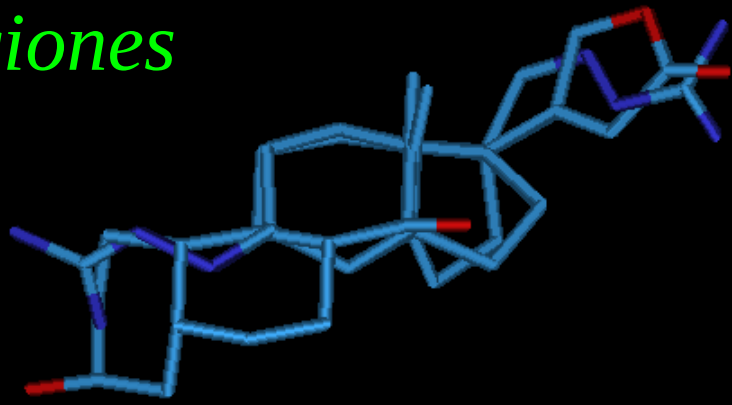
Qf - CIETUS USAL

Grupo DOMOBIO. De Excelencia Científica (JCyL)

Departmento de Química Farmacéutica
Facultad de Farmacia y CIETUS - IBSAL
Universidad de Salamanca (USAL), España

Estructura
Investigación
Colaboraciones



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Dra. Raquel Álvarez. Farmacéutica. Ayudante Doctora

Investigación y Formación en
QF-CIETUS-DOMOBIO -USAL

Áreas de investigación

Fitoquímica, Compuestos Naturales

Quimioinducción y Quimiomodulación de Bioactividad

Diseño, Obtención y Estudio Molecular de Sustancias Bioactivas

Ámbitos terapéuticos:

Quimioterápico:

Cáncer, SIDA, Tuberculosis, Micosis,
Parasitosis: *Plasmodium, Trypanosoma, Leishmania, Schistosoma, Fasciola,...* Vacunas

Farmacodinámico:

CV: Inotrópicos, vasodilatadores, antihipertensores

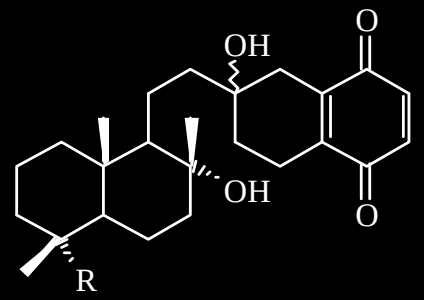
SNC: Ansiolíticos,

Líneas de investigación

A – DISEÑO Y OBTENCIÓN DE AGENTES QUIMIOTERÁPICOS

- Análogos y Heteroanálogos de Lignanos ®
- Combretastatinas. Derivados antineoplásicos y antiparasitarios
- Terpenil-quinonas/hidroquinonas citotóxicas ®
- Compuestos Anti-VIH
- Compuestos Homo- y Heterocíclicos antiparasitarios
- Heterociclos fusionados revertidores de resistencia
- Ciclolignanos derivados de Podofilotoxina y Peltatina ®
- Compuestos Lipídicos antimicobacterianos ®
- Análogos de Productos Marinos

® con patente en ese ámbito



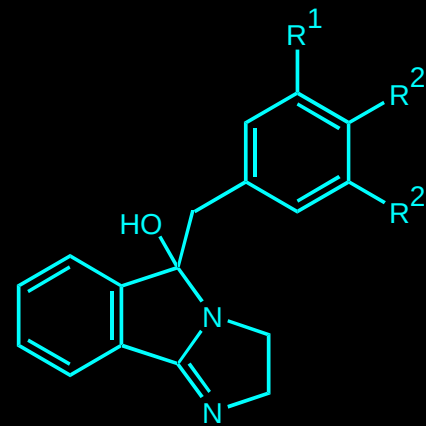
Líneas de investigación

B – DISEÑO Y SINTESIS DE AGENTES FARMACODINAMICOS

- Análogos No-esteroides de Cardenolidas
- Derivados Ciclolignánicos Inmunosupresores ®
- Derivados Lipídicos Antiinflamatorios e Inmunomoduladores
- Sistemas Poliheterocíclicos Vasodilatadores

C – METODOLOGÍAS DE SÍNTESIS ORGÁNICA

- Enaminonas en Síntesis de Compuestos Heterocíclicos
- Sistemas Heterocíclicos Oxigenados
- Aplicaciones de Arilsiloxidienos
- Synthesis de Indazoles e indazoles fusionados



Líneas de investigación

D – AISLAMIENTO Y ESTRUCTURAS DE PRODUCTOS NATURALES

- **Alcaloides y Otros Componentes de Plantas Iberoamericanas**
- **Composición de Plantas Medicinales ®**
- **Composición de Aceites Esenciales**

E – METODOLOGIAS DE DISEÑO Y ESTUDIO MOLECULAR

- **Modelado Molecular**
- **Tutoriales en Farmacoquímica y Nomenclatura.**
- **Bases de Datos Moleculares Interactivas (datos de ^{13}C RMN)**

http:// farmacoquimica.usal.es (Mecanismos de Acción)
http://farmaceutica.usal.es (Nomenclatura de Fármacos)
http://c13.usal.es (Base de datos de RMN-C13 de Comp. nat.)

Articles:

More than 40 peer-reviewed papers in the last 5 years in Medicinal and Organic Chemistry journals, dealing with:

- ***Design, synthesis and evaluation of new bioactive compounds.***
- ***Chemomodulation of bioactive natural compounds***
- ***Study of medicinal plants and new natural compounds.***

Patents:

- ***WO 2008059014 A2 Antituberculosis Agents (lipidic derivatives)***

- ***WO* 2007/010307 A1. *Antineoplastic compounds (lignans)***
  ***GB-0514685.7,* March 07**

Resultados estudios antineoplásicos 1

- ***Eur. J. Med. Chem.*** **58, 377-389,** ***2012***

Lignopurines: A new family of hybrids between cyclolignans and purines.

*Colab.: USAL-**CICáncer***

- ***J. Med. Chem.*** **55, 6724–6737 ,** ***2012***

Synthesis, Antimitotic and Tubulin Interaction Profiles of Novel Pinacol Derivatives of Podophyllotoxins.

*Colab.: USAL-CIB(CSIC)-**PharmaMar***

- ***J. Med. Chem.*** **53, 983–993,** ***2010*****:**

Synthesis and Biological Evaluation of New Podophyllic Aldehyde Derivatives with Cytotoxic and Apoptosis-Inducing Activities.

*Colab.: USAL- **PharmaMar-CICáncer***

- ***Bioorg. Med. Chem.*** **15, 1670-1678,** ***2007:***

Synthesis and cytotoxic evaluation of C-9 oxidized podophyllotoxin derivatives

Colab.:

- ***WO 2007/010307 A1***

Antineoplastic Compounds

Colab.: *USAL-* ***PharmaMar***

2007 - 2012

Resultados estudios antineoplásicos 2

-*Arch. Pharm. Chem. Life Sci.* **342**, 591 – 599, *2009*
Synthesis and Cytotoxic Evaluation of 6-(3-Pyrazolylpropyl) Derivatives of 1,4-Naphthohydroquinone-1,4-diacetate
*Colab: USAL-UCV-**PharmaMar***

*Colab: USAL-UCV-**PharmaMar***
-*Arch. Pharm. Chem. Life Sci. 2008, 341, 301 – 306*
Cytotoxic-Antineoplastic Derivatives of Prenyl-1,2-Naphthohydroquinone
*Colab: USAL-UCV-**PharmaMar***

- *Med Chem Res. DOI 10.1007/s00044-008-9108-1*
Synthesis, characterisation, and antineoplastic cytotoxicity of hybrid naphthohydroquinone–nucleicbase mimic derivatives
*Colab: USAL-UCV-**PharmaMar***

-*Bioorg. Med. Chem.* **15, 5760–5774 2007:**
New cytotoxic diterpenylnaphthohydroquinone derivatives.
*Colab.: USAL-UCV-**PharmaMar***

Resultados estudios antineoplásicos 3
+ otras cooperaciones con grupos de la Red

-*Molecules* **13**, 2915-24, *2008*
A New Cytotoxic Friedelane Acid – Pluricostatic Acid and Other Compounds from the Leaves of *Marila pluricostata*
*Colab: USAL-**UPAN***

- *Nat. Prod. Research*, **21**, 625–631, *2007*
A new coumarin from the fruits of Coutarea hexandra
*Colab: USAL-**UPAN***

- *Tetrahedron Lett.* **52,** 6392-95, *2011:*
Cernumidine and isocernumidine, new type of cyclic guanidine alkaloids from *Solanum cernuum.*
*Colab: USAL-UNISO-UNL-**USEV**-UGR*

Resultados de cooperaciones con grupos de RIBECANCER en otros ámbitos

- *Molecules*, **17**, 9245-9257, *2012*
3-Phenylcoumarins as Inhibitors of HIV-1 Replication
*Colab: USAL-**UPAN**-ISCIII-UCO*

- *Nat. Prod. Research*, 1–4, *2012*
Euglobal-like compounds from the genus *Eugenia*
Colab: USAL-UNIVALI

- *Pharmacological reports*, 62, 849-57, *2010*
New antinociceptive agents related to dihydrosphingosine
Colab: USAL-UNIVALI

- *Phytomedicine*, 15, 520-524, ***2008***
Guatemalan plants extracts as virucides against HIV-1 infection
*Colab: USAL-**USCG-Farmaya**- ISCIII*

European Journal of Medicinal Chemistry 58 (2012) 377–389

Lignopurines: A new family of hybrids between cyclolignans and purines. Synthesis and biological evaluation

Mª Ángeles Castro [a,*], José Mª. Miguel del Corral [a], Pablo A. García [a], Mª Victoria Rojo [a], Ana C. Bento [b], Faustino Mollinedo [b], Andrés M. Francesch [c], Arturo San Feliciano [a]

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[c] PharmaMar S.A. Avda. de los Reyes, P.I. La Mina Norte, E-28770 Colmenar Viejo, Madrid, Spain

ABSTRACT

A new family of hybrids between cyclolignans related to podophyllic aldehyde, a non-lactonic cyclolignan, and purines were prepared and evaluated against several human tumour cell lines. Both fragments, cyclolignan and purine, were linked through aliphatic and aromatic chains. The influence on the cytotoxicity of the purine substitution and the nature of the linker is analyzed. The new family was slightly less cytotoxic than the parent podophyllic aldehyde, although the selectivity is maintained or even improved and among the linkers used, the presence of an aromatic ring gave the most potent and selective derivatives within the new series tested. Cell cycle and confocal studies demonstrate that these derivatives interfere with the tubulin polymerization and arrest cells at the G_2/M phase, in the same way than the parent compounds podophyllotoxin and podophyllic aldehyde do.

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J. Med. Chem. 2012, 55, 6724−6737

Synthesis and Antimitotic and Tubulin Interaction Profiles of Novel Pinacol Derivatives of Podophyllotoxins

Andrés Abad,[†,‡] José L. López-Pérez,[*,†] Esther del Olmo,[†] Luis F. García-Fernández,[§] Andrés Francesch,[§] Chiara Trigili,[∥] Isabel Barasoain,[∥] José M. Andreu,[∥] J. Fernando Díaz,[*,∥] and Arturo San Feliciano[†]

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[§]PharmaMar SA, P. I. La Mina, 28770 Colmenar Viejo, Madrid, Spain

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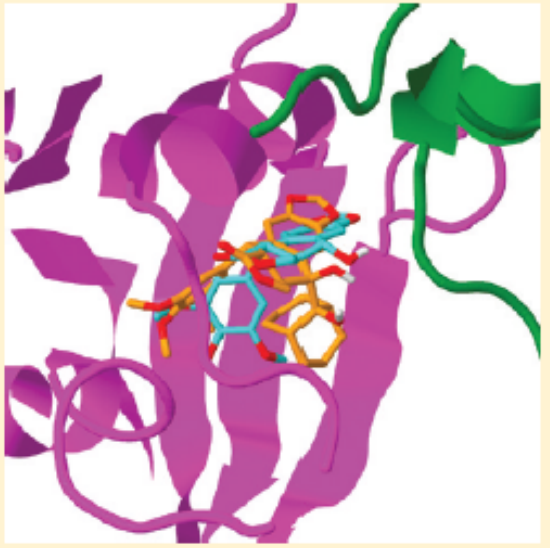
Supporting Information

ABSTRACT: Several pinacol derivatives of podophyllotoxins bearing different side chains and functions at C-7 were synthesized through reductive cross-coupling of podophyllotoxone and several aldehydes and ketones. While possessing a hydroxylated chain at C-7, the compounds retained their respective hydroxyl group with either the 7α (podo) or 7β (epipodo) configuration. Along with pinacols, some C-7 alkylidene and C-7 alkyl derivatives were also prepared. Cytotoxicities against neoplastic cells followed by cell cycle arrest and cellular microtubule disruption were evaluated and mechanistically characterized through tubulin polymerization inhibition and assays of binding to the colchicine site. Compounds of the epipodopinacol (7β-OH) series behaved similarly to podophyllotoxin in all the assays and proved to be the most potent inhibitors. Significantly, 7α-isopropyl-7-deoxypodophyllotoxin (**20**), without any hydroxyl function, appeared as a promising lead compound for a novel type of tubulin polymerization inhibitors. Experimental results were in overall agreement with modeling and docking studies performed on representative compounds of each series.



Qf-CIETUS-DOMOBIO

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25 January 2007 (25.01.2007)

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ANTINEOPLASTIC COMPOUNDS

J. Med. Chem. **2010,** *53,* 983–993

Synthesis and Biological Evaluation of New Podophyllic Aldehyde Derivatives with Cytotoxic and Apoptosis-Inducing Activities

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Received May 27, 2009

Several series of nonlactonic podophyllic aldehyde analogues were prepared and evaluated against several human tumor cell lines. They had different combinations of aldehyde, imine, amine, ester, and amide functions at C-9 and C-9′ of the cyclolignan skeleton. All the compounds synthesized showed cytotoxicity levels in the μM range and below. Within the new series tested, compounds having an aldehyde or imine at C-9 and an ester at C-9′ were the most potent, with GI_{50} values in the nM range, some of them being several times more potent against HT-29 and A-549 carcinoma than against MB-231 melanoma cells. Cell cycle studies and analysis of the microtubule-disrupting capacity have demonstrated the existence of two different mechanisms of cell death induction for compounds with closely related structures.

Arch. Pharm. Chem. Life Sci. 2009, *342*, 591–599

Synthesis and Cytotoxic Evaluation of 6-(3-Pyrazolylpropyl) Derivatives of 1,4-Naphthohydroquinone-1,4-diacetate

Aurora Molinari[1], Alfonso Oliva[1], Claudia Ojeda[1], José M. Miguel del Corral[2], M. Angeles Castro[2], Carmen Cuevas[3], and Arturo San Feliciano[2]

[1] Instituto de Química, Pontificia Universidad Católica de Valparaíso, Valparaiso, Chile
[2] Depto de Química Farmacéutica, Facultad de Farmacia, Universidad de Salamanca, Salamanca, España
[3] Pharma Mar S. A., Madrid, España

Several new 6-(3-pyrazolylpropyl) derivatives of 1,4-naphthohydroquinone-1,4-diacetate (NHQ-DA) have been prepared by chemical modifications of the Diels–Alder adduct of α-myrcene and 1,4-benzoquinone. All these new compounds and precursors have been evaluated *in vitro* for their cytotoxicity against cultured human cancer cells of MB-231 breast-adeno carcinoma, A-549 lung carcinoma, and HT-29 colon carcinoma. GI_{50} values ranged in and below the micromolar concentration level.

Keywords: Antineoplastic cytotoxicity / α-Myrcene / 1,4-Naphthohydroquinone / Pyrazole

Med Chem Res
DOI 10.1007/s00044-008-9108-1

Synthesis, characterisation, and antineoplastic cytotoxicity of hybrid naphthohydroquinone–nucleic base mimic derivatives

Aurora Molinari · Claudia Ojeda · Alfonso Oliva · José M. Miguel del Corral · M. Angeles Castro · Pablo A. García · Carmen Cuevas · Arturo San Feliciano

Abstract From a partially degraded Diels–Alder adduct of α-myrcene and 1,4-benzoquinone, several model compounds belonging to a new series of 1,4-naphthohydroquinone derivatives have been prepared. Phenyl, pyridyl, imidazolyl and some nucleic base mimic heterocycles have been attached to the naphthohydroquinone system through linkers of different size and type, leading to potentially antineoplastic hybrid structures. The new compounds have been evaluated in vitro for their cytotoxicity against cultured human cancer cells of A-549 lung carcinoma, HT-29 colon adenocarcinoma and MDA-MB-231 breast carcinoma. GI_{50} values ranged in the μM level.

Keywords Naphthohydroquinone · Hybrid structures · Antineoplastic cytotoxicity

Arch. Pharm. Chem. Life Sci. 2008, *341*, 301 – 306

Cytotoxic-Antineoplastic Derivatives of Prenyl-1,2-naphthohydroquinone

Aurora Molinari[1], Alfonso Oliva[1], Claudia Ojeda[1], José M. Miguel del Corral[2], M. Angeles Castro[2], Carmen Cuevas[3] and Arturo San Feliciano[2]

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Several new prenyl-1,2-naphthohydroquinone derivatives have been prepared by chemical modifications of Diels–Alder products which were obtained from cycloaddition of α-myrcene to 1,2-benzoquinone and then evaluated *in vitro* for their cytotoxic activity against A-549 lung carcinoma, HT-29 colon carcinoma, and MB-231 breast adeno-carcinoma culture cells. Most of them exhibited GI_{50} values in the μM-concentration level.

Keywords: Antineoplastic cytotoxicity / 1,2-Benzoquinone / α-Myrcene / Naphthohydroquinone

Bioorganic & Medicinal Chemistry 15 (2007) 5760–5774

New cytotoxic diterpenylnaphthohydroquinone derivatives obtained from a natural diterpenoid

José M. Miguel del Corral,[a,*] M. Angeles Castro,[a] M. Lucena Rodríguez,[a] Pablo Chamorro,[a] Carmen Cuevas[b] and Arturo San Feliciano[a]

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[b]*PharmaMar S.A., Avda. de los Reyes, 1 P.I. La Mina-Norte, 28770 Colmenar Viejo, Madrid, Spain*

Abstract—Diterpenylquinone/hydroquinone derivatives were prepared through Diels–Alder cycloaddition between natural myrcecommunic acid or its methyl ester and *p*-benzoquinone (*p*-BQ), using $BF_3{\cdot}Et_2O$ as catalyst or under microwave (Mw) irradiation. Acetyl, methyl and benzyl derivatives of several diterpenylnaphthohydroquinone were prepared from cycloadducts following two basic synthetic strategies, either protection before aromatisation or viceversa. Some of them were further functionalised at the B-ring of the decaline core. Most of the new compounds were evaluated and some of them resulted cytotoxic against several tumour cell lines with IC_{50} values under the μM level.
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Molecules **2008**, *13*, 2915-2924;

A New Cytotoxic Friedelane Acid – Pluricostatic Acid – and Other Compounds from the Leaves of *Marila pluricostata*

Dionisio A. Olmedo [1], José L. López-Pérez [2], Esther del Olmo [2], Yelkaira Vásquez [1], Arturo San Feliciano [2] and Mahabir P. Gupta [1,*]

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[2] Departamento de Química Farmacéutica, Facultad de Farmacia, CIETUS, Universidad de Salamanca, Campus Miguel de Unamuno, E-37007, Salamanca, España. E-mails: lopez@usal.es (J-L. L-P.), olmo@usal.es (E. O.), asf@usal.es (A-S. F.)

Abstract: Bioassay-guided fractionation of the dichloromethane extract of the leaves of *Marila pluricostata* led to the isolation of 2α,3β-dihydroxy-D:A-friedoolean-28-oic acid (pluricostatic acid), a new friedelane triterpenoid, (**1**), ten known triterpenoids and three sterols. Their chemical structures were elucidated through spectroscopic analysis. The less polar fractions, on GC/MS analysis and comparison with a MS library, resulted in the identification of twenty four sesquiterpenoids. The new triterpenoid acid **1** showed cytotoxicity against the MCF-7, H-460, and SF-268 human cancer cell lines with GI_{50} values from 1.2 to 3.3 μg/mL.

Keywords: *Marila pluricostata*; Clusiaceae; Triterpenoids; Cytotoxicity; 2α,3β-dihydroxy-D:A-friedoolean-28-oic acid.

Resultados Recientes

Cernumidine and isocernumidine, new type of cyclic guanidine alkaloids from *Solanum cernuum*

Tetrahedron Letters 52 (2011) 6392–6395

Luciane C. Lopes [a], Bianca Roman [a], Maria A. Medeiros [b], Abhik Mukhopadhyay [c], Pilar Utrilla [d], Julio Gálvez [d], Sofía García Mauriño [e], Virginia Moltiva [f], Ana Lourenço [c,*], Arturo San Feliciano [g]

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A B S T R A C T

Cernumidine and isocernumidine were identified in the ethanol extract of the leaves of *Solanum cernuum* Vell. together with four known phenolic compounds. The alkaloids have a natural (2-aminopyrrolidin-1-yl)carboxamidine alkaloidal base acylated with isofenulic (3-hydroxy-4-methoxycinnamic) acid with *Z* and *E* configurations, respectively. The structures were elucidated on the basis of 1D- and 2D-NMR data and the structure of cernumidine was confirmed by X-ray analysis. Cernumidine displayed inhibition of interleukin-8 production by HT-29 colon carcinoma cells. This fact could orient further research in gastric cancer prevention and treatment.

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A new coumarin from the fruits of *Coutarea hexandra*

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A new 5-*O*-*β*-D-glucopyranosyl-4-(4-hydroxyphenyl)-7-methoxy-2*H*-chromen-2-one (1), together with four known compounds, one coumarin, 5-*O*-*β*-D-galactopyranosyl-4-(4-hydroxyphenyl)-7-methoxy-2*H*-chromen-2-one (2) and three cucurbitacins, 23,24-dihydrocucurbitacin F (3), 23,24-dihydro-25-acetylcucurbitacin F (4) and 2-*O*-*β*-D-glucopyranosyl-23,24-dihydrocucurbitacin F (5) have been isolated and characterised from the ethanol extract of *Coutarea hexandra* fruits. Their structures have been established by spectroscopic analysis (NMR and MS). Interpretation of the HMQC, HMBC, COSY-45 and NOESY experiments permitted us to establish stereochemistry of the natural products. All compounds were tested in cytotoxicity assays against the breast (MCF-7), lung (H-460), and central nervous system (SF-268) human cancer cell lines.

Keywords: Coumarins; Cucurbitacins; Triterpenoids; Cytotoxicity; Coutarea hexandra; Rubiaceae

TABLA RESUMEN. COOPERACIÓN Grupo DOMOBIO. Q. Farmacéutica.

1. Cooperación Internacional: Redes, Proyectos y Grupos

Resultados (leyenda): As (artículo/s), R (Review), CL (capítulo en libro), E (co-edición), Bd (base datos), C (convenio), IT (informe técnico), D (tesis doctoral), G (tesis de Grado/Maestría), Ps (Pasantias), Cs (Cursos, Talleres, Jornadas), Cf (conferencia), Ases (asesoría)

PAIS	Institución	Coordinador	Tema	Result.
Alem.	Heinrich-Heine-Univ. Dusseld Philipps-Uni v. Marburg	**WA Alfermann** **M Petersen**	Biotecnología de lignanos BIO4-CT98-0461	As
Argent.	U. Nac. Rosario U. Nac. San Luis U. Buenos Aires U. La Plata	**Susana Zacchino** **Daniel Enriz** **Mª Inés Ibarra** **Alicia Seldes, G. Cabrera** **G.Burton** **S. Debenedetti**	Antifúngicos. Cal. molecular Síntesis Heterocicl. Colab. Manual RMN Colab. Manual RMN	As Ps, As Cs, Cf, CL 3 Cf
Arg + 12 países	CYTED-Proy. Iberoam. X.7	**Susana Zacchino**	Antifúngicos	
Bolivia	U. Mayor San Andrés. IIFB UMSA-Inst. de Química	**Alberto Giménez** **Giovanna Almanza *Bolivia*** **José A. Bravo**	Antiparasit / libros Colab. Manual RMN Colab. Manual RMN	As CL E CL CL
Bolivia + 9 países	CYTED-Proy. Iberoam. X.5	**Alberto Giménez**	Antiparasitarios	L, Cl, As Cs, Cf

Brasil	U. Bandeirantes. SP (CIBEP)	**Sergio Mendonça**	Helicobacter	
	U. Campinas (grupo CIBEP)	**Joao E. Carvalho**	Cancer-inflamación	
	U. Fed. Minas Gerais.UFMG	**Alaide Braga** **Ydia M. Valadares** **Fernao Castro**	Quinonas Formación Investig. Colab. Manual RMN	As, 2D CL
	U. Fed Santa Catarina. UFSC	**Rosendo Yunes** **Louise D. Chiaradia**	Colab. Libro Farmac. Formación Investig.	1D CL
	U. Est. Bahia	**Simone Gualberto** **Ronan Batista**	Quinonas Bioactivas Formación Investig. Terpenoides	As 2D As, R
	U. Sorocaba (grupo CIBEP)	**Luciane C. Lopes** **Yoko Oshima**	Formación investig. Colab. Libro Antivenenos, Fitoquim.	Cfs CL Ps
	U. Metod. Piracicaba	**Luiz M. Franco**	Antivenenos, Fitoquim.	Ps
	U. Reg. Blumenau	**Angela Malheiros**	Colab. Manual, libro	CL 2
	UNIVALI. Itajaí	**Valdir Cechinel**	Formac. Investig. Fitoquim. Antiinflam. Colab. Libro Farmac.	Cs As CL 2
Brasil + 12 países	CYTED-284-RIBIOFAR	**Valdir Cechinel**	Pro. Nat. Bioactivos Formac. Fitoquim.	Bd, As Cs, Cf Bd

Chile	U de Chile, Fac. Ciencias	Orlando Muñoz	Fitoquímica Colab. Libro	A CL
	U de Chile, Fac. Medicina	Antonio Morello Sergio Mora	Anti paras. Chagas	As Cfs
	U de Chile, Fac. C. Quím. Farm.	Nadine Backhouse Ramiro Araya Claudio Sáitz	Fitoquím. Antiinflam. Colab. Manual RMN Colab. Manual RMN	As CL CL
	U. Católica. Valparaíso	Alfonso Oliva Aurora Molinari Claudia Ojeda	Quinonas bioactivas Formación Investig.	As, Cf Ps 3
	U. Tec. Federico Sta. María	Juan Garbarino	Fitoquímica	A, Cf
	U. Antofagasta	Hernán Sagua	Antiparas. Chagas Formac. Investig.	Ps 1
	U. Católica del Norte	Gabino Garrido	Formación Investig.	Cs
Colomb.	U. Nac. Col. Bogotá	Roberto Pinzón Mario Guerrero	fitoquímica Formac. Investig. Fitoquímica	Cs Ps 3 As D
	U. de Antioquia	Liliana Betancurt Ana C. Mesa	Antineoplásicos, antifúngicos	As
	Pont. U. Javeriana	Juan C. Martínez	Colab. Manual RMN	E CL3
	U. Santa Marta	Juan Dib	Antiparasitarios	

C. Rica	U. de C Rica, CIPRONA	**Alice L. Pérez**	Quinonas bioactivas Colab. Manual RMN	E CL2
Cuba	U. La Habana Inst. Pedro Kourí	**Lourdes Morán** **Carlos Pérez** **Ernesto Montoro**	Síntesis Orgánica Colab. Manual RMN Antituberculosis	As Cs Ps E CL2
Ecuador	U. Guayaquil	**Patricia Ramos**	Plantas Medicinales	Ases
El Salv.	U. de El Salvador	**Salvador Castillo**	Formac. Investig.	Cs
Esp (2) **Port.Ita,** **Pan,Chi,** **Bra Col**	ALFA-RELAPLAMED Red EU-AL de Plantas Medicinales	**A San Feliciano** **E del Olmo**	Formación Investig.	As 9D 1G
Esp + **20 Países**	CYTED - Red Iberoam. X.A de Productos Naturales de uso medicinal. >200 grupos de 21 países	**Olga Lock** **A. San Feliciano** **R. Pinzón**	Prod Nat. Medicinales Formac. Investig.	As Cs Cfs
Esp + **12 países**	CYTED- Red Iberoam. X.D de Productos Marinos	**Agustín Pérez-Aranda**	Prod. Marinos. Bioact. antineoplásicos	As
Esp + **14 países**	CYTED-Red Iberoam. X.F de Determ. Estructural	**Angel G. Ravelo**	Determ. Estructural Formac. Investig.	As Cs
Esp + **15 países** **Esp +** **9 países** **Esp +** **11 países**	CYTED-Proy. Iberoam. X.6 CYTED-Proy. Iber. X.10 CYTED-Proy. Iber. X.11	**Mª José Alcaraz** **Mª José Martín Calero** **Esther del Olmo**	Antiinflamatorios Formac. Investig. Gastrointestinales Antituberculosos	As Ps 2 CL 2 L, E, CL
Guatem.	U. San Carlos, FARMAYA	**Óscar Cóbar** **Armando Cáceres**	Colab. Manual RMN Anti VIH naturales	CL A

Holanda	Univ. Groningen	N Pras	Biotecnología de lignanos BIO4-CT98-0461	As
Italia	U. d. Studi Genova	Luisa Mosti	Formación investig	Ps 3
	U. d. Studi Salerno U. d. Studi Catania	Tina de Tomassi Corrado Tringali	PostGrado PostGrado	Cs Cf
México	C. Inv.Biomed.Sur-IMSS	Jaime Tortoriello	Ansiolíticos Formac. Investig.	As Ps 1
	C.Inv.Biomed.Noreste-IMSS	Salvador Said	Antituberculosos Formación	C Patent2 L, E, Cfs
	Inst. Nac. C. Med. y Nutric	Rogelio Hernández-Pando	Antituberculosos	C Patent2
	U. Baja Calif. Sur	Rosalba Encarnación	Formac. Investig.	Cs
Panamá	U. Panamá	Mahabir P. Gupta	Fitoquím. Antineoplas. Formación Investig. Colab. Manual RMN	As, G2, Ps D2, Cs 3, CL
Parag.	U. Nac. Asunción I Invest. Ciencias de la Salud	Esteban Ferro Antonieta Rojas	Formación Investig. Anti parasitarios	Cs As
Perú	Pontif. U. Católica del Perú	Olga Lock / Ana Pastor	Fitoquím., Formación	Cs 3
	U.Priv. Antenor Orrego	Marlon García-Armas	Fitoquím., Síntesis	As, D2
	U.Nac. Trujillo	Zoila Honores Mario Alva	Formación Síntesis Síntesis heterocicl.	As D As
	U Nac S. Luis Gonzaga, Ica	Haydeé Chávez	Colab. Manual RMN	CL
	U.Nac Amazon. Peru. Iquitos	Lastenia Ruiz	Determ. Estruct.	Cs

Perú	U.Nac Mayor S Marcos. Lima	Pablo Bonilla	Formación Investig.	Cs
	U. S. Martín de Porres. Lima	Lucy Ibáñez	Formación investig.	Ps 2, Cs
	U. San Antonio Abad, Cuzco	Emma Urrunaga	Formación investig	Cs 2, Cf
	U. Alas Peruanas	Fernanda Gallegos	Formación investig	Cs
Portug.	U. Lisboa	Pilar Rauter	Fitoquímica	A
	U. Nova de Lisboa (CIBEP)	Ana M. Lourenço	Fitoquím./ Síntesis Colabor. libro	CL
UK	De Montfort University	RRJ Arroo/ JG Woolley	Biotecnología de lignanos BIO4-CT98-0461	As
Urug.	U. de la República	Eduardo Manta	Colab. Manual RMN	CL
Venez.	U Central Ven. U. Los Andes, Fac. Ciencias U. de Los Andes Fac. Farmac. U. Simón Bolívar	Nelson Ferrigni Balbina Noguera R. Compagnone Trina Colman Andres Abad Carmelo Rosquete Gina Meccia Fernando Simón	Formacion Investig. PNAt, antiinflamat. Colab. Manual RMN Colab. Manual RMN Fitoquimica, síntesis, Antineoplásicos Prod. Naturales Aceit esenciales Formac. Investig. Formac. Investig.	Cs Ps 2, As CL CL D, As, Patent2 D, As As Cs 2, Ps 4 D
TOTAL	72	**96**		

2 Cooperación Nacional con Instituciones y Empresas

Institución/Empresa	Responsable Grupo	Tema	Pub/Patent
Comp. Esp. de Esteroides	Joaquin Solís	Síntesis esteroides	Patent
CSIC Inst.Paras.Bioq.L.Neira	Dolores González Miguel Navarro Francisco Gamarro	Antiplasmodio Mal del Sueño Reversion MDR	
CSIC C. Cien. Medioambient.	Azucena González	Fagorrepelentes	As
GSK	Domingo Gargallo	Agentes antituberculosos	
Inst. BIOMAR SA	Agustín Pérez-Aranda	Antineoplásicos antiangiogénicos	C
ISCIII-Microbiología Majadahonda	José Alcamí	Anti-VIH	As
Lab. Dr. Andreu. Barcelona	JL Bada	antihipertensores	LRU
Lab. FAES FARMA. Lejona	Aurelio Orjales	Antidepresivos	LOU
Lab. Madaus. Barcelona	J. Quintana, José Poch	Plantas Medicinales	LRU. Patent
PharmaMar SA. Tres Cantos.	Carmen Cuevas	antineoplásicos	As Patent 5 C, PETRI
FERRER INTERNAC.	Domingo Gargallo	Antituberculosis	
RICET. Red Nacional de Investigación en Enfermedades Tropicales	Agustín Benito,	Antipalúdicos, Antileismaniásicos Anti-Chagas, Sueño	
RIS. Red Nacional de Investigación en SIDA	J. Alcami	Anti VIH	As

U. Alicante	**M. Yus**	Formac. Investig.	Cs
U. Aut. Barcelona **U. Barcelona**	**Francisco Sánchz-Ferrando** **Lluisa Bennasar**	Estructuras PNat/Sínt. Determ. Estructural	As
U. Complutense Madrid	**Antonio R. Martínez**	Vacunas antiparasit Anti paludicos	As
U. Córdoba	**Eduardo Muñoz** **J. Mª Marinas**	Antivir. VIH Apoptosis Formac. Investig.	As Cs
U. Granada	**Alejandro F. Barrero**	Determ. Estructural Formac. Investig.	As 1
U. La Coruña	**Carlos Jiménez**	Colab. Manual RMN	E, CL2
U. La Laguna, IUBO	**Angel G. Ravelo**	Terpenoides Determ. Estruct. Colab Manual RMN	As, Cs 3 E CL3
USC. Campus Santiago **Campus Lugo**	**L. Castedo** **P. Morrondo**	Formac. Investig Vacunas antiparasit.	Cs As
U. Oviedo	**J. Barluenga**	Espec. Masas Determ. Estruct	As As, Cs
U. País Vasco, San Sebastián **Lejona**	**Miguel Valero** **Isaa Katime**	Formac. Investig. polimeros	Cs
U. Sevilla	**MªJ. Martín Calero** **Mª Jesús Ayuso** **Virginia Motilva (CIBEP)**	Colab. Libro Antineoplásicos Inflam-cáncer	CL A Cs Posgrado 2

U. Valencia	**R Mestre** **Miguel Payá, M.J.Alcaraz** **Jorge Gálvez** **Santos Fustero**	Formac. Investig. Inh. Fosfolip. Antiinfl. Diseño antipalúdicos Determ. Estructuras	Cs As A
U. Valladolid	**Álfonso Glez. Ortega**	Formac. Investig.	Cs, Cfs

3 Cooperación Institucional

Depto/Centro	**Investigador responsable**	**Tema**	**Public**
Cent. Investig. Cáncer	Faustino Mollinedo	antineoplásicos	As
Cent. Investig. Enferm. Tropic. CIETUS.	Antonio Muro	Antiparasitarios y vacunas	As
CSIC. IRNA-Salamanca		Vacunas antiparas.	
Fisiología y Farmacología	Luis San Román	Cardiovasculares Antiprostáticos Prod. Nat	As, Patent As
Q. Orgánica, Ciencias	Julio G. Urones Anna Lithgow J. Rodríguez	Determ. Estructural Colab. Manual RMN Determ. Estructural	As, CL A
Microbiología, Biología	Angel Domínguez	Antifúngicos	
Informática, Ciencias	R Therón	Manual Det. Estruct.	CL

TOTAL	**108 Entidades**	**141 Grupos**

Oferta y Demanda en RIBIOCANCER

Química Estructural y de Modificación Molecular para:

- **modular actividad y perfil fármaco-terapéutico**
- **corregir toxicidad o efectos secundarios**
- **inducir actividad genérica o específica**

- **diseño y cálculo molecular**
- **determinación estructural**

Bioensayos y caracterización de Bioactividad

- **genéricos y/o sobre dianas específicas**
- **establecimiento de mecanismos de acción**