Compounds acting against HIV

Imidazo[1,2-*a*]pyridines as non-nucleoside reverse transcriptase inhibitors (NNRTIs)

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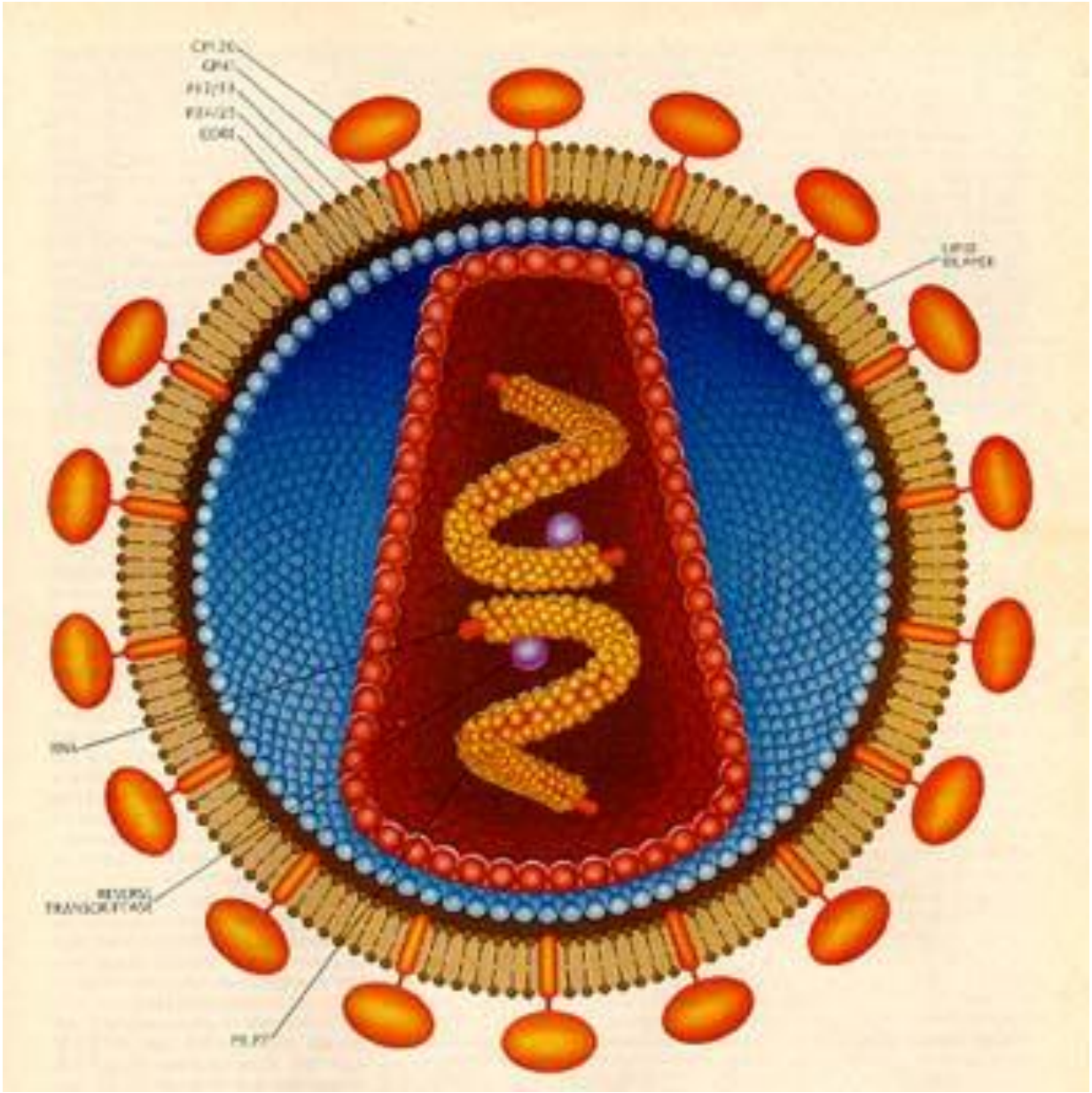
HIV drug targets

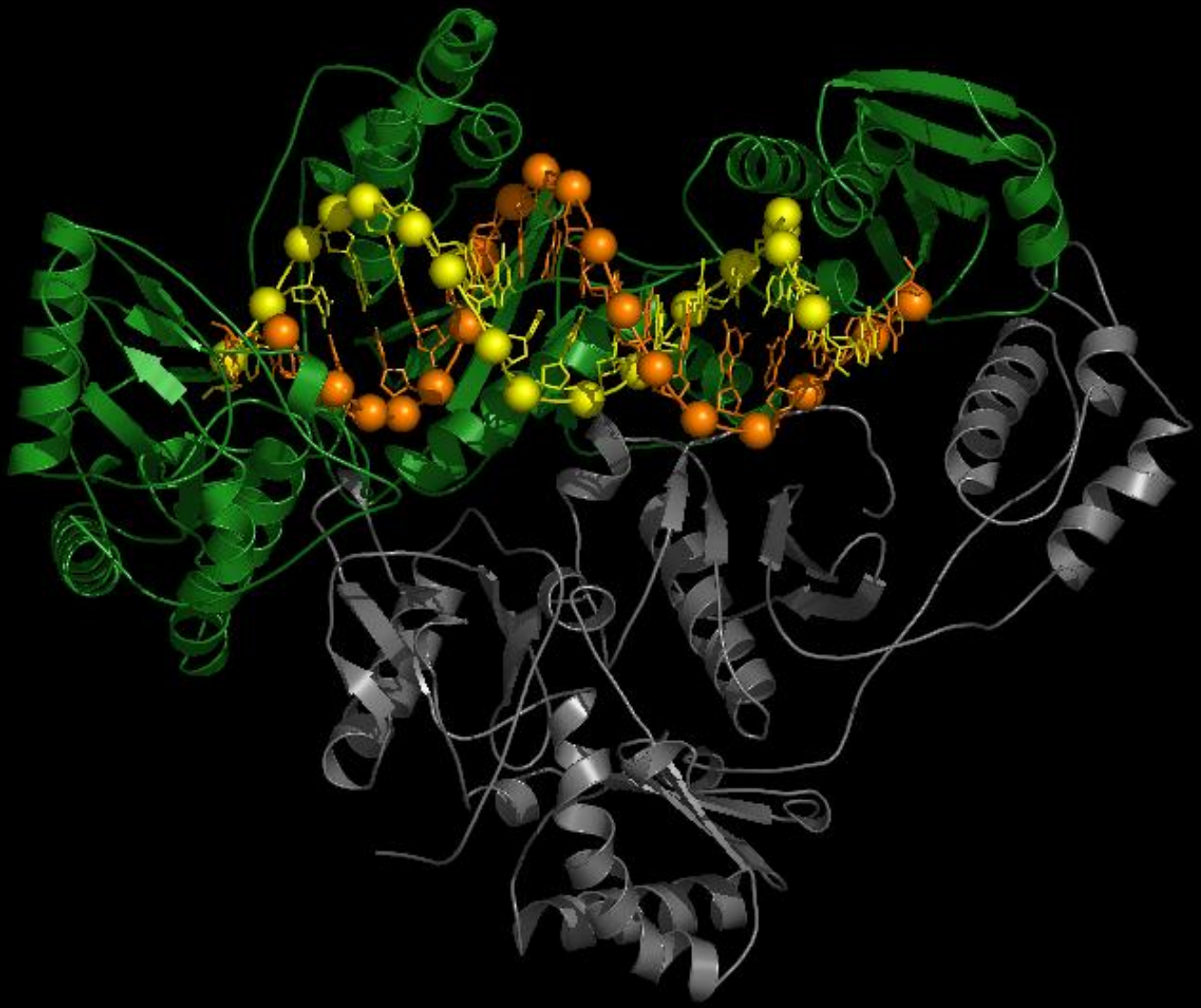
Viral enzymes:

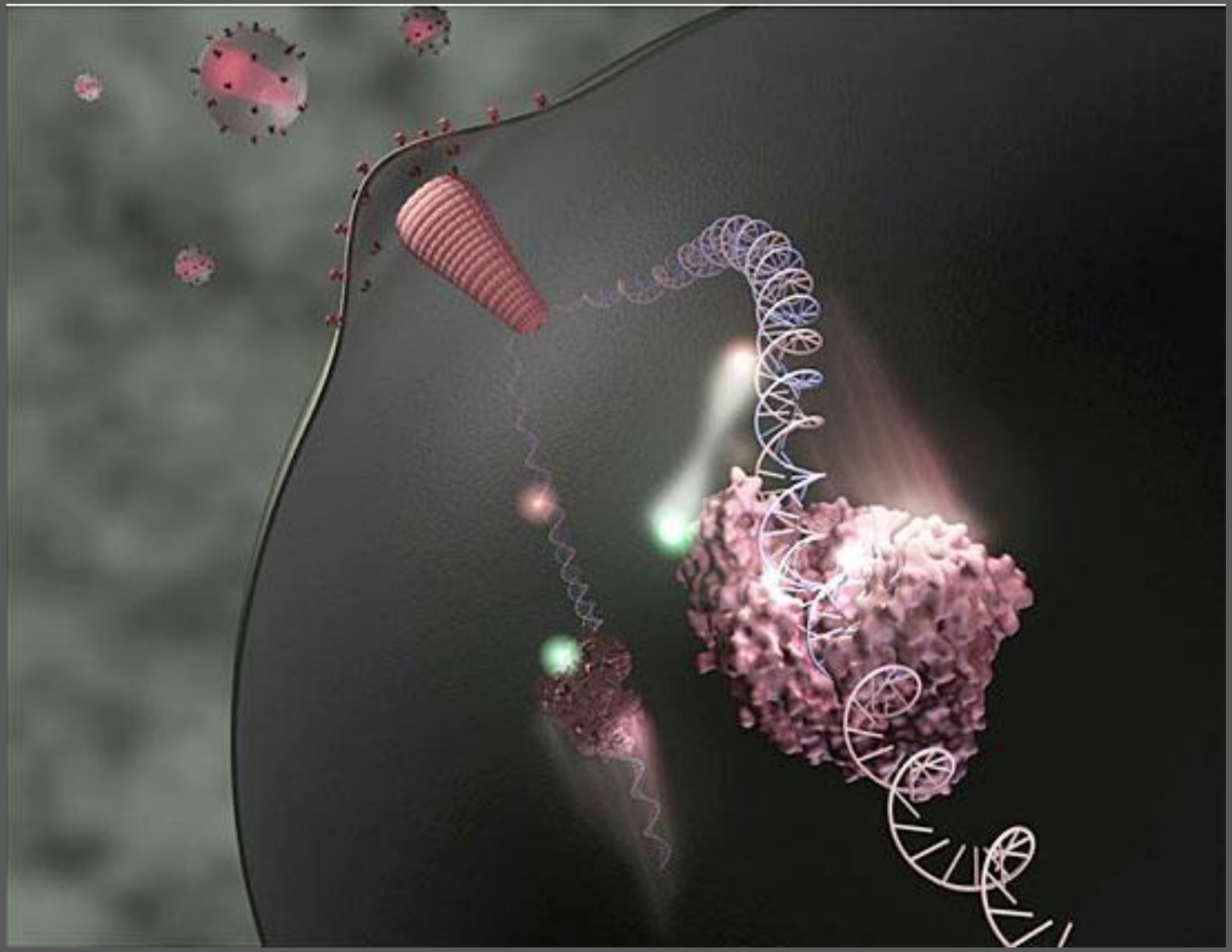
•Reverse Transcriptase

•Protease

•Integrase

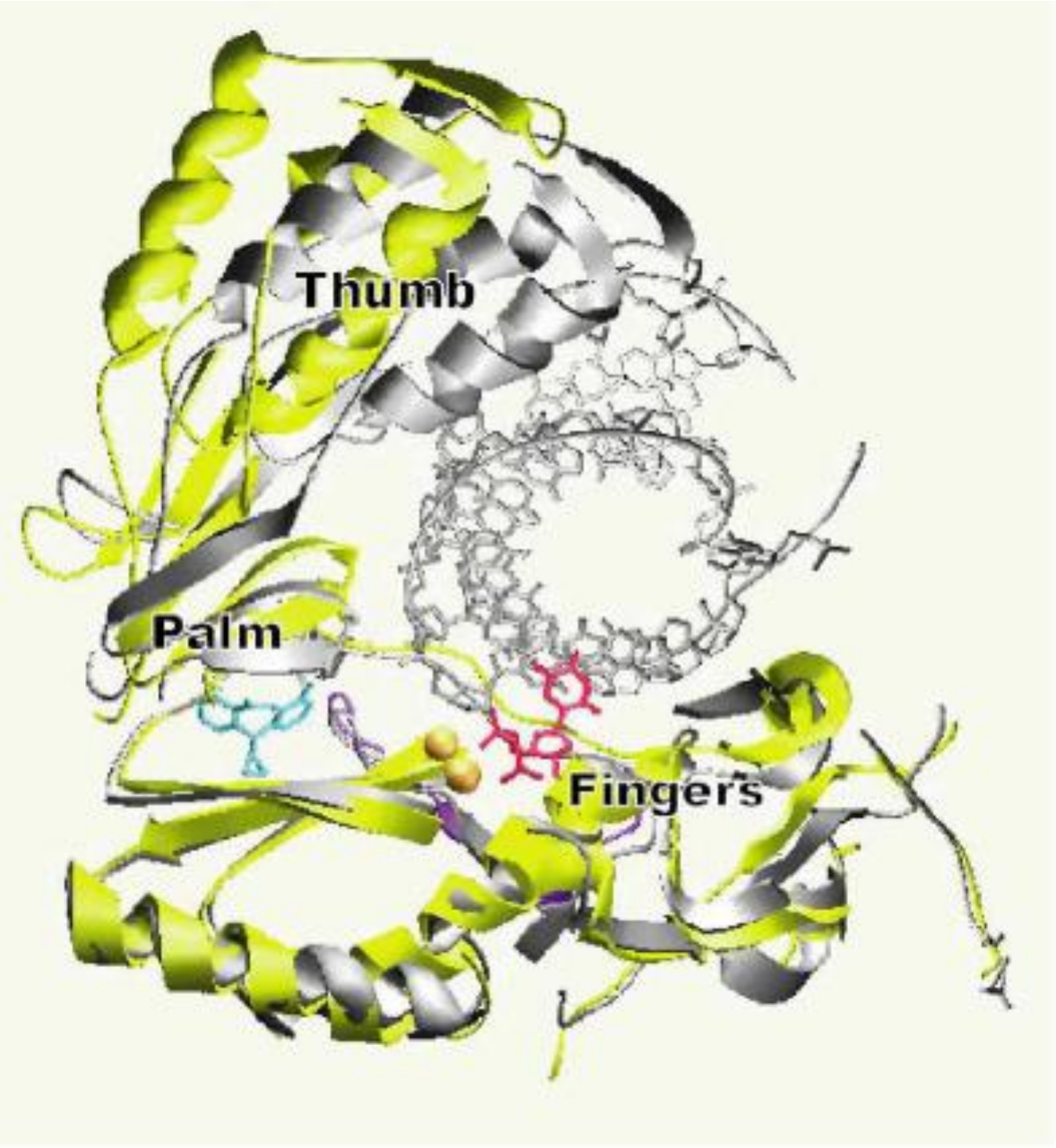






Courtesy Howard Hughes medical centre

Reverse Transcriptase

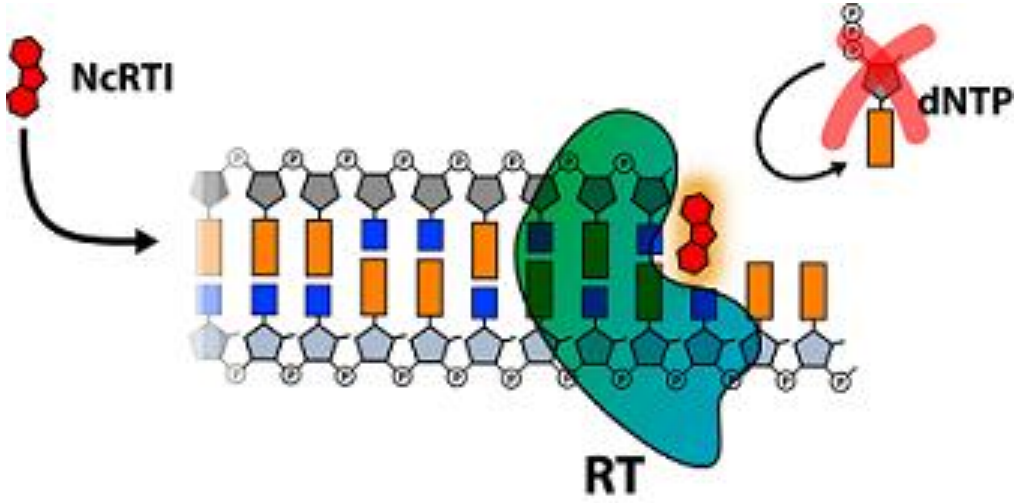


Two types of inhibitors:
NRTIs and NNRTIs

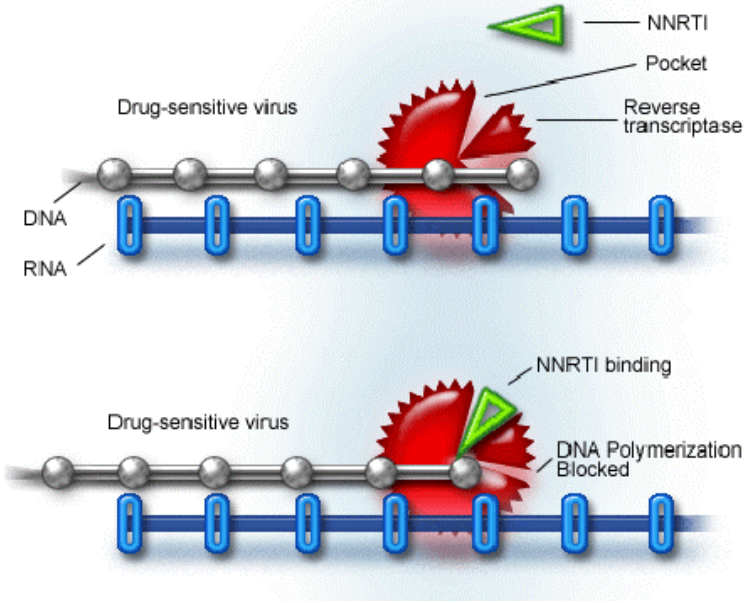
CSIR
our future through science

Inhibitor Modes of action

NRTI



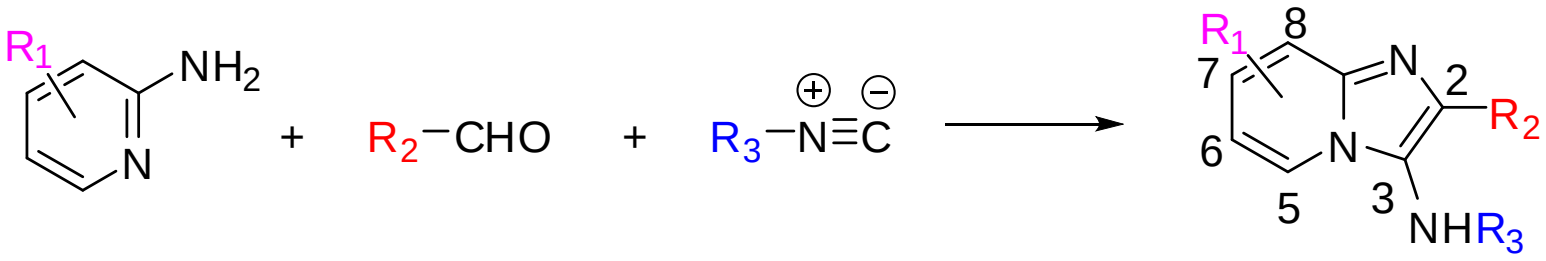
NNRTI



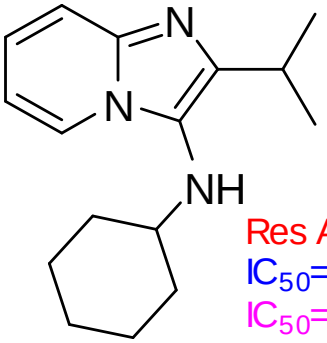
NNRTIs in HIV treatment

- Non-competitive allosteric inhibitors of reverse transcriptase
- Form part of first-line treatment regimen of HAART, eg. nevirapine, efavirenz
- Potent, highly selective anti-HIV agents
- Structurally diverse
- Generally good safety profile

Imidazo[1,2-*a*]pyridines



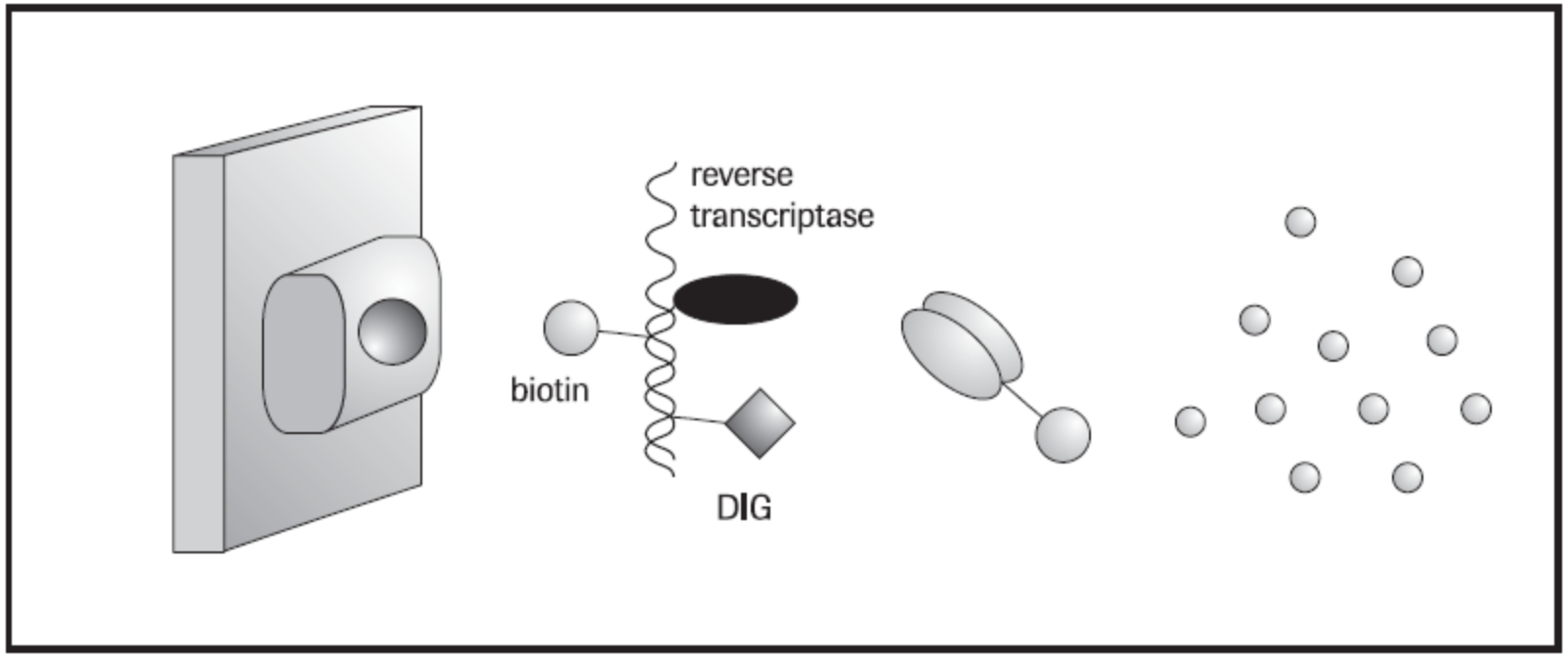
Prepared by the Groebke multi-component coupling reaction



Res Act = 41%
IC_{50}= 29 uM (RT)
IC_{50}= 41 uM (PBMC)

Hit compound identified from an enzymatic RT screen – poorly active in whole cell anti-HIV assay

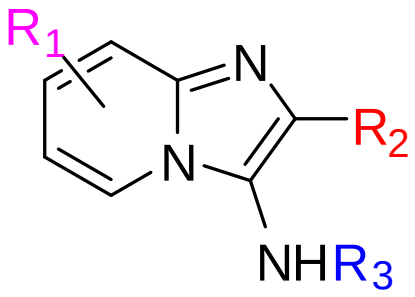
Reverse transcriptase assay



Compounds showing < 20% residual activity in enzymatic assay were submitted to SRI for whole-cell anti-HIV infectivity assay

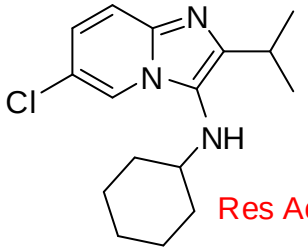
Hit to Lead Development

H
halogen
methyl
cyano
alkoxy

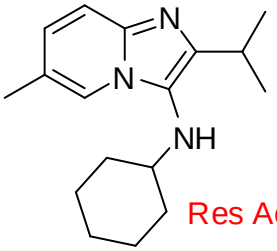


alkyl
branched alkyl
cycloalkyl
phenyl
halogenated phenyl

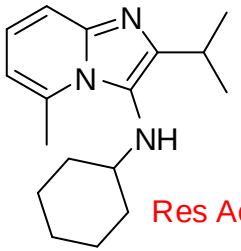
alkyl
branched alkyl
cycloalkyl
aromatic



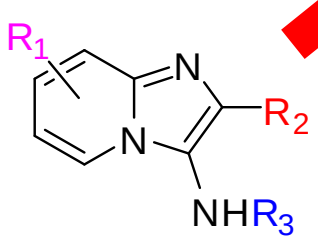
Res Act = 73%

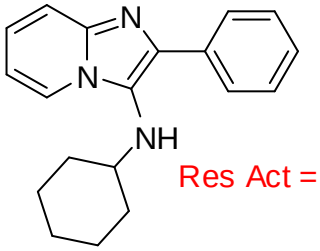


Res Act = 70%

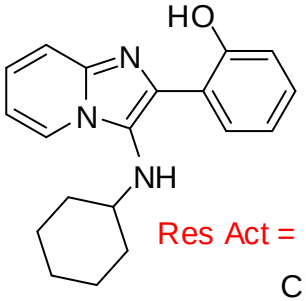


Res Act = 22%

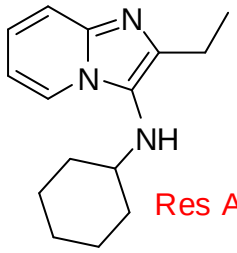




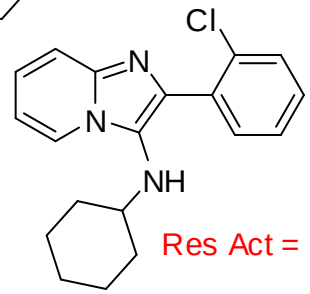
Res Act = 75%



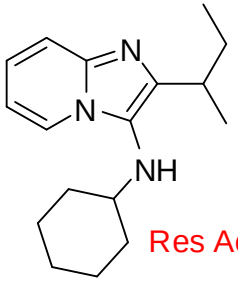
Res Act = 87%



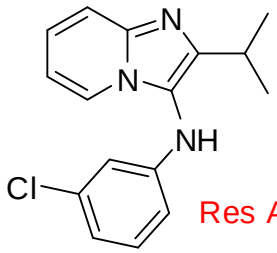
Res Act = 76%



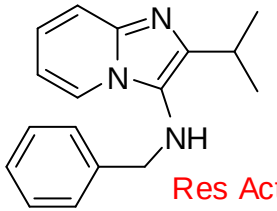
Res Act = 7%



Res Act = 55%

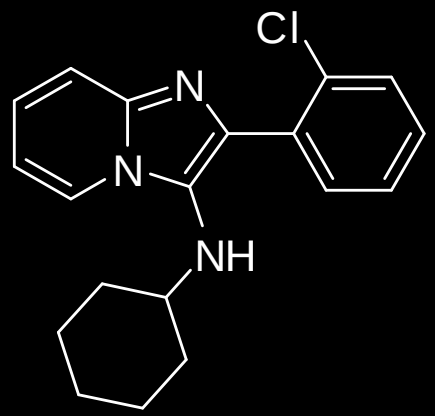


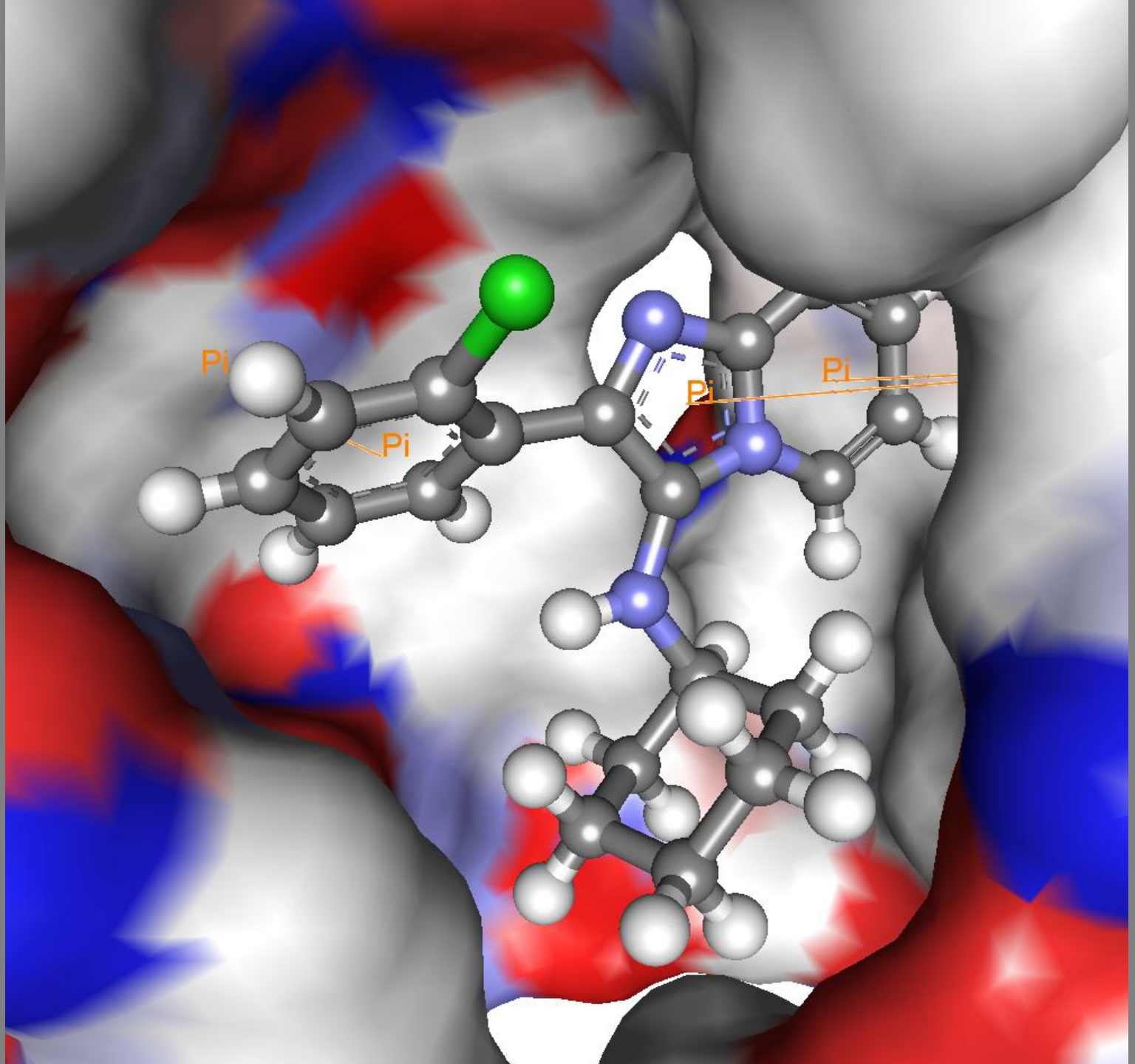
Res Act = 77%



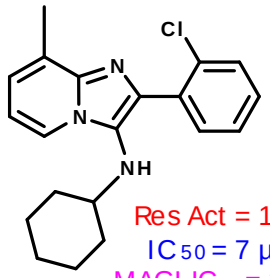
Res Act = 96%

Lead compound identified

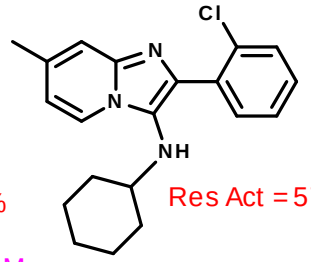



Pi
Pi
Pi
Pi

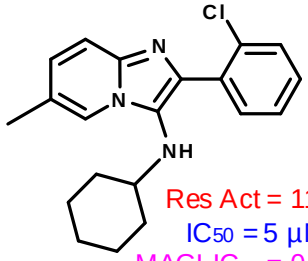
Lead optimisation



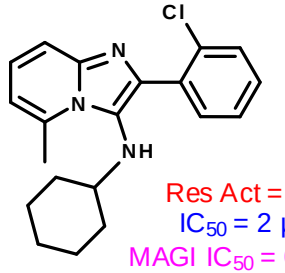
Res Act = 18%
IC_{50} = 7 µM
MAGI IC_{50} = 3 µM



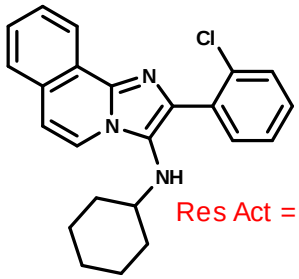
Res Act = 57%



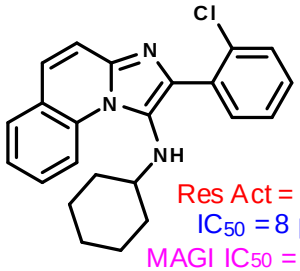
Res Act = 11%
IC_{50} = 5 µM
MAGI IC_{50} = 0.6 µM



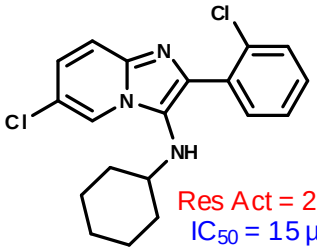
Res Act = 3%
IC_{50} = 2 µM
MAGI IC_{50} = 0.2 µM



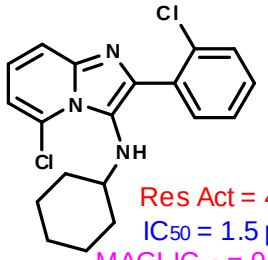
Res Act = 94%



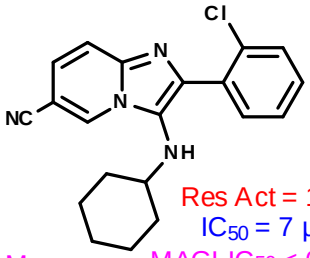
Res Act = 13%
IC_{50} = 8 µM
MAGI IC_{50} = 0.6 µM



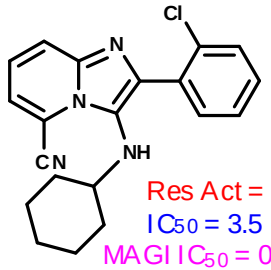
Res Act = 20%
IC_{50} = 15 µM
MAGI IC_{50} = 0.8 µM



Res Act = 4%
IC_{50} = 1.5 µM
MAGI IC_{50} = 0.18 µM

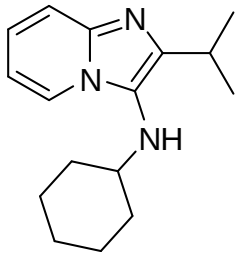


Res Act = 12%
IC_{50} = 7 µM
MAGI IC_{50} < 0.6 µM

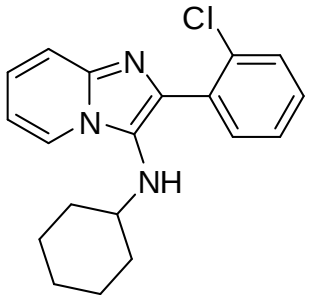


Res Act = 5%
IC_{50} = 3.5 µM
MAGI IC_{50} = 0.18 µM

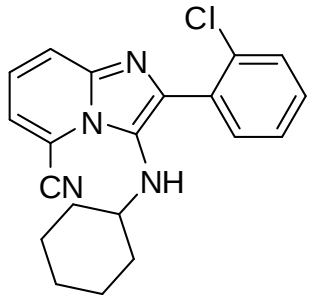
Summary: Activity improvement



IC_{50}= 29 uM (RT)
IC_{50}= 41 uM (PBMC)
cf. Nevirapine
IC_{50}= 0.67 uM (RT)
IC_{50}= 0.033 uM (PBMC)



IC_{50}= 4.4 uM (RT)
IC_{50}= 0.16 uM (PBMC)
IC_{50}= 0.41 uM (MAGI)
cf. Nevirapine
IC_{50}=0.67 uM (RT)
IC_{50}=0.033 uM (PBMC)



IC_{50}= 3.5 uM (RT)
IC_{50}= 0.18uM (MAGI)
cf. Nevirapine
IC_{50}= 0.67uM (RT)
IC_{50}= 0.10 uM (MAGI)

Conclusions

- A compound possessing anti-HIV activity similar to that of FDA-approved nevirapine was developed
- Acts as a non-nucleoside reverse transcriptase inhibitor
- Compound shows good cell permeability
- Quantitative structure activity relationship (QSAR) developed for the compound series