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Pyrazolone-based anaplastic lymphoma kinase (ALK) inhibitors: Control of selectivity by a benzyloxy group

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ABSTRACT

Anaplastic lymphoma kinase (ALK) is transmembrane receptor tyrosine kinase, with oncogenic variants that have been implicated in ALCL, NSCLC and other cancers. Screening of a VEGFR2-biased kinase library resulted in identification of **1** which showed cross-reactivity with ALK. SAR on the indole segment of **1** showed that a subtle structural modification (the ethoxy group of **1** changed to a benzyloxy to generate **5a**) enhanced potency (ALK), selectivity for VEGFR2 and IR along with improvement in metabolic stability. From docking studies of ALK versus VEGFR2 kinase, we postulated that the loss of entropy of the VEGFR2 in the bound form with **5a** might be the origin of the reduced activity against that protein. Modification of the heterocyclic segment showed that thiazole-bearing pyrazolones preserved enzyme potency, and enhanced inhibition of NPM-ALK autophosphorylation in ALK-positive ALCL cells (Karpas-299). SAR of the benzyloxy group resulted in compounds which demonstrated good cellular potency in Karpas-299 cells. Compound **8** showed best overall profile for the series with broad kinome selectivity and liver micorsome stability. Compound **8** showed reasonable iv PK in rat, but with little oral exposure.

Inhibitor promiscuity remains a divisive topic in kinase-based drug discovery due to the common mode of binding for most inhibitors at the conserved adenosine triphosphate (ATP) pocket.[1] Despite this facet, several ATP-competitive compounds with activity against multiple kinase targets have been approved as drugs. One positive aspect of this paradigm is that the parent molecular scaffolds, in principle, have the potential to serve as launching points for alternative kinase programs via judicious structural modifications and structure–activity relationship (SAR). In this communication, we have utilized this structural re-design process, and successfully translated a member of the hetero-substituted pyrazolones (A, Fig. 1), a known class of vascular endothelial growth factor receptor 2 (VEGFR2) inhibitors[2] into potent and selective anaplastic lymphoma kinase (ALK) inhibitors via introduction of a 4-benzyloxy substituent on the indole segment which purportedly acts as a position specific selectivity determinant.[3]

ALK is a transmembrane receptor tyrosine kinase that was originally identified as a part of the nucleophosmin (NPM)-ALK fusion protein derived from t(2,5)(p23,5q35) chromosomal translocation. This translocation was detected in 60–75% of the ALK-positive anaplastic large-cell lymphoma (ALCL) patients.[4] Moreover, additional ALK chimeras, as well as activating mutations in full length ALK have been found in recent years.[5]

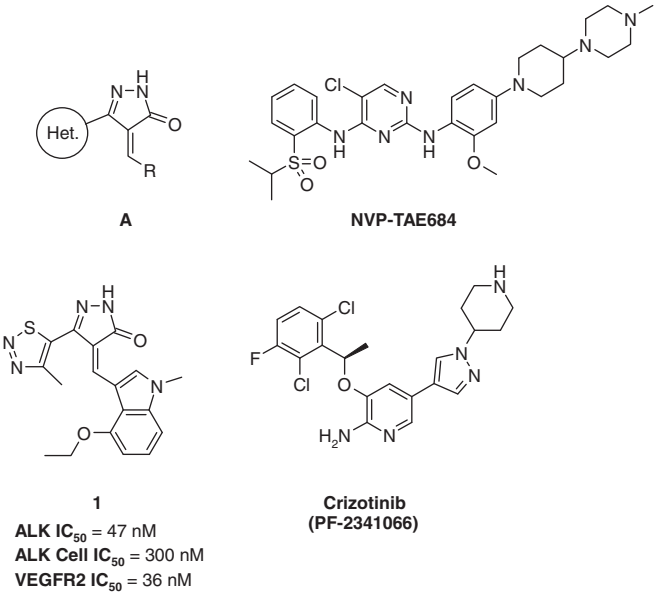

Figure 1. Reported ALK inhibitors and pyrazolones.

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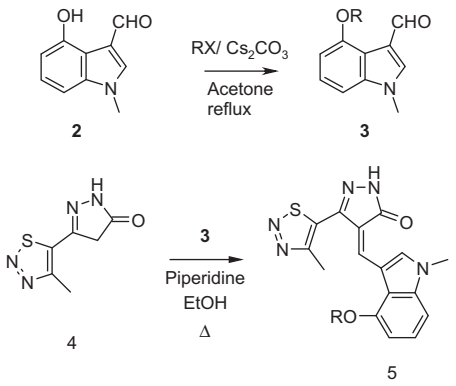


Scheme 1. General synthesis of 4-hydroxy-1-methyl-1*H*-indole-3-carbaldehydes (**3**) and subsequent condensation with the pyrazolone **4**.

Importantly, echinoderm micro-tubule-associated protein-like 4 (EML4)-ALK fusion oncogene has also been identified in non-small cell lung cancer (NSCLC).[5a,b] These ALK fusion genes encode oncoproteins with constitutively active kinases which stimulate anti-apoptotic and mitogenic signaling pathways associated with survival and proliferation of ALCL, NSCLC, and other cancers.[5e]

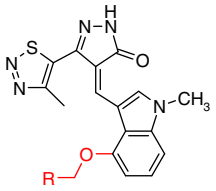
Inhibiting oncogenic signaling through direct ALK kinase inhibition has emerged as an attractive approach to targeted cancer therapy in recent years.[6] Shown in Figure 1 are two prototypical inhibitors in this area of research, a preclinical ALK inhibitor NVP-TAE684[6g] and the c-Met/ALK inhibitor, crizotinib[6i] which recently gained FDA approval for the treatment of ALK-positive NSCLC.

In a program to design ALK inhibitors as a possible therapeutic intervention against such cancers, we screened our internal kinase library, which resulted in identification of a pyrazolone **1** (Fig. 1) as an initial lead from this series. Pyrazolones were designed as a class of potent and selective VEGFR2 kinase inhibitors.[2] The design concept for pyrazolones originated from their structural similarity with the oxindole-based VEGFR2 inhibitors, a series which ultimately provided the drug sunitinib for advanced renal cell carcinoma and malignant gastrointestinal stromal tumor (GIST).[7] The pyrazolone class of compounds can be synthesized readily via condensation of simple, substituted pyrazolones with a suitable aldehyde (generally indole-3-aldehydes or pyrrole-2-aldehydes). As described previously, oral PK has limited the development of this series, ascribed to rapid metabolism, though select members demonstrated acceptable values (cf., $F = 29\%$).[8]

Our initial lead **1** bears a methyl 4-methyl-1,2,3-thiadiazole subunit as the heterocyclic segment that is directly attached to the pyrazolone ring (A, Fig. 1) along with a 4-ethoxy-*N*-methylindole unit. It is potent (IC_{50} values of 47 nM against ALK enzyme and 300 nM in ALK-positive Karpas-299 cell), and has a low molecular weight (367 Da). Ambit KINOMEscan™[9] across a panel of 235 kinases for **1** showed it to be a relatively selective compound, inhibiting only 22 kinases >90% at 1 μM ($S_{90} = 0.09$).[10] Since ALK is a member of insulin receptor (IR)[11] and the inhibition of IR has been documented to impact glucose homeostasis in preclinical animal models, we desired selectivity against this closely related family member.[6h] Importantly, counterscreening of **1** registered 21-fold selectivity against IR (IR $IC_{50} = 998$ nM). The compound **1** also inhibited VEGFR2 kinase with an IC_{50} value of 36 nM as reported earlier.[8] As expected, liver microsome stability (LMS) and rat pharmacokinetics (PK) of **1** were found to be poor with no oral bioavailability.[8] Moreover, aqueous solubility of **1** at pH 7.4 and 2, respectively were low (<1 μg/mL).

Despite the poor aqueous solubility and PK profile, the unique structure of **1** combined with the favorable selectivity profile against IR and the broader kinome warranted further investigation. The challenge, however, was to translate a molecular scaffold, which was initially biased to inhibit a specific kinase (VEGFR2), into another series that would be potent and selective with reduced (or no) affinity for the parent target. Based on the SAR of the internal screening data of the pyrazolones, our initial focus was to modify the 4-ethoxy indole segment of **1** to enhance potency against ALK. As shown in Scheme 1 and 4-hydroxy-1-methyl-1*H*-indole-3-carbaldehyde was alkylated with aryl or heteroaryl methyl halides and the resulting compounds (**3**) were condensed with the pyrazolone **4** in presence catalytic amounts of piperidine at 90 °C. The Knoevenagel condensation products (**5**) were isolated via simple filtration.

Table 1
SAR of the 4-methyl-1,2,3-thiadiazole series



5a-e

Compd	R	ALK IC_{50}[a]	Karpas-299 cell IC_{50}[b]
5a	Ph	23	650
5b	2-Pyridyl	158	–
5c	3-Pyridyl	34	2500
5d	4-Pyridyl	55	1600
5e	2-Me-thiazol-4-yl	2999	–
5f	$Me_2N–CH_2–$	291	–

[a] IC_{50} values are reported as an average of 3 determinations; see Ref. 5d.
[b] Karpas-299 cells; IC_{50} values are reported as a mean of at least two determinations.; see Ref. 5d.

Table 1 shows ALK enzyme and cellular IC_{50} values for **5a–5f**. Compound **5a**, with a benzyloxy substituent, was found to be the most potent, demonstrating an IC_{50} of 23 nM against ALK. Compound **5a** was also found to be twofold more potent than **1** against the enzyme, but was less potent in cells. Benzene replacement of **5a** with pyridyl (**5b–5d**), 2-methyl-thiazole (**5e**) or with an aliphatic segment (**5f**) were found to be less active against the enzyme and ALK-positive ALCL cells (Karpas-299).

Although, **5a** bears an additional aromatic ring (as compared to **1**) LMS data across the species improved dramatically (Table 2). Selectivity against IR also improved considerably (IC_{50} >10 μM). Moreover, the 4-benzyloxy group in **5a** also significantly reduced the affinity for VEGFR2 kinase (Table 2, **5a** vs **1**). This result provided our first structural handle to control selectivity against kinases including IR, VEGFR2 and others.

In order to understand the origin of such selectivity, these ligands (**1** and **5a**) were docked in the ALK (2XB7) and VEGFR2 (3CJG) structures available in the Protein Data Bank (PDB). All the ALK structures in PDB had type I inhibitors with DFG-in structures. VEGFR2 had mostly DFG-out structures for both apo and type I inhibitors. 3CJG is one of the few VEGFR2 structures that

Table 2
Selectivity and liver microsome stability (LMS) of **1** and **5a**

Compd	VEGFR2 IC_{50}[a] (nM)	ALK IC_{50}[a] (nM)	LMS ($t_{1/2}$ in min) human, dog, rat, mouse
1	36	47	6, 5, 5,5
5a	>300	23	32, 29, >40, >40

[a] IC_{50} values are reported as an average of 3 determinations; see Refs. 8 and 5d.

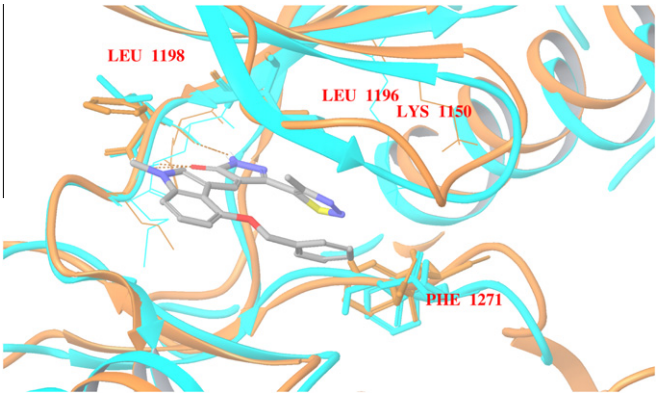
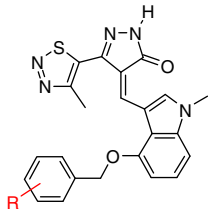


Figure 2. The binding mode of **5a** in ALK is shown in cyan. The binding mode of **5a** in VEGFR2 (orange) was very similar to ALK with a small counter clockwise twist.

Table 3
Effect of benzene substituents on the SAR of the 4-methyl-1,2,3-thiadiazole series



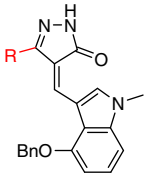
Compd	R	ALK IC_{50}[a] (nM)	Karpas-299 cell[b] (nM)	IR (nM)
5a	H	23	650	>10,000
5g	2-F	13	400	>10,000
5h	3-F	20	1000	>10,000
5i	4-F	12	400	>10,000
5j	2,6-Di-F	12	300	>1000
5k	2,4-Di-F	12	200	>10,000
5l	2-F-6-Cl	21	200	720
5m	2-Cl-3,6-di-F	14	300	661
5n	3-Cl-2,6-di-F	5	400	861

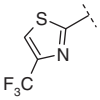
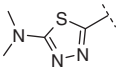
[a] IC_{50} values are reported as an average of 3 determinations; see Ref. 5d.
[b] Karpas-299 cells; IC_{50} values are reported as a mean of at least two determinations.; see Ref. 5d.

had a DFG-in structure. The best scoring binding modes derived by Glide[12] for both **1** and **5a** were consistent with similar ligands, like Sutent,[7] in the PDB. This binding mode is illustrated in Figure 2 (data shown only for **5a**). Even though it was not obvious why the activity of **5a** dropped in VEGFR2 from the docking study with a static DFG-in protein structure, it was not very difficult to interpret the SAR in terms of the high entropy VEGFR2. Several DFG-out VEGFR2 structures either had problem in docking **5a** or had poor docking score. The loss of entropy of the protein in the bound form with **5a** might be responsible for the loss of activity of **5a**.[13]

Based on these encouraging findings, structural modifications of the aromatic group of **5a** were carried out to improve cellular and enzyme potencies against ALK. Table 3 shows SAR for the methyl-thiadiazole series. It was intriguing to find that a variety of halogen substituents on the aromatic ring provided enhancement in potency. A single fluoro substituent on the 2-, 3- and 4-positions of the benezene ring (**5g**–**5i**) provided inhibitors with enhanced potencies over **5a**. However, ALK cellular potency increased only modestly with **5g** and **5i**, and dropped with **5h**. Compounds bearing di- or tri-halo substituents (**5j**–**5n**) also demonstrated acceptable potency against ALK and in one case (**5n**) an IC_{50} value in single digit nM range. However, cellular potency remained in the 200–400 nM range. Moreover, except **5l**–**5n**, all the compounds showed good selectivity against IR.

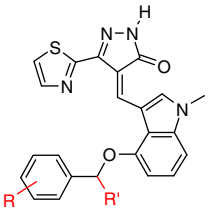
Table 4
Effect of heterocyclic substituents on the SAR of the 4-methyl-1,2,3-thiadiazole replacement series



Compd	R	ALK IC_{50}[a] (nM)
6		54
7		138
8		46
9		10 μM
10		4.6 μM
11		104

[a] IC_{50} values are reported as an average of 3 determinations; see Ref. 5d.

Table 5
Effect of benzyloxy substituents on the SAR of the thiazole series



Compd	R/R′	ALK IC_{50}[a] (nM)	Karpas-299 cell[b] (nM)	IR (nM)
8	H/H	46	300	9124
8a	2-F/H	46	400	>10,000
8b	3-F/H	25	120	>1000
8c	4-F	63	—	—
8d	H/Me	42	500	>10,000
8e	2,6-Di-F/H	9	100	428
8f	2-Cl-6-F/H	13	200	1415
8g	2,3-Di-F/H	14	90	6499
8h	2,5-Di-F/H	17	200	—
8i	2,4-Di-F/H	229	—	—

[a] IC_{50} values are reported as an average of 3 determinations; see Ref. 5d.
[b] Karpas-299 cells; IC_{50} values are reported as a mean of at least two determinations; see Ref. 5d.

We, therefore, turned our attention toward modification of the heterocyclic segment of the inhibitors that is directly attached to the pyrazolone ring to assess impact on potency and physiochemical properties. The condensation of the requisite pyrazolones with 4-benzyloxy-1-methyl-1*H*-indole-3-carbaldehyde was carried out as per the standard protocol to make the final targets **6**–**11** (in very similar fashion as shown in Scheme 1). The pyrazolone starting materials were prepared as per the methods described earlier.[2,8]

As shown in Table 4, thiazole-bearing pyrazolone **8** provided the best result (<50 nM) against ALK. The thiazole compound **8**

Table 6
Profile of the compounds **8**, **8b**, **8e** and **8g**

Compd	ALK Cell IC_{50} (nM)	Selectivity Ambit S_{90}	VEGFR2 (% Inh @ 1 μM)	LMS $t_{1/2}$ (min) H, D, R, M[a]
8	300	0.039[b]	50%	30, 22, 30, 25
8b	120	0.031[c]	50%	10, 8, 8, 6
8e	100	—	—	7, 10, 6, 6
8g	90	—	—	14, 12, 10, 8

[a] H = Human, D = Dog, R = Rat, M = Mouse.
[b] 10/253 kinases showing 90% inh. at 1 μM.
[c] 8/261 kinases showing 90% inh. at 1 μM.

exhibited a cell IC_{50} value of 300 nM (Table 5), which is a slight improvement over the 4-methyl-1,2,3-thiadiazole-based compound **5a**. Moreover, **8** also showed good selectivity against IR.

To improved cellular potency further, substituent effects on the benzyloxy segment of **8** were examined. These results are shown in Table 6. With a single 3-fluoro substituent, **8b** showed ~2-fold improvement in enzyme potency and 2.5-fold increase in ALK cell potency. Selectivity against IR, however, dropped slightly. Addition of a methyl group at the aliphatic carbon of the benzyloxy was not helpful (**8d**). Di-substituted compounds **8e–8g** also showed improvements in enzyme and cellar potencies against ALK. Except for **8e**, selectivity against IR dropped significantly.

The Ambit selectivity profile (S_{90} values) and LMS data for selected thiazole compounds are shown in Table 6. Compounds **8** and **8b** had improved selectivity in comparison to our initial lead (**1**, S_{90} = 0.09). As expected, selectivity improved against VEGFR2 kinase (IC_{50} value of 36 nM for **1** vs 50% inhibition at 1 μM for **8** and **8b**). LMS did not dramatically improve, except for **8**. Halo substituents on the aromatic ring of the benzyloxy group (**8b**, **8e**, and **8g**) did little to enhance stability. Despite acceptable LMS, rat PK data for **8** showed negligible oral exposure, although the iv profile was reasonable (1 mg/kg; $t_{1/2}$ = 0.69 h, V_d = 1.2 L/Kg, Cl = 19.6 mL/min, AUC = 972 ng h/mL, oral at 5 mg/Kg, AUC = 13 ng h/mL).

In conclusion, we have demonstrated that a lead (**1**) from the pyrazolone-based kinase inhibitor series (bearing a 4-methyl-1,2,3-thiadiazole) has been successfully modified to provide potent ALK inhibitors with improved enzyme and cellular potencies, selectivity against IR and other kinases along with enhanced LMS stability. Placement of a 4-benzyloxy group on the indole segment was key structural element acting as a molecular switch to improve selectivity against VEGFR2 kinase. To probe the origin of such selectivity, we carried out modeling of **5a** against ALK and VEGFR2 kinases. Even though it was not obvious why the activity of **5a** dropped in VEGFR2 from the docking study, we postulate that the loss of entropy of that protein in the bound form with **5a** might be responsible for the loss of activity. From the SAR on the heterocyclic part of the inhibitors, thiazole was identified as a good substitute for the 4-methyl-1,2,3-thiadiazole. Benzyloxy modification of the thiazole series resulted in potent compounds **8b**, **8e**, and **8g** with improved cellular activities. The inhibitor **8** had best overall profile with improved kinase selectivity and metabolic stability. The PK data for **8** in rat showed a reasonable iv profile, but with very little oral exposure.

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10. S_{90} value = number of kinases showing 90% inhibition at 1 μM/total number of kinases tested.
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