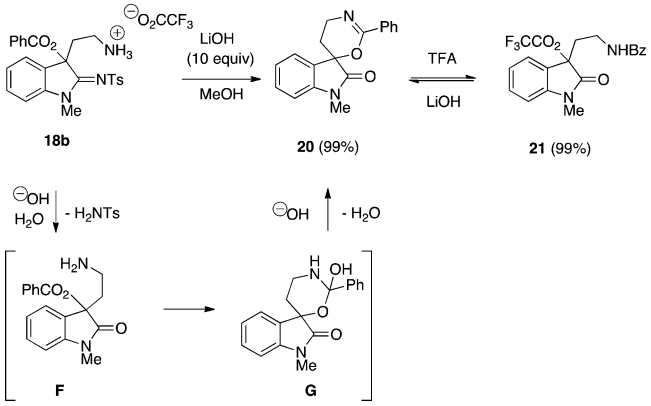
17a,b and **18a,b** to basic conditions affords additional diversification. Treatment with triethylamine generates a free primary amine **D** from **18a**, which initiates quantitative intramolecular acetyl transfer via the tetrahedral intermediate **E** to reestablish the acetamide side chain and provides a benzylic hydroxyl group in **19** (Scheme 5).[27]

Scheme 5. Chemical Transformation of Compound 18a to 19



In contrast, treatment with stronger LiOH base promotes the expected oxindole formation together with the installment of a spiro-dihydrooxazine functionality in **20**.[27] Again, this multiple transformation starts from liberation of the free primary amine **F** and proceeds through the corresponding tetrahedral intermediate **G** with complete selectivity and in quantitative isolated yield (Scheme 6).

Scheme 6. Chemical Transformation of Compound 18b to 21



In the presence of TFA, compound **20** undergoes quantitative opening of the spiro-cyclic arrangement upon concomitant addition of one molecule of TFA to furnish **21** with its benzoylamide side chain and a benzylic trifluoroacetate ester. Exposure to LiOH reverts **21** back to **20** in essentially quantitative manner. These transformations provide access to a unique number of new tryptamine derivatives. In view of the general occurrence of the 3-(aminoethyl)-3-hydroxyoxindole motif (Figure 1),[30] our new methodology provides unique access to derivatives of this core and to the additional, yet

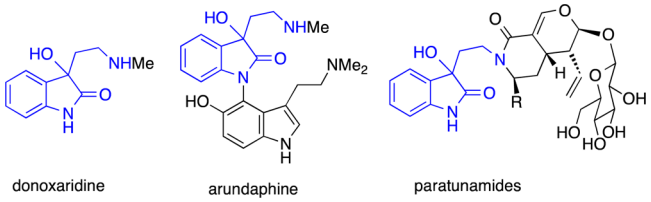


Figure 1. Examples for naturally occurring 3-(aminoethyl)-3-hydroxyoxindoles.

biologically unexplored, classes of 2-imido and allosteric 3-fluoro[31] derivatives.

In summary, we have developed a general strategy for intermolecular C2-amination of indoles and tryptamines. This transformation proceeds selectively in the presence of hypervalent iodine reagents of the general formula PhI[N(SO_2R)(SO_2R′)]$_2$. The corresponding products undergo oxidative fluorination under parallel desulfonylation to provide a new class of tryptamine derivatives. These compounds initiate a number of remarkable transformations, with and without interplay by the ethylenamine side chain. As a result, a higher degree of structural variation is now available for tryptamine derivatives, providing building blocks for future exploration.

EXPERIMENTAL SECTION

General Remarks. Chemicals and solvents for chromatography were used as received. Solvents were obtained from a solvent purification system. Reactions that were monitored by TLC were visualized by a dual short-wave/long-wave UV lamp. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded using an internal deuterium lock on a 300 or a 500 MHz spectrometer. All chemical shifts in NMR experiments are reported as ppm downfield from TMS. *J* couplings are reported in hertz. The following calibrations were used: $CDCl_3$, δ = 7.26 and 77.0 ppm; CD_2Cl_2, δ = 5.32 and 54.00 ppm; MeOD, δ = 3.31 and 49.0 ppm. Infrared spectra were taken in the solid state and were recorded on a FT-IR fitted with an ATR accessory. Absorptions are given in wavenumbers (cm^{-1}). High-resolution mass spectra were obtained on a HRMS-TOF spectrometer.

The following compounds were purchased form commercial suppliers and used as received: tryptamine, 5-benzyloxytryptamine, tosyl chloride, mesyl chloride, triethylamine, acetyl chloride, benzoyl chloride, methyl iodide, trifluoroacetic acid, lithium hydroxide, di(acetoxy)iodobenzene, bis(pyridine)iodonium tetrafluoroborate, tetrafluoroboric acid diethyl etherate, Selectfluor, and 3-methylindole (**1**). The following compounds were synthesized according to literature procedures: **2**,[32] **5a**,[33] **5b**,[7] **5c**,[34] **5d**,[35] **6a**,[33] and **6b**.[33]

*N-(2-(5-(Benzyloxy)-1-methyl-1H-indol-3-yl)ethyl)benzamide (**6c**).* A mixture of the indole **5c**[33] (0.18 g, 0.5 mmol, 1.0 equiv), NaOH (0.06 g, 1.5 mmol, 3 equiv), and Bu_4NOH (8 mg, 0.025 mmol, 5% mol) in CH_2Cl_2 (5 mL) was stirred at 25 °C for 10 min. MeI (0.08 g, 0.55 mmol, 1.1 equiv) was added into the reaction mixture at 25 °C. The reaction mixture was stirred for 12 h. The reaction mixture was quenched with an aqueous solution of 10% HCl and then with an aqueous saturated solution of $NaHCO_3$ and was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, MeOH/CH_2Cl_2, 0.2/10, v/v) to afford the pure product (0.096 g, 50% yield, colorless oil). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.95 (t, *J* = 6.6 Hz, 2H), 3.63−3.70 (m, 5H), 3.79 (td, *J* = 6.8, 6.1 Hz, 2H), 4.91 (s, 2H), 6.22 (s, 1H), 6.80 (s, 1H), 6.88 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.05 (d, *J* = 2.4 Hz, 1H), 7.12 (d, *J* = 8.8 Hz, 1H), 7.22−7.36 (m, 8H), 7.58−7.61 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 25.3 (CH_2), 32.8 (CH_3), 40.7 (CH_2), 71.0 (CH_2), 102.3, 110.2, 111.2, 112.8, 126.9, 127.5, 127.7, 127.8, 128.1, 128.5, 128.6, 131.3, 132.7, 134.7, 137.6, 153.1, 167.4 (C═O). IR ν (cm^{-1}): 3316 (N−H), 3029 (Ar−H), 2926 (Ar−H), 2860 (Ar−H), 1625

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(C═O), 1542, 1488, 1462, 1317, 1218, 1198, 1021, 795, 695. HRMS (ESI-TOF): calcd for $C_{25}H_{25}N_2O_2$ 385.1911, found 385.1914.

General Procedure for Amination Reaction Indoles and Tryptamines. To a solution of the corresponding starting material (0.2 mmol, 1.0 equiv) in CH_2Cl_2 (2.0 mL) was added the corresponding iodine(III) reagent (0.22 mmol, 1.1 equiv), and the mixture was stirred at 25 °C for 12 h. After that time, the solvent was removed under reduced pressure and the crude mixture was purified by column chromatography (silica gel, MeOH/CH_2Cl_2, 0.2/10, v/v) to obtain the pure product.

*4-Ethyl-N-(3-methyl-1H-indol-2-yl)-N-tosylbenzenesulfonamide (**3**).* Yield: 70 mg, 75%, white solid. Mp: 164−165 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.69 (s, 3H), 2.48 (s, 6H), 7.14 (m, 1H), 7.28−7.31 (m, 2H), 7.34 (d, J = 7.7 Hz, 4H), 7.51 (d, J = 8.0 Hz, 1H), 7.82 (brs, 1H), 7.86 (d, J = 8.4 Hz, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 8.0 (CH_3), 21.8 (CH_3), 111.4, 115.6, 119.9, 120.0, 122.7, 124.1, 127.5, 128.6, 129.7, 135.0, 136.4, 145.3. IR ν (cm^{-1}): 3385 (N−H), 2956 (Ar−H), 2923 (Ar−H), 2851 (Ar−H), 1595, 1372, 1345, 1169, 1082, 881, 657, 549. HRMS (ESI-TOF): calcd for $C_{23}H_{21}N_2O_4S_2$ 453.0943, found 453.0927.

*N-(1,3-Dimethyl-1H-indol-2-yl)-4-methyl-N-tosylbenzenesulfonamide (**4a**).* Yield: 85 mg, 92%, brown solid. Mp: 194−196 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.66 (s, 3H), 2.40 (s, 6H), 3.19 (s, 3H), 7.03−7.08 (m, 1H), 7.15−7.23 (m, 2H), 7.26 (d, J = 7.7 Hz, 4H), 7.46 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 8.4 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 8.7 (CH_3), 21.8 (CH_3), 29.5 (CH_3), 109.8, 113.8, 119.4, 120.0, 123.7, 124.6, 126.4, 129.0, 129.7, 136.0, 136.4, 145.5. IR ν (cm^{-1}): 3055 (Ar−H), 2922 (Ar−H), 1594, 1469, 1372, 1357, 1166, 1084, 878, 738. HRMS (ESI-TOF): calcd for $C_{24}H_{24}N_2NaO_4S_2$ 491.1070, found 491.1065.

*N-(1,3-dimethyl-1H-indol-2-yl)-4-methyl-N-(methylsulfonyl)-benzenesulfonamide (**4b**).* Yield: 76 mg, 98%, yellow solid. Mp: 189−191 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.01 (s, 3H), 2.49 (s, 3H), 3.44 (s, 3H), 3.61 (s, 3H), 7.14−7.19 (m, 1H), 7.24−7.32 (m, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 7.9 Hz, 1H), 7.83 (d, J = 8.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 8.8 (CH_3), 21.8 (CH_3), 29.4 (CH_3), 44.4 (CH_3), 109.8, 113.5, 119.5, 120.0, 123.8, 126.3, 129.2, 129.7, 135.1, 135.9, 145.9. IR ν (cm^{-1}): 3055 (Ar−H), 2931 (Ar−H), 1469, 1369, 1354, 1163, 1121, 1087, 966, 872, 737. HRMS (ESI-TOF): calcd for $C_{18}H_{20}N_2NaO_4S_2$ 415.0757, found 415.0743.

*N-(2-(2-(4-Methyl-N-tosylphenylsulfonamido)-1H-indol-3-yl)-ethyl)acetamide (**7a**).* Yield: 87 mg, 83%, white solid. Mp: 170−171 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.79 (s, 3H), 2.16−2.20 (t, J = 6.7, 2H), 2.48 (s, 6H), 3.53 (td, J = 6.2, 5.8 Hz, 2H), 6.24 (brs, 1H), 7.13−7.17 (m, 1H), 7.28−7.35 (m, 2H), 7.36 (d, J = 8.1 Hz, 4H), 7.62 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.4 Hz, 4H), 8.30 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.8 (CH_3), 22.9 (CH_3), 23.0 (CH_2), 38.6 (CH_2), 111.8, 116.2, 120.3, 120.4, 123.4, 124.5, 126.4, 128.7, 129.9, 135.2, 135.8, 145.9, 170.4 (C═O). IR ν (cm^{-1}): 3376 (N−H), 3257 (N−H), 2922 (Ar−H), 1659 (C═O), 1536, 1377, 1353, 1167, 876, 773, 659, 540. HRMS (ESI-TOF): calcd for $C_{26}H_{27}N_3O_5NaS_2$ 548.1290, found 548.1277.

*N-(2-(2-(4-Methyl-N-tosylphenylsulfonamido)-1H-indol-3-yl)-ethyl)benzamide (**7b**).*[7] Yield: 74 mg, 63%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.37 (t, J = 6.7 Hz, 2H), 2.47 (s, 6H), 3.73 (td, J = 6.7, 5.1 Hz, 2H), 6.67 (brs, 1H), 7.10−7.15 (m, 1H), 7.28−7.39 (m, 9H), 7.66−7.69 (m, 2H), 7.72 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 8.4 Hz, 4H), 8.02 (brs, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.8 (CH_3), 23.2 (CH_2), 39.3 (CH_2), 111.7, 116.3, 120.4, 120.7, 123.2, 124.5, 126.6, 127.1, 128.2, 128.7, 129.9, 131.1, 134.4, 135.1, 135.9, 145.8, 167.7 (C═O).

*N-(2-(5-(Benzyloxy)-2-(4-methyl-N-tosylphenylsulfonamido)-1H-indol-3-yl)ethyl)benzamide (**7c**).* Yield: 110 mg, 80%, brown solid. Mp: 109−111 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33 (t, J = 6.6 Hz, 2H), 2.48 (s, 6H), 3.70 (td, J = 6.6, 5.2 Hz, 2H), 4.94 (s, 2H), 6.65 (t, J = 5.2 Hz, 1H), 7.00 (dd, J = 8.8, 2.4 Hz, 1H), 7.19 (d, J = 2.4 Hz, 1H), 7.23 (d, J = 8.9 Hz, 1H), 7.30−7.43 (m, 12H), 7.68−7.70 (m, 2H), 7.85−7.88 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.8 (CH_3), 23.2 (CH_2), 39.2 (CH_2), 70.6 (CH_2), 103.0, 112.6, 116.0, 116.2, 123.6, 127.1, 127.8, 127.8, 128.3, 128.5, 128.7, 130.0, 130.2, 130.3, 131.1, 134.4, 135.9, 137.2, 137.5, 145.8, 153.6, 167.6 (C═O). IR ν (cm^{-1}): 3384 (N−H), 3191 (Ar−H), 3059 (Ar−H), 2922 (Ar−H), 1640 (C═O), 1579, 1485, 1376, 1187, 1165, 1083, 882. HRMS (ESI-TOF): calcd for $C_{38}H_{35}N_3NaO_6S_2$ 716.1859, found 716.1863.

*tert-Butyl (2-(2-(4-Methyl-N-tosylphenylsulfonamido)-1H-indol-3-yl)ethyl)carbamate (**7d**).* Yield: 58 mg, 50%, yellow solid. Mp: 102−107 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (s, 9H), 2.26 (t, J = 7.2 Hz, 2H), 2.48 (s, 6H), 3.24−3.29 (m, 2H), 4.73 (brs, 1H), 7.12−7.16 (m, 1H), 7.28−7.30 (m, 2H), 7.35 (d, J = 7.9 Hz, 4H), 7.68 (d, J = 7.8 Hz, 1H), 7.86 (d, J = 8.4 Hz, 4H), 7.99 (brs, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.7 (CH_3), 24.2 (CH_2), 28.4 (CH_3), 39.8 (CH_2), 78.8, 111.5, 116.6, 120.1, 120.7, 122.9, 124.2, 126.7, 128.7, 129.8, 135.0, 136.0, 145.6, 155.9 (C═O). IR ν (cm^{-1}): 3294 (N−H), 2927 (Ar−H), 1632 (C═O), 1580, 1470, 1282, 1145, 1082, 770, 751, 671, 545, 461. HRMS (ESI-TOF): calcd for $C_{29}H_{33}N_3O_6NaS_2$ 606.1708, found 606.1690.

*N-(2-(2-(4-Methyl-N-(methylsulfonyl)phenylsulfonamido)-1H-indol-3-yl)ethyl)acetamide (**7e**).* Yield: 52 mg, 58%, yellow solid. Mp: 166−172 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.83 (s, 3H), 2.28−2.36 (m, 1H), 2.48 (s, 3H), 2.58−2.64 (m, 1H), 3.57 (td, J = 6.1, 5.5 Hz, 2H), 3.64 (s, 3H), 6.02 (s, 1H), 7.15−7.18 (m, 1H), 7.31−7.35 (m, 4H), 7.64 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 8.4 Hz, 2H), 8.10 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.8 (CH_3), 23.0 (CH_2), 23.3 (CH_3), 38.6 (CH_2), 44.2 (CH_3), 111.8, 115.3, 120.2, 120.3 122.8, 124.4, 126.2, 128.9, 129.9, 134.6, 135.1, 146.2, 170.7 (C═O). IR ν (cm^{-1}): 3358 (N−H), 2928 (Ar−H), 2880 (Ar−H), 1646 (C═O), 1550, 1369, 1347, 1165, 976, 877, 744, 664, 520. HRMS (ESI-TOF): calcd for $C_{20}H_{23}N_3O_5NaS_2$ 472.0966, found 472.0977.

*N-(2-(1-Methyl-2-((4-methyl-N-tosylphenyl)sulfonamido)-1H-indol-3-yl)ethyl)acetamide (**8a**).* Yield: 107 mg, 99%, yellow solid. Mp: 189−190 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.82 (s, 3H), 2.25 (t, J = 6.5 Hz, 2H), 2.53 (s, 6H), 3.36 (s, 3H), 3.57−3.61 (m, 2H), 6.20 (brs, 1H), 7.17−7.20 (m, 1H), 7.32 (d, J = 8.3 Hz, 1H), 7.36−7.39 (m, 1H), 7.40 (d, J = 7.8 Hz, 4H), 7.70 (d, J = 8.1 Hz, 1H), 7.90 (d, J = 8.4 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.8 (CH_3), 23.0 (CH_3), 23.7 (CH_2), 30.0 (CH_3), 38.8 (CH_2), 110.2, 114.7, 120.0, 120.6, 124.1, 125.1, 125.5, 129.2, 129.8, 135.8, 136.3, 146.0, 170.3 (C═O). IR ν (cm^{-1}): 3399 (N−H), 3059 (Ar−H), 2928 (Ar−H), 1652 (C═O), 1595, 1534, 1471, 1431, 1373, 1358, 1166, 1083, 1017. HRMS (ESI-TOF): calcd for $C_{27}H_{30}N_3O_5S_2$ 540.1621, found 540.1630.

*N-(2-(1-Methyl-2-(4-methyl-N-tosylphenyl)sulfonamido)-1H-indol-3-yl)ethyl)benzamide (**8b**).* Yield: 110 mg, 92%, yellow solid. Mp: 178−180 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.46 (t, J = 6.9 Hz, 2H), 2.51 (s, 6H), 3.28 (s, 3H), 3.83 (td, J = 6.9, 5.1 Hz, 2H), 6.70 (t, J = 5.0 Hz, 1H), 7.15−7.18 (m, 1H), 7.28−7.30 (m, 1H), 7.33−7.36 (m, 3H), 7.39−7.44 (m, 5H), 7.70−7.73 (m, 2H), 7.81 (d, J = 8.1 Hz, 1H), 7.92 (d, J = 8.4 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.8 (CH_3), 23.9 (CH_2), 29.8 (CH_3), 39.5 (CH_2), 110.1, 114.6, 120.0, 120.9, 124.0, 125.1, 125.6, 127.0, 128.2, 129.1, 129.8, 131.0, 134.5, 135.9, 136.2, 145.9, 167.6 (C═O). IR ν (cm^{-1}): 3242 (N−H), 3069 (Ar−H), 2923 (Ar−H), 1630 (C═O), 1549, 1492, 1470, 1386, 1357, 1334, 1169, 1084, 1016. HRMS (ESI-TOF): calcd for $C_{33}H_{27}N_7NaOS_2$ 624.1611, found 624.1612.

*N-(2-(5-(Benzyloxy)-1-methyl-2-(4-methyl-N-tosylphenylsulfonamido)-1H-indol-3-yl)ethyl)benzamide (**8c**).* Yield: 133 mg, 95%, orange solid. Mp: 168−170 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.41 (t, J = 6.7 Hz, 2H), 2.51 (s, 6H), 3.26 (s, 3H), 3.80 (td, J = 6.8, 5.2 Hz, 2H), 5.02 (s, 2H), 6.68 (t, J = 5.2 Hz, 1H), 7.08 (dd, J = 8.9, 2.3 Hz, 1H), 7.20 (d, J = 8.9 Hz, 1H), 7.28 (d, J = 2.1 Hz, 1H), 7.33−7.42 (m, 10H), 7.46−7.48 (m, 2H), 7.71−7.73 (m, 2H), 7.91−7.93 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.8 (CH_3), 23.9 (CH_2), 29.9 (CH_3), 39.4 (CH_2), 70.7 (CH_2), 103.1, 111.1, 114.2, 125.2, 125.8, 127.0, 127.1, 127.7, 127.8, 128.3, 128.4, 128.5, 129.1, 129.8, 129.9, 131.1, 131.6, 134.5, 135.9, 137.3, 145.9, 153.4, 167.6 (C═O). IR ν (cm^{-1}): 339 (N−H), 3032 (Ar−H), 2924 (Ar−H), 1645 (C═O), 1596, 1487, 1374, 1166, 1083, 1019, 872. HRMS (ESI-TOF): calcd for $C_{39}H_{37}N_3NaO_6S_2$ 730.2016, found 730.2048.

*N-(2-(1-Methyl-2-((4-methyl-N-(methylsulfonyl)phenyl)-sulfonamido)-1H-indol-3-yl)ethyl)acetamide (**8d**).* Yield: 80 mg,

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87%, yellow solid. Mp: 119−121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.84 (s, 3H), 2.39−2.44 (m, 1H), 2.50 (s, 3H), 2.68−2.73 (m, 1H), 3.39 (s, 3H), 3.54−3.60 (m, 1H), 3.62−3.68 (m, 1H), 3.73 (s, 3H), 5.95 (s, 1H), 7.17−7.20 (m, 1H), 7.31 (d, J = 8.3 Hz, 1H), 7.35−7.37 (m, 3H), 7.68 (d, J = 8.1 Hz, 1H), 7.78 (d, J = 8.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.8 (CH_3), 23.0 (CH_3), 24.1 (CH_2), 29.5 (CH_3), 38.9 (CH_2), 44.6 (CH_3), 110.2, 114.4, 120.1, 120.4, 124.2, 124.6, 125.3, 129.2, 129.9, 134.5, 136.2, 146.3, 170.4 (C═O). IR ν (cm^{-1}): 3316 (N−H), 3017 (Ar−H), 2982 (Ar−H), 2936 (Ar−H), 1642 (C═O), 1549, 1448, 1368, 1355, 1345, 1295, 1167, 1087. HRMS (ESI-TOF): calcd for $C_{21}H_{25}N_3NaO_5S_2$ 486.1128, found 486.1135.

*N-(2-(1-Methyl-2-(4-methyl-N-(methylsulfonyl)phenyl)-sulfonamido)-1H-indol-3-yl)ethyl)benzamide (**8e**).* Yield: 94 mg, 90%, yellow solid. Mp: 182−184 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.48 (s, 3H), 2.57−2.67 (m, 1H), 2.81−2.90 (m, 1H), 3.36 (s, 3H), 3.66 (s, 3H), 3.81−3.89 (m, 2H), 6.55 (s, 1H), 7.14−7.19 (m, 2H), 7.30−7.39 (m, 5H), 7.42−7.45 (m, 1H), 7.68−7.71 (m, 2H), 7.75−7.80 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.8 (CH_3), 24.4 (CH_2), 29.4 (CH_3), 39.6 (CH_2), 44.5 (CH_3), 110.1, 114.4, 120.1, 120.6, 124.1, 124.5, 125.4, 127.1, 128.3, 129.2, 129.9, 131.2, 134.4, 134.6, 136.2, 146.3, 167.7 (C═O). IR ν (cm^{-1}): 3300 (N−H), 3043 (Ar−H), 2929 (Ar−H), 1636 (C═O), 1598, 1579, 1538, 1488, 1470, 1429, 1356, 1309, 1165, 1086. HRMS (ESI-TOF): calcd for $C_{26}H_{27}N_3NaO_5S_2$ 548.1284, found 548.1291.

*N-(2-(5-(Benzyloxy)-1-methyl-2-(4-methyl-N-(methylsulfonyl)-phenyl sulfonamido)-1H-indol-3-yl)ethyl)benzamide (**8f**).* Yield: 115 mg, 92%, orange solid. Mp: 146−148 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.49 (s, 3H), 2.52−2.62 (m, 1H), 2.77−2.87 (m, 1H), 3.34 (s, 3H), 3.66 (s, 3H), 3.83 (td, J = 6.6, 6.0 Hz, 2H), 5.04 (q, J = 11.4 Hz, 2H), 6.53 (t, J = 5.5 Hz, 1H), 7.07 (dd, J = 8.9, 2.4 Hz, 1H), 7.20 (d, J = 8.9 Hz, 1H), 7.24 (d, J = 2.4 Hz, 1H), 7.34−7.47 (m, 10H), 7.69−7.72 (m, 2H), 7.80 (d, J = 8.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.8 (CH_3), 24.4 (CH_2), 29.6 (CH_3), 39.6 (CH_2), 44.5 (CH_3), 70.7 (CH_2), 103.0, 111.1, 113.9, 115.7, 124.6, 125.6, 127.1, 127.7, 128.4, 128.5, 129.2, 129.9, 131.2, 131.6, 134.4, 134.6, 136.2, 137.2, 146.3, 167.6 (C═O). IR ν (cm^{-1}): 3410 (N−H), 3033 (Ar−H), 2928 (Ar−H), 1648 (C═O), 1486, 1370, 1353, 1163, 1086, 1025, 966, 873. HRMS (ESI-TOF): calcd for $C_{33}H_{33}N_3NaO_6S_2$ 654.1703, found 654.1709.

*N-(2-(1-Methyl-2-(N-(methylsulfonyl)methylsulfonamido)-1H-indol-3-yl)ethyl)acetamide (**8g**).* Yield: 54 mg, 71%, white solid. Mp: 209−210 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.90 (s, 3H), 3.06 (t, J = 7.1 Hz, 2H), 3.55 (s, 6H), 3.74−3.78 (m, 5H), 5.99 (s, 1H), 7.19−7.23 (m, 1H), 7.36−7.41 (m, 2H), 7.73 (d, J = 8.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 23.1 (CH_3), 25.1 (CH_2), 29.8 (CH_3), 38.9 (CH_2), 43.3 (CH_3), 110.2, 114.0, 120.3, 120.4, 124.1, 124.4, 125.3, 136.3, 170.4 (C═O). IR ν (cm^{-1}): 3425 (N−H), 3023 (Ar−H), 3002 (Ar−H), 2942 (Ar−H), 2923 (Ar−H), 1663 (C═O), 1531, 1469, 1361, 1347, 1290, 1225, 1158, 1101. HRMS (ESI-TOF): calcd for $C_{15}H_{21}N_3NaO_5S_2$ 410.0815, found 410.0815.

*N-(2-(1-Methyl-2-(N-(methylsulfonyl)methylsulfonamido)-1H-indol-3-yl)ethyl)benzamide (**8h**).* Yield: 69 mg, 77%, white solid. Mp: 166−168 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.19 (t, J = 7.0 Hz, 2H), 3.53 (s, 6H), 3.76 (s, 3H), 3.99 (td, J = 7.0, 5.6 Hz, 2H), 6.59 (s, 1H), 7.18−7.22 (m, 1H), 7.36−7.42 (m, 4H), 7.46−7.50 (m, 1H), 7.72−7.75 (m, 2H), 7.82 (d, J = 8.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 25.3 (CH_2), 29.8 (CH_3), 39.6 (CH_2), 43.2 (CH_3), 110.1, 114.0, 120.4, 120.6, 124.0, 124.4, 125.4, 127.0, 128.4, 131.3, 134.3, 136.3, 167.7 (C═O). IR ν (cm^{-1}): 3308 (N−H), 2932 (Ar−H), 1630 (C═O), 1543, 1472, 1355, 1311, 1164, 962, 874, 748. HRMS (ESI-TOF): calcd for $C_{20}H_{23}N_3NaO_5S_2$ 472.0971, found 472.0979.

*N-(2-(5-(Benzyloxy)-1-methyl-2-(N-(methylsulfonyl)-methylsulfonamido)-1H-indol-3-yl)ethyl)benzamide (**8i**).* Yield: 89 mg, 80%, brown solid. Mp: 157−159 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.12 (t, J = 6.9 Hz, 2H), 3.50 (s, 6H), 3.70 (s, 3H), 3.89−3.94 (m, 2H), 5.03 (s, 2H), 6.55 (t, J = 5.5 Hz, 1H), 7.08 (dd, J = 9.0, 2.4 Hz, 1H), 7.23−7.27 (m, 2H), 7.31−7.45 (m, 8H), 7.70−7.72 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 25.1 (CH_2), 30.0 (CH_3), 39.5 (CH_2), 43.2 (CH_3), 70.8 (CH_2), 103.2, 111.2, 113.5, 115.9, 124.1, 125.6, 127.1, 127.7, 127.9, 128.4, 128.5, 131.4, 131.7, 134.3, 137.2, 153.6, 167.7 (C═O). IR ν (cm^{-1}): 3341 (N−H), 3062 (Ar−H), 3033 (Ar−H), 2930 (Ar−H), 1711 (C═O), 1651, 1532, 1488, 1451, 1366, 1279, 1162, 1128, 1022, 875, 727, 694. HRMS (ESI-TOF): calcd for $C_{27}H_{29}N_3NaO_6S_2$ 578.1390, found 578.1403.

*N-(2-(5-Iodo-2-(4-methyl-N-tosylphenylsulfonamido)-1H-indol-3-yl)ethyl)acetamide (**9**).* To a stirred solution of acetamide **7a** (47.8 mg, 0.091 mmol, 1 equiv) and TFA (2 mL) in CH_2Cl_2 (20 mL) at −78 °C were added $HBF_4{\cdot}Et_2O$ (0.038 mL, 0.3 mmol, 3 equiv) and bis(pyridine)iodonium tetrafluoroborate (0.034 g, 0.091 mmol, 1 equiv). The brown solution was stirred for 2 h. The reaction was quenched with cold water. The two phases were separated, and the organic layer was washed with water and an aqueous saturated solution of sodium thiosulfate. The organic phase was dried over Na_2SO_4, and the solvent was removed under reduced pressure to obtain a crude product, which was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 1/1, v/v) to afford the pure product (46 mg, 78% yield, white solid). Mp: 187−191 °C. ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 1.79 (s, 3H), 2.15 (t, J = 6.7 Hz, 2H), 2.48 (s, 6H), 3.35 (td, J = 6.2, 5.7 Hz, 2H), 7.17 (d, J = 8.7 Hz, 1H), 7.39 (d, J = 7.8 Hz, 4H), 7.52 (dd, J = 8.6, 1.6 Hz, 1H), 7.80 (d, J = 7.8 Hz, 4H), 7.96 (s, 1H). ^{13}C NMR (101 MHz, CD_2Cl_2): δ = 21.9 (CH_3), 22.9 (CH_3), 23.4 (CH_2), 39.1 (CH_2), 83.4 (C−I), 114.3, 115.0, 124.2, 129.0, 129.1, 129.4, 130.3, 132.8, 134.6, 136.1, 146.7, 171.6 (C═O). IR ν (cm^{-1}): 3379 (N−H), 3170 (Ar−H), 2921 (Ar−H), 2582 (Ar−H), 2366 (Ar−H), 1643 (C═O), 1596, 1376, 1353, 1165, 879, 660, 542. HRMS (ESI-TOF): calcd for $C_{26}H_{26}IN_3O_5NaS_2$ 674.0256, found 674.0279.

*N-(2-(5-Iodo-1-methyl-2-(4-methyl-N-tosylphenylsulfonamido)-1H-indol-3-yl)ethyl)acetamide (**10**).* Compound **10** was synthesized from **4a** through an identical procedure as that described for compound **9**. Yield: 59 mg, 98%, white solid. Mp: 196−197 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.82 (s, 3H), 2.15 (t, J = 6.4 Hz, 2H), 2.50 (s, 6H), 3.31 (s, 3H), 3.48−3.52 (m, 2H), 6.11 (t, J = 6.1 Hz, 1H), 7.07 (d, J = 8.7 Hz, 1H), 7.38 (d, J = 8.1 Hz, 4H), 7.58 (dd, J = 8.8, 1.6 Hz, 1H), 7.85 (d, J = 8.4 Hz, 4H), 7.98 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.8 (CH_3), 23.0 (CH_3), 23.5 (CH_2), 30.0 (CH_3), 38.9 (CH_2), 83.4 (C−I), 112.2, 114.1, 125.7, 127.8, 129.1, 129.3, 129.9, 132.4, 135.2, 135.5, 146.13, 170.3 (C═O). IR ν (cm^{-1}): 3290 (N−H), 2923 (Ar−H), 2853 (Ar−H), 1651 (C═O), 1372, 1166, 873, 659, 542, 478. HRMS (ESI-TOF): calcd for $C_{27}H_{28}IN_3O_5NaS_2$ 688.0413, found 688.0437.

*N-(2-(5,6-Diiodo-2-(4-methyl-N-tosylphenylsulfonamido)-1H-indol-3-yl)ethyl)acetamide (**11**) and N-(2-(5,7-Diiodo-2-(4-methyl-N-tosylphenylsulfonamido)-1H-indol-3-yl)ethyl)acetamide (**12**).* To a stirred solution of acetamide **7a** (0.052 g, 0.1 mmol, 1 equiv) and TFA (2 mL) in CH_2Cl_2 (20 mL) at −78 °C were added $HBF_4{\cdot}Et_2O$ (0.086 mL, 0.6 mmol, 6 equiv) and bis(pyridine)iodonium tetrafluoroborate (0.082 g, 0.22 mmol, 2.2 equiv). The brown solution was allowed to stir for 2 h. The reaction was quenched with cold water, and after extraction the organic layer was washed with an aqueous saturated solution of $Na_2S_2O_3$. The combined organic phases were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, CH_2Cl_2/EtOAc, 1/1, v/v) to afford a mixture of the two regioisomers in 1:3 ratio (53 mg, 68% yield, white solid). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.86 (s, 6H), 2.12−2.15 (m, 2H), 2.19−2.22 (m, 2H), 2.52 (s, 6H), 2.53 (s, 6H), 3.43−3.48 (m, 2H), 3.64−3.68 (m, 2H), 6.12 (s, 2H), 7.39−7.44 (m, 8H), 7.84−7.89 (m, 8H), 7.93 (s, 1H), 7.95 (s, 1H), 8.17 (s, 1H), 8.18 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.8 (CH_3), 22.7 (CH_2), 22.8 (CH_2), 23.0 (CH_3), 31.9 (CH_2), 38.7 (CH_2), 96.9 (C−I), 101.7 (C−I), 115.4, 122.4, 124.5, 128.5, 128.7, 128.8, 130.0, 130.1, 130.5, 135.4, 135.5, 146.1, 146.3, 170.5 (C═O). IR ν (cm^{-1}): 3387 (N−H), 2919 (Ar−H), 2850 (Ar−H), 1657 (C═O), 1597, 1540, 1375, 1351, 1164, 1083, 876, 754, 659, 541. HRMS (ESI-TOF): calcd for $C_{26}H_{26}I_2N_3O_5S_2$ 777.9398, found 777.9418.

General Procedure for Fluorination. Selectfluor (0.019 g, 0.06 mmol, 1.2 equiv) was added to a stirred solution of the corresponding starting material (0.027 g, 0.05 mmol, 1.0 equiv) and $NaHCO_3$ (0.005 g, 0.06 mmol, 1.2 equiv) in acetonitrile at 70 °C. The reaction was

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allowed to stir at 70 °C for 16 h. The solvent was removed under reduced pressure, and an aqueous saturated solution of $NaHCO_3$ was added. The residue was extracted with ethyl acetate, the combined organic phases were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, *n*-hexane/EtOAc, 2/3, v/v). The products were obtained as solids in 95−99% isolated yield.

*N-(2-(3-Fluoro-2-(tosylimino)indolin-3-yl)ethyl)acetamide (**13a**).* Yield: 19 mg, 98%, yellow solid. Mp: 230−232 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.87 (s, 3H), 2.27−2.50 (m, 5H), 3.33 (m, 2H), 5.93 (brs, 1H), 7.02 (d, J = 7.9 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.31−7.37 (m, 3H), 7.42 (d, J = 7.5 Hz, 1H) 7.88 (d, J = 8.3 Hz, 2H), 9.82 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.6 (CH_3), 23.1 (CH_3), 33.7 (d, J_{C-F} = 9.8 Hz, CH_2), 35.8 (d, J_{C-F} = 27.9 Hz, CH_2), 97.3 (d, J_{C-F} = 192.2 Hz, C−F), 111.8, 124.6 (d, J_{C-F} = 2.7 Hz), 124.8, 125.6 (d, J_{C-F} = 18.7 Hz), 126.8, 129.7, 131.9 (d, J = 3.1 Hz), 137.5, 141.0, 144.2, 165.1 (d, J_{C-F} = 19.7 Hz), 170.3 (C═O). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −150.3. IR ν (cm^{-1}): 3303 (N−H), 2921 (Ar−H), 2851 (Ar−H), 1615 (C═O), 1469, 1284, 1143, 1082, 752, 665, 546. HRMS (ESI-TOF): calcd for $C_{19}H_{19}FN_3O_3S$ 388.1137, found 388.1137.

*N-(2-(3-Fluoro-2-(tosylimino)indolin-3-yl)ethyl)benzamide (**13b**).* Yield: 21 mg, 95%, yellow solid. Mp: 202−204 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33−2.64 (m, 5H), 3.62 (td, J = 6.4, 6.2 Hz, 2H), 6.52 (t, J = 5.8 Hz, 1H), 7.00 (d, J = 7.8 Hz, 1H), 7.16−7.19 (m, 1H), 7.30 (d, J = 8.2 Hz, 2H), 7.36−7.49 (m, 5H), 7.69−7.72 (m, 2H), 7.86 (d, J = 8.3 Hz, 2H), 9.82 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.6 (CH_3), 34.2 (d, J_{C-F} = 10.1 Hz, CH_2), 35.6 (d, J_{C-F} = 27.2 Hz, CH_2), 99.2 (d, J_{C-F} = 194.5 Hz, C−F) 111.8, 124.7 (d, J_{C-F} = 2.7 Hz), 124.9, 126.8 (d, J_{C-F} = 16.7 Hz), 129.7, 131.5, 131.9, 132.0, 134.0, 137.6, 141.0, 144.1, 164.9 (d, J_{C-F} = 24.3 Hz), 167.3 (C═O). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −149.8. IR ν (cm^{-1}): 3295 (N−H), 2851 (Ar−H), 1616 (C═O), 1532, 1470, 1284, 1142, 1082, 669, 547. HRMS (ESI-TOF): calcd for $C_{24}H_{22}FN_3NaO_3S$ 474.1264, found 474.1260.

*N-(2-(3-Fluoro-1-methyl-2-(tosylimino)indolin-3-yl)ethyl)-acetamide (**14a**).* Yield: 20 mg, 99%, yellow solid. Mp: 47−53 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.87 (s, 3H), 2.44 (s, 3H), 2.64−2.70 (m, 1H), 3.08−3.13 (m, 1H), 3.20−3.38 (m, 5H), 6.32 (s, 1H), 6.90−6.92 (m, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.41−7.44 (m, 2H), 7.92 (d, J = 8.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.6 (CH_3), 23.1 (CH_3), 29.0 (CH_3), 33.9 (d, J_{C-F} = 9.8 Hz, CH_2), 35.6 (d, J_{C-F} = 27.1 Hz, CH_2), 96.9 (d, J_{C-F} = 194.3 Hz, C−I), 110.0, 124.1, 124.7 (d, J_{C-F} = 2.7 Hz), 126.7, 127.1 (d, J_{C-F} = 19.0 Hz), 129.4, 131.8 (d, J_{C-F} = 2.7 Hz), 140.0, 143.0, 143.3 (d, J_{C-F} = 5.1 Hz), 164.8 (d, J_{C-F} = 23.5 Hz), 170.1 (C═O). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −153.0. IR ν (cm^{-1}): 3294 (N−H), 2927 (Ar−H), 1632 (C═O), 1580, 1470, 1282, 1145, 1082, 770, 751, 671, 545, 461. HRMS (ESI-TOF): calcd for $C_{20}H_{22}FN_3O_3NaS$ 426.1258, found 426.1261.

*N-(2-(3-Fluoro-1-methyl-2-(tosylimino)indolin-3-yl)ethyl)-benzamide (**14b**).* Yield: 22 mg, 98%, orange solid. Mp: 128−129 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.46 (s, 3H), 2.73−2.80 (m, 1H), 3.02 (s, 3H), 3.30−3.36 (m, 1H), 3.50−3.71 (m, 2H), 6.90 (d, J = 7.9 Hz, 1H), 7.12−7.14 (m, 1H), 7.20 (t, J = 7.6 Hz, 1H), 7.29−7.32 (m, 2H), 7.38−7.52 (m, 5H), 7.84−7.88 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 21.5 (CH_3), 28.7 (CH_3), 34.5 (d, J_{C-F} = 10.1 Hz, CH_2), 35.3 (d, J_{C-F} = 27.4 Hz, CH_2), 96.9 (d, J_{C-F} = 193.6 Hz, C−I), 110.0, 124.0, 124.7 (d, J = 2.7 Hz), 126.6, 126.8, 127.0, 127.2, 128.4, 129.3, 131.4, 131.8 (d, J_{C-F} = 2.8 Hz), 133.8, 140.0, 142.9, 143.3 (d, J_{C-F} = 5.2 Hz), 165.3 (d, J_{C-F} = 23.5 Hz), 166.8 (C═O). ^{19}F NMR (376 MHz, $CDCl_3$) δ = −152.8. IR ν (cm^{-1}): 3253 (N−H), 3068 (Ar−H), 2920 (Ar−H), 1627 (C═O), 1550, 1381, 1167, 876, 657, 540. HRMS (ESI-TOF): calcd for $C_{25}H_{24}FN_3NaO_3S$ 488.1415, found 488.1422.

*N-(2-(3-Fluoro-2-(4-methyl-N-tosylphenylsulfonamido)-3H-indol-3-yl)ethyl)acetamide (**15**).* Yield: 23 mg, 86%, yellow solid. Mp: 132−134 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.90 (s, 3H), 2.13−2.25 (m, 1H), 2.26−2.40 (m, 1H), 2.51 (s, 6H), 3.15−3.23 (m, 1H), 3.34−3.43 (m, 1H), 5.51 (t, J = 6.0, 1H), 7.36−7.41 (m, 5H), 7.44−7.52 (m, 2H), 7.57 (d, J = 7.6 Hz, 1H), 8.11 (d, J = 8.4, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.8 (CH_3), 23.2 (CH_3), 33.5 (d, J_{C-F} = 26.0 Hz, CH_2), 34.0 (d, J_{C-F} = 6.9 Hz, CH_2), 100.4 (d, J_{C-F} = 197.0 Hz, C−F), 101.4, 122.9, 123.9, 128.8 (d, J_{C-F} = 1.6 Hz), 129.5, 129.7 (d, J_{C-F} = 1.9 Hz), 131.2, 134.4 (d, J_{C-F} = 18.5 Hz), 136.2, 145.8, 149.7 (d, J_{C-F} = 6.3 Hz), 165.4 (d, J_{C-F} = 18.8 Hz), 169.8 (C═O). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −166.6. IR ν (cm^{-1}): 3282 (N−H), 2919 (Ar−H), 2850 (Ar−H), 1650 (C═O), 1563, 1381, 1167, 1082, 886, 659, 538. HRMS (ESI-TOF): calcd for $C_{26}H_{25}FN_3O_5S_2$ 542.1225, found 542.1221.

*N-(2-(3-Fluoro-1-methyl-2-oxoindolin-3-yl)ethyl)acetamide (**16a**).* Compound **14a** (0.045 g, 0.11 mmol, 1 equiv) was dissolved in MeOH (2 mL), and LiOH (0.027, 1.1 mmol, 10 equiv) was added. The reaction mixture was stirred at 25 °C for 16 h. The solvent was removed under reduced pressure. The residue was quenched with water and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, MeOH/CH_2Cl_2, 0.2:10, v/v) to afford the pure product in 85% yield (0.023 g) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.94 (s, 3H), 2.14−2.27 (m, 1H), 2.41−2.52 (m, 1H), 3.22 (s, 3H), 3.43−3.60 (m, 2H), 6.15 (brs, 1H), 6.87 (d, J = 8.3 Hz, 1H), 7.15 (t, J = 7.9 Hz, 1H), 7.40−7.44 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 23.2 (CH_3), 26.3 (CH_3), 33.9 (d, J_{C-F} = 5.9 Hz, CH_2), 34.8 (d, J_{C-F} = 26.8 Hz), 92.4 (d, J_{C-F} = 186.9 Hz, C−F), 108.9, 123.6 (d, J_{C-F} = 2.8 Hz), 124.5, 125.9 (d, J_{C-F} = 18.2 Hz), 126.4, 129.7, 131.5 (d, J_{C-F} = 3.0 Hz), 143.7 (d, J_{C-F} = 5.4 Hz), 170.0 (C═O), 172.8 (d, J_{C-F} = 22.0 Hz, C═O). ^{19}F NMR (101 MHz, $CDCl_3$): δ = −158.5. IR ν (cm^{-1}): 3294 (N−H), 3065 (Ar−H), 2927 (Ar−H), 1724 (C═O), 1615 (C═O), 1470, 1372, 1246, 1113, 750. HRMS (ESI-TOF): calcd for $C_{13}H_{15}FN_2NaO_2$ 273.1010, found 273.1013.

*N-(2-(3-Fluoro-1-methyl-2-oxoindolin-3-yl)ethyl)benzamide (**16b**).* Compound **16b** was synthesized in an analogous manner to that described above for **16a**. Yield: 29 mg, 85%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.23−2.36 (m, 1H), 2.57−2.67 (m, 1H), 3.18 (s, 3H), 3.63−3.71 (m, 1H), 3.78−3.87 (m, 1H), 6.86 (d, J = 7.8 Hz, 1H), 7.02 (brs, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.39−7.52 (m, 5H), 7.76−7.82 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 26.3 (CH_3), 34.3 (d, J_{C-F} = 5.8 Hz, CH_2), 34.8 (d, J_{C-F} = 27.0 Hz, CH_2), 92.5 (d, J_{C-F} = 186.8 Hz, C−F), 109.0, 123.7 (d, J_{C-F} = 2.7 Hz), 124.5, 125.9 (d, J_{C-F} = 18.3 Hz), 126.9, 128.5, 131.4, 131.6 (d, J_{C-F} = 3.2 Hz), 134.3, 143.6 (d, J_{C-F} = 5.4 Hz), 167.0 (C═O), 173.0 (d, J_{C-F} = 22.0 Hz, C═O). ^{19}F NMR (101 MHz, $CDCl_3$): δ = −158.3. IR ν (cm^{-1}): 3327 (N−H), 2923 (Ar−H), 2852 (Ar−H), 1725 (C═O), 1639 (C═O), 1616, 1537, 1491, 1470, 1376, 1306, 1092, 751, 694. HRMS (ESI-TOF): calcd for $C_{18}H_{17}FN_2NaO_2$ 335.1166, found 335.1169.

General Procedure for Treatment of 13a,b and 14a,b with TFA. The corresponding starting material (0.12 mmol, 1 equiv) was dissolved in TFA (4 mL), and the reaction mixture was allowed to stir for 12 h under an atmosphere of argon. The solvent was removed under reduced pressure and the pure product was isolated in quantitative yield.

*2-(3-Acetoxy-2-(tosylimino)indolin-3-yl)ethanaminium trifluoroacetate (**17a**).* Yield: 59 mg, 98%, brown solid. Mp: 112−115 °C. ^{1}H NMR (400 MHz, MeOD): δ = 2.43 (s, 3H), 2.51 (s, 3H), 2.55−2.56 (m, 1H), 2.73−2.81 (m, 1H), 3.77−3.83 (m, 1H), 4.09−4.18 (m, 1H), 7.29−7.35 (m, 2H), 7.49 (d, J = 7.7 Hz, 2H), 7.56−7.62 (m, 2H), 7.93 (d, J = 8.3 Hz, 2H). ^{13}C NMR (101 MHz, MeOD): δ = 21.5 (CH_3), 22.5 (CH_3), 33.8 (CH_2), 37.5 (CH_2), 81.0, 83.5, 87.4, 113.4, 125.0, 125.4, 127.8, 130.6, 130.6, 131.7, 140.0, 142.6, 143.4, 145.2, 170.1 (C═O). ^{19}F NMR (376 MHz, MeOD): δ = −77.5. IR ν (cm^{-1}): 3306 (N−H), 2921 (Ar−H), 2851 (Ar−H), 1599 (C═O), 1469, 1279, 1138, 1082, 753, 666, 547. HRMS (ESI-TOF): calcd for $C_{19}H_{22}N_3O_4S$ 388.1326, found 388.1311.

*2-(3-(Benzoyloxy)-2-(tosylimino)indolin-3-yl)ethanaminium 2,2,2-Trifluoroacetate (**17b**).* Yield: 67 mg, 99%, yellow solid. Mp: 131−135 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.19−2.23 (m, 1H), 2.43 (s, 3H), 3.61−3.64 (m, 1H), 3.74 (td, J = 7.1, 6.9, 2H), 5.38 (s, 1H), 7.07 (d, J = 8.1 Hz, 1H), 7.18−7.54 (m, 8H), 7.74 (d, J = 7.6 Hz, 2H), 7.88 (d, J = 8.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.6

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(CH_3), 34.8 (CH_2), 37.4 (CH_2), 86.6, 111.7, 124.6, 126.5, 126.6, 127.0, 128.5, 128.6, 129.3, 129.7, 130.8, 131.8, 138.0, 144.0, 168.2 (C═O). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −76.0. IR ν (cm^{-1}): 3253 (N−H), 3068 (Ar−H), 2920 (Ar−H), 1627 (C═O), 1550, 1381, 1167, 876, 657, 540. HRMS (ESI-TOF): calcd for $C_{24}H_{24}N_3O_4S$ 450.1482, found 450.1476.

*2-(3-Acetoxy-1-methyl-2-(tosylimino)indolin-3-yl)ethanaminium 2,2,2-Trifluoroacetate (**18a**).* Yield: 61 mg, 99%, yellow solid. Mp: 129−132 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.19−2.23 (m, 1H), 2.46 (s, 3H), 2.55 (s, 3H), 3.20−3.28 (m, 1H), 3.48 (s, 3H), 3.84−3.95 (m, 1H), 4.04−4.11 (m, 1H), 7.05 (d, J = 7.9 Hz, 1H), 7.26−7.30 (m, 1H), 7.36 (d, J = 8.0 Hz, 2H), 7.44 (dd, J = 7.6, 1.1 Hz, 1H), 7.55 (td, J = 7.9, 1.1 Hz, 1H), 7.83−7.96 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 20.0 (CH_3), 21.5 (CH_3), 25.1 (CH_3), 30.4 (CH_2), 34.5 (CH_2), 84.3, 110.5, 123.7, 125.3, 126.3, 127.1, 129.6, 132.9, 138.9, 142.5, 143.8, 162.5, 172.8 (C═O). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −75.9. IR ν (cm^{-1}): 3383 (N−H), 2919 (Ar−H), 1678 (C═O), 1572, 1190, 1148, 1132, 1083, 948, 777, 760, 680. HRMS (ESI-TOF): calcd for $C_{20}H_{24}N_3O_4S$ 402.1488, found 402.1485.

*2-(3-(Benzoyloxy)-1-methyl-2-(tosylimino)indolin-3-yl)-ethanaminium 2,2,2-Trifluoroacetate (**18b**).* Yield: 89 mg, 99%, yellow solid. Mp: 56−58 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.31−2.34 (m, 1H), 2.39 (s, 3H), 3.27−3.34 (m, 1H), 3.53 (s, 3H), 4.09−4.14 (m, 1H), 4.21−4.28 (m, 1H), 7.06 (d, J = 8.0 Hz, 1H), 7.21−7.28 (m, 3H), 7.50−7.55 (m, 4H), 7.70−7.71 (m, 3H), 8.00−8.08 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.5 (CH_3), 25.4 (CH_3), 30.7 (CH_2), 35.1 (CH_2), 84.7, 110.6, 124.0, 124.9, 125.4, 126.3, 127.0, 128.9, 129.4, 129.5, 132.5, 135.9, 138.8, 142.6, 143.7, 162.2, 167.6 (C═O). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −75.9. IR ν (cm^{-1}): 3067 (N−H), 2929 (Ar−H), 1783 (C═O), 1588, 1138, 1084. HRMS (ESI-TOF): calcd for $C_{25}H_{25}N_3NaO_4S$ 486.1463, found 486.1458.

*N-(3-(2-Acetamidoethyl)-3-hydroxy-1-methylindolin-2-ylidene)-4-methylbenzenesulfonamide (**19**).* Compound **18a** (46 mg, 0.1 mmol) was dissolved in CH_2Cl_2 (0.25 mL), and Et_3N (0.5 mL) was added dropwise. After 16 h, additional CH_2Cl_2 (5 mL) and water were added, and the resulting mixture was extracted with diluted HCl (1 M in water). The organic phase was separated and the solvent was removed under reduced pressure. The title compound was isolated as a yellowish solid (40 mg, 0.1 mmol, 99% yield). Mp: 135−138 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.90 (s, 3H), 2.45 (s, 3H), 3.19 (s, 3H), 2.45−2.55 (m, 1H), 2.94−3.17 (m, 3H), 3.19 (s, 3H), 6.31 (brs, 1H), 6.90 (d, J = 8.0 Hz, 1H), 7.19−7.23 (m, 1H), 7.32−7.34 (m, 2H), 7.35−7.41 (m, 2H), 7.88−7.90 (m, 2H), 8.08−8.10 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.6 (CH_3), 23.1 (CH_3), 28.4 (CH_3), 34.5 (CH_2), 38.8 (CH_2), 80.2 (C−O), 109.8, 123.4, 125.0, 126.4, 129.4, 129.7, 130.4, 130.5, 139.1, 142.7, 143.3, 169.9, 171.2 (C═O). IR ν (cm^{-1}): 3411 (O−H), 3376 (N−H), 2921 (Ar−H), 2852 (Ar−H), 1665 (C═O), 1548, 1073, 961, 778, 752, 689, 553. HRMS (ESI-TOF): calcd for $C_{20}H_{23}N_3NaO_4S$ 424.1301, found 424.1307.

*8-Methyl-2,3,3a,8-tetrahydropyrrolo[2,3-b]indol-3a-yl Benzoate (**20**).* Compound **18b** (0.372 g, 0.64 mmol, 1 equiv) was dissolved in MeOH (10 mL), and LiOH (0.154 g, 6.4 mmol, 10 equiv) was added. The reaction mixture was allowed to stir at 25 °C for 16 h. The solvent was removed under reduced pressure. The residue was quenched with water and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure, affording compound **20** in quantitative yield (185 mg, 99%) as a brownish solid. Mp: 45−46 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.07 (ddd, J = 14.0, 7.1, 5.3 Hz, 1H), 2.23 (ddd, J = 14.0, 6.5, 5.3 Hz, 1H), 3.27 (s, 3H), 3.90 (ddd, J = 17.2, 6.5, 5.3 Hz, 1H), 4.17 (ddd, J = 17.2, 7.1, 5.3 Hz, 1H), 6.92 (d, J = 7.9 Hz, 1H), 7.13 (t, J = 7.6 Hz, 1H), 7.34−7.44 (m, 5H), 7.91−7.94 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.4 (CH_3), 27.5 (CH_2), 38.7 (CH_2), 76.7, 108.7, 123.4, 124.1, 127.2, 128.0, 129.1, 130.4, 130.5, 133.5, 143.2, 154.3, 174.2 (C═O). IR ν (cm^{-1}): 3060 (Ar−H), 2924 (Ar−H), 1715 (C═O), 1653, 1613, 1156, 1120, 1091. HRMS (ESI-TOF): calcd for $C_{18}H_{17}N_2O_2$ 293.1285, found 293.1284.

*Trifluoromethyl 3-(2-Benzamidoethyl)-1-methyl-2-oxoindoline-3-carboxylate (**21**).* Compound **20** (58 mg, 0.20 mmol, 1 equiv) was dissolved in CH_2Cl_2 (2 mL), and TFA (0.05 mL, 0.60 mmol, 3 equiv) was added. The reaction mixture was stirred for 16 h at 25 °C. After 16 h, the solvent was removed under reduced pressure to afford the pure product as a yellow oil in 80 mg (99% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.45−2.50 (m, 1H), 2.68−2.74 (m, 1H), 3.29 (s, 3H), 4.09−4.14 (m, 1H), 4.40−4.47 (m, 1H), 7.04 (d, J = 7.9, 1H), 7.26 (t, J = 8.0 Hz, 1H), 7.36−7.59 (m, 3H), 7.74 (t, J = 7.4 Hz, 1H), 7.67−7.77 (m, 1H), 7.98 (d, J = 7.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 25.0 (CH_3), 26.7 (CH_2), 35.8 (CH_2), 81.4, 109.9, 112.0, 114.3, 116.5, 118.8, 123.7, 124.0, 125.0, 128.4, 129.5, 132.8, 136.2, 143.5, 161.3 (q, CF_3C═O), 168.4 (C═O), 170.8 (C═O). ^{19}F NMR (101 MHz, $CDCl_3$): δ = −76.0. IR ν (cm^{-1}): 3325 (N−H), 2926 (Ar−H), 1697 (C═O), 1638 (C═O), 1611 (C═O), 1537, 1490, 1347, 1301, 1128, 1091, 749, 695. HRMS (ESI-TOF): calcd for $C_{20}H_{17}F_3N_2NaO_4$ 429.1038, found 429.1026.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01118.

Crystal data and ORTEP plots from X-ray analyses for compounds **9**, **11**/**12**, **14a**, **18a**, **19**, and **20** and NMR spectra for new compounds (PDF)

X-ray crystallographic data in CIF format for **9** (CIF)

X-ray crystallographic data in CIF format for **11**/**12** (CIF)

X-ray crystallographic data in CIF format for **14a** (CIF)

X-ray crystallographic data in CIF format for **18a** (CIF)

X-ray crystallographic data in CIF format for **19** (CIF)

X-ray crystallographic data in CIF format for **20** (CIF)

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Notes

The authors declare no competing financial interest.

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