Drug Discovery: Towards the Synthesis of Novel CDK2-Spy1 Inhibitors

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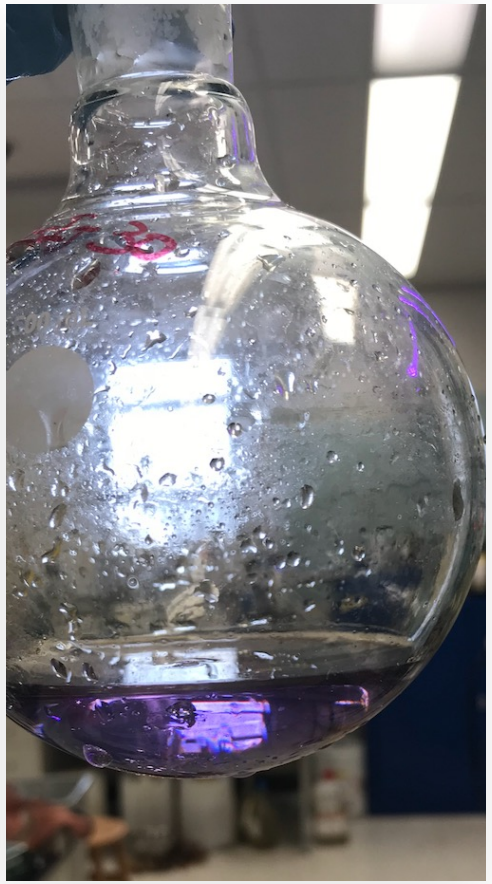
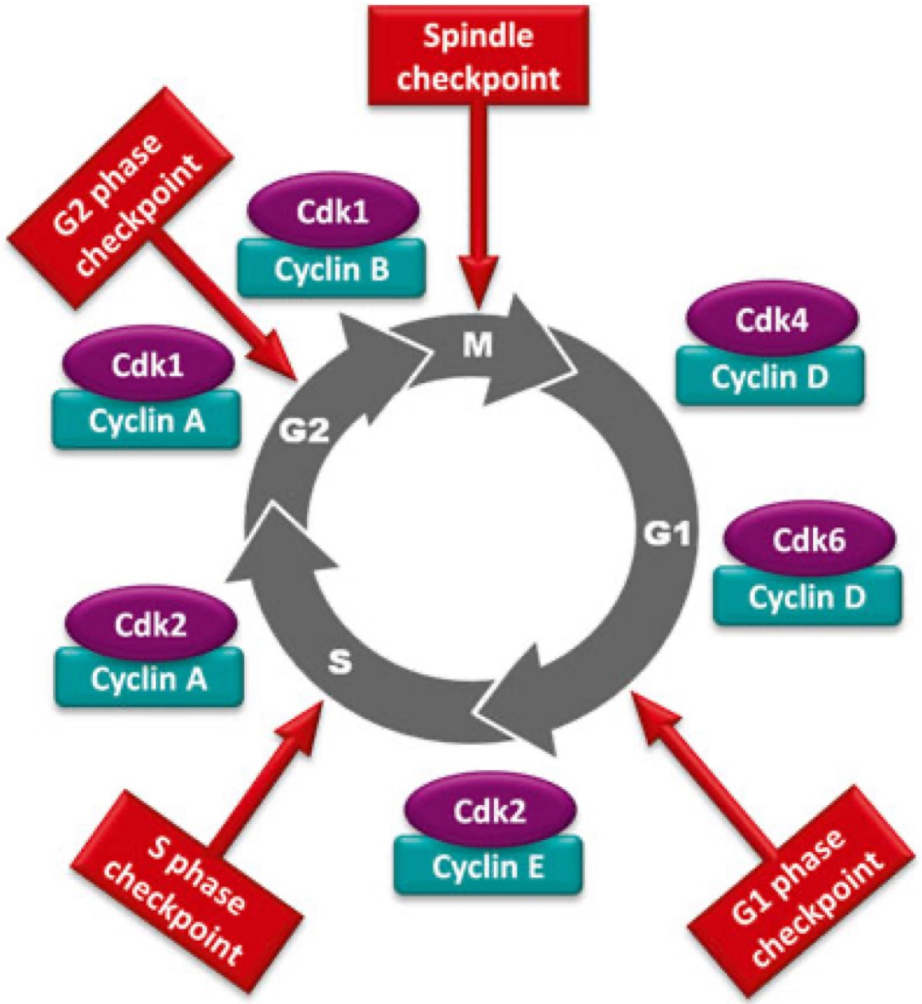
About Me…

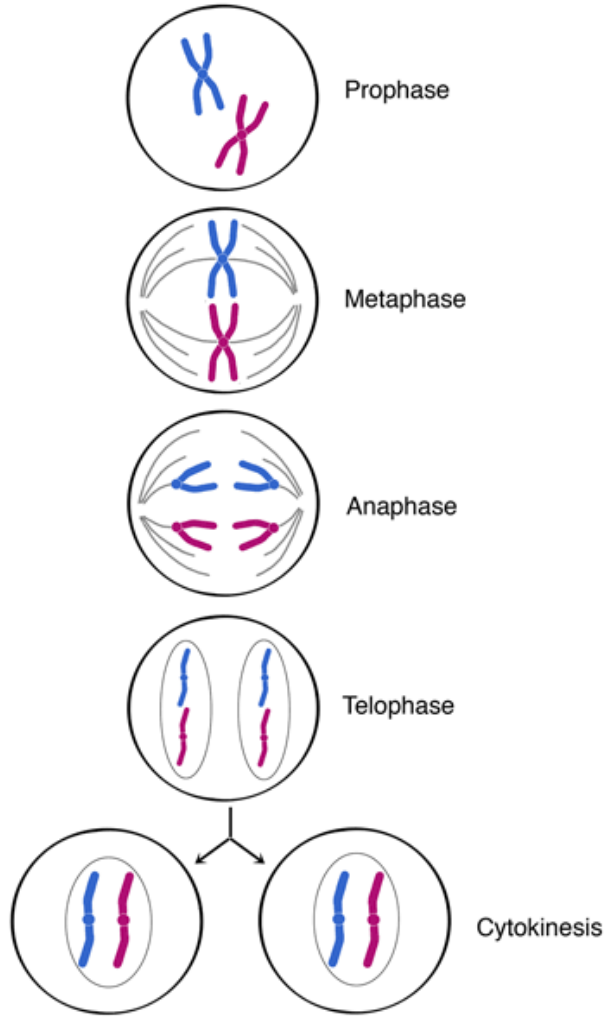


- 4th year Honours Chemistry
- Organic chemistry and total synthesis
- Uyghur international student from Xinjiang
- Supervisor: Dr. John F. Trant

Proteins In Cell Regulation

- CDKs and Cyclins: regulates cell proliferation
- Unregulated CDK complexes lead to uncontrolled cell growth = cancer
- Existing treatments target CDK/Cyclin complexes cause cytotoxicity due to lack of selectivity





Spoerri, L. *et al.* Cell Cycle Checkpoint and DNA Damage Response Defects as Anticancer Targets: From Molecular Mechanisms to Therapeutic Opportunities. in *Stress Response Pathways in Cancer: From Molecular Targets to Novel Therapeutics* 29–49 (2015).

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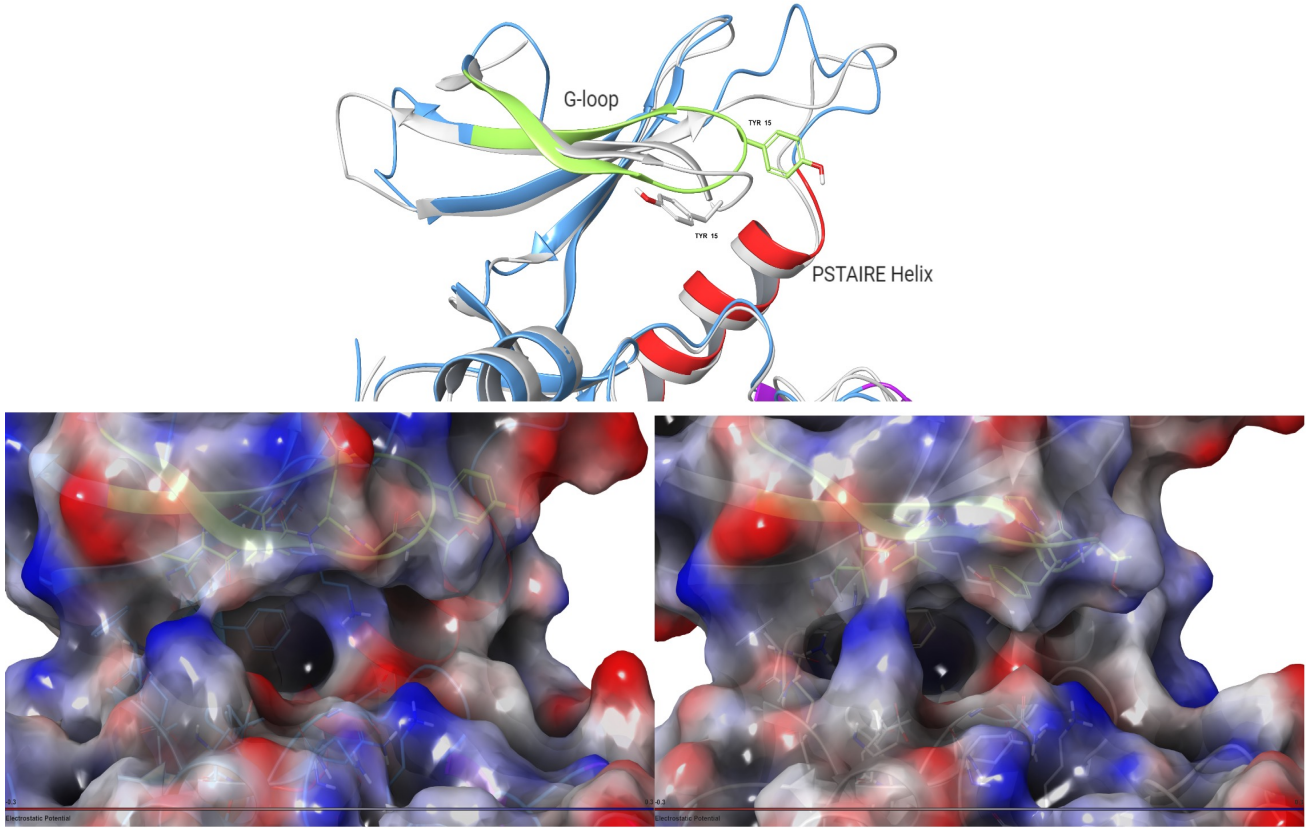
A New Target

- CDK2-Spy1 complex: partner in crime
- Practicality: non-essential protein
- Not been selectively targeted before in terms of CKI (cyclin-dependent kinase inhibitor) therapy
- Current CKIs show decreased affinity to CDK2-Spy1 complex
- Selectivity due to difference in active site conformation



CDK2-Cyclin A **CDK2-Spy1**

McGrath, D. A. *et al.* Structural basis of divergent cyclin-dependent kinase activation by Spy1/RINGO proteins. *EMBO J.* **36**, 2251–2262 (2017).

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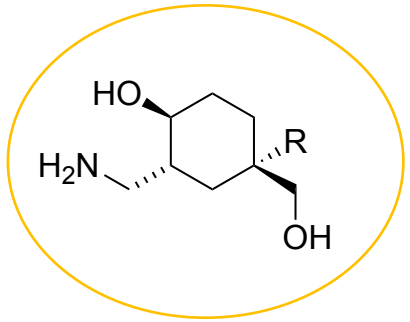
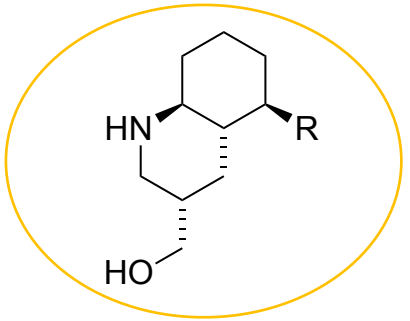
Current Focus

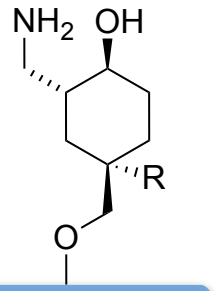
- Synthesis of alcohol moieties based on computational work
- Methodology developed by previous members of Trant Team



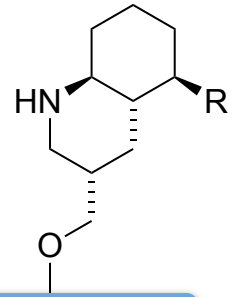
target #1



target #2



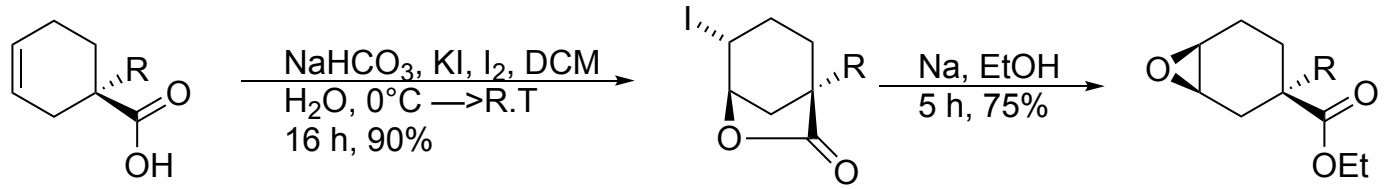
Purine core



Purine core

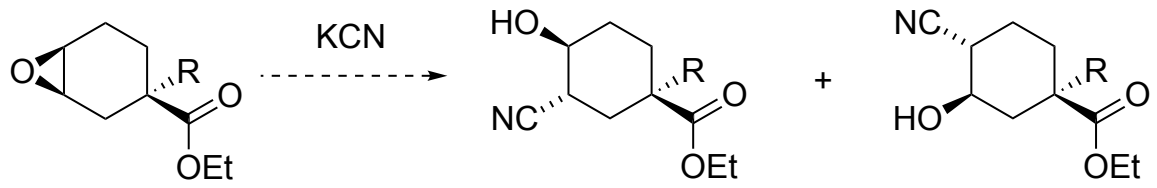
Target #1: Smooth Sailing

- Iodolactonization
- Epoxidation



Base Equiv.	Base	Solvent	Time	Product Yield
1.2	2M NaOH aq.	EtOH	5 h	0%
1.2	NaOH	EtOH	5 h	31%
1.2	Na	EtOH	5 h	75%

Target #1: Bottleneck



Desired isomer

- Solubility issue of cyanide
- Computational work indicates regioselective ring opening is difficult to achieve
- IR, ^{1}H NMR, ^{13}C NMR, 2D NMR used

Cyanide source	Cyanide Equiv.	Temperature	18-Crown-6 Equiv.	Acid Source	Acid Equiv.	Solvent	Time	Product Yield
TMSCN	1.1	0 °C → R.T.	------	$LaCl_3 \cdot 7H_2O$	0.15	DCM	48 h	0%
TMSCN	1.1	0 °C → R.T.	------	$LaCl_3$	0.15	DCM	48 h	0%
TBACN	1.1	0 °C → 40 °C	------	------	------	TFE	120 h	0%
KCN	1.1	0 °C → 40 °C	0.55	------	------	TFE	120 h	0%
KCN	2.2	0 °C → 40 °C	1.1	------	------	TFE	120 h	0%
KCN	1.1	0 °C → 40 °C	1.21	------	------	MeCN	120 h	0%
KCN*	3.5	0 °C → 40 °C	3.6	------	------	HMPA/DME/DMF	120 h	0%
KCN*	3.5	0 °C → 120 °C	3.6	NH_4Cl	1.0	HMPA/DME/DMF	120 h	0%
KCN	1.5	0 °C → 80 °C	------	NH_4Cl	1.0	H_2O	16 h	29%

*TBAI was added for these reactions

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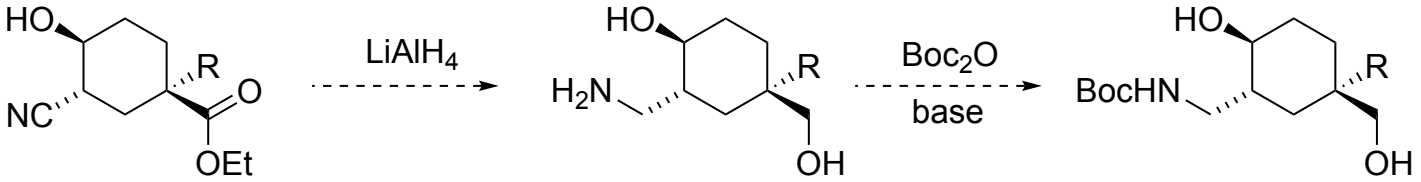
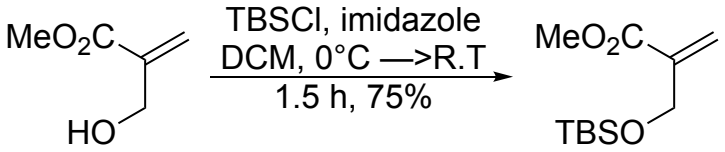
Currently:

- Fieser workup
- Polarity issue
- Purification

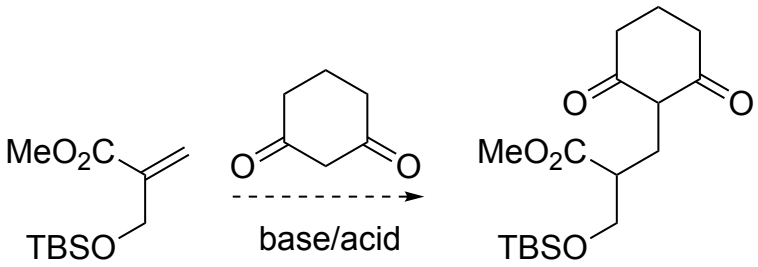


Target #2: Also Smooth Sailing

- TBS protection
- Reduced reaction time
- Simple purification



Target #2: Also… Bottleneck



- Impurity in ketone starting material
- Decomposition of compounds at high temperature
- Difficulty in extraction
- Low mass recovery

Substrate	Base/Acid	Base/Acid Equiv.	Temperature**	Ketone Equiv.	Solvent	Time	Product Yield
R-OH	NaOH	1.0	R.T.	1.2	H_2O	144 h	SM recovered
R-OH	Na	1.2	R.T.	1.2	EtOH	144 h	0%
R-OH	Na	2.4	R.T.	1.2	EtOH	144 h	0%
R-OH	NaH	1.2	R.T. → 80 °C	1.3	DMSO	22 h	0%
R-OH	K_2CO_3	2.0	R.T. → 80 °C	1.2	DMSO	22 h	0%
R-OH	$BF_3{\cdot}OEt_2$	1	R.T.	1.0	THF	22 h	0%
R-OH	$BF_3{\cdot}OEt_2$	0.1	R.T.	1.0	THF	22 h	SM recovered
R	NaH	1.2	R.T. → 80 °C	1.3	DMSO	22 h	0%
R	K_2CO_3	2.0	R.T. → 80 °C	1.2	DMSO	22 h	0%
R-OTBS	NaH	0.8	R.T. → 80 °C	0.8	DMSO	22 h	0%
R-OTBS	NEt_3	2.0	80 °C	1.2	DMSO	96 h	0%
R-OTBS	DBU	2.0	80 °C	1.2	DMSO	96 h	0%
R-OTBS	NEt_3	2.0	R.T.	1.2	DCE	48 h	SM recovered
R-OTBS	NEt_3	2.0	R.T.	1.2	THF	48 h	SM recovered
R-OTBS	DBU	2.0	R.T.	1.2	THF	48 h	SM recovered
R-OTBS	KHMDS	2.0	R.T.	1.2	THF	144 h	0%
R-OTBS	LiHMDS	2.0	R.T.	1.2	THF	144 h	0%
R-OTBS	LDA	1.2	R.T.	1.2	THF	48 h	SM recovered

*R = methyl acrylate

**For R.T. → 80 °C temperature change, the first 16 h is done at R.T. and the last 6 h is done at 80 °C

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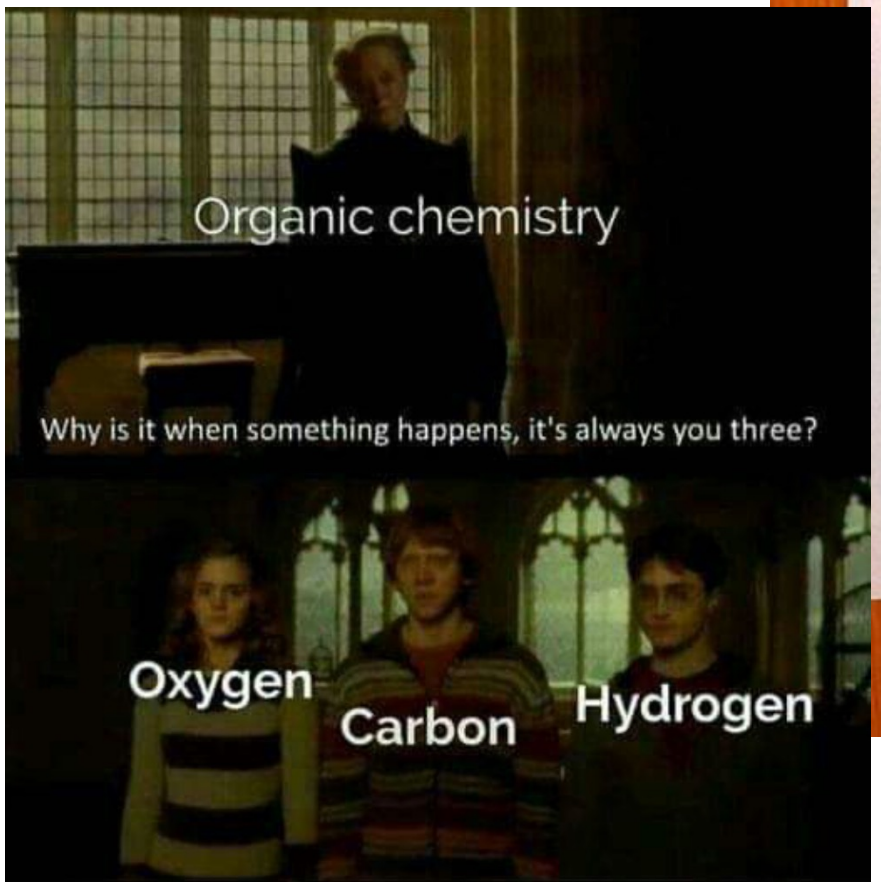
Next Step In The Journey

- Reduction of cyanation product
- Link to the purine core
- Drug testing in collaboration with The Porter Lab
- Screening conditions for Michael addition (ongoing)



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