Next Generation Glucokinase Activators

The Discovery of AZD1656

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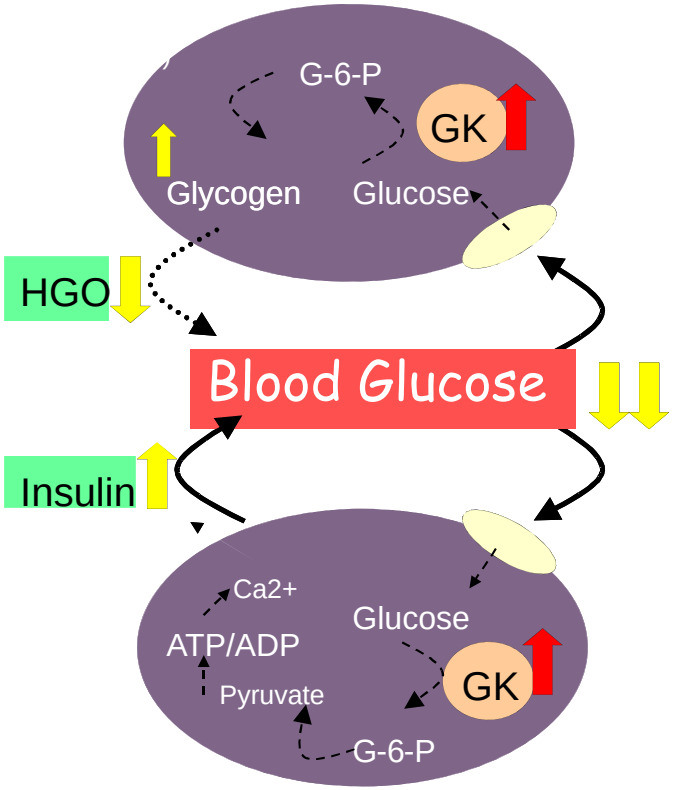
University of Cambridge, Churchill College, Cambridge, UK

AstraZeneca

Glucokinase – The Glucose Sensor

Glucokinase (GK) is expressed in liver and pancreas

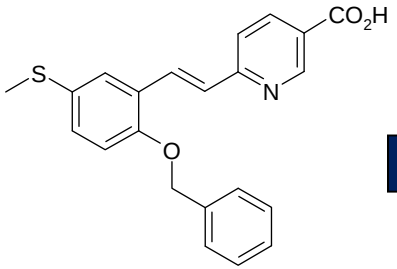
- Controls rate of glucose phosphorylation (utilisation) in liver
- Controls glucose-sensitive release of insulin in pancreas

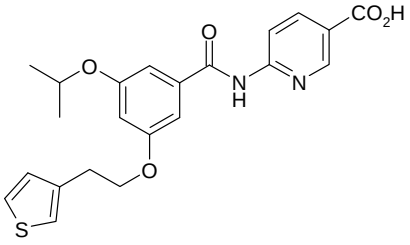


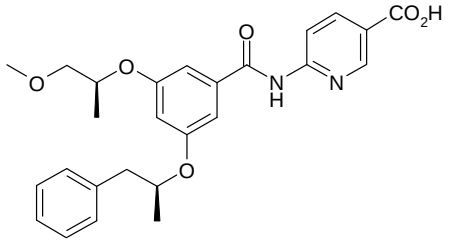
Clinical Target Validation

- Inactivating GK
  - Heterozygous loss of function mutations lead to MODY-2, a rare form of diabetes
- Activating GK
  - Rare activating mutations in man cause hypoglycaemia and hyperinsulinaemia

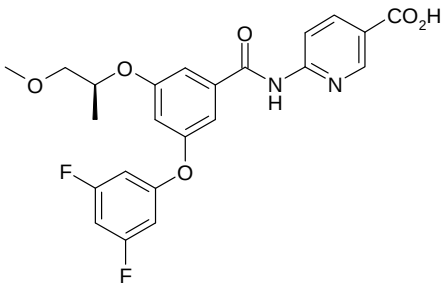
Optimisation of the acid series

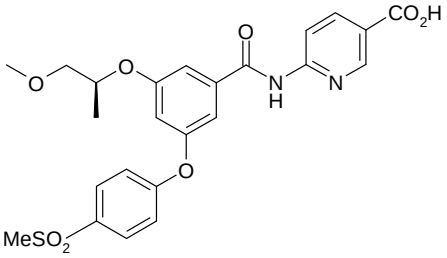






EC_{50} / μM	4.7	0.090	0.030
Solubility / μM	-	48	1350
Cl (r) / $mLmin^{-1}kg^{-1}$	-	3.8	1.9
Cl_u (r)	-	1461	475
LogD	2.5	1.7	1.5

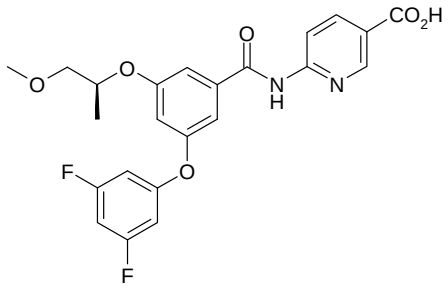


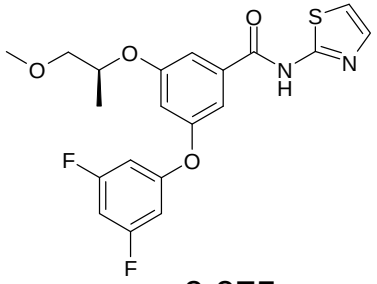


EC_{50} / μM	0.060	0.090
Solubility / μM	>3000	841
Cl (r) / $mLmin^{-1}kg^{-1}$	8.2	0.1
Cl_u (r)	44	43
LogD	-0.4	1.4

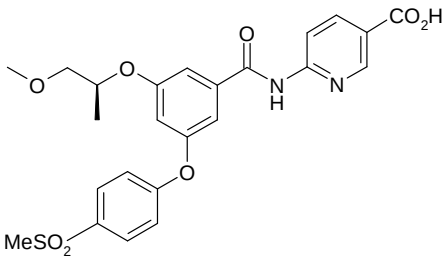
McKerrecher, D. *et al. Bioorg. Med. Chem. Lett.* **2005**, *15*, 2013; McKerrecher D. *et al. Bioorg. Med. Chem. Lett.* **2006**, *16*, 2705; Pike, K. *et al. Bioorg. Med. Chem. Lett.* **2011,** *21,* 3467

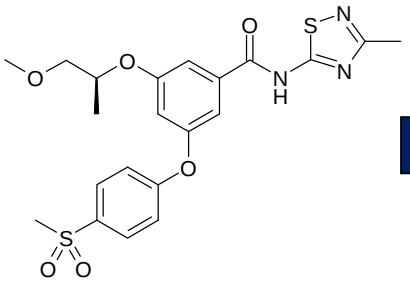
Switching to orally available neutral compounds

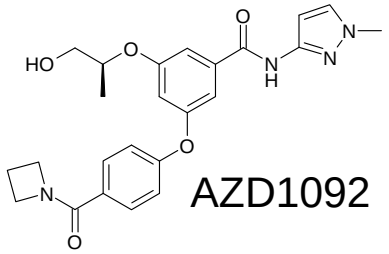




EC_{50} / μM	0.090	0.075
Solubility / μM	841	<1
Caco-2 P_{app}	7.4	-
nAUC (r)	8.2	0
LogD	1.4	4.1



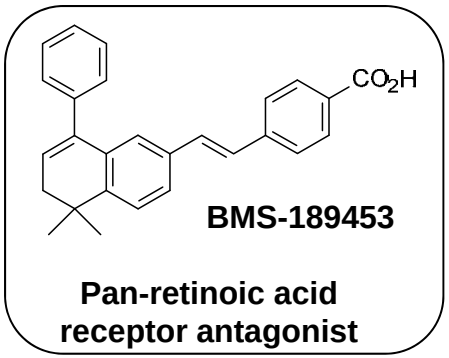


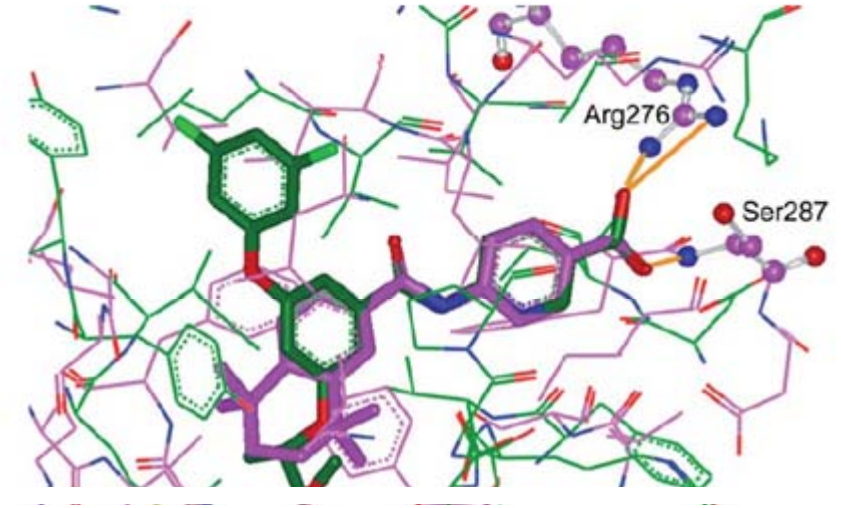


EC_{50} / μM	0.060	0.092	0.031
Solubility / μM	>3000	129	350
Caco-2 P_{app}	0.3	29	1.8
nAUC (r)	0	8.3	1.0
LogD	-0.4	2.9	1.8

Waring et al. Med. Chem. Commun. 2011, 2, 771, Waring et al Med. Chem. Commun. 2011, 2, 775

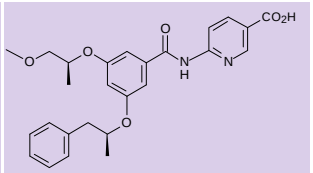
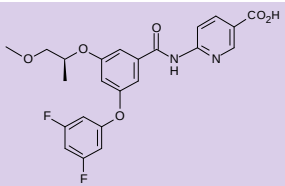
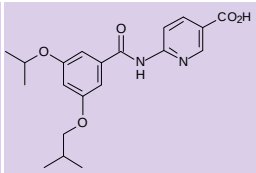
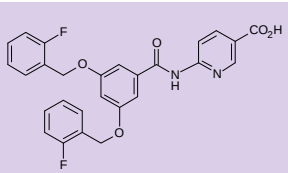
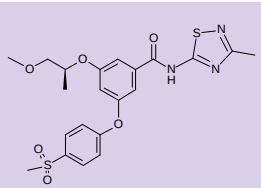
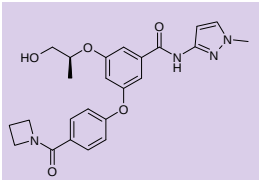
RARα inhibition is likely cause of testicular effects





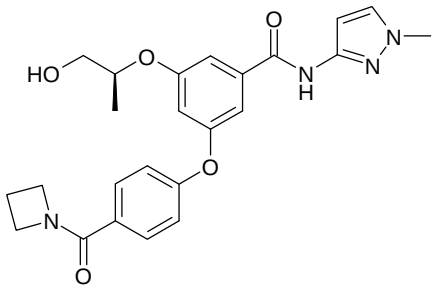
Crystal structures:
Glucokinase
RAR-α

Ligands:
GKA60
Retinoic acid

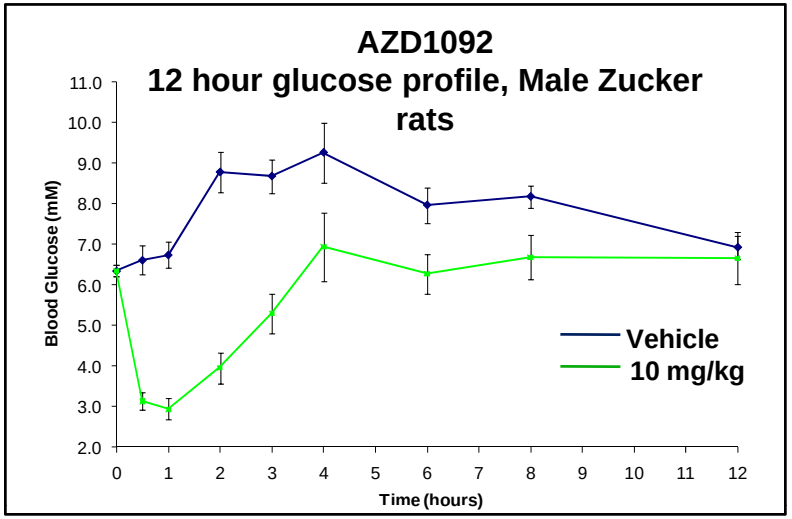
Compound	 GKA50	 GKA60	 1	 2	 GKA71	 AZD1092
RARα IC_{50} / μM	0.47	<0.001	0.011	0.01	>30	>30
RARβ IC_{50} / μM	32	<0.001	0.007	0.135	-	-
RARγ IC_{50} / μM	>1000	19	1.2	22	-	-
Testicular tox?	Yes	Yes	Yes	Yes	No	No

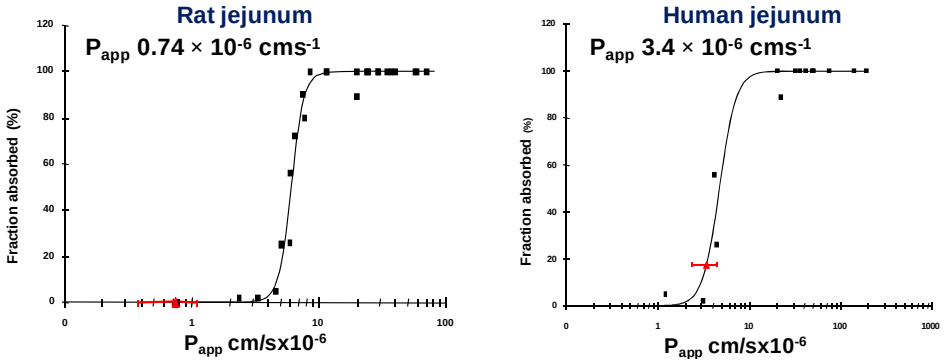
Waring et al. Med. Chem. Commun. 2011, 2, 771

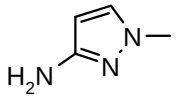
AZD1092



	AZD1092
EC_{50} / μM	30
LogD	1.8
Soly, MDCK P_{app}	350, 1.8
hERG IC_{50} / μM	70
Rat Cl (Cl_u), V_{ss}	14(480), 1.8
Rat F%	30
Dog Cl (Cl_u), V_{ss}	26(113), 3.7
Dog F%	51
OGTT Activity	24% @ 3 mg/kg





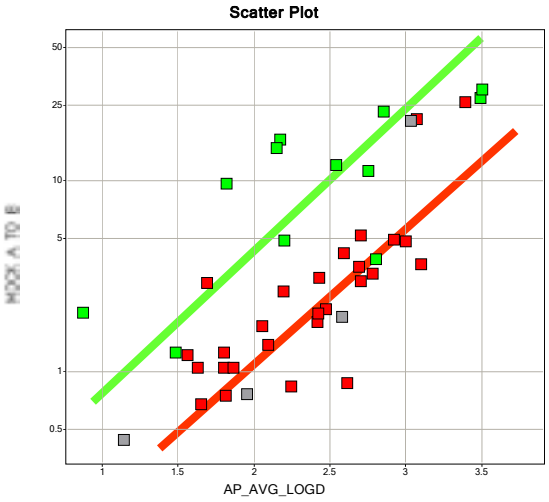


Methylaminopyrazole active in Ames test at 2000ug/plate
Clean in rat bone marrow micronucleus and UDS at 0.5 g.kg iv

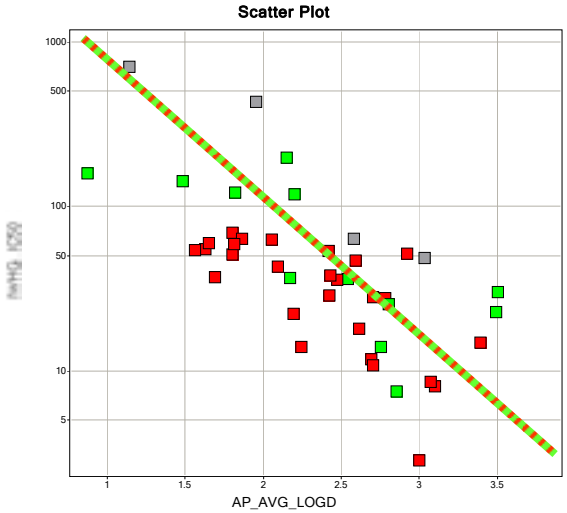
Remit for follow-up campaign

No releasable fragment with Ames liability
Unambiguously high permeability (P_{app} >10 cm/s x 10^{-6})
Matched technical profile in other respects to AZD1092

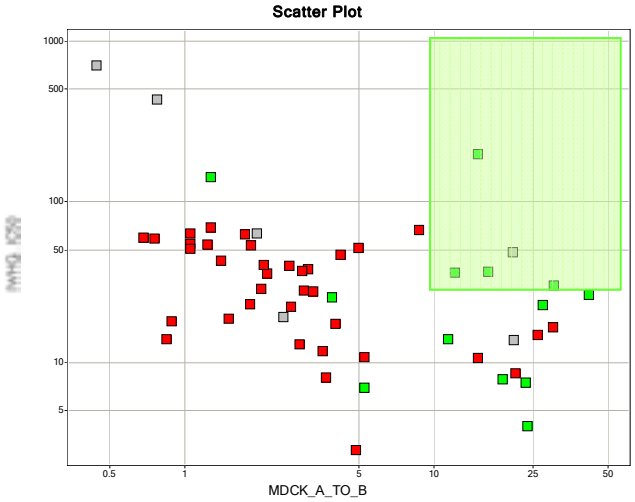
MDCK against logD



hERG against logD

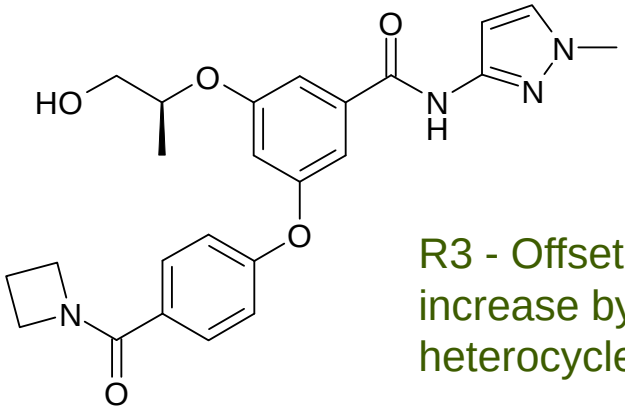


hERG against MDCK



1 donor green, 2 donors red, >2 grey

Molecular Design

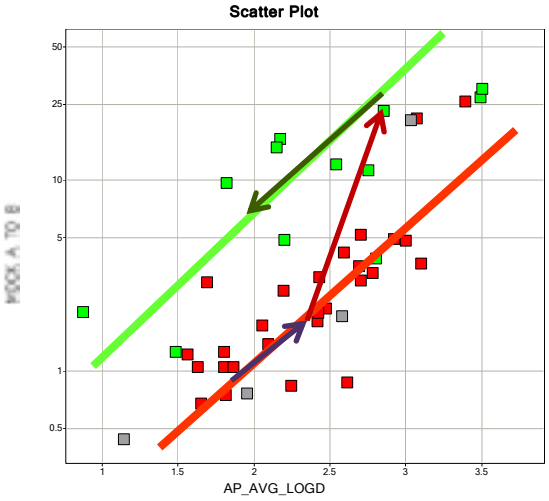


R1 - Replace with Ames inactive heterocyclic amides

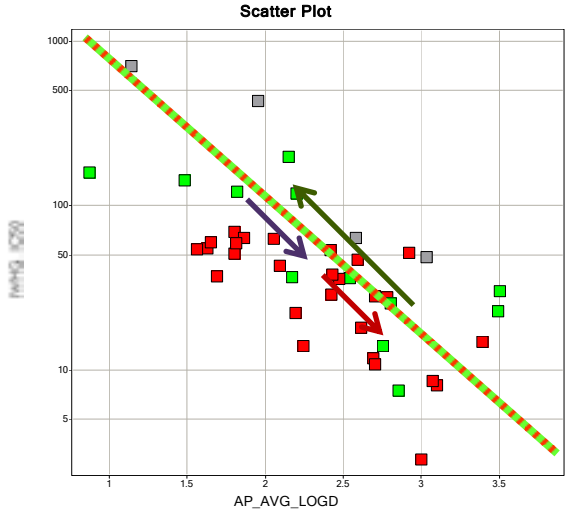
R2 - Remove H-bond donor

R3 - Offset lipophilicity increase by embedding heterocycles

MDCK against logD

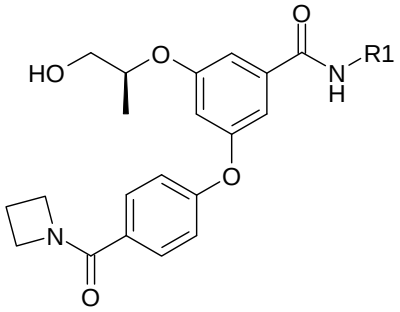


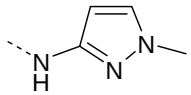
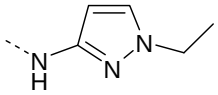
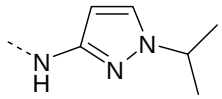
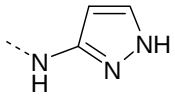
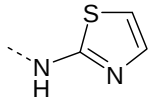
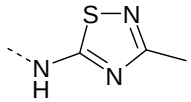
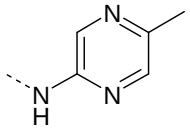
hERG against logD



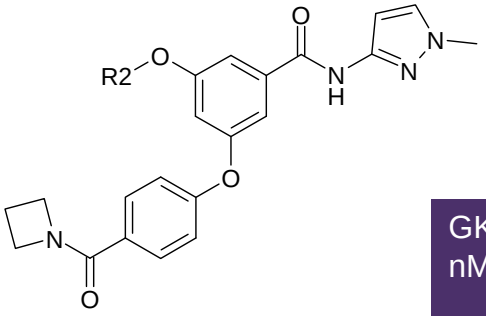
1 donor green, 2 donors red, >2 grey

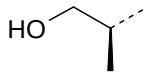
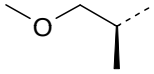
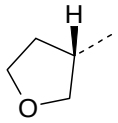
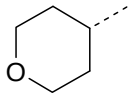
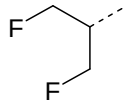
R1 Heterocyclic variations



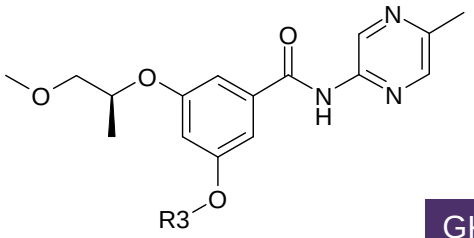
	~~GK EC_{50} / nM~~	~~LogD~~	~~LLE~~	~~Solubility / uM~~	~~MDCK Papp / $cm/sx10^{-6}$~~	~~hERG IC_{50} / uM~~	~~Framgent~~ Ames activity
	30	1.8	5.7	350	1.2	70	Positive
	31	2.4	5.1	280	1.6	54	Positive
	73	2.8	4.3	44		31	Positive
	53	2.0	5.3	670	0.8	>100	Negative
	32	3.1	4.4	9		9	Negative
	35	2.7	4.8	17	5.2	11	Negative
	61	2.4	4.8	17	4.1	38	Negative

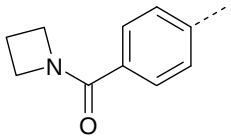
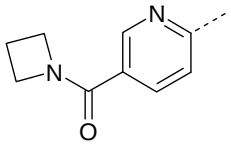
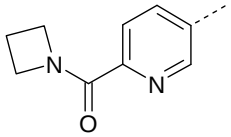
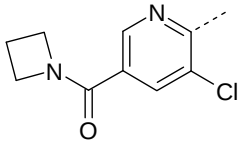
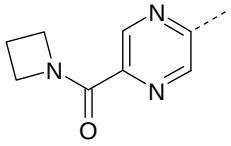
R2 Ether SAR



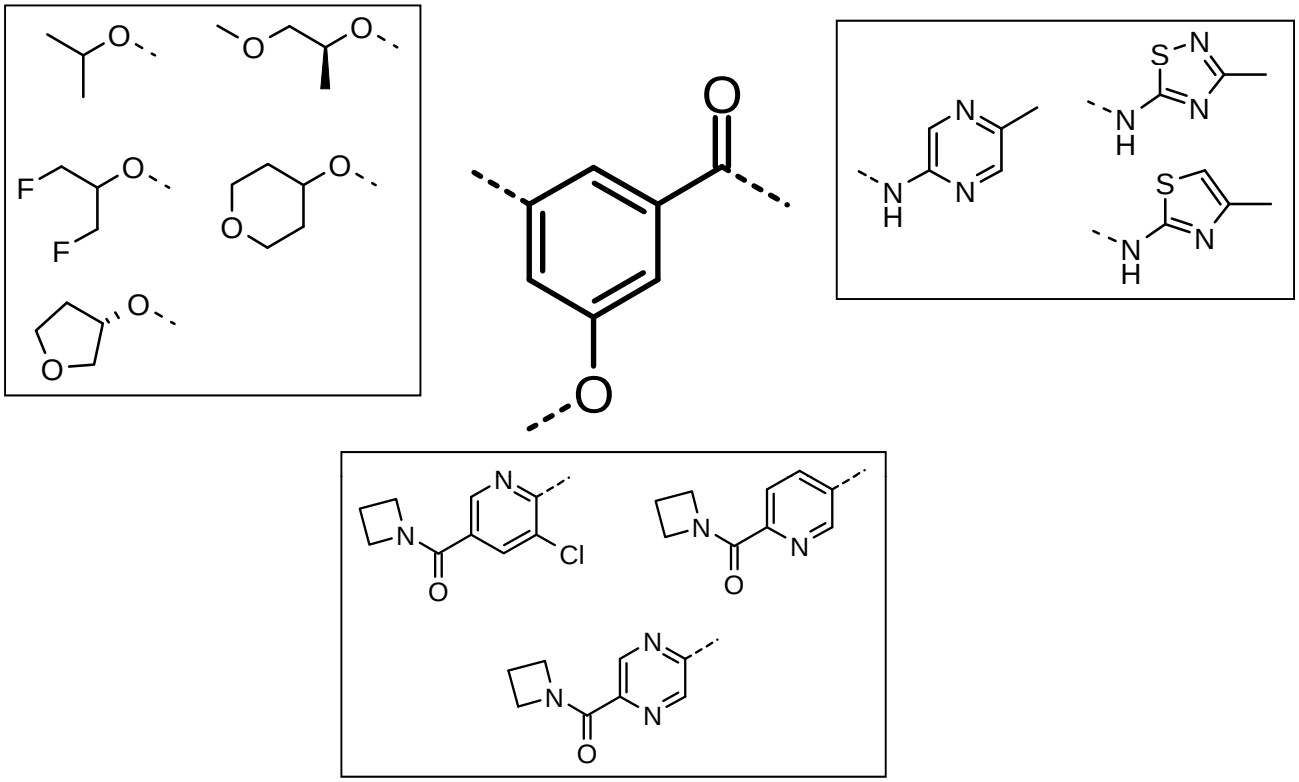
	GK EC_{50} / nM	LogD	LLE	Solubility / uM	MDCK Papp / $cm/sx10^{-6}$	hERG IC_{50} / uM
	30	1.8	5.7	360	1.2	70
	37	2.5	4.9	490	12	36
	110	3.3	3.7	125		27
	79	2.2	4.9	180	6.4	35
	170			170	12	
	47	2.6	4.7	11	7	28

R3 Heterocycle SAR



	GK EC_{50} / nM	LogD	LLE	Solubility / uM	MDCK Papp / $cm/sx10^{-6}$	hERG IC_{50} / uM
	73	2.9	4.2	30	29	18
	370					
	36	2.9	4.5	21	18	40
	60	2.8	4.4	8.0		18
	61	2.4	4.8	260	35	>100

Matrix Enumeration



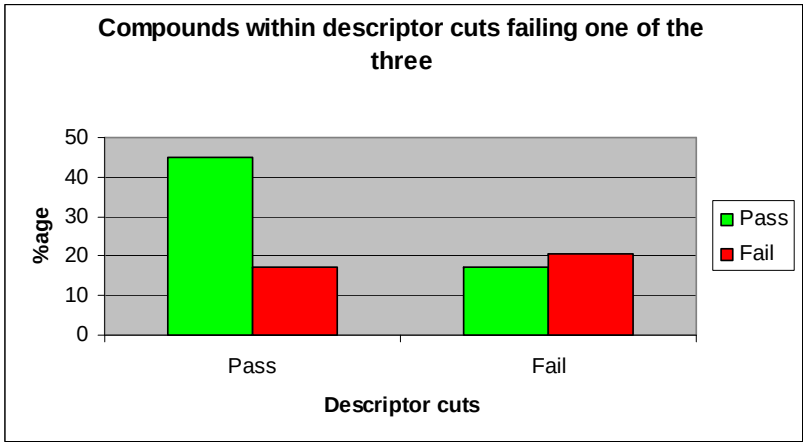
- Matrix of best compounds enumerated computationally
- Refined using predicted logD (< 2.5)
- QSAR models built for solubility, permeability (MDCK) and hERG (RMSE 0.25 – 0.7)
- Best combinations selected for synthesis

Outcome

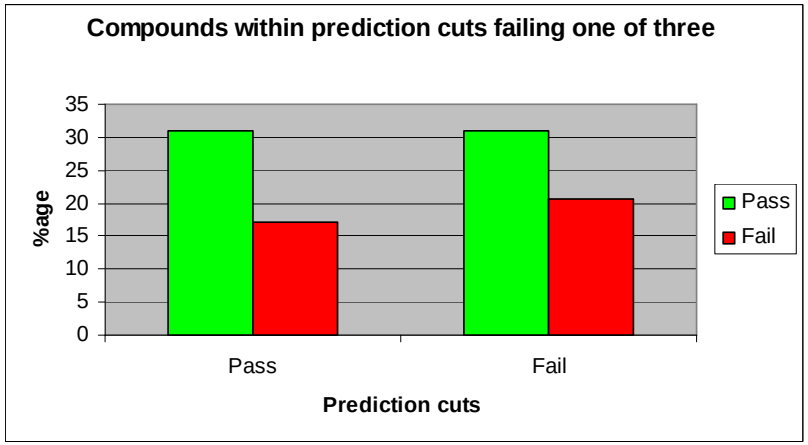
Analyses carried out to consider potent compounds (sub 100 nM) within predicted logD range or predicted to have good MDCK, hERG and solubility against measured data:

MDCK P_{app}	> 2
hERG	> 30 uM
Solubility	> 100 uM

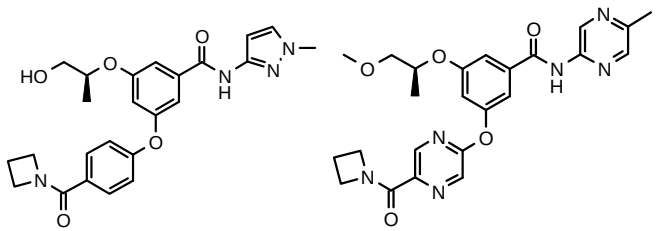
Predicted logD



QSAR models

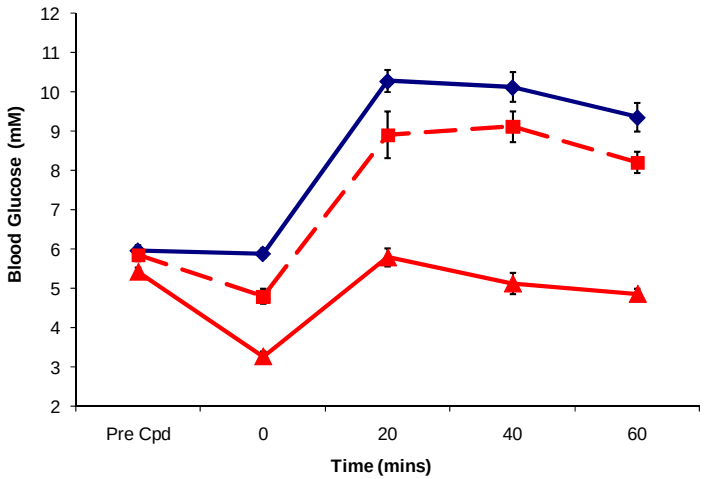


AZD1656

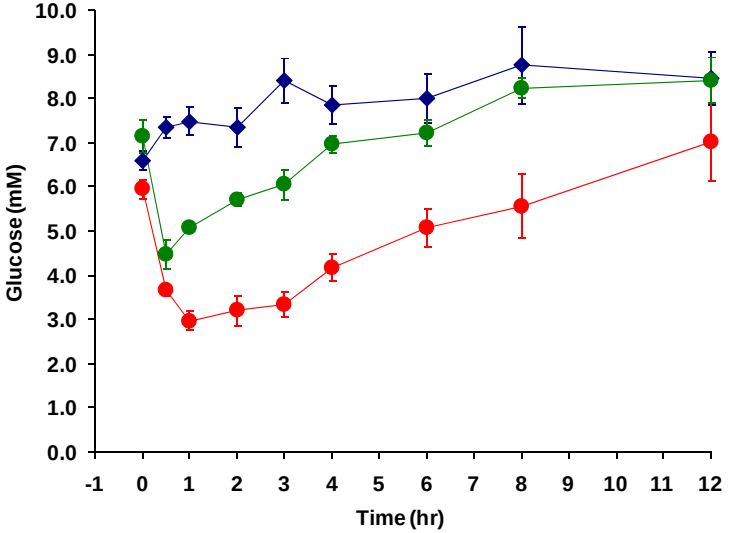


	AZD1092	AZD1656
EC_{50} / nM	30	61
LogD	1.8	2.4
Soly, MDCK P_{app}	350, 1.2	260, 35
hERG IC_{50} / μM	70	>100
Rat Cl (Cl_u), V_{ss}	14(480), 1.8	16 (310), 0.5
Rat F%	30	100
Dog Cl (Cl_u), V_{ss}	26(113), 3.7	8.1 (50), 1.5
Dog F%	51	100
OGTT Activity	24% @ 3 mg/kg	43% @ 1 mg/kg

HFFF Zucker OGTT Response



Free feeding Zucker profile



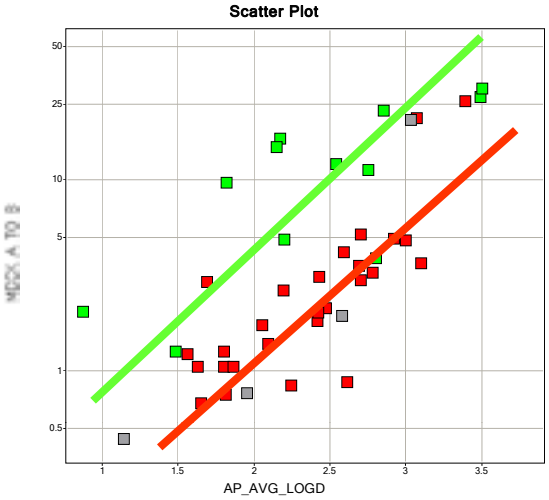
AZD1656 clinical program

- Approximately 20 clinical studies have been completed from Phase I through to completion of Phase IIb
- These studies have evaluated the profile of AZD 1656 primarily in T2DM patients but also included evaluation of AZD 1656 in healthy volunteers. Some mechanistic work was also performed in T1DM patients
- AZD 1656 was clinically evaluated as monotherapy and as a component of dual therapy (add-on to metformin or insulin) and triple therapy (SU+metformin)

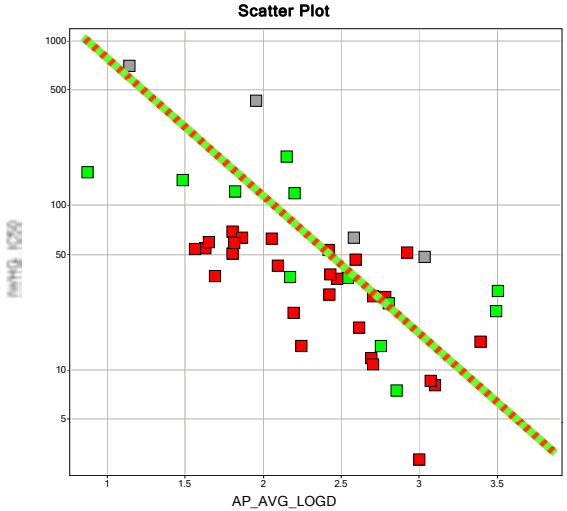
- AstraZeneca has taken the decision not to progress AZD1656 into phase III
- The reason for discontinuing is that the profile achieved in our Phase IIB evaluations did not meet our predefined internal criteria for the product

Chemistry Strategy in Summary

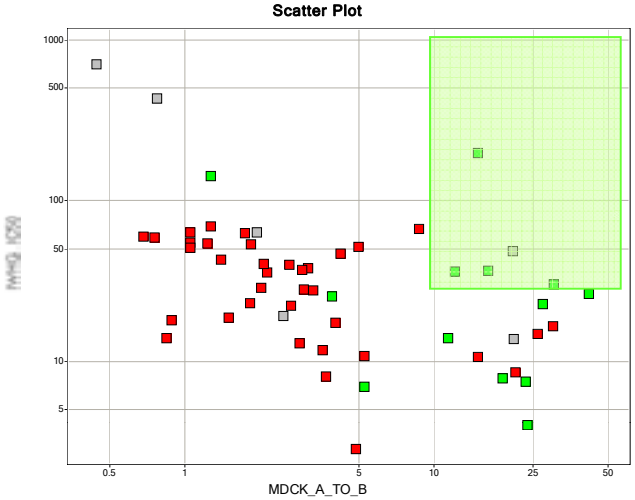
MDCK against logD



hERG against logD

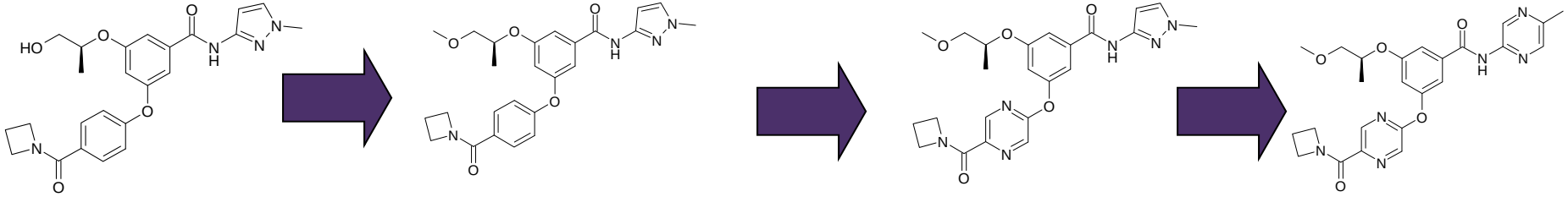


hERG against MDCK



1 donor green, 2 donors red, >2 grey

Structural changes



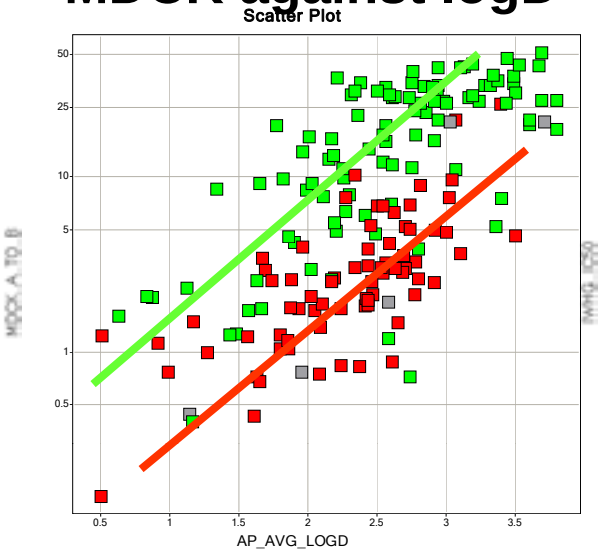
Removal of donor improves permeability but increases logD outside target range

Offset by introducing heteroatoms

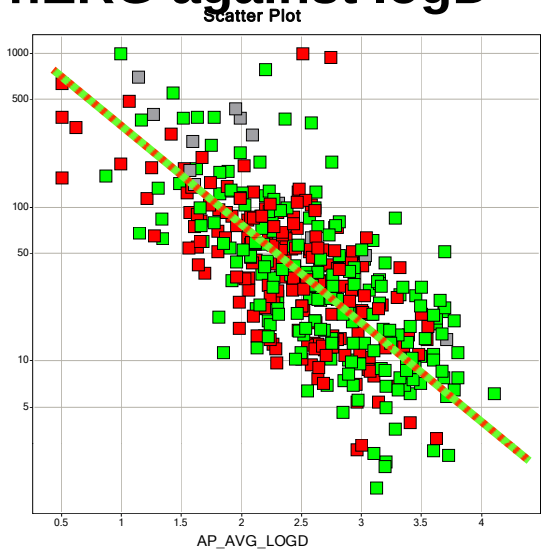
Combine with Ames negative heterocycles

Chemistry Strategy in Summary

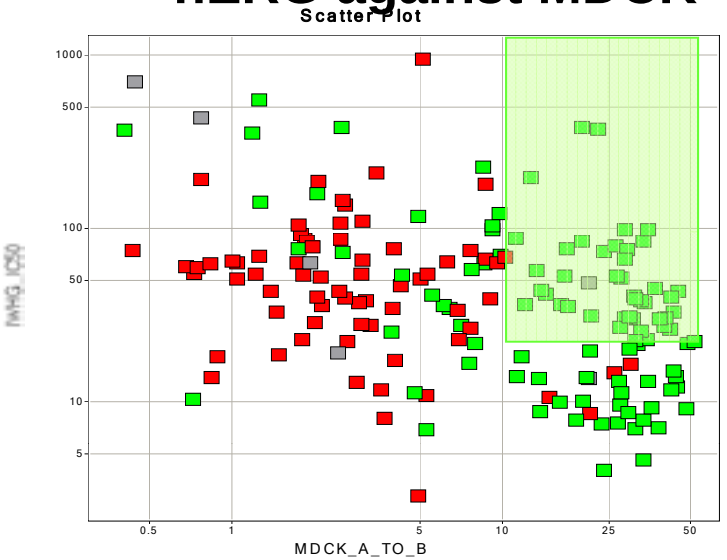
MDCK against logD



hERG against logD



hERG against MDCK



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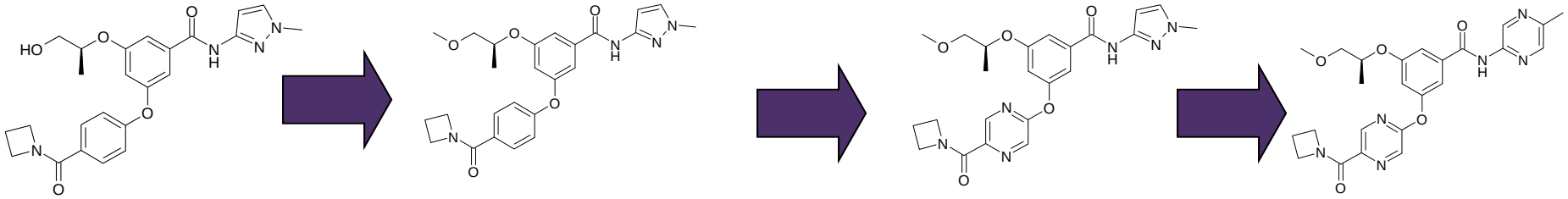
Structural changes



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Thank You
Acknowledgments