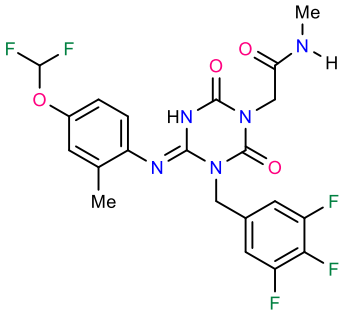
Ensitrelvir

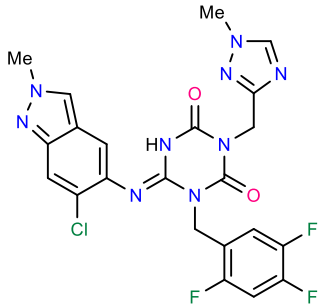
Introduction



initial screening hit

optimization of structure

>600 fold activity improvement



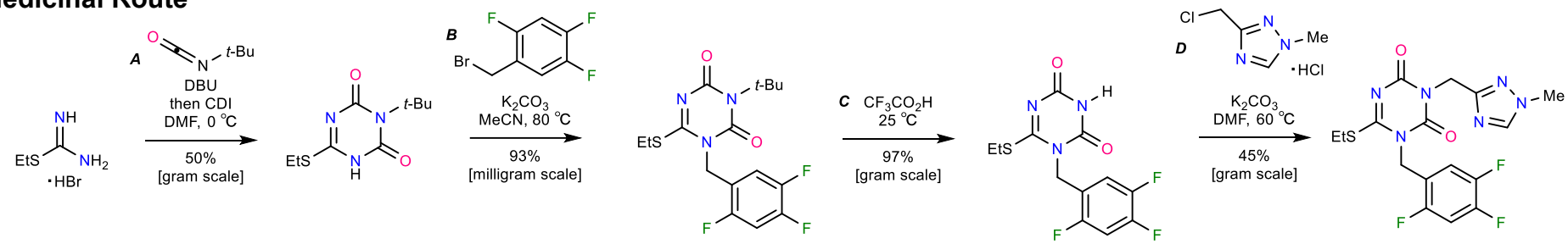
S-217622
Ensitrelvir

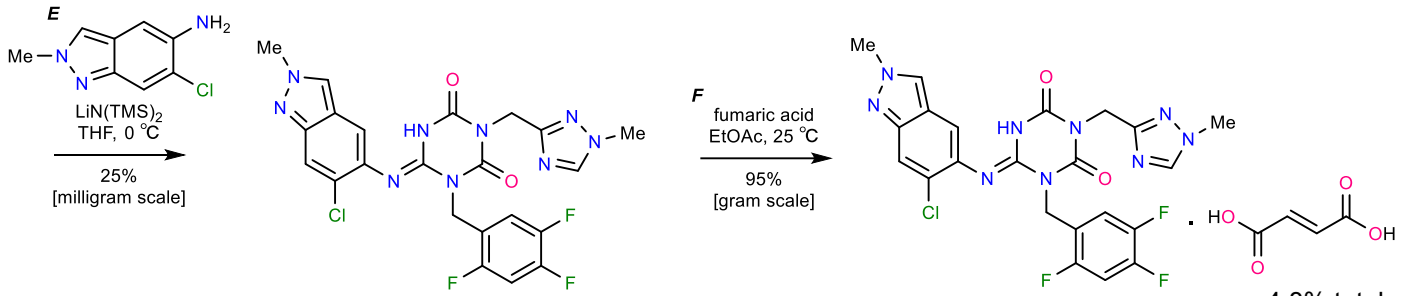
- Noncovalent oral SARS-CoV-2 3CL Protease Inhibitor
- SARS-CoC-2 3CLpro IC_{50}: 0.013 μM
- Favorable DMPK profile
  a. low total clearance
  CL_{tot} = 0.29 mL/min/kg (for monkey), 0.17 mL/min/kg (for dog)
  b. long elimination half times: 10.0 h (for monkey), 29.5 h (for dog)

SHIONOGI

Tachibana, Y. et al. *J. Med. Chem.* **2022**, *26*, 648. https://pubs.acs.org/doi/10.1021/acs.jmedchem.2c00117
Kawajiri, T. et al. *ACS. Cent. Sci.* **2023**, *9*, 836. https://pubs.acs.org/doi/10.1021/acscentsci.2c01203

Medicinal Route





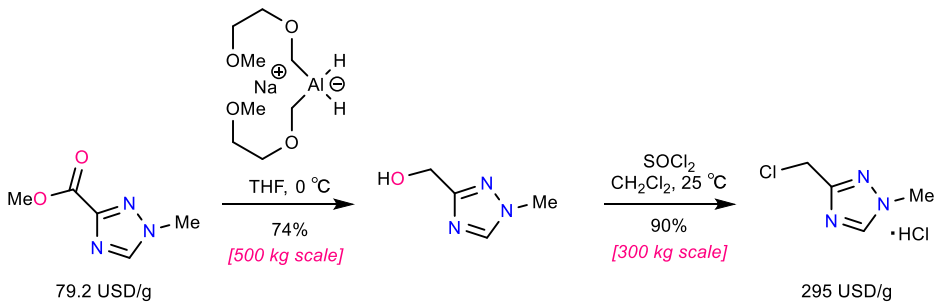
co-crystal of Ensitrelvir with fumaric acid
- excellent solubility and stability

- 4.8% total yield (6 steps)
- two N-containing heteroaromatics are expensive
- rotavap of TFA (solvent amount, step C)
- generation of thiol derivatives (step E)
- silica gel column chromatography (step B, D, and E)

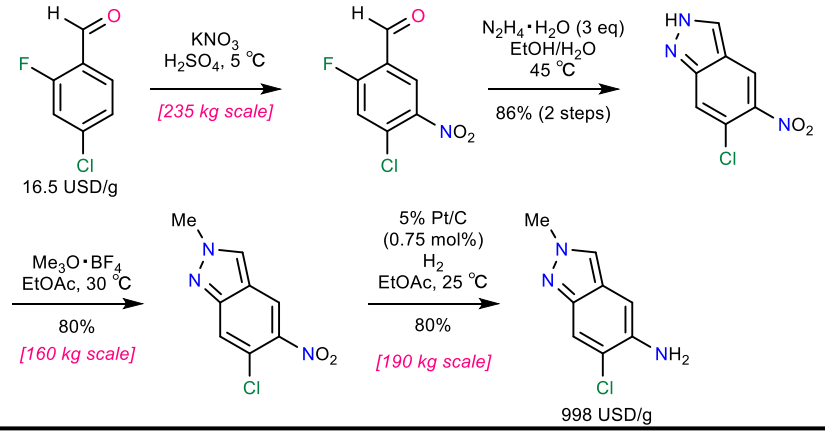
Ensitrelvir

Optimization of fragment syntheses

*1,2,4-triazole motif for step **D***

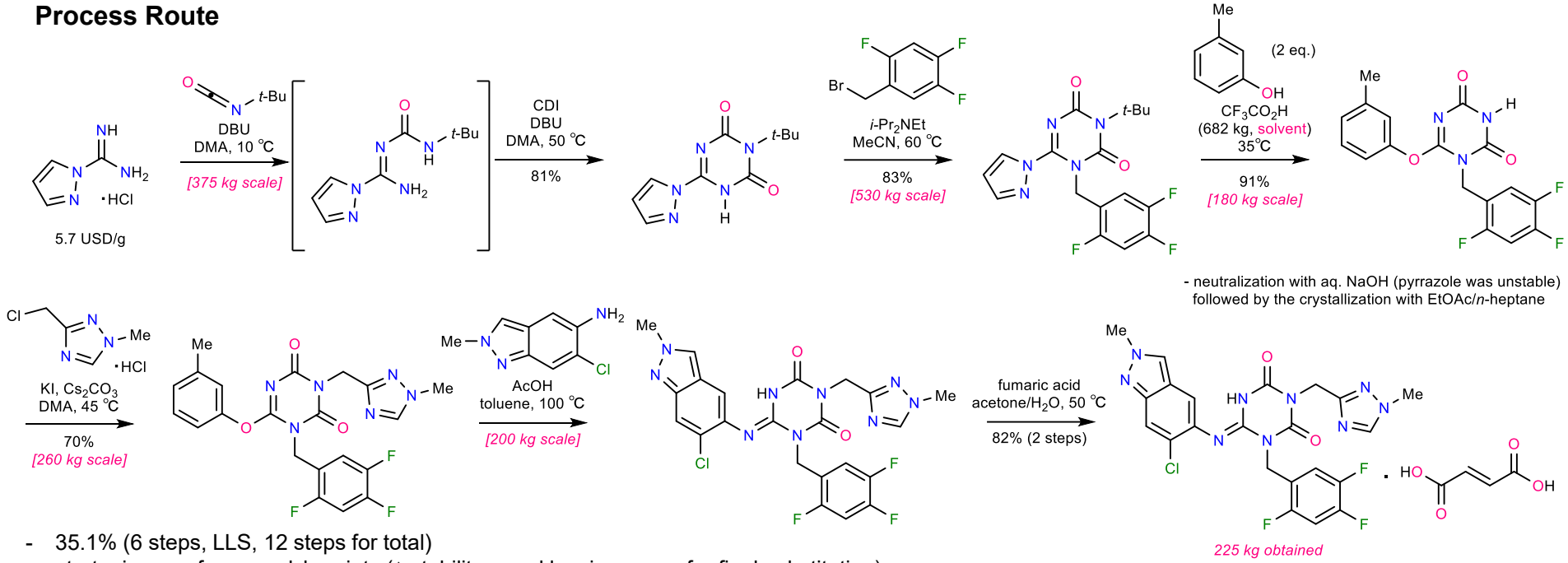


*indazole motif for step **E***



- robust and scalable heterocycle fragment syntheses

Process Route



- neutralization with aq. NaOH (pyrrazole was unstable) followed by the crystallization with EtOAc/*n*-heptane

- 35.1% (6 steps, LLS, 12 steps for total)
- strategic use of *m*-cresolyl moiety (↑ stability, good leaving group for final substitution)
- direct crystallization (9/12 steps)