

# SDDC Early Lead Target Profile - TB

An EarlyLead series should be exemplified by at least one compound which fulfills ALL the attributes shown below

A Qualified Hit Series (HTL start) should be exemplified by > 3 compounds which fulfill the attributes shown below

Attribute	ELTP criteria	Hit-to-Lead Start (QHS) criteria
<b>In vitro assays and potency</b>		
Primary potency (enzyme assay, IC <sub>50</sub> nM)	< 200	< 500
<i>In vitro</i> MIC90 in H37Rv (nM)	< 350	< 500
<i>In vitro</i> MIC90 in common drug resistant strains (nM)	< 500	NOT REQUIRED
Average MIC90/primary potency ratio	< 10	< 10
Relationship between enzyme potency and MIC understood	YES	YES
<b>DMPK, potential safety liabilities</b>		
<i>In vitro</i> metabolic stability: CL <sub>int</sub> in human & mouse MS (Heps)	<50% LBF in both	<70% LBF in both
<i>In vitro</i> plasma stability (mouse, human)	Stable, Stable	Stable, Stable
<i>In vitro</i> plasma protein binding (mouse, human)	<95%	<98%
CYP inhibition: 5 major human isoforms (IC <sub>50</sub> μM)	>10	>10 for 3 of 5 isoforms
<i>In vivo</i> Cl (hepatic extraction % LBF) in rat or mouse	<30%	<50%
<i>In vivo</i> oral BioA (%), oral exposure in rat or mouse	>20	Oral exposure at achievable <i>in vivo</i> dose
<b>Potential safety liabilities</b>		
hERG liability: IC <sub>50</sub> μM (E-phys)	> 20, hERG SAR understood	>5, average
Ames test: +/- SP	Negative	Negative
Safety panel broad screening	No significant issues	Potential series-related issues identified
<b>Target Validation, in vivo efficacy</b>		
Xray co- structure with hit(s)	YES, several	YES
<i>In vivo</i> acute M tb infection in mouse (po dosing)	>1 log reduction at acute tolerated dose	NOT REQUIRED
Evidence of on-target cidal effect on M tb <i>in vitro</i>	YES	YES
<b>Drug-like properties properties</b>		
Average solubility for (n) active cpds, stability in pH7.4 buffer (μM)	>50 ( 5 cpds) , stable	>10, stable
Average LLE (calcd. from primary potency) for (n) active compounds	>3 (5 cpds)	NOT REQUIRED
Average of cLogP for (n) active compounds	<4 ( 5 cpds)	<4 (3 cpds)
Average of MW for (n) active compounds	<450 (5 cpds)	<500 (3 cpds)