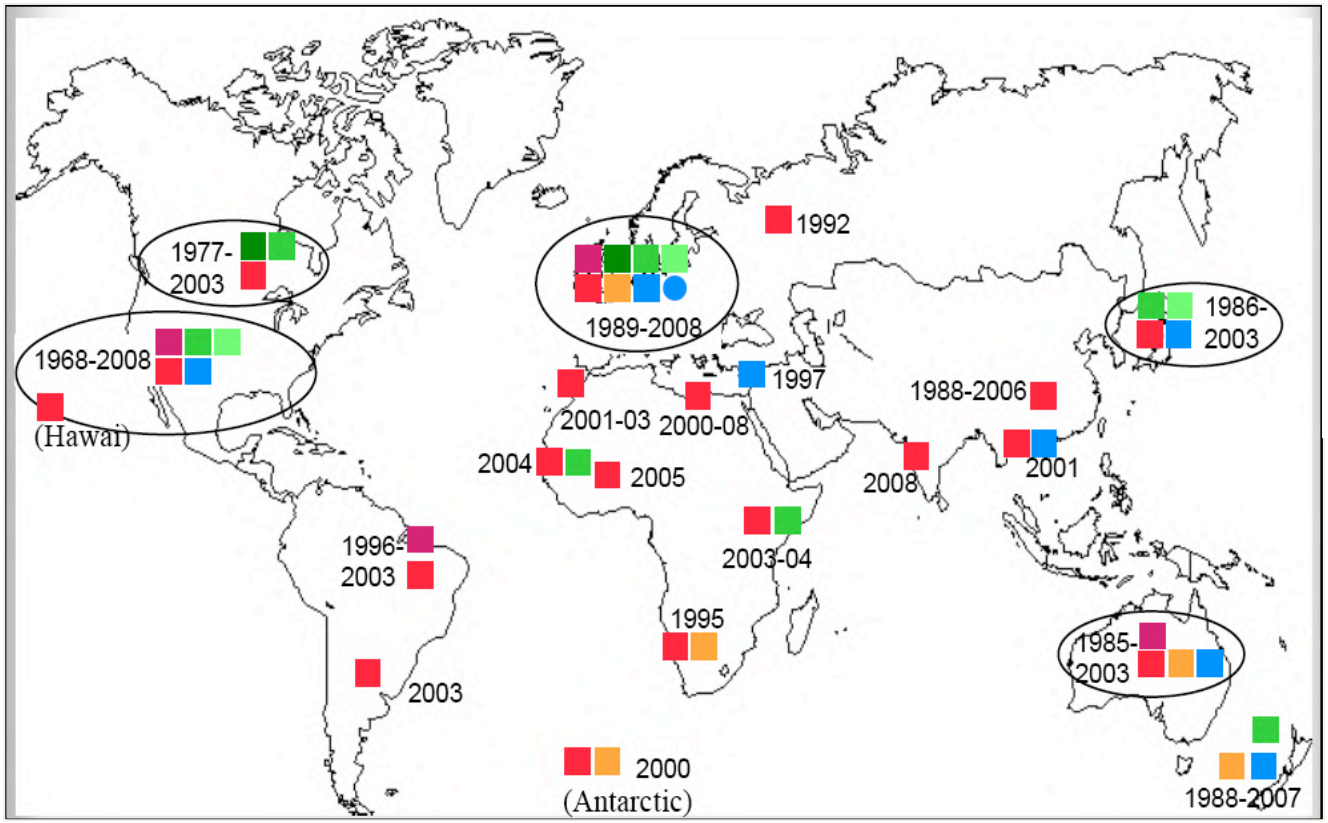
Voies de biosynthèse des produits naturels des cyanobactéries

Institut Pasteur Paris, Université Paris Cité

Muriel GUGGER

Journée FIRE/MCAM, MNHN, 24 avril 2024

Cyanobactéries, efflorescences et leurs produits naturels



NEUROTOXINES:
Anatoxines-a, Guanitoxines, Saxitoxines

(et les marines : Jamaicamides, Antillatoxins, Alotamide A, Hioamides, Palmyramides)

HEPATOTOXINES:
Microcystines, Nodularines, Cylindrospermopsines

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Bien plus de molécules chez les Cyanobactéries

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Les voies de synthèse de ces métabolites

- Ribosomally synthesized and post translationally modified peptides (RiPPs)

- Non ribosomal Peptides Synthetases (NRPS)

- Polyketides Synthases (PKS)

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La voie ‘Ribosomale’

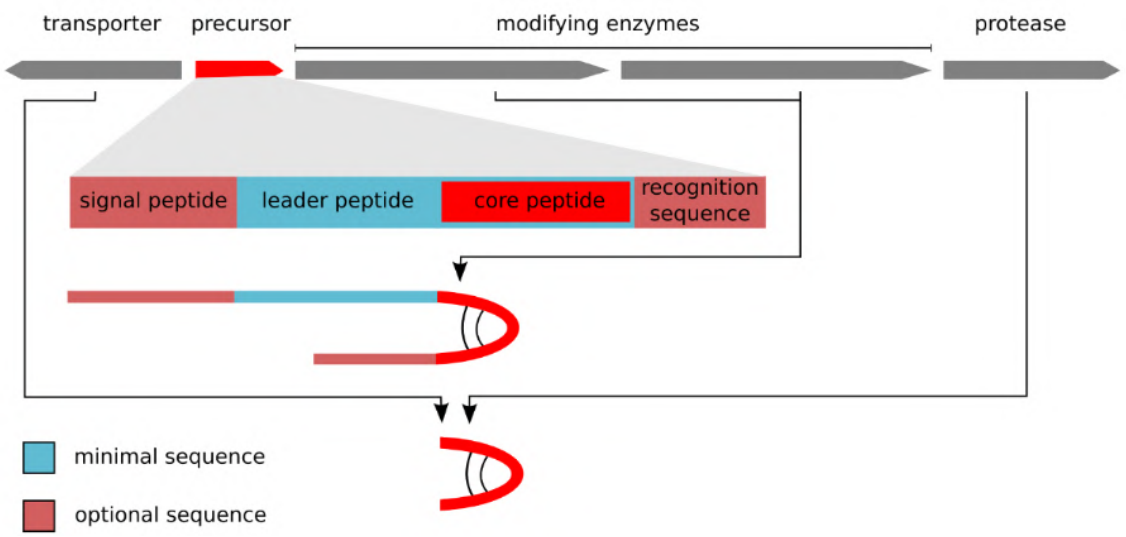
Ribosomally synthesized and post translationally modified peptides (RiPPs)

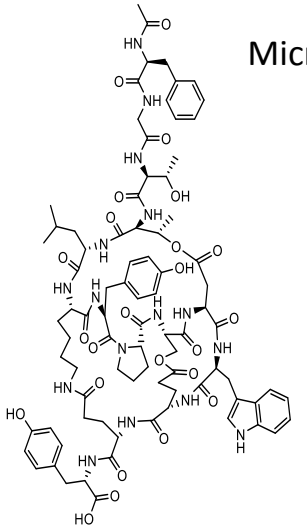
DNA $\xrightarrow{\text{transcription}}$ mRNA $\xrightarrow{\text{translation}}$ Peptide

Cyanobactines : peptides cyclique ou linéaire de petites tailles

Microviridines : peptides multicycliques avec des liaisons

Bacteriocines :petits peptides antimicrobiens





Microviridin

Kehr et al., 2011. Beilstein J. Org. Chem; Schmidt et al., 2005 ; Arnison et al., 2013

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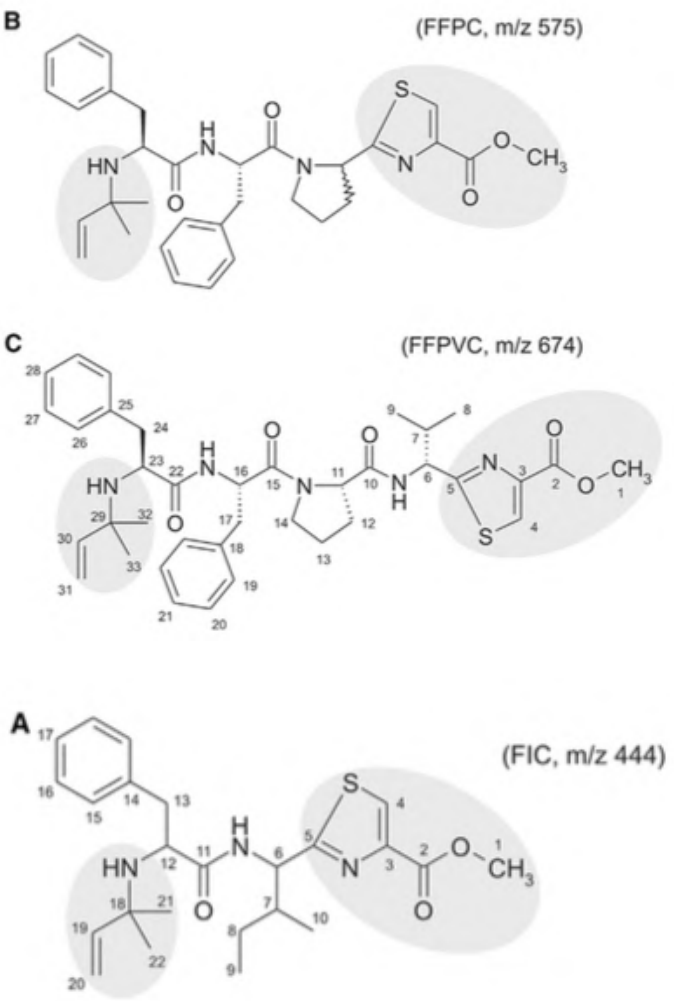
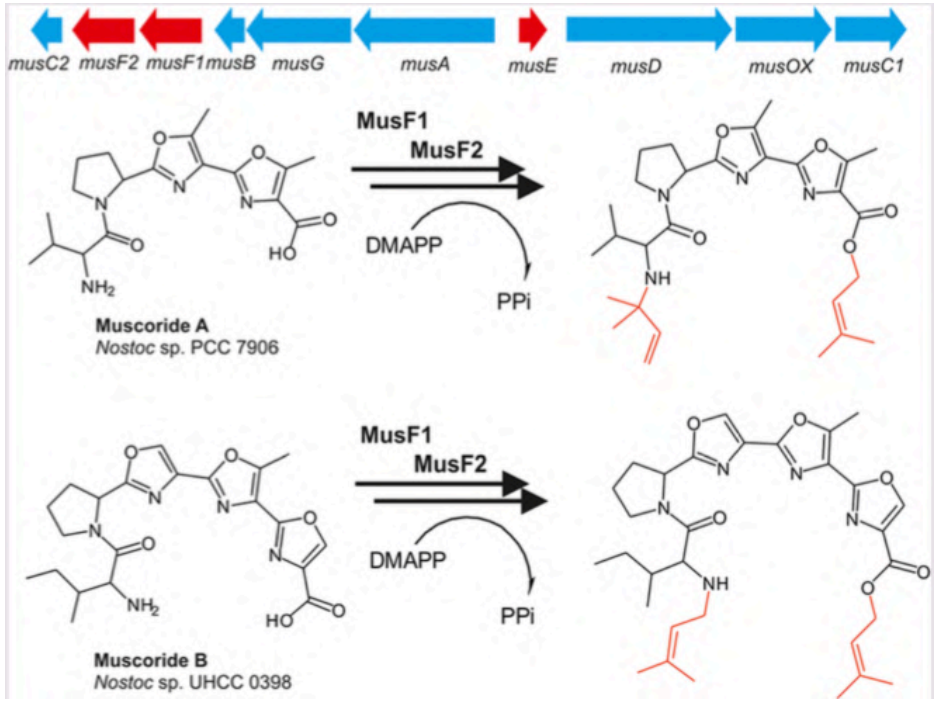
Famille des cyanobactines :
env. 40 types de peptides cycliques ou linéaires



Leikoski et al., 2013 ChemBiol



Mattila et al., 2019 ASC Chem Biol

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Les voies non ribosomales et polyketides

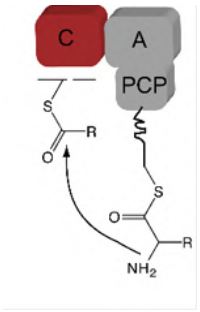
Non-ribosomal peptide synthetase (NRPS)

Polyketide synthase (PKS)

DNA Mod.1, 2 et 3 —transcription→ mRNA —traduction→ Enzymes 1, 2 et 3

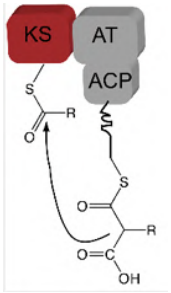
Complexe multienzymatique

NRPS: peptide



Kehr et al., 2011. Beilstein J. Org. Chem ;
Balkus & Walsh, 2010 Science

PKS: polyketide



Kehr et al., 2011. Beilstein J. Org. Chem ;
Mendez Perez et al., 2011 AEM ;
Ueoka et al., 2015 Nat Chem Biol

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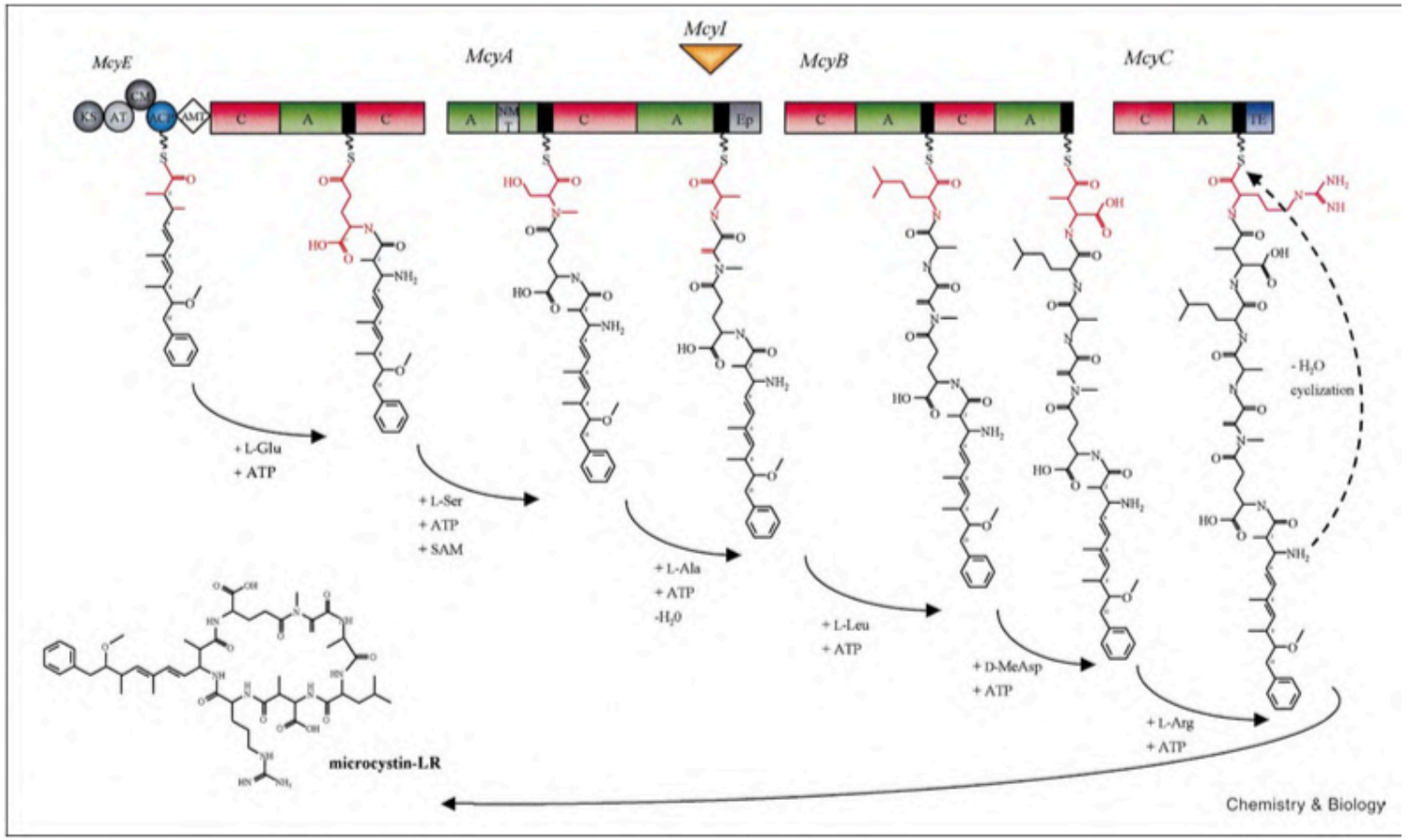
La voie de synthèse des microcystines

PKS/NRPS NRPS NRPS NRPS



Tillett et al., 2000 ChemBiol

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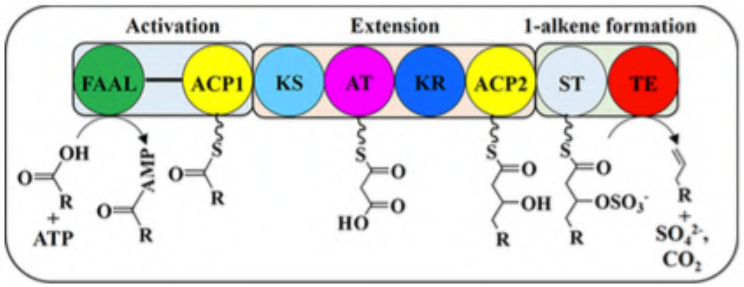
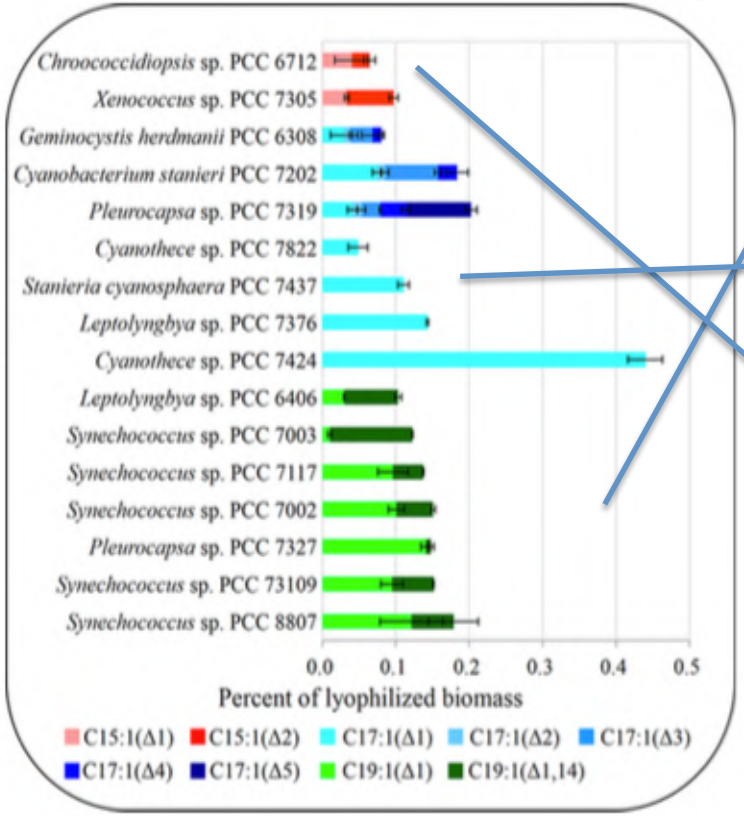
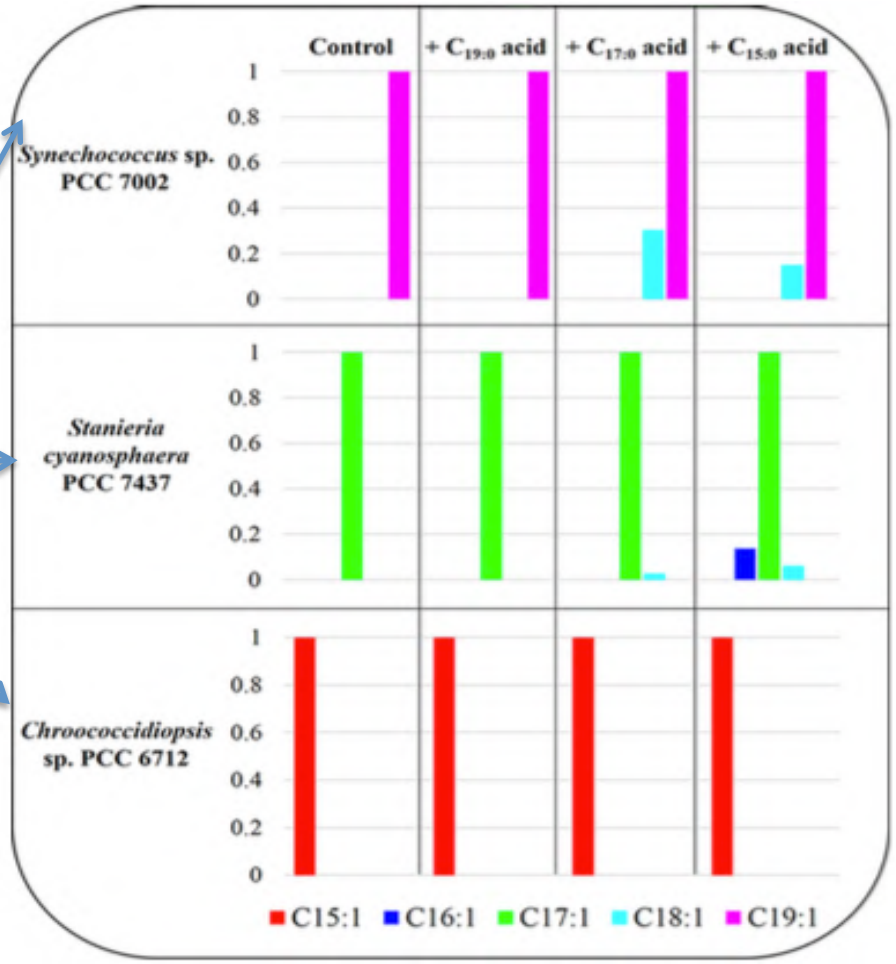
La voie PKS OLS : différents alkènes





Naturellement



Nourris

Zhu et al., 2018 AEM

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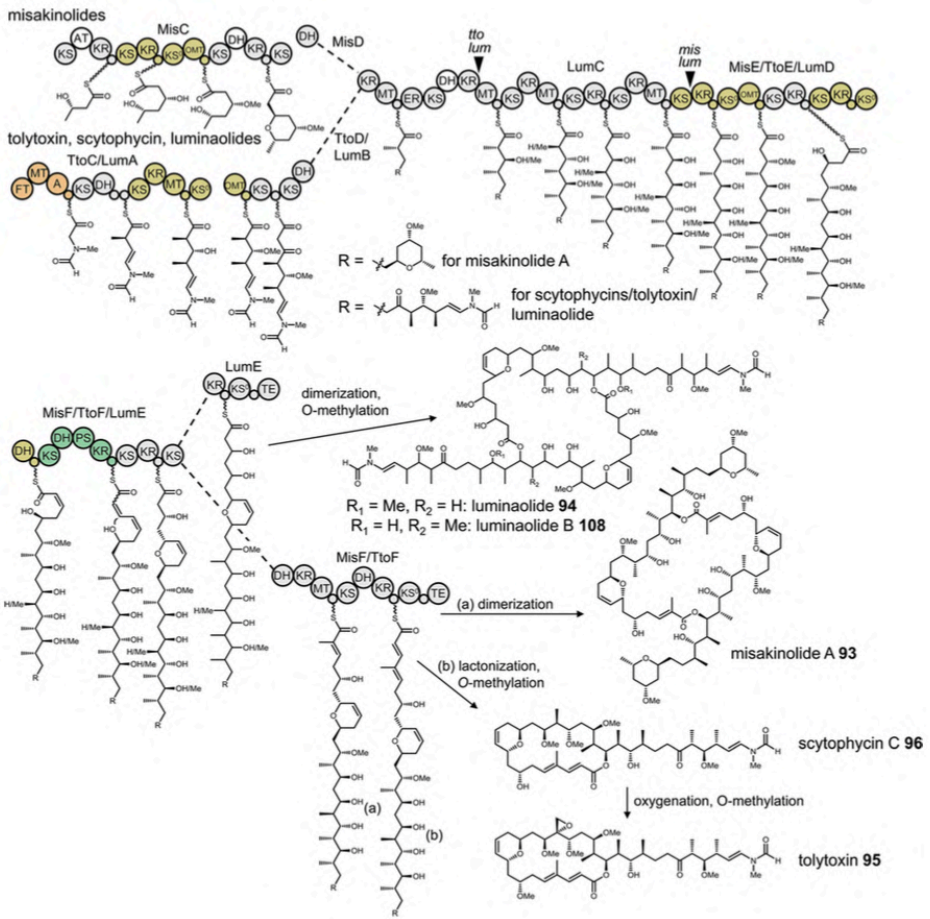
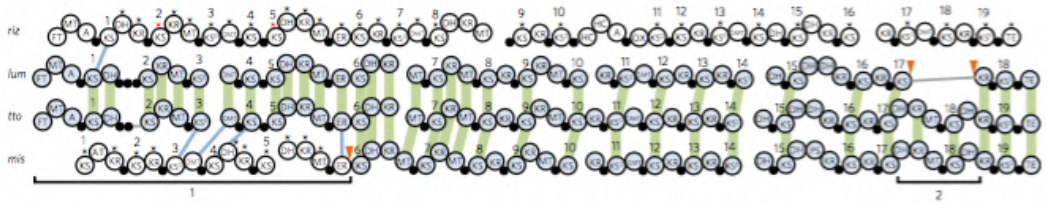
Evolution d'une voie de trans AT PKS





Ueoka et al., 2015 Nat Chem Biol

Les métabolites produits par ces voies de PKS sont des inhibiteurs de la polymérisation de l'actine.

Comparaison de ce cluster de gènes trouvé dans deux cyanobactéries (*tol*, *lum*) et *Escherischia coli* (*mis*) révèle des similarités et des différences.

Une voie homologue en enzyme dans une bactérie du sol (*riz*) révèle que cette voie a été crée au moins deux fois !

Bacterial Natural Products,
ETH Zurich, J. Piel

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Ces voies de synthèse dans le phylum

126 genomes - PhyML tree

- 31 conserved proteins, rooted

Unicellular I

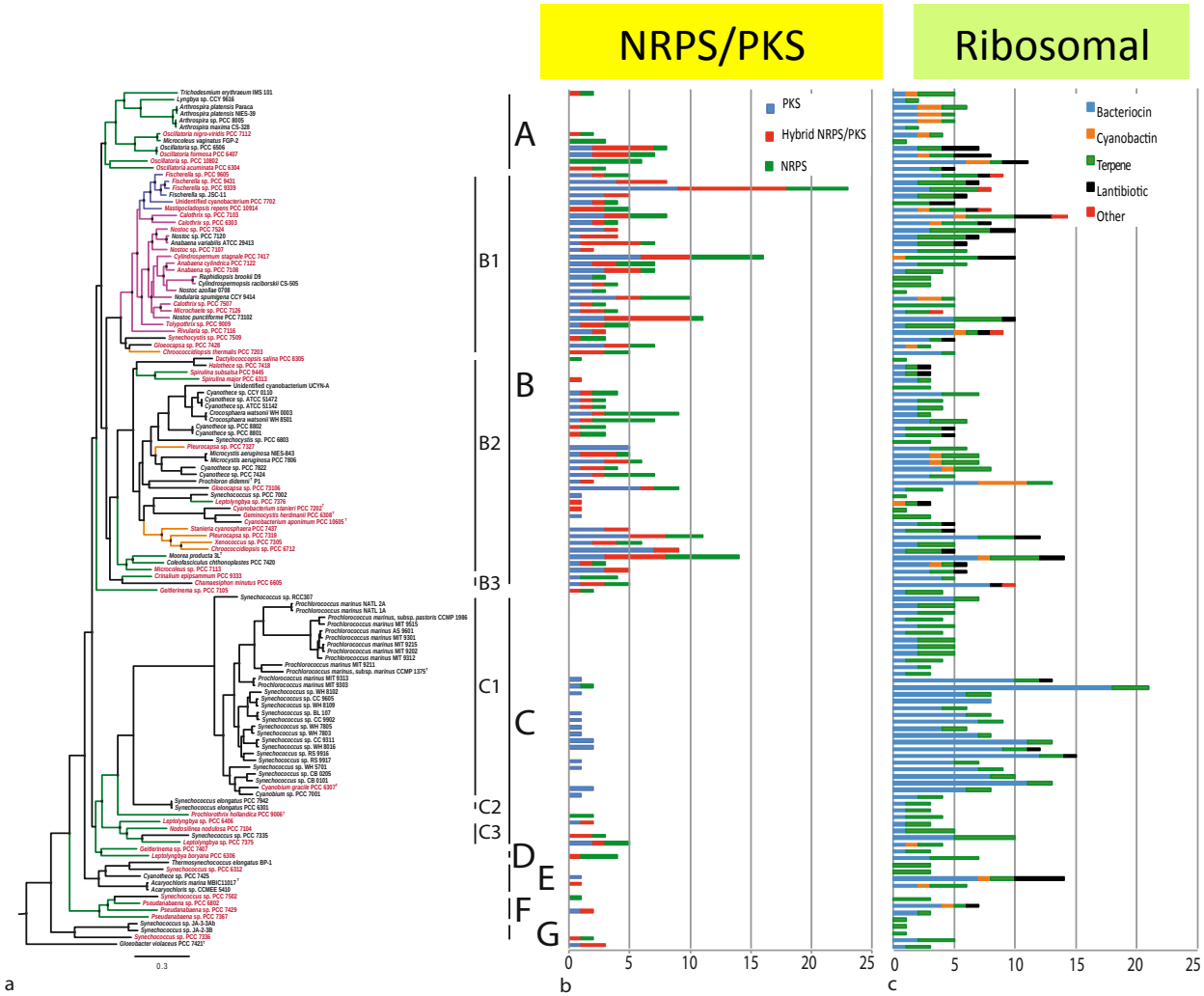
Baeocystous II

Filamentous III

Heterocystous IV

Ramified V

● Bootstrap >70%



Shih *et al.*, 2013 PNAS ; Calteau et al., 2014 BMC genomics

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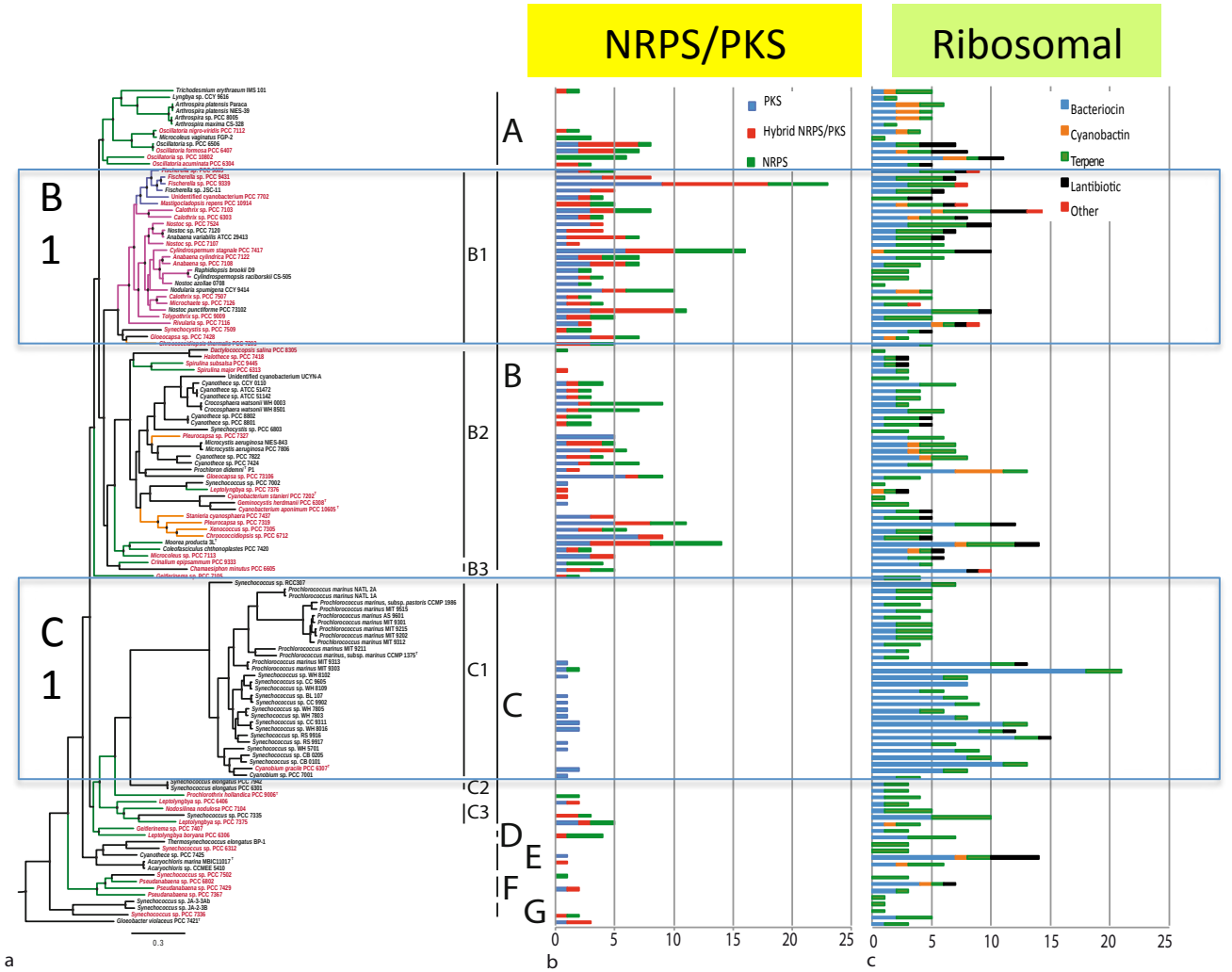

B1 investit une grande partie dans les deux types de voies, alors que C1 en a perdu une !

Shih *et al.*, 2013 PNAS ; Calteau et al., 2014 BMC genomics

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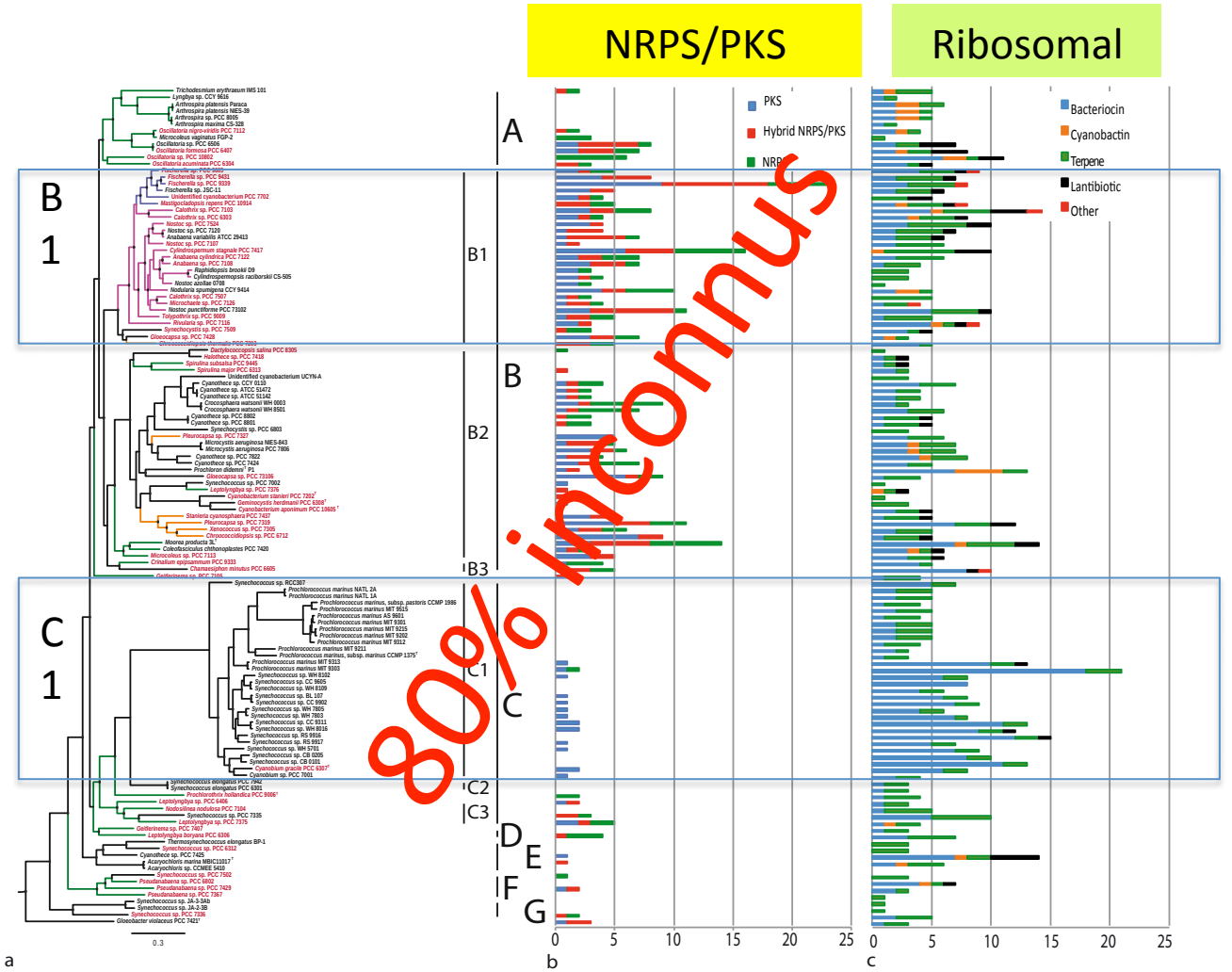

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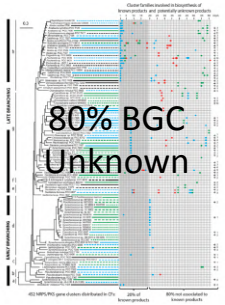
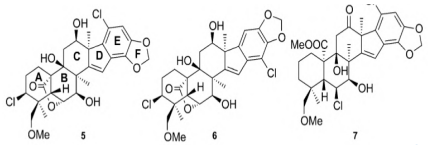
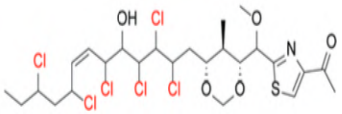


Nouveaux produits naturels



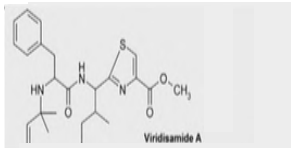
Merosterol

Moosmann et al., 2017 Angew. Chem.

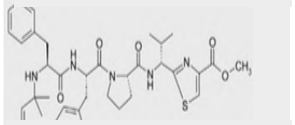


Aranazole

Moosmann et al., 2018 Org. Lett.

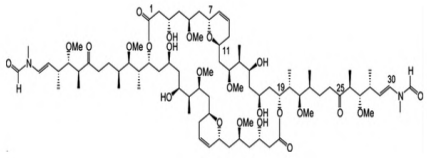


Viridisamide A



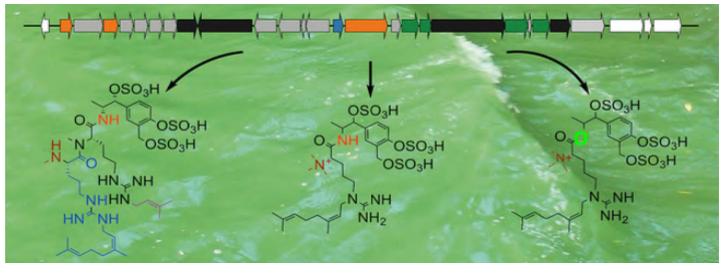
Aeruginosamide

Leikoski et al., 2013 Chem. Biol.

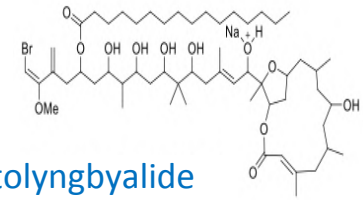


Luminaolide B

Ueoka et al., 2015 Nat. Chem Biol

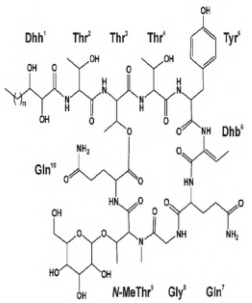


Aeruginoguanidine, Microguanidine amide, Microguanidine *Pancrace et al., 2019 ASC Chem. Biol.*



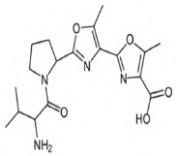
Leptolyngbyalide

Helfrich et al., 2019 Nat. Chem. Biol



Hassallidin E

Pancrace et al., 2017 ASC Chem. Biol.



Muscoride A & B

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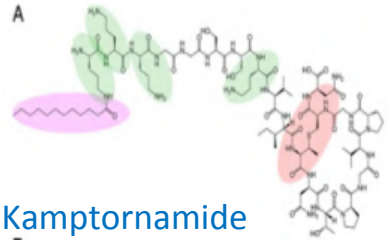
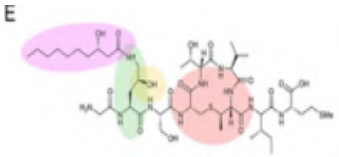
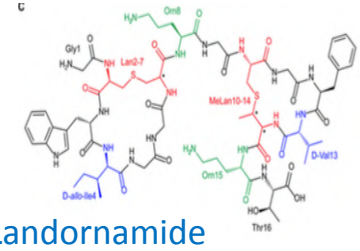


Kamptornamide



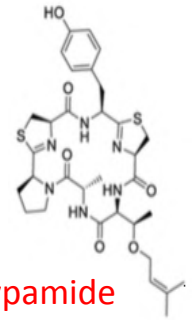
Phaeornamide

***Selinamides**, Hubrich et al., 2022 PNAS*



Landornamide

Bösh et al., 2020 Angew. Chem.



Tolypamide

Purushothaman et al., 2021 Angew. Chem.

Cyanobacteria Research, University of Helsinki ; Bacterial Natural Products, ETH Zurich ; Microbiology, University of Postdam, Leibniz Institute for NP Research and Infection Biology, Hans Knöll Institute, Jena, Friedrich Schiller University Jena ; Morinaka's Lab, National University of Singapore

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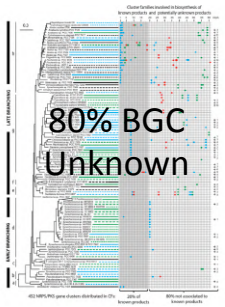
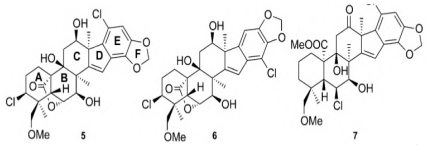


Nouveaux produits naturels



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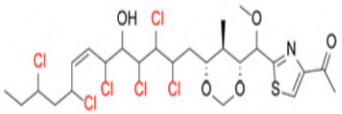

Aranazole

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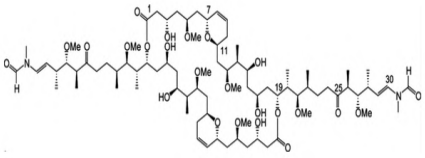

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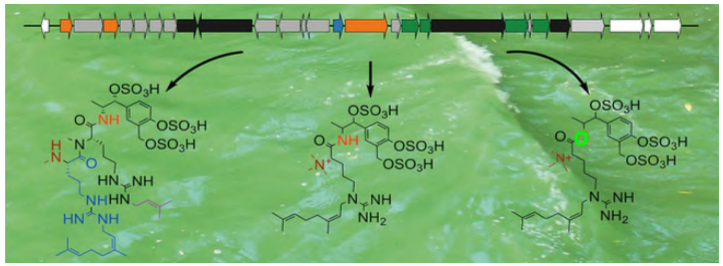

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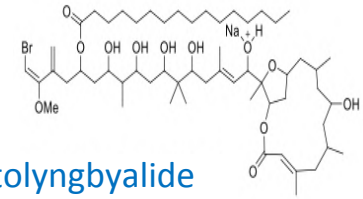

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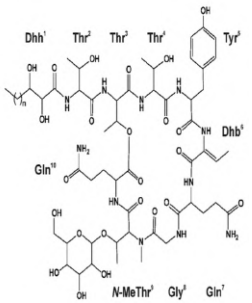

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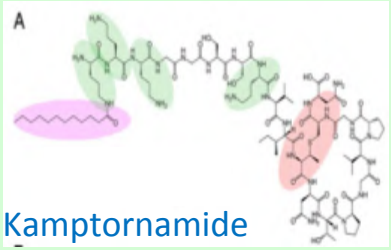
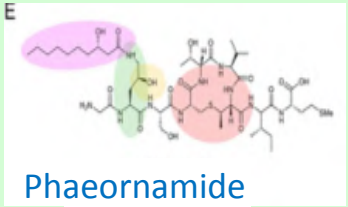


Kamptornamide



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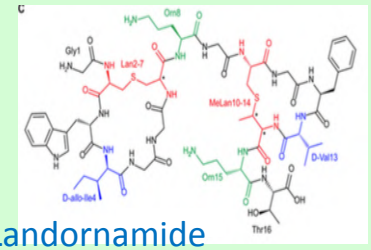

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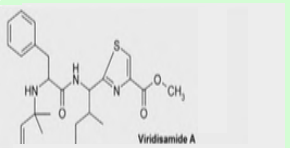
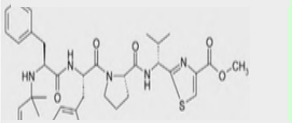


Viridisamide A



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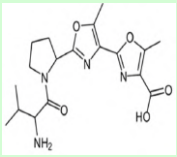

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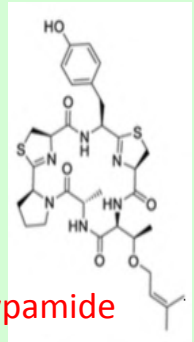

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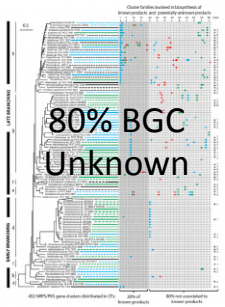

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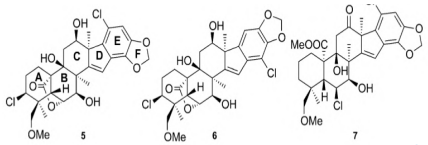

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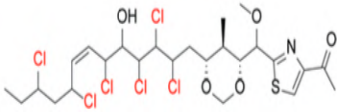

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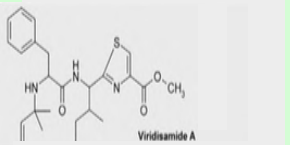
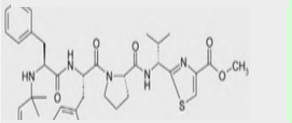
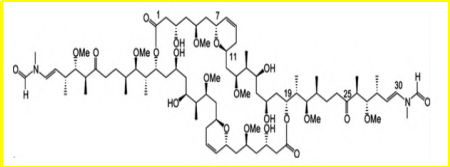


Viridisamide A



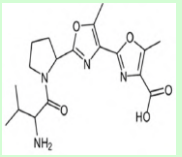
Aeruginosamide

Leikoski et al., 2013 Chem. Biol.



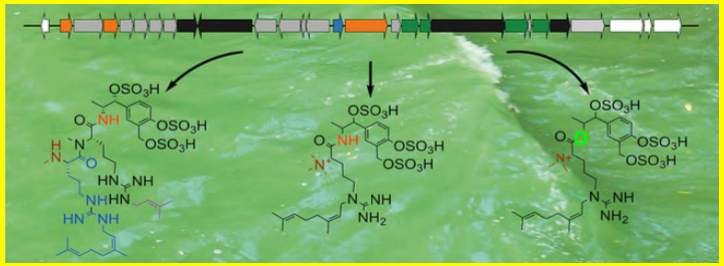
Luminaolide B

Ueoka et al., 2015 Nat. Chem Biol

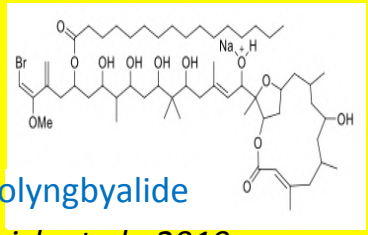


Muscoride A & B

Mattila et al., 2019 ACS Chem. Biol.

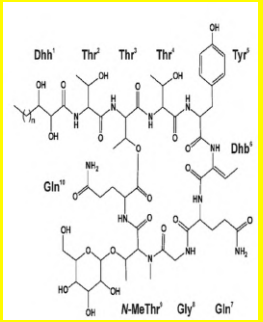


Aeruginoguanidine, Microguanidine amide, Microguanidine *Pancrace et al., 2019 ASC Chem. Biol.*



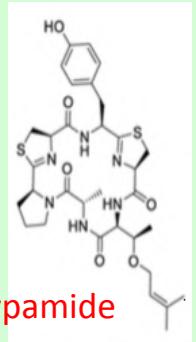
Leptolyngbyalide

Helfrich et al., 2019 Nat. Chem. Biol



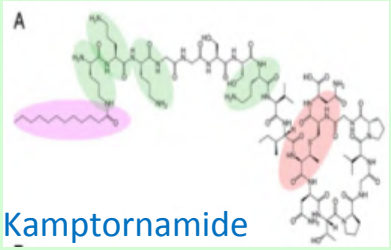
Hassallidin E

Pancrace et al., 2017 ASC Chem. Biol.

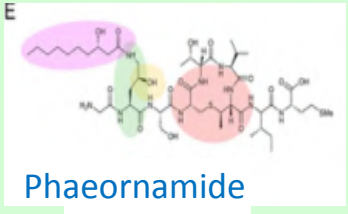


Tolypamide

Purushothaman et al., 2021 Angew. Chem.

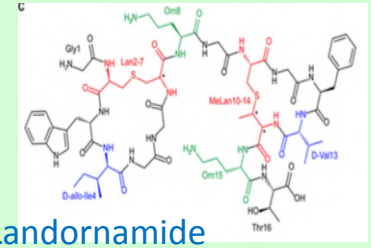


Kamptornamide



Phaeornamide

***Selinamides**, Hubrich et al., 2022 PNAS*



Landornamide

Bösh et al., 2020 Angew. Chem.

Cyanobacteria Research, University of Helsinki ; Bacterial Natural Products, ETH Zurich ; Microbiology, University of Postdam, Leibniz Institute for NP Research and Infection Biology, Hans Knöll Institute, Jena, Friedrich Schiller University Jena ; Morinaka's Lab, National University of Singapore

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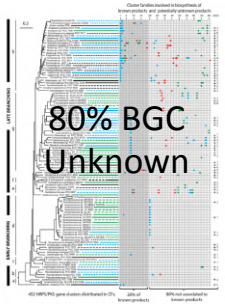
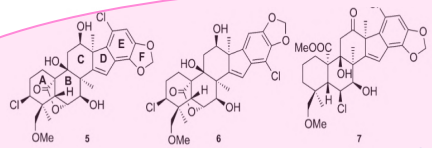
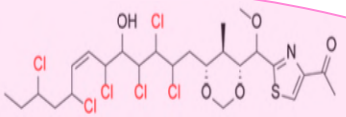


Nouveaux produits naturels



Merosterol

Moosmann et al., 2017 Angew. Chem.



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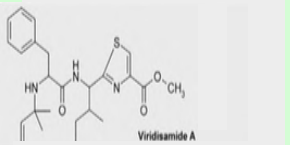

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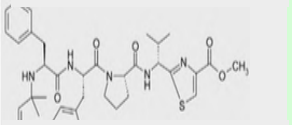

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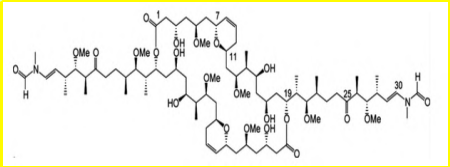

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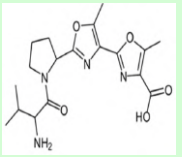

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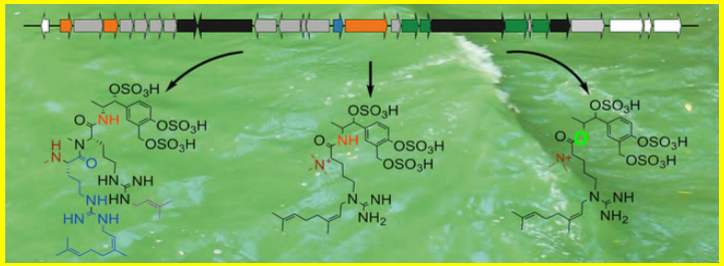

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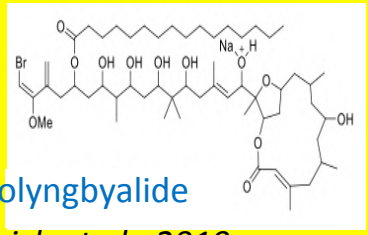

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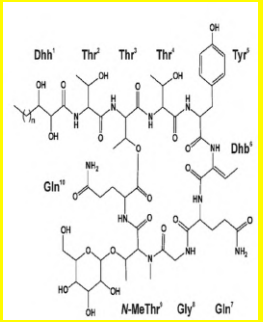

Hassallidin E

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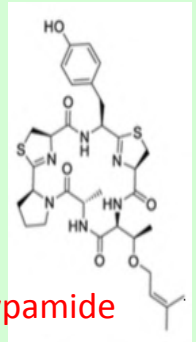
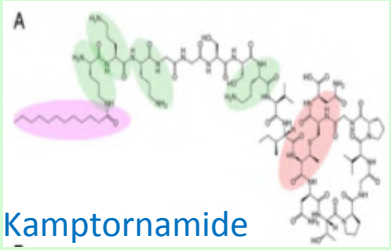
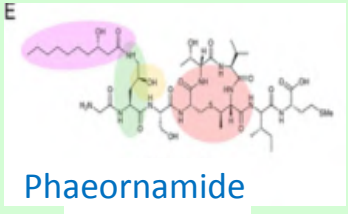


Tolypamide

Purushothaman et al., 2021 Angew. Chem.



Kamptornamide



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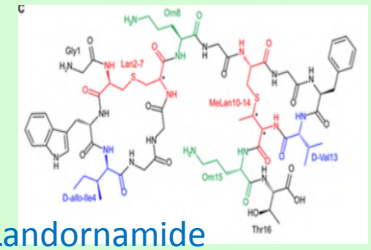

Landornamide

Bösh et al., 2020 Angew. Chem.

Cyanobacteria Research, University of Helsinki ; Bacterial Natural Products, ETH Zurich ; Microbiology, University of Postdam, Leibniz Institute for NP Research and Infection Biology, Hans Knöll Institute, Jena, Friedrich Schiller University Jena ; Morinaka's Lab, National University of Singapore

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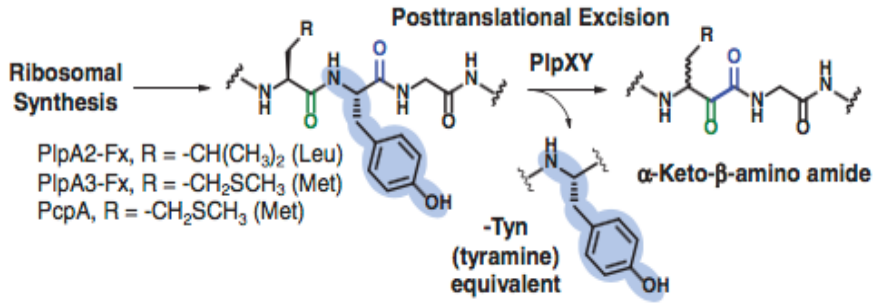
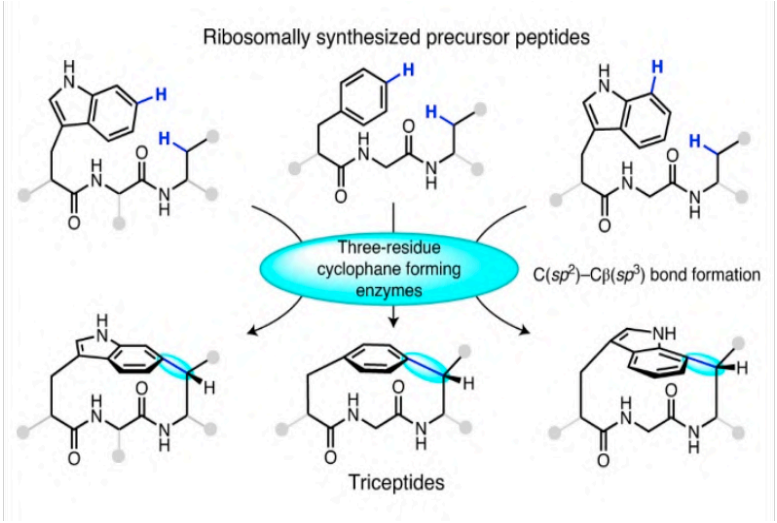
Nouvelles enzymes et nouvelle chimie dans les RIPPs

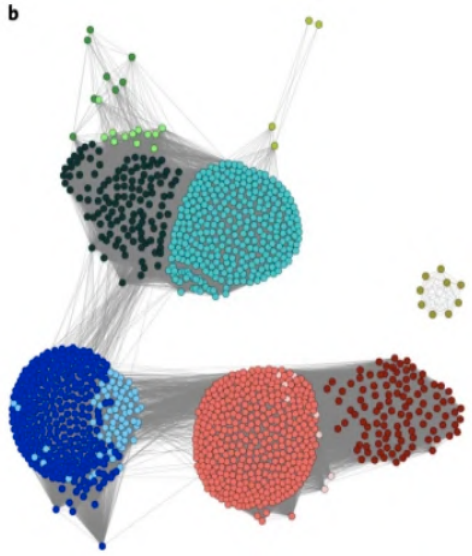


Morinaka et al., 2018 Science

Bacterial Natural Products, ETH Zurich, J. Piel



Protein sequence similarity network constructed for TIGRFAM41 SPASM maturase proteins with characterized members.



Nguyen et al., 2020 Nat. Chemistry

Morinaka's Lab in Department of Pharmacy, National University of Singapore

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Les voies de synthèse de métabolites des cyanobactéries

- Diversifiées dans des classes connues (RiPPs, NRPS, PKS) et d'autres nouvelles
- Une grande diversité de produits naturels bioactifs
- L'activité reste à découvrir pour le producteur et vis-à-vis d'effets potentiellement toxiques

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Voies de biosynthèse des produits naturels des cyanobactéries

Institut Pasteur Paris, Université Paris Cité

Muriel GUGGER, muriel.gugger@pasteur.fr

Journée FIRE/MCAM, MNHN, 24 avril 2024