IASOC - September 21-25, 2014

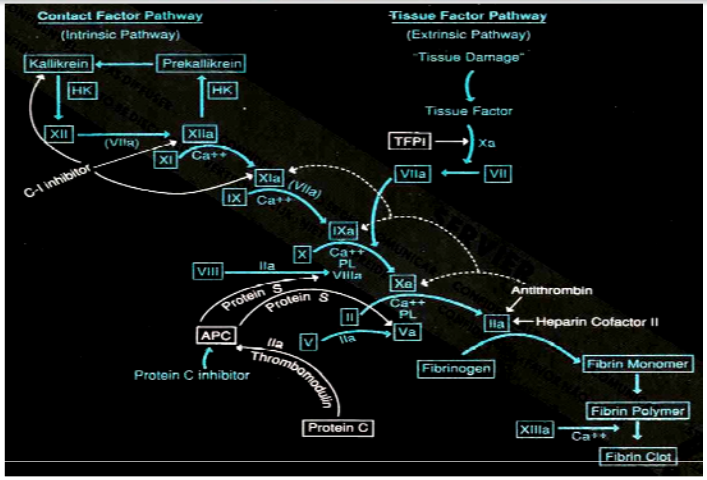
Aspects of cardiovascular drug discovery and development :

Studies towards the discovery of Thrombin and TAFIa inhibitors

Case Study # 1

SYNTHESIS OF NEW TETRAHYDRO-PYRROLO-PYRAZINONE CONTAINING ORALLY BIOAVAILABLE THROMBIN INHIBITORS

COAGULATION CASCADE



THROMBIN (fIIa)

- Proteolytic Enzyme belonging to serine proteases family
- Cleaves soluble fibrinogen to fibrin and stabilizes clots by activation of factor XIII
- Amplifies its own formation by activation of several coagulation factors
  (factors V et VIII)
- Lowers its own formation by binding to thrombomodulin to activate protein C (inactivation of factors Va et VIIIa)

MARKETED ANTITHROMBOTICS

INDIRECT INHIBITORS OF THROMBIN

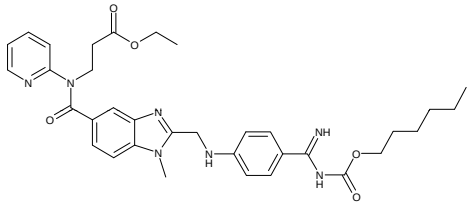
HEPARIN (iv/sc)
- → Polysulfated polysaccharide
- → Potentiate the activity of AT III (neutralisation of thrombin and factor Xa)
- → Thrombopenia

LMWH (iv/sc)
- → Chemical or Enzymatic Depolymerisation Heparin
- → Same activity compared to Heparin

A.V.K. (po)
- → Coumarin derivatives (ex: warfarin)
- → Inhibit vitamin K- dpendent factors
- → Orally active
- → High bleeding risk
- → DDI

MARKETED ANTITHROMBOTICS

DIRECT INHIBITOR OF THROMBIN

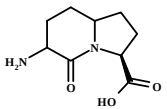


PRADAXA (Dabigatran)
Boerhinger Ingelheim
Launched 2008

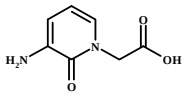
TARGET PRODUCT PROFILE

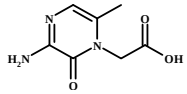
- Potent and selective Inhibitor of Thrombin
- Orally Active (good bioavailability)
- Active on venous / arterial thrombosis models
- Without Food /Drug Interaction
- Once a Day Administration
- No prodrug

PEPTIDOMIMETIC CORES AS Phe-Pro ANALOG

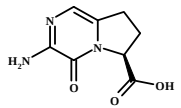


PFIZER ,
NOVARTIS,
....



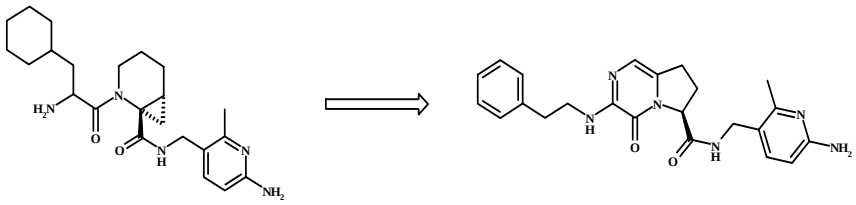


MERCK,
ELI LILLY,
...



SERVIER
(Tetrahedron Lett. 2002, 43, 3499-3501)

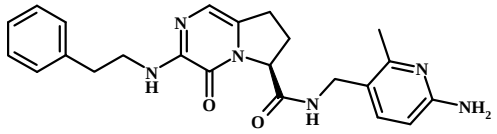
PEPTIDOMIMETIC INHIBITORS



S 34211

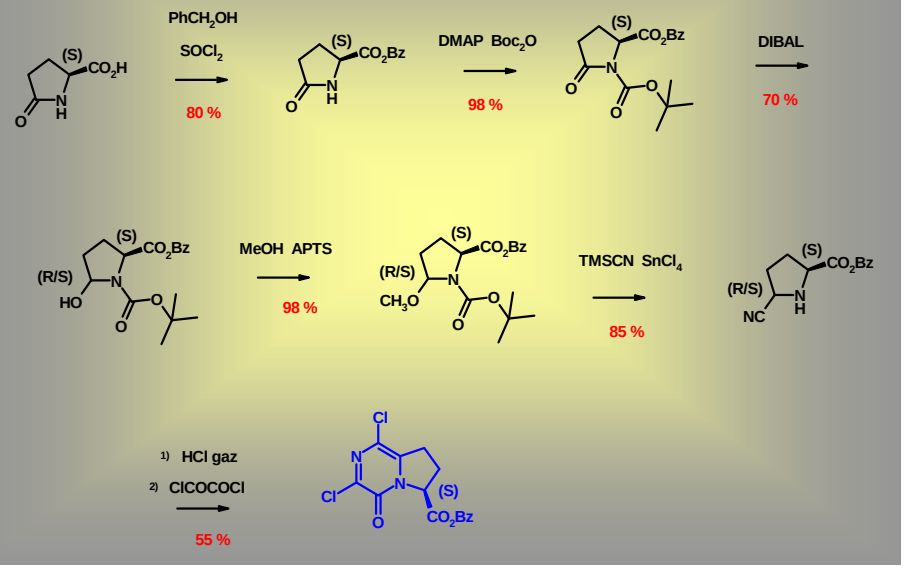
Direct and Reversible Thrombin Inhibitor
Selective
Orally active (F=80 %)
$t_{1/2}$ (1h)

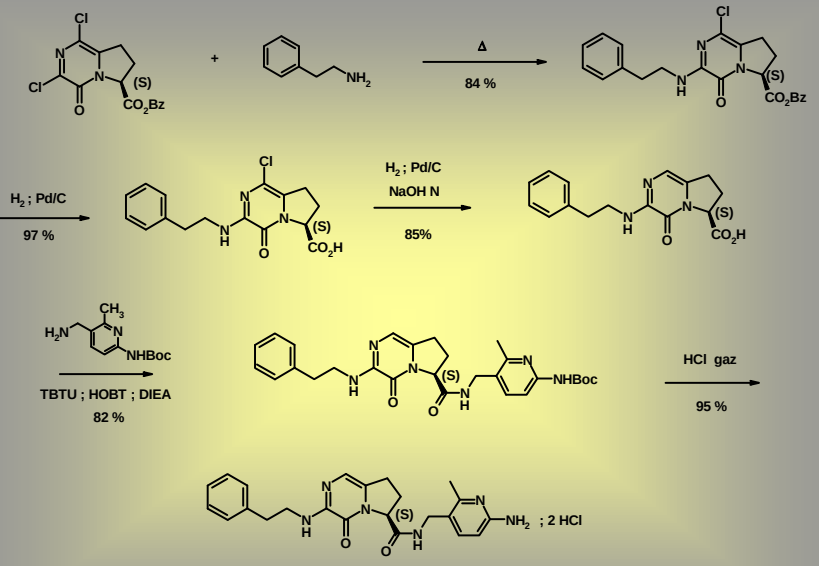
Pharmacological Profile of S 34840



IC_{50}(nM)	SELECTIVITY (nM)	COAGULATION H D R C(TT)2 (µM)	BIOAVAILABILITY Dog Rat	$t_{1/2}$ (h)
34	> 33000	3 3 2	100 56	10

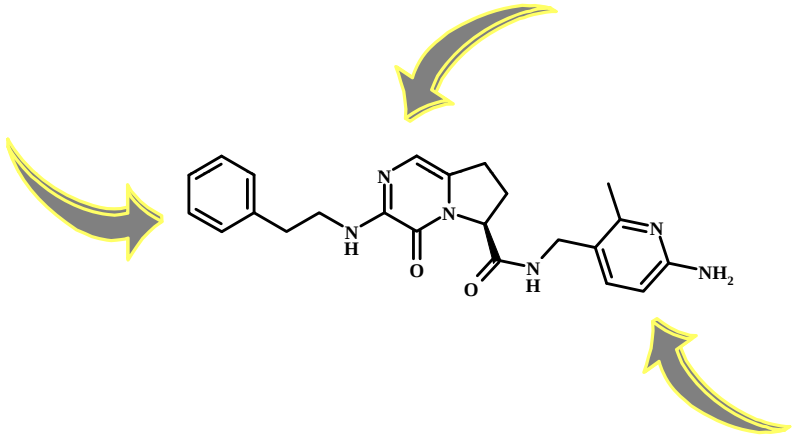
CHEMICAL SYNTHESIS OF S 34840



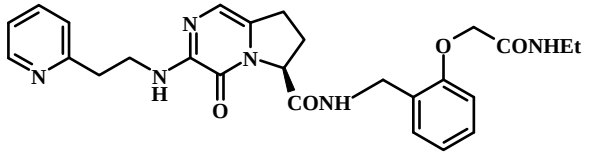


S 34840-1

SAR FROM S 34840



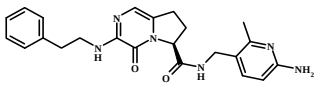
SUMMARY of SAR



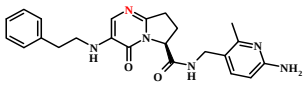
S 35972

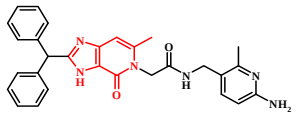
- Potent and selective : IC_{50} = 4nM , C(TT)2 = 0.24µM
- Orally Active : F(*Dog*) = 85 %
- Without food interaction
- Orally active on venous and arterial models of thrombosis
- Half-life = 4 h

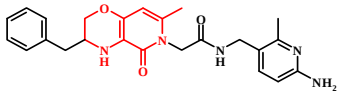
Other scaffolds .....

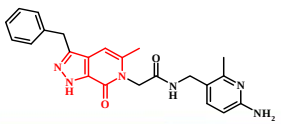


IC_{50} (nM)
34
508
5695
375
810

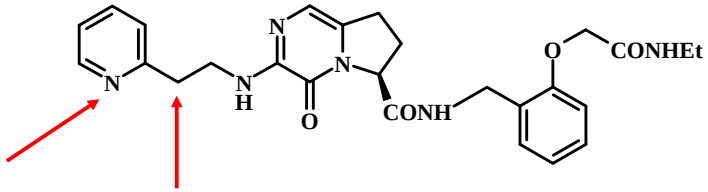








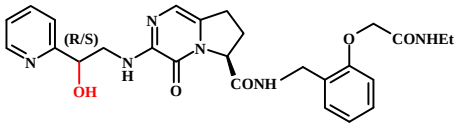
Metabolism Profile of S 35972



S 35972

IC_{50} = 4 nM
$C(TT)_2$ = 0.24 µM
t1/2 = 4 h
F (Dog) = 85%
MF = 32%

Metabolites of S 35972

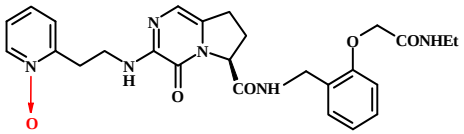


S 40240

IC_{50} = 10 nM
$C(TT)_2$ = 0.22 µM
†1/2 = 3h15
F(Dog) = 50%
MF = 65%

S 40243

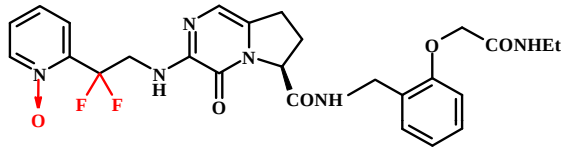
IC_{50} = 43 nM
$C(TT)_2$ = 0.48 µM



S 39733

IC_{50} = 1.8 nM
$C(TT)_2$ = 0.11 µM

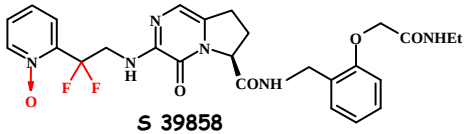
« Protected » S 35972



S 39858

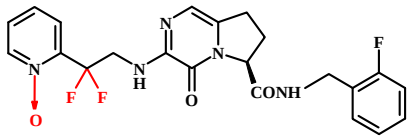
IC_{50} = nd
$C(TT)_2$ = 0.19 µM
F(Dog) = 18%
MF = 67%

Modification on *RHS* of S 35858



S 39858

IC_{50} = nd
$C(TT)_2$ = 0.19 µM
F = 18%
MF = 67%



S 40294

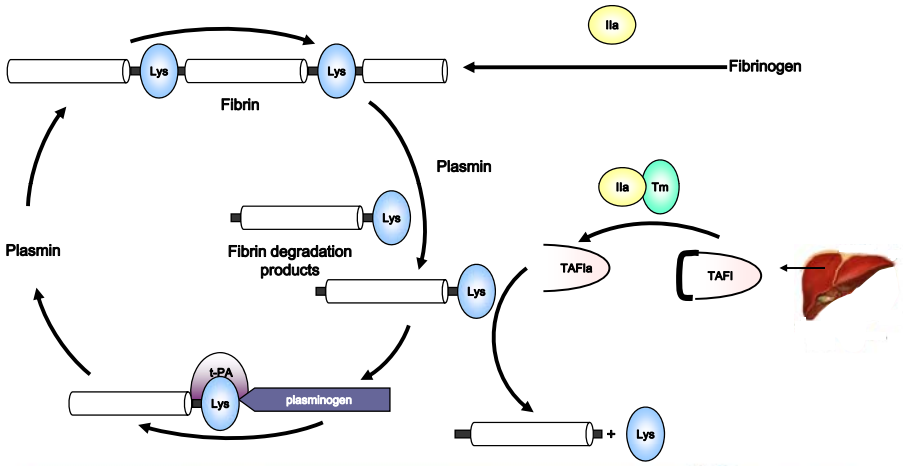
IC_{50} = 16 nM
$C(TT)2$ = 0.15 µM
F= 60%
MF = 92%

Case Study # 2

SYNTHESIS OF NEW TAFIa INHIBITORS

(Thrombin Activable Fibrinolysis Inhibitor Activated)

Role of TAFIa in Thrombosis

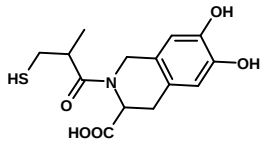


Hit Compounds

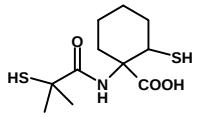
IC_{50} TAFIa (μM)

Captopril inhibitor of TAFIa

V 811, V 812, M 326
20 compounds

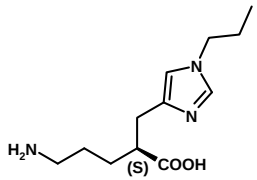


S 8897
25

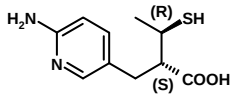


S 9917
20

Competitors

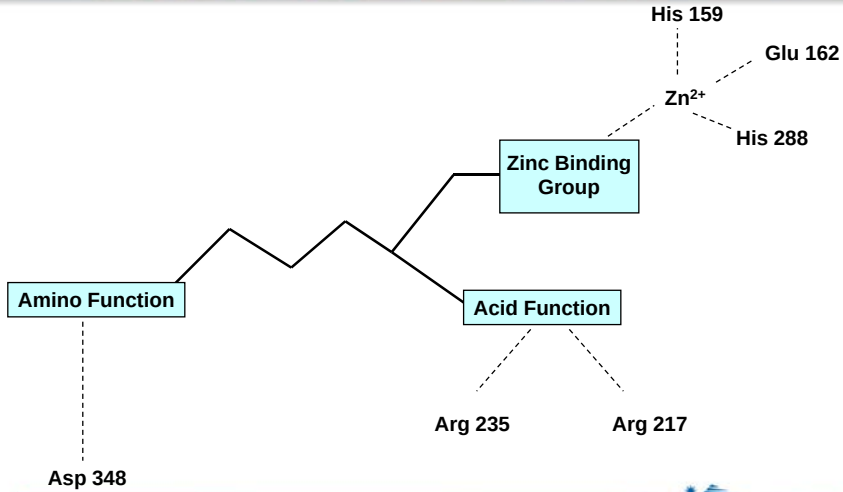


Pfizer (Phase I)
UK-396082



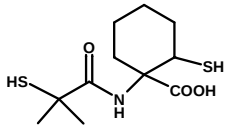
Astra-Zeneca (Phase II)
AZD-9684

Key Interactions in the Active Site



Hit to Lead Exploration

IC_{50} TAFIa (μM)



S 9917
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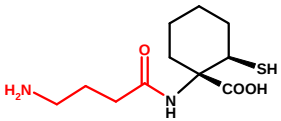
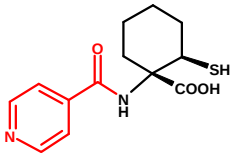
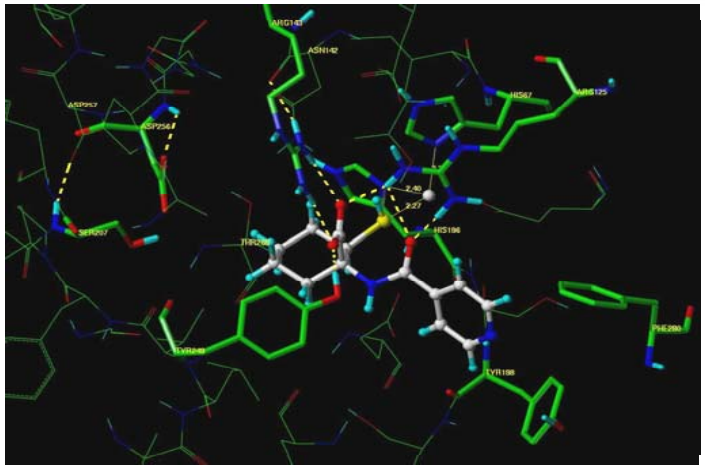


S 43970
> 30



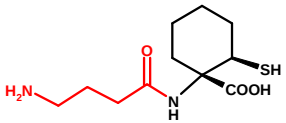
S 46321
> 30

S 43621-1 Binding Mode

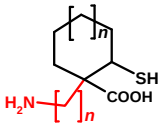


Hit to Lead Optimisation

IC_{50} TAFIa (μM)

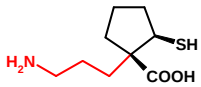


S 43970

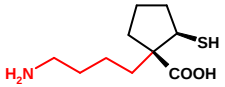


Lead Optimisation

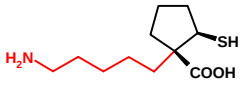
IC_{50} TAFIa (μM)



S 45708
0.014

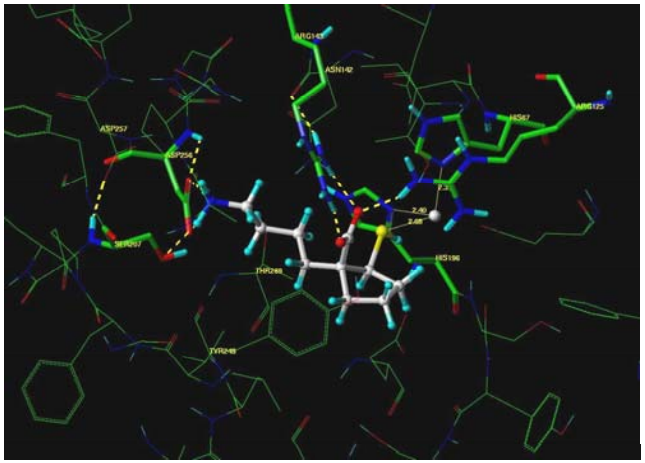


S 44900
0.17



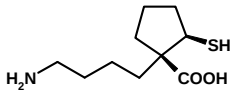
S 45377
1.65

S 44900-1 Binding Mode



S 44900-1 / S 45708-1 Enantiomers Separation

IC_{50} TAFIa (µM)

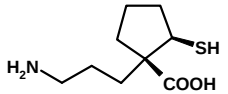


S 44900
0.17

S 45646
2.03

S 45647
0.081

➢ Syn-rac

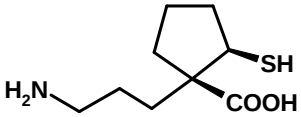


S 45708
0.014

S 46911
5

S 46913
0.005

Lead Optimisation : SAR Results



S 46913

Basic side chain modifications

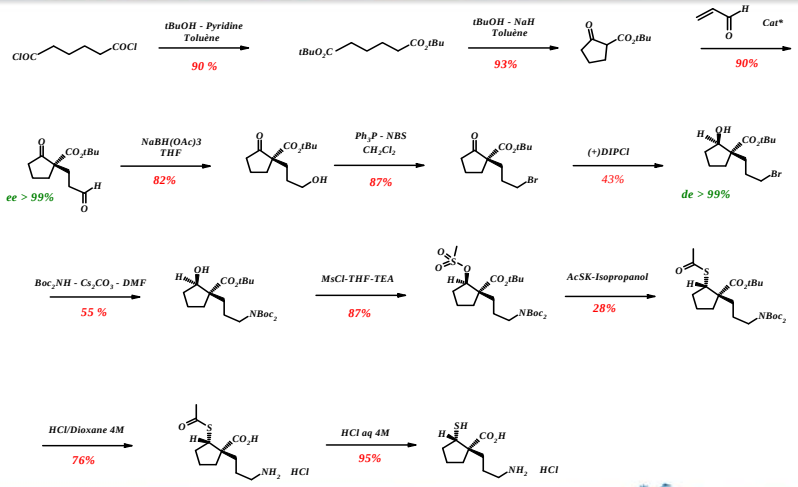
- N-methyl amine
- N,N-dimethyl amine
- Cyclic amine
- Pyridine

Thiol function replacements

- Carboxylic Acid
- Hydroxamic Acid
- Retro-hydroxamic Acid
- Triazole

IC_{50} > µM

Stereoselective synthesis of S 46913



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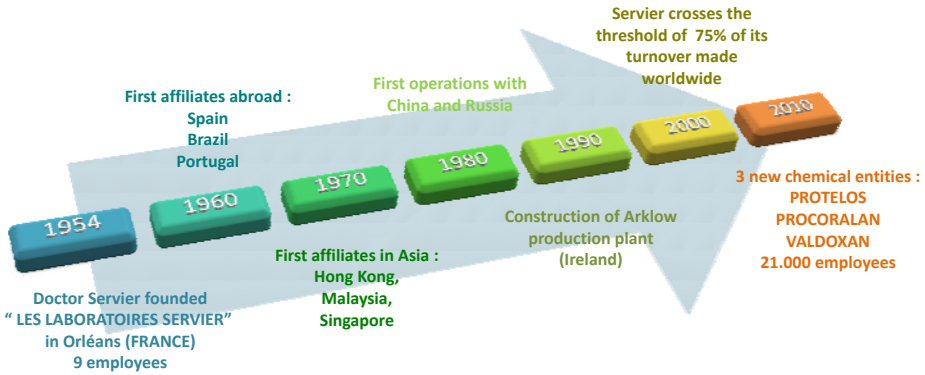
Nicolas BOYER

PHARMACOLOGY

Tony VERBEUREN

Alain RUPIN
Marie-Odile VALLEZ
Philippe MENNECIER
Isabelle RICHARD
Christine MAUCLAIR

Milestones of our company

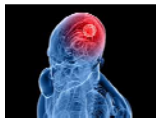


Servier : Research Orientations

Coronary Arterial Disease
Heart Failure
Venous Disease
Ischemia
Arterial Hypertension
CARDIOVASCULAR

Epigenetics
Angiogenesis
Proliferation / Differention Pathways
Cell metabolism
Apoptosis
Immunotherapy
Protein degradation
ONCOLOGY

Depression / Anxiety
Schizophrenia
Cognitive Impairment
Neurodegenerative diseases
(Alzheimer, Parkinson)
CNS



METABOLISM
Type II Diabetes Mellitus

RHUMATOLOGY
Osteoporosis
Osteoarthritis
Inflammatory & auto-immune diseases
Muscular pathologies

Main marketed products

CARDIOVASCULAR
Coversyl Hyperium
Coveram Artex
Preterax Procoralan
Fludex Vastarel

ONCOLOGY
Muphoran

SERVIER

CNS
Valdoxan
Stablon
Trivastal

METABOLISM
Diamicron
Diamicron MR

RHUMATOLOGY
Protelos