Journal of Medicinal Chemistry

Article

Design and synthesis of fungal-selective resorcylate aminopyrazole Hsp90 inhibitors

David Huang, Emmanuelle LeBlanc, Tanvi Shekhar-Guturja, Nicole Robbins, Damian Krysan, Juan Carlos Pizarro, Luke Whitesell, Leah Cowen, and Lauren E. Brown

J. Med. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.jmedchem.9b00826 • Publication Date (Web): 12 Sep 2019

Design and synthesis of fungal-selective resorcylate aminopyrazole Hsp90 inhibitors

David S. Huang[A†‡], *Emmanuelle V. LeBlanc*[B‡], *Tanvi Shekhar-Guturja*[B], *Nicole Robbins*[B], *Damian J. Krysan*[C], *Juan Pizarro*[D], *Luke Whitesell*[B]*, *Leah E. Cowen*[B]* *and Lauren E. Brown*[A]*

[A] Department of Chemistry and Center for Molecular Discovery (BU-CMD), Boston University, Boston, MA, 02215, USA

[B] Department of Molecular Genetics, University of Toronto, Toronto, Ontario, M5G 1M1, Canada.

[C] Departments of Pediatrics and Microbiology/Immunology, Carver College of Medicine, University of Iowa, Iowa City, Iowa, 52242, USA

[D] Department of Tropical Medicine, School of Public Health and Tropical Medicine and Vector-Borne Infectious Disease Research Center, Tulane University, New Orleans, LA, 70112, USA.

ABSTRACT

The molecular chaperone Hsp90, essential in all eukaryotes, plays a multifaceted role in promoting survival, virulence and drug resistance across diverse pathogenic fungal species. The chaperone is also critically important, however, to the pathogen's human host, preventing the use of known clinical Hsp90 inhibitors in antifungal applications due to concomitant host toxicity issues. With the goal of developing Hsp90 inhibitors with acceptable therapeutic indices for the treatment of invasive fungal infections, we initiated a program to design and synthesize potent inhibitors with selective activity against fungal Hsp90 isoforms over their human counterparts. Building on our previously-reported derivatization of resorcylate natural products to produce fungal-selective compounds, we have developed a series of synthetic aminopyrazole-substituted resorcylate amides with broad, potent, and fungal-selective Hsp90 inhibitory activity. Herein we describe the synthesis of this series, as well as biochemical structure-activity relationships driving selectivity for the Hsp90 isoforms expressed by *Cryptococcus neoformans* and *Candida albicans*, two pathogenic fungi of major clinical importance.

INTRODUCTION

The morbidity and mortality caused by fungal infections cripple human health across the globe. Over a billion people are affected by superficial infections, such as ringworm and athlete's foot. Adding to these numbers are the burden of oral and other mucosal infections. Of most concern is the increasing number of invasive systemic infections, which leads to over one million deaths each year.[1] People with compromised immune function, such as patients receiving cancer chemotherapies, organ transplant recipients and those infected with HIV, are most vulnerable to invasive fungal infections. The pathogens responsible for > 90% of invasive mycoses are *Candida albicans, Aspergillus fumigatus* and *Cryptococcus neoformans*. Once diagnosed, treatment options

are limited to only three major classes of antifungal drugs, notoriously hampered by problems with host toxicity, the emergence of resistance, or limited spectrum of activity.[2] In fact, the only new class of antifungals to reach the clinic in decades has no efficacy against *C. neoformans* and related species.[3]

Selective targeting of fungal stress responses provides a promising therapeutic strategy to mitigate resistance and more effectively combat invasive mycoses. The essential molecular chaperone Hsp90 has been extensively validated as a regulator of virulence and antifungal drug resistance in *Candida* and *Aspergillus* species.[4, 5] For instance, in *C. albicans*, genetic depletion or pharmacological inhibition of Hsp90 increases the efficacy of current antifungal drugs, reduces acquired antifungal resistance in clinical isolates, and improves clearance in a mouse model of disseminated candidiasis.[6] Recent studies have demonstrated the critical importance of Hsp90 for *C. neoformans* thermotolerance and shown that Hsp90 inhibition alters capsule assembly and sensitivity to antifungals, influencing virulence of the pathogen.[7, 8]While targeting Hsp90 offers a promising but relatively unexplored strategy for antifungal drug development, the chaperone has been intensively explored as a target in oncology. A structurally diverse array of drugs targeting the ATP-binding pocket of human Hsp90 continue to be evaluated for anticancer activity in patients. In contrast, allosteric approaches to targeting the function of Hsp90 at sites other than its N-terminal ATPase have only been explored in preclinical studies,[9] the exception being a putative C-terminal inhibitor (RTA901) which has recently completed Phase I testing in humans (NCT0266693).

Unfortunately, dose-limiting toxicities coupled with relatively limited therapeutic efficacy have so far precluded FDA approval of any N-terminal Hsp90 inhibitor either alone or in combination with other therapeutic agents. In the course of these anticancer drug development and

testing campaigns, no effort has been devoted to the pursuit of fungal selectivity and an Hsp90 inhibitor with the properties required for use as an antifungal has yet to be reported.

Fungal selectivity is a crucial feature for an Hsp90 inhibitor to be developed as an antifungal given that Hsp90 is essential in all eukaryotes. Its function supports protein quality control mechanisms, productive folding and the stability of conformationally labile proteins, many involved in key signaling cascades.[10] The chaperoning by Hsp90 of its so-called client proteins is ATP-dependent and coordinated by a suite of co-chaperones and accessory factors that impart client selectivity and help regulate progression through the chaperoning cycle. Although Hsp90 is highly conserved across phylogenetic kingdoms, species-specific variations are observed at the level of conformational flexibility, intrinsic ATPase activity, chaperoning dynamics, and the involvement of specific co-chaperone/accessory proteins.[11] Therefore, despite a very high degree of conservation at the primary sequence level, these important functional differences provide hope that species-selectivity can be achieved, either at the classical N-terminal ATP-binding pocket or alternatively *via* allosteric inhibitors acting at other sites.[12]

While efforts to achieve species-selectivity are just beginning, the pursuit of human paralog-specific Hsp90 inhibitors has already achieved considerable success. These efforts have been focused on achieving selectivity at the N-terminal nucleotide-binding domain (NBD) across the four family members expressed in humans: Hsp90α, Hsp90β, Trap1 and Grp94.[13, 14] For example, Blagg and coworkers have described successful efforts to modify the resorcylate scaffold to confer selectivity towards specific human paralogs, including selective Grp94 inhibitors with applications in oncology and glaucoma,[15-19]and more recently, the first Hsp90β selective inhibitor with applications in cancer.[20] In addition, isoform-selective purine mimetics, such as Hsp90α/β-specific inhibitor TAS-116[21] and modified analogs of BIIB021 selectively targeting Trap1[14] have

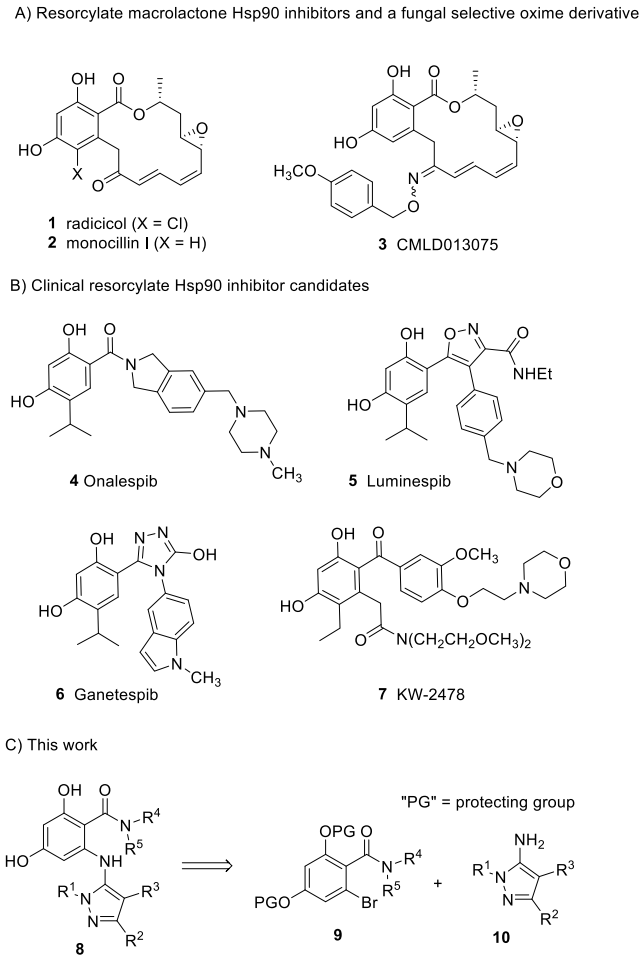
been described. Modified benzamides resembling SNX-2112 have also been diverted to both Hsp90α/β-specific[22] and Trap1-specific[23] activities for neurological applications.

We recently disclosed the discovery of the first fungal-selective Hsp90 inhibitors,[11] with activity against the *C. albicans* Hsp90 isoform, based on semi-synthetic oxime-derivatization of the resorcylate macrocycle natural products radicicol (**1**) and monocillin I (**2**). For therapeutic applications, fungal-selectivity is critical as current inhibitors targeting host Hsp90 have deleterious effects that preclude their use in the context of systemic infection. Our most promising lead from this series, monocillin-derived oxime CMLD013075 (**3**) (Figure 1A), has >25-fold binding selectivity for the *C. albicans* Hsp90 NBD compared to the human ortholog, limits fungal proliferation in whole cell assays, and is less toxic to human cells compared to the non-selective compound radicicol. Importantly, the co-crystal structure of *C. albicans* Hsp90 NBD with CMLD013075 displayed unique structural rearrangements, including remodeling of the ATP-binding site, N-terminus, and lid region of the fungal chaperone. Aided by structural insights, key residues were identified as critical for the fungal selectivity of this derivative. Encouraged by these findings and using **3** as a point of departure, we now report the structure activity relationship (SAR)-guided efforts to develop fully synthetic, non-macrocyclic resorcylate inhibitor chemotypes, focusing on selectivity toward both *C. neoformans* and *C. albicans* Hsp90.

Replacement of the macrolactone of radicicol with acyclic isosteres including amides (Onalespib (**4**)[24-27]), oxazoles (Luminespib (**5**)[28-33]), triazolones (Ganetespib (**6**)[34-42]), and ketones (KW-2478 (**7**)[43-46]) has been a widely successful strategy for the development of multiple classes of synthetic Hsp90 inhibitors currently in clinical evaluation (Figure 1B). Using our macrocyclic oxime CMLD013075 as a lead template, our initial efforts focused on the replacement of the selectivity-imparting oxime with a suitable heterocyclic isostere, with the parallel goals of

removing the isomerizable oxime (which we postulated could obfuscate selectivity analysis), and reducing rotational degrees of freedom to enhance binding affinity. After evaluating various heterocyclic options for similarity and synthetic tractability, we selected the aminopyrazole of general type **8** (Figure 1C) for initial development. We hypothesized that a pendant aminopyrazole could project substituents ($R^1/R^2/R^3$) in orientations similar to that of the CMLD013075 oxime, to impart fungal selectivity in the binding of Hsp90. In addition to the attractiveness of the pyrazole from the standpoint of developability,[47] we also postulated that structure-activity relationships at three points of diversity ($R^1/R^2/R^3$) could be easily elaborated through the coupling of aryl bromide **9** with a combination of commercial and synthetic aminopyrazoles (**10**).

Figure 1. Design of aminopyrazole resorcylate-type inhibitor chemotype **8** based on precedented fungal-selective natural-product-derived inhibitors (A) and truncated resorcylates under clinical evaluation in oncology (B).



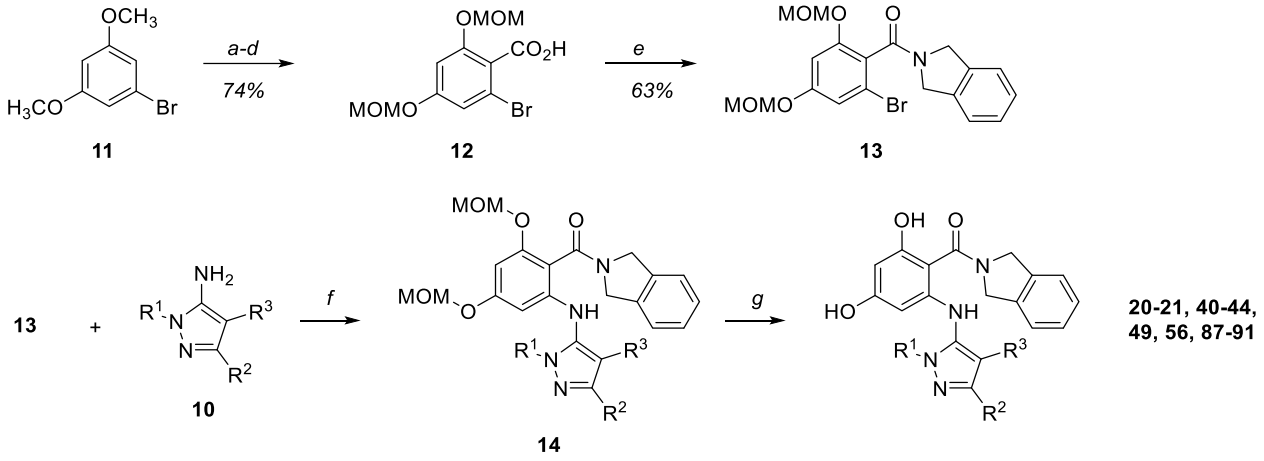
RESULTS AND DISCUSSION

Synthesis of resorcylate aminopyrazole analogs

Our initial synthesis of aminopyrazole resorcylates began with 1-bromo-3,5-dimethoxybenzene **11** (Scheme 1). Formylation, de-methylation, MOM protection, and Pinnick oxidation afforded carboxylic acid **12**, which was then subjected to HATU-mediated amidation with isoindoline to produce amide **13**. We initially selected the isoindoline amide as it is conserved across multiple classes of acyclic resorcylate heat shock protein inhibitors, [48-53] providing a simple,

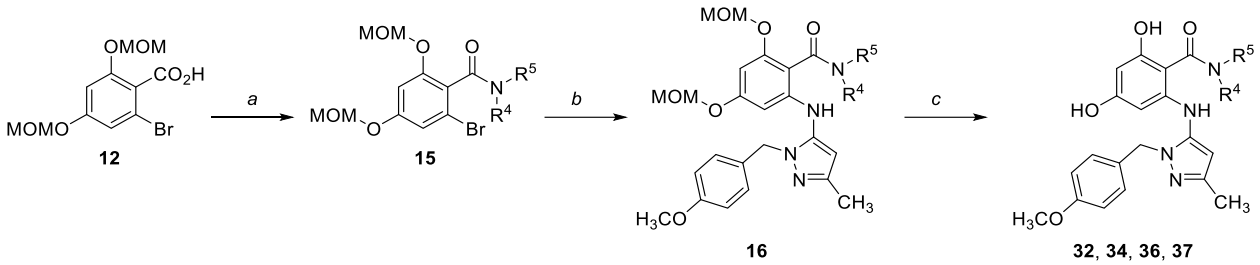
precedented model scaffold on which our selectivity-inducing strategy could be evaluated. We next installed the aminopyrazole using Pd-mediated coupling; after a brief exploration of coupling conditions[54] we ultimately settled on $Pd_2(dba)_3$/Xantphos/NaOPh in dioxane under microwave irradiation[55] as the optimal conditions across a wide scope of substrates. Following amination, acid-mediated MOM deprotection produced the desired aminopyrazole-substituted resorcylates.

Scheme 1. First-generation synthetic route to aminopyrazole/isoindoline resorcylate amides



Conditions: a) $POCl_3$, DMF, 100 °C; b) BBr_3, CH_2Cl_2, -78 °C to RT; c) MOMCl, DIPEA, DMF; d) $NaOCl_2$, NaH_2PO_4•H_2O, 2-methyl-2-butene, THF/^{t}BuOH/H_2O; e) isoindoline•HCl, HATU, Et_3N, THF/CH_2Cl_2; f) ^{t}BuXphos Pd G1 (10 mol%), ^{t}BuXPhos (10 mol%), NaO^{t}Bu, ^{t}BuOH, or $Pd_2(dba)_3$ (4 mol%), Xantphos (8 mol%), NaOPh, dioxane, 60 °C to 120 °C, or $Pd_2(dba)_3$ (10 mol%), Xantphos (10 mol%), NaOPh, dioxane, 170 °C, microwave; g) HCl, methanol, 50 °C.

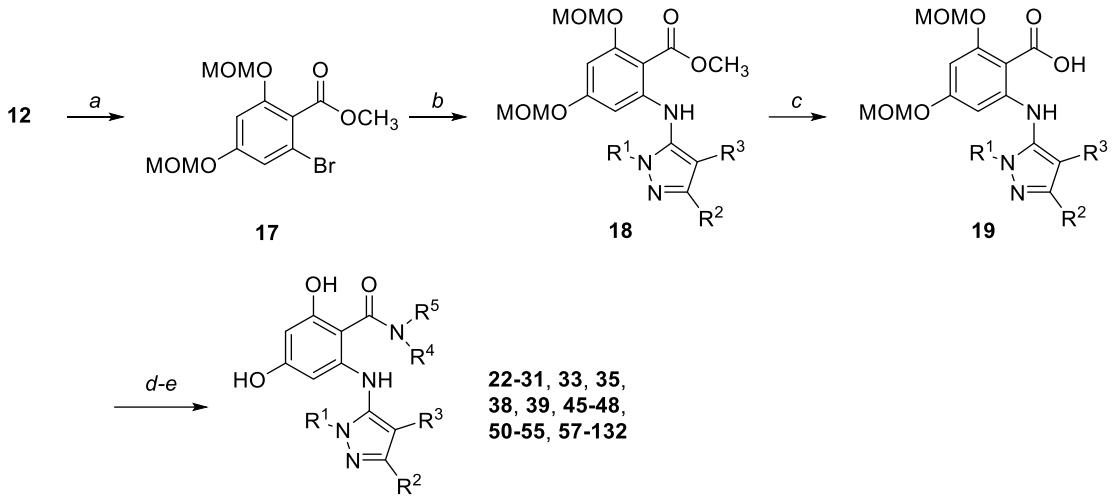
Scheme 2. Early exploration of amide SAR using first-generation synthetic route



Conditions: a) HNR^4R^5, HATU, Et_3N, THF/CH_2Cl_2; b) **10a**, $Pd_2(dba)_3$ (4 mol%), Xantphos (10 mol%), NaOPh, dioxane, 170 °C, microwave; c) HCl, methanol, 50 °C.

We also applied this first-generation synthetic sequence to explore replacement of the isoindoline amide for several early compounds (Scheme 2). During the course of analog synthesis, however, we found that reversing the order of coupling/amidation resulted in a more efficient procedure with improved yields and product purities; the resultant second-generation route is depicted in Scheme 3. Following esterification of carboxylic acid **12**, the resulting ester **17** was subjected to Pd-mediated coupling with **10** to afford intermediate **18**. Following ester hydrolysis, carboxylic acid **19** was subsequently amidated, which was initially performed using the HATU-mediated conditions, and later optimized to employ polymer-supported carbonyldiimidazole (PS-CDI) as a coupling reagent for improved parallel processing. Finally global MOM-deprotection provided the desired products for testing. All tested compounds were purified by mass-targeted HPLC.

Scheme 3. Second-generation synthetic route to aminopyrazole resorcylate amides



Conditions: a) CH_3I, K_2CO_3, DMF, 80 °C; b) **10**, $Pd_2(dba)_3$ (4 mol%), Xantphos (10 mol%), NaOPh; c) KOH, EtOH, 95 °C; d) HNR^4R^5, HATU, Et_3N, CH_2Cl_2/THF, RT or HNR^4R^5, PS-CDI, HOBt•xH_2O, Et_3N, THF/CH_2Cl_2; e) HCl, methanol, 50 °C.

Measurement of fungal Hsp90 binding affinity and selectivity

All analogs were assessed for Hsp90 binding affinity using a fluorescence polarization (FP)-based equilibrium competition assay in fungal and human whole cell lysates. Notably, this approach allows for the assessment of compound binding while the target protein is in native complexes with co-chaperones; and, in the case of human cell lysate, in a biologically relevant mix of Hsp90 paralogs. Using lysates, we were able to measure the relative potency and selectivity for fungal Hsp90 versus the entire ensemble of human Hsp90 isoforms in microplate format using small amounts of test materials. To confirm target engagement with an alternative biochemical approach, the most selective analogs were also assessed by protein thermal shift assays using purified recombinant Hsp90 nucleotide binding domains (NBD) of the relevant fungal species. Thermal shift assays were performed under saturating ligand conditions, i.e. equimolar concentrations (10 μM) of protein and ligand. As a result, they provided qualitative evidence of

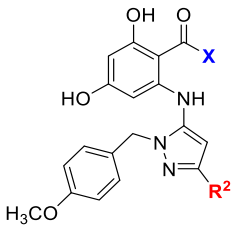
target binding, but not a quantitative measurement of ligand affinity. For quantitation, a ligand dissociation constant (K_i) for key compounds was also determined using purified NBDs in FP assays and KD measurements were made by surface plasmon resonance (SPR) using a Biacore instrument. Finally, all analogs were assessed for whole cell antifungal activity against the pathogens *C. albicans* and *C. neoformans*. Quantitative dose-response assays were performed for all compounds found to inhibit growth at a concentration $\leq$ 50 μM.

Structure activity relationships for resorcylate aminopyrazoles

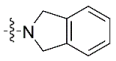
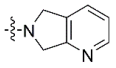
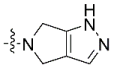
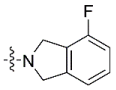
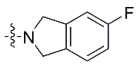
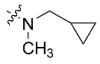
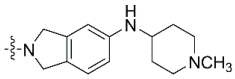
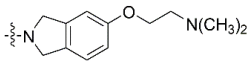
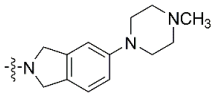
We first examined *N*-(*para*)-methoxybenzyl substituted aminopyrazoles, designed to mimic our parent *Candida*-selective inhibitor CMLD013075. We began by making systematic alterations to the resorcylate amide, with R^2 substitution limited to methyl and phenyl. Our initial amide diversification utilized several pyrrolidine/isoindoline-based heterocycles, which are prevalent among resorcylate amide Hsp90 inhibitors reported by Astex and Pfizer (**20**-**21**, **26**-**29**, **32**-**36, 38**),[49, 50] as well as new isoindoline isosteres (pyrido- and pyrazolopyrrolidines **22**-**25**). We also pursued a small series of acyclic mono- and disubstituted amides, both new (**30**-**31**) and precedented (**37**, **39**).[56] From this initial set, we were pleased to find a number of compounds had < 200 nM EC_{50} values against one or both fungal species (Table 1). Consistent with published inhibitors in this space, larger, substituted isoindoline-type moieties (**32**-**36**) generally exhibited excellent potency, but with no apparent selectivity for the fungal Hsp90 isoforms. In contrast, we found that the pairing of smaller heterobicylic amides with a phenyl group at the R^2 position (compounds **21**, **23**, **25**, **27**, and **29**) afforded modestly fungal-selective compounds; as a general trend, their $R^2 = CH_3$ analogs (**20**, **22**, **24**, **26** and **28**) were more potent but nonselective. Activity was mainly relegated to the heterobicyclic amides; our limited set of acyclic and monocyclic

amides (**30**-**31**, **37**-**39**) were for the most part less active and also nonselective, with the interesting exception of low potency cryptococcal-selective compound **30**. Based on these results, and given our early hypothesis that the installation of functionality at the aminopyrazole would be the key driver in imparting selectivity, we opted to progress forward with the lower-molecular weight isoindoline, pyridopyrrolidine, and pyrazolopyrrolidine amides, selected to represent both precedented and novel resorcylate amide substitutions with varying basicities.

Table 1. Structure-activity relationships for *N*-(4-methoxybenzyl)-substituted aminopyrazoles, exploring variation of the resorcylate amide with methyl- and phenyl-substitution at R^2. Fold-selectivity > 5 for any compound is highlighted in **red**.



20-39

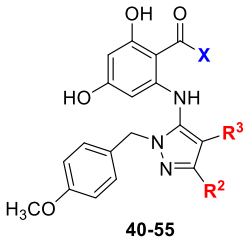
Entry	Compound	X	R^2	*C. neoformans* EC_{50}[a] (μM)	*C. neoformans* fold-selectivity[b]	*C. albicans* EC_{50}[c] (μM)	*C. albicans* fold-selectivity[b]
1	**20**		CH_3	0.040	0.8	0.011	0.9
2	**21**		Ph	0.877	2.5	0.511	2.2
3	**22**		CH_3	0.087	1.2	0.184	0.4
4	**23**		Ph	0.142	4.0	0.068	**6.2**
5	**24**		CH_3	0.063	1.7	0.157	0.5
6	**25**		Ph	0.121	2.7	0.063	3.9
7	**26**		CH_3	0.109	0.6	0.117	0.4
8	**27**		Ph	0.787	2.2	1.089	1.2
9	**28**		CH_3	0.592	0.1	0.054	0.5
10	**29**		Ph	0.705	2.7	1.043	1.3
11	**30**		CH_3	1.330	**5.8**	> 9	-
12	**31**		Ph	> 9	-	> 9	-
13	**32**		CH_3	0.096	1.0	0.171	0.4
14	**33**		Ph	0.146	0.8	0.023	1.8
15	**34**		CH_3	0.086	1.2	0.115	0.7
16	**35**		Ph	0.091	0.8	0.014	1.7
17	**36**		CH_3	0.115	0.9	0.143	0.6
18	**37**		CH_3	4.814	1.6	> 6	0.0
19	**38**		Ph	0.464	2.1	0.282	1.2
20	**39**		Ph	>10	-	>10	-

EC_{50} values were determined by FP-based equilibrium competition assay performed in 384-well format using whole cell lysates prepared from *C. neoformans* (a) and *C. albicans* (c) and serial compound dilutions. All determinations were performed in duplicate. To calculate fold-selectivity (b), the EC_{50} value determined in human HepG2 cell lysate was divided by the EC_{50} value

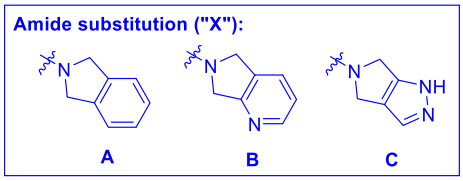
determined in fungal cell lysate. The resulting ratio was then normalized to values determined in the same assay for the non-selective inhibitor geldanamycin using lysate of each cell type. Results for key selective compounds were confirmed by repeat assay (see Supplemental Table 1).

Our next series of analogs explored additional R^2/R^3 substitutions on the aminopyrazole, again keeping the R^1 *para*-methoxybenzyl group intact (Table 2). For the R^2 unsubstituted pyrazoles (**40**-**44**), we found that substitution at R^3 was tolerated, but with decreasing potency as steric bulk increased. Several of these compounds also exhibited modest undesired selectivity toward the human isoform. Based on these results, we opted not to pursue this substitution pattern further. In contrast, and similar to our initial cohort, we identified wider tolerance for substitution at the R^2 position with several acyclic (**45**-**48**) and cyclic (**50**-**53**) aliphatic groups, as well as furan (**54**-**55**) substitution. A drop in potency was limited to the bulkier R^2 = ^{t}Bu analog **49**. Disappointingly, however, none of the inhibitors exhibited the modest fungal selectivity that had been observed in their R^2 = Ph substituted counterparts **21**, **23** and **25** (Table 1).

Table 2. Exploration of SAR at R^2/R^3 for R^1 = *p*-methoxybenzyl substituted aminopyrazoles



40-55



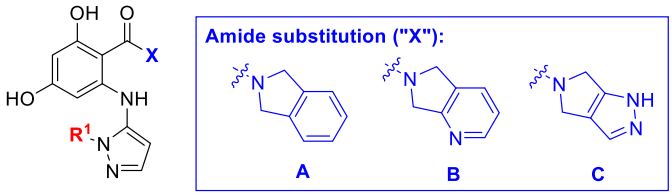
Entry	Compound	X	R^2	R^3	*C. neoformans* EC_{50}[a] (μM)	*C. neoformans* fold-selectivity[b]	*C. albicans* EC_{50}[c] (μM)	*C. albicans* fold-selectivity[b]
1	**40**	**A**	H	H	0.072	0.8	0.041	1.0
2	**41**	**A**	H	CH_3	0.094	0.3	0.022	0.7
3	**42**	**A**	H	^{i}Pr	0.396	0.4	0.147	0.5
4	**43**	**A**	H	Ph	1.623	1.6	0.615	2.1
5	**44**	**A**	H	Bn	1.756	0.5	0.465	1.1
6	**45**	**B**	Et	H	0.022	0.9	0.014	0.5
7	**46**	**C**			0.025	0.7	0.012	0.6
8	**47**	**B**	^{i}Pr	H	0.025	1.0	0.013	0.7
9	**48**	**C**			0.023	0.8	0.009	0.8
10	**49**	**A**	^{t}Bu	H	1.026	1.4	0.816	1.0
11	**50**	**B**		H	0.026	0.9	0.014	0.6
12	**51**	**C**			0.023	0.9	0.014	0.5
13	**52**	**B**		H	0.021	0.7	0.006	1.0
14	**53**	**C**			0.041	0.6	0.009	1.0
15	**54**	**B**		H	0.039	1.3	0.022	0.9
16	**55**	**C**			0.040	0.9	0.018	0.7

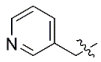
EC_{50} and selectivity values were determined as described for Table 1.

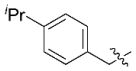
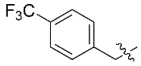
We next assessed replacement of the *p*-methoxybenzyl group at R^1. Initially, this group had been chosen based on analogy to our *Candida*-selective inhibitor CMLD013075. Our X-ray crystallographic analysis[11] (PDB ID: 6CJP) indicates that the aryl ring participates in a key binding

interaction following a major structural rearrangement of the *Candida* Hsp90 lid region, serving as a donor in an N-H…π interaction with *C. albicans* Asn40. However, given the limited scope of radicicol- and monocillin-derived analogs that we previously explored, coupled with a current lack of structural information about the cryptococcal isoform, it is not clear that this group represents an "ideal" binding moiety for either fungal species. As an initial probe, we focused on varying solely the R^1 group across the isoindoline, tetrahydropyrrolopyridine and tetrahydropyrrolopyrazole amides, leaving the R^2 and R^3 sites unsubstituted. The results for this series are summarized in Table 3. We once again identified a wide array (aliphatic, aromatic, heteroaromatic) of aminopyrazole substitutions that afforded in most cases sub-125 nM potencies for both fungal species (**56**, **59**, **62-77** and **80-86**), but all broadly nonselective with the exception of isoindoline **83**. This compound was exemplary as the first compound in our aminopyrazole series to exhibit sub-100 nM EC_{50} with greater than 10-fold selectivity. Interestingly, however, in isolated cases the tetrahydropyrrolopyridine and tetrahydropyrrolopyrazole amides diverged from their isoindoline counterparts with a slight decrease in potency (compounds **78-79**), which was in some cases coupled with a slight increase in cryptococcal selectivity (**57-58** and **60-61**). These compounds, bearing aliphatic *N*-substitutions of varying size, showed 2- to 5-fold selectivity toward *C. neoformans*, with no apparent selectivity toward *C. albicans*.

Table 3. Exploring alternative R^1 substituents on R^2/R^3-unsubstituted aminopyrazoles. Fold selectivity >5 for any compound is highlighted in **red**.



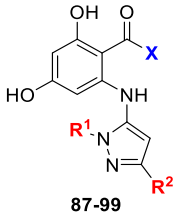
Entry	Compound	R^1	X	*C. neoformans* EC_{50}[a] (μM)	*C. neoformans* fold-selectivity[b]	*C. albicans* EC_{50}[c] (μM)	*C. albicans* fold-selectivity[b]
1	**56**		**A**	0.088	1.5	0.111	0.4
2	**57**	CH_3	**B**	0.286	4.4	0.624	0.7
3	**58**		**C**	0.142	**5.1**	0.377	0.7
4	**59**		**A**	0.125	1.3	0.076	0.7
5	**60**	^{i}Pr	**B**	0.250	2.6	0.309	0.7
6	**61**		**C**	0.097	3.6	0.161	0.7
7	**62**		**A**	0.062	1.1	0.035	0.7
8	**63**	^{i}Bu	**B**	0.103	1.7	0.117	0.6
9	**64**		**C**	0.041	2.3	0.057	0.6
10	**65**		**A**	0.051	0.7	0.009	1.2
11	**66**		**B**	0.026	1.7	0.015	0.9
12	**67**		**C**	0.018	1.3	0.008	0.8
13	**68**		**A**	0.061	0.5	0.014	0.8
14	**69**	Ph	**B**	0.044	0.9	0.021	0.7
15	**70**		**C**	0.037	0.8	0.015	0.8
16	**71**		**A**	0.087	0.4	0.013	0.9
17	**72**	Cy	**B**	0.045	1.0	0.016	1.0
18	**73**		**C**	0.035	1.0	0.014	1.0
19	**74**		**A**	0.052	0.8	0.015	0.8
20	**75**	Bn	**B**	0.043	1.1	0.018	0.8
21	**76**		**C**	0.036	1.1	0.015	0.8
22	**77**		**A**	0.058	1.7	0.041	0.7
23	**78**		**B**	0.207	1.6	0.143	0.7
24	**79**		**C**	0.199	1.8	0.164	0.7
25	**80**		**A**	0.074	0.9	0.033	0.7
26	**81**		**B**	0.106	1.2	0.080	0.6
27	**82**		**C**	0.058	1.4	0.041	0.8

28	**83**		**A**	0.044	**12.8**	0.366	1.1
29	**84**		**B**	0.040	0.8	0.012	0.9
30	**85**		**C**	0.036	0.8	0.012	0.8
31	**86**		**B**	0.063	0.9	0.025	0.8
32	**87**		**C**	0.048	1.1	0.021	0.9

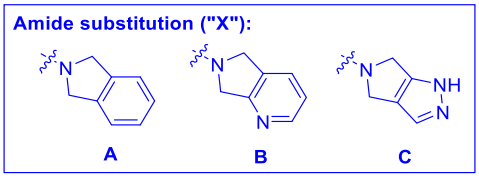
EC_{50} and selectivity values were determined as described for Table 1.

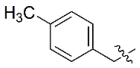
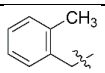
We next progressed to examining the combined modifications of the R^1 *N*-substitution with additional groups at R^2 (Table 4). Again mindful of keeping physicochemical properties such as molecular weight and lipophilicity within an acceptable "druglike" range, we imposed a limitation for this series that each pyrazole should contain a maximum of one aryl ring at either R^1 or R^2, but not at both.[57] This series produced a number of analogs with more modest sub-micromolar potency and cryptococcal selectivity greater than 4-fold (**91**-**95**). Of these, compounds **94** and **95** also exhibited modest selectivity for *C. albicans* Hsp90 over human Hsp90 paralogs, which was consistent with their early near neighbor analogs **21**, **23** and **25** (Table 1).

Table 4. Examining varied parings of R^1/R^2 substitutions on the aminopyrazole ring. Fold selectivity >5 for any compound is highlighted in **red**.



87-99



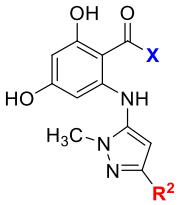
Entry	Compound	X	R^1	R^2	*C. neoformans* EC_{50}[a] (μM)	*C. neoformans* fold-selectivity[b]	*C. albicans* EC_{50}[c] (μM)	*C. albicans* fold-selectivity[b]
1	**88**	**A**		CH_3	0.252	0.2	0.121	0.3
2	**89**	**A**		CH_3	0.560	0.2	0.116	0.4
3	**90**	**A**		CH_3	0.700	0.2	0.134	0.4
4	**91**	**A**			0.078	**9.2**	0.328	0.4
5	**92**	**B**	CH_3	Ph	0.127	**8.2**	0.395	0.8
6	**93**	**C**			0.066	**6.7**	0.213	0.6
7	**94**	**B**			0.517	**9.7**	0.379	3.9
8	**95**	**C**	^{t}Bu	Ph	0.379	**6.7**	0.182	4.1
9	**96**	**B**		Ph	0.615	0.4	0.059	1.7
10	**97**	**C**			0.419	0.3	0.034	1.4
11	**98**	**B**			0.315	1.7	0.100	1.6
12	**99**	**C**	^{i}Bu	Ph	0.147	1.8	0.070	1.4

EC_{50} and selectivity values were determined as described for Table 1.

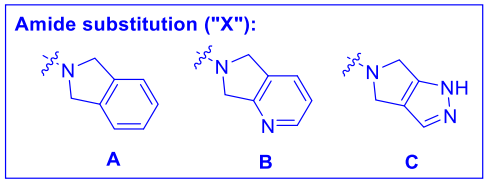
Among our initial fungal-selective leads from this effort, compounds **91-93** stood out as having high cryptococcal selectivity without a concomitant loss in cryptococcal potency as seen

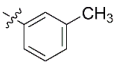
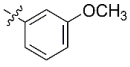
in earlier analogs. To follow up, we designed a final array of analogs *N*-methylated at R^1, probing more diverse aliphatic and aryl substituents at R^2 (Table 5).

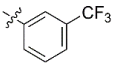
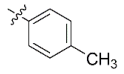
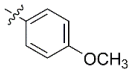
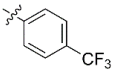
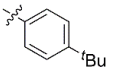
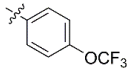
Table 5. Variation of R^2 substituent for *N*-methylated aminopyrazoles yields *C. neoformans*- and *C. albicans*-selective Hsp90 inhibitors with diverging isoform selectivities. Fold selectivities > 5 are highlighted in **red**.



100-132



Entry	Compound	R^2	X	*C. neoformans* EC_{50}[a] (μM)	*C. neoformans* fold-selectivity[b]	*C. albicans* EC_{50}[c] (μM)	*C. albicans* fold-selectivity[b]
1	**100**		**A**	0.087	0.9	0.048	0.6
2	**101**	^{i}Pr	**B**	0.062	1.6	0.156	0.2
3	**102**		**C**	0.040	3.0	0.094	0.5
4	**103**		**A**	0.156	0.7	0.033	1.4
5	**104**	Cy	**B**	0.110	**6.5**	0.670	0.4
6	**105**		**C**	0.037	3.7	0.096	0.6
7	**106**		**A**	0.065	**14.1**	0.599	0.7
8	**107**		**B**	0.139	**12.9**	0.795	0.8
9	**108**		**C**	0.084	**12.4**	0.398	0.9
10	**109**		**A**	0.267	**16.3**	0.573	3.0
11	**110**		**B**	0.421	**15.1**	1.030	2.4
12	**111**		**C**	0.176	**14.6**	0.396	2.5
13	**112**		**A**	0.281	**33.3**	1.642	2.0
14	**113**		**B**	0.852	**27.6**	5.000	1.7

15	**114**		**C**	0.244	**26.5**	1.881	1.3
16	**115**		**A**	4.601	3.2	2.236	2.1
17	**116**		**B**	1.523	**5.5**	0.594	4.4
18	**117**		**C**	0.434	**9.8**	0.294	4.6
19	**118**		**A**	1.318	**6.3**	1.067	2.6
20	**119**		**B**	1.781	**9.5**	1.779	4.0
21	**120**		**C**	0.424	**14.9**	0.636	3.4
22	**121**		**A**	0.630	4.4	0.186	**5.8**
23	**122**		**B**	1.289	**6.9**	1.139	3.1
24	**123**		**C**	0.489	**6.8**	0.376	3.4
25	**124**		**A**	9.530	1.0	1.084	3.1
26	**125**		**B**	5.815	0.8	0.319	4.8
27	**126**		**C**	1.385	1.1	0.103	4.9
28	**127**		**A**	>10	-	1.197	2.1
29	**128**		**B**	8.337	0.4	0.237	4.5
30	**129**		**C**	2.262	0.5	0.071	**5.0**
31	**130**		**A**	5.402	1.0	0.134	**15.3**
32	**131**		**B**	1.262	1.0	0.050	**18.2**
33	**132**		**C**	0.514	1.3	0.016	**15.9**

EC_{50} and selectivity values were determined as described for Table 1.

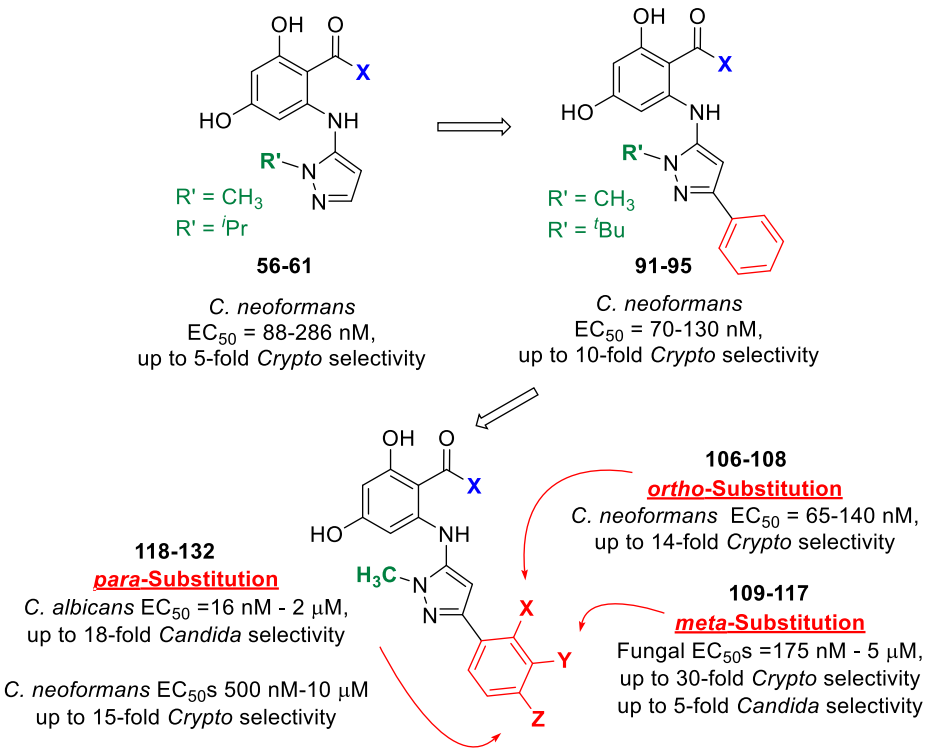
Gratifyingly, this series produced highly selective inhibitors for both the *C. neoformans* and *C. albicans* isoforms of Hsp90. While our exploration of aliphatic substitution was limited, high cryptococcal potency (EC_{50} < 160 nM), and in some cases modestly *Cryptococcus*-selective compounds (3- to 6.5-fold) were observed with isopropyl (**100-102**) and cyclohexyl (**103-105**) substitution at R^2. The most highly selective compounds, however, were observed among the R^2 arylated analogs, with diverging species-selectivity based on the nature and position of the aryl ring substituent. The *ortho*-methylated analogs **106-108** displayed slightly enhanced cryptococcal

selectivity and similar cryptococcal potency (<150 nM) as compared to their unsubstituted congeners **91-93** (Table 4), with no apparent selectivity and significantly lower potencies (≥ 400 nM) in lysate of *C. albicans*. Movement of the methyl substituent from *ortho*- to *meta*- (compounds **109-111**) afforded similarly *Cryptococcus*-selective compounds, albeit with lower potencies. Interestingly, the *meta*-methoxy substituted **112-114** exhibited a significant improvement in cryptococcal selectivity (27- to 33-fold) despite only modest cryptococcal potency (EC_{50}s all >250 nM). Trifluoromethylation at the same *meta*- position (compounds **115-117**), resulted in a dramatic reduction in both cryptococcal selectivity and activity.

Moving from testing in *C. albicans* lysate to *C. neoformans* lysate, the aforementioned *meta*-substituted compounds **109-117** also exhibited modest selectivity, with the best *Candida*-selectivity observed *m*-trifluoromethylated analogs **116** and **117** (4.4- and 4.6-fold, respectively). The *meta*-substituted series also exhibited consistently poor *C. albicans* potencies, with EC_{50} values ranging from ~300 nM to 5 μM. In contrast, improved *C. albicans* selectivities and potencies were observed among the analogs that were *para*-substituted on the R^2 phenyl ring. *para*-Methylated (**119-120**) and *para*-methoxy substituted (**121-123**) aminopyrazoles exhibited moderate selectivities and, in most cases, equivalently low potencies against both fungal species, with EC_{50} values generally ranging from 0.5-2 μM. Incorporation of larger lipophilic substituents at the *para*-position such as trifluoromethyl (**124-126**) and *tert*-butyl (**127-129**) further depressed cryptococcal potency, with EC_{50}s ranging from 2 to >10 μM and no apparent selectivity. In contrast these compounds (**124-129**) maintained improved potencies and similar selectivities against *Candida* Hsp90 to their *para*-methyl- and *para*-methoxy- counterparts **124-127**. This series also highlights what we have observed to be an occasional sensitivity to the nature of the amide/aminopyrazole pairing; for example in direct contrast to the cryptococcal potency trends

observed with unsubstituted analogs **56**-**58**, pairing of the pyrido- and pyrazolopyrrolidine with the bulkier 3-CF_3-Ph (**116**-**117**), 4-CF_3-Ph (**125**-**126**) and 4-^{t}Bu-Ph (**128**-**129**) substituents at R^2 improved *C. albican*s potency and selectivity relative to their isoindoline counterparts **115**, **124** and **127**. This trend did not hold, however, for all analogs. Perhaps most intriguingly, the *para*-trifluoromethoxy substituted compounds **130**-**132**, which were completely nonselective and only modestly potent toward cryptococcal Hsp90, exhibited dramatic improvements in potency toward *C. albicans*, with EC_{50} values ranging from 16-134 nM and 15- to 18-fold *Candida* selectivity. These divergent structure-selectivity trends, wherein *ortho*/*meta*-methyl and *meta*-methoxy compounds exhibited high *Cryptococcus* selectivity and poor *Candida* selectivity, whereas *para*-trifluoromethoxy substitution rendered high *Candida* selectivity and poor *Cryptococcus* activity, are summarized in Figure 2.

Figure 2. Summary of iterative progression to fungal selective inhibitors **106-132** with divergent patterns of species selectivity dependent on position of substitution on the aminopyrazole phenyl ring (*red*)

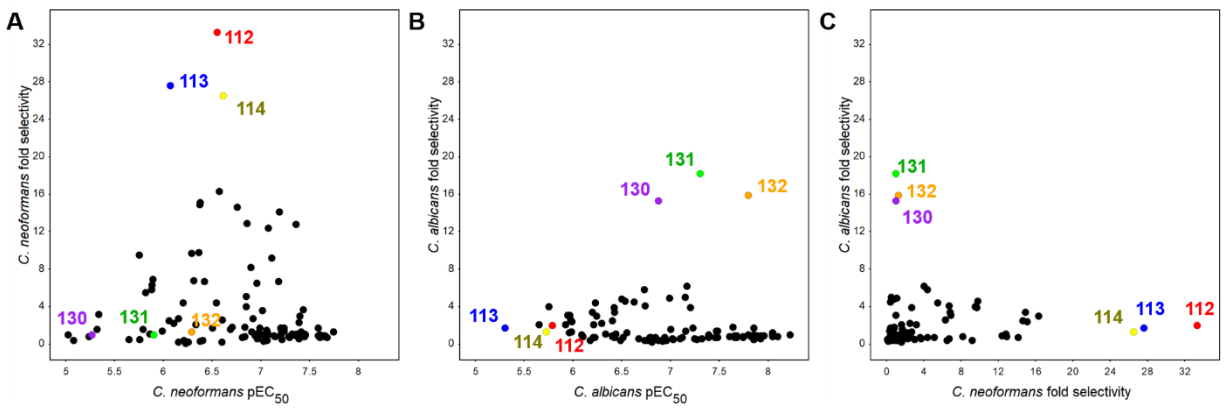


Relationship of fungal to human selectivity

To better understand the phylogenetic origins of the divergent selectivity between fungi, we performed protein::protein BLAST sequence alignments across the different species studied. This analysis indicated that *C. neoformans* and *C. albicans* share 69% sequence identity across the entire Hsp90 protein, and 71% identity across their NBD (residues 1-240). As a comparison, human Hsp90α and Hsp90β share 69% and 67% identity with *C. albicans* Hsp90 across their NBD, respectively. Thus, the two fungal species diverge in primary sequence as greatly from one another as they do from human Hsp90. In light of such sequence divergence, perhaps it is not surprising that while we set out to discriminate against human Hsp90, the potency and selectivity of our

synthetic inhibitors also diverged between the two fungal species studied. A graphic summary of inhibitor potency/selectivity relationships found by screening compounds in *C. neoformans* lysate (Fig 3A) and *C. albicans* lysate (Fig. 3B) highlights the progress made in achieving our goal of achieving fungal selectivity, while the divergence between compound selectivity in regards to *C. neoformans* vs. *C. albicans* is best demonstrated by plotting the selectivity of compounds for one fungus vs. human against selectivity for the other (Fig. 3C). To more accurately define their potency and selectivity, the activity of 27 compounds with a screening EC_{50} < 1μM in lysate of either fungal species was confirmed by repeat testing in two additional experiments, with results provided in Supplemental Table 1.

Figure 3. Scatter plots depict fungal potency (*x-axis*) vs. fungal selectivity (*y-axis*) relationships for all aminopyrazoles when screened using human cell lysate and lysate of either *C. neoformans* (Panel A) or *C. albicans* (Panel B). All potencies are reported as the inverse $\log_{10}$ of compound EC_{50} (pEC_{50} as measured by FP assay). The scatter plot in Panel C compares compound selectivity patterns between the two fungi. Key fungal-selective compounds for each species (**112-114** and **130-132**) are highlighted in color to underscore their divergence in potency and selectivity. Each point represents the mean of duplicate determinations in a single experiment.



Validation of whole cell lysate FP results

To confirm the FP results obtained in lysate for our most potent and selective compounds, we prepared recombinant *Candida, Cryptococcus*, and human Hsp90 NBDs by expression and purification in *E. coli*. Using recombinant proteins, we were able to define assay-independent nanomolar inhibitory constants (K_i) for these compounds (Supplemental Fig. 1). We also confirmed binding of the compounds to their relevant NBD by qualitative thermal shift denaturation assays performed under saturating ligand conditions (Supplemental Fig. 1). Thermal shift assays were performed under saturating ligand conditions, i.e. equimolar concentrations (10 μM) of protein and ligand. As a result, they can provide only qualitative evidence of target binding, but not a quantitative measurement of ligand affinity. This feature of the thermal shift method is well demonstrated in Supplemental Table 2, which presents K_i and thermal shift data for both high and low potency compounds. Here, compounds with K_i values of less than 50 nM for a particular NBD increase its ΔTm to a similar extent irrespective of absolute potency. In contrast, lower affinity compounds (K_i > 100 nM) fail to increase the Tm of the respective NBD.

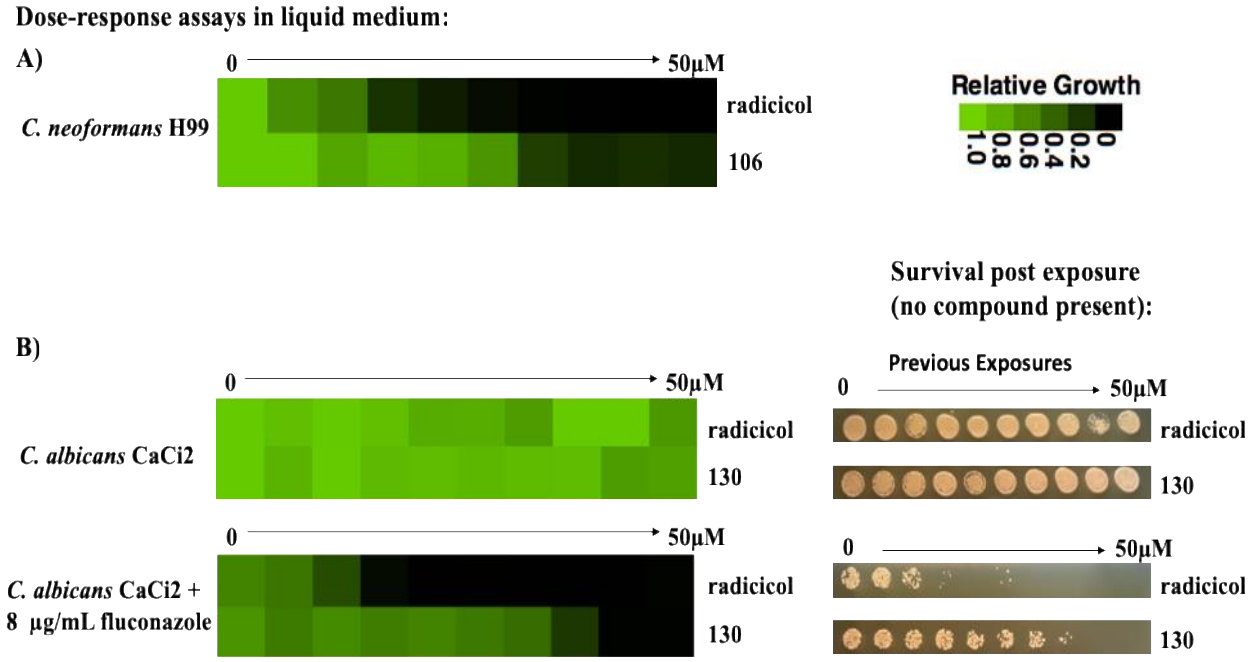
As an orthogonal, highly quantitative approach to FP, we measured the binding affinities of our six lead compounds for *C. albicans, C. neoformans* and human Hsp90 NBDs by surface plasmon resonance (SPR, Supplemental Table 3). The affinity values determined for compounds varied by less than an order of magnitude between the two different experimental techniques. The same pattern of fungal selectivity for compounds demonstrated by FP assay in whole cell lysates was also seen by SPR. The magnitude of selectivity determined by SPR assays compared to FP assays in lysate, however, was reduced. Such a difference might be expected given the absence in SPR assays of native co-chaperone containing complexes and, in the case of human cell lysate, a biologically relevant mix of Hsp90 paralogs.

Whole cell antifungal activity

Having achieved promising potency and species-selectivity for several compounds at the level of fungal target engagement, we next examined the ability of these compounds to inhibit fungal growth. We found that minimal inhibitory concentrations (MICs) for most of the potent and selective analogs highlighted in Table 5 were much higher than their EC_{50} values in lysate, generally > 50 μM. The disparity between whole cell antifungal activity and the EC_{50} values we determined in FP assays is undoubtedly due to poor permeability/accumulation of the compounds in fungal cells. This common problem in the development of antifungals occurs because the fungal cell wall and membrane as well as the diverse drug efflux pumps expressed by fungi render it a challenge to achieve intracellular concentrations of experimental compounds sufficient to inhibit the function of their targets.

Of the fungal Hsp90-selective compounds tested, only the 14-fold *C. neoformans*-selective analog **106** inhibited growth of the organism below 10 μM (Fig. 4A). While triazole antifungals in current clinical use against *Cryptococcus* do have MICs in excess of this range, they also possess far greater selectivity than we have achieved so far and are much less toxic to human cells. As single agents, the MICs of all our *Candida*-selective compounds were >50 μM. To provide a more sensitive read-out, however, we took advantage of the well-established ability of Hsp90 inhibitors to potentiate the activity of conventional antifungals against drug-resistant isolates of *C. albicans*.[5] Testing compounds **130** and **131** in combination with the widely used antifungal fluconazole, we found an MIC of 12.5 μM for the 15-fold *Candida*-selective analog **130** against a moderately fluconazole-resistant clinical isolate of *C. albicans.* This compound also converted the fungistatic activity of fluconazole to fungicidal against the same isolate, an effect consistent with Hsp90 inhibitory activity (Figure 4B).

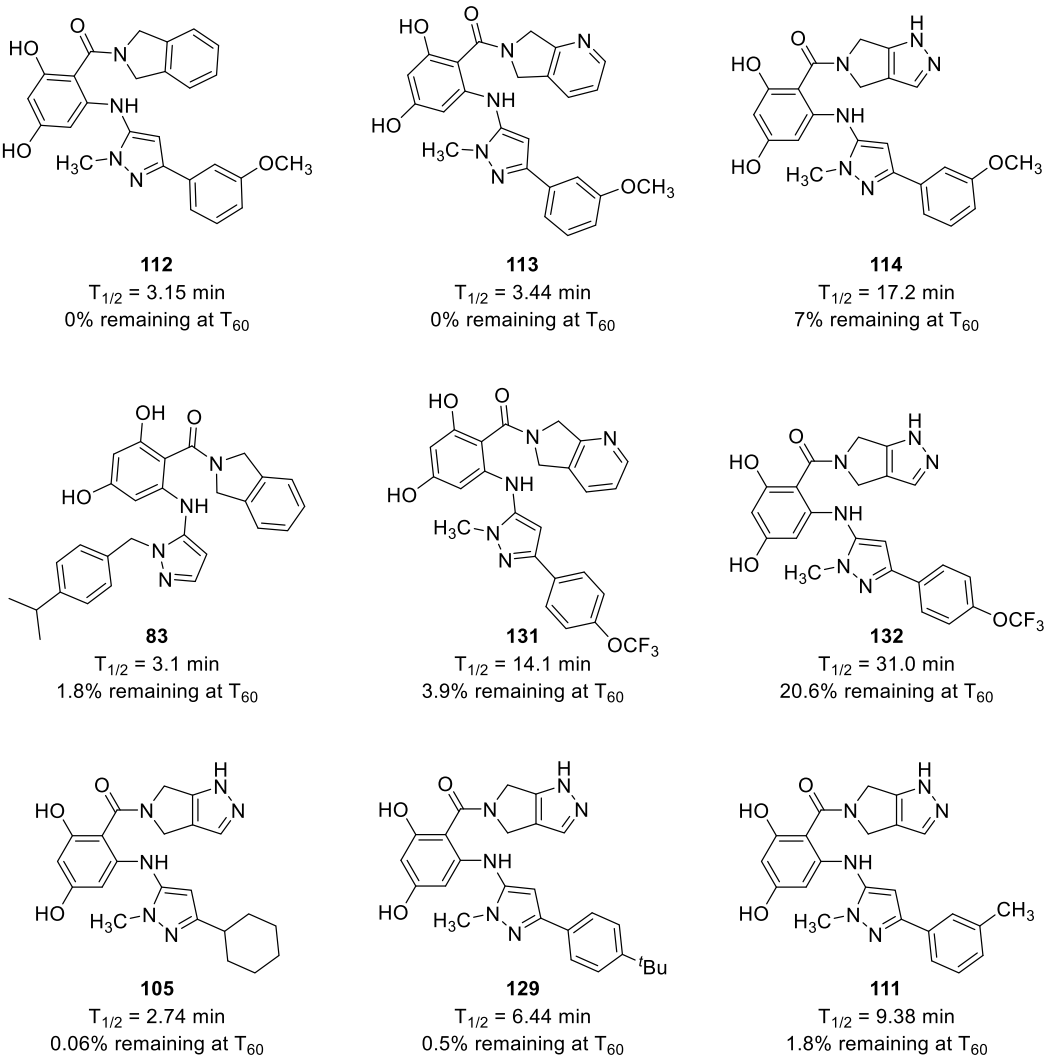
Figure 4. Biological activity of fungal-selective inhibitors.



Panel A: Growth inhibition by fungal-selective aminopyrazoles of *C. neoformans* reference strain H99 cultured in RPMI 1640 medium at 37 °C. **Panel B:** Growth inhibition by fungal-selective aminopyrazoles of a *C. albicans* clinical isolate (CaCi2) with or without a background concentration of 8 μg/mL fluconazole. The effect of 48-hour exposure to inhibitors over a twofold dilution series of concentrations is displayed in heat-map format. Color scale bar: no growth inhibition (green) to complete inhibition (black). Each colored box represents the mean of technical duplicates. The experiment was repeated as an independent biological replicate to confirm results. Following exposure to compounds, aliquots of the cultures in each well were spotted onto compound-free YPD agar and plates incubated at 30 °C for an additional 24 hours before imaging to assess fungicidal activity (Panel B, right).

Thus, although their potency and selectivity require further improvement, the whole cell activity of these resorcylate aminopyrazoles remains consistent with an Hsp90-targeted mode of action. Encouraged by this finding and to aid future efforts in developing the scaffold, we performed an initial evaluation of its stability to P450-mediated metabolism in liver microsomes, a major pharmacological liability of our previous fungal selective macrocyclic oxime **CMLD013075**[11]. Although all the compounds tested suffered from relatively rapid metabolism (Fig. 5 and Supplemental Table 4), important insights were gained into the basis of their instability. Comparing the half-lives of cryptococcal-selective compounds **112**-**114** reveals an apparent stabilizing effect of the pyrazolopyrrolidine amide, which is consistent with the previously reported metabolic instability of isoindolines due to oxidation at the 5/6 position.[24] The isoindoline was chosen for this study despite its known downstream pharmacological liabilities, as it represented a low molecular-weight starting point allowing for the methodical assessment of the relative potency and selectivity of different aminopyrazole substitutions. Assessment of additional analogs **105**, **111**, **129**, and **131**-**132** indicate that additional metabolic liabilities are also likely present at the aminopyrazole, with the *para*-trifluoromethoxy substitution clearly inhibiting metabolism. Still, the relatively short half-life of compound **132** (31 minutes) underscores the need for further optimization of metabolic stability, in addition to fungal penetration, as we advance in future work to compounds with suitable properties for testing *in vivo*. Metabolic stability optimization for resorcylate Hsp90 inhibitors *via* modification of the amide is well-precedented;[24, 50] similar strategies, paired with targeted alterations of the aminopyrazole aryl substituent, are currently under study in our laboratory and will be reported in due course.

Figure 5. Microsomal stability (mouse liver microsomes) of a panel of fungal-selective inhibitors. Assays were performed by Charles River Laboratories (Worcester, MA).



The factors governing the ability of small molecules to cross cell wall and membrane barriers, avoid active efflux and accumulate within fungi are not well defined. To gain initial insights for our resorcylate aminopyrazoles, we expanded the scope of compounds tested *in cellulo* to include all biochemically active compounds (FP $EC_{50} < 10$ μM) irrespective of their selectivity in cell-free lysates. An additional 83 compounds with diverse physicochemical and structural

properties were tested to identify several (**21**, **27**, **29**, **49**, and **89**) with single agent bioactivity against *C. neoformans* (Table 6).

Table 6. Aminopyrazoles with whole cell anti-cryptococcal activity

Entry	Compound	MIC (μM)	EC_{50} (FP, nM))	Selectivity (FP)
1	**21**	6.25	877	2.5
2	**27**	12.5	787	2.2
3	**29**	6.25	705	2.7
4	**49**	12.5	1026	1.4
5	**89**	25	560	0.2

Minimum inhibitory concentration (MIC) value for compounds against *C. neoformans* (Strain H99) was determined in dose-response format, in technical duplicate. Experiments were conducted in RPMI medium at 37 °C for 48 h. Relative viable cell number was measured by standard dye reduction (resazurin) assay.

The pattern of results suggests that enhancement of lipophilicity through the introduction of halogens or bulky aliphatic moieties can improve whole cell activity. To independently verify that the whole cell activity of these compounds was consistent with an ability to engage Hsp90, we complemented primary FP-based testing of **21**, **27, 29**, **49** and **89** and **106** with thermal shift assays using *C. neoformans* NBD (Supplemental Table 5). Whole cell testing of all biochemically active, but non-selective compounds also revealed three inhibitors (**21**, **41**, and **89**) with fungicidal activity in combination with fluconazole against the same clinical isolate of *C. albicans* used in Fig. 4 (Fig. S2). Analogous to our approach with *Cryptococcus*-active compounds, target engagement for *Candida*-active compounds was confirmed by thermal shift assay using *C. albicans* Hsp90 NBD (Supplemental Table 5).

CONCLUSION

Through the iterative design and optimization of a novel aminopyrazole-substituted resorcylate amide chemotype, we have identified advanced analogs with markedly improved potency and selectivity for binding to fungal Hsp90 isoforms as compared to their human counterparts. Interestingly, as fungal selectivity increased, a marked divergence in structure-activity relationship between *C. albicans* and *C. neoformans* became evident. Beyond potent and selective target engagement, the need to increase intracellular accumulation and activity against whole organisms remains to be addressed in future work if useful antifungals are to be developed. By investigating the bioactivity of the entire series of analogs, we have identified key physicochemical properties (e.g. structural modification and lipophilicity enhancement through the introduction of halogens or bulky aliphatic moieties) that appear to contribute to improved whole cell activity and metabolic stability. Targeted exploration of these identified modifications in the context of our fungal-selective aminopyrazole substitutions, as well as medicinal chemistry work to further optimize potency and selectivity of the top fungal-selective leads are ongoing in our efforts to cripple human fungal pathogens by selectively targeting Hsp90.

Experimental Section

Yeast strains and culture conditions. Strains used in this study were *C. albicans* CaCi2 (clinical isolate 2),[58] SC5314,[59] and *C. neoformans* H99.[60] Archives of all fungal strains were maintained at −80 °C in 25% glycerol. Active cultures were maintained on solid (2% agar) yeast extract peptone (YPD, 1% yeast extract, 2% bactopeptone, 2% glucose) at 4 °C for no more than

one month. For growth experiments, strains were cultured in YPD medium or in RPMI medium 1640 (Gibco SKU#318000-089, 3.5% MOPS, 2% glucose, pH 7.0), as indicated in figure legends.

Antifungal sensitivity testing. Minimum inhibitory concentrations (MICs) were determined in flat bottom, 96-well plate format using a modified broth microdilution protocol as previously described,[6, 61] except relative viable cell number was monitored by standard dye reduction assay after a 3-hour incubation with resazurin at 37 °C. Radicicol and all synthetic analogs were formulated in dimethyl sulfoxide (DMSO, Sigma Aldrich Co.); fluconazole was dissolved in sterile ddH_2O. Each compound was tested in duplicate in at least two independent experiments. Minimum inhibitory concentration (MIC) data were quantitatively displayed in heat-map format using the program Java TreeView 1.1.3 (http://jtreeview.sourceforge.net). To test for fungicidal activity, cultures from MIC plates were spotted on YPD agar plates using a spotter (Frogger, V&P Scientific, Inc). Plates were photographed after 24 h of incubation at 30 °C.

FP assays. Whole cell lysates were prepared for FP assays as described previously.[11] Total protein concentration of human and yeast lysates was determined by Bradford assay.[6] Titrations of Cy3-labeled geldanamycin (Cy3-GdA) probe and lysate were evaluated to define conditions that resulted in 75% maximal probe polarization with no competitor present.[11] Serial dilutions of test Hsp90 inhibitors were then assayed under these same conditions to monitor loss of fluorescence polarization as an indicator of probe displacement from Hsp90. All determinations were performed in duplicate wells using 384-well black flat-bottom microtiter plates (Greiner Bio-One; 655076). Titrations of test compound in 25 μL of binding buffer (supplemented with 0.1 mg/mL bovine gamma globulin), were mixed with an equal volume of freshly prepared whole-cell lysate spiked with Cy3-GdA (0.1 nM). Plates were incubated at room temperature for 4.5 h to achieve equilibrium binding for the geldanamycin-based probe. Signal in millipolarization (mP)

units was measured at an excitation wavelength of 535 nm and emission wavelength of 595 nm in a SpectraMax i3 microplate reader (Molecular Devices) using Softmax Pro software (version 5.4.1). Non-linear 4-parameter curve fitting of raw displacement data was performed in GraphPad Prism 5.0 to determine EC_{50} values as a measure of relative Hsp90-binding affinity. Results were normalized to the value determined for GdA in lysate of each cell type. This experiment was repeated for a set of 27 key compounds for SAR in at least three independent experiments.

FP assays were also performed with purified *C. albicans* and *C. neoformans* Hsp90 NBD for the determination of inhibitory constants (K_i) for relevant fungal-selective compounds. Titrations of the Cy3-GdA probe and purified proteins were evaluated to define assay conditions and to determine the dissociation constant K_d of the probe for each NBD. Serial dilutions of test Hsp90 inhibitors were then assayed in triplicate wells under these conditions. Non-linear 4-parameter curve fitting of raw displacement data was performed in GraphPad Prism 5.0 to determine IC_{50} values. Finally, inhibitory constants (K_i) were calculated as described previously.[11, 62]

Protein thermal shift assays. Thermal melting curves were determined using a Protein Thermal Shift Kit (ThermoFisher # 4462263), employing a CFX384 Real-Time PCR System (Bio-Rad, C1000 Touch Thermal Cycler). Reactions were performed in a final volume of 10 μL, and contained purified *C. albicans* or *C. neoformans* Hsp90 NBD diluted to 250 μg/mL in Buffer HBS-P (GE Healthcare Life Sciences, 0.01 M HEPES pH 7.4, 0.15 M NaCl, 0.005% v/v Surfactant P20) with 10 μM synthetic analog or DMSO control, and 1 × Sypro Orange dye solution. Samples were prepared in triplicate in 384-well white plates (Bio-Rad; HSP3805). The instrument was set to melt curve, step 1 (25 °C, 2 min) and step 2 (ramp to 98.6 °C, increasing 0.2 °C per 5 s cycle). Protein

melting temperatures were defined as the temperature at the maximum of the derivative of fluorescence intensity.

NBD expression and purification. Recombinant Hsp90 NBDs were expressed and purified as previously described.[11] Stock protein solutions in 50% glycerol were stored at -20 °C until dilution into relevant buffers and use for FP and thermal shift assays.

SPR assays. For SPR experiments, Hsp90 NBD expression constructs were modified to encode a C-terminal AviTag™ for site-specific on-column biotinylation with a BirA biotin-ligase kit (Avidity LLC; BirA-500). SPR experiments were performed on a Biacore T200 instrument at 25 °C. Biotinylated Hsp90 NBD was diluted to 40 μg/mL and immobilized on a streptavidin chip (Sensor Chip SA, GE Healthcare) at a density of 2000 - 2500 response units (RU) on the biosensor surface. Binding experiments were done in HBS-P (0.01 M HEPES pH 7.4, 0.15 M NaCl, 0.005% v/v Surfactant P20, GE Healthcare) with 5% DMSO at a flow rate of 40 μL/min. Test compounds were injected in two dilutions series, with low concentrations ranging from 6 to 96 nM and high concentrations ranging from 60 to 960 nM, with a 60 s association time and 600 s dissociation time, with the exception of compound **130** for which the injection time was extended to 300 s after observing a very slow on-rate with this molecule. Resulting sensorgrams were analyzed with a fit to a 1:1 binding model, using BIA evaluation software.

Microsome stability testing. The potential susceptibility of compounds to hepatic metabolism was assessed by Charles River Laboratories (Worcester, MA) using standard in-house protocols. Compounds were incubated at 1 μM concentration in mixed-gender CD-1 mouse liver microsomes (0.5 mg/mL) in the presence of 2 μM NADPH. Percent compound remaining was measured by

LC/MS/MS at six timepoints (0, 15, 30, 60, 90 and 120 min) in duplicate. 7-ethoxycoumarin was utilized as a positive control. In addition, NADPH-free control samples were assessed at two timepoints (0 and 15 min) in duplicate to exclude non-CYP450-mediated decomposition. First-order half-lives are calculated from the equation $T_{1/2} = -0.693/x$, where x is the slope found in the linear fit for the plot of ln(% remaining) versus incubation time. Calculated mouse intrinsic hepatic clearance (CL_{int}) in mL/min/kg is extrapolated[63] based on 45 mg microsomes/g liver and 87.5 g liver/kg body weight.

Statistical methods. For FP experiments in support of SAR studies, GraphPad Prism 7.0 was used to perform curve fitting and calculate the concentrations of compounds (EC_{50}) resulting in 50% reduction in maximal polarization signal (EC_{50}). All curve fits demonstrated a correlation coefficient (R^2) >0.95 The number of independent experiments performed and the number of technical replicates in each experiment are provided in the legends of figures and tables characterizing the biochemical and biological activities of compounds. In calculating the error of selectivity determinations, the fractional error of measurements in each species was summed to yield a composite error for the derived ratio.

Chemistry Methods.

General Methods. All melting points are uncorrected. ^{1}H NMR spectra were recorded at 400 or 500 MHz at ambient temperature. ^{13}C NMR spectra were recorded at 101 or 126 MHz at ambient temperature. Chemical shifts are reported in parts per million. Data for ^{1}H NMR are reported as follows: chemical shift, multiplicity (app = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, sxt = sextet, m = multiplet, ovrlp = overlap), coupling constants, and integration. All ^{13}C NMR spectra were recorded with complete proton decoupling. Analytical thin layer chromatography was performed using 0.25 mm silica gel 60-F plates. Flash column

chromatography was performed using 200-400 mesh silica gel (Sorbent Technologies, Inc.). Automated flash chromatography was performed using prepacked columns (SI-HC, puriFlash or Premium Universal, Yamazen) on either an Interchim puriFlash450 or Yamazen Smart Flash EPCLC W-Prep2XY system. All mass-guided preparative HPLC was performed using an acetonitrile:water gradient (mobile phase modified with 0.01% formic acid) on a Waters FractionLynx system equipped with a 600 HPLC pump, a micromass ZQ quadrapole, Waters 996 diode array, and Sedere Sedex 75 ELS detectors, using an XBridge Prep C18 5 μM OBD 19 mm diameter column of either 100 mm or 250 mm length. Isolated yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. All reactions were carried out in oven-dried glassware under an argon atmosphere unless otherwise noted. Analytical LC-MS experiments were performed using a Waters Acquity UPLC (ultraperformance liquid chromatography) with a binary solvent manager, SQ mass spectrometer, Waters 2996 PDA (photodiode array) detector, and evaporative light scattering detector (ELSD). All microwave experiments were performed on a CEM Discover microwave reactor, using a sealed 10 or 35 mL vessel with temperatures monitored by an external sensor. All compounds tested in biological assays were determined to be >95% pure by UPLC-MS-ELSD analysis.

General Procedure A: Synthesis of α-Formyl Nitriles. All α-formyl nitriles used as synthetic precursors for aminopyrazoles **10** were synthesized *via* a procedure adapted from [64]. To a suspension of potassium *tert*-butoxide in THF (2.2 equiv, 1.4 M solution in THF) at room temperature was added a mixture of the requisite nitrile (1 equiv) and ethyl formate (1.05 equiv) in THF (6.3 M relative to nitrile) dropwise. After stirring overnight at room temperature, the reaction mixture was diluted with CH_2Cl_2 and water. The resulting mixture was adjusted to pH = 4 using concentrated HCl (aq.). The layers were separated and aqueous layer was extracted twice

with CH_2Cl_2. The combined organic layers were washed with brine and dried with anhydrous $MgSO_4$. The salts were removed via gravity filtration and volatile materials were condensed *in vacuo*. The crude mixture was purified via automated flash chromatography to give the intermediate α-formyl nitrile.

General Procedure B: Synthesis of α,β-unsaturated Nitriles. All α,β-unsaturated nitriles used as synthetic precursors for aminopyrazoles **10** were generated from commercially-available aldehydes according to the following procedure: To a solution of potassium *tert*-butoxide (2 M in THF, 1.04 equiv) at 0 ºC was added diethyl cyanomethylphosphonate (1.1 equiv) dropwise. After stirring at 0 ºC for 1 h, the requisite aldehyde (1 equiv) was added dropwise and the reaction was allowed the warm to room temperature overnight. The reaction mixture was poured into saturated NH_4Cl (aq.) and diluted with ethyl acetate. The layers were separated and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts from each suspension were removed via gravity filtration and condensed *in vacuo*. The crude mixture was purified via automated flash chromatography to give the intermediate α,β-unsaturated nitrile.

General Procedures C: Syntheses of aminopyrazoles 10

C1: Procedure adapted from [65]. A suspension of 3-aminocrotonitrile (1.08 equiv) and the requisite hydrazine hydrochloride (1 equiv) in 1 M HCl (aq.) (0.72 M concentration of hydrazine) was refluxed for 3 h. The resulting mixture was diluted with water and extracted twice with ethyl acetate. The aqueous layer was basicified with solid $NaHCO_3$ until solid remained. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers from each extraction sequence were separately washed with brine and dried with anhydrous Na_2SO_4. The salts from

each suspension were removed *via* gravity filtration and the mother liquors were combined and condensed *in vacuo*. The crude residues were purified *via* automated flash chromatography.

C2: A mixture of the requisite α-formyl nitrile and 4-(methoxybenzyl)hydrazine hydrochloride (1 equiv) was refluxed overnight in ethanol (0.36 M relative to α-formyl nitrile). The solution was cooled to room temperature and condensed *in vacuo*. The residue was diluted with CH_2Cl_2 and the organic layer was washed twice with saturated $NaHCO_3$ (aq.) and brine. The organic layer was dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were condensed *in vacuo*. The crude mixture was purified via automated flash chromatography.

C3: Procedure adapted from [65]. To a solution of hydrazine monohydrate (1.03 equiv) in THF (5 M relative to hydrazine) at room temperature was added the requisite α,β-unsaturated nitrile (1.02 equiv) and heated to 40 ºC for 2 h. After cooling to room temperature, the requisite aldehyde (1 equiv) was added dropwise. The mixture was heated to 40 ºC for an additional 2 h. After cooling to room temperature, volatile materials were condensed *in vacuo*. The resulting residue was dissolved in ^{i}PrOH (4.5 M relative to benzaldehyde). Sodium *tert*-butoxide (1.03 equiv) was added to the reaction mixture and the resulting suspension was heated to 100 ºC for 2.5 h and then stirred overnight at room temperature. The reaction mixture was diluted with water and extracted twice with diethyl ether. The combined organic layers were washed twice with 1 M HCl . The combined 1 M HCl washes were basified to pH = 14 with 50% NaOH (aq.) and extracted with diethyl ether. The second set of ether extractions were combined and washed with brine and dried with anhydrous Na_2SO_4. The salts from each suspension were removed via gravity filtration and volatile materials were condensed *in vacuo*. The crude mixture was purified via automated flash chromatography.

C4: A solution of requisite oxo-nitrile and (1 equiv) and (4-methoxybenzyl)hydrazine hydrochloride (2 equiv) in EtOH (0.3 M relative to oxo-nitrile) was heated to reflux overnight. After cooling to room temperature, volatile materials were condensed *in vacuo*. The residue was dissolved in CH_2Cl_2 and saturated $NaHCO_3$ (aq.). The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts from each suspension were removed via gravity filtration and volatile materials were condensed *in vacuo*. The crude mixture was purified via automated flash chromatography.

C5: A solution of requisite oxo-nitrile (1 equiv) and methylhydrazine (1 equiv) in methanol (2 M) were irradiated at 120 ºC for 40 min in a microwave reactor. After cooling to room temperature, volatile materials were condensed *in vacuo*. The crude mixture was purified via automated flash chromatography

General Procedures D. Pd-mediated coupling of aryl bromides to aminopyrazoles 10.

D1: Inside a nitrogen glovebox were combined aryl bromide (1 equiv), amine **10** (1.1 equiv), tris(dibenzylideneacetone)dipalladium (0.04 equiv), Xantphos (0.08 equiv), sodium phenoxide (1.5 equiv). Dioxane (0.13 M) was added to the mixture and the reaction vessel was capped and removed from the glovebox. After the reaction was heated in an oil bath at 120 ºC for 2 h, the reaction cooled to room temperature and diluted with ethyl acetate. The resulting mixture was washed 3 times with saturated Na_2CO_3 (aq.), brine, then dried with anhydrous Na_2SO_4. The salts from each suspension were removed via gravity filtration and volatile materials were condensed *in vacuo*. The crude mixture was purified via automated flash chromatography.

D2: Inside a nitrogen glovebox were combined aryl bromide (1 equiv), amine **10** (1.1 equiv), tris(dibenzylideneacetone)dipalladium (0.04 equiv), Xantphos (0.08 equiv), sodium phenoxide

(1.5 equiv) in a 10 mL microwave reaction vessel. Dioxane (0.13 M) was added to the mixture and the reaction vessel was capped and removed from the glovebox. After the reaction was irradiated at 170 ºC for 2 h in a microwave reactor, the reaction cooled to room temperature and diluted with ethyl acetate. The resulting mixture was washed 3 times with saturated Na_2CO_3 (aq.), brine, then dried with anhydrous Na_2SO_4. The salts from each suspension were removed via gravity filtration and volatile materials were condensed *in vacuo*. The crude mixture was purified via automated flash chromatography.

General Procedure E. Hydrolysis conditions to generate crude acids 19. To a solution of ester (1 equiv) in EtOH:water (1:1 ratio, 0.06 M) was added potassium hydroxide (9.2 equiv) and then heated to 95 ºC for 1h. After cooling to room temperature, volatile materials were condensed *in vacuo*. The residue was suspended in saturated NH_4Cl (aq.) and CH_2Cl_2. The layers were separated and the aqueous layer was extracted 3 times with CH_2Cl_2. The combined organic layers were washed twice with water, brine and then dried with anhydrous Na_2SO_4. The salts from each suspension were removed via gravity filtration and volatile materials were condensed *in vacuo*. The crude acid **19** was used without further purification.

General Procedure F: Global MOM-deprotection. To a solution of amide (1 equiv) in methanol (13.7 mM) was added HCl (2 M, 6.5 equiv). The resulting solution was stirred at 50 ºC overnight. After cooling to room temperature, volatile materials were condensed *in vacuo*. The residue was purified on mass-guided preparative HPLC.

General Procedure G: Amidation of acids 19. To a suspension of crude carboxylic acid **19** (1 equiv) and amine (1.5 equiv) in CH_2Cl_2:THF (1:1 mixture, 0.08-0.09 M) was added triethylamine followed by HATU (1.2 equiv). The suspension was stirred overnight at room temperature and then diluted with CH_2Cl_2. The reaction mixture was washed with saturated $NaHCO_3$ (aq.), brine

and then dried with anhydrous Na_2SO_4. The salts from each suspension were removed via gravity filtration and volatile materials were condensed *in vacuo*. The crude mixture was purified via automated flash chromatography.

General Procedures H: Tandem PS-CDI-mediated amidation and MOM deprotection of crude acids **19**.

H1: To a solution of crude carboxylic acid **19** (1 equiv) and isoindoline hydrochloride (1.5 equiv) in THF: CH_2Cl_2 (1:1 ratio, 77 mM) was added trimethylamine (4 equiv) followed by HOBt hydrate (1.2 equiv) and PS-Carbodiimide (1.18 mmol/g loading, 1.2 equiv). The suspension was shaken overnight at room temperature. The resin was removed via filtration and the resulting filtrate was washed twice with saturated $NaHCO_3$ (aq.) and once with brine. The organic layer was dried with anhydrous sodium sulfate and the salts. The salts from each suspension were removed via gravity filtration and volatile materials were condensed *in vacuo*. The resulting residue was dissolved in methanol (20 mM) and HCl (aq.) (2 M, 6.5 equiv) was added to the mixture. The resulting solution was stirred at 50 ºC overnight. After cooling to room temperature, volatile materials were condensed *in vacuo*. The residue was purified on mass-guided preparative HPLC.

H2: Identical to General Procedure H1, except using 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine instead of isoindoline hydrochloride.

H3: Identical to General Procedure H1, except using 1,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole instead of isoindoline hydrochloride.

1-(4-methoxybenzyl)-3-methyl-1*H*-pyrazol-5-amine (10a). Synthesized using General Procedure C1 with (4-methoxybenzyl)hydrazine hydrochloride (250 mg, 1.33 mmol) and purified using automated flash chromatography (5% to 25% ethyl acetate in hexanes) to afford 189 mg of **10a** as a white/orange solid (66% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, J = 8.2 Hz, 2H),

6.86 (d, *J* = 8.4 Hz, 2H), 5.37 (s, 1H), 5.08 (s, 2H), 3.80 – 3.74 (m, 3H), 3.30 (s, 2H), 2.19 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 147.4, 145.2, 129.0, 128.1, 114.2, 91.3, 55.2, 50.8, 13.9. LC/MS (*m/z*): 218.126 [$M+H^+$]; UPLC t_R 1.04 min.

1-(4-methoxybenzyl)-3-phenyl-1*H*-pyrazol-5-amine (10b). A solution of benzoylacetonitrile (350 mg, 2.41 mmol) and (4-methoxybenzyl)hydrazine hydrochloride (910 mg, 4.82 mmol) in ethanol (8 mL) was heated to reflux overnight. After cooling to room temperature, the solution was condensed *in vacuo*. The residue was dissolved in CH_2Cl_2 and saturated $NaHCO_3$ (aq.). The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts from each suspension were removed via gravity filtration and the combined mother liquors condensed *in vacuo*. The crude mixture was purified via automated flash chromatography (1% to 5% ethyl acetate in CH_2Cl_2) to afford 498 mg of **10b** (74% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.38 (dd, *J* = 8.4, 6.9 Hz, 2H), 7.29 (d, *J* = 7.4 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 2H), 6.90 – 6.80 (m, 2H), 5.90 (s, 1H), 5.24 (s, 2H), 3.78 (s, 3H), 3.44 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.3, 144.5, 134.5, 128.5, 127.2, 125.5, 88.9, 56.2, 32.3, 25.8, 25.3. LC/MS (*m/z*): 281.203 [$M+H^+$]; UPLC t_R 1.64 min.

1-(4-methoxybenzyl)-4-methyl-1*H*-pyrazol-5-amine (10c). 2-methyl-3-oxopropanenitrile was synthesized using General Procedure A from propionitrile (0.82 mL, 11.4 mmol) in 6.7% yield after automated flash chromatography (20% to 60% ethyl acetate in hexanes). 2-methyl-3-oxopropanenitrile (64 mg, 0.73 mmol) was subjected to General Procedure C2 to afford 68 mg of **10c** as an off-white solid (41% yield) after purification *via* automated flash chromatography (15% to 85% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (s, 1H), 7.16 – 7.07 (m, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.14 (s, 2H), 3.78 (s, 3H), 3.11 (s, 1H), 1.90 (s, 3H). ^{13}C NMR (101 MHz,

$CDCl_3$) δ 159.1, 141.3, 138.7, 128.9, 128.3, 114.2, 100.5, 55.3, 51.4, 7.9. LC/MS (*m/z*): 218.17 [$M+H^+$]; UPLC t_R 1.11 min.

4-isopropyl-1-(4-methoxybenzyl)-1*H*-pyrazol-5-amine (10d). 2-formyl-3-methylbutanenitrile was synthesized using General Procedure A from isovaleronitrile (1.20 mL, 11.4 mmol) in 24% yield after automated flash chromatography (10% to 30% acetone in hexanes and 5% to 20% ethyl acetate in CH_2Cl_2).

2-formyl-3-methylbutanenitrile (291 mg, 2.62 mmol) was subjected to General Procedure C2 to afford 260 mg of **10d** as a white/yellow solid (40% yield) after purification via automated flash chromatography (15% to 55% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (s, 1H), 7.12 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.14 (s, 2H), 3.78 (s, 3H), 3.13 (s, 2H), 2.62 (p, *J* = 6.9 Hz, 1H), 1.19 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 140.1, 135.8, 129.0, 128.3, 114.2, 112.4, 55.2, 51.2, 23.7, 23.3. Mp: 74-76 ºC. LC/MS (*m/z*): 245.916 [$M+H^+$]; UPLC t_R 1.30 min.

1-(4-Methoxybenzyl)-4-phenyl-1*H*-pyrazol-5-amine (10e). Synthesized using General Procedure C2 from 3-oxo-2-phenylpropanenitrile (250 mg, 1.72 mmol) to afford 223 mg of **10e** (46% yield) as an off-white solid after purification via automated flash chromatography (4% to 12% ethyl acetate in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.46 – 7.33 (m, 4H), 7.25 – 7.11 (m, 3H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.21 (s, 2H), 3.79 (s, 3H), 3.61 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 141.2, 137.3, 133.6, 129.0, 128.4, 128.3, 126.3, 125.6, 114.4, 106.9, 55.3, 51.6. Mp: 154-156 ºC. LC/MS (*m/z*): 281.159 [$M+H^+$]; UPLC t_R 1.68 min.

4-benzyl-1-(4-methoxybenzyl)-1*H*-pyrazol-5-amine (10f). 2-benzyl-3-oxopropanenitrile was synthesized using General Procedure A from 3-phenylpropionitrile (1.50 mL, 11.4 mmol) in 17% yield after automated flash chromatography (10% to 30% acetone in hexanes and 5% to 20% ethyl

acetate in CH_2Cl_2). 2-benzyl-3-oxopropanenitrile (300 mg, 1.88 mmol) was subjected to General Procedure C2 to afford 152 mg of **10f** (27% yield) as a white/brown solid after purification via automated flash chromatography (20% to 60% ethyl acetate in hexanes and 4% to 15% ethyl acetate in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.15 (m, 5H), 7.11 (d, *J* = 8.3 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 5.14 (s, 2H), 3.78 (s, 3H), 3.70 (s, 2H), 3.03 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 141.7, 140.3, 138.7, 128.8, 128.6, 128.3, 126.2, 114.3, 103.9, 55.3, 51.4, 29.7. LC/MS (*m/z*): 295.186 [M+H$^+$]; UPLC t_R 1.54 min.

3-ethyl-1-(4-methoxybenzyl)-1*H*-pyrazol-5-amine (10g). Synthesized using General Procedure C3 from pent-2-enenitrile (239 mg, 2.95 mmol) and *p*-anisaldehyde (0.353 mL, 2.90 mmol) to afford 131 mg of **10g** (19% yield) after purification via automated flash chromatography (10% to 30% acetone in hexanes and 5% to 20% ethyl acetate in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.40 (s, 1H), 5.11 (s, 2H), 3.78 (s, 3H), 3.36 (s, 2H), 2.57 (q, *J* = 7.6 Hz, 2H), 1.22 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 153.6, 144.9, 128.9, 128.1, 114.2, 89.9, 55.3, 50.9, 21.8, 14.0. LC/MS (*m/z*): 231.933 [M+H$^+$]; UPLC t_R 1.14 min.

3-isopropyl-1-(4-methoxybenzyl)-1*H*-pyrazol-5-amine (10h). Synthesized using General Procedure C4 from 4-methyl-3-oxopentanenitrile (100 mg, 0.900 mmol) to afford 278 mg of **10h** (>100% yield) as a yellow oil after purification *via* automated flash chromatography (7% to 20% ethyl acetate in CH_2Cl_2). Chromatographed product was impure and was carried forward to the next step without further purification.

3-(*tert*-butyl)-1-(4-methoxybenzyl)-1*H*-pyrazol-5-amine (10i). Synthesized using General Procedure C4 from 4,4-dimethyl-3-oxopentanenitrile (200 mg, 1.60 mmol) and (4-methoxybenzyl)hydrazine hydrochloride (301 mg, 1.60 mmol) to afford 342 mg of **10i** (83% yield)

as an orange solid after purification via automated flash chromatography (10% to 35% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 – 7.00 (m, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 5.44 (s, 1H), 5.12 (s, 2H), 3.78 (s, 3H), 3.25 (s, 2H), 1.29 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.6, 159.0, 144.5, 129.2, 127.9, 114.2, 88.3, 55.2, 50.9, 32.1, 30.5. Mp: 72-74 ºC. LC/MS (*m/z*): 261.222 [$M+H^+$]; UPLC t_R 1.30 min.

3-cyclopropyl-1-(4-methoxybenzyl)-1*H*-pyrazol-5-amine (10j). Synthesized using General Procedure C4 from 3-cyclopropyl-3-oxopropanenitrile (100 mg, 0.916 mmol) to afford 176 mg of **10j** (79% yield) as an off-white solid after purification via automated flash chromatography (7% to 20% ethyl acetate in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.20 (s, 1H), 5.10 (s, 2H), 3.78 (s, 3H), 3.35 (s, 2H), 1.93 – 1.81 (m, 1H), 0.96 – 0.82 (m, 2H), 0.75 – 0.59 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 154.0, 145.0, 128.9, 128.1, 114.2, 87.4, 55.2, 50.9, 9.5, 7.7. Mp: 113-114 ºC. LC/MS (*m/z*): 245.21 [$M+H^+$]; UPLC t_R 1.19 min.

3-cyclopentyl-1-(4-methoxybenzyl)-1*H*-pyrazol-5-amine (10k). 3-cyclopentylacrylonitrile was synthesized using General Procedure A from cyclopentanecarboxaldehyde (0.50 mL, 4.7 mmol) to afford 390 mg (68% yield) of a 1:1.4 mixture of *E*:*Z* isomers as a colorless oil after purification via automated flash chromatography (1% to 5% ethyl acetate in hexanes). 3-cyclopentylacrylonitrile (387 mg, 3.19 mmol) was subjected to General Procedure C3 with *p*-anisaldehyde (0.381 mL, 3.14 mmol) to afford 68.7 mg of **10k** (8.2% yield) after purification via automated flash chromatography (3% to 15% ethyl acetate in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.39 (s, 1H), 5.09 (s, 2H), 3.77 (s, 3H), 3.31 (s, 2H), 3.06 – 2.89 (m, 1H), 2.09 – 1.94 (m, 2H), 1.83 – 1.53 (m, 6H). ^{13}C NMR (101 MHz,

$CDCl_3$) δ 156.4, 144.9, 129.1, 128.2, 114.3, 88.9, 55.3, 51.0, 39.6, 33.5, 25.5. LC/MS (*m/z*): 272.426 [$M+H^+$]; UPLC t_R 1.08 min.

3-(furan-3-yl)-1-(4-methoxybenzyl)-1*H*-pyrazol-5-amine (10l). To a solution of potassium *tert*-butoxide (2 M in THF, 1.04 equiv) at 0 ºC was added diethyl cyanomethylphosphonate (1.1 equiv) dropwise. After stirring at 0 ºC for 1 h, 3-furancarboxaldehyde (0.50 mL, 5.8 mmol, 1 equiv) was added dropwise and the reaction was allowed the warm to room temperature overnight. The reaction mixture was poured into saturated NH_4Cl (aq.) and diluted with ethyl acetate. The layers were separated and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts from each suspension were removed via gravity filtration and volatile materials were condensed *in vacuo*. The crude mixture was purified via automated flash chromatography(4% to 12% ethyl acetate in CH_2Cl_2) to afford 3-(furan-3-yl)acrylonitrile 600 mg (88% yield) as an oil in a 3.3:1 mixture of *E*:*Z* isomers. 3-(furan-3-yl)acrylonitrile was subjected to General Procedure C3 using *p*-anisaldehyde (0.605 mL, 4.98 mmol) to afford 292 mg of **10l** (22% yield) as a beige solid after purification via automated flash chromatography (3% to 15% ethyl acetate in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.44 (t, *J* = 1.7 Hz, 1H), 7.18 (d, *J* = 8.1 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 6.76 (s, 1H), 5.69 (s, 1H), 5.23 (s, 1H), 3.79 (s, 3H), 3.47 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.1, 159.2, 145.3, 143.1, 139.0, 130.1, 128.5, 128.1, 120.3, 114.3, 108.8, 89.3, 55.3, 51.3. Mp: 140-142 ºC. LC/MS (*m/z*): 270.176 [$M+H^+$]; UPLC t_R 1.45 min.

3-methyl-1-(4-methylbenzyl)-1*H*-pyrazol-5-amine (10m). Synthesized using General Procedure C3 from crotononitrile (0.70 mL, 8.6 mmol) and *p*-tolualdehyde (1.0 mL, 8.5 mmol) to afford 610 mg of **10m** (36% yield) as a yellow solid after purification via automated flash chromatography (5% to 20% ethyl acetate in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, *J* =

7.9 Hz, 2H), 7.06 (d, *J* = 7.8 Hz, 2H), 5.37 (s, 1H), 5.11 (s, 2H), 3.29 (s, 2H), 2.32 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.4, 145.6, 137.1, 134.0, 129.4, 126.7, 90.9, 50.8, 21.1, 13.9. Mp: 102-104 ºC. LC/MS (*m/z*): 202.158 [$M+H^+$]; UPLC t_R 1.13 min.

3-methyl-1-(2-methylbenzyl)-1*H*-pyrazol-5-amine (10n). Synthesized using General Procedure C1 from (2-methylbenzyl)hydrazine hydrochloride (180 mg, 1.33 mmol) to afford 125 mg of **10n** (47% yield) as a white solid after purification via automated flash chromatography (5% to 20% ethyl acetate in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.08 (m, 3H), 6.74 (d, *J* = 7.3 Hz, 1H), 5.41 (s, 1H), 5.13 (s, 2H), 3.36 – 3.18 (m, 2H), 2.33 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.6, 145.6, 135.4, 135.0, 130.4, 127.5, 126.5, 126.1, 91.1, 74.1, 49.4, 19.1, 14.0. Mp: 84-87 ºC. LC/MS (*m/z*): 202.202 [$M+H^+$]; UPLC t_R 1.10 min.

1-(2-chlorobenzyl)-3-methyl-1*H*-pyrazol-5-amine (10o). Synthesized using General Procedure C1 from (2-chlorobenzyl)hydrazine dihydrochloride (300 mg, 1.31 mmol) to afford 245 mg of **10o** (85% yield) as a white solid after purification via automated flash chromatography (3% to 15% ethyl acetate in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.33 (m, 1H), 7.24 – 7.15 (m, 2H), 6.85 – 6.72 (m, 1H), 5.43 (s, 1H), 5.23 (s, 2H), 3.42 (s, 2H), 2.20 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.2, 145.6, 134.7, 131.9, 129.3, 128.7, 127.9, 127.3, 91.1, 48.3, 14.0. Mp: 97-99 ºC. LC/MS (*m/z*): 222.14 [$M+H^+$]; UPLC t_R 1.12 min.

1-methyl-3-phenyl-1*H*-pyrazol-5-amine (10p). Synthesized using General Procedure C5 from benzoylacetonitrile (250 mg, 1.72 mmol) to afford 221 mg of **10p** (74% yield) as a white solid after purification via automated flash chromatography (25% to 40% ethyl acetate in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.67 (m, 2H), 7.36 (td, *J* = 7.2, 6.4, 1.3 Hz, 2H), 7.31 – 7.21 (m, 1H), 5.83 (s, 1H), 3.68 (s, 3H), 3.56 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.7, 145.6, 133.8,

128.5, 127.5, 125.3, 88.5, 34.4. Mp: 127-128 ºC. LC/MS (*m/z*): 174.103 [M+H$^+$]; UPLC t_R 1.14 min.

1-(*tert*-butyl)-3-phenyl-1*H*-pyrazol-5-amine (10q). Synthesized using General Procedure C4 from benzoylacetonitrile (250 mg, 1.72 mmol) and *tert*-butylhydrazine hydrochloride (429 mg, 3.44 mmol) to afford 278 mg of **10q** (85% yield) as a yellow solid after purification via automated flash chromatography (7% to 20% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.62 (d, *J* = 7.5 Hz, 2H), 7.38 – 7.27 (m, 2H), 7.26 – 7.13 (m, 1H), 5.76 (d, *J* = 1.6 Hz, 1H), 4.95 (s, 2H), 1.55 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.5, 145.6, 134.4, 128.5, 127.1, 125.3, 91.3, 58.8, 29.4. Mp: 103-104 ºC. LC/MS (*m/z*): 217.2 [M+H$^+$]; UPLC t_R 1.63 min.

1-cyclohexyl-3-phenyl-1*H*-pyrazol-5-amine (10r). Synthesized using General Procedure C4 from benzoylacetonitrile (250 mg, 1.72 mmol) and cyclohexylhydrazine hydrochloride (519 mg, 3.44 mmol) to afford 326 mg of **10r** (79% yield) as a yellow solid after purification via automated flash chromatography (7% to 20% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.6 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.30 – 7.25 (m, 1H), 5.88 (s, 1H), 3.99 (s, 1H), 3.62 (s, 1H), 2.17 – 1.84 (m, 7H), 1.72 (d, *J* = 11.5 Hz, 1H), 1.48 – 1.11 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.3, 144.5, 134.5, 128.5, 127.2, 125.5, 88.9, 56.2, 32.3, 25.8, 25.3. Mp: 126-128 ºC. LC/MS (*m/z*): 243.225 [M+H$^+$]; UPLC t_R 1.68 min.

1-isobutyl-3-phenyl-1*H*-pyrazol-5-amine (10s). Synthesized using General Procedure C4 from benzoylacetonitrile (100 mg, 0.689 mmol) and isobutylhydrazine hydrochloride (172 mg, 1.38 mmol) to afford 102 mg of **10s** (69% yield) after purification via automated flash chromatography (15% to 40% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.70 (m, 2H), 7.41 – 7.32 (m, 2H), 7.32 – 7.23 (m, 1H), 5.87 (s, 1H), 3.80 (d, *J* = 7.5 Hz, 2H), 3.50 (s, 2H), 2.29 (dt, *J* = 13.8, 6.9 Hz, 1H), 0.97 (d, *J* = 6.7 Hz, 6H).

3-isopropyl-1-methyl-1*H*-pyrazol-5-amine (10t). Synthesized using General Procedure C5 from 4-methyl-3-oxopentanenitrile (200 mg, 1.80 mmol) to afford 205 mg of **10s** (82% yield) as a purple solid after purification via automated flash chromatography (2% to 6% methanol in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38 (s, 1H), 3.61 (s, 3H), 3.42 (s, 2H), 2.83 (p, *J* = 7.0 Hz, 1H), 1.21 (d, *J* = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.9, 144.7, 87.8, 33.9, 28.1, 22.9. Mp: 105-107 ºC. LC/MS (*m/z*): 140.358 [M+H$^+$].; UPLC t_R 0.37 min.

3-cyclohexyl-1-methyl-1*H*-pyrazol-5-amine (10u). Synthesized using General Procedure C5 from 3-cyclohexyl-3-oxopropanenitrile (253 mg, 1.67 mmol) to afford 161 mg of **10u** (54% yield) as a clear crystalline solid after recrystallization of the crude material from ethyl acetate in CH_2Cl_2 mixture. ^{1}H NMR (400 MHz, CD_3OD) δ 5.27 (s, 1H), 3.51 (s, 3H), 2.47 – 2.32 (m, 1H), 1.93 – 1.66 (m, 5H), 1.43 – 1.12 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.1, 144.6, 88.2, 38.0, 33.9, 33.3, 26.4, 26.1. Mp: 170-171 ºC. LC/MS (*m/z*): 181.205 [M+H$^+$]; UPLC t_R 1.16 min.

1-methyl-3-(o-tolyl)-1*H*-pyrazol-5-amine (10v). Synthesized using General Procedure C5 from 3-(2-methylphenyl)-3-oxopropanenitrile (256 mg, 1.61 mmol) to afford 186 mg of **10v** (62% yield) as a brown solid after purification via automated flash chromatography (15% to 40% ethyl acetate in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.45 (m, 1H), 7.23 – 7.17 (m, 3H), 5.73 (s, 1H), 3.74 (s, 3H), 3.51 (s, 2H), 2.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.1, 144.7, 135.9, 133.8, 130.6, 129.0, 127.4, 125.7, 91.8, 34.2, 21.1. Mp: 69-72 ºC. LC/MS (*m/z*): 189.145 [M+H$^+$]; UPLC t_R 1.14 min.

1-methyl-3-(*m*-tolyl)-1*H*-pyrazol-5-amine (10w). Synthesized using General Procedure C5 from 3-(3-methylphenyl)-3-oxopropanenitrile (278 mg, 1.75 mmol) to afford 258 mg of **10w** (79% yield) as a white solid after purification via automated flash chromatography (15% to 40% ethyl acetate in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.49 (d, *J* = 7.7 Hz, 1H), 7.31 –

7.20 (m, 1H), 7.14 – 7.03 (m, 1H), 5.86 (s, 1H), 3.73 (d, *J* = 0.8 Hz, 3H), 3.53 (s, 2H), 2.37 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.8, 145.7, 138.1, 133.7, 128.4, 128.2, 125.9, 122.5, 88.5, 34.3, 21.5. Mp: 103-104 ºC. LC/MS (*m/z*): 188.396 [M+H$^+$]; UPLC t_R 1.27 min.

3-(3-methoxyphenyl)-1-methyl-1*H*-pyrazol-5-amine (10x). Synthesized using General Procedure C5 from 3-(3-methoxyphenyl)-3-oxopropanenitrile (306 mg, 1.75 mmol) to afford 279 mg of **10x** (79% yield) as a yellow solid after purification via automated flash chromatography (15% to 45% ethyl acetate in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.24 (m, 3H), 6.86 – 6.80 (m, 1H), 5.86 (s, 1H), 3.85 (s, 3H), 3.73 (s, 3H), 3.53 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 149.5, 145.8, 135.3, 129.5, 117.9, 113.4, 110.3, 88.6, 74.1, 55.3, 34.3. Mp: 91-92 ºC. LC/MS (*m/z*): 205.158 [M+H$^+$]; UPLC t_R 1.21 min.

1-methyl-3-(3-(trifluoromethyl)phenyl)-1*H*-pyrazol-5-amine (10y). Synthesized using General Procedure C5 from 3-(trifluoromethyl)benzoylacetonitrile (373 mg, 1.75 mmol) to afford 334 mg of **10y** (79% yield) as a white/beige solid after purification via automated flash chromatography (15% to 40% ethyl acetate in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 2.2 Hz, 1H), 7.89 (d, *J* = 7.5 Hz, 1H), 7.48 (dt, *J* = 15.3, 7.7 Hz, 2H), 5.90 (s, 1H), 3.74 (s, 3H), 3.57 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.2, 146.0, 134.7, 130.8 (q, *J* = 31.9 Hz), 129.0, 128.4, 128.4, 124.3 (q, *J* = 272.4 Hz), 123.9 (q, *J* = 4.1 Hz), 121.9 (q, *J* = 4.1 Hz), 88.4, 74.1, 34.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.7. Mp: 87-88 ºC. LC/MS (*m/z*): 243.137 [M+H$^+$]; UPLC t_R 1.60 min.

1-methyl-3-(*p*-tolyl)-1*H*-pyrazol-5-amine. (10z). Synthesized using General Procedure C5 with 3-(4-methylphenyl)-3-oxopropanenitrile (278 mg, 1.75 mmol) to afford 238 mg of **10z** (73% yield) as a white solid after purification via automated flash chromatography (15% to 40% ethyl acetate in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.2 Hz, 2H), 7.22 – 7.09 (m, 2H), 5.84 (s,

1H), 3.72 (s, 3H), 3.52 (s, 2H), 2.35 (s, 3H). Mp: 139-140 ºC. LC/MS (*m/z*): 188.396 [M+H$^+$]; UPLC t_R 1.25 min.

3-(4-methoxyphenyl)-1-methyl-1*H*-pyrazol-5-amine (10aa). Synthesized using General Procedure C5 with 3-(4-methoxyphenyl)-3-oxopropanenitrile (306 mg, 1.75 mmol) to afford 238 mg of **10aa** (67% yield) as an off-white/brown crystalline solid after purification via automated flash chromatography (15% to 45% ethyl acetate in CH_2Cl_2). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.60 – 7.47 (m, 2H), 6.91 – 6.80 (m, 2H), 5.57 (s, 1H), 5.18 (s, 2H), 3.73 (s, 3H), 3.51 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 149.6, 145.5, 126.7, 126.5, 113.9, 88.1, 55.3, 34.3. Mp: 139-142 ºC. LC/MS (*m/z*): 204.364 [M+H$^+$]; UPLC t_R 1.15 min.

1-methyl-3-(4-(trifluoromethyl)phenyl)-1*H*-pyrazol-5-amine (10ab). Synthesized using General Procedure C5 from 4-(trifluoromethyl)benzoylacetonitrile (373 mg, 1.75 mmol) to afford 326 mg of **10ab** (77% yield) as a white solid after purification via automated flash chromatography (15% to 40% ethyl acetate in CH_2Cl_2). ^{1}H NMR (400 MHz, CD_3OD) δ 7.84 (d, *J* = 8.1 Hz, 2H), 7.64 (d, *J* = 8.1 Hz, 2H), 5.89 (s, 1H), 3.67 (s, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 149.8, 149.7, 138.8, 130.1 (q, *J* = 32.2 Hz), 126.6, 125.8 (q, *J* = 271.1 Hz), 126.4 (q, *J* = 3.9 Hz) 88.5, 34.4. ^{19}F NMR (376 MHz, CD_3OD) δ -64.0. Mp: 170-172 ºC. LC/MS (*m/z*): 243.137 [M+H$^+$]; UPLC t_R 1.61 min.

3-(4-(*tert*-butyl)phenyl)-1-methyl-1*H*-pyrazol-5-amine (10ac). Synthesized using General Procedure C5 from 3-(4-*tert*-butylphenyl)-3-oxopropanenitrile (253 mg, 1.26 mmol) to afford 222 mg of **10ac** (77% yield) as a white solid after purification via automated flash chromatography (15% to 40% ethyl acetate in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 5.85 (s, 1H), 3.72 (s, 3H), 1.33 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ

150.4, 149.7, 145.5, 131.1, 125.4, 125.0, 88.4, 74.1, 34.6, 34.3, 31.4. Mp: 143-145 ºC. LC/MS (*m/z*): 231.183 [M+H$^+$]; UPLC t_R 1.59 min.

1-methyl-3-(4-(trifluoromethoxy)phenyl)-1*H*-pyrazol-5-amine (10ad). Synthesized using General Procedure C5 from 4-(trifluoromethoxy)benzoyl acetonitrile (400 mg, 1.75 mmol) to afford 362 mg of **10ad** (81% yield) as a purple solid after purification via automated flash chromatography (15% to 40% ethyl acetate in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.7 Hz, 2H), 7.20 (d, *J* = 7.8 Hz, 2H), 5.85 (s, 1H), 3.73 (s, 3H), 3.55 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.4, 146.0, 132.7, 126.5, 120.5 (q, *J* = 256.8 Hz) 121.0, 88.3, 34.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.8. Mp: 97-99 ºC. LC/MS (*m/z*): 259.105 [M+H$^+$]; UPLC t_R 1.62 min.

2-Bromo-4,6-bis(methoxymethoxy)benzoic acid (12). To a suspension of 2-bromo-4,6-dimethoxybenzaldehyde (3.0 g, 12 mmol) in CH_2Cl_2 (40 mL) was added a freshly-prepared solution of boron tribromide (3.5 mL, 37 mmol) in CH_2Cl_2 (10 mL) via cannula over 15 minutes. The reaction was warmed to room temperature and stirred overnight. The reaction mixture was poured into 200 mL ice water and the resulting mixture was extracted 4 times with ethyl acetate. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were condensed *in vacuo*. The crude mixture was purified via automated flash chromatography (5% to 20% acetone in hexanes) to afford 1.8 g of 2-bromo-4,6-dihydroxybenzaldehyde as a white solid (81% yield). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 12.18 (s, 1H), 11.33 (s, 1H), 9.96 (s, 1H), 6.69 (d, *J* = 2.2 Hz, 1H), 6.29 (d, *J* = 2.2 Hz, 1H). ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 194.5, 165.6, 165.4, 128.2, 113.9, 111.5, 102.3.

To a solution of 2-bromo-4,6-dihydroxybenzaldehyde (1.5 g, 6.9 mmol) and *N*,*N*-diisopropylethylamine (4.8 mL, 28 mmol) in DMF (20 mL) at room temperature was chloromethyl methyl ether (2.1 mL, 28 mmol) dropwise. The reaction was stirred at room temperature overnight.

The reaction mixture was poured into water and the resulting mixture was extracted 4 times with Et_2O. The combined organic layers were washed twice with water and once with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were condensed *in vacuo*. The crude mixture was purified via automated flash chromatography (5% to 25% ethyl acetate in hexanes) to afford 2.1 g of 2-bromo-4,6-bis(methoxymethoxy)benzaldehyde as a white solid (93% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.34 (s, 1H), 7.01 (d, J = 2.3 Hz, 1H), 6.83 (d, J = 2.2 Hz, 1H), 5.26 (s, 2H), 5.20 (s, 2H), 3.51 (s, 3H), 3.48 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.1, 161.9, 161.2, 126.3, 118.3, 115.3, 102.9, 95.0, 94.3, 56.7, 56.5. mp: 60-64 ^{o}C.

To a solution of 2-bromo-4,6-bis(methoxymethoxy)benzaldehyde (350 mg, 1.15 mmol) in ^{t}BuOH (3.6 mL) and THF (1.3 mL) at room temperature was added a solution of sodium chlorite (80%, 260 mg, 2.29 mmol) and sodium phosphate monobasic monohydrate (791 mg, 5.74 mmol) in water (1.9 mL) dropwise. To the yellow solution was added 2-methyl-2-butene (90%, 1.08 mL, 9.18 mmol). After 25 minutes, the orange solution became faint yellow/colorless and diluted with ethyl acetate. The layers were separated, and the organic layer was washed three times with saturated NH_4Cl (aq.). The organic layer was dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were condensed *in vacuo*. The crude carboxylic acid **12** (364 mg, 99% crude yield) was used in the next step without further purification.

(2-bromo-4,6-bis(methoxymethoxy)phenyl)(isoindolin-2-yl)methanone (13). To a suspension of benzoic acid **12** (320 mg, 0.997 mmol) and isoindoline hydrochloride (156 mg, 1.49 mmol) in THF (2.9 mL) and CH_2Cl_2 (2.9 mL) at room temperature was added trimethylamine (0.420 mL, 2.99 mmol) followed by HATU (451 mg, 1.20 mmol). After stirring the suspension was stirred at

room temperature, the reaction mixture was diluted with CH_2Cl_2. The resulting mixture was washed with saturated $NaHCO_3$ (aq.), brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were condensed *in vacuo*. The crude mixture was purified via automated flash chromatography (20% to 50% ethyl acetate in hexanes) to afford 266 mg of **13** as a white solid (63% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 3H), 7.19 – 7.14 (m, 1H), 6.99 (d, *J* = 2.1 Hz, 1H), 6.85 (d, *J* = 2.1 Hz, 1H), 5.21 – 5.10 (m, 4H), 5.07 – 4.94 (m, 2H), 4.68 – 4.48 (m, 2H), 3.49 (s, 3H), 3.42 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6, 158.8, 154.8, 136.3, 136.2, 127.7, 127.5, 123.1, 123.0, 122.5, 119.8, 113.3, 103.1, 94.9, 94.4, 56.4, 56.2, 53.1, 51.7. Mp: 102-104 ˚C**.** LC/MS (*m/z*): 422.128 and 424.133 [M+H$^+$]; UPLC t_R 1.97 min.

Isoindolin-2-yl(2-((1-(4-methoxybenzyl)-3-methyl-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)phenyl)methanone (14a). Synthesized using General Procedure D1 from **13** (45 mg, 110 µmol) and **10a** (25 mg, 170 µmol). Following silica gel flash chromatography (12% to 40% acetone in hexanes), TMT (18 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 52 mg of **14a** (87% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.24 (m, 3H), 7.16 (d, *J* = 7.1 Hz, 1H), 7.06 (d, *J* = 8.6 Hz, 2H), 6.64 (d, *J* = 8.7 Hz, 2H), 6.44 – 6.35 (m, 2H), 6.22 (d, *J* = 2.1 Hz, 1H), 5.85 (s, 1H), 5.15 (q, *J* = 6.7 Hz, 2H), 5.07 (d, *J* = 1.3 Hz, 2H), 5.03 (s, 2H), 4.99 – 4.41 (m, 4H), 3.66 (s, 3H), 3.45 (s, 2H), 3.44 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 159.7, 158.9, 155.3, 147.5, 143.6, 139.3, 136.5, 136.1, 128.6, 128.6, 128.6, 127.7, 127.6, 122.9, 122.5, 113.8, 107.7, 98.5, 96.4, 95.3, 95.0, 94.2, 56.5, 56.2, 55.1, 52.9, 52.0, 51.2, 14.1. LC/MS (*m/z*): 559.299 [M+H$^+$]; UPLC t_R 1.66 min.

Isoindolin-2-yl(2-((1-(4-methoxybenzyl)-3-phenyl-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)phenyl)methanone (14b). Synthesized using General Procedure D1 from **13** (40 mg, 95 μmol) and **10b** (25 mg, 170 μmol). Following silica gel flash chromatography (5% to 30% acetone in hexanes), TMT (18 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 52.6 mg of **14b** (89% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.76 (m, 2H), 7.43 – 7.23 (m, 5H), 7.18 (d, *J* = 7.2 Hz, 1H), 7.16 – 7.09 (m, 2H), 6.70 – 6.61 (m, 2H), 6.48 (s, 1H), 6.42 (d, *J* = 2.1 Hz, 1H), 6.39 (s, 1H), 6.29 (d, *J* = 2.1 Hz, 1H), 5.16 (d, *J* = 7.2 Hz, 4H), 5.06 (s, 2H), 5.01 – 4.49 (m, 4H), 3.67 (s, 3H), 3.45 (s, 3H), 3.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 159.8, 159.0, 155.3, 150.0, 143.5, 140.0, 136.5, 136.1, 133.7, 128.7, 128.5, 128.3, 127.7, 127.6, 127.5, 125.3, 122.9, 122.5, 113.8, 107.8, 96.5, 96.3, 95.3, 95.2, 94.2, 56.5, 56.2, 55.1, 52.9, 52.0, 51.8. LC/MS (*m/z*): 621.311 [M+H$^+$]; UPLC t_R 2.03 min.

Isoindolin-2-yl(2-((1-(4-methoxybenzyl)-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)phenyl)methanone (14c). Synthesized using General Procedure D2 from **13** (45 mg, 110 μmol) and 1-[(4-methoxyphenyl)methyl]-1*H*-pyrazol-5-amine (24 mg, 170 μmol). Following silica gel flash chromatography (10% to 45% ethyl acetate in hexanes), TMT (22 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 66 mg of **14c** (108% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (ddd, *J* = 16.1, 7.2, 2.0 Hz, 3H), 7.17 (d, *J* = 7.3 Hz, 1H), 7.09 (d, *J* = 8.7 Hz, 2H), 6.66 (d, *J* = 8.7 Hz, 2H), 6.45 (s, 1H), 6.40 (d, *J* = 2.2 Hz, 1H), 6.19 (d, *J* = 2.1 Hz, 1H), 6.05 (d, *J* = 2.0 Hz, 1H), 5.16 (dd, *J* = 9.7, 5.0 Hz, 2H), 5.11 (s, 2H), 5.07 – 5.01 (m, 2H), 4.99 – 4.79 (m, 3H), 4.56 (d, *J* =

14.6 Hz, 1H), 3.68 (s, 3H), 3.48 – 3.39 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 159.8, 159.0, 155.4, 143.8, 138.9, 138.8, 136.6, 136.2, 128.9, 128.4, 128.3, 127.7, 127.6, 123.0, 122.5, 114.3, 113.9, 107.7, 99.2, 96.2, 95.3, 95.3, 94.3, 56.5, 56.2, 55.1, 53.0, 52.1, 51.6. LC/MS (*m/z*): 545.185 [M+H$^+$]; UPLC t_R 1.67 min.

Isoindolin-2-yl(2-((1-(4-methoxybenzyl)-4-methyl-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)phenyl)methanone (14d). Synthesized using General Procedure D2 from **13** 45 mg, 110 µmol) and **10c** (25 mg, 120 µmol). Following silica gel flash chromatography (10% to 40% acetone in hexanes), TMT (17 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 49 mg of **14d** (82% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 4H), 7.20 (d, *J* = 7.2 Hz, 1H), 7.07 – 7.01 (m, 2H), 6.66 – 6.54 (m, 2H), 6.36 (d, *J* = 2.1 Hz, 1H), 6.09 (s, 1H), 5.71 (d, *J* = 2.1 Hz, 1H), 5.16 (s, 2H), 5.10 – 4.81 (m, 7H), 4.61 (d, *J* = 14.7 Hz, 1H), 3.68 (s, 3H), 3.46 (s, 3H), 3.42 (s, 3H), 1.86 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 159.9, 158.9, 155.4, 144.6, 139.2, 136.6, 136.3, 135.5, 128.9, 128.9, 127.8, 127.7, 123.1, 122.6, 113.8, 111.5, 107.1, 95.5, 95.3, 94.5, 94.2, 56.6, 56.2, 55.1, 53.1, 52.1, 51.8, 8.3. LC/MS (*m/z*): 559.166 [M+H$^+$]; UPLC t_R 1.81 min.

Isoindolin-2-yl(2-((4-isopropyl-1-(4-methoxybenzyl)-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)phenyl)methanone (14e). Synthesized using General Procedure D2 from **13** (45 mg, 110 µmol) and **10d** (29 mg, 120 µmol). Following silica gel flash chromatography (10% to 30% acetone in hexanes), TMT (15 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 54 mg of **14e** (86% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.39 – 7.27 (m, 3H), 7.21 (d, *J* = 7.2 Hz, 1H),

7.02 (d, *J* = 8.1 Hz, 2H), 6.58 (d, *J* = 8.1 Hz, 2H), 6.35 (d, *J* = 2.2 Hz, 1H), 6.13 (s, 1H), 5.65 (d, *J* = 2.1 Hz, 1H), 5.17 (s, 2H), 5.11 – 4.83 (m, 7H), 4.62 (d, *J* = 14.7 Hz, 1H), 3.66 (s, 3H), 3.46 (s, 3H), 3.39 (s, 3H), 2.67 (p, *J* = 6.9 Hz, 1H), 1.13 (d, *J* = 6.9 Hz, 3H), 1.08 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 159.9, 158.9, 155.5, 145.4, 136.6, 136.6, 136.3, 133.9, 129.0, 128.9, 127.7, 127.7, 123.7, 123.1, 122.6, 113.7, 106.9, 95.5, 95.3, 94.5, 94.2, 56.6, 56.1, 55.1, 53.1, 52.1, 51.6, 23.7, 23.6, 23.3. LC/MS (*m/z*): 587.262 [M+H$^+$]; UPLC t_R 1.96 min.

Isoindolin-2-yl(2-((1-(4-methoxybenzyl)-4-phenyl-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)phenyl)methanone (14f). Synthesized using General Procedure D1 from **13** (40 mg, 95 µmol) and **10e** (29 mg, 100 µmol) for 4 h. Following silica gel flash chromatography (5% to 35% acetone in hexanes), TMT (13 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 25 mg of **14f** (43% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.41 (dt, *J* = 6.2, 1.3 Hz, 2H), 7.38 – 7.26 (m, 3H), 7.22 – 7.02 (m, 6H), 6.65 (d, *J* = 8.3 Hz, 2H), 6.47 (s, 1H), 6.36 (d, *J* = 2.1 Hz, 1H), 5.72 (d, *J* = 2.1 Hz, 1H), 5.24 – 4.94 (m, 6H), 4.93 – 4.81 (m, 3H), 4.58 (d, *J* = 14.7 Hz, 1H), 3.68 (s, 3H), 3.47 (s, 3H), 3.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 159.9, 159.1, 155.5, 144.3, 137.7, 136.6, 136.2, 134.3, 132.1, 129.2, 128.5, 128.4, 127.8, 127.7, 126.3, 126.1, 123.1, 122.5, 116.7, 113.9, 107.3, 95.8, 95.4, 94.8, 94.2, 56.6, 56.2, 55.2, 53.0, 52.2, 51.9. LC/MS (*m/z*): 621.311 [M+H$^+$]; UPLC t_R 1.92 min

(2-((4-Benzyl-1-(4-methoxybenzyl)-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)phenyl)(isoindolin-2-yl)methanone (14g). Synthesized using General Procedure D1 from **13** (40 mg, 95 µmol) and **10f** (31 mg, 100 µmol) for 4 h. Following silica gel flash chromatography (10% to 35% acetone in hexanes), TMT (17 mg) was added to the isolated

residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 45 mg of **14g** (75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 4H), 7.23 – 6.96 (m, 7H), 6.68 – 6.56 (m, 2H), 6.34 (d, *J* = 2.1 Hz, 1H), 6.19 (s, 1H), 5.65 (d, *J* = 2.1 Hz, 1H), 5.16 (d, *J* = 2.4 Hz, 2H), 5.11 – 4.82 (m, 7H), 4.53 (d, *J* = 14.7 Hz, 1H), 3.69 (s, 3H), 3.61 (d, *J* = 3.5 Hz, 2H), 3.46 (s, 3H), 3.41 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 159.8, 159.0, 155.4, 144.8, 140.2, 139.0, 136.6, 136.3, 135.4, 129.1, 128.7, 128.4, 128.2, 127.7, 127.6, 125.9, 123.0, 122.6, 115.6, 113.8, 106.9, 95.4, 95.3, 94.7, 94.1, 56.6, 56.2, 55.2, 53.0, 52.1, 51.8, 29.8. LC/MS (*m/z*): 635.292 [M+H$^+$]; UPLC t_R 1.96 min.

(2-((3-(*tert*-Butyl)-1-(4-methoxybenzyl)-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)phenyl)(isoindolin-2-yl)methanone (14h) Synthesized using General Procedure D1 from **13** (40 mg, 95 µmol) and **10i** (27 mg, 100 µmol) for 4 h. Following silica gel flash chromatography (5% to 25% acetone in hexanes), TMT (18 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 45 mg of **14h** (79% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 3H), 7.16 (d, *J* = 7.2 Hz, 1H), 7.03 (d, *J* = 8.5 Hz, 2H), 6.64 (d, *J* = 8.6 Hz, 2H), 6.38 (d, *J* = 2.1 Hz, 1H), 6.33 – 6.23 (m, 2H), 5.92 (s, 1H), 5.14 (q, *J* = 6.5 Hz, 2H), 5.08 (s, 2H), 5.05 (s, 2H), 4.91 (d, *J* = 14.8 Hz, 1H), 4.84 (s, 2H), 4.51 (d, *J* = 14.6 Hz, 1H), 3.66 (s, 3H), 3.45 (s, 3H), 3.44 (s, 3H), 1.30 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 160.8, 159.8, 158.8, 155.3, 143.7, 138.8, 136.6, 136.2, 128.9, 128.4, 127.7, 127.6, 123.0, 122.5, 113.8, 107.8, 96.5, 95.3, 95.2, 95.1, 94.4, 56.5, 56.2, 55.1, 53.0, 52.0, 51.4, 32.3, 30.5. LC/MS (*m/z*): 601.331 [M+H$^+$]; UPLC t_R 2.04 min.

(2,4-Bis(methoxymethoxy)-6-((1-methyl-1*H*-pyrazol-5-yl)amino)phenyl)(isoindolin-2-yl)methanone (14i). Synthesized using General Procedure D2 from **13** (45 mg, 110 µmol) and 1-methyl-1*H*-pyrazol-5-amine (11 mg, 120 µmol). Following silica gel flash chromatography (30% to 70% ethyl acetate in CH_2Cl_2), TMT (19 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 38 mg of **14i** (82% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 2.0 Hz, 1H), 7.38 – 7.27 (m, 3H), 7.19 (d, *J* = 6.9 Hz, 1H), 6.64 (s, 1H), 6.43 (d, *J* = 2.2 Hz, 1H), 6.08 (d, *J* = 2.1 Hz, 1H), 6.01 (d, *J* = 2.0 Hz, 1H), 5.21 – 5.10 (m, 3H), 5.08 (s, 2H), 5.05 – 4.84 (m, 2H), 4.63 (d, *J* = 14.7 Hz, 1H), 3.68 (s, 3H), 3.45 (s, 3H), 3.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 159.9, 155.5, 144.4, 139.3, 138.6, 136.6, 136.1, 127.8, 127.6, 123.1, 122.5, 107.6, 99.1, 96.2, 95.4, 95.2, 94.2, 56.6, 56.3, 53.1, 52.2, 35.0. LC/MS (*m/z*): 439.33 [M+H$^+$]; UPLC t_R 1.48 min.

Isoindolin-2-yl(2-((1-(4-isopropylbenzyl)-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)phenyl)methanone (14j). Synthesized using General Procedure D2 from **13** (40 mg, 95 µmol) and 1-([4-(propan-2-yl)phenyl]methyl)-1*H*-pyrazol-5-amine (22 mg, 100 µmol). Following silica gel flash chromatography (10% to 30% acetone in hexanes), TMT (15 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 42 mg of **14j** (80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 2.0 Hz, 1H), 7.35 – 7.28 (m, 3H), 7.18 (d, *J* = 7.3 Hz, 1H), 7.06 (d, *J* = 8.1 Hz, 2H), 6.98 (d, *J* = 8.2 Hz, 2H), 6.43 (s, 1H), 6.40 (d, *J* = 2.1 Hz, 1H), 6.20 (d, *J* = 2.1 Hz, 1H), 6.06 (d, *J* = 2.0 Hz, 1H), 5.23 – 5.07 (m, 5H), 5.07 – 5.00 (m, 2H), 5.00 – 4.76 (m, 3H), 4.57 (d, *J* = 14.7 Hz, 1H), 3.45 (s, 6H), 2.76 (p, *J* = 6.9 Hz, 1H), 1.14 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$)

δ 166.9, 159.8, 155.4, 148.2, 143.9, 139.0, 138.9, 136.6, 136.2, 133.6, 127.7, 127.6, 127.5, 127.5, 126.7, 123.0, 122.5, 107.7, 99.4, 96.2, 95.3, 95.2, 94.3, 56.6, 56.3, 53.0, 52.1, 51.9, 33.7, 23.9, 23.8. LC/MS (*m/z*): 557.27 [M+H$^+$]; UPLC t_R 1.93 min

(2,4-Bis(methoxymethoxy)-6-((3-methyl-1-(4-methylbenzyl)-1*H*-pyrazol-5-yl)amino)phenyl)(isoindolin-2-yl)methanone (14k). Synthesized using General Procedure D1 from **13** (45 mg, 110 μmol) and **10m** (24 mg, 120 μmol) and heated for 3 h. Following silica gel flash chromatography (10% to 35% acetone in hexanes), TMT (15 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 40 mg of **14k** (70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 3H), 7.16 (d, *J* = 7.2 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 2H), 6.88 (d, *J* = 7.8 Hz, 2H), 6.39 (d, *J* = 2.1 Hz, 1H), 6.32 (s, 1H), 6.24 (d, *J* = 2.1 Hz, 1H), 5.86 (s, 1H), 5.14 (q, *J* = 6.5 Hz, 2H), 5.07 (d, *J* = 1.3 Hz, 2H), 5.06 (s, 2H), 4.90 (d, *J* = 14.7 Hz, 1H), 4.83 (s, 2H), 4.48 (d, *J* = 14.6 Hz, 1H), 3.46 (s, 3H), 3.43 (s, 3H), 2.24 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 159.8, 155.3, 147.6, 143.7, 139.4, 137.0, 136.6, 136.2, 133.6, 129.2, 127.7, 127.6, 127.0, 122.9, 122.5, 107.8, 98.6, 96.4, 95.3, 95.1, 94.3, 56.5, 56.3, 52.9, 52.0, 51.7, 21.0, 14.2. LC/MS (*m/z*): 543.332 [M+H$^+$]; UPLC t_R 1.76 min.

(2-((1-(2-Chlorobenzyl)-3-methyl-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)phenyl)(isoindolin-2-yl)methanone (14l). Inside a nitrogen glovebox were combined aryl bromide **13** (45 mg, 110 μmol), amine **10o** (26 mg, 170 μmol), tris(dibenzylideneacetone)dipalladium (3.9 mg, 4.3 μmol), Xantphos (6.2 mg, 11 μmol), sodium phenoxide (19 mg, 160 μmol). Dioxane (0.8 mL) was added to the mixture and the reaction vessel was capped and removed from the glovebox. The reaction vessel was heated at 60 ºC for 90 min,

90 ºC for 90 min, and then 120 ºC for 2.5 h. After cooling to room temperature, the reaction was diluted with ethyl acetate. The resulting mixture was washed 3 times with saturated Na_2CO_3 (aq.), brine, then dried with anhydrous Na_2SO_4. The salts from each suspension were removed via gravity filtration and volatile materials were condensed *in vacuo*. Following silica gel flash chromatography (10% to 30% acetone in hexanes), TMT (20 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 47 mg of **14l** (78% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 3H), 7.16 (s, 1H), 7.09 – 6.93 (m, 3H), 6.72 – 6.62 (m, 1H), 6.39 (d, *J* = 2.1 Hz, 1H), 6.37 (s, 1H), 6.20 (d, *J* = 2.1 Hz, 1H), 5.93 (s, 1H), 5.28 – 5.01 (m, 6H), 4.86 (d, *J* = 14.5 Hz, 1H), 4.77 (s, 2H), 4.38 (d, *J* = 14.6 Hz, 1H), 3.46 (s, 3H), 3.42 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 159.8, 155.4, 148.4, 143.8, 140.1, 136.6, 136.1, 134.6, 131.8, 129.1, 128.4, 127.7, 127.6, 127.5, 127.0, 122.9, 122.6, 107.9, 99.4, 96.5, 95.3, 95.2, 94.3, 56.5, 56.3, 52.9, 52.0, 49.1, 14.3. LC/MS (*m/z*): 563.224 [$M+H^+$]; UPLC t_R 1.73 min.

(2,4-Bis(methoxymethoxy)-6-((3-methyl-1-(2-methylbenzyl)-1*H*-pyrazol-5-yl)amino)phenyl)(isoindolin-2-yl)methanone (14m). Inside a nitrogen glovebox were combined aryl bromide **13** (45 mg, 110 µmol), amine **10n** (28 mg, 140 µmol), ^{t}BuXPhos Palladacycle Gen. 1 (7.3 mg, 11 µmol), ^{t}BuXphos (4.5 mg, 11 µmol), sodium *tert*-butoxide (22 mg, 220 µmol). *tert*-Butanol (0.8 mL) was added to the mixture and the reaction vessel was capped and removed from the glovebox. After stirring at room temperature for 2.5 h, the reaction was quenched with saturated NH_4Cl (aq.). The resulting mixture was extracted four times with ethyl acetate. The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. The salts from each suspension were removed via gravity filtration and volatile materials were condensed *in vacuo*.

Following silica gel flash chromatography (40% to 80% ethyl acetate in hexanes), TMT (21 mg) was added to the isolated residue; the mixture was suspended in toluene (1.5 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 25 mg of **14m** (52% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 3H), 7.21 – 7.09 (m, 1H), 7.03 – 6.88 (m, 3H), 6.65 (d, *J* = 7.6 Hz, 1H), 6.39 (d, *J* = 2.1 Hz, 1H), 6.33 – 6.26 (m, 2H), 5.91 (s, 1H), 5.16 – 5.03 (m, 7H), 4.85 (d, *J* = 14.7 Hz, 1H), 4.73 (d, *J* = 9.2 Hz, 2H), 4.38 (d, *J* = 14.7 Hz, 1H), 3.46 (s, 3H), 3.42 (s, 3H), 2.25 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 159.7, 155.3, 147.8, 143.6, 140.1, 136.5, 136.2, 135.1, 134.8, 130.2, 127.7, 127.5, 127.2, 126.4, 126.2, 123.0, 122.5, 107.9, 98.3, 96.5, 95.3, 95.2, 94.3, 56.5, 56.3, 52.8, 51.9, 49.6, 19.0, 14.3. LC/MS (*m/z*): 543.288 [M+H$^+$]; UPLC t_R 1.75 min.

(2,4-Bis(methoxymethoxy)-6-((1-methyl-3-phenyl-1*H*-pyrazol-5-yl)amino)phenyl)(isoindolin-2-yl)methanone (14n). Synthesized using General Procedure D2 from **13** (60 mg, 140 µmol) and **10p** (27 mg, 160 µmol) and purified via automated flash chromatography (30% to 80% ethyl acetate in CH_2Cl_2). To QuadraPure™ MPA resin (1.5 mmol/g loading, 68 mg) soaked in CH_2Cl_2 (1 mL) for 90 min was transferred the purified product using CH_2Cl_2 (3 mL) and shaken overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 65 mg of **14n** (89% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.70 (m, 2H), 7.41 – 7.27 (m, 6H), 7.20 (d, *J* = 7.1 Hz, 1H), 6.72 (s, 1H), 6.45 (d, *J* = 2.1 Hz, 1H), 6.34 (s, 1H), 6.18 (d, *J* = 2.1 Hz, 1H), 5.24 – 5.11 (m, 3H), 5.09 (s, 2H), 5.06 – 4.86 (m, 2H), 4.65 (d, *J* = 14.7 Hz, 1H), 3.73 (s, 3H), 3.46 (d, *J* = 0.8 Hz, 3H), 3.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 160.0, 155.6, 150.0, 144.3, 140.5, 136.6, 136.2, 133.6, 128.6, 128.4, 127.8, 127.6, 127.6, 127.4, 125.2, 123.1, 122.5, 107.7, 96.5, 96.4, 95.4, 95.2, 94.3, 56.6, 56.3, 53.1, 52.3, 35.2. LC/MS (*m/z*): 516.34 [M+H$^+$]; UPLC t_R 1.88 min.

(2-Bromo-4,6-bis(methoxymethoxy)phenyl)(5-((1-methylpiperidin-4-yl)amino)isoindolin-2-yl)methanone (15a). Inside a glovebox under a nitrogen atmosphere were combined, *tert*-butyl 5-bromoisoindoline-2-carboxylate (85 mg, 0.29 mmol), tris(dibenzylideneacetone)dipalladium (13 mg, 0.014 mmol), Johnphos (8.5 mg, 0.029 mmol) and sodium *tert*-butoxide (38 mg, 0.40 mmol) and suspended in toluene (4 mL). 4-Amino-1-methylpiperidine (39 mg mL, 0.34 mmol) was added to the mixture and the reaction vessel was sealed and removed from the glovebox. The reaction mixture was irradiated at 120 ºC for 30 minutes in a microwave reactor. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate, washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were condensed *in vacuo*. The crude mixture was purified via silica gel flash chromatography (95:5:1 CH_2Cl_2:methanol:concentrated NH_4OH (aq.)) to afford 47 mg of *tert*-butyl 5-((1-methylpiperidin-4-yl)amino)isoindoline-2-carboxylate (50% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (dd, *J* = 20.7, 8.1 Hz, 1H), 6.63 – 6.40 (m, 2H), 4.65 – 4.42 (m, 4H), 3.33 – 3.17 (m, 1H), 2.82 (d, *J* = 11.3 Hz, 2H), 2.31 (s, 3H), 2.22 – 2.02 (m, 4H), 1.50 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.5, 154.4, 146.6, 146.6, 138.4, 138.0, 125.6, 125.3, 123.3, 123.0, 113.1, 106.6, 106.5, 79.2, 54.4, 52.3, 52.0, 51.6, 51.3, 46.1, 32.3, 28.4. LC/MS (*m/z*): 332.193 [$M+H^+$]; UPLC t_R 1.19 min

To a solution of *tert*-butyl 5-((1-methylpiperidin-4-yl)amino)isoindoline-2-carboxylate (47 mg, 0.14 mmol) from above in CH_2Cl_2 (0.28 mL) at room temperature was added HCl (4 M in dioxane, 0.45 mL, 1.8 mmol) and stirred overnight. The reaction was then triturated with ether. The suspension was filter and the resulting solid washed with ether to afford 29 mg of N-(1-methylpiperidin-4-yl)isoindolin-5-amine dihydrogenchloride as a viscous gum (66% based on crude mass).

Benzoic acid **12** (68 mg, 0.21 mmol), *N*-(1-methylpiperidin-4-yl)isoindolin-5-amine dihydrogenchloride salt (64 mg, 0.21 mmol) from above, trimethylamine (0.12 mL, 0.84 mmol) and HATU (95 mg, 0.25 mmol) were reacted using the same procedure for the synthesis of amide **13** to afford 57 mg of **15a** (51% yield) after purification via automated flash chromatography (1% to 10% methanol in CH_2Cl_2). ^{1}H NMR (400 MHz, CD_3OD) δ 7.15 – 6.87 (m, 3H), 6.71 – 6.38 (m, 2H), 5.32 – 5.13 (m, 4H), 4.89 (s, 3H), 4.86 – 4.74 (m, 2H), 4.45 (d, *J* = 14.7 Hz, 2H), 3.48 (d, *J* = 1.2 Hz, 2H), 3.42 – 3.38 (m, 3H), 3.35 (s, 1H), 3.02 (t, *J* = 13.6 Hz, 2H), 2.44 (d, *J* = 11.0 Hz, 4H), 2.17 – 1.97 (m, 2H), 1.69 – 1.42 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 166.7, 166.7, 159.3, 159.3, 155.0, 147.8, 147.6, 136.7, 136.5, 123.5, 123.4, 123.1, 122.9, 122.2, 122.1, 119.2, 113.9, 113.7, 112.9, 112.8, 106.4, 106.3, 102.8, 102.8, 94.8, 94.7, 94.3, 55.4, 55.2, 53.7, 53.3, 52.7, 51.6, 51.0, 44.1, 30.7. LC/MS (*m/z*): 534.114 and 536.099 [$M+H^+$]; UPLC t_R 1.31 min.

(2-Bromo-4,6-bis(methoxymethoxy)phenyl)(5-(2-(dimethylamino)ethoxy)isoindolin-2-yl)methanone (15b). A suspension of *tert*-butyl 5-hydroxyisoindoline-2-carboxylate (250 mg, 1.06 mmol), 2-chloro-*N*,*N*-dimethylethylamine hydrochloride (367 mg, 2.55 mmol), and cesium carbonate (1.73 g, 5.31 mmol) in MeCN (4 mL) was heated overnight at 90 ºC. The mixture was cooled to room temperature and diluted with 15% methanol in CH_2Cl_2. The resulting mixture was washed twice with water and once with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were condensed *in vacuo*. The crude mixture was purified via automated flash chromatography (5% to 10% methanol in CH_2Cl_2) to afford 165 mg of *tert*-butyl 5-(2-(dimethylamino)ethoxy)isoindoline-2-carboxylate (51% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (dd, *J* = 20.9, 8.3 Hz, 1H), 6.88 – 6.72 (m, 2H), 4.60 (t, *J* = 15.2 Hz, 4H), 4.05 (td, *J* = 5.7, 2.0 Hz, 2H), 2.74 (t, *J* = 5.7 Hz, 2H), 2.35 (s, 6H), 1.51 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4, 158.4, 154.3, 154.3, 138.5, 138.1, 129.2, 128.8, 123.2, 123.0, 114.3,

114.0, 108.3, 108.2, 79.4, 66.0, 58.1, 52.2, 52.0, 51.6, 51.2, 45.7, 28.4. LC/MS (*m/z*): 307.139 [M+H$^+$]; UPLC t_R 1.18 min.

To a solution of *tert*-butyl 5-(2-(dimethylamino)ethoxy)isoindoline-2-carboxylate from above (135 mg, 0.441 mmol) in CH_2Cl_2 (0.88 mL) at room temperature was added HCl (4 M in dioxane, 1.4 mL, 5.6 mmol) and stirred overnight. The reaction was then triturated with ether. The suspension was filter and the resulting solid washed with ether to afford 103 mg 2-(Isoindolin-5-yloxy)-N,N-dimethylethan-1-amine dihydrochloride as a solid (84% based on crude mass).

Benzoic acid **12** (38 mg, 0.12 mmol), 2-(isoindolin-5-yloxy)-*N*,*N*-dimethylethan-1-amine dihydrochloride salt from above (33 mg, 0.12 mmol), trimethylamine (0.066 mL, 0.47 mmol) and HATU (54 mg, 0.14 mmol) were reacted using the same procedure for the synthesis of amide **13** to afford 60 mg of **15b** (75% yield) after purification via automated flash chromatography (1% to 8% methanol in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (dd, *J* = 75.4, 8.4 Hz, 1H), 6.98 (t, *J* = 2.0 Hz, 1H), 6.94 – 6.66 (m, 3H), 5.25 – 5.05 (m, 4H), 4.92 (dd, *J* = 7.9, 3.4 Hz, 2H), 4.50 (q, *J* = 13.3 Hz, 2H), 4.09 (dt, *J* = 20.4, 5.5 Hz, 2H), 3.57 – 3.45 (m, 3H), 3.41 (s, 3H), 3.18 (q, *J* = 7.3 Hz, 4H), 2.87 (dt, *J* = 16.3, 5.6 Hz, 2H), 2.46 (s, 3H), 2.42 (s, 3H), 1.34 (t, *J* = 7.3 Hz, 4H). LC/MS (*m/z*): 509.062 and 511.047 [M+H$^+$]; UPLC t_R 1.29 min.

(2-Bromo-4,6-bis(methoxymethoxy)phenyl)(5-(4-methylpiperazin-1-yl)isoindolin-2-yl)methanone (15c). Procedure adapted from [66]. Inside a glovebox under a nitrogen atmosphere were combined *tert*-butyl 5-bromoisoindoline-2-carboxylate (300 mg, 1.01 mmol), tris(dibenzylideneacetone)dipalladium (46.1 mg, 0.0503 mmol), Xantphos (29.1 mg, 0.0503 mmol) and sodium *tert*-butoxide (145 mg, 1.51 mmol) and suspended in toluene (3 mL). 1-Methylpiperazine (0.134 mL, 1.21 mmol) was added to the mixture and the reaction vessel was sealed and removed from the glovebox. After heating at 100 ºC overnight, the reaction mixture was cooled to room temperature and diluted with ethyl acetate. The organic mixture was washed with brine and dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and

volatile materials were condensed *in vacuo*. The crude mixture was purified via automated flash chromatography (1% to 7% methanol in CH_2Cl_2) to afford 259 mg of *tert*-butyl 5-(4-methylpiperazin-1-yl)isoindoline-2-carboxylate (81% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (dd, *J* = 20.8, 8.3 Hz, 1H), 6.92 – 6.75 (m, 2H), 4.70 – 4.46 (m, 4H), 3.19 (d, *J* = 5.1 Hz, 4H), 2.58 (t, *J* = 5.0 Hz, 4H), 2.35 (s, 3H), 1.51 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3, 154.3, 151.0, 138.1, 137.7, 128.2, 127.9, 122.9, 122.7, 115.8, 115.6, 110.0, 109.8, 79.2, 54.8, 52.3, 52.0, 51.6, 51.3, 49.4, 49.3, 45.9, 28.3. LC/MS (*m/z*): 318.167 [M+H$^+$]; UPLC t_R 1.04 min.

To a solution of *tert*-butyl 5-(4-methylpiperazin-1-yl)isoindoline-2-carboxylate from above (259 mg, 0.816 mmol) in CH_2Cl_2 (1.6 mL) at room temperature was added HCl (4 M in dioxane, 2.59 mL, 10.4 mmol) and stirred overnight. The reaction was then triturated with ether. The suspension was filter and the resulting solid washed with ether to afford 262 mg of crude 5-(4-methylpiperazin-1-yl)isoindoline dihydrochloride salt (110% crude yield).

Benzoic acid **12** (133 mg, 0.374 mmol), 5-(4-methylpiperazin-1-yl)isoindoline dihydrochloride salt from above (106 mg, 0.365 mmol), trimethylamine (0.208 mL, 1.49 mmol) and HATU (169 mg, 0.448 mmol) were reacted using the same procedure for the synthesis of amide **13** to afford 132 mg of **15c** (68% yield) after purification via automated flash chromatography (1% to 8% methanol in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.6 Hz, 1H), 7.04 (d, *J* = 8.3 Hz, 1H), 6.98 (dd, *J* = 2.1, 1.5 Hz, 1H), 6.96 – 6.82 (m, 3H), 5.30 (s, 1H), 5.23 – 5.07 (m, 4H), 4.93 (d, *J* = 13.0 Hz, 2H), 4.61 – 4.39 (m, 2H), 3.49 (d, *J* = 0.9 Hz, 3H), 3.41 (d, *J* = 2.0 Hz, 3H), 3.27 – 3.12 (m, 5H), 2.64 (dt, *J* = 9.5, 4.7 Hz, 4H), 2.40 (d, *J* = 7.0 Hz, 3H), 1.39 (t, *J* = 7.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7, 165.6, 158.8, 154.8, 151.3, 151.2, 137.2, 137.2, 127.1, 127.1, 123.5, 123.0, 122.7, 119.7, 116.5, 116.0, 113.2, 113.2, 110.4, 109.8, 103.1, 103.0, 94.9, 94.8, 94.4, 77.2, 56.4, 56.2, 54.8, 53.4, 52.7, 51.9, 51.2, 49.1, 49.1, 47.0, 47.0, 45.7, 8.7. LC/MS (*m/z*): 520.089 and 522.073 [M+H$^+$]; UPLC t_R 1.25 min.

***N*-benzyl-2-bromo-4,6-bis(methoxymethoxy)-*N*-methylbenzamide (15d).** The product was synthesized using the same procedure for the synthesis of amide **13**. The reaction with benzoic acid **12** (0.68 g, 2.1 mmol), N-benzylmethylamine (0.41 mL, 3.2 mmol), trimethylamine (0.59 mL, 4.2 mmol) and HATU (0.96 g, 2.5 mmol) to afford 0.55 g of **15d** as a colorless oil (61% yield) after purification via automated flash chromatography (20% to 40% ethyl acetate in hexanes and 5% to 10% ethyl acetate in CH_2Cl_2). Isomer 1: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.5 Hz, 1H), 7.32 (dt, *J* = 20.9, 8.2 Hz, 4H), 6.96 (d, *J* = 2.1 Hz, 1H), 6.79 (d, *J* = 2.1 Hz, 1H), 5.29 – 5.08 (m, 6H), 5.03 – 4.59 (m, 2H), 3.47 (s, 3H), 3.43 (s, 3H), 2.75 (s, 3H). Isomer 2: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.5 Hz, 1H), 7.32 (dt, *J* = 20.9, 8.2 Hz, 4H), 6.96 (d, *J* = 2.1 Hz, 1H), 6.82 (d, *J* = 2.2 Hz, 1H), 5.29 – 5.08 (m, 5H), 4.52 – 4.25 (m, 2H), 3.45 (s, 3H), 3.43 (s, 3H), 3.01 (s, 3H). LC/MS (*m/z*): 424.069 and 426.010 [$M+H^+$]; UPLC t_R 1.69 min.

(2-((1-(4-Methoxybenzyl)-3-methyl-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)phenyl)(5-((1-methylpiperidin-4-yl)amino)isoindolin-2-yl)methanone (16a). Synthesized using General Procedure D2 from **15a** (56.9 mg, 106 µmol) and **10a** (25.4 mg, 117 µmol) in dioxane. The crude mixture was purified via automated flash chromatography (2% to 10% methanol in CH_2Cl_2). To QuadraPure™ MPA resin (1.5 mmol/g loading, 45 mg) soaked in CH_2Cl_2 (2 mL) for 30 min was transferred the purified product using CH_2Cl_2 (3 mL) and shaken overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 41.8 mg of **16a** (59% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 – 6.91 (m, 3H), 6.66 (dd, *J* = 8.6, 1.5 Hz, 2H), 6.53 (q, *J* = 8.9, 8.2 Hz, 2H), 6.41 – 6.16 (m, 3H), 5.84 (s, 1H), 5.23 – 5.09 (m, 2H), 5.09 – 4.97 (m, 4H), 4.88 – 4.67 (m, 3H), 4.43 (t, *J* = 13.1 Hz, 1H), 3.68 (d, *J* = 1.5 Hz, 3H), 3.51 – 3.39 (m, 6H), 3.26 (d, *J* = 28.2 Hz, 1H), 2.83 (d, *J* = 13.5 Hz, 2H), 2.30 (d, *J* = 8.8 Hz, 4H), 2.24 (s, 3H), 2.18 – 1.95 (m, 4H), 1.49 (d, *J* = 11.8 Hz, 1H). ^{13}C

NMR (101 MHz, $CDCl_3$) δ 166.8, 166.7, 159.7, 158.9, 155.3, 147.6, 147.6, 147.1, 146.9, 143.7, 139.3, 137.8, 137.5, 128.7, 128.7, 128.7, 124.8, 124.5, 123.6, 123.2, 113.9, 113.9, 113.5, 113.4, 108.0, 107.9, 106.8, 106.3, 98.7, 98.6, 96.4, 96.4, 95.3, 95.3, 95.1, 95.0, 94.3, 56.5, 56.5, 56.2, 55.1, 55.1, 54.5, 53.2, 52.6, 52.2, 51.6, 51.3, 49.6, 46.2, 46.2, 32.4, 14.2. LC/MS (*m/z*): 671.282 [$M+H^+$]; UPLC t_R 1.45 min.

(5-(2-(Dimethylamino)ethoxy)isoindolin-2-yl)(2-((1-(4-methoxybenzyl)-3-methyl-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)phenyl)methanone (16b). Synthesized using General Procedure D2 from **15b** (41.9 mg, 82.3 µmol) and **10a** (19.7 mg, 90.5 µmol) in dioxane (0.8 mL). The crude mixture was purified via automated flash chromatography (1% to 8% methanol in CH_2Cl_2). To QuadraPure™ MPA resin (1.5 mmol/g loading, 34 mg) soaked in CH_2Cl_2 (2 mL) for 30 min was transferred the purified product using CH_2Cl_2 (3 mL) and shaken overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated *in vacuo* to afford 37.7 mg of **16b** (71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.4 Hz, 1H), 7.05 (t, *J* = 8.8 Hz, 2H), 6.90 – 6.79 (m, 2H), 6.72 – 6.59 (m, 2H), 6.37 (dd, *J* = 7.7, 3.6 Hz, 2H), 6.22 (d, *J* = 2.4 Hz, 1H), 5.84 (s, 1H), 5.14 (q, *J* = 7.1 Hz, 2H), 5.04 (d, *J* = 12.2 Hz, 4H), 4.92 – 4.67 (m, 3H), 4.46 (t, *J* = 12.8 Hz, 1H), 4.05 (dt, *J* = 18.9, 5.7 Hz, 2H), 3.67 (s, 3H), 3.44 (s, 3H), 3.43 (s, 3H), 2.74 (dt, *J* = 11.6, 5.6 Hz, 2H), 2.35 (s, 3H), 2.33 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 166.8, 159.7, 158.9, 158.9, 158.8, 155.3, 147.6, 143.7, 139.3, 137.9, 137.5, 128.7, 128.6, 128.5, 128.2, 127.7, 126.4, 125.8, 125.3, 123.7, 123.3, 121.5, 120.7, 114.8, 114.5, 113.9, 108.6, 108.5, 107.8, 98.6, 96.4, 95.3, 95.3, 95.1, 94.3, 66.3, 66.2, 58.2, 58.2, 56.5, 56.5, 56.2, 55.1, 53.1, 52.5, 52.2, 51.5, 51.3, 45.8, 45.8, 14.2. LC/MS (*m/z*): 646.275 [$M+H^+$]; UPLC t_R 1.47 min.

(2-((1-(4-Methoxybenzyl)-3-methyl-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)phenyl)(5-(4-methylpiperazin-1-yl)isoindolin-2-yl)methanone (16c). Synthesized using General Procedure D2 from **15c** (41 mg, 79 μmol) and **10a** (19 mg, 87 μmol) in dioxane (0.8 mL). The crude mixture was purified via automated flash chromatography (1% to 7% methanol in CH_2Cl_2). To QuadraPure™ MPA resin (1.5 mmol/g loading, 34 mg) soaked in CH_2Cl_2 (2 mL) for 30 min was transferred the purified product using CH_2Cl_2 (3 mL) and shaken overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated *in vacuo* to afford 39 mg of **16c** (75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 – 6.99 (m, 3H), 6.94 – 6.82 (m, 2H), 6.71 – 6.58 (m, 2H), 6.40 – 6.31 (m, 2H), 6.21 (dd, *J* = 5.1, 2.1 Hz, 1H), 5.84 (s, 1H), 5.19 – 5.08 (m, 2H), 5.08 – 4.97 (m, 4H), 4.91 – 4.71 (m, 3H), 4.46 (t, *J* = 13.0 Hz, 1H), 3.67 (d, *J* = 3.6 Hz, 3H), 3.51 – 3.40 (m, 6H), 3.29 – 3.10 (m, 4H), 2.59 (dt, *J* = 10.0, 4.7 Hz, 4H), 2.36 (d, *J* = 7.7 Hz, 3H), 2.24 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 166.7, 159.7, 158.9, 155.3, 151.5, 151.4, 147.6, 143.7, 139.3, 137.7, 137.3, 128.7, 128.7, 128.7, 127.5, 127.3, 123.4, 123.0, 116.4, 116.1, 113.9, 110.3, 109.8, 107.9, 107.8, 98.7, 98.6, 96.4, 95.3, 95.3, 95.1, 95.0, 94.3, 56.5, 56.2, 55.1, 55.0, 55.0, 53.2, 52.6, 52.3, 51.6, 51.3, 49.5, 49.5, 46.1, 46.1, 14.2. LC/MS (*m/z*): 657.301 [M+H$^+$]; UPLC t_R 0.89 min.

***N*-Benzyl-2-((1-(4-methoxybenzyl)-3-methyl-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)-N-methylbenzamide (16d)**. Synthesized using General Procedure D2 from **15d** (30 mg, 71 μmol) and **10a** (17 mg, 78 μmol). Following silica gel flash chromatography (10% to 35% acetone in hexanes), TMT (15 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 39 mg **16d** (98% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.07 (m, 8H), 7.06 – 6.97 (m, 1H), 6.87 – 6.74 (m,

2H), 6.43 – 6.30 (m, 1H), 6.23 (dd, *J* = 15.2, 2.1 Hz, 1H), 5.84 (d, *J* = 12.4 Hz, 1H), 5.19 – 4.96 (m, 7H), 4.65 – 4.17 (m, 1H), 3.72 (d, *J* = 6.6 Hz, 3H), 3.46 – 3.35 (m, 6H), 2.91 – 2.78 (m, 3H), 2.27 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0, 168.0, 159.6, 159.6, 159.0, 155.2, 155.0, 147.7, 147.6, 144.2, 144.1, 139.9, 139.5, 136.8, 136.4, 128.9, 128.8, 128.7, 128.7, 128.6, 128.6, 128.1, 127.7, 127.6, 127.4, 114.2, 114.1, 114.0, 106.9, 106.5, 98.4, 97.5, 97.0, 96.4, 95.0, 94.9, 94.9, 94.3, 94.3, 94.2, 91.4, 56.5, 56.3, 56.2, 56.2, 55.3, 55.2, 54.8, 51.2, 51.0, 50.9, 50.4, 35.8, 32.4, 14.3. LC/MS (*m/z*): 561.284 [M+H$^+$]; UPLC t_R 1.80 min.

Synthesis of methyl 2-bromo-4,6-bis(methoxymethoxy)benzoate (17). To a suspension of benzoic acid **12** (1.26 g, 3.93 mmol) and K_2CO_3 (0.951 g, 6.88 mmol) in DMF (39 mL) at room temperature was added iodomethane (0.428 mL, 6.88 mmol) dropwise. The suspension was heated to 80 ºC and stirred for 1 h. After cooling to room temperature, the reaction was quenched with saturated NH_4Cl (aq.). The resulting mixture was extracted 4 times with ether. The combined organic layers were washed twice with water, brine and then dried with anhydrous Na_2SO_4. The salts from each suspension were removed via gravity filtration and volatile materials were condensed *in vacuo*. The crude mixture was purified via automated flash chromatography (5% to 20% ethyl acetate in hexanes twice) to afford 1.02 g of **17** (77% yield) as a clear colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (d, *J* = 2.1 Hz, 1H), 6.79 (d, *J* = 2.1 Hz, 1H), 5.15 (s, 2H), 5.14 (s, 2H), 3.92 (s, 3H), 3.46 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 159.0, 155.6, 120.7, 119.9, 113.0, 102.8, 94.7, 94.4, 56.3, 56.2, 52.6. LC/MS (*m/z*): [M+H$^+$]; UPLC t_R min (d*H*-109-763).

Methyl 2-((1-(4-methoxybenzyl)-3-methyl-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoate (18a). Synthesized using General Procedure D2 from **17** (130 mg, 390 µmol) and **10a** (93 mg, 430 µmol). Following silica gel flash chromatography (20% to 60% ethyl acetate in hexanes and 15% to 50% ethyl acetate in hexanes), TMT (59 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary

evaporator to afford 161 mg of **18a** (88% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.17 – 7.10 (m, 2H), 6.82 – 6.73 (m, 2H), 6.24 (d, *J* = 2.3 Hz, 1H), 6.10 (d, *J* = 2.3 Hz, 1H), 5.88 (s, 1H), 5.17 (s, 2H), 5.06 (s, 2H), 5.03 (s, 2H), 3.84 (s, 3H), 3.76 (s, 3H), 3.52 (s, 3H), 3.42 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 161.3, 159.7, 158.9, 149.2, 147.7, 138.9, 128.9, 128.8, 113.9, 99.9, 99.5, 95.2, 95.0, 95.0, 93.9, 56.4, 56.2, 55.1, 51.8, 51.1, 14.2. LC/MS (*m/z*): 473.16 [M+H$^+$]; UPLC t_R 1.70 min.

Methyl 2-((1-(4-methoxybenzyl)-3-phenyl-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoate (18b). Synthesized using General Procedure D2 from **17** (203 mg, 606 µmol) and **10b** (186 mg, 666 µmol). Following silica gel flash chromatography (7% to 25% ethyl acetate in hexanes), TMT (115 mg) was added to the isolated residue; the mixture was suspended in toluene (4 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 270 mg of **18b** (84% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 7.85 – 7.76 (m, 2H), 7.44 – 7.36 (m, 2H), 7.31 (d, *J* = 7.4 Hz, 1H), 7.20 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 6.42 (d, *J* = 0.7 Hz, 1H), 6.26 (d, *J* = 2.3 Hz, 1H), 6.15 (d, *J* = 2.3 Hz, 1H), 5.19 (s, 2H), 5.18 (s, 2H), 5.01 (s, 2H), 3.85 (s, 3H), 3.76 (s, 3H), 3.53 (s, 3H), 3.41 (s, 3H), 1.56 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 161.4, 159.7, 159.0, 150.2, 149.0, 139.6, 133.7, 128.9, 128.5, 128.5, 127.5, 125.3, 113.9, 100.1, 97.3, 95.2, 95.2, 95.1, 93.9, 56.4, 56.3, 55.1, 51.8, 51.6. LC/MS (*m/z*): 535.438 [M+H$^+$]; UPLC t_R 2.01 min

Methyl 2-((3-ethyl-1-(4-methoxybenzyl)-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoate (18c). Synthesized using General Procedure D2 from **17** (100 mg, 298 µmol) and **10g** (75.9 mg, 328 µmol). Following silica gel flash chromatography (15% to 40% ethyl acetate in hexanes), TMT (40 mg) was added to the isolated residue; the mixture was

suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 123 mg of **18c** (85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (s, 2H), 6.80 (d, *J* = 8.3 Hz, 2H), 6.25 (s, 1H), 6.14 (s, 1H), 5.93 (s, 1H), 5.17 (s, 2H), 5.11 (s, 2H), 5.03 (s, 2H), 3.83 (s, 3H), 3.76 (s, 3H), 3.52 (s, 3H), 3.42 (s, 3H), 2.65 (q, *J* = 7.7 Hz, 2H), 1.25 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 161.4, 159.7, 159.0, 153.9, 149.2, 138.9, 128.9, 128.9, 113.9, 100.0, 98.0, 95.3, 95.1, 94.0, 56.4, 56.3, 55.2, 51.8, 51.2, 22.1, 13.9. LC/MS (*m/z*): 487.318 [M+H$^+$]; UPLC t_R 1.80 min.

Methyl 2-((3-isopropyl-1-(4-methoxybenzyl)-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoate (18d). Synthesized using General Procedure D2 from **17** 100 mg, 298 µmol) and **10h** (80.5 mg, 328 µmol). Following silica gel flash chromatography (12% to 35% ethyl acetate in hexanes), TMT (42 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 112 mg of **18d** (75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.14 (d, *J* = 8.2 Hz, 2H), 6.86 – 6.71 (m, 2H), 6.24 (d, *J* = 2.2 Hz, 1H), 6.13 (s, 1H), 5.93 (s, 1H), 5.17 (s, 2H), 5.10 (s, 2H), 5.01 (s, 2H), 3.82 (s, 3H), 3.76 (s, 3H), 3.51 (s, 3H), 3.42 (s, 3H), 2.97 (p, *J* = 6.9 Hz, 1H), 1.27 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 161.4, 159.7, 159.0, 158.3, 149.2, 138.8, 129.0, 128.8, 113.9, 100.1, 96.5, 95.3, 95.2, 95.2, 94.0, 56.4, 56.2, 55.2, 51.8, 51.2, 28.3, 22.9. LC/MS (*m/z*): 501.344 [M+H$^+$]; UPLC t_R 1.89 min.

Methyl 2-((3-cyclopropyl-1-(4-methoxybenzyl)-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoate (18e). Synthesized using General Procedure D2 from **17** (100 mg, 298 µmol) and **10j** (80.0 mg, 328 µmol). Following silica gel flash chromatography (8% to 50% ethyl acetate in hexanes), TMT (44 mg) was added to the isolated residue; the mixture was

suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 133 mg of **18e** (89% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.15 (d, *J* = 8.2 Hz, 2H), 6.85 – 6.73 (m, 2H), 6.24 (d, *J* = 2.2 Hz, 1H), 6.11 (s, 1H), 5.72 (s, 1H), 5.16 (s, 2H), 5.07 (s, 2H), 5.02 (s, 2H), 3.82 (s, 3H), 3.76 (s, 3H), 3.51 (s, 3H), 3.42 (s, 3H), 1.93 (dq, *J* = 8.8, 5.1, 4.4 Hz, 1H), 0.90 (dd, *J* = 7.7, 5.5 Hz, 2H), 0.77 – 0.63 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 161.4, 159.7, 159.0, 154.3, 149.1, 138.9, 128.9, 128.9, 113.9, 100.0, 95.7, 95.3, 95.2, 94.0, 56.4, 56.3, 55.2, 51.8, 51.2, 9.7, 7.9. LC/MS (*m/z*): 499.315 [M+H$^+$]; UPLC t_R 1.81 min.

Methyl 2-((3-cyclopentyl-1-(4-methoxybenzyl)-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoate (18f). Synthesized using General Procedure D2 from **17** (81 mg, 240 µmol) and **10k** (67 mg, 240 µmol) in dioxane (1.2 mL). Following silica gel flash chromatography (8% to 25% ethyl acetate in hexanes), TMT (36 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 90 mg of **18f** (71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.15 (d, *J* = 8.2 Hz, 2H), 6.80 (d, *J* = 8.6 Hz, 2H), 6.24 (s, 1H), 6.15 (s, 1H), 5.92 (s, 1H), 5.17 (s, 2H), 5.10 (s, 2H), 5.02 (s, 2H), 3.82 (s, 3H), 3.76 (s, 3H), 3.51 (s, 3H), 3.42 (s, 3H), 3.08 (t, *J* = 8.1 Hz, 1H), 2.06 (s, 2H), 1.83 – 1.45 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 161.4, 159.7, 159.0, 156.6, 149.2, 138.9, 129.0, 128.8, 113.9, 100.1, 97.0, 95.3, 95.2, 95.2, 94.0, 56.4, 56.3, 55.2, 51.8, 51.2, 39.6, 33.4, 25.4. LC/MS (*m/z*): 527.366 [M+H$^+$]; UPLC t_R 2.02 min.

Methyl 2-((3-(furan-3-yl)-1-(4-methoxybenzyl)-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoate (18g). Synthesized using General Procedure D2 from **17** (88.4 mg, 328 µmol) and **10l** (88.4 mg, 328 µmol). Following silica gel flash chromatography (12% to

35% ethyl acetate in hexanes), TMT (44 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 111 mg of **18g** (71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.77 (dd, *J* = 1.6, 0.9 Hz, 1H), 7.45 (t, *J* = 1.7 Hz, 1H), 7.17 (d, *J* = 8.6 Hz, 2H), 6.85 – 6.78 (m, 2H), 6.76 (dd, *J* = 1.9, 0.9 Hz, 1H), 6.26 (d, *J* = 2.3 Hz, 1H), 6.22 – 6.18 (m, 1H), 6.14 (d, *J* = 2.2 Hz, 1H), 5.18 (s, 2H), 5.16 (s, 2H), 5.02 (s, 2H), 3.84 (s, 3H), 3.76 (s, 3H), 3.52 (s, 3H), 3.41 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 161.4, 159.8, 159.1, 149.0, 143.7, 143.2, 139.5, 139.1, 128.9, 128.6, 120.2, 113.9, 108.8, 100.2, 97.6, 95.3, 95.3, 95.2, 94.0, 56.5, 56.3, 55.2, 51.9, 51.6. LC/MS (*m/z*): 524.279 [M+H$^+$]; UPLC t_R 1.81 min.

Methyl 2,4-bis(methoxymethoxy)-6-((1-methyl-1*H*-pyrazol-5-yl)amino)benzoate (18h). Synthesized using General Procedure D2 from **17** (100 mg, 207 µmol) and 1-methyl-1*H*-pyrazol-5-amine (31.9 mg, 328 µmol). Following silica gel flash chromatography (10% to 35% ethyl acetate in hexanes), TMT (30 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 80.6 mg of **18h** (77% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (s, 1H), 7.47 (d, *J* = 2.0 Hz, 1H), 6.27 (d, *J* = 2.3 Hz, 1H), 6.08 (dd, *J* = 8.0, 2.1 Hz, 2H), 5.18 (s, 2H), 5.07 (s, 2H), 3.91 (s, 3H), 3.73 (s, 3H), 3.52 (s, 3H), 3.42 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 161.6, 160.0, 149.5, 139.0, 138.6, 99.4, 95.3, 95.2, 94.6, 93.9, 56.5, 56.3, 52.0, 35.0. LC/MS (*m/z*): 353.233 [M+H$^+$]; UPLC t_R 1.34 min.

Methyl 2-((1-isopropyl-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoate (18i). Synthesized using General Procedure D2 from **17** (150 mg, 448 µmol) and 1-(propan-2-yl)-1*H*-pyrazol-5-amine (61.6 mg, 492 µmol). Following silica gel flash chromatography (10% to 30%

ethyl acetate in hexanes), TMT (47 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 124 mg of **18i** (73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 7.53 (d, *J* = 1.9 Hz, 1H), 6.24 (d, *J* = 2.3 Hz, 1H), 6.05 (dd, *J* = 5.1, 2.0 Hz, 2H), 5.18 (s, 2H), 5.05 (s, 2H), 4.48 (p, *J* = 6.6 Hz, 1H), 3.91 (s, 3H), 3.52 (d, *J* = 1.2 Hz, 3H), 3.40 (d, *J* = 0.8 Hz, 3H), 1.45 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 161.6, 160.0, 150.4, 138.6, 137.4, 100.2, 99.4, 95.3, 95.1, 94.5, 93.9, 56.4, 56.2, 51.9, 48.6, 22.4. LC/MS (*m/z*): 381.329 [$M+H^+$]; UPLC t_R 1.61 min.

Methyl 2-((1-isobutyl-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoate (18j). Synthesized using General Procedure D2 from **17** (150 mg, 448 µmol) and 1-(2-methylpropyl)-1*H*-pyrazol-5-amine (68.3 mg, 492 µmol). Following silica gel flash chromatography (12% to 33% ethyl acetate in hexanes), TMT (50 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 136 mg of **18j** (77% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 7.50 (d, *J* = 2.0 Hz, 1H), 6.25 (d, *J* = 2.3 Hz, 1H), 6.18 (d, *J* = 2.3 Hz, 1H), 6.07 (d, *J* = 1.9 Hz, 1H), 5.18 (s, 2H), 5.06 (s, 2H), 3.90 (s, 3H), 3.80 (d, *J* = 7.4 Hz, 2H), 3.52 (s, 3H), 3.42 (s, 3H), 2.22 (hept, *J* = 7.0 Hz, 1H), 0.90 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 161.6, 160.0, 149.7, 138.9, 138.6, 99.6, 99.2, 95.3, 95.2, 94.7, 93.9, 56.4, 56.2, 55.1, 51.9, 29.4, 19.9. LC/MS (*m/z*): 395.355 [$M+H^+$]; UPLC t_R 1.73 min.

Methyl 2-((1-(cyclohexylmethyl)-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoate (18k). Synthesized using General Procedure D2 from **17** (139 mg, 415 µmol) and 1-(cyclohexylmethyl)-1*H*-pyrazol-5-amine (81.8 mg, 456 µmol). Following silica gel flash

chromatography (8% to 25% ethyl acetate in hexanes), TMT (44 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 130 mg of **18k** (72% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H), 7.49 (d, *J* = 2.0 Hz, 1H), 6.25 (d, *J* = 2.3 Hz, 1H), 6.16 (d, *J* = 2.3 Hz, 1H), 6.09 – 5.97 (m, 1H), 5.18 (s, 2H), 5.06 (s, 2H), 3.91 (s, 3H), 3.82 (d, *J* = 7.3 Hz, 2H), 3.53 (s, 3H), 3.41 (s, 3H), 1.91 (tt, *J* = 7.5, 3.7 Hz, 1H), 1.75 – 1.54 (m, 6H), 1.32 – 1.07 (m, 3H), 0.96 (q, *J* = 11.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 161.6, 159.9, 149.7, 139.0, 138.6, 99.7, 99.1, 95.3, 95.2, 94.7, 93.9, 56.4, 56.3, 53.9, 51.9, 38.5, 30.6, 26.3, 25.7. LC/MS (*m/z*): 435.405 [M+H$^+$]; UPLC t_R 1.93 min.

Methyl 2,4-bis(methoxymethoxy)-6-((1-phenyl-1*H*-pyrazol-5-yl)amino)benzoate (18l). Synthesized using General Procedure D2 from **17** (150 mg, 448 µmol) and 1-phenyl-1*H*-pyrazol-5-amine (78.4 mg, 492 µmol). Following silica gel flash chromatography (12% to 33% ethyl acetate in hexanes), TMT (47 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 132 mg of **18l** (71% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 7.66 (d, *J* = 2.0 Hz, 1H), 7.60 – 7.53 (m, 2H), 7.49 – 7.40 (m, 2H), 7.38 – 7.32 (m, 1H), 6.46 (d, *J* = 2.3 Hz, 1H), 6.30 – 6.19 (m, 2H), 5.16 (s, 2H), 5.09 (s, 2H), 3.79 (s, 3H), 3.50 (s, 3H), 3.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 161.5, 159.7, 148.2, 140.3, 139.3, 138.5, 129.2, 127.6, 124.0, 100.5, 99.1, 95.7, 95.2, 95.2, 94.0, 56.4, 56.3, 51.9. LC/MS (*m/z*): 415.292 [M+H$^+$]; UPLC t_R 1.67 min.

Methyl 2-((1-cyclohexyl-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoate (18m). Synthesized using General Procedure D2 from **17** (150 mg, 448 µmol) and 1-cyclohexyl-1*H*-pyrazol-5-amine (81.4 mg, 492 µmol). Following silica gel flash chromatography (10% to 30%

ethyl acetate in hexanes), TMT (60 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 152 mg of **18m** (81% yield) as a clear yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 2H), 7.51 (d, *J* = 1.9 Hz, 2H), 6.24 (d, *J* = 2.3 Hz, 2H), 6.13 – 5.96 (m, 1H), 5.19 (s, 1H), 5.05 (s, 2H), 4.09 – 3.97 (m, 1H), 3.91 (s, 3H), 3.53 (d, *J* = 1.0 Hz, 3H), 3.40 (s, 3H), 1.99 – 1.81 (m, 7H), 1.72 – 1.64 (m, 1H), 1.46 – 1.06 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 161.6, 160.0, 150.4, 138.5, 137.6, 99.9, 99.5, 95.3, 95.1, 94.5, 93.8, 56.4, 56.3, 56.2, 51.9, 32.7, 25.6, 25.2. LC/MS (*m/z*): 421.379 [M+H$^+$]; UPLC t_R 1.83 min.

Methyl 2-((1-benzyl-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoate (18n). Synthesized using General Procedure D2 from **17** (140 mg, 418 μmol) and 1-benzyl-1*H*-pyrazol-5-amine (79.6 mg, 460 μmol). Following silica gel flash chromatography (10% to 30% ethyl acetate in hexanes), TMT (44 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 116 mg of **18n** (65% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 7.54 (d, *J* = 2.0 Hz, 1H), 7.31 – 7.23 (m, 3H), 7.22 – 7.17 (m, 2H), 6.25 (d, *J* = 2.3 Hz, 1H), 6.11 (d, *J* = 2.0 Hz, 1H), 6.09 (d, *J* = 2.3 Hz, 1H), 5.20 (s, 2H), 5.17 (s, 2H), 5.01 (s, 2H), 3.82 (s, 3H), 3.51 (s, 3H), 3.41 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 161.4, 159.8, 149.3, 139.2, 138.9, 136.5, 128.6, 127.7, 127.6, 100.2, 100.0, 95.3, 95.3, 94.9, 93.9, 56.5, 56.3, 52.0, 51.9. LC/MS (*m/z*): 429.362 [M+H$^+$]; UPLC t_R 1.71 min.

Methyl 2,4-bis(methoxymethoxy)-6-((1-(pyridin-3-ylmethyl)-1*H*-pyrazol-5-yl)amino)benzoate (18o). Synthesized using General Procedure D2 from **17** (150 mg, 448 μmol) and 1-(pyridin-3-ylmethyl)-1*H*-pyrazol-5-amine (85.8 mg, 492 μmol) and purified via silica gel

flash chromatography (10% to 30% acetone in CH_2Cl_2). To QuadraPure™ MPA resin (1.5 mmol/g loading, 192 mg) soaked in CH_2Cl_2 (3 mL) for 30 min was transferred the purified product using CH_2Cl_2 (2 mL) and shaken overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 135 mg of **18o** (71% yield) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.31 (dd, *J* = 8.5, 7.3 Hz, 2H), 7.18 (dd, *J* = 8.5, 1.3 Hz, 2H), 7.07 – 6.99 (m, 1H), 6.59 (d, *J* = 2.2 Hz, 1H), 6.26 (d, *J* = 2.3 Hz, 1H), 5.18 (s, 2H), 5.08 (s, 2H), 3.88 (s, 3H), 3.52 (s, 3H), 3.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 160.9, 159.4, 148.1, 141.1, 129.3, 123.0, 121.5, 101.8, 95.7, 95.2, 95.2, 94.0, 56.4, 56.2, 51.9. LC/MS (*m/z*): 429.582 [M+H$^+$]; UPLC t_R 1.16 min.

Methyl 2-((1-(furan-2-ylmethyl)-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoate (18p). Synthesized using General Procedure D2 from **17** (150 mg, 448 µmol) and 1-(furan-2-ylmethyl)-1*H*-pyrazol-5-amine (80.3 mg, 492 µmol). Following silica gel flash chromatography (12% to 35% ethyl acetate in hexanes), TMT (60 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 145 mg of **18p** (78% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 7.51 (d, *J* = 1.9 Hz, 1H), 7.41 – 7.33 (m, 1H), 6.35 – 6.28 (m, 2H), 6.28 (d, *J* = 2.2 Hz, 1H), 6.17 (d, *J* = 2.2 Hz, 1H), 6.09 (d, *J* = 2.0 Hz, 1H), 5.19 (s, 4H), 5.05 (s, 2H), 3.90 (s, 3H), 3.52 (d, *J* = 0.9 Hz, 3H), 3.42 (d, *J* = 0.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 161.4, 159.8, 149.4, 149.2, 142.8, 139.3, 139.0, 110.4, 108.7, 100.2, 99.9, 95.4, 95.3, 95.0, 93.9, 56.4, 56.3, 51.9, 44.7. LC/MS (*m/z*): 419.35 [M+H$^+$]; UPLC t_R 1.57 min.

Methyl 2-((1-(4-isopropylbenzyl)-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoate (18q). Synthesized using General Procedure D2 from **17** (80 mg,

240 µmol) and 1-([4-(propan-2-yl)phenyl]methyl)-1*H*-pyrazol-5-amine (57 mg, 270 µmol). Following silica gel flash chromatography (7% to 25% ethyl acetate in hexanes), TMT (21 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 55 mg of **18q** (49% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.52 (d, *J* = 2.0 Hz, 1H), 7.14 (s, 4H), 6.24 (d, *J* = 2.3 Hz, 1H), 6.10 (t, *J* = 2.2 Hz, 2H), 5.17 (s, 2H), 5.16 (s, 2H), 5.00 (s, 2H), 3.83 (s, 3H), 3.52 (s, 3H), 3.41 (s, 3H), 2.85 (p, *J* = 7.0 Hz, 1H), 1.20 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 161.4, 159.8, 149.3, 148.3, 139.1, 138.8, 133.8, 127.7, 126.7, 100.1, 100.0, 95.3, 95.3, 94.9, 93.9, 56.4, 56.3, 51.9, 51.7, 33.8, 23.9. LC/MS (*m/z*): 470.381 [$M+H^+$]; UPLC t_R 1.96 min.

Methyl 2,4-bis(methoxymethoxy)-6-((1-(4-(trifluoromethyl)benzyl)-1*H*-pyrazol-5-yl)amino)benzoate (18r). Inside a nitrogen glovebox were combined aryl bromide **17** (145 mg, 432 µmol), 1-([4-(trifluoromethyl)phenyl]methyl)-1*H*-pyrazol-5-amine hydrochloride (100 mg, 360 µmol), tris(dibenzylideneacetone)dipalladium (16.5 mg, 18.0 µmol). Xantphos (25.0 mg, 43.2, µmol) and sodium phenoxide (155 mg, 1.33 mmol). Dioxane (3.4 mL) was added to the mixture and the reaction vessel was capped and removed from the glovebox. After the reaction was irradiated at 170 ºC for 2 h in a microwave reactor, the reaction cooled to room temperature and diluted with ethyl acetate. The resulting mixture was washed 3 times with saturated Na_2CO_3 (aq.), brine, then dried with anhydrous Na_2SO_4. The salts from each suspension were removed via gravity filtration and volatile materials were condensed *in vacuo*. Following silica gel flash chromatography (10% to 40% ethyl acetate in hexanes), TMT (30 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to

afford 66 mg of **18r** (37% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 7.55 (d, *J* = 1.9 Hz, 1H), 7.53 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 6.25 (d, *J* = 2.3 Hz, 1H), 6.13 (d, *J* = 1.9 Hz, 1H), 6.04 (d, *J* = 2.3 Hz, 1H), 5.26 (s, 2H), 5.17 (s, 2H), 5.01 (s, 2H), 3.83 (s, 3H), 3.51 (s, 3H), 3.40 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 161.5, 159.9, 149.2, 140.4, 140.4, 139.5, 139.1, 129.9 (q, *J* = 32.6 Hz), 127.9, 125.6 (q, *J* = 3.7 Hz), 124.0 (q, *J* = 272.0 Hz), 100.4, 99.9, 95.4, 95.3, 94.8, 93.9, 56.4, 56.3, 51.9, 51.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.6. LC/MS (*m/z*): 497.33 [$M+H^+$]; UPLC t_R 1.88 min.

Methyl 2,4-bis(methoxymethoxy)-6-((1-methyl-3-phenyl-1*H*-pyrazol-5-yl)amino)benzoate (18s). Synthesized using General Procedure D2 from **17** (50 mg, 150 µmol) and **10p** (28 mg, 160 µmol). Following silica gel flash chromatography (10% to 35% MTBE in hexanes), TMT (21 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 55 mg of **18s** (86% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 7.81 – 7.72 (m, 2H), 7.48 – 7.34 (m, 2H), 7.34 – 7.27 (m, 1H), 6.51 – 6.36 (m, 1H), 6.29 (d, *J* = 2.3 Hz, 1H), 6.18 (d, *J* = 2.2 Hz, 1H), 5.20 (s, 2H), 5.08 (s, 2H), 3.92 (s, 3H), 3.78 (s, 3H), 3.53 (s, 3H), 3.42 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.7, 160.1, 150.1, 149.4, 140.1, 133.6, 128.6, 127.6, 125.3, 99.8, 96.6, 95.3, 95.3, 94.9, 94.0, 56.5, 56.3, 52.0, 35.2. LC/MS (*m/z*): 429.23 [$M+H^+$]; UPLC t_R 1.76 min.

Methyl 2-((1-(*tert*-butyl)-3-phenyl-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoate (18t). Synthesized using General Procedure D2 from **17** (69.4 mg, 207 µmol) and **10q** (49.0 mg, 227 µmol) in dioxane (1.6 mL). Following silica gel flash chromatography (7% to 20% MTBE in hexanes), TMT (29 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered

through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 65.5 mg of **18t** (68% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 7.83 – 7.73 (m, 2H), 7.47 – 7.35 (m, 2H), 7.33 – 7.22 (m, 1H), 6.47 – 6.38 (m, 1H), 6.28 – 6.19 (m, 2H), 5.19 (s, 2H), 5.05 (s, 2H), 3.91 (s, 3H), 3.54 (s, 3H), 3.40 (s, 3H), 1.68 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 161.6, 160.0, 150.4, 147.8, 139.2, 134.1, 128.5, 127.3, 125.2, 100.0, 99.3, 95.4, 95.0, 94.7, 94.0, 59.8, 56.5, 56.3, 51.9, 29.8. LC/MS (*m/z*): 471.263 [M+H$^+$]; UPLC t_R 2.15 min.

Methyl 2-((1-cyclohexyl-3-phenyl-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoate (18u). Synthesized using General Procedure D2 from **17** (100 mg, 298 µmol) and **10r** (79.2 mg, 323 µmol). Following silica gel flash chromatography (8% to 25% MTBE in hexanes), TMT (44 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 111 mg of **18u** (75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 7.84 – 7.75 (m, 2H), 7.38 (t, *J* = 7.7 Hz, 2H), 7.30 – 7.27 (m, 1H), 6.40 – 6.33 (m, 1H), 6.26 (d, *J* = 2.3 Hz, 1H), 6.17 (d, *J* = 2.3 Hz, 1H), 5.20 (s, 2H), 5.05 (s, 2H), 4.07 (td, *J* = 11.2, 5.5 Hz, 1H), 3.92 (s, 3H), 3.54 (s, 3H), 3.40 (s, 3H), 2.12 – 1.87 (m, 6H), 1.74 – 1.66 (m, 1H), 1.47 – 1.16 (m, 3H).

Methyl 2-((1-isobutyl-3-phenyl-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoate (18v). Synthesized using General Procedure D2 from **17** (100 mg, 298 µmol) and **10s** (66.4 mg, 308 µmol). Following silica gel flash chromatography (7% to 20% ethyl acetate in hexanes), TMT (42 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 118 mg of **18v** (84% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 7.84 – 7.78 (m, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.3 Hz, 1H), 6.40 (s, 1H), 6.29

(d, *J* = 2.1 Hz, 2H), 5.20 (s, 2H), 5.08 (s, 2H), 3.92 (s, 3H), 3.88 (d, *J* = 7.4 Hz, 2H), 3.54 (s, 3H), 3.42 (s, 3H), 2.40 – 2.21 (m, 1H), 0.94 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 161.6, 160.0, 150.0, 149.6, 140.0, 133.8, 128.6, 127.5, 125.4, 99.7, 96.4, 95.3, 95.2, 95.0, 94.0, 56.5, 56.3, 55.2, 52.0, 29.5, 20.0. LC/MS (*m/z*): 471.307 [M+H$^+$]; UPLC t_R 2.05 min.

Methyl 2-((3-isopropyl-1-methyl-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoate (18w). Synthesized using General Procedure D2 from **17** (150 mg, 448 µmol) an amine **10t** (68.5 mg, 492 µmol). Following silica gel flash chromatography (15% to 45% ethyl acetate in hexanes), TMT (55 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 129 mg of **18w** (78% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.26 (d, *J* = 2.3 Hz, 1H), 6.14 (d, *J* = 2.2 Hz, 1H), 5.89 (s, 1H), 5.18 (s, 2H), 5.08 (s, 2H), 3.89 (d, *J* = 0.9 Hz, 3H), 3.66 (s, 3H), 3.52 (d, *J* = 0.6 Hz, 3H), 3.43 (d, *J* = 0.6 Hz, 3H), 2.92 (p, *J* = 6.9 Hz, 1H), 1.26 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 161.6, 159.9, 158.1, 149.5, 139.1, 99.7, 95.8, 95.3, 95.1, 94.9, 94.0, 56.4, 56.2, 51.9, 34.6, 28.3, 22.8. LC/MS (*m/z*): 395.355 [M+H$^+$]; UPLC t_R 1.68 min.

Methyl 2-((3-cyclohexyl-1-methyl-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoate (18x). Synthesized using General Procedure D2 from **17** (150 mg, 448 µmol) an amine **10u** (88.3 mg, 492 µmol). Following silica gel flash chromatography (15% to 40% ethyl acetate in hexanes), TMT (42 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 108 mg of **18x** (56% yield) as a clear yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 6.26 (d, *J* = 2.3 Hz, 1H), 6.12 (d, *J* = 2.3 Hz, 1H), 5.87 (s, 1H), 5.18 (s, 2H), 5.07 (s, 2H), 3.89 (s, 3H), 3.66 (s, 3H),

3.52 (s, 3H), 3.43 (s, 3H), 2.64 – 2.50 (m, 1H), 2.05 – 1.90 (m, 2H), 1.86 – 1.75 (m, 2H), 1.75 – 1.62 (m, 1H), 1.50 – 1.15 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 161.6, 159.9, 157.3, 149.5, 139.0, 99.7, 96.1, 95.3, 95.1, 94.9, 94.0, 56.4, 56.2, 51.9, 38.1, 34.6, 33.2, 26.4, 26.1. LC/MS (*m/z*): 435.405 [M+H$^+$]; UPLC t_R 1.97 min.

Methyl 2,4-bis(methoxymethoxy)-6-((1-methyl-3-(o-tolyl)-1*H*-pyrazol-5-yl)amino)benzoate (18y). Synthesized using General Procedure D2 from **17** (150 mg, 448 µmol) and **10v** (92.2 mg, 492 µmol). Following silica gel flash chromatography 10% to 30% ethyl acetate in hexanes), TMT (48 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 139 mg of **18y** (70% yield) as a clear yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.27 – 7.21 (m, 2H), 6.30 – 6.16 (m, 3H), 5.20 (s, 2H), 5.08 (s, 2H), 3.92 (s, 3H), 3.79 (s, 3H), 3.53 (s, 3H), 3.42 (s, 3H), 2.48 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 161.7, 160.0, 150.4, 149.5, 139.2, 135.8, 133.5, 130.7, 129.0, 127.6, 125.8, 99.7, 95.3, 95.3, 94.7, 94.0, 56.5, 56.3, 52.0, 35.1, 21.1. LC/MS (*m/z*): 443.388 [M+H$^+$]; UPLC t_R 1.93 min.

Methyl 2,4-bis(methoxymethoxy)-6-((1-methyl-3-(m-tolyl)-1*H*-pyrazol-5-yl)amino)benzoate (18z). Synthesized using General Procedure D2 from **17** (170 mg, 570 µmol) and **10w** (104 mg, 558 µmol). Following silica gel flash chromatography 10% to 30% ethyl acetate in hexanes), TMT (66 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 155 mg of **18z** (69% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 7.63 (s, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 7.7 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 6.42 – 6.32 (m, 1H), 6.29 (d, *J* = 2.3 Hz, 1H), 6.17 (d, *J* = 2.3 Hz, 1H), 5.20 (s, 2H), 5.08 (s, 2H), 3.92 (s, 3H), 3.77 (s, 3H), 3.53 (s, 3H), 3.42 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (101

MHz, $CDCl_3$) δ 169.2, 161.7, 160.1, 150.2, 149.5, 140.1, 138.2, 133.5, 128.5, 128.4, 125.8, 122.5, 99.8, 96.7, 95.3, 95.2, 94.9, 94.0, 56.5, 56.3, 52.0, 35.1, 21.5.

Methyl 2,4-bis(methoxymethoxy)-6-((3-(3-methoxyphenyl)-1-methyl-1*H*-pyrazol-5-yl)amino)benzoate (18aa) Synthesized using General Procedure D2 from **17** (150 mg, 448 µmol) and **10x** (100 mg, 492 µmol). Following silica gel flash chromatography 10% to 40% ethyl acetate in hexanes), TMT (64 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 161 mg of **18aa** (79% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 7.39 – 7.29 (m, 3H), 6.86 (dd, *J* = 7.8, 2.2 Hz, 1H), 6.39 (s, 1H), 6.30 (dd, *J* = 2.3, 1.0 Hz, 1H), 6.18 (t, *J* = 2.4 Hz, 1H), 5.20 (s, 2H), 5.08 (s, 2H), 3.92 (s, 3H), 3.87 (s, 3H), 3.78 (d, *J* = 2.1 Hz, 3H), 3.53 (s, 3H), 3.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 161.7, 160.1, 159.9, 149.9, 149.4, 140.1, 135.0, 129.6, 117.9, 113.7, 110.2, 99.8, 96.8, 95.3, 95.2, 94.9, 93.9, 56.5, 56.3, 55.3, 52.0, 35.2. LC/MS (*m/z*): 459.399 [$M+H^+$]; UPLC t_R 1.85 min.

Methyl 2,4-bis(methoxymethoxy)-6-((1-methyl-3-(3-(trifluoromethyl)phenyl)-1*H*-pyrazol-5-yl)amino)benzoate (18ab). Synthesized using General Procedure D2 from **17** (150 mg, 448 µmol) and **10y** (119 mg, 492 µmol). Following silica gel flash chromatography 10% to 30% ethyl acetate in hexanes), TMT (65 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 165 mg of **18ab** (74% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (s, 1H), 8.04 (s, 1H), 7.95 (d, *J* = 7.5 Hz, 1H), 7.58 – 7.43 (m, 2H), 6.47 – 6.40 (m, 1H), 6.31 (d, *J* = 2.3 Hz, 1H), 6.20 (d, *J* = 2.3 Hz, 1H), 5.20 (s, 2H), 5.09 (s, 2H), 3.92 (s, 3H), 3.79 (s, 3H), 3.53 (s, 3H), 3.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2,

161.7, 160.1, 149.2, 148.6, 140.6, 134.5, 130.9 (q, *J* = 32.2 Hz), 129.0, 128.4, 124.2 (q, *J* = 272.4 Hz), 124.1 (q, *J* = 3.8 Hz), 122.0 (q, *J* = 3.9 Hz)., 99.8, 96.5, 95.4, 95.3, 94.9, 94.0, 56.4, 56.3, 52.0, 35.2. ^{9}F NMR (376 MHz, $CDCl_3$) δ -62.7. LC/MS (*m/z*): 497.286 [$M+H^+$]; UPLC t_R 2.09 min.

Methyl 2,4-bis(methoxymethoxy)-6-((1-methyl-3-(p-tolyl)-1*H*-pyrazol-5-yl)amino)benzoate (18ac). Synthesized using General Procedure D2 from **17** (150 mg, 448 µmol) and **10z** (92.2 mg, 492 µmol). Following silica gel flash chromatography 10% to 30% ethyl acetate in hexanes), TMT (59 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 160 mg of **18ac** (81% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 7.66 (d, *J* = 7.9 Hz, 2H), 7.20 (d, *J* = 7.9 Hz, 2H), 6.36 (s, 1H), 6.29 (d, *J* = 2.2 Hz, 1H), 6.18 (d, *J* = 2.3 Hz, 1H), 5.19 (s, 2H), 5.08 (s, 2H), 3.91 (d, *J* = 0.9 Hz, 3H), 3.76 (s, 3H), 3.53 (s, 3H), 3.42 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 161.7, 160.1, 150.2, 149.5, 140.0, 137.3, 130.8, 129.3, 125.2, 99.8, 96.4, 95.3, 95.2, 94.9, 94.0, 56.5, 56.3, 52.0, 35.1, 21.2. LC/MS (*m/z*): 443.388 [$M+H^+$]; UPLC t_R 1.94 min.

Methyl 2,4-bis(methoxymethoxy)-6-((3-(4-methoxyphenyl)-1-methyl-1*H*-pyrazol-5-yl)amino)benzoate (18ad). Synthesized using General Procedure D2 from **17** (150 mg, 448 µmol) and **10aa** (100 mg, 492 µmol). Following silica gel flash chromatography 15% to 45% ethyl acetate in hexanes), TMT (57 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 161 mg of **18ad** (78% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 7.70 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 8.6 Hz, 2H), 6.32 (s, 1H), 6.29 (d, *J* = 2.3 Hz, 1H), 6.18 (d, *J* = 2.3 Hz, 1H), 5.19 (s, 2H), 5.08 (s, 2H), 3.92 (s, 3H),

3.84 (s, 3H), 3.75 (s, 3H), 3.53 (s, 3H), 3.42 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 161.7, 160.1, 159.3, 150.0, 149.5, 140.0, 126.5, 126.5, 114.0, 99.7, 96.1, 95.3, 95.2, 94.9, 94.0, 56.5, 56.3, 55.3, 52.0, 35.0. LC/MS (*m/z*): 459.354 [M+H$^+$]; UPLC t_R 1.80 min.

Methyl 2,4-bis(methoxymethoxy)-6-((1-methyl-3-(4-(trifluoromethyl)phenyl)-1*H*-pyrazol-5-yl)amino)benzoate (18ae). Synthesized using General Procedure D2 from **17** (150 mg, 448 µmol) and **10ab** (119 mg, 492 µmol). Following silica gel flash chromatography 10% to 30% ethyl acetate in hexanes), TMT (60 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 180 mg of **18ae** (81% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (s, 1H), 7.88 (d, *J* = 8.1 Hz, 2H), 7.64 (d, *J* = 8.1 Hz, 2H), 6.45 (s, 1H), 6.31 (d, *J* = 2.3 Hz, 1H), 6.19 (d, *J* = 2.2 Hz, 1H), 5.20 (s, 2H), 5.09 (s, 2H), 3.92 (s, 3H), 3.79 (s, 3H), 3.53 (s, 3H), 3.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 161.7, 160.1, 149.2, 148.6, 140.5, 137.0, 137.0, 129.3 (q, *J* = 32.3 Hz), 128.8, 125.53 (q, *J* = 3.8 Hz), 124.3 (q, *J* = 271.8 Hz), 123.0, 120.3, 99.8, 96.8, 95.4, 95.3, 94.9, 94.0, 56.5, 56.3, 52.0, 35.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.4. LC/MS (*m/z*): 497.33 [M+H$^+$]; UPLC t_R 2.06 min.

Methyl 2-((3-(4-(*tert*-butyl)phenyl)-1-methyl-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoate (18af). Synthesized using General Procedure D2 from **17** (150 mg, 448 µmol) and **10ac** (113 mg, 492 µmol). Following silica gel flash chromatography 10% to 30% ethyl acetate in hexanes), TMT (58 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 174 mg of **18af** (80% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.42 (d, *J* = 8.2 Hz, 2H), 6.37 (s, 1H), 6.28 (d, *J* = 2.2 Hz, 1H), 5.19 (s, 2H), 5.07 (s, 2H), 3.92 (s, 2H), 3.76

(s, 3H), 3.53 (s, 3H), 3.42 (s, 3H), 1.34 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 161.7, 160.0, 150.6, 150.1, 149.5, 140.0, 130.8, 129.0, 128.2, 125.5, 125.3, 125.0, 99.7, 96.5, 95.3, 95.2, 94.9, 94.0, 56.5, 56.3, 52.0, 35.1, 34.6, 31.3. LC/MS (*m/z*): 485.377 [M+H$^+$]; UPLC t_R 2.20 min.

Methyl 2,4-bis(methoxymethoxy)-6-((1-methyl-3-(4-(trifluoromethoxy)phenyl)-1*H*-pyrazol-5-yl)amino)benzoate (18ag). Synthesized using General Procedure D2 from **17** (150 mg, 448 µmol) and **10ad** (127 mg, 492 µmol). Following silica gel flash chromatography (12% to 33% ethyl acetate in hexanes), TMT (66 mg) was added to the isolated residue; the mixture was suspended in toluene (3 mL) and stirred overnight. The suspension was filtered through a plug of Celite® and the filtrate was concentrated using a rotary evaporator to afford 183 mg of **18ag** (80% yield) as a white/yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 1H), 7.83 – 7.71 (m, 2H), 7.25 – 7.19 (m, 2H), 6.41 – 6.34 (m, 1H), 6.30 (d, *J* = 2.3 Hz, 1H), 6.17 (d, *J* = 2.2 Hz, 1H), 5.20 (s, 2H), 5.08 (s, 2H), 3.92 (s, 3H), 3.77 (s, 3H), 3.53 (s, 3H), 3.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 161.7, 160.1, 149.3, 148.8, 140.4, 132.5, 126.6, 121.1, 120.5 (q, *J* = 256.9 Hz), 99.8, 96.5, 95.3, 95.3, 94.9, 94.0, 56.4, 56.3, 52.0, 35.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.8. LC/MS (*m/z*): 513.296 [M+H$^+$]; UPLC t_R 2.04 min.

2-((1-(4-Methoxybenzyl)-3-methyl-1*H*-pyrazol-5-yl)amino)-4-(methoxymethoxy)-6-((methoxymethyl)peroxy)benzoic acid (19a). Ester **18a** (105 mg, 0.222 mmol) was hydrolyzed using General Procedure E to afford 95.1 mg of crude acid **19a** (93% crude yield).

2-((1-(4-Methoxybenzyl)-3-phenyl-1*H*-pyrazol-5-yl)amino)-4-(methoxymethoxy)-6-((methoxymethyl)peroxy)benzoic acid (19b). Ester **18b** (267 mg, 500 µmol) was hydrolyzed using General Procedure E to afford 235 mg of crude acid **19b** (90% crude yield).

2-((3-Ethyl-1-(4-methoxybenzyl)-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoic acid (19c). Ester **18c** (123 mg, 253 µmol) was hydrolyzed using General Procedure E to afford 112 mg of crude acid **19c** (94% crude yield).

2-((3-Isopropyl-1-(4-methoxybenzyl)-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoic acid (19d) Ester **18d** (112 mg, 224 µmol) was hydrolyzed using General Procedure E to afford 111 mg of crude acid **19d** (102% crude yield).

2-((3-Cyclopropyl-1-(4-methoxybenzyl)-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoic acid (19e) Ester **18e** (132 mg, 265 µmol) was hydrolyzed using General Procedure E to afford 118 mg of crude acid **19e** (92% crude yield).

2-((3-Cyclopentyl-1-(4-methoxybenzyl)-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoic acid (19f). Ester **18f** (90.1 mg, 171 µmol) was hydrolyzed using General Procedure E to afford 90 mg of crude acid **19f** (103% crude yield).

2-((3-(Furan-3-yl)-1-(4-methoxybenzyl)-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoic acid (19g). Ester **18g** (110 mg, 210 µmol) was hydrolyzed using General Procedure E to afford 104 mg of crude acid **19g** (97% crude yield).

2,4-Bis(methoxymethoxy)-6-((1-methyl-1*H*-pyrazol-5-yl)amino)benzoic acid (19h). Ester **18h** (79.8 mg, 227 µmol) was hydrolyzed using General Procedure E to afford 27.6 mg of crude acid **19h** (36% crude yield).

2-((1-Isopropyl-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoic acid (19i). Ester **18i** (124 mg, 327 µmol) was hydrolyzed using General Procedure E to afford 98.8 mg of crude acid **19i** (83% crude yield).

2-((1-Isobutyl-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoic acid (19j). Ester **18j** (135 mg, 343 μmol) was hydrolyzed using General Procedure E to afford 119 mg of crude acid **19j** (91% crude yield).

2-((1-(Cyclohexylmethyl)-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoic acid (19k). Ester **18k** (125 mg, 288 μmol) was hydrolyzed using General Procedure E to afford 105 mg of crude acid **19k** (87% crude yield).

2,4-Bis(methoxymethoxy)-6-((1-phenyl-1*H*-pyrazol-5-yl)amino)benzoic acid (19l). Ester **18l** (131 mg, 317 μmol) was hydrolyzed using General Procedure E to afford 114 mg of crude acid **19l** (90% crude yield).

2-((1-Cyclohexyl-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoic acid (19m). Ester **18m** (152 mg, 362 μmol) was hydrolyzed using General Procedure E to afford 152 mg of crude acid **19m** (103% crude yield).

2-((1-Benzyl-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoic acid (19n). Ester **18n** (115 mg, 269 μmol) was hydrolyzed using General Procedure E to afford 106 mg of crude acid **19n** (95% crude yield).

2,4-Bis(methoxymethoxy)-6-((1-(pyridin-3-ylmethyl)-1*H*-pyrazol-5-yl)amino)benzoic acid (19o). Ester **18o** (135 mg, 315 μmol) was hydrolyzed using General Procedure E to afford 90.1 mg of crude acid **19o** (69% crude yield).

2-((1-(Furan-2-ylmethyl)-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoic acid (19p). Ester **18p** (145 mg, 347 μmol) was hydrolyzed using General Procedure E to afford 128 mg of crude acid **19p** (91% crude yield).

2-((1-(4-Isopropylbenzyl)-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoic acid (19q). Ester **18q** (55.1 mg, 117 µmol) was hydrolyzed using General Procedure E to afford 47.9 mg of crude acid **19q** (90% crude yield).

2,4-Bis(methoxymethoxy)-6-((1-(4-(trifluoromethyl)benzyl)-1*H*-pyrazol-5-yl)amino)benzoic acid (19r) Ester **18r** (66 mg, 133 µmol) was hydrolyzed using General Procedure E to afford 57 mg of crude acid **19r** (89% crude yield).

2,4-Bis(methoxymethoxy)-6-((1-methyl-3-phenyl-1*H*-pyrazol-5-yl)amino)benzoic acid (19s). Ester **18s** (65.7 mg, 154 µmol) was hydrolyzed using General Procedure E to afford 64.1 mg of crude acid **19s** (101% crude yield).

2-((1-(*tert*-Butyl)-3-phenyl-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoic acid (19t). Ester **18t** (65.5 mg, 140 µmol) was hydrolyzed using General Procedure E to afford 62.2 mg of crude acid **19t** (98% crude yield).

2-((1-Cyclohexyl-3-phenyl-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoic acid (19u). Ester **18u** (111 mg, 224 µmol) was hydrolyzed using General Procedure E to afford 104 mg of crude acid **19u** (96% crude yield).

2-((1-Isobutyl-3-phenyl-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoic acid (19v). Ester **18v** (118 mg, 251 µmol) was hydrolyzed using General Procedure E to afford 112 mg of crude acid **19v** (98% crude yield).

2-((3-Isopropyl-1-methyl-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoic acid (19w). Ester **18w** (124 mg, 316 µmol) was hydrolyzed using General Procedure E to afford 124 mg of crude acid (104% crude yield).

2-((3-Cyclohexyl-1-methyl-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoic acid (19x). Ester **18x** (105 mg, 242 μmol) was hydrolyzed using General Procedure E to afford 102 mg of crude acid (101% crude yield).

2,4-Bis(methoxymethoxy)-6-((1-methyl-3-(o-tolyl)-1*H*-pyrazol-5-yl)amino)benzoic acid (19y). Ester **18y** (138 mg, 313 μmol) was hydrolyzed using General Procedure E to afford 133 mg of crude acid (100% crude yield).

2,4-Bis(methoxymethoxy)-6-((1-methyl-3-(m-tolyl)-1*H*-pyrazol-5-yl)amino)benzoic acid (19z). Ester **18z** (154 mg, 349 μmol) was hydrolyzed using General Procedure E to afford 166 mg of crude acid (112% crude yield).

2,4-Bis(methoxymethoxy)-6-((3-(3-methoxyphenyl)-1-methyl-1*H*-pyrazol-5-yl)amino)benzoic acid (19aa) Ester **18aa** (161 mg, 352 μmol) was hydrolyzed using General Procedure E to afford 142 mg of crude acid **S7** (91% crude yield).

2,4-Bis(methoxymethoxy)-6-((1-methyl-3-(3-(trifluoromethyl)phenyl)-1*H*-pyrazol-5-yl)amino)benzoic acid (19ab). Ester **S6ab** (161 mg, 325 μmol) was hydrolyzed using General Procedure E to afford 152 mg of crude acid **S7ab** (97% crude yield).

2,4-Bis(methoxymethoxy)-6-((1-methyl-3-(p-tolyl)-1*H*-pyrazol-5-yl)amino)benzoic acid (19ac). Ester **18ac** (146 mg, 331 μmol) was hydrolyzed using General Procedure E to afford 142 mg of crude acid (100% crude yield).

2,4-Bis(methoxymethoxy)-6-((3-(4-methoxyphenyl)-1-methyl-1*H*-pyrazol-5-yl)amino)benzoic acid (19ad). Ester **18ad** (155 mg, 339 μmol) was hydrolyzed using General Procedure E to afford 144 mg of crude acid (96% crude yield).

2,4-Bis(methoxymethoxy)-6-((1-methyl-3-(4-(trifluoromethyl)phenyl)-1*H*-pyrazol-5-yl)amino)benzoic acid (19ae). Ester **S6ae** (174 mg, 351 µmol) was hydrolyzed using General Procedure E to afford 174 mg of crude acid **S7ae** (105% crude yield).

2-((3-(4-(*tert*-Butyl)phenyl)-1-methyl-1*H*-pyrazol-5-yl)amino)-4,6-bis(methoxymethoxy)benzoic acid (19af). Ester **18af** (167 mg, 345 µmol) was hydrolyzed using General Procedure E to afford 138 mg of crude acid **19af** (85% crude yield).

2,4-Bis(methoxymethoxy)-6-((1-methyl-3-(4-(trifluoromethoxy)phenyl)-1*H*-pyrazol-5-yl)amino)benzoic acid (19ag). Ester **18ag** (175 mg, 342 µmol) was hydrolyzed using General Procedure E to afford 156 mg of crude acid (92% crude yield).

4-(2,3-dihydro-1*H*-isoindole-2-carbonyl)-5-((1-((4-methoxyphenyl)methyl)-3-methyl-1*H*-pyrazol-5-yl)amino)benzene-1,3-diol (20). Amide **14a** (38 mg, 68 µmol) was deprotected using General Procedure F to afford 24 mg of **20** (74% yield). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 9.66 (s, 1H), 9.31 (s, 1H), 7.45 – 7.13 (m, 3H), 7.13 – 6.92 (m, 3H), 6.68 (d, *J* = 8.5 Hz, 1H), 5.85 (d, *J* = 2.1 Hz, 1H), 5.78 (s, 1H), 5.71 (d, *J* = 2.0 Hz, 1H), 4.89 (s, 2H), 4.72 (s, 2H), 3.62 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (126 MHz, $(CD_3)_2SO$) δ 166.6, 159.2, 158.4, 155.4, 146.0, 143.8, 143.7, 140.1, 129.3, 128.8, 127.2, 122.8, 113.6, 103.7, 98.0, 94.3, 92.8, 55.0, 50.0, 40.4, 13.9. LC/MS (*m/z*): 471.207 [$M+H^+$]; UPLC t_R 1.31 min.

4-(2,3-dihydro-1*H*-isoindole-2-carbonyl)-5-((1-((4-methoxyphenyl)methyl)-3-phenyl-1*H*-pyrazol-5-yl)amino)benzene-1,3-diol (21). Amide **14b** was deprotected using General Procedure F (52.6 mg, 84.7 µmol) to afford 25.9 mg of **21** (57% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.75 – 7.66 (m, 2H), 7.42 – 7.32 (m, 3H), 7.32 – 7.21 (m, 5H), 7.06 (d, *J* = 8.7 Hz, 2H), 6.65 (d, *J* = 8.7 Hz, 2H), 6.46 (s, 1H), 5.93 (dd, *J* = 14.2, 2.1 Hz, 2H), 5.17 (s, 2H), 4.96 – 4.59 (m, 4H), 3.63 (s, 3H). ^{13}C NMR (126 MHz, $(CD_3)_2SO$) δ 166.6, 159.4, 158.5, 155.6, 148.7, 143.6, 141.2, 136.6 (br),

133.5, 129.0, 128.8, 128.5, 127.4, 127.3, 124.8, 122.8, 113.7, 104.0, 96.1, 94.6, 93.0, 55.0, 50.6, 40.4. LC/MS (*m/z*): 533.257 [M+H$^+$]; UPLC t_R 1.63 min.

5-((1-((4-Methoxyphenyl)methyl)-3-methyl-1*H*-pyrazol-5-yl)amino)-4-(5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridine-6-carbonyl)benzene-1,3-diol (22). Crude acid **19a** (31.7 mg, 69.3 µmol) was coupled with 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine dihydrochloride (20.1 mg, 104 µmol), and triethylamine (72 µL, 520 µmol) using General Procedure G to give 21.8 mg of MOM-protected intermediate (56% yield) after purification via automated flash chromatography (10% to 50% acetone in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 – 8.42 (m, 1H), 7.67 – 7.43 (m, 1H), 7.21 (ddd, *J* = 13.1, 7.7, 4.9 Hz, 1H), 7.06 (ddd, *J* = 9.9, 6.0, 2.6 Hz, 2H), 6.70 – 6.57 (m, 2H), 6.45 (d, *J* = 2.5 Hz, 1H), 6.39 (dd, *J* = 7.5, 2.1 Hz, 1H), 6.23 (dd, *J* = 13.2, 2.1 Hz, 1H), 5.84 (s, 1H), 5.30 – 4.72 (m, 9H), 4.61 – 4.41 (m, 1H), 3.68 (d, *J* = 2.8 Hz, 3H), 3.44 (dd, *J* = 4.3, 2.0 Hz, 6H), 2.23 (d, *J* = 3.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 167.2, 159.9, 159.0, 158.9, 157.6, 157.2, 155.4, 155.4, 149.4, 149.3, 147.6, 147.6, 143.9, 143.8, 139.4, 139.2, 131.0, 130.6, 130.3, 129.9, 128.8, 128.6, 128.5, 122.5, 122.4, 113.9, 113.8, 107.1, 98.5, 98.5, 96.5, 95.4, 95.3, 95.1, 95.1, 94.3, 94.2, 56.6, 56.5, 56.3, 56.2, 55.2, 55.1, 53.8, 53.4, 52.6, 51.4, 51.3, 51.3, 50.5, 29.3, 14.2, 14.2. LC/MS (*m/z*): 560.225 [M+H$^+$]; UPLC t_R 1.41 min

The MOM-protected intermediate (21.8 mg, 39.0 µmol) was deprotected using General Procedure F to afford 3.0 mg of **22** (16% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.44 (d, *J* = 5.0 Hz, 1H), 7.76 (s, 1H), 7.40 – 7.30 (m, 1H), 7.00 (d, *J* = 8.7 Hz, 2H), 6.66 (d, *J* = 8.7 Hz, 2H), 5.96 – 5.85 (m, 2H), 5.83 (d, *J* = 2.1 Hz, 1H), 5.04 (s, 2H), 4.96 – 4.43 (m, 4H), 3.65 (s, 3H), 2.13 (s, 3H). LC/MS (*m/z*): 472.234 [M+H$^+$]; UPLC t_R 1.12 min.

5-((1-((4-Methoxyphenyl)methyl)-3-phenyl-1*H*-pyrazol-5-yl)amino)-4-(5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridine-6-carbonyl)benzene-1,3-diol (23). Acid **19b** (31.7 mg, 69.3 µmol) was

coupled with 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine dihydrochloride (20.1 mg, 104 µmol), and triethylamine (72 µL, 520 µmol) using General Procedure G to give 43.2 mg of MOM-protected intermediate (77% yield) after purification *via* automated flash chromatography (4% to 40% acetone in hexanes and 0% to 3% methanol in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 – 8.40 (m, 1H), 7.78 (dq, *J* = 6.4, 1.4 Hz, 2H), 7.66 – 7.46 (m, 1H), 7.42 – 7.34 (m, 2H), 7.33 – 7.18 (m, 2H), 7.18 – 7.06 (m, 2H), 6.73 – 6.58 (m, 2H), 6.53 (d, *J* = 4.4 Hz, 1H), 6.46 – 6.34 (m, 2H), 6.30 (dd, *J* = 18.9, 2.1 Hz, 1H), 5.16 (d, *J* = 17.6 Hz, 4H), 5.06 (d, *J* = 3.8 Hz, 2H), 5.02 – 4.78 (m, 3H), 4.56 (d, *J* = 16.2 Hz, 1H), 3.69 (d, *J* = 3.1 Hz, 3H), 3.52 – 3.40 (m, 6H). (Proton not clean so didn't include carbon) LC/MS (*m/z*): 622.237 [M+H$^+$]; UPLC t_R 1.71 min.

The MOM-protected intermediate (43.2 mg, 69.5 µmol) was deprotected using General Procedure F to afford 11.5 mg of **23** (31% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (500 MHz, CD_3OD) δ 8.40 (d, *J* = 5.1 Hz, 1H), 7.75 (d, *J* = 7.5 Hz, 1H), 7.72 – 7.63 (m, 2H), 7.38 – 7.30 (m, 2H), 7.30 – 7.20 (m, 1H), 7.15 – 7.04 (m, 2H), 6.73 – 6.66 (m, 2H), 6.45 (s, 1H), 6.01 – 5.90 (m, 1H), 5.19 (s, 2H), 4.99 – 4.49 (m, 4H), 3.65 (s, 2H), 2.65 (s, 3H). LC/MS (*m/z*): 535.173 [M+H$^+$]; UPLC t_R 1.40 min.

5-((1-((4-Methoxyphenyl)methyl)-3-methyl-1*H*-pyrazol-5-yl)amino)-4-(1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole-5-carbonyl)benzene-1,3-diol (24). Acid **19a** (39 mg, 85 µmol) was coupled with 1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole (14 mg, 130 µmol), and triethylamine (24 µL, 170 µmol) using General Procedure G to give 28.1 mg of MOM-protected intermediate (60% yield) after purification via automated flash chromatography (15% to 60% acetone in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.17 (m, 2H), 7.13 – 6.98 (m, 2H), 6.73 – 6.61 (m, 2H), 6.43 – 6.31 (m, 2H), 6.20 (d, *J* = 2.1 Hz, 1H), 5.84 (d, *J* = 2.3 Hz, 1H), 5.20 – 5.10 (m, 2H), 5.09 – 4.97 (m, 4H), 4.77 – 4.56 (m, 3H), 4.31 (dd, *J* = 13.6, 7.2 Hz, 1H), 3.68 (d, *J* = 1.0 Hz, 3H), 3.48 – 3.38

(m, 6H), 2.23 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 159.8, 159.7, 159.0, 158.9, 155.2, 147.6, 143.6, 139.4, 139.3, 128.7, 128.6, 128.6, 128.6, 113.9, 113.9, 107.7, 107.6, 98.7, 98.6, 96.5, 96.4, 95.2, 95.1, 95.1, 94.2, 56.5, 56.5, 56.2, 55.1, 55.1, 53.7, 51.2, 51.2, 46.6, 46.4, 45.6, 45.3, 29.2, 14.1.LC/MS (*m/z*): 549.199 [M+H$^+$]; UPLC t_R 1.28 min.

The MOM-protected intermediate (28.1 mg, 51.2 μmol) was deprotected using General Procedure F to afford 3.6 mg of **24** (15% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.44 (s, 1H), 7.06 – 6.95 (m, 2H), 6.75 – 6.65 (m, 2H), 5.95 – 5.87 (m, 2H), 5.82 (d, *J* = 2.1 Hz, 1H), 5.03 (s, 2H), 4.77 – 4.22 (m, 4H), 3.68 (s, 3H), 2.65 (s, 3H), 2.15 (s, 3H). LC/MS (*m/z*): 461.207 [M+H$^+$]; UPLC t_R 0.94 min.

5-((1-((4-Methoxyphenyl)methyl)-3-phenyl-1*H*-pyrazol-5-yl)amino)-4-(1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole-5-carbonyl)benzene-1,3-diol (25). Acid **19b** (90 mM in 1:1 CH_2Cl_2:THF, 1.0 mL, 90 μmol) was coupled with 1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole (15 mg, 140 μmol), and triethylamine (25 μL, 180 μmol) using General Procedure G to give 33 mg of MOM-protected intermediate (61% yield) after purification via automated flash chromatography (10% to 40% acetone in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.75 (m, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 8.2 Hz, 2H), 6.76 – 6.65 (m, 2H), 6.50 – 6.35 (m, 3H), 6.29 (dd, *J* = 8.7, 1.9 Hz, 1H), 5.15 (s, 1H), 5.05 (s, 2H), 4.83 – 4.50 (m, 3H), 4.35 (t, *J* = 12.4 Hz, 1H), 3.71 (dd, *J* = 2.1, 0.9 Hz, 3H), 3.45 (s, 3H), 3.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 159.8, 159.8, 159.0, 158.9, 155.2, 150.1, 143.4, 143.4, 140.1, 140.0, 133.6, 128.7, 128.5, 128.3, 128.2, 127.6, 125.3, 113.9, 113.9, 107.7, 107.7, 96.6, 96.4, 95.3, 95.2, 94.2, 56.5, 56.5, 56.2, 55.1, 55.1. LC/MS (*m/z*): 611.255 [M+H$^+$]; UPLC t_R 1.61 min.

The MOM-protected intermediate (33.5 mg, 54.9 μmol) was deprotected using General Procedure F to afford 7.2 mg of **25** (25% yield) after purification using mass-guided preparative HPLC. ^{1}H

NMR (500 MHz, CD_3OD) δ 7.71 (dd, *J* = 8.0, 1.4 Hz, 2H), 7.46 – 7.31 (m, 3H), 7.30 – 7.21 (m, 1H), 7.13 – 7.00 (m, 2H), 6.75 – 6.68 (m, 2H), 6.46 (s, 1H), 5.92 (dd, *J* = 17.4, 2.1 Hz, 2H), 5.18 (s, 2H), 4.77 – 4.17 (m, 4H), 3.68 (d, *J* = 0.6 Hz, 3H). LC/MS (*m/z*): 523.132 [$M+H^+$]; UPLC t_R 1.31 min.

4-(4-Fluoro-2,3-dihydro-1*H*-isoindole-2-carbonyl)-5-((1-((4-methoxyphenyl)methyl)-3-methyl-1*H*-pyrazol-5-yl)amino)benzene-1,3-diol (26). Acid **19a** (30 mg, 66 μmol) was coupled with 4-fluoroisoindoline (13 mg, 98 μmol), and triethylamine (18 μL, 130 μmol) using General Procedure G to give 38 mg of MOM-protected intermediate (78% yield) after purification via automated flash chromatography (10% to 45% acetone in hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 7.9, 5.2 Hz, 1H), 7.17 – 7.03 (m, 2H), 7.03 – 6.88 (m, 1H), 6.72 – 6.61 (m, 2H), 6.46 – 6.33 (m, 2H), 6.25 (dd, *J* = 13.2, 2.1 Hz, 1H), 5.85 (d, *J* = 2.5 Hz, 1H), 5.16 (dd, *J* = 9.5, 3.3 Hz, 2H), 5.06 (d, *J* = 10.6 Hz, 4H), 5.00 – 4.76 (m, 3H), 4.53 (d, *J* = 14.9 Hz, 1H), 3.68 (d, *J* = 7.4 Hz, 3H), 3.49 – 3.38 (m, 6H), 2.24 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -117.44 (dd, *J* = 9.1, 5.1 Hz), -117.90 (dd, *J* = 9.1, 5.0 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 166.8, 159.9, 159.9, 159.0, 158.9, 156.8, 156.5, 155.3, 147.6, 147.6, 143.8, 143.7, 140.0, 139.9, 139.5, 139.5, 139.3, 139.3, 129.9, 129.9, 129.8, 128.7, 128.6, 128.5, 123.4, 118.7, 118.6, 118.2, 114.3, 114.1, 114.1, 114.0, 113.9, 113.9, 107.5, 107.2, 98.5, 98.3, 96.5, 95.4, 95.3, 95.1, 95.1, 94.3, 56.6, 56.3, 55.1, 55.1, 53.0, 52.3, 51.4, 51.3, 50.0, 49.2, 14.2. LC/MS (*m/z*): 578.22 [$M+H^+$]; UPLC t_R 1.65 min.

The MOM-protected intermediate (27.5 mg, 47.7 μmol) was deprotected using General Procedure F to afford 6.9 mg of **26** (30% yield) after purification using mass-guided preparative HPLC. ^1H NMR (400 MHz, CD_3OD) δ 7.33 (q, *J* = 7.7 Hz, 1H), 7.09 (s, 1H), 7.04 – 6.94 (m, 3H), 6.66 (d, *J*

= 8.7 Hz, 2H), 5.96 – 5.87 (m, 2H), 5.84 (d, *J* = 2.1 Hz, 1H), 5.03 (s, 2H), 4.92 – 4.53 (m, 4H), 3.64 (s, 3H), 2.13 (s, 3H). LC/MS (*m/z*): 489.214 [M+H$^+$]; UPLC t_R 1.36 min.

4-(4-Fluoro-2,3-dihydro-1*H*-isoindole-2-carbonyl)-5-((1-((4-methoxyphenyl)methyl)-3-phenyl-1*H*-pyrazol-5-yl)amino)benzene-1,3-diol (27). Acid **19b** (90 mM in 1:1 CH_2Cl_2:THF, 1.0 mL, 90 µmol) was coupled with 4-fluoroisoindoline (17 mg, 140 µmol), and triethylamine (25 µL, 180 µmol) using General Procedure G to give 42 mg of MOM-protected intermediate (72% yield) after purification via automated flash chromatography (8% to 30% acetone in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.73 (m, 2H), 7.39 (t, *J* = 7.7 Hz, 2H), 7.35 – 7.23 (m, 2H), 7.19 – 7.08 (m, 3H), 6.98 (dt, *J* = 12.5, 8.4 Hz, 1H), 6.73 – 6.65 (m, 2H), 6.52 (d, *J* = 3.3 Hz, 1H), 6.46 – 6.37 (m, 2H), 6.32 (dd, *J* = 16.3, 2.1 Hz, 1H), 5.29 (s, 1H), 5.25 – 5.11 (m, 4H), 5.07 (s, 2H), 5.03 – 4.81 (m, 3H), 4.56 (dd, *J* = 14.7, 5.9 Hz, 1H), 3.69 (d, *J* = 8.1 Hz, 3H), 3.48 – 3.43 (m, 6H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -117.44 (dd, *J* = 9.1, 4.9 Hz), -117.88 (dd, *J* = 9.4, 5.1 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 166.8, 160.0, 159.9, 159.3, 159.1, 159.0, 156.8, 155.4, 150.1, 150.1, 143.7, 143.5, 140.0, 140.0, 139.9, 139.5, 133.7, 130.0, 129.9, 129.8, 128.7, 128.7, 128.6, 128.4, 128.2, 127.6, 125.4, 123.6, 123.4, 123.3, 123.1, 118.6, 118.2, 114.3, 114.2, 114.1, 114.0, 113.9, 113.9, 107.6, 107.3, 96.6, 96.3, 96.0, 95.4, 95.3, 95.3, 95.3, 94.3, 94.3, 56.6, 56.3, 55.1, 55.1, 53.1, 52.3, 51.9, 51.8, 50.0, 49.3. LC/MS (*m/z*): 639.306 [M+H$^+$]; UPLC t_R 2.00 min.

The MOM-protected intermediate (41.7 mg, 65.3 µmol) was deprotected using General Procedure F to afford 19.2 mg of **27** (53% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (500 MHz, CD_3OD) δ 7.76 – 7.52 (m, 3H), 7.41 – 7.20 (m, 4H), 7.06 (d, *J* = 8.5 Hz, 3H), 6.98 (t, *J* = 8.8 Hz, 1H), 6.74 – 6.62 (m, 2H), 6.46 (d, *J* = 0.9 Hz, 1H), 5.93 (ddd, *J* = 14.0, 2.1, 0.9 Hz, 2H), 5.18 (s, 2H), 4.93 – 4.53 (m, 4H), 3.64 (d, *J* = 0.9 Hz, 3H). ^{13}C NMR (126 MHz, $(CD_3)_2SO$) δ 166.6, 159.5, 158.5, 157.2 (d, $^1J_{C\text{-}F}$ = 244.1 Hz), 155.7, 148.7, 143.7, 141.2, 133.5,

129.9 (d, $^{3}J_{C\text{-}F}$ = 4.8 Hz), 129.0, 128.7, 128.5, 127.3, 124.7, 123.1 (br), 119.1, 113.67 (app d, ovrlp), 113.63, 103.7, 96.2, 94.6, 93.2, 54.9, 50.5, 40.4. LC/MS (*m/z*): 551.250 [M+H$^+$]; UPLC t_R 1.65 min.

4-(5-Fluoro-2,3-dihydro-1*H*-isoindole-2-carbonyl)-5-((1-((4-methoxyphenyl)methyl)-3-methyl-1*H*-pyrazol-5-yl)amino)benzene-1,3-diol (28). Acid **19a** (31.1 mg, 68.0 µmol) was coupled with 5-fluoroisoindoline hydrochloride (17.7 mg, 102 µmol), and triethylamine (28 µL, 204 µmol) using General Procedure G to give 33.3 mg of MOM-protected intermediate (85% yield) after purification via automated flash chromatography (20% to 50% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 – 6.80 (m, 4H), 6.66 (dd, *J* = 8.6, 1.8 Hz, 2H), 6.43 – 6.34 (m, 2H), 6.24 (dd, *J* = 2.1, 0.7 Hz, 1H), 5.85 (s, 1H), 5.15 (q, *J* = 6.6 Hz, 2H), 5.05 (dd, *J* = 11.3, 1.7 Hz, 4H), 4.96 – 4.74 (m, 3H), 4.55 – 4.40 (m, 1H), 3.68 (s, 3H), 3.51 – 3.37 (m, 6H), 2.24 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.63 – -114.72 (m), -114.72 – -114.83 (m). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 166.8, 163.9, 163.8, 161.4, 161.3, 159.9, 159.9, 158.9, 155.3, 155.3, 147.6, 143.8, 143.7, 139.3, 138.6, 138.6, 138.3, 138.2, 132.0, 131.7, 128.7, 128.7, 128.6, 124.3, 124.2, 123.8, 123.7, 115.1, 115.0, 114.9, 114.8, 113.9, 110.3, 110.1, 109.8, 109.6, 107.5, 107.5, 98.5, 98.4, 96.5, 95.4, 95.3, 95.1, 94.3, 56.6, 56.3, 55.1, 55.1, 52.9, 52.3, 52.0, 52.0, 51.5, 51.3, 14.2. LC/MS (*m/z*): 577.206 [M+H$^+$]; UPLC t_R 1.71 min.

The MOM-protected intermediate (29.9 mg, 51.9 µmol) was deprotected using General Procedure F to afford 9.1 mg of **28** (36% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.25 (s, 1H), 7.07 – 6.91 (m, 4H), 6.72 – 6.57 (m, 2H), 5.93 – 5.84 (m, 2H), 5.83 (d, *J* = 2.1 Hz, 1H), 5.03 (s, 2H), 4.91 – 4.48 (m, 4H), 3.65 (s, 3H), 2.14 (d, *J* = 6.9 Hz, 4H). LC/MS (*m/z*): 489.244 [M+H$^+$]; UPLC t_R 1.34 min

4-(5-Fluoro-2,3-dihydro-1*H*-isoindole-2-carbonyl)-5-((1-((4-methoxyphenyl)methyl)-3-phenyl-1*H*-pyrazol-5-yl)amino)benzene-1,3-diol (29). Acid **19b** (90 mM in 1:1 CH_2Cl_2:THF, 1.0 mL, 90 μmol) was coupled with 5-fluoroisoindoline hydrochloride (23 mg, 140 μmol), and triethylamine (38 μL, 270 μmol) using General Procedure G to give 39 mg of MOM-protected intermediate (68% yield) after purification via automated flash chromatography (8% to 30% acetone in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.74 (m, 2H), 7.38 (dd, *J* = 8.4, 6.9 Hz, 2H), 7.32 – 7.27 (m, 1H), 7.12 (ddd, *J* = 11.7, 7.9, 3.6 Hz, 2H), 7.04 – 6.80 (m, 2H), 6.72 – 6.59 (m, 2H), 6.48 (d, *J* = 5.9 Hz, 1H), 6.43 – 6.36 (m, 2H), 6.30 (t, *J* = 1.9 Hz, 1H), 5.16 (d, *J* = 9.5 Hz, 4H), 5.06 (s, 2H), 4.98 – 4.73 (m, 3H), 4.57 – 4.43 (m, 1H), 3.69 (s, 3H), 3.50 – 3.38 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 166.8, 163.9, 163.8, 161.5, 161.4, 159.9, 159.9, 159.0, 155.4, 155.4, 150.1, 143.6, 143.6, 140.0, 140.0, 138.6, 138.5, 138.3, 138.2, 133.7, 132.0, 132.0, 131.7, 131.7, 128.7, 128.6, 128.6, 128.4, 128.3, 127.6, 125.4, 124.3, 124.2, 123.9, 123.8, 115.1, 115.0, 114.9, 114.8, 113.9, 110.3, 110.1, 109.8, 109.6, 107.6, 107.6, 96.7, 96.2, 96.2, 95.4, 95.4, 95.3, 94.3, 56.6, 56.3, 55.1, 55.1, 52.9, 52.4, 52.0, 51.8, 51.5. LC/MS (*m/z*): 639.306 [M+H$^+$]; UPLC t_R 1.98 min.

The MOM-protected intermediate (39.3 mg, 61.5 μmol) was deprotected using General Procedure F to afford 6.6 mg of **29** (19% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (500 MHz, CD_3OD) δ 7.72 – 7.60 (m, 2H), 7.34 (dd, *J* = 8.4, 6.9 Hz, 2H), 7.28 – 7.22 (m, 1H), 7.21 (s, 1H), 7.08 – 7.00 (m, 2H), 6.98 (dd, *J* = 9.0, 7.0 Hz, 2H), 6.72 – 6.64 (m, 2H), 6.45 (s, 1H), 5.93 (dd, *J* = 12.7, 2.1 Hz, 2H), 5.17 (s, 2H), 4.97 – 4.43 (m, 4H), 3.65 (s, 3H). ^{13}C NMR (126 MHz, $(CD_3)_2SO$) δ 166.5, 161.8 (d, $^1J_{C-F}$ = 241.3 Hz), 159.4, 158.5, 155.6, 148.7, 143.6, 141.2, 133.4, 129.0, 128.8, 128.5, 127.3, 124.7, 124.5 (d, $^3J_{C-F}$ = 9.5 Hz), 114.3 (d, $^2J_{C-F}$ = 22.9

Hz), 113.6, 110.0 (d, $^{2}J_{C\text{-}F}$ = 22.9 Hz), 103.9, 96.2, 94.6, 93.1, 55.0, 50.5, 40.4. LC/MS (*m/z*): 551.250 [M+H^{+}]; UPLC t_R 1.64 min.

***N*-(Cyclopropylmethyl)-2,4-dihydroxy-6-((1-((4-methoxyphenyl)methyl)-3-methyl-1*H*-pyrazol-5-yl)amino)-*N*-methylbenzamide (30).** Acid **19a** (49 mg, 110 µmol) was coupled with (cyclopropylmethyl)methylamine (27 mg, 320 µmol), and triethylamine (30 µL, 210 µmol) using General Procedure G to give 43 mg of MOM-protected intermediate (76% yield) after purification via automated flash chromatography (10% to 35% acetone in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 – 7.07 (m, 2H), 6.80 (t, *J* = 8.6 Hz, 2H), 6.43 – 6.26 (m, 1H), 6.25 – 6.15 (m, 1H), 5.84 (d, *J* = 8.5 Hz, 1H), 5.19 – 4.92 (m, 6H), 3.75 (d, *J* = 4.1 Hz, 3H), 3.50 – 3.30 (m, 7H), 3.10 – 2.87 (m, 3H), 2.31 – 2.17 (m, 3H), 1.07 – -0.15 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 167.2, 159.5, 159.4, 159.0, 159.0, 155.0, 154.7, 147.7, 147.6, 143.9, 143.9, 139.7, 139.6, 128.9, 128.8, 128.8, 128.7, 114.0, 113.9, 107.4, 107.2, 98.3, 97.9, 96.6, 96.4, 95.0, 95.0, 94.8, 94.7, 94.3, 94.3, 56.4, 56.3, 56.2, 56.2, 55.4, 55.2, 55.2, 51.1, 51.0, 36.2, 32.4, 14.2, 9.9, 9.2, 3.9, 3.5, 3.4, 3.4. LC/MS (*m/z*): 525.249 [M+H^{+}]; UPLC t_R 1.66 min

The MOM-protected intermediate (42.7 mg, 81.4 µmol) was deprotected using General Procedure F to afford 19.2 mg of **30** (54% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.07 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 5.89 (s, 1H), 5.87 – 5.79 (m, 2H), 5.05 (s, 2H), 3.74 (s, 3H), 3.19 (dd, *J* = 6.9, 4.6 Hz, 2H), 3.02 (s, 3H), 2.20 (s, 4H), 0.99 – 0.82 (m, 1H), 0.53 – 0.32 (m, 2H), 0.12 (ddt, *J* = 37.2, 9.5, 4.8 Hz, 2H). LC/MS (*m/z*): 437.213 [M+H^{+}]; UPLC t_R 1.28 min.

***N*-(Cyclopropylmethyl)-2,4-dihydroxy-6-((1-((4-methoxyphenyl)methyl)-3-phenyl-1*H*-pyrazol-5-yl)amino)-*N*-methylbenzamide (31).** Acid **19b** (90 mM in 1:1 CH_2Cl_2:THF, 1.0 mL, 90 µmol) was coupled with (cyclopropylmethyl)methylamine (23 mg, 270 µmol), and

triethylamine (25 µL, 180 µmol) using General Procedure G to give 40 mg of MOM-protected intermediate (75% yield) after purification via automated flash chromatography (8% to 30% acetone in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dt, *J* = 8.2, 1.6 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.33 – 7.27 (m, 1H), 7.22 (dd, *J* = 8.8, 2.6 Hz, 2H), 6.87 – 6.71 (m, 2H), 6.41 – 6.31 (m, 2H), 6.30 – 6.24 (m, 1H), 5.29 – 5.09 (m, 4H), 5.03 (s, 2H), 3.76 (d, *J* = 4.5 Hz, 3H), 3.50 – 3.30 (m, 7H), 3.17 – 2.92 (m, 4H), 1.04 – -0.10 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 167.2, 159.5, 159.4, 159.1, 159.1, 155.1, 154.8, 150.1, 150.1, 143.8, 143.7, 140.5, 140.3, 133.8, 133.7, 128.9, 128.9, 128.5, 128.5, 128.4, 127.6, 125.4, 114.0, 114.0, 107.5, 107.3, 96.8, 96.6, 96.0, 95.5, 95.1, 95.0, 94.8, 94.3, 94.3, 56.4, 56.4, 56.3, 56.2, 55.2, 55.2, 51.6, 51.6, 51.1, 36.2, 32.5, 10.0, 9.3, 3.9, 3.5, 3.5, 3.4. LC/MS (*m/z*): 587.306 [M+H$^+$]; UPLC t_R 1.95 min

The MOM-protected intermediate (39.8 mg, 54.9 µmol) was deprotected using General Procedure F to afford 5.7 mg of **19b** (17% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (500 MHz, CD_3OD) δ 7.78 – 7.73 (m, 2H), 7.38 (dd, *J* = 8.3, 7.0 Hz, 2H), 7.32 – 7.26 (m, 1H), 7.18 – 7.12 (m, 2H), 6.87 – 6.81 (m, 2H), 6.45 (s, 1H), 5.93 (d, *J* = 2.1 Hz, 1H), 5.88 (d, *J* = 2.1 Hz, 1H), 5.20 (s, 2H), 3.75 (s, 3H), 3.26 – 3.15 (m, 2H), 3.03 (s, 3H), 0.99 – 0.84 (m, 1H), 0.50 – 0.33 (m, 2H), 0.12 (ddq, *J* = 42.7, 9.6, 4.8 Hz, 2H). LC/MS (*m/z*): 499.182 [M+H$^+$]; UPLC t_R 1.60 min

5-((1-((4-methoxyphenyl)methyl)-3-methyl-1*H*-pyrazol-5-yl)amino)-4-(5-((1-methylpiperidin-4-yl)amino)-2,3-dihydro-1*H*-isoindole-2-carbonyl)benzene-1,3-diol (32). Amide **16a** (41.8 mg, 62.3 µmol) was deprotected using General Procedure F to afford 3.3 mg of **32** (9.1% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.52 (s, 1H), 7.08 – 6.94 (m, 3H), 6.63 (d, *J* = 8.7 Hz, 4H), 5.91 (d, *J* = 2.1 Hz, 1H), 5.88 (s, 1H), 5.82 (d, *J* = 2.0 Hz, 1H), 5.01 (s, 3H), 4.84 – 4.29 (m, 4H), 3.64 (s, 3H), 3.51 (s, 1H),

3.03 – 2.81 (m, 4H), 2.72 (s, 3H), 2.65 (s, 1H), 2.14 (s, 5H), 1.66 (s, 1H). LC/MS (*m/z*): 583.336 [M+H$^+$]; UPLC t_R 0.88 min.

5-((1-((4-Methoxyphenyl)methyl)-3-phenyl-1*H*-pyrazol-5-yl)amino)-4-(5-((1-methylpiperidin-4-yl)amino)-2,3-dihydro-1*H*-isoindole-2-carbonyl)benzene-1,3-diol (33). Acid **19b** 77 mM in 1:1 CH_2Cl_2:THF, 1.0 mL, 77 µmol) was coupled with *N*-(1-methylpiperidin-4-yl)isoindolin-5-amine dihydrogenchloride (25 mg, 81 µmol), and triethylamine (85 µL, 610 µmol) using General Procedure G to give 35 mg of MOM-protected intermediate (59% yield) after purification via silica gel flash chromatography (96:4:1 CH_2Cl_2:methanol:conc. NH_4OH (aq.)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.6 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.30 (d, *J* = 7.2 Hz, 1H), 7.21 – 7.05 (m, 2H), 6.71 – 6.61 (m, 2H), 6.60 – 6.46 (m, 1H), 6.40 (dd, *J* = 12.6, 10.4 Hz, 3H), 6.26 (dd, *J* = 8.6, 2.1 Hz, 1H), 5.15 (d, *J* = 6.9 Hz, 4H), 5.05 (d, *J* = 2.0 Hz, 2H), 4.81 (dt, *J* = 21.1, 14.4 Hz, 3H), 3.68 (d, *J* = 1.6 Hz, 3H), 3.47 – 3.35 (m, 6H), 2.81 (s, 1H), 2.30 (d, *J* = 8.6 Hz, 3H), 2.20 – 1.92 (m, 3H), 1.49 (d, *J* = 11.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 166.7, 159.7, 159.0, 155.4, 150.1, 147.1, 147.0, 143.5, 140.0, 137.8, 137.5, 133.7, 128.8, 128.5, 128.4, 127.6, 125.4, 124.8, 124.5, 123.7, 123.2, 113.9, 113.6, 113.4, 106.8, 106.3, 96.5, 96.4, 95.3, 94.3, 56.5, 56.3, 55.1, 54.5, 52.6, 52.2, 51.8, 51.6, 46.2, 32.4. LC/MS (*m/z*): 733.603 [M+H$^+$]; UPLC t_R 1.45 min

The MOM-protected intermediate (34.7 mg, 47.4 µmol) was deprotected using General Procedure F to afford 7.7 mg of **33** (25% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.52 (s, 1H), 7.76 – 7.63 (m, 2H), 7.42 – 7.22 (m, 3H), 7.10 – 6.94 (m, 2H), 6.71 – 6.60 (m, 3H), 6.55 (s, 1H), 6.44 (s, 1H), 5.92 (dd, *J* = 16.0, 2.1 Hz, 1H), 5.15 (s, 2H), 4.83 – 4.43 (m, 4H), 3.64 (s, 3H), 3.52 (s, 1H), 3.36 (d, *J* = 14.5 Hz, 2H), 2.99 (s, 2H), 2.76 (s, 3H), 2.18 (d, *J* = 14.2 Hz, 2H), 1.68 (s, 2H). LC/MS (*m/z*): 645.481 [M+H$^+$]; UPLC t_R 1.21 min

4-(5-(2-(Dimethylamino)ethoxy)-2,3-dihydro-1*H*-isoindole-2-carbonyl)-5-((1-((4-methoxyphenyl)methyl)-3-methyl-1*H*-pyrazol-5-yl)amino)benzene-1,3-diol (34). Amide **16b** (37.7 mg, 58.4 µmol) was deprotected using General Procedure F to afford 8.2 mg of **34** (25% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.52 (s, 1H), 7.19 (s, 1H), 7.02 – 6.96 (m, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 6.65 (d, *J* = 8.7 Hz, 2H), 5.92 (d, *J* = 2.1 Hz, 1H), 5.88 (s, 1H), 5.83 (d, *J* = 2.1 Hz, 1H), 5.02 (s, 3H), 4.85 – 4.45 (m, 3H), 4.22 (t, *J* = 5.3 Hz, 2H), 3.65 (s, 3H), 3.25 – 3.18 (m, 2H), 2.70 (s, 7H), 2.65 (s, 5H), 2.13 (s, 3H). LC/MS (*m/z*): 558.328 [$M+H^+$]; UPLC t_R 0.90 min.

4-(5-(2-(Dimethylamino)ethoxy)-2,3-dihydro-1*H*-isoindole-2-carbonyl)-5-((1-((4-methoxyphenyl)methyl)-3-phenyl-1*H*-pyrazol-5-yl)amino)benzene-1,3-diol (35). To a suspension of crude carboxylic acid **19b** (57 mg, 110 µmol) and 2-(isoindolin-5-yloxy)-*N*,*N*-dimethylethan-1-amine dihydrochloride (24 mg, 86 µmol) in CH_2Cl_2 (0.7 mL) and THF (0.7 mL) was added triethylamine (60 µL, 430 µmol) followed by HATU (26 mg, 69 µmol). After the suspension was stirred overnight at room temperature, additional 2-(isoindolin-5-yloxy)-*N*,*N*-dimethylethan-1-amine dihydrochloride (12 mg, 43 µmol), triethylamine (60 µL, 430 µmol) and HATU (13 mg, 34 µmol) were added to the reaction. After stirring overnight, the reaction was diluted with CH_2Cl_2. The reaction mixture was washed with saturated $NaHCO_3$ (aq.), brine and then dried with anhydrous Na_2SO_4. The salts from each suspension were removed via gravity filtration and volatile materials were condensed *in vacuo*. The crude mixture was purified via automated flash chromatography (2% to 5% methanol in CH_2Cl_2) to afford 47 mg of MOM-protected intermediate (60% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.73 (m, 2H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.30 (d, *J* = 7.1 Hz, 1H), 7.23 – 7.01 (m, 3H), 6.91 – 6.80 (m, 1H), 6.66 (d, *J* = 8.6 Hz, 2H), 6.45 (d, *J* = 5.8 Hz, 1H), 6.42 – 6.33 (m, 2H), 6.28 (dd, *J* = 3.4, 2.1 Hz, 1H), 5.16 (d, *J* =

7.4 Hz, 4H), 5.05 (d, *J* = 1.9 Hz, 2H), 4.95 – 4.73 (m, 3H), 4.55 – 4.43 (m, 1H), 4.07 (dt, *J* = 17.1, 5.6 Hz, 2H), 3.68 (d, *J* = 1.0 Hz, 3H), 3.44 (t, *J* = 1.4 Hz, 6H), 2.80 (dt, *J* = 9.2, 5.5 Hz, 2H), 2.40 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 166.8, 159.8, 159.1, 158.8, 158.7, 155.4, 150.1, 143.6, 140.1, 138.0, 137.6, 133.8, 128.7, 128.5, 128.4, 127.5, 125.4, 123.7, 123.3, 114.8, 114.6, 114.0, 108.8, 108.6, 108.0, 96.7, 96.4, 95.4, 94.4, 66.0, 58.1, 56.5, 56.2, 55.1, 53.1, 52.5, 52.2, 51.8, 51.5, 45.7. LC/MS (*m/z*): 708.551 [M+H$^+$]; UPLC t_R 1.45 min.

To a solution of the resulting MOM-protected intermediate (46.7 mg, 66.0 µmol) in methanol (6.4 mL) at room temperature was added HCl (aq.) (2 M, 0.21 mL, 420 µmol) and stirred at 50 ºC overnight. Additional HCl (aq.) (2 M, 0.21 mL, 420 µmol) was added to the reaction mixture and stirred at 50 ºC overnight. The reaction was cooled the room temperature and volatile materials were condensed *in vacuo*. The crude residue was purified using mass-guided preparative HPLC to afford 29.2 mg of **35** (71% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.68 (dt, *J* = 6.4, 1.3 Hz, 2H), 7.37 – 7.28 (m, 2H), 7.28 – 7.20 (m, 1H), 7.16 (d, *J* = 8.6 Hz, 1H), 7.10 – 6.99 (m, 2H), 6.97 – 6.79 (m, 2H), 6.74 – 6.59 (m, 2H), 6.43 (s, 1H), 5.94 (dd, *J* = 14.2, 2.0 Hz, 2H), 5.16 (s, 2H), 4.85 – 4.45 (m, 4H), 4.25 (t, *J* = 5.1 Hz, 2H), 3.64 (s, 3H), 3.41 (t, *J* = 4.9 Hz, 2H), 3.34 (s, 1H), 2.84 (s, 6H). LC/MS (*m/z*): 620.473 [M+H$^+$]; UPLC t_R 1.20 min.

5-((1-((4-Methoxyphenyl)methyl)-3-methyl-1*H*-pyrazol-5-yl)amino)-4-[5-(4-methylpiperazin-1-yl)-2,3-dihydro-1*H*-isoindole-2-carbonyl)benzene-1,3-diol (36). Amide **16c** (38.8 mg, 59.1 µmol) was deprotected using General Procedure F to afford 14.6 mg of **36** (43% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.04 – 6.92 (m, 4H), 6.68 – 6.58 (m, 2H), 5.92 (d, *J* = 2.1 Hz, 1H), 5.88 (s, 1H), 5.83 (d, *J* = 2.1 Hz, 1H), 5.01 (s, 3H), 4.68 (d, *J* = 59.6 Hz, 4H), 3.63 (s, 3H), 3.30 (dt, *J* = 3.7, 1.9 Hz, 4H), 3.01

(d, *J* = 5.1 Hz, 4H), 2.66 – 2.61 (m, 3H), 2.13 (s, 3H). LC/MS (*m/z*): 569.311 [M+H$^+$]; UPLC t_R 0.77 min.

***N*-Benzyl-2,4-dihydroxy-6-((1-((4-methoxyphenyl)methyl)-3-methyl-1*H*-pyrazol-5-yl)amino)-*N*-methylbenzamide (37).** Amide **16d** (39.1 mg, 69.7 µmol) was deprotected using General Procedure F to afford 12.6 mg of **37** (38% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.19 (q, *J* = 4.2, 3.4 Hz, 5H), 7.10 – 7.02 (m, 2H), 6.83 – 6.73 (m, 2H), 5.95 – 5.82 (m, 3H), 5.04 (s, 2H), 4.53 (d, *J* = 14.7 Hz, 2H), 3.70 (s, 3H), 2.84 (s, 3H), 2.21 (s, 3H). LC/MS (*m/z*): 473.16 [M+H$^+$]; UPLC t_R 1.49 min.

5-((1-((4-Methoxyphenyl)methyl)-3-phenyl-1*H*-pyrazol-5-yl)amino)-4-(pyrrolidine-1-carbonyl)benzene-1,3-diol (38). Acid **19b** (31.5 mg, 60.6 µmol) was coupled with pyrrolidine (6.5 mg, 91 µmol), and triethylamine (17 µL, 120 µmol) using General Procedure G to give 22.6 mg of MOM-protected intermediate (65% yield) after purification via automated flash chromatography (30% to 60% ethyl acetate in hexanes, 10% to 20% ethyl acetate in CH_2Cl_2, and 10% to 30% acetone in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.76 (m, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.25 – 7.16 (m, 2H), 6.86 – 6.74 (m, 2H), 6.69 (s, 1H), 6.40 – 6.32 (m, 2H), 6.28 (d, *J* = 2.1 Hz, 1H), 5.26 – 5.09 (m, 4H), 5.03 (s, 2H), 3.76 (s, 3H), 3.47 (s, 6H), 3.42 (s, 3H), 3.21 (s, 1H), 2.80 (s, 3H), 1.90 (d, *J* = 6.3 Hz, 3H), 1.76 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 159.5, 159.1, 155.3, 150.1, 143.5, 140.4, 133.8, 129.0, 128.5, 127.6, 125.4, 114.0, 108.5, 96.6, 95.7, 95.3, 95.2, 94.3, 56.4, 56.2, 55.2, 51.6, 47.5, 45.6, 25.8, 24.5. LC/MS (*m/z*): 573.457 [M+H$^+$]; UPLC t_R 1.87 min

The MOM-protected intermediate (22.6 mg, 39.5 µmol) was deprotected using General Procedure F to afford 8.5 mg of **38** (44% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.82 – 7.66 (m, 2H), 7.38 (dd, *J* = 8.2, 6.8 Hz, 2H), 7.32 – 7.24 (m,

1H), 7.14 (s, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.45 (s, 1H), 5.89 (d, *J* = 4.1 Hz, 2H), 5.19 (s, 2H), 3.75 (s, 3H), 3.41 – 3.23 (m, 5H), 1.98 – 1.69 (m, 4H). LC/MS (*m/z*): 485.377 [M+H$^+$]; UPLC t_R 1.53 min.

***N*,*N*-Diethyl-2,4-dihydroxy-6-((1-((4-methoxyphenyl)methyl)-3-phenyl-1*H*-pyrazol-5-yl)amino)benzamide (39).** Acid **19b** (35.6 mg, 68.5 µmol) was coupled with diethylamine (7.5 mg, 100 µmol), and triethylamine (19 µL, 140 µmol) using General Procedure G to give 25.2 mg of MOM-protected intermediate (64% yield) after purification via automated flash chromatography (20% to 50% ethyl acetate in hexanes and 10% to 30% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.76 (m, 2H), 7.43 – 7.36 (m, 2H), 7.33 – 7.28 (m, 1H), 7.24 – 7.14 (m, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 6.38 – 6.36 (m, 1H), 6.35 (d, *J* = 2.1 Hz, 1H), 6.27 (d, *J* = 2.1 Hz, 1H), 6.11 (s, 1H), 5.29 – 5.10 (m, 4H), 5.02 (s, 2H), 3.76 (s, 3H), 3.64 (dq, *J* = 13.7, 6.9 Hz, 1H), 3.46 (s, 3H), 3.42 (s, 3H), 3.33 (dp, *J* = 14.3, 7.1 Hz, 2H), 3.18 (dq, *J* = 14.3, 7.1 Hz, 1H), 1.14 (t, *J* = 7.1 Hz, 3H), 1.02 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 159.3, 159.1, 154.7, 150.2, 143.4, 140.5, 133.7, 128.8, 128.5, 128.5, 127.6, 125.4, 114.1, 108.2, 96.8, 95.8, 95.1, 95.0, 94.3, 56.4, 56.2, 55.2, 51.5, 43.0, 39.0, 14.3, 12.9. LC/MS (*m/z*): 575.485 [M+H$^+$]; UPLC t_R 1.95 min.

The MOM-protected intermediate (25.4 mg, 44.2 µmol) was deprotected using General Procedure F to afford 13.5 mg of **39** (63% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.79 – 7.71 (m, 2H), 7.38 (td, *J* = 7.3, 6.4, 1.3 Hz, 2H), 7.32 – 7.26 (m, 1H), 7.21 – 7.10 (m, 2H), 6.94 – 6.78 (m, 2H), 6.44 (s, 1H), 5.91 (dd, *J* = 14.7, 2.1 Hz, 2H), 5.19 (s, 2H), 3.75 (s, 3H), 3.43 (dq, *J* = 14.1, 7.1 Hz, 2H), 3.36 – 3.24 (m, 2H), 1.07 (t, *J* = 7.1 Hz, 6H). LC/MS (*m/z*): 487.406 [M+H$^+$]; UPLC t_R 1.61 min.

4-(2,3-Dihydro-1*H*-isoindole-2-carbonyl)-5-((1-((4-methoxyphenyl)methyl)-1*H*-pyrazol-5-yl)amino)benzene-1,3-diol (40). Amide **14c** (62.4 mg, 114 µmol) was deprotected using General Procedure F to afford 23.8 mg of **40** (46% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.43 (d, *J* = 2.1 Hz, 1H), 7.28 (s, 4H), 7.02 – 6.96 (m, 2H), 6.67 – 6.59 (m, 2H), 6.10 (d, *J* = 2.1 Hz, 1H), 5.92 (d, *J* = 2.1 Hz, 1H), 5.77 (d, *J* = 2.1 Hz, 1H), 5.10 (s, 2H), 4.98 – 4.56 (m, 4H), 3.63 (s, 3H). ^{13}C NMR (126 MHz, $(CD_3)_2SO$) δ 166.6, 159.3, 158.5, 155.5, 143.7, 143.6, 139.73, 139.66, 138.1, 129.1, 128.8, 127.3, 122.8, 122.8, 113.6, 103.3, 98.8, 94.4, 92.6, 55.0, 50.4, 40.4. LC/MS (*m/z*): 457.227 [M+H$^+$]; UPLC t_R 1.30 min.

4-(2,3-Dihydro-1*H*-isoindole-2-carbonyl)-5-((1-((4-methoxyphenyl)methyl)-4-methyl-1*H*-pyrazol-5-yl)amino)benzene-1,3-diol (41). Amide **14d** (49.1 mg, 87.9 µmol) was deprotected using General Procedure F to afford 12.2 mg of **41** (30% yield) after purification using mass-guided preparative HPLC ^{1}H NMR (400 MHz, CD_3OD) δ 7.31 (d, *J* = 14.5 Hz, 5H), 6.98 (d, *J* = 8.6 Hz, 2H), 6.65 – 6.54 (m, 3H), 5.87 (d, *J* = 2.1 Hz, 1H), 5.34 (d, *J* = 2.0 Hz, 1H), 5.03 (s, 2H), 4.94 – 4.73 (m, 4H), 3.63 (s, 3H), 1.90 (s, 3H). ^{13}C NMR (126 MHz, $(CD_3)_2SO$) δ 166.6, 159.3, 158.4, 155.5, 144.4, 138.4, 136.7 (br), 136.6, 129.4, 128.9, 127.3, 122.9, 113.5, 109.9, 103.4, 93.8, 91.6, 55.0, 50.5, 40.4, 8.3. LC/MS (*m/z*): 471.251 [M+H$^+$]; UPLC t_R 1.34 min.

4-(2,3-Dihydro-1*H*-isoindole-2-carbonyl)-5-((1-((4-methoxyphenyl)methyl)-4-(propan-2-yl)-1*H*-pyrazol-5-yl)amino)benzene-1,3-diol (42). Amide **14e** (53.7 mg, 91.5 µmol) was deprotected using General Procedure F to afford 22.4 mg of **42** (49% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.39 (s, 1H), 7.29 (s, 4H), 6.98 (d, *J* = 8.2 Hz, 2H), 6.62 – 6.50 (m, 3H), 5.88 (d, *J* = 2.1 Hz, 1H), 5.31 (d, *J* = 2.1 Hz, 1H), 5.00 (s, 2H), 4.97 – 4.70 (m, 4H), 3.61 (s, 3H), 2.73 (p, *J* = 6.9 Hz, 1H), 1.14 (d, *J* = 6.9 Hz, 6H). LC/MS (*m/z*): 499.255 [M+H$^+$]; UPLC t_R 1.47 min.

4-(2,3-Dihydro-1*H*-isoindole-2-carbonyl)-5-((1-((4-methoxyphenyl)methyl)-4-phenyl-1*H*-pyrazol-5-yl)amino)benzene-1,3-diol (43). Amide **14f** (25.4 mg, 40.9 µmol) was deprotected using General Procedure F to afford 15.0 mg of **43** (69% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.81 (s, 1H), 7.50 – 7.44 (m, 2H), 7.33 – 7.16 (m, 9H), 7.10 (dd, *J* = 13.6, 7.6 Hz, 3H), 6.65 (d, *J* = 8.2 Hz, 2H), 5.87 (d, *J* = 2.1 Hz, 1H), 5.37 (d, *J* = 2.1 Hz, 1H), 5.12 (s, 2H), 3.65 (s, 3H). LC/MS (*m/z*): 533.257 [M+H$^+$]; UPLC t_R 1.53 min.

5-((4-Benzyl-1-((4-methoxyphenyl)methyl)-1*H*-pyrazol-5-yl)amino)-4-(2,3-dihydro-1*H*-isoindole-2-carbonyl)benzene-1,3-diol (44). Amide **14g** (45.3 mg, 71.4 µmol) was deprotected using General Procedure F to afford 23.5 mg of **44** (60% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.29 (d, *J* = 4.5 Hz, 5H), 7.09 (d, *J* = 5.6 Hz, 4H), 7.04 – 6.95 (m, 3H), 6.67 – 6.56 (m, 3H), 5.88 (d, *J* = 2.1 Hz, 1H), 5.36 (d, *J* = 2.1 Hz, 1H), 5.05 (s, 2H), 4.96 – 4.57 (m, 4H), 3.68 – 3.59 (m, 5H). LC/MS (*m/z*): 547.17 [M+H$^+$]; UPLC t_R 1.70 min.

(5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)(2-((3-ethyl-1-(4-methoxybenzyl)-1*H*-pyrazol-5-yl)amino)-4,6-dihydroxyphenyl)methanone (45). Acid **19c** (51.7 mg, 110 µmol) was coupled with 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine dihydrochloride (31.7 mg, 164 µmol), and triethylamine (115 µL, 822 µmol) using General Procedure G to give 33.2 mg of MOM-protected intermediate (53% yield) after purification via silica gel flash chromatography (1% to 4% methanol in CH_2Cl_2) and manual flash chromatography (20:80:1 CH_2Cl_2:ethyl acetate:conc. NH_4OH (aq.)) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 – 8.41 (m, 1H), 7.21 (ddd, *J* = 13.4, 7.6, 4.9 Hz, 1H), 7.08 (dd, *J* = 8.4, 5.9 Hz, 2H), 6.67 (dd, *J* = 8.7, 3.2 Hz, 2H), 6.47 (d, *J* = 2.8 Hz, 1H), 6.40 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.26 (dd, *J* = 11.8, 2.1 Hz, 1H), 5.88 (d, *J* = 2.1 Hz, 1H), 5.22 – 5.00 (m, 6H), 4.99 – 4.78

(m, 3H), 4.52 (d, *J* = 15.5 Hz, 1H), 3.69 (d, *J* = 2.6 Hz, 3H), 3.45 (dd, *J* = 4.4, 1.7 Hz, 6H), 2.61 (qd, *J* = 7.7, 1.9 Hz, 2H), 1.29 – 1.14 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 167.1, 159.9, 159.0, 158.9, 157.6, 157.2, 155.4, 155.3, 153.7, 153.7, 149.4, 149.3, 143.8, 143.7, 139.4, 139.2, 131.0, 130.6, 130.3, 129.9, 128.8, 128.6, 128.6, 128.5, 122.5, 122.4, 113.9, 113.8, 107.1, 96.9, 96.8, 96.6, 95.4, 95.2, 95.2, 95.1, 94.3, 94.3, 56.6, 56.5, 56.2, 56.2, 55.2, 55.1, 53.4, 52.5, 51.4, 51.4, 51.3, 50.5, 22.0, 13.9. LC/MS (*m/z*): 574.383 [M+H$^+$]; UPLC t_R 1.51 min.

The MOM-protected intermediate (33.2 mg, 57.9 µmol) was deprotected using General Procedure F to afford 22.9 mg of **45** (81% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.43 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.74 (s, 1H), 7.33 (dd, *J* = 7.8, 5.0 Hz, 1H), 7.06 – 6.95 (m, 2H), 6.65 (d, *J* = 8.7 Hz, 2H), 5.93 (d, *J* = 3.1 Hz, 2H), 5.83 (d, *J* = 2.1 Hz, 1H), 5.05 (s, 2H), 4.97 – 4.48 (m, 4H), 3.64 (s, 3H), 2.51 (q, *J* = 7.6 Hz, 2H), 1.17 (t, *J* = 7.6 Hz, 3H). LC/MS (*m/z*): 486.259 [M+H$^+$]; UPLC t_R 1.16 min.

5-((3-Ethyl-1-((4-methoxyphenyl)methyl)-1*H*-pyrazol-5-yl)amino)-4-(1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole-5-carbonyl)benzene-1,3-diol (46). Acid **19c** (54.0 mg, 115 µmol) was coupled with 1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole (18.8 mg, 172 µmol), and triethylamine (32 µL, 230 µmol) using General Procedure G to give 26.9 mg of MOM-protected intermediate (42% yield) after purification via silica gel flash chromatography (12% to 35% acetone in CH_2Cl_2) and manual flash chromatography (96:4 CH_2Cl_2:methanol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.6 Hz, 2H), 6.70 (d, *J* = 8.7 Hz, 2H), 6.38 (dd, *J* = 7.1, 2.1 Hz, 1H), 6.32 (d, *J* = 13.6 Hz, 1H), 6.24 (dd, *J* = 4.2, 2.1 Hz, 1H), 5.88 (d, *J* = 1.7 Hz, 1H), 5.15 (td, *J* = 7.3, 5.2 Hz, 2H), 5.06 (d, *J* = 2.5 Hz, 4H), 4.82 – 4.59 (m, 3H), 4.32 (t, *J* = 12.4 Hz, 1H), 3.71 (d, *J* = 1.8 Hz, 3H), 3.50 – 3.39 (m, 6H), 2.62 (q, *J* = 7.6 Hz, 2H), 1.23 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 159.8, 159.8, 159.0, 158.9, 155.2, 153.8, 143.6, 139.3, 139.2, 128.8, 128.6, 128.6, 118.3, 117.8,

113.9, 113.9, 107.7, 107.6, 97.1, 97.0, 96.6, 95.3, 95.2, 94.3, 56.5, 56.2, 55.2, 55.2, 51.3, 46.6, 46.4, 45.6, 45.3, 22.0, 13.9. LC/MS (*m/z*): 563.401 [M+H$^+$]; UPLC t_R 1.39 min.

The MOM-protected intermediate (26.9 mg, 47.8 µmol) was deprotected using General Procedure F to afford 15.3 mg of **46** (67% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.43 (s, 1H), 7.00 (d, *J* = 8.7 Hz, 2H), 6.69 (d, *J* = 8.7 Hz, 2H), 5.98 – 5.89 (m, 2H), 5.82 (d, *J* = 2.1 Hz, 1H), 5.04 (s, 2H), 4.83 – 4.28 (m, 4H), 3.67 (s, 3H), 2.53 (q, *J* = 7.6 Hz, 2H), 1.19 (t, *J* = 7.6 Hz, 3H). LC/MS (*m/z*): 475.321 [M+H$^+$]; UPLC t_R 1.04 min

5-((1-((4-Methoxyphenyl)methyl)-3-(propan-2-yl)-1*H*-pyrazol-5-yl)amino)-4-(5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridine-6-carbonyl)benzene-1,3-diol (47). Acid **19d** (53.2 mg, 110 µmol) was coupled with 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine dihydrochloride (31.7 mg, 164 µmol), and triethylamine (115 µL, 822 µmol) using General Procedure G to give 44.1 mg of MOM-protected intermediate (68% yield) after purification via silica gel flash chromatography (1% to 4% methanol in CH_2Cl_2) and manual flash chromatography (20:80:1 CH_2Cl_2:ethyl acetate:conc. NH_4OH (aq.)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 – 8.42 (m, 1H), 7.56 (dd, *J* = 66.5, 7.7 Hz, 1H), 7.25 – 7.17 (m, 1H), 7.08 (dd, *J* = 8.3, 5.8 Hz, 2H), 6.68 (dd, *J* = 8.7, 2.9 Hz, 2H), 6.48 (d, *J* = 9.5 Hz, 1H), 6.40 (dd, *J* = 9.2, 2.1 Hz, 1H), 6.29 (dd, *J* = 10.5, 2.0 Hz, 1H), 5.89 (d, *J* = 3.2 Hz, 1H), 5.24 – 5.01 (m, 6H), 5.01 – 4.71 (m, 3H), 4.52 (d, *J* = 15.3 Hz, 1H), 3.69 (d, *J* = 2.7 Hz, 3H), 3.45 (d, *J* = 1.4 Hz, 3H), 3.44 (d, *J* = 1.9 Hz, 3H), 2.94 (p, *J* = 6.9 Hz, 1H), 1.25 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 167.1, 160.0, 159.0, 158.8, 158.2, 158.2, 157.6, 157.2, 155.4, 155.3, 149.4, 149.3, 143.8, 143.7, 139.2, 139.0, 131.0, 130.6, 129.9, 128.8, 128.6, 128.5, 128.5, 122.5, 122.4, 113.9, 113.8, 107.2, 107.2, 96.7, 95.4, 95.3, 95.2, 95.2, 95.1, 94.4, 94.3, 56.6, 56.5, 56.2, 56.2, 55.2, 55.1, 53.4, 52.5, 51.4, 51.4, 51.3, 50.5, 28.3, 22.8. LC/MS (*m/z*): 588.408 [M+H$^+$]; UPLC t_R 1.61 min.

The MOM-protected intermediate (44.1 mg, 71.0 μmol) was deprotected using General Procedure F to afford 24.8 mg of **47** (66% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.43 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.74 (s, 1H), 7.33 (dd, *J* = 7.8, 5.0 Hz, 1H), 6.98 (d, *J* = 8.7 Hz, 2H), 6.65 (d, *J* = 8.7 Hz, 2H), 5.99 – 5.87 (m, 2H), 5.83 (d, *J* = 2.1 Hz, 1H), 5.06 (s, 2H), 4.97 – 4.49 (m, 4H), 3.63 (s, 3H), 2.84 (hept, *J* = 6.9 Hz, 1H), 1.20 (d, *J* = 6.9 Hz, 6H). LC/MS (*m/z*): 500.285 [M+H$^+$]; UPLC t_R 1.25 min.

5-((1-((4-Methoxyphenyl)methyl)-3-(propan-2-yl)-1*H*-pyrazol-5-yl)amino)-4-(1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole-5-carbonyl)benzene-1,3-diol (48). Acid **19d** (57.5 mg, 118 μmol) was coupled with 1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-c]pyrazole (19.4 mg, 178 μmol), and triethylamine (33 μL, 240 μmol) using General Procedure G to give 23.2 mg of MOM-protected intermediate (34% yield) after purification via silica gel flash chromatography (12% to 35% acetone in CH_2Cl_2) and manual flash chromatography (96:4 CH_2Cl_2:methanol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.19 (m, 1H), 7.09 (d, *J* = 8.1 Hz, 2H), 6.70 (d, *J* = 8.4 Hz, 2H), 6.44 – 6.27 (m, 2H), 6.26 (t, *J* = 2.1 Hz, 1H), 5.89 (d, *J* = 2.2 Hz, 1H), 5.21 – 5.00 (m, 6H), 4.78 – 4.57 (m, 3H), 4.38 – 4.22 (m, 1H), 3.71 (d, *J* = 1.4 Hz, 3H), 3.44 (d, *J* = 1.3 Hz, 6H), 2.94 (p, *J* = 6.9 Hz, 1H), 1.25 (dd, *J* = 7.0, 2.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 159.8, 159.8, 159.0, 158.9, 158.2, 155.2, 143.5, 143.4, 139.3, 139.2, 128.7, 128.6, 113.9, 113.9, 107.8, 107.7, 96.7, 96.6, 95.5, 95.4, 95.3, 95.2, 94.4, 56.5, 56.2, 55.2, 55.1, 51.3, 51.3, 46.6, 46.4, 45.6, 45.3, 28.3, 22.8. LC/MS (*m/z*): 577.382 [M+H$^+$]; UPLC t_R 1.47 min.

The MOM-protected intermediate (23.2 mg, 40.2 μmol) was deprotected using General Procedure F to afford 15.3 mg of **48** (78% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.43 (s, 1H), 7.05 – 6.92 (m, 2H), 6.74 – 6.63 (m, 2H), 5.99 – 5.88

(m, 2H), 5.82 (d, *J* = 2.1 Hz, 1H), 5.05 (s, 2H), 4.79 – 4.22 (m, 4H), 3.67 (s, 3H), 2.85 (h, *J* = 6.9 Hz, 1H), 1.21 (d, *J* = 6.9 Hz, 6H). LC/MS (*m/z*): 489.303 [M+H$^+$]; UPLC t_R 1.13 min.

(2-((3-(*tert*-Butyl)-1-(4-methoxybenzyl)-1*H*-pyrazol-5-yl)amino)-4,6-dihydroxyphenyl)(isoindolin-2-yl)methanone (49). Amide **14h** (45.0 mg, 74.9 µmol) was deprotected using General Procedure F to afford 12.5 mg of **49** (33% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.33 – 7.17 (m, 4H), 6.93 (d, *J* = 8.7 Hz, 2H), 6.61 (d, *J* = 8.7 Hz, 2H), 5.98 (s, 1H), 5.91 (d, *J* = 2.1 Hz, 1H), 5.82 (d, *J* = 2.1 Hz, 1H), 5.07 (s, 2H), 4.93 – 4.56 (m, 4H), 3.61 (s, 3H), 1.26 (s, 9H). ^{13}C NMR (126 MHz, $(CD_3)_2SO$) δ 166.6, 159.32, 159.27, 158.4, 155.5, 143.7, 139.8, 136.7 (br), 129.4, 128.5, 127.2, 122.8, 113.6, 103.8, 94.6, 94.4, 92.9, 54.9, 50.2, 40.4, 31.9, 30.3. LC/MS (*m/z*): 513.208 [M+H$^+$]; UPLC t_R 1.73 min

(2-((3-cyclopropyl-1-(4-methoxybenzyl)-1*H*-pyrazol-5-yl)amino)-4,6-dihydroxyphenyl)(5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)methanone (50). Acid **19e** (52.5 mg, 109 µmol) was coupled with 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine dihydrochloride (31.5 mg, 163 µmol), and triethylamine (114 µL, 814 µmol) using General Procedure G to give 43.7 mg of MOM-protected intermediate (69% yield) after purification via automated flash system (1% to 4% methanol in CH_2Cl_2) and manual flash chromatography (20:80:1 CH_2Cl_2:ethyl acetate:conc. NH_4OH (aq.)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 – 8.44 (m, 1H), 7.68 – 7.40 (m, 1H), 7.25 – 7.16 (m, 1H), 7.08 (dd, *J* = 8.5, 5.0 Hz, 2H), 6.67 (dd, *J* = 8.7, 2.6 Hz, 2H), 6.48 (d, *J* = 7.3 Hz, 1H), 6.40 (dd, *J* = 8.9, 2.1 Hz, 1H), 6.29 – 6.20 (m, 1H), 5.69 (s, 1H), 5.24 – 4.97 (m, 7H), 5.00 – 4.79 (m, 3H), 4.51 (d, *J* = 15.8 Hz, 1H), 3.69 (d, *J* = 2.2 Hz, 3H), 3.45 (d, *J* = 1.5 Hz, 3H), 3.44 (d, *J* = 1.8 Hz, 3H), 1.89 (dtd, *J* = 8.9, 5.6, 5.2, 2.8 Hz, 1H), 0.89 (dd, *J* = 8.6, 2.0 Hz, 2H), 0.68 (dd, *J* = 5.2, 2.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 167.1, 159.9, 159.0, 158.9, 157.5, 157.2, 155.4, 155.3,

154.2, 154.1, 149.4, 149.3, 143.6, 143.6, 139.5, 139.3, 131.0, 130.6, 130.3, 129.9, 128.7, 128.6, 128.5, 128.5, 122.5, 122.4, 113.9, 113.8, 107.2, 107.2, 96.7, 95.4, 95.3, 95.2, 95.2, 94.6, 94.5, 94.3, 94.3, 56.6, 56.5, 56.3, 56.2, 55.2, 55.1, 53.4, 52.5, 51.4, 51.4, 51.3, 50.5, 9.6, 7.9. LC/MS (*m/z*): 586.38 [M+H$^+$]; UPLC t_R 1.46 min.

The MOM-protected intermediate (43.7 mg, 74.6 µmol) was deprotected using General Procedure F to afford 25.3 mg of **50** (68% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.43 (dd, *J* = 5.1, 1.5 Hz, 1H), 7.74 (s, 1H), 7.33 (dd, *J* = 7.7, 5.0 Hz, 1H), 7.03 – 6.90 (m, 2H), 6.72 – 6.57 (m, 2H), 5.92 (d, *J* = 2.1 Hz, 1H), 5.81 (d, *J* = 2.1 Hz, 1H), 5.74 (s, 1H), 5.03 (s, 2H), 4.94 – 4.44 (m, 4H), 3.64 (s, 4H), 1.78 (tt, *J* = 8.4, 5.0 Hz, 1H), 0.83 (dd, *J* = 8.5, 2.1 Hz, 2H), 0.61 (dd, *J* = 5.1, 2.0 Hz, 2H). LC/MS (*m/z*): 498.3 [M+H$^+$]; UPLC t_R 1.19 min

5-((3-Cyclopropyl-1-((4-methoxyphenyl)methyl)-1*H*-pyrazol-5-yl)amino)-4-(1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole-5-carbonyl)benzene-1,3-diol (51). Acid **19e** (59.7 mg, 123 µmol) was coupled with 1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole (20.2 mg, 185 µmol), and triethylamine (34 µL, 250 µmol) using General Procedure G to give 31.4 mg of MOM-protected intermediate (44% yield) after purification via automated flash system (12% to 35% acetone in CH_2Cl_2) and manual flash chromatography (96:4 CH_2Cl_2:methanol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.4 Hz, 2H), 6.75 – 6.63 (m, 2H), 6.38 (dd, *J* = 7.1, 2.1 Hz, 1H), 6.29 (d, *J* = 15.5 Hz, 1H), 6.22 (dd, *J* = 5.2, 2.1 Hz, 1H), 5.69 (s, 1H), 5.21 – 5.09 (m, 2H), 5.04 (d, *J* = 4.3 Hz, 5H), 4.78 – 4.65 (m, 2H), 4.64 (s, 1H), 4.30 (t, *J* = 12.6 Hz, 1H), 3.71 (d, *J* = 2.1 Hz, 3H), 3.48 – 3.37 (m, 6H), 1.89 (td, *J* = 8.6, 4.3 Hz, 1H), 0.89 (dd, *J* = 8.5, 2.2 Hz, 2H), 0.76 – 0.57 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 159.8, 159.8, 159.0, 158.9, 155.2, 154.2, 143.5, 139.4, 139.3, 128.7, 128.6, 128.6, 128.6,

118.2, 117.7, 113.9, 113.9, 107.7, 107.7, 96.6, 95.3, 95.2, 94.9, 94.8, 94.3, 56.5, 56.5, 56.2, 55.2, 55.1, 51.3, 46.6, 46.4, 45.6, 45.3, 9.7, 7.9. LC/MS (*m/z*): 575.397 [M+H$^+$]; UPLC t_R 1.41 min.

The MOM-protected intermediate (31.4 mg, 54.6 µmol) was deprotected using General Procedure F to afford 17.7 mg of **51** (67% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.43 (s, 1H), 6.99 (d, *J* = 8.7 Hz, 2H), 6.69 (d, *J* = 8.7 Hz, 2H), 5.90 (d, *J* = 2.1 Hz, 1H), 5.80 (d, *J* = 2.1 Hz, 1H), 5.74 (s, 1H), 5.02 (s, 2H), 4.77 – 4.18 (m, 4H), 3.67 (s, 4H), 1.82 (tt, *J* = 8.4, 5.0 Hz, 1H), 0.86 (dd, *J* = 8.5, 2.1 Hz, 2H), 0.64 (dd, *J* = 5.1, 2.1 Hz, 2H). LC/MS (*m/z*): 487.318 [M+H$^+$]; UPLC t_R 1.08 min.

5-((3-Cyclopentyl-1-((4-methoxyphenyl)methyl)-1*H*-pyrazol-5-yl)amino)-4-(5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridine-6-carbonyl)benzene-1,3-diol (52). Acid **19f** (44.7 mg, 87.4 µmol) was coupled with 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine dihydrochloride (25.3 mg, 131 µmol), and triethylamine (91.4 µL, 655 µmol) using General Procedure G to give 41.2 mg of MOM-protected intermediate (77% yield) after purification via automated flash system (1% to 4% methanol in CH_2Cl_2) and manual flash chromatography (55:45:1 CH_2Cl_2:ethyl acetate:conc. NH_4OH (aq.) to 40:60:1 CH_2Cl_2:ethyl acetate:conc. NH_4OH (aq.)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 – 8.38 (m, 1H), 7.68 – 7.38 (m, 1H), 7.24 – 7.15 (m, 1H), 7.08 (dd, *J* = 8.4, 5.7 Hz, 2H), 6.67 (dd, *J* = 8.7, 3.0 Hz, 2H), 6.46 (d, *J* = 6.2 Hz, 1H), 6.40 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.29 (dd, *J* = 11.1, 2.1 Hz, 1H), 5.88 (d, *J* = 2.7 Hz, 1H), 5.27 – 4.98 (m, 6H), 4.98 – 4.78 (m, 3H), 4.51 (d, *J* = 15.6 Hz, 1H), 3.69 (d, *J* = 2.7 Hz, 3H), 3.45 (dd, *J* = 5.0, 1.7 Hz, 6H), 3.04 (t, *J* = 8.2 Hz, 1H), 2.03 (d, *J* = 9.1 Hz, 2H), 1.85 – 1.33 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 159.9, 158.8, 157.6, 157.2, 156.5, 156.5, 155.4, 155.3, 149.4, 149.3, 143.8, 143.7, 139.3, 139.1, 131.0, 130.6, 130.3, 129.9, 128.8, 128.6, 128.6, 128.5, 122.5, 122.4, 113.9, 113.8, 107.1, 96.6, 95.8, 95.7, 95.4, 95.2, 95.2,

95.1, 94.4, 94.3, 56.6, 56.5, 56.2, 56.2, 55.2, 55.1, 53.4, 51.4, 51.3, 50.5, 39.5, 33.4, 25.4. LC/MS (*m/z*): 614.431 [M+H$^+$]; UPLC t_R 1.72 min

The MOM-protected intermediate (40.8 mg, 66.5 µmol) was deprotected using General Procedure F to afford 22.9 mg of **52** (66% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.43 (dd, *J* = 4.9, 1.5 Hz, 1H), 7.74 (s, 1H), 7.33 (dd, *J* = 7.8, 5.1 Hz, 1H), 6.98 (d, *J* = 8.7 Hz, 2H), 6.65 (d, *J* = 8.7 Hz, 2H), 5.92 (d, *J* = 2.6 Hz, 2H), 5.83 (d, *J* = 2.1 Hz, 1H), 5.05 (s, 2H), 4.88 (s, 9H), 3.64 (s, 3H), 2.92 (d, *J* = 8.1 Hz, 1H), 1.96 (s, 2H), 1.80 – 1.48 (m, 6H). ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 166.8, 159.5, 158.4, 157.3, 155.6, 154.8, 148.8, 143.9, 140.0, 131.3, 129.4, 128.7, 122.4, 113.6, 103.4, 95.8, 94.4, 93.0, 55.0, 50.1, 40.4, 32.7, 24.9 LC/MS (*m/z*): 526.308 [M+H$^+$]; UPLC t_R 1.36 min

5-((3-Cyclopentyl-1-((4-methoxyphenyl)methyl)-1*H*-pyrazol-5-yl)amino)-4-(1*H*,4H,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole-5-carbonyl)benzene-1,3-diol (53). Acid **19f** (45.3 mg, 88.6 µmol) was coupled with 1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole (14.5 mg, 133 µmol), and triethylamine (35 µL, 180 µmol) using General Procedure G to give 27.1 mg of MOM-protected intermediate (51% yield) after purification via automated flash system (12% to 35% acetone in CH_2Cl_2) and manual flash chromatography (96:4 CH_2Cl_2:methanol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 – 6.99 (m, 2H), 6.70 (d, *J* = 8.2 Hz, 2H), 6.44 – 6.29 (m, 2H), 6.27 (q, *J* = 1.9 Hz, 1H), 5.88 (d, *J* = 2.2 Hz, 1H), 5.24 – 4.95 (m, 6H), 4.78 – 4.58 (m, 3H), 4.31 (t, *J* = 12.4 Hz, 1H), 3.71 (t, *J* = 1.4 Hz, 3H), 3.44 (d, *J* = 1.5 Hz, 6H), 3.06 (q, *J* = 8.1 Hz, 1H), 2.04 (s, 2H), 1.82 – 1.48 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 159.8, 159.8, 159.0, 158.9, 156.5, 156.5, 155.2, 143.4, 139.4, 139.3, 128.7, 128.6, 113.9, 113.9, 107.8, 107.7, 96.7, 96.7, 95.9, 95.8, 95.3, 95.3, 94.4, 56.5, 56.2, 55.2, 55.1, 51.3, 51.3, 46.6, 46.4, 45.6, 45.3, 39.5, 33.4, 33.4, 25.4. LC/MS (*m/z*): 603.404 [M+H$^+$]; UPLC t_R 1.59 min.

The MOM-protected intermediate (27.1 mg, 45.0 μmol) was deprotected using General Procedure F to afford 16.1 mg of **53** (70% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.42 (s, 1H), 6.99 (d, *J* = 8.7 Hz, 2H), 6.69 (d, *J* = 8.7 Hz, 2H), 6.01 – 5.87 (m, 2H), 5.82 (d, *J* = 2.1 Hz, 1H), 5.05 (s, 2H), 4.82 – 4.24 (m, 4H), 3.67 (s, 3H), 2.92 (s, 1H), 1.98 (d, *J* = 10.7 Hz, 2H), 1.87 – 1.43 (m, 6H). LC/MS (*m/z*): 515.325 [M+H$^+$]; UPLC t_R 1.25 min.

5-((3-(Furan-3-yl)-1-((4-methoxyphenyl)methyl)-1*H*-pyrazol-5-yl)amino)-4-(5*H*,6*H*,7*H*-pyrrolo[3,4-b]pyridine-6-carbonyl)benzene-1,3-diol (54). Acid **19g** (52.5 mg, 103 μmol) was coupled with 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine dihydrochloride (29.8 mg, 155 μmol), and triethylamine (108 μL, 773 μmol) using General Procedure G to give 48.6 mg of MOM-protected intermediate (77% yield) after purification via automated flash system (0% to 3% methanol in CH_2Cl_2) and manual flash chromatography (55:45:1 CH_2Cl_2:ethyl acetate:conc. NH_4OH (aq.) to 40:60:1 CH_2Cl_2:ethyl acetate:conc. NH_4OH (aq.)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (dd, *J* = 21.5, 4.9 Hz, 1H), 7.75 (q, *J* = 1.2 Hz, 1H), 7.70 – 7.61 (m, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.44 (q, *J* = 1.7 Hz, 1H), 7.24 – 7.16 (m, 1H), 7.12 (dd, *J* = 8.7, 6.7 Hz, 2H), 6.74 (dd, *J* = 1.9, 0.9 Hz, 1H), 6.73 – 6.59 (m, 2H), 6.53 (d, *J* = 5.5 Hz, 1H), 6.42 (dd, *J* = 7.9, 2.1 Hz, 1H), 6.29 (dd, *J* = 15.9, 2.1 Hz, 1H), 6.16 (d, *J* = 2.0 Hz, 1H), 5.16 (dd, *J* = 11.1, 7.1 Hz, 5H), 5.07 (d, *J* = 2.5 Hz, 3H), 5.01 – 4.78 (m, 4H), 4.53 (d, *J* = 15.1 Hz, 1H), 3.69 (d, *J* = 3.1 Hz, 4H), 3.47 – 3.42 (m, 6H), 2.80 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 167.1, 160.0, 159.1, 159.0, 157.4, 157.1, 155.5, 155.4, 149.3, 149.2, 143.5, 143.5, 143.5, 143.2, 143.2, 140.0, 139.8, 139.1, 131.1, 130.7, 130.3, 129.9, 128.6, 128.6, 128.4, 128.2, 122.5, 122.5, 120.1, 113.9, 113.9, 108.7, 107.2, 96.7, 96.3, 95.4, 95.3, 95.3, 94.3, 94.2, 56.6, 56.6, 56.3, 56.3, 55.2, 55.2, 53.4, 52.5, 51.7, 51.6, 51.4, 50.6, 47.4, 38.6, 8.7. LC/MS (*m/z*): 612.358 [M+H$^+$]; UPLC t_R 1.55 min.

The MOM-protected intermediate (48.6 mg, 79.5 µmol) was deprotected using General Procedure F to afford 28.7 mg of **54** (69% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.39 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.76 (dd, *J* = 1.6, 0.8 Hz, 1H), 7.70 (s, 1H), 7.46 (t, *J* = 1.7 Hz, 1H), 7.29 (dd, *J* = 7.8, 5.0 Hz, 1H), 7.04 (d, *J* = 8.7 Hz, 2H), 6.72 – 6.59 (m, 3H), 6.26 (s, 1H), 5.95 (d, *J* = 2.1 Hz, 1H), 5.91 (d, *J* = 2.1 Hz, 1H), 5.14 (s, 2H), 5.02 – 4.45 (m, 4H). LC/MS (*m/z*): 524.279 [M+H$^+$]; UPLC t_R 1.25 min.

5-((3-(Furan-3-yl)-1-((4-methoxyphenyl)methyl)-1*H*-pyrazol-5-yl)amino)-4-(1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole-5-carbonyl)benzene-1,3-diol (55). Acid **19g** (51.7 mg, 101 µmol) was coupled with 1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole (16.6 mg, 152 µmol), and triethylamine (28 µL, 200 µmol) using General Procedure G to give 33.3 mg of MOM-protected intermediate (55% yield) after purification via automated flash system (10% to 30% acetone in CH_2Cl_2) and manual flash chromatography (96:4 CH_2Cl_2:methanol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.48 – 7.31 (m, 1H), 7.17 (d, *J* = 7.8 Hz, 2H), 6.80 – 6.66 (m, 3H), 6.43 (d, *J* = 8.6 Hz, 1H), 6.31 (s, 1H), 6.16 (d, *J* = 2.4 Hz, 1H), 5.16 (d, *J* = 11.2 Hz, 4H), 5.06 (s, 2H), 4.86 – 4.55 (m, 3H), 4.33 (s, 1H), 3.72 (d, *J* = 1.9 Hz, 3H), 3.51 – 3.35 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 159.8, 159.8, 159.1, 159.0, 155.3, 143.5, 143.3, 143.3, 140.0, 140.0, 139.1, 139.1, 128.7, 128.3, 128.2, 120.1, 114.0, 113.9, 108.8, 107.9, 107.8, 96.7, 96.6, 96.5, 95.4, 95.3, 94.3, 56.5, 56.3, 55.2, 55.2, 51.6, 46.6, 46.5, 45.6, 45.4. LC/MS (*m/z*): 601.331 [M+H$^+$]; UPLC t_R 1.35 min

The MOM-protected intermediate (32.9 mg, 55.8 µmol) was deprotected using General Procedure F to afford 18.9 mg of **55** (67% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.84 – 7.78 (m, 1H), 7.49 (t, *J* = 1.7 Hz, 1H), 7.41 (s, 1H), 7.05 (d, *J* = 8.7 Hz, 2H), 6.76 – 6.66 (m, 3H), 6.27 (s, 1H), 5.93 (d, *J* = 2.1 Hz, 1H), 5.89 (d, *J* = 2.1 Hz, 1H), 5.14 (s, 2H), 4.79 – 4.27 (m, 4H), 3.67 (s, 3H). LC/MS (*m/z*): 513.296 [M+H$^+$]; UPLC t_R 1.15 min.

(2,4-dihydroxy-6-((1-methyl-1*H*-pyrazol-5-yl)amino)phenyl)(isoindolin-2-yl)methanone (56). Amide **14i** (37.0 mg, 84.4 µmol) was deprotected using General Procedure F to afford 17.1 mg of **56** (58% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.36 (d, *J* = 2.0 Hz, 1H), 7.28 (s, 4H), 6.03 (d, *J* = 2.1 Hz, 1H), 5.92 (d, *J* = 2.1 Hz, 1H), 5.61 (d, *J* = 2.1 Hz, 1H), 5.07 – 4.70 (m, 4H), 3.64 (s, 3H). LC/MS (*m/z*): 351.292 [M+H$^+$]; UPLC t_R 1.09 min.

5-((1-Methyl-1*H*-pyrazol-5-yl)amino)-4-(5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridine-6-carbonyl)benzene-1,3-diol (57). Acid **19h** (27.6 mg, 81.8 µmmol) was coupled with 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine dihydrochloride (23.7 mg, 123 µmol), and triethylamine (86 µL, 610 µmol) using General Procedure G to give 13.3 mg of MOM-protected intermediate (37% yield) after purification via an automated flash system (1% to 5% methanol in CH_2Cl_2) and manual flash chromatography (60:40:1 CH_2Cl_2:acetone:conc. NH_4OH (aq.)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (dd, *J* = 19.1, 5.0 Hz, 1H), 7.77 – 7.50 (m, 1H), 7.44 (d, *J* = 2.0 Hz, 1H), 7.26 (s, 1H), 6.79 (d, *J* = 15.3 Hz, 1H), 6.45 (dd, *J* = 10.5, 2.1 Hz, 1H), 6.13 (dd, *J* = 4.4, 2.1 Hz, 1H), 6.03 (d, *J* = 2.2 Hz, 1H), 5.18 (d, *J* = 9.2 Hz, 3H), 5.11 – 4.81 (m, 4H), 4.79 – 4.53 (m, 1H), 3.70 (s, 3H), 3.46 (s, 3H), 3.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 160.1, 160.1, 157.6, 157.2, 155.7, 155.6, 149.5, 149.3, 144.6, 144.4, 138.6, 131.1, 130.6, 129.9, 122.6, 122.4, 106.9, 99.0, 96.3, 96.2, 95.5, 95.3, 95.3, 95.2, 94.3, 94.2, 56.6, 56.6, 56.3, 56.2, 53.5, 52.7, 51.5, 50.7, 35.1. LC/MS (*m/z*): 440.426 [M+H$^+$]; UPLC t_R 1.13 min

The MOM-protected intermediate (13.3 mg, 30.3 µmol) was deprotected using General Procedure F to afford 5.1 mg of **57** (48% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.44 (dd, *J* = 5.1, 1.5 Hz, 1H), 7.80 (d, *J* = 7.7 Hz, 1H), 7.36 (d, *J* =

2.0 Hz, 2H), 6.03 (d, *J* = 2.1 Hz, 1H), 5.92 (d, *J* = 2.1 Hz, 1H), 5.62 (d, *J* = 2.1 Hz, 1H), 4.90 (s, 4H), 3.65 (s, 3H). LC/MS (*m/z*): 352.218 [M+H$^+$]; UPLC t_R 0.77 min.

5-((1-Methyl-1*H*-pyrazol-5-yl)amino)-4-(1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole-5-carbonyl)benzene-1,3-diol (58). Acid **19h** (16.8 mg, 49.8 μmmol) was coupled with 1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole (8.2 mg, 75 μmol), and triethylamine (14 μL, 100 μmol) using General Procedure G to afford 4.2 mg of MOM-protected intermediate (20% yield) after purification via automated flash system (1% to 5% methanol in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 2.0 Hz, 1H), 7.34 (d, *J* = 46.2 Hz, 1H), 6.59 (d, *J* = 7.2 Hz, 1H), 6.42 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.07 (d, *J* = 2.1 Hz, 1H), 6.01 (t, *J* = 1.9 Hz, 1H), 5.16 (q, *J* = 6.3, 4.9 Hz, 2H), 5.07 (d, *J* = 2.5 Hz, 2H), 4.98 – 4.64 (m, 3H), 4.42 (dd, *J* = 13.5, 6.5 Hz, 1H), 3.67 (s, 3H), 3.45 (s, 3H), 3.43 (d, *J* = 1.6 Hz, 3H). LC/MS (*m/z*): 429.318 [M+H$^+$]; UPLC t_R 1.03 min.

The MOM-protected intermediate (4.2 mg, 9.8 μmol) was deprotected using General Procedure F to afford 2.3 mg of **58** (69% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.45 (s, 1H), 7.38 (d, *J* = 2.1 Hz, 1H), 6.04 (d, *J* = 2.1 Hz, 1H), 5.91 (d, *J* = 2.1 Hz, 1H), 5.60 (d, *J* = 2.1 Hz, 1H), 4.80 – 4.43 (m, 4H), 3.65 (s, 3H). LC/MS (*m/z*): 341.235 [M+H$^+$]; UPLC t_R 0.66 min.

4-(2,3-Dihydro-1*H*-isoindole-2-carbonyl)-5-((1-(propan-2-yl)-1*H*-pyrazol-5-yl)amino)benzene-1,3-diol (59). To a mixture of carboxylic acid **19i** (34.9 mg, 95.5 μmmol) and isoindoline hydrochloride (22.3 mg, 143 μmol) in THF (0.62 mL) and CH_2Cl_2 (0.62 mL) was added triethylamine (53 μL, 380 μmol) followed by PyBOP (59.7, 115 μmol). After the reaction was stirred at room temperature overnight, the reaction mixture was diluted with CH_2Cl_2. The reaction mixture was washed twice with saturated $NaHCO_3$ (aq.), once with brine and then dried with anhydrous Na_2SO_4. The salts were removed via gravity filtration and volatile materials were

condensed *in vacuo*. The crude residue was dissolved in methanol (4.8) and HCl (2 M, 310 µL, 620 µmol) was added to the resulting mixture. The reaction was stirred at 50 ºC overnight. After cooling to room temperature, volatile materials were condensed *in vacuo*. The crude residue was purified using mass-guided preparative HPLC to afford 8.7 mg of **59** (24% yield over 2 steps). ^{1}H NMR (400 MHz, CD_3OD) δ 7.43 (d, *J* = 2.0 Hz, 1H), 7.29 (d, *J* = 1.7 Hz, 4H), 6.03 (d, *J* = 2.0 Hz, 1H), 5.89 (d, *J* = 2.1 Hz, 1H), 5.60 – 5.55 (m, 1H), 4.90 (s, 4H), 4.55 (p, *J* = 6.7 Hz, 1H), 1.36 (d, *J* = 6.7 Hz, 6H). LC/MS (*m/z*): 379.344 [M+H$^+$]; UPLC t_R 1.25 min

(5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)(2,4-dihydroxy-6-((1-isopropyl-1*H*-pyrazol-5-yl)amino)phenyl)methanone (60). Synthesized using the same procedure for the synthesis of **59** with **19i** (37.6 mg, 103 µmol), 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine dihydrochloride (29.8 mg, 154 µmol) and triethylamine (110 µL, 770 µmol) followed by MOM deprotection with HCl (2 M, 330 µL, 670 µmol) in methanol at 50 ºC overnight to afford 6.6 mg of **60** (17% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.55 (s, 1H), 8.45 (d, *J* = 4.8 Hz, 1H), 7.82 (d, *J* = 7.4 Hz, 1H), 7.43 (d, *J* = 1.6 Hz, 1H), 7.36 (dd, *J* = 7.4, 4.8 Hz, 1H), 6.04 (d, *J* = 1.6 Hz, 1H), 5.90 (d, *J* = 2.0 Hz, 1H), 5.59 (d, *J* = 2.0 Hz, 1H), 4.65-4.53 (m, 2H), 1.67 (d, *J* = 6.6 Hz, 6H). LC/MS (*m/z*): 380.359 [M+H$^+$]; UPLC t_R 0.93 min.

5-((1-(Propan-2-yl)-1*H*-pyrazol-5-yl)amino)-4-(1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole-5-carbonyl)benzene-1,3-diol (61). Synthesized using the same procedure for the synthesis of **59** with **19i** (36.7 mg, 100 µmol), 1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole (16.4 mg, 151 µmol) and triethylamine (28 µL, 200 µmol) followed by MOM deprotection with HCl (2 M, 330 µL, 650 µmol) in methanol at 50 ºC overnight to afford 11.7 mg of **61** (32% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.45 (t, *J* = 2.8 Hz, 2H), 6.04 (d,

J = 2.0 Hz, 1H), 5.88 (d, *J* = 2.1 Hz, 1H), 5.56 (d, *J* = 2.1 Hz, 1H), 4.80 – 4.42 (m, 5H), 1.37 (d, *J* = 6.6 Hz, 6H). LC/MS (*m/z*): 369.332 [M+H$^+$]; UPLC t_R 0.82 min.

4-(2,3-Dihydro-1*H*-isoindole-2-carbonyl)-5-((1-(2-methylpropyl)-1*H*-pyrazol-5-yl)amino)benzene-1,3-diol (62). Carboxylic acid **19j** (45 mg, 120 µmol) was subjected to General Procedure H1 to afford 17 mg of **62** (37% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.40 (d, *J* = 2.0 Hz, 1H), 7.28 (s, 4H), 6.06 (d, *J* = 2.0 Hz, 1H), 5.92 (d, *J* = 2.1 Hz, 1H), 5.74 (d, *J* = 2.1 Hz, 1H), 5.14 – 4.69 (m, 4H), 3.75 (d, *J* = 7.6 Hz, 2H), 3.34 (s, 2H), 2.09 (dh, *J* = 12.5, 6.3, 5.9 Hz, 1H), 0.79 (d, *J* = 6.7 Hz, 6H). LC/MS (*m/z*): 393.238 [M+H$^+$]; UPLC t_R 1.38 min

5-((1-(2-Methylpropyl)-1*H*-pyrazol-5-yl)amino)-4-(5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridine-6-carbonyl)benzene-1,3-diol (63). Carboxylic acid **19j** (46 mg, 120 µmol) was subjected to General Procedure H2 to afford 4.7 mg of **63** (9.9% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.44 (dd, *J* = 5.2, 1.5 Hz, 1H), 7.80 (d, *J* = 7.7 Hz, 1H), 7.40 (d, *J* = 2.0 Hz, 1H), 7.35 (dd, *J* = 7.8, 5.0 Hz, 1H), 6.06 (d, *J* = 2.0 Hz, 1H), 5.92 (d, *J* = 2.1 Hz, 1H), 5.75 (d, *J* = 2.1 Hz, 1H), 5.04 – 4.57 (m, 4H), 3.77 (d, *J* = 7.5 Hz, 2H), 2.12 (hept, *J* = 7.0 Hz, 1H), 0.81 (d, *J* = 6.7 Hz, 6H). LC/MS (*m/z*): 394.341 [M+H$^+$]; UPLC t_R 1.08 min.

5-((1-(2-Methylpropyl)-1*H*-pyrazol-5-yl)amino)-4-(1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole-5-carbonyl)benzene-1,3-diol (64). Carboxylic acid **19j** (46 mg, 120 µmol) was subjected to General Procedure H3 to afford 13.2 mg of **64** (28% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.46 (s, 1H), 7.42 (d, *J* = 2.0 Hz, 1H), 6.06 (d, *J* = 2.1 Hz, 1H), 5.91 (d, *J* = 2.1 Hz, 1H), 5.72 (d, *J* = 2.1 Hz, 1H), 4.88 (s, 4H), 3.76 (d, *J* = 7.5 Hz, 2H), 2.12 (p, *J* = 6.9 Hz, 1H), 0.81 (d, *J* = 6.7 Hz, 6H). LC/MS (*m/z*): 383.27 [M+H$^+$]; UPLC t_R 0.95 min.

5-((1-(Cyclohexylmethyl)-1*H*-pyrazol-5-yl)amino)-4-(2,3-dihydro-1*H*-isoindole-2-carbonyl)benzene-1,3-diol (65). Carboxylic acid **19k** (30.9 mg, 73.4 µmol) was subjected to General Procedure H1 to afford 12.4 mg of **65** (39% yield) after purification using mass-guided preparative HPLC ^{1}H NMR (400 MHz, CD_3OD) δ 7.40 (d, *J* = 2.1 Hz, 1H), 7.29 (s, 5H), 6.06 (d, *J* = 2.1 Hz, 1H), 5.92 (d, *J* = 2.0 Hz, 1H), 5.69 (d, *J* = 2.0 Hz, 1H), 5.10 – 4.65 (m, 4H), 3.75 (d, *J* = 7.4 Hz, 2H), 1.77 (ddd, *J* = 11.1, 7.5, 3.6 Hz, 1H), 1.63 – 1.40 (m, 5H), 1.16 – 0.72 (m, 5H). ^{13}C NMR (126 MHz, 2:1 $(CD_3)_2SO$: CD_3OD) δ 167.6, 159.8, 155.8, 144.4, 140.4, 138.1, 136.9, 127.7, 123.1, 104.0, 99.5, 94.6, 92.9, 53.7, 40.4, 38.3, 30.4, 26.1, 25.5. LC/MS (*m/z*): 433.596 [M+H$^+$]; UPLC t_R 1.46 min.

5-((1-(Cyclohexylmethyl)-1*H*-pyrazol-5-yl)amino)-4-(5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridine-6-carbonyl)benzene-1,3-diol (66). Synthesized using General Procedure H2 from carboxylic acid **19k** (36.4 mg, 86.8 µmol) was subjected to General Procedure H2 to afford 13.8 mg of **66** (37% yield) after purification using mass-guided preparative HPLC ^{1}H NMR (400 MHz, CD_3OD) δ 8.44 (dd, *J* = 5.0, 1.4 Hz, 1H), 7.81 (d, *J* = 7.7 Hz, 1H), 7.40 (d, *J* = 2.0 Hz, 1H), 7.36 (dd, *J* = 7.8, 5.0 Hz, 1H), 6.06 (d, *J* = 2.0 Hz, 1H), 5.93 (d, *J* = 2.0 Hz, 1H), 5.71 (d, *J* = 2.1 Hz, 1H), 4.89 (s, 4H), 3.77 (d, *J* = 7.4 Hz, 2H), 1.86 – 1.72 (m, 1H), 1.68 – 1.39 (m, 5H), 1.18 – 0.74 (m, 5H). LC/MS (*m/z*): 434.39 [M+H$^+$]; UPLC t_R 1.22 min.

5-((1-(Cyclohexylmethyl)-1*H*-pyrazol-5-yl)amino)-4-(1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole-5-carbonyl)benzene-1,3-diol (67). The product **67** was synthesized following General Procedure H3 from carboxylic acid **19k** (37.2 mg, 88.7 µmol) was subjected to General Procedure H3 to afford 14.8 mg of **67** (40% yield) after purification using mass-guided preparative HPLC ^{1}H NMR (400 MHz, CD_3OD) δ 7.46 (s, 1H), 7.41 (d, *J* = 2.0 Hz, 1H), 6.06 (d, *J* = 2.0 Hz, 1H), 5.92 (d, *J* = 2.0 Hz, 1H), 5.69 (d, *J* = 2.1 Hz, 1H), 5.04 – 4.38 (m, 4H), 3.76 (d, *J* = 7.4 Hz, 2H), 1.79 (ddq, *J*

= 11.3, 7.4, 3.7 Hz, 1H), 1.67 – 1.43 (m, 5H), 1.18 – 0.76 (m, 5H). LC/MS (*m/z*): 423.363 [M+H$^+$]; UPLC t_R 1.08 min.

4-(2,3-Dihydro-1*H*-isoindole-2-carbonyl)-5-((1-phenyl-1*H*-pyrazol-5-yl)amino]benzene-1,3-diol (68). Synthesized using General Procedure H1 from carboxylic acid **19l** (42 mg, 110 µmol) was subjected to General Procedure H1 to afford 2.4 mg of **68** (5.5% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.61 (d, *J* = 2.0 Hz, 1H), 7.49 – 7.40 (m, 2H), 7.34 – 7.16 (m, 8H), 6.26 (d, *J* = 2.0 Hz, 1H), 5.89 (d, *J* = 2.1 Hz, 1H), 5.85 (d, *J* = 2.1 Hz, 1H), 4.98 – 4.42 (m, 4H). LC/MS (*m/z*): 413.307 [M+H$^+$]; UPLC t_R 1.39 min.

5-((1-Phenyl-1*H*-pyrazol-5-yl)amino)-4-(5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridine-6-carbonyl)benzene-1,3-diol (69). Synthesized using General Procedure H2 from carboxylic acid **19l** (43 mg, 110 µmol) was subjected to General Procedure H2 to afford 5.1 mg of **69** (11% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.45 (d, *J* = 5.0 Hz, 1H), 7.77 (s, 1H), 7.61 (d, *J* = 2.0 Hz, 1H), 7.50 – 7.41 (m, 2H), 7.39 – 7.29 (m, 3H), 7.29 – 7.18 (m, 1H), 6.26 (d, *J* = 2.0 Hz, 1H), 5.91 – 5.84 (m, 2H), 5.12 – 4.44 (m, 4H). LC/MS (*m/z*): 414.277 [M+H$^+$]; UPLC t_R 1.08 min.

5-((1-Phenyl-1*H*-pyrazol-5-yl)amino)-4-(1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole-5-carbonyl)benzene-1,3-diol (70). Synthesized using General Procedure H3 from carboxylic acid **19l** (44 mg, 110 µmol) was subjected to General Procedure H3 to afford 6.6 mg of **70** (15% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.62 (d, *J* = 2.0 Hz, 1H), 7.52 – 7.41 (m, 3H), 7.39 – 7.24 (m, 3H), 6.26 (d, *J* = 2.0 Hz, 1H), 5.85 (dd, *J* = 17.7, 2.1 Hz, 2H), 4.73 – 4.07 (m, 4H). LC/MS (*m/z*): 403.295 [M+H$^+$]; UPLC t_R 0.97 min.

5-((1-Cyclohexyl-1*H*-pyrazol-5-yl)amino)-4-(2,3-dihydro-1*H*-isoindole-2-carbonyl)benzene-1,3-diol (71). Synthesized using General Procedure H1 from carboxylic acid **19m** (48.8 mg, 120

μmol) was subjected to General Procedure H1 to afford 18.3 mg of **71** (36% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.41 (d, *J* = 2.0 Hz, 1H), 7.37 – 7.20 (m, 4H), 6.03 (d, *J* = 2.0 Hz, 1H), 5.90 (d, *J* = 2.1 Hz, 1H), 5.59 (d, *J* = 2.1 Hz, 1H), 5.03 – 4.76 (m, 4H), 4.09 (d, *J* = 11.4 Hz, 1H), 1.98 – 1.71 (m, 9H), 1.63 (d, *J* = 10.8 Hz, 1H), 1.23 (dd, *J* = 26.4, 15.1 Hz, 2H). LC/MS (*m/z*): 419.041 [M+H$^+$]; UPLC t_R 1.46 min

5-((1-Cyclohexyl-1*H*-pyrazol-5-yl)amino)-4-(5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridine-6-carbonyl)benzene-1,3-diol (72). Synthesized using General Procedure H2 from carboxylic acid **19m** (54.4 mg, 134 μmol) was subjected to General Procedure H2 to afford 14.3 mg of **72** (25% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.44 (dd, *J* = 5.1, 1.5 Hz, 1H), 7.86 – 7.74 (m, 1H), 7.40 (d, *J* = 2.0 Hz, 1H), 7.36 (dd, *J* = 7.8, 5.0 Hz, 1H), 6.03 (d, *J* = 2.0 Hz, 1H), 5.90 (d, *J* = 2.1 Hz, 1H), 5.61 (d, *J* = 2.1 Hz, 1H), 4.88 (s, 4H), 4.12 (dt, *J* = 11.3, 6.4 Hz, 1H), 1.96 – 1.71 (m, 7H), 1.71 – 1.59 (m, 1H), 1.44 – 1.08 (m, 3H). LC/MS (*m/z*): 420.32 [M+H$^+$]; UPLC t_R 1.18 min.

5-((1-Cyclohexyl-1*H*-pyrazol-5-yl)amino)-4-(1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole-5-carbonyl)benzene-1,3-diol (73). Synthesized using General Procedure H3 from carboxylic acid **19m** (58.8 mg, 145 μmol) was subjected to General Procedure H3 to afford 22.5 mg of **73** (38% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.46 (s, 1H), 7.43 (d, *J* = 2.0 Hz, 1H), 6.04 (d, *J* = 2.0 Hz, 1H), 5.89 (d, *J* = 2.1 Hz, 1H), 5.58 (d, *J* = 2.1 Hz, 1H), 4.80 – 4.43 (m, 4H), 4.11 (dt, *J* = 10.9, 6.4 Hz, 1H), 1.92 – 1.72 (m, 7H), 1.71 – 1.61 (m, 1H), 1.44 – 1.12 (m, 3H). LC/MS (*m/z*): 409.337 [M+H$^+$]; UPLC t_R 1.05 min.

5-((1-Benzyl-1*H*-pyrazol-5-yl)amino)-4-(2,3-dihydro-1*H*-isoindole-2-carbonyl)benzene-1,3-diol (74). Acid **19n** (42.1 mg, 102 μmol) was subjected to General Procedure H1 to afford 3.3 mg of **74** (7.6% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz,

CD_3OD) δ 7.45 (d, *J* = 2.0 Hz, 1H), 7.34 – 7.18 (m, 4H), 7.10 (dd, *J* = 4.0, 2.5 Hz, 3H), 7.03 (dd, *J* = 6.8, 3.0 Hz, 2H), 6.12 (d, *J* = 2.1 Hz, 1H), 5.92 (d, *J* = 2.1 Hz, 1H), 5.79 (d, *J* = 2.1 Hz, 1H), 5.18 (s, 2H), 5.01 – 4.52 (m, 4H). LC/MS (*m/z*): 427.333 [$M+H^+$]; UPLC t_R 1.37 min.

5-((1-Benzyl-1*H*-pyrazol-5-yl)amino)-4-(5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridine-6-carbonyl)benzene-1,3-diol (75). Acid **19n** (42.6 mg, 103 μmol) was subjected to General Procedure H2 to afford 2.9 mg of **75** (6.6% yield) after purification using mass-guided preparative HPLC. ^1H NMR (400 MHz, CD_3OD) δ 8.44 (d, *J* = 5.1 Hz, 1H), 7.76 (s, 1H), 7.45 (d, *J* = 2.0 Hz, 1H), 7.41 – 7.31 (m, 1H), 7.17 – 6.99 (m, 5H), 6.13 (d, *J* = 2.1 Hz, 1H), 5.92 (d, *J* = 2.1 Hz, 1H), 5.79 (d, *J* = 2.1 Hz, 1H), 5.19 (s, 2H), 5.05 – 4.11 (m, 4H). LC/MS (*m/z*): 428.347 [$M+H^+$]; UPLC t_R 1.08 min.

5-((1-Benzyl-1*H*-pyrazol-5-yl)amino)-4-(1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole-5-carbonyl)benzene-1,3-diol (76). Acid **19n** (43 mg, 100 μmol) was subjected to General Procedure H3 to afford 5.0 mg of **76** (12% yield) after purification using mass-guided preparative HPLC. ^1H NMR (400 MHz, CD_3OD) δ 7.51 – 7.33 (m, 2H), 7.15 (dd, *J* = 5.2, 1.9 Hz, 4H), 7.06 (dd, *J* = 6.9, 2.7 Hz, 2H), 6.12 (d, *J* = 2.0 Hz, 1H), 5.91 (d, *J* = 2.1 Hz, 1H), 5.78 (d, *J* = 2.1 Hz, 1H), 5.19 (s, 3H), 4.80 – 4.21 (m, 4H). LC/MS (*m/z*): 417.321 [$M+H^+$]; UPLC t_R 0.96 min.

4-(2,3-Dihydro-1*H*-isoindole-2-carbonyl)-5-((1-((pyridin-3-yl)methyl)-1*H*-pyrazol-5-yl)amino)benzene-1,3-diol (77). Acid **19o** (41.5 mg, 100 μmol) was subjected to General Procedure H1 to afford 4.0 mg of **77** (9.3% yield) after purification using mass-guided preparative HPLC. ^1H NMR (400 MHz, CD_3OD) δ 8.32 (d, *J* = 6.5 Hz, 2H), 7.61 (d, *J* = 1.9 Hz, 1H), 7.47 (d, *J* = 2.0 Hz, 1H), 7.25 (d, *J* = 18.7 Hz, 6H), 6.13 (d, *J* = 2.0 Hz, 1H), 5.91 (d, *J* = 2.1 Hz, 1H), 5.64 (d, *J* = 2.1 Hz, 1H), 5.25 (s, 2H), 5.00 – 4.41 (m, 4H). LC/MS (*m/z*): 428.347 [$M+H^+$]; UPLC t_R 0.98 min.

5-((1-((Pyridin-3-yl)methyl)-1*H*-pyrazol-5-yl)amino)-4-(5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridine-6-carbonyl)benzene-1,3-diol (78). Acid **19o** (42.4 mg, 102 μmol) was subjected to General Procedure H2 to afford 2.5 mg of **78** (5.7% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.44 (d, *J* = 5.1 Hz, 1H), 8.38 – 8.29 (m, 2H), 7.75 – 7.59 (m, 2H), 7.46 (d, *J* = 2.1 Hz, 1H), 7.41 – 7.32 (m, 1H), 7.32 – 7.19 (m, 2H), 6.13 (d, *J* = 2.0 Hz, 1H), 5.91 (d, *J* = 2.1 Hz, 1H), 5.64 (d, *J* = 2.0 Hz, 1H), 5.27 (s, 2H), 5.04 – 4.49 (m, 4H). LC/MS (*m/z*): 429.362 [$M+H^+$]; UPLC t_R 0.76 min.

5-((1-((Pyridin-3-yl)methyl)-1*H*-pyrazol-5-yl)amino)-4-(1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole-5-carbonyl)benzene-1,3-diol (79). Acid **19o** (46.6 mg, 112 μmol) was subjected to General Procedure H3 to afford 4.2 mg of **79** (9.0% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.40 (dd, *J* = 5.0, 1.6 Hz, 1H), 8.39 – 8.31 (m, 2H), 7.67 – 7.56 (m, 1H), 7.49 (d, *J* = 2.1 Hz, 1H), 7.36 (ddd, *J* = 7.9, 4.9, 0.9 Hz, 1H), 6.09 (d, *J* = 2.0 Hz, 1H), 5.77 (s, 2H), 5.27 (s, 2H), 5.01 – 4.45 (m, 4H). LC/MS (*m/z*): 418.335 [$M+H^+$]; UPLC t_R 0.63 min.

4-(2,3-Dihydro-1*H*-isoindole-2-carbonyl)-5-((1-((furan-2-yl)methyl)-1*H*-pyrazol-5-yl)amino)benzene-1,3-diol (80). Acid **19p** (47.1 mg, 117 μmol) was subjected to General Procedure H1 to afford 12.7 mg of **80** (26% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.40 (d, *J* = 2.0 Hz, 1H), 7.26 (d, *J* = 11.9 Hz, 5H), 6.23 (t, *J* = 1.6 Hz, 2H), 6.08 (d, *J* = 2.0 Hz, 1H), 5.94 (d, *J* = 2.1 Hz, 1H), 5.15 (s, 2H), 5.00 – 4.65 (m, 4H). LC/MS (*m/z*): 417.321 [$M+H^+$]; UPLC t_R 1.29 min.

5-((1-((Furan-2-yl)methyl)-1*H*-pyrazol-5-yl)amino)-4-(5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridine-6-carbonyl)benzene-1,3-diol (81). Acid **19p** (49.6 mg, 123 μmol) was subjected to General Procedure H2 to afford 7.6 mg of **81** (15% yield) after purification using mass-guided preparative

HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.44 (dd, *J* = 5.1, 1.4 Hz, 1H), 7.85 – 7.70 (m, 1H), 7.40 (d, *J* = 2.1 Hz, 1H), 7.35 (dd, *J* = 7.8, 5.0 Hz, 1H), 7.28 (dd, *J* = 1.8, 0.9 Hz, 1H), 6.25 (dd, *J* = 3.2, 1.3 Hz, 2H), 6.08 (d, *J* = 2.1 Hz, 1H), 5.94 (d, *J* = 2.1 Hz, 1H), 5.79 (d, *J* = 2.1 Hz, 1H), 5.16 (s, 2H), 5.03 – 4.72 (m, 4H). LC/MS (*m/z*): 418.291 [$M+H^+$]; UPLC t_R 0.98 min.

5-((1-((Furan-2-yl)methyl)-1*H*-pyrazol-5-yl)amino)-4-(1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole-5-carbonyl)benzene-1,3-diol (82). Acid **19p** (55.5 mg, 138 μmol) was subjected to General Procedure H3 to afford 8.5 mg of **82** (15% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.45 (s, 1H), 7.41 (d, *J* = 2.1 Hz, 1H), 7.34 – 7.27 (m, 1H), 6.26 (t, *J* = 1.4 Hz, 2H), 6.08 (d, *J* = 2.0 Hz, 1H), 5.93 (d, *J* = 2.1 Hz, 1H), 5.78 (d, *J* = 2.1 Hz, 1H), 5.16 (s, 2H), 4.80 – 4.33 (m, 4H). LC/MS (*m/z*): 407.308 [$M+H^+$]; UPLC t_R 0.89 min.

(2,4-Dihydroxy-6-((1-(4-isopropylbenzyl)-1*H*-pyrazol-5-yl)amino)phenyl)(isoindolin-2-yl)methanone (83). Amide **14j** (42.1 mg, 75.6 μmol) was deprotected using General Procedure F to afford 7.8 mg of **83** (22% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.45 (d, *J* = 2.1 Hz, 1H), 7.29 (s, 4H), 6.96 (d, *J* = 1.0 Hz, 4H), 6.11 (d, *J* = 2.1 Hz, 1H), 5.92 (d, *J* = 2.1 Hz, 1H), 5.75 (d, *J* = 2.1 Hz, 1H), 5.13 (s, 2H), 4.95 – 4.59 (m, 4H), 2.72 (p, *J* = 6.9 Hz, 1H), 1.11 (d, *J* = 6.9 Hz, 6H). LC/MS (*m/z*): 469.234 [$M+H^+$]; UPLC t_R 1.59 min

5-((1-((4-(Propan-2-yl)phenyl)methyl)-1*H*-pyrazol-5-yl)amino)-4-(5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridine-6-carbonyl)benzene-1,3-diol (84). Acid **19q** (24.6 mg, 54.0 μmmol) was coupled with 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine dihydrochloride (15.6 mg, 81.0 μmol), and triethylamine (57 μL, 410 μmol) using General Procedure G to give 20.7 mg of MOM-protected intermediate (69% yield) after purification via an automated flash system (25% to 70% ethyl

acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (ddd, *J* = 19.6, 5.0, 1.5 Hz, 1H), 7.67 – 7.44 (m, 2H), 7.21 (ddd, *J* = 12.8, 7.7, 4.9 Hz, 1H), 7.07 (dd, *J* = 8.2, 3.7 Hz, 2H), 7.00 (dd, *J* = 8.2, 3.3 Hz, 2H), 6.51 (d, *J* = 6.0 Hz, 1H), 6.40 (dd, *J* = 6.7, 2.1 Hz, 1H), 6.20 (dd, *J* = 17.0, 2.1 Hz, 1H), 6.12 – 6.01 (m, 1H), 5.24 – 5.09 (m, 4H), 5.05 (d, *J* = 3.9 Hz, 2H), 4.93 (dt, *J* = 25.1, 13.4 Hz, 3H), 4.57 (dd, *J* = 15.1, 7.2 Hz, 1H), 3.44 (t, *J* = 1.9 Hz, 6H), 2.83 – 2.71 (m, 1H), 1.14 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3, 167.2, 160.0, 157.6, 157.2, 155.5, 155.4, 149.4, 149.3, 148.5, 148.2, 144.0, 139.0, 138.9, 133.7, 133.6, 130.9, 130.6, 130.3, 129.9, 127.5, 126.7, 126.7, 126.6, 122.5, 122.4, 106.9, 99.3, 99.2, 96.3, 96.2, 95.4, 95.3, 95.3, 95.2, 94.3, 94.2, 56.6, 56.6, 56.3, 56.2, 53.4, 52.6, 51.9, 51.9, 51.5, 50.6, 33.7, 23.9. LC/MS (*m/z*): 558.417 [M+H$^+$]; UPLC t_R 1.60 min.

The MOM-protected intermediate (20 mg, 36 µmol) was deprotected using General Procedure F to afford 8.5 mg of **84** (50% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.44 (dd, *J* = 5.1, 1.5 Hz, 1H), 7.77 (s, 1H), 7.44 (d, *J* = 2.1 Hz, 1H), 7.35 (dd, *J* = 7.8, 5.0 Hz, 1H), 6.99 (s, 4H), 6.11 (d, *J* = 2.1 Hz, 1H), 5.92 (d, *J* = 2.1 Hz, 1H), 5.73 (d, *J* = 2.1 Hz, 1H), 5.14 (s, 2H), 4.89 (s, 25H), 2.73 (p, *J* = 6.9 Hz, 1H), 1.11 (d, *J* = 6.9 Hz, 6H). LC/MS (*m/z*): 470.381 [M+H$^+$]; UPLC t_R 1.36 min.

5-((1-((4-(Propan-2-yl)phenyl)methyl)-1*H*-pyrazol-5-yl)amino)-4-(1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole-5-carbonyl)benzene-1,3-diol (85). Acid **19q** (27.7 mg, 60.8 µmmol) was coupled with 1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole (10 mg, 109 µmol), and triethylamine (17 µL, 120 µmol) using General Procedure G to give 17.2 mg of MOM-protected intermediate (52% yield) after purification via automated flash system (2% to 5% methanol in CH_2Cl_2) and manual flash chromatography (40:59:1 CH_2Cl_2:ethyl acetate: saturated NH_4OH (aq.)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 2.0 Hz, 1H), 7.32 (d, *J* = 43.7 Hz, 1H), 7.09 (d, *J* = 7.8 Hz, 2H), 7.04

(d, *J* = 8.1 Hz, 2H), 6.45 – 6.31 (m, 2H), 6.20 (dd, *J* = 3.7, 2.1 Hz, 1H), 6.07 (d, *J* = 1.9 Hz, 1H), 5.24 – 5.08 (m, 4H), 5.04 (s, 2H), 4.69 (d, *J* = 20.0 Hz, 2H), 4.36 (dd, *J* = 13.5, 8.5 Hz, 1H), 3.50 – 3.33 (m, 6H), 2.80 (q, *J* = 7.0, 6.5 Hz, 1H), 1.16 (dd, *J* = 7.0, 1.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 159.9, 159.8, 155.3, 148.4, 148.2, 143.8, 139.1, 139.0, 138.9, 133.6, 133.6, 127.5, 126.7, 126.7, 107.6, 99.4, 99.3, 96.3, 95.3, 95.3, 94.2, 56.5, 56.2, 51.8, 46.6, 33.7, 23.9, 23.9. LC/MS (*m/z*): 547.434 [M+H$^+$]; UPLC t_R 1.53 min.

The MOM-protected intermediate (17.2 mg, 31.5 µmol) was deprotected using General Procedure F to afford 7.5 mg of **85** (52% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.45 (d, *J* = 2.0 Hz, 2H), 7.08 – 6.91 (m, 4H), 6.11 (d, *J* = 2.0 Hz, 1H), 5.91 (t, *J* = 1.4 Hz, 1H), 5.74 (d, *J* = 2.0 Hz, 1H), 5.14 (s, 2H), 4.80 – 4.36 (m, 4H), 2.77 (p, *J* = 6.9 Hz, 1H), 1.14 (d, *J* = 6.9 Hz, 6H). LC/MS (*m/z*): 459.354 [M+H$^+$]; UPLC t_R 1.23 min.

4-(5*H*,6*H*,7*H*-Pyrrolo[3,4-*b*]pyridine-6-carbonyl)-5-((1-((4-(trifluoromethyl)phenyl)methyl)-1*H*-pyrazol-5-yl)amino]benzene-1,3-diol (86). Acid **19r** (35.1 mg, 65 µmol) was subjected to General Procedure H2 to afford 10.3 mg of **86** (32% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.43 (dd, *J* = 5.0, 1.4 Hz, 1H), 7.75 (s, 1H), 7.52 – 7.42 (m, 3H), 7.34 (dd, *J* = 7.8, 5.0 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 6.14 (d, *J* = 2.1 Hz, 1H), 5.92 (d, *J* = 2.0 Hz, 1H), 5.68 (d, *J* = 2.1 Hz, 1H), 5.28 (s, 2H), 5.07 – 4.44 (m, 4H). LC/MS (*m/z*): 496.316 [M+H$^+$]; UPLC t_R 1.31 min

4-(1*H*,4*H*,5*H*,6*H*-Pyrrolo[3,4-*c*]pyrazole-5-carbonyl)-5-((1-((4-(trifluoromethyl)phenyl)methyl)-1*H*-pyrazol-5-yl)amino]benzene-1,3-diol (87). Acid **19r** (31.6 mg, 66 µmol) was subjected to General Procedure H3 to afford 10.6 mg of **87** (33% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.54 – 7.38 (m, 4H), 7.25 (d, *J* = 8.0 Hz, 2H), 6.14 (d, *J* = 2.0 Hz, 1H), 5.91 (d, *J* = 2.1 Hz, 1H), 5.67 (d,

J = 2.1 Hz, 1H), 5.28 (s, 2H), 4.82 – 4.20 (m, 4H). ^{19}F NMR (376 MHz, CD_3OD) δ -64.1. LC/MS (*m/z*): 485.289 [M+H$^+$]; UPLC t_R 1.20 min.

4-(2,3-Dihydro-1*H*-isoindole-2-carbonyl)-5-((3-methyl-1-((4-methylphenyl)methyl)-1*H*-pyrazol-5-yl)amino)benzene-1,3-diol (88). Amide **14k** (40.4 mg, 74.5 µmol) was deprotected using General Procedure F to afford 28.8 mg of **88** (85% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.29 (d, *J* = 8.8 Hz, 4H), 6.89 (s, 4H), 5.96 – 5.88 (m, 2H), 5.85 (d, *J* = 2.1 Hz, 1H), 5.05 (s, 2H), 4.95 – 4.46 (m, 4H), 2.14 (s, 3H), 2.13 (s, 3H). LC/MS (*m/z*): 455.208 [M+H$^+$]; UPLC t_R 1.55 min.

5-((1-((2-Chlorophenyl)methyl)-3-methyl-1*H*-pyrazol-5-yl)amino)-4-(2,3-dihydro-1*H*-isoindole-2-carbonyl)benzene-1,3-diol (89). Amide **14l** (46.5 mg, 82.3 µmol) was deprotected using General Procedure F to afford 30.4 mg of **89** (78% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.31 – 7.19 (m, 4H), 7.17 – 7.11 (m, 1H), 7.10 – 6.99 (m, 2H), 6.64 – 6.53 (m, 1H), 5.97 (s, 1H), 5.92 (d, *J* = 2.1 Hz, 1H), 5.88 (d, *J* = 2.1 Hz, 1H), 5.20 (s, 2H), 4.85 – 4.29 (m, 4H), 2.14 (s, 3H). ^{13}C NMR (126 MHz, $(CD_3)_2SO$) δ 166.4, 159.2, 155.5, 146.7, 143.7, 141.3, 136.5, 135.0, 131.3, 129.0, 128.8, 128.6, 127.2, 127.1, 122.8, 104.1, 98.4, 94.5, 93.1, 48.0, 40.4, 13.9. LC/MS (*m/z*): 475.573 [M+H$^+$]; UPLC t_R 1.41 min

4-(2,3-Dihydro-1*H*-isoindole-2-carbonyl)-5-((3-methyl-1-((2-methylphenyl)methyl)-1*H*-pyrazol-5-yl)amino)benzene-1,3-diol (90). Amide **14m** (21.3 mg, 39.3 µmol) was deprotected using General Procedure F to afford 9.7 mg of **90** (54% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.28 (dt, *J* = 7.1, 3.6 Hz, 2H), 7.22 (d, *J* = 7.4 Hz, 2H), 7.01 – 6.94 (m, 2H), 6.91 – 6.83 (m, 1H), 6.49 (d, *J* = 7.6 Hz, 1H), 5.97 – 5.93 (m, 2H), 5.92 (d, *J* = 2.1 Hz, 1H), 5.11 (s, 2H), 4.82 – 4.32 (m, 4H), 2.16 (s, 3H), 2.14 (s, 3H). LC/MS (*m/z*): 455.164 [M+H$^+$]; UPLC t_R 1.51 min.

4-(2,3-Dihydro-1*H*-isoindole-2-carbonyl)-5-((1-methyl-3-phenyl-1*H*-pyrazol-5-yl)amino]benzene-1,3-diol (91). Amide **14n** (65.0 mg, 126 µmol) was deprotected using General Procedure F to afford 32.8 mg of **91** (61% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.70 – 7.53 (m, 2H), 7.34 – 7.27 (m, 2H), 7.24 (s, 5H), 6.35 (s, 1H), 5.95 (d, *J* = 2.1 Hz, 1H), 5.78 (d, *J* = 2.1 Hz, 1H), 5.03 – 4.71 (m, 4H), 3.69 (s, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 170.2, 161.6, 157.5, 151.6, 145.8, 143.7, 137.7, 134.7, 129.7, 128.9, 128.8, 126.4, 123.9, 105.3, 98.3, 95.9, 95.2, 40.6, 35.3. LC/MS (*m/z*): 428.347 [M+H$^+$]; UPLC t_R 1.58 min

5-((1-Methyl-3-phenyl-1*H*-pyrazol-5-yl)amino)-4-(5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridine-6-carbonyl)benzene-1,3-diol (92). Acid **19s** (44.1 mg, 107 µmmol) was coupled with 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine dihydrochloride (30.9 mg, 160 µmol), and triethylamine (110 µL, 800 µmol) using General Procedure G to give 48.3 mg of MOM-protected intermediate (88% yield) after purification via an automated flash system (0% to 4% methanol in CH_2Cl_2) and manual chromatography (70:30:1 CH_2Cl_2:acetone: saturated NH_4OH (aq.)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 – 8.46 (m, 1H), 7.75 (ddd, *J* = 8.3, 2.5, 1.3 Hz, 2H), 7.63 (dd, *J* = 51.9, 7.7 Hz, 1H), 7.38 (ddd, *J* = 7.9, 6.8, 2.1 Hz, 2H), 7.32 – 7.27 (m, 1H), 6.81 (s, 1H), 6.47 (dd, *J* = 7.4, 2.1 Hz, 1H), 6.34 (s, 1H), 6.26 – 6.16 (m, 1H), 5.19 (d, *J* = 10.6 Hz, 3H), 5.10 (d, *J* = 0.9 Hz, 3H), 4.99 – 4.83 (m, 1H), 4.75 – 4.51 (m, 1H), 3.74 (s, 3H), 3.47 (s, 3H), 3.46 – 3.42 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 161.6, 160.0, 150.4, 149.7, 138.6, 134.1, 128.5, 127.3, 125.4, 99.6, 97.2, 95.4, 95.1, 94.8, 93.9, 56.7, 56.5, 56.3, 52.0, 32.7, 25.7, 25.2. LC/MS (*m/z*): 516.251 [M+H$^+$]; UPLC t_R 1.43 min.

The MOM-protected intermediate (48.3 mg, 94 µmol) was deprotected using General Procedure F to afford 25 mg of **92** (62% yield) after purification using mass-guided preparative HPLC. ^{1}H

NMR (400 MHz, CD_3OD) δ 8.34 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.68 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.61 – 7.53 (m, 2H), 7.34 – 7.14 (m, 4H), 6.35 (s, 1H), 5.96 (d, *J* = 2.1 Hz, 1H), 5.82 (d, *J* = 2.1 Hz, 1H), 5.01 – 4.60 (m, 4H), 3.72 (s, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 170.4, 161.8, 158.2, 157.6, 151.4, 149.6, 146.1, 144.0, 134.6, 133.4, 129.7, 128.8, 126.3, 124.3, 111.5, 104.9, 98.2, 96.0, 95.7, 40.6, 35.3. LC/MS (*m/z*): 428.259 [M+H$^+$]; UPLC t_R 1.11 min.

5-((1-Methyl-3-phenyl-1*H*-pyrazol-5-yl)amino)-4-(1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole-5-carbonyl)benzene-1,3-diol (93). Acid **19s** (64.1 mg, 155 μmmol) was coupled with 1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole (25 mg, 230 μmol), and triethylamine (43 μL, 310 μmol) using General Procedure G to give 17.2 mg of MOM-protected intermediate (52% yield) as a solid after purification via automated flash system (20% to 60% acetone in CH_2Cl_2). ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.88 – 7.77 (m, 2H), 7.51 (d, *J* = 24.4 Hz, 1H), 7.43 – 7.32 (m, 2H), 7.30 – 6.88 (m, 1H), 6.49 (d, *J* = 5.2 Hz, 1H), 6.45 (dd, *J* = 5.0, 2.1 Hz, 1H), 6.18 (q, *J* = 2.1 Hz, 1H), 5.32 – 5.15 (m, 2H), 5.13 (d, *J* = 2.3 Hz, 2H), 4.82 – 4.48 (m, 3H), 4.43 (d, *J* = 13.0 Hz, 1H), 3.70 (d, *J* = 3.3 Hz, 3H), 3.43 (d, *J* = 2.5 Hz, 3H), 3.40 (s, 3H). LC/MS (*m/z*): 505.269 [M+H$^+$]; UPLC t_R 1.34 min.

The MOM-protected intermediate (41.6 mg, 82 μmol) was deprotected using General Procedure F to afford 24.5 mg of **93** (71% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.67 – 7.61 (m, 2H), 7.38 (s, 1H), 7.36 – 7.28 (m, 2H), 7.28 – 7.22 (m, 1H), 6.37 (s, 1H), 5.94 (d, *J* = 2.1 Hz, 1H), 5.77 (d, *J* = 2.1 Hz, 1H), 4.78 – 4.44 (m, 4H), 3.71 (s, 3H). LC/MS (*m/z*): 417.233 [M+H$^+$]; UPLC t_R 1.01 min.

5-((1-*tert*-Butyl-3-phenyl-1*H*-pyrazol-5-yl)amino)-4-(5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridine-6-carbonyl)benzene-1,3-diol (94). Acid **19t** (41.5 mg, 91.1 μmmol) was coupled with 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine dihydrochloride (26.4 mg, 140 μmol), and triethylamine (100 μL, 680

μmol) using General Procedure G to give 39.9 mg of MOM-protected intermediate (79% yield) after purification via an automated flash system (0% to 3% methanol in CH_2Cl_2) and manual chromatography (70:30:1 CH_2Cl_2:ethyl acetate: saturated NH_4OH (aq.)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (dd, *J* = 18.4, 4.9 Hz, 1H), 7.84 – 7.74 (m, 2H), 7.60 (dd, *J* = 59.2, 7.8 Hz, 1H), 7.36 (t, *J* = 7.7 Hz, 2H), 7.27 – 7.17 (m, 2H), 6.75 (d, *J* = 7.3 Hz, 1H), 6.51 – 6.36 (m, 2H), 6.30 (dd, *J* = 9.4, 2.1 Hz, 1H), 5.32 – 5.01 (m, 6H), 4.94 (d, *J* = 16.5 Hz, 1H), 4.68 (d, *J* = 14.7 Hz, 1H), 3.47 (s, 3H), 3.44 (d, *J* = 1.9 Hz, 3H), 2.80 (s, 3H), 1.64 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 167.6, 160.1, 160.1, 157.7, 157.2, 155.7, 155.6, 149.4, 149.3, 147.7, 147.7, 145.2, 145.2, 139.5, 139.4, 134.0, 131.1, 130.6, 129.9, 128.5, 127.2, 125.2, 122.5, 122.4, 106.5, 106.4, 99.3, 99.1, 96.5, 96.3, 95.5, 95.4, 94.6, 94.5, 94.3, 94.2, 59.7, 59.7, 56.7, 56.6, 56.3, 56.2, 53.5, 52.7, 51.5, 50.8, 38.6, 29.7. LC/MS (*m/z*): 558.328 [M+H$^+$]; UPLC t_R 1.84 min.

The MOM-protected intermediate (39.9 mg, 72 μmol) was deprotected using General Procedure F to afford 24.3 mg of **94** (72% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.42 (dd, *J* = 5.1, 1.5 Hz, 1H), 7.78 (d, *J* = 7.7 Hz, 1H), 7.74 – 7.65 (m, 2H), 7.41 – 7.26 (m, 3H), 7.26 – 7.18 (m, 1H), 6.45 (s, 1H), 5.89 (d, *J* = 2.1 Hz, 1H), 5.80 (d, *J* = 2.0 Hz, 1H), 5.08 – 4.70 (m, 4H), 1.63 (s, 9H). ^{13}C NMR (101 MHz, CD_3OD) δ 170.7, 161.8, 158.3, 157.4, 149.7, 149.5, 147.3, 142.2, 135.5, 133.4, 132.6, 129.6, 128.5, 126.3, 124.3, 103.8, 101.9, 95.1, 94.5, 61.2, 40.6, 30.4. LC/MS (*m/z*): 470.337 [M+H$^+$]; UPLC t_R 1.51 min.

5-((1-*tert*-Butyl-3-phenyl-1*H*-pyrazol-5-yl)amino)-4-(1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole-5-carbonyl)benzene-1,3-diol (95). Acid **19t** (62.2 mg, 137 μmmol) was coupled with 1H,4H,5H,6*H*-pyrrolo[3,4-c]pyrazole (22.3 mg, 205 μmol), and triethylamine (38 μL, 270 μmol) using General Procedure G to give 44.4 mg of MOM-protected intermediate (59% yield) as a solid after purification via automated flash system (10% to 30% acetone in CH_2Cl_2). ^{1}H NMR (400

MHz, $(CD_3)_2SO$) δ 12.70 (s, 1H), 7.80 – 7.71 (m, 3H), 7.71 – 7.62 (m, 1H), 7.53 (d, *J* = 31.5 Hz, 1H), 7.45 – 7.30 (m, 3H), 7.28 – 7.20 (m, 1H), 7.04 (d, *J* = 2.7 Hz, 1H), 6.60 (d, *J* = 9.9 Hz, 1H), 6.27 (t, *J* = 2.5 Hz, 1H), 5.85 (dd, *J* = 10.4, 2.1 Hz, 1H), 5.24 – 5.11 (m, 3H), 5.10 – 4.99 (m, 3H), 4.66 (dd, *J* = 14.4, 6.5 Hz, 1H), 4.56 – 4.39 (m, 3H), 4.34 (d, *J* = 12.9 Hz, 1H), 3.28 (s, 6H), 2.87 (s, 3H), 1.54 (d, *J* = 1.1 Hz, 9H). LC/MS (*m/z*): 547.346 [$M+H^+$]; UPLC t_R 1.60 min.

The MOM-protected intermediate (43.4 mg, 79 μmol) was deprotected using General Procedure F to afford 15.5 mg of **95** (43% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.78 – 7.70 (m, 2H), 7.45 (s, 1H), 7.39 – 7.29 (m, 2H), 7.27 – 7.21 (m, 1H), 6.46 (s, 1H), 5.87 (d, *J* = 2.1 Hz, 1H), 5.77 (t, *J* = 1.9 Hz, 1H), 4.84 – 4.44 (m, 4H), 1.63 (s, 9H). LC/MS (*m/z*): 459.266 [$M+H^+$]; UPLC t_R 1.40 min.

5-((1-Cyclohexyl-3-phenyl-1*H*-pyrazol-5-yl)amino)-4-(5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridine-6-carbonyl)benzene-1,3-diol (96). Acid **19u** (51.9 mg, 108 μmmol) was coupled with 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine dihydrochloride (31.2 mg, 162 μmol), and triethylamine (110 μL, 810 μmol) using General Procedure G to give 39.5 mg of MOM-protected intermediate (63% yield) after purification via an automated flash system (0% to 3% methanol in CH_2Cl_2) and manual chromatography (65:35:1 CH_2Cl_2:ethyl acetate: saturated NH_4OH (aq.)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 – 8.44 (m, 1H), 7.83 – 7.74 (m, 2H), 7.61 (dd, *J* = 59.5, 7.7 Hz, 1H), 7.42 – 7.30 (m, 2H), 7.31 – 7.17 (m, 3H), 6.62 (d, *J* = 3.9 Hz, 1H), 6.43 (dd, *J* = 8.5, 2.1 Hz, 1H), 6.32 (d, *J* = 3.0 Hz, 1H), 6.22 (dd, *J* = 7.2, 2.1 Hz, 1H), 5.19 (d, *J* = 5.7 Hz, 3H), 5.08 (s, 3H), 4.96 (d, *J* = 14.1 Hz, 1H), 4.69 (d, *J* = 14.1 Hz, 1H), 4.03 (td, *J* = 11.2, 4.1 Hz, 1H), 3.47 (d, *J* = 1.0 Hz, 3H), 3.43 (d, *J* = 1.3 Hz, 3H), 2.80 (s, 3H), 2.09 – 1.75 (m, 6H), 1.75 – 1.57 (m, 1H), 1.25 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 167.5, 160.0, 157.6, 155.6, 155.5, 149.6, 149.5, 149.3, 145.1, 145.0, 138.9, 138.8, 134.0, 131.1, 130.6, 128.5, 127.3, 127.3, 125.3, 122.5, 106.9, 106.8, 96.8, 96.7, 96.5,

96.4, 95.5, 95.4, 95.1, 95.0, 94.2, 94.2, 56.8, 56.8, 56.6, 56.6, 56.2, 56.2, 53.6, 52.7, 51.6, 50.7, 38.6, 32.8, 32.4, 25.6, 25.2. LC/MS (*m/z*): 584.351 [M+H$^+$]; UPLC t_R 1.88 min.

The MOM-protected intermediate (43.4 mg, 79 µmol) was deprotected using General Procedure F to afford 15.5 mg of **96** (43% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.36 (dd, *J* = 5.1, 1.5 Hz, 1H), 7.71 (d, *J* = 7.7 Hz, 1H), 7.67 – 7.55 (m, 2H), 7.39 – 7.05 (m, 4H), 6.33 (s, 1H), 5.93 (d, *J* = 2.1 Hz, 1H), 5.79 (d, *J* = 2.1 Hz, 1H), 5.21 – 4.68 (m, 4H), 4.19 (p, *J* = 7.9 Hz, 1H), 2.08 – 1.76 (m, 6H), 1.72 – 1.59 (m, 1H), 1.49 – 1.20 (m, 3H). LC/MS (*m/z*): 496.271 [M+H$^+$]; UPLC t_R 1.54 min.

5-((1-Cyclohexyl-3-phenyl-1*H*-pyrazol-5-yl)amino)-4-(1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole-5-carbonyl)benzene-1,3-diol (97). Acid **19u** (54.8 mg, 114 µmmol) was coupled with 1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole (18.6 mg, 172 µmol), and triethylamine (32 µL, 230 µmol) using General Procedure G1. The resulting suspension was diluted with CH_2Cl_2 and saturated $NaHCO_3$ (aq.). The layers were separated and the organic layer was washed with brine. The organic layer was dried with anhydrous sodium sulfate. The desired amide was collected along with sodium sulfate following vacuum filtration through a Celite®. The desired product and residual Celite® was separated from sodium sulfate and used without purification.

To a mixture of the intermediate amide and residual Celite® in methanol (8.3 mL) was add HCl (2 M, 0.37 µL, 740 µmol). The resulting mixture was stirred at 50 ºC three nights. Additional HCl (2 M, 0.37 µL, 740 µmol) was added to the mixture and stirred at 50 ºC overnight. The mixture was cooled to room temperature and volatile material were condensed *in vacuo*. The residue was dissolved in DMSO and the residual Celite® was removed via filtration. The crude mixture was purified using mass-guided preparative HPLC to afford 13.7 mg of **97** (25% yield over 2 steps). ^{1}H NMR (400 MHz, CD_3OD) δ 7.73 – 7.61 (m, 2H), 7.41 (s, 1H), 7.33 (dd, *J* = 8.3, 6.7 Hz, 2H),

7.28 – 7.12 (m, 1H), 6.36 (s, 1H), 5.91 (d, *J* = 2.1 Hz, 1H), 5.73 (d, *J* = 2.1 Hz, 1H), 4.81 – 4.45 (m, 4H), 4.16 (p, *J* = 9.3, 8.7 Hz, 1H), 2.04 – 1.78 (m, 6H), 1.67 (d, *J* = 10.9 Hz, 1H), 1.48 – 1.10 (m, 3H). LC/MS (*m/z*): 485.245 [M+H$^+$]; UPLC t_R 1.41 min.

5-((1-(2-Methylpropyl)-3-phenyl-1*H*-pyrazol-5-yl)amino)-4-(5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridine-6-carbonyl)benzene-1,3-diol (98). Acid **19v** (52.5 mg, 115 µmmol) was coupled with 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine dihydrochloride (33.4 mg, 173 µmol), and triethylamine (120 µL, 860 µmol) using General Procedure G to give 46.6 mg of MOM-protected intermediate (73% yield) after purification via an automated flash system (1% to 4% methanol in CH_2Cl_2) and manual chromatography (20:80:1 CH_2Cl_2:ethyl acetate: saturated NH_4OH (aq.)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (dd, *J* = 21.5, 4.8 Hz, 1H), 7.80 – 7.71 (m, 2H), 7.71 – 7.45 (m, 1H), 7.37 (td, *J* = 7.4, 1.3 Hz, 2H), 7.33 – 7.15 (m, 2H), 6.79 (d, *J* = 7.2 Hz, 1H), 6.45 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.38 – 6.30 (m, 2H), 5.14 (d, *J* = 32.1 Hz, 6H), 4.94 (d, *J* = 15.8 Hz, 1H), 4.67 (d, *J* = 14.2 Hz, 1H), 3.82 (dd, *J* = 7.5, 2.4 Hz, 2H), 3.47 (d, *J* = 0.9 Hz, 3H), 3.45 (d, *J* = 1.0 Hz, 3H), 2.80 (s, 3H), 2.32 – 2.17 (m, 1H), 0.88 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 167.4, 160.1, 157.6, 157.2, 155.7, 155.6, 149.9, 149.5, 149.3, 144.4, 144.3, 140.3, 140.2, 133.8, 131.1, 130.6, 130.3, 129.8, 128.5, 127.5, 127.5, 125.3, 122.5, 122.5, 107.0, 106.9, 96.7, 96.6, 95.8, 95.7, 95.5, 95.4, 95.2, 95.1, 94.3, 94.3, 56.6, 56.6, 56.3, 56.2, 55.3, 55.2, 53.5, 52.7, 51.6, 50.8, 38.6, 29.4, 20.0.. LC/MS (*m/z*): 558.372 [M+H$^+$]; UPLC t_R 1.72 min.

The MOM-protected intermediate (46.6 mg, 79 µmol) was deprotected using General Procedure F to afford 26.0 mg of **98** (66% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.37 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.71 (d, *J* = 7.7 Hz, 1H), 7.66 – 7.56 (m, 2H), 7.38 – 7.19 (m, 4H), 6.39 (s, 1H), 5.94 (dd, *J* = 12.6, 2.1 Hz, 2H), 5.16 – 4.61 (m, 4H), 3.83 (d, *J* = 7.5 Hz, 2H), 2.19 (hept, *J* = 6.9 Hz, 1H), 0.86 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (101

MHz, CD_3OD) δ 170.5, 161.8, 158.2, 157.6, 151.5, 149.7, 146.1, 143.6, 134.8, 133.4, 132.5, 129.7, 128.8, 126.5, 124.3, 104.8, 98.1, 96.0, 95.4, 56.3, 40.6, 30.7, 20.4. LC/MS (*m/z*): 470.293 [$M+H^+$]; UPLC t_R 1.38 min.

5-((1-(2-Methylpropyl)-3-phenyl-1*H*-pyrazol-5-yl)amino)-4-(1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole-5-carbonyl)benzene-1,3-diol (99). Acid **19v** (59.0 mg, 130 μmmol) was coupled with 1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole (21.2 mg, 195 μmol), and triethylamine (36 μL, 260 μmol) using General Procedure G1. The reaction mixture was diluted with CH_2Cl_2 and saturated $NaHCO_3$ (aq.). The layers were separated and brine was added to the organic layer. The combined mixture was filtered through a Celite® plug and the plug was washed with water, methanol and CH_2Cl_2. The organic layer from the combined filtrate evaporated to leave a fine powder. The remaining water layer was decanted from the solid. The solid was dried to afford 33.9 mg of impure MOM-protected amide which was used without further purification.

The impure MOM-protected amide from above was deprotected using General Procedure F to afford 15.3 mg of **99** (59% overall yield) after purification using mass-guided preparative HPLC. ^1H NMR (400 MHz, CD_3OD) δ 7.73 – 7.64 (m, 2H), 7.41 (s, 1H), 7.38 – 7.31 (m, 2H), 7.30 – 7.17 (m, 1H), 5.93 (d, *J* = 2.1 Hz, 1H), 5.88 (d, *J* = 2.1 Hz, 1H), 4.67 (s, 4H), 3.82 (d, *J* = 7.5 Hz, 2H), 2.19 (hept, *J* = 6.9 Hz, 1H), 0.87 (d, *J* = 6.7 Hz, 6H). LC/MS (*m/z*): 459.31 [$M+H^+$]; UPLC t_R 1.27 min.

4-(2,3-Dihydro-1*H*-isoindole-2-carbonyl)-5-((1-methyl-3-(propan-2-yl)-1*H*-pyrazol-5-yl)amino)benzene-1,3-diol (100). Acid **19w** (45 mg, 120 μmol) was subjected to General Procedure H1 to afford 15.3 mg of **100** (33% yield) after purification using mass-guided preparative HPLC ^1H NMR (400 MHz, CD_3OD) δ 7.28 (s, 4H), 5.93 (dd, *J* = 12.6, 2.0 Hz, 1H),

5.84 (s, 1H), 5.67 (d, *J* = 2.1 Hz, 1H), 5.06 – 4.67 (m, 4H), 3.58 (s, 4H), 2.76 (p, *J* = 7.0 Hz, 1H), 1.15 (d, *J* = 7.0 Hz, 6H). LC/MS (*m/z*): 393.106 [M+H$^+$]; UPLC t_R 1.30 min.

5-((1-Methyl-3-(propan-2-yl)-1*H*-pyrazol-5-yl)amino)-4-(5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridine-6-carbonyl)benzene-1,3-diol (101). Acid **19w** (45 mg, 120 µmol) was subjected to General Procedure H2 to afford 9.9 mg of **101** (21% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.44 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.80 (d, *J* = 7.7 Hz, 1H), 7.35 (dd, *J* = 7.8, 5.0 Hz, 1H), 5.92 (d, *J* = 2.1 Hz, 1H), 5.85 (s, 1H), 5.68 (d, *J* = 2.1 Hz, 1H), 5.09 – 4.72 (m, 4H), 3.59 (s, 3H), 2.76 (hept, *J* = 6.6 Hz, 1H), 1.14 (d, *J* = 6.9 Hz, 6H). LC/MS (*m/z*): 394.253 [M+H$^+$]; UPLC t_R 1.29 min.

5-((1-Methyl-3-(propan-2-yl)-1*H*-pyrazol-5-yl)amino)-4-(1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole-5-carbonyl)benzene-1,3-diol (102). Acid **19w** (45 mg, 120 µmol) was subjected to General Procedure H3 to afford 12.5 mg of **102** (28% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.45 (s, 1H), 5.91 (d, *J* = 2.1 Hz, 1H), 5.85 (s, 1H), 5.66 (d, *J* = 2.1 Hz, 1H), 4.85 – 4.44 (m, 4H), 3.59 (s, 3H), 2.78 (dq, *J* = 13.9, 6.9 Hz, 1H), 1.17 (d, *J* = 6.9 Hz, 6H). LC/MS (*m/z*): 383.314 [M+H$^+$]; UPLC t_R 0.92 min.

5-((3-Cyclohexyl-1-methyl-1*H*-pyrazol-5-yl)amino)-4-(2,3-dihydro-1*H*-isoindole-2-carbonyl)benzene-1,3-diol (103). Acid **19x** (38.9 mg, 92.7 µmol) was subjected to General Procedure H1 to afford 16.1 mg of **103** (40% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.28 (s, 4H), 5.92 (d, *J* = 2.1 Hz, 1H), 5.80 (s, 1H), 5.69 (d, *J* = 2.1 Hz, 1H), 5.09 – 4.64 (m, 4H), 3.58 (s, 3H), 2.44 – 2.21 (m, 1H), 1.99 – 1.62 (m, 5H), 1.48 – 1.09 (m, 5H). LC/MS (*m/z*): 433.376 [M+H$^+$]; UPLC t_R 1.51 min.

5-((3-Cyclohexyl-1-methyl-1*H*-pyrazol-5-yl)amino)-4-(5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridine-6-carbonyl)benzene-1,3-diol (104). Acid **19x** (39.9 mg, 95.1 µmol) was subjected to General

Procedure H2 to afford 3.3 mg of **104** (8.0% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.54 (s, 1H), 8.44 (dd, *J* = 5.1, 1.5 Hz, 1H), 7.79 (d, *J* = 7.7 Hz, 1H), 7.35 (dd, *J* = 7.8, 5.0 Hz, 1H), 5.92 (d, *J* = 2.1 Hz, 1H), 5.81 (s, 1H), 5.71 (d, *J* = 2.1 Hz, 1H), 5.04 – 4.38 (m, 4H), 3.59 (s, 4H), 2.39 (d, *J* = 10.8 Hz, 1H), 1.73 (dq, *J* = 23.1, 11.6, 8.8 Hz, 6H), 1.27 (hept, *J* = 11.6 Hz, 4H). LC/MS (*m/z*): 434.346 [$M+H^+$]; UPLC t_R 1.32 min.

5-((3-Cyclohexyl-1-methyl-1*H*-pyrazol-5-yl)amino)-4-(1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole-5-carbonyl)benzene-1,3-diol (105). Acid **19x** (44 mg, 100 µmol) was subjected to General Procedure H3 to afford 12.5 mg of **105** (28% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.44 (s, 1H), 5.91 (d, *J* = 2.1 Hz, 1H), 5.81 (s, 1H), 5.68 (d, *J* = 2.1 Hz, 1H), 4.78 – 4.36 (m, 4H), 3.59 (s, 3H), 2.51 – 2.27 (m, 1H), 1.89 – 1.61 (m, 5H), 1.43 – 1.09 (m, 5H). LC/MS (*m/z*): 423.363 [$M+H^+$]; UPLC t_R 1.15 min.

4-(2,3-Dihydro-1*H*-isoindole-2-carbonyl)-5-((1-methyl-3-(2-methylphenyl)-1*H*-pyrazol-5-yl)amino)benzene-1,3-diol (106). Acid **19y** (50.3 mg, 118 µmol) was subjected to General Procedure H1 to afford 18.8 mg of **106** (36% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.34 (dd, *J* = 7.1, 1.3 Hz, 1H), 7.27 (s, 4H), 7.22 – 7.17 (m, 2H), 7.17 – 7.09 (m, 1H), 6.17 (s, 1H), 5.94 (d, *J* = 2.1 Hz, 1H), 5.75 (d, *J* = 2.1 Hz, 1H), 5.01 – 4.72 (m, 4H), 3.70 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 170.2, 161.6, 157.5, 151.9, 145.9, 142.8, 137.7, 137.2, 134.7, 131.7, 130.3, 129.0, 128.8, 126.9, 123.9, 105.3, 101.6, 95.9, 94.9, 40.6, 35.3, 21.3. LC/MS (*m/z*): 441.315 [$M+H^+$]; UPLC t_R 1.65 min.

5-((1-Methyl-3-(2-methylphenyl)-1*H*-pyrazol-5-yl)amino)-4-(5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridine-6-carbonyl)benzene-1,3-diol (107). Acid **19y** (50.4 mg, 118 µmol) was subjected to General Procedure H1 to afford 14.6 mg of **107** (28% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.40 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.75 (d, *J* = 7.7

Hz, 1H), 7.44 – 7.27 (m, 2H), 7.27 – 7.16 (m, 2H), 7.16 – 7.08 (m, 1H), 6.17 (s, 1H), 5.94 (d, *J* = 2.1 Hz, 1H), 5.77 (d, *J* = 2.1 Hz, 1H), 5.02 – 4.65 (m, 4H), 3.72 (s, 3H), 2.37 (s, 3H). LC/MS (*m/z*): 442.329 [M+H$^+$]; UPLC t_R 1.40 min.

5-((1-Methyl-3-(2-methylphenyl)-1*H*-pyrazol-5-yl)amino)-4-(1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole-5-carbonyl)benzene-1,3-diol (108). Acid **19y** (50.4 mg, 118 µmol) was subjected to General Procedure H3 to afford 14.6 mg of **108** (28% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.42 (s, 1H), 7.36 (dd, *J* = 7.0, 1.6 Hz, 1H), 7.25 – 7.11 (m, 3H), 6.18 (s, 1H), 5.93 (d, *J* = 2.1 Hz, 1H), 5.74 (d, *J* = 2.1 Hz, 1H), 4.80 – 4.47 (m, 4H), 3.71 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 170.7, 161.6, 157.4, 152.0, 145.9, 142.9, 137.2, 134.7, 131.7, 130.3, 129.0, 126.9, 105.2, 101.7, 95.9, 95.0, 40.6, 35.3, 21.3. LC/MS (*m/z*): 431.347 [M+H$^+$]; UPLC t_R 1.31 min.

4-(2,3-Dihydro-1*H*-isoindole-2-carbonyl)-5-((1-methyl-3-(3-methylphenyl)-1*H*-pyrazol-5-yl)amino)benzene-1,3-diol (109). Acid **19z** (54.1 mg, 127 µmol) was subjected to General Procedure H1 to afford 20.2 mg of **109** (36% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.49 – 7.36 (m, 2H), 7.24 (s, 4H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.06 (d, *J* = 7.6 Hz, 1H), 6.34 (s, 1H), 5.94 (d, *J* = 2.1 Hz, 1H), 5.78 (d, *J* = 2.1 Hz, 1H), 4.96 – 4.70 (m, 4H), 3.69 (s, 3H), 2.31 (s, 3H). LC/MS (*m/z*): 441.094 [M+H$^+$]; UPLC t_R 1.57 min.

5-((1-Methyl-3-(3-methylphenyl)-1*H*-pyrazol-5-yl)amino)-4-(5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridine-6-carbonyl)benzene-1,3-diol (110). Acid **19z** (56.7 mg, 133 µmol) was subjected to General Procedure H2 to afford 16.2 mg of **110** (28% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.34 (dd, *J* = 4.9, 1.4 Hz, 1H), 7.73 – 7.62 (m, 1H), 7.46 – 7.29 (m, 2H), 7.24 (dd, *J* = 7.7, 5.0 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 7.6

Hz, 1H), 6.33 (s, 1H), 5.95 (d, *J* = 2.1 Hz, 1H), 5.83 (d, *J* = 2.1 Hz, 1H), 5.02 – 4.65 (m, 4H), 3.72 (s, 3H), 2.31 (s, 3H). LC/MS (*m/z*): 442.329 [M+H$^+$]; UPLC t_R 1.29 min.

5-((1-Methyl-3-(3-methylphenyl)-1*H*-pyrazol-5-yl)amino)-4-(1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole-5-carbonyl)benzene-1,3-diol (111). Acid **19z** (57.6 mg, 135 µmol) was subjected to General Procedure H3 to afford 20.3 mg of **111** (35% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.51 – 7.40 (m, 2H), 7.38 (s, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.13 – 7.05 (m, 1H), 6.34 (s, 1H), 5.94 (d, *J* = 2.1 Hz, 1H), 5.78 (d, *J* = 2.1 Hz, 1H), 4.79 – 4.45 (m, 4H), 3.70 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 170.6, 161.6, 157.4, 151.7, 145.8, 143.7, 139.4, 134.6, 129.6, 127.0, 123.6, 105.2, 98.4, 95.9, 95.3, 40.6, 35.3, 21.7. LC/MS (*m/z*): 431.347 [M+H$^+$]; UPLC t_R 1.22 min

4-(2,3-Dihydro-1*H*-isoindole-2-carbonyl)-5-((3-(3-methoxyphenyl)-1-methyl-1*H*-pyrazol-5-yl)amino)benzene-1,3-diol (112). Acid **19aa** (48.6 mg, 110 µmol) was subjected to General Procedure H1 to afford 18.2 mg of **112** (36% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.54 (s, 1H), 7.34 – 7.09 (m, 7H), 6.82 (s, 1H), 6.36 (s, 1H), 5.94 (s, 1H), 5.77 (s, 1H), 5.17 – 4.70 (m, 4H), 3.80 (s, 3H), 3.70 (s, 3H). ^{13}C NMR (101 MHz, $(CD_3)_2SO$) δ 166.4, 159.5, 159.3, 155.5, 148.1, 143.9, 143.8, 141.5, 141.4, 135.0, 129.6, 127.2, 122.9, 117.1, 113.1, 109.6, 104.0, 96.9, 94.3, 92.7, 55.0, 40.4, 35.0. LC/MS (*m/z*): 457.061 [M+H$^+$]; UPLC t_R 1.58 min.

5-((3-(3-Methoxyphenyl)-1-methyl-1*H*-pyrazol-5-yl)amino)-4-(5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridine-6-carbonyl)benzene-1,3-diol (113). Acid **19aa** (52.6 mg, 119 µmol) was subjected to General Procedure H2 to afford 6.7 mg of **113** (12% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.34 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.67 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.23 (dd, *J* = 7.8, 5.0 Hz, 1H), 7.21 – 7.07 (m, 3H), 6.78 (ddd, *J* = 7.9, 2.6, 1.3

Hz, 1H), 6.34 (s, 1H), 5.95 (d, *J* = 2.1 Hz, 1H), 5.83 (d, *J* = 2.1 Hz, 1H), 4.98 – 4.63 (m, 4H), 3.79 (s, 3H), 3.72 (s, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 170.4, 161.8, 161.5, 158.1, 157.6, 151.2, 149.6, 146.2, 144.0, 135.9, 133.3, 132.5, 130.7, 124.2, 118.8, 114.6, 111.4, 104.9, 98.3, 96.0, 95.9, 55.8, 40.6, 35.4. LC/MS (*m/z*): 458.296 [M+H$^+$]; UPLC t_R 1.30 min.

5-((3-(3-Methoxyphenyl)-1-methyl-1*H*-pyrazol-5-yl)amino)-4-(1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole-5-carbonyl)benzene-1,3-diol (114) Acid **19aa** (55.5 mg, 125 µmol) was subjected to General Procedure H3 to afford 21.6 mg of **114** (37% yield) after purification using mass-guided preparative HPLC.. ^{1}H NMR (400 MHz, CD_3OD) δ 7.38 (s, 1H), 7.30 – 7.15 (m, 3H), 6.82 (ddd, *J* = 7.6, 2.6, 1.7 Hz, 1H), 6.37 (s, 1H), 5.94 (d, *J* = 2.1 Hz, 1H), 5.77 (d, *J* = 2.1 Hz, 1H), 4.80 – 4.47 (m, 4H), 3.80 (s, 3H), 3.71 (s, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 170.7, 161.6, 161.5, 157.4, 151.4, 145.8, 143.7, 136.0, 130.8, 119.0, 114.7, 111.5, 98.6, 95.9, 95.3, 55.8, 40.6, 35.3. LC/MS (*m/z*): 447.313 [M+H$^+$]; UPLC t_R 1.25 min.

4-(2,3-Dihydro-1*H*-isoindole-2-carbonyl)-5-((1-methyl-3-(3-(trifluoromethyl)phenyl)-1*H*-pyrazol-5-yl)amino)benzene-1,3-diol (115). Acid **19ab** (50.5 mg, 105 µmol) was subjected to General Procedure H1 to afford 22 mg of **115** (42% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.94 (s, 1H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.49 (dt, *J* = 15.4, 7.8 Hz, 2H), 7.20 (s, 4H), 6.44 (s, 1H), 5.96 (d, *J* = 2.1 Hz, 1H), 5.81 (d, *J* = 2.1 Hz, 1H), 4.98 – 4.65 (m, 4H), 3.72 (s, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ 170.1, 161.6, 157.6, 149.7, 145.73, 145.66, 144.2, 137.6, 135.8, 132.0 (q, $^2J_{C\text{-}F}$ = 32.5 Hz), 130.6, 129.9, 128.8, 125.8 (q, $^1J_{C\text{-}F}$ = 270.0 Hz), 125.1 (q, $^3J_{C\text{-}F}$ = 3.8 Hz), 123.8, 122.6 (q, $^3J_{C\text{-}F}$ = 3.7 Hz), 105.5, 98.5, 96.1, 95.6, 40.6, 35.5. ^{19}F NMR (376 MHz, CD_3OD) δ -64.2. LC/MS (*m/z*): 495.301 [M+H$^+$]; UPLC t_R 1.78 min.

5-((1-Methyl-3-(3-(trifluoromethyl)phenyl)-1*H*-pyrazol-5-yl)amino)-4-(5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridine-6-carbonyl)benzene-1,3-diol (116). Acid **19ab** (56.4 mg, 117 µmol) was subjected to General Procedure H2 to afford 18.7 mg of **116** (32% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.30 (dd, *J* = 5.0, 1.4 Hz, 1H), 7.89 (d, *J* = 2.2 Hz, 1H), 7.79 (d, *J* = 7.5 Hz, 1H), 7.66 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.54 – 7.40 (m, 2H), 7.20 (dd, *J* = 7.8, 5.0 Hz, 1H), 6.45 (s, 1H), 5.97 (d, *J* = 2.1 Hz, 1H), 5.85 (d, *J* = 2.1 Hz, 1H), 4.98 – 4.63 (m, 4H), 3.75 (s, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ 170.4, 161.8, 158.2, 157.7, 149.62, 149.59, 146.1, 144.5, 135.7, 133.3, 132.0 (q, $^{2}J_{C\text{-}F}$ = 31.5 Hz), 130.6, 129.8, 125.8 (q, $^{1}J_{C\text{-}F}$ = 267.0 Hz), 125.1 (q, $^{3}J_{C\text{-}F}$ = 3.8 Hz), 124.2, 122.5 (q, $^{3}J_{C\text{-}F}$ = 4.8 Hz), 105.1, 98.3, 96.2, 96.1, 40.6, 35.6. ^{19}F NMR (376 MHz, CD_3OD) δ -64.2. LC/MS (*m/z*): 496.316 [M+H$^+$]; UPLC t_R 1.52 min.

5-((1-Methyl-3-(3-(trifluoromethyl)phenyl)-1*H*-pyrazol-5-yl)amino)-4-(1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole-5-carbonyl)benzene-1,3-diol (117). Acid **19ab** (57.2 mg, 119 µmol) was subjected to General Procedure H3 to afford 18.9 mg of **117** (33% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.97 (s, 1H), 7.86 (d, *J* = 7.3 Hz, 1H), 7.60 – 7.47 (m, 2H), 7.36 (s, 1H), 6.47 (s, 1H), 5.95 (d, *J* = 2.1 Hz, 1H), 5.80 (d, *J* = 2.1 Hz, 1H), 4.82 – 4.45 (m, 4H), 3.73 (s, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ 170.6, 161.6, 157.4, 149.8, 145.7, 144.2, 135.9, 132.1 (q, $^{2}J_{C\text{-}F}$ = 31.5 Hz), 130.6, 129.9, 125.8 (q, $^{1}J_{C\text{-}F}$ = 270.8 Hz), 125.2 (q, $^{3}J_{C\text{-}F}$ = 4.8 Hz), 122.7 (q, $^{3}J_{C\text{-}F}$ = 3.8 Hz), 105.4, 98.5, 96.1, 95.6, 40.6, 35.6. ^{19}F NMR (376 MHz, CD_3OD) δ -64.2. LC/MS (*m/z*): 485.289 [M+H$^+$]; UPLC t_R 1.45 min.

4-(2,3-Dihydro-1*H*-isoindole-2-carbonyl)-5-((1-methyl-3-(4-methylphenyl)-1*H*-pyrazol-5-yl)amino)benzene-1,3-diol (118). Acid **19ac** (44.5 mg, 104 µmol) was subjected to General Procedure H1 to afford 18.2 mg of **118** (40% yield) after purification using mass-guided

preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.58 – 7.43 (m, 2H), 7.24 (s, 4H), 7.12 (d, *J* = 8.0 Hz, 2H), 6.31 (s, 1H), 5.94 (d, *J* = 2.1 Hz, 1H), 5.76 (d, *J* = 2.1 Hz, 1H), 4.96 – 4.69 (m, 4H), 3.68 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 170.2, 161.6, 157.5, 151.7, 145.8, 143.6, 138.8, 137.7, 131.9, 130.3, 128.8, 126.4, 123.9, 105.2, 98.1, 95.9, 95.1, 40.6, 35.3, 21.4. LC/MS (*m/z*): 441.094 [$M+H^+$]; UPLC t_R 1.66 min.

5-((1-Methyl-3-(4-methylphenyl)-1*H*-pyrazol-5-yl)amino)-4-(5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridine-6-carbonyl)benzene-1,3-diol (119). Acid **19ac** (46.6 mg, 109 µmol) was subjected to General Procedure H2 to afford 14.2 mg of **119** (30% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.69 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.52 – 7.42 (m, 2H), 7.25 (dd, *J* = 7.8, 5.0 Hz, 1H), 7.09 (d, *J* = 7.9 Hz, 2H), 6.30 (s, 1H), 5.95 (d, *J* = 2.1 Hz, 1H), 5.81 (d, *J* = 2.1 Hz, 1H), 4.99 – 4.64 (m, 4H), 3.70 (s, 3H), 2.31 (s, 3H). LC/MS (*m/z*): 442.329 [$M+H^+$]; UPLC t_R 1.40 min.

5-((1-Methyl-3-(4-methylphenyl)-1*H*-pyrazol-5-yl)amino)-4-(1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole-5-carbonyl)benzene-1,3-diol (120). Acid **19ac** (50.8 mg, 119 µmol) was subjected to General Procedure H3 to afford 16.5 mg of **120** (32% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.58 – 7.46 (m, 2H), 7.38 (s, 1H), 7.14 (d, *J* = 7.9 Hz, 2H), 6.32 (s, 1H), 5.93 (d, *J* = 2.1 Hz, 1H), 5.76 (d, *J* = 2.1 Hz, 1H), 4.79 – 4.45 (m, 4H), 3.69 (s, 3H), 2.32 (s, 3H). LC/MS (*m/z*): 431.303 [$M+H^+$]; UPLC t_R 1.32 min.

4-(2,3-Dihydro-1*H*-isoindole-2-carbonyl)-5-((3-(4-methoxyphenyl)-1-methyl-1*H*-pyrazol-5-yl)amino)benzene-1,3-diol (121). Acid **19ad** (54.2 mg, 122 µmol) was subjected to General Procedure H1 to afford 21.4 mg of **121** (38% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.58 – 7.47 (m, 2H), 7.24 (s, 4H), 6.93 – 6.81 (m, 2H), 6.27 (s, 1H), 5.94 (d, *J* = 2.1 Hz, 1H), 5.77 (d, *J* = 2.1 Hz, 1H), 4.99 – 4.72 (m, 4H), 3.78

(s, 3H), 3.67 (s, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 170.2, 161.6, 161.0, 157.5, 151.5, 145.9, 143.6, 137.7, 128.8, 128.1, 127.7, 127.4, 123.9, 115.1, 105.3, 97.8, 95.9, 95.2, 55.8, 40.6, 35.2. LC/MS (*m/z*): 457.105 [M+H$^+$]; UPLC t_R 1.47 min.

5-((3-(4-Methoxyphenyl)-1-methyl-1*H*-pyrazol-5-yl)amino)-4-(5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridine-6-carbonyl)benzene-1,3-diol (122). Acid **19ad** (55.4 mg, 125 µmol) was subjected to General Procedure H2 to afford 14.4 mg of **122** (25% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.36 (dd, *J* = 5.1, 1.5 Hz, 1H), 7.69 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.58 – 7.42 (m, 2H), 7.26 (dd, *J* = 7.8, 5.0 Hz, 1H), 6.88 – 6.74 (m, 2H), 6.26 (s, 1H), 5.95 (d, *J* = 2.1 Hz, 1H), 5.82 (d, *J* = 2.1 Hz, 1H), 5.09 – 4.66 (m, 4H), 3.79 (s, 3H), 3.70 (s, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 170.4, 161.8, 161.0, 158.2, 157.6, 151.4, 149.6, 146.2, 143.9, 133.4, 127.6, 127.3, 124.3, 115.1, 104.9, 97.7, 96.0, 95.7, 55.9, 40.6, 35.2. LC/MS (*m/z*): 458.241 [M+H$^+$]; UPLC t_R 1.04 min.

5-((3-(4-Methoxyphenyl)-1-methyl-1*H*-pyrazol-5-yl)amino)-4-(1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole-5-carbonyl)benzene-1,3-diol (123). Acid **19ad** (55.6 mg, 125 µmol) was subjected to General Procedure H3 to afford 12.9 mg of **123** (23% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.61 – 7.51 (m, 2H), 7.39 (s, 1H), 6.93 – 6.82 (m, 2H), 6.28 (s, 1H), 5.93 (d, *J* = 2.1 Hz, 1H), 5.76 (d, *J* = 2.1 Hz, 1H), 4.85 – 4.41 (m, 4H), 3.79 (s, 3H), 3.68 (s, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ 170.7, 161.6, 161.1, 157.4, 151.6, 145.9, 143.7, 127.7, 127.4, 115.1, 105.3, 97.9, 95.9, 95.3, 55.9, 40.6, 35.2. LC/MS (*m/z*): 447.216 [M+H$^+$]; UPLC t_R 0.98 min.

4-(2,3-Dihydro-1*H*-isoindole-2-carbonyl)-5-((1-methyl-3-(4-(trifluoromethyl)phenyl)-1*H*-pyrazol-5-yl)amino)benzene-1,3-diol (124). Acid **19ae** (61.4 mg, 128 µmol) was subjected to General Procedure H1 to afford 20.5 mg of **124** (32% yield) after purification using mass-guided

preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.81 – 7.71 (m, 2H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.21 (s, 4H), 6.45 (s, 1H), 5.96 (d, *J* = 2.1 Hz, 1H), 5.81 (d, *J* = 2.1 Hz, 1H), 4.98 – 4.68 (m, 4H), 3.73 (s, 3H). ^{19}F NMR (376 MHz, CD_3OD) δ -64.1. LC/MS (*m/z*): 495.301 [$M+H^+$]; UPLC t_R 1.78 min.

5-((1-Methyl-3-(4-(trifluoromethyl)phenyl)-1*H*-pyrazol-5-yl)amino)-4-(5H,6H,7*H*-pyrrolo[3,4-*b*]pyridine-6-carbonyl)benzene-1,3-diol (125). Acid **19ae** (61.5 mg, 128 µmol) was subjected to General Procedure H2 to afford 15.2 mg of **125** (24% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.30 (d, *J* = 5.0 Hz, 1H), 7.76 – 7.69 (m, 2H), 7.65 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.20 (dd, *J* = 7.8, 5.0 Hz, 1H), 6.45 (s, 1H), 5.97 (d, *J* = 2.1 Hz, 1H), 5.85 (d, *J* = 2.1 Hz, 1H), 4.96 – 4.59 (m, 4H), 3.75 (s, 3H). ^{19}F NMR (376 MHz, CD_3OD) δ -64.0. LC/MS (*m/z*): 496.271 [$M+H^+$]; UPLC t_R 1.53 min.

5-((1-Methyl-3-(4-(trifluoromethyl)phenyl)-1*H*-pyrazol-5-yl)amino)-4-(1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole-5-carbonyl)benzene-1,3-diol (126). Acid **19ae** (62.2 mg, 129 µmol) was subjected to General Procedure H3 to afford 15 mg of **126** (24% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.81 (d, *J* = 8.1 Hz, 2H), 7.61 (d, *J* = 8.1 Hz, 2H), 7.37 (s, 1H), 6.47 (s, 1H), 5.95 (d, *J* = 2.1 Hz, 1H), 5.79 (d, *J* = 2.1 Hz, 1H), 4.79 – 4.41 (m, 4H), 3.74 (s, 3H). ^{19}F NMR (376 MHz, CD_3OD) δ -64.0. LC/MS (*m/z*): 485.289 [$M+H^+$]; UPLC t_R 1.47 min.

5-((3-(4-*tert*-Butylphenyl)-1-methyl-1*H*-pyrazol-5-yl)amino)-4-(2,3-dihydro-1*H*-isoindole-2-carbonyl)benzene-1,3-diol (127). Acid **19af** (59 mg, 130 µmol) was subjected to General Procedure H1 to afford 18.4 mg of **127** (30% yield) after purification using mass-guided preparative HPLC ^{1}H NMR (400 MHz, CD_3OD) δ 7.62 – 7.47 (m, 2H), 7.38 – 7.30 (m, 2H), 7.23

(s, 4H), 6.32 (s, 1H), 5.94 (d, *J* = 2.1 Hz, 1H), 5.78 (d, *J* = 2.1 Hz, 1H), 5.05 – 4.68 (m, 4H), 3.69 (s, 3H), 1.31 (s, 9H). LC/MS (*m/z*): 483.392 [M+H$^+$]; UPLC t_R 1.90 min.

5-((3-(4-*tert*-Butylphenyl)-1-methyl-1*H*-pyrazol-5-yl)amino)-4-(5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridine-6-carbonyl)benzene-1,3-diol (128). Acid **19af** (59.8 mg, 127 µmol) was subjected to General Procedure H2 to afford 18.1 mg of **128** (29% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.33 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.68 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.54 – 7.42 (m, 2H), 7.36 – 7.28 (m, 2H), 7.23 (dd, *J* = 7.8, 5.0 Hz, 1H), 6.32 (s, 1H), 5.95 (d, *J* = 2.1 Hz, 1H), 5.83 (d, *J* = 2.1 Hz, 1H), 4.93 – 4.66 (m, 4H), 3.72 (s, 3H), 1.31 (s, 9H). LC/MS (*m/z*): 484.363 [M+H$^+$]; UPLC t_R 1.64 min.

5-((3-(4-*tert*-Butylphenyl)-1-methyl-1*H*-pyrazol-5-yl)amino)-4-(1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole-5-carbonyl)benzene-1,3-diol (129). Acid **19af** (61.7 mg, 131 µmol) was subjected to General Procedure H3 to afford 18.1 mg of **129** (29% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.57 (d, *J* = 8.5 Hz, 2H), 7.42 – 7.31 (m, 3H), 6.34 (s, 1H), 5.93 (d, *J* = 2.1 Hz, 1H), 5.76 (d, *J* = 2.1 Hz, 1H), 4.81 – 4.47 (m, 4H), 3.70 (s, 3H), 1.32 (s, 9H). LC/MS (*m/z*): 473.336 [M+H$^+$]; UPLC t_R 1.57 min.

4-(2,3-Dihydro-1*H*-isoindole-2-carbonyl)-5-((1-methyl-3-(4-(trifluoromethoxy)phenyl)-1*H*-pyrazol-5-yl)amino)benzene-1,3-diol (130). Acid **19ag** (51.3 mg, 103 µmol) was subjected to General Procedure H1 to afford 21.3 mg of **130** (40% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.72 – 7.55 (m, 2H), 7.21 (s, 4H), 7.20 – 7.12 (m, 2H), 6.36 (s, 1H), 5.96 (d, *J* = 2.1 Hz, 1H), 5.80 (d, *J* = 2.1 Hz, 1H), 4.99 – 4.66 (m, 4H), 3.71 (s, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ 170.2, 161.6, 157.5, 150.0, 149.9, 145.8, 144.1, 137.7, 134.0, 128.8, 127.9, 123.9, 122.3, 122.1 (q, $^1J_{C\text{-}F}$ = 253.8 Hz), 105.5, 98.3, 96.1, 95.7, 40.6, 35.4. ^{19}F NMR (376 MHz, CD_3OD) δ -59.5. LC/MS (*m/z*): 511.162 [M+H$^+$]; UPLC t_R 1.61 min.

5-((1-Methyl-3-(4-(trifluoromethoxy)phenyl)-1*H*-pyrazol-5-yl)amino)-4-(5*H*,6*H*,7*H*-pyrrolo[3,4-*b*]pyridine-6-carbonyl)benzene-1,3-diol (131). Acid **19ag** (53.1 mg, 107 µmol) was subjected to General Procedure H2 to afford 18.6 mg of **131** (34% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 8.31 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.69 – 7.59 (m, 3H), 7.21 (dd, *J* = 7.8, 5.0 Hz, 1H), 7.19 – 7.11 (m, 2H), 6.37 (s, 1H), 5.96 (d, *J* = 2.1 Hz, 1H), 5.85 (d, *J* = 2.1 Hz, 1H), 4.97 – 4.64 (m, 4H), 3.73 (s, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ 170.4, 161.7, 158.1, 157.6, 149.9, 149.7, 149.4, 133.8, 133.5, 132.6, 127.7, 124.7, 122.1 (q, $^{1}J_{C\text{-}F}$ = 253.8 Hz), 105.1, 98.2, 96.24, 96.17, 40.6, 35.4. ^{19}F NMR (376 MHz, CD_3OD) δ -59.4. LC/MS (*m/z*): 512.326 [M+H$^+$]; UPLC t_R 1.48 min.

5-((1-Methyl-3-(4-(trifluoromethoxy)phenyl)-1*H*-pyrazol-5-yl)amino)-4-(1*H*,4*H*,5*H*,6*H*-pyrrolo[3,4-*c*]pyrazole-5-carbonyl)benzene-1,3-diol (132). Acid **19ag** (54.4 mg, 109 µmol) was subjected to General Procedure H3 to afford 17 mg of **132** (31% yield) after purification using mass-guided preparative HPLC. ^{1}H NMR (400 MHz, CD_3OD) δ 7.77 – 7.67 (m, 2H), 7.37 (s, 1H), 7.28 – 7.17 (m, 2H), 6.39 (s, 1H), 5.94 (d, *J* = 2.1 Hz, 1H), 5.78 (d, *J* = 2.1 Hz, 1H), 4.79 – 4.45 (m, 4H), 3.72 (s, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ 170.6, 161.5, 157.4, 150.0, 149.9, 145.6, 144.1, 134.0, 127.9, 124.1, 122.3, 122.1 (q, $^{1}J_{C\text{-}F}$ = 255.0 Hz), 105.4, 98.2, 96.1, 95.6, 40.6, 35.4. ^{19}F NMR (376 MHz, CD_3OD) δ -59.5. LC/MS (*m/z*): 501.151 [M+H$^+$]; UPLC t_R 1.28 min.

ASSOCIATED CONTENT

Supporting Information.

The following files are available free of charge.

Supporting Information: Figures S1 & S2 and Supplementary Tables 1-5 (PDF)

Molecular formula strings and associated biological data (CSV)

AUTHOR INFORMATION

Corresponding Authors

*L.W.: email, luke.whitesell@utoronto.ca

*L.E.C.: email, leah.cowen@utoronto.ca

*L.E.B.: email, brownle@bu.edu

Present Addresses

† D.S.H.: Foghorn Therapeutics, 100 Binney St. Cambridge, MA 02142, USA

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. ‡These authors contributed equally.

Notes

L.E.C. is a co-founder, Chief Scientific Officer, and shareholder in Bright Angel Therapeutics, a platform company for the development of novel antifungal therapeutics. L.E.C. is a consultant for Boragen, a small molecule development company focused on leveraging the unique chemical

properties of boron chemistry for crop protection and animal health. L.W. is a co-founder and shareholder in Bright Angel Therapeutics. L.E.B. D.S.H., L.E.C. and L.W. are named as inventors on a provisional patent application pertaining to findings reported here.

ACKNOWLEDGMENT

This work was supported by a grant from the National Institutes of Health (Grant R01AI120958 to L.E.C., L.E.B., and D.K). L.E.C. holds a Canada Research Chair in Microbial Genomics & Infectious Disease and is Co-Director of the CIFAR Program, Fungal Kingdom: Threats & Opportunities. The authors thank Dr. Han Yueh for assistance in acquiring LC/MS purity data, Dr. Paul Ralifo for assistance with NMR analysis, Gaurang Patel and Adrian Sheldon (Charles River Laboratories) for assistance with microsomal stability assays, and the Ontario Institute for Cancer Research (M. Mohammed and R. Marcellus) for assistance with SPR assays.

ABBREVIATIONS

Hsp90, heat shock protein 90; Trap1, TNF receptor associated protein 1; Grp94, 94 kDa glucose-regulated protein; NBD, nucleotide binding domain; HATU, hexafluorophosphate azabenzotriazole tetramethyl uronium; DIPEA, *N*,*N*-diisopropylethylamine; UPLC, ultraperformance liquid chromatography; PS-CDI, polymer-supported carbonyldiimidazole;

REFERENCES

1. Brown, G. D.; Denning, D. W.; Gow, N. A.; Levitz, S. M.; Netea, M. G.; White, T. C., Hidden killers: human fungal infections. *Sci. Transl. Med.* **2012,** *4* (165), 165rv113.
2. Robbins, N.; Wright, G. D.; Cowen, L. E., Antifungal drugs: the current armamentarium and development of new agents. In *The Fungal Kingdom*, Heitman, J.; Howlett, B.; Crous,

P.; Stukenbrock, E.; James, T.; Gow, N., Eds. ASM Press: Washington DC., 2017; Vol. 4, pp 903-922.

3. McKenzie, C. G.; Koser, U.; Lewis, L. E.; Bain, J. M.; Mora-Montes, H. M.; Barker, R. N.; Gow, N. A.; Erwig, L. P., Contribution of Candida albicans cell wall components to recognition by and escape from murine macrophages. *Infect. Immun.* **2010,** *78* (4), 1650-1658.

4. Cowen, L. E.; Singh, S. D.; Kohler, J. R.; Collins, C.; Zaas, A. K.; Schell, W. A.; Aziz, H.; Mylonakis, E.; Perfect, J. R.; Whitesell, L.; Lindquist, S., Harnessing Hsp90 function as a powerful, broadly effective therapeutic strategy for fungal infectious disease. *Proc. Natl. Acad. Sci. USA* **2009,** *106* (8), 2818-2823.

5. Cowen, L. E.; Lindquist, S., Hsp90 potentiates the rapid evolution of new traits: drug resistance in diverse fungi. *Science* **2005,** *309* (5744), 2185-2189.

6. Singh, S. D.; Robbins, N.; Zaas, A. K.; Schell, W. A.; Perfect, J. R.; Cowen, L. E., Hsp90 governs echinocandin resistance in the pathogenic yeast Candida albicans via calcineurin. *PLoS Pathog.* **2009,** *5* (7), e1000532.

7. Chatterjee, S.; Tatu, U., Heat shock protein 90 localizes to the surface and augments virulence factors of Cryptococcus neoformans. *PLoS Negl. Trop. Dis.* **2017,** *11* (8), e0005836.

8. Cordeiro Rde, A.; Evangelista, A. J.; Serpa, R.; Marques, F. J.; de Melo, C. V.; de Oliveira, J. S.; Franco Jda, S.; de Alencar, L. P.; Bandeira Tde, J.; Brilhante, R. S.; Sidrim, J. J.; Rocha, M. F., Inhibition of heat-shock protein 90 enhances the susceptibility to antifungals and reduces the virulence of Cryptococcus neoformans/Cryptococcus gattii species complex. *Microbiology (Reading, England)* **2016,** *162* (2), 309-317.

9. Ferraro, M.; D'Annessa, I.; Moroni, E.; Morra, G.; Paladino, A.; Rinaldi, S.; Compostella, F.; Colombo, G., Allosteric modulators of HSP90 and HSP70: dynamics meets function through structure-based drug design. *J. Med. Chem.* **2019,** *62* (1), 60-87.

10. Taipale, M.; Jarosz, D. F.; Lindquist, S., HSP90 at the hub of protein homeostasis: emerging mechanistic insights. *Nat. Rev. Mol. Cell Biol.* **2010,** *11*, 515-528.

11. Whitesell, L.; Robbins, N.; Huang, D. S.; McLellan, C. A.; Shekhar-Guturja, T.; LeBlanc, E. V.; Nation, C. S.; Hui, R.; Hutchinson, A.; Collins, C.; Chatterjee, S.; Trilles, R.; Xie, J. L.; Krysan, D. J.; Lindquist, S.; Porco, J. A.; Tatu, U.; Brown, L. E.; Pizarro, J.; Cowen, L. E., Structural basis for species-selective targeting of Hsp90 in a pathogenic fungus. *Nat. Commun.* **2019,** *10* (1), 402.

12. Rehn, A.; Moroni, E.; Zierer, B. K.; Tippel, F.; Morra, G.; John, C.; Richter, K.; Colombo, G.; Buchner, J., Allosteric regulation points control the conformational dynamics of the molecular chaperone Hsp90. *J. Mol. Biol.* **2016,** *428* (22), 4559-4571.

13. Gewirth, D. T., Paralog specific Hsp90 inhibitors - a brief history and a bright future. *Curr. Top. Med. Chem.* **2016,** *16* (25), 2779-2791.

14. Lee, C.; Park, H. K.; Jeong, H.; Lim, J.; Lee, A. J.; Cheon, K. Y.; Kim, C. S.; Thomas, A. P.; Bae, B.; Kim, N. D.; Kim, S. H.; Suh, P. G.; Ryu, J. H.; Kang, B. H., Development of a mitochondria-targeted Hsp90 inhibitor based on the crystal structures of human TRAP1. *J. Am. Chem. Soc.* **2015,** *137* (13), 4358-4367.

15. Crowley, V. M.; Khandelwal, A.; Mishra, S.; Stothert, A. R.; Huard, D. J. E.; Zhao, J.; Muth, A.; Duerfeldt, A. S.; Kizziah, J. L.; Lieberman, R. L.; Dickey, C. A.; Blagg, B. S. J., Development of glucose regulated protein 94-selective inhibitors based on the BnIm and radamide scaffold. *J. Med. Chem.* **2016,** *59* (7), 3471-3488.

16. Patel, P. D.; Yan, P.; Seidler, P. M.; Patel, H. J.; Sun, W.; Yang, C.; Que, N. S.; Taldone, T.; Finotti, P.; Stephani, R. A.; Gewirth, D. T.; Chiosis, G., Paralog-selective Hsp90 inhibitors define tumor-specific regulation of HER2. *Nat. Chem. Biol.* **2013,** *9*, 677-684.

17. Duerfeldt, A. S.; Peterson, L. B.; Maynard, J. C.; Ng, C. L.; Eletto, D.; Ostrovsky, O.; Shinogle, H. E.; Moore, D. S.; Argon, Y.; Nicchitta, C. V.; Blagg, B. S., Development of a Grp94 inhibitor. *J. Am. Chem. Soc.* **2012,** *134*, 9796-9804.

18. Stothert, A. R.; Suntharalingam, A.; Tang, X.; Crowley, V. M.; Mishra, S. J.; Webster, J. M.; Nordhues, B. A.; Huard, D. J. E.; Passaglia, C. L.; Lieberman, R. L.; Blagg, B. S. J.; Blair, L. J.; Koren, J.; Dickey, C. A., Isoform-selective Hsp90 inhibition rescues model of hereditary open-angle glaucoma. *Sci. Rep.* **2017,** *7* (1), 17951.

19. Muth, A.; Crowley, V.; Khandelwal, A.; Mishra, S.; Zhao, J.; Hall, J.; Blagg, B. S. J., Development of radamide analogs as Grp94 inhibitors. *Bioorg. Med. Chem.* **2014,** *22* (15), 4083-4098.

20. Khandelwal, A.; Kent, C. N.; Balch, M.; Peng, S.; Mishra, S. J.; Deng, J.; Day, V. W.; Liu, W.; Subramanian, C.; Cohen, M.; Holzbeierlein, J. M.; Matts, R.; Blagg, B. S. J., Structure-guided design of an Hsp90β N-terminal isoform-selective inhibitor. *Nat. Commun.* **2018,** *9* (1), 425.

21. Ohkubo, S.; Kodama, Y.; Muraoka, H.; Hitotsumachi, H.; Yoshimura, C.; Kitade, M.; Hashimoto, A.; Ito, K.; Gomori, A.; Takahashi, K.; Shibata, Y.; Kanoh, A.; Yonekura, K., TAS-116, a highly selective inhibitor of heat shock protein 90α and β, demonstrates potent antitumor activity and minimal ocular toxicity in preclinical models. *Mol. Cancer Ther.* **2015,** *14* (1), 14-22.

22. Ernst, J. T.; Neubert, T.; Liu, M.; Sperry, S.; Zuccola, H.; Turnbull, A.; Fleck, B.; Kargo, W.; Woody, L.; Chiang, P.; Tran, D.; Chen, W.; Snyder, P.; Alcacio, T.; Nezami, A.; Reynolds, J.; Alvi, K.; Goulet, L.; Stamos, D., Identification of novel HSP90 α/β isoform selective inhibitors using structure-based drug design. Demonstration of potential utility in treating CNS disorders such as Huntington's Disease. *J. Med. Chem.* **2014,** *57* (8), 3382-3400.

23. Ernst, J. T.; Liu, M.; Zuccola, H.; Neubert, T.; Beaumont, K.; Turnbull, A.; Kallel, A.; Vought, B.; Stamos, D., Correlation between chemotype-dependent binding conformations of HSP90 α/β and isoform selectivity—Implications for the structure-based design of HSP90 α/β selective inhibitors for treating neurodegenerative diseases. *Bioorg. Med. Chem. Lett.* **2014,** *24* (1), 204-208.

24. Woodhead, A. J.; Angove, H.; Carr, M. G.; Chessari, G.; Congreve, M.; Coyle, J. E.; Cosme, J.; Graham, B.; Day, P. J.; Downham, R.; Fazal, L.; Feltell, R.; Figueroa, E.; Frederickson, M.; Lewis, J.; McMenamin, R.; Murray, C. W.; O'Brien, M. A.; Parra, L.; Patel, S.; Phillips, T.; Rees, D. C.; Rich, S.; Smith, D. M.; Trewartha, G.; Vinkovic, M.; Williams, B.; Woolford, A. J., Discovery of (2,4-dihydroxy-5-isopropylphenyl)-[5-(4-methylpiperazin-1-ylmethyl)-1,3-dihydrois oindol-2-yl]methanone (AT13387), a novel inhibitor of the molecular chaperone Hsp90 by fragment based drug design. *J. Med. Chem.* **2010,** *53*, 5956-5969.

25. Do, K.; Speranza, G.; Chang, L.-C.; Polley, E. C.; Bishop, R.; Zhu, W.; Trepel, J. B.; Lee, S.; Lee, M.-J.; Kinders, R. J.; Phillips, L.; Collins, J.; Lyons, J.; Jeong, W.; Antony, R.; Chen, A. P.; Neckers, L.; Doroshow, J. H.; Kummar, S., Phase I study of the heat shock protein 90 (Hsp90) inhibitor onalespib (AT13387) administered on a daily for 2

consecutive days per week dosing schedule in patients with advanced solid tumors. *Invest. New Drug.* **2015,** *33* (4), 921-930.

26. Wagner, A. J.; Agulnik, M.; Heinrich, M. C.; Mahadevan, D.; Riedel, R. F.; von Mehren, M.; Trent, J.; Demetri, G. D.; Corless, C. L.; Yule, M.; Lyons, J. F.; Oganesian, A.; Keer, H., Dose-escalation study of a second-generation non-ansamycin HSP90 inhibitor, onalespib (AT13387), in combination with imatinib in patients with metastatic gastrointestinal stromal tumour. *Eur. J. Cancer* **2016,** *61*, 94-101.

27. Canella, A.; Welker, A. M.; Yoo, J. Y.; Xu, J.; Abas, F. S.; Kesanakurti, D.; Nagarajan, P.; Beattie, C. E.; Sulman, E. P.; Liu, J.; Gumin, J.; Lang, F. F.; Gurcan, M. N.; Kaur, B.; Sampath, D.; Puduvalli, V. K., Efficacy of onalespib, a long-acting second-generation HSP90 inhibitor, as a single agent and in combination with temozolomide against malignant gliomas. *Clin. Cancer Res.* **2017,** *23* (20), 6215-6226.

28. Stühmer, T.; Zöllinger, A.; Siegmund, D.; Chatterjee, M.; Grella, E.; Knop, S.; Kortüm, M.; Unzicker, C.; Jensen, M. R.; Quadt, C.; Chène, P.; Schoepfer, J.; García-Echeverría, C.; Einsele, H.; Wajant, H.; Bargou, R. C., Signalling profile and antitumour activity of the novel Hsp90 inhibitor NVP-AUY922 in multiple myeloma. *Leukemia* **2008,** *22*, 1604-1612.

29. Jensen, M. R.; Schoepfer, J.; Radimerski, T.; Massey, A.; Guy, C. T.; Brueggen, J.; Quadt, C.; Buckler, A.; Cozens, R.; Drysdale, M. J.; Garcia-Echeverria, C.; Chène, P., NVP-AUY922: a small molecule HSP90 inhibitor with potent antitumor activity in preclinical breast cancer models. *Breast Cancer Res.* **2008,** *10* (2), R33.

30. Doi, T.; Onozawa, Y.; Fuse, N.; Yoshino, T.; Yamazaki, K.; Watanabe, J.; Akimov, M.; Robson, M.; Boku, N.; Ohtsu, A., Phase I dose-escalation study of the HSP90 inhibitor

AUY922 in Japanese patients with advanced solid tumors. *Cancer Chemother. Pharmacol.* **2014,** *74* (3), 629-636.

31. Seggewiss-Bernhardt, R.; Bargou, R. C.; Goh, Y. T.; Stewart, A. K.; Spencer, A.; Alegre, A.; Bladé, J.; Ottmann, O. G.; Fernandez-Ibarra, C.; Lu, H.; Pain, S.; Akimov, M.; Iyer, S. P., Phase 1/1B trial of the heat shock protein 90 inhibitor NVP-AUY922 as monotherapy or in combination with bortezomib in patients with relapsed or refractory multiple myeloma. *Cancer* **2015,** *121* (13), 2185-2192.

32. Renouf, D. J.; Hedley, D.; Krzyzanowska, M. K.; Schmuck, M.; Wang, L.; Moore, M. J., A phase II study of the HSP90 inhibitor AUY922 in chemotherapy refractory advanced pancreatic cancer. *Cancer Chemother. Pharmacol.* **2016,** *78* (3), 541-545.

33. Bendell, J. C.; Bauer, T. M.; Lamar, R.; Joseph, M.; Penley, W.; Thompson, D. S.; Spigel, D. R.; Owera, R.; Lane, C. M.; Earwood, C.; Burris, H. A., A phase 2 study of the Hsp90 inhibitor AUY922 as treatment for patients with refractory gastrointestinal stromal tumors. *Cancer Invest.* **2016,** *34* (6), 265-270.

34. Lin, T.-Y.; Bear, M.; Du, Z.; Foley, K. P.; Ying, W.; Barsoum, J.; London, C., The novel HSP90 inhibitor STA-9090 exhibits activity against Kit-dependent and -independent malignant mast cell tumors. *Exp. Hematol.* **2008,** *36* (10), 1266-1277.

35. Ying, W. W.; Du, Z. J.; Sun, L. J.; Foley, K. P.; Proia, D. A.; Blackman, R. K.; Zhou, D.; Inoue, T.; Tatsuta, N.; Sang, J.; Ye, S. X.; Acquaviva, J.; Ogawa, L. S.; Wada, Y.; Barsoum, J.; Koya, K., Ganetespib, a unique triazolone-containing Hsp90 inhibitor, exhibits potent antitumor activity and a superior safety profile for cancer therapy. *Mol. Cancer Ther.* **2012,** *11* (2), 475-484.

36. Lock, R. B.; Carol, H.; Maris, J. M.; Kang, M. H.; Reynolds, C. P.; Kolb, E. A.; Gorlick, R.; Keir, S. T.; Billups, C. A.; Kurmasheva, R. T.; Houghton, P. J.; Smith, M. A., Initial testing (stage 1) of ganetespib, an Hsp90 inhibitor, by the pediatric preclinical testing program. *Pediatr. Blood Cancer* **2013,** *60* (7), E42-E45.

37. Jhaveri, K.; Wang, R.; Teplinsky, E.; Chandarlapaty, S.; Solit, D.; Cadoo, K.; Speyer, J.; D'Andrea, G.; Adams, S.; Patil, S.; Haque, S.; O'Neill, T.; Friedman, K.; Esteva, F. J.; Hudis, C.; Modi, S., A phase I trial of ganetespib in combination with paclitaxel and trastuzumab in patients with human epidermal growth factor receptor-2 (HER2)-positive metastatic breast cancer. *Breast Cancer Res.* **2017,** *19* (1), 89.

38. Thakur, M. K.; Heilbrun, L. K.; Sheng, S.; Stein, M.; Liu, G.; Antonarakis, E. S.; Vaishampayan, U.; Dzinic, S. H.; Li, X.; Freeman, S.; Smith, D.; Heath, E. I., A phase II trial of ganetespib, a heat shock protein 90 Hsp90) inhibitor, in patients with docetaxel-pretreated metastatic castrate-resistant prostate cancer (CRPC)-a prostate cancer clinical trials consortium (PCCTC) study. *Invest. New Drug.* **2016,** *34* (1), 112-118.

39. Goyal, L.; Wadlow, R. C.; Blaszkowsky, L. S.; Wolpin, B. M.; Abrams, T. A.; McCleary, N. J.; Sheehan, S.; Sundaram, E.; Karol, M. D.; Chen, J.; Zhu, A. X., A phase I and pharmacokinetic study of ganetespib (STA-9090) in advanced hepatocellular carcinoma. *Invest. New Drug.* **2015,** *33* (1), 128-137.

40. Socinski, M. A.; Goldman, J.; El-Hariry, I.; Koczywas, M.; Vukovic, V.; Horn, L.; Paschold, E.; Salgia, R.; West, H.; Sequist, L. V.; Bonomi, P.; Brahmer, J.; Chen, L.-C.; Sandler, A.; Belani, C. P.; Webb, T.; Harper, H.; Huberman, M.; Ramalingam, S.; Wong, K.-K.; Teofilovici, F.; Guo, W.; Shapiro, G. I., A multicenter phase II study of

ganetespib monotherapy in patients with genotypically defined advanced non–small cell lung cancer. *Clin. Cancer Res.* **2013,** *19* (11), 3068-3077.

41. Jhaveri, K.; Chandarlapaty, S.; Lake, D.; Gilewski, T.; Robson, M.; Goldfarb, S.; Drullinsky, P.; Sugarman, S.; Wasserheit-Leiblich, C.; Fasano, J.; Moynahan, M. E.; D'Andrea, G.; Lim, K.; Reddington, L.; Haque, S.; Patil, S.; Bauman, L.; Vukovic, V.; El-Hariry, I.; Hudis, C.; Modi, S., A phase II open-label study of ganetespib, a novel heat shock protein 90 inhibitor for patients with metastatic breast cancer. *Clin. Breast Cancer* **2014,** *14* (3), 154-160.

42. Goldman, J. W.; Raju, R. N.; Gordon, G. A.; El-Hariry, I.; Teofilivici, F.; Vukovic, V. M.; Bradley, R.; Karol, M. D.; Chen, Y.; Guo, W.; Inoue, T.; Rosen, L. S., A first in human, safety, pharmacokinetics, and clinical activity phase I study of once weekly administration of the Hsp90 inhibitor ganetespib (STA-9090) in patients with solid malignancies. *BMC Cancer* **2013,** *13* (1), 152.

43. Nakashima, T.; Ishii, T.; Tagaya, H.; Seike, T.; Nakagawa, H.; Kanda, Y.; Akinaga, S.; Soga, S.; Shiotsu, Y., New molecular and biological mechanism of antitumor activities of KW-2478, a novel nonansamycin heat shock protein 90 inhibitor, in multiple myeloma cells. *Clin. Cancer Res.* **2010,** *16* (10), 2792-2802.

44. Ishii, T.; Seike, T.; Nakashima, T.; Juliger, S.; Maharaj, L.; Soga, S.; Akinaga, S.; Cavenagh, J.; Joel, S.; Shiotsu, Y., Anti-tumor activity against multiple myeloma by combination of KW-2478, an Hsp90 inhibitor, with bortezomib. *Blood Cancer J.* **2012,** *2*, e68.

45. Yong, K.; Cavet, J.; Johnson, P.; Morgan, G.; Williams, C.; Nakashima, D.; Akinaga, S.; Oakervee, H.; Cavenagh, J., Phase I study of KW-2478, a novel Hsp90 inhibitor, in patients with B-cell malignancies. *Br. J. Cancer* **2015,** *114*, 7-13.

46. Cavenagh, J.; Oakervee, H.; Baetiong-Caguioa, P.; Davies, F.; Gharibo, M.; Rabin, N.; Kurman, M.; Novak, B.; Shiraishi, N.; Nakashima, D.; Akinaga, S.; Yong, K., A phase I/II study of KW-2478, an Hsp90 inhibitor, in combination with bortezomib in patients with relapsed/refractory multiple myeloma. *Br. J. Cancer* **2017,** *117*, 1295-1302.

47. Ritchie, T. J.; Macdonald, S. J. F.; Peace, S.; Pickett, S. D.; Luscombe, C. N., The developability of heteroaromatic and heteroaliphatic rings – do some have a better pedigree as potential drug molecules than others? *MedChemComm* **2012,** *3* (9), 1062-1069.

48. Khandelwal, A.; Crowley, V. M.; Blagg, B. S. J., Resorcinol-based Grp94-selective inhibitors. *ACS Med. Chem. Lett* **2017,** *8* (10), 1013-1018.

49. Kung, P.-P.; Funk, L.; Meng, J.; Collins, M.; Zhou, J. Z.; Catherine Johnson, M.; Ekker, A.; Wang, J.; Mehta, P.; Yin, M.-J.; Rodgers, C.; Davies, J. F.; Bayman, E.; Smeal, T.; Maegley, K. A.; Gehring, M. R., Dihydroxylphenyl amides as inhibitors of the Hsp90 molecular chaperone. *Bioorg. Med. Chem. Lett.* **2008,** *18* (23), 6273-6278.

50. Kung, P.-P.; Huang, B.; Zhang, G.; Zhou, J. Z.; Wang, J.; Digits, J. A.; Skaptason, J.; Yamazaki, S.; Neul, D.; Zientek, M.; Elleraas, J.; Mehta, P.; Yin, M.-J.; Hickey, M. J.; Gajiwala, K. S.; Rodgers, C.; Davies, J. F.; Gehring, M. R., Dihydroxyphenylisoindoline amides as orally bioavailable inhibitors of the heat shock protein 90 (Hsp90) molecular chaperone. *J. Med. Chem.* **2010,** *53* (1), 499-503.

51. Murray, C. W.; Carr, M. G.; Callaghan, O.; Chessari, G.; Congreve, M.; Cowan, S.; Coyle, J. E.; Downham, R.; Figueroa, E.; Frederickson, M.; Graham, B.; McMenamin,

R.; O'Brien, M. A.; Patel, S.; Phillips, T. R.; Williams, G.; Woodhead, A. J.; Woolford, A. J., Fragment-based drug discovery applied to Hsp90. Discovery of two lead series with high ligand efficiency. *J. Med. Chem.* **2010,** *53*, 5942-5955.

52. Patel, B. H.; Barrett, A. G. M., Total synthesis of resorcinol amide Hsp90 inhibitor AT13387. *J. Org. Chem.* **2012,** *77* (24), 11296-11301.

53. Ren, J.; Li, J.; Wang, Y.; Chen, W.; Shen, A.; Liu, H.; Chen, D.; Cao, D.; Li, Y.; Zhang, N.; Xu, Y.; Geng, M.; He, J.; Xiong, B.; Shen, J., Identification of a new series of potent diphenol HSP90 inhibitors by fragment merging and structure-based optimization. *Bioorg. Med. Chem. Lett.* **2014,** *24* (11), 2525-2529.

54. Moss, T. A.; Addie, M. S.; Nowak, T.; Waring, M. J., Room-temperature palladium-catalyzed coupling of heteroaryl amines with aryl or heteroaryl bromides. *Synlett* **2012,** *2012* (02), 285-289.

55. Schulte II, J. P.; Tweedie, S. R., Palladium-catalyzed couplings of heteroaryl amines with aryl halides using sodium phenolate as the stoichiometric base. *Synlett* **2007,** *2007* (15), 2331-2336.

56. Park, S. Y.; Oh, Y. J.; Lho, Y.; Jeong, J. H.; Liu, K.-H.; Song, J.; Kim, S.-H.; Ha, E.; Seo, Y. H., Design, synthesis, and biological evaluation of a series of resorcinol-based N-benzyl benzamide derivatives as potent Hsp90 inhibitors. *Eur. J. Med. Chem.* **2018,** *143*, 390-401.

57. Ritchie, T. J.; Macdonald, S. J., The impact of aromatic ring count on compound developability--are too many aromatic rings a liability in drug design? *Drug Discov. Today* **2009,** *14* (21-22), 1011-1020.

58. White, T. C., Increased mRNA levels of ERG16, CDR, and MDR1 correlate with increases in azole resistance in Candida albicans isolates from a patient infected with human immunodeficiency virus. *Antimicrob. Agents Chemother.* **1997,** *41* (7), 1482-1487.

59. Odds, F. C.; Brown, A. J.; Gow, N. A., Candida albicans genome sequence: a platform for genomics in the absence of genetics. *Genome Biol.* **2004,** *5* (7), 230.

60. Granger, D. L.; Perfect, J. R.; Durack, D. T., Virulence of Cryptococcus neoformans. Regulation of capsule synthesis by carbon dioxide. *J. Clin. Invest.* **1985,** *76* (2), 508-516.

61. LaFayette, S. L.; Collins, C.; Zaas, A. K.; Schell, W. A.; Betancourt-Quiroz, M.; Gunatilaka, A. A.; Perfect, J. R.; Cowen, L. E., PKC signaling regulates drug resistance of the fungal pathogen Candida albicans via circuitry comprised of Mkc1, calcineurin, and Hsp90. *PLoS Pathog.* **2010,** *6* (8), e1001069.

62. Rossi, A. M.; Taylor, C. W., Analysis of protein-ligand interactions by fluorescence polarization. *Nat. Protoc.* **2011,** *6* (3), 365-387.

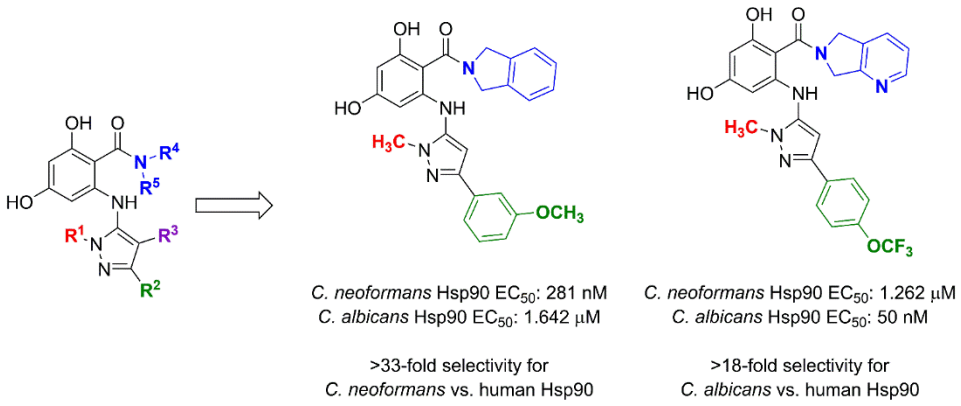
63. Houston, J. B., Utility of in vitro drug metabolism data in predicting in vivo metabolic clearance. *Biochem. Pharmacol.* **1994,** *47* (9), 1469-1479.

64. Jung, F. H.; Morgentin, R. R.; Ple, P. Quinoline derivatives. WO2007099323, 2007.

65. Nikolovska-Coleska, Z.; Abulwerdi, F.; Showalter, H.; Miao, L.; Stuckey, J.; Mady, A. Small molecule inhibitors of MCL-1 and uses thereof. WO2015153959, 2015.

66. Jefson, M. R.; Lowe, J. A.; Dey, F.; Bergmann, A.; Schoop, A.; Fuller, N. O. Hetero-halo inhibitors of histone deacetylase. WO2017007756, 2017.

Table of Contents graphic



C. neoformans Hsp90 EC_{50}: 281 nM
C. albicans Hsp90 EC_{50}: 1.642 μM

>33-fold selectivity for
C. neoformans vs. human Hsp90

C. neoformans Hsp90 EC_{50}: 1.262 μM
C. albicans Hsp90 EC_{50}: 50 nM

>18-fold selectivity for
C. albicans vs. human Hsp90