



UMR CNRS 6005

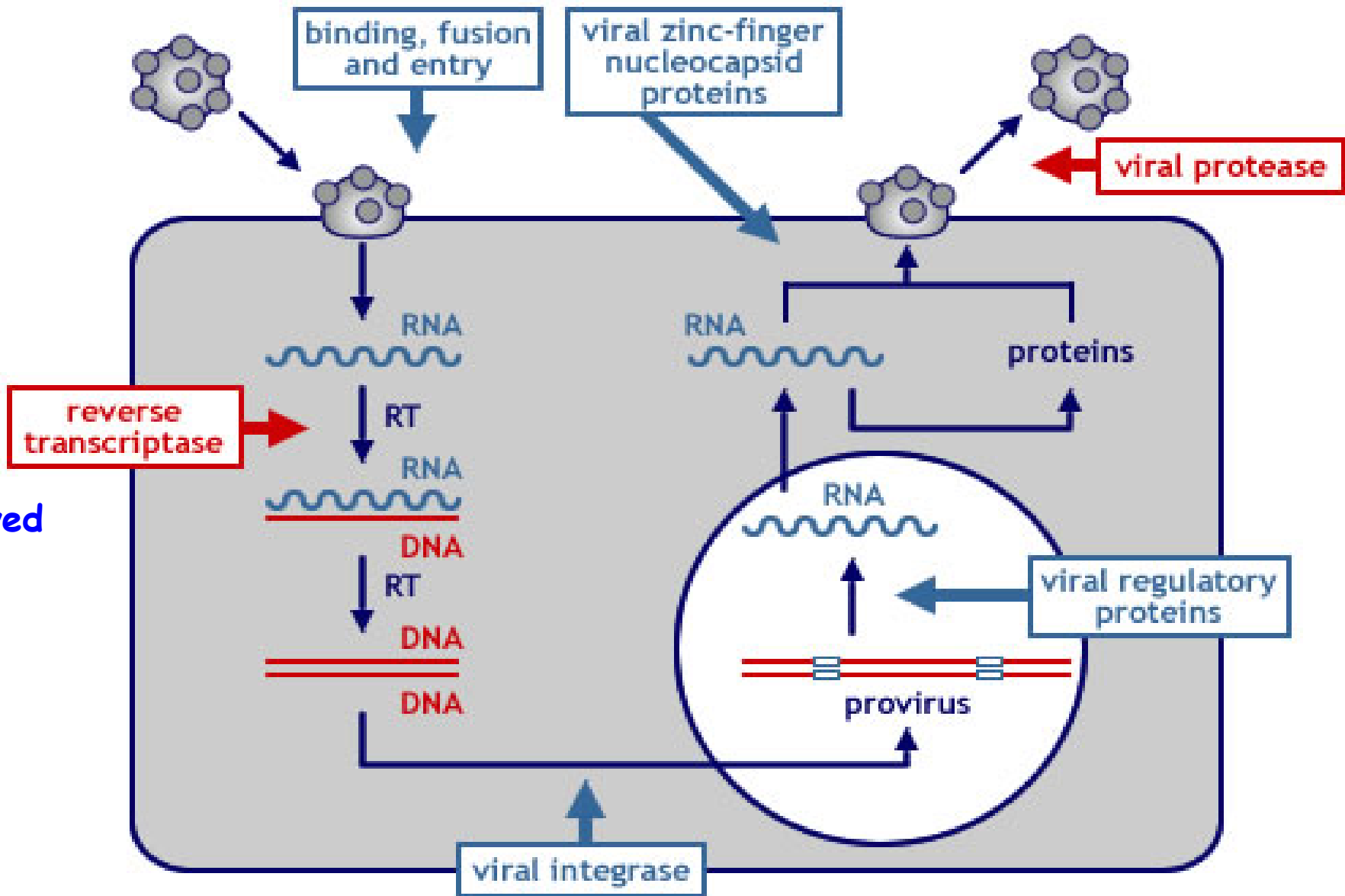


Synthesis of Oxazolopyrimidines Targeting an anti-HIV Activity

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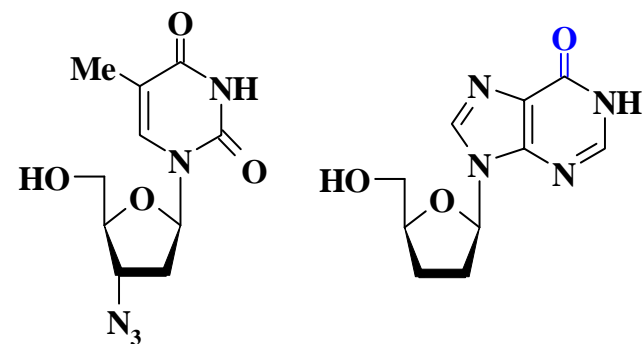
>> Potential New Targets <<



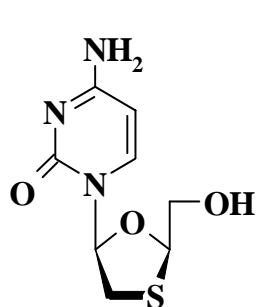
11 approved drugs

8 Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

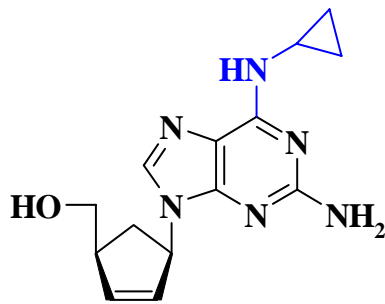
Name	Trade Name™	Laboratories	Acronyme	Approval (FDA)
<i>Zidovudine</i>	<i>Retrovir</i>	<i>GlaxoSmithKline</i>	<i>AZT</i>	<i>1987</i>
<i>Didanosine</i>	<i>Videx</i>	<i>Bristol-Myers Squibb</i>	<i>ddI</i>	<i>1991</i>
<i>Zalcitabine</i>	<i>Hivid</i>	<i>Roche Laboratories</i>	<i>ddC</i>	<i>1992</i>
<i>Stavudine</i>	<i>Zerit</i>	<i>Bristol-Myers Squibb</i>	<i>d4T</i>	<i>1994</i>
<i>Lamivudine</i>	<i>Epivir</i>	<i>GlaxoSmithKline</i>	<i>3TC</i>	<i>1995</i>
<i>Abacavir</i>	<i>Ziagen</i>	<i>GlaxoSmithKline</i>	<i>ABC</i>	<i>1998</i>
<i>Tenofovir</i>	<i>Viread</i>	<i>Gilead Sciences</i>	<i>TDF</i>	<i>2001</i>
<i>Emtricitabine</i>	<i>Emtriva</i>	<i>Gilead Sciences</i>	<i>FTC</i>	<i>2003</i>



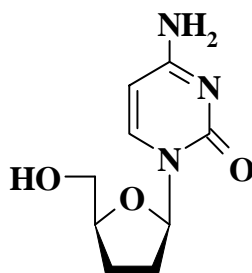
Zidovudine, Rétrovir, AZT *Didanosine, Videx, ddI*



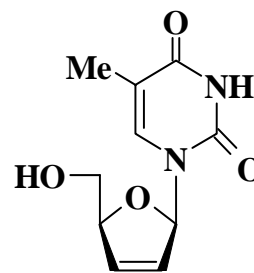
Lamivudine, Epivir, 3TC



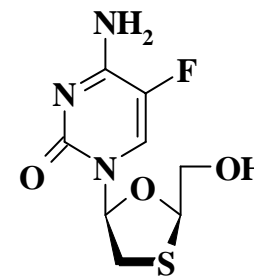
Abacavir, Ziagen, ABC



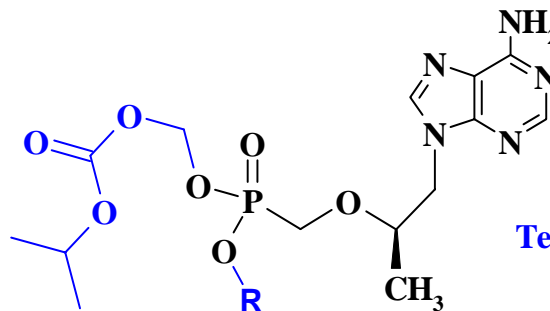
Zalcitabine, Hivid, ddC



Stavudine, Zerit, d4T

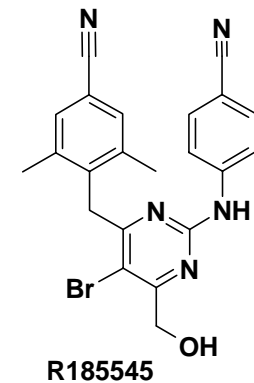
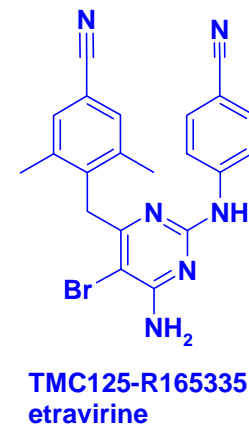
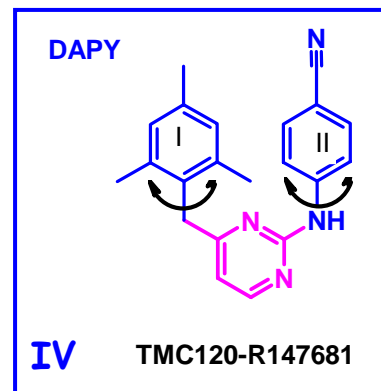
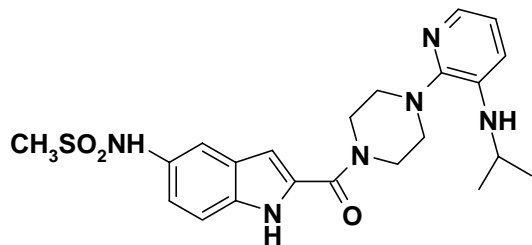
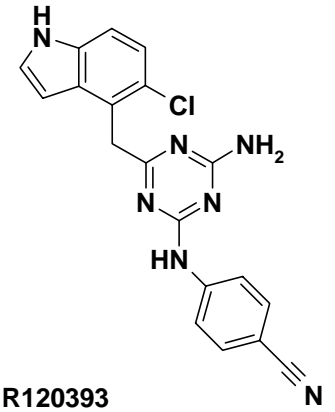
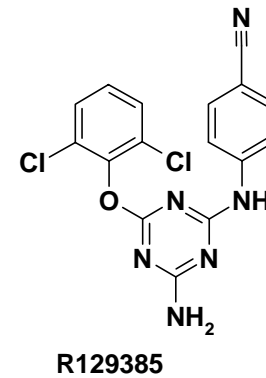
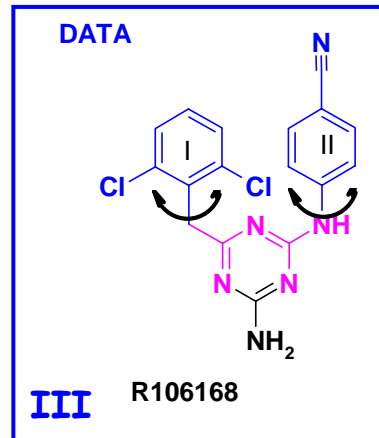
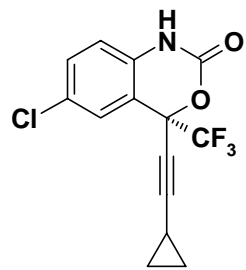
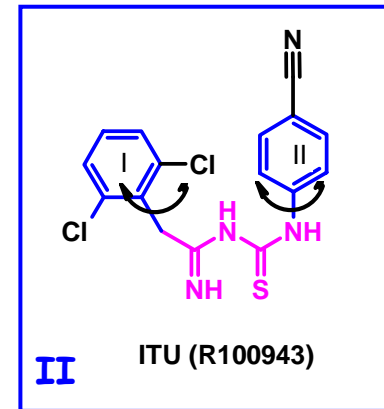
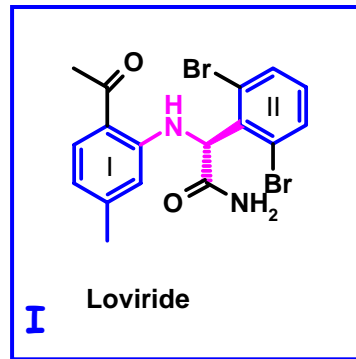
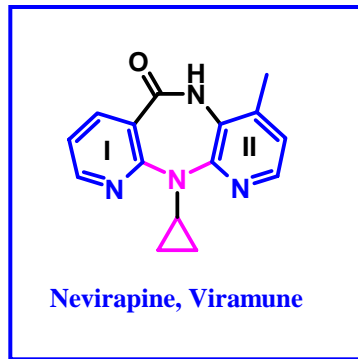


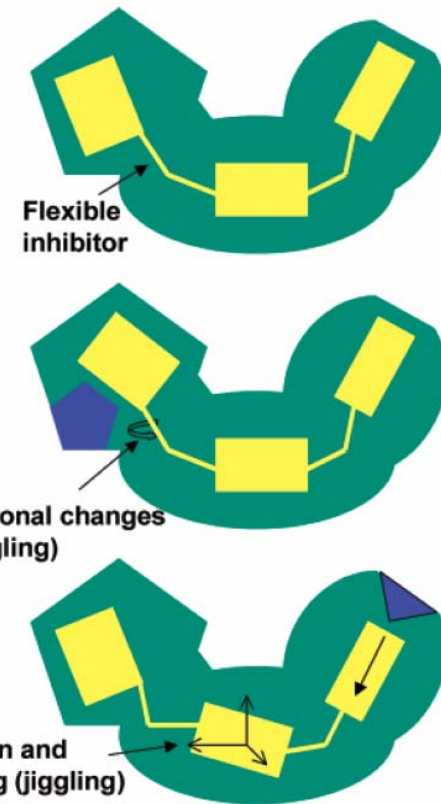
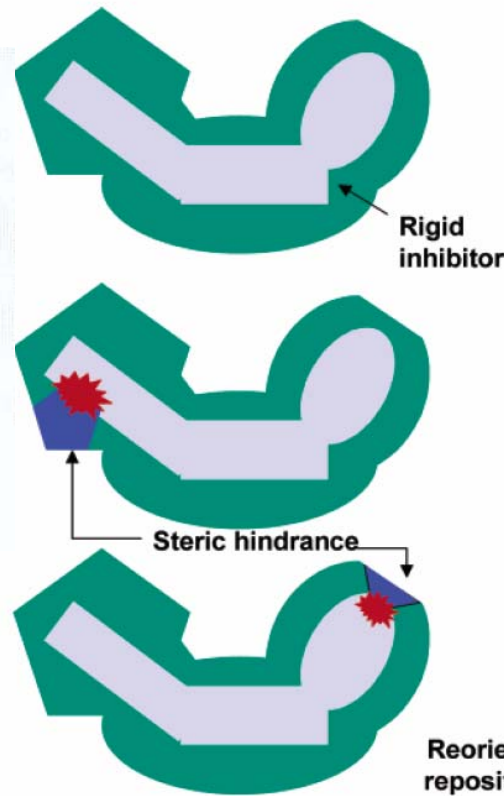
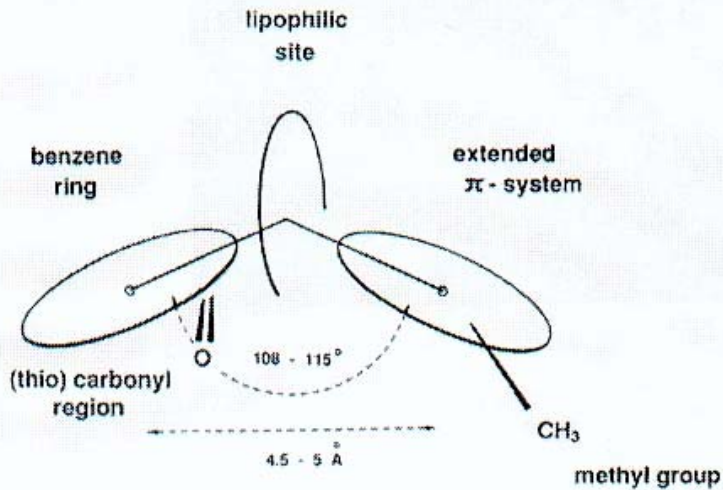
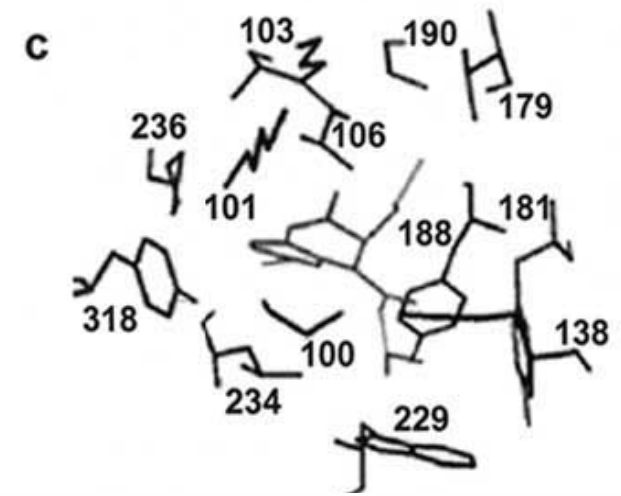
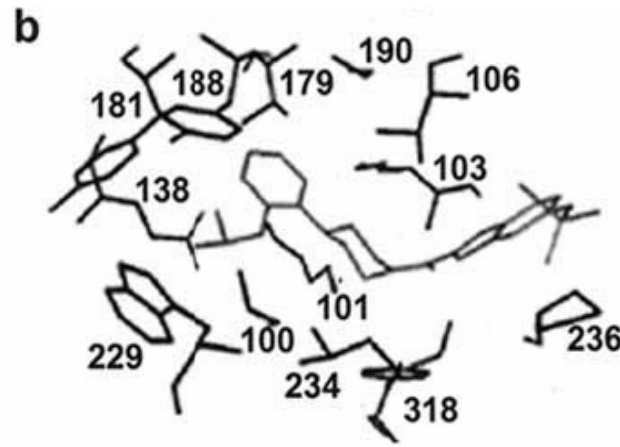
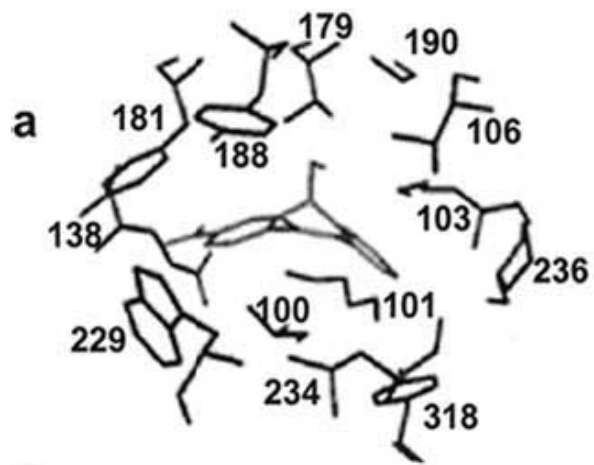
Emtricitabine, Emtriva, (-)-FTC



Tenofovir disoproxil fumarate, Viread , TDF

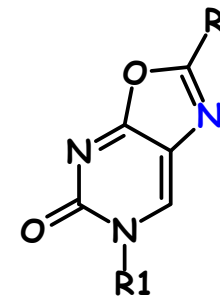
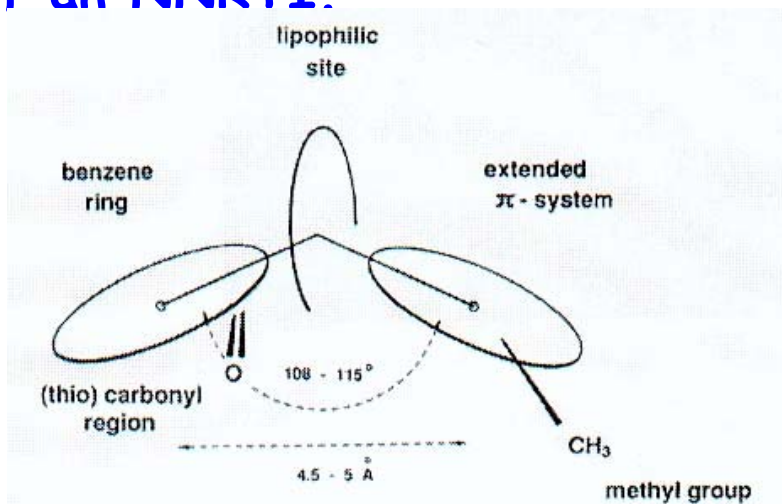
3 Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)





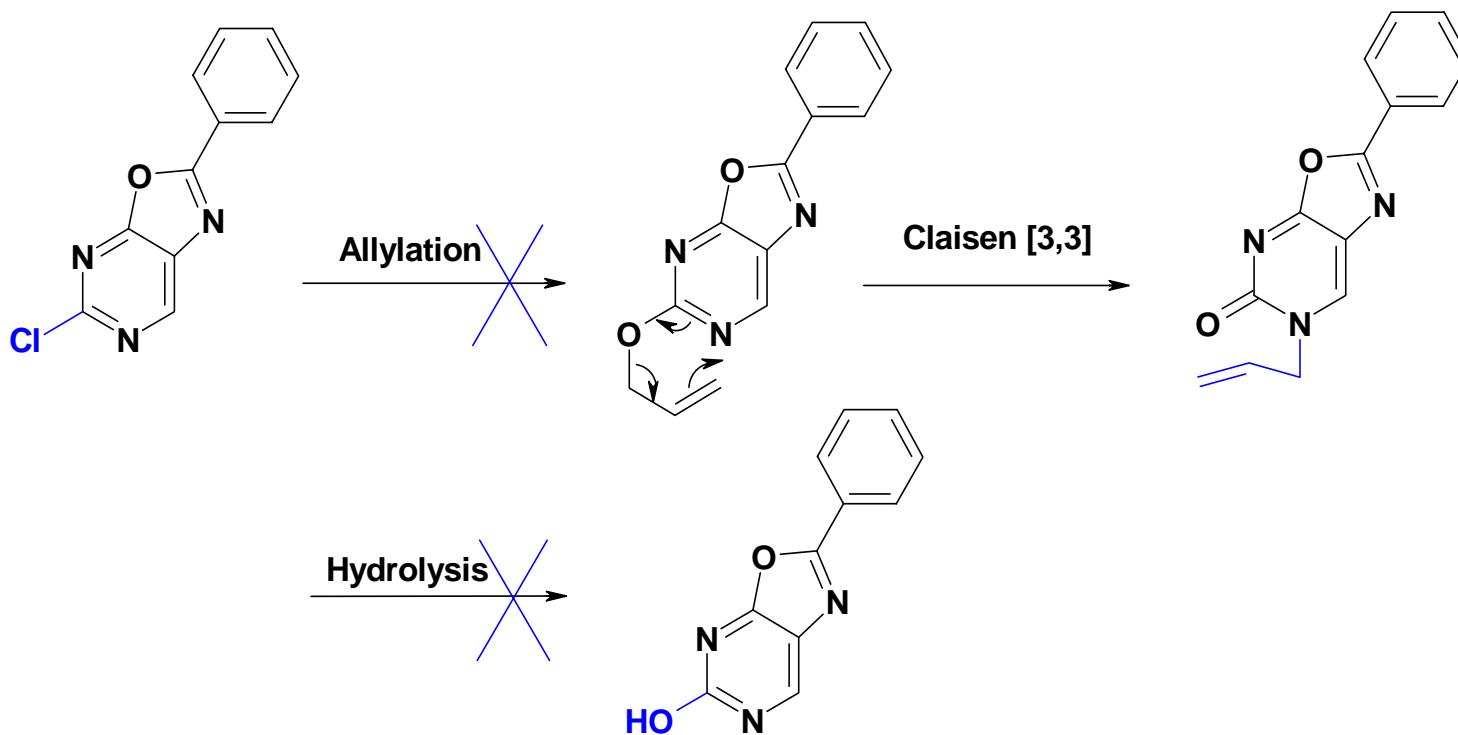
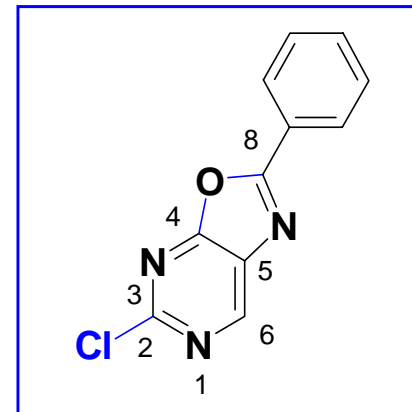
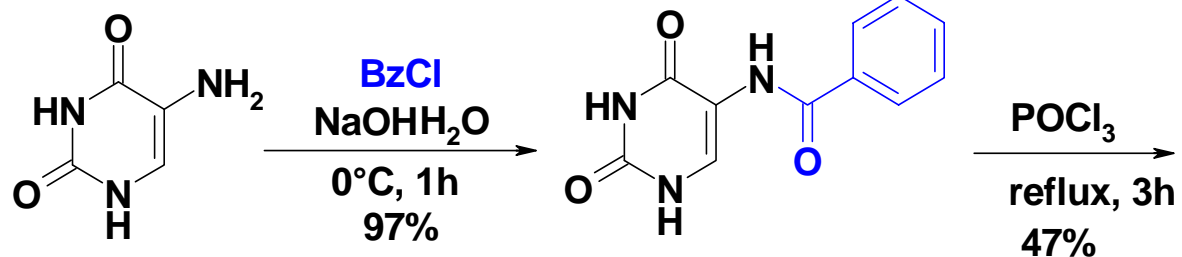
hydrophobic (aromatic) pocket

1. NNRTIs are chemically diverse
2. NNRTIs bind to HIV-1 RT in a hydrophobic pocket (NNIBP) that contains side chains of aromatic and hydrophobic aa
3. NNRTIs develop extensive hydrophobic residues (van der Waals and π - π interactions with aromatic rings)
4. We termed a « butterfly-like » binding mode and wing I, wing II and body/linker as modular segments
5. The NNIBP is elastic and its conformation depends on the size, shape, specific chemical composition, and binding mode of an NNRTI.

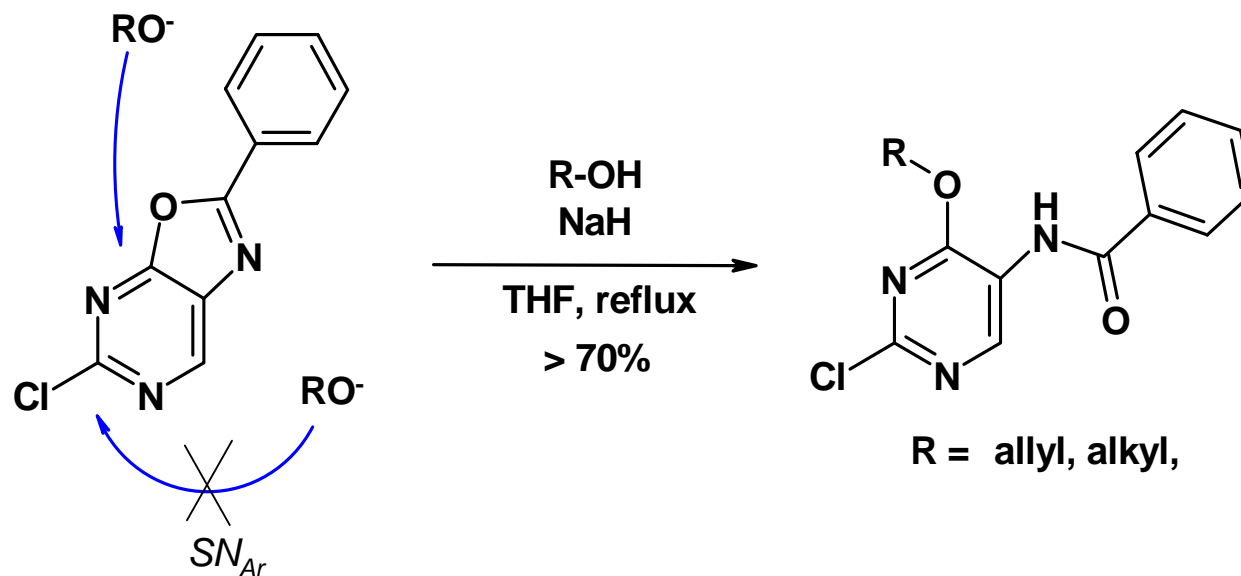


Oxazolopyrimidines

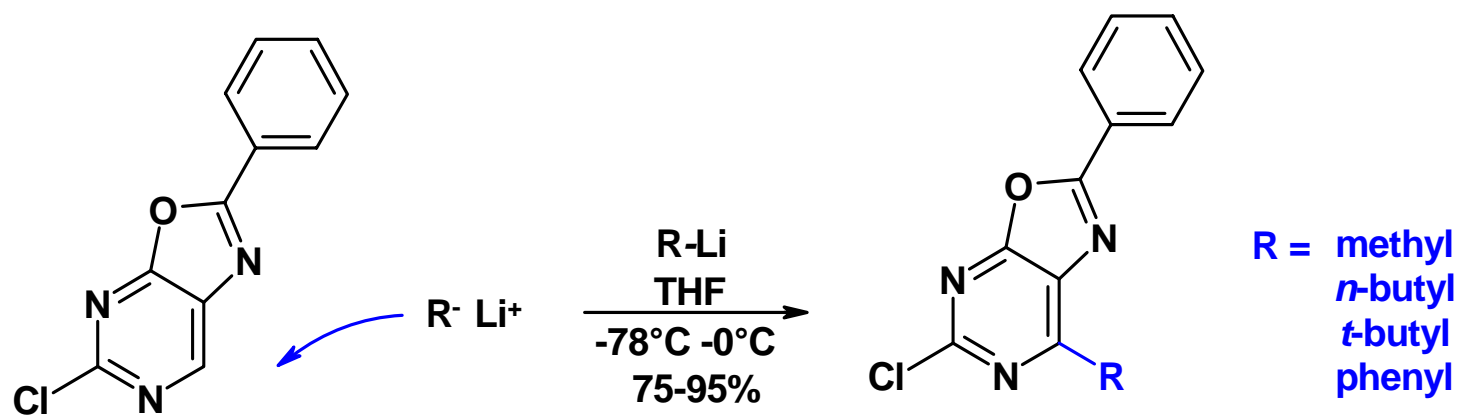
Synthesis of Oxazolopyrimidines



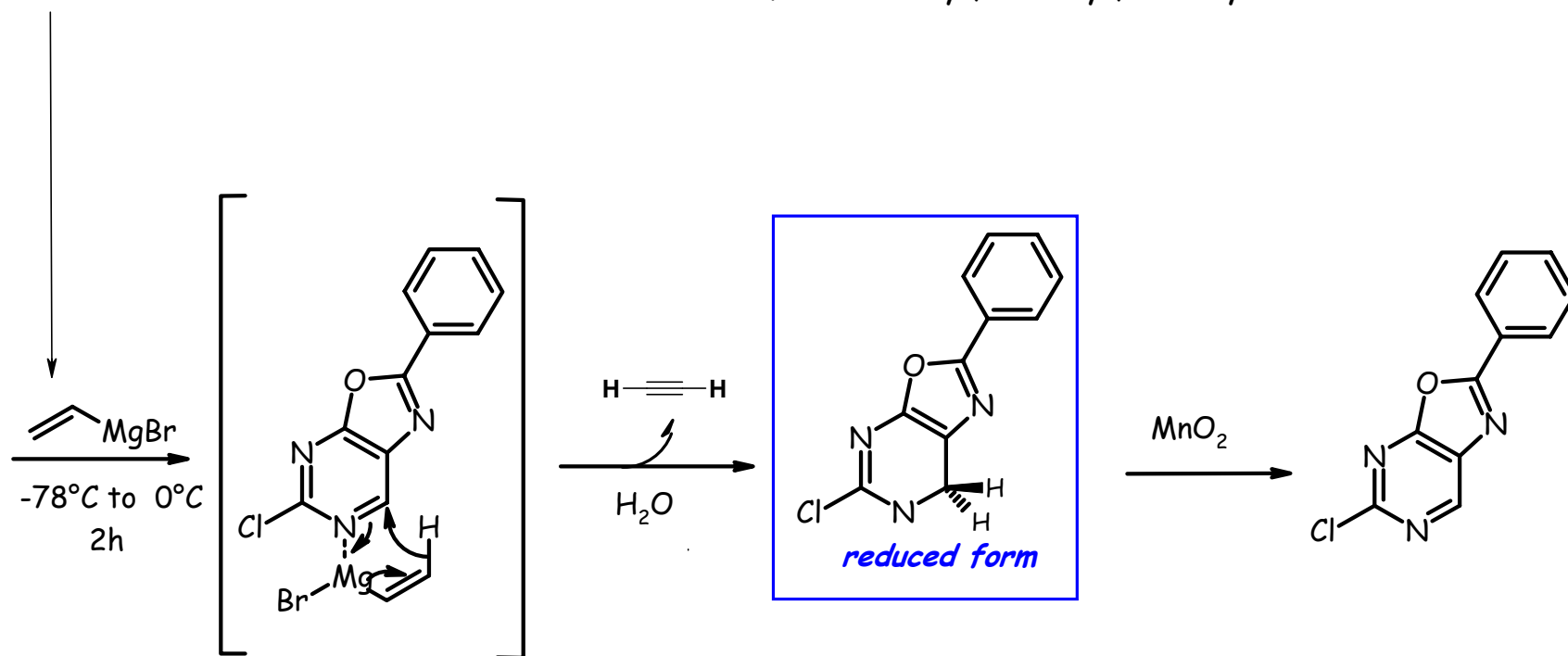
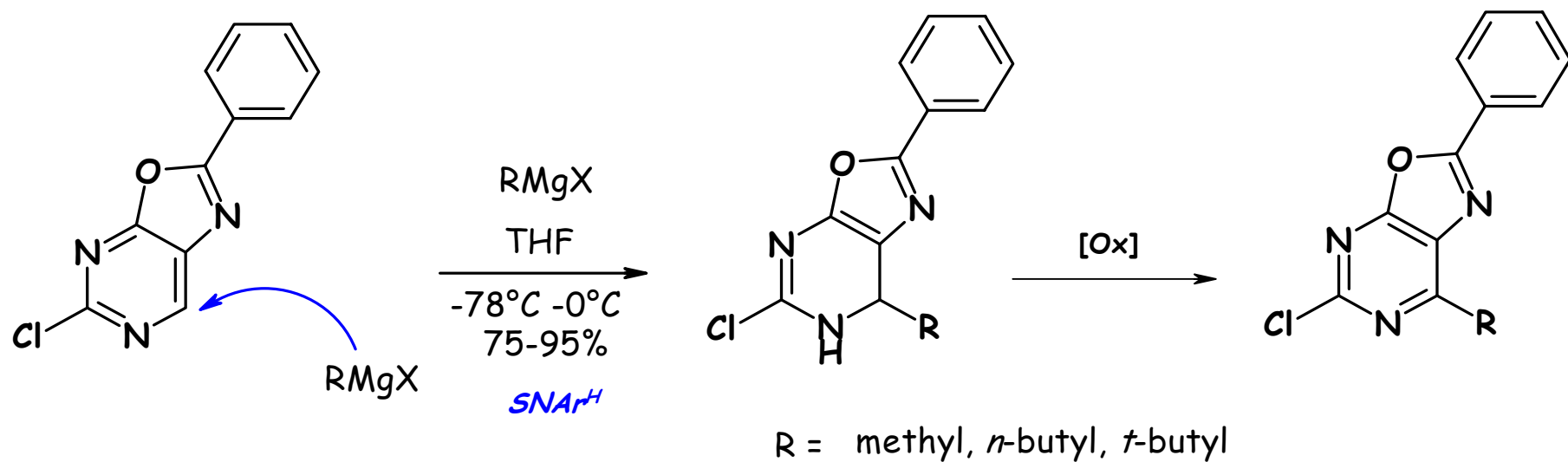
Reactivity towards alcoholates



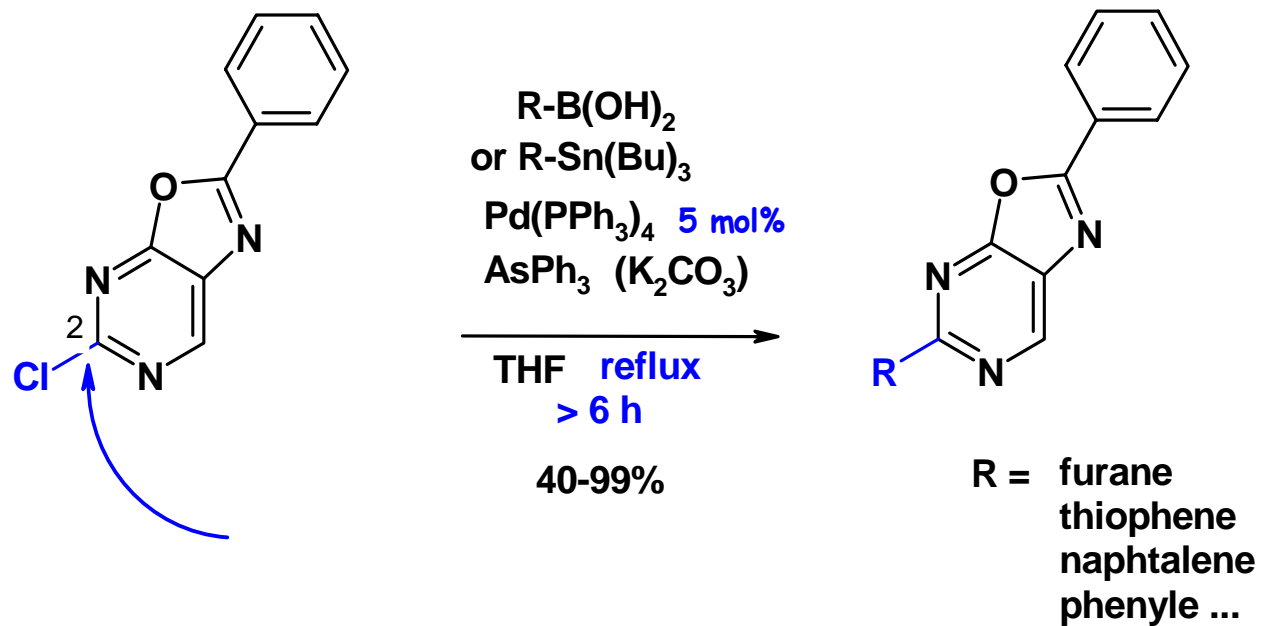
Reactivity towards organolithium



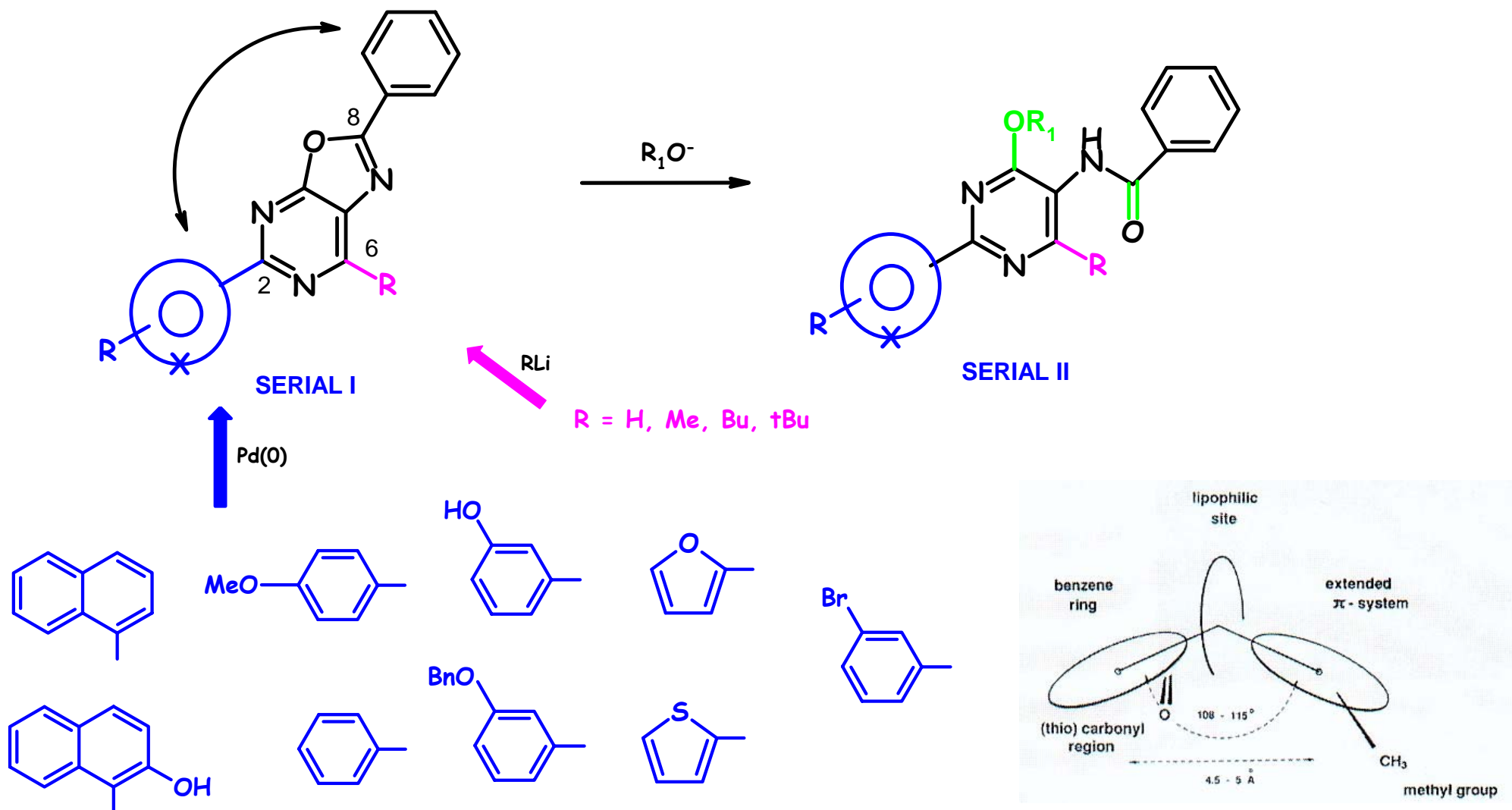
Reactivity towards organomagnesium

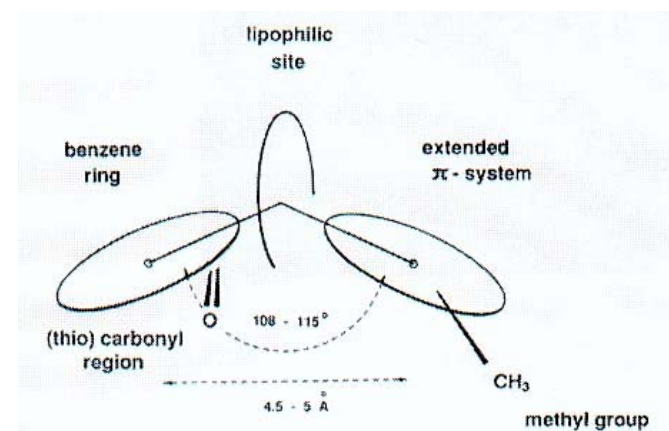
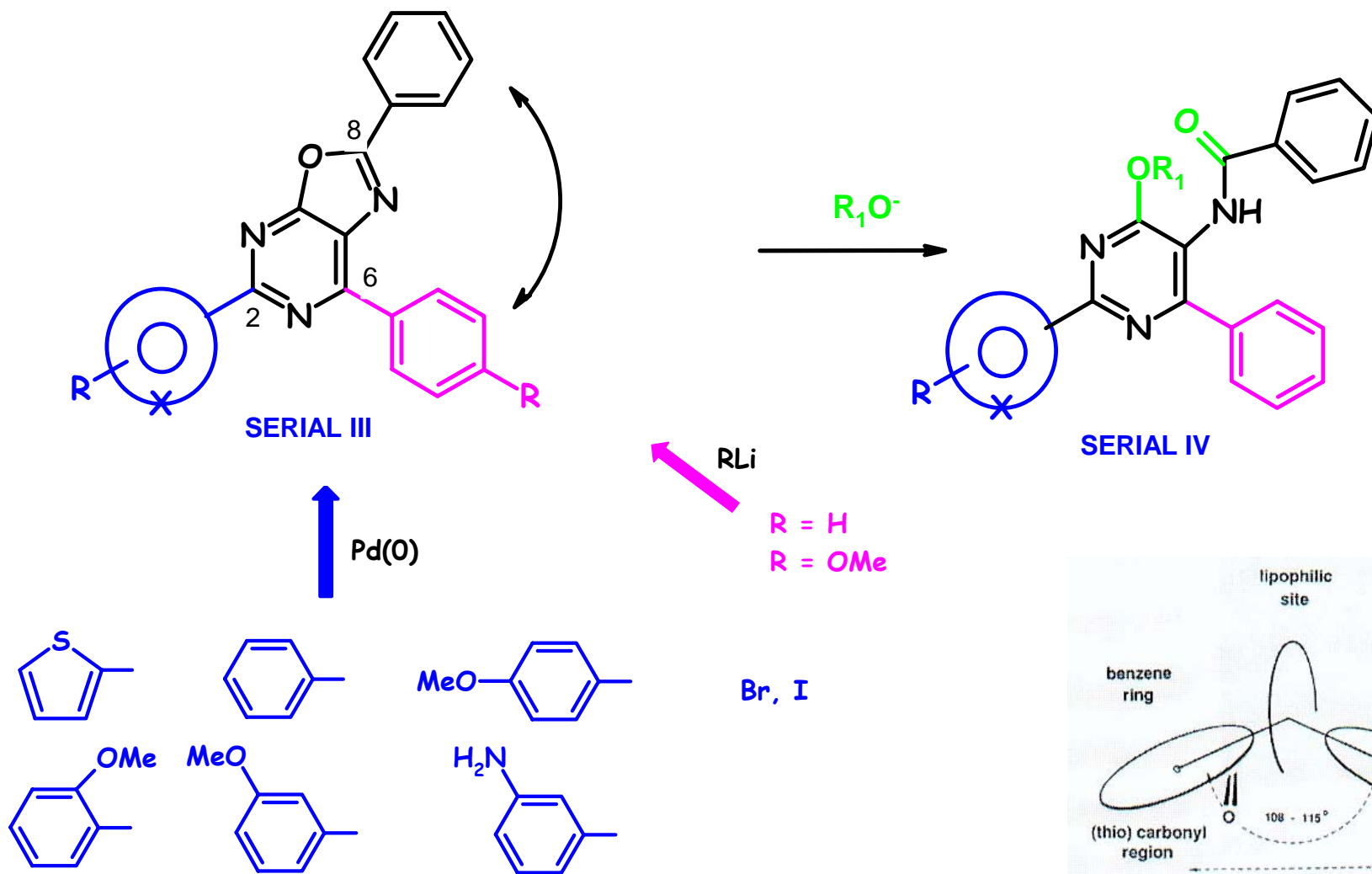


Reactivity towards Pd(0) reactions

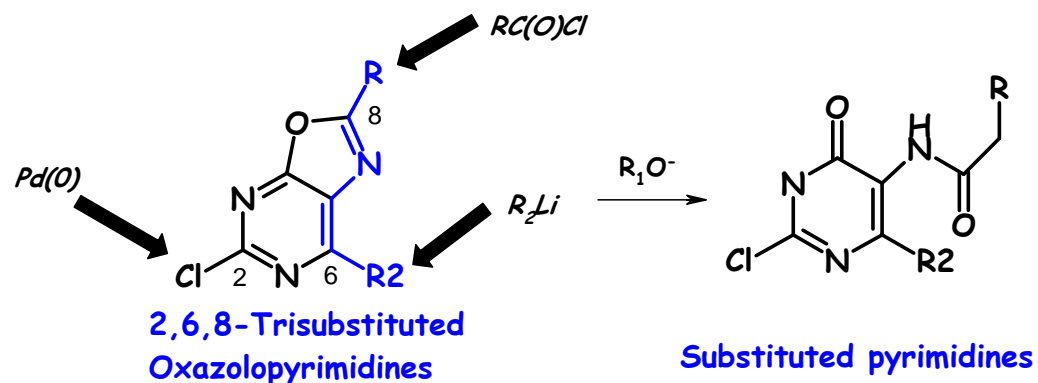


Overview of obtained oxazolopyrimidines and their opened forms

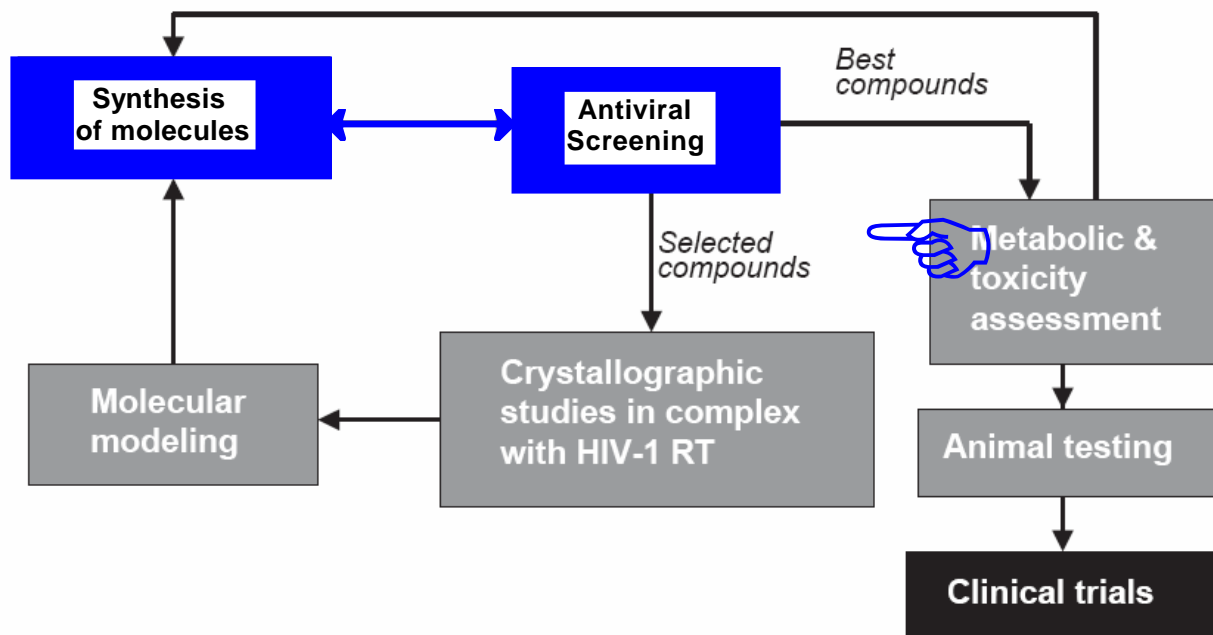




Conclusion



- Brief overview of new heterocycles - NNRTIs like -
- Interest into 6,8-disubstituted oxazopyrimidines
- Access to a large diversity using Pd(0), RLi, RO⁻ chemistry
- Towards small libraries introducing more flexibility
- Evaluation on drug-resistant strains of HIV-1



ACKNOWLEDGMENTS

Synthesis

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Collaborations

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- Région Centre
- CNRS

