Glecaprevir (ABT-493)

abbvie

ENANTA Pharmaceuticals

- First proof-of-concept in the P2-P4 macrocyclic series by evaluation of different core structures for next-generation HCV protease inhibitor with pan-genotypic activity, excellent activity against resistant mutants, and favorable pharmacokinetic properties
- Targets HCV NS3 and NS4A genes
- Acylsulfonamide improves potency and metabolic stability
- Difluoroalkyl cyclopentyl ether linker improves metabolic stability and yields approximately a 4-fold improvement in antiviral activity without significant PPAR-γ activity
- In a 5 mg/kg iv dose rat PK study possess a plasma half-life of 2.8 h and AUC of 25 μg h/mL with an oral bioavailability of 90%
- Active against a replicon-containing protease from genotype 3, the most difficult-to-treat HCV genotype
- Maintains activity against replicons containing key resistance-associated substitutions for NS5A and NS5B inhibitors

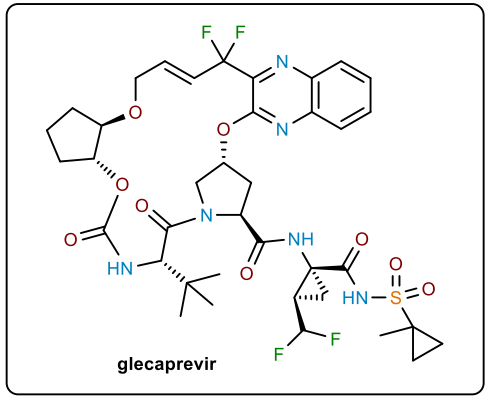
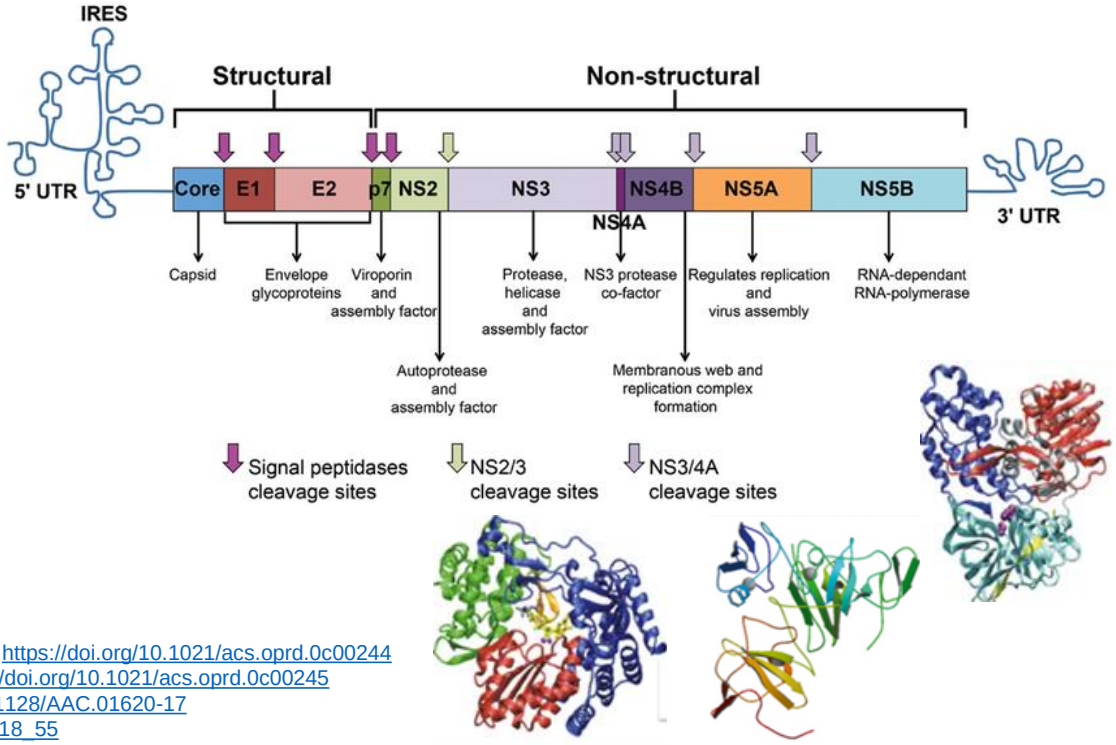


TABLE 1 Activity of glecaprevir against HCV NS3/4A proteases and human proteases in biochemical assays

Protease	HCV subtype or human protease[a]	Mean IC_{50} ± SD (nM)[b]
HCV	GT1a	4.6 ± 0.76
	GT1b	8.9 ± 1.6
	GT2a	3.5 ± 0.22
	GT2b	3.8 ± 0.96
	GT3a	7.9 ± 0.29
	GT4a	6.1 ± 1.9
	GT5a	8.1 ± 0.93
	GT6a	11.3 ± 1.8
Human	Chymase	>200,000
	Chymotrypsin type II	>200,000
	Chymotrypsin type VII	>200,000
	Elastase	>200,000
	Kallikrein	>200,000
	Urokinase	>200,000
	Cathepsin B	>200,000

[a]GT, genotype.
[b]Values were determined in ≥3 independent experiments. IC_{50}, half-maximal (50%) inhibitory concentration.



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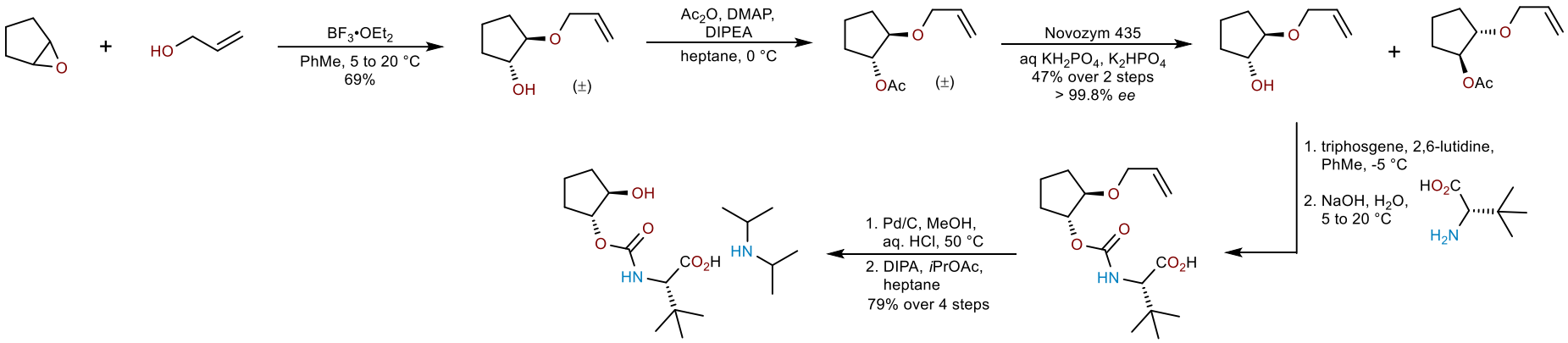

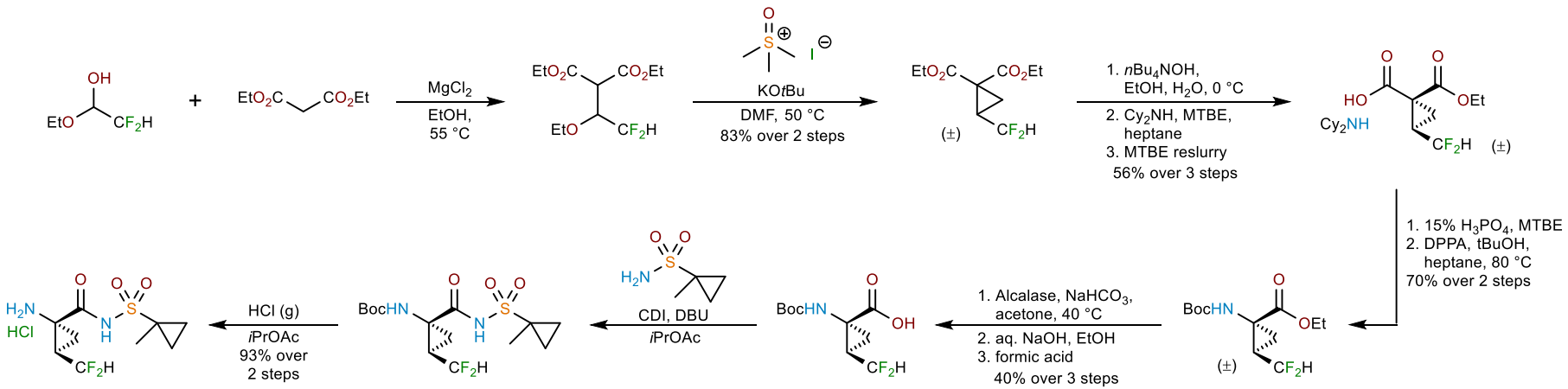

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