University of Athens
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Ancient medical texts: a valuable source of knowledge for drug discovery

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Pharmacognosy

- Pharmacon + gnosis
- Φάρμακον + γνώσις
- Knowledge of drugs
- Discrimination between therapeutic and toxic plants
- Historically, this knowledge was a result of “trials” on humans

Natural Pharmacopoeia

- The therapeutic use of plants and natural drugs has been systematically exploited for thousands years all over the world.
- In the western civilization, the most important source of knowledge about the therapeutic use of plants comes from the ancient doctors of the classic Greek and Roman period that created the base of the pharmacopoeia in Europe up to the 16th century

Dioscorides

- Centuries of medical experience on human beings (not animals), described in astonishing details by Hippocrates, Dioscorides, Galenus, Theophrastus, Aetius, Oreibasios, Nikolaos Myrepsos etc have been recorded in thousands of pages including:

- Botanical description
- Mode of extraction
- Dosology
- Disease

More than two thousands of recipes related with more than 1000 taxa have been reported for a great variety of diseases.

Electronic revolution

- Thousands pages of knowledge from all the ancient doctors up to the Middle ages are now accessible in electronic form through TLG

THESAURUS LINGUAE GRAECAE®

A Digital Library of Greek Literature

Thesaurus Linguae Graecae:

- TLG Project started in 1972 (University of California, Irvine)
- Electronic access to the full text of all the ancient Greek literature
- In 2001 the TLG-team developed a search engine and made the corpus available online.
- Today the Online TLG contains more than 100 million words from 9,958 works from the time of Homer up to 1453 AC associated with 2,314 authors and is constantly updated and improved
- TLG A was the first compact disk that did not contain music

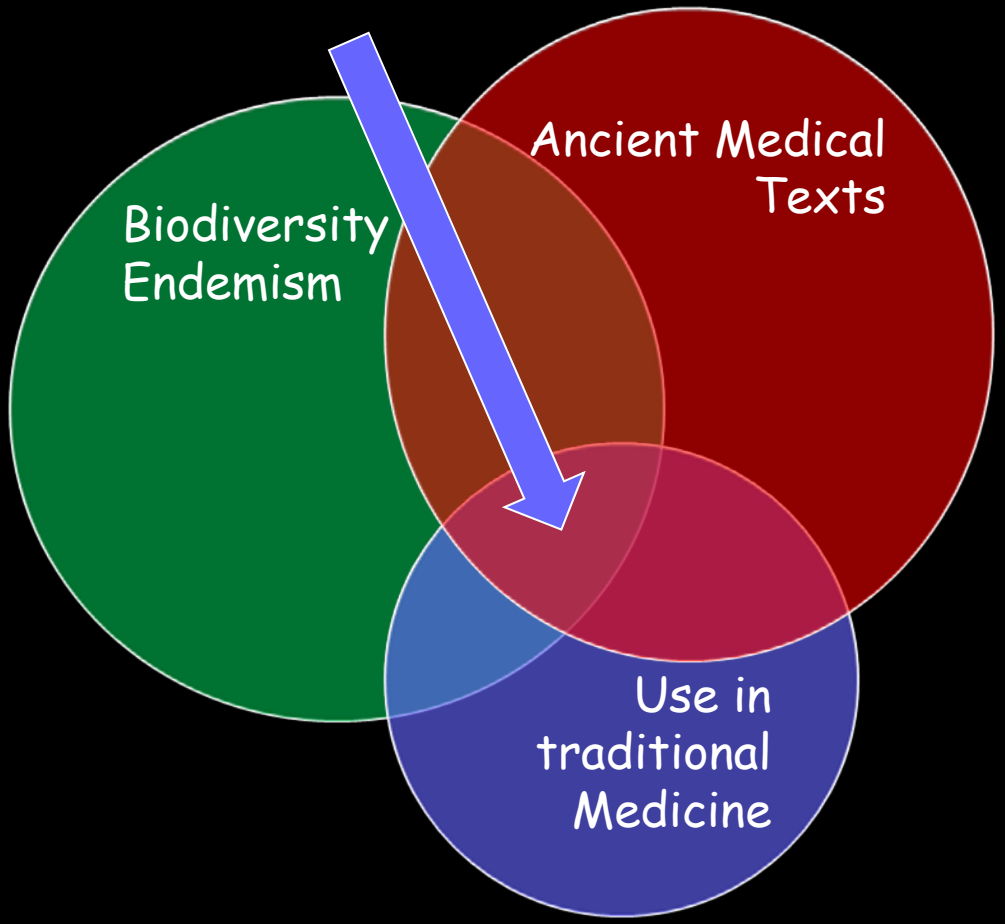
Problems

- Language (translation, obscure terms)
- Medical Terminology
- Botanical names
- Complex multidrug prescriptions
- Lost practical experience

- It is extremely astonishing that a great number of plants mentioned repetitively from several ancient authors for a period of more than 1500 years have never been studied towards the correct disease and with the proposed mode of preparation
- The systematic, cross checked study of ancient recipes can lead to surprising discoveries
- The success is hidden in the details: plant part, mode of extraction, correct interpretation of disease.
- A new concept: ARCHAEOPHARMACOLOGY
- Instead of looking at plants from exotic origin or organisms from the deep oceans we should first study the organisms mentioned in medical texts

Priority criteria for selection of plants

- Strategy:
- Collection of plants (>1000)
- Dereplication
- Isolation
- Pharmacological evaluation
- Molecular modelling
- Synthesis of derivatives



*DIOS database for in silico screening

Rollinger JM, Stuppner H et al, J. Chem. Inf. Comput. Sci., 2004, 44 (2), pp 480–488

Successful examples

- Paeonia
- Sesame
- Mastic
- Olive –olive oil
- Tyrian purple-Indirubin

Paeonia

Dioscorides in his work *De materia medica* states that the seeds of *Paeonia* could be used in wine to calm pains of the womb (uterus) = female genital disorders.

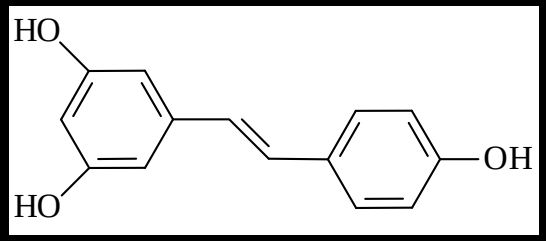
Botanical source
Plant part
Mode of extraction
Dosology
Application

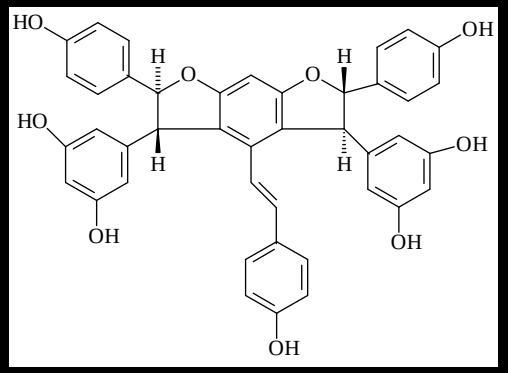
Although there are numerous phytochemical studies on the roots of Asian Paeonia spp, the seeds of European spp. had never been studied or correlated with gynecological problems

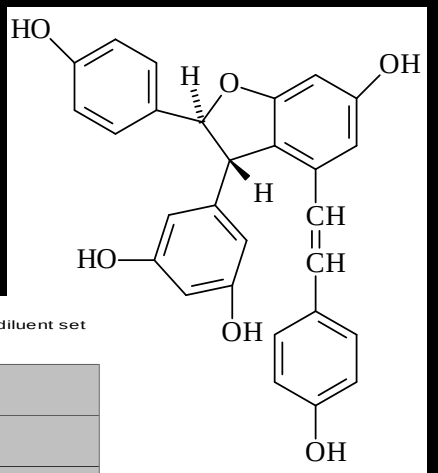
Dioscorides Pedanius Med., Περὶ παιωνίας καὶ ὅσα ποιεῖν δύναται.
καὶ ὀδύνας μήτρας ἐν μελικράτῳ οἴνῳ ὅσον ιε κόκκοι πινόμενοι ποιοῦσι.

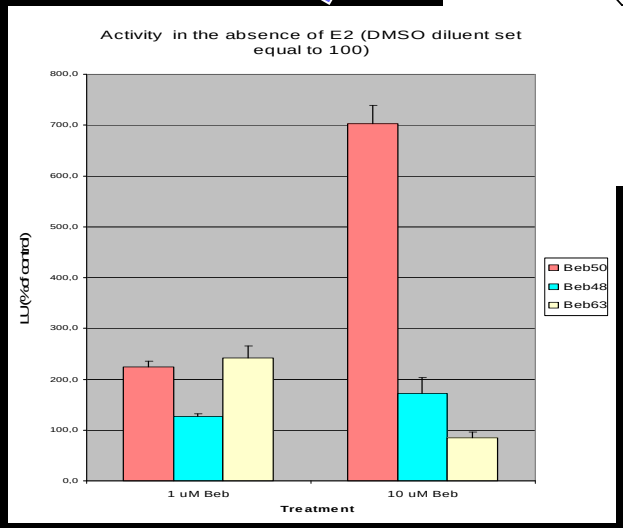
Scientific proof of ancient use

- 50 g of seeds contain
- trans-resveratrol (100 mg)
- gnetin-H (550 mg)
- trans-ε-viniferin (170 mg)
- Amount of resveratrol equal to 100-300 glasses of red wine
- Total resveratrol in Red Wines = 0.30 - 1.07 mg/150mL
- Resveratrol has established estrogen-modulatory effects (Cancer Res. 2001;61(20):7456-63)
- The conclusion is that the ancient text indeed contained important and specific information that nobody had ever studied









Paeonia root-anticonvulsant activity

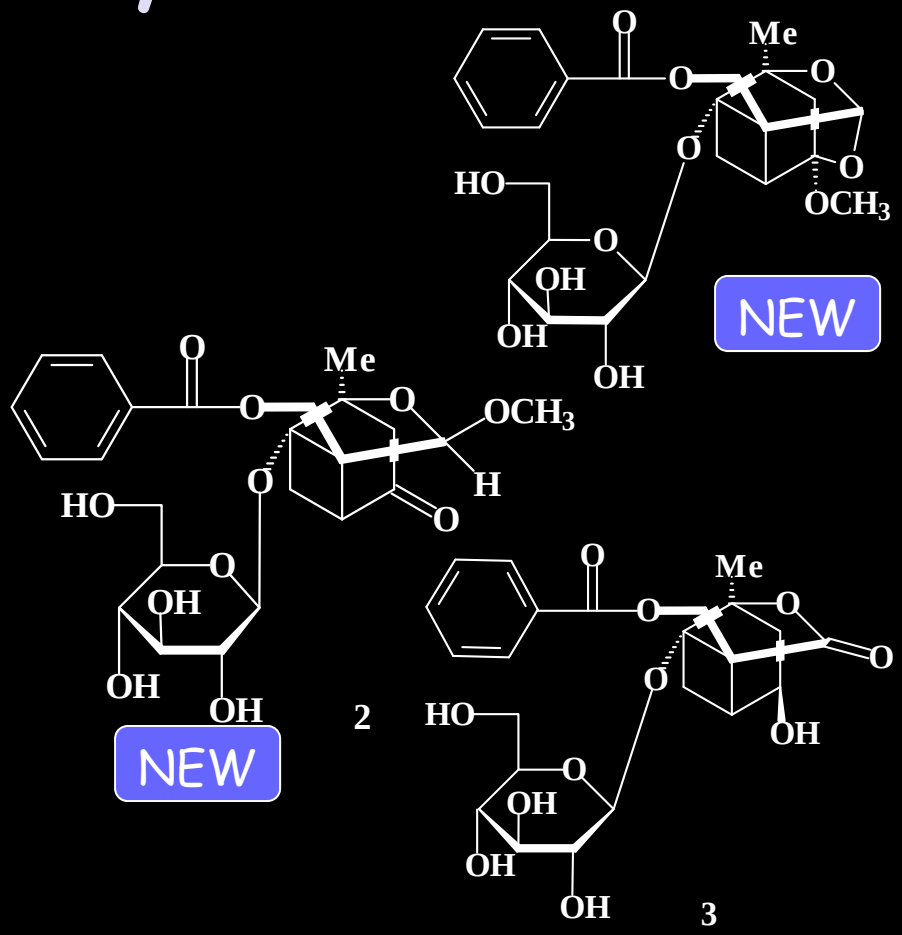
- Phytochemical study of Paeonia spp roots described by Dioscorides and Aetius and in vivo anticonvulsant activity (never tested)

Aëtius Med., *Iatricorum liber i.*

Γλυκυσίδης ἢ παιωνία. εὐλόγως πεπιστεῦσθαι παίδων ἐπιληψίας ἰᾶσθαι·

Table 1: Results of the tested *Paeonia* extracts at dose of 100 mg/Kg in the 6 Hz test using 32 mA and 22 mA.

Time (h)		0.25	0.5	1	2	4
Tested extract	**Intensity**	**N/F**	**N/F**	**N/F**	**N/F**	**N/F**
P.parnassica water extract	32 mA	**2/4**	0/4	0/4	1/4	0/4
	22 mA	1/4	**2/4**	**2/4**	**2/4**	-
P. parnassica MeOH extract	32 mA	1/4	1/4	1/4	1/4	0/4



Magiatis, P. et al, "Phytochemical investigation and anticonvulsant activity of *Paeonia parnassica* radix" **Natural Products Communications** 2007, *2*, 351-356.

Sesame

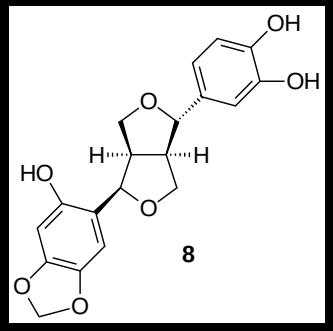
- Hippocrates describes the action of the whole seed on female genital problems (in combination with flaxseed) and for the secretion of milk during breastfeeding

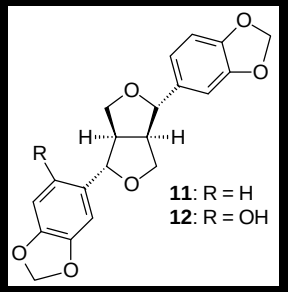
- The hull (seed coat) of the sesame seed had never been studied and never correlated with the female hormone system
- Grougnet, R., Magiatis, P., Mitaku, S., Terzis, A., Tillequin, F., Skaltsounis, A.-L. New lignans from the perisperm of Sesamum indicum (2006) Journal of Agricultural and Food Chemistry, 54 (20), pp. 7570-7574.

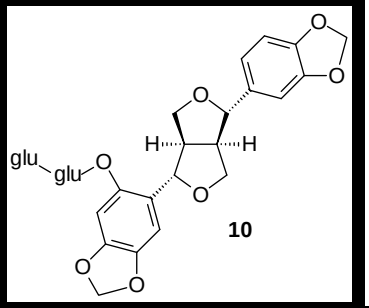
Hippocrates et Corpus Hippocraticum Med., *De mulierum affectibus i–iii*.

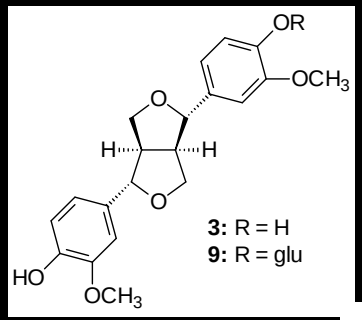
Καὶ ἄγνου καρπὸν ἐν οἴνῳ διδόναι πίνειν· καὶ **γάλα πουλὺ ποιέει** τεύτλου χυλὸς καὶ **σησάμου ἁπλύτου** καὶ κριθέων τριμηνιαίων, ἐμβαλὼν ἐς θυείαν, τρίψας πάντα, δι' ὀθονίου ἐκχυλίσας, παραμίξας μέλι ἢ ἀμαμηλίδας, εἶτα ἐπ' οἴνῳ μέλανι διδόναι πίνειν.

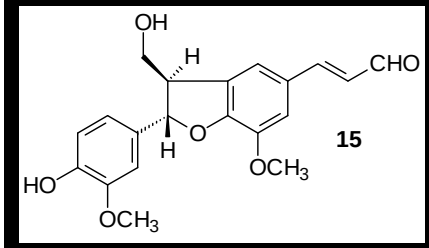
Phytochemical study of sesame seed coat

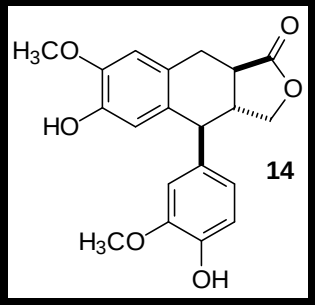


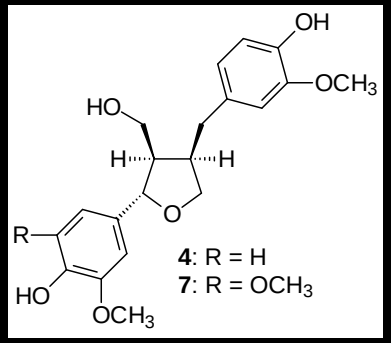


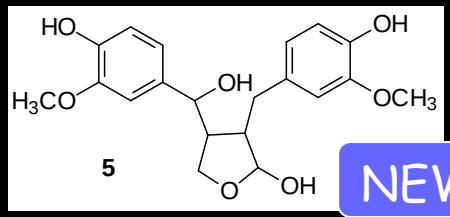












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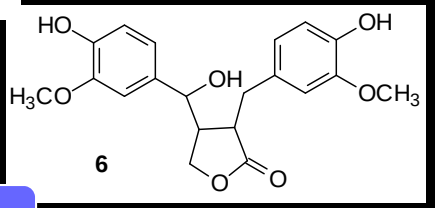

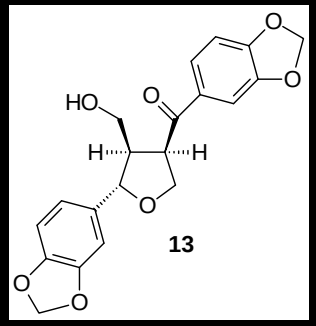

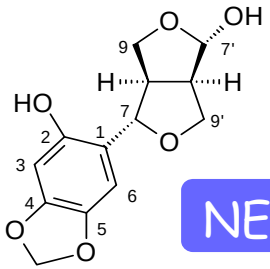

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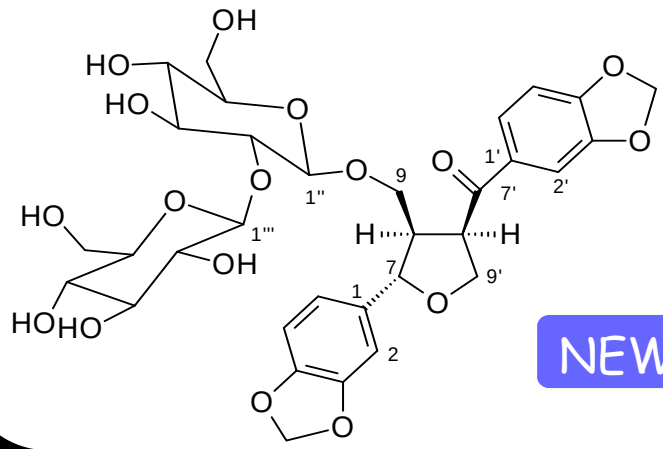


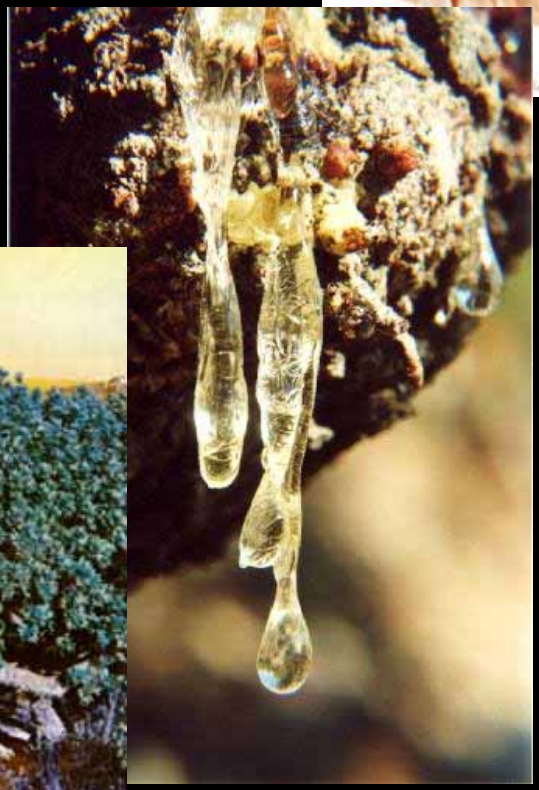
NEW

In vivo studies

- 10 times more rich in lignans than the dehulled seed
- The lignan extract of sesame hull in mice showed estrogenic activity

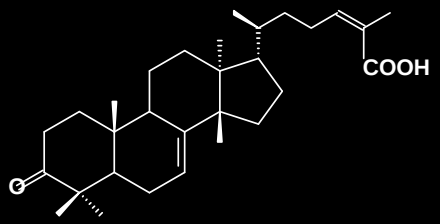
Mastic

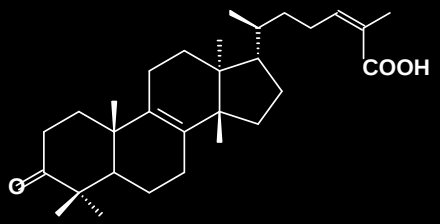
- Galen (22 volumes and over 20,000 pages in length):
- Among the resins he states that mastic is the most powerful for the treatment of stomach inflammation
- Only from the island of Chios (Pistacia lentiscus var.chia)

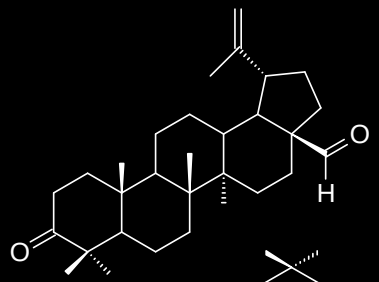


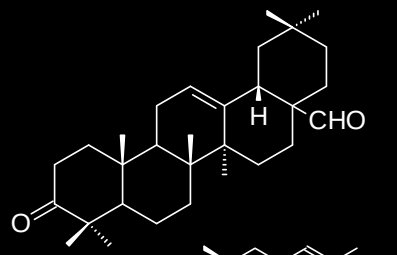
Galenus Med., De simplicium medicamentorum temperamentis ac facultatibus libri xi. Volume 12 page 68 line 14. στ. Περί μαστίχης. Μαστίχη, μεν λευκή καί Χία συνήθως ὀνομαζομένη σύνθετός πώς ἐστιν ἐξ ἐναντίων δυνάμεων στυπτικῆς καὶ μαλακτικῆς. διὸ καὶ **στομάχου** καὶ κοιλίας καὶ ἐντέρων καὶ ἥπατος **φλεγμοναῖς** ἁρμόττει

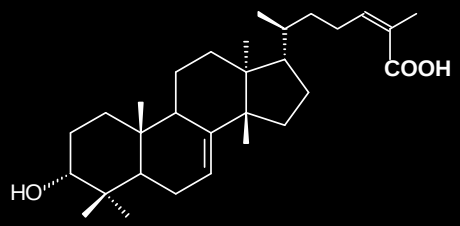
Phytochemical study of mastic resin

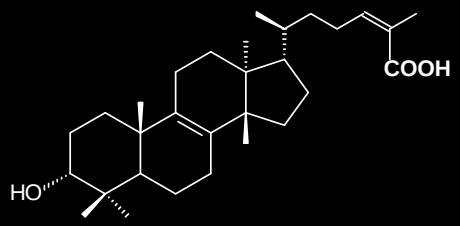


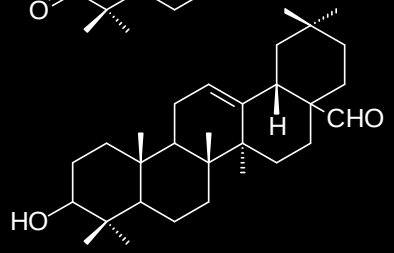


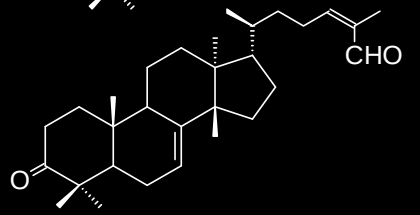


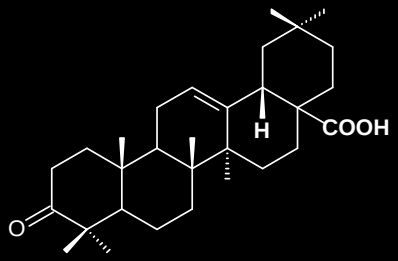


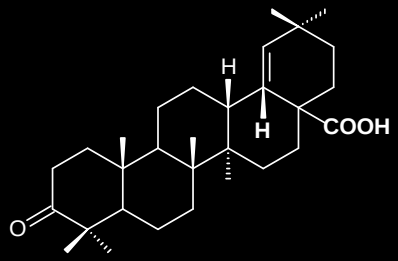


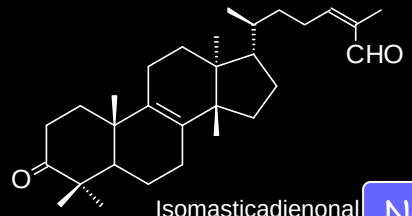












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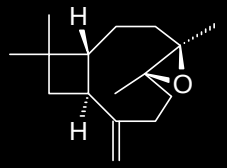
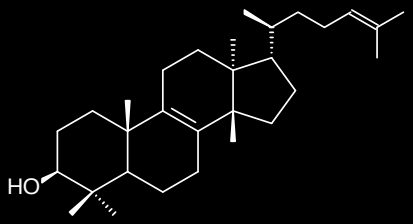
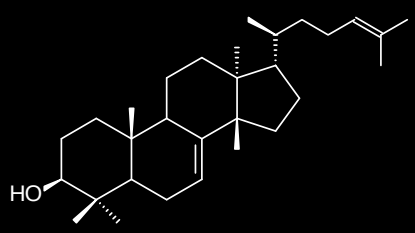
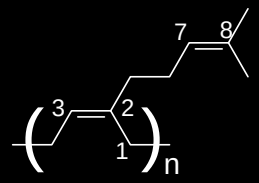
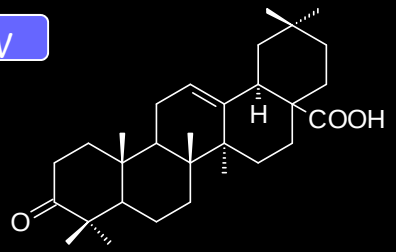
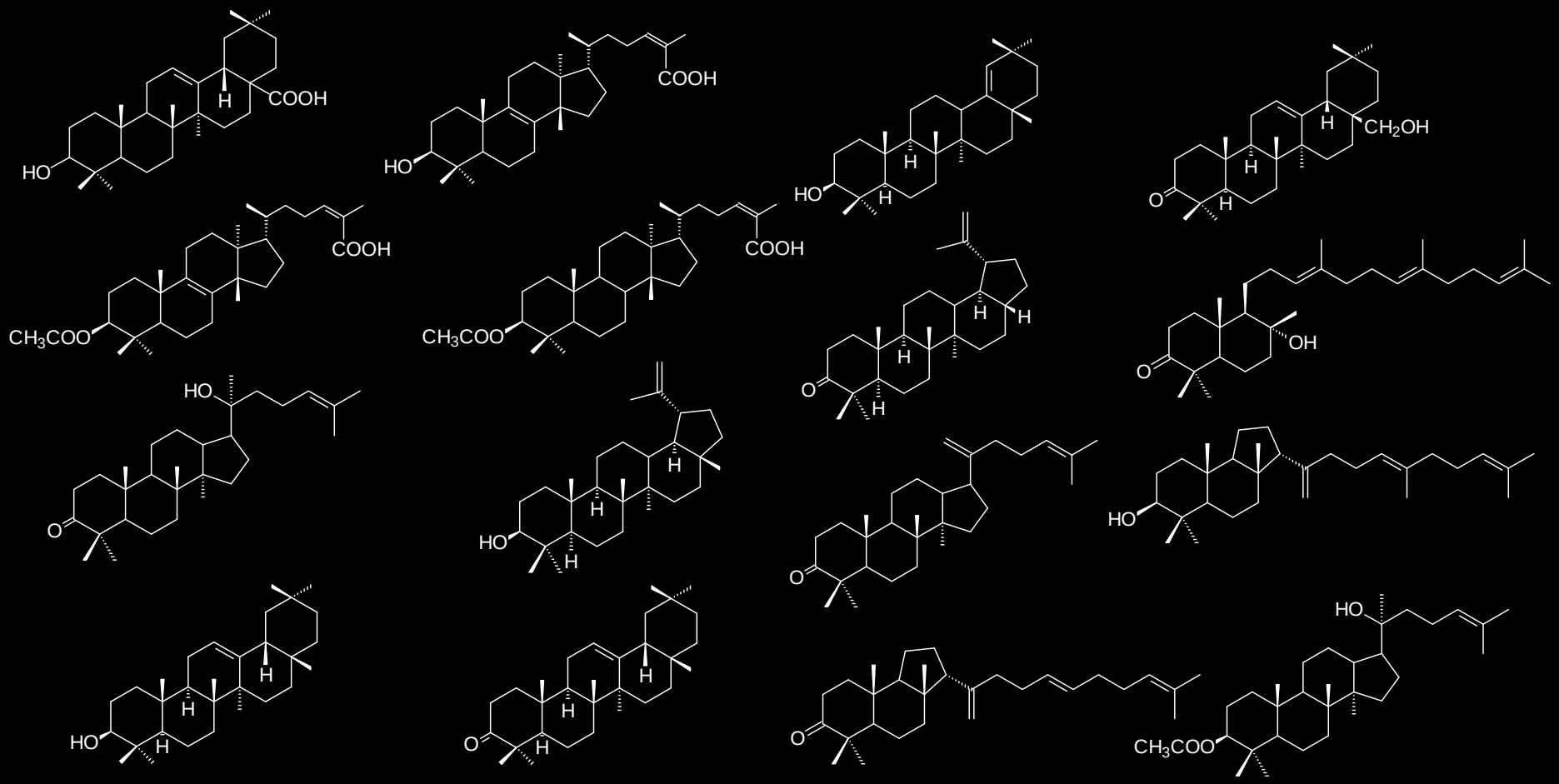












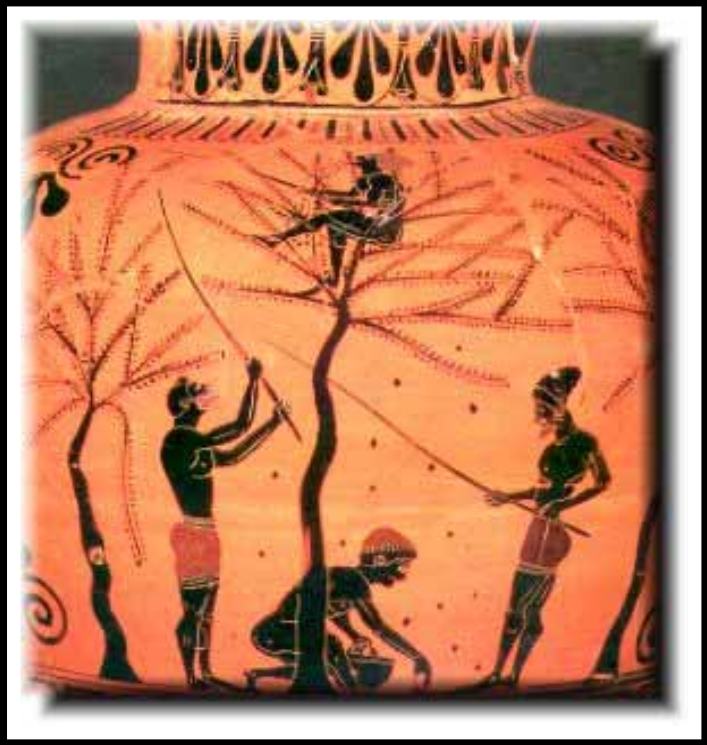
Paraschos, S., Magiatis, P., Mitakou, S., Petraki, K., Kalliaropoulos, A., Maragkoudakis, P., Mentis, A., Sgouras, D., Skaltsounis, A.-L. In vitro and in vivo activities of chios mastic gum extracts and constituents against Helicobacter pylori (2007) Antimicrobial Agents and Chemotherapy, 51 (2), pp. 551-559.

- Phytochemical study of mastic resin, mastic oil, mastic water (poster)
- Isolation of triterpenic acids
- In vitro- in vivo studies

- Although mastic does not eradicate H.pylori as initially believed (Huwez et al., N Engl J Med 339(26):1946, 1998) it reduces in vivo (in mice) the colonization of H.pylori and the grade of inflammation as originally stated in the ancient texts!!
- The activity is attributed to the acid fraction and to specific triterpenic acids

Olive- olive oil

- Dioscorides and after him all the ancient doctors insist that the best health effects come from the fresh olive oil from unripe olives and especially from the wild variety (Olea europaea, var. sylvestris
- Numerous applications are reported including headache, toothache
- Obvious indications of antinflammatory activity

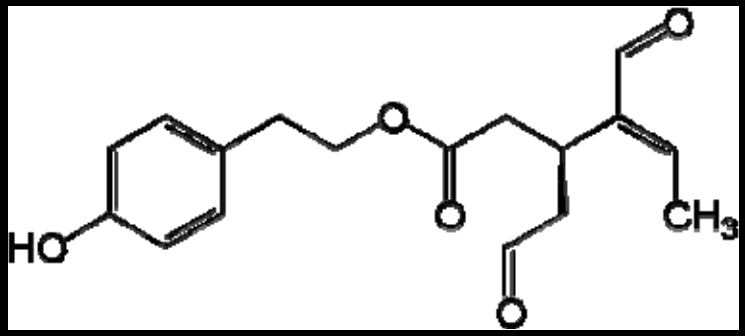


Olive harvest.
Pot of the 6th century BC.

Dioscorides Pedanius Med., *De materia medica*.
ἔλαιον πρὸς τὴν ἐν ὑγιείᾳ χρῆσιν ἄριστον τὸ ὠμοτριβές, ὃ καὶ ὀμφάκινον καλοῦσι.

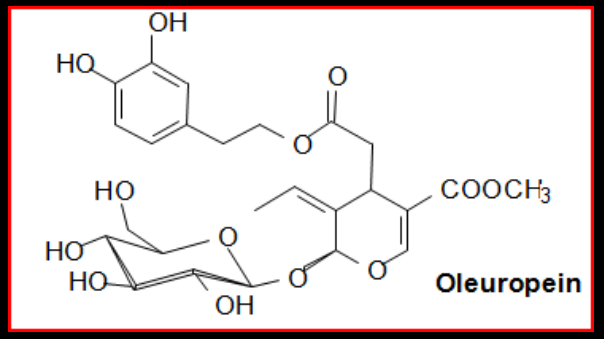
Oleocanthal

- Oleocanthal posseses antiinflammatory activity similar to Ibuprofen
- Following the ancient guidelines we have recently identified olive oil varieties with high concentration of oleocanthal

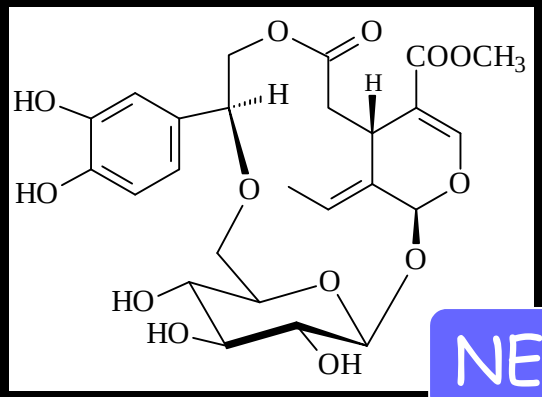


- "Phytochemistry: Ibuprofen-like activity in extra-virgin olive oil." Beauchamp, Gary K. et al. *Nature* (2005), 437(7055), 45-46

Oleuropein



- The bitter principle of olive leaves and fruits
- The ancient texts mention the use of the olive leaf decoction and the brine of the table olives
- Phytochemical study
- Protects from myocardial infarction and lowers cholesterol



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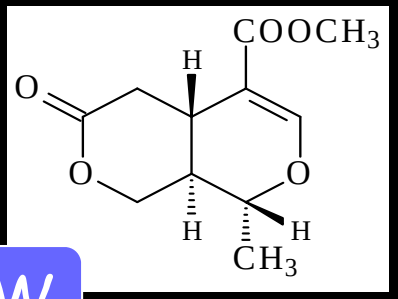
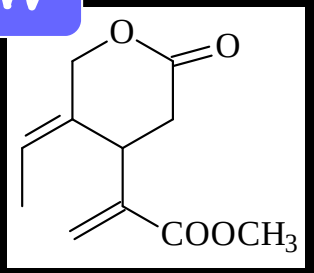
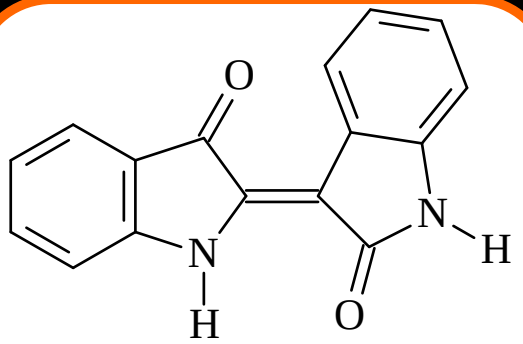




- "The olive constituent oleuropein exhibits anti-ischemic, antioxidative, and hypolipidemic effects in anesthetized rabbits" I. Andreadou, E. Iliodromitis, E. Mikros, M. Constantinou, A. Agalias, P. Magiatis, A. Skaltsounis, E. Kamber, A. Tsantili-Kakoulidou, D. Kremastinos. *J. Nutrition* 2006, 136, 2213-2219.

Indirubin

- Ten years ago, indirubin was identified as the main active ingredient of a traditional Chinese medicinal recipe, Danggui Longhui Wan, used successfully to treat chronic myelocytic leukemia (CML)
- The activity of indirubin against CML was confirmed in clinical trials performed in China.
- The action of indirubin was first identified to be mediated through the inhibition of cyclin-dependent kinases (CDKs) but it was also quite potent on glycogen synthase kinase (GSK-3) inhibition.



INDIRUBIN

Nature Cell Biology, 1999,1,60-67

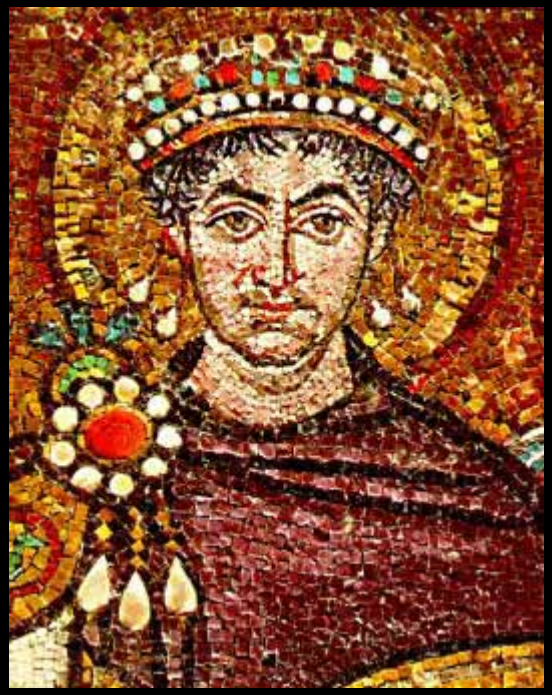
Danggui Longhui Wan

当归龙荟丸

- Based on the importance of CDKs or GSK-3 inhibition in the treatment of cancer or several other serious diseases, in our laboratory in the Univ. of Athens we decided to start a research for new natural indirubin derivatives as kinase inhibitors.

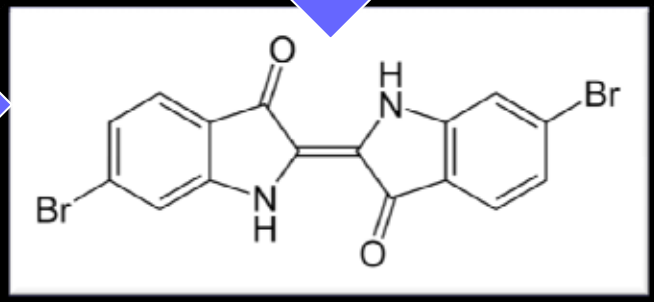
Natural sources of indirubins

- Indirubins, have been found in over 200 species of indigo-producing plants.
- Indirubins, along with indigo, are also produced by various bacterial strains
- But the most famous source of indirubins is the Gastropod mollusks, of the *Muricidae* family that have been used as the source of the vivid purplish red dye, known as "Tyrian purple" or "Royal Blue" around the Mediterranean Sea.



Byzantine Emperor Justinian clad in Tyrian purple

- The main chemical constituent of the Tyrian dye was discovered by Paul Friedländer in 1909 to be 6,6′-dibromoindigo
- Dioscorides states 2000 years ago that the tyrian dye is similar to indigo!!



Dioscorides Pedanius Med., *De materia medica*. {**0656.001**
τοῦ δὲ λεγομένου Ἰνδικοῦ τὸ μὲν αὐτομάτως γίνεται, οἱονεὶ ἔκβρασμα ὂν τῶν Ἰνδικῶν καλάμων· τὸ δὲ βαφικόν ἐστιν ἐπανθισμὸς πορφύρας, ἐπαιωρούμενος τοῖς χαλκείοις, ὃν ἀπο-

Numerous pharmacological activities are reported from all ancient medical texts including Malignant ulcers, sarcomas, hair loss, wound healing, burns, spleen oedema etc.....

Never studied

Gastropods used for the production of Tyrian purple

- *1. Murex brandaris* (synonym *Bolinus brandaris*)
- *2. Hexaplex trunculus* (synonym *Phyllonotus* or *Trunculariopsis*)

But Aristotle (Historia animalium) clearly states two different types of dye coming from two different species

1. Κήρυξ = Ceryx =herald's trumpet (Friedländer)
2. Πορφύρα = Purple shellfish (not studied)

SALAMIS

ATHENS

Extraction procedure

The snails were removed by hand from the shell

Crucial information by Aristotle

exposed to sunlight for 1 h

The hypobranchial glands and their excretions changed from colorless to green and rapidly to purple

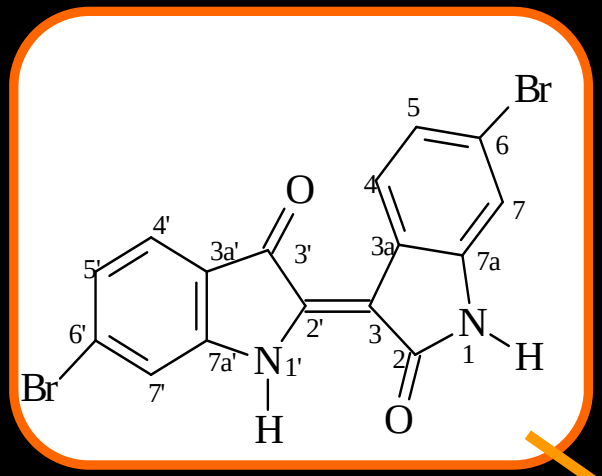
Then the material was lyophilized

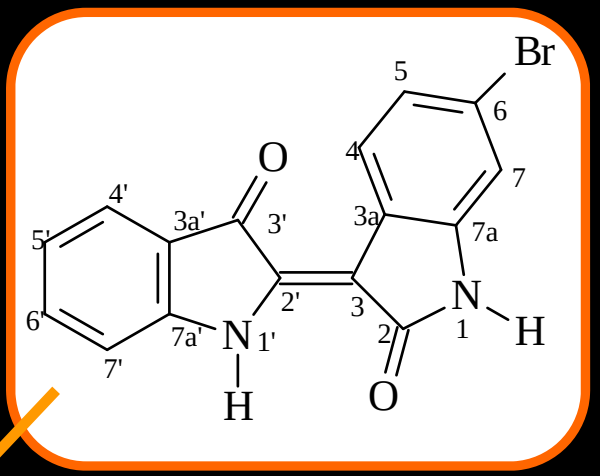
and extracted repeatedly with dichloromethane.

Using as starting material 60 Kg of mollusc….

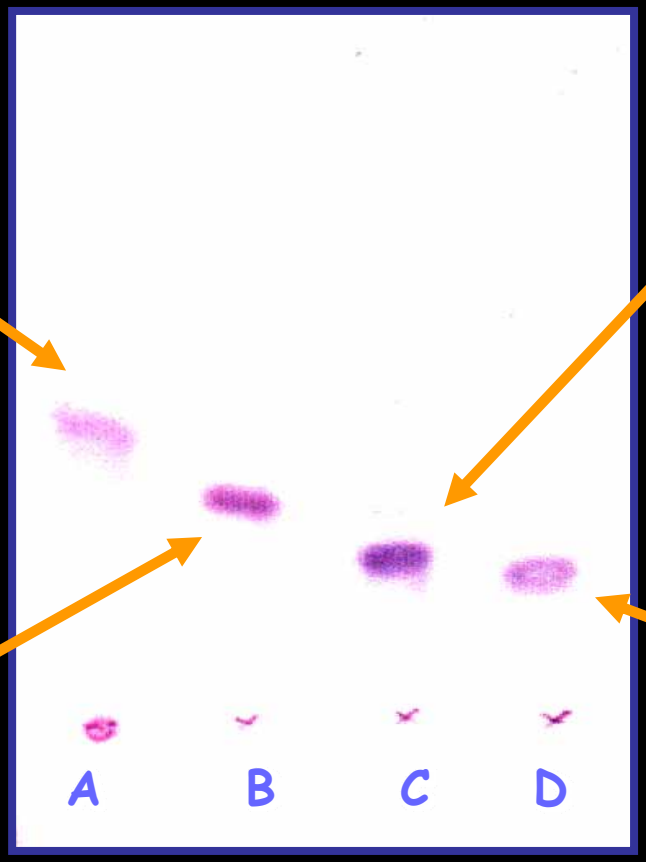
- After several chromatographic separations we isolated four pure compounds with vivid red color (2-3 mg each)
- NMR and MS study led to the structure elucidation of each compound

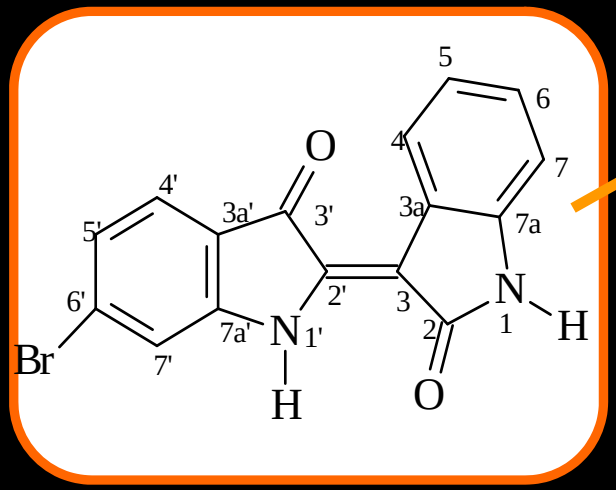
Final purification

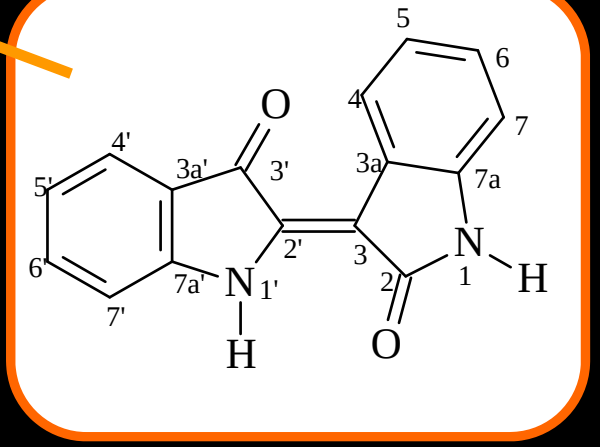




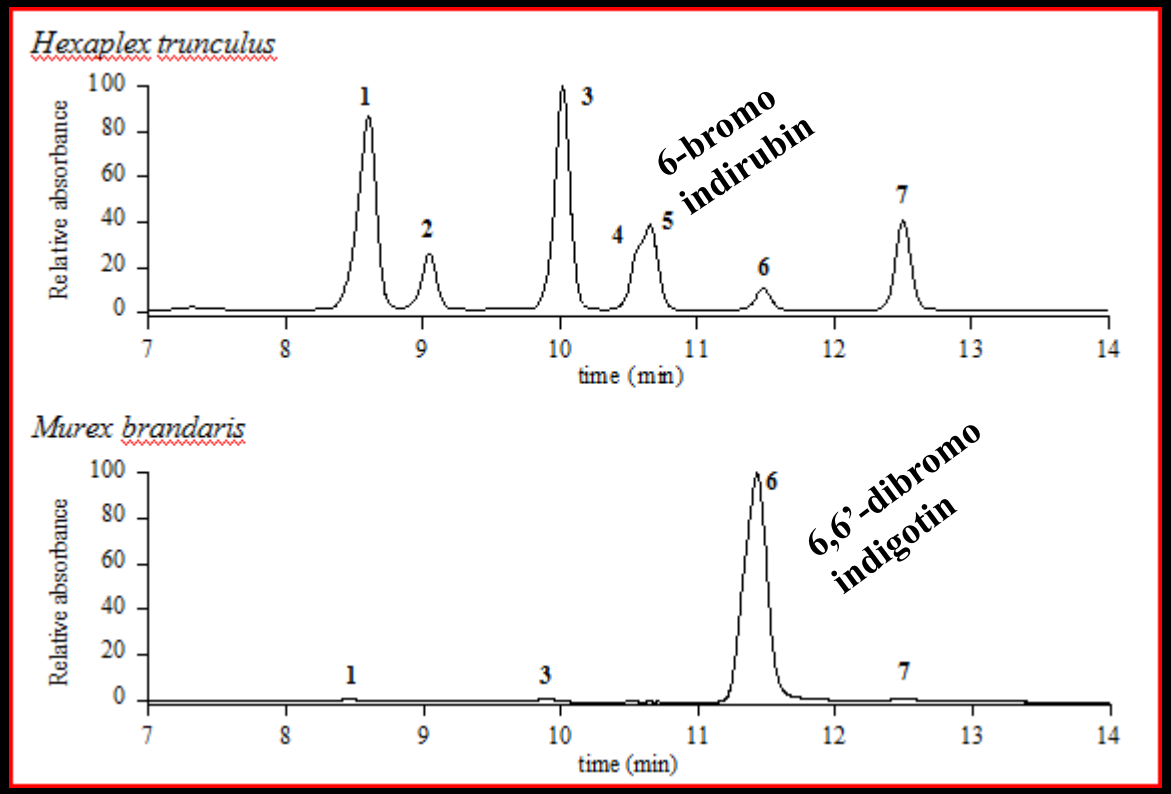
6-bromo-indirubin
First time described
as natural product







Only from *Hexaplex*!!



Aristotle was right

HPLC analysis of the extracts, using the above isolated authentic samples revealed surprisingly that 6-bromo-indirubin was found only in *H. trunculus* and not in the other Tyrian purple producing gastropod

"Identification of the Coloring Constituents of Four Indigoid Dyestuffs" Karapanagiotis, I.; V Violaine de Villemereuil; Magiatis, P.; Polychronopoulos, P.; Vougogiannopoulou, K.; Skaltsounis, AL ***J. Liquid Chromatography,*** 2006, *29*, 1491-1502

A long history

- The oldest sample of "Tyrian" purple (17th century BC) was recently identified in frescos from Santorini island before the volcano eruption. The research was performed by a Greek art diagnosis center (Ormylia) and was based on the authentic samples of colorants from *Hexaplex trunculus*.

The complex chemical technology for the production of the purple dye was first discovered by the Aegean civilization and then transfered to Pheonicia

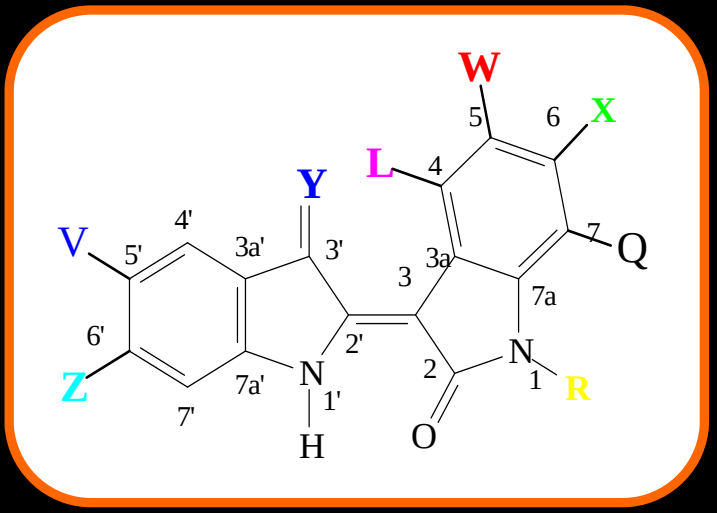
Pharmacological evaluation of pure natural compounds

Pure compounds	CDK1	CDK5	GSK3β
	IC_{50} (μM)	IC_{50} (μM)	IC_{50} (μM)
6,6′-dibromo-indirubin	>100	>100	3.000
6′-bromo-indirubin	>100	>100	>100
6-bromo-indirubin	>100	>100	0.040
indirubin	10.000	5.500	0.700

Magiatis, P. et al, Chemistry & Biology, 2003, 10, 1255-1266

The small quantity of the natural indirubins led us to investigate their total synthesis as well as the synthesis of several derivatives

Additionally to the natural indirubins we synthesized:

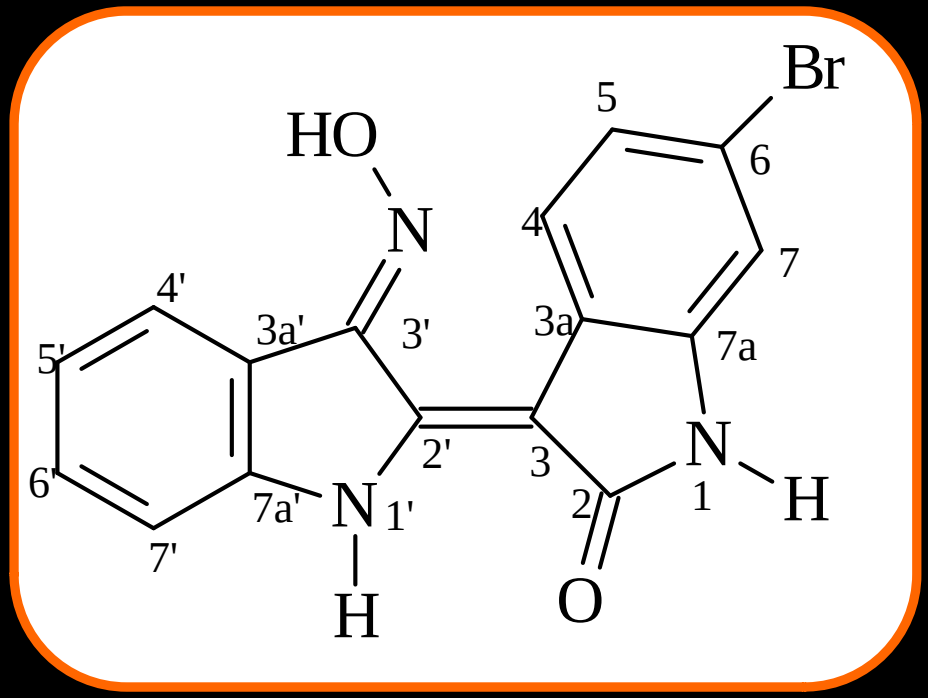


A total of >250 derivatives bearing: Br, Cl, F, I, NO_2, CH_3, $CH=CH_2$, COOH, CH2OH, CHO, at positions 4,5,6,7, 5',6' in combination with =O, =NOH, =NOAc, $=NOCH_3$ at position 3' and with N1-H or N1-CH_3.

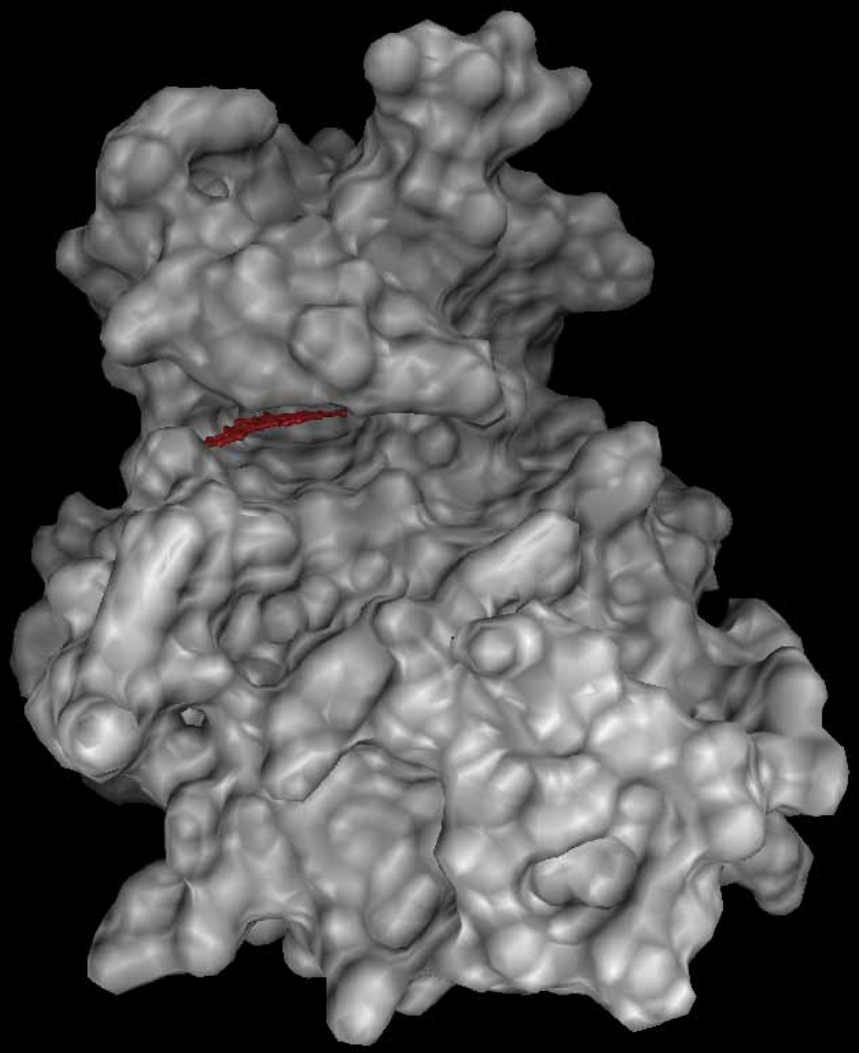
Magiatis, P. et al, J. Med. Chem 2004, *47*, 935-946.
Magiatis, P. *et al*, ***J Med Chem*** 2006, *49*, 4638-4649.
Magiatis, P. *et al*, ***J. Med Chem*** 2007, *50*, 4027-4037.

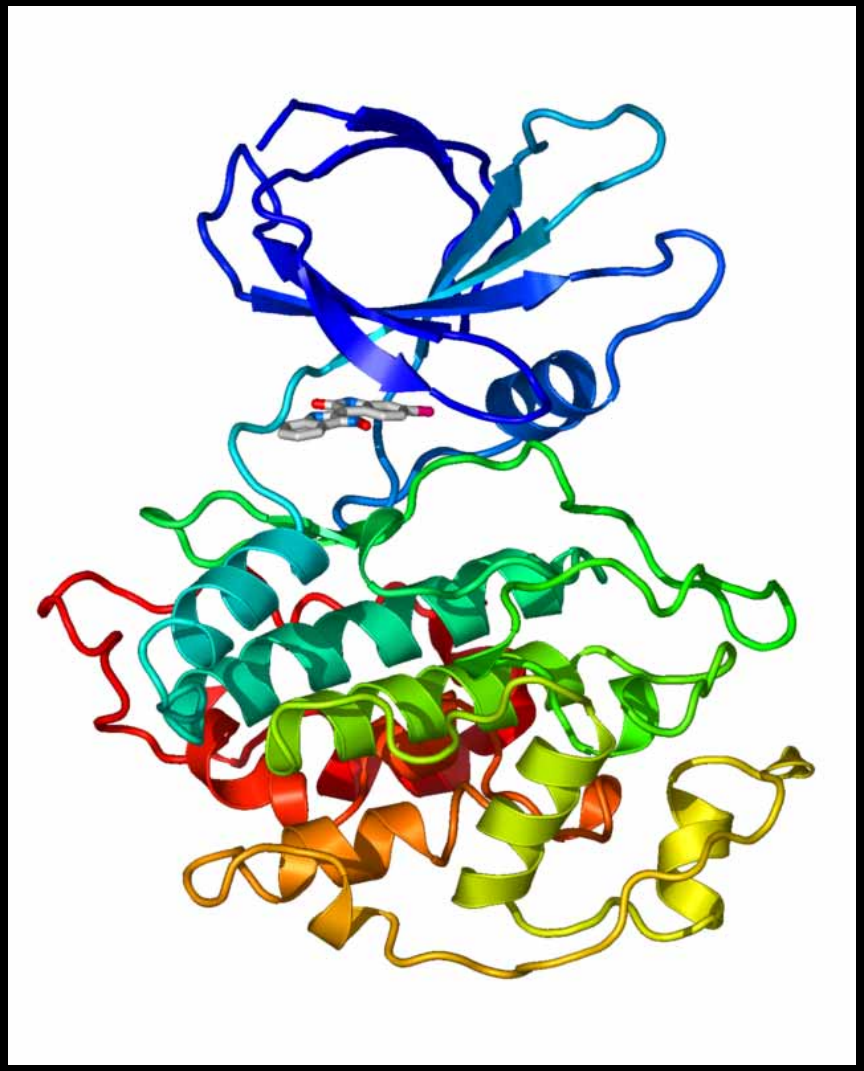
6BIO

- The most interesting among all the synthesized derivatives was 6-bromo-indirubin-3'-oxime (6BIO) which combined a high potency (**5 nM**) 10-100 fold selectivity for GSK-3.

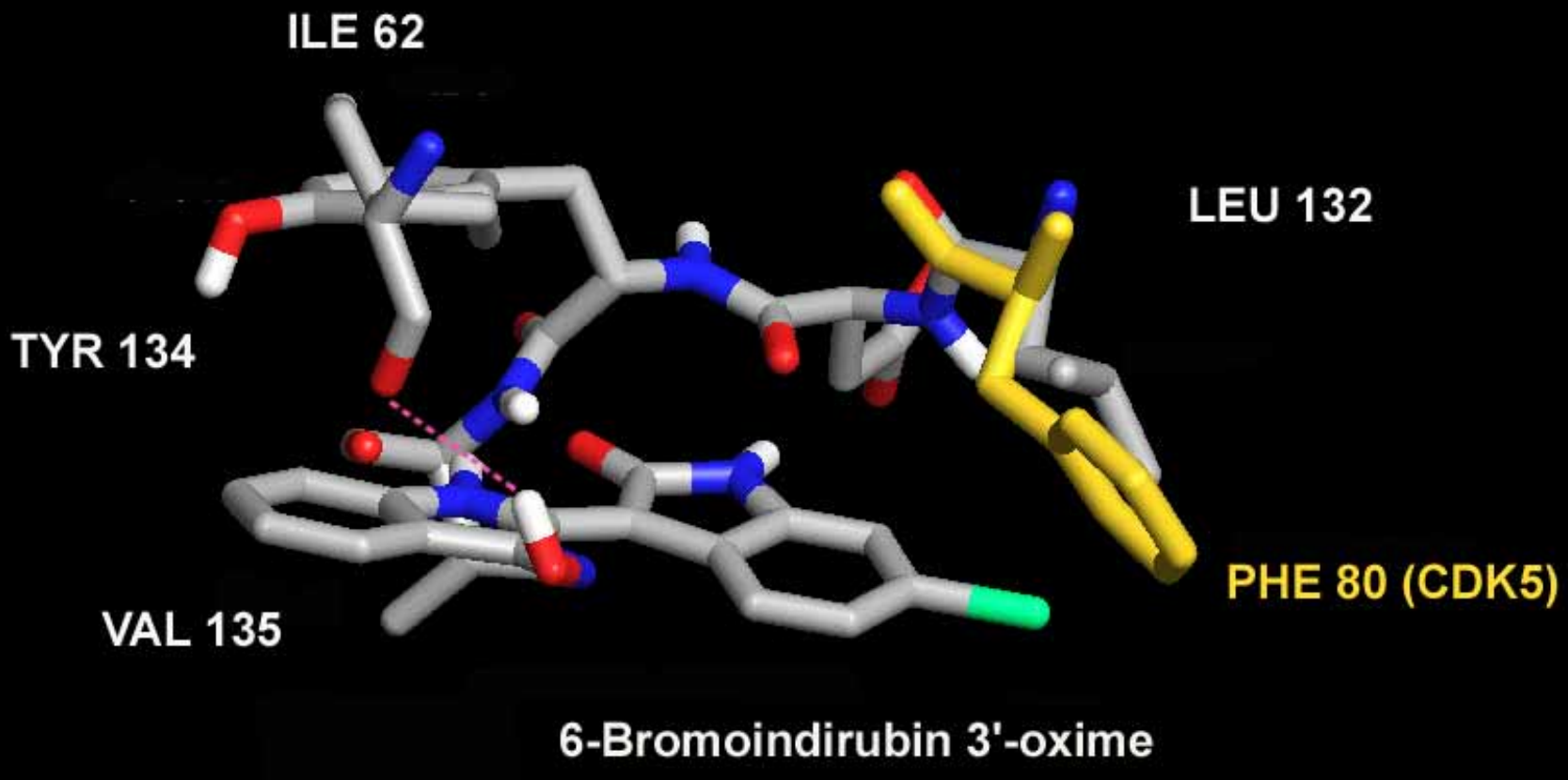


6BIO into the ATP pocket of GSK-3. Crystallographic studies





Explanation of the selectivity of 6BIO against GSK3 in comparison to CDKs

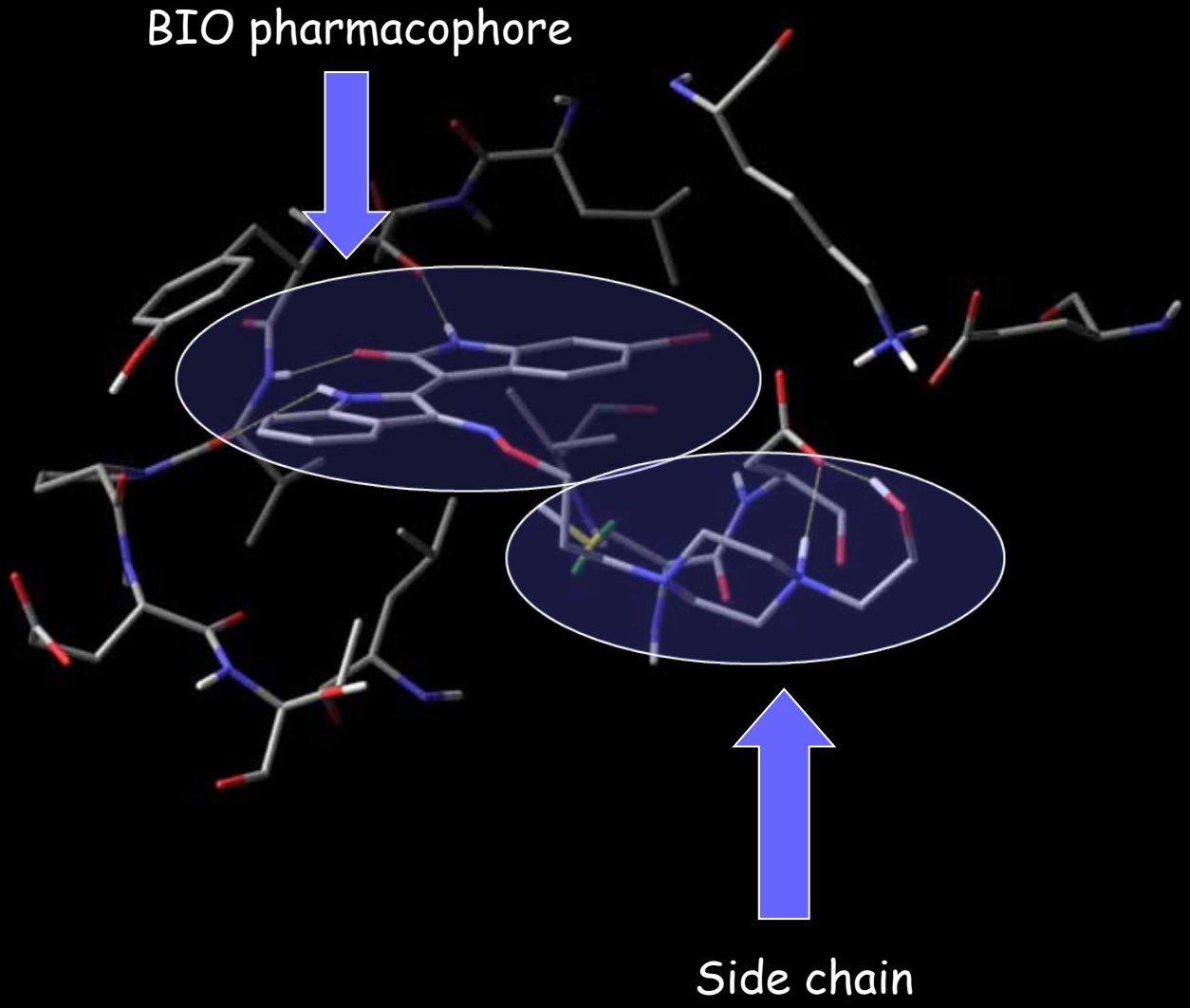


The solubility problem

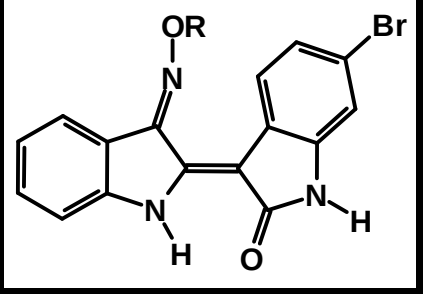
- The solubility of BIO in water is about 12 mg/lt. This solubility is sufficient for in vitro tests or tests in cellular level but not for in vivo administration.
- Target: amelioration of water solubility (minimum 40 mg/lt) with retention of low nanomolar activity (100 nM) and high selectivity (10 fold).

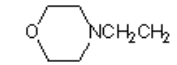
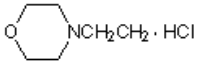
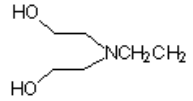
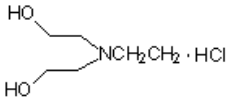
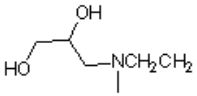
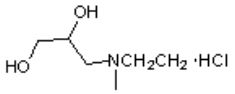
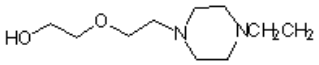
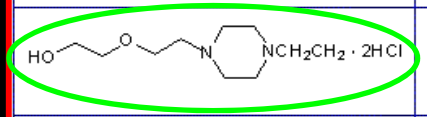
Molecular modeling design

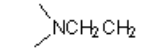
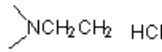
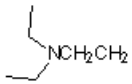
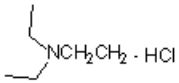
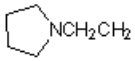
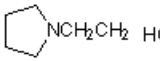
There was enough space to attach a hydrophilic side chain on the 3´-oxime group of BIO without affecting the binding sites in the ATP pocket



SYNTHESIS AND IN VITRO KINASE INHIBITION OF 3'-DERIVATIVES WITH AMINO SIDE CHAINS



ΠΑΡΑΓΩΓΟ ΙΝΤΙΡΟΥΜΠΙΝΗΣ	ΠΡΟΪΟΝ	p25 / CDK5	cyclinB / CDK1	GSK-3α/β	SI*
	(8)	0.170	1.000	0.060	1.22
	(15)	0.400	1.700	0.110	1.19
	(9)	–	0.800	0.040	1.30
	(16)	–	1.000	0.041	1.39
	(10)	0.240	0.240	0.067	0.55
	(17)	0.130	0.150	0.023	0.81
	(11)	–	51.000	0.014	3.56
	(18)	–	80.000	0.033	3.26
OH	BIO	–	0.320	0.005	1.8

	(5)	–	0.490	0.033	1.17
	(12)	–	0.500	0.029	1.24
	(6)	–	23.000	0.035	2.82
	(13)	–	2.500	0.027	1.97
	(7)	0.160	0.800	0.026	1.49
	(14)	0.180	0.700	0.054	1.11

Increase of selectivity for GSK-3 by 180% !

Water Solubility = 4.253 g/l !!

- Selectivity index =

-log IC50 (GSK-3) / IC50 (CDK1)

"Soluble 3',6-substituted indirubins with enhanced selectivity toward glycogen synthase kinase -3 alter circadian period" Vougogiannopoulou, K.; Ferandin, Y.; Bettayeb, K.; Myrianthopoulos, V.; Lozach, O.; Fan, Y.; Johnson, C.H.; Magiatis, P.; Skaltsounis, A.-L.; Mikros, E.; Meijer, L. *Journal of Medicinal Chemistry* 2008, *51*, 6421-6431.

APPLICATIONS OF INDIRUBINS FROM OUR LAB AND CO-WORKERS

- Proliferation of Stem cells : *Nature Medicine, 2004, 10, 55-6*
- Effect on circadian rhythm. *Journal of Medicinal Chemistry* 2008, *51*, 6421-6431.
- "7-bromo-indirubins induce caspase-independent cell death", L. *Oncogene* 2006, *25*, 6304-6318.
- Indirubin is one of the most powerfull ligands of AhR (dioxin receptor) causing G1 arrest. "Independent actions on cyclin-dependent kinases and aryl hydrocarbon receptor mediate the anti-proliferative effects of indirubins" *Oncogene* 2004, *23,* 4400-4412 .
- Against Leishmania : *Antimicrobial agents & Chemotherapy, 2004, 3033-3042*
- *6-Br-5-methyl indirubin -3'-oxime against Leishmania. Int. J. Parasitology 2009*
- Against human Papilloma virus: *Oncogene, 2004, 23, 8206-8215*

APPLICATIONS FROM LABS ALL OVER THE WORLD

- *Replication and survival of pancreatic beta cells: J.Biol. Chem. 2007,* 282, 12030-12037
- Regulation of Hedgehog signaling: *Biochem. Biophys. Res. Comm.* 2007, 353, 501-508
- Proliferation of Mammalian Cardiomyocytes: *Chem. Biol. 2006,* 13, 957-963
- Diabetic nephropathy: *J.Am. Soc. Nephrology* 2006, 17, 2812-2820
- regulation of melanogenesis, 2008 *Cellular Signalling* 20 (10), pp. 1750-1761
- Adipocyte differentiation, 2008 *BMC Cell Biology*
- Downregulation of total tau proteins in cultured neurons *2009, Brain Research, 1252, 66-75*

Applications

- More than 50 publications exploring the pharmacological applications of 6BIO have appeared during 2004-2009
- More than 300 citations of the two main publications concerning the isolation of natural 6-bromoindirubin, the synthesis of 6BIO and the first bioactivity tests on GSK3

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Stem-cell 'secret of youth' found

Chemical might help human cells reach clinic.

23 December 2003

ERIKA CHECK

Human embryonic stem cells are currently grown on mouse cells.
© GettyImages

A humble marine snail has helped scientists to unravel the signals that keep stem cells young.

Human embryonic stem (ES) cells can give rise to almost all of the body's different cell types. They could eventually provide patients with replacement tissues - but there are some roadblocks that currently prevent researchers from putting the cells into patients' bodies.

One problem is that scientists don't yet know how to control the cells' transformations into other types. Another is that the cells cannot be grown without help from mouse cells, which means that they could be contaminated with mouse proteins.

Ali Brivanlou of Rockefeller University in New York says that he and his colleagues may have found a partial solution to

related stories
- Instant stem cells - just add water *19 December 2003*
- Long-lived stem cells heal heart attacks *11 August 2003*
- Excess DNA prompts stem-cell rethink *31 March 2003*
- Stem cells fingerprinted *13 September 2002*
- Stem cells rescue retina *29 July 2002*
- Stem cell hopes double *21 June 2002*
- Stem-cell powers challenged *14 March 2002*

more news
- Perfect pterosaur found in fossil egg *10 June 2004*
- Brain learns like a robot *10 June 2004*
- Gene therapy treats brain wasting disease

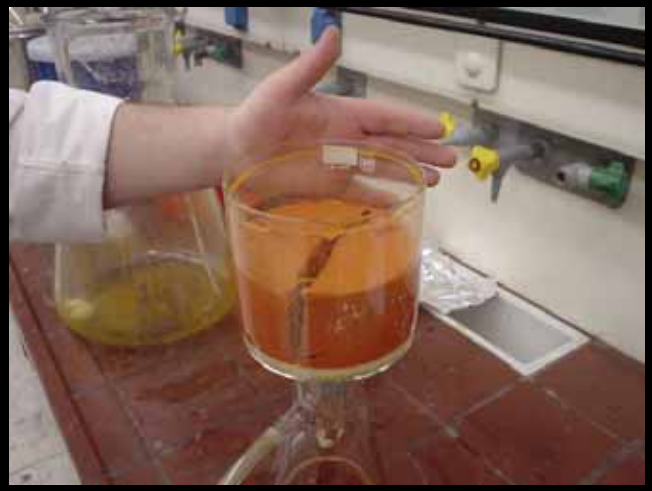
About five years ago, in the website of Nature appeared a hot article entitled:

"stem-cell secret of youth found"

That article described the action of a small molecule named **BIO** coming from a "humble" Mediterranean snail on the differentiation of stem cells. This molecule was reported as a **highly potent and selective inhibitor of an enzyme named GSK-3** which was found to posses a key role in the procedure of cell differentiation in the Wnt pathway. The addition of this compound in the culture media of the stem cells permitted their proliferation, without loosing their pluripotency, something that had never been achieved before.

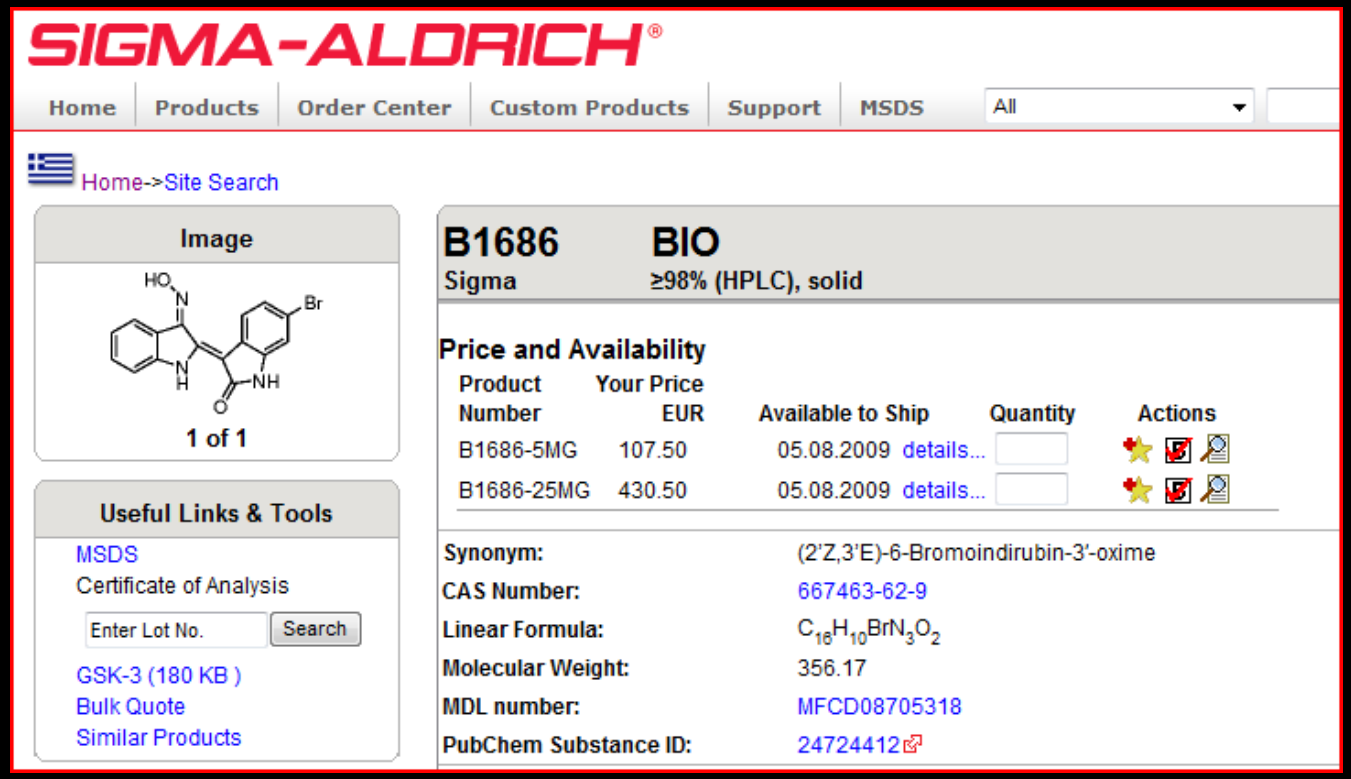
SATO N., MEIJER L., SKALTSOUNIS L., GREENGARD P., BRIVANLOU A. H *Nature Medicine* 2004, 10, 55 – 63

Pilot scale production of BIO



50 gr 6BIO

6BIO, N-Me-6BIO, 6BIO-acetoxime and 7BIO are now commercially available by SIGMA-ALDRICH, MERCK, ALEXIS etc



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Product Number	Your Price EUR	Available to Ship	Quantity	Actions
B1686-5MG	107.50	05.08.2009 details...		
B1686-25MG	430.50	05.08.2009 details...		

Synonym:	(2'Z,3'E)-6-Bromoindirubin-3'-oxime
CAS Number:	667463-62-9
Linear Formula:	$C_{16}H_{10}BrN_3O_2$
Molecular Weight:	356.17
MDL number:	MFCD08705318
PubChem Substance ID:	24724412

Before many centuries Tyrian purple was as valuable as gold.

Today BIO (20€/mg) and its derivatives are 1000 times more valuable than gold (20€/g).

Indirubin and Malassezia

- Surprisingly we found that indirubin is a metabolite of Malassezia spp, a yeast that causes seborrhoic dermatitis, pityriasis versicolor and dandruff and lives on the skin of everybody
- Role unknown
- Potential implication in development of basal cell skin cancer

University of Athens, Faculty of Pharmacy


HITEMA

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