Examples for Recent Successes in Drug Discovery

Torsten Hoffmann, September 25-29, IASOC 2010



A Brief Look Back

The Way We Work Today

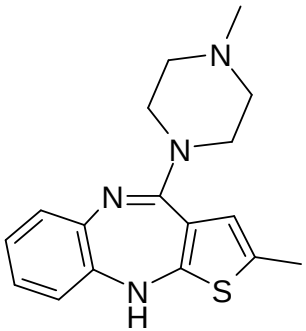
Outlook Into Our Future

How Were Benzodiazepines Discovered?
"The Benzodiazepine Story", Leo Sternbach

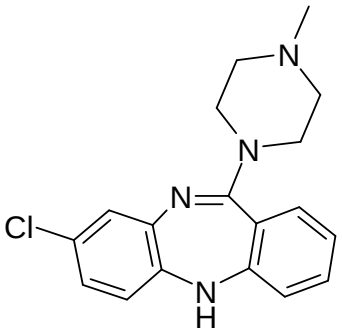
- 1955: Tranquilizers showed considerable clinical value
- Produce a novel, patentable compound with superior properties
- Pharmacological effects of Librium first discovered in animals in May 1957
- ca. 15'000 patients treated by 1960
- NDA submitted in 1960
- Valium as "second generation" was introduced in 1963

Another Complication: Polypharmacology

Receptor binding (K_i [nM]) olanzapine and clozapine



Olanzapine



Clozapine

	Olanzapine	Clozapine
D_1	31	85
D_2	11	125
D_4	27	21
$5HT_{2A}$	4	12
$5HT_{2C}$	11	8
$5HT_3$	57	69
m_1	1.9	1.9
m_2	18	10
m_3	25	14
m_4	13	18
α_1	19	7
α_2	230	8
H_1	7	6

[F.P. Bymaster et al., Neuropsychopharm. 1996, 14, 87-96]



'That's Dr Arnold Moore. He's conducting an experiment to test the theory that most great scientific discoveries were hit on by accident.'

Drawing by Hoff; © 1957
The New Yorker Magazine, Inc.

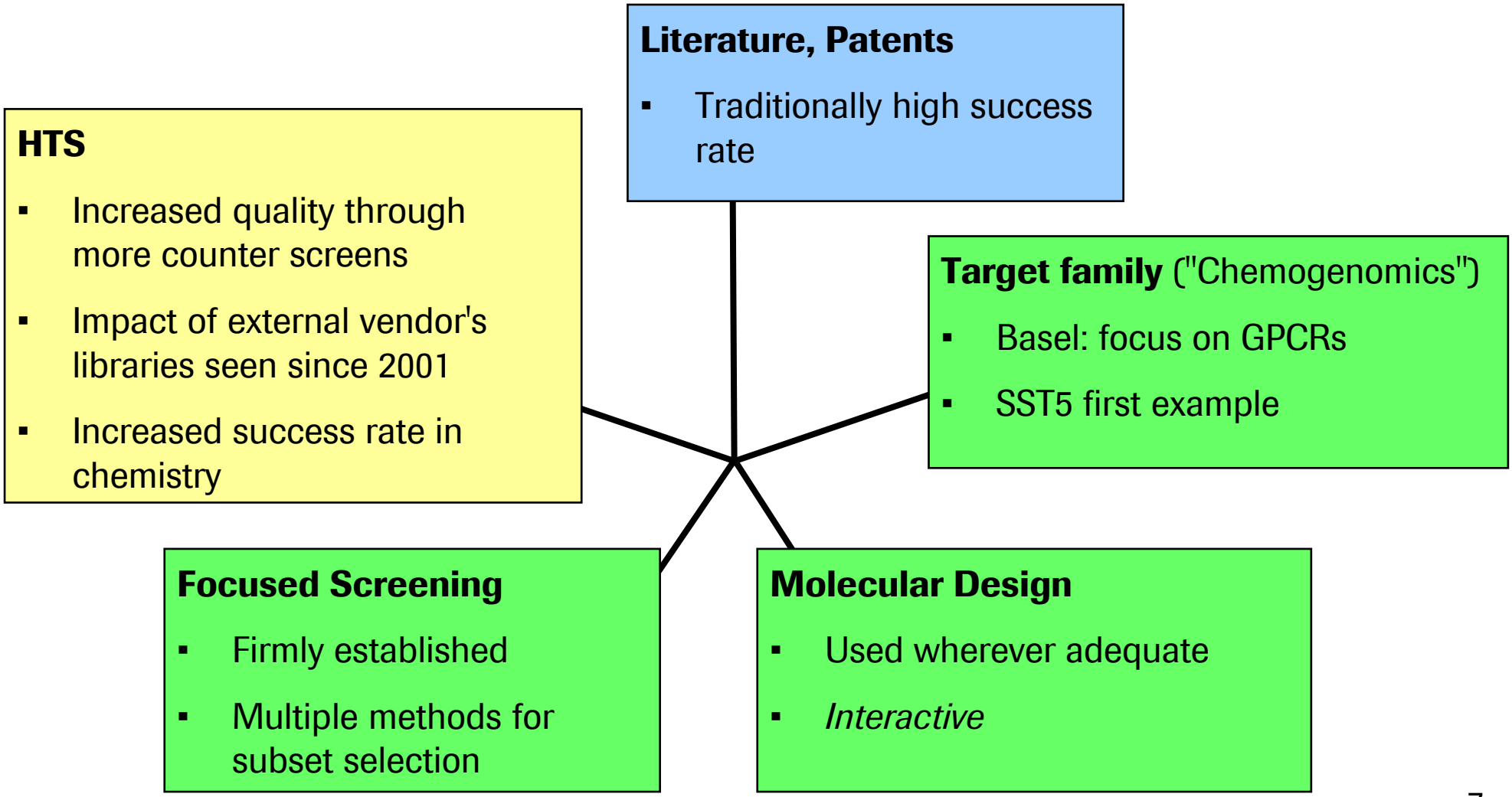
A Brief Look Back

The Way We Work Today

Outlook Into Our Future

Identification of Entry Points in Chemistry

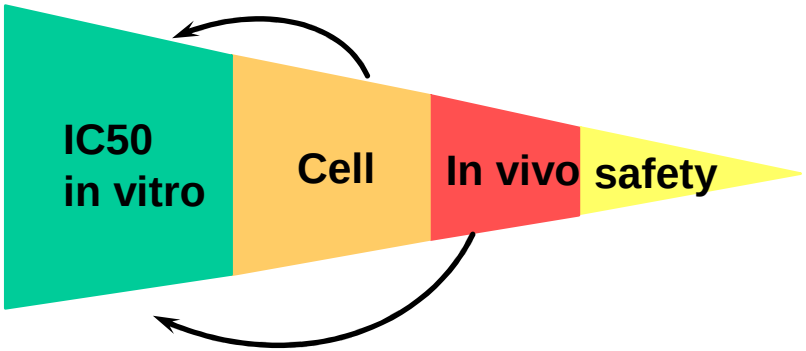
All methods used in an unbiased manner



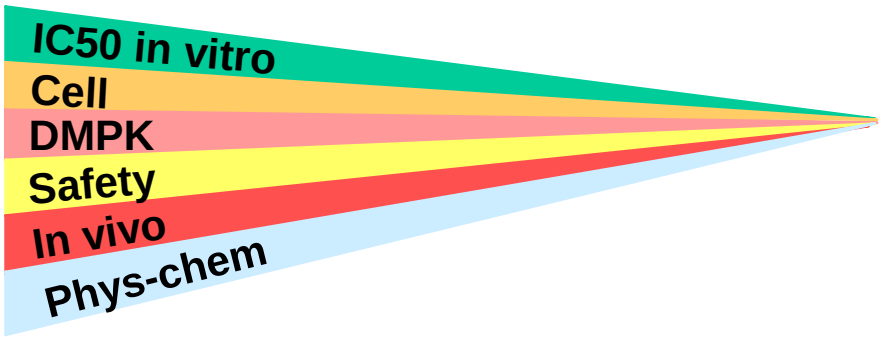
The Way We Work

The multidimensional optimization concept

Sequential Testing



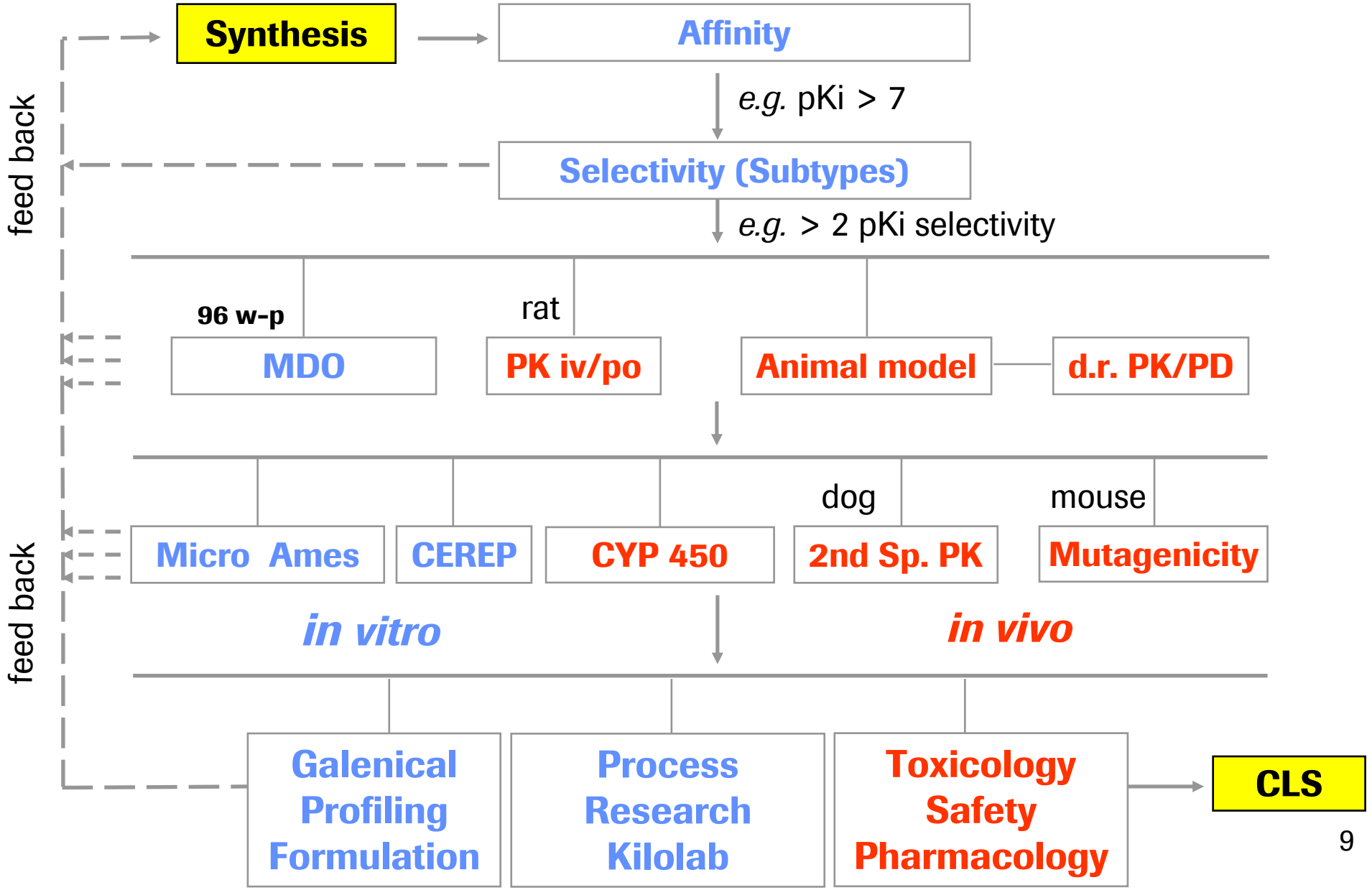
Parallel Multiobjective ("MDO")



Increased productivity through

- Addressing key issues early
- Avoiding optimization dead-ends
- Saving cost

Typical, Iterative and Parallel Screening Cascade



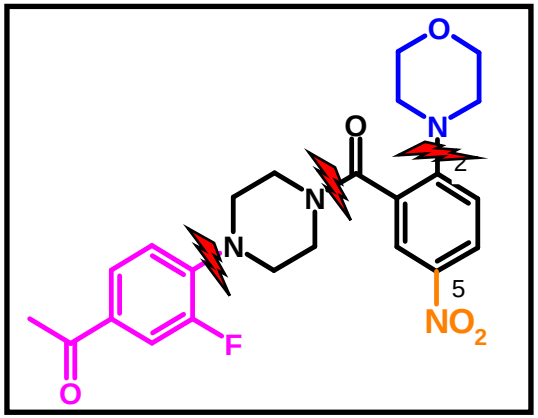
RG1678: A Potent and Selective GlyT1 Inhibitor for the Treatment of Schizophrenia

Antipsychotic treatment with the potential to improve both, positive and negative symptoms in schizophrenia patients



Benzoylpiperazine Hit identified through HTS

A good starting point



hGlyT1 EC_{50} [µM]	0.015

Selectivity

hGlyT2 EC_{50} [µM]	5

Physico-chemical properties:

LogD	2.36
Solubility [µg/ml]	9
PAMPA [10^{-6}cm/s]	4.7

Metabolic Stability:

Cl. (mic.) [µl/min/mg], Human	35
Cl. (mic.) [µl/min/mg], mouse	106

DMPK, mouse:

Cl. (i.v.) [ml/min/kg]	66
F (%)	10

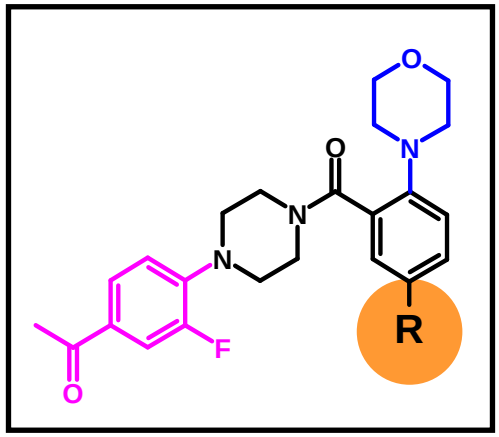
In Vivo, L687,414, mouse

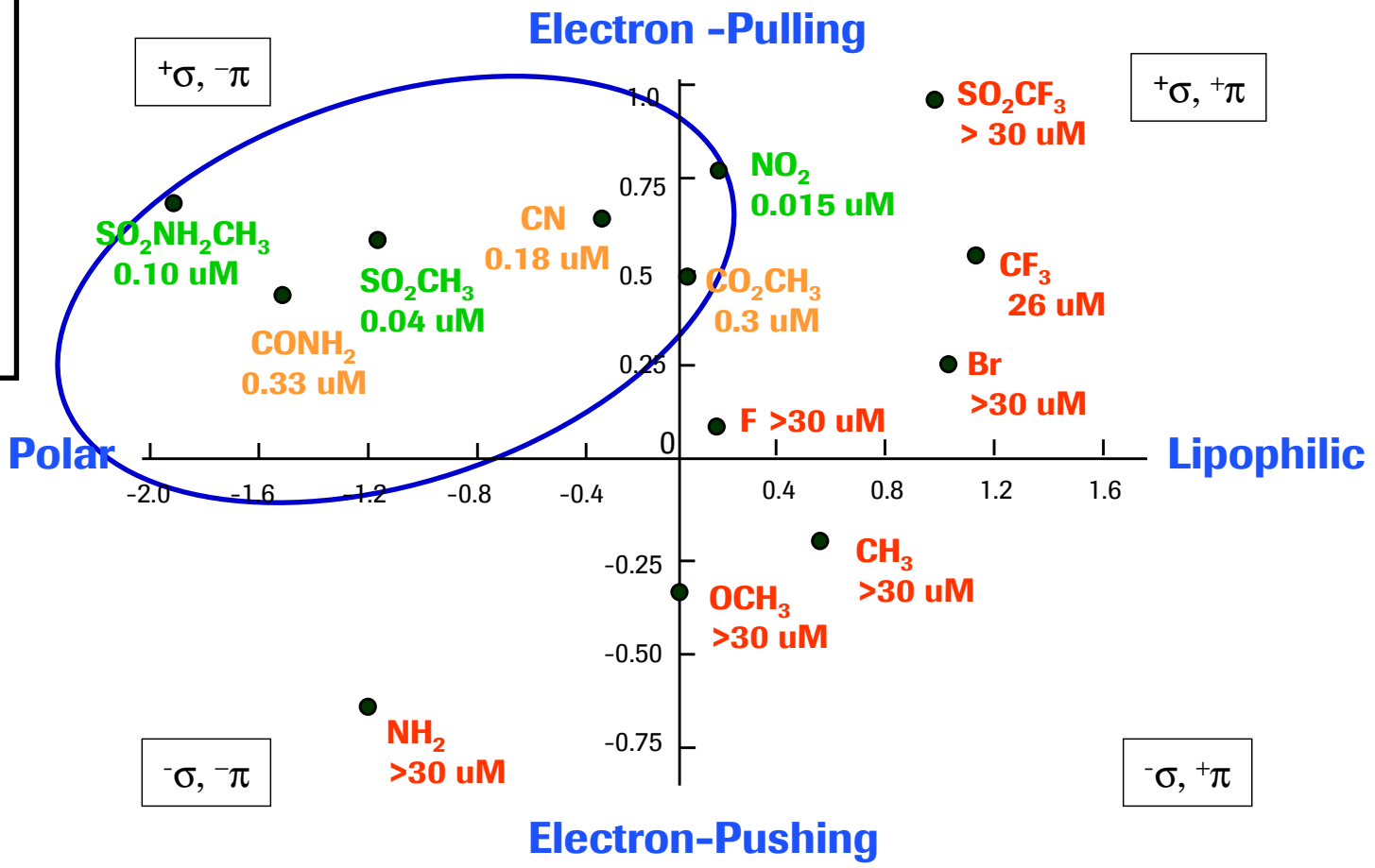
ID50 (mg/kg) **ip**	20

- ✓ **High GlyT1 potency**
- ✓ **Simple structure– Fast chemistry**
- ✓ **Overall, attractive profile**
- × **Nitro Group (potential for mutagenicity)**
- × **High metabolic clearance / Low F%, No oral activity**

Finding a Replacement for the Nitro Group

Best surrogate identified: methylsulfone

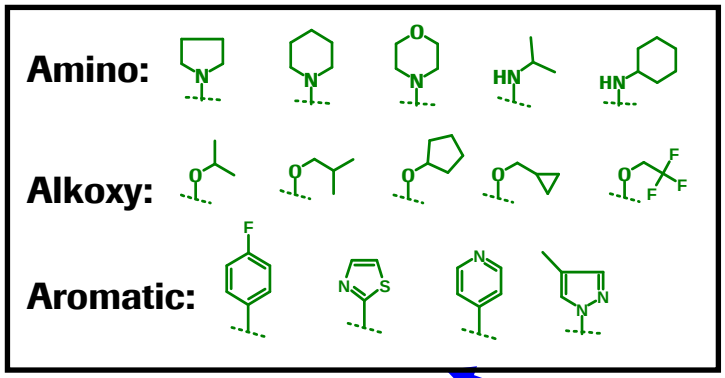




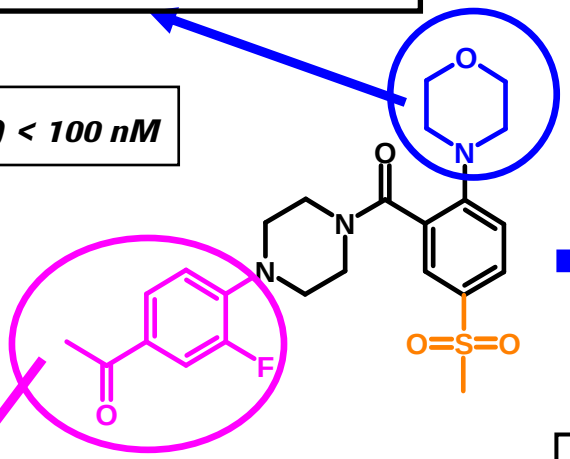
hGLYT1 EC50

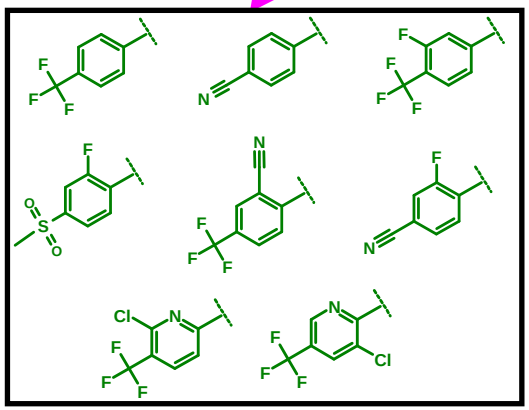
Exploration of SAR at morpholine and western Ar ring

Large scope; Best profiles with alkoxy derivatives



: GlyT1 (EC_{50}) < 100 nM





In vitro MDO profiling

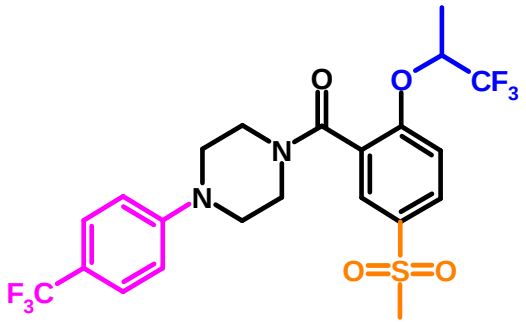
- Solubility
- Permeability
- Microsomal clerance
- Cyp

In vivo profiling

- L-687,414 (mouse)

(In house discovered model)

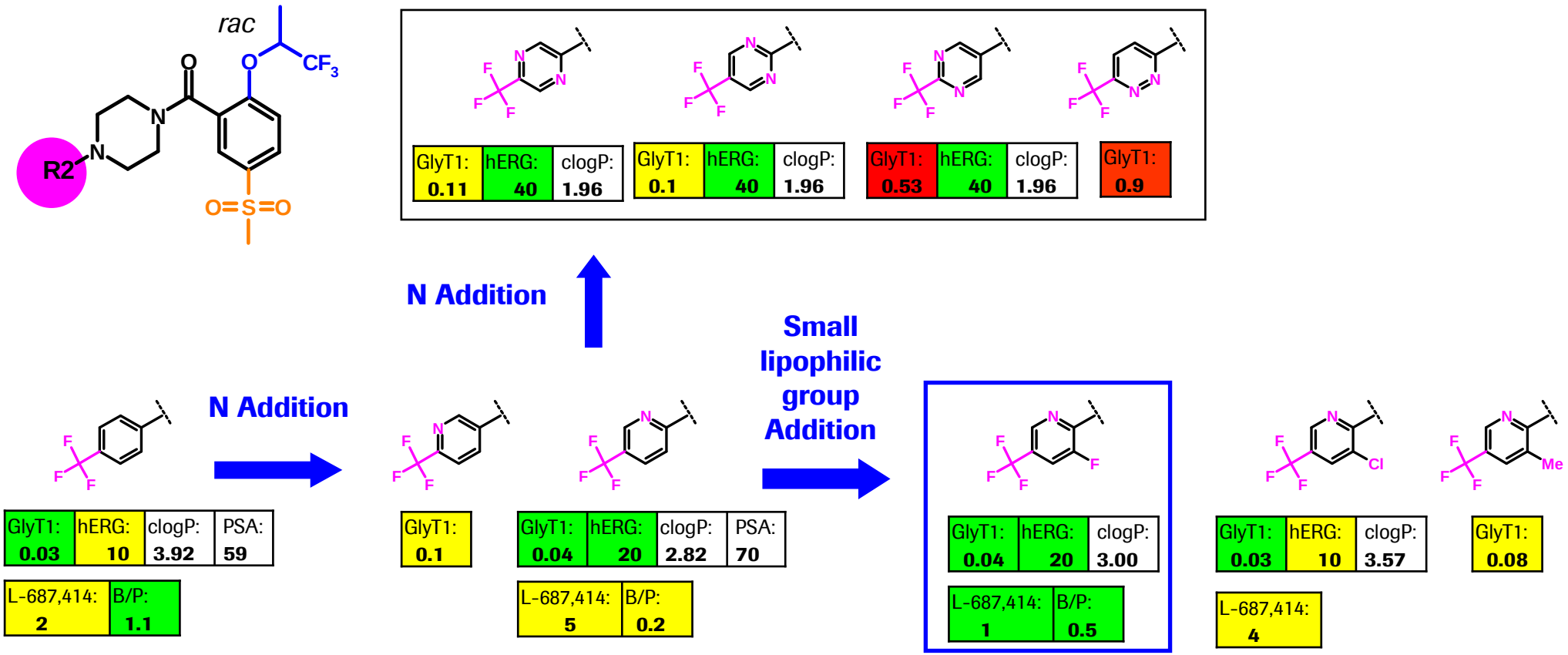
Lead series: Alkoxy methyl sulfone



- ✓ Good overall physico-chem. properties
- ✓ High metabolic stability
- ✓ Oral activity- Bioavailability
- ✓ No Cyp and off target activity (CEREP)
- ✓ Patentable scaffold

Optimization of hERG and oral in vivo activity

Heteroaromatic switch and Fluorine addition



- ✓ **Aryl to Heteroaryl switch reduces hERG**
- ✓ **Beneficial effect of Fluorine on brain penetration / in vivo activity**
- ✓ **Great and optimal profile with 3-F, 5-CF_3 pyridine-piperazine fragment**

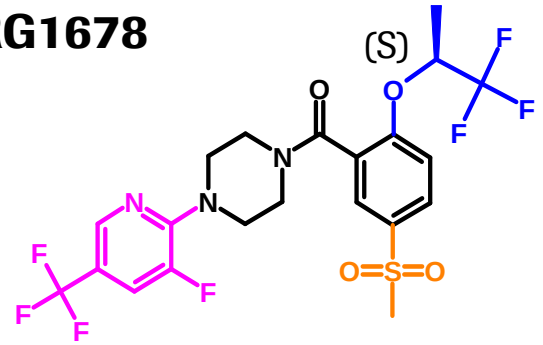
RG1678

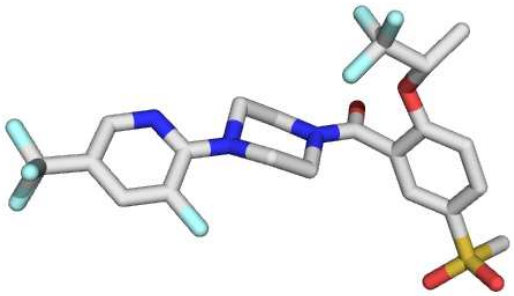
An excellent overall profile

in vitro potency, and selectivity

GLYT1 EC_{50} [µM]	0.03
GLYT2 EC_{50} [µM]	>30
Cerep: 92 receptors, at 10 µM	Clean

RG1678





Physico-chemical properties:

LogD	3.03
Aqueous solubility [µg/ml]	1
FaSSIF solubility [µg/ml]	20
FeSSIF solubility [µg/ml]	60
PAMPA [10^{-6} cm/s]	3.2

In vitro safety profile

Cyps IC_{50} [µM]	>24
hERG IC_{50} [µM]	17
Genotox assays: Ames, MNT	Neg.
Phototoxicity	Neg.

PK properties:

	Rat	Cyno	Human
CL. (i.v.) [ml/min/kg]	4.3	3.6	1*
Vss (L/Kg)	3.58	1.98	3.6*
T1/2 (h)	5.8	6.4	40*
F (%)	78	56	
Brain/Plasma	0.7		
Protein Binding	97	97	98

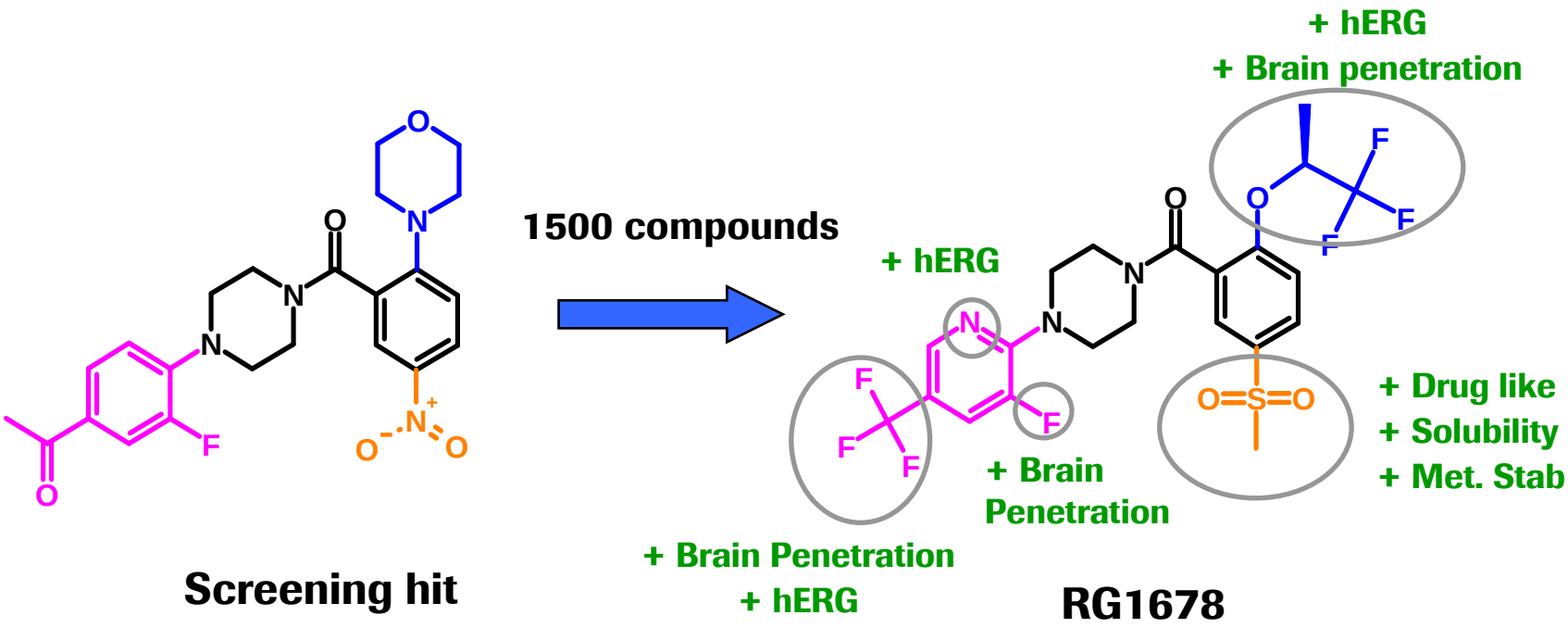
In Vivo

* predicted

L-687,414, ID_{50} mg/kg	0.5
Fold increase glycine 10 mg/kg po	2.3

RG1678

A highly optimized GlyT1 inhibitor



✓ **Each group has specific role and contribute to the overall excellent compound profile**

RG1678

First potent and selective, clinically efficacious GlyT1 inhibitor

- **Phase I in healthy volunteers:**
  - Safe and well tolerated
  - Excellent PK profile

- **Phase II in schizophrenic patients stabilized with antipsychotics with prominent negative symtoms:**
  - Safe and well tolerated
  - Positive Phase II results annonced in Nov. 2009:

  RG1678 improved the negative symptoms of patients with schizophrenia

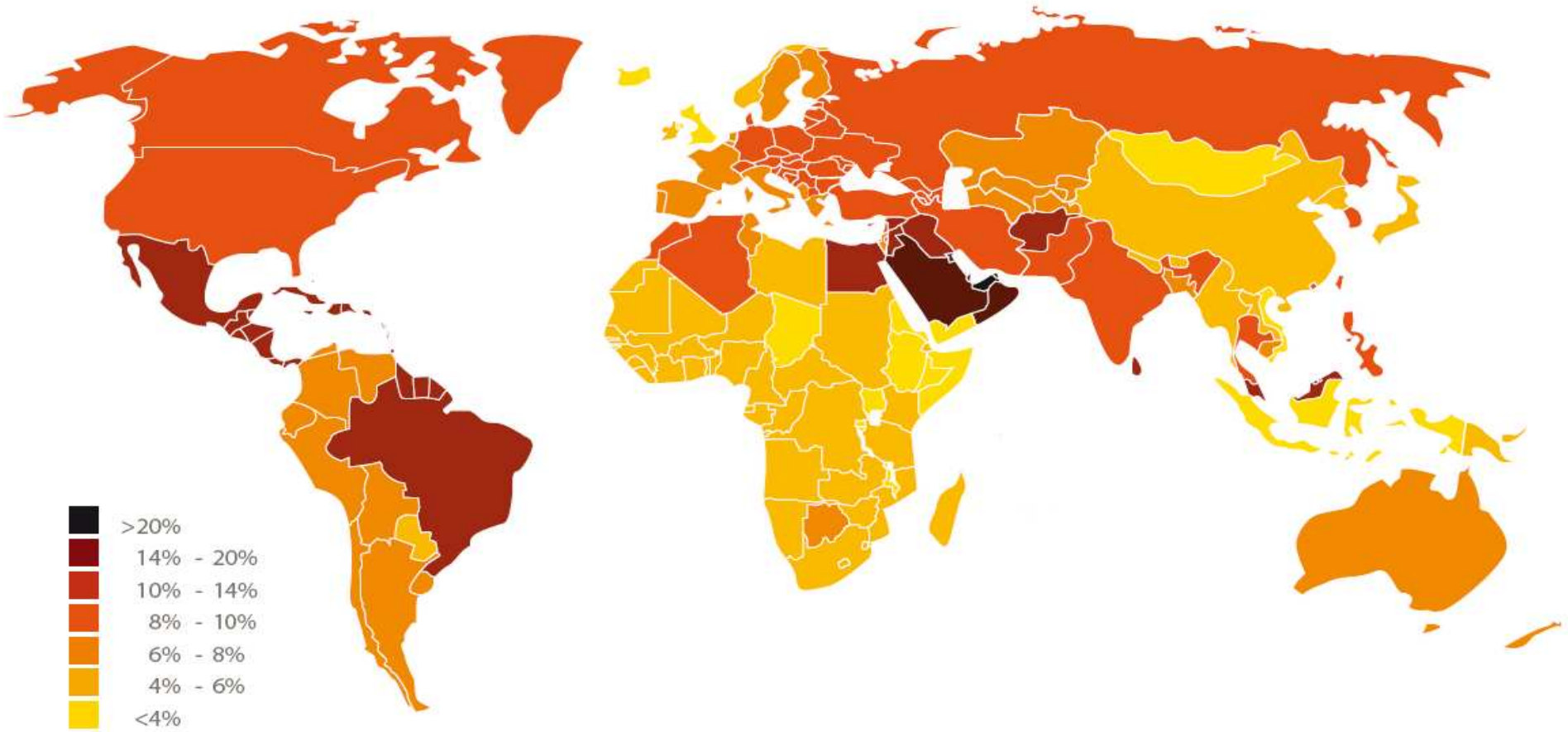
- **Phase III scheduled for 2010**

ALEGLITAZAR, A POTENT AND BALANCED DUAL PPARα/γ AGONIST FOR THE TREATMENT OF TYPE II DIABETES

Combine the fuel storing and insulin sensitizing effect of PPARγ with the fuel burning, lipid modulating effect of PPARα



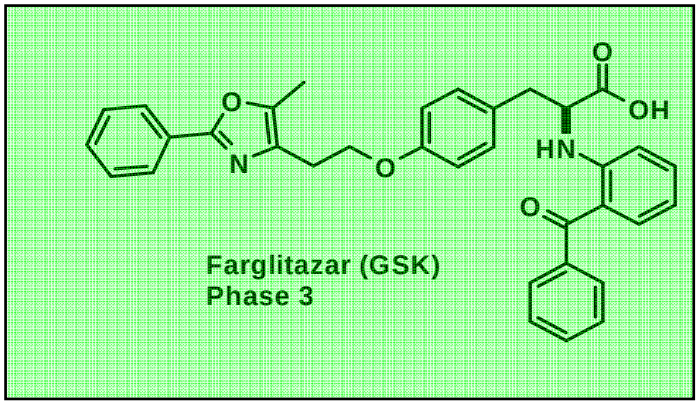
Prevalence estimates of diabetes, 2025

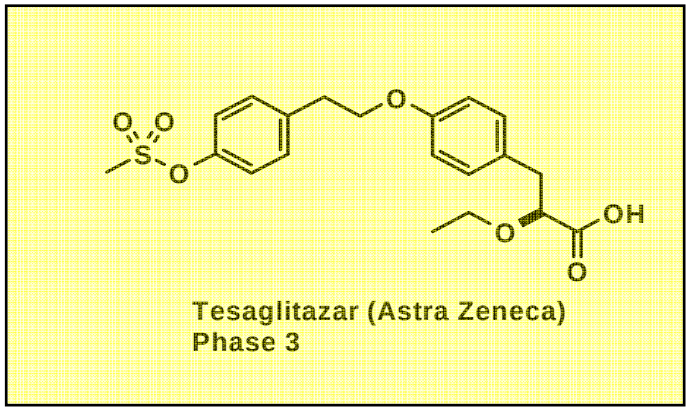


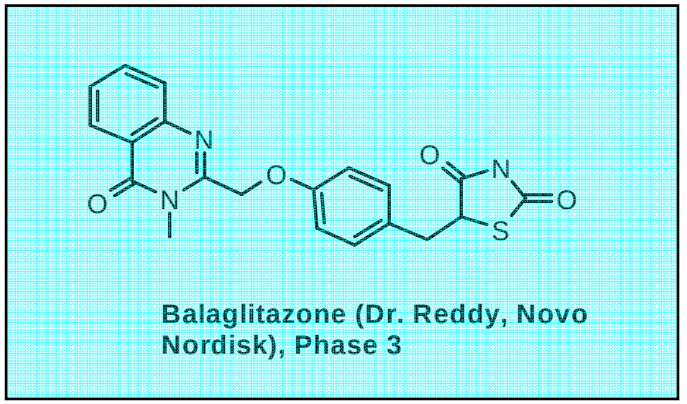
SOURCE: *DIABETES ATLAS THIRD EDITION,* © INTERNATIONAL DIABETES FEDERATION, 2006

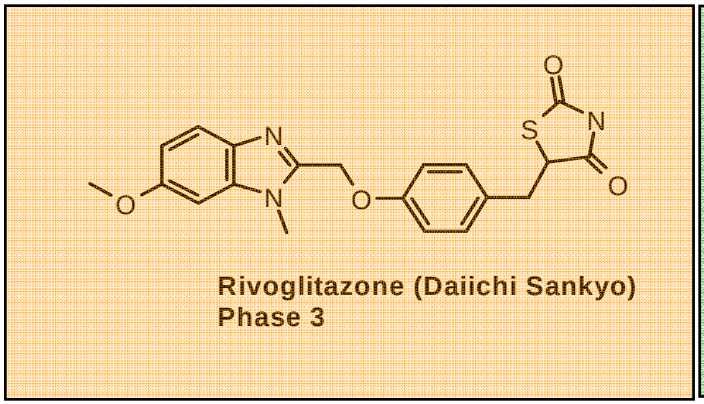
Adapted from Diabetes Atlas, third edition, International Diabetes Association, 2006

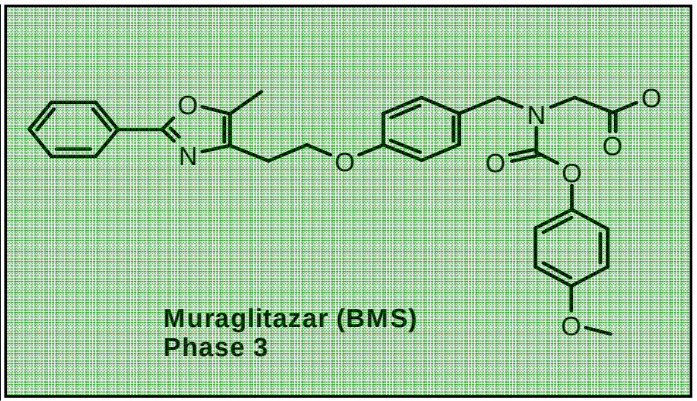
Competitive Landscape

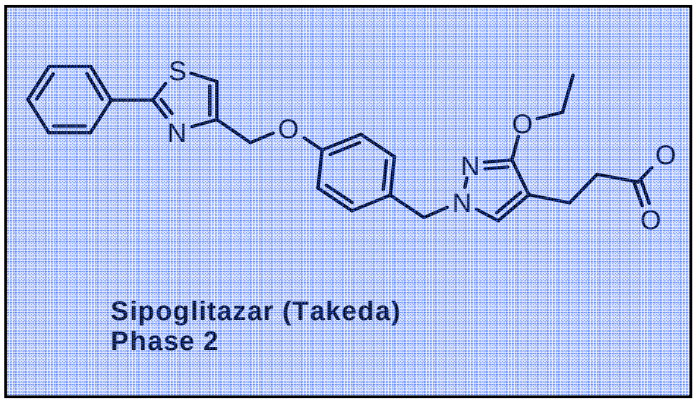




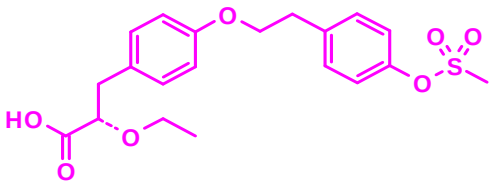








X-Ray Guided Rational Design



PPARα
AZ242=Tesaglitazar
IC_{50} α/γ/δ [nM] 653/345/>10^4

hPPARα / AZ242 x-ray

His 440 (helix-11, PPARα)

Tyr 314 (helix-5, PPARα)

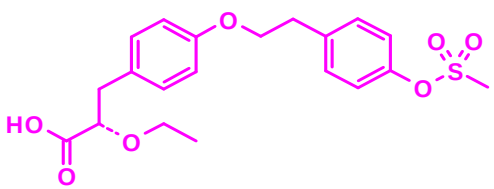
Tyr 464 (AF2 helix, PPARα)

Molecular recognition of carboxylate

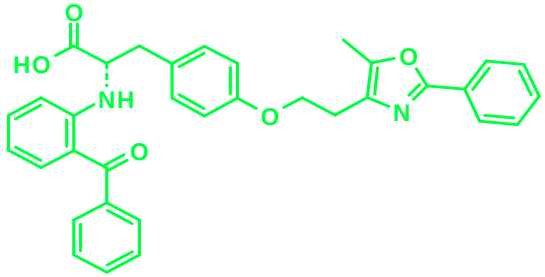
"Banana"-like shape of binding site

X-Ray Guided Rational Design

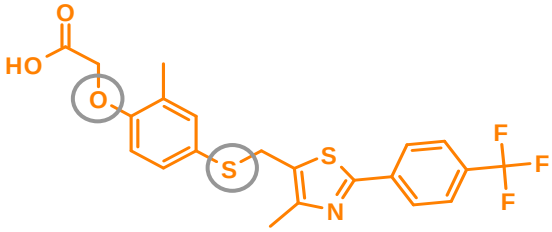
PPARα
AZ242=Tesaglitazar
IC_{50} α/γ/δ [nM] 653/345/>10^4



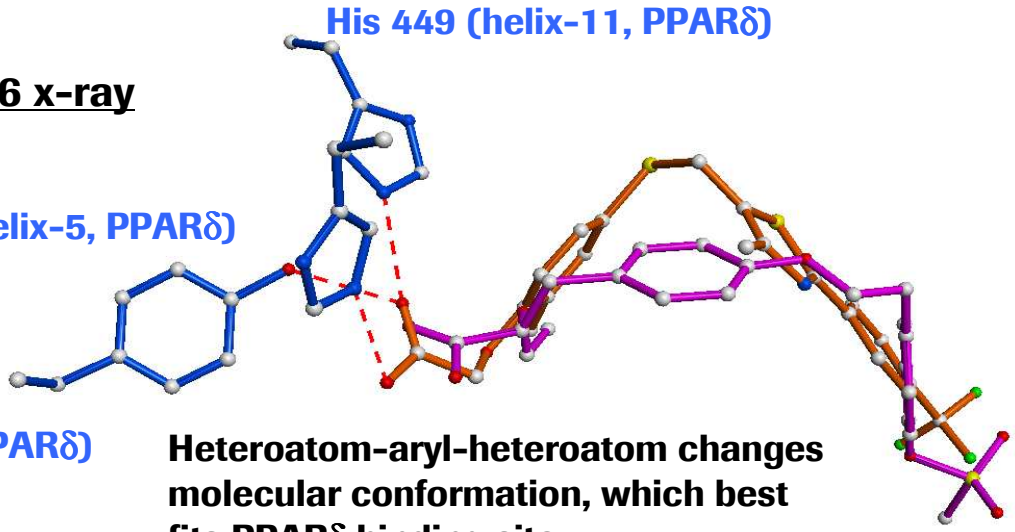
PPARγ
GW2570=Farglitazar
IC_{50} α/γ/δ [nM] 341/1/471



PPARδ
GW501516
IC_{50} α/γ/δ [nM] 133/>10^4/1



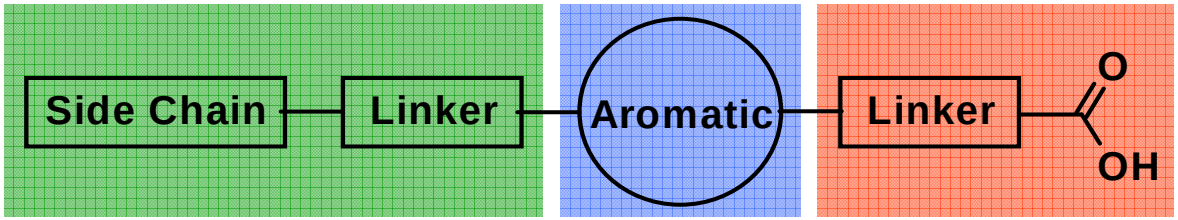
hPPARδ / GW1516 x-ray

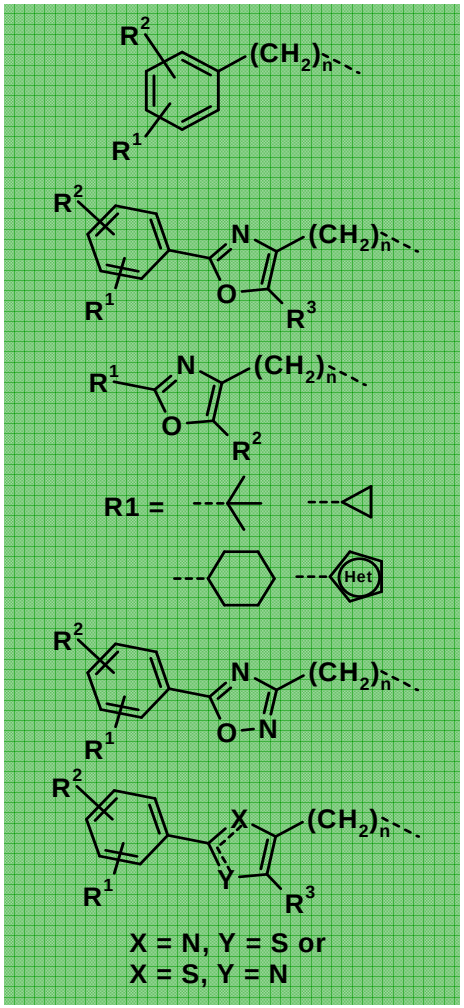


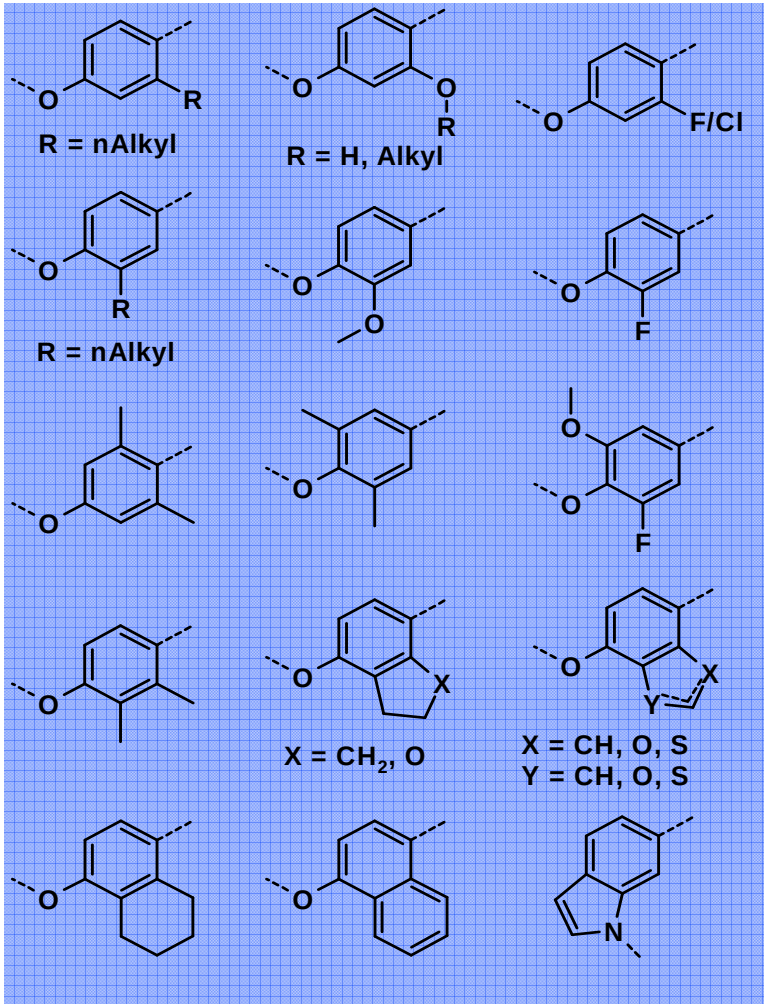
Heteroatom-aryl-heteroatom changes molecular conformation, which best fits PPARδ binding site

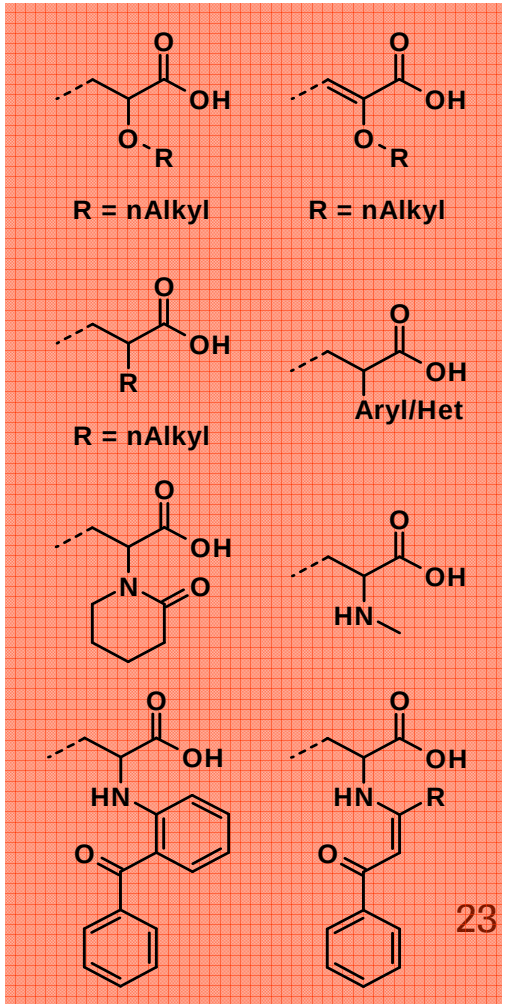
Several residue differences in the ligand binding pocket affect substructure selectivity

Modeling Supported Synthetic Strategy



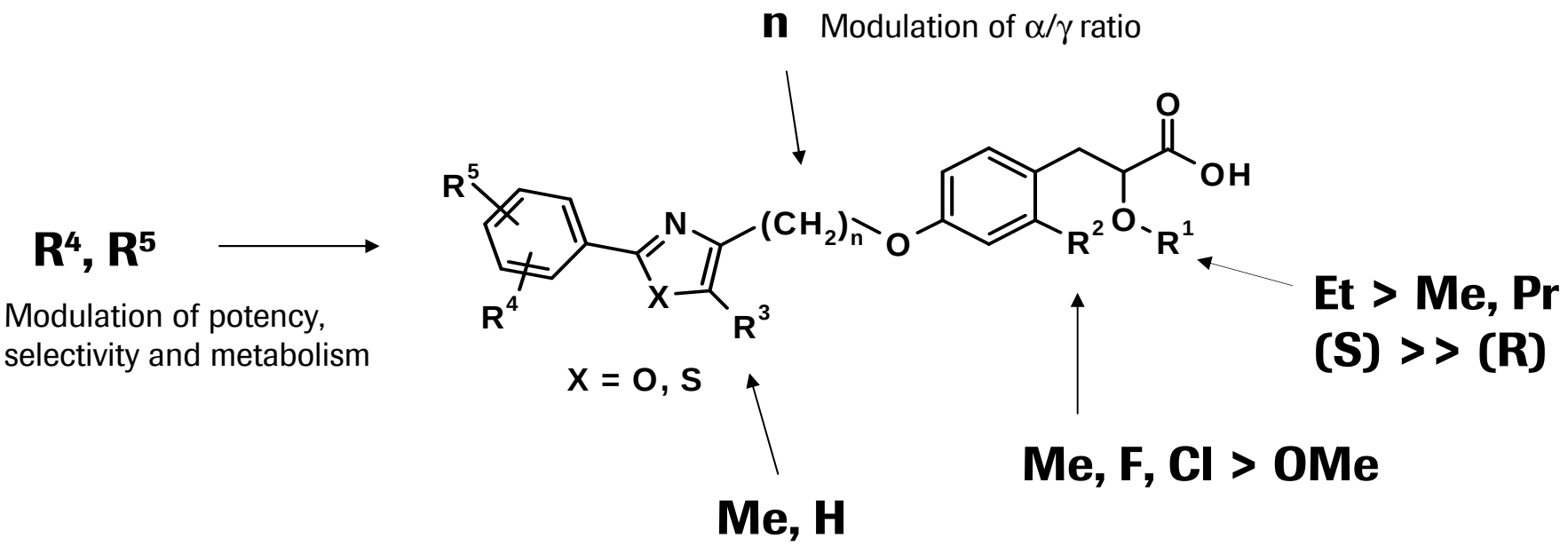






o-Substituted Phenylpropionic Acids

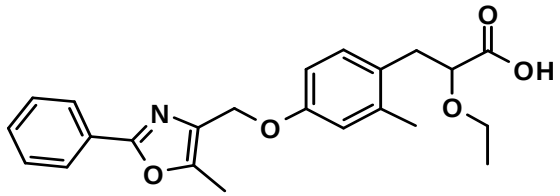
A promising subclass



Fine tuning for optimal balance and potency

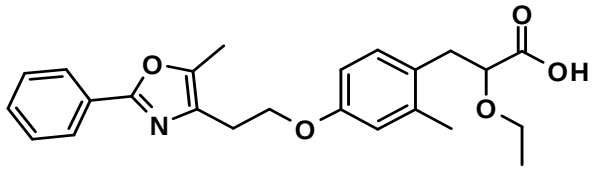
Phenylpropionic Acids

Linker length optimzation



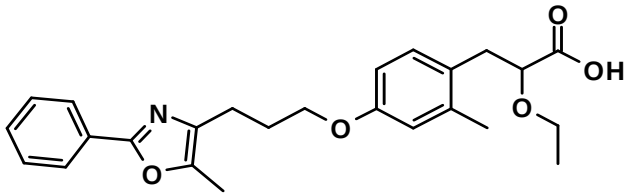
C1 linker

PPAR	α	γ	δ
IC_{50} [nM]	234	460	5890
EC_{50} [nM]	66	60	2217 (20)



C2 linker

α	γ	δ
3210	4	-
550	32	2540 (27)



C3 linker

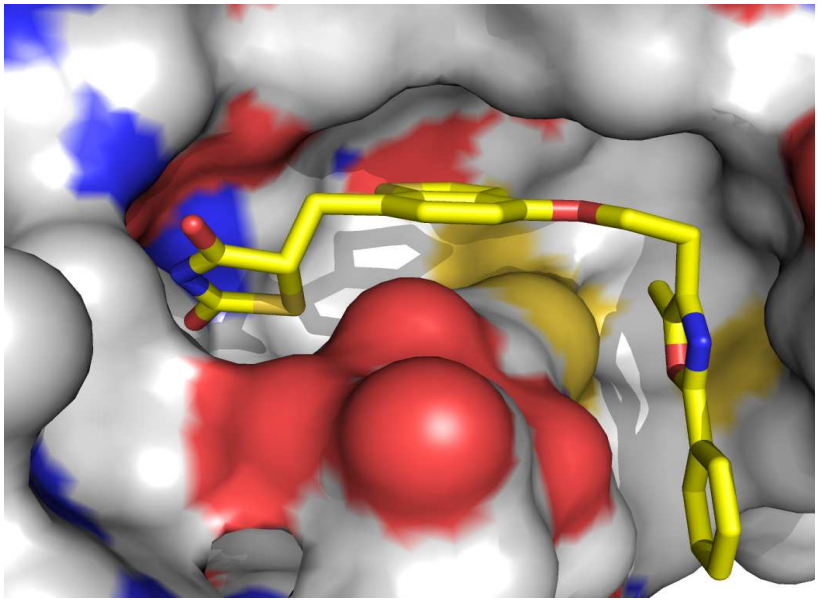
α	γ	δ
131	33	-
150	57	2657 (16)

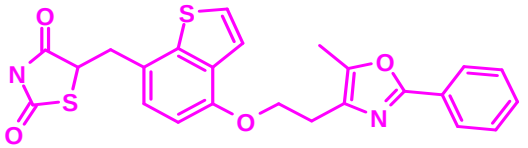
PPARα/γpotency ratio around 1 with C_1-O linkage

X-Ray of Edaglitazone

Another source of inspiration

hPPARγco-crystal x-ray structure



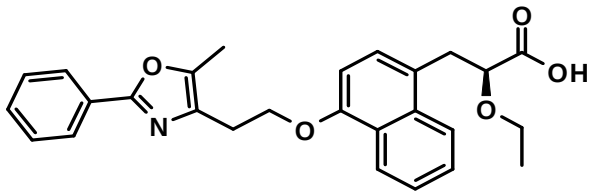


Edaglitazone

PPAR	α	γ	δ
IC_{50} [nM]	5720	12	n. d.
EC_{50} [nM]	n. d.	70	n. d.

Explore and exploit bicyclic spacers

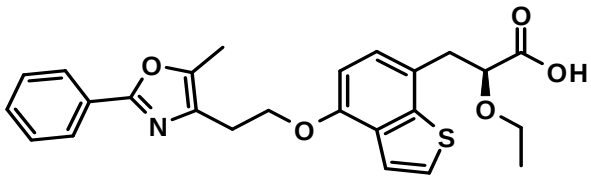
Phenylpropionic Acids with Bicyclic Linker



(S)

Naphthalene

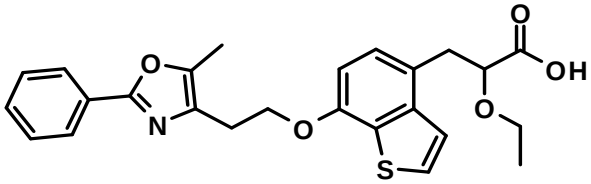
PPAR	α	γ	δ
IC_{50} [nM]	198	36	-
EC_{50} [nM]	11	37	169 (64)



(S)

Benzothiophene

α	γ	δ
53	21	16
27	21	117 (99)



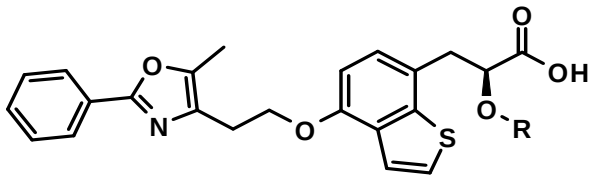
(R/S)

Isomeric Benzothiophene

α	γ	δ
333	13	9
58	7	17 (45)

PPARα/γratio close to 1 with benzothiophene
Absolute potency excellent

Screening the Alkoxy Chain



R = Me

PPAR	α	γ	δ
IC_{50} [nM]	35	66	21
EC_{50} [nM]	53	32	444(22)

R = Et

α	γ	δ
53	21	16
27	21	117 (99)

R = Pr

α	γ	δ
393	2	7
13	4	45 (92)

R = Bu

PPAR	α	γ	δ
IC_{50} [nM]	162	1	5
EC_{50} [nM]	17	63	30 (153)

R = CF_3CH_2

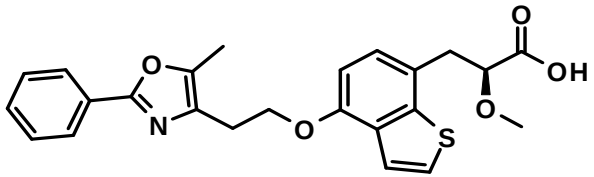
α	γ	δ
60	3	45
555	151	514 (89)

R = CH_2=CH-CH_2CH_2

α	γ	δ
21	2	5
27	32	57 (105)

Limited space in α-receptor, but butenyl can accommodate

Aleglitazar
Preclinical DMPK profile

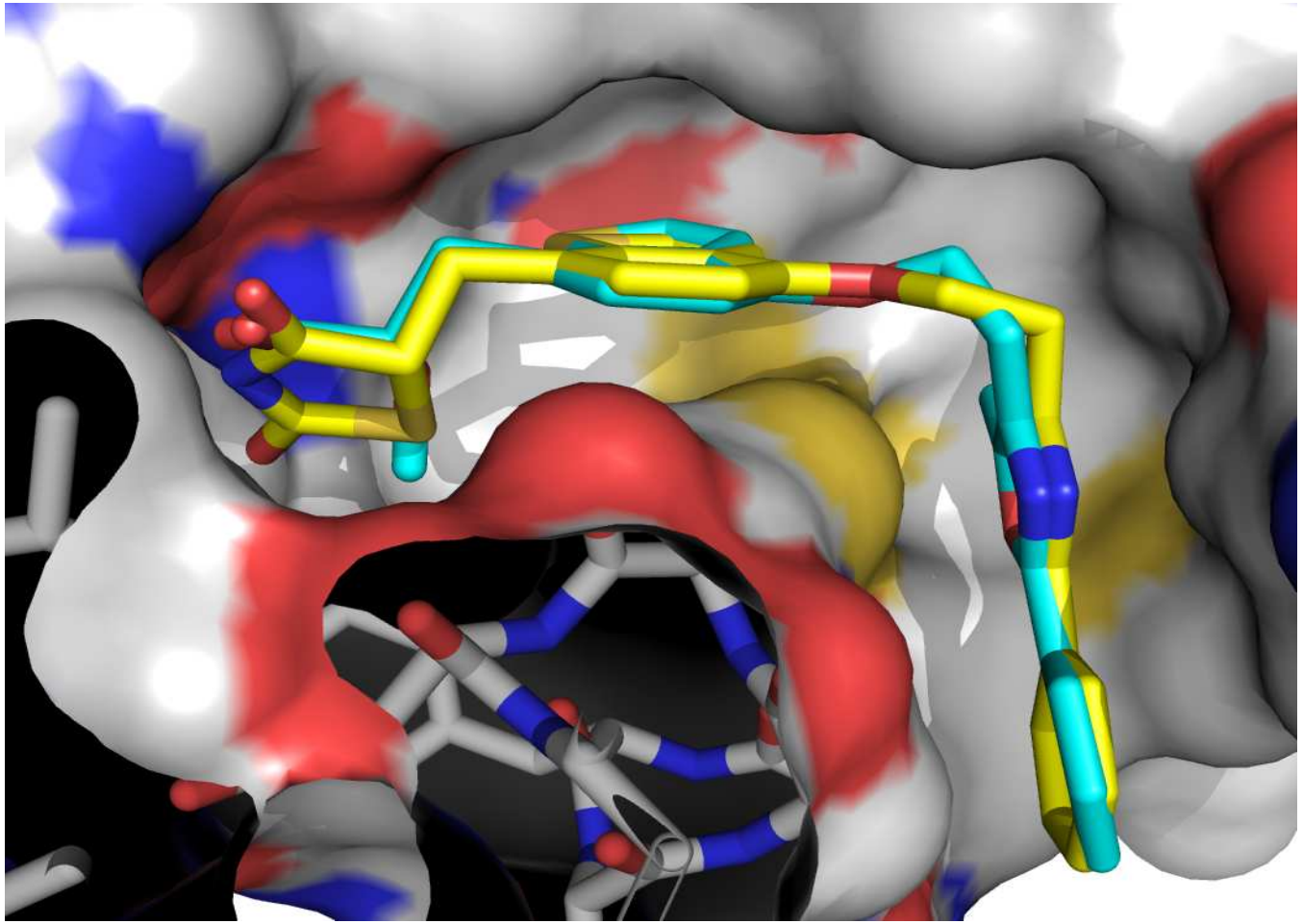


RO0728804-000

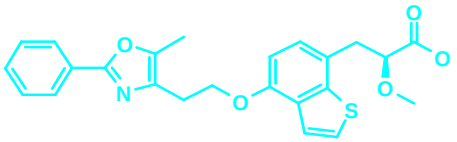
***In vitro* Activity**	IC_{50} α/γ/δ [nM]	35 / 66 / 21		
	EC_{50} α/γ/δ [nM]	53 / 32 / 444 (22%)		
Physicochemical	Solubility	15µg / mL		8000 µg / mL (pH 9)
Properties	Log D	1.18		mp. 153°
	Caco-2	34.5 x 10^{-6} cm / sec		
Pharmacokinetics	Total clearance	6.2 ml/min/kg		1.6 ml/min/kg
(Rat)	Vss	1.3 l/kg	**(Primate)**	0.4 l/kg
	Bioavailability	70 %		68 %
	T1/2	4 h		12.9 h
Safety (*in vitro*)	Cyp	3A4 19; 2C9 4.0; 1A2 >50		2D6 >50; 2C19 12 µM
	hERG	negative		
	Ames/MNT	negative		
	Phsopholipidosis	negative		
	Phototoxicity	negative		

Comparison of Aleglitazar and Edaglitazone

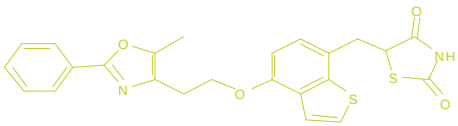
hPPARγ-LBD



Aleglitazar



Edaglitazone

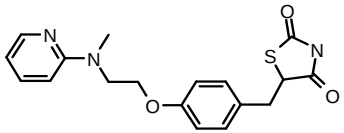


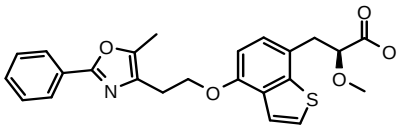
In vivo Efficacy: T2D Model-1

Efficacy on glucose lowering

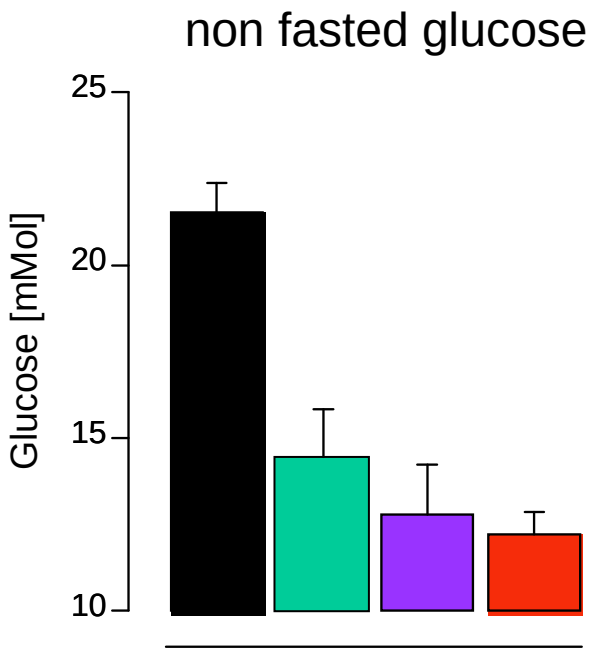
Treatment of db/db mice for 12 days

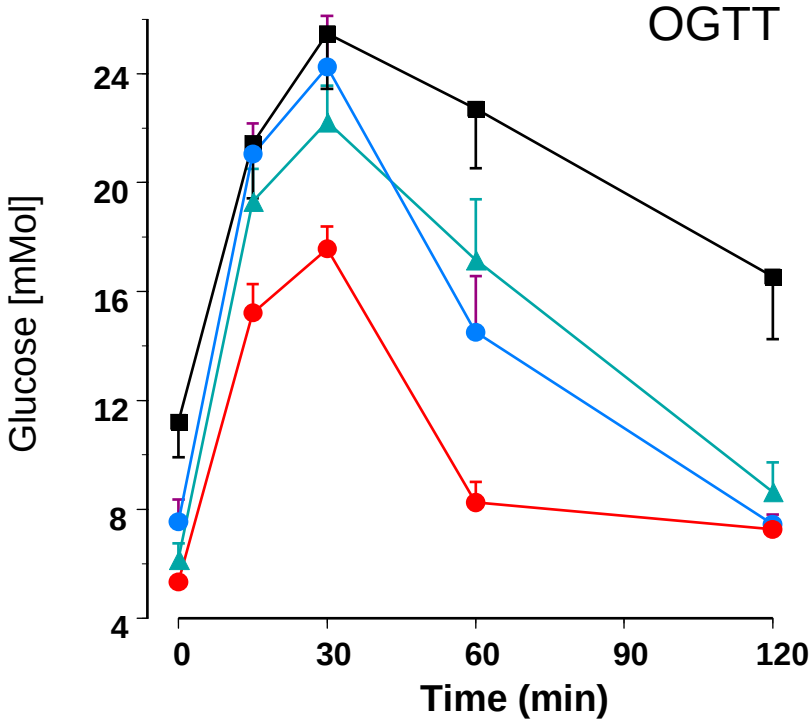
Rosiglitazone





Aleglitazar





Placebo

RSG 3 mkd

RO0728804 0.3 mkd

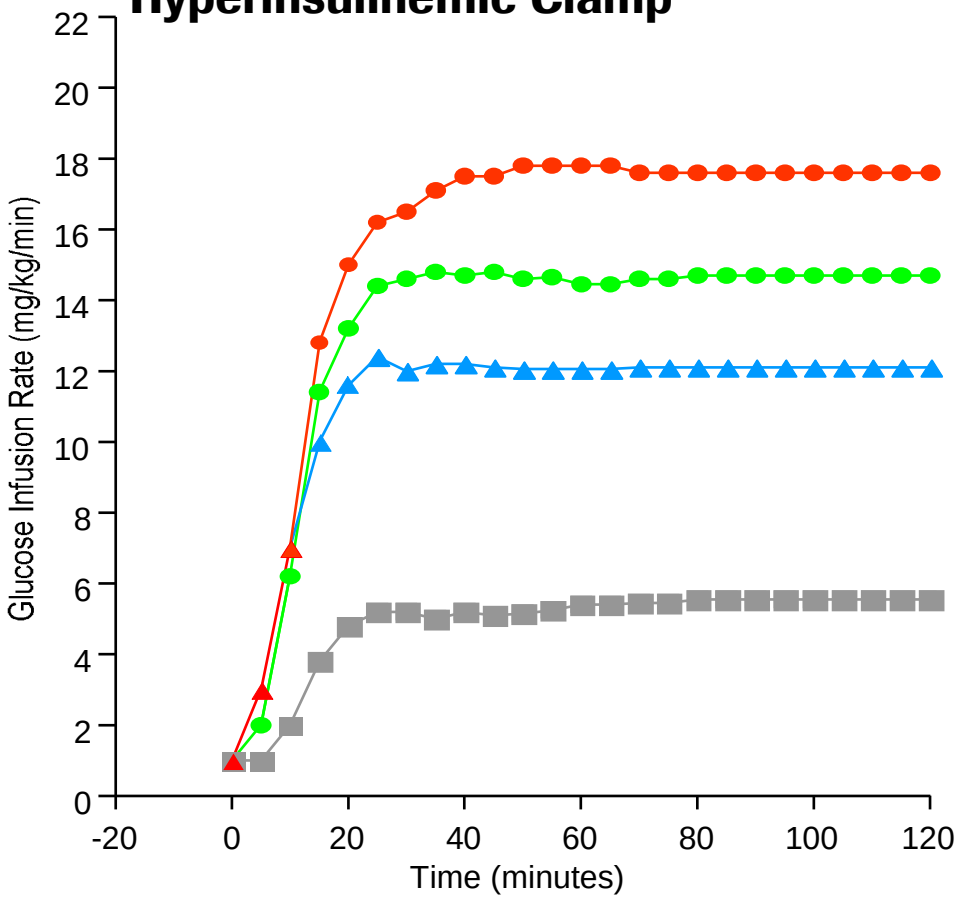
RO0728804 3.0 mkd

In vivo Efficacy: T2D Model-2

Efficacy on insulin sensitization

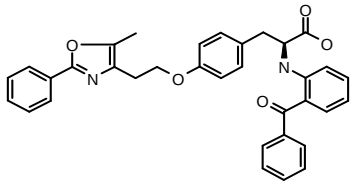
Treatment of Zucker fa/fa rats for 7 days

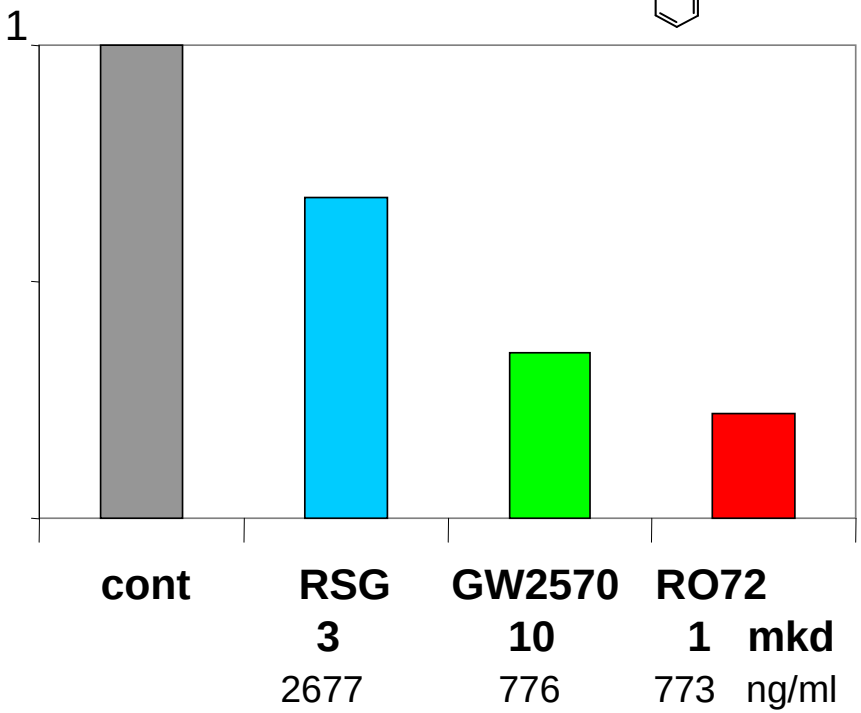
GIR measured during Euglycemic Hyperinsulinemic Clamp



Relative insulin resistance (fasting insulin x fasting glucose)

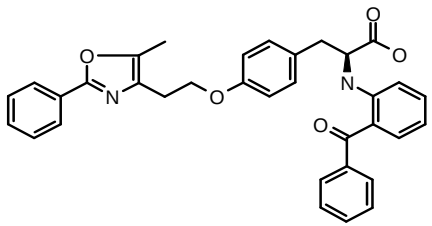
GW2570





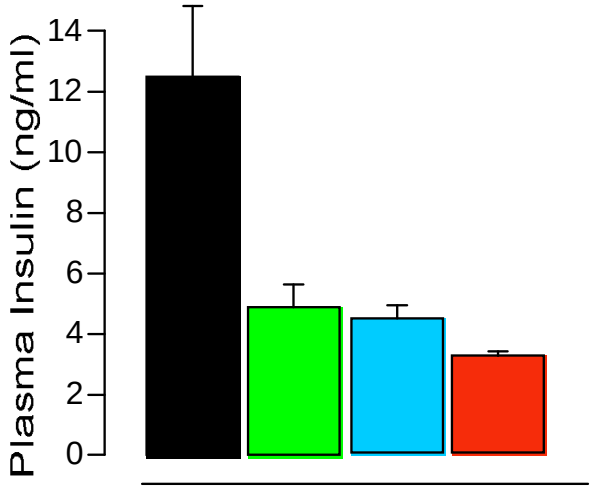
In vivo Efficacy: T2D Model-3

Efficacy on insulin lowering

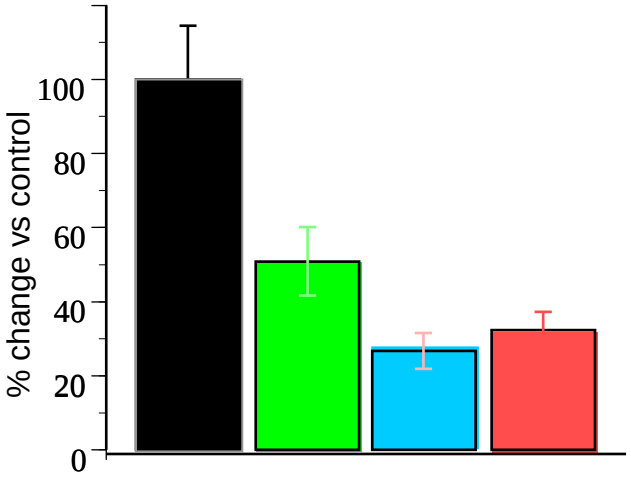


GW2570 = Farglitazar

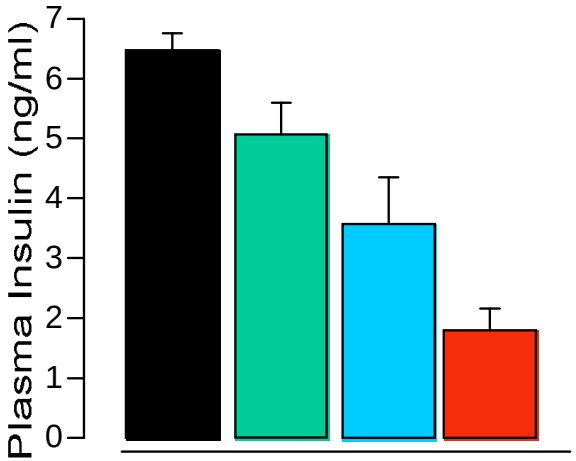
Zucker fa/fa rat
7 days



HFF-SD rat
12 days



ob/ob mouse
12 days



Placebo

GW2570
10 mkd

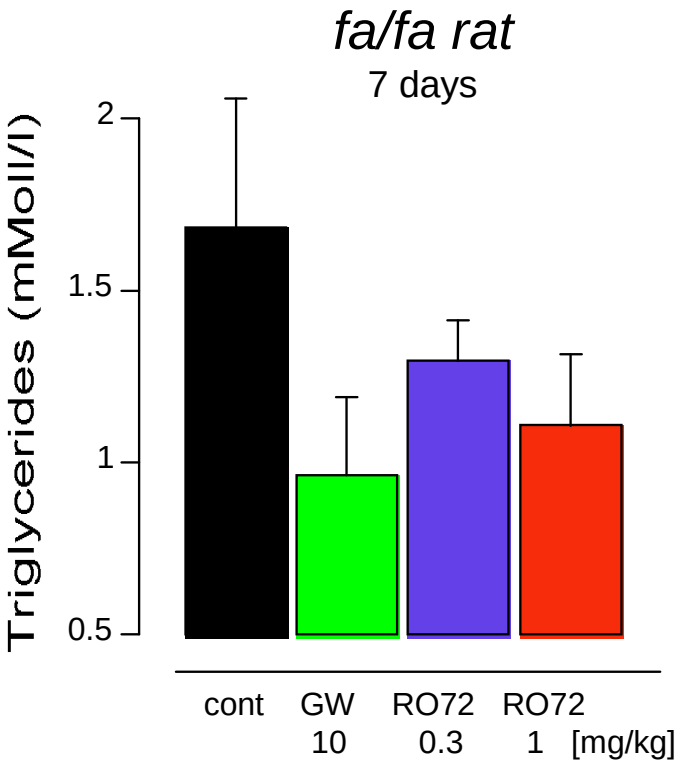
Rosiglitazone
3 mkd

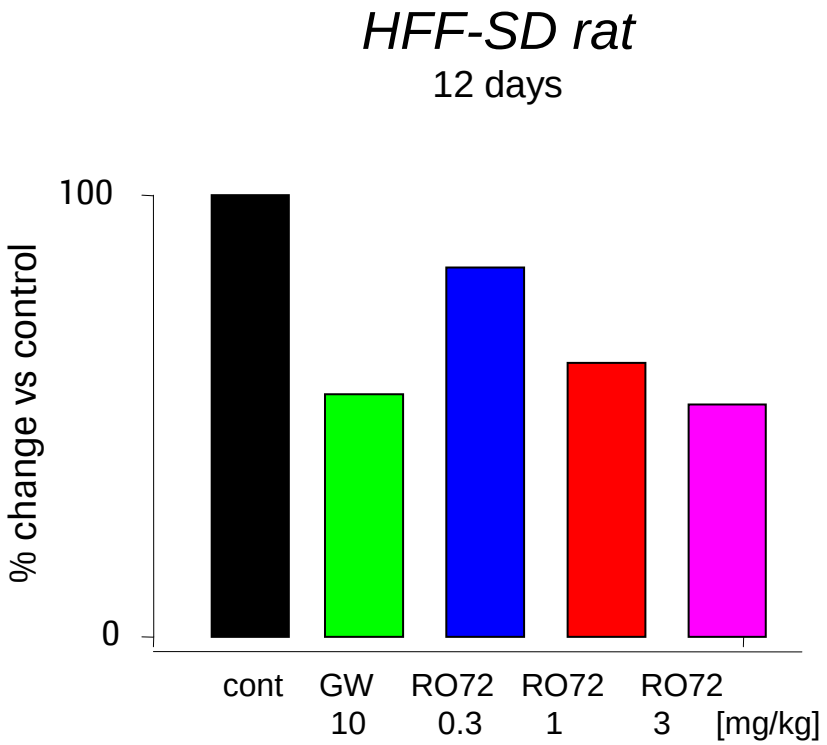
RO0728804
0.3 mkd

RO0728804
1.0 mkd

In vivo Efficacy: Dyslipidemia Model-1

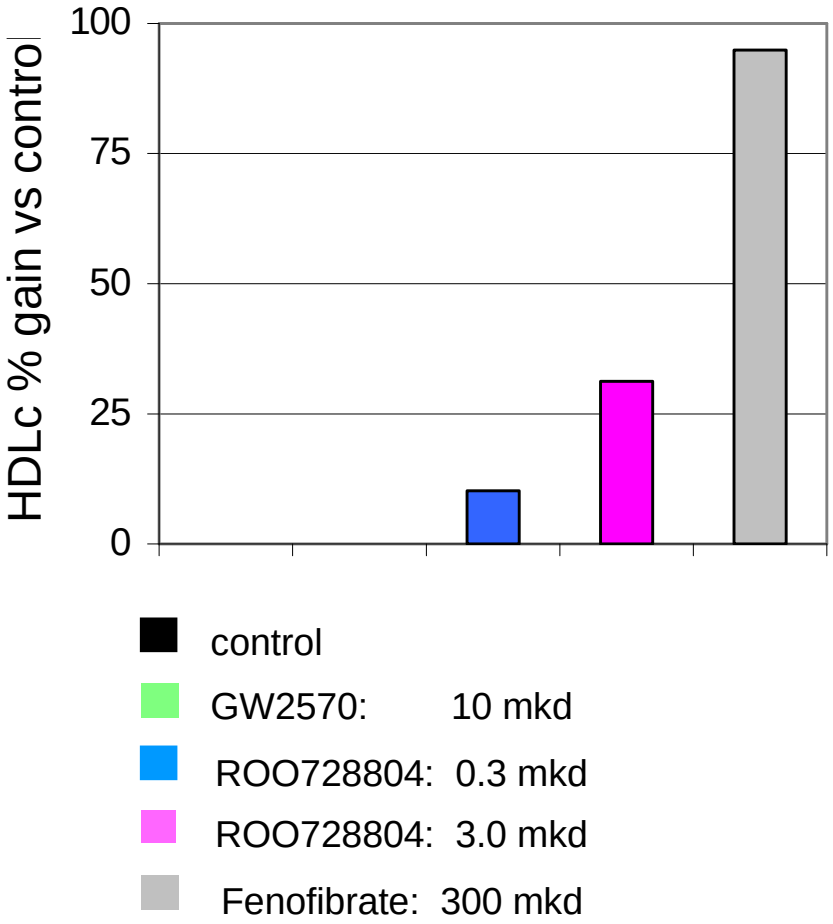
Efficacy on triglycerides

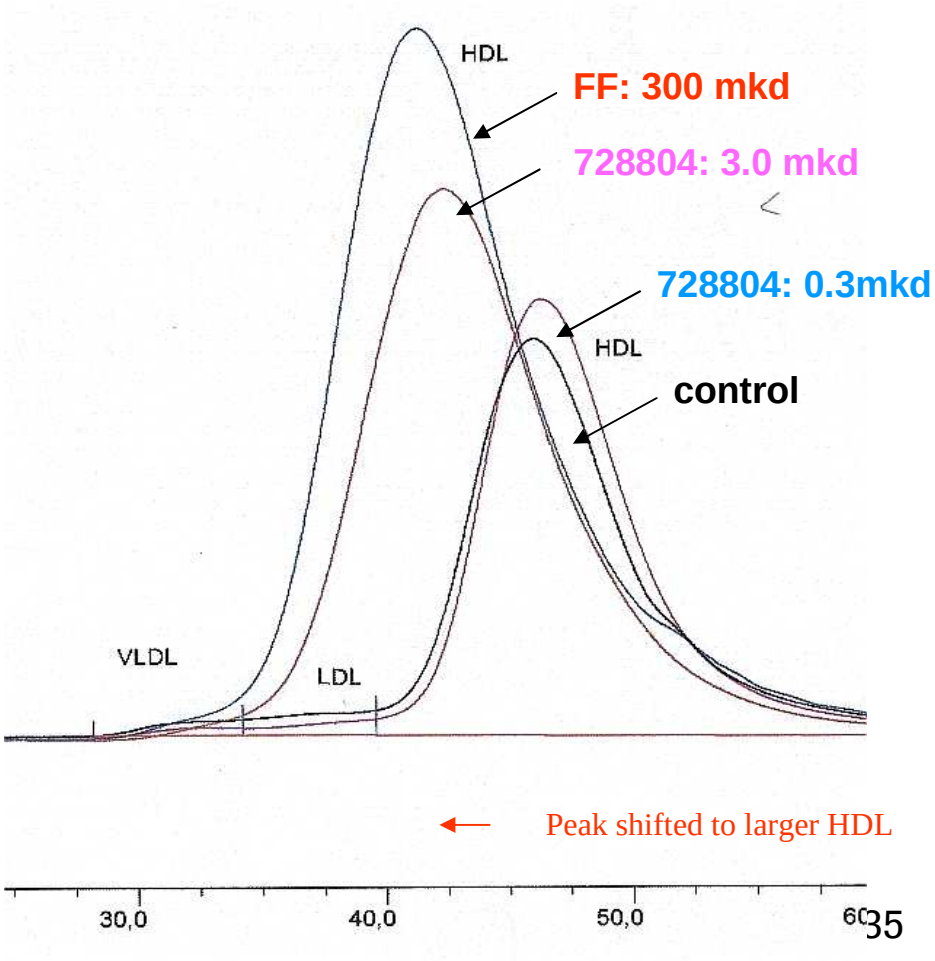




In vivo Efficacy: Dyslipidemia Model-2

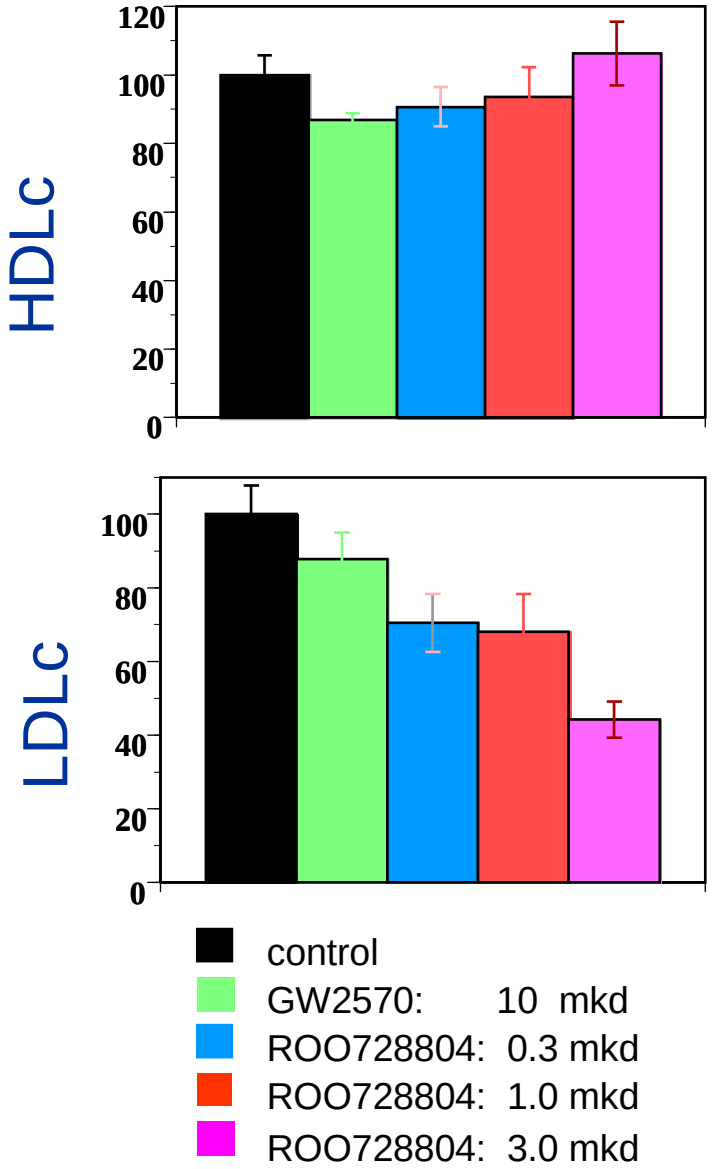
Efficacy on HDL in human ApoAI-transgenic mice

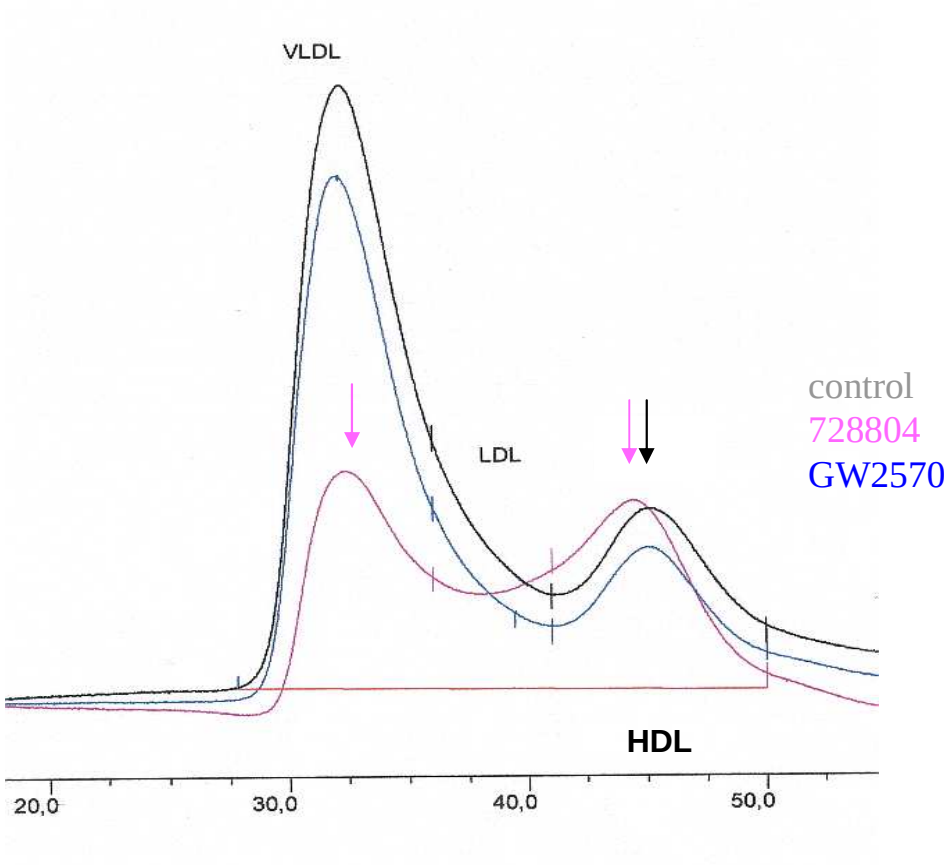




In vivo Efficacy: Dyslipidemia Model-3

Efficacy on lipoprotein profile in HF rats





In high fat fed rats Aleglitazar is strongly decreasing LDLc and weakly increasing HDLc

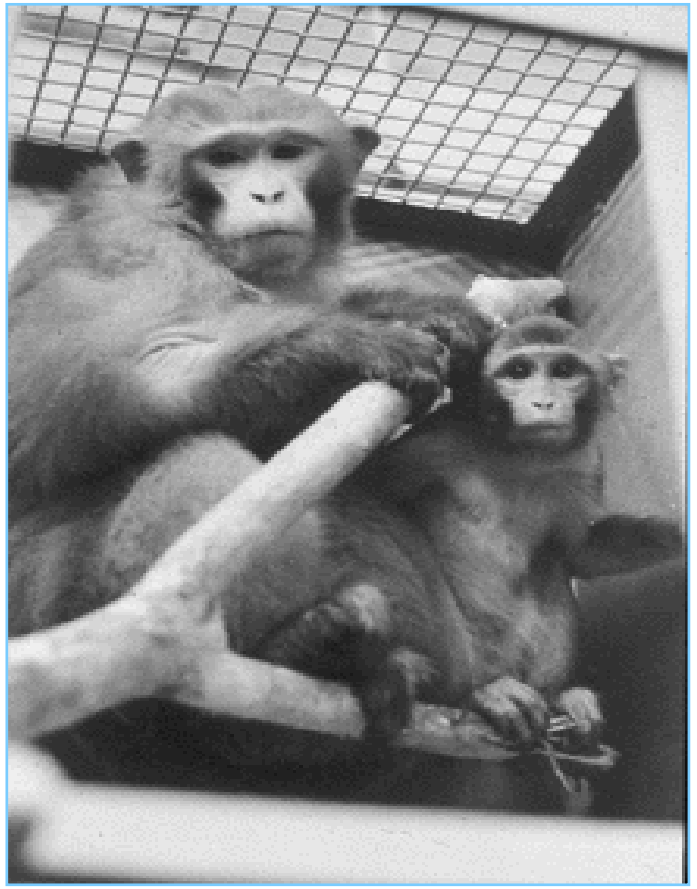
Aleglitazar has an Outstanding Efficacy Profile in *(Pre-) Diabetic rhesus monkeys*

- **6-week, 0.03 mg/kg/day; AUC 300 ng·mL/h:**

- **Effects on hyperglycemia and insulin resistance**
  - HbA1C (BL 8.4%) - 2.1%
  - Fasting plasma glucose - 17%
  - Fasting insulin - 60%
  - Insulin sensitivity + 68%

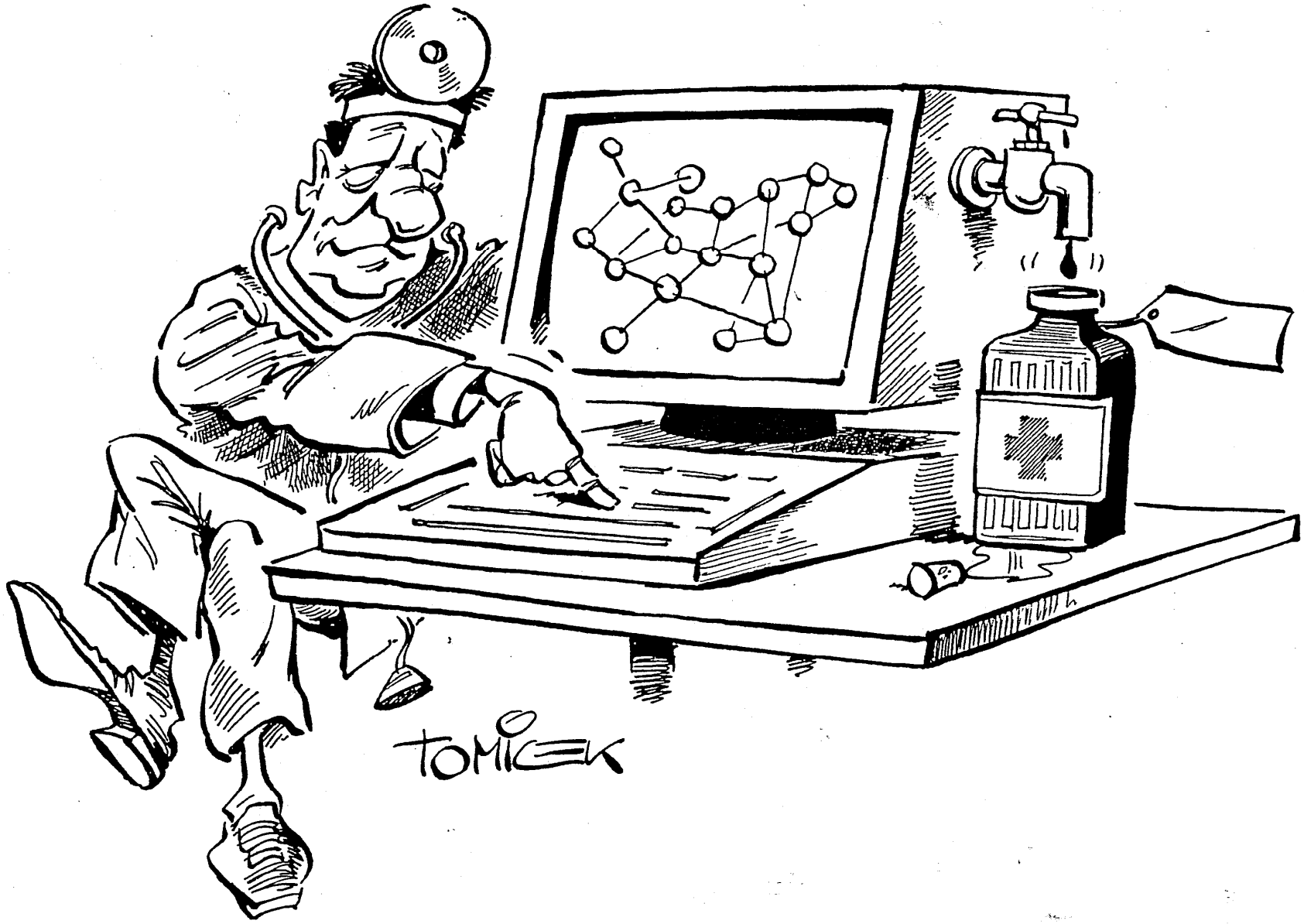
- **Anti-dyslipidemic effects**
  - TG + VLDLc - 88%
  - HDL-C + 111%
    (sdHDLc: - 58%)
  - LDL-C -37%
    (large LDLc: + 110%)

- **Tendency for lowering blood pressure**



Summary

- X-Ray supported semirational design led to novel bicyclic aryl-propionic acid series, showing high and balanced agonistic activity towards both PPARα and γ.
- Side chain variations within this series allowed to fine tune absolute potency and relative PPARα/γ ratio.
- Many molecules exhibit excellent physicochemical and pharmacokinetic profiles.
- Selected compounds show high efficacy in *in vivo* models of T2D and dyslipidemia.
- Aleglitazar was chosen for clinical development.
- X-Ray structures confirm its smooth fit into both binding cavities.
- Completed Phase I and II studies look very promising with efficacious dose 150 µg/day.
- Phase III studies ongoing: Cardioprotective antidiabetic treatment for CV risk patients


TOMICEK

A Brief Look Back

The Way We Work Today

Outlook Into Our Future

Future Trends of Discovery Chemistry
The classical approach

- Microfluidics - from flow chemistry to flow biology
- Chemically diverse, high quality screening library
- Novel building blocks and functional groups – e.g. “modules”
- Chemogenomics and scaffold hopping
- Early availability of 3D target structure
  - virtual screening
  - *de novo* design
  - fragment-based screening
- Effective tools to drive SAR/SER
  - predictive high-throughput tests, *in vitro* and *in vivo*
  - *in silico* prediction tools

Future Trends of Discovery Chemistry
The broadened approach

- Phenotypic screening, e.g. insulin resistant pancreatic beta-cells
- SER by in vivo pharmacology approaches using computational algorithms
- SER/SAR-based knowledge management for “pattern recognition”
- Intracellular delivery of polar macromolecules
  - cell penetrating peptides
  - siRNA conjugates delivered through endocytosis
- Regenerative medicine
  - mechanisms for cellular self-renewal
  - iPS cells from somatic cells and redirection of cell fate
- RNA as drug target
  - small molecules that regulate gene expression
  - rRNA, tRNA, mRNA - 5‘UTR binding molecules

Acknowledgments

All colleagues in Roche chemistry

GlyT1: Emmanuel Pinard and team

Aleglitazar: Peter Mohr and team



We Innovate Healthcare