TAROS

discovering the world of chemistry

Small Molecule Drug Discovery Chemistry

Winter 2022

Taros – Your Trusted Chemistry CRO

100 % Privately Owned – Successful Organic Growth Over 20 Years

1999	2004	2009	2013	2022
3 Employees	**13 Employees**	**24 Employees**	**50 Employees**	**70 Employees**
Inception of Taros Custom Chemicals in Marburg	Rebranding and Relocation to Dortmund	Inception of Mithros Chemicals, Hyderabad	Project Executive European Lead Factory	Portfolio of Drug Discovery Services

- 2013-2018: Leading the Chemistry Consortium of IMI's € 196 m ELF drug discovery platform
- Headquarter in Dortmund, GERMANY
  - 50 Laboratory staff / 35 PhD level
  - Work in shifts → Total 14 h/d
  - 1500 m^2 Laboratory space, 52 fume hoods
- Own facilities in Hyderabad, INDIA
  - 50 Laboratory staff
  - Large scale synthesis and scale-up

- Small scale synthesis
- Route scouting and optimization
- Chemical process development and scale up to pilot plant
- Medicinal chemistry
- Computational chemistry and molecular modeling
- Department for parallel chemistry, library design and production

Small Molecule Drug Discovery Chemistry

Introduction To Our Core Competences

Click to skip to each section

1 Custom organic synthesis

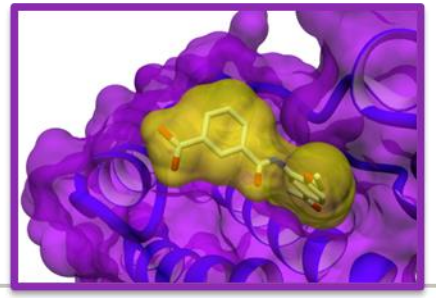
- Excellence in synthetic chemistry
- Route scouting & optimization
- Proactive consulting

2 Process research & scale-up

- Small & large scale synthesis
- Process optimization & development
- Scale-up to 20 kg per batch (non-GMP)

3 Library design & Parallel synthesis

- Literature inspired
- Focused & screening libraries
- SAR expansion arrays



4 Computational chemistry

- Computer aided drug design
- Cheminformatics & virtual screening
- Bioinformatics & Chemogenomics

5 Medicinal chemistry research

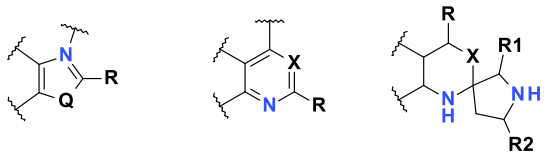
- Hit validation & expansion
- Lead generation & optimization

Custom Organic Synthesis 1

Broad Chemistry Expertise For Small Molecule Drug Discovery (1)

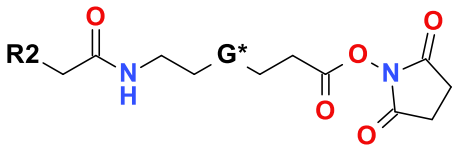
Heterocyclic chemistry (as experienced pharmaceutical CRO)

- Traditional heterocyclic chemistry
- Since ELF (2013) also experienced in design and synthesis of non-planar heterocyclic compounds (libraries)



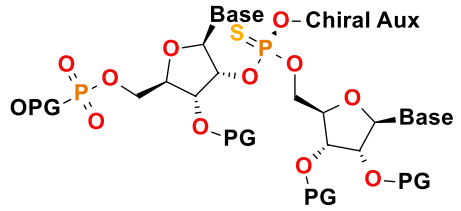
Labelled compounds (2H and 13C)

- E.g.: for LC-MS-MS analyses of peptides



Nucleotides

- Customized nucleosides/nucleotides, dinucleotides, phosphoroamidates, thiophosphates, triphosphates, and monophosphates → e.g.: Labelled
- Chiral thiophosphate units
- Analytical equipment and purification in-house or available at our university partner

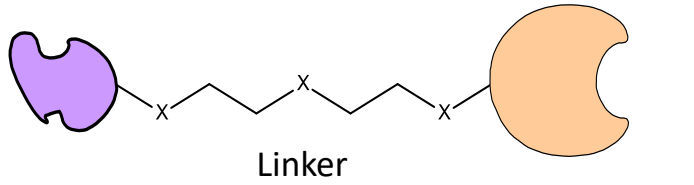


Custom Organic Synthesis 1

Broad Chemistry Expertise For Small Molecule Drug Discovery (2)

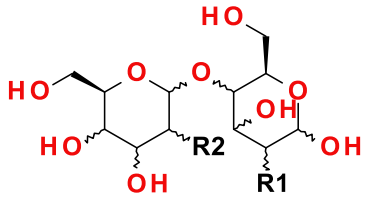
Targeted Protein Degradation (TPD)

- Capability to develop unique linkers and molecular glues to meet current discovery demands
- PROTACs, partial PROTACs, functionalization of a wide range of ligands
- Small scale as well as large scale synthetic support



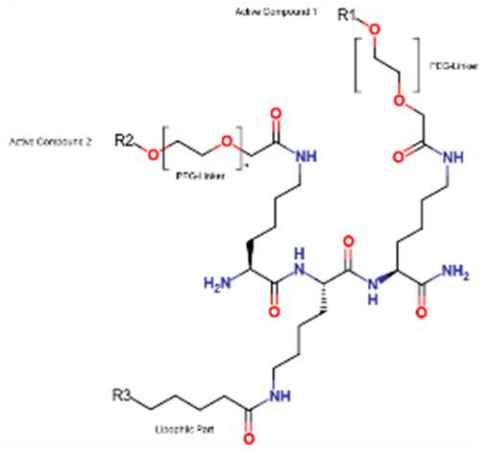
Carbohydrate chemistry

- Customized saccharides
- Oligo-saccharides



Peptide chemistry

- Long, cyclic or dimeric peptides
- Different linkers, spacers and PEGs
- Peptidomimetics



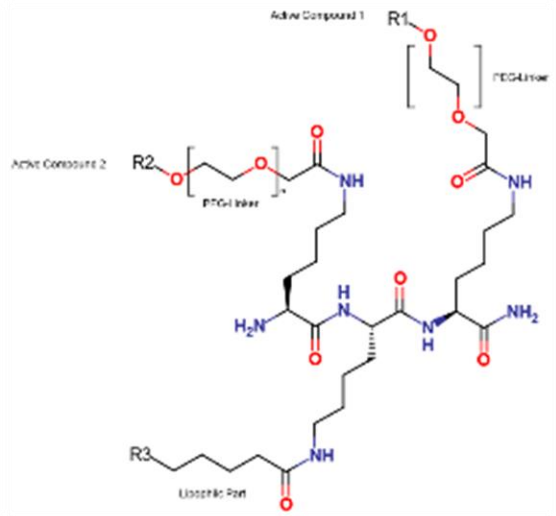
Custom Organic Synthesis 1

Syntheses Of Complex Peptides And Peptide Conjugates

Taros delivers molecular design, medicinal chemistry and synthesis of peptide-small molecule conjugates

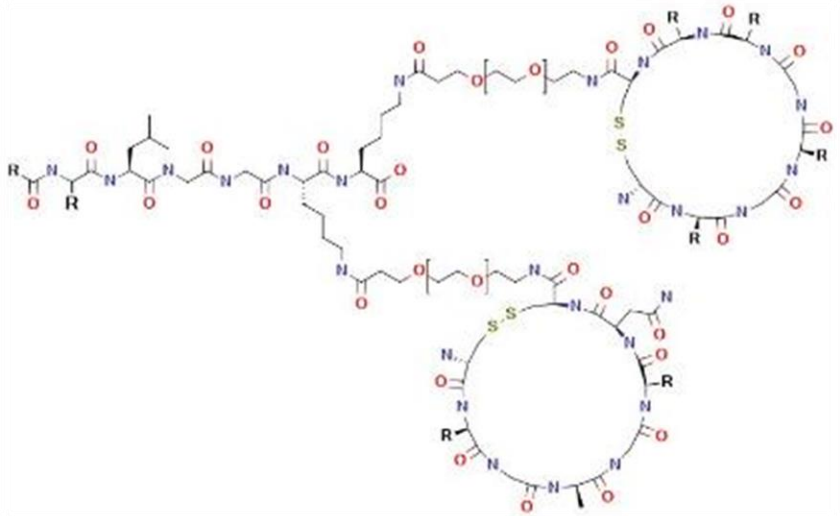
Integrated approach to treating a specific disease

- Conjugates designed by Taros
- Retro-synthetic analysis and development of an efficient synthesis
- Over all 34 steps to multiple variations of the peptide-small molecule conjugates



Custom large peptides

- Cyclic and linear special peptides
- Retro-synthetic analysis and development of an efficient synthesis
- Up to multi-gram scale isolation
- Over 27 steps



Process Development And Scale-up 2

From Lab To Large Scale Synthesis

- Small and large scale synthesis (probes, metabolites, impurities, radiolabelled tracers)
- Process optimization (route scouting , optimisation) and development
- Scale-up to 20 kg per batch (non-GMP), 500kg per year
- Synthesis of impurities (synthesis of standards for impurity profiling, degradation derivatives)

Route Scouting

- Aliphatic, aromatic and heterocyclic chemistry
- Microwave chemistry
- Combinatorial chemistry
- Polymer chemistry (only dispersions)
- Dye chemistry
- Flow Chemistry

Product and test samples

- Facilities in Dortmund up to few kg
- Facilities in Hyderabad, India up to 1 t/a

Process Development

- Route optimization – Design of experiment
- Raw materials availability
- Mass Balance
- Scalability
- Safety (Mettler-Toledo Optimax 1001, Linseis TG-DSC)

Synthesis of impurities

- Synthesis of standards for impurity profiling
- Degradation derivatives

Process Development And Scale-up 2

Our Laboratories For Large Scale Organic Synthesis in Germany (Dortmund)

Laboratories

- 50 Laboratory staff / 35 PhD level; work in shifts → Total 14 h/d
- 1500 m^2 Laboratory space; 52 fume hoods

Characterization of products and side-products

In-house analytical equipment

- Bruker 300 MHz NMR (1H, 13C)(1D, 2D)
- Magritek Benchtop 80MHz NMR (31P, 19F, in flow)
- Waters HPLC-MS
- Agilent uHPLC-MS
- Agilent GC-MS
- KF-titrator
- Kern Moisture Analyzer

Contractual access to TU Dortmund

- Bruker range of NMRs up to 900 MHz (1H, 13C, 19F, 31P)
- Polarimeter
- SECcurity GPC System
- Bruker ATR-FT-IR
- Bohlin Instrument Rheometer
- Malvern DLS
- Raman Spectroscopy

Purification

Flash column chromatography

- System Reveleris X2 and Büchi Pure C-815
- Flow until 200 mL/min
- Pressure until 200 psi
- Detectors UV (200-800 nm) and ELSD
- All kind of classical solvent and buffer
- Normal phase until 150 g substance
- Reverse phase until 12 g substance

Recrystallization

- Large experience from kg scale activities

Sublimation

- Standard equipment

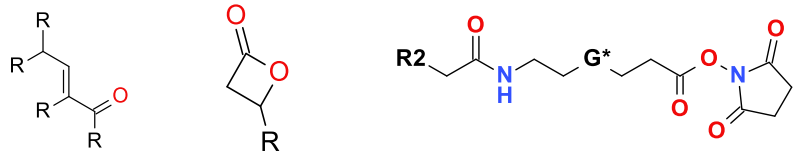
Process Development And Scale-up 2

From Lab To Large Scale Synthesis

Expertise and Trained Personnel Covering the Full Range of Organic Chemistry

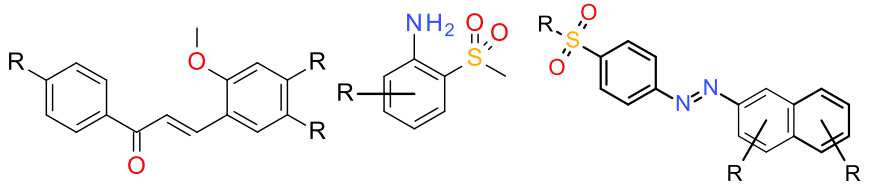
Aliphatic chemistry

- ✓ Typical 1 to 5 steps linear
- ✓ 5 g to 500 g target amount



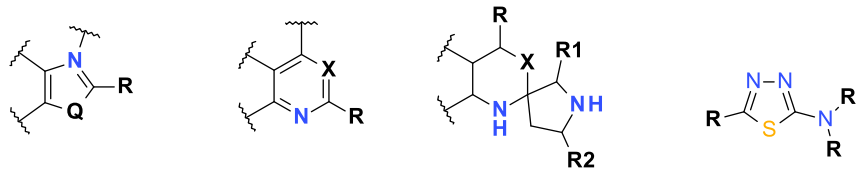
Aromatic chemistry

- ✓ Typical 3 to 13 steps linear
- ✓ 100 mg to 500 g target amount



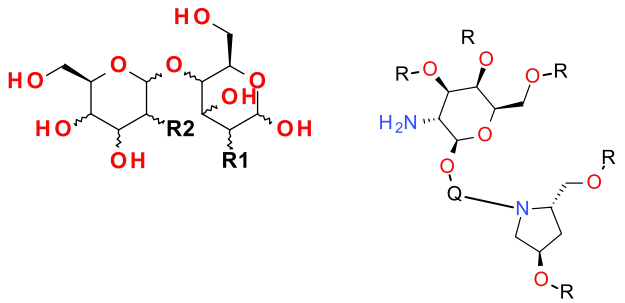
Heterocyclic chemistry

- ✓ Typical 1 to 10 steps linear
- ✓ 100 mg to 200 g target amount



Carbohydrate chemistry

- ✓ Typical 5 to 19 steps linear
- ✓ 5 g to 10 g target amount



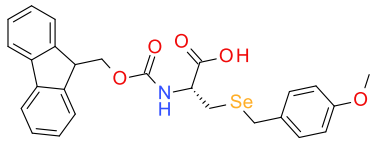
Process Development And Scale-up 2

From Lab To Large Scale Synthesis

Expertise and Trained Personnel Covering the Full Range of Organic Chemistry

Amino acid chemistry

- ✓ 4 to 15 steps linear
- ✓ 5 g to 80 g target amount
- ✓ Selenium chemistry in g to 100 g scale e.g seleno aminoacids



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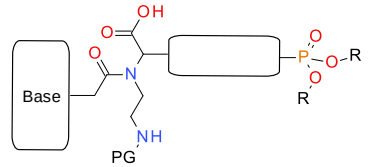
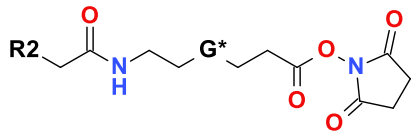


Labelled compounds

- ✓ 3 to 6 steps linear
- ✓ 10 mg to 500 mg target amount



High-pressure reactions/ Hydrogenations

- ✓ Pd/Ru catalysed asymmetric reductions up to 500 g
- ✓ Expertise in optimising asymmetric hydrogenation by using ligands scalable for multig gram or kg production

Metabolite/impurity/reference synthesis

- ✓ 4 to 12 steps linear
- ✓ 50 mg to 15 g

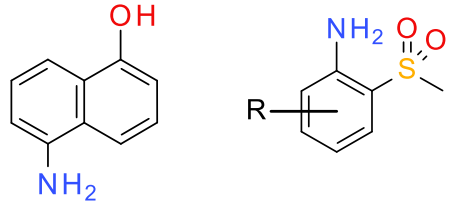
Process Development And Scale-up 2

From Lab To Large Scale Synthesis

Expertise and Trained Personnel Covering the Full Range of Organic Chemistry

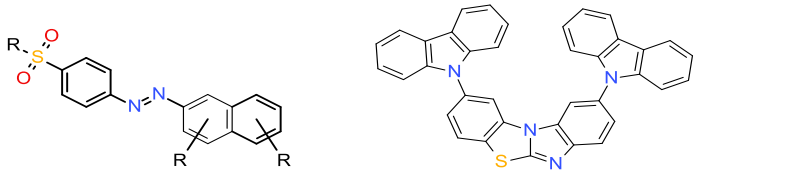
Building blocks for dye industry

- ✓ 4 to 6 steps linear
- ✓ 500 g to 240 kg target amount



Azo dyes/Dyes

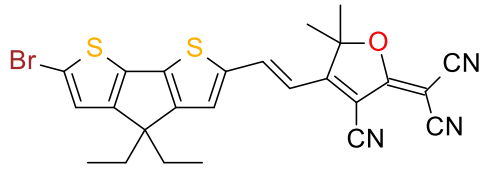
- ✓ 4 to 6 steps linear
- ✓ 500 g to 400 kg target amount



Angew. Chem. Int. Ed. **2016**, *55*, 6864 –6868

OLED materials

- ✓ 2 to 6 steps
- ✓ 500 g to 10 kg target amount



RSC Adv., 2014, **4**, 42044–42053

Compound Library Design And Production 3

Our Library Designs Target Underpopulated Druglike Chemical Space

European Lead Factory

- European Lead Factory: € 196 Million Budget and 30 Partners
- 2013-2018: Taros led the chemistry consortium building 200,000 compounds from scratch
- Taros started its library activities and built its own subset of 40,000 compounds for commercialization

Scaffolds with or without 3D character

- ✓ Polarity, structural complexity and 3D elements engineered in scaffolds
- ✓ Not solely deriving from decoration reagents
- ✓ New structural shape and topology
- ✓ More sphere-like shaped compounds

Complementary chemical space

- ✓ Spiro, bridged and fused ring systems
- ✓ Saturation, conjugation and substitution
- ✓ Minimal overlap with corporate collections and commercial vendors

Balanced design

- ✓ Absence of chemical liability
- ✓ Selection of diversity reagents ensures good balance between availability of related pairs of molecules to discern SAR during hit evaluation and wide sampling of chemical space.

High diversification potential

- ✓ Higher number of diversification points and their good practical exploitation

Library Production 3

Library Production – Work Flow

Design

Literature Search and In-house procedures

Chemistry Validation

Scaffold´s route validation and scale up to Multi g-scale

Parallel setup validation
Test block
- ✓ Rxn´s yield
- ✓ Crude Isolation method
- ✓ Purification method
- ✓ (Acidic or Basic HPLC-MS)

Typical Chemistry transformations in parallel:
- Amide coupling
- Ureas
- Triazole formation
- Sulfonylation
- Suzuki coupling
- Boc deprotection
- Saponifincation, etc.

Production

Enumeration

Parallel setup

Mettler Toledo Blocks
- ✓ In 0,5 ml- 20 ml rxn
- ✓ 24-48 rxns/d, 4 d/week
- ✓ Under air or inert atmosphere
- ✓ Low or high temperature

Eppendorf and Bio-shaker
- ✓ In 24-96 well-plates
- ✓ In 0,5 ml- 2 ml rxn
- ✓ 24-96 rxns/d, 4 d/week
- ✓ Under air
- ✓ Room to 99 °C.

Purification

HPLC-MS directed purification

Injection Volume
1.5 ml in 24/96 deep well plate format

Average purity:
95 % by uHPLC

Library Purification 3

HPLC-MS purification

Throughput and Cyclic time

Throughput

24 – 48 cpds /day
4 day/week

Cycle time

2-2.5 weeks
Start of purification until delivery

Purification

Crude amount

10 -200 mg (solubility dependent) of crude material

Injection Volume

1.5 ml in **24/48/96 deep well plate** format

Mobile Phase Conditions

- ✓ Basic (ammonium carbonate buffer) and Acidic (formic acid, TFA)
- ✓ Solvent: ACN/Water; 32 ml/min; 11 min run

Preparative Columns

- ✓ 2 x XBridge Prep C18 5µm OBD; Kromasil 300-10C4

Analytical Columns

- ✓ XBridge C18 3.5µm 19x150mm; Acquity UPLC BEH C18 1.7µm 2.1x50mm; Acquity UPLC HSS T3 1.8µm 2.1x50mm; Kromasil 300-5-C4 4.6x150mm; Symmetry C8 5µm 4.6x250mm

Peak collection

- ✓ Mass guided, UV, or UV + mass guided, retention time
- ✓ Diode array detection (200 to 300 nm)

Purification System

System

2 x Mass directed 1620 Agilent Infinity HPLC purification system

Detection methods

- ✓ 1260 Agilent Infinity Quadrupole Mass Detector
- ✓ Diode array detection (200 to 300 nm)

Ionization method

Multimode ESI/APCI

Final Sample Analysis

System

1 x 1620, 1920 Agilent Infinity UHPLC-MS system

Detection methods

- ✓ 1260 Agilent Infinity Quadrupole Mass Detector
- ✓ Diode array detection (200 to 300 nm)

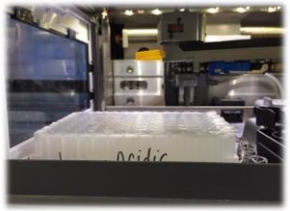
Ionization method

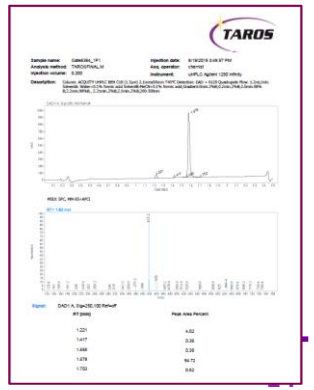
Multimode ESI/APCI

Final Sample and Data Format

7 ml Chromacol barcoded powder vials or Matrix vials.

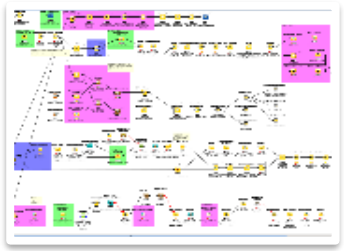
Analytical data as PDF files, Vial taras and gross weights.





Compound Library Design And Production 3

Our Recipe For Success And The Equipment



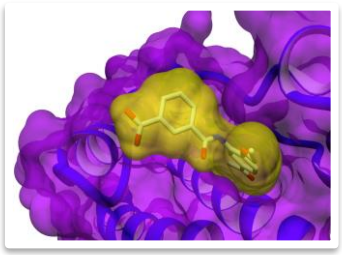
Enumeration

Preparative HPLC

Shipping

1 2 3 4 5 6

Design and Validation



Parallel Setup

Final analysis

Equipment

- 1 Zinsser Analytics Calli weigh station
- 2 Agilent 1260 Infinity mass-directed auto-preparative HPLC systems
- 1 Agilent 1290 Infinity analytical UHPLC-MS
- 1 Waters Alliance analytical HPLC-MS
- 1 Grace Reveleris X2 FlashMaster
- 2 x Büchi Pure C-815 Flash

- 2 Genevac HT-4X centrifuges for sample drying
- 1 Genevac EZ2 centrifuge for sample drying
- 1 Eppendorf centrifuge 5804 for sample filtration
- 10 Mettler Toledo MiniBlock XT Solution Phase Synthesizers
- 1 Eppendorf shaker, 2 Bio-shakers iQ
- 4 Radleys Carousel Reaction Stations
- 2 BioShake iQ (parallel shaker with temperature control)
- 1 Xelsius parallel synthesis reactor (with 10 parallel different temperatures)

Compound Library Design And Production 3

Our Library Designs Ensure Diversity And Novelty

Diversity is ensured at the scaffold level and within the library with regards to the enumeration of the final compounds.

1. **Substructure search**
   We are checking the core structure in comparison with commercially available reagents based on internally cured eMolecules collection. The substructure search needs to usually retrieve an empty result to proceed with the scaffold.

2. **Scaffold similarity**
   The central core (scaffold) is compared to Taros libraries already offered to the costumer. We accept scaffolds with 2D Tanimoto similarity coefficient less than 0.75. Further analysis of novelty and diversity of the compounds is accessed by comparison to commercially available screening sets, Chembl and chemical patent space.

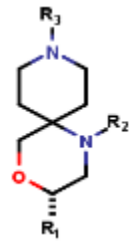
3. **Structural diversity of final compounds**
   The scaffolds are enumerated with final diversification reagents. Most of the final compounds have the 2D Tanimoto similarity score between 0.15-0.4.

4. **Physicochemical properties**
   At the same time, a set of physicochemical properties (e.g. MW, logP, fsp3, TPSA) are calculated.

Compound Library Design And Production 3

Scaffold design

Monocycles

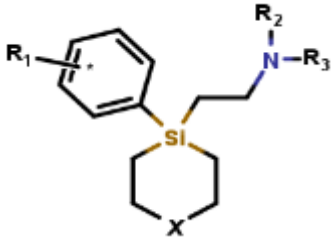


Decoration

R1: alkyl and aryl
R2: alkyl and aryl
R3: alkyl and aryl
(amines, urea, sulphonamides)

Decoration

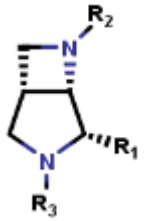
R1: aryl
R2: alkyl
R3: alkyl and aryl
(amines, amides, urea, sulphonamides)



Decoration

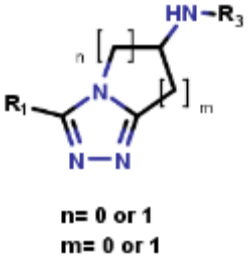
R1: alkyl, alkoxy and halide
R2, R3: 2°amines

Fused Cycles



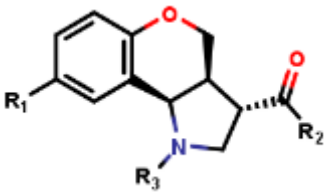
Decoration

R1: alkyl and aryl
R2: alkyl and aryl
R3: alkyl and aryl
(amines, urea, sulphonamides)



Decoration

R1: alkyl and aryl
R3: alkyl and aryl
(amines, amides, urea, sulphonamides)



Decoration

R1: H and halide
R2: OH and alkyl
R3: alkyl and aryl
(amines, amides, urea, sulphonamides)

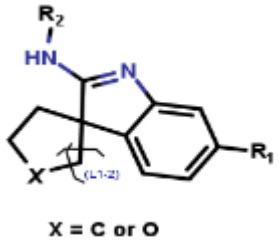
Spiro Bicycles and Tricycles

Decoration

R1: alkylacyl
R2: alkyl and aryl
(amines, amides, urea, sulphonamides)

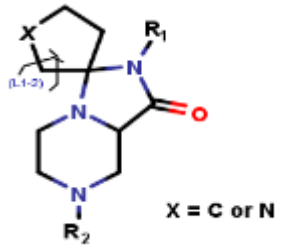
Decoration

R2: alkyl
R3: alkyl and aryl
(amines, amides, urea, sulphonamides)



Decoration

R1: H and halide
R2: alkyl and aryl
(amines, amides, urea, sulphonamides)



Decoration

R1: alkyl
R2: alkyl and aryl
(amines, amides, urea, sulphonamides)

Decoration

R1: alkyl
R2: alkyl and aryl
R3: alkyl and aryl
(amines, amides, urea, sulphonamides)

Compound Library Design And Production 3

Case Studies

Large Libraries

European Lead Factory

IMI Collaboration 2013-2018

- ✓ Taros led the chemistry consortium that built a screening collection of 200,000 compounds
- ✓ > **65 Scaffolds**
- ✓ **> 40,000 compounds**
- ✓ **5-30 mg** scale
- ✓ > 90 % Purity

Medium Libraries

Commercial Screening Compounds

Commercial collaboration

- ✓ **Spiro, polycycles, heterocycles**
- ✓ **> 10 Scaffolds innovative high 3D carachter scaffolds**
- ✓ **4,000 compounds**
- ✓ **50-100 mg scale**
- ✓ **> 90 % Purity**

Focus Libraries

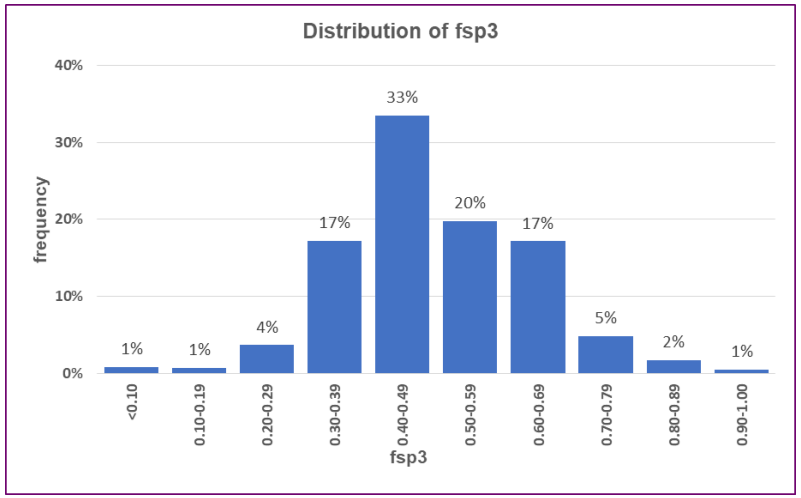
SAR series

Commercial collaboration

- ✓ **Substitutes hydrazide and guanidines**
- ✓ **3 Scaffolds**
- ✓ **> 100 compounds**
- ✓ **2-4 steps in parallel setup**
- ✓ **50-100 mg scale**
- ✓ **> 95 % Purity**

Taros´ Compound Collection 3

Taros´ small In-house screening compound collection Ca. 4,000 cpds



Taros´ In-house screening compound collection

- 4,000 cpds from > 10 library scaffolds

Format

- Glass Barcoded vials
- Matrix vials

Purity

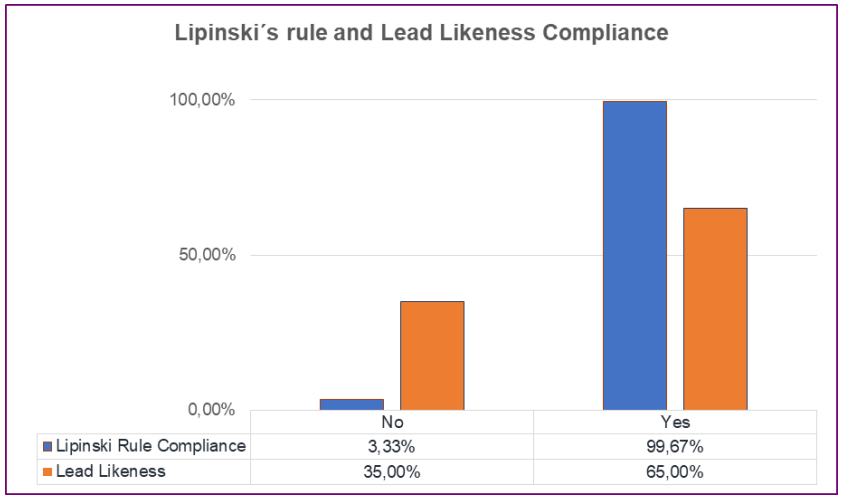
- > 90 % uHPLC (95 % average purity)

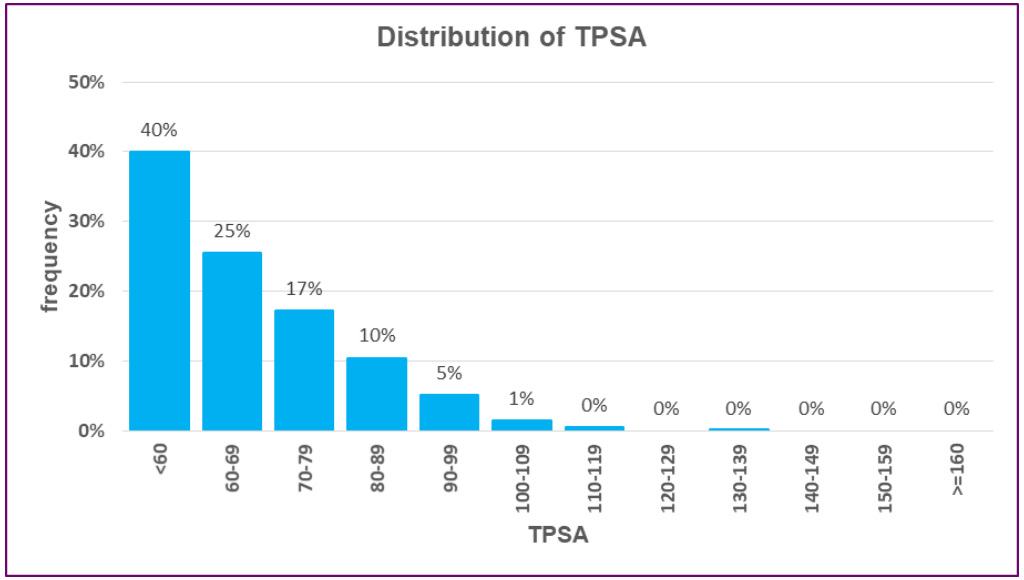
Amount

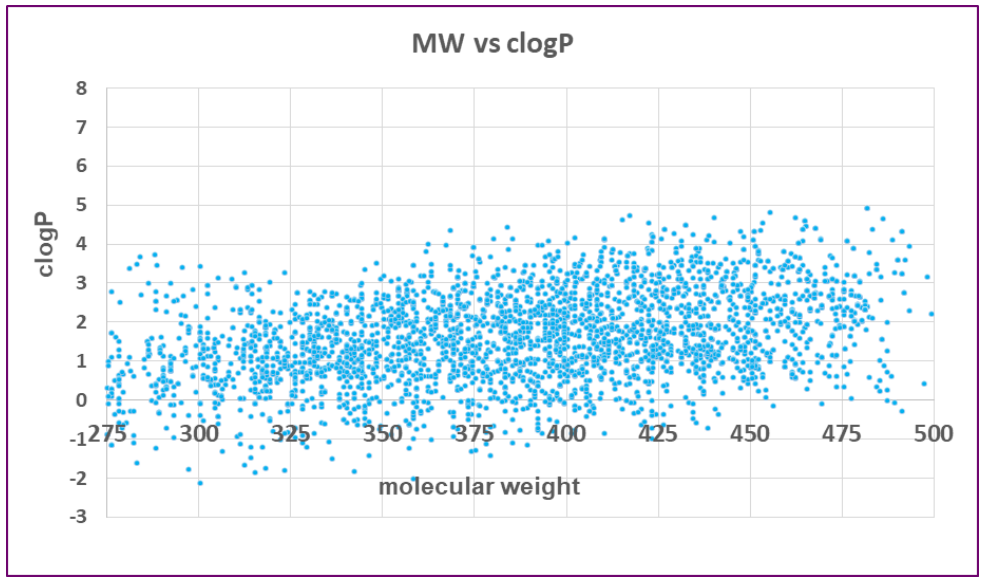
- Multi-mg scale available

Resynthesis and analogues

- All synthesis protocols are available in-house

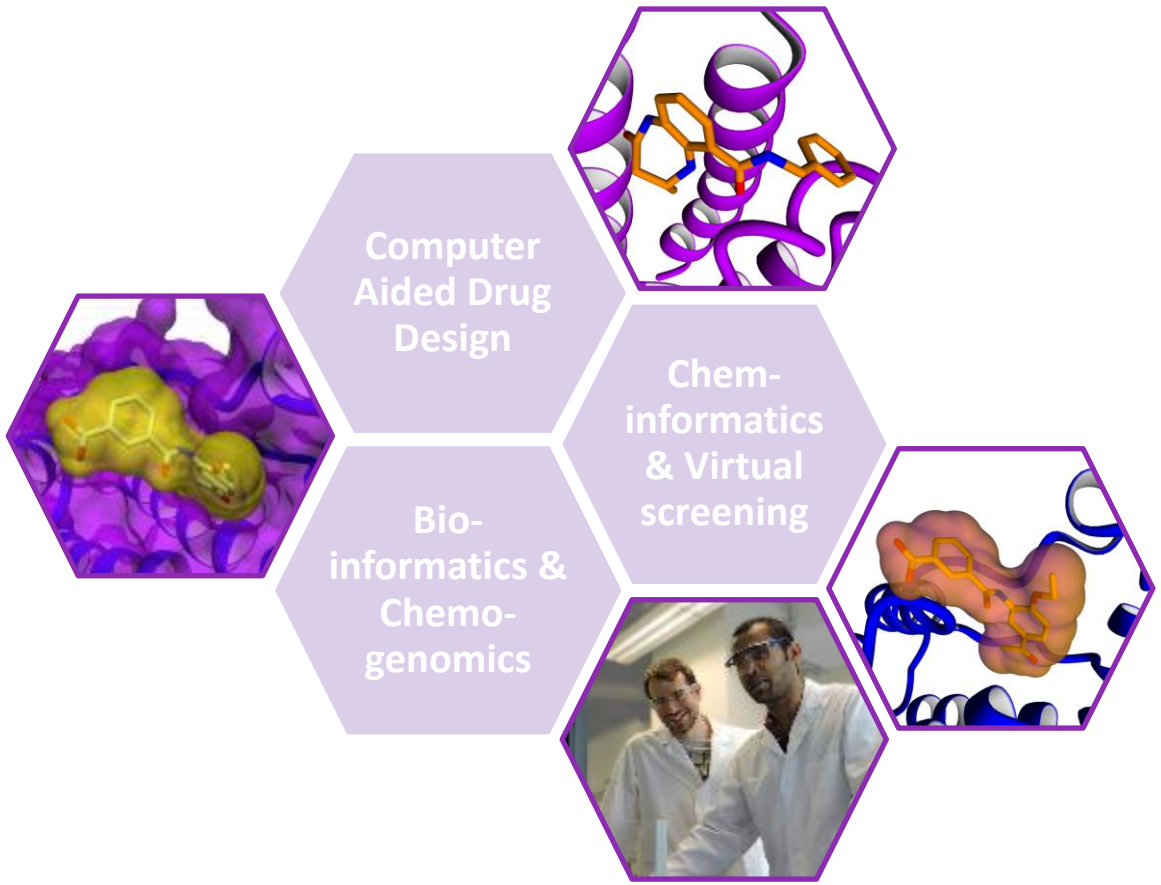






Computational Chemistry 4

Broad Access To Cheminformatics And Molecular Modeling



Computational resources available at Taros include:

- 3.2 GHz Intel Xeon W, 16-cores, 32 threads and supports 2933 MHz memory
- Computational resources available at Taros include over 8160 CPU cores, 30 Terabytes of RAM, and 1.28 Petabyte of storage across a dozen clusters connected by 40 Gb high-speed Ethernet interconnects

State-of-the-art software packages:

- Schrodinger drug discovery suite
- MolSoft ICM suite

Medicinal Chemistry Research 5

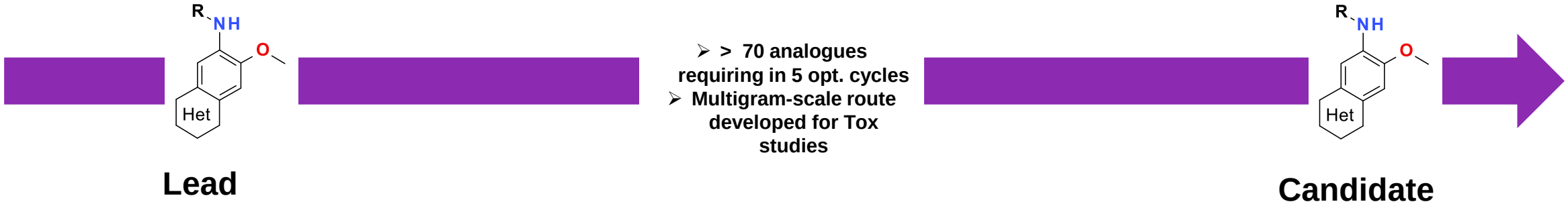
Support From Hit Validation To Lead Optimization

Services

- Hit validation and expansion
- Lead generation and optimization
- MDO concept
- Screening data analysis and SAR development
- Enhancement of target activity and selectivity
- Improvement of ADME/PK and safety profile
- Carving, enlarging and securing new IP space

KomIT: Competence Center For Innovative Diabetic Therapies 5

Lead To Canditate



1 year Lead to candidate campaign

Optimized parameters

- Solubility
- Clint
- Oral availability

Results

- Oral available and soluble compound
- High efficacy *in-vivo* mice models

Chemistry

- Compound design and synthesis for 5 optimization cycles, focusing on varios modifications on the easter and wester part of the lead structure.
- > 70 analogues requiring > 10 synthesis steps per analogue involving heteromatic and cross coupling chemistry.
- Multigram-scale route developed for *in-vivo* studies. > 20 g in > 99 % purity.

Optimized parameters	Kom56
Caco-2 A=>B B=>A Efflux	**1.7** **38.6** **36.2**
Solubility SolRank [µM]	461
Clint [uL/min/mg] mouse / human	38/10.4
PPB [%] mouse / human	39
hERG	14 %

Targeted Protein Degradation (TPD) 5

Synthesis of PROTACs and molecular glues

Synthesis of PROTACs and partial PROTACs as well as design and functionalization of a wide range of ligands, such as CRBN and VHL.

Capability to develop unique linkers to meet discovery demands.

Ability to synthesize a wide range of linkers required for connecting E3-Ligase ligands to the target-binding ligands, such as PEG linkers and carbon-based chains with a wide range of end functionalities, such as -NH2, -CO2H, -N3, -CCH, -CHO, -X, and -OH etc.

Capability to provide both small scale as well as large scale synthetic supports.

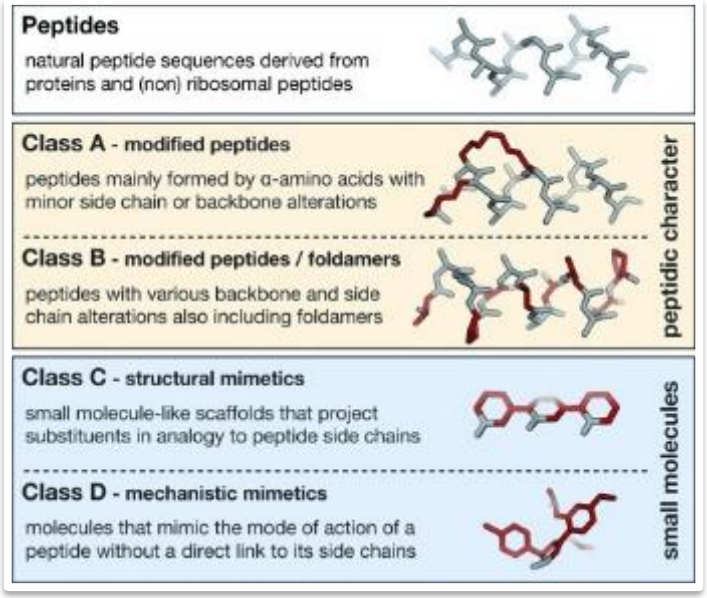
Depending on the goals we can additionally provide parallel library synthesis support.

MiVaKa: Vascular Calcification Inhibitors 5

Design Of Stabilised Peptidomimetics

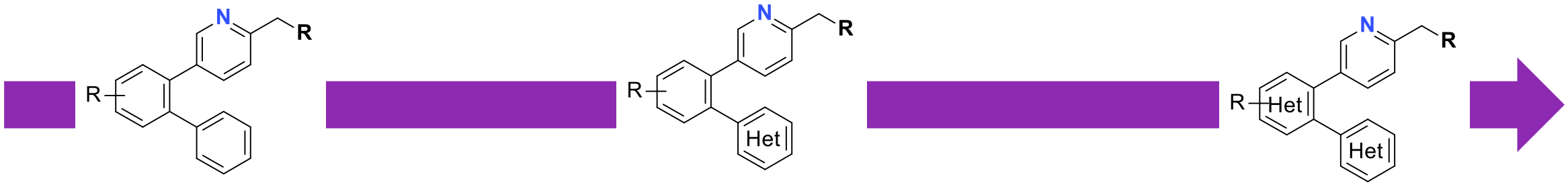
Active Peptide | Fragmentation | Pharmacophore | Medicinal Chemistry | Peptidomimetics

1. From a 19 aa peptide a systematic fragmentation towards the most active fragment.
2. 44 peptide fragments were synthesized and tested in *ex-vivo* and *in-vivo* experiments.
3. A peptido mimetic design and synthesis campaign is ongoing in order to deccrease excresion and increase metabolic stability.



DDHD Project: Kinase Inhibitors 5

Lead To Candidate



1 year Lead to candidate campaign

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Chemistry

- Compound design and synthesis for 3 optimization cycles, focusing on varios modifications on the easter and wester part of the lead structure.
- > 40 analogues requiring > 10 synthesis steps per analogue involving heteromatic and cross coupling chemistry.
- Multigram-scale route developed for *in-vivo* studies. > 20 g in > 99 % purity.

Optimized Parameters	Lead	Candidate
Activity Caco-2 A=>B B=>A Efflux	1 nM 0.04 12.9 299	9 nM 6.3 5.7 0.9
Solubility SolRank [µM]	13	29
Clint [uL/min/mg] mouse / human	31 / 7	178 / 27
PPB [%] mouse / human	98.6 / 99.9	99.3 / -
LogP (Seurat)	5.0	5.1
PSA (Seurat)	116	76

Do Not Hesitate To Contact Us

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