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Synthesis of Spiropiperidine Lactam Acetyl-CoA Carboxylase Inhibitors

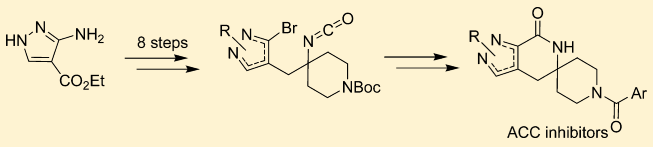
Kim Huard,[†] Scott W. Bagley,[†] Elnaz Menhaji-Klotz,*[,†] Cathy Préville,[†] James A. Southers, Jr.,[†] Aaron C. Smith,[†] David J. Edmonds,[†] John C. Lucas,[†] Matthew F. Dunn,[†] Nigel M. Allanson,[‡] Emma L. Blaney,[‡] Carmen N. Garcia-Irizarry,[†] Jeffrey T. Kohrt,[†] David A. Griffith,[†] and Robert L. Dow[†]

[†]Pfizer Worldwide Research & Development, Eastern Point Road, Groton, Connecticut 06340, United States

[‡]Peakdale Molecular Ltd, Peakdale Science Park, Sheffield Road, Chapel-en-le-Frith, High Peak, SK23 0PG, United Kingdom

Supporting Information

ABSTRACT: The synthesis of 4′,6′-dihydrospiro[piperidine-4,5′-pyrazolo[3,4-*c*]pyridin]-7′(2′*H*)-one-based acetyl-CoA carboxylase inhibitors is reported. The hitherto unknown N-2 *tert*-butyl pyrazolospirolactam core was synthesized from ethyl 3-amino-1*H*-pyrazole-4-carboxylate in a streamlined 10-step synthesis requiring only one chromatography procedure. The described synthetic strategy provides pyrazolo-fused spirolactams from halogenated benzylic arenes and cyclic carboxylates. Key steps include a regioselective pyrazole alkylation providing the N-2 *tert*-butyl pyrazole and a Curtius rearrangement under both conventional and flow conditions to install the hindered amine via a stable and isolable isocyanate. Finally, a Parham-type cyclization was used to furnish the desired spirolactam. An analogous route provided efficient access to the related N-1 isopropyl lactam series. Elaboration of the lactam cores via amidation enabled synthesis of novel ACC inhibitors and the identification of potent analogues.



INTRODUCTION

Type 2 diabetes mellitus (T2DM) is associated with a fundamental imbalance in lipid metabolism, and these alterations are hypothesized to contribute to the molecular pathogenesis of insulin resistance. Fatty acid oxidation is suppressed, and the rate of hepatic de novo lipogenesis is increased in the insulin-resistant state.[1] Acetyl-CoA carboxylase (ACC) serves as a critical switch, regulating the transition from lipogenic to oxidative lipid metabolism. Inhibition of ACC activity is expected to have a favorable impact on both skeletal muscle and hepatic insulin sensitivity by rebalancing the alterations in lipid metabolism associated with the pathogenesis of insulin resistance. Consequently, pharmacologic ACC inhibitors may have utility in the treatment of T2DM.[2]

Pyrazole spiropyranone **1** was recently reported by Pfizer as a potent ACC inhibitor.[3] A chemical stability issue involving base-mediated retro-Michael-type ring-opening reaction and subsequent olefin migration was addressed with carbocyclic variant **2**.[4,5] To explore alternative SAR, we sought to replace the ketone in compound **2** with a lactam core as exemplified by compound **3**.[6]

Described here is the route that provided the desired N-2 *tert*-butyl pyrazolo-lactam scaffold (**40**) related to **3**. This regioselective, robust, and scalable sequence provided the desired pyrazole spirolactam in 27% overall yield and only one chromatography step. Synthesis of the isomeric N-1 isopropyl series is also illustrated. This synthesis provided access to analogues and enabled investigation of the in vitro activity for this class of compounds. Compounds derived from the spirolactam core structures are currently being investigated for the treatment of T2DM.

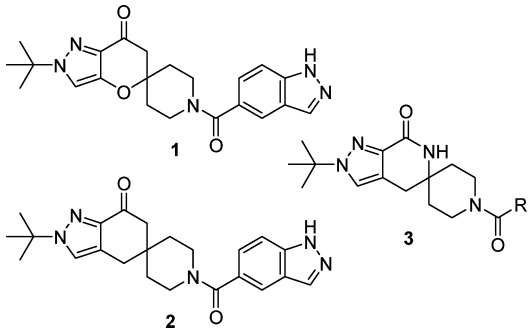


Figure 1. Examples of Pfizer ACC inhibitors.

RETROSYNTHETIC ANALYSIS

A search for existing literature around the pyrazolo spirolactam scaffold did not provide any precedents, and we were dismayed to find only limited examples of spiro-fused dihydroisoquinolones such as compounds **6**, **9**, **11**, **13**, and **16** (Scheme 1). Two examples (transformations a and b in Scheme 1) demonstrated nucleophilic attack of a benzylic carbon upon a ketimine derived from cyclohexanone or piperidinone, respectively, with subsequent ring closure.[7,8] Both of these examples would require lactam N-deprotection. Additional examples made use

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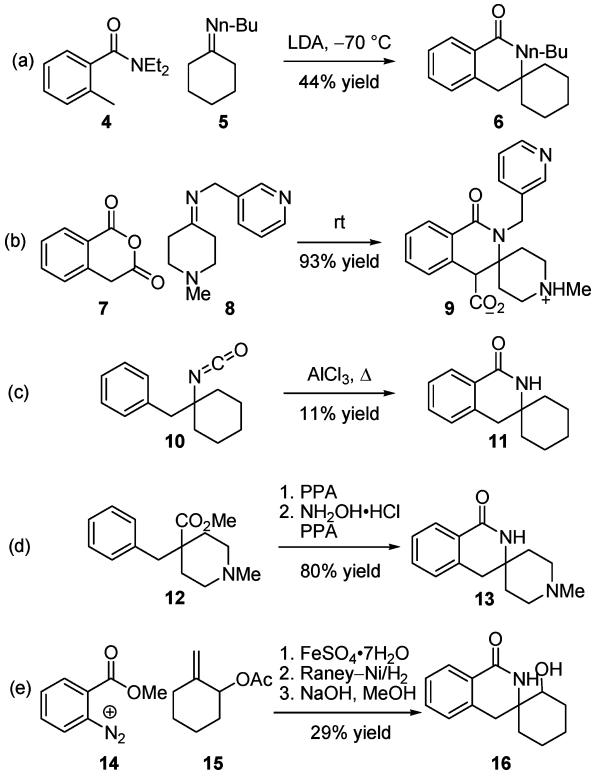
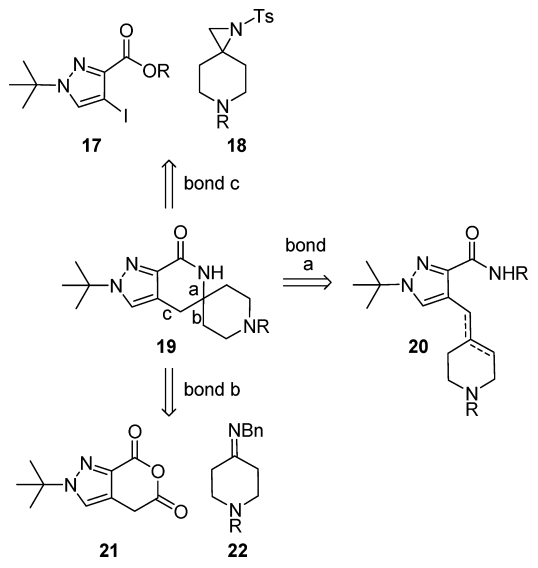
Scheme 1. Synthesis of Spirocyclic Dihydroisoquinolones



of a Lewis or protic acid (equations c and d, respectively) to form the desired C−C bond of **11** and **13**.[7,9] Equation d used a Beckmann rearrangement to form the lactam from an intermediate spiroindanone. This reference described a spirolactam with a fused thiophene, the only literature example of a heterofused spirocyclic lactam that we noted in our research. Most recently, a literature report described radical carboamination of aryl diazonium salts and olefins to access spirocarbocyclic dihydroisoquinolones (equation e).[10]

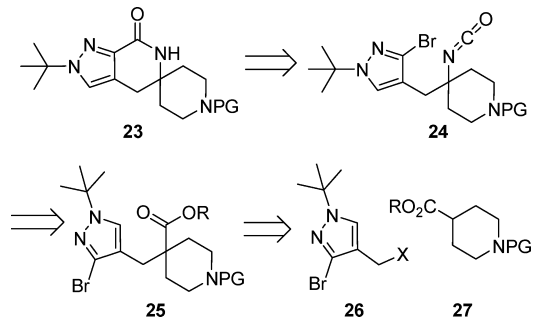
Scheme 2 summarizes some of our initial attempts to synthesize the desired spirolactam **19** in light of the limited literature precedents and illustrates the synthetic challenge of working with the pyrazole scaffold. For example, disconnection of bond a via iodolactamization[11] or hydroamidation[12] resulted in no reaction. Nitrene cyclization[13] of olefinic precursor **20** did not provide the desired spirolactam. Addition of a nucleophilic pyrazole derivative to an imine to form bond b resulted in low conversion[8] to the desired product, and addition of pyrazole **17** to aziridine[14] to form bond c also proved fruitless.

Scheme 2. Attempted Routes toward the Lactam Core



The retrosynthetic strategy that provided access to the spirolactam core is described in Scheme 3. We imagined late-stage deprotection of lactam **23** would reveal the piperidine nitrogen that could undergo amide coupling and serve as the point of diversity for preparing lactam-containing ACC inhibitors. We hoped to target pyrazolo spirolactam **23** from isocyanate **24** via Parham-type cyclization as demonstrated by Quin et al. in their synthesis of isoindolinones.[15−17] We imagined that a Curtius rearrangement of a carboxy ester derivative such as **25** would install the isocyanate and establish the tertiary alkyl nitrogen atom. The all-carbon quaternary center could be introduced via alkylation of ester **27**, with a suitably functionalized pyrazole derivative (**26**).

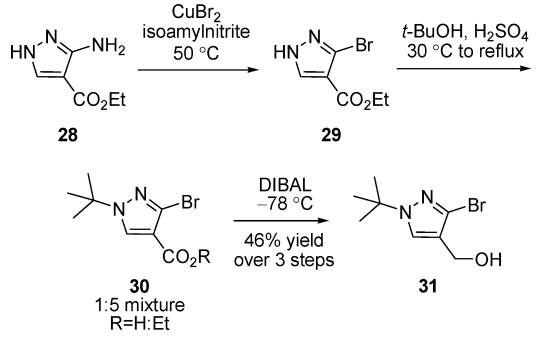
Scheme 3. Retrosynthetic Strategy



RESULTS AND DISCUSSION

The primary alcohol of pyrazole **31** was envisioned to be a suitable precursor to generate the desired alkylating agent, **26**. To access **31**, the synthetic sequence began with the commercially available ethyl 3-amino-1*H*-pyrazole-4-carboxylate **28** (Scheme 4). Sandmeyer reaction with copper(II) bromide provided bromide **29**, which was used without further purification. The crude material was alkylated with *in situ* prepared isobutylene (*t*-BuOH in sulfuric acid[18]) to furnish the *tert*-butyl pyrazole as a mixture of the carboxylic acid and ethyl ester (1:5 respectively) with complete regioselectivity of alkylation as confirmed by NOE. The mixture of carboxy

Scheme 4. Synthesis of Primary Alcohol 31



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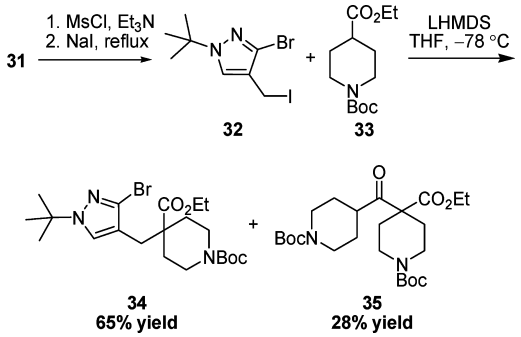
derivatives was treated with DIBAL at low temperature to generate alcohol **31**. Purification by column chromatography provided the desired alcohol in 46% yield, over three steps from the commercially available amino pyrazole **28**.

Bromination of alcohol **31** with PBr_3, to generate a good leaving group, proved capricious with variable yields. Instead, iodide **32** was prepared in a two-step sequence of mesylation/chlorination and a subsequent Finkelstein reaction with NaI (Scheme 5). This fast and reproducible method provided an

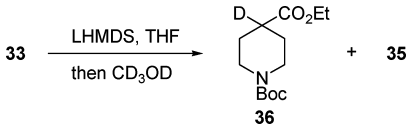
Scheme 5. Initial Alkylation Conditions



active electrophile without the need for purification. Alcohol **31** was treated with MsCl to provide the chloride as an oil. After aqueous workup, the chloride was exchanged with sodium iodide in acetone at reflux to provide pyrazolo iodide **32** which was used crude in the subsequent alkylation. Our initial alkylation conditions (addition of LHMDS to **33**, followed by addition of **32**) resulted in formation of the desired product **34**, albeit with large quantities of the Claisen condensation side-product **35**.

Deuterium exchange experiments were undertaken to explore the best conditions for lithium enolate formation, and the results are summarized in Table 1. We found that while the

Table 1. Deuterium Quenching Experiments



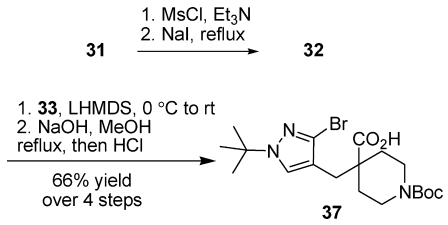
entry	conditions[a]	temp of LHMDS addition, °C	temp of CD_3OD quench, °C	% yield **35**[b]
1	A	−78	−78	n/a[c]
2	A	5	5	40
3	B	0	0	10
4	B	0	23	25
5	B	23	23	30

[a]Reaction conditions: (A) 1.2 equiv of LHMDS was added to a 0.12 M solution of ester (1.0 equiv) in THF. Reaction conditions: (B) A 0.5 M solution of ester (1 equiv) was added to a 0.12 M solution of LHMDS (1.2 equiv) in THF. [b]Determined by ^1H NMR, relative to ethyl *N*-Boc-piperidine-4-carboxylate. [c]No enolate formation.

desired enolate was not formed at −78 °C (entry 1), the Claisen condensation side product formed to a greater extent as the reaction temperature was raised. For example, adding base to a solution of **33** at 5 °C and quenching with CD_3OD at 5 °C resulted in significant formation of **35** (entry 2). When the order of addition was reversed, i.e., a solution of the ester was added to a solution of the LHMDS at 0 °C and quenched with CD_3OD at 0 °C, we found a significant drop in Claisen condensation (entry 3). When the reaction was warmed to room temperature and quenched with CD_3OD, once again Claisen condensation produced more of the troublesome side product (entries 4 and 5). In summary, addition of the ester to the base at 0 °C was identified as the most efficient procedure.

Having identified conditions to minimize side-product formation, we set out to complete the desired homologation sequence with iodide **32** (Scheme 6). In the event, excess

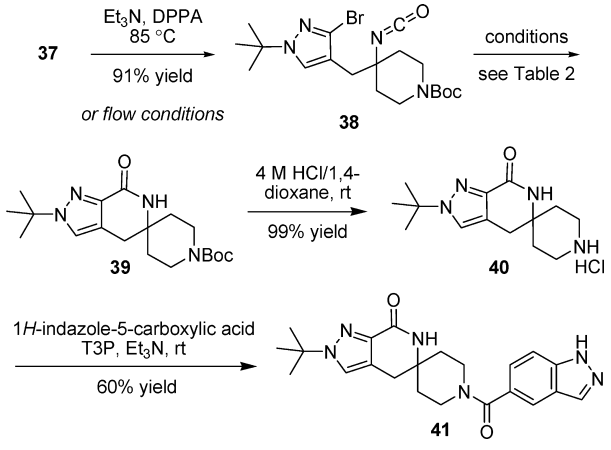
Scheme 6. Synthesis of Carboxylic Acid 37



amounts of ester **33** were used to consume iodide **32**. This meant that the crude reaction mixture contained ester **33** as well as some Claisen condensation product **35** which necessitated a chromatography step to isolate desired product **34**. We found the best way to avoid chromatographic purification was to hydrolyze the crude mixture containing ester **34** with sodium hydroxide in methanol. The sodium carboxylate salt of the desired product was moderately soluble in ethyl acetate and could be extracted from the aqueous layer. The combined organic extracts were concentrated in vacuo to provide a solid which was triturated with dichloromethane and heptane to remove organic impurities. Finally, the sodium salt was treated with aqueous 1 N HCl to isolate carboxylic acid **37** as an analytically pure and colorless solid. Acid **37** was made in 66% yield over four steps from primary alcohol **31**.

Appropriately functionalized carboxylic acid **37** was used to generate the lactam core in a two-step process (Scheme 7).

Scheme 7. Elaboration of Acid 37 to ACC Inhibitor 41



First, compound **37** was treated with DPPA and Et_3N to effect a Curtius rearrangement and install the tertiary alkyl amine functionality, in the form of isocyanate **38**, in 91% yield. While we found that the isocyanate was stable enough to survive column chromatography, it was isolated from the crude reaction mixture as a gum and used without further purification. Because of safety concerns associated with running large-scale

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Curtius reactions, conditions were developed for this transformation in a flow reactor.[19] ISCO pumps were used to combine a toluene solution of acid **37** and Et_3N with a toluene solution of diphenylphosphoryl azide within a flow reactor. The reactor residence time was approximately 90 min, and the loop was maintained at 120 °C and 500 psi. As with the conventional heating conditions, aqueous workup of the flow eluent provided crude material that was used without further purification.

Cyclization of isocyanate **38** was investigated under a range of conditions (Table 2). Reaction of **38** with either *sec*-butyllithium or *tert*-butyllithium at −78 °C afforded a high yield of the desired spirolactam core. Running the reaction at −42 °C was also successful in furnishing the desired C−C bond and is more amenable to large-scale synthesis. In attempts to replace the more pyrophoric organolithium reagents with *i*-PrMgCl, addition of the Grignard reagent to the isocyanate was observed. Treatment of **38** with Mg turnings also failed to provide the desired product.

Table 2. Lactam Cyclization

conditions[a]	% yield of **39**[b]
t-BuLi (2 equiv), −78 °C	99
s-BuLi (2 equiv), −78 °C	96
s-BuLi (2 equiv), −42 °C	99
i-PrMgCl (1 equiv), −78 °C	0
Mg turnings (10 equiv), rt → reflux	0

[a]Typical reaction conditions: Base was added to a 0.1 M solution of isocyanate in THF at the designated temperature. After being stirred for 1 h, the reaction was warmed to RT and quenched. [b]Isolated yield.

During our synthesis, *tert*-butyllithium was used to form lactam **39** in quantitative yield on greater than a 15 g scale, and the structure of the cyclization product was confirmed by NOESY. Hydrogen chloride in dioxane was used to deprotect the piperidine amine group and provide the HCl salt of the lactam core in quantitative yield. This route provided the lactam core with an overall yield of 27% over 10 steps from the commercially available amino pyrazole. The spirolactam core was then elaborated into ACC inhibitors via amide formation.[20] This is exemplified by product **41** which proved to be a potent ACC inhibitor with an IC_{50} value of 67 nM.[21]

The favorable properties of the N-2 *tert*-butyl pyrazole lactams generated interest in the related N-1 isopropyl analogues. Scheme 8 describes the synthesis of a representative N-1 pyrazole analogue using the same key bond disconnections to form the spirolactam. Commercially available ethyl (ethoxymethylene) cyanoacetate was converted to N-1 pyrazole **44** in two steps via regioselective condensation using isopropylhydrazine[22] followed by a subsequent Sandmeyer reaction. With the isopropyl group appropriately installed at N-1, ethyl ester **44** was then converted to the desired isopropyl lactam **48** in a similar synthetic sequence as discussed above for the N-2 *tert*-butyl series.[23] The isopropyl lactam was acylated to generate final analogues for biological evaluation against ACC inhibition. Amide **49** is a representative example with an IC_{50} of 174 nM.[24]

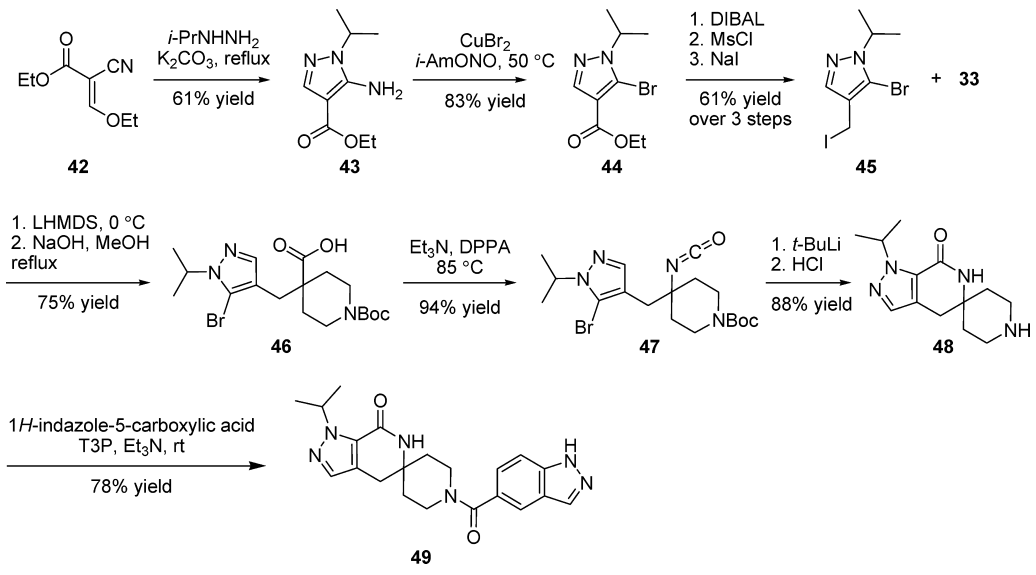
CONCLUSION

Our interest in developing ACC inhibitors led us to explore a number of pyrazole cores including an N-2 *tert*-butyl spirolactam-based template. Challenges in synthesizing these hitherto unknown scaffolds led to the exploration of several reactions traditionally circumvented in an industrial setting due to safety concerns upon scale-up. Rapid access to the lactam provided a number of active compounds which underscored our desire to access this structural motif. These successes led to an internal campaign to optimize the route for efficiency and safety. In this regard, an optimized reaction sequence of 10 steps from commercially available materials provided **40** in 27% overall yield and facilitated advanced analogue production. From a broader perspective, this work describes synthetic access to fused pyrazolo spirolactams from halogenated benzylic arenes and cyclic carboxylates and could be applied to the synthesis of other spirocyclic systems.

EXPERIMENTAL SECTION

General Experimental Methods. All chemicals, reagents, and solvents were purchased from commercial sources and used without further purification. ^{1}H NMR spectra were recorded with 400 or 500 MHz spectrometers and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical

Scheme 8. Synthesis of N-1 *i*-Pr Lactam Core



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shift (δ ppm), multiplicity, coupling constant (Hz), and integration. The multiplicities are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; spt, septet; m, multiplet; br s, broad singlet. ^{13}C NMR spectra were recorded at 100 or 125 MHz. Data for ^{13}C NMR spectra are reported in terms of chemical shift (δ ppm). IR spectra are reported by frequency of absorption (cm^{-1}). High resolution mass spectrometry (HRMS) was performed via electrospray ionization (ESI) source. The system used was an Agilent 1200 DAD (G1315C): 190−400 nm scan; 4 nm slit, and Agilent 6220 MS (TOF). Silica gel chromatography was performed using a medium pressure Biotage or ISCO system and columns prepackaged by various commercial vendors including Biotage and ISCO. Whatman precoated silica gel plates (250 μm) were used for analytical thin-layer chromatography (TLC). The terms "concentrated" and "evaporated" refer to the removal of solvent at reduced pressure on a rotary evaporator with a water bath temperature not exceeding 60 °C.

Ethyl 3-Bromo-1*H*-pyrazole-4-carboxylate (29). A three-neck flask equipped with a mechanical stirrer was charged with ethyl 3-amino-1*H*-pyrazole-4-carboxylate (98.6 g, 635 mmol), $CuBr_2$ (144 g, 640 mmol), and MeCN (1.27 L). The mixture was cooled in an ice bath, and isoamyl nitrite (110 mL, 820 mmol) was added. After 15 min of stirring at this temperature, the reaction was slowly warmed to an internal temperature of 50 °C and stirred for 2 h. The dark green reaction mixture was then cooled to room temperature, quenched with a 1 M aqueous solution of HCl (700 mL), and washed with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the desired product as a thick, dark green oil (124 g) that was used without further purification. For characterization purposes, an aliquot was purified by silica gel chromatography (20−40% EtOAc/heptanes), and the desired product was isolated as a white solid: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.63 (br s, 1H), 8.15 (s, 1H), 4.36 (q, J = 7.2 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.9, 135.0, 127.8, 114.0, 61.0, 14.5; HRMS (ESI) m/z [M + 2 + H]$^+$ calcd for $C_6H_8BrN_2O_2$, 220.9744, found 220.9746; mp = 85−88 °C; IR: 3147, 2978, 1707, 1207, 1054, 769.

3-Bromo-1-*tert*-butyl-1*H*-pyrazole-4-carboxylic Acid (30). A mixture of pyrazole **29** (124 g) and *t*-BuOH (252 g, 3.40 mmol) was heated to 30 °C to give a homogeneous green solution. Concentrated H_2SO_4 (54.2 mL, 1.01 mol) was slowly added, and the solution was stirred at this temperature until bubbling stopped. The reaction mixture was then heated to gentle reflux for 2.5 h, which caused the solution to turn from green to brown. After being cooled to room temperature, the reaction mixture was diluted with EtOAc. The organic layer was washed with water, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a brown gum (149 g). NMR analysis of this brown gum is consistent with a mixture (1:5) of the desired 3-bromo-1-*tert*-butyl-1*H*-pyrazole-4-carboxylic acid (**30**) and its ethyl ester. This mixture of carboxylic acid and ester (149 g) was used without further purification. For characterization purposes, an aliquot (240 mg, 1.44 mmol) was dissolved in THF (3 mL) and treated with a 1 M aqueous solution of LiOH (5 mL, 5 mmol) at 60 °C for 4 h. The solution was acidified to pH of ∼3 with a 1 M aqueous solution of HCl. The aqueous solution was washed with DCM. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the desired carboxylic acid as a white solid (320 mg, 90%). This white solid can be further purified by trituration in heptanes: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.05 (s, 1H), 1.62 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.3, 132.9, 128.0, 112.3, 60.9, 29.6; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_8H_{11}BrN_2NaO_2$, 268.9896, found 268.9901; mp = 165−168 °C; IR: 2979, 2591, 1681, 1531, 1245, 1057, 768, 730. The regioselectivity was confirmed by NOESY NMR ($CDCl_3$, 500 MHz) between the *tert*-butyl group (1.62 ppm) and the aromatic proton (8.05 ppm).

(3-Bromo-1-*tert*-butyl-1*H*-pyrazol-4-yl)methanol (31). A three-neck flask was charged with the mixture of carboxylic acid and ester obtained from the previous step (149 g) and THF (1.00 L). The solution was cooled to −78 °C, and a 1.5 M solution of DIBAL in toluene (1.08 L, 1.62 mol) was added over 30 min. During the addition, the internal temperature was monitored to stay below −40 °C. The reaction was stirred for 1 h in the dry ice/acetone bath and 1 h in an ice bath. The mixture was cooled back to −78 °C, and EtOAc (100 mL) was slowly added. A separate three-neck flask equipped with a mechanical stirrer was charged with a saturated aqueous solution of Rochelle's salt (1.5 L). The organic solution was slowly poured with stirring into the Rochelle's salt solution, and the mixture was stirred at room temperature for 1 h. The layers of the biphasic mixture were separated, and the aqueous layer was washed with EtOAc. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting material was purified by silica gel chromatography (10−80% EtOAc/heptanes), and the desired alcohol was isolated as clear oil (68.4 g, 46% over three steps): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.48 (s, 1H), 4.51 (d, J = 5.9 Hz, 2H), 1.65 (t, J = 5.8 Hz, 1H), 1.55 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 127.0, 125.5, 120.0, 59.7, 56.0, 29.8; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_8H_{14}BrN_2O$, 233.0284, found 233.0283; IR: 3367, 2978, 2876, 1553, 1410, 1369, 1216, 1004.

3-Bromo-1-*tert*-butyl-4-(chloromethyl)-1*H*-pyrazole (50). Starting (pyrazol-4-yl)methanol **31** (45.6 g, 196 mmol) was dissolved in dry DCM (1.00 L) and cooled in an ice bath. Et_3N (38.1 mL, 273 mmol) was added followed by methylsulfonyl chloride (19.8 mL, 254 mmol). After being stirred for 15 min, the reaction was warmed to room temperature and stirred for 2 h. The reaction was quenched with water (1 L) and diluted with DCM. The phases were separated, and the aqueous layer was extracted with DCM. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the desired product as a clear oil (48.8 g) that was used without further purification. For characterization purposes, an aliquot was purified by silica gel chromatography (5−15% EtOAc/heptanes), and the desired product was isolated as a clear oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.53 (s, 1H), 4.50 (s, 2H), 1.58 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 127.6, 126.3, 117.3, 60.1, 36.7, 29.8; HRMS (ESI) m/z [M + 2 + H]$^+$ calcd for $C_8H_{13}BrClN_2$, 252.9923, found 252.9928; IR: 2979, 2938, 2910, 1552, 1402, 1369, 1213, 732.

3-Bromo-1-*tert*-butyl-4-(iodomethyl)-1*H*-pyrazole (32). Starting 4-(chloromethyl)pyrazole **50** (48.6 g) was dissolved in acetone (200 mL), and NaI (57.9 g, 386 mmol) was added. The suspension was heated for 2 h at reflux. The brown suspension was cooled to room temperature and concentrated to dryness. The resulting dark brown solid was partitioned between EtOAc and water, the layers were separated, and the aqueous phase was extracted with EtOAc. The combined organics were washed with a saturated aqueous solution of sodium thiosulfate, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the desired product as a yellow oil (58.6 g), which was used without further purification. For characterization purposes, an aliquot was purified by silica gel chromatography (5−10% EtOAc/heptanes), and the desired product was isolated as a yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.53 (s, 1H), 4.29 (s, 2H), 1.57 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 127.0, 126.5, 118.3, 60.1, 29.8, −6.1; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_8H_{13}BrIN_2$, 342.9301, found 342.9299; IR: 2978, 2935, 1683, 1548, 1384, 1370, 1208.

1-*tert*-Butyl 4-Ethyl 4-(1-(carbonyl)piperidine-4-carbonyl)-piperidine-1,4-dicarboxylate: Claisen Condensation Product (35). For characterization purposes, the Claisen condensation product **35** was obtained during the optimization of the enolate formation procedure (Table 1), purified by silica gel chromatography (0−40% EtOAc/heptanes) and isolated as a clear oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.23 (q, J = 7.1 Hz, 2H), 4.07−4.18 (m, 2H), 3.69 (d, J = 10.7 Hz, 2H), 3.17−3.21 (m, 2H), 2.77−2.83 (m, 1H), 2.68 (br s, 2H), 2.20−2.08 (m, 2H), 1.82−1.93 (m, 2H), 1.51−1.68 (m, 4H), 1.45 (s, 9H), 1.45 (s, 9H), 1.28 (t, J = 7.1 Hz, 3H)); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 208.0, 171.1, 154.5, 154.5, 79.8, 79.7, 61.7, 59.6, 53.4, 44.6, 31.8, 29.5, 29.0, 28.4, 22.7, 14.1; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{24}H_{41}N_2O_7$, 469.2908, found 469.2915; IR: 2975, 1689, 1420, 1365, 1279, 1240, 1164, 1127, 1012, 979, 920, 866, 768, 731.

4-((3-Bromo-1-*tert*-butyl-1*H*-pyrazol-4-yl)methyl)-1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic Acid (37). A solution of 1-*tert*-butyl 4-ethylpiperidine-1,4-dicarboxylate (**33**) (76.0 g, 290 mmol) in THF (250 mL) was added over 45 min to a 1 M solution of LHMDS in THF (300 mL, 300 mmol) at 0 °C. After the reaction

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mixture was stirred for 20 min, a solution of 4-(iodomethyl)pyrazole **32** (58.6 g) in THF (250 mL) was added over 45 min. During the addition, the internal temperature was monitored to stay below 5 °C. After being stirred for 15 min, the reaction was allowed to warm to room temperature. The reaction was quenched with a saturated aqueous solution of NH_4Cl and diluted with water. The aqueous layer was extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting orange oil was dissolved in MeOH (825 mL), treated with a 6 M aqueous solution of NaOH (825 mL, 4.90 mol), and heated at reflux for 18 h. The MeOH and most of the water was removed in vacuo. The remaining solution was diluted with EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organics were concentrated in vacuo to give a peach-colored foam. This material was suspended in DCM (350 mL) and heptanes (100 mL) and stirred for 1 h. The sodium salt of the desired product is a white insoluble solid, which was filtered and washed with heptanes. The resulting white solid was dissolved in water, treated with a 1 N aqueous solution of HCl, and extracted with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the desired product as a fluffy white solid (57.3 g, 63% over four steps): ^{1}H NMR (CD_3OD, 400 MHz) δ7.44 (s, 1H), 3.88 (dt, J = 13.7, 3.3 Hz, 2H), 2.84−2.95 (m, 2H), 2.66 (s, 2H), 2.01 (d, J = 13.9 Hz, 2H), 1.51 (s, 9H), 1.43 (s, 9 H), 1.36−1.40 (m, 2H); ^{13}C NMR (CD_3OD, 100 MHz) δ 177.2, 155.3, 127.7, 127.2, 115.1, 79.9, 59.4, 47.2, 46.8, 34.0, 32.8, 28.5, 27.5; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{19}H_{30}BrN_3NaO_4$, 468.1294, found 468.1293; mp = 177−181 °C; IR: 3133, 2976, 2929, 1727, 1694, 1429, 1367, 1172.

1-*tert*-Butyl 4-Ethyl 4-((3-Bromo-1-tert-butyl-1*H*-pyrazol-4-yl)methyl)piperidine-1,4-dicarboxylate (34). For characterization purposes, prior to hydrolysis with NaOH, a sample from the enolate alkylation reaction was subjected to purification by silica gel chromatography (0−75% EtOAc/heptanes). The desired product **34** was isolated as a clear oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.15 (s, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.92 (d, J = 13.4 Hz, 2H), 2.87 (t, J = 11.7 Hz, 2H), 2.66 (s, 2H), 2.09 (d, J = 12.9 Hz, 2H), 1.54 (s, 9H), 1.40−1.50 (m, 11H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.3, 155.1, 127.6, 126.6, 115.1, 79.7, 60.9, 59.5, 47.2, 41.7, 34.6, 33.2, 29.8, 28.7, 14.5; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{21}H_{34}BrN_3NaO_4$, 494.1625, found 494.1621; IR: 2977, 1722, 1686, 1421, 1388, 1366, 1277, 1211, 1170, 1091, 1074, 1025, 965, 865, 729, 647.

***tert*-Butyl 4-((3-Bromo-1-*tert*-butyl-1*H*-pyrazol-4-yl)methyl)-4-isocyanatopiperidine-1-carboxylate (38).** A three-neck flask, equipped with a mechanical stirrer, was charged with carboxylic acid **37** (15.8 g, 35.5 mmol) and toluene (120 mL). Et_3N (4.94 mL, 35.5 mmol) and diphenylphosphoryl azide (8.17 mL, 37.2 mmol) were added. The heterogeneous mixture was heated to an internal temperature of 85 °C and stirred for 2 h. The reaction mixture was then cooled to room temperature and diluted with EtOAc and water. The organic layer was washed with water, and the combined aqueous layers were extracted with EtOAc. The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the desired product as a clear gum (14.2 g, 91%) that was used without further purification. The ^{1}H NMR of this material was comparable to an analytically pure sample: clear gum, purified by silica gel chromatography (5−40% EtOAc/heptanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 (s, 1H), 4.01 (br s, 2H), 2.95 (br s, 2H), 2.67 (s, 2H), 1.60−1.62 (m, 4H), 1.56 (s, 9H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.8, 127.7, 127.6, 122.9, 113.9, 80.0, 60.8, 59.8, 40.2, 38.2, 37.1, 29.8, 28.6; HRMS (ESI) m/z [M + 2 + NH_4]$^+$ calcd for $C_{19}H_{33}BrN_5O_3$, 460.1743, found 460.1740; IR: 2976, 2255, 1691, 1419, 1245.

Set-up and Conditions for Formation of *tert*-Butyl 4-((3-Bromo-1-tert-butyl-1*H*-pyrazol-4-yl)methyl)-4-isocyanatopiperidine-1-carboxylate (38) by Flow Chemistry. A solution of carboxylic acid **37** (30.0 g, 53.3 mmol) and Et_3N (9.40 mL, 63.7 mmol) in toluene (150 mL) was placed in a glass bottle. In a separate glass container, diphenylphosphoryl azide (18.0 mL, 82.2 mmol) was dissolved in toluene (180 mL). Using an ISCO syringe pump for each container, the solutions were combined and fed to the jacketed, 275 mL coil flow reactor at a rate of 1.5 mL/min. The reactor residence time was approximately 90 min, and the reactor was maintained at 120 °C and 500 psi. The resulting toluene solution was concentrated in vacuo to a total of ∼200 mL. The solution was diluted with EtOAc (350 mL) and washed with water (350 mL). The aqueous phase was extracted with additional EtOAc (350 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the crude material as a clear gum (28.9 g, 96%) that was used without further purification.

Boc-Protected Lactam 39 Using *t*-BuLi. Isocyanate **38** (17.7 g, 40.3 mmol) was dissolved in dry THF (400 mL) under nitrogen atmosphere. The solution was cooled to −78 °C and a 1.7 M solution of *t*-BuLi in pentane (47.4 mL, 80.5 mmol) was added dropwise. The mixture was stirred in the dry ice/acetone bath for 1 h and was then allowed to warm to room temperature. After a total of 1.5 h, the reaction was quenched with a saturated aqueous solution of NH_4Cl and stirred for 15 min. The reaction mixture was diluted with water (750 mL), EtOAc (1.75 L), and DCM (500 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The desired lactam was isolated as a yellowish solid (14.6 g, 99%) and was used without further purification. The ^{1}H NMR of this material was comparable to an analytically pure sample: white solid, purified by silica gel chromatography (0−5% MeOH/DCM); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39 (s, 1H), 5.88 (s, 1H), 3.53−3.68 (m, 2H), 3.34−3.39 (m, 2H), 2.81 (s, 2H), 1.67−1.82 (m, 4H), 1.64 (s, 9H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.3, 154.8, 141.1, 123.8, 117.9, 80.2, 60.1, 55.0, 39.8, 36.8, 31.2, 30.1, 28.6; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{19}H_{31}N_4O_3$, 364.2421, found 364.2427; mp = 267−269 °C; IR: 3221, 2976, 2936, 1672, 1423, 1159, 566.

Boc-Protected Lactam 39 Using *s*-BuLi. Isocyanate **38** (300 mg, 0.68 mmol) was dissolved in dry THF (5 mL) under nitrogen atmosphere. The solution was cooled to −42 °C, and a 1.3 M solution of *s*-BuLi in cyclohexane (1.1 mL, 1.4 mmol) was added dropwise. The mixture was stirred in the dry ice/MeCN bath for an additional 15 min. The reaction was quenched with a saturated aqueous solution of NH_4Cl and was then allowed to warm to room temperature. The reaction mixture was diluted with water (3 mL) and DCM (20 mL). The layers were separated, and the aqueous layer was extracted with DCM (15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The desired lactam was isolated as a white solid (250 mg, 99%) and was used without further purification.

Lactam 40. Boc-protected lactam **39** (18.7 g, 51.6 mmol) was dissolved in DCM (500 mL). A 4 M solution of HCl in dioxane (130 mL, 516 mmol) was added, and the reaction was stirred at room temperature for 30 min. The clear solution turned into a white suspension. The solvent was removed in vacuo to afford the desired product as a white solid (17.2 g, 99%), which was used without further purification. The ^{1}H NMR of this material was comparable to an analytically pure sample: white solid, purified by trituration in DCM; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.99 (br s, 2H), 7.93 (s, 1H), 7.75 (s, 1H), 3.14−3.24 (m, 2H), 3.01−3.12 (m, 2H), 2.77 (s, 2H), 1.72−1.90 (m, 4H), 1.52 (s, 9H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 161.8, 141.3, 125.4, 117.9, 59.8, 53.2, 39.8, 33.5, 31.0, 30.2; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{14}H_{23}N_4O$, 263.1866, found 263.1869; mp = 328−336 (decomposition) °C; IR: 3419, 2977, 2802, 1662, 1490, 1207.

2′-(*tert*-Butyl)-1-(1*H*-indazole-5-carbonyl)-4′,6′-dihydrospiro[piperidine-4,5′-pyrazolo[3,4-*c*]pyridin]-7′(2′*H*)-one (41). 1*H*-Indazole-5-carboxylic acid (100 mg, 0.617 mmol) was dissolved in DMF (6 mL). Lactam **40** (207 mg, 0.617 mmol) and Et_3N (0.43 mL, 3.1 mmol) were added, and the solution was stirred at room temperature for 15 min. A 50% solution of propylphosphonic anhydride in EtOAc (0.41 mL, 0.68 mmol) was added, and the reaction mixture was stirred for 16 h. The reaction mixture was diluted with a saturated aqueous solution of $NaHCO_3$ and water and then extracted with DCM. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by silica gel chromatography (0−50% of 20% MeOH in DCM/DCM) to afford **41** as a white solid (150 mg,

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60%): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 13.23 (s, 1H), 8.14 (s, 1H), 7.81 (s, 1H), 7.73 (s, 1H), 7.70 (s, 1H), 7.57 (d, J = 8.5 Hz, 1H), 7.36 (d, J = 8.7 Hz, 1H), 3.37−3.94 (br m, 4H), 2.81 (s, 2H), 1.67 (br s, 4H), 1.51 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.1, 161.9, 141.6, 140.6, 135.0, 128.8, 125.9, 125.2, 122.8, 120.4, 118.2, 110.8, 59.7, 55.2, 36.8, 30.3, 30.1; HMS (ESI) m/z [M + H]$^+$ calcd for $C_{22}H_{26}N_6O_2$, 407.2190, found 407.2191; mp = 184−184 °C; IR: 3230, 2977, 2941, 1669, 1623, 1439.

Ethyl 5-Amino-1-isopropyl-1*H*-pyrazole-4-carboxylate (43). *N*-Isopropylhydrazine (3.45 g, 31.2 mmol), ethyl (ethoxymethylene)-cyanoacetate (5.41 g, 31.0 mmol), and K_2CO_3 (4.33 g, 31.3 mmol) were dissolved in EtOH (100 mL), and the reaction mixture was heated to reflux for 6 h. The reaction was cooled to room temperature, and the solvent was removed in vacuo. The residue was partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc. The combined organics were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (0−85% EtOAc/heptanes), and the desired aminopyrazole was isolated as clear gum (3.77 g, 61%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63 (s, 1H), 5.05 (br s, 2H), 4.24 (q, J = 7.2 Hz, 2H), 4.20 (spt, J = 6.6 Hz, 1H), 1.45 (d, J = 6.6 Hz, 6H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.8, 148.4, 139.1, 96.3, 59.7, 48.7, 21.6, 14.7; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_9H_{16}N_3O_2$, 198.1237, found 198.1237; IR: 2975, 1691, 1158, 730.

Ethyl 5-Bromo-1-isopropyl-1*H*-pyrazole-4-carboxylate (44). Starting amino pyrazole **43** (3.76 g, 19.1 mmol) was dissolved in MeCN (40 mL). Copper(II) bromide (6.29 g, 28.0 mmol) and isoamyl nitrite (3.45 mL, 24.8 mmol) were added, and the reaction mixture was heated to 50 °C for 4.5 h. The reaction was cooled to room temperature and quenched with a 1 M aqueous solution of HCl. The aqueous layer was extracted with EtOAc. The combined organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (0−50% EtOAc/heptanes), and the desired bromopyrazole was isolated as clear oil (4.14 g, 83%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.00 (s, 1H), 4.81 (spt, J = 6.7 Hz, 1H), 4.33 (q, J = 7.2 Hz, 2H), 1.50 (d, J = 6.6 Hz, 6H), 1.37 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.3, 142.2, 116.6, 113.5, 60.5, 52.2, 22.2, 14.6; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_9H_{13}BrNaN_2O_2$, 283.0053, found 283.0052; IR: 2981, 2939, 1720, 1532, 1409, 1214, 1046.

(5-Bromo-1-isopropyl-1*H*-pyrazol-4-yl)methanol (51). Pyrazole **51** was prepared from ester **44** (4.14 g, 15.9 mmol) using the protocol described for compound **31**. The desired material was purified by silica gel chromatography (0−75% EtOAc/heptanes) and isolated as a white solid (3.21 g, 92%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.60 (s, 1H), 4.68 (spt, J = 6.6 Hz, 1H), 4.52 (s, 2H), 1.95 (br s, 1H), 1.48 (d, J = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.5, 120.4, 112.4, 55.9, 51.9, 22.3; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_7H_{12}BrN_2O$, 219.0128, found 219.0124; IR: 3333, 2980, 2936, 2874, 1553, 1400, 1369, 1346, 1248, 1183, 1084, 993, 855, 755, 675.

5-Bromo-1-isopropyl-4-(chloromethyl)-1*H*-pyrazole (52). Chloride **52** was prepared from alcohol **51** (1.59 g, 7.26 mmol) using the protocol described for compound **50**. The desired material was purified by silica gel chromatography (7−60% EtOAc/heptanes) and isolated as a clear oil (1.39 g, 81%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.63 (s, 1H), 4.68 (spt, J = 6.7 Hz, 1H), 4.50 (s, 2H), 1.49 (d, J = 6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.8, 117.5, 113.4, 52.2, 36.7, 22.3; IR: 2981, 1550, 1420, 1399, 1262, 1242, 1203, 996, 901, 737, 707. Due to instability of the product, HRMS could not be attained.

5-Bromo-1-isopropyl-4-(iodomethyl)-1*H*-pyrazole (45). Iodide **45** was prepared from chloride **52** (913 mg, 3.84 mmol) using the protocol described for compound **32**. The desired material was purified by silica gel chromatography (0−30% EtOAc/heptanes) and isolated as a clear oil (1.04 g, 82%): ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 7.60 (s, 1H), 4.66 (spt, J = 6.7 Hz, 1H), 4.33 (s, 2H), 1.46 (d, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.4, 124.5, 119.0, 58.1, 28.3, 0.00; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_7H_{11}BrIN_2$, 328.9145, found 328.9130; IR: 2978, 2935, 1543, 1418, 1395, 1242,1198, 1157, 996, 728, 675.

4-((5-Bromo-1-isopropyl-1*H*-pyrazol-4-yl)methyl)-1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic Acid (46). Carboxylic acid **46** was prepared from ester **33** (1.13 g, 4.39 mmol) and iodide **45** (850 mg, 2.58 mmol) using the protocol described for compound **37**. The desired material was isolated as a white solid (831 mg, 75%) that was analytically pure: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.40 (s, 1H), 4.60 (spt, J = 6.6 Hz, 1H), 3.71 (d, J = 12.0 Hz, 2H), 2.84 (br s, 2H), 2.54 (s, 2H), 1.86 (d, J = 12.9 Hz, 2H), 1.35 (s, 9H), 1.34 (d, J = 6.6 Hz, 6H), 1.16−1.22 (m, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 159.4, 145.3, 145.2, 121.0, 118.3, 84.0, 83.9, 56.4, 51.4, 39.3, 38.0, 33.5, 27.4; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{18}H_{28}BrN_3NaO_4$, 452.1155, found 452.1137; IR: 3452, 2976, 1689, 1551, 1477, 1424, 1393, 366, 1277, 1246, 1172, 1150, 1075, 1000, 965, 865, 736.

***tert*-Butyl 4-((5-Bromo-1-isopropyl-1*H*-pyrazol-4-yl)methyl)-4-isocyanatopiperidine-1-carboxylate (47).** Isocyanate **47** was prepared from carboxylic acid **46** (400 mg, 0.93 mmol) using the protocol described for compound **38**. The desired material was isolated as a clear oil which solidified upon standing (372 mg, 94%) and was analytically pure: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.48 (s, 1H), 4.69 (spt, J = 6.6 Hz, 1H), 4.02 (br s, 2H), 2.96 (br s, 2H), 2.68 (s, 2H), 1.63−1.70 (m, 2H), 1.54−1.624 (m, 2H), 1.48 (d, J = 6.6 Hz, 6H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.8, 140.4, 130.3, 114.3, 114.1, 80.1, 60.5, 52.1, 40.0, 38.4, 37.1, 28.6, 22.3; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{18}H_{27}BrN_4NaO_3$, 449.1159, found 449.1166; IR: 3979, 2363, 2258, 1694, 1420, 1366, 1247, 1174, 1148, 1000, 967.

Boc-Protected Lactam (53). Lactam **53** was prepared from isocyanate **47** (372 mg, 0.87 mmol) using the protocol described for compound **39** using *t*-BuLi. The desired material was purified by silica gel chromatography (0−80% EtOAc/heptanes) and isolated as a white solid (271 mg, 89%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36 (s, 1H), 6.57 (s, 1H), 5.46 (spt, J = 6.7 Hz, 1H), 3.57 (d, J = 12.9 Hz, 2H), 3.41−3.47 (m, 2H), 2.80 (s, 2H), 1.65−1.81 (m, 4H), 1.48 (d, J = 6.8 Hz, 6H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.7, 154.8, 135.6, 128.9, 120.3, 80.1, 55.3, 52.2, 39.7, 36.7, 31.5, 28.6, 22.7; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{18}H_{29}N_4O_3$, 349.2234, found 349.2236; IR: 3230, 2975, 1666, 1551, 1502, 1422, 1365, 1274, 1247, 1158, 779.

Lactam 48. Lactam **48** was prepared from compound **53** (3.82 g, 11.0 mmol) using the protocol described for compound **40**. The desired material was isolated as a white solid (3.48 g, 99%): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.23 (br s, 1H), 9.12 (br s, 1H), 8.10 (s, 1H), 7.39 (s, 1H), 5.39 (spt, J = 6.7 Hz, 1H), 3.13−3.27 (m, 2H), 2.98−3.11 (m, 2H), 2.80 (s, 2H), 1.78−1.94 (m, 4H), 1.36 (d, J = 6.6 Hz, 6H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 159.3, 135.9, 129.3, 120.3, 53.7, 51.5, 39.8, 33.2, 30.9, 23.1; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{13}H_{21}N_4O$, 249.171, found 249.1712; IR: 3388, 3975, 2802, 1667, 1502, 1427, 1393, 1335, 1305, 1130, 1049, 3779, 667.

1-(1*H*-Indazole-5-carbonyl)-1′-isopropyl-4′,6′-dihydrospiro-[piperidine-4,5′-pyrazolo[3,4-*c*]pyridin]-7′(1′*H*)-one (49). Amide **49** was prepared from 1*H*-indazole-5-carboxylic acid (100 mg, 0.617 mmol) and lactam **48** (198 mg, 0.616 mmol) using the protocol described for compound **41**. The desired material was purified by silica gel chromatography (0−50% of 20% MeOH in DCM/DCM) to afford **49** as a white solid (188 mg, 78%): ^{1}H NMR (DMSO-d_6, 500 MHz) δ 13.23 (s, 1H), 8.13 (s, 1H), 7.88 (s, 1H), 7.81 (s, 1H), 7.57 (d, J = 8.5 Hz, 1H), 7.39 (s, 1H), 7.36 (d, J = 8.3 Hz, 1H), 5.41 (sept, J = 6.5 Hz, 1H), 3.49−3.85 (br m, 4H), 2.84 (s, 2H), 1.69 (br s, 4H), 1.36 (d, J = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.1, 159.4, 140.6, 135.9, 135.0, 129.5, 128.7, 125.9, 122.8, 120.5, 120.4, 110.8, 55.7, 51.5, 36.7, 31.9, 30.3, 23.1; HRMS (ESI) calcd for $C_{21}H_{25}N_6O_2$ (m/z) [M + H]$^+$ 393.2034, found 393.2045; mp = 148−150 °C; IR: 3225, 2941, 1666, 1609, 1439.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: Elnaz.Menhaji-Klotz@Pfizer.com.

Notes

The authors declare no competing financial interest.

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