Laboratorio di Preparazioni Estrattive

Estrattiva
Farmaci di Origine Naturale e Sintetica

SAPIENZA
UNIVERSITÀ DI ROMA

Farmaci di origine naturale (1)

L'uomo ha utilizzato per millenni sostanze provenienti dalla natura a scopo medicinale.

I primi documenti che testimoniano l'uso di piante a scopo medicinale risalgono a circa 2600 anni prima di Cristo; essi sono costituiti da centinaia di tavolette di argilla, ritrovate in Mesopotamia, in cui sono descritte in caratteri cuneiformi circa 1000 preparazioni ottenute da piante ed utilizzate a scopo medicinale; tra queste ritroviamo l'olio di cedro (Cedrus) e di cipresso (Cupressus sempervirens), la liquirizia (Glycyrrhiza glabra), mirra (specie Commiphora), e del Papaver somniferum (alcune delle sostanze attive presenti in tali estratti sono ancora oggi utilizzate in terapia)

Farmaci di origine naturale (2)

La medicina egiziana risale a circa il 2900 a. C.; il più noto documento farmaceutico egiziano è il papiro Ebers, datato 1500 a. C., che descrive oltre 700 farmaci (derivati principalmente da piante, ma anche da organi animali e dal regno minerale) formulati come impiastri, pillole, unguenti, infusioni, gargarismi, e veicolati con miele, vino, birra, latte.

La Materia Medica cinese, il cui primo documento risale al 1100 a. C., è stata insegnata per secoli. Analoghe documentazioni sono state ritrovate per la medicina indiana e tibetana.

Farmaci di origine naturale (3)

Nel mondo occidentale, i greci fornirono un contributo sostanziale allo sviluppo razionale di farmaci derivati da erbe.

- Teofrasto, filosofo e naturalista greco, (300 a. C.), nella sua Storia delle piante, descrive le proprietà delle erbe mettendo in evidenza i cambiamenti delle loro caratteristiche che si verificano durante la coltivazione (vita vegetativa).
- Dioscoride, un medico greco al seguito delle armate romane (100 d. C.), annotò accuratamente la raccolta, la conservazione e l'uso di erbe medicinali che ebbe modo di conoscere durante i suoi viaggi.
- Galeno (130-200 d. C.) praticò ed insegnò farmacia e medicina a Roma e pubblicò almeno 30 libri di argomento medico, con complesse descrizioni e formule per la preparazione di farmaci (le cosiddette preparazioni galaniche)

Farmaci di origine naturale (4a)

Durante il medioevo, dal quinto al dodicesimo secolo d.C., nei monasteri inglesi, francesi, irlandesi e tedeschi queste conoscenze furono tramandate ed arricchite, con l'apporto di conoscenze provenienti anche dalla Cina e dall'India.

Avicenna (980-1037), farmacista, medico, poeta e filosofo persiano di cultura araba, contribuì molto alla scienza farmaceutica e medica con opere quali la Canon Medicinae. Tale opera, tradotta in latino da Gerardo da Cremona poco dopo la metà del sec. XII, è considerata la codificazione complessiva della medicina greco-romana e fu adottata quale testo principale nelle facoltà mediche rimanendo in auge fino al sec. XVI.

Questi ed altri furono formalmente codificati in Inghilterra nel 1618 nella London Pharmacopoeia.

Farmaci di origine naturale (4b)

Canon Medicinae:

Poderosa enciclopedia medica divisa in cinque parti, che tratta della medicina teorico-pratica in generale, dell'anatomia, dei medicamenti e delle singole malattie

Farmaci di origine naturale (5)

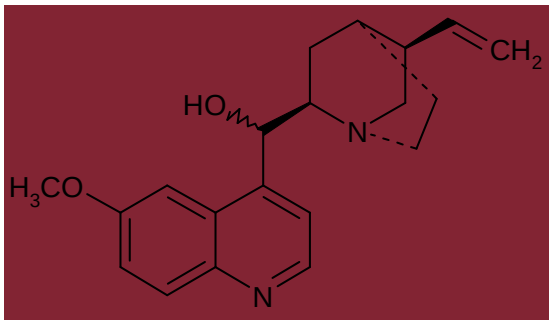
Un grosso progresso nella scienza farmaceutica si è avuto quando, all'inizio del XIX sec., sono stati messi a punto protocolli per l'isolamento dei principi attivi presenti in un campione naturale. Infatti, la possibilità di utilizzare il composto puro, piuttosto che la pianta,o un suo estratto, consente di poter dosare accuratamente il principio attivo, evitando sovra- o sottodosaggi, sempre possibili quando vengono somministrati preparati il cui tenore di principio attivo può variare in dipendenza da vari fattori (metodo di coltivazione, raccolta, essiccamento, conservazione, composizione del terreno, clima, etc.).

Farmaci di origine naturale (6a)

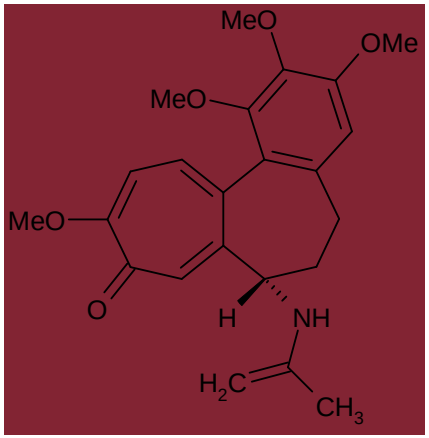
La morfina fu isolata da Serturner nel 1806 e posta in commercio come prodotto puro nel 1826; la codeina fu isolata da Robiquet nel 1832, la papaverina da Merck nel 1848 e poi successivamente efedrina (1887), chinina, ergotamina, atropina, reserpina, colchicina e ajmalina (nella metà del XX secolo) e gli alcaloidi della Vinca, negli anni '60

Farmaci di origine naturale (6b)

Chinina/Chinidina

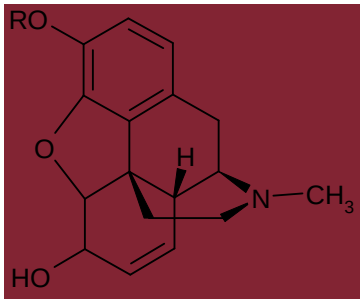


Colchicina

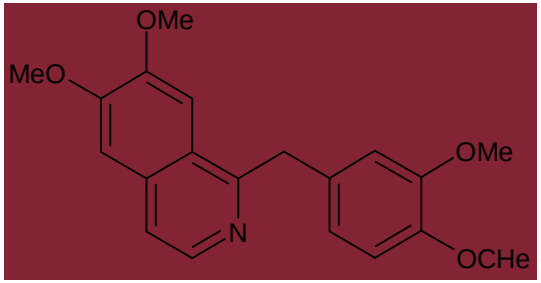


Morfina R = H (1806)

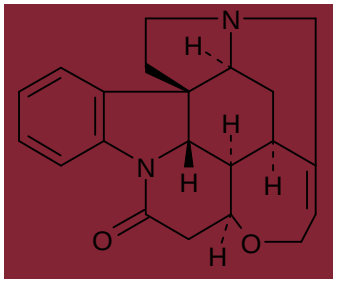
Codeina R = CH3 (1832)



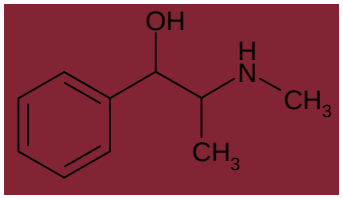
Papaverina (1848)



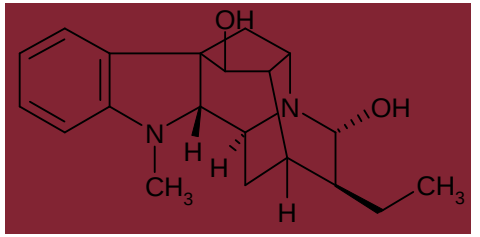
Farmaci di origine naturale (6c)



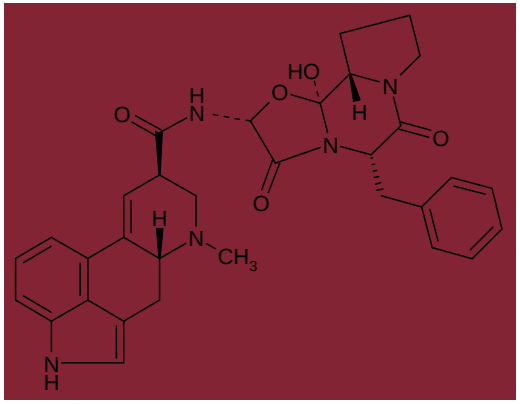
Stricnina



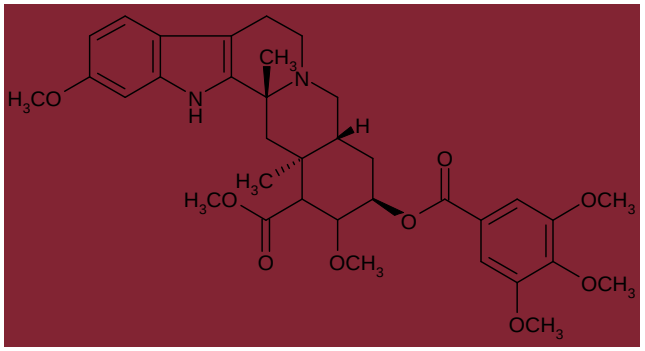
efedrina



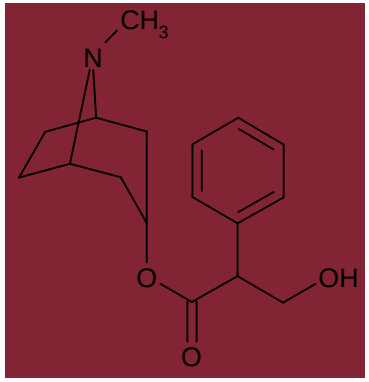
Ajmalina



Ergotamina



Reserpina



Atropina

Farmaci di origine naturale (7)

La nascita dell'estrattiva può quindi essere collocata storicamente in questo periodo. I prodotti naturali hanno quindi formato per millenni la base per la medicina tradizionale. Fino al 1930 la quasi totalità dei farmaci era di origine naturale (vegetale, animale, minerale). Negli anni '90 si calcolava che circa il 25% dei farmaci prescritti conteneva principi attivi estratti da piante

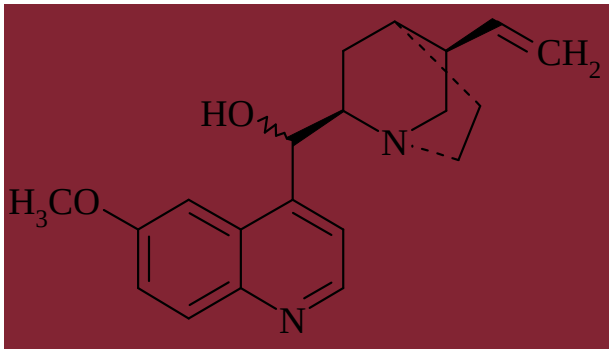
Farmaci di origine naturale (8)

L'industria farmaceutica ha rivolto verso i prodotti d'origine naturale un interesse decrescente negli anni compresi tra il 1960 ed il 1985. Un articolo apparso nei primi anni settanta, in piena era degli antibiotici, prospettava un futuro tetro per i prodotti naturali. Si riteneva infatti che la scoperta di nuovi farmaci da questa via fosse un processo troppo costoso, lento ed inefficiente.

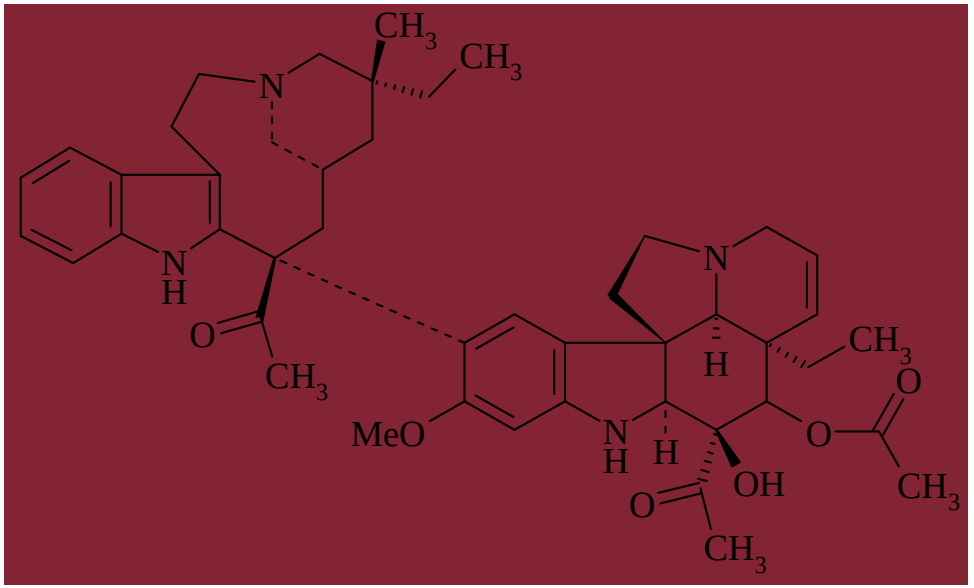
Farmaci di origine naturale (9a)

Inoltre, la produzione di farmaci mediante estrazione da una fonte naturale pone in genere dei problemi di carattere logistico, quali il rifornimento di grandi biomasse ed il successivo isolamento da esse, a volte in basse %, del principio attivo. Ad esempio, la produzione degli alcaloidi della china (principalmente chinina e chinidina) richiede circa 5.000-10.000 tonnellate di corteccia di china per ottenere 300-500 tonnellate di alcaloidi (5%); bisogna tra l'altro ricordare che l'albero della china impiega 10-12 anni per rigenerarsi. La vincristina e la vinblastina sono estratte dal Catharantus roseus e dalla Vinca rosea in ragione di 2 g per tonnellata di pianta fresca (2x10-4 %).

Farmaci di origine naturale (9a)



Chinina / Chinidina

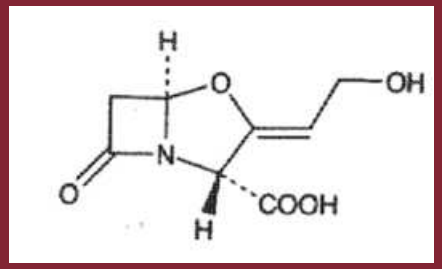


Vincristina / Vinblastina

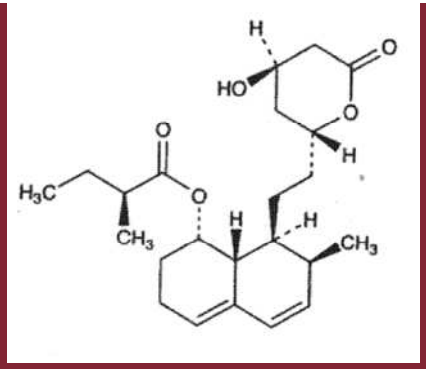
Farmaci di origine naturale (10a)

Successivamente, grazie anche ad un numero di scoperte molto significative, incluse quelle dell'acido clavulanico, ciclosporina A, mevastatina, avermectina, si è registrato un aumento degli sforzi da parte della industria farmaceutica tesi alla scoperta di nuovi farmaci basati su prodotti naturali.

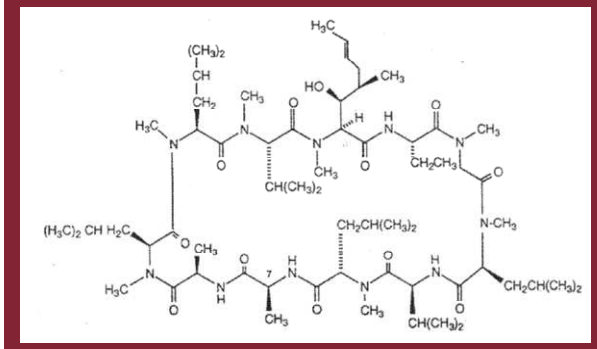
Farmaci di origine naturale (10b)



Acido Clavulanico



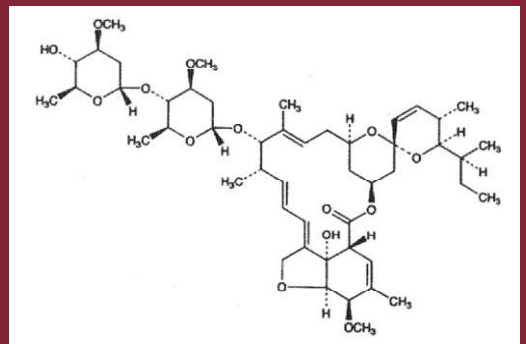
Mevastatina



Ciclosporina A

(Trichederma polisporum)

<u>attività:</u> immunosoppressivo



Avermectina

Farmaci di origine naturale (11a)

Ciò dipende sia dagli importanti sviluppi nelle tecnologie in grado di accelerare la purificazione e l'identificazione di un composto (HPLC, NMR, MS), sia dal riconoscimento dell'importanza che la diversità (intesa come varietà e complessità strutturale) riveste nella scoperta di nuovi farmaci.

Farmaci di origine naturale (11b)

The pharmaceutical industry's productivity continues to be dismal. This state of affairs is due to many factors, and one may have been the diminished interest in natural products drug discovery as the industry embraced promising and exciting new technologies, particularly combinatorial chemistry. However, the tide may be turning, for three reasons.

- combinatorial chemistry's promise to fill drug development pipelines with de novo synthetic small-molecule drug candidates is unfulfilled.
- the practical difficulties of natural products drug discovery are being overcome by advances in separation technologies and in the speed and sensitivity of structure elucidation.
- a compelling case is being made for the intrinsic utility of natural products as sources of drug leads

Farmaci di origine naturale (12)

Un esame delle liste dei farmaci più venduti negli ultimi anni mostra diversi prodotti naturali o loro derivati.

Sintesi 49 %

Semi-Sintesi 10 %

Naturali ~35 %

Sieri e Vaccini ~ 5%

Farmaci di origine naturale (13a)

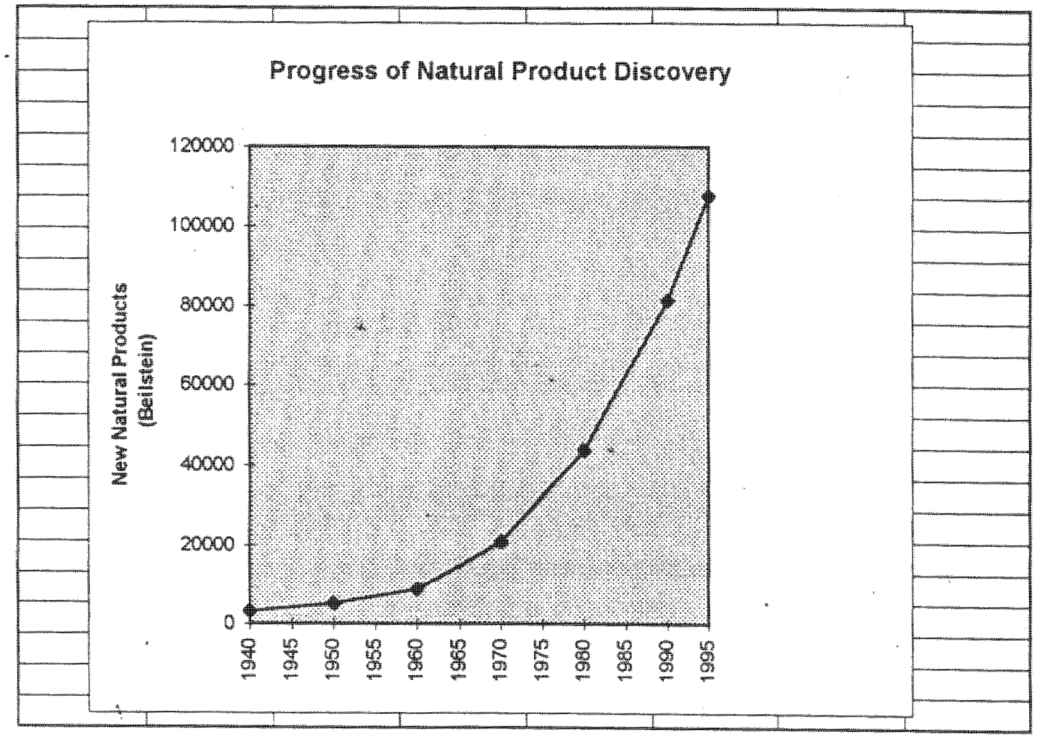


Fig. 13. Numbers of new natural products discovered over past 60 yr (data from **ref. *66***).

Farmaci di origine naturale (13b)

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Reviews

Natural Products as Sources of New Drugs over the Period 1981−2002

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Received March 7, 2003

This review is an updated and expanded version of a paper that was published in this journal in 1997. The time frame has been extended in both directions to include the 22 years from 1981 to 2002, and a new secondary subdivision related to the natural product source but applied to formally synthetic compounds has been introduced, using the concept of a "natural product mimic" or "NM" to join the original primary divisions. From the data presented, the utility of natural products as sources of novel structures, but not necessarily the final drug entity, is still alive and well. Thus, in the area of cancer, the percentage of small molecule, new chemical entities that are nonsynthetic has remained at 62% averaged over the whole time frame. In other areas, the influence of natural product structures is quite marked, particularly in the antihypertensive area, where of the 74 formally synthetic drugs, 48 can be traced to natural product structures/mimics. Similarly, with the 10 antimigraine drugs, seven are based on the serotonin molecule or derivatives thereof. Finally, although combinatorial techniques have succeeded as methods of optimizing structures and have, in fact, been used in the optimization of a number of recently approved agents, we have not been able to identify a *de novo* combinatorial compound approved as a drug in this time frame.

Farmaci di origine naturale (13c)

Classification of Bioactive Molecules by Source

"B": Biological; usually a large (>45 residues) peptide or protein either isolated from an organism/cell line or produced by biotechnological means in a surrogate host.

"N": Natural product.

"ND": Derived from a natural product and is usually a semisynthetic modification.

"S": Totally synthetic drug, often found by random screening/modification of an existing agent.

"S*": Made by total synthesis, but the pharmacophore is/was from a natural product.

"V": Vaccine.

Farmaci di origine naturale (13d)

Table 1. New Chemical Entities and Medical Indications by Source of Compound[a,b]

indication	total	origin of drug						indication	total	origin of drug					
		B	N	ND	S	S*	V			B	N	ND	S	S*	V
analgesic	15				13	2		antiviral	35	2		1	8	24	
anesthetic	5				5			anxiolytic	10				10		
anti-Alzheimer's	4		1		3			benign prostatic hypertrophy	4		1	2	1		
anti-Parkinsonism	10			2	4	4		bronchodilator	8			2		6	
antiallergic	15		1	3	11			calcium metabolism	17			8	9		
antianginal	4				4			cardiotonic	13			3	5	5	
antiarrhythmic	15		1		12	2		chelator & antidote	5				5		
antiarthritic	12	2		1	9			contraception	6			6			
antiasthmatic	12			2	8	2		diuretic	4				4		
antibacterial	90		9	61	19	1		gastroprokinetic	4				3	1	
anticancer	79	12	9	21	25	10	2	hematopoiesis	5	5					
anticoagulant	16	3		12		1		hemophilia	9	9					
antidepressant	21				19	2		hepatitis	17	7				1	9
antidiabetic	23	12	1	2	7	1		hormone	20	10		10			
antiemetic	7				1	6		hormone replacement therapy	4			4			
antiepileptic	10			1	6	3		hypnotic	11				11		
antifungal	24	1		2	21			hypocholesterolemic	9		3	1	2	3	
antiglaucoma	13			4	5	4		hypolipidemic	8		1		7		
antihistamine	12				12			immunostimulant	10	4	3	2	1		
antihyperprolactinemia	4			4				immunosuppressant	10	4	5	1			
antihypertensive	75			1	40	34		muscle relaxant	10			4	3	3	
antiinflammatory	50	1		13	36			neuroleptic	10				8	2	
antimigraine	10				3	7		nootropic	8			3	5		
antiparasitic	13		2	5	4	2		platelet aggregation inhibitor	4			3	1		
antipsoriatic	4			3		1		respiratory distress syndrome	6	3	1		2		
antipsychotic	7				5	2		vasodilator	6			3	3		
antithrombotic	28	13	1	5	7	2		vulnerary	5	2		2	1		
antiulcer	32	1	1	12	18			grand total	868	91	40	209	386	131	11

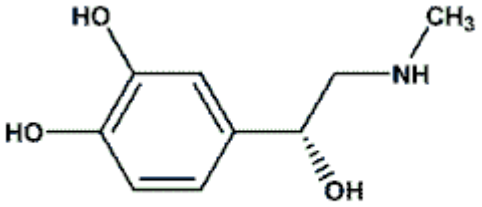
Farmaci di origine naturale (13e)

Rationale for the Use of the Subclassification
of "NM" or "Natural Product Mimic".
One of the more interesting meta-analyses that can be performed on the structural data that we have assembled is to attempt to decide whether a given compound or series of similar compounds is derived from knowledge gained from a study of the original natural product-derived drug or, more usually, lead or initial hit, even though the final product of such a synthetic campaign may not bear much, if any, resemblance to the original natural product. As a result of such an analysis, we have given the subdesignation "NM" to a fairly substantial number of compounds that apparently fall into the category of "designed from knowledge gained from a natural product" or, in some cases, "discovered by using an assay whereby the compound is designed to displace the natural substrate in a competitive fashion", and are thus "Natural Product Mimics" or "NM". In practice, both methods and other information such as X-ray binding studies (ab initio or in silico), may well be involved in the derivation of the final drug

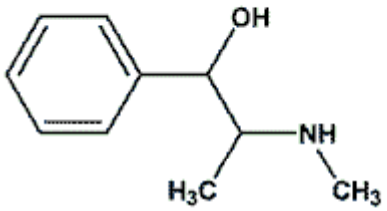
Farmaci di origine naturale (13f)

There are two limit cases, representing an obvious natural product relationship at one extreme, to the nonobvious cases at the opposite extreme, that can be considered in such analyses. In the first, where the drug entity is considered to be an "S*" (totally synthetic but based on a natural product pharmacophore), the relationship may be relatively obvious. Examples would be the ACE inhibitors that were designed to mimic the C-terminal sequence of angiotensin I (AT I) and thus prevent the production of angiotensin II (AT II) by removal of the C-terminal dipeptide following the work originally started from studies on teprotide. Another obvious example would be the -blockers or -agonists (selective or general) that are modeled upon the biogenic amines, and the subsets of dopamine receptor antagonists and serotonin receptor blockers derived from the base dopamine or serotonin structures (with modifications to aid in binding). In these cases (structures 1-6), the structural relationships are relatively obvious. We have identified the mechanism of action of all compounds that fall into the "S*/NM" subcategory, and these are available in database format from the authors.

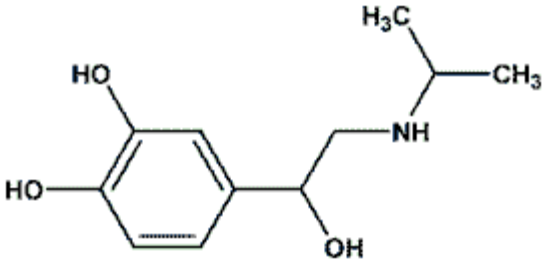
Farmaci di origine naturale (13g)



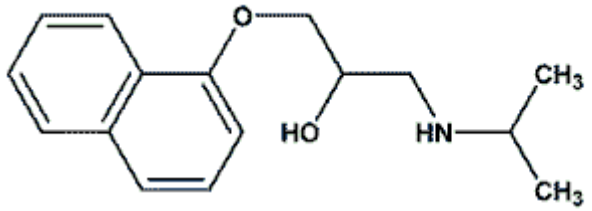
1 Epinephrine



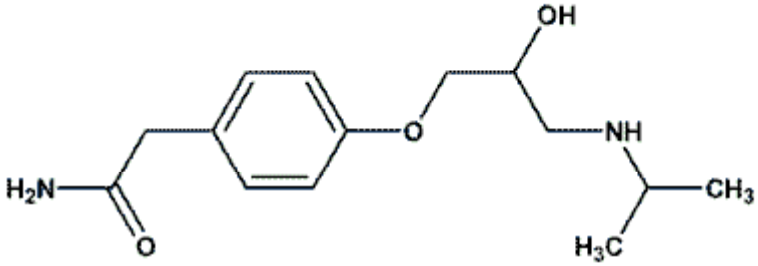
2 Ephedrine



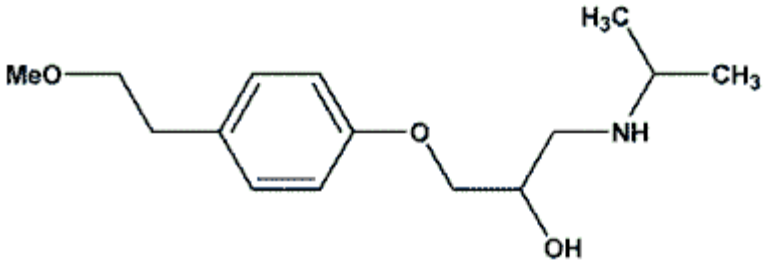
3 Isoprenaline



4 Propranolol



5 Atenolol



6 Metaprolol

Farmaci di origine naturale (13h)

In the second limit case, those compounds classified as "S" for totally synthetic, the relationships are frequently nonobvious and require some "structural forensics" to determine any relationship to a natural product. Where they have been identified by direct competitive assays against the natural product substrate, the relationship will be similar to the second "S*/NM" case discussed above, i.e., where there is a direct displacement of the natural substrate. However, in a number of cases the genesis of the synthetic drug can be derived directly from publications, and one can show how the compound(s) evolved from the natural product(s) structural information.

Perhaps the best examples to consider initially are those derived from the use of peptide isosteres and pseudopeptides (peptidomimetics), as the final product(s) in these cases bear little formal structural relationship to the original peptide(s). There are a series of excellent reviews, one published in 199348 and the others in 2002, that can aid materially in this type of study, and we recommend that readers who are interested in this aspect of the analyses consult them in detail.

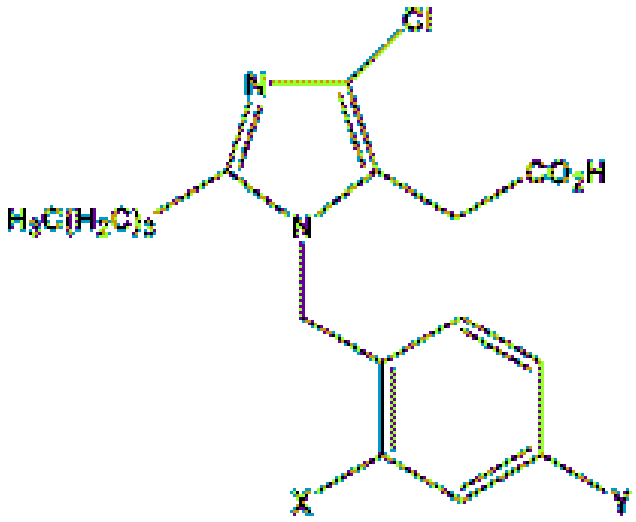
Farmaci di origine naturale (13i)

One example that demonstrates the point is the history of the angiotensin II receptor (AT1R) blocker, losartan, which we define as an "S/NM", both on the basis of its mechanism/assay and, in particular, from the following discussion. In this discussion there is a potential for confusion. The conventional shorthand biochemical designation for the pharmacologically active octapeptide that results from the action of angiotensin-converting enzyme (ACE) upon the decapeptide angiotensin I (or AT I) is AT II. However, from biochemical pharmacology nomenclature, the receptor for this octapeptide ligand is designated as the angiotensin 1 receptor (AT1R). Thus, AT1R is the receptor for the octapeptide AT II, the active ligand produced by ACE action upon angiotensin I (AT I), not, as some may expect, the receptor for the ACE substrate, AT I.
From structure activity (SAR) studies on multiple peptide analogues of the octapeptide AT II, whose formal sequence is H2N-Asp1-Arg2-Val3-Tyr4-Ile5-His6-Pro7-Phe8-CO2H, there were suggestions that the His6 residue was required for receptor recognition and that the agonist activity required the phenyl ring of the Phe8, the hydroxyl group of the Tyr4, and the C-terminal carboxylate. Thus, a working hypothesis for the binding pocket in AT1R for the ligand, AT II, would be a positively charged site, a lipophilic pocket or pockets, and a hydrogen bond acceptor.

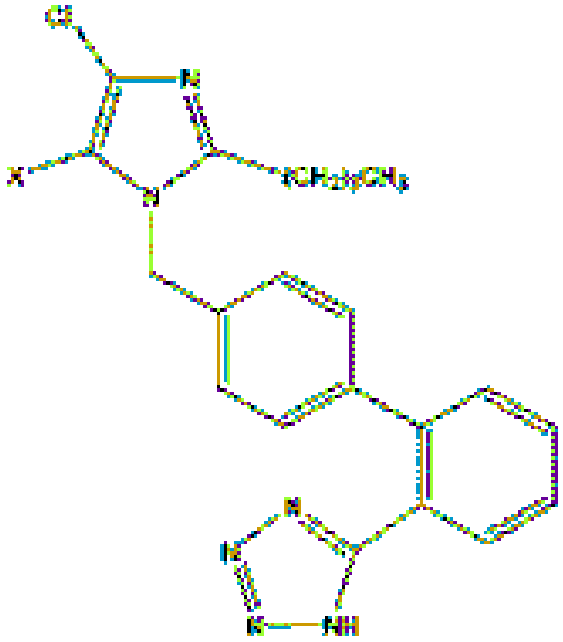
Farmaci di origine naturale (13l)

The first lead to a nonpeptidic structure that demonstrated AT1R inhibition was actually from nature. In 1982, workers at Takeda reported in a U.S. patent the structures of three microbial metabolites (structures 7-9) that had low potency as antihypertensive agents. Using simple modeling methods, both Dreiding models and simple computerized techniques, workers at DuPont postulated that these compounds, which at high concentrations demonstrated a small reduction in blood pressure via blockade of AT1R, bound to the receptor in a manner such that the carboxylic acid was equivalent to the C-terminal carboxylate of AT II; the imidazole nitrogens were comparable with the histidine residue; and the benzyl group pointed toward the N-terminus of AT II, with the para position of that residue holding the most promise for a systematic extension toward the amino-terminus of AT II. By making the (correct) assumption that a second carboxylate in the para position of the phenyl ring would give a negative charge in the vicinity of the Tyr4 hydroxyl and the Asp1 -carboxylic acid, the compound was prepared (structure 10) and demonstrated a 10-fold increase in binding affinity. The rest of the story of the derivation of what finally became the first approved AT1R antagonist (losartan) is told in three excellent papers by the DuPont group with a clinical efficacy review in 1996 in the New England Journal of Medicine,56 and recently an excellent QSAR study of this and later drugs with a similar mechanism of action (MOA) has been published by Hansch and associates.

Farmaci di origine naturale (13m)



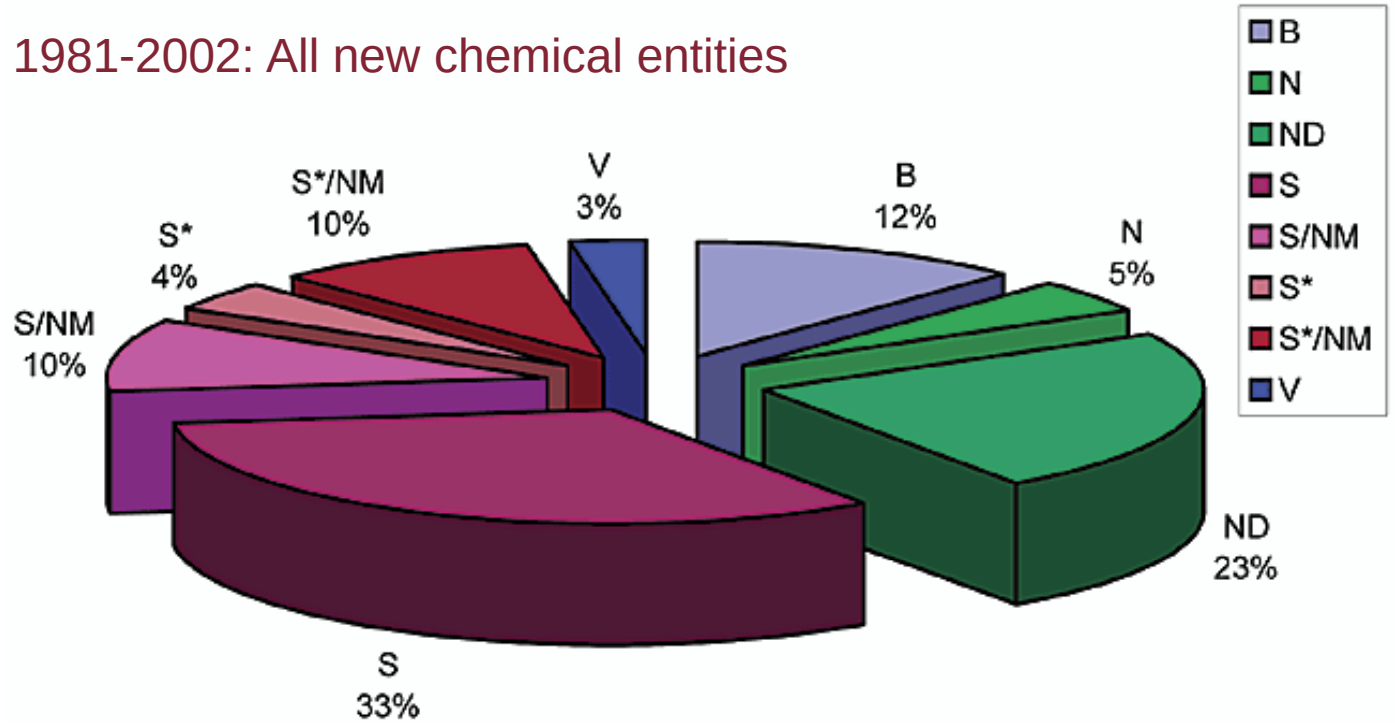
7 X = NO_2 Y = H
8 X = Cl; Y = H
9 X = H; Y = H
10 X = H; Y = CO_2H



11 Losartan; X = CH_2OH
12 EXP3174; X = CO_2H

Farmaci di origine naturale (13n)

1981-2002: All new chemical entities



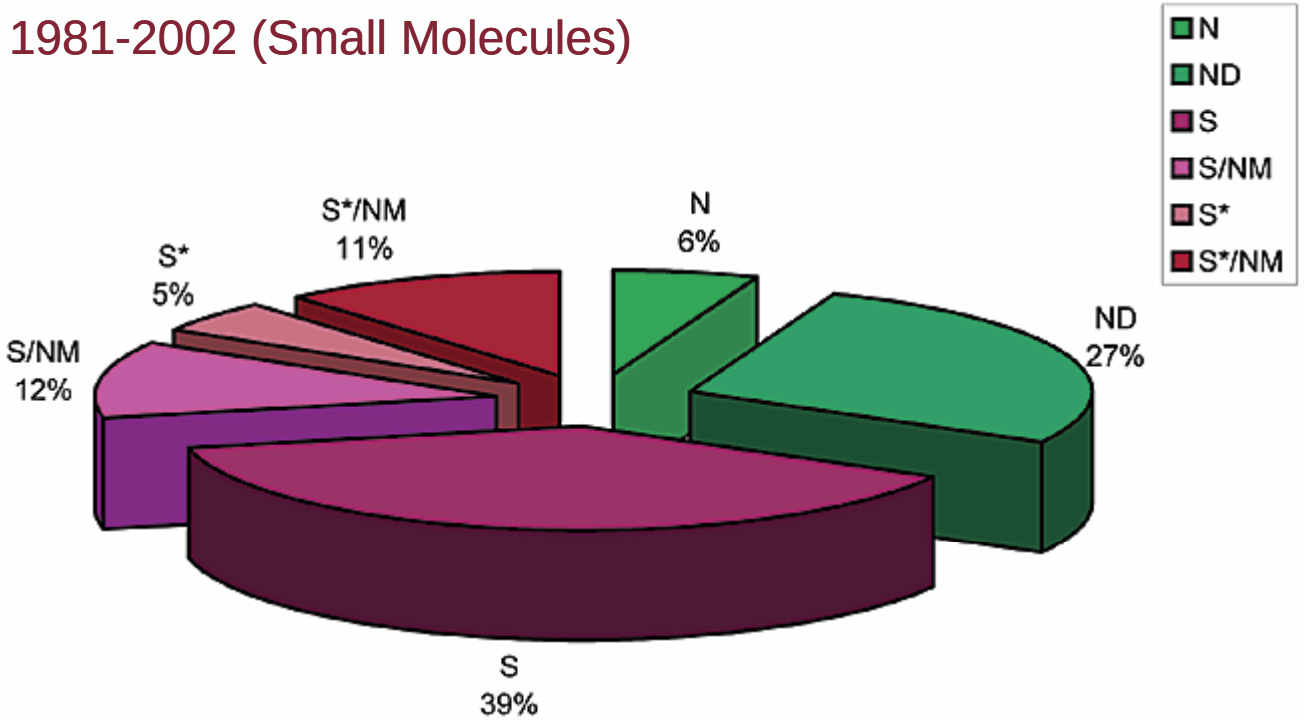
"B": Biological; usually a large (>45 residues) peptide or protein either isolated from an organism/cell line or produced by biotechnological means in a surrogate host.
"N": Natural product.
"ND": Derived from a natural product and is usually a semisynthetic modification.

"S": Totally synthetic drug, often found by random screening/modification of an existing agent.
"S*": Made by total synthesis, but the pharmacophore is/was from a natural product.
"V": Vaccine.

NM: Natural Product Mimic

Farmaci di origine naturale (13o)

1981-2002 (Small Molecules)



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NM: Natural Product Mimic

Nature is Vital to Drug Product Discovery [April 15, 2005, American Journal of Health-System Pharmacy News]

Envenomation by a cone snail
Venomous cone snails use a highly developed projectile apparatus to deliver their cocktail of toxic conotoxins into their prey. In fish-eating species such as Conus magus (seen below) the cone detects the presence of the fish using chemosensors in its siphon and when close enough extends its proboscis and fires a hollow harpoon-like tooth containing venom into the fish. This immobilizes the fish and enables the cone snail to wind it into its mouth via an attached filament. The fish is then digested

http://pubs.acs.org/cen/coverstory/8141/8141pharmaceuticals.html

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REDISCOVERING NATURAL PRODUCTS

Cast aside for years, natural products drug discovery appears to be reclaiming attention and on the verge of a comeback

A. MAUREEN ROUHI, C&EN WASHINGTON

The pharmaceutical industry's productivity continues to be dismal. This state of affairs is due to many factors, and one may have been the diminished interest in natural products drug discovery as the industry embraced promising and exciting new technologies, particularly combinatorial chemistry.