From Almokalant to AZD7009 and AZD1305

A Medicinal Chemistry Journey

Discovery of clinical candidates for treatment of atrial fibrillation

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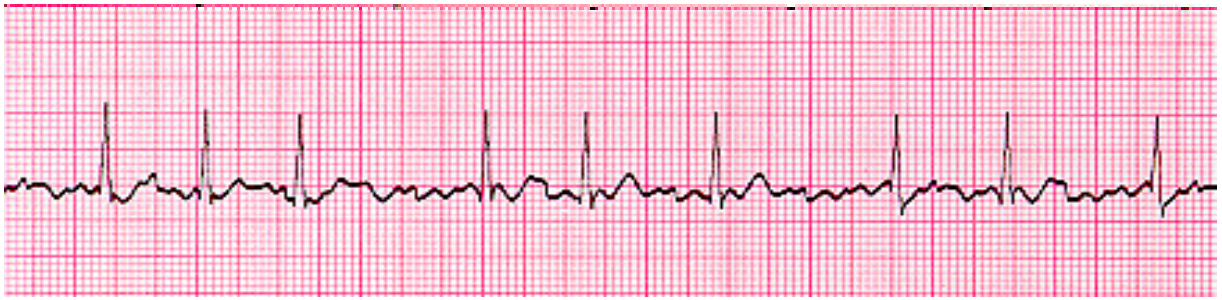
AstraZeneca

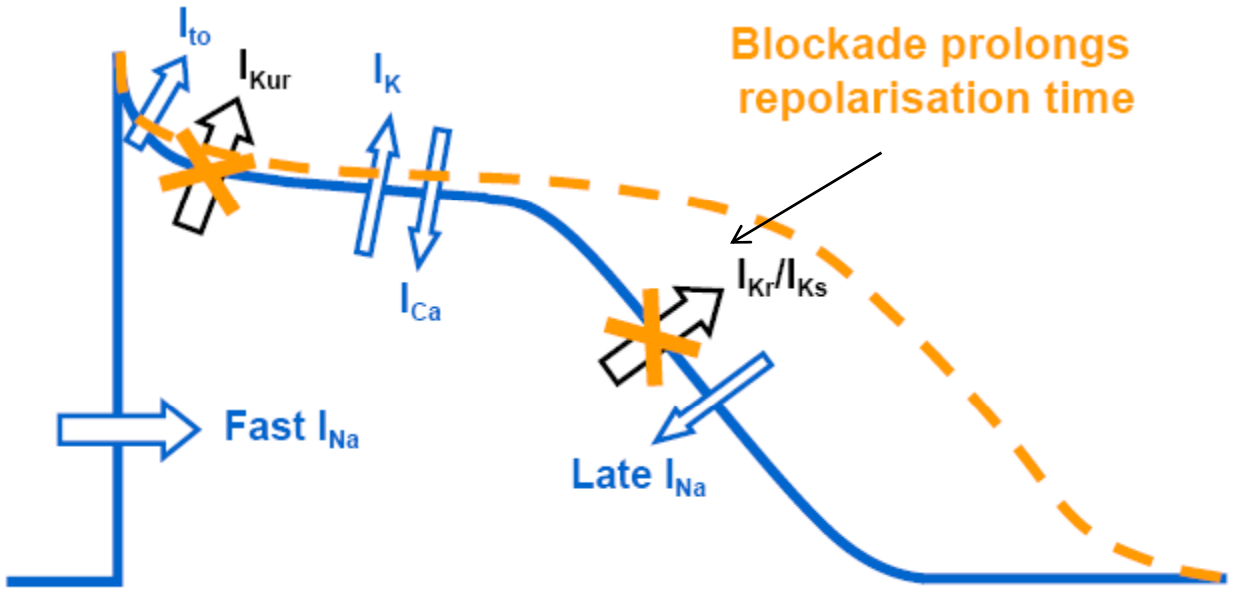
Atrial Fibrillation - Introduction

- Most common arrhythmia in clinical praxis (high health care costs)
- Large medical need
- Increasing with age
- High and irregular ventricular rate (driving heart failure)
- Increased risk of stroke, cardiomyopathy and heart failure
- Bothersome symptoms, negative impact on quality of life
- Increases morbidity & mortality



Potassium channel blockade (IKr; hERG) can restore and maintain normal heart rhythm

Some rhythm control therapies work by prolonging the action potential duration



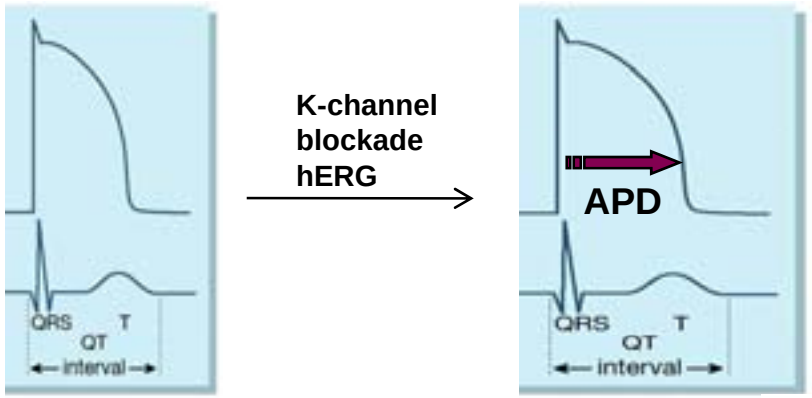
Movement of cations during the action potential of a cardiomyocyte

This is how it works

- Prolongation of the action potential duration in the heart muscle cells
- Increases the Effective Refractory Period in the whole heart
- Gives a longer resting period between consecutive heart beats
- Reduces the risk of arrhythmias

In the beginning

Primary screen in vivo



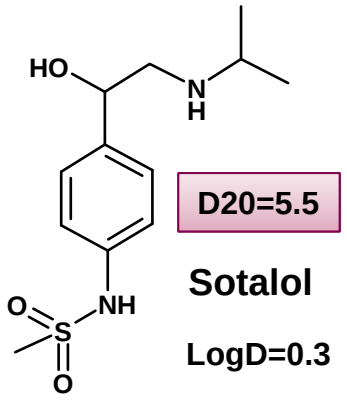
Screening model in Guinea Pig measures the APD prolongation

Screening critera
20% APD prolongation at a dose <0.1 μmol/kg i.v. *in vivo*

D20>7

Starting Points

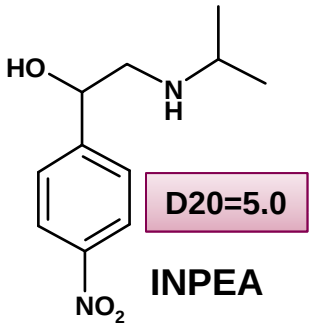
Beta blockers lead structures of low potency



D20=5.5

Sotalol

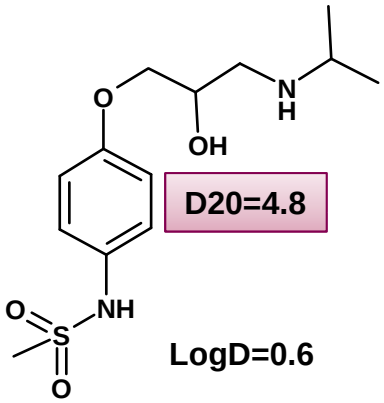
LogD=0.3



D20=5.0

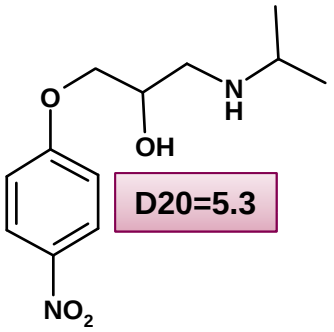
INPEA

LogD=1.3



D20=4.8

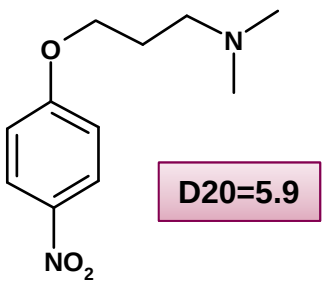
LogD=0.6



D20=5.3

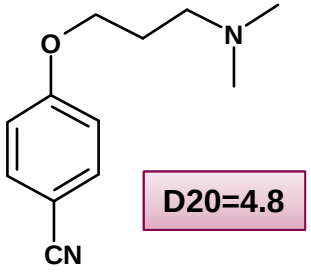
LogD=2.0

Alkylating the nitrogen increases APD potency and decreases beta-blocking potency



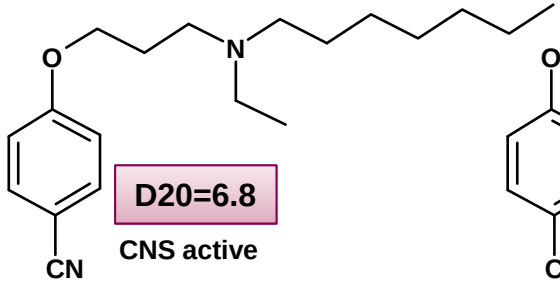
D20=5.9

LogD=2.0



D20=4.8

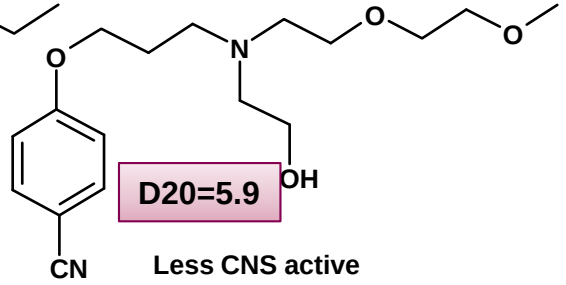
LogD=1.8



D20=6.8

CNS active

LogD=5.5



D20=5.9

Less CNS active

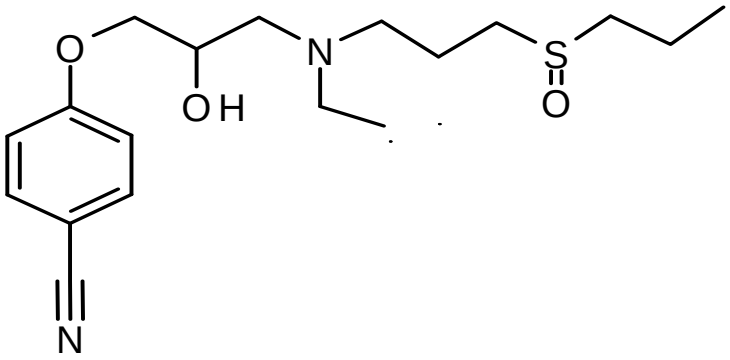
LogD=0.2

Decrease lipophilicity

Important change NO_2 to CN
CN more hydrophilic, and less risk of toxicity

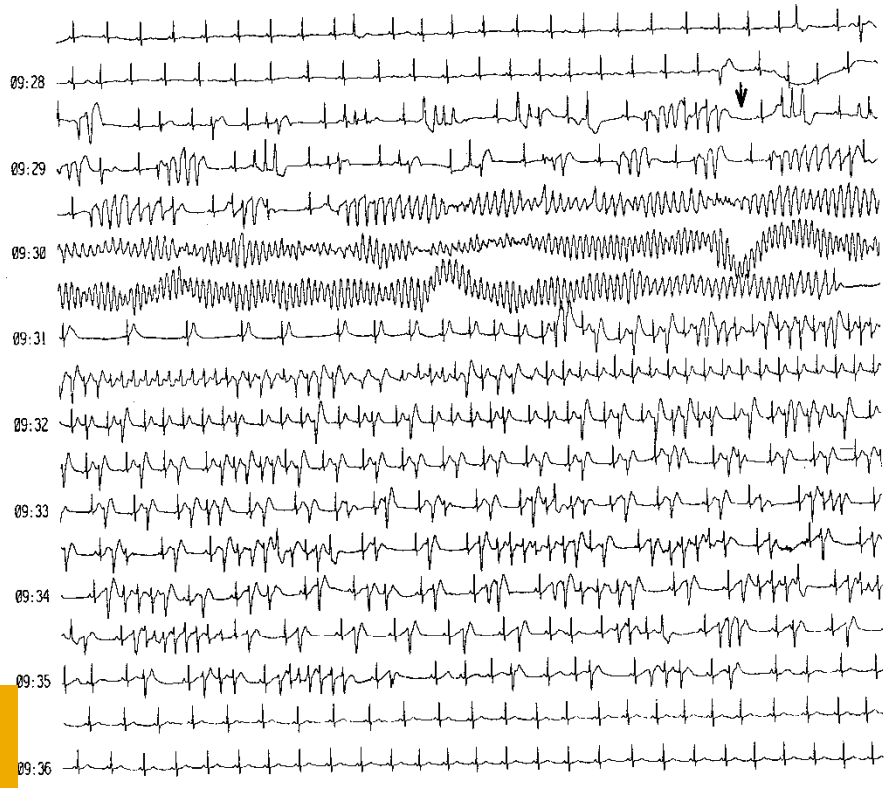
Introduce the beta chain once again

Almokalant first CD to man



D20=7.3
t1/2>100 min (human S9 liver homogenate)
No CNS issues
LogD=1.8

Promising electrophysiological characteristics demonstrated in Phase II studies



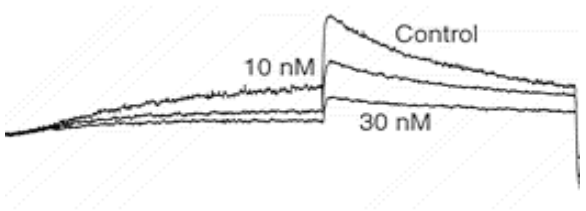
TdP incidence 2.9% (8/273)

Wiesfeld et al., Am Heart J 1993;126:1008.

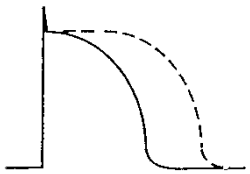
BUT……

B Darpö, O Almgren, Cardiovascular Drug Reviews Vol 14, No. 1, pp 60-83 (1996)

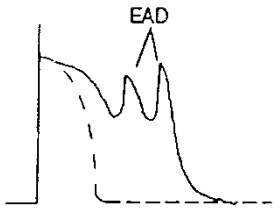
PROARRHYTHMIA RISK
Delay of repolarisation can cause a life-threatening arrhythmia
Torsades de Pointes



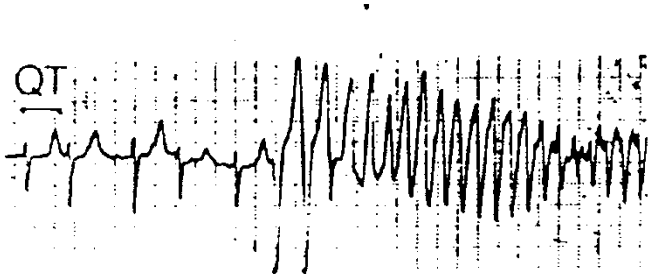
Block of K current (hERG)



APD prolongation

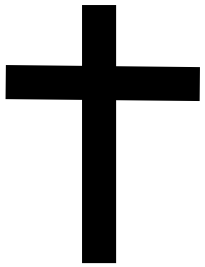


EADs in Purkinje Fibres

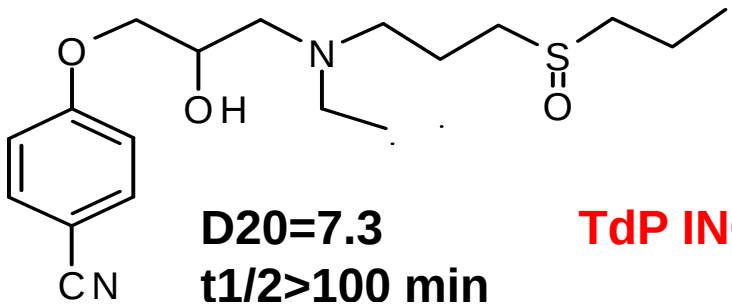


Torsades de pointes (TdP)

Ventricular Fibrillation



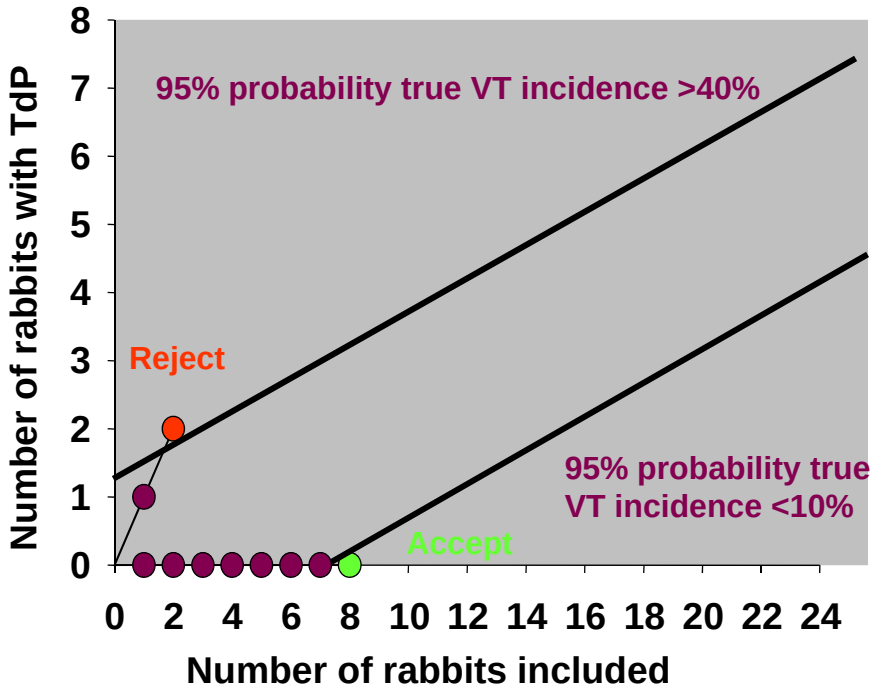
Almokalant stopped and project continued with new screening model



D20=7.3
t1/2>100 min

TdP INC in rabbit model=100% (in patients 2.9%)

Sequential Testing of TdP Potential in the Anaesthetised Rabbit



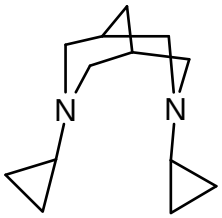
New Screening Criteria
D20>6.5
t1/2> 100 min
TdP incidence <10%

Falling on the ACCEPT side in sequential testing in a rabbit model using a dose 20 times D20 in Guinea Pig

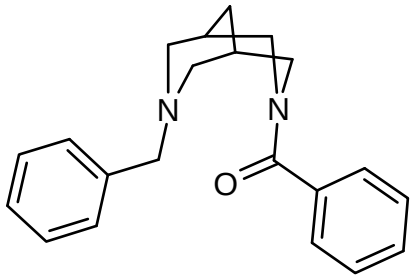
Carlsson L,Pharmacol Ther. 2008 Aug;119(2):160-7

The Bispidine Family

Lead compounds with antiarrhythmic effect



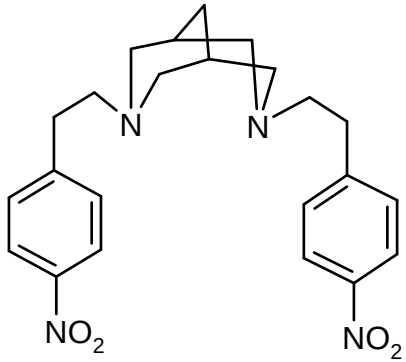
Tedisamil (Solvay)
D20=6.1



Ambasilide (Knoll)
D20<5.5

One basic nitrogen needed for effect
Dibasic compounds more potent

Explore the bispidine scaffold with the aim to reduce the propensity to induce TdP

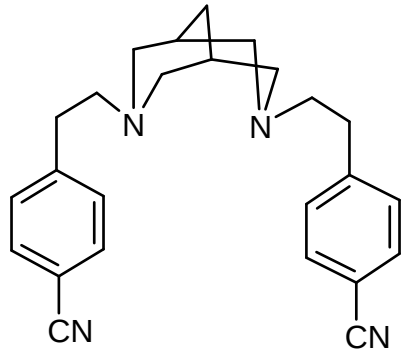


D20=8.0
TdP INC=100%

LogD=4.2

EWG in para position give potent compounds
Still TdP issue

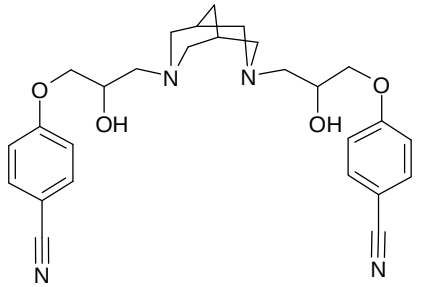
Modify with polar side chains



D20=7.6
TdP INC=100%

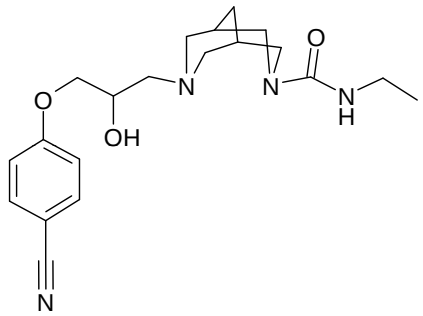
LogD=3.6

The Bispidine Series
Compounds close to fulfilling the screening goals



D20=6.9
INC=42%
t1/2 >100 min
LogD=3.8

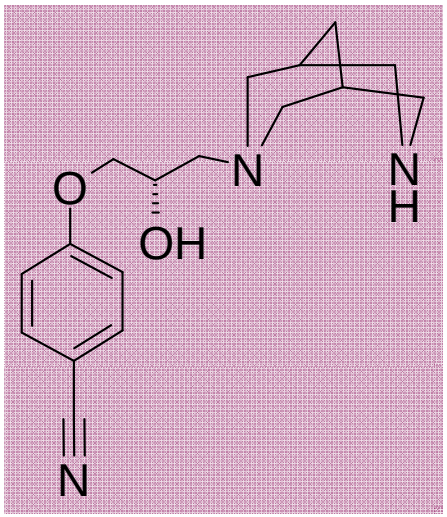
Dibasic compounds



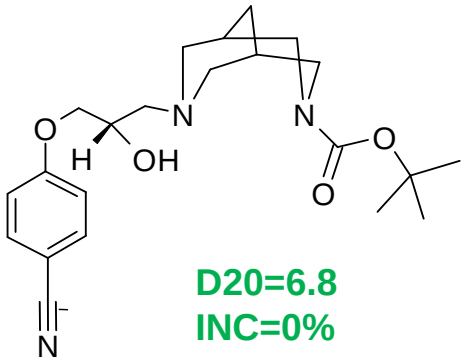
D20=6.7
INC=20%
t1/2>100 min
LogD=2.3

Acylated bispidines have low TdP potential, but it seemed difficult to reach the screening goals Project closure a big threat

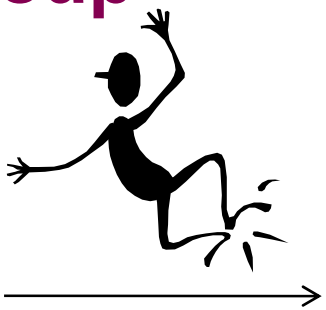
When planning for additional compounds a key intermediate was synthesised

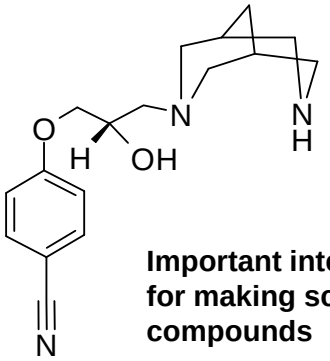


The Magic Boc-group



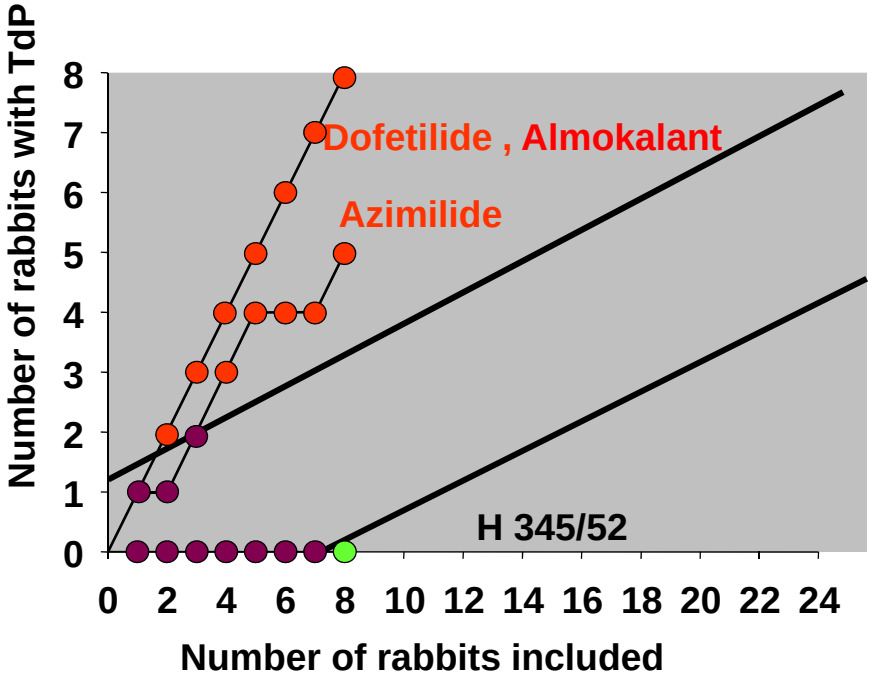
D20=6.8
INC=0%





Important intermediate for making screening compounds

H 345/52 a starting material was sent to screen



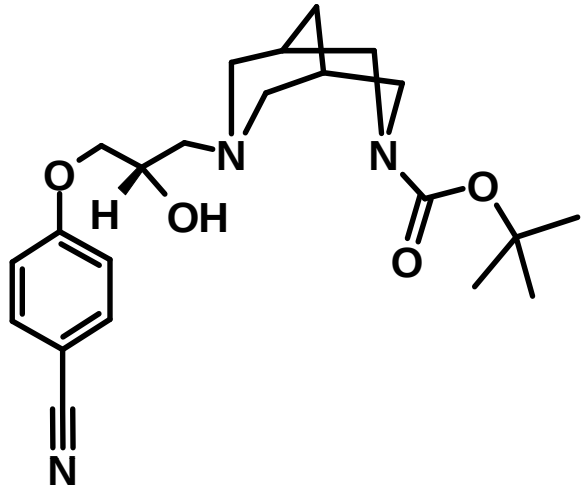
It is possible to make compounds with low TdP potential
The project got another chance!

BUT.....Pharmacokinetics H 345/52 an issue

t1/2 (in vitro human liver homogenates) 6 min

High Clearance in dog and rat

Oral bioavailability dog and rat: 0%



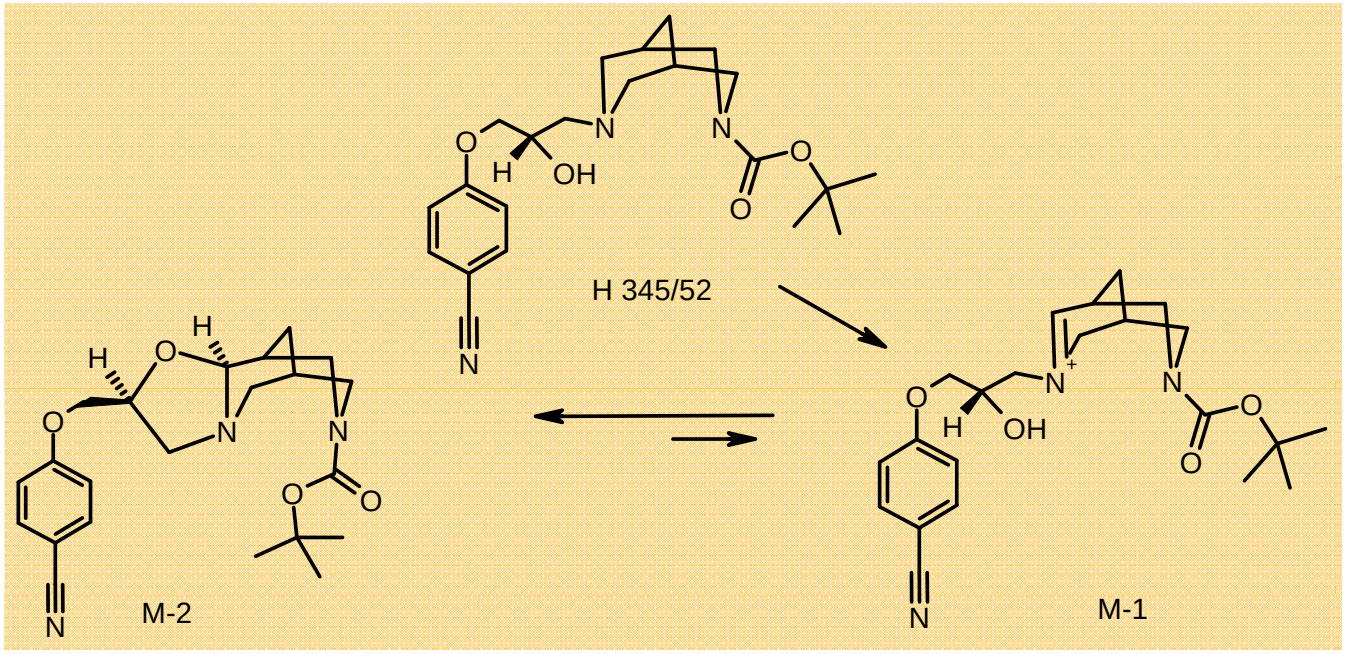
First CD for for i.v *conversion* of atrial fibrillation

Metabolically unstable

Guess why?

Metabolism of H 345/52

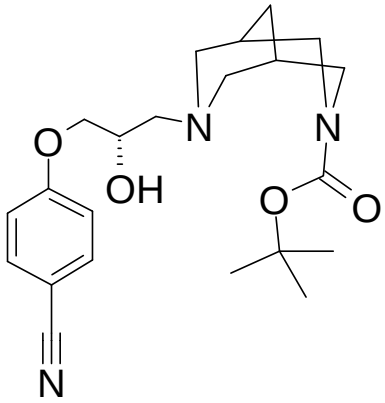
Ames positive with metabolic activation ☹



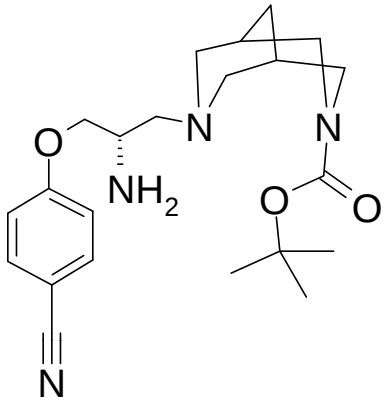
Metabolite Ames positive without metabolic activation ☹

- The compound passed in vivo genotox studies and was considered safe to give as a single intravenous dose to man
- Given to ~300 AF patients for restoration of sinus rhythm
- No TdP cases
- Oral compound with better PK and lack of reactive metabolites needed

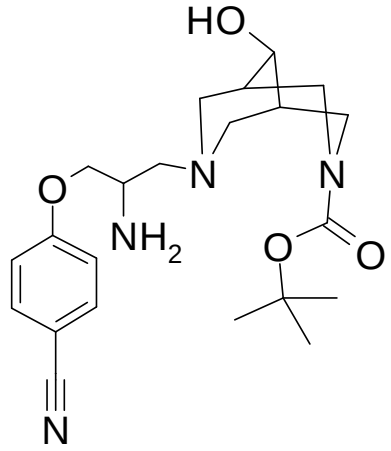
Fine-tuning of H 345/52



Decrease lipophilicity



Decrease lipophilicity



D20=6.8
INC=0%
t1/2=6 min

LogD=3.1

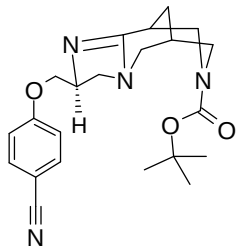
D20=6.3
INC=0%
t1/2=47 min

LogD=2.3

D20=6.6
INC=0%
t1/2 >100 min

LogD=1.1

Active metabolite with TdP
Ames positive

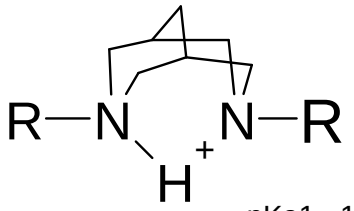


Two chiral centra
4 stereoisomers
None worked in isolation!
Weak Ames positive

Stop for the Bispidine series

New Strategy:

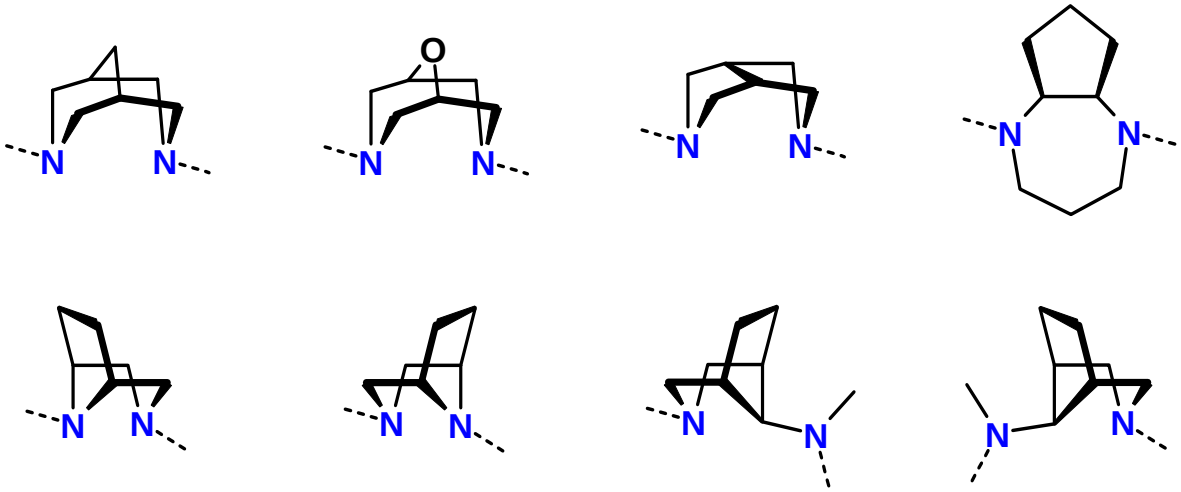
Explore alternative ring systems



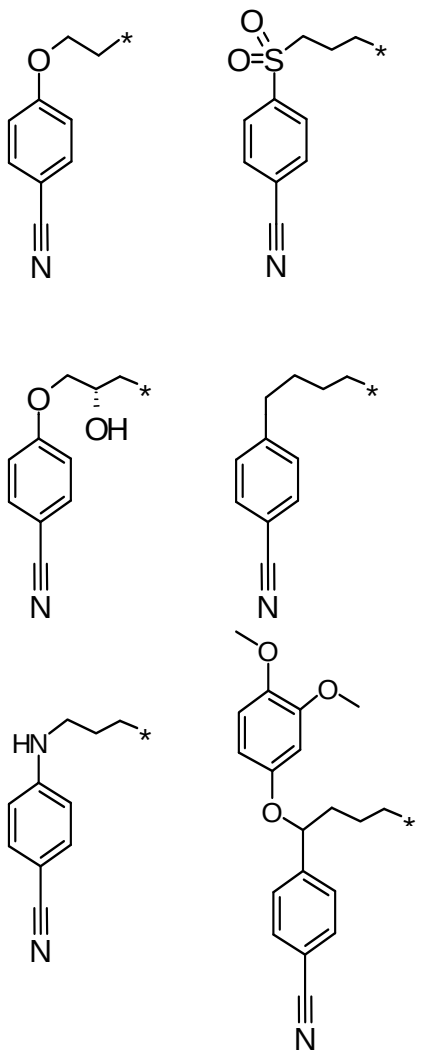
pKa1 ~10-14
pKa2 ~2

- **Keep the pharmacodynamic properties**
- **Increase metabolic stability**

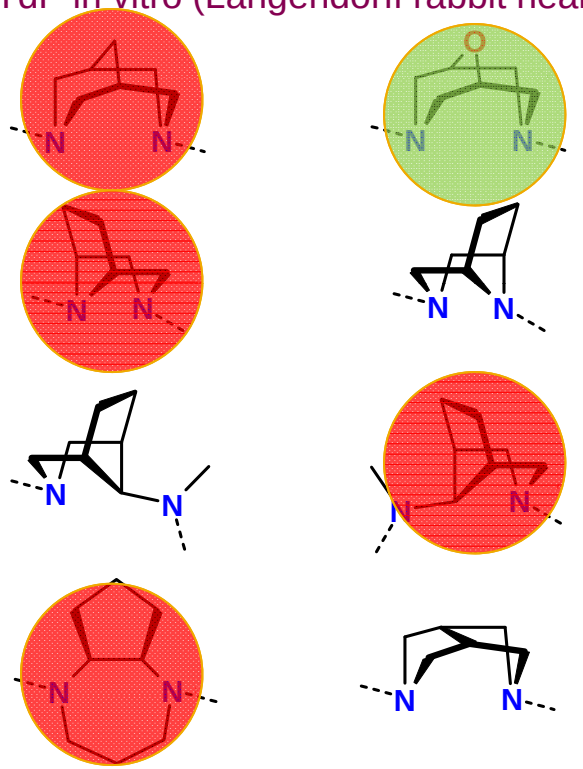
Rings were selected based on modelling where the distance between the 3,7-nitrogens in the bispidine and the dihedral angle, i.e. positioning of the N-substituents, guided the selection of alternative ring systems



Late LO scaffold hopping and library design

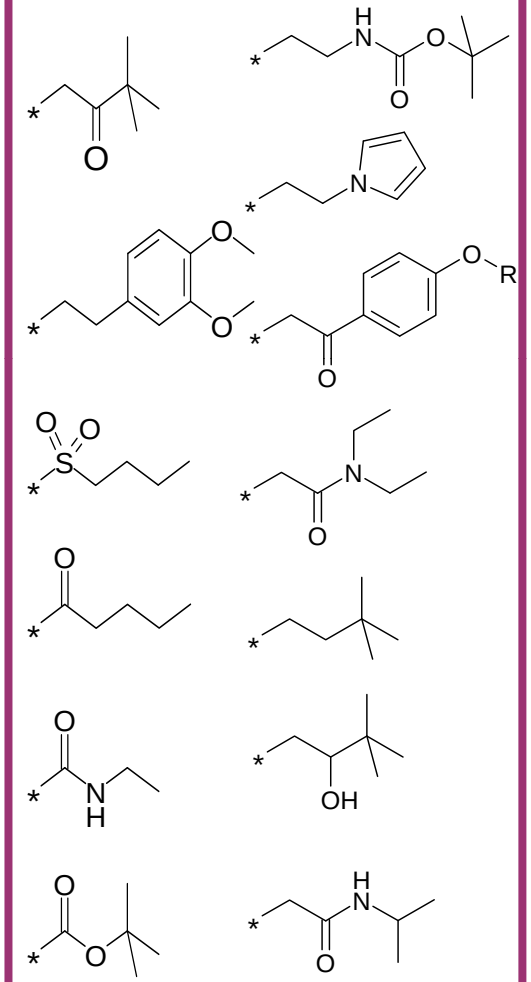


Libraries based on bispidine side chains
Filtration based on in vitro data
Potency in vitro (hERG) correlates to GP-data
Metabolic stability in vitro
TdP in vitro (Langendorff rabbit hearts)

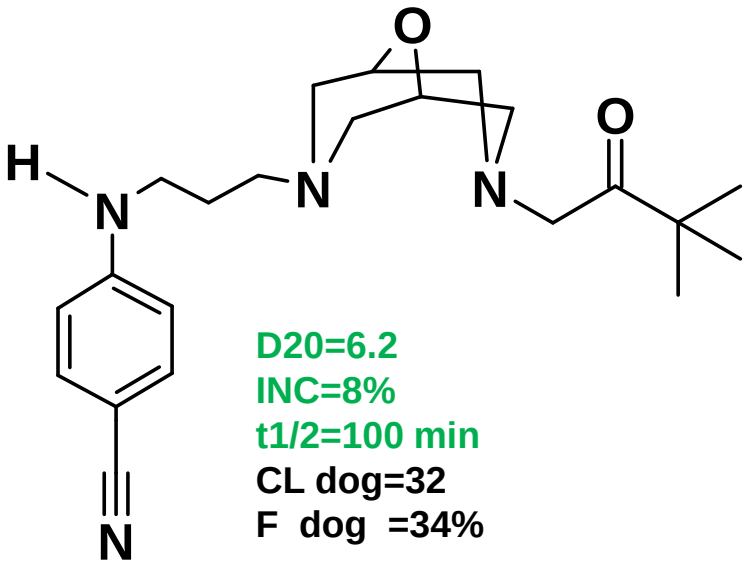


Optimising 4 scaffolds
With designed right side chains

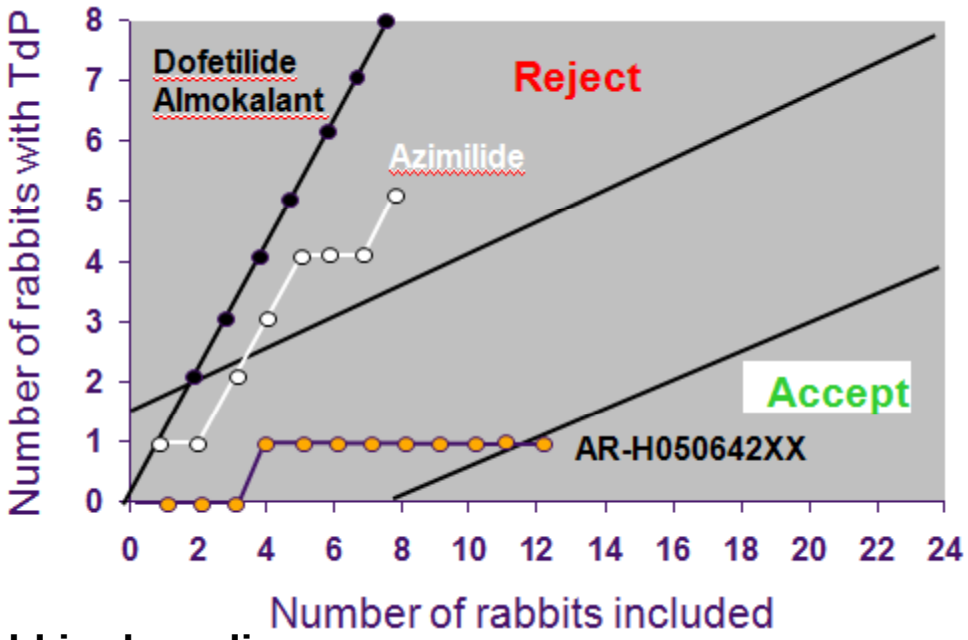
Oxabispidines



AR-H050642 CD from the first oxabispidine library

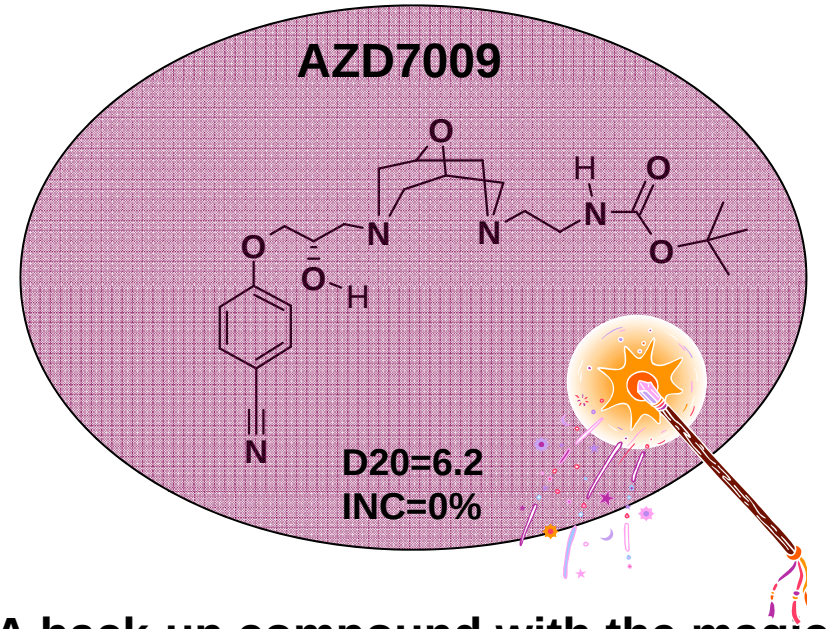


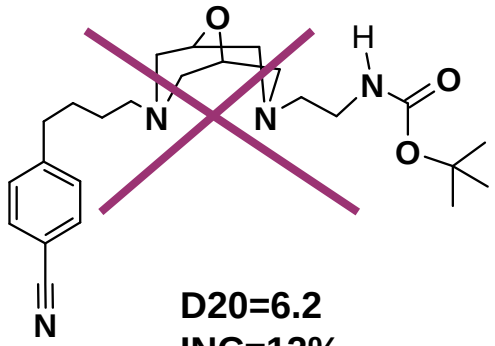
D20=6.2
INC=8%
t1/2=100 min
CL dog=32
F dog =34%



- Oxabispidine an AstraZeneca unique scaffold in drug discovery
- 1999 were no patent published with this fragment
- Project team was eager to further explore this scaffold
- With a very limited timeframe the team made 40 additional compounds

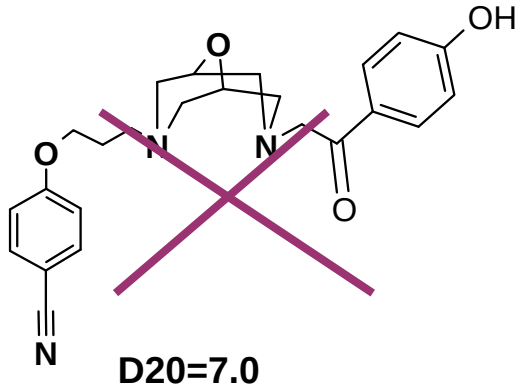
A small illicit optimisation- 10% fulfilled TdP -criteria



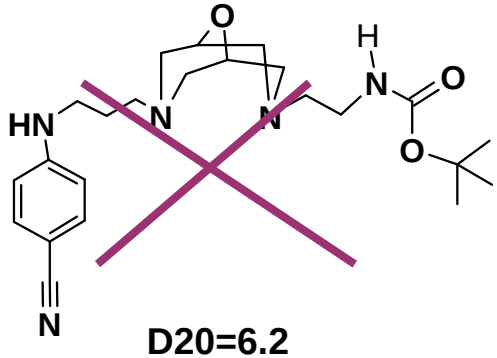


CYP2D6 inhibition

A back-up compound with the magic Boc-group



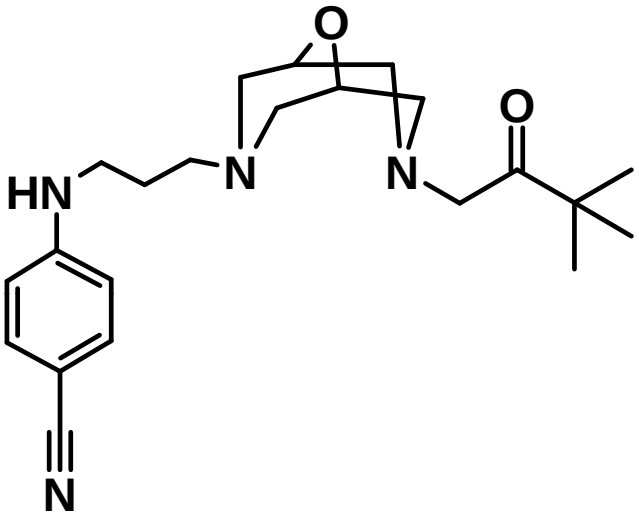
Poor bioavailability



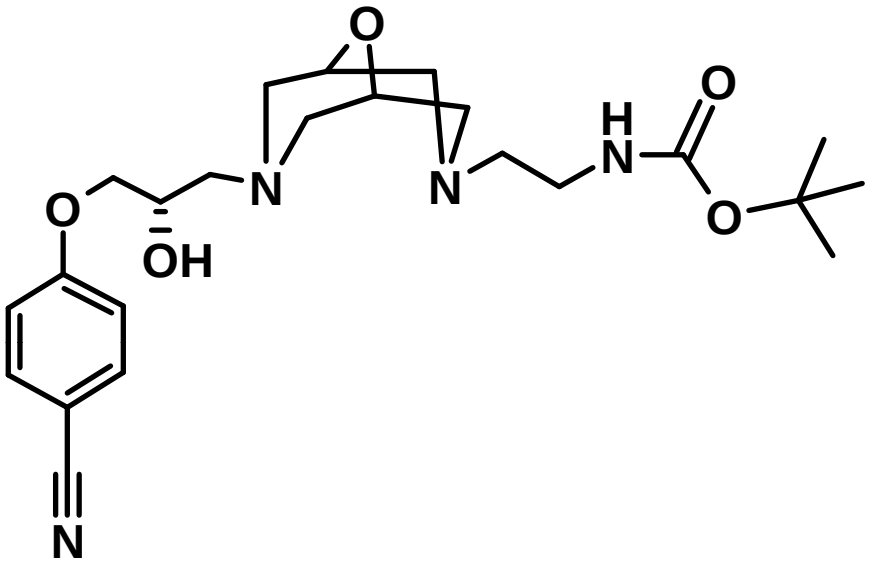
We prefer not to use anilines

AR-H050642 Closed

AZD7009 New Clinical Candidate

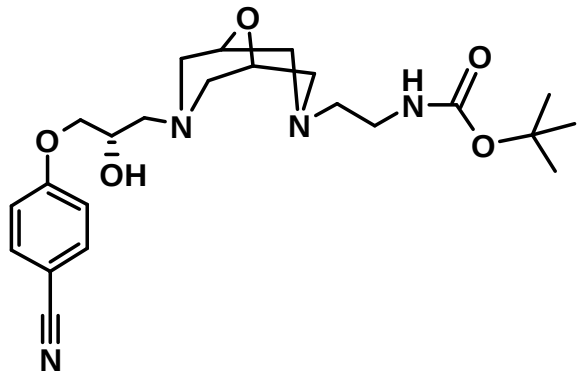


AR-H050642
Closed due to liver toxicity in dogs

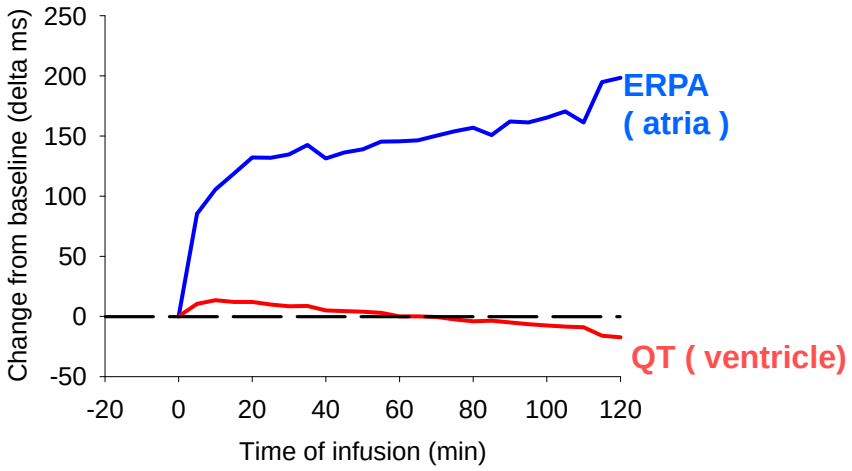


AZD7009 passed toxicology studies
No liver toxicity
No genotox issues

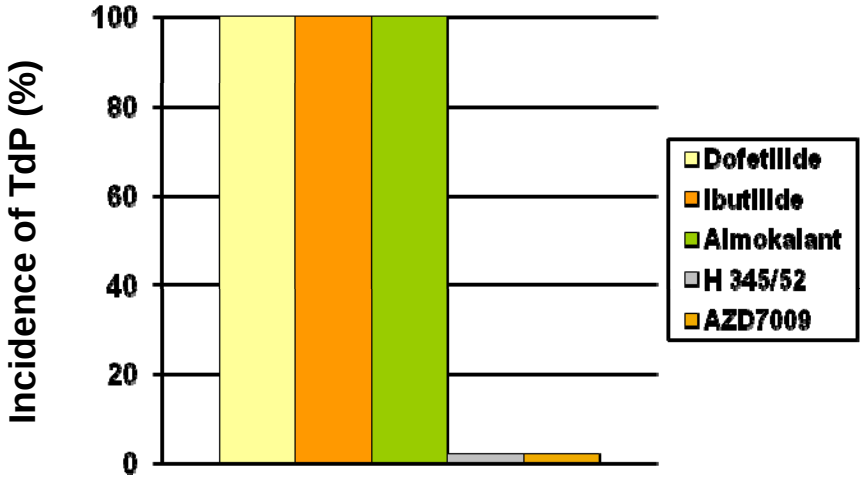
Unique Electrophysiological Characteristics of AZD7009



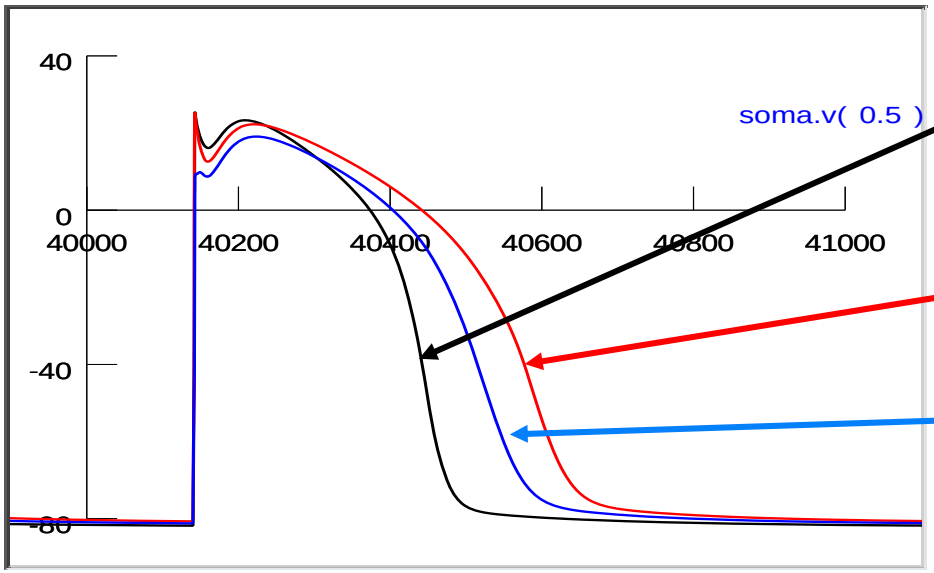
Atrial selectivity in the anaesthetised dog



Lack of TdP liability in the anaesthetised rabbit Competitor comparison



The Secret of AZD7009 - a Mixed Ion Channel Blocker



Control

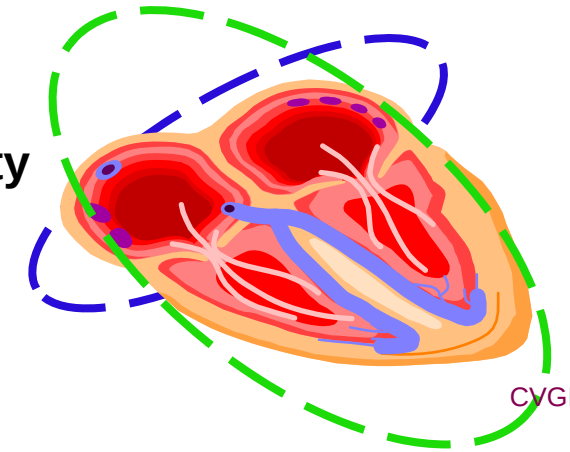
Block I_{Kr}

Block I_{Kr} + I_{CaL} + I_{Na}

AZD7009

AZD7009 prevents excessive APD (and QT) prolongation due to Na and Ca-channel blockade

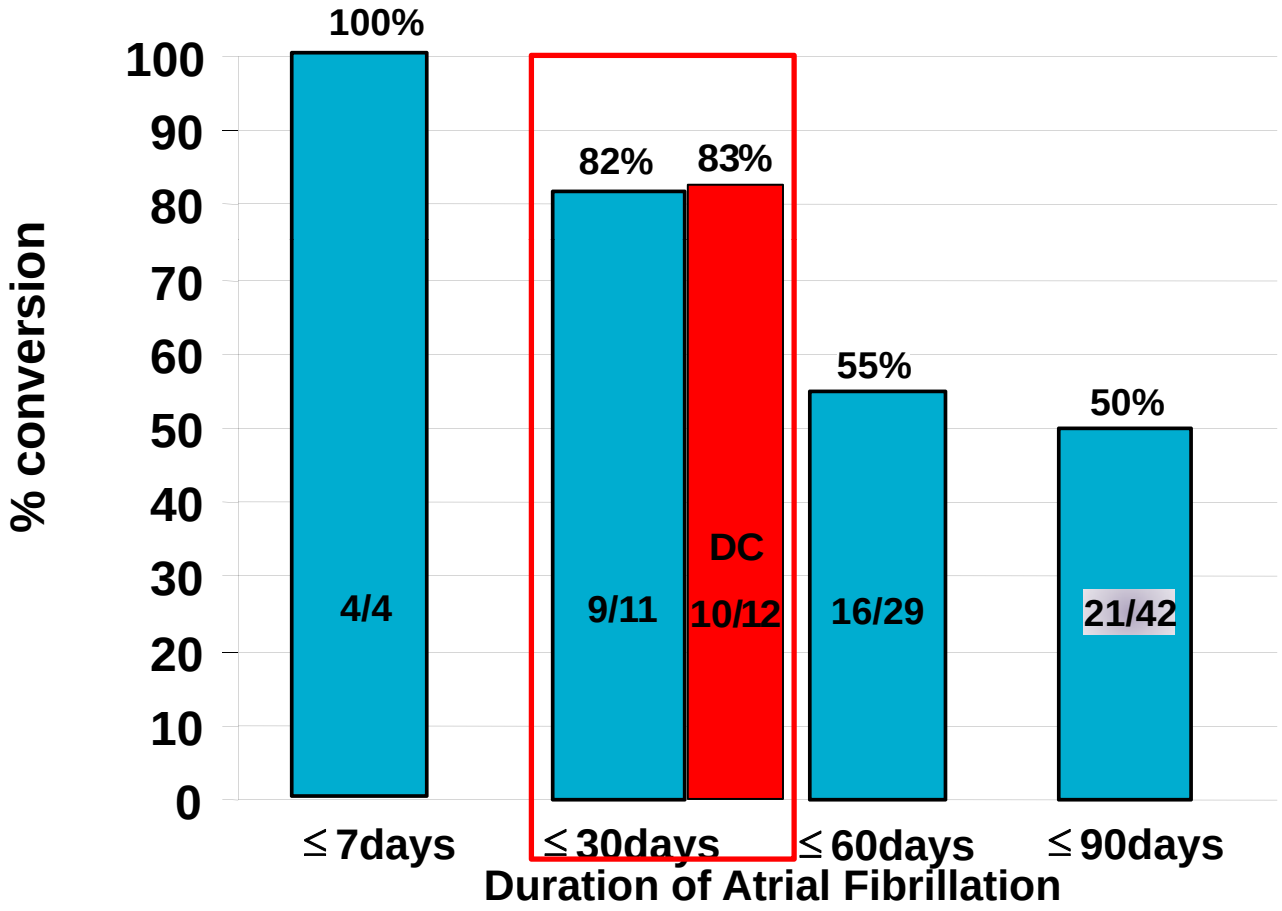
- **Protection from TdP**
- **Contributes to atrial selectivity**



AZD7009 shows similar efficacy as electrical cardioversion in patients with AF duration <30 days

The best chemical defibrillator ever

AZD7009: dose finding study i.v. conversion



Geller et al. J Clin Pharmacol 2009;49:312-322

AZD7009 DMPK Parameters
Predictions vs Clinical data

Parameter	Human Predicted	Clinical data
CL (Lh^{-1})	63	70 - 90
F (%)	24	ca. 20

ER as first formulation

High CL a risk for of high daily dose

A follow- up project was started

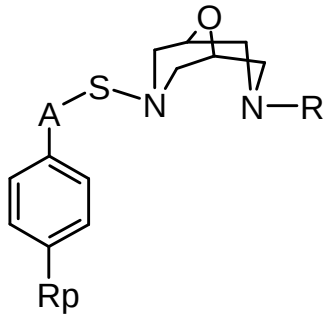
AZD7009 an Excellent Starting Point for Further Optimisation

Optimize the side chains

Keep or improve the pharmacodynamical properties.

Improve the DMPK properties

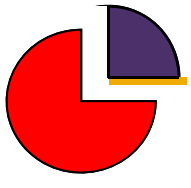
Reduce the predicted daily dose with at least a factor of 4



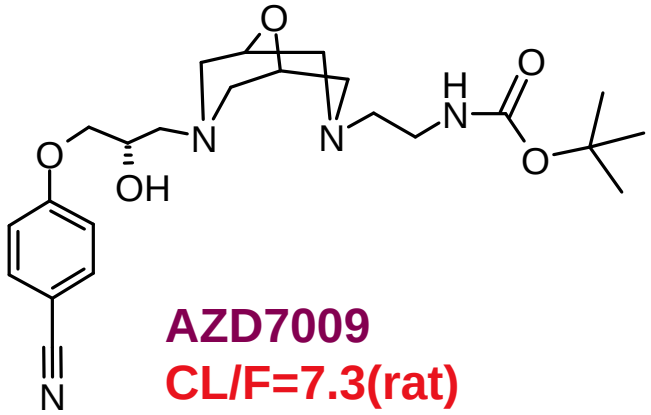
SAR from previous LO campaign

Rp: CN or halogen
A: CH_2, O, SO_2, NHCO, $N(Me)_2SO_2$, CONH, *etc*.
S+A: 3-6 atom distances
R: widely varied

Dose= $\frac{CL \bullet C_{ss} \bullet \tau}{F}$



CL = total plasma clearance
C_{ss} = steady-state plasma concentration
τ = dosing interval
F = oral bioavailability



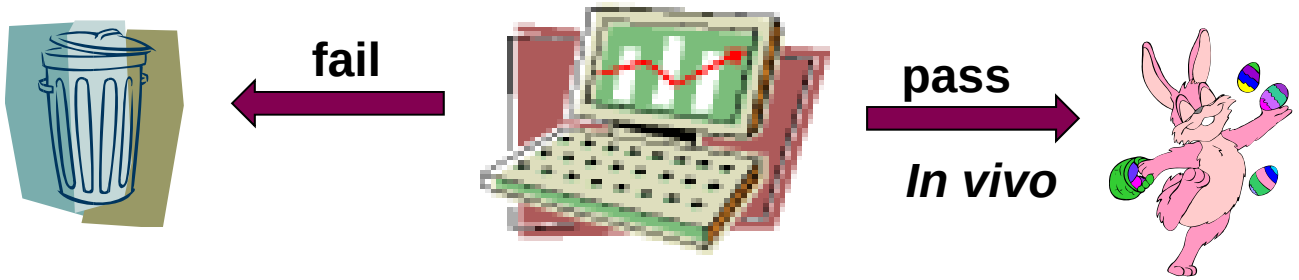
AZD7009
CL/F=7.3(rat)
Inc=0%

The Key to Potency and Low Incidence:

The Right Balance Between K , Na and Ca blockade

A faster design/ make/ test loop and reduction of number of in vivo experiments

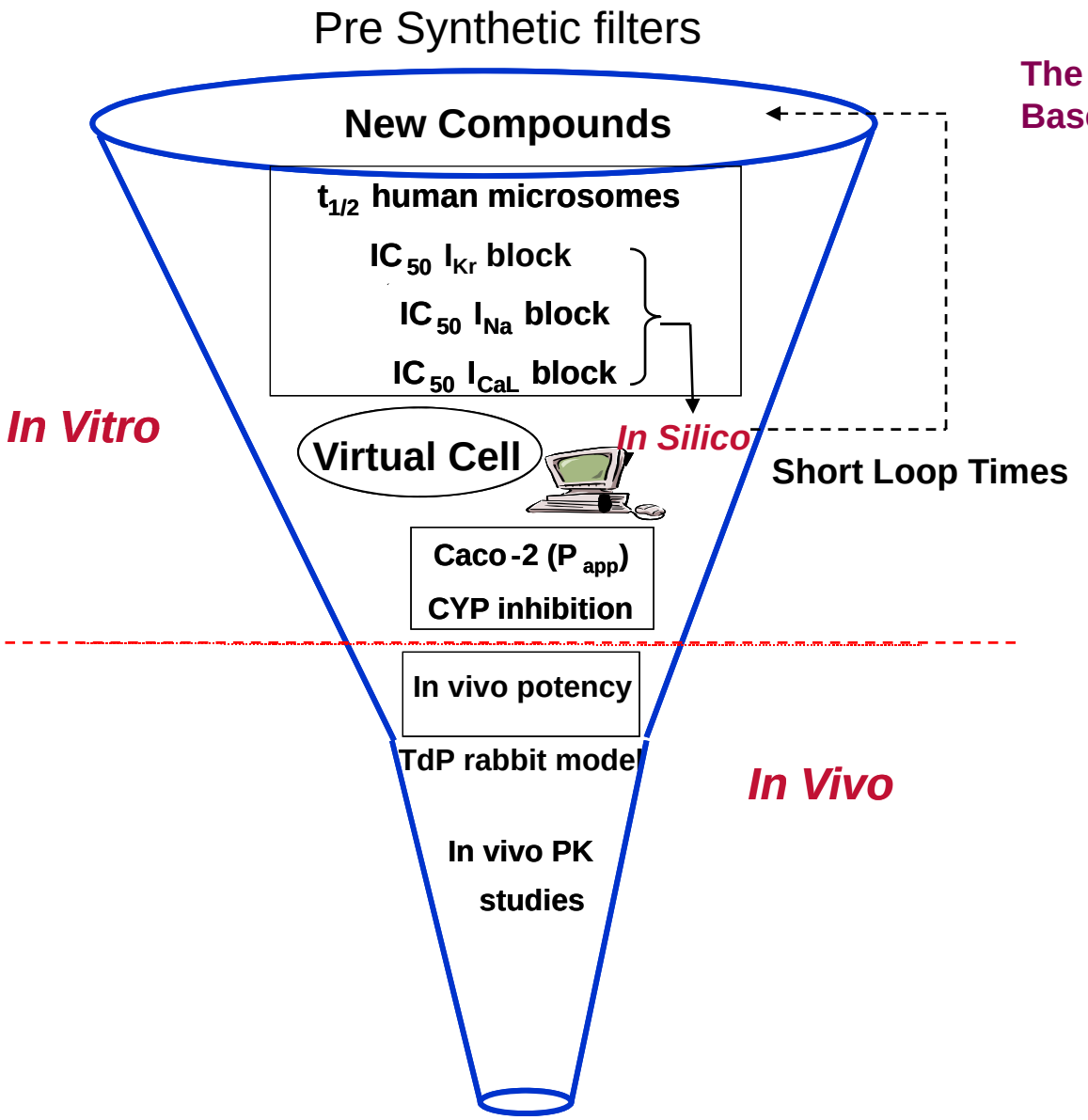
- New and old compounds were screened on hERG, Na and Ca blockade
- Based on historical *in vivo* TdP-data, a limit on APD was set
- Data was used to predict APD in a computer model, a virtual ventricular myocyte



The Virtual Ventricular Myocyte

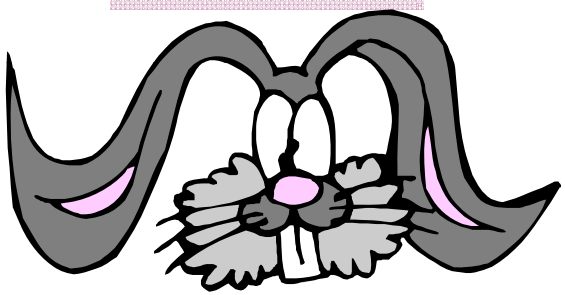
- **Incorporates the present knowledge of the function of cardiac ion-channels and transporters**
- **Gives predictions on the dynamics of a highly complex system**

Screening Loop for Follow-up Program



The Pre-Synthesis "Rabbit" Filter
Based on data from previous LO-campaign

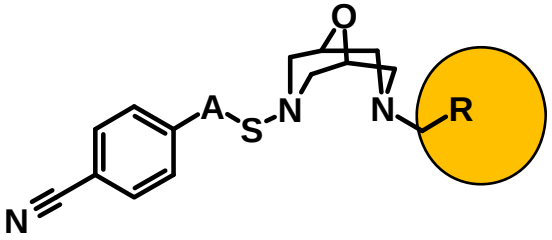
ClogP <4.5
ACDlogD>0.75
11<NPAT<21
6<PAT<11
7<N-rot bonds<13
75<PSA<130



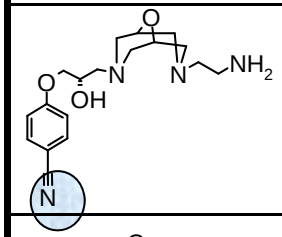
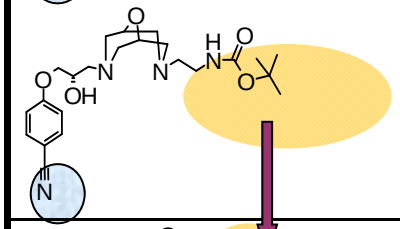
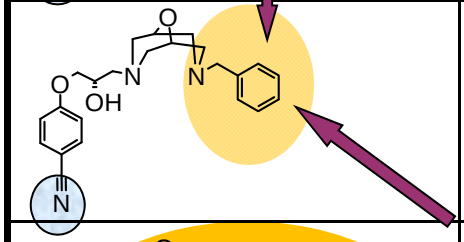
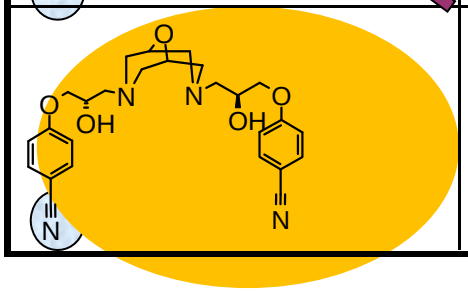
New screening criteria

D20>6
CL/F <2
INC=0%

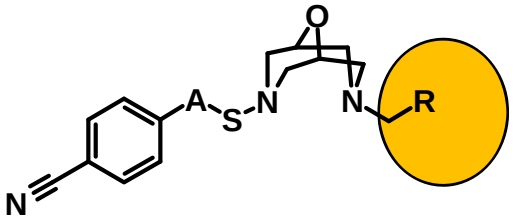
SAR for Potassium Channel (hERG) Blockade



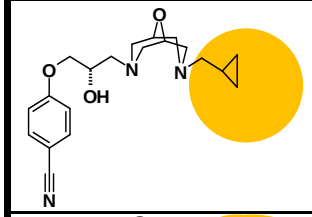
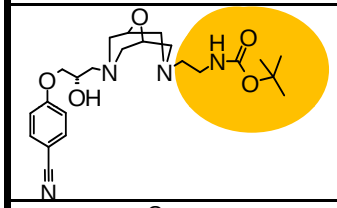
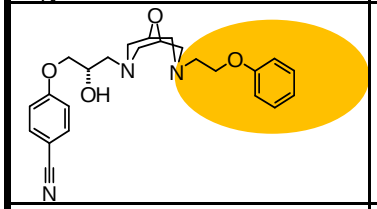
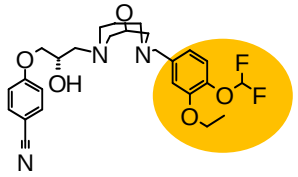
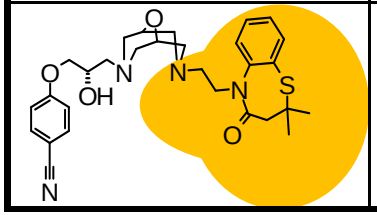
- R should have a lipophilic end-point
- Potency will be increased by replacing an alifatic side chain by an aromatic
- Symmetrical molecules give high potency.
- Potency can be increased by adding an electron withdrawing group to the aromatic ring in the right side chain
- Para-CN substituent is important for potency and *low incidence* in the oxabispidine family

A structure family	pIC50 hERG
	4.5
	5.3
	6.0
	6.5

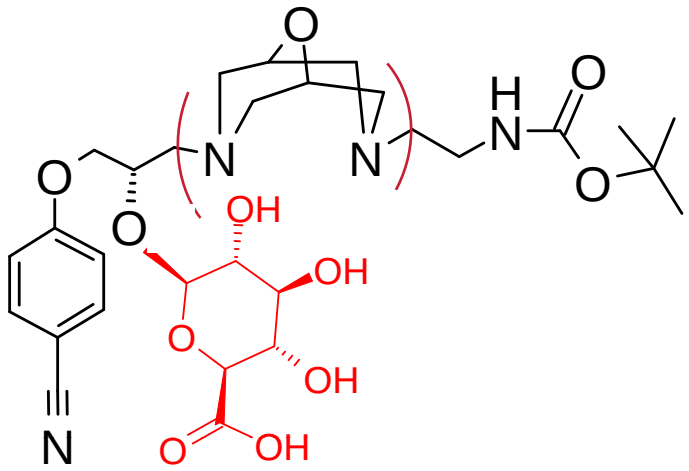
SAR for Sodium and Calcium Channel Blockade



- Small alifatic side chains of low potency
- A lipofilic endpoint is advantageous. Polar functionalities in the side chains often favourable
- The sequence C-C-O-R , C-C-N-R gives high potency
- Bensyl and phenetyl groups give potent Na and Ca channel blockers
- Potency can be modified by using fragments from known Na and Ca blockers
- Ca and Na blockade correlates which simplifies the design of new compounds.

Structure	pKi50 Na	pKi50 Ca
	4.5	<4
	5.5	5.4
	5.7	6.2
	6.3	6.4
	6.3	6.9

Improve DMPK properties



AZD7009
Mainly metabolised by glucuronidation of the β–OH group
Dealkylations of side chains
Relatively low permeability

- **Minimise the number of heteroatoms**
- **Aim for logD between 2 and 3**
- **Avoid glucuronide formation**

In the middle of the follow-up programme

Problems for AZD7009

Non cardiac side-effect

- Unspecific inflammatory reaction

- Fever, elevated CRP, often ”flu-like” symptoms after repeated dosing with ER formulation

- No obvious explanation

- Nothing similiar was seen in toxicological studies

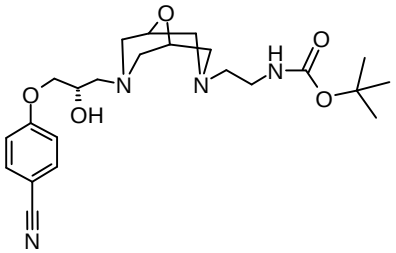
An urgent need for a *Back-up* compound

The optimization continues with high speed

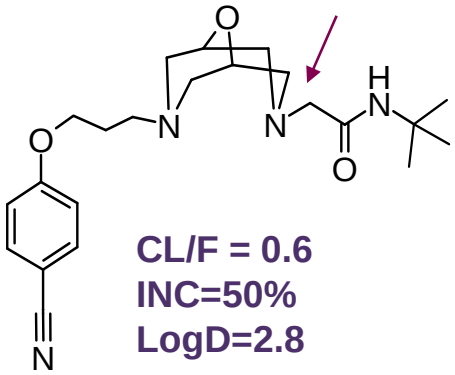
Using our Medicinal Chemistry Toolbox

KHA10

Minimise dealkylations

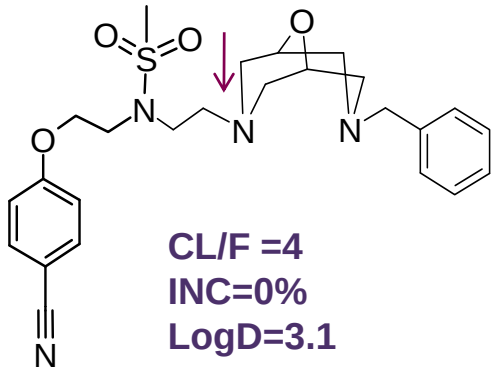


No *N*-dealkylation



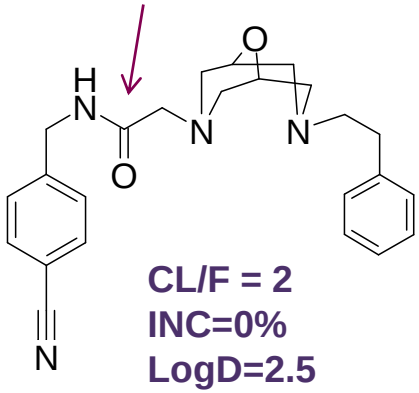
CL/F = 0.6
INC=50%
LogD=2.8

No *N*-dealkylation



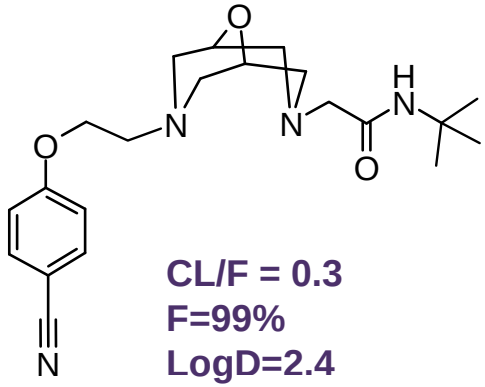
CL/F =4
INC=0%
LogD=3.1

No *N*-dealkylation

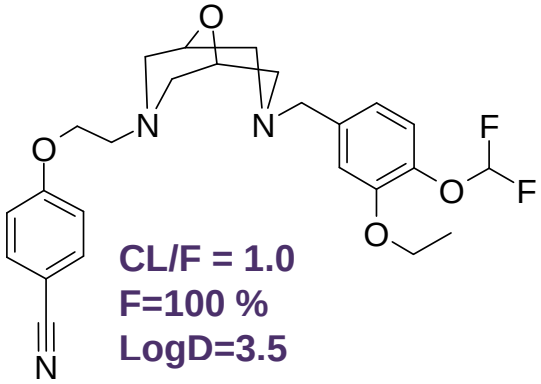


CL/F = 2
INC=0%
LogD=2.5

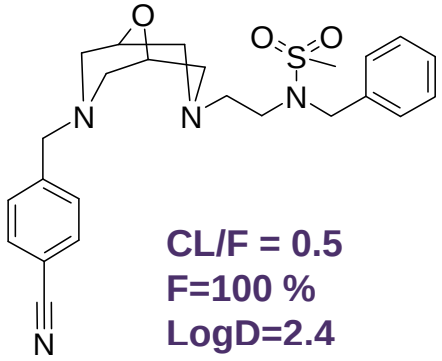
Improve Bioavailability



CL/F = 0.3
F=99%
LogD=2.4



CL/F = 1.0
F=100 %
LogD=3.5



CL/F = 0.5
F=100 %
LogD=2.4

Short side chains increase bioavailability

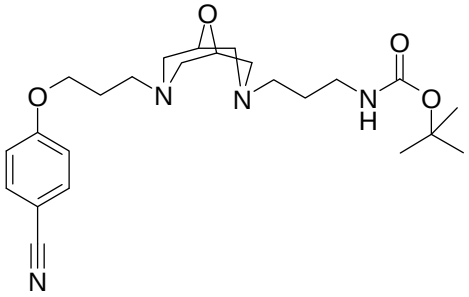
KHA10 log D vid strukturerna

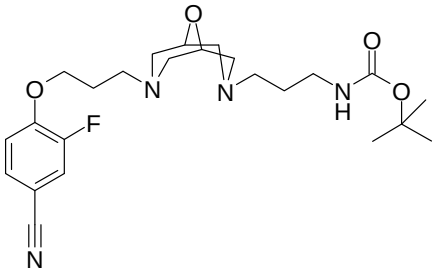
Kjell H Andersson, 23/06/2011

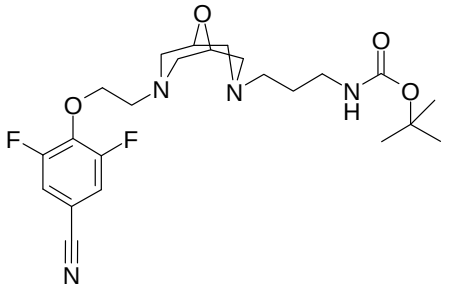
1000 compounds later made by parallel chemistry

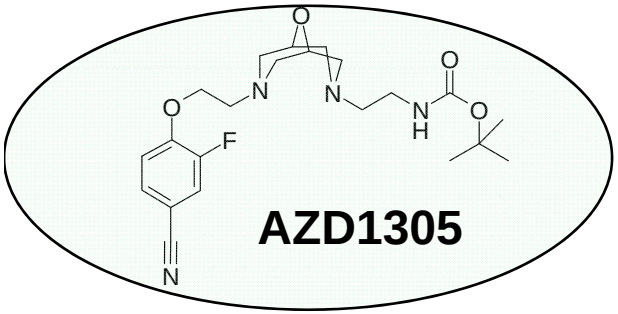
- **70% fulfil the criteria for a balanced K, Na and Ca channel blockade based on data from the *virtual cell***
- **15 % remain after Caco-2, CYP2D6 and CLint screening**
- **12 compounds fulfilled the *in vivo* screening criteria and have been evaluated as potential pre-CDs**

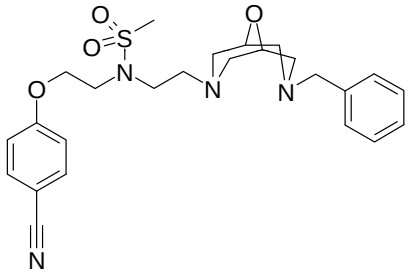
12 compounds with low proarrhythmia liability in the rabbit model was evaluated as potential pre-CD candidates

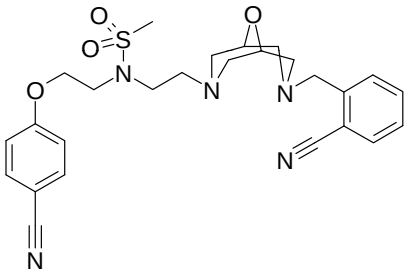


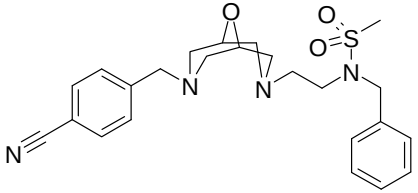


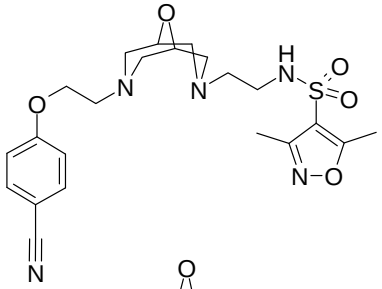


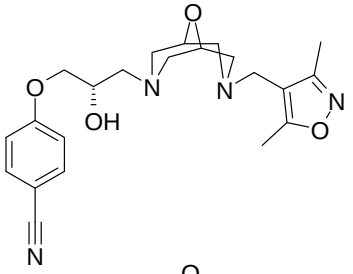


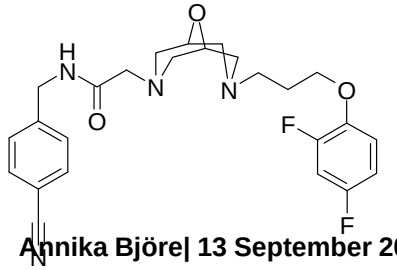


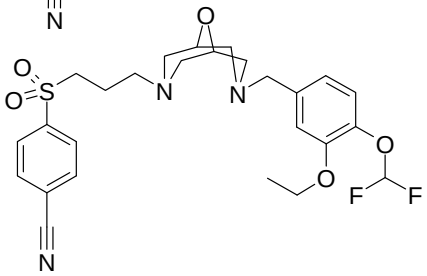


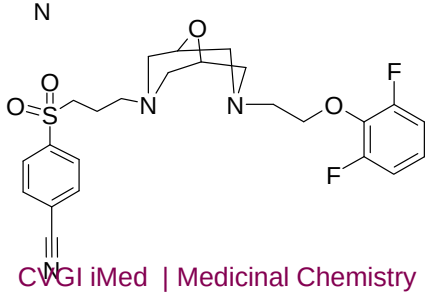




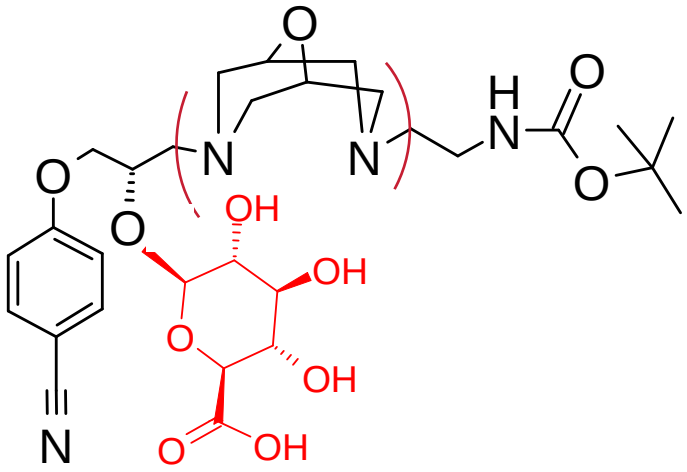


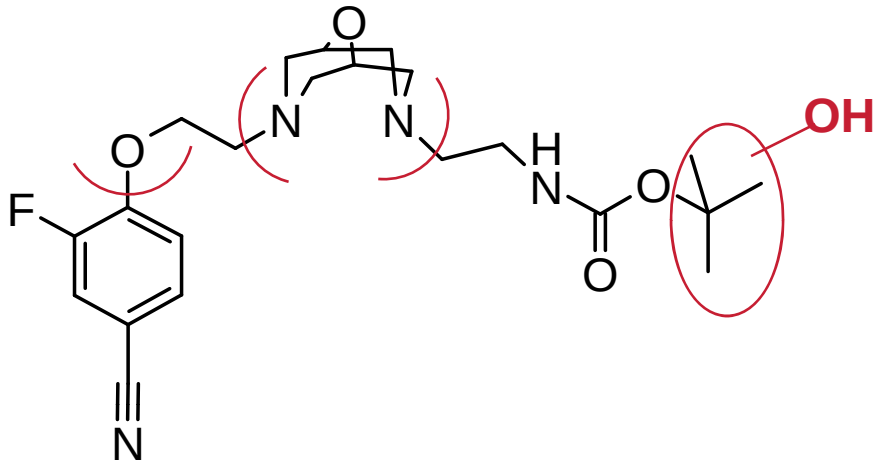






Lower Dose with AZD1305





AZD7009
Mainly metabolised by glucuronidation of the β–OH Group

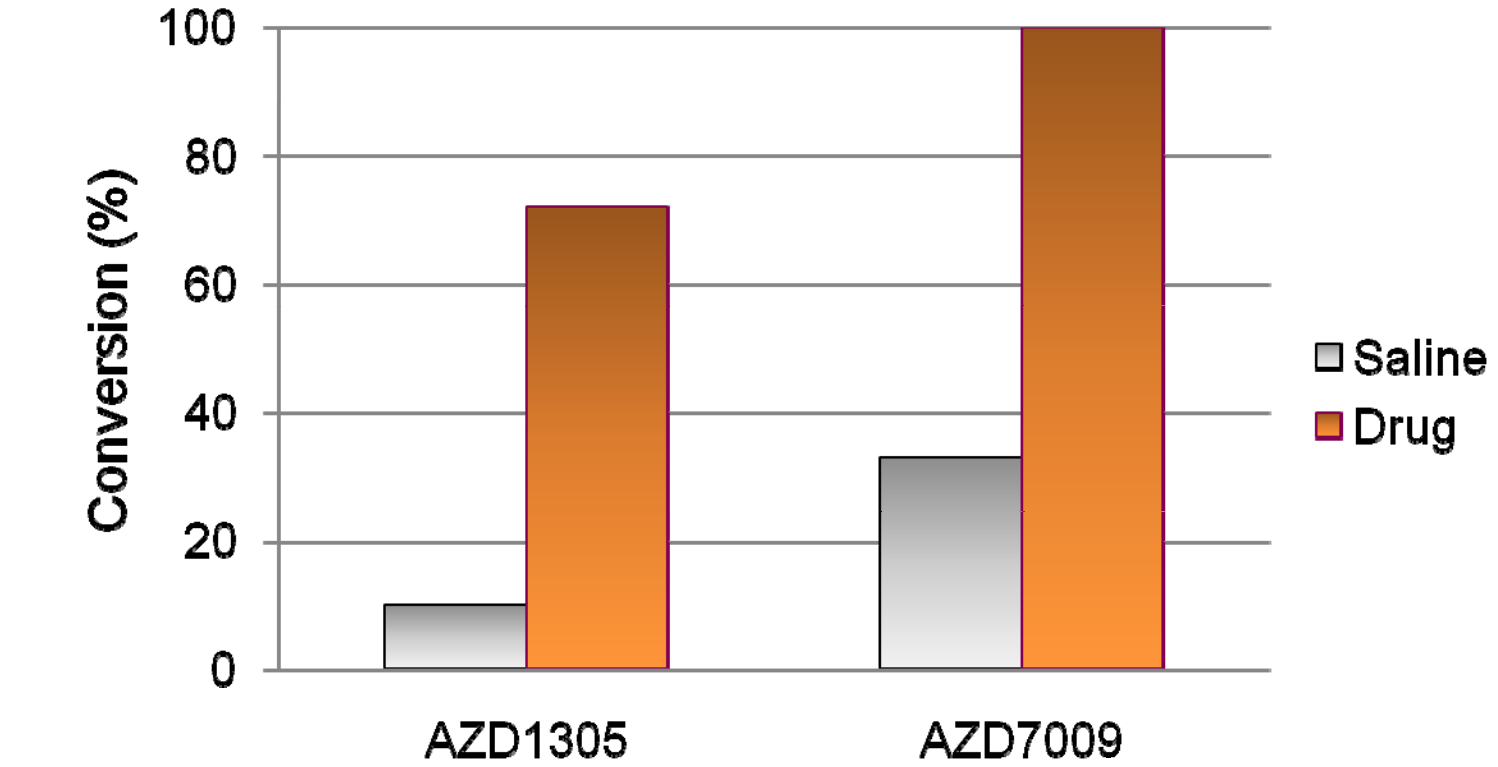
Remove OH, C and add F

AZD1305
A 75% reduction of the predicted daily dose

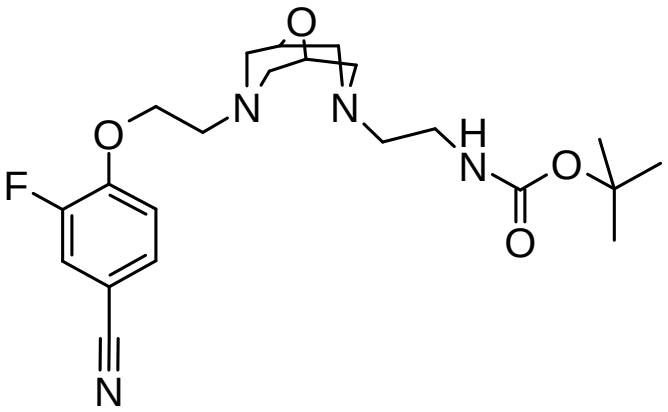
LogD=2.7

LogD=2.6

AZD1305 and AZD7009 Effectively Restore Sinus Rhythm in the Dog



AZD1305



- ✓ **Excellent efficacy in Phase II clinical trials for AZD1305**
- ✓ **No “fever” problem**
- ✓ **“Safe QT-prolongation” in most patients, but risk for ventricular arrhythmia remaining in some predisposed individuals**
- ✓ **Compound metabolised solely by CYP3A4 with an increased risk for drug-drug interactions**

Project stopped in phase II

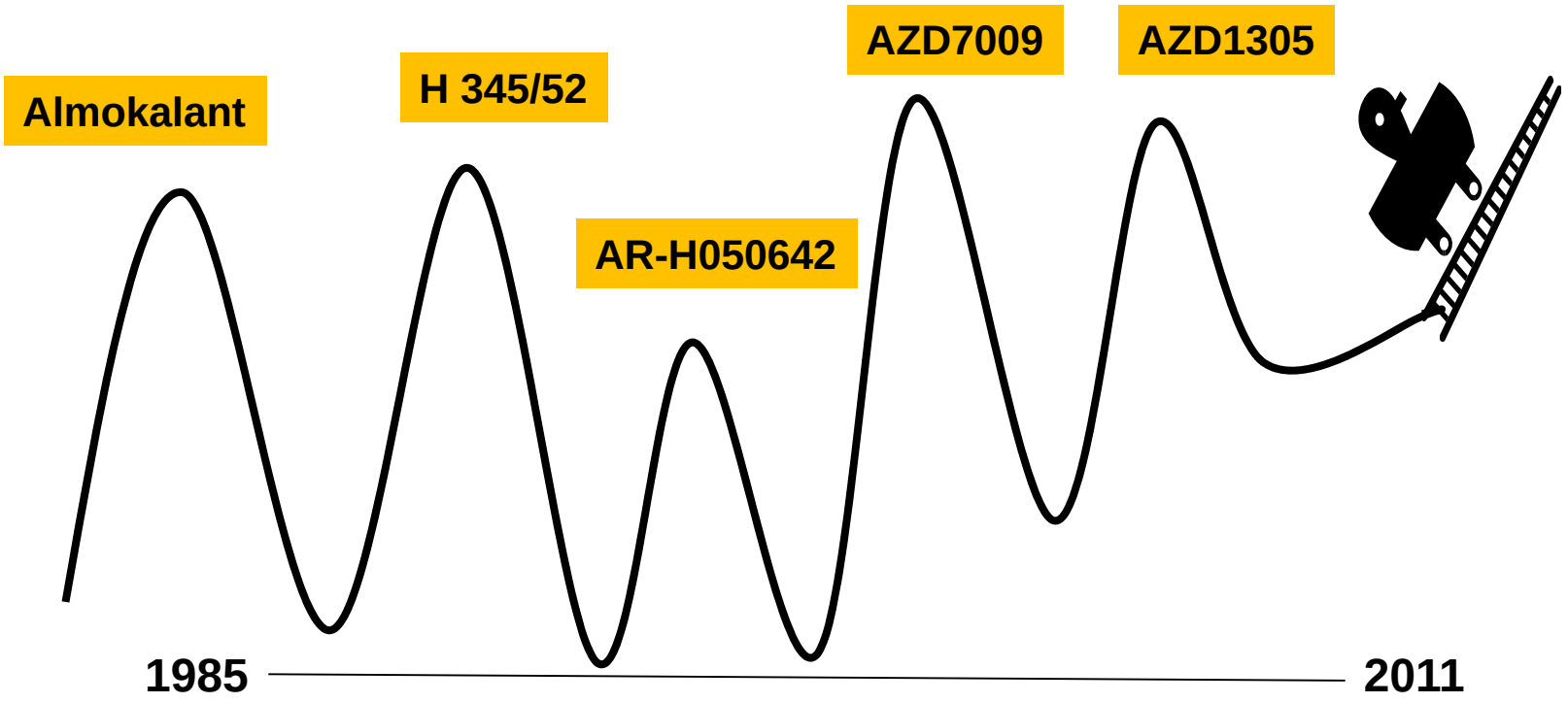
Summary

- From selective hERG blockers to more safe mixed ion channel blockers
- From in vivo studies to virtual models
- Use of High Throughput Chemistry in late LO
- Scaffold hopping in late LO
- Discovery of the unique oxabispidine ringsystem

AZD7009 and AZD1305 are so far the most efficacious antiarrhythmic drugs ever clinically tested for AF conversion

We nearly made it!

A Roller Coaster Ride



The future

Use the knowledge and animal models in new atrial selective targets

“A good drug is hard to find.
The perfect one takes longer “

Dr. Robert N. Young

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