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Note

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One-pot Synthesis of Indole-3-Acetic Acid Derivatives through Cascade Tsuji-Trost Reaction and Heck Coupling

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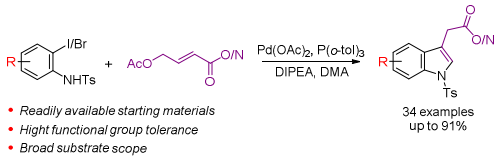


Abstract: A practical palladium-mediated cascade Tsuji-Trost reaction/Heck coupling of N-Ts *o*-bromoanilines with 4-acetoxy-2-butenonic acid derivatives using a $Pd(OAc)_2$/P(*o*-tol)$_3$/DIPEA system is described for a straightforward synthesis of indole-3-acetic acid derivatives. This methodology was successfully applied to synthesize various substituted indole/azaindole-3-acetic acid derivatives and Almotriptan, which is a drug for the acute treatment of migraine. Moreover, a plausible cyclization mechanism has been proposed.

Indole-3-acetic acid is an endogenous growth hormone in plants. Its scaffold (Figure 1) is frequently found in a series of biologically active compounds such as Bunodosine 391[1] and therapeutically effective drugs such as Indomethacin[2], Sumatriptan[3] and Rizatriptan[4]. Owing to its great importance in medicinal chemistry, much effort has been focused on the development of more effective synthetic methods over the past years (Scheme 1. A).

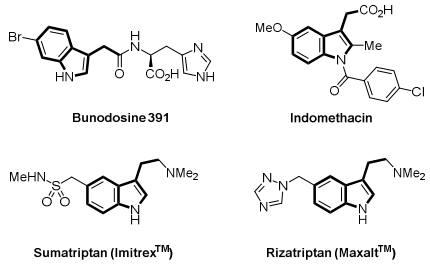
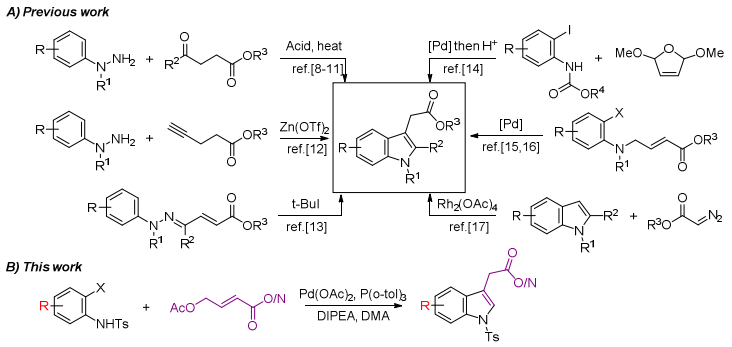


Figure 1. Examples of bioactive molecules containing indole-3-acetic acid scaffold.

Among these synthetic methods[5-7], Fischer indole synthesis[8-11] is the most widely used method which relies on the use of phenylhydrazines and ketones or aldehydes and especially works well for 5-substituted electron-rich indoles. Other variant approaches, for examples, domino synthesis of indoles through Zinc-promoted hydrohydrazination of terminal alkynes[12] and reductive Fischer indolization of N-aryl conjugated hydrazones with tert-butyl iodide[13], provide more choices for

the preparation of indole-3-acetic acid compounds. However, Fischer method has suffered from some problems when it was applied to synthesize 4- or 6-monosubstituted indoles due to its selectivity. During the past few decades, transition-metal-catalyzed reactions have offered a powerful tool for construction of C-C and C-heteroatom bonds. The application of these reactions such as Heck coupling catalyzed by palladium[14-16] and C-H functionalization by $Rh_2(OAc)_4$[17] in the synthesis of indole-3-acetic acid derivatives which greatly enriched the diversity of substrate structures has also been explored. Despite these advances, the development of a straightforward method to access indole-3-acetic acid through one-pot process would be of great value. Herein, we report a novel palladium-mediated cascade Tsuji-Trost reaction[18-22]/Heck coupling[23-27] to synthesize indole-3-acetic acid and its derivatives from readily available starting materials (Scheme 1. B).

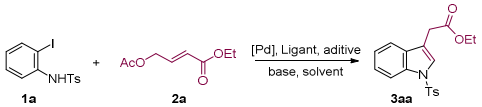
Scheme 1. Synthetic Routes for the Preparation of Indole-3-acetic acid Compounds



The reaction of N-Ts *o*-iodoaniline (**1a**) and ethyl (*E*)-4-acetoxybut-2-enoate (**2a**) was used to screen for suitable reaction conditions. At first, the reaction was performed in DMA at 100°C in the presence of $Pd(OAc)_2$ (5 mol %), P(*o*-tol)$_3$ (10 mol %), *n*-Bu_4NBr (1.2 equiv)[28-30] and K_2CO_3 (3.0 equiv). Disappointedly, the reaction did not give any products after 16h (Table 1, entry 1). However, after the base K_2CO_3 was replaced with KOAc and the amounts of catalyst and ligand were increased at the same time, the reaction afforded the desired product **3aa** in 32% yield after 24h (Table 1, entry 2). Encouraged by the result, we investigated other bases and the results revealed that the type of the base had a significant effect on the outcome of the reaction. Among the screened bases, organic bases such as TEA and DIPEA gave the better results than inorganic bases such as K_2CO_3 and KOAc (Table 1, entries 1–3). Next, we tried to optimize the amounts of catalyst and ligand, and found that the yield would decrease significantly when the amounts of $Pd(OAc)_2$ and P(*o*-tol)$_3$ were reduceed to 3 mol % and 6 mol % respectively (Table 1, entries 3-5). Interestedly, the absence of *n*-Bu_4NBr had no effect on the result (Table 1, entries 4 and 6). Furthermore, the investigation showed that the ligands play a favorable role in the reaction and P(*o*-tol)$_3$ could improve the reaction rate more apparently than PPh_3 (Table 1, entries 6-8). A survey of palladium source on the reaction showed that $Pd(OAc)_2$ and $Pd_2(dba)_3$ have similar catalytic activities (Table 1, entries 6 and 9). Toluene, 1,4-dioxane and CH_3CN were screened as solvents and no one was found to afford a comparable result to DMA (Table 1, entries 10-12). The amino of aniline without protection or protected with other protective groups such as CH_3CO, CF_3CO, $MeSO_2$, Boc and PMB were also investigated under the condition of entry 6, however,

they gave quite poor results. Finally, the optimal reaction conditions were determined as follows: **1a** (1 equiv), **2a** (1.2 equiv), $Pd(OAc)_2$ (5 mol %), P(*o*-tol)$_3$ (10 mol %) and TEA (or DIPEA) (3 equiv) in DMA.

Table 1. Optimization of the Reaction Conditions

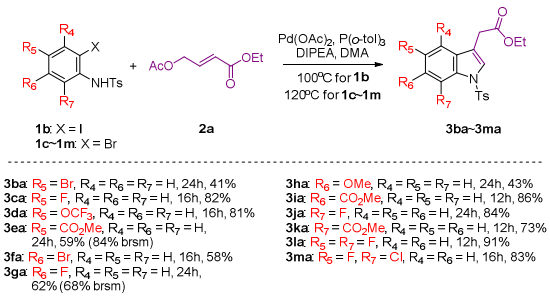


Entry	Cat. (5 mol %)	L (10 mol %)	Base (3.0 eq.)	Additive (1.2 eq.)	Solvent[a]	Temp. (°C)	Time (h)	**3aa**[b] (yield, %)
1	$Pd(OAc)_2$	P(*o*-tol)$_3$	K_2CO_3	*n*-Bu_4NBr	DMA	100	16	NR
2[c]	$Pd(OAc)_2$	P(*o*-tol)$_3$	KOAc	*n*-Bu_4NBr	DMA	100	24	32[d]
3[c]	$Pd(OAc)_2$	P(*o*-tol)$_3$	TEA[e]	*n*-Bu_4NBr	DMA	100	24	84
4	$Pd(OAc)_2$	P(*o*-tol)$_3$	TEA	*n*-Bu_4NBr	DMA	100	12	83
5[f]	$Pd(OAc)_2$	P(*o*-tol)$_3$	TEA	*n*-Bu_4NBr	DMA	100	16	23[d]
6	**$Pd(OAc)_2$**	**P(*o*-tol)$_3$**	**TEA**	**---**	**DMA**	**100**	**10**	**82**
7	$Pd(OAc)_2$	---	TEA	---	DMA	100	12	34[d]
8	$Pd(OAc)_2$	PPh_3	TEA	---	DMA	100	24[g]	83
9	$Pd_2(dba)_3$	P(*o*-tol)$_3$	TEA	---	DMA	100	12	84
10	$Pd_2(dba)_3$	P(*o*-tol)$_3$	TEA	---	Toluene	100	12	14
11	$Pd_2(dba)_3$	P(*o*-tol)$_3$	TEA	---	1,4-dioxane	100	12	7
12	$Pd(OAc)_2$	P(*o*-tol)$_3$	TEA	---	CH_3CN	80	16	72

Conditions: **1a** (1.0 mmol), **2a** (1.2 mmol), *c* = 0.2 M. [a] anhydrous solvent, under N_2 atmosphere; [b] isolated yields; [c] $Pd(OAc)_2$ (12 mol %), P(*o*-tol)$_3$ (20 mol %); [d] **1a** has remained; [e] DIPEA gave a similar result; [f] $Pd(OAc)_2$ (3 mol %), P(*o*-tol)$_3$ (6 mol %); [g] **1a** has remained after18h, disappeared after 24h.

Based on the optimized reaction conditions, the scope of this one-pot process was then examined. Diverse substituted indole-3-ethyl acetate compounds were obtained in moderate to good yields (Schemes 2). As shown in Scheme 2, for the substrate N-Ts *o*-haloanilines, a variety of substituents (-Br, -Cl, -F, $-OCF_3$, -OMe and $-CO_2Me$) were applicable, affording products **3ba**~**3ma** in 41~91% yields. The position and electronic nature of aromatic substituents seem to affect the yields: electron-donating substituents at *para*-position of halogen on anilines lead to poorer yields (**3ha**), while electron-withdrawing substituents give better yields (**3ga** and **3ia**); for substituents at *meta*-position of halogen on anilines, the electronic effects do not seem to play an important role in reaction yields (**3ba**, **3ca**, **3da** and **3ea**); for electron-withdrawing substituents at *orth*-position of nitrogen on anilines, the reactions can also give good results (**3ja**, **3ka** and **3la**). Besides, the substituents have a big influence on the reaction rate: the substrates **1e** and **1g** were not consumed completely after 24h, while the reaction was finished for **1i**, **1k** and **1l** after 12h.

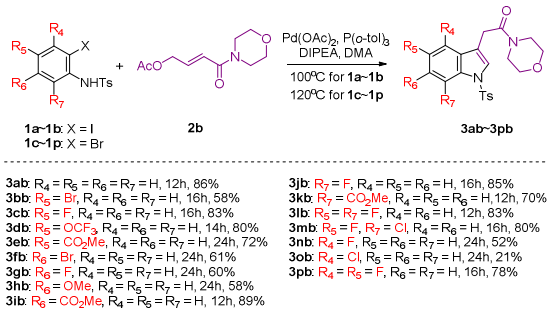
Scheme 2. Scope of Cascade Tsuji-Trost/Heck Reaction to Form Substituted Indole-3-Acetates (3xa)[ab]



[a]Conditions: **1b~1m** (1.0 mmol), **2a** (1.2 mmol), $Pd(OAc)_2$ (5 mol %), P(*o*-tol)$_3$ (10 mol %), DIPEA (3 mmol), anhydrous DMA (5 mL), under N_2 atmosphere; [b]Isolated yield after chromatography.

In order to expand the diversity of the substrates, we examined the cyclization reaction of N-Ts *o*-haloanilines with amide **2b** (Scheme 3). The investigation showed that the substrate amide **2b** gave equivalent or better results (**1ab**~**1mb** except for **1lb**) than its corresponding ester **2a**, while the effects of the position and electronic nature of aromatic substituents were similar to those displayed for the reactions of **1a**~**1m** with **2a**. Interestingly, for substituents at *orth*-position of halogen on anilines, the reactions gave better results (**3nb**, **3ob** and **3pb**) than its corresponding ester **2a**, while there was almost no reaction between **2a** and **1n**, **1o**, **1p**.

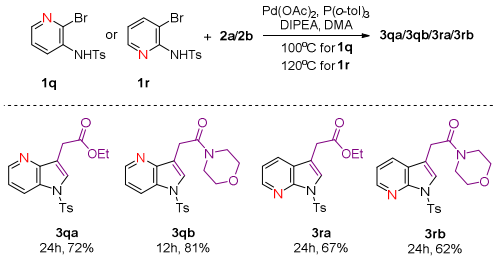
Scheme 3. Scope of Cascade Tsuji-Trost/Heck Reaction to Form Substituted Indole-3-Acetamides (3xb)[ab]



[a]Conditions: **1a~1i** (1.0 mmol), **2b** (1.2 mmol), $Pd(OAc)_2$ (5 mol %), P(*o*-tol)$_3$ (10 mol %), DIPEA (3 mmol), anhydrous DMA (5 mL), under N_2 atmosphere; [b]Isolated yield after chromatography.

The scope of this process was further expanded by utilizing N-Ts bromo-aminopyridines as substrates (Scheme 4). As expected, azaindoles[31-32] were obtained smoothly. The substrate **1q** gave ester **3qa** or amide **3qb** at 100°C for 24h in 72% yield or for 12h in 81% yield respectively, while **1r** afforded **3ra** or **3rb** at 120°C for 24h in 67% or 62% yield respectively.

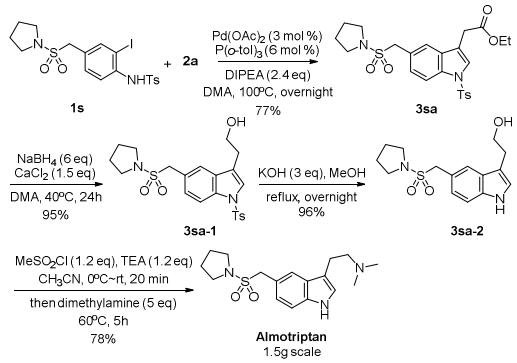
Scheme 4. Scope of Cascade Tsuji-Trost/Heck Reaction to Form Azaindoles [ab]



[a]Conditions: **1q**/**1r** (1.0 mmol), **2a**/**2b** (1.2 mmol), $Pd(OAc)_2$ (5 mol %), P(*o*-tol)$_3$ (10 mol %), DIPEA (3 mmol), anhydrous DMA (5 mL), under N_2 atmosphere; [b]Isolated yield after chromatography.

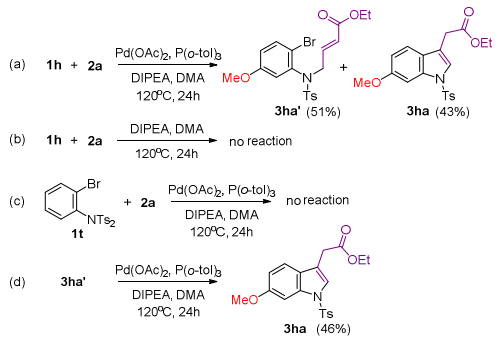
With this newly established methodology, an efficient approach to the synthesis of Almotriptan[33], a specific serotonin 5-HT 1B/1D agonist for the acute treatment of migraine, has been accomplished on gram scale (Scheme 5). It is easy to conduct the reaction of **1s** and **2a** to afford **3sa** in 77% yield. Subsequent reduction and deprotection lead to **3sa-2** in high yield. Finally, Almotriptan was obtained successfully through a one-pot process from **3sa-2** in 78% yield.

Scheme 5. Application in the synthesis of Almotriptan



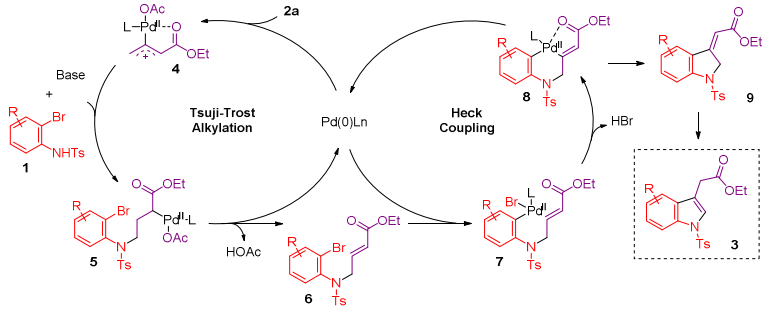
The cascade Tsuji-Trost/Heck reaction mechanism for the cyclization was preliminarily confirmed by the phenomena observed during the synthesis of **3ha**. Besides desired product **3ha**, another product **3ha'** was separated contemporaneously in 51% yield (Scheme 6, eq (a)), which indicated cyclization probably started from Tsuji-Trost alkylation. To further establish the mechanism of the cyclization reaction, three control experiments were performed. When **1h** and **2a** were mixed under the conditions without palladium catalyst and ligand, the reaction did not proceed (Scheme 6, eq (b)), which indicated that **3ha'** was generated via Tsuji-Trost alkylation. Under the same conditions as eq (a), **1t** was not react with **2a** (Scheme 6, eq (c)), while **3ha'** could be converted into **3ha** (Scheme 6, eq (d)) through Heck coupling[34].

Scheme 6. The Evidence for the Cascade Tsuji-Trost/Heck Reaction Process



On the basis of the above results and previous reports, a plausible mechanism for this cascade reaction has been proposed (Scheme 7). It involves, as a first step, oxidative addition of allyl ester **2a** to the palladium complex, forming the electrophilic η^3–allyl Pd(II) complex, which subsequently reacts with nucleophilic N-Ts *o*-haloaniline in the presence of base to produce intermediate **6** and regenerate the Pd(0) catalyst. The next step is the intramolecular Heck coupling, that is, the palladium-mediated cyclization of **6**, to afford cyclization product **9**. The Heck reaction proceeds well under the help of ester group which could stabilize the palladium species by coordination. The last step is the isomerization of **9**, providing indole-3-actic ester **3**.

Scheme 7. Proposed Mechanism for Cyclization



In conclusion, we have developed a practical protocol for the synthesis of substituted indole-3-actic acid derivatives through palladium catalyzed Tsuji-Trost alkylation and Heck coupling. The cascade reaction could be successfully performed from readily available substrates: substituted N-Ts *o*-haloanilines and allyl ester/amide. This methodology provided an alternative for the synthesis of indole-3-actic acid scaffold valuable in medicinal chemistry.

Experimental Section

General Information. Unless otherwise noted, all solvents and reagents are commercially available and used without further purification. $Pd(OAc)_2$ and $P(o\text{-tol})_3$ were purchased from J&K Scientific Ltd.. Substituted *o*-haloaniline and anhydrous DMA were purchased from Energy Chemical. Normal-phase column chromatography was performed using silica gel (200–300 mesh). Unless otherwise noted, all reagents were weighed and handled in air at room temperature. The yields of all the reactions refer to isolated yields. ^{1}H NMR spectra were recorded on a Brucker Avance 400 and 600MHz NMR spectrometer, ^{13}C NMR spectra were recorded on a Brucker Avance 100 and 150MHz NMR spectrometer. Chemical shifts were reported in parts per million (ppm, δ) ($CDCl_3$: δ = 7.26 ppm for ^{1}H NMR and δ = 77.1 ppm for ^{13}C NMR; DMSO-*d6*: δ = 2.50 ppm for ^{1}H-NMR and δ = 39.5 ppm for ^{13}C-NMR). Proton coupling patterns are described as

singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). IR spectra were measured on a PE Spectrum Two. HRMS spectra were measured on a Waters Xevo G2-XS QTof.

General produce for the preparation of Ts protected *o*-haloanilines. To a stirred solution of substituted *o*-haloaniline (10 mmol) in Pyr/THF (18 mL/6 mL) was added TsCl (12 mmol) slowly at room temperature. The reaction mixture was allowed to stir at 40°C overnight. After the solvent was removed under reduced pressure, ethyl acetate (100 mL) was added, and the mixture was washed with brine (50 mL×2), and dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure and the residue was purified by column chromatography to yield corresponding compounds **1a**[35], **1b**[36], **1c**[37], **1d**[38], **1e**[39], **1f**[40], **1g**[38], **1h**[41], **1q**[42], **1r**[43] and **1t**[44].

Methyl 4-bromo-3-((4-methylphenyl)sulfonamido)benzoate (1i): EtOAc/PE = 1/10, 2.7 g, 70%, white solid. **Mp**:124-125°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 10.11 (s, 1H), 7.77-7.73 (m, 1H), 7.60 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 3.83 (s, 3H), 2.37 (s, 3H)； **^{13}C NMR** (100 MHz, DMSO-d_6) δ (ppm): 165.5, 143.9, 137.7, 136.1, 134.3 130.2, 130.1, 128.4, 128.0, 127.2, 125.9, 53.0, 21.5; **HRMS** (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{15}H_{15}BrNO_4S$ 383.9905/385.9885, found 383.9902/385.9882.

***N*-(2-bromo-6-fluorophenyl)-4-methylbenzenesulfonamide(1j)：** EtOAc/PE = 1/10, 2.1g, 61%, white solid. Mp:184-186°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 9.93 (s, 1H), 7.61 (d, J = 8.4 Hz, 2H), 7.51-7.49 (m, 1H), 7.37 (d, J = 8.8 Hz, 2H), 7.29-7.25 (m, 2H), 2.31 (s, 3H); **^{13}C NMR** (150 MHz, DMSO-d_6) δ (ppm): 160.0 (d, $J_{C,F}$ = 251 Hz), 143.4, 139.2, 130.7 (d, $J_{C,F}$ = 7.4 Hz), 129.9, 129.3, 127.1, 125.8, 124.2, 124.1, 116.3 (d, $J_{C,F}$ = 21.5 Hz), 21.5; **ATR-IR**: *v* 3249, 1594, 1339, 1156 cm^{-1}; **HRMS** (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{13}H_{12}BrFNO_2S$ 343.9756/345.9736, found 343.9759/345.9738.

Methyl 3-bromo-2-((4-methylphenyl)sulfonamido)benzoate(1k): EtOAc/PE = 1/10, 1.4g, 36%, white solid. Mp:152-153°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 9.98 (s, 1H), 7.80 (dd, J = 8.0, 2.0 Hz, 1H), 7.68 (dd, J = 8.0, 1.6 Hz, 1H), 7.42 (d, J = 8.4 Hz, 2H), 7.34-7.30 (m, 3H), 3.66 (s, 3H), 2.37 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 166.6, 143.9,137.9, 136.1, 135.4, 129.8, 129.4, 128.9, 127.9, 127.7, 124.6, 52.5, 21.6; **ATR-IR**: *v* 3238, 1596, 1397, 1158 cm^{-1}; **HRMS** (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{15}H_{15}BrNO_4S$ 383.9905/385.9885, found 383.9899/385.9880.

***N*-(2-bromo-4,6-difluorophenyl)-4-methylbenzenesulfonamide (1l):** EtOAc/PE = 1/10, 1.5g, 41%, white solid. Mp:179-181°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 9.95 (s, 1H), 7.61 (d, J = 8.0 Hz, 2H), 7.55 (dt, J = 8.0, 2.4 Hz, 1H), 7.42 (dd, J = 10.0, 3.2 Hz, 1H), 7.38 (d, J = 8.4 Hz, 2H), 2.39 (s, 3H); **^{13}C NMR** (150 MHz, DMSO-d_6) δ (ppm): 161.1 (dd, $J_{C,F}$ = 249.3, 13.7 Hz), 160.1 (dd, $J_{C,F}$ = 253.1, 14.9 Hz), 143.5, 139.0, 130.0, 127.1, 126.6 (d, $J_{C,F}$ = 13.1 Hz), 121.2 (d, $J_{C,F}$ = 15.6 Hz), 116.9 (d, $J_{C,F}$ = 24.0 Hz), 105.2 (t, $J_{C,F}$ = 25.8 Hz), 21.5; **ATR-IR**: *v* 3243, 1590, 1340, 1166 cm^{-1}; **HRMS** (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{13}H_{11}BrF_2NO_2S$ 361.9662/363.9641, found 361.9650/363.9630.

***N*-(2-bromo-6-chloro-4-fluorophenyl)-4-methylbenzenesulfonamide (1m):** EtOAc/PE = 1/10, 984mg, 26%, white solid. Mp:163-166°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 10.03 (s, 1H), 7.70 (dd, J = 7.6, 2.4 Hz, 1H), 7.63-7.58 (m, 3H), 7.38 (d, J = 8.0 Hz, 2H), 2.39 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ (ppm): 160.4 (d, $J_{C,F}$ = 250.8 Hz), 143.4, 139.7, 136.1 (d, $J_{C,F}$ = 112.6 Hz), 130.4 (d, $J_{C,F}$ = 3.9 Hz), 129.9, 127.5 (d, $J_{C,F}$ = 10.9 Hz), 127.1, 120.1 (d, $J_{C,F}$ = 24.2 Hz), 117.5 (d, $J_{C,F}$ = 25.1 Hz), 21.5; **ATR-IR**: *v* 3266, 1590, 1339, 1162 cm^{-1}; **HRMS** (ESI-TOF) *m/z* $[M]^+$ calcd for $C_{13}H_{10}BrClFNO_2S$ 376.9288, found 376.9294; *m/z* $[M+Na]^+$ calcd for

$C_{13}H_{10}BrClFNO_2SNa$ 401.9165, found 401.9164.

***N*-(2-bromo-3-fluorophenyl)-4-methylbenzenesulfonamide (1n):** EtOAc/PE = 1/10, 2.3g, 67%, white solid. Mp:105-107°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 10.05 (s, 1H), 7.63 (d, J = 8.0 Hz, 2H), 7.39-7.23 (m, 3H), 7.21 (td, J = 8.4, 1.2 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 2.38 (s, 3H); **^{13}C NMR** (150 MHz, DMSO-d_6) δ (ppm): 159.3 (d, $J_{C,F}$ = 242.1 Hz), 143.9, 137.9, 137.6, 130.2, 129.5 (d, $J_{C,F}$ = 9.2 Hz), 127.2, 122.9, 114.4 (d, $J_{C,F}$ = 22.8 Hz), 107.5 (d, $J_{C,F}$ = 20.9 Hz), 21.5; **ATR-IR**: v 3277, 1597, 1322, 1154 cm^{-1}; **HRMS** (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{13}H_{12}BrFNO_2S$ 343.9756/345.9736, found 343.9754/345.9733.

***N*-(2-bromo-3-chlorophenyl)-4-methylbenzenesulfonamide (1o):** EtOAc/PE = 1/10, 2.3g, 64%, white solid. Mp:110-111°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 10.05 (s, 1H), 7.63 (d, J = 8.0 Hz, 2H), 7.46 (dd, J = 8.0, 1.6 Hz, 1H), 7.38 (d, J = 8.4 Hz, 2H), 7.33 (t, J = 8.4 Hz, 1H), 7.13 (dd, J = 8.4, 1.6 Hz, 1H), 2.38 (s, 3H); **^{13}C NMR** (150 MHz, DMSO-d_6) δ (ppm): 143.9, 137.9, 137.8, 134.8, 130.2, 129.3, 128.4, 127.2, 125.9, 121.0, 21.5; **ATR-IR**: v 3270, 1595, 1377, 1167 cm^{-1}; **HRMS** (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{13}H_{12}BrClNO_2S$ 359.9461/361.9440, found 359.9460/361.9437.

***N*-(2-bromo-3,4-difluorophenyl)-4-methylbenzenesulfonamide (1p):** EtOAc/PE = 1/10, 1.5g, 42%, white solid. Mp:100-101°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 10.09 (s, 1H), 7.59 (d, J = 8.4 Hz, 2H), 7.46 (q, J = 9.2 Hz, 1H), 7.38 (d, J = 8.0 Hz, 2H), 7.02-6.98 (m, 1H), 2.38 (s, 3H); **^{13}C NMR** (150 MHz, DMSO-d_6) δ (ppm): 148.7 (dd, $J_{C,F}$ = 247.4, 13.8 Hz), 147.7 (dd, $J_{C,F}$ = 243.5, 14.6 Hz), 143.9, 137.7, 133.1, 130.2, 127.2, 124.0 (d, $J_{C,F}$ = 4.8 Hz), 116.9 (d, $J_{C,F}$ = 18.0 Hz), 110.4 (d, $J_{C,F}$ = 18.6 Hz), 21.5; **ATR-IR**: v 3254, 1595, 1378, 1167 cm^{-1}; **HRMS** (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{13}H_{11}BrF_2NO_2S$ 361.9662/363.9641, found 361.9656/363.9633.

***N*-(2-iodo-4-((pyrrolidin-1-ylsulfonyl)methyl)phenyl)-4-methylbenzenesulfonamide (1s):** To a stirred solution of 4-((pyrrolidin-1-ylsulfonyl)methyl)aniline (3.6 g, 15 mmol) in dichloromethane (4 mL) and pyridine (3.6g, 45 mmol) was added iodine (8.4 g, 33 mmol) at 0°C. After stirred for 4h at room temperature, the reaction mixture was added TsCl (3.4 g, 18 mmol) and stirred for another 3h at room temperature. Then the mixture was added dichloromethane (60 mL), H_2O (45 mL) and $Na_2S_2O_3$ (4.8 g, 30 mmol). After stirred for 10 minutes at 0°C, the mixture solution was adjusted pH to 4~5 with 12M HCl solution. Then the organic layer was separated, washed with H_2O (45 mL×2) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (20 mL) while stirring at 80°C. After cooling to room temperature, the mixture was filtered to obtain a pale yellow solid (6.2 g, 79%). **Mp**:215-217°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 9.73 (s, 1H), 7.87 (d, J = 2.0 Hz, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 2.0 Hz, 1H), 7.04 (d, J = 8.4 Hz, 1H), 4.39 (s, 2H), 3.12-3.09 (m, 4H), 2.38 (s, 3H), 1.78-1.75 (m, 4H); **^{13}C NMR** (150 MHz, DMSO-d_6) δ (ppm): 143.6, 142.1, 138.5, 138.1, 131.7, 130.6, 130.1, 127.3, 126.9, 98.3, 52.4, 48.1, 25.8, 21.5; **ATR-IR**: v 3238, 2972, 1596, 1327, 1165 cm^{-1}; **HRMS** (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{18}H_{22}IN_2O_4S_2$ 521.0066; Found 521.0067.

Ethyl (*E*)-4-acetoxybut-2-enoate (2a)[45]. (Method A) To a stirred solution of (*E*)-4-acetoxybut-2-enoic acid[46] (46 mmol) and K_2CO_3 (23 mmol) in DMF (100 mL) was added iodoethane (50.6 mmol) slowly at 0°C. The reaction mixture was allowed to stir for 2h at room temperature. The solvent was then removed under reduced pressure and ethyl acetate (150 mL) was added. The organic mixture was washed with brine (50 mL×3), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column

chromatography (EtOAc/PE = 1/10) to yield corresponding compound as colorless oil (6.9g, 87%).

(Method B) A mixture of ethyl (*E*)-4-bromobut-2-enoate (52 mmol) and KOAc (104 mmol) in CH_3CN (100 mL) was stirred at room temperature for 5h. The solvent was then removed under reduced pressure and ethyl acetate (150 mL) was added. The organic mixture was washed with brine (50 mL×2), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography (EtOAc/PE = 1/10) to yield corresponding compound as colorless oil (7.2g, 81%). The characterization data were consistent with those reported previously.

(*E*)-4-morpholino-4-oxobut-2-en-1-yl acetate (2b)[47]**.** To a stirred solution of (*E*)-4-acetoxybut-2-enoic acid (50 mmol), EDCI (60 mol) and DMAP (1 mmol) in DCM (150 mL) was added morpholine (50 mmol) slowly at 0°C. The reaction mixture was allowed to stirred for 3h, then washed with 1N HCl (50 mL) and brine (50 mL×2) successively, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography (EtOAc/PE = 1/1) to yield corresponding compound as colorless oil (8.7g, 82%). The characterization data were consistent with those reported previously.

General produce for the cascade Tsuji-Trost reaction and Heck coupling. A three-necked round bottom flask charged with a magnetic stir bar, **1** (1 mmol), **2** (1.2 mmol), $Pd(OAc)_2$ (0.05 mmol), P(*o*-tol)$_3$ (0.1 mmol), DIPEA (3 mmol) was equipped with a condenser, and then evacuated and backfilled with N_2. Anhydrous DMA (5 mL) was added through syringe and the reaction mixture was stirred for 12~24 h at 100 °C (for iodoaniline) or 120 °C (for bromoaniline) under nitrogen atmosphere. After the reaction mixture was cooled to room temperature, the solvent was removed under reduced pressure and ethyl acetate (60 mL) was added. The organic mixture was washed with brine (20 mL×6), and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography to yield corresponding compound.

Ethyl 2-(1-tosyl-1H-indol-3-yl)acetate (3aa)[48]**:** Et_3N as base, 12h, EtOAc/PE = 1/15, 293mg, 82%, pale yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 8.00 (d, *J* = 8.4 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.60 (s, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 4.19 (q, *J* = 6.8 Hz, 2H), 3.70 (s, 2H), 2.34 (s, 3H), 1.26 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ (ppm): 170.5, 144.9, 135.3, 135.0, 130.5, 129.9, 126.8, 124.8, 124.7, 123.2, 119.6, 115.2, 113.6, 61.1, 31.1, 21.5, 14.2; **ATR-IR**: *v* 2981, 1733, 1596 , 1367, 1171 cm^{-1}; **HRMS** (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{20}NO_4S$ 358.1113; Found 358.1107.

1-Morpholino-2-(1-tosyl-1H-indol-3-yl)ethan-1-one (3ab): 12h, EtOAc/PE = 1/1, 343mg, 86%, white solid. **Mp**:134-135°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 7.92 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.70 (s, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.39-7.32 (m, 3H), 7.25 (t, *J* = 7.2 Hz, 1H), 3.80 (s, 2H), 3.51-3.42 (m, 8H), 2.31 (s, 3H); **^{13}C NMR** (150 MHz, DMSO-d_6) δ (ppm):168.4, 145.9, 134.8, 134.7, 131.2, 130.7, 127.1, 125.2, 125.1, 123.6, 120.9, 117.6, 113.5, 66.5, 66.5, 46.3, 42.2, 30.0, 21.5; **ATR-IR**: *v* 2969, 1649, 1598, 1361, 1170 cm^{-1}; **HRMS** (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{21}H_{23}N_2O_4S$ 399.1379; Found 399.1380.

Ethyl 2-(5-bromo-1-tosyl-1H-indol-3-yl)acetate (3ba): (24h, EtOAc/PE = 1/20, 178mg, 41%), pale yellow solid. **Mp**:80-81°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 7.88 (d, *J* = 9.2 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.793-7.788 (m, 2H), 7.50 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.39 (d, *J* = 8.4

Hz, 2H), 4.09 (q, *J* = 7.2 Hz, 2H), 3.81 (s, 2H), 2.32 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, DMSO-d_6) δ (ppm): 170.7, 146.2, 134.4, 133.5, 132.8, 130.8, 127.9, 127.1, 127.0, 123.5, 116.5, 115.9, 115.5, 60.9, 30.3, 21.5, 14.5; **ATR-IR**: *v* 2974, 1738, 1593, 1366, 1168 cm^{-1}; **HRMS** (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{19}BrNO_4S$ 436.0218/438.0198; Found 436.0212/438.0193.

2-(5-Bromo-1-tosyl-1H-indol-3-yl)-1-morpholinoethan-1-one (3bb): 16h, EtOAc/PE = 1/1, 272 mg, 58%, white solid. **Mp**:178-180°C; **^{1}H NMR** (600 MHz, DMSO-d_6) δ (ppm): 7.88 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.81 (s, 1H), 7.76 (s, 1H), 7.49 (d, *J* = 9.0 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 2H), 3.81 (s, 2H), 3.51-3.44 (m, 8H), 2.33 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-d_6) δ (ppm): 168.2, 146.2, 134.4, 133.6, 133.2, 130.8, 127.8, 127.1, 126.5, 123.6, 117.2, 116.4, 115.5, 66.5, 66.4, 46.2, 42.1, 29.7, 21.5; **ATR-IR**: *v* 2965, 1638, 1598, 1370, 1173 cm^{-1}; **HRMS** (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{21}H_{22}BrN_2O_4S$ 477.0484/479.0463; Found 477.0484/479.0465.

Ethyl 2-(5-fluoro-1-tosyl-1H-indol-3-yl)acetate (3ca): (16h, EtOAc/PE = 1/20, 309mg, 82%), pale yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.93 (dd, *J* = 4.4, 9.2 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.61 (s, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.17 (dd, *J* = 2.4, 9.2 Hz, 1H), 7.06 (dd, *J* = 2.4, 9.2 Hz, 1H), 4.19 (q, *J* = 6.8 Hz, 2H), 3.65 (d, *J* = 1.2 Hz, 2H), 2.37 (s, 3H), 1.27 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ (ppm): 170.3, 159.6 (d, $J_{C,F}$ = 239.7 Hz), 145.1, 135.1, 131.6 (d, $J_{C,F}$ = 9.3 Hz), 131.4, 129.9, 126.8, 126.4, 115.1 (d, $J_{C,F}$ = 3.5 Hz), 114.7 (d, $J_{C,F}$ = 8.0 Hz), 112.9 (d, $J_{C,F}$ = 23.7 Hz), 105.4 (d, $J_{C,F}$ = 25.0 Hz), 61.2, 31.1, 21.6, 14.1; **ATR-IR**: *v* 2982, 1733, 1595, 1369, 1168 cm^{-1}; **HRMS** (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{19}FNO_4S$ 376.1019; Found 376.1009.

2-(5-Fluoro-1-tosyl-1H-indol-3-yl)-1-morpholinoethan-1-one (3cb): 16h, EtOAc/PE = 1/1, 345 mg, 83%, white solid. **Mp**:152-153°C; **^{1}H NMR** (600 MHz, DMSO-d_6) δ (ppm): 7.92 (dd, *J* = 4.2, 9.0 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.77 (s, 1H), 7.40-7.37 (m, 3H), 7.20 (dt, *J* = 8.0, 9.0 Hz, 1H), 3.79 (s, 2H), 3.53-3.43 (m, 8H), 2.33 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ (ppm): 168.2, 159.3 (d, $J_{C,F}$ = 236.2 Hz), 146.1, 134.4, 132.5 (d, $J_{C,F}$ = 9.8 Hz), 131.2, 130.7, 127.1, 127.0, 117.7 (d, *J* = 3.6 Hz), 115.0 (d, *J* = 8.7 Hz), 113.0 (d, *J* = 26.2 Hz), 106.7 (d, *J* = 24.8 Hz), 66.5, 66.5, 46.2, 42,2, 29.8, 21.5; **ATR-IR**: *v* 2971, 1636, 1594, 1366, 1169 cm^{-1}; **HRMS** (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{21}H_{22}FN_2O_4S$ 417.1284; Found 417.1282.

Ethyl 2-(1-tosyl-5-(trifluoromethoxy)-1H-indol-3-yl)acetate (3da): 16h, EtOAc/PE = 1/20, 359mg, 81%, pale yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.99 (d, *J* = 9.2 Hz, 1H), 7.79 (d, *J* = 8.8 Hz, 2H), 7.66 (s, 1H), 7.38 (d, *J* = 1.2 Hz, 1H), 7.74 (d, *J* = 8.8 Hz, 2H), 7.20 (dd, *J* = 1.2, 8.8 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.68 (d, *J* = 0.8 Hz, 2H), 2.38 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ (ppm): 170.2, 145.3, 135.0, 133.2, 131.2, 130.0, 127.6, 126.9, 126.5, 120.6 (d, $J_{C,F}$ = 256.5 Hz), 118.4, 115.0, 14.6, 112.3, 61.2, 31.0, 21.6, 14.1; **ATR-IR**: *v* 2984, 1734, 1596, 1372, 1162 cm^{-1}; **HRMS** (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{20}H_{19}F_3NO_5S$ 442.0936; Found 442.0931.

1-Morpholino-2-(1-tosyl-5-(trifluoromethoxy)-1H-indol-3-yl)ethan-1-one (3db): 14h, EtOAc/PE = 1/1, 389 mg, 80%, white solid. **Mp**:141-142°C; **^{1}H NMR** (600 MHz, DMSO-d_6) δ (ppm): 8.02 (d, *J* = 9.6 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 2H), 7.85 (s, 1H), 7.60 (s, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 9.6 Hz, 1H), 3.83 (s, 2H), 3.52-3.42 (m, 8H), 2.33 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ (ppm): 168.3, 146.3, 144.8, 144.8, 134.4, 133.1, 132.2, 130.8, 127.19, 127.16, 120.6 (d, $J_{C,F}$ = 254.0 Hz), 118.5, 117.6, 114.9, 113.7, 66.5, 66.5, 46.2, 42.2, 29.6, 21.5; **ATR-IR**: *v* 3122, 1654, 1597, 1365, 1171 cm^{-1}; **HRMS** (ESI-TOF) *m/z* $[M+H]^+$ calcd for

$C_{22}H_{22}F_3N_2O_5S$ 483.1202; Found 483.1204.

Methyl 3-(2-ethoxy-2-oxoethyl)-1-tosyl-1H-indole-5-carboxylate (3ea): 24h, EtOAc/PE = 1/15, 244mg, 59%；recovered start material **1e** 94mg, 84% brsm, pale yellow solid. **Mp**:133-134°C; **^{1}H NMR** (600 MHz, DMSO-d_6) δ (ppm): 8.20 (s, 1H), 8.06 (d, J = 9.0 Hz, 1H), 7.96 (d, J = 9.0 Hz, 1H), 7.89-7.87 (m, 3H), 7.41 (d, J = 8.4 Hz, 2H), 4.10 (q, J = 7.2 Hz, 2H), 3.88 (s, 2H), 3.86 (s, 3H), 2.32 (s, 3H), 1.18 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ (ppm): 170.7, 166.6, 146.3, 137.2, 134.4, 130.9, 130.7, 127.2, 127.0, 126.1, 125.2, 122.6, 116.8, 113.7, 61.0, 52.6, 30.4, 21.5, 14.5; **ATR-IR**: v 2979, 1735, 1721, 1609, 1593, 1370, 1164 cm^{-1}; **HRMS** (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{21}H_{22}NO_6S$ 416.1168; Found 416.1165.

Methyl 3-(2-morpholino-2-oxoethyl)-1-tosyl-1H-indole-5-carboxylate (3eb): (24h, EtOAc/PE = 1/1, 330 mg, 72%), white solid, **Mp**:208-209°C; **^{1}H NMR** (600 MHz, DMSO-d_6) δ (ppm): 8.23 (s, 1H), 8.05 (d, J = 9.0 Hz, 1H), 7.95 (d, J = 9.0 Hz, 1H), 7.88 (d, J = 7.8 Hz, 2H), 7.83 (s, 1H), 7.41 (d, J = 7.8 Hz, 2H), 3.88 (s, 2H), 3.86 (s, 3H), 3.54-3.44 (m, 8H), 2.33 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ (ppm): 168.3, 168.7, 146.3, 137.3, 134.4, 131.2, 130.8, 127.2, 126.5, 126.1, 122.9, 118.1, 113.6, 66.5, 52,6, 46.2, 42.2, 29.7, 21.5; **ATR-IR**: v 2953, 1729, 1648, 1613, 1597, 1364, 1174 cm^{-1}; **HRMS** (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{23}H_{25}N_2O_6S$ 457.1433; Found 457.1430.

Ethyl 2-(6-bromo-1-tosyl-1H-indol-3-yl)acetate (3fa): 16h, EtOAc/PE = 1/15, 253 mg, 58%, pale yellow solid. **Mp**:86-87°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 8.04 (d, J = 1.6 Hz, 1H), 7.87 (d, J = 8.4 Hz, 2H), 7.79 (s, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.45 (dd, J = 1.6, 8.4 Hz, 1H), 7.42 (d, J = 8.4 Hz, 1H), 4.08 (q, J = 7.2 Hz, 2H), 3.80 (s, 2H), 2.33 (s, 3H), 1.16 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, DMSO-d_6) δ (ppm): 170.6, 146.3, 135.4, 134.4, 130.9, 129.9, 127.1, 126.79, 126.3, 122.6, 118.0, 116,3, 116.0, 60.9, 30.3, 21.5, 14.5; **ATR-IR**: v 2982, 1740, 1594, 1369, 1170 cm^{-1}; **HRMS** (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{19}H_{19}BrNO_4S$ 436.0218/438.0198; Found 436.0207/438.0190.

2-(6-Bromo-1-tosyl-1H-indol-3-yl)-1-morpholinoethan-1-one (3fb): 24h, EtOAc/PE = 1/2, 292 mg, 61%, white solid. **Mp**:99-100°C; **^{1}H NMR** (600 MHz, DMSO-d_6) δ (ppm): 8.04 (s, 1H), 7.86 (d, J = 9.6 Hz, 2H), 7.75 (s, 1H), 7.55 (d, J = 9.6 Hz, 1H), 7.45-7.42 (m, 3H), 3.81 (s, 2H), 3.51-3.42 (m, 8H), 2.34 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ (ppm): 168.2, 146.3, 135.4, 130.9, 130.3, 127.1, 126.7, 125.8, 122.9, 117.9, 117.6, 115.9, 66.5, 66.4, 46.2, 42.2, 29.8, 21.5; **ATR-IR**: v 3103, 1647, 1595, 1375, 1167 cm^{-1}; **HRMS** (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{21}H_{22}BrN_2O_4S$ 477.0484/479.0463; Found 477.0482/479.0463.

Ethyl 2-(6-fluoro-1-tosyl-1H-indol-3-yl)acetate (3ga) 24h, EtOAc/PE = 1/20, 233mg, 62%；recovered start material **1g** 31mg, 68% brsm, pale yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.78 (d, J = 8.0 Hz, 2H), 7.72 (dd, J = 2.4, 9.6 Hz, 1H), 7.55 (s, 1H), 7.45 (dd, J = 5.6, 8.8 Hz, 1H), 7.26 (d, J = 7.6 Hz, 2H), 7.02 (dt, J = 2.4, 8.8 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 3.67 (d, J = 0.8 Hz, 2H), 2.38 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ (ppm): 170.4, 161.0 (d, $J_{C,F}$ = 239.7 Hz), 145.2, 135.2 (d, $J_{C,F}$ = 12.5 Hz), 135.1, 130.0, 126.9, 126.7, 124.9 (d, $J_{C,F}$ = 3.8 Hz), 120.5 (d, $J_{C,F}$ = 9.8 Hz), 115.0, 111.7 (d, $J_{C,F}$ = 24.0 Hz), 101.0 (d, $J_{C,F}$ = 27.8 Hz), 61.1, 31.1. 21.6, 14.1; **ATR-IR**: v 2924, 1733, 1597, 1369, 1170 cm^{-1}; **HRMS** (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{19}H_{19}FNO_4S$ 376.1019; Found 376.1010.

2-(6-Fluoro-1-tosyl-1H-indol-3-yl)-1-morpholinoethan-1-one (3gb): 24h, EtOAc/PE = 1/1, 249 mg, 60%, white solid. **Mp**:160-162°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 7.88 (d, J = 8.8 Hz, 2H), 7.71-7.68 (m, 2H), 7.59 (dd, J = 5.6, 8.8 Hz, 1H), 7.41 (d, J = 8.0 Hz, 2H), 7.15 (dt, J =

1.6, 8.8 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 2H), 3.50-3.41 (m, 8H), 2.33 (s, 3H); **^{13}C NMR** (150 MHz, DMSO-d_6) δ (ppm): 168.3, 160.6 (d, $J_{C,F}$ = 239.7 Hz), 146.2, 134.8 (d, $J_{C,F}$ = 12.3 Hz), 134.4, 130.8, 127.8, 127.2, 125.5 (d, $J_{C,F}$ = 3.2 Hz), 122.4 (d, $J_{C,F}$ = 10.2 Hz), 117.6, 111.9 (d, $J_{C,F}$ = 22.7 Hz), 100.6 (d, $J_{C,F}$ = 27.8 Hz), 66.5, 66.5, 42.2, 46.3, 29.9, 21.5; **ATR-IR**: *v* 2966, 1651, 1598, 1361, 1169 cm^{-1}; **HRMS** (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{21}H_{22}FN_2O_4S$ 417.1284; Found 417.1284.

Ethyl 2-(6-methoxy-1-tosyl-1H-indol-3-yl)acetate (3ha): 24h, EtOAc/PE = 1/20, 166 mg, 43%, pale yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.76 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 2.0 Hz, 1H), 7.46 (s, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.89 (dd, *J* = 2.0, 8.4 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.89 (s, 3H), 3.65 (s, 2H), 2.36 (s, 3H), 1.25 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ (ppm): 170.6, 158.1, 144.9, 136.1, 135.3, 129.8, 126.8, 124.3, 123.4, 120.1, 115.3, 112.3, 98.0, 61.0, 55.8, 31.2, 21.6, 14.2; **ATR-IR**: *v* 2981, 1732, 1596, 1365, 1168 cm^{-1}; **HRMS** (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{20}H_{22}NO_5S$ 388.1219; Found 388.1216.

Ethyl (E)-4-((N-(2-bromo-5-methoxyphenyl)-4-methylphenyl)sulfonamido)but-2-enoate (3ha'): 24h, EtOAc/PE = 1/20, 198 mg, 51%, pale yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.768 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 9.2 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.90 (dt, *J* = 6.4, 16.0 Hz, 1H), 6.81-6.77 (m, 2H), 5.88 (dt, *J* = 1.2, 14.8 Hz, 1H), 4.41-4.28 (m, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.76 (s, 3H), 2.46 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm):165.6, 159.1, 143.9, 141.8, 138.1, 136.5, 134.1, 129.6, 127.9, 124.4, 118.2, 116.3, 115,1, 60.5, 55.6, 51.9, 21.6, 14.2; **ATR-IR**: *v* 2980, 1717, 1592, 1352, 1159 cm^{-1}; **HRMS** (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{20}H_{23}BrNO_5S$ 468.0480/470.0460; Found 468.0479/470.0458.

2-(6-Methoxy-1-tosyl-1H-indol-3-yl)-1-morpholinoethan-1-one (3hb): 24h, EtOAc/PE = 1/2, 248 mg, 58%, white solid, **Mp**:181-182°C; **^{1}H NMR** (600 MHz, DMSO-d_6) δ (ppm): 7.83 (d, *J* = 7.8 Hz, 2H), 7.54 (s, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.40-7.39 (m, 3H), 6.90 (d, *J* = 9.0 Hz, 1H), 3.83 (s, 3H), 3.75 (s, 2H), 3.49-3.42 (m, 8H), 2.32 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ (ppm): 168.4, 158.1, 145.9, 135.9, 134.5, 130.7, 127.1, 124.8, 123.6, 121.6, 117.6, 112.4, 97.9, 66.5, 66.4, 56.0, 46.3, 42.1, 30.2,21.5; **ATR-IR**: *v* 3109, 1647, 1596, 1372, 1167 cm^{-1}; **HRMS** (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{22}H_{25}N_2O_5S$ 429.1484; Found 429.1482.

Methyl 3-(2-ethoxy-2-oxoethyl)-1-tosyl-1H-indole-6-carboxylate (3ia): 12h, EtOAc/PE = 1/15, 358 mg, 86%, pale yellow solid, **Mp**:99-100°C; **^{1}H NMR** (600 MHz, DMSO-d_6) δ (ppm): 8.52 (s, 1H), 7.98 (s, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 4.09 (q, *J* = 7.2 Hz, 2H), 3.91 (s, 3H), 3.85 (s, 2H), 2.32 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 3H), **^{13}C NMR** (100 MHz, DMSO-d_6) δ (ppm): 170.6, 166.7, 146.3, 134.6, 134.5, 134.3, 130.9, 128.9, 127.0, 126.4, 124.3, 121.0, 116.6, 114.6, 61.0, 52.8, 30.3, 21.5, 14.5; **ATR-IR**: *v* 2955, 1719, 1706, 1594, 1371, 1303, 1170 cm^{-1}; **HRMS** (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{21}H_{22}NO_6S$ 416.1168; Found 416.1164.

Methyl 3-(2-morpholino-2-oxoethyl)-1-tosyl-1H-indole-6-carboxylate (3ib): 12h, EtOAc/PE = 1/2, 406 mg, 89%, white solid, **Mp**:212-213°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 8.52 (d, *J* = 0.8 Hz, 1H), 7.93 (s, 1H), 7.86 (dd, *J* = 1.4, 8.2 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 3.91 (s, 3H), 3.85 (s, 2H), 3.51-3.42 (m, 8H), 2.32 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6) δ (ppm): 168.2, 168.7, 146.3, 135.0, 134.5, 134.3, 130.9, 128.49, 126.9, 126.3, 124.3, 121.3, 117.9, 114.6, 66.5, 66.5, 52.8, 46.2, 42.2, 29.7, 21.5; **ATR-IR**: *v* 2967, 1710, 1645, 1593, 1370, 1169 cm^{-1}; **HRMS** (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{23}H_{25}N_2O_6S$ 457.1433; Found 457.1435.

Ethyl 2-(7-fluoro-1-tosyl-1H-indol-3-yl)acetate (3ja): 24h, EtOAc/PE = 1/10~1/5, 316mg, 84%, pale yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.85 (d, J = 7.6 Hz, 2H), 7.79 (s, 1H), 7.32-7.28 (m, 3H), 7.19-7.14 (m, 1H), 7.00-6.95 (m, 1H), 4.21 (q, J = 7.2 Hz, 2H), 3.73 (s, 2H), 2.40 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 170.4, 149.7 (d, $J_{C,F}$ = 249.1 Hz), 145.0, 135.5, 134.7 (d, $J_{C,F}$ = 249.1 Hz), 129.8, 127.7 (d, $J_{C,F}$ = 3.0 Hz), 127.2, 123.9 (d, $J_{C,F}$ = 7.4 Hz), 122.1 (d, $J_{C,F}$ = 10.9 Hz), 115.4 (d, $J_{C,F}$ = 3.6 Hz), 113.8 (d, $J_{C,F}$ = 2.1 Hz), 111.4 (d, $J_{C,F}$ = 19.8 Hz), 61.2, 31.0, 21.6, 14.2; **ATR-IR**: v 2982, 1595, 1369, 1171 cm^{-1}; **HRMS** (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{19}H_{19}FNO_4S$ 376.1019, found 376.1017.

2-(7-fluoro-1-tosyl-1H-indol-3-yl)-1-morpholinoethan-1-one (3jb): 16h, EtOAc/PE = 1/1~1/3, 353mg, 85%, pale yellow solid. Mp:190-192°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 7.84 (s, 1H), 7.78 (d, J = 7.6 Hz, 2H), 7.45-7.41 (m, 3H), 7.25-7.20 (m, 1H), 7.14-7.09 (m, 1H), 3.86 (s, 2H), 3.57-3.45 (m, 8H), 2.35 (s, 3H); **^{13}C NMR** (150 MHz, DMSO-d_6) δ (ppm): 168.2, 149.3 (d, $J_{C,F}$ = 246.0 Hz), 145.9, 135.6, 135.1, 130.7, 127.7, 127.5, 124.7 (d, $J_{C,F}$ = 6.2 Hz), 121.5 (d, $J_{C,F}$ = 9.2 Hz), 117.1, 116.6, 111.7 (d, $J_{C,F}$ = 21.0 Hz), 66.6, 46.3, 42.2, 29.7, 21.5; **ATR-IR**: v 2980, 1655, 1596, 1365, 1171 cm^{-1}; **HRMS** (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{21}H_{22}FN_2O_4S$ 417.1284, found 417.1285.

Methyl 3-(2-ethoxy-2-oxoethyl)-1-tosyl-1H-indole-7-carboxylate (3ka): 12h, EtOAc/PE = 1/10, 302mg, 73%, pale yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.61-7.51 (m, 5H), 7.33 (t, J = 7.6 Hz, 1H), 7.17 (d, J = 8.4 Hz, 2H), 4.14 (q, J = 6.8 Hz, 2H), 3.95 (s, 3H), 3.63 (s, 2H), 2.34 (s, 3H), 1.22 (t, J = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 170.0, 168.9, 144.7, 134.7, 132.7, 132.2, 129.4, 128.2, 126.9, 125.8, 123.8, 122.7, 122.1, 117.6, 61.1, 52.6, 31.0, 21.5, 14.1; **ATR-IR**: v 2982, 1727, 1595, 1368, 1171 cm^{-1}; **HRMS** (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{21}H_{22}NO_6S$ 416.1168, found 416.1165.

Methyl 3-(2-morpholino-2-oxoethyl)-1-tosyl-1H-indole-7-carboxylate (3kb): 12h, EtOAc/PE = 1/1~1/2, 319mg, 70%, pale yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 7.65 (dd, J = 8.0, 1.2 Hz, 1H), 7.65 (d, J = 8.0, 1.2 Hz, 2H), 7.55 (dd, J = 7.2, 0.8 Hz, 1H),7.40 (s, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.19 (d, J = 8.0 Hz, 2H), 3.94 (s, 3H), 3.70 (s, 2H), 3.64-3.32 (m, 8H), 2.35 (s, 3H); **^{13}C NMR** (100 MHz, , $CDCl_3$) δ (ppm): 168.8, 167.9, 144.9, 134.9, 132.5, 132.2, 129.6, 127.3, 126.8, 126.0, 123.9, 122.7, 122.2, 118.1, 66.7, 66.4, 52.6, 46.5, 42.1, 30.7, 21.6; **ATR-IR**: v 2922, 1727, 1595, 1365, 1173 cm^{-1}; **HRMS** (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{23}H_{25}N_2O_6S$ 457.1433, found 457.1431.

Ethyl 2-(5,7-difluoro-1-tosyl-1H-indol-3-yl)acetate (3la): 12h, EtOAc/PE = 1/10~1/6, 357mg, 91%, pale yellow solid. Mp:93-94°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 7.96 (s, 1H), 7.78 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.31 (dd, J = 8.8, 2.0 Hz, 1H), 7.22 (td, J = 9.6, 2.0 Hz, 1H), 4.11 (q, J = 6.8 Hz, 2H), 3.85 (s, 2H), 2.36 (s, 3H), 1.20 (t, J = 6.8 Hz, 3H); **^{13}C NMR** (150 MHz, DMSO-d_6) δ (ppm): 170.6, 158.5 (dd, $J_{C,F}$ = 238.7, 10.5 Hz), 148.8 (dd, $J_{C,F}$ = 250.5, 13.8 Hz), 146.2, 135.3 (dd, $J_{C,F}$ = 10.5, 3.8 Hz), 134.8, 130.8, 129.9, 127.5, 118.4 (d, $J_{C,F}$ = 11.9 Hz), 115.6, 61.0, 30.1, 21.5; **ATR-IR**: v 2983, 1740, 1597, 1362, 1164 cm^{-1}; **HRMS** (ESI-TOF) m/z $[M+H]^+$ calcd for $C_{19}H_{18}F_2NO_4S$ 394.0925, found 394.0918.

2-(5,7-difluoro-1-tosyl-1H-indol-3-yl)-1-morpholinoethan-1-one (3lb): 12h, EtOAc/PE = 1/1, 361mg, 83%, pale yellow solid. Mp:185-188°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 7.92 (s, 1H), 7.78 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.30 (dd, J = 8.4, 2.0 Hz, 1H), 7.21 (td, J = 9.2, 2.0 Hz, 1H), 3.84 (s, 2H), 3.57-3.45 (m, 8H), 2.36 (s, 3H); **^{13}C NMR** (150 MHz, DMSO-d_6) δ (ppm): 168.2, 158.5 (dd, $J_{C,F}$ = 239.7, 11.4 Hz), 148.8 (dd, $J_{C,F}$ = 249.3, 12.5 Hz), 146.1, 135.7 (d,

$J_{C,F}$ = 6.5 Hz), 134.9, 130.8, 129.5, 127.5, 118.4 (d, $J_{C,F}$ = 11.7 Hz), 116.9, 103.0 (dd, $J_{C,F}$ = 23.6 Hz), 101.1 (dd, $J_{C,F}$ = 30.5, 23.9 Hz), 66.5, 66.5, 46.2, 29.5, 21.5; **ATR-IR**: *v* 2963, 1637, 1603, 1364, 1170 cm^{-1}; **HRMS** (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{21}H_{21}F_2N_2O_4S$ 435.1190, found435.1190.

Ethyl 2-(7-chloro-5-fluoro-1-tosyl-1H-indol-3-yl)acetate (3ma): 16h, EtOAc/PE = 1/10~1/5, 340mg, 83%, pale yellow solid. Mp:82-84°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 8.05 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.48 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.32 (dd, *J* = 9.2, 2.4 Hz, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.88 (s, 2H), 2.38 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, DMSO-d_6) δ (ppm): 170.6, 158.4 (d, $J_{C,F}$ = 239.3 Hz), 145.7, 136.3, 135.6 (d, $J_{C,F}$ = 9.9 Hz), 131.5, 130.6, 128.5, 127.3, 119.0 (d, $J_{C,F}$ = 13.2 Hz), 115.0 (d, $J_{C,F}$ = 29.9 Hz), 115.0 (d, $J_{C,F}$ = 5.0 Hz), 105.8 (d, $J_{C,F}$ = 23.6 Hz), 61.0, 30.1, 21.5, 14.5; **ATR-IR**: *v* 2987, 1739, 1596, 1365, 1171 cm^{-1}; **HRMS** (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{19}H_{18}ClFNO_4S$ 410.0629, found 410.0630.

2-(7-chloro-5-fluoro-1-tosyl-1H-indol-3-yl)-1-morpholinoethan-1-one (3mb): 16h, EtOAc/PE = 2/1, 359mg, 80%, pale yellow solid. Mp:199-200°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 8.0 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.48 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.31 (dd, *J* = 8.8, 2.0 Hz, 1H), 3.87 (s, 2H), 3.60-3.47 (m, 8H), 2.38 (s, 3H); **^{13}C NMR** (150 MHz, DMSO-d_6) δ (ppm): 168.2, 158.3 (d, $J_{C,F}$ = 242.0 Hz), 145.7, 136.3, 136.1 (d, $J_{C,F}$ = 10.4 Hz), 131.1, 130.6, 128.5, 127.3, 118.9 (d, $J_{C,F}$ = 11.3 Hz), 116.3 (d, $J_{C,F}$ = 2.9 Hz), 114.9 (d, $J_{C,F}$ = 28.7 Hz), 106.0 (d, $J_{C,F}$ = 23.4 Hz), 66.6, 66.5, 46.2, 42.2, 29.4, 21.5; **ATR-IR**: *v* 2972, 1641, 1604, 1346, 1170 cm^{-1}; **HRMS** (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{21}H_{21}ClFN_2O_4S$ 451.0895, found 451.0894.

2-(4-fluoro-1-tosyl-1H-indol-3-yl)-1-morpholinoethan-1-one (3nb): 24h, EtOAc/PE = 1/1~1/2, 216mg, 52%, pale yellow solid. Mp:204-206°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 7.87 (d, *J* = 8.8 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.64 (s, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.35-7.29 (m, 1H), 7.03-6.99 (m, 1H), 3.84 (s, 2H), 3.59-3.45 (m, 8H), 2.34 (s, 3H); **^{13}C NMR** (150 MHz, DMSO-d_6) δ (ppm): 168.6, 156.4 (d, $J_{C,F}$ = 246.3 Hz), 146.2, 137.0 (d, $J_{C,F}$ = 9.8 Hz), 134.4, 130.8, 127.2, 126.2 (d, $J_{C,F}$ = 5.9 Hz), 125.5, 119.8 (d, $J_{C,F}$ = 19.5 Hz), 115.7, 110.0, 109.3 (d, $J_{C,F}$ = 18.6 Hz), 66.6, 66.6, 46.0, 42.2, 30.4, 21.5; **ATR-IR**: *v* 2959, 1641, 1591, 1373, 1177 cm^{-1}; **HRMS** (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{21}H_{22}FN_2O_4S$ 417.1284, found 417.1287.

2-(4-chloro-1-tosyl-1H-indol-3-yl)-1-morpholinoethan-1-one (3ob): 24h, EtOAc/PE = 1/1~1/2, 91mg, 21%, pale yellow solid. Mp:216-218°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 7.91 (d, *J* = 7.6 Hz, 1H), 7.86 (d, *J* = 7.2 Hz, 2H), 7.73 (s, 1H), 7.41 (d, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 3.94 (s, 2H), 3.60-3.34 (m, 8H), 2.33 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 169.0, 145.3, 136.4, 134.8, 130.0, 127.1, 126.9, 126.5, 125.8, 125.4, 124.4, 115.8, 112.5, 66.9, 66.6, 46.3, 42.2, 31.5, 21.6; **ATR-IR**: *v* 2958, 1637, 1591, 1371, 1172 cm^{-1}; **HRMS** (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{21}H_{22}ClN_2O_4S$ 433.0989, found 433.0987.

2-(4,5-difluoro-1-tosyl-1H-indol-3-yl)-1-morpholinoethan-1-one (3pb): 16h, EtOAc/PE = 1/1~1/2, 340mg, 78%, pale yellow solid. Mp:166-168°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 7.87 (d, *J* = 8.0 Hz, 2H), 7.75-7.72 (m, 2H), 7.43-7.35 (m, 3H), 3.86 (s, 2H), 3.60-3.45 (m, 8H), 2.34 (s, 3H); **^{13}C NMR** (150 MHz, DMSO-d_6) δ (ppm): 168.3, 146.4 (dd, $J_{C,F}$ = 240.2, 10.1 Hz), 145.5, 143.6 (dd, $J_{C,F}$ = 249.0, 14.1 Hz), 134.7, 132.4 (d, $J_{C,F}$ = 6.9 Hz), 130.1, 126.9, 126.3, 120.7 (dd, $J_{C,F}$ = 15.5 Hz), 114.2 (d, $J_{C,F}$ = 20.9 Hz), 109.5 (t, $J_{C,F}$ = 5.5 Hz), 66.9, 66.6, 46.3, 42.3, 30.5, 21.6; **ATR-IR**: *v* 2960, 1637, 1591, 1373, 1170 cm^{-1}; **HRMS** (ESI-TOF) *m/z* $[M+H]^+$ calcd for

$C_{21}H_{21}F_2N_2O_4S$ 435.1190, found 435.1187.

Ethyl 2-(1-tosyl-1H-pyrrolo[3,2-b]pyridin-3-yl)acetate (3qa): 100°C, 24h, EtOAc/PE = 1/15, 259mg, 72%, pale yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 8.54 (dd, *J* = 1.6, 4.8 Hz, 1H), 8.26 (dd, *J* = 1.6, 8.8 Hz, 1H), 7.87 (s, 1H), 7.77 (d, *J* = 8.8 Hz, 2H), 7.27-7.25 (m, 3H), 4.21 (q, *J* = 7.2 Hz, 2H), 3.86 (s, 2H), 2.37 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 170.7, 147.7, 146.0, 145.4, 135.0, 130.1, 128.5, 127.7, 126.8, 120.9, 119.3, 116.3, 61.1, 29.2, 21.6, 14.2; **ATR-IR**: *v* 2981, 1732, 1597, 1366, 1168 cm^{-1}; **HRMS** (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{18}H_{19}N_2O_4S$ 359.1066; Found 359.1066.

1-Morpholino-2-(1-tosyl-1H-pyrrolo[3,2-b]pyridin-3-yl)ethan-1-one (3qb): 12h, EtOAc/PE = 1/4, 324mg, 81%, white solid. **Mp**:136-137°C; **^{1}H NMR** (600 MHz, DMSO-*d*$_6$) δ (ppm): 8.50 (d, *J* = 4.8 Hz, 1H), 8.30 (d, *J* = 8.4 Hz, 2H), 7.95 (s, 1H), 7.89 (d, *J* = 7.8 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.37 (dd, *J* = 4.8, 5.6 Hz, 1H), 3.82 (s, 2H), 3.56-3.44 (m, 8H), 2.33 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-*d*$_6$) δ (ppm): 168.4, 148.0, 146.3, 146.2, 134.4, 130.8, 128.4, 128.0, 127.2, 121.1, 120.0, 118.5, 66.5, 46.2, 42.2, 28.2, 21.5; **ATR-IR**: *v* 3100, 1651, 1601, 1369, 1168 cm^{-1}; **HRMS** (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{20}H_{22}N_3O_4S$ 400.1331; Found 400.1326.

Ethyl 2-(1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)acetate (3ra): 24h, EtOAc/PE = 1/20, 241mg, 67%, pale yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 8.45 (dd, *J* = 1.6, 4.4 Hz, 1H), 8.09 (d, *J* = 8.8 Hz, 2H), 7.88 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.71 (s, 1H), 7.28 (d, *J* = 7.6 Hz, 2H), 7.20 (dd, *J* = 4.4, 8.0 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.69 (d, *J* = 0.8 Hz, 2H), 2.38 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$ δ (ppm): 170.3, 147.3, 145.1, 145.1, 135.5, 129.6, 128.3, 128.0, 124.6, 122.8, 118.7, 111.6, 61.2, 31.4, 21.6, 14.2; **ATR-IR**: *v* 2981, 1732, 1596, 1370, 1173 cm^{-1}; **HRMS** (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{18}H_{19}N_2O_4S$ 359.1066; Found 359.1062.

1-Morpholino-2-(1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)ethan-1-one (3rb): 24h, EtOAc/PE = 1/2, 248mg, 62%, white solid. **Mp**:134-136°C; **^{1}H NMR** (600 MHz, DMSO-*d*$_6$) δ (ppm): 8.36 (d, *J* = 3.6 Hz, 1H), 8.00-7.96 (m, 3H), 7.81 (s, 1H), 7.41 (d, *J* = 7.8 Hz, 2H), 7.29 (dd, *J* = 4.8, 7.8 Hz, 1H), 3.85 (s, 2H), 3.56-3.44 (m, 8H), 2.34 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-*d*$_6$) δ (ppm): 168.4, 147.1, 145.9, 145.1, 135.2, 130.4, 129.8, 127.9, 124.9, 123.5, 119.4, 114.47, 66.5, 66.5, 46.3, 42.2, 29.9, 21.5; **ATR-IR**: *v* 2963, 1665, 1589, 1353, 1158 cm^{-1}; **HRMS** (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{20}H_{22}N_3O_4S$ 400.1331; Found 400.1329.

Ethyl 2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1-tosyl-1H-indol-3-yl)acetate (3sa): A three-necked round bottom flask charged with a magnetic stir bar, **1l** (6.0 g, 11.5 mmol), **2** (2.0 g, 11.5 mmol), $Pd(OAc)_2$ (78 mg, 0.35 mmol), P(*o*-tol)$_3$ (213 mg, 0.70 mmol), DIPEA (3.6 g, 27.8 mmol) was added anhydrous DMA (50 mL), then equipped with a condenser, evacuated and backfilled with N_2. The reaction mixture was stirred overnight at 100°C under nitrogen atmosphere and then was added water (5 mL) and stirred for another 1 minute. After cooling to room temperature, the mixture was stilled for 2h and filtered. The solid was washed successively with ethyl acetate (20 mL) and ethanol (10 mL), and then was dissolved in ethyl acetate (20 mL) while stirring at 80°C. After cooling to room temperature, the mixture was filtered to obtain a white solid (4.4 g, 76%). **Mp**:216-218°C; **^{1}H NMR** (400 MHz, DMSO-*d*$_6$) δ (ppm): 7.92 (d, *J* = 8.8 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.76 (s, 1H), 7.56 (s, 1H), 7.41 (d, *J* = 1.6 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 2H), 4.47 (s, 2H), 4.09 (d, *J* = 7.2 Hz, 2H), 3.78 (s, 2H), 3.12-3.08 (m, 4H), 2.31 (s, 3H), 1.75-1.72 (m, 4H), 1.18 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, DMSO-*d*$_6$) δ (ppm): 170.7, 146.1, 134.43, 134.38, 130.8, 130.7, 128.1, 127.1, 126.3, 125.6, 122.8, 116.2, 113.5, 61.0, 53.6, 48.0, 30.5, 25.7, 21.5, 14.5; **ATR-IR**: *v* 2978, 1721, 1594, 1327, 1177 cm^{-1}; **HRMS** (ESI-TOF)

m/z $[M+H]^+$ calcd for $C_{24}H_{29}N_2O_6S_2$ 505.1467; Found 505.1461.

2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1-tosyl-1H-indol-3-yl)ethan-1-ol (3sa-1): To a solution of **3la** (4.2 g, 8.3 mmol) in DMA (30 mL) was added anhydrous $CaCl_2$ (1.4 g, 12.6 mmol) and $NaBH_4$ (1.9 g, 50 mmol). The reaction mixture was stirred for 24h at 40 °C. Then the mixture was adjusted pH to 2~3 with 1M HCl solution at 0°C, and then added water (60 mL). After stilled for 2h, the mixture was filtered. The solid was washed with ethyl acetate (20 mL) and ethanol (10 mL), and then was dissolved in ethyl acetate (20 mL) while stirring at 80°C. After cooling to room temperature, the mixture was filtered to obtain a white solid (3.6 g, 95%). **Mp**:204-206°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 7.89 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.61 (s, 2H), 7.38-7.35 (m, 3H), 4.77 (t, J = 5.4 Hz, 1H), 4.48 (s, 2H), 3.67 (q, J = 5.6 Hz, 2H), 3.11-3.08 (m, 4H), 2.78 (t, J = 6.8 Hz, 2H), 2.31 (s, 3H), 1.75-1.72 (m, 4H); **^{13}C NMR** (150 MHz, DMSO-d_6) δ (ppm): 145.8, 134.5, 131.4, 130.6, 127.8, 127.1, 125.4, 124.8, 122.7, 120.8, 113.5, 60.7, 53.6, 48.0, 28.5, 25.7, 21.5; **ATR-IR**: *v* 3496, 3104, 1594, 1317, 1171 cm^{-1}; **HRMS** (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{22}H_{26}N_2O_5S_2Na$ 485.1181; Found 485.1174.

2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethan-1-ol (3sa-2): To a solution of **3la-1** (3.3 g, 7.1 mmol) in MeOH (30 mL) was added KOH (1.2 g, 21.3 mmol). The reaction mixture was stirred for overnight at 70 °C. The mixture was adjusted pH to 7 with 1M HCl solution at 0°C, and then MeOH was removed under reduced pressure. The residue mixture was extracted with ethyl acetate (50 mL×2). The organic layer was combined and then washed with saturated NaCl solution (60 mL), dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (EtOAc/PE = 1:1) to obtain a white solid (2.1g, 96%). **Mp**:186-188°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 10.87 (s, 1H), 7.56 (s, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.16 (d, J = 2.0 Hz, 1H), 7.11 (dd, J = 8.4, 1.2 Hz, 1H), 4.66 (t, J = 5.4 Hz, 1H), 4.45 (s, 2H), 3.64 (q, J = 6.6 Hz, 2H), 3.12-3.09 (m, 4H), 2.84 (t, J = 7.4 Hz, 2H), 1.77-1.73 (m, 4H); **^{13}C NMR** (150 MHz, DMSO-d_6) δ (ppm): 136.3, 127.8, 124.2, 124.0, 121.4, 119.7, 112.0, 111.5, 62.1, 54.7, 48.1, 29.3, 25.8; **ATR-IR**: *v* 3497, 3273, 2934, 1627, 1302, 1113 cm^{-1}; **HRMS** (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{15}H_{20}N_2O_3SNa$ 331.1092; Found 331.1093.

N,N-dimethyl-2-(5-((pyrrolidin-1-ylsulfonyl)methyl)-1H-indol-3-yl)ethan-1-amine (Almotriptan): To a solution of **3la-2** (1.8 g, 5.8 mmol) in CH_3CN (30 mL) was added TEA (708 mg, 7.0 mmol) at 0 °C. After stirring for 10mins, the mixture was slowly added $MeSO_2Cl$ (802 mg, 7.0 mmol) and then warmed to room temperature. After stirring for another 20mins, the mixture was added dimethylamine (40% in water, 3.9g, 35 mmol) in one portion and then heated to 60 °C. The solvent was removed under reduced pressure after 5h and the residue was added ethyl acetate (80 mL). The organic layer was then washed with saturated NaCl solution (50 mL×2), dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was crystallized with acetone to obtain a white solid (1.5g, 78%). **Mp**:110-112°C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ (ppm): 10.86 (s, 1H), 7.56 (s, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.17 (d, J = 2.0 Hz, 1H), 7.12 (dd, J = 8.4, 1.2 Hz, 1H), 4.46 (s, 2H), 3.12-3.09 (m, 4H), 2.81 (t, J = 8.0 Hz, 2H), 2.51 (t, J = 8.0 Hz, 2H), 2.21 (s, 6H), 1.76-1.73 (m, 4H); **^{13}C NMR** (150 MHz, DMSO-d_6) δ (ppm): 136.3, 127.6, 124.2, 123.7, 121.3, 119.7, 113.1, 111.6, 60.5, 54.8, 48.1, 45.6, 25.8, 23.6; **ATR-IR**: *v* 2849, 1624, 1317, 1146 cm^{-1}; **HRMS** (ESI-TOF) *m/z* $[M+H]^+$ calcd for $C_{17}H_{26}N_3O_2S$ 336.1746; Found 336.1744.

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

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