Farmacología y Farmacoterapia I

Grado en Farmacia - UAH

Tema 10 (curso 2021-2022)

Estrategias generales empleadas en la identificación, diseño y descubrimiento de fármacos y profármacos.

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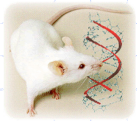
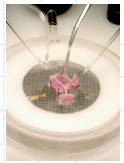
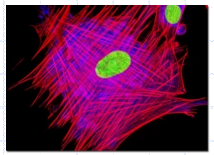
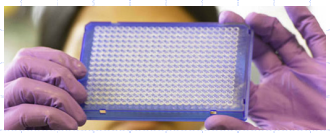
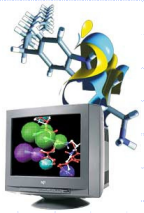
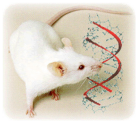
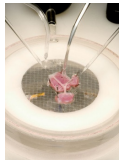
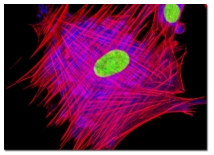
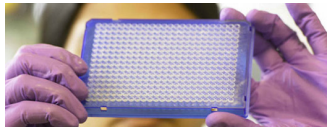
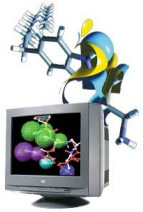
Evolución de la Medicina y la Farmacia

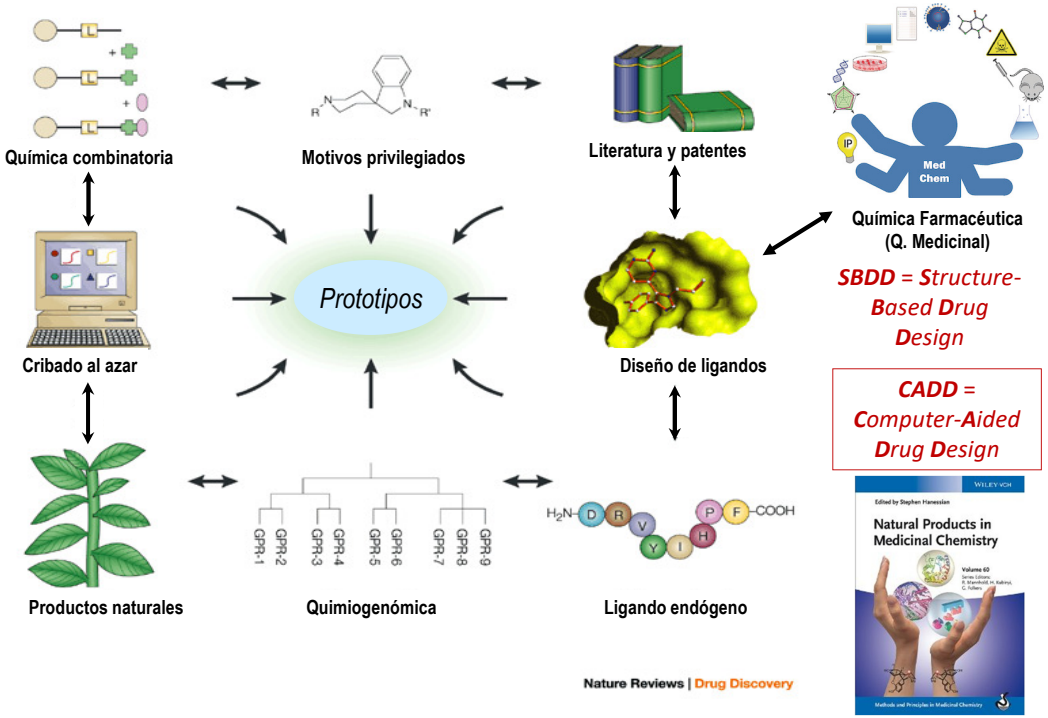
Magia	→	Ciencia
Superstición	→	Experimentación
Milagro	→	Descubrimiento
Revelación	→	Exploración

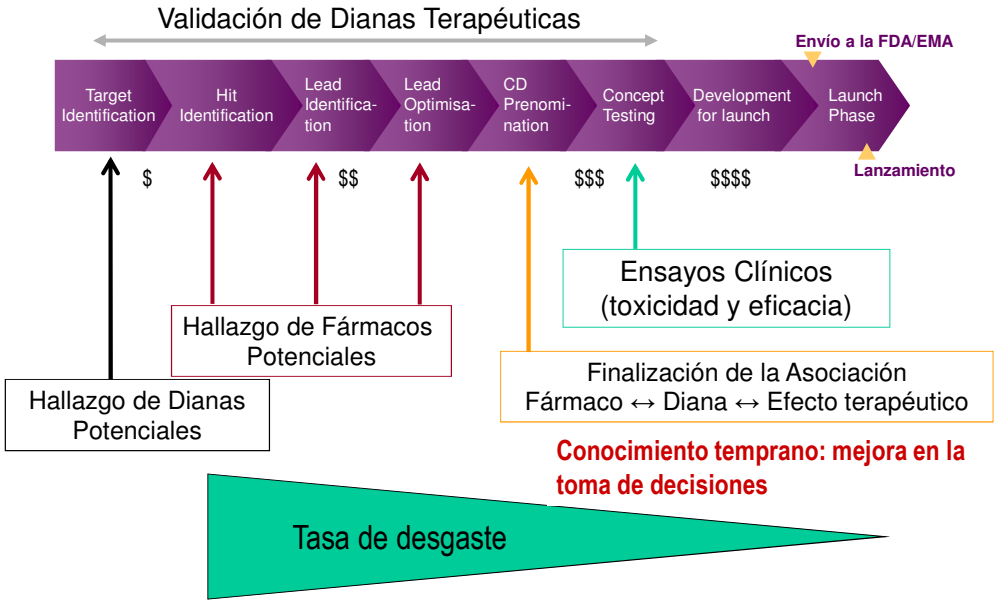
Desarrollo de la Investigación en Nuevos Fármacos (recuerdo del tema 4)

Tiempo	Materiales	Sistemas de ensayo
- antigüedad	plantas, venenos, minerales...	seres humanos
- 1806	morfina	
- 1850	sustancias químicas	
- 1890	productos sintéticos, colorantes	animales
- 1920		animales, órganos aislados
- 1970		enzimas, membranas
- 1990	quimiotecas combinatorias	proteínas humanas, HTS
- 2000	quimiotecas enfocadas	uHTS, cribado virtual

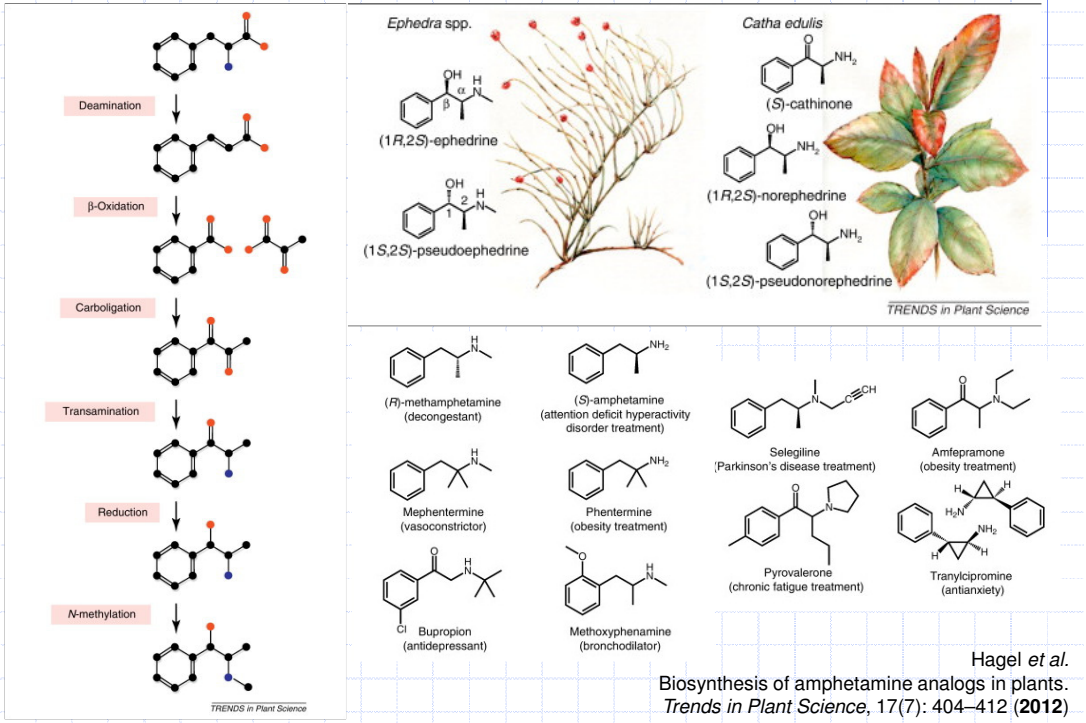


"The Drug Discovery Pipeline"



Estrategias en Identificación y Diseño de Fármacos (1/3)

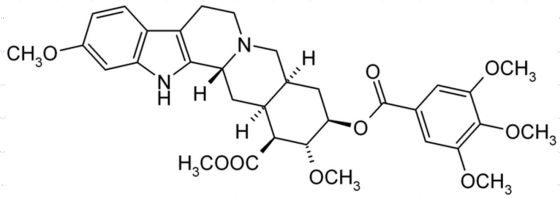
- Purificación del principio activo de una planta o extracto vegetal usado en medicina tradicional y popular ("folclórica"),: *e.g.* "digitálicos", morfina, efedrina, reserpina, paclitaxel, artemisinina
- Diseño, síntesis y evaluación de análogos del principio activo (incluyendo venenos) presente en una especie animal o vegetal: *e.g.* AAS, metformina, neostigmina (=prostigmina), docetaxel, hirudina[56-65], warfarina
- Diseño, síntesis y evaluación de peptidomiméticos y moléculas pequeñas a partir de péptidos naturales con la actividad biológica buscada: *e.g.* desmopresina (~vasopresina), buserelina (~GnRH), captopril
- Búsqueda de actividad (o indicación) en productos obtenidos de fuentes naturales, incluyendo microorganismos del suelo: *e.g.* antimicrobianos, hipocolesterolemiantes, toxina botulínica, ivermectina
- Modificaciones estructurales sistemáticas en una molécula "cabeza de serie": *e.g.* arsenicales orgánicos, sulfamidas, sulfonilureas, tiazidas



Hagel *et al.*
Biosynthesis of amphetamine analogs in plants.
Trends in Plant Science, 17(7): 404–412 (**2012**)

Observaciones clínicas en pacientes tratados con un remedio tradicional

Rauwolfia serpentina



Reserpina

✓ La raíz utilizada en la India (*Sarpaganda*), durante siglos para el tratamiento de enfermos mentales agitados.

✓ El alcaloide fue utilizado durante años para tratar la hipertensión arterial:
- un ~20% de los pacientes desarrollaban estados depresivos e incluso ideas suicidas.
- sus efectos fueron determinantes para el desarrollo de la hipótesis monoaminérgica de la depresión.
- hoy sabemos que inhibe la captación y almacenamiento de NA y DA en las vesículas sinápticas al bloquear a los transportadores vesiculares de monoaminas (**VMAT**).

Otro ejemplo de DESCUBRIMIENTO procedente de plantas

the Taxol® (paclitaxel) STORY

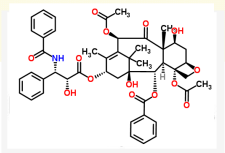
1958
The U. S. National Cancer Institute (NCI) initiates a program to screen 35,000 plant species for anticancer activity.

1963
As part of a National Cancer Institute program to screen plant species for anticancer activity, the U.S. Forest Service collects Pacific yew tree bark and ships it to the NCI for study. Drs. Monroe Wall and M.C. Wani of Research Triangle Institute, North Carolina subsequently find that an extract of the bark has antitumor activity.

1971
Drs. Monroe Wall and M.C. Wani of Research Triangle Institute, North Carolina, identify compound 17, the active ingredient in Pacific yew tree bark, as paclitaxel. However, development is later suspended because experimental models do not show superior activity and there are problems with producing, extracting, and processing paclitaxel.

1979
Paclitaxel's unique mechanism of action – tubulin stabilization – is identified by Susan Horwitz, Ph.D., at Albert Einstein College of Medicine, New York. Paclitaxel prevents cell division by promoting the assembly of and inhibiting the disassembly of microtubules – skeletal structures that assemble and divide throughout the life of a cell.

1983
The NCI sponsors phase I clinical trials of paclitaxel against numerous cancers. However, allergic reactions, attributed to the solvent in the formula, cause some trials to be discontinued and others to be delayed.



1985
The NCI begins phase II trials of paclitaxel.

1989
Researchers a
patients with a
shortages still
in just 15 trials
ovarian cance
invitation to p
commercial de
inquired about
(CRADA) and
Company amo

1958 59 60 61 62 **63** 64 65 66 67 68 69 70 **71** 72 73 74 75 76 77 78 **79** 80 81 82 **83** 84 **85** 86 8

'bioactivity-directed fractionation'

https://www.acs.org/content/acs/en/education/whatischemistry/landmarks/camptothecintaxol.html

Otro ejemplo de DESCUBRIMIENTO procedente de plantas

1993
In further developing TAXOL, Bristol-Myers Squibb Company files 3 supplemental New Drug Applications with the Food and Drug Administration (FDA). One of these supplemental New Drug Applications was the result of Bristol-Myers Squibb Company discovering that there were medical advantages to giving TAXOL infusions over a shorter time period compared to 24-hour administration. Also, the company ends Pacific yew bark harvesting for the manufacture of TAXOL and begins to develop other renewable sources for the drug.

1994
Bristol-Myers Squibb Company receives FDA clearance of its TAXOL supplemental New Drug Applications for: treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within six months of adjuvant chemotherapy, with the stipulation that prior therapy should have included an anthracycline unless clinically contraindicated; also for a 3-hour infusion schedule in ovarian and breast cancer patients.

1995
The semisynthetic form of paclitaxel, manufactured from renewable sources, receives clearance for marketing from the FDA

1996
FDA approves the clearance of TAXOL multidose vials

1997
FDA approves semisynthetic TAXOL for the second-line treatment of AIDS-related Kaposi's sarcoma. In June, Bristol-Myers Squibb Company files supplemental New Drug Applications for TAXOL for non-small cell lung cancer and for the first-line treatment of ovarian cancer.

1998
FDA approves semisynthetic TAXOL in combination with cisplatin, for the first-line treatment of advanced carcinoma of the ovary. To facilitate more efficient preparation of TAXOL for administration to patients, Bristol-Myers Squibb Company introduces TAXOL 300-mg multidose vials.

1999
FDA approves semisynthetic TAXOL in combination with cisplatin, for the first-line treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation therapy. FDA approves semisynthetic TAXOL for the adjuvant treatment of node-positive breast cancer administered sequentially to standard doxorubicin-containing combination chemotherapy. In the clinical trial, there was an overall favorable effect on disease-free and overall survival in the total population of patients with receptor-positive and receptor-negative tumors, but the benefit has been specifically demonstrated by available data (median follow-up 30 months) only in the patients with estrogen and progesterone receptor-negative tumors. (Please see TAXOL label information for details on the clinical study.

for use after failure of
ient chemotherapy for the
static carcinoma of the
RADA, in less than two
rs Squibb Company had
ity, and production
an initial FDA marketing
an producing and
TAXOL for all the patients

1993 • 1994 • 1995 • 1996 • 1997 • 1998 • 1999 • 2000

https://www.acs.org/content/acs/en/education/whatischemistry/landmarks/camptothecintaxol.html

Premio Nobel en Fisiología o Medicina 2015

Streptomyces avermectinius

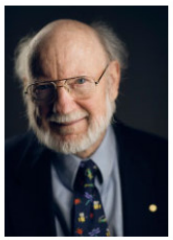
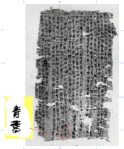


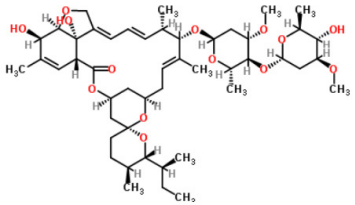
Photo: A. Mahmoud
William C. Campbell
Prize share: 1/4

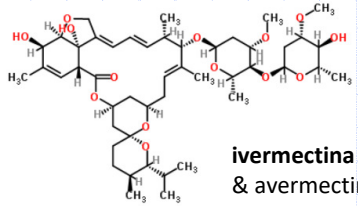
Photo: A. Mahmoud
Satoshi Ōmura
Prize share: 1/4

Photo: A. Mahmoud
Youyou Tu
Prize share: 1/2

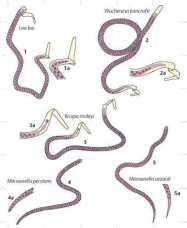


Qing Hao

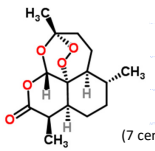




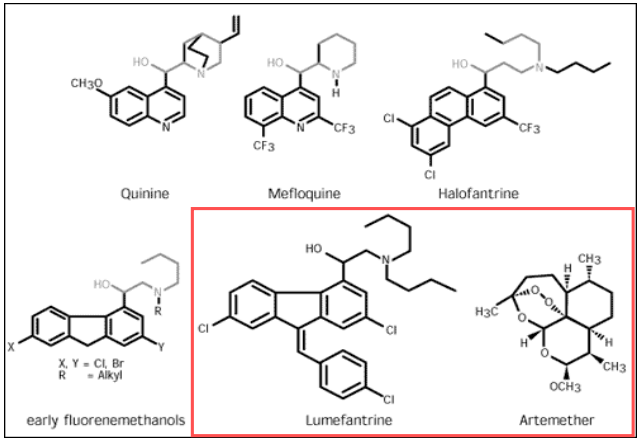
ivermectina
& avermectina →

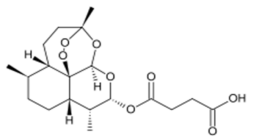


artemisinina → malaria

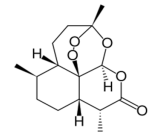


(7 centros quirales)





Artesunato



Artemisinina

Coste del curso de tratamiento por niño y adulto: 0,9 y 2,4 $, respectivamente

World Health Organization

ACTs (*Artemisinin-based Combination Therapies*): artesunato, artemether y dihidroartemisinina

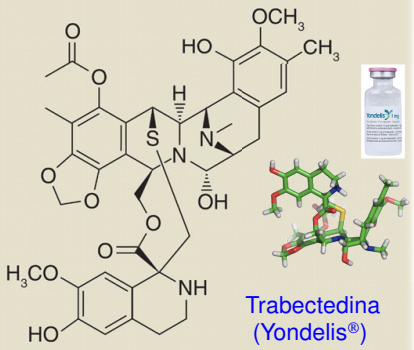
Fármacos recientes de origen marino

A *Conus magus*

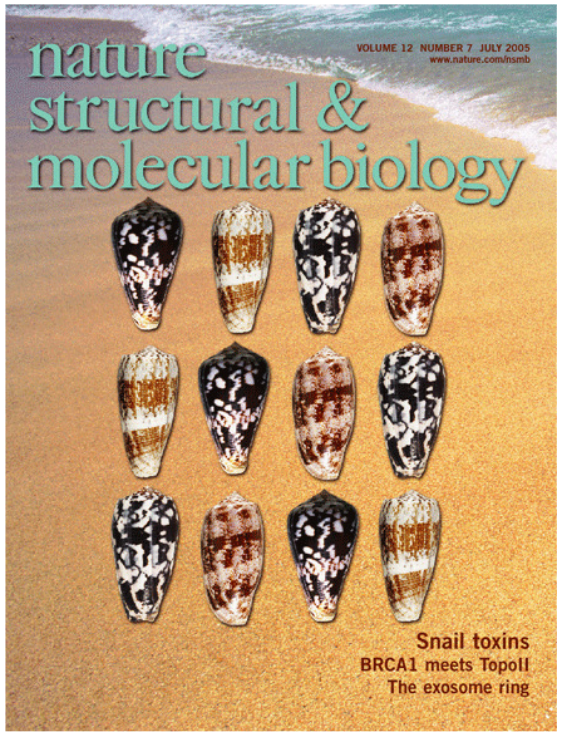
H_2N–CKGKGAKCSRLMYDCCTGSCRSGKC–$CONH_2$

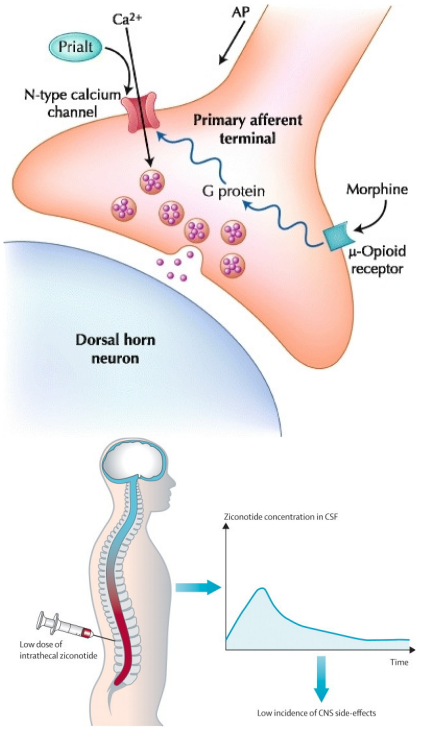
Ziconotida (Prialt®)

B *Ecteinascidia turbinata*



Trabectedina (Yondelis®)

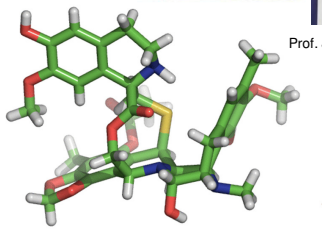




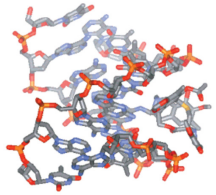
Pharma Mar

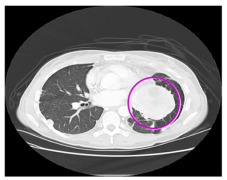
Trabectedina

Prof. José María Fernández Sousa-Faro

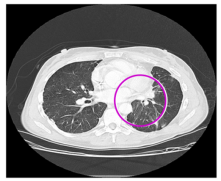


Ecteinascidia turbinata

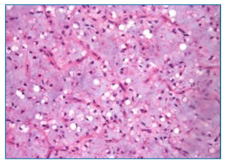


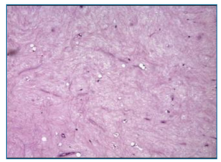


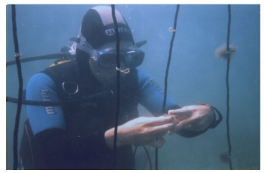
Pretratamiento

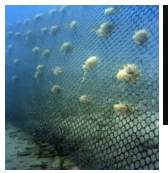


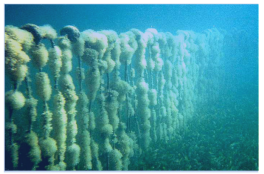
Yondelis 28w

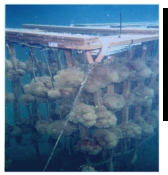


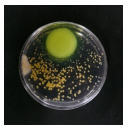




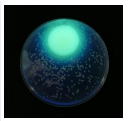


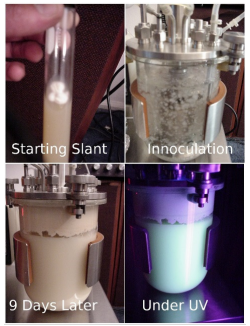






Pseudomonas fluorescens

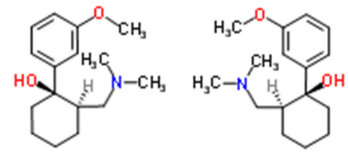


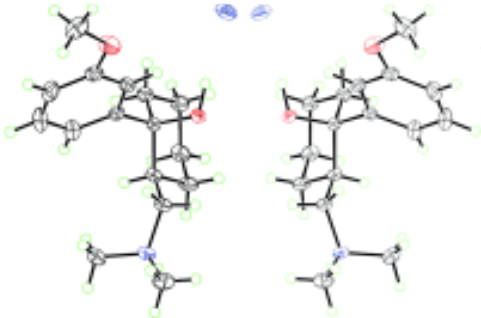


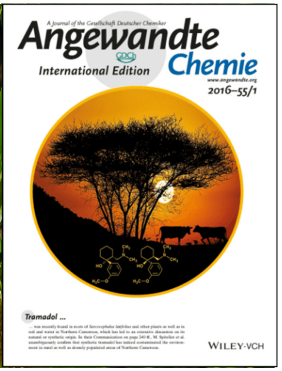
cianosafracina B → trabectedina

Occurrence of the Synthetic Analgesic Tramadol in an African Medicinal Plant:

a rare example of a contaminant synthetic drug that occurs at considerable concentrations in nature

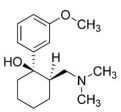




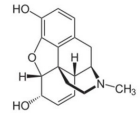


Nauclea latifolia [Sarcocephalus latifolius]
("pin cushion tree")

Anthropogenic contamination!



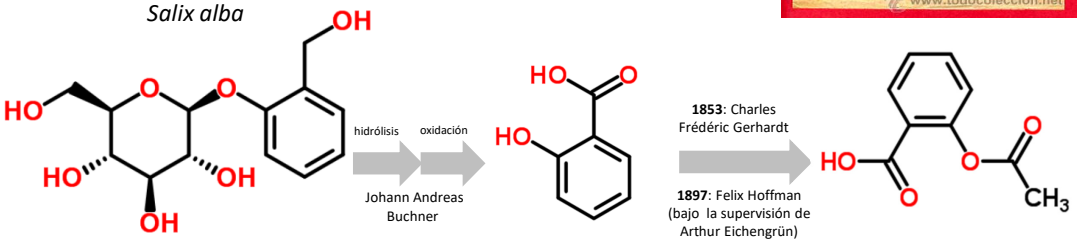
Tramadol



Morfina

Boumendjel et al. (**2013**), *Angew. Chem. Int. Ed.*, 52: 11780–11784
doi: 10.1002/anie.201305697

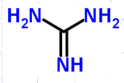
Salix alba



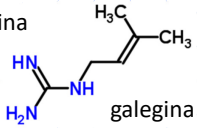
Salicina | **Ácido salicílico** | **Ácido acetilsalicílico (AAS)**

Metformina: del uso tradicional de una planta a la terapia oral de primera línea actualmente para la diabetes tipo 2

Galega officinalis
(Prof. Weed en los EE.UU.)



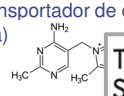
guanidina



galegina

- Riesgo de acidosis láctica (9:100000 personas/año): uso escaso y restringido durante mucho tiempo (la **fenformina** fue retirada por esta causa).
- Ampliamente utilizado hoy día como un antidiabético muy eficaz.
- Suprime la gluconeogénesis hepática

OCT1 = Transportador de cationes orgánicos (e.g. tiamina)

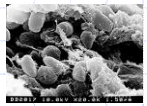


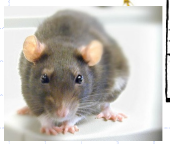
Observaciones en animales:

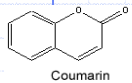
descubrimiento de los anticoagulantes orales

Laboratorio de Karl Paul Link

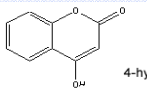
Heno dulce fermentado



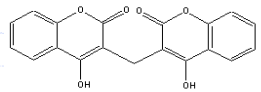




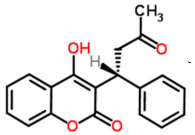
Coumarin



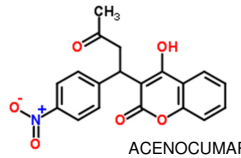
4-hydroxycoumarin



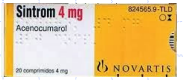
Dicoumarol



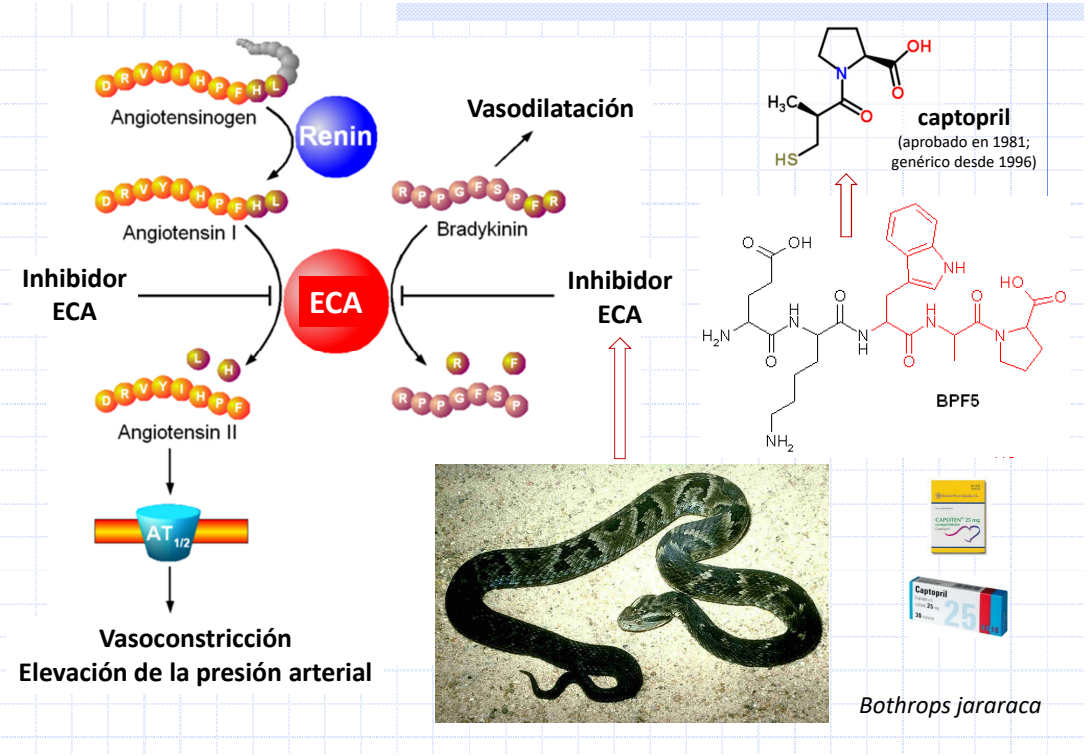
WARFARINA



ACENOCUMAROL



1mg | 3mg | 5mg



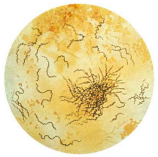
Modificaciones sistemáticas para disminuir toxicidad y aumentar eficacia del ácido arsanílico (Atoxyl®)

Paul Ehrlich (1909):

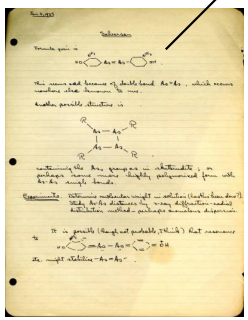
*"The discoveries of those uncivilized peoples represented the sum of limitless testing of thousands of natural materials. By contrast with their selection of medicines by pure chance, we have to find first certain compounds, for example some arsenic derivatives, which show at least a low degree of therapeutic effect. Once this is done through more or less laborious tests, the purely empirical screening is replaced by preparing chemical variations, homologs and other derivatives whose efficacy has to be tested. But even at best chemical drugs are **not magic bullets**, and will not always hit only the center of the target, that is the disease-causing organisms. Moreover, nothing is as simple as to ascertain the lethal or the maximal well-tolerated dose, and the curative dose in a given animal species. In humans the determination of dosages is infinitely more difficult as one has to start with low doses and increase them gradually until they become therapeutically active. This is further aggravated by the occurrence of congenital or acquired idiosyncrasies from most medicines… and it cannot justly be demanded that a decision be made within a few months as to the merits or demerits of such new agents."*

El primer agente quimioterapéutico moderno: la arsfenamina (606 / ***Salvarsan***) para el tratamiento de la sífilis y la tripanosomiasis.

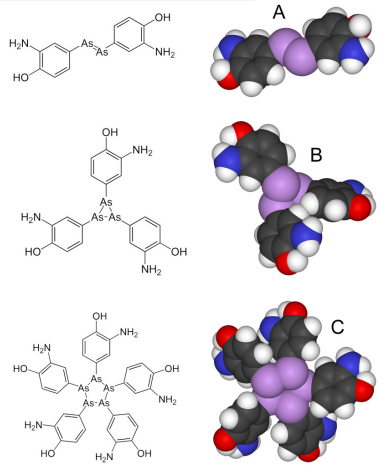
compuesto nº 606 sintetizado para su ensayo !!!

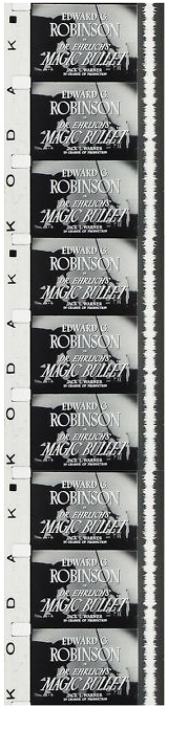


Sahachiro Hata
Paul Ehrlich



NEO-SALVARSAN IS NO. "914."
German Newspapers Just Publishing the Facts About New Serum.
Special Cable to THE NEW YORK TIMES.





LOOK'S NEW MOVIE PREVIEW

THE MAGIC BULLET

HOLLYWOOD'S FIRST MAJOR FEATURE ABOUT SYPHILIS
THE STORY OF DR. EHRLICH, WHO DISCOVERED "606"

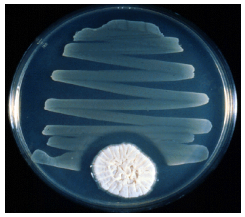
HALF THE BATTLE against syphilis was won in 1910 when a German doctor, Paul Ehrlich, found its cure. The other half will be won when the public is well-informed and unblushing about the disease. "The Magic Bullet," Warner Bros.' new film based on Ehrlich's life, is a bold step in this direction. And it is A-1 entertainment. The laboratory war scenes are convincing drama, and, as Dr. Ehrlich, Edward G. Robinson gives his best performance to date.

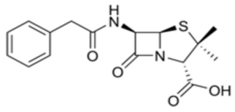
CAST OF CHARACTERS
Dr. Paul Ehrlich...Edward G. Robinson
Frau Ehrlich.....Ruth Gordon
Dr. Emil von Behring....Otto Kruger
Minister Althoff.....Donald Crisp
Frau Speyer.....Maria Ouspenskaya
Dr. Hartmann.....Montague Love
Dr. Robert Koch...Albert Basserman

3 Ehrlich goes to Egypt, with his wife, for rest and cure. While there he is called upon to treat a native father and son who have been bitten by an adder. The boy dies, but the father suffers no ill effects. He tells Ehrlich that he has been bitten three times before, that the reactions were successively milder. Sensing a clue to the mystery of immunization, Ehrlich, finally recovered from tuberculosis, returns home and plunges into laboratory research on antitoxins.

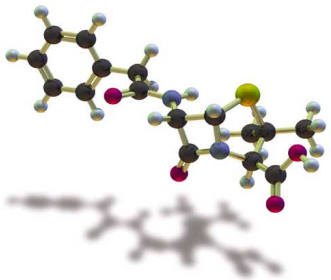
4 Coincidentally, a diphtheria epidemic rages through Germany. Ehrlich and von Behring hurl feverishly for a new serum, make one that works perfectly on horses, and rush with it to the Kaiser Wilhelm Institute where scores of children are dying. Hartmann orders them to use it on only half the children—he wants a controlled experiment. Determined to give all of the children a chance to live, they disobey. It is a tremendous risk—justified when every child recovers.

54



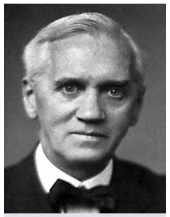


Alexander Fleming (1881-1955) descubrió los efectos bactericidas del *Penicillium notatum* cuyo principio activo (penicilina) fue identificado y purificado 15 años más tarde por Ernst B. Chain y Howard W. Florey.



The Nobel Prize in Physiology or Medicine 1945

"for the discovery of penicillin and its curative effect in various infectious diseases"



Sir Alexander Fleming

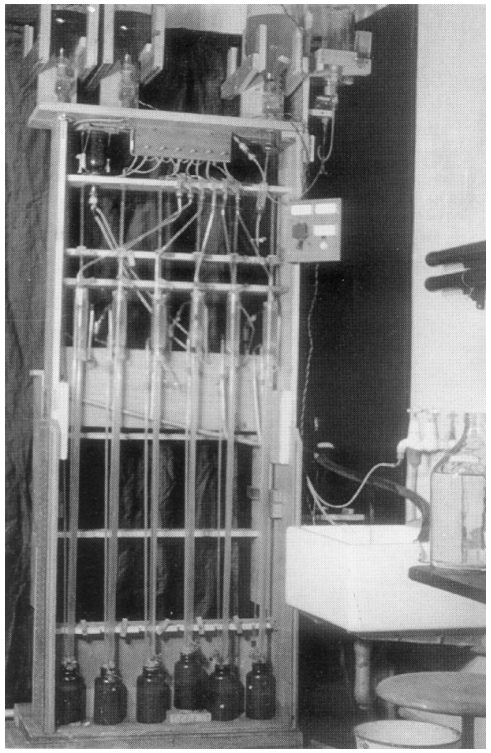
1/3 of the prize

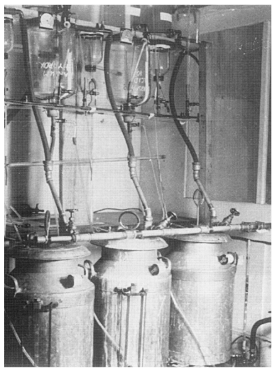
Ernst Boris Chain

1/3 of the prize

Sir Howard Walter Florey

1/3 of the prize





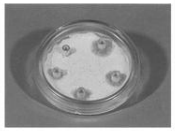
"Without Fleming, no Chain or Florey;
without Florey, no Heatley;
without Heatley, no penicillin."

Sir Henry Harris
(sucesor de H. Florey como Professor of Pathology)

12 Oxford Road,
Old Marston

Penicillin's Forgotten Man: Norman Heatley

Although he's been overlooked, his skills in growing penicillin were a key to Florey and Chain's clinical trials



Green thumb. *Heatley's penchant for training things to grow extends from penicillin cultures to a four-tiered espaliered pear tree in the garden of his Oxford home.*

FOR HALF A CENTURY, NORMAN HEATLEY has lived in the shadow of Alexander Fleming, Howard Florey, and Ernst Chain. A soft-spoken biochemist, Heatley was a key member of the Oxford University team that helped launch a new era of medicine 50 years ago, when it proved that a substance—penicillin—secreted by an obscure mold has remarkable healing powers. But while Fleming, who discovered the mold in 1928, and Florey and Chain, who demonstrated penicillin's medicinal properties 12 years later, went on to receive fame, glory, and the Nobel Prize, Heatley had gone largely unrecognized—until recently. Last October, Heatley, now 80 years old, was awarded an honorary Doctorate of Medicine from Oxford. What makes the honor particularly remarkable is that Heatley is the only person to receive that award in the university's 800-year history.

The honor recognizes Heatley's singular contribution to the penicillin project: to produce the compound in sufficient quantities to carry out the first clinical trials. Bulk production of penicillin had defeated previous workers, but Heatley did it by devising new extraction methods and by cobbling together an amazing array of makeshift equipment. "All of us following the Oxford project knew Norman Heatley's exceptional work," says Rollin D. Hotchkiss, emeritus professor of Rockefeller University who worked on gramicidin in 1939–40. But Hotchkiss also recalls that once the 1945 Nobel Prize was awarded to Heatley's colleagues and postwar jockeying for market share of penicillin began, "Norman's crucial role faded in world memory."

Notable for his modesty, Heatley shows not a trace of bitterness. Speaking of his award, which was presented during penicillin's golden jubilee year, Heatley says in a gentle voice, choosing his words carefully: "This is an enormous privilege, since I am not medically qualified…I have been picked out to represent the whole team involved in the difficult process of extracting and purifying penicillin. I am absolutely staggered that this award has been made at all."

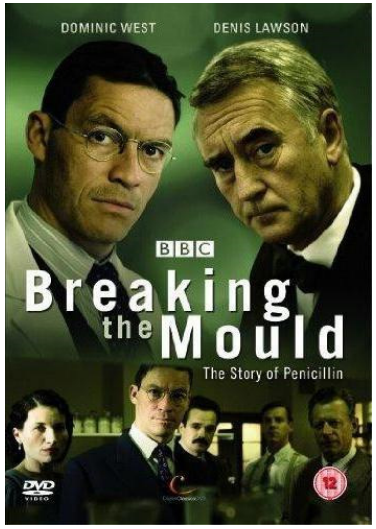
Heatley is a small, almost vanishingly thin, spry man with elfin twinkles around his eyes and mouth. His specialty, for which he was duly honored, was in training things to grow. Indeed, he still does it, proudly exhibiting an immense espaliered pear tree in his garden, one of the largest he knows. The one exception to his desire to see things grow is apparently his own renown: When it comes to discussing the precious units of penicillin he grew at Oxford in 1940–41, Heatley becomes reticent: "I was a third-rate scientist whose only merit was to be in the right place at the right time." Not so. What his modesty will not allow him to admit is that he was also just the right person.

In 1939, when Florey assembled a group to study antimicrobial substances, including the penicillin discovered 11 years earlier by Fleming in London, he selected Chain, a chemist, to analyze the nature of penicillin and to try to purify its active ingredient. Florey appointed himself to head a small team that investigated penicillin's biological, and later clinical, effects. And he chose Heatley as his personal assistant and put him in charge of producing enough penicillin for the researchers to study.

At that time, a crude mold juice containing penicillin could be easily grown. But no one knew how to extract an active substance from temperamental mold cultures. Earlier chemists had tried, had encountered penicillin's notorious instability, and concluded penicillin vanished while they looked on.

Heatley was well suited to Florey's task and team. This Cambridge-trained biochemist, according to Florey's biographer, historian Gwyn Mcfarlane, had "technical skills of optics, glass- and metal-working, plumbing, carpentry, and as much electric work as was needed. Above all he could improvise—making use of the most unlikely bits of laboratory or household equipment to do a job with the least possible waste of time." Heatley's gifts of improvisation and micro-engineering were to prove invaluable in establishing the world's first penicillin factory in the laboratories of Oxford's Sir William Dunn School of Pathology.

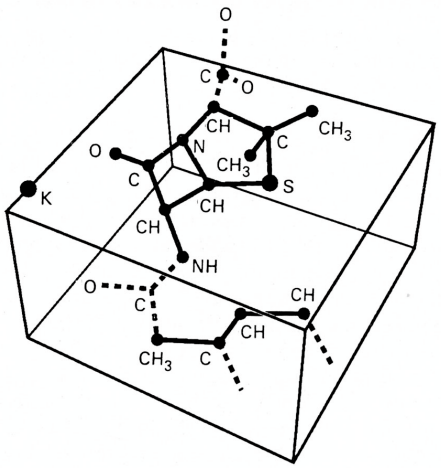
Heatley's initial contribution—the first in a remarkable series—was the "cylinder plate," or "penicillinder," to determine how powerful this unknown substance was. The assay plates contained short lengths of glass tubing, embedded into bacteria-laden agar, and each tube was filled with a different penicillin solution. The diameter of the

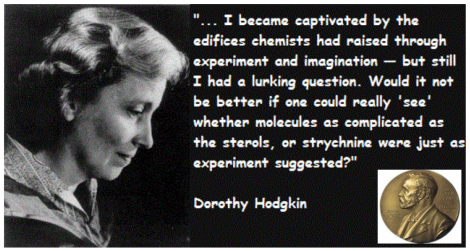


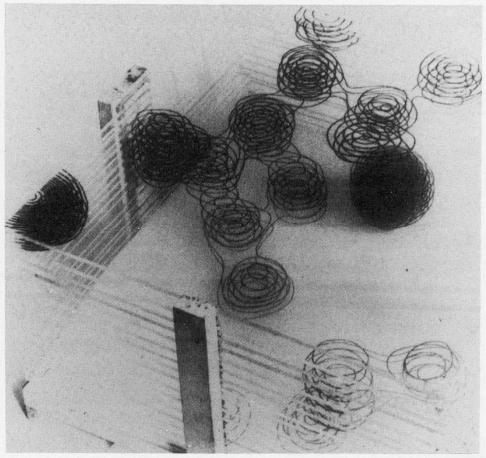
The following drama is based on real people and events.

For the purposes of the narrative some scenes have been invented.

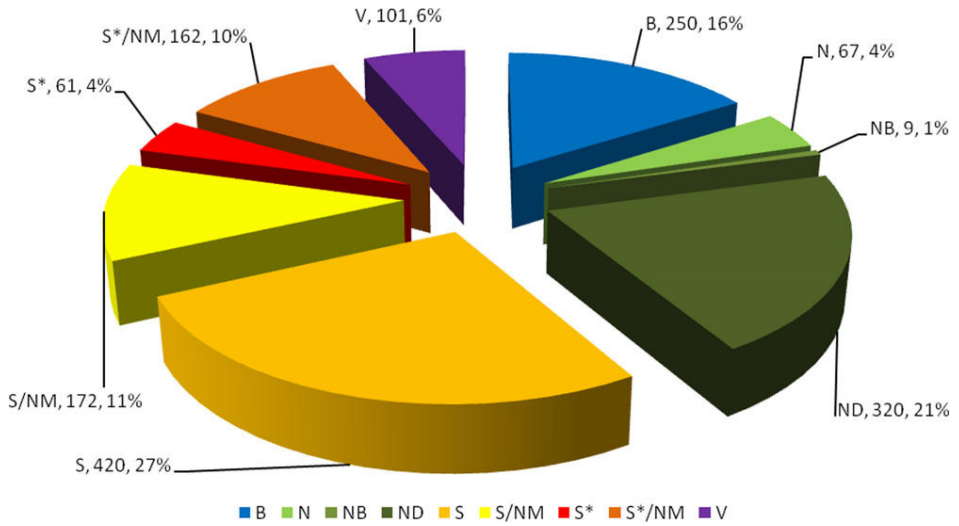
Estructura de la penicilina obtenida a partir de los mapas cristalográficos de difracción de rayos X (D. Hodgkin, 1946)







Nuevos fármacos aprobados entre 1981 y 2014; n = 1562

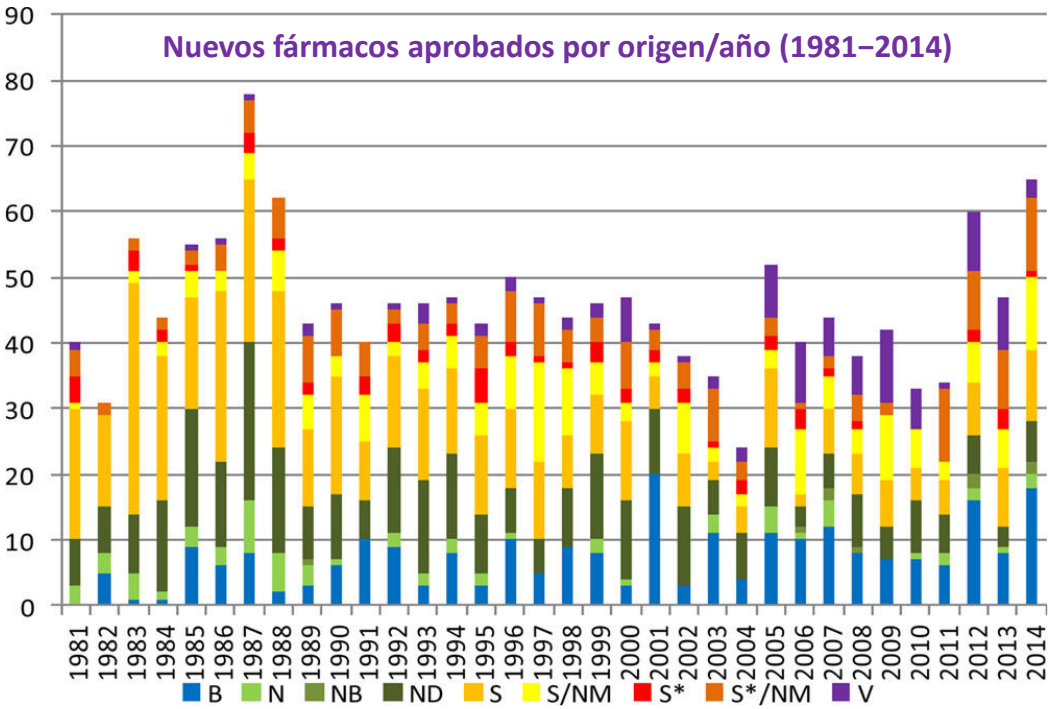


B Biological macromolecule, 1997
N Unaltered natural product, 1997
NB Botanical drug (defined mixture), 2012
ND Natural product derivative, 1997

S Synthetic drug, 1997
S* Synthetic drug (NP pharmacophore), 1997
V Vaccine, 2003
/NM Mimic of natural product

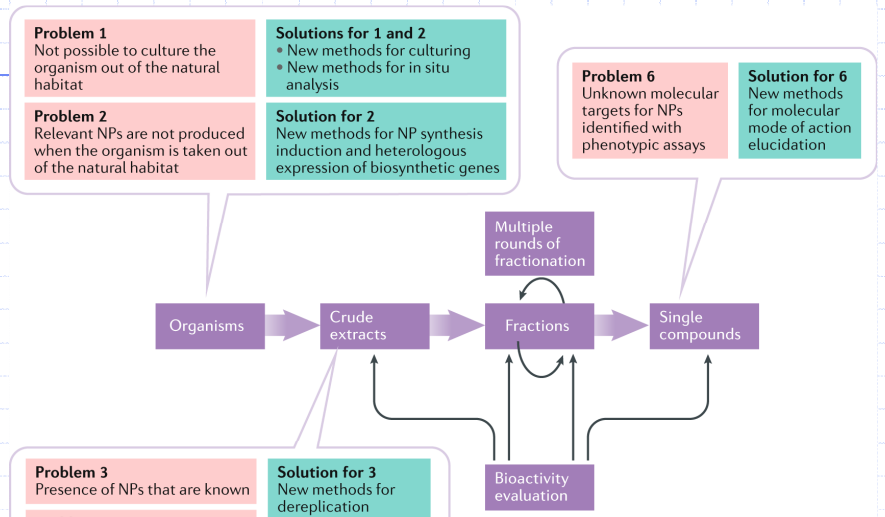
JOURNAL OF NATURAL PRODUCTS
DOI: 10.1021/acs.jnatprod.5b01055

Nuevos fármacos aprobados por origen/año (1981–2014)



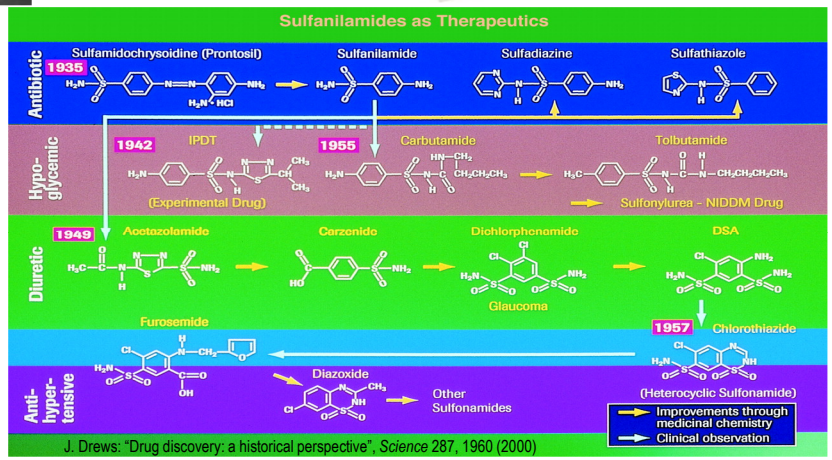
DOI: 10.1021/acs.jnatprod.5b01055

Esquema de los pasos tradicionales de **aislamiento guiado por la bioactividad** en el descubrimiento de fármacos a partir de productos naturales.

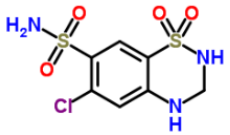


Atanasov AG, Zotchev SB, Dirsch VM; International Natural Product Sciences Taskforce, Supuran CT. Natural products in drug discovery: advances and opportunities. *Nat Rev Drug Discov*. 20(3):200-216 (**2021**)

Gerhard Domagk (1895-1964) protegió con *Prontosil rubrum* a ratones y conejos frente a dosis letales de estafilococos y estreptococos.



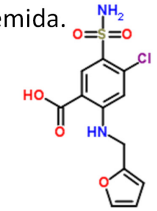
NCC: Co-transportador de Na^+ y Cl^- (= *symporter* Na^+/Cl^-)
Se expresa en el riñón en el túbulo contorneado distal.
Diana de diuréticos tiazídicos, e.g. hidroclorotiazida.

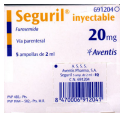


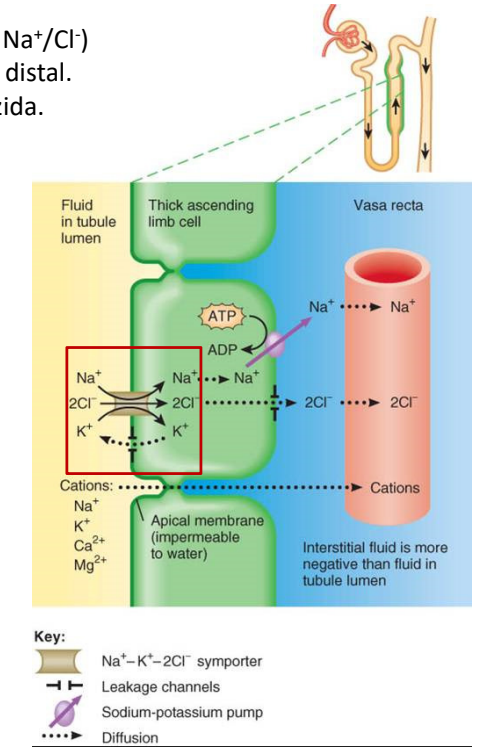
NKCC1 y **NKCC2:**
Co-transportador de Na^+, K^+ y Cl^-

NKCC2 se expresa en el riñón, en la porción gruesa del asa ascendente de Henle

NKCC1 no es exclusivo del riñón, también se encuentra en otros tejidos. Diana de los diuréticos del asa, e.g. furosemida.







Estrategias en Identificación y Diseño de Fármacos (2/3)

- Identificación de moléculas candidatas mediante cribado de actividades farmacológicas utilizando quimiotecas (colecciones de pequeñas moléculas) de origen natural, procedentes de química combinatoria, antiguas colecciones corporativas, etc
- Diseño de "antimetabolitos", *e.g.* 6-tioguanina, aciclovir, trimetoprim
- Diseño de agonistas y antagonistas a partir de agonistas endógenos o productos naturales con afinidad por una diana macromolecular dada
- "Serendipia", *e.g.* clonidina, litio, valproato, talidomida, sildenafilo
- Diseño de inhibidores enzimáticos a partir de la estructura (calculada) del estado de transición, *e.g.* inhibidores de la proteasa del VIH

La estrategia de descubrimiento de fármacos más habitual hoy día: proceso iterativo de *sintetizar* y *ensayar*

s. XXI: una nueva era debido a la sinergia de:

✓ Genómica y Proteómica

✓ Grandes colecciones de moléculas biológicamente activas

✓ Ensayos de altas prestaciones (*high-throughput*)

Descubrimiento de Fármacos Guiado por la Genómica

Bases de Datos de secuencias de genes

Initial Gene Index (IGI)

·Definición de límites intrón-exón
·Polimorfismos de un único nucleótido
·Búsqueda de motivos de secuencia
·Ayuste de ARN

Secuencias genómicas

Dianas terapéuticas validadas

Determinación estructural

Estructuras 3-D de proteínas

Bases de Datos de secuencias de proteínas

Initial Protein Index (IPI)

· Modelado por homología
· Análisis de los sitios
· Determinación de motivos estructurales

Sitios de unión de ligandos

Diseño de ligandos basado en la estructura

Nuevos candidatos

Bailey, D. et al.
Nat. Biotech., *19*, 207-209 (**2001**)

Construcción de quimiotecas: QUÍMICA ORGÁNICA COMBINATORIA

CRIBADO AMPLIO

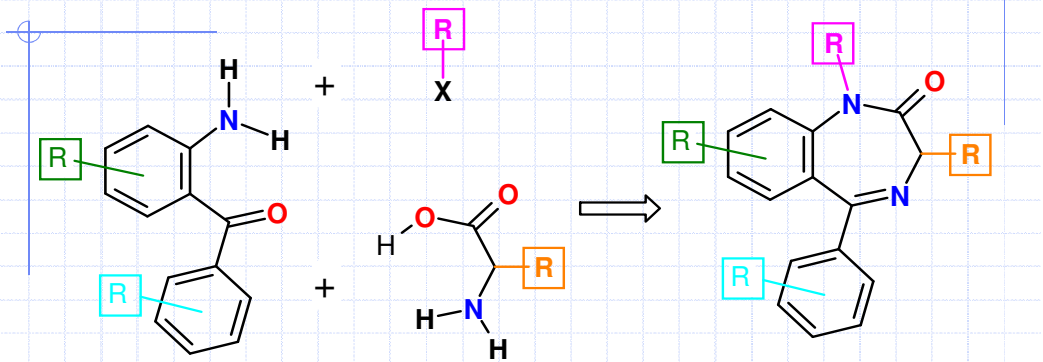
- **Quimioteca de tamaño inmenso**
- **Diversidad estructural lo mayor posible**
- **No hay una meta estructural inicial específica**
- **Bloques de construcción variopintos**
- **Orden de reacción indefinido**
- **Estrategia sintética flexible**
- **Espaciador no crucial**
- **Posibilidad de que el ligando no se pueda desacoplar**
- **Evolución por selección simple**

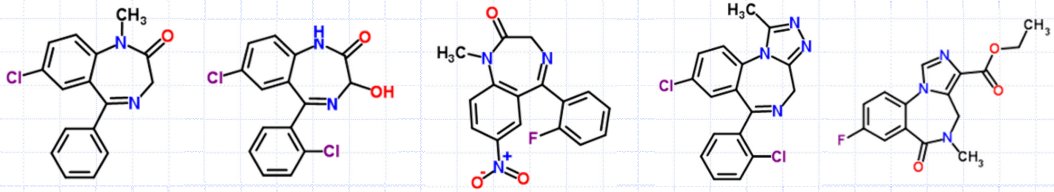
ANÁLOGOS QUÍMICOS / OPTIMIZACIÓN

- **Quimioteca de tamaño modesto**
- **Diversidad estructural relativamente estrecha**
- **Meta estructural específica**
- **Bloques de construcción retrocombinatoriales específicos**
- **Orden específico de combinación**
- **Estrategia sintética bien definida**
- **Espaciador crucial**
- **El ligando debería ser liberable**
- **Evolución acumulativa de la selección**

COMPONENTES DE UNA QUIMIOTECA DE **BENZODIAZEPINAS**

(uno de los farmacóforos más notables de la Química Médico-Farmacéutica)

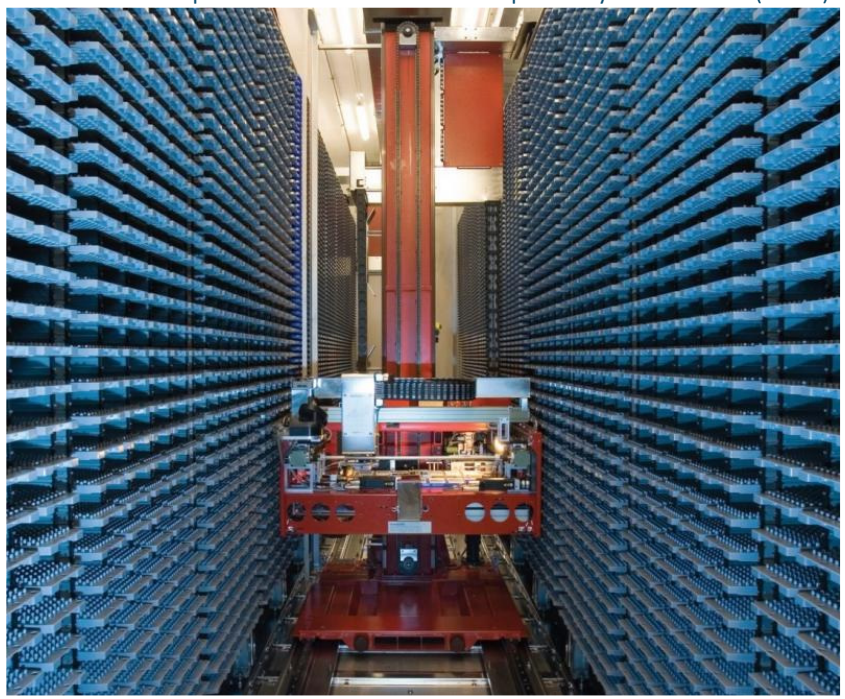




diazepam **lorazepam** **flunitrazepam** **triazolam** **flumazenilo**

Almacén de compuestos automatizado en la empresa Bayer HealthCare (Berlín)

Q U I M I O T E C A



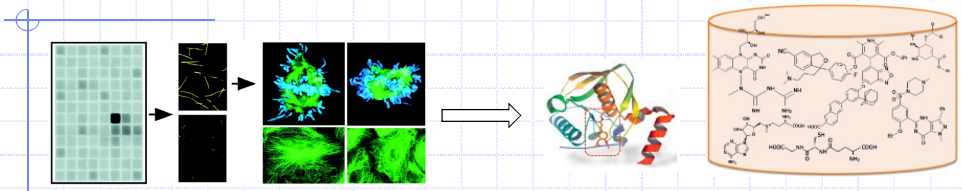
https://www.ddw-online.com/enabling-technologies/p217861-library-logistics:-managing-comprehensive-compound-collections.html

Procesado de compuestos en un instrumento de altas prestaciones (Bayer HealthCare, Berlín)

Compound Logistics Lab

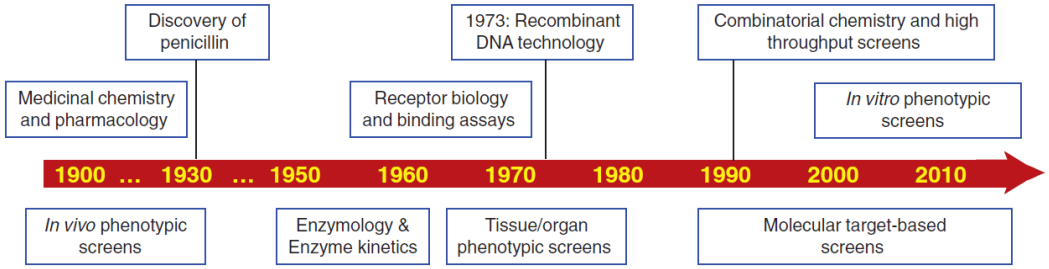
https://www.ddw-online.com/enabling-technologies/p217861-library-logistics:-managing-comprehensive-compound-collections.html

Evolución del cribado farmacológico y el descubrimiento de nuevos cabezas de serie



(1) cribado fenotípico

(2) cribado basado en la estructura 3D de la diana



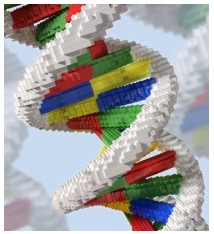
Zheng W, Thorne N, McKew JC.
Phenotypic screens as a renewed approach for drug discovery.
Drug Discovery Today 18(21-22):1067-73 (**2013**)

Pioneros de los antimetabolitos

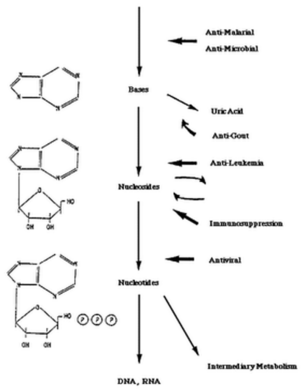
George Hitchings (1905 - 1998) and Gertrude Elion (1918 - 1999)

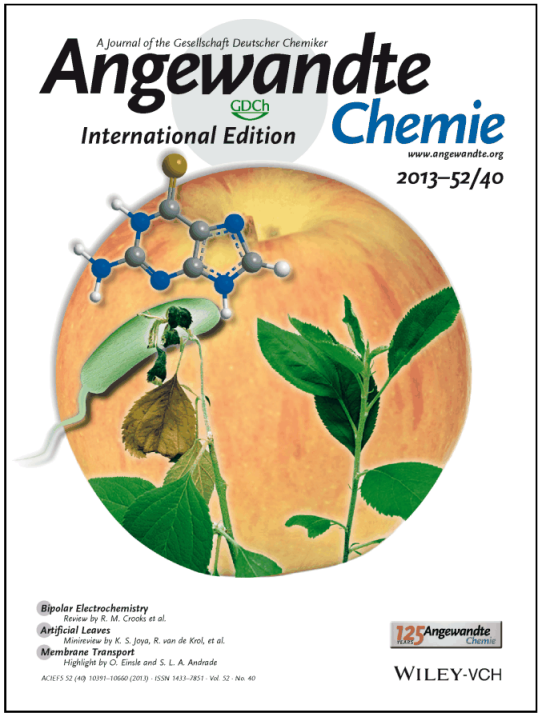
Table II. Clinical use of drugs developed by Elion and Hitchings.

Purine and pyrimidine analogues	Indications
6-Mercaptopurine, thioguanine	Leukemia
Azathioprine	To prevent rejection after organ transplantation
	Autoimmune diseases
Allopurinol	Gout
	Uric acid accumulation after treatment with cytostatic drugs
Acyclovir	Herpes virus infections
Pyrimethamine	Malaria
Trimethoprim (often combined with sulfa)	Bacterial infections, mainly urinary tract infection
	Pulmonary infections caused by e.g. Pneumocystis carinii (complication to decreased immune defence at transplantation and AIDS)

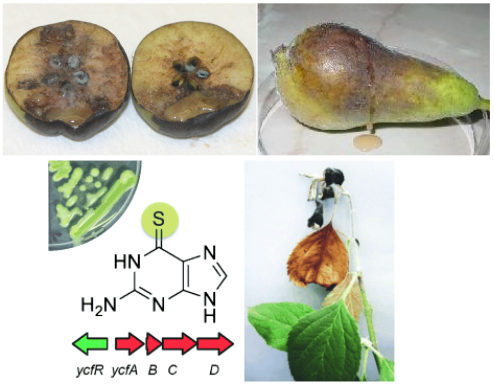


Life building blocks

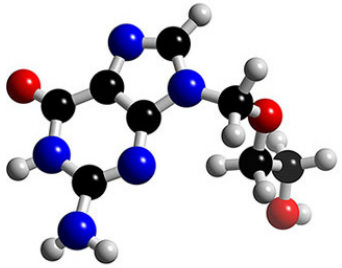




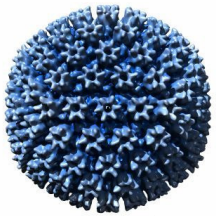
6-tioguanina: metabolito producido por la bacteria *Erwinia amylovora,* causante del "fuego bacteriano" en rosáceas.



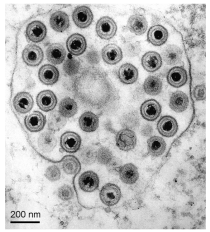
The molecular basis for the biosynthesis of the antimetabolite 6-thioguanine (6TG) was unveiled in *Erwinia amylovora*, the causative agent of fire blight. Bioinformatics, heterologous pathway reconstitution in *E. coli*, and mutational analyses indicate that the protein YcfA mediates guanine thionation in analogy to 2-thiouridylase. Assays in planta and in cell cultures reveal for the first time a crucial role of 6TG in fire blight pathogenesis.

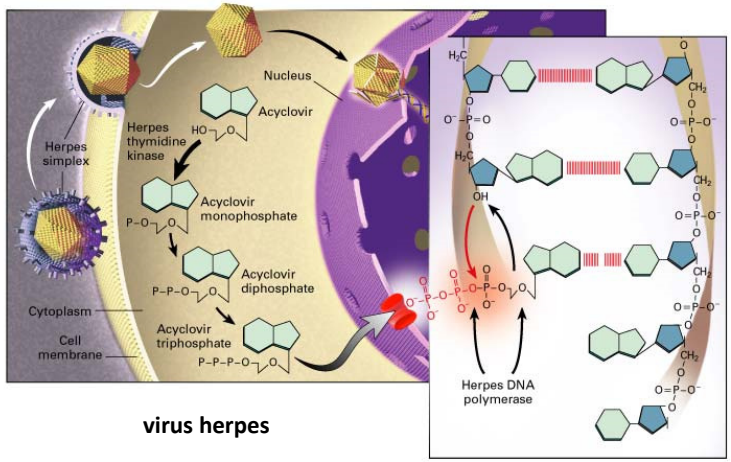


ACICLOVIR



Cytomegalovirus





virus herpes

El transportador de péptidos hPepT1

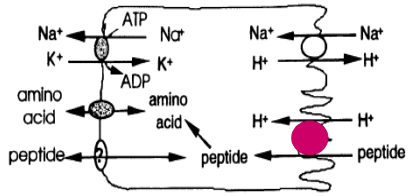
(*human peptide transporter 1*)

- Se expresa en la membrana luminal del epitelio mucoso intestinal
- Es un transportador de oligopéptidos acoplado al transporte de protones
- Presenta baja afinidad y alta capacidad

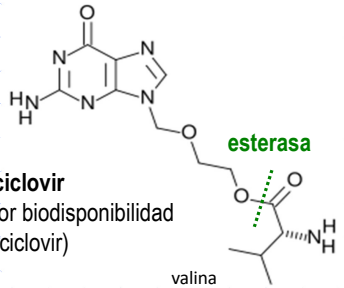
Fármacos transportados por hPepT1:

- penicilinas: amoxicilina, ampicilina
- cefalosporinas: cefalexina, cefadroxilo
- IECAs: captopril, enalapril
- antivirales: **valaciclovir**, valganciclovir

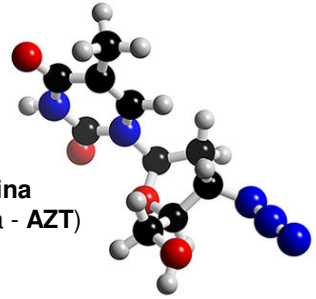
lado basolateral **lado apical**



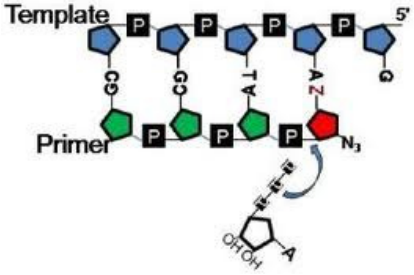
célula del epitelio intestinal

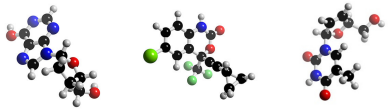


Valaciclovir
(profármaco: mejor biodisponibilidad que aciclovir)

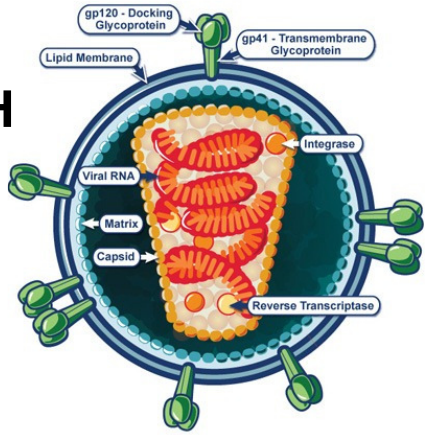


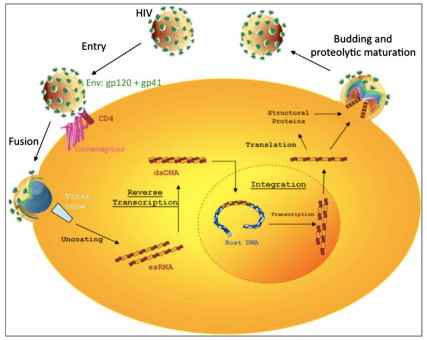
Zidovudina
(azidotimidina - **AZT**)



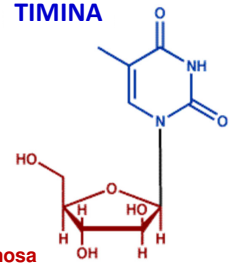


VIH





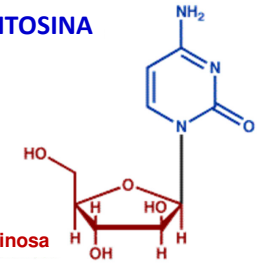
TIMINA



arabinosa

arabinósido de timidina

CITOSINA



arabinosa

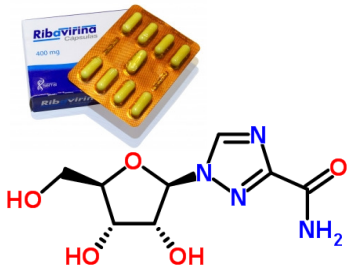
arabinósido de citosina

CITARABINA
(tto. leucemia mieloide aguda, etc)

espongotimidina

Tectithecya crypta

VIDARABINA
(antivírico)



RIBAVIRINA
(antivírico)

Premio Nobel en Fisiología o Medicina (1957): Daniel Bovet

"for his discoveries relating to **synthetic compounds that inhibit the action of certain body substances**, and especially their action on the vascular system and the skeletal muscles".

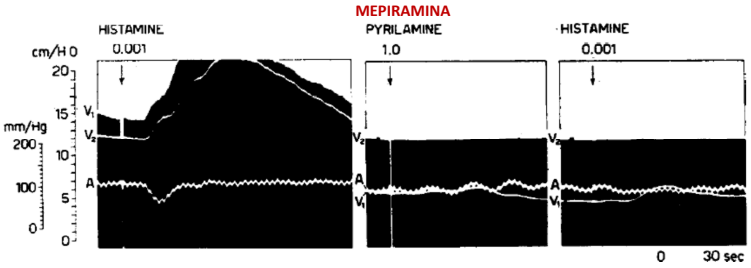
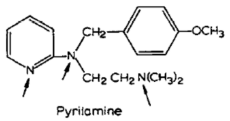


Fig. 7. Antagonistic action of pyrilamine with respect to the vasodilating effects of histamine in cerebral circulation.

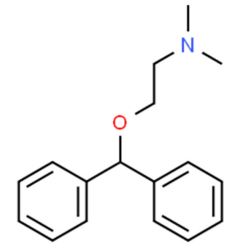
Dog, under chloralose anaesthesia - A = femoral artery pressure (mmHg); V_1 = pressure measured in catheter introduced centrifugally in the external jugular vein (nun H_2O); V_2 = pressure in the internal jugular vein (mm H_2O). Injections in the saphenous vein, doses in mg/kg. (After Virno, Gertner, and Bovet, 1956.)



Pyrilamine
MEPYRAMINE

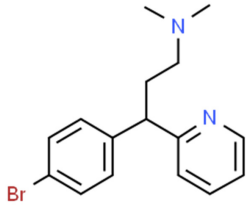
- Studies in animals of the **relationships** between the chemical **structure** and the biological **effect**.

- Systematic variations and progressive structural simplifications led to simple chemical compounds which proved themselves, which proved themselves, from the point of view of specificity and the absence of undesirable side-effects, **much more useful than naturally occurring substances**.

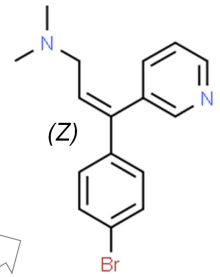


Difenhidramina

ANTIHISTAMÍNICOS

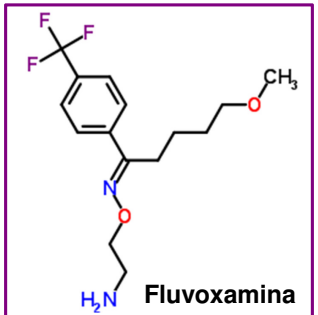


Bromfeniramina



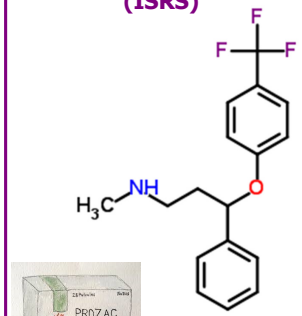
Zimelidina

Síndrome de Guillain–Barré → retirada

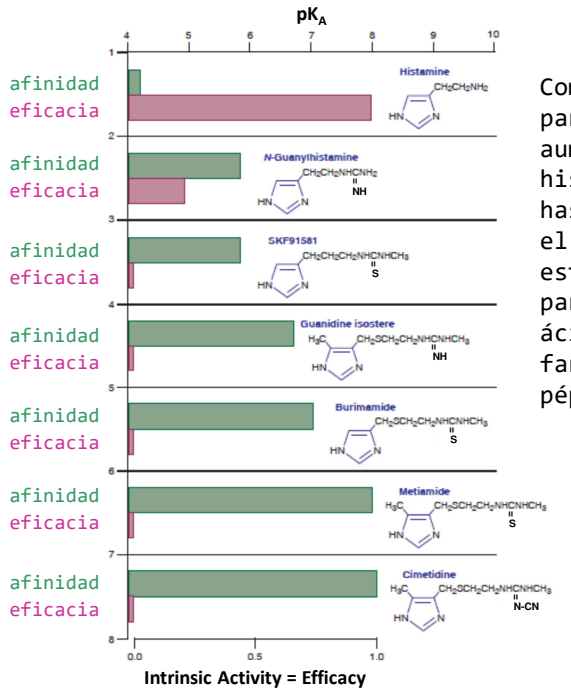


Fluvoxamina

ANTIDEPRESIVOS (ISRS)



Fluoxetina

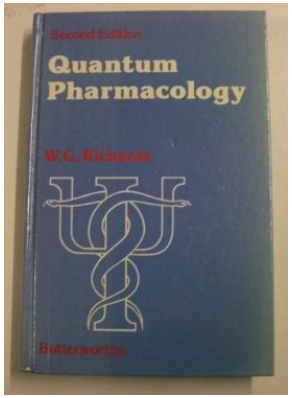


Compuestos clave sintetizados para eliminar la eficacia y aumentar la afinidad de la histamina por los **receptores H_2** hasta llegar a la cimetidina, el primer **antagonista** frente a este receptor que se utilizó para disminuir la secreción ácida gástrica y tratar farmacológicamente la úlcera péptica en los seres humanos.

. . . we knew the receptor bound histamine, so it was a matter of keeping affinity and losing efficacy . . .

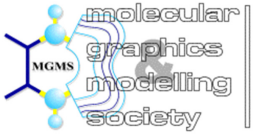
—Sir James W. Black

Black, J. W.
A personal view of pharmacology.
Ann. Rev. Pharmacol. Toxicol. 36:1-33 (**1996**)

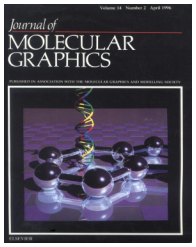


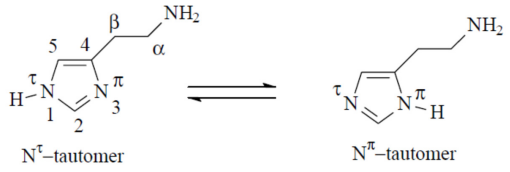
Prof. W. Graham Richards

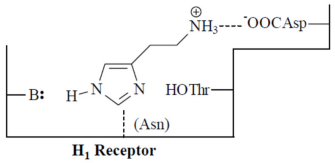
Oxford Molecular

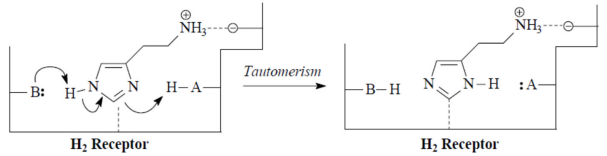


Screensaver Lifesaver









Sir James W. Black
The Nobel Prize in Physiology or Medicine 1988

Gran potencial farmacoterapéutico de fármacos que bloquean (o activan) receptores de neurotransmisores

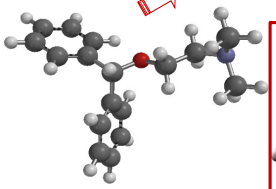
Neuronas, glándulas → HISTAMINA → Receptor H_1 → Alergia

Mastocitos → HISTAMINA → Receptor H_2 → Secreción gástrica

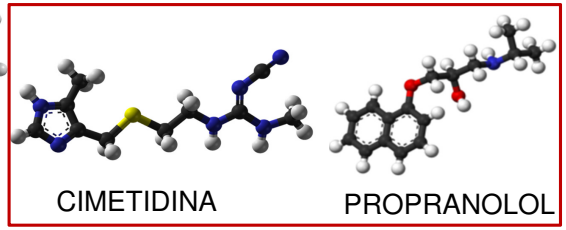
Nervios simpáticos → ADRENALINA NORADRENALINA → Receptor α → Contracción m. liso, ↓ flujo sanguíneo, ↓ NA

Glándula adrenal → ADRENALINA NORADRENALINA → Receptor β → Relajación m. liso, Estimulación cardiaca, Dilatación alveolos, ↑ metabolismo

Dr. George Rieveschl (1943)

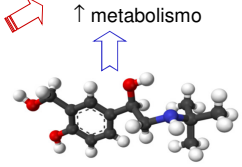


DIFENHIDRAMINA



CIMETIDINA

PROPRANOLOL



SALBUTAMOL

Sir James W. Black
The Nobel Prize in Physiology or Medicine 1988

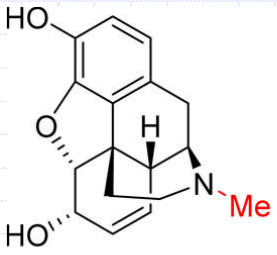
Neuronas, glándulas → HISTAMINA → Receptor H_1 → Alergia

Mastocitos → HISTAMINA → Receptor H_2 → Secreción gástrica

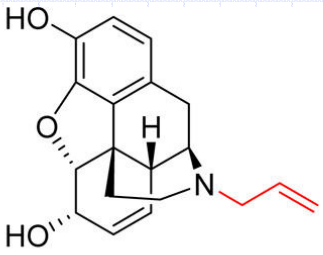
Nervios simpáticos → ADRENALINA NORADRENALINA → Receptor α → Contracción m. liso, ↓ flujo sanguíneo, ↓ NA

Glándula adrenal → ADRENALINA NORADRENALINA → Receptor β → Relajación m. liso, Estimulación cardiaca, Dilatación alveolos, ↑ metabolismo

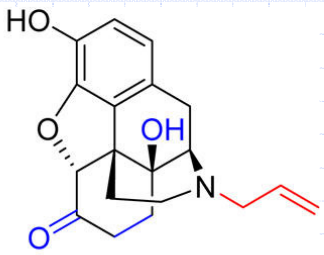
Otro ejemplo de eliminación de eficacia y aumento de afinidad por los receptores opioides



MORFINA
agonista opioide μ

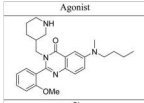
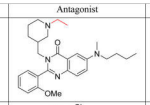
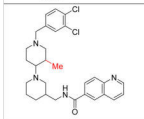
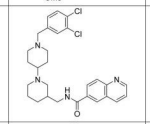
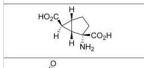
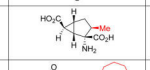
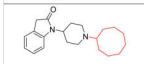
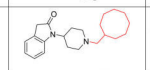
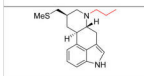
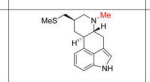
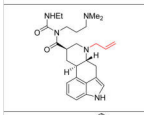
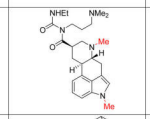
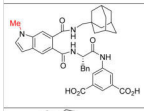
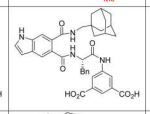
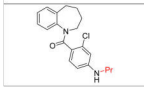
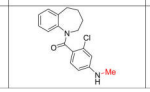


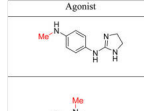
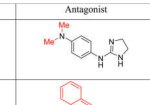
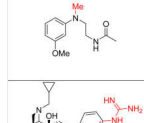
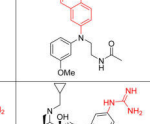
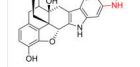
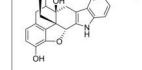
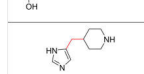
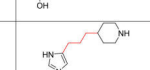
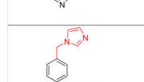
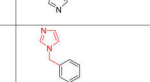
NALORFINA
antagonista opioide μ
agonista parcial opioide κ



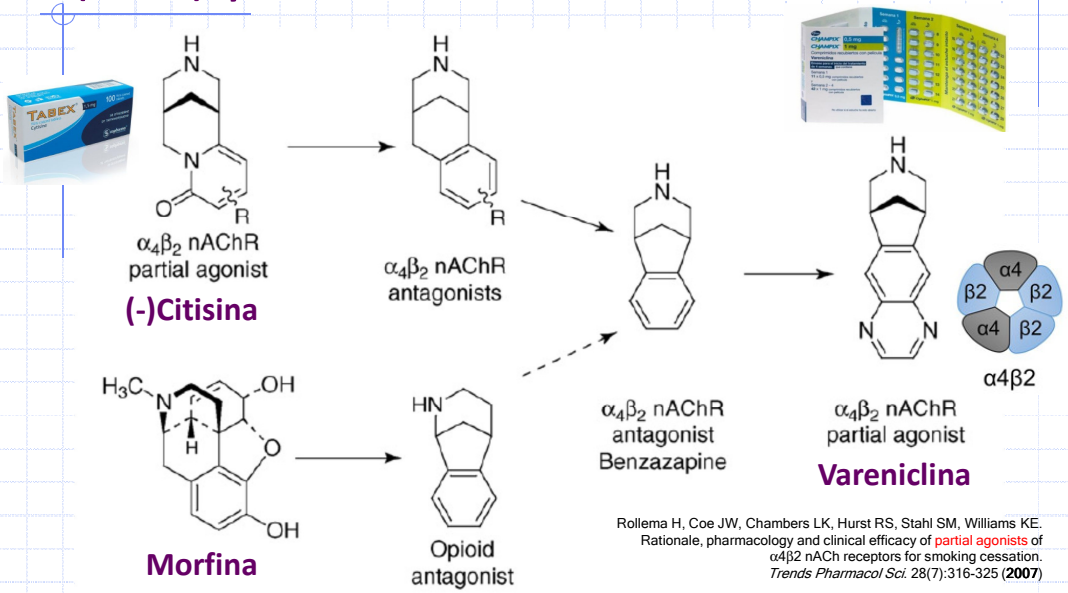
NALOXONA
antagonista opioide μ
antagonista opioide κ

Ejemplos de pequeñas modificaciones estructurales que convierten **Agonistas** GPCR en **Antagonistas**

Agonist	Antagonist	Receptor	Category[a]	Ref
		Ghrelin	N, B	12
		CCR3	N, B	13
		mGlu2/ mGlu3	N, B	15
		Nociceptin	N, B	17
		5-HT_{2B}	N, B	19
		5-HT_{2B}	N, B, A	23
		CCK_2	N	26
		V_2	N	27

Agonist	Antagonist	Receptor	Category[a]	Ref
		α2	N	28
		MT_2	N	29
		*k*-opioid	N, B	30
		H_3	N, B	31
		AT_2	N, B	34
		MT_2	O	36
		α2	O	37
		α2	O	37

Ruta desde subestructuras de **citisina** (R=H) y morfina hasta la **vareniclina**



Rollema H, Coe JW, Chambers LK, Hurst RS, Stahl SM, Williams KE. Rationale, pharmacology and clinical efficacy of partial agonists of α4β2 nACh receptors for smoking cessation. *Trends Pharmacol Sci.* 28(7):316-325 (**2007**)

Distinción entre descubrimiento e invención

Descubrimiento: elucidación de algo que existía previamente, lo entendamos o no (por ejemplo, la estructura del ADN o la acción antibacteriana de la penicilina).

La invención no existe hasta que el investigador la ha creado (por ejemplo, la molécula de propranolol).

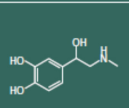
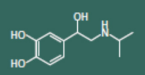
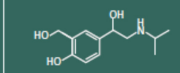
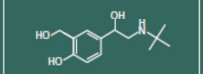
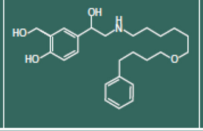
Sir James W. Black
The Nobel Prize in Physiology or Medicine 1988

"*Research is to see what everybody else has seen, and to think what nobody else has thought.*"
-- Albert Szent-Györgi,
Premio Nobel en Fisiología o Medicina 1937

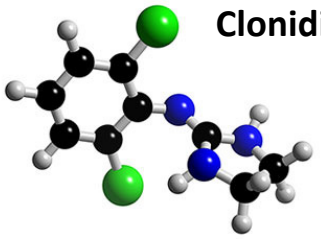
RESUMEN DE LAS MODIFICACIONES ESTRUCTURALES REALIZADAS SOBRE LA ADRENALINA PARA LA OBTENCIÓN DE FÁRMACOS ANTIASMÁTICOS

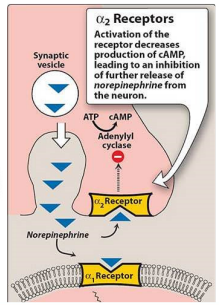
EpiPen®

(+ fluticasone)

Compound	Structure	Effects	Duration of action	Activity α_1 α_2 β_1 β_2
adrenalina		• broncodilatador eficaz • produce ansiedad • estimulación del corazón • aumento presión arterial	very short	✓ ✓ ✓ ✓
isoprenalina		• mayor eficacia sobre la relajación de la musculatura bronquial y la contracción del corazón	short	✓ ✓
adrenalina triol		• broncodilatador • aumento frecuencia cardiaca	short	✓ ✓
salbutamol		• broncodilatador • sin efectos secundarios destacables	short	✓
salmeterol		• broncodilatador • sin efectos secundarios destacables	long	✓

Clonidina





Boehringer Ingelheim

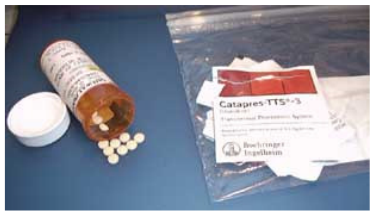


Table 3
Clinical Utility of Clonidine*

Cardiovascular/Circulatory
Hypertension (FDA-approved indication)
Hypertensive emergency
Atrial fibrillation
Congestive heart failure
Orthostatic hypotension
Portal pressure

Analgesia
Allodynia
Intraoperative and postoperative
Pediatric caudal anesthesia (ages 1 to 7 years)
Intractable cancer pain
Cluster headache prophylaxis
Chronic headaches
Migraine headaches
Labor analgesia
Postoperative pain in children
Reflex sympathetic dystrophy
Spinal cord injury pain

Neurology
Akathisia
Peripheral neuropathy
Neuropathic orofacial pain
Diabetic gastroparesis
Essential tremor
Memory enhancement in Korsakoff's psychosis
Postepidural shivering
Postanesthesia shivering
Restless legs syndrome
Hypertonicity
Tetanus-induced autonomic dysfunction
Hyperkinetic movement disorders
Tourette's syndrome

Psychology
Substance withdrawal
Acute anorexia nervosa
Attention-deficit/hyperactivity disorder and conduct disorder
Behavioral symptoms of HIV-1 encephalopathy
Bipolar disorder
Narcolepsy
Panic disorder
Posttraumatic stress disorder
Schizophrenia
Sleep disorders
Social phobia

Gastrointestinal
Carcinoid-associated diarrhea
High intestinal output associated with small bowel transplant
Ulcerative colitis and proctitis

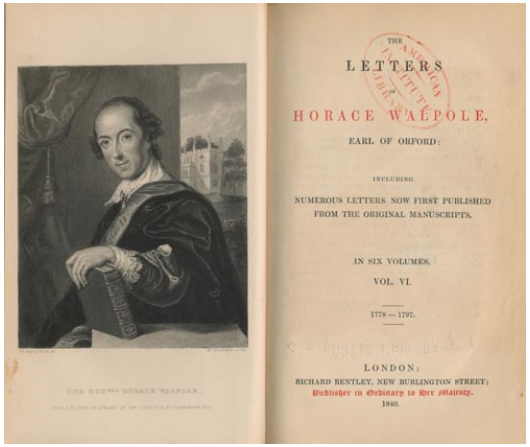
Anesthesia/Sedation/Surgery
Antiemetic in children
Maintenance of stable hemodynamics
Laryngoscopy
Liver transplantation
Intraoperative propofol requirements
Pharmacy cost in preoperative administration
Rhinoplasty
Sedation in intensive care

Endocrinology
Hyperthyroidism
Treatment of growth delay

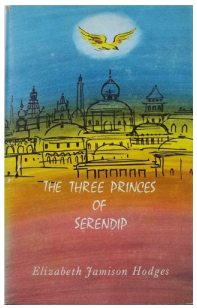
Miscellaneous
Prevention of cyclosporine-induced nephrotoxicity
Excessive sweating
Hot flashes
Trichorrhexis nodosa
Diagnostic tool

* FDA and non-FDA approved. Source: References 4, 6-82.

“SERENDIPITY”



The title page of Tramezzino's 1557 edition of the *Peregrinaggio*. Courtesy of the British Museum



Serendipity... You will understand it better by the derivation than by the definition. I once read a silly fairy tale, called 'The Three Princes of Serendip': as their Highnesses traveled, they were always making discoveries, by accidents and sagacity, of things which they were not in quest of.

‘Serendib’ que se transformó en ***‘Serendip’*** es la palabra persa y urdu (hablado en India y Pakistán) para Ceilán (hoy Sri Lanka)

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Serendipitous Discovery of a Potent Influenza Virus A Neuraminidase Inhibitor†

Dr. Sankar Mohan, Dr. Philip S. Kerry, Nicole Bance, Prof. Dr. Masahiro Niikura, Prof. Dr. B. Mario Pinto

First published: 11 December 2013 Full publication history
DOI: 10.1002/anie.201308142 View/save citation

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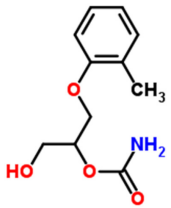
Volume 53, Issue 4
January 20, 2014
Pages 1076–1080

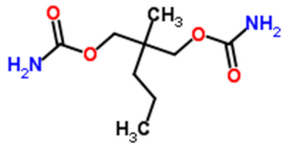
Abstract

We have previously reported a potent neuraminidase inhibitor that comprises a carbocyclic analogue of zanamivir in which the hydrophilic glycerol side chain is replaced by the hydrophobic 3-pentyloxy group of oseltamivir. This hybrid inhibitor showed excellent inhibitory properties in the neuraminidase inhibition assay (K_i=0.46 nM; $K_{i\,(zanamivir)}$=0.16 nM) and in the viral replication inhibition assay in cell culture at 10^{-8} M. As part of this lead optimization, we now report a novel spirolactam that shows comparable inhibitory activity in the cell culture assay to that of our lead compound at 10^{-7} M. The compound was discovered serendipitously during the attempted synthesis of the isothiourea derivative of the original candidate. The X-ray crystal structure of the spirolactam in complex with the N8 subtype neuraminidase offers insight into the mode of inhibition.

PDB **4MJU**

MEFENESINA: conservante para la penicilina → efectos sedantes en roedores (*Myanesin*)



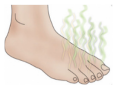


MEPROBAMATO

el primer psicotropo “blockbuster” de la historia en EE.UU. (fármaco milagro en 1954)

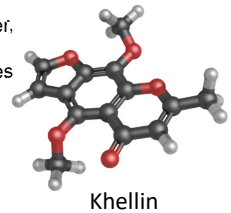
- Clase D durante el embarazo: riesgo aumentado de defectos en el feto y pasa a la leche materna, pudiendo afectar al lactante.
- 1970: sustancia controlada por ser capaz de producir dependencia física y psíquica.
- retirado del mercado en la UE en 2012.

Valeriana officinalis L.

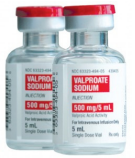


Ácido valérico

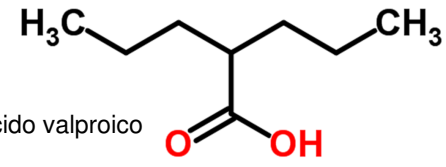
H. Meunier, G. Carraz, Y. Meunier, P. Eymard and P. Aimard, “Propriétés Pharmacodynamiques de L`acide nDipropylacétique”, *Therapie*, 18:435-438 (1963)



Khellin

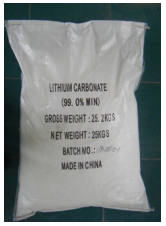


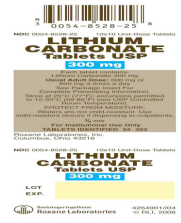
antiepiléptico más vendido del mundo

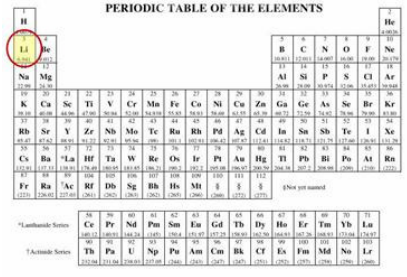


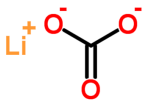
Ácido valproico

Observaciones en pacientes tratados por otra causa: restricción de sal





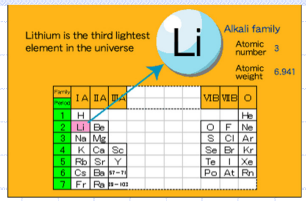




1929: Bib-Label Lithiated Lemon-Lime Soda

1936: 7UP

El fármaco más pequeño de la farmacopea: el ión litio

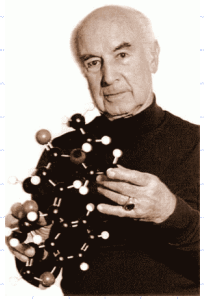


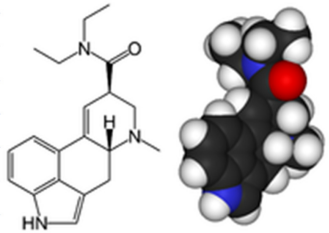
- Más frecuentemente prescrito como carbonato de litio.
- Introducido por el australiano Cade en 1949 para controlar episodios maníacos en pacientes hospitalizados.
- Potencial de producir intoxicaciones por sobredosis: necesidad de monitorizar concentraciones plasmáticas.
- Eficaz en el tratamiento de la manía en el trastorno bipolar.
- Sin efectos psicotrópicos en personas normales
- Ejemplos de mecanismos de acción propuestos:
  - Inhibición no-competitiva de la enzima inositol monofosfatasa, con el resultado final de una menor formación de inositol trifosfato.
  - Inhibición de la glucógeno sintasa kinasa 3β (GSK3β)

http://www.who.int/docstore/bulletin/pdf/2000/issue4/classics.pdf

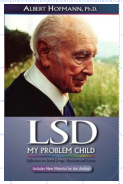
Observaciones en el propio investigador:
el caso de Albert Hofmann (1906–2008)

Cornezuelo del centeno
(***Claviceps purpurea***)





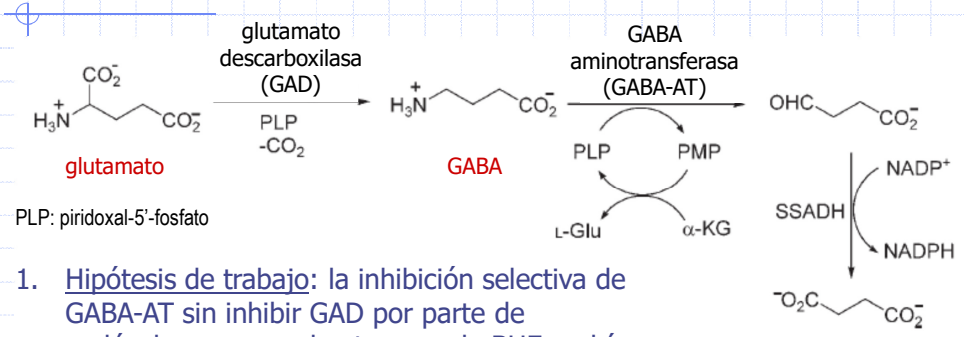
Dietilamida del ácido lisérgico
(LSD-25)



- Químico suizo que trabajaba en un programa para purificar y sintetizar principios activos aislados de plantas medicinales para su posible uso como fármacos.
- Probó con la punta de la lengua una cantidad minúscula de una sustancia que estaba intentando cristalizar.
- Al poco tiempo experimentó una "condición de intoxicación no-desagradable, caracterizada por una imaginación extremadamente estimulada...".
- Repitió la experiencia (con una cantidad de 250 microgramos) tres días después en presencia de su asistente: efectos psicodélicos.

http://es.wikipedia.org/wiki/Albert_Hofmann

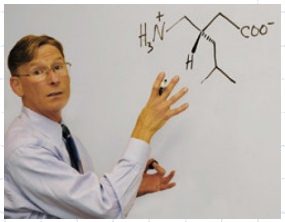
Sorpresas en la interconversión de neurotransmisión excitadora e inhibidora



PLP: piridoxal-5'-fosfato

1. Hipótesis de trabajo: la inhibición selectiva de GABA-AT sin inhibir GAD por parte de moléculas capaces de atravesar la BHE podría conducir a nuevos agentes antiepilépticos.

2. Síntesis de análogos más lipófilos de GABA, que no sólo no inhibían GABA-AT sino que resultaron ser activadores de GAD y poseían actividad anticonvulsivante: ↑[GABA]



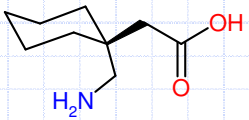
R.B. Silverman
Angew. Chem. Int. Ed. 47, 3500 – 3504 (**2008**)

Sorpresas en la interconversión de neurotransmisión excitadora e inhibidora

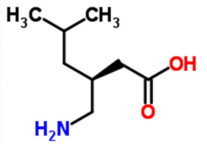
3. Desarrollo de la **pregabalina** (*Lyrica*®) y descubrimiento de que su verdadera diana es la subunidad $\alpha_2\delta$ del canal de calcio operado por voltaje (a la que también se une de forma selectiva la **gabapentina**). Su unión al canal ocasiona una atenuación del flujo de iones Ca^{2+} hacia el interior de la neurona, inhibiéndose así la liberación de sustancia P y glutamato de terminales nerviosas excitadoras.

4. La ↓[Glu] cumple el mismo objetivo que la ↑[GABA].

5. Pregabalina es mucho más potente que otros análogos porque atraviesa la BHE de forma activa al ser sustrato del transportador de leucina, pero es inactivo sobre todos los receptores de GABA ensayados, no afecta a la captación o la degradación de GABA, y no modifica las concentraciones cerebrales de GABA.



Gabapentina



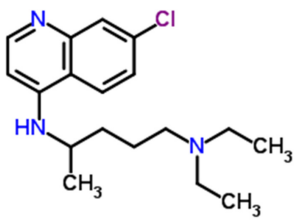
(*S*)-(+)3-isobutil-GABA =
Pregabalina

Indicaciones:

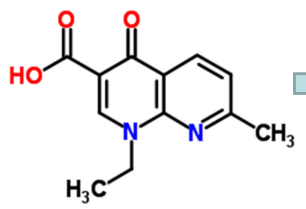
- Dolor neuropático (diabetes y neuralgia postherpética)
- Fibromialgia

Ventas globales en 2014 por Pfizer: 5.168.000.000 $

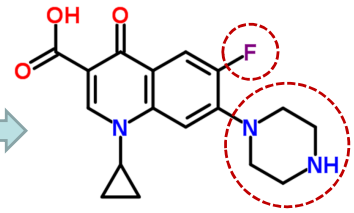
Origen de las quinolonas antibacterianas



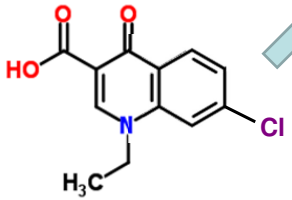
cloroquina



ácido nalidíxico
(esqueleto de 1,8-naftiridona)



ciprofloxacino ("cipro")
(esqueleto de quinolona)



"impureza o producto secundario activo" en la síntesis de cloroquina (@Sterling, 1950s)

ácido pipemídico
(esqueleto de piridopirimidina)

enoxacino
levofloxacino
moxifloxacino
...

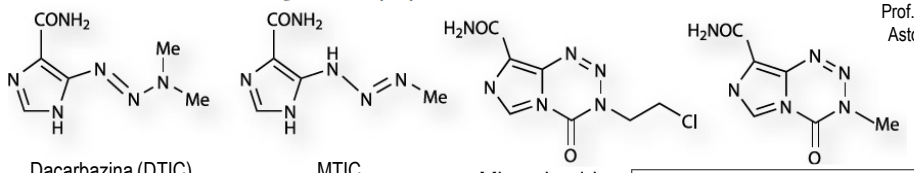
DOI: 10.1021/jm501881c
J. Med. Chem. 58, 4874–4882 (**2015**)

Temozolomide – birth of a blockbuster

Chemistry World | July 2009 |

The history of anticancer drug temozolomide can be traced back over 30 years – and it all started with some novel nitrogen chemistry, says Clare Sansom

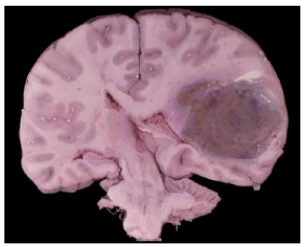
Prof. Malcolm Stevens
Aston University, GB



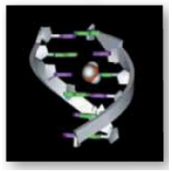
Dacarbazina (DTIC) [profármaco] → MTIC [metabolito activo]

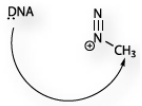
Mitozolomida (Azolastona)

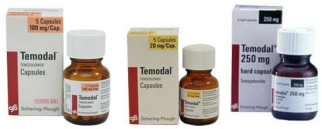
Temozolomida **TMZ**

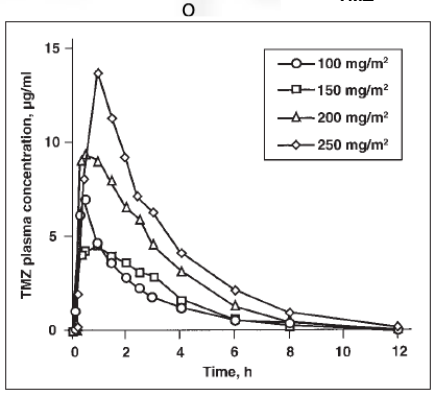


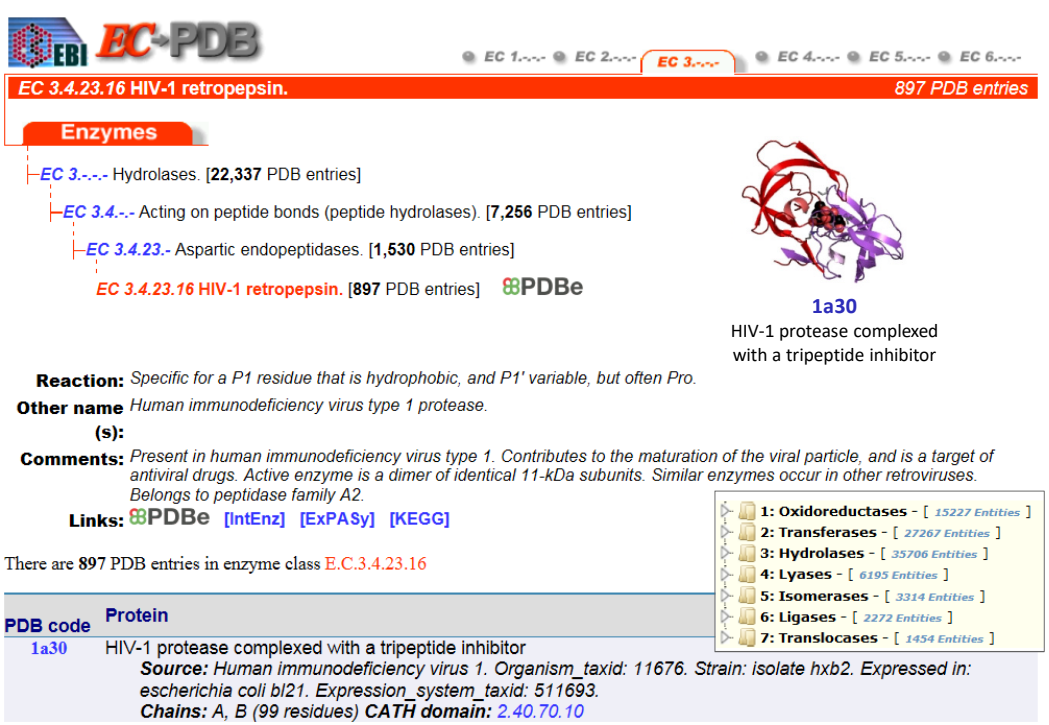
Glioblastoma multiforme



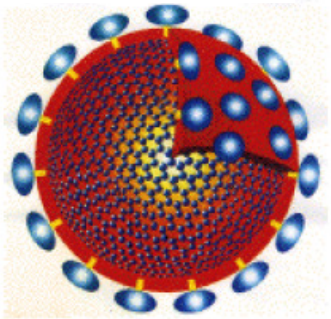


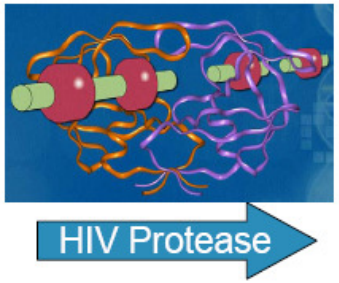




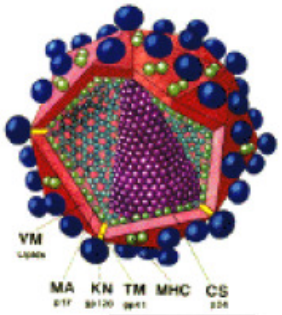


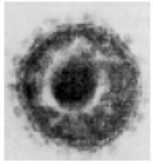
VIH inmaduro

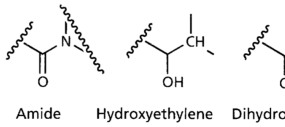


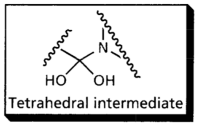


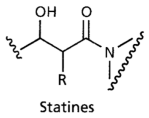
VIH maduro

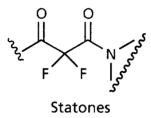






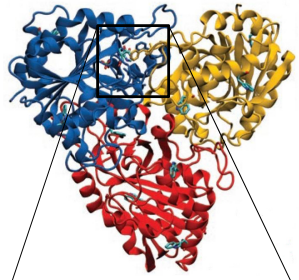


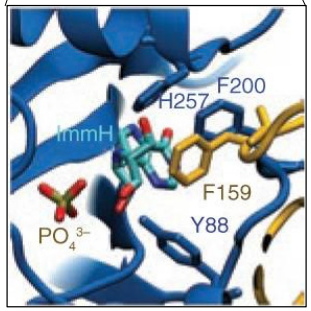


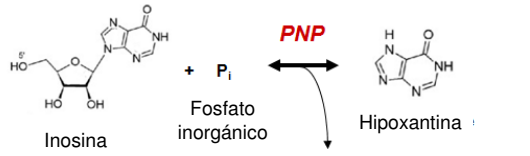


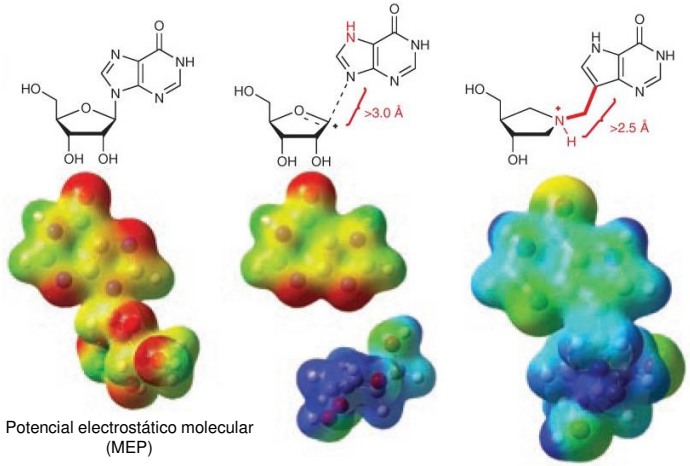
Isósteros del estado de transición

Purina Nucleósido Fosforilasa (PNP) humana









Potencial electrostático molecular (MEP)

Inosina
K_M = 40 µM

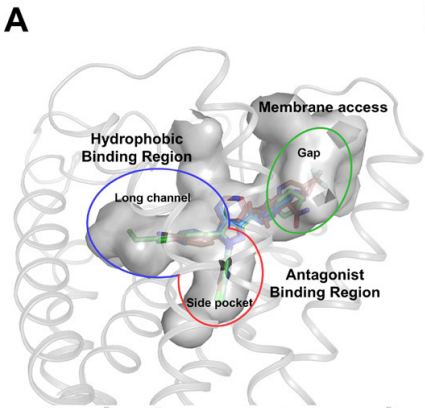
Estado de transición en el sitio active de la hPNP

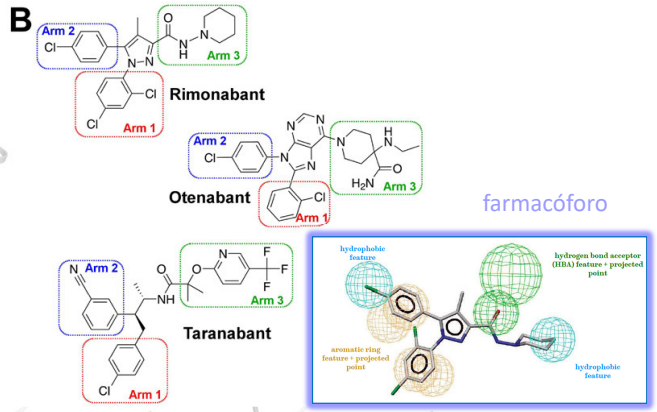
DADMe-ImmH
K_d = 8,5 pM

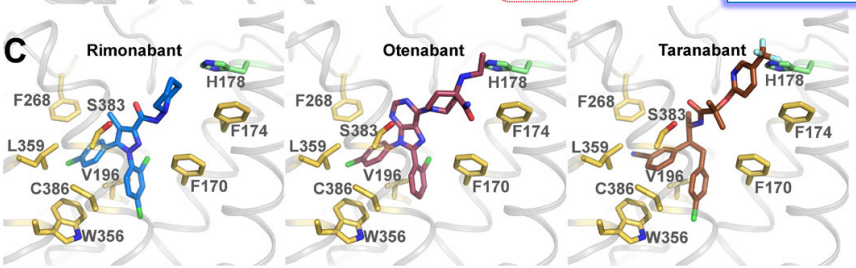
Estrategias en Identificación y Diseño de Fármacos (3/3)

- Diseño basado en una hipótesis de "farmacóforo"
- Diseño *de novo* basado en la estructura tridimensional del sitio receptor en la macromolécula receptora
- Cribado virtual sobre la estructura tridimensional de la macromolécula diana mediante técnicas automatizadas de acoplamiento ligando-receptor ("*docking*") para:
  - priorizar posibles ligandos existentes en las quimiotecas virtuales (*Ligand-Based Drug Discovery*, LBDD).
  - Identificar fragmentos con afinidad por el sitio de unión (*Fragment-Based Drug Discovery*, FBDD).

Estructuras cristalográficas del **receptor cannabinoide humano CB_1**







Código PDB: 5TGZ

Journal of Medicinal Chemistry
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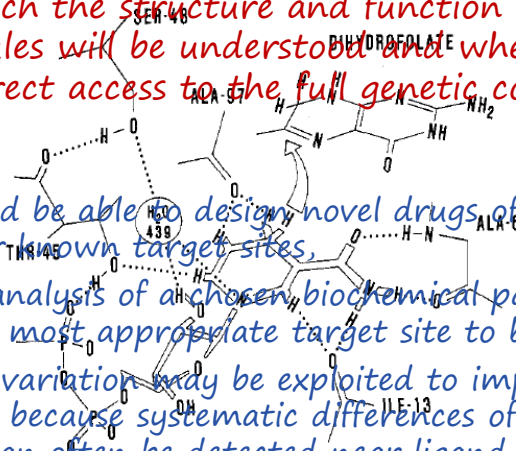
Volume 27, Number 5 May 1984

Drug Design by the Method of Receptor Fit

Peter J. Goodford
Laboratory of Molecular Biophysics, Oxford, England. *Received October 17, 1983*

What, then, does the **method of receptor fit** offer for a future in which the structure and function of macromolecules will be understood and where doctors may have direct access to the full genetic code of every patient?



- ✓ One should be able to design novel drugs of very high **affinity** for known target sites,
- ✓ Systems analysis of a chosen biochemical pathway will enable the most appropriate target site to be identified,
- ✓ Sequence variation may be exploited to improve **specificity**, because systematic differences of protein sequence can often be detected near ligand binding sites.
- ✓ All receptors are different until proved identical.

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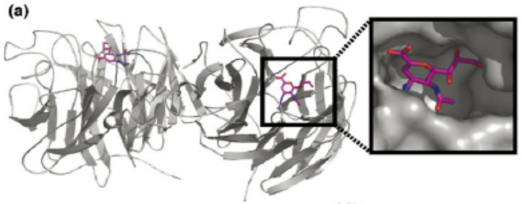
These tentative forecasts point toward:

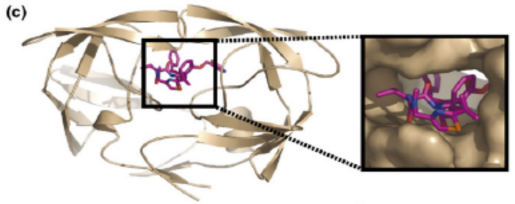
- ➢ a new generation of more potent, specific, effective therapeutic agents with less toxicity, reduced side effects, and fewer aberrant responses, which is what people and society at large are seeking.
- ➢ more costly research, which is the price that must be paid.

One last conclusion seems very probable. Mountaineers climb because the mountains are there and offer them a worthwhile challenge, and scientists will try to design drugs to fit receptors for similar reasons.

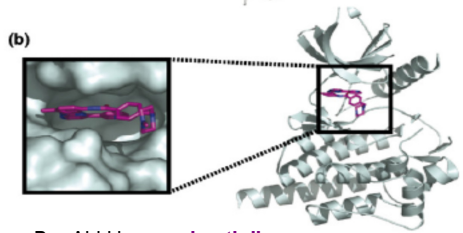
Ejemplos de estructuras de alta resolución de complejos fármaco-receptor

Neuraminidasa del virus de la gripe + **zanamivir**

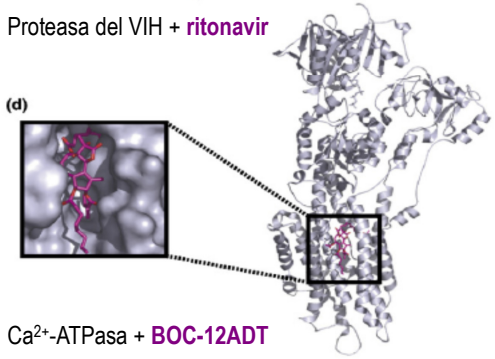




Proteasa del VIH + **ritonavir**

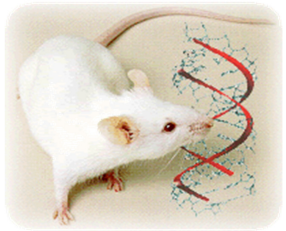


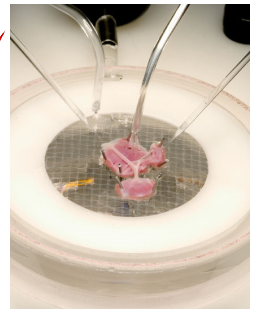
Bcr-Abl kinasa + **imatinib**

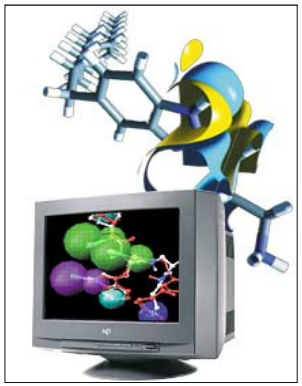


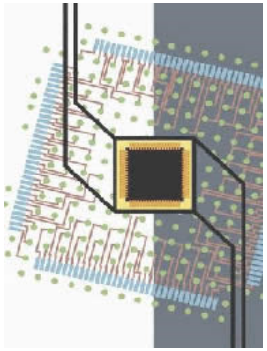
Ca^{2+}-ATPasa + **BOC-12ADT**

De la farmacología *in vivo* e *in vitro* ... a la farmacología *in silico*

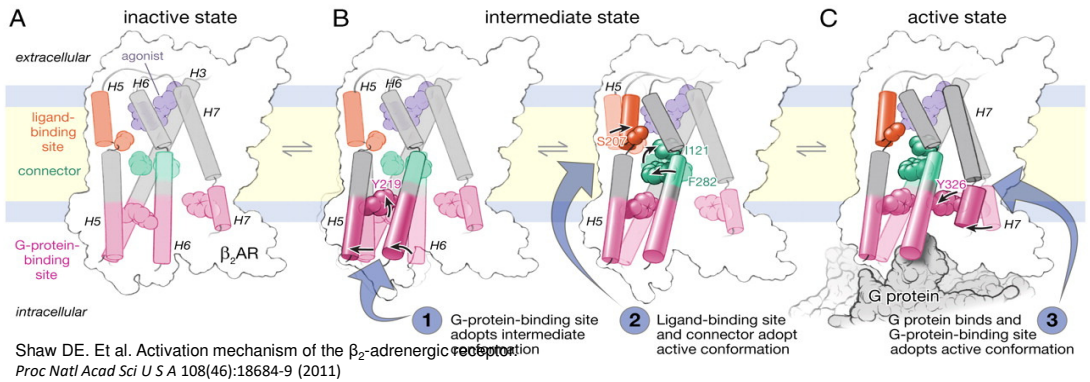




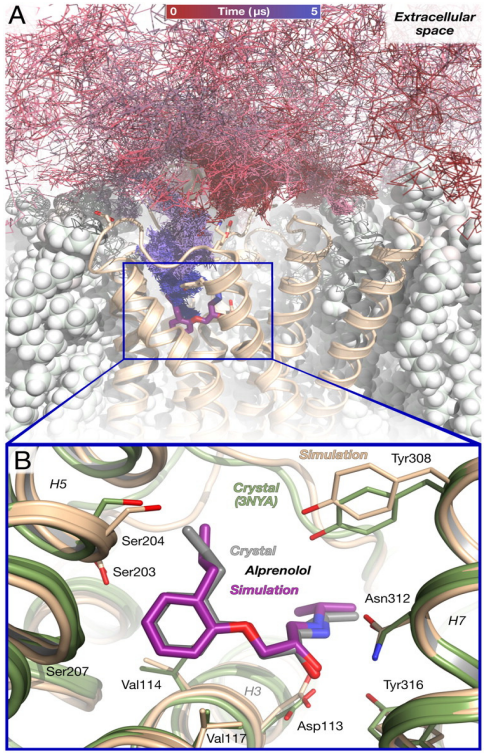


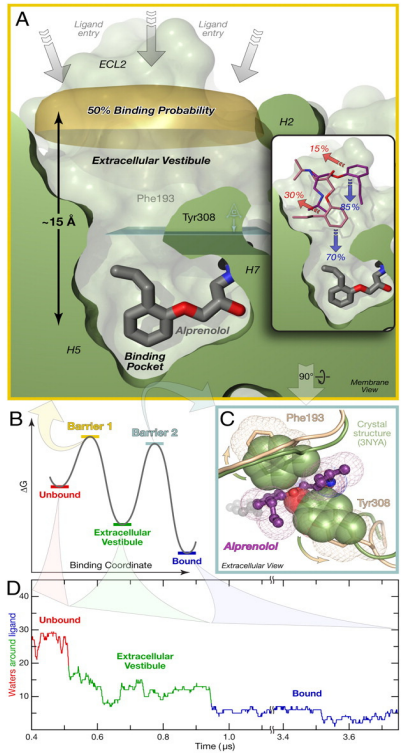


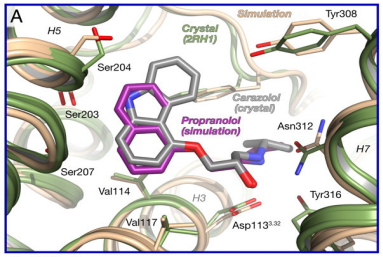
Farmacología *in silico*

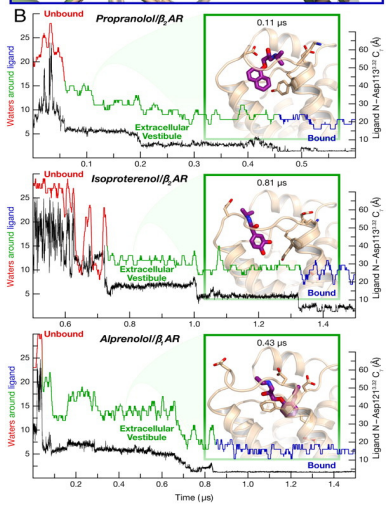


Shaw DE. Et al. Activation mechanism of the β_2-adrenergic receptor. *Proc Natl Acad Sci U S A* 108(46):18684-9 (2011)

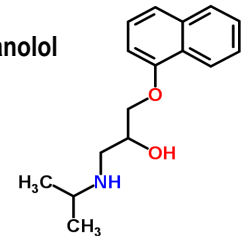


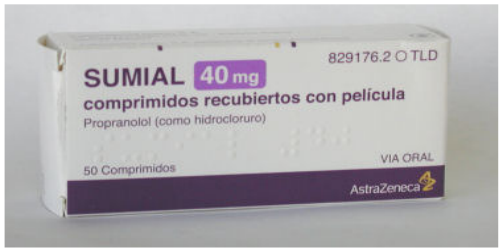






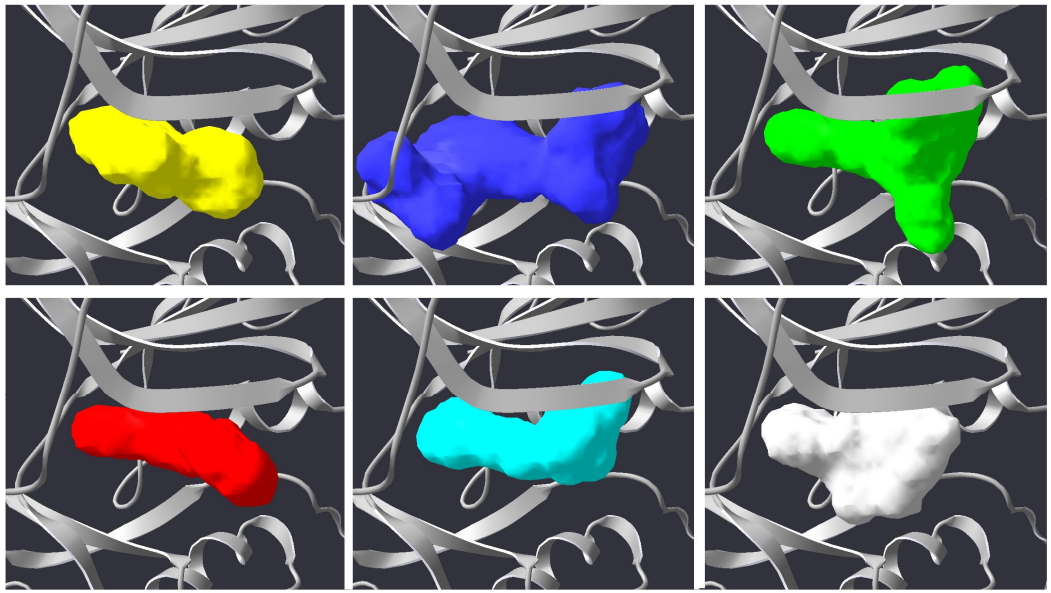
Propranolol





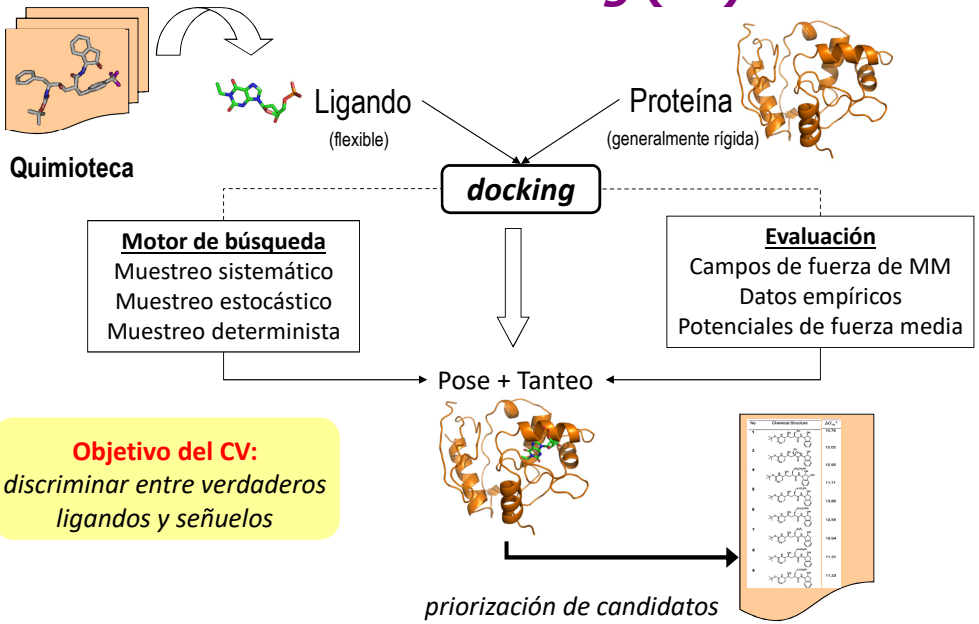
Dror RO, Pan AC, Arlow DH, Borhani DW, Maragakis P, Shan Y, Xu H, Shaw DE. **Pathway and mechanism of drug binding to G-protein-coupled receptors.** *Proc Natl Acad Sci U S A* 108(32):13118-23 (**2011**)

Diseño de inhibidores dentro del sitio activo de la macromolécula diana



Cribado Virtual (CV)

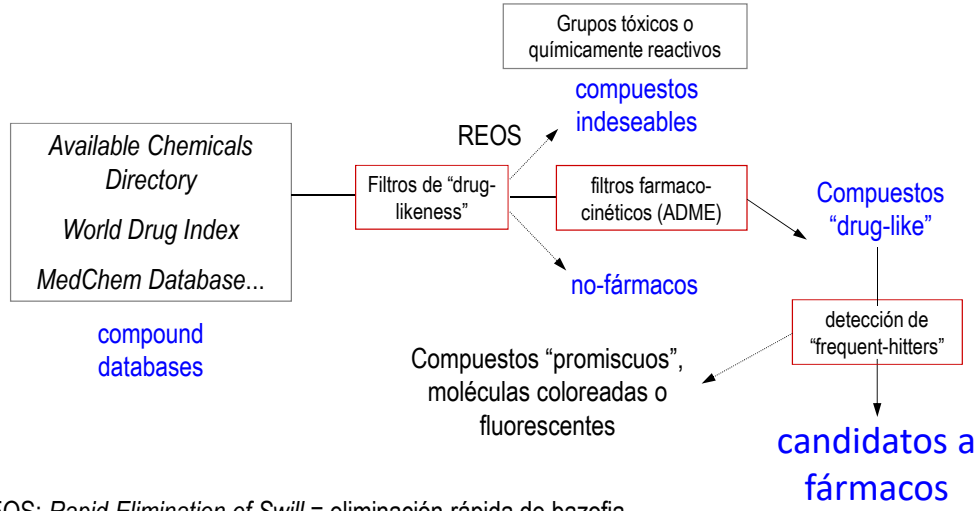
Virtual Screening (VS)



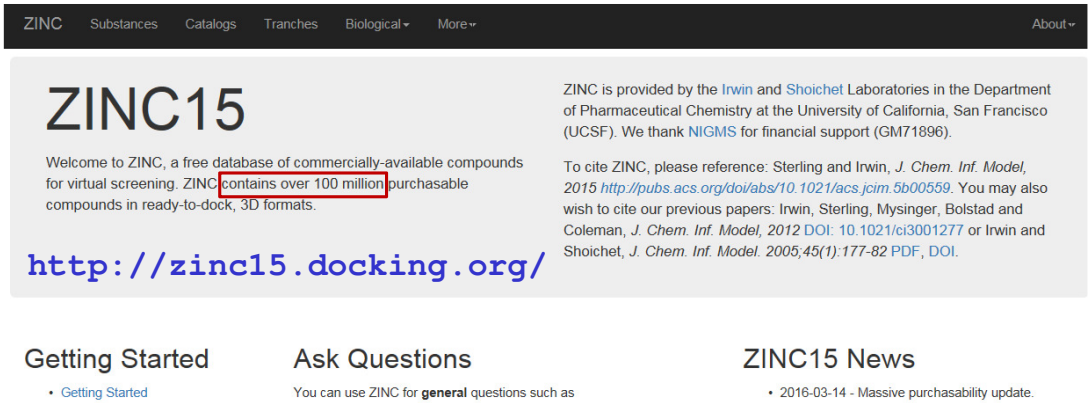
Objetivo del CV:
discriminar entre verdaderos ligandos y señuelos

Uso de filtros en **CRIBADO VIRTUAL** *in silico* y DISEÑO FOCALIZADO DE QUIMIOTECAS

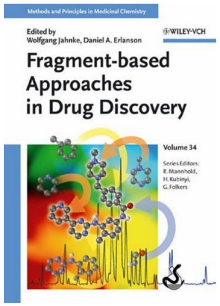
Estructuras "casi perfectas" en un mundo imperfecto



REOS: *Rapid Elimination of Swill* = eliminación rápida de bazofia

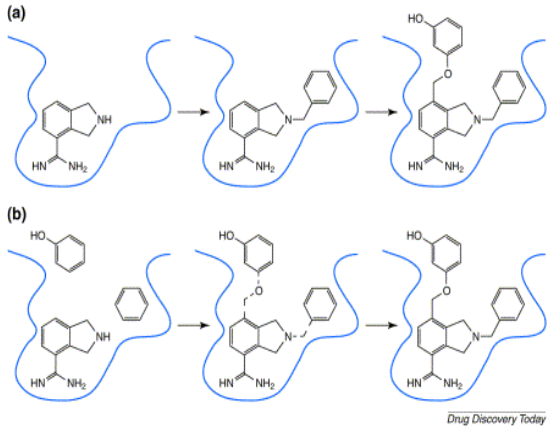


Teague Sterling & John J. Irwin
ZINC 15 – Ligand Discovery for Everyone
J. Chem. Inf. Model. 55(11): 2324–2337 (**2015**)



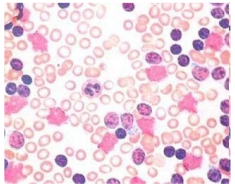
Dos estrategias para el ensamblado de una molécula a partir de fragmentos dentro del sitio de unión

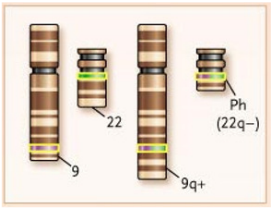
- **Crecimiento secuencial:**
- **Colocación de fragmentos y posterior conexión:**



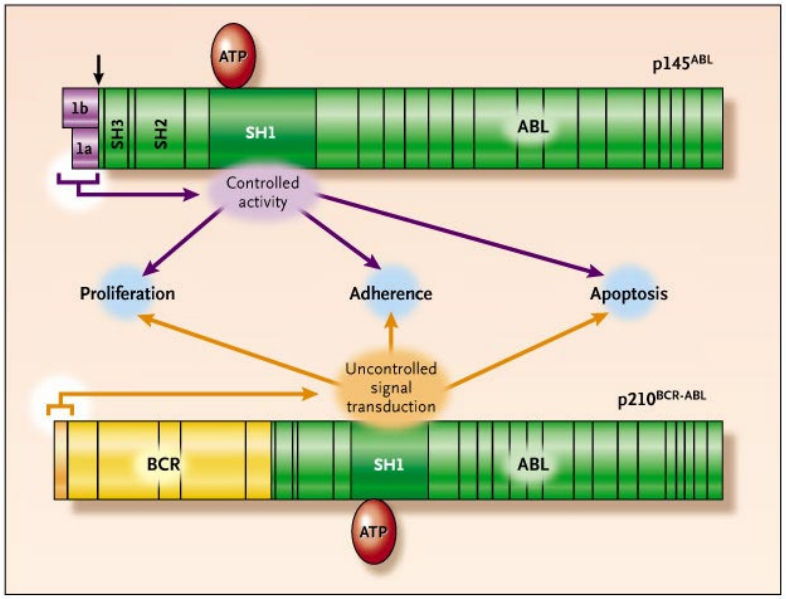
bolsillo de unión en la superficie de una proteína

Leucemia mieloide crónica





BCR-ABL oncogene
t(9;22)(q34;q11)

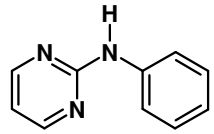


Regulación fisiológica por la proteína ABL normal y desregulación por la BCR-ABL oncogénica de procesos celulares claves, como proliferación, adhesión y apoptosis

Un ejemplo de éxito real: Glivec (STI571/ Imatinib)

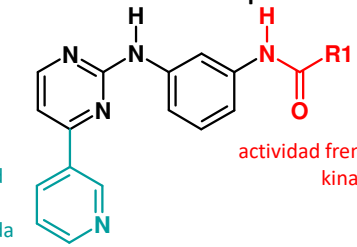
un fármaco antitumoral dirigido desarrollado racionalmente sobre una base estructural frente a una diana específica: Bcr-Abl

a



cabeza de serie

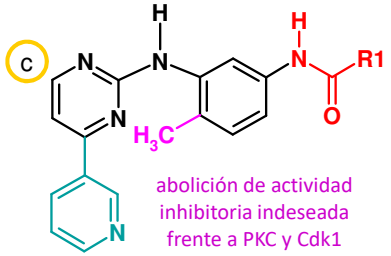
b



actividad celular aumentada

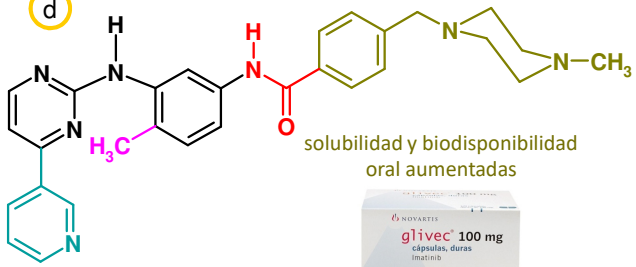
actividad frente a tirosina kinasas

c



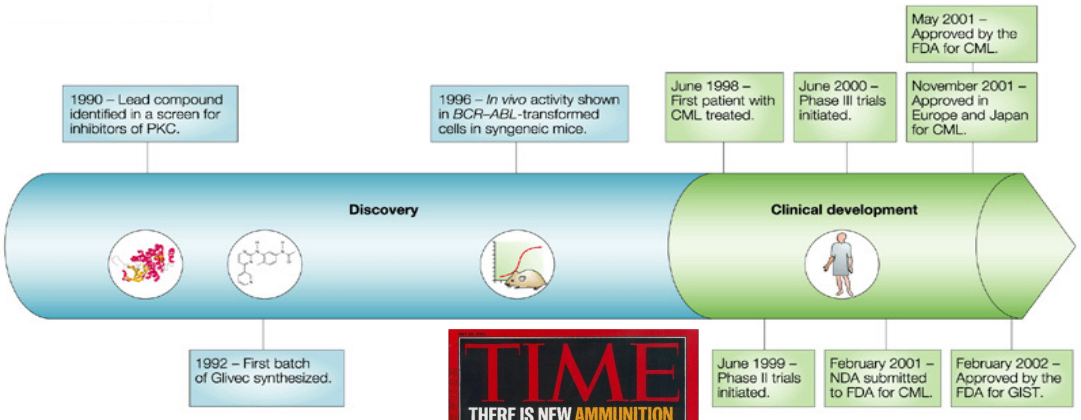
abolición de actividad inhibitoria indeseada frente a PKC y Cdk1 ("metilo bandera")

d

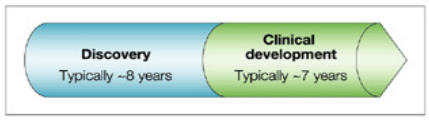


solubilidad y biodisponibilidad oral aumentadas

Calendario del desarrollo de Glivec



Typical development timeline



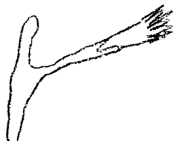
Nuevos inhibidores:
- dasatinib
- nilotinib, ...

Nature Reviews | Drug Discovery

"Considering the enormous number of chemical combinations which are taken into consideration in a struggle with diseases, it will always be a caprice of chance, or fortune, or of intuition, which decides which investigator gets into his hands the substances which turn out to be the best materials for fighting the diseases or the basal substances for the discovery of such"

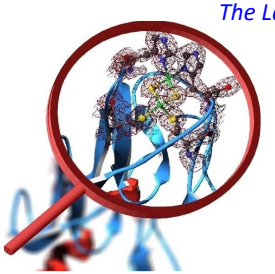
Paul Ehrlich

"Address in Pathology on Chemotherapeutics: Scientific Principles, Methods, and Results"
The Lancet, 445 (1913)



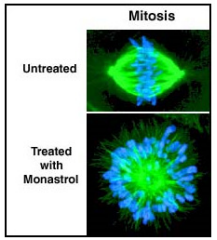
"amboceptor"
(1901)

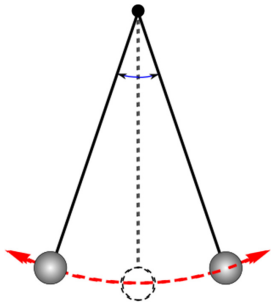
100 years →



→ ?

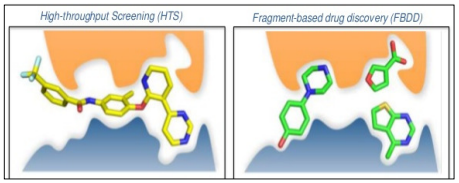
DESCUBRIMIENTO DE NUEVOS FÁRMACOS



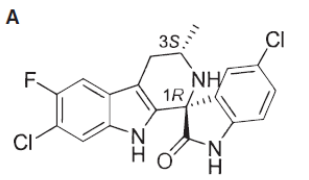


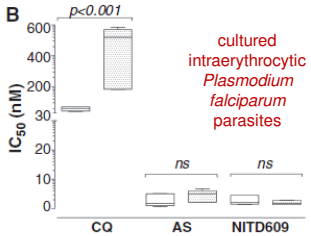
CRIBADO FENOTÍPICO
(respuesta biológica en células enteras u organismos modelo)

HTS **FBDD**

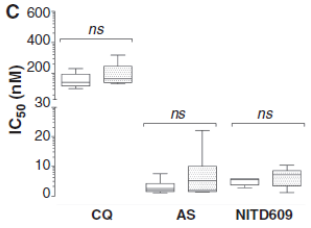


CRIBADO ORIENTADO A DIANA(S) FARMACOLÓGICA(S)

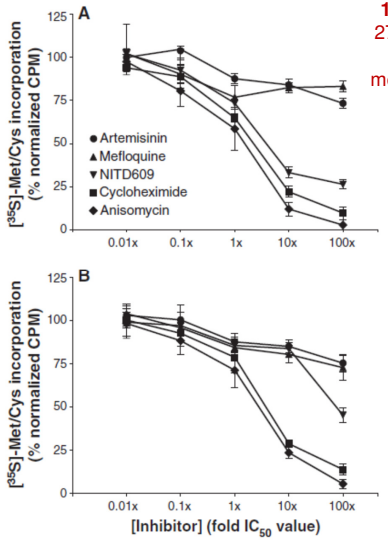




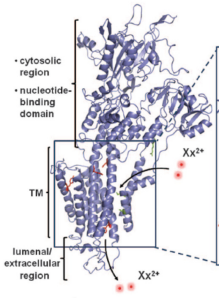
cultured intraerythrocytic *Plasmodium falciparum* parasites



Spiroindolones, a Potent Compound Class for the Treatment of Malaria

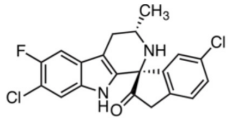


12000 compounds tested; 275 active; **1** with favorable PK properties and a mechanism of action distinct from that of existing antimalarial drugs

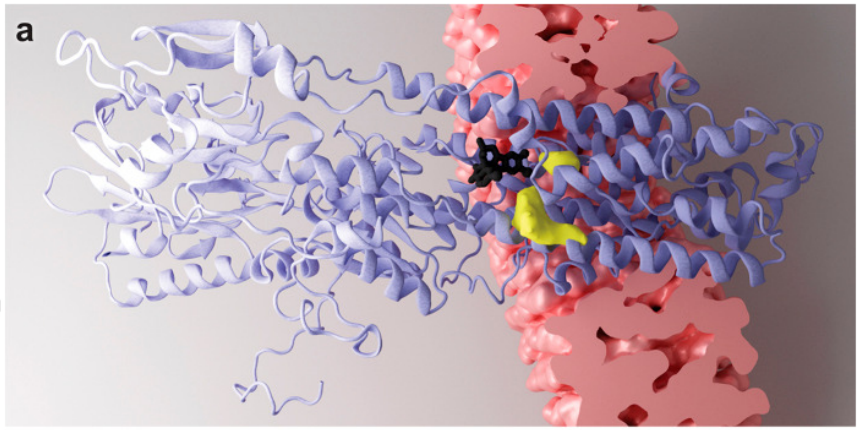


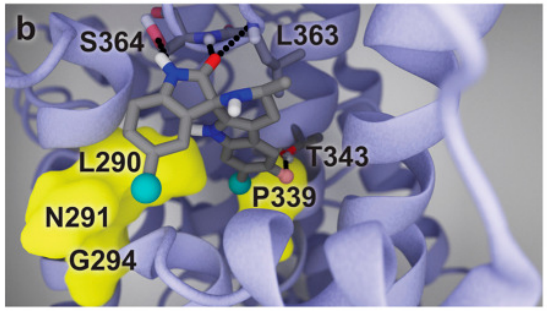
P. berghei

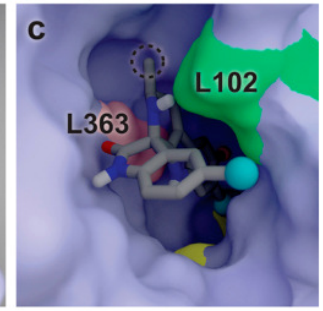
J Med Chem. 53(14):5155-5164 (**2010**) // *Science* 329(5996):1175-1180 (**2010**)



KAE609
(Cipargamin)
is a **P-type ATPase** inhibitor

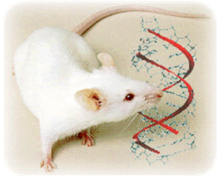






Sci Rep. 6:27806 (**2016**)

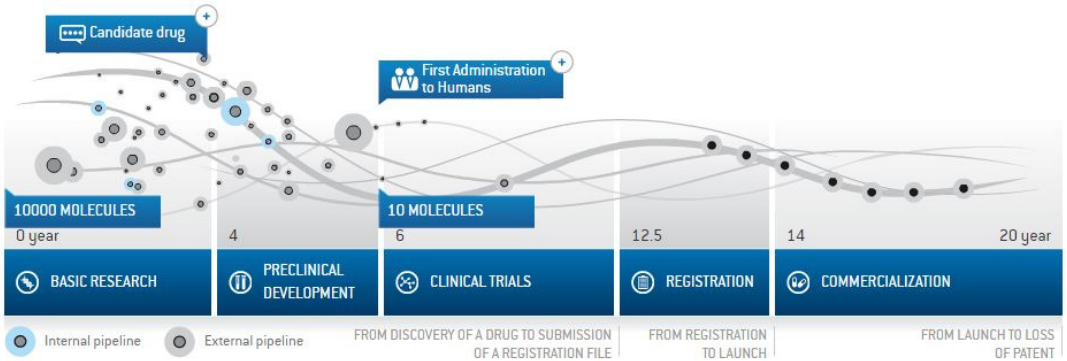
¿Qué es un mejor fármaco?
¿Cómo se puede reconocer?



"A better drug is obviously not a new molecule

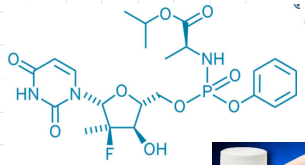
From Molecule to Medicine

There are a great many medical problems that remain unsolved. And there could be a whole lot more to come. There is a global need for new treatments for (chronic) diseases - such as HIV, cancer and central nervous system disorders.



*The chances of any one chemist discovering a drug that works—a molecule that is safe and improves people's lives in a meaningful way—**are small**.*
*The chances of discovering an actual cure? **Minuscule**.*

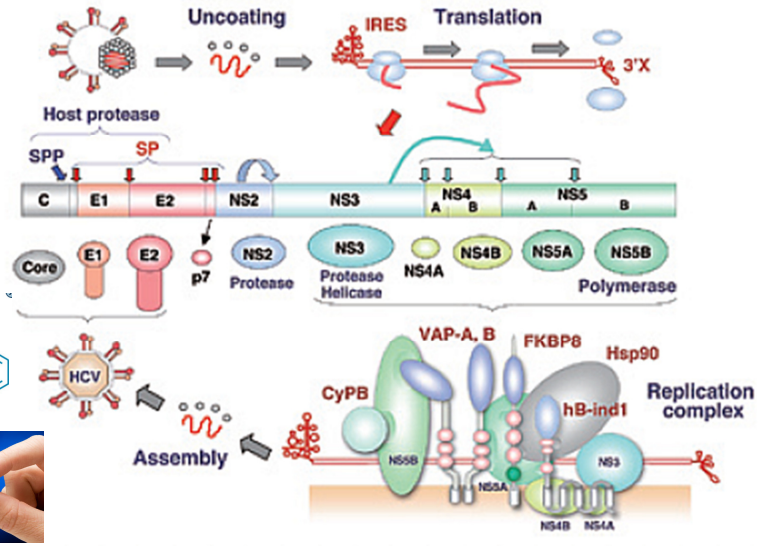
Michael Sofia



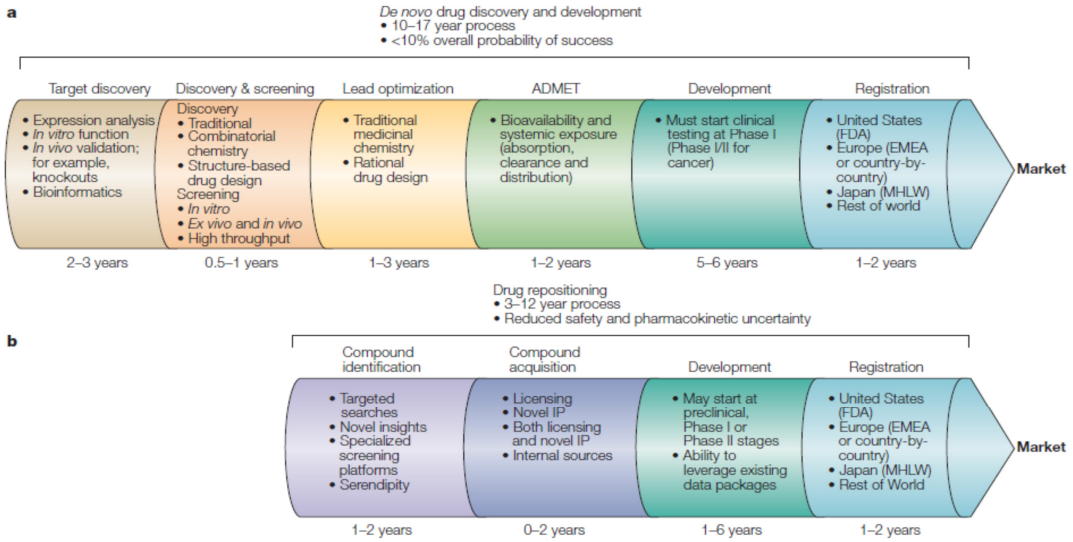
Sofosbuvir

GILEAD
Advancing Therapeutics. Improving Lives.

Infection and replication of HCV



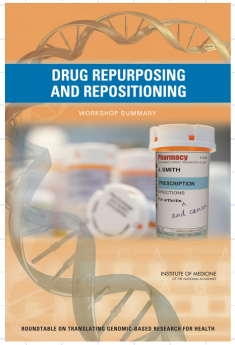
COMPARACIÓN ENTRE EL DESCUBRIMIENTO Y DESARROLLO DE FÁRMACOS *DE NOVO* Y EL REPOSICIONAMIENTO DE UN FÁRMACO



Ashburn TT, Thor KB. Drug repositioning: identifying and developing new uses for existing drugs. *Nat Rev Drug Discov*. 3:673-683 (**2004**)

EJEMPLOS DE REPOSICIONAMIENTO O "CAMBIO DE PROPÓSITO" DE UN FÁRMACO

Reconocimiento (en gran medida, de forma no intencionada o "por serendipia") de efectos sobre una diana diferente de la original (*off target*) o de efectos sobre la misma diana que podrían ser utilizados para identificar una nueva indicación.



- **AAS**: menos utilizado como AINE por sus efectos gastrolesivos pero amplio uso a dosis bajas como antiagregante plaquetar.
- **Talidomida**: retirada del mercado por sus efectos teratogénicos, se ha demostrado su utilidad en el tratamiento de la lepra y del mieloma múltiple.
- **Sildenafilo**: originalmente desarrollado como antihipertensivo, sus indicaciones actuales son la hipertensión arterial pulmonar y la disfunción eréctil
  (> $ 2 000 000 000 de ventas mundiales en 2012).

- **Minoxidilo**
- **Finasterida**
- **Bimatoprost, etc.**

"Knowing is not enough; we must apply. Willing is not enough; we must do."
—Goethe

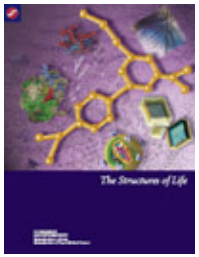
http://www.ncbi.nlm.nih.gov/books/NBK202175/

National Institute of General Medical Sciences
Basic Discoveries for Better Health

Activity
How well the drug candidate binds to its target and generates the desired biological response

Solubility
Affects how well the drug [illegible] orbed [illegible] orally

A drug candidate must pass many hurdles to earn the description "good medicine". It must have the best possible activity, solubility, bioavailability, half-life, and metabolic profile. Attempting to improve one of these factors often affects other factors. For example, if you structurally alter a lead compound to improve its activity, you may also decrease its solubility or shorten its half-life. The final result must always be the best possible compromise.



[illegible] idate [illegible] ate tissue(s) in its active form when given orally

Half-Life
How long the drug candidate stays in its active form in the body

https://publications.nigms.nih.gov/structlife/structlife.pdf

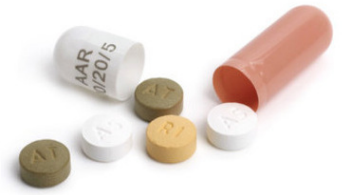
A drug candidate must pass many hurdles to earn the description "good medicine". It must have the best possible activity, solubility, bioavailability, half-life, and metabolic profile. Attempting to improve one of these factors often affects other factors. For example, if you structurally alter a lead compound to improve its activity, you may also decrease its solubility or shorten its half-life. The final result must always be the best possible compromise.

Nuevos medicamentos que contienen dosis fijas de varios fármacos en una misma forma farmacéutica para prevenir enfermedades cardiovasculares:

Table 1 | Fixed-dose combination strategies for cardiovascular prevention

Polypill name	Company	Indication	Active components (mg)
Red Heart Pill 1™	Dr. Reddy's Laboratories (Hyderabad, Andhra Pradesh, India)	Secondary prevention	Aspirin (75), atenolol (50), lisinopril (10), simvastatin (20)
Red Heart Pill 2™	Dr. Reddy's Laboratories	Primary prevention	Aspirin (75), hydrochlorothiazide (12.5), lisinopril (10), simvastatin (20)*
Polycap®	Cadila Pharmaceuticals (Ahmedabad, Gujarat, India)	Primary prevention	Aspirin (100), atenolol (50), hydrochlorothiazide (12.5), ramipril (5), simvastatin (20)
Polycap® DS	Cadila Pharmaceuticals	Primary prevention	Atenolol (100), hydrochlorothiazide (25), ramipril (10), simvastatin (40)
Zycad-4™	Zydus Cadila Healthcare (Ahmedabad, Gujarat, India)	Secondary prevention	Aspirin (75), atorvastatin (10), metoprolol (50), ramipril (5)
Ramitorva™	Zydus Cadila Healthcare	Secondary prevention	Aspirin (75), atorvastatin (10), ramipril (5)
Polytorva™	USV (Govandi East, Mumbai, India)	Secondary prevention?	Aspirin (75), atorvastatin (5), ramipril (10)
PolyIran 1™	Alborz Darou Pharmaceutical Company (Tehran, Iran)	Primary or secondary prevention?	Aspirin (81), atorvastatin (20), enalapril (5), hydrochlorothiazide (25)
PolyIran 2™	Alborz Darou Pharmaceutical Company	Primary or secondary prevention?	Aspirin (81), atorvastatin (20), hydrochlorothiazide (25), valsartan (40)
Polypill‡	Hypermarcas SA (São Paulo, Brazil)	Primary prevention?	Atorvastatin (10), lisinopril (50), hydrochlorothiazide (12.5)
Trinomia®	Ferrer Internacional (Barcelona, Spain)	Secondary prevention	Aspirin (100), ramipril (2.5, 5, or 10), simvastatin (40)

*In a new formulation, the dose of simvastatin has been increased to 40 mg. ‡No trade name given.

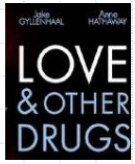


nature REVIEWS CARDIOLOGY

Sanz, G. & Fuster, V.
Polypills for cardiovascular prevention: a step forward?
Nat. Rev. Cardiol. doi:10.1038/nrcardio.2013.157 (**2013**)

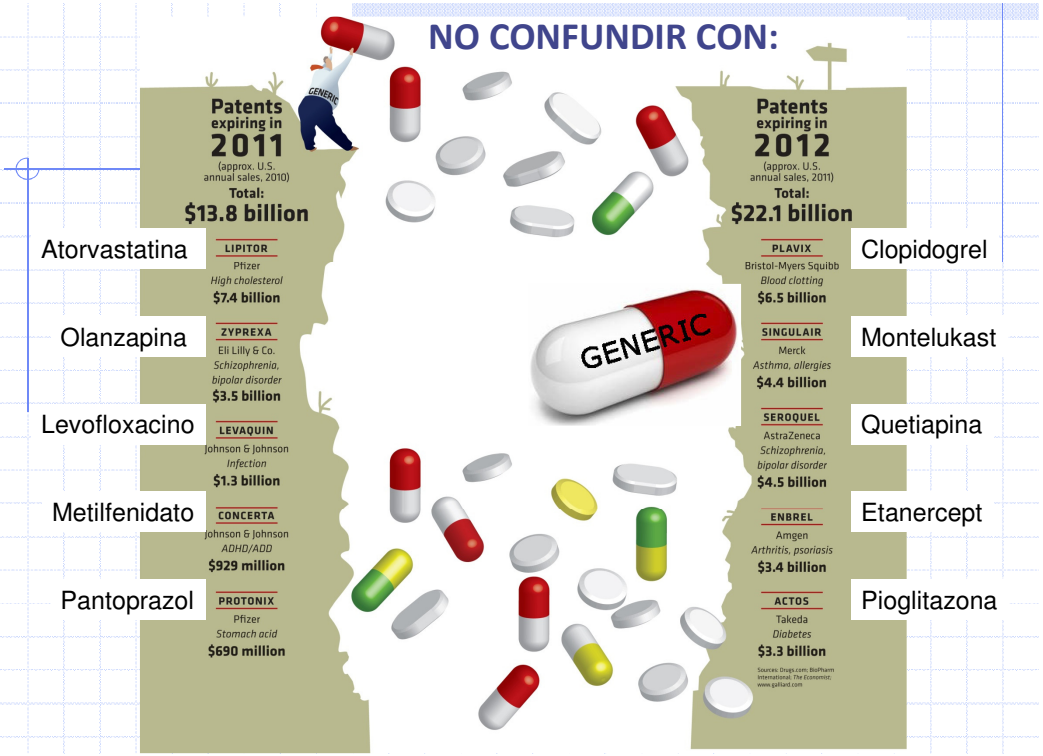
Fármacos *me-too* ("yo también")

Goddard Cartoon ©PharmaVentures; all rights reserved



Un fármaco que sigue (en un momento dado) a una terapia "primera en su clase" (*first-in-class*) y actúa esencialmente a través del mismo mecanismo, pero.....
- no hay dos fármacos que sean realmente iguales (e.g. inhibidores de kinasas en oncología)
- si varias compañías están trabajando sobre el mismo tipo de fármaco, intentando superarse unas a otras en el camino hacia la comercialización, podría parecer que el resultado final es un fármaco "imitamonos" (*copycat*) que se ha desarrollado a costa y riesgo de la molécula que llegó primero al mercado (e.g. vildagliptina y sitagliptina como inhibidores DPP-IV para la diabetes.
- los fármacos *me-too* crean competencia y, en consecuencia, los precios pueden bajar.

NO CONFUNDIR CON:



Colaboraciones

universidad-empresa

"BIG PHARMA"

"ACADEMIA"

Pharma Companies

- Expiring patents on blockbuster drugs
- Limited internal product pipeline
- Declining opportunities with biotech companies
- Streamlined access to university IP

Universities

- Access to pharma's expertise
- Emphasis on translational medicine
- Access to pharma's compound libraries
- Funding concerns

Larger-scale collaboration and umbrella agreements

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

What's on the regulator's mind?