JOC The Journal of Organic Chemistry

Note

Synthesis of Differentially Protected Azatryptophan Analogs via Pd2(dba)3/XPhos Catalyzed Negishi Coupling of N-Ts Azaindole Halides with Zinc Derivative from Fmoc-protected tert-Butyl (R)-2-amino-3-iodopropanoate

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.0c00973 • Publication Date (Web): 10 Aug 2020

Just Accepted

Synthesis of Differentially Protected Azatryptophan Analogs via $Pd_2(dba)_3$/XPhos Catalyzed Negishi Coupling of *N*-Ts Azaindole Halides with Zinc Derivative from Fmoc-protected *tert*-Butyl (*R*)-2-amino-3-iodopropanoate

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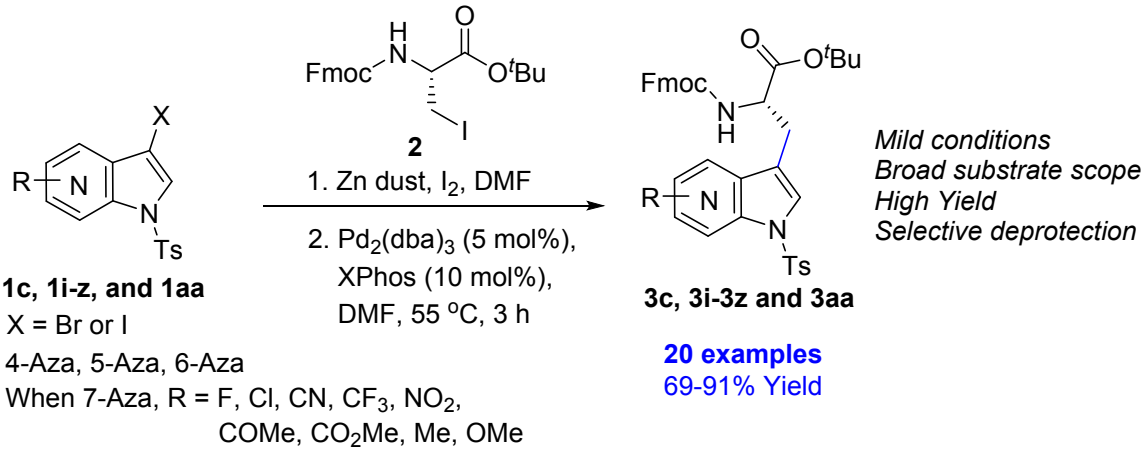
ABSTRACT: Unnatural amino acids play an important role in peptide based drug discovery. Herein, we report a class of differentially protected azatryptophan derivatives synthesized

from *N*-tosyl-3-haloazaindoles **1** and Fmoc-protected *t*-butyl iodoalanine **2** via a Negishi coupling. Through ligand screening, $Pd_2(dba)_3$/XPhos was found to be a superior catalyst for the coupling of **1** with the zinc derivative of **2** to give *tert*-butyl (***S***)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-(1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)propanoate derivatives **3** in 69-91% isolated yields. In addition, we have demonstrated that the protecting groups, namely, Ts, Fmoc and ^{t}Bu, can be easily removed selectively.



Unnatural amino acids are important tools for modern drug discovery research.[1,2] They are widely used as chiral building blocks due to their structural diversity, functional versatility and play a significant role in expanding the potential application of peptide-based drugs.[3] Therefore, the synthesis of unnatural amino acids has attracted much attention in recent years and several methodologies[1,4] have been developed to synthesize these novel building blocks.

Nickel- and palladium-catalyzed Negishi cross coupling[5] is a versatile method for carbon-carbon bond formation. In the past few decades, extensive development[6] in this area has led to the widespread applications of the Negishi reaction in the synthesis of complex natural products,[7-9] including the synthesis of unnatural amino acids.[10,11]

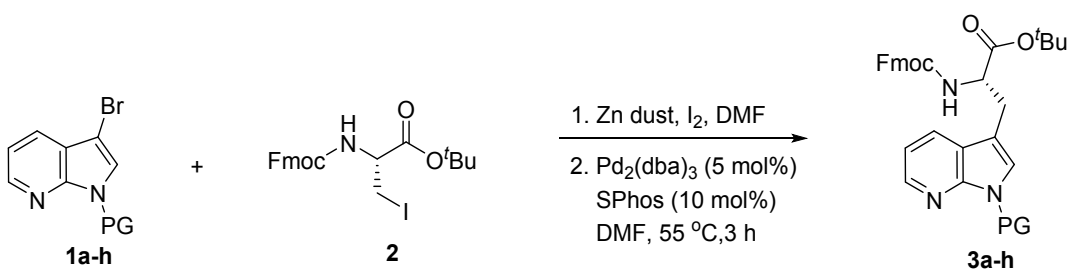
Heteroaromatic unnatural amino acids are especially attractive as structural motifs for the construction of biologically active compounds.[12] In particular, 7-azatryptophan possesses

interesting spectral properties and its incorporation can be of broad applicability in the study of protein folding and protein-protein interactions.[13, 14] In this regard, Gobel and co-workers demonstrated that a few heteroaromatic unnatural amino acid derivatives can be synthesized using a Nickel catalyzed Negishi cross-coupling approach.[15] Similarly, a wide range of novel heteroaryl amino acids containing pyridine, indole, furyl, and thiophene have been successfully prepared using Palladium catalyzed Negishi coupling.[16-18] Yokoyama and co-workers have also reported the synthesis of chiral tryptophan derivatives using Negishi cross-coupling.[19] It must be mentioned that Jackson and co-workers[20-22] performed pioneering work on the synthesis of novel alkyl, aryl and heteroaryl amino acid derivatives using Negishi coupling of the zinc reagent derived from iodoalanine with aryl halides and elaborated additional improvements.[23] However, it is important to realize that, despite the availability of a large number of synthetic procedures, no single method can be universally applied to all substrates and reaction protocols have to be modified as per the needs of the synthesis of the corresponding amino acid scaffolds. For an internal peptide-based drug discovery program, we were interested in an efficient and general synthesis of azatryptophan derivatives bearing both *N*-Fmoc and *t*-butyl ester, which was not reported in the literature. Herein, we describe the development of a methodology for the synthesis of this class of the differentially protected 7-azatryptophans **3** via a Negishi coupling of the zinc derivative of the iodoalanine **2** with *N*-tosyl-3-haloazaindoles **1** catalyzed by $Pd_2(dba)_3$/XPhos. These products are of importance as the three orthogonal protecting groups can be removed independently. This allows flexibility in carrying out selective transformation from the corresponding Negishi product for the incorporation into a *C*- or *N*-terminal peptide following one deprotection reaction.

As aforementioned our objective was to use an Fmoc/*t*-Bu protecting strategy to synthesize azatryptophans (Scheme 1) that would be compatible with Fmoc solid-phase

peptide synthesis (SPPS). It should be noted that there are only a few examples of novel amino acids being prepared via the Negishi coupling of orthogonally protected iodoalanines in which Fmoc has been employed as the protecting group.[21,24] Initially, following the Negishi conditions developed by Jackson,[23] the orthogonally protected organozinc reagent[21] obtained from iodoalanine **2** and *N*-Boc protected 3-bromo azaindole **1b** were coupled using $Pd_2(dba)_3$ and SPhos as the catalyst at room temperature. Unfortunately, during the reaction, substantial Boc deprotection of starting material was observed without any desired product formation. However, when the reaction temperature was increased to 55 ºC it resulted in an extremely low conversion (14%) of **3b** (Table 1, entry 2) along with unreacted deprotected starting material. Based on this observation, we decided to investigate suitable *N*-protecting groups for 3-bromo azaindole that would offer compatibility with the Negishi conditions, as summarized in Table 1. A set of seven reactions were screened using the unprotected azaindole and the azaindoles protected with SEM, PMB, Cbz, *t*-BuSO, Ts and Ns. As anticipated, there was no reaction with the unprotected azaindole **1a** (Table 1, entry 1). The reactions of the azaindoles **1d-g** protected with SEM, PMB, Cbz and ^{t}BuSO groups, respectively, were sluggish, with very poor conversions (Table1, entries 4–7). Both the Ts and Ns protected azaindoles **1c** and **1h** (Table 1, entries 3 and 8) showed moderate conversion (37% and 31%, respectively, by HPLC), without the formation of side products.

Scheme 1. Synthetic Approach to the Preparation of Fmoc/*t*-Bu Protected Azatryptophans



Reaction Conditions: i) Zn-dust (3.0 eq.), I_2 (0.3 eq.), DMF, rt, 30 min
ii) **1** (1.0 eq.), **2** (1.5 eq.), $Pd_2(dba)_3$ (0.05 eq.), SPhos (0.1 eq.), 55 ^{o}C, 3 h

Table 1. Effect of Protecting Groups (PG) on the Yield**s** of **3a-h**

Entry	3-Bromoazaindole derivative **1**	% of unreacted **1**[b]	Product **3**	% of **3**[b]
1	**1a**, PG = H	nd[a]	**3a**	nd[a]
2	**1b**, PG = Boc	nd[a]	**3b**	14
3	**1c**, PG = Ts	10	**3c**	37
4	**1d**, PG = SEM	29	**3d**	10.3
5	**1e**, PG = PMB	36	**3e**	10.6
6	**1f**, PG = Cbz	nd[a]	**3f**	10
7	**1g**, PG = ^{t}BuSO	nd[a]	**3g**	12
8	**1h**, PG = Ns	7	**3h**	31

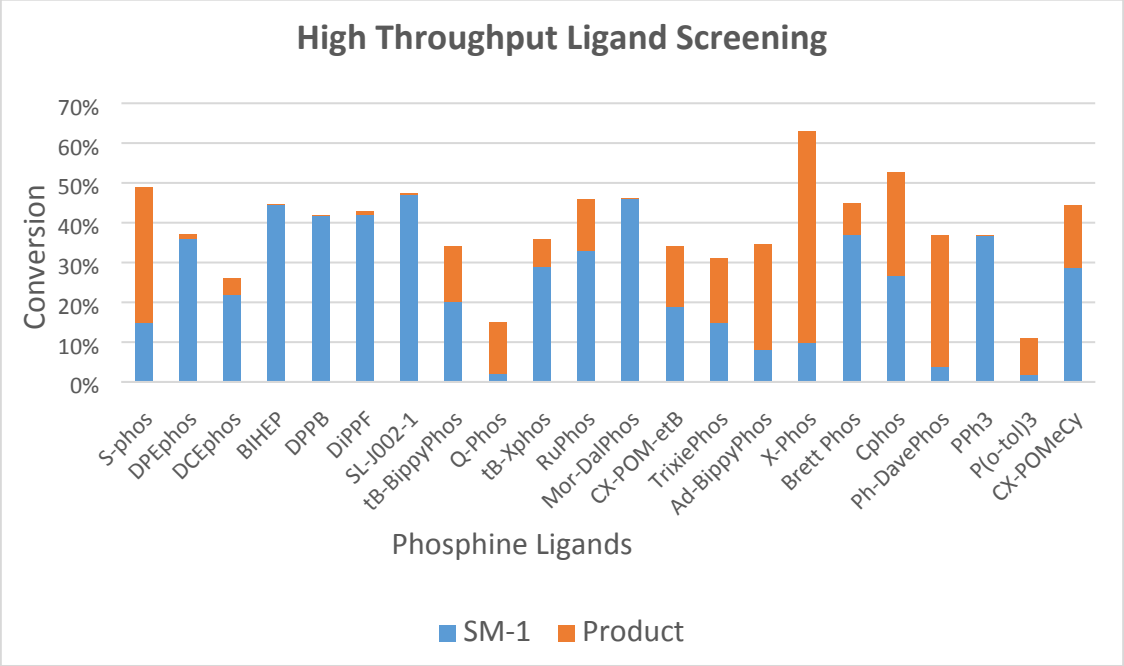
[a] Not detected. [b] HPLC conversion

With consideration for the ease of selective deprotection, the Ts-protected azaindole **1c** was selected for further optimization by screening various catalyst ligands. A high throughput screening experiment was designed using selected commercially-available phosphine ligands and the reactions were conducted in a glovebox (Figure 1). $Pd_2(dba)_3$ was chosen as the precatalyst since it is well documented in the literature[23] that the use of $Pd_2(dba)_3$ as a palladium source with bulky phosphine ligands in a 1:2 molar ratio is highly efficient for the Negishi cross-coupling of aryl and heteroaryl halides with an organozinc reagent derived from the iodoalanine intermediate **2**. As shown in Figure 1, with bidentate phosphine ligands such as BIHEP, DPPB and Mor-Dalphos, the reaction did not proceed at all. A moderate conversion was observed with S-Phos, Ad-BippyPhos, CPhos, Ph-DavePhos,

and CX-POMeCy. With XPhos the reaction was clean and gave the best conversion (55% product by HPLC) with 10% unreacted *N*-tosyl-3-bromoazaindole (**1c**).

It would be pertinent to mention a report of a similar Negishi reaction on 4- and 7-azaindoles in the supplementary data of a literature reference,[17] where SPhos was used as the ligand to afford the corresponding products in good yields from 3-iodo azaindoles at the temperature of 35 ºC. However, in our hands we found that the reaction of Ts-protected 3-bromo-7-azaindole **1c** was sluggish with < 60% conversion after 12 h at 35 ºC.

Figure 1. High Throughput Catalyst Screening of *N*-Tosyl-3-bromoazaindole (1c) with Zinc derivative of iodoalanine **2**



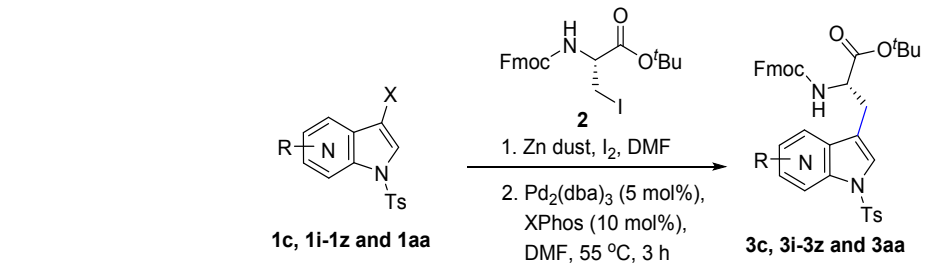
Reaction Conditions: i) Zn-dust (3.0 eq), I_2 (0.3 eq.), DMF, rt, 30 min; ii) 1 (1.0 eq.), 2 (1.5 eq.), $Pd_2(dba)_3$ (0.05 eq.), ligand (0.1 eq.), 55 ºC, 3 h

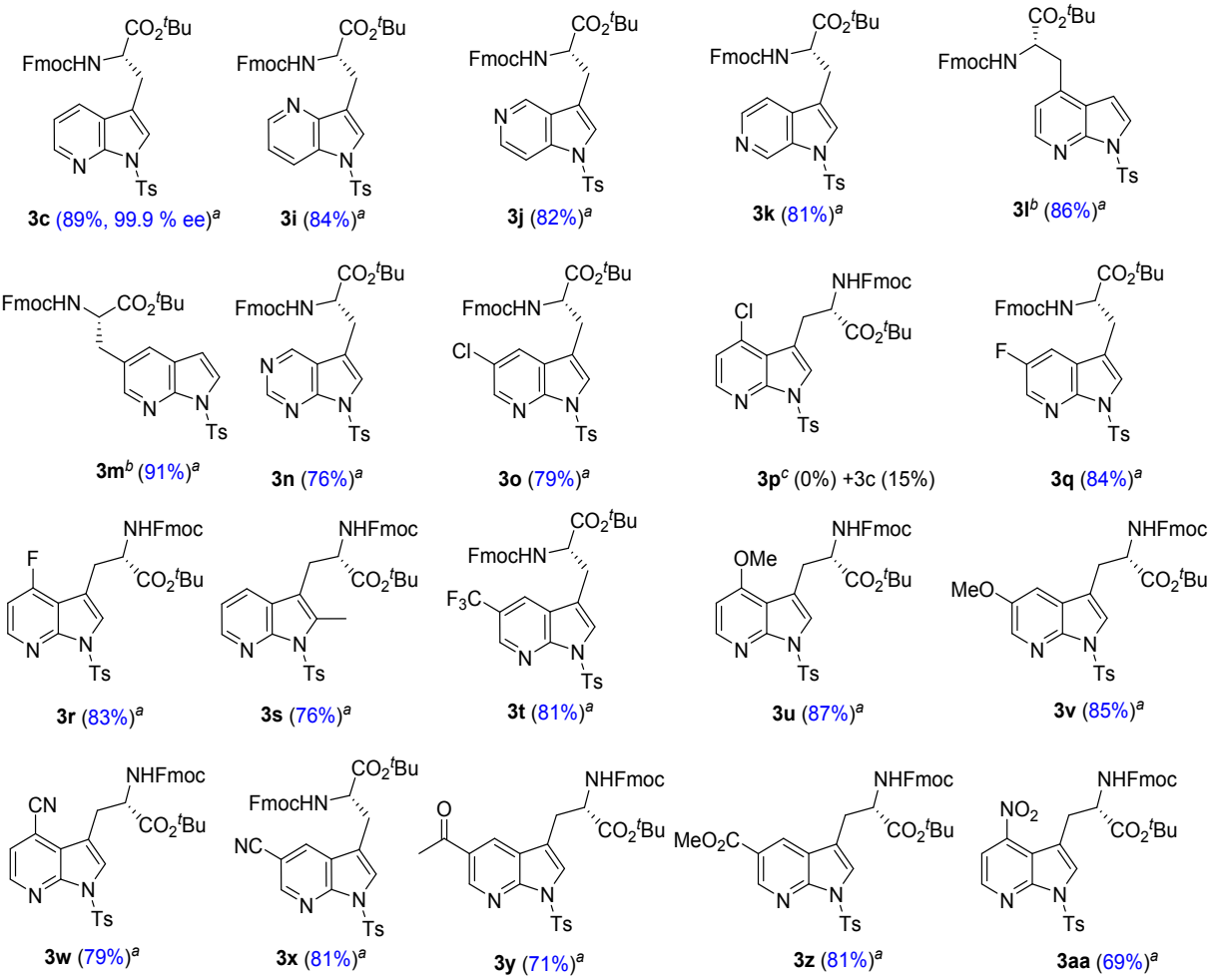
Having found the best catalyst/ligand combination for conducting Negishi coupling of **1c**, the next task was to explore the scalability and reproducibility of the reaction outside of a glove box. Under standard laboratory reaction conditions, using $Pd_2(dba)_3$/XPhos at a molarity of 0.1 M in DMF, the reaction did not go to completion. Further experiments

revealed that the reaction concentration played a critical role. At a concentration of 0.05 M, the reaction was complete in 3 h and provided *N*-Ts-7-azatryptophan **3c** in 89% isolated yield and the same was successfully scaled-up to 3g (76 %). Notably, racemization was not observed under these reaction conditions and the enantiomeric excess (ee) of **3c** was determined to be 99.9% by chiral HPLC analysis.

To further explore the scope of the reaction, various positional isomers of *N*-Ts-azaindole halides and substituted *N*-Ts-azaindole halides were reacted under the optimized conditions using $Pd_2(dba)_3$/XPhos with the zinc derivative of iodoalanine **2**. The results are summarized in Table 2.

Table 2. Negishi Cross-Coupling of **2** with Ts-azaindoles **1c**, **1i-z** and **1aa**





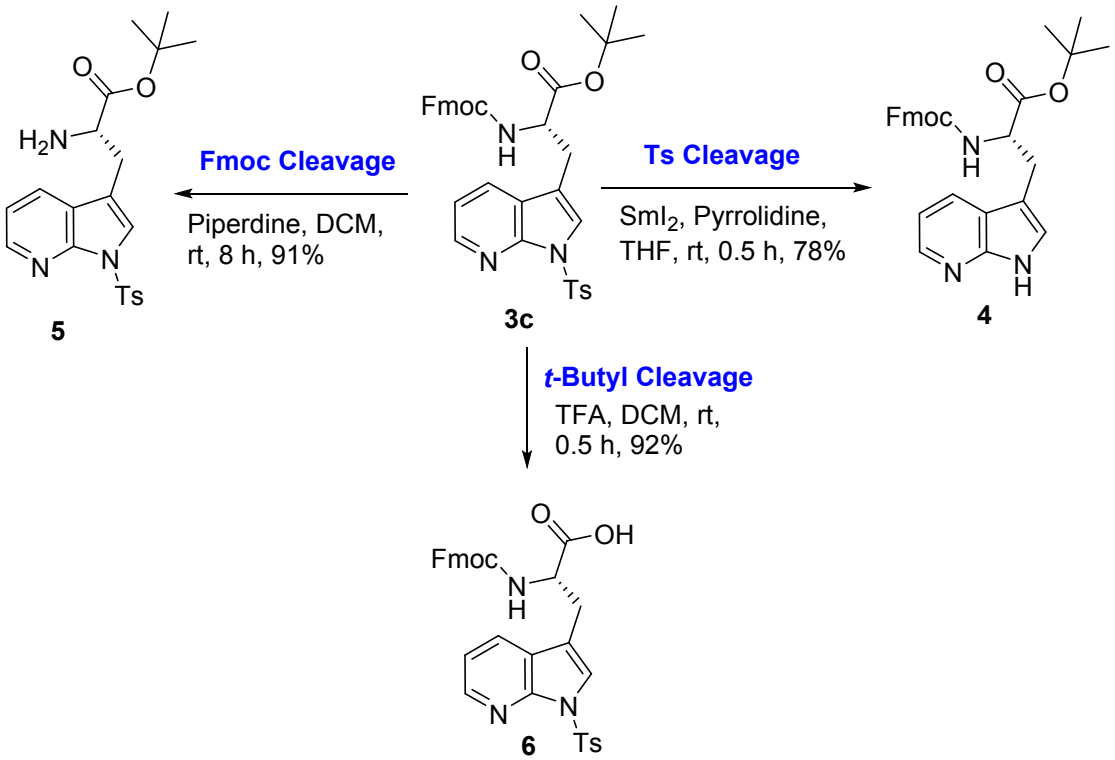
[a] Isolated yield. All reactions were carried out using 0.569 mmol of *N*-Ts-azaindole **1** (1 eq.) in DMF (12 mL), compound **2** (1.5 eq.), Zn (3.0 eq.), Iodine (0.3 eq.), $Pd_2(dba)_3$ (5 mol%) and XPhos (10 mol%).
[b] Product derived from **4** and 5-bromo azaindole respectively. [c] Compound **1p** gave only des chlorinated product **3c**.

Negishi cross-coupling with all four positional isomers of *N*-Ts protected 3-bromo azaindoles (4-, 5-6- and 7-azaindoles) furnished **3c**, **3i**, **3j**, and **3k**, respectively, in excellent yields. Moreover, 4-bromo and 5-bromo *N*-Ts-azaindole participated in this process to afford **3l** and **3m** in 86% and 91% yield, respectively. In the case of *N*-Ts protected 5-bromo-7-deazapurine, the reaction proceeded cleanly in 76% isolated yield (Table 2, entry **3n**).

Although substrates bearing chloro and fluoro substituents on the ring were well-tolerated and generated the corresponding products in excellent yields (Table 2, entry **3o, 3q-3r**), in the case of 4-chloro-3-bromo *N*-Ts-azaindole **1p** no desired product **3p** was formed and 15% of the des-chloro product **3c** was observed by LCMS. Notably, the sterical hindrance associated with a 2-methyl substituent did not interfere, providing the desired product in good yield (Table 2, entry **3s**). Substrates bearing electronically rich substituents such as the 4- and 5-OMe moieties (Table 2, entry **3u** and **3v**) and electron-deficient substituents such as 4- and 5-CN, 5-COMe, 5-CO_2Me, and 4-NO_2 were successfully transformed to the corresponding products in good yields (Table 2, entry **3w-3aa**).

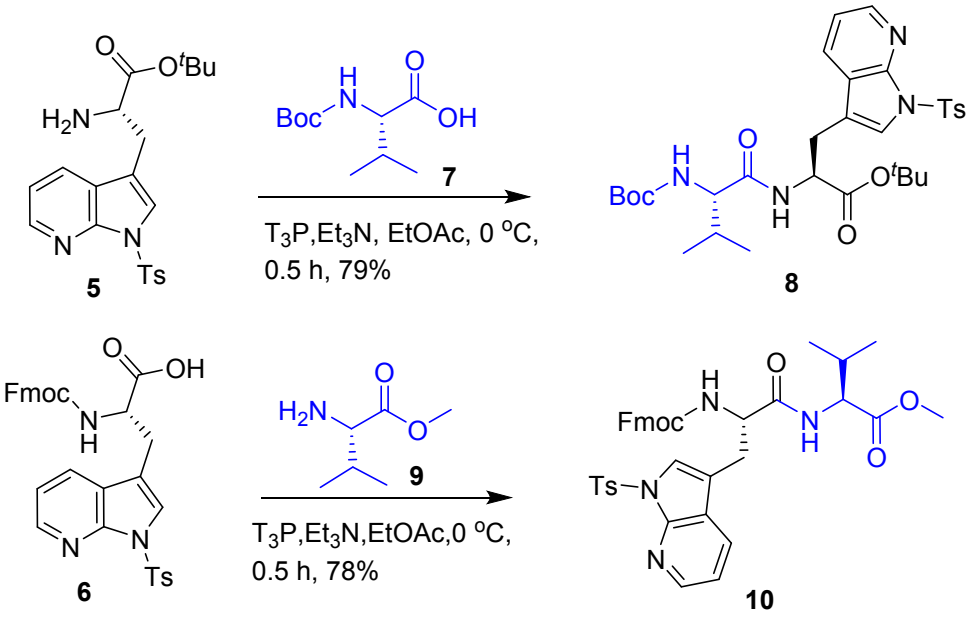
Having successfully demonstrated the Negishi coupling on a wide range of substituted azaindoles, we explored the selectivity of deprotection and for this purpose, 7-azatryptophan **3c** was selected as the prototype.

Scheme 2. Selective Deprotection of Differentially Protected 7-Azatryptophan **3c**



The primary objective of this phase of the study was to find specific reaction conditions that allow selective removal of the Fmoc, ^{t}Bu and *N*-Ts moieties while preserving the other two groups. The selective Fmoc deprotection of 7-azatryptophan **3c** was achieved using piperidine in CH_2Cl_2 to afford compound **5** in 91% isolated yield. The selective deprotection of the *t*-butyl group was accomplished using CF_3CO_2H in CH_2Cl_2 affording **6** in 92% isolated yield. While it was relatively straightforward to identify deprotection conditions to selectively remove the Fmoc and ^{t}Bu moieties, identifying the right conditions for selective *N*-Ts deprotection proved to be considerably more challenging. The majority of the known reaction conditions [25-27] for *N*-Ts deprotection led to deprotection of either the Fmoc or ^{t}Bu under basic or acidic conditions, respectively.[28,29] After numerous attempts, selective deprotection of *N*-Ts group on the 7-azatryptophan **3c** was achieved by using a 0.1 M solution of SmI_2[30] in THF in the presence of pyrrolidine which furnished **4** in 78% isolated yield. The applications of the selectively deprotected Negishi products were further demonstrated in the synthesis of dipeptides at both C- and N-terminals. 7-Azatryptophans **5** and **6** were successfully coupled with Boc-L-valine **7** and L-valine methyl ester **9** to obtain dipeptides **8** and **10** in good yields (Scheme 3).

Scheme 3. Synthesis of Dipeptides **8** and **10**



In summary, we have developed an efficient method to synthesize differentially protected azatryptophan analogs **3** via a Negishi cross-coupling reaction using $Pd_2(dba)_3$/XPhos as the catalyst. A variety of functional groups are tolerated under the reaction conditions and the protective groups can be selectively removed to allow further synthetic manipulation of the products as demonstrated by the synthesis of dipeptides. The versatility of these unnatural amino acids make them a valuable tool for the synthesis of novel therapeutic peptides.

EXPERIMENTAL SECTION

A) General Information: Commercially available reagents were used without additional purification, unless otherwise stated. The heating reactions were conducted in an oil bath with IKA magnetic stirrer. Thin layer chromatography was carried out using plates coated with Kieselgel 60F254. For column chromatography, Teledyne Isco CombiFlash system and Redi-Sep Silica columns were used. NMR characterization of the isolated products was carried out in $CDCl_3$ or DMSO-d_6 at 25 °C. ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded on a Bruker Avance III-400 MHz and Varian 500 MHz spectrometers. Coupling constants (J) are reported

in hertz (Hz). High resolution mass spectra were obtained on an Agilent 6540 UHD Q-TOF with ESI source. SOR was measured on RUDOLPH Autopol® V automatic polarimeter. Compound purities were determined by analytical reverse phase HPLC in Agilent 1200 series instrument. Chiral purity was determined by SFC-HPLC-Hybrid-Analytical Agilent 1260 Infinity II. Melting points were recorded in BUCHI M-560 instrument.

B) Experimental procedure for the synthesis of 1b, 1d-1h

*Tert-butyl 3-bromo-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (**1b**):* Following the literature procedure[31a], to a solution of 3-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (0.2 g, 1.02 mmol) in THF (4.0 mL) under nitrogen atmosphere was added DMAP (0.012 g, 0.11 mmol). The resulting reaction mixture was cooled to -20 ^{0}C followed by addition of di-*tert*-butyl pyrocarbonate (0.259 mL, 1.12 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 2 h. Reaction progress was monitored by LC-MS. The reaction was diluted with water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude was purified by flash column chromatography (5% EtOAc in petroleum ether) to obtain **1b** as colorless liquid (0.17 g, 56%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.61 - 8.55 (m, 1H), 7.89 - 7.72 (m, 2H), 7.32 - 7.27 (m, 1H), 1.69 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 146.2, 128.0, 125.4, 122.4, 94.9, 84.7, 28.0.

*3-Bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine(**1d**)*:

To a solution of 3-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (0.5 g, 2.5 mmol) in THF (15 mL) under nitrogen atmosphere was added NaH (0.163 g, 4 mmol) at 0 °C and the reaction was stirred for 1 h. To this was added (2-Chloromethoxyethyl) trimethylsilane (0.55 g, 3.3 mmol) and the reaction mixture was allowed to warm to room temperature and stirred overnight. Reaction progress was monitored by LC-MS. The reaction was quenched with water (10 mL),

extracted with EtOAc (10 mL), washed with brine solution (10 mL) and dried over anhydrous Na_2SO_4. The organic layer was evaporated to obtain the crude compound. The crude compound was purified by flash column chromatography (5% EtOAc in petroleum ether) to afford the title compound **1d** as a colorless liquid (0.6 g, 93%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.38 (dd, J = 1.5, 4.5 Hz, 1H), 7.87 (dd, J = 1.5, 8.0 Hz, 1H), 7.40 (s, 1H), 7.23 - 7.14 (m, 1H), 3.60 - 3.53 (m, 2H), 0.95 – 0.91 (m, 2H), 0.05 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$,101 MHz) δ 147.2, 144.4, 127.6, 126.8, 120.0, 117.0, 90.1, 72.8, 66.4, 17.8, 1.44 (3C); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{13}H_{20}BrN_2OSi$ 327.0450; Found 327.0525.

*3-Bromo-1-(4-methoxybenzyl)-1H-pyrrolo[2,3-b]pyridine (**1e**)*: To a solution of 3-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (2 g, 10.5 mmol) in THF (40 mL) under nitrogen atmosphere was added NaH (0.365 g, 15.23 mmol) at 0 °C. The reaction was stirred at 0 °C for 1 h. To this 1-(bromomethyl)-4-methoxybenzene (2.40 g, 12.18 mmol) was added and the reaction mixture was allowed to warm to room temperature and stirred for 2 h. Reaction progress was monitored by LC-MS. The reaction was quenched with water (30 mL), extracted with EtOAc (30 mL), washed with brine solution (30 mL) and dried over anhydrous Na_2SO_4. The organic solvents were evaporated to obtain the crude compound. The crude compound was purified by flash column chromatography (5% EtOAc in petroleum ether) to afford title compound **1e** as colorless liquid (2.12 g, 66%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.42 (dd, J = 1.0, 5.0 Hz, 1H), 7.90 (dd, J = 1.3, 7.8 Hz, 1H), 7.23 - 7.15 (m, 4H), 6.88 (d, J = 8.5 Hz, 2H), 5.45 (s, 2H), 3.80 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 159.3, 143.7, 129.2 (3C), 128.9, 127.9, 126.7, 120.2, 116.4, 114.2 (2C), 88.6, 55.2, 47.6; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{14}BrN_2O$ 317.0211; Found 317.0297.

*Benzyl 3-bromo-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (**1f**)*: To a solution of 3-bromo-

1*H*-pyrrolo[2,3-*b*]pyridine (0.4 g, 2.0 mmol) in DCM (4.0 mL) under nitrogen atmosphere was added Et_3N (0.7 mL, 5.08 mmol) at 0 °C. To this resulting reaction mixture was added benzyl chloroformate (0.44 mL, 5.05 mmol). The reaction mixture was allowed to warm up to room temperature and stirred for 2 h. Reaction progress was monitored by LC-MS. The reaction mixture was quenched with sat. sodium bicarbonate (25 mL) and extracted with DCM (2 x 15 mL). The combined organic layer was washed with brine solution (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Title compound **1f** was purified by flash column chromatography (10% EtOAc in petroleum ether) to obtain as off-white solid (0.7 g, 94%); mp: 69-71 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.59 (dd, J = 1.3, 4.8 Hz, 1H), 7.94 - 7.79 (m, 2H), 7.55 (d, J = 6.5 Hz, 2H), 7.45 – 7.39 (m, 3H), 7.34 – 7.29 (m, 1H), 5.53 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 146.8, 146.4, 134.7, 128.7, 128.7, 128.6 (3C), 128.2, 125.2, 122.6, 119.4, 95.9, 69.2; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{12}BrN_2O_2$ 330.0004; Found 330.0083.

*3-Bromo-1-(tert-butyl)-1H-pyrrolo[2,3-b]pyridine compound with sulfurmonoxide (**1g**):* To a solution of 3-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (0.5 g, 2.5 mmol), in THF (10 mL), under nitrogen atmosphere was added NaH (0.365 g, 15.23 mmol) at 0 °C. The reaction was stirred at 0 °C for 1 h. To this was added, *tert*-butylsulfinyl chloride (0.48 g, 3.1 mmol) and stirred. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. Reaction progress was monitored by LC-MS. The reaction was quenched with water (30 mL), extracted with EtOAc (30 mL), washed with brine solution (30 mL) and dried over anhydrous Na_2SO_4. The organic layer was evaporated to obtain a crude compound which was purified by flash column chromatography (20% EtOAc in petroleum ether) to afford title compound **1g** as white solid (0.53 g, 69%) mp: 131-133 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.40 (dd, J = 1.5, 5.0 Hz, 1H), 7.91 (dd, J = 1.5, 8.0 Hz, 1H), 7.62 (s, 1H), 7.28 - 7.24 (m,

1H), 1.36 (s, 9H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 101 MHz) δ 148.9, 145.1, 128.3, 122.0, 121.4, 118.3, 93.9, 61.1, 22.2 (3C); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{11}H_{13}BrN_2OS$ 300.9932; Found 301.0044.

*3-Bromo-1-((4-nitrophenyl)sulfonyl)-1H-pyrrolo[2,3-b]pyridine (**1h**)*: To a solution of 3-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (0.5 g, 2.5 mmol) in THF (25 mL) under nitrogen atmosphere were added pyridine (1.03 mL, 12.69 mmol) and *p*-toluenesulfonyl chloride (0.675 g, 3.05 mmol) and refluxed for 36 h. Reaction progress was monitored by LC-MS. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The title compound **1h** was purified by flash column chromatography (20% EtOAc in petroleum ether) to obtain as off-white solid (0.235 g, 24%); mp: 197-199 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.62 - 8.39 (m, 3H), 8.38 - 8.25 (m, 2H), 7.91 - 7.82 (m, 1H), 7.81 - 7.76 (m, 1H), 7.36 - 7.28 (m, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 101 MHz) δ 146.3, 145.9, 143.1, 129.7 (3C), 128.9, 124.4, 124.3 (2C), 122.6, 120.0, 96.8; (ESI) m/z: $[M + H]^+$ Calcd for $C_{13}H_{18}BrN_3O_4S$ 381.9419; Found 381.9497.

C) General experimental procedure for Tosylazindole intermediates (1c, 1i-1aa): To a solution of azaindole (1.0 eq.) in THF (15 mL), cooled to 0 °C, NaH (1.5 to 3.0 eq. 60 % dispersion in mineral oil) was added and the reaction stirred for 1 h. To the reaction mixture *p*-toluenesulfonyl chloride (1.3 eq.), was added and the reaction mixture was allowed to warm to room temperature and stirred overnight. Reaction progress was monitored by LC-MS. The reaction was quenched with water (10 mL), extracted with EtOAc (10 mL), washed with brine solution (10 mL) and dried over anhydrous Na_2SO_4. The organic layer was evaporated to obtain the crude compound which was purified by flash column chromatography (5-40% EtOAc in petroleum ether) to afford the pure compound.

*3-Bromo-1-tosyl-1H-pyrrolo[2,3-b]pyridine (**1c**):* Following the literature procedure [31c], using 3-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (5 g, 25.4 mmol), NaH (0.913 g, 38.1 mmol) and *p*-toluenesulfonyl chloride (7.26 g, 38.1 mmol), **1c** was obtained by flash column chromatography (40% EtOAc in petroleum ether) as off-white solid (7 g, 79%); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.45 (dd, J = 1.5, 5.0 Hz, 1H), 8.20 (s, 1H), 8.01 (d, J = 8.0 Hz, 2H), 7.93 (dd, J = 1.5, 8.0 Hz, 1H), 7.44 - 7.38 (m, 3H), 2.32 (s, 3H); ^{13}C{^{1}H} NMR (DMSO-d_6, 101 MHz) 145.9, 145.8, 145.3, 134.1, 130.0, 128.5 (2C), 127.6 (2C), 125.6, 121.6, 120.0, 94.9, 21.0.

*3-Bromo-1-tosyl-1H-pyrrolo[3,2-b]pyridine (**1i**)*: Following the general procedure, using 3-bromo-1*H*-pyrrolo[3,2-*b*]pyridine (1.0 g, 5.08 mmol), NaH (0.365 g , 15.23 mmol) and *p*-Toluenesulfonyl chloride (1.064 g, 5.58 mmol), **1i** was obtained by flash column chromatography (30% EtOAc in petroleum ether) as off-white solid (0.9 g, 50%); mp: 197-199 ^{o}C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.59 = 8.58 (dd, J = 1.2, 4.6 Hz, 1H), 8.46 (s, 1H), 8.37 (dd, J = 1.1, 8.4 Hz, 1H), 7.94 (d, J = 8.3 Hz, 2H), 7.46 (dd, J = 4.6, 8.3 Hz, 1H), 7.37 (d, J = 8.1 Hz, 2H), 2.37 - 2.26 (m, 3H); ^{13}C{^{1}H} NMR (DMSO-d_6,101 MHz) δ 147.4, 146.7, 145.1, 133.9, 130.9 (2C), 129.3, 127.7, 127.4 (2C), 121.7, 121.1, 100.4, 21.5; HRMS (ESI) m/z: [M + H]$^+$ $C_{14}H_{11}BrN_2O_2S$ 350.9797; Found 350.9783.

*3-Bromo-1-tosyl-1H-pyrrolo[3,2-c]pyridine (**1j**)*: Following the general procedure, using 3-bromo-1*H*-pyrrolo[3,2-*c*]pyridine (1.0 g, 5.08 mmol), NaH (0.365 g , 15.23 mmol) and *p*-toluenesulfonyl chloride (1.064 g, 5.58 mmol), **1j** was obtained by flash column chromatography (10% EtOAc in petroleum ether) as off-white solid (0.9 g, 88%); mp: 198 ^{o}C; mp: 163-165 ^{o}C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.78 (s, 1H), 8.56 (d, J = 5.9 Hz, 1H), 8.26 (s, 1H), 8.04 - 7.93 (m, 3H), 7.44 (d, J = 8.1 Hz, 2H), 2.38 (s, 3H); ^{13}C{^{1}H} NMR (DMSO-d_6, 101 MHz) δ 146.4, 145.2, 142.4, 138.0, 133.3, 130.5 (2C), 127.0 (2C), 126.4, 125.0, 107.9, 96.4, 21.0; HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{14}H_{11}BrN_2O_2S$ 350.9797; Found 350.9804.

*3-Bromo-1-tosyl-1H-pyrrolo[2,3-c]pyridine (**1k**):* Following the literature procedure[31b], using 3-bromo-1*H*-pyrrolo[2,3-*c*]pyridine (1.0 g, 5.25 mmol), NaH (0.19 g, 7.87 mmol) and *p*-toluenesulfonyl chloride (1.24 g, 6.82 mmol), **1k** was obtained by flash column chromatography (10% EtOAc in petroleum ether) as off-white solid (1.08 g, 60%); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.27 (s, 1H), 8.51 (d, J = 5.1 Hz, 1H), 8.43 (s, 1H), 8.04 (d, J = 8.3 Hz, 2H), 7.54 (dd, J = 1.0, 5.4 Hz, 1H), 7.44 (d, J = 8.6 Hz, 2H), 2.35 (s, 3H); ^{13}C{^{1}H} NMR (DMSO-d_6, 101 MHz) δ 146.3, 143.1, 135.2, 134.6, 133.3, 130.5 (2C), 130.4, 129.1, 127.1 (2C), 113.9, 97.3, 21.0.

*4-Bromo-1-tosyl-1H-pyrrolo[2,3-b]pyridine (**1l**):* Following the literature procedure[31c], using 4-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (1.0 g, 5.25 mmol), NaH (0.19 g, 7.87 mmol) and *p*-toluenesulfonyl chloride (1.24 g, 6.82 mmol), **1l** was obtained by flash column chromatography (10% EtOAc in petroleum ether) as off-white solid (1.48 g, 82%); ^{1}H NMR (CDCl3, 400 MHz) δ 8.24 (d, J = 5.3 Hz, 1H), 8.08 (d, J = 8.5 Hz, 2H), 7.80 (d, J = 4.0 Hz, 1H), 7.37 (d, J = 5.3 Hz, 1H), 7.32 - 7.30 (m, 2H), 6.65 (d, J = 4.0 Hz, 1H), 2.39 (s, 3H); ^{13}C{^{1}H} NMR (CDCl3, 101 MHz) δ 146.7, 145.4, 144.9, 135.0, 129.6 (2C), 128.1 (2C), 126.9, 125.6, 124.3, 122.0, 104.8, 21.6.

*5-Bromo-1-tosyl-1H-pyrrolo[2,3-b]pyridine (**1m**):* Following the literature procedure[31c], using 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (1.0 g, 5.12 mmol), NaH (0.365 g, 15.23 mmol) and *p*-toluenesulfonyl chloride (1.06 g, 5.58 mmol), **1m** was obtained by flash column chromatography (30% EtOAc in petroleum ether) as off-white solid (1.1 g, 62%); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.46 (d, J = 2.0 Hz, 1H), 8.32 (d, J = 2.5 Hz, 1H), 7.99 - 7.94 (m, 3H), 7.42 (d, J = 8.5 Hz, 2H), 6.79 (d, J = 4.0 Hz, 1H), 2.34 (s, 3H).

*5-Bromo-7-tosyl-7H-pyrrolo[2,3-d]pyrimidine (**1n**):* Following the literature procedure [31b], using 5-bromo-7*H*-pyrrolo[2,3-*d*]pyrimidine (1.0 g, 5.25 mmol), NaH (0.19 g, 7.87 mmol) and *p*-toluenesulfonyl chloride (1.24 g, 6.82 mmol), **1n** was obtained by flash column

chromatography (petroleum ether/EtOAc, 9:1) as off-white solid (0.99 g, 55%); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.04 (s, 1H), 9.01 (s, 1H), 8.30 (s, 1H), 8.05 (d, J = 8.6 Hz, 2H), 7.45 (d, J = 7.8 Hz, 2H), 2.34 (s, 3H); ^{13}C{^{1}H} NMR (DMSO-d_6, 101 MHz) δ 153.7, 149.8, 149.4, 146.4, 133.6, 130.2 (2C), 127.7 (2C), 126.5, 93.1, 21.0.

*3-Bromo-5-chloro-1-tosyl-1H-pyrrolo[2,3-b]pyridine (**1o**):* Following the literature procedure [31d], using 3-bromo-5-chloro-1*H*-pyrrolo[2,3-*b*]pyridine (1.0 g, 5.25 mmol), NaH (0.19 g, 7.87 mmol) and *p*-toluenesulfonyl chloride (1.24 g, 6.82 mmol), **1o** was obtained by flash column chromatography (10% EtOAc in petroleum ether) as off-white solid (0.81 g, 45 %); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.41 (d, J = 2.3 Hz, 1H), 8.07 (d, J = 8.5 Hz, 2H), 7.83 (s, 1H), 7.80 (s, 1H), 7.33 (s, 1H), 7.31 - 7.28 (m, 1H), 2.41 (s, 3H); ^{13}C{^{1}H} NMR (DMSO-d_6, 101 MHz) δ 146.0, 143.0, 135.9, 135.2, 134.3, 131.0, 130.2 (3C), 127.8, 127.0, 114.0, 97.9, 21.5.

*3-Bromo-4-chloro-1-tosyl-1H-pyrrolo[2,3-b]pyridine(**1p**)*: Following the general procedure, using 3-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (1.2 g, 5.18 mmol), NaH (0.373 g, 15.55 mmol) and *p*-toluenesulfonyl chloride (1.087 g, 5.7 mmol), **1p** was obtained by flash column chromatography (30% EtOAc in petroleum ether) as off-white solid (0.25 g, 12%); mp: 159-161 ^{o}C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.37 (d, J = 5.0 Hz, 1H), 8.30 (s, 1H), 8.02 (d, J = 8.5 Hz, 2H), 7.50 - 7.42 (m, 3H), 2.35 (s, 3H); ^{13}C{^{1}H} NMR (DMSO-d_6, 101 MHz) δ 146.9, 146.8, 146.3, 136.5, 134.4, 130.7 (2C), 128.4 (3C), 127.9, 121.5, 92.6, 21.7; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{14}H_{10}BrClN_2O_2S$ 384.9408; Found 384.9417.

*3-Bromo-5-fluoro-1-tosyl-1H-pyrrolo[2,3-b]pyridine (**1q**):* Following the literature procedure[31d], using 3-bromo-5-fluoro-1*H*-pyrrolo[2,3-*b*]pyridine (1.2 g, 5.58 mmol), NaH (0.402 g, 16.74 mmol) and *p*-toluenesulfonyl chloride (1.17 g, 6.14 mmol), **1q** was obtained by flash column chromatography (30% EtOAc in petroleum ether) as off-white solid (1.4 g,

66 %); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.50 - 8.46 (m, 1H), 8.31 (s, 1H), 8.00 (d, J = 7.8 Hz, 2H), 7.95 - 7.90 (m, 1H), 7.44 (d, J = 8.0 Hz, 2H), 2.35 (s, 3H).

*3-Bromo-4-fluoro-1-tosyl-1H-pyrrolo[2,3-b]pyridine (**1r**)*: Following the general procedure, using *3-Bromo-4-fluoro*-1*H*-pyrrolo[2,3-*b*]pyridine (0.5 g, 2.33 mmol), NaH (0.167 g, 6.98 mmol) and *p*-toluenesulfonyl chloride (0.488 g, 2.56 mmol), **1r** was obtained by flash column chromatography (30% EtOAc in petroleum ether) as off-white solid (0.28 g, 33%); mp: 211-213 ^{o}C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.45 (dd, J = 5.8, 7.5 Hz, 1H), 8.22 (s, 1H), 8.03 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 8.3 Hz, 2H), 7.32 (br d, J = 5.5 Hz, 1H), 2.35 (s, 3H); ^{13}C{^{1}H} NMR (DMSO-d_6, 101 MHz) δ 164.9, 146.5, 146.2, 133.8, 131.5 (d, J = 71.9 Hz), 130.2, 127.2, 124.5, 122.1, 64.4, 52.5, 21.1; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{14}H_{10}BrFN_2O_2S$ 368.9703; Found 368.9703.

*3-Bromo-2-methyl-1-tosyl-1H-pyrrolo[2,3-b]pyridine (**1s**):* Following the literature procedure[31d], using 3-bromo-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (1.0 g, 4.74 mmol), NaH (0.34 g, 14.21 mmol) and *p*-toluenesulfonyl chloride (0.994 g, 5.21 mmol), **1s** was obtained by flash column chromatography (30% EtOAc in petroleum ether) as off-white solid (1 g, 57 %); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.38 (d, J = 4.6 Hz, 1H), 8.00 (d, J = 8.1 Hz, 2H), 7.81 (d, J = 7.8 Hz, 1H), 7.46 - 7.29 (m, 3H), 2.74 (s, 3H), 2.28 (s, 3H).

*3-Iodo-1-tosyl-5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridine (**1t**):* Following the literature procedure[31d], using 3-iodo-5-(trifluoromethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (1 g, 3.20 mmol), NaH (0.23 g, 9.61 mmol) and *p*-toluenesulfonyl chloride (0.672 g, 3.53 mmol), **1t** was obtained by flash column chromatography (30% EtOAc in petroleum ether) as off-white solid (1.1 g, 71%); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.80 (s, 1H), 8.37 (s, 1H), 8.18 - 8.09 (m, 1H), 8.04 (d, J = 7.8 Hz, 2H), 7.45 (d, J = 8.1 Hz, 2H), 2.35 (s, 3H).

*3-Bromo-4-methoxy-1-tosyl-1H-pyrrolo[2,3-b]pyridine (**1u**)*: Following the general

procedure, using 3-bromo-4-methoxy-1*H*-pyrrolo[2,3-*b*]pyridine (1.0 g, 4.40 mmol), NaH (0.32 g, 13.21 mmol) and *p*-toluenesulfonyl chloride (0.92 g, 4.84 mmol), **1u** was obtained by flash column chromatography (30% EtOAc in petroleum ether) as off-white solid (1.4 g, 83%); mp: 179-181 ^{o}C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.29 (d, J = 5.5 Hz, 1H), 8.04 - 7.96 (m, 2H), 7.94 (s, 1H), 7.46 - 7.35 (m, 2H), 6.95 (d, J = 6.0 Hz, 1H), 3.93 (s, 3H), 2.35 (s, 3H); ^{13}C{^{1}H} NMR (DMSO-d_6,101 MHz) δ 160.5, 148.4, 147.4, 146.2, 134.6, 130.4 (2C), 128.2 (2C), 124.1, 110.6, 102.8, 92.2, 56.6, 21.5; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{13}BrN_2O_3S$ 380.9903; Found 380.9887.

*3-Bromo-5-methoxy-1-tosyl-1H-pyrrolo[2,3-b]pyridine (**1v**):* Following the literature procedure[31d], using 3-bromo-5-methoxy-1*H*-pyrrolo[2,3-*b*]pyridine (0.5 g, 2.20 mmol), NaH (0.16 g, 6.61 mmol), and *p*-toluenesulfonyl chloride (0.462 g, 2.42 mmol), **1v** was obtained by flash column chromatography (30% EtOAc in petroleum ether) as off-white solid (0.5 g, 60 %); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.19 - 8.12 (m, 2H), 7.97 (d, J = 8.5 Hz, 2H), 7.46 - 7.35 (m, 3H), 3.86 (s, 3H), 2.33 (s, 3H); ^{13}C{^{1}H} NMR (DMSO-d_6, 101 MHz) δ 153.6, 145.7, 139.8, 136.2, 134.1, 130.0 (3C), 127.4 (2C), 126.4, 110.4, 56.1, 21.0.

*3-Iodo-1-tosyl-1H-pyrrolo[2,3-b]pyridine-4-carbonitrile (**1w**)*: Following the general procedure, using 3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine-4-(1 g, 3.72 mmol), NaH (0.27 g, 11.15 mmol) and *p*-toluenesulfonyl chloride (0.78 g, 4.09 mmol), **1w** was obtained by flash column chromatography (30% EtOAc in petroleum ether) as off-white solid (1.0 g, 64%); mp: 161-163 ^{o}C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.57 (d, J = 5.1 Hz, 1H), 8.42 (s, 1H), 8.03 (d, J = 8.3 Hz, 2H), 7.84 (d, J = 4.9 Hz, 1H), 7.42 (d, J = 8.1 Hz, 2H), 2.33 (s, 3H); ^{13}C{^{1}H} NMR (DMSO-d_6, 101 MHz) δ 146.2, 145.5, 145.3, 133.9, 133.6 (2C), 130.1, 127.8, 123.7, 121.1, 113.9, 112.6, 60.3, 21.0; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{10}IN_3O_2S$ 423.9611; Found 423.9582.

*3-Bromo-1-tosyl-1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (**1x**)*: Following the general procedure, using 3-bromo-1*H*-pyrrolo[2,3-*b*]pyridine-5-carbonitrile (1 g, 4.50 mmol), NaH (0.324 g, 13.51 mmol) and *p*-toluenesulfonyl chloride (0.94 g, 4.95 mmol), **1x** was obtained by flash column chromatography (30% EtOAc in petroleum ether) as off-white solid (1.1 g, 60%); mp: 173-175 ^{o}C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.87 (d, J = 1.8 Hz, 1H), 8.58 (d, J = 1.8 Hz, 1H), 8.43 (s, 1H), 8.04 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 8.3 Hz, 2H), 2.35 (s, 3H); ^{13}C{^{1}H} NMR (DMSO-d_6, 101 MHz) δ 148.5, 146.4, 145.9, 133.7, 133.3, 130.2 (2C), 128.1, 127.8 (2C), 121.3, 116.9, 105.0, 94.7, 21.1; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{10}BrN_3O_2S$ 375.9750; Found: 375.9735.

*1-(3-Iodo-1-tosyl-1H-pyrrolo[2,3-b]pyridin-5-yl)ethan-1-one (**1y**)*: Following the general procedure, using 1-(3-iodo-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)ethan-1-one (1.2 g, 4.19 mmol), NaH (0.30 g, 12.58 mmol) and *p*-toluenesulfonyl chloride (0.880 g, 4.61 mmol), **1y** was obtained by flash column chromatography (30% EtOAc in petroleum ether) as off-white solid (1.10 g, 60%); mp: 173-175 ^{o}C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.97 (d, J = 2.0 Hz, 1H), 8.29 (s, 1H), 8.19 (d, J = 2.0 Hz, 1H), 8.07 - 8.03 (m, 2H), 7.48 - 7.42 (m, 2H), 2.68 (s, 3H), 2.35 (s, 3H); ^{13}C{^{1}H} NMR (DMSO-d_6, 101 MHz) δ 196.6, 147.6, 146.6, 146.3, 134.1, 131.9, 130.3, 130.2 (2C), 129.1, 127.9 (2C), 124.6, 27.3, 21.2; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{13}IN_2O_3S$ 440.9764; Found: 440.9745.

*Methyl 3-iodo-1-tosyl-1H-pyrrolo[2,3-b]pyridine-5-carboxylate (**1z**)*: Following the general procedure, using methyl 3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (0.5 g, 1.66 mmol), NaH (0.12 g, 4.97 mmol) and *p*-toluenesulfonyl chloride (0.35 g, 1.82 mmol), **1z** was obtained by flash column chromatography (30% EtOAc in petroleum ether) as off-white solid (0.35 g, 46%); mp: 164-166 ^{o}C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.91 (d, J = 2.0 Hz, 1H), 8.29 (s, 1H), 8.16 (d, J = 2.0 Hz, 1H), 8.05 (d, J = 8.3 Hz, 2H), 7.43 (d, J = 8.5 Hz, 2H),

3.90 (s, 3H), 2.34 (s, 3H); $^{13}C\{^{1}H\}$ NMR (DMSO-d_6, 101 MHz) δ 165.4, 148.1, 147.0, 146.7, 134.4, 132.3, 131.6, 130.6 (2C), 128.3 (2C), 125.9, 124.9, 122.6, 64.9, 53.0, 21.6; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{13}IN_2O_4S$ 456.9713; found 456.9699.

*3-Iodo-4-nitro-1-tosyl-1H-pyrrolo[2,3-b]pyridine(**1aa**)*: Following the general procedure, using methyl 3-iodo-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate (1 g, 3.46 mmol), NaH (0.25 g, 10.38 mmol) and *p*-toluenesulfonyl chloride (0.73 g, 3.81 mmol), **1aa** was obtained by flash column chromatography (30% EtOAc in petroleum ether) as yellow solid (0.8 g, 51%); mp: 197-199 ^{o}C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.66 (d, J = 5.1 Hz, 1H), 8.45 (s, 1H), 8.10 - 8.01 (m, J = 8.3 Hz, 2H), 7.89 (d, J = 5.1 Hz, 1H), 7.48 - 7.40 (m, J = 8.3 Hz, 2H), 2.34 (s, 3H); $^{13}C\{^{1}H\}$ NMR (DMSO-d_6, 101 MHz) δ 148.7, 147.2, 146.4, 146.3, 135.1, 133.5 (2C), 130.1 (2C), 127.9, 112.7, 112.7, 57.2, 21.0; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{14}H_{10}IN_3O_4S$ 443.9509; Found 443.9500.

D) General experimental procedure for the synthesis of 3c-3aa: To a stirred suspension of zinc dust (112 mg, 1.71 mmol) in DMF (5.0 mL) was added 0.5 mL of a solution of iodine (43.4 mg, 0.17 mmol) in DMF (1.0 mL). After observing colour change, *tert*-butyl (*R*)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-iodopropanoate **2** (421 mg, 0.85 mmol) was added in one potion followed by addition of the remaining 0.5 mL of the iodine solution. The solution was stirred at room temperature for 35 min; the supernatant liquid was transferred to a mixture of *N*-Ts-3-haloazaindoles (1 eq., 0.57 mmol), $Pd_2(dba)_3$ (26.1 mg, 0.03 mmol), and XPhos (27.1 mg, 0.06 mmol) in DMF (6 mL) via a syringe. The reaction mixture was stirred at 55 ^{o}C in oil bath for 3 h. The completion of reaction was monitored by LCMS. The reaction mixture was concentrated to remove DMF, then diluted with EtOAc (50 mL) and passed through a celite pad. The organic layer was washed with water (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum to give the crude product

which was purified by silica gel column chromatography (eluted with 30-40 % EtOAc in petroleum ether) followed by recrystallization using MTBE/Heptane to afford the pure product.

For the large-scale synthesis, the general procedure was adapted: To a stirred suspension of zinc dust (1.68 g, 25.65 mmol) in DMF (75.0 mL) was added 7.5 mL of a solution of iodine (0.65 g, 2.55 mmol) in DMF (15.0 mL). After observing colour change, *tert*-butyl (*R*)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-iodopropanoate **2** (6.32 g, 12.81 mmol) was added in one potion followed by addition of the remaining 7.5 mL of the iodine solution. The solution was stirred at room temperature for 35 min; the supernatant liquid was transferred to a mixture of 3-bromo-1-tosyl-1H-pyrrolo[2,3-b]pyridine **1c** (3.0 g, 8.54 mmol), $Pd_2(dba)_3$ (0.39 g, 0.45 mmol), and XPhos (0.41 g, 0.9 mmol) in DMF (90 mL) via a syringe. The reaction mixture was stirred at 55 ^oC in oil bath for 3 h. The reaction mixture was concentrated to remove DMF, then diluted with EtOAc (750 mL) and passed through a celite pad. The organic layer was washed with water (300 mL), brine (300 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum to give the crude product which was purified by silica gel column chromatography (eluted with 30-40 % EtOAc in petroleum ether) followed by recrystallization using MTBE/Heptane to afford tert-Butyl (*S*)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)propanoate (**3c**) in 76% yield (4.2 g).

Spectroscopic and analytical data for isolated compounds are given below:

*tert-Butyl (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)propanoate (**3c**)*: The title compound was purified by flash silica-gel column chromatography (30% EtOAc in petroleum ether) to obtain off-white solid (323 mg, 89%, >99% ee); mp: 137-139 ^oC; $[\alpha]^{25}_D$ = +14.8 (c = 1.0, $CHCl_3$); ^1H NMR (500 MHz,

DMSO-d_6) δ 8.36 (d, J = 4.4 Hz, 1H), 8.08 (d, J = 7.8 Hz, 1H), 7.91 (br dd, J = 8.1, 14.4 Hz, 5H), 7.77 (s, 1H), 7.66 (dd, J = 4.4, 6.8 Hz, 2H), 7.46 - 7.37 (m, 2H), 7.35 - 7.24 (m, 5H), 4.35 - 4.09 (m, 4H), 3.18 - 3.08 (m, 1H), 3.06 - 2.96 (m, 1H), 2.27 (s, 3H), 1.27 (s, 9H); $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 171.1, 156.3, 147.0, 145.8, 145.0, 144.2, 144.1, 140.1, 141.1, 135.1, 130.3 (2C), 129.1 (2C), 128.1 (2C),127.8 (2C), 127.5 (2C), 125.7, 124.9, 123.1, 120.6 (2C), 119.5, 115.6, 81.2, 66.7, 54.8, 47.0, 27.9 (3C), 26.9, 21.4; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{36}H_{35}N_3O_6S$ 638.2319; Found 638.2294.

*tert-Butyl (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(1-tosyl-1H-pyrrolo[3,2b]pyridin-3-yl)propanoate (**3i**)*: The title compound was purified by flash silica-gel column chromatography (30% EtOAc in petroleum ether) to obtain off-white solid (305 mg, 84%); mp: 69-71 ^oC; $[\alpha]^{25}_D$ = +1.4 (c = 2.0, $CHCl_3$); ^1H NMR (400 MHz, DMSO-d_6) δ 8.52 (d, J = 4.9 Hz, 1H), 8.31 (br d, J = 8.3 Hz, 1H), 8.04 (br d, J = 7.3 Hz, 1H), 8.00 (s, 1H), 7.88 (dd, J = 8.1, 18.3 Hz, 4H),7.67 (t, J = 7.1 Hz, 2H), 7.47 - 7.36 (m, 3H), 7.35 - 7.23 (m, 4H), 4.48 - 4.40 (m, 1H), 4.32 - 4.26 (m, 1H), 4.23 - 4.11 (m, 2H), 3.23 - 3.12 (m, 1H), 3.06 (br dd, J = 8.8, 14.7 Hz, 1H), 2.26 (s, 3H), 1.19 (s, 9H); $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 171.1, 156.3, 147.9, 146.2, 146.1, 144.2, 144.1 (2C), 134.3, 130.8 (2C), 128.6 (2C), 128.2, 128.1, 128.0, 127.5 (2C), 127.2 (2C), 125.7, 125.6, 121.2, 120.6 (2C), 120.0, 119.1, 80.9, 66.1, 54.1, 47.0, 27.8 (3C), 26.3, 21.4; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{36}H_{35}N_3O_6S$ 638.2319; Found 638.2305.

*tert-Butyl (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(1-tosyl-1H-pyrrolo[3,2-c]pyridin-3-yl)propanoate (**3j**)*: The title compound was purified by flash silica-gel column chromatography (30% EtOAc in petroleum ether) to obtain off-white solid (298 mg, 82%); mp: 85-87 ^oC; $[\alpha]^{25}_D$ = +12.6 (c = 2.0, $CHCl_3$); ^1H NMR (400 MHz, DMSO-d_6) δ 8.95 (s, 1H), 8.45 (br d, J = 6.0 Hz, 1H), 7.94 - 7.82 (m, 6H), 7.75 (s, 1H), 7.64 (br dd, J = 2.0, 7.5 Hz, 2H), 7.46 - 7.37 (m, 2H), 7.35 - 7.21 (m, 4H), 4.34 - 4.08 (m, 4H), 3.21 - 3.00

(m, 2H), 2.25 (s, 3H), 1.23 (s, 9H); $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6) δ 171.0, 156.3, 146.3, 144.6, 144.2, 144.1 (2C), 143.4, 141.1 (2C), 139.0, 134.3, 130.9 (2C), 130.8, 128.1 (2C), 127.5, 127.4, 127.3, 126.9, 125.7 (2C), 120.6 (2C), 117.9, 108.4, 81.2, 66.2, 54.9, 47.0, 27.8 (3C), 26.6, 21.4; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{36}H_{35}N_3O_6S$ 638.2319; Found 638.2306.

*tert-Butyl (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(1-tosyl-1H-pyrrolo[2,3-c]pyridin-3-yl)propanoate (**3k**)*: The title compound was purified by flash silica-gel column chromatography (30% EtOAc in petroleum ether) to obtain off-white solid (294 mg, 81%); mp: 90-92 ^{o}C; $[\alpha]^{25}_{D}$ = +11.1 (c = 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.16 (s, 1H), 8.37 (d, J = 5.5 Hz, 1H), 7.95 - 7.81 (m, 6H), 7.72 - 7.57 (m, 3H), 7.40 (br dd, J = 1.8, 7.3 Hz, 2H), 7.34 - 7.21 (m, 4H), 4.34 - 4.12 (m, 4H), 3.16 - 3.07 (m, 1H), 3.06 - 2.96 (m, 1H), 2.24 (s, 3H), 1.25 (s, 9H); $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6) δ 171.0, 156.3, 146.3, 144.2, 144.1, 142.8, 141.1, 136.5, 135.4, 134.2, 131.6, 130.8 (2C), 128.6 (2C), 128.1 (2C), 127.5 (2C), 127.3 (2C), 125.7, 125.6, 120.6 (2C), 118.3, 115.1, 81.2, 66.2, 54.7, 47.0, 27.9 (3C), 27.3, 21.4; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{36}H_{35}N_3O_6S$ 638.2319; Found 638.2302.

*tert-Butyl (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(1-tosyl-1H-pyrrolo[2,3-b]pyridin-4-yl)propanoate (**3l**)*: The title compound was purified by flash silica-gel column chromatography (30% EtOAc in petroleum ether) to obtain off-white solid (312 mg, 86%); mp: 90-92 ^{o}C; $[\alpha]^{25}_{D}$ = +5.1 (c = 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (d, J = 5.0 Hz, 1H), 7.90 (dd, J = 8.3, 11.3 Hz, 4H), 7.85 - 7.81 (m, 2H), 7.62 (d, J = 7.5 Hz, 2H), 7.44 - 7.38 (m, 2H), 7.34 - 7.31 (m, 4H), 7.17 (d, J = 5.0 Hz, 1H), 6.91 (d, J = 4.0 Hz, 1H), 4.30 - 4.18 (m, 2H), 4.16 - 4.08 (m, 2H), 3.25 - 3.10 (m, 2H), 2.27 (s, 3H), 1.20 (s, 9H); $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6) δ 170.8, 156.2, 147.0, 145.9, 144.9, 144.2, 144.1, 141.2, 141.1, 135.0, 130.3 (2C), 128.1 (2C), 128.0 (2C), 127.5 (2C), 126.8 (2C), 125.7,

125.6, 122.9, 120.6 (2C), 120.2, 104.8, 81.3, 66.0, 55.1, 47.0, 27.8 (3C), 27.3, 21.5; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{36}H_{35}N_3O_6S$ 638.2319; Found 638. 2296.

*tert-Butyl (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(1-tosyl-1H-pyrrolo[2,3-b]pyridin-5-yl)propanoate (**3m**)*: The title compound was purified by flash silica-gel column chromatography (30% EtOAc in petroleum ether) to obtain off-white solid (330 mg, 91%); mp: 190-192 ^oC; $[\alpha]^{25}_D$ = +2.0 (c = 2.0, $CHCl_3$); ^1H NMR (400 MHz, DMSO-d_6) δ 8.25 (s, 1H), 7.97 - 7.91 (m, 3H), 7.90 - 7.80 (m, 4H), 7.62 (br t, J = 8.8 Hz, 2H), 7.42 - 7.29 (m, 5H), 7.23 (br t, J = 7.3 Hz, 1H), 6.75 (br d, J = 4.0 Hz, 1H), 4.25 - 4.11 (m, 4H), 3.13 - 3.02 (m, 1H), 3.02 - 2.90 (m, 1H), 2.27 (s, 3H), 1.22 (s, 9H); $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 171.2, 156.3, 146.1 (2C), 145.9, 144.1 (2C), 141.1 (2C), 135.0, 130.8, 130.4 (2C), 129.1, 128.1 (2C), 127.9 (2C), 127.5 (2C), 127.4 (2C), 125.6, 122.6, 120.6 (2C), 106.2, 81.1, 66.1, 56.5, 47.0, 27.9 (3C), 27.3, 21.5; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{36}H_{35}N_3O_6S$ 638.2319; Found 638. 2300.

*tert-Butyl (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)propanoate (**3n**)*: The title compound was purified by flash silica-gel column chromatography (40% EtOAc in petroleum ether) to obtain off-white solid (276 mg, 76%); mp: 90-92 ^oC; $[\alpha]^{25}_D$ = +17.6 (c = 2.0, $CHCl_3$); ^1H NMR (400 MHz, DMSO-d_6) δ 9.19 (s, 1H), 8.96 (s, 1H), 7.97 (d, J = 8.5 Hz, 2H), 7.93 - 7.82 (m, 4H), 7.62 (dd, J = 2.0, 7.5 Hz, 2H), 7.43 - 7.35 (m, 4H), 7.28 (d, J = 7.0 Hz, 2H), 4.38 - 4.28 (m, 1H), 4.27 - 4.11 (m, 3H), 3.22 - 3.14 (m, 1H), 3.13 - 3.04 (m, 1H), 2.29 (s, 3H), 1.25 (s, 9H); $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 170.9, 156.3, 153.3, 150.7 (2C), 146.5, 144.1 (2C), 141.1 (2C), 134.5, 130.6 (2C), 128.1 (2C), 128.0 (3C),127.5 (2C), 125.6 (2C), 121.1, 120.6 (2C), 114.9, 81.2, 66.2, 54.9, 47.0, 27.9 (3C), 26.8, 21.5; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{35}H_{34}N_4O_6S$ 639.2272; Found 639.2254.

*tert-Butyl (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(5-chloro-1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)propanoate (**3o**)*: The title compound was purified by flash silica-gel column chromatography (30% EtOAc in petroleum ether) to obtain off-white solid (302 mg, 79%); mp: 145-147 °C; $[\alpha]^{25}_{D}$ = +16.6 (c = 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (d, J = 2.0 Hz, 1H), 8.30 (d, J = 2.0 Hz, 1H), 7.95 - 7.83 (m, 6H), 7.62 (dd, J = 3.0, 7.0 Hz, 2H), 7.43 - 7.38 (m, 2H), 7.33 (br d, J = 8.0 Hz, 2H), 7.30 - 7.22 (m, 2H), 4.32 - 4.12 (m, 4H), 3.18 - 3.07 (m, 1H), 3.06 - 2.95 (m, 1H), 2.27 (s, 3H), 1.27 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 171.0, 156.3, 146.1, 145.2, 144.2, 144.1, 143.2, 141.1 (2C), 134.8, 130.4 (2C), 128.9, 128.1 (2C), 127.8 (2C), 127.5 (2C), 127.0, 126.8, 125.6 (2C), 124.4, 120.6 (2C), 115.4, 81.2, 66.2, 54.8, 47.0, 27.9 (3C), 27.8, 21.5; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{36}H_{34}ClN_3O_6S$ 672.1930; Found 672.1901.

*tert-Butyl (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(5-fluoro-1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)propanoate (**3q**)*: The title compound was purified by flash silica-gel column chromatography (30% EtOAc in petroleum ether) to obtain off-white solid (313 mg, 84%); mp: 80-82 °C; $[\alpha]^{25}_{D}$ = +16.9 (c = 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 - 8.31 (m, 1H), 8.09 (dd, J = 2.5, 9.0 Hz, 1H), 7.94 - 7.81 (m, 6H), 7.63 (br d, J = 7.5 Hz, 2H), 7.40 (br t, J = 7.3 Hz, 2H), 7.35 - 7.30 (m, 2H), 7.29 - 7.19 (m, 2H), 4.32 - 4.10 (m, 4H), 3.17 - 3.07 (m, 1H), 3.05 - 2.93 (m, 1H), 2.27 (s, 3H), 1.28 (s, 9H); ^{19}F NMR (377 MHz, DMSO-d_6) δ -134.48 (s, 1F); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 171.0, 157.1 (d, J = 246.9 Hz), 156.3, 146.0, 144.2, 144.1, 143.4, 141.1, 134.9, 133.3 (d, J = 30.2 Hz) 130.4 (2C), 128.1 (2C), 127.8 (2C), 127.5 (2C), 127.4 (2C), 125.6 (2C), 124.2 (d, J = 6.3 Hz), 120.6 (2C), 115.8, 115.7 (d, J = 26.5 Hz), 81.2, 66.7, 54.8, 47.0, 27.9 (3C), 26.8, 21.5; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{36}H_{34}FN_3O_6S$ 656.2225; Found 656.2205.

*tert-Butyl (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(4-fluoro-1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)propanoate (**3r**)*: The title compound was purified by flash silica-

gel column chromatography (30% EtOAc in petroleum ether) to obtain off-white solid (310 mg, 83%); mp: 81-83 °C; $[\alpha]^{25}_{D}$ = +7.3 (c = 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (dd, J = 5.8, 7.8 Hz, 1H), 8.02 - 7.81 (m, 5H), 7.77 (s, 1H), 7.66 (t, J = 7.5 Hz, 2H), 7.45 - 7.36 (m, 2H), 7.35 - 7.12 (m, 5H), 4.31 - 4.13 (m, 4H), 3.16 (br d, J = 6.0 Hz, 1H), 3.08 - 2.97 (m, 1H), 2.27 (s, 3H), 1.24 (s, 9H); ^{19}F NMR (377MHz, DMSO-d_6) δ -111.13 (s, 1F); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 171.0, 162.4 (d, J = 263.7 Hz), 156.4, 149.7 (br d, J = 10.0 Hz), 147.6, 147.5, 146.2, 144.2, 144.1, 141.2, 134.7, 130.4 (2C), 128.1 (2C), 128.0 (2C), 127.5 (2C), 125.7 (2C), 125.4, 120.6 (2C), 113.2, 111.6 (br d, J = 16.6 Hz), 106.7, 81.2, 66.2, 55.0, 47.1, 28.3, 27.9 (3C), 21.5; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{36}H_{34}FN_3O_6S$ 656.2225; Found 656.2236.

*tert-Butyl (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(2-methyl-1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)propanoate (**3s**)*: The title compound was purified by flash silica-gel column chromatography (30% EtOAc in petroleum ether) to obtain off-white solid (282 mg, 76%); mp: 90-92 °C; $[\alpha]^{25}_{D}$ = +4.2 (c = 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (dd, J = 1.3, 4.8 Hz, 1H), 7.95 (dd, J = 1.3, 7.8 Hz, 1H), 7.92 - 7.74 (m, 5H), 7.64 (dd, J = 4.5, 7.5 Hz, 2H), 7.44 - 7.39 (m, 2H), 7.36 - 7.10 (m, 5H), 4.26 - 4.00 (m, 4H), 3.11 - 3.02 (m, 1H), 3.02 - 2.88 (m, 1H), 2.61 (s, 3H), 2.23 (s, 3H), 1.19 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 171.1, 156.2, 148.1, 145.4, 144.2, 144.1, 143.9, 143.8, 141.1, 136.2, 135.3, 130.2 (2C), 128.1, 128.0, 127.7, 127.6 (2C), 127.5 (2C), 125.7, 125.6, 122.4, 120.6 (2C), 119.5, 113.3, 81.0, 66.1, 54.9, 46.9, 27.8 (3C), 27.3, 21.4, 13.3; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{37}H_{37}N_3O_6S$ 652.2476; Found 652.2457.

*tert-Butyl (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(1-tosyl-5-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)propanoate (**3t**)*: The title compound was purified by flash silica-gel column chromatography (30% EtOAc in petroleum ether) to obtain off-white solid (325 mg, 81%); mp: 114-116 °C; $[\alpha]^{25}_{D}$ = +19.7 (c = 2.0, $CHCl_3$); ^{1}H

NMR (400 MHz, DMSO-d_6) δ 8.75 (s, 1H), 8.61 (s, 1H), 8.02 - 7.93 (m, 3H), 7.88 (br dd, J = 3.3, 7.8 Hz, 3H), 7.61 (br t, J = 6.5 Hz, 2H), 7.43 - 7.32 (m, 4H), 7.29 - 7.18 (m, 2H), 4.39 - 4.08 (m, 4H), 3.22 - 3.05 (m, 2H), 2.28 (s, 3H), 1.25 (s, 9H); ^{19}F NMR (377 MHz, DMSO-d_6) δ -59.05 (s, 3F); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 171.0, 156.4, 148.3, 146.3, 144.2, 144.1, 141.8 (2C), 141.2, 141.1, 134.8, 130.5 (2C), 128.1 (2C), 128.0 (2C), 127.5 (2C), 127.4, 125.6 (2C), 124.8 (q, J = 273.4 Hz), 122.8, 121.2 (q, J = 31.4 Hz), 120.6 (2C), 116.1, 81.2, 66.2, 54.9, 47.0, 27.9 (3C), 26.7, 21.5; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{37}H_{34}F_3N_3O_6S$ 706.2193; Found 706.2173.

*tert-Butyl (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(4-methoxy-1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)propanoate (**3u**)*: The title compound was purified by flash silica-gel column chromatography (40% EtOAc in petroleum ether) to obtain off-white solid (330 mg, 87%); mp: 118-120 ^{o}C; $[\alpha]^{25}_D$ = +12.8 (c = 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (d, J = 5.5 Hz, 1H), 7.93 - 7.84 (m, 4H), 7.79 (d, J = 8.0 Hz, 1H), 7.67 (dd, J = 7.3, 12.3 Hz, 2H), 7.56 (s, 1H), 7.43-7.41 (m, 3H), 7.32 (s, 1H), 7.27 (d, J = 8.0 Hz, 2H), 6.89 (d, J = 5.5 Hz, 1H), 4.32 - 4.22 (m, 2H), 4.20 - 4.10 (m, 2H), 3.92 (s, 3H), 3.21 (dd, J = 5.3, 14.3 Hz, 1H), 2.93 (dd, J = 9.5, 14.1 Hz, 1H), 2.24 (s, 3H), 1.31 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 171.5, 160.9, 156.3, 148.7, 147.4, 145.7, 144.2, 144.1, 141.2, 141.1, 135.1, 130.3, 130.2 (2C), 128.1 (2C), 127.9 (2C), 127.5, 125.7 (2C), 123.1, 120.6 (2C), 115.0, 112.0, 102.4, 80.9, 66.1, 56.5, 55.3, 47.0, 28.0 (3C), 27.3, 21.4; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{37}H_{37}N_3O_7S$ 668.2425; Found 668.2411.

*tert-Butyl (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(5-methoxy-1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)propanoate (**3v**)*: The title compound was purified by flash silica-gel column chromatography (40% EtOAc in petroleum ether) to obtain off-white solid (323 mg, 85%); mp: 99-101 ^{o}C; $[\alpha]^{25}_D$ = +9.4 (c = 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 (d, J = 3.0 Hz, 1H), 7.87 (t, J = 8.0 Hz, 5H), 7.71 (s, 1H), 7.68 (d, J = 2.5 Hz, 1H),

7.63 (t, *J* = 6.5 Hz, 2H), 7.44 - 7.36 (m, 2H), 7.32 - 7.23 (m, 4H), 4.30 - 4.11 (m, 4H), 3.81 (s, 3H), 3.18 - 3.08 (m, 1H), 3.02 – 2.96 (m, 1H), 2.26 (s, 3H), 1.30 (s, 9H); $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO- d_6) δ 171.1, 156.4, 153.4, 145.7, 144.2, 144.1, 141.8 (2C), 135.3, 134.8, 130.3 (2C), 128.1 (3C), 127.7 (2C), 127.5 (2C), 125.9 (2C), 125.6, 123.8, 120.6 (2C), 115.9, 112.0, 81.2, 66.2, 56.5, 55.0, 47.0, 28.0 (3C), 26.9, 21.5; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{37}H_{37}N_3O_7S$ 668.2425; Found 668.2438.

*tert-Butyl (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(4-cyano-1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)propanoate (**3w**)*: The title compound was purified by flash silica-gel column chromatography (40% EtOAc in petroleum ether) to obtain off-white solid (298 mg, 79%); mp: 144-146 ^{o}C; $[\alpha]^{25}_{D}$ = -2.3 (c = 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (d, *J* = 4.5 Hz, 1H), 8.06 (s, 1H), 7.97 - 7.84 (m, 5H), 7.80 (d, *J* = 5.0 Hz, 1H), 7.67 (dd, *J* = 3.5, 7.5 Hz, 2H), 7.40 (td, *J* = 3.7, 7.2 Hz, 2H), 7.35 - 7.21 (m, 4H), 4.41 - 4.31 (m, 1H), 4.31 - 4.22 (m, 1H), 4.22 - 4.11 (m, 2H), 3.39 (br dd, *J* = 5.5, 15.1 Hz, 1H), 3.20 - 3.09 (m, 1H), 2.27 (s, 3H), 1.30 (s, 9H); $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6) δ 170.9, 156.4, 146.9, 146.5, 145.2, 144.2, 144.1, 141.1 (2C), 134.4, 130.5 (2C), 128.8 (2C), 128.1 (3C), 127.5 (2C), 125.7 (2C), 122.9, 121.6, 120.6 (2C), 116.2, 114.2, 111.2, 81.3, 66.2, 54.7, 47.0, 27.9 (3C), 27.3, 21.5; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{37}H_{34}N_4O_6S$ 663.2272; Found 663.2253.

*tert-Butyl (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(5-cyano-1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)propanoate (**3x**)*: The title compound was purified by flash silica-gel column chromatography (40% EtOAc in petroleum ether) to obtain off-white solid (305 mg, 81%); mp: 135-137 ^{o}C; $[\alpha]^{25}_{D}$ = +16.5 (c = 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (dd, *J* = 1.8, 9.3 Hz, 2H), 8.03 - 7.91 (m, 3H), 7.91 - 7.80 (m, 3H), 7.61 (br d, *J* = 7.5 Hz, 2H), 7.45 - 7.37 (m, 2H), 7.35 (br d, *J* = 8.5 Hz, 2H), 7.30 - 7.23 (m, 2H), 4.36 - 4.10 (m, 4H), 3.21 - 3.11 (m, 1H), 3.09 - 2.99 (m, 1H), 2.28 (s, 3H), 1.28 (s, 9H)**;** $^{13}C\{^{1}H\}$ NMR (126

MHz, DMSO-d_6) δ 170.9, 156.3, 147.7, 147.4, 146.5, 144.1 (2C), 141.1 (3C), 134.5, 134.2, 130.6 (2C), 128.1, 128.0 (2C), 127.5 (2C), 127.4, 125.6 (2C), 122.8, 120.6 (2C), 118.0, 115.8, 104.3, 81.2, 66.2, 54.7, 47.0, 27.9 (3C), 26.6, 21.5; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{37}H_{34}N_4O_6S$ 663.2272; Found 663.2258.

*tert-Butyl (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(5-acetyl-1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)propanoate (**3y**)*: The title compound was purified by flash silica-gel column chromatography (40% EtOAc in petroleum ether) to obtain off-white solid (275 mg, 71%); mp: 97-99 ^oC; $[\alpha]^{25}_D$ = +9.4 (c = 2.0, $CHCl_3$); ^1H NMR (400 MHz, DMSO-d_6) δ 8.93 (d, J = 1.5 Hz, 1H), 8.63 (d, J = 2.0 Hz, 1H), 7.95 (d, J = 8.0 Hz, 2H), 7.89 (s, 3H), 7.69 (d, J = 7.5 Hz, 1H), 7.61 (dd, J = 2.5, 7.0 Hz, 2H), 7.41 (d, J = 7.5 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H), 7.29 - 7.20 (m, 2H), 4.29 - 4.13 (m, 4H), 3.18 (br d, J = 6.0 Hz, 1H), 3.11 (br d, J = 9.5 Hz, 1H), 2.61 (s, 3H), 2.28 (s, 3H), 1.29 (s, 9H); $^{13}C\{^1H\}$ NM**R** (126 MHz, DMSO-d_6) δ 196.7, 170.5, 156.6, 155.8, 148.1, 145.7, 145.4, 143.9, 143.6, 140.6, 134.4, 129.9 (2C), 128.9, 128.1, 127,6 (2C), 127.5 (2C), 127.0, 126.9, 126.0, 125.1 (2C), 122.4, 120.0 (2C), 116.0, 80.8, 65.7, 64.9, 54.5, 46.7, 27.4 (3C), 27.0, 21.0; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{38}H_{37}N_3O_7S$ 680.2425; Found 680.2424.

*Methyl (S)-3-(2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(tert-butoxy)-3-oxopropyl)-1-tosyl-1H-pyrrolo[2,3-b]pyridine-5-carboxylate (**3z**)*: The title compound was purified by flash silica-gel column chromatography (40% EtOAc in petroleum ether) to obtain off-white solid (321 mg, 81%); mp: 144-146 ^oC; $[\alpha]^{25}_D$ = +2.2 (c = 2.0, $CHCl_3$); ^1H NMR (400 MHz, DMSO-d_6) δ 8.87 (d, J = 1.5 Hz, 1H), 8.60 (d, J = 2.0 Hz, 1H), 7.96 (d, J = 8.0 Hz, 2H), 7.91 - 7.81 (m, 4H), 7.60 (d, J = 7.5 Hz, 2H), 7.43 - 7.31 (m, 4H), 7.27 - 7.19 (m, 2H), 4.32 - 4.10 (m, 4H), 3.83 (s, 3H), 3.22 - 3.04 (m, 2H), 2.28 (s, 3H), 1.27 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 170.4, 165.3, 155.8, 148.2, 145.8, 145.5, 143.6, 140.6 (3C), 134.3, 130.0, 129.9 (2C), 127.6, 127.5 (3C), 126.9 (2C), 126.2, 125.1, 122.4,

121.1, 120.0 (2C), 115.8, 114.5, 80.8, 65.7, 54.5, 52.3, 46.5, 27.4 (3C), 26.1, 21.0; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{38}H_{37}N_3O_8S$ 696.2374; Found 696.2383.

*tert-Butyl (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(4-nitro-1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)propanoate (**3aa**)*: The title compound was purified by flash silica-gel column chromatography (40% EtOAc in petroleum ether) to obtain yellow solid (268 mg, 69%); mp: 90-92 ^oC; $[\alpha]^{25}_D$ = -24.2 (c = 2.0, $CHCl_3$); ^1H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, J = 5.0 Hz, 1H), 8.17 (s, 1H), 7.99 - 7.92 (m, 3H), 7.91 - 7.81 (m, 3H), 7.66 (dd, J = 3.5, 7.5 Hz, 2H), 7.41 (br d, J = 3.5 Hz, 2H), 7.35 - 7.23 (m, 4H), 4.29 - 4.22 (m, 1H), 4.20 - 4.04 (m, 3H), 3.25 (br dd, J = 5.8, 14.8 Hz, 1H), 3.03 (dd, J = 9.5, 14.6 Hz, 1H), 2.27 (s, 3H), 1.27 (s, 9H); $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ 171.1, 156.3, 149.1, 148.9, 146.6, 145.8, 144.2, 144.1, 141.1 (2C), 134.2, 130.5 (2C), 128.2 (2C), 128.1 (2C), 127.5 (2C), 125.7, 125.6 (2C), 120.6 (2C), 113.9, 113.5, 113.2, 81.2, 66.2, 55.0, 47.0, 27.9 (3C), 27.3, 21.5; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{36}H_{34}N_4O_8S$ 683.2170; Found 683.2147.

E) Experimental procedure for deprotected compounds 4, 5 and 6

*tert-Butyl-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(1H-pyrrolo[2,3-b]pyridin-3-yl)propanoate (**4**)*: *tert*-Butyl-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(1-tosyl-1H-pyrrolo [2,3-b]pyridin-3-yl)propanoate **3c** (100 mg, 0.16 mmol) and samarium(II) iodide (4.70 mL, 0.47 mmol) were charged into 50 mL RB flask at room temperature, to this was added water (8.47 µl, 0.47 mmol) and pyrrolidine (0.03 mL, 0.31 mmol). The reaction mixture was stirred for 30 min under nitrogen and it was concentrated under vacuum. The crude mixture was diluted with DCM (25 mL) passed through a celite pad, and washed with DCM (20 mL). The filtrate was concentrated and the crude product was purified by flash silica-gel column chromatography (eluted with 50 % EtOAc in Pet-ether) to obtain *tert*-butyl-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(1H-pyrrolo[2,3-b]pyridin-3-yl)propanoate (**4**) (60 mg, 78 % yield) as off-white solid; mp: 65-67

°C; $[\alpha]^{25}_D$ = +14.4 (c = 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (br s, 1H), 8.28 (br d, *J* = 4.5 Hz, 1H), 7.93 (br d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 7.5 Hz, 2H), 7.59 (dd, *J* = 4.5, 7.0 Hz, 2H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.35 - 7.29 (m, 2H), 7.10 (s, 1H), 7.05 (dd, *J* = 4.8, 7.8 Hz, 1H), 5.58 (br d, *J* = 7.5 Hz, 1H), 4.73 - 4.63 (m, 1H), 4.53 - 4.44 (m, 1H), 4.44 - 4.33 (m, 1H), 4.23 (br t, *J* = 7.0 Hz, 1H), 3.36 - 3.21 (m, 2H), 1.41 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 171.0, 155.8, 148.4, 143.9, 143.7, 143.1, 141.3 (3C), 127.7 (2C), 127.5 (2C), 127.1, 125.1, 123.2, 120.3, 120.0 (2C), 115.7, 109.0, 82.4, 66.8, 55.0, 47.2, 28.3, 28.0 (3C); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{29}H_{29}N_3O_4$ 484.2231; Found 484.2219.

*tert-Butyl-2-amino-3-(1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)propanoate (**5**)*:

To a solution of *tert*-butyl-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)propanoate (125 mg, 0.20 mmol) in DCM (5 mL) was added piperidine (0.06 mL, 0.59 mmol). The reaction mixture was stirred at room temperature for 8 h under nitrogen atmosphere. The reaction mixture was concentrated under vacuum to give the crude product. The crude was purified by flash silica-gel column chromatography (eluted with 70 % EtOAc in Pet-ether) to obtain *tert*-butyl-2-amino-3-(1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)propanoate (**5**) (75 mg, 91% yield) as gummy liquid; $[\alpha]^{25}_D$ = +8.0 (c = 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (dd, *J* = 1.5, 5.0 Hz, 1H), 8.06 (d, *J* = 8.5 Hz, 2H), 7.89 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.61 (s, 1H), 7.29 - 7.27 (m, 1H), 7.25 (s, 1H), 7.18 (dd, *J* = 4.8, 7.8 Hz, 1H), 3.66 (dd, *J* = 5.8, 7.3 Hz, 1H), 3.14 - 3.04 (m, 1H), 2.98 - 2.87 (m, 1H), 2.37 (s, 3H), 1.40 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 174.0, 147.3, 145.0, 135.6, 129.6, 129.5 (2C), 128.2, 128.0 (2C), 124.2, 123.3, 118.6, 115.0, 81.5, 55.2, 30.7, 28.0 (3C), 21.6; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{21}H_{25}N_3O_4S$ 416.1639; Found 416.1651.

*2-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-3-(1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)propanoic acid (**6**)*: To a solution of *tert*-butyl (*S*)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)propanoate (125 mg,

0.20 mmol) in DCM (5 mL), TFA (0.08 mL, 0.98 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 30 min under nitrogen atmosphere. The reaction mixture was concentrated under vacuum to obtain 2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)propanoic acid (**6**) (105 mg, 92%) as off-white solid; $[\alpha]^{25}_{D}$ = +6.0 (c = 0.1, CH_3OH); ^{1}H NMR (400 MHz, METHANOL-d_4) δ 8.31 (dd, J = 1.3, 4.8 Hz, 1H), 8.04 (dd, J = 1.5, 8.0 Hz, 1H), 7.86 (d, J = 8.0 Hz, 2H), 7.79 (d, J = 8.0 Hz, 2H), 7.70 (s, 1H), 7.54 (t, J = 8.3 Hz, 2H), 7.39 - 7.33 (m, 2H), 7.27 - 7.20 (m, 3H), 7.16 (br d, J = 8.0 Hz, 2H), 4.51 (s, 1H), 4.27 - 4.15 (m, 3H), 4.12 (br d, J = 7.0 Hz, 1H), 3.13 (s, 1H), 2.20 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 173.0, 155.9, 146.7, 145.3, 144.5, 143.7, 143.6, 140.7 (2C), 134.7, 129.8 (3C), 128.6, 127.6, 127.3 (3C), 125.6, 125.2, 124,5 (2C), 122.7, 120.1 (2C), 119.0, 115.5, 65.8, 53.8, 40.6, 26.4, 20.9; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{32}H_{27}N_3O_6S$ 582.1693; Found 582.1704.

F) Experimental procedure for dipeptide derivatives 8 and 10

*tert-butyl (S)-2-((S)-2-((tert-butoxycarbonyl)amino)-3-methylbutanamido)-3-(1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)propanoate (**8**)*: To a solution of *tert-Butyl-2-amino-3-(1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)propanoate* (143 mg, 0.35 mmol) and (tert-butoxycarbonyl)-L-valine (75 mg, 0.35 mmol) in ethyl acetate (2 mL) was added triethylamine (0.17 mL, 1.21 mmol) and the reaction mixture was stirred at 0 ^{o}C for 10 min. under nitrogen atmosphere. A solution of propylphosphonic anhydride 48% in ethyl acetate (0.54 mL, 0.86 mmol) was added dropwise and the reaction mixture was stirred at 0 ^{o}C for 0.5 h under nitrogen atmosphere. The reaction mixture was diluted with ethyl acetate (15 mL), washed with water (2 x 5 mL) followed by brine (10 mL) and concentrated to obtained crude. The crude was purified by flash silica-gel column chromatography (eluted with 35 % acetone in DCM) to obtain tert-butyl (S)-2-((S)-2-((tert-butoxycarbonyl)amino)-3-methylbutanamido)-3-(1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)propanoate (**8**) (168 mg, 79%)

as off-white solid; mp: 81-83 °C; $[\alpha]^{25}_{D}$ = +32.0 (c = 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (dd, *J* = 1.5, 4.5 Hz, 1H), 8.10 - 8.01 (m, 2H), 7.93 (dd, *J* = 1.5, 7.5 Hz, 1H), 7.57 (s, 1H), 7.29 (s, 1H), 7.27 (s, 1H), 7.23 - 7.16 (m, 1H), 6.50 (br d, *J* = 6.5 Hz, 1H), 5.03 (br d, *J* = 7.5 Hz, 1H), 4.83 - 4.74 (m, 1H), 3.90 (t, *J* = 6.5 Hz, 1H), 3.25 - 3.11 (m, 2H), 2.38 (s, 3H), 2.11 (qd, *J* = 6.7, 13.0 Hz, 1H), 1.47 (s, 9H), 1.35 (s, 9H), 0.95 (d, *J* = 7.0 Hz, 3H), 0.87 (br d, *J* = 6.0 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.3, 170.0, 147.2, 145.1, 145.1, 135.5, 129.6 (3C), 128.5, 128.0 (2C), 124.4, 123.2, 118.8, 113.9, 83.0, 77.2, 52.8, 30.9, 28.3 (3C), 28.2, 27.9 (3C), 21.6, 19.2 (2C); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{31}H_{42}N_4O_7S$ 615.2847; Found 615.2869.

*methyl ((S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)propanoyl)-L-valinate (**10**)*: To a solution of 2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)propanoic acid (125 mg, 0.18 mmol) and L-Valine methyl ester hydrochloride (30.1 mg, 0.18 mmol) in ethyl acetate (2 mL) was added triethylamine (0.13 mL, 0.90 mmol) and the reaction mixture was stirred at 0 °C for 10 minutes under nitrogen atmosphere. To this was added a solution of propylphosphonic anhydride 48% in ethyl acetate (0.28 mL, 0.45 mmol) dropwise, and the reaction mixture was stirred at 0 °C for 30 min under nitrogen atmosphere. The reaction mixture was diluted with ethyl acetate (15 mL), washed with water (2 x 5 mL) followed by brine (10 mL) and concentrated to obtained crude. The crude was purified by flash silica-gel column chromatography (eluted with 35 % acetone in DCM) to obtain *methyl ((S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)propanoyl)-L-valinate* (**10**) (98 mg, 78%) as off-white solid; mp: 87-89 °C; $[\alpha]^{25}_{D}$ = -8.0 (c = 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (dd, *J* = 1.5, 4.5 Hz, 1H), 8.13 - 8.01 (m, 2H), 7.95 (br d, *J* = 6.5 Hz, 1H), 7.80 (d, *J* = 7.5 Hz, 2H), 7.64 (br s, 1H), 7.58 (br d, *J* = 7.0 Hz, 2H), 7.42 (t, *J* = 7.3 Hz, 2H), 7.32 (t, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.17 (dd, *J* = 4.8, 7.8 Hz,

1H), 6.21 (br d, J = 8.0 Hz, 1H), 5.58 (br d, J = 6.0 Hz, 1H), 4.57 - 4.33 (m, 4H), 4.22 (t, J = 6.8 Hz, 1H), 3.71 (br s, 3H), 3.28 - 3.06 (m, 2H), 2.35 (s, 3H), 2.14 - 2.04 (m, 1H), 0.82 (br dd, J = 6.8, 12.8 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 171.5, 170.3, 147.4, 145.2, 145.1, 143.7, 143.6, 141.3, 141.3, 135.5, 129.6, 128.2, 128.0, 127.8, 127.1, 127.1, 125.0, 125.0, 124.9, 122.8, 120.0, 120.0, 67.3, 67.2, 57.4, 52.4, 47.1, 31.1, 28.6, 21.6, 18.8, 17.7; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{38}H_{38}N_4O_7S$ 695.2534; Found 695.2558.

ASSOCIATED CONTENT

***Supporting Information**

^{1}H, $^{13}C\{1H\}$ NMR, HPLC details and chiral SFC spectra of all compounds.

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ACKNOWLEDGMENT

Authors are thankful to Discovery Analytical Department, Biocon Bristol-Myers Squibb Research Centre (BBRC), Syngene, Bangalore (India) for Analytical support.

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