SAPIENZA
UNIVERSITÀ DI ROMA

Facoltà di Farmacia

Corso di Laurea in Scienze e Tecnologia dei Prodotti Erboristici

Tesi Compilativa di Laurea in Chimica Farmaceutica e Tossicologica I

Inibitori di origine naturale della Heat Shock Protein 90 (HSP90) come potenziali agenti anticancro

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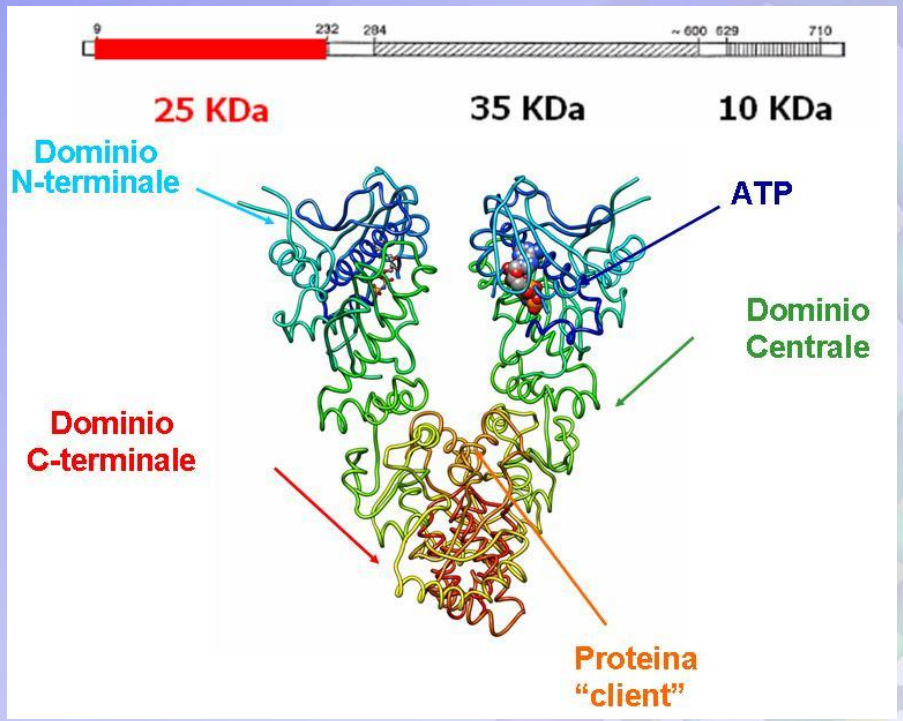
Anno Accademico 2008-2009

Heat Shock Protein 90

- Chaperone molecolare ubiquitario ad attività ATPasica
- Interazione con proteine clients e co-chaperoni
- Espressione aumentata in molte forme tumorali umane
- Struttura altamente conservata all'interno della famiglia



HSP90 e cancro

1. Autosufficienza signaling di crescita

ErbB2 EGFR

2. Insensibilità signaling anti-crescita

CDK4 Ciclina D

6. Invasione tissutale e metastasi

c-MET MMP

Progressione tumorale[1-2]

3. Evasione apoptotica

IGF-1R AKT Survivina

5. Angiogenesi sostenuta

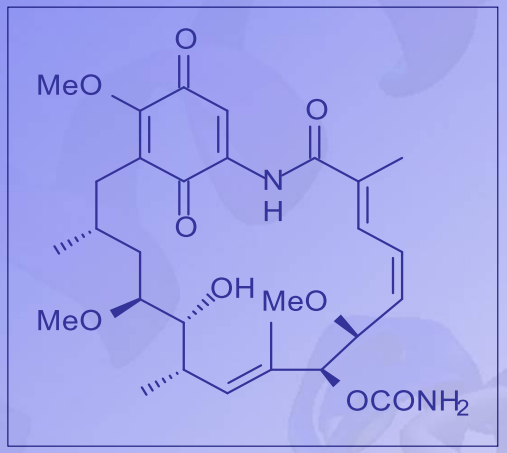
VEGFR HIF-1α

4. Replicazione potenzialmente illimitata

Telomerasi (h-TERT)

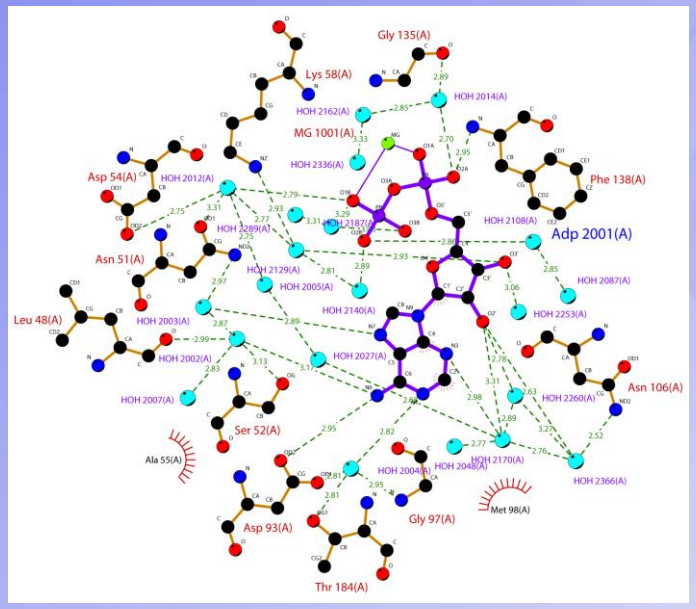
[1]Hanahan et al. Cell. 2000; 100, 57-70. [2]Zhang et al. J Mol Med 2004; 82, 488–499

GELDANAMICINA

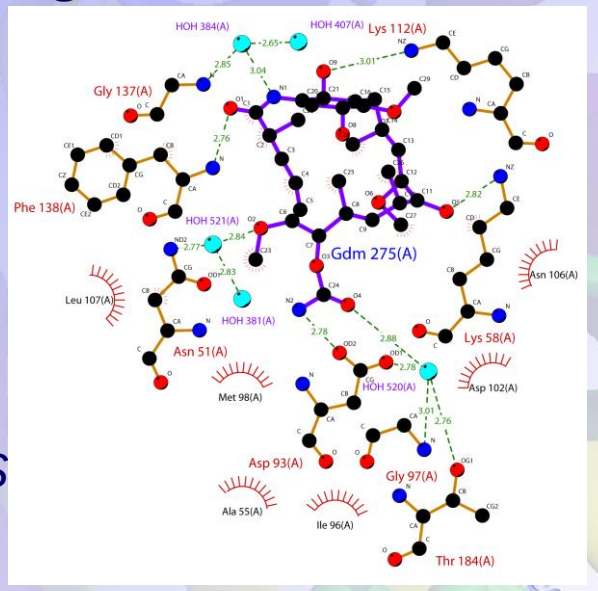


Geldanamicina
Inibitore N-terminale[2]
K_d = 1,2 nM[3]
IC_{50} < 200 nM[4]

Strutture cristallografiche



Dominio N-terminale Hsp90/ADP
PDB: 1yet[5]

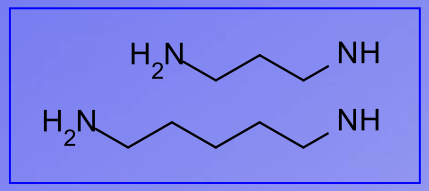


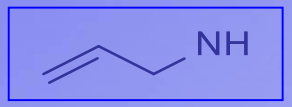
Dominio N-terminale Hsp90/GDA
PDB: 1a4h[6]

[1]DeBoer et al. *J. Antibiot.* 1970, *23*, 442-7. [2]Whiteshell et al. *Proc. Natl. Acad. Sci. USA* 1994, *91*, 8324-8. [3]Neckers et al. Invest. New Drugs 1999; 17, 361-73. [4]Whiteshell et al Cancer Res. 1992; 52, 1721-8. [5]Stebbins et al. Cell 1997; 89, 239-50. [6]Roe et al. J.Med Chem. 1999; 42, 260-6.

GDA: Relazioni Struttura - Attività

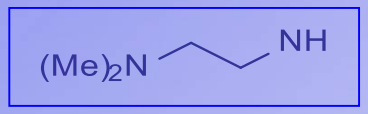
Sostituzione tollerata





17-AAG[1]

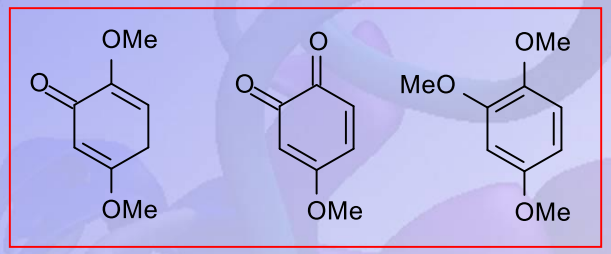
IC_{50} SK-BR3 = 31 nM
K_d = 1,3 µM

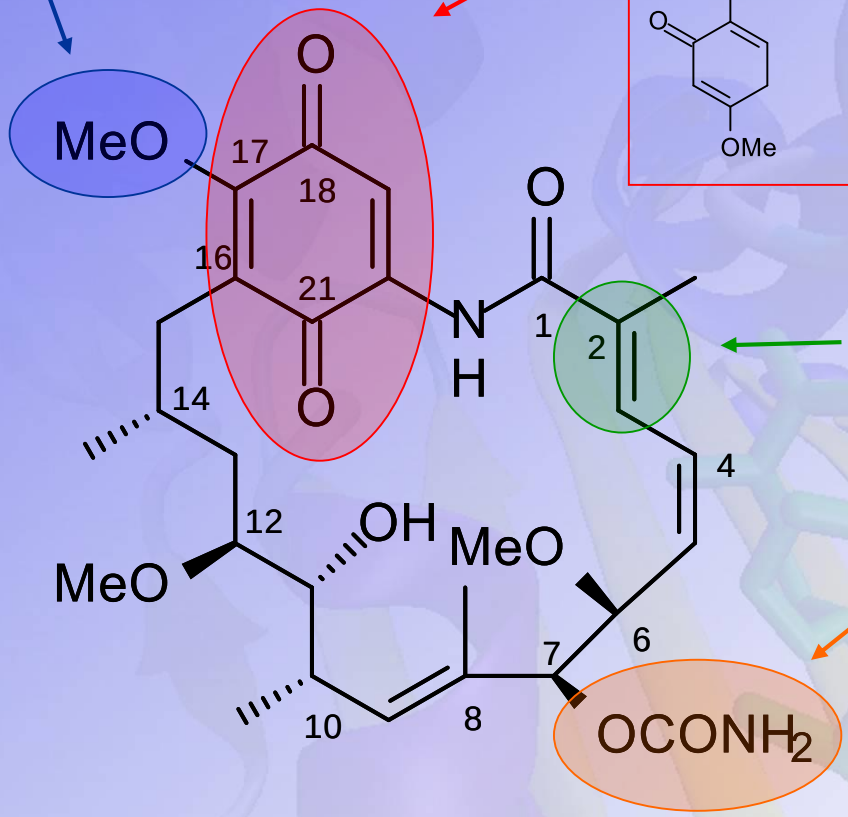


17-DMAG[2]

IC_{50} SK-BR3 = 24 nM
K_d = 0,5 µM

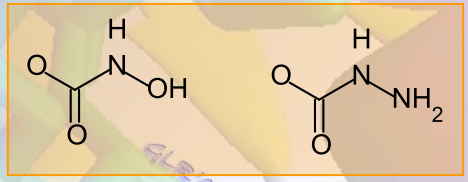
Diminuzione attività





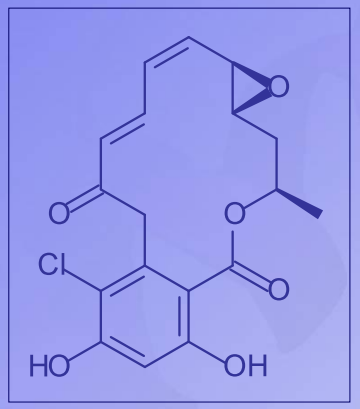
Diminuzione attività

Diminuzione attività



[1]Schulte et al. Cancer Chemoter. Pharmacol. 1998; 42, 273-79. [2]Egorin MJ et al. Cancer Chemoter. Pharmacol. 2002; 49, 7-19.

RADICICOLO e POCHONINE

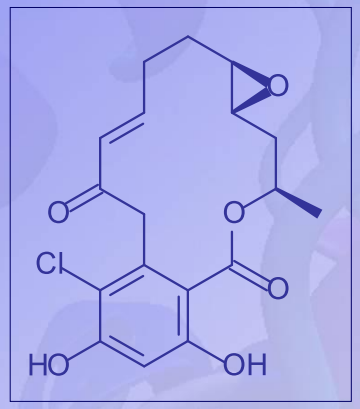


Radicicolo[1]

Inibitore N-terminale

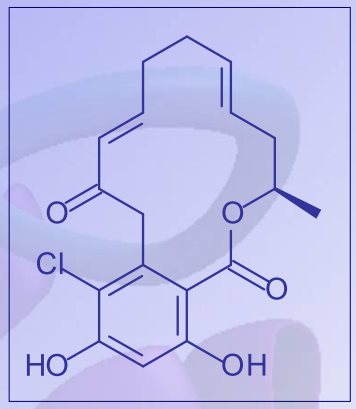
K_d = 19 nM[2]

IC_{50} = 9 µM[3]



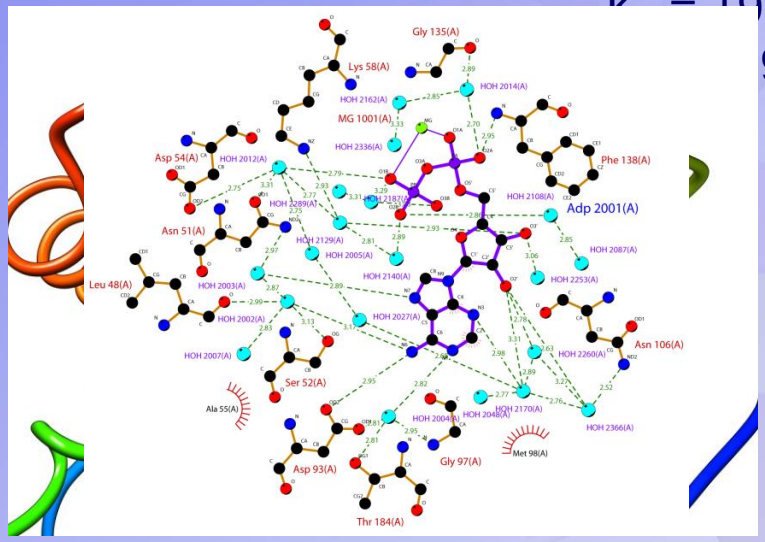
Pochonina A

IC_{50} = ~ 80 nM[5]

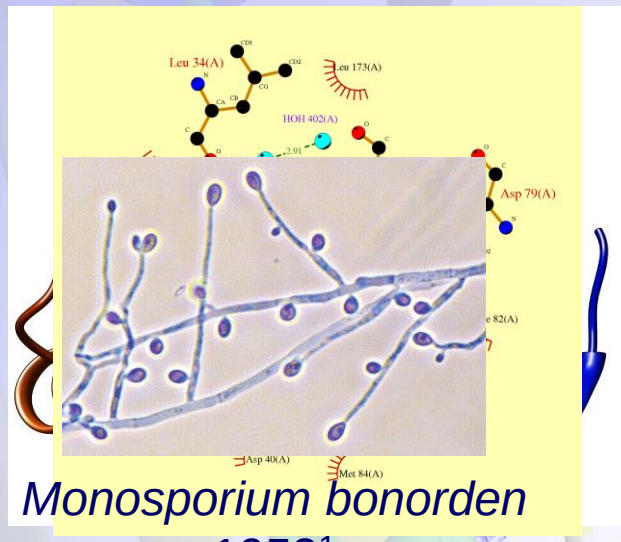


Pochonina D[4]

Strutture cristallografiche



Dominio N-terminale Hsp90/ADP
PDB: 1yet[6]



Monosporium bonorden 1953[1]

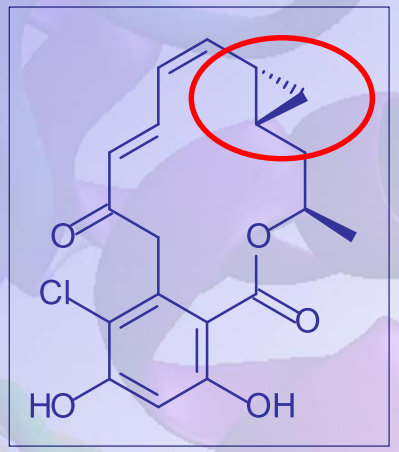
Dominio N-terminale Hsp90/RDC
PDB: 1bgq[7]

[1]Delmotte et al. Nature 1953; 171, 344. [2]Roe et al. J.Med Chem. 1999; 42, 260-6. [3] Rowlands et al. Anal. Biochem. 2004; 327, 176-83. [4]Hellwig et al. J. Nat. Prod. 2003; 66, 829-37. [5]Moulin et al. J. Am. Chem. Soc. 2005; 127, 6999-7004. [6]Stebbins et al. Cell 1997; 89, 239-50. [7]Roe et al. J.Med Chem. 1999; 42, 260-66.

RDC: Relazioni Struttura - Attività

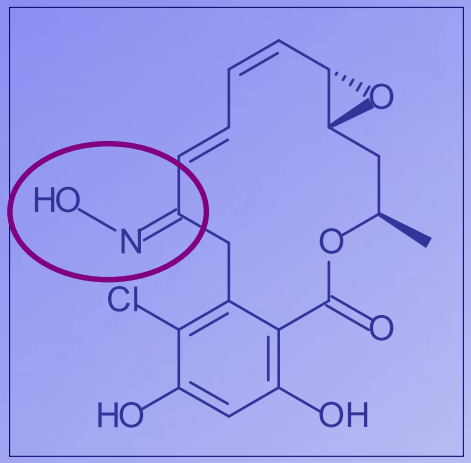
Non essenziali

Mantenimento attività
con bioisostere

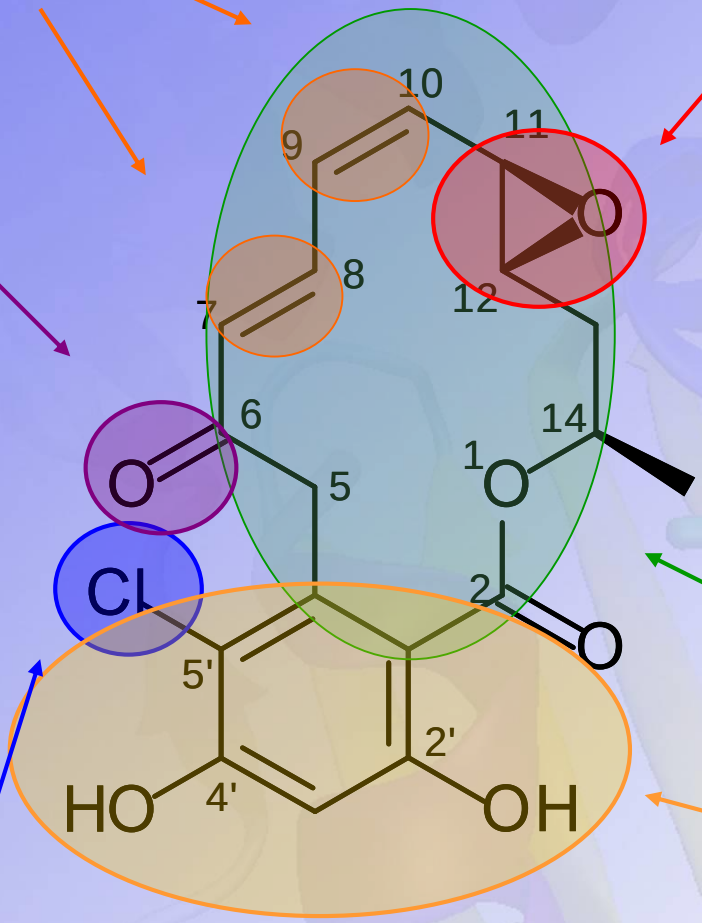


C-RDC
IC_{50} MCF-7 = 43 nM

Aumento attività
con C sp^2
ossima > chetone



KF25706
IC_{50} = 6 - 25 nM

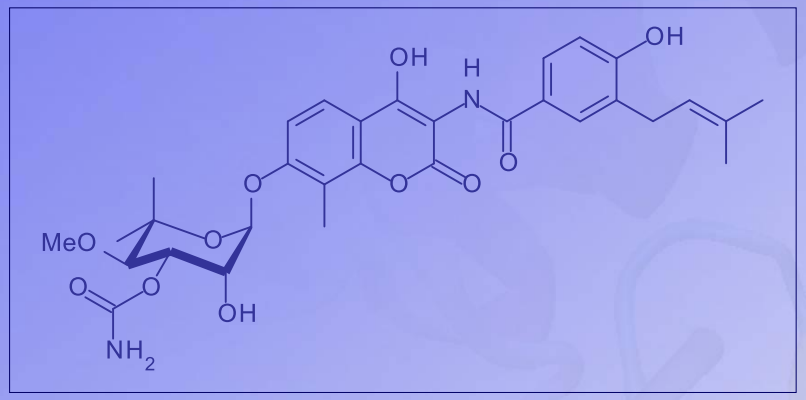


Essenziale

Essenziale

Non essenziale

NOVOBIOCINA
CUMERMICINA A1

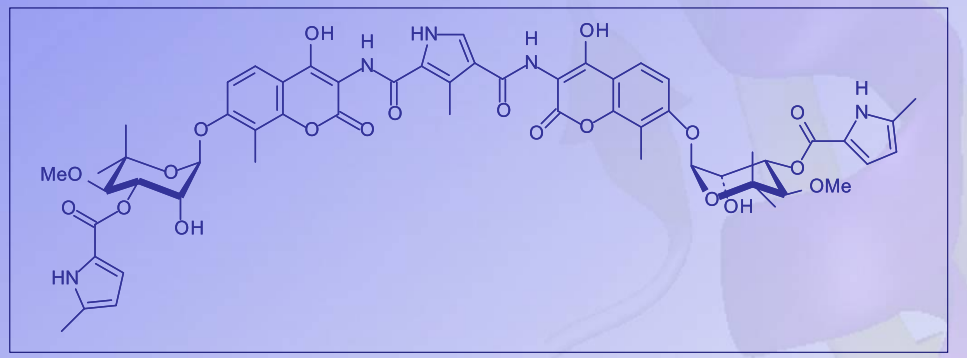


Novobiocina[2]

Inibitore C-terminale[3-4]

IC_{50} SK-BR3 = 700 µM[5]

Streptomyces spheroids[1]



Cumermicina A1[2]

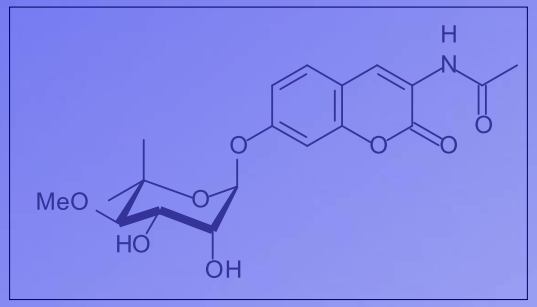
Inibitore C-terminale[3-4]

IC_{50} SK-BR3 = 70 µM[5]

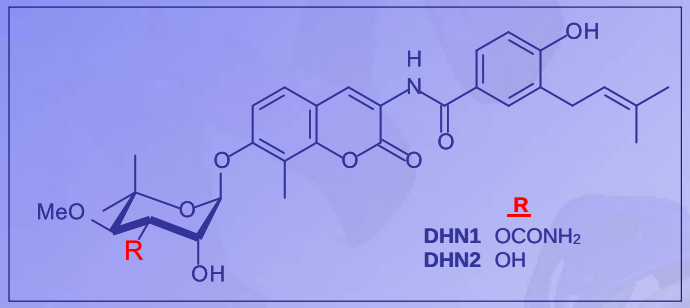
Inibitore della dimerizzazione[6]

[1]Hooper et al. Antimicrob. Agents Chemother. 1982; 22, 662-71. [2]Burlison et al. J. Am. Chem. Soc. 2006; 128, 15529-36. [3]Marcu et al. J. Biol. Chem. 2000; 275, 37181-86. [4]Yun et al. Biochemistry 2004; 43, 8217-29. [5]Marcu et al. J. Natl. Canc. Inst. 2000; 92, 242-48. [6]Allan et al. J. Biol. Chem. 2006; 281, 7161-71

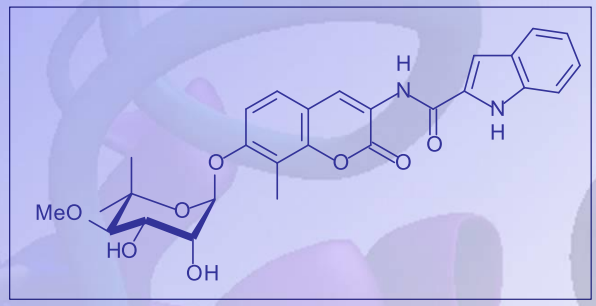
NOVOBIOCINA
Relazioni Struttura - Attività



A4[2]



DHN1 e DHN2[2]

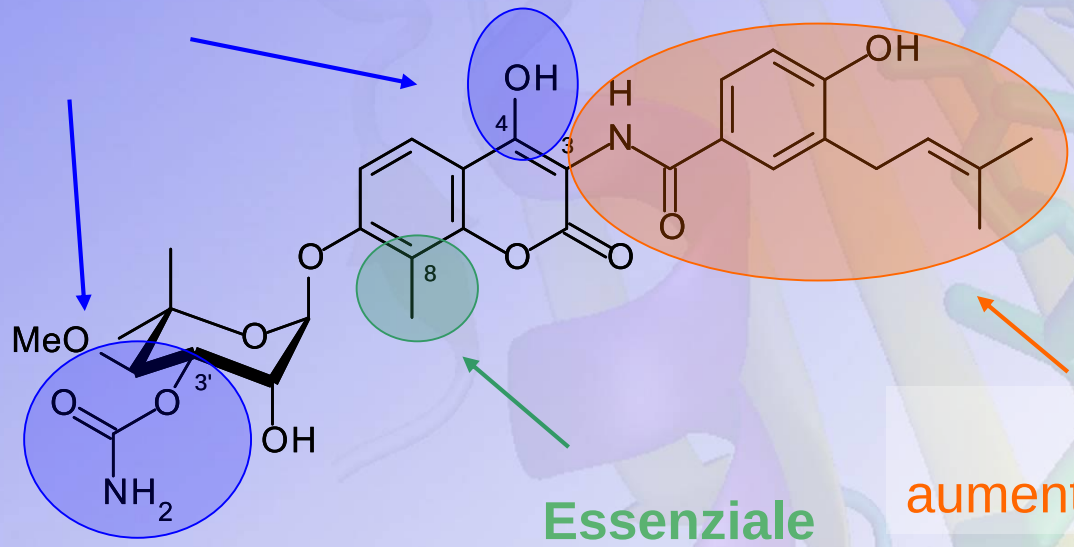


KU-122[7]

IC_{50} SK-BR3 = 0,37 µM

IC_{50} HCT-116 = 0,17 µM

Non Essenziale

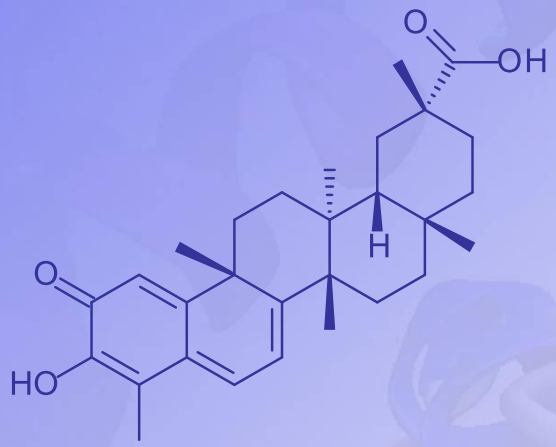


Essenziale

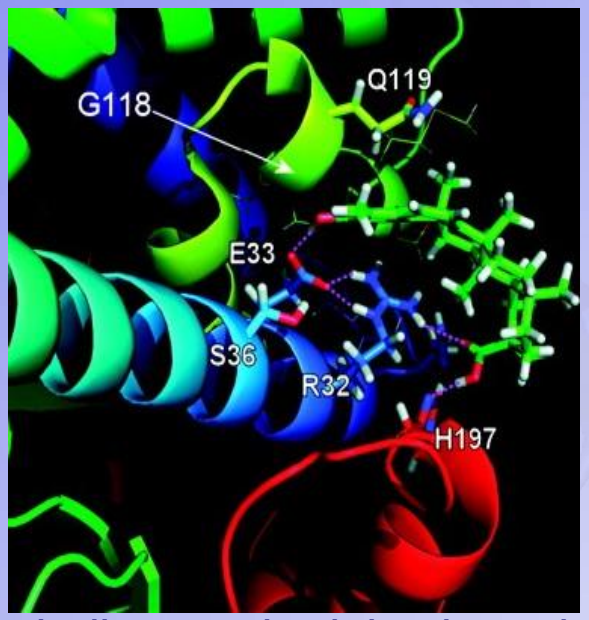
Essenziale
aumento attività con indolo

[2]Burlison et al. J. Am. Chem. Soc. 2006; 128, 15529-36. [7]Burlison et al. J. Org. Chem. 2008; 73, 2130-37.

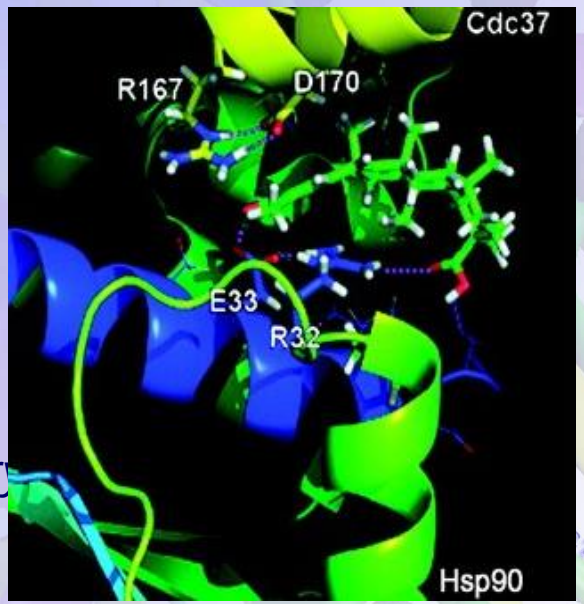
CELASTROLO



Celastrolo[1]
Inibitore interazione
Hsp90-Cdc37
IC_{50} Panc-1 = 3 µM



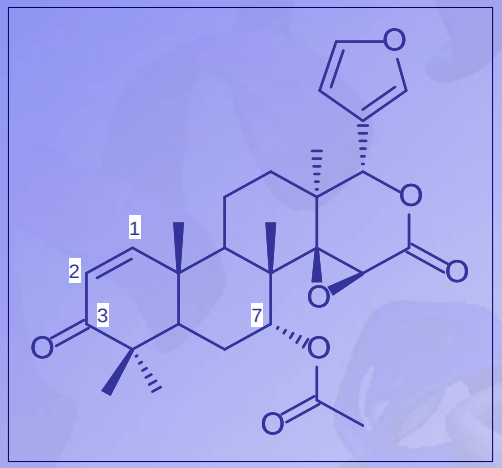
Binding-mode del celastrolo



Modello Hsp90-celastrolo/Cdc37

[1]Zhang et al. Mol. Cancer Ther. 2008; 7, 162-70.

GEDUNINA



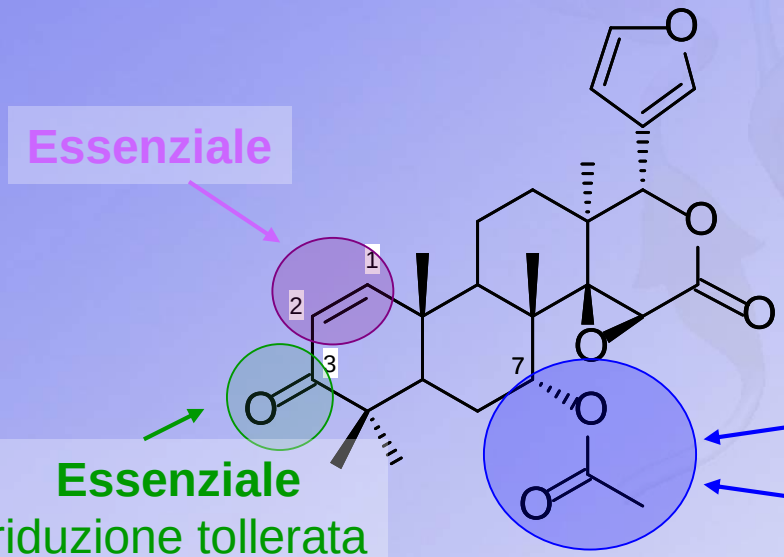
Gedunina

IC_{50} CaCo-2 = 16,83 µM[2]

IC_{50} MCF-7 = 8,84 µM[3]

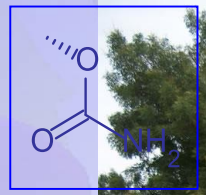
IC_{50} SK-BR3 = 3,22 µM[3]

Relazioni Struttura - Attività



Essenziale

Essenziale
riduzione tollerata



3f[3]

IC_{50} MCF-7 = 9,79 µM

IC_{50} SK-BR3 = 7,05 µM

4[3]

IC_{50} MCF-7 = 10,90 µM

IC_{50} SK-BR3 = 4,49 µM

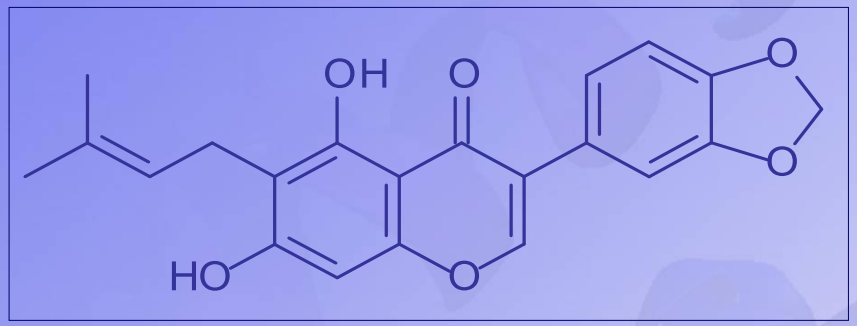
Aumento attività

Diminuzione attività
OMe, OEt, OPr

Azadirachta indica A.Juss[1]

[1]Khalid et al. J. Nat. Prod. 1989; 52, 922-6 . [2]Uddin et al. Phytother. Res.2007; 21, 757-61 . [3]Brandt et al. J. Med. Chem. 2008; 51, 6495-502 .

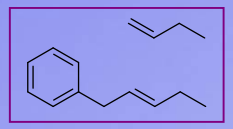
DERRUBONE



Derrubone[2]
IC_{50} MCF-7 = 12 µM[3]
IC_{50} SK-BR3 = 9 µM

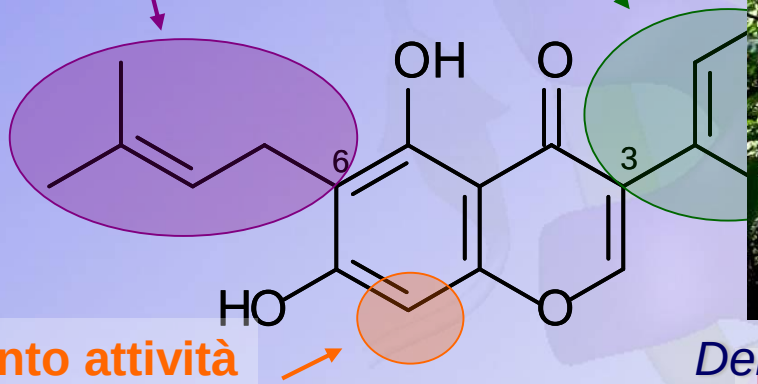
Relazioni Struttura - Attività

Sostituzione tollerata



Essenziale

Aumento attività



Lieve aumento attività
catena prenilata

Derris robusta Benth.

Diminuzione attività

	R_1	R_2
22a	H	OMe
22c	Cl	Cl

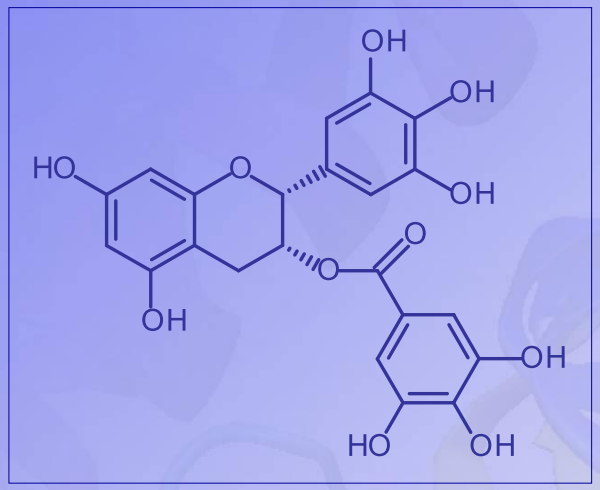
22a[3]
IC_{50} MCF-7 = 5,5 µM
IC_{50} SK-BR3 = 7,3 µM

22c[3]
IC_{50} MCF-7 = 7,3 µM
IC_{50} SK-BR3 = 5,2 µM

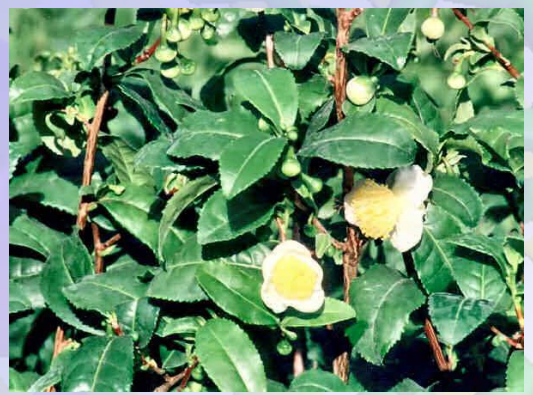
1969[1]

[1]East et al. J. Chem. Soc. C. Org. 1969; 3, 365-74 . [2]Galam et al. Bioorg Med Chem. 2007; 15, 1939-46. [3]Hastings et al. J. Org. Chem 2008; 73, 369-73.

(-)-Epigallocatechin-3-gallato



(-)-epigallocatechin-3-gallato[1]
Antagonizza gli effetti mediati dal legame TCDD-AhR[2]
Inibitore C-terminale[3]



Camellia sinensis L.

[1]Mittal et al. Int. J. Oncol. 2004; 24, 703-10 . [2]Palermo et al. Biochemistry 2005; 44, 5041-52 . [3]Yin et al. Biochemistry 2009;48, 336-45 .

CONCLUSIONI

- Le ricerche effettuate negli ultimi 20 anni hanno evidenziato la proteina Hsp90 come un target selettivo per la cura del cancro e la sua inibizione rappresenta un approccio sempre più importante nello sviluppo di nuovi farmaci chemioterapici.

- Numerose sostanze di origine naturale hanno mostrato la capacità di inibire Hsp90, interagendo con i domini N- o C-terminali e bloccandone l'attività ATPasica, ma anche mediante l'interruzione delle interazioni tra Hsp90, i suoi co-chaperoni e le proteine clients.

- Per questi motivi i composti attivi isolati da fonti naturali rappresentano una risorsa fondamentale nella ricerca e possono essere considerati dei "lead compounds" per lo sviluppo di nuovi farmaci antitumorali.