

Innovative Fluorination Methods & New Fluorinated Building Blocks For Life Science

Dr. Andreas Stolle
Head of Business Line Pharma

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Saltigo - A Global Player

saltigo
customized competence

A globally active custom manufacturing services provider with the business lines:

PHARMA and AGRO/ SPECIALITIES

saltigo
customized competence

Saltigo Key Facts & Figures

saltigo
customized competence

Employees	1400
CEO	Wolfgang Schmitz
Customers	~ 150
Markets	Worldwide
Headquarters	Langenfeld, Germany
Production sites	Leverkusen, Germany
	Dormagen, Germany
	Redmond, USA (Lanxess Corporation)

Saltigo's Key Technology Areas

Chiral chemistry

Asymmetric hydrogenation, SMB chromatography, enzymes

Coupling reactions

Cross and aromatic C-hetero coupling

Challenging chemistry

Metal hydrides, high pressure, hydrogenation, phosgene, low temperature

Fluorine chemistry

HF, Halogen exchange reactions (Halex), PBSF



Fluorine Chemistry at Saltigo

Why are we working on Fluorine Chemistry ?

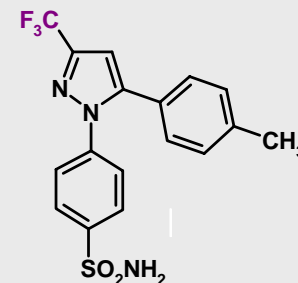
„As many as 30-40% of agrochemicals and 20% of pharmaceuticals on the market are estimated to contain fluorine, including half of the top 10 drugs sold in 2005. Developmental pipelines are predicted to contain even more.“

Chemical & Engineering News, 2006

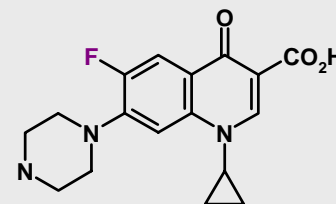
⇒ high future potential of fluorine chemistry

selective introduction of fluorine at the right position of a biologically active compound can lead to a significantly enhanced activity

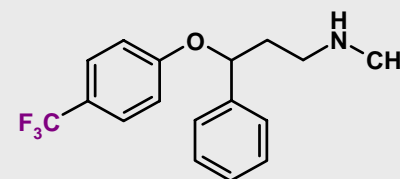
mild fluorination methods and suitable fluorinated building blocks permit an easy and elegant introduction of fluorine



Celecoxib (Celebrex®, PFIZER)
anti-inflammatory, 3.3 Bn\$



Ciprofloxacin (Cipro®, BAYER)
antibiotic, 1.5 Bn\$



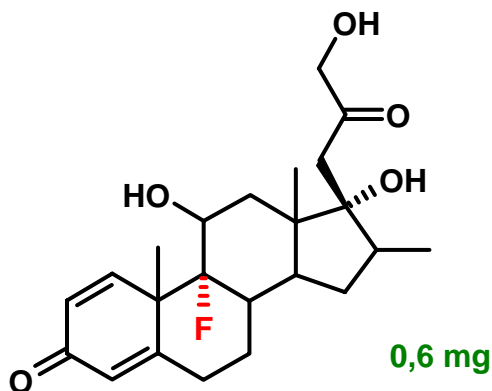
Fluoxetine (Prozac®, ELI LILLY)
antidepressant, 2.5 Bn\$

What Makes Fluorine so Different ?

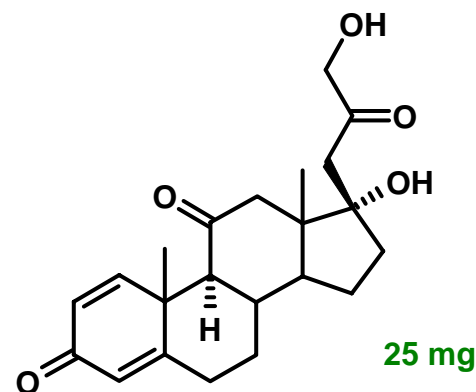
Effects of Fluorine in Drugs

- **Fluorine has a very small van der Waals Radius (1.35 Å)**
 - bioisosteric substitute of hydrogen (1.20 Å) at an enzyme receptor site
- **Fluorine is the most electronegative element**
 - affects acidity / basicity of neighboring groups
 - induces a dipole moment
 - ⇒ increased rate of absorption & transport
 - ⇒ better binding to the enzyme

				18	
	14	15	16	17	He 2
	C 6	N 7	O 8	F 9	Ne 10
	Si 14	P 15	S 16	Cl 17	Ar 18
	Ge 32	As 33	Se 34	Br 35	Kr 36
	Sn 50	Sb 51	Te 52	I 53	Xe 54



Betamethasone

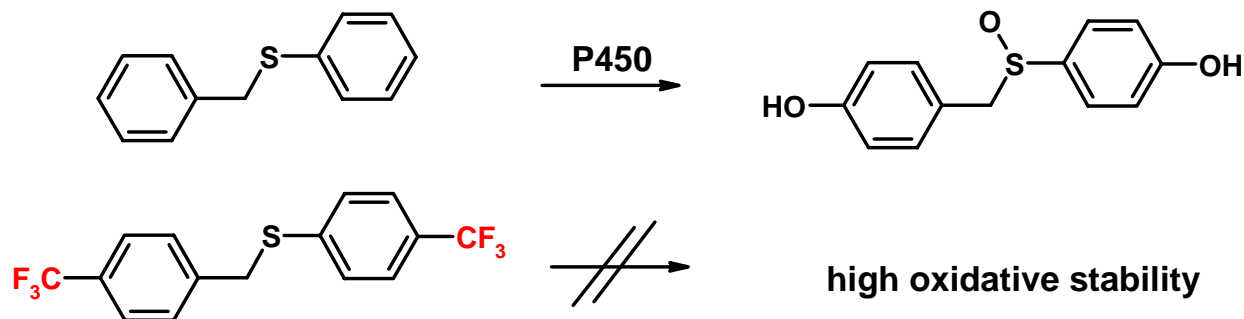


Cortisone

What Makes Fluorine so Different ?

Effects of Fluorine in Drugs

- **one fluorine is hydrophilic whereas more fluorines (CF₃-, OCF₃-, SCF₃-group) are strongly lipophilic**
 - increased lipophilicity
 - ⇒ improved bioavailability & pharmacological activity
- **strength of the C-F bond exceeds that of the C-H bond**
 - increased oxidative stability against enzymatic attack
 - ⇒ higher and broader range of activity
 - ⇒ reduced toxicity by metabolic stabilisation

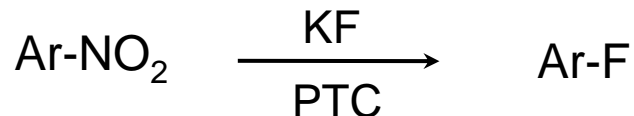


Selective Introduction of Fluorine in Aromatic Compounds

Nucleophilic Substitution Cl (Br) or NO₂ → F



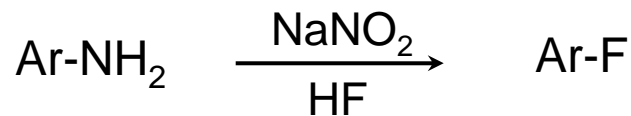
Halex Reaction



Fluorodenitration

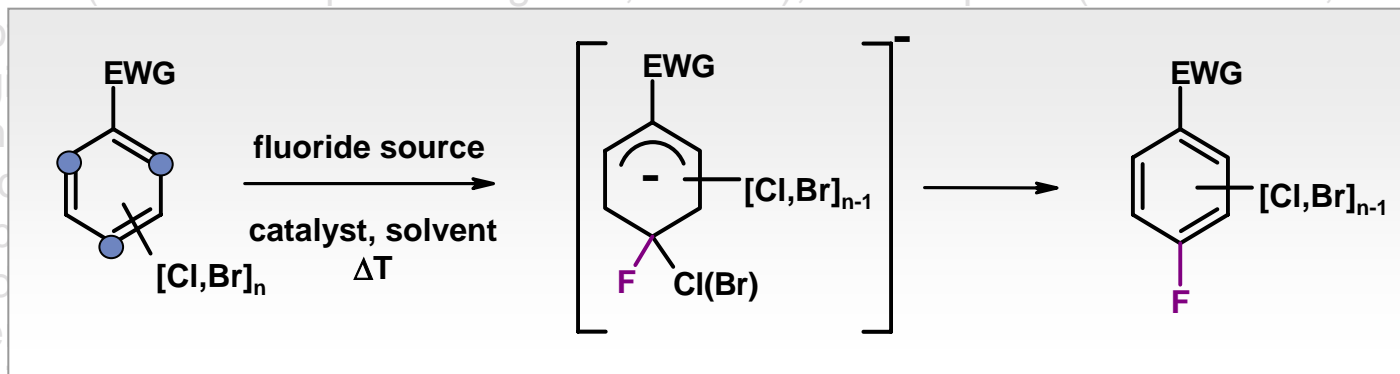
Activation by electron withdrawing groups
in *ortho* and/or *para*-position

Diazotization of anilines and fluorination with HF or HBF₄



“Schiemann” Reaction

The Classical HALEX-Reaction



EWG= $-NO_2$ (strong activation)

$-CF_3, CN, CHO, COCl \rightarrow COF$ (medium activation)

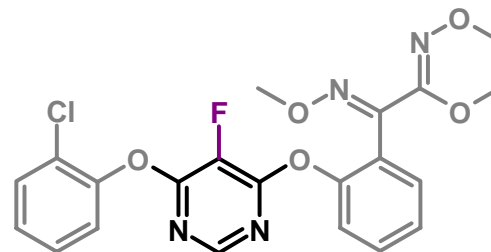
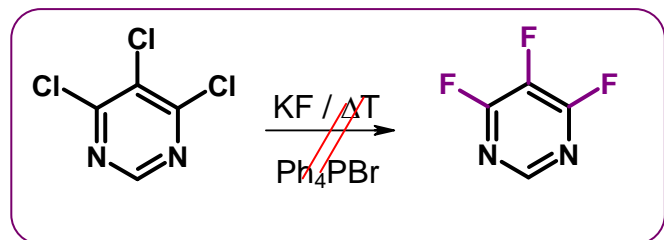
$-Cl, Br$ (weak activation)

Requirements for HALEX-reaction:

- activated substrate & high reaction temperature
- fluoride sources: KF, CsF, NaF...
- dipolar aprotic solvent: sulfolane, DMF, NMP, ...
- phase-transfer catalysts: e.g. Ph_4PBr

The Ultimate Challenge in HALEX-Chemistry

Low Activated Substrates

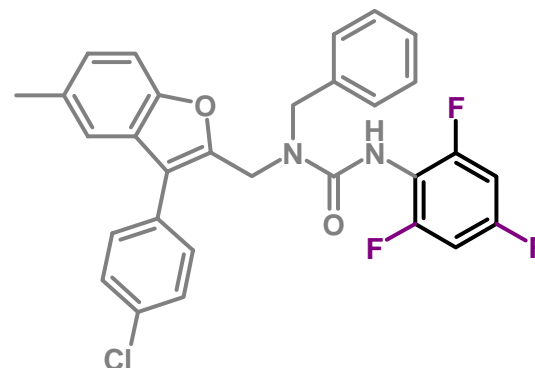
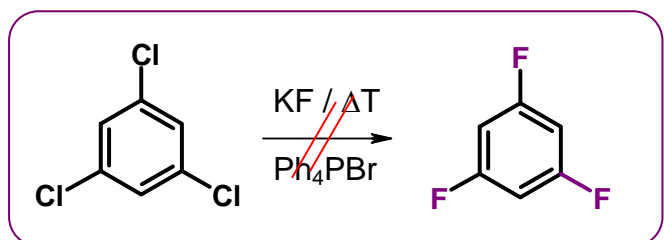


Fluoxastrobin
fungicide
(BayerCropScience)
2005

HALEX-reaction fails for low activated substrates using traditional phase-transfer catalysts (e.g. Ph_4PBr)



Limitation in HALEX-chemistry

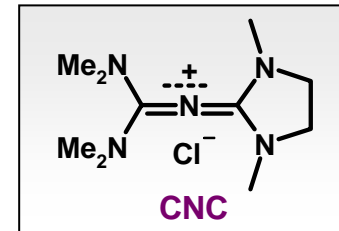


FR-145237
atherosclerosis
(Fuhisawa
Pharmaceuticals)

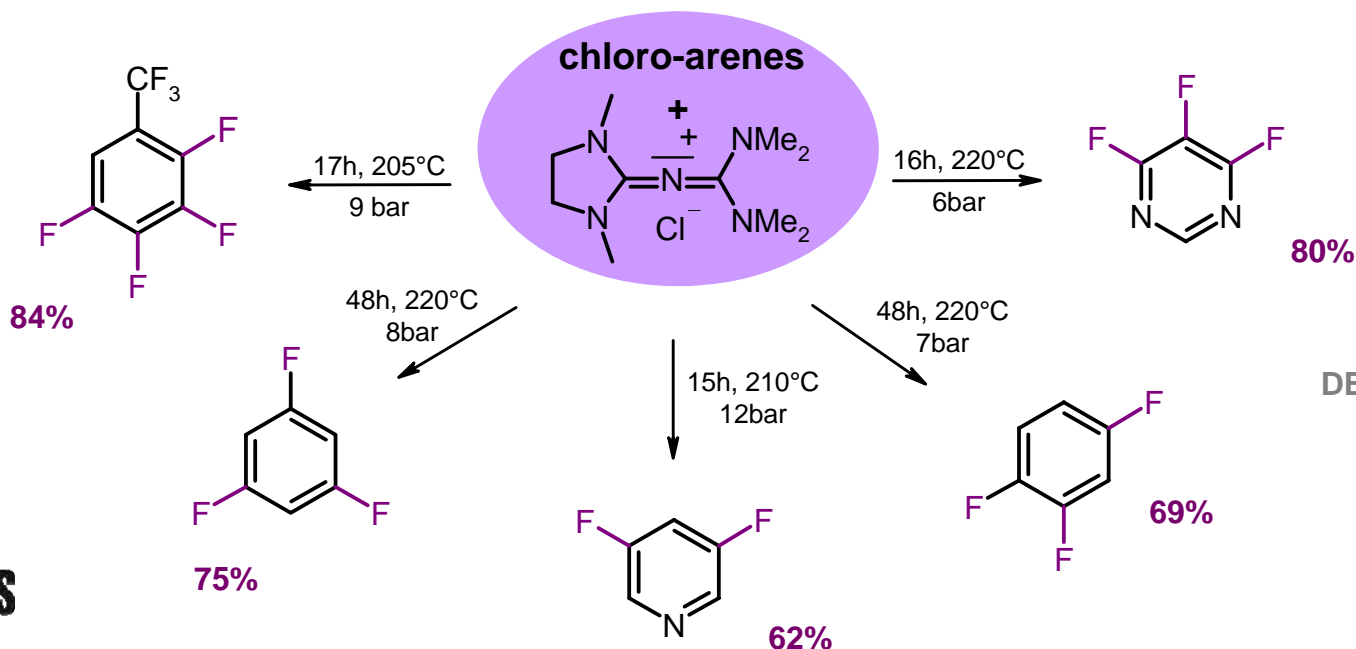
New Building Blocks Through Effective HALEX-Catalysts

SALTIGO's new generation of CNC-type HALEX-catalysts

- high activity at high temperature
- non-toxic & obtained by low-cost synthesis

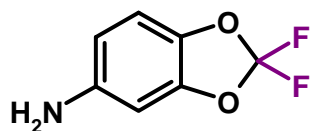


...enable the Halex-reaction of low & non-activated substrates and provide straightforward access to challenging fluorinated building blocks for life science.

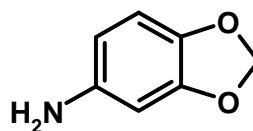


2,2-Difluorobenzodioxoles as Building Blocks for Active Ingredients

2,2-Difluorobenzodioxoles – Increased Lipophilicity

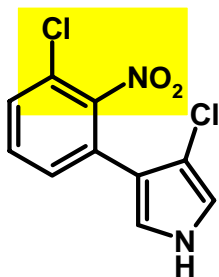


π 2,33



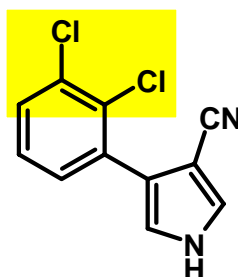
π 0,8

Fungicides



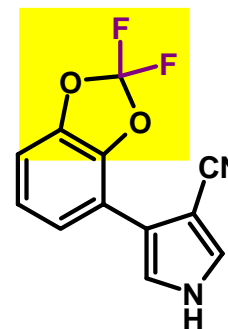
Pyrrolnitril:

natural product
antifungal activity



Fenpiclonil

„lead compound“
launch in 1988



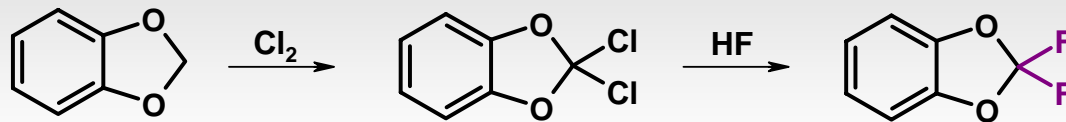
Fludioxonil (Celest®)

8 x more active
launch in 1993
(Ciba Geigy)

good mimic

2,2-Difluorobenzodioxoles & Derivatives for Active Ingredients

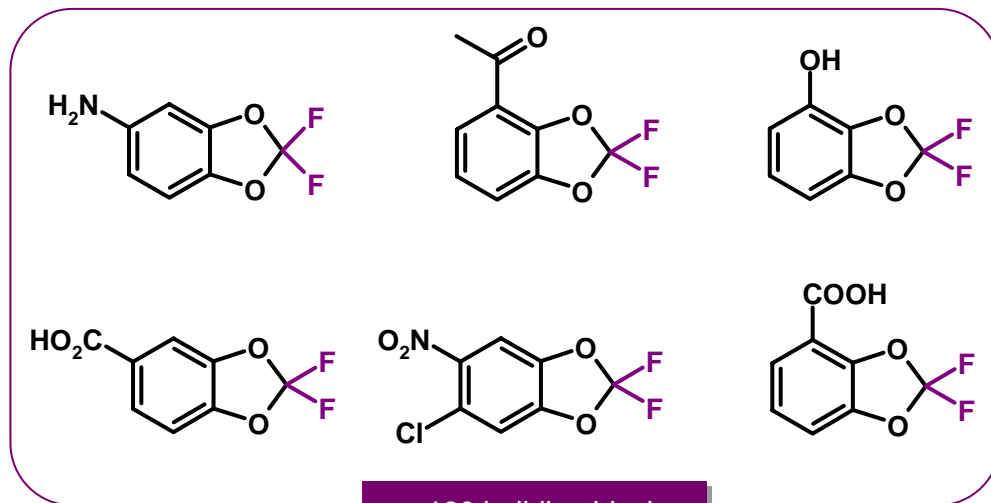
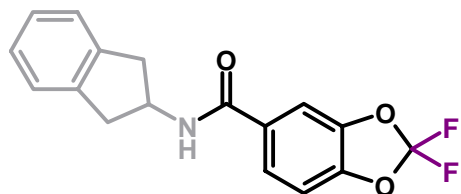
Saltigo: HF-based manufacturing process



DE 2819788 (Lanxess)

established process

Development of new drugs:
> 70 potential drug candidates

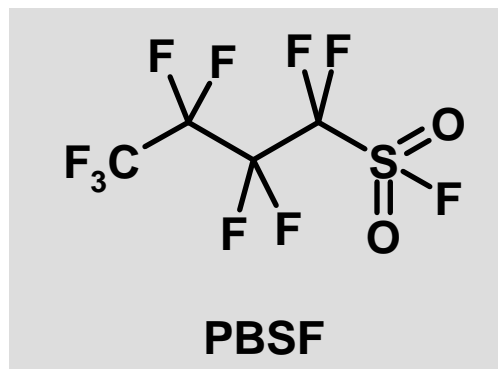


~ 120 building blocks

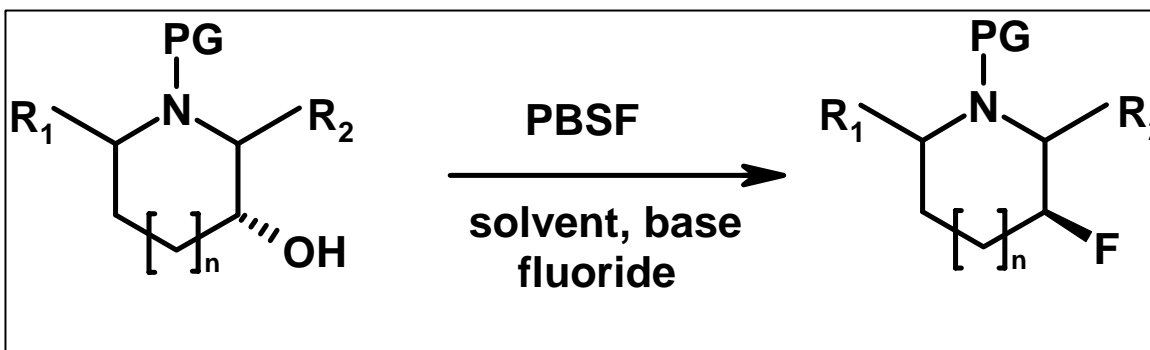
Saltigo's Fluorinating Reagent PBSF

Perfluoro-1-butanesulfonyl fluoride

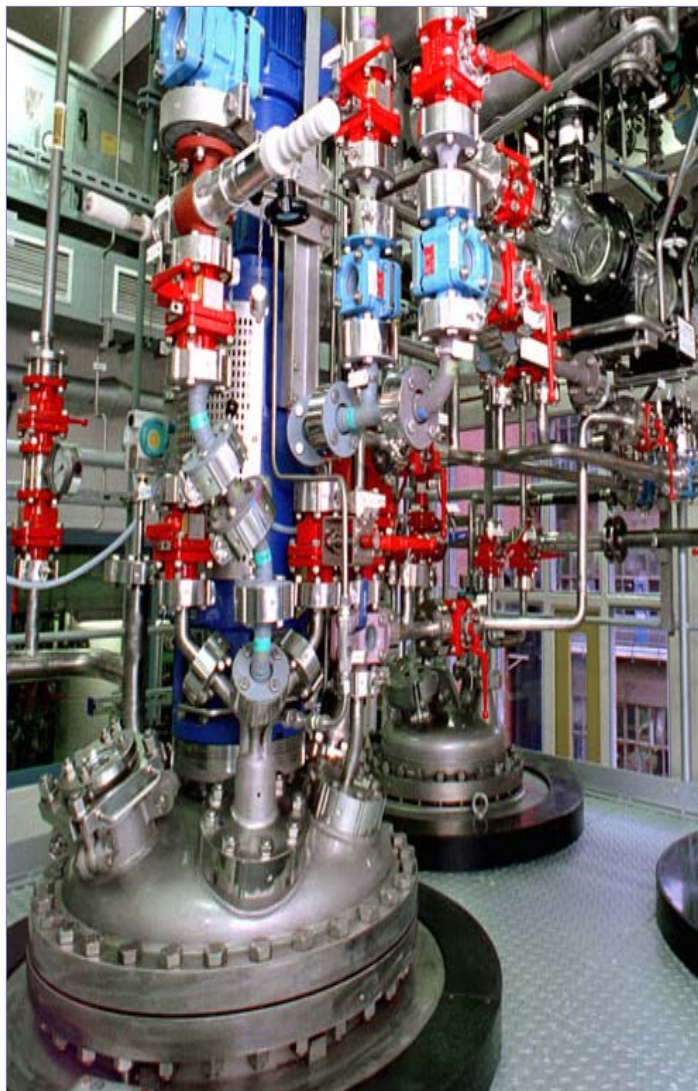
- Colorless liquid
- Low reactivity to moisture and air
- Not ignitable
- Protecting groups widely tolerated
- Used as precursor for flame retardants
- Produced at LANXESS in several metric tons per year



Scale-up Challenge: Racemization and price of reagents



Final Process for Scale-up



- ◆ Solvent toluene
- ◆ 1.25 eq. fluorinating agent
- ◆ 0.5 eq. additional fluoride
- ◆ Reaction at slightly elevated temperature
- ◆ Appr. 80% overall yield
- ◆ Low levels of residual reagent and by-products

Successful Scale-Up at the 1000 L Scale



- ◆ Run at multiple 100 kg -scale
- ◆ Scale-up from 1 L to 1000 L
- ◆ Robust process
- ◆ All batches in spec.
- ◆ Racemization-free fluorination

Why Outsource Fluorine Chemistry ?

Special Know How & Expertise required to succeed in fluorine chemistry

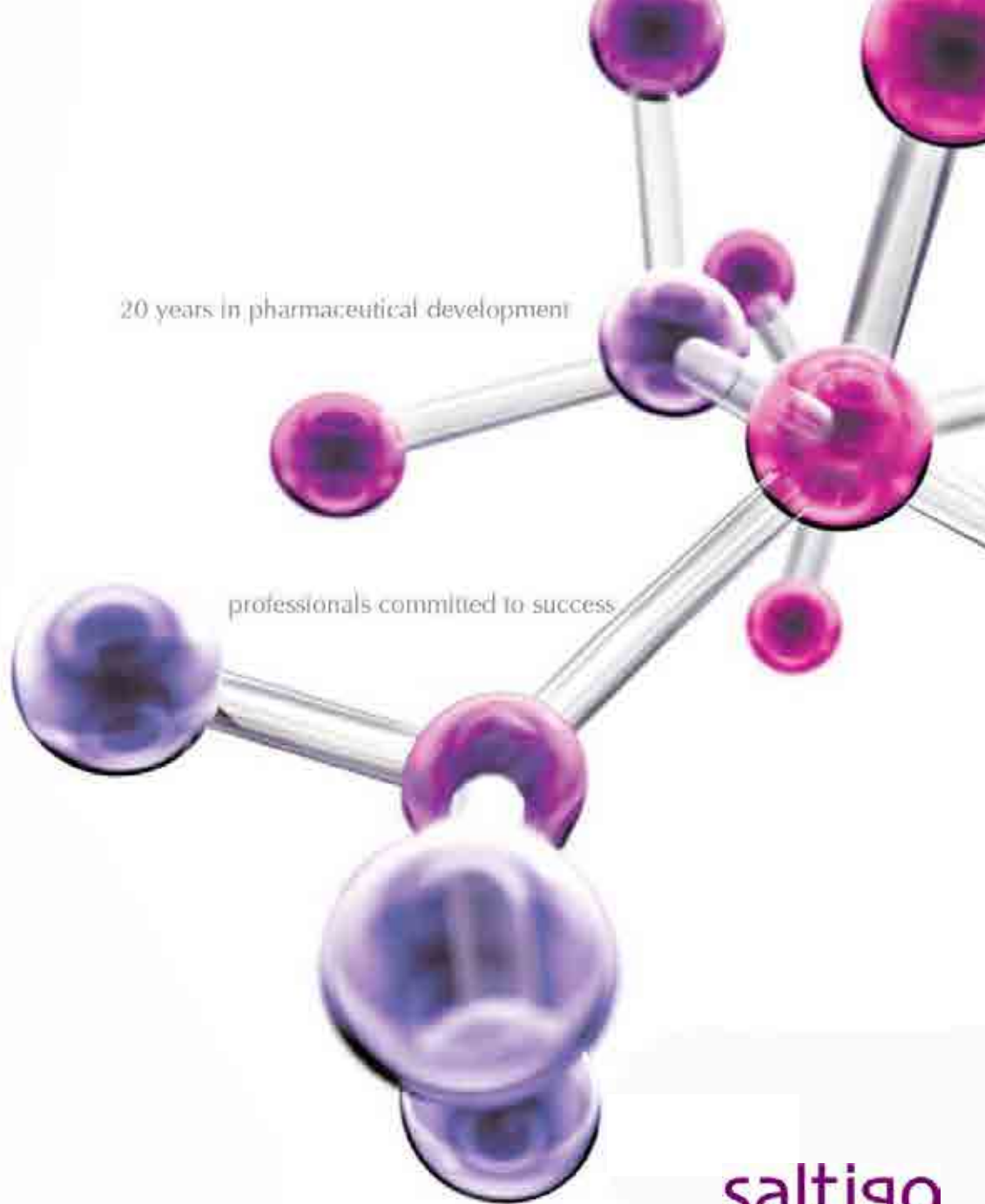
- Safe handling of toxic & corrosive reagents (e.g. HF, BF₃, DAST, ...)
- Special apparatus & technical equipment (PTFE, hastelloy, ...)
- Properties of fluoro compounds (stability, reactivity, toxicity)
- Fluorination methods
- Building blocks & commercial intermediates
- Saltigo has more than 45 years of expertise in fluorine chemistry

Fluorine Chemistry will remain an expert's field !



20 years in pharmaceutical development

professionals committed to success



saltigo
customized competence