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Synthesis of an aryloxy oxo pyrimidinone library that displays ALK-selective inhibition

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ABSTRACT

We report the synthesis of a pyrimidinone library that targets anaplastic lymphoma kinase (ALK), an oncogenic receptor tyrosine kinase. This library was generated in three steps from a versatile commercially available starting material. Some compounds within this library showed single digit micromolar inhibition of ALK in vitro, while showing minimal inhibition of other homologous insulin receptor family kinases including the human insulin receptor kinase (IRK), at the highest concentrations investigated. We also present initial ALK structure–activity relationships for this library.

Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase (RTK) and a member of the insulin receptor superfamily.[1,2] Mutant forms of ALK, for example, NPM (nucleophosmin) -ALK and EML4 (echinoderm microtubule-associated protein-like 4) -ALK, have been identified as oncogenic drivers in ALCL (anaplastic large cell lymphoma),[3,4] non-small-cell lung cancer,[5,6] and neuroblastoma[7–9] among other malignancies. Furthermore, ALK knock-out mice show no phenotypic abnormalities,[10] suggesting that inhibition of ALK for the treatment of ALK-driven cancers should not be associated with significant target-associated toxicity. The initial clinical success of Pfizer's dual ALK/MET inhibitor PF-2341066[11–14] (crizotinib® **1**, Fig. 1) for the therapy of ALK-driven subsets of lung cancer[6,15] has confirmed the efficacy and safety of ALK inhibition for the management of ALK-driven tumors.

We set out to generate a small library of ALK-selective kinase inhibitors from a flexible and commercially available starting material. Given the ALK-inhibitory activity of PF-2341066, ChemBridge's ALK inhibitor[16] (**2**, Fig. 1), our previously published ALK 'hit' compound[17] (**3**, Fig. 1), and other amino-pyrimidine/pyridines recently reviewed,[18] we envisioned that a pyridone or pyrimidi-

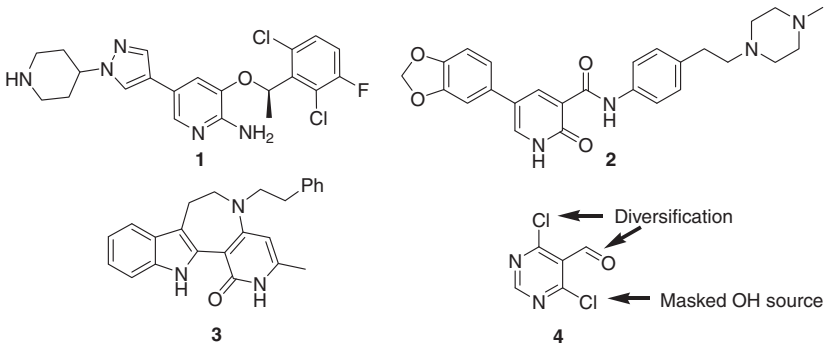

Figure 1. Literature examples of ALK inhibitors.

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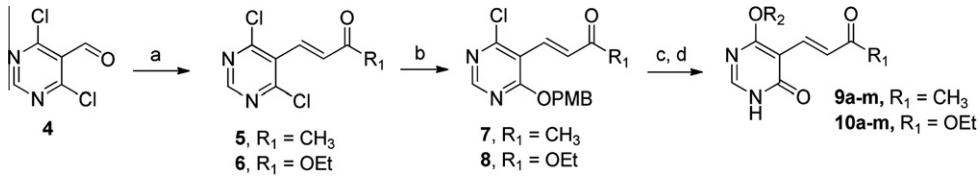
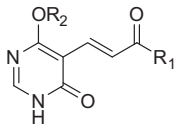
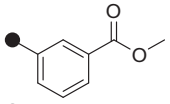
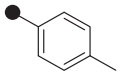
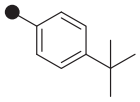
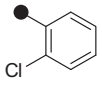
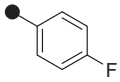
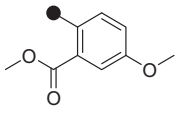
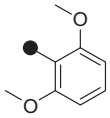
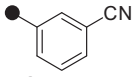
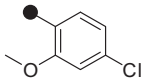
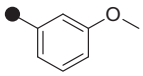
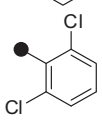


Scheme 1. Reagents and conditions: (a) 1-(triphenylphosphoranylidene)propan-2-one or ethyl 2-(triphenylphosphoranylidene)acetate, THF, 67 °C, 4 h; (b) *para*-methoxy benzyl alcohol, potassium carbonate, neat, 50 °C, 16 h; (c) substituted phenol, potassium carbonate, DME, 80 °C, 16 h; (d) TFA, DCM, rt, 16 h.

Table 1
Yields of phenoxy-displacement/PMB-cleavage reactions and biochemical evaluation of pyrimidinone library versus ALK, IRK and MET using the in vitro enzymatic kinase assay previously reported[17]



ID	R_1	R_2	Yield[a] (%)	ALK IC_{50}[b]	IRK IC_{50}	MET IC_{50}
9a	CH_3		48	3.03	>40	4.01
10a	OEt		59	>40	>40	>40
9b	CH_3		51	>40	>40	>40
10b	OEt		66	>40	>40	>40
9c	CH_3		49	>40	>40	>40
10c	OEt		64	>40	>40	>40
9d	CH_3OEt		35	>40	>40	>40
10d			63	>40	>40	>40
9e	CH_3		33	>40	>40	>40
10e	OEt		60	>40	>40	>40
9f	CH_3		53	>40	>40	>40
10f	OEt		60	>40	>40	>40
9g	CH_3		50	>40	>40	>40
10g	OEt		25	>40	>40	>40
9h	CH_3		27	>40	>40	>40
10h	OEt		84	>40	>40	>40
9i	CH_3		36	>40	>40	>40
10i	OEt		68	>40	>40	>40
9j	CH_3		57	>40	>40	>40
10j	OEt		79	>40	>40	>40
9k	CH_3		25	>40	>40	>40
10k	OEt		12	>40	>40	>40
1				0.6	0.65	0.00078

[a] Yields determined after reverse phase HPLC purification.
[b] All IC_{50} value determinations were done in triplicate and are reported in μM.

none-based library could serve as the starting template for selective ALK-targeted compounds. Since chloropyrimidines are generally more reactive than their pyridine counterpart, we started with the commercially available 2,4-dichloro-pyrimidin-5-carbaldehyde (**4**, Fig. 1). We envisioned that the initial chloride displacement of **4** would allow for the introduction of the masked oxygen component of the pyrimidine, followed by subsequent selective diversification by displacement of the other chloride with various