Synthesis of Selective CDK2/SPY1 Inhibitors employing Stereochemical Control - An invaluable tool in an Organic Chemist's belt

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An invaluable tool in an Organic Chemist's belt

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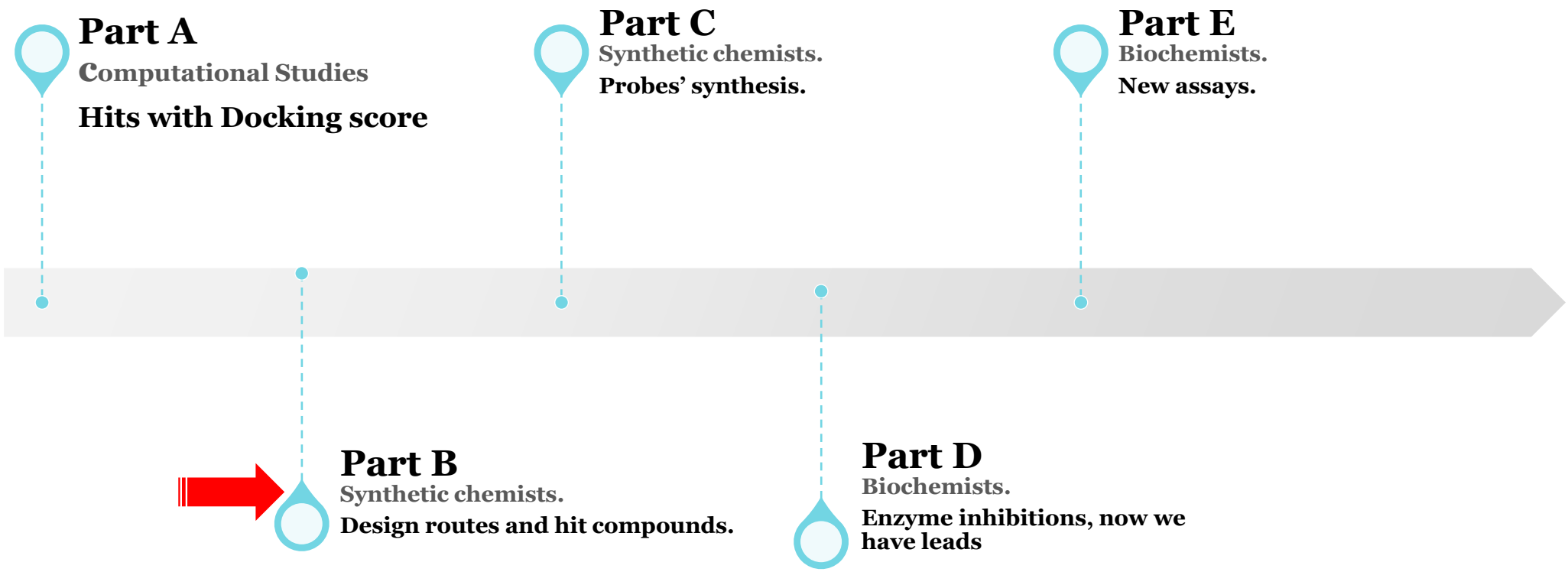
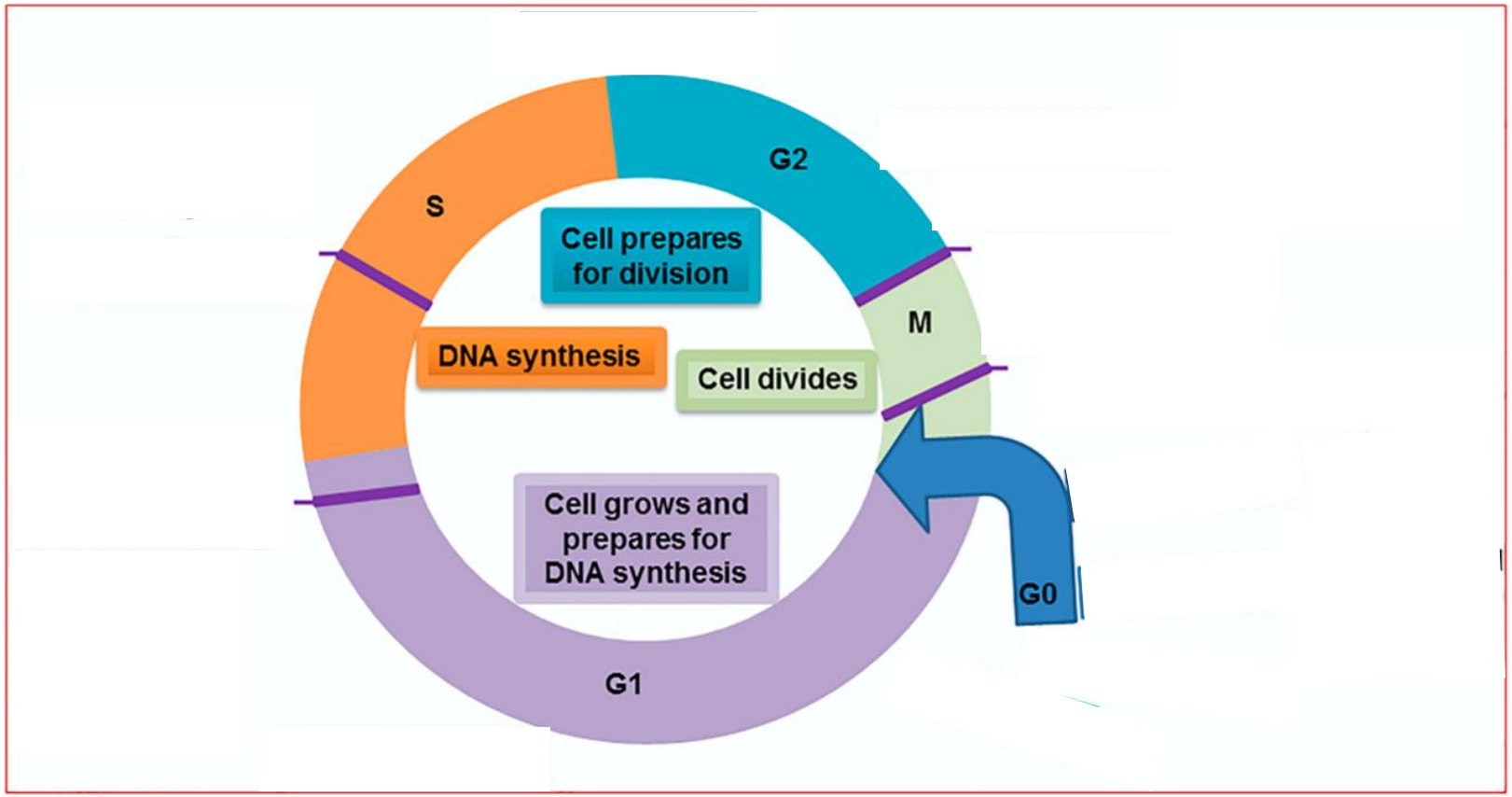
CDK2 Project – A sneak peek



Cell division cycle, role of CDKs and checkpoints.



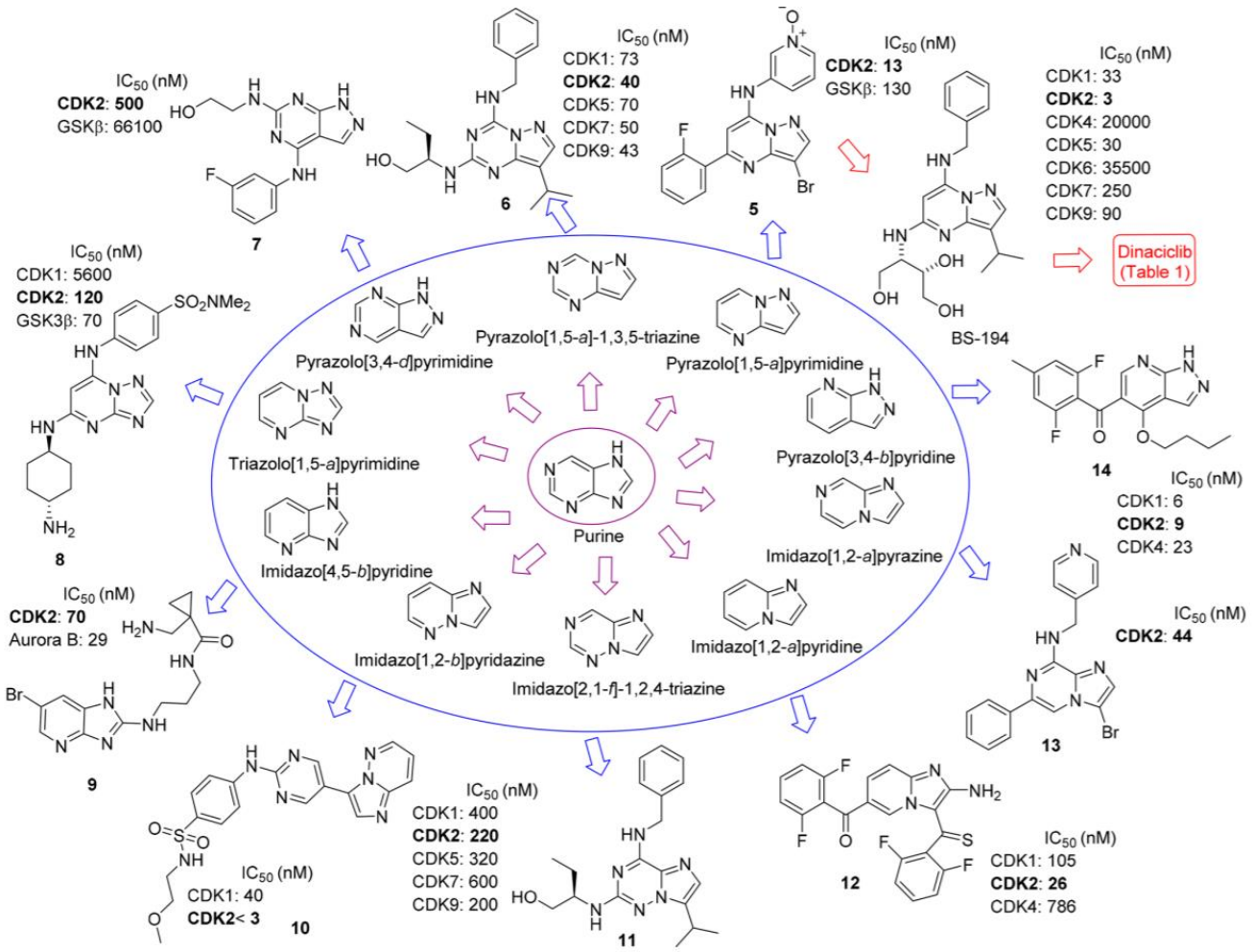
Challenge in CDK2 inhibitor - selectivity.

Table 1. Percent (%) Sequence Similarity between CDK2 and Other CDKs[a]

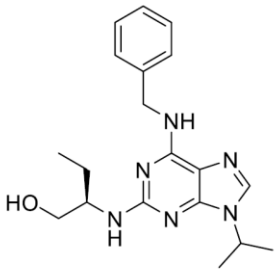
CDK	% sequence identity
CDK 3	74
CDK 1	65
CDK 5	58
CDK 6	44
CDK 4	43
CDK 7	38
CDK 20	37
CDK 10	36
CDK 18	33
CDKs 9, 14, 15, and 16	32
CDK 17	30
CDK 8	24
CDK 19	23
CDK 11	16
CDKs 12 and 13	9

[a]Sequence alignments were performed and % sequence similarity determined by using the UniPort database (http://www.uniprot.org/align/).

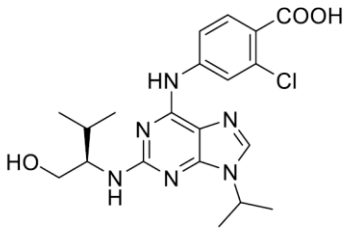
Purine – a central scaffold to CKI inhibitors.



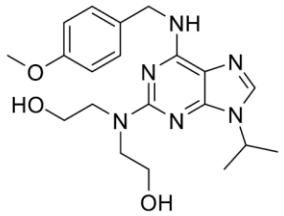
CKIs



Roscovitine
IC50
CDK1: 650 nM
CDK2: 700 nM
CDK4: >100000 nM
CDK6: >100000 nM

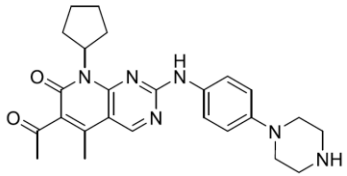


Purvalanol B
IC50
CDK1: 6 nM
CDK2: 6 nM
CDK4: >10000 nM
CDK6: -

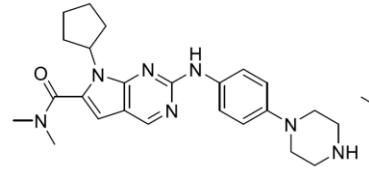


CVT-313
IC50
CDK1: 4200 nM
CDK2: 500 nM
CDK4: >100000 nM
CDK6: -

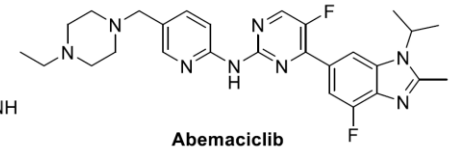
Figure 1.6. First generation CKIs: Roscovitine, Purvalanol B, and CVT-313.[45,46,48]



Palbociclib
IC50
CDK1: >10000 nM
CDK2: >10000 nM
CDK4: 11 nM
CDK6: 16 nM



Ribociclib
IC50
CDK1: >50000 nM
CDK2: >50000 nM
CDK4: 10 nM
CDK6: 39 nM



Abemaciclib
IC50
CDK1: >1000 nM
CDK2: >1000 nM
CDK4: 2 nM
CDK6: 10 nM

Figure 1.7. Second generation CKIs approved for CDK4/6 inhibition.[55]

NU2058 series

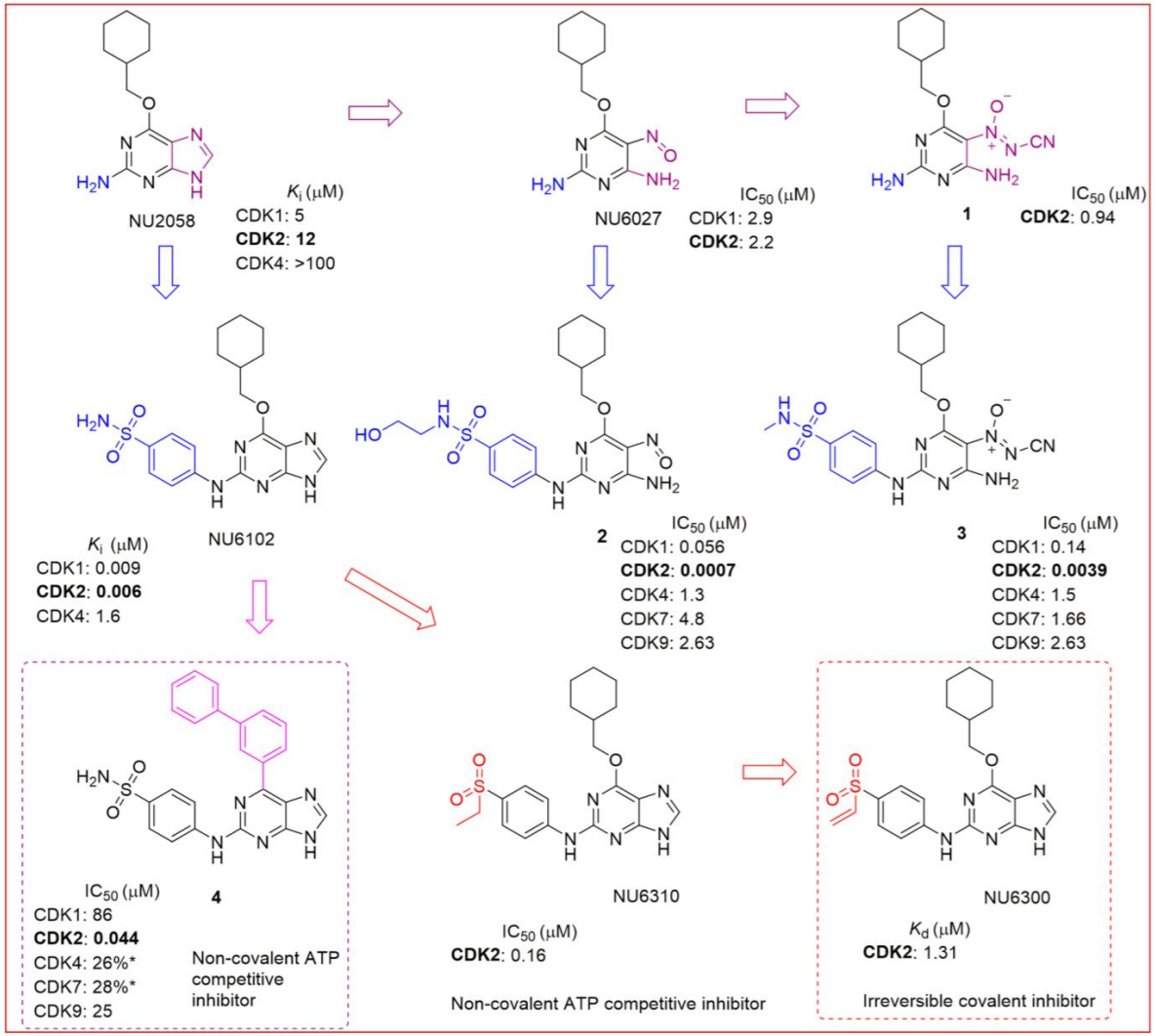
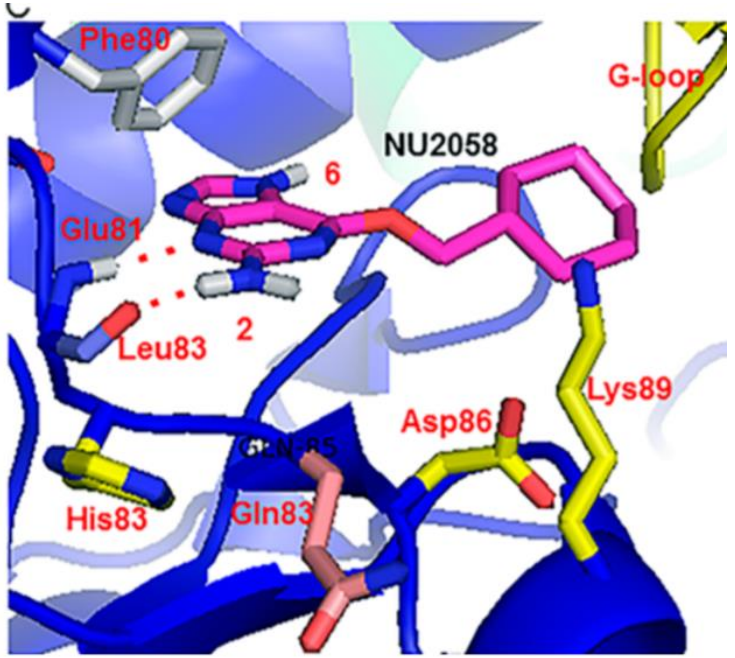
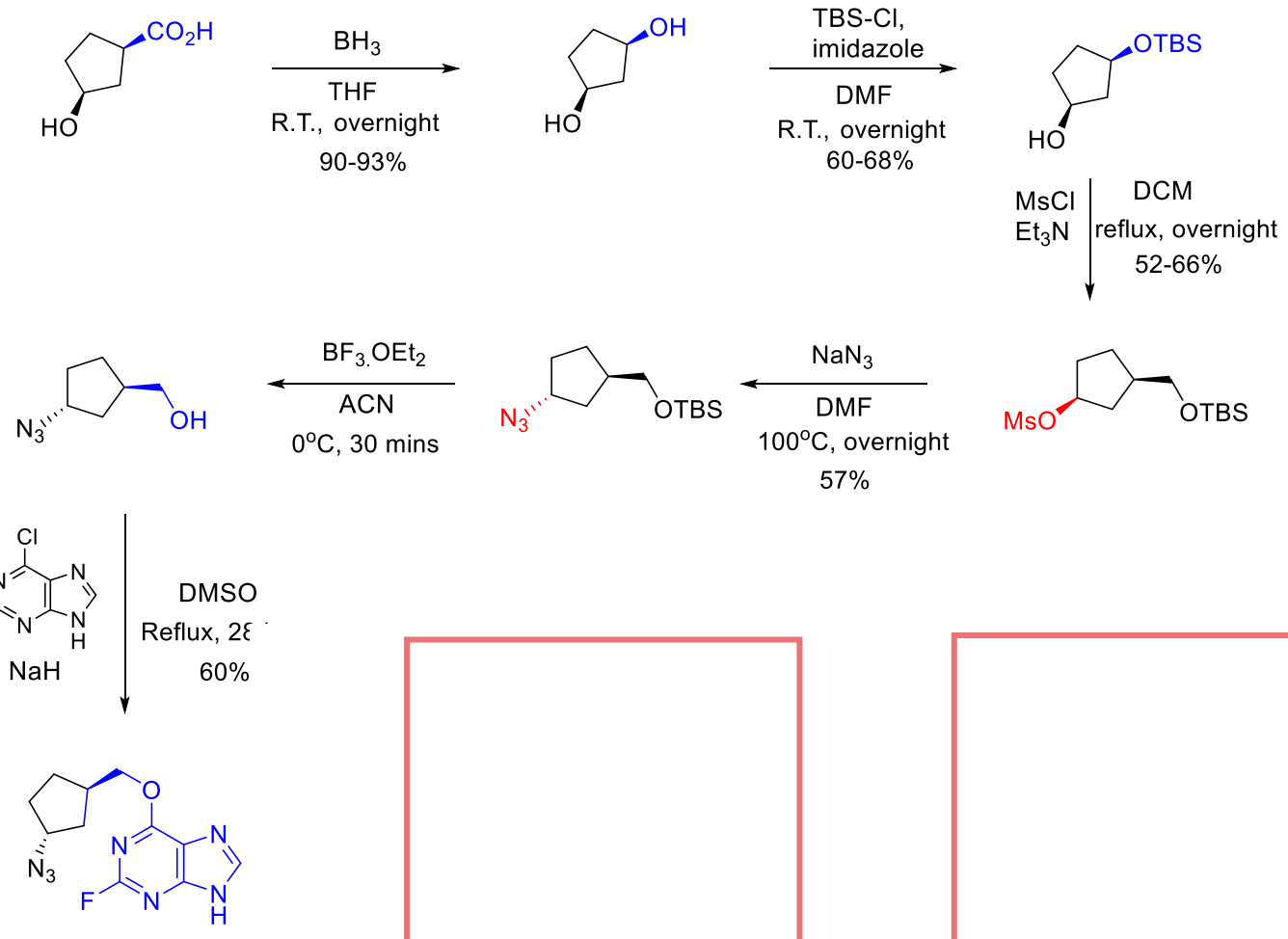


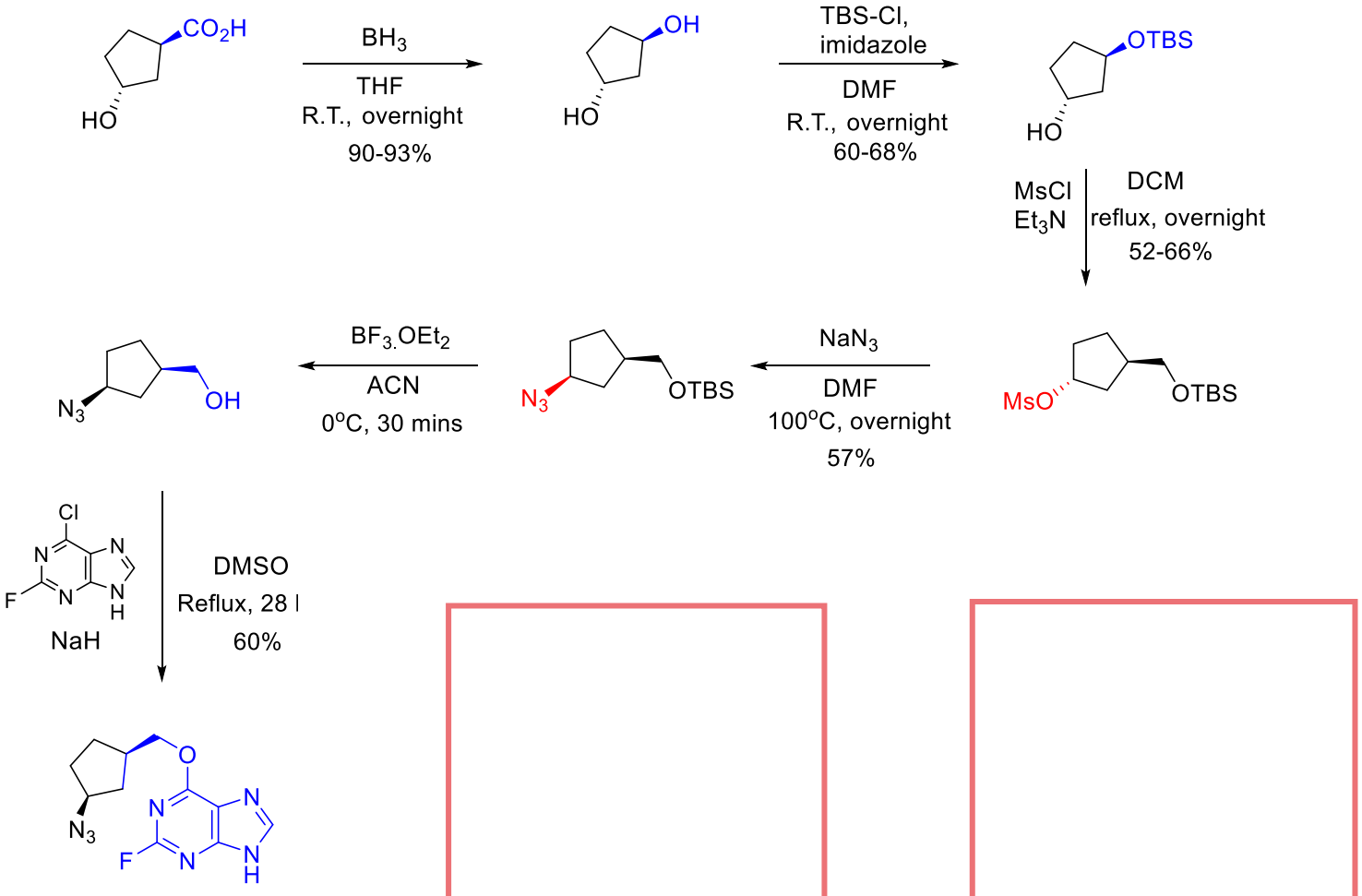
Figure 4. Identification and optimization of 2-amino-6-oxypurine core as CDK2 inhibitors. * represents inhibition at 100 μM.



Synthetic route – from cis to trans molecules.



Synthetic route – from trans to cis molecules.




Thank
you