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Article

Structure–Property Optimization of a Series of Imidazopyridines for Visceral Leishmaniasis

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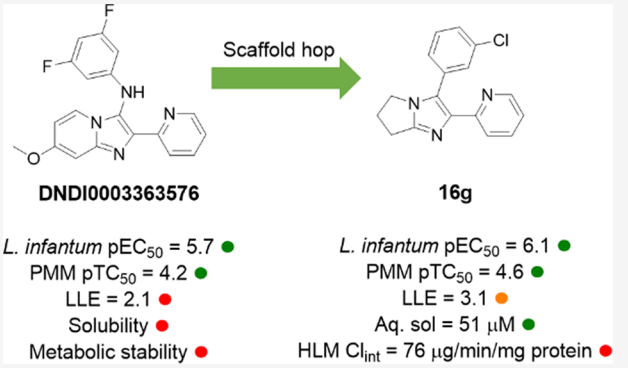
ABSTRACT: Leishmaniasis is a collection of diseases caused by more than 20 *Leishmania* parasite species that manifest as either visceral, cutaneous, or mucocutaneous leishmaniasis. Despite the significant mortality and morbidity associated with leishmaniasis, it remains a neglected tropical disease. Existing treatments have variable efficacy, significant toxicity, rising resistance, and limited oral bioavailability, which necessitates the development of novel and affordable therapeutics. Here, we report on the continued optimization of a series of imidazopyridines for visceral leishmaniasis and a scaffold hop to a series of substituted 2-(pyridin-2-yl)-6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazoles with improved absorption, distribution, metabolism, and elimination properties.



KEYWORDS: *leishmaniasis, neglected tropical diseases, structure–property optimization*

Neglected tropical diseases (NTDs) are a collection of 20 infectious diseases identified by the World Health Organization (WHO), for which over 1 billion people worldwide received chemotherapy between 2015 and 2019.[1] These communicable diseases are often found in tropical and subtropical regions of the world. The most vulnerable populations are those living in poverty, often with inadequate means of sanitation in densely populated regions proximal to disease vectors.[2] These diseases are designated as NTDs due to the lack of dedicated funding by the for-profit sector for the discovery and development of new drugs, further diluting the limited financial resources available.

Leishmaniasis is caused by a variety of *Leishmania* species and subspecies and is the third most common[3] parasitic disease worldwide. The disease commonly presents in three forms, visceral (VL), which is the most serious and often fatal if left untreated, cutaneous which is the most common and causes disfiguring skin lesions, and mucocutaneous, which destroys mucous membranes. Existing treatments for VL have variable efficacy and significant toxicity, and there are limited oral medications that exist (miltefosine),[4] which necessitates the development of novel, affordable, and orally available drugs.

Although large compound libraries have been screened against *Leishmania* spp., the discovery of quality leads remains challenging. As a consequence, the modest hit selection criteria of pEC_{50} > 5.3 against intracellular *L. donovani* has been described.[5] The Drugs for Neglected Diseases *initiative* (DND*i*) developed a program that utilizes extensive proprietary chemical libraries of partner pharmaceutical companies in an iterative, noncompetitive environment. A hit identified in this effort, referred to as the "Booster Program", was typified by the imidazo[1,2-*a*]pyridine (**DNDI0003363576**),[6] which was progressed to a pharmacokinetic (PK) study to assess the translation based on a series of in vitro absorption, distribution, metabolism, and elimination (ADME) parameters and in vivo bioavailability. Insufficient exposure of the compound was observed to warrant advancement into an in vivo proof-of-concept infection study. We report the continued optimization of this hit, with a focus on improving oral bioavailability. To inform the optimization campaign and to ensure the future success of a pre-clinical candidate, more stringent target candidate properties (TCP) were identified (Table 1). The full suite of ADME was not obtained for **DNDI0003363576**; however, the series suffered from poor solubility, selectivity, and low metabolic stability. Furthermore, improvements that

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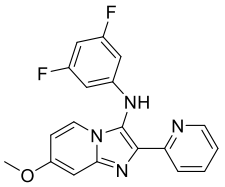
Table 1. TCP Summary of Desired Potency, Toxicity, ADME, and Physicochemical Properties



		Desired criteria	DNDI0003363576
Potency	pEC_{50} *Leish* spp	>5.3	5.7
	Leish LLE[a]	≥4	2.1
Toxicity	PMM[b] pCC_{50}	>10	4.2
ADME and physicochemical properties	*M*W	≤360	350
	*c*Log*P*	≤3	3.6
	$LogD_{7.4}$	≤2	3.6
	MLM[c] Cl_{int}	≤60	62
	revised ADME assessment criteria		
	RH[d] Cl_{int}	≤27	
	HLM[e] Cl_{int}	≤47	
	Aq. Sol.[f]	>10	
	PK exposure	free plasma concentration > EC_{90}	

[a]Ligand lipophilicity efficiency $pEC_{50} - LogD_{7.4}$. [b]Primary mouse macrophage. [c]Mouse liver microsomes μL/min/mg protein. [d]Rat hepatocyte μL/min/10^6 cells; 5.1 ≤ moderate ≤27. [e]Human liver microsomes μL/min/mg protein; 8.6 ≤ moderate ≤47. [f]Thermodynamic aqueous solubility μM.

positively modified the structure−property relationships (SPR) detrimentally affected the structure−activity relationships (SAR).

CHEMISTRY

Synthesis of the hetericyclic core was achieved via a three-step synthesis represented in Scheme 1. Amines **1a−e** were converted to the corresponding isocyanides **2a−e** using the Hoffmann isocyanide synthesis,[7] followed by the Groebke−Blackburn−Bienaymé three component reaction,[8] which provided rapid access to the desired imidazo[1,2-*a*]-heterocycles **3a−ai**.[8] *N*-alkyl derivatives **4a−n** were synthesized using the corresponding alkyl halide.

There were some examples where the isocyanide synthesis was not achievable due to instability of the reactants (Scheme 2). The synthesis could be achieved starting from differently substituted pyridine amines which were converted to the corresponding derivatives **6a**,**b**. The removal of the *tert*-butyl group with HBr provided amines **7a**,**b**, followed by Buchwald−Hartwig coupling to achieve the desired imidazo[1,2-*a*]-heterocycle **8**.[9] Alternatively, bromination of ketone **9** provided **10** as a HBr salt which was cyclized with the corresponding 2-aminoaryl to provide **11a-b**. Treatment of **11b** with NCS provided **12**; the Vilsmeier−Haack reaction provided aldehyde **13**, and subsequent reductive amination in the presence of $NaCNBH_3$ provided **14**.

An alternative scaffold could be synthesized with condensation of dihydropyrrolamine and α-bromoketone **10** providing intermediate **15a**. Subsequent bromination with NBS afforded **15b**. A final Suzuki coupling provides the desired substituted 6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazoles **16a−ad** (Scheme 3).

RESULTS AND DISCUSSION

To better understand the SPR and the pharmacophore required for potent activity, we synthesized a series of truncated analogues (Table 2, **7b**, **11a−b**, **12**). The introduction of a 7-methoxy group (**11a** vs **11b**) resulted in a modest boost in parasite selectivity versus primary mouse macrophages (PMM), although this was at the expense of microsomal stability, potentially due to *o*-demethylation. Introduction of the amine in the 3-position (**7b** vs **11b**) was tolerated with a significant increase in the lipophilic ligand efficiency (LLE) and provided a handle for future modifications. However, the aqueous solubility of these analogues was reduced, suggesting that hydrogen bonding with the adjacent pyridyl may increase the planarity of the series. Compounds without 3-arylamine had rapid human microsomal and low rat hepatocyte intrinsic clearance, necessitating the re-introduction of the arylamine functionality.[10]

We first synthesized the unadorned imidazopyridine **3a** to act as a reference point to the exploration of the core. This compound had a reasonable selectivity index [SI, expressed as the ratio CC_{50} μM (cell line)/EC_{50} μM(*L.inf*), rounded to the nearest integer] (16-fold), although aqueous solubility was poor and metabolism was high. We hypothesized that there was a correlation between selectivity and the electronics and, to understand this, a fluorine and methoxy scan was conducted (Table 3, **3b**, **3c**, **3e**, **3f**, **3h**, **3i**, **3k**, **3l**). Fluorine afforded minimal preference to substitution, with no position affording SI greater than ten-fold. Conversely, a strong correlation with SI was observed for the methoxy substitutions, with the best SI observed for the 6-methoxy (**3f**) derivative and no selectivity for the 5- or 7-methoxy substitutions (**3c** and **3i**). Given this, we sought to further explore the substituent at the 6-position (**3n−q**) of the imidazopyridine and explore alternate scaffolds that incorporated additional heteroatoms to modulate the ADME and physicochemical properties. The introduction of an additional nitrogen into any position (**3d**, **3g**, **3j**, **3m**) or thiazole (**3r**) failed to improve the SI with only small gains in aqueous solubility.

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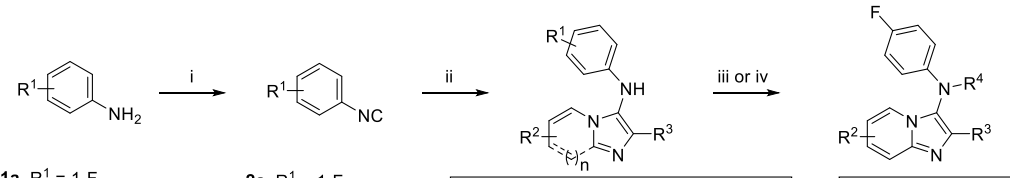
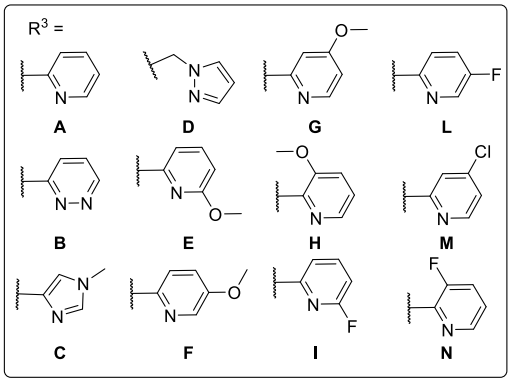
Scheme 1. Synthesis of Diarylimidazole Derivatives 3a−ai and 4a−n[a]



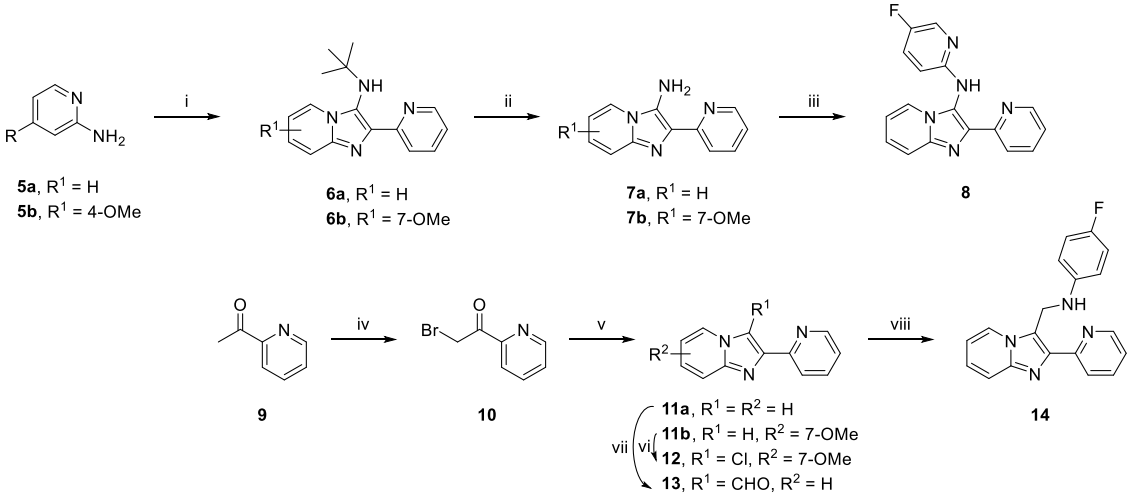
	R^1	R^2	n	R^3
3a	4-F	H	1	A
3b	4-F	5-F	1	A
3c	4-F	5-OMe	1	A
3d	4-F	5-[N]	1	A
3e	4-F	6-F	1	A
3f	4-F	6-OMe	1	A
3g	4-F	6-[N]	1	A
3h	4-F	7-F	1	A
3i	4-F	7-OMe	1	A
3j	4-F	7-[N]	1	A
3k	4-F	8-F	1	A
3l	4-F	8-OMe	1	A
3m	4-F	8-[N]	1	A
3n	4-F	6-SMe	1	A
3o	4-F	6-SO_2Me	1	A
3p	4-F	6-cyclopropyl	1	A
3q	4-F	6-(4-isoxazole)	1	A
3r	4-F	[S]	0	A
3s	3,5-diF	H	1	A
3t	2,4-diF	H	1	A
3u	3-CF_3	H	1	A
3v	2,3-dioxole	H	1	A
3w	4-F	H	1	B
3x	4-F	H	1	C
3y	4-F	H	1	D
3z	4-F	H	1	E
3aa	4-F	H	1	F
3ab	4-F	H	1	G
3ac	4-F	H	1	H
3ad	4-F	H	1	I
3ae	4-F	H	1	L
3af	4-F	H	1	M
3ag	4-F	H	1	N
3ah	4-F	6-OMe	1	G
3ai	4-F	6-OMe	1	F

	R^2	R^3	R^4
4a	H	A	CH_3
4b	H	A	CD_3
4c	H	A	Ethyl
4d	H	A	Propyl
4e	H	A	Methylcyclopropane
4f	H	A	Isobutyl
4g	H	A	Isopentyl
4h	H	A	Propyl-OTBS
4i	H	A	Ethyl-OTBS
4j	H	A	Acetyl
4k	H	G	CH_3
4l	H	F	CH_3
4m	6-OCH_3	F	CH_3
4n	6-OCH_3	A	CH_3



[a]*Reagents and reaction conditions:* (i) NaOH (50% v/v), TEAC, CH_3Cl, CH_2Cl_2, 40 °C, 3−8 h; (ii) appropriate pyridin-2-amine or 2-aminothiazole, aldehyde, $Yb(OTf)_3$, 120 °C, microwave, 40 min; (iii) alkyl halide, Cs_2CO_3, DMF, 55 °C, 24 h; (iv) alkyl halide, pyridine, CH_2Cl_2, room temperature, 17 h.

Scheme 2. Synthesis of Imidazo[1,2-*a*] Heterocycles 8, 11a,b, 12, and 14[a]



[a]*Reagents and reaction conditions:* (i) pyridine-2-carboxaldehyde, *tert*-butyl isocyanide, $Yb(OTf)_3$, 120 °C, microwave, 40 min; (ii) HBr, H_2O, 110 °C, 4 h; (iii) 2-bromo-5-fluoropyridine, NaOtBu, XPhos Pd G2, *t*-BuOH, 75 °C, 2 h; (iv) HBr, Br_2, room temperature, overnight; (v) 2-aminoaryl, Na_2CO_3, DMF, 85 °C, 18 h; (vi) NCS, ACN, room temperature, 1 h; (vii) $POCl_3$, 1,2-DCA, DMF, 70 °C, 2 h; (viii) $NaCNBH_3$, MeOH, AcOH, room temperature, 1 h.

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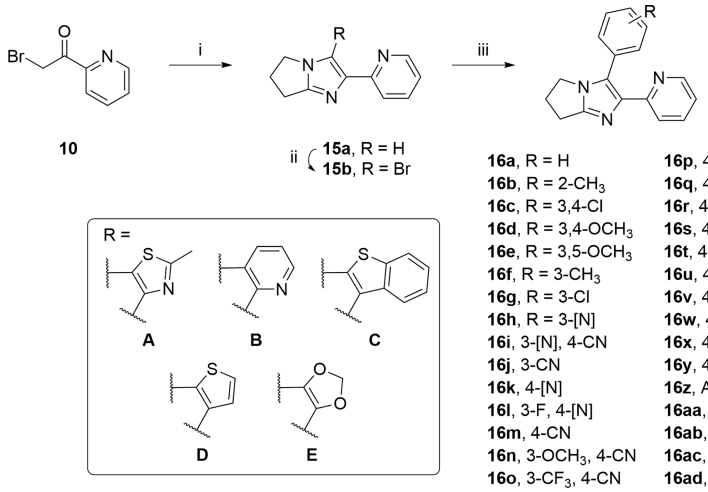
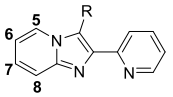
Scheme 3. Synthesis of Substituted 6,7-Dihydro-5*H*-pyrrolo[1,2-*a*]imidazoles 16a–ad[a]



[a]*Reagents and reaction conditions:* (i) dihydropyrrolamine, Na_2CO_3, DMF, 50 °C, overnight; (ii) NBS, CH_2Cl_2, room temperature, 1 h; (iii) appropriate aryl boronic acid or pinacol boronic ester, $Pd(PPh_3)_4$, toluene/MeOH (3:1 v/v, 0.2 M), Na_2CO_3 (aq. 2 M), 120 °C 18 h or microwave, 40 min.

Table 2. Biological Activity and Physicochemical Properties of Truncated Analogues[a]



ID	R	7	*L.inf* pEC_{50}	PMM pCC_{50}	SI	aq. sol.[b]	HLM clint[c]	RH clint[d]	LLE[e]
7b	NH_2	OMe	4.5	4.2	2	290	120	7.1	4.1
11a	H	H	4.3	4.2	1	828	130	140	2.6
11b	H	OMe	4.6	4.2	3	723	>300	53	2.4
12	Cl	OMe	4.8	4.5	2	562	>300	17	2.2

[a]*nt*, not tested. [b]Thermodynamic aqueous solubility μM. [c]μL/min/mg protein. [d]μL/min/10^6 cells. [e]LLE = pEC_{50} − $LogD_{7.4}$.

Attention was directed toward optimizing the 3-position substituent (Table 4). This region was previously explored and identified as having the potential to positively affect leishmanicidal activity.[6] Small lipophilic alkyl groups demonstrated moderate antiparasitic activities as well as *N*-phenyl derivatives adorned with polar heteroatoms and halogens. When compared to **3a**, difluoro and trifluoromethyl compounds (**3s**, **3t**, and **3u**) had reduced selectivity and only **3s** demonstrated improved solubility. Compounds **3v** and **8** had improved metabolic stability, although it was still classified as moderate in human liver microsomes for both compounds and high and moderate, respectively, in rat hepatocytes; however, this came at the expense of antiparasitic activity. The presence of a short methylene linker between the imidazopyridine core and aniline portion was found to be detrimental to antiparasitic potency (**14**).

Due to the lipophilic nature of the binding sites of metabolizing enzymes, reduction in lipophilicity has been demonstrated to be an effective method to improve metabolic stability.[11−13] Hence, we next explored modifications to the 2-pyridyl moiety utilizing an unadorned core to allow an improved understanding of the SPR (Table 5). We replaced the pyridyl with more polar nitrogen-containing heterocycles, and while **3y** exhibited the highest LLE to date, the pyrazole detrimental to selectivity. Improved solubility and metabolic stability were obtained with several other compounds, although this was at the expense of selectivity. X-ray crystallography of **3a** and **3ac** indicated that the improved aqueous solubility of the *ortho*-methoxy-substituted compound likely resulted from increased dihedral rotation to reduce steric interaction, reducing the planarity of the compound (Table S1).

The final area of exploration was alkylation of the exocyclic amine (Table 6). Improvement to the solubility was observed for the *N*-methyl derivative (**4a**) when compared to the *N*-H derivative (**3a**), presumably via interruption of the planarity reinforced by hydrogen bonding. However, this was accompanied by a reduction in selectivity. This selectivity could be restored by replacing the methyl with the deuterium-labeled isostere (**4b**) with no loss of potency. Incorporation of deuterium isosteres has been shown to positively modulate pharmacokinetics due to the stronger deuterium-carbon bond;[14] however, **4b** failed to improve metabolic stability. Increasing the alkyl-chain length resulted in a lipophilicity-driven reduction in aqueous solubility and selectivity (**4a** vs **4c** vs **4d**). In general, the improved antiparasitic activity of the *N*-alkyl compounds was coupled with erosion of metabolic stability.

The synthesis of compounds that encompassed the optimal modifications from each of the explored regions was done with the goal of achieving additive improvements to SAR and SPR (Table 7). Re-introduction of the 6-methoxy group into the core with methoxy-substituted pyridyl **3ah** and **3ai** improved the SI relative to their unadorned analogues (Table 4, **3aa** and **3ab**). The introduction of the ionizable *N*-methyl-linked substituted pyridyl (**4m**) improved aqueous solubility with comparable SI to **3ah**. *N*-methylated derivatives **4k** and **4l** did provide some SI improvement, although metabolism was still high.

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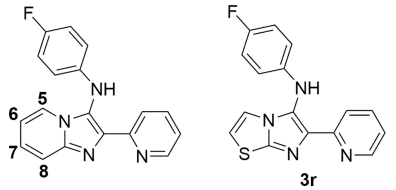
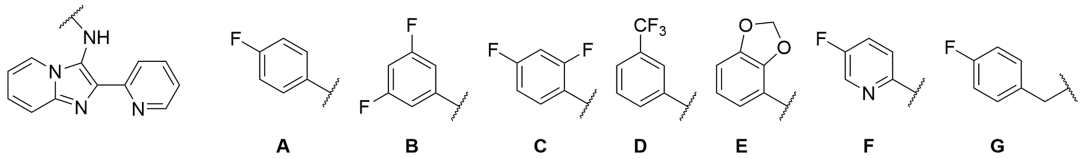
Table 3. Biological Activity and Physicochemical Properties of the Imidazo[1,2-*a*]-Pyridine



ID	5	6	7	8	*L.inf* pEC_{50}	PMM pCC_{50}	SI	aq. sol.[a]	HLM clint[b]	RH clint[c]	LLE[d]
3a	H	H	H	H	5.4	4.2	16	8	137	>300	2
3b	F	H	H	H	5.1	4.2	8	26	60	190	1.6
3c	OMe	H	H	H	5.1	5.1	1	62	28	30	0.6
3d	[N]	H	H	H	4.8	4.5	2	68	212	>300	3.2
3e	H	F	H	H	5.1	4.3	6	25	>300	>300	
3f	H	OMe	H	H	5.7	4.5	16				
3g	H	[N]	H	H	4.3	4.2	1	64			
3h	H	H	F	H	4.6	4.2	3	0.1	>300	146	
3i	H	H	OMe	H	5.1	5.1	1				
3j	H	H	[N]	H	4.2	4.2	1	61	202	64.2	2.7
3k	H	H	H	F	4.4	4.2	2	12	220	101	1.4
3l	H	H	H	OMe	5.1	4.2	8	2	143	29	1.7
3m	H	H	H	[N]	4.3	4.2	1	180	42.4	64.8	1.7
3n	H	SMe	H	H	5.1	5.1	1	0.5	247	>300	1.8
3o	H	SO_2Me	H	H	4.5	4.5	1	5	92	>300	2.1
3p	H	cyclopropyl	H	H	5.2	5.1	1	0.7	91.6	148	1.1
3q	H	4-isoxazole	H	H	4.6	4.2	3	3	75	128	0.7
3r					5.1	4.5	4	76	270	>300	0.9

[a]Thermodynamic aqueous solubility μM. [b]μL/min/mg protein. [c]μL/min/10^6 cells. [d]LLE = pEC_{50} − $LogD_{7.4}$.

Table 4. Biological Activity and Physicochemical Properties of the 3-Position Substituent[a]



ID	R	*L.inf* pEC_{50}	PMM pCC_{50}	SI	aq. sol.[b]	HLM clint[c]	RH clint[d]	LLE[e]
3a	A	5.4	4.2	16	8	140	>300	2
3s	B	5.3	4.5	6	32	64	131	1.9
3t	C	5.1	4.5	4	0.8	96	194	3.9
3u	D	5.2	4.8	3	2	59	>300	1.9
3v	E	4.8	4.5	2	8	25	88	2.9
8	F	4.2	4.2	1	220	44	18	1.6
14	G	4.9	4.3	4	*nd*	*nd*	*nd*	*NA*

[a]*NA*, not applicable; *nd*, not determined. [b]Thermodynamic aqueous solubility μM. [c]μL/min/mg protein. [d]μL/min/10^6 cells. [e]LLE = pEC_{50} − $LogD_{7.4}$.

Acknowledging that the presence of basic nitrogens and high lipophilicity can correlate to potential liabilities,[15,16] we sought to get a better understanding of the limitations of this series. Representative compounds of the series were selected for further in vitro biological screening. We investigated blockage of the potassium ion channel coded by the human ether-a-go-go related gene (hERG) which has been associated with long QT syndrome and has led to the withdrawal of several marketed drugs, such as sertindole.[17] The series exhibits micromolar activity against hERG (Table 8); however, the SAR shows that strategies to mitigate this activity, such as reduction of lipophilicity and modulation of basic nitrogen pK_a via steric and electronic alteration, are tolerated, suggesting that this liability may be mitigated. Inhibition of cytochrome P450 (CYP450) enzymes blocks the metabolic activity of the enzyme which can result in clinically significant drug−drug interactions that can cause adverse reactions or therapeutic failures. The most clinically significant CYP450 isoforms are CYP3A4 and CYP2D6 as they account for 23.6 and 13.8% of known CYP450-drug interactions, respectively.[18] Only moderate inhibition of these CYPs was observed for **3p** (Table 8), with strong inhibition for **3ak** (Table S6), indicating that structural modifications of the series can impact this liability.

We assessed the bioavailability of the series by progressing **4n** (Table 7) into PK studies, as it had the best balance of potency (*L. infantum* pEC_{50}: 6.1), SI (10-fold), and LLE (3.2) for the series, with moderate aqueous solubility (17 μM) (Figure 1). However, this compound did not possess the desired metabolic stability outlined in the TCP (Table 1) and it was hypothesized that co-dosing with the pan-CYP450 inhibitor, 1-amino-

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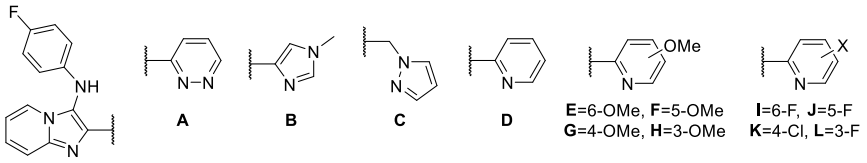
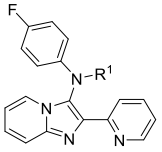
Table 5. Biological Activity and Physicochemical Properties of the 2-Position Substituent[a]

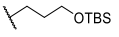
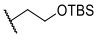


ID	R	*L.inf* pEC_{50}	PMM pCC_{50}	SI	aq. sol.[b]	HLM clint[c]	RH clint[d]	log$D_{7.4}$	LLE[e]
3a	D	5.4	4.2	16	8	140	>300	3.4	2
3w	A	4.5	4.2	2	190	64	290	1.6	2.9
3x	B	5.1	4.8	2	4	17	14	*nd*	*NA*
3y	C	4.2	4.2	1	410	45	51	−0.1	4.3
3z	E	4.2	4.2	1	4	137	>300	4.5	−0.3
3aa	F	5.3	4.7	4	3	35	88	3.8	1.5
3ab	G	5.3	4.8	3	0.2	120	190	4.0	1.3
3ac	H	4.5	4.2	2	690	19	29	1.7	2.8
3ad	I	4.8	4.2	4	13	130	>300	4.5	0.3
3ae	J	4.9	4.2	5	2	89	>300	3.9	1
3af	K	5.0	4.8	2	2	160	>300	*nd*	*NA*
3ag	L	4.7	4.2	3	49	86	100	3.5	1.2

[a]*NA*, not applicable; *nd*, not determined. [b]Thermodynamic aqueous solubility μM. [c]μL/min/mg protein. [d]μL/min/10^6 cells. [e]LLE = pEC_{50} − Log$D_{7.4}$.

Table 6. Biological Activity and Physicochemical Properties of *N*-Alkyl Substituents



ID	R^1	*L.inf* pEC_{50}	PMM pCC_{50}	SI	Aq. Sol.[a]	HLM Clint[b]	RH Clint[c]	Log$D_{7.4}$	LLE
3a	H	5.4	4.2	16	8	140	>300	3.4	2
4a	methyl	6.0	5.4	4	120	110	>300	3.7	2.3
4b	CD_3	5.9	4.5	25	120	140	>300	2.6	3.3
4c	ethyl	6.0	5.1	8	31	180	150	2.8	3.2
4d	propyl	5.8	5.7	1	3	62	110	3.6	2.2
4e	methylcyclopropane	5.8	5.4	3	2	110	140	4	1.8
4f	isobutyl	6.1	4.6	32	8	59	230	4.6	1.5
4g	isopentyl	6.1	5.7	3	14	110	> 300	3.9	2.2
4h		6.1	5.4	5	0.2	>300	42	5.6	0.5
4i		5.7	4.8	8	0.3	> 300	53	>4.7	<1
4j	acetyl	4.2	4.2	1	10	20	81	2.5	1.7

[a]Thermodynamic aqueous solubility μM. [b]μL/min/mg protein. [c]μL/min/10^6 cells. [d]LLE = pEC_{50} − Log$D_{7.4}$.

benzotriazole (ABT), would increase exposure. Two studies were run in parallel: the first was **4n** only, and the second included a 50 mg/kg dose of ABT 2 h prior to dosing with **4n**. In both studies, **4n** was dosed at 50 mg/kg P.O. in fasted male CD1 mice. When accounting for the low (2%) free plasma concentration, the criterion for progression into the in vivo proof-of-concept efficacy study was not met (criteria: free plasma concentration > EC_{90}) in either study.

At this point, we connected with the Open Science Antibiotics (OSA) consortium who were working on a related chemotype that came from the Published Kinase Inhibitor Set[19] (**SB-400868**) for *Methicillin-resistant Staphylococcus aureus* (MRSA). Compound **SB-400868** was originally generated in an effort targeting transforming growth factor beta receptor I (TGFBR1/ALK5)[20] and identified at University of North Carolina, Chapel Hill, as a hit against *Mycobacterium tuberculosis*. Preliminary optimization leading to compounds with activity against MRSA was carried out to yield OSA-822 (Figure 2).

The Log*D* was generally improved for this series, and we tested compounds for the in vitro *L. infantum* potency, host cell toxicity, and ADME profile. From this set, we identified several compounds that met or exceeded the aqueous solubility threshold as well as demonstrated improved metabolic stability. Substituent exploration of the northern aromatic region revealed that introduction of a pyridyl nitrogen (Table 9, **16h,i** and **16k,l**) significantly improved the ADME profile, with millimolar solubility and clearance in the medium to low range for both HLM and RH, although this was also accompanied by abrogation of potency. The *para* substituent could also be modified to improve the ADME profile, although this was

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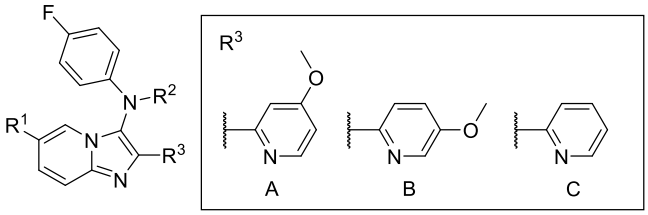
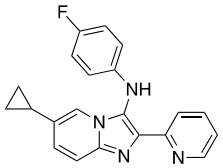
Table 7. Hybrid Analogues That Combine the Most Promising Modifications for *L. infantum* Activity and Physicochemical Property Modulation



ID	R^1	R^2	R^3	*L.inf* pEC_{50}	PMM pCC_{50}	SI	aq. sol.[a]	HLM clint[b]	RH clint[c]	$logD_{7.4}$	LLE[d]
3ah	OMe	H	A	5.9	5.1	6	0.4	240	>300	5.2	0.7
3ai	OMe	H	B	5.6	4.8	6	1	44	76	4.8	0.8
4m	OMe	Me	B	6.1	5.4	5	27	260	>300	3.7	2.4
4k	H	Me	A	6.3	4.5	63	26	210	>300	3.4	2.9
4l	H	Me	B	6.3	5.1	16	10	93	>300	3.7	2.6
4a	H	Me	C	6.0	5.4	4	120	110	>300	3.7	2.3
4n	OMe	Me	C	6.1	5.1	10	17	250	>300	2.9	3.2

[a]Thermodynamic aqueous solubility μM. [b]μL/min/mg protein. [c]μL/min/10^6 cells. [d]LLE = pEC_{50} − $LogD_{7.4}$.

Table 8. Further Biological Profiling of Compound 3p



L. inf pEC_{50}	5.2
PMM pCC_{50}	5.1
hERG pIC_{50}[a]	4.9
MDCK P_{app} A-B[b]	16.7×10^{-6} cm/s
kinetic aq. sol.	3 μM
CYP isoform	inhibition
CYP1A2	0.59 μM, strong inhibitor
CYP2C19	1.8 μM, moderate inhibitor
CYP2C8	4.9 μM, moderate inhibitor
CYP2C9	0.76 μM, strong inhibitor
CYP2D6	1.5 μM, moderate inhibitor
CYP3A4	1.6 μM, moderate inhibitor

[a]Human ether-a-go-go. [b]Madin-Darby canine kidney Apparent permeability.

similarly accompanied by loss of potency (cf. **16u−16w**). The best compounds from this series, when considering potency, selectivity, and ADME, were **16f, 16g,** and **16t**. Nevertheless, the narrow therapeutic window of **16f** and **16t,** and the high clearance of **16g** advocated against advancing these compounds further.

While we were unable to achieve our original goal of increasing in vivo exposure for the imidazopyridines, we did identify a modification that led to a boost in potency (*N*-alkylation), and we were able to modulate the aqueous solubility by lowering $LogD_{7.4}$. We serendipitously uncovered a novel scaffold for *Leishmania*, the 6,7-dihydro-5*H*-pyrrolo[1,2-*a*]-imidazoles, with superior $LogD_{7.4}$ and improved aqueous solubility and metabolic stability. While **16g** is currently untested in an in vivo PK study to determine its exposure, this latter series serves as a potential starting point for continued optimization as a therapeutic for leishmaniasis, given the dearth of leads for this NTD.

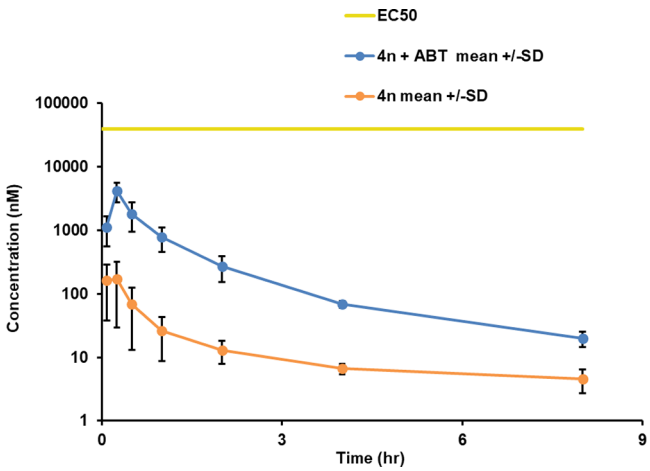


Figure 1. Mean plasma levels of **4n** in fasted male CD1 mice, with and without ABT. **4n** was dosed at 50 mg/kg P.O. (formulation: 5% DMSO, 45% PEG400, 50% MilliQ water; pH 4.0−5.0), and ABT was dosed 2 h before compound (P.O., in saline).

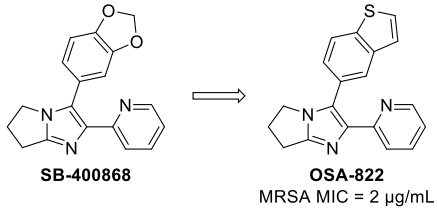


Figure 2. Origin of the OSA series from **SB-400868**.

METHODS

General Procedures for Biological Evaluation. Test compounds were formulated in 100% dimethyl sulfoxide (DMSO) at 20 mM and were 4-fold serially diluted to obtain 10 concentrations. Following an intermediate dilution in MilliQ water, the highest in-test concentration of 64 μM was obtained while assuring a DMSO concentration of <1%. Compounds were evaluated against intramacrophage amastigotes. Briefly, *L. infantum* (MHOM/MA(BE)/67/ITMAP263) amastigotes were derived from the spleens of heavily infected Syrian golden

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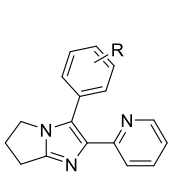
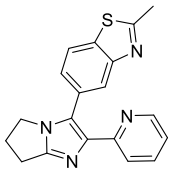
Table 9. Derivatives of SB-400868 and their Activity against *L. infantum* and Associated ADME Data[a]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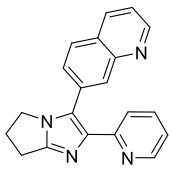
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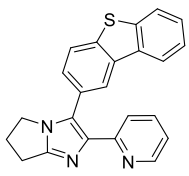
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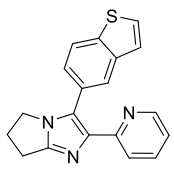
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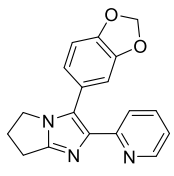
16ad

ID	R	*L.inf* pEC_{50}	PMM pCC_{50}	SI	aq. sol.[b]	HLM clint[c]	RH clint[d]	log$D_{7.4}$	LLE[e]
16a		5.7	5.1	4	180	64	26	2.2	3.5
16b	**2-Me**	6.0	5.7	2	*nt*	*nt*	*nt*	*nt*	*NA*
16c	**3,4-Cl**	6.2	5.1	13	3	100	38	3.4	2.8
16d	**3,4-OMe**	5.7	4.5	16	*nt*	*nt*	*nt*	*nt*	*NA*
16e	**3,5-OMe**	5.9	5.1	6	97	53	>300	2.4	3.5
16f	**3-Me**	6.2	5.1	13	560	76	63	2.8	2.4
16g	**3-Cl**	6.1	4.6	32	51	140	51	3.0	3.1
16h	**3-[N]**	4.2	4.2	1	>1000	24	2.4	1.1	3.1
16i	**3-[N], 4-CN**	4.2	4.2	1	*nt*	*nt*	*nt*	*nt*	*NA*
16j	**3-CN**	5.0	4.2	6	37	44	23	2.0	3.0
16k	**4-[N]**	4.2	4.2	1	>1000	26	4.8	1.2	3.0
16l	**3-F, 4[N]**	4.6	4.5	1	*nt*	*nt*	*nt*	*nt*	*NA*
16m	**4-CN**	4.5	4.2	2	38	99	8.0	1.9	2.6
16n	**3-OMe, 4-CN**	4.6	4.2	3	*nt*	*nt*	*nt*	*nt*	*NA*
16o	**3-CF_3, 4-CN**	4.6	4.2	3	*nt*	*nt*	*nt*	*nt*	*NA*
16p	**4-Cl**	5.8	5.1	5	4	170	22	3.0	2.8
16q	**4-F**	5.5	4.5	10	*nt*	*nt*	*nt*	*nt*	*NA*
16r	**4-Me**	6.3	5.7	4	32	82	49	2.7	3.6
16s	**4-CF_3**	5.7	4.5	16	*nt*	*nt*	*nt*	*nt*	*NA*
16t	**4-OCF_3**	6.2	5.1	13	38	62	54	2.9	3.3
16u	**4-SOMe**	4.7	4.2	3	760	<3	<1	0.9	3.8
16v	**4-SO_2Me**	4.2	4.2	1	320	<3	<1	1.2	3.0
16w	**4-CON$(Me)_2$**	4.4	4.2	2	780	<3	<1	1.1	3.3
16x	**4-COMe**	5.2	4.5	5	*nt*	*nt*	*nt*	*nt*	*NA*
16y	**4-NH_2**	5.6	5.1	3	*nt*	*nt*	*nt*	*nt*	*NA*
16z		5.5	4.3	16	10	34	49	2.6	2.9
16aa		5.4	4.5	8	*nt*	*nt*	*nt*	*nt*	*NA*
16ab		6.5	5.7	6	3	43	150	4.1	2.4
16ac		6.5	5.7	6	3	62	>300	2.9	3.6
16ad		5.9	5.1	6	*nt*	*nt*	*nt*	*nt*	*NA*

[a]*NA*, not applicable; *nt*, not tested. [b]Thermodynamic aqueous solubility μM. [c]μL/min/mg protein. [d]μL/min/10^6 cells. [e]LLE = pEC_{50} − log$D_{7.4}$.

hamsters (*Mesocricetus auratus*) and used to infect primary peritoneal mouse macrophages (PMM) of Swiss mice. PMM (3×10^4) were infected with 4.5×10^5 parasites/well in 190 μL. Compound dilutions (10 μL) were added after 2 h of infection. Cells were maintained at 37 °C and 5% CO_2 atmosphere in RPMI-1640 medium, supplemented with 2 mM L-glutamine, 16.5 mM $NaHCO_3$, and 5% inactivated fetal calf serum. After 5 days of incubation, parasite burdens (mean number of amastigotes/PMM) were determined microscopically after staining with a 10% Giemsa solution. Percentage (%) reduction in growth compared to untreated controls was used to calculate pEC_{50} values. Cytotoxicity toward PMM was scored semi-quantitatively by observation of compound-induced cell detachment, lysis and granulation of at least 500 cells. The percentage reduction in cell viability compared to untreated controls was used to calculate pCC_{50} values.

Pharmacokinetic Study. The study was performed under the protocol approved by the Institutional Animal Ethical Committee (IAEC) at TCGLS as per guidelines of Committee for Purpose of Control and Supervision of Experiments on Animals (CPCSEA). IAEC protocol number: TCGLS/M-PK/21-20.

General Chemistry. Reagents purchased were used as received, unless otherwise noted. Purification of intermediates and final compounds was performed using silica gel or reverse phase chromatography using the Biotage Isolera, or Selekt flash purification systems. LCMS analysis was performed using either of the following:

a. Waters Alliance reverse phase HPLC (columns Waters SunFire C18 4.6 × 50 mm, 3.5 μm, or Waters SunFire C8 4.6 × 50 mm, 3.5 μm) using a multiwavelength photodiode array detector from 210 to 600 nm and either a Waters Micromass ZQ detector (electrospray ionization) or Waters Micromass QDA detector.
b. Waters Alliance reverse phase HPLC (2695; Xbridge C18 4.6 × 50 mm, 3.5 μm), using a multi-wavelength photodiode array detector from 210 to 600 nm and Waters Micromass QDA detector.
c. Agilent 1260 Infinity HPLC (Agilent SB-C18 column (1.8 μm, 2.1 × 50 mm)), using a multiwavelength photodiode array detector monitoring 210, 230, 254, and

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280 nm coupled to an Agilent 6120 single quad MS (ESI source).

All compounds tested had a purity of >95% as measured by LCMS, unless otherwise noted. ^{1}H NMR spectra were obtained with Bruker NMR systems, operating at either 400 or 500 MHz at room temperature. Chemical shifts (δ, ppm) are reported relative to the solvent peak ($CDCl_3$: 7.26 [^{1}H]; DMSO-d_6: 2.50 [^{1}H]; or CD_3OD: 3.31 [^{1}H]). Data for ^{1}H NMR spectra are reported as follows: chemical shift (ppm), multiplicity (s for singlet, d for doublet, t for triplet, dd for doublet of doublet, m for multiplet), coupling constant (Hz), and integration.

General Procedure a for the Synthesis of Isocyanides. To a vigorously stirred solution of a 50% NaOH in water (36 mL), TEAC (0.18 equiv) was added. The reaction mixture was efficiently stirred and heated at 40 °C; then, a solution of the selected amine (1 equiv) and $CHCl_3$ (1.05 equiv) in CH_2Cl_2 (36 mL) was added dropwise over 50 min. The reaction was stirred and heated at 40 °C for 3−8 h. After completion, the reaction mixture was allowed to cool to room temperature and cold water (150 mL) was added. The aqueous phase was extracted with CH_2Cl_2. The organic layers were combined and washed with brine, dried over Na_2SO_4, and evaporated to give an oil which was then purified via a bulb-to-bulb distillation condensing with reaction dewar acetone dry ice (55 °C, 0.2 mbar).

General Procedure B for the Synthesis of Imidazopyridines. Amine (1 equiv), aldehyde (1.2 equiv), appropriate fluorophenyl isocyanide (1.2 equiv), and ytterbium(III) trifluoromethanesulfonate (0.01 equiv) were combined in a microwave vial and irradiated at 120 °C for 40 min. The reaction was cooled to room temperature, dissolved in a minimal amount of DMSO, and purified via a 30 g Biotage SH-C18 reverse phase column. The purified fractions were partially concentrated until a precipitate formed which was collected on a Hirsch funnel. The precipitate was then dried overnight with a high vacuum pump to provide the titled compound.

General Procedure C for N-Alkylation. To a solution of the corresponding imidazopyridine (1 equiv) in DMF (1−2 mL), cesium carbonate (2 equiv) and appropriate alkyl halide (1.2−1.5 equiv) were added. The resultant mixture was stirred at 55 °C for 24 h. After cooling to room temperature, the reaction mixture was partitioned between EtOAc and water. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue that was dissolved in a minimal amount of DMSO and purified via a 30 g Biotage SH-C18 reverse chromatography. The purified fractions were partially concentrated until a precipitate formed which was collected on a Hirsch funnel. The precipitate was then dried overnight with a high vacuum pump to provide the title compound.

General Procedure D for the Synthesis of 3-Aryl-2-(pyridyl)imidazoles. A reaction vial was charged with the corresponding 3-bromo-2-(pyridyl)imidazole (1 equiv), the appropriate aryl boronic acid or pinacol boronic ester (1.3 equiv), and $Pd(PPh_3)_4$ (0.12 equiv). The vial was sealed with a Teflon septum, evacuated, and backfilled with nitrogen (this sequence was carried out three times). Under an inert atmosphere, a mixture of toluene and methanol (3:1, v/v, 0.2 M) was added via a syringe, followed by the addition of 2 M aqueous Na_2CO_3 (4 equiv). The mixture was heated at 120 °C for 18 h or in the microwave at 120 °C for 30 min. After cooling to room temperature, the mixture was either diluted with CH_2Cl_2 and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure; or alternatively, the reaction mixture was diluted with MeOH, filtered through celite, and concentrated. The crude residue was purified by flash chromatography on silica and the product triturated to afford a fine powder.

General Procedure E for the Synthesis of 2-(Pyridyl)-imidazoles. 2-Bromo-1-(pyridyl)ethan-1-one hydrobromide (1 equiv), heterocycloalkenyl, or heteroaryl amine (1 equiv), and Na_2CO_3 (2 equiv) were stirred in EtOH (15−20 mL) at 85 °C for 1 h. After cooling to room temperature, the solvent was evaporated under reduced pressure and the crude reaction mixture was diluted with water and neutralized using 2 N HCl, then extracted twice with CH_2Cl_2. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue that was purified by flash chromatography on silica.

*5-(Isoxazol-4-yl)pyridin-2-amine (**1f**).* A reaction vial was charged with 5-bromopyridin-2-amine (100 mg, 0.58 mmol), 4-isoxazoleboronic acid pinacol ester (135 mg, 0.69 mmol), potassium fluoride (101 mg, 1.73 mmol), and $PdCl_2$dppf complex (47 mg, 0.58 mmol). The vial was sealed with a Teflon septum, evacuated, and backfilled with N_2 three times. Under an inert atmosphere, a mixture of DMF and H_2O (2:1, v/v) was added via a syringe and stirred at 50 °C for 4 h. After cooling to room temperature, the reaction mixture was filtered through celite, washed with MeOH, and concentrated under reduced pressure to give a residue that was purified by column chromatography (20/80 EtOAc:Hex) to afford a light brown solid (46 mg, 49%).

*1-Fluoro-4-isocyanobenzene (**2a**).* Compound **2a** was synthesized using 4-fluoroaniline (2.1 g, 18.90 mmol) according to General Procedure A. The crude product was purified by distillation to yield the title compound as a faint green oil (yield: 60%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.68 (dd, J = 4.9, 8.8 Hz, 2H), 7.37 (t, J = 8.8 Hz, 2H).

*1,3-Difluoro-5-isocyanobenzene (**2b**).* Compound **2b** was synthesized using 1,3-difluoroaniline (1.4 g, 10.84 mmol) according to General Procedure A. The crude product was used as is without further purification.

*2,4-Difluoro-1-isocyanobenzene (**2c**).* Compound **2c** was synthesized using 3,5-difluoroaniline (100 mg, 0.79 mmol) according to General Procedure A. The crude product was used as is without further purification.

*1-Isocyano-3-(trifluoromethyl)benzene (**2d**).* Compound **2d** was synthesized using 3-trifluoromethylaniline (150 mg, 0.12 mmol) according to General Procedure A. The crude product was used as is without further purification.

*4-Isocyanobenzo[d][1,3]dioxole (**2e**).* Compound **2e** was synthesized using benzo[d][1,3]dioxol-4-amine (100 mg, 0.73 mmol) according to General Procedure A. The crude product was used as is without further purification.

*N-(4-Fluorophenyl)-2-(pyridin-2-yl)imidazo[1,2-a]pyridin-3-amine (**3a**).* Compound **3a** was synthesized using 2-aminopyridine (400 mg, 4.25 mmol), picolinaldehyde (546 mg, 5.10 mmol), and **2a** (882 mg, 5.10 mmol) according to General Procedure B. The crude product was purified by reverse phase chromatography (35−100% MeOH:H_2O) to yield the title compound as a beige solid (996 mg, 77%). LCMS $[M + H]^+$ 305.3 m/z.[a] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (d, J = 4.5 Hz, 1H), 8.34 (s, 1H), 8.22 (d, J = 8.4 Hz, 1H), 7.79 (t, J = 7.9 Hz, 1H), 7.66 (d, J = 9.3 Hz, 1H), 7.60 (d, J = 6.8 Hz, 1H), 7.13−7.23 (m, 2H), 6.95 (t, J = 8.4 Hz, 2H), 6.78 (t, J = 6.8 Hz, 1H), 6.64 (dd, J = 4.5, 7.9 Hz, 2H).

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*5-Fluoro-N-(4-fluorophenyl)-2-(pyridin-2-yl)imidazo[1,2-a]pyridin-3-amine (**3b**).* Compound **3b** was synthesized using 6-fluoropyridin-2-amine (60 mg, 0.54 mmol), picolinaldehyde (69 mg, 0.64 mmol), and **2a** (78 mg, 0.64 mmol) according to General Procedure B. The crude product was purified by reverse phase chromatography (35−100% MeOH:H_2O) to yield the title compound as a beige solid (116 mg, 67%). LCMS $[M + H]^+$ 323.0 *m/z*.[b] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (d, J = 4.4 Hz, 1H), 8.14−8.27 (m, 2H), 7.74−7.84 (m, 1H), 7.43 (d, J = 9.3 Hz, 1H), 7.10−7.23 (m, 2H), 6.93 (t, J = 8.6 Hz, 2H), 6.69 (dd, J = 4.4, 8.6 Hz, 2H), 6.34 (t, J = 6.8 Hz, 1H).

*N-(4-Fluorophenyl)-5-methoxy-2-(pyridin-2-yl)imidazo-[1,2-a]pyridin-3-amine (**3c**).* Compound **3c** was synthesized using 6-methoxypyridin-2-amine (150 mg, 0.54 mmol), picolinaldehyde (155 mg, 1.45 mmol), and **2a** (176 mg, 1.45 mmol) according to General Procedure B. The crude product was purified by reverse phase chromatography (35−100% MeOH:H_2O) to yield the title compound as a beige solid (309 mg, 76%). LCMS $[M + H]^+$ 335.0 *m/z*.[b] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (d, J = 4.9 Hz, 1H), 8.35 (br. s., 1H), 8.22 (d, J = 7.3 Hz, 1H), 7.76 (t, J = 7.8 Hz, 1H), 7.27−7.31 (m, 1H), 7.10−7.20 (m, 2H), 6.90 (t, J = 8.5 Hz, 2H), 6.62−6.72 (m, 2H), 5.95 (d, J = 7.3 Hz, 1H), 3.63 (s, 3H).

*N-(4-Fluorophenyl)-2-(pyridin-2-yl)imidazo[1,2-b]-pyridazin-3-amine (**3d**).* Compound **3d** was synthesized using 3-aminopyridazine (100 mg, 1.05 mmol), picolinaldehyde (135 mg, 1.26 mmol), and **2a** (153 mg, 1.26 mmol) according to General Procedure B. The crude product was purified by reverse phase chromatography (35−100% MeOH:H_2O) to yield the title compound as a brown solid (158 mg, 50%). LCMS $[M + H]^+$ 306.0 *m/z*.[b] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.61 (d, J = 4.7 Hz, 1H), 8.31 (d, J = 4.7 Hz, 1H), 8.24 (d, J = 8.2 Hz, 1H), 7.95 (d, J = 9.4 Hz, 1H), 7.81 (t, J = 8.2 Hz, 1H), 7.17−7.25 (m, 1H), 6.90−7.04 (m, 3H), 6.75 (dd, J = 4.7, 8.2 Hz, 2H).

*6-Fluoro-N-(4-fluorophenyl)-2-(pyridin-2-yl)imidazo[1,2-a]pyridin-3-amine (**3e**).* Compound **3e** was synthesized using 5-fluoropyridin-2-amine (50 mg, 0.45 mmol), picolinaldehyde (96 mg, 0.89 mmol), and **2a** (108 mg, 0.89 mmol) according to General Procedure B. The crude product was purified by reverse phase chromatography (40−80% MeOH:H_2O) to yield the title compound as a white solid (60 mg, 42%). LCMS $[M + H]^+$ 323.1 *m/z*.[a] ^{1}H NMR (500 MHz, CD_3OD) δ 8.62−8.56 (m, 1H), 8.01 (dt, J = 8.0, 1.2 Hz, 1H), 7.88−7.85 (m, 1H), 7.83 (td, J = 7.6, 1.8 Hz, 1H), 7.66 (dd, J = 9.9, 4.8 Hz, 1H), 7.35 (ddd, J = 10.1, 8.2, 2.4 Hz, 1H), 7.28 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 6.96−6.87 (m, 2H), 6.60−6.52 (m, 2H).

*N-(4-Fluorophenyl)-6-methoxy-2-(pyridin-2-yl)imidazo-[1,2-a]pyridin-3-amine (**3f**).* Compound has been synthesized as previously reported in the literature.[6]

*N-(4-Fluorophenyl)-2-(pyridin-2-yl)imidazo[1,2-c]-pyrimidin-3-amine (**3g**).* Compound **3g** was synthesized using 4-aminopyrimidine (200 mg, 2.10 mmol), picolinaldehyde (270 mg, 2.52 mmol), and **2a** (270 mg, 2.52 mmol) according to General Procedure B. The crude product was purified by reverse phase chromatography (35−100% MeOH:H_2O) to yield the title compound as an orange solid (95 mg, 18%). LCMS $[M + H]^+$ 306.2 *m/z*.[a] ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.76 (s, 1H), 9.55 (d, J = 1.0 Hz, 1H), 8.72 (d, J = 4.4 Hz, 1H), 8.00 (d, J = 5.9 Hz, 1H), 7.79−7.88 (m, 1H), 7.61−7.69 (m, 2H), 7.42−7.49 (m, 1H), 7.12−7.19 (m, 1H), 7.01−7.09 (m, 2H).

*7-Fluoro-N-(4-fluorophenyl)-2-(pyridin-2-yl)imidazo[1,2-a]pyridin-3-amine (**3h**).* Compound **3h** was synthesized using 4-fluoropyridin-2-amine (150 mg, 1.34 mmol), picolinaldehyde (172 mg, 1.61 mmol), and **2a** (194 mg, 1.61 mmol) according to General Procedure B. The crude product was purified by reverse phase chromatography (40−70% MeOH:H_2O) to yield the title compound as a beige solid (105 mg, 24%). LCMS $[M + H]^+$ 323.1 *m/z*.[a] ^{1}H NMR (500 MHz, CD_3OD) δ 8.59 (ddd, J = 4.9, 1.8, 1.0 Hz, 1H), 7.99 (dt, J = 7.9, 1.0 Hz, 1H), 7.95 (dd, J = 7.5, 5.6 Hz, 1H), 7.82 (td, J = 7.9, 1.8 Hz, 1H), 7.34−7.24 (m, 2H), 6.95−6.88 (m, 3H), 6.60−6.53 (m, 2H).

*N-(4-Fluorophenyl)-7-methoxy-2-(pyridin-2-yl)imidazo-[1,2-a]pyridin-3-amine (**3i**).* Compound **3i** has been synthesized as previously reported in the literature.[6]

*N-(4-Fluorophenyl)-2-(pyridin-2-yl)imidazo[1,2-a]pyrazin-3-amine (**3j**).* Compound **3j** was synthesized using 2-aminopyrazine (100 mg, 1.05 mmol), picolinaldehyde (135 mg, 1.26 mmol), and **2a** (153 mg, 1.26 mmol) according to General Procedure B. The crude product was purified by reverse phase chromatography (35−100% MeOH:H_2O) to yield the title compound as a brown solid (51 mg, 16%). LCMS $[M + H]^+$ 306.0 *m/z*.[b] ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (s, 1H), 8.79 (s, 1H), 8.59 (d, J = 4.3 Hz, 1H), 8.28 (d, J = 7.8 Hz, 1H), 7.83 (t, J = 7.8 Hz, 1H), 7.78 (d, J = 4.7 Hz, 1H), 7.39 (d, J = 4.7 Hz, 1H), 7.17−7.26 (m, 1H), 7.00 (t, J = 8.4 Hz, 2H), 6.68 (dd, J = 4.3, 8.4 Hz, 2H).

*8-Fluoro-N-(4-fluorophenyl)-2-(pyridin-2-yl)imidazo[1,2-a]pyridin-3-amine (**3k**).* Compound **3k** was synthesized using 3-fluoropyridin-2-amine (150 mg, 1.34 mmol), picolinaldehyde (172 mg, 1.61 mmol), and **2a** (194 mg, 1.61 mmol) according to General Procedure B. The crude product was purified by reverse phase chromatography (35−100% MeOH:H_2O) to yield the title compound as a beige solid (182 mg, 42%). LCMS $[M + H]^+$ 323.0 *m/z*.[b] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (d, J = 5.1 Hz, 1H), 8.49 (br. s., 1H), 8.31 (d, J = 8.4 Hz, 1H), 7.80 (dt, J = 1.5, 7.7 Hz, 1H), 7.40 (d, J = 6.7 Hz, 1H), 7.19 (dd, J = 5.1, 6.7 Hz, 1H), 6.95 (t, J = 8.4 Hz, 2H), 6.89 (dd, J = 7.7, 10.2 Hz, 1H), 6.61−6.71 (m, 3H).

*N-(4-Fluorophenyl)-8-methoxy-2-(pyridin-2-yl)imidazo-[1,2-a]pyridin-3-amine (**3l**).* Compound **3l** was synthesized using 3-methoxypyridin-2-amine (150 mg, 1.21 mmol), picolinaldehyde (155 mg, 1.45 mmol), and **2a** according to General Procedure B. The crude product was purified by reverse phase chromatography (35−100% MeOH:H_2O) to yield the title compound as a beige solid (350 mg, 87%). LCMS $[M + H]^+$ 335.0 *m/z*.[b] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (d, J = 4.9 Hz, 1H), 8.40 (s, 1H), 8.34 (d, J = 8.3 Hz, 1H), 7.76 (t, J = 7.8 Hz, 1H), 7.26 (d, J = 6.8 Hz, 1H), 7.14 (dd, J = 5.9, 6.8 Hz, 1H), 6.93 (t, J = 8.8 Hz, 2H), 6.59−6.72 (m, 3H), 6.48 (d, J = 7.8 Hz, 1H), 4.08 (s, 3H).

*N-(4-Fluorophenyl)-2-(pyridin-2-yl)imidazo[1,2-a]-pyrimidin-3-amine (**3m**).* Compound **3m** was synthesized using 2-aminopyrimidine (100 mg, 1.05 mmol), picolinaldehyde (135 mg, 1.26 mmol), and **2a** (153 mg, 1.26 mmol) according to General Procedure B. The crude product was purified by reverse phase chromatography (35−100% MeOH:H_2O) to yield the title compound as a beige solid (55 mg, 17%). LCMS $[M + H]^+$ 306.0 *m/z*.[b] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50−8.60 (m, 3H), 8.38 (d, J = 8.5 Hz, 1H), 7.78−7.87 (m, 2H), 7.17−7.23 (m, 1H), 6.98 (t, J = 8.5 Hz, 2H), 6.82 (dd, J = 3.9, 6.8 Hz, 1H), 6.68 (dd, J = 4.4, 8.5 Hz, 2H).

*N-(4-Fluorophenyl)-6-(methylsulfanyl)-2-(pyridin-2-yl)-imidazo[1,2-a]pyridin-3-amine (**3n**).* Compound **3n** was synthesized using 5-(methylthio)pyridin-2-amine (150 mg, 1.07 mmol), 4-methoxypicolinaldehyde (138 mg, 1.28 mmol), and **2a** (156 mg, 1.28 mmol) according to General Procedure B.

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The crude product was purified by reverse phase chromatography (35−100% MeOH:H_2O) to yield the title compound as a beige solid (320 mg, 85%). LCMS $[M + H]^+$ 351.0 *m/z*.[b] ^1H NMR (500 MHz, $CDCl_3$) δ 8.56 (d, J = 4.4 Hz, 1H), 8.39 (br. s., 1H), 8.22 (d, J = 7.7 Hz, 1H), 7.80 (t, J = 7.7 Hz, 1H), 7.60 (d, J = 9.3 Hz, 1H), 7.46 (s, 1H), 7.14−7.23 (m, 2H), 6.96 (t, J = 8.6 Hz, 2H), 6.64 (dd, J = 4.4, 8.6 Hz, 2H), 2.38 (s, 3H).

*N-(4-Fluorophenyl)-6-methanesulfonyl-2-(pyridin-2-yl)-imidazo[1,2-a]pyridin-3-amine (**3o**).* Compound **3o** was synthesized using 5-(methylsulfonyl)pyridin-2-amine (140 mg, 0.81 mmol),[21] picolinaldehyde (105 mg, 0.96 mmol), and **2a** (118 mg, 0.96 mmol) according to General Procedure B. The crude product was purified by reverse phase chromatography (35−100% MeOH:H_2O) to provide a yellow solid (206 mg, 66%). LCMS $[M + H]^+$ 383.0 *m/z*.[b] ^1H NMR (500 MHz, $CDCl_3$) δ 8.59 (d, J = 4.4 Hz, 1H), 8.44 (s, 1H), 8.28 (s, 1H), 8.23 (d, J = 7.8 Hz, 1H), 7.82 (dt, J = 1.5, 7.8 Hz, 1H), 7.76 (d, J = 9.3 Hz, 1H), 7.53 (dd, J = 1.7, 9.5 Hz, 1H), 7.22 (dd, J = 5.1, 6.6 Hz, 1H), 6.97 (t, J = 8.5 Hz, 2H), 6.61−6.70 (m, 2H), 3.10 (s, 3H).

*6-Cyclopropyl-N-(4-fluorophenyl)-2-(pyridin-2-yl)-imidazo[1,2-a]pyridin-3-amine (**3p**).* Compound **3p** was synthesized using 5-cyclopropylpyridin-2-amine (40 mg, 0.30 mmol),[22] picolinaldehyde (64 mg, 0.60 mmol), and **2a** (72 mg, 0.60 mmol) according to General Procedure B. The crude product was purified by reverse phase chromatography (50−70% MeOH:H_2O) to provide a beige solid (33 mg, 32%). LCMS $[M + H]^+$ 345.2 *m/z*.[a] ^1H NMR (500 MHz, $CDOD_3$) δ 8.59 (d, J = 4.9 Hz, 1H), 8.00 (d, J = 8.3 Hz, 1H), 7.82 (d, J = 1.5 Hz, 1H), 7.65 (s, 1H), 7.53 (d, J = 9.3 Hz, 1H), 7.24−7.29 (m, 1H), 7.13 (dd, J = 1.5, 9.3 Hz, 1H), 6.91 (t, J = 8.8 Hz, 2H), 6.52−6.58 (m, 2H), 1.93 (s, 1H), 0.96 (dd, J = 1.5, 8.3 Hz, 2H), 0.66 (d, J = 6.4 Hz, 2H).

*N-(4-Fluorophenyl)-6-(1,2-oxazol-4-yl)-2-(pyridin-2-yl)-imidazo[1,2-a]pyridin-3-amine (**3q**).* Compound **3q** was synthesized using **1f** (45 mg, 0.28 mmol), picolinaldehyde (60 mg, 0.56 mmol), and **2a** (68 mg, 0.56 mmol) according to General Procedure B. The crude product was purified by reverse phase chromatography (30−60% MeOH:H_2O) to provide a beige solid (39 mg, 38%). LCMS $[M + H]^+$ 372.2 *m/z*.[a] ^1H NMR (500 MHz, $CDOD_3$) δ 9.13 (s, 1H), 8.83 (s, 1H), 8.60 (d, J = 4.9 Hz, 1H), 8.23 (s, 1H), 8.02 (d, J = 7.8 Hz, 1H), 7.84 (s, 1H), 7.68−7.73 (m, 1H), 7.63−7.67 (m, 1H), 7.29 (d, J = 4.9 Hz, 1H), 6.91 (t, J = 8.8 Hz, 2H), 6.59 (dd, J = 4.4, 8.8 Hz, 2H).

*N-(4-Fluorophenyl)-6-(pyridin-2-yl)imidazo[2,1-b][1,3]-thiazol-5-amine (**3r**).* Compound **3r** was synthesized using 2-aminothiazole (50 mg, 0.50 mmol), picolinaldehyde (107 mg, 1.00 mmol), and **2a** (121 mg, 1.00 mmol) according to General Procedure B. The crude product was purified by reverse phase chromatography (35−100% MeOH:H_2O) to yield the title compound as an orange solid (27 mg, 17%). LCMS $[M + H]^+$ 311.1 *m/z*.[a] ^1H NMR (500 MHz, DMSO-d_6) δ 8.48 (d, J = 4.5 Hz, 1H), 8.29 (s, 1H), 7.93−7.86 (m, 1H), 7.78 (td, J = 7.8, 1.8 Hz, 1H), 7.37 (d, J = 4.5 Hz, 1H), 7.26 (d, J = 4.5 Hz, 1H), 7.17 (ddd, J = 7.4, 4.8, 1.2 Hz, 1H), 6.99 (t, J = 8.8 Hz, 2H), 6.67−6.59 (m, 2H).

*N-(3,5-Difluorophenyl)-2-(pyridin-2-yl)imidazo[1,2-a]-pyridin-3-amine (**3s**).* Compound **3s** was synthesized using pyridin-2-amine (90 mg, 0.96 mmol), picolinaldehyde (123 mg, 1.15 mmol), and **2b** (160 mg, 1.15 mmol) according to General Procedure B. The crude product was purified by reverse phase chromatography (35−100% MeOH:H_2O) to yield the title compound as a brown solid (243 mg, 78%). LCMS $[M + H]^+$ 323.2 *m/z*.[a] ^1H NMR (500 MHz, $CDCl_3$) δ 8.55−8.62 (m, 1H), 8.18−8.25 (m, 2H), 7.79 (dt, J = 1.7, 7.7 Hz, 1H), 7.65−7.72 (m, 2H), 7.23−7.27 (m, 1H), 7.19 (ddd, J = 1.0, 5.5, 6.7 Hz, 1H), 6.86 (t, J = 6.7 Hz, 1H), 6.36 (tt, J = 2.2, 9.0 Hz, 1H), 6.07−6.22 (m, 2H).

*N-(2,4-Difluorophenyl)-2-(pyridin-2-yl)imidazo[1,2-a]-pyridin-3-amine (**3t**).* Compound **3t** was synthesized using pyridin-2-amine (50 mg, 0.53 mmol), picolinaldehyde (114 mg, 1.06 mmol), and **2c** (148 mg, 1.06 mmol) according to General Procedure B. The crude product was purified by reverse phase chromatography (5−70% MeOH:H_2O) to yield the title compound as a brown solid (53 mg, 31%). LCMS $[M + H]^+$ 323.1 *m/z*.[a] ^1H NMR (500 MHz, $CDOD_3$) δ 8.58 (ddd, J = 4.9, 1.8, 1.1 Hz, 1H), 8.03 (dt, J = 7.8, 1.1 Hz, 1H), 7.99 (dt, J = 6.9, 1.1 Hz, 1H), 7.84 (td, J = 7.8, 1.8 Hz, 1H), 7.64 (dt, J = 9.2, 1.1 Hz, 1H), 7.40 (ddd, J = 9.2, 6.9, 1.3 Hz, 1H), 7.28 (ddd, J = 7.8, 4.9, 1.1 Hz, 1H), 7.05−6.97 (m, 2H), 6.67−6.60 (m, 1H), 6.14 (td, J = 9.4, 5.4 Hz, 1H).

*2-(Pyridin-2-yl)-N-[3-(trifluoromethyl)phenyl]imidazo[1,2-a]pyridin-3-amine (**3u**).* Compound **3u** was synthesized using pyridin-2-amine (50 mg, 0.53 mmol), picolinaldehyde (114 mg, 1.06 mmol), and **2d** (182 mg, 1.06 mmol) according to General Procedure B. The crude product was purified by reverse phase chromatography (30−70% MeOH:H_2O) to yield the title compound as a yellow solid (80 mg, 42%). LCMS $[M + H]^+$ 355.1 *m/z*.[a] ^1H NMR (500 MHz, $CDOD_3$) δ 8.59 (ddd, J = 4.9, 1.9, 1.1 Hz, 1H), 8.00 (ddt, J = 14.4, 6.8, 1.1 Hz, 2H), 7.83 (td, J = 7.8, 1.8 Hz, 1H), 7.66 (dt, J = 9.1, 1.1 Hz, 1H), 7.42 (ddd, J = 9.1, 6.8, 1.1 Hz, 1H), 7.32−7.25 (m, 2H), 7.05 (d, J = 7.8 Hz, 1H), 7.00 (td, J = 6.8, 1.1 Hz, 1H), 6.86 (t, J = 1.9 Hz, 1H), 6.71−6.64 (m, 1H).

*N-(Benzo[d][1,3]dioxol-4-yl)-6-methoxy-2-(pyridin-2-yl)-imidazo[1,2-a]pyridin-3-amine (**3v**).* Compound **3v** was synthesized using pyridin-2-amine (20 mg, 0.21 mmol), picolinaldehyde (45 mg, 0.43 mmol), and **2e** (47 mg, 0.32 mmol) according to General Procedure B. The crude product was purified by reverse phase chromatography (40−65% MeOH:H_2O) to yield the title compound as a beige solid (14 mg, 20%). LCMS $[M + H]^+$ 331.1 *m/z*; ^1H NMR (500 MHz, Methanol-d_4) δ 8.60 (d, J = 4.9 Hz, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.97 (dt, J = 6.8, 1.2 Hz, 1H), 7.84 (td, J = 7.7, 1.7 Hz, 1H), 7.61 (dt, J = 9.1, 1.2 Hz, 1H), 7.37 (ddd, J = 9.2, 6.7, 1.3 Hz, 1H), 7.28 (dd, J = 7.4, 5.1 Hz, 1H), 6.96 (td, J = 6.8, 1.1 Hz, 1H), 6.59 (t, J = 8.1 Hz, 1H), 6.39 (dd, J = 7.9, 1.0 Hz, 1H), 5.89 (s, 2H), 5.87 (dd, J = 8.3, 1.1 Hz, 1H).

*N-(4-Fluorophenyl)-2-(pyridazin-3-yl)imidazo[1,2-a]-pyridin-3-amine (**3w**).* Compound **3w** was synthesized using pyridin-2-amine (90 mg, 0.96 mmol), pyridazine-3-carbaldehyde (124 mg, 1.15 mmol), and **2a** (174 mg, 1.15 mmol) according to General Procedure B. The crude product was purified by reverse phase chromatography (20−70% MeOH:-H_2O) to yield the title compound as a dark brown solid (80 mg, 27%). LCMS $[M + H]^+$ 306.6 *m/z*.[a] ^1H NMR (500 MHz, $CDCl_3$) δ 9.04 (dd, J = 1.4, 4.9 Hz, 1H), 8.38 (dd, J = 1.4, 8.5 Hz, 1H), 8.23 (s, 1H), 7.59−7.69 (m, 2H), 7.57 (dd, J = 4.9, 8.8 Hz, 1H), 7.20−7.25 (m, 1H), 6.94 (t, J = 8.5 Hz, 2H), 6.80 (t, J = 6.6 Hz, 1H), 6.60−6.68 (m, 2H).

*N-(4-Fluorophenyl)-2-(1-methyl-1H-imidazol-4-yl)-imidazo[1,2-a]pyridin-3-amine (**3x**).* Compound **3x** was synthesized using pyridin-2-amine (90 mg, 0.96 mmol), 1-methyl-1*H*-imidazole-4-carbaldehyde (172 mg, 1.15 mmol), and **2a** (154 mg, 1.15 mmol) according to General Procedure B. The crude product was purified by reverse phase chromatog-

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raphy (20−70% MeOH:H_2O) to yield the title compound as a beige solid (115 mg, 40%). LCMS $[M + H]^+$ 308.2 *m/z*.[a] ^1H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, J = 6.8 Hz, 1H), 7.58 (d, J = 9.3 Hz, 1H), 7.42 (s, 2H), 7.13−7.20 (m, 1H), 7.06 (s, 1H), 6.89 (t, J = 8.8 Hz, 2H), 6.75 (t, J = 6.3 Hz, 1H), 6.49−6.59 (m, 2H), 3.70 (s, 3H).

*N-(4-Fluorophenyl)-2-[(1H-pyrazol-1-yl)methyl]imidazo-[1,2-a]pyridin-3-amine (**3y**).* Compound **3y** was synthesized using pyridin-2-amine (45 mg, 0.48 mmol), 2-(1*H*-pyrazol-1-yl)acetaldehyde (105 mg, 0.96 mmol), and **2a** (116 mg, 0.96 mmol) according to General Procedure B. The crude product was purified by reverse phase chromatography (30−60% MeOH:H_2O) to yield the title compound as a beige solid (9 mg, 6%). LCMS $[M + H]^+$ 308.1 *m/z*.[a] ^1H NMR (500 MHz, $CDOD_3$) δ 7.94 (dt, J = 6.9, 1.3 Hz, 1H), 7.63 (d, J = 2.3 Hz, 1H), 7.53 (d, J = 9.0 Hz, 1H), 7.43 (d, J = 1.9 Hz, 1H), 7.36 (ddd, J = 9.0, 6.9, 1.3 Hz, 1H), 6.94 (td, J = 6.9, 1.3 Hz, 1H), 6.90−6.83 (m, 2H), 6.48−6.42 (m, 2H), 6.24 (t, J = 2.3 Hz, 1H), 5.39 (s, 2H).

*N-(4-Fluorophenyl)-2-(6-methoxypyridin-2-yl)imidazo-[1,2-a]pyridin-3-amine (**3z**).* Compound **3z** was synthesized using pyridin-2-amine (90 mg, 0.96 mmol), 6-methoxypicolinaldehyde (158 mg, 1.15 mmol), and **2a** (174 mg, 1.15 mmol) according to General Procedure B. The crude product was purified by reverse phase chromatography (30−80% MeOH:-H_2O) to yield the title compound as a yellow solid (50 mg, 16%). LCMS $[M + H]^+$ 335.6 *m/z*.[a] ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.12−8.18 (m, 1H), 7.95−8.03 (m, 1H), 7.62 (s, 2H), 7.16−7.22 (m, 2H), 6.89−6.97 (m, 2H), 6.74−6.81 (m, 1H), 6.61 (d, J = 4.3 Hz, 2H), 3.89 (s, 3H).

*N-(4-Fluorophenyl)-2-(5-methoxypyridin-2-yl)imidazo-[1,2-a]pyridin-3-amine (**3aa**).* Compound **3aa** was synthesized using 2-aminopyridine (200 mg, 2.13 mmol), 5-methoxypicolinaldehyde (350 mg, 2.55 mmol), and **2a** (309 mg, 2.55 mmol) according to General Procedure B. The crude product was purified by reverse phase chromatography (35−100% MeOH:-H_2O) to yield the title compound as a colorless powder (49 mg, 31%). LCMS $[M + H]^+$ 335.5 *m/z*.[a] ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 3.1 Hz, 1H), 8.15 (d, J = 9.0 Hz, 1H), 7.97−8.02 (m, 1H), 7.57−7.66 (m, 1H), 7.29−7.33 (m, 2H), 7.15−7.22 (m, 1H), 6.90−6.96 (m, 2H), 6.74−6.80 (m, 1H), 6.60 (dd, J = 4.3, 9.0 Hz, 2H), 3.89 (s, 3H).

*11,111 (**3ab**).* Compound **3ab** was synthesized using 2-aminopyridine (45 mg, 0.48 mmol), 4-methoxypicolinaldehyde (79 mg, 0.57 mmol), and **2a** (87 mg, 0.57 mmol) according to General Procedure B. The crude product was purified by reverse phase chromatography (35−100% MeOH:H_2O) to yield the title compound as a beige solid (55 mg, 35%). LCMS $[M + H]^+$ 335.5 *m/z*.[a] ^1H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.36 (d, J = 5.5 Hz, 1H), 7.75 (d, J = 2.4 Hz, 1H), 7.65 (d, J = 9.0 Hz, 1H), 7.56 (d, J = 7.0 Hz, 1H), 7.14−7.23 (m, 1H), 6.94 (t, J = 8.6 Hz, 2H), 6.76 (t, J = 7.0 Hz, 1H), 6.70 (dd, J = 2.4, 5.5 Hz, 1H), 6.63 (dd, J = 4.5, 8.6 Hz, 2H), 3.96 (s, 3H).

*N-(4-Fluorophenyl)-2-(3-methoxypyridin-2-yl)imidazo-[1,2-a]pyridin-3-amine (**3ac**).* Compound **3 ac** was synthesized using 2-aminopyridine (45 mg, 0.48 mmol), 3-methoxypicolinaldehyde (45 mg, 0.48 mmol), and **2a** (87 mg, 0.57 mmol) according to General Procedure B. The crude product was purified by reverse phase chromatography (35−100% MeOH:-H_2O) to yield the title compound as a faint brown solid (35 mg, 22%). LCMS $[M + H]^+$ 335.5 *m/z*.[a] ^1H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, J = 3.9 Hz, 1H), 7.64−7.74 (m, 2H), 7.33 (s, 1H), 7.31 (d, J = 8.7 Hz, 1H), 7.14−7.25 (m, 2H), 6.86 (t, J = 8.7 Hz, 2H), 6.77 (t, J = 6.8 Hz, 1H), 6.44−6.54 (m, 2H), 3.90 (s, 3H).

*N-(4-Fluorophenyl)-2-(6-fluoropyridin-2-yl)imidazo[1,2-a]pyridin-3-amine (**3ad**).* Compound **3ad** was synthesized using 2-aminopyridine (45 mg, 0.48 mmol), 6-fluoropicolinaldehyde (72 mg, 0.57 mmol), and **2a** (87 mg, 0.57 mmol) according to General Procedure B. The crude product was purified by reverse phase chromatography (35−100% MeOH:-H_2O) to yield the title compound as a brown solid (68 mg, 44%). LCMS $[M + H]^+$ 323.5 *m/z*.[a] ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 5.8 Hz, 1H), 7.87 (q, J = 8.2 Hz, 1H), 7.72 (s, 1H), 7.64 (d, J = 8.6 Hz, 2H), 7.18−7.26 (m, 1H), 6.95 (t, J = 8.6 Hz, 2H), 6.74−6.84 (m, 2H), 6.61 (dd, J = 4.3, 8.9 Hz, 2H).

*N-(4-Fluorophenyl)-2-(5-fluoropyridin-2-yl)imidazo[1,2-a]pyridin-3-amine (**3ae**).* Compound **3ae** was synthesized using 2-aminopyridine (45 mg, 0.48 mmol), 5-fluoropicolinaldehyde (72 mg, 0.57 mmol) and **2a** (87 mg, 0.57 mmol) according to General Procedure B. The crude product was purified by reverse phase chromatography (35−100% MeOH:-H_2O) to yield the title compound as a brown solid (38 mg, 25%). LCMS $[M + H]^+$ 323.5 *m/z*.[a] ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 2.7 Hz, 1H), 8.23 (dd, J = 4.4, 8.9 Hz, 1H), 7.88 (s, 1H), 7.59−7.67 (m, 2H), 7.50 (dt, J = 2.7, 8.6 Hz, 1H), 7.17−7.25 (m, 1H), 6.94 (t, J = 8.6 Hz, 2H), 6.75−6.82 (m, J = 6.4, 6.4 Hz, 1H), 6.60 (dd, J = 4.4, 8.9 Hz, 2H).

*2-(4-Chloropyridin-2-yl)-N-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-amine (**3af**).* Compound **3af** was synthesized using 2-aminopyridine (45 mg, 0.48 mmol), 4-chloropicolinaldehyde (81 mg, 0.57 mmol), and **2a** (87 mg, 0.57 mmol) according to General Procedure B. The crude product was purified by reverse phase chromatography (35−100% MeOH:H_2O) to yield the title compound as a brown solid (52 mg, 32%). LCMS $[M + H]^+$ 339.5 *m/z*.[a] ^1H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, J = 5.5 Hz, 1H), 8.27 (s, 1H), 8.18 (s, 1H), 7.64 (d, J = 9.4 Hz, 1H), 7.58 (d, J = 6.5 Hz, 1H), 7.13−7.24 (m, 2H), 6.95 (t, J = 8.4 Hz, 2H), 6.77 (t, J = 6.5 Hz, 1H), 6.64 (d, J = 4.5 Hz, 2H).

*N-(4-Fluorophenyl)-2-(3-fluoropyridin-2-yl)imidazo[1,2-a]pyridin-3-amine (**3ag**).* Compound **3ag** was synthesized using 2-aminopyridine (90 mg, 0.96 mmol), 3-fluoropicolinaldehyde (144 mg, 1.15 mmol), and **2a** (174 mg, 1.15 mmol) according to General Procedure B. The crude product was purified by reverse phase chromatography (35−100% MeOH:-H_2O) to yield the title compound as a faint beige solid (123 mg, 40%). LCMS $[M + H]^+$ 323.5 *m/z*.[a] ^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, J = 4.7 Hz, 1H), 7.79 (s, 1H), 7.73 (d, J = 8.9 Hz, 1H), 7.67 (d, J = 7.0 Hz, 1H), 7.49−7.58 (m, 1H), 7.17−7.26 (m, 2H), 6.91 (t, J = 8.9 Hz, 2H), 6.80 (t, J = 7.0 Hz, 1H), 6.56 (dd, J = 4.7, 8.9 Hz, 2H).

*N-(4-Fluorophenyl)-6-methoxy-2-(4-methoxypyridin-2-yl)imidazo[1,2-a]pyridin-3-amine (**3ah**).* Compound **3ah** was synthesized using 5-methoxypyridin-2-amine (90 mg, 0.72 mmol), 4-methoxypicolinaldehyde (119 mg, 0.87 mmol) and **2a** (132 mg, 0.87 mmol), according to General Procedure B. The crude product was purified by reverse phase chromatography (35−100% MeOH:H_2O) to yield the title compound as a white solid (110 mg, 42%). LCMS $[M + H]^+$ 365.7 *m/z*.[a] ^1H NMR (500 MHz, $CDCl_3$) δ 8.54 (br. s., 1H), 8.34 (d, J = 5.8 Hz, 1H), 7.70 (d, J = 2.4 Hz, 1H), 7.54 (d, J = 9.3 Hz, 1H), 6.92−7.02 (m, 4H), 6.69 (dd, J = 2.4, 5.8 Hz, 1H), 6.59−6.66 (m, 2H), 3.95 (s, 3H), 3.68 (s, 3H).

*N-(4-Fluorophenyl)-6-methoxy-2-(5-methoxypyridin-2-yl)imidazo[1,2-a]pyridin-3-amine (**3ai**).* Compound **3ai** was synthesized using 5-methoxypyridin-2-amine (150 mg, 1.21

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mmol), 5-methoxypicolinaldehyde (199 mg, 1.45 mmol) and **2a** (176 mg, 1.45 mmol) according to General Procedure B. The crude product was purified by reverse phase chromatography (35−100% MeOH:H_2O) to yield the title compound as a yellow solid (135 mg, 31%). LCMS $[M + H]^+$ 365.1 *m/z*.[b] ^1H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, J = 2.9 Hz, 1H), 8.12 (d, J = 8.8 Hz, 1H), 7.99 (s, 1H), 7.54 (d, J = 9.8 Hz, 1H), 7.30 (dd, J = 2.9, 8.8 Hz, 1H), 7.07 (d, J = 1.5 Hz, 1H), 6.99 (d, J = 9.8 Hz, 1H), 6.94 (t, J = 8.5 Hz, 2H), 6.60 (dd, J = 4.4, 8.8 Hz, 2H), 3.88 (s, 3H), 3.70 (s, 3H).

*N-(4-Fluorophenyl)-N-methyl-2-(pyridin-2-yl)imidazo[1,2-a]pyridin-3-amine (**4a**).* Compound **4a** was synthesized using **3a** (100 mg, 0.33 mmol) and iodomethane (21.5 μL, 0.34 mmol) according to General Procedure C. The crude product was then purified by Rilas technologies to afford the title compound as a yellow solid (66 mg, 64%). LCMS $[M + H]^+$ 319.0 *m/z*.[b] ^1H NMR (500 MHz, $CDCl_3$) δ 8.62 (d, J = 4.4 Hz, 1H), 7.93 (d, J = 7.8 Hz, 1H), 7.76 (d, J = 6.8 Hz, 1H), 7.63−7.73 (m, 2H), 7.25 (d, J = 8.7 Hz, 1H), 7.14 (dd, J = 5.4, 6.8 Hz, 1H), 6.90 (t, J = 8.7 Hz, 2H), 6.80 (t, J = 6.8 Hz, 1H), 6.47−6.58 (m, 2H), 3.41 (s, 3H).

*N-(4-Fluorophenyl)-N-(methyl-d_3)-2-(pyridin-2-yl)-imidazo[1,2-a]pyridin-3-amine (**4b**).* Compound **4b** was synthesized using **3a** (56 mg, 0.18 mmol) and iodomethane-d_3 (13 μL, 0.19 mmol) according to General Procedure C. The crude product was then purified by Rilas technologies to afford the title compound as a yellow solid (34 mg, 58%). LCMS $[M + H]^+$ 322.0 *m/z*.[b] ^1H NMR (500 MHz, $CDCl_3$) δ 8.63 (d, J = 4.4 Hz, 1H), 7.94 (d, J = 7.8 Hz, 1H), 7.78 (d, J = 6.8 Hz, 1H), 7.66−7.74 (m, 2H), 7.24−7.28 (m, 1H), 7.16 (dd, J = 5.4, 6.8 Hz, 1H), 6.91 (t, J = 9.0 Hz, 2H), 6.81 (t, J = 6.8 Hz, 1H), 6.54 (dd, J = 4.0, 9.0 Hz, 2H).

*N-Ethyl-N-(4-fluorophenyl)-2-(pyridin-2-yl)imidazo[1,2-a]pyridin-3-amine (**4c**).* Compound **4c** was synthesized from **3a** (50 mg, 0.16 mmol) and iodoethane (0.16 μL, 0.20 mmol) according to General Procedure C. The crude product was purified by reverse phase chromatography (35−100% MeOH:-H_2O) to yield the title compound as a light orange solid (26 mg, 49%). LCMS $[M + H]^+$ 333.2 *m/z*.[a] ^1H NMR (500 MHz, DMSO-d_6) δ 8.48 (s, 1H), 8.12 (d, J = 8.0 Hz, 1H), 8.01 (d, J = 6.8 Hz, 1H), 7.82 (t, J = 7.6 Hz, 1H), 7.66 (d, J = 9.2 Hz, 1H), 7.35 (t, J = 8.0 Hz, 1H), 7.23 (s, 1H), 6.94 (t, J = 8.8 Hz, 3H), 6.44 (d, J = 5.0 Hz, 2H), 3.82 (d, J = 36.1 Hz, 2H), 1.11−0.92 (m, 3H).

*N-(4-Fluorophenyl)-N-propyl-2-(pyridin-2-yl)imidazo[1,2-a]pyridin-3-amine (**4d**).* Compound **4d** was prepared from **3a** (50 mg, 0.16 mmol) and 1-iodopropane (33.5 μL, 0.20 mmol) according to General Procedure C. The crude product was purified by reverse phase chromatography (35−100% MeOH:-H_2O) to yield the title compound as a yellow solid (26 mg, 46%). LCMS $[M + H]^+$ 347.1 *m/z*.[b] ^1H NMR (500 MHz, CD_3OD) δ 8.63−8.54 (m, 1H), 7.96 (dt, J = 6.7, 1.3 Hz, 1H), 7.88−7.83 (m, 1H), 7.79 (td, J = 7.7, 1.8 Hz, 1H), 7.66 (dt, J = 9.0, 1.1 Hz, 1H), 7.41 (ddd, J = 9.0, 6.7, 1.3 Hz, 1H), 7.28 (ddd, J = 7.5, 4.9, 1.3 Hz, 1H), 6.97 (td, J = 6.7, 1.3 Hz, 1H), 6.94−6.89 (m, 2H), 6.59−6.54 (m, 2H), 3.71 (br. s, 2H), 1.56 (br. s, 2H), 0.85 (t, J = 7.4 Hz, 3H).

*N-(Cyclopropylmethyl)-N-(4-fluorophenyl)-2-(pyridin-2-yl)imidazo[1,2-a]pyridin-3-amine (**4e**).* Compound **4e** was synthesized from **3a** (50 mg, 0.16 mmol) and (iodomethyl)-cyclopropane (18.4 μL, 19.72 mmol) according to General Procedure C. The crude product was purified by reverse phase chromatography (35−100% MeOH:H_2O) to yield the title compound as a beige solid (13 mg, 22%). LCMS $[M + H]^+$ 359.2 *m/z*.[a] ^1H NMR (500 MHz, DMSO-d_6) δ 8.51−8.44 (m, 1H), 8.13 (d, J = 8.0 Hz, 1H), 8.09 (d, J = 6.9 Hz, 1H), 7.81 (td, J = 7.8, 1.8 Hz, 1H), 7.65 (d, J = 9.0 Hz, 1H), 7.34 (dd, J = 9.0, 6.9 Hz, 1H), 7.22 (dd, J = 7.4, 4.9 Hz, 1H), 6.94 (td, J = 8.8, 7.8, 4.3 Hz, 3H), 6.45 (dd, J = 9.2, 4.3 Hz, 2H), 3.90−3.74 (m, 1H), 3.61−3.41 (m, 1H), 0.95−0.81 (m, 1H), 0.13 (d, J = 13.3 Hz, 3H), −0.21 (s, 1H).

*N-(4-Fluorophenyl)-N-isobutyl-2-(pyridin-2-yl)imidazo-[1,2-a]pyridin-3-amine (**4f**).* Compound **4f** was synthesized using **3a** (50 mg, 0.16 mmol) and 1-iodo-2-methylpropane (28.3 μL, 0.24 mmol) according to General Procedure C. The crude product was purified by reverse phase chromatography (35−100% MeOH:H_2O) to yield the title compound as a colorless solid (18 mg, 31%). LCMS $[M + H]^+$ 361.6 *m/z*.[a] ^1H NMR (500 MHz, $CDCl_3$) δ 8.66 (d, J = 4.4 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 6.8 Hz, 1H), 7.65−7.73 (m, 2H), 7.24−7.26 (m, 1H), 7.17 (ddd, J = 1.0, 5.5, 6.8 Hz, 1H), 6.90 (t, J = 8.4 Hz, 2H), 6.81 (dt, J = 1.0, 6.8 Hz, 1H), 6.54 (td, J = 3.9, 8.4 Hz, 2H), 3.39−3.75 (m, 2H), 1.89 (spt, J = 6.6 Hz, 1H), 0.70−1.02 (m, 6H).

*N-(4-Fluorophenyl)-N-(3-methylbutyl)-2-(pyridin-2-yl)-imidazo[1,2-a]pyridin-3-amine (**4g**).* Compound **4 g** was synthesized from **3a** (50 mg, 0.16 mmol) and 1-bromo-3-methylbutane (30 μL, 0.25 mmol) according to General Procedure C. The crude product was purified by reverse phase chromatography (35−100% MeOH:H_2O) to yield the title compound as a brown oil (10 mg, 16%). LCMS $[M + H]^+$ 375.8 *m/z*.[a] ^1H NMR (500 MHz, $CDCl_3$) δ 8.65 (d, J = 3.9 Hz, 1H), 7.90 (d, J = 8.3 Hz, 1H), 7.75 (d, J = 6.8 Hz, 1H), 7.61−7.72 (m, 2H), 7.24 (ddd, J = 1.2, 6.8, 9.0 Hz, 1H), 7.11−7.18 (m, 1H), 6.84−6.93 (m, 2H), 6.78 (dt, J = 1.0, 6.8 Hz, 1H), 6.49−6.55 (m, 2H), 3.74 (br. s., 2H), 1.30−1.64 (m, 3H), 0.75−0.90 (m, 6H).

*N-{3-[(tert-Butyldimethylsilyl)oxy]propyl}-N-(4-fluorophenyl)-2-(pyridin-2-yl)imidazo[1,2-a]pyridin-3-amine (**4h**).* Compound **4 h** was synthesized from **3a** (50 mg, 0.16 mmol) and (3-bromopropoxy)(tert-butyl)dimethylsilane (57 μL, 0.25 mmol) according to General Procedure C. The crude product was purified by Rilas technologies to afford the title compound as a brown solid (20 mg, 26%). LCMS $[M + H]^+$ 477.9 *m/z*.[a] ^1H NMR (500 MHz, $CDCl_3$) δ 8.65 (d, J = 4.9 Hz, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 6.8 Hz, 1H), 7.64−7.73 (m, 2H), 7.26 (d, J = 1.5 Hz, 1H), 7.10−7.18 (m, 1H), 6.89 (t, J = 8.4 Hz, 2H), 6.79 (s, 1H), 6.55−6.65 (m, 2H), 3.76−4.14 (m, 2H), 3.59 (br. s., 2H), 1.61−1.96 (m, 2H), 0.87 (s, 9H), −0.01 (s, 6H).

*N-{2-[(tert-Butyldimethylsilyl)oxy]ethyl}-N-(4-fluorophenyl)-2-(pyridin-2-yl)imidazo[1,2-a]pyridin-3-amine (**4i**).* Compound **4i** was synthesized from **3a** (100 mg, 0.33 mmol) and (2-bromoethoxy)(tert-butyl)dimethylsilane (94 mg, 0.39 mmol) according to General Procedure C. The crude product was purified by reverse phase chromatography (35−100% MeOH:-H_2O) to yield the title compound as a yellow solid (10 mg, 6%). LCMS $[M + H]$ + 463.2 *m/z*.[c] ^1H NMR (500 MHz, $CDCl_3$) δ 8.58−8.69 (m, 1H), 8.00 (d, J = 7.8 Hz, 1H), 7.91 (d, J = 6.8 Hz, 1H), 7.68 (d, J = 10.3 Hz, 2H), 7.22−7.26 (m, 1H), 7.13−7.19 (m, 1H), 6.87 (t, J = 8.8 Hz, 2H), 6.75 (s, 1H), 6.62 (dd, J = 4.4, 9.3 Hz, 2H), 3.45−4.18 (m, 4H), 0.80 (s, 9H), −0.27−0.06 (m, 6H).

*N-(4-Fluorophenyl)-N-(2-(pyridin-2-yl)imidazo[1,2-a]-pyridin-3-yl)acetamide (**4j**).* An oven-dried 8 mL vial had added **3a** (200 mg, 0.66 mmol), CH_2Cl_2 (3.3 mL) and pyridine (58 μL, 0.72 mmol). The reaction was then cooled with an external ice

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bath before the dropwise addition of acetyl chloride (50 μL, 0.69 mmol). The reaction was then slowly warmed to room temperature and stirred for 17 h. To the solution was added CH_2Cl_2 (15 mL) and then diluted HCl till pH was adjusted to ∼5−6. The two phases are separated, and combined organic washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in a minimal amount of DMSO and purified by reverse phase chromatography (40−100% MeOH:H_2O) to yield the title compound as a yellow solid (55 mg, 24%). LCMS $[M + H]^+$ 379.0 *m/z*.[b] ^1H NMR (500 MHz, $CDCl_3$) δ 8.65 (d, J = 4.9 Hz, 1H), 8.29 (d, J = 8.3 Hz, 1H), 7.99 (d, J = 6.8 Hz, 1H), 7.82 (t, J = 7.8 Hz, 1H), 7.69 (d, J = 9.3 Hz, 1H), 7.39 (br. s., 2H), 7.32 (t, J = 7.8 Hz, 1H), 7.24−7.27 (m, 1H), 6.88−7.01 (m, 3H), 2.02 (br. s., 3H).

*N-(4-Fluorophenyl)-2-(4-methoxypyridin-2-yl)-N-methylimidazo[1,2-a]pyridin-3-amine (**4k**).* Compound **4 k** was synthesized from **3ab** (100 mg, 0.30 mmol) and iodomethane (20 μL, 0.31 mmol) according to General Procedure C. The crude product was then purified by Rilas technologies to afford the title compound as a yellow solid (55 mg, 53%). LCMS $[M + H]^+$ 349.0 *m/z*.[b] ^1H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, J = 5.4 Hz, 1H), 7.79 (d, J = 6.6 Hz, 1H), 7.70 (d, J = 9.3 Hz, 1H), 7.49 (d, J = 2.4 Hz, 1H), 7.22−7.31 (m, 1H), 6.90 (t, J = 8.8 Hz, 2H), 6.81 (t, J = 6.6 Hz, 1H), 6.70 (dd, J = 2.4, 5.4 Hz, 1H), 6.52 (dd, J = 4.4, 8.8 Hz, 2H), 3.81 (s, 3H), 3.42 (s, 3H).

*N-(4-Fluorophenyl)-2-(5-methoxypyridin-2-yl)-N-methylimidazo[1,2-a]pyridin-3-amine (**4l**).* Compound **4l** was synthesized from **3aa** (100 mg, 0.30 mmol) and iodomethane (20 μL, 0.31 mmol) according to General Procedure C. The crude product was then purified by reverse phase chromatography (35−100% MeOH:H_2O) to yield the afford the title compound as a brown solid (10 mg, 10%). LCMS $[M + H]^+$ 349.1 *m/z*.[a] ^1H NMR (500 MHz, $CDCl_3$) δ 8.32 (br. s., 1H), 7.85 (d, J = 8.5 Hz, 1H), 7.75 (t, J = 8.5 Hz, 2H), 7.24−7.32 (m, 1H), 7.20 (td, J = 1.5, 8.5 Hz, 1H), 6.86−6.93 (m, 2H), 6.82 (t, J = 6.6 Hz, 1H), 6.45−6.57 (m, 2H), 3.86 (d, J = 1.5 Hz, 3H), 3.39 (s, 3H).

*N-(4-Fluorophenyl)-6-methoxy-2-(5-methoxypyridin-2-yl)-N-methylimidazo[1,2-a]pyridin-3-amine (**4m**).* Compound **4 m** was synthesized using **3ai** (115 mg, 0.32 mmol) and iodomethane (29.5 μL, 0.47 mmol) according to General Procedure C. The crude product was then purified by Rilas technologies to afford the title compound as a yellow solid (25 mg, 24%). LCMS $[M + H]^+$ 379.0 *m/z*.[c] ^1H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, J = 5.4 Hz, 1H), 7.59 (d, J = 9.8 Hz, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.27−7.29 (m, 1H), 7.05 (dd, J = 2.2, 9.5 Hz, 1H), 6.91 (t, J = 8.5 Hz, 2H), 6.67 (dd, J = 2.4, 5.9 Hz, 1H), 6.51−6.58 (m, 2H), 3.80 (s, 3H), 3.75 (s, 3H), 3.41 (s, 3H).

*N-(4-Fluorophenyl)-6-methoxy-N-methyl-2-(pyridin-2-yl)-imidazo[1,2-a]pyridin-3-amine (**4n**).* Compound **4n** was prepared using **3f** (50 mg, 0.15 mmol) and iodomethane (11 μL, 0.18 mmol) according to General Procedure C. The crude product was purified by reverse phase chromatography (35−100% MeOH:H_2O) to yield the title compound as a light yellow solid (14 mg, 27%). LCMS $[M + H]^+$ 349.2 *m/z*.[a] ^1H NMR (500 MHz, DMSO-d_6) δ 8.44−8.38 (m, 1H), 8.08−8.03 (m, 1H), 7.78 (td, J = 7.8, 1.8 Hz, 1H), 7.60 (d, J = 9.6 Hz, 1H), 7.49 (d, J = 2.3 Hz, 1H), 7.18 (ddd, J = 7.4, 4.8, 1.2 Hz, 1H), 7.14 (dd, J = 9.6, 2.3 Hz, 1H), 6.94 (t, J = 8.8 Hz, 2H), 6.48−6.38 (m, 2H), 3.71 (s, 3H), 3.35 (s, 3H).

*N-(tert-Butyl)-7-methoxy-2-(pyridin-2-yl)imidazo[1,2-a]-pyridin-3-amine (**6b**).* Compound **6b** was synthesized using 4-methoxypyridin-2-amine **5b** (200 mg, 1.61 mmol), pyridine-2-carboxaldehyde (305 μL, 3.22 mmol), and *tert*-butyl isocyanide (364.4 μL, 3.22 mmol) according to General Procedure B. The crude product was purified by flash chromatography (5:95 EtOAc/Hex) to yield the title compound as a solid (318 mg, 71%). LCMS $[M + H]^+$ 297.1 *m/z*.[a] ^1H NMR (500 MHz, $CDCl_3$) δ 8.54 (ddd, J = 4.9, 1.9, 1.0 Hz, 1H), 8.12−8.08 (m, 2H), 7.73 (td, J = 7.8, 1.8 Hz, 1H), 7.12 (ddd, J = 7.5, 4.8, 1.2 Hz, 1H), 6.78 (d, J = 2.3 Hz, 1H), 6.46 (dd, J = 7.6, 2.4 Hz, 1H), 5.36 (s, 1H), 3.85 (s, 3H), 1.13 (s, 9H).

*2-(Pyridin-2-yl)imidazo[1,2-a]pyridin-3-amine (**7a**).* A suspension of *N*-(*tert*-butyl)-amine **6a** (660 mg, 2.48 mmol)[8] in water (30 mL) was treated with HBr (9.8 mL, ∼8.95 M in water), and stirred at 110 °C for 4 h. After the reaction was complete, the pH has been raised to ∼12, and the was precipitate collected by filtration (430 mg, 83%). ^1H NMR (500 MHz, $CDCl_3$) δ 8.57 (d, J = 3.9 Hz, 1H), 8.20 (d, J = 7.8 Hz, 1H), 7.81 (d, J = 6.5 Hz, 1H), 7.71−7.79 (m, 1H), 7.56 (d, J = 9.3 Hz, 1H), 7.03−7.16 (m, 2H), 6.81 (t, J = 6.5 Hz, 1H), 5.41 (br. s., 2H).

*7-Methoxy-2-(pyridin-2-yl)imidazo[1,2-a]pyridin-3-amine (**7b**).* A suspension of **6b** (340 mg, 1.15 mmol) in 3 M HBr (20 mL) was stirred at 110 °C for 3 h. After the reaction was complete, the pH has been raised to ∼12, and the precipitate was collected by filtration (220 mg, 80%). LCMS $[M + H]^+$ 241.1 *m/z*.[a] ^1H NMR (500 MHz, $CDCl_3$) δ 8.53 (d, J = 4.8 Hz, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.77−7.68 (m, 1H), 7.63 (d, J = 7.5 Hz, 1H), 7.06 (t, J = 6.2 Hz, 1H), 6.83−6.74 (m, 1H), 6.51 (dd, J = 7.6, 2.3 Hz, 1H), 5.22 (s, 2H), 3.85 (s, 3H).

*5-Fluoro-N-[2-(pyridin-2-yl)imidazo[1,2-a]pyridin-3-yl]-pyridin-2-amine (**8**).* Compound **8** was synthesized using amine **7a** (100 mg, 0.48 mmol) and 2-bromo-5-fluoropyridine (100 mg, 0.57 mmol), in the presence of NaOtBu and XPhos Pd G2 (19 mg, 0.24 mmol) in *t*-BuOH (2 mL). The reaction was stirred at 75 °C for 2 h, then quenched with brine (30 mL) and extracted with CH_2Cl_2 (3 × 40 mL), dried over Na2SO4, filtered, and concentrated under vacuum. The crude product was purified by reverse phase chromatography (20−80% MeOH:H_2O) to yield the title compound as a yellow solid (141 mg, 97%). LCMS $[M + H]^+$ 306.0 *m/z*.[b] ^1H NMR (500 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.59 (d, J = 3.9 Hz, 1H), 8.21 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 2.4 Hz, 1H), 7.72−7.81 (m, 2H), 7.64 (d, J = 9.3 Hz, 1H), 7.27−7.32 (m, 1H), 7.22 (ddd, J = 1.2, 7.3, 8.4 Hz, 1H), 7.16 (ddd, J = 1.0, 5.0, 7.7 Hz, 1H), 6.75−6.83 (m, 1H), 6.55 (dd, J = 3.4, 8.8 Hz, 1H).

*2-(Pyridin-2-yl)imidazo[1,2-a]pyridine (**11a**).* Compound **11a** was synthesized using pyridin-2-amine (258 mg, 2.74 mmol) according to General Procedure E. The crude product was then purified by flash chromatography (35−100% MeOH in CH_2Cl_2) to yield the title compound as a brown solid (10 mg, 10%). LCMS $[M + H]^+$ 196.0 *m/z*.[a] ^1H NMR (500 MHz, $CDOD_3$) δ 8.58 (d, J = 4.9 Hz, 1H), 8.49 (d, J = 6.8 Hz, 1H), 8.38 (s, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.92 (td, J = 7.7, 1.8 Hz, 1H), 7.61−7.56 (m, 1H), 7.36 (tdd, J = 8.0, 4.2, 1.4 Hz, 2H), 6.95 (td, J = 6.8, 1.1 Hz, 1H).

*7-Methoxy-2-(pyridin-2-yl)imidazo[1,2-a]pyridine (**11b**).* Compound **11b** was synthesized using 4-methoxypyridin-2-amine (127 mg, 1.02 mmol) according to General Procedure E. The crude product was then purified by flash chromatography (30:70 EtOAc/Hex) to yield the title compound as a white solid (136 mg, 67%). LCMS $[M + H]^+$ 226.0 *m/z*.[a] ^1H NMR (500 MHz, $CDCl_3$) δ 8.60 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H), 8.15 (d, J = 7.9 Hz, 1H), 8.08 (s, 1H), 7.96 (d, J = 7.4 Hz, 1H), 7.76 (td, J =

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7.8, 1.8 Hz, 1H), 7.20 (ddd, J = 7.5, 4.8, 1.2 Hz, 1H), 6.92 (d, J = 2.4 Hz, 1H), 6.54 (dd, J = 7.4, 2.4 Hz, 1H), 3.87 (s, 3H).

*3-Chloro-7-methoxy-2-(pyridin-2-yl)imidazo[1,2-a]-pyridine (**12**).* To a solution of **11b** (100 mg, 0.44 mmol) in ACN (5 mL) was added *N*-chlorosuccinimide (59.28 mg, 0.44 mmol), and the mixture was stirred at room temperature for 4 h. After the reaction was complete, all the volatiles were removed under vacuum. The residue was diluted with CH_2Cl_2 and washed with a saturated solution of NaCl. The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by RP chromatography (40−60% MeOH:H_2O) to give the title compound as light orange solid (57 mg, 50%). LCMS $[M + H]^+$ 260.1 m/z.[a] ^{1}H NMR (500 MHz, $CDOD_3$) δ 8.67 (d, J = 4.9 Hz, 1H), 8.23 (d, J = 7.5 Hz, 1H), 8.05 (d, J = 7.9 Hz, 1H), 7.93 (td, J = 7.8, 1.8 Hz, 1H), 7.39 (dd, J = 7.5, 5.0 Hz, 1H), 6.95 (d, J = 2.4 Hz, 1H), 6.84 (dd, J = 7.5, 2.4 Hz, 1H), 3.93 (s, 3H).

*2-(Pyridin-2-yl)imidazo[1,2-a]pyridine-3-carbaldehyde (**13**).* A mixture of DMF (7.5 mL) and $POCl_3$ (7.5 mL) was stirred in an ice bath for 15 min under argon. After being warmed to room temperature, it was stirred for 30 min. Then, **10** (490 mg, 2.5 mmol) in CH_2Cl_2 (60 mL) was added. Then the temperature was raised to 70 °C, and the mixture was stirred for additional 2 h. The reaction mixture was cooled to room temperature, and slowly poured into NH_3 H_2O under ice-cold conditions. After being warmed to room temperature, the reaction mixture was further stirred for 30 min and extracted with CH_2Cl_2. The organic layers were combined, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The pure product was obtained as a white solid (300 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.04 (s, 1H), 9.75 (d, J = 7.0 Hz, 1H), 8.72 (d, J = 4.3 Hz, 1H), 8.36 (d, J = 8.2 Hz, 1H), 7.87 (t, J = 7.8 Hz, 1H), 7.81 (d, J = 9.0 Hz, 1H), 7.57 (t, J = 8.0 Hz, 1H), 7.33−7.42 (m, 1H), 7.13 (t, J = 6.8 Hz, 1H).

*4-Fluoro-N-{[2-(pyridin-2-yl)imidazo[1,2-a]pyridin-3-yl]-methyl}aniline (**14**).* To a suspension of previously prepared aldehyde **13** (110 mg, 0.49 mmol)[23] in MeOH (2 mL), acetic acid (141 μL, 2.46 mmol) is added, followed by 4-fluoroaniline (109 mg, 0.93 mmol) and $NaCNBH_3$ (124 mg, 1.97 mmol). After stirring for 1 h, the reaction was quenched with $NaHCO_3$ solution and extracted with EtOAc, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield the title compound as a faint beige powder (560 mg, quantitative). The residue was used in the subsequent reaction without purification. LCMS $[M + H]^+$ 319.1 m/z.[b] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 4.7 Hz, 1H), 8.26 (d, J = 7.8 Hz, 1H), 8.20 (d, J = 6.6 Hz, 1H), 7.81 (t, J = 7.8 Hz, 1H), 7.65 (d, J = 9.0 Hz, 1H), 7.23 (d, J = 7.0 Hz, 2H), 6.80−6.99 (m, 3H), 6.67−6.80 (m, 2H), 5.02 (s, 2H), 4.52 (br. s., 1H).

*2-(Pyridin-2-yl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole (**15a**).* Compound **15a** was synthesized using 3,4-dihydro-2*H*-pyrrol-5-amine hydrochloride (521 mg, 4.32 mmol) according to General Procedure E. The crude product was then purified by flash chromatography (0−10% MeOH in CH_2Cl_2) to yield the title compound as an orange solid (242 mg, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89−8.82 (m, 1H), 8.38−8.30 (m, 1H), 7.94 (dt, J = 7.9, 2.0 Hz, 1H), 7.19−7.14 (m, 1H), 7.13 (s, 1H), 3.88 (t, J = 7.0 Hz, 2H), 2.80 (t, J = 7.6 Hz, 2H), 2.57−2.43 (m, 2H).

*3-Bromo-2-(pyridin-2-yl)-6,7-dihydro-5H-pyrrolo[1,2-a]-imidazole (**15b**).* To a solution of the **15a** (150 mg, 0.81 mmol) in CH_2Cl_2 (4 mL) was added *N*-bromosuccinimide (151 mg, 0.85 mmol) and the mixture was stirred at 25 °C for 1 h. On completion, the volatiles were evaporated. The residue was diluted with EtOAc and washed with a saturated solution of $NaHCO_3$ and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the desired product as a brown solid, which was used without further purification (205 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (ddd, J = 4.9, 1.8, 0.9 Hz, 1H), 7.93 (dt, J = 8.0, 1.1 Hz, 1H), 7.66 (ddd, J = 8.1, 7.5, 1.9 Hz, 1H), 7.11 (ddd, J = 7.5, 4.9, 1.2 Hz, 1H), 3.98−3.90 (m, 2H), 3.00−2.90 (m, 2H), 2.64−2.50 (m, 2H).

*3-Phenyl-2-(pyridin-2-yl)-6,7-dihydro-5H-pyrrolo[1,2-a]-imidazole (**16a**).* Synthesized as reported in a previous study.[24]

*2-(Pyridin-2-yl)-3-(o-tolyl)-6,7-dihydro-5H-pyrrolo[1,2-a]-imidazole (**16b**).* Synthesized as reported in a previous study.[24]

*3-(3,4-Dichlorophenyl)-2-(pyridin-2-yl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole (**16c**).* Synthesized as reported in a previous study.[24]

*3-(3,4-Dimethoxyphenyl)-2-(pyridin-2-yl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole (**16d**).* Synthesized as reported in a previous study.[24]

*3-(3,5-Dimethoxyphenyl)-2-(pyridin-2-yl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole (**16e**).* Compound **16e** was prepared using **15** (75 mg, 0.28 mmol) and 2-(3,5-dimethoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (98 mg, 0.37 mmol) according to General Procedure D. The crude product was purified by reverse phase chromatography (35−100% MeOH:-H_2O) to yield the title compound as a faint beige solid (21 mg, 22%). LCMS $[M + H]^+$ 322.0 m/z.[b] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (d, J = 4.4 Hz, 1H), 7.52−7.61 (m, 2H), 7.05 (ddd, J = 1.2, 5.4, 6.6 Hz, 1H), 6.59 (d, J = 2.0 Hz, 2H), 6.44 (t, J = 2.0 Hz, 1H), 3.98 (t, J = 7.3 Hz, 2H), 3.74 (s, 6H), 2.98 (t, J = 7.3 Hz, 2H), 2.55−2.66 (m, 2H).

*2-(Pyridin-2-yl)-3-(m-tolyl)-6,7-dihydro-5H-pyrrolo[1,2-a]-imidazole (**16f**).* Synthesized as reported in a previous study.[24]

*3-(3-Chlorophenyl)-2-(pyridin-2-yl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole (**16g**).* Compound **16g** was prepared using **15** (75 mg, 0.28 mmol) and (3-chlorophenyl)boronic acid (58 mg, 0.37 mmol) according to General Procedure D. The crude product was purified by reverse phase chromatography (35−100% MeOH−H_2O) to yield the title compound as a colorless solid (10 mg, 12%). LCMS $[M + H]^+$ 296.2 m/z.[a] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (d, J = 3.9 Hz, 1H), 7.70 (d, J = 8.3 Hz, 1H), 7.61 (dt, J = 1.6, 7.8 Hz, 1H), 7.47 (d, J = 1.5 Hz, 1H), 7.28−7.37 (m, 3H), 7.05−7.10 (m, 1H), 3.99 (t, J = 7.3 Hz, 2H), 3.01 (t, J = 7.3 Hz, 2H), 2.65 (quin, J = 7.3 Hz, 2H).

*2-(Pyridin-2-yl)-3-(pyridin-3-yl)-6,7-dihydro-5H-pyrrolo-[1,2-a]imidazole (**16h**).* Compound **16h** was prepared using **15** (75 mg, 0.28 mmol) and pyridin-3-ylboronic acid (45 mg, 0.37 mmol) according to General Procedure D. The crude product was purified by reverse phase chromatography (35−100% MeOH:H_2O) to yield the title compound as a colorless solid (10 mg, 11%). LCMS $[M + H]^+$ 263.1 m/z.[a] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (d, J = 1.5 Hz, 1H), 8.57 (dd, J = 1.5, 4.9 Hz, 1H), 8.38−8.43 (m, 1H), 7.85 (td, J = 1.9, 7.8 Hz, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.64 (dt, J = 1.9, 7.8 Hz, 1H), 7.30−7.37 (m, 1H), 7.08 (ddd, J = 1.5, 4.9, 7.3 Hz, 1H), 4.01 (t, J = 7.1 Hz, 2H), 3.03 (t, J = 7.6 Hz, 2H), 2.68 (quin, J = 7.3 Hz, 2H).

*5-(2-(Pyridin-2-yl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-3-yl)picolinonitrile (**16i**).* Synthesized as reported in a previous study.[24]

*3-(2-(Pyridin-2-yl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-3-yl)benzonitrile (**16j**).* Synthesized as reported in a previous study.[24]

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*2-(Pyridin-2-yl)-3-(pyridin-4-yl)-6,7-dihydro-5H-pyrrolo-[1,2-a]imidazole (**16k**).* Compound **16k** was prepared using **15** (75 mg, 0.28 mmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (76 mg, 0.37 mmol) according to General Procedure D. The crude product was purified by reverse phase chromatography (35−100% MeOH−H_2O) to yield the title compound as a colorless solid (12 mg, 16%). LCMS $[M + H]^+$ 263.1 *m/z*.[a] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (d, J = 6.3 Hz, 2H), 8.45 (d, J = 4.9 Hz, 1H), 7.79 (d, J = 7.8 Hz, 1H), 7.67 (dt, J = 1.5, 7.8 Hz, 1H), 7.34−7.41 (m, 2H), 7.13 (dd, J = 5.4, 6.8 Hz, 1H), 4.06 (t, J = 7.1 Hz, 2H), 3.03 (t, J = 7.6 Hz, 2H), 2.69 (quin, J = 7.3 Hz, 2H).

*3-(2-Fluoropyridin-4-yl)-2-(pyridin-2-yl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole (**16l**).* Synthesized as reported in a previous study.[24]

*4-(2-(Pyridin-2-yl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-3-yl)benzonitrile (**16m**).* Synthesized as reported in a previous study.[24]

*2-Methoxy-4-(2-(pyridin-2-yl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-3-yl)benzonitrile (**16n**).* Synthesized as reported in a previous study.[24]

*4-(2-(Pyridin-2-yl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-3-yl)-2-(trifluoromethyl)benzonitrile (**16o**).* Synthesized as reported in a previous study.[24]

*3-(4-Chlorophenyl)-2-(pyridin-2-yl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole (**16p**).* Synthesized as reported in a previous study.[24]

*3-(4-Fluorophenyl)-2-(pyridin-2-yl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole (**16q**).* Synthesized as reported in a previous study.[24]

*2-(Pyridin-2-yl)-3-(p-tolyl)-6,7-dihydro-5H-pyrrolo[1,2-a]-imidazole (**16r**).* Synthesized as reported in a previous study.[24]

*2-(Pyridin-2-yl)-3-(4-(trifluoromethyl)phenyl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole (**16s**).* Synthesized as reported in a previous study.[24]

*2-(Pyridin-2-yl)-3-(4-(trifluoromethoxy)phenyl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole (**16t**).* Synthesized as reported in a previous study.[24]

*3-(4-(Methylsulfinyl)phenyl)-2-(pyridin-2-yl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole (**16u**).* Synthesized as reported in a previous study.[24]

*3-(4-(Methylsulfonyl)phenyl)-2-(pyridin-2-yl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole (**16v**).* Synthesized as reported in a previous study.[24]

*N,N-Dimethyl-4-(2-(pyridin-2-yl)-6,7-dihydro-5H-pyrrolo-[1,2-a]imidazol-3-yl)benzamide (**16w**).* Synthesized as reported in a previous study.[24]

*1-(4-(2-Pyridin-2-yl)-6,7-dihydro-5H-pyrrolo[1,2-a]-imidazol-3-yl)phenyl)ethan-1-one (**16x**).* Synthesized as reported in a previous study.[24]

*4-(2-(Pyridin-2-yl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-3-yl)aniline (**16y**).* Synthesized as reported in a previous study.[24]

*2-Methyl-5-(2-(pyridin-2-yl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-3-yl)benzo[d]thiazole (**16z**).* Synthesized as reported in a previous study.[24]

*7-(2-(Pyridin-2-yl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-3-yl)quinoline (**16aa**).* Synthesized as reported in a previous study.[24]

*3-(Dibenzo[b,d]thiophen-2-yl)-2-(pyridin-2-yl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole (**16ab**).* Synthesized as reported in a previous study.[24]

*3-(Benzo[b]thiophen-5-yl)-2-(pyridin-2-yl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole (**16ac**).* Synthesized as reported in a previous study.[24]

*3-(Benzo[d][1,3]dioxol-5-yl)-2-(pyridin-2-yl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole (**16ad**).* Synthesized as reported in a previous study.[20]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsinfecdis.3c00040.

Supplementary biological and ADME data; X-ray crystallography data; additional PK parameters; ADME protocols; and synthetic procedures (PDF)

Molecular formula strings (CSV)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

ABT, 1-aminobenzotriazole; ADME, absorption distribution metabolism excretion; Cl_{int}, intrinsic clearance; HLM, human liver microsomes; HTS, high-throughput screen; PO, Per os; LLE, lipophilic ligand efficiency; MLM, mouse liver microsomes; NBS, *N*-bromosuccinimide; NTD, neglected tropical disease; PK, pharmacokinetic; PPB, plasma protein binding; RH, rat hepatocytes; TCP, target candidate profile; TEAC, tetraethylammonium chloride; TPSA, topological polar surface area; VL, visceral leishmaniasis; WHO, World Health Organization

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