

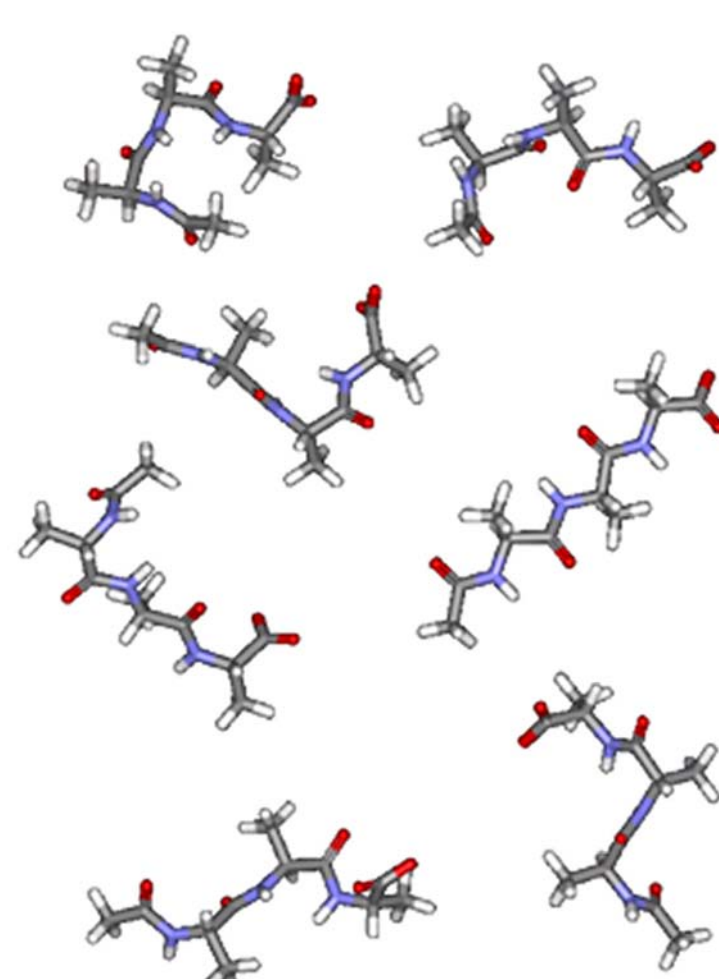
## Summary

- No target limitations
- Validated drug discovery technology
- Confirmed hit to clinical candidate in as rapid as 18 months
- Robust manufacturing processes for large batches at high yields
- Generated multiple clinical drug candidates
- Unencumbered intellectual property landscape

## Small Macrocyclus With Drug-Like Properties

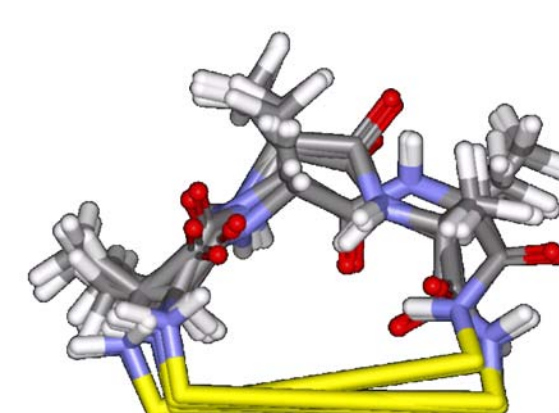
A proprietary drug discovery strategy based upon the efficient construction of diverse libraries of novel macrocyclic compounds is presented. These conformationally-defined molecules in combination with high throughput screening have generated multiple potent and selective hits against a wide range of pharmacological targets, including GPCRs, protein-protein interactions, proteases and ion channels. The unique chemical and biological features of this strategy include ease of SAR development, accelerated lead-to-clinic optimization, favorable safety and ADME properties, straightforward scalability, and an unencumbered patent landscape. Among the case studies that will be described are the identification and optimization of modulators of critical GPCR targets in the gastrointestinal tract that have led to compounds with appropriate properties to be developed as pharmaceuticals. The most advanced of these clinical candidates has now reached Phase III trials.

### Linear peptide ligands



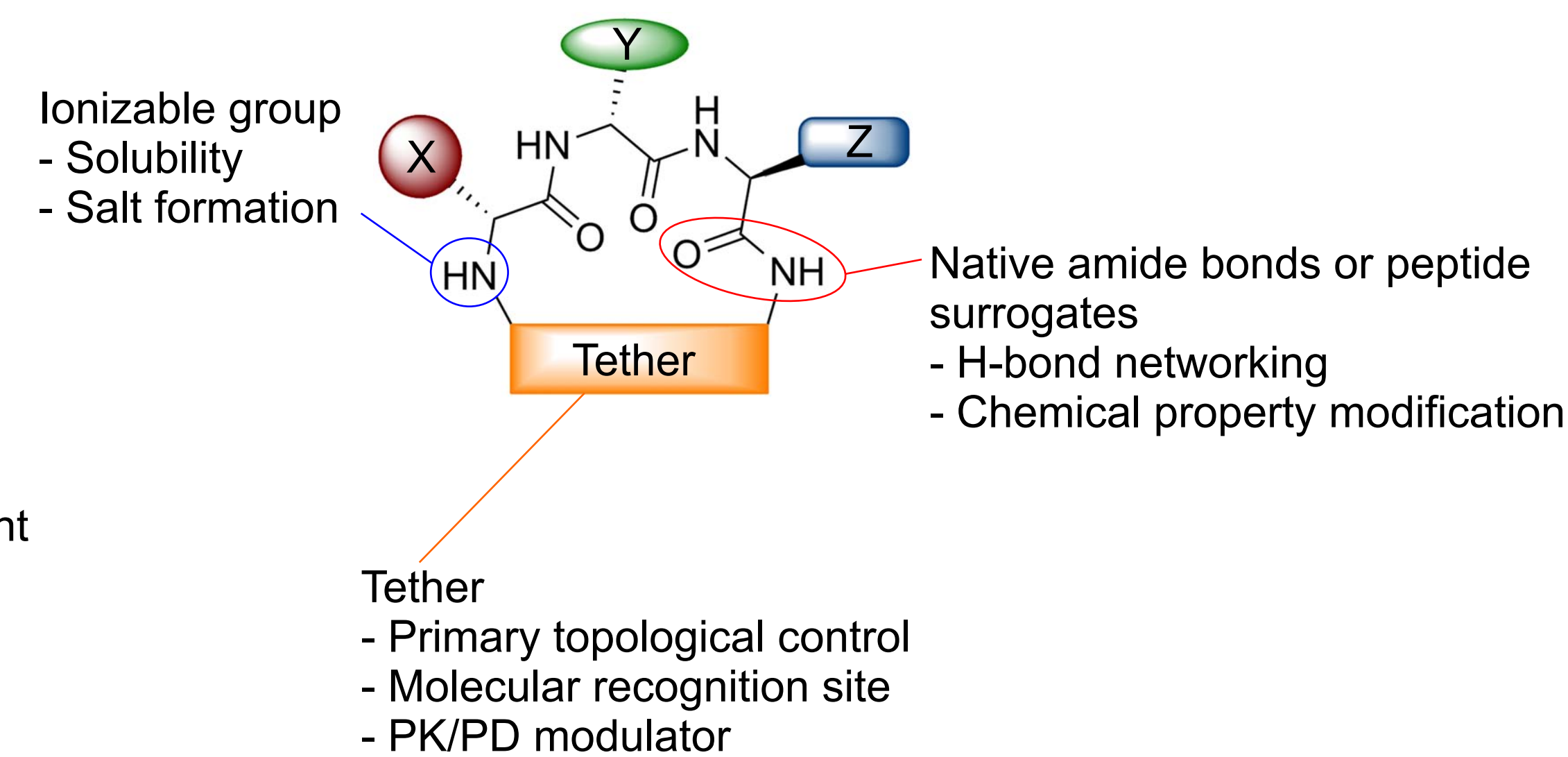
- Numerous uncontrolled conformers
- Substrate for proteases

### Macrocyclus ligands



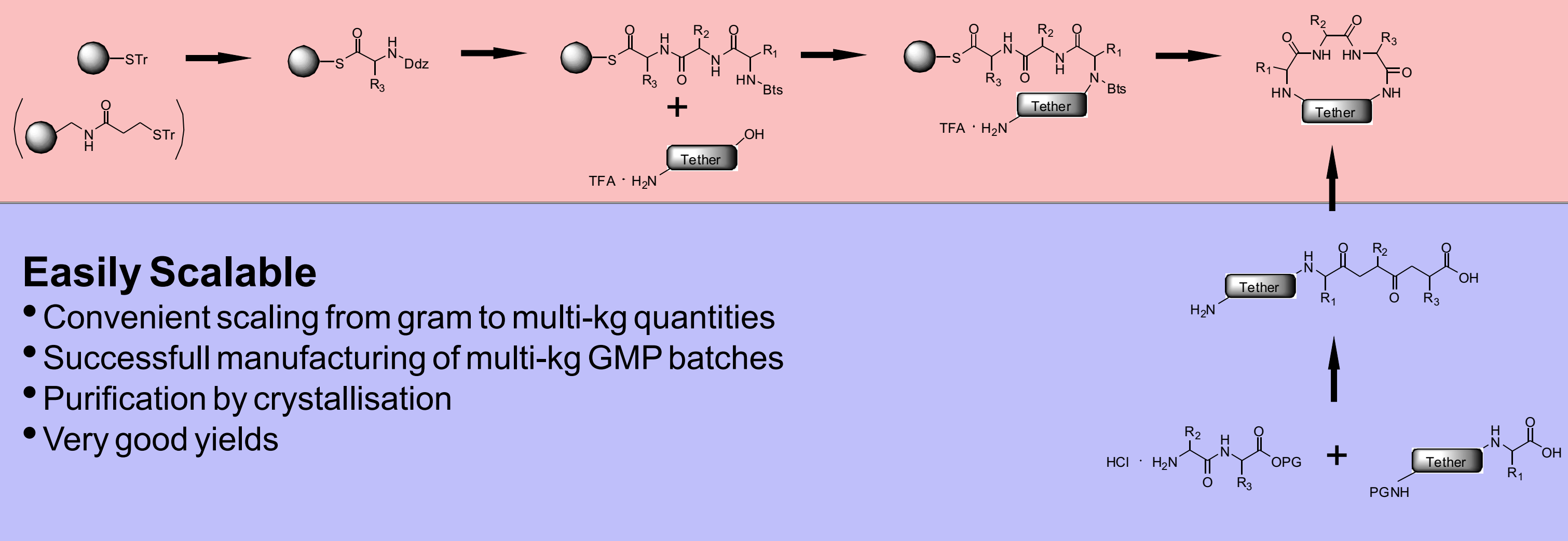
- Conformationally locked
- Reduced binding entropy / more potent
- High proteolytic stability
- Improved specificity and selectivity
- Solid SAR
- Recognized in drug discovery

Molecular Recognition Elements X, Y, Z  
- Variable hydrophobicity / electrostatics  
- Variable steric environment  
- Variable orientation



## MATCH™ (Macrocyclus Template Chemistry) - Easily Scalable, Unique And Versatile Library Design

### High Throughput Parallel Synthesis => Rapid Library Generation => Instant SAR



#### Easily Scalable

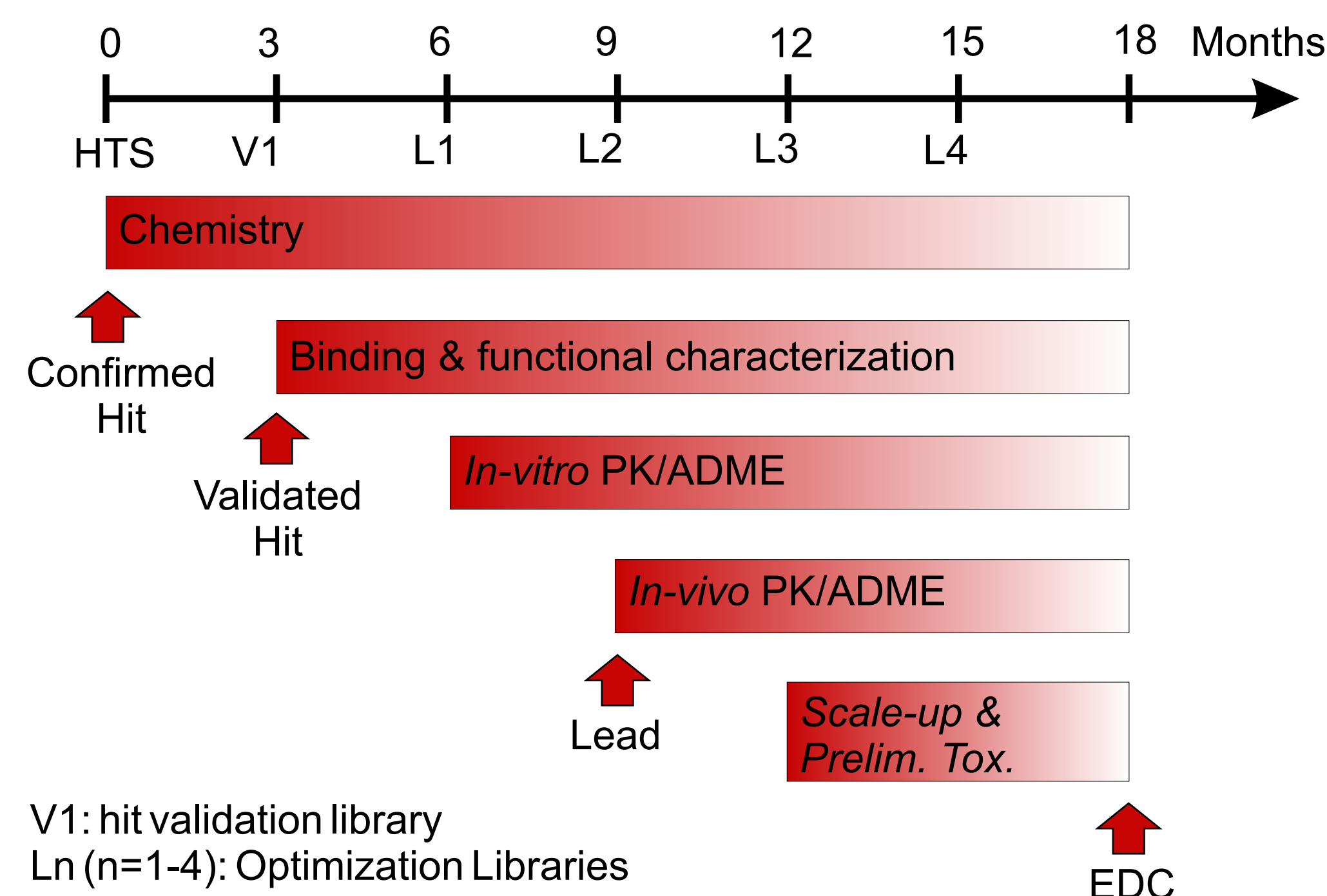
- Convenient scaling from gram to multi-kg quantities
- Successful manufacturing of multi-kg GMP batches
- Purification by crystallisation
- Very good yields

### Compelling Reasons to Employ MATCH™ and HITCREATE™

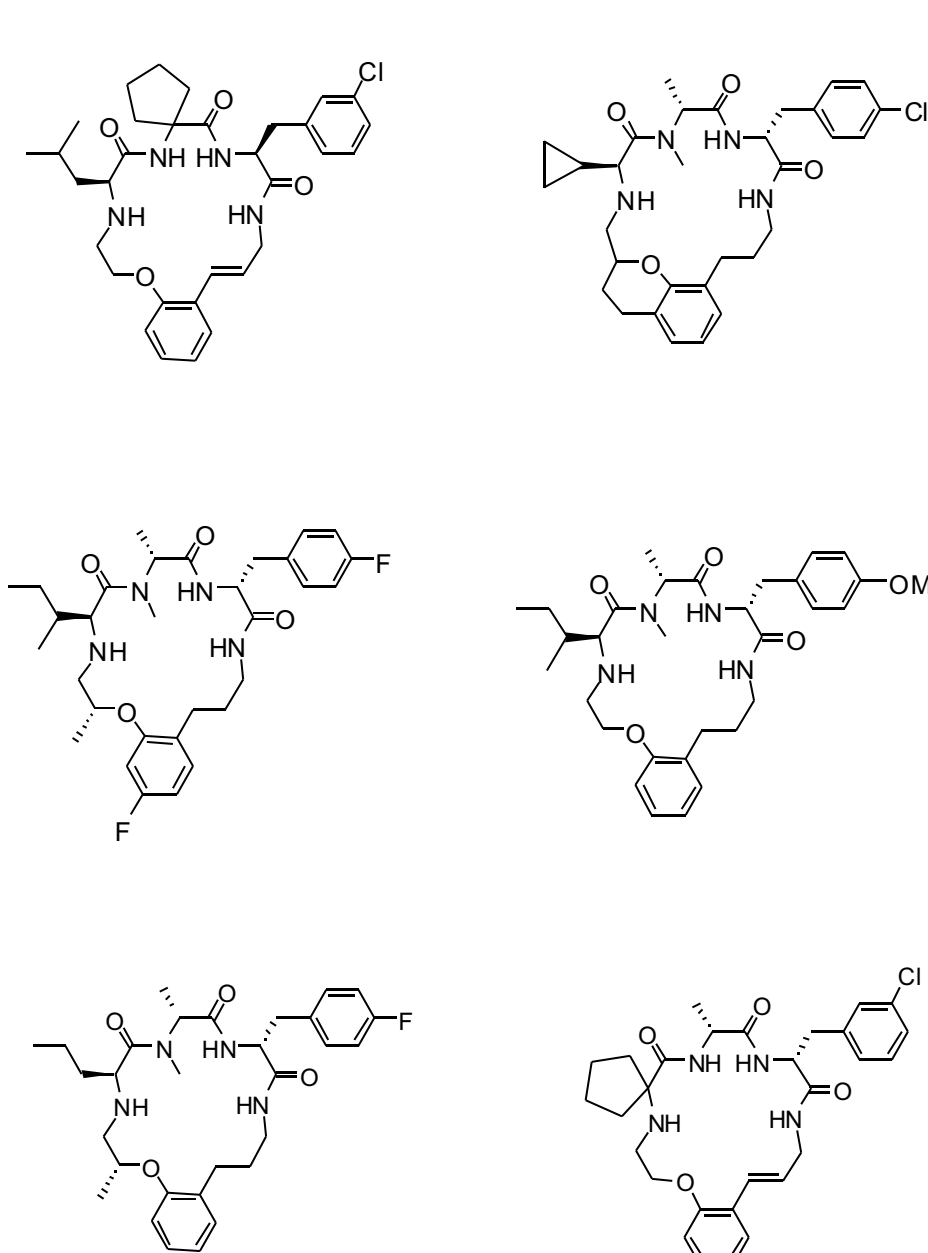
- Unique small macrocyclus (MWt ~500)
- Multiple recognition elements
- Tight topological control
- Unmatched diversity
- Ideal for rational design
- Straight-forward parallel synthesis
- High quality hit generation
- Accelerated, resource-efficient lead optimization
- Easily scalable chemistry
- Excellent chemical and metabolic stability
- Good oral bioavailability
- Superior safety profile
- No target limitations
- Successful clinical drug
- Strong IP position worldwide
- 40,000 compounds synthesized
- 20,000 compounds available for screening
- Hit rate of 0.2-0.5%
- High hit potency: initial K<sub>i</sub> frequently < 500 nM
- Hit validation rate up to 50%
- High selectivity against liability targets (> 300 fold)
- Successfully applied to diverse target classes
  - GPCRs, ion channels, protein-protein, proteases

## HITCREATE™ In Drug Discovery - HT Parallel Synthesis For Lead Optimization

### Competitive Timelines from Hit to Clinical Candidate



### Representative Ghrelin Receptor Agonist Structures

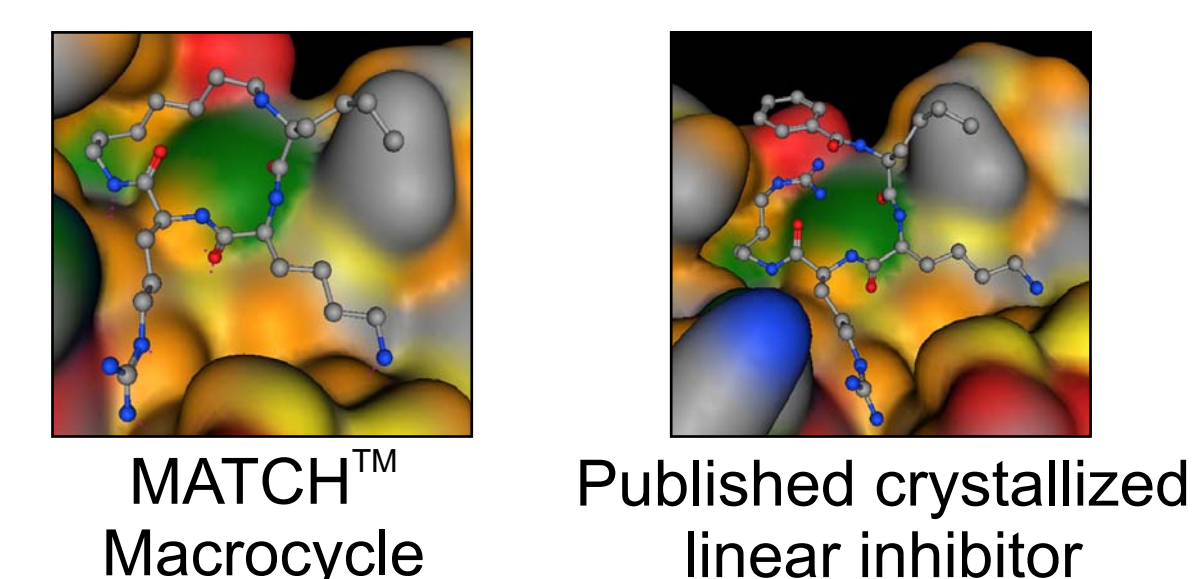


### Key Properties of the Clinical Ghrelin

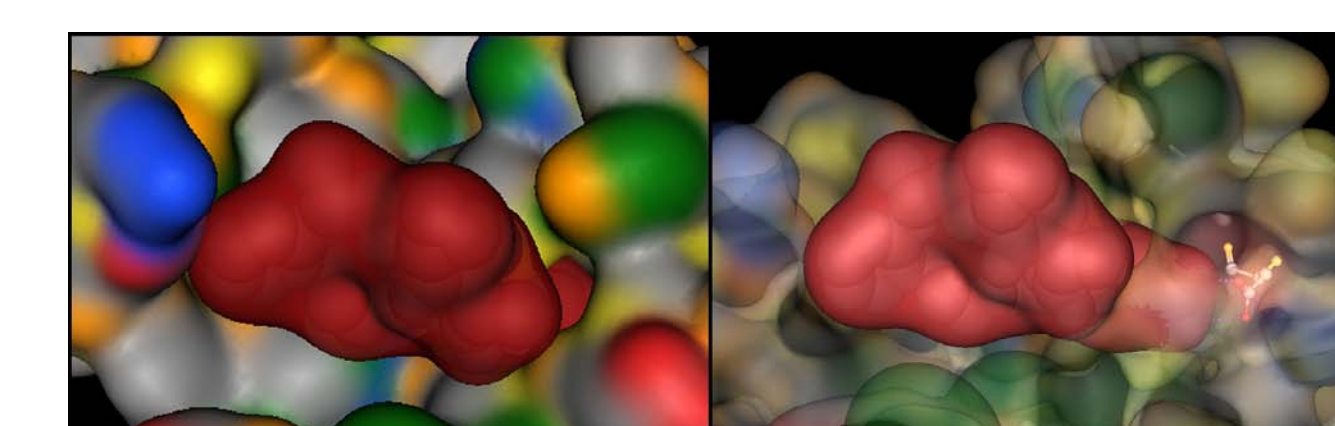
| Property                          | TZP-101          | TZP-102        |
|-----------------------------------|------------------|----------------|
| Molecular Weight                  | ~ 500            | ~ 500          |
| ClogP                             | 5.3              | 4.5            |
| pK <sub>a</sub>                   | 7.17 ± 0.04      | 6.23 ± 0.11    |
| K <sub>i</sub> (hGRLN)            | 22 nM            | 12 nM          |
| EC <sub>50</sub> (hGRLN)          | 27 nM            | 11 nM          |
| ED <sub>GE</sub> (rat, iv bolus)  | 0.1 mg/kg        | ND             |
| ED <sub>GE</sub> (rat, oral)      | >3 mg/kg         | 3 mg/kg        |
| ED <sub>POI</sub> (rat, iv bolus) | 0.1 mg/kg        | ND             |
| IC <sub>50</sub> CYP3A4           | >0.5 μM (BFC/BQ) | >5 μM (BFC/BQ) |
| IC <sub>50</sub> Other CYPs*      | >50 μM           | >100 μM        |
| BBB Perm.                         | 0.1 %            | 1.3 %          |
| Oral BAV Rat                      | 16 %             | 13 %           |
| Dog                               | ND               | 25 %           |
| Monkey                            | 23 %             | 26 %           |
| Man                               | ND               | ca 85 %        |

\* CYP2D6, 2C9, 2C8, 2C19, 2B6, 2A6, 1A2

### MATCH™ Macrocyclus Appear to Fit in the Active Site of Viral Proteases



### A Potent and Selective Oncogenic Non-MMP Protease Inhibitor Hit



Primary hit docked into substrate binding site  
- Primary screen (~ 50 cpds): 3 hits, K<sub>i</sub> ~ 1.5 μM  
- Small optimization library (~ 30 cpds): K<sub>i</sub> 245 nM

## Successful Programs - You Have The Target, We Have Its MATCH™

### Tranzyme's Motilin Receptor Antagonist Portfolio

| Compound | Pharmacodynamics |                  |                 |                  | PK/ADME          |              |                 |
|----------|------------------|------------------|-----------------|------------------|------------------|--------------|-----------------|
|          | Binding          | Antagonist       | Ex Vivo         | In Vivo          | Rat, i.v. PK     |              | Bio. Avail. (F) |
|          | K <sub>i</sub>   | IC <sub>50</sub> | Rabbit Atrium   | Strain Gauge     | t <sub>1/2</sub> | Clearance Cl |                 |
| 1        | nM               | nM               | pA <sub>2</sub> | Dog i.v. (mg/kg) | minutes          | ml/min/kg    | <1              |
| 2        | 4.6              | 7.5              | 7.76            | >0.3             | 146              | 57           | <1              |
| 3*       | 2.1              | 0.53             | 8.11            | <0.3             | 139              | 33           | 4.5             |
| 4        | 1.2              | 0.12             | 8.35            | >0.3             | 24               | 45           | 13              |
|          | 10.3             | 5.4              | 7.8             | >0.3             | 25               | 65           | 11.4            |

- Proof-of-concept achieved in preclinical dog CID model - Compound 3: efficacious at 2.5 & 7.5 mg/kg (dog, i.v.)
- Clinical candidate (TZP-201) selected

### Selective Hits on Three Protein-Protein Interaction Targets

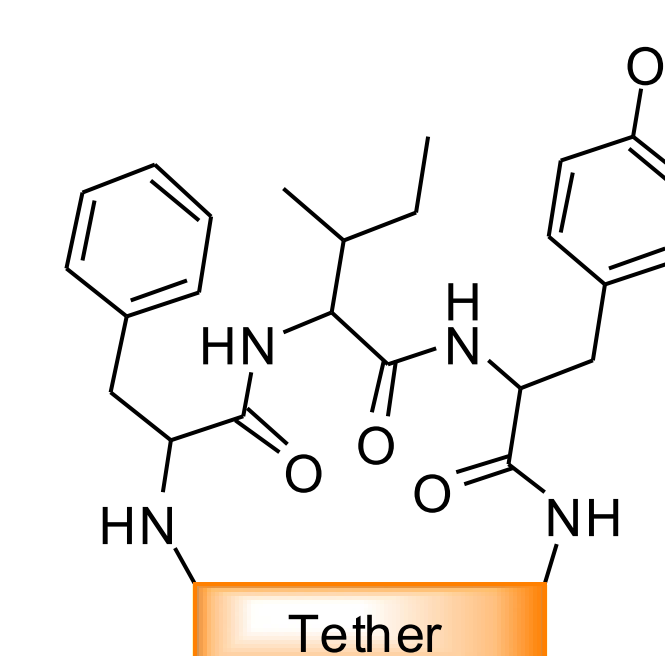
| Target Number | Primary hits n/20K cpds | Confirmed Hits/Tested | Validated Hits/Tested | K <sub>i</sub> in μM (# of cpds) |
|---------------|-------------------------|-----------------------|-----------------------|----------------------------------|
| 1             | 1948                    | 82/192 (43%)          | 34/54 (64%)           | <10 (10)                         |
| 2             | 2375                    | 85/86 (99%)           | 16/41 (39%)           | <10 (5)                          |
| 3             | 390                     | 132/170 (78%)         | 2/56 (4%)             | 22 (2)                           |

### Highly Potent & Selective Primary Hits on Ion Channels

| Hit Number | Primary Target IC <sub>50</sub> (μM) | Liability Target IC <sub>50</sub> (μM) | Fold Selectivity |
|------------|--------------------------------------|--|------------------|
| 1          | 0.11                                 | 42                                     | 382              |
| 2          | 0.02                                 | 5                                      | 250              |
| 3          | 0.21                                 | >30                                    | >142             |
| 4          | 0.39                                 | >30                                    | >77              |
| 5          | 0.79                                 | 21                                     | 27               |

### Motilin Receptor Agonists

Motilin Agonist (EC<sub>50</sub> = 39 nM)



- Design based on key elements of motilin pharmacophores - Phe<sup>1</sup>, Ile<sup>4</sup>, Tyr<sup>7</sup>
- One library designed (n ~30 molecules)
  - Constant amino acid sequence
  - Variable macrocyclic ring size
- Hit potency dependent on macrocyclic ring size:
  - 16 atoms: K<sub>i</sub> = 106 nM
  - 17 & 18 atoms: K<sub>i</sub> = 2 mM