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Design and synthesis of a novel tyrosine kinase inhibitor template

P. Jake Slavish [a], Qin Jiang [b], Xiaoli Cui [b], Stephan W. Morris [b,c], Thomas R. Webb [a,*]

[a] Department of Chemical Biology and Therapeutics, St. Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN 38105-3678, United States
[b] Department of Pathology, St. Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN 38105-3678, United States
[c] Department of Oncology, St. Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN 38105-3678, United States

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ABSTRACT

We report the design and synthesis of an insulin receptor kinase family-targeted inhibitor template using the inhibitor conformation observed in an IGF1R/inhibitor co-crystal complex by application of a novel molecular design approach that we have recently published. The synthesis of the template involves a one pot Opatz cyclization reaction that provides a versatile indole ester in good yields. We also developed the required chemistry to elaborate this template with additional substituents and have used this chemistry to prepare some initial compounds that show selective inhibition of anaplastic lymphoma kinase (ALK).

1. Introduction

Often the discovery of new lead structures for drug discovery projects starts from active molecules (hits) that are found from the screening of compound libraries using in vitro assays or cell-based high-throughput screening. However, in some cases, it is possible to design 'hits' if sufficient information is available. We have recently published a detailed report on a novel and general method for de novo protein ligand design that uses pharmacophore-based geometry queries, or other similar information, to search virtual hydrocarbon databases for rigid frameworks that match the *geometry* of the query.[1] These new frameworks can then be used as starting points in the design of new structures that contain the constrained pharmacophore interaction features.[1] One of the general applications of this design method makes use of a pharmacophore query derived from the bound conformation of an inhibitor, as observed in a protein-inhibitor crystal structure.[2] A specific application of this approach to the inactive form of an oncogenic tyrosine kinase has previously been presented.[3] The development of new inhibitors of certain tyrosine kinases in the insulin receptor superfamily is of great interest since compounds that demonstrate an appropriate inhibition selectivity profile show promise as potential drugs for the treatment of human malignancies caused by specific gain-of-function oncogenic kinase mutations.[4–8] We report here details of the design of a novel kinase inhibitor template as well as the synthesis of a partially elaborated template and initial activity data.

Using the general published approach,[1] we searched a virtual framework library (VFL) using the pharmacophore shown in Figure 1, which was derived from a co-crystal structure of a ligand bound to the non-activated IGF1R kinase domain.[2] We utilized a pharmacophore with all of the interaction features converted to hydrophobic for the initial search of the VFL, as previously described.[1–3] This search yielded a large number of polycyclic framework hits that were then subjected to selection based on synthetic and medicinal chemistry expertise. This led to the selection of framework hit **1a** (see Fig. 2) since it was a close match to four of the five features and also had a synthetically attractive framework. We then targeted the synthesis of compounds containing this core template as a starting point for the design of selective inhibitors of relevant oncogenic tyrosine kinases in the insulin receptor superfamily by the stabilization of the inactive form of their kinase domains.

2. Results

As outlined in our retrosynthetic plan (Fig. 3) the synthesis of tetracyclic pyridone **1** can start with compounds such as ester **4/5**, which can be prepared from commercially available 2-iodoaniline (or 5-chloro-2-iodoaniline, Scheme 1) by iodo-vinyl exchange using phosphine-free, thermal Heck conditions[9] in 86/92% yield. Treatment of the resulting ester **4/5** with aldehyde **6** (made from the commercially available ester)[10] using modified Opatz conditions[11,12] provided the indole ester **7/8** in 73/68% yield.

* Corresponding author. Tel.: +1 901 595 3928; fax: +1 901 595 5715.
E-mail address: thomas.webb@stjude.org (T.R. Webb).

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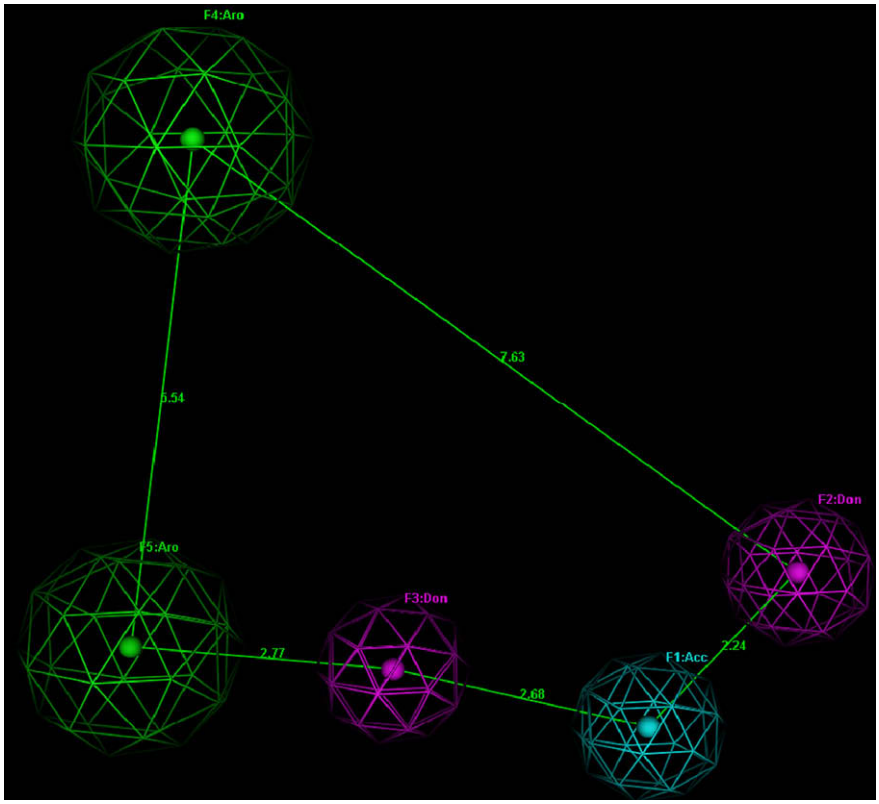


Figure 1. A detailed view of the pharmacophore including measurements in angstroms derived from the bound conformation of a ligand/IGF1R kinase domain co-crystal structure.[2,3] This pharmacophore was used to search the virtual framework library. The colour coding is as follows: Green = aromatic (Aro); Purple = hydrogen-bond donor (Don); Cyan = hydrogen-bond acceptor (Acc). The size of each sphere is to scale with the query that was used to search the VFL.[1] The radius dimensions are as follows: Aro = 1.2 Å; Don = 0.8 Å; Acc = 0.8 Å.

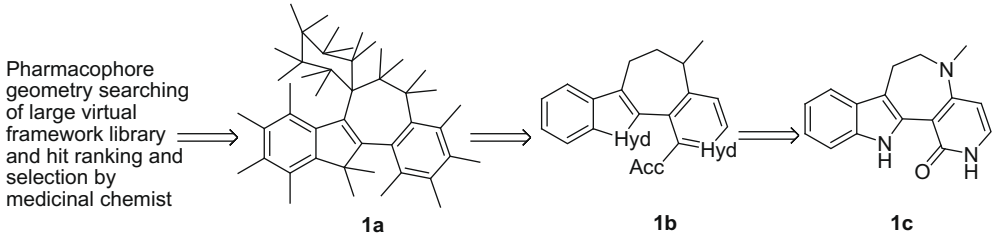


Figure 2. The evolution of scaffold **1c** from initial computational hit **1a**. Abbreviations: Hyd = hydrogen-bond donor; Acc = hydrogen-bond acceptor.

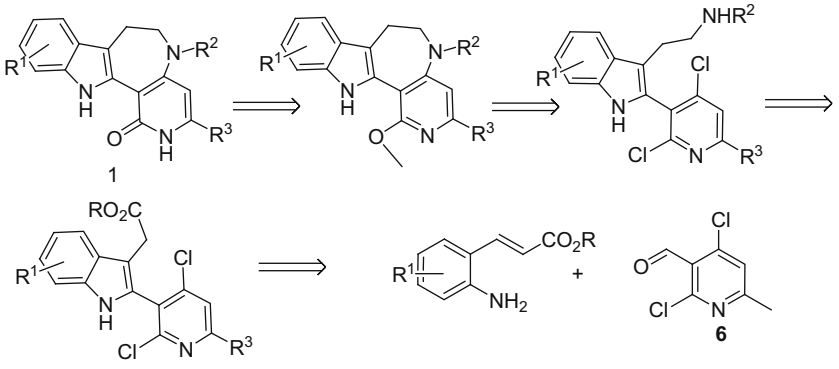
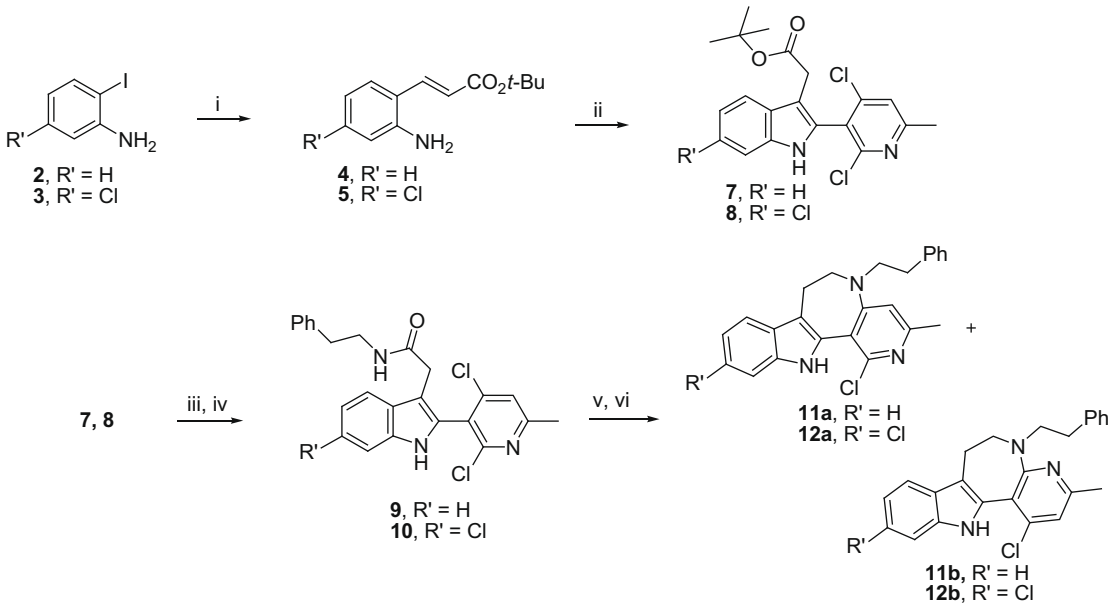


Figure 3. The general retrosynthetic approach to scaffold **1**.

Deprotection of the *t*-butyl ester, followed by amide coupling gave indole amide **9/10** in 80/74% overall yield. We initially investigated the direct base-catalyzed cyclization to form the seven-membered lactam[13,14] using **9/10** as a substrate, but the yield of the desired cyclized product was quite low. However, we found that amide reduction followed by base treatment yielded the tetracyclic pyri-



Scheme 1. The syntheses of the tetracyclic intermediates **11a/12a** and **11b/12b**. Reagents and conditions: (i) *t*-butyl acrylate, cat. $Pd(OAc)_2$, $NaHCO_3$, DMF; (ii) (a) **6**, HOAc, EtOH; (b) KCN, HOAc, EtOH; (iv) trifluoroacetic acid, DCM; (v) phenethylamine, HBTU, *N*-methyl morpholine, DMF; (vi) 1.0 M borane–THF complex, trifluoroborane–methyl etherate, THF; (vii) triethylamine, DMF.

dines **11a/12a** and **11b/12b** in 34% and 24/21% yields, respectively, over two steps. Acid-promoted cyclization of the amine[15] failed to provide the desired tetracyclic compound.

Though the cyclization was not regioselective, these compounds were readily separable and we viewed the diversity of these structures as an opportunity for our envisioned kinase inhibitory structure–activity studies on final compounds derived from both of these two templates (Scheme 1, see Fig. 4).

Direct conversion of chlorides **11a/12a** and **11b/12b** to the corresponding pyridones, using the published acidic conditions (HOAc,[16] HCl[17]) and basic conditions (KOH/DMSO)[18] failed to provide the desired products. For this reason, we chose to convert the chloro intermediates to the corresponding ethers, which could serve as a precursor to the pyridone (see Scheme 2). While sodium methoxide (in methanol or toluene)[19] under reflux conditions and DMAP yielded only partial chloro to methoxy conversion, we found that barium hydroxide (octahydrate) in the presence of excess DMAP in refluxing methanol provided complete conversion to ethers **13a/14a** and **13b** in 54/51% and 54% yield (Scheme 2). Though barium hydroxide is used quite often as the base for Suzuki couplings[20,21] and as an ester saponification reagent,[22,23] the aforementioned exchange catalyzed by barium hydroxide appears rather new. Ether **13a** could readily be converted to pyridone **1**,[24] in a modest yield of 63% after recrystallization. Structural confirmation of pyridone **1** was achieved via X-ray crystal determination (Fig. 5). Using Buchwald conditions, ether **14a** was converted to its

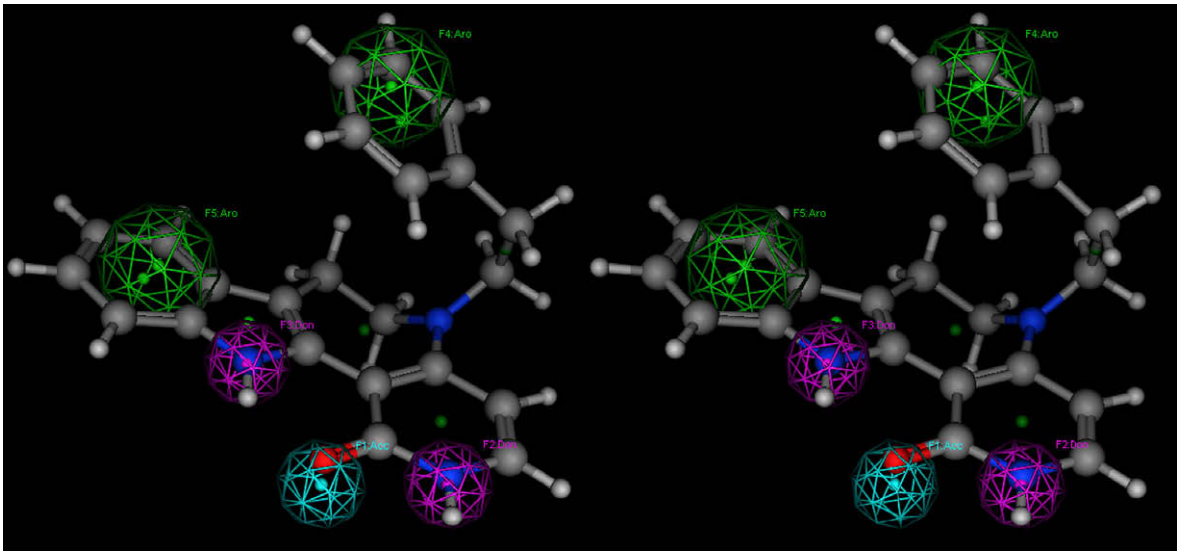
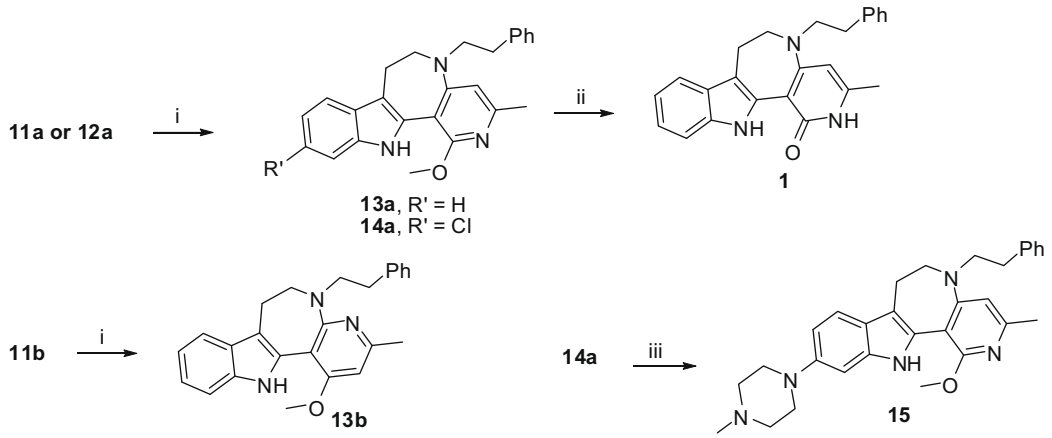


Figure 4. A right-left stereoview of a low energy conformation of **1** (the methyl group on the pyridine is omitted for simplicity) with an overlay of the pharmacophore from Figure 1 generated in MOE. The colour coding is as follows: Green = aromatic (Aro); Purple = hydrogen-bond donor (Don); Cyan = hydrogen-bond acceptor (Acc). The size of each sphere is to scale with the query that was used to search the VFL.[1] The radius dimensions are as follows: Aro = 1.2 Å; Don = 0.8 Å; Acc = 0.8 Å. Small green dots represent centroids recognized by MOE. See Figure 1 for a detailed view of the pharmacophore.



Scheme 2. The synthesis of pyridone or methoxy pyridine inhibitors. Reagents and conditions: (i) barium hydroxide (octahedrate), DMAP, CH_3OH; (ii) 4 M HCl (aq), THF; (iii) $Pd_2(dba)_3$, *N*-methyl-piperazine, X-Phos®, lithium hexamethyldisilazide, THF.

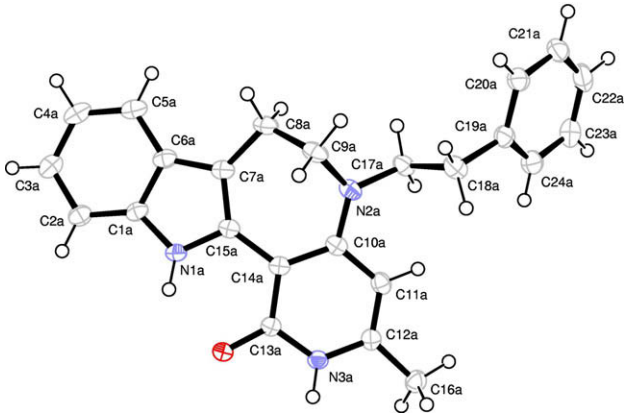
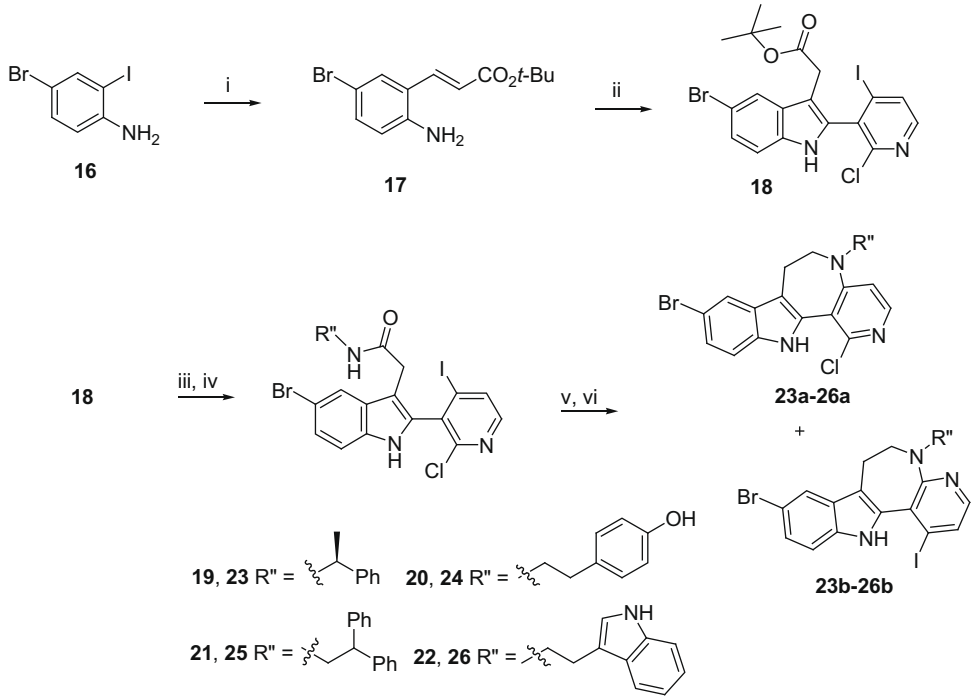


Figure 5. The single crystal X-ray structure of **1**, which confirms our structural assignment (see Supplementary data).

amino analogue **15**. Using a synthetic approach similar to Scheme 1 we synthesized various aryl analogues (Scheme 3).

3. Discussion

With this initial set of compounds in hand, we investigated their inhibitory effects on a set of kinases using in vitro enzymatic assays, performed as previously reported.[5] As can be seen (Table 1), depending on the position of the regioisomer and the substituents, we were able to identify initial compounds with the desirable selectivity for the oncogenic human anaplastic lymphoma kinase (ALK).[5,25] For example, compounds such as **24b**, **25a** and **26a** showed selectivity for ALK as compared to the highly homologous (and clinically relevant due to the possibility of iatrogenic diabetes with its inhibition) human insulin receptor kinase (IRK), exhibiting IC_{50}s in the single-digit micromolar range for ALK and greater than the highest compound concentration tested (40 μM) for the IRK. We have previously



Scheme 3. Synthesis of aryl analogues. Reagents and conditions: (i) *t*-butyl acrylate, cat. $Pd(OAc)_2$, $NaHCO_3$, DMF; (ii) (a) 2-chloro-4-iodo-nicotinaldehyde, HOAc, EtOH; (b) KCN, HOAc, EtOH; (iii) trifluoroacetic acid, DCM; (iv) amine, HBTU, *N*-methyl morpholine, DMF; (v) 1.0 M borane–THF complex, trifluoroborane–methyl etherate, THF; (vi) triethylamine, DMF.

Table 1
Biochemical evaluation of pyridone **1** and analogs (using the in vitro enzymatic kinase assay previously described in the Supplementary data)[5]

ID	ALK[a]	IRK	IGF1R	JAK2	MET
11a	21.3	30.5	24.7	33.5	26.1
11b	11.8	19.8	12.6	>40	12.4
13a	>40	>40	>40	>40	>40
13b	>40	>40	>40	>40	>40
1	18.0	15.6	11.8	16.9	19.7
15	5.1	3.5	4.5	5.1	5.5
23b	8.3	>40	ND[b]	ND	>40
23a	5.8	11.9	ND	ND	12.9
24b	6.2	11.1	ND	ND	9.7
24a	7.1	>40	ND	ND	12.5
25b	5	>40	ND	ND	8.6
25a	>40	>40	ND	ND	>40
26a	9.3	>40	ND	ND	>40

[a] All IC_{50} values (μM) are averages from triplicate assays.
[b] Not determined.

observed that this degree of selectivity at the hit stage indicates that these 'hits' may be converted into more potent and selective compounds. The relative potency of regioisomers such as **25b** versus **25a** was unexpected and could be due to difference in the kinase domain structure of ALK versus IGF1R, X-ray crystal structure of ALK remain unpublished at this time. The observed potencies are 'hit-like' and demonstrates the utility of our framework design method to identify compounds that are suitable starting points for further optimization into more potent selective inhibitors for additional iterations of medicinal chemistry.

4. Conclusion

We report the details on the specific application of our recently published 'framework' design[1] of a new kinase inhibitor template and the synthesis of the subject of this design, a novel tetracyclic pyridone tyrosine kinase inhibitor template, which was accomplished in eight steps.[26] This synthesis involves a one pot di-*ortho*-substituted aldehyde condensation, followed by the cyanide-catalyzed cyclization, which gave the key indole intermediate in >70% yield. In addition, we report the first example of barium hydroxide-catalyzed chloro-to-methoxy pyridine conversion. Finally, we present initial structure–activity data showing that representative examples of compounds based on these templates demonstrate activity and initial selectivity for anaplastic lymphoma kinase (ALK), thus indicating that they are suitable starting points for the development of more active 'lead-like' inhibitors through the usual process of 'hit-to-lead' chemistry. A future avenue of research will be the exploration of these templates for the discovery of new therapeutic leads against oncogenic tyrosine kinases in the insulin receptor superfamily such as ALK.[5,25]

5. Experimental

5.1. General remarks

All reactions were performed under an atmosphere of nitrogen. Flash chromatography purifications employed Silica Gel 60 from EMD Chemicals (particle size: 0.040–0.063 mm, 230–400 mesh ASTM). Thin layer chromatography was performed on silica gel with UV-254 indicator (250 μm thickness). All TLC visualizations were conducted with UV light. Nuclear magnetic resonance experiments were conducted using a 400 MHz II instrument (Bruker Avance II). Microwave reactions were conducted using a Biotage Initiator 60 (N = 100–300 W, H = 50–150 W, VH = 40–90 W). HPLC analyses were accomplished using an UPLC/UV/ELSD/SQD (Single Quadrapole Detector) with stationary phase: BEH C18, 1.7 μm, solvents: A: 0.1% formic acid in water, B: 0.1% formic acid in acetonitrile, detector types: PDA (210–400 nm) and ELSD.

5.2. X-ray crystallographic data

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 711726. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

5.3. (*E*)-*tert*-Butyl 3-(2-aminophenyl)acrylate (4)

To a solution of iodoaniline (5.5 g, 25.0 mmol), acrylate (3.8 mL, 26.2 mmol) and sodium bicarbonate (5.3 g, 62.4 mmol) in DMF (8 mL) was added palladium acetate (0.3 g, 1.3 mmol) in one portion. The resulting mixture was heated to 70 °C for 16 h. The mixture was then diluted with EtOAc and filtered through Celite. After concentrating under reduced pressure, crude product was purified via column chromatography (EtOAc/hexanes, 10:90) to provide the ester 4 (4.72 g, 86%) as a yellow solid. Mp 76–78 °C. ^{1}H NMR ($CDCl_3$) δ 7.75 (d, J = 15.8 Hz, 1H), 7.38 (dd, J = 7.8, 1.3 Hz, 1H), 7.17 (t, J = 7.5, 1.6 Hz, 1H), 6.78 (t, J = 7.6, 1.5 Hz, 1H), 6.72 (d, J = 8.1 Hz, 1H), 6.32 (d, J = 15.8 Hz, 1H), 3.93 (br s, 2H), 1.56 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 166.7, 145.4, 139.1, 128.1, 120.2, 120.1, 118.9, 116.7, 80.5, 28.3. HRMS (ESI) *m/z* calcd for $C_{13}H_{18}NO_2$ $(M+1)^+$ 220.1338, found 220.1332.

5.4. (*E*)-*tert*-Butyl 3-(2-amino-4-chlorophenyl)acrylate (5)

Compound **5** was prepared in a similar manner to conditions for ester **2** to give ester **5** (92%) as a yellow solid. Mp 63–65 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, 1H, J = 15.8 Hz), 7.20 (d, 1H, J = 8.1 Hz), 6.63 (m, 2H), 6.18 (d, J = 15.8 Hz, 1H), 1.44 (s, 9H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 146.2, 137.9, 136.5, 129.2, 120.7, 119.1, 118.6, 116.1, 100.0, 80.7, 28.3. HRMS (ESI) *m/z* calcd for $C_{13}H_{16}NO_2Cl$ $(M+1)^+$ 253.08695, found 253.08688.

5.5. *tert*-Butyl 2-(2-(2,4-dichloro-6-methylpyridin-3-yl)-1*H*-indol-3-yl)acetate (7)

To a solution of amine **4** (1.4 g, 6.4 mmol) and aldehyde **6** (1.5 g, 7.7 mmol) in EtOH (5 mL) was added HOAc (0.6 mL, 10.2 mmol). After 2 h, the solvent was removed under reduced pressure. The resulting crude imine was treated with potassium cyanide (0.9 g, 14.1 mmol) and additional acetic acid (0.37 mL, 6.4 mmol). The reaction mixture was heated to 70 °C stirred for 22 h. Once deemed complete, the solvent was removed under reduced pressure. Crude product was taken up in EtOAc and washed with satd aq $NaHCO_3$ solution. The organic phase was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude ester was purified via column chromatography (EtOAc/hexanes, 20:80) to furnish the indole ester **7** (1.84 g, 73%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.90 (s, 1H), 7.66 (d, J = 7.9 Hz, 1H), 7.33 (d, J = 8.1 Hz, 1H), 7.24 (s, 1H), 7.19 (m, 3H), 7.12 (t, J = 7.5 Hz, 1H), 3.43 (d, J = 1.0 Hz, 2H), 2.54 (s, 3H), 1.48 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 170.2, 160.3, 152.4, 147.5, 136.2, 122.8, 127.5, 123.0, 120.1, 119.9, 111.1, 110.1, 80.7, 32.5, 27.9, 24.0. HRMS (ESI) *m/z* calcd for $C_{20}H_{21}N_2O_2Cl_2$ $(M+1)^+$ 391.0980, found 391.0976.

5.6. *tert*-Butyl 2-(6-chloro-2-(2,4-dichloro-6-methylpyridin-3-yl)-1*H*-indol-3-yl)acetate (8)

Compound **8** was prepared in a similar manner to the conditions above for **4** to give **8** (68%) as a off-white solid. Mp 72–

74 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.79 (d, J = 1.8 Hz, 1H), 7.20 (m, 3H), 3.36 (d, J = 3.3 Hz, 2H), 2.50 (s, 3H), 1.28 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 160.6, 152.3, 147.5, 136.5, 129.0, 128.2, 126.3, 123.2, 121.1, 111.1, 110.3, 80.9, 32.4, 27.9, 24.0. HRMS (ESI) m/z calcd for $C_{20}H_{20}N_2O_2Cl_3$ $(M+1)^+$ 425.0590, found 425.0571.

5.7. 2-(2-(2,4-Dichloro-6-methylpyridin-3-yl)-1*H*-indol-3-yl)-*N*-phenethylacetamide (9)

A solution of indole ester **5** (1.7 g, 4.0 mmol) in dichloromethane (3 mL) was treated with trifluoroacetic acid (3.0 mL, 40.0 mmol). The solution stirred at rt for 1 h. The solvent was then removed under reduced pressure. The crude acid was dissolved in DMF, treated with 4-methylmorpoline (1.3 mL, 12.0 mmol) followed by HBTU (2.3 g, 6.0 mmol) and phenethylamine (0.6 mL, 4.8 mmol) in one portion. After 1 h, the mixture was diluted with EtOAc and washed with satd aq $NaHCO_3$ solution, dried with sodium sulfate, filtered and concentrated under reduced pressure. Crude product was purified via column chromatography (EtOAc/hexanes, 1:1) to yield indole amide **9** (0.50 g, 80%) as an off-white solid. Mp 165–167 °C. ^{1}H NMR ($CDCl_3$) δ 8.02 (s, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 8.2 Hz, 1H), 7.29 (t, J = 7.5 Hz, 1H), 7.20–7.15 (m, 3H), 7.05–6.90 (m, 3H), 6.67 (d, J = 6.9 Hz, 2H), 5.62 (s, 1H), 3.47 (q, J = 17.5 Hz, 2H), 3.39–3.22 (m, 2H), 2.55–2.48 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 170.2, 161.3, 152.5, 147.3, 138.3, 135.9, 128.6, 127.5, 126.2, 123.4, 120.6, 119.1, 111.4, 109.4, 40.3, 35.6, 32.6, 24.0. Anal. Calcd for $C_{24}H_{21}Cl_2N_3O$: C, 65.76; H, 4.83; N, 9.59. Found: C, 65.22; H, 4.81; N, 9.39. HRMS (ESI) m/z calcd for $C_{24}H_{22}N_3OCl_2$ $(M+1)^+$ 438.1140, found 438.1144.

5.8. 2-(6-Chloro-2-(2,4-dichloro-6-methylpyridin-3-yl)-1*H*-indol-3-yl)-*N*-phenethylacetamide (10)

Compound **10** was prepared in a similar manner to above conditions for **5** to give amide **10** (74%) as a transparent oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 7.47–7.42 (m, 2 H), 7.22 (s, 1H), 7.16 (dd, J = 8.4, 1.4 Hz, 1H), 7.11–7.01 (m, 3H), 6.76 (m, 2H), 5.65 (t, J = 5.6 Hz, 1H), 3.53–3.27 (m, 4H), 2.78 (s, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 161.0, 152.1, 147.2, 138.2, 136.8, 129.4, 128.5, 128.4, 125.8, 123.4, 123.2, 121.3, 120.1, 111.6, 109.1, 40.5, 38.6, 35.4, 32.6, 24.0. HRMS (ESI) m/z calcd for $C_{24}H_{20}N_3OCl_3$ $(M+1)^+$ 472.0750, found 472.0758.

5.9. Compounds 11a and 11b

A refluxing mixture of amide **9** (0.6 g, 1.3 mmol) and boron trifluoride dimethyl etherate (0.2 mL, 2.2 mmol) in THF (3 mL) was exposed to 1.0 M borane-THF complex (3.9 mL, 3.9 mmol in THF) for 3 h. After this time, the reaction was cooled to 0 °C and quenched with 4.5 N HCl (3 mL). The mixture was stirred for 1 h and then at rt for 1 h. The mixture was then cooled to 0 °C and basified to pH 13 with solid KOH and extracted with CH_2Cl_2 (10 mL) three times. The organic solution was dried (sodium sulfate), filtered and concentrated to afford the amine, which was diluted in DMF (5 mL) and treated triethylamine (0.2 mL, 1.3 mmol). The reaction was heated to 70 ° C for 16 h, then quenched via the addition of water (5 mL) at rt. The aqueous layer was extracted with EtOAc (5 mL). The organic layer was dried, filtered and concentrated under reduced pressure. The regioisomers were separated via column chromatography (EtOAc/hexanes, 9:1 to 4:1) to afford pure 2-chlroro pyridine **11a** (0.17 g, 34%) as an off-white solid. Mp 165–166 °C. ^{1}H NMR ($CDCl_3$) δ 8.95 (s, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.18–7.00 (m, 7H), 6.57 (s, 1H), 3.53 (t, J = 7.6 Hz, 2H), 3.46 (t, J = 5.6 Hz, 2H), 2.97 (t, J = 5.6, 2H), 2.86 (t, J = 7.6 Hz, 2H), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 161.5, 154.0, 139.8, 139.4, 135.4, 134.7, 127.2, 126.3, 126.0, 122.8, 118.8, 116.7, 115.5, 110.3, 109.2, 53.5, 51.9, 34.7, 27.1, 23.6. HRMS (ESI) m/z calcd for $C_{24}H_{23}N_3Cl$ $(M+1)^+$ 388.1581, found 388.1589. 4-Chloro pyridine **11b** (0.12 g, 24%) was a yellow solid. Yield: 24%, mp 155–156 °C. ^{1}H NMR ($CDCl_3$) δ 8.92 (s, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.19–7.00 (m, 7H), 6.8 (s, 1H), 3.86 (t, J = 7.7 Hz, 2H), 3.57 (t, J = 7.5 Hz, 2H), 3.09 (t, J = 5.4 Hz, 2H), 3.02 (t, J = 7.7 Hz, 2H), 2.45 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 160.6, 154.8, 147.0, 138.8, 135.4, 128.9, 127.2, 126.7, 123.2, 118.5, 116.1, 113.5, 110.6. 109.5, 54.2, 53.9, 34.7, 26.5, 23.9. HRMS (ESI) m/z calcd for $C_{20}H_{21}N_2O_2Cl_2$ $(M+1)^+$ 388.1581, found 388.1563.

5.10. Compounds 12a and 12b

These compounds were prepared in a similar manner to the above cyclization from amide **10** to give 2-chloro pyridine **12a** (34%) as an off-white solid. Mp 152–154 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 7.41 (d, J = 1.7 Hz, 1H), 7.36 (d, 1H, J = 8.4 Hz), 7.18–7.05 (m, 6H), 6.66 (s, 1H), 3.63 (t, J = 7.4 Hz, 2H), 3.52 (t, J = 5.6 Hz, 2H), 3.00–2.92 (m, 4H), 2.46 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 155.0, 146.9, 138.7, 135.2, 128.7, 128.5, 128.0, 126.6, 126.3, 120.1, 119.6, 116.0, 113.2, 110.4, 109.5, 54.6, 53.9, 34.4, 26.6, 24.0, HRMS (ESI) m/z calcd for $C_{24}H_{21}Cl_2N_3$ $(M+1)^+$ 422.1191, found 422.1197. 4-Chloro pyridine **12b** (21%) was a yellow solid. Mp 175–177 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.35 (d, J = 1.6 Hz, 1H), 7.17–7.13 (m, 5H), 7.08 (dd, J = 8.4, 1.8 Hz, 1H), 6.79 (s, 1H), 3.86 (t, J = 7.6 Hz, 2H), 3.53 (t, J = 5.5 Hz, 2H), 3.05–2.97 (m, 4H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 153.7, 140.2, 139.3, 135.3, 128.9, 128.3, 128.1, 126.5, 120.1, 119.7, 116.7, 115.7, 110.3, 108.7, 53.7, 51.8, 34.7, 26.8, 23.8. HRMS (ESI) m/z calcd for $C_{24}H_{21}Cl_2N_3$ $(M+1)^+$ 422.1191, found 422.1187.

5.11. Compound 13a

2-Chloro pyridine (0.2 g, 0.4 mmol) and DMAP (0.4 g, 3.6 mmol) was dissolved in methanolic barium hydroxide octahydrate solution (1.2 g, 7.2 mmol $Ba(OH)_2{\cdot}8H_2O$, 8 mL methanol). The resulting solution was heated to reflux for 16 h. The methanol was removed under reduced pressure; the crude product was dissolved in EtOAc and washed with water. The organic solution was dried with sodium sulfate, filtered, concentrated and purified via column chromatography (EtOAc/hexanes, 1:9) to yield ether **13a** (0.07 g, 54%) as a white solid. Mp 137–139 °C. ^{1}H NMR ($CDCl_3$) δ 10.1 (s, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.40 (d, J = 8.1 Hz, 1H), 7.30–7.20 (m, 6H), 7.12 (t, J = 7.4 Hz, 1H), 6.48 (s, 1H), 4.18 (s, 3H), 3.64 (t, J = 7.8 Hz, 2H), 3.50 (t, J = 5.4 Hz, 2H), 3.12 (t, J = 5.3 Hz, 2H), 3.03 (t, J = 7.8 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 160.9, 158.7, 152.1, 139.3, 134.4, 128.6, 128.2, 126.5, 122.1, 118.1, 113.7, 110.3, 105.9, 100.9, 55.2, 53.8, 52.0, 34.7, 27.8, 24.1. Anal. Calcd for $C_{25}H_{25}N_3O$: C, 78.30; H, 6.57; N, 10.96. Found: C, 77.95; H, 6.62; N, 10.75.

5.12. Compound 13b

This compound was prepared in a similar manner to the above methoxy displacement to give ether **13b** (51%) as an off-white solid. Mp 80–82 °C. ^{1}H NMR ($CDCl_3$) δ 9.75 (s, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.26–7.23 (m, 4H), 7.19 (t, J = 8.0 Hz, 2H), 7.10 (t, J = 7.0 Hz, 1H), 6.42 (s, 1H) 4.06 (s, 3H), 3.88 (t, J = 7.8 Hz, 2H), 3.53 (t, J = 5.3 Hz, 2H), 3.12–3.08 (m, 4H), 2.48 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 140.6, 134.7, 129.0, 128.4, 128.1, 126.1, 122.1, 118.8, 118.4, 113.4, 110.3, 98.5, 56.0, 54.5, 50.9, 34.9, 29.7, 27.8, 24.8. HRMS (ESI) m/z calcd for $C_{25}H_{26}N_3O$ $(M+1)^+$ 384.2076, found 384.2069.

5.13. Compound 14a

This compound was prepared in a similar manner to the above methoxy displacement to give ether **14a** (54%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.98 (s, 1H), 7.28 (d, J = 1.8 Hz, 1H) 7.27 (d, J = 8.7 Hz, 1H), 7.18–7.07 (m, 7H), 6.96 (dd, J = 8.4, 1.8 Hz, 1H), 6.38 (s, 1H), 4.05 (s, 3H), 3.54 (t, J = 7.7 Hz, 2H), 3.37 (t, J = 5.2 Hz, 2H), 2.95–2.86 (m, 4H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 156.8, 150.6, 137.4, 132.9, 127.0, 126.8, 125.9, 125.1, 124.7, 117.7, 117.1, 111.9, 108.4, 98.8, 53.4, 52.0, 50.2, 32.8, 25.8, 22.4. HRMS (ESI) m/z calcd for $C_{25}H_{25}N_3OCl$ $(M+1)^+$ 418.1686, found 418.1680.

5.14. 3-Methyl-6-*N*-phenethyl-5,6,7,12-tetrahydroindolo[2,1-*d*]pyrido[4,3-*b*]azepin-1(2*H*)-one (1)

To a solution of *O*-methyl pyridine (0.05 g, 140 μmol) in dioxane (0.2 mL) was added 4 M HCl (aq). The mixture was heated to 65 °C for 5 h. Crude product was purified via recrystallization (EtOAc/hexanes) to afford pyridone **1** (32 mg, 63%) as a tan solid. Yield: 63%, mp 244 °C. ^{1}H NMR ($CDCl_3$) δ 12.4 (s, 1H), 9.94 (s, 1H), 7.49 (d, J = 7.5 Hz, 1H), 7.41 (d, J = 7.5 Hz, 1H), 7.36–7.24 (m, 6H), 7.17 (t, J = 7.0 Hz, 1H), 7.09 (t, J = 7. 0 Hz, 1H), 5.85 (s, 1H), 3.65 (t, J = 7.6 Hz, 2H), 3.51 (t, J = 4.8 Hz, 2H), 3.12 (t, J = 4.9 Hz, 2H), 3.08 (t, J = 7.6 Hz, 2 H), 2.30 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 165.7, 158.1, 140.9, 138.7, 133.7, 132.1, 128.8, 128.0, 126.7, 121.1, 118.5, 117.5, 111.2, 110.6, 100.4, 99.8, 55.4, 51.3, 34.8, 29.7, 26.9, 19.1.

5.15. Compound 15

A mixture of **14a** (0.08 g, 0.2 mmol), dicyclohexyl(2′,4′,6′-triisopropylbiphenyl-2-yl)phosphine (X-Phos®, 6 mg, 0.01 mmol), and $Pd_2(dba)_3$ (16 mg, 0.02 mmol) was treated with a solution of *N*-methyl piperazine (0.03 mL, 0.2 mmol) in THF (1 mL). This solution was treated with LiHMDS (0.6 mL, 1 M in THF) in one portion. The reaction was heated to 70 °C in a sealed tube overnight. The reaction mixture was dissolved in EtOAc, washed with satd aq $NaHCO_3$ solution, dried over magnesium sulfate, filtered and concentrated under reduced pressure. Crude product was purified via reverse phase HPLC. Ether **15** (11 mg, 10%) was a tan oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.4 (s, 1H), 8.25 (s, 1H), 7.30–7.25 (m, 6H), 6.96 (d, J = 1.9 Hz, 1H), 6.75 (dd, J = 8.6, 2.0 Hz, 1H), 4.05 (s, 3H), 3.57 (t, J = 7.8 Hz, 4H), 3.44 (t, J = 5.2 Hz, 4H), 3.12 (t, J = 4.8 Hz, 4H), 3.00–2.92 (m, 5H), 2.32 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 160.2, 158.1, 150.8, 147.5, 139.4, 135.6, 128.8, 127.0, 126.1, 121.8, 117.9, 112.9, 110.9, 105.4, 100.5, 97.5, 54.8, 54.3, 53.3, 51.5, 50.0, 45.7, 33.7, 27.2, 23.8. HRMS (ESI) m/z calcd for $C_{30}H_{35}N_5O$ $(M+1)^+$ 482.2920, found 482.2912.

5.16. (*E*)-*tert*-Butyl 3-(2-amino-4-bromophenyl)acrylate (17)

Compound **17** was prepared in a similar manner to conditions for **2** to give ester **17** (92%) as yellow solid. Mp 63–65 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 15.8 Hz, 1H), 7.48 (d, J = 2.3 Hz, 1H), 7.23 (dd, J = 8.5, 2.2 Hz, 1H), 6.59 (d, J = 8.5 Hz, 1H), 6.29 (d, J = 15.7 Hz, 1H), 3.96 (s, 2H), 1.55 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 155.3, 144.3, 137.5, 133.4, 130.3, 121.9, 121.5, 118.2, 110.6, 80.8, 28.2. HRMS (ESI) m/z calcd for $C_{13}H_{17}NO_2Br$ $(M+1)^+$ 298.0443, found 298.0442.

5.17. *tert*-Butyl 2-(5-bromo-2-(2-chloro-4-iodopyridin-3-yl)-1*H*-indol-3-yl)acetate (18)

Compound **18** was prepared in a similar manner to the conditions above for **4** to give indole ester **18** (66%) as a yellow solid. Mp 181–184 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 8.00 (d, J = 5.2 Hz, 1H), 7.83 (s, 1H), 7.79 (d, J = 5.2 Hz, 1H), 7.28 (dd, J = 8.6, 1.8 Hz, 1H), 7.24–7.18 (m, 2H), 3.36 (d, J = 4.6 Hz, 2H), 1.31 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 151.7, 149.9, 134.6, 134.0, 133.2, 133.2, 129.4, 126.1, 123.1, 114.8, 113.5, 112.8, 108.8, 81.2, 32.5, 28.1. HRMS (ESI) m/z calcd for $C_{19}H_{18}N_2O_2ClBrI$ $(M+1)^+$ 546.9285, found 546.9272.

5.18. 2-(5-Bromo-2-(2-chloro-4-iodopyridin-3-yl)-1*H*-indol-3-yl)-*N*-((*S*)-1-phenylethyl)acetamide (19)

Compound **19** was prepared in a similar manner to above conditions for **5** to give amide **19** (68%) as a tan oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J = 9.9 Hz, 1H), 8.03 (dd, J = 5.2, 2.2 Hz, 1H), 7.75 (dd, J = 6.2, 5.4 Hz, 1H), 7.68 (dd, J = 8.8, 1.8 Hz, 1H), 7.33 (dt, J = 8.6, 1.9 Hz, 1H), 7.24 (dd, J = 10.0, 1.2 Hz, 1H), 7.20–7.10 (m, 4H), 7.01 (m, 2H), 5.84 (d, J = 8.0 Hz, 1H), 4.99 (qn, J = 7.2 Hz, 1H), 3.46 (dd, J = 17.5, 5.5 Hz, 1H), 3.36 (dd, J = 17.5, 4.5 Hz, 1H), 1.25 (dd, J = 6.9, 5.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 168.9, 151.4, 151.4, 150.4, 142.9, 142.8, 135.0, 133.3, 132.7, 127.3, 126.1, 122.3, 114.7, 114.0, 113.2, 108.1, 108.0, 49.0, 33.0, 21.8. HRMS (ESI) m/z calcd for $C_{23}H_{19}N_3OClBrI$ $(M+1)^+$ 593.9445, found 593.9445.

5.19. 2-(5-Bromo-2-(2-chloro-4-iodopyridin-3-yl)-1*H*-indol-3-yl)-*N*-(2-(4-hydroxyphenyl)ethyl) acetamide (20)

Compound **20** was prepared in a similar manner to above conditions for **5** to give amide **20** (39%) as a brown oil. ^{1}H NMR (400 MHz, acetone) δ 10.64 (s, 1H), 8.20 (br s, 1H) 8.15 (t, J = 4.9 Hz, 1H), 8.04 (t, J = 4.9 Hz, 1H), 7.98 (d, J = 2.4 Hz, 1H), 7.47 (dd, J = 8.6, 4.4 Hz, 1H), 7.36 (m, 1H), 6.83 (m, 2H), 6.63 (m, 3H), 3.46 (t, J = 5.3 Hz, 2H), 3.31 (m, 2H), 2.58 (m, 2H). ^{13}C NMR (101 MHz, acetone) δ 169.8, 156.7, 151.9, 150.9, 136.3, 136.0, 134.4, 134.3, 130.8, 130.6, 130.5, 126.1, 123.4, 116.1, 115.6, 114.3, 113.2, 109.3, 41.8, 35.7, 33.4. HRMS (ESI) m/z calcd for $C_{22}H_{19}N_3O_2ClBrI$ $(M+1)^+$ 609.9394, found 609.9421.

5.20. 2-(5-Bromo-2-(2-chloro-4-iodopyridin-3-yl)-1*H*-indol-3-yl)-*N*-(2,2-diphenylethyl)acetamide (21)

Compound **21** was prepared in a similar manner to above conditions for **5** to give amide **21** (94%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.95 (d, J = 5.2 Hz, 1H), 7.70 (d, J = 5.2 Hz, 1H), 7.65 (d, J = 1.7 Hz, 1H), 7.37 (dd, J = 8.6, 1.8 Hz, 1H), 7.25 (d, J = 8.6 Hz, 1H), 7.05–6.97 (m, 6H), 6.90–6.84 (m, 4H), 5.53 (t, J = 5.4 Hz, 1H), 3.82 (t, J = 7.6 Hz, 1H), 3.73 (t, J = 6.7 Hz, 2H), 3.33 (d, J = 5.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 151.4, 150.3, 141.5, 141.4, 135.1, 134.7, 133.0, 132.6, 128.8, 128.6, 128.0, 127.9, 126.8, 126.7, 122.1, 114.7, 114.1, 113.1, 107.8, 50.4, 43.6, 32.7. HRMS (ESI) m/z calcd for $C_{29}H_{23}N_3OClBrI$ $(M+1)^+$ 669.9758, found 669.9736.

5.21. *N*-(2-(1*H*-Indol-3-yl)ethyl)-2-(5-bromo-2-(2-chloro-4-iodopyridin-3-yl)-1*H*-indol-3-yl)acetamide (22)

Compound **22** was prepared in a similar manner to above conditions for **5** to give amide **22** (58%) as a tan solid. Mp 240–242 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.45 (s, 1H), 10.77 (s, 1H), 8.16 (d, J = 5.2 Hz, 1H), 8.08 (d, J = 5.1 Hz, 1H) 7.94 (d, J = 1.9 Hz, 1H), 7.84 (t, J = 5.7 Hz, 1H), 7.49 (d, J = 7.9 Hz, 1H), 7.35 (d, J = 8.6 Hz, 1H), 7.32 (d, J = 8.1 Hz, 1H), 7.30 (dd, J = 8.6, 2.0 Hz, 1H), 7.06–7.03 (m, 2H), 6.95 (dt, J = 7.5, 1.0 Hz, 1H), 3.30 (m, 5H), 2.72 (t, J = 7.5 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 169.1, 150.3, 149.9, 136.2, 134.9, 134.4, 133.3, 133.2, 129.5, 127.1, 124.2, 122.5, 122.4, 120.9, 118.2, 116.5, 113.3, 111.7, 111.4, 108.1, 31.9, 25.3, HRMS (ESI) m/z calcd for $C_{25}H_{20}N_4OClBrI$ $(M+1)^+$ 632.9554, found 632.9537.

5.22. Compounds 23a/b

These compounds were prepared in a similar manner to the above cyclization from amide **10** except the cyclization step was heated to 170 °C for 1 h using microwave heating (absorbance: normal) to provide **23a** (11%) as a tan solid. Mp 142–146 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 7.83 (d, J = 5.7 Hz, 1H), 7.51 (s, 1H), 7.29–7.22 (m, 7H), 6.68 (d, J = 5.7 Hz, 1H), 4.96 (q, J = 6.8 Hz, 1H), 3.49 (t, J = 5.5 Hz, 2H), 2.93 (dt, J = 16.7, 5.7 Hz, 1H), 2.72 (dt, J = 16.7, 5.4 Hz, 1H), 1.67 (d, J = 6.9 Hz, 3H), ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 147.0, 144.2, 139.6, 132.5, 128.4, 127.8, 127.4, 126.6, 125.9, 125.2, 120.4, 114.7, 113.7, 111.5, 111.1, 110.0, 58.2, 47.6, 26.4, 17.4. HRMS (ESI) *m/z* calcd for $C_{23}H_{20}N_3BrCl$ $(M+1)^+$ 452.0529, found 452.0509. *Compound* **23b** was a tan oil (7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.61 (d, J = 4.9 Hz, 1H), 7.47 (d, J = 1.6 Hz, 1H), 7.23 (m, 8H), 5.83 (q, J = 6.9 Hz, 1H), 3.40 (ddd, J = 14.5, 6.5, 4.4 Hz, 1H), 3.18 (ddd, J = 14.3, 8.2, 3.6 Hz, 1H), 2.78 (ddd, J = 16.7, 6.2, 3.7 Hz, 1H), 2.46 (ddd, J = 16.7, 8.2, 4.3 Hz, 1H), 1.61 (d, J = 6.9 Hz, 3H), ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.9, 143.0, 140.7, 132.3, 129.0, 128.9, 127.3, 126.9, 126.6, 126.1, 125.0, 120.7, 114.7, 114.4, 111.6, 111.0, 100.9, 54.5, 45.1, 25.9, 15.5, HRMS (ESI) *m/z* calcd for $C_{23}H_{20}N_3BrI$ $(M+1)^+$ 543.9885, found 543.9873.

5.23. Compounds 24a/b through 26a/b

These compounds were prepared in a similar manner to the above cyclization from amide **10.** *Compound* **24a** was a tan solid (22%). Mp 217–219 °C. ^{1}H NMR (400 MHz, acetone) δ 10.29 (s, 1H), 8.07 (s, 1H), 8.02 (s, 1H), 7.95 (d, J = 5.6 Hz, 1H), 7.66 (d, J = 1.9 Hz, 1H), 7.46 (d, J = 8.6 Hz, 1H), 7.28 (dd, J = 8.6, 1.9 Hz, 1H), 7.07 (d, J = 5.7 Hz, 1H), 7.05 (d, J = 8.4 Hz, 2H), 6.65 (d, J = 8.5 Hz, 2H), 3.65 (m, 4H), 3.12 (t, J = 5.8 Hz, 2H), 2.91 (t, J = 7.7 Hz, 2H). ^{13}C NMR (101 MHz, acetone) δ 217.5, 214.9, 213.8, 212.7, 212.3, 206.1, 206.1, 161.3, 156.8, 149.1, 146.3, 135.3, 130.7, 130.7, 130.4, 130.2, 126.2, 121.8, 116.4, 116.1, 116.0, 113.8, 112.5, 111.3, 55.6, 55.2, 33.9, 26.8. HRMS (ESI) *m/z* calcd for $C_{23}H_{20}N_3OBrCl$ $(M+1)^+$ 468.0478, found 468.0469. *Compound* **24b** was a brown solid (10%). Mp 208–212 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.80 (s, 1H), 9.17 (s, 1H), 7.76 (d, J = 4.9 Hz, 1H), 7.73 (d, J = 1.7 Hz, 1H), 7.47 (d, J = 4.9 Hz, 1H), 7.40 (d, J = 8.6 Hz, 1H), 7.30 (dd, J = 8.6, 1.9 Hz, 1H), 7.04 (d, J = 8.4 Hz, 2H), 6.64 (d, J = 8.4 Hz, 2H), 3.72 (t, J = 7.7 Hz, 2H), 3.58 (t, J = 5.4 Hz, 2H), 3.08 (t, J = 5.6 Hz, 2H), 2.85 (t, J = 7.7 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 161.2, 155.5, 144.2, 134.2, 131.5, 129.8, 129.5, 129.4, 127.1, 124.8, 120.8, 117.1, 115.0, 114.1, 113.3, 111.1, 104.9, 52.5, 33.1, 25.5. HRMS (ESI) *m/z* calcd for $C_{23}H_{20}N_3OBrI$ $(M+1)^+$ 559.9835, found 559.9857. *Compound* **25a** was an off-white solid (24%). Mp 112–114 °C. ^{1}H NMR (400 MHz, acetone) δ 10.13 (s, 1H), 7.99 (d, J = 5.6 Hz, 1H), 7.33 (d, J = 1.9 Hz, 1H), 7.28 (dd, J = 8.6, 0.4 Hz, 1H), 7.13 (dd, J = 8.6, 1.9 Hz, 1H), 7.00 (dd, J = 7.6, 1.6 Hz, 5H), 6.89 (t, J = 1.8 Hz, 1H), 6.87 (dd, J = 5.8, 1.4 Hz, 3H), 6.84 (t, J = 1.5 Hz, 1H), 6.83 (t, J = 3.0 Hz, 1H), 4.18 (d, J = 8.6, 6.9 Hz, 1H), 4.09 (d, J = 3.9 Hz, 2H), 3.48 (t, J = 5.8 Hz, 2H), 2.57 (d, J = 5.8 Hz, 2H).^{13}C NMR (101 MHz, acetone) δ 161.1, 149.2, 146.3, 143.5, 135.3, 130.4, 129.9, 128.9, 128.9, 127.1, 125.9, 121.9, 117.4, 116.6, 113.6, 112.1, 112.1, 58.8, 57.2, 50.6, 26.4, HRMS (ESI) *m/z* calcd for $C_{29}H_{24}N_3ClBr$ $(M+1)^+$ 528.0842, found 528.0848. *Compound* **25b** was a tan oil (3%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.60 (d, J = 4.9 Hz, 1H), 7.35 (d, J = 1.7 Hz, 1H), 7.29 (d, J = 5.0 Hz, 1H), 7.23 (dd, J = 8.6, 1.8 Hz, 1H), 7.19 (s, 2H), 7.14 (d, J = 8.5 Hz, 1H), 6.96 (m, 10H), 4.25 (m, 3H), 3.37 (t, J = 5.7 Hz, 2H), 2.40 (t, J = 5.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.3, 144.1, 142.9, 133.3, 129.8, 129.7, 128.2, 128.1, 128.1, 126.2, 125.9, 121.9, 117.8, 115.9, 112.3, 111.8, 102.3, 57.4, 54.6, 49.9, 25.8. HRMS (ESI) *m/z* calcd for $C_{29}H_{24}N_3BrI$ $(M+1)^+$ 620.0198, found 620.0211. *Compound* **26a** was a light brown solid (30%). Mp 248–252 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.99 (s, 1H), 10.81 (s, 1H), 7.98 (d, J = 5.6 Hz, 1H), 7.69 (s, 1H), 7.56 (d, J = 7.4 Hz, 1H), 7.38 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.25 (d, J = 6.7 Hz, 1H), 7.17 (s, 1H), 7.06 (m, 2H), 6.95 (t, J = 7.1 Hz, 1H), 3.64 (br s, 4H), 3.10 (br s, 2H), 3.06 (br s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 160.1, 147.9, 145.4, 136.1, 134.2, 129.2, 128.8, 127.1, 124.8, 122.9, 120.9, 120.6, 118.3, 114.8, 114.5, 113.3, 111.3, 111.3, 111.0, 110.39, 54.2, 53.1, 25.5, 23.1. HRMS (ESI) *m/z* calcd for $C_{25}H_{21}N_4ClBr$ $(M+1)^+$ 491.0638, found 491.0646. *Compound* **26b** was a tan solid (5%). Mp 208–212 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.76 (s, 2H), 7.75 (t, J = 4.3 Hz, 1H), 7.69 (br s, 1H), 7.63 (m, 1H), 7.44 (t, J = 4.7, 1H), 7.36 (dd, J = 8.3, 5.3 Hz, 1H), 7.31 (dd, J = 7.9, 4.8 Hz, 1H), 7.25 (m, 1H), 7.11 (br s, 1H), 7.05 (m, 1H), 6.96 (m, 1H), 3.80 (m, 2H), 3.60 (m, 2H), 3.08 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 161.3, 144.2, 136.2, 134.3, 131.5, 129.4, 127.3, 127.0, 124.8, 122.5, 120.8, 118.5, 118.2, 116.9, 114.1, 113.3, 112.1, 111.3, 111.2, 104.9, 52.3, 51.3, 25.6, 23.6. HRMS (ESI) *m/z* calcd for $C_{25}H_{21}N_4BrI$ $(M+1)^+$ 582.9994, found 583.0003.

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Supplementary data

Supplementary data (all additional experimental details including methods for the kinase inhibition determination, NMR spectra and HPLC purity data) associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2009.03.046.

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