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The Discovery of (*S*)-1-(6-(3-((4-(1-(Cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenyl)amino)-2,3-dihydro-1*H*-inden-4-yl)pyridin-2-yl)-5-methyl-1*H*-pyrazole-4-carboxylic Acid, a Soluble Guanylate Cyclase Activator Specifically Designed for Topical Ocular Delivery as a Therapy for Glaucoma

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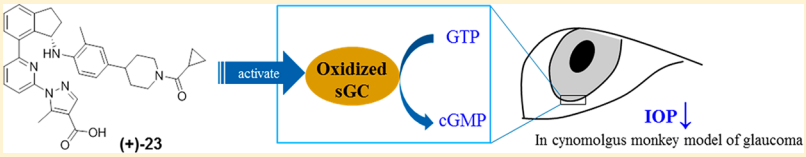
Supporting Information



ABSTRACT: Soluble guanylate cyclase (sGC), the endogenous receptor for nitric oxide (NO), has been implicated in several diseases associated with oxidative stress. In a pathological oxidative environment, the heme group of sGC can be oxidized becoming unresponsive to NO leading to a loss in the ability to catalyze the production of cGMP. Recently a dysfunctional sGC/NO/cGMP pathway has been implicated in contributing to elevated intraocular pressure associated with glaucoma. Herein we describe the discovery of molecules specifically designed for topical ocular administration, which can activate oxidized sGC restoring the ability to catalyze the production of cGMP. These efforts culminated in the identification of compound (+)-**23**, which robustly lowers intraocular pressure in a cynomolgus model of elevated intraocular pressure over 24 h after a single topical ocular drop and has been selected for clinical evaluation.

INTRODUCTION

Glaucoma, a neurodegenerative disease of the retina and optic nerve, is one of the leading causes of blindness in the world. The estimated number of glaucoma cases globally is over 60 million. In the USA alone, over 120 000 patients are legally blind from glaucoma.[1] The only accepted modifiable risk factor for glaucoma is the lowering of intraocular pressure (IOP), which is elevated in the most common form of glaucoma, primary open angle glaucoma (POAG). For each mmHg reduction in IOP, a 10% reduction in disease progression can be observed.[2] It is believed that the primary cause of increased IOP is inadequate drainage of intraocular fluid (aqueous humor) due to a dysfunctional outflow pathway. Dysfunctional outflow is thought to arise from extensive oxidative stress and extracellular matrix deposition, which can result in functional impairment of the trabecular meshwork (TM), the tissue that is the major site of resistance to aqueous humor outflow. The recent clinical success of Rhopressa (netarsudil, a rho kinase inhibitor)[3] and Vyzulta (latanoprostene bunod, a dual-action drug that produces nitric oxide and latanoprost),[4] which improve conventional outflow facility (or trabecular outflow), have increased interest in targeting the TM.[5] Clinically and preclinically, nitric oxide (NO) can lead to a reduction in IOP by producing the vasorelaxant signaling molecule cyclic guanosine monophosphate (cGMP), presumably acting on the TM.[4,6] The endogenous receptor for NO is soluble guanylate cyclase (sGC). sGC is a heterodimer composed of either an α1 or an α2 subunit combined with the β1 subunit, which has a heme prosthetic group. Under physiological conditions, upon binding of NO to the reduced iron of the heme, the enzyme is activated and catalyzes the conversion of

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guanosine-5′-triphosphate (GTP) to cGMP.[7] Under pathological conditions involving oxidative stress, the heme moiety of sGC can become oxidized (from ferrous to ferric state) and become nonresponsive to NO. Furthermore, upon oxidation, the prosthetic heme can detach from the enzyme, leaving it incapable of catalyzing the conversion of GTP to cGMP.[8]

The NO/sGC/cGMP pathway has been implicated in a several different diseases, in particular cardiovascular and pulmonary diseases. This has led to identification of molecules that activate or stimulate sGC.[7a,9] The greatest clinical success has been achieved using stimulators, with riociguat approved to treat pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH).[10] However, stimulators require the heme of sGC to be present in the reduced state to afford an enhancement in cGMP production. Activators, on the other hand, preferentially bind to oxidized, or heme free, sGC and restore the enzyme's catalytic activity. We hypothesized that in glaucoma, oxidative stress may lead to an increase in nonfunctional, oxidized sGC, and thus sGC activators may prove beneficial in reducing elevated IOP. Further evidence for the relevance of the NO/sGC/cGMP pathway comes from several reports of modulators of this pathway lowering IOP in preclinical glaucoma models.[6,11]

At the start of our work, two sGC activators had been evaluated clinically for cardiovascular indications, cinaciguat and ataciguat, **1** and **2** (Figure 1). However, to the best of

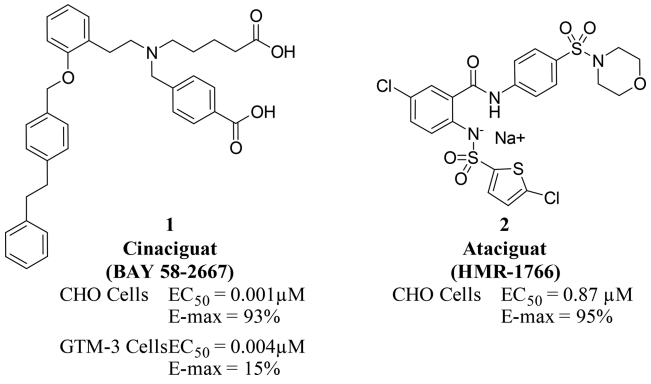

Figure 1. Previously reported sGC activators tested in clinical trials.

knowledge, at the time our program was initiated, there were no reports of the development of topically administered sGC activators for the treatment of glaucoma.[12]

Compound **1** served as a useful tool to explore the potential of this mechanism to lower IOP. To this end, compound **1** was evaluated in our primary *in vivo* model, a laser-induced elevated IOP cynomolgus monkey model (cyno-IOP model).[13] In this model, a laser-induced trabeculoplasty of the TM in one eye leads to elevated IOP. Upon b.i.d. instillation of **1** employing topical eye drops, a modest reduction in IOP was observed (up to 10%). The need for twice-a-day dosing and substandard IOP lowering were clearly discouraging.[14] Compound **1** potently activates sGC (EC_{50}/E-max; maximal cGMP produced from the dose response curve) in a high throughput Chinese hamster ovary (CHO) cell assay, which was used as our initial assay for compound evaluation. However, **1** proved to be a partial activator of sGC when evaluated in a potentially more relevant cell line, immortalized glaucomatous trabecular meshwork cells (GTM-3) expressing endogenous levels of sGC.[15] We reasoned that an activator with greater *in vitro* efficacy (increase in E-max) in the GTM-3 cell assay may afford more robust IOP lowering. Therefore, we set out to identify sGC activators with excellent *in vitro* potency and efficacy, which were suitable for topical ocular administration.

RESULTS AND DISCUSSION

An internal high-throughput screening (HTS) campaign identified **3**[16] as a potential starting point (Figure 2) with an EC_{50} of 162 nM and an E-max of 105% in a CHO cell line overexpressing sGC. Pharmacophore modeling, which overlaid **3** with several literature described sGC activators,[9c,17] guided our efforts to improve upon **3**.

This pharmacophore model suggested potency could be gained by elaborating **3** at the northern most ring. This led to the design of **4**, incorporating a thiophene ring to position the piperidine containing "tail" moiety in the appropriate orientation. We were pleased to see that upon synthesis, **4** afforded a ∼7-fold improvement in potency relative to **3.** Compound **4** served as a lead for our optimization campaign, which began with exploration of the substitution of the aryl ring of the "tail" (Table 1). Addition of a methyl group alpha to the oxygen (R^2 = Me, **5**) resulted in an enhancement in potency in the CHO cell assay. This improvement in potency warranted evaluation in the more relevant and stringent GTM cell assay. Gratifyingly, **5** afforded maximal efficacy (E-max = 97%) with an EC_{50} of 370 nM. On the strength of this data, we evaluated **5** in the laser-induced elevated IOP cynomolgus monkey model (cyno-IOP model).

When a single 30 μL drop containing 100 μg of **5**, formulated as a suspension, was dosed in the cyno-IOP model, a modest 17% reduction in IOP was observed at 6 h and a 10% reduction was observed after 24 h. When a higher concentration of 300 μg in 30 μL was administered, mild hyperemia and ocular

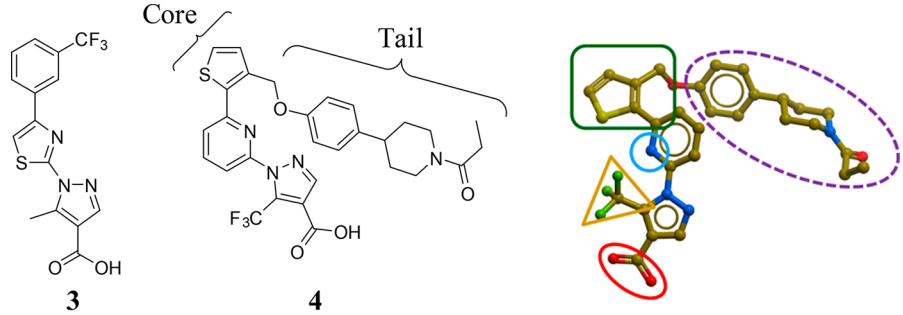

Figure 2. HTS hit (**3**), lead molecule (**4**), and pharmacophore model on **4**. Common feature points are carboxylic acid (red), hydrophobic groups (yellow and green), and a hydrogen bond acceptor (cyan), whereas occupancy of a tail group (purple dotted circle) varies depending on a molecule.

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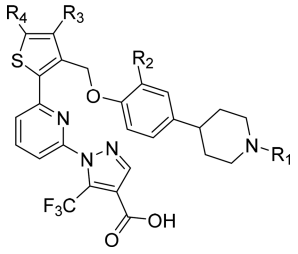
Table 1. SAR of the Thiophene Analogues



cpd	R_1	R_2	R_3	R_4	CHO EC_{50} (μM) / E-max (%)	GTM-3 EC_{50} (μM) / E-max (%)
4		H	H	H	0.025 / 101	(ND)
5		Me	H	H	0.0055 / 100	0.37 / 97
6	H	Me	H	H	4.2 / 73	(ND)[a]
7		Me	H	H	0.43 / 88	(ND)[a]
8		Me	H	H	0.0045 / 102	(ND)[a]
9		Me	H	Me	<0.0001 / 101	0.053 / 100
10		Me	H	Cl	0.00015 / 99	0.52 / 97
11		Me	H	Et	0.002 / 103	0.18 / 68
12		Me	Et	Me	0.001 / 101	0.012 / 93
13		Me	Me	H	<0.0005 / 100	0.04 / 100
14		Me	Et	H	0.006 / 105	0.16 / 70

[a](ND) = not determined.

discharge were observed in the eyes of both rabbits and monkeys, limiting further evaluation at this dose. Although encouraged by the ability of **5** to demonstrate *in vivo* efficacy, there was room for further improvement. We initially focused on the piperidine of the tail (Table 1), recognizing that this region offered one of the few areas to dramatically affect the physicochemical properties of the scaffold. Removal of the ethyl amide to reveal the free piperidine NH (**6**) afforded a dramatic loss of *in vitro* potency, as did N-alkylation (**7**). The amide appeared essential to retain potency, with a slight preference for cyclopropyl amide. We next explored the importance of substitution around the thiophene portion of the core. Installation of a methyl group at the 5-position (R^4) improved CHO cellular potency (**8** vs **9**), and more importantly led to improved potency in the GTM-3 assay. Further exploration of the 5-position revealed that an electron withdrawing group or larger alkyl groups than methyl were less preferred (**10** and **11**) in the GTM-3 assay. Modification of the thiophene 4-position (e.g., R^3 in **12**–**14**) retained *in vitro* potency with addition of either methyl or ethyl groups. Recognizing that substitutions at both the 4 and 5 positions of the thiophene were tolerated or offered enhanced potency encouraged us to explore alternative core units to further increase the *in vitro* potency and also enrich the chemical diversity.

We hypothesized that substitution at the 5 position may be filling a pocket within the protein, leading to the improved potency, while substitution at the 4 position may be altering the conformation of the piperidine tail to a more preferred orientation. These two hypotheses directed our efforts as we investigated replacements of the thiophene. Guided by our pharmacophore model, we identified 5- and 6-membered cycloalkenes and indanes as potential replacements for the thiophene (Table 2).

As anticipated, the cycloalkenes were tolerated, with a preference for the larger 6-membered ring system (**16**), consistent with substitution of the 5-position of the thiophene offering improved potency. Returning to the concept of altering the orientation of the piperidine tail, we then explored alkylation of the cyclohexene. A monomethyl substitution at the 3-position of the cyclohexene ring, somewhat mimicking substitution of the 4-position of the thiophene, proved beneficial, with the (+)-enantiomer of **17** furnishing a 14-fold improvement in potency relative to **16** in the GTM-3 assay. Interestingly, the other methyl enantiomer, or the gem-dimethyl analogue **18**, resulted in a decrease in potency relative to **16**. Of note, additional SAR (data not shown) indicated that substitution of the 2 position of the phenol (as in **16**) with a methyl group, or the 3 position with an ethyl group afforded similar activity, with a modest preference for the 3-ethyl motif. Highly encouraged by the ability to morph from the thiophene to the cyclohexene, we turned our attention to the indane concept.

Replacement of the dialkyl thiophene of **12** with an indane led to compound **19**, which afforded similar potency in the GTM-3 cellular assay as **12**; of note, the corresponding enantiomer (−)-**19** was far less potent, supporting our previous observations about a preferred tail orientation. Although we were encouraged by the potency of (+)-**19**, there were concerns about the chemical stability of the benzylic ether linkage when considering that ideally a successful topical ocular molecule needs to be stable in an aqueous-based formulation for >12 months. Thus, we examined replacement of the potentially labile oxygen linker with a nitrogen (**20**), which proved equally potent. Aiming for further potency enhancement, we explored the 6 position of the indane core (R^5), as that seemed to overlay with the 5-position of the thiophene core (e.g., **9**). Surprisingly, addition of a methyl to the indane core, (+)-**21**, decreased the GTM cellular potency by 18-fold relative to (+)-**20**.

Chemistry. 4-Piperidylphenols and 4-piperidylaniline tail pieces were prepared according to Scheme 1. Boronic ester **25** was coupled to the appropriate bromophenol utilizing Suzuki-type coupling conditions, followed by hydrogenation over Pd/C, to give 4-Boc-piperidylphenols **26**. Removal of the Boc protecting group and acylation with cyclopropylcarbonyl chloride gave rise to both N- and O-acylation, with the *O*-acyl group being selectively removed *in situ* with MeOH and K_2CO_3, to give free phenols **27**. Preparation of aniline **30** was accomplished using similar conditions to the 4-piperidylphenols, but the Boc removal and N-acylation were performed before reducing both the olefin and nitro group of **29** via hydrogenation over Pd/C.

The general syntheses of activators **4**–**14** are outlined in Scheme 2. The core was constructed starting with commercially available 2-bromo-6-hydrazinyl-pyridine (**31**) and ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate, which were reacted in EtOH at room temperature, followed by trituration with water, to provide **32**. A Suzuki coupling between **32** and (3-formylthiophen-2-yl)boronic acid was best achieved by

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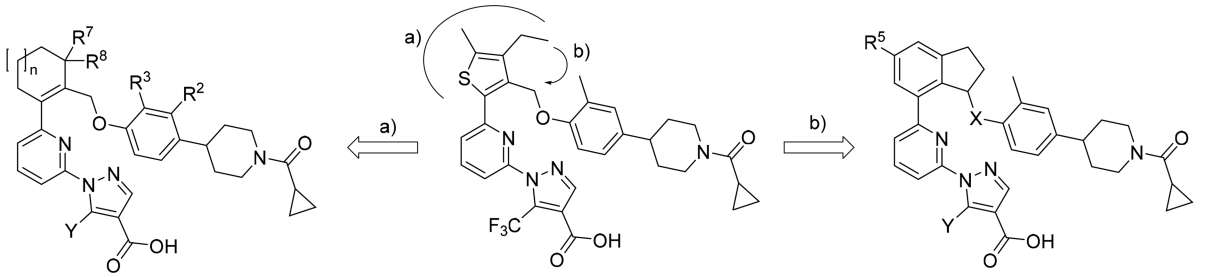
Table 2. Cycloalkene and Indane Analogs Derived from 12



15 (n = 0, R^2 = H, R^3 = Me, R^7 = R^8 = H, Y = CF_3)
16 (n = 1, R^2 = H, R^3 = Me, R^7 = R^8 = H, Y = CF_3)
(+)- and (-)- **17** (n = 1, R^2 = Et, R^3 = H, R^7 = Me, R^8 = H, Y = CF_3)
18 (n = 1, R^2 = Et, R^3 = H, R^7 = R^8 = Me, Y = CF_3)
(+)- and (-)- **24** (n = 1, R^2 = Et, R^3 = H, R^7 = Me, R^8 = H, Y = Me)

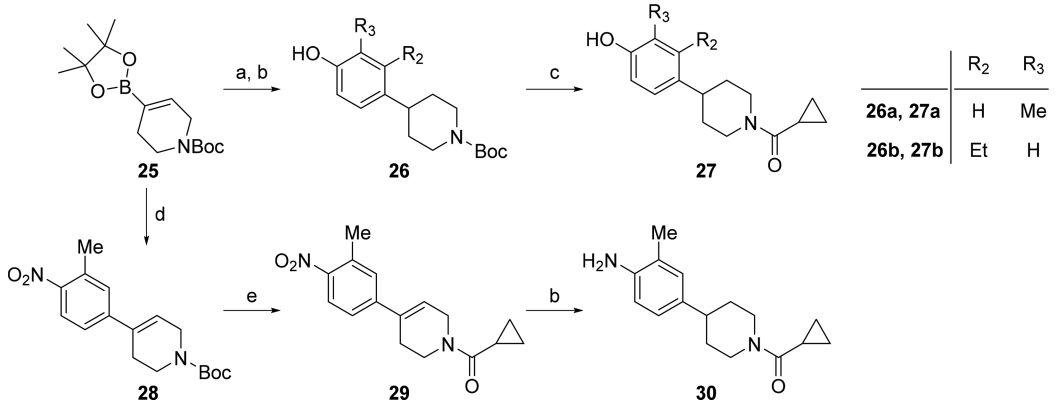
12

(+)- and (-)-**19** (R^5 = H, X = O, Y = CF_3)
(+)- and (-)-**20** (R^5 = H, X = NH, Y = CF_3)
(+)- and (-)-**21** (R^5 = Me, X = NH, Y = CF_3)
(+)-**22** (R^5 = H, X = O, Y = H)
(+)- and (-)-**23** (R^5 = H, X = NH, Y = Me)

compd	CHO EC_{50} (μM)/E-max (%)	GTM-3 EC_{50} (μM)/E-max (%)	compd	CHO EC_{50} (μM)/E-max (%)	GTM-3 EC_{50} (μM)/E-max (%)
15	0.0025/101	*a*	(−)-**20**	0.037/101	1.2/97
16	0.00035/101	0.085/110	(+)-**21**	0.001/101	0.055/85
(+)-**17**	0.001/102	0.006/85	(−)-**21**	0.024/99	*a*
(−)-**17**	0.009/100	0.17/63	(+)-**22**	0.0025/103	0.32/70
18	0.001/99	0.14/71	(+)-**23**	<0.0005/104	0.005/106
(+)-**19**	0.001/102	0.01/100	(−)-**23**	0.017/102	0.49/82
(−)-**19**	0.007/100	*a*	(+)-**24**	<0.0005/101	0.009/120
(+)-**20**	<0.0005/100	0.003/89	(−)-**24**	0.003/101	*a*

[a]Not determined.

Scheme 1. Synthesis of Activator Tails[a]



	R_2	R_3
26a, 27a	H	Me
26b, 27b	Et	H

[a]Reagents and conditions: (a) 4-bromo-2-methyl phenol (for **26a**) or 4-chloro-3-ethylphenol (for **26b**), $PdCl_2(dppf)\cdot CH_2Cl_2$ adduct, aq. K_3PO_4, CH_3CN, 80 °C; or SPhos-Pd (first generation), aq. K_3PO_4, DMF, 110 °C; (b) H_2, Pd/C 5%, MeOH, rt; (c) (1) TFA, CH_2Cl_2, 0 °C; (2) cyclopropanecarbonyl chloride, *i*-Pr_2NEt, CH_2Cl_2, 0 °C; (3) K_2CO_3, MeOH, rt; (d) 4-bromo-2-methyl-1-nitrobenzene, $PdCl_2(dppf)\cdot CH_2Cl_2$ adduct, aq. K_3PO_4, CH_3CN, 80 °C; (e) (1) TFA, CH_2Cl_2, 0 °C; (2) cyclopropanecarbonyl chloride, *i*-Pr_2NEt, CH_2Cl_2, 0 °C.

employing $((t\text{-Bu})_3P)_2Pd$ as the catalyst and potassium fluoride as the base in THF at room temperature followed by reduction of the aldehyde to give alcohol **33**. Coupling **33** with 4-piperidylphenol **26** was achieved by a Mitsunobu-type reaction, to afford phenoxyether **37**. When the piperidine nitrogen was protected with a Boc group, it was further functionalized by deprotection with TFA, followed by either acylation, coupling with a carboxylic acid, or alkylation. Finally, saponification of the ethyl ester afforded activators with the general structure of **38** (where R^4 = R^5 = H).

Regioselective modification at the 5-position of the thiophene was achieved by treatment of **33** with *N*-bromosuccinimide (X^1 = Br) or *N*-chlorosuccinimide (X^1 = Cl), with only a single regioisomer observed. Converting the 5-bromothiophene **34** to 5-alkylthiophene **35** was accomplished with dimethyl or diethyl zinc in the presence of $((t\text{-Bu})_3P)_2Pd$ in THF. Compound **35** was then successfully coupled with 4-piperidylphenol **26** under Mitsunobu-type reaction conditions, followed by saponification of the ethyl ester to give activators **38** (where R^4 = H and R^5 = alkyl or Cl). 5-Alkylthiophene **35** could be further functionalized at the 4 position by treating with NBS, followed by diethyl zinc, to give rise to 4,5-dialkyl thiophenes **36**, which could be carried forward as described above to **38** (where R^4 = Et and R^5 = Me). To selectively prepare activators with only substitution at the 4-position of the thiophene, we used previously described selective C−H functionalization.[18]

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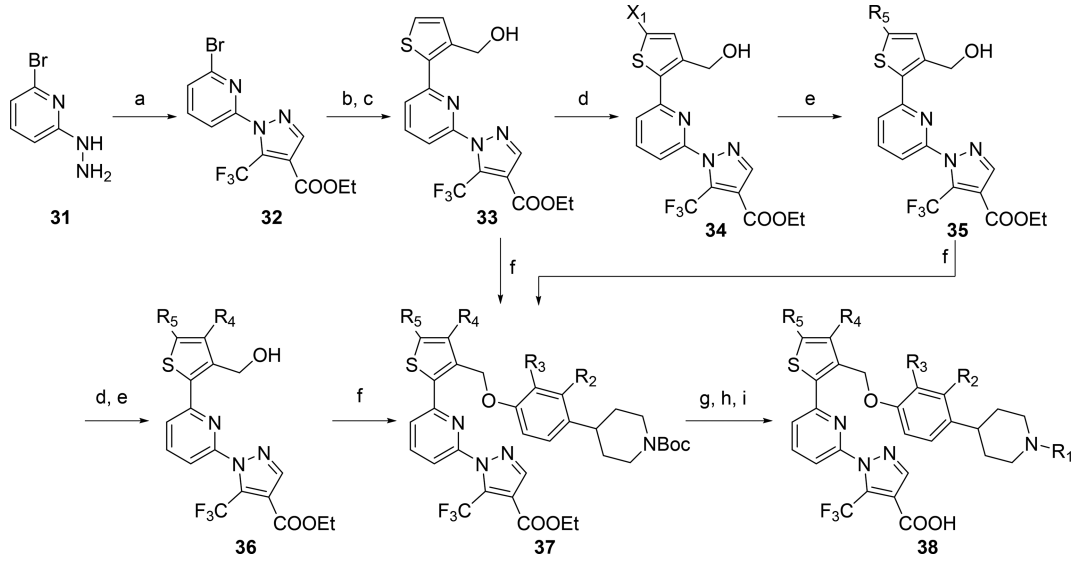
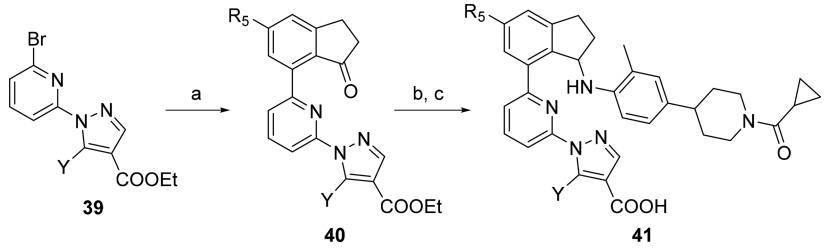
Scheme 2. General Synthesis of Activators 4−14[a]



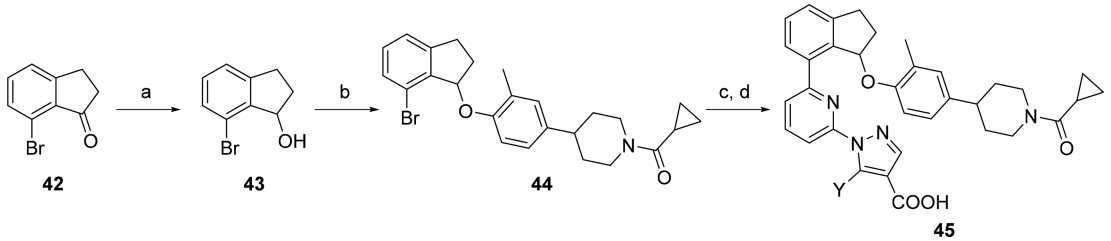
[a]Reagents and conditions: (a) ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate, EtOH, rt; (b) (3-formylthiophen-2-yl)boronic acid, KF, Pd(*t*-Bu_3P)$_2$, THF, rt; (c) $NaBH_4$, EtOH, 0 °C; (d) NBS, DMF, rt; or NCS, DMF; (e) corresponding dialkylzinc, Pd(*t*-Bu_3P)$_2$, THF, rt; (f) **26**, DIAD, PPh_3, THF; (g) TFA, CH_2Cl_2, rt; (h) propionyl chloride, Et_3N, CH_2Cl_2; or cyclopropylmethyl bromide, Cs_2CO_3, DMF, 50 °C; or 2-cyclopropylacetic acid, HATU, *i*-Pr_2NEt, DMF, rt; (i) LiOH, THF, MeOH, H_2O, 50 °C.

Scheme 3. Synthesis of Indane Amine Activators[a]



[a]Reagents and conditions: (a) (1) bis(pinacolato)diboron, KOAc, SPhos−Pd (first generation), dioxane, 120 °C (microwave); (2) **42**, aq. Na_2CO_3, SPhos−Pd (first generation), dioxane, 110 °C conventional heating (one pot); (b) (1) **30**, cat. TsOH, 130 °C with Dean−Stark apparatus; (2) $NaBH_4$, EtOH, 0 °C to rt; (c) LiOH, MeOH/THF/H_2O, 50 °C.

Scheme 4. Synthesis of Indane Ether Activators[a]



[a]Reagents and conditions: (a) $NaBH_4$, MeOH, 0 °C to rt; or RuCl[(*R*,*R*)-Tsdpen](p-cymene), TEA·HC(O)OH, DMF, 60 °C; (b) **27**, azodicarboxylic dimorpholide, *n*-Bu_3P, THF, rt; (c) bis(pinacolato)diboron, KOAc, SPhos-Pd (first generation), dioxane, 120 °C (microwave); (2) aq. Na_2CO_3, SPhos-Pd (first generation), dioxane, 110 °C conventional heating (one pot); (d) LiOH, MeOH/THF/H_2O, 50 °C.

Activators with the general structure of **41** were accessed via Scheme 3, starting with a two-step, one-pot Miyaura borylation and Suzuki coupling with either **32** or **39** (Y = H or Me) to afford the ketone intermediate **40**. Reductive amination followed by saponification afforded the final activators **41**.

Scheme 4 outlines the synthesis of indane activators with an ether linkage. The 7-bromo-2,3-dihydro-1*H*-inden-1-one (**42**) was either reduced under standard $NaBH_4$ conditions to give the racemic indanol **43**, or **42** was reduced in an asymmetric fashion, using RuCl[(*R*,*R*)-Tsdpen](p-cymene), to give the enantiomerically enriched indanol **43**.[19] The indanols underwent a Mitsunobu reaction with phenol **27** to afford ether **44**. A one pot Miyaura borylation−Suzuki coupling with pyridine halides **32** or **39** and saponification of the ester furnishes activators **45**.

The synthesis of cycloalkenyl activators is outlined in Scheme 5. TBS protected cycloalkenyl intermediates **46** were prepared from previously reported intermediates.[20] A two step, one pot

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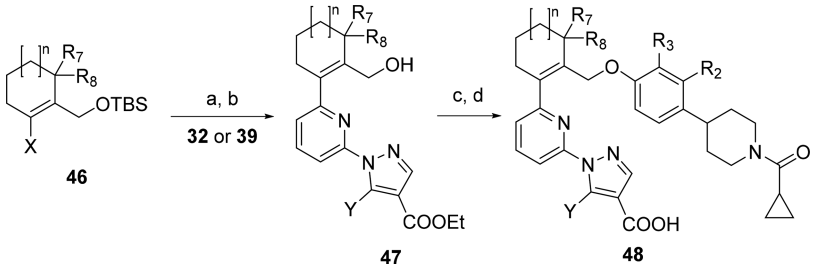
Scheme 5. Synthesis of Cycloalkenyl Activators[a]



[a]Reagents and conditions: (a) (1) bis(pinacolato)diboron, potassium acetate, SPhos–Pd (first generation), dioxane, 110 °C; (2) corresponding cycloalkene intermediate, aq. Na_2CO_3, SPhos–Pd (first generation) (one pot); (b) TBAF, THF, rt; (c) **27**, DIAD, PPh_3, THF; (d) LiOH, THF, MeOH, H_2O, 50 °C.

cross-coupling was performed to couple **46** and 2-bromo pyridyl **32** or **39**. Removal of the TBS group using TBAF in THF afforded **47**. The free alcohols **47** were then coupled with 4-piperidylphenol **27** via a Mitsunobu-type reaction, followed by saponification, to provide activators **48**.

***In Vivo* Pharmacology.** With acceptable potency and efficacy observed in the GTM-3 cellular assay for the thiophene, cyclohexene, and indane cores, we next selected representative examples from each scaffold for *in vivo* evaluation. Compounds **12**, (+)-**17**, and (+)-**20** were profiled first in an acute rabbit ocular tolerability study to assess the maximum dose that afforded acceptable ocular tolerability. Each compound was formulated at 1%, 0.3%, and 0.1% concentrations (300 μg, 100 μg, and 30 μg, respectively) in a 30 μL drop to test in the rabbit ocular tolerability study to identify a suitable dose to evaluate in the cyno-IOP model. Thiophene **12** was sufficiently tolerated up to 300 μg, although mild ocular discharge was noted in the majority of animals. In the cyno-IOP model, thiophene **12** afforded improved IOP lowering compared to progenitor compound **5**; however a 3-fold higher dose was required; furthermore some mild ocular irritation was noted in a subset of animals (Figure 3). In the case of cyclohexene (+)-**17** and

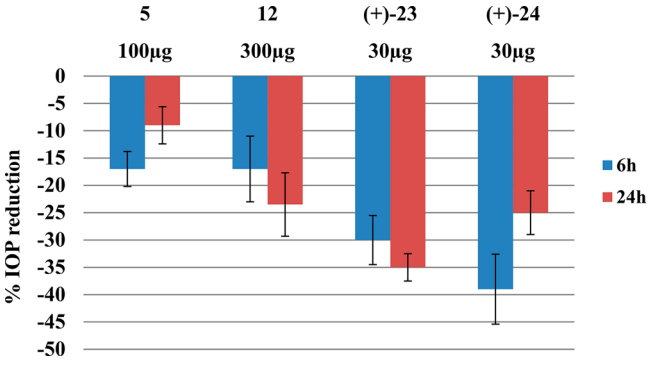


Figure 3. IOP reduction (%) in the cynomolgus monkey laser-induced hypertensive model.

indane (+)-**20**, even a dose as low as 30 μg afforded suboptimal tolerability with hyperemia and excessive blinking observed in subsets of rabbits. The fact that ocular tolerability limited dosing to <30 μg for (+)-**17** and (+)-**20** and that several of the compounds evaluated (e.g., **5** and **12**) also exhibited signs of irritation was a concern. While it was not clear what was causing the acute ocular tolerability issues, one hypothesis was the relatively acidic 5-(trifluoromethyl)-pyrazole-4-carboxylic acid moiety that was common to most compounds across scaffolds, for example, the pK_a of the carboxylic acid of (+)-**21** was determined to be only 3.1. Replacing the electron withdrawing CF_3 moiety with a methyl as in (+)-**23** raises the pK_a over a full log unit to 4.3, without impacting cellular activity. Of note, completely removing substitution at the 5-position of the pyrazole led to a substantial loss in cellular activity (e.g., (+)-**22**). When (+)-**23** was evaluated in an acute rabbit tolerability study, we were delighted to see that at a dose of 300 μg (1%), the highest dose tested, this molecule was well tolerated. Performing the same transformation on cyclohexene (+)-**17** afforded (+)-**24**; this also afforded a much improved rabbit ocular tolerability profile, up to a dose of 300 μg. While we recognize that ocular tolerability is almost certainly governed by a wide range of parameters and that there may not be a general strict correlation of pK_a to tolerability, in this instance, empirically, it appears to be a factor.[21] With (+)-**23** and (+)-**24** offering improved dose flexibility, they were evaluated in the cyno-IOP model. Both (+)-**23** and (+)-**24** afforded robust IOP lowering with excellent ocular tolerability at a dose of 30 μg (Figure 3). However, what differentiated indane (+)-**23** from cyclohexene (+)-**24** was the trend that for (+)-**23** the reduction in IOP was maintained or even increased from 6 h to 24 h time points, whereas there was a clear attenuation in efficacy for (+)-**24** in going from 6 to 24 h time point. The importance of being able to maintain effective IOP lowering over a 24 h time period, and the ability to lower IOP to levels that compare favorably to other approved therapies in this model,[14] led to the selection of compound (+)-**23** for clinical evaluation.[22]

CONCLUSION

In conclusion, SAR development starting from **4** identified *in vitro* potent thiophene containing sGC activators, which afforded modest *in vivo* efficacy in a cynomolgus monkey model of elevated IOP. Subsequent core modifications led to the identification of cyclohexene and indane scaffolds. Further refinement addressed ocular tolerability concerns and led to well tolerated molecules with robust IOP lowering in the cyno-IOP model. These efforts culminated with the discovery of (+)-**23**, an sGC activator specifically designed for once a day topical ocular dosing for the treatment of elevated IOP associated with glaucoma. Additional preclinical and clinical pharmacology and safety studies with (+)-**23** will be reported in due course.

EXPERIMENTAL SECTION

Pharmacophore Modeling. Eight representative sGC activators from the literature[9c,17] were selected to maximize chemical

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dissimilarity and presumable maintenance of a similar binding site based on their electronic and steric features as well as reported SAR. The activators employed are described in refs 9c and 17 are 5-(trifluoro-methyl)-1-(6-(2-((4-(4-(trifluoro-methyl)-cyclohexyl)-phenyl)-methoxy)-phenyl)-pyridin-2-yl)-1*H*-pyrazole-4-carboxylic acid, 1-(4-(2-((4-(4-cyano-phenyl)-2-methyl-phenyl)-methoxy)-5-methyl-phenyl)-pyrimidin-2-yl)-piperidine-4-carboxylic acid, 1-(6-(3-chloro-phenyl)-pyridin-2-yl)-5-(trifluoro-methyl)-1*H*-pyrazole-4-carboxylic acid, 1-((5-methyl-2-(3-(trifluoro-methyl)-phenyl)-thiazol-4-yl)-methyl)-1*H*-pyrazole-4-carboxylic acid, 1-(3-(2-cyclopentyl-2-(4-((2-fluoro-7-oxo-8-aza-bicyclo[4.3.0]nona-1(6),2,4-trien-8-yl)-methyl)-phenyl)-acetylamino)-benzyl)-cyclopropanecarboxylic acid, 3-(4-chloro-3-(2-(4-chloro-phenyl)-4,4,4-trifluoro-3-methyl-butyrylamino)-phenyl)-4-cyclopropyl-butanoic acid, 1-(3-(2-(4-chloro-phenyl)-2-cyclopentyl-acetylamino)-benzyl)-cyclopropanecarboxylic acid, and 1-(6-(5-chloro-2-(4-(4-(2,2,2-trifluoro-ethyl)-piperazin-1-yl)-phenyl)-phenyl)-pyridin-2-yl)-5-(trifluoro-methyl)-1*H*-pyrazole-4-carboxylic acid.

Low energy conformations of these molecules were generated with MacroModel v9.6,[23] followed by B3LYP/6-31+G(d,p) with a continuum water model with Gaussian 03.[24] An initial overlay model was built based on similarity of local molecular size, shape, electronic properties, and reported SAR within low energy conformations of these molecules. The model was further refined with MOE flexible alignment.[25]

***In Vitro* Cellular Assays.** *CHO Cellular Assay.* CHO cells overexpressing sGC were generated to test the effect of sGC activators in a cellular context. Human cDNAs for GUCYA3 (the Reference Sequence NM_000856.3) and GUCYB3 (the Reference Sequence NM_000857.1) were amplified by PCR from a HUVEC (human umbilical vein endothelial cells) cDNA library and cloned into mammalian expression vectors. CHO K1 cells (ATCC CCL-61) were transfected using Lipofectamine 2000 following manufacturer's instructions and stably expressing clones were identified by antibiotic selection. CHO GUCY clone 8E10 was used for subsequent experiments. Cells were seeded at a density of 3000 cells/well in white 384-well proxyplates (PerkinElmer) and incubated overnight, then the medium was removed, and cells were washed with assay buffer (Hanks' balanced salt solution (HBSS), 0.1% BSA, 1 mM IBMX, 20 μM ODQ). sGC activators were serially diluted in DMSO, then diluted in assay buffer prior to adding to cells (10 μL/well, final DMSO concentration 0.5%). Cells were incubated with compounds for 1 h at room temperature and then assayed for cGMP production using Cisbio cGMP HTRF kit (62GM2PEC) according to manufacturer's instructions. The EC_{50} values are calculated based on the amount of cGMP interpolated from the standard curve, using a 4-parameter sigmoidal dose−response. The % E-max (maximal cGMP produced) was calculated in reference to 1-{6-[5-chloro-2-({4-[*trans*-4-(trifluoromethyl)cyclohexyl]-benzyl}oxy)phenyl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid.[9c,26]

GTM-3 Cellular Assay. GTM-3 cells (SV40-transformed human GTM cells, Alcon Laboratories) were used for additional profiling of selected sGC activators. Cells were plated in 96-well plates at a density of 50 000 cells/well and incubated overnight. Medium was removed, and cells were incubated with assay buffer (Dulbecco's modified Eagle's medium (DMEM), 1 mM IBMX, 0.1% BSA, 20 μM ODQ) for 15 min, then sGC activators serially diluted in DMSO were added (final DMSO concentration 0.1%). Cells were incubated 30 min at 37 °C, then cGMP was quantitated using CatchPoint Cyclic-GMP Fluorescent Assay Kit (Molecular Devices) following manufacturer's instructions.

The EC_{50} values are calculated based on the amount of cGMP interpolated from the standard curve, using a 4-parameter sigmoidal dose−response. The % E-max (maximal cGMP produced) was calculated in reference to 1-{6-[5-chloro-2-({4-[*trans*-4-(trifluoromethyl)cyclohexyl]-benzyl}oxy)phenyl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid.[9c,26]

***In Vivo* Pharmacology Experiments.** All animal related procedures were conducted under Novartis Institutional Animal Care and Use Committee (IACUC) approved protocols in compliance with Animal Welfare Act (AWA) regulations and the Guide for the Care and Use of Laboratory Animals.

Determination of IOP in Lasered (Hypertensive) Eyes of Cynomolgus Monkeys. The induction of elevated IOP in cynomolgus monkeys and the determination of IOP have been described in detail in ref 13. However, in brief, conscious IOP was determined with an Alcon Pneumatonometer (Alcon Laboratories, Inc., Fort Worth, TX.) after light corneal anesthesia with 0.25% proparacaine. Right eyes were hypertensive as a result of laser trabeculoplasty. Left eyes were intact and with normal IOP. After a baseline IOP measurement, the animals were randomly divided into two groups with similar group mean of IOP. Compound-containing formulation was administered as a single 30 μL topical ocular drop to both eyes in 8−9 conscious ocular hypertensive cynomolgus monkeys. Vehicle was instilled in both eyes of 8−9 additional animals as control. Subsequent IOP measurements were taken at prescribed time points. Average baseline IOP in the hypertensive eye ranged from 35 to 40 mmHg (n = 9−10 animals/group). Group mean and standard error of the mean (SEM) were calculated. Statistical significance of IOP change from baseline and also versus treatment groups were determined by repeated measures ANOVA and Bonferroni t test at $p < 0.05$. For this manuscript the formulation employed in all instances was comprised of: hydroxypropyl methylcellulose USP 2910 E4M (0.5%), dibasic sodium phosphate anhydrous (0.2%), sodium chloride (0.65%), polysorbate 80 (0.05%), sodium hydroxide and hydrochloric acid (to adjust to pH 7.4), and purified water (q.s. 100%).

Rabbit Ocular Tolerability Assessments Following Topical Ocular Dosing. The compound was instilled as a single 30 μL topical ocular drop on the cornea of New Zealand albino rabbits employing concentrations as specified. Conjunctival hyperemia (mild, medium, and severe, based on area of blood vessel coverage), conjunctival discharge (mild, inner portion of eye; moderate, around eyelid/hair; severe, marked discharge around periocular skin), and swelling (mild or moderate, lid misalignment; severe, eversion) were assessed up to 2 h postdose and followed up at 24 h after dosing. Up to 20 rabbits (10 eyes/dose) were evaluated following a single topical ocular dose. Percent of eyes with varying degrees of ocular tolerability were noted for each dose and compared with that observed following vehicle treatment.

Synthetic Methods and Procedures. *General Chemical Methods.* Starting materials, reagents, and solvents were obtained from commercial sources and used as received. THF and diethyl ether were anhydrous grade. Progress of the reactions was monitored by analytical LC-MS using an Agilent 1100 series with UV detection at 214 and 254 nm and an electrospray mode (ESI) coupled with a Waters ZQ single quad mass detector. Progress of the reactions was also monitored by analytical LC-MS using a Waters Classic AcQuity UPLC with UV detection at 214 and 254 nm and an electrospray mode (ESI) coupled with a Waters SQ single quad mass detector. Purification of intermediates and final products was carried out using CombiFlash Companion from Teledyne Isco, Inc., and RediSep Rf disposable normal phase silica gel columns (4−300 g). HPLC was performed on a Waters preparative HPLC system controlled by MassLynx. Systems were run with acetonitrile/water gradient with 10 mM NH_4OH modifier on X-Bridge C18 5 μm particle column (RP-HPLC-B) or 0.1% TFA modifier on SunFire C18 μm particle column (RP-HPLC-A). Preparative supercritical fluid chromatography (SFC) was performed employing WatersThar-80 system with UV detection based collection. In the case of racemic samples, including intermediates, enantiomers were separated by SFC using a chiral stationary phase with the provided conditions. Optical rotations were measured at the sodium D line with a Jasco P-2000 digital polarimeter in a qualitative manner. NMR spectra were recorded on a Bruker Avance II 400 MHz spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane or deuterated solvent as the internal standard. The following abbreviations are used to denote signal patterns: s = singlet, d = doublet, t = triplet, m = multiplet, and br = broad. The purity of all exemplified compounds was ≥95%, as determined by both ^{1}H NMR and HPLC-UV at a wavelength of 214 nm.

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General Procedure for the Saponification. Method A. A mixture of ethyl ester (1 equiv) and LiOH (10 equiv) in 1:1 THF/H_2O (0.5 M) was stirred at 40 °C for 16 h, and then partially concentrated. The resulting residue was rendered pH ≈ 5 with 2 N aq. HCl and then extracted twice with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and then concentrated.

Method B. A mixture of ethyl ester (1 equiv) and 1 M aq LiOH (3 equiv) in acetonitrile (0.02 M) was stirred at 50 °C for 2 h. Aqueous HCl (3.3 equiv of 1 M) was added to resulting precipitates, which were collected and then washed with H_2O and MeOH to furnish the title compound. In some instances, further HPLC purification was performed under the provided conditions.

Method C. A mixture of ethyl ester (1 equiv) and 1 M aq LiOH (10 equiv) in 1:1 THF/MeOH (0.02 M) was stirred at rt for 1.5 h and then rendered acidic with 1 N aq HCl. The mixture was then extracted with EtOAc. The organic phase was dried over Na_2SO_4, filtered, and then concentrated.

General Procedure for the Mitsunobu-type Reaction. Method D. To a solution of alcohol (1.1 equiv), phenol (1 equiv), and PPh_3 (1.1 equiv) in THF (0.2 M) at 0 °C was added diisopropyl azodicarboxylate (DIAD, 1.1 equiv). The mixture was stirred at rt for 16 h and then concentrated.

Method E. A mixture of alcohol (1 equiv), phenol (1.5 equiv), and 2-(tributylphosphoranylidene)acetonitrile (2 equiv) in toluene (1 M) was stirred at 80 °C for 4 h. The reaction mixture was then concentrated.

General Procedure for a Pd Mediated Cross Coupling with Corresponding Zincate. Method F. To a solution aryl halide (1 equiv) in THF (10 mL) was added dialkylzinc (4 equiv as a solution), followed by $Pd(t\text{-}Bu_3P)_2$ (10 mol %). The mixture was stirred at rt for 16 h and then quenched with EtOH. The mixture was diluted with EtOAc. The mixture was filtered through a plug of silica gel, which was rinsed with EtOAc. The filtrate was then concentrated.

General Procedure of a Pd Mediated Two-Step One-Pot Cross-Coupling. Method G. Step 1. 2-Halo pyridine (1 equiv), bis-(pinacolato)diboron (1 equiv), and KOAc (1.5 equiv) were added to a microwave vial with a stir bar and dioxane (0.2 M). S-Phos Pd G1 (CAS registry number 1028206-58-7, 10 mol %) was added, and the head space was purged with N_2. The vial was sealed and heated to 120 °C under microwave irradiation for 45 min.

Step 2. Aryl halide (1.2 equiv) in dioxane (0.2 M) was added to the reaction mixture, followed by 1 M aq Na_2CO_3 (3 equiv) and S-Phos Pd G1 (10 mol %). The reaction mixture was heated to 110 °C under microwave irradiation for 30 min. The reaction mixture was diluted with EtOAc and washed with H_2O before the organic phase was passed through an Isolute Phase Separator and concentrated.

*1-(6-(3-((4-(1-Propionylpiperidin-4-yl)phenoxy)methyl)thiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic Acid (**4**).* Step 1. A mixture of 2-bromo-3-(bromomethyl)-thiophene (1.50 g, 5.9 mmol), *tert*-butyl 4-(4-hydroxyphenyl)piperidine-1-carboxylate (0.93 g, 5.9 mmol), and K_2CO_3 (0.81 g, 5.9 mmol) in DMF (56 mL) was stirred at 70 °C for 22 h. The reaction mixture was cooled to rt, and then diluted with EtOAc. The organic layer was then washed twice with H_2O. The organic layer was further washed with brine, and then dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by FCC (20% EtOAc in heptane) to afford *tert*-butyl 4-(4-((2-bromothiophen-3-yl)methoxy)phenyl)piperidine-1-carboxylate (0.65 g, 24% yield). MS (ESI+) *m/z* 395.1 (M − *t*Bu + 2H). Step 2. To a suspension of **32** (500 mg, 1.373 mmol), bis(pinacolato)diboron (384 mg, 1.51 mmol), potassium acetate (404 mg, 4.12 mmol), and X-Phos (98 mg, 0.21 mmol) in dioxane (13 mL) was added $Pd(OAc)_2$ (12 mg, 0.053 mmol). The mixture was then stirred at 100 °C for 3 h and cooled to rt. The mixture was then filtered through a plug of Celite. The filtrate was then concentrated. The resulting residue was suspended in 1,4-dioxane (12 mL). To the suspension were added *tert*-butyl 4-(4-((2-bromothiophen-3-yl)methoxy)phenyl)piperidine-1-carboxylate (500 mg, 1.1 mmol), 2 M aq. sodium carbonate (2.21 mL, 4.4 mmol), and $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ adduct. The mixture was stirred at 80 °C for 30 h and then cooled to rt. The mixture was diluted with EtOAc and then washed successively with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by FCC (20% EtOAc in heptane) to afford *tert*-butyl 4-(4-((2-(6-(4-(ethoxycarbonyl)-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)pyridin-2-yl)-thiophen-3-yl)methoxy)phenyl)piperidine-1-carboxylate (0.30 g, 42%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.35 (s, 1H), 8.18 (t, *J* = 7.8 Hz, 1H), 7.84 (d, *J* = 7.5 Hz, 1H), 7.72−7.70 (m, 2H), 7.26 (d, *J* = 5.1 Hz, 1H), 7.13−7.10 (m, 2H), 6.90−6.87 (m, 2H), 5.28 (s, 2H), 4.31 (q, *J* = 7.2 Hz, 2H), 4.06−4.00 (m, 2H), 2.82−2.75 (m, 2H), 2.65−2.55 (m, 1H), 1.72−1.68 (m, 2H), 1.45−1.40 (m, 1H), 1.39 (s, 9H), 1.29 (t, *J* = 7.2 Hz, 3H). MS (ESI+) *m/z* 657.4 (M + H). Step 3. Deprotection of the Boc group on *tert*-butyl 4-(4-((2-(6-(4-(ethoxycarbonyl)-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)pyridin-2-yl)-thiophen-3-yl)methoxy)phenyl)piperidine-1-carboxylate was achieved by a similar method as described for the synthesis of **27a** to afford ethyl 1-(6-(3-((4-(piperidin-4-yl)phenoxy)methyl)thiophen-2-yl)-pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, which was used in the next step without any further purification (crude yield). MS (ESI+) *m/z* 557.3 (M + H). Step 4. To a solution of ethyl 1-(6-(3-((4-(piperidin-4-yl)phenoxy)methyl)thiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (0.25 g, 0.45 mmol) and Et_3N (0.15 mL, 1.12 mmol) in CH_2Cl_2 (20 mL) was added propionyl chloride (0.05 mL, 0.054 mmol). The mixture was stirred at rt for ca. 80 min and then diluted with CH_2Cl_2. The organic phase was washed successively with H_2O (three times) and brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by FCC (50% EtOAc in heptane) to afford ethyl 1-(6-(3-((4-(1-propionylpiperidin-4-yl)phenoxy)methyl)thiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (0.20 g, 74% yield). ^{1}H NMR (300 MHz, DMSO- d_6) δ 8.20 (s, 1H), 8.18 (t, *J* = 8.1 Hz, 1H), 7.84 (d, *J* = 7.2 Hz, 1H), 7.72−7.69 (m, 2H), 7.26 (d, *J* = 5.1 Hz, 1H), 7.13−7.11 (m, 2H), 6.90−6.88 (m, 2H), 5.28 (s, 2H), 4.58−4.52 (m, 1H), 4.31 (q, *J* = 6.9 Hz, 2H), 3.94−3.89 (m, 1H), 3.04−3.00 (m, 2H), 2.70−2.63 (m, 1H), 2.56−2.50 (m, 1H), 2.31 (q, *J* = 7.5 Hz, 2H), 1.80−1.70 (m, 2H), 1.58−1.48 (m, 2H), 1.29 (t, *J* = 6.9 Hz, 3H), 0.98 (t, *J* = 7.5 Hz, 3H). MS (ESI+) *m/z* 613.4 (M + H). Step 5. Method A employing ethyl 1-(6-(3-((4-(1-propionylpiperidin-4-yl)-phenoxy)methyl)thiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate afforded **4** (0.09 g, 82% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.15 (s, 1H), 8.07 (dd, *J* = 7.80, 8.00 Hz, 1H), 7.84 (dd, *J* = 0.60, 8.00 Hz, 1H), 7.59 (dd, *J* = 0.60, 8.00 Hz, 1H), 7.53 (d, *J* = 5.26 Hz, 1H), 7.26 (d, *J* = 5.13 Hz, 1H), 7.08−7.13 (m, 2H), 6.82−6.88 (m, 2H), 5.31 (s, 2H), 4.63−4.70 (m, 1H), 4.01−4.09 (m, 1H), 3.14−3.22 (m, 1H), 2.64−2.79 (m, 2H), 2.45 (q, *J* = 7.54 Hz, 2H), 1.80−1.92 (m, 2H), 1.46−1.66 (m, 2H), 1.14 (t, *J* = 7.46 Hz, 3H). HRMS calculated for $C_{29}H_{28}F_3N_4O_4S$ (M + H) 585.1783, found 585.1808.

*1-(6-(3-((2-Methyl-4-(1-propionylpiperidin-4-yl)phenoxy)methyl)-thiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic Acid (**5**).* Step 1. Method D employing **33** and **26a**, followed by FCC purification (0−30% EtOAc/heptane) afforded *tert*-butyl 4-(4-((2-(6-(4-(ethoxycarbonyl)-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)-pyridin-2-yl)thiophen-3-yl)methoxy)-3-methylphenyl)piperidine-1-carboxylate (2.4 g, 71% yield). MS (ESI+) *m/z* 615.2 (M − *t*Bu + 2H). Step 2. Following the procedure as described for the preparation of **29**, a reaction of *tert*-butyl 4-(4-((2-(6-(4-(ethoxycarbonyl)-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)pyridin-2-yl)thiophen-3-yl)-methoxy)-3-methylphenyl)piperidine-1-carboxylate with propionyl chloride in place of cyclopropane carbonyl chloride afforded ethyl 1-(6-(3-((2-methyl-4-(1-propionylpiperidin-4-yl)phenoxy)methyl)-thiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (160 mg, 98% yield). MS (ESI+) *m/z* 627.3 (M + H). Step 3. Method B employing ethyl 1-(6-(3-((2-methyl-4-(1-propionylpiperidin-4-yl)phenoxy)methyl)thiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, followed by RP-HPLC-B purification, afforded **5** (23 mg, 15% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.03 (dd, *J* = 7.8, 8.0 Hz, 1H), 8.00 (s, 1H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 5.1 Hz, 1H), 7.26 (d, *J* = 5.1 Hz, 1H), 6.97−7.00 (m, 1H), 6.92−6.96 (m, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 5.33 (s, 2H), 4.62−4.70 (m, 1H), 4.02−4.08 (m, 1H), 3.12−3.22 (m, 1H), 2.66−2.75 (m, 2H), 2.44 (q, *J* = 7.5 Hz, 2H), 2.14 (s, 3H),

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1.79−1.91 (m, 2H), 1.46−1.65 (m, 2H), 1.14 (t, J = 7.5 Hz, 3H). HRMS calculated for $C_{30}H_{30}F_3N_4O_4S$ (M + H) 599.1940, found 599.1999.

*1-(6-(3-((2-Methyl-4-(piperidin-4-yl)phenoxy)methyl)thiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic Acid (**6**).* Deprotection of the Boc group on *tert*-butyl 4-(4-((2-(6-(4-(ethoxycarbonyl)-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)pyridin-2-yl)-thiophen-3-yl)methoxy)-3-methylphenyl)piperidine-1-carboxylate was achieved by a similar method as described for the synthesis of **27a** and was followed by method B affording **6** (30 mg, quantitative yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.16 (d, J = 0.7 Hz, 1H), 8.07 (t, J = 7.9 Hz, 1H), 7.85 (dd, J = 7.9, 0.8 Hz, 1H), 7.59 (dd, J = 7.9, 0.7 Hz, 1H), 7.54 (d, J = 5.2 Hz, 1H), 7.27 (d, J = 5.2 Hz, 1H), 7.01 (d, J = 2.3 Hz, 1H), 6.95 (dd, J = 8.3, 2.4 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 5.36 (s, 2H), 3.50−3.43 (m, 2H), 3.15−3.05 (m, 2H), 2.84−2.73 (m, 1H), 2.14 (s, 3H), 2.08−1.99 (m, 2H), 1.90−1.77 (m, 2H). HRMS calculated for $C_{27}H_{26}F_3N_4O_3S$ (M + H)$^+$ 543.1678, found 543.1687.

*1-(6-(3-((4-(1-(Cyclopropylmethyl)piperidin-4-yl)-2-methylphenoxy)methyl)thiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic Acid (**7**).* To a solution of **6** (60 mg, 0.105 mmol) in DMF (1 mL) was added Cs_2CO_3 (103 mg, 0.315 mmol), followed by (bromomethyl)cyclopropane (28.4 mg, 0.210 mmol). The mixture was stirred at 50 °C for 16 h, and then insoluble materials were filtered off. To the DMF solution was added a solution of 1 M aq. LiOH (0.52 mL), and then the mixture was stirred at for 50 °C for 2 h. The reaction mixture was rendered acidic by aq. HCl, and resulting precipitates were removed by filtration. The filtrate was then directly purified by RP-HPLC-B to afford **7** (7 mg, 10% yield over 2 steps). ^{1}H NMR (400 MHz, CD_3OD) δ 8.02 (t, J = 7.9 Hz, 1H), 7.94−7.88 (m, 1H), 7.77 (dd, J = 7.9, 0.8 Hz, 1H), 7.58−7.49 (m, 2H), 7.29 (d, J = 5.2 Hz, 1H), 6.96 (d, J = 9.2 Hz, 2H), 6.79 (d, J = 8.2 Hz, 1H), 5.37 (s, 2H), 3.67 (d, J = 12.2 Hz, 2H), 2.98 (d, J = 7.0 Hz, 4H), 2.72 (s, 1H), 2.13 (s, 3H), 2.04 (d, J = 14.3 Hz, 2H), 1.93 (t, J = 13.4 Hz, 2H), 1.20−1.07 (m, 1H), 0.81−0.73 (m, 2H), 0.48−0.37 (m, 2H). HRMS calculated for $C_{31}H_{32}F_3N_4O_3S$ (M + H) 597.2147, found 597.2151.

*1-(6-(3-((4-(1-(Cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenoxy)methyl)thiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic Acid (**8**).* Step 1. A solution of cyclopropane-carboxylic acid (19.6 mg, 0.23 mmol) and HATU (66.6 mg, 0.175 mmol) in DMF (2 mL) was stirred at rt for 30 min. To the mixture were added **6** (100 mg, 0.175 mmol) and diisopropylethylamine (0.061 mL, 0.350 mmol), and then the mixture was stirred at rt for 16 h. The reaction mixture was filtered, and the filtrate was directly purified by RP-HPLC-B to afford ethyl 1-(6-(3-((4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenoxy)methyl)-thiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (90 mg, 80% yield). MS (ESI+) m/z 639.1 (M + H). Step 2. The obtained ethyl ester was saponified by utilizing method B to provide **8** after RP-HPLC-B purification (52 mg, 60% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.07−7.98 (m, 2H), 7.78 (dd, J = 7.9, 0.8 Hz, 1H), 7.58 (dd, J = 8.0, 0.7 Hz, 1H), 7.52 (d, J = 5.1 Hz, 1H), 7.26 (d, J = 5.2 Hz, 1H), 6.99 (d, J = 2.2 Hz, 1H), 6.95 (dd, J = 8.4, 2.3 Hz, 1H), 6.80 (d, J = 8.3 Hz, 1H), 5.32 (s, 2H), 4.63 (d, J = 12.9 Hz, 1H), 4.44 (d, J = 13.6 Hz, 1H), 3.28−3.18 (m, 1H), 2.73 (tt, J = 11.0, 3.3 Hz, 2H), 2.15 (s, 3H), 2.05−1.95 (m, 1H), 1.95−1.75 (m, 2H), 1.72−1.44 (m, 2H), 0.95−0.75 (m, 4H). HRMS calculated for $C_{31}H_{30}F_3N_4O_4S$ (M + H) 611.1940, found 611.1934.

*1-(6-(3-((4-(1-(Cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenoxy)methyl)-5-methylthiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic Acid (**9**).* Step 1. A solution of **33** (2 g, 5.03 mmol) and NBS (1.1 g, 6.18 mmol) in DMF (20 mL) was stirred at rt for 14 h. The reaction mixture was diluted with H_2O. The whole mixture was stirred at rt for 0.5 h. The resulting solid was collected by filtration. The collected solid was purified by FCC (heptane/EtOAc = 8/2 to 6/4) to afford ethyl 1-(6-(5-bromo-3-(hydroxymethyl)thiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (2.0 g, 83% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (s, 1H), 8.23 (t, J = 8.0 Hz, 1H), 7.91 (dd, J = 7.9, 0.7 Hz, 1H), 7.74 (dd, J = 8.0, 0.7 Hz, 1H), 7.31 (s, 1H), 5.53 (t, J = 5.5 Hz, 1H), 4.67 (d, J = 5.5 Hz, 2H), 4.34 (q, J = 7.1 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H). MS (ESI+) m/z 475.9 (M + H). Step 2. Following method F, ethyl 1-(6-(5-bromo-3-(hydroxymethyl)thiophen-2-yl)-pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate and dimethylzinc (2 M in toluene) afforded ethyl 1-(6-(3-(hydroxymethyl)-5-methylthiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate after FCC purification (heptane/EtOAc = 67/33) (1.0 g, 77% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (d, J = 0.6 Hz, 1H), 8.16 (t, J = 7.9 Hz, 1H), 7.85 (dd, J = 8.0, 0.8 Hz, 1H), 7.64 (dd, J = 7.9, 0.7 Hz, 1H), 6.94 (d, J = 1.2 Hz, 1H), 5.34 (t, J = 5.5 Hz, 1H), 4.62 (d, J = 5.5 Hz, 2H), 4.34 (q, J = 7.1 Hz, 2H), 2.46 (d, J = 1.1 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H). MS (ESI+) m/z 412.1. Step 3. Following method E, ethyl 1-(6-(3-(hydroxymethyl)-5-methylthiophen-2-yl)-pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate and **27a** afforded ethyl 1-(6-(3-((4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenoxy)methyl)-5-methylthiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate after FCC purification (15−40% EtOAc/heptane) (30 mg, 63% yield). MS (ESI+) m/z 653.1 (M + H). Step 4. Method C was employed for the hydrolysis, followed by RP-HPLC-A purification to afford **9** (11 mg, 21% yield over 2 steps). ^{1}H NMR (+5 μL TFA, 400 MHz, CD_3OD) δ 8.15 (s, 1H), 8.02 (t, J = 7.9 Hz, 1H), 7.74 (dd, J = 0.6, 7.9 Hz, 1H), 7.52 (dd, J = 0.6, 7.9 Hz, 1H), 6.95−7.01 (m, 2H), 6.92 (dd, J = 2.3, 8.4 Hz, 1H), 6.76 (d, J = 8.4 Hz, 1H), 5.25 (s, 2H), 4.58−4.69 (m, 1H), 4.39−4.51 (m, 1H), 3.17−3.26 (m, 1H), 2.65−2.79 (m, 2H), 2.50 (d, J = 1 Hz, 3H), 2.13 (s, 3H), 1.95−2.05 (m, 1H), 1.76−1.94 (m, 2H), 1.44−1.70 (m, 2H), 0.74−0.94 (m, 4H). HRMS calculated for $C_{32}H_{32}F_3N_4O_4S$ (M + H) 625.2096, found 625.2115.

*1-(6-(5-Chloro-3-((4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenoxy)methyl)thiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic Acid (**10**).* Step 1. Ethyl 1-(6-(5-chloro-3-(hydroxymethyl)thiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate was synthesized by a similar method as described for the synthesis of ethyl 1-(6-(5-bromo-3-(hydroxymethyl)thiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, starting with NCS in the place of NBS. MS (ESI+) m/z 432.2 (M + H). Step 2. Following method E, **34** (X_1 = Cl, prepared in the step 1 above) and **27a** afforded ethyl 1-(6-(5-chloro-3-((4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenoxy)-methyl)thiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate. MS (ESI+) m/z 673.4 (M + H). Step 3. Method C, followed by HPLC purification (RP-HPLC-A), afforded **10** (3% yield over 3 steps). ^{1}H NMR (TFA salt, 400 MHz, CD_3OD) δ 8.17 (s, 1H), 8.07 (dd, J = 7.80, 8.00 Hz, 1H), 7.75−7.80 (m, 1H), 7.63 (d, J = 7.96 Hz, 1H), 7.15 (s, 1H), 7.00−7.04 (m, J = 2.00 Hz, 1H), 6.94−6.99 (m, 1H), 6.82 (d, J = 8.34 Hz, 1H), 5.25 (s, 2H), 4.60−4.69 (m, 1H), 4.39−4.50 (m, 1H), 3.20−3.29 (m, 1H), 2.67−2.79 (m, 2H), 2.14 (s, 3H), 1.96−2.03 (m, 1H), 1.87−1.95 (m, 1H), 1.78−1.87 (m, 1H), 1.46−1.70 (m, 2H), 0.75−0.93 (m, 4H). HRMS calculated for $C_{31}H_{29}ClF_3N_4O_4S$ (M + H) 645.1550, found 645.1581.

*1-(6-(3-((4-(1-(Cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenoxy)methyl)-5-ethylthiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic Acid (**11**).* Step 1. Following method F, ethyl 1-(6-(5-bromo-3-(hydroxymethyl)thiophen-2-yl)-pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate and diethylzinc (1 M in hexane), followed by FCC purification (0−30% EtOAc in heptane), afforded ethyl 1-(6-(5-ethyl-3-(hydroxymethyl)thiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (136 mg, 66% yield). MS (ESI+) m/z 425.90 (M + H). Step 2. To a solution of ethyl 1-(6-(5-ethyl-3-(hydroxymethyl)thiophen-2-yl)-pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (220 mg, 0.517 mmol) and diisopropylethylamine (270 μL, 1.55 mmol) in anhydrous DCM (5 mL) at rt was added methanesulfonyl chloride (72 μL, 0.931 mmol), and then the mixture was stirred at rt for 18 h. The reaction mixture was then washed with H_2O. The aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was used in the next step without any further purification. MS (ESI+) m/z 443.8 (M + H). Step 3. To a solution of the resulting residue above (230 mg as a crude, 0.52 mmol) in anhydrous DMF (6 mL) was added potassium carbonate (239 mg, 1.73 mmol), followed

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by **26a** (151 mg, 0.52 mmol). The mixture was stirred at 50 °C for 18 h. The reaction mixture was diluted with EtOAc, which was then washed with H_2O. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by FCC (100% heptane) to afford *tert*-butyl 4-(4-((2-(6-(4-(ethoxycarbonyl)-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)pyridin-2-yl)-5-ethylthiophen-3-yl)methoxy)-3-methylphenyl)piperidine-1-carboxylate (330 mg, 91% yield). MS (ESI+) *m/z* 699.8 $[M + H]^+$. Step 4. Deprotection of the Boc group of *tert*-butyl 4-(4-((2-(6-(4-(ethoxycarbonyl)-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)pyridin-2-yl)-5-ethylthiophen-3-yl)methoxy)-3-methylphenyl)piperidine-1-carboxylate and subsequent acylation were achieved by a similar method as described for the synthesis of **27a** to furnish ethyl 1-(6-(3-((4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenoxy)methyl)-5-ethylthiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (240 mg, 76% yield). MS (ESI+) *m/z* 667.0 (M + H). Step 5. Following method C, ethyl 1-(6-(3-((4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenoxy)methyl)-5-ethylthiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate afforded **11**, after RP-HPLC-A purification (100 mg, 98% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.97 (t, *J* = 8.0 Hz, 1H), 7.91 (s, 1H), 7.68 (dd, *J* = 0.7, 7.9 Hz, 1H), 7.52 (dd, *J* = 0.7, 8.0 Hz, 1H), 6.93−7.01 (m, 3H), 6.80 (d, *J* = 8.4 Hz, 1H), 5.27 (s, 2H), 4.58−4.68 (m, 1H), 4.40−4.49 (m, 1H), 3.19−3.26 (m, 1H), 2.87 (dq, *J* = 0.9, 7.6 Hz, 2H), 2.67−2.79 (m, 2H), 2.17 (s, 3H), 1.96−2.04 (m, 1H), 1.87−1.95 (m, 1H), 1.77−1.86 (m, 1H), 1.46−1.70 (m, 2H), 1.33 (t, *J* = 7.6 Hz, 3H), 0.77−0.93 (m, 4H). HRMS calculated for $C_{33}H_{34}F_3N_4O_4S$ (M + H) 639.2253, found 639.2275.

*1-(6-(3-((4-(1-(Cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenoxy)methyl)-4-ethyl-5-methylthiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic Acid (**12**).* Step 1. The bromination of ethyl 1-(6-(3-(hydroxymethyl)-5-methylthiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate was achieved by a similar method as described for the synthesis of ethyl 1-(6-(5-bromo-3-(hydroxymethyl)thiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate after FCC purification (0−40% EtOAc/heptane). MS (ESI+) *m/z* 489.9 (M + H). Step 2. Following method F, ethyl 1-(6-(4-bromo-3-(hydroxymethyl)-5-methylthiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate and diethylzinc (1 M in hexane) afforded ethyl 1-(6-(4-ethyl-3-(hydroxymethyl)-5-methylthiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate after FCC purification (35% EtOAc/heptane) (78% yield over 2 steps). MS (ESI+) *m/z* 440.3 (M + H). Step 3. Method E employing **27a** and ethyl 1-(6-(4-ethyl-3-(hydroxymethyl)-5-methylthiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, followed by FCC purification (16−67% EtOAc/heptane), afforded ethyl 1-(6-(3-((4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenoxy)methyl)-4-ethyl-5-methylthiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (65 mg, 28% yield). MS (ESI+) *m/z* 681.3 (M + H). Step 4. Method C employing the product in the step 4 above, followed by RP-HPLC-A purification, afforded **12** (25 mg, 35% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.09 (s, 1H), 7.96 (dd, *J* = 7.80, 8.00 Hz, 1H), 7.69 (dd, *J* = 0.67, 7.89 Hz, 1H), 7.53 (dd, *J* = 0.67, 7.89 Hz, 1H), 6.94−7.00 (m, 2H), 6.89−6.93 (m, 1H), 5.12 (s, 2H), 4.59−4.69 (m, 1H), 4.40−4.51 (m, 1H), 3.21−3.27 (m, 1H), 2.70−2.80 (m, 2H), 2.61−2.70 (m, 2H), 2.46 (s, 3H), 2.07 (s, 3H), 1.97−2.05 (m, 1H), 1.89−1.97 (m, 1H), 1.80−1.89 (m, 1H), 1.47−1.71 (m, 2H), 1.15 (t, *J* = 7.52 Hz, 3H), 0.77−0.95 (m, 4H). HRMS calculated for $C_{34}H_{36}F_3N_4O_4S$ (M + H) 653.2404, found 665.2424.

*1-(6-(3-((4-(1-(Cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenoxy)methyl)-4-methylthiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic Acid (**13**).* Step 1. To a solution of 1 M LDA in THF (14.77 mL, 14.77 mmol) at −78 °C was added a solution of 4-methylthiophene-3-carboxylic acid (1 g, 7.03 mmol) in THF (5 mL) over 0.25 h, and then the mixture was stirred at −78 °C for 0.5 h. To the solution was then added a solution of CBr_4 (2.57 g, 7.74 mmol) in THF (8 mL) dropwise over 15 min. The mixture was stirred at −78 °C for 0.5 h, and then allowed to warm to rt over 1 h. The reaction mixture was then rendered acidic with 1 M aq. HCl to a pH of 1. The mixture was then extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and then concentrated. The resulting residue was purified by FCC (0−100% EtOAc in heptane) to afford 2-bromo-4-methylthiophene-3-carboxylic acid (1.2 g, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (s, 1H), 2.45 (s, 3H). Step 2. To a solution of 2-bromo-4-methylthiophene-3-carboxylic acid (1.22 g, 5.52 mmol) in THF (8 mL) at rt was added BH_3-THF in THF (16.56 mL, 16.56 mmol). The mixture was then stirred at rt for 2 h. The reaction was quenched with MeOH. The mixture was then concentrated. The resulting residue was purified by FCC (0−30% EtOAc in heptane) to afford (2-bromo-4-methylthiophen-3-yl)methanol (920 mg, 81% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.02 (d, *J* = 1.0 Hz, 1H), 4.45−4.60 (m, 2H), 2.29 (d, *J* = 1.0 Hz, 3H). Step 3. Following method D, (2-bromo-4-methylthiophen-3-yl)methanol and **27a**, followed by FCC purification (0−100% EtOAc/heptane), afforded (4-(4-((2-bromo-4-methylthiophen-3-yl)methoxy)-3-methylphenyl)-piperidin-1-yl)(cyclopropyl)methanone (80 mg, 35% yield). MS (ESI +) *m/z* 448.0 (M + H). Step 4. Following method G, **32** and (4-(4-((2-bromo-4-methylthiophen-3-yl)methoxy)-3-methylphenyl)-piperidin-1-yl)(cyclopropyl)methanone, followed by FCC purification (0−50% EtOAc/heptane), afforded ethyl 1-(6-(3-((4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenoxy)methyl)-4-methylthiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (54 mg, 46% yield). MS (ESI+) *m/z* 448.0 (M + H). Step 5. Method C employing ethyl 1-(6-(3-((4-(1-(cyclopropanecarbonyl)-piperidin-4-yl)-2-methylphenoxy)methyl)-4-methylthiophen-2-yl)-pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate afforded **13**, without any further purification (22 mg, 43% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.08 (d, *J* = 0.8 Hz, 1H), 8.00 (t, *J* = 7.9 Hz, 1H), 7.74 (dd, *J* = 7.9, 0.8 Hz, 1H), 7.59 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.22 (d, *J* = 1.1 Hz, 1H), 6.98 (d, *J* = 2.2 Hz, 1H), 6.95 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.88 (d, *J* = 8.3 Hz, 1H), 5.19 (s, 2H), 4.64 (d, *J* = 13.1 Hz, 1H), 4.45 (d, *J* = 13.7 Hz, 1H), 3.27−3.20 (m, 1H), 2.74 (tt, *J* = 12.2, 3.7 Hz, 2H), 2.30 (d, *J* = 1.0 Hz, 3H), 2.07 (s, 3H), 2.00 (tt, *J* = 8.0, 4.8 Hz, 1H), 1.96−1.87 (m, 1H), 1.83 (d, *J* = 13.2 Hz, 1H), 1.71−1.45 (m, 2H), 0.94−0.86 (m, 2H), 0.85−0.78 (m, 2H). HRMS calculated for $C_{32}H_{32}F_3N_4O_4S$ (M + H) 625.2018, found 625.2121.

*1-(6-(3-((4-(1-(Cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenoxy)methyl)-4-ethylthiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic Acid (**14**).* Step 1. A mixture of thiophene-3-carboxylic acid (2.24 g, 17.5 mmol), propylphosphonic anhydride (T_3P, 2 M in DMF, 12.5 mL, 25 mmol), diisopropylethylamine (6.2 mL, 35.5 mmol) and 2,3,5,6-tetrafluoro-4-(trifluoromethyl)aniline (4.45 g, 19.1 mmol) was stirred at 100 °C for 18 h and then cooled to rt. The reaction mixture was poured into saturated aq. NH_4Cl and then stirred for 0.5 h. The resulting precipitates were collected by filtration. The precipitates were triturated with CH_2Cl_2 (ca. 60 mL). The solids were collected by filtration and rinsed with CH_2Cl_2 to afford *N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)thiophene-3-carboxamide (3.7 g, 62% yield). MS (ESI+) *m/z* 344.0 (M + H). Step 2. A mixture of *N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)thiophene-3-carboxamide (2.33 g, 6.8 mmol), **32** (1.98 g, 5.43 mmol), $Pd(OAc)_2$ (121 mg, 0.54 mmol), Cs_2CO_3 (5.31 g, 16.30 mmol), and triphenylphosphine (547 mg, 2.09 mmol) in toluene (9.9 mL) was sparged with N_2, and then the mixture was stirred at 100 °C for 1.5 h. The reaction mixture was cooled to rt and then diluted with EtOAc and saturated aq. NH_4Cl. The organic layer was separated and then successively washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by FCC (15−40% EtOAc/heptane) to afford ethyl 1-(6-(3-((2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-carbamoyl)thiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (2.5 g, 74% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.20 (s, 1H), 8.36 (s, 1H), 8.18 (t, *J* = 7.9 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 5.3 Hz, 1H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.45 (d, *J* = 5.1 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H). MS (ESI+) *m/z* 627.0 (M + H). Step 3. To a mixture of ethyl 1-(6-(3-((2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)carbamoyl)thiophen-

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2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (503.8 mg, 0.804 mmol), potassium acetate (281.7 mg, 2.87 mmol), and NBS (217.1 mg, 1.220 mmol) in DCE (5 mL) was added bis[(pentamethylcyclopentadienyl)dichloro-rhodium] (25.4 mg, 0.041 mmol). The mixture was then stirred at 80 °C for 1 h. To the mixture was then added an additional amount of NBS (168.2 mg, 0.945 mmol), and the mixture continued to be stirred at 80 °C for 0.5 h. To the mixture was then added bis[(pentamethylcyclopentadienyl)-dichloro-rhodium] (33.2 mg, 0.054 mmol) and stirred at 80 °C for 0.5 h. The reaction mixture was then cooled to rt and filtered through a plug of Celite, which was rinsed with EtOAc. The filtrate was then concentrated. The resulting residue was purified by FCC (15−30% EtOAc/heptane) to afford ethyl 1-(6-(4-bromo-3-((2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)carbamoyl)thiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (254 mg, 45% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.52 (s, 1H), 8.37 (s, 1H), 8.25 (t, J = 7.9 Hz, 1H), 8.06 (s, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 4.33 (q, J = 7.1 Hz, 2H), 1.31 (t, J = 7.1 Hz, 3H). MS (ESI+) m/z 704.8 (M + H). Step 4. A mixture of ethyl 1-(6-(4-bromo-3-((2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)carbamoyl)thiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (1.47 g, 2.08 mmol) and MsOH (7.5 mL) was stirred at 70 °C for 2.25 h and then cooled to rt. The mixture was poured into ice/H_2O and then stirred for 0.75 h. The resulting precipitate was collected by filtration to furnish 4-bromo-2-(6-(4-(ethoxycarbonyl)-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)pyridin-2-yl)thiophene-3-carboxylic acid (469 mg, 46% yield). MS (ESI+) m/z 489.9 (M + H). Step 5. To a solution of BH_3-THF complex (6.6 mL, 6.60 mmol) at 4 °C was added a solution of 4-bromo-2-(6-(4-(ethoxycarbonyl)-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)pyridin-2-yl)thiophene-3-carboxylic acid (644 mg, 1.31 mmol) in THF (5 mL). The mixture was then stirred for 3 h at rt. To the mixture was added additional BH_3-THF complex (6.6 mL, 6.6 mmol), and then the mixture was stirred at rt for an additional 3 h. The reaction was quenched with MeOH (6.0 mL). The mixture was then concentrated. The resulting residue was purified by FCC (15−40% EtOAc/heptane) to afford ethyl 1-(6-(4-bromo-3-(hydroxymethyl)-thiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (250 mg, 40% yield). MS (ESI+) m/z 475.9 (M + H). Step 6. Following method F, ethyl 1-(6-(4-bromo-3-(hydroxymethyl)-thiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (370 mg, 0.777 mmol) and diethylzinc (1 M in hexane, 1.5 mL), followed by FCC purification (33% isocratic EtOAc/heptane), afforded ethyl 1-(6-(4-ethyl-3-(hydroxymethyl)thiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (190 mg, 57% yield). MS (ESI+) m/z 426.2 (M + H). *Step 7.* To a solution of ethyl 1-(6-(4-ethyl-3-(hydroxymethyl)thiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (150 mg, 0.353 mmol) and CBr_4 (150 mg, 0.452 mmol) in CH_2Cl_2 (1 mL) at rt was added PPh_3 (150 mg, 0.572 mmol). The reaction mixture was then stirred at rt for 1.5 h. To the reaction mixture were added **27a** (140 mg, 0.540 mmol) and K_2CO_3 (140 mg, 1.013 mmol), and then the reaction mixture was diluted with DMF (3 mL). The reaction mixture was then stirred at rt for 16 h. The reaction mixture was diluted with EtOAc, and the organic layer was washed successively with half saturated aq. $KHSO_4$, H_2O, and brine, dried over Na_2SO_4, filtered, and then concentrated. The residue was purified by FCC (2−7% EtOAc/CH_2Cl_2) to afford ethyl 1-(6-(3-((4-(1-(cyclopropanecarbonyl)-piperidin-4-yl)-2-methylphenoxy)methyl)-4-ethylthiophen-2-yl)-pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (140 mg, 60% yield). MS (ESI+) m/z 667.4 (M + H). Step 8. Method C employing ethyl 1-(6-(3-((4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenoxy)methyl)-4-ethylthiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate afforded **14** without any further purification (110 mg, 80% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.94−8.01 (m, 2H), 7.71 (dd, J = 0.67, 7.89 Hz, 1H), 7.59 (dd, J = 0.61, 7.95 Hz, 1H), 7.26 (s, 1H), 6.95−7.01 (m, 2H), 6.90 (d, J = 8.20 Hz, 1H), 5.16 (s, 2H), 4.59−4.68 (m, 1H), 4.40−4.50 (m, 1H), 3.20−3.27 (m, 1H), 2.66−2.80 (m, 4H), 2.08 (s, 3H), 1.97−2.05 (m, 1H), 1.89−1.96 (m, 1H), 1.79−1.88 (m, 1H), 1.47−1.72 (m, 2H), 1.28 (t, J = 7.52 Hz, 3H), 0.76−0.95 (m, 4H). HRMS calculated for $C_{33}H_{34}F_3N_4O_4S$ (M + H) 639.2253, found 639.2253.

*1-(6-(2-((4-(1-(Cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenoxy)methyl)cyclopent-1-en-1-yl)pyridin-2-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic Acid (**15**).* Step 1. To a solution of (2-bromocyclopent-1-en-1-yl)methanol (1.95 g, 11.01 mmol) and imidazole (0.86 g, 12.7 mmol) in DMF (10 mL) was added TBS-Cl (1.83 g, 12.12 mmol). The mixture was stirred at rt for 18 h. The reaction was quenched with a mixture of H_2O and saturated aq NH_4Cl. The mixture was extracted with a solvent mixture of EtOAc/heptane (ca. 2/1). The organic layer was washed with H_2O and brine and dried over Na_2SO_4. The organic layer was filtered and concentrated to afford ((2-bromocyclopent-1-en-1-yl)methoxy)(*tert*-butyl)dimethylsilane (3.04 g, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (s, 2H), 2.60−2.53 (m, 2H), 2.35 (t, J = 7.2 Hz, 2H), 1.86 (app. quin, J = 7.6 Hz, 2H), 0.82 (s, 9H), 0.00 (s, 6H). Step 2. Following method G, **32** and ((2-bromocyclopent-1-en-1-yl)-methoxy)(*tert*-butyl)dimethylsilane, followed by FCC purification (0−75% EtOAc in heptane), afforded ethyl 1-(6-(2-(((*tert*-butyldimethylsilyl)oxy)methyl)cyclopent-1-en-1-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (34% yield). MS (ESI+) m/z 496.3 (M + H). Step 3. To a solution of ethyl 1-(6-(2-(((*tert*-butyldimethylsilyl)oxy)methyl)cyclopent-1-en-1-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (0.19 g, 0.383 mmol) in THF (5 mL) at rt was added TBAF (1 M in THF; 0.65 mL, 0.65 mmol). The mixture was stirred at rt for 30 min. The reaction mixture was diluted with EtOAc. The organic layer was then washed with saturated aq NH_4Cl, dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by FCC (0−30% EtOAc/DCM) to afford ethyl 1-(6-(2-(hydroxymethyl)cyclopent-1-en-1-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (134 mg, 92% yield). MS (ESI+) m/z 382.2 (M + H). Step 4. Following method E, a reaction of **27a** with ethyl 1-(6-(2-(hydroxymethyl)cyclopent-1-en-1-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, followed by FCC purification (0−20% EtOAc/DCM), afforded ethyl 1-(6-(2-((4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenoxy)methyl)cyclopent-1-en-1-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate. MS (ESI+) m/z 623.3 (M + H). Step 5. Method A employing ethyl 1-(6-(2-((4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenoxy)methyl)-cyclopent-1-en-1-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, followed by RP-HPLC-B purification, afforded **15** (64 mg, 55% yield over 2 steps). ^{1}H NMR (400 MHz, CD_3OD) δ 13.44 (br. s., 1H), 8.29 (s, 1H), 8.14 (t, J = 7.9 Hz, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.00 (d, J = 1.8 Hz, 1H), 6.87 (dd, J = 2.1, 8.3 Hz, 1H), 6.62 (d, J = 8.4 Hz, 1H), 5.04 (s, 2H), 4.49 (d, J = 12.1 Hz, 1H), 4.34 (d, J = 12.2 Hz, 1H), 3.12 (t, J = 12.1 Hz, 1H), 2.88 (t, J = 7.2 Hz, 2H), 2.73 (t, J = 7.2 Hz, 2H), 2.69−2.61 (m, 2H), 2.11 (s, 3H), 2.02−1.88 (m, 3H), 1.82−1.66 (m, 2H), 1.55−1.31 (m, 2H), 0.80−0.66 (m, 4H). HRMS calculated for $C_{32}H_{34}F_3N_4O_4$ (M + H) 595.2532, found 595.2549.

*1-(6-(2-((4-(1-(Cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenoxy)methyl)cyclohex-1-en-1-yl)pyridin-2-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic Acid (**16**).* Step 1. Following method G, a reaction of **32** (1.43 g, 3.93 mmol) with ((2-bromocyclohex-1-en-1-yl)methoxy)(*tert*-butyl)dimethylsilane (1 g, 3.28 mmol), followed by FCC purification (0−10% EtOAc in heptane), afforded ethyl 1-(6-(2-(((*tert*-butyldimethylsilyl)oxy)-methyl)cyclohex-1-en-1-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (569 mg, 34% yield). MS (ESI+) m/z 510.3 (M + H). Step 2. Deprotection of the TBS group on ethyl 1-(6-(2-(((*tert*-butyldimethylsilyl)oxy)methyl)cyclohex-1-en-1-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate was achieved by a similar method as described for the synthesis of **15**, followed by purification by FCC (0−100% EtOAc/heptane), to afford ethyl 1-(6-(2-(hydroxymethyl)cyclohex-1-en-1-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (2.26 g, 92% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (d, J = 0.6 Hz, 1H), 8.08 (t, J = 7.8 Hz, 1H), 7.65 (dd, J = 8.0, 0.8 Hz, 1H), 7.57 (dd, J = 7.7, 0.9 Hz, 1H), 4.74 (t, J = 5.3 Hz, 1H), 4.32 (q, J = 7.1 Hz, 2H), 3.83 (d, J = 5.3 Hz, 2H), 2.40−2.31

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(m, 2H), 2.31−2.18 (m, 2H), 1.65 (t, J = 3.2 Hz, 4H), 1.31 (t, J = 7.1 Hz, 3H). MS (ESI+) m/z 396.2 (M + H). Step 3. Following method D, a reaction of ethyl 1-(6-(2-(hydroxymethyl)cyclohex-1-en-1-yl)-pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate with **26a**, followed by FCC purification (0−25% EtOAc in heptane), afforded *tert*-butyl 4-(4-((2-(6-(4-(ethoxycarbonyl)-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)pyridin-2-yl)cyclohex-1-en-1-yl)methoxy)-3-methylphenyl)piperidine-1-carboxylate (566 mg, 69% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 (s, 1H), 8.09 (t, J = 7.8 Hz, 1H), 7.71−7.65 (m, 1H), 7.53−7.48 (m, 1H), 6.99−6.96 (m, 1H), 6.87 (dd, J = 8.3, 2.3 Hz, 1H), 6.60 (d, J = 8.5 Hz, 1H), 4.40 (s, 2H), 4.33 (q, J = 7.1 Hz, 2H), 4.07−3.99 (m, 2H), 3.29 (s, 2H), 2.45−2.38 (m, 2H), 2.34−2.28 (m, 2H), 2.11 (s, 3H), 1.74−1.63 (m, 6H), 1.46−1.35 (m, 12H), 1.31 (t, J = 7.1 Hz, 3H). MS (ESI+) m/z 669.3 (M + H). Step 4. To a solution of *tert*-butyl 4-(4-((2-(6-(4-(ethoxycarbonyl)-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)pyridin-2-yl)cyclohex-1-en-1-yl)methoxy)-3-methylphenyl)piperidine-1-carboxylate (396 mg, 0.592 mmol) in DCM (5 mL) at 0 °C was added TFA (5 mL, 64.9 mmol) dropwise. The mixture was then stirred for 30 min at 0 °C. Acetonitrile (10 mL) was added to the mixture, which was then was concentrated. The resulting residue was diluted with DCM and saturated. aq. $NaHCO_3$ and then passed through an ISOLUTE Phase Separator. The organic layer was concentrated to furnish ethyl 1-(6-(2-((2-methyl-4-(piperidin-4-yl)phenoxy)methyl)cyclohex-1-en-1-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (337 mg, quantitative yield). MS (ESI+) m/z 569.4 (M + H). Step 5. To a solution of ethyl 1-(6-(2-((2-methyl-4-(piperidin-4-yl)phenoxy)methyl)cyclohex-1-en-1-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (38 mg, 0.067 mmol) and diisopropylethylamine (0.035 mL, 0.200 mmol) in DCM (2 mL) at 0 °C was added cyclopropylcarbonyl chloride (6 μL, 0.100 mmol). The mixture was stirred for 30 min at 0 °C, and then H_2O was added. The mixture was then passed through an ISOLUTE Phase Separator. The organics were concentrated. The resulting residue was purified by FCC (heptane to 50% EtOAc in heptane) to afford ethyl 1-(6-(2-((4-(1-(cyclopropanecarbonyl)-piperidin-4-yl)-2-methylphenoxy)methyl)cyclohex-1-en-1-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (36 mg, 85% yield). MS (ESI+) m/z 637.3 (M + H). Step 6. Method C employing ethyl 1-(6-(2-((4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenoxy)methyl)cyclohex-1-en-1-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate, followed by RP-HPLC-B purification, afforded **16** (10 mg, 44% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.44 (s, 1H), 8.28 (s, 1H), 8.08 (t, J = 7.8 Hz, 1H), 7.67 (dd, J = 8.0, 0.8 Hz, 1H), 7.50 (dd, J = 7.8, 0.9 Hz, 1H), 7.00 (d, J = 2.2 Hz, 1H), 6.89 (dd, J = 8.3, 2.2 Hz, 1H), 6.60 (d, J = 8.4 Hz, 1H), 4.53−4.43 (m, 1H), 4.40 (s, 2H), 4.38−4.30 (m, 1H), 3.12 (t, J = 12.8 Hz, 1H), 2.71−2.53 (m, 2H), 2.43 (s, 2H), 2.32 (dd, J = 5.0, 2.5 Hz, 2H), 2.11 (s, 3H), 2.04−1.92 (m, 1H), 1.79−1.66 (m, 6H), 1.49 (d, J = 13.1 Hz, 1H), 1.37 (s, 1H), 0.77−0.65 (m, 4H). HRMS calculated for $C_{33}H_{36}F_3N_4O_4$ (M + H) 609.2689, found 609.2682.

*(+)-1-(6-(2-((4-(1-(Cyclopropanecarbonyl)piperidin-4-yl)-3-ethylphenoxy)methyl)-3-methylcyclohex-1-en-1-yl)pyridin-2-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic Acid ((+)-**17**).* Step 1. Methyl acetoacetate (1.85 mL, 17.2 mmol) was added dropwise to a suspension of NaH (0.76 g, 18.9 mmol, 60% in mineral oil) and THF (60 mL) at 0 °C. After 10 min, *n*-BuLi (7.58 mL, 18.9 mmol, 2.5 M in heptane) was added dropwise. After an additional 10 min, crotonyl bromide (1.77 mL, 17.2 mmol) was added, and the reaction was allowed to slowly warm to rt. After 2 h, the reaction was quenched with 1 M aq. HCl, and the mixture was extracted with Et_2O (200 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated. The residue was purified by FCC (5% EtOAc/heptane) to give methyl 3-oxooct-6-enoate as a mixture of *E*- and *Z*-isomers (2.7 g, 84% yield). MS (ESI+) m/z 171.1 (M + H). Step 2. A mixture of methyl 3-oxooct-6-enoate (4.35 g, 25.6 mmol), ytterbium(III) trifluoromethanesulfonate (4.76 g, 7.67 mmol), and dichlorobis-(acetonitrile)palladium(II) (0.66 g, 2.56 mmol) in dioxane (250 mL) was stirred at 50 °C for 30 h and then concentrated. The resulting residue was passed through a silica gel plug, eluting with 30% EtOAc/heptane, to furnish *rac*-methyl 2-methyl-6-oxocyclohexanecarboxylate, which was used without any further purification (3.2 g, 74% yield). MS (ESI+) m/z 171.1 (M + H). Step 3. To a solution of *rac*-methyl 2-methyl-6-oxocyclohexanecarboxylate (1.00 g, 5.88 mmol) in DCM (30 mL) at 0 °C was added NaH (0.305 g, 7.64 mmol, 60% in mineral oil). The suspension was allowed to warm to rt and stir for 10 min. The reaction mixture was then cooled to −78 °C. To the mixture at −78 °C was added triflic anhydride (1.29 mL, 14.1 mmol), and the mixture was allowed to gradually warm to rt. After 1 h, the reaction at rt was quenched with the slow addition of 10% aq. citric acid. The mixture was then diluted with DCM and H_2O. The layers were mixed and then separated. The aqueous layer was further extracted with DCM. The combined organic layers were then dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by FCC (0−10% EtOAc/heptane) to afford *rac*-methyl 6-methyl-2-(((trifluoromethyl)-sulfonyl)oxy)cyclohex-1-enecarboxylate (1.55 g, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 3H), 2.91−2.78 (m, 1H), 2.40−2.21 (m, 2H), 1.85−1.73 (m, 1H), 1.73−1.62 (m, 2H), 1.45−1.35 (m, 1H), 1.02 (d, J = 6.9 Hz, 3H). Step 4. To a solution of *rac*-methyl 6-methyl-2-(((trifluoromethyl)sulfonyl)oxy)cyclohex-1-enecarboxylate (5.1 g, 16.9 mmol) in DCM (170 mL) at −78 °C was added a THF solution of 1 M DIBAL-H (35.4 mL, 35.4 mmol). The reaction was allowed to slowly warm to rt over 1 h, at which point the reaction showed complete conversion according to TLC (25% EtOAc/heptane, $KMnO_4$ stain). The reaction was then quenched with an addition of 2.1 mL of H_2O with vigorous stirring at rt over 0.25 h, followed by addition of 2.1 mL of 15% aqueous NaOH. The mixture was vigorously stirred until solids formed. The solids were removed by filtration, and the filtrate was concentrated to afford *rac*-2-(hydroxymethyl)-3-methylcyclohex-1-en-1-yl trifluoromethanesulfonate, which was used without any further purification (2.45 g, 53% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 4.40 (d, J = 12.8 Hz, 1H), 4.05 (d, 1H), 2.62−2.76 (m, 1H), 2.30−2.39 (m, 2H), 1.64−1.95 (m, 3H), 1.37−1.50 (m, 1H), 1.15 (d, J = 7.0 Hz, 3H). Step 5. To a solution of *rac*-2-(hydroxymethyl)-3-methylcyclohex-1-en-1-yl trifluoromethanesulfonate (6.0 g, 21.9 mmol) in DMF (220 mL) were added imidazole (1.71 g, 25.2 mmol) and TBS-Cl (3.63 g, 24.1 mmol) at rt. The mixture was then stirred at rt for 3 h. The reaction mixture was filtered through a pad of Celite, which was rinsed with 25% EtOAc−heptane. The resulting solution was concentrated. The resulting residue was suspended in H_2O and then extracted with ca. 1/1 mixture of EtOAc/heptane. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford *rac*-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-methylcyclohex-1-en-1-yl trifluoromethanesulfonate, which was used in the next reaction without any further purification (5.9 g, 69% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 4.40 (d, J = 12.4 Hz, 1H), 4.07−4.14 (m, 1H), 2.55−2.67 (m, 1H), 2.18−2.30 (m, 2H), 1.72−1.85 (m, 1H), 1.57−1.72 (m, 2H), 1.30−1.41 (m, 1H), 1.06 (d, J = 7.0 Hz, 3H), 0.83 (s, 9H), 0.01 (d, J = 5.2 Hz, 6H). Step 6. Following method G, **32** and *rac*-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-methylcyclohex-1-en-1-yl trifluoromethanesulfonate (534 mg, 1.37 mmol) afforded *rac*-ethyl 1-(6-(2-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-methylcyclohex-1-en-1-yl)-pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate after FCC purification (0−100% EtOAc in heptane) (141 mg, 20% yield). MS (ESI+) m/z 524.3 (M + H). Step 7. To a solution of *rac*-ethyl 1-(6-(2-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-methylcyclohex-1-en-1-yl)-pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (1.0 g, 1.92 mmol) in THF (19.3 mL) at room temperature was added a solution of TBAF in THF (1 M, 2.9 mL, 2.9 mmol). The mixture was stirred at room temperature for 3 h, and then diluted with EtOAc. The mixture was washed successively with H_2O and brine, dried over Na_2SO_4, filtered, and then concentrated. The resulting residue was purified by FCC (0−100 EtOAc/heptane) to afford *rac*-ethyl 1-(6-(2-(hydroxymethyl)-3-methylcyclohex-1-en-1-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (546 mg, 69% yield). MS (ESI+) m/z 410.6 (M + H). Step 8. Following method D, **27b** and *rac*-ethyl 1-(6-(2-(hydroxymethyl)-3-methylcyclohex-1-en-1-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate afforded *rac*-ethyl 1-(6-(2-((4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-3-ethylphenoxy)-methyl)-3-methylcyclohex-1-en-1-yl)pyridin-2-yl)-5-(trifluoromethyl)-

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1*H*-pyrazole-4-carboxylate after FCC purification (0−100% EtOAc in heptane) (230 mg, 46% yield). MS (ESI+) *m/z* 665.3 (M + H). Step 9. Resolution of the racemate was achieved by chiral SFC using Daicel CHIRALPAK AD-H column with a gradient 5−55% MeOH in CO_2 to afford ethyl 1-(6-(2-((4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-3-ethylphenoxy)methyl)-3-methylcyclohex-1-en-1-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (enantiomer 1, t_R = 2.3 min, >99% ee) and ethyl 1-(6-(2-((4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-3-ethylphenoxy)methyl)-3-methylcyclohex-1-en-1-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (enantiomer 2, t_R = 2.5 min, >99% ee). Step 10. Method C employing ethyl 1-(6-(2-((4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-3-ethylphenoxy)methyl)-3-methylcyclohex-1-en-1-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (enantiomer 1, t_R = 2.3 min) afforded (+)-**17** without any further purification (79 mg, 86% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.06 (s, 1H), 7.95 (t, *J* = 7.8 Hz, 1H), 7.56 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.45 (dd, *J* = 7.7, 0.9 Hz, 1H), 6.96−7.05 (m, 1H), 6.52−6.63 (m, 2H), 4.64 (d, *J* = 13.1 Hz, 1H), 4.32−4.54 (m, 3H), 2.93−3.07 (m, 1H), 2.68−2.80 (m, 1H), 2.50−2.67 (m, 4H), 2.31−2.44 (m, 1H), 2.27 (t, *J* = 7.4 Hz, 1H), 1.93−2.06 (m, 1H), 1.46−1.92 (m, 8H), 1.21 (d, *J* = 7.0 Hz, 3H), 1.14 (t, *J* = 7.5 Hz, 3H), 0.75−0.99 (m, 4H). HRMS calculated for $C_{35}H_{40}F_3N_4O_4$ (M + H) 637.2996, found 637.3014.

*(−)-1-(6-(2-((4-(1-(Cyclopropanecarbonyl)piperidin-4-yl)-3-ethylphenoxy)methyl)-3-methylcyclohex-1-en-1-yl)pyridin-2-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic Acid ((−)-**17**).* Method C employing ethyl 1-(6-(2-((4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-3-ethylphenoxy)methyl)-3-methylcyclohex-1-en-1-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (enantiomer 2, t_R = 2.5 min) afforded (−)-**17** without any further purification (9 mg, 93% yield). The analytical data were substantially identical to (+)-**17**.

*1-(6-(2-((4-(1-(Cyclopropanecarbonyl)piperidin-4-yl)-3-ethylphenoxy)methyl)-3,3-dimethylcyclohex-1-en-1-yl)pyridin-2-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic Acid (**18**).* Step 1. A TBS protection of 2-(hydroxymethyl)-3,3-dimethylcyclohex-1-en-1-yl trifluoromethanesulfonate was achieved by a similar method as described for the synthesis of 2-(((*tert*-butyldimethylsilyl)oxy)-methyl)-3-methylcyclohex-1-en-1-yl trifluoromethanesulfonate to afford 2-(((*tert*-butyldimethylsilyl)oxy)methyl)-3,3-dimethylcyclohex-1-en-1-yl trifluoromethanesulfonate (7.4 g, 79% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 4.30 (t, *J* = 1.0 Hz, 2H), 2.36 (t, *J* = 6.4 Hz, 2H), 1.77−1.88 (m, 2H), 1.46−1.54 (m, 2H), 1.19 (d, *J* = 2.0 Hz, 6H), 0.91 (d, *J* = 1.6 Hz, 9H), 0.10 (s, 6H). Step 2. Following method G, **32** and 2-(((*tert*-butyldimethylsilyl)oxy)methyl)-3,3-dimethylcyclohex-1-en-1-yl trifluoromethanesulfonate afforded ethyl 1-(6-(2-(((*tert*-butyldimethylsilyl)oxy)methyl)-3,3-dimethylcyclohex-1-en-1-yl)-pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate after FCC purification (0−100% EtOAc in heptane) (257 mg, 6% yield). MS (ESI+) *m/z* 538.3 (M + H). Step 3. Deprotection of the TBS group on ethyl 1-(6-(2-(((*tert*-butyldimethylsilyl)oxy)methyl)-3,3-dimethylcyclohex-1-en-1-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate was achieved by a similar method as described for the synthesis of **15** to afford ethyl 1-(6-(2-(hydroxymethyl)-3,3-dimethylcyclohex-1-en-1-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate after FCC purification (0−100% EtOAc in heptane) (45 mg, 22% yield). (ESI+) *m/z* 424.4 (M + H). Step 4. Following method D, ethyl 1-(6-(2-(hydroxymethyl)-3,3-dimethylcyclohex-1-en-1-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate and **26b** afforded *tert*-butyl 4-(4-((2-(6-(4-(ethoxycarbonyl)-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)pyridin-2-yl)-6,6-dimethylcyclohex-1-en-1-yl)methoxy)-2-ethylphenyl)piperidine-1-carboxylate after FCC purification (0−100% EtOAc in heptane) (62 mg, 82% yield). (ESI+) *m/z* 711.5 (M + H). Step 5. Deprotection of the Boc group on *tert*-butyl 4-(4-((2-(6-(4-(ethoxycarbonyl)-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)-pyridin-2-yl)-6,6-dimethylcyclohex-1-en-1-yl)methoxy)-2-ethylphenyl)piperidine-1-carboxylate was achieved by a similar method as described for the synthesis of **27a** to afford ethyl 1-(6-(2-((3-ethyl-4-(piperidin-4-yl)phenoxy)methyl)-3,3-dimethylcyclohex-1-en-1-yl)-pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate after FCC purification (0−20% MeOH/DCM) (34 mg, 64% yield). MS (ESI+) *m/z* 611.5 (M + H). Step 6. To a solution of ethyl 1-(6-(2-((3-ethyl-4-(piperidin-4-yl)phenoxy)methyl)-3,3-dimethylcyclohex-1-en-1-yl)-pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (35 mg, 0.057 mmol) and diisopropylethylamine (0.03 mL, 0.17 mmol) in DCM (3 mL) was added cyclopropanecarbonyl chloride (0.01 mL, 0.110 mmol). The mixture was stirred at rt for 1 h. The reaction mixture was directly loaded onto silica gel and was purified by FCC (20% EtOAc in heptane) to afford ethyl 1-(6-(2-((4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-3-ethylphenoxy)methyl)-3,3-dimethylcyclohex-1-en-1-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (35 mg, 91% yield). MS (ESI+) *m/z* 679.5 (M + H). Step 7. Method C employing ethyl 1-(6-(2-((4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-3-ethylphenoxy)methyl)-3,3-dimethylcyclohex-1-en-1-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate afforded **18** without any further purification (12 mg, 32% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.11 (s, 1H), 7.87 (t, *J* = 7.8 Hz, 1H), 7.56 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.51 (dd, *J* = 8.0, 0.9 Hz, 1H), 6.98−7.07 (m, 1H), 6.59 (dt, *J* = 4.4, 2.4 Hz, 2H), 4.65 (d, *J* = 13.3 Hz, 1H), 4.46 (d, *J* = 13.3 Hz, 1H), 4.30 (s, 2H), 3.01 (t, *J* = 12.0 Hz, 1H), 2.74 (t, *J* = 12.9 Hz, 1H), 2.65 (q, *J* = 7.5 Hz, 2H), 2.48 (t, *J* = 6.3 Hz, 2H), 2.27 (t, *J* = 7.4 Hz, 1H), 1.95−2.07 (m, 1H), 1.49−1.93 (m, 9H), 1.21 (s, 6H), 1.17 (t, *J* = 7.5 Hz, 3H), 0.73−0.99 (m, 4H). HRMS calculated for $C_{36}H_{42}F_3N_4O_4$ (M + H) 651.3153, found 651.3165.

*(+)-1-(6-(3-(4-(1-(Cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenoxy)-2,3-dihydro-1H-inden-4-yl)pyridin-2-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic Acid ((+)-**19**).* Step 1. Sodium borohydride (0.090 g, 2.369 mmol) was added to a solution of **42** (0.5 g, 2.369 mmol) in MeOH (24 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h then let warm to rt. After 2 h, TLC indicated complete consumption of the starting material. The reaction mixture was diluted with H_2O and DCM, and then saturated aq. NH_4Cl was added to neutralize the aqueous layer to a pH of 7. The mixture was passed through an ISOLUTE Phase Separator, and the organic phase was concentrated to afford *rac*-7-bromo-2,3-dihydro-1*H*-inden-1-ol (505 mg, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.33 (m, 1H), 7.25−7.20 (m, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 5.41−5.34 (m, 1H), 3.30−3.17 (m, 1H), 2.97−2.84 (m, 1H), 2.51−2.35 (m, 1H), 2.20−2.09 (m, 1H). Step 2. To a solution of *rac*-7-bromo-2,3-dihydro-1*H*-inden-1-ol (335 mg, 1.57 mmol), **27a** (489 mg, 1.89 mmol), and tri-*n*-butylphosphine (490 μL, 1.89 mmol) in THF (6.3 mL), azodicarboxylic dimorpholide (483 mg, 1.89 mmol) was added at rt, and the reaction mixture was stirred for 2 h. The reaction mixture was diluted with DCM and H_2O and then passed through a phase separator and concentrated. The residue was purified by FCC (0−50% EtOAc/heptane) to afford *rac*-(4-(4-((7-bromo-2,3-dihydro-1*H*-inden-1-yl)oxy)-3-methylphenyl)piperidin-1-yl)(cyclopropyl)methanone (248 mg, 34.7% yield). MS (ESI+) *m/z* 456.2 (M + H). Step 3. Following method G, *rac*-(4-(4-((7-bromo-2,3-dihydro-1*H*-inden-1-yl)oxy)-3-methylphenyl)piperidin-1-yl)(cyclopropyl)methanone and **32** afforded *rac*-ethyl 1-(6-(3-(4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenoxy)-2,3-dihydro-1*H*-inden-4-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate after FCC purification (0−50% EtOAc/heptane gradient) (55% yield). MS (ESI+) *m/z* 659.4 (M + H). Step 4. Resolution of the racemate was achieved by chiral SFC using Daicel CHIRALCEL OJ-H column with a gradient 5% to 55% MeOH in CO_2 to give (+)-ethyl 1-(6-(3-(4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenoxy)-2,3-dihydro-1*H*-inden-4-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (t_R = 2.02 min) and (−)-ethyl 1-(6-(3-(4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenoxy)-2,3-dihydro-1*H*-inden-4-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (t_R = 2.19 min). Step 5. Method C employing (+)-ethyl 1-(6-(3-(4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenoxy)-2,3-dihydro-1*H*-inden-4-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (t_R = 2.02 min) afforded (+)-**19** after RP-HPLC-B purification (31 mg, 32% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.97 (s, 1H), 7.93 (t, *J* = 7.9 Hz, 1H), 7.82−7.78 (m, 1H), 7.68−7.63 (m, 1H), 7.55−7.51 (m, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.45−7.41 (m, 1H), 6.82−6.75 (m, 2H), 6.69 (d, *J* = 8.2 Hz, 1H), 6.39−6.34 (m, 1H), 4.64

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(d, J = 13.0 Hz, 1H), 4.45 (d, J = 13.6 Hz, 1H), 3.24−3.16 (m, 2H), 3.05−2.95 (m, 1H), 2.78−2.64 (m, 2H), 2.59−2.47 (m, 1H), 2.18−2.08 (m, 1H), 2.05−1.97 (m, 1H), 1.92 (d, J = 13.1 Hz, 1H), 1.84 (d, J = 13.5 Hz, 1H), 1.63 (s, 3H), 1.61−1.44 (m, 2H), 0.93−0.86 (m, 2H), 0.86−0.78 (m, 2H). HRMS calculated for $C_{35}H_{34}F_3N_4O_4$ (M + H) 631.2532, found 631.2572.

*(−)-1-(6-(3-(4-(1-(Cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenoxy)-2,3-dihydro-1H-inden-4-yl)pyridin-2-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic Acid ((−)-**19**).* Method C employing (−)-ethyl 1-(6-(3-(4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenoxy)-2,3-dihydro-1*H*-inden-4-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (t_R = 2.19 min) afforded (−)-**19** after RP-HPLC-B purification (56 mg, 59%). The analytical data were substantially identical to (+)-**19**.

*(+)- and (−)-1-(6-(3-((4-(1-(Cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenyl)amino)-2,3-dihydro-1H-inden-4-yl)pyridin-2-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic Acid ((+)- and (−)-**20**).* Step 1. Following method G, **32** and **42**, followed by FCC purification (0−40% EtOAc/heptane), afforded ethyl 1-(6-(3-oxo-2,3-dihydro-1*H*-inden-4-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (422 mg, 53% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.19 (d, J = 0.7 Hz, 1H), 8.07 (t, J = 7.9 Hz, 1H), 7.85 (dd, J = 7.8, 0.9 Hz, 1H), 7.77−7.69 (m, 2H), 7.65 (dq, J = 7.7, 1.0 Hz, 1H), 7.56 (dq, J = 7.4, 0.8 Hz, 1H), 4.36 (q, J = 7.1 Hz, 2H), 3.26−3.18 (m, 2H), 2.77−2.68 (m, 2H), 1.37 (t, J = 7.1 Hz, 3H). Step 2. To a solution of **30** (60 mg, 0.232 mmol) and ethyl 1-(6-(3-oxo-2,3-dihydro-1*H*-inden-4-yl)-pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (106 mg, 0.255 mmol) in anhydrous toluene (2.3 mL) was added TsOH (4.42 mg, 0.023 mmol), the reaction flask was fitted with a Dean−Stark trap, and the reaction mixture was stirred at 130 °C for 22 h. The reaction mixture was then concentrated. The residue was dissolved in anhydrous EtOH (2.3 mL) and cooled to 0 °C, and then sodium borohydride (8.79 mg, 0.232 mmol) was added. The mixture was stirred at 0 °C for 1.5 h. The reaction was quenched with H_2O and saturated aq $NaHCO_3$, and then the mixture was extracted with EtOAc. The organic layer was concentrated onto Celite. The residue was purified by FCC (0−50% EtOAc/heptane) to afford *rac*-ethyl 1-(6-(3-((4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenyl)-amino)-2,3-dihydro-1*H*-inden-4-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (32 mg, 21% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.97−7.92 (m, 2H), 7.90 (dd, J = 7.9, 1.1 Hz, 1H), 7.63 (dd, J = 5.6, 3.3 Hz, 1H), 7.49 (dd, J = 7.6, 1.0 Hz, 1H), 7.43 (d, J = 5.6 Hz, 2H), 6.80 (dd, J = 8.3, 2.2 Hz, 1H), 6.71 (d, J = 2.2 Hz, 1H), 6.54 (d, J = 8.3 Hz, 1H), 5.24 (d, J = 6.5 Hz, 1H), 4.64 (d, J = 13.0 Hz, 1H), 4.45 (d, J = 13.3 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 3.21 (dt, J = 16.3, 8.2 Hz, 2H), 2.94 (ddd, J = 16.1, 8.7, 3.5 Hz, 1H), 2.73 (t, J = 12.7 Hz, 1H), 2.65 (tt, J = 12.0, 3.6 Hz, 1H), 2.37 (dtd, J = 12.8, 8.5, 6.7 Hz, 1H), 2.15−2.06 (m, 1H), 2.04−1.97 (m, 1H), 1.95−1.88 (m, 1H), 1.87−1.79 (m, 1H), 1.69 (s, 3H), 1.66−1.45 (m, 2H), 1.40 (t, J = 7.1 Hz, 3H), 0.94−0.85 (m, 2H), 0.85−0.78 (m, 2H). MS (ESI+) m/z 658.5 (M + H). Step 3. Method A employing *rac*-ethyl 1-(6-(3-((4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenyl)amino)-2,3-dihydro-1*H*-inden-4-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate afforded (±)-**20** after RP-HPLC-B purification. Step 4. Resolution of the racemate was achieved by chiral SFC using Daicel CHIRALCEL OJ-H column with 20% (5 mM NH_4OH in MeOH) in CO_2 to afford (+)-**20** (t_R = 3.10 min, > 97% ee) and (−)-**20** (t_R = 4.40 min, > 97% ee). ^{1}H NMR (400 MHz, CD_3OD) δ 7.98−7.91 (m, 2H), 7.91−7.87 (m, 1H), 7.67−7.61 (m, 1H), 7.51−7.47 (m, 1H), 7.43 (d, J = 5.9 Hz, 2H), 6.85−6.80 (m, 1H), 6.74−6.71 (m, 1H), 6.55 (d, J = 8.2 Hz, 1H), 5.24 (s, 1H), 4.63 (d, J = 13.0 Hz, 1H), 4.45 (d, J = 13.3 Hz, 1H), 3.26−3.16 (m, 2H), 2.98−2.89 (m, 1H), 2.79−2.61 (m, 2H), 2.42−2.31 (m, 1H), 2.16−2.07 (m, 1H), 2.05−1.97 (m, 1H), 1.93 (d, J = 13.2 Hz, 1H), 1.84 (d, J = 12.9 Hz, 1H), 1.70 (s, 3H), 1.67−1.45 (m, 2H), 0.93−0.78 (m, 4H). HRMS calculated for $C_{35}H_{35}F_3N_5O_3$ $(M + H)^+$ 630.2692, found 630.2451.

*(+)- and (−)-1-(6-(3-((4-(1-(Cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenyl)amino)-6-methyl-2,3-dihydro-1H-inden-4-yl)-pyridin-2-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic Acid ((+)- and (−)-**21**).* Step 1. A mixture of *m*-tolyl 3-chloropropanoate (3.92 g, 19.7 mmol) and $AlCl_3$ (10.5 g, 79 mmol) was heated at 100 °C for 1 h, then at 180 °C for 2 h, and subsequently cooled to rt. The excess $AlCl_3$ was carefully quenched with 1 M aq HCl. The resulting mixture was extracted with DCM. The combined organic layers were washed with water and passed through an ISOLUTE Phase Separator. The filtrate was concentrated to afford 7-hydroxy-5-methyl-2,3-dihydro-1*H*-inden-1-one, which was used in the next reaction without further purification (946 mg, 30% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (s, 1H), 6.80−6.72 (m, 1H), 6.64−6.52 (m, 1H), 3.08−3.03 (m, 2H), 2.71−2.67 (m, 2H), 2.38 (s, 3H). Step 2. To a solution of 7-hydroxy-5-methyl-2,3-dihydro-1*H*-inden-1-one (217 mg, 1.34 mmol) and pyridine (325 μL, 4.01 mmol) in DCM (13.4 mL) at 0 °C was added trifluoromethanesulfonic anhydride (316 μL, 1.87 mmol) dropwise. The resulting suspension was stirred at 0 °C for 1 h. The reaction was quenched with H_2O, and then the mixture was diluted with 1 N aq HCl. The resulting mixture was passed through an ISOLUTE Phase Separator. The organic phase was concentrated to furnish 6-methyl-3-oxo-2,3-dihydro-1*H*-inden-4-yl trifluoromethanesulfonate, which was used in the next step without any further purification (335 mg, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.21 (m, 1H), 6.90 (s, 1H), 3.11−3.02 (m, 2H), 2.70−2.63 (m, 2H), 2.41 (s, 3H). MS (ESI+) m/z 295.2 (M + H). Step 3. Following method G, **32** and 6-methyl-3-oxo-2,3-dihydro-1*H*-inden-4-yl trifluoromethanesulfonate afforded ethyl 1-(6-(6-methyl-3-oxo-2,3-dihydro-1*H*-inden-4-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate after FCC purification (0−50% EtOAc/heptane) (303 mg, 56.2% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.19 (d, J = 0.8 Hz, 1H), 8.06 (t, J = 7.9 Hz, 1H), 7.86 (dd, J = 7.8, 0.9 Hz, 1H), 7.71 (dd, J = 8.0, 0.9 Hz, 1H), 7.46 (dq, J = 1.8, 0.9 Hz, 1H), 7.41 (dd, J = 1.7, 0.9 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 3.20−3.15 (m, 2H), 2.73−2.68 (m, 2H), 2.49 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H). MS (ESI+) m/z 430.3 (M + H). Step 4. A mixture of **30** (90 mg, 0.349 mmol), ethyl 1-(6-(6-methyl-3-oxo-2,3-dihydro-1*H*-inden-4-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (150 mg, 0.349 mmol), and TsOH (3.32 mg, 0.017 mmol) in anhydrous toluene (3.5 mL) was charged to a flask equipped with a condenser and a Dean−Stark trap. The mixture was stirred at 130 °C for 22 h, and then concentrated. The residue was then dissolved in anhydrous EtOH (3.5 mL). To the solution at 0 °C was added sodium borohydride (13.2 mg, 0.35 mmol). The mixture was stirred at rt for 3 h, with the addition of sodium borohydride (13.2 mg, 0.35 mmol) each hour, for a total of 3 additions. The reaction was quenched with H_2O and saturated aq. NH_4Cl. The mixture was then extracted with DCM. The organic layer was passed through an ISOLUTE Phase Separator and concentrated onto Celite. The residue was purified by FCC (0−50% EtOAc/heptane) to afford *rac*-ethyl 1-(6-(3-((4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenyl)-amino)-6-methyl-2,3-dihydro-1*H*-inden-4-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (130 mg, 55% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.97−7.91 (m, 2H), 7.89 (dd, J = 7.9, 1.1 Hz, 1H), 7.49−7.45 (m, 2H), 7.25 (s, 1H), 6.81 (dd, J = 8.2, 2.2 Hz, 1H), 6.71 (d, J = 2.1 Hz, 1H), 6.54 (d, J = 8.3 Hz, 1H), 5.16 (d, J = 6.4 Hz, 1H), 4.64 (d, J = 13.0 Hz, 1H), 4.45 (d, J = 13.7 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 3.25 (s, 1H), 3.17 (dd, J = 16.4, 8.4 Hz, 1H), 2.88 (ddd, J = 16.1, 8.7, 3.3 Hz, 1H), 2.74 (t, J = 12.3 Hz, 1H), 2.64 (tt, J = 12.1, 3.8 Hz, 1H), 2.44 (s, 3H), 2.40−2.29 (m, 1H), 2.15−2.05 (m, 1H), 2.05−1.97 (m, 1H), 1.92 (d, J = 13.0 Hz, 1H), 1.83 (d, J = 12.9 Hz, 1H), 1.69 (s, 3H), 1.59 (dd, J = 41.5, 16.5 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H), 0.94−0.86 (m, 2H), 0.85−0.78 (m, 2H). MS (ESI+) m/z 672.4 (M + H). Step 5. Method C employing ethyl 1-(6-(3-((4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenyl)amino)-6-methyl-2,3-dihydro-1*H*-inden-4-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate afforded *rac*-**21** without any further purification (63% yield).

Resolution of the racemate was achieved by chiral SFC using Daicel CHIRALCEL OJ-H column with isocratic 20% MeOH in CO_2 to afford (+)-**21** (t_R = 3.23 min, 99% ee) and (−)-**21** (t_R = 4.73 min, >99% ee). ^{1}H NMR (400 MHz, CD_3OD) δ 7.94−7.89 (m, 2H), 7.89−7.85 (m, 1H), 7.49−7.45 (m, 2H), 7.25−7.23 (m, 1H), 6.84−6.81 (m, 1H), 6.75−6.71 (m, 1H), 6.55 (d, J = 8.2 Hz, 1H), 5.20−5.16 (m, 1H), 4.63 (d, J = 13.1 Hz, 1H), 4.43 (d, J = 13.1 Hz, 1H), 3.28−

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3.21 (m, 1H), 3.19−3.12 (m, 1H), 2.93−2.84 (m, 1H), 2.77−2.61 (m, 2H), 2.43 (s, 3H), 2.39−2.28 (m, 1H), 2.15−2.06 (m, 1H), 2.05−1.96 (m, 1H), 1.96−1.89 (m, 1H), 1.87−1.80 (m, 1H), 1.70 (s, 3H), 1.67−1.44 (m, 2H), 0.92−0.79 (m, 4H). HRMS calculated for $C_{36}H_{37}F_3N_5O_3$ $(M + H)^+$ 644.2848, found 644.2841.

*(+)-1-(6-(3-(4-(1-(Cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenoxy)-2,3-dihydro-1H-inden-4-yl)pyridin-2-yl)-1H-pyrazole-4-carboxylic Acid ((+)-**22**).* Step 1. To a suspension of **42** (10 g, 47.4 mmol) and (*R*,*R*)-RuCl(TsDPEN)(p-Cymene) (CAS registry number 192139-92-7, 40 mg, 0.063 mmol) in DMF (40 mL) was added formic acid−triethylamine complex, 5:2 (8 mL). The mixture was then stirred at 60 °C for 22 h and cooled to rt. The mixture was poured into ice/water (ca. 1/1 v/v). The resulting solid was collected by filtration. The solid was then dissolved in CH_2Cl_2, and the solution was dried over $MgSO_4$ and filtered through a plug of silica gel. The silica gel cake was rinsed with a mixture of CH_2Cl_2/EtOAc (ca. 9/1). The combined organic layers were concentrated to furnish (−)-*R*-7-bromo-2,3-dihydro-1*H*-inden-1-ol without any further purification (7.5 g, 35.2 mmol, 74.3% yield, > 98% ee determined by SFC using Daicel CHIRALPAK OD-H, 10% isocratic IPA in CO_2; (−)-enantiomer 1 (t_R = 4.87 min) and (+)-enantiomer 2 (t_R = 5.58 min)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.33 (m, 1H), 7.25−7.20 (m, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 5.41−5.34 (m, 1H), 3.30−3.17 (m, 1H), 2.97−2.84 (m, 1H), 2.51−2.35 (m, 1H), 2.20−2.09 (m, 1H). Step 2. Following the procedure described for the synthesis of **32**, a reaction of 2-bromo-6-hydrazinylpyridine with ethyl 3-(dimethylamino)-2-formyl acrylate afforded ethyl 1-(6-bromopyridin-2-yl)-1*H*-pyrazole-4-carboxylate (1.2 g, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (d, *J* = 0.7 Hz, 1H), 8.10 (d, *J* = 0.7 Hz, 1H), 7.95 (dd, *J* = 8.1, 0.8 Hz, 1H), 7.70 (t, *J* = 7.9 Hz, 1H), 7.47−7.41 (m, 1H), 4.38−4.30 (m, 2H), 1.38 (t, *J* = 7.1 Hz, 3H). MS (ESI+) *m*/*z* 298.0 (M + H). *Step 3.* Following the procedure as described for the preparation of *rac*-(4-(4-((7-bromo-2,3-dihydro-1*H*-inden-1-yl)oxy)-3-methylphenyl)piperidin-1-yl)(cyclopropyl)-methanone, a reaction starting with (−)-*R*-7-bromo-2,3-dihydro-1*H*-inden-1-ol afforded (+)-(4-(4-((7-bromo-2,3-dihydro-1*H*-inden-1-yl)-oxy)-3-methylphenyl)piperidin-1-yl)(cyclopropyl)methanone (438 mg, 41% yield, 97% ee determined by SFC (stationary phase CHIRALCEL OJ-H; mobile phase, gradient 5−55% IPA in CO_2; (+)-enantiomer (t_R = 2.38 min) and (−)-enantiomer (t_R = 2.70 min)). MS (ESI+) *m*/*z* 456.2 (M + H). Step 4. Following method G, ethyl 1-(6-bromopyridin-2-yl)-1*H*-pyrazole-4-carboxylate and (+)-(4-(4-((7-bromo-2,3-dihydro-1*H*-inden-1-yl)oxy)-3-methylphenyl)piperidin-1-yl)(cyclopropyl)methanone, followed by FCC purification (0−50% EtOAc/heptane), afforded ethyl 1-(6-(3-(4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenoxy)-2,3-dihydro-1*H*-inden-4-yl)pyridin-2-yl)-1*H*-pyrazole-4-carboxylate (70 mg, 50% yield). MS (ESI+) *m*/*z* 591.4 (M + H). Step 5. Method C employing ethyl 1-(6-(3-(4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenoxy)-2,3-dihydro-1*H*-inden-4-yl)pyridin-2-yl)-1*H*-pyrazole-4-carboxylate, followed by RP-HPLC-B purification afforded (+)-**22** (30 mg, 43% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.60 (d, *J* = 0.7 Hz, 1H), 7.94−7.89 (m, 1H), 7.88 (d, *J* = 0.7 Hz, 1H), 7.77−7.72 (m, 1H), 7.62−7.56 (m, 2H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.45−7.41 (m, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.79−6.75 (m, 1H), 6.62−6.57 (m, 2H), 4.63−4.54 (m, 1H), 4.40 (d, *J* = 13.4 Hz, 1H), 3.25−3.17 (m, 1H), 3.11−3.03 (m, 0H), 2.90−2.79 (m, 1H), 2.67 (t, *J* = 12.6 Hz, 1H), 2.58−2.48 (m, 1H), 2.23−2.13 (m, 1H), 2.03−1.95 (m, 1H), 1.82−1.64 (m, 2H), 1.53−1.33 (m, 5H), 0.94−0.77 (m, 4H). HRMS calculated for $C_{34}H_{35}N_4O_4$ $(M + H)^+$ 563.2658, found 563.2669.

*(+)-(S)-1-(6-(3-((4-(1-(Cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenyl)amino)-2,3-dihydro-1H-inden-4-yl)pyridin-2-yl)-5-methyl-1H-pyrazole-4-carboxylic Acid ((+)-**23**).* Step 1. A mixture of **31** (5.04 g, 26.8 mmol) and ethyl 2-acetyl-3-(dimethylamino)acrylate (4.96 g, 26.8 mmol) in EtOH (81 mL) was heated to 70 °C for 1.5 h. The reaction mixture was then allowed to cool to rt and a precipitate formed. H_2O (80 mL) was then added to the mixture, and the resulting heterogeneous mixture was filtered. The filter cake was washed with H_2O and dried under reduced pressure to yield ethyl 1-(6-bromopyridin-2-yl)-5-methyl-1*H*-pyrazole-4-carboxylate (7.1 g, 86 mmol). MS (ESI+) *m*/*z* 310.1 (M + H). Step 2. To a mixture of ethyl 1-(6-bromopyridin-2-yl)-5-methyl-1*H*-pyrazole-4-carboxylate (1.03 g, 3.31 mmol), bis(pinacolato) diboron (0.84 g, 3.31 mmol), and KOAc (0.65 g, 6.61 mmol) in dioxane (11 mL) was added SPhos Pd G1 (0.11 g, 0.165 mmol). The reaction mixture was then stirred at 120 °C under microwave irradiation for 45 min. To the mixture was then added a solution of **42** (0.66 g, 3.14 mmol) in dioxane (11 mL), followed by sodium carbonate (1 M in H_2O, 8.3 mL, 8.3 mmol) and $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ adduct (0.14 g, 0.165 mmol). The reaction mixture was then stirred under microwave irradiation for 30 min at 110 °C. Celite was added to the reaction mixture, and the mixture was concentrated. The residue was purified by FCC (0−50% EtOAc/heptane) to afford ethyl 5-methyl-1-(6-(3-oxo-2,3-dihydro-1*H*-inden-4-yl)pyridin-2-yl)-1*H*-pyrazole-4-carboxylate (908 mg, 80% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.06−8.00 (m, 2H), 7.80 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.74 (t, *J* = 7.6 Hz, 1H), 7.66 (ddd, *J* = 8.0, 7.1, 0.9 Hz, 2H), 7.54 (dq, *J* = 7.4, 0.8 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.26−3.20 (m, 2H), 2.83 (s, 3H), 2.75−2.70 (m, 2H), 1.36 (t, *J* = 7.1 Hz, 3H). MS (ESI+) *m*/*z* 362.3 (M + H). Step 3. A Dean−Stark trap was fitted to a flask containing a solution of **30** (162 mg, 0.627 mmol), ethyl 5-methyl-1-(6-(3-oxo-2,3-dihydro-1*H*-inden-4-yl)pyridin-2-yl)-1*H*-pyrazole-4-carboxylate (260 mg, 0.627 mmol), and TsOH (12 mg, 0.063 mmol) in anhydrous toluene (6 mL). The reaction mixture was heated at 130 °C for 22 h, at which point the mixture was concentrated. The resulting residue was dissolved in anhydrous EtOH (6 mL) and cooled to 0 °C. Sodium borohydride (23.74 mg, 0.627 mmol) was added to the cooled solution,and the reaction mixture was allowed to warm to rt. After 3 h, an additional portion of sodium borohydride (23.74 mg, 0.627 mmol) was added at rt. One hour later, the reaction mixture was quenched with H_2O and saturated aq. NH_4Cl. The aqueous layer was extracted twice with EtOAc. Celite was added to the combined organic layers, and the mixture was concentrated. The resulting residue was purified by FCC (0−50% EtOAc/heptane gradient) to afford ethyl 1-(6-(3-((4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenyl)amino)-2,3-dihydro-1*H*-inden-4-yl)pyridin-2-yl)-5-methyl-1*H*-pyrazole-4-carboxylate (113 mg, 30% yield). MS (ESI+) *m*/*z* 657.4 (M + H). Step 4. Resolution of the racemate was achieved by chiral SFC using Daicel CHIRALPAK AD-H column with a gradient 5% to 55% MeOH in CO_2 to afford (+)-ethyl 1-(6-(3-((4-(1-(cyclopropanecarbonyl)-piperidin-4-yl)-2-methylphenyl)amino)-2,3-dihydro-1*H*-inden-4-yl)-pyridin-2-yl)-5-methyl-1*H*-pyrazole-4-carboxylate (t_R = 2.74 min, >99% ee) and (−)-ethyl 1-(6-(3-((4-(1-(cyclopropanecarbonyl)-piperidin-4-yl)-2-methylphenyl)amino)-2,3-dihydro-1*H*-inden-4-yl)-pyridin-2-yl)-5-methyl-1*H*-pyrazole-4-carboxylate (t_R = 3.70 min, >99% ee). Step 5. (+)-Ethyl 1-(6-(3-((4-(1-(cyclopropanecarbonyl)-piperidin-4-yl)-2-methylphenyl)amino)-2,3-dihydro-1*H*-inden-4-yl)-pyridin-2-yl)-5-methyl-1*H*-pyrazole-4-carboxylate ((+)-isomer, t_R = 2.74 min, 168 mg, 0.278 mmol) was dissolved in MeOH (2.8 mL) and THF (2.8 mL) at rt, and the reaction mixture was heated to 50 °C for 2 h. Upon completion, the reaction mixture was cooled to rt and 1 M aq. HCl (2.9 mL) was added. The resulting mixture was extracted with EtOAc, and the combined organic layers were concentrated to provide the title compound after RP-HPLC-B purification (115 mg, 72% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.89 (s, 1H), 7.82 (t, *J* = 7.9 Hz, 1H), 7.69−7.65 (m, 1H), 7.58−7.54 (m, 1H), 7.53−7.50 (m, 1H), 7.44−7.37 (m, 2H), 6.83−6.79 (m, 1H), 6.74−6.71 (m, 1H), 6.56 (d, *J* = 8.2 Hz, 1H), 5.38 (s, 1H), 4.61 (d, *J* = 12.9 Hz, 1H), 4.43 (d, *J* = 13.2 Hz, 1H), 3.24−3.15 (m, 2H), 3.02−2.93 (m, 1H), 2.75−2.59 (m, 5H), 2.54−2.43 (m, 1H), 2.13−2.04 (m, 1H), 2.03−1.96 (m, 1H), 1.90 (d, *J* = 13.1 Hz, 1H), 1.80 (d, *J* = 13.4 Hz, 1H), 1.67 (s, 3H), 1.64−1.41 (m, 2H), 0.92−0.78 (m, 4H). HRMS calculated for $C_{35}H_{38}N_5O_3$ $(M + H)^+$ 576.2975, found 576.3015. The absolute stereochemistry of (+)-**23** was determined by single crystal X-ray crystallography.[27]

*(−)-1-(6-(3-((4-(1-(Cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenyl)amino)-2,3-dihydro-1H-inden-4-yl)pyridin-2-yl)-5-methyl-1H-pyrazole-4-carboxylic Acid ((−)-**23**).* Method C employing (−)-ethyl 1-(6-(3-((4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-2-methylphenyl)amino)-2,3-dihydro-1*H*-inden-4-yl)pyridin-2-yl)-5-

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methyl-1*H*-pyrazole-4-carboxylate (t_R = 3.70 min) afforded (−)-**23** after RP-HPLC-B purification. The analytical data were substantially identical to (+)-**23**.

*(+)-1-(6-(2-((4-(1-(Cyclopropanecarbonyl)piperidin-4-yl)-3-ethylphenoxy)methyl)-3-methylcyclohex-1-en-1-yl)pyridin-2-yl)-5-methyl-1H-pyrazole-4-carboxylic Acid ((+)-**24**).* Step 1. Following method D, *rac*-2-(hydroxymethyl)-3-methylcyclohex-1-en-1-yl trifluoromethanesulfonate and **26b** afforded *rac-tert*-butyl 4-(2-ethyl-4-((6-methyl-2-(((trifluoromethyl)sulfonyl)oxy)cyclohex-1-en-1-yl)methoxy)phenyl)piperidine-1-carboxylate after FCC purification (0−60% EtOAc in heptane) (49% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, J = 8.8 Hz, 1H), 6.76−6.70 (m, 2H), 4.79 (d, J = 11.7 Hz, 1H), 4.53−4.47 (m, 1H), 4.25 (d, J = 13.3 Hz, 2H), 2.86−2.76 (m, 3H), 2.74−2.61 (m, 3H), 2.43−2.38 (m, 2H), 1.95−1.77 (m, 2H), 1.74−1.56 (m, 5H), 1.50 (s, 9H), 1.47−1.39 (m, 1H), 1.22 (t, J = 7.5 Hz, 3H), 1.16 (d, J = 7.0 Hz, 3H). *Step 2.* A mixture of *rac-tert*-butyl 4-(2-ethyl-4-((6-methyl-2-(((trifluoromethyl)sulfonyl)oxy)cyclohex-1-en-1-yl)methoxy)phenyl)piperidine-1-carboxylate (450 mg, 0.80 mmol), KOAc (142 mg, 1.44 mmol), bis(pinacolato) diboron (305 mg, 1.2 mmol), and $PdCl_2$(dppf)·CH_2Cl_2 adduct (33 mg, 0.04 mmol) in dioxane (4 mL) was stirred at 60 °C under N_2 for 24 h. The reaction mixture was filtered, concentrated, and purified by FCC (0−50% EtOAc in heptane) to afford *rac-tert*-butyl 4-(2-ethyl-4-((6-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-1-en-1-yl)methoxy)phenyl)piperidine-1-carboxylate (345 mg, 80% yield). MS (ESI+) m/z 538.5 (M + H). Step 3. A suspension of S-Phos Pd G1 (22.4 mg, 0.03 mmol), 2 M aq K_3PO_4 (0.43 mL, 0.87 mmol), *rac-tert*-butyl 4-(2-ethyl-4-((6-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-1-en-1-yl)methoxy)phenyl)piperidine-1-carboxylate (396 mg, 0.73 mmol), and ethyl 1-(6-bromopyridin-2-yl)-5-methyl-1*H*-pyrazole-4-carboxylate (207 mg, 0.67 mmol) in dioxane (4 mL) was stirred at 100 °C for 20 h. The reaction mixture was concentrated, and the resulting residue was purified by FCC (0−70% EtOAc in heptane) to afford *rac-tert*-butyl 4-(4-((2-(6-(4-(ethoxycarbonyl)-5-methyl-1*H*-pyrazol-1-yl)pyridin-2-yl)-6-methylcyclohex-1-en-1-yl)methoxy)-2-ethylphenyl)piperidine-1-carboxylate (154 mg, 35% yield). MS (ESI+) m/z 643.7 (M + H). Step 4. Deprotection of the Boc group of *rac-tert*-butyl 4-(4-((2-(6-(4-(ethoxycarbonyl)-5-methyl-1*H*-pyrazol-1-yl)pyridin-2-yl)-6-methylcyclohex-1-en-1-yl)methoxy)-2-ethylphenyl)piperidine-1-carboxylate and subsequent acylation was achieved by a similar method as described for the synthesis of **27a** to furnish *rac*-ethyl 1-(6-(2-((4-(1-(cyclopropanecarbonyl)-piperidin-4-yl)-3-ethylphenoxy)methyl)-3-methylcyclohex-1-en-1-yl)-pyridin-2-yl)-5-methyl-1*H*-pyrazole-4-carboxylate after FCC purification (0−70% EtOAc in heptane) (60% yield). MS (ESI+) m/z 611.5 (M + H). Step 5. Resolution of the racemate was performed by chiral SFC using Daicel CHIRALPAK AD-H column, a gradient 5−55% IPA in CO_2, 5 mL/min to afford (+)-ethyl 1-(6-(2-((4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-3-ethylphenoxy)methyl)-3-methylcyclohex-1-en-1-yl)pyridin-2-yl)-5-methyl-1*H*-pyrazole-4-carboxylate (t_R = 3.02 min, >98% ee) and (−)-ethyl 1-(6-(2-((4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-3-ethylphenoxy)methyl)-3-methylcyclohex-1-en-1-yl)pyridin-2-yl)-5-methyl-1*H*-pyrazole-4-carboxylate (t_R = 3.17 min, >98% ee). Step 6. Method C employing (+)-ethyl 1-(6-(2-((4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-3-ethylphenoxy)methyl)-3-methylcyclohex-1-en-1-yl)pyridin-2-yl)-5-methyl-1*H*-pyrazole-4-carboxylate (t_R = 3.02 min) afforded (+)-**24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.68 (s, 1H), 7.97−7.89 (m, 2H), 7.67 (d, J = 8.1 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 7.02 (d, J = 8.3 Hz, 1H), 6.63−6.57 (m, 2H), 4.56−4.46 (m, 2H), 4.42−4.31 (m, 2H), 3.21−3.11 (m, 1H), 2.93−2.84 (m, 1H), 2.79 (s, 3H), 2.63−2.58 (m, 4H), 2.41−2.37 (m, 1H), 2.03−1.94 (m, 1H), 1.85−1.74 (m, 2H), 1.72−1.32 (m, 6H), 1.15 (d, J = 7.0 Hz, 1H), 1.07 (t, J = 7.5 Hz, 3H), 0.81−0.64 (m, 4H). HRMS calculated for $C_{35}H_{43}N_4O_4$ (M + H)$^+$ 583.3284, found 583.3253.

*(−)-1-(6-(2-((4-(1-(Cyclopropanecarbonyl)piperidin-4-yl)-3-ethylphenoxy)methyl)-3-methylcyclohex-1-en-1-yl)pyridin-2-yl)-5-methyl-1H-pyrazole-4-carboxylic Acid ((−)-**24**).* Method C employing (−)-ethyl 1-(6-(2-((4-(1-(cyclopropanecarbonyl)piperidin-4-yl)-3-ethylphenoxy)methyl)-3-methylcyclohex-1-en-1-yl)pyridin-2-yl)-5-methyl-1*H*-pyrazole-4-carboxylate (t_R = 3.17 min) afforded (−)-**24**. The analytical data were substantially identical to (+)-**24**.

*tert-Butyl 4-(4-Hydroxy-3-methylphenyl)piperidine-1-carboxylate (**26a**).* Step 1. To a suspension of 4-bromo-2-methyl phenol (5 g, 26.7 mmol), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2*H*)-carboxylate, **25** (8.27 g, 26.7 mmol), and K_3PO_4 (2 M in H_2O, 26.7 mL, 53.5 mmol) in acetonitrile (54 mL) was added $PdCl_2$(dppf)·CH_2Cl_2 adduct (1.09 g, 1.33 mmol). The mixture was stirred at 80 °C for 3 h and then cooled to rt. The reaction mixture was added to Celite and then concentrated. The resulting residue was purified by FCC (0−100% EtOAc/heptane) to afford *tert*-butyl 4-(4-hydroxy-3-methylphenyl)-5,6-dihydropyridine-1(2*H*)-carboxylate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18−7.12 (m, 1H), 7.12−7.06 (m, 1H), 6.73 (d, J = 8.3 Hz, 1H), 5.98−5.85 (m, 1H), 4.04 (q, J = 2.9 Hz, 2H), 3.62 (t, J = 5.7 Hz, 2H), 2.48 (dtd, J = 6.1, 3.2, 1.8 Hz, 2H), 2.25 (s, 3H), 1.49 (s, 9H). MS (ESI+) m/z 290.1 (M + H). Step 2. A mixture of the above product (4.4 g, 15.21 mmol) and Pd/C (5% w/w, 0.8 g) in MeOH (50 mL) was stirred under H_2 atmosphere at rt for 2 h. The reaction mixture was then filtered through a plug of Celite. The filtrate was then concentrated to furnish **26a** (4.4 g, 58% yield over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, J = 2.2 Hz, 1H), 6.92 (dd, J = 8.2, 2.3 Hz, 1H), 6.73 (d, J = 8.2 Hz, 1H), 4.24 (ddt, J = 13.4, 4.0, 1.9 Hz, 2H), 2.86−2.75 (m, 2H), 2.56 (tt, J = 12.2, 3.6 Hz, 1H), 2.26 (s, 3H), 1.85−1.76 (m, 2H), 1.59 (dtd, J = 13.4, 12.3, 4.2 Hz, 2H), 1.50 (s, 9H). MS (ESI−) m/z 290.2 (M − H).

*tert-Butyl 4-(2-Ethyl-4-hydroxyphenyl)piperidine-1-carboxylate (**26b**).* Step 1. To a mixture of 4-chloro-3-ethylphenol (3 g, 19.16 mmol), **25** (7.70 g, 24.90 mmol), and SPhos Pd G1 methyl-*tert*-butylether adduct (CAS registry number. 1375325-64-6, 0.644 g, 0.958 mmol) in DMF (96 mL) was added 2 M aq. K_3PO_4 (28.7 mL, 57.5 mmol). The mixture was stirred at 110 °C for 1 h and then cooled to rt. The reaction mixture was diluted with EtOAc and H_2O. The organic layer was then separated, and dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by FCC (heptane/EtOAc = 1/0 to 6/4) to afford *tert*-butyl 4-(2-ethyl-4-hydroxyphenyl)-5,6-dihydropyridine-1(2*H*)-carboxylate. MS (ESI+) m/z 248.2 (M − *t*Bu + 2H). Step 2. A mixture of the product from step 1 (5.4 g, 17.80 mmol) and 10% Pd/C (1.89 g) in MeOH (250 mL) was stirred under H_2 atmosphere at rt for 1 h. The reaction mixture was filtered through a plug of Celite, which was then washed with MeOH. The filtrate was then concentrated to furnish the title compound without any further purification (4.3 g, 76% yield over 2 steps). MS (ESI+) m/z 250.2 (M − *t*Bu + 2H).

*Cyclopropyl(4-(4-hydroxy-3-methylphenyl)piperidin-1-yl)-methanone (**27a**).* Step 1. To a solution of **26a** (3.98 g, 13.66 mmol) in CH_2Cl_2 (137 mL) at 0 °C was added TFA (12.63 mL, 164 mmol). The mixture was stirred for 1.5 h and then concentrated to furnish 2-methyl-4-(piperidin-4-yl)phenol as the TFA salt, which was used in the next step without any further purification. MS (ESI+) m/z 192.1 (M + H). Step 2. To a solution of the product obtained in step 1 (2.6 g, 13.59 mmol) in CH_2Cl_2 (68 mL) at 0 °C was added diisopropylethylamine (9.5 mL, 54.4 mmol), followed by cyclopropanecarbonyl chloride (2.47 mL, 27.2 mmol). The mixture was then stirred at 0 °C for 1 h. The reaction was quenched with H_2O. The mixture was extracted with CH_2Cl_2. The organic layer was concentrated. A mixture of the resulting residue and K_2CO_3 (9.39 g, 68 mmol) in MeOH (68 mL) was stirred for 2 h at rt and then diluted with CH_2Cl_2 and H_2O. The mixture was passed through an ISOLUTE Phase Separator. The resulting organic layer was concentrated to furnish the title compound without any further purification (3.4 g, 96% yield over 2 steps). ^{1}H NMR (400 MHz, CD_3OD) δ 6.92 (d, J = 2.3 Hz, 1H), 6.85 (dd, J = 8.2, 2.3 Hz, 1H), 6.66 (d, J = 8.2 Hz, 1H), 4.62 (d, J = 13.2 Hz, 1H), 4.43 (d, J = 13.4 Hz, 1H), 3.23 (td, J = 12.7, 11.4, 2.9 Hz, 1H), 2.70 (dtt, J = 15.8, 7.6, 4.4 Hz, 2H), 2.15 (s, 3H), 1.99 (tt, J = 8.0, 4.8 Hz, 1H), 1.85 (dd, J = 36.3, 13.3 Hz, 2H), 1.70−1.44 (m, 2H), 0.95−0.75 (m, 4H). MS (ESI+) m/z 260.1 (M + H).

*Cyclopropyl(4-(2-ethyl-4-hydroxyphenyl)piperidin-1-yl)-methanone (**27b**).* The title compound was synthesized from **26b** analogously to the preparation of **27a**. MS (ESI+) m/z 274.3 (M + H).

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*tert-Butyl 4-(3-Methyl-4-nitrophenyl)-5,6-dihydropyridine-1(2H)-carboxylate (**28**).* To a suspension of 4-bromo-2-methyl nitrobenzene (10 g, 46.3 mmol), **25** (14.3 g, 46.3 mmol), and 2 M aq K_3PO_4 (46.3 mL, 93 mmol) in acetonitrile (154 mL) was added $PdCl_2(dppf)\cdot CH_2Cl_2$ adduct (1.89 g, 2.31 mmol). The mixture was then stirred at 80 °C for 3 h and cooled to rt. The reaction mixture was concentrated with Celite. The resulting residue was purified by FCC (0−20% EtOAc in heptane) to afford **28** (10.6 g, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.4 Hz, 1H), 7.36−7.32 (m, 2H), 6.20 (s, 1H), 4.14 (q, J = 2.9 Hz, 2H), 3.67 (t, J = 5.7 Hz, 2H), 2.65 (s, 3H), 2.58−2.52 (m, 2H), 1.52 (s, 9H). MS (ESI−) m/z 317.2 (M − H).

*Cyclopropyl(4-(3-methyl-4-nitrophenyl)-5,6-dihydropyridin-1(2H)-yl)methanone (**29**).* Step 1. Deprotection of the Boc group on **28** was achieved by a similar method as described for the synthesis of **27a**. The product was used in the next step without any further purification (quantitative yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.99 (d, J = 8.5 Hz, 1H), 7.60−7.47 (m, 2H), 6.34 (dt, J = 3.5, 1.8 Hz, 1H), 3.89 (q, J = 2.7 Hz, 2H), 3.49 (t, J = 6.1 Hz, 2H), 2.83 (tq, J = 5.7, 1.9 Hz, 2H), 2.60 (s, 3H). MS (ESI+) m/z 219.2 (M + H). Step 2. Cyclopropanecarbonyl chloride (0.509 mL, 5.61 mmol) was added dropwise to a solution of 4-(3-methyl-4-nitrophenyl)-1,2,3,6-tetrahydropyridine (1.165 g, 5.34 mmol) and diisopropylethylamine (2.80 mL, 16.02 mmol) in DCM (53 mL) at 0 °C. The mixture was stirred at 0 °C for 90 min before being quenched with half saturated aq sodium bicarbonate. The resulting mixture was passed through an ISOLUTE Phase Separator, and the organic layer was concentrated. The resulting residue was purified by FCC (0−50% EtOAc in heptane) to afford **29** (quantitative yield). MS (ESI+) m/z 287.3 (M + H).

*(4-(4-Amino-3-methylphenyl)piperidin-1-yl)(cyclopropyl)-methanone (**30**).* A mixture of **29** (5.98 g, 20.89 mmol) and Pd/C (1.11 g) in EtOH (104 mL) was stirred under H_2 atmosphere at rt for 16 h. The mixture was filtered through a plug of Celite, which was rinsed with EtOH. The filtrate was concentrated, and the resulting residue was purified by FCC (0−100% [0.2% Et_3N in EtOAc] in [0.2% Et_3N in heptane]) to afford the title compound (quantitative yield). ^{1}H NMR (400 MHz, CD_3OD_4) δ 6.87 (d, J = 2.7 Hz, 1H), 6.84 (dd, J = 8.1, 2.2 Hz, 1H), 6.67 (d, J = 8.0 Hz, 1H), 4.62 (d, J = 13.2 Hz, 1H), 4.43 (d, J = 13.5 Hz, 1H), 3.27−3.19 (m, 1H), 2.77−2.62 (m, 2H), 2.14 (s, 3H), 2.03−1.95 (m, 1H), 1.89 (d, J = 13.0 Hz, 1H), 1.80 (d, J = 13.3 Hz, 1H), 1.69−1.44 (m, 2H), 0.92−0.76 (m, 4H).MS (ESI+) m/z 259.3 (M + H).

*Ethyl 1-(6-Bromopyridin-2-yl)-5-(trifliuoromethyl)-1H-pyrazole-4-carboxylate (**32**).* A solution of 2-bromo-6-hydrazinylpyridine, **31** (12.63 g, 67 mmol), in THF (350 mL) was cooled in an acetone/dry ice bath, and then ethyl 2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutyrate (13.72 mL, 71 mmol) was added dropwise. Once the addition was complete, the reaction mixture was gradually allowed to warm to rt over 2 h. The reaction mixture was concentrated, and then the resulting residue was dissolved in EtOAc. The organic layer was washed successively with saturated aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by FCC (10% EtOAc in heptane) to afford **32** (15.8 g, 65% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.19 (s, 1H), 7.96 (t, J = 7.82 Hz, 1H), 7.74−7.80 (m, 2H), 4.37 (q, J = 7.13 Hz, 2H), 1.38 (t, J = 7.15 Hz, 3H). MS (ESI+) m/z 364.0, 366.0 (M + H).

*Ethyl 1-(6-(3-(Hydroxymethyl)thiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate (**33**).* Step 1. To a suspension of **32** (4.44 g, 12.19 mmol), (3-formylthiophen-2-yl)boronic acid (3.75 g, 24.04 mmol), and potassium fluoride (4.19 g, 72.1 mmol) in THF (60 mL) was added $Pd(t\text{-}Bu_3P)_2$ (0.5 g, 0.978 mmol). The mixture was stirred at rt for 18 h. The reaction mixture was diluted with CH_2Cl_2 and then filtered. The filtrate was concentrated. The resulting residue was purified by FCC (0−100% EtOAc in heptane) to afford ethyl 1-(6-(3-formylthiophen-2-yl)-pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate. MS (ESI +) m/z 396.1 (M + H). Step 2. To a solution of ethyl 1-(6-(3-formylthiophen-2-yl)pyridin-2-yl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (4.42 g, 11.18 mmol) in EtOH (56 mL) at 0 °C was added sodium borohydride (0.423 g, 11.2 mmol) portion-wise. The mixture was stirred at rt for 2 h, and then diluted with H_2O and CH_2Cl_2. The organic layer was passed through an ISOLUTE Phase Separator. The organic layer was then concentrated. The resulting residue was purified by FCC (0−100% EtOAc in heptane) to afford **33** (4.0 g, 83% yield over 2 steps). MS (ESI+) m/z 398.1 (M + H).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jmedchem.8b00007.

Molecular formula strings for exemplified compounds (CSV)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

sGC, soluble guanylate cyclase; IOP, intraocular pressure; POAG, primary open angle glaucoma; TM, trabecular meshwork; GTM, glaucomatous trabecular meshwork; CHO, Chinese hamster ovary; dppf, 1,1′-bis(diphenylphosphino)-ferrocene; DIPEA, diisopropylethylamine; DIAD, diisopropyl azodicarboxylate; HATU, 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate; TsDPEN, *N*-(2-amino-1,2-diphenylethyl)-4-methylbenzenesulfonamide; IBMX, 3-isobutyl-1-methylxanthine; ODQ, 1*H*-[1,2,4]oxadiazolo[4,3-*a*]quinoxalin-1-one; FCC, flash silica gel column chromatography.

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