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Identification of 3-substituted-6-(1-(1*H*-[1,2,3]triazolo[4,5-*b*]pyrazin-1-yl)ethyl)quinoline derivatives as highly potent and selective mesenchymal-epithelial transition factor (c-Met) inhibitors via metabolite profiling-based structural optimization

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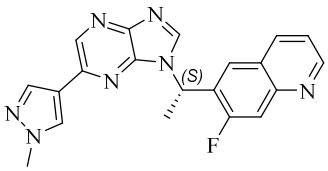
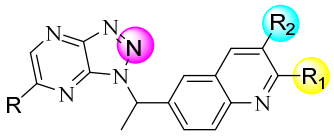


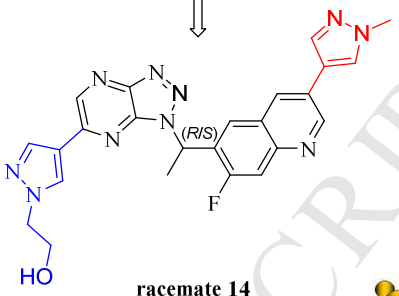
compound 1

IC_{50} = 1.45 nM (enzyme)
IC_{50} = 24.7 nM (H1993)
IC_{50} = 11.8 nM (SNU-5)

Metabolite profiling-based structural optimization



Filtration by SAR studies



racemate 14

IC_{50} = 0.6 nM (enzyme)
IC_{50} = 1.1 nM (H1993)
IC_{50} = 2.0 nM (SNU-5)
$T_{1/2}$ = 3.7 h F = 12.1%

Xenograft models
H1993 TGI (10mg/kg): 90.8%
SNU-5 PTR (3mg/kg): 87.9%