Astex Pharmaceuticals

Identification of Oral Bioavailable, Type2 Inhibitors of Discoidin Domain-containing Receptor 1/2 (DDR1/DDR2) using “Back-to-Front” X-Ray FBDD

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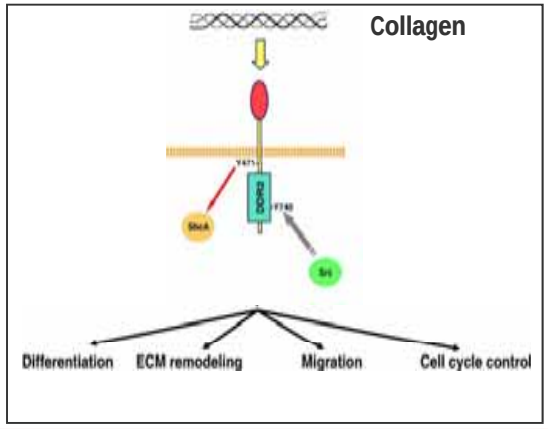
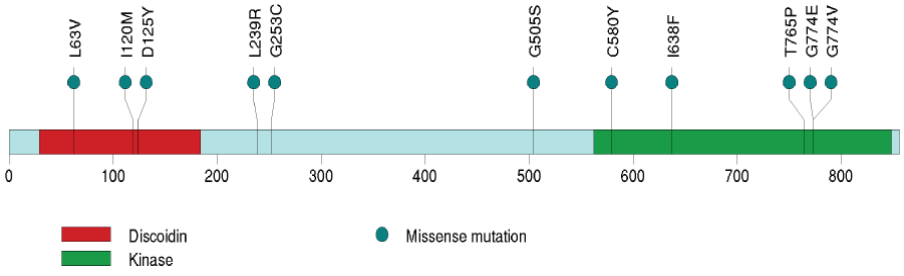
Lung Squamous Cell Cancer (SCC) and DDR2

- **Lung cancer is the leading cause of cancer-related mortality in the US**
  - >157000 deaths projected in 2010
- **Non-small-cell lung cancer (NSCLC) accounts for 85% of cases**
  - Lung squamous cell cancer (SCC) accounts for 25% of NSCLC
  - Unmet need for targeted treatment for lung SCC
- **Mutations of the Discoidin Domain Receptor 2 (DDR2) reported in ~4% of SCC***
  - Data suggest these are gain-of-function mutations
  - Multi-targeted kinase inhibitors (Dasatinib and Nilotinib) showed anti tumour activity in DDR2-mutant cell lines
- **DDR1 & 2 are non-integrin receptors for collagen**
- **Regulate cell-adhesion, proliferation and extracellular remodelling**

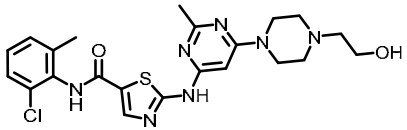




* Hammerman S. P. *et al.*; *Cancer Discovery*, **2011**, *1* (1), 78-98

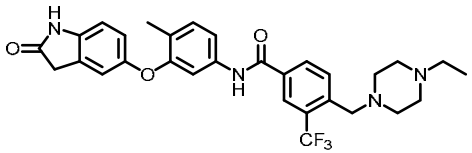
DDR1/2 inhibitors in the literature

- **Most DDR1/2 inhibitors in the literature derived from cross screening of existing kinase inhibitors**
  - Generally lack selectivity:



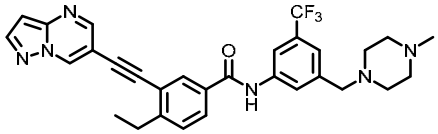
Dasatinib
DDR2 IC_{50} = 2 nM
C-src IC_{50} < 1 nM
C-Kit IC_{50} < 1 nM

- **More recent examples show a higher degree of selectivity:**



DDR1 IC_{50} = 105 nM
DDR2 IC_{50} = 413 nM
C-Kit IC_{50} > 10 µM

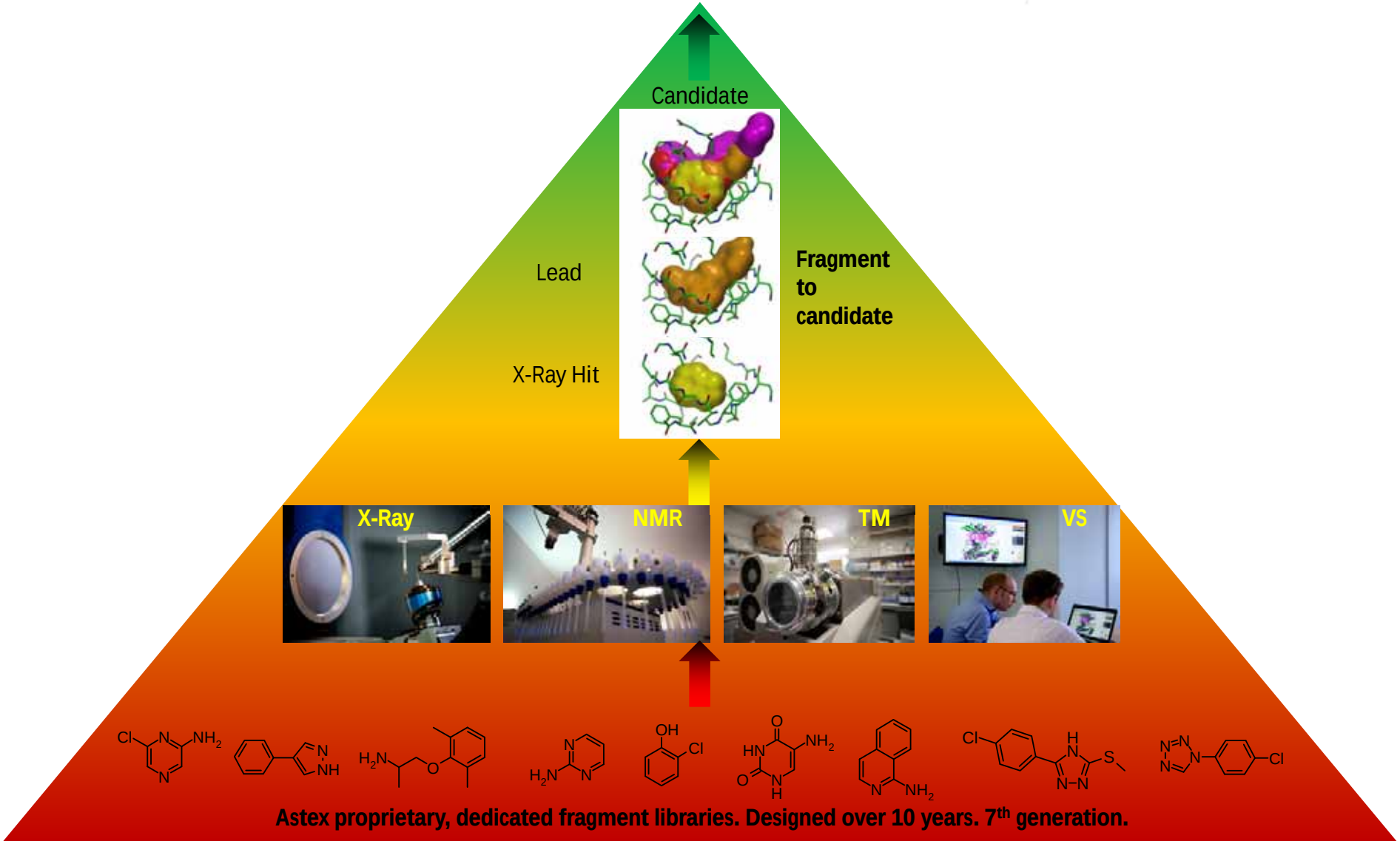
Nathanael S. Gray et al. ACS Chem Biol, 2013, 8, 2145



DDR1 IC_{50} = 6.8 nM
DDR2 IC_{50} = 101 nM
C-Kit IC_{50} > 10 µM

Ke Ding *et al.* JMC, 2013, *56*, 3281

Fragment Based Drug Design at Astex – Pyramid ™



Astex proprietary, dedicated fragment libraries. Designed over 10 years. 7th generation.

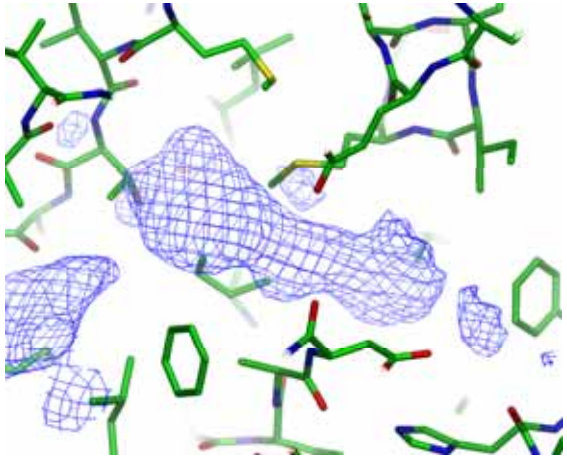
Fragment hits

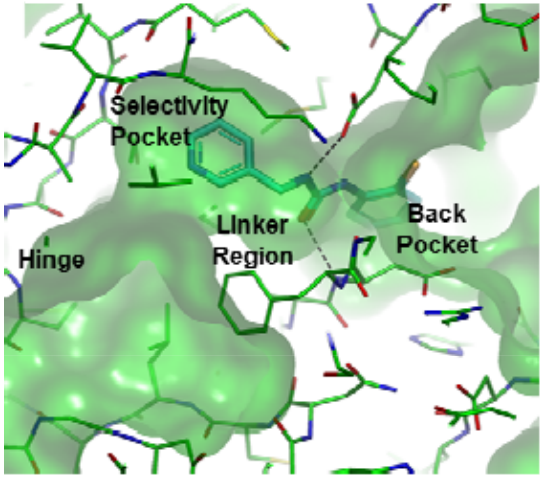
~40 hinge binders

Thermal Shift (T_M) *X-Ray*

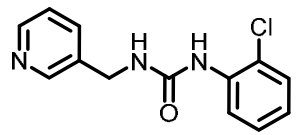
~ 1500 fragments screened against DDR1 → Hits progressed into X-ray crystallography → ~ 50 fragment-protein structures determined

~10 fragments in the back pocket





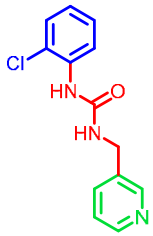
"Fragment 1"



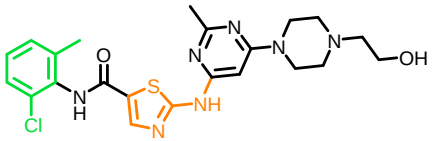
DDR2 > 100 µM LE < 0.3

AstexMerge*

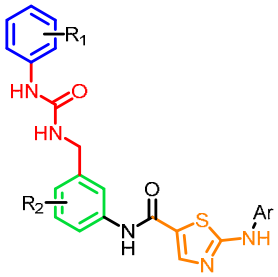
Fragment 1



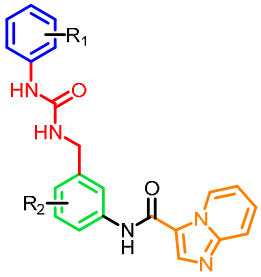
Dasatinib

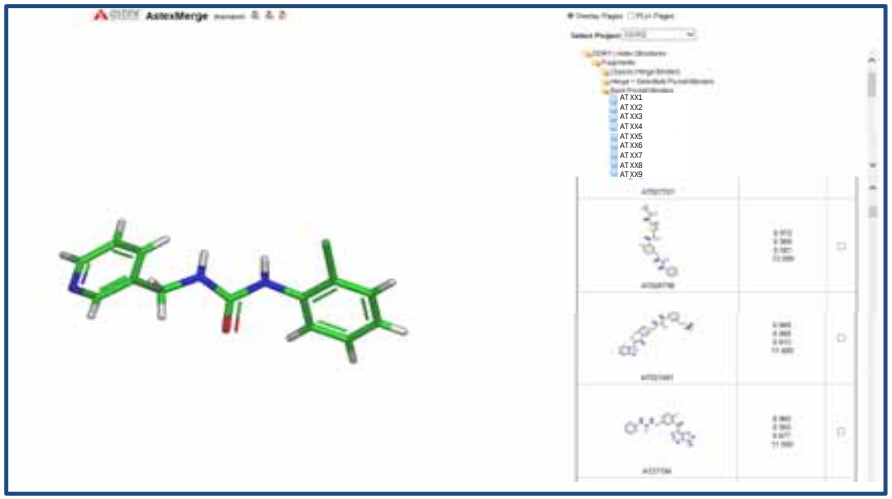


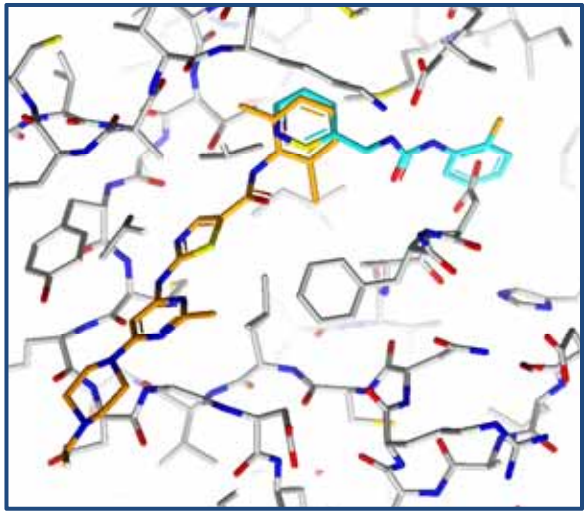
Merge Molecules



Scaffold Morph

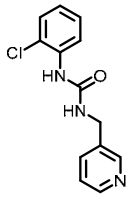
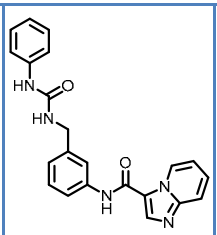
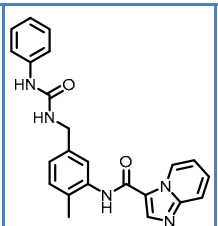
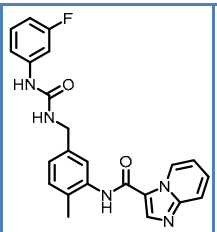
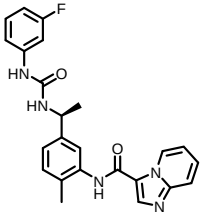
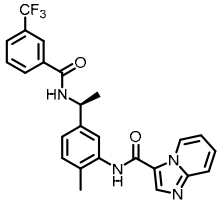
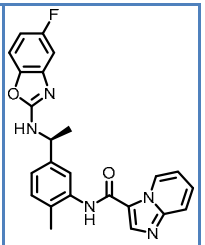






*Pierce, A. C.; Rao, G.; Bemis, G. W.; *J. Med. Chem.*, **2004**, *47*, 2768

H2L – The story of two magic methyls

	 1	 2	 3	 4	 5	 6	 7
MW	261	385	399	417	431	467	430
ClogP	1.8	3.7	3.6	4.0	4.3	5.1	4.6
DDR2 IC_{50} (nM) (LE)	> 100000 (< 0.3)	280 (0.31)	8.2 (0.37)	3.3 (0.37)	4.5 (0.36)	5.8 (0.33)	6.1 (0.35)
DDR1 IC_{50} (nM)	-	140	-	~ 1.5	~ 1.5	~ 1.5	~ 5
C-src IC_{50} (nM)	-	~ 100000	~ 10000	> 3000	> 10000	~ 10000	~ 10000
C-Kit IC_{50} (nM)	-	180	9.8	19	140	~ 3000	160

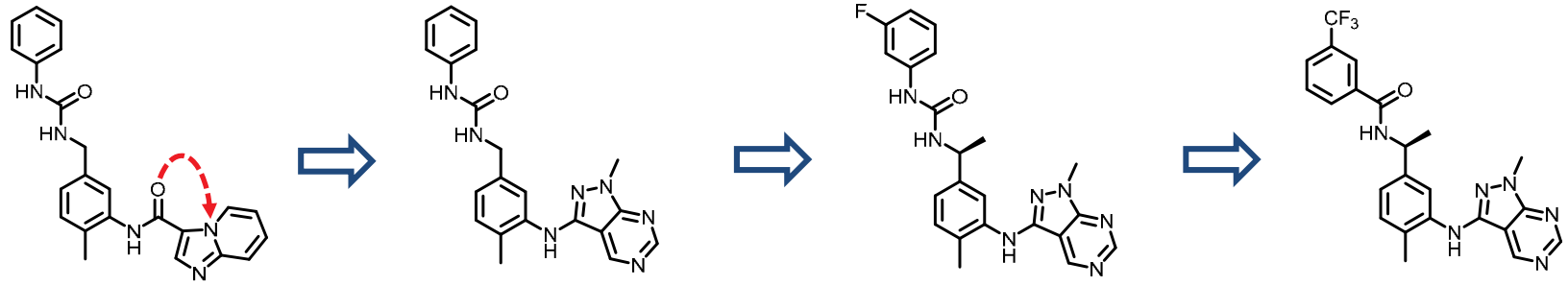
Selectivity:
> 2000 fold over Src
> 30 fold over Kit

> 300 fold
DDR2 IC_{50}

> 30 fold
DDR2 IC_{50}

- 7 fold
C-Kit IC_{50}

Pyrazolopyrimidine series



3

MW 399
ClogP 3.6

DDR2 8.2 nM (LE 0.37)
DDR1 -
C-src ~ 10 µM
C-Kit 9.8 nM

8

MW 387
ClogP 3.2

DDR2 27 nM (LE 0.36)
DDR1 -
C-src > 10 µM
C-Kit 360 nM

9

MW 419
ClogP 4.0

DDR2 24 nM (LE 0.34)
DDR1 -
C-src > 100 µM
C-Kit > 10 µM

10

MW 454
ClogP 4.75

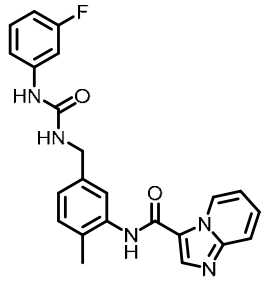
DDR2 7.5 nM (LE 0.34)
DDR1 ~ 5 nM
C-src > 100 µM
C-Kit > 100 µM

- 30 fold
C-Kit IC_{50}

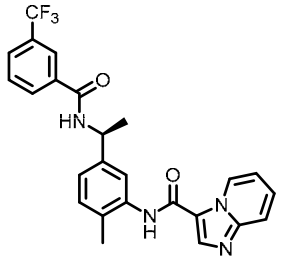
Potency and selectivity of 10 similar to best cmpd in the main series

Astex Viewer

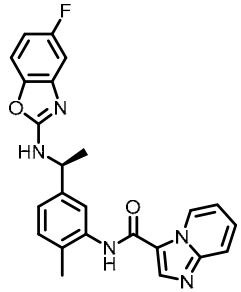
Lead compounds – DMPK



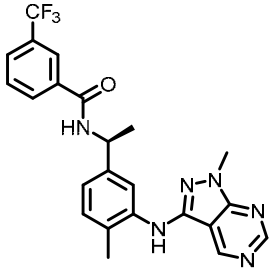
4



6



7

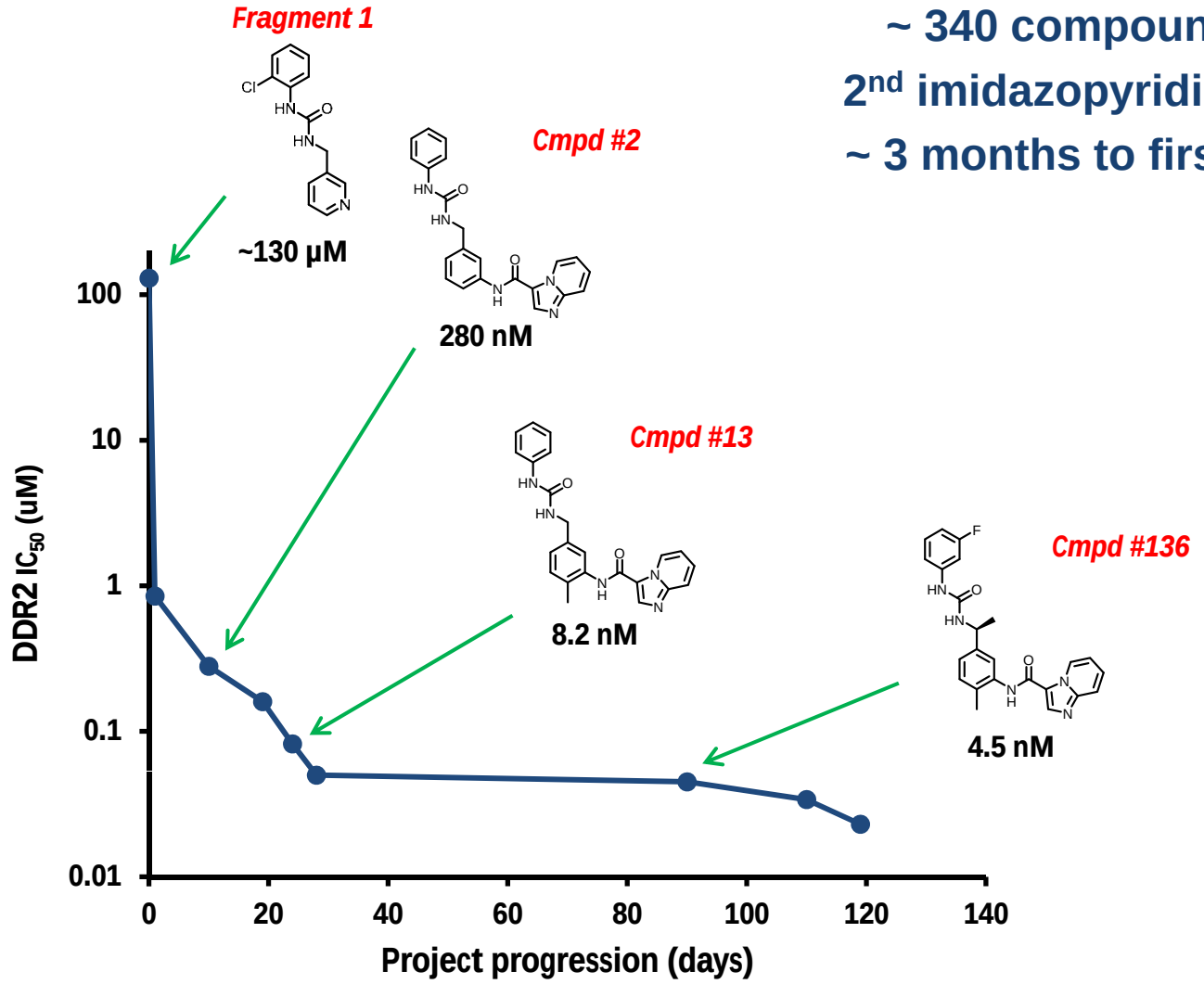


10

	ClogP (MW)	DDR2 IC_{50} (nM) (LE)	DDR1 IC_{50} (nM)	C-src (nM)	C-Kit (nM)	Cl (mL/min/kg)	Vss (L/Kg)	$t_{½}$ (h)	F%
4	4.0 (417)	3.3 (0.37)	~ 1.5	> 3000	19	7.65	0.42	0.83	62
6	5.1 (467)	5.8 (0.33)	~ 1.5	~ 10000	~ 3000	2.99	0.31	1.4	55
7	4.6 (430)	6.1 (0.35)	~ 5	~ 10000	160	16.6	1.9	1.8	97
10	4.75 (454)	7.5 (0.34)	~ 5	> 100000	> 100000	79	1.2	0.47	14

Compounds from the imidazopyridine series (4,6,7) show superior PK than compound 10 from the pyrazolopyrimidien series

Project Progression

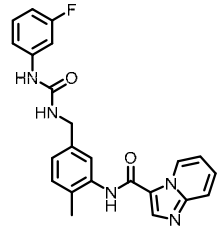


~ 340 compounds synthesised

2nd imidazopyridine cmpd = 8.2 nM

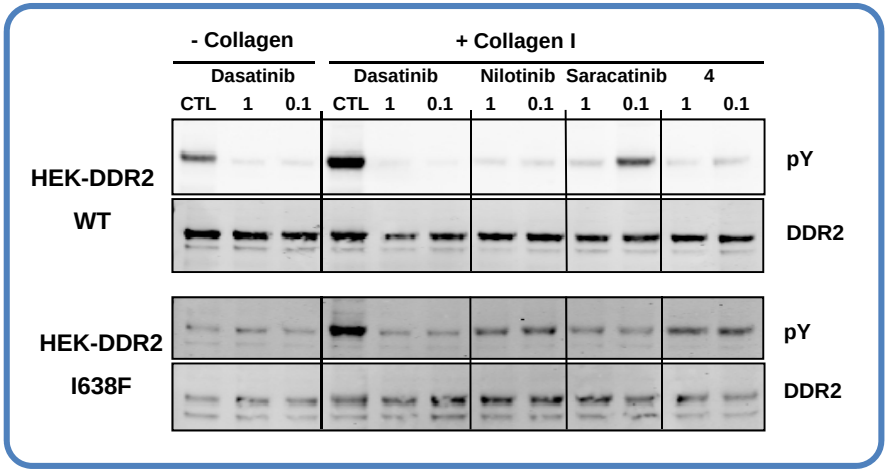
~ 3 months to first lead compound

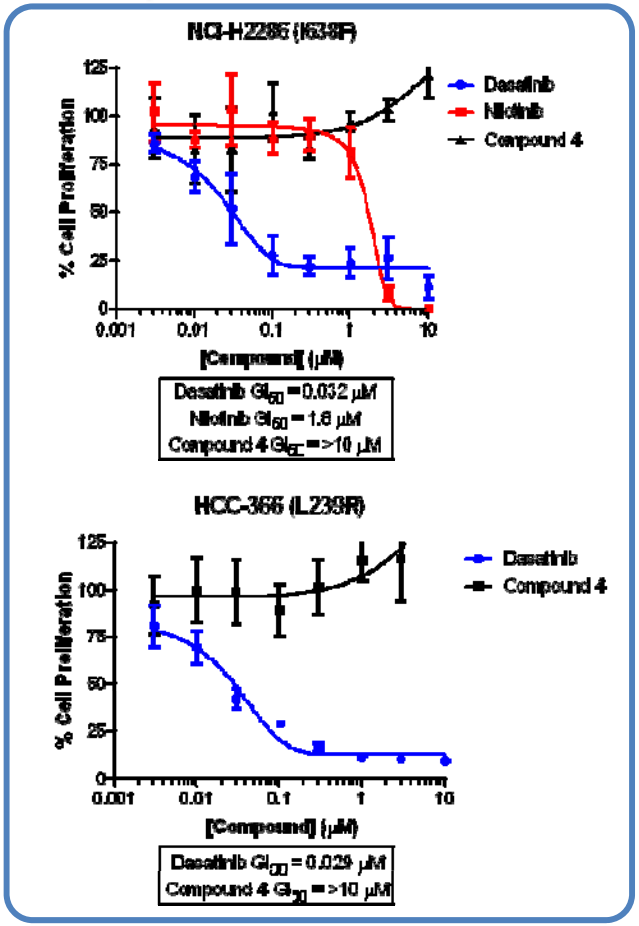
Probing the role of DDR2 in lung cancer



4

	4	Dasatinib	Nilotinib	Saracatinib
DDR2	3.3 nM	2 nM	5.6 nM	300 nM
DDR1	~ 1 nM	ND	ND	ND
c-Kit	19 nM	< 3 nM	ND	540 nM
c-Src	> 3 µM	< 3 nM	810 nM	3.8 nM





- **Compound 4 potently inhibits pDDR2 in cells**
- **Compound 4 does <u>not</u> have an effect on DDR2-mutant cells proliferation**
  - Dasatinib and Nilotinib show anti-proliferative effect in same cell lines

Conclusions

- **Potent and selective DDR1/2 inhibitors generated using FBDD**
  - Novel benzyl urea fragment identified in the “back pocket”
  - “Back-to-front” design and AstexMerge successfully employed to identify lead series
  - Fragment hit quickly progressed into potent and selective DDR1/2 inhibitors
- **Magic methyls**
  - Two methyl groups essential to achieve desired levels of potency and selectivity
  - Methyl on the sp^3 centre in the linker region effective with a variety of linker groups
- **Biological data on compound 4, and other independent data*, suggest that selective inhibitors of DDR2 may not be interesting for treatment of lung SCC**
  - Although compound **4** potently inhibit pDDR2 in cells it does not have an effect on DDR2-mutant cells proliferation
- **Our selective inhibitors could be used as chemical probes to investigate the role of DDR1 or DDR2 in other indications**

*Paul H. Huang, *Biochem. J.*, **2013**,*454*,501

Acknowledgements

Astex Pharmaceuticals

Thanks to all Astex staff

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Otsuka