CRTh2: Can Residence Time help ?

25th Symposium on Medicinal Chemistry in Eastern England

Fielder Centre,
Hatfield, Hertfordshire, UK

Thursday 24th April 2014

Almirall

Solutions with you in mind

Rick Roberts
Almirall
Barcelona, Spain

Introduction

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

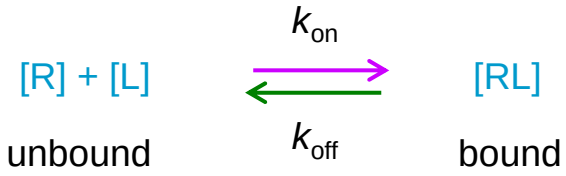
“A substance will not work unless it is bound”

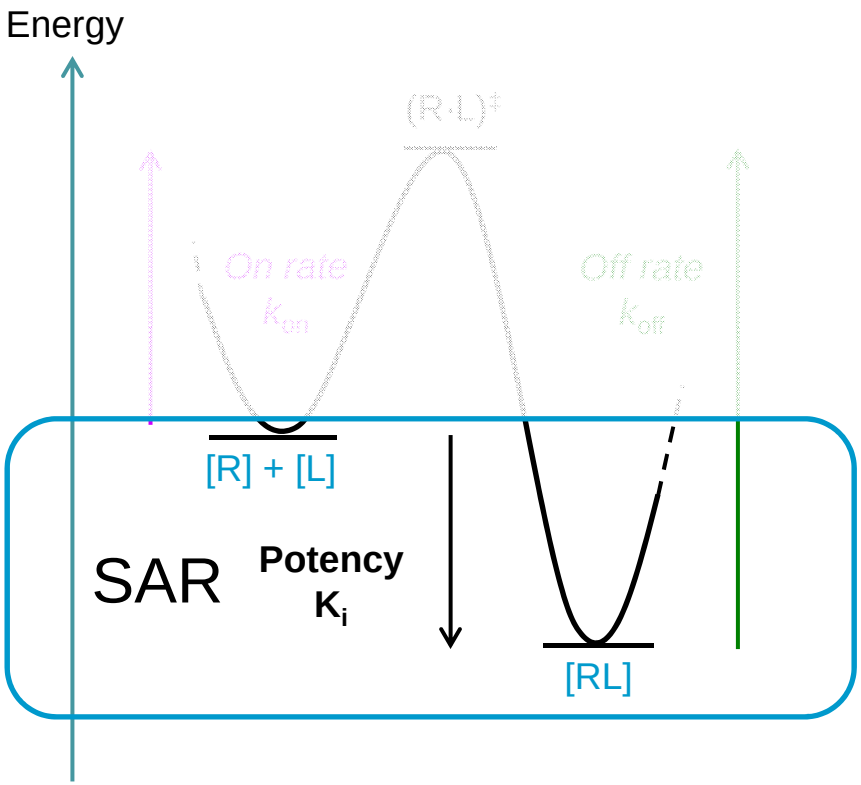
100 years on:

“how long it’s bound determines how it works”

Energetic concept of Residence Time

Standard model





Potency is determined by the difference between two **rates**

$$K_i = \frac{k_{off}}{k_{on}}$$

$$\frac{\cancel{per\ second}}{\cancel{per\ second} \cdot per\ concentration}$$

Potency = concentration

Equilibrium binding assays
measure potency but **ignore kinetics**

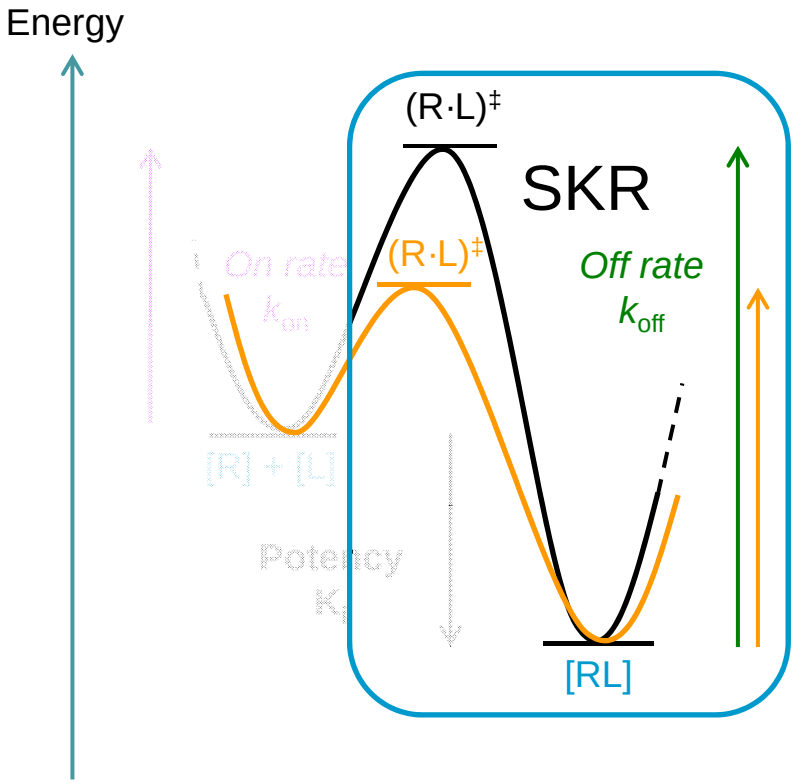
Almirall

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 binding kinetics are controlled by the transition state energy

slow associating compounds that are slow dissociating

fast associating compounds that are fast dissociating

⇩

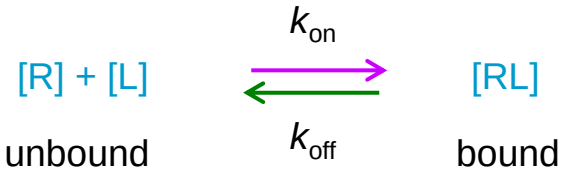
Are all equipotent

If we can control the transition state energy, we can control the binding kinetics

Almirall

What is the transition state (R·L)‡ ?

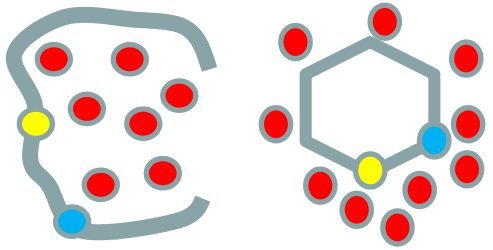
Standard model



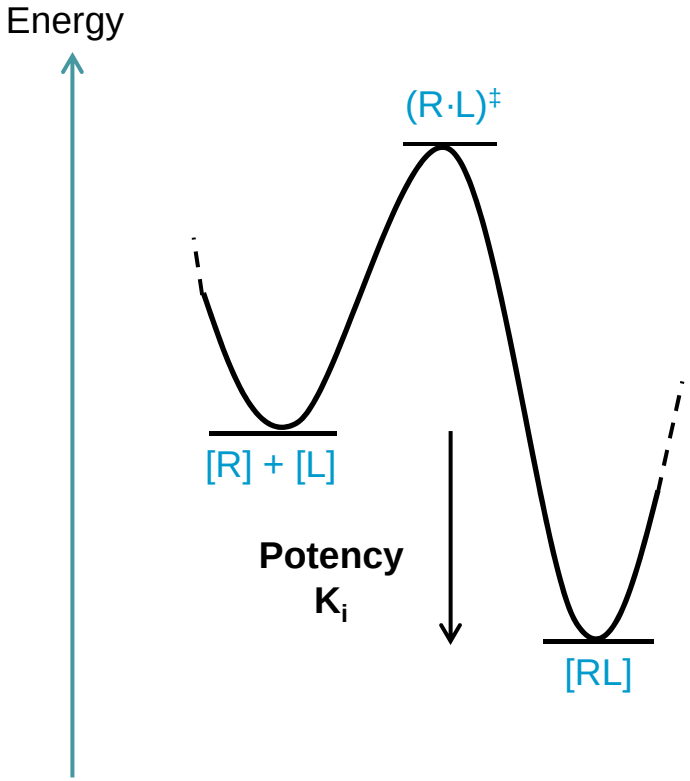
"Home"

[R] + [L]

Solvated Receptor [R]



Solvated Ligand [L]



Fleeting existence

Protein conformational changes?

Entropy?

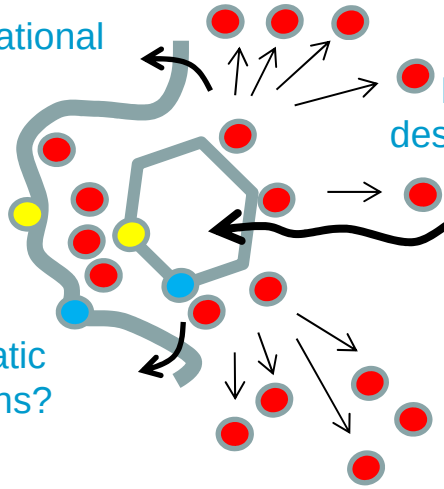
Partial desolvations ?

"Journey"

(R·L)‡

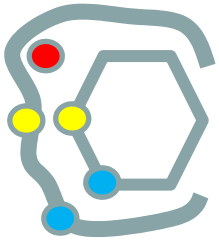
Partial electrostatic interactions?

A physical process



"Destination"

[RL]



Water molecules

Molecular interaction points

Almirall

What is the transition state (R·L)‡ ?

Standard model

[R] + [L] ⇌ [RL]

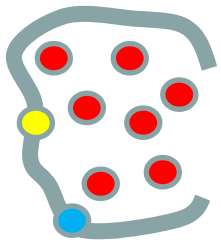
k_{on} / k_{off}

unbound / bound

"Destination"

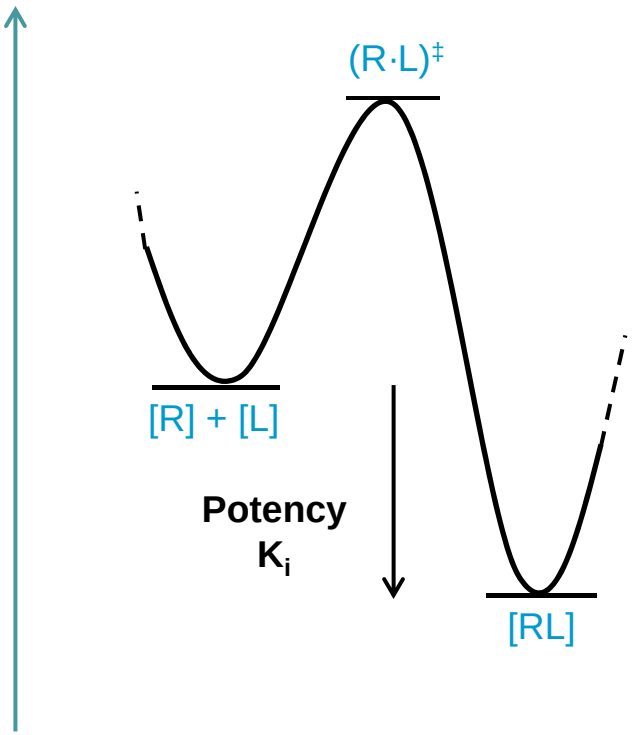
[R] + [L]

Solvated Receptor [R]



Solvated Ligand [L]

Energy



Fleeting existence

Entropy?

Protein conformational changes?

Partial solvations?

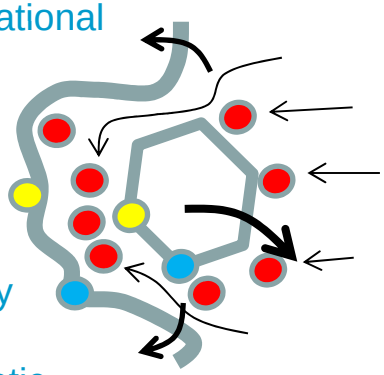
"Journey"

(R·L)‡

Purely qualitative

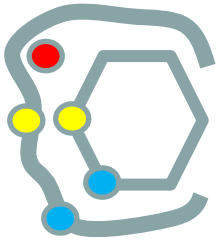
Partially break electrostatic interactions?

A physical process



"Home"

[RL]



Water molecules

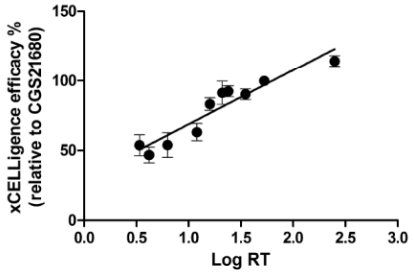
Molecular interaction points

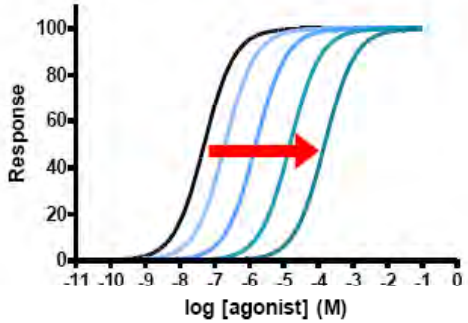
Almirall

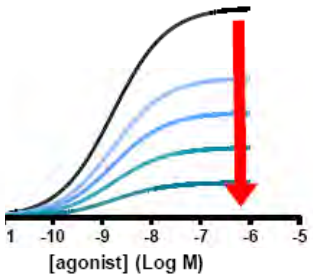
Why bother to control Binding Kinetics ?

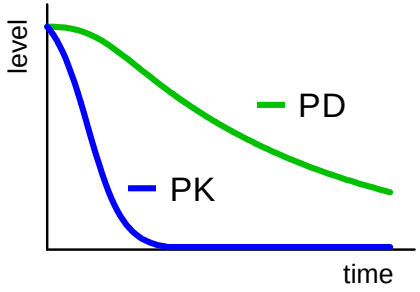
Residence time / Dissociation half-life

seconds — minutes — hours — days









Mechanistic | Surmountable | Insurmountable | Pharmacodynamic

Potency has little influence over these behaviours

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

Almirall

The CRTh2 Programme

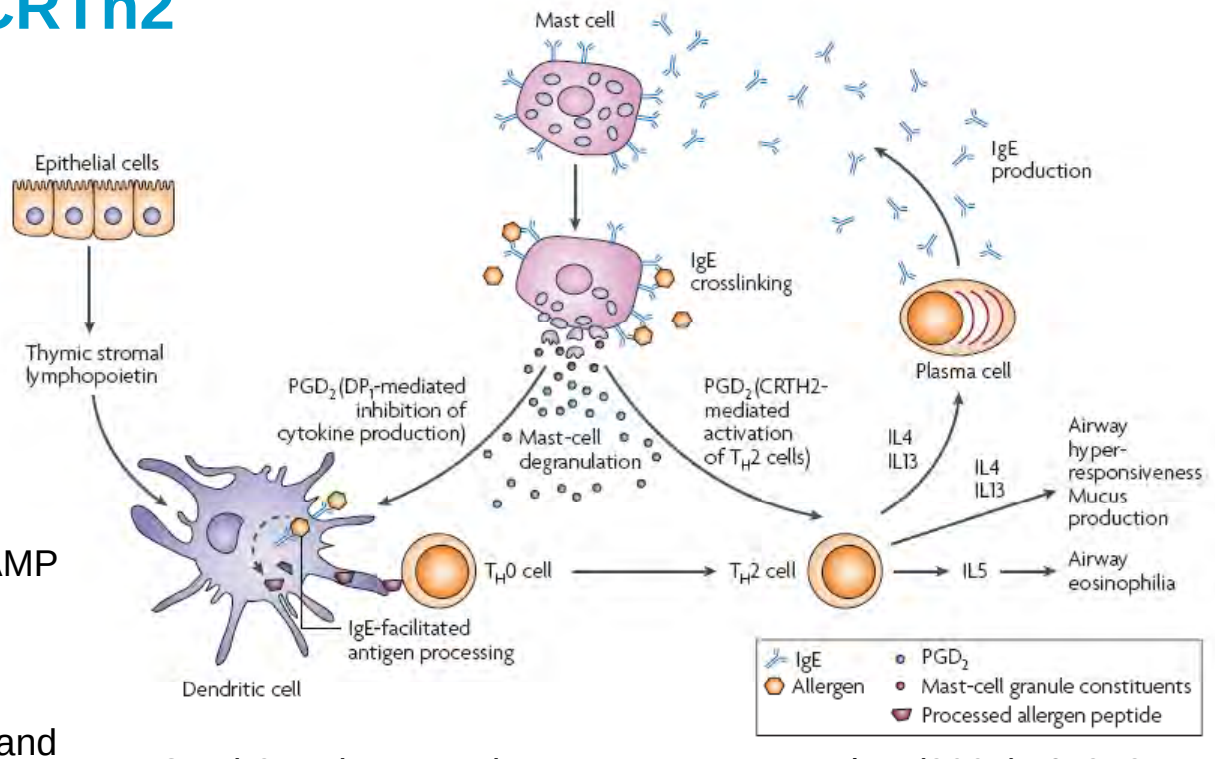
Brief introduction to CRTh2

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

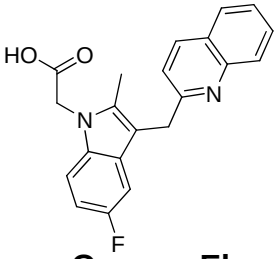
CRTh2 antagonism:

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

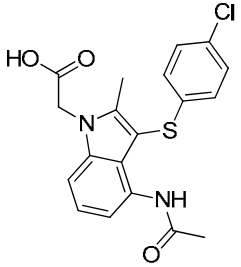
Almirall

Why Long Residence Time in CRTh2 ?

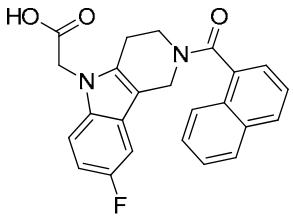
Indole acetic acids



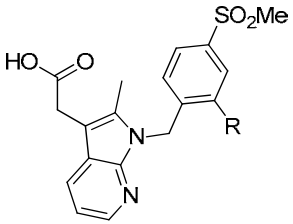
Oxagen-Eleventa
OC-459
Phase III



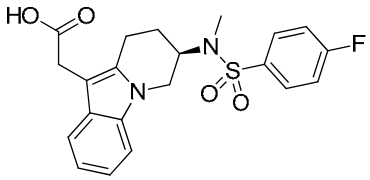
AstraZeneca
AZD-1981
Phase II



Actelion
Setipiprant
Phase III



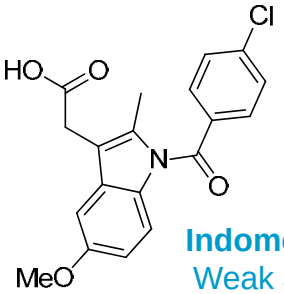
Novartis
R = CF_3 QAV-039
R = H QAW-680
Phase II/II



Merck
MK-7246
Phase I

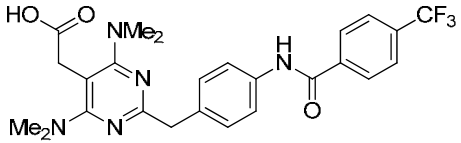
Pulmagen-Teijin
ADC-3680
Phase II

?

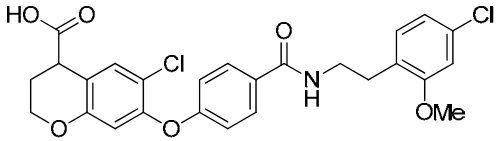


Indomethacin
Weak agonist

Aryl acetic acids



Boehringer
BI671800
Phase II

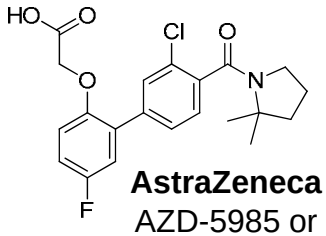


Array
ARRY-502
Phase II

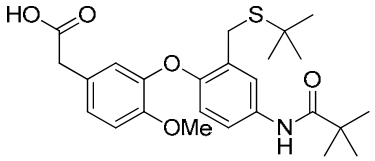
Roche
RG-7581
Phase I

?

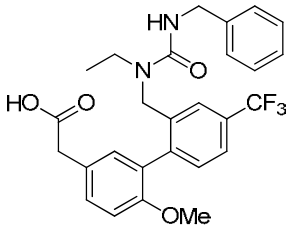
Phenoxyacetic acids



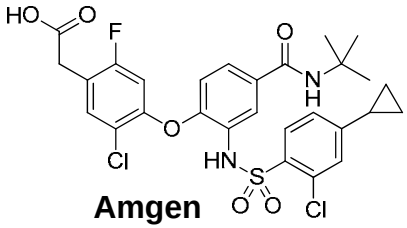
AstraZeneca
AZD-5985 or
AZD-8075
Phase I/I



Panmira
AM461
Phase I



Panmira
AM211
Phase I



Amgen
AMG-853
Phase II

Almirall

Our internal programme

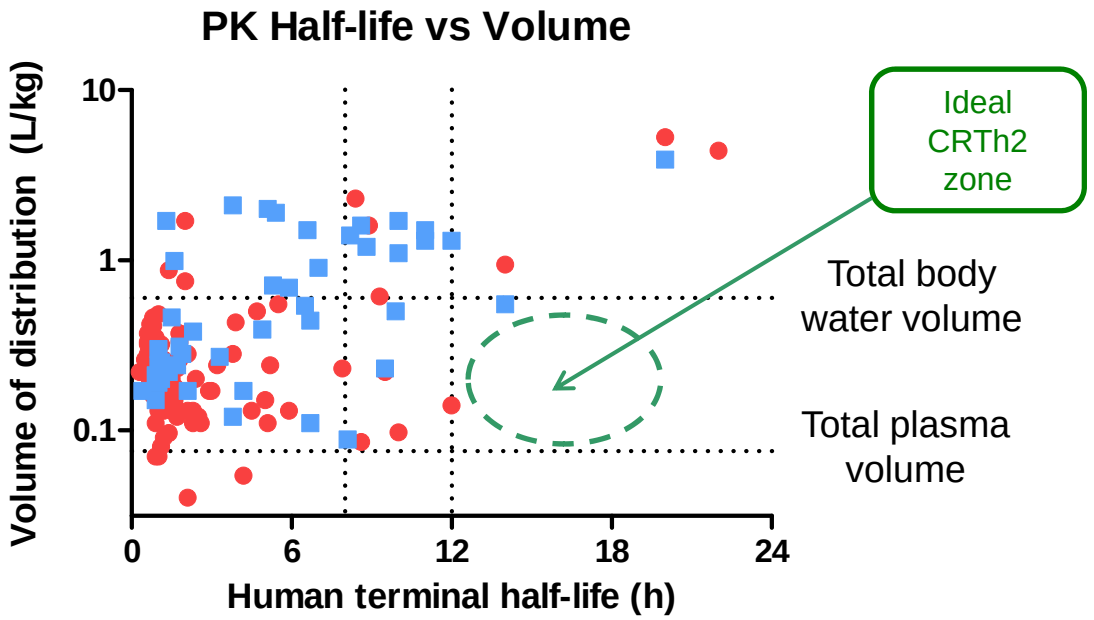
We want to find a once a day, oral, low dose (≤ 10 mg) CRTh2 antagonist for mild-moderate asthma

- All antagonists are acids.
- Acids generally have poor PK

Acid
Zwitterion

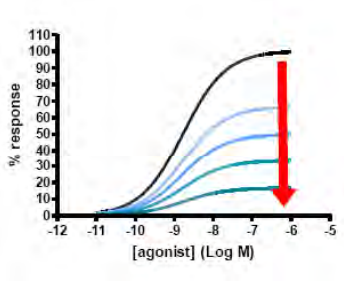
Human PK profiles of 150 carboxylic acids

Adapted from Obach, *Drug.Metab.Disp.* (2008), 36, 1385

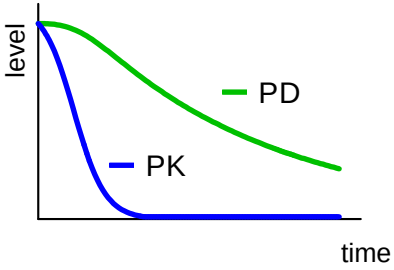


- Clinical dosing of first CRTh2 antagonists – high dose and twice daily

- 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



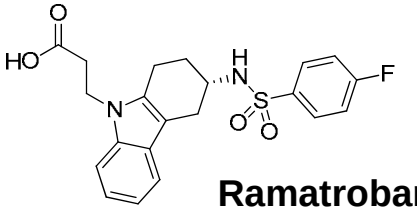
Insurmountable



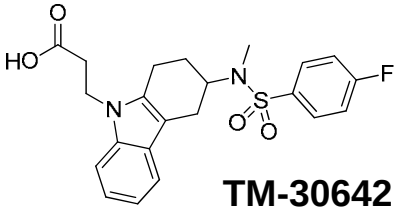
Pharmacodynamic

Almirall

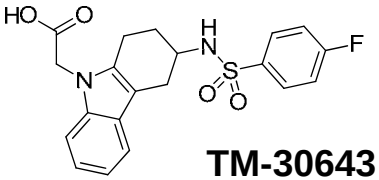
Are there slow-dissociating CRTh2 antagonists?



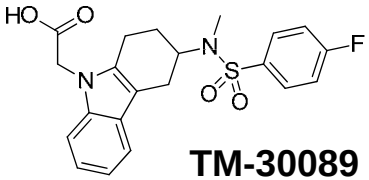
Ramatroban



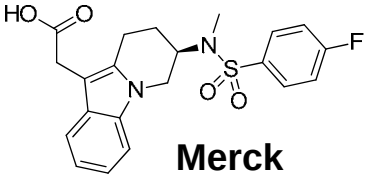
TM-30642



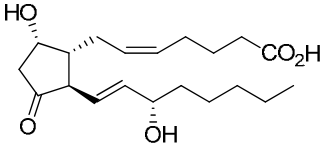
TM-30643



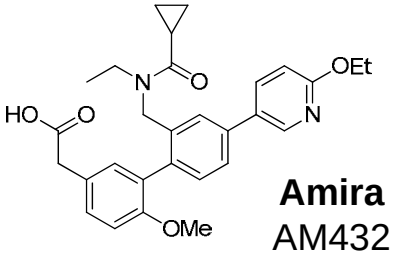
TM-30089
(CAY-10471)



Merck
MK-7246



PGD_2



Amira
AM432

Structure not disclosed

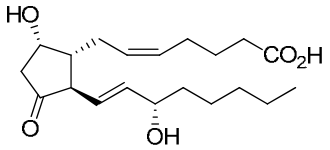
Pulmagen
ADC-3680

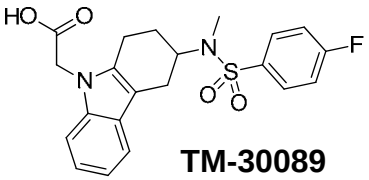
Compound	Potency		Dissociation half-life*	Reference
Ramatroban	pA_2	36 nM	**5 min**	*Mol. Pharmacol*. (2006), *69*, 1441
TM-30642	pA_2	20 nM	**8 min**	--- / / ---
TM-30643	pA_2	4 nM	*(12.8 years)*	--- / / ---
TM-30089	pA_2		*(13.5 years)*	--- / / ---
MK-7246	K_i	2.5 nM	**33 min**	*Mol. Pharmacol*. (2011), *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

Almirall

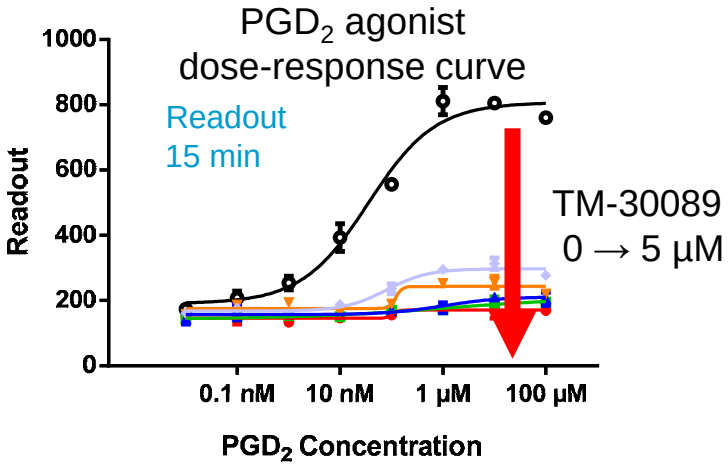
In vitro dissociation assays CRTh2

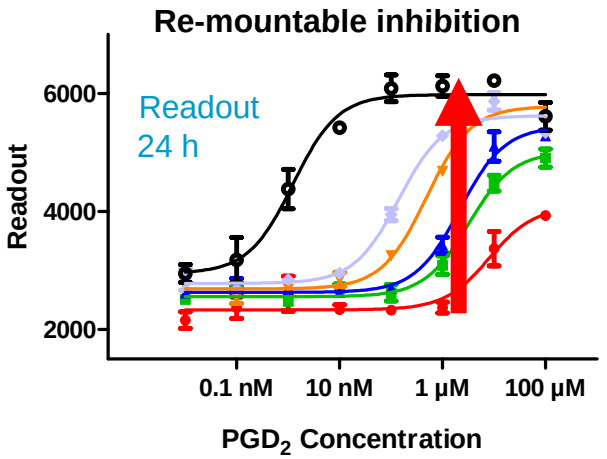
Surmountability vs Insurmountability





TM-30089
(CAY-10471)

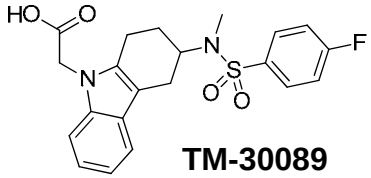




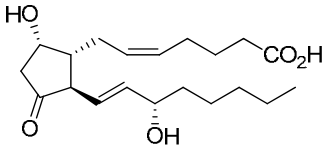
15 min < TM-30089 Dissociation half-life < 24 h

Surmountability is just a question of time

in vitro washout Dissociation assay

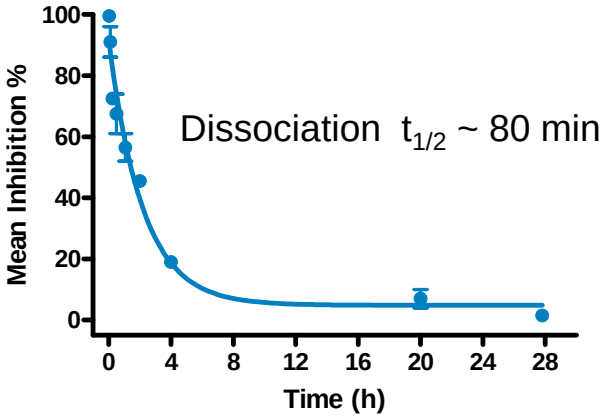


TM-30089
at 10 × IC_{50}



Then PGD_2
at 10000 × EC_{50}

- "Worst case" scenario for dissociation half-life
- No rebinding possible.
- Physiological system may be less demanding

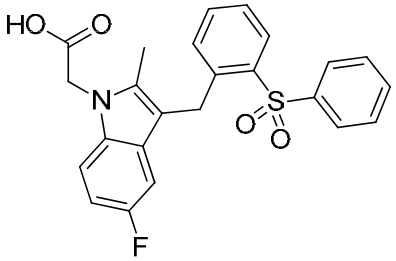


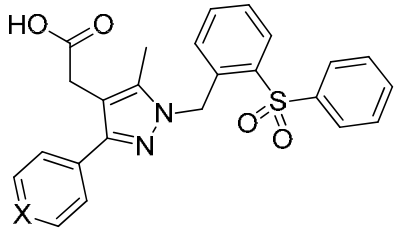
Dissociation $t_{1/2}$ ~ 80 min

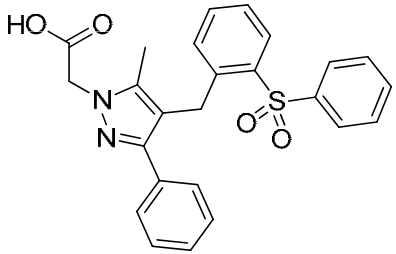
Almirall

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

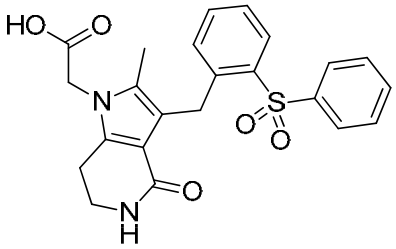
Pyrazoles series abandoned for general lack of Residence time

Almirall

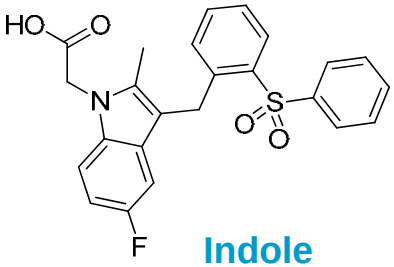
Pipas

- Third series of Pyrazolopyrimidinones (Pipas) gave active compounds with long residence (manuscript in preparation)

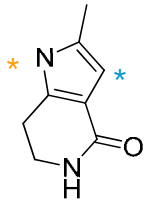
- Core SAR flat. Core SKR varied

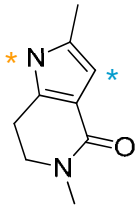


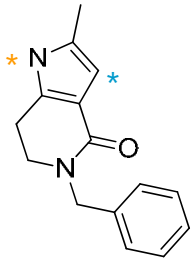
Pyrazolopyrimidinones (Pipas)

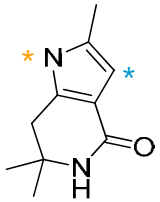


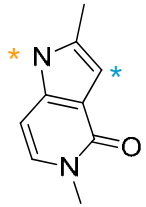
Indole

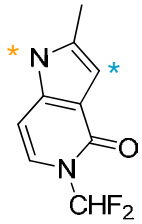








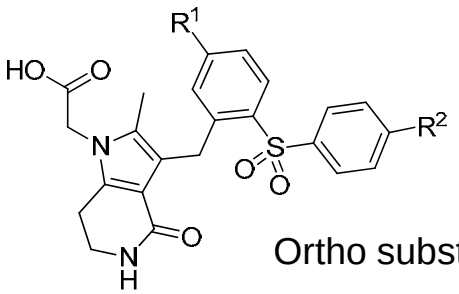




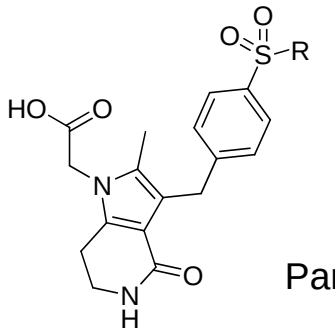
	Oxagen	PiPa	N-Me	N-Bn	diMe	N-Me*	N-CHF_2*
GTPγS IC_{50} (nM)	14	5	5	1	4	5	2
Dissociation t½ (h)	1.3	2.3	5.3	**6.6**	**10**	**8**	**21**

Pipas

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



Ortho substitution



Para 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**

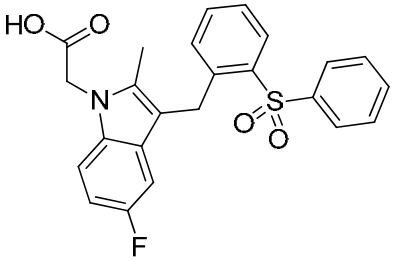
R	GTPγS IC_{50}	Dissociation t½
Ph	170 nM	n.d.
Me	900 nM	n.d.
Bn	3 nM	0.9 h

Ultimately Potent but no duration

- Pipa series was essentially impermeable.
- Not suitable for an oral program
- **Still, a valuable tool to validate the PK-PD disconnection in guinea pig**

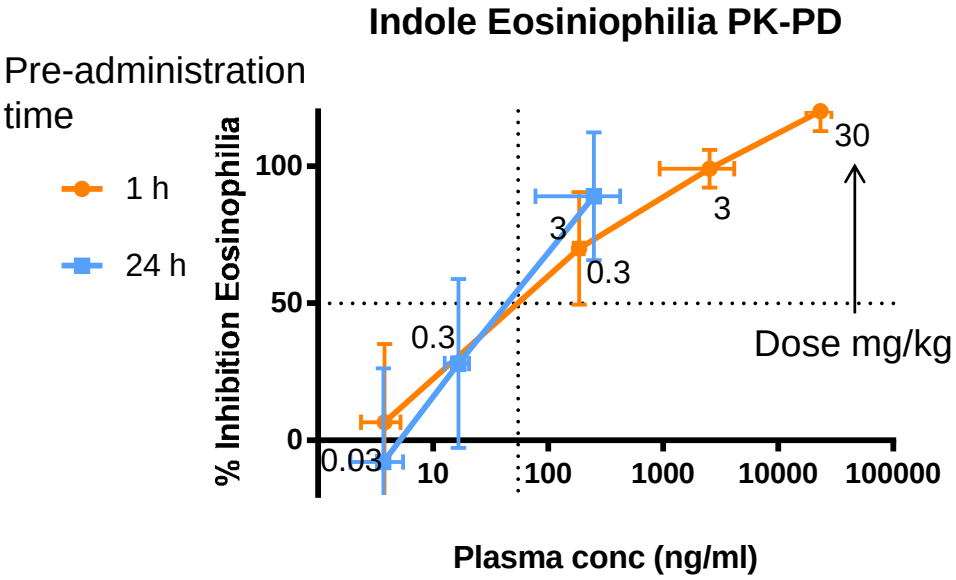
Almirall

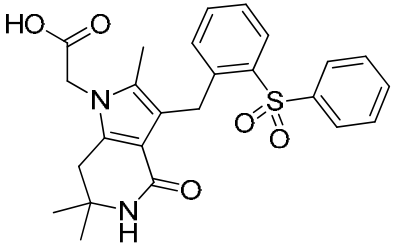
PK-PD Disconnection Model



F-Indole guinea pig data
Dissociation t½ **1.3 h <** PK t½ **5.3 h**

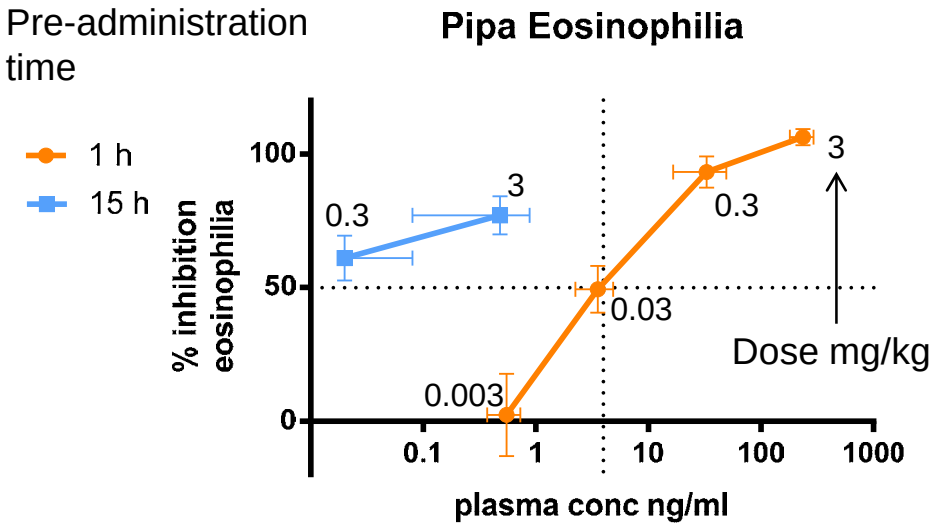
- Inhibition of eosinophilia (PD) is purely dependant upon systemic levels (PK)
- **No PK-PD disconnection**





diMe-Pipa guinea pig data
Dissociation t½ **20 h >>** PK t½ **0.9 h**

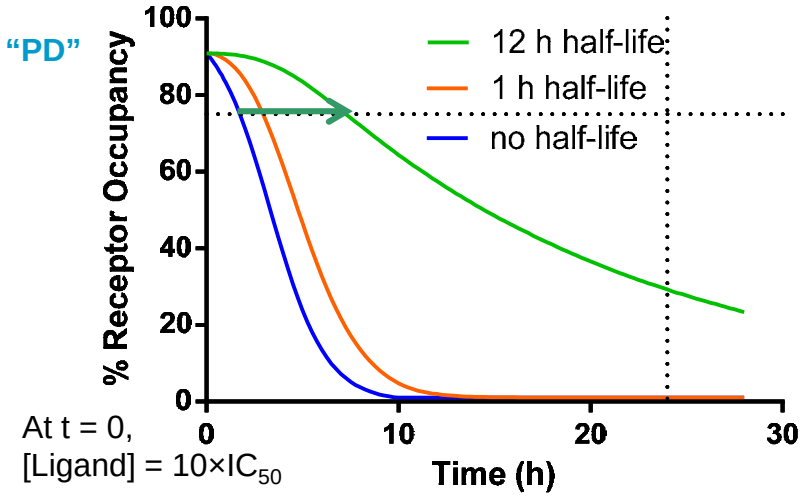
- Inhibition of eosinophilia (PD) outlasts drop in systemic levels (PK) at 17h after dosing
- **PK-PD disconnection** (hysteresis)



Almirall

PK-PD Disconnection Simulations

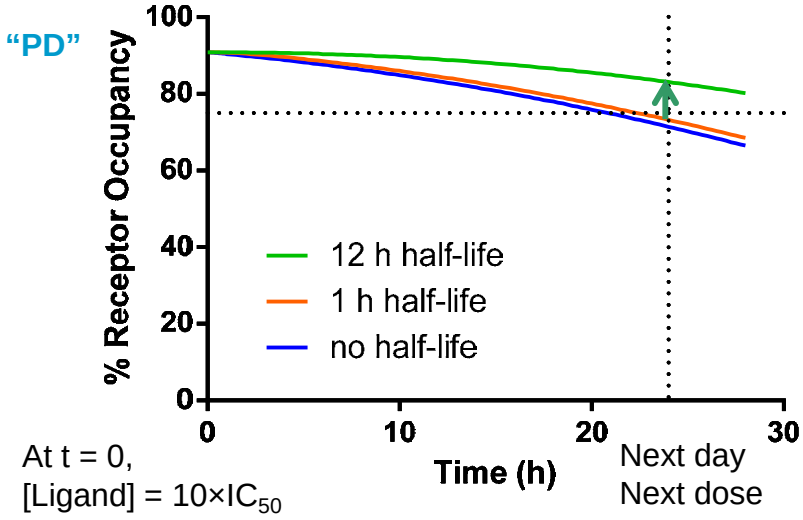
PK half-life 1 h



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

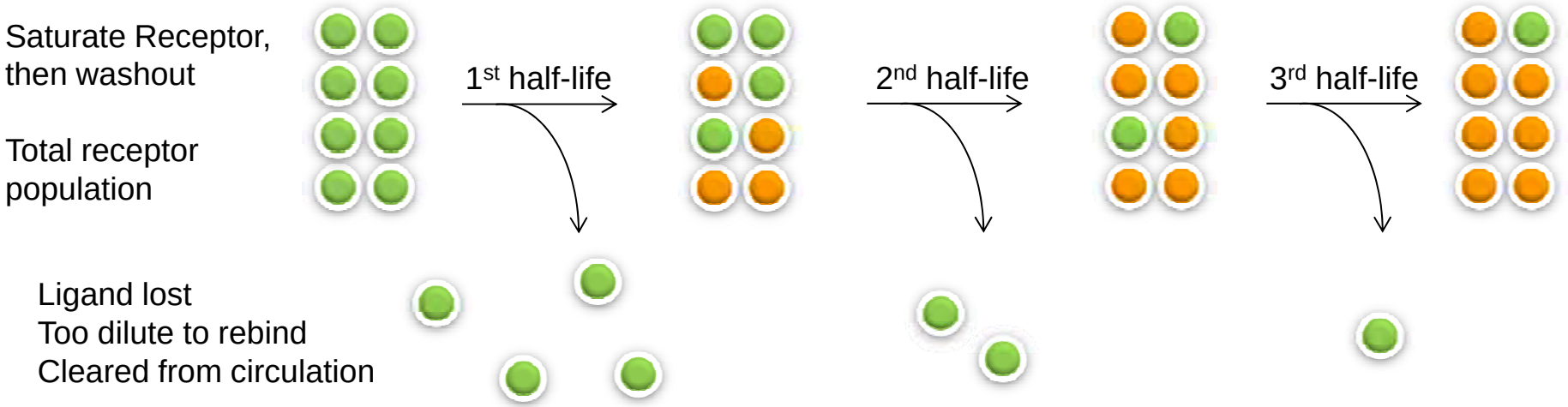
A 12 h Dissociation half-life is barely noticeable
A great drug is really efficacious over 24 h

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

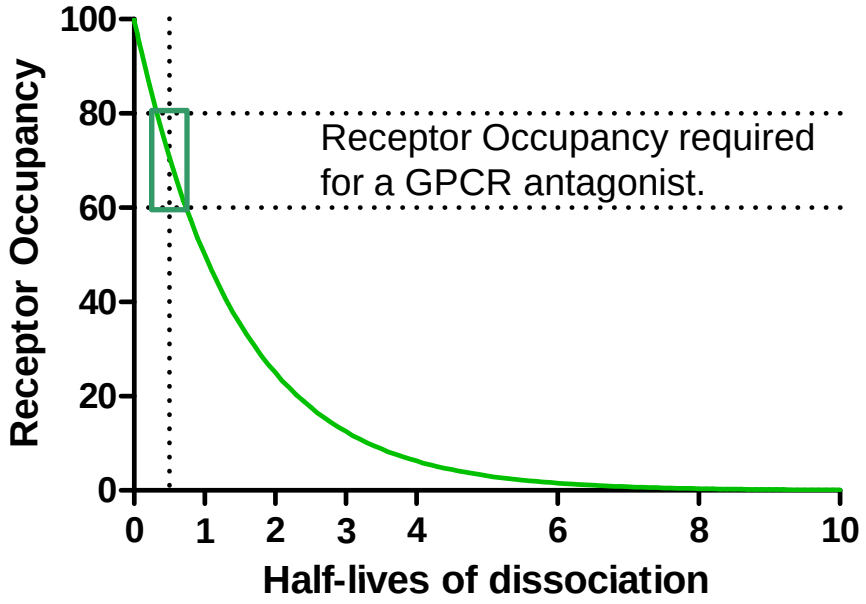
For a recent article, see *Drug Disc. Today* (2013), 18, 697

Almirall

How long is long residence ?



Receptor Occupancy by exponential decay



An antagonist fully saturating a GPCR will lose robust efficacy after about half a Dissociation Half-life

A twice-daily compound achieves 12 h PD coverage due to PK levels

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

Pharmacol. Therap. (2009), *122*, 281-301

Almirall

Molecular Determinants of Long Residence:

Structure Kinetic Relationships (SKR)

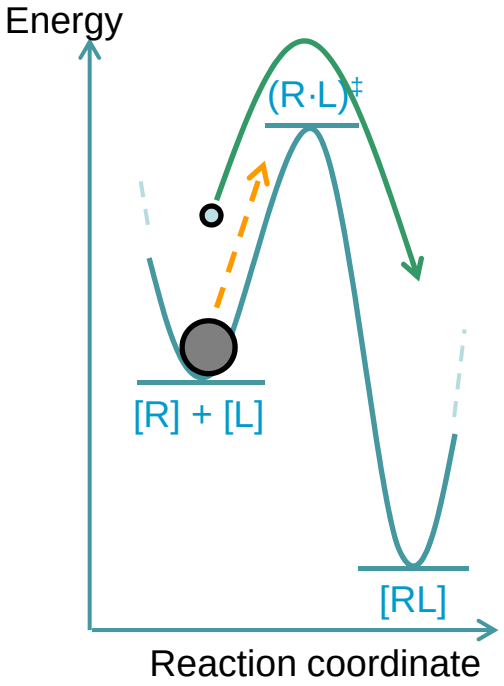
Where is long Residence?

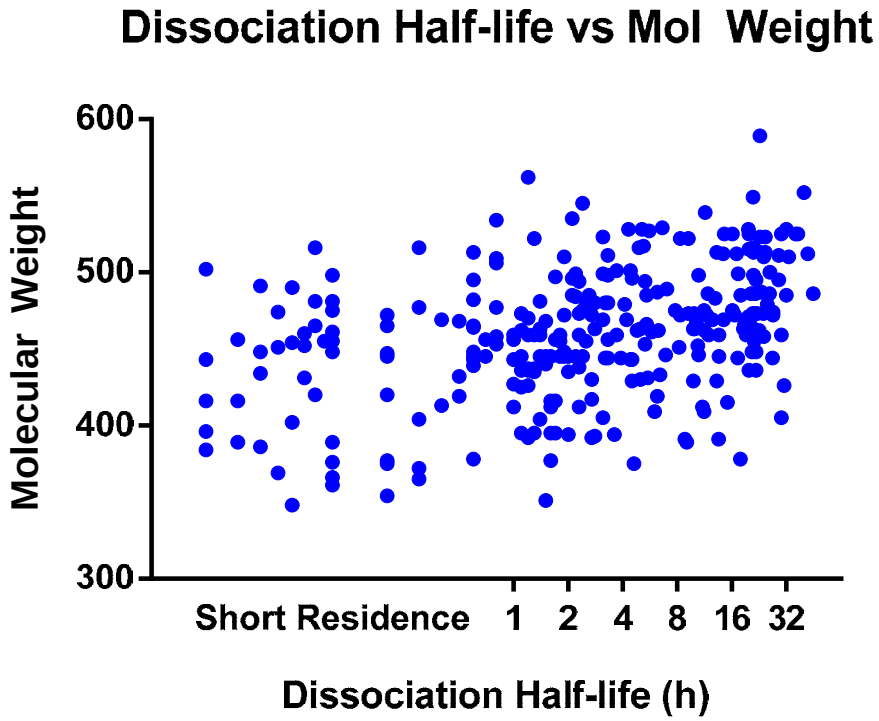
Selected lit reports or Structure Kinetic Relationships (SKRs)

- 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 ?
Don't know ?

Are Bigger compounds longer resident?





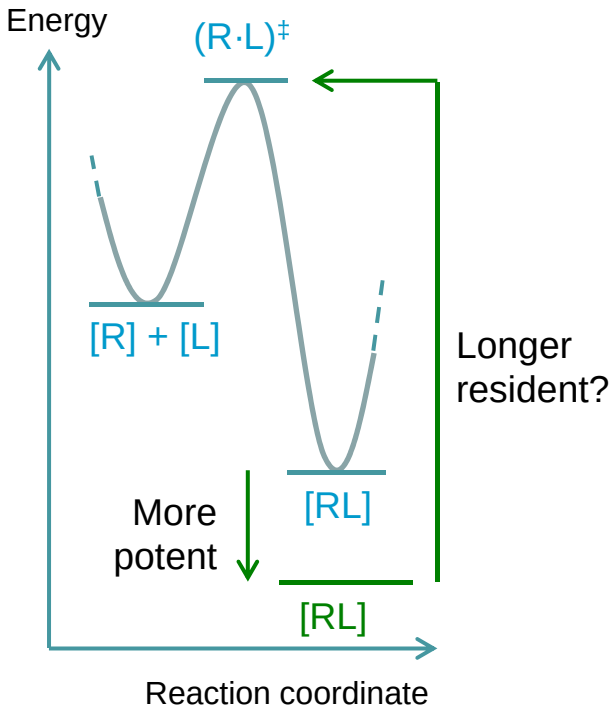
Nope. Not diffusion controlled

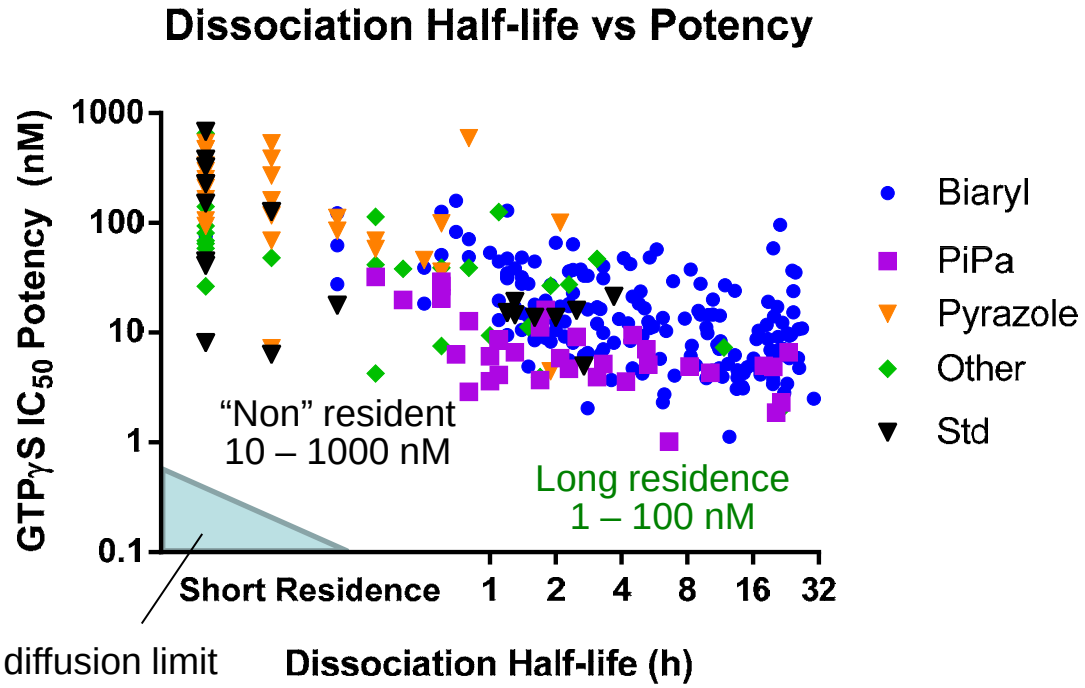
No "Kinetic Efficiency"

Almirall

Where is long Residence?

Are more potent compounds longer resident ?





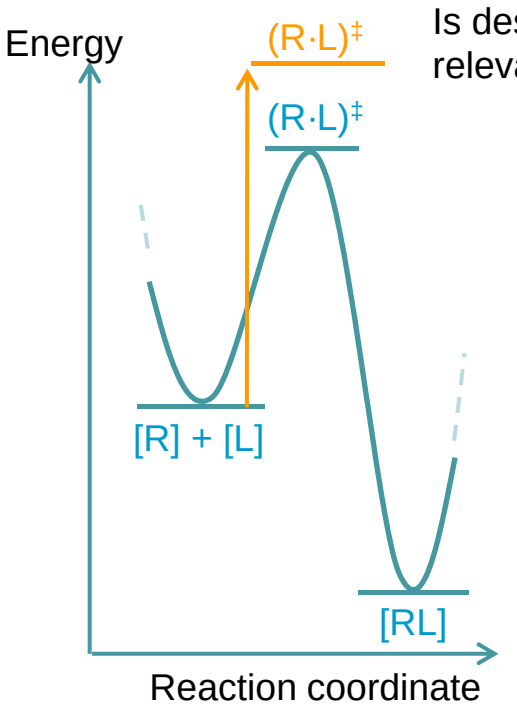
Intuitive, but not that helpful

We want the most potent compounds anyway

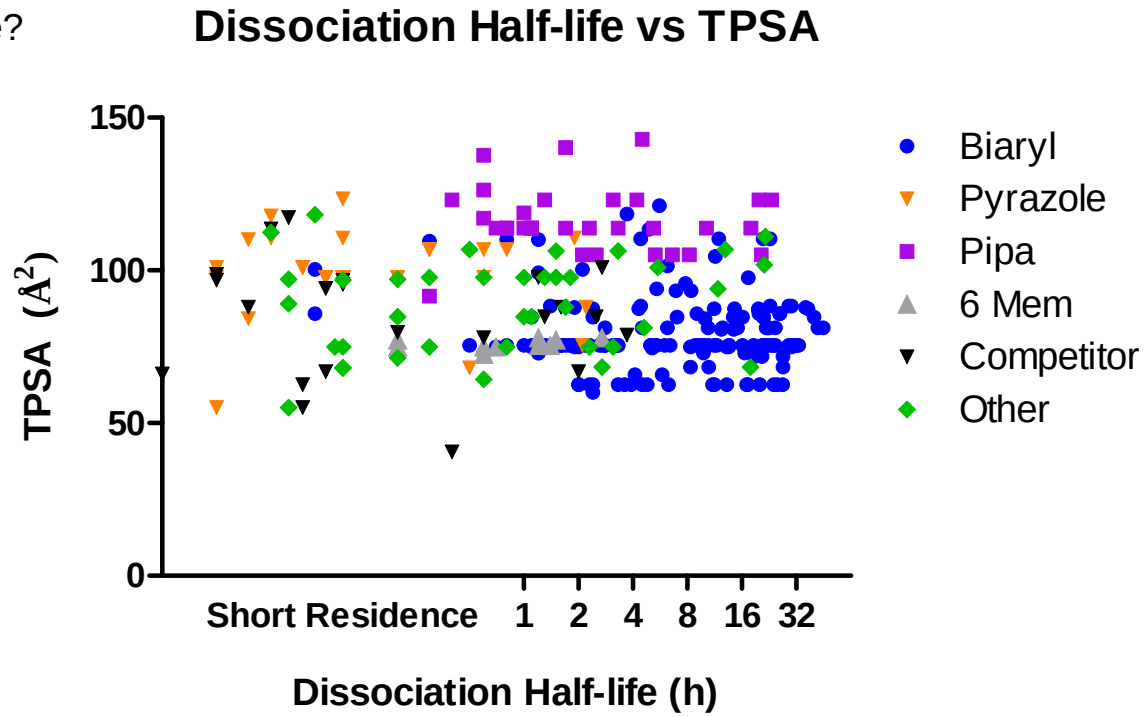
Almirall

Where is long Residence?

Are more polar molecules longer resident?



Is desolvation relevant here?



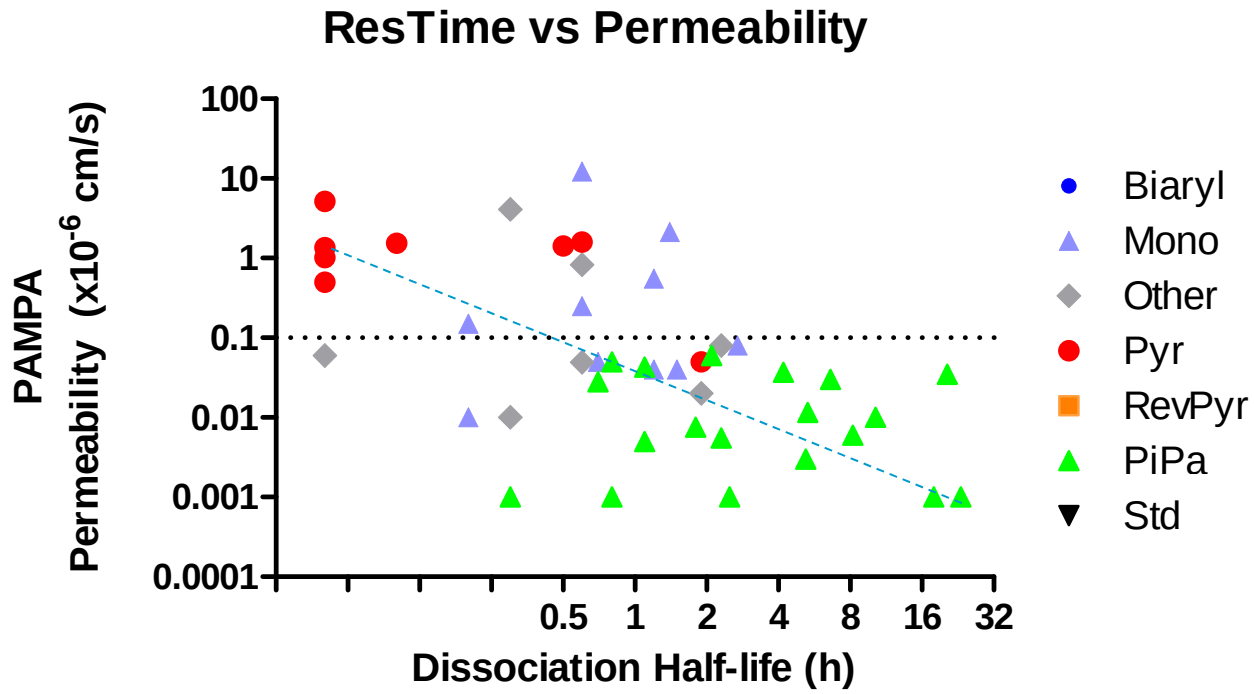
No.

Freedom to adapt polar surface area to modulate physicochemical properties

Almirall

Where is long Residence?

Are Impermeable compounds are Long Resident in CRTh2 ?

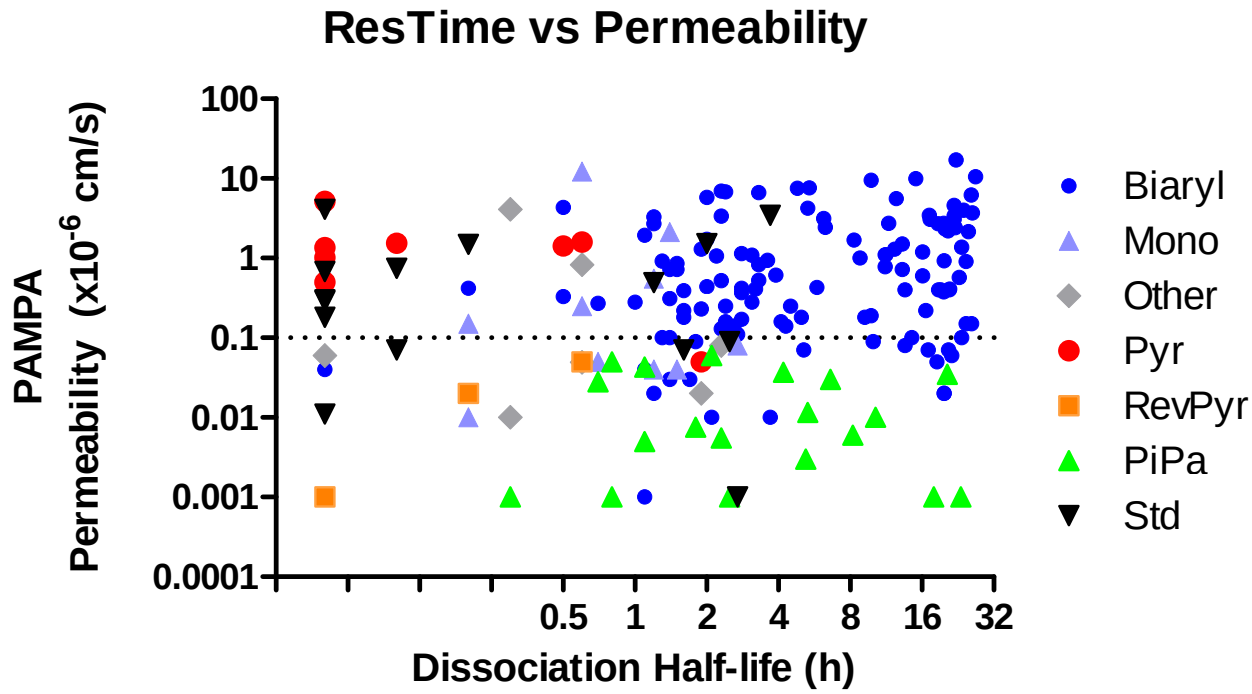


Not Intuitive

Almirall

Where is long Residence?

Are Impermeable compounds are Long Resident in CRTh2 ?



Not Intuitive
And ultimately not true

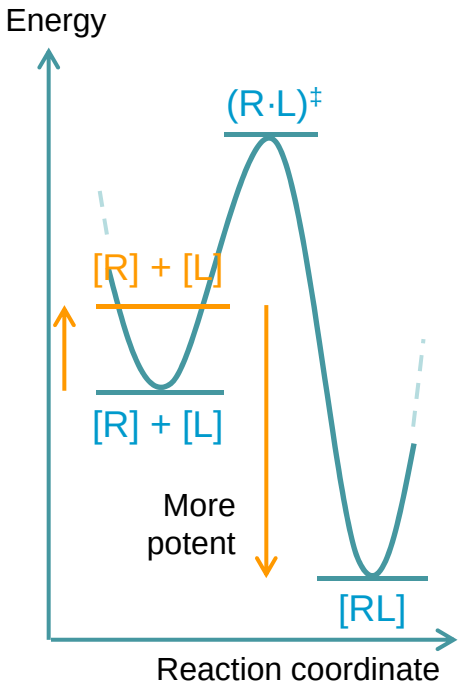
Initially looking at an incomplete picture

Design permeable compounds for oral delivery

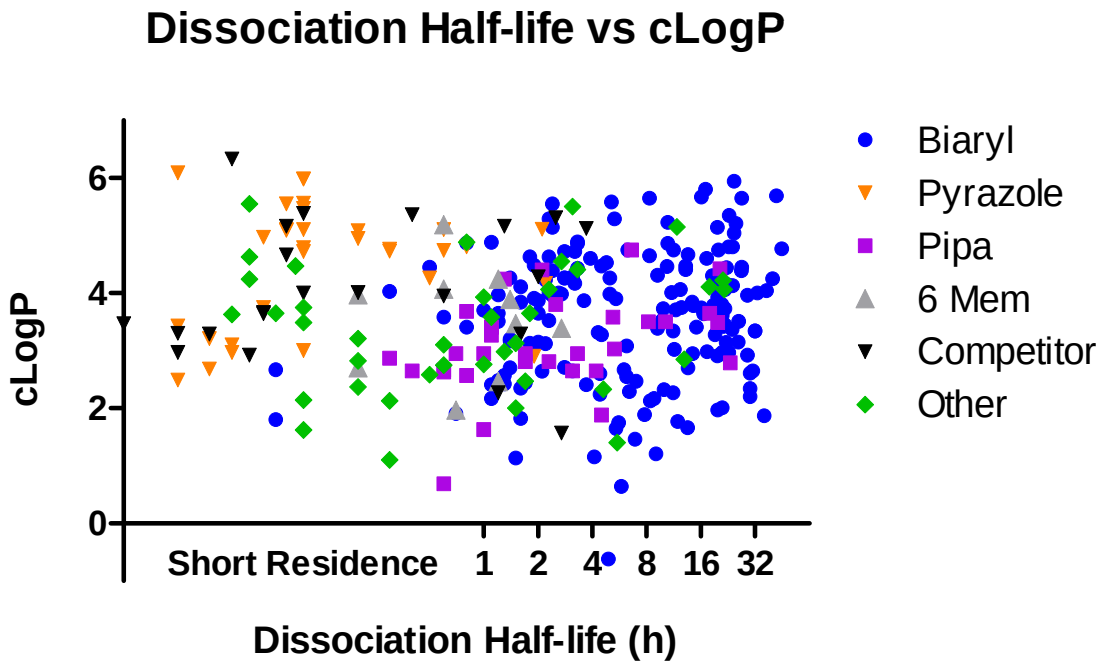
Almirall

Where is long Residence?

Are more lipophilic compounds longer resident?



Probably just pushes up
energy of [L] in free water



Lipophilic molecules are often more potent,

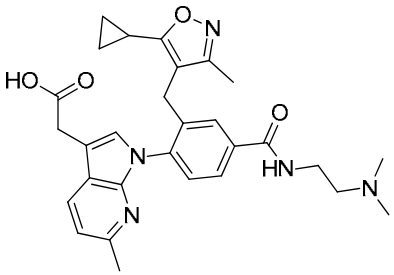
because once bound, the molecule doesn't want to go back into the surrounding water

Almirall

Where is long Residence?

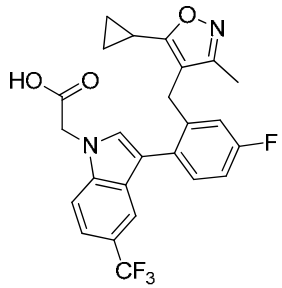
Are more lipophilic compounds longer resident?

Within particular sub-series, there was often a relationship



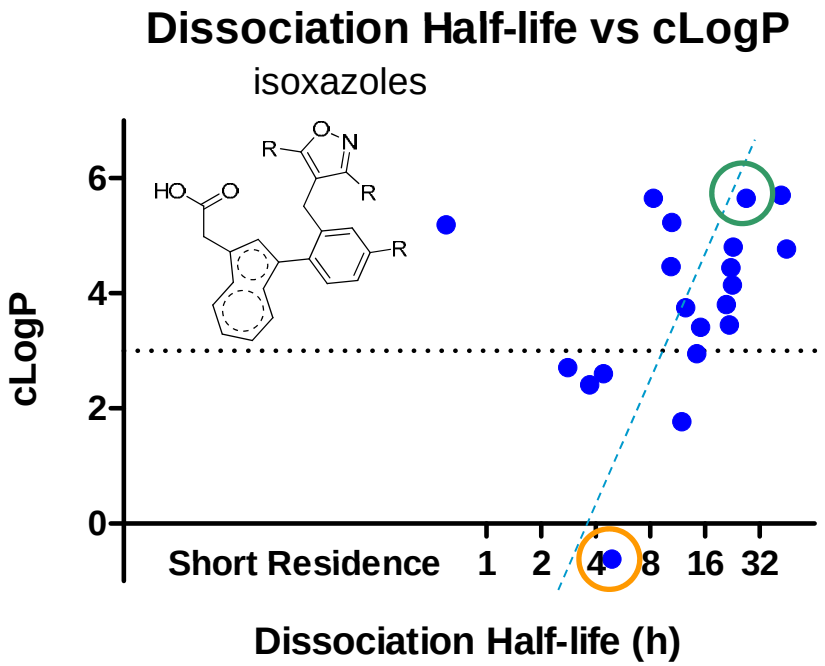
7-Azaindole

IC_{50}	21 nM
Diss t½	**5 h**
cLogP	**-0.6**



CF_3-Indole

IC_{50}	37 nM
Diss t½	**27 h**
cLogP	**5.9**



5-fold increase in Dissociation half-life

For a 1,000,000-fold increase in lipophilicity

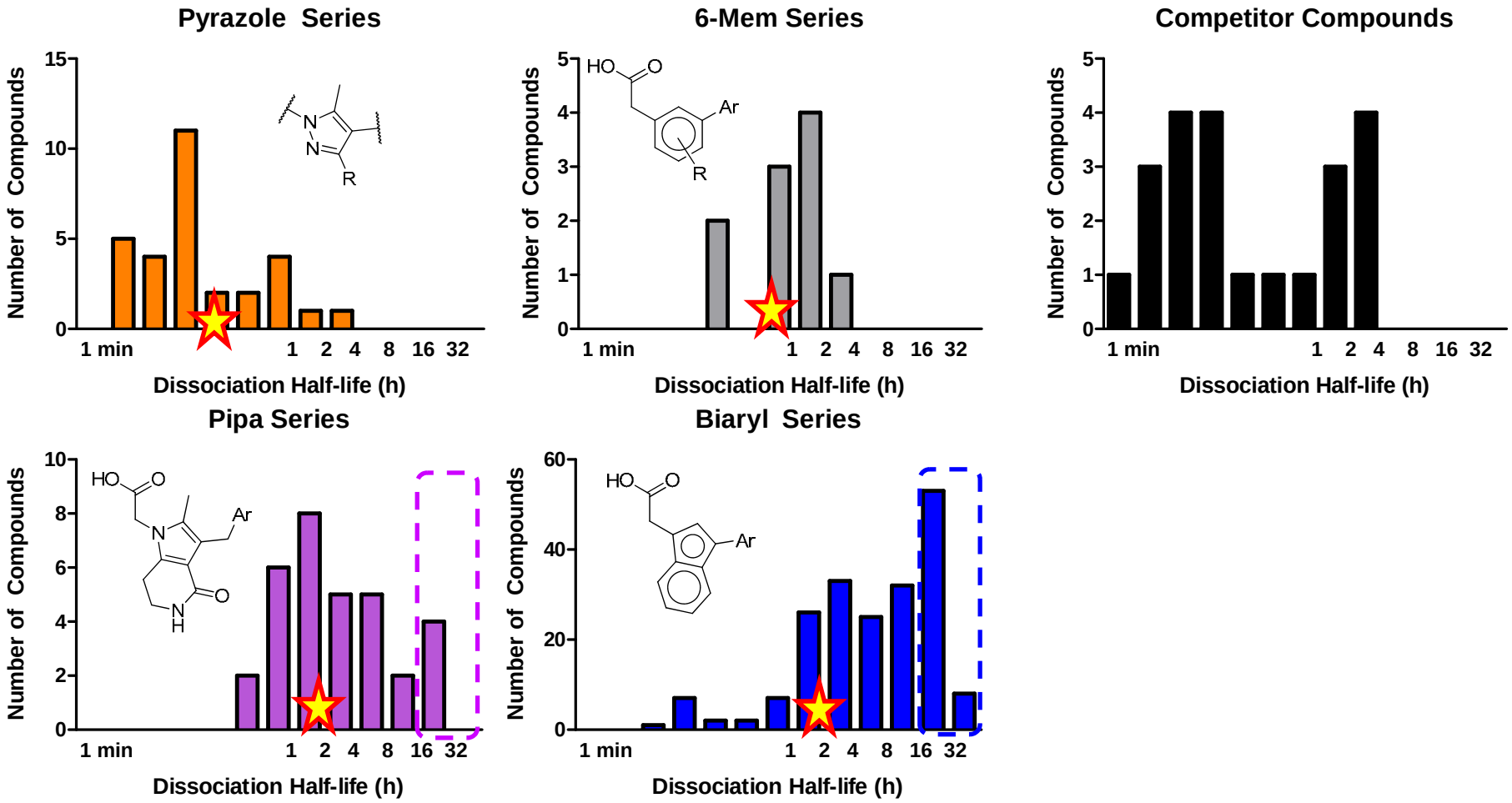
Workable in final optimisation, but not without its associated risks for oral delivery

Almirall

Where is long Residence?

Series by series

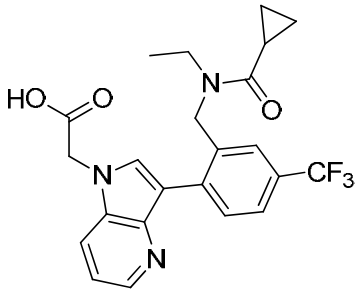
First example of series

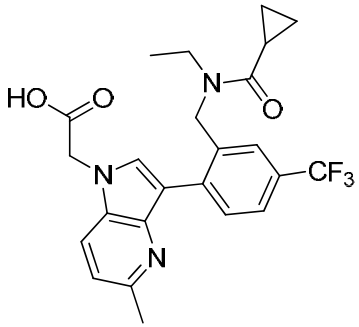


- **Chemical series drives Residence Time: If you've got it, you've got it and if you don't, you don't**
- **First compound of series dictates the trend.**

Almirall

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**

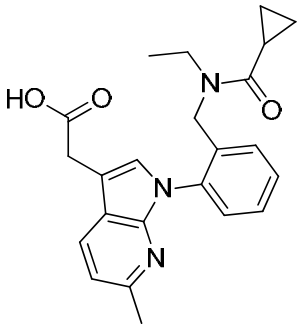
A Magic Methyl for SKR ?

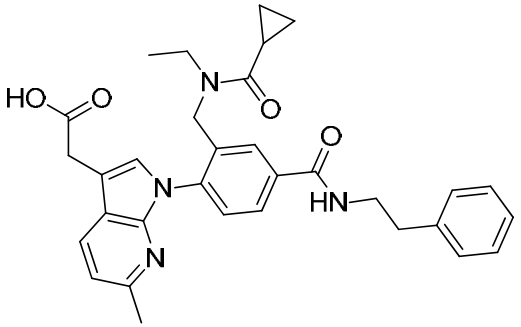
Almirall

Homing in on Residence Time in the Biaryl series

IC_{50} 5 nM

Dissociation half-life 9 h

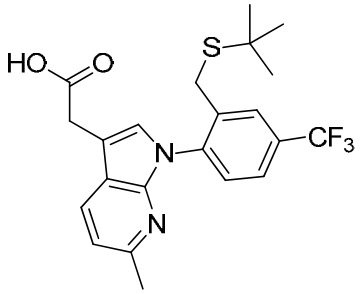


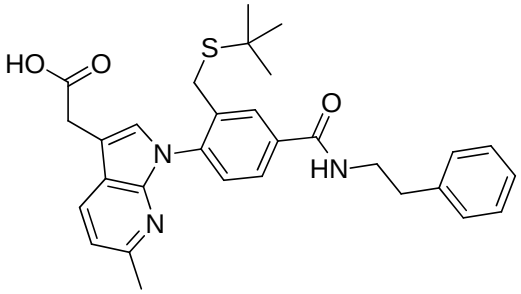


IC_{50} 8 nM

Dissociation half-life 11 h

inactive





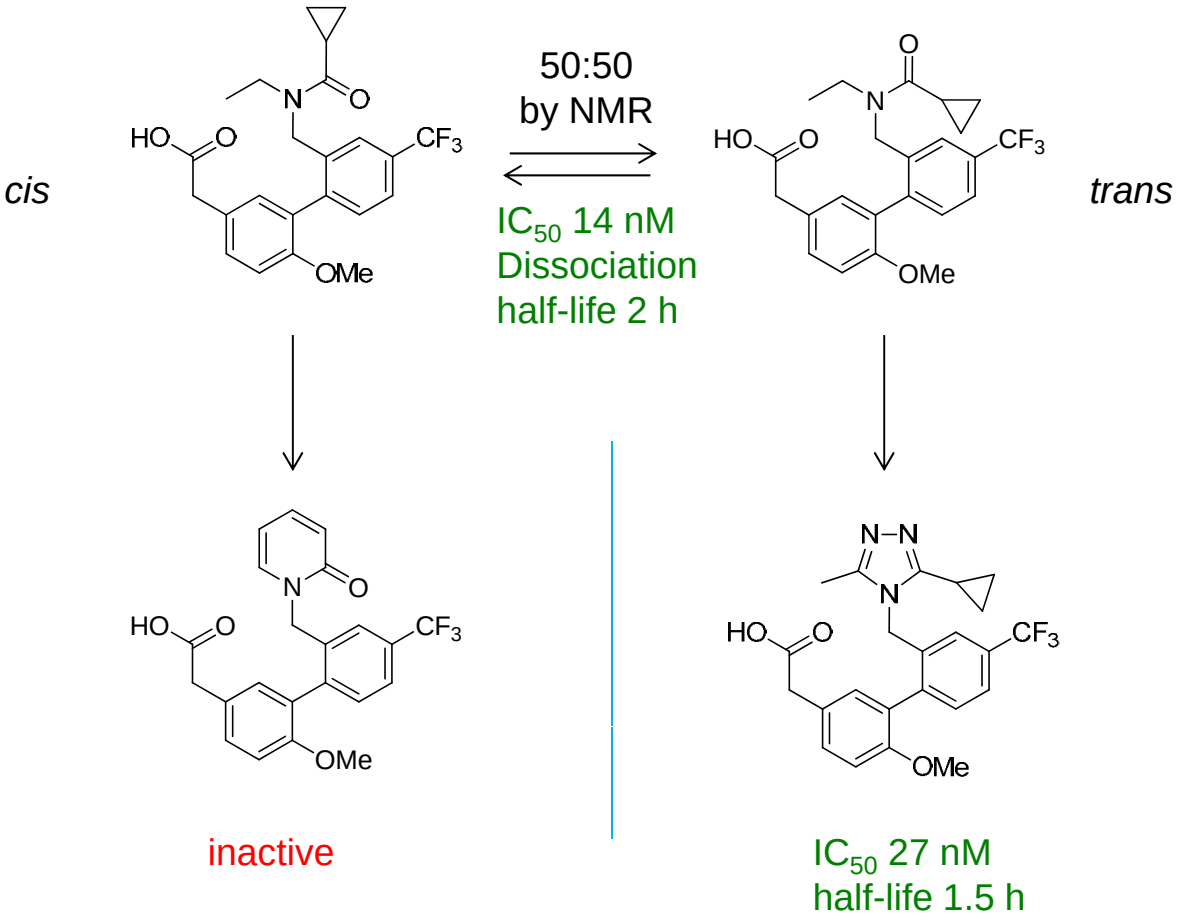
IC_{50} 4 nM

Dissociation half-life 25 min

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

Almirall

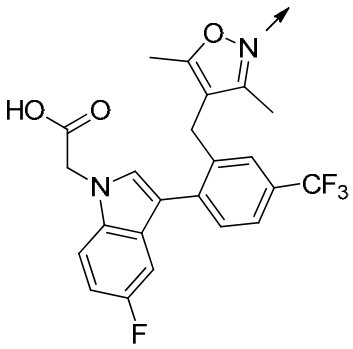
Amide Rotamers



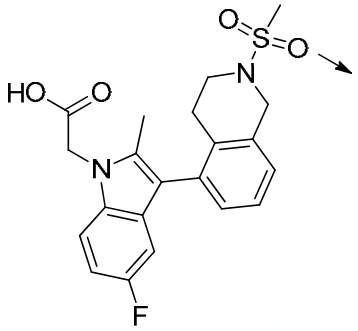
Long Residence Time in the Biaryls comes from an H-Bond Acceptor in a specific orientation

Almirall

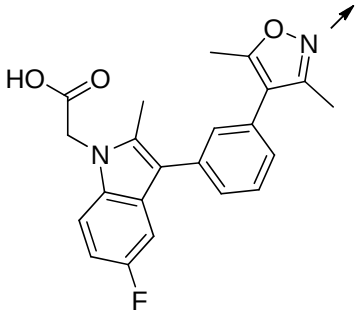
Can we check the H-Bond Acceptor location?



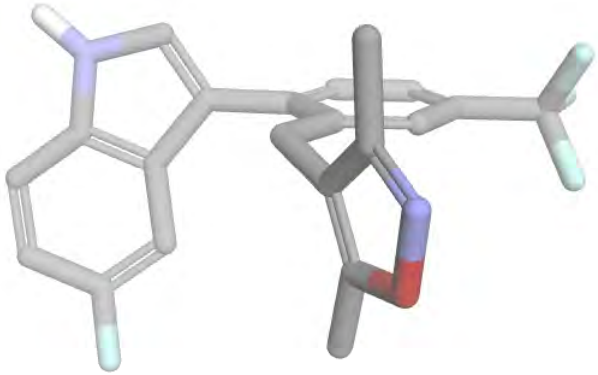
1

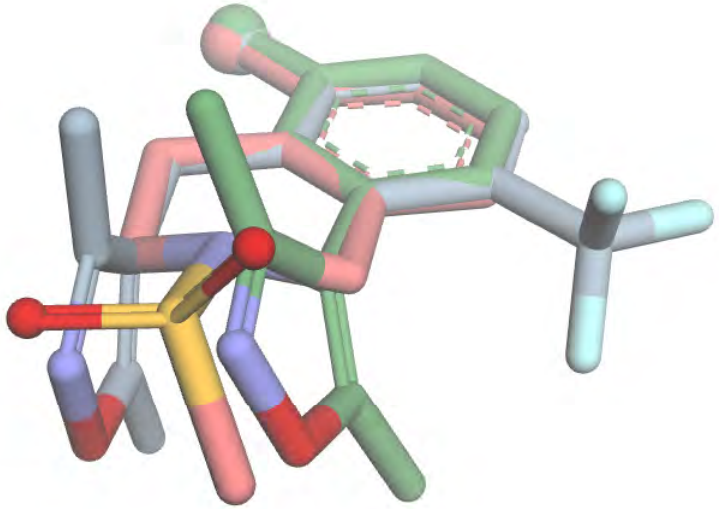


2



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**

Almirall

Can we achieve truly long residence?

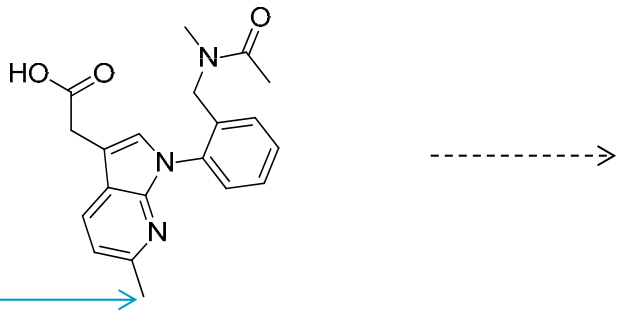
Position-by-position analysis of good structural features for Residence Time

Minimum expression of potency and long residence

3º amide as H-bond acceptor

Acetic acid

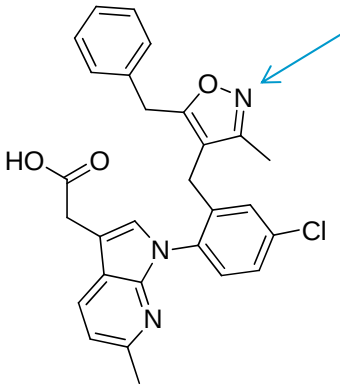
methyl stub



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

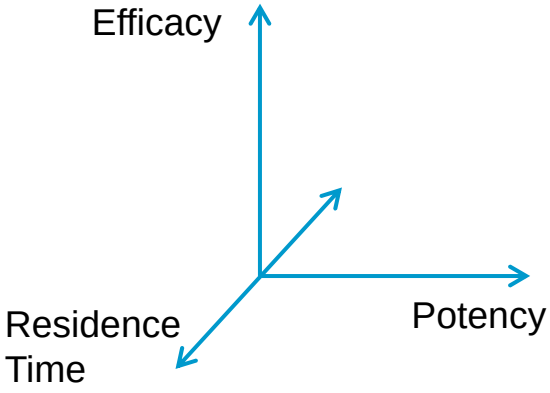
	Azaindole
GTPγS IC_{50} (nM)	**2.5 nM**
Dissociation t½ (h)	**46 ± 15 h**
cLogP	4.8
cLogD	2.4

Once-a-day purely from Residence Time ?

Almirall

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
- We are pretty good at explaining what's behind Structure-Activity Relationships (SAR)
  Structure-Kinetic Relationships (SKR) are in their infancy and/or qualitative
- To find Long Residence, you need to look for it



Acknowledgements

Medicinal Chemistry
Juan Antonio Alonso
Mª Antonia Buil
Oscar Casado
Marcos Castillo
Jordi Castro
Paul Eastwood
Cristina Esteve
Manel Ferrer
Pilar Forns
Elena Gómez
Jacob González
GalChimia
Sara López
Marta Mir
Imma Moreno
Sara Sevilla
Bernat Vidal
Laura Vidal
Pere Vilaseca

ADME
Manel de Luca
Peter Eichhorn
Laura Estrella
Dolores Marin
Juan Navarro
Montse Vives
Miriam Zanuy

Respiratory Therapeutic Area
Mónica Bravo
Marta Calbet
José Luís Gómez
Encarna Jiménez
Martin Lehner
Isabel Pagan

Biological Reagents and Screening
Fani Alcaraz
Miriam Andrés
Julia Díaz
Teresa Domènech
Vicente García
Rosa López
Adela Orellana
Sílvia Petit
Israel Ramos
Enric Villanova

Integrative Pharmacology
Clara Armengol
Laia Benavent
Luis Boix
Elena Calama
Amadeu Gavaldà
Beatríz Lerga
Sonia Sánchez

Computational and Structural Chemistry and Biology
Sandra Almer
Yolanda Carranza
Sònia Espinosa
Estrella Lozoya

Pathology and Toxicology
Ana Andréa
Mariona Aulí
Cloti Hernández
Neus Prats

Development
Cesc Carrera
Nieves Crespo
Juan Pérez Andrés
Juan Pérez García
Gemma Roglan
Francisco Sánchez
Carme Serra

Intellectual Property
Houda Meliana
Eulàlia Pinyol

Management
Paul Beswick
Jordi Gràcia
Victor Matassa
Monste Miralpeix