CRTh2: Can Residence Time Help ?

RSC-SCI Symposium on GPCR2 in Medicinal Chemistry

Allschwil, Basel
15-17 September 2014

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Solutions with you in mind

Rick Roberts
Almirall
Barcelona, Spain

Introduction

Paul Ehrlich, *The Lancet* (1913), 182, 445

“A substance will not work unless it is bound”

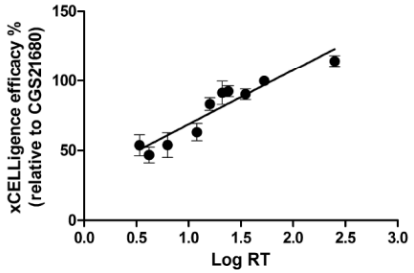
100 years on:

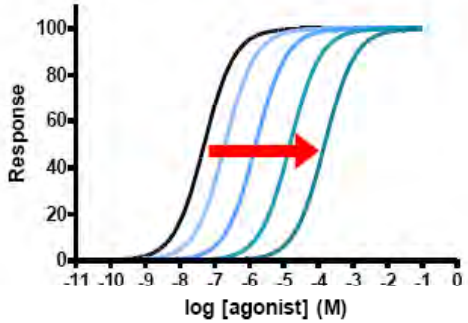
“What a substance does once it’s bound
may depend on how long it’s bound for”

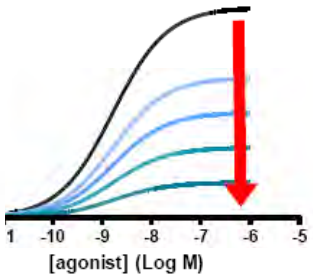
The influence of Binding Kinetics

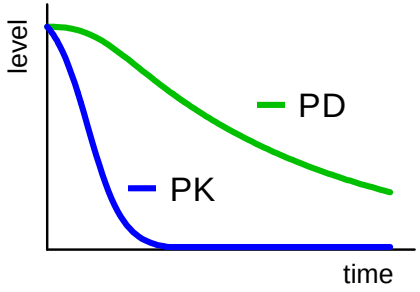
Residence time / Dissociation half-life

seconds — minutes — hours — days









Mechanistic | Surmountable | Insurmountable | Pharmacodynamic

Partial vs Full agonism

- M3 agonists
- A_{2A} agonists

Efficacy vs substrate concentration

- Lovastatin — Candasartan

Mechanism-based toxicity

- Clozapine — Haloperidol
- Celecoxib — Aspirin

Duration of Action

- Ipratropium vs Aclidinium

Kinetic Selectivity

- M3 vs M2 antagonism

Potency has little influence over these behaviours

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The CRTh2 Programme

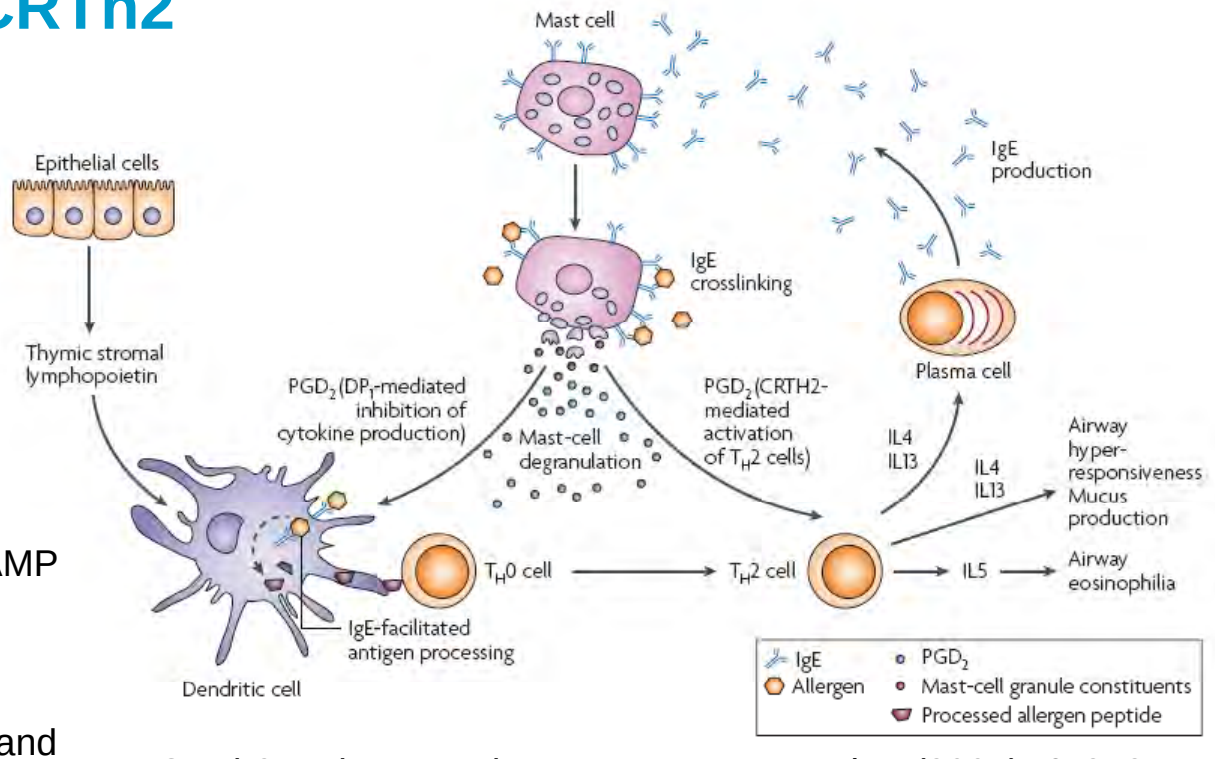
Brief introduction to CRTh2

Real name:

- **C**hemoattractant **R**eceptor-homologous molecule expressed on **T**-**H**elper **2** cells
- Also known as DP2

CRTh2 activation:

- induces a reduction of intracellular cAMP and calcium mobilization.
- is involved in chemotaxis of Th2 lymphocytes, eosinophils, mast cells and basophils.
- inhibits the apoptosis of Th2 lymphocytes
- stimulates the production of IL4, IL5, and IL13, leading to:
  - eosinophil recruitment and survival
  - mucus secretion
  - airway hyper-responsiveness
  - immunoglobulin E (IgE) production
  - etc



CRTh2 and DP1 review. *Nat. Rev. Drug Disc.* (2007), *6*, 313

CRTh2 antagonism:

- Should block pro-inflammatory PGD_2 effects on key cell types
- Potential benefit in:
  - asthma
  - allergic rhinitis
  - atopic dermatitis.

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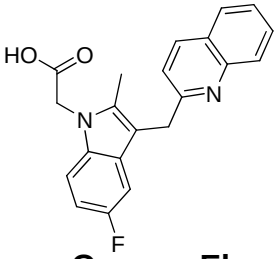
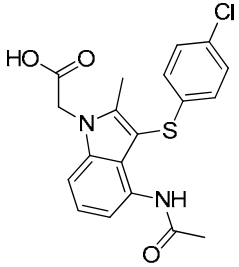
CRTh2 – A Target of interest

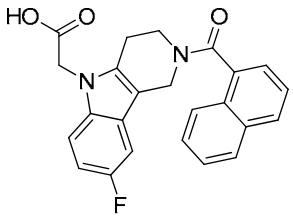
Indole acetic acids



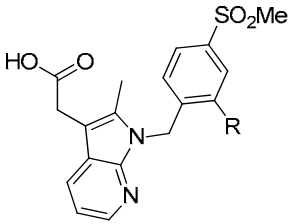
Oxagen-Eleventa
OC-459
Phase III



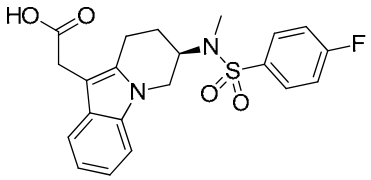
AstraZeneca
AZD-1981
Phase II



Actelion
Setipiprant
Phase III



Novartis
R = CF_3 QAW-039
R = H QAV-680
Phase II/II

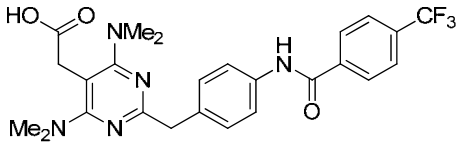


Merck
MK-7246
Phase I

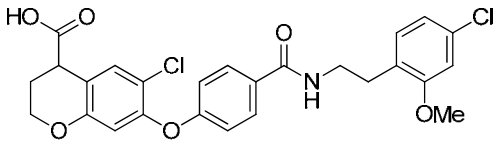
Pulmagen-Teijin
ADC-3680
Phase II

?

Aryl acetic acids



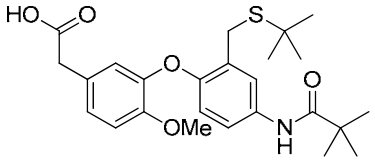
Boehringer
BI671800
Phase II



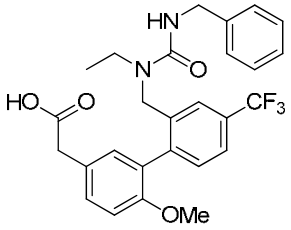
Array
ARRY-502
Phase II

?

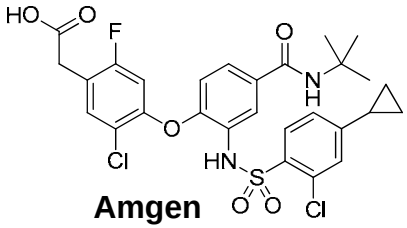
Roche
RG-7581
Phase I



Panmira
AM461
Phase I

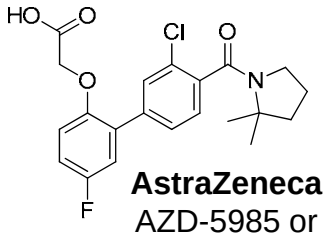


Panmira
AM211
Phase I



Amgen
AMG-853
Phase II

Phenoxyacetic acids



AstraZeneca
AZD-5985 or
AZD-8075
Phase I/I

- **All compounds are acids**
- **Plenty of Competition**
- **Plenty of Attrition**
- **First compounds high dose and/or BID**

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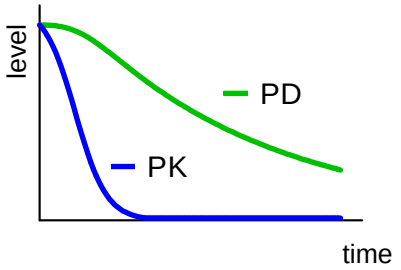
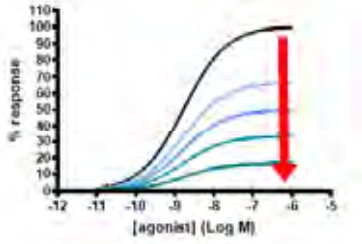
Our internal programme

We want to find a
Once-a-day
Oral
low dose (≤ 10 mg)
CRTh2 antagonist for mild-moderate asthma

- Therefore, we chose to deliberately look for slowly dissociating CRTh2 antagonists:
  - To maintain receptor occupancy beyond normal PK and extend duration of action
  - to reduce the pressure of finding a carboxylic acid with desirable PK properties
  - to add the possibility of extra protection due to insurmountability against PGD_2 burst



Pharmacodynamic



Insurmountable

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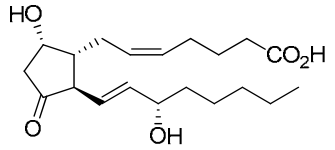
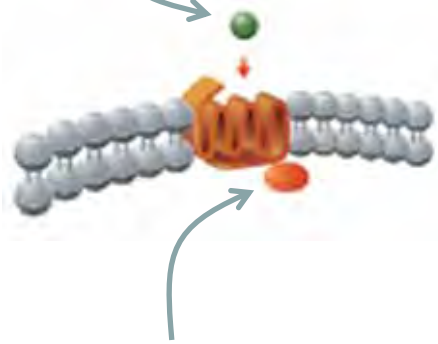
Assays

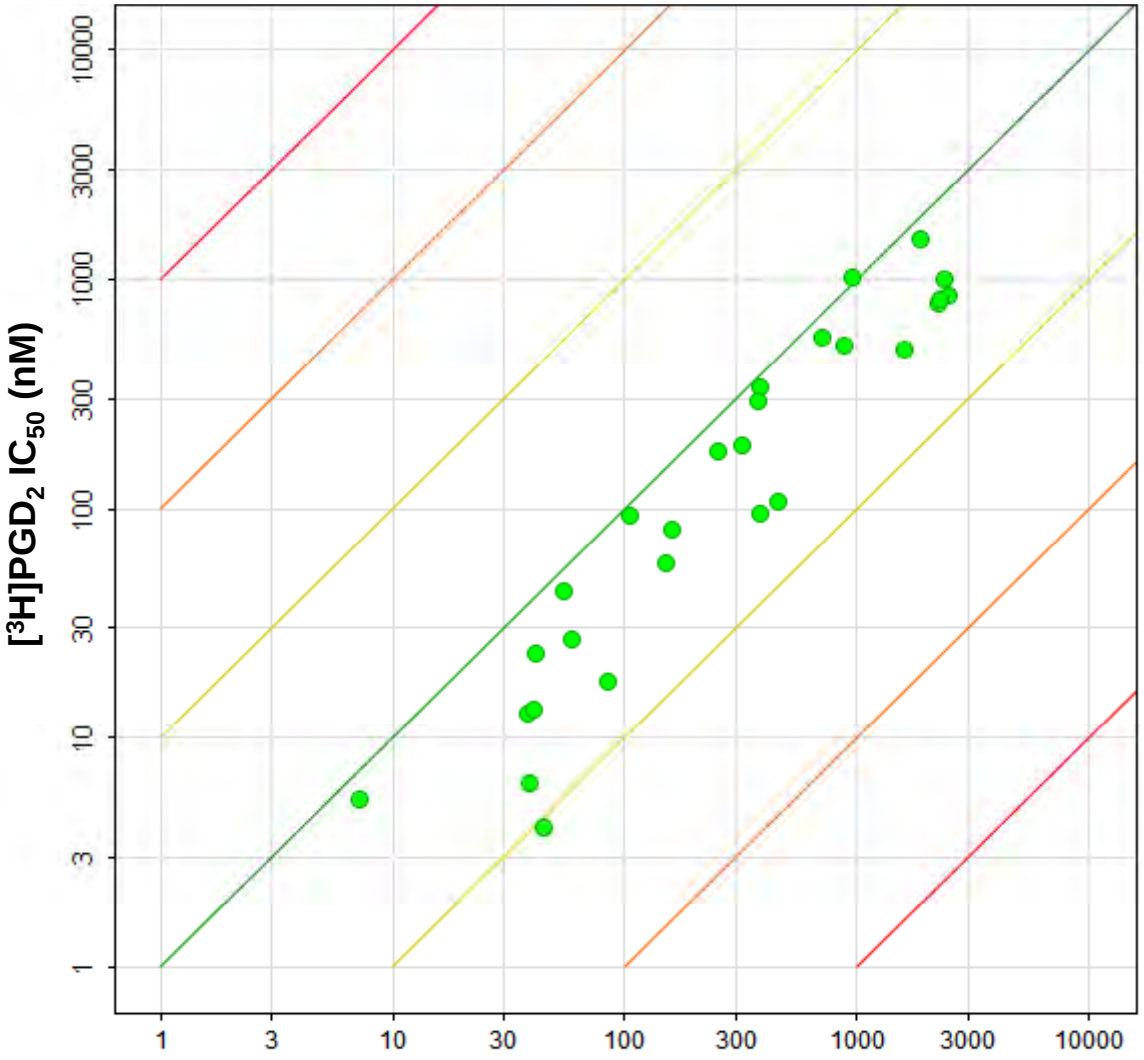
GTPγS vs PGD_2 binding



[^{3}H]PGD_2



[^{35}S]GTPγS



Good correlation
[^{35}S]GTPγS Assay favoured

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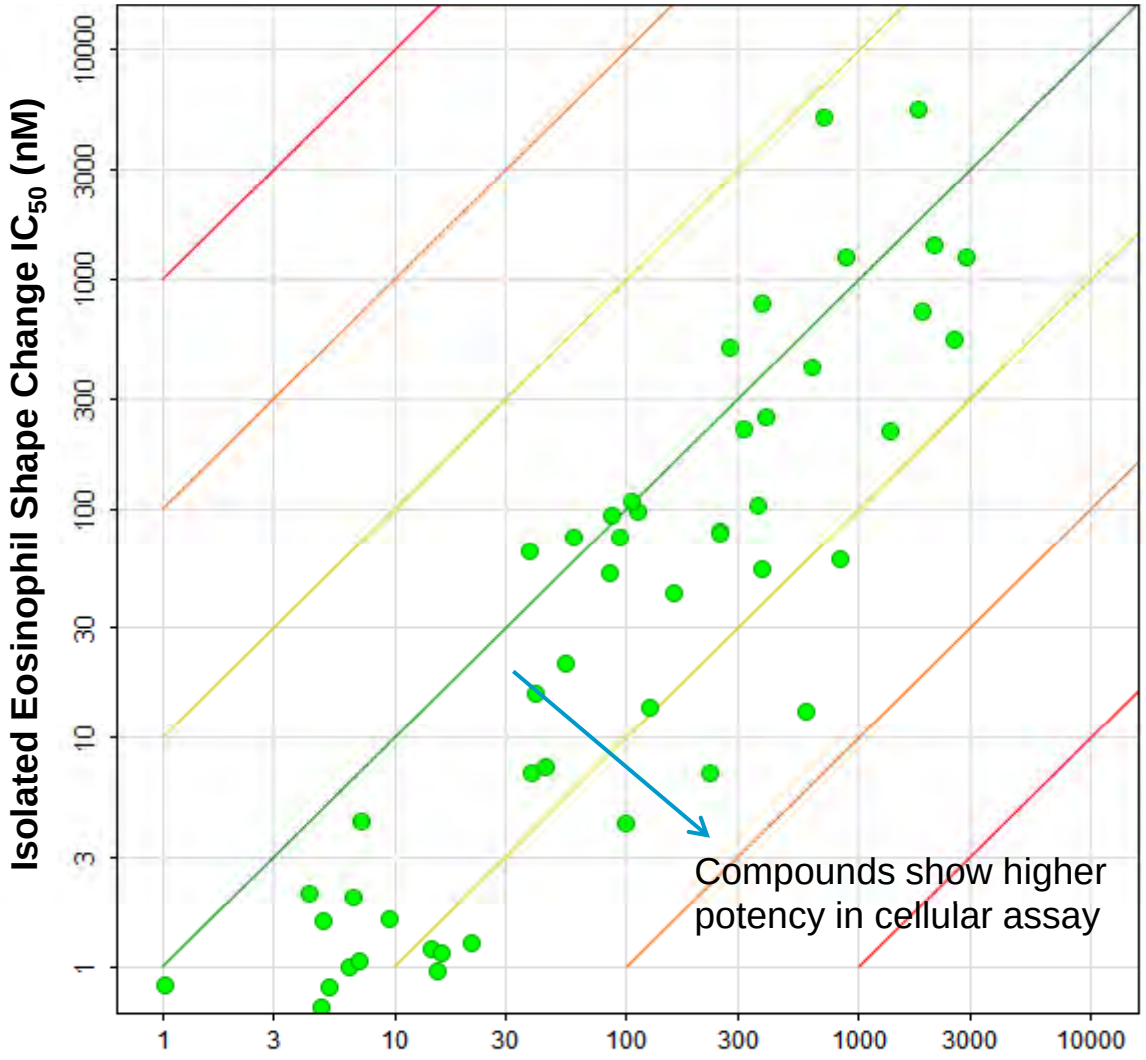
GTPγS vs ESC Isolated cell

Whole cell

membranes

+ 0.1% BSA



Protein binding plays a role

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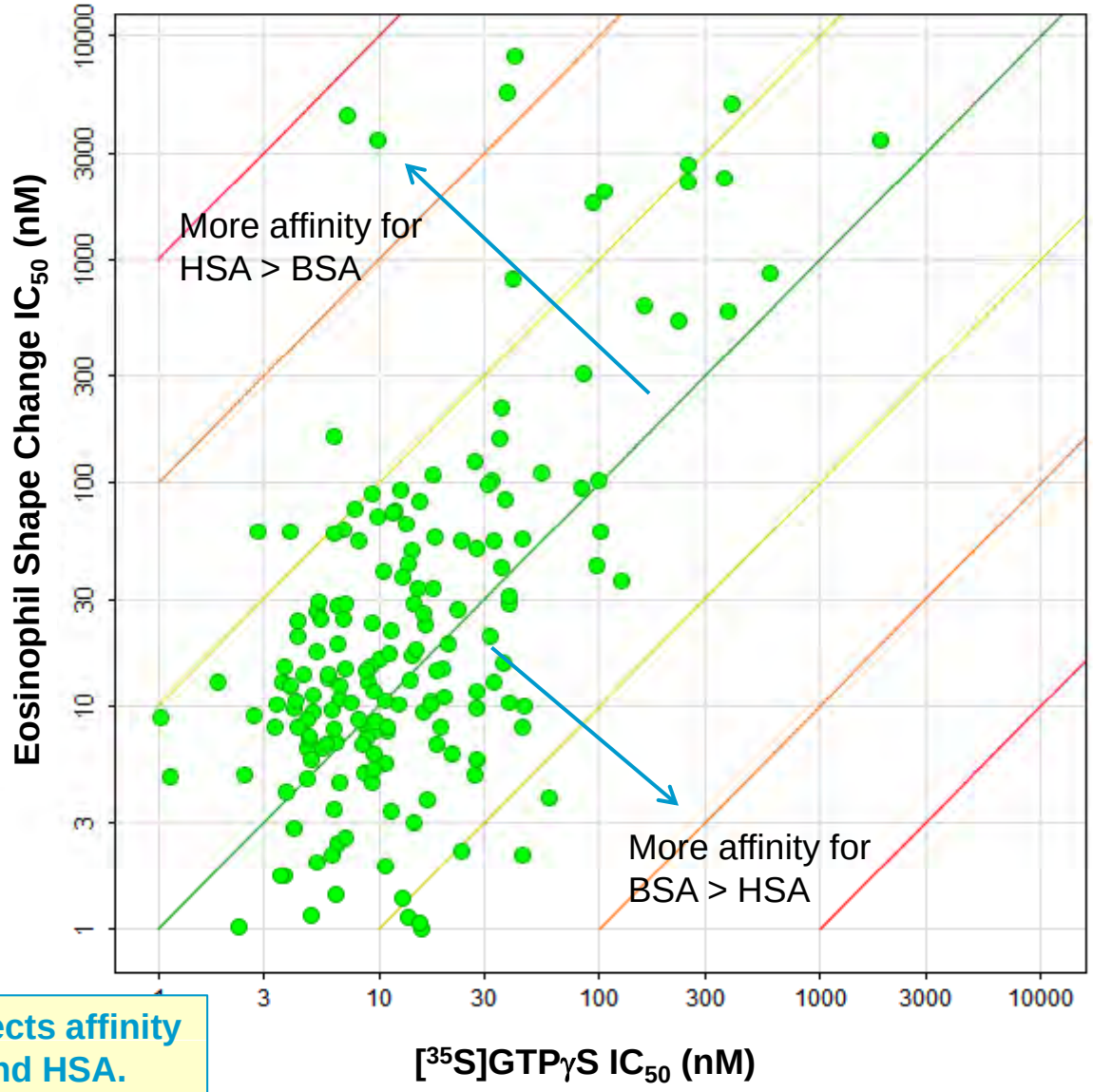
GTPγS vs ESC Human Whole Blood

Whole cell

+ 4% HSA

membranes

+ 0.1% BSA



"Shift" assay simply reflects affinity of compounds for BSA and HSA. ESC IC_{50} is "Real" Potency

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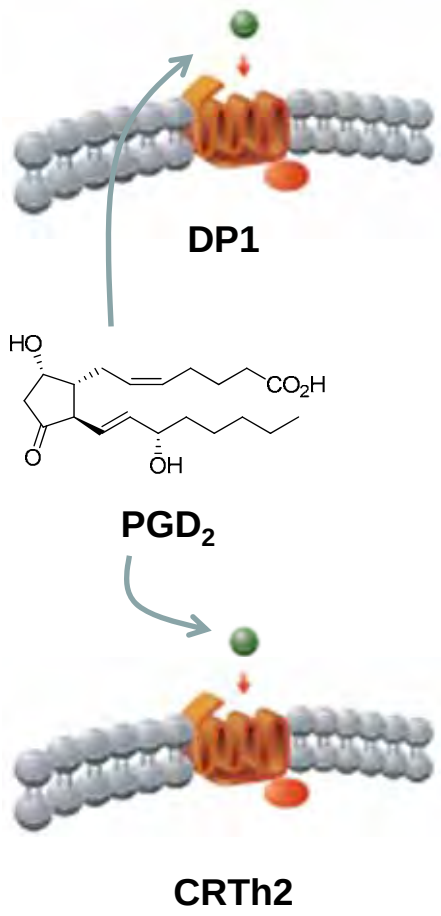
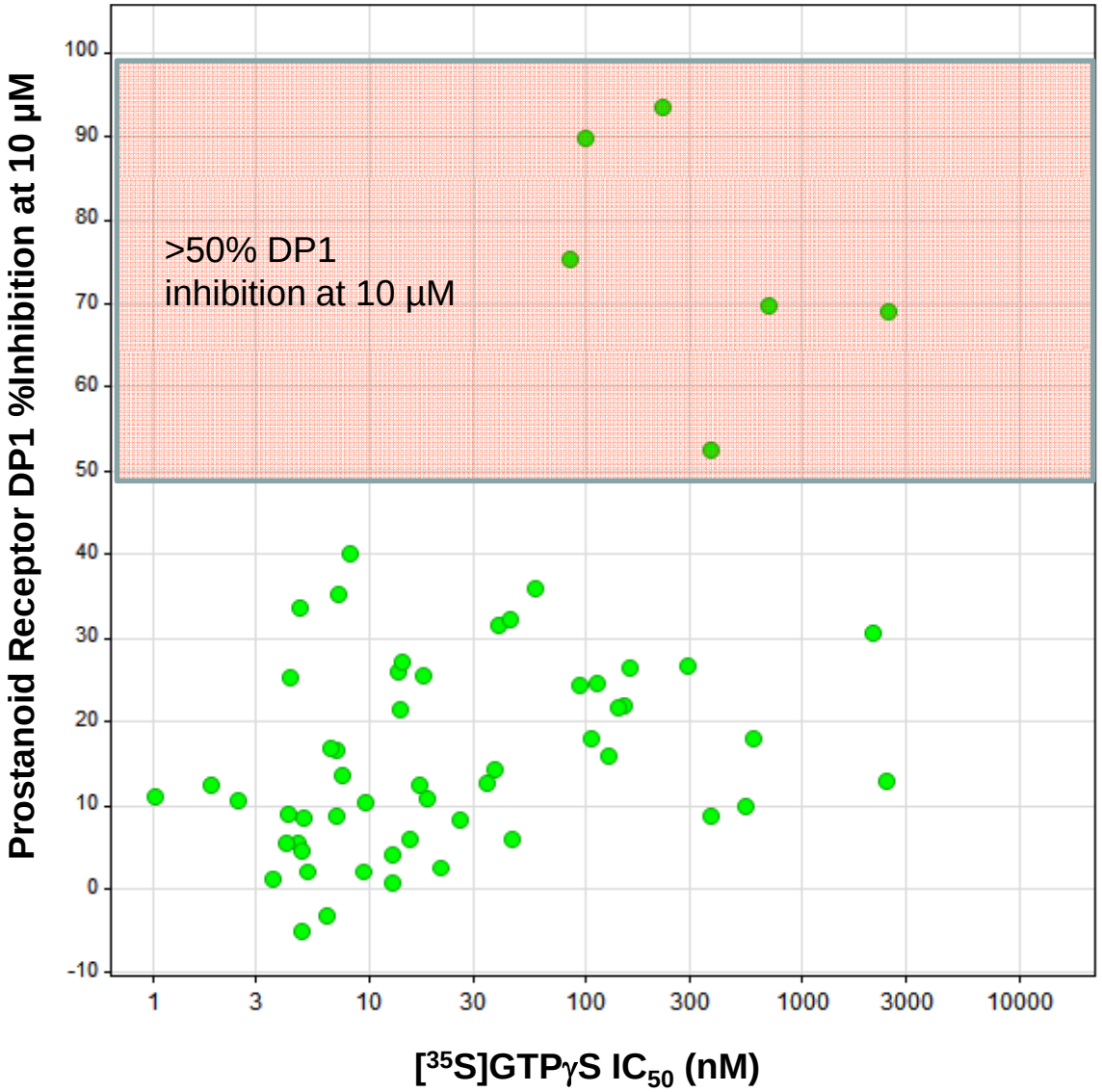
GTPγS vs DP1 Receptor Selectivity





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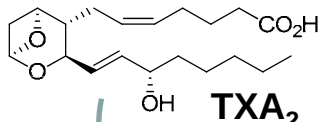
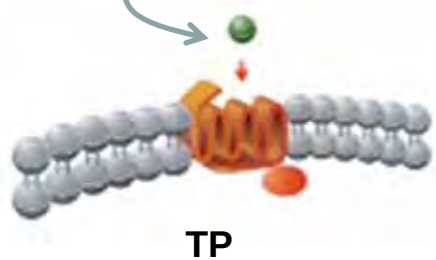
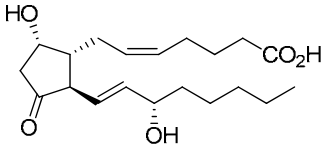
GTPγS vs TP Receptor Selectivity



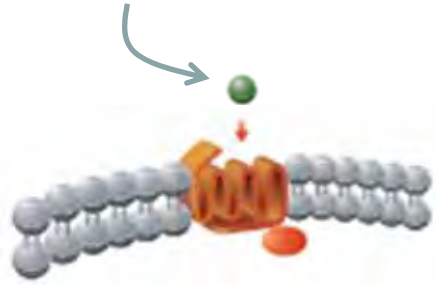
TXA_2



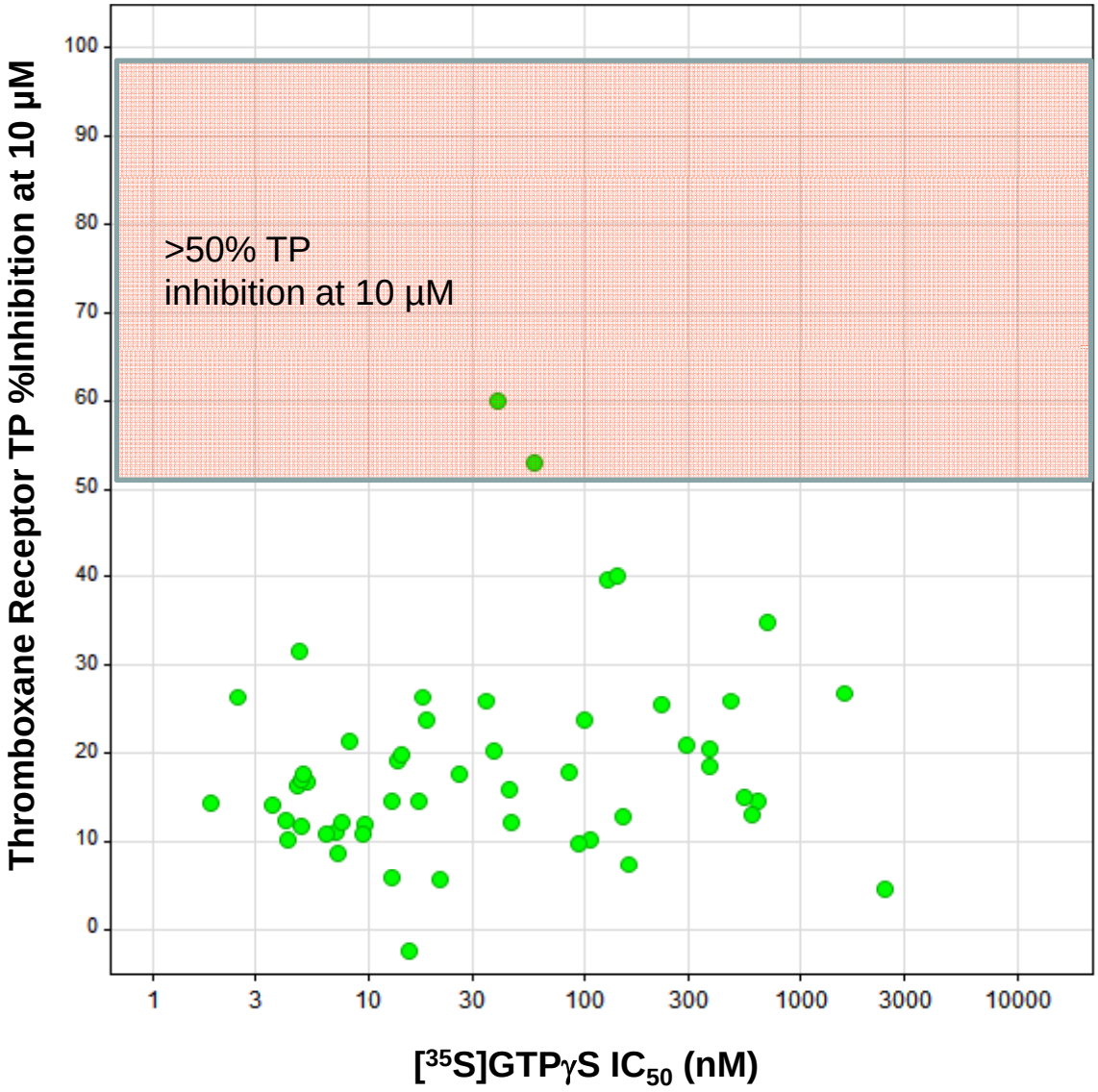
TP



PGD_2



CRTh2



Compounds are CRTh2 selective

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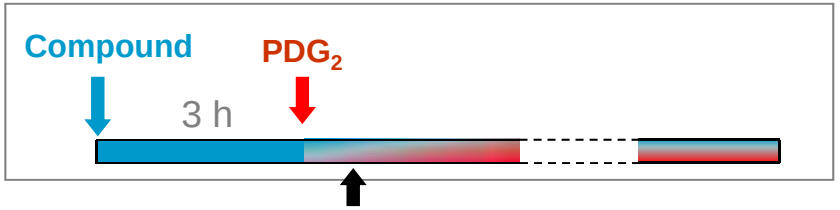
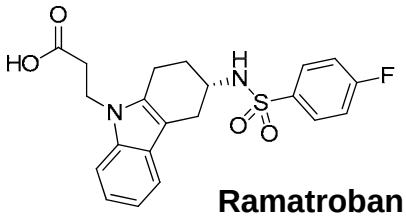
In vitro dissociation assays CRTh2

GTPγS binding

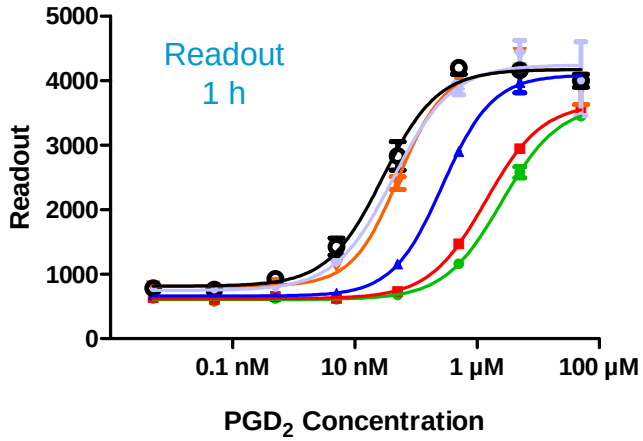
- Membranes over-expressing human CRTh2
- PGD_2 agonism produces allows [^{35}S]-GTPγS binding, detected by radioactivity

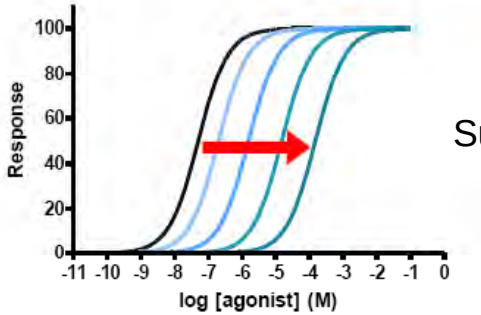




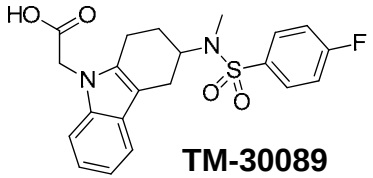
Ramatroban

Ramatroban 0 → 10 µM

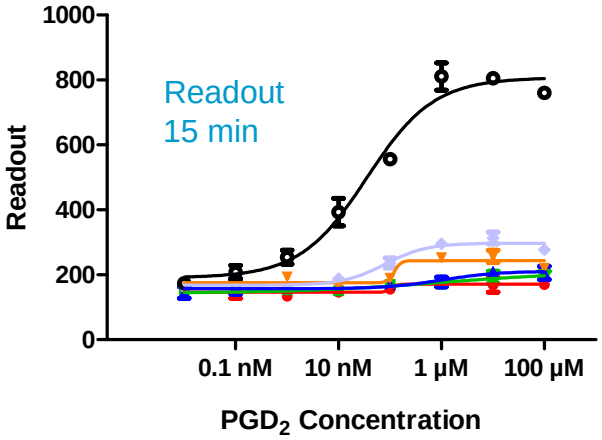


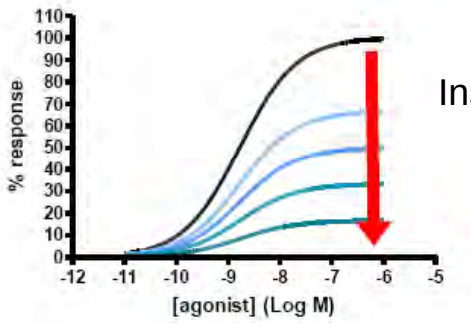


Classical Surmountable inhibition



TM-30089 (CAY-10471)





Classical Insurmountable inhibition

CAY-10471 0 → 5 µM

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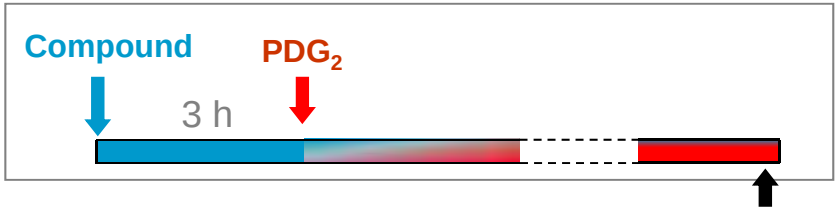
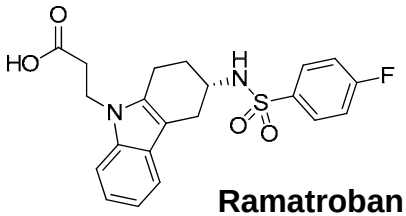
In vitro dissociation assays CRTh2

Surmountability vs Insurmountability

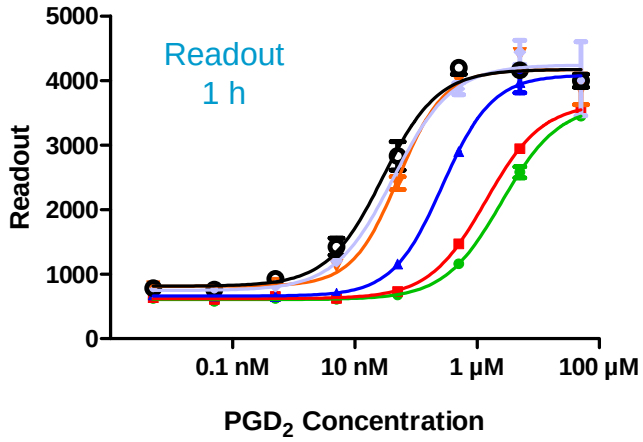
- Membranes over-expressing human CRTh2
- PGD_2 agonism produces allows [^{35}S]GTPγS binding, detected by radioactivity

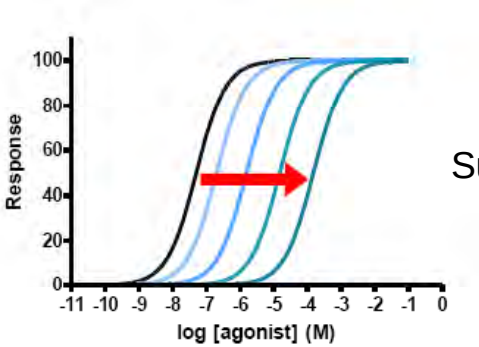




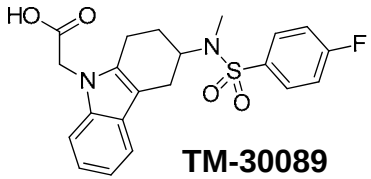
Ramatroban

Ramatroban 0 → 10 µM

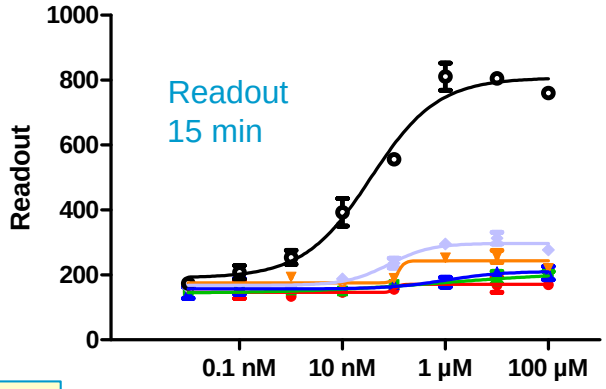




Classical Surmountable inhibition

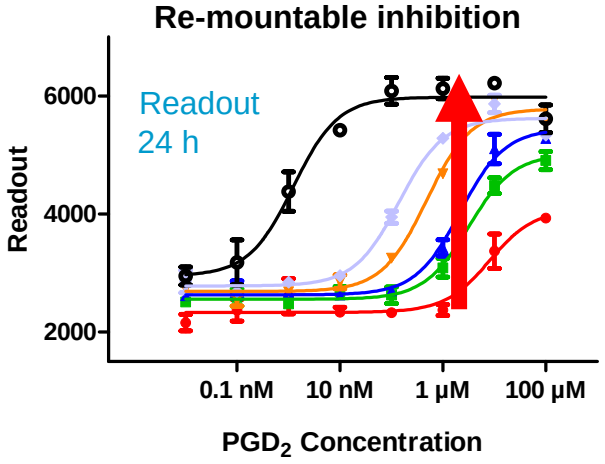


TM-30089 (CAY-10471)



CAY-10471 0 → 5 µM

Re-mountable inhibition



Surmountability is just a question of time

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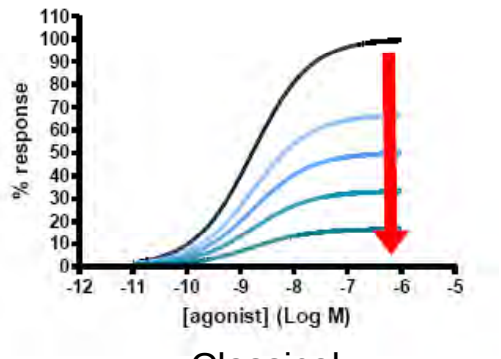
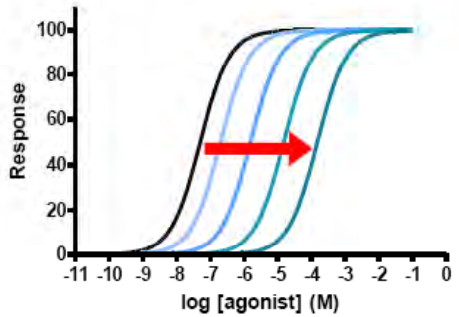
When is the insurmountable surmountable ?

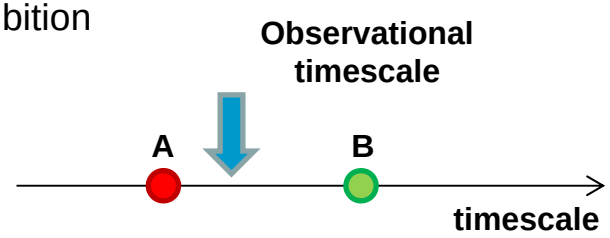


Classical
Insurmountable inhibition

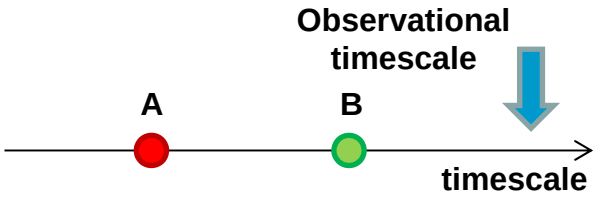


Classical
Surmountable inhibition

Competitive compounds with different kinetics



B seems immobile in the experiment: Insurmountable



A and B reach equilibrium during the experiment. Surmountable behaviour

Long resident CRTh2 antagonists will have an insurmountable behaviour against PGD_2 burst

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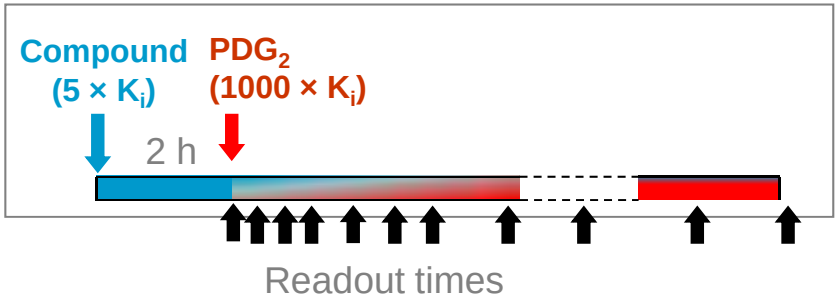
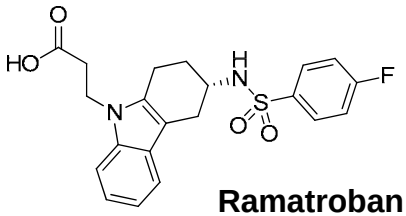
In vitro dissociation assays CRTh2

Washout experiments

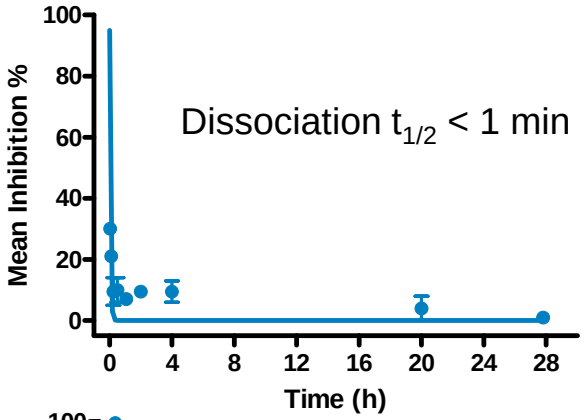
- Membranes pre-incubated with compound
- Antagonist effectively swamped by agonist
- Decay of inhibition followed by time
- Automated Filtration reading in 96-well format
- Readings from 2 min to 28 h



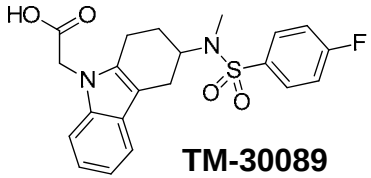


Ramatroban

Surmountable

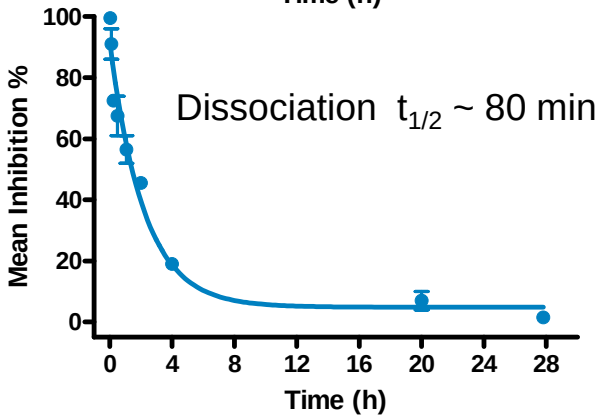


Dissociation $t_{1/2}$ < 1 min



TM-30089
(CAY-10471)

Insurmountable



Dissociation $t_{1/2}$ ~ 80 min

"Worst case" scenario for dissociation half-life

- No rebinding possible.
- Physiological system may be less demanding

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Mechanisms of slow dissociation

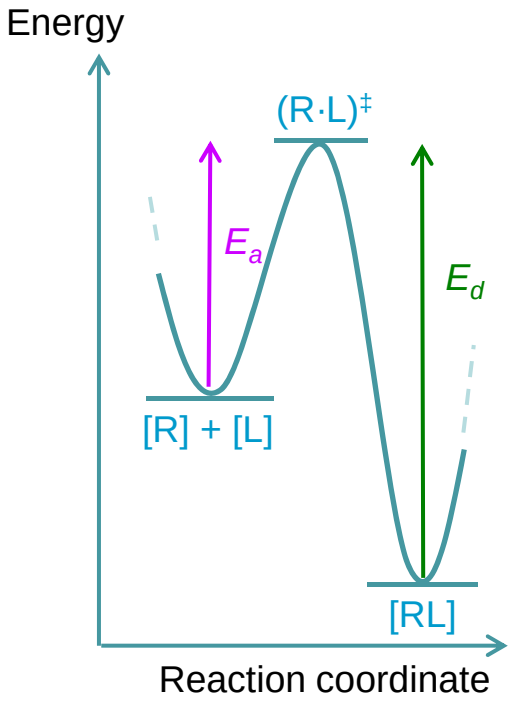
On rates by mechanism – also independent of potency

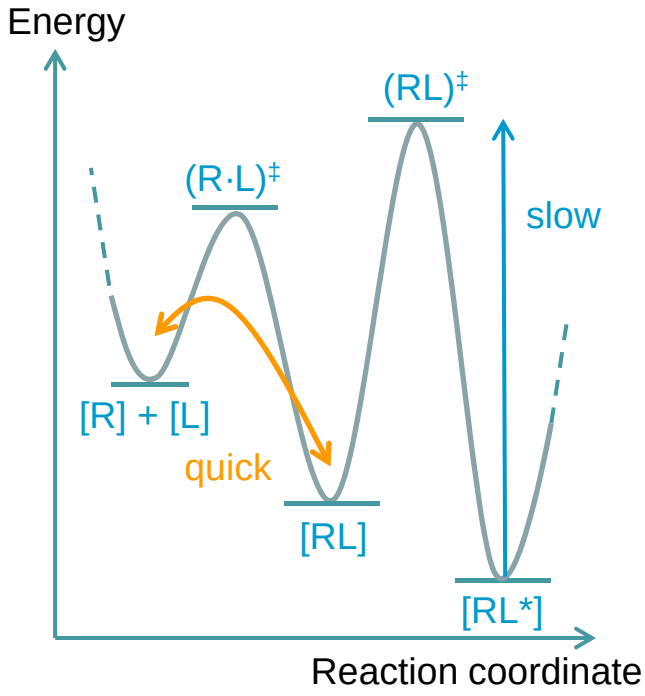
Simple fit

$$[R] + [L] \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} [RL]$$

Induced fit

$$[R] + [L] \underset{k_2}{\overset{k_1}{\rightleftharpoons}} [RL] \underset{k_4}{\overset{k_3}{\rightleftharpoons}} [RL^*]$$





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On rates by mechanism

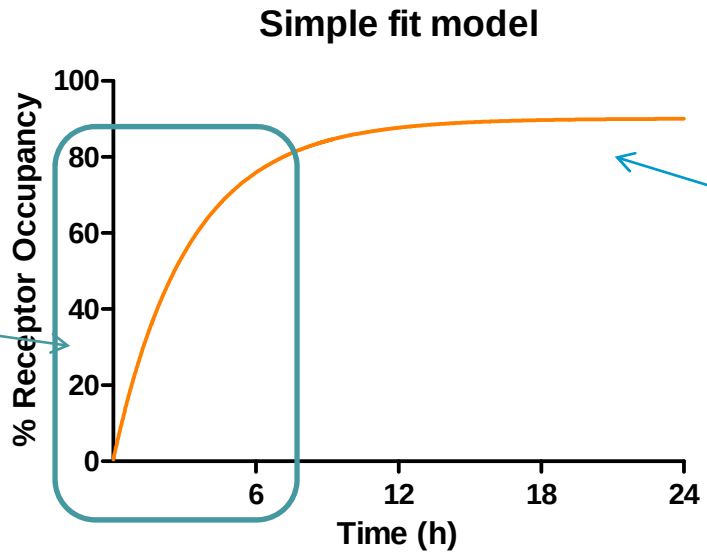
Simple fit

$$[R] + [L] \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} [RL]$$

- If the off rate is slow, the on rate is also slow

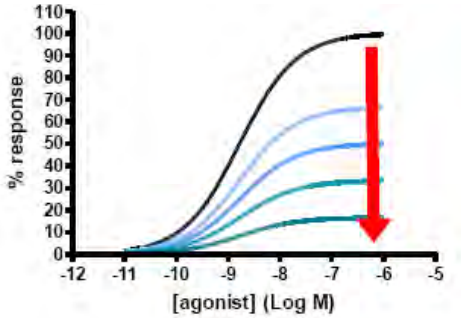
However, the time to "get on" is about 6 h.

Before this time the ligand is a partial antagonist



Simulation: Dissociation half-life 24 h
Concentration of [L] at 10 × IC_{50}

Once "on", the ligand behaves as an insurmountable antagonist



Sufficient PK levels needed for sufficient time to ensure receptor becomes saturated

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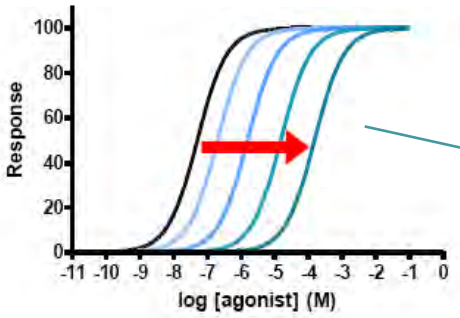
On rates by mechanism

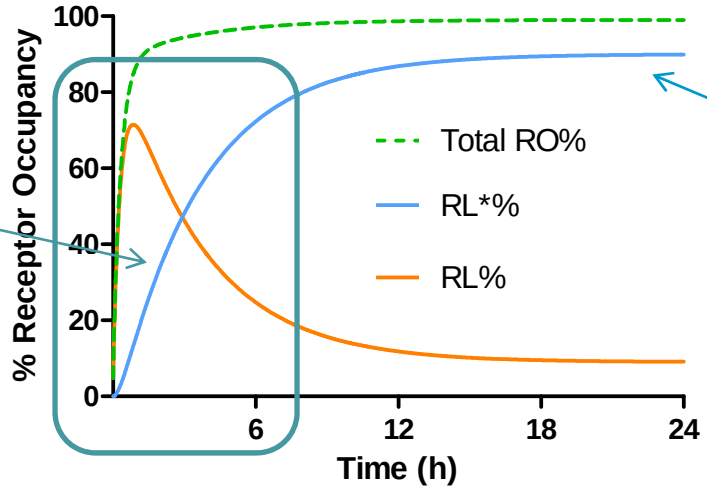
Induced fit

$$[R] + [L] \underset{k_2}{\overset{k_1}{\rightleftharpoons}} [RL] \underset{k_4}{\overset{k_3}{\rightleftharpoons}} [RL^*]$$

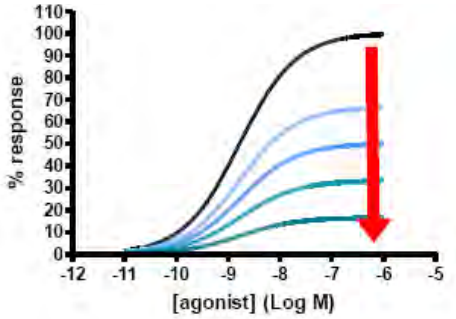
The ligand binds quickly (Total RO%)
However at this point it behaves as a classical surmountable ligand



Induced fit model



Once “on”, the ligand behaves as an insurmountable antagonist



Simulation: k_4 Dissociation half-life 24 h
Concentration of [L] at 10 × IC_{50}

Sufficient PK levels needed for sufficient time to ensure receptor becomes saturated

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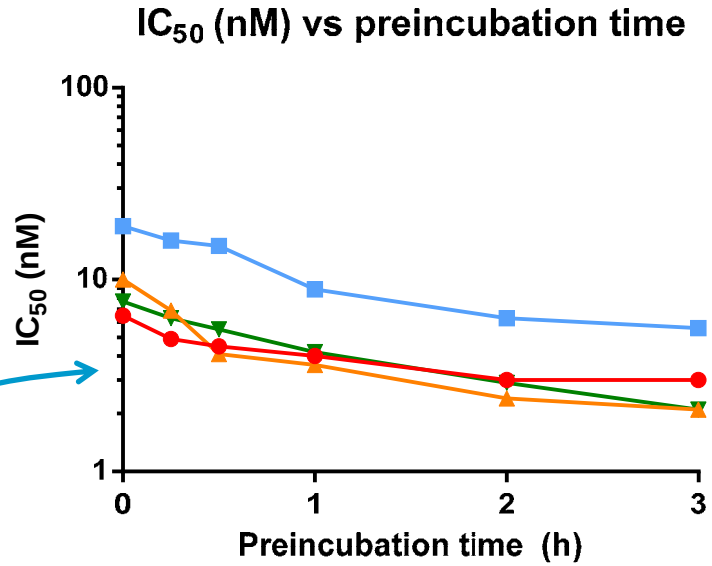
Which mechanism is it ?

- No radio-labelled ligands
- No Biacore
- Slow dissociating compounds get more potent with time



Compound Dissociation half-life

- 2.2 h
- 2.5 h
- 10 h
- 23 h

Compounds are active from t=0

Changes in potency not sufficient to estimate which mechanism is acting

"Real" potency may be better than in vitro potency

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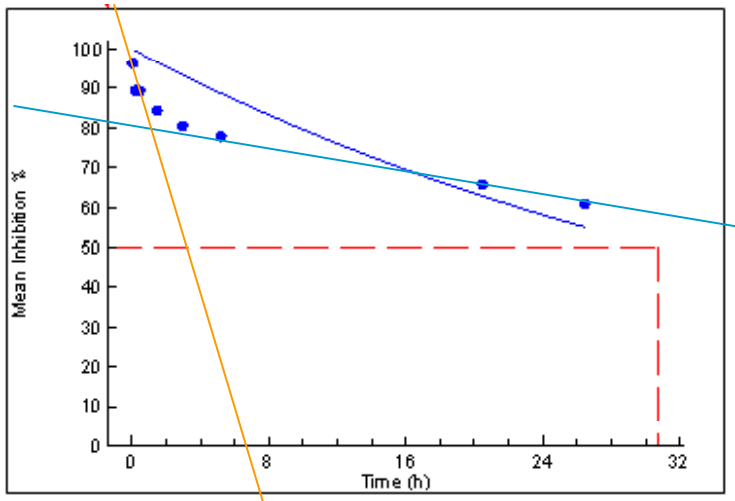
Which mechanism is it ?

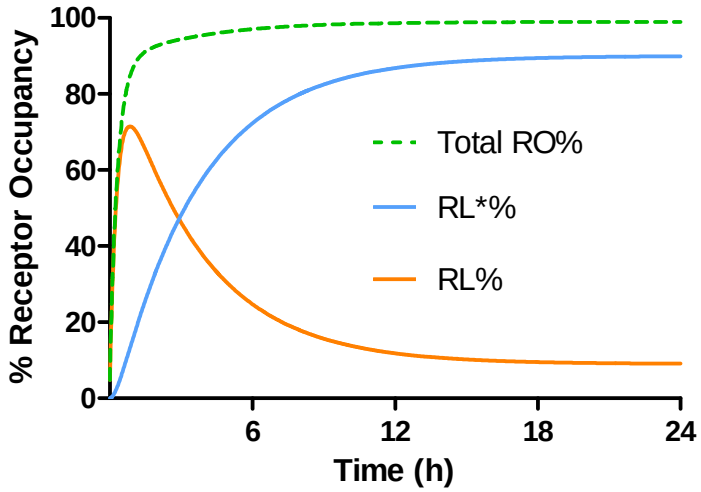
2 h Pre-incubation at 10 × IC_{50}
Dissociation $t_{1/2}$ 25 h ± 3.5



Majority [RL*] fast Dissociation

Residual [RL] fast Dissociation

Induced fit model



Mechanism unknown, but induced fit suspected

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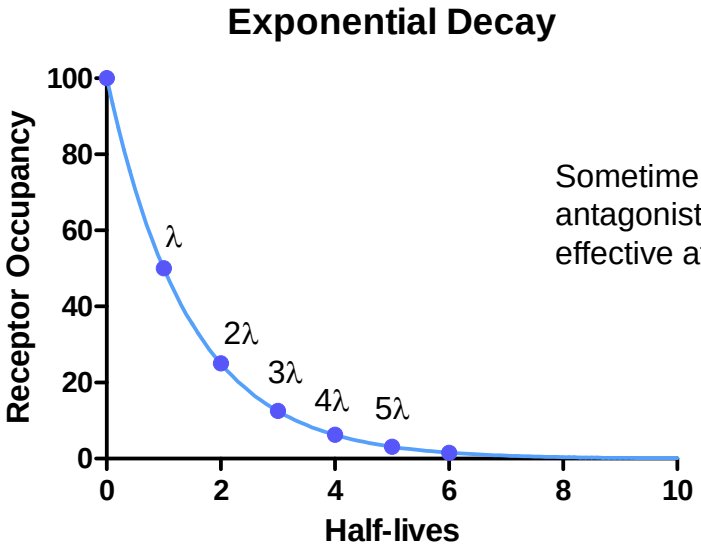
How long is long? Mechanistic or Pharmacodynamic?

Necessary Receptor Occupancy for efficacy - Pharmacodynamic

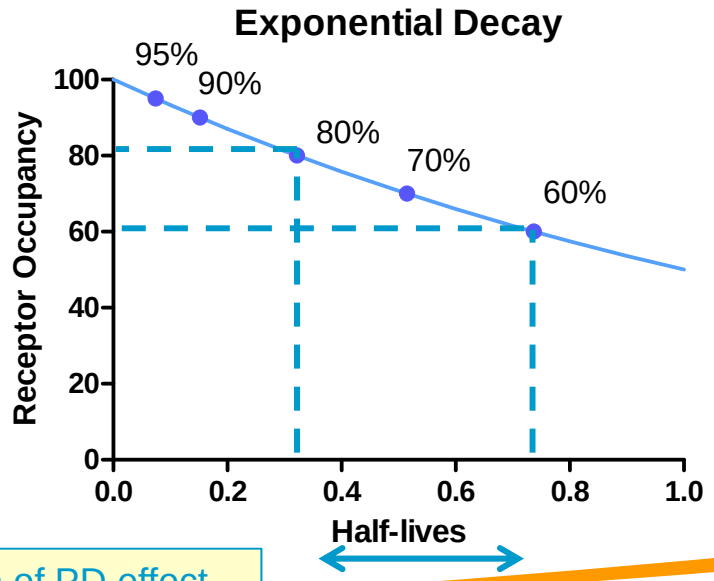
Target	Class	Receptor Occupancy
GPCR	Antagonist	60-80%
	Agonist high efficacy	2-30%
	Agonist low efficacy	60-95%
Ligand-gated ion channels	Antagonist	65-95%
	Agonist	5-80%
Transporters	All	60-85%
Enzyme	Inhibitors	70-99%

Grimwood and Hartig, Pharm. Therap. 122, 281, 2009



Sometime here, a GPCR antagonist will stop being effective after washout

Expanded zone: 0 – 1 half-life



For a GPCR antagonist, count on about **half a half-life** extra of PD effect

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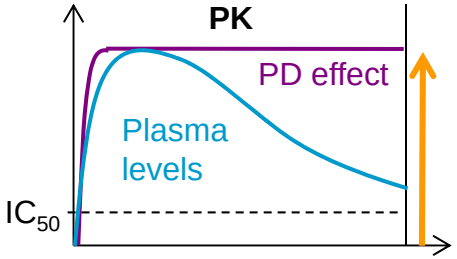
DoA Scenarios for full coverage over 24h

Many CRTh2 antagonists in the clinic are twice daily

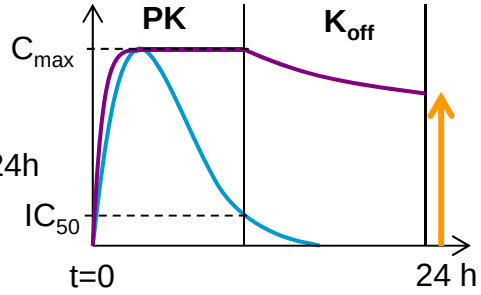
PK only effect:
"classic" drug. PK-PD relationship



- Dissociation Half-life = not necessary

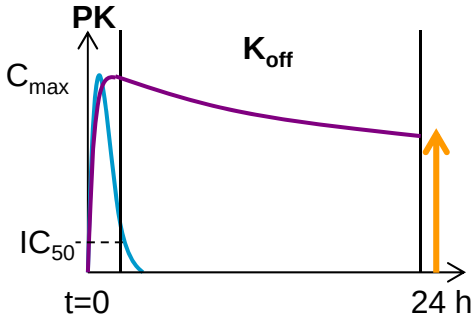
Residual activity at 24h

Some PK
Some residence time



- Dissociation Half-life **~ 24 h**

Little PK
Really long residence time



- Dissociation Half-life **~ 48 h**

To turn a twice-daily compound into a once-daily compound, we want to add on a **Dissociation half-life of ≥ 24h**

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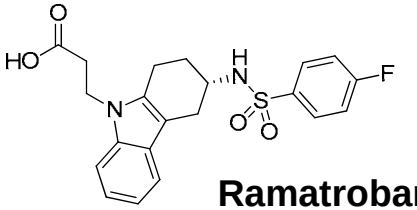
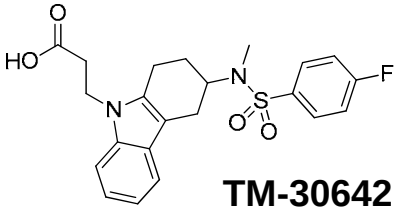
Chemical Series

Structure-Activity Relationships (SAR)
Structure-Kinetic Relationships (SKR)

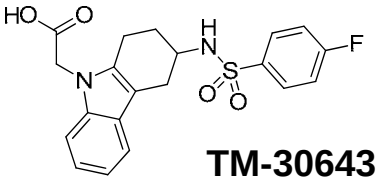
Are there slow-dissociating CRTh2 antagonists?



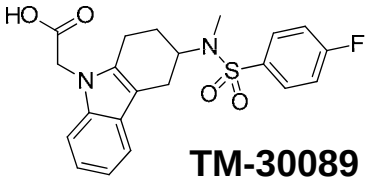
Ramatroban



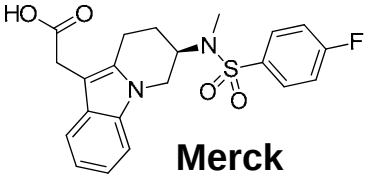
TM-30642



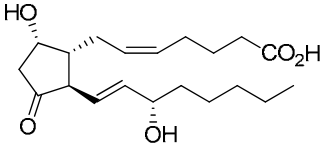
TM-30643



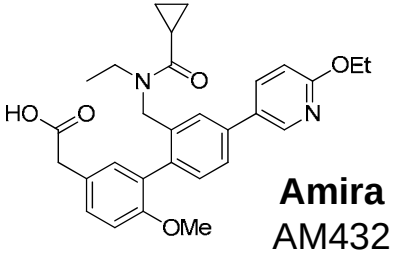
TM-30089 (CAY-10471)



Merck
MK-7246



PGD_2



Amira
AM432

Structure not disclosed

Pulmagen
ADC-3680

Compound	Potency		Dissociation half-life*	Reference
Ramatroban	pA_2	36 nM	**5 min**	*Mol. Pharmacol*. (2006), *69*, 1441
TM-30642	pA_2	20 nM	**8 min**	--- / / ---
MK-7246	K_i	2.5 nM	**33 min**	*Mol. Pharmacol*. (2011), *79*, 69
PGD_2	K_D	11 nM	**11 min**	*Bioorg. Med. Chem. Lett.* (2011), *21*, 1036
AM432	IC_{50}	6 nM	**89 min**	--- / / ---
ADC-3680	K_i	1.6 nM	**20 min**	*American Thoracic Society (ATS),* May 17-22, 2013
QAW-039	K_d	1 nM	**12 min**	*ERS 8 September 2014*
QAV-680	K_d	15 nM	**1 min**	*ERS 8 September 2014*

Published residence times are all "short"

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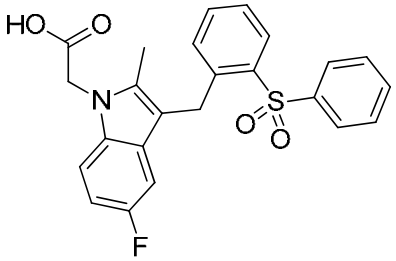
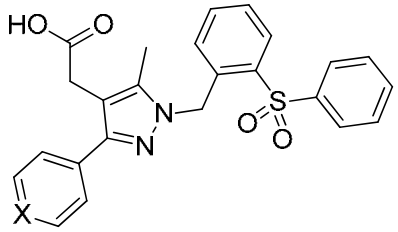
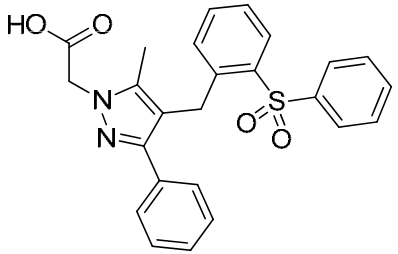
Pyrazoles

- Indole nucleus developed by Oxagen. Beginnings of slow dissociation observed
- First series of Pyrazoles gave active compounds, but no significant residence time (BMCL, 2013, 23, 3349)
- Second series of Reverse Pyrazoles gave a similar story (Eur J Med Chem, 2014, 71, 168)







	Indole	Pyrazoles			Reverse Pyrazoles	
	Oxagen	X = CH	X = N	General	Ph	General
GTPγS IC_{50} (nM)	14	7	4	4 – 100	35	32 – 450
Dissociation t½ (h)	1.3	0.2	1.9	0.02 – 0.7	0.2	0.04 – 0.7

SAR pretty good. No SKR advances observed in either core or tail sections

Pyrazoles series abandoned for general lack of Residence time

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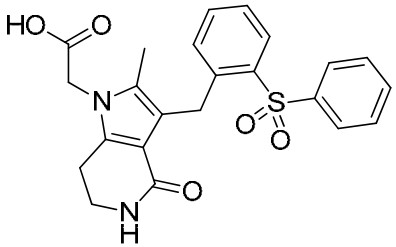
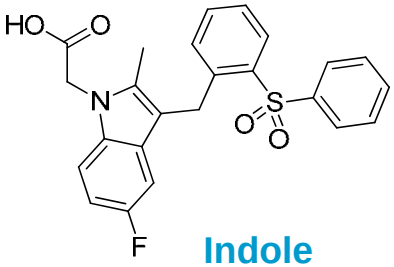
Pipas

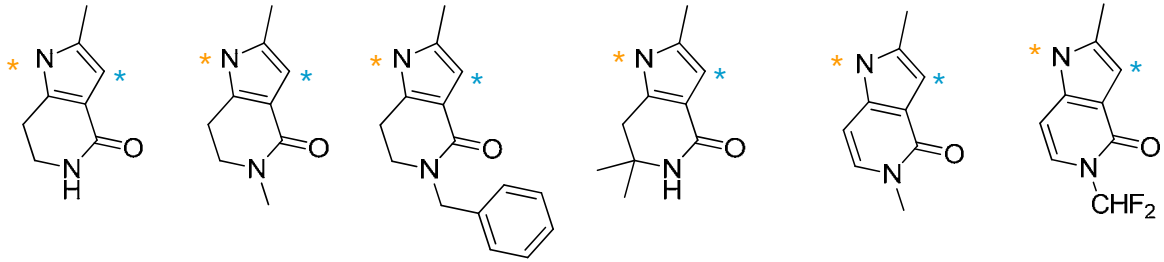
- Third series of Pyrazolopyrimidinones (Pipas) gave active compounds with long residence (BMCL Accepted for publication)
- Core SAR flat. Core SKR varied



Pyrazolopyrimidinones (Pipas)



Indole



	Oxagen	PiPa	N-Me	N-Bn	diMe	N-Me*	N-CHF_2*
GTPγS IC_{50} (nM)	14	5	5	1	4	5	2
Dissociation t½ (h)	1.3	2.3	5.3	**6.6**	**10**	**8**	**21**

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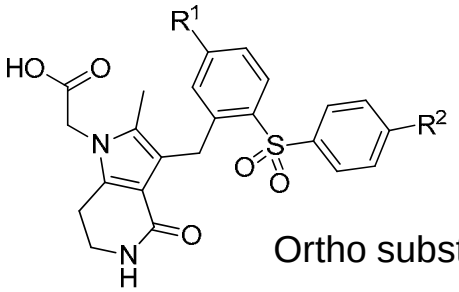
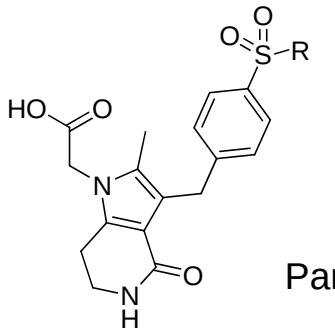
Pipas

- Tail SAR flat. Tail SKR varied
- Sulphone positioning ultimately affects SKR



Ortho substitution

R^1	R^2	GTPγS IC_{50}	Dissociation t½
H	H	5 nM	2.3 h
MeO	H	4 nM	4.2 h
H	F	5 nM	3.3 h
MeO	F	7 nM	**23 h**



Para substitution

R	GTPγS IC_{50}	Dissociation t½
Ph	170 nM	n.d.
Me	900 nM	n.d.
Bn	3 nM	0.9 h

Ultimately Potent but no duration

- Pipa series was essentially impermeable.
- Not suitable for an oral programme.
- Series abandoned due to impermeability

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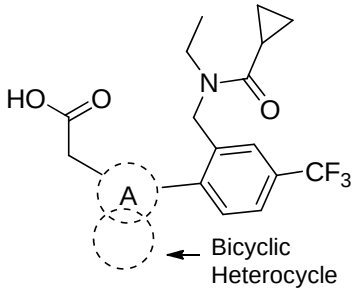
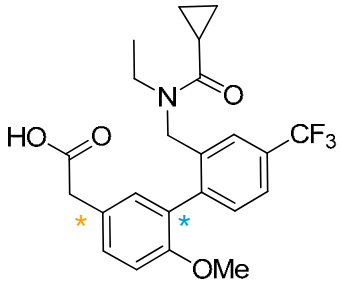
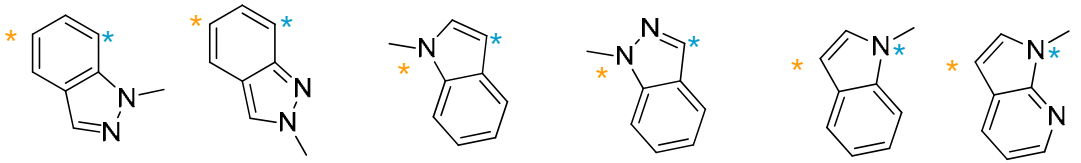
Biaryl series

- Fourth series of diverse biaryl compounds finally gave good activity and long residence time (BMCL Accepted for publication)
- Core SAR and SKR varied







6,5-ring *5,6-ring*

	Amira	Indazole	Indazole	Indole	Indazole	Indole	Azaindole
GTPγS IC_{50} (nM)	16	48	48	19	19	37	9
Dissociation t½ (h)	2	1.4	1.2	**4.0**	1.6	2.5	2.3

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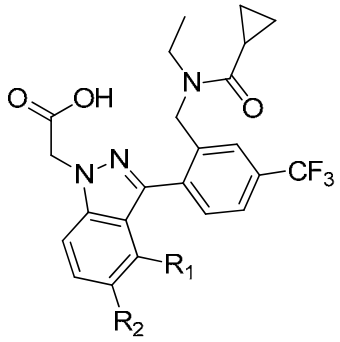
Biaryl series – Indazole core

- 6 member ring SAR flat. SKR varied



R^1	R^2	GTPγS IC_{50}	Dissociation t½
H	H	19 nM	1.6 h
Cl	H	6 nM	3.2 h
F	H	4 nM	**5 h**
H	Cl	16 nM	2.8 h
F	Cl	15 nM	**10.5 h**

- Small substituents in R_1 led to moderate increased in both potency and dissociation $t_{1/2}$
- Substitution in R_2 led to minimal changes in binding potency

Good starting point for the search of the desired Residence time

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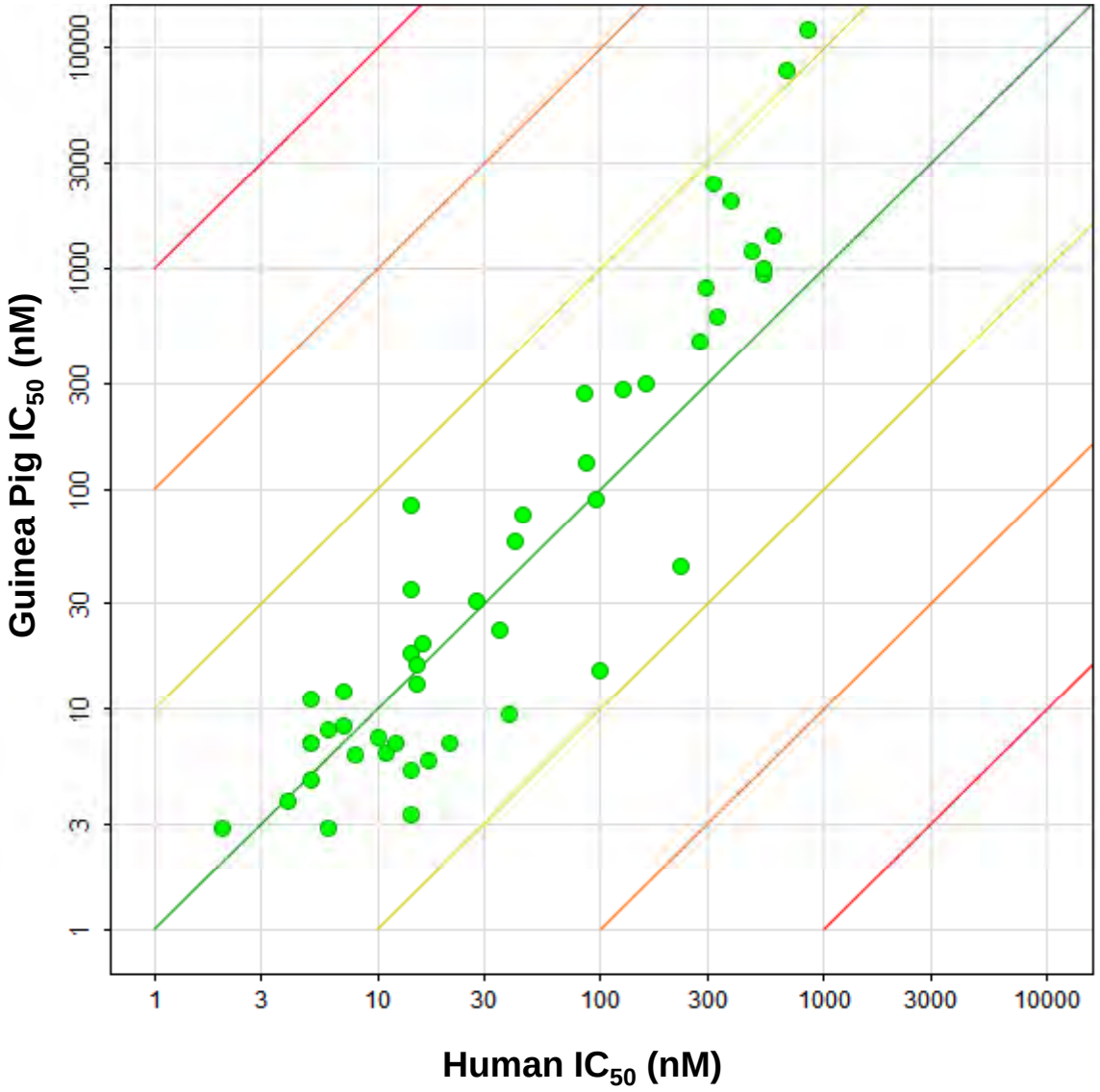
Species differences

Percentage of identical residues among all ungapped positions between the pairs.

	Human	Guinea Pig	Rat	Mouse
Human	100%	73%	78%	80%
Guinea Pig		100%	69%	70%
Rat			100%	94%
Mouse				100%

How similar are these species ?

GTPγS potencies human vs GP



Similar Potencies

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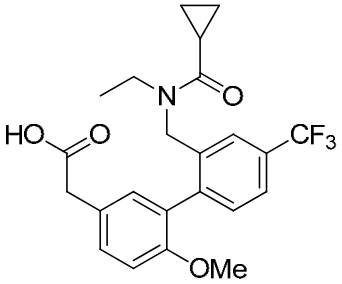
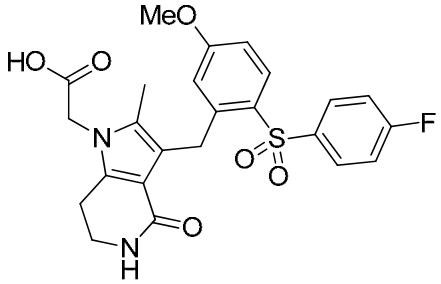
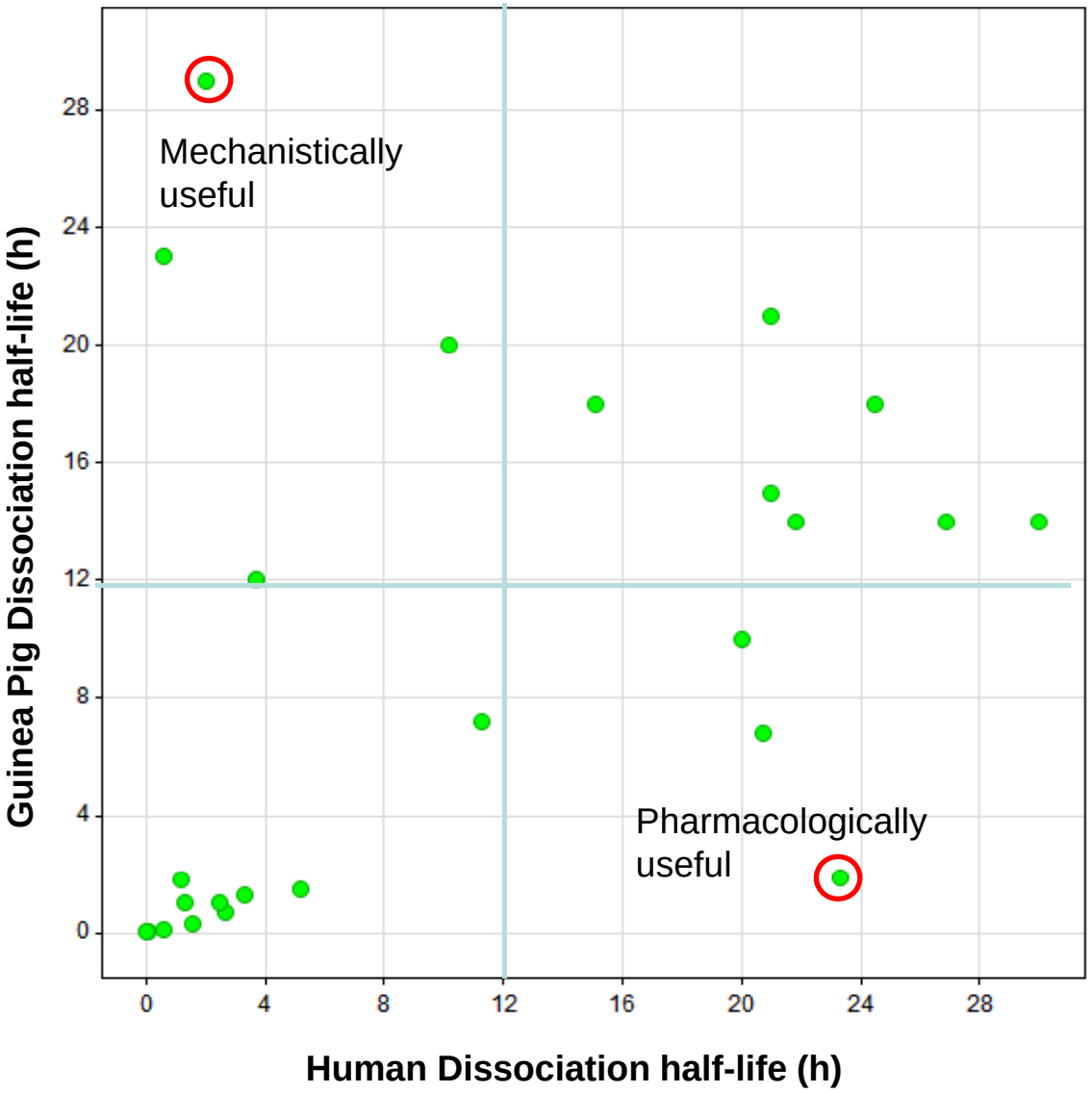
GTP human vs GP Residence Time



species	t½
Human	2 h
Guinea pig	29 h



species	t½
Human	23 h
Guinea pig	1.9 h



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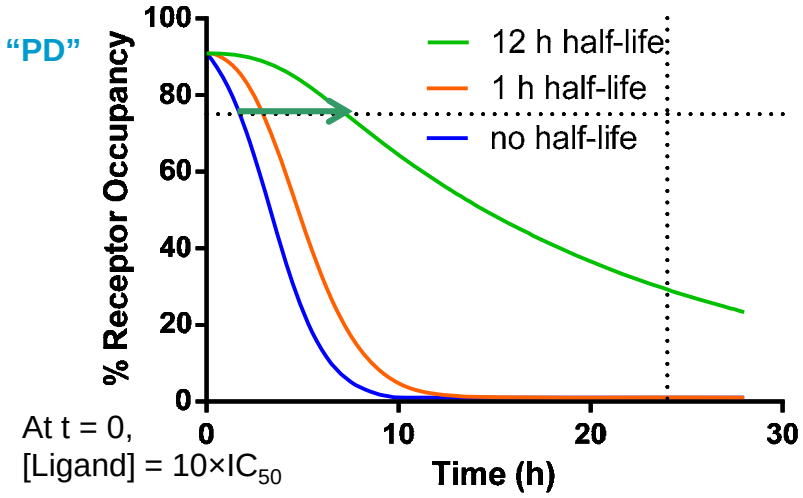
PK-PD Disconnection Simulations

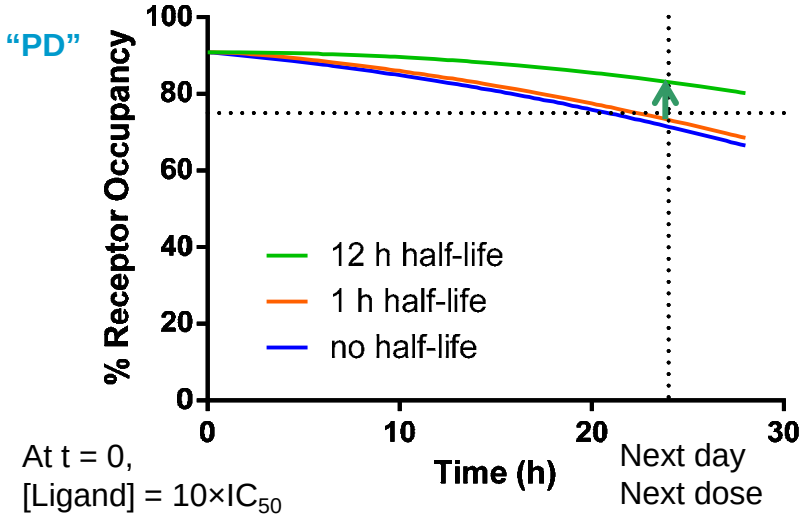
PK half-life 1 h



A 1 h Dissociation half-life is barely noticeable in the PD
Poor drug – short duration of action

A 12 h Dissociation half-life is definitely observable
A short acting drug keeps working long beyond its expectations

PK half-life 12 h



A 1 h Dissociation half-life goes completely unnoticed
Good PK means once-a-day dosing

A 12 h Dissociation half-life is barely noticeable
A great drug is really efficacious over 24 h

For the greatest observable effect, Dissociation half-life >> PK half-life

For a recent article, see *Drug Disc. Today* (2013), 18, 697

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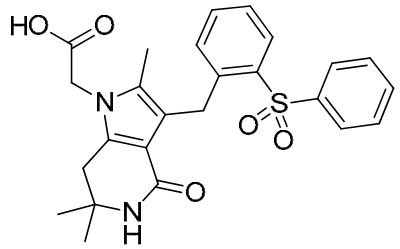
PK-PD disconnection model



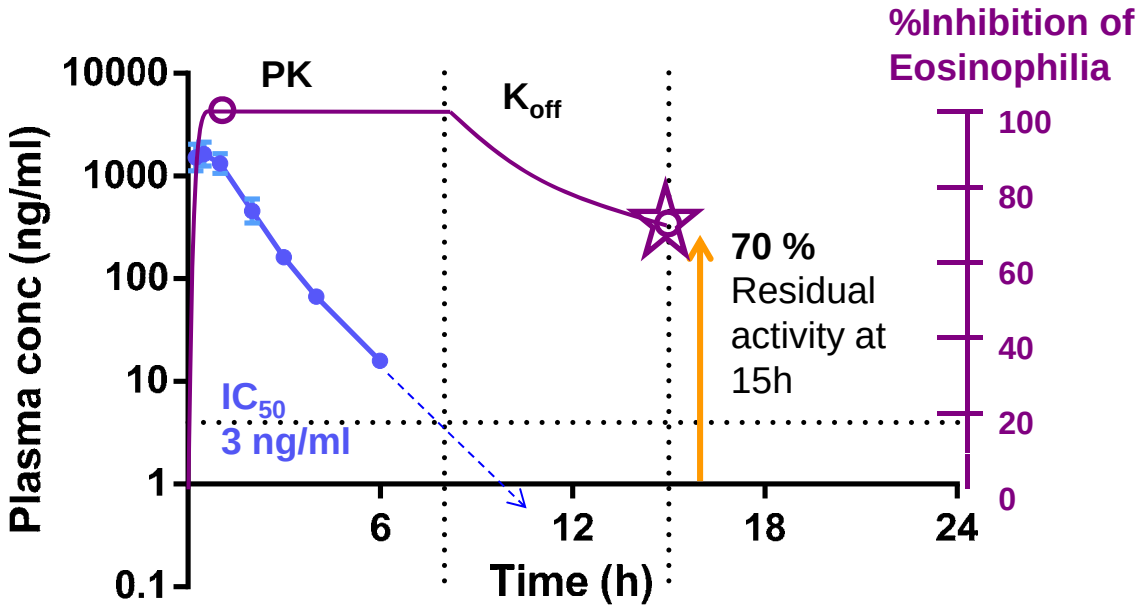
diMe-Pyrrolopiridinone guinea pig profile

Eosinophilia IC_{50}	3 ng/ml
Dissociation t½	**20 h**
PK t½	**0.9 h**

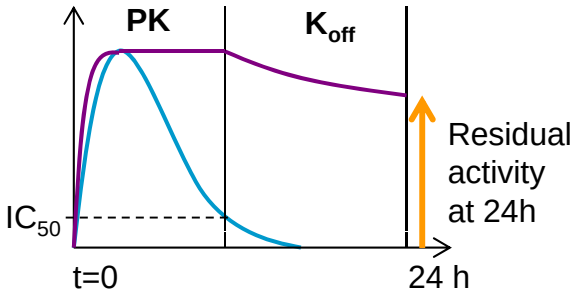
3 mg / kg dose

Timepoint	Plasma levels	Eosinophilia Inhibition
1 h	1300 ng/ml	100%
15 h	undetectable	70%

Guinea pig PK 3 mg/kg s.c.



Short PK, Long residence time
PK-PD disconnection



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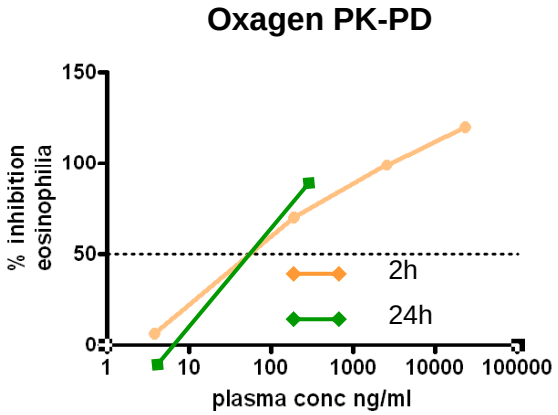
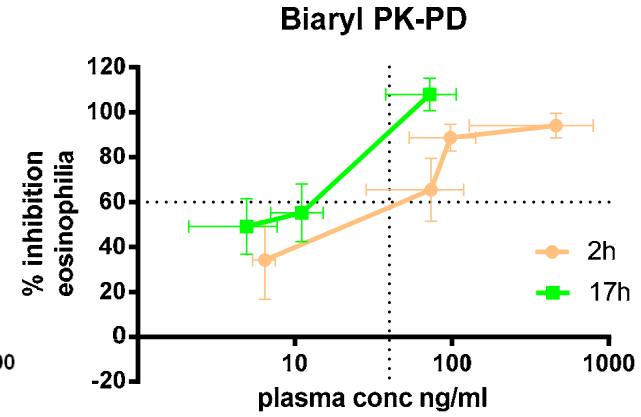
PK-PD Disconnection in Guinea Pig Eosinophilia

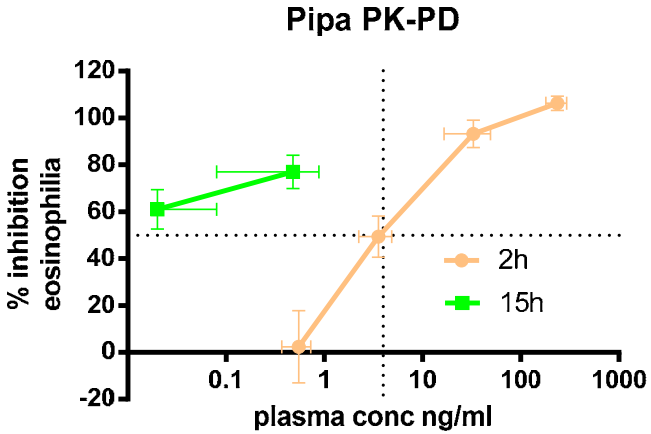
	Oxagen	BiAryl	PiPas
Eosinophilia IC_{50} (ng/ml)	~50	~40	~5
Gp Dissociation Half-life	1 h	15 h	20 h
Gp Pharmacokinetic Half-life	5 h	3 h	0.9 h



Good PK
Short Dissociation
No separation PK-PD



OK PK
Good Dissociation
Small separation PK-PD



Poor PK
Good Dissociation
Large separation PK-PD

Long residence time translates to a PK-PD disconnection
Remember: half a half-life

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Molecular Determinants of Long Residence

Where is long Residence?

Selected **general reports or Structure Kinetic Relationships** (SKRs)

- Trend analysis of D2 antagonists. *Bioorg. Med. Chem* (2011), 19, 2231.
- Trend analysis of Pfizer and literature data. *Med. Chem. Comm*. (2012), 3, 449
- Review of molecular determinants. *Drug Disc. Today*. (2013), 18, 667

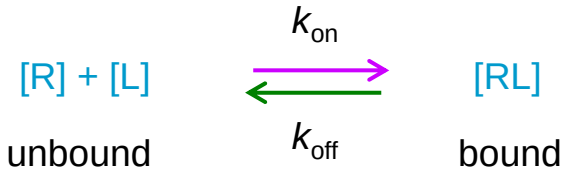
Molecular size / weight ?
Lipophilicity ?
Charged state ?
Rigidity ?
Don't know ?

Selected **specific reports or Structure Kinetic Relationships** (SKRs)

- Therapeutic Complement Inhibitors. *J. Mol. Recognit*. (2009), 22, 495
- Slow dissociation M3 antagonists. *J. Med. Chem.* (2011), 54, 6888
- CCR2 antagonists. *J. Med. Chem*. (2013), 56, 7706
- CDK8/CycC inhibitors. *PNAS* (2013), 110, 8081.
- Adenosine A1 Receptor antagonists. *J. Med. Chem*. (2014), 57, 3213

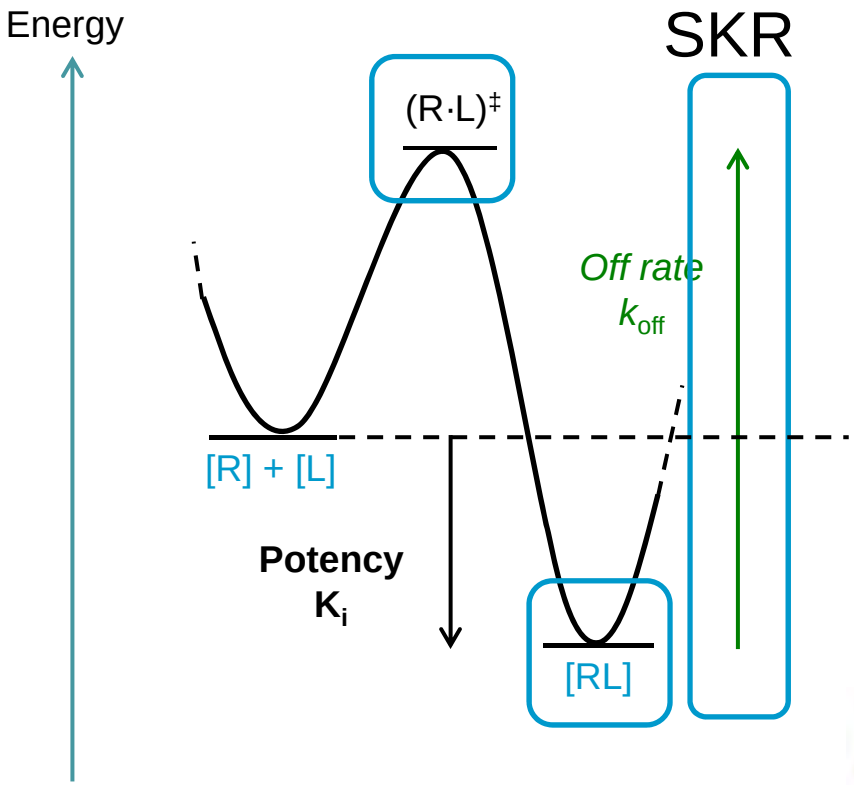
Energetic concept of Residence Time

Standard model



Structure Kinetic Relationships (SKRs) have been largely ignored:

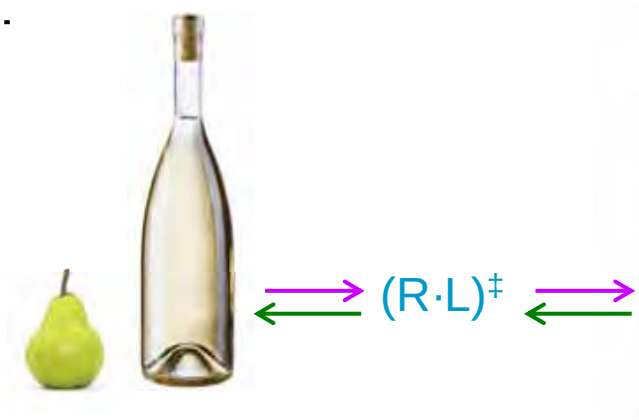
- Residence Time
- Dissociation half-life
- Slow or fast kinetics
- Off-rate, k_{off}



The Dissociation rate is controlled by 2 factors:

(1) The potency (SAR)

(2) The Transition state energy



Potency can be measured
If we can control the transition state energy, we can control the binding kinetics

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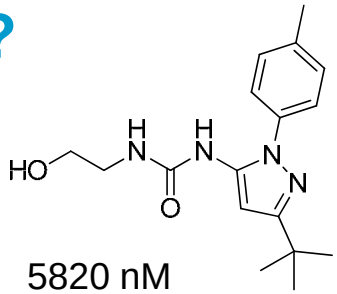
Where is Long Residence ?

Are more active compounds longer resident ?

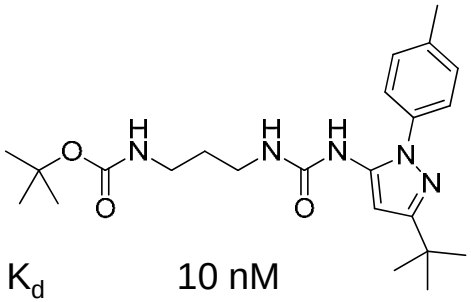
CDK8/CycC inhibitors

PNAS (2013), 110, 8081.



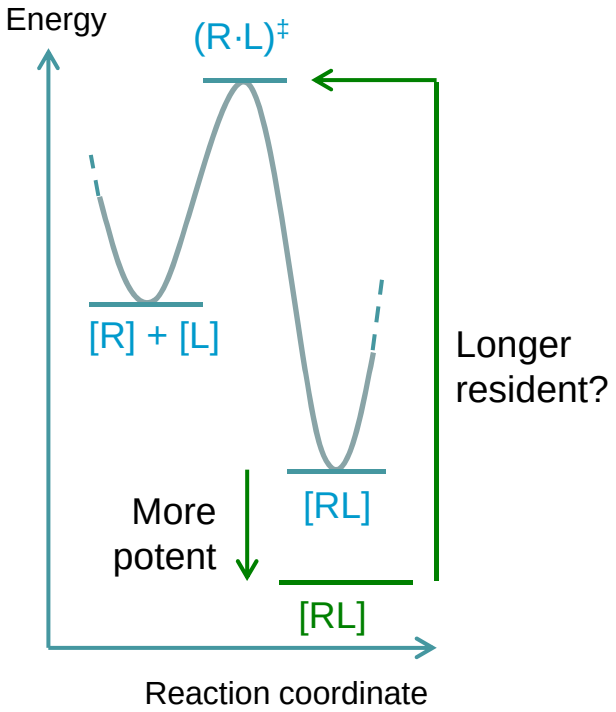
K_d 5820 nM

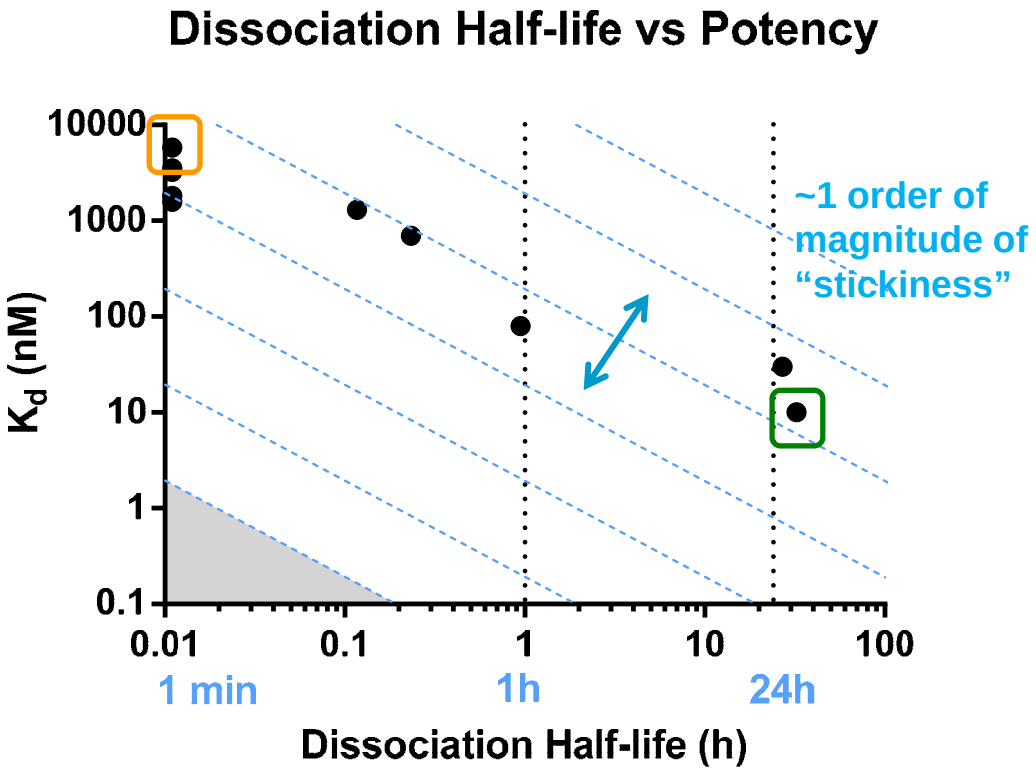
Diss t½ **< 1.4 min**



K_d 10 nM

Diss t½ **32 h**





Clearly, Residence Time is linked to Potency

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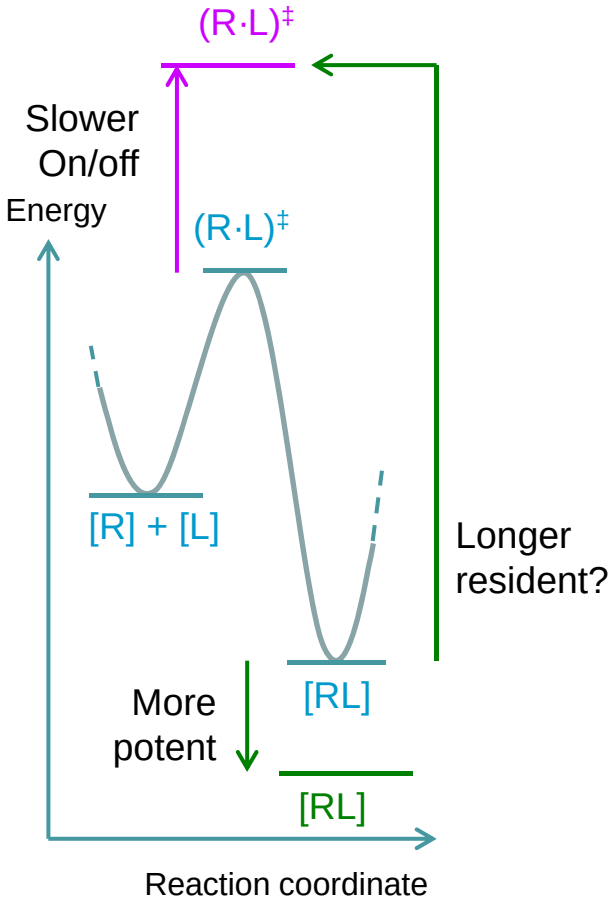
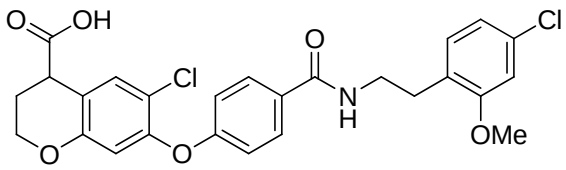
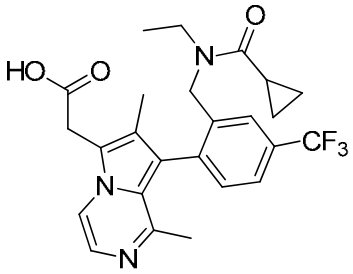
Where is long Residence?

Are more active compounds longer resident ?

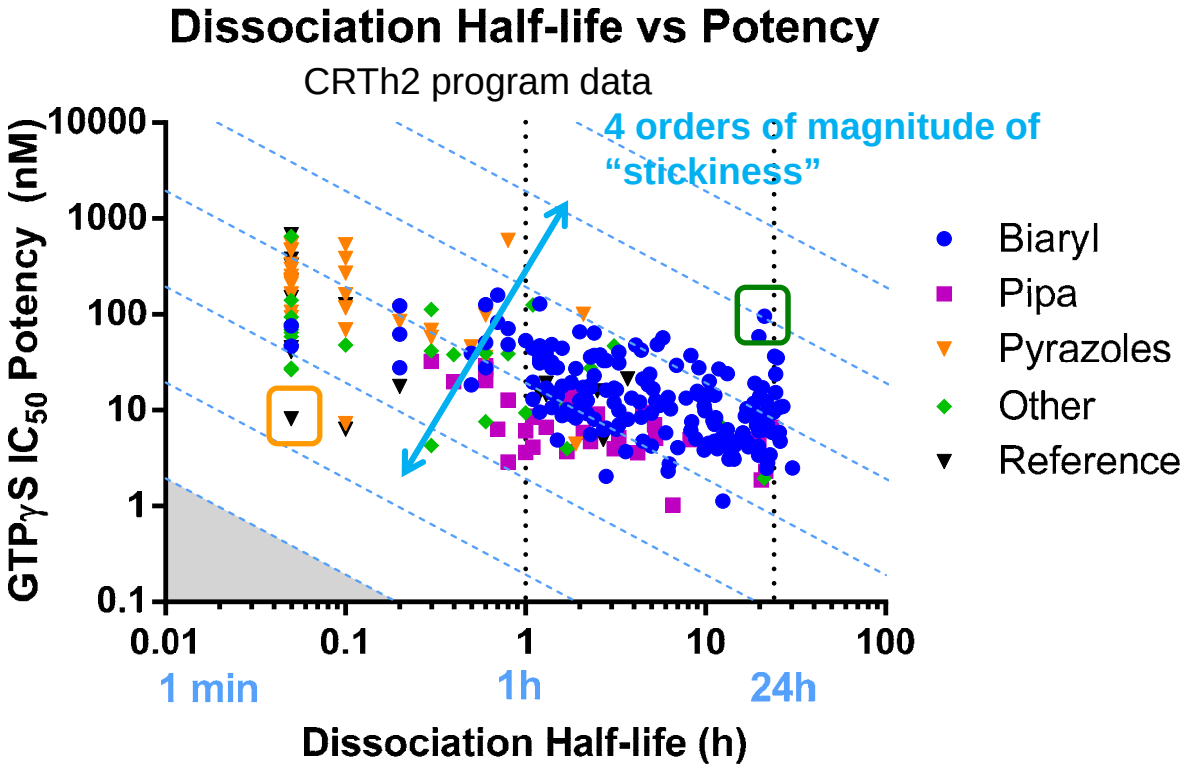




IC_{50} 8 nM
Diss t½ **5 min**



IC_{50} 98 nM
Diss t½ **21 h**



We are affecting the transition state more than the final binding position

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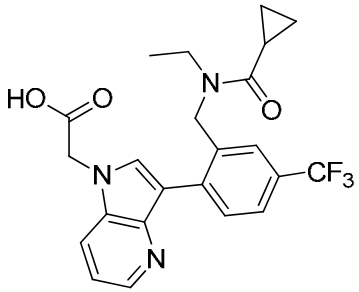
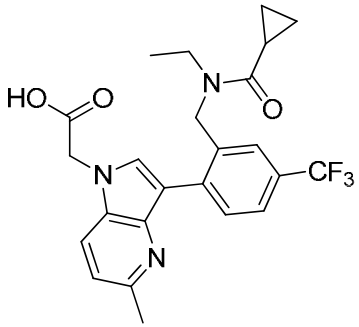
Homing in on Residence Time in the Biaryl series





	4-Azaindole	Me-4-Azaindole
GTPγS IC_{50} (nM)	14	16
Dissociation t½ (h)	1.3	**21**

A Magic Methyl for SKR ?

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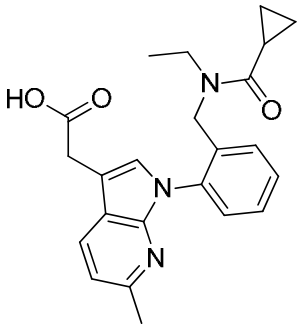
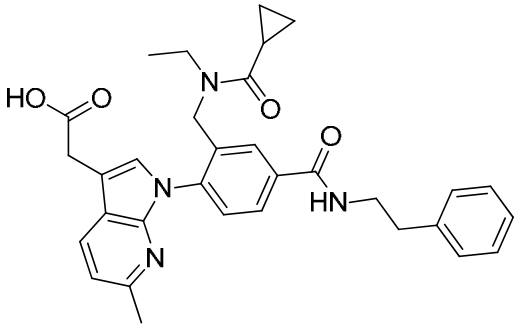
Homing in on Residence Time in the Biaryl series

IC_{50} 5 nM

Dissociation half-life 9 h

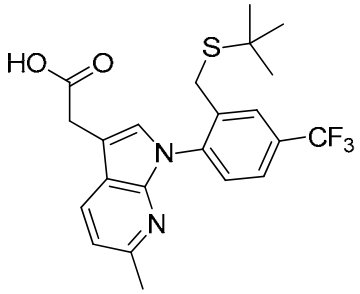


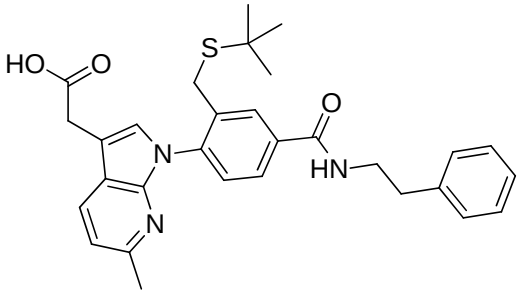


IC_{50} 8 nM

Dissociation half-life 11 h

inactive





IC_{50} 4 nM

Dissociation half-life 25 min

Long Residence Time in the Biaryls comes from an H-Bond Acceptor in ortho

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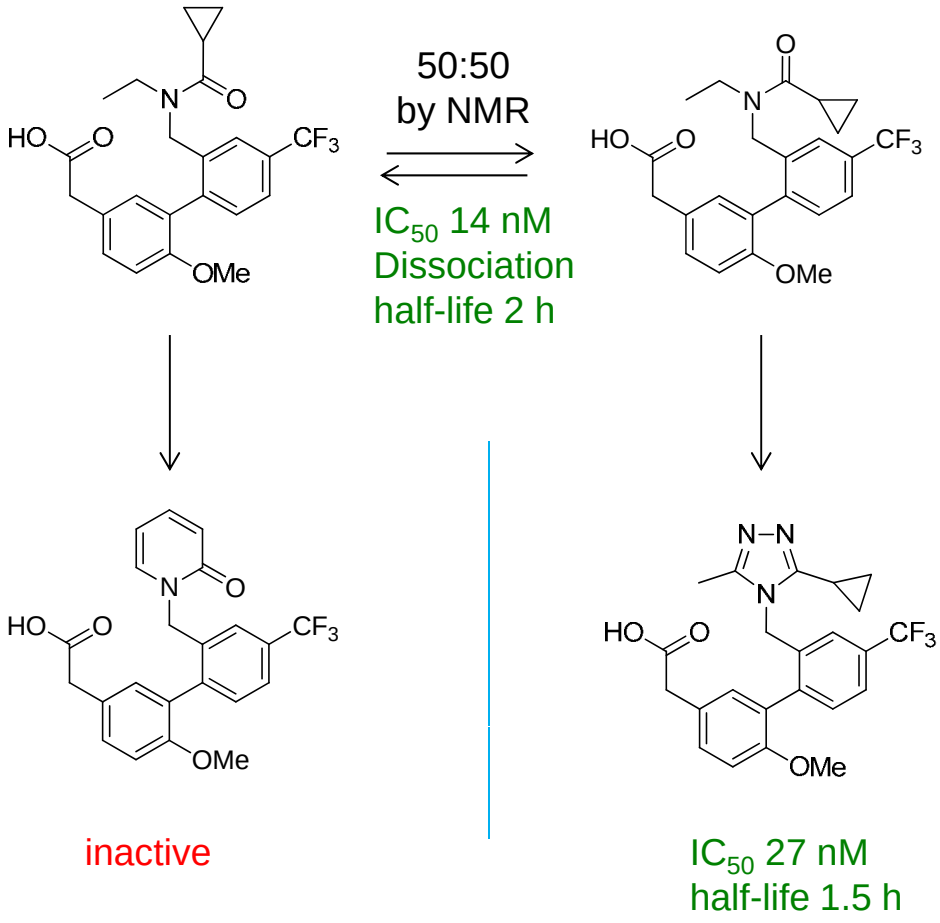
Amide Rotamers



Long Residence Time in the Biaryls comes from an H-Bond Acceptor in ortho in a specific position

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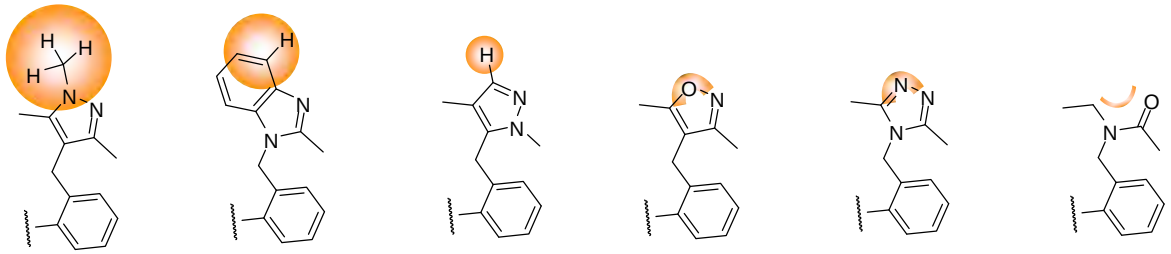
H-Bond Acceptors – Steric requirements

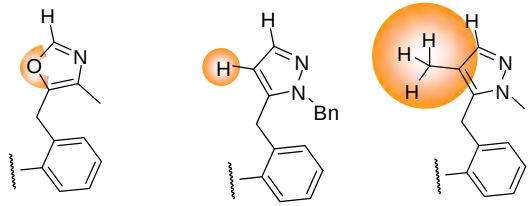
Do very subtle steric effects first determine Potency binding, then residence binding?

R^3



	Me	Fused	Pyrazole	Isoxazole	Triazole	Amide
R3 Sterics	Large	Medium	Small	Minimum	Minimum	-
Potency	Low	Medium	High	High	High	High
Residence	-	Low	Medium	High	High	High

R^1

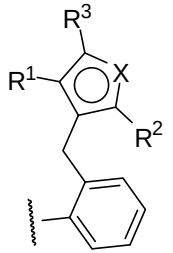


	Oxazole	Pyrazole	Pyrazole
R1 Sterics	Minimum	Small	Large
Potency	Low	Medium	High
Residence	-	-	Medium

Steric Requirements for HBA

$R^3 \leq H$

$R^1 > H$



$R^2 > H$

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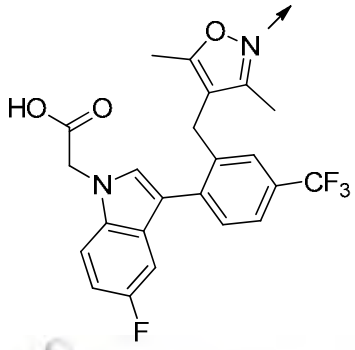
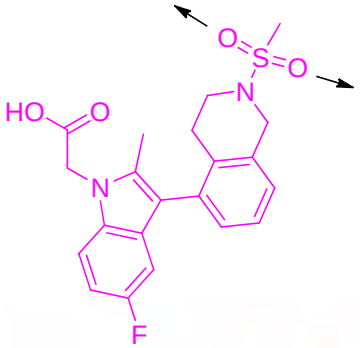
Can we check the H-Bond Acceptor location?



1



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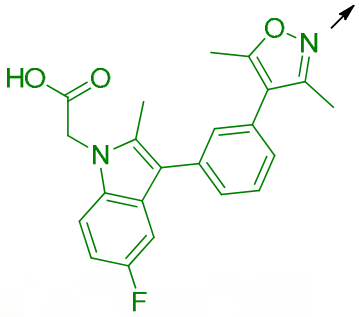
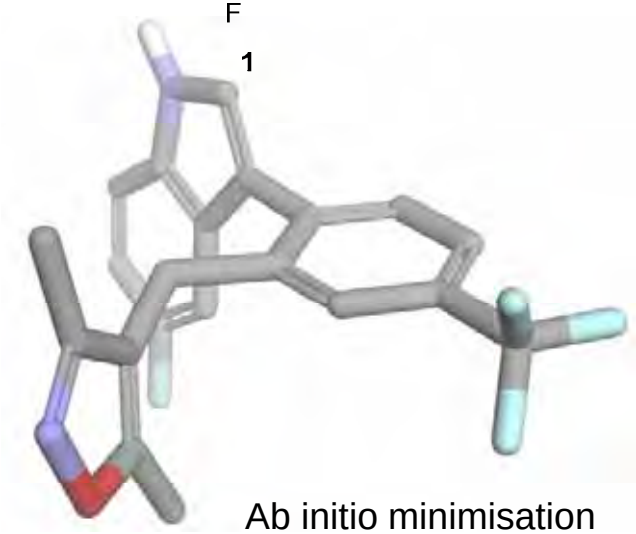
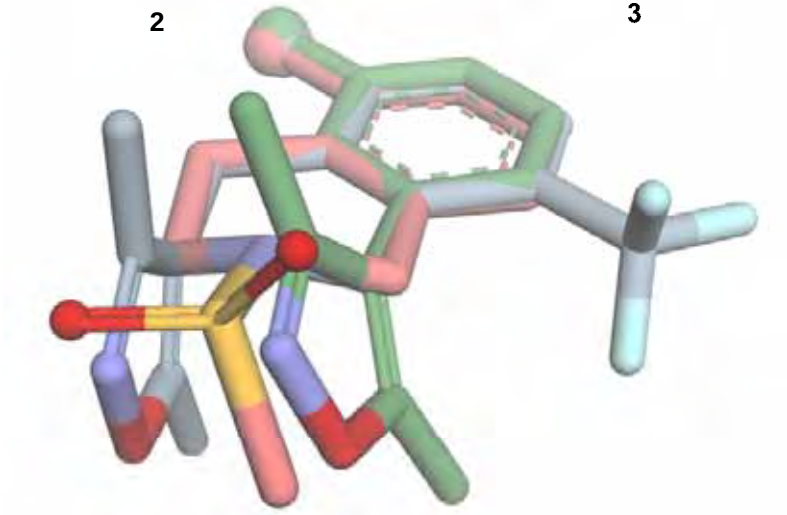


3



Ab initio minimisation



Compound	1	2	3
GTPγS IC_{50}	**20 nM**	**4 nM**	**6 nM**
Dissociation t½	**10 h**	1.7 h	**18 h**

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Can we achieve truly long residence?

If we understand it, we can harness it.

Position-by-position analysis of good structural features for Residence Time

Minimum expression of potency and long residence

3º amide as H-bond acceptor

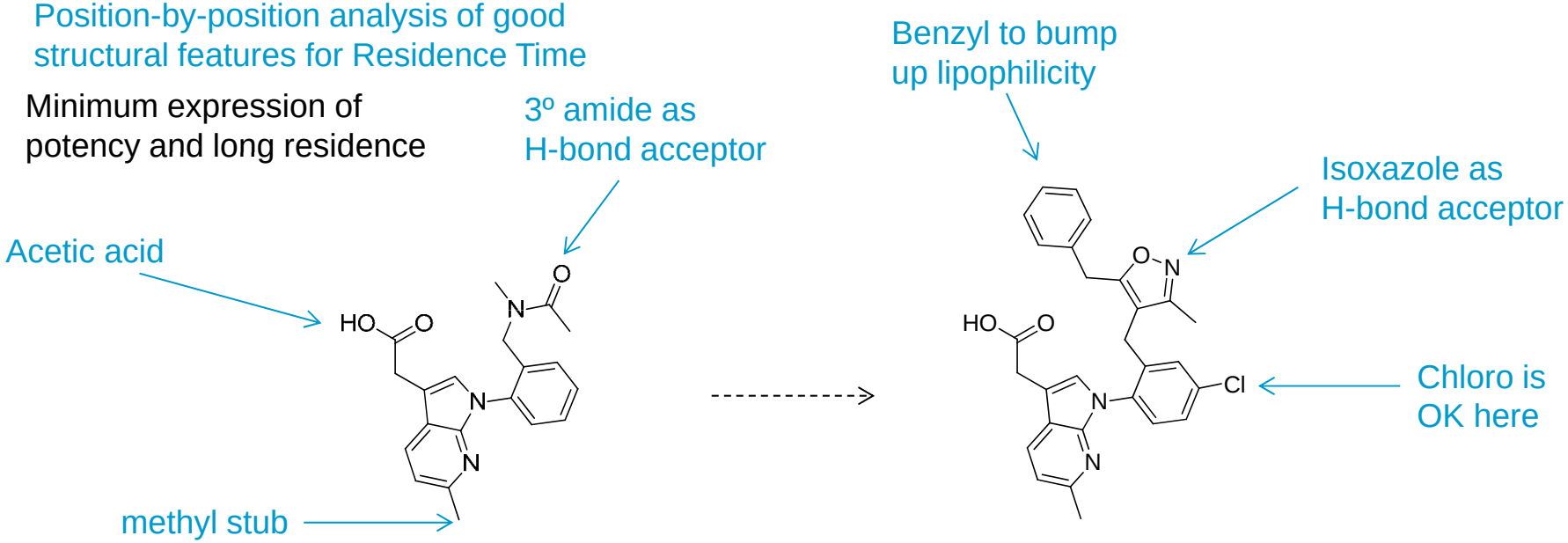
Acetic acid

methyl stub

Benzyl to bump up lipophilicity

Isoxazole as H-bond acceptor

Chloro is OK here



	Azaindole
GTPγS IC_{50} (nM)	**14 nM**
Dissociation t½ (h)	**1.5 h**
cLogP	1.1
cLogD	-1.1

	Azaindole
GTPγS IC_{50} (nM)	**2.5 nM**
Dissociation t½ (h)	**46 ± 15 h**
cLogP	4.8
cLogD	2.4

Once-a-day purely from Residence Time ?

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Lead Compound Profile

In vitro and In vivo	
human GTPγS IC_{50}	4 nM
ESC hWB IC_{50}	**3 nM**
Dissociation t½ (h)	**22 h**
gp GTPγS IC_{50} (nM)	3 nM
Dissociation t½ (h)	14 h
Eosinophilia IC_{50}	4 nM
Eosinophilia ID_{50} at 2 h	0.020 mg/kg
PK-PD Disconnection	**Yes**

Physical Chemistry	
Solubility pH 1 and 7.4	> 1 mg/ml
LogD	1.3
Caco (AB/BA)	24 / 6

Pharmacokinetics	
Rat Clearance	9 ml/min/kg
Volume	0.5 L/kg
Terminal half-life	1.6 h
Bioavailability	80%
Dog Clearance	2 ml/min/kg
Volume	0.9 L/kg
Terminal half-life	8 h
Bioavailability	51%
***Pred. Human** Clearance*	*2 ml/min/kg*
Pred. Volume	*1.4 L/kg*
Pred. Terminal half-life	*biphasic*
PK-PD dose simulation	***2-6 mg QD***

Safety	
hERG, $Na_v1.5$, $Ca_v1.2$	**> 10 µM**
Working heart	**Clean**
Cytotox	**> 100 µM**
GreenScreen	**Clean**
CYP3A4	**20 µM**
Major metabolite	Glucuronide
Acyl Glucuronide stability	t½ > 4 h

An oral, low dose (<10 mg), once-a-day CRTh2 Antagonist

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CRTh2: Can Residence Time Help ?

- For a purely antagonistic effect, prolonging Receptor Occupancy prolongs PD effect
- You will only really appreciate a PK-PD disconnection if Dissociation half-life > PK terminal half-life
- For GPCR antagonism, you should count on extending the PD effect by half a half-life
- A “PK phase” of antagonism is needed to “set” the ligand in the receptor, regardless of mechanism
- We are pretty good at explaining what’s behind Structure-Activity Relationships (SAR)
  Structure-Kinetic Relationships (SKR) are in their infancy and/or qualitative
- **Residence Time can be designed**
- To find Long Residence, you need to look for it

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