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Discovery, synthesis and characterization of a series of 7-aryl-imidazo[1,2-*a*]pyridine-3-ylquinolines as activin-like kinase (ALK) inhibitors

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Graphical Abstract

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Design, synthesis and characterization of a series of 7-aryl-imidazo[1,2-*a*]pyridin-3-ylquinolines as activin-like kinase (ALK) inhibitors

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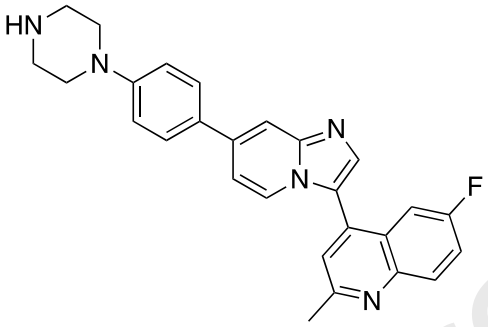

19b
ALK1, IC_{50} = 166 nM
ALK2, IC_{50} = 11 nM
ALK2 (R206H), IC_{50} = 5.6 nM
ALK3, IC_{50} = < 5 nM

CLp = 12.9 mL/min/kg
$t_{1/2}$ (h) = 5.9
%F = 40
B:P = 1.6

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Discovery, synthesis and characterization of a series of 7-aryl-imidazo[1,2-*a*]pyridine-3-ylquinolines as activin-like kinase (ALK) inhibitors

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ABSTRACT

The activin-like kinases are a family of kinases that play important roles in a variety of disease states. Of this class of kinases, ALK2, has been shown by a gain-of-function to be the primary driver of the childhood skeletal disease fibrodysplasia ossificans progressiva (FOP) and more recently the pediatric cancer diffuse intrinsic pontine glioma (DIPG). Herein, we report our efforts to identify a novel imidazo[1,2-*a*]pyridine scaffold as potent inhibitors of ALK2 with good *in vivo* pharmacokinetic properties suitable for future animal studies.

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The bone morphogenetic proteins (BMPs) play critical roles in embryonic pattern formation.[1-3] There have been more than a dozen BMP proteins identified in mammals and these can be further subclassified depending on their structures.[3] The BMP-1 receptors activate intracellular proteins, such as Smad, and have seven different types of receptors, termed activin-like kinase (ALK1-7).[1] Of these, three receptors have been shown to bind BMP ligands during mammalian skeletal development (ALK2, ALK3 and ALK6)[4], in addition to a variety of other disease states such as iron-refractory iron-deficient anemia (IRIDA)[5, 6], non-alcoholic steatohepatitis (NASH)[7], Duchenne muscular dystrophy (DMD)[8, 9], cancer[10-12] and liver fibrosis.[13] More recent, genetic studies have shown that two of these receptors play critical roles in two devastating childhood diseases: fibrodysplasia ossificans progressiva (FOP)[14, 15] and diffuse intrinsic pontine glioma (DIPG).[16, 17] Genetic studies have found that FOP patients and ~20% of DIPG patients experience a gain-of-function mutation in the *ACVR1* gene which encodes ALK2.[18, 19] FOP is an autosomal dominant disorder characterized by heterotopic ossification and is caused by the *ACVR1* mutation; however, the role in DIPG is under study. There are no effective treatments for FOP, although a clinical trial with a monoclonal antibody that blocks Activin A is underway[20], and a trial for an RAR-γ agonist (palovarotene) was recently halted due to safety concerns.[21] Thus, identification of new, small molecules is still a major unmet medical need for this devastating disease.

Our laboratory has been interested in developing a selective ALK2 inhibitor for some time and we have recently published our efforts in the area. In addition, other laboratories have published work on the same pyrazolo[1,5-*a*]pyrimidine scaffold, with the most recent publication possessing the sulfonamide moiety.[22] The first compounds discovered in this area were dorsomorphin (**1**)[23] followed by LDN-193189 (**2**)[24], followed by DMH1 (**3**)[25] and these compounds were shown to be active in *in vivo* models of FOP. These compounds were followed by ML347 (**4**)[26] and LDN-212854 (**5**)[27], two compounds that were ALK2 preferring inhibitors (compared to ALK3, 337-fold and 66-fold selectivity, respectively). More recently, compound **6** was reported as a selective ALK2 inhibitor (715-fold selectivity).[22] In addition to the pyrazolo[1,5-*a*]pyrimidine scaffold, compounds based off the K02288, **7**, trimethoxyaryl moiety, leading to **8**, have been recently reported.[28, 29] Although these compounds represent breakthroughs in the area, they still suffer from some pharmacokinetic (PK) liabilities and thus, new compounds are needed in order to further investigate therapies for these diseases. Herein, we report our efforts toward an imidazo[1,2-*a*]pyridine scaffold as potent ALK inhibitors.

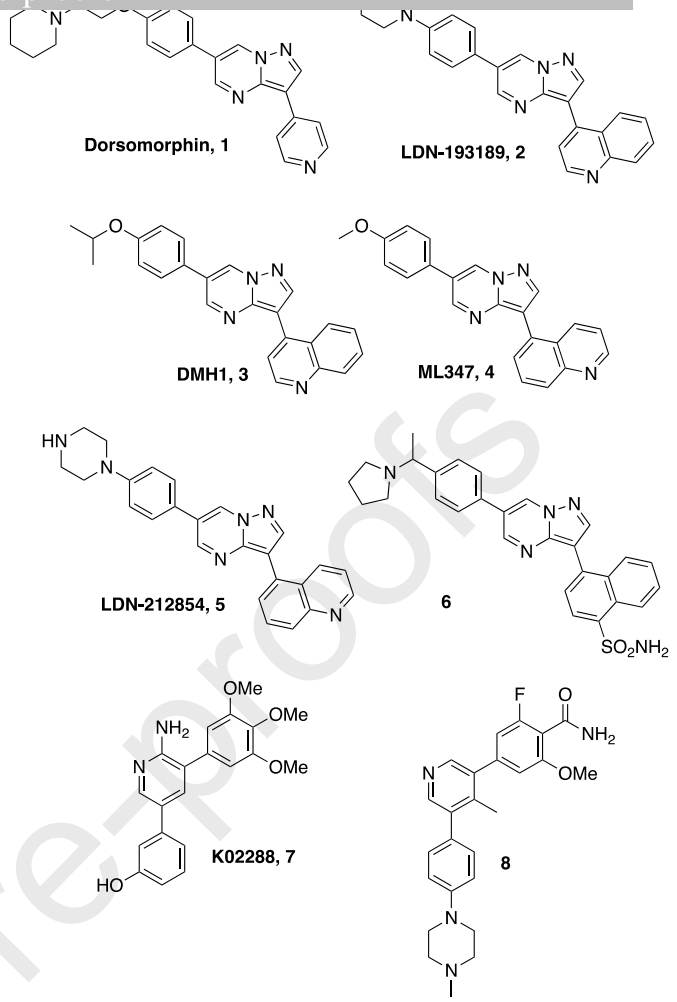
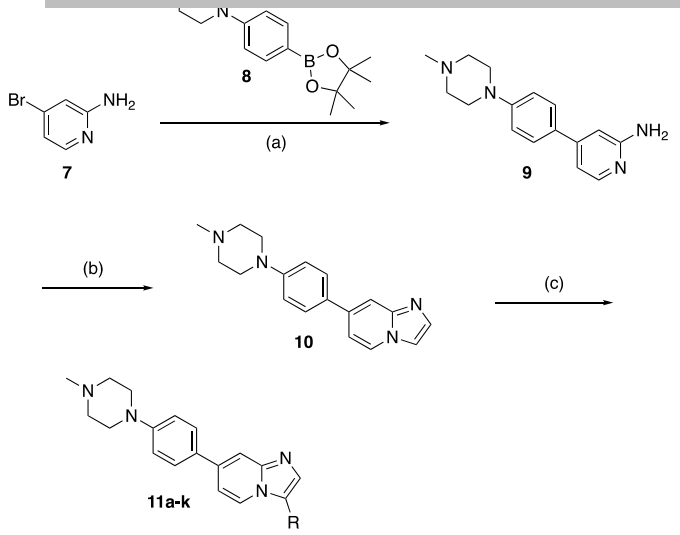


Figure 1. Previously reported pyrazolo[1,5-*a*]pyrimidine scaffold as ALK inhibitors.

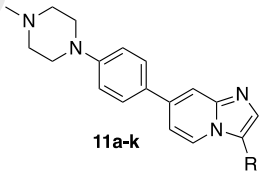
Our efforts were concentrated on the development of a new, core scaffold for this series of compounds. After several attempts, we identified the imidazo[1,2-*a*]pyridine core as a suitable replacement system as potent ALK inhibitors. The synthesis of the imidazo[1,2-*a*]pyridine compounds is shown in Scheme 1. 4-bromo-2-aminopyridine, **7**, was reacted with the boronic ester, **8**, under palladium cross-coupling conditions to yield **9**.[30] Next, the 2-aminopyidine was cyclized to the imidazo[1,2-*a*]pyridine, **10**, using chloroacetaldehyde under basic conditions. The final targets were realized by reacting the appropriate aryl chloride or aryl bromide under palladium catalysis to directly access the coupled products, **11a-k**.

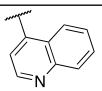
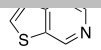
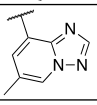
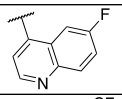
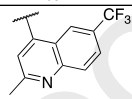
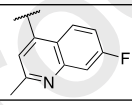
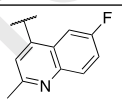
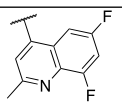


Scheme 1. Synthesis of the imidazo[1,2-*a*]pyridine scaffold. Reagents and conditions: (a) $Pd(dppf)Cl_2$, 1,4-dioxane, K_3PO_4, H_2O, μW, 120 °C, 30 min; (b) chloroacetaldehyde, $NaHCO_3$, EtOH, reflux; (c) R-Cl or R-Br, KOAc, $Pd(OAc)_2$, DMA, μW, 200 °C, 30 min.

Our initial efforts centered around the southern portion of the molecule as represented in Table 1. Starting with the 4-quinoline, **11a**, which has been used in the previous scaffold, was shown to be active against ALK2 (IC_{50} = 24 nM). As this particular moiety has been shown to have significant metabolic liabilities (oxidation of the 2-position), we wanted to move away from the unsubstituted 4-quinoline and thus investigated alternative heterocyclic replacements. The 3-thieno[3,2-*d*]pyrimidine, **11b**, was potent against ALK2 (IC_{50} = 56 nM) and moving the nitrogen one spot to the 3-thieno[2,3-*b*]pyrazine, **11c**, led to a significant improvement in ALK2 potency (IC_{50} = 1 nM). Rearranging the attachment from the 3-position of the 6,5-systems to the 7-position led to compounds **11d-f**. The 7-benzo[*d*]thiazole, **11d**, and 7-thieno[3,2-*b*]pyridine, **11f**, were active against ALK2 (IC_{50} = 10 and 14 nM, respectively), and, interestingly, the 6-methyl-[1,2,4]triazolo[1,5-*a*]pyridine, **11e**, was much less active against ALK2 (IC_{50} = 148 nM). Reinvestigation of the 4-quinoline moiety led to the identification of potent compounds, starting with the 6-fluoro-4-quinoline, **11g** (IC_{50} = 15 nM). Incorporation of a substituent in the 2-position in order to alleviate the metabolic liability (2-methyl), led to compounds that all retained activity (**11i-k**), with the exception of the 2-methyl-6-trifluoromethyl (**11h**), which was much less potent.

Table 1.
SAR around the southern portion of the imidazo[1,2-a]scaffold.



Cmpd	Structure	ALK2[a] (IC_{50}, nM)
11a		24
11b		55.8
11c		1
11d		10.4
11e		148
11f		14
11g		15
11h		135
11i		38.1
11j		17.3
11k		17.8

[a]ALK2 data were obtained at Reaction Biology (Malvern, PA)

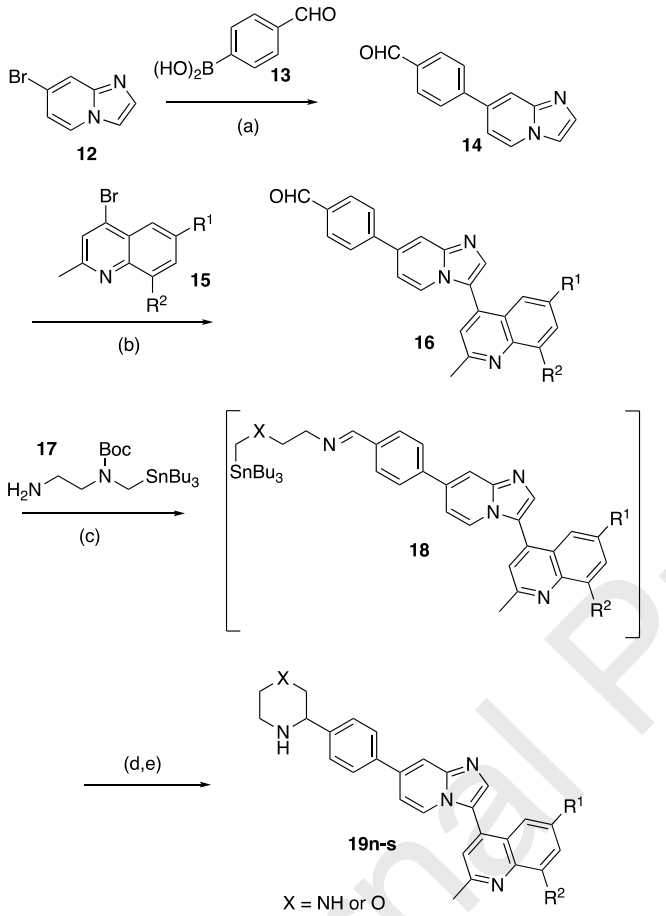
Having identified ALK2 potent compounds, we next evaluated these compounds for hepatic microsomal stability in an established intrinsic clearance assay (Table 2). All of the compounds tested showed high instability in both human and mouse liver microsomes. In order to better understand the reason for the instability, we performed a soft-spot analysis and it was revealed that *N*-demethylation of the piperazine ring was the primary source of instability.

Table 2.
Hepatic microsomal stability of selected compounds.

	Human liver microsomes (mL/min/kg)[a]		Mouse liver microsomes (mL/min/kg)[a]	
Cmpd	CL_{INT}	CL_{HEP}	CL_{INT}	CL_{HEP}
11b	100	17.4	2481	86.8
11d	192	18.9	1263	84.0
11e	47.7	14.6	201	62.1
11j	118	17.8	1492	84.9
11k	120	17.9	1078	83.1
[a]Data obtained at Warren Center for Neuroscience Drug Discovery, Vanderbilt University, Franklin, TN				

In order to identify compounds with better microsomal stability, we investigated alternative substituents on the piperazine system including removal of the *N*-substituent as well as adding steric bulk in order to minimize the demethylation. In addition, we introduced carbon-linked analogs as the *N*-linked analogs could, potentially, release an aniline upon metabolism. These analogs were synthesized as described in Scheme 2. Starting material **12**, was reacted with the boronic acid, **13**, under normal coupling

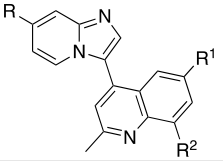
conc ges
bromoquinoline, **15**, was coupled directly with the imidazo[1,2-*a*]pyridine, **14** ($Pd(OAc)_2$, KOAc, μW, 130 °C), to yield the precursor material to the final cyclization. The aldehyde, **16**, was subjected to the initiation of the SnAP chemistry (tin(Sn) Amine Protocol) pioneered by Bode *et al.* by condensation with the respective amino tin reagents, **17**, under anhydrous conditions (4 Å MS, CH_2Cl_2, rt) to yield the imine intermediate, **18**.[31-33] This intermediate was subjected to the copper-mediated cyclization ($Cu(OTf)_2$, HFIP, 2,6-lutidine, CH_2Cl_2, 12 h, rt) to yield the cyclized material, which was then subjected to acid mediated Boc removal to obtain the desired compounds, **19**.

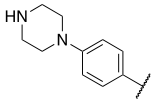
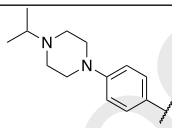
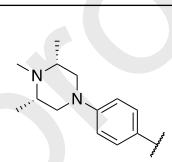
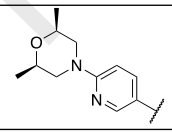
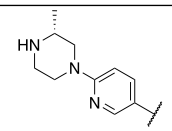
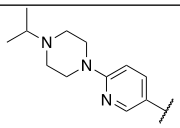
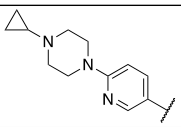
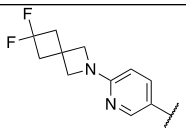
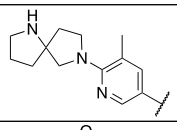
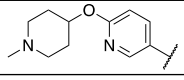
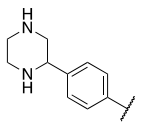


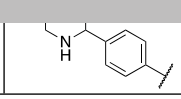
Scheme 2. Synthesis of carbon-linked analogs. Reagents and conditions: (a) Cs_2CO_3, $Pd(dppf)Cl_2$, 1,4-dioxane/H_2O, μW, 120 °C, 15 min., 67%; (b) $Pd(OAc)_2$, KOAc, DMF, μW, 130 °C, 10 min., 68%; (c) 4 Å MS, CH_2Cl_2, 12 h, rt; (d) $Cu(OTf)_2$, HFIP, 2,6-lutidine, CH_2Cl_2, 12 h, rt, 30-50%; (e) when X = NHBoc: TFA, CH_2Cl_2, rt, 12 h, 45-65%.

Having identified three southern quinoline moieties that had ALK2 potency, we utilized these in our next round of SAR as they have also been shown to impart stability to the quinoline ring system (Table 3). We utilized the 2-methyl fluorinated quinolines as the southern moiety for this SAR exploration as these were all shown to be potent. Thus, incorporation of the *N*H-piperazine (**19a-c**) was well tolerated (IC_{50} = 8 – 32 nM). Addition of the larger isopropyl group produced an active compound (**19d**, IC_{50} = <5 nM), and introduction of methyl groups flanking the N-Me piperazine were moderately active (**19e**) to active (**19f**) (IC_{50} = 216 and 32 nM, respectively) as was the bulky morpholine, **19g** (IC_{50} = 46 nM). In addition to the phenyl spacer, we examined the pyridine replacement with good results (**19g-19l**) (IC_{50} = 6.3 – 148 nM). The ether linked compound, however, was inactive (**19m**, IC_{50} = 10,000 nM). Lastly, introduction of the carbon-linked 2-leading to the promising analogs (**19n-s**, IC_{50} = < 5 nM).

Table 3.
SAR around the northern portion of the molecule.



Cmpd	R	R^1	R^2	ALK2[a] (IC_{50}, nM)
19a		H	H	8.0
19b		F	H	10.9
19c		F	F	32.2
19d		F	F	<5
19e		F	H	216
19f		F	F	31.7
19g		H	H	46.3
19h		F	H	14.7
19i		H	H	6.3
19j		H	H	15.6
19k		H	H	148
19l		H	H	37
19m		F	H	>10,000
19n		H	H	<5
19o		F	H	<5
19p		F	F	<5
19q		H	H	<5
19r		F	H	<5

19s		F	F	5.6

[a]ALK2 data were obtained at Reaction Biology (Malvern, PA)

Having identified the next generation of compounds, we tested these compounds for hepatic microsomal stability (Table 4). Removing the *N*-alkyl group improved the stability (**19a-c**) in human and mouse liver microsomes, with **19b,c** being stable in human. Introducing steric bulk to the piperidine ring system provided some improvement (**19d-f**); however, the compounds were not stable enough to progress. Introducing the pyridine ring system as a replacement for the central phenyl ring led to significant instability (**19g,k**). Moving to the carbon-linked series, the piperazine containing compounds showed improved stability over the morpholine based compounds (**19n-o** vs. **19q-s**) in both human and mouse liver microsomes.

Table 4.
Hepatic microsomal stability of selected compounds

	Human liver microsomes (mL/min/kg)		Mouse liver microsomes (mL/min/kg)	
Cmpd	CL_{INT}	CL_{HEP}	CL_{INT}	CL_{HEP}
19a[a]	28.9	12.2	87.7	44.4
19b[a]	12.3	7.7	207	62.7
19c[a]	**0.82**	**0.79**	**131**	**53.4**
19d[a]	33.3	12.9	27.3	21.0
19e[a]	92.4	17.1	130	53.2
19f[a]	113	17.7	186	60.6
19g[a]	106	17.5	265	67.2
19k[a]	98.1	17.3	352	71.7
19n[b]	<23.3	<10.7	<49.5	<32.9
19o[b]	32.8	12.4	<49.5	<32.9
19p[b]	46.7	14.0	<49.5	<32.9
19q[b]	139	17.5	198	97.8
19r[b]	134	17.4	100	47.4
19s[b]	139	17.5	97.1	47.7

[a]Data obtained at Warren Center for Neuroscience Drug Discovery, Vanderbilt University, Franklin, TN. [b]Data obtained at Q2 Solutions, Indianapolis, IN.

Having identified more stable compounds, we next evaluated the compounds in a selectivity panel against the other ALK receptors as well as the important ALK2 mutation (R206H) (Table 5). The lead compounds were all selective against ALK4, ALK5, BMPR2, TGFβR2, KDR and PDGFRβ. Each of the compounds, however, did retain activity against ALK1, ALK3 and ALK6. Importantly, the compounds were potent inhibitors of the R206H mutation in ALK2, an important mutation found in fibrodysplasia ossificans progressiva (FOP), a rare inherited connective tissue disorder. Compounds **19a-c** were also profiled against a 369 kinase panel (Reaction Biology, Malvern, PA) in order to assess their selectivity against a wider range of receptors. The compounds were inactive against the panel with the exceptions of ABL2, TNIK, DDR1, SIK1, SIK2 and LIMK1.

Table 5.
Off-target selectivity of lead compounds **19a-c,n,p**

Receptor	**19a**	**19b**	**19c**	**19n**	**19p**
ALK1/ ACVRL1	39.1	166.3	308.8	<5	89.2
ALK2/ ACVR1 (R206H)	8.0	10.9	32.2	<5	<5
ALK3/ BMPR1A	<5	<5	<5	<5	<5
ALK4	464	568.7	596.1	192	390
ALK5	1,260	1,267	1,285	310	717
ALK6	18.4	29.4	40.9	54.5	188
BMPR2	>10,000	>50,000	>50,000	>50,000	>50,000
TGFβR2	1,250	587.2	170.7	4,590	498
AMPK	>10,000	13,590	18,600	20,000	11,500
KDR	5,930	13,410	20,560	9,350	36,900
PDGFRβ	1,250	7,450	>10,000	2,820	6,903

[a]Selectivity data were obtained at Reaction Biology (Malvern, PA)

Next, we further evaluated the three top compounds based on stability and selectivity in additional assays including plasma protein binding, CYP inhibition and *in vivo* pharmacokinetic (PK) studies in animals to assess their potential as drug candidates (Table 6). The compounds had modest free fraction in both human and mouse plasma (%f_u = 1.0 – 2.2), with **19c** having the best overall binding profile. In addition, the compounds did not have any significant CYP inhibition in the five CYP enzymes tested (1A2, 3A4, 2D6, 2C9, 2C19). Next, we performed an IV/PO pharmacokinetic cross-over study in rats. All three compounds showed modest clearance in rats (CLp = 13 – 17 mL/min/kg) and excellent half-life ($t_{1/2}$ = 5 hr) and showed good oral bioavailability (F = 30 – 45%). Lastly, the compounds were evaluated in a plasma:brain tissue distribution study in order to evaluate their ability to cross the blood-brain barrier (BBB). The compounds were dosed (10 mg/kg) and then measured for brain penetration at 1 h. **19b** showed excellent brain penetration (Brain:Plasma (B:P) 1.6) while **19a** and **19c** displayed modest brain penetration. Overall, these compounds display *in vivo* PK attributes that would be amenable to a once-a-day dosing regimen. Recently, **19b**, was shown to be active in an animal model of iron-refractory iron-deficient anemia (IRIDA), further bolstering this scaffold as a potential translatable scaffold.

Table 6.
Further profiling of the lead compounds[a].

	19a	**19b**	**19c**
Plasma Protein Binding (%F_u)			
hPPB (%f_u)	1.4	1.0	1.4
mPPB (%f_u)	1.8	1.0	2.2
Rat *in vivo* PK			
IV dosing (0.5 mg/kg, 5% DMSO/5% solutol:EtOH (1:1, v:v)/90% saline)			
CLp (mL/min/kg)	17.1	12.9	16.7
$t_{1/2}$ (h)	5.9	5.9	5.4
C_{max} (ng/mL)	133.2	144	83.6
V_{dss} (L/kg)	7.3	5.5	6.8
$AUC_{0-\infty}$ (hr*ng/mL)	489.6	701	503.9
PO dosing (3 mg/kg, suspension, 0.1% Tween80 and 0.5% methyl cellulose)			
$t_{1/2}$ (h)	4.7	3.9	3.8
C_{max} (ng/mL)	127.7	163	95.7
t_{max} (hr)	4	4	4
$AUC_{0-\infty}$ (hr*ng/mL)	1289	1683	920.5
%F	45.3	40.0	29.8
Plasma:Brain Study (10 mg/kg, PO, 1 h)			
Plasma (ng/mL)	240	101	145
Brain (ng/g)	84	163	41
B:P	0.35	1.61	0.3

[a]*In vivo* PK studies performed at Jubilent Biosys.

In summary, we have identified a novel imidazo[1,2-*a*]pyridine scaffold as a new entry into ALK inhibitors. The lead optimization

northern piperazine moiety with 2-methyl-fluorinated quinoline as the southern portion. These compounds are potent ALK2 inhibitors, including the important R206H mutation, and display selectivity against other related receptors. Further profiling showed that these compounds have balanced *in vivo* PK properties (low clearance, oral bioavailability, $t_{1/2}$) amenable to further advancement into IND-enabling studies. Further progression of these lead molecules will be reported in due course.

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Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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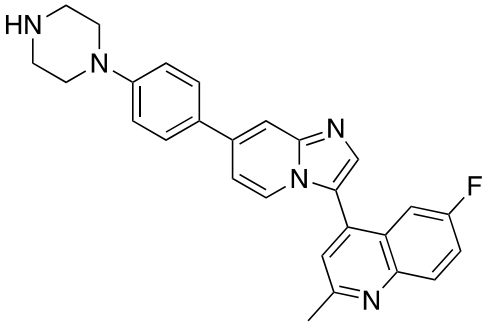
Graphical Abstract:



19b
ALK1, IC_{50} = 166 nM
ALK2, IC_{50} = 11 nM
ALK2 (R206H), IC_{50} = 5.6 nM
ALK3, IC_{50} = < 5 nM

CLp = 12.9 mL/min/kg
$t_{1/2}$ (h) = 5.9
%F = 40
B:P = 1.6