

Article

Design and Synthesis of 7-(N-Aryl Pyrrolidinyl) Indoles as Potential DCAF15 Binders

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Abstract: We describe the design and synthesis of a series of 7-(N-aryl pyrrolidinyl) indoles and oxo-analogs as isosteric mimics of the DCAF15 binder E7820, a well-known member of aryl sulfonamides known as SPLAMs. The functionalization of C-7 in indoles was achieved by metal-catalyzed CH-activation with unexpected results. Binding assays revealed the pyrrolidine N-aryl carboxylic acid analog to be as equally active as E7820.

Keywords: molecular glues; DCAF15 binders; indole derivatives



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1. Introduction

The phenomenal success in developing new medicines over the past century has been due in major part to the invention of pharmacologically active small molecules that target, among others, receptors and enzymes involved in complex mechanisms at the molecular level [1,2]. There are, however, many instances where a disease can be caused by the involvement of a protein that cannot be targeted by small molecules because of an inability to be recognized in conventional ways. The term ‘undruggable’ has been used for such recalcitrant protein targets [3,4].

Proteolysis is an important process for the body to eliminate dysregulated proteins [5,6]. This is accomplished in a remarkable sequence of molecular events, whereby enzymes called ligases recognize specific amino acid sequences in certain proteins called degrons to generate secondary complexes, whereby the recruited protein of interest (POI) undergoes ubiquitination, leading to degradation via the proteasomal machinery [6,7]. Somewhat indirectly, if not serendipitously, it has been found that small organic molecules can bind to proteins such as ligases to create neo-proteins that can recruit proteins of interest forming a ternary complex, eventually leading to ubiquitination and degradation. Acting as chemical inducers of proximity (CIPs) [8], such organic compounds have been called molecular glues [9–13]. The process has been exploited to target disease-causing proteins with small molecules and to eliminate them through an induced process mediated by ligases [14]. However, without prior knowledge of their ability to bind and induce protein–protein interactions [15], it is difficult to rationally design such small molecules for therapeutic

purposes. Nevertheless, the discovery of novel molecular glues often arises from serendipity, such as during the clarification of the mode of action (MOA) of biologically active compounds, including small molecules with anticancer activities [16,17]. These molecules consist of sulfonamides such as indisulam and E7820, also termed SPLAMS (SPlicing inhibitor SulfonAMides), which have an indole moiety in common (Figure 1). Interest in the field was heightened with the watershed report by Nijhawan [18,19] that indisulam mediates the recruitment of essential pre-mRNA splicing factor RBM39 to CUL4^{DCAF15} E3 ligase, leading to the degradation of RBM39. Furthermore, treatment of tumors derived from parental HCT-116 colon carcinoma cell lines with indisulam resulted in complete regression. DeBussiere and coworkers provided the precise molecular mechanism by which indisulam mediates the interaction between RBM39 and the DCAF15 E3 ligase substrate receptor DCAF15–DDB1–DDA1 [20]. The structure of the ternary complex was resolved by X-ray crystallography and cryogenic electron microscopy (cryo-EM) at 2.30 Å and 3.54 Å, respectively. No interactions between RBM39 and DCAF15-complex were observed in the absence of indisulam and other SPLAMs, thereby supporting their involvement as molecular glues. The authors concluded that indisulam binds to DCAF15 and enhances the binding of RBM39 forming a ternary complex leading to ubiquitination and proteasomal degradation. More recently, Fischer and coworkers reported the X-ray and cryoEM structure of the DDB1–DCAF15–DDA1 core ligase complex bound to RBM39 and E7820 at a resolution of 4.4 Å, highlighting details of the interactions [21]. Coomar and Gillingham reported that despite significant chemical modification, indisulam can still promote CUL4^{DCAF15}-dependent degradation of RBM39 [22]. A selection of DCAF15 binders, some of which have been designated as molecular glues, is shown in Figure 1 [23–28]. With the discovery of new ligases and better small-molecule binders, further exciting developments can be achieved as heterobifunctional compounds called PROTACS (Proteolysis Targeting Chimeras) for targeted protein degradation using a designed approach [29]. PROTACs contain a small-molecule binder for a selected E3 ligase linked by a spacer element to another small molecule that binds to the POI. Binding simultaneously to these two proteins creates a ternary complex, and in an optimal situation, the necessary proximity to ubiquitinate and degrade the POI via the proteasome. Although a PROTAC was developed with E7820, its activity was weak [30]. However, the prospects for new clinical candidates based on PROTACS are promising [31]. The fact that E3 ligases are tissue-, cell-type-, and cell-compartment-specific offers great opportunities to exploit the targeted protein degradation (TPD) paradigm for therapeutic purposes. Therefore, increasing the toolbox of applicable E3 ligases via new small-molecule binders provides exciting opportunities for new approaches to drug discovery through a TPD modality [32].

SPLAMs have a sulfonamide linker in common which defines sites of interaction with DCAF15 as H-bond-accepting units [20,21]. Considering the available structural information in the ternary complex involving E7820 [21], we devised surrogates of E7820 as possible isosteres by diversifying the nature of the linker between the indole and aryl sulfonamide units. We chose to synthesize compounds in which the cyanophenyl sulfonamide group in E7820 was replaced with a N-arylpyrrolidine unit, as well as an N-aryl pyrrolidinone and an N-aryl succinimide. We surmised that the presence of one or more oxo-groups in a pyrrolidine ring could possibly act as H-bond acceptor sites leading to binding to DCAF15. To address the spatial environment of the N-aryl group as an exit vector, we also considered the corresponding N-benzyl pyrrolidines and pyrrolidinones.

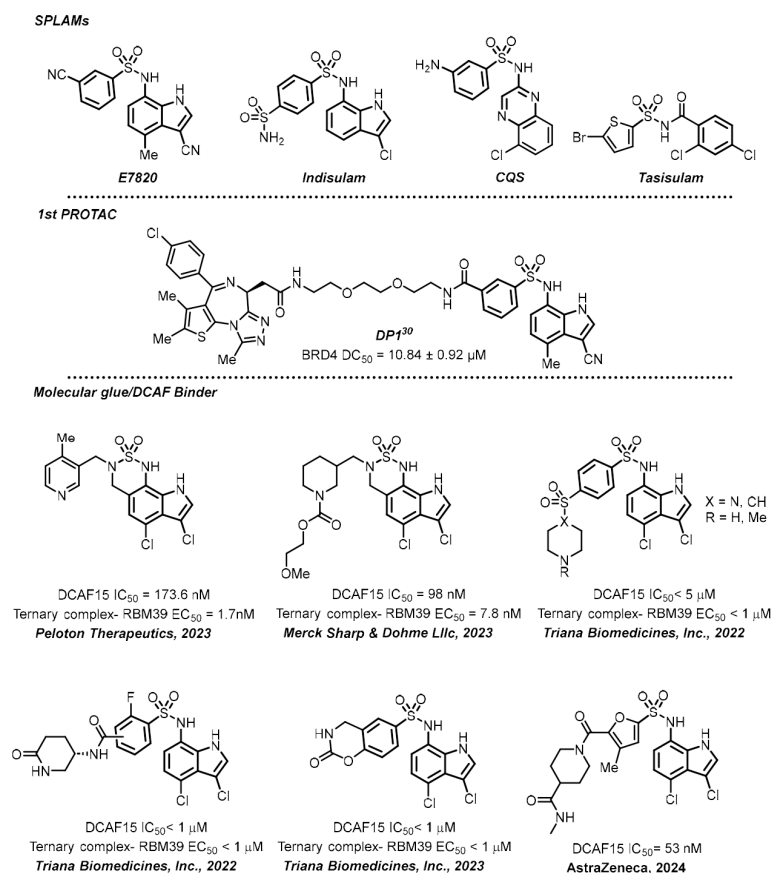


Figure 1. Structures of SPLAMs, a PROTAC with E-7820, and molecular glues (SPLAMs) [23–28].

We were aware that the structural data for DCAF15 and E7820 involved a ternary complex with RBM39 [21]. To engage in the design of surrogates of E7820 as potential DCAF15 binders would assume that the position of the E7820 vis-à-vis DCAF15 in the ternary complex would remain unchanged in the absence of RBM39. With the inevitable uncertainties as to the successful outcome of such a study, we nevertheless proceeded with the synthesis of two groups of 4-methyl-7-indolyl surrogates of E7820 consisting of N-arylpyrrolidines, N-arylpyrrolidinones, and the corresponding N-benzyl variants as linkers exemplified by the composite structure shown in Figure 2. The aryl group within each series was substituted with a carboxylic acid, the corresponding methyl ester, and n-propyl amide in the meta position. Here, we describe synthetic methods leading to the compounds displayed in Figure 2 as well as preliminary data on their binding to DCAF15. A variety of aryl sulfonamides have been reported to bind to DCAF15 [22]. However, to the best of our knowledge, and with the exception of patented compounds [23–28] (Figure 1), analogs of E7820 have only been reported as potential binders to DCAF15 in connection with RBM39 degradation.

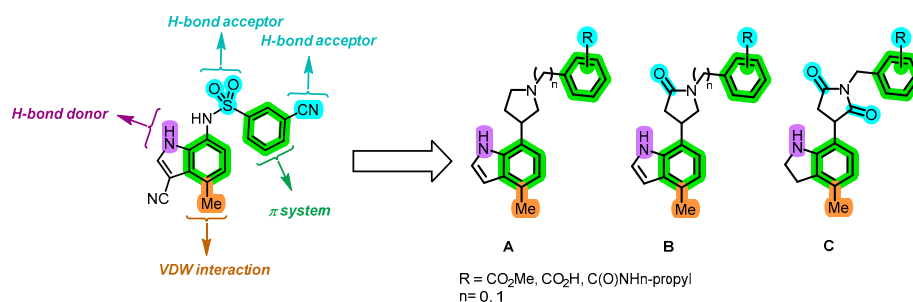
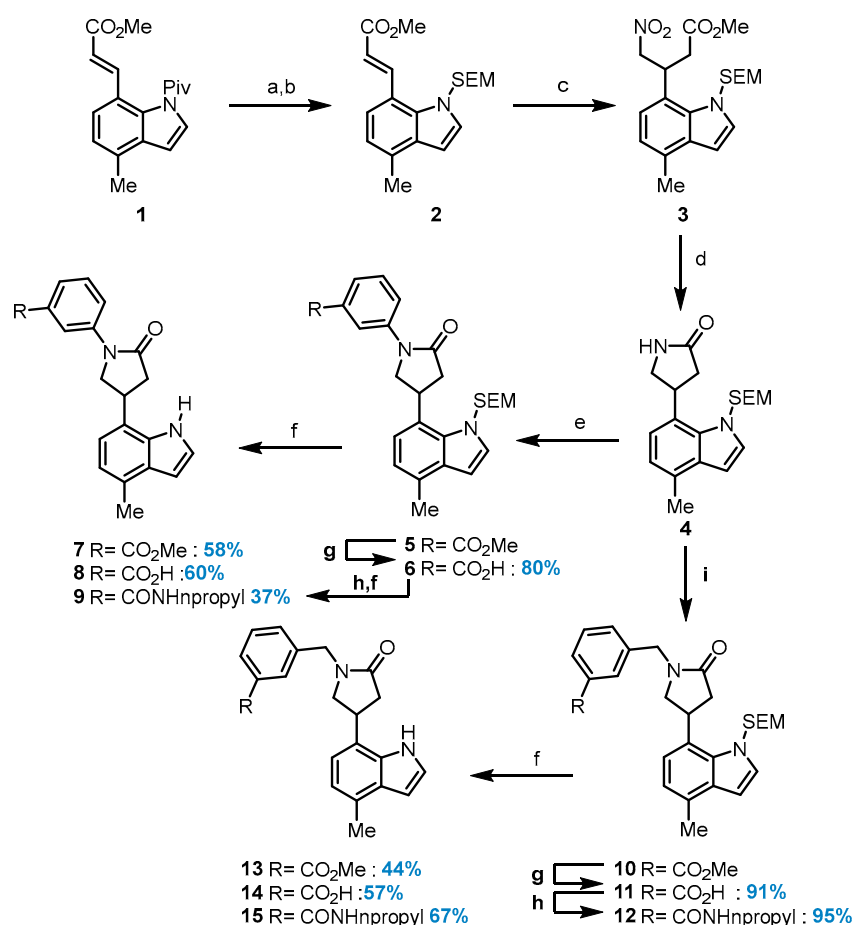


Figure 2. Proposed analogs of E7820 containing an azacyclic linker.

2. Results

2.1. N-Aryl and N-Benzyl Pyrrolidinones in the Indole Series

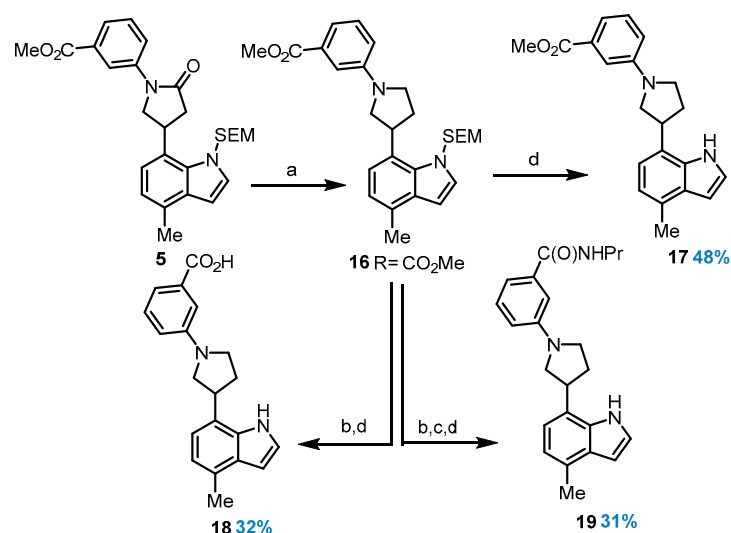
The synthesis commenced with the cleavage of the N-pivaloyl group in the known α,β -unsaturated ester **1** prepared according to Ma [33] followed by replacing the Piv group with SEM to give indole **2** [34] (Scheme 1). Subsequently, reaction with nitromethane in the presence of tetramethyl guanidine led to nitro ester **3**. When this reaction was carried out on N-Piv indole **1**, an undesirable cyclization product was obtained due to the deprotection of the indole and the intramolecular attack of the nitrogen atom on the ester. Reduction of the nitro group with $\text{NiCl}_2\text{-NaBH}_4$ [35] led to the corresponding amine which cyclized to lactam **4**. Buchwald–Hartwig coupling [36] was carried out with methyl 3-bromobenzoate to give the m-methoxycarbonyl phenyl lactam **5**. Saponification afforded carboxylic acid **6**, which was converted to n-propyl amide **7**. Cleavage of the SEM group with 1M TBAF solution in the presence of ethylenediamine [37] at 80 °C afforded the m-substituted aryl analogs **7–9**. For the N-benzyl series, lactam **4** was alkylated in presence of NaH with methyl 3-(bromomethyl) methyl benzoate to give **10**. Following the same protocol as described above led to N-benzyl analogs **13–15** as racemates.



Scheme 1. Synthesis of N-aryl lactams **7–9** and N-benzyl lactams **13–15**.

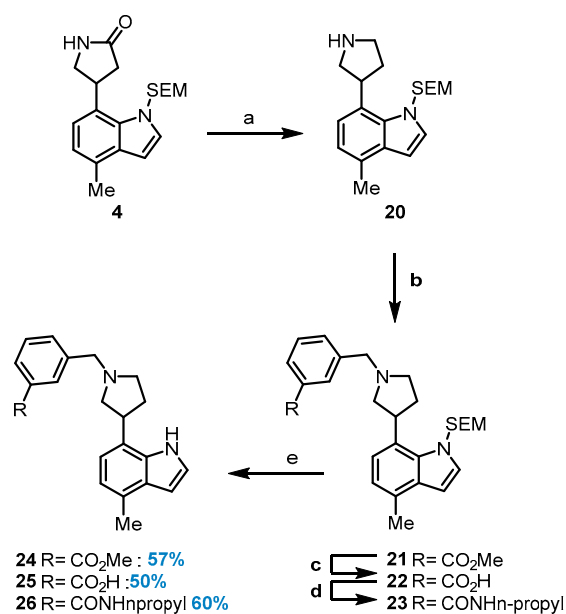
2.2. N-Aryl and N-Benzyl Pyrrolidines in the Indole Series

N-aryl pyrrolidine analog **16** was easily obtained from γ -lactam **5** by treatment with BH_3 . THF complex. Following the same reaction sequence as described above, racemic N-aryl pyrrolidine analogs **17–19** were obtained (Scheme 2).



Scheme 2. Synthesis of N-aryl pyrrolidines 17–19.

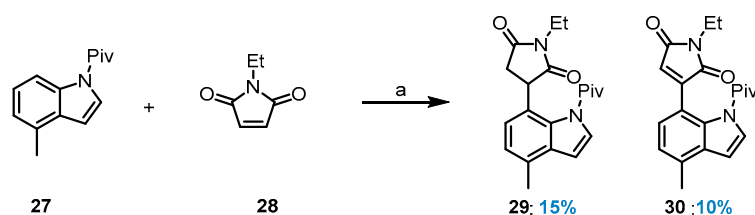
For the N-benzyl pyrrolidine series, treatment of γ -lactam **10** with borane under the same conditions as for the lactams proved unsuccessful. Consequently, selective reduction of racemic lactam **4** was performed with LiAlH_4 , and the resulting pyrrolidine was alkylated with (3-bromomethyl) methyl benzoate to give **21**. Following the same protocol described above led to N-benzyl pyrrolidine analogs **24–26** (Scheme 3).



Scheme 3. Synthesis of N-benzyl pyrrolidines 24–26.

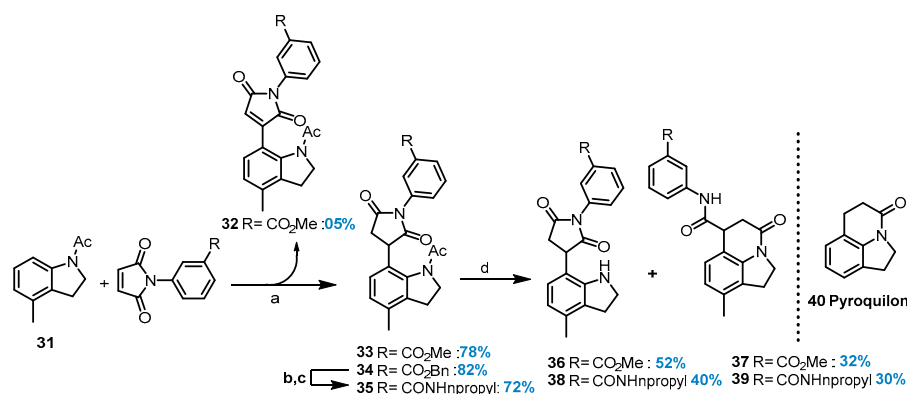
2.3. N-Aryl and N-Benzyl Succinimides in the Indoline Series

Attempts to prepare a C-7 succinimide analog replacing the lactam in **4** proved to be challenging. Following the method reported by Song [38] using N-ethylsuccinimide as a model in the presence of (5 mol%) $[\text{RhCp}^*\text{Cl}_2]_2$, AgSbF_6 (20 mol%), Ag_2O (2.0 equiv.), and TFE (2 mL) at 80 °C resulted in very low yields of the desired hydroarylation product **29** (15%) and the undesired Heck product **30** (10%) (Scheme 4). Unfortunately, numerous attempts to fine-tune the catalytic system to obtain 7-(N-substituted succinimidyl) indoles as major products were unsuccessful (see Table S1 in Supplementary Information). We therefore opted to synthesize analogs using an indoline scaffold.



Scheme 4. Synthesis of N-phenyl indole succinimides **29** and **30**.

Naturally occurring indolines and synthetic indolines are endowed with a variety of biological activities [39,40]. We surmised that 7-N-aryl lactam and N-aryl succinimide indoline analogs of E7820 would complement the examples shown above in the indole series. Indoline N-(m-methoxycarbonyl phenyl) lactam was synthesized following the same procedure as described above for the indole series (Scheme 1), whereas a Piv-protecting group was used throughout the sequences (see Scheme S1 in Supplementary Information). The synthesis of 7-indoline N-(m-methoxycarbonyl phenyl)succinimide following the method developed by Yu [41] using the catalytic system $[\text{RhCp}^*\text{Cl}_2]_2$ (5 mol%), AgSbF_6 (20 mol%), AgOAc (20 mol%), HOAc (0.4 mmol), and DCE (2.0 mL), under N_2 , at 120 °C for 24 h, led to a mixture of Heck product **32** (30%) and the desired hydroarylation product **33** (60%) (Scheme 5). We optimized the conditions using Ag_2O (two equiv.) and three equiv. of AcOH to minimize Heck product **32** (5%) in favor of **33** (78%) (see Table S2 in Supplementary Information). Methyl ester **36** and amide **38** were obtained using the same strategy as before with relatively similar yields. During the deprotection step, we observed the formation of δ -lactams **37** and **39** in addition to the expected indolines **36** and **38**. This resulted from an intramolecular attack of indoline nitrogen on the proximal succinimide carbonyl group. The tricyclic core structure in **37** corresponds to pyroquilon (**40**), which is an inhibitor of the rice blast fungal enzyme trihydroxy naphthalene reductase [42]. N-Benzyl succinimide analogs were prepared from the corresponding succinimides (see Scheme S2 in Supplementary Information).

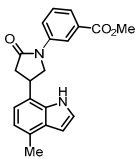
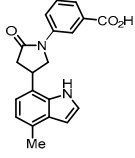
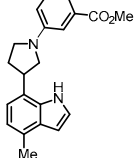
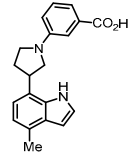


Scheme 5. Synthesis of N-phenyl succinimides **36** and **38** and tricyclic lactams **37** and **39**.

With a diverse set of racemic compounds in hand, we conducted preliminary binding tests from each series by the fluorescence polarization method using a fluorescent derivative of E7820 as tracer (see Scheme S3 in Supplementary Information) [43]. We also tested selected compounds against colon carcinoma cell line HCT116 in vitro (see Table S5 in Supplementary Information). Although the esters and amides were weaker binders compared to the free carboxylic acids, a clear SAR was not evident, particularly between the phenyl and benzyl series (see Tables S3 and S4 in Supplementary Information). Surprisingly, the N-aryl carboxylic acid with pyrrolidine linker **18** was active with an AC_{50} of 7.7 μM compared to E7820 (AC_{50} = 10 μM). The corresponding methyl ester **17** and n-propyl amide

19 were inactive (Table 1 and Table S3 in Supplementary Information). Carboxylic acid lactam analogs **8** and **14** demonstrated comparable activity to E7820, with AC_{50} values of 15 μ M and 23 μ M, respectively (see Table S3 in Supplementary Information). Only weak in vitro inhibition was observed against colon carcinoma cell line HCT116 for analogs **14** and **19** (AC_{50} = 19 μ M) and Tasisulam (AC_{50} = 24 μ M). On the other hand, a possible correlation between binding (AC_{50} = 10 μ M) and HTC inhibition (AC_{50} = 0.7 μ M) was observed in the case of E7820. However, the colon carcinoma cell line HCT116 activities cannot be attributed to DCAF15 binding activity without further experimentation.

Table 1. Binding affinity of selected analogs.

Entry	Compound nb	Structure	Binding Affinity AC_{50} (μ M)
1	7		67
2	8		15
3	17		>100
4	18		7.7
5	E7820		10

Data represent the mean of experiments performed in triplicate. A fluorescence polarization assay was performed.

3. Discussion

The tested compounds exhibited significant differences in their biological activity. Carboxylic acid analogs **8** and **18** demonstrated binding activity comparable to or even higher than that of E7820, whereas their methyl ester analogs (**7** and **17**) showed little to no activity. Furthermore, compound **8**, based on a pyrrolidine linker, displayed better activity than its lactam counterpart **18**; an unexpected result considering the possible loss of hydrogen bonding interactions.

To compare the interactions of compounds **7**, **8**, **17**, and **18** with DCAF15 and to formulate hypotheses explaining the experimental results, we performed molecular docking studies using AutoDock Vina 1.1.2 (La Jolla, CA, USA) [44,45].

The docking poses of lactams **7** and **8** (Figure 3B,D and Figures S3 and S4 in Supplementary Information) showed that they retained the characteristic interactions involving the indole unit as observed for E7820 (Figure 3A and Figure S2 in Supplementary Information). These interactions include a hydrogen bond between the NH of the indole part and the Phe231residue, as well as a hydrogen bond between the carbonyl group of the lactam and residues Ala234 and Phe235. Compounds **8** and **18**, derived from pyrrolidine linker units, adopted the same pose as their lactam counterparts despite the absence of the carbonyl group. Instead of forming hydrogen bonds with Ala234 and Phe235, the

pyrrolidine unit engaged in hydrophobic interactions with these residues (Figure 3B,C and Figures S6–S8 in Supplementary Information). A charge interaction between the carboxylic acid group of compounds **8** and **18** and residue Lys238 was observed (Figure 3B,C) which was absent in methyl ester analogs **7** and **17**, possibly accounting for their reduced activity. Thus, the carboxylic acid group appears to play a critical role in stabilizing the interaction with DCAF15. Additionally, we investigated the impact of enantiomeric differences on binding interactions. The docking poses of both enantiomers of compound **8** (lactam series) were compared (Figure S5 in Supplementary Information), revealing that one enantiomer loses the hydrogen bonds with residues Ala234 and Phe235. This observation suggests that, in the lactam series, the presence of a less favorable enantiomer in the racemic mixture could contribute to the overall decrease in biological activity.

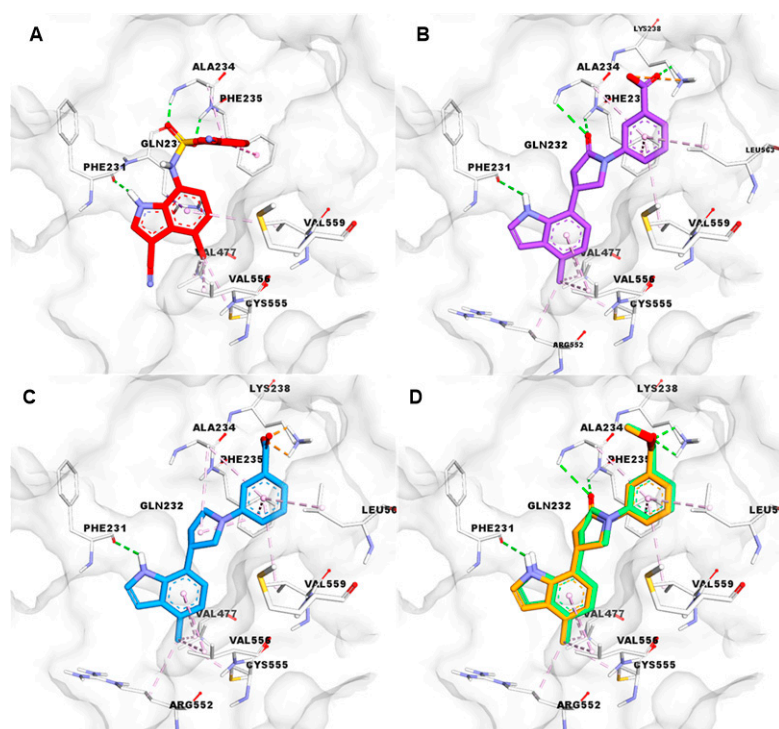


Figure 3. (A) E7820 in DCAF15. (B) Docking pose and interactions of compound **8** with DCAF15. (C) Docking pose and interactions of compound **18** with DCAF15. (D) Superposition of docking pose of compound **24** (orange) and interactions of compound **7** (green) with DCAF15.

4. Conclusions

In conclusion, a series of 7-indolyl 3-aryl pyrrolidine and pyrrolidinones were synthesized as surrogates for E7820 relying on catalytic reactions and conventional synthetic methods. Preliminary testing of selected compounds as binders to DCAF15 was disappointing, even though the pyrrolidine analog **18** matched the activity of E7820. The results of the docking study suggest that the hydrophobic interactions of pyrrolidines can probably compensate for the absence of hydrogen bonding with Ala234 and Phe235 and that the presence of a carboxylic acid group is essential for optimal interaction with DCAF15, particularly through a charged interaction with Lys238.

Although it appears that some of our compounds interact with DCAF15 as deduced from the binding assay results, the nature of the interactions beyond the docking study is unclear. In the case of glue-type molecules, a binding pocket created from two proteins forms only in the presence of the small molecule. Therefore, a binding pocket derived from a ternary complex in the absence of one partner (here RBM39) presents a conundrum for

molecular modeling. Further studies are needed to extend the scope and implications of these results.

Lucas and coworkers [28] recently disclosed their detailed results on the design of ligands for the E3 ligase DCAF15 and the prospects of developing PROTAC degraders with the most active synthetic analogs to target BRD4 using (+)-JQ1 as a binder. No degradation of RBM39 was observed, which led the authors to suggest that the glue modality of the developed binders was mostly abolished. However, based on their experiments, they suggested the involvement of alternative mechanisms of degradation of BRD4 that were not mediated by DCAF15. These highly relevant observations by the AstraZeneca scientists should serve as guidelines for further research dealing with reliance on single ligases in drug design related to targeted protein degradation.

5. Materials and Methods

5.1. DCAF15 Target Engagement—Polarized Fluorescence

A total of 100 nL of each tested compound was dispensed in 11 dose–response steps in a 384-well plate (Perkin Elmer, Waltham, USA), targeting a maximum final concentration of 100 μ M in DMSO (semi-log dilution step). A solution of 12.5 nM final concentration of the tracer was prepared as well as a solution of 5 nM final concentration of DCAF15 (provided by NOVALIX, Lyon, France) [43]. To start the experiment, 4 μ L of a freshly prepared buffer (50 mM HEPES, 200 mM NaCl, 4% DMSO, and 0.01% BSA, pH 7.5), 3 μ L of the DCAF15 solution, and 3 μ L of the tracer solution were dispensed. The plate was centrifuged for 2 min at 900 rpm and then incubated at room temperature for 10 min. The fluorescence polarization (FP 635-20/680-20 module) was read in a PheraSTAR plate reader (BMG Labtech, Offenburg, Germany) as the total fluorescence intensity (FI 640/680 module).

5.2. General Information

Physical data and spectroscopic measurement NMR spectra were recorded on a Bruker 300 spectrometer (Offenburg, Germany) (75 MHz for ^{13}C), a Bruker AVANCETM 400 RG spectrometer (400 MHz for ^1H), and a Bruker AVANCETM 500 Ultrashield Plus spectrometer (Offenburg, Germany) (500 MHz for ^1H , 126 MHz for ^{13}C , and 471 MHz for ^{19}F) in chloroform- d , d_6 , or methanol- d_4 . Spectra were recorded in the indicated solvent at ambient temperature. Chemical shifts (δ) are given in parts per million (ppm) with tetramethylsilane as an internal standard. Multiplicities are recorded as follows: s = singlet, d = doublet, t = triplet, q = quartet, br = broad. Coupling constants (J values) are given in Hz. Structural assignments were made with additional information from gCOSY, gHSQC, and gHMBC experiments. Accurate mass measurements were performed on an LC-TOF instrument from Agilent Technologies in positive electrospray mode. Protonated molecular ions $(\text{M}+\text{H})^+$ and/or sodium adducts $(\text{M}+\text{Na})^+$ were used for empirical formula confirmation. Melting points were determined on a Büchi B-540 melting point apparatus. Crystal measurements were performed on a Bruker Venture Metaljet diffractometer (Offenburg, Germany). Thin-layer chromatography (TLC) was performed on pre-coated Silicycle silica gel (250 μM , 60 Å) plates with F-254 indicator. Visualization was performed with a UV light (254 nm) or with stains (KMnO_4 , p -anisaldehyde, or ninhydrin). ZEO prep 60 (0.040–0.063 mm) silica gel was used for all column chromatography.

All reactions involving air- or moisture-sensitive compounds were performed under a nitrogen atmosphere in flame-dried glassware. Other solvents used for reactions were purified according to standard procedures. Starting reagents were purchased from commercial suppliers and used without further purification unless otherwise specified.

5.3. Experiments

- General Procedure A: saponification

Methyl ester derivative (1.0 equiv.) was dissolved in MeOH (40 μ M), and a solution of 2 N NaOH (5.0 equiv.) was added. The resulting solution was stirred for 24 h at room temperature. After completion, the reaction mixture was then evaporated to dryness. The residue was dissolved in CH₂Cl₂ and washed with 2 N HCl and brine. Drying over Na₂SO₄, filtration, and concentration yielded the crude carboxylic acid.

- General Procedure B: amide coupling

HATU (1.3 equiv.), 4-Dimethylaminopyridine (0.2 equiv.), and N,N-Diisopropylethylamine (2.2 equiv.) were added to a stirred solution of carboxylic acid (1.0 eq.) in dry DMF (30 μ M). The reaction mixture turned yellow. After 1 h, Propylamine (2.0 equiv.) was added. The resulting mixture was stirred at room temperature overnight. The reaction was quenched with 3 volumes of 1 M HCl, diluted with 3 volumes of EtOAc, and extracted with EtOAc (3 $\times$ 2 volumes). The organic layer was collected and washed sequentially with 1 M HCl (4 $\times$ 4 volumes), NaHCO₃ (2 $\times$ 2 volumes), and brine (2 $\times$ 2 volumes). It was then dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was quickly purified by chromatography to yield the corresponding amide.

- General Procedure C: SEM deprotection

To a solution of protected indole (1.0 equiv.) in THF (59 μ M), tetrabutylammonium fluoride (10 equiv.) was added, and the mixture was heated at 80 °C overnight. The reaction mixture was cooled to rt, diluted with EtOAc (2 volumes), and washed sequentially with water (2 volumes $\times$ 3) and brine (2 volumes $\times$ 1). The organic layer was dried with Na₂SO₄, and the solvent was removed under reduced pressure and purified by chromatography to afford unprotected indole.

- General Procedure D: SEM deprotection with additive

To a solution of protected indole (1.0 equiv.) in THF (59 μ M), ethylenediamine (6.0 equiv.) and tetrabutylammonium fluoride (10 equiv.) were added, and the mixture was heated at 80 °C overnight. The reaction mixture was cooled to rt, diluted with EtOAc (2 volumes), and washed with water (3 $\times$ 2 volumes) and brine (1 $\times$ 2 volumes). The organic layer was dried over Na₂SO₄, and the solvent was removed under reduced pressure. The crude product was purified by chromatography to afford the unprotected indole.

- General Procedure E: C7 alkylation using maleimides

To a pre-dried seal tube, indoline derivatives (0.2 mmol, 1.0 equiv.), [RhCp*Cl₂]₂ (5 mol%), AgSbF₆ (20 mol%), Ag₂O (2.0 equiv.), maleimide derivatives (1.5 equiv.), and AcOH (3.0 equiv.) were added. To this mixture, DCE (2 mL) was then added. The vial was flushed with argon gas while tightly capped and placed in a pre-heated (100 °C) oil bath. After 24 h, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and passed through a short pad of Celite. The organic layer was concentrated under reduced pressure, and the crude product was purified on a silica gel column using an ethyl acetate/hexane mixture to afford 65–95% yield (a trace amount of Heck-type product was also observed).

- General Procedure F: deacetylation

To a pre-dried seal tube, C7 alkylated indoline derivatives (0.2 mmol, 1.0 equiv.) was added, and to this, 4M HCl in dioxane was added (1 mL). The vial was capped and placed in a pre-heated (100 °C) oil bath. After 30 min, the reaction mixture was cooled to room temperature and diluted with ethyl acetate; the reaction mixture was neutralized with

sat, aq. and sodium bicarbonate solution; and the aqueous layer was extracted twice with EtOAc. The combined organic layer was dried over sodium sulfate. The organic layer was concentrated under reduced pressure (25 °C), and the crude product was purified on a silica gel column using ethyl acetate/hexane (if the reaction proceeded for more than 30 min, the formation of pyroquilon product was observed).

Methyl (E)-3-(4-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indol-7-yl)acrylate (2): To a solution of indole **1** (2.58 g, 8.62 mmol) in MeOH (17.2 mL) at room temperature, triethylamine (18.5 mL, 132 mmol) was added. The reaction mixture was stirred for 24 h under reflux and then concentrated under reduced pressure. The residue was washed with hexane to afford the free indole as a yellow solid. (1.86 g, 90%). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.55 (s, 1H), 8.00 (d, *J* = 16.0 Hz, 1H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.28 (dd, *J* = 3.3, 2.5 Hz, 1H), 6.96 (d, *J* = 7.5 Hz, 1H), 6.63 (dd, *J* = 3.3, 2.0 Hz, 1H), 6.45 (d, *J* = 16.0 Hz, 1H), 3.84 (s, 3H), 2.59 (s, 3H). ¹³C NMR (101 MHz, Chloroform-*d*) δ 167.9, 141.6, 133.9, 128.7, 124.2, 122.9, 120.7, 116.3, 116.0, 101.9, 51.8, 19.1. A stirring, ice-cooled solution of the free indole (250 mg, 1.16 mmol) in DMF (13.0 mL) was treated with sodium hydride (74.3 mg, 1.86 mmol), and the reaction mixture was stirred at room temperature for 45 min. After cooling to 0 °C, 2-(trimethylsilyl)ethoxymethyl chloride (308 µL, 1.74 mmol) was added dropwise. The reaction mixture was stirred at room temperature overnight and then partitioned between H₂O (50 mL) and Et₂O (50 mL). The aqueous layer was extracted with Et₂O (2 × 50 mL), and the combined organic phases were washed with water and brine and then dried over MgSO₄. The product was purified by chromatography to afford **2** (390 mg, 96%) as a white solid. ¹H NMR (500 MHz, Chloroform-*d*) δ 8.61 (d, *J* = 15.6 Hz, 1H), 7.33 (d, *J* = 7.5 Hz, 1H), 7.13 (d, *J* = 3.3 Hz, 1H), 7.00–6.94 (m, 1H), 6.54 (d, *J* = 3.3 Hz, 1H), 6.38 (d, *J* = 15.6 Hz, 1H), 5.47 (s, 2H), 3.81 (s, 3H), 3.63–3.56 (m, 2H), 2.56 (s, 3H), 1.00–0.93 (m, 2H), 0.02 (s, 9H). ¹³C NMR (101 MHz, Chloroform-*d*) δ 167.5, 143.1, 133.0, 130.5, 129.8, 122.1, 121.0, 118.8, 118.7, 100.9, 65.4, 51.6, 34.7, 31.6, 25.3, 22.7, 18.8, 17.7, 1.4; HRMS (M+H)⁺ calcd. for C₁₉H₂₈NO₃Si 346.18330, found 346.18270.

Methyl 3-(4-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indol-7-yl)-4-nitrobutanoate (3): Indole **2** (3.17 g, 9.17 mmol) was dissolved in nitromethane, >96% (13.8 mL, 241 mmol), after which 1,1,3,3-tetramethylguanidine (576 µL, 4.59 mmol) was added with stirring, and the mixture was heated overnight at 50 °C. An additional amount of base (1 equiv.) was added, and the reaction was stirred at 50 °C for an additional period (1 h). The reaction mixture was concentrated at reduced pressure to afford an orange-colored oil which was purified by chromatography (10% EtOAc in Hexane) to give **3** as an oil (2.85 g, 76%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.14 (d, *J* = 3.3 Hz, 1H), 7.00–6.93 (m, 2H), 6.54 (d, *J* = 3.3 Hz, 1H), 5.91 (d, *J* = 11.4 Hz, 1H), 5.63 (d, *J* = 11.4 Hz, 1H), 5.02–4.91 (m, 1H), 4.85–4.76 (m, 2H), 3.64 (s, 3H), 3.58–3.50 (m, 2H), 3.05–2.85 (m, 2H), 2.54 (d, *J* = 0.7 Hz, 3H), 0.93 (ddd, *J* = 9.5, 8.2, 7.1 Hz, 2H), 0.02 (s, 9H). ¹³C NMR (101 MHz, Chloroform-*d*) δ 171.7, 130.6, 129.9, 120.9, 120.6, 120.3, 100.6, 79.2, 65.4, 51.8, 38.1, 33.4, 18.5, 17.6; HRMS (M+H)⁺ calcd. for C₂₀H₃₁N₂O₅Si 407.19968, found 407.19890.

4-(4-Methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indol-7-yl)pyrrolidine-2-one (4): To a solution of compound **3** (1.54 g, 3.79 mmol) and nickel(ii) chloride hexahydrate (908 mg, 3.79 mmol) in EtOH (20.2 mL), sodium borohydride (1.52 g, 41.7 mmol) was added at 4 °C. The reaction mixture was stirred at 4 °C for 1 h before it was diluted with EtOH. A 6 M NaOH solution was added, and the mixture was stirred for 30 min at room temperature before being treated slowly with saturated NH₄Cl solution. The solution was extracted with CH₂Cl₂, dried over Na₂SO₄, filtered through Celite, and concentrated under reduced pressure, and it was then purified by chromatography (10% EtOAc in Hexane) to give compound **4** (1.29 g, 99%) as a white foam. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.18 (d, *J* = 7.5 Hz, 1H), 7.12 (d, *J* = 3.3 Hz, 1H), 7.01 (dd, *J* = 7.5, 1.0 Hz, 1H), 6.57 (d, *J* = 3.3 Hz, 1H),

5.80 (s, 1H), 5.58 (d, $J = 11.8$ Hz, 1H), 5.51 (d, $J = 11.8$ Hz, 1H), 4.67 (p, $J = 7.4$ Hz, 1H), 3.88 (dd, $J = 9.4, 8.1$ Hz, 1H), 3.57 (dd, $J = 9.5, 5.6$ Hz, 1H), 3.53–3.48 (m, 2H), 2.85 (dd, $J = 17.0, 9.1$ Hz, 1H), 2.64 (dd, $J = 17.0, 6.7$ Hz, 1H), 2.57 (d, $J = 0.8$ Hz, 3H), 0.95–0.86 (m, 2H), 0.01 (s, 9H). ^{13}C NMR (126 MHz, Chloroform- d) δ 177.6, 133.0, 131.0, 130.4, 129.2, 124.9, 121.1, 120.1, 100.8, 65.4, 50.3, 38.9, 33.9, 18.5, 17.8; HRMS ($\text{M}+\text{K}$) $^{+}$ calcd. for $\text{C}_{19}\text{H}_{28}\text{N}_2\text{O}_2\text{SiK}$ 383.15516, found 383.15554.

Methyl 3-(4-(4-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indol-7-yl)-2-oxopyrrolidin-1-yl)benzoate (5): A flame-dried pressure vial was charged with 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (36.2 mg, 62.6 mmol), compound 4 (89.7 mg, 417 mmol), tris(dibenzylideneacetone)-dipalladium (0) (19.5 mg, 20.9 mmol), and cesium carbonate (192 mg, 584 mmol). The vial was capped with a septum, evacuated, and then filled with argon twice. 1,4-Dioxane (1 mL/mmol aryl halide) was added using a syringe, and then the septum was replaced with a Teflon screwcap, and the mixture was stirred at 100 °C for 16 h until the starting aryl halide had been completely consumed. The reaction mixture was then allowed to cool to room temperature, diluted with dichloromethane (10 mL), filtered over Celite, and concentrated under reduced pressure. The crude material was purified by chromatography on silica gel to afford compound 5 as a white solid (182 mg, 91%). ^1H NMR (500 MHz, Chloroform- d) δ 8.16 (ddd, $J = 8.2, 2.4, 1.1$ Hz, 1H), 8.10 (t, $J = 1.9$ Hz, 1H), 7.87 (dt, $J = 7.8, 1.3$ Hz, 1H), 7.50 (t, $J = 8.0$ Hz, 1H), 7.17 (d, $J = 7.5$ Hz, 1H), 7.14 (d, $J = 3.2$ Hz, 1H), 7.00 (d, $J = 7.6$ Hz, 1H), 6.58 (d, $J = 3.3$ Hz, 1H), 5.64–5.54 (m, 2H), 4.68 (q, $J = 7.2$ Hz, 1H), 4.36 (dd, $J = 9.6, 7.8$ Hz, 1H), 4.08 (dd, $J = 9.6, 5.5$ Hz, 1H), 3.95 (s, 3H), 3.53 (ddd, $J = 9.3, 8.1, 3.3$ Hz, 2H), 3.16 (dd, $J = 17.2, 8.8$ Hz, 1H), 2.96 (dd, $J = 17.1, 6.5$ Hz, 1H), 2.57 (s, 3H), 0.93 (d, $J = 8.3$ Hz, 2H), 0.01 (s, 9H). ^{13}C NMR (101 MHz, Chloroform- d) δ 173.5, 166.8, 139.5, 133.1, 131.2, 130.8, 130.5, 129.4, 129.0, 125.6, 124.8, 124.2, 121.2, 120.2, 120.1, 119.9, 100.9, 65.5, 56.5, 52.3, 41.4, 30.7, 18.5, 17.8; HRMS ($\text{M}+\text{H}$) $^{+}$ calcd. for $\text{C}_{27}\text{H}_{35}\text{N}_2\text{O}_4\text{Si}$ 479.23606, found 479.23650.

3-(4-(4-Methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indol-7-yl)-2-oxopyrrolidin-1-yl)benzoic acid (6): Compound 6 was prepared following General Procedure A from methyl ester 5 (59.0 mg, 113 mmol). Compound 6 was obtained as a white solid (46.0 mg, 80%). ^1H NMR (400 MHz, Chloroform- d) δ 8.26 (ddd, $J = 8.3, 2.4, 1.0$ Hz, 1H), 8.12 (t, $J = 2.0$ Hz, 1H), 7.93 (dt, $J = 7.9, 1.3$ Hz, 1H), 7.53 (t, $J = 8.0$ Hz, 1H), 7.23–7.13 (m, 2H), 7.01 (dd, $J = 7.3, 1.0$ Hz, 1H), 6.59 (d, $J = 3.3$ Hz, 1H), 4.77–4.61 (m, 1H), 4.39 (dd, $J = 9.6, 7.8$ Hz, 1H), 4.13–4.06 (m, 1H), 3.59–3.48 (m, 2H), 3.23–3.12 (m, 1H), 3.01 (d, $J = 6.5$ Hz, 1H), 2.57 (d, $J = 0.8$ Hz, 3H), 0.98–0.89 (m, 2H), 0.01 (s, 9H). ^{13}C NMR (101 MHz, Chloroform- d) δ 173.68, 170.9, 133.1, 131.2, 130.5, 130.0, 129.4, 129.1, 128.9, 126.2, 125.6, 124.2, 121.2, 120.6, 120.2, 119.9, 100.9, 65.6, 56.5, 41.3, 30.7, 18.5, 17.8; HRMS ($\text{M}+\text{Na}$) $^{+}$ calcd. for $\text{C}_{26}\text{H}_{32}\text{N}_2\text{O}_4\text{SiNa}$ 487.20236, found 487.20329.

Methyl 3-(4-(4-methyl-1H-indol-7-yl)-2-oxopyrrolidin-1-yl)benzoate (7): Compound 7 was prepared following General Procedure C from the protected indole 5 (40.0 mg, 83.6 μmol) and obtained as a white solid (17.0 mg, 58%). ^1H NMR (500 MHz, Chloroform- d) δ 8.66 (s, 1H), 8.09–8.04 (m, 2H), 7.83 (dt, $J = 7.8, 1.3$ Hz, 1H), 7.47–7.41 (m, 1H), 7.05 (d, $J = 7.4$ Hz, 1H), 6.95 (dd, $J = 7.4, 1.0$ Hz, 1H), 6.65 (dd, $J = 3.3, 2.0$ Hz, 1H), 4.28 (dd, $J = 9.6, 8.1$ Hz, 1H), 4.17–4.11 (m, 1H), 4.02 (t, $J = 8.3$ Hz, 1H), 3.91 (s, 3H), 3.15–2.98 (m, 2H), 2.58 (d, $J = 0.8$ Hz, 3H). ^{13}C NMR (101 MHz, Chloroform- d) δ 173.3, 166.7, 139.2, 133.6, 130.8, 129.8, 129.1, 128.4, 125.8, 124.7, 123.9, 121.0, 120.3, 120.2, 119.3, 102.1, 54.3, 52.3, 39.1, 33.2, 18.6; HRMS ($\text{M}+\text{H}$) $^{+}$ calcd. for $\text{C}_{21}\text{H}_{20}\text{N}_2\text{O}_3$ 349.1554, found 349.1546.

3-(4-(4-Methyl-1H-indol-7-yl)-2-oxopyrrolidin-1-yl)benzoic acid (8): Compound 8 was prepared following General Procedure C from the protected indole 6 (36.0 mg, 77.5 μmol) and obtained as a colorless oil (12.5 mg, 48%). ^1H NMR (400 MHz, Methanol- d_4) δ 8.02 (s, 1H), 7.92 (d, $J = 8.1$ Hz, 1H), 7.80 (d, $J = 7.6$ Hz, 1H), 7.40 (t, $J = 7.9$ Hz, 1H), 7.27 (d,

$J = 3.2$ Hz, 1H), 7.01 (d, $J = 7.3$ Hz, 1H), 6.83 (d, $J = 7.3$ Hz, 1H), 6.53 (d, $J = 3.2$ Hz, 1H), 4.45–4.36 (m, 1H), 4.13 (dd, $J = 15.4, 8.1$ Hz, 2H), 3.07 (dd, $J = 16.8, 8.2$ Hz, 1H), 2.93 (dd, $J = 16.7, 8.0$ Hz, 1H), 2.51 (s, 3H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 134.5, 128.3, 128.0, 125.1, 119.6, 118.3, 100.7, 54.2, 39.0, 23.5, 18.9, 13.9. HRMS ($\text{M}+\text{H}$) $^+$ calcd. for $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_3$ 335.1389, found 335.1390.

3-(4-(4-Methyl-1*H*-indol-7-yl)-2-oxopyrrolidin-1-yl)-*N*-propylbenzamide (**9**): General Procedure B was applied using carboxylic acid **6** (47.0 mg, 100 μmol) to give the corresponding *n*-propylamide (17.0 mg, 73%) as a colorless oil. ^1H NMR (400 MHz, Chloroform- d) δ 8.09 (t, $J = 2.0$ Hz, 1H), 7.89–7.83 (m, 1H), 7.61–7.55 (m, 1H), 7.47 (t, $J = 8.0$ Hz, 1H), 7.18–7.12 (m, 2H), 7.00 (d, $J = 7.7$ Hz, 1H), 6.58 (d, $J = 3.3$ Hz, 1H), 5.63–5.52 (m, 3H), 4.69 (p, $J = 7.3$ Hz, 2H), 4.36 (dd, $J = 9.6, 7.8$ Hz, 2H), 4.09 (dd, $J = 9.6, 5.3$ Hz, 1H), 3.55–3.49 (m, 2H), 3.50–3.43 (m, 2H), 3.16 (dd, $J = 17.1, 8.9$ Hz, 2H), 2.95 (dd, $J = 17.1, 6.3$ Hz, 1H), 2.57 (d, $J = 0.8$ Hz, 3H), 1.71–1.65 (m, 2H), 1.03 (t, $J = 7.4$ Hz, 3H), 0.92 (t, $J = 1.2$ Hz, 2H), 0.01 (s, 9H). ^{13}C NMR (126 MHz, Chloroform- d) δ 173.6, 167.2, 162.6, 135.6, 133.1, 131.2, 130.5, 129.4, 129.1, 124.2, 122.8, 122.6, 121.2, 118.1, 100.9. General Procedure D was applied directly on the propylamide to give the corresponding unprotected indole **9** (6.1 mg, 55%) as colorless oil. ^1H NMR (400 MHz, Chloroform- d) δ 9.38 (s, 1H), 8.08 (t, $J = 2.0$ Hz, 1H), 7.70 (ddd, $J = 8.2, 2.3, 1.0$ Hz, 1H), 7.56 (dt, $J = 7.7, 1.3$ Hz, 1H), 7.40 (d, $J = 7.9$ Hz, 1H), 7.03 (d, $J = 7.3$ Hz, 1H), 6.94 (d, $J = 7.0$ Hz, 1H), 6.64 (dd, $J = 3.3, 1.9$ Hz, 1H), 6.53 (d, $J = 6.0$ Hz, 1H), 4.26 (dd, $J = 9.1, 7.6$ Hz, 1H), 4.01 (dt, $J = 24.9, 8.3$ Hz, 2H), 3.46–3.37 (m, 2H), 3.08 (dd, $J = 17.0, 9.1$ Hz, 1H), 2.97 (dd, $J = 17.1, 8.5$ Hz, 1H), 2.59 (s, 3H), 1.66–1.59 (m, 2H), 0.99 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (101 MHz, Chloroform- d) δ 173.8, 167.4, 139.3, 135.6, 133.8, 129.7, 129.2, 128.5, 124.2, 123.04, 122.4, 120.7, 120.1, 119.1, 118.1, 101.7, 54.4, 41.9, 38.9, 33.4, 29.7, 22.8, 18.6, 11.5; HRMS ($\text{M}+\text{H}$) $^+$ calcd. for $\text{C}_{23}\text{H}_{26}\text{N}_3\text{O}_2$ 376.2013, found 376.2019.

Methyl-3-((4-(4-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-7-yl)-2-oxopyrrolidin-1-yl)methyl) benzoate (**10**): Indole **4** (100 mg, 290 μmol) in DMF (1.45 mL) and 15-CROWN-5 (80.4 mL, 406 μmol) was treated with sodium hydride (23.2 mg, 581 μmol) at 0 $^\circ\text{C}$, and the suspension was stirred at room temperature for 1 h. The solution as cooled, and methyl 4-(bromomethyl)-3-methoxybenzoate (160 mg, 598 μmol) in THF was added at 0 $^\circ\text{C}$, and the solution was stirred for 6h at room temperature. EtOAc and water were added, and the organic phase was extracted three times with EtOAc and then washed with water and brine. The organic extracts were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by chromatography (0–90% EtOAc in hexanes) to afford compound **10** (97.1 mg, 64%) as a colorless oil. ^1H NMR (400 MHz, Chloroform- d) δ 7.96 (dt, $J = 7.7, 1.7$ Hz, 1H), 7.93 (d, $J = 1.8$ Hz, 1H), 7.48 (dd, $J = 7.6, 1.7$ Hz, 1H), 7.41 (t, $J = 7.6$ Hz, 1H), 7.05 (d, $J = 3.3$ Hz, 1H), 6.96 (d, $J = 7.5$ Hz, 1H), 6.89 (d, $J = 7.5$ Hz, 1H), 6.50 (d, $J = 3.3$ Hz, 1H), 5.52–5.39 (m, 2H), 4.64–4.54 (m, 2H), 4.48 (ddd, $J = 8.7, 7.0, 4.3$ Hz, 1H), 3.91 (s, 3H), 3.69 (dd, $J = 9.9, 8.0$ Hz, 1H), 3.42 (dd, $J = 8.9, 7.6$ Hz, 2H), 3.36 (dd, $J = 9.8, 4.9$ Hz, 1H), 2.98 (dd, $J = 17.0, 9.2$ Hz, 1H), 2.76–2.70 (m, 1H), 2.50 (s, 3H), 0.80 (td, $J = 7.7, 1.6$ Hz, 2H), 0.07 (s, 9H). ^{13}C NMR (101 MHz, Chloroform- d) δ 136.8, 132.8, 130.9, 130.3, 129.3, 129.0, 128.9, 128.9, 125.3, 121.1, 119.8, 100.7, 65.4, 54.9, 52.2, 46.4, 30.4, 18.4, 17.7; HRMS ($\text{M}+\text{Na}$) $^+$ calcd. for $\text{C}_{28}\text{H}_{36}\text{N}_2\text{O}_4\text{SiNa}$ 515.2337, found 515.2327.

3-((4-(4-Methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-7-yl)-2-oxopyrrolidin-1-yl)methyl)benzoic acid (**11**): Compound **11** was prepared following General Procedure A from methyl ester **10** (20.0 mg, 40.6 μmol) and was obtained as a colorless oil (17.7 mg, 91%). ^1H NMR (400 MHz, Chloroform- d) δ 8.09–8.02 (m, 2H), 7.57 (dt, $J = 7.7, 1.5$ Hz, 1H), 7.48 (t, $J = 7.7$ Hz, 1H), 7.08 (d, $J = 3.3$ Hz, 1H), 7.02 (d, $J = 7.6$ Hz, 1H), 6.95 (dd, $J = 7.5, 1.0$ Hz, 1H), 6.53 (d, $J = 3.3$ Hz, 1H), 5.56–5.42 (m, 2H), 4.71–4.57 (m, 2H), 4.59–4.49 (m, 1H), 3.76 (dd, $J = 9.8, 8.1$ Hz, 1H), 3.44 (ddd, $J = 14.6, 9.3, 6.3$ Hz, 3H), 3.04 (dd, $J = 17.1, 9.2$ Hz, 1H), 2.80 (dd, $J = 17.1, 5.8$ Hz, 1H), 2.54 (d, $J = 0.8$ Hz, 3H), 0.88–0.82 (m, 2H), 0.04 (s, 9H). ^{13}C NMR

(101 MHz, Chloroform-*d*) δ 174.5, 170.7, 136.9, 133.4, 132.9, 130.9, 130.3, 130.0, 129.8, 129.6, 129.1, 125.2, 121.1, 119.9, 100.7, 65.4, 55.0, 46.4, 39.9, 30.5, 18.4, 17.7; HRMS (M+Na)⁺ calcd. for C₂₇H₃₄N₂O₄SiNa 501.2180, found 501.2182.

3-((4-(4-Methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-7-yl)-2-oxopyrrolidin-1-yl)methyl)-*N*-propylbenzamide (**12**):

Compound **12** was prepared following General Procedure B from carboxylic acid **11** (10 mg, 50.6 μ mol) and obtained as a colorless oil (10 mg, 95%). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.74 (d, *J* = 1.3 Hz, 1H), 7.66 (q, *J* = 1.3 Hz, 1H), 7.45–7.40 (m, 2H), 7.09 (d, *J* = 3.3 Hz, 1H), 6.99 (d, *J* = 7.5 Hz, 1H), 6.93 (dd, *J* = 7.5, 1.0 Hz, 1H), 6.54 (d, *J* = 3.3 Hz, 1H), 6.22 (s, 1H), 5.54–5.41 (m, 2H), 4.60 (s, 2H), 4.52 (s, 1H), 3.74 (dd, *J* = 9.8, 8.0 Hz, 1H), 3.50–3.43 (m, 4H), 3.41 (dd, *J* = 9.8, 4.8 Hz, 1H), 3.04–2.98 (m, 2H), 2.76 (dd, *J* = 17.1, 5.7 Hz, 1H), 2.54 (d, *J* = 0.8 Hz, 3H), 1.73–1.64 (m, 3H), 1.03 (t, *J* = 7.4 Hz, 3H), 0.84 (td, *J* = 7.8, 1.8 Hz, 2H), 0.04 (s, 9H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 174.3, 136.9, 135.4, 133.0, 131.1, 130.9, 130.3, 129.1, 129.1, 126.5, 126.4, 120.9, 119.7, 100.8, 65.4, 54.9, 46.4, 41.8, 39.9, 38.6, 30.4, 22.9, 18.4, 17.7, 11.5; HRMS (M+Na)⁺ calcd. for C₃₀H₄₁N₃O₃SiNa 542.2818, found 542.2809.

Methyl 3-((4-(4-methyl-1*H*-indol-7-yl)-2-oxopyrrolidin-1-yl)methyl)benzoate (**13**):

Compound **13** was prepared following General Procedure D from the protected indole **10** (25.0 mg, 50.7 μ mol) and obtained as a colorless oil (8 mg, 44%). ¹H NMR (500 MHz, Chloroform-*d*) δ 8.13 (s, 1H), 8.00–7.94 (m, 2H), 7.52 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.15–7.12 (m, 1H), 6.92–6.81 (m, 2H), 6.57 (dd, *J* = 3.3, 1.9 Hz, 1H), 4.65–4.56 (m, 2H), 3.92 (s, 3H), 3.88–3.79 (m, 1H), 3.72 (dd, *J* = 9.9, 8.5 Hz, 1H), 3.48 (dd, *J* = 9.8, 6.4 Hz, 1H), 2.98 (dd, *J* = 17.2, 9.3 Hz, 1H), 2.83–2.73 (m, 1H), 2.52 (d, *J* = 0.8 Hz, 3H). ¹³C NMR (101 MHz, Chloroform-*d*) δ 174.1, 141.4, 130.2, 129.5, 128.2, 123.8, 120.1, 119.3, 101.9, 52.6, 52.2, 46.5, 37.7, 33.2, 18.6; HRMS (M+H)⁺ calcd. for C₂₂H₂₃N₂O₃ 363.1694, found 363.1703.

3-((4-(4-Methyl-1*H*-indol-7-yl)-2-oxopyrrolidin-1-yl)methyl)benzoic acid (**14**): Compound **14** was synthesized following General Procedure D from the protected indole **11** (17.0 mg, 35.5 μ mol) and obtained as a colorless oil (7 mg, 57%). ¹H NMR (500 MHz, Methanol-*d*₄) δ 7.91–7.88 (m, 2H), 7.38–7.35 (m, 2H), 7.23–7.20 (m, 1H), 6.87 (d, *J* = 7.3 Hz, 1H), 6.78 (d, *J* = 7.3 Hz, 1H), 6.49 (d, *J* = 3.2 Hz, 1H), 4.76 (d, *J* = 14.8 Hz, 1H), 4.43 (d, *J* = 14.8 Hz, 1H), 4.03 (s, 1H), 3.83 (dd, *J* = 9.9, 8.1 Hz, 1H), 3.47 (dd, *J* = 9.9, 6.8 Hz, 1H), 2.95 (dd, *J* = 16.8, 8.8 Hz, 1H), 2.79–2.71 (m, 1H), 2.48 (d, *J* = 0.9 Hz, 2H). ¹³C NMR (126 MHz, Methanol-*d*₄) δ 132.3, 128.9, 128.7, 128.6, 119.1, 117.1, 52.8, 45.7, 37.5, 32.3, 31.4, 29.4, 22.3, 17.3, 13.0; HRMS (M+H)⁺ calcd. for C₂₁H₂₁N₂O₃ 349.1546, found 349.1531.

3-((4-(4-Methyl-1*H*-indol-7-yl)-2-oxopyrrolidin-1-yl)methyl)-*N*-propylbenzamide (**15**):

Compound **15** was prepared following General Procedure D from the protected indole **12** (10 mg, 26.9 μ mol) and obtained as a colorless oil (5 mg, 67%). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.72 (s, 1H), 7.78–7.67 (m, 2H), 7.43 (dd, *J* = 4.4, 2.0 Hz, 2H), 7.21 (t, *J* = 2.7 Hz, 1H), 6.95–6.86 (m, 2H), 6.60 (dd, *J* = 3.4, 1.3 Hz, 1H), 6.42 (s, 1H), 4.69 (d, *J* = 14.8 Hz, 1H), 4.51 (d, *J* = 14.7 Hz, 1H), 3.90 (d, *J* = 8.1 Hz, 1H), 3.82–3.73 (m, 1H), 3.47 (dq, *J* = 23.6, 6.6 Hz, 3H), 2.97 (dd, *J* = 17.3, 9.1 Hz, 1H), 2.84 (dd, *J* = 17.1, 8.1 Hz, 1H), 2.56 (d, *J* = 0.8 Hz, 3H), 1.70–1.64 (m, 2H), 1.01 (d, *J* = 7.4 Hz, 3H). ¹³C NMR (101 MHz, Chloroform-*d*) δ 129.4, 129.2, 126.6, 119.9, 101.7, 41.9, 33.3, 22.9, 18.6; HRMS (M+H)⁺ calcd. for C₂₄H₂₈N₃O₂ 390.2167, found 390.2176, (M+Na)⁺ calcd. for C₂₄H₂₇N₃O₂Na 407.2431, found 407.2442.

Methyl 3-(3-(4-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indol-7-yl)pyrrolidin-1-yl)benzoate (**16**): To a solution of compound **5** (70.0 mg, 146 μ mol) in THF (439 mL), a solution of Borane-THF complex 1M in THF (190 mL, 190 μ mol) was added. The reaction mixture was stirred at room temperature overnight and then quenched by slowly adding MeOH (1 mL) followed by H₂O. The above mixture was then extracted with EtOAc, and the organic layer was washed with H₂O and brine, dried over Na₂SO₄, filtered, and

concentrated. Purification by chromatography (0–30% EtOAc/Hex) gave compound **16** (44.2 mg, 65%) as a clear, colorless oil. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.42–7.31 (m, 3H), 7.15 (d, J = 3.3 Hz, 1H), 7.06 (d, J = 7.5 Hz, 1H), 6.94 (d, J = 7.5 Hz, 1H), 6.82 (ddd, J = 8.1, 2.7, 1.1 Hz, 1H), 6.58 (d, J = 3.3 Hz, 1H), 5.71–5.53 (m, 2H), 4.54–4.44 (m, 1H), 3.94 (s, 3H), 3.83 (dd, J = 9.5, 7.2 Hz, 1H), 3.66–3.58 (m, 2H), 3.56–3.49 (m, 3H), 2.56 (s, 3H), 2.49 (dt, J = 13.0, 6.3 Hz, 1H), 2.28 (dq, J = 13.2, 6.8 Hz, 1H), 0.97–0.88 (m, 2H), 0.01 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.89, 147.4, 130.9, 130.8, 130.3, 129.1, 128.7, 125.1, 120.9, 120.1, 116.6, 115.9, 112.4, 100.7, 65.4, 55.1, 52.0, 47.2, 37.6, 33.8, 18.6, 17.7; HRMS ($\text{M}+\text{H}$) $^+$ calcd. for $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}_2$ 335.1763, found 335.1754.

Methyl 3-(3-(4-methyl-1*H*-indol-7-yl)pyrrolidin-1-yl)benzoate (**17**): Compound **17** was prepared following General Procedure D from the protected indole **16** (100 mg, 209 μmol) and obtained as a colorless oil (46.6 mg, 48%). ^1H NMR (400 MHz, Chloroform-*d*) δ 8.88 (s, 1H), 7.52–7.47 (m, 1H), 7.43 (dd, J = 2.6, 1.5 Hz, 1H), 7.37 (t, J = 7.9 Hz, 1H), 7.22 (t, J = 2.8 Hz, 1H), 7.00 (d, J = 7.3 Hz, 1H), 6.96–6.87 (m, 2H), 6.63 (dd, J = 3.2, 2.1 Hz, 1H), 3.95 (s, 3H), 3.89–3.75 (m, 3H), 3.70 (dd, J = 9.5, 8.0 Hz, 1H), 3.41 (dt, J = 9.3, 7.8 Hz, 1H), 2.59 (d, J = 0.8 Hz, 3H), 2.55 (p, J = 4.1, 3.6 Hz, 1H), 2.41–2.29 (m, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 148.1, 131.0, 129.3, 128.9, 124.1, 123.6, 120.1, 119.9, 118.4, 117.5, 114.0, 101.5, 54.0, 53.8, 52.1, 48.8, 40.5, 32.1, 20.8, 18.6, 14.1; HRMS ($\text{M}+\text{H}$) $^+$ calcd. for $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}_2$ 335.1763, found 335.1754.

3-(3-(4-Methyl-1*H*-indol-7-yl)pyrrolidin-1-yl)benzoic acid (**18**): General Procedure A was applied to methyl ester **16** (47.0 mg, 100 μmol) to give the corresponding carboxylic acid (30 mg, 66%) as a colorless oil: ^1H NMR (400 MHz, Chloroform-*d*) δ 7.43 (d, J = 7.6 Hz, 1H), 7.36–7.28 (m, 2H), 7.10 (d, J = 3.3 Hz, 1H), 7.03 (d, J = 7.5 Hz, 1H), 6.90 (d, J = 7.5 Hz, 1H), 6.82 (dd, J = 8.1, 2.6 Hz, 1H), 6.54 (d, J = 3.3 Hz, 1H), 5.63 (dd, J = 11.6, 2.5 Hz, 1H), 5.52 (d, J = 11.6 Hz, 1H), 4.50–4.39 (m, 1H), 3.84–3.74 (m, 1H), 3.62–3.54 (m, 2H), 3.49 (t, J = 8.1 Hz, 3H), 2.52 (s, 3H), 2.47 (dd, J = 12.5, 5.9 Hz, 1H), 2.25 (dd, J = 12.4, 6.6 Hz, 1H), 0.93–0.84 (m, 3H), 0.06 (s, 9H). General Procedure D was applied directly to the carboxylic acid to give the corresponding unprotected indole **18** (10 mg, 48%) as a colorless oil. ^1H NMR (400 MHz, Methanol-*d*₄) δ 7.28 (d, J = 10.1 Hz, 2H), 7.23 (d, J = 3.2 Hz, 2H), 6.90 (s, 1H), 6.77 (d, J = 7.3 Hz, 1H), 6.72 (d, J = 7.5 Hz, 1H), 6.49 (d, J = 3.2 Hz, 1H), 3.91 (q, J = 6.8, 6.0 Hz, 1H), 3.83 (t, J = 8.3 Hz, 1H), 3.56 (s, 1H), 3.49 (d, J = 8.2 Hz, 2H), 2.49 (s, 4H), 2.27 (dd, J = 12.3, 8.0 Hz, 1H). ^{13}C NMR (101 MHz, Methanol-*d*₄) δ 127.9, 127.4, 123.5, 118.9, 117.6, 99.7, 39.3, 31.5, 17.3; HRMS ($\text{M}+\text{H}$) $^+$ calcd. for $\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_2$ 321.1582, found 321.1598.

3-(3-(4-Methyl-1*H*-indol-7-yl)pyrrolidin-1-yl)-*N*-propylbenzamide (**19**): General Procedure A was applied to methyl ester **16** (47.0 mg, 100 μmol) to give the corresponding carboxylic acid (30 mg, 66%) as a colorless oil which was directly used in General Procedure B to obtain the corresponding propylamide (30 mg, 68%) as a colorless oil. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.37 (q, J = 7.4, 6.9 Hz, 2H), 7.18 (d, J = 7.7 Hz, 1H), 7.14 (d, J = 3.3 Hz, 1H), 7.11 (d, J = 7.6 Hz, 1H), 7.04 (s, 1H), 6.96 (d, J = 7.5 Hz, 1H), 6.57 (d, J = 3.3 Hz, 1H), 6.21 (s, 1H), 5.70–5.55 (m, 2H), 4.62–4.52 (m, 1H), 3.92–3.85 (m, 1H), 3.74–3.67 (m, 2H), 3.62 (t, J = 7.5 Hz, 1H), 3.57–3.41 (m, 4H), 2.56 (s, 3H), 2.54 (d, J = 6.2 Hz, 1H), 2.36 (dd, J = 12.8, 6.9 Hz, 1H), 1.68 (q, J = 7.3 Hz, 2H), 1.03 (t, J = 7.4 Hz, 3H), 0.91 (dd, J = 9.3, 7.1 Hz, 2H), 0.02 (s, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 136.2, 133.4, 130.9, 130.4, 129.6, 121.0, 120.1, 100.7, 65.4, 41.8, 37.7, 33.8, 22.9, 18.5, 17.7, 11.5. General Procedure D was applied directly on the propylamide to give the corresponding unprotected indole **19** (5 mg, 68%) as a white solid. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.88 (s, 1H), 7.31 (d, J = 7.9 Hz, 1H), 7.20–7.16 (m, 2H), 7.04 (dt, J = 7.8, 1.1 Hz, 1H), 6.95 (d, J = 7.3 Hz, 1H), 6.86 (dd, J = 7.3, 0.9 Hz, 1H), 6.80 (ddd, J = 8.2, 2.6, 0.9 Hz, 1H), 6.59 (dd, J = 3.2, 2.0 Hz, 1H), 6.12 (s, 1H), 3.85–3.70 (m, 3H), 3.46–3.32 (m, 4H), 2.55 (d, J = 0.9 Hz, 3H), 2.52–2.47 (m, 1H), 2.29 (dd, J = 12.7, 7.8 Hz, 1H), 1.66–1.61 (m, 2H), 0.98 (d, J = 7.4 Hz, 3H). ^{13}C NMR

(101 MHz, Chloroform-*d*) δ 168.2, 148.3, 136.1, 133.5, 129.4, 128.2, 124.1, 123.7, 120.0, 119.8, 115.78, 114.6, 111.9, 101.5, 53.9, 48.7, 41.8, 40.5, 32.1, 22.9, 18.6, 11.5; HRMS (M+H)⁺ calcd. for C₂₃H₂₈N₃O 362.2216, found 362.2227.

4-Methyl-7-(pyrrolidin-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indole (20): To a 1M solution of lithium aluminum hydride (755 μ L, 755 μ mol) in anhydrous THF (677 μ L), a solution of indole **4** (130 mg, 377 μ mol) in anhydrous THF (1.43 mL) was added dropwise at 0 °C for 1h. The reaction was refluxed for 2 h and then quenched with water at 0 °C. The resulting mixture was filtered, and the filter cake was washed with a mixture of DCM and MeOH (1/1 (v/v), 10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by chromatography (10% MeOH in DCM) to give the free pyrrolidine **20** as a yellow solid (104 mg, 83%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.08 (d, *J* = 3.3 Hz, 1H), 7.04 (d, *J* = 7.5 Hz, 1H), 6.93 (d, *J* = 7.5 Hz, 1H), 6.51 (d, *J* = 3.3 Hz, 1H), 5.55 (s, 2H), 4.13 (p, *J* = 6.8 Hz, 1H), 3.51–3.48 (m, 2H), 3.32 (dd, *J* = 11.1, 7.3 Hz, 1H), 3.24 (ddd, *J* = 11.2, 8.3, 5.7 Hz, 1H), 3.11 (ddd, *J* = 11.2, 8.2, 6.5 Hz, 1H), 3.01 (dd, *J* = 11.1, 6.1 Hz, 1H), 2.51 (s, 3H), 2.30–2.19 (m, 1H), 2.08–1.95 (m, 1H), 0.93–0.84 (m, 2H), 0.05 (s, 9H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 140.0, 134.1, 131.0, 130.2, 128.2, 120.8, 120.0, 104.1, 100.6, 81.1, 78.1, 65.3, 29.9, 18.4, 17.7, 2.0, 1.4; HRMS (ESI) *m/z*: [M+H]⁺ calculated for C₁₉H₃₁N₂OSi: 331.21941, found 331.22002.

Methyl 3-((3-(4-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indol-7-yl)pyrrolidin-1-yl)methyl)benzoate (21): To a stirred solution of pyrrolidine **20** (375 mg, 1.13 mmol) in CH₂Cl₂ (2.05 mL), Et₃N (398 μ L, 2.84 mmol) was added at 0 °C followed by methyl 3-(bromomethyl)benzoate (345 μ L, 1.59 mmol) in CH₂Cl₂ (1.37 mL). The mixture was stirred for 30 min at 0 °C and then warmed to room temperature and stirred for an additional 2 h. The above mixture was washed with saturated NaHCO₃ solution, and the organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification by chromatography (0–10% EtOAc in Hexanes) gave **21** as a colorless oil (443 mg, 82%). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.04 (d, *J* = 1.8 Hz, 1H), 7.93 (dt, *J* = 7.9, 1.5 Hz, 1H), 7.65–7.59 (m, 1H), 7.40 (t, *J* = 7.7 Hz, 1H), 7.30 (d, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 3.3 Hz, 1H), 6.96 (dd, *J* = 7.5, 1.0 Hz, 1H), 6.49 (d, *J* = 3.3 Hz, 1H), 5.59–5.44 (m, 2H), 4.30–4.17 (m, 1H), 3.92 (s, 3H), 3.80–3.70 (m, 2H), 3.46 (dd, *J* = 8.8, 7.6 Hz, 2H), 2.99 (dd, *J* = 9.3, 7.9 Hz, 1H), 2.87 (dt, *J* = 8.5, 4.3 Hz, 1H), 2.77 (ddd, *J* = 8.5, 6.5, 2.8 Hz, 2H), 2.54–2.49 (m, 3H), 2.38 (dddd, *J* = 13.0, 9.7, 7.7, 5.4 Hz, 1H), 2.02 (dtd, *J* = 12.7, 6.4, 2.0 Hz, 1H), 0.85 (td, *J* = 7.8, 1.9 Hz, 2H), 0.06 (s, 9H). ¹³C NMR (126 MHz, Chloroform-*d*) δ 167.2, 140.0, 139.9, 133.5, 133.4, 130.4, 130.1, 129.8, 128.2, 127.8, 121.0, 120.9, 100.5, 78.1, 65.2, 63.0, 60.3, 54.8, 52.1, 36.6, 34.8, 18.4, 17.7, 1.4; HRMS (ESI) *m/z*: [M+H]⁺ calculated for C₂₈H₃₉N₂O₃Si: 479.27245, found 479.27164.

3-((3-(4-Methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indol-7-yl)pyrrolidin-1-yl)methyl)benzoic acid (22): Compound **22** was synthesized following General Procedure A from methyl ester **21** (340 mg, 710 μ mol). Compound **22** was obtained as a colorless oil (306 mg, 93%). ¹H NMR (400 MHz, Chloroform-*d*): δ 8.08 (s, 1H), 7.96 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.67 (s, 1H), 7.49–7.39 (m, 1H), 7.32 (d, *J* = 7.5 Hz, 1H), 6.52 (d, 1H), 5.59 (d, *J* = 11.5 Hz, 1H), 5.51 (d, *J* = 11.5 Hz, 1H), 4.35–4.17 (m, 1H), 3.95 (s, 3H), 3.80 (s, 2H), 3.50 (t, 2H), 2.98 (s, 1H), 2.91 (s, 1H), 2.54 (s, 3H), 2.48–2.37 (m, 1H), 1.29 (s, 1H), 0.96–0.82 (m, 2H), −0.03 (s, 9H); ¹³C NMR (101 MHz, Chloroform-*d*) δ 170.5, 133.4, 132.6, 131.1, 130.6, 129.3, 128.6, 121.9, 121.2, 120.3, 100.6, 78.2, 77.4, 77.1, 76.7, 65.3, 59.6, 58.9, 53.5, 53.1, 36.6, 18.4, 17.7, −1.4; HRMS (ESI) *m/z*: [M+H]⁺ calculated for C₂₇H₃₇N₂O₃Si: 465.25680, found 465.25658.

3-((3-(4-Methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indol-7-yl)pyrrolidin-1-yl)methyl)-N-propylbenzamide (23): Compound **23** was synthesized following General Procedure B from carboxylic acid **22** (150 mg, 323 μ mol). Compound **23** was obtained as a colorless oil (155 mg, 95%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.89 (d, *J* = 1.8 Hz, 1H), 7.83 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.49 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.39 (t, *J* = 7.7 Hz, 1H), 7.15 (d, *J* = 7.5 Hz, 1H), 7.05

(d, $J = 3.3$ Hz, 1H), 6.72 (t, $J = 5.7$ Hz, 1H), 6.49 (d, $J = 3.3$ Hz, 1H), 5.56–5.46 (m, 2H), 4.46 (p, $J = 8.5$ Hz, 1H), 4.18 (s, 2H), 3.62–3.53 (m, 1H), 3.45–3.27 (m, 6H), 3.17 (t, $J = 10.0$ Hz, 1H), 2.50 (d, $J = 0.8$ Hz, 3H), 2.34–2.20 (m, 1H), 2.05 (d, $J = 6.4$ Hz, 1H), 1.65 (h, $J = 7.4$ Hz, 2H), 0.96 (t, $J = 7.4$ Hz, 3H), 0.85–0.70 (m, 2H), −0.07 (s, 9H); ^{13}C NMR (101 MHz, Chloroform- d) δ 167.0, 135.9, 133.3, 132.4, 131.1, 130.6, 129.4, 129.3, 128.5, 127.8, 121.2, 120.3, 100.7, 78.2, 65.4, 61.6, 59.8, 54.9, 42.0, 36.6, 32.9, 22.6, 18.4, 17.7, 11.4, −1.5; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{30}\text{H}_{44}\text{N}_3\text{O}_2\text{Si}$: 506.31973, found 506.32176.

Methyl 3-((3-(4-methyl-1H-indol-7-yl)pyrrolidin-1-yl)methyl)benzoate (**24**): Compound **24** was prepared following General Procedure C from the protected indole **21** (50 mg, 104 μmol) and obtained as a white solid (20.7 mg, 57%). ^1H NMR (400 MHz, Chloroform- d) δ 11.66 (s, 1H), 8.16–8.14 (m, 1H), 7.95 (dt, $J = 7.8, 1.5$ Hz, 1H), 7.56 (dt, $J = 7.7, 1.5$ Hz, 1H), 7.42 (t, $J = 7.7$ Hz, 1H), 7.28–7.25 (m, 1H), 6.79 (d, $J = 7.1$ Hz, 1H), 6.74–6.71 (m, 1H), 3.96 (s, 3H), 6.53 (dd, $J = 3.1, 2.2$ Hz, 1H), 3.87 (d, $J = 12.6$ Hz, 1H), 3.72 (d, $J = 12.5$ Hz, 1H), 3.59–3.48 (m, 1H), 3.35–3.27 (m, 1H), 3.16 (d, $J = 10.1$ Hz, 1H), 2.59 (t, $J = 9.4$ Hz, 1H), 2.52 (d, $J = 0.9$ Hz, 3H), 2.43–2.28 (m, 2H), 2.06–1.92 (m, 1H); ^{13}C NMR (101 MHz, Chloroform- d) δ 167.0, 139.1, 133.4, 133.1, 130.7, 130.1, 128.8, 128.8, 128.5, 128.3, 128.1, 123.4, 120.7, 118.8, 100.6, 60.0, 59.9, 55.8, 52.3, 41.4, 32.6, 18.8; HRMS ($\text{M}+\text{H}$) $^+$ calcd. for $\text{C}_{22}\text{H}_{25}\text{N}_2\text{O}_2$ 349.19105, found 349.19110.

3-((3-(4-Methyl-1H-indol-7-yl)pyrrolidin-1-yl)methyl)benzoic acid (**25**): Compound **25** was synthesized following General Procedure C from the protected indole **22** (92 mg, 198 μmol). Compound **25** was obtained as a white solid (33 mg, 50%). ^1H NMR (400 MHz, Chloroform- d) δ 11.40 (s, 1H), 8.90 (s, 1H), 8.21 (d, $J = 7.5$ Hz, 1H), 7.50–7.28 (m, 3H), 6.95 (d, $J = 7.3$ Hz, 1H), 6.85 (d, $J = 7.2$ Hz, 1H), 6.54 (t, $J = 2.3$ Hz, 1H), 4.61–3.86 (m, 4H), 3.33 (s, 2H), 2.71 (s, 2H), 2.56 (s, 3H), 2.35 (s, 1H); ^{13}C NMR (101 MHz, Chloroform- d) δ 148.2, 130.7, 129.6, 128.3, 125.2, 119.1, 100.3, 59.6, 55.6, 18.8; HRMS ($\text{M}+\text{H}$) $^+$ calcd. for $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}_2$ 335.17540, found 335.17611.

3-((3-(4-Methyl-1H-indol-7-yl)pyrrolidin-1-yl)methyl)-N-propylbenzamide (**26**): Compound **26** was synthesized following General Procedure C from the protected indole **23** (50 mg, 98.9 μmol). Compound **26** was obtained as a white solid (22.5 mg, 60%).

^1H NMR (400 MHz, Chloroform- d) δ 11.66 (s, 1H), 8.18–8.12 (m, 1H), 7.95 (dt, $J = 7.8, 1.5$ Hz, 1H), 7.56 (dt, $J = 7.7, 1.5$ Hz, 1H), 7.42 (t, $J = 7.7$ Hz, 1H), 7.28–7.25 (m, 1H), 6.79 (d, $J = 7.1$ Hz, 1H), 6.72 (dq, $J = 7.0, 0.8$ Hz, 1H), 6.53 (dd, $J = 3.1, 2.2$ Hz, 1H), 3.96 (s, 3H), 3.87 (d, $J = 12.6$ Hz, 1H), 3.72 (d, $J = 12.5$ Hz, 1H), 3.59–3.47 (m, 1H), 3.37–3.27 (m, 1H), 3.16 (d, $J = 10.1$ Hz, 1H), 2.59 (t, $J = 9.4$ Hz, 1H), 2.52 (d, $J = 0.9$ Hz, 3H), 2.43–2.28 (m, 2H), 2.06–1.92 (m, 1H); ^{13}C NMR (101 MHz, Chloroform- d) δ 167.0, 139.1, 133.4, 133.1, 130.7, 130.1, 128.8, 128.8, 128.5, 128.3, 128.1, 123.4, 120.7, 118.8, 100.6, 60.0, 59.9, 55.8, 52.3, 41.4, 32.6, 18.8; HRMS ($\text{M}+\text{H}$) $^+$ calcd. for $\text{C}_{24}\text{H}_{30}\text{N}_3\text{O}$ 376.23834, found 376.23780.

1-Ethyl-3-(4-methyl-1-pivaloyl-1H-indol-7-yl)pyrrolidine-2,5-dione (**29**) and 1-Ethyl-3-(4-methyl-1-pivaloyl-1H-indol-7-yl)-1H-pyrrole-2,5-dione (**30**): To a pre-dried sealed tube, 2,2-dimethyl-1-(4-methyl-1H-indol-1-yl)propan-1-one (0.2 mmol, 1.0 equiv.), N-ethyl maleimide (0.6 mmol), $[\text{RhCp}^*\text{Cl}_2]_2$ (5 mol%), AgSbF_6 (20 mol%), and Ag_2O (2.0 equiv.) were added. To this mixture, TFE (2 mL) was added, and the vial was tightly capped and placed in a pre-heated (80 $^\circ\text{C}$) oil bath. After 24h, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (5 mL) and water (5 mL), and then aqueous layers were extracted three times with ethyl acetate (5 mL). The organic layer was concentrated under reduced pressure, and the crude product was purified on a silica gel column using an ethyl acetate/hexane mixture to afford the desired hydroarylation product (**29**, 10.0 mg, 15%) and the undesired Heck product (**30**, 6.5 mg, 10%).

1-Ethyl-3-(4-methyl-1-pivaloyl-1H-indol-7-yl)pyrrolidine-2,5-dione (**29**): This compound was obtained as a brownish liquid, ^1H NMR (400 MHz, Chloroform- d) δ 7.64 (d,

$J = 3.9$ Hz, 1H), 7.06 (dd, $J = 7.6$, 0.9 Hz, 1H), 6.94 (d, $J = 7.7$ Hz, 1H), 6.67 (d, $J = 3.9$ Hz, 1H), 4.52 (dd, $J = 8.6$, 5.0 Hz, 1H), 3.67–3.59 (m, 2H), 3.31 (dd, $J = 18.4$, 9.3 Hz, 1H), 2.87 (dd, $J = 18.5$, 5.1 Hz, 1H), 2.50 (d, $J = 0.7$ Hz, 3H), 1.23 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (101 MHz, Chloroform- d) δ 179.4, 178.5, 176.9, 150.9, 134.9, 131.8, 130.2, 126.2, 124.7, 123.4, 106.4, 44.2, 41.9, 37.2, 34.0, 29.3, 18.4, 13.3. HRMS ($\text{M}+\text{H}$) $^{+}$ calcd. for $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_3$ 341.1859, found 341.1857.

1-Ethyl-3-(4-methyl-1-pivaloyl-1H-indol-7-yl)-1H-pyrrole-2,5-dione (**30**): This compound was obtained as yellowish liquid, ^1H NMR (400 MHz, Chloroform- d) δ 7.70 (d, $J = 3.9$ Hz, 1H), 7.18 (d, $J = 7.5$ Hz, 1H), 7.09 (dd, $J = 7.5$, 0.8 Hz, 1H), 6.69–6.67 (m, 1H), 6.43 (s, 1H), 3.57 (q, $J = 7.2$ Hz, 2H), 2.55 (s, 3H), 1.22 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (101 MHz, Chloroform- d) δ 179.0, 171.5, 170.8, 149.9, 134.3, 133.4, 131.1, 127.6, 126.1, 124.1, 120.5, 115.6, 105.9, 41.5, 32.9, 32.8, 28.7, 18.8, 14.2, 14.1. HRMS ($\text{M}+\text{H}$) $^{+}$ calcd. for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_3$ 339.1703, found 339.1699.

Methyl 3-(3-(1-acetyl-4-methylindolin-7-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoate (**32**): This compound was prepared following General Procedure E and was obtained as a yellow liquid (4.2 mg, 05%). ^1H NMR (500 MHz, Chloroform- d) δ 8.08–8.04 (m, 1H), 8.00 (d, $J = 7.9$ Hz, 1H), 7.59 (d, $J = 8.1$ Hz, 1H), 7.56–7.48 (m, 1H), 7.18 (d, $J = 7.9$ Hz, 1H), 6.98 (d, $J = 7.7$ Hz, 1H), 6.47 (s, 1H), 4.16 (t, $J = 8.0$ Hz, 2H), 3.90 (s, 3H), 3.07 (t, $J = 8.1$ Hz, 2H), 2.29 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (126 MHz, Chloroform- d) δ 170.0, 168.9, 168.9, 166.4, 149.7, 140.0, 137.2, 134.4, 133.3, 131.2, 130.6, 129.6, 129.1, 128.5, 127.4, 126.2, 119.4, 115.7, 52.3, 49.7, 27.8, 24.1, 18.9. HRMS ($\text{M}+\text{H}$) $^{+}$ calcd. for $\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_5$ 405.1445, found 405.1443.

Methyl 3-(3-(1-acetyl-4-methylindolin-7-yl)-2,5-dioxopyrrolidin-1-yl)benzoate (**33**): This compound was prepared following General Procedure E and was obtained as a gum (63.3 mg, 78%). ^1H NMR (400 MHz, Chloroform- d) δ 8.11–7.99 (m, 2H), 7.59–7.51 (m, 2H), 6.98 (s, 2H), 4.52 (dd, $J = 9.6$, 5.8 Hz, 1H), 4.15 (m, 1H), 4.11–4.01 (m, 1H), 3.91 (s, 3H), 3.61–3.43 (m, 2H), 3.05 (m, 2H), 2.91 (m, 1H), 2.28 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (101 MHz, Chloroform- d) δ 177.4, 176.0, 169.5, 166.2, 140.6, 134.2, 133.8, 132.7, 131.4, 131.2, 129.6, 129.3, 128.0, 127.5, 127.2, 125.4, 52.4, 50.7, 45.0, 37.5, 28.5, 24.2, 18.6. HRMS ($\text{M}+\text{H}$) $^{+}$ calcd. for $\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_5$ 407.1604, found 407.1598.

Benzyl 3-(3-(1-acetyl-4-methylindolin-7-yl)-2,5-dioxopyrrolidin-1-yl) benzoate (**34**): This compound was prepared following General Procedure E and was obtained as a gel (79 mg, 82%). ^1H NMR (400 MHz, Chloroform- d) δ 8.14–8.07 (m, 1H), 8.05 (q, $J = 1.4$ Hz, 1H), 7.59–7.52 (m, 2H), 7.46–7.31 (m, 5H), 6.98 (s, 2H), 5.37 (s, 2H), 4.52 (dd, $J = 9.6$, 5.9 Hz, 1H), 4.21–4.00 (m, 2H), 3.55 (dd, $J = 18.7$, 9.6 Hz, 1H), 3.06 (ddd, $J = 21.7$, 17.9, 7.3 Hz, 2H), 2.92 (ddd, $J = 15.5$, 8.7, 4.3 Hz, 1H), 2.27 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (101 MHz, Chloroform- d) δ 177.4, 176.1, 169.5, 165.6, 140.6, 135.9, 134.2, 133.9, 132.8, 131.5, 129.9, 129.4, 128.8, 128.5, 128.2, 127.5, 127.3, 125.4, 67.1, 50.7, 45.1, 37.5, 28.5, 24.2, 18.6. HRMS ($\text{M}+\text{H}$) $^{+}$ calcd. for $\text{C}_{29}\text{H}_{26}\text{N}_2\text{O}_5$ 483.1914, found 483.1910.

3-(3-(1-Acetyl-4-methylindolin-7-yl)-2,5-dioxopyrrolidin-1-yl)-N-propylbenzamide (**35**): To a stirred solution of benzyl 3-(3-(1-acetyl-4-methylindolin-7-yl)-2,5-dioxopyrrolidin-1-yl)benzoate **34** (62.7 mg, 0.130 mmol) in EtOAc/MeOH (3:1, 2 mL), Pd/C (15 mol%) was added under argon. The reaction mixture was hydrogenated (balloon) for 24h, and the reaction mixture was passed through a Celite pad and washed with methanol. The solvent was evaporated, and the crude product was subjected to the next step without purification. To a solution containing HATU (1.3 equiv.), 4-dimethylaminopyridine (20 mol%) and N, N-diisopropylethylamine (2.2 equiv.) in dry DMF (2.0 mL). was added to the acid (0.127 mmol) under a N_2 atmosphere. After 1h, LCMS showed the formation of the activated ester intermediate. Propylamine (2.0 equiv.) was added, and the resulting mixture was stirred at room temperature overnight. The solution was diluted with ethyl acetate, a saturated solution of aqueous sodium bicarbonate was added, and the organic layer was dried with

MgSO₄, filtered, and evaporated in vacuo. The crude was purified by chromatography (80% EtOAc in Hexanes) to give amide **36** (30 mg, 72%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.81 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.73 (t, *J* = 1.9 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.48 (dt, *J* = 8.2, 1.5 Hz, 1H), 6.99 (s, 2H), 6.17 (s, 1H), 4.52 (dd, *J* = 9.6, 5.8 Hz, 1H), 4.21–4.13 (m, 1H), 4.11–4.01 (m, 1H), 3.55 (dd, *J* = 18.7, 9.6 Hz, 1H), 3.44–3.36 (m, 2H), 3.13–3.00 (m, 2H), 2.97–2.86 (m, 1H), 2.29 (s, 3H), 2.25 (s, 3H), 1.62 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (101 MHz, Chloroform-*d*) δ 177.4, 176.0, 169.5, 166.5, 136.0, 134.1, 133.8, 132.6, 129.4, 127.5, 127.1, 125.3, 125.0, 77.4, 77.0, 76.7, 50.7, 44.9, 41.9, 37.3, 28.4, 24.1, 22.9, 18.5, 11.5. HRMS (M+H)⁺ calcd. for C₂₅H₂₇N₃O₄ 434.2079, found 434.2071.

Methyl 3-(3-(4-methylindolin-7-yl)-2,5-dioxopyrrolidin-1-yl)benzoate (**36**): This compound was prepared following General Procedure F and was obtained as a gum (47 mg, 52%). ¹H NMR (400 MHz, Acetone-*d*₆) δ 8.12–7.98 (m, 2H), 7.72–7.59 (m, 2H), 6.93 (d, *J* = 7.8 Hz, 1H), 6.54 (dd, *J* = 7.7, 0.8 Hz, 1H), 4.37 (dd, *J* = 9.6, 5.5 Hz, 1H), 3.92 (s, 3H), 3.65–3.56 (m, 2H), 3.38 (dd, *J* = 18.1, 9.6 Hz, 1H), 3.09–2.87 (m, 3H), 2.19 (s, 3H). ¹³C NMR (101 MHz, Acetone-*d*₆) δ 205.3, 177.1, 174.9, 165.6, 150.2, 133.5, 133.1, 131.5, 131.0, 129.1, 128.8, 127.9, 125.5, 120.0, 116.5, 51.7, 46.3, 42.2, 35.3, 29.5, 29.4, 29.2, 29.0, 28.8, 28.6, 28.5, 28.4, 17.8. HRMS (M+H)⁺ calcd. for C₂₁H₂₀N₂O₄ 365.1495, found 365.1498.

Methyl 3-(9-methyl-4-oxo-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-*ij*]quinoline-6-carboxamido)benzoate (**37**): This compound was prepared following General Procedure F and was obtained as a gel (31.4 mg, 35%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.46 (s, 1H), 8.27 (t, *J* = 1.9 Hz, 1H), 7.82 (ddd, *J* = 8.2, 2.3, 1.1 Hz, 1H), 7.64 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.45 (t, *J* = 7.9 Hz, 1H), 7.15 (d, *J* = 7.7 Hz, 1H), 6.78–6.66 (m, 1H), 4.03 (td, *J* = 7.2, 5.0 Hz, 1H), 3.99–3.86 (m, 2H), 3.84 (s, 3H), 3.05 (t, *J* = 8.4 Hz, 2H), 2.83–2.67 (m, 2H), 2.16 (s, 3H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 171.0, 166.0, 165.5, 140.9, 139.3, 133.7, 130.1, 129.3, 128.2, 128.1, 125.1, 124.0, 123.6, 119.7, 115.6, 59.7, 52.2, 44.8, 42.7, 33.9, 26.1, 18.1, 17.9, 14.1. HRMS (M+H)⁺ calcd. for C₂₁H₂₀N₂O₄ 365.1495, found 365.1504.

3-(3-(4-Methylindolin-7-yl)-2,5-dioxopyrrolidin-1-yl)-N-propylbenzamide (**38**): This compound was prepared following General Procedure F and was obtained as a sticky liquid (18 mg, 40%). ¹H NMR (400 MHz, Acetone-*d*₆) δ 7.96–7.81 (m, 3H), 7.60–7.53 (m, 1H), 7.50 (ddd, *J* = 7.9, 2.0, 1.2 Hz, 1H), 6.89 (d, *J* = 7.8 Hz, 1H), 6.59–6.42 (m, 1H), 4.33 (dd, *J* = 9.6, 5.3 Hz, 1H), 3.58 (dd, *J* = 9.2, 8.1 Hz, 2H), 3.42–3.32 (m, 3H), 3.06–2.89 (m, 3H), 2.18 (s, 3H), 1.68–1.58 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (101 MHz, Acetone-*d*₆) δ 177.1, 175.0, 165.4, 150.7, 136.1, 133.8, 132.9, 129.5, 128.8, 128.6, 126.5, 126.1, 125.3, 119.7, 116.3, 46.2, 42.1, 41.4, 35.3, 28.5, 22.6, 17.8, 10.8. HRMS (M+H)⁺ calcd. for C₂₃H₂₅N₃O₃ 392.1968, found 392.19830.

9-Methyl-4-oxo-N-(3-(propylcarbamoyl)phenyl)-1,2,5,6-tetrahydro-4H-pyrrolo[3,2,1-*ij*]quinoline-6-carboxamide (**39**): This compound was prepared following General Procedure F and was obtained as a brown solid (14mg, 30%). ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.01 (t, *J* = 1.9 Hz, 1H), 7.70 (ddd, *J* = 8.1, 2.2, 1.1 Hz, 1H), 7.58–7.49 (m, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.13 (d, *J* = 7.7 Hz, 1H), 6.86–6.80 (m, 1H), 4.16–3.99 (m, 3H), 3.38–3.31 (m, 4H), 3.15 (t, *J* = 8.3 Hz, 2H), 2.92–2.88 (m, 2H), 2.25 (s, 3H), 1.63 (h, *J* = 7.4, 6.9 Hz, 2H), 0.98 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (101 MHz, MeOD) δ 173.3, 169.9, 168.7, 141.6, 139.8, 136.8, 135.9, 130.1, 130.1, 126.3, 126.0, 124.1, 124.0, 120.2, 117.2, 46.4, 44.6, 42.8, 35.3, 27.6, 23.7, 18.2, 11.8. HRMS (M+H)⁺ calcd. for C₂₃H₂₅N₃O₃ 392.1968, found 392.1973.

Supplementary Materials: The following supporting information can be downloaded at <https://www.mdpi.com/article/10.3390/reactions6010020/s1>, Figure S1: Superposition of crystal structure of E7820 and docked pose obtained for E7820 (yellow) in the DCAF15 using Autodock Vina; Figure S2: A. X-ray visualization of E7820 inside DCAF15. B. E7820 interactions with proximal residues inside DCAF15; Figure S3: A. Docking pose of analog 7 inside DCAF15. B. Interactions of 7 with proximal residues inside DCAF15; Figure S4: A. Docking pose of analog 8 inside DCAF15. B. Interactions of 8

with proximal residues inside DCAF15; Figure S5: A. Docking pose of analog 8 (other enantiomer) inside DCAF15. B. Superposition of the docking pose for both enantiomers of analog 8 inside DCAF15; Figure S6: A. Docking pose of analog 17 inside DCAF15. B. Interactions of 17 with proximal residues inside DCAF15; Figure S7: A. Docking pose of analog 18 inside DCAF15. B. Interactions of 18 with proximal residues inside DCAF15; Figure S8: Superposition of the docking pose for E7820 (yellow), 7 (orange), 8 (purple), 17 (green) and 18 (blue) inside DCAF15; Table S1: Binding affinity of analogs; Table S2: Optimization of C-H activation on Indoline; Table S3: Cellular activity of selected analogs on colon carcinoma cell lines HCT116; Scheme S1: Synthesis of N-aryl indoline lactams S7 and S8; Scheme S2: Synthesis of benzyl succinimides S13 and S14; Scheme S3: Synthesis of DCAF15 tracer S18.

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