

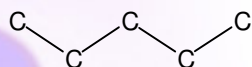
Can Macrocycles Get It Done (this time)

A NON-confidential introduction
to ODIN Industries, LLC

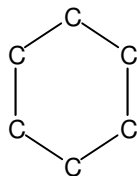
March 2015



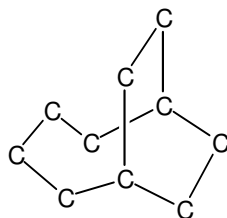
Macrocycles Are Among The Most Diverse & Valuable Molecules Known



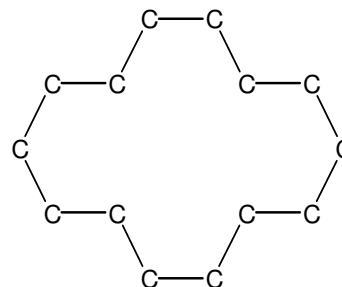
linear



cycle

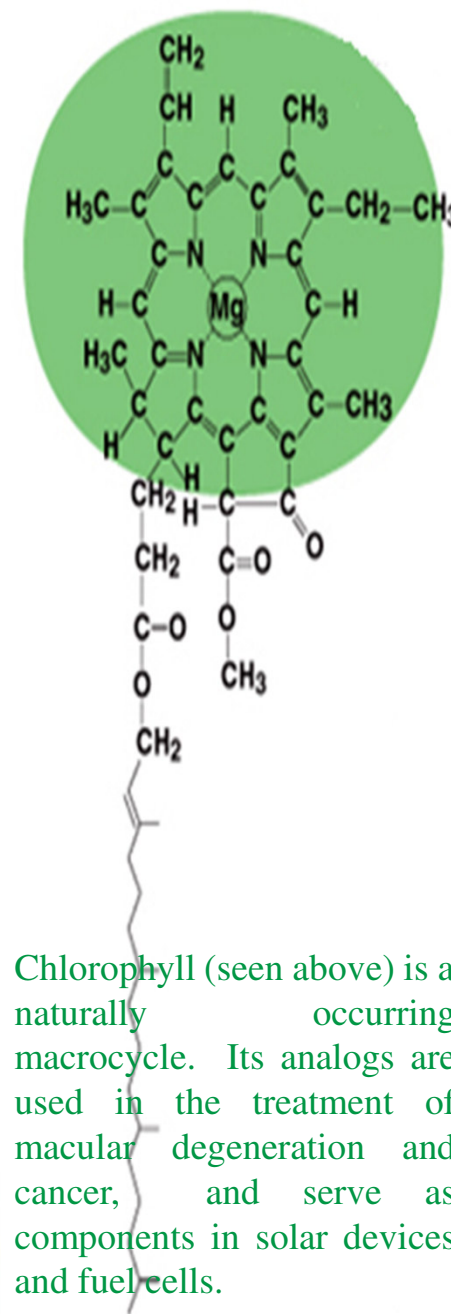


bicycle



macrocycle

They are small to medium sized natural, semi-natural, or synthetic molecules where the atoms are connected in such a fashion that they form a ring. The ring gives the molecule's functional groups structure – locking them into their active form.



Chlorophyll (seen above) is a naturally occurring macrocycle. Its analogs are used in the treatment of macular degeneration and cancer, and serve as components in solar devices and fuel cells.

Macrocycles Make Better Drugs

Naturally-occurring macrocycles are highly evolved, highly specific, and can be highly effective toward the gene products with which they coevolved. Macrocycles, compounds that occupy the whitespace between small molecules and proteins, are not just bigger versions of small molecules, but can be considered as the smallest examples of biomolecules that can interact with both the active site of an enzyme and/or the surface of a protein.

What's for sure is that macrocyclic compounds are underrepresented in the drug industry...

And the chemical space that they cover is probably not something that other compounds can easily pick up.

Derek Lowe, Ph.D.

Typically, Macrocycles Exhibit Vastly Improved Pharmacodynamics When Compared To Their Linear Small-Molecule Counter Parts

Macrocycles exhibit :

- improved binding affinity
- improved selectivity
- improved half lives
- lower dosing requirements
- reduced side effects
- improved oral availability
- improved membrane permeability
- blood-brain barrier permeability

Macrocycles also:

- operate outside of Lipinski's Rules
- possess greater diversity than traditional small-molecule leads
- demonstrate higher hit rates in libraries than linear leads
- target new & unique sites that will aid in the discovery of new treatments for difficult-to-treat diseases, and
- open the door to the development of individualized treatments



And macrocycles are one of a very few number of classes of molecules that selectively disrupt protein-protein interactions!

Macrocycles in Medicine

Accordingly, macrocycles constitute a major class of pharmaceutical agents currently under preclinical and clinical investigation for the treatment of virtually every disease.

Thus, thousands of macrocycle leads have been developed in virtually every therapeutic area.

Macrocyclization is a well-precedented technique to enhance potency by conformational preorganization, and in many cases, the physical properties of the inhibitors were also improved.

Dr. Shawn Stachel
Merck & Co

A Few Examples of Macrocycles in Medicine

- All Cancer
 - ✓ Bladder Cancer
 - ✓ Brain Tumors
 - ✓ Breast Cancer
 - ✓ Cervical Cancer
 - ✓ Colorectal Cancer
 - ✓ Esophageal Cancer
 - ✓ Lymphoid Cancer
 - ✓ Leukemia
 - ✓ Liver Cancer
 - ✓ Lung Cancer
 - ✓ Ovarian Cancer
 - ✓ Pancreatic Cancer
 - ✓ Prostate Cancer
 - ✓ Skin Cancer
 - ✓ Thyroid Cancer
- Alzheimer's
- Antibiotics
- Antifungals
- Antivirals (HCV & HIV)
- Coronary Artery Disease
- Dementia
- Diabetes
- Drug Addiction
- Epilepsy
- Fragile X Syndrome
- Lou Gehrig's Disease-ALS
- Macular Degeneration
- Mad Cow Disease-TSE
- Nerve Regeneration
- Obesity
- Pain
- Parkinson's Disease
- Rheumatoid Arthritis
- Stroke

Conformational restriction by ring-closing increased the specificity of responses among active compounds and was the dominant factor in global activity patterns.

Stuart Schreiber
Harvard

Macrocycles: Going Where No Drugs Have Gone Before?

Thus, (re)-inspired by nature, but still challenged by chemistry, the quest for synthetic macrocycles is taking on new life in the pharmaceutical industry.

At least a dozen start-ups are now developing platforms for synthesizing or screening macrocycle libraries, and there have been more than 50 discovery partnerships initiated in the last five years.



By Frits Ahlefeldt

For these compounds, the cyclization step is usually the main challenge and their preparation often involves complex synthetic methodologies which require the use of specific reactions, selective protection/deprotection steps and high dilution techniques.

Juan F. Miravet
University Jaume



The elephant in the room, however, is that NONE of these partnerships can optimize & commercialize their leads

- there are no general synthetic methods; reactions are often *ad hoc* for a specific ring size or family of compound; this makes SAR studies practically impossible and forces companies to pursue un-optimized drug leads
- many leads are prepared using biological methods, and
- for leads prepared using chemical synthesis
 - reaction schemes involve many steps prior to cyclization;
 - reaction conditions are oftentimes limiting;
 - reactions are typically performed very dilute;
 - reaction results can be difficult to reproduce;
 - reactions afford very low yields of the desired compound;
 - reactions require extensive purification; and
- in either case, scale up of bench-top reactions is practically impossible.

Without new technology, companies will soon re-discover that macrocycles are hard to make and expensive - This will limit their potential, slow important research, and force companies to market inferior products.

The Macrocycle Paradox

The macrocycle is the poster-child for the ‘laboratory to market dilemma’; bringing discoveries from the laboratory to the market. Although it is the ring-like structure that gives macrocycles their valuable chemical, physical and biological properties, the cyclic nature of this class of molecules has made it extremely difficult and expensive to obtain them.

Some macrocycles can cost millions of dollars per kilogram to produce while others cannot be obtained in commercially-viable quantities at any price.



So you see, you really aren't in macrocycles
unless you can commercialize them!



THIS IS A TEST

IF YOU CAN

READ THIS

ALL THE WAY

DOWN TO HERE

FEEL

IT

Worse yet, macrocycles hold such promise that if someone else develops an economical way to produce them, they will control the drug market for years to come!



EVERYONE
NEEDS AN
EYE EXAM



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About ODIN

ODIN Industries is a molecular engineering company specialized in research and development, manufacturing, technology assessment, and product pipeline development. The company's platform technology for the preparation of highly sought after cyclic, bicyclic, polycyclic and macrocyclic compounds impacts more than 20 different industries by allowing companies to commercialize innovative pharmaceuticals and technologies that have fallen out of the pipeline in the gap between development and manufacturing.



Through internal and external programs, out-licensing, and partnerships, ODIN Industries is working to deliver big profits on down-stream products that, until now, have had little or no commercial viability. Market-ready prototypes from, for example, the pharmaceutical, solar photovoltaic, fuel cell, engineering plastics, defense and clean water industries, which currently teeter on the edge of success, will quickly emerge with ODIN's components inside.



Opportunities in Medicine



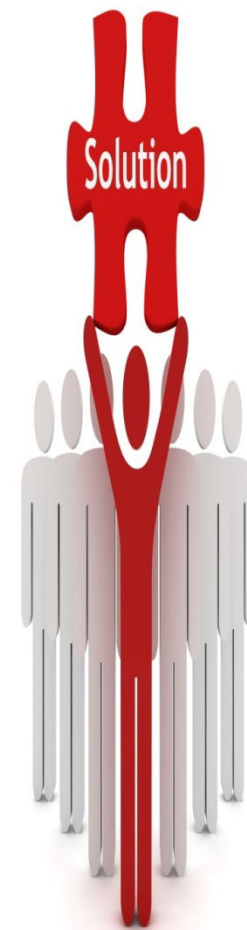
ODIN Industries

Bringing Discoveries from the Laboratory to Life

ODIN Industries has patented a revolutionary new platform for the development and manufacture of highly sought-after cyclic, bicyclic, polycyclic and macrocyclic molecules that serve as the critical ingredients in thousands of cutting-edge pharmaceuticals.

Simply put, without ODIN's technology, these products CANNOT be commercialized!

The lack of economic competition to produce these goods and the lack of viable substitute goods puts ODIN and its partners in a very strong position in both established and emerging markets.



Setting Your Own Rhythm

Unlike most innovations that have a particular rhythm as the new technology is born, develops, matures, and then balloons, ODIN's technology provides a platform to bring an immense back-log of products from the laboratory to market within a very short period of time.



ODIN's Core Capabilities

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- **Synthesis, analog development & scale-up of virtually ALL natural, semi-synthetic and synthetic macrocycles**
 - Increased yields of existing cyclization reactions
 - Increased scale, higher throughput: 10-to-10,000 fold plus
 - New intellectual property protection for leads and intermediates
- **Rapid analog development by:**
 - variations in ring size (expansion or contraction)
 - variations in peripheral functionalization
 - changes in atom or residue order (retro-inverso peptides)
 - changes in the type of atoms in ring
 - use of unnatural amino acids
 - use of mimics

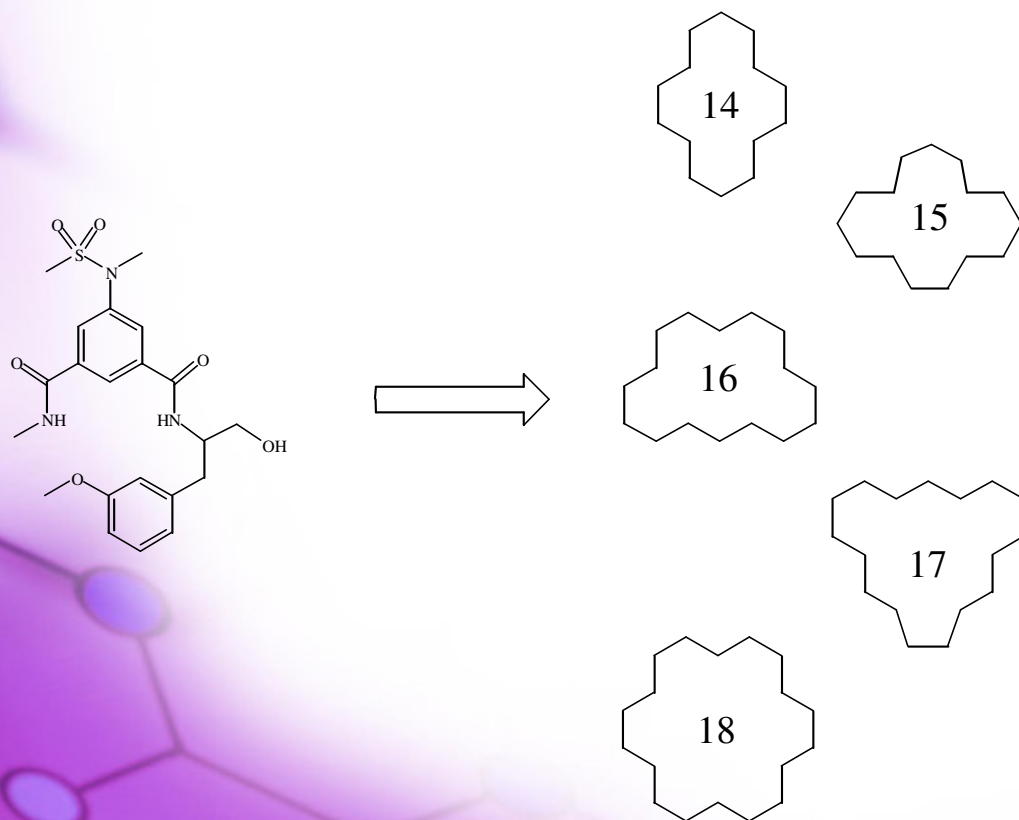
ODIN's Core Capabilities

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- **Macrocyclization of linear, small-molecule leads**
 - to improve pharmacodynamics of linear leads, including:
 - ✓ affinity & selectivity
 - ✓ bioavailability
 - ✓ bioretention
 - ✓ side-effects
 - to create new intellectual property
 - to create first-in-class leads
 - to reduce structural complexity of lead compounds
 - ✓ fewer structural elements such as stereocenters
 - to re-purpose biological target research and linear leads that have lost patent protection
 - to re-purpose library research and development

Instead of continuing to search for new leads or abandon unique therapeutic targets, ODIN uses macrocyclization to enhance the pharmacodynamics of linear compounds that do not possess high enough efficacies to move through the pipeline. This allows are partners to re-purpose costly and time-consuming data to jumpstart new initiatives.

Linear Leads into Cyclic Leads

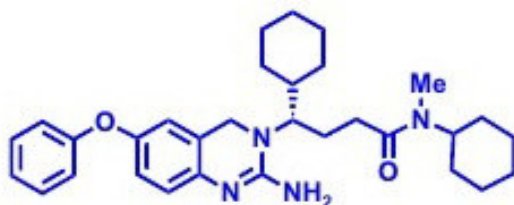


Variations in the ring size of a macrocycle is a powerful tool for SAR development since the change of a single atom in the ring can dramatically alter the pharmacodynamics of the molecule.

This is in contrast to single atom modification of a linear lead which has little or no effect.

Acyclic versus Macrocyclic Ligands

Design of BACE-1 Inhibitors for Treatment of Alzheimer's

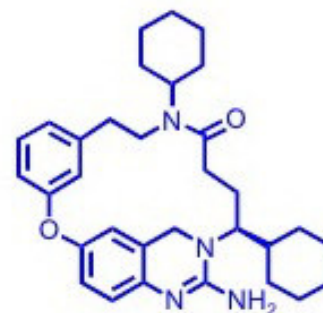


$$K_i = 8 \text{ nM}$$

$$A\beta \text{ (CHO) cellular } IC_{50} = 44 \text{ nM}$$

$$hERG K_i = 84 \text{ nM}$$

No in vivo activity



$$K_i = 5 \text{ nM}$$

$$A\beta \text{ (CHO) cellular } IC_{50} = 17 \text{ nM}$$

$$hERG K_i = 1900 \text{ nM}$$

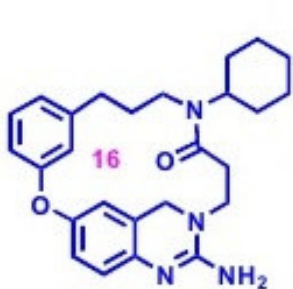
Plasma A β lowering in mice

22% at 25 mpk, PO/dose

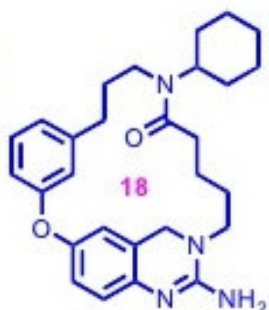
74% at 2 mpk, iv/dose in rat

$$K_i = (\text{Conc. Ligand}) \times (\text{Conc. Receptor}) / (\text{Conc. of Ligand Receptor Complex})$$

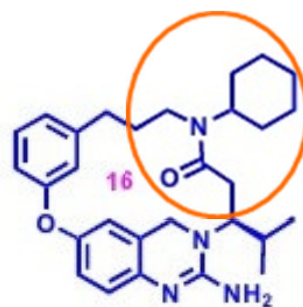
A Tunable Ring



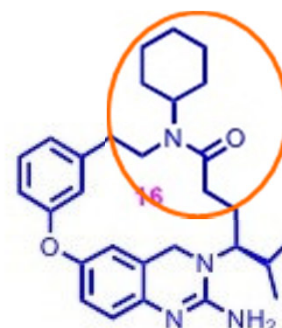
$K_i = 51 \text{ nM}$
Cellular $A\beta$ $IC_{50} = 516 \text{ nM}$



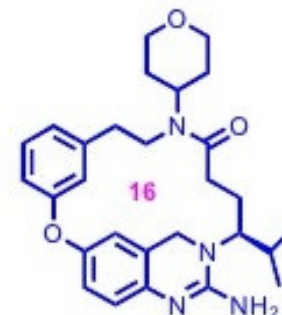
$K_i = 44 \text{ nM}$



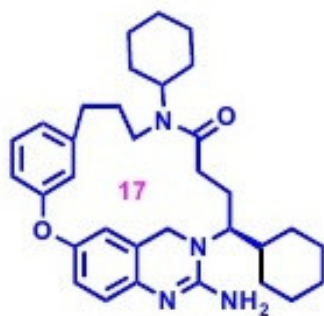
inactive



$K_i = 8 \text{ nM}$
Cellular $IC_{50} = 81 \text{ nM}$
hERG $K_i = 1500 \text{ nM}$



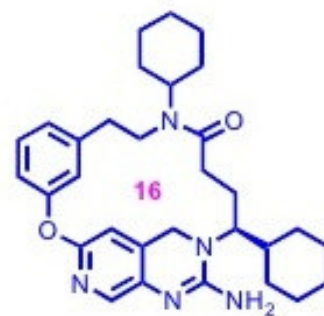
$K_i = 22 \text{ nM}$
Cellular $IC_{50} = 660 \text{ nM}$
hERG $K_i = 3500 \text{ nM}$



$K_i = 31 \text{ nM}$
Cellular $A\beta$ $IC_{50} = 35 \text{ nM}$



$K_i = 17 \text{ nM}$
hERG $K_i = 3500 \text{ nM}$



$A\beta$ (CHO) cellular $IC_{50} = 6.6 \text{ nM}$
hERG $K_i = 4000 \text{ nM}$



$K_i = 5 \text{ nM}$
 $A\beta$ (CHO) cellular $IC_{50} = 17 \text{ nM}$
hERG $K_i = 1900 \text{ nM}$

Things Don't Have to be Straight

“If you take a linear peptide [for example] and inject it into the bloodstream the half-life is less than two minutes. Nature gets around this by making peptides circular... If you inject a cyclic peptide into the blood stream it doesn't get chewed up and degraded. Its half-life is 40 hours or more.”

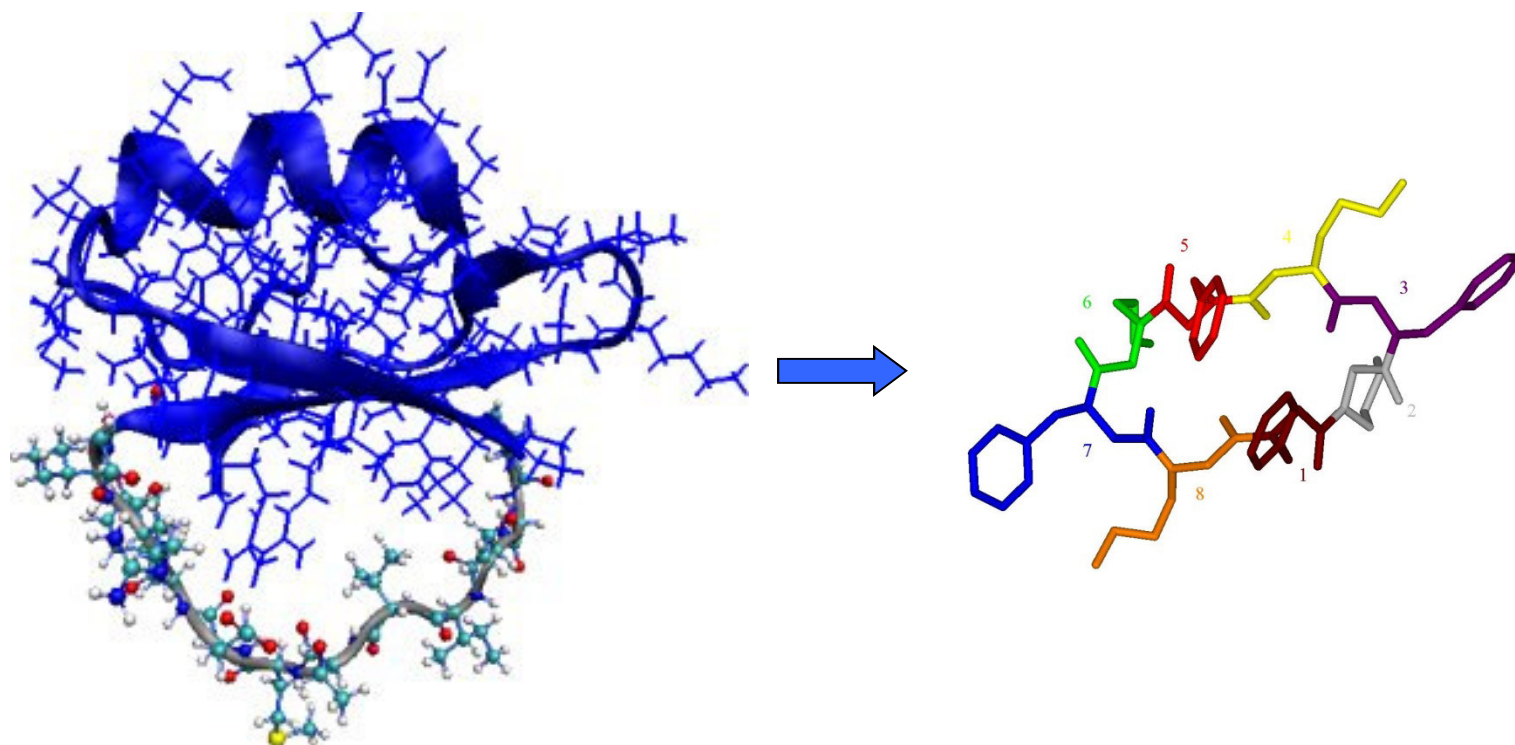
Danith Ly
Carnegie Mellon University



ODIN's Core Capabilities

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- **Transform protein leads into orally-available macrocycles**



Ask us more about this!

ODIN's Core Capabilities

page 4 of 5

- **Synthetic macrocycle vaccines**
- **Macrocycle supplements that aid manufacturing of traditional vaccines by reducing the time and cost to market**



Ask us more about this too!

ODIN's Core Capabilities

page 5 of 5

- **Process Development & Manufacturing Advantages**
 - Synthetic schemes with high selectivity, and significant cost reductions
 - Modular synthetic schemes that utilize
 - ✓ lowest-cost starting materials, and
 - ✓ provide rapid access to structurally-related analogs
 - Efficient methods of ensuring unchanged product quality and performance during scale-up
 - Automated flow reactors, high concentration reactions, simplified purification, improved robustness, reduced environmental impact, and improved safety.

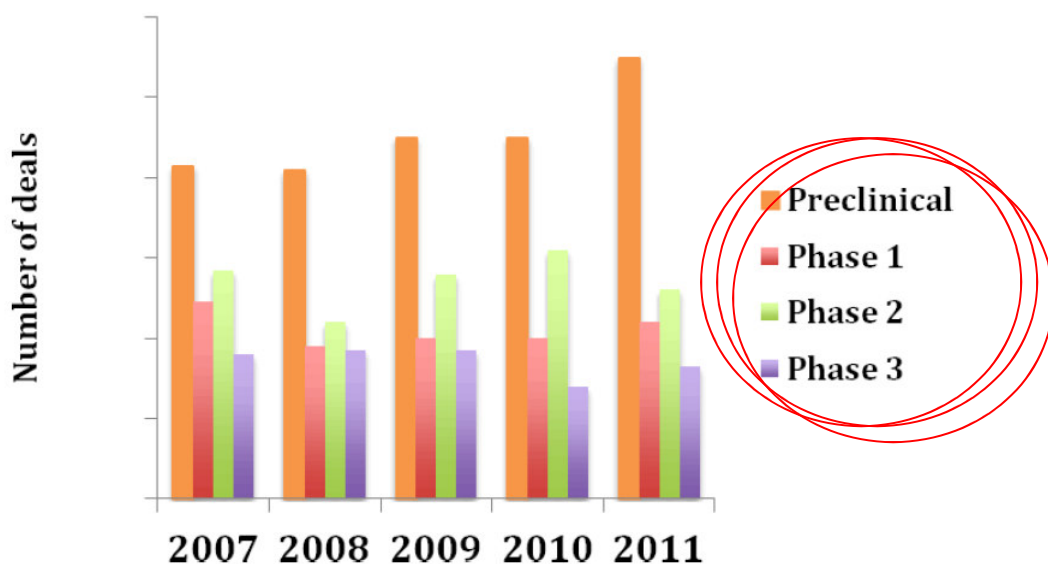
ODIN Industries also possesses

- proprietary search algorithms, assessment tools, and extensive databases that include biological testing data (biological targeting assays, animal testing & human trials), and SAR data that provides insight into key structural properties that dictate macrocycle pharmacodynamics,
- an immense IP portfolio of under-valued, 3rd-party macrocycle lead compounds that can provide quick entry into new drug development whitespace for virtually every disease, and
- key relationships with institutions, companies, and universities to provide access to unique biological targets, NMEs and libraries.

Comparison of Macrocyclic Platforms

Capability	Aileron	Bicycle	Ensemble	ODIN	Peptidream	RA	Tranzyme
Research	+++	+++	+++	+++	+++	+++	+++
Development	+++	+++	+++	+++	+++	+++	+++
Manufacturing				+++			
Synthetic and natural analogs				+++			
Linear leads into macrocycle leads				+++			
Protein leads into macrocycle leads				+++			
Reduce complexity of lead				+++			
Dramatically reduce cost of development of leads				+++			
Access to all macrocycles				+++			

Overview of Partnerships By Development Stage

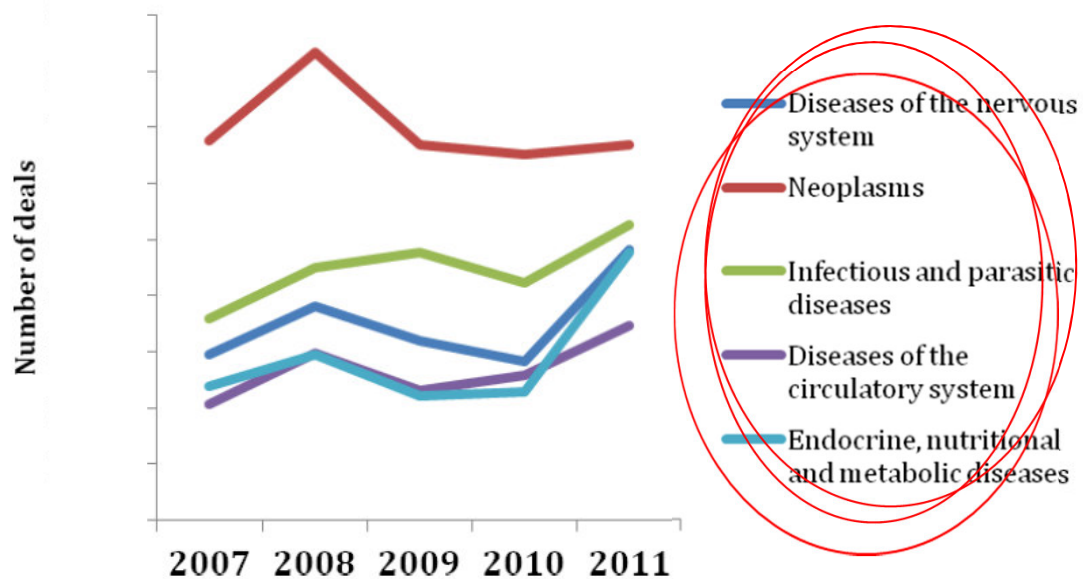


← ODIN's Platform is critical for ALL stages including manufacturing!

Figure 6: Number of licensing deals by development stage 2007-2011

(Source: PharmaDeals® v4)

Overview of Partnerships by Therapeutic Area



ODIN's Platform supports development in ALL therapeutic areas!

Figure 9: Number of deals by therapy area (selected therapy areas only)

(Source: PharmaDeals® v4)

And We Have Identified Thousands Of Compounds That Are Supported By ODIN's Platform Technology

A partial list of cycles, bicycles, polycycles, and macrocycles including:

- Alkaloids
- Bis-indolylmaleimides
- Calixarenes
- Calix[n]pyrroles
- Carbocycles
- Crown Ethers
- Cyclic peptides
- Cyclic peptideomimetics
- Diterpenoids
- Fungal metabolites
- Macrocyclic lactams
- Macrocyclic lactones
- Macrocyclic olefins
- Macrolides
- Phallotoxins
- Polyazamacrocycles
- Polyketides
- Porphyrins

So If It's Cyclic, ODIN's Technology Can Be Used To Prepare It!

ODIN's technology is a general and enabling platform without limitation to the class of compound, reaction type or starting material. It can be operational in research laboratories throughout the world within months using existing facilities and brain trust.



Return on Investment

Simplifying Synthesis Will Drive Innovation!

- You get the molecule you want (**ask us about this too!**)
- Quick entry into new drug development whitespace
- New composition of matter; first-in-class leads
- New, proprietary routes for the synthesis of lead compounds
 - rapid scale up
 - ability to engineer around existing process patents
- New intermediates for the synthesis of proprietary molecules
- New reactions to replace existing reactions
- New functional groups
- New catalysts

Re-establish strong patent protection by exploring vast undeveloped chemical space!



How We Establish Patent Protection

- Process Patent Protection
- Composition of Matter
- Application
 - ✓ First in Class
 - ✓ New Therapeutic Targets
- ODIN Improvement Technology
 - ✓ new catalysts
 - ✓ new functional groups
 - ✓ new reaction parameters
 - ✓ new reactor technology



<u>Small Molecules</u>	<u>Macrocycles</u>	<u>Large Molecules</u>
➤ nonspecific	➤ highly specific	➤ highly specific
➤ orally available	➤ orally available	➤ IV available
➤ metabolically unstable	➤ metabolically stable	➤ metabolically stable
➤ small pipeline	➤ large pipeline	➤ large pipeline
➤ low cost of manufacturing	➤ high cost of manufacturing	➤ high cost of manufacturing

Summary

The biological profile of macrocycles makes them an extremely attractive target for the pharmaceutical industry...

Whoever can make them affordable will advance patient care & make a lot of money at the same time!



the
bottom line
+ is

ODIN's technology makes ALL macrocycles commercially viable now, and accelerates research in emerging areas that would not otherwise be viable for many years into the future.



ODIN's Intellectual Property Position

ODIN controls proprietary platform technology (DOCC) relating to the synthesis of cyclic compounds that is the subject of U.S. and many other international patents and patent applications. Based on a review of the technology by the United States Patent & Trade Office and by many international patent examiners, DOCC is a novel and fundamental enabling technology for the synthesis of cyclic compounds. The technology resolves a number of basic problems that have limited the prior commercial synthesis of macrocyclic compounds to small yield and small-volume production involving costly and complex purification procedures. By enabling high yields of macrocyclic compounds to be economically achieved at high volume, the technology makes these compounds widely available at low costs.

The first of ODIN's patents have issued in the United States, China, Mexico, Russia, Israel, the EU and other major international markets. Many other applications are patent pending and are expected to issue over the next few years.



Contact Us

To learn more about the DOCC platform, please contact us for an informational presentation. We welcome the opportunity to work with you.

info@odinindustries.com

