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Non-oxime pyrazole based inhibitors of B-Raf kinase

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ABSTRACT

The synthesis and biological evaluation of non-oxime pyrazole based B-Raf inhibitors is reported. Several oxime replacements have been prepared and have shown excellent enzyme activity. Further optimization of fused pyrazole **2a** led to compound **38**, a selective and potent B-Raf inhibitor.

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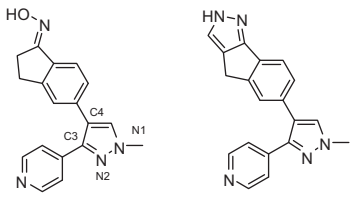
Raf kinases, part of the mitogen-activated protein kinase pathway (MAPK), exist in three isoforms, A-Raf, B-Raf, and C-Raf (Raf-1), have been shown to be critical for mediating cell proliferation and survival.[1] The Ras-Raf-MEK-ERK pathway has been implicated in up to 30% of human cancers. Much focus has been centered around the serine/threonine kinase B-Raf, which is mutated in 7% of human cancers. Activating mutations in Raf have been observed in melanoma (50–70%), thyroid cancers (40–70%), and ovarian cancer (35%).[2] The most frequent mutation in B-Raf is the valine for glutamic acid substitution (V600E), which is found in the activation segment of the B-Raf kinase domain.[3] This accounts for a 500-fold increase in the basal rate of MEK phosphorylation over wild-type B-Raf, essentially rendering ^{V600E}B-Raf constitutively active.[4] This makes B-Raf an attractive target for therapeutic intervention.

Significant effort has been ongoing to develop a potent and selective B-Raf inhibitor. A handful of small molecules that are selective have entered clinical trials, such as PLX-4032, XL-281, and RAF265, with others in preclinical development.[5] We recently reported on pyrazole based B-Raf inhibitors that incorporate an oxime moiety **1a** (Fig. 1).[6] The oxime provides both a donor and acceptor to a hydrogen bond network that is crucial to the potency and selectivity of the series (Fig. 2). However, compound **1a** showed degradation to its indane ketone with a half-life of 1.3 hours in a simulated gastric fluid assay. To address the oxime chemical instability and potential metabolic liability,[7] we sought to identify a suitable compound that retained potency and selectivity.

In our previous Letter,[6] a small number of modified oximes and oxime replacements were reported. The 2,4-dihydroindeno [1,2-*c*]pyrazole (herein referred to as the fused pyrazole) in compound **2a** (Fig. 1) showed excellent enzyme potency, encouraging cellular activity, and no degradation in a simulated gastric fluid assay. Although pyrazole **2a** is a potent inhibitor, the matched indane oxime is significantly more active. We determined that the tautomer preference for the pyrazole does favor the desired donor–acceptor arrangement (Fig. 3a), and that the difference most likely arises from less optimal distances for the NH::Glu501 contact (Fig. 3b). Despite the lower activity, the potential for improvements in metabolic stability inspired us to further develop the fused pyrazole, as well as to explore other compounds that might provide a similar hydrogen bonding network.

We began by exploring the properties of the fused pyrazole (Table 1).[10] By removing the methylene bridge in the fused pyrazole **2a**, the pendant pyrazole **3a** showed a 30-fold drop in potency



1a
BRafIC$_{50}$ = 0.02 nM
pERKIC$_{50}$ = 33 nM

2a
BRafIC$_{50}$ = 2.2 nM
pERKIC$_{50}$ = 1900 nM

Figure 1. Oxime and non-oxime pyrazole based B-Raf inhibitors.

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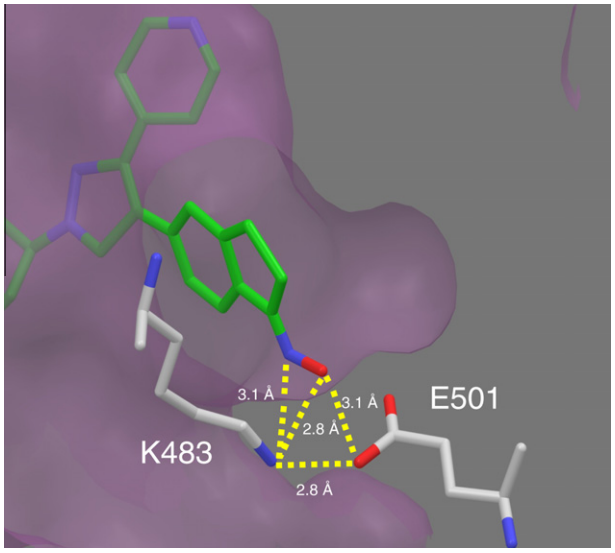
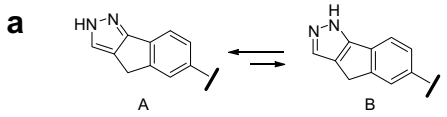


Figure 2. X-ray crystal structure (2.8 Å resolution) of B-Raf in complex with a pyridinyl-pyrazole oxime inhibitor.[8] The view highlights the hydrogen-bonding network that involves the oxime moiety. The indane ring occupies the largely hydrophobic gatekeeper pocket.



Tautomer	E*rel* Kcal/mol	ΔΔG*solv* Kcal/mol
A	0	-11.49
B	1.49	-9.57

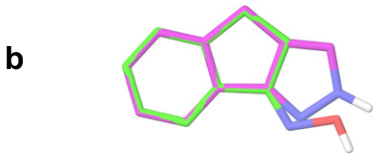
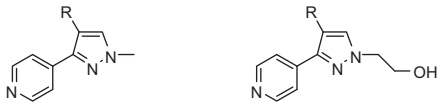
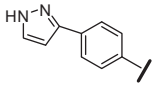
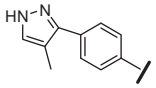
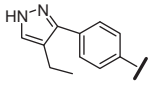
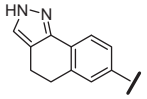
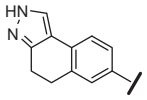
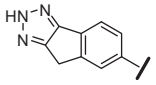
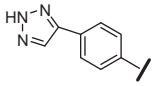
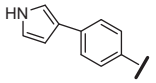
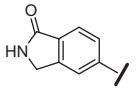
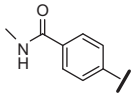
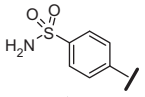
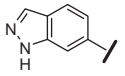
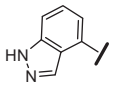
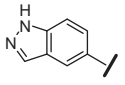
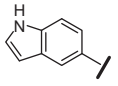
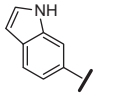
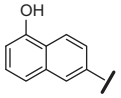


Figure 3. Stereoelectronic comparison of a simplified indane oxime and a fused pyrazole. (a) Relative energies and estimated free energies of solvation for the desired (A) and undesired (B) tautomers of the fused pyrazole suggests that the solution population of A should be dominant.[9] (b) Comparison of the optimized geometries for the oxime (green) and fused pyrazole (violet) suggests that the ring constraint of the pyrazole prevents close approach of the proton donor to Glu501 if the position of the benzo-fusion is to be retained in its hydrophobic pocket; the oxime hydroxyl also benefits from some rotational flexibility.

owing to lost hydrophobic contact of the methylene with Ala481 and Thr529.[11] Methyl substitution on the pendant pyrazole (**4a**) restored a significant amount of this contact, while ethyl substitution proved sterically excessive (**5a**). Tethering the ethyl group into a six-membered fused pyrazole (**6a**) restored most of the activity; the 10-fold drop in potency versus **2a** is likely caused by residual steric crowding in this very tight space. Repositioning of the donor–acceptor pair from the 4,5-dihydro-2*H*-benzo[*g*]indazole **6a** to the 4,5-dihydro-2*H*-benzo[*e*]indazole **7a** causes a loss of potency that underscores the requirement for interaction with Lys483 and Glu501. Fused triazole **8a** and pendant triazole **9a** displayed similar behavior to their pyrazole counterparts. When compared to the pendant pyrazole **3a** and triazole **9a**, pyrrole **10a** was 4–14-fold less potent in the enzyme assay, again emphasizing the importance of the hydrogen bond acceptor for Lys483 (Fig. 2).

Table 1
B-Raf enzyme activity of oxime replacements



Compound	R	B-Raf IC_{50} (nM)
3a		68
4a		7
5a		>1000
6a		23
7a		>1000
8a		11
9a		55
10a		788
11a		94
12a		647
13a		>1000
14a		139
15a		468
16a		>1000
17a		861
18a		328
19a		1.4

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