SpiroChem
GET INSPIRED. INNOVATE.

The chemistry of the future, today.

www.spirochem.com

Outsourcing your chemistry: why SpiroChem is your best choice?

SpiroFacts

Continuous Growth

- Since foundation in 2011
- ETH-Zürich spin-off

Location (since 2017)

- Basel, Switzerland - fully-equipped R&D facilities
- Lab capacity: 140 fumehoods

Team of 100+ experts (92 research chemists)

- Handpicked* experts with successful academic and industrial experience
- Objective end 2023: 130

Expertise

- High ratio of PhD/MSc covering all aspects of modern synthetic chemistry
- Hands on management

Clients

- Life science companies with high expectations
- Over 350 clients in 30+ countries

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*Continual recruitment policy: we hire when the best are available, not only when we need them

What we believe in

[Skills x Quality] = Normal expectation

[Skills x Quality x **Speed**] = Value

- To reduce discovery chemistry costs: DON'T MAKE IT CHEAP … MAKE IT FAST !

Structural complexity is a matter of perception

With knowledge, creativity and technology, we decorrelate complexity from actual synthetic accessibility

[Skills x Quality x **Knowledge x Speed**] = Real Value

- **Don't be limited by perceived structural complexity**
- **Make the molecules you should, not only the ones you could**

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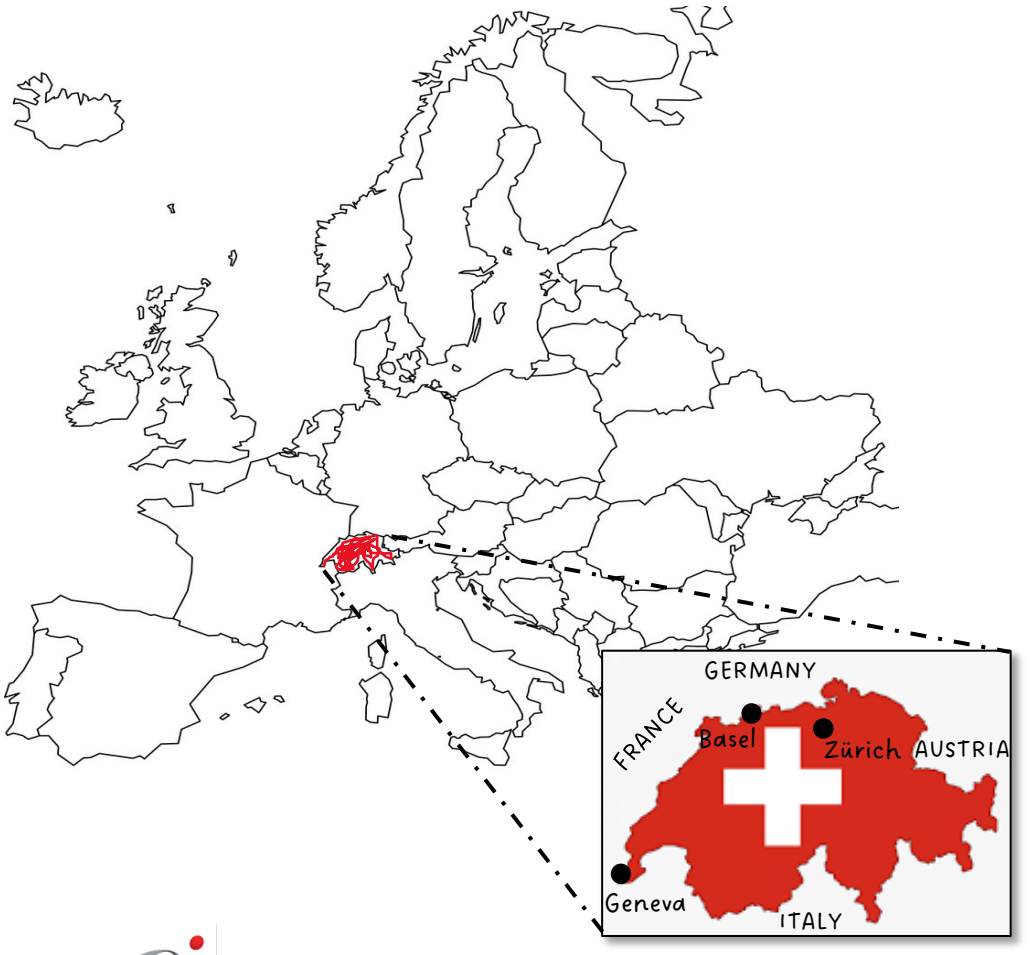

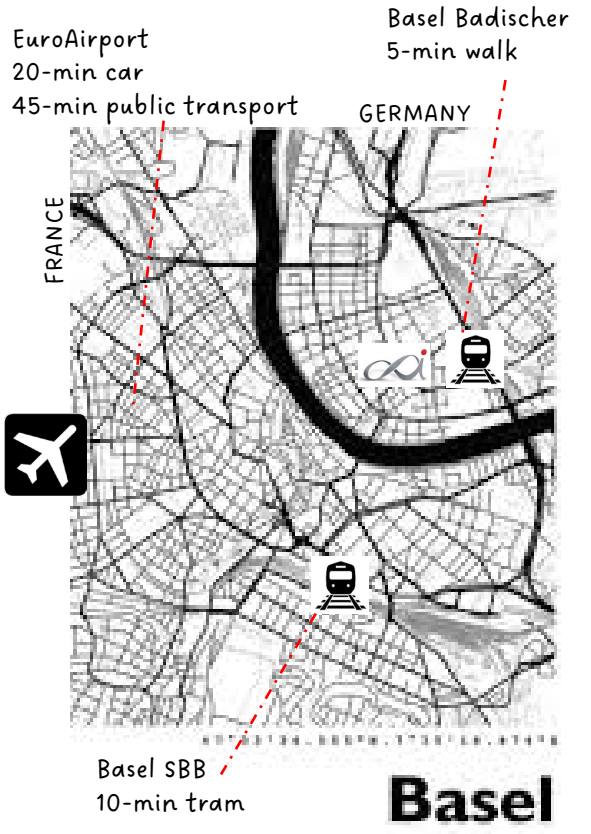

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Evolution of SpiroChem's business model

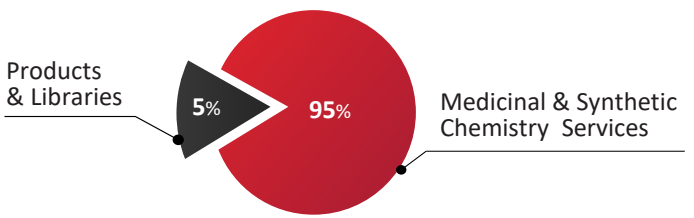
2011 **Catalog company:** Catalog continually growing, inventory over 14'000 references

2013 **Service - Custom-made products:** Spirocycles, complex molecules, natural products, ...

2017 **Solution Provider under FTE-model:**
- Medicinal chemistry
- MedChem enabling platforms
- Route scouting

2018 **Libraries:**
- Sp^3-rich Fragment
- Multifunctionalized scaffolds for DELt

2022 Revenue Balance



2020 **SpiroKits™**

High Potent Lab (research)

2022 **SpiroSpace Library™** (virtual) + **CompChem**

2023: **Macrocyclic platform** and more ...

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Logistics: SpiroChem has shipped compounds to over 350 clients in 30+ countries

Pharma | BioTech | Material Sciences | Ag Tech | CRO | Screening | Food Sciences | CDMO&CMO | Animal Health

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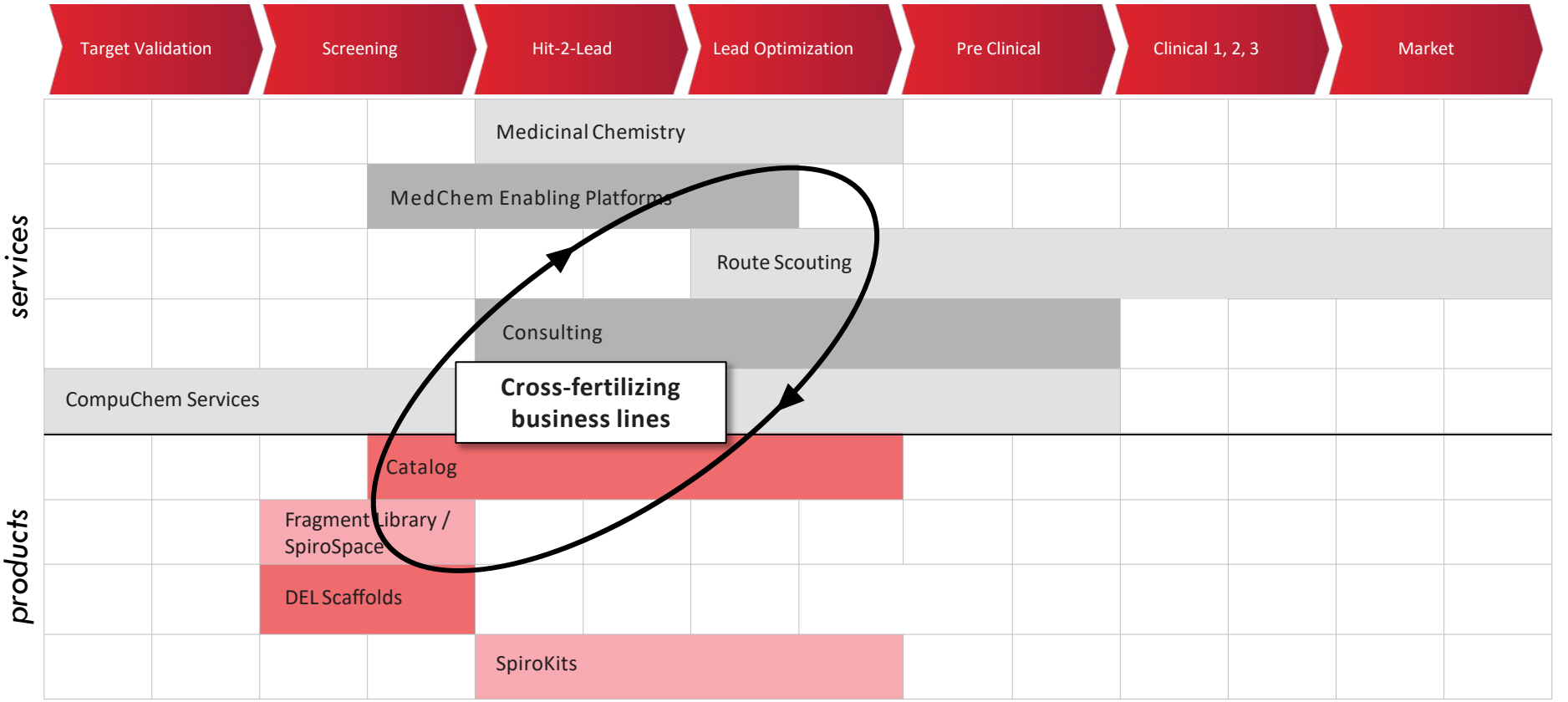
SpiroChem's services and solutions

We support you at each stage of the Discovery Program ... and beyond!



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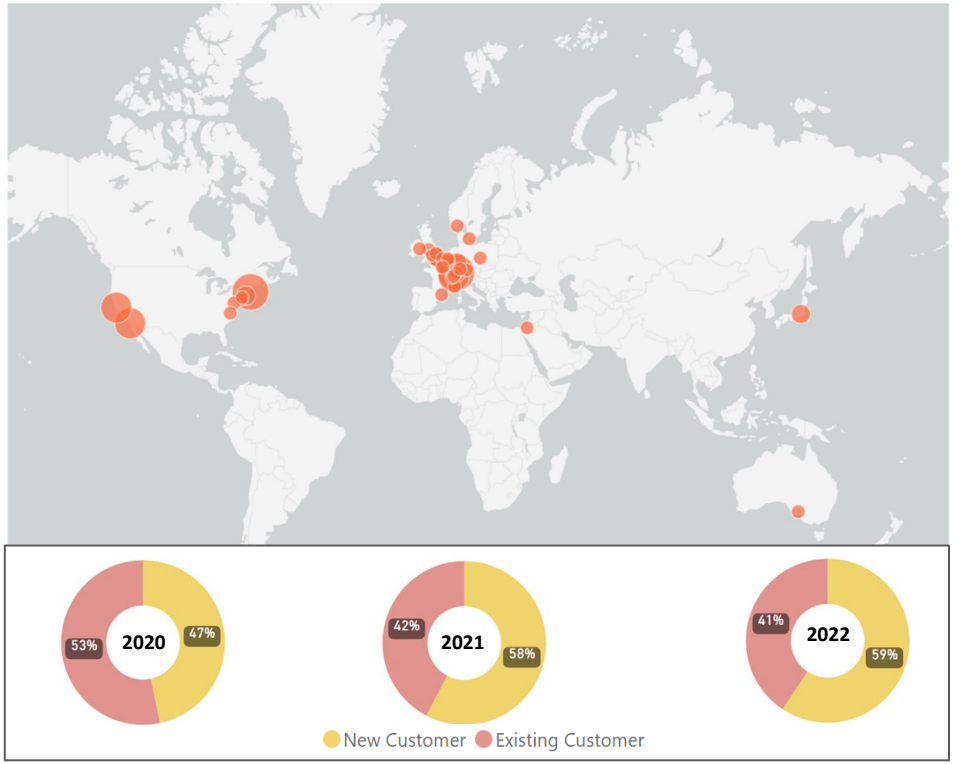
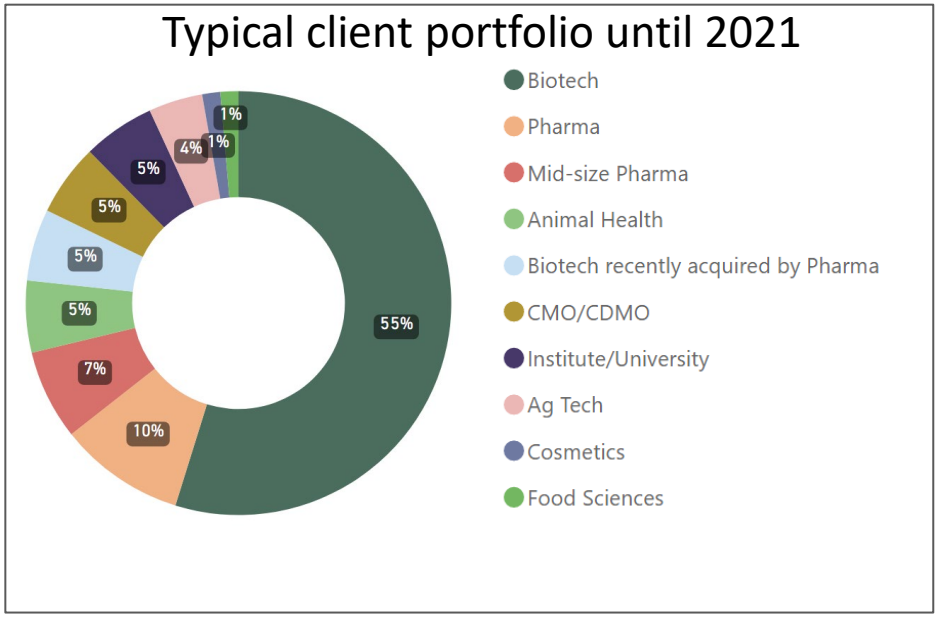
SpiroChem's Clients : where and who?





- Since 2022: client portfolio composition is shifting – increasing Pharma component
- Forecast 2023: Pharma / Large CDMO will represent about 50 % of revenues

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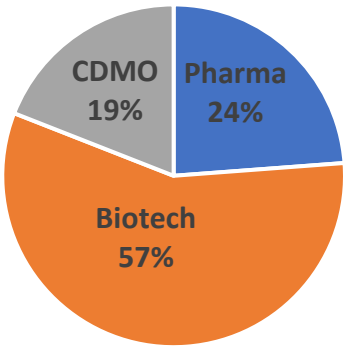
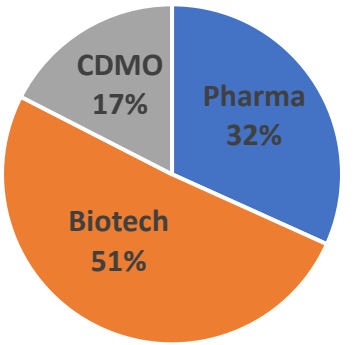
Overview of current projects (March 2023)

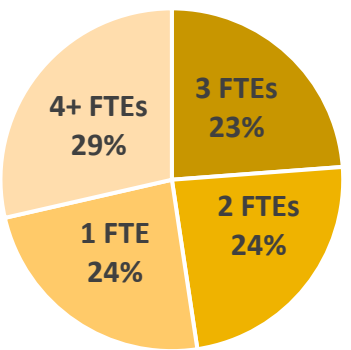
Pharma / Biotech / CDMO



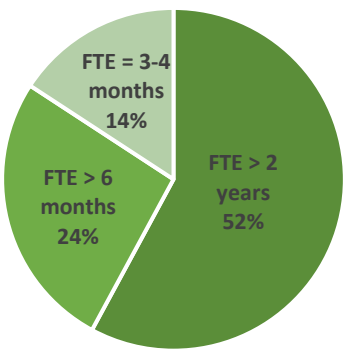
Pharma / Biotech / CDMO
(by the number of FTEs)



FTE per project



FTE contract duration



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SpiroChem's Discovery Services

Medicinal Chemistry Projects

Full medchem programs from hit validation to identification of a preclinical candidate

Support for a specific phase of your project

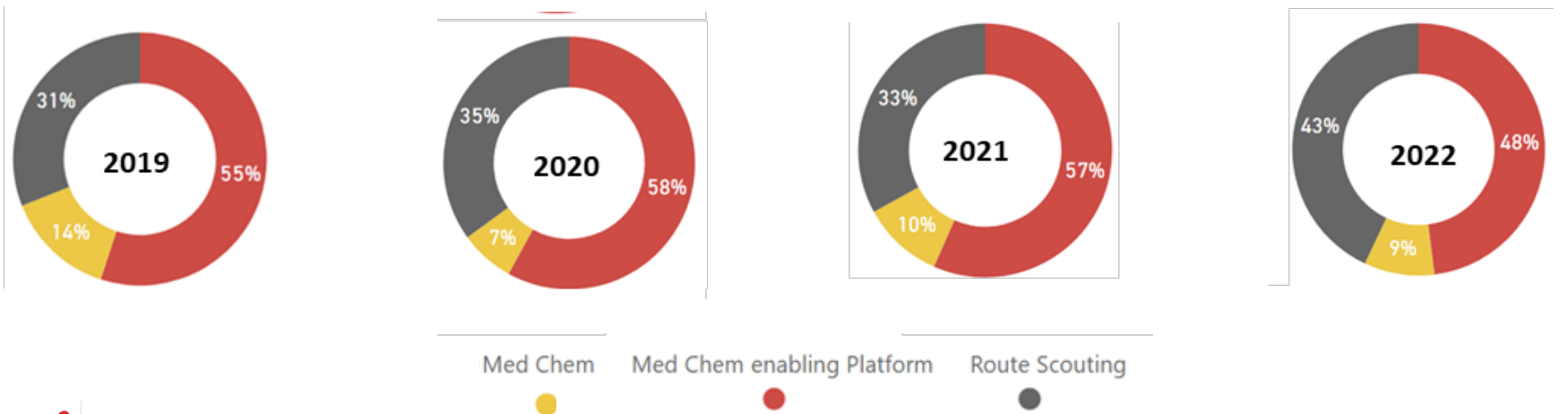
MedChem Enabling Platforms

NOVEL chemical space made accessible

High flexibility required – Agile switch between projects / types chemistry

Route Scouting

We design and implement de novo synthetic routes and strategies for molecules of interest.



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SpiroChem growth and financial stability

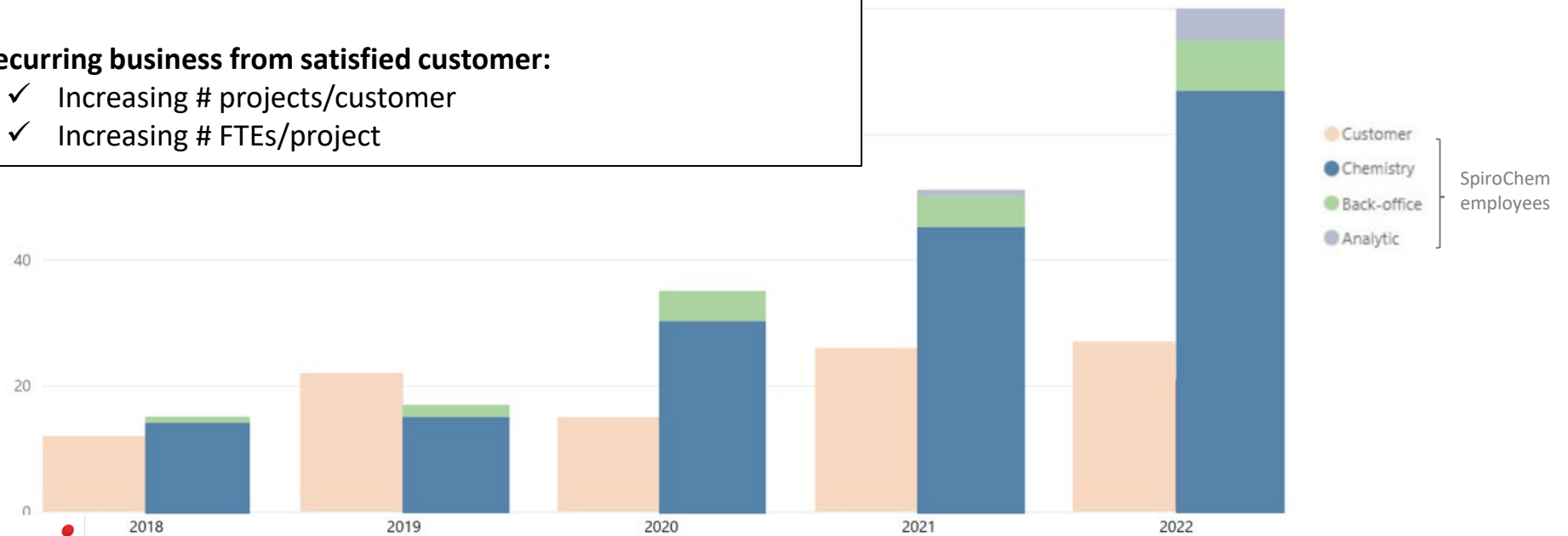
- **Acceleration of growth since 2018**
  - ✓ Opening of an analytical department and increasing back-office to support the growth
  - ✓ Early 2023: opening of a additional lab space:
    - 1 additional high-potent lab
    - 20 additional fumehoods
    - Increasing lab capacity and tech support

- **Recurring business from satisfied customer:**
  - ✓ Increasing # projects/customer
  - ✓ Increasing # FTEs/project

Steady Revenue growth:

- 2020 → 2021: 55%
- 2021→ 2022: 45 %
- 2022 → 2023: 50%+ (forecast)

Profitable, no debt



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What we do matters

H3 Biomedicine
Human. Health. Hope.

"Our collaboration with SpiroChem has enhanced our ability to investigate novel chemical space. The SpiroChem team and our tec partnership, working closely to resolve tough synthetic areas, which - without their expertise - would have been cl communication, rapid delivery with uncompromised c solutions makes SpiroChem a highly recommended partner

Stephanos Ioannidis
Vice President, Head of Chemistry

actio BIOSCIENCES

With a complex pharmacophore to deal with and the need to devise a succinct and scalable route for development, we turned to SpiroChem for assistance. Their knowledgeable chemists made quick work c strides in developing an optimized route. Th and will not shy away from a challenge! Give hesitate in recommending the SpiroChem synthetic chemistry guidance and support.

Nicholas Stock, Ph.D.
Senior Vice President and Head of Che

AsahiKASEI
ASAHI KASEI PHARMA

SpiroChem is a reliable partner for our lead optimization programs. We have been working with SpiroChem for several years in a fruitful and trustworthy relationship. The SpiroChem team - based on strong knowledge of synthetic and medicinal chemistry – always performs effectively to boost our structure-activity relationship studies. And when it comes to the synthesis of challenging targets, SpiroChem also solved many synthetic issues with unique and sophisticated ideas that no other CRO can provide. It is stimulating us and brings great results and value to our projects. For this reason, SpiroChem is a highly recommended partner for discovery.

Masakazu Atobe
ory for Drug Discovery

HORIZON

When only the best chemistry team will do, I turn to Spirochem. For 10 years now, I have collaborated with chemists at Spirochem to solve my project's most complex synthetic challenges in medicinal and process chemistry.

Denis Billen
Associate Director, Small molecule API Chemistry

CYBREXA THERAPEUTICS

d Spirochem support its research chemistry efforts, focus on research projects requiring a high level of istry insight, rigor and experience. I have not only d with the quality and timeliness of Spirochem's with the "added value" their chemists have shown with creative and practical suggestions for moving the project forward. Cybrexa has now focused all of its "high cost" challenging synthesis work at Spirochem.

Rob Maguire
Director of Chemistry

asser

"SpiroChem is an excellent partner for several reasons. They have strong chen collaborative, creative, knowledgeable, innovative, and hard working. Over the course of a one-year Route Scouting project, they generated many ideas for new synthetic routes and aggressively explored each of the ideas for application to a very challenging structural motif that required a broad understanding and good command of asymmetric methodologies. In addition to generating and applying new ideas, they were also quite successful at making measurable improvements to existing synthetic processes. They are reliable and productive. All meetings went as scheduled and were always strongly supported with detailed updates covering many experiments that the project chemists could always speak to confidently and authoritatively. They are flexible and responsive. The project demanded good judgement and abrupt changes in direction at several points and the SpiroChem team was able to quickly pivot and move to higher priority activities when needed. I have no reservations in recommending SpiroChem as a partner for challenging Route Scouting projects. The SpiroChem chemists that I worked with are professional chemists who are committed to high quality Science and I look forward to working with the team again on a future project."

Michael D. Wallace
Director, Process Development and Manufacturing

"In our medicinal chemistry collaboration, SpiroChem quickly learned about our project goals and used their expertise in SBDD and medicinal chemistry to suggest innovative, yet accessible targets. Following up with this initial effort, SpiroChem was able to translate those ideas into synthetic plans and generated new compounds, addressing synthetic challenges along the way. Throughout our collaboration, we enjoyed their clear and honest communication style, their flexibility, and high quality of work which, bundled together, made SpiroChem a good partner to work with."

Jean Kim
SVP Head of Chemistry of Kadmon

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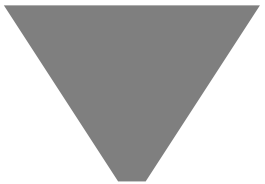
Our people: a stringent recruitment process to attract talents

2022 statistics



• 1000+	CVs reviewed	(triage)
• 240	1st-round	(potential)
• 80	2nd-round	(technical)
• 30	3rd round	(scientific, cultural and philosophical alignement)
• 24	new researchers	**Onboarding period takes 1-3 months**

Where do they come from?

- 9 nationalities (**Swiss**, **EU**, US, Canada, India, Korea) (Note: 17 different nationalities at SpiroChem)

High education level:

- PhD/Postdoc level: Top tier universities / academic research groups, accomplished researchers.
- MSc level: selected universities and chemistry schools across Europe, preferably with prior industry experience

Diverse expertise:

Natural product synthesis, methodology, carbohydrate, lipids, nucleic acids, etc.

Prior professional experience:

- Chemical industry, Pharma, **Contract Research Organizations**

We keep training our people:

- New employees present and share their research with team
- Emulation: brainstorming sessions on projects, sharing of knowledge across company
- Invited academic lectures
- Training courses from consultants and advisors
- Attendance to International Conference

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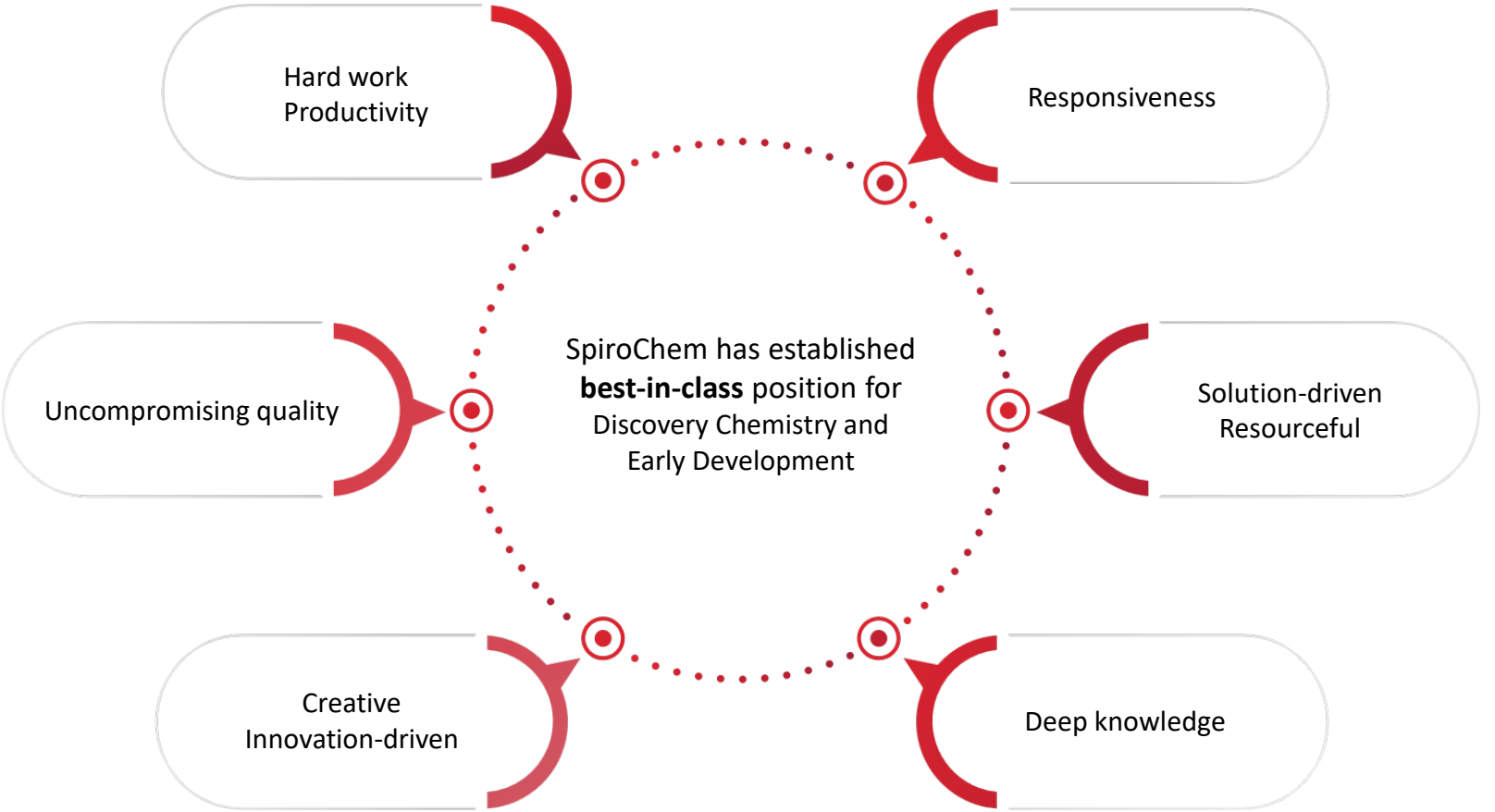
Company Values must be understood by our employees BEFORE joining



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Beyond KPIs*: SpiroChem stands out of the **CRO**wd for quality

Top-notch scientific team, at <u>all</u> levels

- Interpretation of data, experimental observations
- Diligent and rigourous scientists
- Data management: electronic notebooks used since 2011
- Low maintenance: rapid and autonomous problem-solving
- Smooth and transparent communication («chemist to chemist»)
- Project leaders are **<u>researchers</u>** and spend most of the time **<u>in the lab with their team</u>**

Solution-oriented, focusing on client needs

- Agility and flexibility: priorities have changed? Not a problem!

** KPI: Key Performance Indicator*

Importance of continuous R&D … not the usual CRO model …

Internal R&D

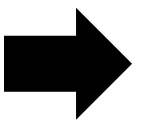
- Maintaining an internal pool of chemists for R&D

Sponsoring of multiple academic collaborations (Switzerland, USA, Italy, France, …)

- Ad-hoc collaborations and spot financing
- 5 PhD scholarships
- 2 Postdocs
  - ➢ "SpiroChem Academy"

Multiple ongoing research grants:

- Swiss federal grants:
  - HES-SO (Geneva, AI – ML) (+ 2 postdocs)
  - ETH (Zürich, novel late-stage transformation paradigms) (+ 2 postdocs)
- European Union:
  - Eurostars: mRNA inhibitors (+ 2 researchers)
  - ITN: expanding the ADC toolbox (+ 1 PhD student)



R&D is in our DNA:

- *continuous development of new molecules (products) or new methods (services)*
- *Training our staff*
- *Benefits directly our partners and clients*

SpiroChem is already a trusted partner for many research companies in Life Science

Type of client	Location	# FTE	Duration	Type of support
Pharma	Global	5	12 month, renewed yearly	Synthetic platform, exploration of new chemical space
Pharma	Japan	10	12 month, renewed yearly	Synthetic chemistry support to medicinal chemistry team (several projects), problem solving
Pharma	Germany	6	12 month, renewed yearly	High-potent chemistry Linkers New building blocks for chemical space exploration
Pharma	Japan	1-2	Renewed every 6 months since 4 years	Medicinal chemistry (design) Route scouting
Biotech	Switzerland	2-3	Permanent FTE	Medicinal chemistry (design) 2 development candidates selected Route Scouting
Biotech	USA	6	12 months- contract, renewable	Synthesis of libraries of meolecular glues Support in PROTACs design
Biotech	USA	6	12 month contract	Synthetic chemistry support
CDMO	Europe	7	24-month contract, renewable	Route scouting for multiple projects

+ SpiroChem works on 30-40 projects per year (6-12 months) with clients in Europe, USA and Japan

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Collaborations and partnerships

Government-partially funded collaboration

Innosuisse - Swiss Innovation Agency

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Hes·so
Haute Ecole Spécialisée de Suisse occidentale
Fachhochschule Westschweiz
University of Applied Sciences and Arts Western Switzerland

Prof. Dr. Douglas Teodoro
AI and ML

ETH
Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

Prof. Dr. Bill Morandi
Late-stage functionalization

saverna therapeutics

mRNA targeting molecules

SpiroChem-funded collaboration (more to be announced)

Uni Pavia / Uni Illinois
Prof. Dr. David Sarlah

Uni Indiana
Prof. Dr. Kevin Brown

University of Nottingham
UK | CHINA | MALAYSIA

Prof. Dr. Hon Lam

Strategic partners

ChemAlive™

Accurate computational calculation for quantum chemical data

ZOBIO

Biophysical screening platform

CRYSTALS FIRST

Rapid generation of high-resolution X-ray co-crystal structure

INVENesis

Rapid in vitro and cell-based screening Compound Management

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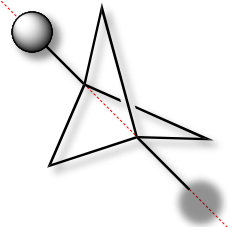
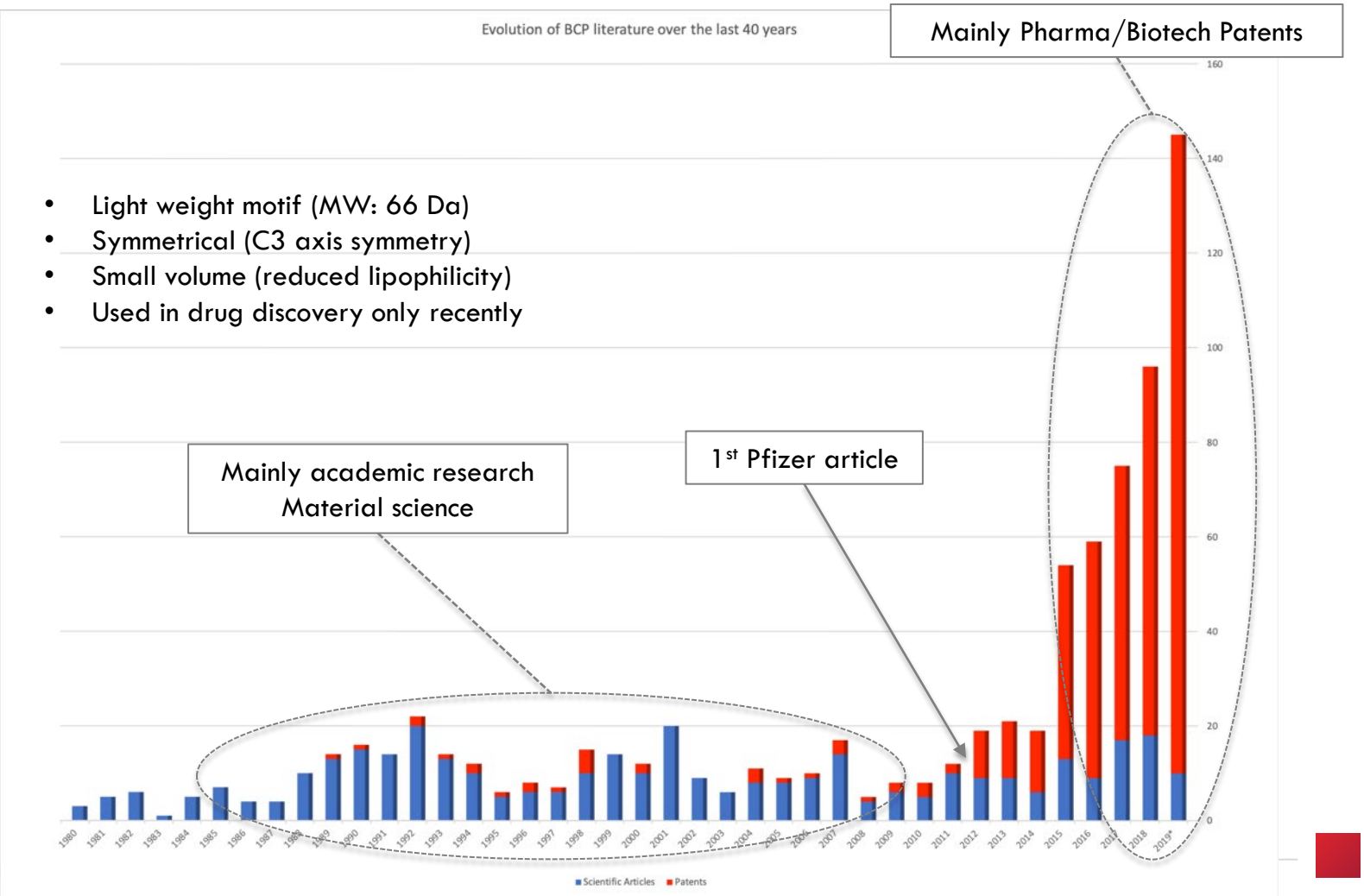
Bicyclo[1.1.1]pentanes

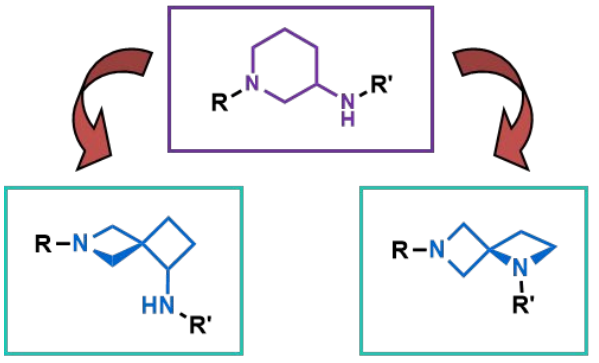


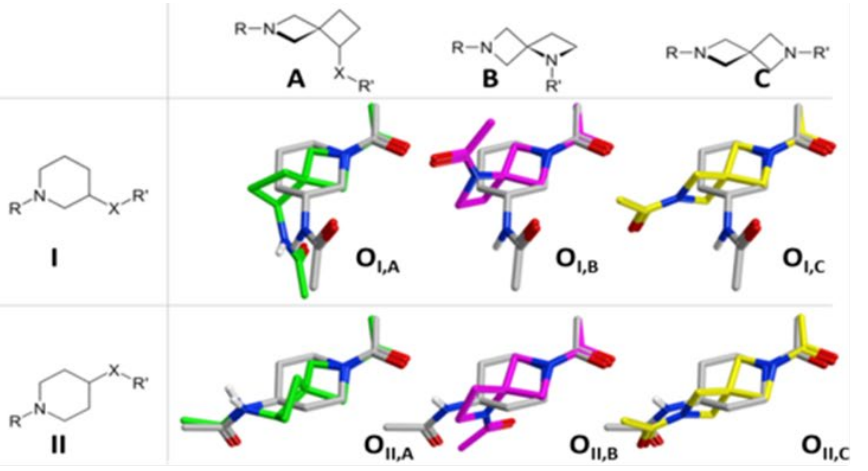
- Light weight motif (MW: 66 Da)
- Symmetrical (C3 axis symmetry)
- Small volume (reduced lipophilicity)
- Used in drug discovery only recently



SpiroChem data | SciFinder search

SpiroChem's Portfolio of Bioisoteric Solutions - Spiro-switch concept

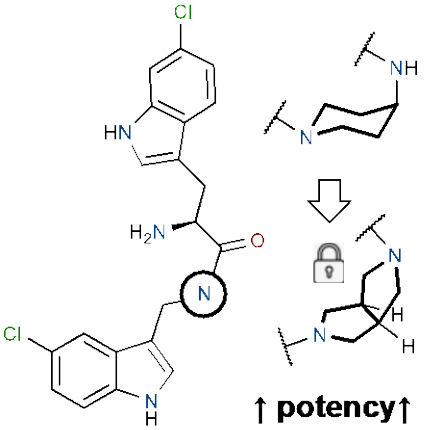




- Replacement of piperidine moieties by azaspiro[3.3]heptane scaffold
- Good match of exit vectors often found due to the high diversity of spirocycles
- Entropy gain often observed due to conformational restriction of spirocycles
- Full analysis of the vectorial space surrounding spirocycles available from SpiroChem

Example of recent innovative project – Dewar pyridines – with Sarlah group

Real problem and a possible solution



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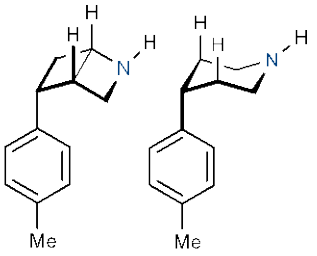
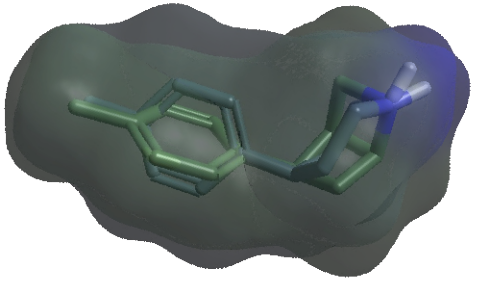
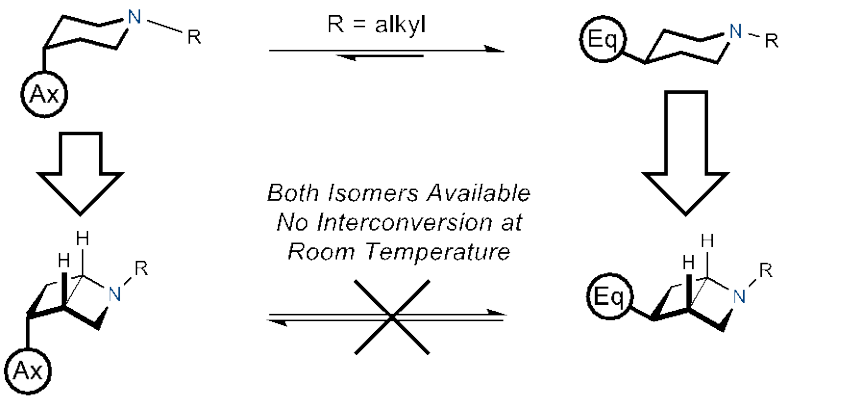
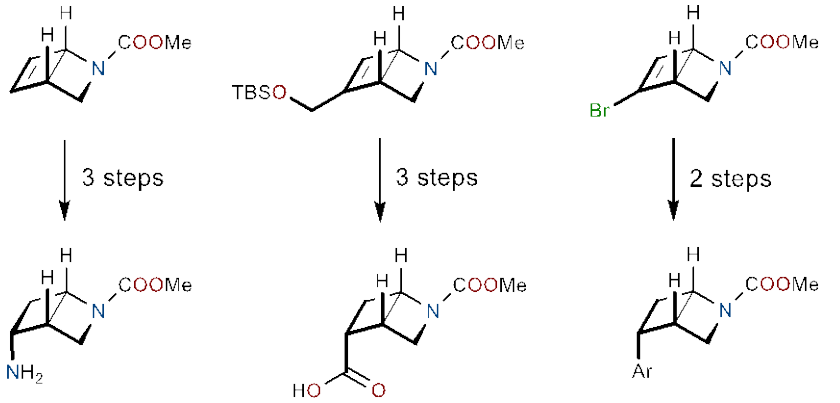




Volumes of replacement are almost identical!





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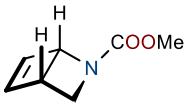
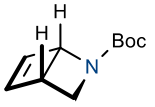
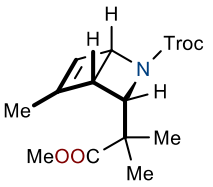
Example of recent innovative project – Dewar pyridines – with Sarlah group



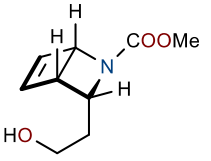
(69%, 35%)



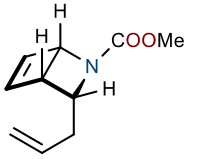
(53%, 96%, 29%)



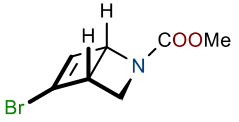
(36%, 37%)



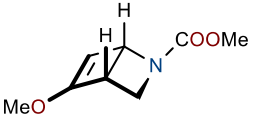
(71%, 73%, 26%)



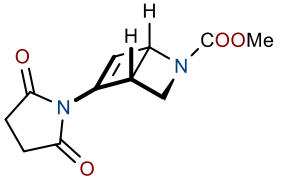
(17%, 11%)



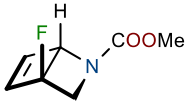
(68%, 46%)



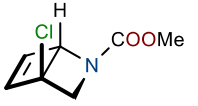
(81%, 71%)



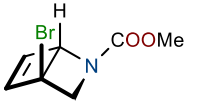
(76%, 54%)



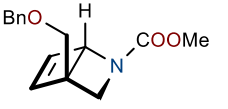
(50%, 13%)



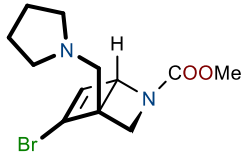
(60%, 9%)



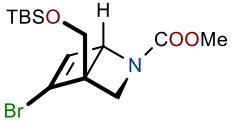
(67%, 17%)



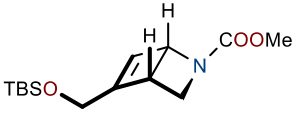
(81%, 18%)



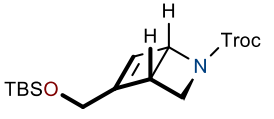
(75%, 23%)



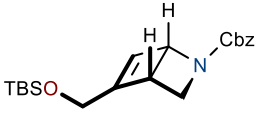
(92%, 35%)



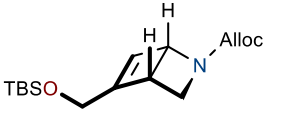
(80%, 55%)



(86%, 14%)



(88%, 31%)



(89%, 43%)

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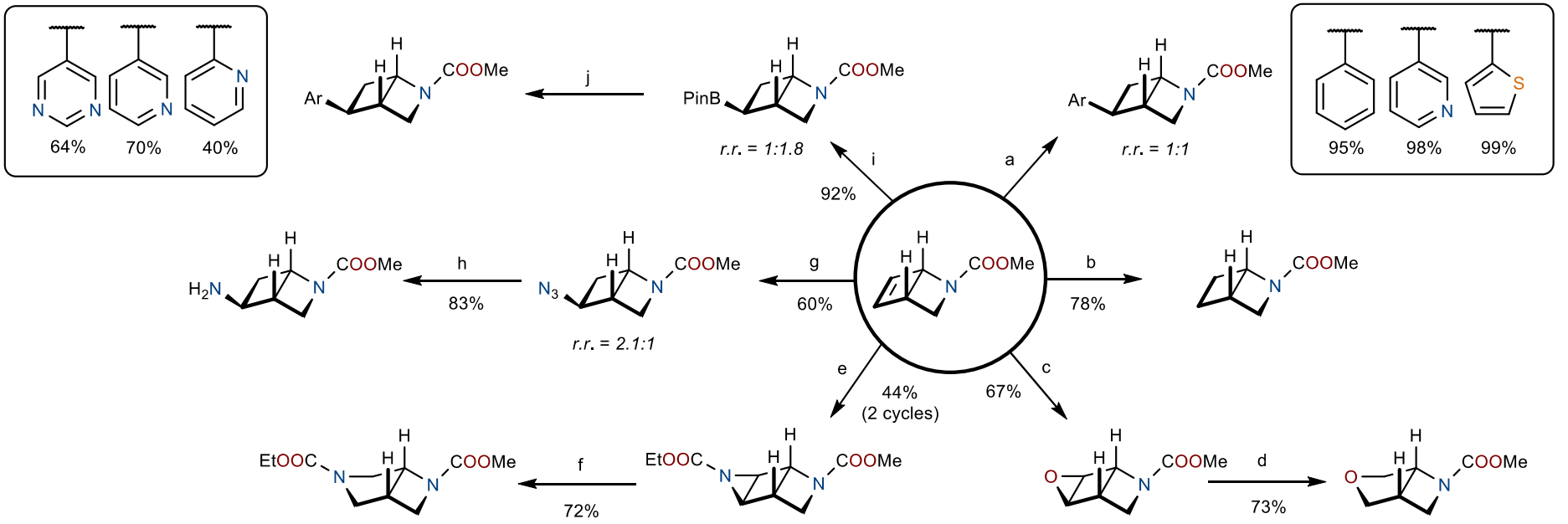
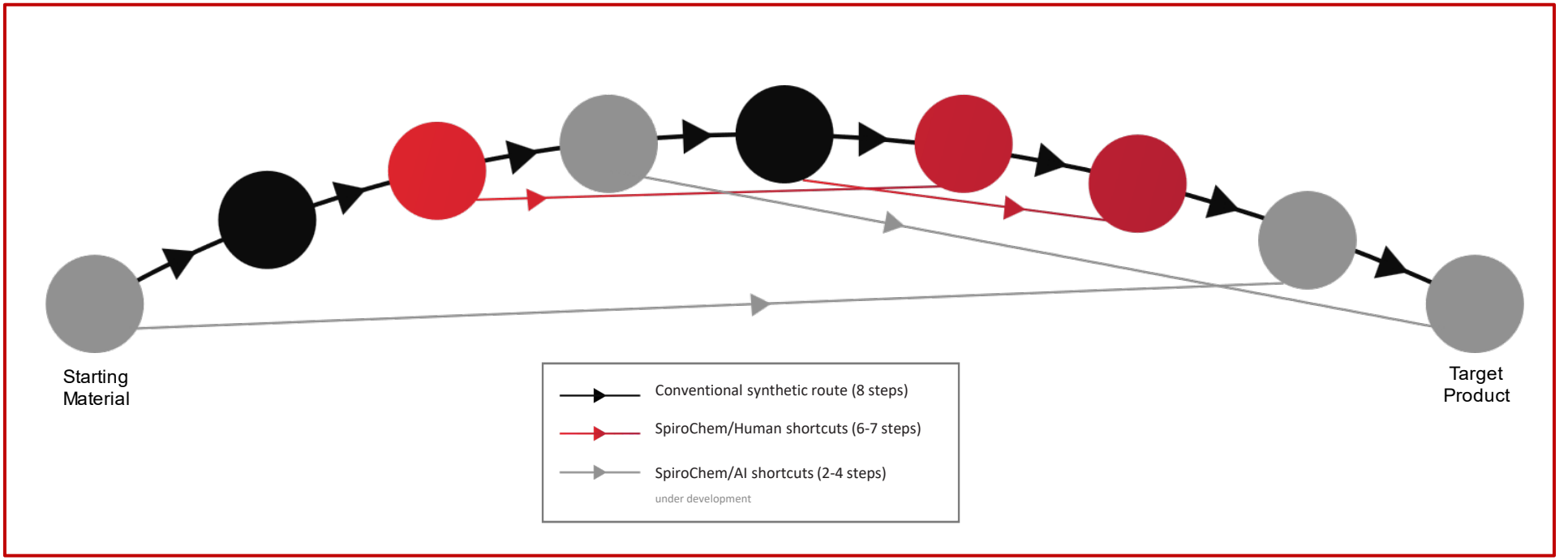
Example of recent innovative project – Dewar pyridines – with Sarlah group



- 3 grad students + 3 postdocs sponsored by SpiroChem over the last 3 years -> SpiroChem academy
- Ongoing discussions with Merck for joint evaluation of properties
- Dr. Yaroslav Boyko (Chemistry), Carl Monopoli (BDL/TTO)

SpiroChem's MedChem enabling platforms – Concept



- Use modern synthetic chemistry method to introduce complexity at a late stage
- Technological support: photochemistry (photoredox), electrochemistry, …
- Pragmatic and agile approach to develop flexible synthetic strategies

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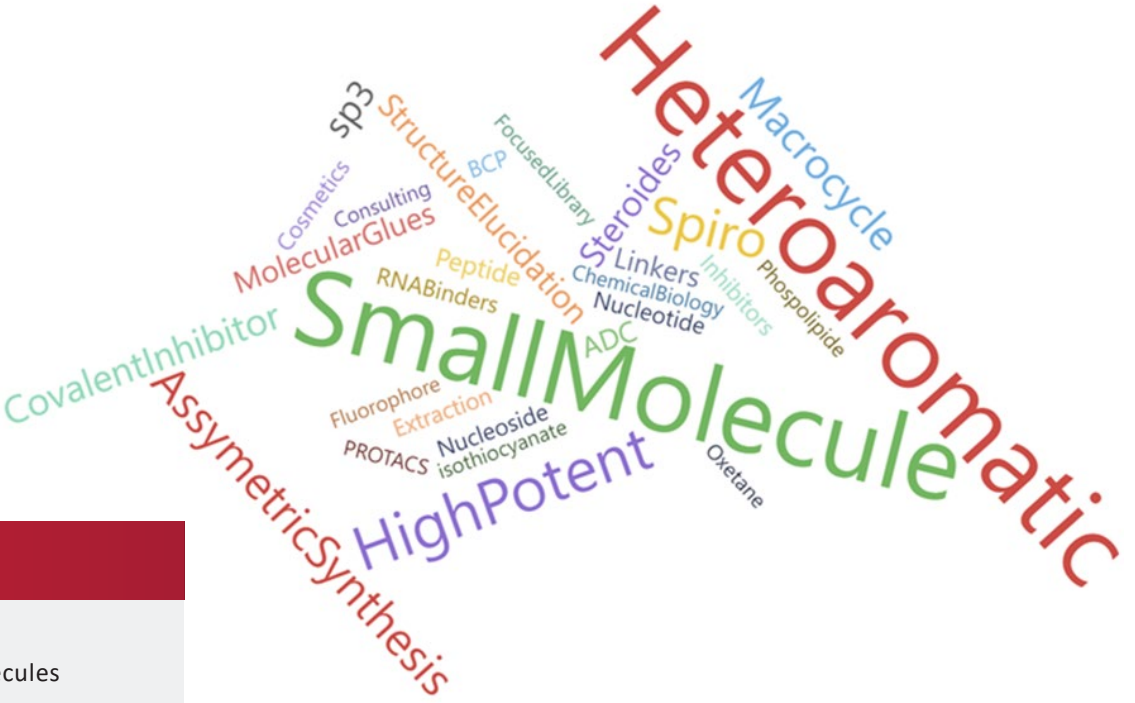
SpiroChem niche and specialty expertise

- SpiroSPACE: enabled Virtual Fragment Library
- New modalities: Covalent inhibition (with SpiroCOVE: subset of SpiroSPACE for covalent inhibitors)
- CADD and Bio-isosteric Switch
- DEL scaffolds
- Linkers
- New Modalities: macrocycles
- New modalities: Degraders
- New modalities: ADCs
- Route scouting

SpiroChem's Chemistry Expertise

Mastering Cutting-edge technologies

- Photochemistry
- Flow Chemistry
- Electrochemistry
- Microwave-assisted chemistry



Mastering Specific Chemistry Skills

- Heterocyclic chemistry
- Radical chemistry, organocatalysis, cross-coupling reactions
- Synthesis of hybrid sp^2-sp^3 scaffolds
- Synthesis of conformationally restricted scaffolds (spirocycles, bicycloalkanes)
- Preparation of biomolecules (glycochemistry, fatty acids, polypeptides, macrocycles, nucleotides/sides)
- Chemical biology (probes, linker)
- Total synthesis of natural products

We provide a tailored team of experts to fit your needs.

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SpiroChem's Portfolio of Bioisoteric Solutions

SpiroChem has developed a diverse portfolio of solutions via isosteric switches for :

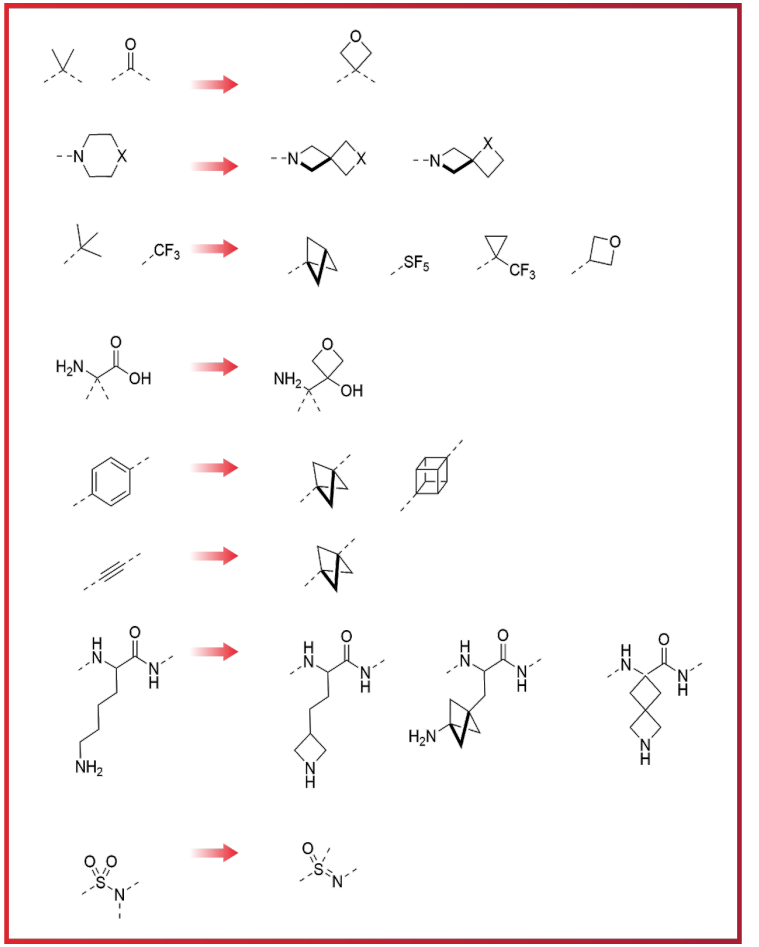
- Finding solutions for ADME optimization
- Fostering scaffold hopping
- Generating IP through exploration and exploitation of novel structural and property diversity

In particular, SpiroChem is world-leading expert in the chemistry of cage molecules and conformationally-restricted motifs.

syngenta

SpiroChem is a truly outstanding partner for the synthesis of customized building blocks, combining high technical expertise, creativity and a strong commitment with a very collaborative approach and a focus on delivery. Excellent communication, innovative ideas at the start of the project and proactive problem-solving by the SpiroChem team contribute to the success of projects. I have no hesitation in recommending SpiroChem.

Fredrik Cederbaum
Head of Fungicide Chemistry & Chemistry Operations



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NEW

Small-Molecule Macrocycles

The Ideal Tool for the Discovery of Breakthrough Drugs Against Challenging Disease Targets

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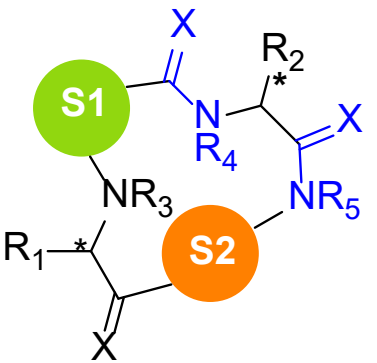
Specific CMRT™ Designs – BBP Example

Design Examples for PPI and BBP Compounds
(Constrained **M**acrocycles for **R**ecognition of **T**opologies)



Calculated properties of representative BBP library

MW:	320-500 Da
tPSA:	70-126 (Mean: 93 Å^2)
clogP:	0.7-5.9 (Mean: 3.7)

Specific Considerations

- Small surface area and low MW focus
- Diverse topologies
- Lipophilic aliphatic and heterocyclic functionalities preferred
- Amino acids with short, aliphatic, alicyclic or small lipophilic, heterocyclic, side chains preferred
- Amide nitrogen frequently methylated
- MW not exceeding 500 Da

NEW

CMRT™ Design Considerations

CMRT™ constitutes SpiroChem's proprietary small-molecule macrocycle technology

Molecules with MW < 1000 Da and ring sizes of 12-30 atoms preferred

Maximization of chemical and topological diversity through use of bifunctional building blocks (3-8 per compound)

- L- and D- natural and unnatural amino acids with/without modifiable side chains
- Linkers and spacers containing
  - Aliphatic, aromatic, alicyclic, heterocyclic elements with/without options for secondary modifications
  - Structural elements prone to inducing alpha- and beta-turns, structural constraints
- Allowing attachment through a variety of reaction methodologies to provide alternative linkages, in addition to amides and amide isosteres/surrogates

Introduction of secondary conformational constraints through N-alkylation, ring type/size, specific pharmacophore groups, internal hydrogen-bonds, fused rings

Expansion of diversity by adding side chain extensions and functionalities

Target agnostic with exceptions of PPI and CNS-penetrant designs

NEW

QUEST Library – Structural Diversity

Current Stock

8269 Compounds

- 7,830 cyclic compounds
- 20 cyclic dimers (cd)
- 193 acyclic congeners
- 226 advanced fragments

Ring sizes comprising 10 to 60 atoms

Rings containing 3 to 8 building blocks

Incorporation of up to 459 unique building blocks per position in various combinations across different ring sizes

Providing a representative cross-section of the initially synthesized 16,677 compounds and their attributes relating to:

Sizes and topologies

Physico-chemical properties

Utility for a broad spectrum of target classes

NEW

QUEST Library – Structural Diversity

Current Stock

Unique Building Blocks (BB) per Ring Position

BB Position	1	2	3	4	5	6	7	8
No. of BBs	391	437	459	379	157	77	29	21

Unique Compounds per Ring Size

Ring Size	10	11	12	13	14	15	16	17	18	19
Compounds	1	2	263	53	168	831	711	1845	2192	346

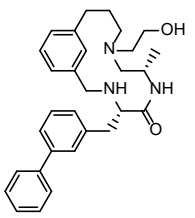
Ring Size	20	21	22	23	24	25	26	27	28	29
Compounds	478	307	64	69	60	19	17	55	35	55

Ring Size	30	31	34	36
Compounds	232	14	9	2

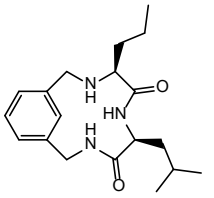
Ring Size	cd24	cd30	cd32	cd34	cd38	cd56	cd58	cd60
Compounds	1	4	2	6	1	1	2	3

NEW

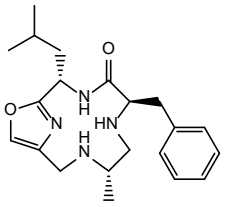
Specific CMRT™ Designs – BBP Examples



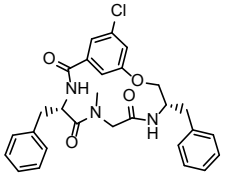
Molecular Weight: 471.64
tPSA: 64.6
CLogP: 5.3804



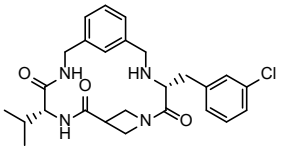
Molecular Weight: 331.46
tPSA: 70.23
CLogP: 3.431



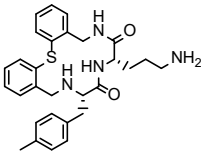
Molecular Weight: 370.50
tPSA: 74.75
CLogP: 2.2306



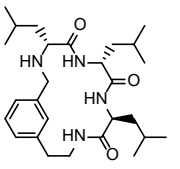
Molecular Weight: 506.00
tPSA: 87.74
CLogP: 5.55044



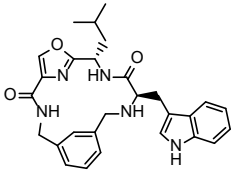
Molecular Weight: 483.01
tPSA: 90.54
CLogP: 3.8516



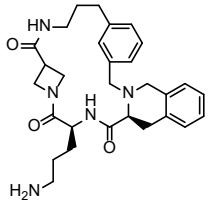
Molecular Weight: 502.68
tPSA: 96.25
CLogP: 4.462



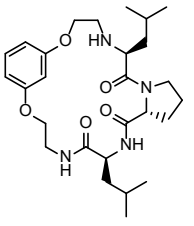
Molecular Weight: 472.67
tPSA: 99.33
CLogP: 5.9124



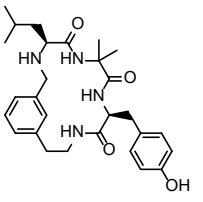
Molecular Weight: 485.59
tPSA: 103.85
CLogP: 3.4936



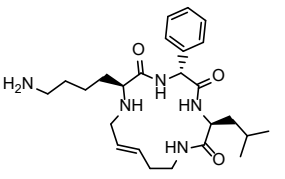
Molecular Weight: 503.65
tPSA: 107.77
CLogP: 2.7048



Molecular Weight: 502.66
tPSA: 109
CLogP: 5.1441



Molecular Weight: 494.64
tPSA: 119.56
CLogP: 4.2684



Molecular Weight: 457.62
tPSA: 125.35
CLogP: 2.7934

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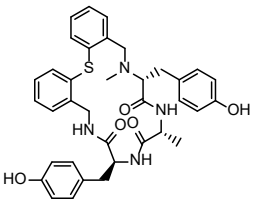
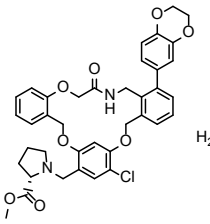
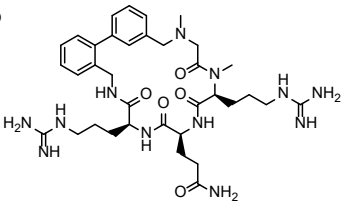
Specific CMRT™ Designs – PPI Examples



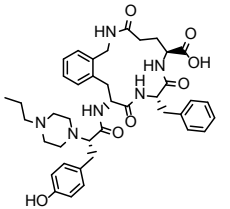
Molecular Weight: 638.78
tPSA: 131
CLogP: 5.6756



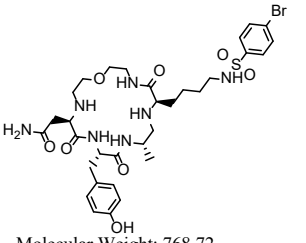
Molecular Weight: 685.17
tPSA: 104.79
CLogP: 7.4255



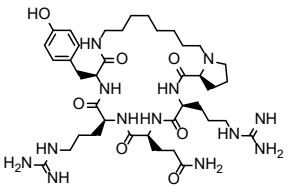
Molecular Weight: 720.88
tPSA: 277.74
CLogP: -1.4954



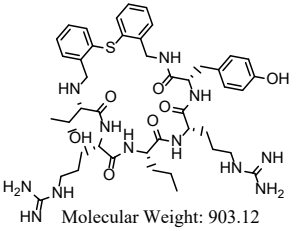
Molecular Weight: 726.88
tPSA: 180.41
CLogP: -0.2335



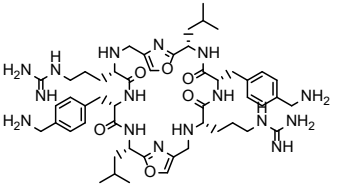
Molecular Weight: 768.72
tPSA: 230.08
CLogP: 1.65065



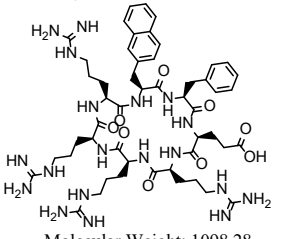
Molecular Weight: 828.03
tPSA: 335.86
CLogP: -1.4008



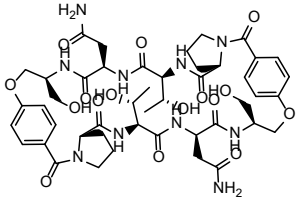
Molecular Weight: 903.12
tPSA: 321.79
CLogP: 1.24135



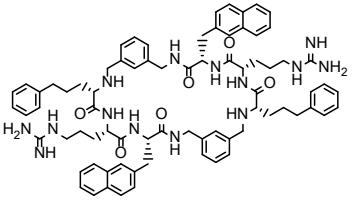
Molecular Weight: 997.26
tPSA: 359.48
CLogP: -1.456



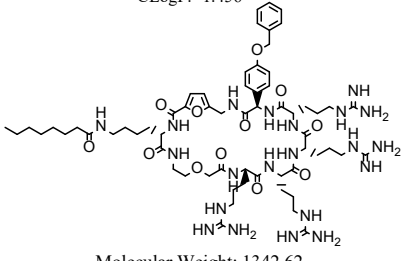
Molecular Weight: 1098.28
tPSA: 488.6
CLogP: -5.3592



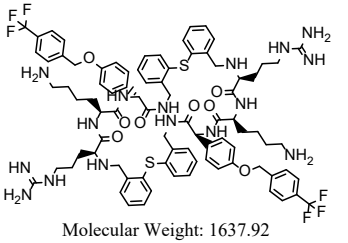
Molecular Weight: 1011.06
tPSA: 400.78
CLogP: -2.8974



Molecular Weight: 1295.65
tPSA: 322.46
CLogP: 8.7628



Molecular Weight: 1342.62
tPSA: 537.19
CLogP: -2.5059



Molecular Weight: 1637.92
tPSA: 392.96
CLogP: 10.1608

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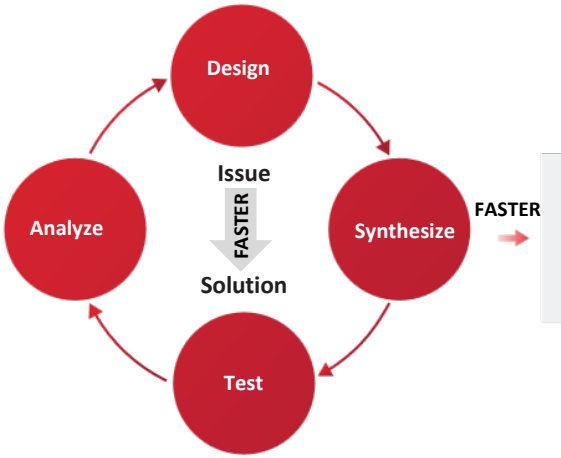
Typical SpiroChem **MedChem** project workflow

CDA → Disclosure of the project → Definition of the goals timelines and specifications → High-level evaluation to define scope and tentative budget →



→ **Project success**

The client can share:

- *Biological target*
- *Existing SAR*
- *Preliminary results/data*
- *X-ray data*
- *Chemistry procedures*

…

Our medicinal chemistry group combines expertise across :

- *multiple therapeutics areas (e. g. oncology, CNS, antibiotics, antiviral, metabolic disorders, pulmonary diseases, obesity, …)*
- *various biological mechanisms (e. g. kinase, ion channel, reverse transcriptase, protein degrader, GPCR, Ppi, covalent inhibitor, …)*

SpiroChem's impact on chemistry program PRODUCTIVITY

Troubleshooting and high speed of implementation to:

- Deliver compounds earlier
- Reach conclusions faster
- Rapid shifting of priorities when required by project

SHORTER optimization cycles
Get access to your go/no-go decisions earlier

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Let’s collaborate!

Be in touch.

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WRO-1047-3, Mattenstrasse 24
4058 Basel Switzerland

Tel: + 41 61 685 95 00
E-mail: laurence.jung@spirochem.com
www.spirochem.com

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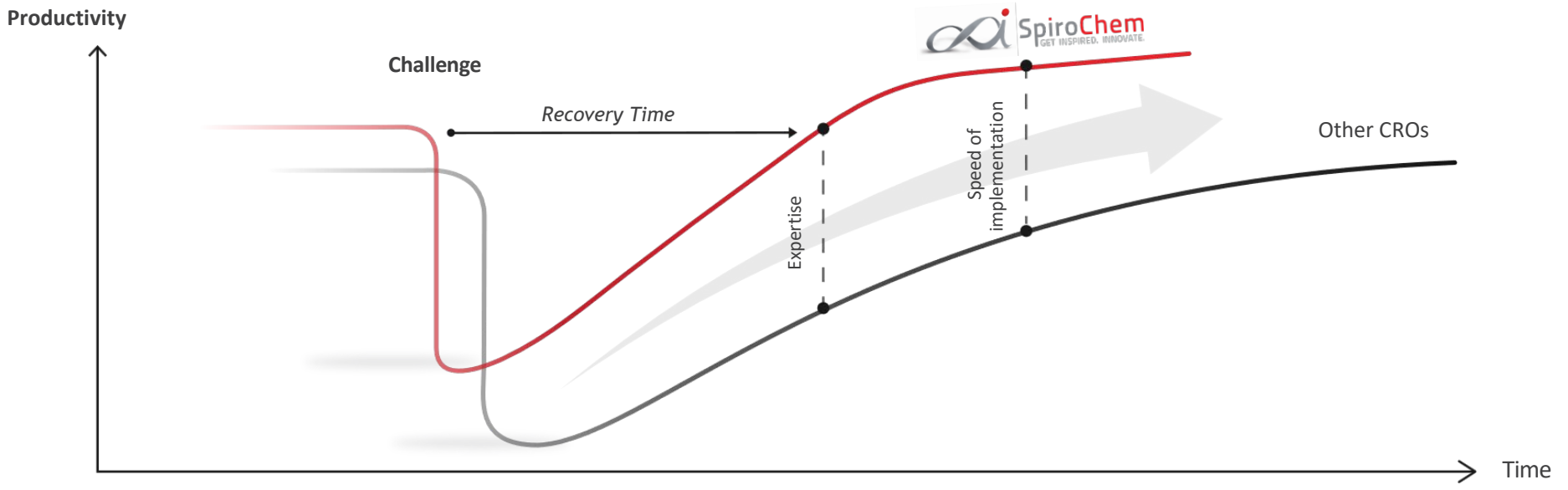
Speed + Expertise = Budget Optimization

SpiroChem's impact on chemistry programs:

- Delivering compounds earlier
- Shorter test cycles
- Reaching conclusions faster

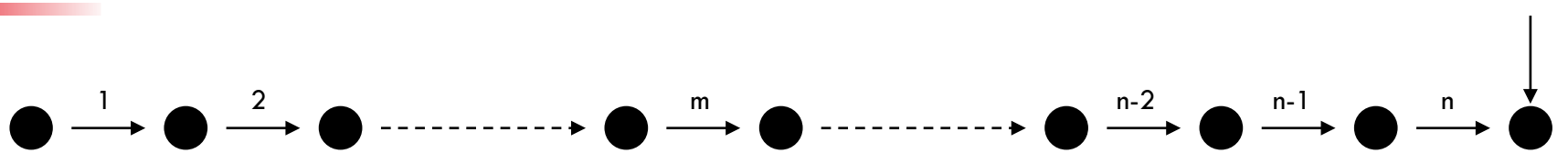
SpiroChem's **impact on project budget:**

- Less down-time for other CROs/internal resources
- Lower overall project costs



We face the same problems as others... but we avoid them or solve them faster.

Number of steps needed per final target/compound



n = number of linear steps

P_x = average success rate per reaction for step *x* (1 = 100%, 0.5 = 50%)

N = average number of synthetic steps per final product

$$N = \frac{1}{P_1} + \frac{1}{P_2} + \cdots + \frac{1}{P_n} = \sum_{i=1}^{n} \frac{1}{P_i}$$

Example:

- 10-step synthesis
- 6 easy steps
- 3 medium complexity
- 1 difficult step

Assumptions Probability per step	P_{easy}	P_{medium}	$P_{complex}$	N	N_{20} (20 compounds)
Good chemist	0.9	0.75	0.5	12.7	253
Less good chemist	0.8	0.5	0.2	18.5	370

+46%

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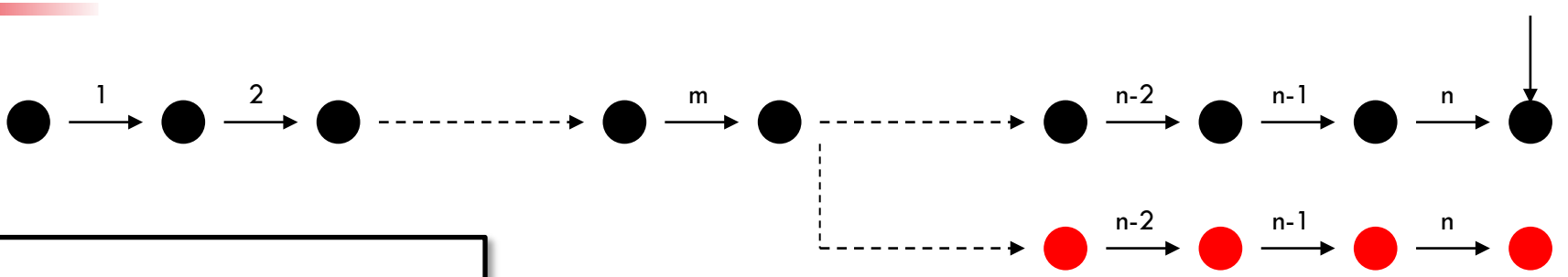
Illustrative values

Metrics for focused library synthesis (H2L, LeadOpt)



$$N_i = \sum_{i=1}^{m} \frac{1}{P_i} + j \cdot \sum_{i=m}^{n} \frac{1}{P_i}$$

n = number of linear steps
m = number of steps before divergence
P_x = average success rate per reaction for step *x* (1 = 100%, 0.5 = 50%)
N_i = number of synthetic steps for ***i*** final products

Assumptions Probability per step	*m*	P_{easy}	P_{medium}	$P_{complex}$	N_{20} *j* = 20 compounds
creative chemist	8	0.9	0.75	0.5	59
"conservative" chemist	5	0.9	0.75	0.5	86

+45%

Example:

- 10-step synthesis
- 6 easy steps E
- 3 medium complexity M
- 1 difficult step D
- Sequence: EEMEMEEDME

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Illustrative values

“Complexity scale”: depends on who you ask !

Chemist 1 (SpiroChem)

Easy (works 9 times out of 10)

-Suzuki
-Sonogashira
-Amide coupling
-Reductive amination
-Esterification
-Wittig/HWE
-[2+2] photocycloaddition
-Nickel-photoredox Csp3-Csp2 coupling

Medium (works 6-8 times out of 10)

-Buchwald Hartwig
-Ullmann C-N coupling
-Etherification
-Mitsunobu
-Nickel photoredox Csp3-Csp3 coupling

Difficult (works 3-5 times out of 10 or requires some optimization)

-Pd-catalyzed C-O coupling
-Nickel photoredox C-N coupling
-Nickel-photoredox C-O coupling
-Krapcho

Chemist 2 (SpiroChem)

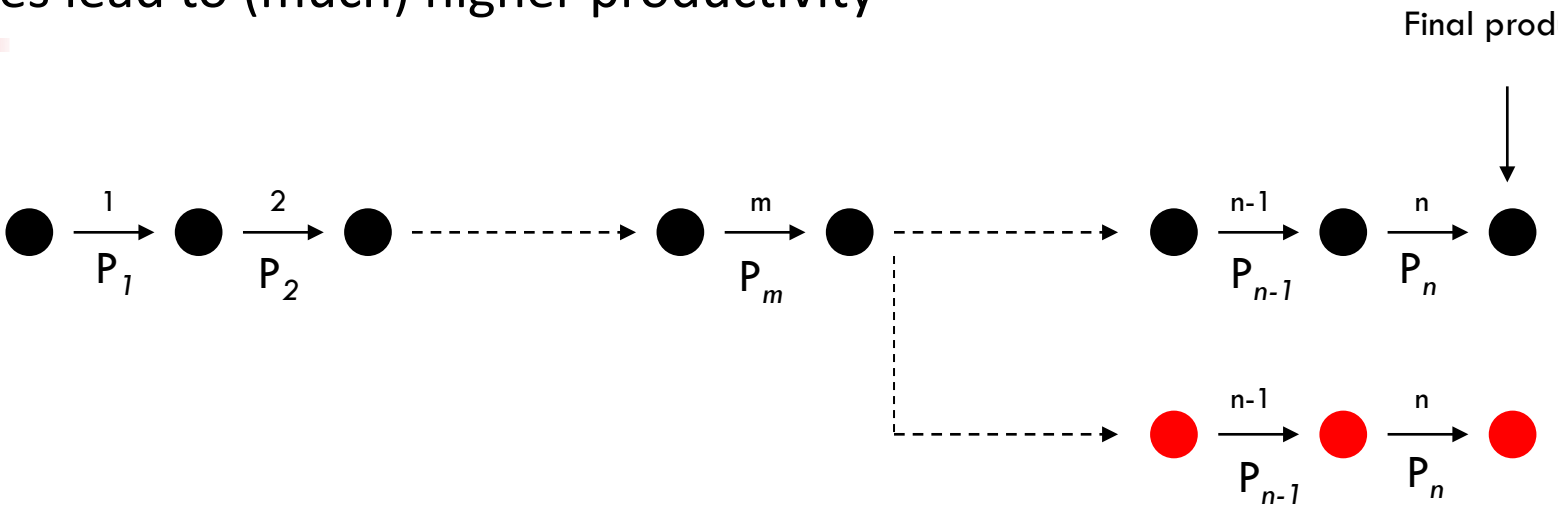
Easy (works 9 times out of 10)

- carboxylate chemistry (sapo, petide coupling, etc
- carbonyl chemistry (addition, condensation, reductive amination, etc)
- SNAr
- palladium catalysed cross coupling (various)
- FG interconversion (most redox, protecting group and activation strategies)

Medium (works 6-8 times out of 10)
- spirocycle formation
- metathesis (cross, ring-closing)
- cryogenic reactions involving hard organometallic species
- glycosylation
- photochemical transformations

Difficult (~~works 3-5 times out of 10 or~~ requires some optimization)
- macrocyclization (all)
- biocatalytic transformations
- C-H functionalisation
- unprecedented enantioselective transformations
- reactions requiring extreme conditions (-100 °C, high pressure, >150 °C)

Synergies lead to (much) higher productivity

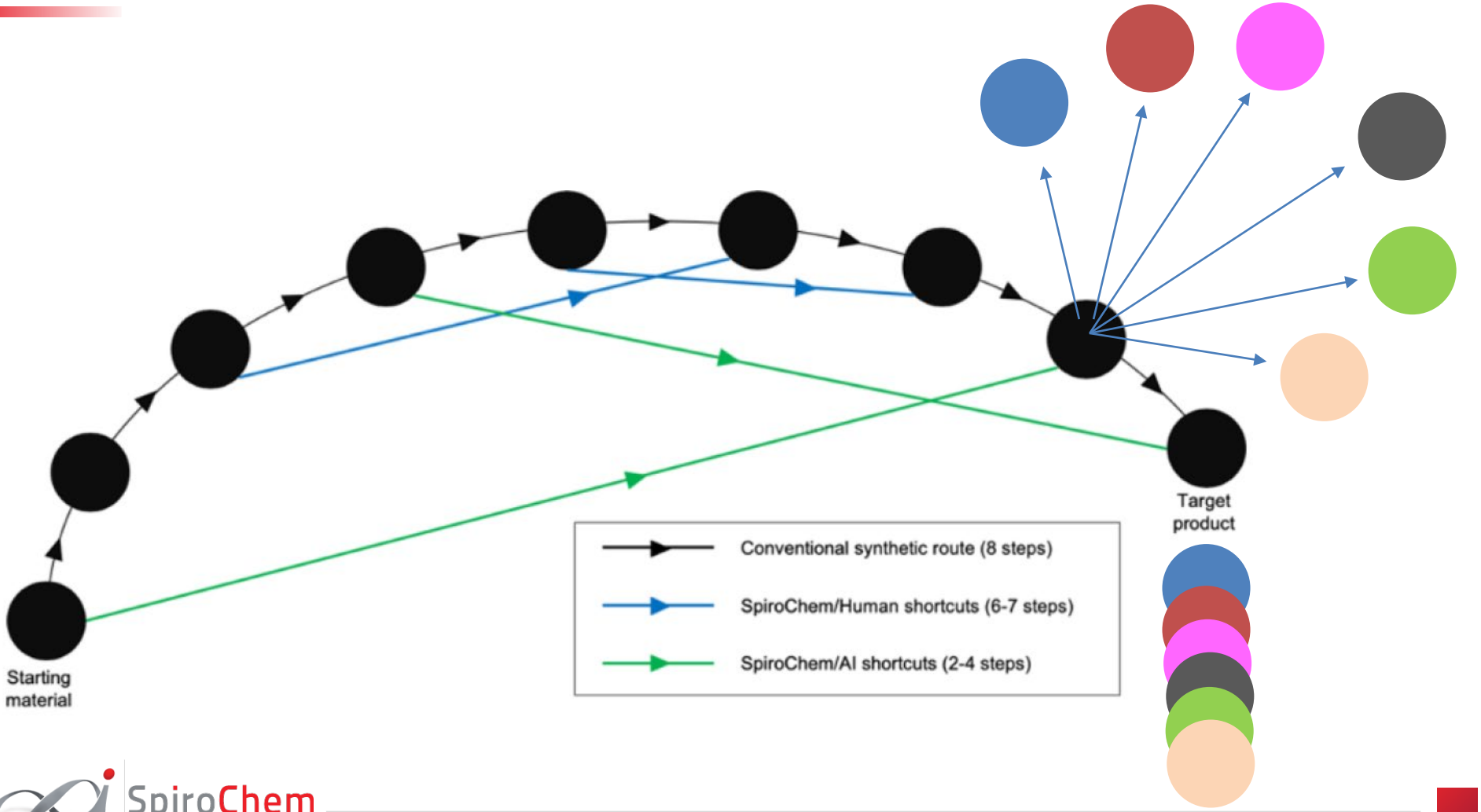


- SpiroChem always evaluate synthetic strategy to reduce "n" and increase "m"
- SpiroChem chemsits are highly trained, hence higher P_i

- Synergy of effects means that efficiency of SpiroChem chemists is at a multiple of industry standards
- SpiroChem skills can be used to:
  - Work on long and/or complex synthetic sequences
  - Remove bottlenecks to facilitate downstream chemistry (3rd party ?)
  - Blitz projects: focused libraries

SpiroChem's MedChem-Enabling Platforms: Concept

Late-stage transformations



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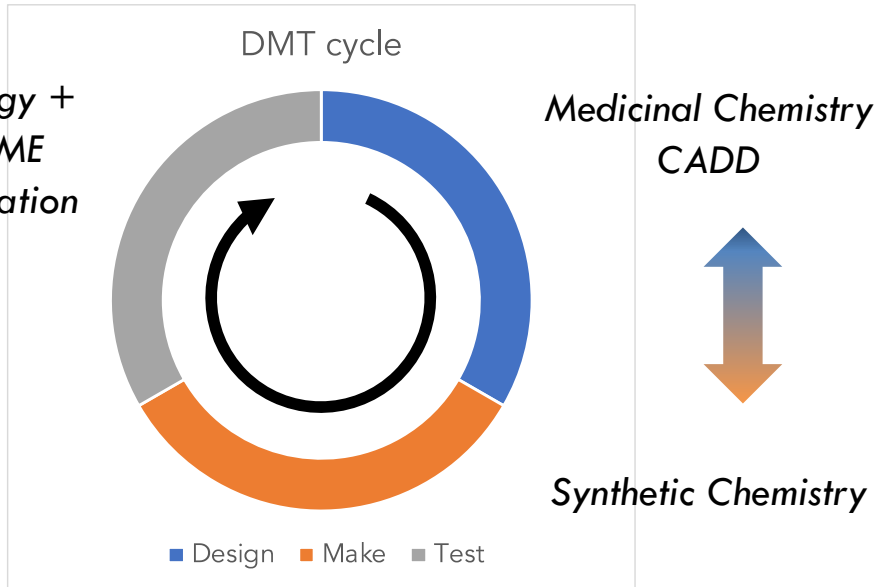
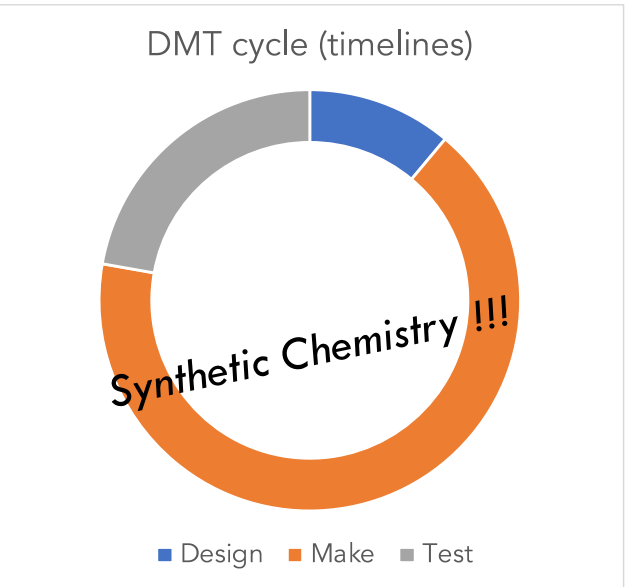
Important role of synthetic chemistry in drug discovery





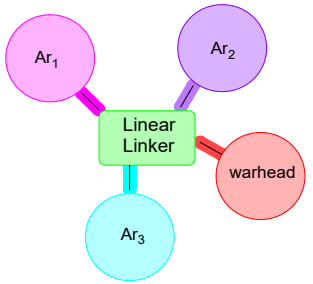
Conclusions:

- Synthetic chemistry has the highest potential to accelerate drug discovery
- Synthetic accessibility should not be a limitation to designers/medicinal chemists
- Novel methodologies and supporting technologies are needed

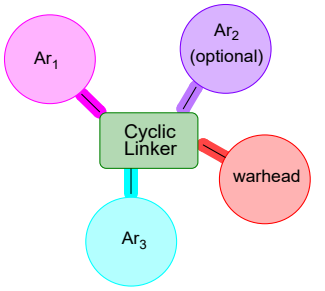
Case Study 1 – Hit-to-Lead supported by 3D design

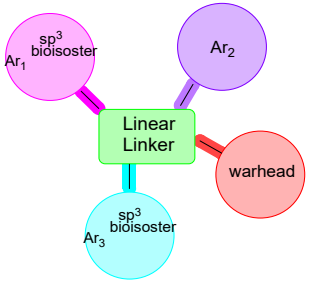
Customer : European Biotech
Collaboration : 5 FTEs, 12 months

Project goal : Design new IP secured chemical series compatible with oral bioavailability (protein degraders program)



Linear Linker replaced with cyclic linker
or
Ar group replacement (bioisosteric solutions)





- ❑ Design (IP + chemical feasibility)
- ❑ Docking (215 docked structures)
- ❑ Selection of 9 chemical series
- ❑ Route scouting : selection of 6 chemical series
- ❑ Synthesis of representatives of each series

1240 experiments

- ❑ Selection of 4 series

760 experiments

- ❑ Analog production / SAR / properties optimization supported with docking (485 docked structures)

❑ Outcome:

- Activity maintained
- IP space identified
- Improved solubility
- Decreased logP

❑ KPIs:

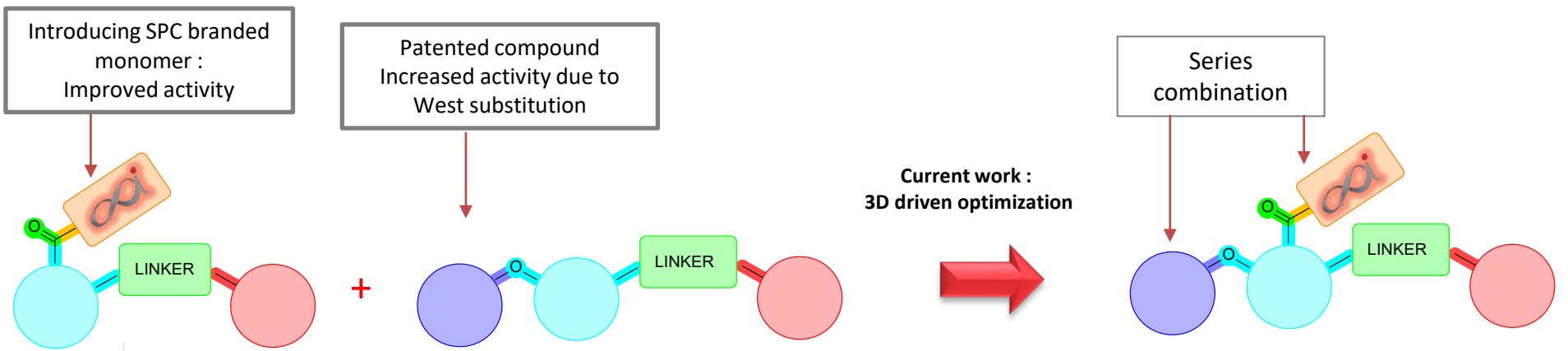
- Number of final targets: 100
- Average steps/target : 5.2 (without considering the key BB production)

Case Study 2 : Patent Gap Analysis – Novel Hit Identification – Hit-to-Lead

Customer : European Biotech
Collaboration : 2 FTEs, 3 months then 2 FTEs, 3 months

Project goal : Identify **novel hits for a know target** and initiate Hit-to-Lead program (antiviral)

- ❑ Patent analysis -> Analysis of **patent gaps** of 127 patents
- ❑ 3D design using **structure-based pharmacophore models**
- ❑ Suggestion of 12 chemical series
- ❑ Selection of 10 chemical series by the customer
- ❑ Synthesis of representatives of each of the 10 series
- ❑ Promising biological results for 2 series
- ❑ Initiation of Hit-to-Lead program driven by 3D design (series combination)



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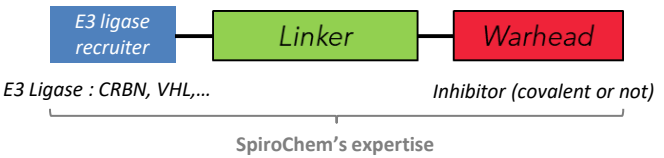
Expertise in Protein Degraders (multiple projects)

PROTACs



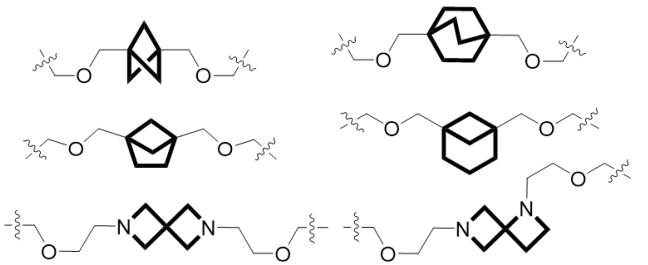
- Design of tool compounds
- Access to novel E3 ligase recruiters

Ex: VHL and CRBN analogs:

optimisation of synthetic strategy, new anchoring strategy)

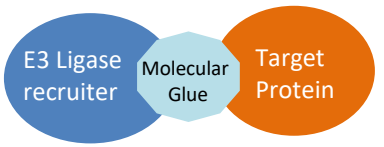
- Design and Optimization of novel linkers :
  - ✓ Improved bifunctional molecule properties
  - ✓ Choose the suitable coupling handle for easy anchory
  - ✓ Secure IP

Examples:



Our objective : Escape from PEGLand!

MOLECULAR GLUES



- Multiple synthesis of focused and medium-size diverse libraries

Expertise in Protein Degraders (multiple projects)

- Linkers are NOT INERT elements of a bi-functional molecule

  (Typically 1/3 of MW of bifunctional small molecule)
- Many parameters can be modulated, each with specific applications

- SpiroChem has expertise in applying SpiroLinkers concepts in:
  - PROTACs
  - Bifunctional molecules (beyond degradation, i.e. polypharmacology)
  - ADCs
  - Chemical Biology tools

Case Study 3 : PROTACS Project

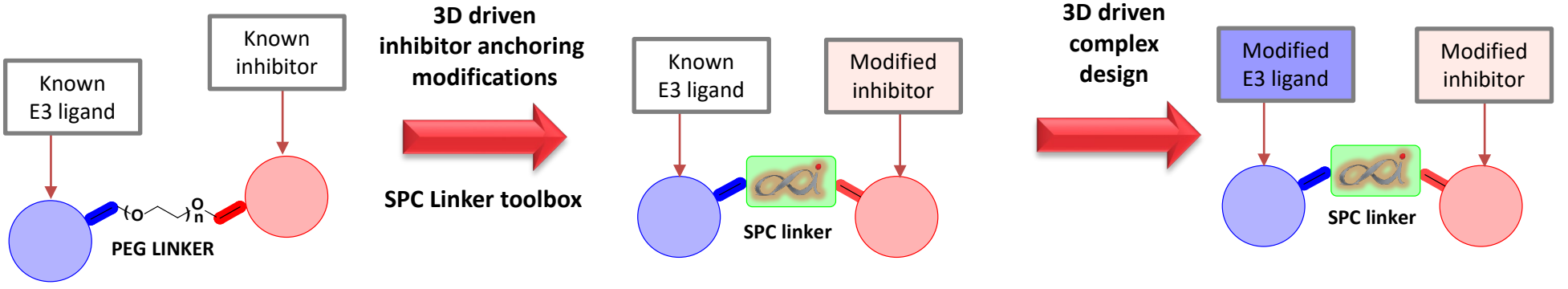
Customer : European Biotech
Collaboration : 2 FTEs, 2 months then 4 FTEs, 6 months

Project goal : Design and synthesize novel PROTACS derivatives (oncology program)

- ❑ Starting point : moderate active PROTAC : known inhibitor + PEG linker + known E3 ligase ligand
- ❑ 3D design to suggest new inhibitor anchoring
- ❑ Complex properties optimization : SPC linker variation
- ❑ 3D design to suggest modified E3 ligand

- ❑ Deliverables:
  - 15 final compounds
  - Modified E3 ligand produced at 100mg scale and shipped to a low-cost CRO working also on the project

Target amount : 10-15 mg
Steps/target : 10-15
Number of reactions per week/chemist : 11



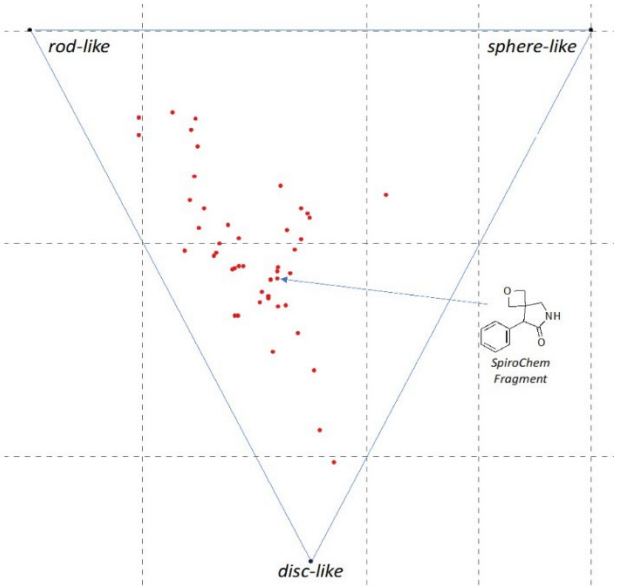
MedChem Enabling Platform

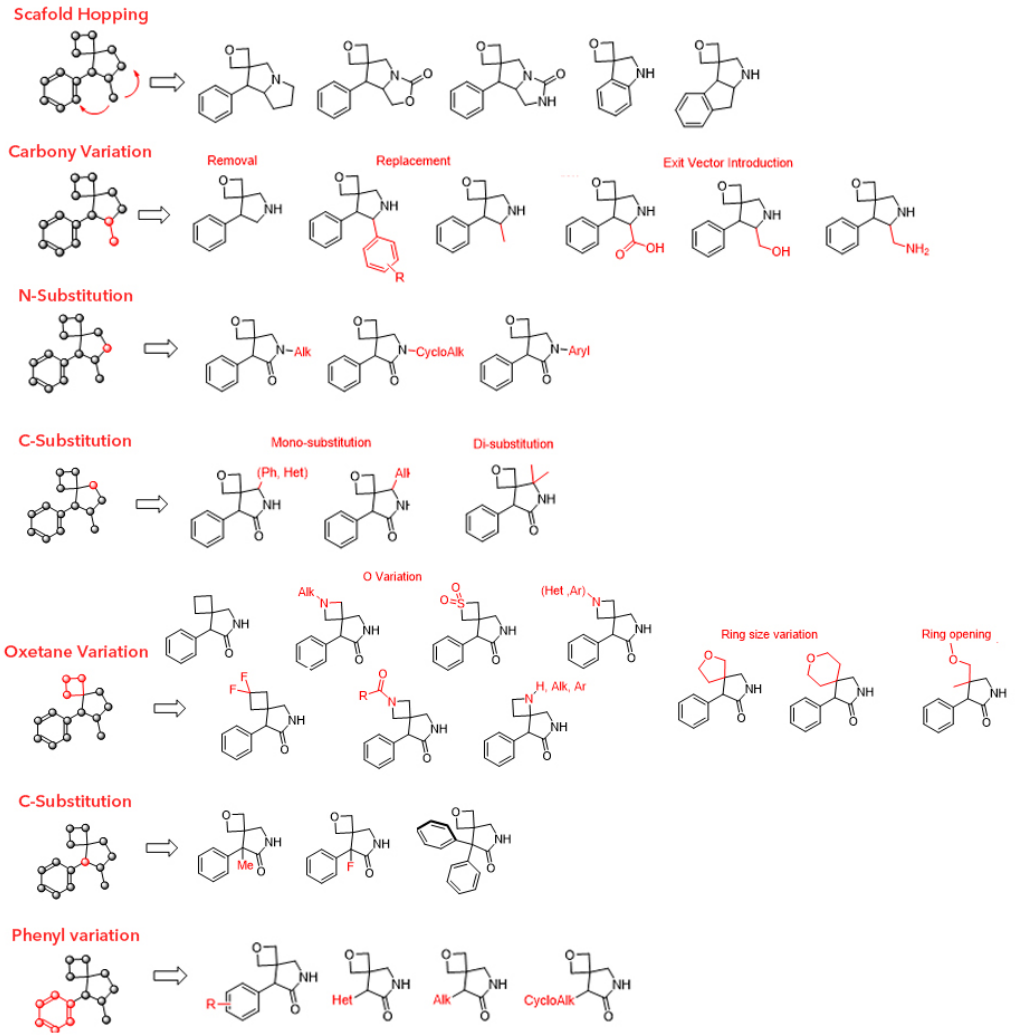
Goal : Unleash design potential by reducing synthetic challenges

NOVEL chemical space made accessible

HOW:

- Opening of new exit vectors
- Implementation of late-stage functionalization strategy
- Preparation of focused smart sets of novel compounds





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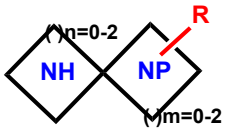
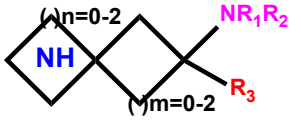
Case Study 1 – Preparation of novel spirocycles

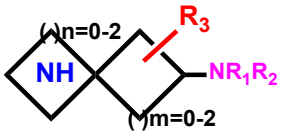
Customer : European Big Pharma
Collaboration : 2 FTEs, 3 months

Project goal : Preparation of novel spirocycles for a high-priority MedChem program (properties optimization + IP securing)



NP : N-Protected





13 requested spirocycles
Objective : Use SpiroChem knowledge and knowhow to get fast and efficient access to the spiro monomers

❑ Deliverables:
- 8 completed compounds
- 4 compounds obtained as advanced intermediates
- 1 not started

Amount : 20 - 600mg
Average steps/target : 7.2
Number of reactions per week/chemist : 11

❑ Customer's feedback:
- High-level technical input
- Fast problem solving
- Transfer of valuable knowledge
- High responsiveness
- Seamless communication

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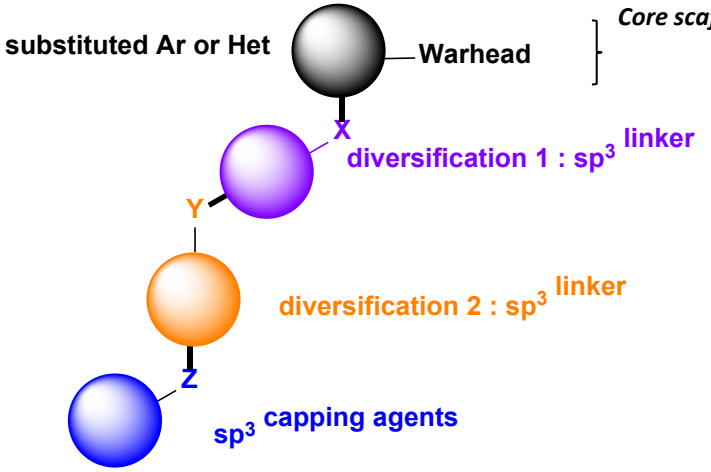
Case Study 2 – Molecular Glues project

US Biotech Company, 12-month collaboration, 5 to 6 chemists

***Goal of the project**: synthesize focused sets in the field of molecular glues using standard like warhead derivatives and focusing on diversity leveraging high sp^3 content*



Core scaffolds : synthesis in up to 6 steps each (some reported in literature, some completely new).

Diversification**:** up to 5 steps
(diversification 1, deprotection, diversification 2, deprotection, capping)

Sp^3 monomers : synthesis in up to 4 steps each
Only one was introduced among the 3 diversifications points

Type of chemistry explored:
- Amide coupling, Mitsunobu reactions, O-alkylations, reductive aminations
- Copper-mediated A3 couplings
- Suzuki and Sonogashira couplings, Minisci reactions
- C-N coupling (SNAr, metal catalysis, nickel-photoredox dual catalysis)
- C-O coupling (SNAr, nickel-photoredox dual catalysis)
- C-C coupling (nickel-photoredox cross-electrophile coupling)

KPIs

First period: 5 chemists for 6 months
Second period: 6 chemists for 6 months

2611 reactions

365 final products

Customer's satisfaction:
- Access to a collection of innovative compounds
- High sp^3 content
- High diversity

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Case Study 3 – Covalent Fragment Set

US Biotech Company, 6-month collaboration

***Goal of the project**: Explore, unlock and exemplify innovative chemistry for covalent fragment synthesis, focusing on druglikeness and library diversity leveraging high sp^3 content and heteroaromatic scaffolds.*

Project workflow:

Benchmarking : 2 chemists/1 month

100+ recent literature articles

Client selection

8 suitable transformations

SpiroChem knowledge + in-lab expertise

4 validated transformations

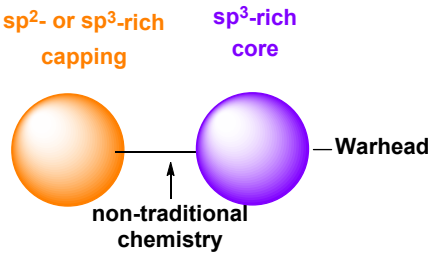
SpiroChem experimental optimization

5 chemists / 3 months
6 chemists / 2 months

Scope and limitations evaluation of each transformation

SpiroChem experimental production

Library synthesis with high success rate



Reaction benchmarking required

KPIs

4 chemists for 6 months

919 reactions

186 final products

Type of chemistry explored:

- Photoredox-nickel dual catalysis
- Copper-mediated radical chemistry
- Palladium-catalyzed cross-coupling
- Ex-situ toxic gas handling with a two-chamber reactor

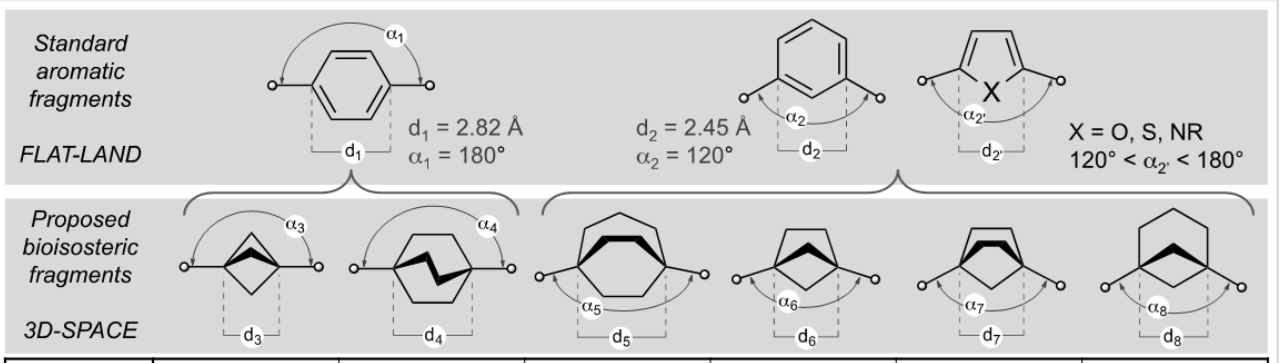
Fast access to smart sp^3-rich monomers (part of SpiroKit Collections)

Customer's satisfaction:

- Access to uncharted chemical space
- High diversity
- Efficient hybride model
  - ✓ low cost CROs : Easy chemistry
  - ✓ SpiroChem : Innovation

SpiroChem's Portfolio of Bioisoteric Solutions – sp^2 to sp^3 switch

Many sp^2-rich lead molecules fail due their propensity to generate reactive metabolites or because of their poor pharmacokinetic properties. Switching to sp^3 modules give opportunity to modulate the PhysChem and ADME properties but also to fine tune the geometry of the molecule and have a direct impact on the activity and selectivity.

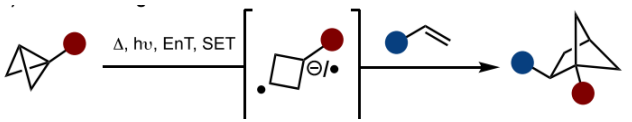


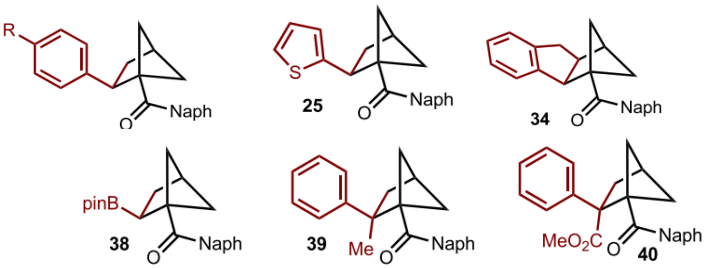
Bicyclo	[1.1.1]pentane	[2.2.2]octane	[3.2.2]nonane	[2.1.1]hexane	[2.2.1]heptane	[3.1.1]heptane
angle	α_3 = 180°	α_4 = 180°	180° > α_5 > α_6 > α_7 > α_8 > 120°			
distance	d_3 = 1.84 Å	d_4 = 2.65 Å	d_5 = 2.84 Å	d_6 = 1.86 Å	d_6 = 2.23 Å	d_7 = 2.06 Å

Figure 2. *Rationale for the development of implementation of the bicyclo[x.y.z]alkane repertoire*

Collaboration with Kevin Brown (U. of Indiana)

JACS 2022 focusing on new exit vectors on 2.1.1 rings





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