LUMC Leiden University Medical Center

Acurx Pharmaceuticals

A unique inhibitor conformation selectively targets Gram+ bacterial DNA replication

Nat Commun (2025)

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Art by
Ella Maru Studio

LED3 PhD/Postdoc symposium 2026

The urgent need for novel antibiotics

- Predicted to cause 10 million deaths annually by 2050 (WHO)
- Last 30 years: only 1 novel antibiotic with new mode-of-action

We need:

- **new chemotypes**
- **new targets**

PolC is a clinically unexploited target

- Only in low-GC Gram+ bacteria → specific
- The replicative DNA polymerase → essential
- Distinct from human polymerase → druggable

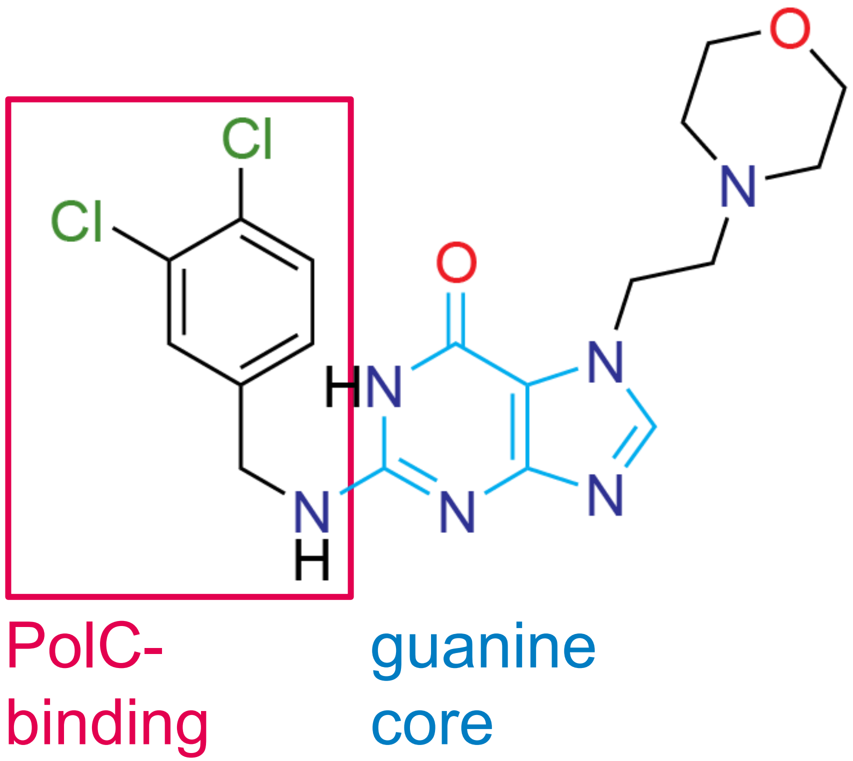
Clostridioides difficile

Staphylococcus aureus

Enterococcus faecium

CDC:
Antibiotic
Resistance
Threats in the
United States,
2019

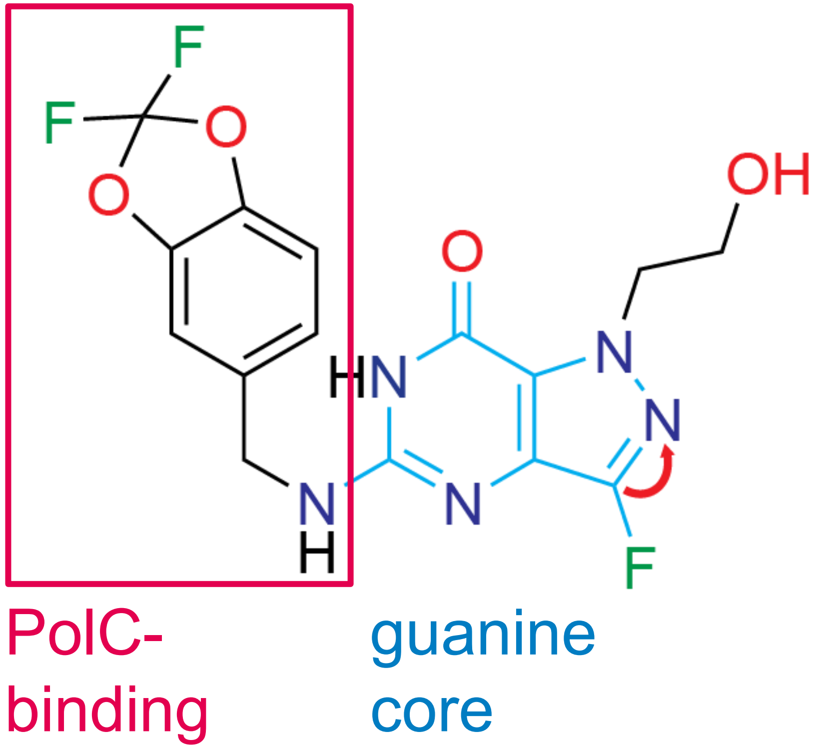
First-in-class PolC inhibitor: ibezapolstat



Acurx Pharmaceuticals

- Mimics guanine (DNA building block)
- Competes with dGTP to inhibit replication
- Phase 3 trials for *C. difficile* infections
- Narrow spectrum: microbiome-sparing

Expanding PolC inhibition beyond *C. diff*: ACX-801



Acurx Pharmaceuticals

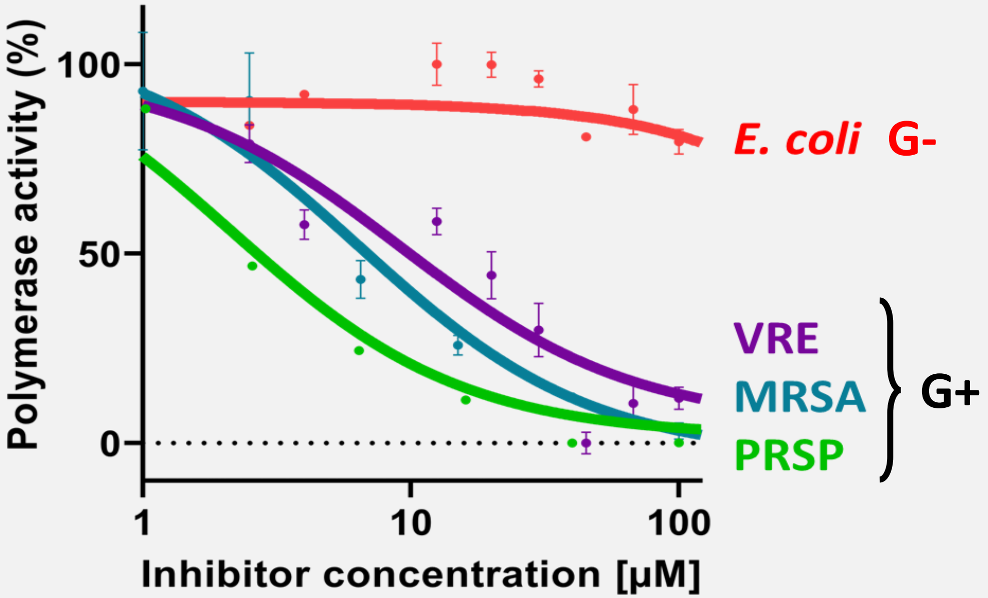
- IBZ: only suitable in gastro-intestinal tract
- ACX: modified core improves absorption
- Infections: *S. aureus, E. faecium*
- PolC-specificity via N2-aromatic group

Disrupting DNA replication is detrimental & PolC-specific

Polymerase activity → inhibition

PolC polymerases

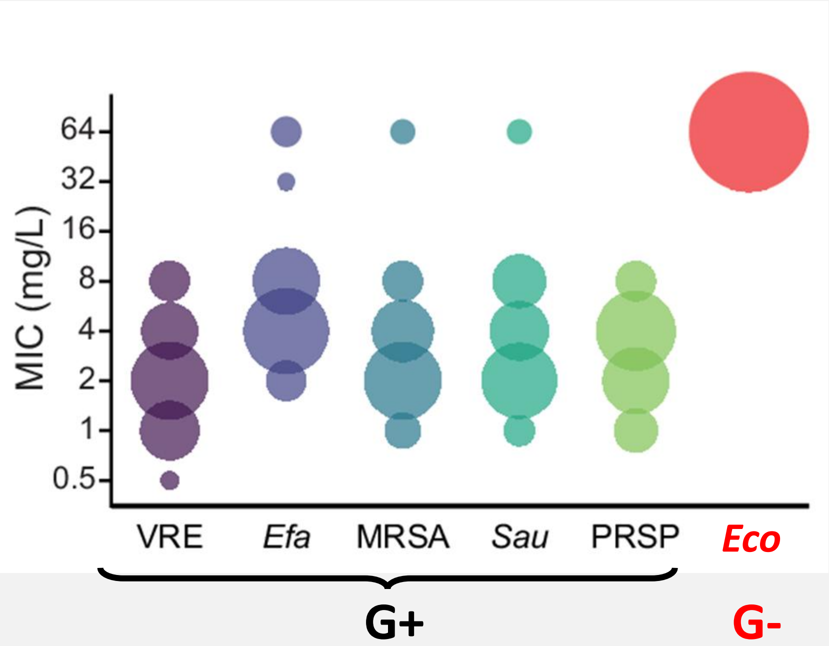
IC50 ≤ 15 µM



Bacterial growth → inhibition

Gram+ species

MIC ≤ 2 mg/L



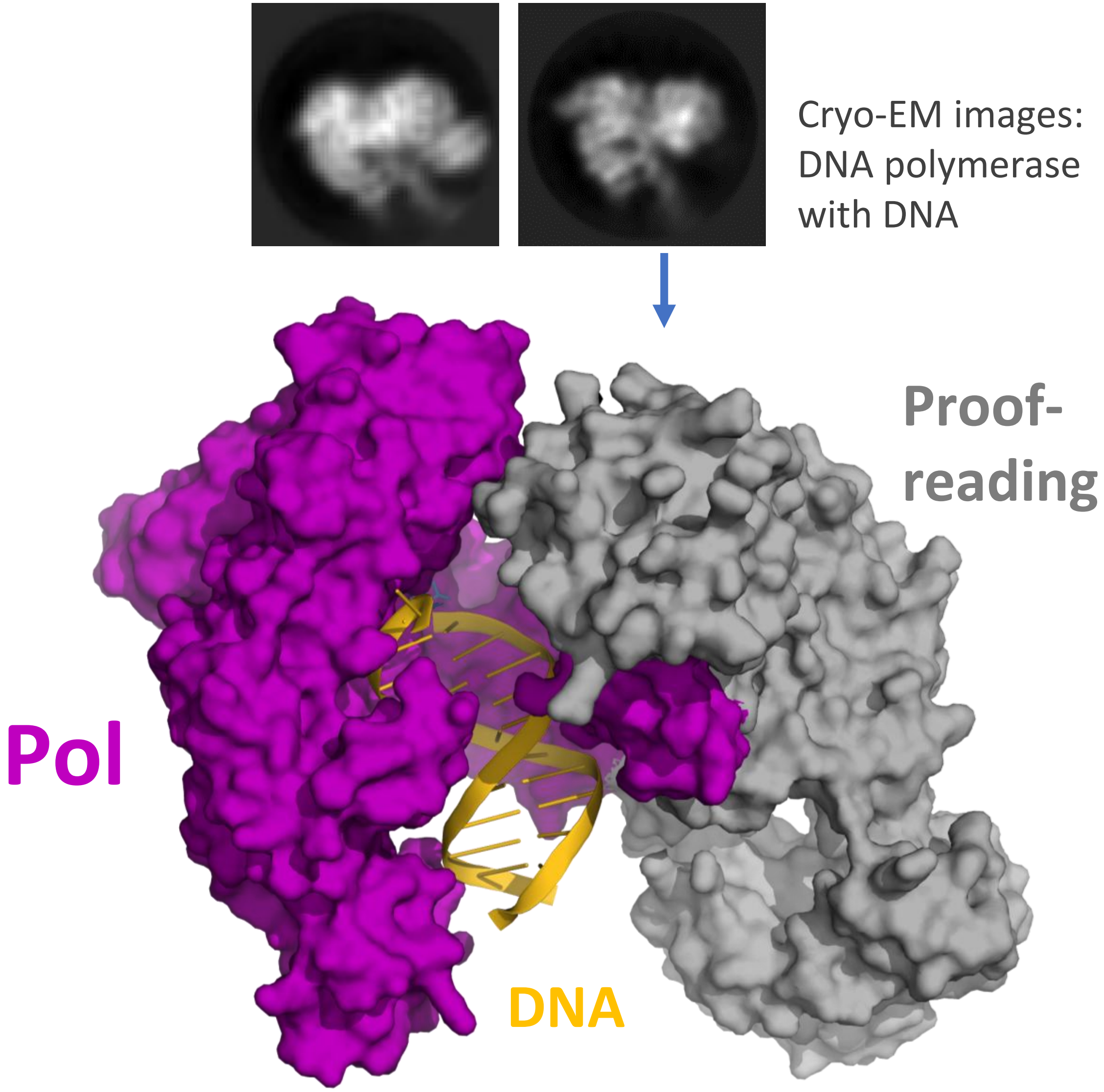
Structure reveals the inhibitor binding mode

- High resolution cryo-EM

NeCEN

- *E. faecium* PolC
  - Bound to DNA with ACX-801 (2.8 Å) or IBZ (3.2 Å)
  - PolC apo (no DNA/inhibitor; 3.1 Å)

- Detailed view of inhibitor binding

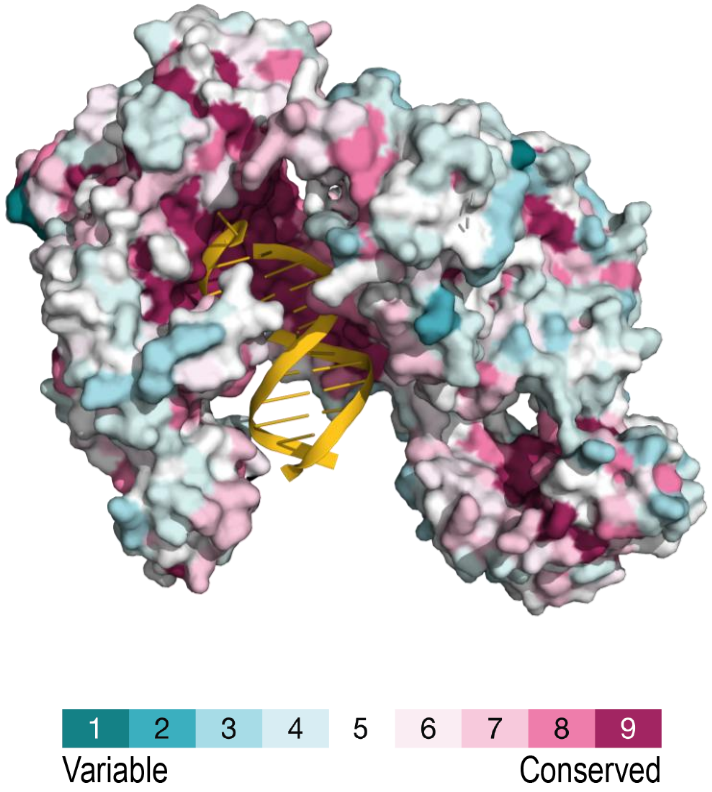


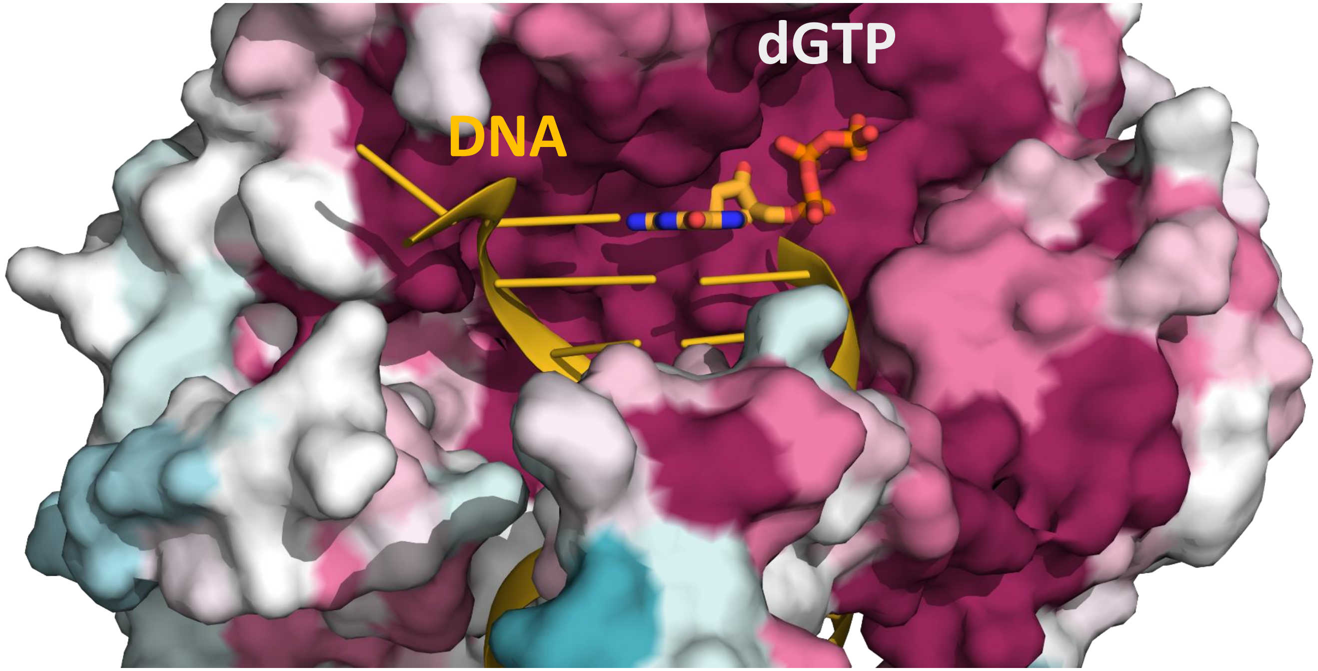
Cryo-EM images: DNA polymerase with DNA

Urem et al. *Nat Commun* (2025)

PolC polymerase active site is conserved

- *E. faecium* PolC: representative model of Gram+ bacteria
- Key residues & pocket: conserved in >220 other Gram+ species



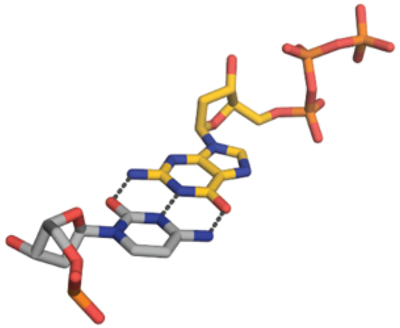


Polymerase active site

dGTP from *Geob* PolC structure

Str: Urem et al. *Nat Commun* (2025); dGTP: Evans (2008) *Proc Natl Acad Sci*

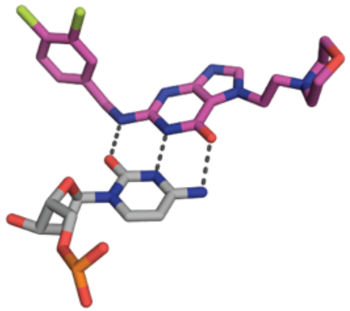
Inhibitors base-pair with template dCMP



dCMP:dGTP

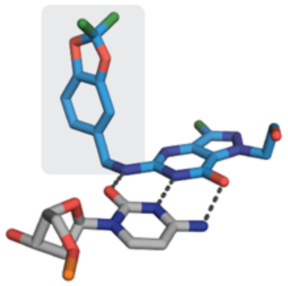
Evans (2008) *Proc Natl Acad Sci*

3F2C



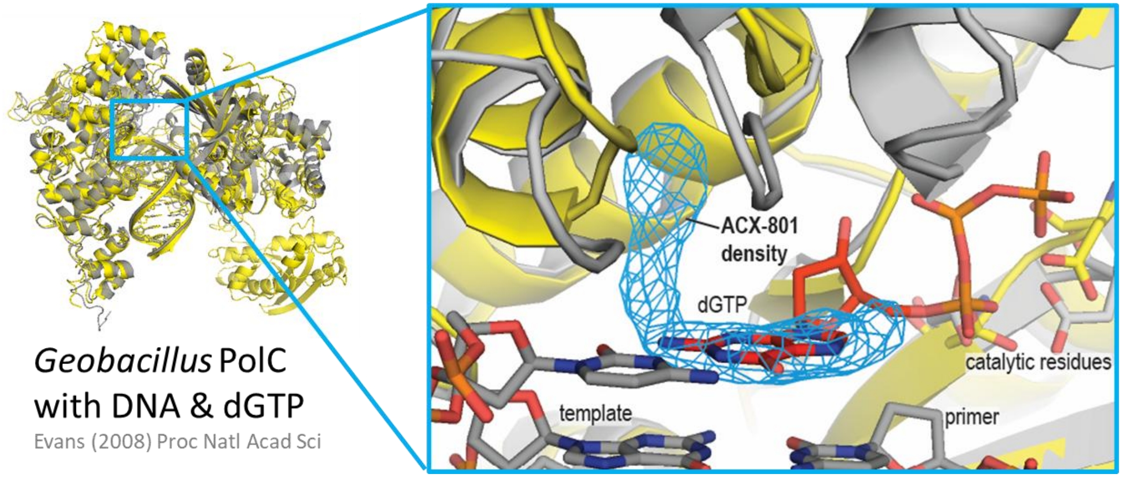
dCMP:**IBZ**

9QRL



dCMP:**ACX-801**

9QPC

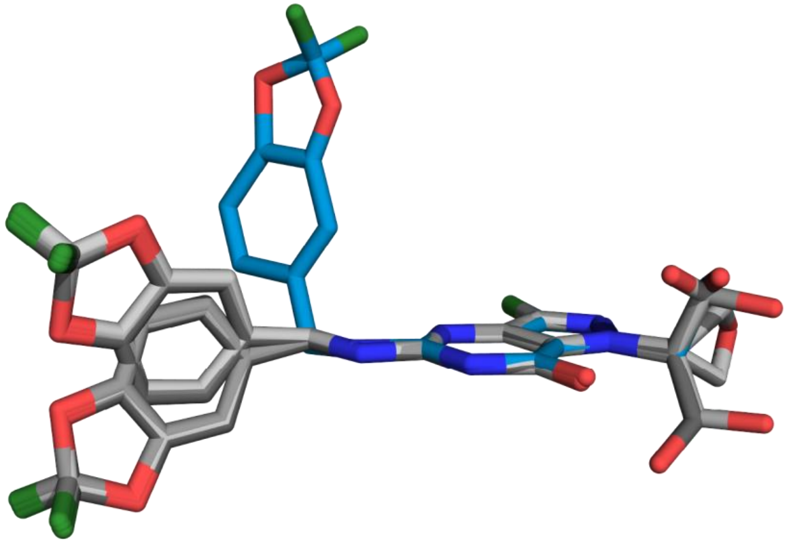


Geobacillus PolC
with DNA & dGTP

Evans (2008) Proc Natl Acad Sci

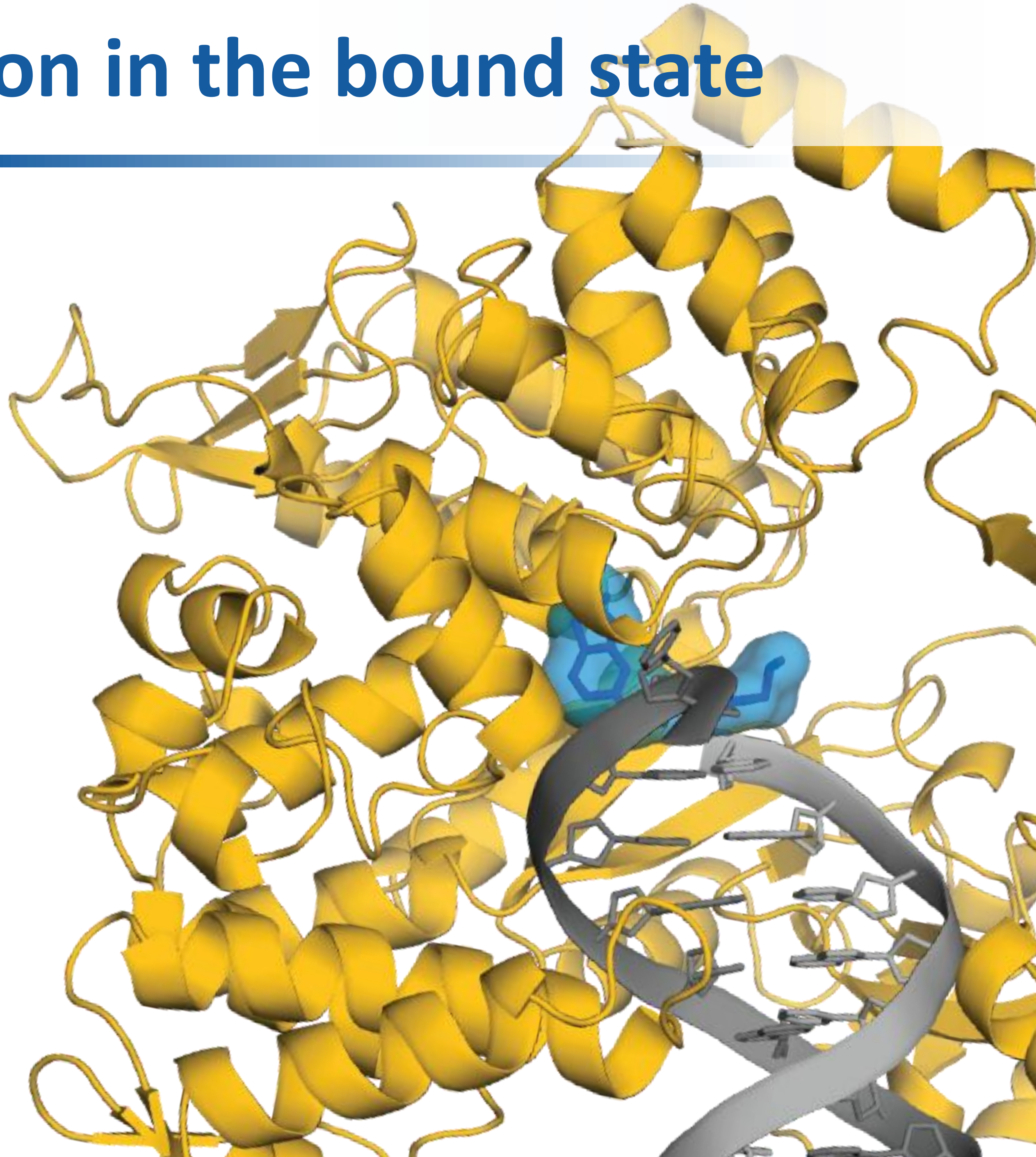
- Occupy polymerase active site
- Bind in place of dGTP
- Competition blocks DNA extension

Key: non-planar conformation in the bound state



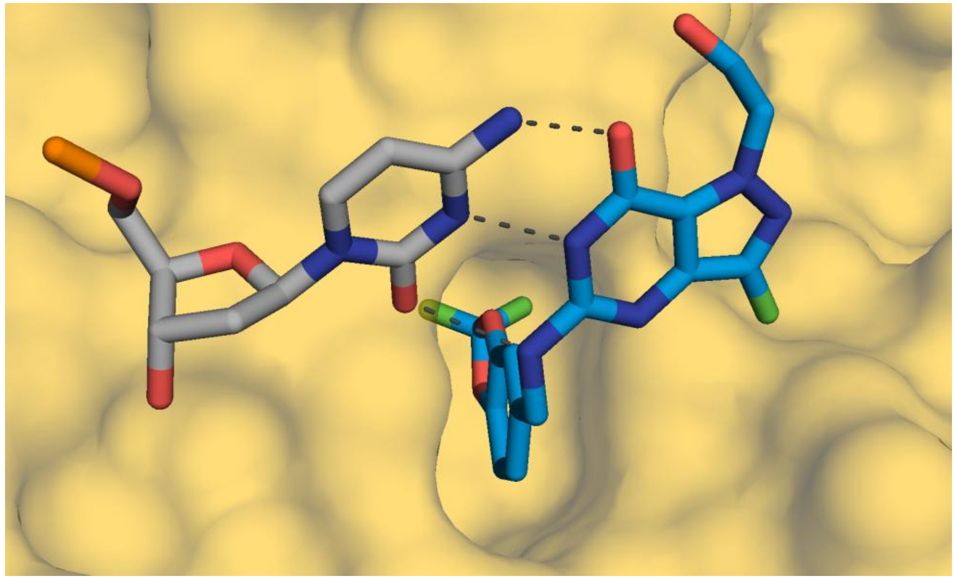
- Prediction: lowest energy conformation → planar (grey)

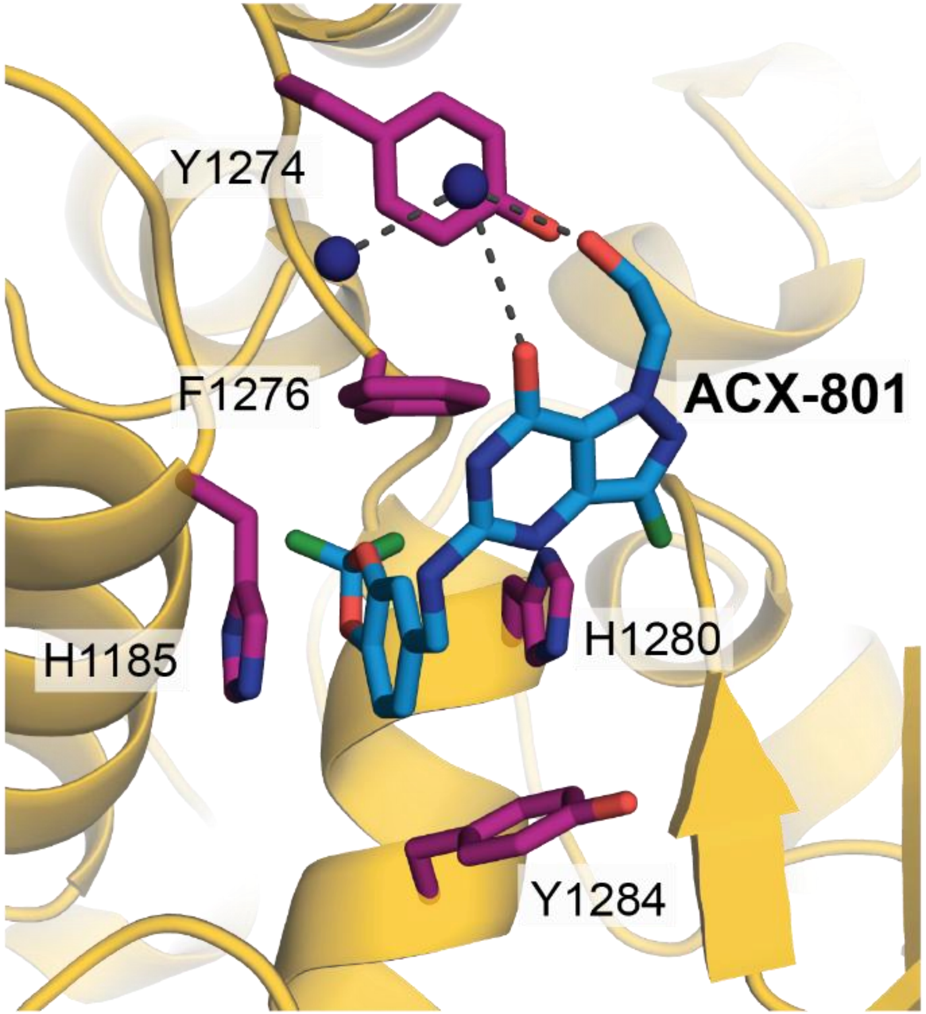
- Structure: N2-aromatic group almost perpendicular to nucleobase



N2-aromatic inhibitory group anchored within PolC

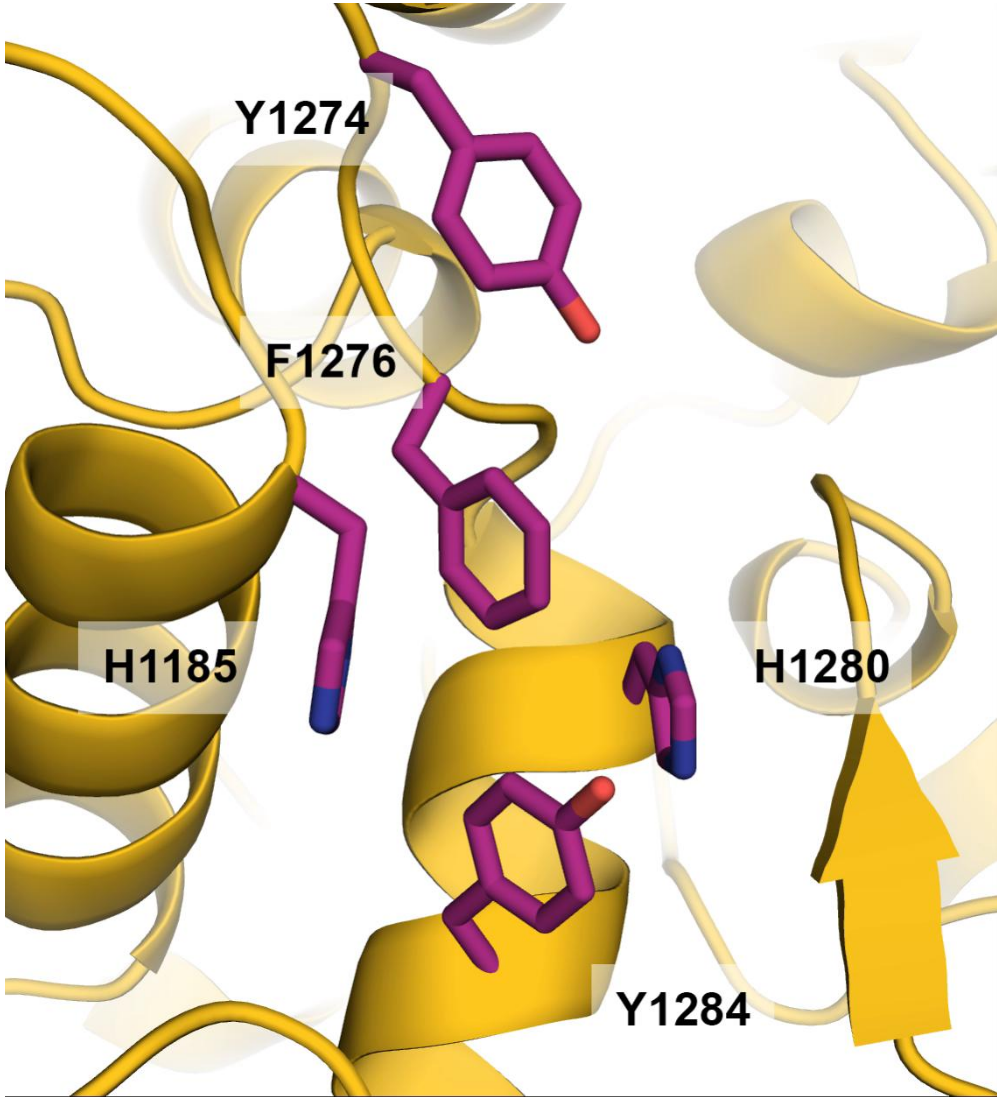
- Binding pocket: 4 aromatic residues
- Interactions with inhibitory group
- F1276: also edge-to-face with interactions with nucleobase core



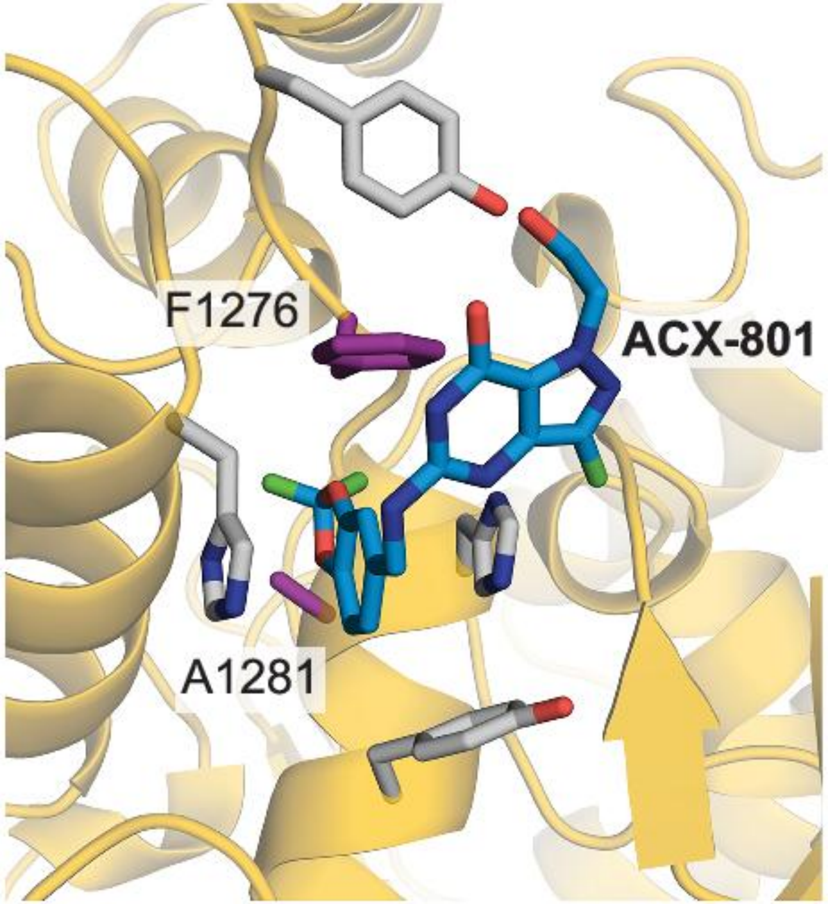


Induced fit: F1276 is the gatekeeper of the binding pocket

ACX-801 vs apo

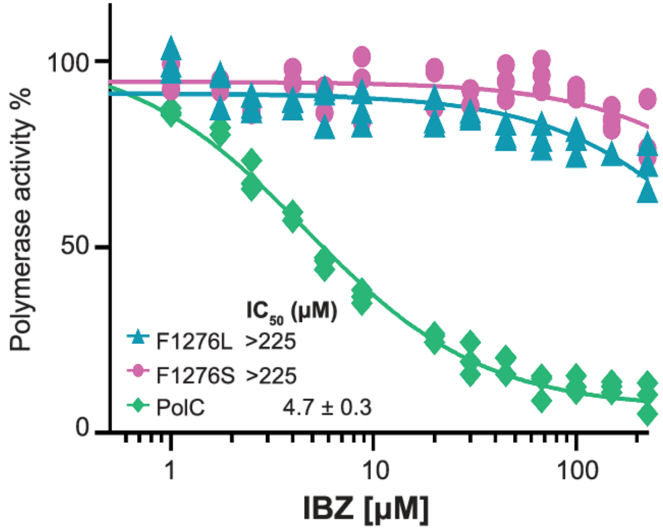


F1276 is also a hotspot for lab-evolved mutations



- No resistance observed in *Cdiff* clinical isolates
  (van Eijk (2019), Murray (2020), Bassères (2024))

- F1276 is most common

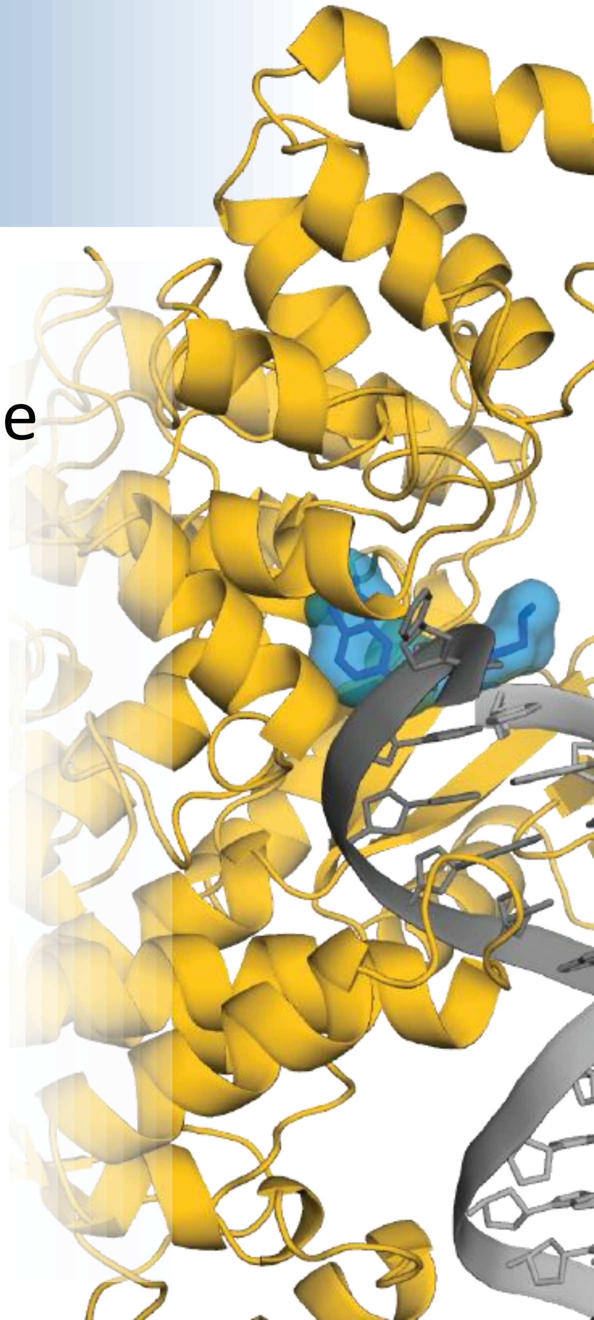


F>S introduction polar group

F>L loss of aromatic group

WT

Key for PolC inhibition:
non-planar inhibitor conformation & induced-fit



- Cryo-EM structures were essential to determine binding mode
  - Non-planar inhibitor: anchored to PolC while base-pairing DNA
  - Induced fit: pocket absent in apo
  - F1276: gatekeeper & hotspot for mutations

- IBZ progressing to Ph. 3 clinical trials

- Structure provides a framework for future inhibitor design

Leiden University
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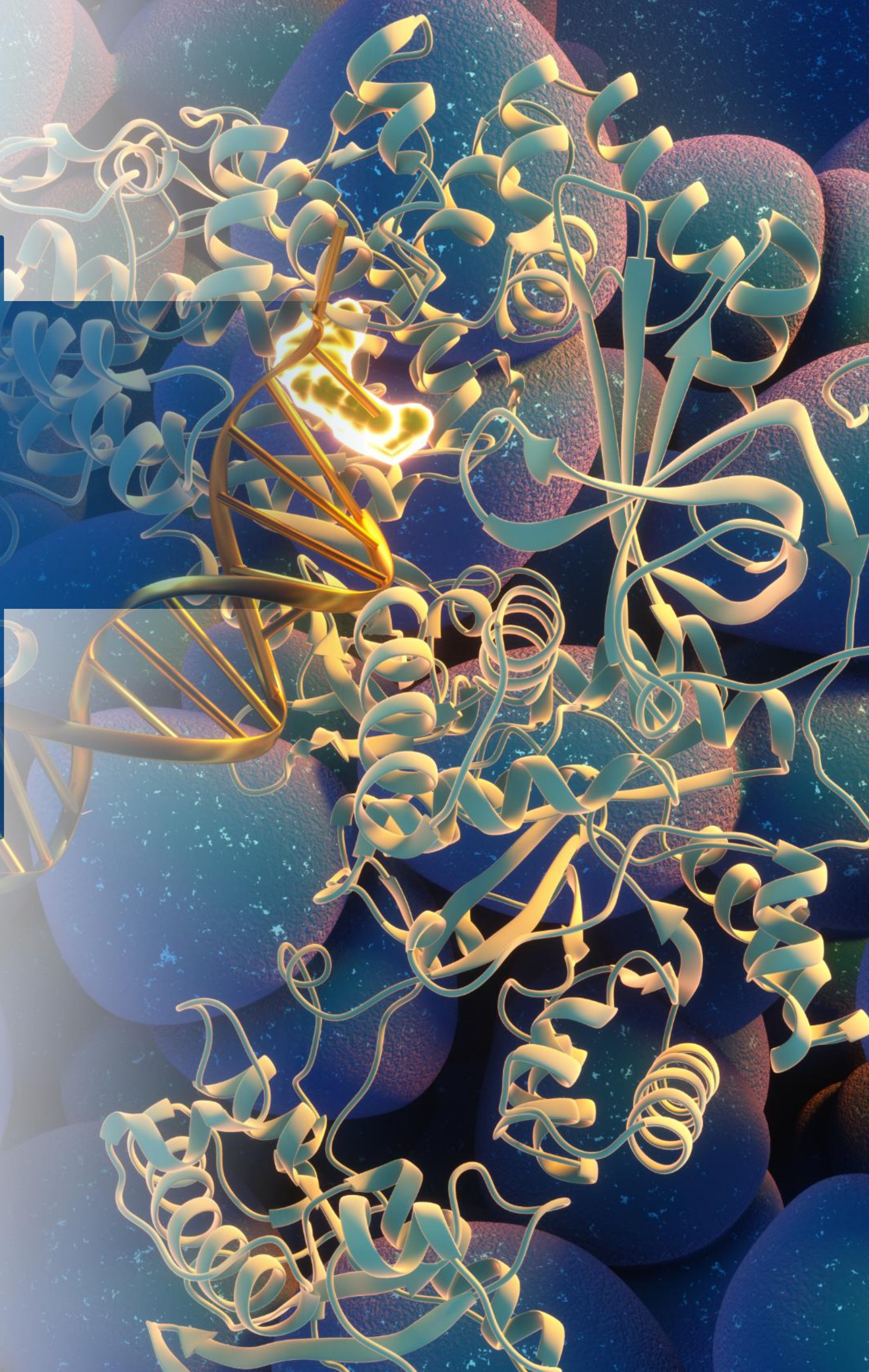
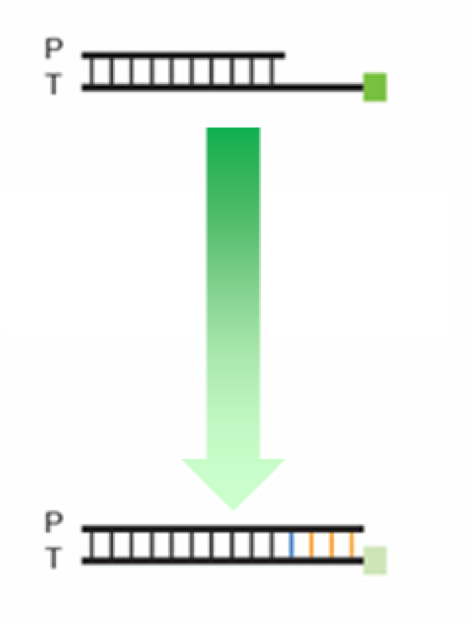
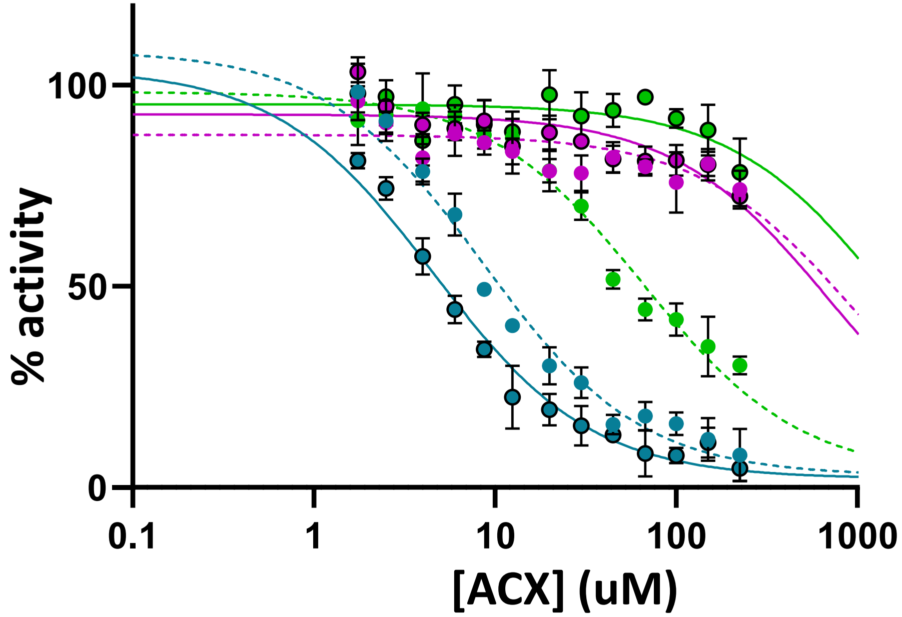


Health~Holland

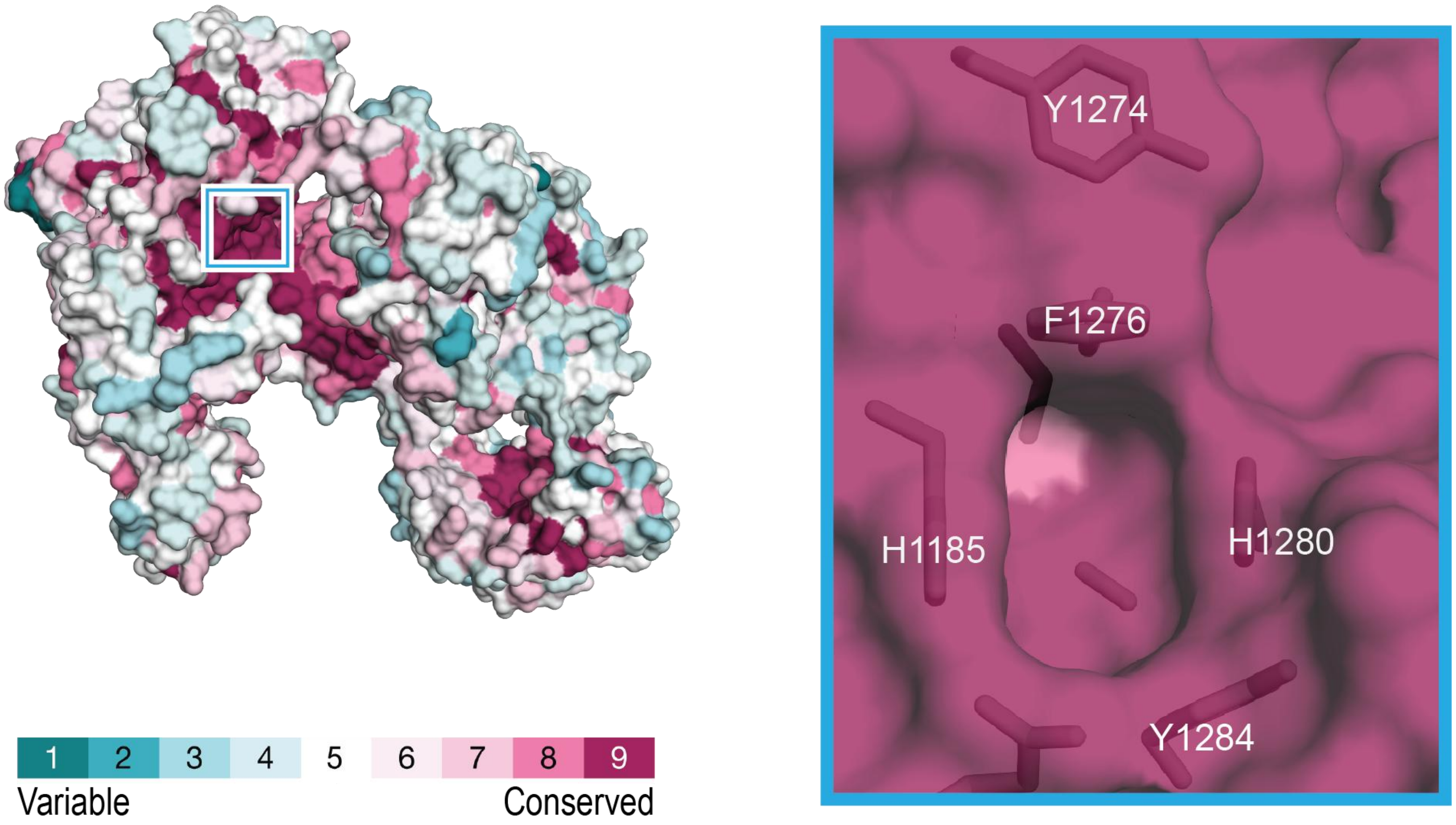
NEMI NeCEN

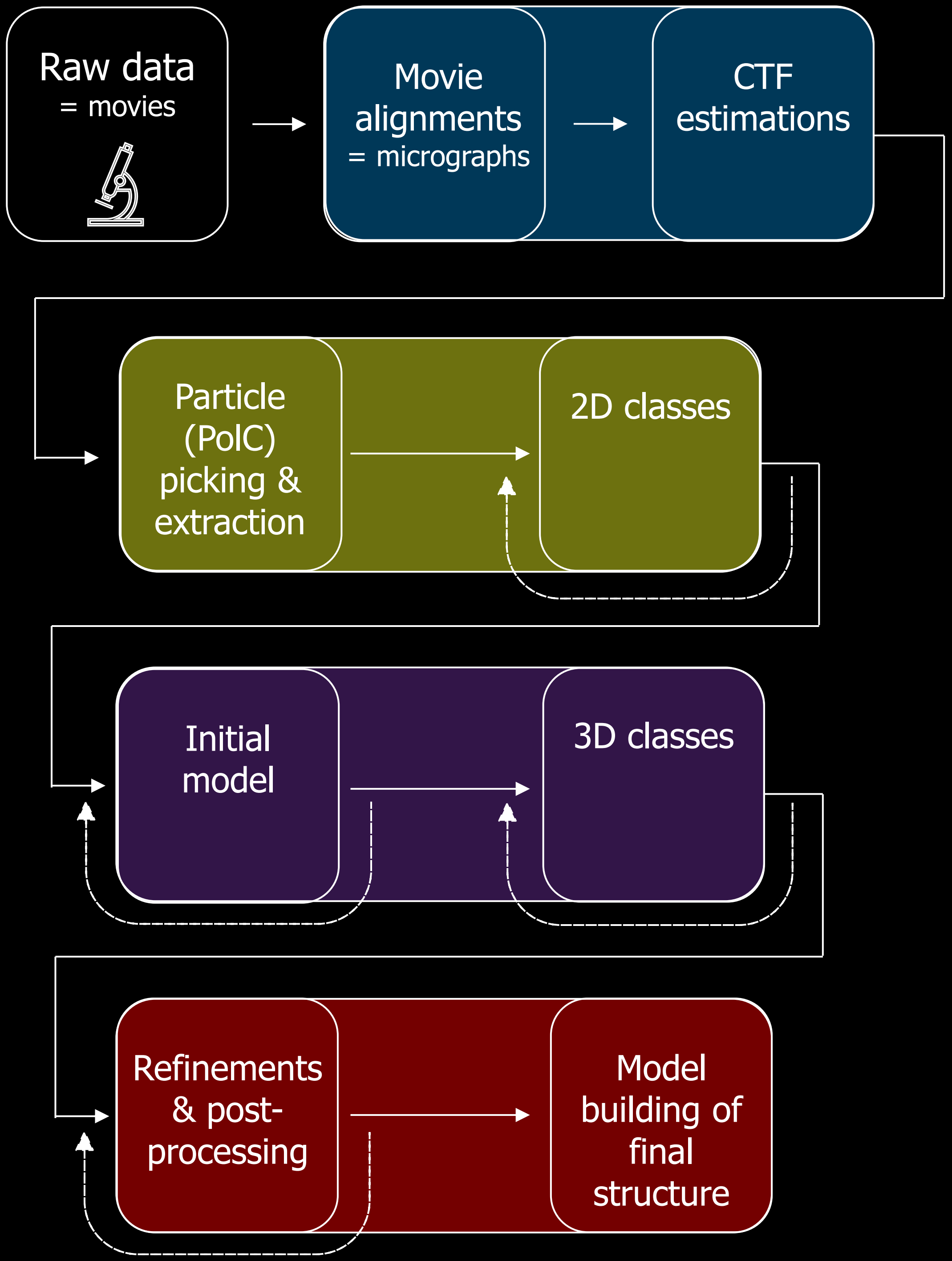




Condition	IC$_{50}$ (uM)
PolC + IBZ	9
PolC + ACX-801	5
PolC^{F1276L} + IBZ	993
PolC^{F1276L} + ACX-801	717
PolC^{F1276S} +IBZ	66
PolC^{F1276S} + ACX-801	1545

The aromatic residues are highly conserved in PolC





Raw data
= movies

Movie alignments
= micrographs

CTF estimations

Particle (PolC) picking & extraction

2D classes

Initial model

3D classes

Refinements & post-processing

Model building of final structure