Eighteen-year partnership in diabetes research between Novo Nordisk and Apigenex

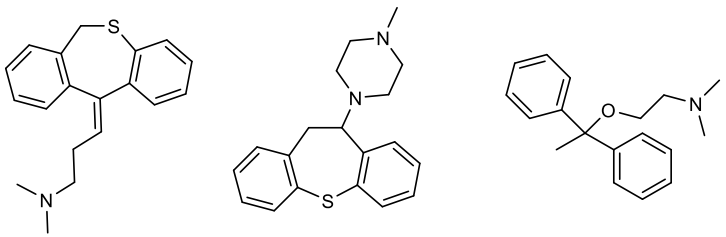
An on-going story

Outline

1. Scientific background
2. Lucky chance
3. Early cooperation
4. PPAR project
5. Fatal decision
6. Refocusing on peptides
7. Current APIGENEX
8. Outside partnership

1. Scientific background

- Research Institute for Pharmacy and Biochemistry in Prague (VUFB)
- 3rd Department of organic synthesis (OS III) led by **Dr. Protiva** (more than 500 publications and 800 patents)
- agents acting at the vegetative and central nervous system
- antihistaminic, spasmolytic, hypotensive and antidepressant drugs (TCA)
- **Dosulepine** (Prothiaden), Bisulepin (Dithiaden), Moxastine (Kinedryl), Clotepin
- 26 original drugs in pharmaceutical market, 23 original substances reaching the stage of clinical trials



M. Protiva, *Collect. Czech. Chem. Commun.* **1991**, *56*, 2501-2772

2. A bit of luck

- VUFB – gradual decline in pharmaceutical research after 1989, cancellation of agreements with Czechoslovak pharmaceutical industry
- redirecting research into antagonists of NMDA receptors, GABA-mimetics
- introduction of faster in-vitro screenings on different receptors
- contacted by Tine Krogh Jorgensen from Novo Nordisk (4 samples) in **1994**


Collect. Czech. Chem. Commun. **1994**, *59*, 667-674
doi:10.1135/cccc19940667

Antihistamine Substances. Tricyclic Analogues of *N*-(4,4-Diphenyl-3-butene-1-yl)nipecotic Acid and Some Related Compounds

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Research Institute for Pharmacy and Biochemistry, 130 00 Prague 3, Czech Republic

- one of the lead compounds in NN arthritis-related research was published in this article
- **28th of September 1995** – visit in NN, quickly created contract based upon structurally related research (cmpds on stock at VUFB)

Z. Polívka, et al. *Collect. Czech. Chem. Commun.* **1991**, *59*, 667-674

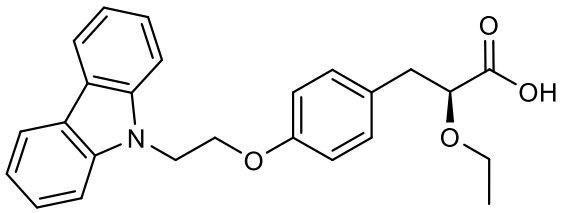
3. Early cooperation

- initial agreement for organic synthesis (30 cmpds from stock, syntheses of 40 new cmpds, mutual publication and patent activities) within VUFB
- cooperation with Dr. Lundt‘s team – custom synthesis
- extension of the agreement every year
- quarterly meetings (Prague-Copenhagen)
- cooperation in in-vivo experimental pharmacology from **1997**
- foundation of RE&D VÚFB independently on VUFB in **1999**
- starting to participate on the PPAR project
- forced moving from the Institute to a rented location (instability of research activities with kind tolerance from NN) in **2001**

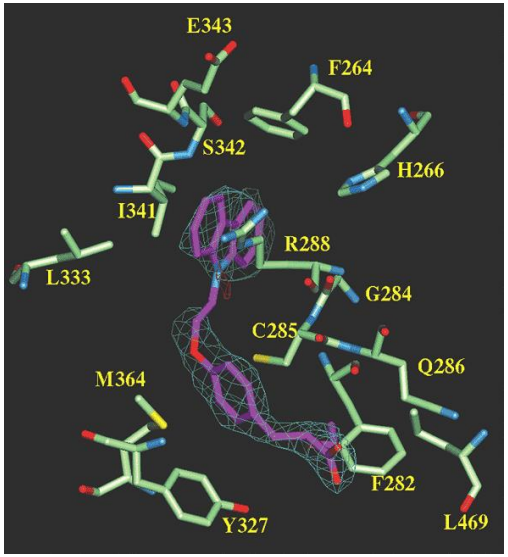
4. PPAR project

- cooperation with the team of Per Sauerberg
- open project cooperation (sharing results, designing own structures)
- by the end of 2006 – 6 FTE for chemistry, 6 FTE for pharmacology

From selective PPARα or γ to dual agonist + in-vivo testing on db/db mice



	PPARα		PPARγ	
	EC50 (μM)	% max	EC50 (μM)	% max
NN-ReaD cmpd	0.36	140	0.17	108
Rosiglitazon	4.10	43	0.14	**100**
WY 14643	12.00	**100**	29.00	22

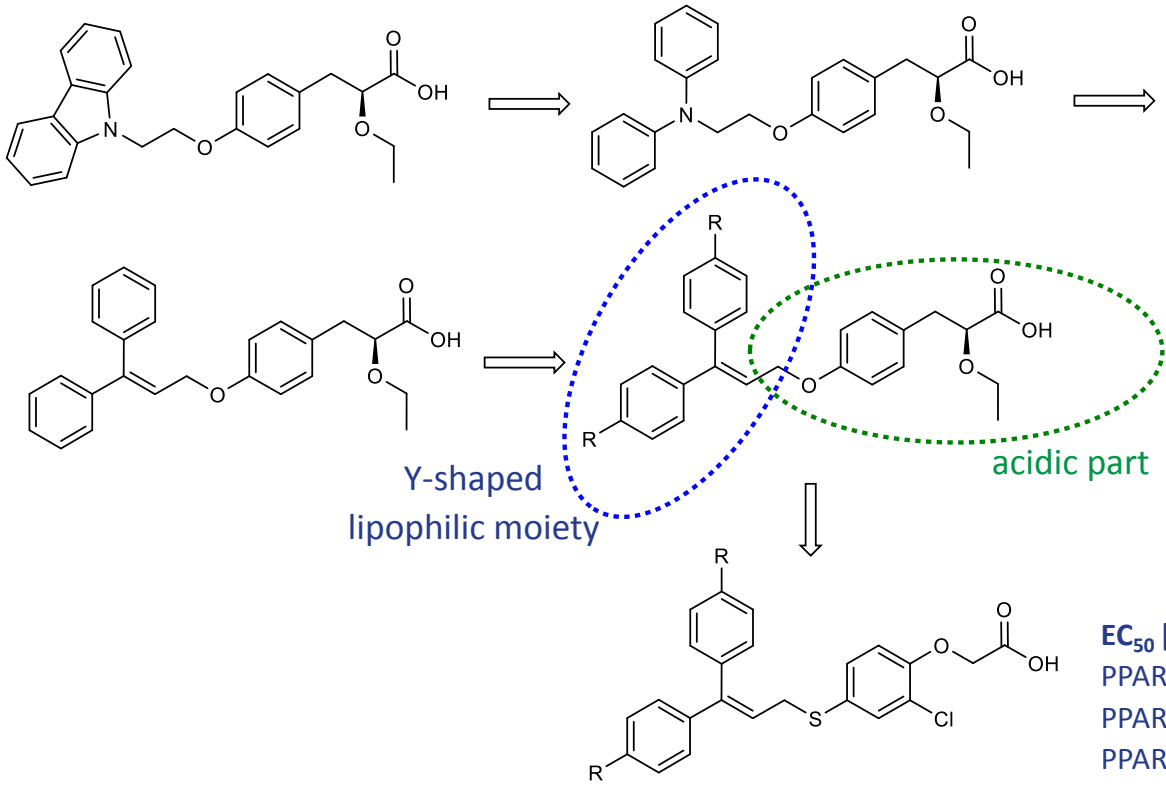


P. Sauerberg, et al. *J. Med. Chem.* **2002,** *45*, 789-804

4. PPAR project

Through PPAR α/γ/δ triple activators to selective PPARδ agonists modifying the structure to understand SAR and to get BACK-UP candidates

EC_{50} [μM] (% max)
PPARα 0.4 (140 %)
PPAR□γ 0.2 (108 %)
PPAR□δ ---

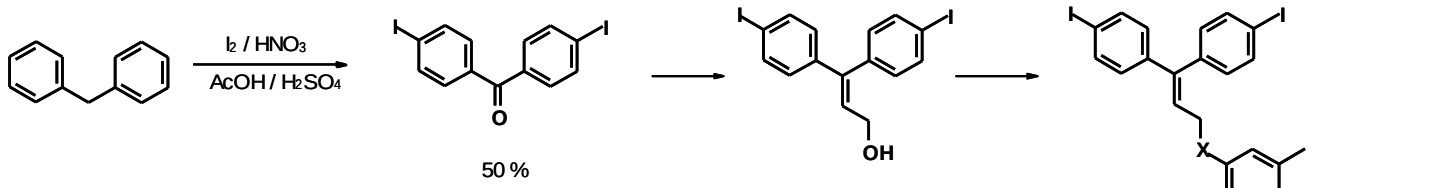


R = Br
EC_{50} [μM] (% max)
PPARα 0.3 (132 %)
PPARγ 0.9 (85 %)
PPARδ 0.4 (239 %)

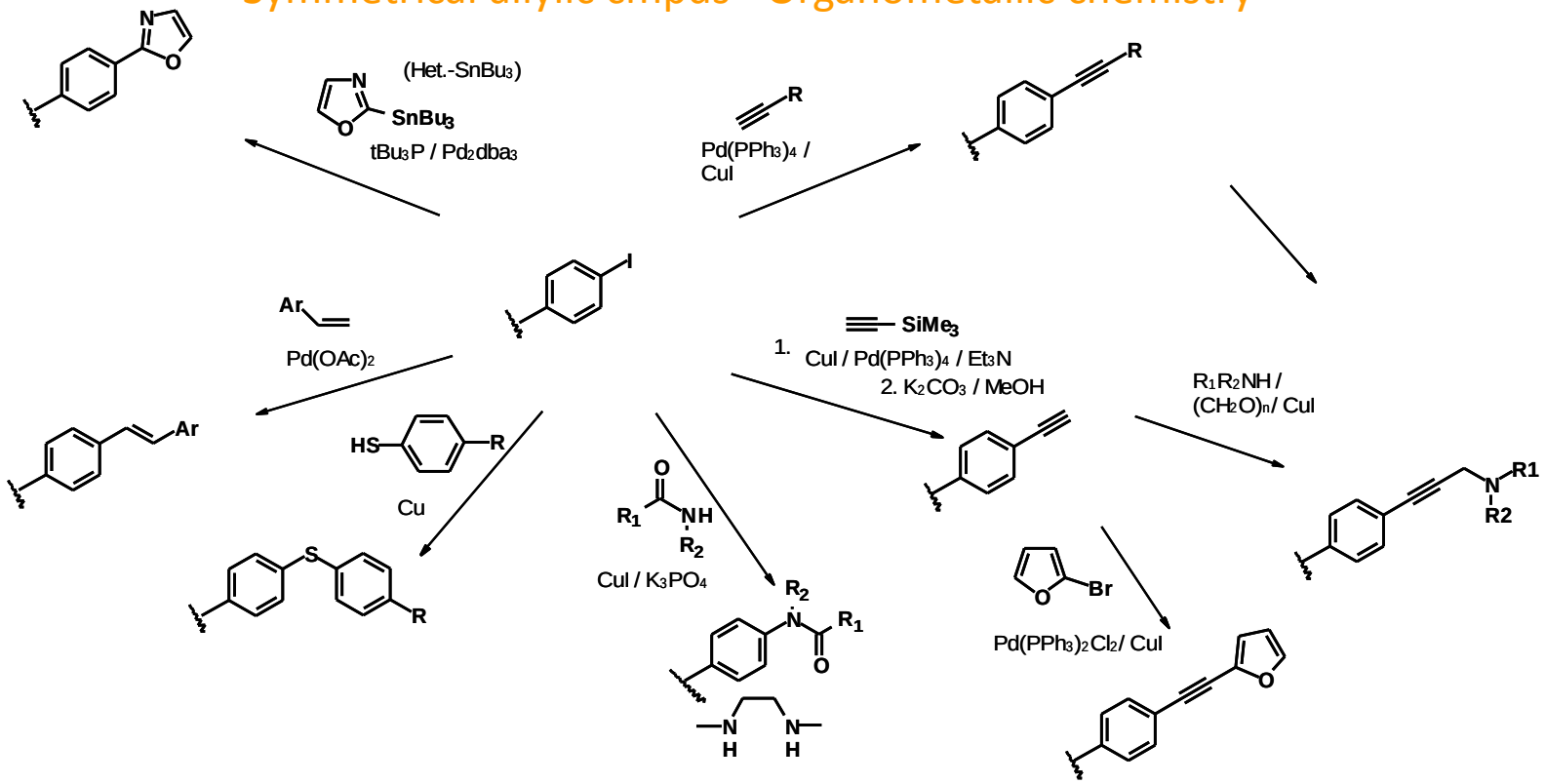
R = Br
EC_{50} [μM] (% max)
PPARα >10 (12 %)
PPARγ >10 (18 %)
PPARδ 0.053 (200 %)

J. P. Mogensen et al. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 257–260
P. Sauerberg et al. *J. Med. Chem.* **2007,** *50,* 1495-1503

4. PPAR project



Symmetrical allylic cmpds - Organometallic chemistry



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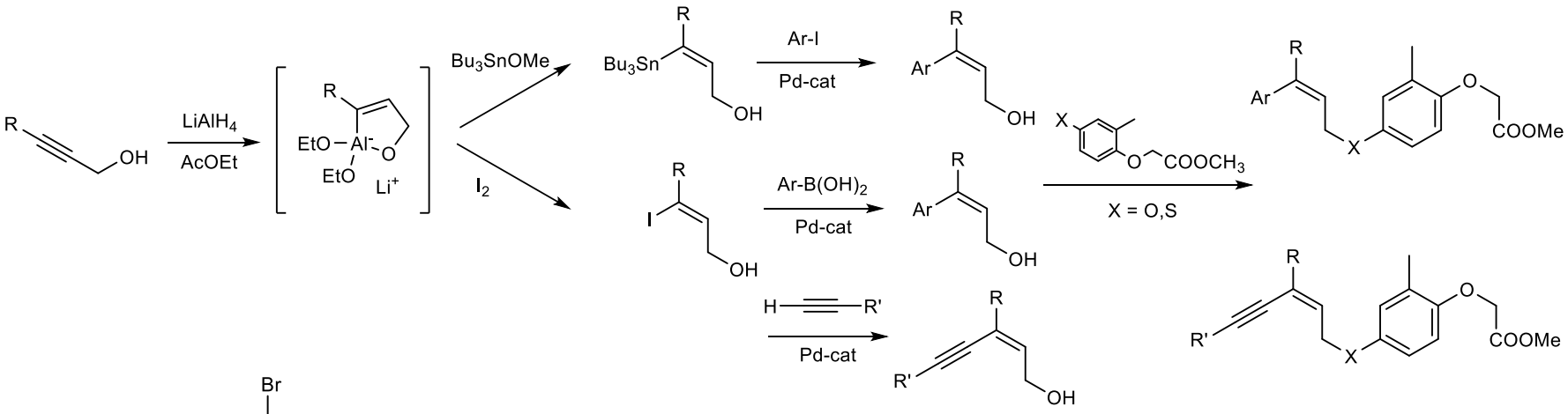
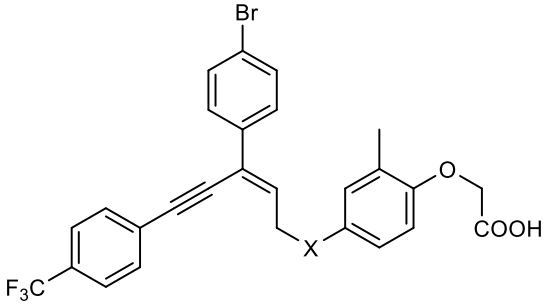
4. PPAR project

Non-symmetrical allylic cmpds - hydroaluminations



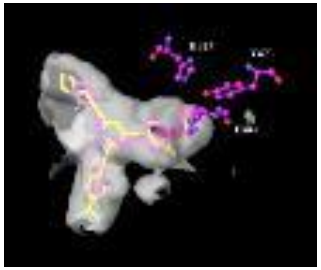


EC_{50} [μM] (% max)

PPARα >10 (19 %)

PPARγ >10 (<10 %)

PPARδ 0.13 (185 %)



M. Havranek et al. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4144–4149

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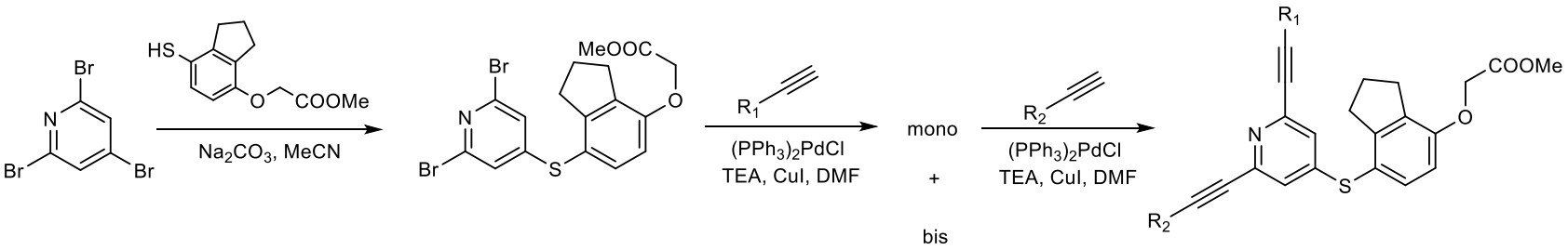
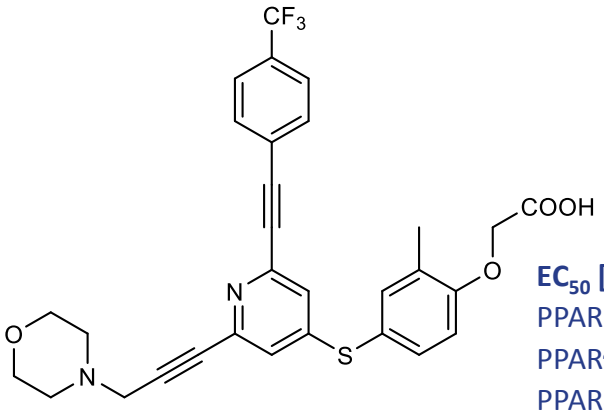
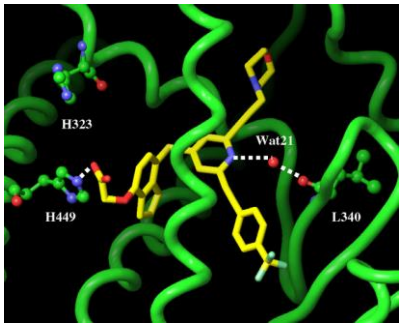
4. PPAR project

Trisubstituted benzenes, pyridines, triazines etc. – PPARδ partial





EC_{50} [μM] (% max)
PPARα 0.1 (50 %)
PPARγ 5.5 (28 %)
PPARδ 0.05 (87 %)



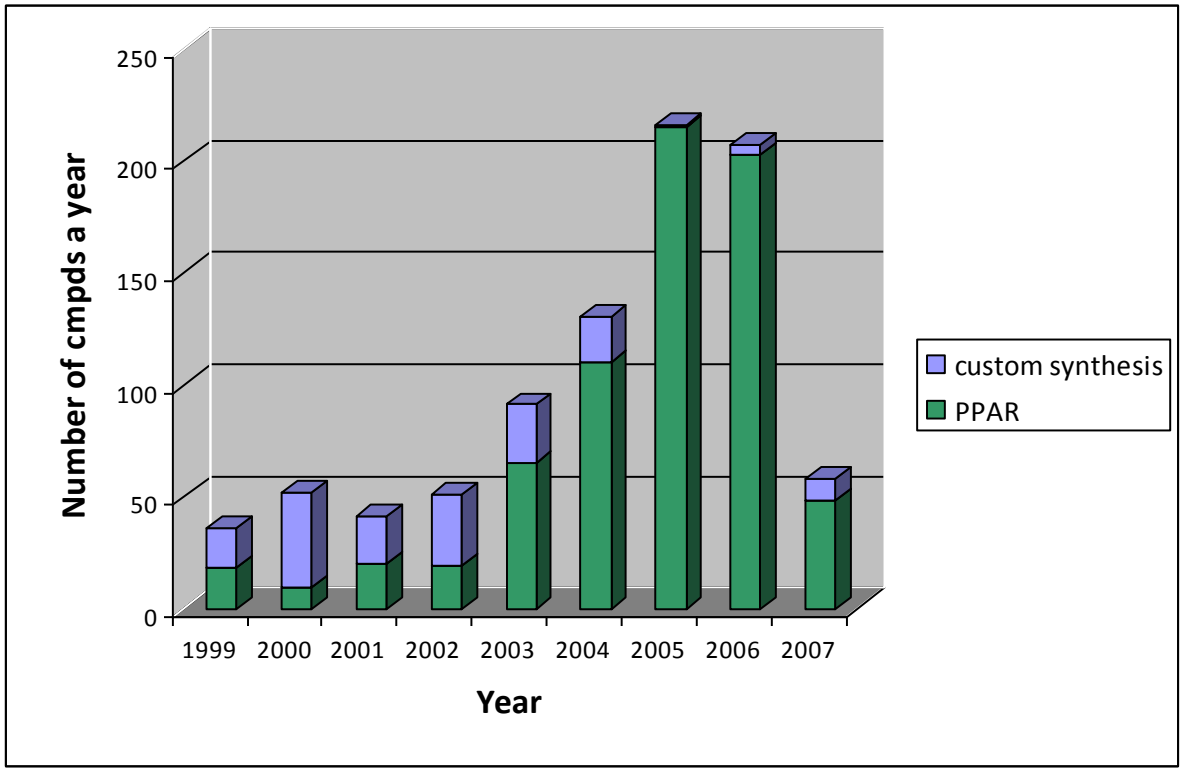
One of the most potent

EC_{50} [μM] (% max)
PPARα n.d. (<10 %)
PPARγ 1.3 (19 %)
PPARδ 0.005 (252 %)

I. Pettersson et al. *Bioorg. Med. Chem. Lett.* **2007**, *17,* 4625–4629

4. PPAR project

Synthesized compounds during the PPAR project



4. PPAR project

Pharmacological models of metabolic syndrome

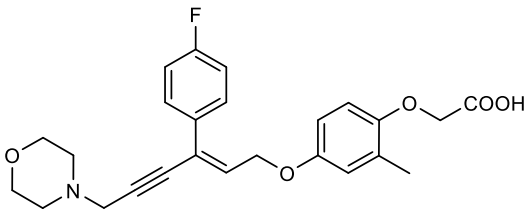
High cholesterol diet-induced dyslipidemia	Zucker fatty rats
Db/db mice	Diabetic Zucker fatty rats
Ob/ob mice	DIO rats and mice

Complete M1 pharmacology documentation for lead compound NN-61-5920

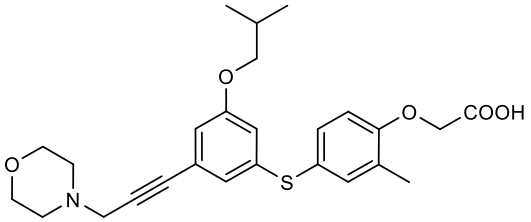
In-vivo pharmacology for other NN projects

2004-2007	**Inhibitors of 11β-HSD1**
2005-2007	**Glucokinase activators**

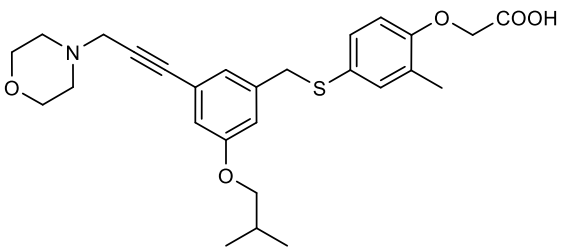
Scale-up and synthesis of 3 SQs as back-up compounds in 200 g batches



NNC-61-6593



NNC-61-0203



NNC-61-0230

4. PPAR project

A year in the life of Novo Nordisk

Therapeutic proteins take R&D lead
15 January: Novo Nordisk discontinues R&D within small molecules and focuses research and development on therapeutic proteins. See p 8.

JANUARY

US hiring blitz
The US diabetes sales force is expand

- direct impact on 180 NN-staff
- cancellation of agreement
- significant drop in R&D activities

Novo Nordisk Annual Report 2007

5. Tough years

In-vivo pharmacology

- continuing in established pharmacological models (NN, Transtech Pharma, Recepticon)
- introducing new models to get new customers (Nycomed)

Chemistry department

- occasional custom synthesis (Polyphor, Recepticon, Novo Nordisk)
- 2 FTE (small molecules) and 2 FTE (pharmacology) for NN in **2008**
- hiring experienced peptide chemists in **2009** → 2 FTE for peptide chemistry
- adapting staff and equipment to meet biopharmaceutical focus of NN
- steady annual increase in FTE since **2009** (developing partnership)

RE&D VÚFB → in 2010 → APIGENEX

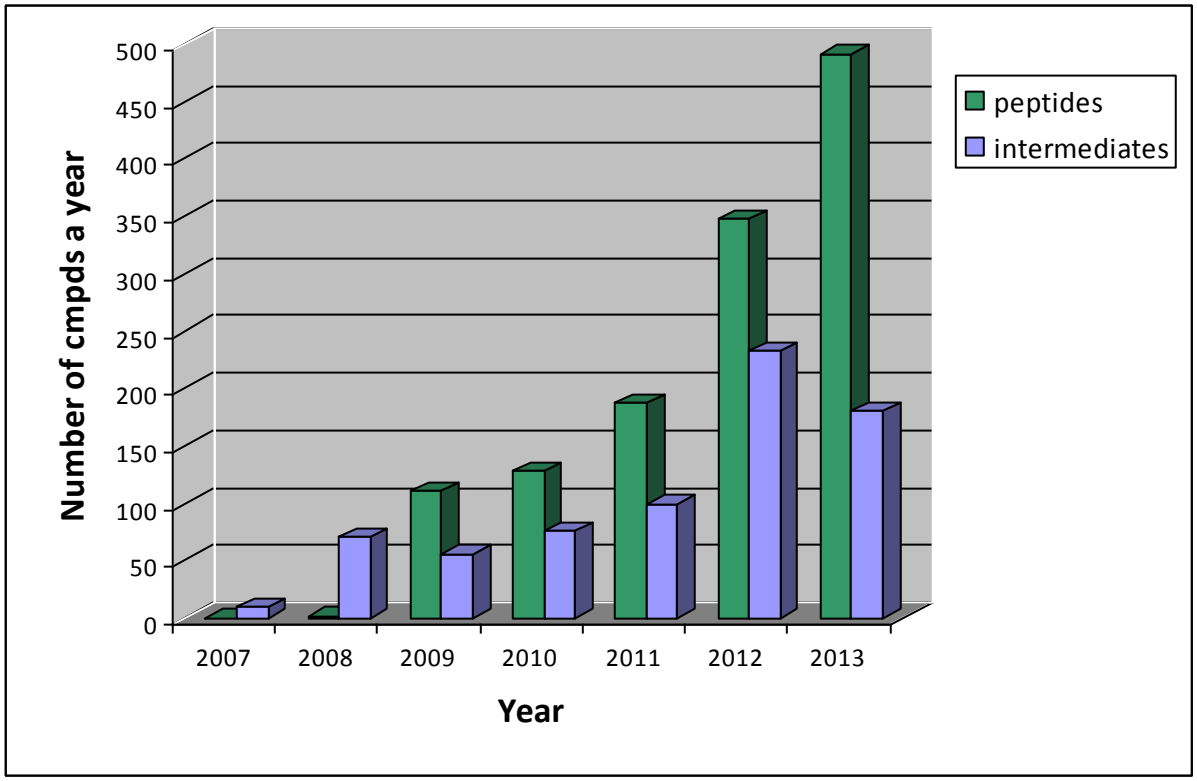
6. Refocusing on peptides

Chemistry department

„Small“ molecules - intermediates

- Building blocks for SPPS
- Side-chains
- Smaller peptides

Peptide synthesis



- Manual or robotic
- Modified peptides

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7. Present peptide synthesis

30-45 derivatized peptides per month typically 20-40 amino acids 1 mg to 100 g

2 **Preludes** 6-channel parallel peptide synthesizer up to 1.3 g of resin

2 **Symphonies** 12-channel multiplex peptide synthesizer up to 1.3 g of resin

2 **CS Bio 536 XT** 50-500 mL RV up to 50 g of resin

purification lab equipped with preparative HPLCs and lyophilization stations

analytical and QC data obtained from UPLC and LCMS

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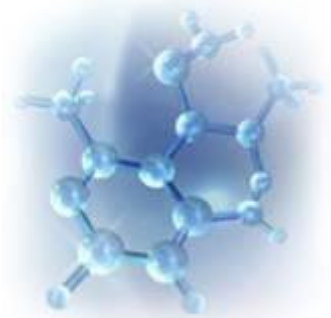
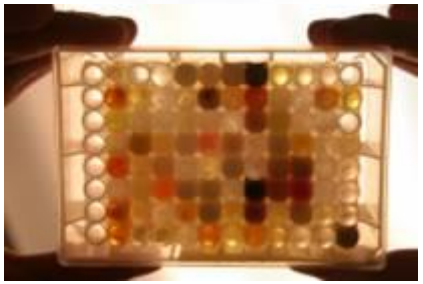
7. Present medicinal chemistry



- **design and synthesis** of novel low molecular weight compounds from 0.1 mg up to 1 kg
- synthesis of **building blocks** and precursors for peptide synthesis



- small **focused libraries** of purified compounds
- **solid phase synthesis**, parallel solution phase synthesis

- **scale-up** of known synthesis to robust protocols for GMP production
- supported by **NMR**, **LCMS**, flash purification systems, preparative LCMS

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7. Present exp. pharmacology

pharmacokinetic and pharmacodynamic studies

acute toxicity MTD

anti-inflammatory and immunomodulatory activities of drug candidates

diabetes type 2
dyslipidemia
obesity
autoimmune diseases

long-term experience in pharmacology of acute and chronic inflammation

Pharmacological models

Acute inflammation
Neurogenic inflammation
Alergic inflammation
DTH/Contact sensitivity
Septic shock

Adjuvant arthritis
Colagen-induced arthritis
Monoclonal antibody/LPS induced arthritis
Acute EAE

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7. Present exp. pharmacology

day capacity of 5 400 mice, 2 160 rats, 750 hamsters and 240 guinea pigs

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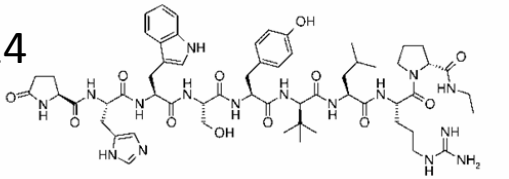
Activities outside partnership

GMP production of peptides

- Lecirelin –completed SMF and DMF, launching this year 2014
- Depherelin – to be completed and launched this year 2014



Participating on research projects with Academia

- 5 on-going projects with several Czech academic institutions

INSTITUTE OF CHEMICAL TECHNOLOGY PRAGUE

Institute of Microbiology

Palacký University

IOCB TTO www.iocb-tto.cz

Institute of Experimental Medicine AS CR, v.v.i. EU Centre of Excellence

Institute of Physiology Academy of Sciences of the Czech Republic

IMG

Key factors of our partnership

- high scientific standard
- open and direct communication
- tolerance towards struggles of small company
- focused effort to meet the demands
- adapting to NN global standards
- mutual confidence
- good-quality agreements
- helpful, open-minded and co-operative people

Thank you for your attention