Available Libraries: What's Special and how to Choose

Moderator: Geoffrey Greene (UChicago)
Panel Members: Sergey Kozmin (UChicago), Brian Murphy (UIC), Karl Scheidt (NU)

Available Chemical Libraries – Univ of Chicago

THE UNIVERSITY OF CHICAGO MEDICAL CENTER

Cellular Screening Center
http://igsb.org/services/csc/
Sam Bettis, Technical Director

UCCCC Drug Discovery Core
Geoffrey Greene, Director

Compound Collections: Automated storage and retrieval for ~200,000 compounds; diverse scaffolds that cover as much chemical space as possible.

MicroSource Spectrum library: ~2,000 cpds - 50% (800 USP/USAN + 200 INN & BAN & JAN) known drugs, 30% (580) natural products, 20% (420) other bioactive compounds.
http://www.msdiscovery.com/spectrum.html

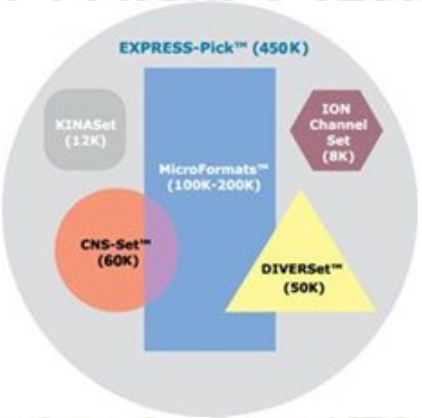
Prestwick Chemical Library: 1200 FDA approved drugs.
http://www.prestwickchemical.com/index.php?pa=26

The Prestwick Chemical Library® contains 1200 small molecules, 100% FDA approved drugs, thus it presents the greatest possible degree of "drug-likeliness". The active compounds were selected for their high chemical and pharmacological diversity as well as for their known bioavailability and safety in humans. The Prestwick Chemical Library ® contains a limited number of highly diverse drug molecules for which bioavailability and toxicity studies have already been performed and which have proven usefulness in humans.

Available Chemical Libraries – Univ of Chicago

THE UNIVERSITY OF CHICAGO MEDICAL CENTER

Chembridge Express-Pick collection - 130,000 cpds from the MicroFormat library. Stock compounds are selected using novelty, diversity, drug-like property analysis, and medicinal chemistry expertise.
In addition, 50,000 compounds available as pooled plates - 8 cpds/well. These cpds come from the 130,000 cpd collection.
http://igsb.org/services/csc/



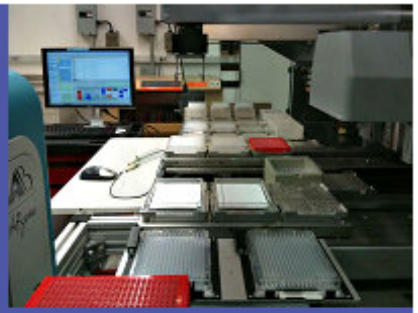
Chembridge DIVERSet Collection (from UIC): 50,000 cpds
Extensive pharmacophore coverage for primary screening. Stringent drug-like and desirable chemical group filters coupled with a 3D conformer analysis are used in selecting a premium set of 50,000 drug-like compounds with maximum pharmacophore coverage and chemical diversity

CTCMLD collection: ~10,000 diverse cpds
Chicago Tri-Institutional Center for Chemical Methods and Library Development
Sergey Kozmin, Director
Karl Scheidt, Project 1 Leader
http://ctcmld.uchicago.edu

UIC Research Resources Center

High-Throughput Screening (HTS)

The **High-Throughput Screening (HTS)** facility offers users the ability to screen biological targets against a library of over 100,000 unique chemical compounds in a time-efficient manner. We offer assistance with many of the early drug-discovery stages, including assay development and optimization, robotic screening, data analysis and interpretation, and hit validation. Users interested in structural biology can perform automated screening of their purified protein against hundreds of crystallization conditions.



Small Molecule Libraries

Kiira Ratia, Director of High-Throughput Screening
http://www.rrc.uic.edu/hts

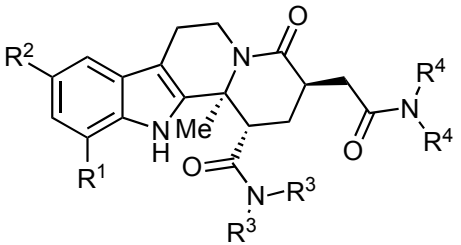
Prestwick Chemical Library: 1200 FDA approved drugs.
http://www.prestwickchemical.com/index.php?pa=26

Maybridge HitFinder Library: 14,400 diverse, drug-like compounds.

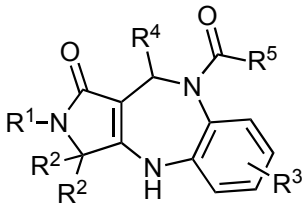
ChemBridge DiverSet Collection: 75,000 compounds of diverse chemical structure.
http://www.chembridge.com/screening_libraries/

Current CTCMLD Collection: About 10,000 Diverse Compounds

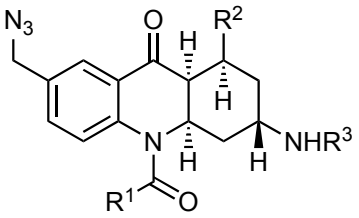
Sergey Kozmin
http://ctcmld.uchicago.edu



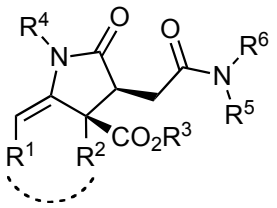
Tetracyclic Lactams
476 compounds



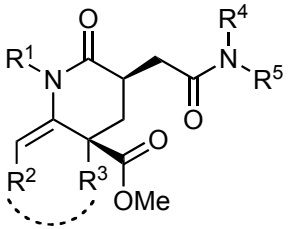
Triazatricyclamides
936 compounds



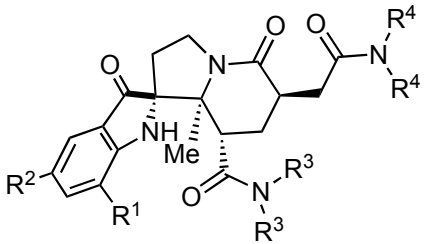
Dihydroquinolones
966 compounds



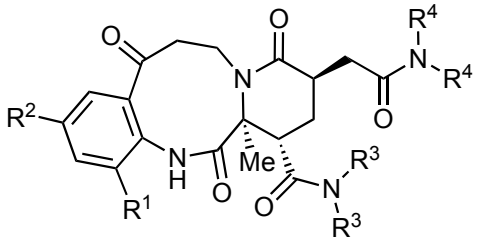
Pyrrolidinones
955 compounds



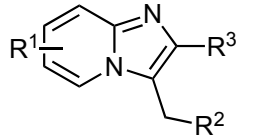
Bicyclic Piperidinones
1536 compounds



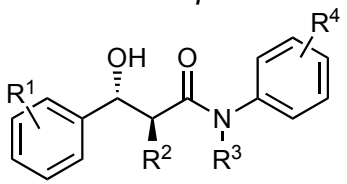
Spirocyclic Lactams
83 compounds



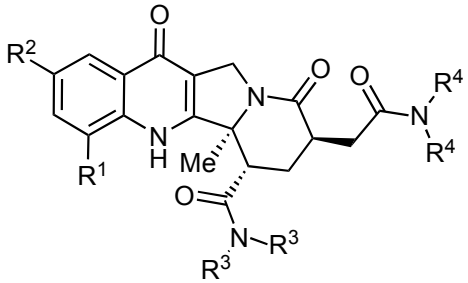
Tricyclic Lactams
96 compounds



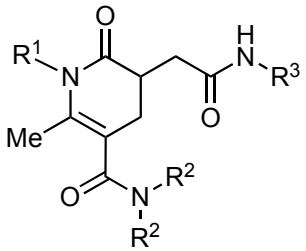
Imidazolepyridines
960 Compounds



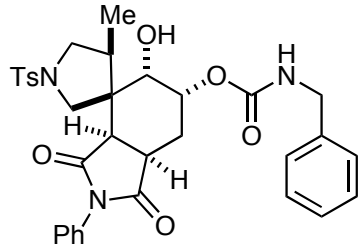
Hydroxyamides
48 compounds



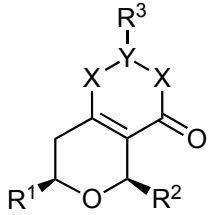
Tetracyclic Quinolones
96 compounds



Unsaturated Lactams
480 compounds

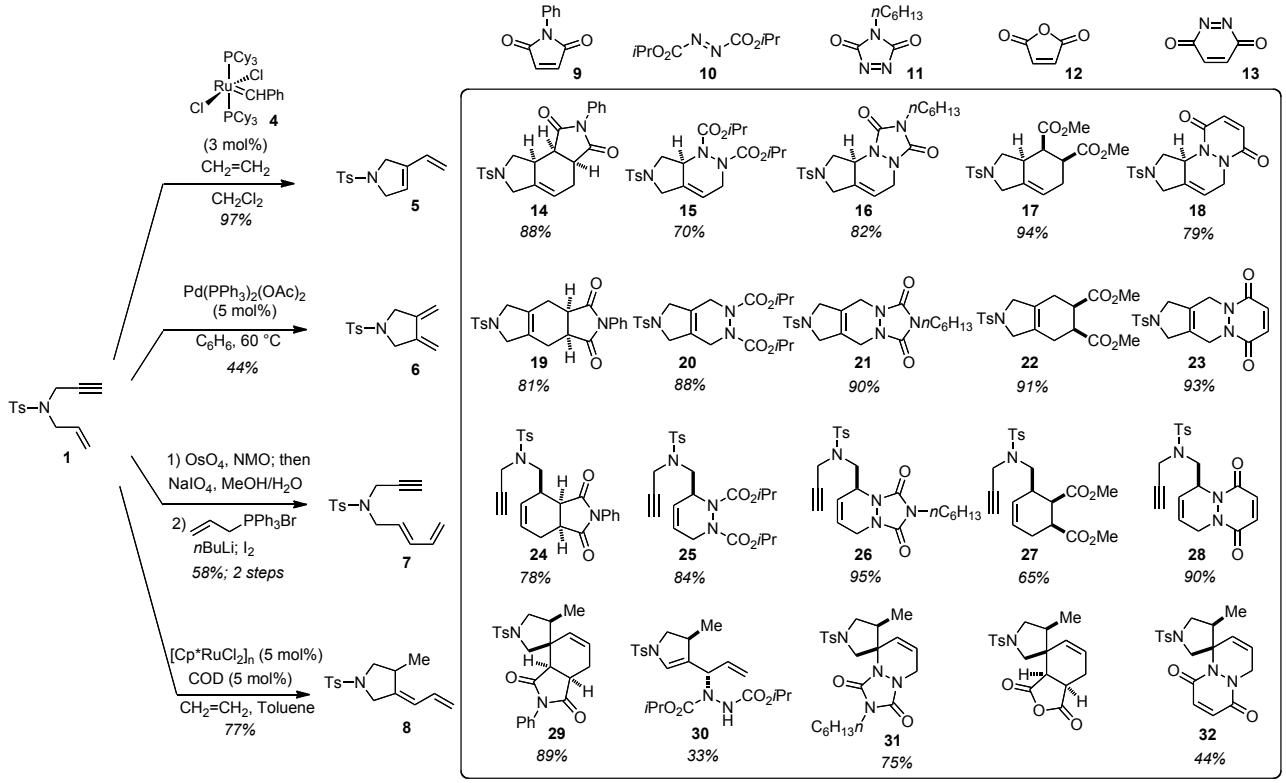


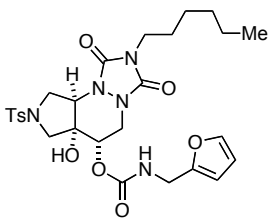
Skeletally Diverse Carbamates
representative structure
191 compounds



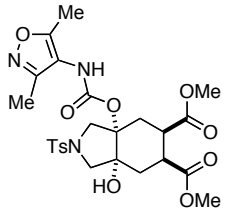
Bicyclic Dioxinones
240 compounds

Diversity Analysis using Principal Moments of Inertia (PMI)

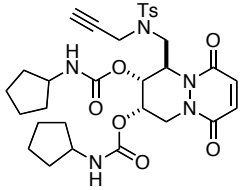




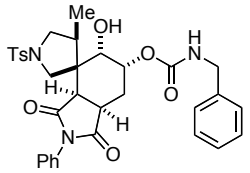
Yield: 18.0 mg (72%);
Purity (ELSD): 100%
MW: 589.7
Average ClogP: 2.41



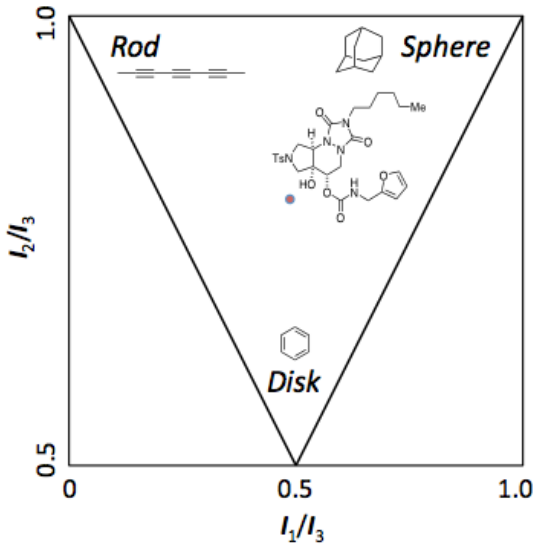
Yield: 23.0 mg (87%);
Purity (ELSD): 100%
MW: 565.6
Average ClogP: 1.09

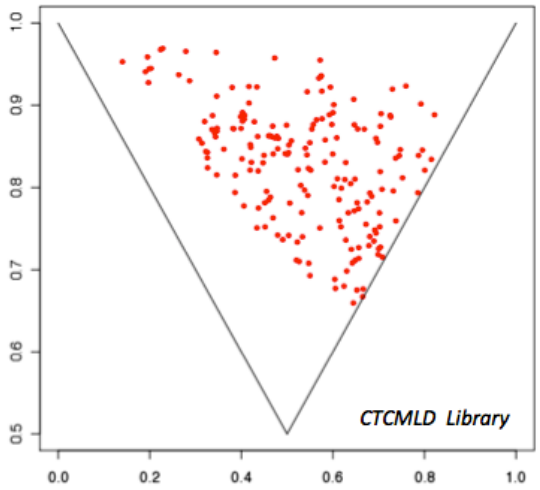


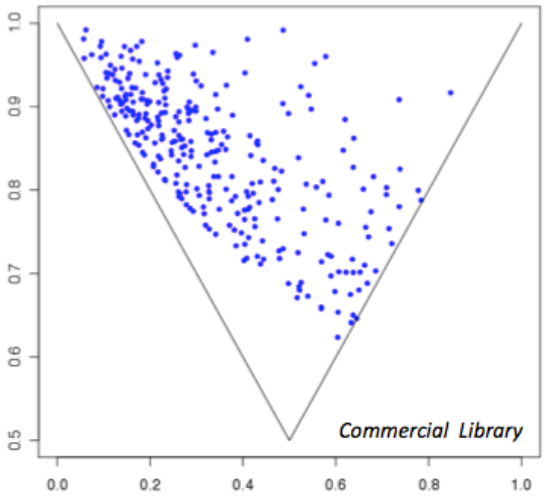
Yield: 21.9 mg (72%);
Purity (ELSD): 100%
Mw: 641.3
Average ClogP: 3.29



Yield: 19.7 mg (86%);
Purity (ELSD): 100%
MW: 589.7
Average ClogP: 3.39







Screening of CTCMLD Compounds at NIH by MLPCNs

3208
Number of compounds on PubChem

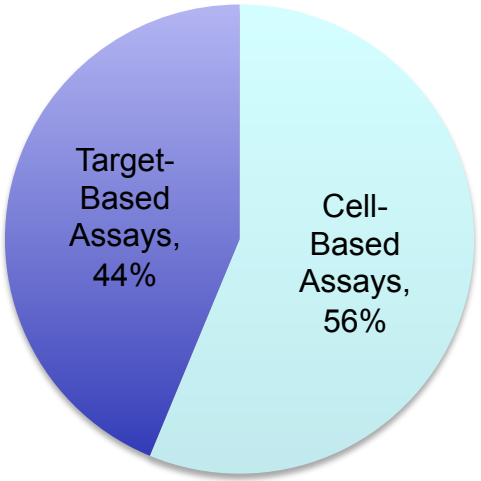
2439
Total number of compounds tested

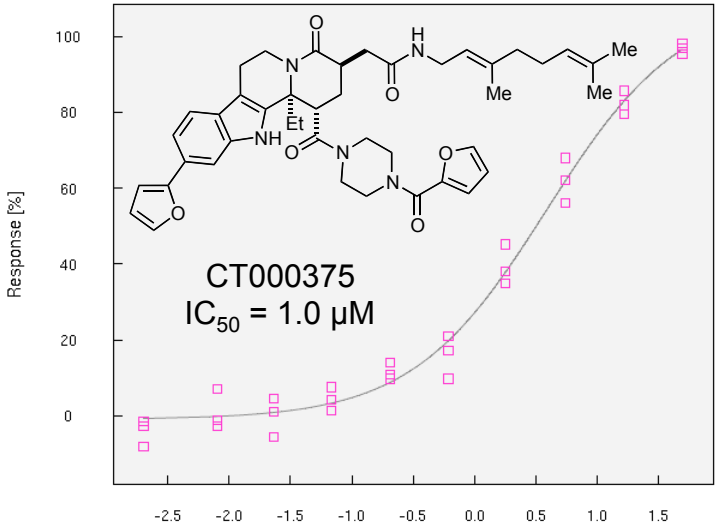
524
Total number of compounds active in at least one assay

360
Total number of assays subjected to

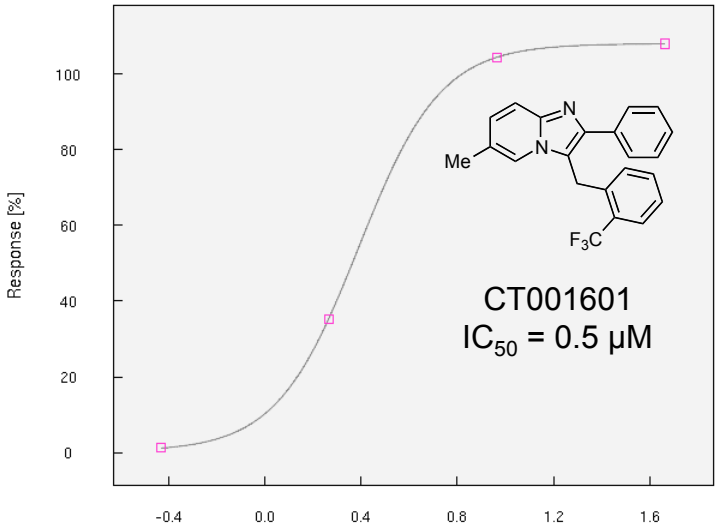
148
Total number of assays with at least one active compound

33
Confirmatory assays with unique targets





Antagonist of orexin 1 receptor
Potential treatment of drug addiction, sleep disorder and behavioral plasticity.



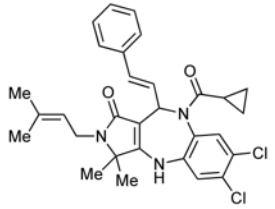
Activator of BRCA1 expression
Potential enhancer of the effects of anti-estrogenic agents in treating breast cancer

CMLD Biology Outreach and Collaboration

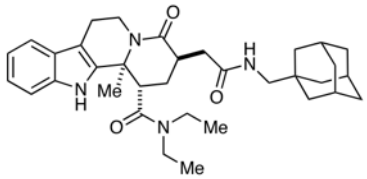
Format: 384 or 96 well plates, 5 mM DMSO stock solutions ready for target-directed and cell-based assays

Availability: current CTCMLD library is readily available to our biology collaborators

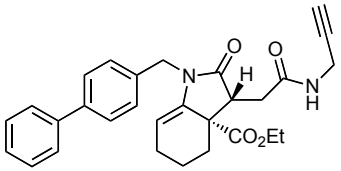
Examples of other chemical probes discovered from CTCMLD library



Potent Apoptosis Inducer: GI_{50} 150 nM



Inhibitor of *M. tuberculosis* : MIC 18 μM



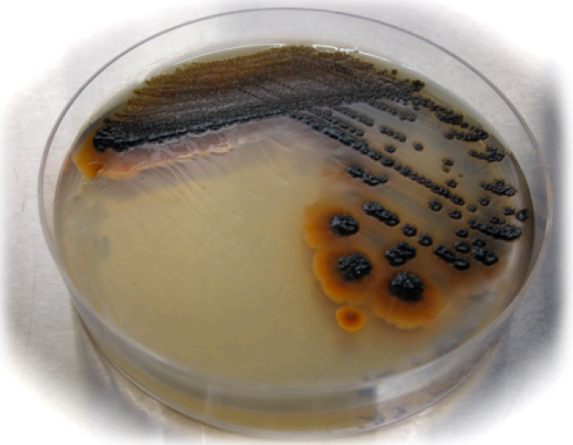
Selective Anti-Colon Cancer Agent: IC_{50} 8 μM

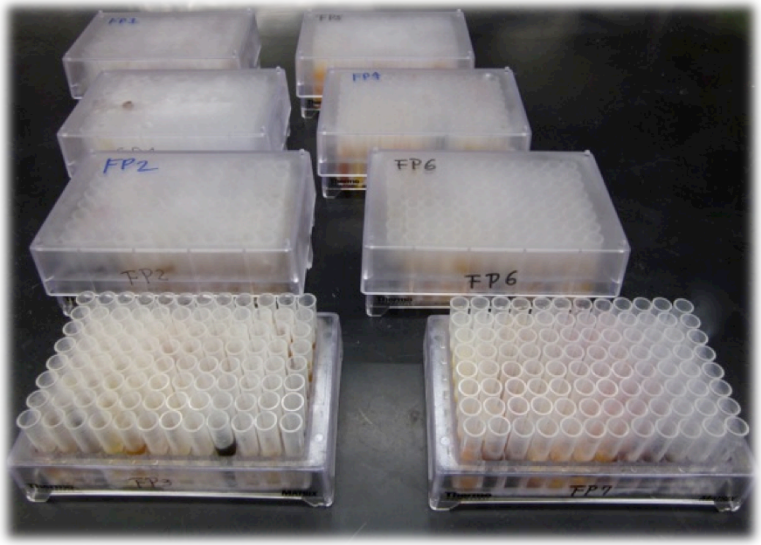
Selected Ongoing CTCMLD Collaborations

Richard van Breemen	Mass spectrometry-based enzymatic screening	UIC, Med Chemistry and Pharmacognosy
Wonhwa Cho	Search for small molecule inhibitors for PH domains	UIC, Chemistry
Scott Franzblau	HTS for new antituberculosis agents	UIC, Institute for Tuberculosis Research
Robert Haselkorn	Discovery of inhibitors of acetylCoA carboxylase	UC, BMB and MGCB
David Kovar	Identification of small-molecule formin modulators	UC, BMB and MGCB
Ronald Rock	Search for inhibitors of motor proteins	UC, BMB
Howard Shuman	Small-molecule modulators of *Legionella pneumophila*	UC and Argonne, Microbiology
Chuan He	Development of inhibitors of bacterial virulence	UC, Chemistry
Steven Kron	Identification of modulators of cellular senescence	UC, BMB
Kenan Onel	HTS for anti-leukemic compounds	UC, Pediatrics
Paul Schumacker	Identification of modulators of energy metabolsim	NU, Pediatrcis
Douglas Vaughan	Development of new PAI-1 inhibitors	NU, Medicine-Cardiology
Dane Chetkovich	Hit-to-lead development for novel neurological target	NU, Neurology
Karla Satchell	HTS for new antibiotic agents	NU, Microbiology
Steven Rosen	Development of new nucleoside analogs	NU, Medicine-Oncology
John Crispino	Design and synthesis of novel kinase inhibitors	NU, Medicine-Hematology/Oncology

Brian Murphy Lab (UIC) – Secondary metabolite fraction library

- >300 aquatic actinomycete strains; 1,084 metabolite fractions
- Global collection locations; library expansion is continuous
- Crude metabolites extracted; separated by polarity into four fractions (10 mg/mL stock solution in DMSO)
- PKS and NRPS biosynthetic pathways; few terpenes
- Structural diversity and chemical space are immense



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Illinois
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Data SIO, NOAA, U.S. Navy, NGA, GEBCO
Google earth


Florida Keys
+25° 00.479', -80° 2
+24° 55.395', -80° 30.532'
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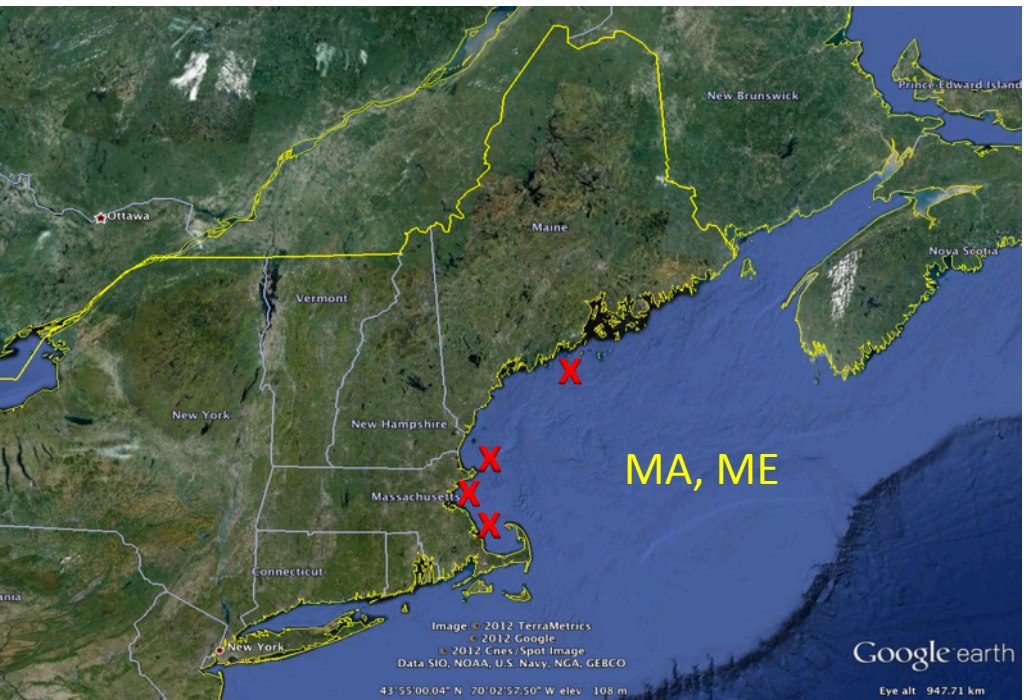
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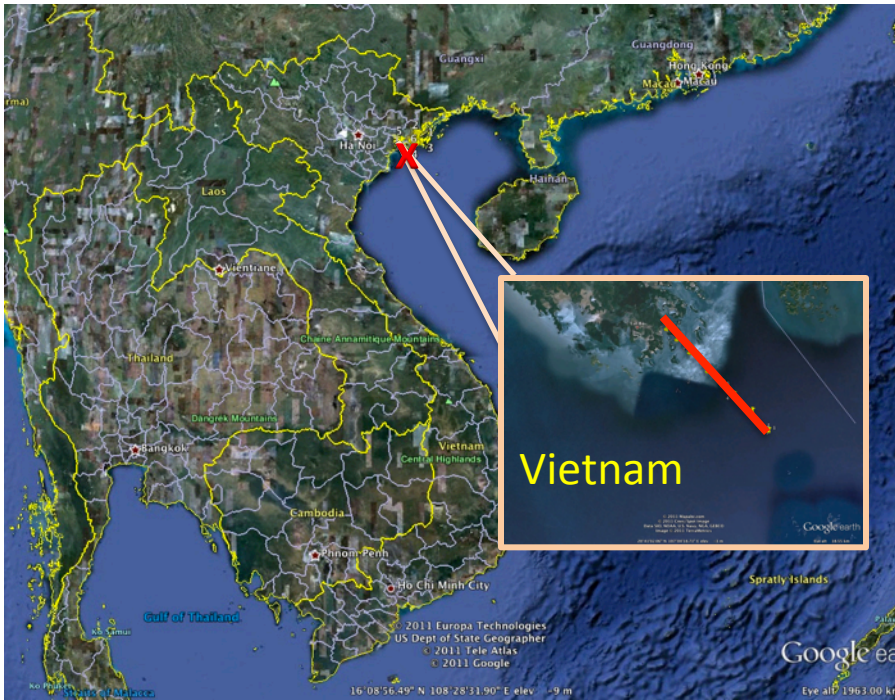
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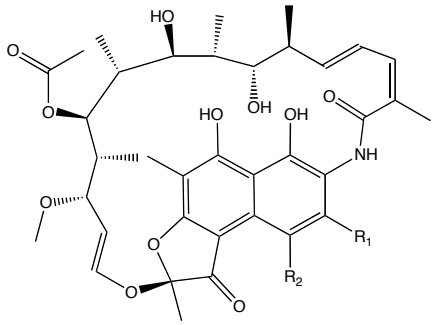
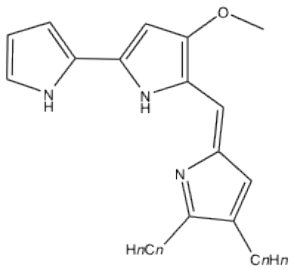
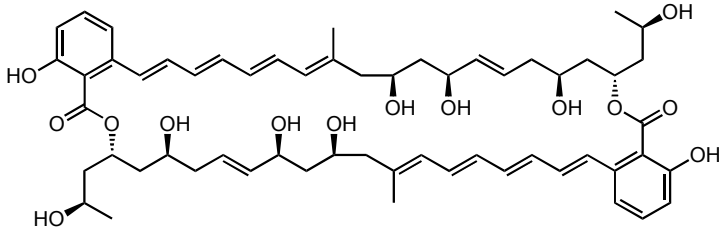
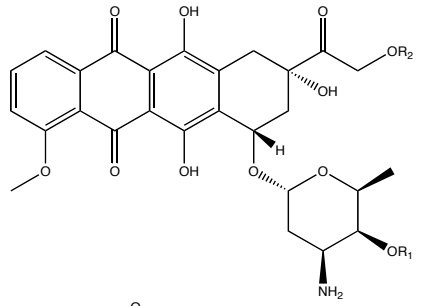
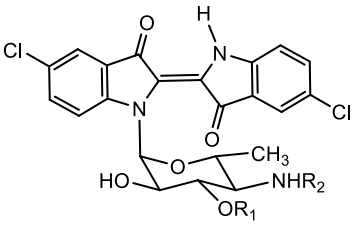
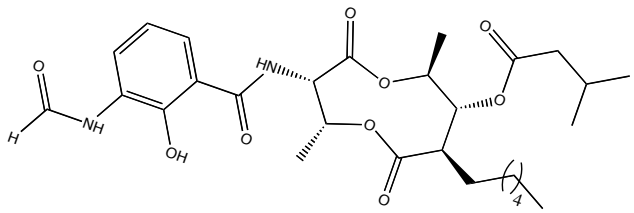
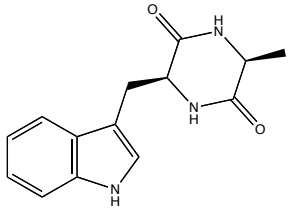
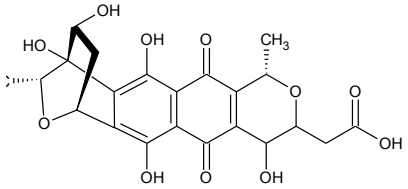
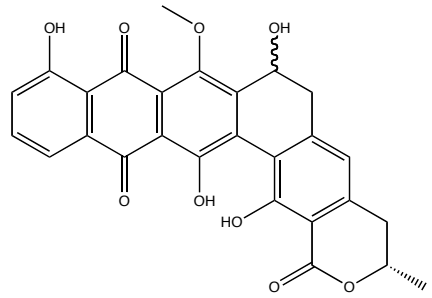
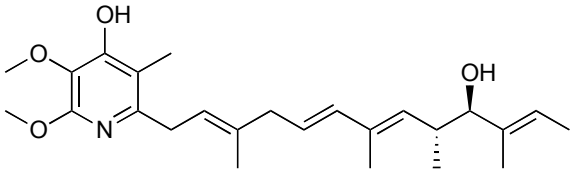
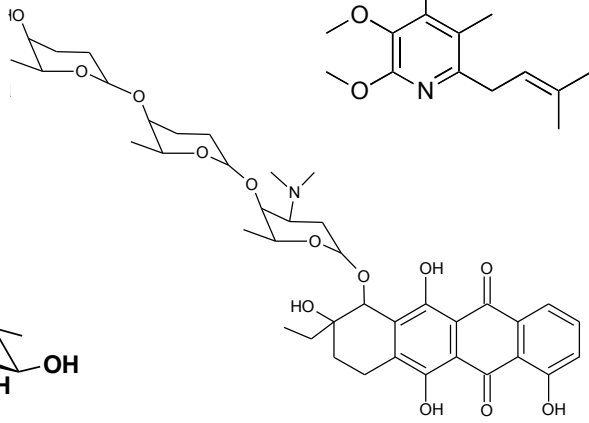
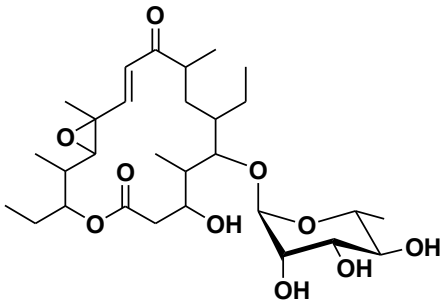
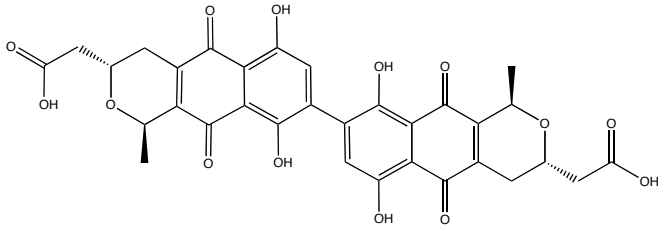
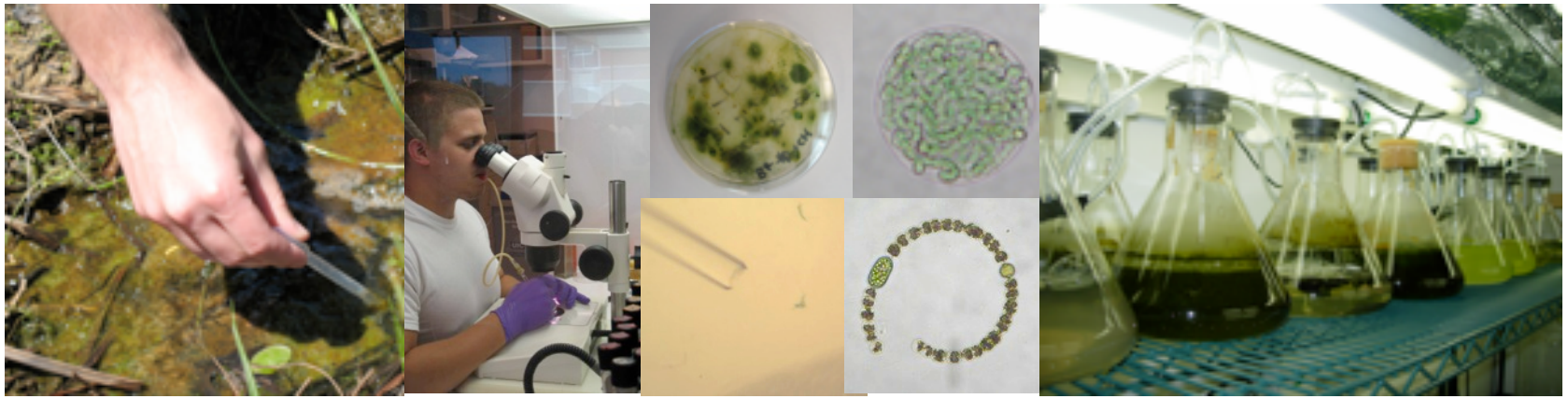














Structural diversity from Murphy Lab library

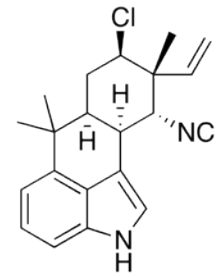
btmurphy@uic.edu

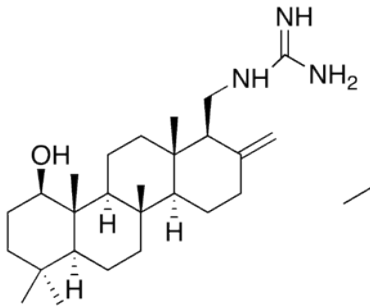
Orjala Lab (UIC) - Secondary metabolite fraction library from cyanobacteria

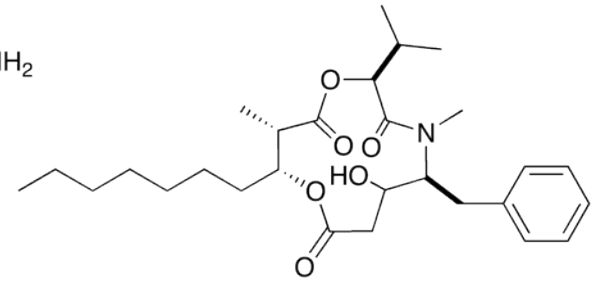
- Collection contains 651 cyanobacterial strains (mainly terrestrial and aquatic)
- Library currently contains 3069 metabolite fractions; expansion is continuous
- Collections from continental US
- Crude metabolite extracts separated by polarity into seven fractions (10 mg/mL stock solution in DMSO)

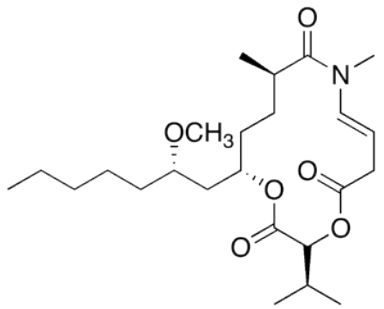


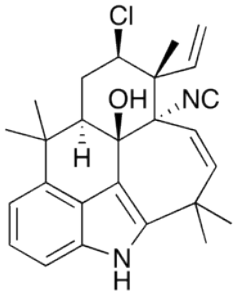
Examples of structures obtained in Orjala Lab

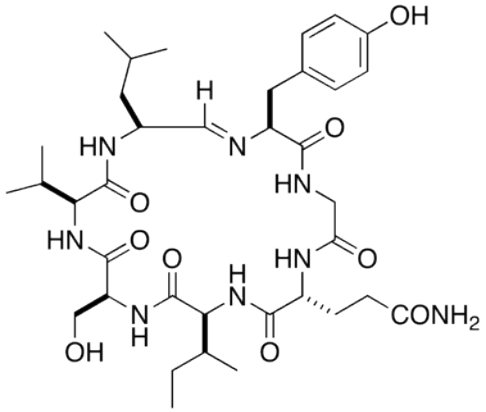


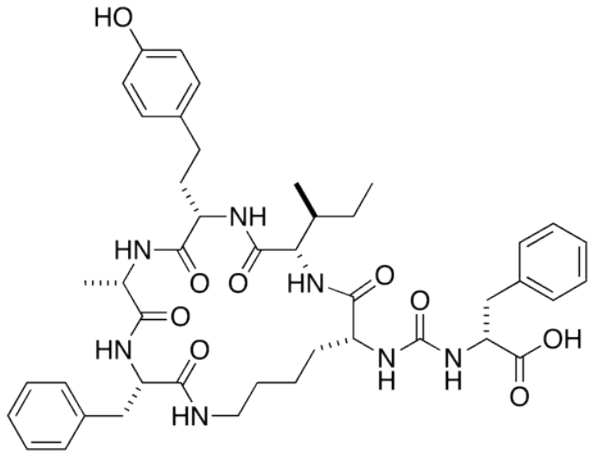


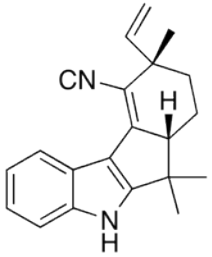


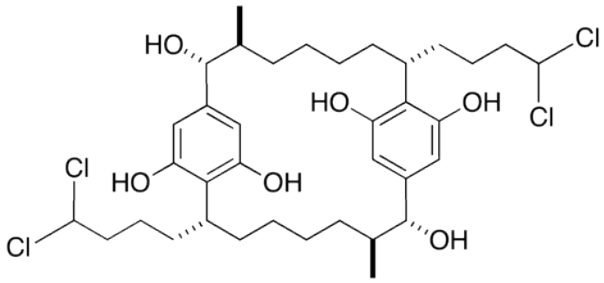


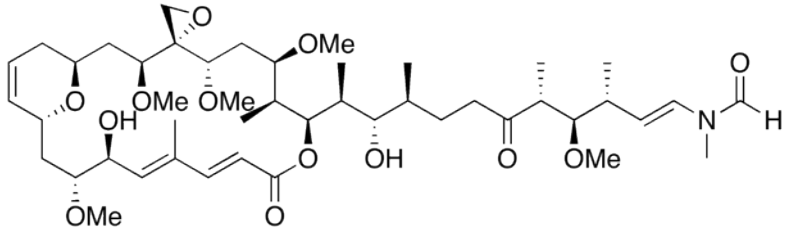












Small Molecule Compound Libraries

Eric Weiss, Chi-Hao Luan http://groups.molbiosci.northwestern.edu/hta/compound.htm

ChemDiv Structural-Diversity Set: The library includes 30,000 compounds of diverse chemical structure.

ChemBridge Drug-Like Set: The library includes 20,000 compounds of diverse chemical structure.

ASDI Library: 6800 compounds of diverse chemical structure.

NCC Set: The NIH Clinical Collection prepared by BioFocus DPI includes compounds currently in NIH clinical trials. Includes over 400 compounds.

Spectrum Collection: The collection is composed of 2000 compounds from MicroSource Discovery Systems and covers; (i) drugs that have been introduced in the US, Europe and Japan and have known pharmacological profiles, (ii) natural products with unknown biological properties and (iii) other bioactive compounds such as non-drug enzyme inhibitors, receptor blockers, membrane active compounds, and cellular toxins.

The NCI/DTP Open Chemical Repository: The HTA has acquired four sets of synthetic compounds and natural products from the National Cancer Institute: the structural diversity set, the mechanistic set, the natural products set, and the challenge set, in all totally over 3200 compounds.

Enzo Kinase Inhibitor Library: 80 compounds including inhibitors of these important kinases: BTK, CaM Kinase, CDK, CKI & II, EGFR, GSK, IKK, Insulin receptor, JAK, JNK, MAPK, MEK, MLCK, PI 3-Kinase, PDGFR, PKA, PKC, RAF, SAPK, Src-family, VEGFR, and more.