Discovering the Future

10 YEARS
2008-2018

La farmacia del mar: fármacos de origen marino

Fernando Reyes

Fundación MEDINA

FUNDACIÓN
CENTRO DE EXCELENCIA
EN INVESTIGACIÓN DE
MEDICAMENTOS INNOVADORES
EN ANDALUCÍA

Interreg
Atlantic Area
European Regional Development Fund

EUROPEAN UNION

Blue Human

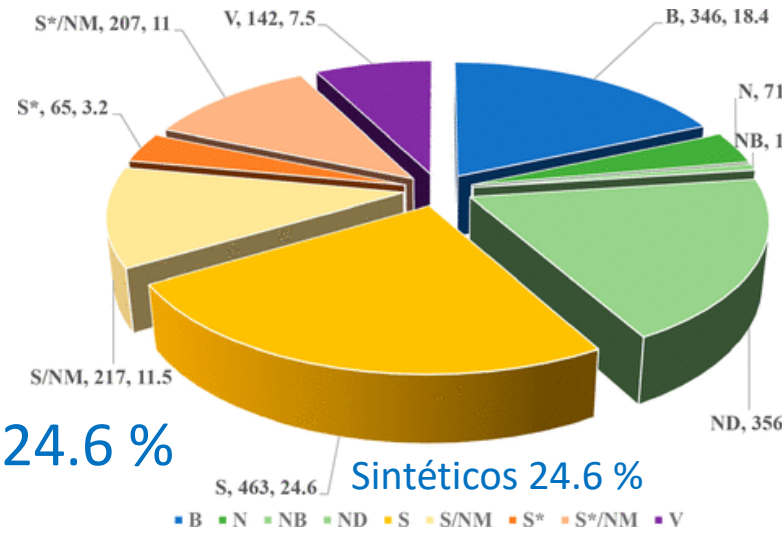
Papel Fundamental de los Productos Naturales en el Descubrimiento de Fármacos

- **Ocupan un espacio químico único** en comparación con los productos sintéticos.
- **Poseen una potencia y selectividad** derivadas de una amplia selección evolutiva.
- **Existen muchas fuentes naturales no exploradas** de nuevos compuestos.
- Los **productos naturales bioactivos** han sido frecuentemente usados como **punto de partida** en el **desarrollo de nuevos candidatos a fármacos**.
- **Poseen estructuras privilegiadas** que constituyen **excelentes modelos** para la sintesis de nuevos derivados biológicamente activos.

Productos naturales y nuevos fármacos

Sintéticos inspirados en Naturales 25.7 %

Fármacos Aprobados ENE1981-SEP2019



Naturales 3.8 %

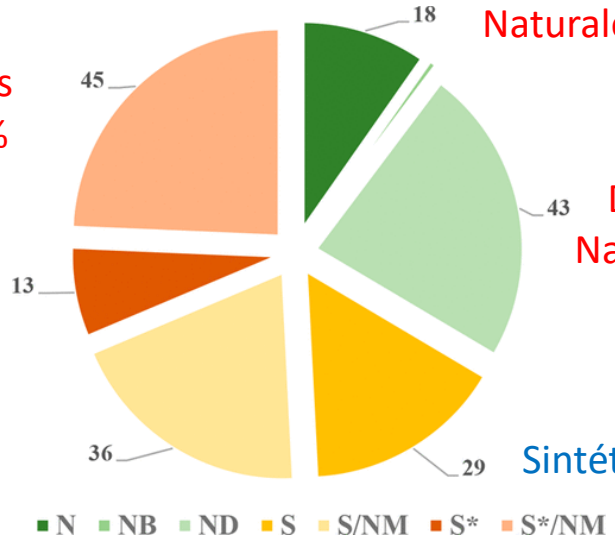
Derivados de Naturales 18.9 %

Sintéticos 24.6 %

Naturales* 48.4 %/Sintéticos 24.6 %

Sintéticos inspirados en Naturales 51.1 %

Anticancerígenos (small molecules) ENE1981-SEP2019



Naturales 9.8%

Derivados de Naturales 23.4 %

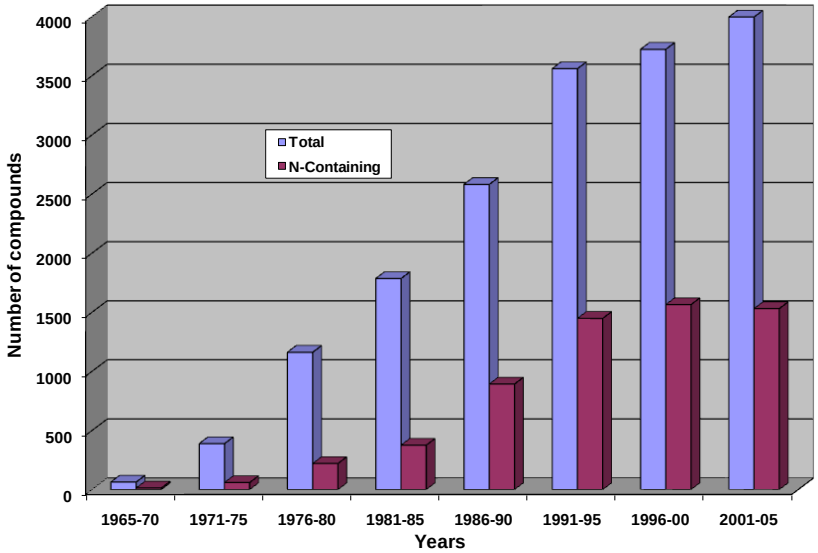
Sintéticos 15.8 %

Naturales* 84.2 %/Sintéticos 15.8 %

Newman, D. J.; Gragg, G. M. *J. Nat. Prod.* **2020**, *83*, 770-803.

Biodiversidad: el mar frente a la tierra

John W. Blunt et al. *Nat. Prod. Rep.* 2007, *24*, 31-86.



Marinlit: > 35.000 productos naturales marinos

Biodiversidad: Marina > Terrestre

Alta Biodiversidad = Alta Diversidad Química

Oportunidad: No se ha explorado gran parte de la biodiversidad del mar

Expediciones y Colección

EXPEDICIONES

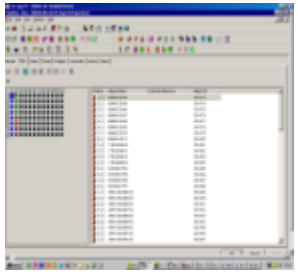
Recolección y Logística

CLASIFICACION

Taxonomía y Etiquetado

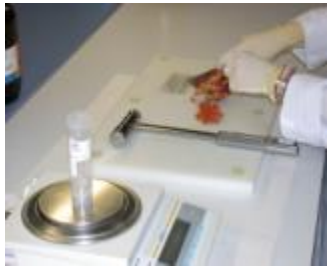
ALMACENAMIENTO

Colección, Seguridad



Datos GPS, Imágenes

GESTION DE DATOS



Preparación en laboratorio

TRATAMIENTO

Microbiología

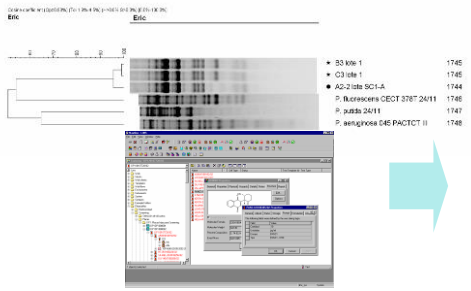
Muestras → Aislamiento → DR molecular → Colección → Fermentación → Screening → De-replicación → Escalado

Invertebrado marino /planta/sedimento /tierra/agua

Homogeneizado

Aislamiento de Microorganismos

Bacterias
Actinomicetos
Hongos



Desreplicación molecular

Colección de Microorganismos

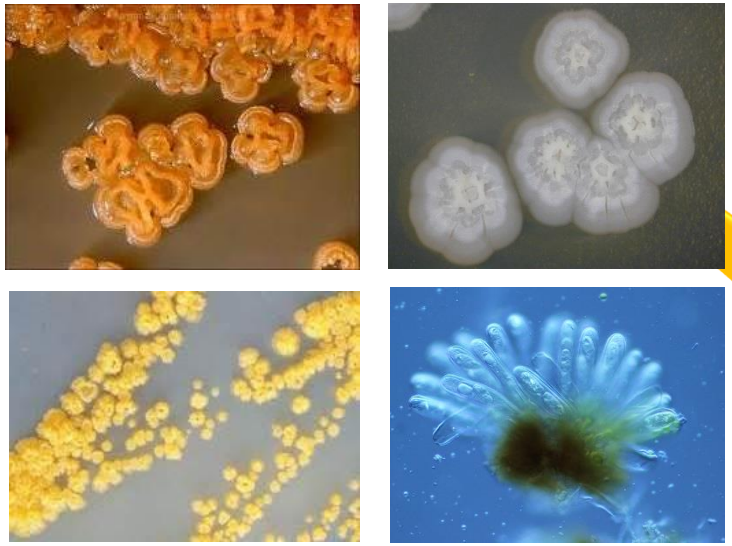
- Fermentación
- Extracción
- Detección de actividad

Escalado de extractos activos

Nuevas Cepas:

HPLC-MS
De replicación

Microbiological Approaches to Maximize Chemical Diversity



- Genes encoding biosynthetic enzymes in bacteria and fungi outnumber known secondary metabolites
- We are missing large part of NP biosynthetic capacity
- Only a subset of pathways is expressed in laboratory conditions
- Access to this reservoir of molecules needs activation of cryptic genes

- **Culture conditions** (OSMAC)
- **Stress factors**
- **Addition chemical inducers**
- **Interspecies crosstalk: Co-culturing**
- **Epigenetic modifiers**

Descubrimiento de moléculas bioactivas

Extractos de macroorganismos/cultivos de microorganismos marinos

High Throughput Screening (HTS)
Confirmación de actividad y desreplicación mediante LC/MS

Selección de cepas y condiciones para fermentación a pequeña escala y confirmación de la actividad

Extractos y cepas seleccionados para escalado de la purificación

Purificación cromatográfica guiada por bioensayo

Moléculas bioactivas

Conversión de biodiversidad en fármacos

BioDiversidad → Moléculas Bioactivas

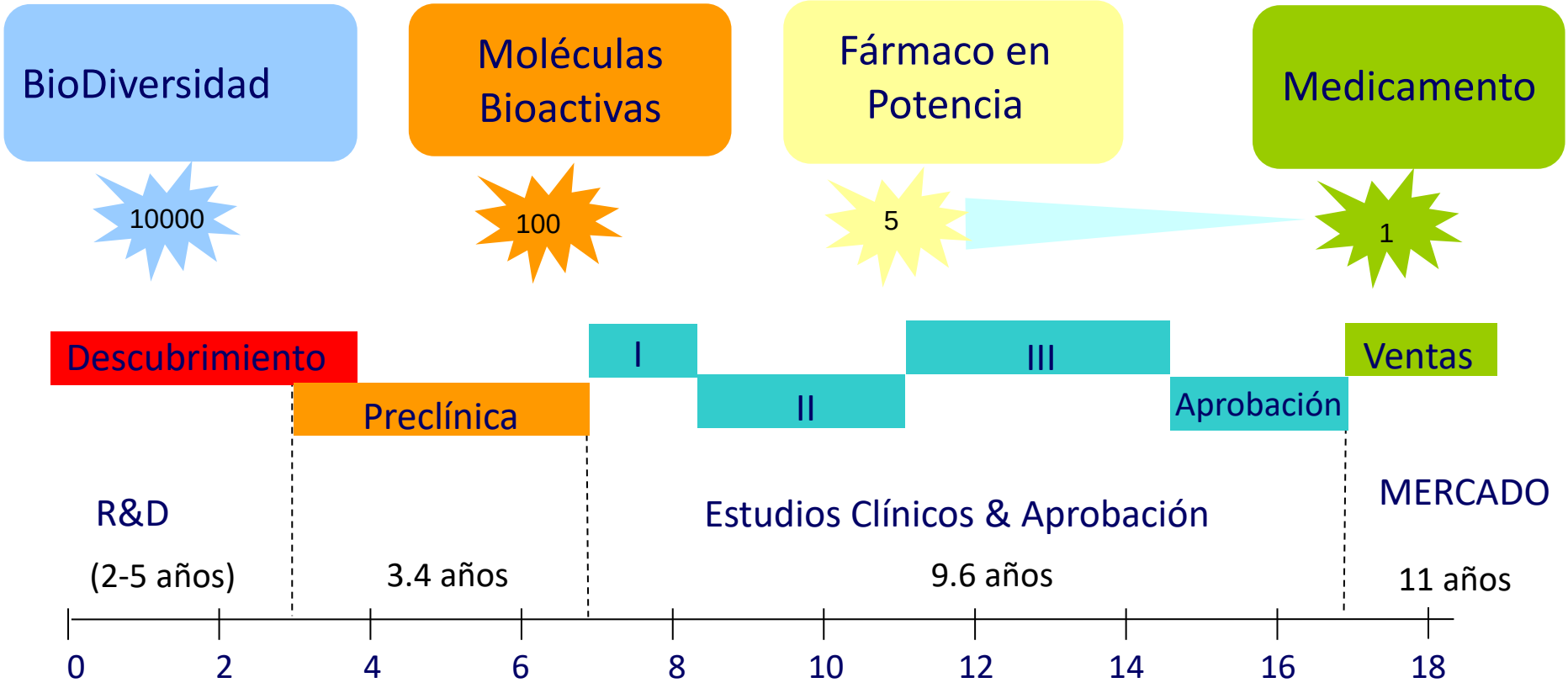
Moléculas Bioactivas → Fármaco en Potencia → Medicamento

Industria Farmacéutica y afines

Molécula Bioactiva ≠ Fármaco en Potencia

Actividad *in vitro* no garantiza actividad *in vivo* o buenas propiedades como potencial fármaco.

Proceso de desarrollo de un fármaco



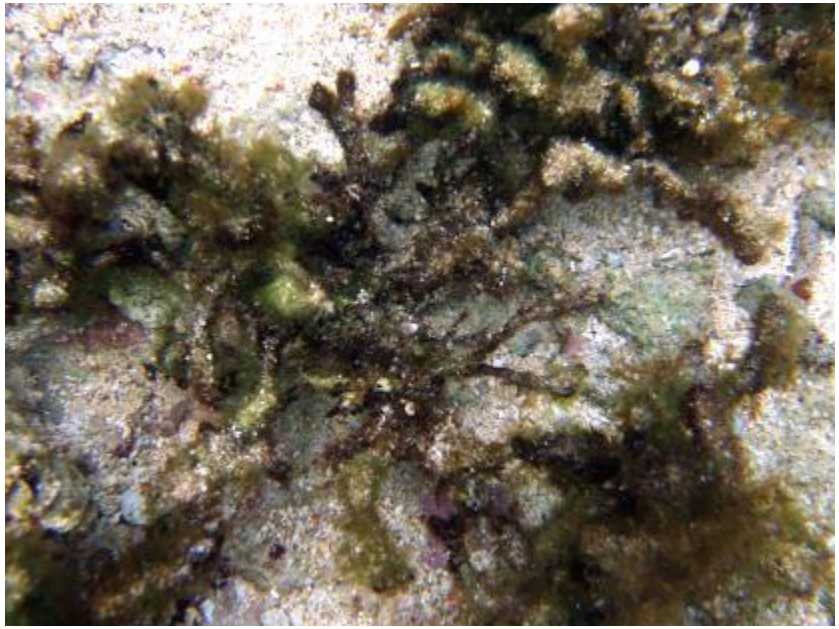
Paclitaxel (TAXOL) : > 20 años desde la Determinación Estructural (Molécula Bioactiva) hasta la Aprobación por la FDA

Costes ~ $ 1.395 mill.*

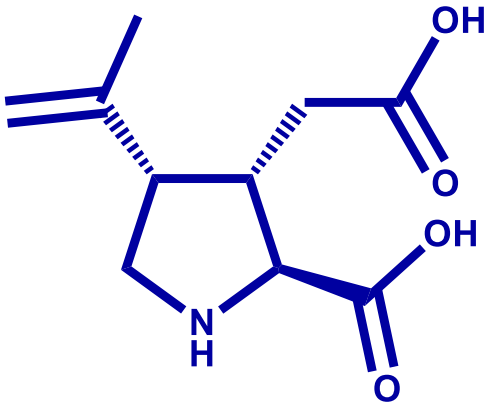
* *J. Health Econ.* 2016, 47, 20-33

Fármacos marinos

Ácido kaínico



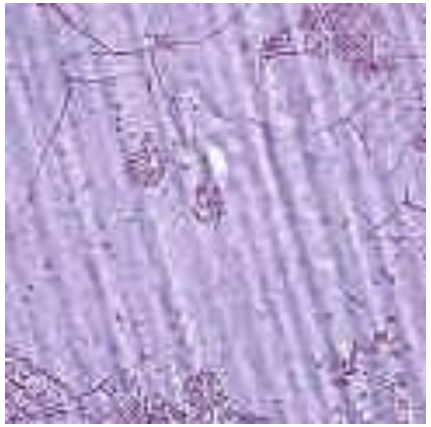
Digenea simplex
Alga parda



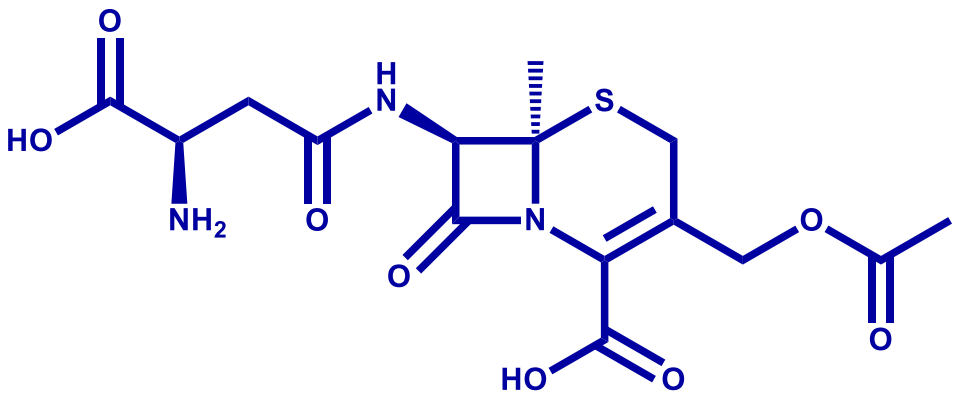
Ácido kaínico

- **Comercializado en 1954**
- **Antihelmíntico**

Cefalosporina C



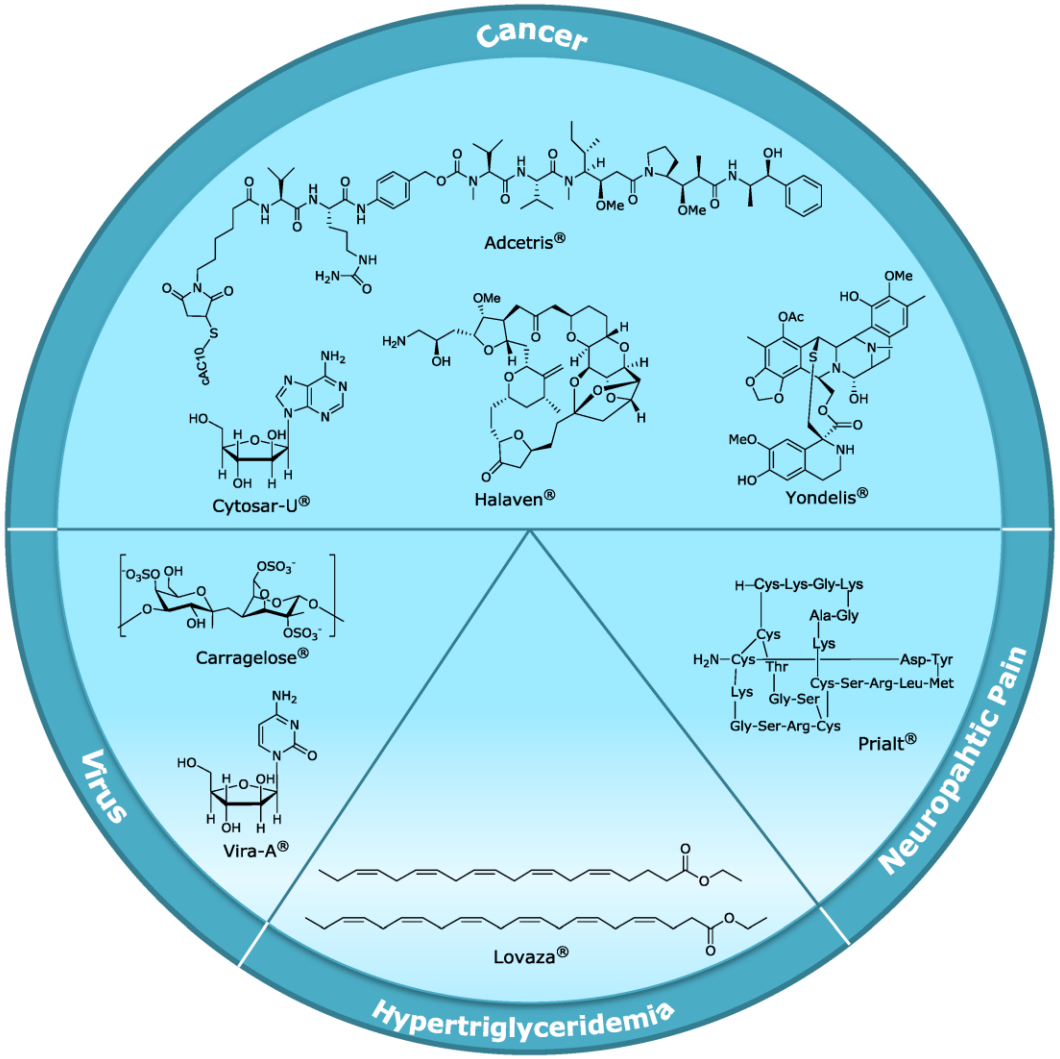
Cephalosphorium acremonium
Hongo microscópico



Cefalosporina C

- **Antibiótico**
- **En 1992 empezó a desarrollarse la 4ª generación**

Productos Naturales Marinos en uso clínico



Mar. Drugs 2014, *12*(2), 1066-1101; https://doi.org/10.3390/md12021066

Productos Naturales Marinos en uso clínico (2014)

Compound	NP or Derivative	Original NP/Source Organism	Company/Institution (Country)	Therapeutic Area	Status 2004	Status 2009	Status 2013
Cytarabine (Cytosar-U®; Depocyt®)	NP derivative	Spongothymidine/sponge *Cryptotethya crypta*	Bedford (USA); Enzon (USA)	Cancer	FDA/EMEA approved	Approved	Approved
Vidarabine (Vira-A®)	NP derivative	Spongouridine/sponge *Cryptotethya crypta*	King Pharma (USA)	Anti-viral	FDA/EMEA approved	Approved	US discontinued
Ziconotide (Prialt®)	NP	ω-Conotoxin/marine snail *Conus magus*	Elan Corporation (Ireland)	Neuropahtic Pain	FDA approved	FDA/EMEA approved	Approved
Omega-3-acid ethyl esters (Lovaza®)	NP derivative	Omega-3-fatty acids/fish	GlaxoSmithKline (UK)	Hypertriglyceridemia	FDA approved	FDA/EMEA approved	Approved
Trabectedin (Yondelis®)	NP	Ecteinascidin 743/tunicate *Ecteinascidia turbinata*	PharmaMar (Spain)	Cancer	Phase II/III	EMEA approved	EMEA approved
Eribulin mesylate (Halaven®)	NP derivative	Halichondrin B/sponge *Halichondria okadai*	Eisai (Japan)	Cancer	Phase I	Phase III	FDA/EMEA approved
Brentuximab vedotin (SGN-35) (Adcetris®)	NP derivative	Dolastatin 10/sea hare *Dolabella auricularia*	Seattle Genetics (USA); Takeda GRDC (Japan)	Cancer	-	Phase II	FDA/EMEA approved
Iota-carrageenan (Carragelose®)	NP	Iota-carrageenan/red Algae *Eucheuma/Cnondus*	Marinomed (Austria); Boehringer Ingelheim (Germany)	Anti-viral	-	-	Over-the-counter drug (OTC)

Mar. Drugs 2014, *12*(2), 1066-1101; https://doi.org/10.3390/md12021066

Web sobre Farmacología Marina

https://www.marinepharmacology.org/

Marine Pharmacology

Home | About | General Publications | Clinical Pipeline | Preclinical Pipeline | Links

The Global Marine Pharmaceuticals Pipeline

The marine pharmaceuticals website has been prepared with the generous help of several researchers from academia, industry, and government who are currently involved in the global marine pharmaceuticals pipeline, which involves both preclinical and clinical research on the pharmacology of marine-derived chemicals.

The content of the website is aimed at researchers in academia, industry, and government with an interest in the preclinical and clinical pharmacology of marine compounds,

Contact Us

Midwestern University
College of Graduate Studies
Department of Pharmacology
555 31st Street
Downers Grove, IL 60515
USA

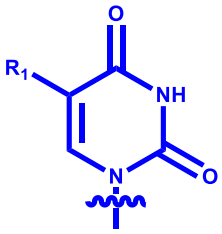
A.M.S Mayer, Ph.D.
Email: amayer@midwestern.edu

Phone: (630) 515-6951

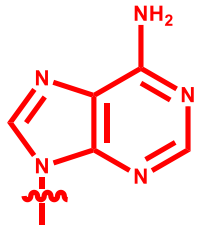
Fax: (630) 515-6295

Ara C y Ara A

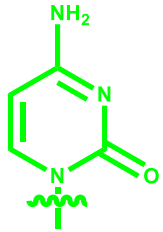
Cryptotethya crypta **(esponja)**
Ara U y Spongotimidina



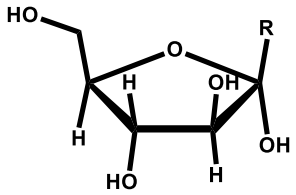
1 R_1=H Uracilo
2 R_1=CH_3 Timina



3= Adenina

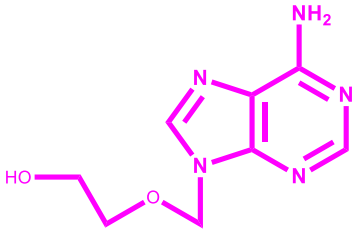


4=citosina

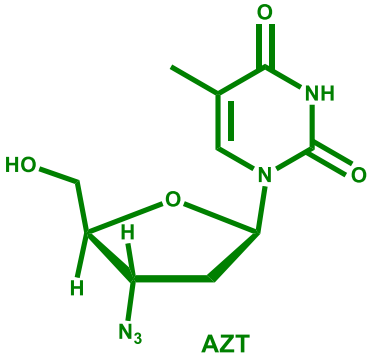


Arabinosa

Ara U (Spongouridina) R=1
Spongotimidina R=2
Ara A (Vidarabina) R=3
Ara C (Citarabina) R=4



Aciclovir



AZT

Eunicella cavolini **(coral blando)**
Ara A y Ara U

- Ara C (Cytosar-U®): Linfoma no Hodking y leucemia mielocítica aguda
- Ara A (Vira-A®): Antiviral

Prialt® (Ziconotide)

Conus magus

Conus pennaceus

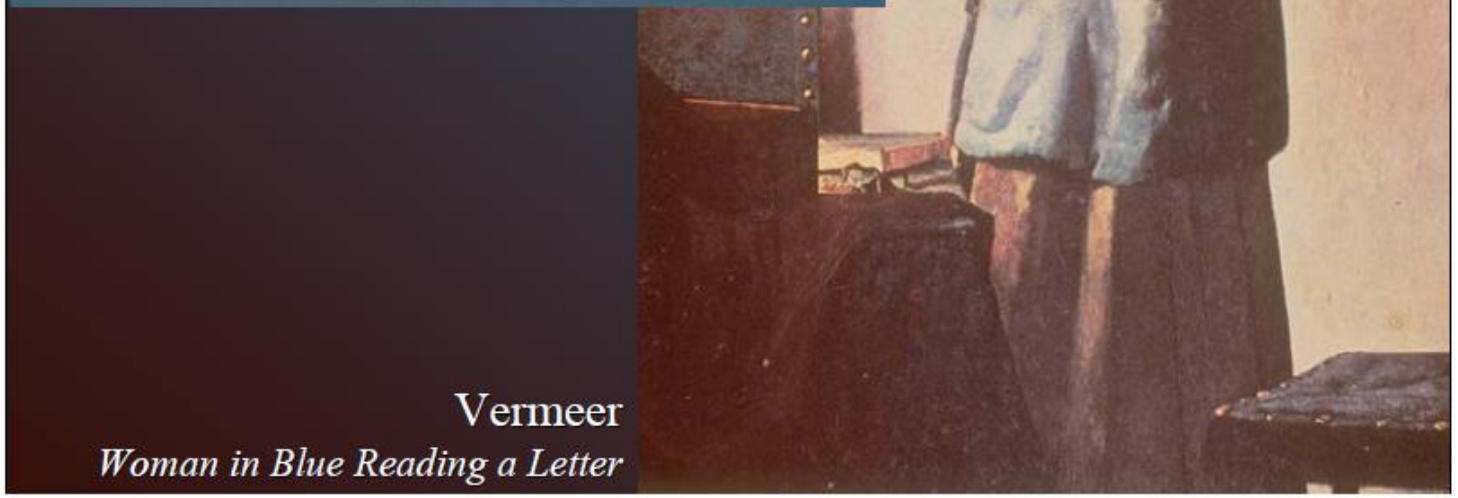
Especies del género *Conus*

•Tamaño variable (hasta 25 cm).
•Carnívoros.
•Productores de conotoxinas: Péptidos neurotóxicos (10-30 aminoácidos).
•Mecanismo de ataque con propiedades paralizantes.

- Conus Geographicus
- Conus magus

Prialt® (Ziconotide)

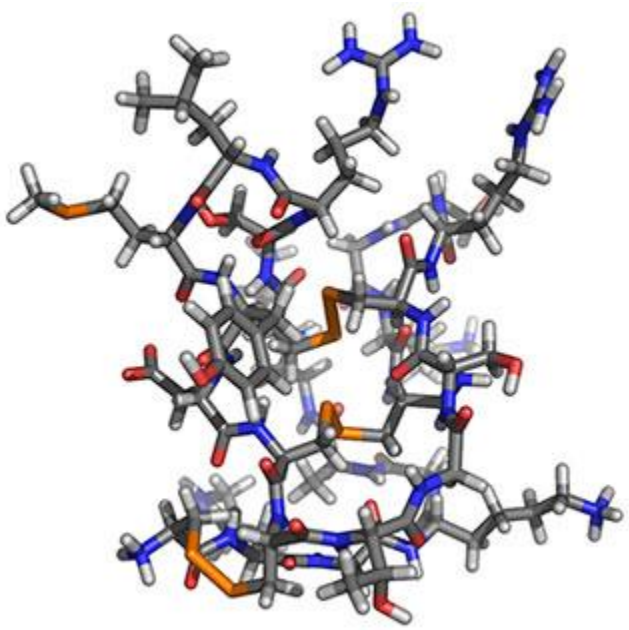
Conus cedonulli ("the matchless cone")

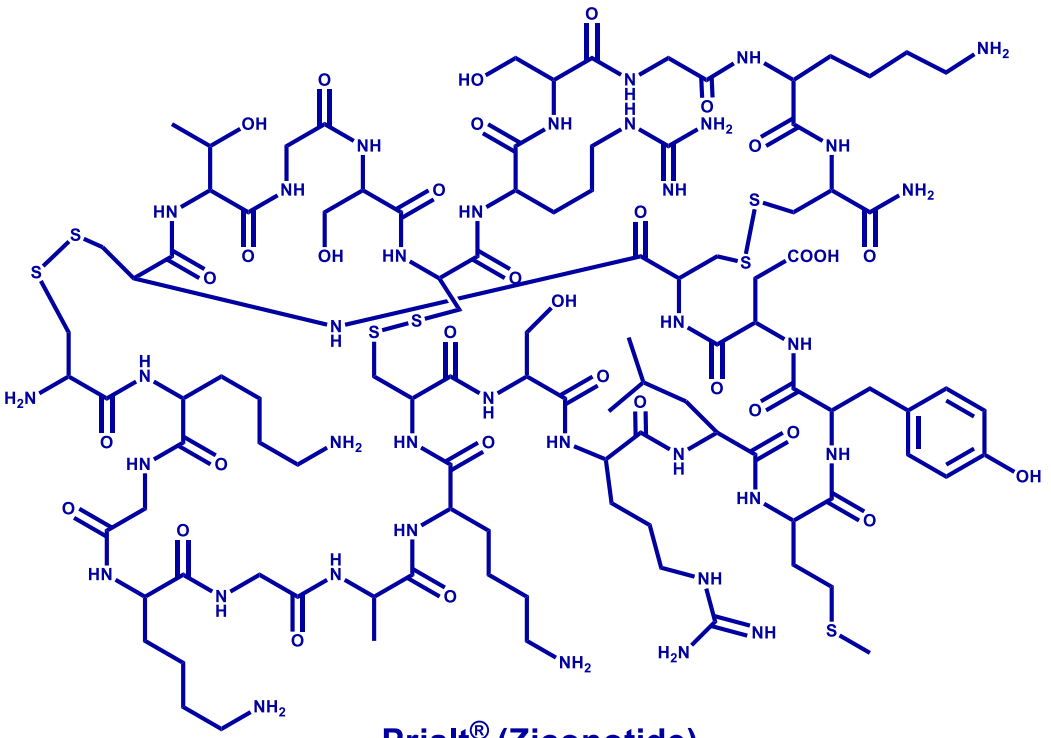


Vermeer

Woman in Blue Reading a Letter

Prialt® (Ziconotide)

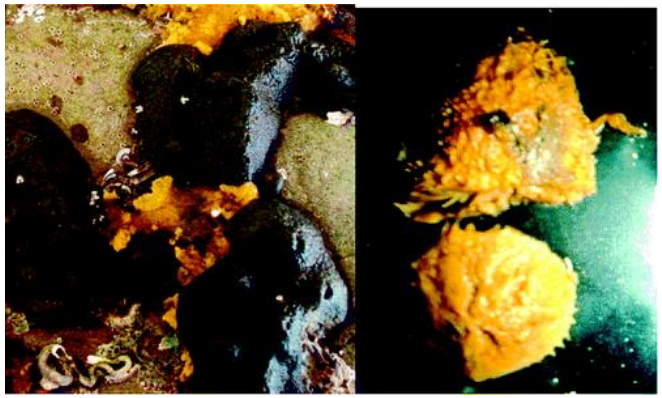




Prialt® (Ziconotide)

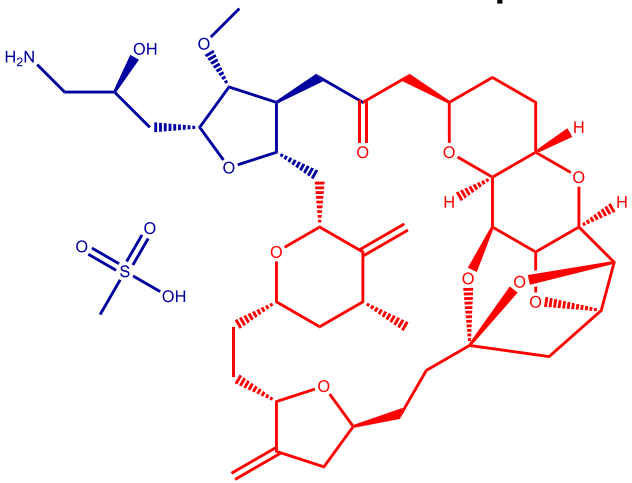
- Obenido de *Conus magus*
- Inicialmente conocido como ω-conotoxina M-VII-A
- Agente bloqueante del canal de calcio tipo N
- Tratamiento del dolor neuropático persistente y resistente a todo tipo de tratamiento
- Administración por inyección intracatecal

Mesilato de Eribulin (E7879, Halaven®)



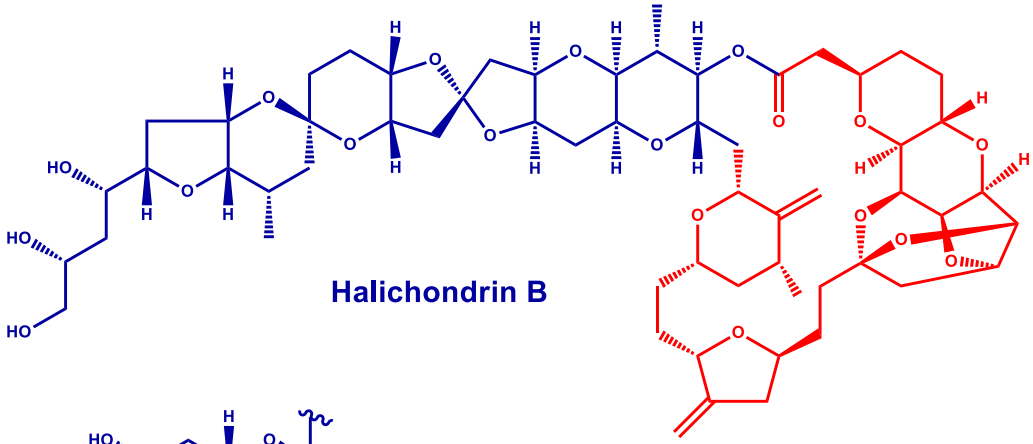
Halichondria okadai

***Lissodendoryx* sp.**

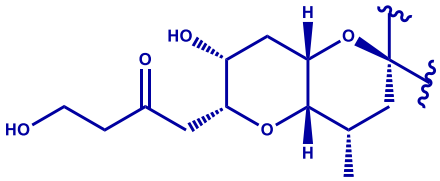


Mesilato de Eribulin

Eisai Co., Ltd



Halichondrin B

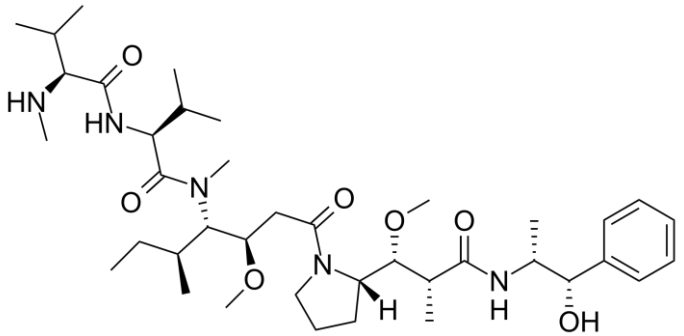


Isohomohalichondrin B

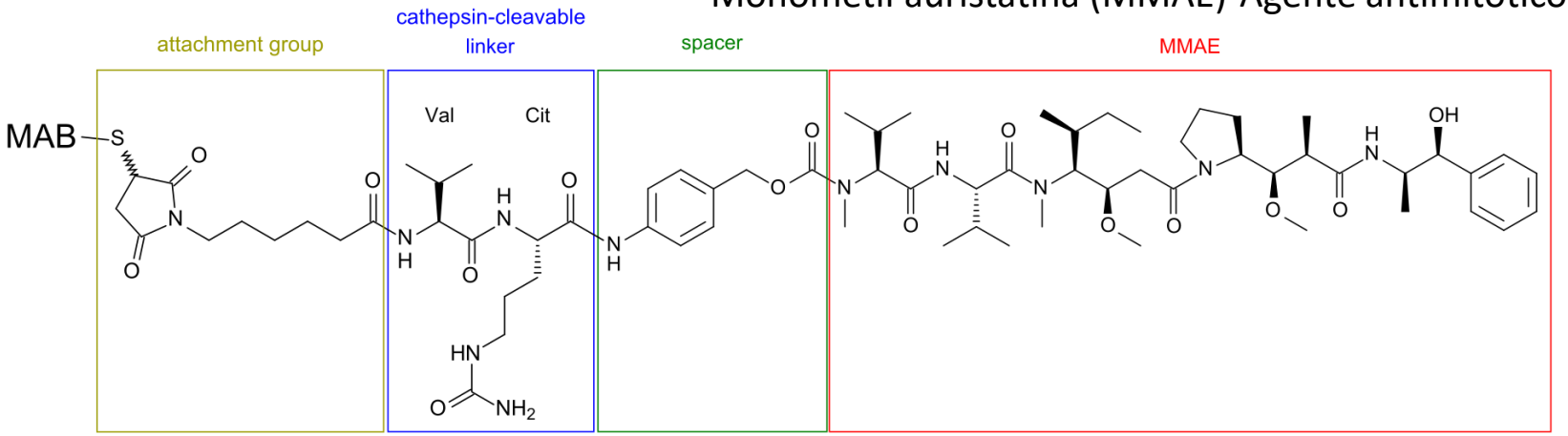
- **Halichondrins y halistatins aisladas de varias especies de esponjas por los grupos de Uemura, Petit y Blunt y Munro**
- ***Lissondendoryx* sp. Rindió 300 mg de halichondrin B e isohomohalichondrin B a partir de 1TM de esponja.**
- **Síntesis total desarrollada por el grupo de Kishi.**
- **Agente antimitótico que interfiere en la formación de microtúbulos**
- **Mesilato de Eribulin aprobado por la FDA para el tratamiento del cáncer de mama refractario en 2010**

ADC (Antibody drug conjugates) de Monometil auristatina (MMAE)

Dolabella auricularia



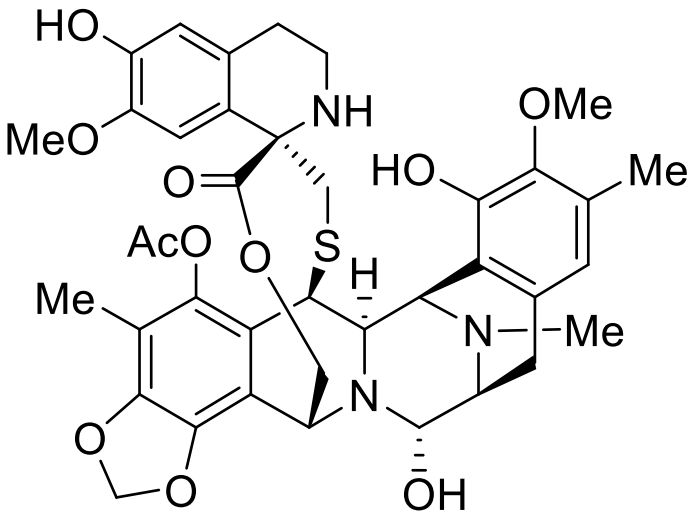
Monometil auristatina (MMAE)-Agente antimitótico



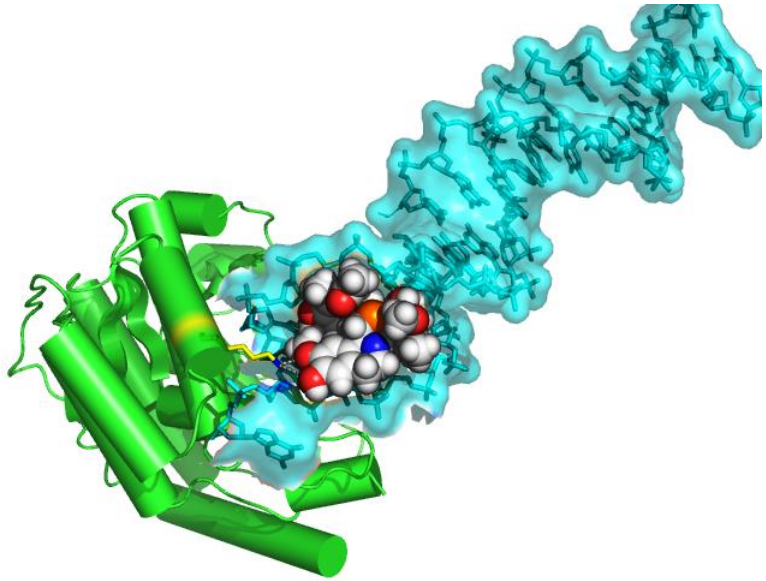
1) **Adcetris® (2011)** directed to CD30, transmembrane receptor expressed in classical hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (sALCL).
2) **Polivy™ (2019)** directed to CD79b, a B-cell specific surface protein, indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma.
3) **PADCEV™ (2019)** directed to Nectin-4, an adhesion protein located on the surface of cells, indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer

Yondelis® (Trabectedin, ET-743)-PharmaMar

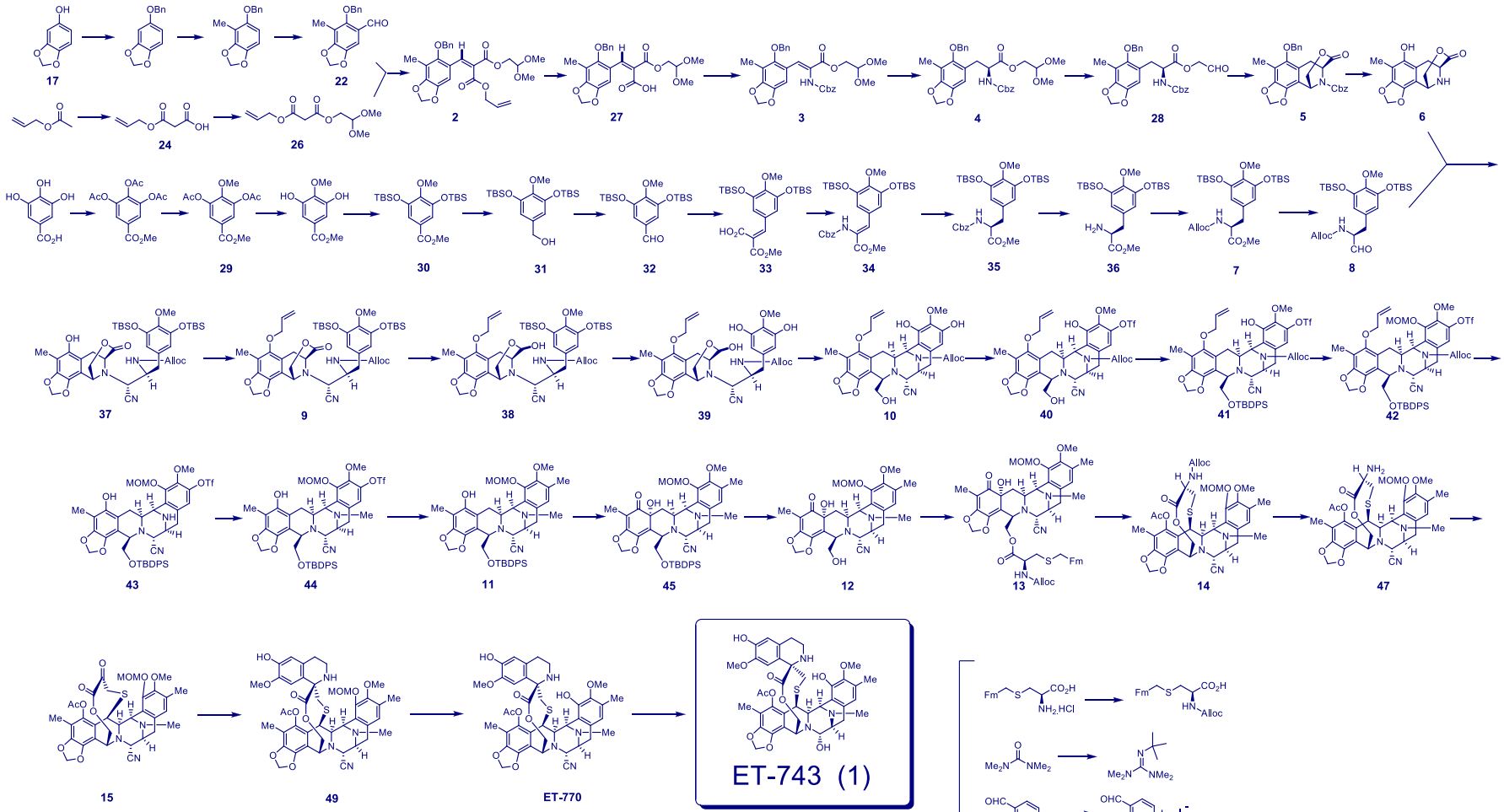
Ecteinascidia turbinata **(tunicado)**



- Múltiple e Innovador Mecanismo de Acción
- Unión al surco menor de DNA
- Inhibidor de ciclo celular en G2/M
- Interacción con mecanismos de reparación de DNA (TC-NER)
- Inhibición de la activación de expresión de genes involucrados en cáncer
- Fuerte inductor de apoptosis

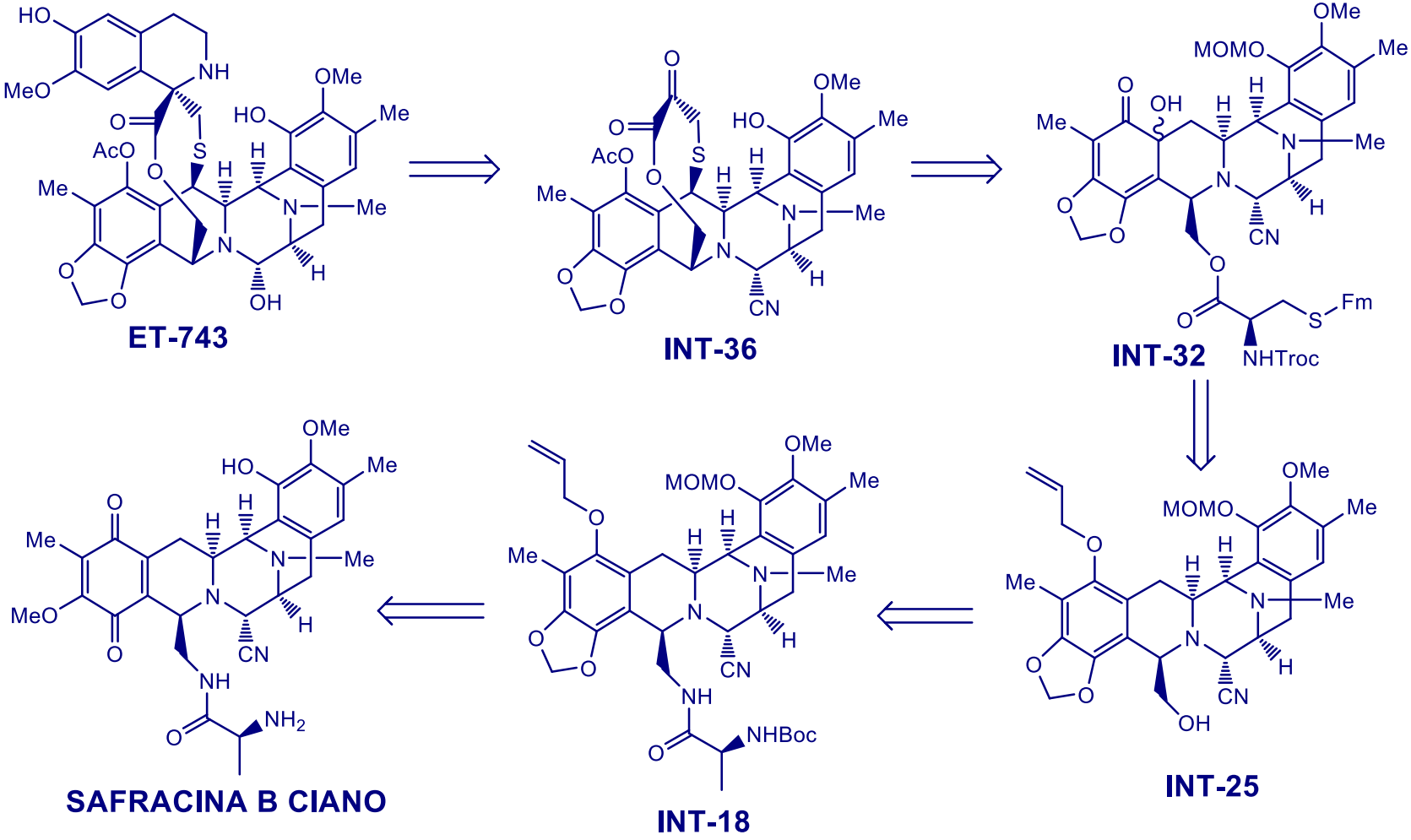


Síntesis total de Yondelis®



Corey et al., *J. Am. Chem. Soc.* **1996**, *118*, 9202.

Semisíntesis de Yondelis®



C. Cuevas et al, *Org Lett*. **2000**, *2*, 2545

Yondelis® (Trabectedin, ET-743)-PharmaMar

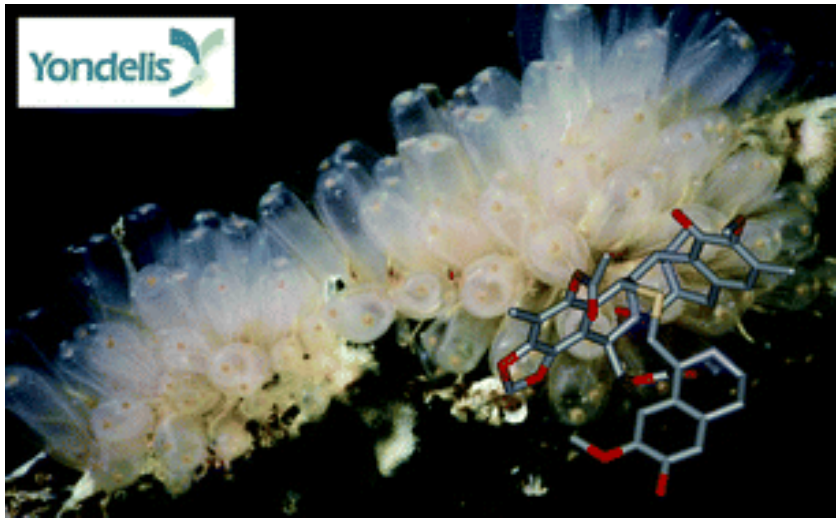
Review

Nat. Prod. Rep., 2009, **26**, 322 - 337, **DOI:** 10.1039/b808331m

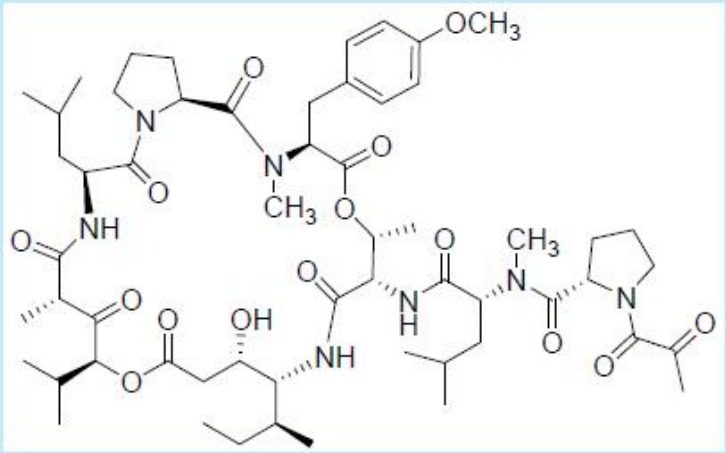
Development of Yondelis® (trabectedin, ET-743). A semisynthetic process solves the supply problem

Carmen Cuevas and Andrés Francesch

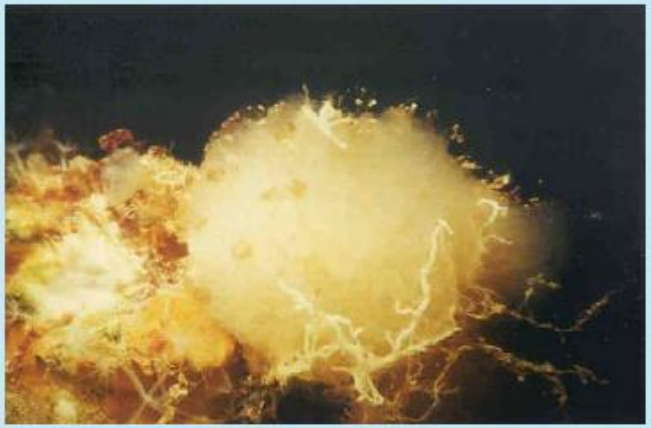
Covering: up to 2008



Aplidin® (Plitidepsin)-PharmaMar



Plitidepsin (depsipeptide)



Aplidium albicans **(**seasquirt)

(Phylum Chordata, Subphylum:Tunicata)

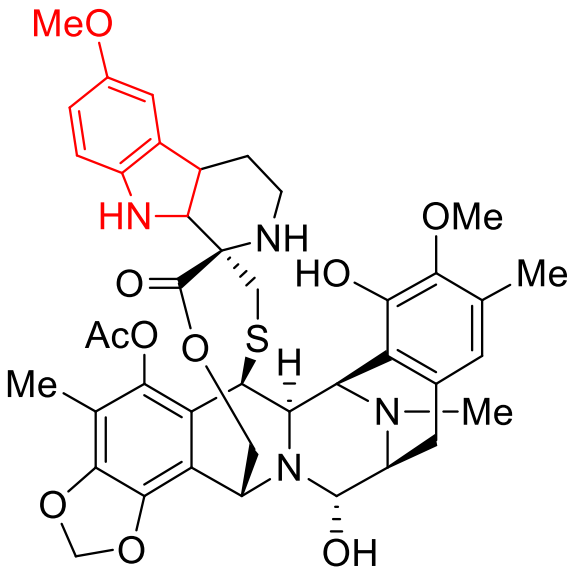
Aprobado en diciembre de 2018 Australia para el tratamiento del mieloma multiple en combinación con dexametasona

En fase II de estudios clínicos frente a SARS-CoV-2

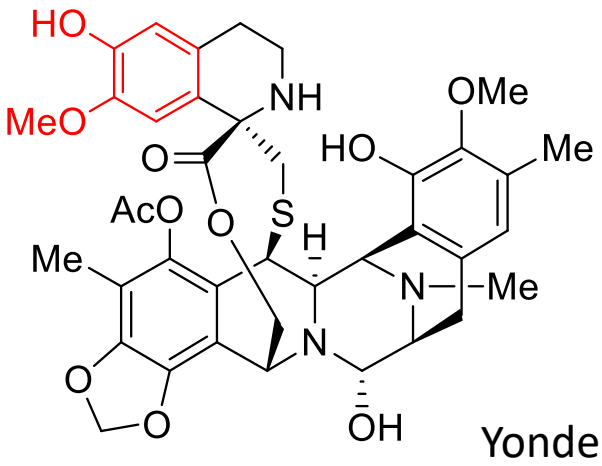
ZEPZELCA™ (Lurbinectedin)-PharmaMar

Ecteinascidia turbinata **(tunicado)**

- Agente alquilante de ADN
- Aprobado de manera acelerada por la FDA para el tratamiento de cáncer microcítico de pulmón



ZEPZELCA™

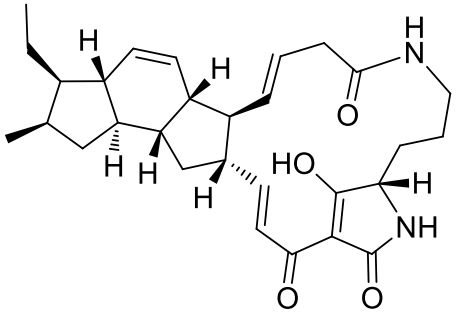


Yondelis®

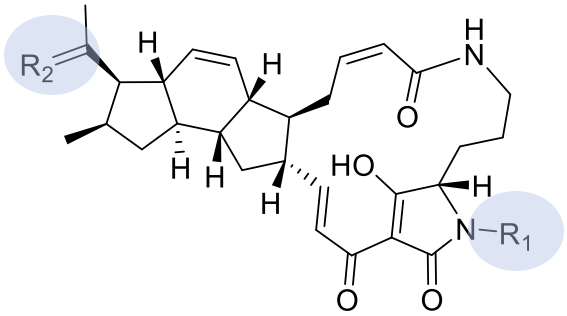
Productos Naturales Marinos Bioactivos en Fundación MEDINA

New ikarugamycins

Streptomyces zhaozhouensis CA-185989



Isoikarugamycin



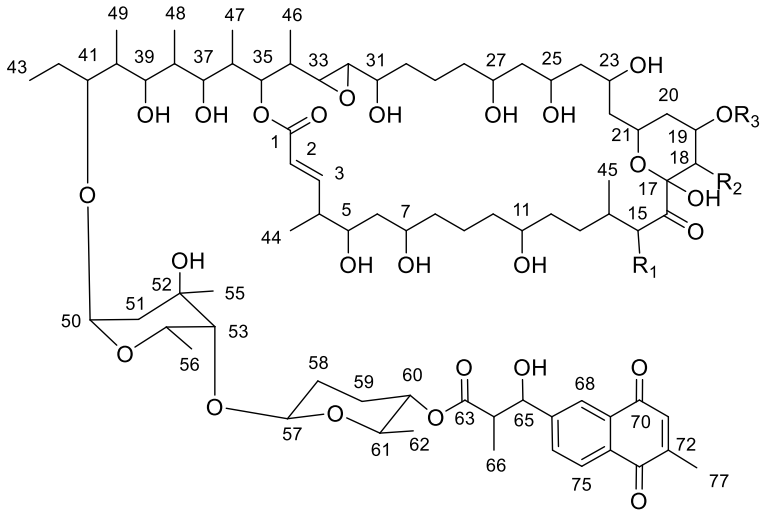
R_1= H R_2=H Ikarugamycin
R_1= CH_3 R_2=H 28-N-methylIkarugamycin New
R_1= CH_3 R_2=O 30-oxo-28-N-methylIkarugamycin New

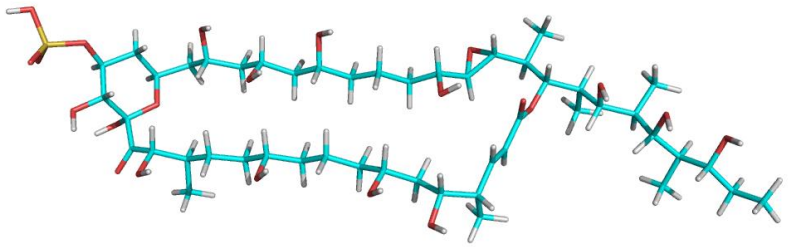
Biological activity	MIC [μg/mL]		
Compound ID	***MRSA***	***C. albicans***	***A. fumigatus***
Isoikarugamycin	2-4	2-4	4-8
Ikarugamycin	2-4	4	4-8
28-N-methylIkarugamycin	1-2	4	4-8
30-oxo-28-N-methylIkarugamycin	32-64	>64	>64

Mar. Drugs, **2015**, *13*, 128-140.

New antifungal macrolides

Streptomyces caniferus **CA-271066**

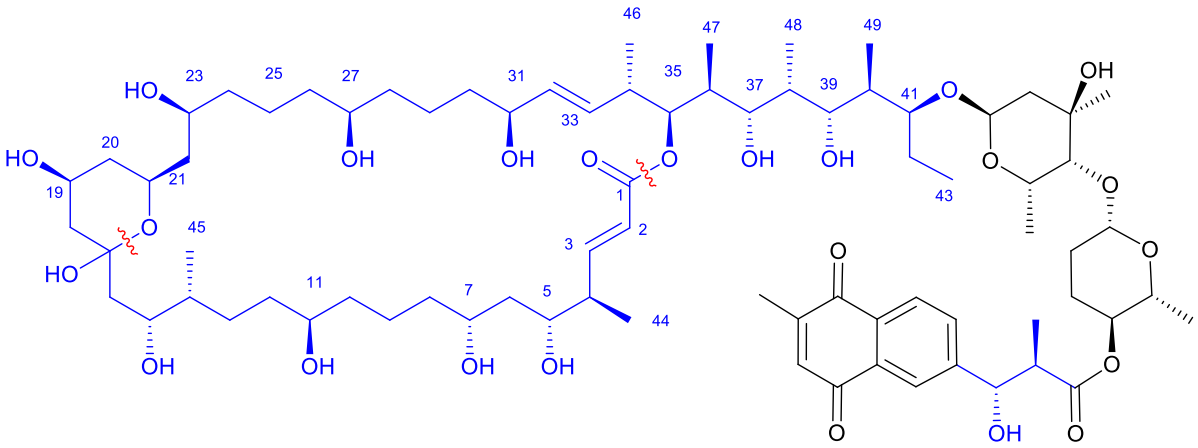




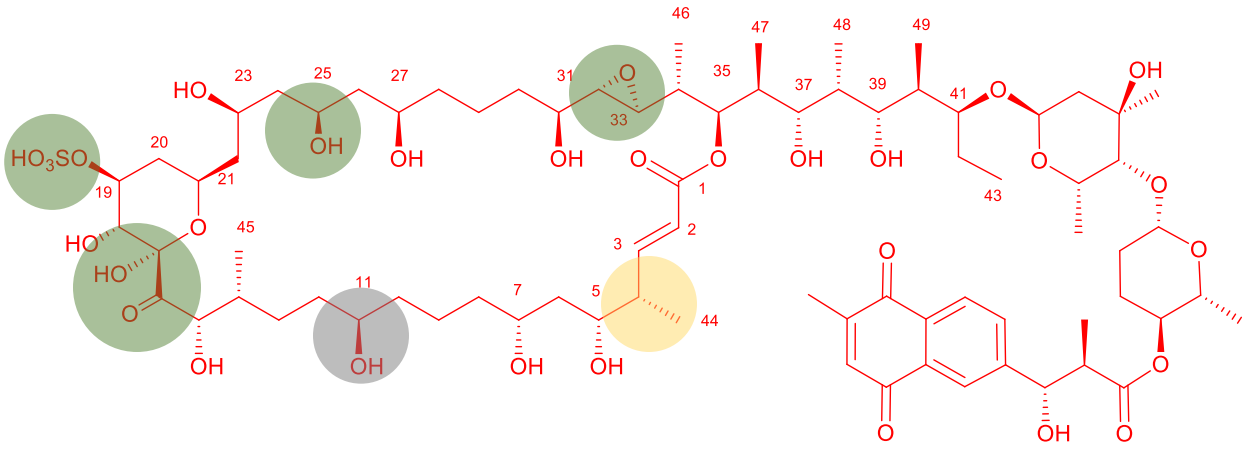
R_1= -OH	R_2= -H	R_3= -H	**Compound 1**
R_1= -OH	R_2= -OH	R_3= -H	**GT-35**
R_1= -H	R_2= -OH	R_3= $-SO_3H$	**Compound 2**
R_1= -OH	R_2= -OH	R_2= $-SO_3H$	**Compound 3**

		MIC values (μg/mL)			
Fungal strains	**Strain number**	**Compound 1**	**Compound 2**	**Compound 3**	**Compound 4**
C. albicans	ATCC64124	0.5-1	2	0.5-1	8
C. tropicalis	ATCC750	0.5-1	2	0.5-1	8
C. glabrata	ATCC90030	0.5-1	2	0.5-1	8
C. krusei	ATCC6258	0.5-1	1	0.5-1	8
C. parapsilosis	ATCC22019	0.5-1	2	0.5-1	16
A. fumigatus	ATCC46645	4	4	4	8

Full absolute configuration of macrolides



Bioinformatic prediction



Bioinformatic + NMR prediction

Post-Tailoring NMR predicted

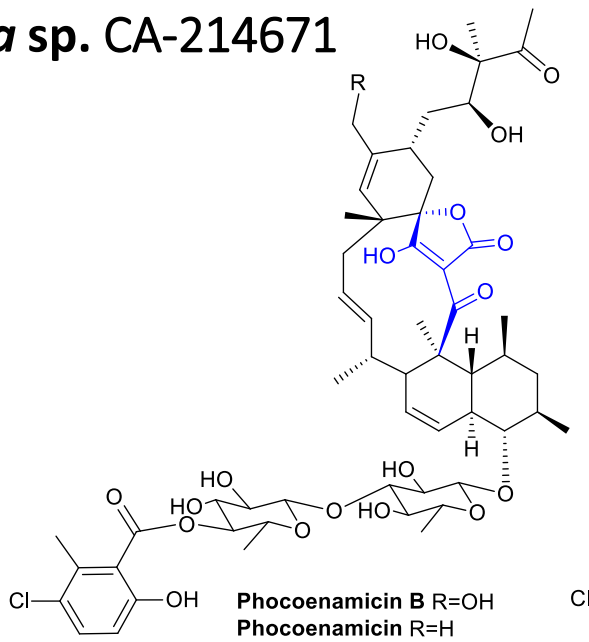
Bioinformatic prediction

DISCREPANCY

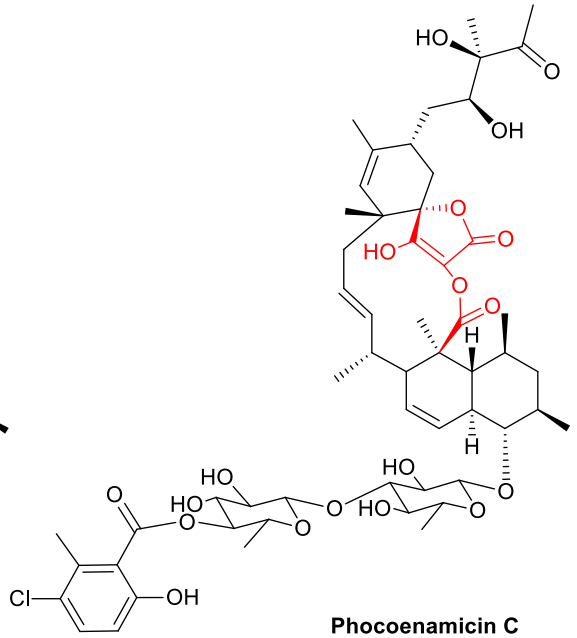
Org. Biomol. Chem., **2019**, *17*, 2954-2971

New spirotetronate derivatives. Phocoenamicins

***Micromonospora* sp.** CA-214671



Phocoenamicin B R=OH
Phocoenamicin R=H



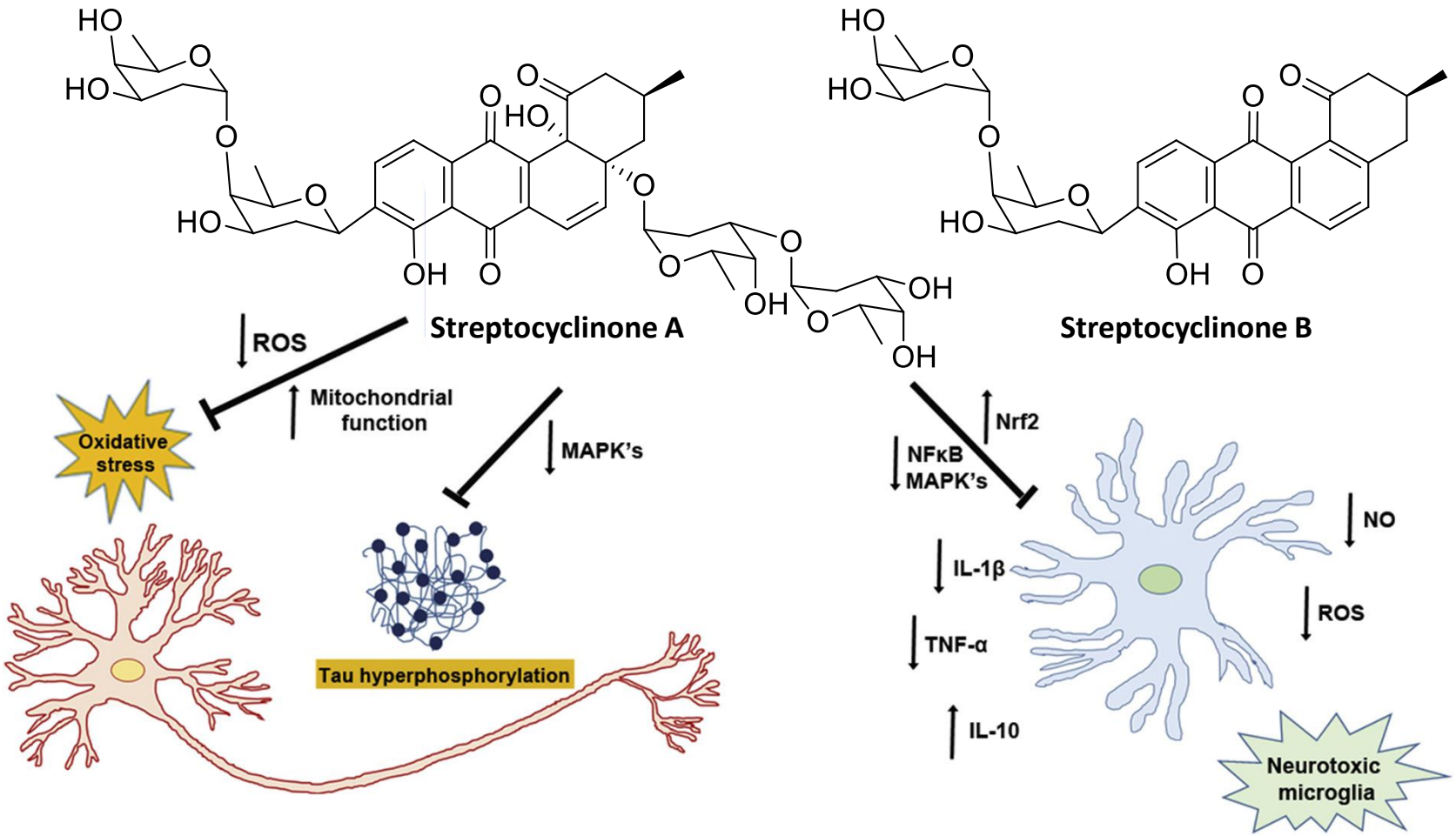
Phocoenamicin C

compounds	MIC (mg/mL)				ZOI* mm(mg)
	S. Aureus MB5393	*M. tuberculosis* ATCC 25177	*M. bovis* ATCC 35734	*E. faecium* MB5571	*B. subtilis* MB964
phocoenamicin B	8-16	>128	>128	>128	7 (2)
phocoenamicin C	32-64	32	>128	>128	7 (4)
phocoenamicin	4-8	16-32	>128	32-64	7 (4)
vancomycin	2-4			>128	
streptomycin		1.6-3.2	0.4-0.8		
gentamicin					8 (0.25)
penicillin G					19 (0.06)

Mar. Drugs, **2018**, *16*, 95.

New C-glycosilated angucycline derivatives

Streptomyces sp. CA-237351



Neuropharmacology, **2018**, *141*, 283-295

Contact: Dr. Fernando Reyes– Head of Chemistry

fernando.reyes@medinaandalucia.es

www.medinadiscovery.com

Gracias