AXL BIOLOGY & Downstream Effects

- Binding of Gaist to AXL on the tumor cell surface induces AXL autophosphorylation.
- AXL activation induces PI3K-AKT pathway signaling, resulting in upregulation of genes associated with EMT & DNA damage repair leading to therapeutic resistance to multiple agents.

STRUCTURAL BIOLOGY AND RATIONALE OF AXL RECEPTOR Tyrosine Kinase Inhibition

Upon GAS6-induced AXL dimerization, tyrosine residues within the intracellular domain are phosphorylated by action of the intracellular kinase domain, including the catalytic tyrosine (K) residue (Figure 2). Alternatively, phosphorylation is mitigated through small molecule inhibition of the intracellular kinase domain (Figure 3A & 3B).

We embarked upon the design of novel AXL Inhibitors, utilizing a pharmacophore mapping approach based on existing commercial and academic molecules. Axitinib from Phosphorus specifically we sought to avoid AXL and TYRO3 inhibition to reduce any unwanted off-target effects. Due to the high homology of these catalytic domains, design of AXL-selective inhibitors is challenging.

Pharmacokinetics and Safety Characterization

Both Compound A and Compound B exhibit favorable in vitro pharmacokinetic profiles with low hERG and hAXL interaction.

In combination with our in vivo pharmacokinetic studies, we have developed a comprehensive preclinical pharmacokinetic and safety profile.

Study in Vivo Pharmacokinetics

- Table 4. Summary of pharmacokinetic parameters. Rat Compound A was orally administered at 25 mg/kg in 5% DMSO/75% PEG 400 via gavage (p.o.).

CYP Isoform and hERG Inhibition of Compound B

<table>
<thead>
<tr>
<th>Compound</th>
<th>CYP 2A10 (IC50, µM)</th>
<th>CYP 2B6 (IC50, µM)</th>
<th>CYP 2C8 (IC50, µM)</th>
<th>CYP 2C9 (IC50, µM)</th>
<th>CYP 3A4 (IC50, µM)</th>
<th>CYP 1A2 (IC50, µM)</th>
<th>CYP 1B1 (IC50, µM)</th>
<th>hERG IC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound B</td>
<td>0.15</td>
<td>1.8</td>
<td>0.4</td>
<td>0.6</td>
<td>0.8</td>
<td>0.3</td>
<td>0.15</td>
<td>&gt;10000 (data not shown)</td>
</tr>
</tbody>
</table>

Table 3. Summary of hERG IC50 values for various compounds.

<table>
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<tr>
<th>Compound</th>
<th>Rat Pharmacokinetic Parameters</th>
<th>Man Pharmacokinetic Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound A</td>
<td>T1/2 (h)</td>
<td>CL (L/min/kg)</td>
</tr>
<tr>
<td>Compound B</td>
<td>T1/2 (h)</td>
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</tr>
</tbody>
</table>

Table 4. Summary of pharmacokinetic parameters. Rat Compound A was orally administered at 25 mg/kg in 5% DMSO/75% PEG 400 via gavage (p.o.).

REFERENCES


SUMMARY

- Two unique AXL inhibitors have been discovered and characterized in functional biochemical and cellular assays.
- These inhibitors showed improved potency and selectivity compared to previous small-molecule AXL inhibitors (Table 1).
- Compound B showed a good pan-linac kinase selectivity profile, suggesting minimal off-target effects within the inhibitor class.
- In vitro kinase selectivity is low hAXL and hERG IC50s (Table 2).
- Both AXL inhibitors show promising pharmacokinetic profiles with low in vivo clearance and desirable half-lives.
- Compound B exhibited a good safety profile, with no observed CYP and hERG inhibition (Tables 3 & 4).

Figure 2. Kinase Selectivity of Arcus AXL Inhibitors

- Table 1. Characterization and comparison of optimized AXL and benchmark BTK inhibitors.

Table 2. Characterization and comparison of optimized AXL and benchmark BTK inhibitors.

- Table 3. Summary of hERG IC50 values for various compounds.

- Table 4. Summary of pharmacokinetic parameters. Rat Compound A was orally administered at 25 mg/kg in 5% DMSO/75% PEG 400 via gavage (p.o.).