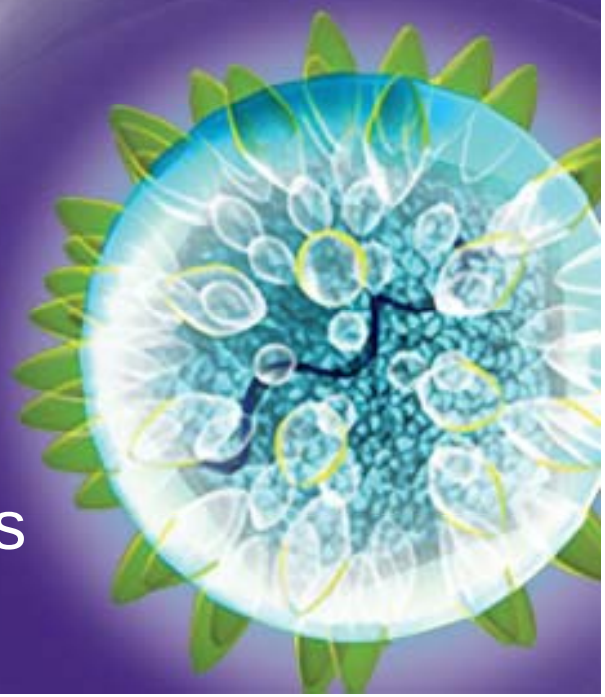
Design and synthesis of kinase inhibitors using novel heterocyclic systems



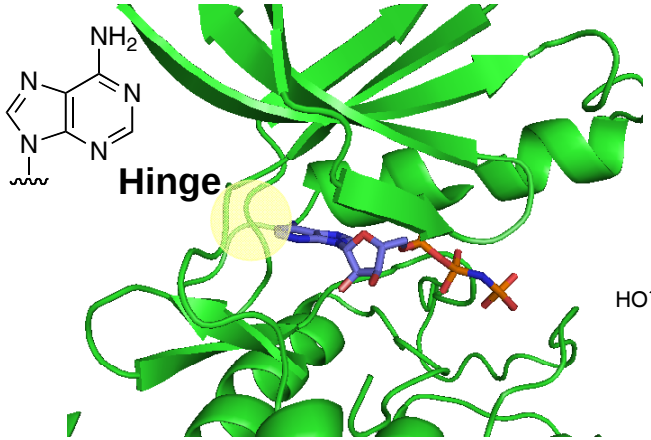
Dr Steven Durrant

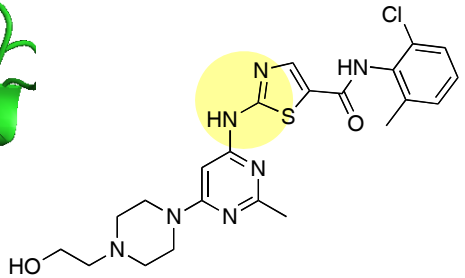
Vertex Pharmaceuticals

23rd March 2011

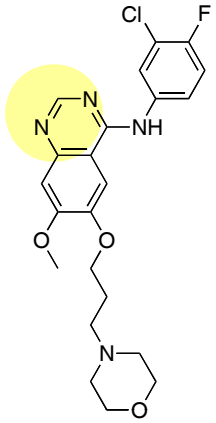
VERTEX

Development of Kinase Inhibitors

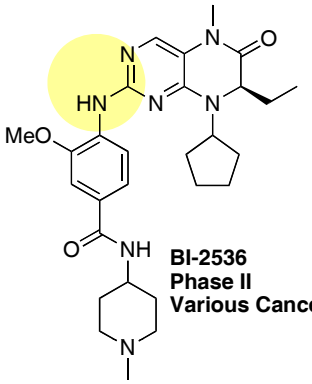




Sprycel
Bristol-Myers Squibb
Leukemia



Iressa
AstraZeneca
Various Cancer Types



BI-2536
Phase II
Various Cancer Types

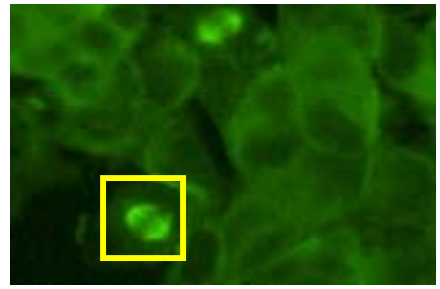
- 9 kinase inhibitors have reached the market
  - Many more have entered clinical trials
- ATP competitive inhibitors bind to “hinge” region using HBA/HBD motifs that mimic adenosine
- Mimicking this interaction leads to inherently flat aromatic systems
  - Poor physical properties result in need to append solubilising groups

Review: *J. Med. Chem.* 2011, 54, 1539-1554

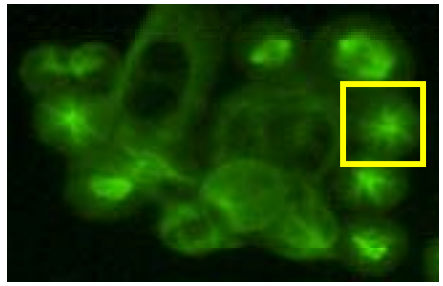
Plk1 is a promising oncology drug target

- Plk1 is overexpressed in multiple human tumours
  - Overexpression correlates with poor disease prognosis
- Plk family (1-4) are essential for accurate cell cycle progression
  - Plk1 plays a key role in the regulation of mitosis
  - Plks 2-4 have roles in tumour suppression / DNA damage response
- Small molecule inhibitors of Plk1 cause mitotic arrest and cell death (apoptosis) by activation of the mitotic checkpoint
- Development of ATP-competitive, Plk1-selective inhibitors could lead to a novel cancer therapy
  - Plk inhibitors are currently progressing through clinical trials

Control

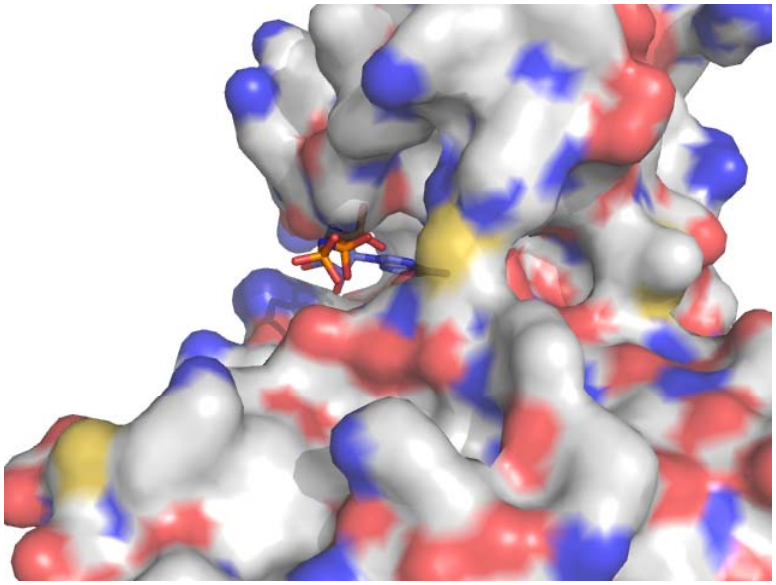


Plk1 inhibitor

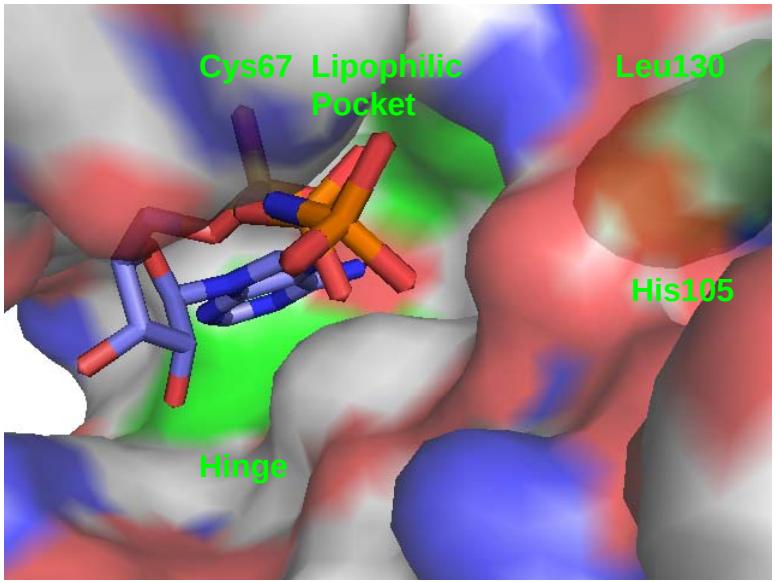


Review: Nature Reviews Drug Discovery 2010, 643-660

Overview of the Plk active site



Overview of whole kinase



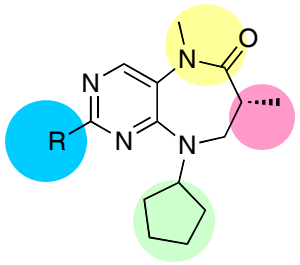
Key residues

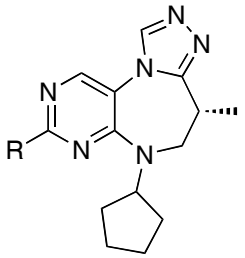
- Overall structure typical of many kinases
  - Cleft where ATP binds
- Two areas believed to be important for potency and selectivity
  - Lipophilic pocket defined by Leu130/Cys67
  - His105

3-Dimensionality can be engineered to improve drug-likeness

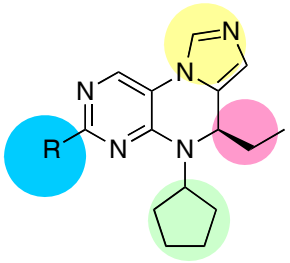
6:7 Scaffold

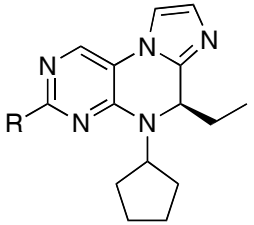
6:7:5 Scaffold

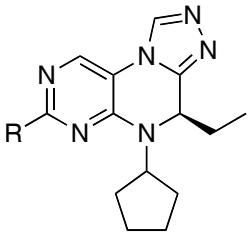




6:6:5 Scaffolds

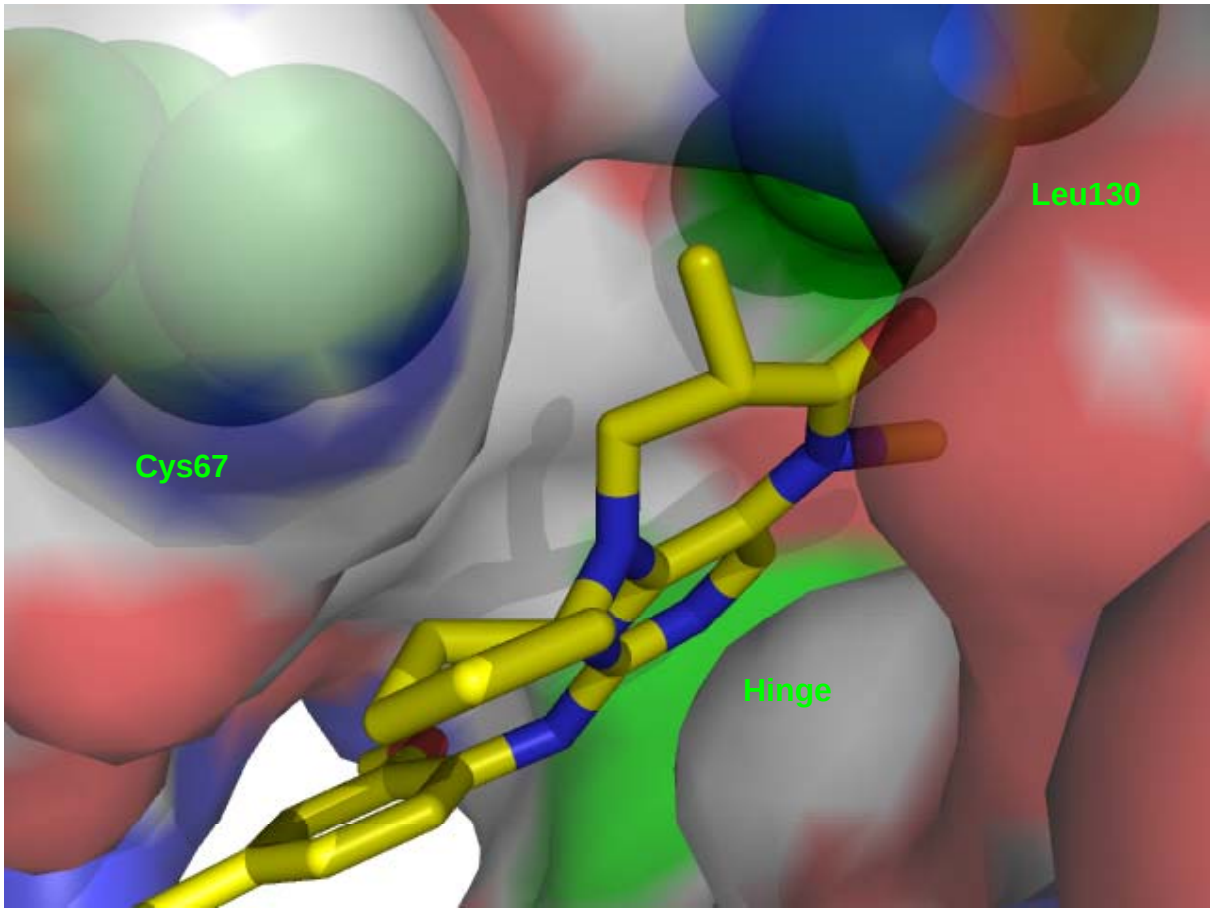


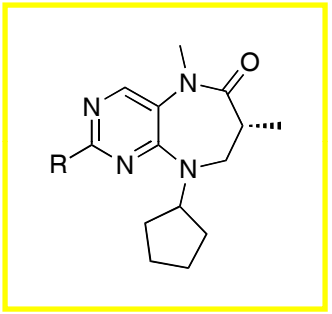




- Array of novel related scaffolds offer a degree of 3-dimensionality
  - Expectation of good drug-like properties (*e.g.* solubility)
  - Opportunity to target 4 points of diversity

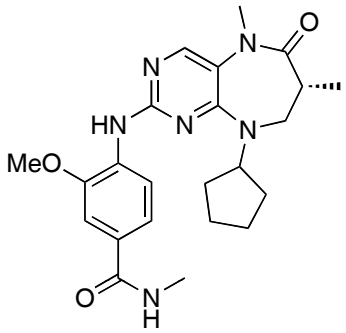
7-Membered Ring offers great potential for 3-D molecules





- Natural pucker of 7 membered ring allows good interaction with lipophilic pocket
  - Additional substitution enhances 3-dimensionality further

8,9-Dihydro-5H-pyrimido[4,5-*b*][1,4]diazepin-6(*7H*)-one scaffold (*a.k.a.* 6:7 scaffold)



Mw: 438.5 $gmol^{-1}$
cLogP: 2.73
PSA: 100 $Å^2$

Compound 1

Plk1 K_i: 3 nM

Plk2 K_i: 162 nM

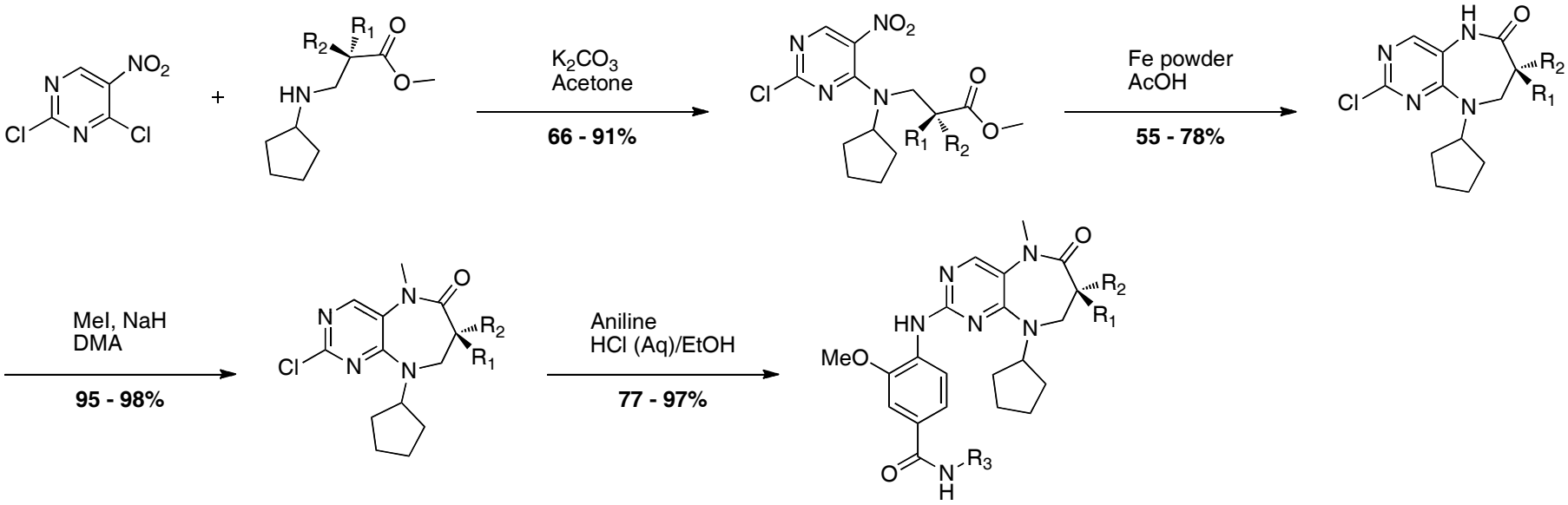
Plk3 K_i: 126 nM

HCT-116 IC_{50}: 140 nM

Solubility at $pH_{7.4}$: > 200 μM

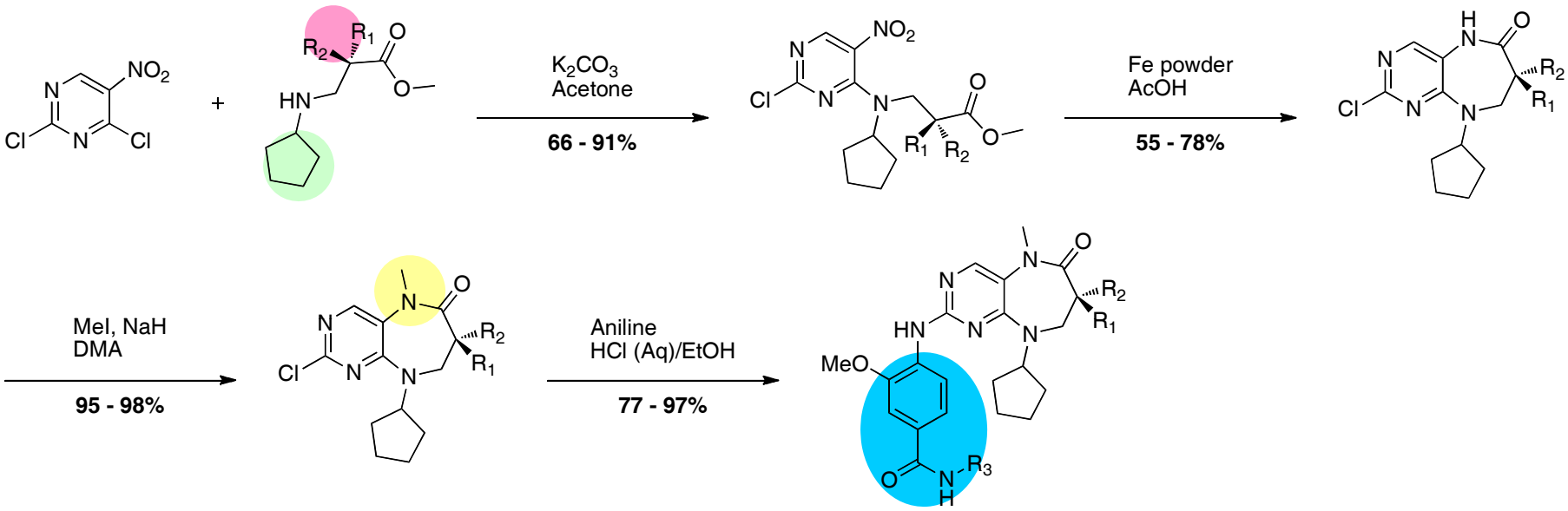
- 6:7 scaffold gives potency and selectivity consistent with drug candidate
- High solubility without need to append traditional solubilising groups

Synthesis of the 6:7 scaffold



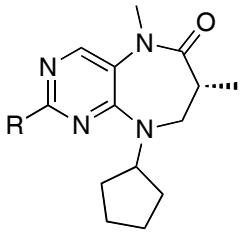
- Novel system can be accessed using optionally substituted β-amino acids
- Rapid, high yielding and versatile
  - 4 points of diversity to be manipulated

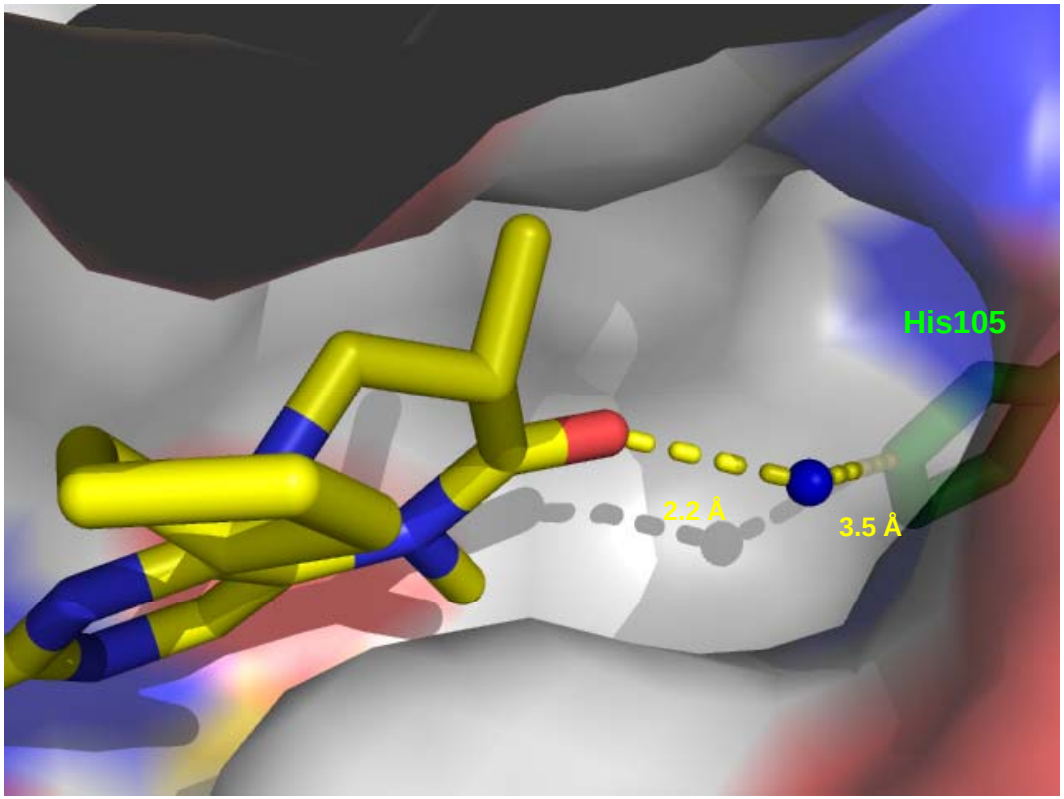
Synthesis of the 6:7 scaffold



- Novel system can be accessed using optionally substituted β-amino acids
- Rapid, high yielding and versatile
  - 4 points of diversity to be manipulated

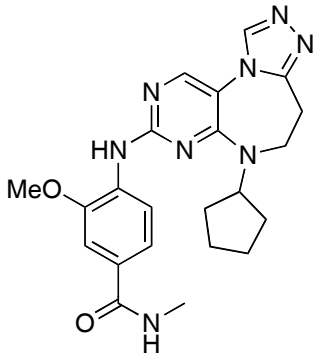
Interaction with Plk specific His105 Residue





- 6-Carbonyl makes water mediated interaction with specific His105 residue as shown through X-ray structures
- Objective: Make direct interaction with His105 as it is predicted to be energetically favourable

5,6-Dihydro-4*H*-pyrimido[4,5-*b*][1,2,4]triazolo[4,3-*d*][1,4]diazepine (*a.k.a.* 6:7:5 scaffold)



Mw: 434.5 $gmol^{-1}$ l
cLogP: 0.71
PSA: 110 $Å^2$

Compound 2

Plk1 K_i: 19 nM

Plk2 K_i: 2850 nM

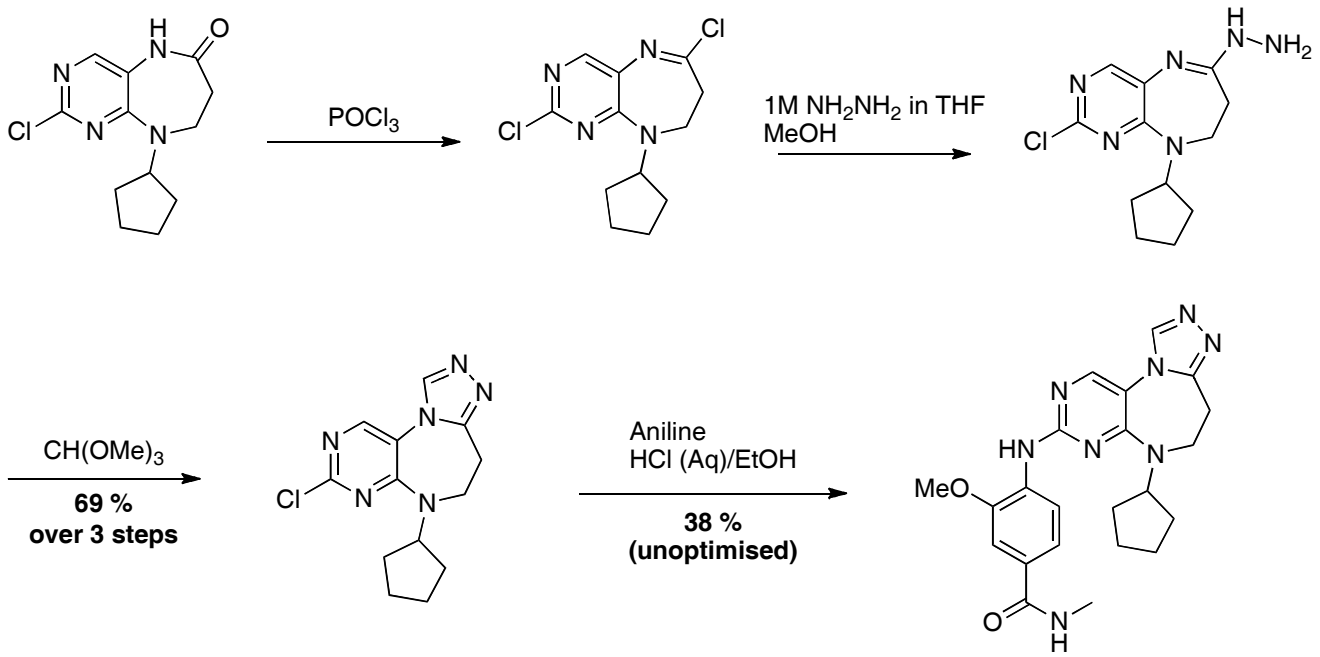
Plk3 K_i: 357 nM

HCT-116 IC_{50}: > 2000 nM

- Direct interaction with His105 with 6:7:5 scaffold suboptimal
- 7-ring no longer able to adopt appropriate conformation to interact in lipophilic pocket
- Small lipophilic substitutions failed to re-adjust binding complementarity

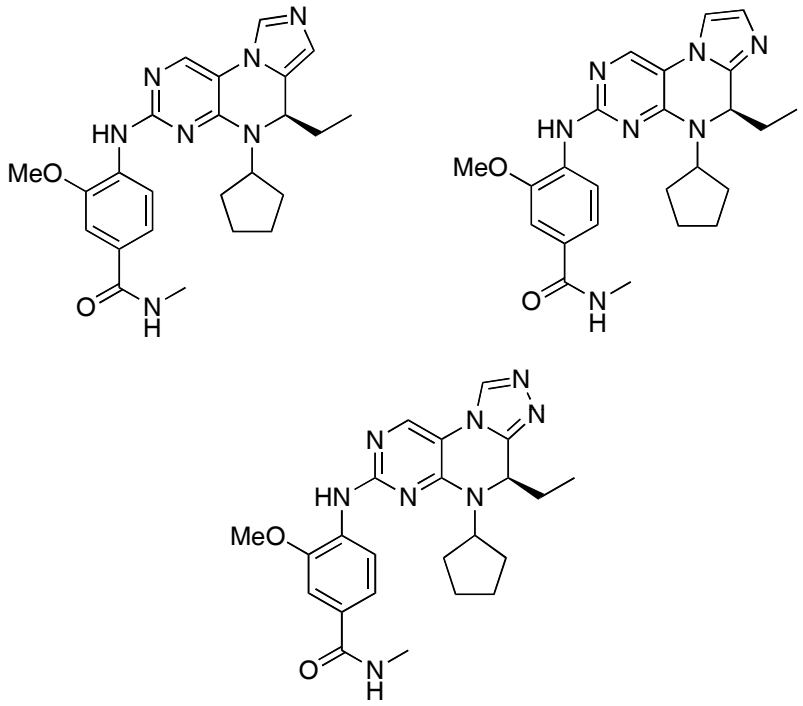
VERTEX

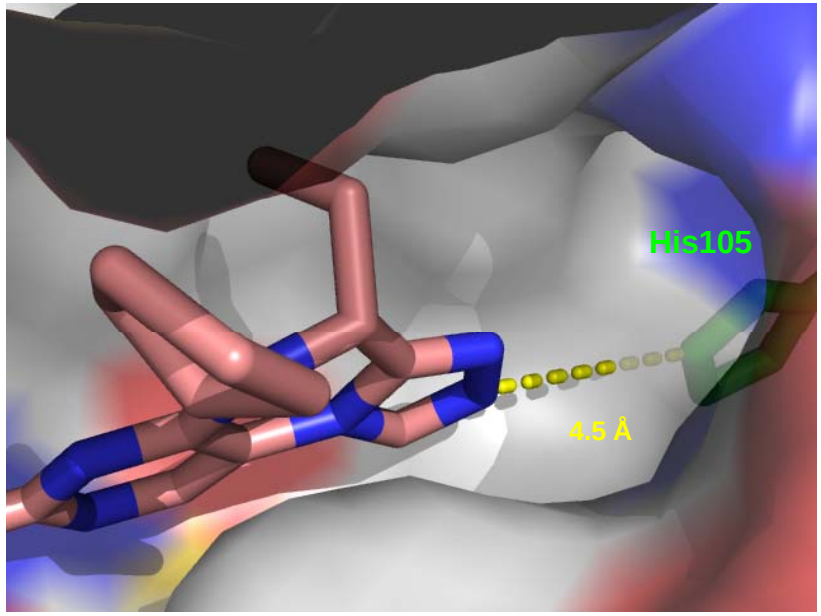
Synthesis of the 6:7:5 scaffold



- Novel tricyclic system accessed *via* same intermediate as bicyclic system
- Need to use non-aqueous hydrazine to obtain high yield
- Safety concerns: toxicity, explosive

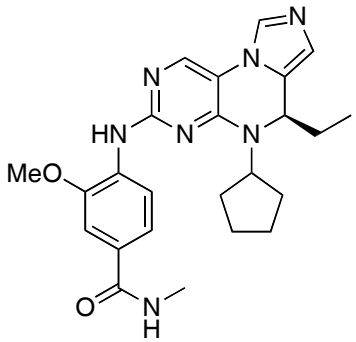
6:6:5 Scaffolds





- 3 potential scaffolds identified
  - All predicted to interact efficiently with His105 with no water mediated hydrogen bond
  - More rigid system enables substituents to adopt preferred conformation more easily

Optimising 5-membered ring interactions



Compound 3

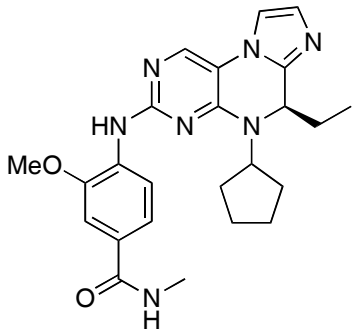
Plk1 K_i: 0.2 nM

Plk2 K_i: < 10 nM

Plk3 K_i: < 10 nM

HCT-116 IC_{50}: 45 nM

Solubility at $pH_{7.4}$: 24 μM



Compound 4

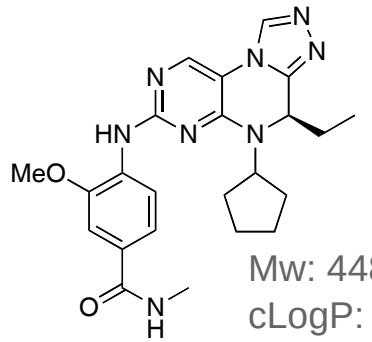
Plk1 K_i: 0.4 nM

Plk2 K_i: 19 nM

Plk3 K_i: 56 nM

HCT-116 IC_{50}: 179 nM

Solubility at $pH_{7.4}$: 31 μM



Mw: 448.5 $gmol^{-1}$

cLogP: 1.54

PSA: 110 $Å^2$

Compound 5

Plk1 K_i: 0.1 nM

Plk2 K_i: < 10 nM

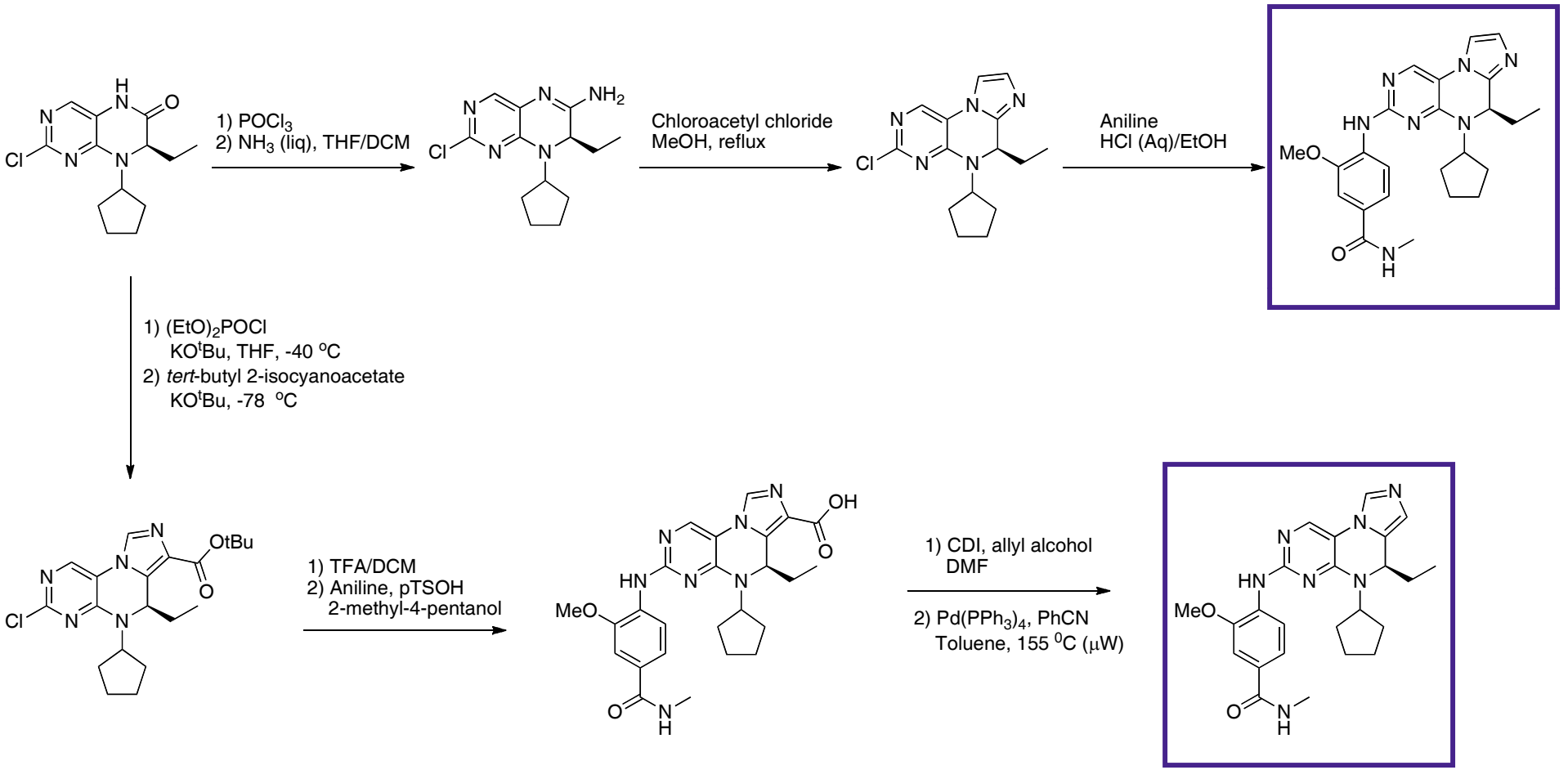
Plk3 K_i: < 10 nM

HCT-116 IC_{50}: 7 nM

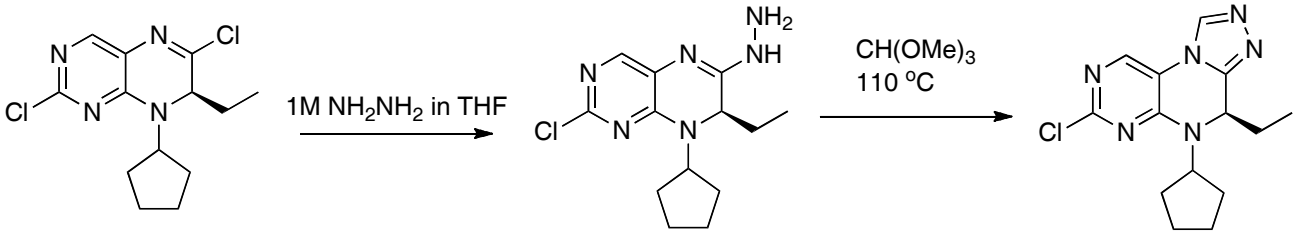
Solubility at $pH_{7.4}$: > 200 μM

- Fused ring systems provides potent Plk inhibitors
- Good solubility with no traditional solubilising group
  - Triazolo variant preferred for its optimal physical properties

Synthesis of Imidazolo 6:6:5 scaffold variants



Triazolo 6:6:5 scaffold - pro's and con's



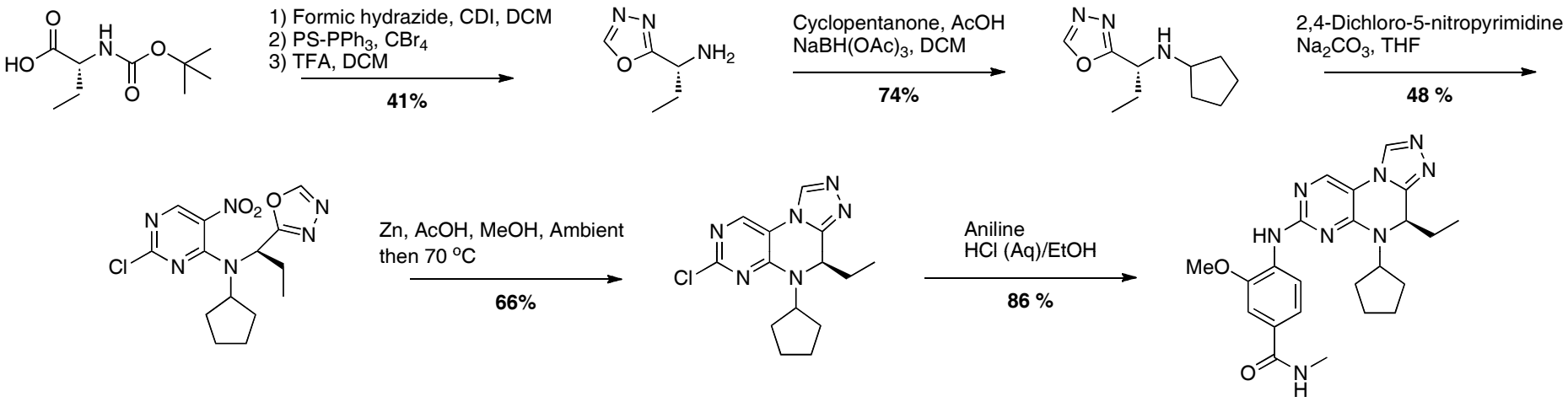
✓4,5-Dihydro-[1,2,4]triazolo[4,3-*f*]pteridine core scaffold allows very potent druglike inhibitors to be developed

✕Route requires use of non-aqueous hydrazine

– Introduces safety concerns particularly on large scale

- In order to safely produce large quantities of the core scaffold an alternative route was required

A safe synthesis of triazolo 6:6:5 *via* key reductive cyclisation



- Use of 1,3,4-oxadiazole allows incorporation of hydrazine motif in a safe manner
- Key step: One-pot reduction of nitro group with concomitant cyclisation leads to formation of triazole ring in good yield

For similar cyclisation reaction see WO2005121152

Conclusions

- 5 novel scaffolds have been identified for potent kinase inhibition
- Inherent three dimensionality confers good solubility to all these scaffolds without need to append traditional solubilising groups
- Safe route developed to triazolo 6:6:5 scaffold
  - Key reductive cyclisation step avoids the use of non-aqueous hydrazine

Acknowledgements

Chemistry

- Jean-Damien Charrier
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- Ronald Knegtel

Vertex: A Global Health Sciences Company

- Founded in 1989; public since 1991
- 6 major locations worldwide including 5 R&D sites with standalone discovery capabilities and numerous field locations
  - Cambridge MA (headquarters)
  - San Diego, CA
  - Coralville, IA
  - Milton Park, UK
  - Laval, Canada
  - Washington, D.C.
- 1,700+ employees worldwide, 70% in R&D