

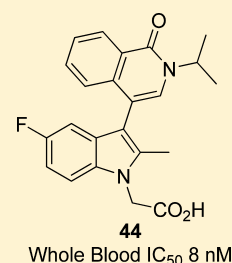
Discovery of Isoquinolinone Indole Acetic Acids as Antagonists of Chemoattractant Receptor Homologous Molecule Expressed on Th2 Cells (CRTH2) for the Treatment of Allergic Inflammatory Diseases

Neelu Kaila,* Bruce Follows, Louis Leung, Jennifer Thomason, Adrian Huang, Alessandro Moretto, Kristin Janz, Michael Lowe, Tarek S. Mansour, Cedric Hubeau, Karen Page, Paul Morgan, Susan Fish, Xin Xu, Cara Williams, and Eddine Saiah

Pfizer Research and Development, Cambridge, Massachusetts 02140, United States

S Supporting Information

ABSTRACT: Previously we reported the discovery of CRA-898 (**1**), a diazine indole acetic acid containing CRTH2 antagonist. This compound had good in vitro and in vivo potency, low rates of metabolism, moderate permeability, and good oral bioavailability in rodents. However, it showed low oral exposure in nonrodent safety species (dogs and monkeys). In the current paper, we wish to report our efforts to understand and improve the poor PK in nonrodents and development of a new isoquinolinone subseries that led to identification of a new development candidate, CRA-680 (**44**). This compound was efficacious in both a house dust mouse model of allergic lung inflammation (40 mg/kg qd) as well as a guinea pig allergen challenge model of lung inflammation (20 mg/kg bid).



INTRODUCTION

Arachidonic acid (AA) is released upon catalytic action of cytosolic phospholipase A2 (cPLA2) on membrane phospholipids, which in turn is initiated by activation of mast cells.^{1,2} Once the AA cascade is triggered, several metabolites are produced. PGD2 is a downstream metabolite and is a major prostanoid; it binds to three different receptors: thromboxane type prostanoid receptor (TP), the PGD2 receptor (DP), and the chemoattractant receptor homologous molecule expressed on Th2 cells (CRTH2). CRTH2 is a promiscuous receptor and in addition to PGD2 binds to several of its metabolites.³ It is a seven transmembrane Gi coupled receptor expressed on Th2 cells, eosinophils, basophils, and monocytes. Signaling through CRTH2 results in an inhibition of cAMP, resulting in T cell, eosinophil, basophil, and monocyte chemotaxis as well as stimulation of Th2 T cell cytokine production. Activation of CRTH2 contributes to Th2/eosinophilic type responses associated with allergy and asthma. A comparison of CRTH2 expression with chemotactic behavior of eosinophils in healthy and atopic individuals revealed higher mRNA and protein levels of CRTH2 in eosinophils from atopic subjects compared with those in healthy controls. In agreement with the increased number of CRTH2 receptors in eosinophils from atopic individuals, chemotaxis that is induced by PGD2 was significantly higher in these cells.⁴ There is also evidence that genetic alterations of CRTH2 are linked to the severity of allergic asthma.⁵ These findings indicate that higher levels of CRTH2 expression and increased responsiveness to its ligand PGD₂ might be the biological basis for its association with asthma.

CRTH2 antagonists have been moved to clinical trials for treatment of allergic rhinitis, asthma, and COPD.⁶ Recent clinical data has come from AstraZeneca (AZD1981), Oxagen

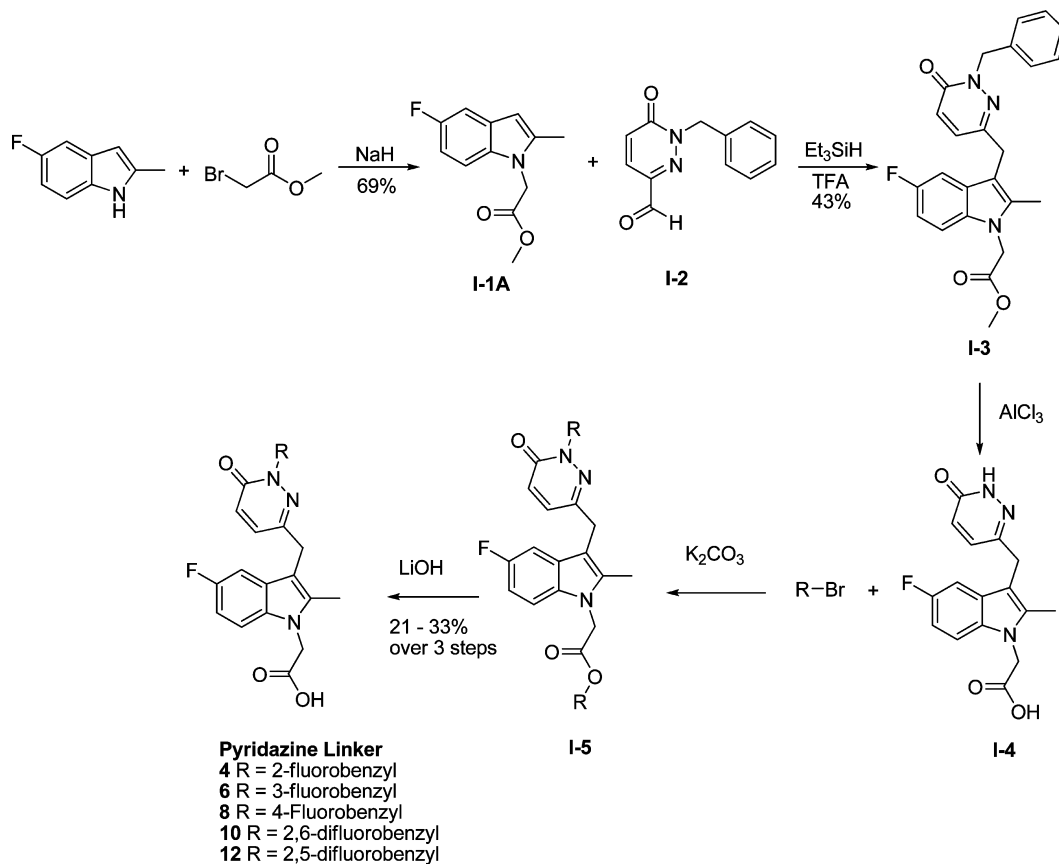
(OC000459), and Array Biopharma (ARRY-502). Although no beneficial effect was observed with AZD1981 in patients with moderate to severe COPD,⁷ clinical data from Oxagen looks promising. Their orally active CRTH2 antagonist, OC000459, when dosed at 200 mg twice daily for 16 days, showed a 25% reduction in the late asthmatic response area under the curve as measured by forced expiratory volume in 1 s (FEV1) to inhaled allergen change.⁸ Array BioPharma also observed positive results from a phase 2 trial; their oral CRTH2 antagonist, ARRY-502, improved FEV1 by 3.9% versus placebo in mild to moderate persistent allergic asthma when dosed at 200 mg twice daily for 4 weeks, achieving statistical significance ($P = 0.02$).⁹ These results have stimulated interest in discovering potent, selective, and orally active CRTH2 antagonists for the treatment of asthma.

Indomethacin was identified as a CRTH2 receptor agonist soon after the discovery of the CRTH2 receptor.¹⁰ After indomethacin was discovered, a number of bicyclic indole acetic acids and related analogues were disclosed as potent CRTH2 antagonists. Over the years, aryl acetic acid is a common pharmacophore for a large number of CRTH2 antagonists reported in literature.^{6,11} We recently reported discovery of a new class of CRTH2 antagonists, the pyridazine linker containing indole acetic acids.⁶ We had started from an initial phthalazinone indole acetic acid hit, which had good potency but poor permeability, metabolic stability, and PK. Optimization led to CRA-898 (**1**), a compound with good potency, low rates of metabolism, moderate permeability, and good oral bioavailability in rodents. It was efficacious in mouse models of contact hypersensitivity (1 mg/kg bid) and house dust allergen induced

Received: September 27, 2013

Published: February 10, 2014

Scheme 1. Synthesis of Pyridazine Linker Analogues



Scheme 2. Synthesis of {3-[(1-Benzyl-6-oxo-1,6-dihydropyridin-3-yl)methyl]-5-fluoro-2-methyl-1H-indol-1-yl}acetic Acid

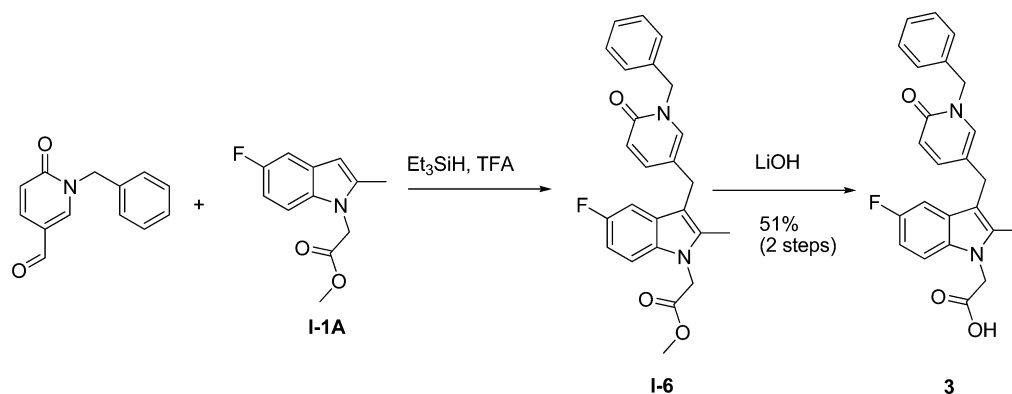


Table 1. PK Properties of Compound 1

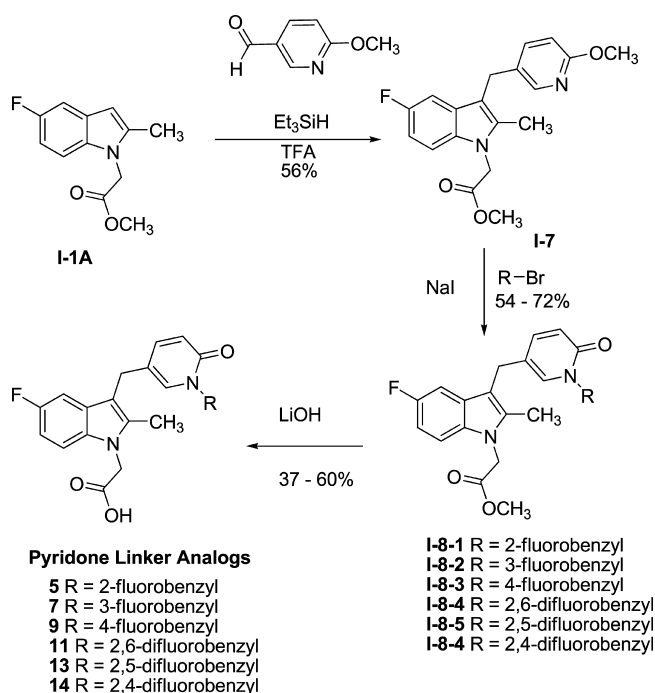
species	iv Cl ^a (mL/min/kg)	t _{1/2} ^a h	V _{ss} ^a (L/kg)	AUC _{0-inf} ^b (h·kg·ng/mL/mg)	C _{max} ^b (ng/mL)	bioavailability (%)
rat	12	3	1.6	5066	772	37
dog	20	2.3	0.4	678	716	8
monkey	21	2.3	0.4	1154	246	12

^aIntravenous dose, 2 mg/kg. ^bOral dose, 10 mg/kg.

lung inflammation (20 mg/kg qd) when dosed orally. However, compound 1 showed low oral exposure in nonrodent safety species (dogs and monkeys) (Table 1). In the current paper, we wish to report our efforts to understand and improve the poor PK in nonrodents and to describe the development of a new isoquinolinone subseries that led to identification of a new development candidate, 44.

CHEMISTRY

N-Benzyl Pyridazine Linker Analogues. The pyridazine linker compounds (4, 6, 8, 10, and 12, Scheme 1) were prepared by reductive alkylation of methyl 2-(5-fluoro-2-methyl-1H-indol-1-yl)acetate (I-1A) with 1-benzyl-6-oxo-1,6-dihydropyridin-3-carbaldehyde (I-2)⁶ using triethyl silane/TFA mixture as the reducing agent (Scheme 1).¹² The resulting intermediate I-3

Scheme 3. Synthesis of Substituted *N*-Benzyl Pyridone Linker Analogues

was debenzylated using aluminum chloride. In this reaction, the methyl ester was hydrolyzed as well. The resulting pyridazine carboxylic acid (**I-4**) was alkylated using substituted benzyl bromides to give the dibenzylated intermediates **I-5**. Base hydrolysis of benzyl esters gave the final products.

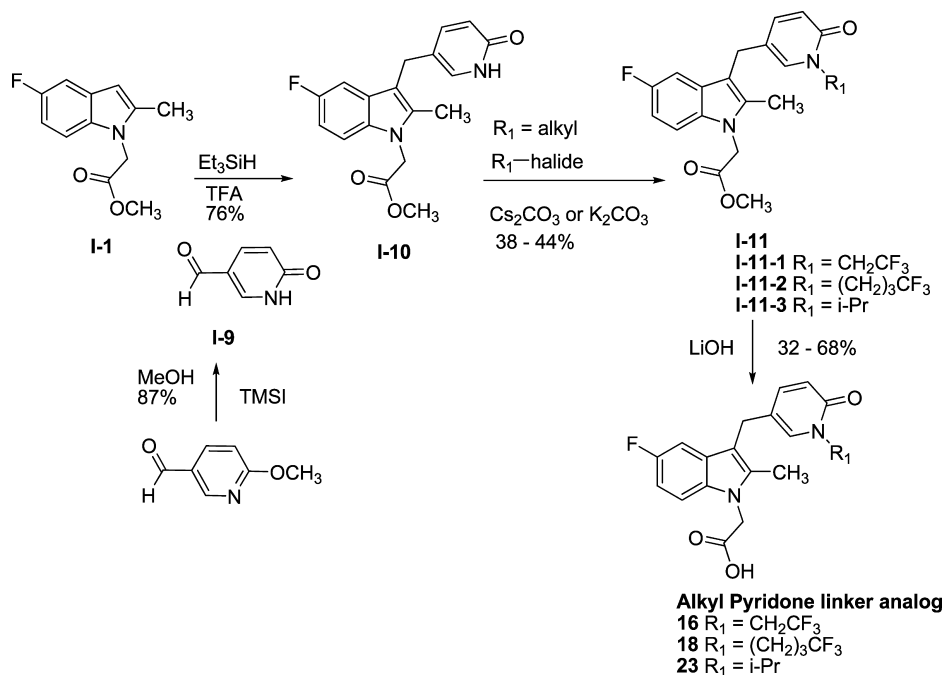
***N*-Benzyl Pyridone Linker Analogues.** To obtain the *N*-benzylated pyridone linker analogues, reductive alkylation was done either with 1-benzyl-6-oxo-1,6-dihydropyridine-3-carbaldehyde (Scheme 2) or 6-methoxy pyridine carbaldehyde (Scheme 3) to give intermediates **I-6** or **I-7**, respectively. The

N-benzyl pyridone linker analogue **3** was obtained by hydrolysis of **I-6** (Scheme 2). To obtain the substituted *N*-benzylated pyridone linker analogues (**5**, **7**, **9**, **11**, **13**, and **14**, Scheme 3), a procedure by Bowman et al.¹³ was used, **I-7** was reacted with benzyl bromides activated by sodium iodide, and the products (**I-8**) were hydrolyzed with base.

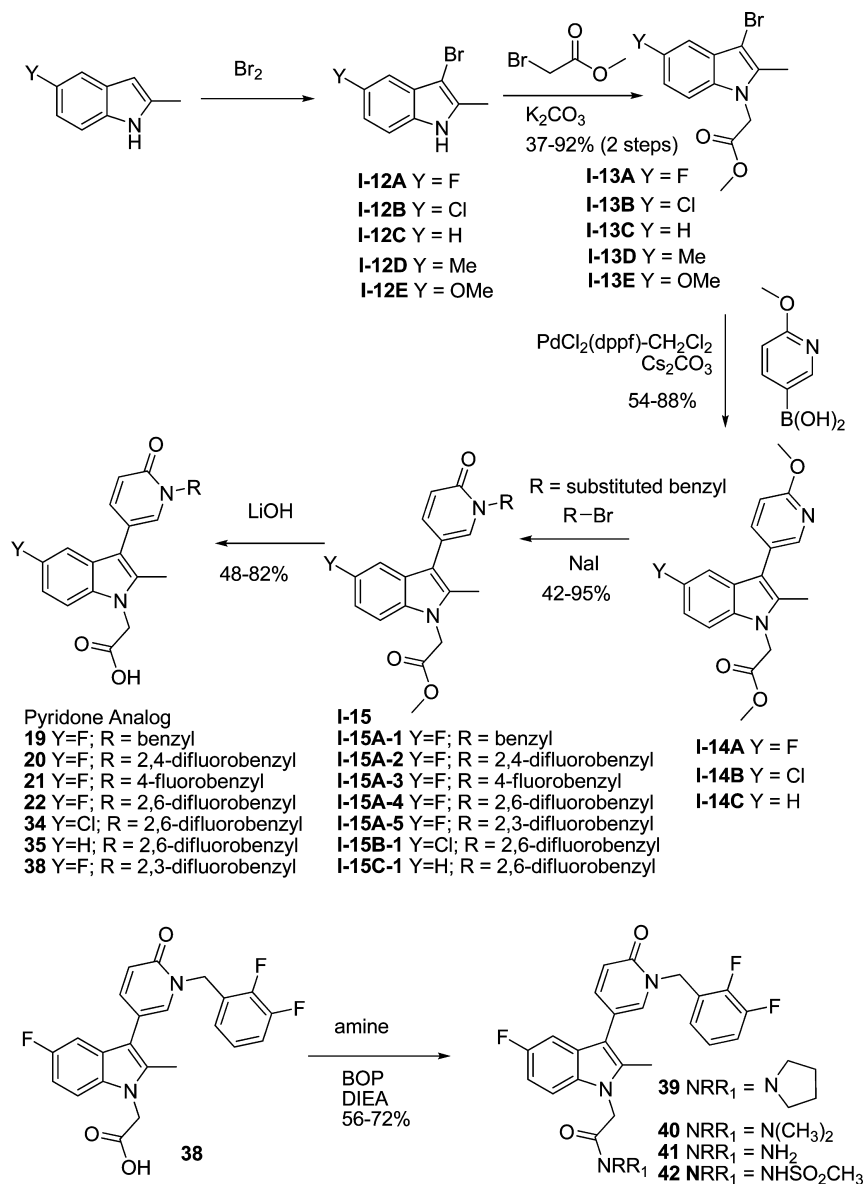
***N*-Alkyl Pyridone Linker Analogues.** Synthesis of the alkyl pyridone linker analogues was less straightforward (Scheme 4); alkylation of **I-7**, using alkyl halides, was not successful because the alkyl halides were not electrophilic enough to react with the pyridyl nitrogen. Therefore, the methoxy group was cleaved using TMSI, and the intermediate **I-9** thus obtained was reacted with **I-1A** to give **I-10**. Amide **I-10** was treated with alkyl halide and a base to give **I-11**. The latter were hydrolyzed to get the *N*-alkylated pyridone linker analogues (**16**, **18**, **23**). Small amounts of *O*-alkylated side products were also observed.

***N*-Benzyl Pyridones.** The direct linked *N*-benzylated pyridones (**19**–**22**, **34**, **35**, **38** Scheme 5) were prepared by benzylation of the methoxy pyridine **I-14** followed by hydrolysis of the methyl ester of intermediate **I-15**. Intermediates **I-14** were acquired by palladium mediated coupling of 3-bromo indoles (**I-13**) with 6-methoxypyridin-3-ylboronic acid. Intermediates **I-13** were obtained in 2 steps from 5-fluoro-2-methyl indole; first bromination, followed by reaction with methylbromo acetate. A similar Scheme 7 was followed to access **32** and **33**, except *tert*-butyl ester (**I-18**–**I-20**) was used as a protecting group instead of methyl ester because better yields were obtained with the former. The 2-methyl propionic acids (**43a** and **43b** Scheme 8) were prepared by benzylation of **I-22** followed by hydrolysis of the methyl ester **I-23**. **I-22** were acquired via **I-21** by following a procedure similar to Scheme 5.

***N*-Alkyl Pyridones.** To access the *N*-alkylated pyridones (**24**–**31**, and **36**, Scheme 6), the methyl ether in **I-14** was removed using acid and the product **I-16** was alkylated with alkyl bromides using potassium carbonate to give **I-17**, which was hydrolyzed to give the final products. A minor amount of *O*-alkylated analogue **37** was isolated alongside of *N*-alkylated

Scheme 4. Synthesis of *N*-Alkyl Pyridone Linker Analogues

Scheme 5. Synthesis of Substituted *N*-Benzyl Pyridone Analogues

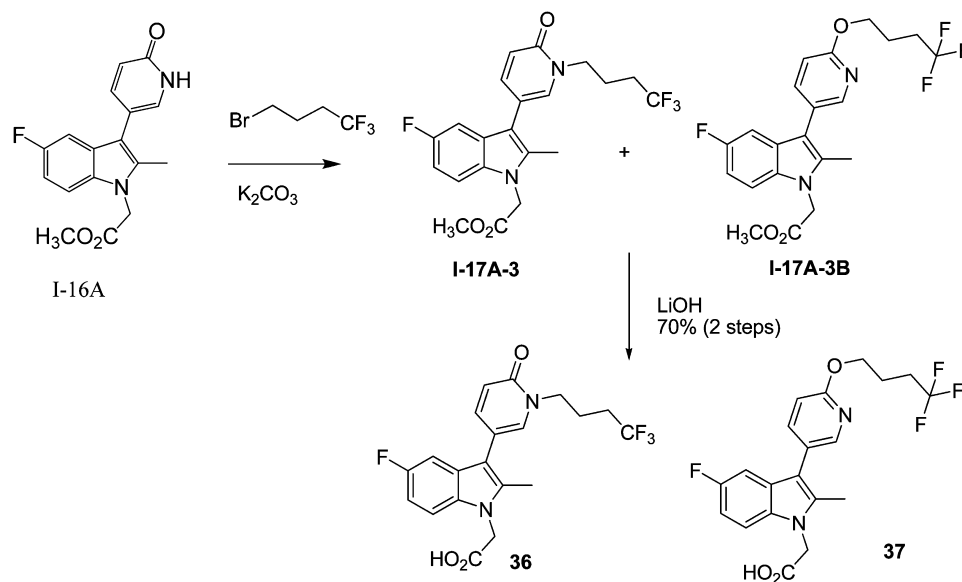
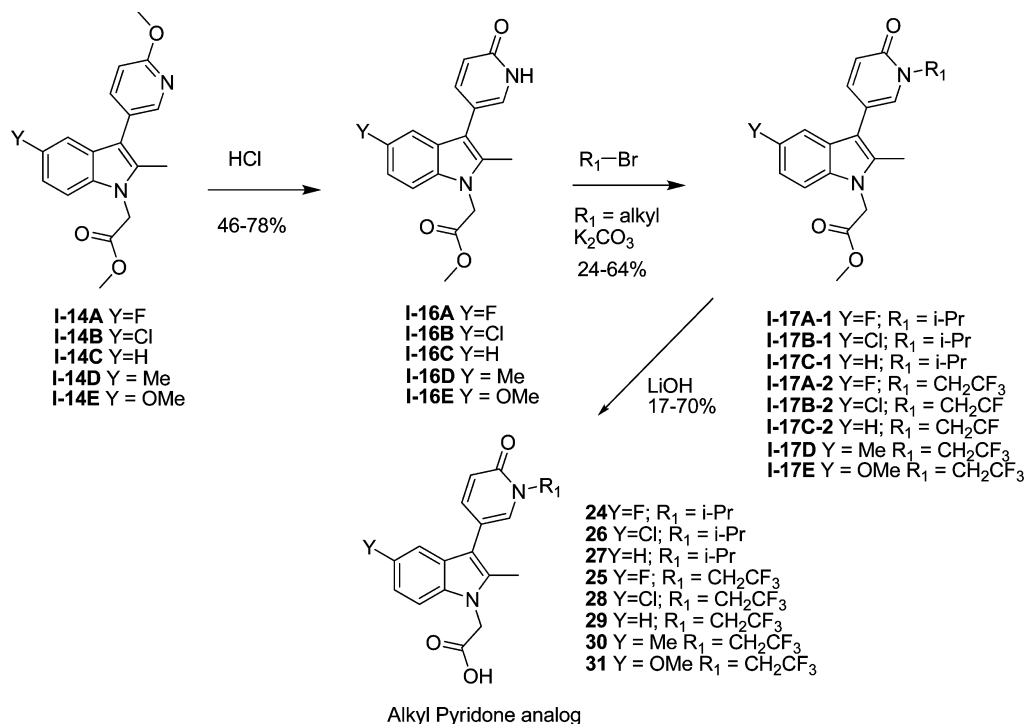


analogue **36**. The reaction conditions for synthesis of **I-16** required some optimization; conventional heating for 48 h gave moderate yield, and heating in the microwave improved the yields.

N-Benzyl Isoquinolinone. Initially, the synthesis of the isoquinolinone analogues was tried using the same approach taken for the synthesis of the pyridone analogues shown in Scheme 5. Following this sequence, 4-bromo-methoxyisoquinoline was converted to the pinacol boronic ester and subsequently coupled to 3-bromoindole in low but acceptable yields (28% and 45%, Scheme 9A). No reaction was observed, however, when the methoxyisoquinoline analogue was subjected to sodium iodide and benzylbromide. The ring system in this example seems to be more stable than the methoxypyridine (**I-14**) example described above in Scheme 5. In fact, when the methoxyisoquinoline was subjected to conditions typically used to cleave arylmethoxy groups, such as HBr in acetic acid, no reaction took place. Scheme 9B illustrates another unsuccessful attempt, where isoquinolinone-4-boronic acid (or its *N*-benzyl derivative) was directly coupled to the indole core. Unfortunately, these

couplings were unsuccessful, giving in most cases the reduced form of the indole ring as the major side product.

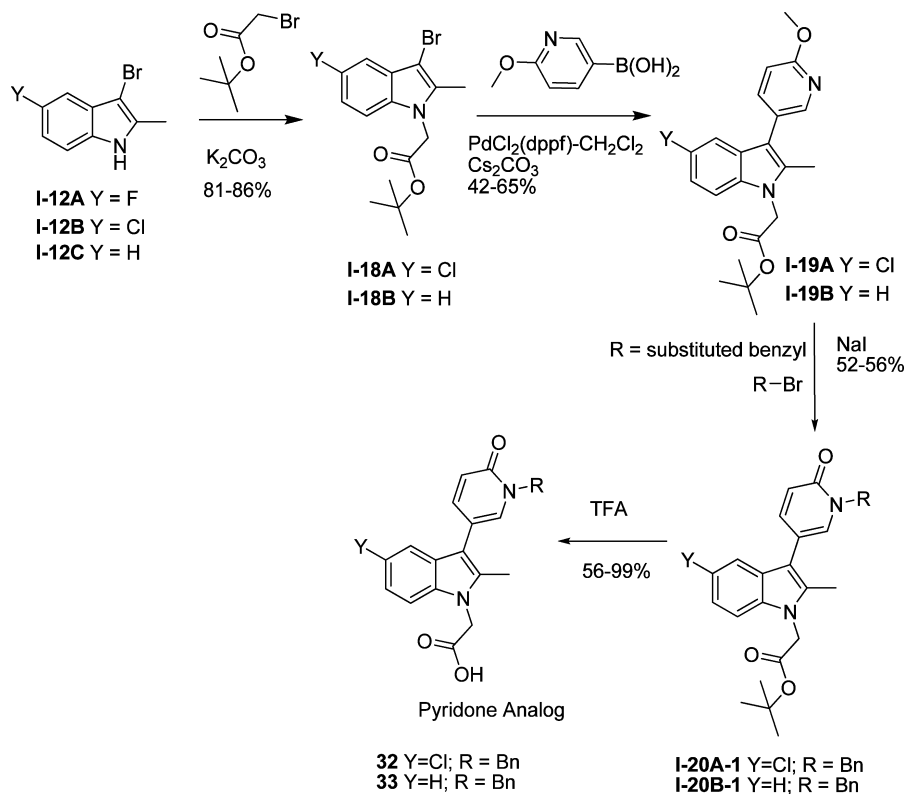
In a third approach to a synthetic route to the benzyl isoquinolinone (**48**), coupling of 3-boronic ester indole with 4-bromoquinolinone was tried (Scheme 9C). This route examined the effect of switching the boronic ester and the aryl halide components of the Suzuki reaction. The literature revealed that most of the Suzuki reactions with 3-boronic acid indoles require an electron withdrawing group at the indole nitrogen such as a sulfonamide. Using a sulfonamide protecting group on the nitrogen atom of the indole (Scheme 9C; step 1), the 3-bromoindole was converted to the 3-boronic ester indole, giving a separable mixture of the desired product and the reduced form of the indole as a side product (ratio 2:3). Unfortunately, coupling of the boronic ester with 4-bromo isoquinolinone did not give the desired product. On the basis of the observations above, we suspected that 4-bromoisquinolinone may be a poor partner in the Suzuki coupling reactions. The coupling described in Scheme 7 was different in that the halide coupling partner was aromatic. On the basis of this observation, a benzyl group

Scheme 6. Synthesis of *N*-Alkyl Pyridone Analogues

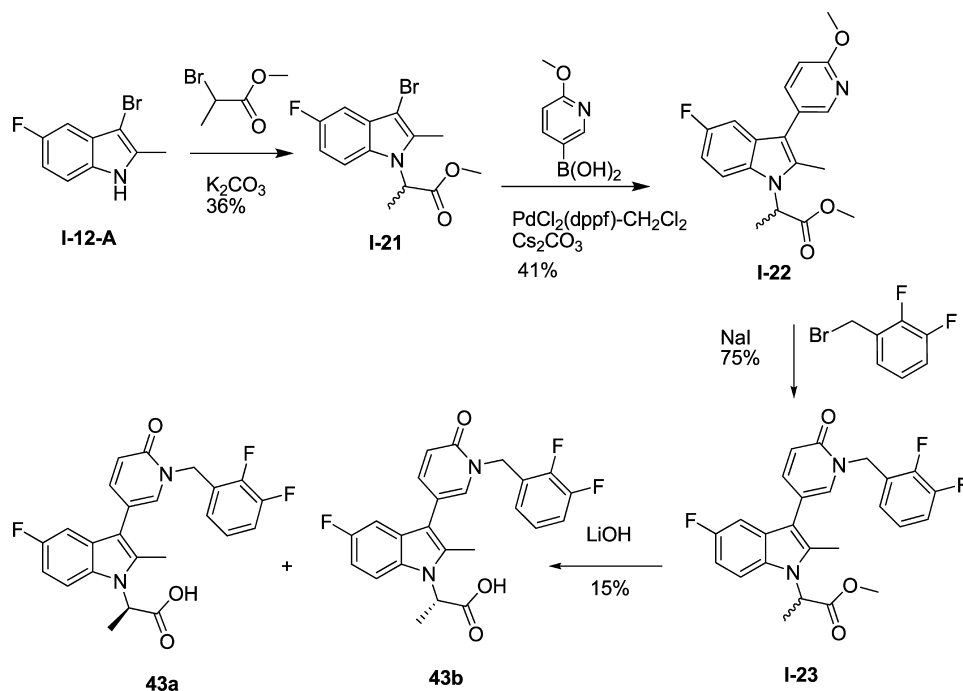
was used as a protecting group on the oxygen during the Suzuki coupling (Scheme 9D). The *O*-benzyl starting material was prepared via Mitsunobu reaction from 4-bromoisoquinolin-1(2*H*)-one.¹⁴ Coupling of the boronic ester with 3-bromoindole using PdCl₂(dppf)-CH₂Cl₂ provided the desired product in 56%, a much improved yield in the coupling step. A variety of conditions were tried to cleave benzyl groups, but none were successful. The entire sequence was also run using a PMB protecting group. Cleavage should have occurred easily with either DDQ or TFA, however, neither condition worked. Scheme 10A illustrates direct coupling of isoquinoline to the indole core, followed by a benzylation/oxidation protocol to convert the isoquinoline to an benzyloisoquinolinone as described in literature.¹⁵ The benzylation step proceeded as expected,

however, when the intermediate obtained from the benzylation was treated with the oxidant, K₃Fe(CN)₆, overoxidation took place to give unwanted side products. By changing the protecting group to BOC on the indole nitrogen, the oxidation step took place cleanly to afford the desired benzyloisoquinolinone product (**I-26**, Scheme 10B). In the last three steps of the route, the BOC group was cleaved with TFA and elaborated to the carboxylic side chain to give a 37% overall yield in the 5-step transformation.

***N*-Alkyl Isoquinolinones.** To access the *N*-alkyl isoquinolinone analogues (**44–47** Scheme 10C), the alkyl isoquinolinone boronic ester (**I-29**) was coupled with 3-iodo indole (**I-30**). **I-29** was prepared in 2 steps from 2-alkylisoquinolin-1(2*H*)-one (**I-27**) via the 4-iodo-2-alkylisoquinolin-1(2*H*)-one (**I-28**).

Scheme 7. Synthesis of *N*-Benzyl 5-Chloro- and 5-*H* Pyridones

Scheme 8. Synthesis of 2-Methyl Propionoc Acid Pyridone Analogues

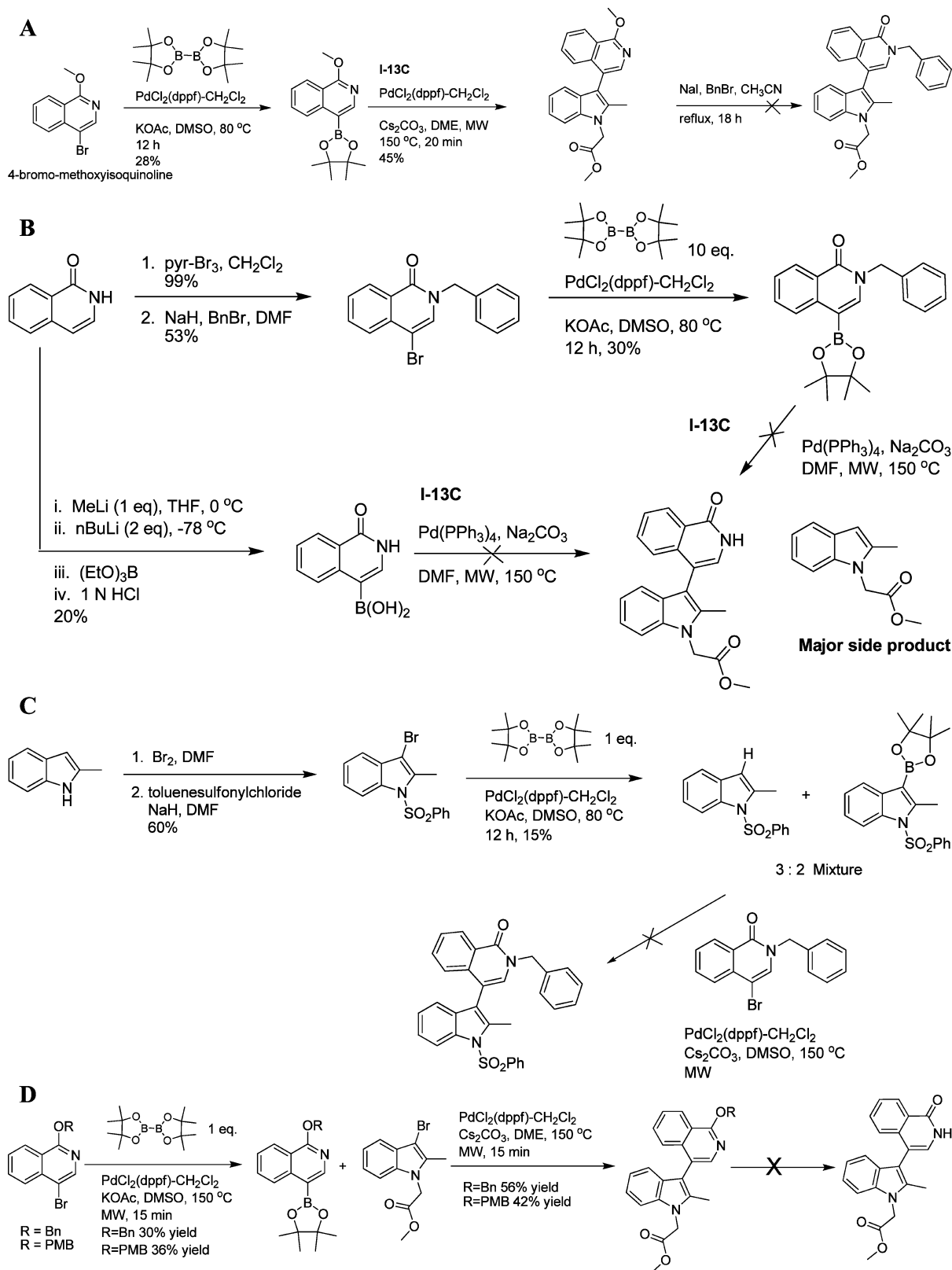


Saturated Isoquinolinones. The saturated isoquinolinones (Scheme 11) were synthesized using a similar approach as the alkyl isoquinolinones (Scheme 10C). The required boronic esters (**I-34**) were prepared in 3 steps (via **I-32** and **I-33**) from the tetrahydroisoquinolin-1(2*H*)-one **I-31**. The latter was prepared by platinum oxide reduction of the commercially available isoquinolin-1(2*H*)-one.¹⁶ Palladium catalyzed coupling

of **I-34** with indole **I-30**, followed by hydrolysis, gave final products (**49–52**).

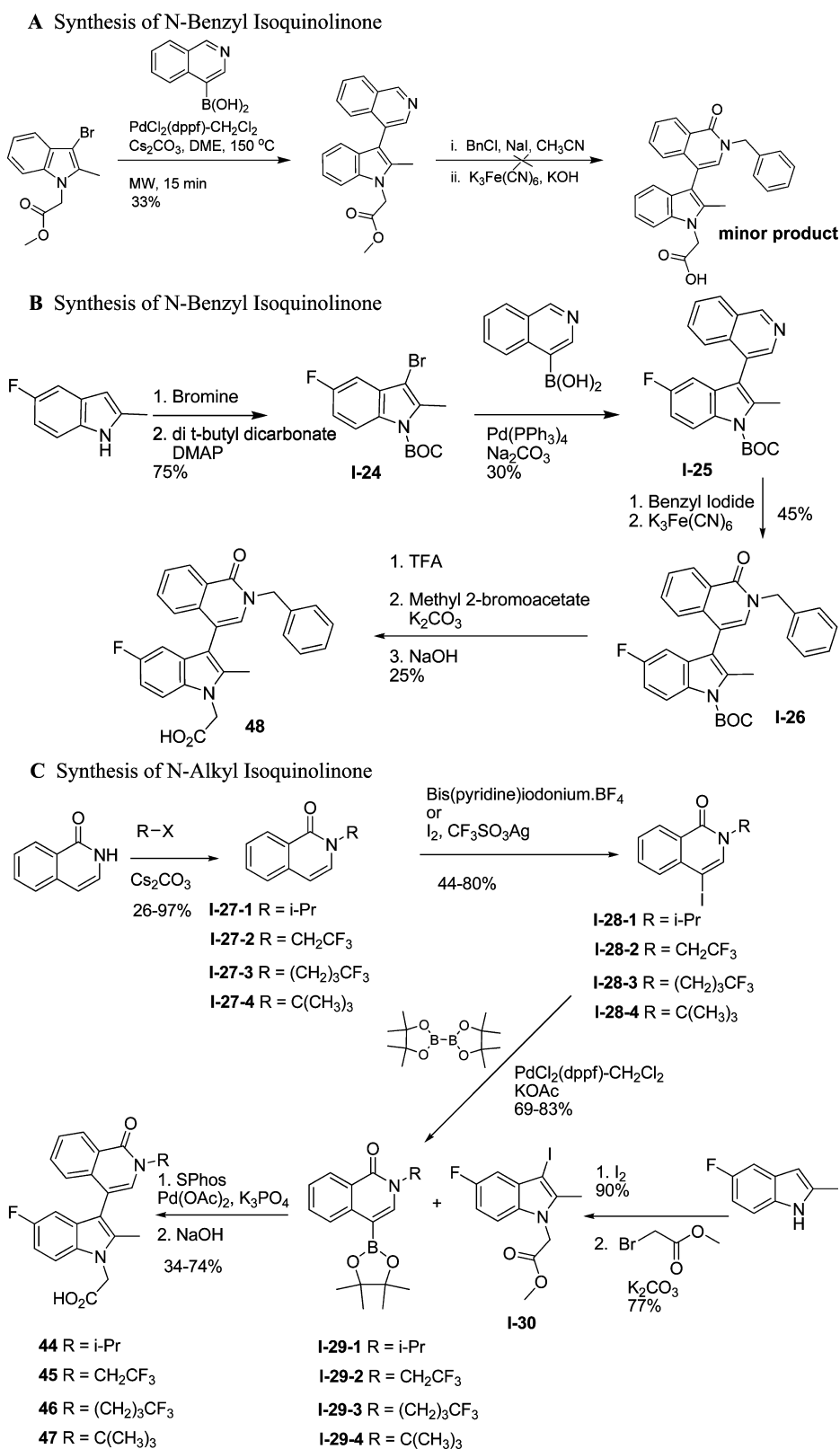
RESULTS AND DISCUSSION

Compound **1**, our first development track candidate, showed good potency in cell based, binding and whole blood assays. This compound exhibited a good PK profile in rodents and was

Scheme 9. Synthesis of *N*-Benzyl Isoquinolinone

efficacious in mouse models of contact hypersensitivity and house dust allergen induced lung inflammation when dosed orally. However, compound **1** showed low oral exposure in nonrodent safety species (dogs and monkey). PK properties of **1** in preclinical animal species are shown in Table 1. A large interspecies variability

was observed in plasma clearance (relative to hepatic blood flow) in preclinical animal species (dog > monkey > rat). This was an unexpected result because earlier studies with cryopreserved hepatocytes from each of the species had shown low intrinsic metabolic clearance (<5 $\mu\text{L}/\text{min}/10^6$ cells). Further studies were

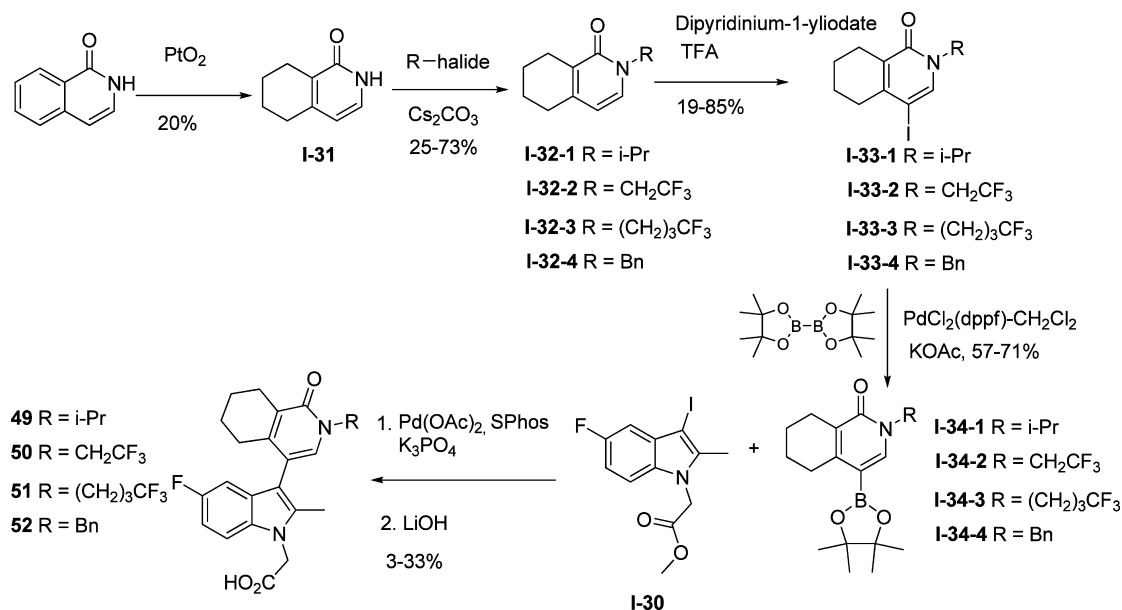
Scheme 10. (A) Synthesis of *N*-Benzyl Isoquinolinone, (B) Synthesis of *N*-Benzyl Isoquinolinone, (C) Synthesis of *N*-Alkyl Isoquinolinone

performed to examine alternative clearance pathways (e.g., renal, biliary) in addition to metabolic clearance.

Biliary excretion studies in bile duct cannulated rats showed that following a single iv dose of 5 mg/kg of **1**, the average plasma clearance was 14 mL/min/kg, with about 27% of the parent drug

recovered in bile and none in urine over a period of 24 h. These results suggest that metabolism is the major elimination pathway in rat with biliary excretion of unchanged drug a relatively modest clearance pathway. Nevertheless, a different picture was observed in dogs. A single intravenous dose of 5 mg/kg of **1** was administered,

Scheme 11. Synthesis of Saturated Isoquinolinone



and quantification of unchanged drug and drug-related products in urine and feces over a 24 h period was assessed by ¹⁹F-NMR and LC/MS. A majority of the administered dose (>90%) was recovered as unchanged drug in feces. These results suggest that in dogs, unlike rats, fecal excretion potentially via biliary excretion represents a major clearance pathway of **1**.

Additional experiments were conducted to further investigate the difference in biliary clearance observed in rats (low) and dogs (high). We reasoned that **1** may have different hepatobiliary uptake or efflux in different species. Permeability of **1** was measured in the Caco-2 cell line at reduced pH 6.5. Compound **1** exhibited reasonable permeability (P_{app} 7.1×10^{-6} cm/s) across Caco-2 monolayers, suggesting that the brush-border (microvilli) region of the jejunum segment of the small intestine (where the pH is slightly acidic) may be a predominant site of absorption. Results from initial studies using Caco-2 cell monolayers and selective P-gp (verapamil) or MRP2 (MK-571) inhibitors indicated that MRP2 and to a lesser extent P-gp was involved in the efflux of **1**.

Because MRP2 seemed to be largely responsible for the efflux of **1** in Caco-2 monolayers, membrane vesicles prepared from Sf9 cells expressing Mrp2/MRP2 from rats, dogs, monkeys, or humans were used to further assess potential species differences in biliary efflux of **1**. Figure 1 shows the uptake of **1** into inside-out membrane vesicles. The uptake in dog vesicles was found to be 3–4-fold higher than that in rat, monkey, and human, suggesting species differences in transporter-mediated efflux.

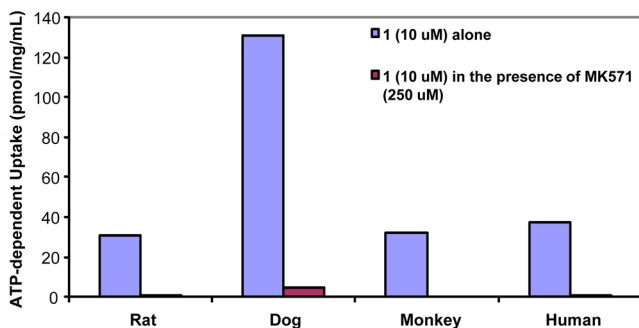


Figure 1. Uptake of **1** into Sf9 cells expressing Mrp2/MRP2.

To further characterize the hepatobiliary disposition of **1**, sandwich-cultured hepatocytes from rat and human were used as an in vitro model. Sandwich-cultured hepatocytes form functional bile canalicular networks and maintain the expression and function of key uptake and efflux transporters relative to hepatocytes in vivo. In rat, the in vitro intrinsic biliary clearance was determined to be low (<2.6 μ L/min/ μ g) and seemed to be consistent with the low in vivo biliary clearance (3.8 mL/min/kg). The in vitro intrinsic biliary clearance was also determined to be low (<1 μ L/min/ μ g) in human sandwich-cultured hepatocytes. However, it should be kept in mind that the use of sandwich-cultured hepatocytes to accurately predict biliary clearance in humans remains to be fully established. As a result, despite the low predicted human clearance, the decision was made to identify a different development candidate with improved PK properties in nonrodent species.

A cAMP cell based competitive immunoassay (hCRTH2 FRET) using Eu³⁺ cryptate-labeled anti-cAMP and d₂-labeled cAMP was used as a primary in vitro screen. Additionally, three secondary assays were used to evaluate compounds: (a) A basophil chemotaxis assay to examine CRTH2 mediated cell migration. This assay was run in a 96-transwell format with human CRTH2+ basophils, derived from IL-3 treated CD34+ progenitor cells, in the presence of 10 nM PGD₂. An initial set of compounds were tested in the chemotaxis assay, and a very good correlation was observed between the FRET and chemotaxis assays (Figure 2A). (b) A human CRTH2 competitive binding assay with tritium labeled PGD₂. A good correlation was observed between the binding assay and the FRET assay, confirming that the FRET potency was coming from direct binding to hCRTH2 (Figure 2B). Because a good correlation was established between the FRET versus chemotaxis and FRET versus binding assays, only selected compounds were tested in these assays. (c) A human whole blood eosinophil shape change assay (hEOS). Eosinophil shape change is a consequence of cytoskeleton reorganization and is a prerequisite for leukocyte movement, transmigration, and activation, and it can be quantified by flow cytometry through changes in forward light scatter. In this assay, human whole blood was stimulated with PGD₂ and analyzed by flow cytometry. Eosinophils were

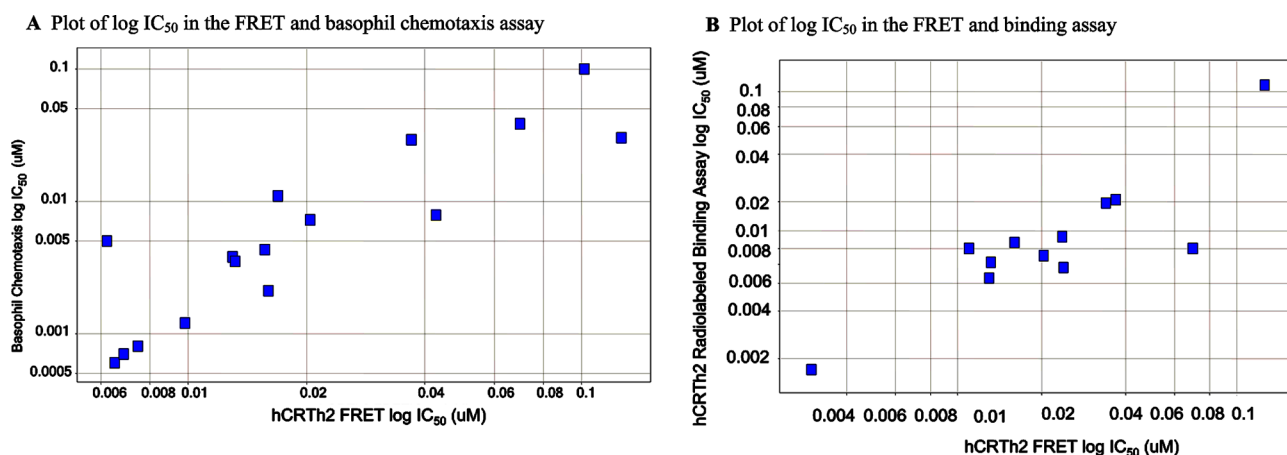


Figure 2. (A) Plot of log IC_{50} in the FRET and basophil chemotaxis assay. (B) Plot of log IC_{50} in the FRET and binding assay.

selected based on their autofluorescence in the FL2 channel. Shape change was estimated based on mean forward light scatter values. This assay was used as a secondary assay and could potentially be used as a biomarker in in vivo models and clinical trials. A good correlation was seen between the FRET and hEOS (free) assay (Figure 3). Potency in the FRET assay ($IC_{50} \leq 50$ nM) and good chemical properties were used as filters to advance compounds to the hEOS assay.

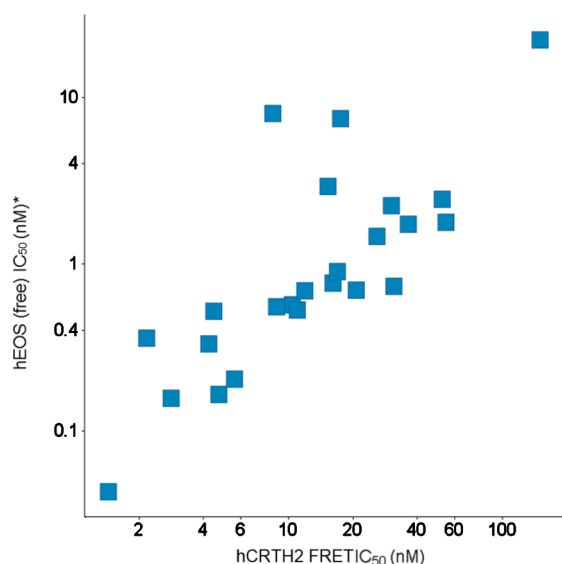
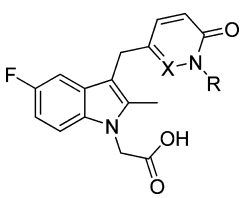


Figure 3. Plot of log IC_{50} in the FRET and hEOS (free) assay. *Calculated human plasma protein binding used to determine hEOS (free) values

Ligands for the receptors in the prostaglandin family show some degree of cross-reactivity, and there is potential for small molecule inhibitors to do the same. Therefore, selectivity of these compounds against two other prostaglandin receptors (DP1 and TXB2) was investigated using assays described previously.⁶ Representative examples from the series were tested and found to be greater than thousand-fold selective for CRTH2. Early compounds were also tested for affinity to the mouse CRTH2 receptor. A good correlation was seen between the human and murine CRTH2. This result is of importance for the feasibility of in vivo pharmacological studies in mouse models. Compounds were tested in these assays before advancing to in vivo models.

Our initial strategy to improve the permeability and oral bioavailability of the diazine class of compounds was to lower the TPSA. One of the nitrogen atoms in the diazine was replaced with carbon giving pyridine indoles. Table 2 shows comparison

Table 2. Potency in the FRET Assay for Diazine and Pyridone Indoles

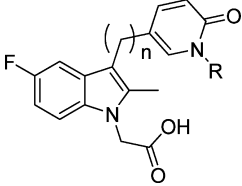


compd	X	R	FRET IC_{50} (nM)
2	N	Bn	10
3	CH	Bn	11
4	N	2-F	3
5	CH	2-F	8
6	N	3-F	8
7	CH	3-F	4
8	N	4-F	6
9	CH	4-F	3
10	N	2,6-diF	5
11	CH	2,6-diF	7
12	N	2,5-diF	2
13	CH	2,5-diF	8
1 (CRA-898)	N	2,4-DiF	2
14 ^a	CH	2,4-DiF	4
15	N	CH ₂ CF ₃	18
16	CH	CH ₂ CF ₃	52
17	N	(CH ₂) ₃ CF ₃	11
18	CH	(CH ₂) ₃ CF ₃	150

^aPK rat (iv 2 mg/kg, PO 10 mpk) Cl = 32 mL/min/kg; F = 4%.

of the diazine and pyridine indoles synthesized. In general, the *N*-benzyl pyridones showed improved IC_{50} s but comparable LipE to the diazine indoles. The *N*-alkyl pyridones showed loss in potency (**15** versus **16** and **17** versus **18**). Compound **14** was evaluated in in vivo rat pharmacokinetic studies. The compound had high clearance and poor bioavailability (Table 2). In an effort to address the high clearance of these compounds, the metabolically labile methylene group was removed. The direct linked pyridine compounds (Table 3) showed comparable potency to

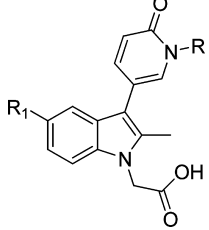
Table 3. Potency in the FRET Assay for Pyridone Indoles



compd	n	R	FRET IC ₅₀ (nM)
3	1	Bn	11
19 ^a	0	Bn	5
14	1	2,4-DiF	5
20	0	2,4-DiF	17
9	1	4-F	3
21	0	4-F	6
11	1	2,6-diF	7
22	0	2,6-diF	6
23	1	i-Pr	137
24	0	i-Pr	70
16 ^b	1	CH ₂ CF ₃	52
25	0	CH ₂ CF ₃	84

^aPK rat (iv 2 mg/kg, PO 10 mpk) Cl = 15 mL/min/kg; F < 10%. ^bPK rat (iv 2 mg/kg, PO 10 mpk) Cl = 7 mL/min/kg; F 20%.

Table 4. SAR at the 5-Position



compd	R ₁	R	FRET IC ₅₀ (nM)
26	Cl	i-Pr	195
24	F	i-Pr	70
27	H	i-Pr	556
28	Cl	CH ₂ CF ₃	148
25	F	CH ₂ CF ₃	84
29	H	CH ₂ CF ₃	711
30	Me	CH ₂ CF ₃	1120
31	OMe	CH ₂ CF ₃	2000
32	Cl	Bn	10
19	F	Bn	5
33	H	Bn	42
34	Cl	2,6-DiF	8
22	F	2,6-DiF	7
35	H	2,6-DiF	21

linker pyridines. The SAR of this series was further expanded. Substitution at the 5 position of the indole was studied for the *N*-alkyl and *N*-benzyl subseries (Table 4). Substituents at the 5-position had an important effect on activity. In both subseries, chloro (26) or fluoro (24) substitution at the 5 position improved potency. Polar groups like methoxy had a detrimental effect on activity (31).

Transferring the substituent from the nitrogen to the oxygen in the pyridone ring was not tolerated. Greater than 40-fold loss in potency was observed (Table 5). Conversion of the acid to amide (39), substituted amide (40 and 41), and aliphatic sulfonamide (42) all resulted in loss of potency. Likewise,

addition of a methyl group at the methylene next to the carboxylic acid reduced potency (43A, 43B).

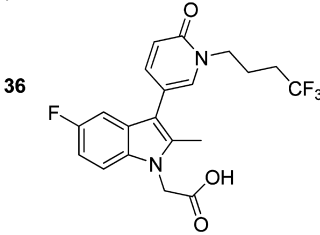
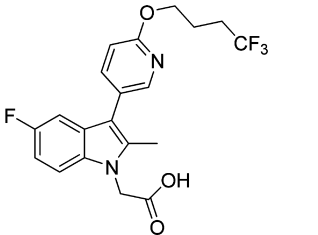
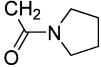
One of the pyridone analogues, 19, was taken forward for rat pharmacokinetic studies. The compound had moderate clearance and poor bioavailability (Table 3). So far, the *N*-benzyl pyridones had shown poor rat PK properties (14, 19), therefore we decided to select an *N*-alkyl pyridone (16) for evaluation in in vivo rat pharmacokinetic studies (Table 3). This compound showed low clearance and improved bioavailability. A quick calculation using an in-house model showed that the predicted kinetic solubility at pH 6.5 in PBS buffer for the alkyl pyridone (16, solubility = 240 µg/mL) was higher than the benzyl pyridones (19, solubility = 63 µg/mL; 14, solubility = 17 µg/mL), which could result in improved absorption leading to higher bioavailability observed with 16. Regrettably, thus far the alkyl pyridones had shown low potency (16, 18, 23–29). A plot of cLogP and FRET IC₅₀s (Figure 4) for the pyridones showed that the optimal range for clogP to achieve a potency less than 20 nM in the FRET assay is 3.5 and 5. We decided to pursue the isoquinolinone series to modulate the lipophilicity of the *N*-alkyl pyridones. The *N*-alkyl isoquinolinone (44–47) showed 10–20-fold improvement in potency against CRTH2 in the FRET assay with improved or comparable LipE (Table 6). The *N*-benzyl isoquinolinone (48) had similar potency but lower LipE compared to the pyridone. The good potency of the *N*-alkyl isoquinolinones was confirmed in the human whole blood hEOS assay, and these compounds were then advanced to in vivo studies. Additional ways to modulate the lipophilicity of this scaffold include saturating the ring adjacent to the isoquinoline ring. However, these compounds (49–52) showed loss in potency.

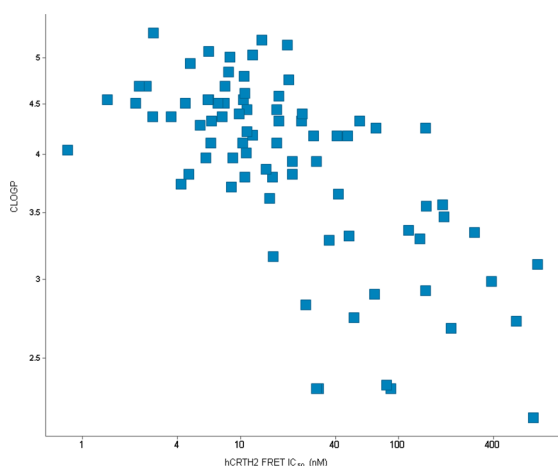
IN VIVO STUDIES

We utilized an oxazolone induced contact hypersensitivity (CHS) model in the mouse as a primary in vivo screen. In this model, mice were sensitized with oxazolone on their shaved abdomen and then challenged on day 5 by painting their ears with oxazolone. On the day of challenge, the test compound was administered and inhibition of ear swelling was determined as a measure of efficacy. A 40% reduction in ear swelling was observed with CRTH2 knockout mice. Selected compounds were tested in this model at 3 mg/kg po b.i.d. Figure 5 shows results for compounds 44–47. All compounds showed reduction in ear swelling in the oxazolone CHS model at 3 mg/kg po bid. Compound 47 was not taken further due to its physicochemical properties. Compounds 44, 45, and 46 were progressed into in vivo rat pharmacokinetic studies. To establish pharmacokinetic profiles, compounds were dosed intravenously in rats at 3 mg/kg and orally at 10 mg/kg. Compounds 44 (Table 7) and 45 (Cl = 20 mL/min/kg; F = 35%) showed moderate clearance and oral bioavailability, whereas compound 46 had moderate clearance (35 mL/min/kg) but poor oral bioavailability (<5%). Compound 45 had poor oral exposure in guinea pigs, and because our efficacy model was the guinea pig allergen induced pulmonary inflammation model, it would have been very challenging to dose compound 45. On the other hand, the po exposure in guinea pigs was acceptable for compound 44. Similarly, its PK profile was acceptable in dog and monkey (Table 7). Therefore, this compound was selected for evaluation in efficacy models.

First, we sought to evaluate the potential of compound 44 to modulate house dust mite (HDM)-induced allergic airway disease in mice (Figure 6). This model has been previously described⁶ and uses dexamethasone (Dex) intraperitoneally at 1 mg/kg (qd) as a positive control. Airway inflammation was almost completely abrogated with Dex. Compound 44 was

Table 5. SAR of the Pyridone Indoles

Compound	FRET IC ₅₀ (nM)	Compound	FRET IC ₅₀ (nM)
	16		689
Compound	R	R ₁	FRET IC ₅₀ (nM)
38	2,3 di-FBenzyl	CH ₂ CO ₂ H	0.8
39	2,3 di-FBenzyl	CH ₂ CONH ₂	> 2000
40	2,3 di-FBenzyl	CH ₂ CON(CH ₃) ₂	> 2000
41	2,3 di-FBenzyl		> 2000
42	2,3 di-FBenzyl	CH ₂ CO ₂ NHSO ₂ CH ₃	> 2000
43a	2,3 di-FBenzyl	(R)-CH(CH ₃)CO ₂ H	> 2000
43b	2,3 di-FBenzyl	(S)-CH(CH ₃)CO ₂ H	> 2000

Figure 4. Plot of cLogP versus FRET IC₅₀ (nM).

administered orally at 40 mg/kg (qd), and the eosinophilic component of HDM-induced allergic airway disease was significantly decreased. These anti-inflammatory effects of **44** treatment on airway neutrophilia were observed along with significantly decreased total BAL cellularity as well as significantly decreased BAL counts of eosinophils and lymphocytes. However, BAL macrophage numbers were unaffected by **44** treatment. Next, **44** was tested in a guinea pig allergen challenge model; guinea pig airway allergen challenge models have been used routinely in preclinical development of numerous molecules targeted towards asthma and are recognized to elicit robust allergic pulmonary inflammation that consists primarily of eosinophils. Guinea pigs were sensitized by IP injection with 100 μ g of ovalbumin (OVA) emulsified in 100 mg of alum on days 1 and 5. Animals were then challenged via the airways with an aerosol of 0.01% OVA for 60 min on day 15. Compound was dosed at 20 mg/kg bid 1 h prior to challenge and 6 h post

Table 6. SAR of Isoquinolinone Indoles

compd	R	FRET IC ₅₀ (nM)	LipE	compd	R ₁	FRET IC ₅₀ (nM)	LipE	hEOS IC ₅₀ (nM)	compd	R ₂	FRET IC ₅₀ (nM)
24	i-Pr	70	4.01	44	i-Pr	6	4.46	8	49	i-Pr	107
25	CH ₂ CF ₃	84	3.97	45	CH ₂ CF ₃	4	4.55	19	50	CH ₂ CF ₃	1000
36	(CH ₂) ₃ CF ₃	16	4.53	46	(CH ₂) ₃ CF ₃	1	4.41	3	51	(CH ₂) ₃ CF ₃	123
				47	CH ₂ C(CH ₃) ₃	3	4.04	18			
19	Bn	5	4.9	48	Bn	14	3.52		52	Bn	192

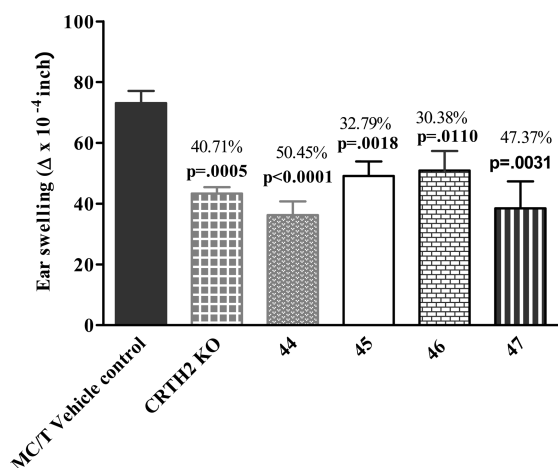


Figure 5. In vivo efficacy in CHS model.

challenge on day 15. Animals were sacrificed on day 16 and bronchoalveolar cavities lavaged with 2×10 mL of warm PBS. Total BAL cell counts and cell differentials were quantified as described previously.¹⁷ Compound **44** significantly attenuated total BAL cellularity, and BAL eosinophil, numbers 24 h post OVA challenge (Figure 7). The efficacious doses in the CHS, HDM, and OVA models were different; however, the exposures at these doses were within 2-fold (exposures were predicted based on pharmacokinetic studies).

To explore efficacy in a nonrodent species and to determine effects on lung function, **44** was evaluated in a sheep model

of *Ascaris* induced airway bronchoconstriction and AHR (Figure 8A).¹⁸ Compound **44**, when dosed at 3 mg/kg iv bid the day prior to challenge and then again 1 h prior to challenge, completely blocked the late phase allergic airway bronchoconstriction (LAR). The animals were also given a fourth dose of **44**, 8 h post challenge, to evaluate attenuation of airway hyper-responsiveness (AHR) to aerosolized carbachol that was measured the day following allergen challenge. Using this dosing regimen, **44** (3 mg/kg iv) completely blocked the allergen induced AHR to carbachol. **44** was also evaluated for efficacy following subchronic administration at 1 mg/kg iv qd for 7 days prior to challenge. Using this dosing regimen, the compound completely blocked the LAR and AHR. Following measurement of AHR, three bronchi from each sheep were lavaged and cell counts determined. **44** reduced BAL inflammation at this dose (Figure 8B).

Preliminary studies also point to a role for CRTH2 in driving impaired airway mucociliary clearance after allergen challenge. Tracheal mucus velocity (TMV), a marker of airway mucociliary clearance, was measured in sheep by a technique described previously.⁶ Administration of **44** at 3 mg/kg iv resulted in a more rapid return to baseline levels with a TMV of approx 70% of baseline at 4 h and a TMV of 98% of baseline at 8 h compared to an 8 h TMV of 47% of baseline with vehicle treated animals (Figure 8C). Five sheep were used for these studies.

Compound **44** was further profiled in safety and selectivity studies (Table 8). The potential for clinical metabolic drug–drug interactions was considered low based on in vitro CYP inhibition results (CYP1A2, 2A6, 2B6, 2C19, 2D6, and 3A4 IC₅₀s >100 μM, CYP2C9 IC₅₀ = 55 μM). Compound was clean in the AMES assay.

Table 7. PK Properties of **44**

species	iv CI ^a (mL/min/kg)	t _{1/2} ^a h	V _{ss} ^a (L/kg)	AUC _{0–inf} ^b (h·kg·ng/mL/mg)	C _{max} ^b (ng/mL)	bioavailability (%)
rat	18	2.7	1.2	1676	253	20
dog	5.6	3.4	0.7	9459	2011	32
monkey	6.1	4.1	0.95	19675	2967	69

^aIntravenous dose, 2 mg/kg. ^bOral dose, 10 mg/kg.

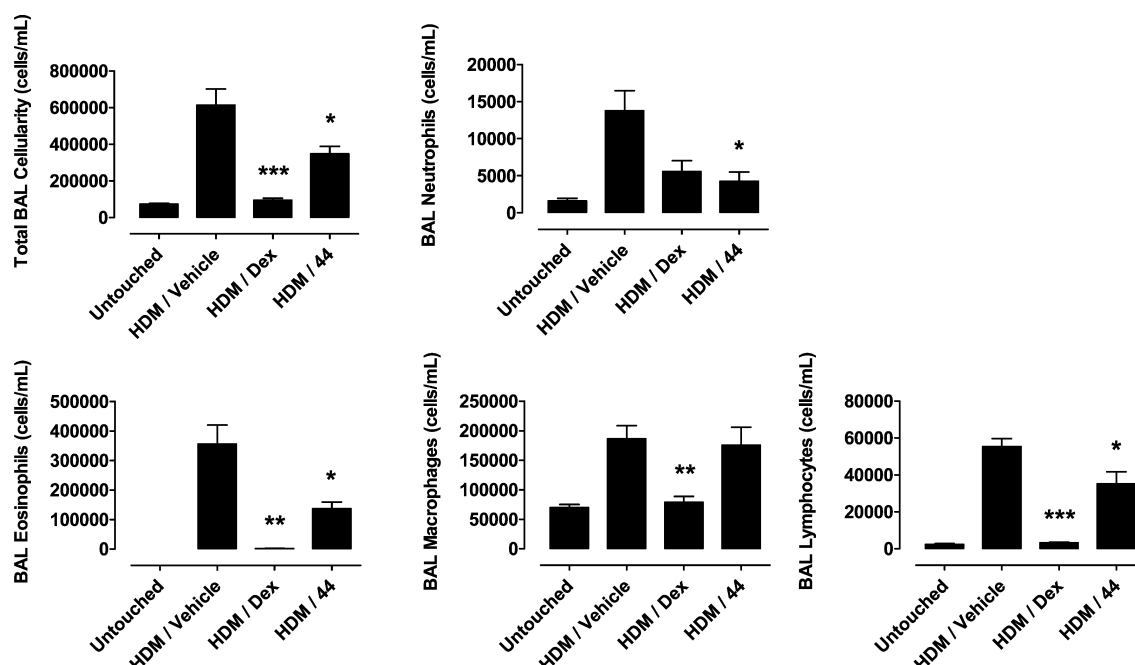


Figure 6. Modulation of HDM-induced allergic airway disease in BALB/c mice with **44** and dexamethasone (Dex). Total cellularity and eosinophil, macrophage, lymphocyte, and neutrophil cell numbers in BAL samples collected 72 h post-HDM challenge.

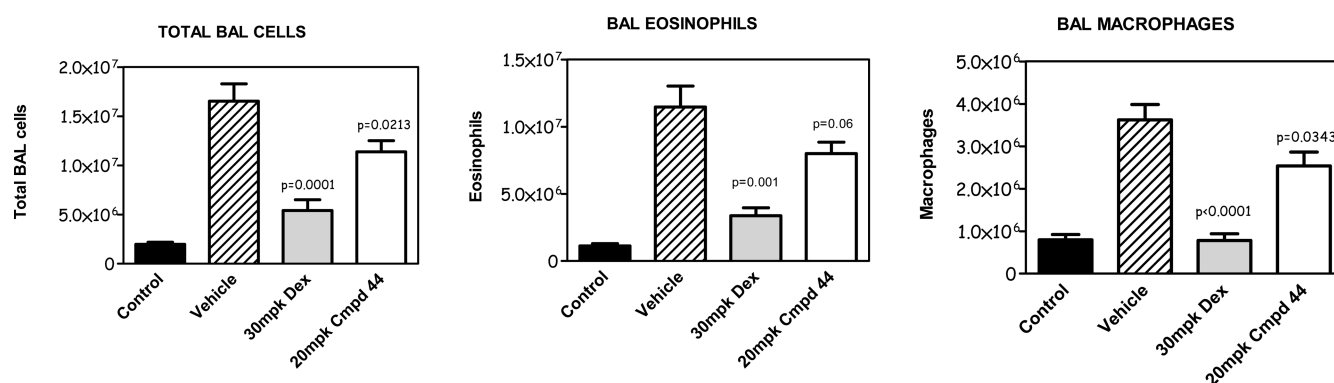


Figure 7. Modulation of OVA-induced allergic lung inflammation in the guinea pig: total cellularity and eosinophils, in BAL samples collected 24 h post-OVA challenge. Solid bars are OVA sensitized, PBS challenged animals; hatched bars are OVA sensitized OVA challenged animals that received vehicle orally 1 h prior to challenge and 6 h post challenge (1 mL of 0.5 Tween 80 in FlavoRX Cherry blast syrup) $N = 15$ animals; gray bars are animals that have been treated with dexamethasone orally at 30 mg/kg 1 h prior to challenge. $N = 9$ animals; open bars are animals that have been treated with compound **44** orally at 20 mg/kg 1 h prior to challenge and 6 h post challenge. $N = 14$ animals. P values as determined by student's unpaired t test compared with vehicle treated animals are provided above the relevant bars.

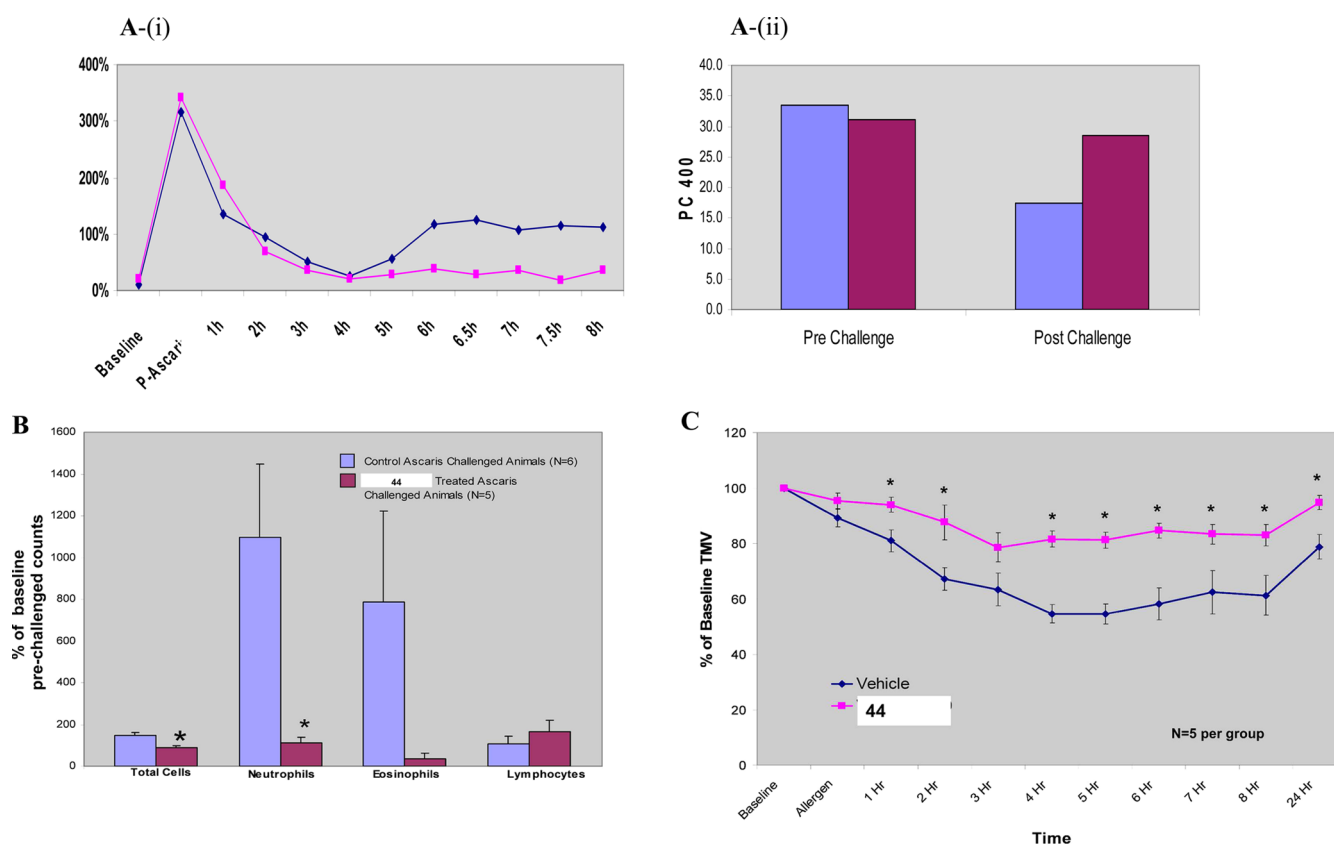


Figure 8. (A) Administration of compound **44** at 3 mg/kg iv in a sheep model of allergic airway bronchoconstriction and AHR. (i) While compound **44** (pink line) did not attenuate EAR as determined by increases in airway resistance above baseline, it completely ablated the *Ascaris suum* allergen induced LAR compared to untreated historical control values observed after allergen challenge in the same animals. (ii) Compound **44** blocks AHR to aerosolized carbachol (pink bar) as determined by an increase in PC400 values (the cumulative carbachol breath units that increased specific lung resistance by 400% (PC400) following allergen challenge compared to historical untreated control values in the same animals (blue bar). (B) Compound **44** attenuates *Ascaris* induced BAL fluid inflammation at 1 mg/kg iv qd for 7 days in sheep. (C) Reduction in mucociliary clearance in sheep with **44** at 3 mpk iv.

No hERG inhibition was seen at 33 μ M. Greater than 800-fold selectivity was seen against DP1 and TP receptors and in the Novascreen and nuclear receptor panel. On the basis of these results and in vivo efficacy, **44** (CRA-680) was advanced to development track.

In summary, we started with **1**, a compound with good in vitro and in vivo potency, good oral bioavailability in rodents, but low

oral exposure in nonrodent species (dogs and monkeys) (Table 1). Key medicinal chemistry optimization changes included decreasing polar surface area and eliminating metabolically labile methylene group. This led to a new development candidate **44** with comparable potency to **1**, moderate bioavailability in rats, and improved PK in dogs and monkeys (Table 7).

Table 8. Overall Profile of Compound 44

hCRTH ₂ FRET (IC ₅₀ nM)	hCRTH ₂ binding (IC ₅₀ nM)	basophil chemotaxis (IC ₅₀ nM)	hEOS (IC ₅₀ nM)	mCRTH ₂ binding (IC ₅₀ nM)	DP ₁ FRET (IC ₅₀ nM)	TXA ₂ binding (IC ₅₀ nM)	Caco2 permeability at (pH 6) cm/s
8	1.4	1.2	8	4	16000	>1000	2.7 × 10 ⁶

EXPERIMENTAL SECTION

Chemistry. Reactions were run using commercially available starting materials and solvents without further purification. Proton NMR spectra were recorded at 300 MHz on a Varian Gemini 2000 or at 400 MHz on a Bruker AV-400 spectrometer using TMS (δ 0.0) as a reference. The microwave procedures were carried out with a Biotage microwave. Preparative HPLC was run using a Waters reverse phase prep HPLC with Xterra C18 5 μ M, 30 mm × 100 mm column. The flow rate was 40 mL/min and mobile phase A was water, mobile phase B was CH₃CN, and triethylamine was used as a modifier. Purity in H₂O–CH₃CN was determined using an Agilent 1100 HPLC instrument, and all compounds analyzed were >95% pure.

Biology. All procedures performed on these animals were in accordance with regulations and established guidelines and were reviewed and approved by an Institutional Animal Care and Use Committee or through an ethical review process.

General Procedure A (Scheme 1). Methyl 2-(5-fluoro-2-methyl-1H-indol-1-yl)acetate (**I-1A**). In a 500 mL 2-necked round-bottomed flask, 5-fluoro-2-methylindole (5.00 g) was taken up with 100 mL anhydrous DMF, under nitrogen. NaH (1.69 g of a 60 wt % suspension in mineral oil, 1.01 g, 42.2 mmol) was added in small aliquots, and the mixture allowed to stir at room temperature for 30 min. Methyl bromoacetate (3.9 mL, 6.5 g, 42 mmol) was added all at once by syringe, and the reaction was allowed to stir overnight. It was then quenched by addition of 20 mL of brine, via syringe, and partitioned between 400 mL each ethyl acetate and brine. The aqueous layer was extracted with additional ethyl acetate (2×), and the combined organic extracts washed with brine (3×), dried over anhydrous magnesium sulfate, filtered, evaporated, and purified by flash chromatography over silica gel (2–20% ethyl acetate in hexanes) to give a white solid that gradually turned pink over several days (5.39 g, 69% yield).

Methyl 2-(3-((1-benzyl-6-oxo-1,6-dihydropyridazin-3-yl)methyl)-5-fluoro-2-methyl-1H-indol-1-yl)acetate (**I-3**). To a 250 mL round-bottom flask under an atmosphere of nitrogen was added **I-1A** (3.26 g, 14.77 mmol, 1.0 equiv), 1-benzyl-6-oxo-1,6-dihydropyridazine-3-carbaldehyde (**I-2**) (3.46g, 16.24 mmol, 1.1 equiv), and 100 mL of anhydrous methylene chloride. The resulting solution was cooled to 0 °C in an ice/water bath, and triethylsilane (8.26 mL, 51.69 mmol, 3.5 equiv) and trifluoroacetic acid (3.3 mL, 44.30 mmol, 3.0 equiv) were added dropwise. The mixture was allowed to warm to room temperature and then stirred for 24 h. The mixture was then poured into satd NaHCO_{3(aq)} and the aqueous layer extracted with two 50 mL portions of methylene chloride. The combined organic layers were then washed with water and brine and dried over magnesium sulfate. Filtration and removal of solvent in vacuo gave the crude material, which was then purified by silica gel chromatography to give a white solid (2.66g, 43%).

2-(5-Fluoro-2-methyl-3-((6-oxo-1,6-dihydropyridazin-3-yl)methyl)-1H-indol-1-yl)acetic acid (**I-4**). To a 5 mL microwave reaction vessel was added **I-3** (0.197g, 0.47 mmol, 1.0 equiv), aluminum trichloride (0.375g, 2.84 mmol, 6.0 equiv), and 5 mL of toluene. The vessel was sealed and the mixture heated to 140 °C in a microwave reactor for 1 h. The mixture was then poured into 50 mL of water and extracted with three 50 mL portions of ethyl acetate. The combined organic layers were washed with water and brine then dried over MgSO₄. Filtration and concentration in vacuo gave the crude product which was taken to the next step.

2-(3-((1-Substituted-6-oxo-1,6-dihydropyridazin-3-yl)methyl)-5-fluoro-2-methyl-1H-indol-1-yl)ester **I-5**. To a 100 mL round-bottom flask under a nitrogen atmosphere was added intermediate **I-4** (0.069 g, 0.22 mmol, 1.0 equiv), selected bromide (0.67 mmol, 3.0 equiv), potassium carbonate (0.123g, 0.89 mmol, 4.0 equiv), and 40 mL of DMF. The resulting suspension was heated to 85 °C for 16 h. The mixture was then allowed to cool to room temperature and then poured into 200 mL of water. This was extracted with three 50 mL portions of ethyl acetate. The combined organic

layers were washed with water and brine and dried over MgSO₄. Filtration and concentration in vacuo gave a tan solid. The crude material was purified by silica gel chromatography.

Pyridazine Linker Analogue. To a 50 mL round-bottom flask under an atmosphere of nitrogen was added **I-5** (0.06 mmol, 1.0 equiv) and 20 mL of methanol. To this was added 0.12 mL of 5.0 N NaOH. The resulting mixture was allowed to stir for 16 h at room temperature. Mixture was poured into 100 mL of 1.2 N HCl and extracted with three 50 mL portions of ethyl acetate. The combined organic layers were washed with water and brine and dried over MgSO₄. Filtration and concentration in vacuo gave crude material which was purified by reverse phase HPLC. The isolated material was then suspended in acetonitrile/water, frozen, and lyophilized to give the desired product (the yields have been reported over three steps).

3-([1-(2-Fluorobenzyl)-6-oxo-1,6-dihydropyridazin-3-yl]methyl)-5-fluoro-2-methyl-1H-indol-1-yl)acetic Acid (**4**). General procedure A was followed to make this compound in 33% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.03 (br s, 1H), 7.32–7.40 (m, 2H), 7.11–7.25 (m, 5H), 6.84–6.90 (m, 2H), 5.28 (s, 2H), 4.93 (s, 2H), 3.93 (s, 2H), 2.28 (s, 3H).

3-([1-(3-Fluorobenzyl)-6-oxo-1,6-dihydropyridazin-3-yl]methyl)-5-fluoro-2-methyl-1H-indol-1-yl)acetic Acid (**6**). General procedure A was followed to make this compound in 23.1% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.31–7.40 (m, 2H), 7.06–7.19 (m, 5H), 6.82–6.89 (m, 2H), 5.24 (s, 2H), 4.87 (s, 2H), 3.96 (s, 2H), 2.30 (s, 3H).

3-([1-(4-Fluorobenzyl)-6-oxo-1,6-dihydropyridazin-3-yl]methyl)-5-fluoro-2-methyl-1H-indol-1-yl)acetic Acid (**8**). General procedure A was followed to make this compound in 21.2% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.23–7.33 (m, 3H), 7.02–7.12 (m, 4H), 6.74–6.84 (m, 2H), 5.14 (s, 2H), 4.85 (s, 2H), 3.88 (s, 2H), 2.23 (s, 3H).

3-([1-(2,6-Difluorobenzyl)-6-oxo-1,6-dihydropyridazin-3-yl]methyl)-5-fluoro-2-methyl-1H-indol-1-yl)acetic Acid (**10**). General procedure A was followed to make this compound in 28% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.13 (br s, 1H), 7.52 (tt, *J* = 6.66, 8.37 Hz, 1H), 7.38 (dd, *J* = 4.42, 8.97 Hz, 1H), 7.12–7.22 (m, 3H), 7.09 (dd, *J* = 2.53, 9.85 Hz, 1H), 6.86–6.95 (m, 2H), 5.36 (s, 2H), 4.95 (s, 2H), 3.89 (s, 2H), 2.26 (s, 3H).

3-([1-(2,5-Difluorobenzyl)-6-oxo-1,6-dihydropyridazin-3-yl]methyl)-5-fluoro-2-methyl-1H-indol-1-yl)acetic Acid (**12**). General procedure A was followed to make this compound in 22% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.16–7.38 (m, 4H), 7.12 (dd, *J* = 2.53, 9.85 Hz, 1H), 7.02 (ddd, *J* = 3.28, 5.62, 8.78 Hz, 1H), 6.83–6.91 (m, 2H), 5.28 (s, 2H), 4.92 (s, 2H), 3.94 (s, 2H), 2.30 (s, 3H).

3-([1-(Benzyl-6-oxo-1,6-dihydropyridin-3-yl)methyl]-5-fluoro-2-methyl-1H-indol-1-yl)acetic Acid (**3**) (Scheme 2). The procedure described above for **I-3** was followed, reacting 1-benzyl-6-oxo-1,6-dihydropyridine-3-carbaldehyde¹⁹ with **I-1A** to give methyl 2-(3-((1-benzyl-6-oxo-1,6-dihydropyridin-3-yl)methyl)-5-fluoro-2-methyl-1H-indol-1-yl)acetate (**I-6**). To a 100 mL round-bottom flask was added intermediate **I-6** (0.335g, 0.80 mmol, 1.0 equiv) and 20 mL of THF. To this was added a solution of lithium hydroxide (0.096g, 4.0 mmol, 5.0 equiv) in 10 mL of water. To the resulting biphasic mixture was added methanol dropwise until a single layer formed. The resulting solution was stirred for 2 h at room temperature. It was then poured into 1.2 N HCl_(aq), and the aqueous layer was extracted with three 50 mL portions of ethyl acetate. The combined organic layers were washed with water and brine and dried over magnesium sulfate. Filtration and removal of solvent in vacuo gave the crude material. This was purified by reverse phase HPLC and the isolated product lyophilized to give a powder (0.161g, 51% yield.). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.74 (d, *J* = 2.02 Hz, 1H), 7.22–7.37 (m, 6H), 7.19 (td, *J* = 2.53, 9.35 Hz, 2H), 6.86 (td, *J* = 2.65, 9.28 Hz, 1H), 6.31 (d, *J* = 9.35 Hz, 1H), 5.05 (s, 2H), 4.92 (s, 2H), 3.72 (s, 2H), 2.30 (s, 3H).

General Procedure B (Scheme 3). Methyl 2-(5-fluoro-3-((6-methoxypyridin-3-yl)methyl)-2-methyl-1H-indol-1-yl)acetate (**I-7**).

I-1A (1.00 g, 4.52 mmol) was reacted with 6-methoxy-3-pyridinecarboxaldehyde (0.620 g, 4.52 mmol) using the procedure for intermediate **I-3** to give **I-7** (0.861 g, 56% yield).

Methyl 2-(3-((1-substituted benzyl-6-oxo-1,6-dihydropyridin-3-yl)methyl)-5-fluoro-2-methyl-1H-indol-1-yl)acetate **I-8**. Intermediate **I-7** (0.954 mmol) and sodium iodide (0.286 g, 1.91 mmol) were taken up in 10 mL of anhydrous acetonitrile, and selected bromide (1.9 mmol) was added. The mixture was refluxed overnight then poured into a mixture of 50 mL each brine and 5% sodium thiosulfate and extracted into ethyl acetate (2×). The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, evaporated, and purified by flash chromatography over silica gel.

Pyridone Linker Analogue. Intermediate **I-8** (0.513 mmol) was taken up in 15 mL of methanol and 5 mL of tetrahydrofuran. A solution of lithium hydroxide monohydrate (0.430 g, 10.3 mmol) in 5 mL of water was added, and the reaction stirred at room temperature for 55 min until LC-MS analysis showed complete hydrolysis of the ester. The reaction mixture was then acidified with concentrated hydrochloric acid, extracted into ethyl acetate (3×), washed with brine, dried over anhydrous magnesium sulfate, filtered, evaporated, and purified by preparative HPLC (water/acetonitrile with 0.1% formic acid).

2-(5-Fluoro-3-((1-(2-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)methyl)-2-methyl-1H-indol-1-yl)acetic Acid (5). Methyl 2-(5-fluoro-3-((1-(2-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)methyl)-2-methyl-1H-indol-1-yl)acetate (**I-8-1**). General procedure B was followed to make **I-8-1** from **I-7** and 2-fluorobenzyl bromide in 66% yield.

General procedure A was followed to make **5** from **I-8-1** in 39% yield. ¹H NMR (DMSO-*d*₆) δ 12.99 (br s, 1H), 7.67 (d, *J* = 2.0 Hz, 1H), 7.30–7.38 (m, 2H), 7.16–7.24 (m, 3H), 7.05–7.16 (m, 2H), 6.86 (td, *J* = 9.1, 2.5 Hz, 1H), 6.32 (d, *J* = 9.3 Hz, 1H), 5.09 (s, 2H), 4.94 (s, 2H), 3.74 (s, 2H), 2.30 (s, 3H).

2-(5-Fluoro-3-((1-(3-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)methyl)-2-methyl-1H-indol-1-yl)acetic Acid (7). Methyl 2-(5-fluoro-3-((1-(3-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)methyl)-2-methyl-1H-indol-1-yl)acetate (**I-8-2**). General procedure B was followed to make **I-8-2** from **I-7** and 3-fluorobenzyl bromide in 64% yield.

General procedure A was followed to make **7** from **I-8-2** in 39% yield. ¹H NMR (DMSO-*d*₆) δ 7.76 (d, *J* = 2.0 Hz, 1H), 7.31–7.40 (m, 2H), 7.19 (dd, *J* = 9.5, 2.7 Hz, 2H), 7.05–7.14 (m, 3H), 6.86 (td, *J* = 9.2, 2.5 Hz, 1H), 6.33 (d, *J* = 9.1 Hz, 1H), 5.06 (s, 2H), 4.94 (s, 2H), 3.73 (s, 2H), 2.31 (s, 3H).

2-(5-Fluoro-3-((1-(4-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)methyl)-2-methyl-1H-indol-1-yl)acetic Acid (9). Methyl 2-(5-fluoro-3-((1-(4-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)methyl)-2-methyl-1H-indol-1-yl)acetate (**I-8-3**). General procedure B was followed to make **I-8-3** from **I-7** and 4-fluorobenzyl bromide in 54% yield.

General procedure B was followed to make **9** from **I-8-3** in 55% yield. ¹H NMR (DMSO-*d*₆) δ 12.97 (br s, 1H), 7.73 (d, *J* = 2.0 Hz, 1H), 7.30–7.37 (m, 3H), 7.09–7.20 (m, 4H), 6.86 (td, *J* = 9.1, 2.5 Hz, 1H), 6.31 (d, *J* = 9.3 Hz, 1H), 5.03 (s, 2H), 4.93 (s, 2H), 3.72 (s, 2H), 2.30 (s, 3H).

2-(3-((1-(2,6-Difluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)methyl)-5-fluoro-2-methyl-1H-indol-1-yl)acetic Acid (11). Methyl 2-(3-((1-(2,6-difluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)methyl)-5-fluoro-2-methyl-1H-indol-1-yl)acetate (**I-8-4**). General procedure B was followed to make **I-8-4** from **I-7** and 2,6-difluorobenzyl bromide in 72% yield.

General procedure B was followed to make **11** from **I-8-4** in 60% yield. ¹H NMR (DMSO-*d*₆) δ 12.98 (br s, 1H), 7.56 (s, 1H), 7.40 (tt, *J* = 8.3, 6.6 Hz, 1H), 7.34 (dd, *J* = 8.8, 4.3 Hz, 1H), 7.16 (td, *J* = 9.3, 2.5 Hz, 2H), 7.01–7.09 (m, 2H), 6.86 (td, *J* = 9.2, 2.7 Hz, 1H), 6.25 (d, *J* = 9.3 Hz, 1H), 5.07 (s, 2H), 4.94 (s, 2H), 3.74 (s, 2H), 2.29 (s, 3H).

2-(3-((1-(2,5-Difluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)methyl)-5-fluoro-2-methyl-1H-indol-1-yl)acetic Acid (13). Methyl 2-(3-((1-(2,5-difluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)methyl)-5-fluoro-2-methyl-1H-indol-1-yl)acetate (**I-8-5**). General procedure B was followed to make **I-8-5** from **I-7** and 2,5-difluorobenzyl bromide in 68% yield.

General procedure B was followed to make **13** from **I-8-5** in 37% yield. ¹H NMR (DMSO-*d*₆) δ 13.27 (s, 1H), 7.69 (d, *J* = 1.8 Hz, 1H), 7.14–7.36 (m, 5H), 6.80–6.91 (m, 2H), 6.33 (d, *J* = 9.3 Hz, 1H), 5.07 (s, 2H), 4.90 (s, 2H), 3.74 (s, 2H), 2.31 (s, 3H).

2-(3-((1-(2,4-Difluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)methyl)-5-fluoro-2-methyl-1H-indol-1-yl)acetic Acid (14). Intermediate **I-8-6**. Methyl 2-(3-((1-(2,4-difluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)methyl)-5-fluoro-2-methyl-1H-indol-1-yl)acetate. General procedure B was followed to make **I-8-6** in 56% yield.

General procedure B was followed to make **14** from **I-8-6** in 44% yield. ¹H NMR (DMSO-*d*₆) δ 7.63 (d, *J* = 2.5 Hz, 1H), 7.16–7.29 (m, 4H), 7.13 (dd, *J* = 9.9, 2.5 Hz, 1H), 6.98–7.06 (m, *J* = 8.5, 8.5, 2.6, 0.9 Hz, 1H), 6.82 (td, *J* = 9.2, 2.5 Hz, 1H), 6.31 (d, *J* = 9.3 Hz, 1H), 5.05 (s, 2H), 4.70 (s, 2H), 3.72 (s, 2H), 2.29 (s, 3H).

General Procedure C (Scheme 4). 6-Oxo-1,6-dihydropyridine-3-carbaldehyde (**I-9**). In a flame-dried 250 mL 2-necked round-bottomed flask fitted with a condenser, 6-methoxy-3-pyridinecarboxaldehyde (3.43 g, 24.9 mmol) was taken up in 30 mL of anhydrous dichloromethane under nitrogen. Iodotrimethylsilane (5.0 g, 25 mmol) was added by syringe. The mixture was stirred at room temperature for 2.5 h then refluxed for 1.5 h. After cooling to room temperature, 4.1 mL of methanol was added by syringe. The solvent was evaporated, and the residue purified by flash chromatography over silica gel (7–60% acetone in dichloromethane) to give pure product (2.67 g, 87% yield).

Methyl 2-(5-fluoro-2-methyl-3-((6-oxo-1,6-dihydropyridin-3-yl)methyl)-1H-indol-1-yl)acetate (**I-10**). The procedure described above for **I-7** was followed, reacting **I-1A** (2.52 g, 11.4 mmol) with intermediate **I-9** (1.40 g, 11.4 mmol) in the presence of triethylsilane (5.1 mL, 3.7 g, 32 mmol) and trifluoroacetic acid (1.8 mL, 2.6 g, 23 mmol). Because of the relative insolubility of the product, the workup was modified as follows: the cooled reaction mixture was partitioned between saturated sodium bicarbonate and dichloromethane and the organic layer washed with water and evaporated (product was already starting to precipitate out, so drying over magnesium sulfate and filtering was concluded to be a bad idea). The crude product was purified by recrystallization from acetonitrile, collecting two crops of pure product (2.82 g, 76% yield).

Methyl 2-(3-((1-alkyl-6-oxo-1,6-dihydropyridin-3-yl)methyl)-5-fluoro-2-methyl-1H-indol-1-yl)acetate (**I-11**). In a 100 mL round-bottomed flask under nitrogen, **I-10** (1.75 mmol) and cesium carbonate or potassium carbonate (8.8 mmol) were taken up in 25 mL of anhydrous DMF and selected alkyl halide (8.8 mmol) was added. The mixture was heated to 55–85 °C until almost complete conversion to product had occurred. The cooled reaction mixture was poured into 250 mL of water and extracted into ethyl acetate; the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, evaporated, and purified by flash chromatography over silica gel to give pure product.

Alkyl Pyridone Linker Analogue. The procedure described above for pyridone linker analogue (in Scheme 4) was followed, reacting **I-11** (0.764 mmol) with lithium hydroxide monohydrate (0.642 g, 15.3 mmol). The crude product was purified by recrystallization.

2-(5-Fluoro-2-methyl-3-((6-oxo-1-(2,2,2-trifluoroethyl)-1,6-dihydropyridin-3-yl)methyl)-1H-indol-1-yl)acetic Acid (16). Methyl 2-(5-fluoro-2-methyl-3-((6-oxo-1-(2,2,2-trifluoroethyl)-1,6-dihydropyridin-3-yl)methyl)-1H-indol-1-yl)acetate (**I-11-1**). General procedure C was followed reacting **I-10** with and 1,1,1-trifluoro-2-iodoethane to make **I-11-1** in 44% yield.

2-(5-Fluoro-2-methyl-3-((6-oxo-1-(4,4,4-trifluorobutyl)-1,6-dihydropyridin-3-yl)methyl)-1H-indol-1-yl)acetic Acid (18). Methyl 2-(5-fluoro-2-methyl-3-((6-oxo-1-(4,4,4-trifluorobutyl)-1,6-dihydropyridin-3-yl)methyl)-1H-indol-1-yl)acetic acid (**I-11-2**). General procedure C was followed reacting **I-10** with 4-bromo-1,1,1-trifluorobutane to make **I-11-2** in 38% yield.

General procedure C was followed to make **18** from **I-11-2** in 40% yield. ¹H NMR (DMSO-*d*₆) δ 13.00 (br s, 1H), 7.62 (d, *J* = 2.0 Hz, 1H), 7.35 (dd, *J* = 9.0, 4.4 Hz, 1H), 7.22 (dd, *J* = 10.1, 2.5 Hz, 1H), 7.17 (dd, *J* = 9.3, 2.5 Hz, 1H), 6.86 (td, *J* = 9.1, 2.5 Hz, 1H), 6.29 (d, *J* = 9.3 Hz, 1H), 4.95 (s, 2H), 3.90 (t, *J* = 6.9 Hz, 2H), 3.73 (s, 2H), 2.32 (s, 3H), 2.16–2.31 (m, 2H), 1.84 (quin, *J* = 7.6 Hz, 2H).

2-(5-Fluoro-2-methyl-3-((6-oxo-1-(4,4,4-trifluorobutyl)-1,6-dihydropyridazin-3-yl)methyl)-1H-indol-1-yl)acetic Acid (15). The procedure described in Scheme 5A of ref 6 was followed to make this compound in 63% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.35 (dd, *J* = 4.29, 8.84 Hz, 1H), 7.23 (dd, *J* = 2.53, 9.85 Hz, 1H), 7.14 (d, *J* = 9.60 Hz, 1H),

6.88 (td, $J = 2.40, 9.16$ Hz, 1H), 6.81 (d, $J = 9.35$ Hz, 1H), 4.90 (s, 2H), 3.95 (s, 2H), 3.91 (s, 2H), 2.34 (s, 3H), 0.95 (s, 9H).

(5-Fluoro-2-methyl-3-[(6-oxo-1-(2,2,2-trifluoroethyl)-1,6-dihydropyridazin-3-yl)methyl]-1H-indol-1-yl)acetic Acid (**17**). The procedure described in Scheme 5A of ref 6 was followed to make this compound in 37% yield. ^1H NMR (400 MHz, DMSO- d_6) δ 7.27 (dd, $J = 4.55, 8.84$ Hz, 1H), 7.10–7.18 (m, 2H), 6.76–6.87 (m, 2H), 4.77–4.90 (m, 4H), 3.89 (s, 2H), 2.26 (s, 3H).

General Procedure D (Scheme 5). 3-bromo-5-halo-2-methyl-1H-indole (**I-12**). To a round-bottom flask containing 5-halo-2-methyl-1H-indole (15.3 mmol) in DMF (50 mL) was added bromine (0.8 mL, 15.3 mmol). The reaction was stirred at room temperature for 30 min and diluted with EtOAc (400 mL). The solution was washed with H_2O (3×250 mL), 0.1 M $\text{Na}_2\text{S}_2\text{O}_3$ (75 mL), and brine (75 mL). The organic layer was dried (MgSO_4) and filtered. The solvent was removed under reduced pressure to give the desired product.

Methyl 2-(3-bromo-5-halo-2-methyl-1H-indol-1-yl)acetate (**I-13**). To a round-bottom flask containing **I-12** (19 mmol), K_2CO_3 (10.5 g, 76 mmol) in DMF (250 mL) was added methylbromoacetate (3.5 mL, 38 mmol). The reaction was heated to 85 °C for 3 h and cooled to room temperature. The reaction was diluted with EtOAc (500 mL) and washed with H_2O (3×200 mL) and brine (100 mL). The organic layer was dried (MgSO_4) and filtered. The solvent was removed under reduced pressure to give the product.

Methyl 2-(5-halo-3-(6-methoxypyridin-3-yl)-2-methyl-1H-indol-1-yl)acetate (**I-14**). To a microwave vessel was added **I-13** (1.3 mmol), 6-methoxypyridin-3-ylboronic acid (0.47 g, 3.1 mmol), $\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$ (49 mg, 0.07 mmol), and Cs_2CO_3 (2.0 g, 6.1 mmol) in DME (10.3 mL). The contents were degassed with nitrogen and sealed. The reaction was heated at 150 °C for 20 min in the microwave. The reaction was diluted with EtOAc (250 mL) and washed with H_2O (3×100 mL). The organic layer was dried (MgSO_4) and filtered. The solvent was removed under reduced pressure, and the crude material was purified by silica gel column chromatography.

Methyl 2-(3-(1-substituted benzyl-6-oxo-1,6-dihydropyridin-3-yl)-5-halo-2-methyl-1H-indol-1-yl)acetate (**I-15**). To a flask containing **I-14** (1.1 mmol) in CH_3CN (6 mL) was added sodium iodide (321 mg, 2.1 mmol) and selected bromide (2.1 mmol). The reaction was heated to reflux for 15 h and cooled to room temperature. The contents of the reaction were poured into 0.1 M $\text{Na}_2\text{S}_2\text{O}_3$ (50 mL) and brine (25 mL) and extracted with EtOAc (3×50 mL). The organic layer was dried (MgSO_4) and filtered. The solvent was removed under reduced pressure, and the crude material was purified by silica gel column chromatography.

Pyridone Analogue. The method described for pyridone linker analogue in Scheme 4 was used. The crude material was purified by chromatography.

2-(3-(1-Benzyl-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-methyl-1H-indol-1-yl)acetic Acid (**19**). 3-Bromo-5-fluoro-2-methyl-1H-indole (**I-12A**). General procedure D was followed to give the desired product.

Methyl 2-(3-bromo-5-fluoro-2-methyl-1H-indol-1-yl)acetate (**I-13A**). General procedure D was followed to give **I-13A** from **I-12A** in 37% yield (2 steps).

Methyl 2-(5-fluoro-3-(6-methoxypyridin-3-yl)-2-methyl-1H-indol-1-yl)acetate (**I-14A**). General procedure D was followed to give **I-14A** from **I-13A** in 56% yield.

Methyl 2-(3-(1-benzyl-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-methyl-1H-indol-1-yl)acetate (**I-15A-1**). General procedure D was followed to give **I-15A-1** from **I-14A** and benzyl bromide in 95% yield.

General procedure D was followed to make **19** from **I-15A-1** in 48% yield. ^1H NMR (400 MHz, DMSO- d_6) δ 13.10 (br s, 1H), 7.84 (d, $J = 2.02$ Hz, 1H), 7.56 (dd, $J = 2.65, 9.22$ Hz, 1H), 7.45 (dd, $J = 4.29, 8.84$ Hz, 1H), 7.27–7.41 (m, 5H), 7.10 (dd, $J = 2.53, 9.85$ Hz, 1H), 6.95 (td, $J = 2.53, 9.09$ Hz, 1H), 6.55 (d, $J = 9.09$ Hz, 1H), 5.21 (s, 2H), 5.03 (s, 2H), 2.30 (s, 3H).

2-(3-(1-(2,4-Difluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-methyl-1H-indol-1-yl)acetic Acid (**20**). Methyl 2-(3-(1-(2,4-difluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-methyl-1H-indol-1-yl)acetate (**I-15A-2**). General procedure D was followed to make **I-15A-2** from **I-14A** and 2,4-difluorobenzyl bromide in 61% yield.

General procedure D was followed to make **20** from **I-15A-2** in 76% yield. ^1H NMR (400 MHz, DMSO- d_6) δ 7.74 (d, 1H), 7.57 (dd, $J = 2.65, 9.22$ Hz, 1H), 7.23–7.43 (m, 3H), 7.05–7.15 (m, 2H), 6.89 (td, $J = 2.53, 9.22$ Hz, 1H), 6.53 (d, $J = 9.35$ Hz, 1H), 5.21 (s, 2H), 4.56 (br s, 2H), 2.30 (s, 3H).

2-(5-Fluoro-3-(1-(4-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)-2-methyl-1H-indol-1-yl)acetic Acid (**21**). Methyl 2-(5-fluoro-3-(1-(4-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)-2-methyl-1H-indol-1-yl)acetate (**I-15A-3**). General procedure D was followed to make **I-15A-3** from **I-14A** and 4-fluorobenzyl bromide in 42% yield.

General procedure D was followed to make **21** from **I-15A-3** in 76% yield. ^1H NMR (400 MHz, DMSO- d_6) δ 7.88 (d, $J = 2.02$ Hz, 1H), 7.56 (dd, $J = 2.65, 9.22$ Hz, 1H), 7.43–7.50 (m, 3H), 7.17–7.22 (m, 2H), 7.12 (dd, $J = 2.27, 9.85$ Hz, 1H), 6.97 (td, $J = 2.65, 9.16$ Hz, 1H), 6.55 (d, 1H), 5.19 (s, 2H), 5.17 (s, 2H), 3.70 (s, 3H), 2.31 (s, 3H).

2-(3-(1-(2,6-Difluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-methyl-1H-indol-1-yl)acetic Acid (**22**). Methyl 2-(3-(1-(2,6-difluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-methyl-1H-indol-1-yl)acetate (**I-15A-4**). General procedure D was followed to make **I-15A-4** from **I-14A** and 2,6-difluorobenzyl bromide in 53% yield.

General procedure D was followed to make **22** from **I-15A-4** in 78% yield. ^1H NMR (400 MHz, DMSO- d_6) δ 13.16 (br s, 1H), 7.81 (s, 1H), 7.55 (dd, $J = 2.53, 9.35$ Hz, 1H), 7.37–7.51 (m, 2H), 7.07–7.19 (m, 3H), 6.97 (td, $J = 2.53, 9.09$ Hz, 1H), 6.46 (d, $J = 9.35$ Hz, 1H), 5.24 (s, 2H), 5.03 (s, 2H), 2.33 (s, 3H).

General Procedure E (Scheme 6). Methyl 2-(5-halo-2-methyl-3-(6-oxo-1,6-dihydropyridin-3-yl)-1H-indol-1-yl)acetate (**I-16**). To a microwave vessel was added **I-14** (2.25 mmol), MeOH (10 mL), and concentrated HCl (0.5 mL, 16.5 mmol). The reaction was heated at 125 °C for 60 min in the microwave. The solvent was removed under reduced pressure, and the crude material was purified by silica gel column chromatography.

Methyl 2-(5-halo-3-(1-alkyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methyl-1H-indol-1-yl)acetate **I-17**. To a microwave vessel was added **I-16** (1 mmol), potassium carbonate (0.7 g, 5 mmol), and DMF (12 mL). Then selected bromide (2 mmol) was added and the vessel sealed. The reaction was heated at 65 °C for 20 h on an oil bath. The reaction was diluted with EtOAc (100 mL) and washed with brine (3×100 mL). The organic layer was dried (MgSO_4) and filtered. The solvent was removed under reduced pressure, and the crude material was purified by silica gel column chromatography.

Alkyl Pyridone Analogue. The method described for pyridone linker analogue in Scheme 4 was used. The crude material was purified by HPLC.

2-(5-Fluoro-3-(1-isopropyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methyl-1H-indol-1-yl)acetic Acid (**24**). Methyl 2-(5-fluoro-2-methyl-3-(6-oxo-1,6-dihydropyridin-3-yl)-1H-indol-1-yl)acetate (**I-16A**). General procedure E was followed to make **I-16A** from **I-14A** in 75% yield.

Methyl 2-(5-fluoro-3-(1-isopropyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methyl-1H-indol-1-yl)acetate (**I-17A-1**). General procedure E was followed to make **I-17A-1** from **I-16A** and 2-bromo propane in 64% yield.

General procedure E was followed to make **24** from **I-17A-1** in 70% yield. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.33 (d, $J = 6.3$ Hz, 6H), 2.35 (s, 3H), 5.05 (s, 2H), 5.24–5.35 (m, 1H), 6.85 (d, $J = 8.3$ Hz, 1H), 6.97 (td, $J = 9.1, 2.5$ Hz, 1H), 7.16 (dd, $J = 9.9, 2.5$ Hz, 1H), 7.47 (dd, $J = 8.8, 4.5$ Hz, 1H), 7.75 (dd, $J = 8.5, 2.4$ Hz, 1H), 8.19 (d, $J = 2.5$ Hz, 1H), 13.11 (br s, 1H).

2-(5-Fluoro-2-methyl-3-(6-oxo-1-(2,2,2-trifluoroethyl)-1,6-dihydropyridin-3-yl)-1H-indol-1-yl)acetic Acid (**25**). Methyl 2-(5-fluoro-2-methyl-3-(6-oxo-1-(2,2,2-trifluoroethyl)-1,6-dihydropyridin-3-yl)-1H-indol-1-yl)acetate (**I-17A-2**). General procedure E was followed to make **I-17A-2** from **I-16A** in 24% yield.

General procedure E was followed to make **24** from **I-17A-2** in 70% yield. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 2.34 (s, 3H), 4.97 (q, $J = 9.3$ Hz, 2H), 5.05 (s, 2H), 6.61 (d, $J = 9.3$ Hz, 1H), 6.98 (td, $J = 9.2, 2.3$ Hz, 1H), 7.18 (dd, $J = 9.9, 2.5$ Hz, 1H), 7.47 (dd, $J = 9.0, 4.4$ Hz, 1H), 7.64 (dd, $J = 9.6, 2.5$ Hz, 1H), 7.75 (d, $J = 2.0$ Hz, 1H), 13.12 (s, 1H).

2-(5-Fluoro-3-(1-isopropyl-6-oxo-1,6-dihydropyridazin-3-yl)-2-methyl-1H-indol-1-yl)acetic Acid (**23**). Methyl 2-(5-fluoro-3-(1-isopropyl-6-oxo-1,6-dihydropyridin-3-yl)methyl)-2-methyl-1H-indol-1-yl)acetate (**I-11-3**). General procedure C was followed reacting **I-10**

with and 2-bromopropane to make **I-11-3**. Crude product was taken forward.

General procedure C was followed to make **23** from **I-11-3** in 68% yield. ^1H NMR (400 MHz, DMSO- d_6) δ 7.72 (d, J = 9.60 Hz, 1H), 7.49–7.55 (m, 2H), 7.43–7.48 (m, 2H), 6.97–7.06 (m, 2H), 5.22–5.30 (m, 1H), 5.09 (s, 2H), 1.36 (d, J = 6.57 Hz, 6H).

2-(5-Chloro-3-(1-isopropyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methyl-1H-indol-1-yl)acetic Acid (**26**). 3-Bromo-5-chloro-2-methyl-1H-indole (**I-12B**). Intermediate **I-12B** was prepared according to the method described for **I-12-A** and the crude product carried forward.

Methyl 2-(3-bromo-5-chloro-2-methyl-1H-indol-1-yl)acetate (**I-13B**). Intermediate **I-13B** was prepared according to the method described for intermediate **I-13A**. 63% yield (2 steps).

Methyl 2-(5-chloro-3-(6-methoxypyridin-3-yl)-2-methyl-1H-indol-1-yl)acetate (**I-14B**). Intermediate **I-14B** was prepared according to the method described for intermediate **I-14A**. 81% yield.

Methyl 2-(5-chloro-2-methyl-3-(6-oxo-1,6-dihydropyridin-3-yl)-1H-indol-1-yl)acetate (**I-16B**). Intermediate **I-16B** was prepared according to the method described for **I-16A**. 63% yield.

Methyl 2-(5-chloro-3-(1-isopropyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methyl-1H-indol-1-yl)acetate (**I-17B-1**). Intermediate **I-17B-1** was prepared according to the method described for intermediate **I-17A**. 62% yield.

The title compound was prepared according to the method described for **24**. 66% yield. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.34 (d, J = 6.1 Hz, 6H), 2.36 (s, 3H), 5.07 (s, 2H), 5.19–5.36 (m, 1H), 6.86 (d, J = 8.3 Hz, 1H), 7.14 (dd, J = 8.6, 2.0 Hz, 1H), 7.40 (d, J = 2.0 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.76 (dd, J = 8.3, 2.5 Hz, 1H), 8.19 (d, J = 2.5 Hz, 1H), 13.13 (s, 1H).

2-(3-(1-Isopropyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methyl-1H-indol-1-yl)acetic Acid (**27**). 3-Bromo-2-methyl-1H-indole (**I-12C**). Intermediate **I-12C** was prepared according to the method described for intermediate **I-12A**.

Methyl 2-(3-bromo-2-methyl-1H-indol-1-yl)acetate (**I-13C**). Intermediate **I-13C** was prepared according to the method described for intermediate **I-13A**. 80% yield. (2 steps).

Methyl 2-(3-(6-methoxypyridin-3-yl)-2-methyl-1H-indol-1-yl)acetate (**I-14C**). Intermediate **I-14C** was prepared according to the method described for intermediate **I-14A**. 88% yield.

Methyl 2-(2-methyl-3-(6-oxo-1,6-dihydropyridin-3-yl)-1H-indol-1-yl)acetate (**I-16C**). Intermediate **I-16C** was prepared according to the method described for intermediate **I-16A**. 75% yield.

Methyl 2-(3-(1-isopropyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methyl-1H-indol-1-yl)acetate (**I-17C-1**). Intermediate **I-17C-1** was prepared according to the method described for intermediate **I-17A**.

The title compound was prepared from **I-17C-1** according to the method described for **24**. 44% yield. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.34 (d, J = 6.3 Hz, 6H), 2.36 (s, 3H), 5.04 (s, 2H), 5.23–5.35 (m, 1H), 6.86 (d, J = 8.3 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1H), 7.13 (td, J = 7.6, 1.1 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H), 7.76 (dd, J = 8.6, 2.5 Hz, 1H), 8.20 (d, J = 2.5 Hz, 1H), 13.08 (br s, 1H).

2-(5-Chloro-2-methyl-3-(6-oxo-1-(2,2,2-trifluoroethyl)-1,6-dihydropyridin-3-yl)-1H-indol-1-yl)acetic Acid (**28**). Methyl 2-(5-chloro-2-methyl-3-(6-oxo-1-(2,2,2-trifluoroethyl)-1,6-dihydropyridin-3-yl)-1H-indol-1-yl)acetate (**I-17-B2**). Intermediate **I-17B-2** was prepared according to the method described for **I-17A**. 33% yield.

The title compound was prepared according to the method described for **24**. 58% yield. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 2.34 (s, 3H), 4.97 (q, J = 9.2 Hz, 2H), 5.06 (s, 2H), 6.61 (d, J = 9.3 Hz, 1H), 7.14 (dd, J = 8.6, 2.0 Hz, 1H), 7.43 (d, J = 2.3 Hz, 1H), 7.50 (d, J = 8.6 Hz, 1H), 7.64 (dd, J = 9.3, 2.5 Hz, 1H), 7.77 (d, J = 1.5 Hz, 1H), 13.14 (s, 1H).

2-(2-Methyl-3-(6-oxo-1-(2,2,2-trifluoroethyl)-1,6-dihydropyridin-3-yl)-1H-indol-1-yl)acetic Acid (**29**). Methyl 2-(2-methyl-3-(6-oxo-1-(2,2,2-trifluoroethyl)-1,6-dihydropyridin-3-yl)-1H-indol-1-yl)acetate (**I-17C-2**). Intermediate **I-17C-2** was prepared according to the method described for **I-17A**. 50% yield.

The title compound was prepared from **I-17C-2** according to the method described for **24**. 60% yield. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 2.35 (s, 3H), 4.97 (q, J = 9.3 Hz, 2H), 5.04 (s, 2H), 6.61 (d, J = 9.3 Hz, 1H), 7.06 (t, J = 7.6 Hz, 1H), 7.13 (t, J = 8.0 Hz, 1H), 7.44

(d, J = 8.6 Hz, 2H), 7.65 (dd, J = 9.5, 2.7 Hz, 1H), 7.74 (d, J = 2.3 Hz, 1H), 13.08 (br s, 1H).

2-(2,5-Dimethyl-3-(6-oxo-1-(2,2,2-trifluoroethyl)-1,6-dihydropyridin-3-yl)-1H-indol-1-yl)acetic Acid (**30**). 3-Bromo-2,5-dimethyl-1H-indole (**I-12D**). Intermediate **I-12D** was prepared according to the method described for **I-12A**.

Methyl 2-(3-bromo-2,5-dimethyl-1H-indol-1-yl)acetate (**I-12D**). Intermediate **I-12D** was prepared according to the method described for **I-13A**. Yield 76% (2 steps).

Methyl 2-(3-(6-methoxypyridin-3-yl)-2,5-dimethyl-1H-indol-1-yl)acetate (**I-14D**). Intermediate **I-14D** was prepared according to the method described for **I-14A**. Yield 66%.

Methyl 2-(2,5-dimethyl-3-(6-oxo-1,6-dihydropyridin-3-yl)-1H-indol-1-yl)acetate (**I-16D**). Intermediate **I-16D** was prepared according to the method described for **I-16A**. Yield 78%.

Methyl 2-(2,5-dimethyl-3-(6-oxo-1-(2,2,2-trifluoroethyl)-1,6-dihydropyridin-3-yl)-1H-indol-1-yl)acetate (**I-17D**). Intermediate **I-17D** was prepared according to the method described for intermediate **I-17A**. Yield 38%.

The title compound was prepared from **I-17A** according to the method described for **24**. Yield 72%. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 2.32 (s, 3H), 2.36 (s, 3H), 4.87–5.05 (m, 4H), 6.61 (d, J = 9.3 Hz, 1H), 6.95 (dd, J = 8.5, 1.4 Hz, 1H), 7.22 (s, 1H), 7.31 (d, J = 8.3 Hz, 1H), 7.64 (dd, J = 9.5, 2.7 Hz, 1H), 7.71 (d, J = 2.3 Hz, 1H), 13.02 (br s, 1H).

2-(5-Methoxy-2-methyl-3-(6-oxo-1-(2,2,2-trifluoroethyl)-1,6-dihydropyridin-3-yl)-1H-indol-1-yl)acetic Acid (**31**). 3-Bromo-5-methoxy-2-methyl-1H-indole (**I-12E**). Intermediate **I-12E** was prepared according to the method described for **I-12A**.

Methyl 2-(3-bromo-5-methoxy-2-methyl-1H-indol-1-yl)acetate (**I-13E**). Intermediate **I-13E** was prepared according to the method described for **I-13A**. Yield 92% (2 steps).

Methyl 2-(5-methoxy-3-(6-methoxypyridin-3-yl)-2-methyl-1H-indol-1-yl)acetate (**I-14E**). Intermediate **I-14E** was prepared according to the method described for **I-14A**. Yield 54%.

Methyl 2-(5-methoxy-2-methyl-3-(6-oxo-1,6-dihydropyridin-3-yl)-1H-indol-1-yl)acetate (**I-16E**). Intermediate **I-16E** was prepared according to the method described for intermediate **I-16D**. Yield 46%.

Methyl 2-(5-methoxy-2-methyl-3-(6-oxo-1-(2,2,2-trifluoroethyl)-1,6-dihydropyridin-3-yl)-1H-indol-1-yl)acetate (**I-17E**). Intermediate **I-17E** was prepared according to the method described for **I-17A**. The product was carried on to the next step without purification.

The title compound was prepared from **I-17E** according to the method described for **24**. Yield 17% for 2 steps. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 2.32 (s, 3H), 3.74 (s, 3H), 4.89–5.02 (m, 4H), 6.61 (d, J = 9.3 Hz, 1H), 6.77 (dd, J = 8.8, 2.3 Hz, 1H), 6.91 (d, J = 2.3 Hz, 1H), 7.34 (d, J = 8.6 Hz, 1H), 7.64 (dd, J = 9.5, 2.7 Hz, 1H), 7.73 (d, J = 2.5 Hz, 1H), 13.01 (br s, 1H).

2-(3-(1-Benzyl-6-oxo-1,6-dihydropyridin-3-yl)-5-chloro-2-methyl-1H-indol-1-yl)acetic Acid (**32**). *tert*-Butyl 2-(3-bromo-5-chloro-2-methyl-1H-indol-1-yl)acetate (**I-18A**). Intermediate **I-18A** was prepared according to the method described for **I-13A** reacting **I-12B** with *tert*-butyl bromo acetate. Yield 81% (2 steps).

tert-Butyl 2-(5-chloro-3-(6-methoxypyridin-3-yl)-2-methyl-1H-indol-1-yl)acetate (**I-19A**). Intermediate **I-19A** was prepared according to the method described for **I-14A**. Yield 42%.

tert-Butyl 2-(3-(1-benzyl-6-oxo-1,6-dihydropyridin-3-yl)-5-chloro-2-methyl-1H-indol-1-yl)acetate **I-20A-1**. Intermediate **I-20A-1** was prepared according to the method described for **I-15A**. Yield 52%.

The title compound was prepared according to this method. A round-bottom flask containing **I-20A-1** (0.7 mmol) was treated with TFA (4 mL) at room temperature for 30 min. The solution was concentrated under reduced pressure, and the crude material was purified by HPLC to give **32** in 99% yield. ^1H NMR (400 MHz, DMSO- d_6) δ 13.12 (br s, 1H), 7.86 (d, J = 2.02 Hz, 1H), 7.55 (dd, J = 2.53, 9.35 Hz, 1H), 7.48 (d, J = 8.59 Hz, 1H), 7.27–7.43 (m, 6H), 7.12 (dd, J = 2.15, 8.72 Hz, 1H), 6.55 (d, J = 9.35 Hz, 1H), 5.21 (s, 2H), 5.04 (s, 2H), 2.31 (s, 3H).

2-(3-(1-Benzyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methyl-1H-indol-1-yl)acetic Acid (**33**). *tert*-Butyl 2-(3-bromo-2-methyl-1H-indol-1-yl)acetate (**I-18B**). Intermediate **I-18B** was prepared according to the

method described for **I-13A** reacting **I-12C** with *tert*-butyl bromoacetate. Yield 86% (2 steps).

tert-Butyl 2-(3-(6-methoxypyridin-3-yl)-2-methyl-1*H*-indol-1-yl)-acetate (**I-19B**). Intermediate **I-19B** was prepared according to the method described for **I-14A**.

tert-Butyl 2-(3-(1-benzyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methyl-1*H*-indol-1-yl)acetate (**I-20B-1**). Intermediate **I-20B-1** was prepared according to the method described for **I-15A**. Yield 65%.

The title compound was prepared from **I-20B-1** according to the method described for **32** (Yield 56%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.15 (s, 1H), 7.81 (d, *J* = 2.53 Hz, 1H), 7.57 (dd, *J* = 2.53, 9.35 Hz, 1H), 7.34–7.44 (m, 6H), 7.31 (dd, *J* = 3.16, 5.43 Hz, 1H), 7.07–7.15 (m, 1H), 6.97–7.06 (m, 1H), 6.55 (d, *J* = 9.35 Hz, 1H), 5.21 (s, 2H), 4.96 (s, 2H), 2.31 (s, 3H).

2-(5-Chloro-3-(1-(2,6-difluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)-2-methyl-1*H*-indol-1-yl)acetic Acid (**34**). Methyl 2-(5-chloro-3-(1-(2,6-difluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)-2-methyl-1*H*-indol-1-yl)acetate (**I-15B-1**). General procedure D was followed to make **I-15B-1** from **I-14B**, and the product was carried on to the next step without purification.

General procedure D was followed to make **34** from **I-15B-1** in 63% yield for 2 steps. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.33 (s, 3 H), 5.05 (s, 2 H), 5.25 (s, 2 H), 6.47 (d, *J* = 9.3 Hz, 1 H), 7.07–7.17 (m, 3 H), 7.38 (d, *J* = 2.0 Hz, 1 H), 7.39–7.48 (m, 1 H), 7.49 (d, *J* = 8.3 Hz, 1 H), 7.55 (dd, *J* = 9.3, 2.5 Hz, 1 H), 7.82 (s, 1 H), 13.14 (br s, 1 H).

2-(3-(1-(2,6-Difluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)-2-methyl-1*H*-indol-1-yl)acetic Acid (**35**). Methyl 2-(3-(1-(2,6-difluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)-2-methyl-1*H*-indol-1-yl)-acetate (**I-15C-1**). General procedure D was followed to make **I-15C-1** from **I-15B** in 68% yield.

General procedure D was followed to make **35** from **I-15C-1** in 76% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.34 (s, 3 H), 5.02 (s, 2 H), 5.24 (s, 2 H), 6.47 (d, *J* = 9.3 Hz, 1 H), 7.05 (t, *J* = 7.5 Hz, 1 H), 7.08–7.18 (m, 3 H), 7.35–7.50 (m, 3 H), 7.56 (dd, *J* = 9.3, 2.5 Hz, 1 H), 7.78 (s, 1 H), 13.07 (br s, 1 H).

2-(5-Fluoro-2-methyl-3-(6-oxo-1-(4,4,4-trifluorobutyl)-1,6-dihydropyridin-3-yl)-1*H*-indol-1-yl)acetic Acid (**36**) and 2-(5-Fluoro-2-methyl-3-(6-(4,4,4-trifluorobutoxy)pyridin-3-yl)-1*H*-indol-1-yl)acetic Acid (**37**). Methyl 2-(5-fluoro-2-methyl-3-(6-oxo-1-(4,4,4-trifluorobutyl)-1,6-dihydropyridin-3-yl)-1*H*-indol-1-yl)acetate (**I-17A-3**) and methyl 2-(5-fluoro-2-methyl-3-(6-(4,4,4-trifluorobutoxy)pyridin-3-yl)-1*H*-indol-1-yl)acetate (**I-17A-3B**). General procedure E was followed to make **I-17A-3** and **I-17A-3B** from **I-16A**, and the mixture was carried on to the next step without purification.

General procedure E was followed to make **36** and **37** from mixture of **I-17A-3** and **I-17A-3B**. The mixture was separated by column chromatography.

36 in 70% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.87–2.01 (m, 2 H), 2.23–2.42 (m, 5 H), 4.05 (t, *J* = 7.3 Hz, 2 H), 5.02 (s, 2 H), 6.51 (d, *J* = 9.1 Hz, 1 H), 6.95 (td, *J* = 9.2, 2.5 Hz, 1 H), 7.18 (dd, *J* = 9.9, 2.5 Hz, 1 H), 7.44 (dd, *J* = 8.8, 4.3 Hz, 1 H), 7.54 (dd, *J* = 9.2, 2.7 Hz, 1 H), 7.75 (d, *J* = 2.3 Hz, 1 H), 13.24 (br s, 1 H).

37 in 70% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.20 (d, *J* = 1.77 Hz, 1H), 7.79 (dd, *J* = 2.53, 8.59 Hz, 1H), 7.46 (dd, *J* = 4.29, 8.84 Hz, 1H), 7.15 (dd, *J* = 2.53, 9.85 Hz, 1H), 6.92–7.00 (m, 2H), 5.02 (s, 2H), 4.37 (t, *J* = 6.44 Hz, 2H), 2.38–2.45 (m, 2H), 2.35 (s, 3H), 1.94–2.03 (m, 2H).

2-(3-(1-(2,3-Difluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-methyl-1*H*-indol-1-yl)acetic Acid (**38**). Methyl 2-(3-(1-(2,3-difluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-methyl-1*H*-indol-1-yl)acetate (**I-15A-5**). General procedure D was followed to make **I-15A-5** from **I-14A** and 2,3-difluorobenzyl bromide in 78% yield.

General procedure D was followed to make **38** from **I-15A-5** in 82% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.32 (s, 3 H), 4.85 (s, 2 H), 5.29 (s, 2 H), 6.54 (d, *J* = 9.1 Hz, 1 H), 6.92 (td, *J* = 9.2, 2.5 Hz, 1 H), 7.05 (td, *J* = 7.1, 1.5 Hz, 1 H), 7.14 (dd, *J* = 10.0, 2.4 Hz, 1 H), 7.17–7.25 (m, 1 H), 7.33–7.45 (m, 2 H), 7.60 (dd, *J* = 9.2, 2.7 Hz, 1 H), 7.81 (d, *J* = 2.5 Hz, 1 H).

1-(2,3-Difluorobenzyl)-5-(5-fluoro-2-methyl-1-(2-oxo-2-(pyrrolidin-1-yl)ethyl)-1*H*-indol-3-yl)pyridin-2(1*H*)-one (**39**). To a round-bottom flask containing **38** (200 mg, 0.469 mmol), BOP (228 mg,

0.52 mmol), and pyrrolidine (43 μ L, 0.52 mmol) in DMF (5 mL) was added DIEA (122 μ L, 0.7 mmol) to give an orange solution. This was stirred at room temp for 18 h until complete by TLC and LC/MS. Aqueous workup followed by prep HPLC purification and lyophilization afforded the title compound as a white solid. 56% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.76–1.87 (m, 2 H), 1.91–2.03 (m, 2 H), 2.29 (s, 3 H), 3.31–3.36 (m, 2 H), 3.65 (t, *J* = 6.8 Hz, 2 H), 5.06 (s, 2 H), 5.30 (s, 2 H), 6.55 (d, *J* = 9.3 Hz, 1 H), 6.93 (td, *J* = 9.2, 2.7 Hz, 1 H), 7.05 (td, *J* = 6.3, 1.5 Hz, 1 H), 7.15 (dd, *J* = 9.9, 2.5 Hz, 1 H), 7.17–7.26 (m, 1 H), 7.32–7.46 (m, 2 H), 7.60 (dd, *J* = 9.2, 2.7 Hz, 1 H), 7.81 (d, *J* = 2.5 Hz, 1 H).

2-(3-(1-(2,3-Difluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-methyl-1*H*-indol-1-yl)-*N,N*-dimethylacetamide (**40**). The title compound was prepared according to the method described for **39**. 60% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.27 (s, 3 H), 2.86 (s, 3 H), 3.16 (s, 3 H), 5.15 (s, 2 H), 5.30 (s, 2 H), 6.55 (d, *J* = 9.3 Hz, 1 H), 6.92 (td, *J* = 9.2, 2.5 Hz, 1 H), 7.05 (td, *J* = 6.3, 1.5 Hz, 1 H), 7.14 (dd, *J* = 10.0, 2.4 Hz, 1 H), 7.17–7.26 (m, 1 H), 7.32–7.44 (m, 2 H), 7.60 (dd, *J* = 9.2, 2.7 Hz, 1 H), 7.80 (d, *J* = 2.5 Hz, 1 H).

2-(3-(1-(2,3-Difluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-methyl-1*H*-indol-1-yl)acetamide (**41**). The title compound was prepared according to the method described for **39**. 75% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.34 (s, 3 H), 4.81 (s, 2 H), 5.30 (s, 2 H), 6.55 (d, *J* = 9.3 Hz, 1 H), 6.96 (td, *J* = 9.2, 2.5 Hz, 1 H), 7.02–7.09 (m, 1 H), 7.15 (dd, *J* = 10.0, 2.4 Hz, 1 H), 7.18–7.25 (m, *J* = 8.1, 8.1, 5.1, 1.5 Hz, 1 H), 7.28 (s, 1 H), 7.34–7.43 (m, 2 H), 7.60 (dd, *J* = 9.3, 2.5 Hz, 2 H), 7.80 (d, *J* = 2.5 Hz, 1 H).

2-(3-(1-(2,3-Difluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-methyl-1*H*-indol-1-yl)-*N*-(methylsulfonyl)acetamide (**42**). The title compound was prepared according to the method described for **39**. 58% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.33 (s, 3 H), 3.27 (s, 3 H), 5.05 (s, 2 H), 5.30 (s, 2 H), 6.55 (d, *J* = 9.3 Hz, 1 H), 6.92–7.09 (m, 2 H), 7.11–7.27 (m, 2 H), 7.33–7.49 (m, 2 H), 7.60 (dd, *J* = 9.3, 2.5 Hz, 1 H), 7.83 (d, *J* = 2.3 Hz, 1 H).

(*R*)-2-(3-(1-(2,3-Difluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-methyl-1*H*-indol-1-yl)propanoic Acid (**43a**) and (*S*)-2-(3-(1-(2,3-Difluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-methyl-1*H*-indol-1-yl)propanoic Acid (**43b**). Methyl 2-(3-bromo-5-fluoro-2-methyl-1*H*-indol-1-yl)propanoate (**I-21**). Intermediate **I-21** was prepared according to the method described for **I-13**. 36% yield.

Methyl 2-(5-fluoro-3-(6-methoxypyridin-3-yl)-2-methyl-1*H*-indol-1-yl)propanoate (**I-22**). Intermediate **I-22** was prepared according to the method described for **I-14**. 41% yield.

Methyl 2-(3-(1-(2,3-difluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-methyl-1*H*-indol-1-yl)propanoate (**I-23**). Intermediate **23** was prepared according to the method described for **I-15**. Purification by flash chromatography afforded the product in a 75% yield.

The title compound was prepared from **I-23** according to the method described for pyridine analogue Scheme 5. 15% yield for **43a**. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.62 (d, *J* = 7.1 Hz, 3 H), 2.38 (s, 3 H), 5.29 (s, 2 H), 5.44 (q, *J* = 6.3 Hz, 1 H), 6.54 (d, *J* = 9.3 Hz, 1 H), 6.95 (td, *J* = 9.0, 2.3 Hz, 1 H), 7.05 (t, *J* = 6.9 Hz, 1 H), 7.14 (dd, *J* = 9.9, 2.3 Hz, 1 H), 7.17–7.27 (m, 1 H), 7.29–7.46 (m, 2 H), 7.60 (dd, *J* = 9.3, 2.3 Hz, 1 H), 7.84 (d, *J* = 1.8 Hz, 1 H), 13.20 (br s, 1 H). 15% yield for **43b**. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.62 (d, *J* = 7.3 Hz, 3 H), 2.38 (s, 3 H), 5.28 (s, 2 H), 5.46 (q, *J* = 7.2 Hz, 1 H), 6.54 (d, *J* = 9.1 Hz, 1 H), 6.96 (td, *J* = 9.2, 2.7 Hz, 1 H), 7.02–7.09 (m, 1 H), 7.14 (dd, *J* = 9.9, 2.5 Hz, 1 H), 7.21 (qd, *J* = 8.1, 5.1, 1.5 Hz, 1 H), 7.30–7.44 (m, 2 H), 7.60 (dd, *J* = 9.2, 2.7 Hz, 1 H), 7.83 (d, *J* = 2.5 Hz, 1 H), 13.13 (br s, 1 H).

2-(3-(2-Benzyl-1-oxo-1,2-dihydroisoquinolin-4-yl)-5-fluoro-2-methyl-1*H*-indol-1-yl)acetic Acid (**48**) (Scheme 10B). *tert*-Butyl 3-bromo-5-fluoro-2-methyl-1*H*-indole-1-carboxylate (**I-24**). To a 1000 mL round-bottom flask containing 5-fluoro-2-methyl-1*H*-indole (5.66 g, 38 mmol) and DMF (127 mL) was added bromine (2.0 mL, 38 mmol). After 15 min, the reaction was diluted with EtOAc (800 mL) and washed with water (500 mL) and brine (500 mL) and dried (MgSO₄). The suspension was filtered and concentrated. The residue was dissolved in THF (381 mL) and treated with BOC₂ (8.3 g, 38 mmol) and DMAP (232 mg, 1.9 mmol). After 3 h, the reaction was concentrated to remove the THF. The residue was diluted with EtOAc (500 mL) and washed with water (250 mL) and brine (250 mL). The organic layer was dried

(MgSO₄), filtered, and concentrated. The crude material was purified by Biotage to give a beige solid (12.45 g, 75% yield).

tert-Butyl 5-fluoro-3-(isoquinolin-4-yl)-2-methyl-1*H*-indole-1-carboxylate (**I-25**). To a microwave vial containing **I-24** (1.03 g, 3.1 mmol), isoquinolin-4-ylboronic acid (1.02 g, 3.1 mmol), Na₂CO₃ (640 mg, 6.1 mmol), and THF–H₂O (20 mL, 1:1) was added Pd(PPh₃)₄ (200 mg, 0.15 mmol). The vessel was sealed and heated at 150 °C for 15 min. The reaction was filtered through filter paper and diluted with EtOAc (200 mL) and water (100 mL). The organic layer was dried (MgSO₄), filtered, and concentrated. The crude material was purified by silica gel chromatography, eluting with an EtOAc/hexane gradient to give a red solid (1.18g, 30% yield).

tert-Butyl 3-(2-benzyl-1-oxo-1,2-dihydroisoquinolin-4-yl)-5-fluoro-2-methyl-1*H*-indole-1-carboxylate (**I-26**). To a flask containing **I-25** (159 mg, 0.42 mmol) in CH₃CN (4.5 mL) was added benzyl iodide (100 mg, 0.46 mmol). The reaction was heated at reflux for 3 h. The solution was cooled and diluted with EtOAc (100 mL). The organic layer was washed with water (50 mL) and brine (50 mL). The organic layer was dried (MgSO₄), filtered, and concentrated to give an amber oil. To the amber oil was added hexane (~5–10 mL), and the suspension was agitated and stirred until a powdery light-brown solid appeared. The hexane was decanted, and the solid was dried in the vacuum oven. To the material was added water (2 mL) and THF (2 mL). An aqueous solution of KOH (1.8 M, 1.68 mmol, 0.93 mL) was added immediately, followed by addition of a solution of K₃Fe(CN)₆ (415 mg, 1.26 mmol) in water (0.5 M, 2.5 mL). DMF was slowly added to the mixture until the reaction appeared to be homogeneous. The reaction was diluted with EtOAc (50 mL) and washed with water (50 mL). The eluent was concentrated, and the product was taken into the next step without further purification (91 mg, 45% yield).

Compound 48. To a flask containing **I-26** (202 mg, 0.42 mmol) was added TFA (2 mL). The reaction was stirred for 20 min and then concentrated. The residue was dissolved in EtOAc (50 mL) and washed with H₂O (25 mL). The organic layer was dried (MgSO₄), filtered, and concentrated. The crude material was dissolved in DMF (4 mL) and treated with methylbromoacetate (116 µL, 1.3 mmol) and potassium carbonate (232 mg, 1.7 mmol). The reaction was heated to 90 °C for 4 h and cooled to room temperature. The solution was diluted with EtOAc (75 mL) and washed with water (3 × 50 mL). The organic layer was concentrated to remove the EtOAc. The residue was dissolved in THF–MeOH–H₂O (15 mL, 1:1:1) and treated with 1 M NaOH (2 mL). The reaction was stirred for 2–3 h and then concentrated to remove the volatile solvent. The aqueous layer was made acidic by addition of 1 M HCl. The product was extracted with EtOAc (3 × 15 mL) and purified by reverse phase HPLC to give a beige solid, yield 25%. ¹H NMR (400 MHz, MeOD) δ 8.47 (dd, 1H), 7.52–7.68 (m, 2H), 7.25–7.44 (m, 8H), 6.90 (td, *J* = 2.65, 9.16 Hz, 1H), 6.71 (dd, *J* = 2.53, 9.60 Hz, 1H), 5.20–5.45 (m, 2H), 4.96 (s, 2H), 2.21 (s, 3H).

General Procedure F (Scheme 10C). 2-Alkylisoquinolin-1(2*H*)-one (**I-27**). In a 1000 mL round-bottom flask was isoquinolin-1(2*H*)-one (14.27 g, 98 mmol), selected alkylhalide (98 mmol), and cesium carbonate (32.0 g, 98 mmol) in DMF (328 mL) to give a pale-yellow suspension. The reaction was heated to 50 °C in an oil bath for 3 h. The reaction mixture was diluted with ethyl acetate (600 mL). The organic layer was washed with water (4 × 250 mL) and dried (MgSO₄). The suspension was filtered, and the solvent was removed under reduced pressure. A solution of the material in CH₂Cl₂ and MeOH was added to a Biotage samplet. The samplet was then put in a chamber and evacuated to remove the excess solvent. Purification using a Biotage column yielded 2-alkylisoquinolin-1(2*H*)-one.

4-Iodo-2-alkylisoquinolin-1(2*H*)-one (**I-28**). To a cooled 500 mL round-bottomed flask of Et₂O (103 mL) containing a suspension of silver trifluoromethanesulfonate (13.19 g, 51.3 mmol), potassium hydroxide (2.88 g, 51.3 mmol), and **I-27** (51.3 mmol) was added iodine (13.03 g, 51.3 mmol) at 0 °C to give a cloudy suspension. After 2 h, the suspension was diluted with diethylether (200 mL) and filtered to remove the silver. The organic layer was washed with 0.1 M sodium thiosulfate (200 mL) and brine (200 mL) and dried (MgSO₄). The solution was filtered and concentrated. The residue was purified via Biotage.

2-Alkyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2*H*)-one (**I-29**). In a 500 mL round-bottomed flask was bis(pinacolato)-diboron (5.68 g, 22.35 mmol) and **I-28** (22.35 mmol), acetic acid, and potassium acetate (6.58 g, 67.1 mmol) in DMSO (112 mL) to give a dark-orange solution. The reaction was purged with nitrogen gas, and then PdCl₂(dppf)-CH₂Cl₂ adduct (1.095 g, 1.341 mmol) was added. The reaction was heated at 80 °C for 18 h and then cooled to room temperature. The reaction mixture was diluted with EtOAc (800 mL) and washed with water (3 × 300 mL) and saturated NaCl (1 × 300 mL). The organic layer was dried (MgSO₄), filtered and concentrated. The residue was purified via Biotage.

Methyl 2-(5-fluoro-3-iodo-2-methyl-1*H*-indol-1-yl)acetate (**I-30**). To a 500 mL round-bottomed flask under an atmosphere of nitrogen was added 5-fluoro-3-iodo-2-methyl-1*H*-indole (8.3 g, 30.2 mmol), methyl 2-bromoacetate (11.10 mL, 121 mmol), and potassium carbonate (20.85 g, 151 mmol) in 150 mL of DMF to give a brown suspension. This was heated to 90 °C and allowed to stir for 16 h. The mixture was cooled to room temperature and poured into 800 mL of water. This was extracted with three 250 mL portions of ethyl acetate. The combined organic layers were washed with water and brine then dried over MgSO₄. Filtration and concentration in vacuo gave the crude material which was purified by silica gel chromatography (6–50% EtOAc/Hex; 340 g SNAP column) to give a tan solid (8.08 g, 77% yield).

To a 500 mL round-bottomed flask under an atmosphere of nitrogen was added 5-fluoro-3-iodo-2-methyl-1*H*-indole (8.3 g, 30.2 mmol), methyl 2-bromoacetate (11.10 mL, 121 mmol), and potassium carbonate (20.85 g, 151 mmol) in 150 mL of DMF to give a brown suspension. This was heated to 90 °C and allowed to stir for 16 h. The mixture was cooled to room temperature and poured into 800 mL of water. This was extracted with three 250 mL portions of ethyl acetate. The combined organic layers were washed with water and brine then dried over MgSO₄. Filtration and concentration in vacuo gave the crude material which was purified by silica gel chromatography to give **I-30** as a tan solid (8.08 g, 77% yield).

Alkyl Isoquinolinone. To a 75 mL sealed vessel was added **I-29** (18.65 mmol), methyl 2-(5-fluoro-3-iodo-2-methyl-1*H*-indol-1-yl)acetate (9.71 g, 28.0 mmol, **I-30**), potassium phosphate tribasic monohydrate (7.92 g, 37.3 mmol), and 2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl (0.765 g, 1.865 mmol) in butan-1-ol (133 mL) and water (53.3 mL) to give a suspension. The reaction was purged with nitrogen. The catalyst, palladium(II) acetate (0.209 g, 0.932 mmol), was added, and the vessel was sealed. The tube was heated at 100 °C in an oil bath for 18 h. To the aqueous layer was added 1 N HCl until the solution was acidic by litmus test. The solution was stirred rigorously for 5 min and allowed to partition into two layers. The aqueous layer was decanted using a pipet. The organic layer was filtered through filter paper to remove the catalyst and then concentrated under reduced pressure to remove the *n*BuOH. The material was dissolved in MeOH (80 mL) and THF (80 mL) and treated with 50 mL of 1N aqueous NaOH. After stirring for 20 min, the organic layer was removed under reduced pressure and the aqueous layer was rendered acidic by addition of 1N HCl (50 mL). The product was extracted with EtOAc (3 × 200 mL). The organic layer was dried (MgSO₄), filtered, and concentrated to give the crude material. The crude material was purified to give the final product.

2-(5-Fluoro-3-(2-isopropyl-1-oxo-1,2-dihydroisoquinolin-4-yl)-2-methyl-1*H*-indol-1-yl)acetic Acid (**44**). 2-Isopropylisoquinolin-1(2*H*)-one (**I-27-1**). General procedure F was followed to give **I-27-1** from isoquinolin-1(2*H*)-one and 2-iodopropane in 26% yield.

4-Iodo-2-isopropylisoquinolin-1(2*H*)-one (**I-28-1**). General procedure F was followed to give **I-28-1** from **I-27-1** in 44% yield.

2-Isopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-isoquinolin-1(2*H*)-one (**I-29-1**). General procedure F was followed to give **I-29-1** from **I-28-1** in 83% yield.

General procedure F was followed to convert **I-29-1** to **44** in 74% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.11 (s, 1H), 8.32–8.40 (m, 1H), 7.63 (td, *J* = 1.39, 7.64 Hz, 1H), 7.48–7.56 (m, 2H), 7.42 (s, 1H), 7.22 (s, 1H), 6.97 (td, *J* = 2.65, 9.16 Hz, 1H), 6.81 (dd, *J* = 2.53, 9.85 Hz, 1H), 5.22–5.36 (m, 1H), 5.10 (d, *J* = 2.53 Hz, 2H), 2.22 (s, 3H), 1.39 (dd, *J* = 3.79, 6.82 Hz, 6H).

2-(5-Fluoro-2-methyl-3-(2-neopentyl-1-oxo-1,2-dihydroisoquinolin-4-yl)-1*H*-indol-1-yl)acetic Acid (**45**). 2-(2,2,2-Trifluoroethyl)-isoquinolin-1(2*H*)-one (**I-27-2**). General procedure F was followed

to give **I-27-2** from isoquinolin-1(2*H*)-one and 1,1,1-trifluoro-2-iodoethane, 97% yield.

4-Iodo-2-(2,2,2-trifluoroethyl)isoquinolin-1(2*H*)-one (**I-28-2**). Bis-(pyridine)iodonium tetrafluoroborate (5.67 g, 15.25 mmol) was dissolved in dry dichloromethane (69.3 mL) and added slowly to **I-27-2** (3.15 g, 13.87 mmol) and trifluoromethanesulfonic acid (2.71 mL, 30.5 mmol) in CH₂Cl₂. After completion of the reaction by TLC, the reaction was quenched by the addition of 0.1 M sodium thiosulfate (~100 mL) and washed with saturated NaCl (250 mL). The organic layer was isolated, dried (MgSO₄), filtered, and concentrated to give a dark-orange solid. The solid was purified to give an orange solid (3.9 g; 80% yield).

4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(2,2,2-trifluoroethyl)-isoquinolin-1(2*H*)-one (**I-29-2**). General procedure F was followed to give **I-29-2** from **I-28-2**, 69% yield.

General procedure F was followed to convert **I-29-2** to **45**, yield 34%. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.13 (s, 1H), 8.34–8.41 (m, 1H), 7.71 (ddd, *J* = 1.52, 7.14, 8.27 Hz, 1H), 7.60 (ddd, *J* = 1.26, 7.07, 8.08 Hz, 1H), 7.53 (dd, *J* = 4.29, 9.09 Hz, 1H), 7.48 (s, 1H), 7.26 (d, *J* = 7.33 Hz, 1H), 6.98 (td, *J* = 2.53, 9.22 Hz, 1H), 6.83 (dd, *J* = 2.40, 9.73 Hz, 1H), 5.12 (s, 2H), 4.93–5.09 (m, 2H), 2.23 (s, 3H).

2-(5-Fluoro-3-(1-oxo-2-(4,4,4-trifluorobutyl)-1,2-dihydroisoquinolin-4-yl)-1*H*-indol-1-yl)acetic Acid (**46**). 2-(4,4,4-Trifluorobutyl)-isoquinolin-1(2*H*)-one (**I-27-3**). General procedure F was followed to give **I-27-3** from isoquinolin-1(2*H*)-one and 4-bromo-1,1,1-trifluorobutane, 93% yield.

4-Iodo-2-(4,4,4-trifluorobutyl)isoquinolin-1(2*H*)-one (**I-28-3**). General procedure F was followed to give **I-28-3** from **I-27-3** in 58% yield.

4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(4,4,4-trifluorobutyl)isoquinolin-1(2*H*)-one (**I-29-3**). General procedure F was followed to give **I-29-3** from **I-28-3**, 71% yield.

General procedure F was followed to convert **I-29-3** to **46**, yield 64%. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.09 (br s, 1H), 8.31–8.39 (m, 1H), 7.61–7.68 (m, 1H), 7.50–7.58 (m, 2H), 7.50 (s, 1H), 7.21 (d, *J* = 7.58 Hz, 1H), 6.96 (td, *J* = 2.53, 9.22 Hz, 1H), 6.86 (dd, *J* = 2.53, 9.60 Hz, 1H), 5.10 (s, 2H), 4.07–4.18 (m, 2H), 2.35 (d, *J* = 11.37 Hz, 2H), 2.22 (s, 3H), 1.98 (d, *J* = 7.07 Hz, 2H).

2-(5-Fluoro-3-(2-neopentyl-1-oxo-1,2-dihydroisoquinolin-4-yl)-1*H*-indol-1-yl)acetic Acid (**47**). 2-Neopentylisoquinolin-1(2*H*)-one (**I-27-4**). General procedure F was followed to give **I-27-3** from isoquinolin-1(2*H*)-one and 1-bromo-2,2-dimethylpropane, yield 57%.

4-Iodo-2-neopentylisoquinolin-1(2*H*)-one (**I-28-4**). Intermediate **I-28-4** was prepared according to the method described for intermediate **I-28-3**, 73% yield.

2-Neopentyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-isoquinolin-1(2*H*)-one (**I-29-4**). General procedure F was followed to give **I-29-4** from **I-28-4**, 50% yield.

General procedure F was followed to convert **I-29-4** to **47**, yield 47%. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.11 (br s, 1H), 8.35 (dd, *J* = 1.01, 8.08 Hz, 1H), 7.63 (td, *J* = 1.52, 7.58 Hz, 1H), 7.47–7.56 (m, 2H), 7.35 (s, 1H), 7.19 (d, *J* = 7.58 Hz, 1H), 6.96 (td, *J* = 2.65, 9.16 Hz, 1H), 6.80 (dd, *J* = 2.53, 9.60 Hz, 1H), 5.10 (s, 2H), 3.85–4.07 (m, 2H), 2.22 (s, 3H), 0.99 (s, 9H).

General Procedure G. 5,6,7,8-Tetrahydroisoquinolin-1(2*H*)-one (intermediate **I-31**). To a 100 mL round-bottomed flask under an atmosphere of nitrogen was added isoquinolin-1(2*H*)-one (0.5 g, 3.44 mmol) in 20 mL of acetic acid to give a colorless solution. Platinum(IV) oxide (0.235 g, 1.033 mmol) was added. Hydrogen gas was sparged through the solution via a needle attached to a balloon for 10 min. The reaction was then allowed to stir for 16 h under one atmosphere of nitrogen. The catalyst was filtered off and the acetic acid removed by azeotroping with hexane. The residue was purified by silica gel chromatography to give the desired product as a white solid (0.100g, 20% yield).

2-Substituted-5,6,7,8-tetrahydroisoquinolin-1(2*H*)-one (**I-32**). To a 20 mL microwave vial was added intermediate **I-31** (1.01 g, 6.77 mmol) and cesium carbonate (4.41 g, 13.54 mmol) in 10 mL of DMF to give a white suspension. Selected halide (20.31 mmol) was added. The vial was sealed and the mixture heated to 50 °C. The reaction was allowed to stir 16 h. The mixture was then poured into water and extracted with

3 × 100 mL portions of ethyl acetate. The combined organic layers were washed with water and brine and then dried over MgSO₄ and filtered. The resulting solution was concentrated, and the residue was purified by silica gel chromatography to give the desired product.

4-Iodo-2-substituted-5,6,7,8-tetrahydroisoquinolin-1(2*H*)-one (**I-33**). To a 50 mL round-bottomed flask under an atmosphere of nitrogen was added intermediate **I-32** (1.694 mmol) and trifluoromethanesulfonic acid (0.331 mL, 3.73 mmol) in 20 mL of dichloromethane to give a tan solution. Dipyrindinium-1-ylidate(I), BF₄[−] (0.693 g, 1.863 mmol) was added slowly as a solution in 5 mL of dichloromethane, and the resulting solution was allowed to stir 1 h. The reaction was then quenched with 100 mL of 0.1 M sodium thiosulfate. The organic layer was washed with brine and dried over MgSO₄ and then filtered and concentrated in vacuo to give an orange solid. The residue was purified by silica gel chromatography to give the desired product.

2-Substituted-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6,7,8-tetrahydroisoquinolin-1(2*H*)-one (**I-34**). To a 50 mL round-bottomed flask under an atmosphere of nitrogen was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.401 g, 1.578 mmol), intermediate **I-33** (1.435 mmol), and potassium acetate (0.422 g, 4.30 mmol) in 25 mL of DMSO to give an orange solution. PdCl₂(dppf)-CH₂Cl₂ adduct (0.070 g, 0.086 mmol) was added. The reaction was heated to 80 °C and allowed to stir for 16 h. The mixture was then poured into 100 mL of water and extracted with three 50 mL portions of ethyl acetate. The combined organic layers were washed with water and brine, dried over magnesium sulfate, filtered, and concentrated. The residue was purified by silica gel to give the desired product.

Saturated Isoquinolinone. To a 5 mL microwave vessel was added intermediate **I-30** (0.571 g, 1.645 mmol), intermediate **I-34** (0.823 mmol), and potassium phosphate tribasic monohydrate (0.349 g, 1.645 mmol) in 4 mL of butan-1-ol and 1.6 mL water to give a tan suspension. 2-Dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl (0.034 g, 0.082 mmol) was added. The vial was purged with nitrogen, and palladium(II) acetate (9.24 mg, 0.041 mmol) was added. The vessel was sealed and heated to 100 °C in an oil bath and allowed to stir for 16 h. The reaction mixture was then poured into 50 mL of water extracted with three 25 mL portions of ethyl acetate. The combined organic layers were washed with water and brine. The organic was dried over MgSO₄, filtered, and concentrated in vacuo. The residue was redissolved into 10 mL of THF. To this was added lithium hydroxide (0.073 g, 3.06 mmol) dissolved into 5 mL of water. Methanol was added until solution was monophasic. The mixture was stirred for 30 min and was then poured into 100 mL of 1.2 N HCl. The aqueous layer was extracted with three 50 mL portions of ethyl acetate. The combined organic layers were washed with water and brine. The organic was dried MgSO₄, filtered, and concentrated. The crude material was then purified.

2-(5-Fluoro-3-(2-isopropyl-1-oxo-1,2,5,6,7,8-hexahydroisoquinolin-4-yl)-2-methyl-1*H*-indol-1-yl)acetic Acid (**49**). 2-Isopropyl-5,6,7,8-tetrahydroisoquinolin-1(2*H*)-one (**I-32-1**). General procedure G was followed to give **I-32-1** from **I-31** and 2-iodopropane, yield 25%.

4-Iodo-2-isopropyl-5,6,7,8-tetrahydroisoquinolin-1(2*H*)-one (**I-33-1**). General procedure G was followed to give **I-33-1** from **I-32-1**, yield 85%.

2-Isopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6,7,8-tetrahydroisoquinolin-1(2*H*)-one (**I-34-1**). General procedure G was followed to give **I-34-1** from **I-33-1**, 57% yield.

General procedure G was followed to convert **I-34-1** to **49** yield 23%. ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.30 (d, 6 H) 1.41–1.61 (m, 2 H) 1.68 (quin, *J* = 5.9 Hz, 2 H) 2.01–2.25 (m, 5 H) 2.44 (d, *J* = 5.6 Hz, 2 H) 5.02 (d, *J* = 1.0 Hz, 2 H) 5.14 (quin, *J* = 6.8 Hz, 1 H) 6.84–6.97 (m, 2 H) 7.29 (s, 1 H) 7.43 (dd, *J* = 9.0, 4.4 Hz, 1 H) 13.07 (br s, 1 H).

2-(5-Fluoro-2-methyl-3-(1-oxo-2-(2,2,2-trifluoroethyl)-1,2,5,6,7,8-hexahydroisoquinolin-4-yl)-1*H*-indol-1-yl)acetic Acid (**50**). 2-(2,2,2-Trifluoroethyl)-5,6,7,8-tetrahydroisoquinolin-1(2*H*)-one (**I-32-2**). General procedure G was followed to give **I-32-2** from **I-31** and 1,1,1-trifluoro-2-iodoethane, 66% yield.

4-Iodo-2-(2,2,2-trifluoroethyl)-5,6,7,8-tetrahydroisoquinolin-1(2*H*)-one (**I-33-2**). General procedure G was followed to give **I-33-2** from **I-32-2**, 19% yield.

4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(2,2,2-trifluoroethyl)-5,6,7,8-tetrahydroisoquinolin-1(2H)-one (**I-34-2**). General procedure G was followed to give **I-34-2** from **I-33-2**, 61% yield.

General procedure G was followed to convert **I-34-2** to **50**, 25% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.45–1.63 (m, 2 H) 1.64–1.75 (m, 2 H) 2.04–2.28 (m, 5 H) 2.39–2.53 (m, 2 H) 4.78–4.98 (m, 2 H) 5.03 (d, *J* = 1.5 Hz, 2 H) 6.85–6.97 (m, 2 H) 7.37 (s, 1 H) 7.45 (dd, *J* = 8.8, 4.3 Hz, 1 H) 13.09 (br s, 1 H).

2-(5-Fluoro-2-methyl-3-(1-oxo-2-(4,4,4-trifluorobutyl)-1,2,5,6,7,8-hexahydroisoquinolin-4-yl)-1H-indol-1-yl)acetic Acid (**51**). 2-(4,4,4-Trifluorobutyl)-5,6,7,8-tetrahydroisoquinolin-1(2H)-one (**I-32-3**). General procedure G was followed to give **I-32-3** from **I-31** and 4-bromo-1,1,1-trifluorobutane, 53% yield.

4-Iodo-2-(4,4,4-trifluorobutyl)-5,6,7,8-tetrahydroisoquinolin-1(2H)-one (**I-33-3**). General procedure G was followed to give **I-33-2** from **I-32-2** in 21% yield.

4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(4,4,4-trifluorobutyl)-5,6,7,8-tetrahydroisoquinolin-1(2H)-one (**I-34-3**). General procedure G was followed to give **I-34-3** from **I-33-3**, 61% yield.

General procedure G was followed to convert **I-34-3** to **51**, 33% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.42–1.60 (m, 2 H) 1.61–1.74 (m, 2 H) 1.90 (quin, *J* = 7.6 Hz, 2 H) 2.04–2.23 (m, 5 H) 2.23–2.36 (m, 2 H) 2.40–2.45 (m, 2 H) 3.89–4.03 (m, 2 H) 5.02 (d, *J* = 1.3 Hz, 2 H) 6.84–6.97 (m, 2 H) 7.38 (s, 1 H) 7.43 (dd, *J* = 8.7, 4.4 Hz, 1 H) 13.08 (br s, 1 H).

2-(3-(2-Benzyl-1-oxo-1,2,5,6,7,8-hexahydroisoquinolin-4-yl)-5-fluoro-2-methyl-1H-indol-1-yl)acetic Acid (**52**). 2-Benzyl-5,6,7,8-tetrahydroisoquinolin-1(2H)-one (**I-32-4**). General procedure G was followed to give **I-32-4** from **I-31** and benzyl bromide, 73% yield.

2-Benzyl-4-iodo-5,6,7,8-tetrahydroisoquinolin-1(2H)-one (**I-33-4**). General procedure G was followed to give **I-33-4** from **I-32-4**, 53% yield.

2-Benzyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6,7,8-tetrahydroisoquinolin-1(2H)-one (**I-34-4**). General procedure G was followed to give **I-34-4** from **I-33-4**, 71% yield.

General procedure G was followed to convert **I-34-4** to **52**, 33% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.47–1.66 (m, 2 H) 1.68–1.80 (m, 2 H) 2.05–2.31 (m, 5 H) 2.42–2.68 (m, 2 H) 5.07 (s, 2 H) 5.20 (d, *J* = 4.8 Hz, 2 H) 6.90 (dd, *J* = 9.6, 2.3 Hz, 1 H) 6.98 (td, *J* = 9.1, 2.5 Hz, 1 H) 7.29–7.37 (m, 1 H) 7.37–7.44 (m, 4 H) 7.49 (dd, *J* = 8.7, 4.4 Hz, 1 H) 7.54 (s, 1 H).

Membrane Vesicles and Sandwich-Cultured Hepatocytes Studies. Membrane vesicles prepared from Mrp2/MRP2 expressing Sf9 insect cells were purchased from Invitrogen (Carlsbad, CA). Incubations were performed according to the vendor's recommended procedures using a substrate concentration of 10 μM, 50 μg protein/incubation, and an incubation time of 5 min at 37 °C in the presence or absence of ATP and an ATP generating system. MK571 (250 μM), a Mrp2/MRP2 inhibitor, was included in separate incubations. Net uptake activity was obtained by subtracting activity in the presence of ATP from that in the presence of AMP. Rat and human sandwich-cultured hepatocytes were purchased from Qualyst (Durham, NC), and incubations were performed according to the vendor's recommended procedures using substrate concentrations of 1–50 μM (rat) or 1–10 μM (human). The amount of substrate excreted into the bile canalicular network was calculated as the difference between the amount of substrate accumulated in the hepatocytes when incubations were conducted in the presence or absence of Ca²⁺. In vitro intrinsic biliary clearance was calculated by the amount of substrate excreted in the bile divided by the concentration of substrate present with time.

hCRTH2 FRET Assay. The cAMP TR-FRET assay was performed by incubating a dilution series of compound concentrations with 30000 cells per assay well of CHO-K1 cells expressing the recombinant human CRTH2 receptor (Euroscreen, Belgium). Incubations were performed at room temperature for 30 min in the presence of 10 μM forskolin and 10 nM PGD2. The assay buffer used contained 25 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES), pH 7.4, 124 mM sodium chloride, 5 mM potassium chloride, 1.45 mM calcium chloride, 1.25 mM magnesium chloride, 1.25 mM potassium dihydrogen phosphate, 13.3 mM glucose, and 0.5 g/L BSA. Following the 30 min incubation at room

temperature, *d*₂-cAMP and europium-labeled antibody supplied with the Hi-Range Assay Reagent kit (Cisbio, Bedford, MA) were separately diluted into the supplier-provided cell lysis buffer, and each was added to the assay plate, as per manufacturer's directions. Data was collected on the Envision plate reader (Perkin-Elmer, Waltham, MA) using λ_{exc}, 340 nm, and λ_{em}, 615/665. Samples containing cells and DMSO alone were included as a control in order to measure the maximal signal.

Human Eosinophil Shape Change Assay (hEOS). Peripheral blood from healthy human donors, prescreened for having greater than 3% eosinophils, was collected into sodium heparin tubes. Blood was incubated with compound for 10 min at room temperature and then activated with 50 nM PGD2 for 10 min at 37 °C. The reaction was stopped by transferring the plates to ice and adding 1% paraformaldehyde fixative. The samples were then transferred to ammonium chloride lysis solution, mixed gently, and incubated on ice for 40 min. Eosinophil shape change was analyzed by flow cytometry using a FACSCalibur outfitted with a 96-well autosampler. Individual cell populations were separated based on their forward and side scatter properties. Gross cellular toxicity was noted as a reduced or abnormal forward/side scatter pattern compared to untreated or placebo treated blood cell populations. Granulocytes were gated and assessed for autofluorescence in the FL1 and FL2 channels. Eosinophils were isolated based on their higher autofluorescence in both channels. Finally, shape change was measured by alterations in the mean forward scatter of the eosinophils in response to PGD2.

Contact Hypersensitivity Mouse Ear Model (CHS). Inflammation was measured in the ear skin of mice. One week prior to challenge, mice were sensitized on the shaved abdomen by applying 100 μL of 2% oxazolone made in 100% ethanol. Five days later, baseline ear thickness measurements were taken on the left and right ears using a Mitutoyo micrometer. Compound was given orally prior to challenge. One hour after treatment, the left ears of the mice were challenged topically with 10 μL of 2% oxazolone on the left ear, and as a negative control 10 μL of 100% ethanol on the right ear. Mice received another dose of compound orally 7 h post challenge. The following day (24 h) ear swelling was measured again with the micrometer, and the swelling was expressed postchallenge–prechallenge thickness (Δ) (Student's unpaired *t* test used for statistical analysis).

House Dust Mite Model. Mouse model of house dust mite-induced allergic airway disease: Age-matched 6–12 week old female BALB/c mice were obtained from Taconic Farms (Hudson, NY). All in vivo experiments were performed in accordance with animal use protocols approved by Pfizer's Institutional Animal Care and Use Committee. On day 0, 7, and 14 of the protocol, mice were anesthetized with isoflurane and received house dust mite extract from *Dermatophagoides pteronyssinus* (HDM, Greer Laboratories, Lenoir, NC). Briefly, 100 μg HDM extract in 40 μL of saline were instilled intratracheally using a 100 μL Hamilton glass syringe terminated with a 1.5 in. polyethylene catheter mounted on a 30G needle. The catheter was introduced through the animal's vocal cords into the trachea using an otoscope terminated with a 2 mm speculum. When indicated, mice were treated (qd) either intraperitoneally with dexamethasone (1 mg/kg) or perorally with compound **44** (40 mg/kg). All mice were euthanized by CO₂ asphyxiation on day 17 of the protocol to collect bronchoalveolar lavage (BAL) fluid and various tissue samples for analysis. BAL collection was performed as previously described.¹⁷ Because systemic inflammation is minimal in this model, no blood samples were collected.

Statistical Analysis. Results represent the mean ± SEM. Statistical significance for all results was determined using a Mann–Whitney *U* test. Results were considered significant for *P* values <0.05.

Guinea Pig Allergen Challenge Model. Female Hartley guinea pigs between the weight range of 375 and 425 g (5–7 weeks) were obtained from Charles River. On days 1 and 5, guinea pigs were anesthetized with isoflurane inhalation prior to receiving a 1 mL intraperitoneal injection of 100 μg of OVA (Ovalbumin; grade V, minimum 98% agarose gel electrophoresis; batch no. 087K7004; A5503-50G; Sigma) with 100 mg of aluminum hydroxide (reagent grade; batch no. 09712JE; Sigma no. 239186-500G) in PBS. On day 15, animals were exposed to an aerosol of 0.01% OVA allergen in PBS for 60 min. Animals were dosed per os with test articles 1 h prior to and 6 h post OVA

allergen challenge. To facilitate oral dosing, animals were anesthetized with isoflurane inhalation. An infant feeding tube was then placed into the stomach, and compounds were dosed in a 1 mL volume in 0.5% Tween made up in Cherry Blast FlavoRX syrup. All animals were euthanized by pentobarbital overdose on day 16 of the protocol in order to collect bronchoalveolar lavage (BAL) fluid and various tissue samples for analysis. For BAL fluid collection lungs were lavaged with 2×10 mL of PBS. Recovered total cell numbers were pooled and counted using a hemocytometer. Evans Blue exclusion was used to assess cell viability. In terms of cell viability, there were no differences between vehicle treated and compound treated animals. Cell differentials were quantified from cells smears (prepared by spinning a 100 μ L aliquot (106 cells/mL) in a Cytospin (Shandon) centrifuge) that were fixed using a solution of methanol for 10 s and stained with buffered eosin (10 s) and methylene blue/Azur (5 s). A total of 500 cells per smear were counted by light microscopy under oil immersion ($\times 1000$).

■ ASSOCIATED CONTENT

■ Supporting Information

Analytical data for intermediates. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*Phone: (617) 665-5626. E-mail: neelu.kaila@pfizer.com.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Seonghee Park, Aram Oganessian, Jianyao Wang, and Robert Espina for the in vitro and in vivo ADME studies and Professor William Abraham from the University of Miami for sheep studies. We would also like to thank the DAC group for analytical data.

■ ABBREVIATIONS USED

CRTH2, chemoattractant receptor homologous molecule expressed on Th2 cells; PGD2, prostaglandin D2; cPLA2, cytosolic phospholipase A2; TP, thromboxane type prostanoid receptor; DP, the PGD2 receptor; TXB2, 11-dehydrothromboxane B2; FEV1, forced expiratory volume in 1 s; AHR, airway hyperresponsiveness; LAR, late airway response; EAR, early airway response; FRET, fluorescence resonance energy transfer; BOP, benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate; P_{app} , apparent permeability coefficient; pH, potential hydrogen; nM, nanomolar; HDM, house dust mite; BAL, bronchoalveolar lavage; $MgSO_4$, magnesium sulfate; HCl, hydrochloric acid; SEM, standard error of the mean; P-gp, P-glycoprotein 1; MRP, multidrug resistant protein; LipE, lipophilic efficiency

■ REFERENCES

- (1) (a) Haeggstrom, J. Z.; Rinaldo-Matthis, A.; Wheelock, C. E.; Wetterholm, A. Advances in eicosanoid research, novel therapeutic implications. *Biochem. Biophys. Res. Commun.* **2010**, *21*, 135–139.
- (2) Castellani, M. L.; Felaco, M.; Pandolfi, F.; Salini, V.; De Amicis, D.; Orso, C.; Vecchiet, J.; Tete, S.; Ciampoli, C.; Conti, F.; Cerulli, G.; Caraffa, A.; Antinolfi, P.; Cuccurullo, C.; Felaco, P.; Kempuraj, D.; Boscolo, P.; Sabatino, G.; Shaik, Y. B. Mast cells and arachidonic acid cascade in inflammation. *Eur. J. Inflammation* **2009**, *7*, 131–137.
- (3) (a) Nagata, K.; Hirai, H.; Tanaka, K.; Ogawa, K.; Aso, T.; Sugamura, K.; Nakamura, M.; Takano, S. CRTH2, an orphan receptor of T-helper-2-cells, is expressed on basophils and eosinophils and responds to mast cell-derived factor(s). *FEBS Lett.* **1999**, *459*, 195–199.
- (b) Nagata, K.; Hirai, H. The second PGD(2) receptor CRTH2:

structure, properties, and functions in leukocytes. *Prostaglandins, Leukotrienes Essent. Fatty Acids* **2003**, *69*, 169–177. (c) Kostenis, E.; Ulven, T. Emerging roles of DP and CRTH2 in allergic inflammation. *Trends Mol. Med.* **2006**, *12*, 148–158. Epub. (d) Cosmi, L.; Annunziato, F.; Galli, G.; Manetti, R.; Maggi, E.; Romagnani, S. CRTH2: marker for the detection of human Th2 and Tc2 cells. *Adv. Exp. Med. Biol.* **2001**, *495*, 25–29.

(4) Hirai, H.; Tanaka, K.; Yoshie, O.; Ogawa, K.; Kenmotsu, K.; Takamori, Y.; Ichimasa, M.; Sugamura, K.; Nakamura, M.; Takano, S. Prostaglandin D2 Selectively Induces Chemotaxis in T Helper Type 2 Cells, Eosinophils, and Basophils via Seven-Transmembrane Receptor CRTH2. *J. Exp. Med.* **2001**, *193*, 255–262.

(5) Huang, J.-L.; Gao, P.-S.; Mathias, R. A.; Yao, T.-C.; Chen, L.-C.; Kuo, M.-L.; Hsu, S.-C.; Plunkett, B.; Togias, A.; Barnes, K. C. Sequence variants of the gene encoding chemoattractant receptor expressed on Th2 cells (CRTH2) are associated with asthma and differentially influence mRNA stability. *Hum. Mol. Genet.* **2004**, *13*, 2691–2697.

(6) Kaila, N.; Huang, A.; Moretto, A.; Follows, B.; Janz, K.; Lowe, M.; Thomason, J.; Mansour, T. S.; Hubeau, C.; Page, K.; Morgan, P.; Fish, S.; Xu, X.; Williams, C.; Saiah, E. Diazine Indole Acetic Acids as Potent, Selective, and Orally Bioavailable Antagonists of Chemoattractant Receptor Homologous Molecule Expressed on Th2 Cells (CRTH2) for the Treatment of Allergic Inflammatory Diseases. *J. Med. Chem.* **2012**, *55*, 5088–5109.

(7) Snell, N.; Foster, M.; Vestbo, J. Efficacy and safety of AZD1981, a CRTH2 receptor antagonist, in patients with moderate to severe COPD. *Respir. Med.* **2013**, *107*, 1722–1730.

(8) Singh, D.; Cadden, P.; Hunter, M.; Collins, L. P.; Perkins, M.; Pettipher, R.; Townsend, E.; Vinall, S.; O'Connor, B. Inhibition of the asthmatic allergen challenge response by the CRTH2 antagonist OC000459. *Eur. Respir. J.* **2013**, *41*, 46–52.

(9) Arry-502/CRTH2 Antagonist. <http://www.arraybiopharma.com/ProductPipeline/Inflammation/CRTH2.asp> (accessed December 20, 2013).

(10) Hirai, H.; Tanaka, K.; Takano, S.; Ichimasa, M.; Nakamura, M.; Nagata, K. Cutting edge: agonistic effect of indomethacin on a prostaglandin D2 receptor, CRTH2. *J. Immunol.* **2002**, *168*, 981–985.

(11) (a) Fretz, H.; Valdenaire, A.; Pothier, J.; Hilpert, K.; Gnerre, C.; Peter, O.; Leroy, X.; Riederer, M. A. Identification of 2-(2-(1-Naphthoyl)-8-fluoro-3,4-dihydro-1H-pyrido[4,3-b]indol-5(2H)-yl)-acetic Acid (Setiprant/ACT-129968), a Potent, Selective, and Orally Bioavailable Chemoattractant Receptor-Homologous Molecule Expressed on Th2 Cells (CRTH2) Antagonist. *J. Med. Chem.* **2013**, *56*, 4899–4911. (b) Tumey, L. N. CRTH2 antagonists. In *Anti-Inflammatory Drug Discovery*; RSC Drug Discovery Series, Vol. 26; Royal Society of Chemistry: London, 2012; pp 104–134. (c) Valdenaire, A.; Pothier, J.; Renneberg, D.; Riederer, M. A.; Peter, O.; Leroy, X.; Gnerre, C.; Fretz, H. Evolution of novel tricyclic CRTH2 receptor antagonists from a (E)-2-cyano-3-(1H-indol-3-yl)acrylamide scaffold. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 944–948. (d) Andres, M.; Bravo, M.; Buil, M. A.; Calbet, M.; Castro, J.; Domenech, T.; Eichhorn, P.; Ferrer, M.; Gomez, E.; Lehner, M. D.; Moreno, I.; Roberts, R. S.; Sevilla, S. 2-(1H-Pyrazol-4-yl)acetic acids as CRTH2 antagonists. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3349–3353. (e) Lamers, C.; Flesch, D.; Schubert-Zsilavecz, M.; Merk, D. Novel prostaglandin receptor modulators: a patent review (2002–2012), part I: Non-EP receptor modulators. *Expert Opin. Ther. Pat.* **2013**, *23*, 47–77. (f) Sandham, D. A.; Arnold, N.; Aschauer, H.; Bala, K.; Barker, L.; Brown, L.; Brown, Z.; Budd, D.; Cox, B.; Docx, C.; Dubois, G.; Duggan, N.; England, K.; Everatt, B.; Furegati, M.; Hall, E.; Kalthoff, F.; King, A.; Leblanc, C. J.; Manini, J.; Meingassner, J.; Profit, R.; Schmidt, A.; Simmons, J.; Sohal, B.; Stringer, R.; Thomas, M.; Turner, K. L.; Walker, C.; Watson, S. J.; Westwick, J.; Willis, J.; Williams, G.; Wilson, C. Discovery and characterization of NVP-QAV680, a potent and selective CRTH2 receptor antagonist suitable for clinical testing in allergic diseases. *Bioorg. Med. Chem.* **2013**, *21*, 6582–6591.

(12) Mahadevan, A.; Sard, H.; Gonzalez, M.; McKew, J. C. A general method for C3 reductive alkylation of indoles. *Tetrahedron Lett.* **2003**, *44*, 4589–4591.

(13) Bowman, W. R.; Bridge, C. F. *Synth. Commun.* **1999**, *29* (22), 4051.

- (14) Ferrer, S.; Naughton, D. P.; Parveen, I.; Threadgill, M. D. *N*- and *O*-Alkylation of isoquinolin-1-ones in the Mitsunobu reaction: development of potential drug delivery systems. *J. Chem. Soc., Perkin Trans. 1* **2002**, 335–340.
- (15) Horning, D. E.; Lacasse, G.; Muchowski, J. M. *Can. J. Chem.* **1971**, 49, 2785–2796.
- (16) Peukert, S.; Schwahn, U.; Güssregen, S.; Schreuder, H.; Hofmeister, A. Poly(ADP-ribose) polymerase-1 (PARP-1) inhibitors based on a tetrahydro-1(2*H*)-isoquinolinone scaffold: synthesis, biological evaluation and X-ray crystal structure. *Synthesis* **2005**, 1550–1554.
- (17) Long, A. J.; Sypek, J. P.; Askew, R.; Fish, S. C.; Mason, L. E.; Williams, C. M.; Goldman, S. J. Gob-5 contributes to goblet cell hyperplasia and modulates pulmonary tissue inflammation. *Am. J. Respir. Cell Mol. Biol.* **2006**, 35, 357–365.
- (18) (a) Abraham, W. M.; Ahmed, A.; Sabater, J. R.; Lauredo, I. T.; Botvinnikova, Y.; Bjercke, R. J.; Hu, X.; Revelle, B. M.; Kogan, T. P.; Scott, I. L. Selectin blockade prevents antigen-induced late bronchial responses and airway hyperresponsiveness in allergic sheep. *Am. J. Respir. Crit. Care Med.* **1999**, 159, 1205–1214. (b) Abraham, W. M. Modeling of asthma, COPD and cystic fibrosis in sheep. *Pulm. Pharmacol. Ther.* **2008**, 21, 743–754.
- (19) Mellor, B. J.; Murray, P. E.; Thomas, E. J. Aspects of the Chemistry of Dioxolanes: Synthesis of C-Nucleoside Analogues. *Tetrahedron* **1998**, 54, 243–256.

“Supporting Information”

Title:

Discovery of Isoquinolinone indole acetic acids as Antagonists of Chemoattractant Receptor Homologous Molecule Expressed on Th2 cells (CRTH2) for the Treatment of Allergic Inflammatory Diseases

Authors

Neelu Kaila*, Bruce Follows, Louis Leung, Jennifer Thomason, Adrian Huang, Alessandro Moretto, Kristin Janz, Michael Lowe, Tarek S Mansour, Cedric Hubeau, Karen Page, Paul Morgan, Susan Fish, Xin Xu, Cara Williams and Eddine Saiah

Content:

Analytical data for intermediates

Characterization data for intermediates

Methyl 2-(5-fluoro-2-methyl-1*H*-indol-1-yl)acetate (**I-1A**). ¹H NMR (CHLOROFORM-*d*) δ 7.18 (dd, *J* = 9.6, 2.5 Hz, 1H), 7.08 (dd, *J* = 8.8, 4.3 Hz, 1H), 6.89 (td, *J* = 9.1, 2.5 Hz, 1H), 6.28 (t, *J* = 0.8 Hz, 1H), 4.78 (s, 2H), 3.76 (s, 3H), 2.40 (d, *J* = 1.0 Hz, 3H).

Methyl 2-(5-fluoro-3-((6-methoxypyridin-3-yl)methyl)-2-methyl-1*H*-indol-1-yl)acetate (**I-7**). ¹H NMR (DMSO-*d*₆) δ 8.07 (d, *J* = 2.3 Hz, 1H), 7.46 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.35 (dd, *J* = 8.8, 4.3 Hz, 1H), 7.18 (dd, *J* = 9.9, 2.5 Hz, 1H), 6.87 (td, *J* = 9.2, 2.5 Hz, 1H), 6.69 (d, *J* = 9.1 Hz, 1H), 5.09 (s, 2H), 3.94 (s, 2H), 3.78 (s, 3H), 3.68 (s, 3H), 2.32 (s, 3H).

Methyl 2-(5-fluoro-3-((1-(2-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)methyl)-2-methyl-1*H*-indol-1-yl)acetate (**I-8-1**). ¹H NMR (DMSO-*d*₆) δ 7.67 (d, *J* = 2.0 Hz, 1H), 7.30 - 7.39 (m, 2H), 7.16 - 7.24 (m, 3H), 7.05 - 7.15 (m, 2H), 6.87 (td, *J* = 9.1, 2.5 Hz, 1H), 6.33 (d, *J* = 9.3 Hz, 1H), 5.09 (s, 2H), 5.08 (s, 2H), 3.74 (s, 2H), 3.67 (s, 3H), 2.30 (s, 3H).

Methyl 2-(5-fluoro-3-((1-(3-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)methyl)-2-methyl-1*H*-indol-1-yl)acetate (**I-8-2**). ¹H NMR (DMSO-*d*₆) δ 7.78 (d, *J* = 2.0 Hz, 1H), 7.32 - 7.40 (m, 2H), 7.19 (td, *J* = 9.8, 2.4 Hz, 2H), 7.05 - 7.15 (m, 3H), 6.87 (td, *J* = 9.2, 2.5 Hz, 1H), 6.33 (d, *J* = 9.3 Hz, 1H), 5.08 (s, 2H), 5.06 (s, 2H), 3.73 (s, 2H), 3.67 (s, 3H), 2.30 (s, 3H).

Methyl 2-(5-Fluoro-3-((1-(4-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)methyl)-2-methyl-1*H*-indol-1-yl)acetate (**I-8-3**). ¹H NMR (DMSO-*d*₆) δ 7.76 (d, *J* = 2.0 Hz, 1H), 7.31 - 7.38 (m, 3H), 7.10 - 7.22 (m, 4H), 6.87 (td, *J* = 9.2, 2.7 Hz, 1H), 6.31 (d, *J* = 9.3 Hz, 1H), 5.07 (s, 2H), 5.03 (s, 2H), 3.72 (s, 2H), 3.67 (s, 3H), 2.30 (s, 3H).

Methyl 2-(3-((1-(2,6-Difluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)methyl)-5-fluoro-2-methyl-1*H*-indol-1-yl)acetate (**I-8-4**). ¹H NMR (DMSO-*d*₆) δ 7.58 (s, 1H), 7.37 - 7.45 (m, 1H), 7.35 (dd, *J* = 9.0, 4.4 Hz, 1H), 7.16 (dd, *J* = 9.3, 2.5 Hz, 2H), 7.01 - 7.09 (m, 2H), 6.87 (td, *J* = 9.1, 2.5 Hz, 1H), 6.25 (d, *J* = 9.3 Hz, 1H), 5.08 (s, 2H), 5.07 (s, 2H), 3.74 (s, 2H), 3.67 (s, 3H), 2.29 (s, 3H).

Methyl 2-(3-((1-(2,5-Difluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)methyl)-5-fluoro-2-methyl-1*H*-indol-1-yl)acetate (**I-8-5**). ¹H NMR (DMSO-*d*₆) δ 7.69 (d, *J* = 2.5 Hz, 1H), 7.35 (dd, *J* = 8.8, 4.3 Hz, 1H), 7.24 - 7.31 (m, 1H), 7.16 - 7.23 (m, 3H), 6.83 - 6.90 (m, 2H), 6.33 (d, *J* = 9.1 Hz, 1H), 5.08 (s, 4H), 3.75 (s, 2H), 3.67 (s, 3H), 2.31 (s, 3H).

Methyl 2-(3-((1-(2,4-Difluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)methyl)-5-fluoro-2-methyl-1*H*-indol-1-yl)acetate (**I-8-6**). ¹H NMR (CHLOROFORM-*d*) δ 7.40 (td, *J* = 8.5, 6.4 Hz, 1H), 7.19 (dd, *J* = 9.3, 2.5 Hz, 1H), 7.09 (dd, *J* = 8.7, 4.2 Hz, 1H), 7.03 (s, 1H), 6.87 - 6.97 (m, 2H), 6.74 - 6.85 (m, 2H), 6.50 (d, *J* = 9.3 Hz, 1H), 5.03 (s, 2H), 4.80 (s, 2H), 3.73 - 3.78 (m, 5H), 2.31 (s, 3H).

6-Oxo-1,6-dihydropyridine-3-carbaldehyde (**I-9**). ¹H NMR (DMSO-*d*₆) δ 12.32 (br. s., 1H), 9.59 (d, *J* = 1.0 Hz, 1H), 8.25 (dd, *J* = 2.5, 0.5 Hz, 1H), 7.75 (dd, *J* = 9.6, 2.5 Hz, 1H), 6.41 (d, *J* = 9.6 Hz, 1H).

Methyl 2-(5-fluoro-2-methyl-3-((6-oxo-1,6-dihydropyridin-3-yl)methyl)-1*H*-indol-1-yl)acetate (**I-10**). ¹H NMR (DMSO-*d*₆) δ 11.32 (br. s., 1H), 7.36 (dd, *J* = 8.8, 4.3 Hz, 1H), 7.22 (ddd, *J* = 9.8, 7.4, 2.5 Hz, 2H), 7.14 (d, *J* = 2.0 Hz, 1H), 6.87 (td, *J* = 9.2, 2.5 Hz, 1H), 6.23 (dd, *J* = 9.5, 0.6 Hz, 1H), 5.09 (s, 2H), 3.72 (s, 2H), 3.67 (s, 3H), 2.30 (s, 3H).

Methyl 2-(5-fluoro-2-methyl-3-((6-oxo-1-(2,2,2-trifluoroethyl)-1,6-dihydropyridin-3-yl)methyl)-1*H*-indol-1-yl)acetate (**I-11-1**). ¹H NMR (DMSO-*d*₆) δ 7.59 (s, 1H), 7.36 (dd, *J* = 8.8, 4.3 Hz, 1H), 7.23 (ddd, *J* = 9.8, 5.9, 2.5 Hz, 2H), 6.88 (td, *J* = 9.1, 2.5 Hz, 1H), 6.39 (d, *J* = 9.3 Hz, 1H), 5.09 (s, 2H), 4.80 (q, *J* = 9.3 Hz, 2H), 3.75 (s, 2H), 3.67 (s, 3H), 2.32 (s, 3H).

Methyl 2-(5-fluoro-2-methyl-3-((6-oxo-1-(4,4,4-trifluorobutyl)-1,6-dihydropyridin-3-yl)methyl)-1*H*-indol-1-yl)acetic acid (**I-11-2**). ¹H NMR (DMSO-*d*₆) δ 7.62 (d, *J* = 2.0 Hz, 1H), 7.35 (dd, *J* =

8.8, 4.3 Hz, 1H), 7.23 (dd, $J = 10.0, 2.4$ Hz, 1H), 7.17 (dd, $J = 9.3, 2.5$ Hz, 1H), 6.87 (td, $J = 9.2, 2.5$ Hz, 1H), 6.29 (d, $J = 8.8$ Hz, 1H), 5.08 (s, 2H), 3.90 (t, $J = 7.2$ Hz, 2H), 3.73 (s, 2H), 3.67 (s, 3H), 2.32 (s, 3H), 2.16 - 2.30 (m, 2H), 1.84 (dt, $J = 15.2, 7.7$ Hz, 2H).

Methyl 2-(3-bromo-5-fluoro-2-methyl-1H-indol-1-yl)acetate (**I-13A**). ^1H NMR (400 MHz, DMSO- d_6) δ 7.51 (dd, $J = 4.17, 9.22$ Hz, 1H), 7.09 (dd, $J = 2.40, 9.22$ Hz, 1H), 7.02 (td, 1H), 5.20 (s, 2H), 3.69 (s, 3H), 2.34 (s, 3H).

Methyl 2-(5-fluoro-3-(6-methoxypyridin-3-yl)-2-methyl-1H-indol-1-yl)acetate (**I-14A**). ^1H NMR (400 MHz, DMSO- d_6) δ 8.21 (dd, $J = 0.76, 2.53$ Hz, 1H), 7.78 (dd, $J = 2.53, 8.34$ Hz, 1H), 7.47 (dd, $J = 4.42, 8.97$ Hz, 1H), 7.15 (dd, $J = 2.53, 9.85$ Hz, 1H), 6.93 - 7.01 (m, 2H), 5.06 (s, 2H), 3.91 (s, 3H), 2.34 (s, 3H), 1.44 (s, 9H).

Methyl 2-(3-(1-benzyl-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-methyl-1H-indol-1-yl)acetate (**I-15A-1**). ^1H NMR (400 MHz, DMSO- d_6) δ 7.83 (d, $J = 2.02$ Hz, 1H), 7.55 (dd, $J = 2.65, 9.22$ Hz, 1H), 7.44 (dd, $J = 4.29, 8.84$ Hz, 1H), 7.26 - 7.40 (m, 5H), 7.10 (dd, $J = 2.53, 9.85$ Hz, 1H), 6.96 (td, $J = 2.65, 9.16$ Hz, 1H), 6.55 (d, $J = 8.84$ Hz, 1H), 5.21 (s, 2H), 5.02 (s, 2H), 2.29 (s, 3H), 1.43 (s, 9H).

Methyl 2-(3-(1-(2,4-difluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-methyl-1H-indol-1-yl)acetate (**I-15A-2**). ^1H NMR (400 MHz, DMSO- d_6) δ 7.81 (d, 1H), 7.59 (dd, $J = 2.65, 9.22$ Hz, 1H), 7.47 (dd, $J = 4.42, 8.97$ Hz, 1H), 7.37 (td, $J = 6.57, 8.72$ Hz, 1H), 7.30 (ddd, $J = 2.65, 9.22, 10.61$ Hz, 1H), 7.16 (dd, $J = 2.53, 9.85$ Hz, 1H), 7.11 (tt, $J = 1.45, 8.53$ Hz, 1H), 6.98 (td, $J = 2.53, 9.09$ Hz, 1H), 6.54 (d, $J = 9.35$ Hz, 1H), 5.22 (s, 2H), 5.18 (s, 2H), 3.71 (s, 3H), 2.32 (s, 3H).

Methyl 2-(5-fluoro-3-(1-(4-fluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)-2-methyl-1H-indol-1-yl)acetate (**I-15A-3**). ^1H NMR (400 MHz, DMSO- d_6) δ 13.11 (br. s., 1H), 7.86 (d, $J = 2.53$ Hz, 1H), 7.55 (dd, $J = 2.53, 9.35$ Hz, 1H), 7.41 - 7.50 (m, 3H), 7.16 - 7.23 (m, 2H), 7.11 (dd, $J = 2.53, 9.85$ Hz, 1H), 6.95 (td, $J = 2.40, 9.16$ Hz, 1H), 6.54 (d, $J = 9.09$ Hz, 1H), 5.19 (s, 2H), 5.02 (s, 2H), 2.30 (s, 3H).

Methyl 2-(3-(1-(2,6-difluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-methyl-1H-indol-1-yl)acetate (**I-15A-4**). ^1H NMR (400 MHz, DMSO- d_6) δ 7.83 (s, 1H), 7.56 (dd, $J = 2.53, 9.35$ Hz, 1H), 7.39 - 7.50 (m, 2H), 7.09 - 7.18 (m, 3H), 6.98 (td, $J = 2.53, 9.09$ Hz, 1H), 6.47 (d, $J = 9.35$ Hz, 1H), 5.25 (s, 2H), 5.18 (s, 2H), 3.71 (s, 3H), 2.33 (s, 3H).

Methyl 2-(5-fluoro-2-methyl-3-(6-oxo-1,6-dihydropyridin-3-yl)-1H-indol-1-yl)acetate (**I-16A**). ^1H NMR (400 MHz, DMSO- d_6) δ ppm 2.32 (s, 3 H), 3.70 (s, 3 H), 5.14 (s, 2 H), 6.46 (d, $J=9.6$ Hz, 1 H), 7.05 (td, $J=7.4, 0.9$ Hz, 1 H), 7.12 (td, $J=7.6, 1.1$ Hz, 1 H), 7.33 (d, $J=2.3$ Hz, 1 H), 7.41 (dd, $J=8.0, 3.2$ Hz, 2 H), 7.56 (dd, $J=9.3, 2.5$ Hz, 1 H), 11.70 (br. s., 1 H)

Methyl 2-(5-fluoro-3-(1-isopropyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methyl-1H-indol-1-yl)acetate (**I-17A-1**). ^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.33 (d, $J=6.1$ Hz, 6 H), 2.35 (s, 3 H), 3.71 (s, 3 H), 5.19 (s, 2 H), 5.24 - 5.35 (m, 1 H), 6.86 (d, $J=8.3$ Hz, 1 H), 6.98 (td, $J=9.1, 2.5$ Hz, 1 H), 7.16 (dd, $J=9.9, 2.5$ Hz, 1 H), 7.47 (dd, $J=8.8, 4.3$ Hz, 1 H), 7.76 (dd, $J=8.5, 2.4$ Hz, 1 H), 8.19 (d, $J=2.5$ Hz, 1 H)

Methyl 2-(5-fluoro-2-methyl-3-(6-oxo-1-(2,2,2-trifluoroethyl)-1,6-dihydropyridin-3-yl)-1H-indol-1-yl)acetate (**I-17A-2**). ^1H NMR (400 MHz, DMSO- d_6) δ ppm 2.34 (s, 3 H), 3.70 (s, 3 H), 4.97 (q, $J=9.4$ Hz, 2 H), 5.19 (s, 2 H), 6.61 (d, $J=9.6$ Hz, 1 H), 6.99 (td, $J=9.1, 2.5$ Hz, 1 H), 7.18 (dd, $J=9.9, 2.5$ Hz, 1 H), 7.48 (dd, $J=9.0, 4.4$ Hz, 1 H), 7.64 (dd, $J=9.3, 2.5$ Hz, 1 H), 7.75 (s, 1 H)

Methyl 2-(3-bromo-5-chloro-2-methyl-1H-indol-1-yl)acetate (**I-13B**). ^1H NMR (400 MHz, DMSO- d_6) δ ppm 2.34 (s, 3 H), 3.69 (s, 3 H), 5.21 (s, 2 H), 7.18 (dd, $J=8.7, 2.1$ Hz, 1 H), 7.34

(d, $J=2.3$ Hz, 1 H), 7.53 (d, $J=8.8$ Hz, 1 H)

Methyl 2-(5-chloro-3-(6-methoxypyridin-3-yl)-2-methyl-1H-indol-1-yl)acetate (**I-14B**). ^1H NMR (400 MHz, DMSO- d_6) δ ppm 2.36 (s, 3 H), 3.72 (s, 3 H), 3.91 (s, 3 H), 5.21 (s, 2 H), 6.95 (d, $J=8.3$ Hz, 1 H), 7.15 (dd, $J=8.6$, 2.0 Hz, 1 H), 7.41 (d, $J=2.0$ Hz, 1 H), 7.51 (d, $J=8.8$ Hz, 1 H), 7.80 (dd, $J=8.6$, 2.5 Hz, 1 H), 8.22 (d, $J=2.5$ Hz, 1 H)

Methyl 2-(5-chloro-2-methyl-3-(6-oxo-1,6-dihydropyridin-3-yl)-1H-indol-1-yl)acetate (**I-16B**). ^1H NMR (400 MHz, DMSO- d_6) δ ppm 2.31 (s, 3 H), 3.70 (s, 3 H), 5.17 (s, 2 H), 6.47 (d, $J=9.6$ Hz, 1 H), 7.13 (dd, $J=8.6$, 2.0 Hz, 1 H), 7.37 (t, $J=2.8$ Hz, 2 H), 7.48 (d, $J=8.8$ Hz, 1 H), 7.55 (dd, $J=9.3$, 2.8 Hz, 1 H), 11.76 (br. s., 1 H)

Methyl 2-(5-chloro-3-(1-isopropyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methyl-1H-indol-1-yl)acetate (**I-17B-1**). ^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.34 (d, $J=6.1$ Hz, 6 H), 2.35 (s, 3 H), 3.71 (s, 3 H), 5.21 (s, 2 H), 5.24 - 5.36 (m, 1 H), 6.87 (d, $J=8.3$ Hz, 1 H), 7.14 (dd, $J=8.6$, 2.0 Hz, 1 H), 7.41 (d, $J=2.0$ Hz, 1 H), 7.51 (d, $J=8.8$ Hz, 1 H), 7.76 (dd, $J=8.6$, 2.5 Hz, 1 H), 8.20 (d, $J=2.3$ Hz, 1 H).

Methyl 2-(3-bromo-2-methyl-1H-indol-1-yl)acetate (**I-13C**). ^1H NMR (400 MHz, DMSO- d_6) δ ppm 2.34 (s, 3 H), 3.69 (s, 3 H), 5.18 (s, 2 H), 7.10 - 7.20 (m, 2 H), 7.33 - 7.37 (m, 1 H), 7.46 (dd, $J=7.2$, 0.9 Hz, 1 H)

Methyl 2-(3-(6-methoxypyridin-3-yl)-2-methyl-1H-indol-1-yl)acetate (**I-14C**). ^1H NMR (400 MHz, DMSO- d_6) δ ppm 2.36 (s, 3 H), 3.71 (s, 3 H), 3.91 (s, 3 H), 5.18 (s, 2 H), 6.95 (d, $J=8.6$ Hz, 1 H), 7.02 - 7.10 (m, 1 H), 7.10 - 7.17 (m, 1 H), 7.45 (dd, $J=8.1$, 4.8 Hz, 2 H), 7.79 (dd, $J=8.3$, 2.5 Hz, 1 H), 8.23 (d, $J=1.5$ Hz, 1 H)

Methyl 2-(2-methyl-3-(6-oxo-1,6-dihydropyridin-3-yl)-1H-indol-1-yl)acetate (**I-16C**). ^1H NMR (400 MHz, DMSO- d_6) δ ppm 2.32 (s, 3 H), 3.70 (s, 3 H), 5.14 (s, 2 H), 6.46 (d, $J=9.6$ Hz, 1 H), 7.05 (td, $J=7.4$, 0.9 Hz, 1 H), 7.12 (td, $J=7.6$, 1.1 Hz, 1 H), 7.33 (d, $J=2.3$ Hz, 1 H), 7.41 (dd, $J=8.0$, 3.2 Hz, 2 H), 7.56 (dd, $J=9.3$, 2.5 Hz, 1 H), 11.70 (br. s., 1 H)

Methyl 2-(3-(1-isopropyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methyl-1H-indol-1-yl)acetate (**I-17C-1**). ^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.34 (d, $J=6.3$ Hz, 6 H), 2.36 (s, 3 H), 3.71 (s, 3 H), 5.18 (s, 2 H), 5.23 - 5.37 (m, 1 H), 6.86 (d, $J=8.6$ Hz, 1 H), 7.06 (t, $J=7.5$ Hz, 1 H), 7.13 (td, $J=7.5$, 1.1 Hz, 1 H), 7.45 (t, $J=7.7$ Hz, 2 H), 7.76 (dd, $J=8.3$, 2.5 Hz, 1 H), 8.20 (d, $J=2.5$ Hz, 1 H)

Methyl 2-(5-chloro-2-methyl-3-(6-oxo-1-(2,2,2-trifluoroethyl)-1,6-dihydropyridin-3-yl)-1H-indol-1-yl)acetate (**I-17B-2**). ^1H NMR (400 MHz, DMSO- d_6) δ ppm 2.34 (s, 3 H), 3.70 (s, 3 H), 4.97 (q, $J=9.1$ Hz, 2 H), 5.20 (s, 2 H), 6.61 (d, $J=9.3$ Hz, 1 H), 7.15 (dd, $J=8.6$, 2.0 Hz, 1 H), 7.43 (d, $J=2.0$ Hz, 1 H), 7.51 (d, $J=8.8$ Hz, 1 H), 7.64 (dd, $J=9.3$, 2.5 Hz, 1 H), 7.78 (d, $J=2.0$ Hz, 1 H)

Methyl 2-(2-methyl-3-(6-oxo-1-(2,2,2-trifluoroethyl)-1,6-dihydropyridin-3-yl)-1H-indol-1-yl)acetate (**I-17C-2**). ^1H NMR (400 MHz, DMSO- d_6) δ ppm 2.35 (s, 3 H), 3.70 (s, 3 H), 4.97 (q, $J=9.3$ Hz, 2 H), 5.17 (s, 2 H), 6.62 (d, $J=9.3$ Hz, 1 H), 7.07 (t, $J=7.1$ Hz, 1 H), 7.14 (t, $J=7.6$ Hz, 1 H), 7.45 (d, $J=8.1$ Hz, 2 H), 7.65 (dd, $J=9.5$, 2.7 Hz, 1 H), 7.74 (d, $J=2.0$ Hz, 1 H)

Methyl 2-(3-bromo-2,5-dimethyl-1H-indol-1-yl)acetate (**I-12D**). ^1H NMR (400 MHz, DMSO- d_6) δ ppm 2.32 (s, 3 H), 2.39 (s, 3 H), 3.66 - 3.70 (m, 3 H), 5.13 (s, 2 H), 6.98 (d, $J=8.1$ Hz, 1 H), 7.13 (s, 1 H), 7.32 (d, $J=8.1$ Hz, 1 H)

Methyl 2-(3-(6-methoxypyridin-3-yl)-2,5-dimethyl-1H-indol-1-yl)acetate (**I-14D**). ^1H NMR (400 MHz, DMSO- d_6) δ ppm 2.33 (s, 3 H), 2.36 (s, 3 H), 3.70 (s, 3 H), 3.91 (s, 3 H), 5.13 (s, 2 H), 6.89 - 7.00 (m, 2 H), 7.24 (s, 1 H), 7.32 (d, $J=8.3$ Hz, 1 H), 7.78 (dd, $J=8.5$, 2.4 Hz, 1 H), 8.21 (d, $J=1.8$ Hz, 1 H)

Methyl 2-(2,5-dimethyl-3-(6-oxo-1,6-dihydropyridin-3-yl)-1H-indol-1-yl)acetate (**I-16D**). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.29 (s, 3 H), 2.36 (s, 3 H), 3.69 (s, 3 H), 5.09 (s, 2 H), 6.46 (d, *J*=9.3 Hz, 1 H), 6.94 (dd, *J*=8.6, 1.3 Hz, 1 H), 7.19 (s, 1 H), 7.25 - 7.34 (m, 2 H), 7.54 (dd, *J*=9.3, 2.5 Hz, 1 H), 11.68 (br. s., 1 H).

Methyl 2-(2,5-dimethyl-3-(6-oxo-1-(2,2,2-trifluoroethyl)-1,6-dihydropyridin-3-yl)-1H-indol-1-yl)acetate (**I-17D**). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.32 (s, 3 H), 2.36 (s, 3 H), 3.69 (s, 3 H), 4.96 (q, *J*=9.2 Hz, 2 H), 5.12 (s, 2 H), 6.61 (d, *J*=9.3 Hz, 1 H), 6.96 (dd, *J*=8.5, 1.4 Hz, 1 H), 7.22 (s, 1 H), 7.31 (d, *J*=8.3 Hz, 1 H), 7.63 (dd, *J*=9.5, 2.7 Hz, 1 H), 7.71 (d, *J*=2.5 Hz, 1 H)

Methyl 2-(3-bromo-5-methoxy-2-methyl-1H-indol-1-yl)acetate (**I-13E**). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.31 (s, 3 H), 3.68 (s, 3 H), 3.78 (s, 3 H), 5.13 (s, 2 H), 6.74 - 6.84 (m, 2 H), 7.35 (dd, *J*=8.3, 1.3 Hz, 1 H)

Methyl 2-(5-methoxy-3-(6-methoxypyridin-3-yl)-2-methyl-1H-indol-1-yl)acetate (**I-14E**). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.32 (s, 3 H), 3.67 - 3.77 (m, 6 H), 3.91 (s, 3 H), 5.12 (s, 2 H), 6.77 (dd, *J*=8.8, 2.5 Hz, 1 H), 6.87 - 6.98 (m, 2 H), 7.34 (d, *J*=8.8 Hz, 1 H), 7.78 (dd, *J*=8.6, 2.5 Hz, 1 H), 8.23 (d, *J*=1.8 Hz, 1 H)

Methyl 2-(5-methoxy-2-methyl-3-(6-oxo-1,6-dihydropyridin-3-yl)-1H-indol-1-yl)acetate (**I-16E**). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.28 (s, 3 H), 3.69 (s, 3 H), 3.73 (s, 3 H), 5.09 (s, 2 H), 6.46 (d, *J*=9.3 Hz, 1 H), 6.75 (dd, *J*=8.8, 2.3 Hz, 1 H), 6.87 (d, *J*=2.3 Hz, 1 H), 7.26 - 7.37 (m, 2 H), 7.55 (dd, *J*=9.5, 2.7 Hz, 1 H), 11.65 (br. s., 1 H)

tert-butyl 2-(3-bromo-5-chloro-2-methyl-1H-indol-1-yl)acetate (**I-18A**). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.52 (d, *J* = 8.84 Hz, 1H), 7.33 (d, *J* = 2.02 Hz, 1H), 7.18 (dd, *J* = 2.15, 8.72 Hz, 1H), 5.08 (s, 2H), 2.33 (s, 3H), 1.35 - 1.45 (m, 9H).

tert-Butyl 2-(5-chloro-3-(6-methoxypyridin-3-yl)-2-methyl-1H-indol-1-yl)acetate (**I-19A**). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.21 (dd, *J* = 0.76, 2.53 Hz, 1H), 7.79 (dd, *J* = 2.40, 8.46 Hz, 1H), 7.50 (d, *J* = 9.09 Hz, 1H), 7.40 (d, *J* = 1.77 Hz, 1H), 7.15 (dd, *J* = 2.02, 8.84 Hz, 1H), 6.95 (dd, *J* = 0.76, 8.59 Hz, 1H), 5.07 (s, 2H), 3.91 (s, 3H), 2.34 (s, 3H), 1.43 (s, 9H).

tert-Butyl 2-(3-(1-benzyl-6-oxo-1,6-dihydropyridin-3-yl)-5-chloro-2-methyl-1H-indol-1-yl)acetate (**I-20A-1**). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.86 (d, *J* = 2.27 Hz, 1H), 7.55 (dd, *J* = 2.53, 9.35 Hz, 1H), 7.47 (d, *J* = 8.84 Hz, 1H), 7.27 - 7.42 (m, 6H), 7.12 (dd, *J* = 2.15, 8.72 Hz, 1H), 6.55 (d, *J* = 9.35 Hz, 1H), 5.21 (s, 2H), 5.04 (s, 2H), 2.29 (s, 3H), 1.42 (s, 9H).

tert-Butyl 2-(3-bromo-2-methyl-1H-indol-1-yl)acetate (**I-18B**). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.44 (d, 1H), 7.29 - 7.38 (m, 1H), 7.05 - 7.21 (m, 2H), 5.03 (s, 2H), 2.33 (s, 3H), 1.42 (s, 9H).

tert-Butyl 2-(3-(1-benzyl-6-oxo-1,6-dihydropyridin-3-yl)-2-methyl-1H-indol-1-yl)acetate (**I-20B-1**). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.81 (d, 1H), 7.56 (dd, *J* = 2.53, 9.35 Hz, 1H), 7.34 - 7.43 (m, 6H), 7.12 (td, *J* = 1.26, 7.58 Hz, 1H), 7.00 - 7.06 (m, 1H), 6.55 (d, *J* = 9.35 Hz, 1H), 5.21 (s, 2H), 5.00 (s, 2H), 2.30 (s, 3H), 1.43 (s, 9H).

Methyl 2-(3-(1-(2,6-difluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)-2-methyl-1H-indol-1-yl)acetate (**I-15C-1**). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.33 (s, 3 H), 3.70 (s, 3 H), 5.16 (s, 2 H), 5.24 (s, 2 H), 6.47 (d, *J*=9.3 Hz, 1 H), 7.06 (t, *J*=7.3 Hz, 1 H), 7.09 - 7.18 (m, 3 H), 7.37 - 7.49 (m, 3 H), 7.56 (dd, *J*=9.3, 2.5 Hz, 1 H), 7.79 (s, 1 H)

Methyl 2-(3-(1-(2,3-difluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-methyl-1H-indol-1-yl)acetate (**I-15A-5**). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 2.33 (s, 3 H), 3.70 (s, 3 H), 5.17 (s, 2 H), 5.29 (s, 2 H), 6.55 (dd, *J*=9.3, 0.5 Hz, 1 H), 6.97 (td, *J*=9.2, 2.5 Hz, 1 H), 7.02 - 7.09 (m, 1 H), 7.16 (dd, *J*=9.9, 2.5 Hz, 1 H), 7.18 - 7.25 (m, 1 H), 7.34 - 7.43 (m, 1 H), 7.46 (dd, *J*=9.0, 4.4 Hz, 1 H), 7.60 (dd, *J*=9.3, 2.5 Hz, 1 H), 7.84 (d, *J*=2.5 Hz, 1 H)

Methyl 2-(3-bromo-5-fluoro-2-methyl-1H-indol-1-yl)propanoate (**I-21**). ¹H NMR (400 MHz,

DMSO- d_6) δ ppm 1.64 (d, $J=7.1$ Hz, 3 H), 2.38 (s, 3 H), 3.66 (s, 3 H), 5.62 (q, $J=7.2$ Hz, 1 H), 7.01 (td, $J=9.2, 2.5$ Hz, 1 H), 7.09 (dd, $J=9.1, 2.3$ Hz, 1 H), 7.35 (dd, $J=9.0, 4.2$ Hz, 1 H)

Methyl 2-(5-fluoro-3-(6-methoxypyridin-3-yl)-2-methyl-1H-indol-1-yl)propanoate (**I-22**). ^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.66 (d, $J=7.1$ Hz, 3 H), 2.38 (s, 3 H), 3.68 (s, 3 H), 3.91 (s, 3 H), 5.63 (q, $J=7.1$ Hz, 1 H), 6.89 - 7.02 (m, 2 H), 7.14 (dd, $J=9.7, 2.4$ Hz, 1 H), 7.31 (dd, $J=8.8, 4.3$ Hz, 1 H), 7.79 (dd, $J=8.6, 2.5$ Hz, 1 H), 8.22 (dd, $J=2.5, 0.8$ Hz, 1 H)

Methyl 2-(3-(1-(2,3-difluorobenzyl)-6-oxo-1,6-dihydropyridin-3-yl)-5-fluoro-2-methyl-1H-indol-1-yl)propanoate (**I-23**). ^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.64 (d, $J=7.1$ Hz, 3 H), 2.36 (s, 3 H), 3.67 (s, 3 H), 5.28 (s, 2 H), 5.60 (q, $J=7.2$ Hz, 1 H), 6.54 (d, $J=9.3$ Hz, 1 H), 6.96 (td, $J=9.2, 2.7$ Hz, 1 H), 7.02 - 7.08 (m, 1 H), 7.15 (dd, $J=9.7, 2.4$ Hz, 1 H), 7.21 (qd, $J=8.1, 5.2, 1.6$ Hz, 1 H), 7.29 (dd, $J=9.1, 4.3$ Hz, 1 H), 7.34 - 7.45 (m, 1 H), 7.60 (dd, $J=9.3, 2.5$ Hz, 1 H), 7.84 (d, $J=2.5$ Hz, 1 H)

tert-Butyl 3-bromo-5-fluoro-2-methyl-1H-indole-1-carboxylate (**I-24**). ^1H NMR (400 MHz, DMSO- d_6) δ 8.03 - 8.15 (m, 1H), 7.13 - 7.26 (m, 2H), 2.60 (s, 3H), 1.64 (s, 9H).

tert-Butyl 5-fluoro-3-(isoquinolin-4-yl)-2-methyl-1H-indole-1-carboxylate (**I-25**). ^1H NMR (400 MHz, CHLOROFORM- d) δ 9.33 (s, 1H), 8.49 (s, 1H), 8.17 (dd, $J = 4.80, 9.09$ Hz, 1H), 8.05 - 8.13 (m, 1H), 7.56 - 7.70 (m, 3H), 7.01 (td, $J = 2.65, 9.03$ Hz, 1H), 6.70 (dd, $J = 2.53, 8.84$ Hz, 1H), 2.46 (s, 3H), 1.73 (s, 9H).

tert-Butyl 3-(2-benzyl-1-oxo-1,2-dihydroisoquinolin-4-yl)-5-fluoro-2-methyl-1H-indole-1-carboxylate (**I-26**). ^1H NMR (400 MHz, DMSO- d_6) δ 8.42 (dd, $J = 1.52, 8.08$ Hz, 1H), 8.20 (d, $J = 8.34$ Hz, 1H), 7.65 - 7.75 (m, 2H), 7.57 - 7.65 (m, 1H), 7.31 - 7.49 (m, 6H), 7.07 - 7.29 (m, 3H), 5.26 - 5.39 (m, 2H), 2.47 (s, 3H), 1.73 (s, 9H).

2-Isopropylisoquinolin-1(2H)-one (**I-27-1**). ^1H NMR (400 MHz, DMSO- d_6) δ 8.23 (d, $J = 8.08$ Hz, 1H), 7.61 - 7.74 (m, 2H), 7.44 - 7.59 (m, 2H), 6.67 (d, $J = 7.58$ Hz, 1H), 5.20 (dt, $J = 6.66, 13.71$ Hz, 1H), 1.33 (d, 6H).

4-iodo-2-isopropylisoquinolin-1(2H)-one (**I-28-1**). ^1H NMR (400 MHz, DMSO- d_6) δ 8.17 - 8.30 (m, 1H), 7.93 (s, 1H), 7.83 (ddd, $J = 1.52, 7.14, 8.27$ Hz, 1H), 7.62 - 7.66 (m, 1H), 7.56 - 7.61 (m, 1H), 5.13 (quin, $J = 6.82$ Hz, 1H), 1.36 (d, $J = 6.82$ Hz, 6H).

2-Isopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2H)-one (**I-29-1**). ^1H NMR (400 MHz, DMSO- d_6) δ 8.32 (d, $J = 7.58$ Hz, 1H), 8.26 (dq, $J = 0.71, 7.99$ Hz, 1H), 7.70 - 7.78 (m, 2H), 7.47 - 7.54 (m, 1H), 5.13 (quin, $J = 6.82$ Hz, 1H), 1.36 (d, $J = 7.07$ Hz, 6H), 1.34 (s, 12H).

2-(2,2,2-Trifluoroethyl)isoquinolin-1(2H)-one (**I-27-2**). ^1H NMR (400 MHz, DMSO- d_6) δ 8.21 - 8.30 (m, 1H), 7.73 - 7.80 (m, 1H), 7.67 - 7.72 (m, 1H), 7.56 (ddd, $J = 1.26, 7.01, 8.15$ Hz, 1H), 7.47 (d, $J = 7.33$ Hz, 1H), 6.72 (d, $J = 7.07$ Hz, 1H), 4.94 (q, 2H).

4-Iodo-2-(2,2,2-trifluoroethyl)isoquinolin-1(2H)-one (**I-28-2**). ^1H NMR (400 MHz, DMSO- d_6) δ 8.23 - 8.28 (m, 1H), 8.03 (s, 1H), 7.90 (td, $J = 1.39, 7.64$ Hz, 1H), 7.69 (d, $J = 7.58$ Hz, 1H), 7.62 - 7.67 (m, 1H), 4.92 (q, $J = 9.35$ Hz, 2H).

4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(2,2,2-trifluoroethyl)isoquinolin-1(2H)-one (**I-29-2**). ^1H NMR (400 MHz, DMSO- d_6) δ 8.21 - 8.31 (m, 1H), 8.03 (s, 1H), 7.86 - 7.93 (m, 1H), 7.69 (d, $J = 7.58$ Hz, 1H), 7.65 (ddd, 1H), 4.93 (q, 2H), 1.17 (s, 12H).

2-(4,4,4-trifluorobutyl)isoquinolin-1(2H)-one (**I-27-3**). ^1H NMR (400 MHz, DMSO- d_6) δ 8.23 (d, $J = 8.08$ Hz, 1H), 7.63 - 7.75 (m, 2H), 7.43 - 7.55 (m, 2H), 6.65 (d, $J = 7.33$ Hz, 1H), 3.97 - 4.08 (m, 2H), 2.23 - 2.43 (m, 2H), 1.92 (dt, $J = 7.64, 15.03$ Hz, 2H).

4-Iodo-2-(4,4,4-trifluorobutyl)isoquinolin-1(2H)-one (**I-28-3**). ^1H NMR (400 MHz, DMSO- d_6) δ 8.20 - 8.27 (m, 1H), 8.05 (s, 1H), 7.80 - 7.87 (m, 1H), 7.65 (d, $J = 7.58$ Hz, 1H), 7.59 (ddd, $J =$

1.26, 7.14, 8.02 Hz, 1H), 3.99 - 4.06 (m, 2H), 2.23 - 2.41 (m, 2H), 1.84 - 1.97 (m, 2H).
4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(4,4,4-trifluorobutyl)isoquinolin-1(2H)-one (**I-29-3**). ^1H NMR (400 MHz, DMSO- d_6) δ 8.33 (d, 1H), 8.25 (dd, $J = 1.01$, 8.08 Hz, 1H), 7.83 (s, 1H), 7.74 (ddd, $J = 1.52$, 7.07, 8.34 Hz, 1H), 7.51 (ddd, $J = 1.26$, 7.01, 8.15 Hz, 1H), 4.09 (t, $J = 7.45$ Hz, 2H), 2.21 - 2.45 (m, 2H), 1.79 - 1.97 (m, 2H), 1.34 (s, 12H).

2-Neopentylisoquinolin-1(2H)-one (**I-27-4**). ^1H NMR (400 MHz, DMSO- d_6) δ 8.19 - 8.25 (m, 1H), 7.67 - 7.72 (m, 1H), 7.63 - 7.66 (m, 1H), 7.49 (ddd, $J = 1.39$, 6.88, 8.15 Hz, 1H), 7.37 (d, $J = 7.58$ Hz, 1H), 6.58 (d, $J = 6.82$ Hz, 1H), 3.86 (s, 2H), 0.94 (s, 9H).

2-Neopentyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinolin-1(2H)-one (**I-29-4**). ^1H NMR (400 MHz, DMSO- d_6) δ 8.31 (d, $J = 7.58$ Hz, 1H), 8.25 (dd, $J = 1.01$, 8.08 Hz, 1H), 7.74 (ddd, $J = 1.52$, 6.95, 8.21 Hz, 1H), 7.70 (s, 1H), 7.49 (td, $J = 1.26$, 7.58 Hz, 1H), 3.95 (s, 2H), 1.30 - 1.37 (m, 12H), 0.93 (s, 9H).

Methyl 2-(5-fluoro-3-iodo-2-methyl-1H-indol-1-yl)acetate. ^1H NMR (400 MHz, CHLOROFORM- d) δ 2.44 (s, 3 H) 3.74 (s, 3 H) 4.82 (s, 2 H) 6.89 - 6.97 (m, 1 H) 7.02 - 7.09 (m, 2 H).

Methyl 2-(5-fluoro-3-iodo-2-methyl-1H-indol-1-yl)acetate (**I-30**). ^1H NMR (400 MHz, CHLOROFORM- d) δ 2.44 (s, 3 H) 3.74 (s, 3 H) 4.82 (s, 2 H) 6.89 - 6.97 (m, 1 H) 7.02 - 7.09 (m, 2 H).

5,6,7,8-Tetrahydroisoquinolin-1(2H)-one (Intermediate **I-31**). ^1H NMR (400 MHz, CHLOROFORM- d) δ 1.65 - 1.83 (m, 4 H) 2.47 - 2.65 (m, 4 H) 6.02 (d, $J = 6.6$ Hz, 1 H) 7.17 (d, $J = 6.6$ Hz, 1 H) 12.92 (br. s., 1 H).

2-Isopropyl-5,6,7,8-tetrahydroisoquinolin-1(2H)-one (**I-32-1**). ^1H NMR (400 MHz, CHLOROFORM- d) δ 1.32 (d, 6 H) 1.62 - 1.82 (m, 4 H) 2.39 - 2.62 (m, 4 H) 5.30 (spt, $J = 6.9$ Hz, 1 H) 5.97 (d, $J = 7.1$ Hz, 1 H) 7.09 (d, $J = 7.1$ Hz, 1 H).

4-iodo-2-isopropyl-5,6,7,8-tetrahydroisoquinolin-1(2H)-one (**I-33-1**). ^1H NMR (400 MHz, CHLOROFORM- d) δ 1.34 (d, 6 H) 1.65 - 1.81 (m, 4 H) 2.38 - 2.49 (m, 2 H) 2.51 - 2.59 (m, 2 H) 5.23 (spt, $J = 6.8$ Hz, 1 H) 7.50 (s, 1 H).

2-Isopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6,7,8-tetrahydroisoquinolin-1(2H)-one (**I-34-1**). ^1H NMR (400 MHz, CHLOROFORM- d) δ 1.30 (s, 12 H) 1.36 (d, $J = 6.8$ Hz, 6 H) 1.64 - 1.77 (m, 4 H) 2.49 - 2.57 (m, 2 H) 2.73 - 2.82 (m, 2 H) 5.25 (quin, $J = 6.9$ Hz, 1 H) 7.64 (s, 1 H).

2-(2,2,2-Trifluoroethyl)-5,6,7,8-tetrahydroisoquinolin-1(2H)-one (**I-32-2**). ^1H NMR (400 MHz, CHLOROFORM- d) δ 1.65 - 1.82 (m, 4 H) 2.47 - 2.61 (m, 4 H) 4.59 (q, $J = 8.8$ Hz, 2 H) 5.98 (d, $J = 7.3$ Hz, 1 H) 7.03 (dd, $J = 7.1$, 0.8 Hz, 1 H).

4-Iodo-2-(2,2,2-trifluoroethyl)-5,6,7,8-tetrahydroisoquinolin-1(2H)-one (**I-33-2**). ^1H NMR (400 MHz, CHLOROFORM- d) δ 1.63 - 1.80 (m, 4 H) 2.41 - 2.50 (m, 2 H) 2.52 - 2.59 (m, 2 H) 4.58 (q, $J = 8.7$ Hz, 2 H) 7.52 (s, 1 H).

4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(2,2,2-trifluoroethyl)-5,6,7,8-tetrahydroisoquinolin-1(2H)-one (**I-34-2**). ^1H NMR (400 MHz, CHLOROFORM- d) δ 1.30 (s, 12 H) 1.66 - 1.76 (m, 4 H) 2.45 - 2.59 (m, 2 H) 2.74 - 2.83 (m, 2 H) 4.60 (q, $J = 8.6$ Hz, 2 H) 7.58 (s, 1 H).

2-(4,4,4-Trifluorobutyl)-5,6,7,8-tetrahydroisoquinolin-1(2H)-one (**I-32-3**). ^1H NMR (400 MHz, CHLOROFORM- d) δ 1.64 - 1.81 (m, 4 H) 1.94 - 2.08 (m, 2 H) 2.09 - 2.24 (m, 2 H) 2.49 - 2.57 (m, 4 H) 3.97 (t, $J = 7.1$ Hz, 2 H) 5.95 (d, $J = 7.1$ Hz, 1 H) 6.99 (d, $J = 7.1$ Hz, 1 H).

4-Iodo-2-(4,4,4-trifluorobutyl)-5,6,7,8-tetrahydroisoquinolin-1(2H)-one (**I-33-3**). ^1H NMR (400 MHz, CHLOROFORM-*d*) δ 1.64 - 1.82 (m, 4 H) 1.94 - 2.07 (m, 2 H) 2.10 - 2.25 (m, 2 H) 2.42 - 2.49 (m, 2 H) 2.54 (t, $J=5.7$ Hz, 2 H) 3.95 (t, $J=7.2$ Hz, 2 H) 7.47 (s, 1 H).

4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(4,4,4-trifluorobutyl)-5,6,7,8-tetrahydroisoquinolin-1(2H)-one (**I-34-3**). ^1H NMR (400 MHz, CHLOROFORM-*d*) δ 1.31 (s, 12 H) 1.71 (dt, $J=6.4, 3.1$ Hz, 4 H) 1.97 - 2.09 (m, 2 H) 2.09 - 2.25 (m, 2 H) 2.46 - 2.59 (m, 2 H) 2.72 - 2.83 (m, 2 H) 3.98 (t, $J=7.2$ Hz, 2 H) 7.55 (s, 1 H).

2-Benzyl-5,6,7,8-tetrahydroisoquinolin-1(2H)-one (**I-32-4**). ^1H NMR (400 MHz, CHLOROFORM-*d*) δ 1.62 - 1.84 (m, 4 H) 2.48 - 2.54 (m, 2 H) 2.56 (t, $J=5.8$ Hz, 2 H) 5.91 (d, $J=7.1$ Hz, 1 H) 7.04 (d, $J=7.1$ Hz, 1 H) 7.22 - 7.37 (m, 5 H).

2-Benzyl-4-iodo-5,6,7,8-tetrahydroisoquinolin-1(2H)-one (**I-33-4**). ^1H NMR (400 MHz, CHLOROFORM-*d*) δ 1.58 - 1.80 (m, 4 H) 2.43 (t, $J=5.1$ Hz, 2 H) 2.57 (t, $J=5.3$ Hz, 2 H) 5.08 (s, 2 H) 7.23 - 7.38 (m, 5 H) 7.51 (s, 1 H).

2-Benzyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6,7,8-tetrahydroisoquinolin-1(2H)-one (**I-34-4**). ^1H NMR (400 MHz, CHLOROFORM-*d*) δ 1.28 (s, 12 H) 1.62 - 1.80 (m, 4 H) 2.46 - 2.60 (m, 2 H) 2.73 - 2.85 (m, 2 H) 5.12 (s, 2 H) 7.21 - 7.36 (m, 5 H) 7.67 (s, 1 H).