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Scienze Chimiche
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"Scegli i tuoi
esperimenti"

Sintesi di prodotti biologicamente attivi: puzzle 3D o domino? Ecco il nostro gioco

Sintesi di prodotti naturali e non con attività:

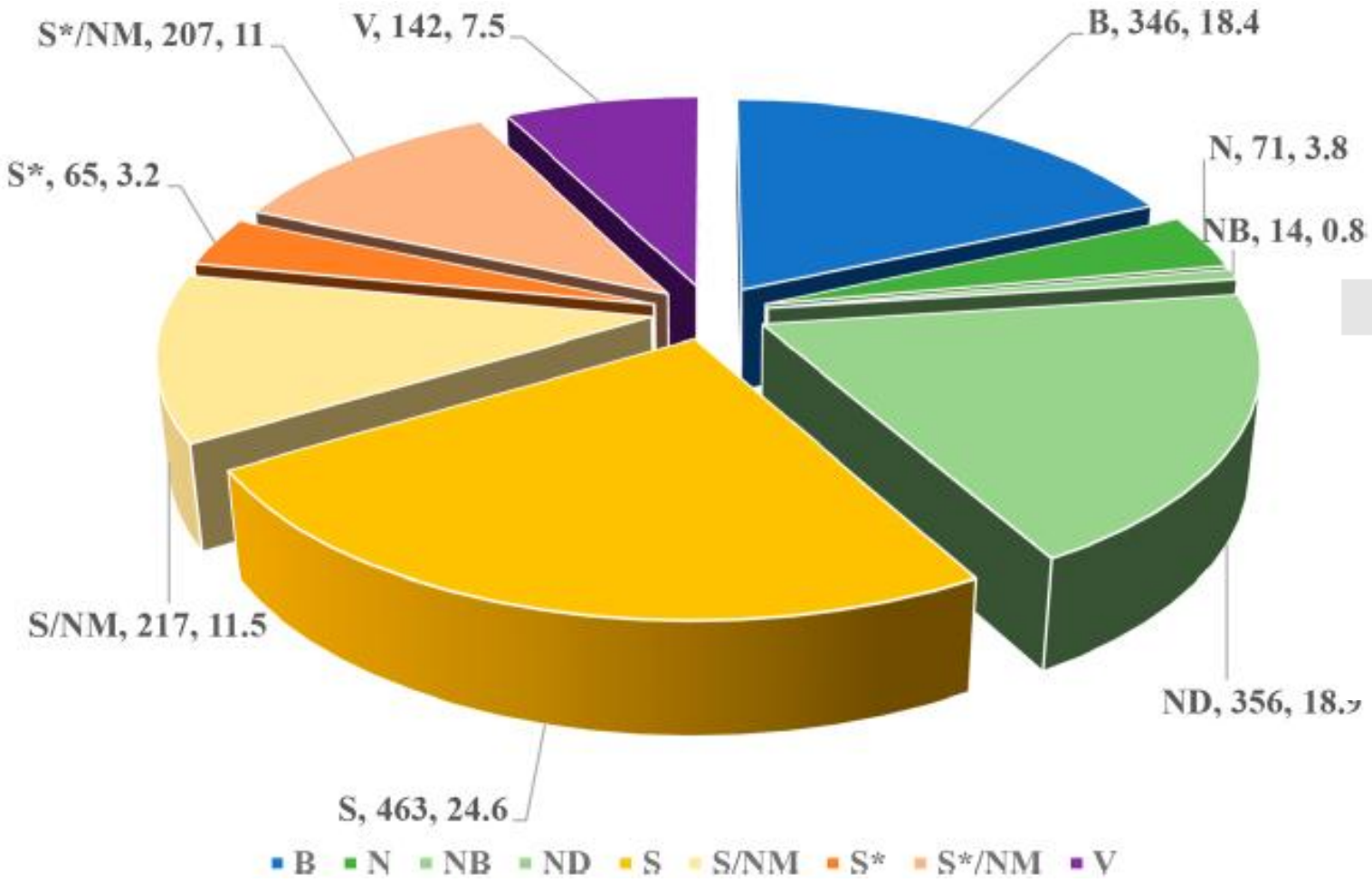
1. **Anti-tumorali (dimeri del resveratrolo)**
2. **Anti-Alzheimer (diarileptanoidi ciclici , derivati della curcumina)**
3. **Anti-virali e anti-tumorali (inibitori dell'HIV proteasi, peptidomimetici)**

Laboratorio: **Composti organici biologicamente attivi «*Carlo Cesare Bonini*»**

Prof.ssa Funicello Maria **Dott.ssa Chiummiento Lucia**

Dottorandi: Alessandro Santarsiere, Pierantonio Galgano **Studenti: Nunzio Iovine**

Natural Products as Sources of New Drugs over the Nearly Four Decades from 01/1981 to 09/2019



code	brief definition/year
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, 2003

Figure 1. All new approved drugs 01JAN81 to 30SEP19; n = 1881.

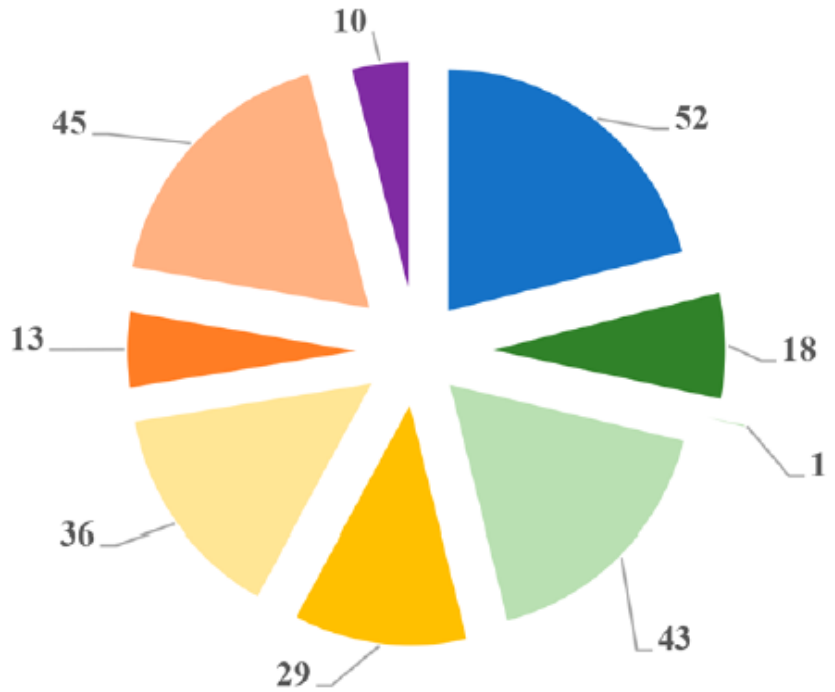


Figure 15. All anticancer drugs 01JAN81–30SEP19, $n = 247$.

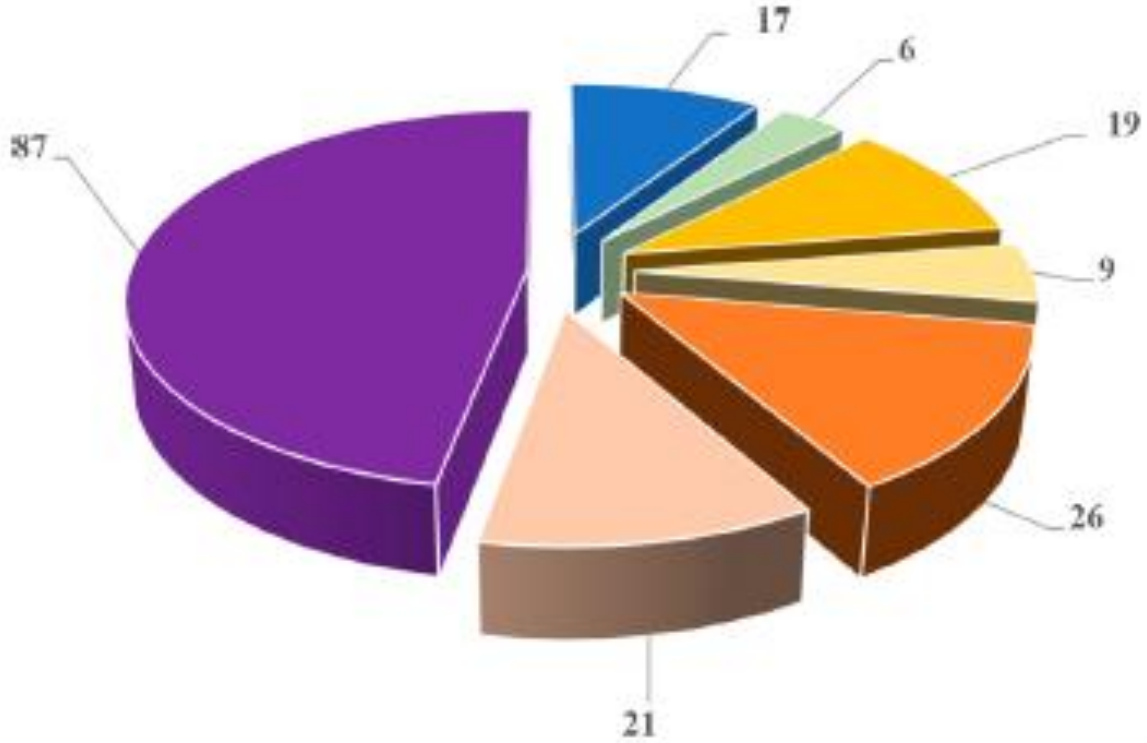
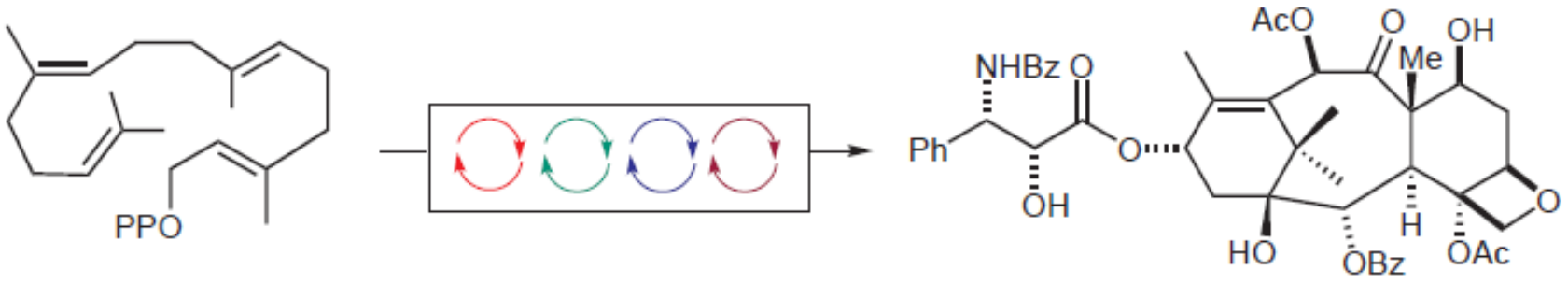


Figure 13. Antiviral Drugs by Source.

Natura insegna:

- Strutture complesse costruite in modo semplice ed efficiente

- Generalmente composti chirali e otticamente puri



2
GGPP

1
Taxol

Enzymatic cascade catalysis applied in the biosynthesis of taxol

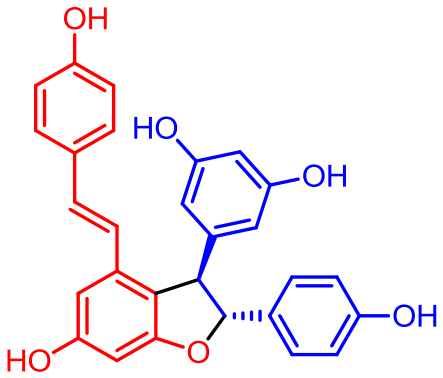
Natura insegna:

- Strutture complesse costruite in modo semplice ed efficiente

- Generalmente composti chirali e otticamente puri

- Ispirazione per «scaffolds» nuovi,
  per metodologie nuove e/o biomimetiche,
- Nuova sfide!!!

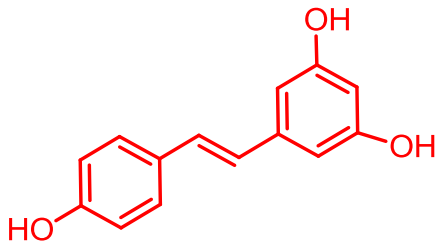
DIMERI DEL RESVERATROLO ED ATTIVITA' BIOLOGICA



trans-ε-Viniferina

- **Antitumorale**
- **Antileucemico**
- **Antiossidante**

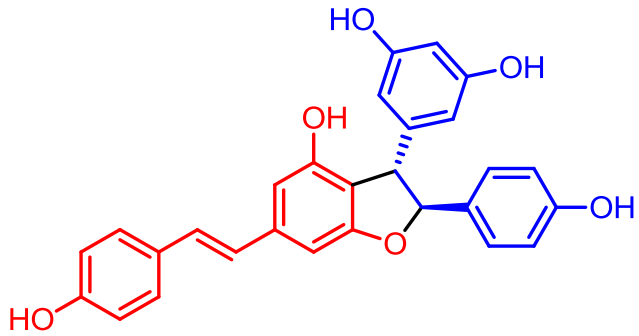
Biochimie, ***2008*** *, 90, (11–12), 1674–1684*



trans-Resveratrolo

- **Antitumorale**
- **Antiossidante**
- **Antiaggregante**

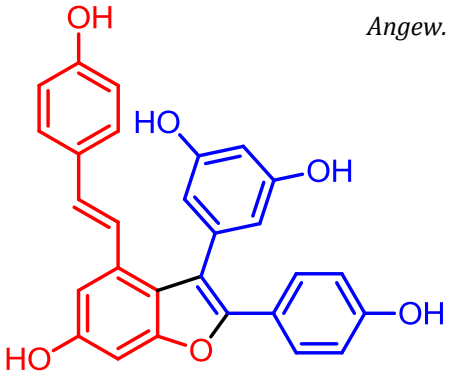
Angew. Chem. Int. Ed. **2012**, *51, 6824–6826*



Gnetina C

- **Antiaggregante**
- **Antiossidante**
- **Inibitore dell'angiogenesi**

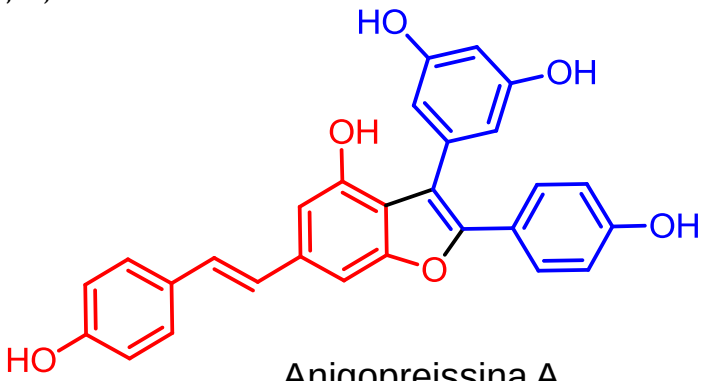
Bioorg. Med. Chem. Lett. **2010**, *20, 3441*



Amurensina H

- **Antiinfiammatorio**
- **Anti asmatico**
- **Inibitore del fattore TNF –α**

Acta Pharmacologica Sinica ***2006****, 27, 735*

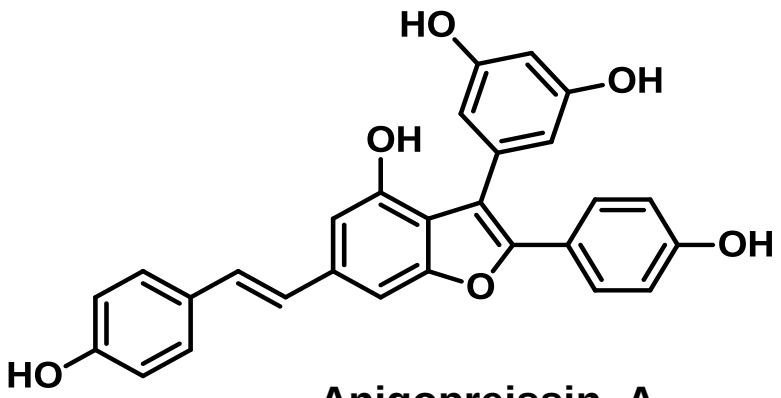


Anigopreissina A

- *Anigozanthos preissi* 250 g di radici 2,4 mg

- *Musa cavendish* 50 g di rizomi 100 µg

- *Macropidia fuliginosa* 77 g di bulbi 12.2 mg



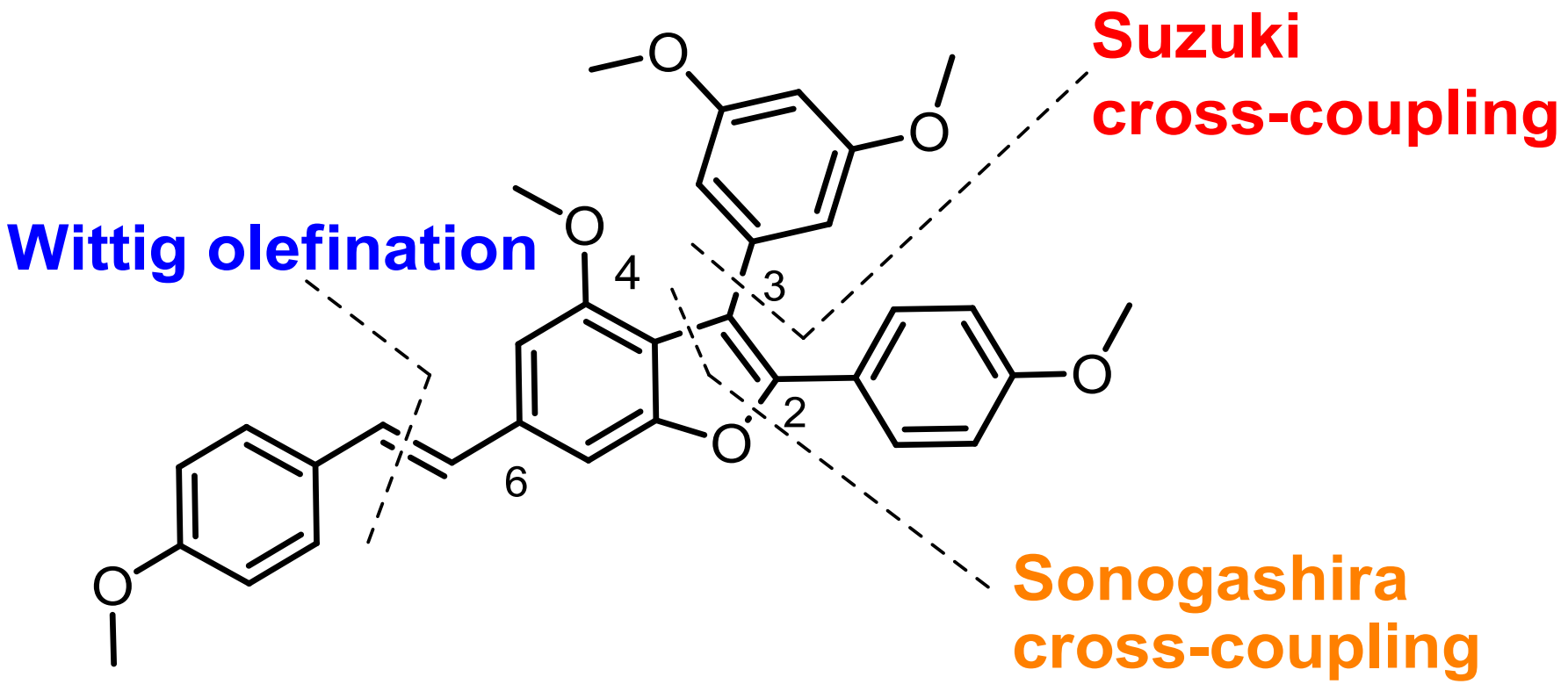
Anigopreissin A

- It prevents and/or fights against the wrinkles of the skin
- It has low antimicrobial activity against *S. aures* e *S. pyogenes.*
- It inhibits HIV-1 reverse transcriptase

B. Schneider *et al. Phytochemistry* ***1996***, 471.

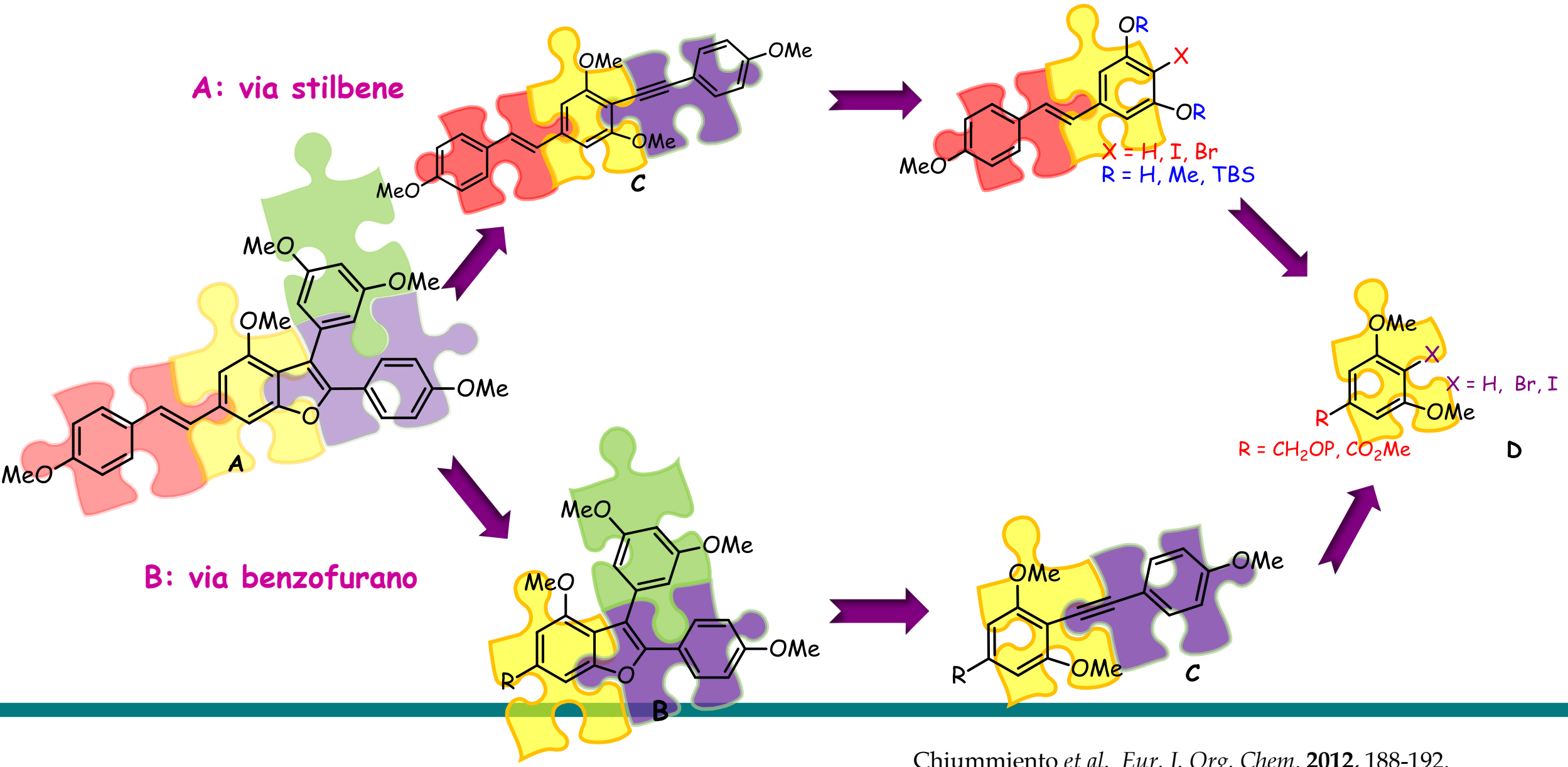
S. Urban *et al. J. Nat. Prod,* **2015**, *78*, 1600.

M. Elofsson *et al. Advanced Synthesis & Catalysis,* **2016**, *358*(24), 4085.



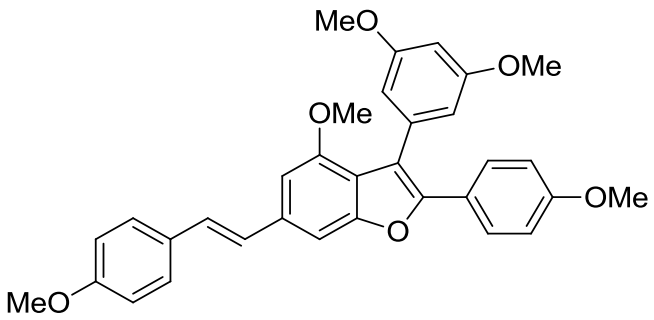
Permethylated anigopreissin A

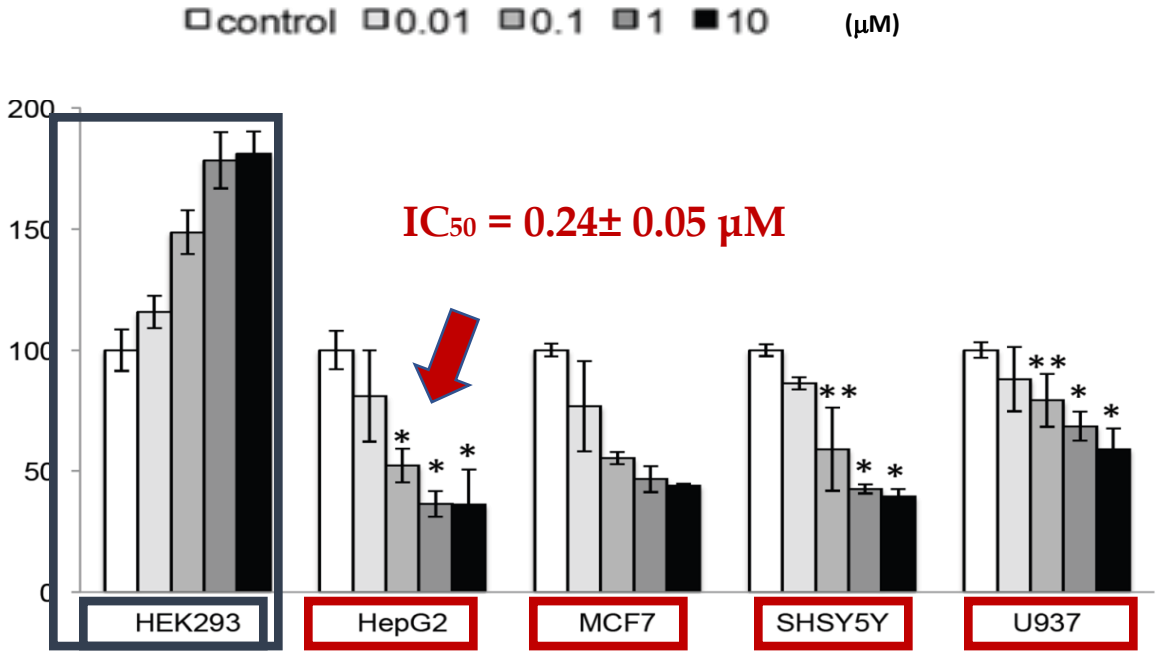
Chiummiento *et al.* *Eur. J. Org. Chem.* **2012**, 188-192.



Chiummiento *et al. Eur. J. Org. Chem.* **2012**, 188-192.

Permethylated anigopreissin A





Metilazione dei gruppi ossidrilici

↑ Permeabilità membrana cellular[3]

↑ Biodisponibilità

↑ Stabilità metabolica

Sintesi PAA in grandi quantità:

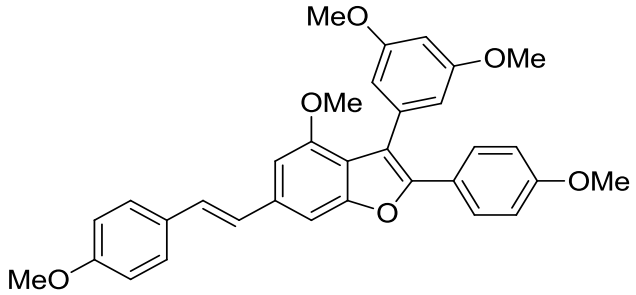
- Replicabile su scale maggiori
- Indagine attività antitumorale

8 passaggi Resa Totale 20%

Hepatoma cells treated with Permethylated Anigopreissin A arrest their cell cycle in G1 phase

Permethylated Anigopreissin A triggered cell death occurs by apoptosis.

Permethylated Anigopreissin A kills liver cancer cells through intrinsic apoptotic pathway

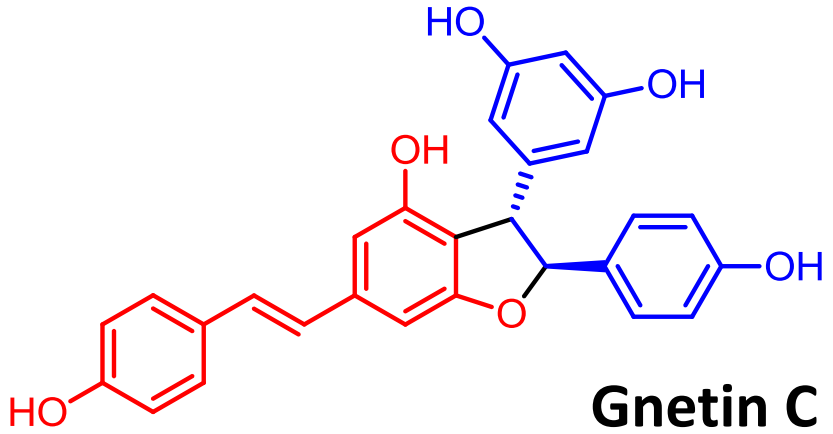


Permethylated anigopreissin A

Chiummiento *et al.*, *Chemico-Biological Interactions*, **2015**, *237*, 1.

Todisco, S. et al. Biomedicines, 2021,

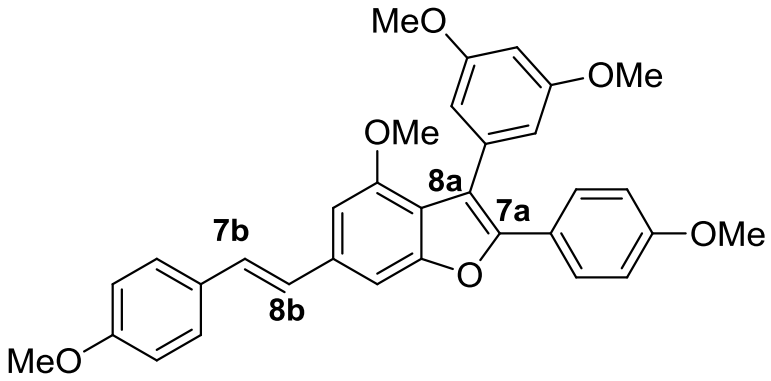
Dai semi di Melinjo
Gnetum gnemon (Gnetaceae)

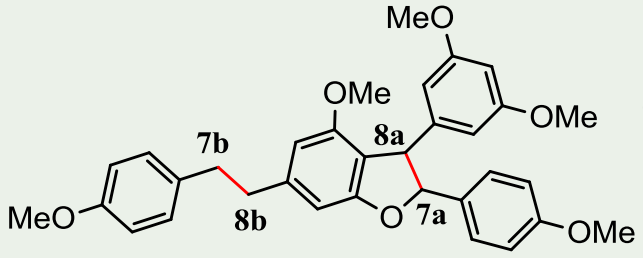
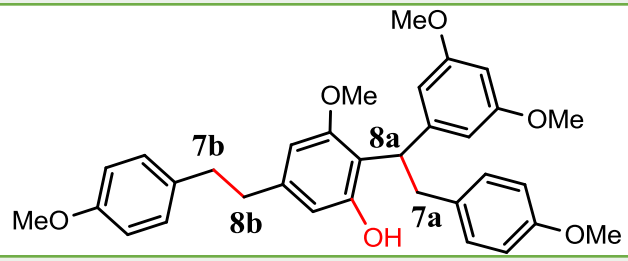
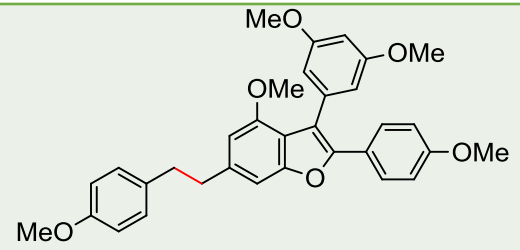


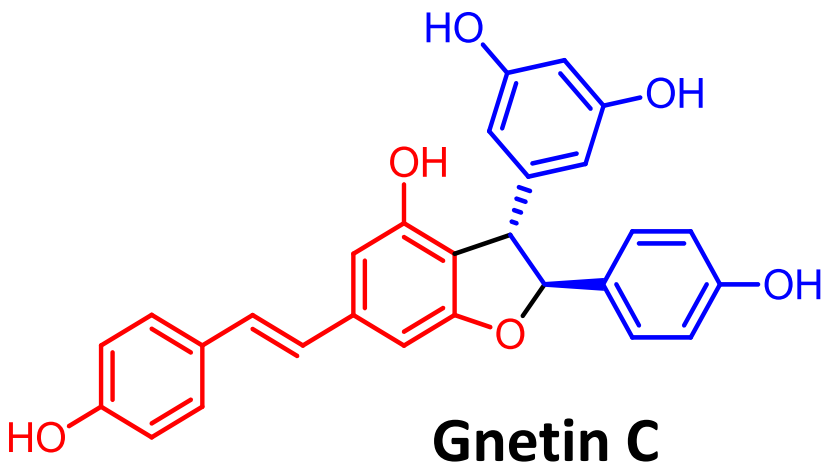
Gnetin C

- Inibitore dell'attività della tirosinasi e quindi della biosintesi della melanina (trattamento contro iperpigmentazione, agente sbiancante);
- Inibitore dell'angiogenesi (prevenzione e trattamento del cancro);
- Moderata attività antimicrobica;
- Inibitore aggregazione piastrinica;
- Inibitore delle placche b-amiloidi
- Fase preclinica nel trattamento cancro prostatico

J Nat Prod . **1982**, *45*, 754–761.

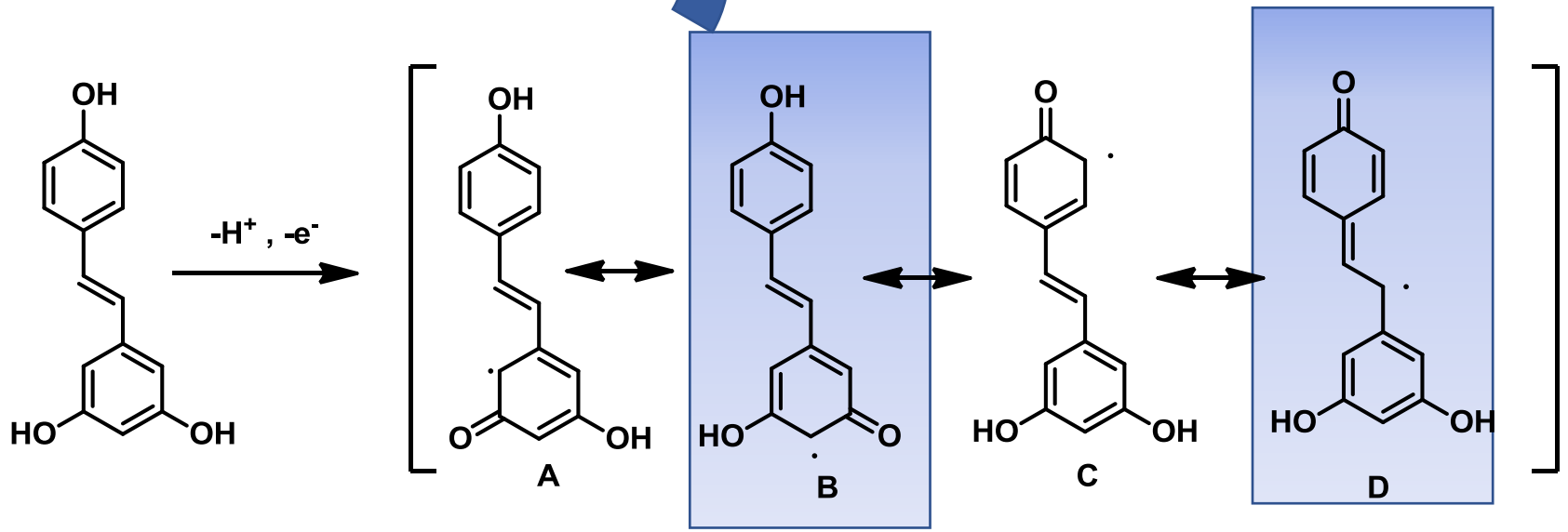


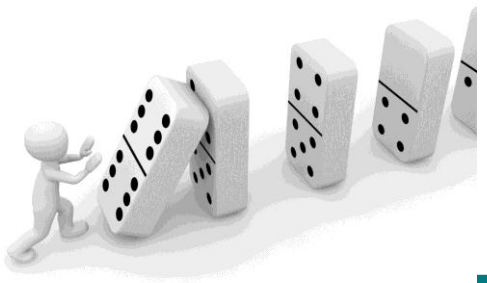
REAGENTI	RISULTATO
H_2, Pd/C acetone	 + Altri Prodotti
ET_3SiH (3,0 eq) CF_3COOH	 + Altri Prodotti
ET_3SiH Pd/C (10%) Metanolo	Nessuna reazione
NH_2NH_2 (4,0 eq.) $FeCl_3 \cdot 6_2H$ O (cat.) Etanolo	Nessuna reazione
NH_2NH_2(8 eq.) 2-Nitrobenzensolfonil-cloruro(2 eq.), CH_3CN	Presenza di 



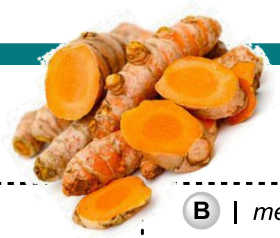
Gnetin C

B + D

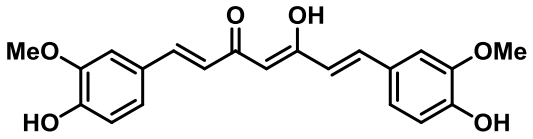




Diarylheptanoides

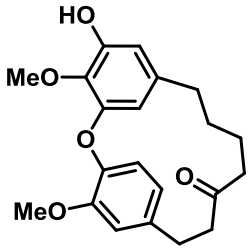


A | Diarylheptanoïde linéaire

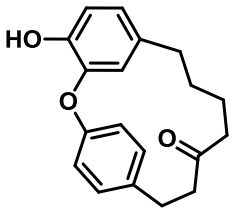


curcumine

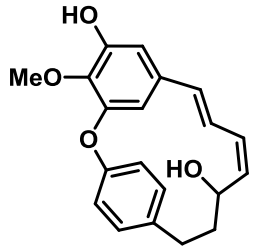
B | *méta,para*-diarylheptanoïdes diphényléthers cycliques



juglanine A

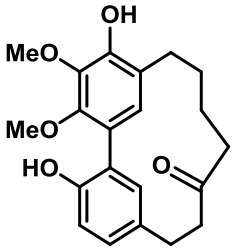


acérogénine C

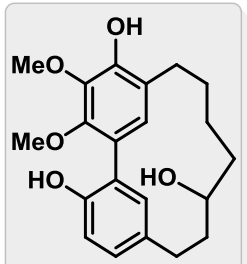


giffonine H

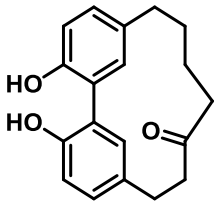
C | *méta,méta*-diarylheptanoïdes cycliques



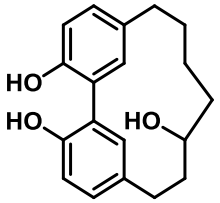
myricanone



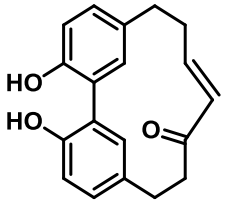
myricanol



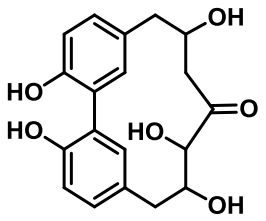
acérogénine E



acérogénine K

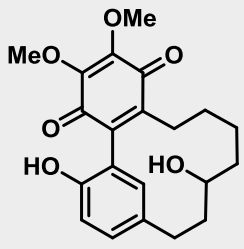


alnusone

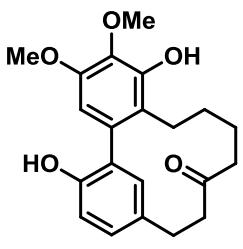


asadanine

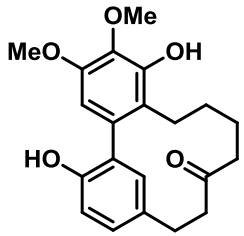
D | *ortho,méta*-diarylheptanoïdes cycliques



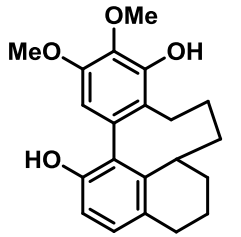
actinidione



isomyricanone

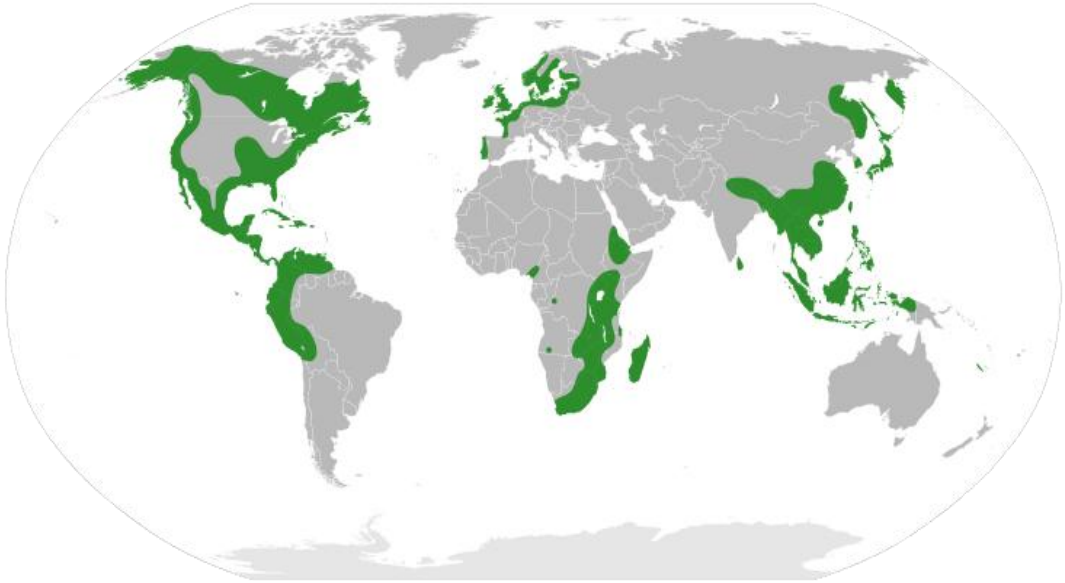


isomyricanol



tétraline

Les *myricacées*



- *Myrica gale*

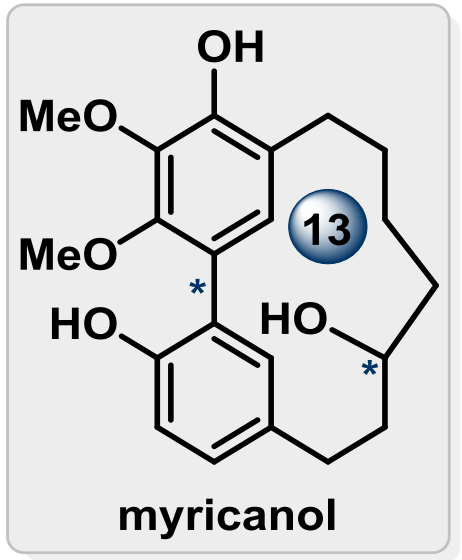
- Utilisées en médecine traditionnelle pour ses propriétés versatiles et « miraculeuses »

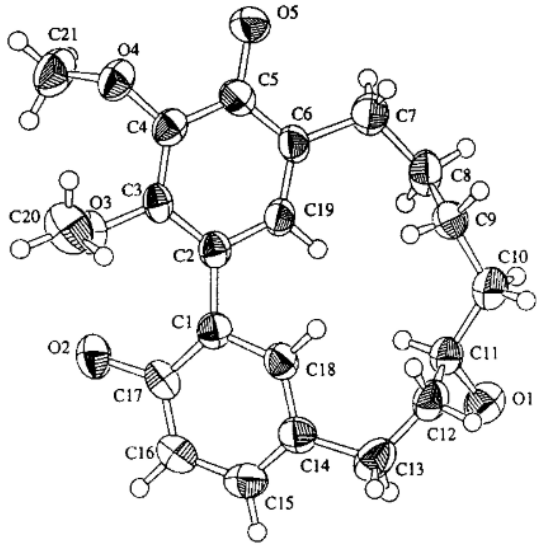
- *Myrica cerifera*

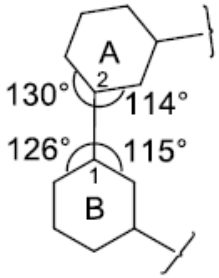
- *Myrica Rubra*

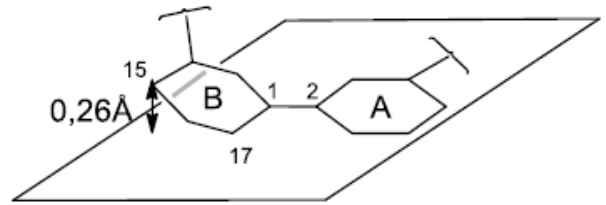
- Fraise chinoise

Myricanol









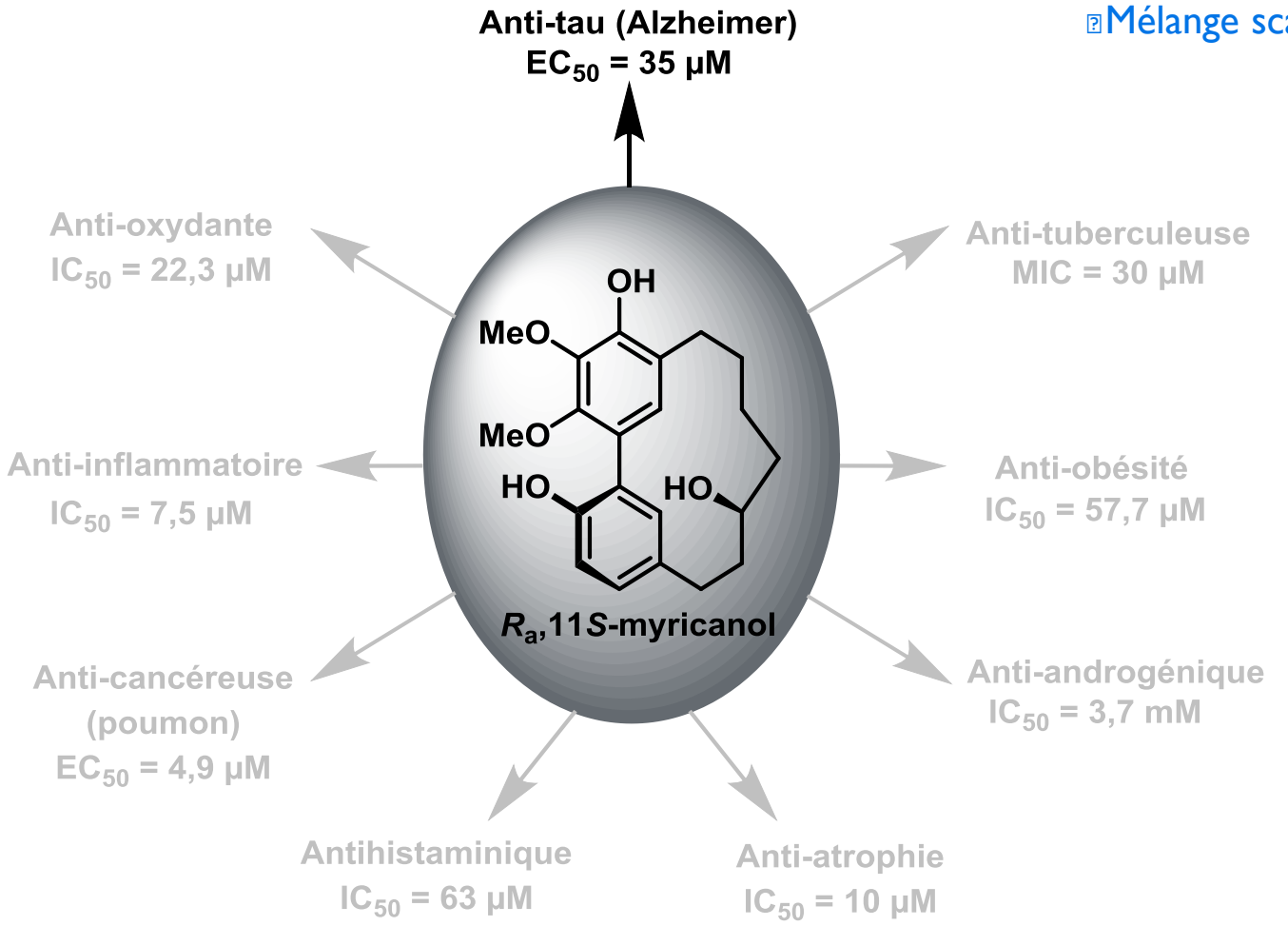
- Isolé en 1970
  - < 0,005% de la masse totale
- Deux cycles aromatiques
- Chaîne heptyle linéaire et oxygénée
- Macrocycle à 13 chaînons *méta,méta*-ponté
- Chiralité centrale et atropoisomérie

- Structure RX (Joshi, 1996)
- Angle dièdre : 33°

- Flexion et distorsion du motif biphényle

📖 D.A.Whiting *et al. Chem. Commun.* **1970**, 1207–1208. 📖 P.S. Baran *et al. Nat. Prod. Rep.* **2012**, *29*, 899–934. 📖 B.S. Joshi *et al. J. Nat. Prod.* **1996**, *59*, 759-764.

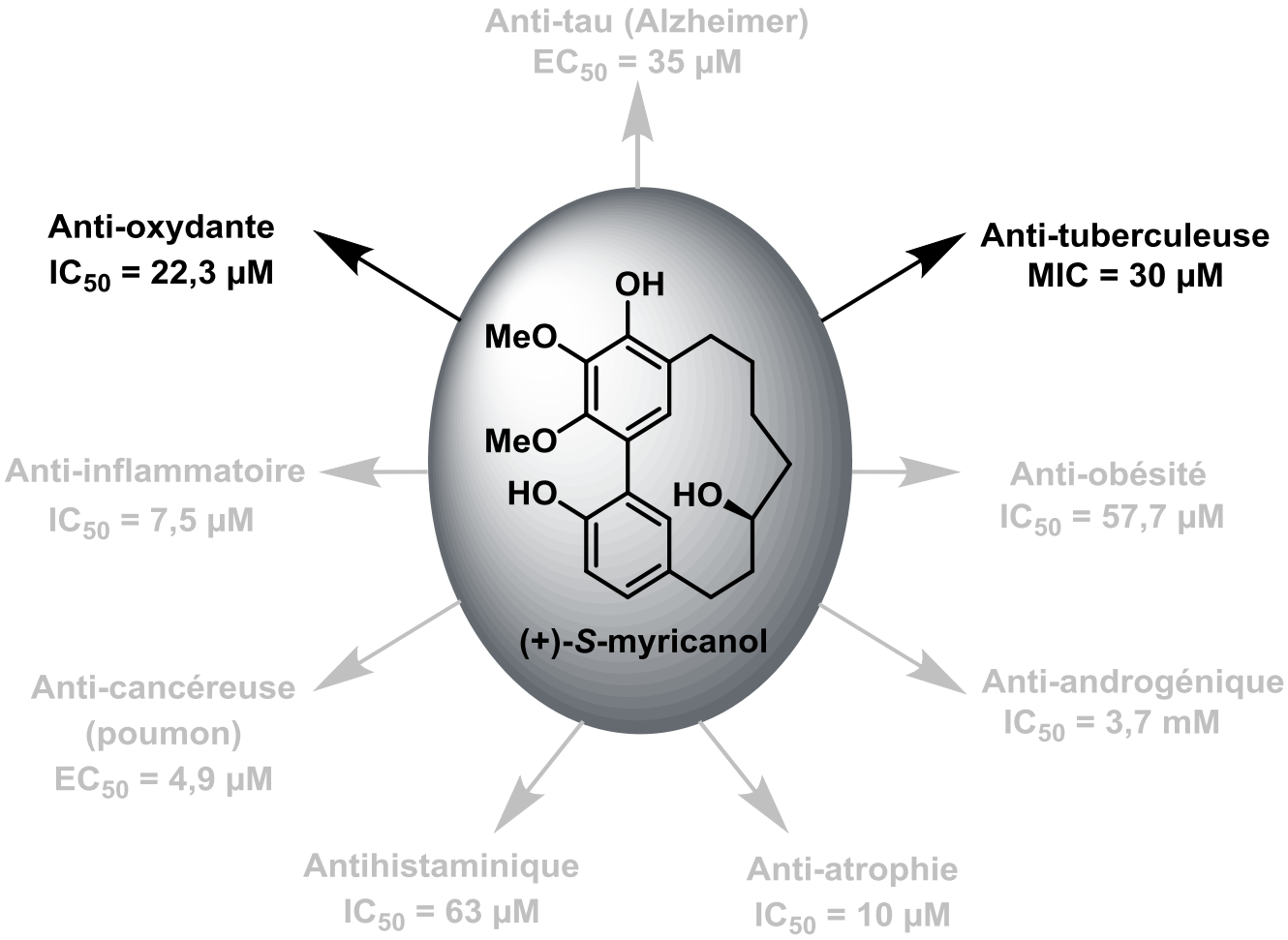
Activités biologiques



Mélange scalémique dans *Myrica Cerifera*:
e.e. = 86%

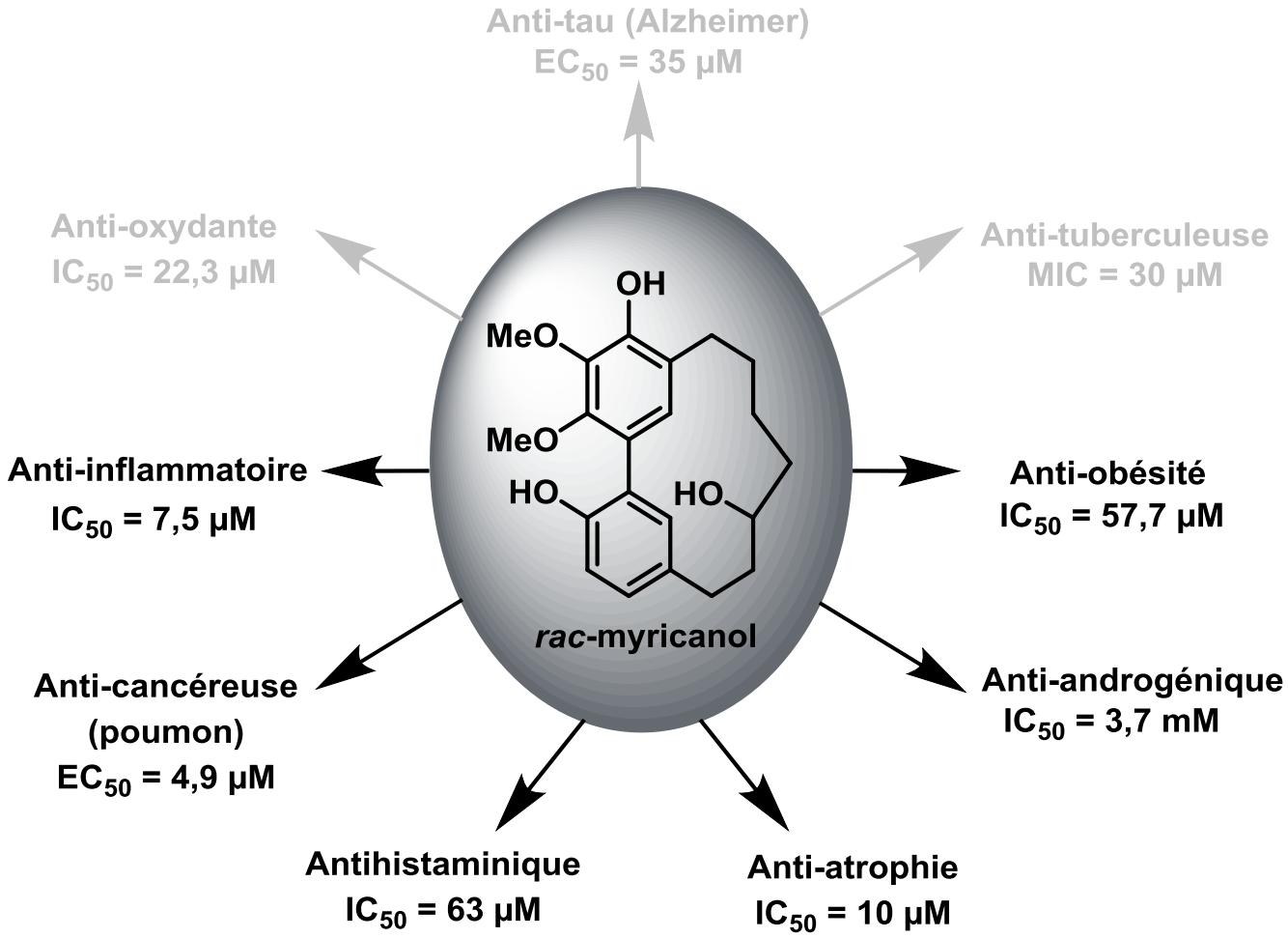
📖 C. Dickey *et al. ACS Chem. Biol.* **2015**, *10*, 1099–1109. 📖 C. Dickey *et al. J. Nat. Prod.* **2011**, *74*, 38–44. 📖 M. Yoshikawa *et al. Bioorg. Med. Chem.* **2002**, *10*, 4005–4012. 📖 F. Yang *et al. Phytomedicine* **2014**, *21*, 1490–1496. 📖 Patent CN 108434127 A, (*issued* August 24th 2018). 📖 H. Matsuda *et al. Biol. Pharm. Bull.* **2002**, *24*, 259–263. 📖 L. Lin *et al. Food Chem.* **2019**, *270*, 305–314. 📖 L. Lin *et al. J. Cachexia. Sarcopenia Muscle* **2019**, *10*, 429–444. 📖 L. Lin *et al. Br. J. Pharmacol.* **2019**, *176*, 3983-4001. 📖 S. Chen *et al. Phytochemistry* **2014**,

Activités biologiques

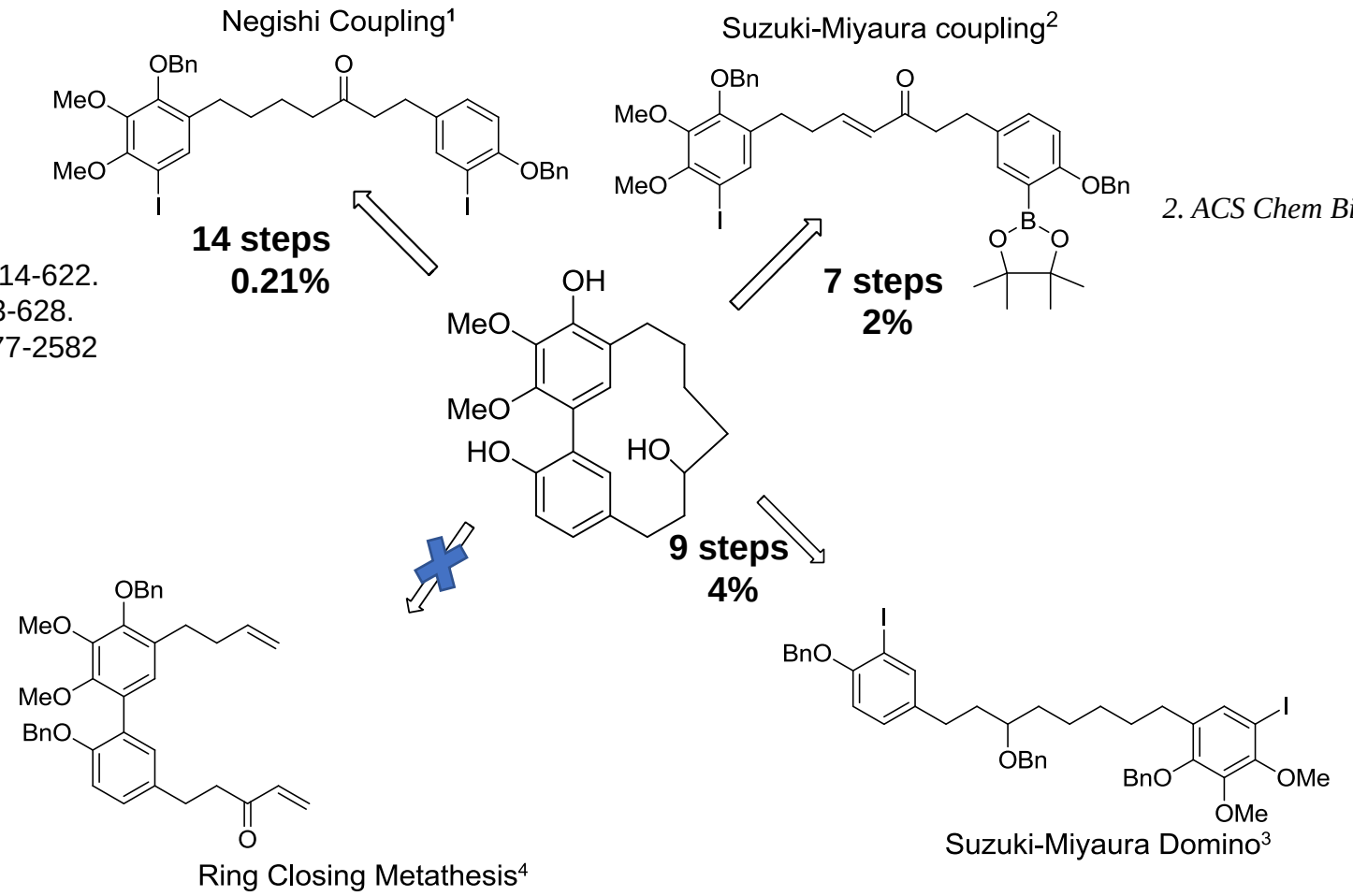


📖 C. Dickey *et al. ACS Chem. Biol.* **2015**, *10*, 1099–1109. 📖 C. Dickey *et al. J. Nat. Prod.* **2011**, *74*, 38–44. 📖 M. Yoshikawa *et al. Bioorg. Med. Chem.* **2002**, *10*, 4005–4012. 📖 F. Yang *et al. Phytomedicine* **2014**, *21*, 1490–1496. 📖 Patent CN 108434127 A, (*issued* August 24th 2018). 📖 H. Matsuda *et al. Biol. Pharm. Bull.* **2002**, *24*, 259–263. 📖 L. Lin *et al. Food Chem.* **2019**, *270*, 305–314. 📖 L. Lin *et al. J. Cachexia. Sarcopenia Muscle* **2019**, *10*, 429–444. 📖 L. Lin *et al. Br. J. Pharmacol.* **2019**, *176*, 3983-4001. 📖 S. Chen *et al. Phytochemistry* **2014**,

Activités biologiques



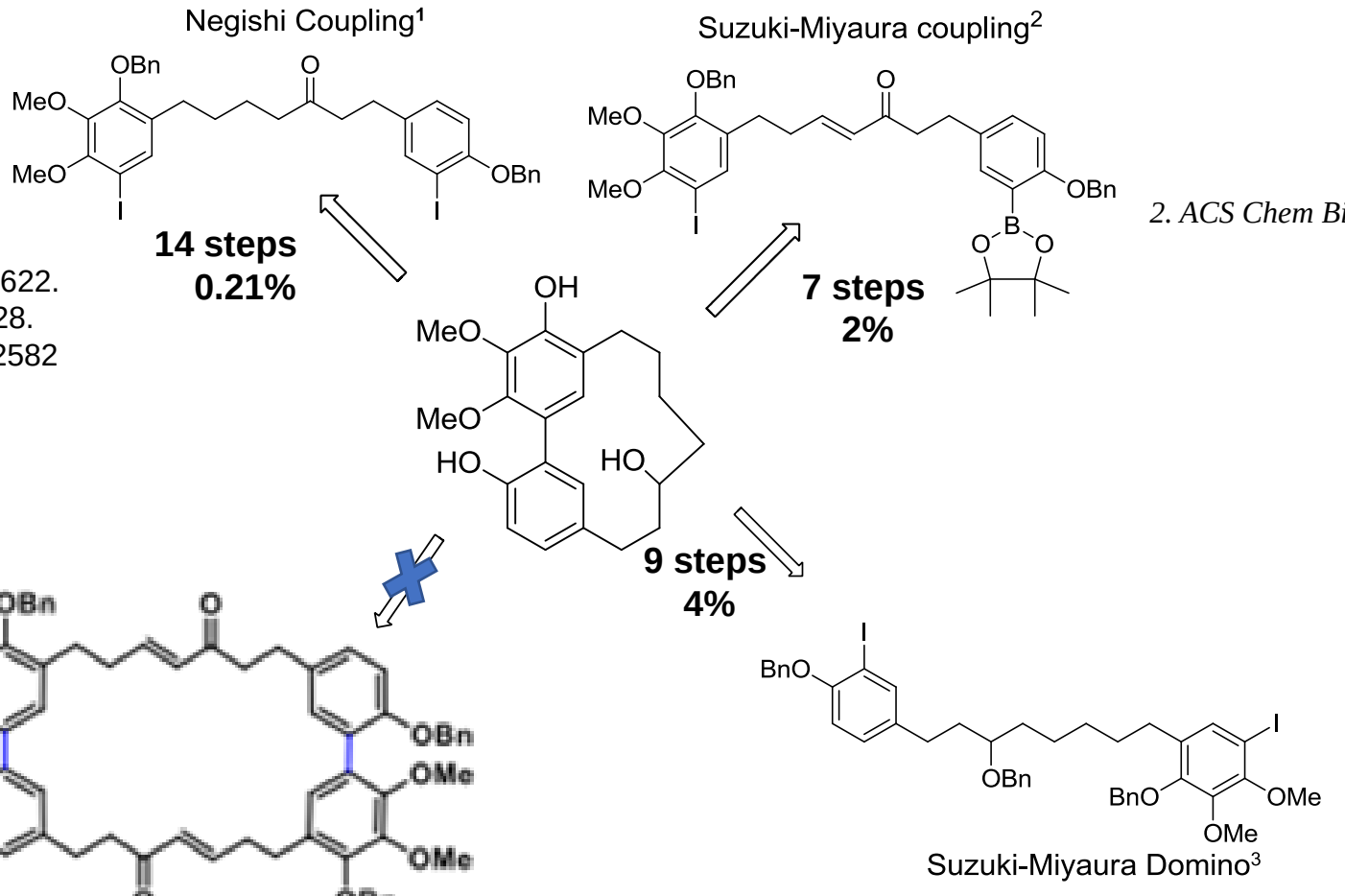
📖 C. Dickey *et al. ACS Chem. Biol.* **2015**, *10*, 1099–1109. 📖 C. Dickey *et al. J. Nat. Prod.* **2011**, *74*, 38–44. 📖 M. Yoshikawa *et al. Bioorg. Med. Chem.* **2002**, *10*, 4005–4012. 📖 F. Yang *et al. Phytomedicine* **2014**, *21*, 1490–1496. 📖 Patent CN 108434127 A, (*issued* August 24th 2018). 📖 H. Matsuda *et al. Biol. Pharm. Bull.* **2002**, *24*, 259–263. 📖 L. Lin *et al. Food Chem.* **2019**, *270*, 305–314. 📖 L. Lin *et al. J. Cachexia. Sarcopenia Muscle* **2019**, *10*, 429–444. 📖 L. Lin *et al. Br. J. Pharmacol.* **2019**, *176*, 3983-4001. 📖 S. Chen *et al. Phytochemistry* **2014**,



1.a) *J. Chem. Soc. Perkin 1*, **1980**, 614-622.
b) J. Chem. Soc. Perkin 1, **1980**, 623-628.
c) *J. Chem. Soc. Perkin 1*, **1983**, 2577-2582

2. *ACS Chem Biol.* **2015** , 10(4):1099-109.

3. *Org. Biomol. Chem.*, **2018**, 16, 8859-8869.
4. Synlett **2020**; 31, 559-564.



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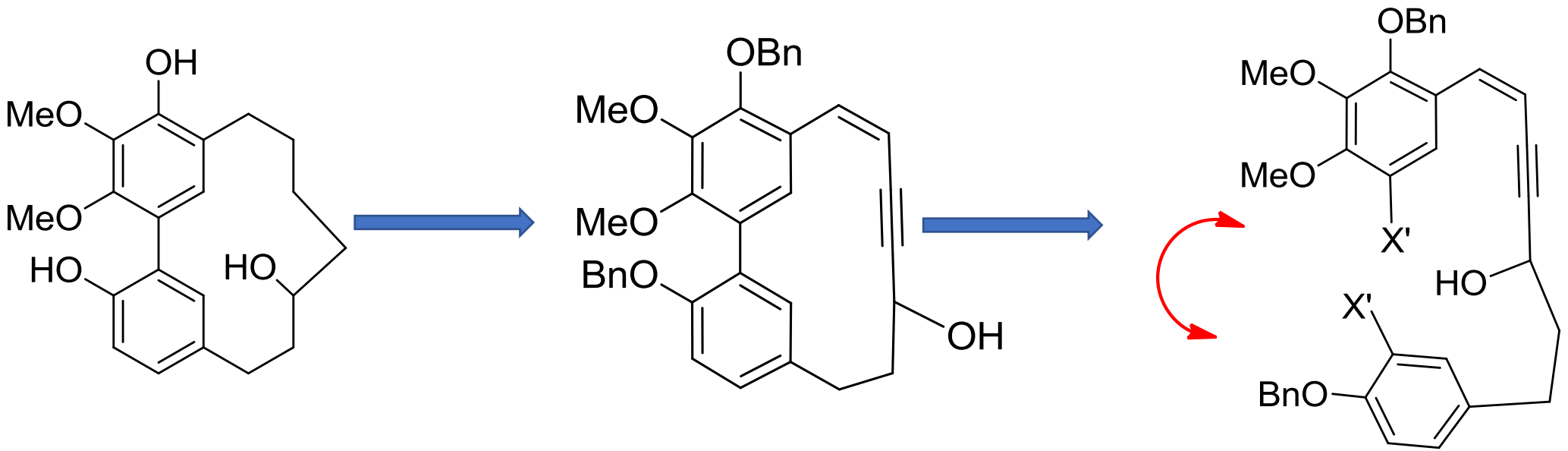
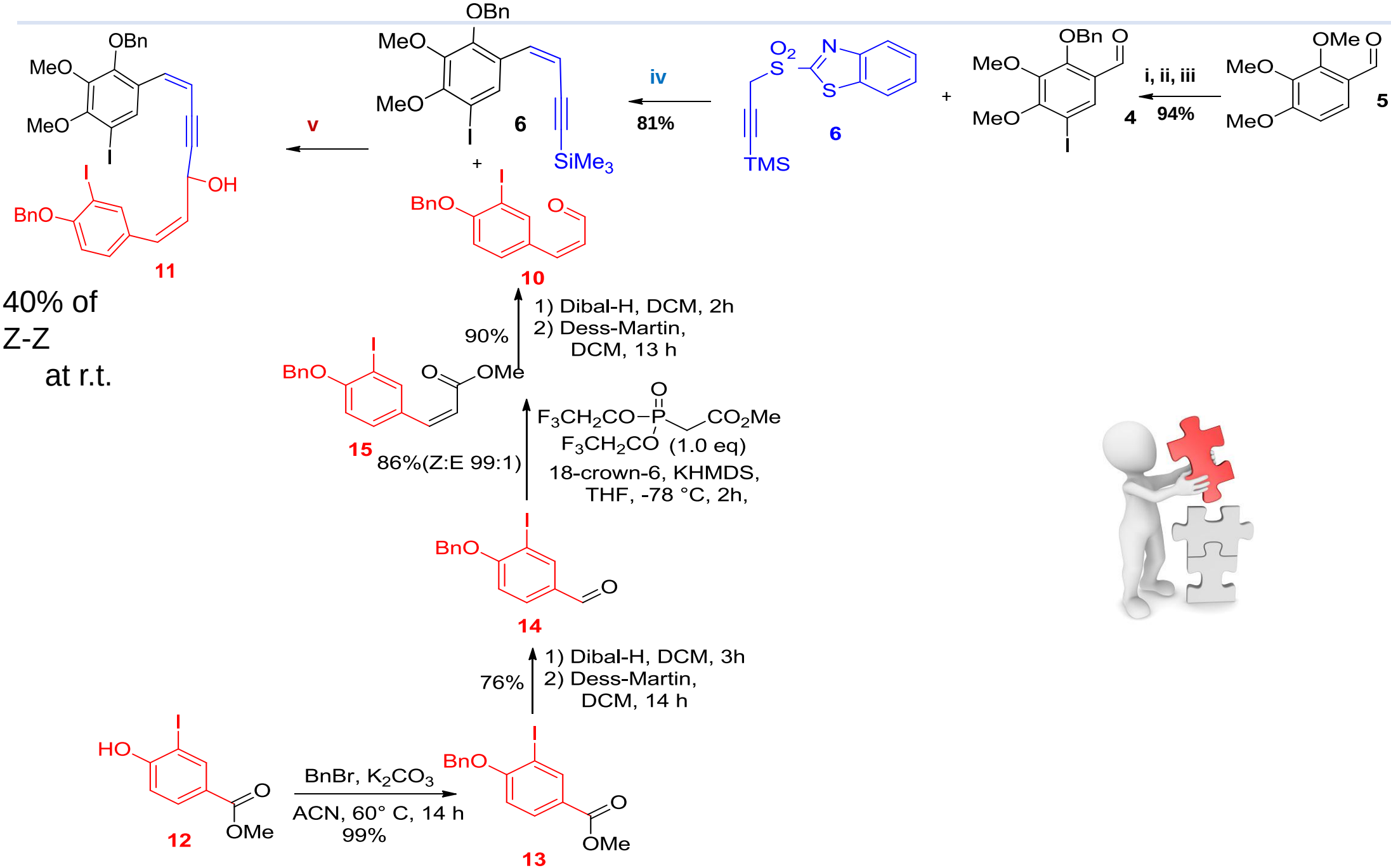
4. Synlett **2020**; 31, 559-564.

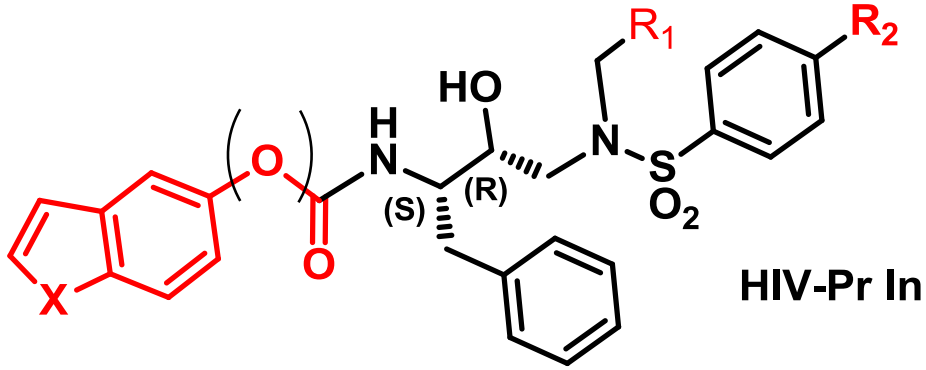
Retrosintesi



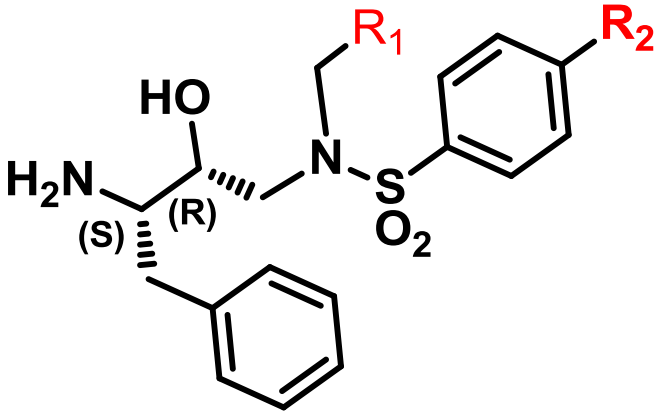

OBn
MeO
MeO
I
OH
BnO
11
v
6
SiMe3
+
BnO
O
10
iv
81%
O2
N
S
S
TMS
6
+
OBn
O
MeO
MeO
I
i, ii, iii
4
94%
OMe
O
MeO
MeO
5
40% of
Z-Z
at r.t.
90%
1) Dibal-H, DCM, 2h
2) Dess-Martin,
DCM, 13 h
BnO
O
OMe
15
86%(Z:E 99:1)
F3CH2CO–P
O
CO2Me
F3CH2CO (1.0 eq)
18-crown-6, KHMDS,
THF, -78 °C, 2h,
BnO
O
14
76%
1) Dibal-H, DCM, 3h
2) Dess-Martin,
DCM, 14 h
HO
I
O
OMe
12
BnBr, K2CO3
ACN, 60° C, 14 h
99%
BnO
O
OMe
13

Quali altri bersagli ci attendono?

Nuovi potenziali inibitori dell'HIV proteasi……



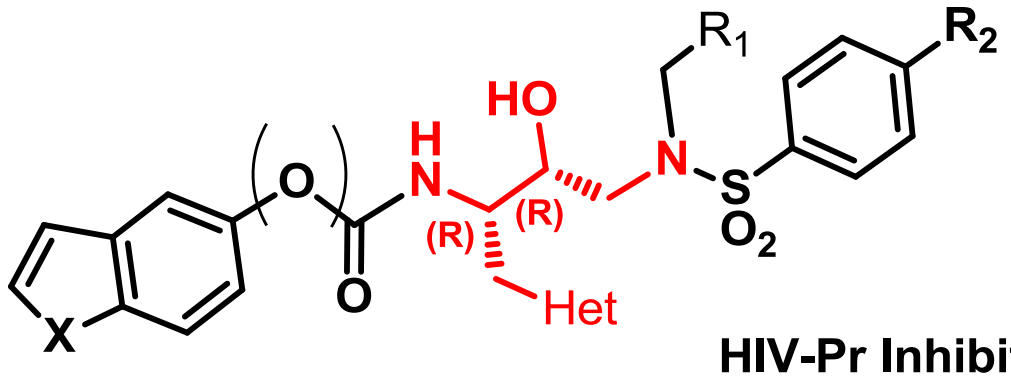
HIV-Pr Inhibitors



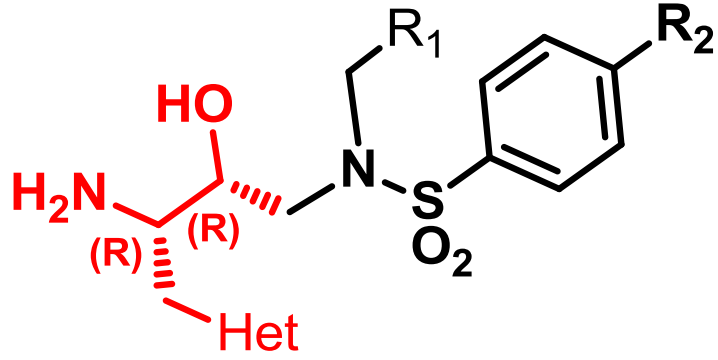
Attività antitumorale

X = O, NH, S
R_1 = iPr, Ph
R_2 = 4-OMe, 4-NO_2, 3,4-diMeO

IC_{50} = ≤0.6 nM (X=O,NH, S)



HIV-Pr Inhibitors



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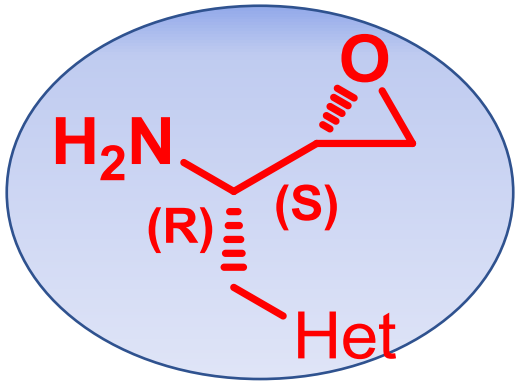

Via aspettiamo numerosi!!!