



SAPIENZA
UNIVERSITÀ DI ROMA

Facoltà di Farmacia

Corso di Laurea in Farmacia

Tesi Compilativa di Laurea in Chimica Farmaceutica e Tossicologica I

**Inibitori della Heat Shock Protein 90 (HSP90)
quali potenziali agenti anticancro**

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Laureando: Nicola Folino (Matr. 313332)

Anno Accademico 2007-2008

Proteine Shock Termico

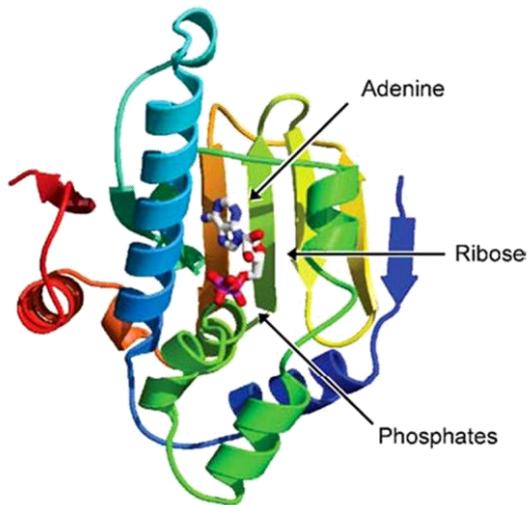
- ✚ Le proteine dello shock termico (Heat Shock Proteins, HSPs) rappresentano un ampio gruppo di polipeptidi presenti nelle cellule di tutte le forme di vita.
- ✚ La loro funzione predominante è la prevenzione di associazioni non corrette e aggregazione di catene polipeptidiche non ripiegate, sia in condizioni fisiologiche che in condizioni di stress.
- ✚ Le HSP possono essere classificate in base al peso molecolare in 7 famiglie principali: HSP10, HSP27, HSP40, HSP60, HSP70, HSP90 e HSP110.



HSP90

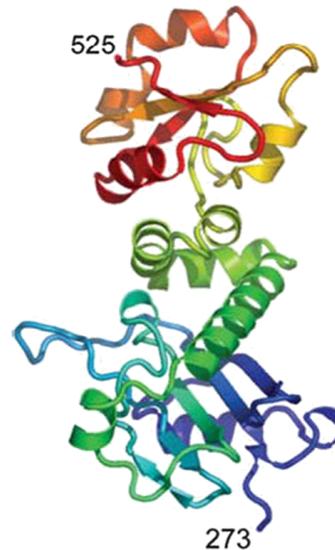


Dominio N-terminale
24-28 KDa



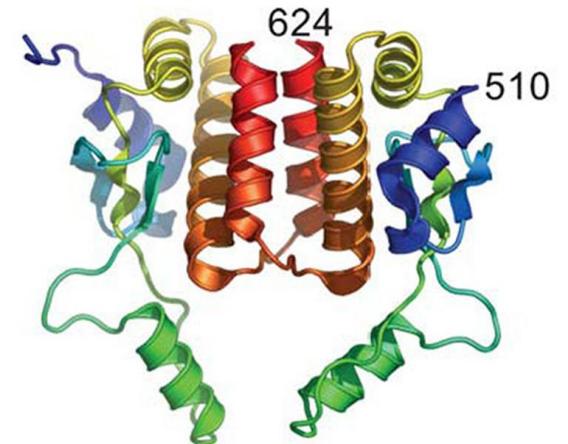
Codice PDB: 1ah6

Dominio centrale
38-44 KDa



Codice PDB: 1hk7

Dominio C-terminale
11-15 kDa

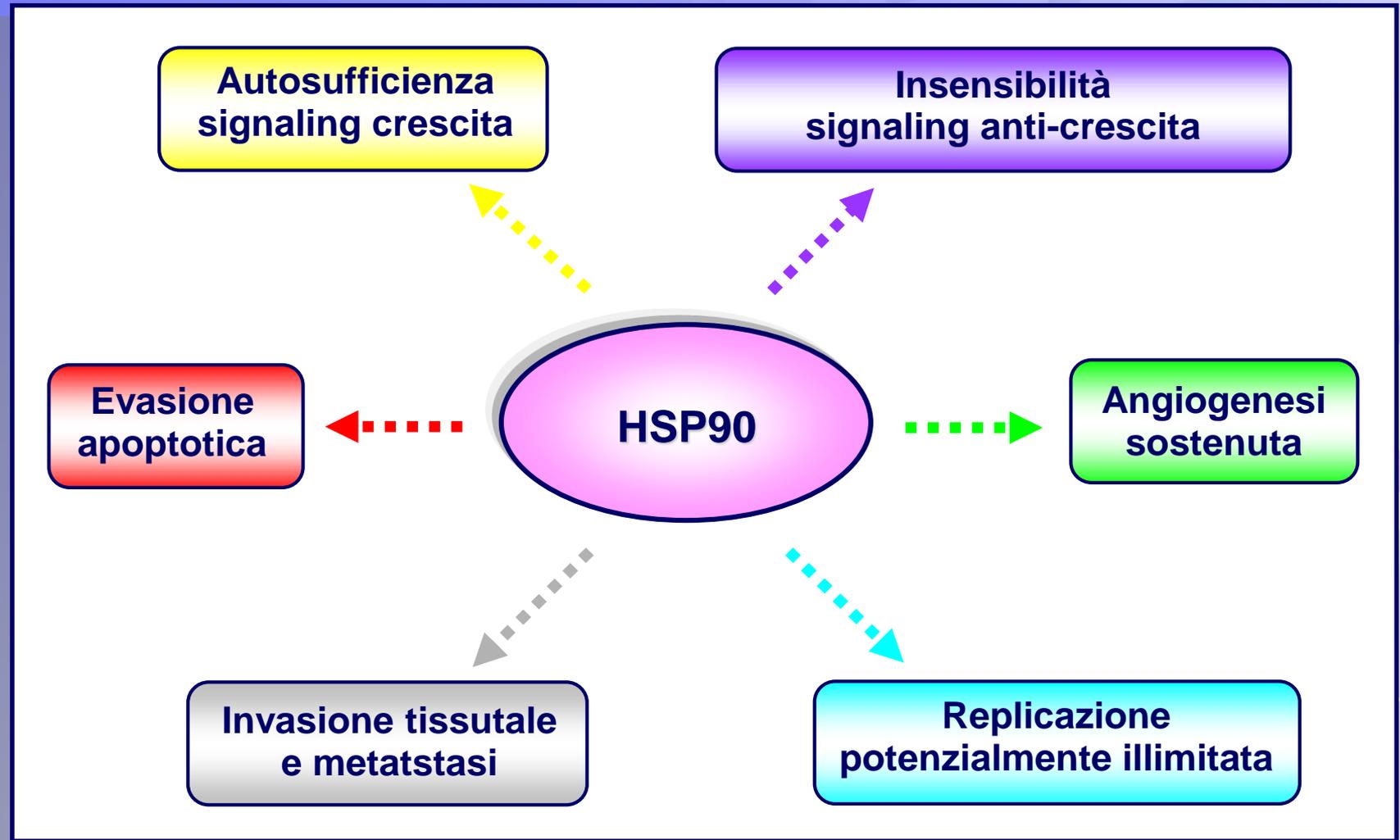


Codice PDB: 1sf8

corretto folding, la stabilità e la specifica attività.



HSP90 e Cancro



Inibitori HSP90

+ *Inibitori N-terminali*

- ✓ Naturali: geldanamicina, radicololo
- ✓ Semisintetici: derivati geldanamicina e radicololo
- ✓ Sintetici: inibitori chimerici, purine, pirazoli, benzisossazoli, solfonamidi, chinazolinoni, pirimidine

+ *Inibitori C-terminali*

- ✓ Naturali: novobiocina, cumermicina A1, (-)-epigallocatechin-3-gallato
- ✓ Semisintetici: derivati novobiocina
- ✓ Sintetici: cisplatino

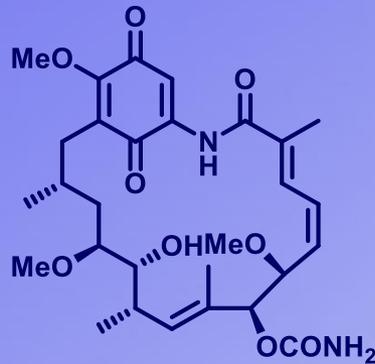
+ *Altri inibitori*

- ✓ Naturali: celastrolo, derrubone
- ✓ Semisintetici: derivati novobiocina
- ✓ Sintetici: derivati celastrolo



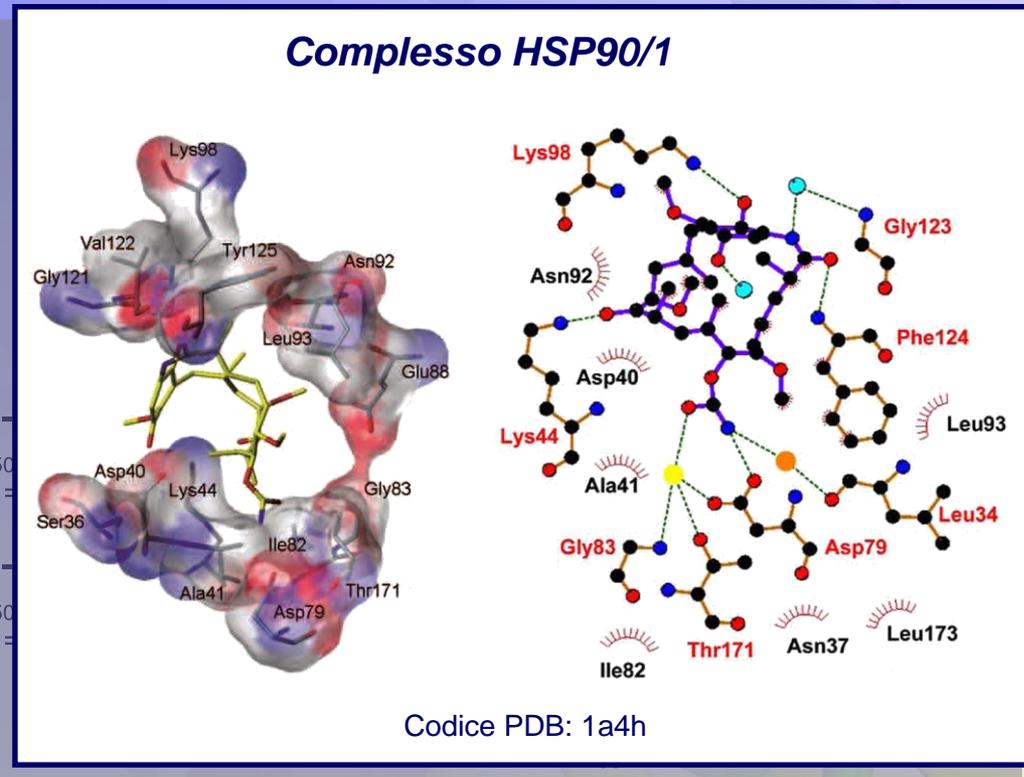
Inibitori N-terminali

+ Geldanamicina e derivati



Geldanamicina^{1,2} (1)
Streptomyces hygroscopicus
 $IC_{50} < 200$ nM

17
 IC_{50}
 K_d
 17
 IC_{50}
 K_d

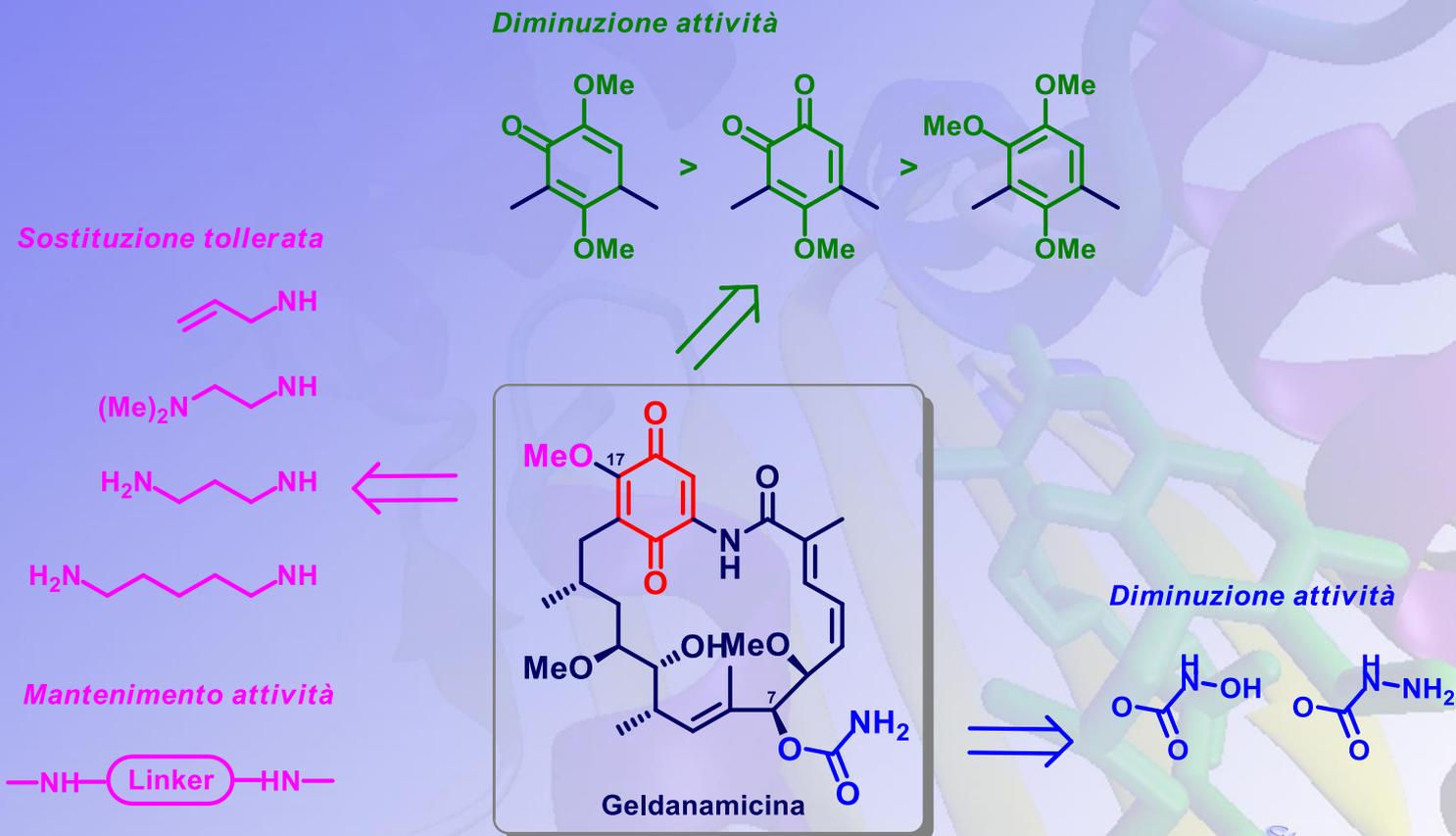


¹DeBoer et al. *J. Antibiot.* **1970**, 23, 442-447. ²Whitesell et al. *Proc. Natl. Acad. Sci. USA* **1994**, 91, 8324-8328. ³Schulte et al. *Cancer Chemother. Pharmacol.* **1998**, 42, 273-279. ⁴Snader et al. *PCT Int. Appl.* **2002**, WO2002079167. ⁵Yin et al. *Clin. Cancer Res.* **2005**, 11, 3889-3896.



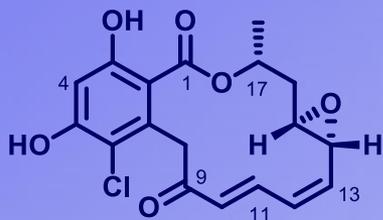
Inibitori N-terminali

+ Geldanamicina e derivati: relazione struttura-attività

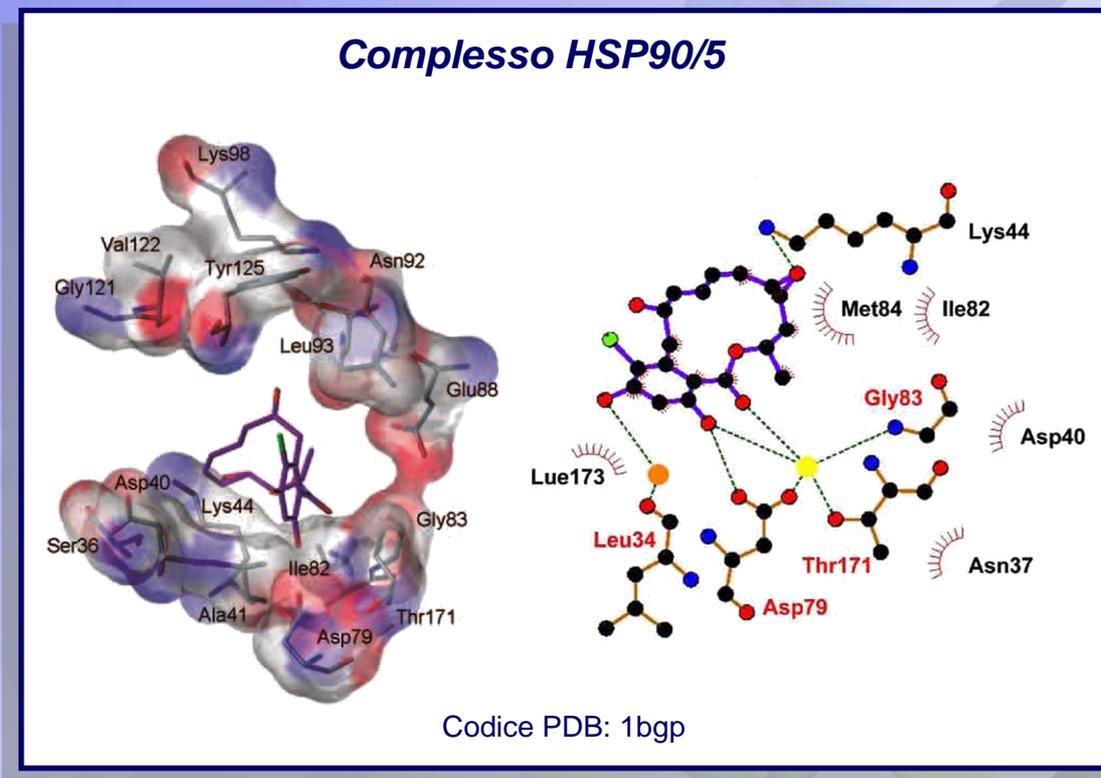


Inibitori N-terminali

+ Radicicolo e derivati



Radicicolo¹ (5)
Monosporium bonorden
 $K_d = 19$ nM

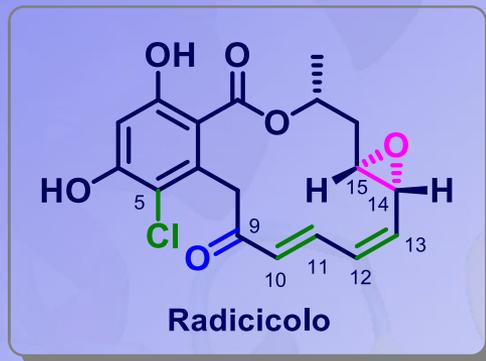


¹Delmotte et al. *Nature* **1953**, 171, 344; Sharma et al. *Oncogene* **1998**, 16, 2639-2645. ²Soga et al. *Cancer Res.* **1999**, 59, 2931-2938. ³Ikuina et al. *J. Med. Chem.* **2003**, 46, 2534-2541. ⁴Yamamoto et al. *Angew. Chem. Int. Ed. Engl.* **2003**, 42, 1280-1284. ⁵Yang et al. *J. Am. Chem. Soc.* **2004**, 126, 7881-7889.

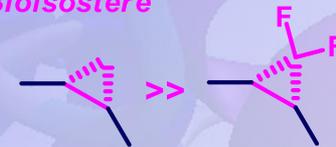


Inibitori N-terminali

+ Radicicolo e derivati: relazioni struttura-attività



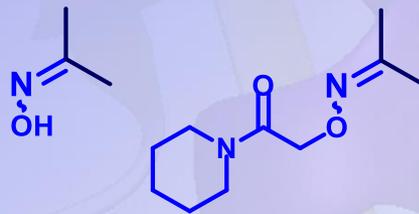
Bioisostere



Esenziale

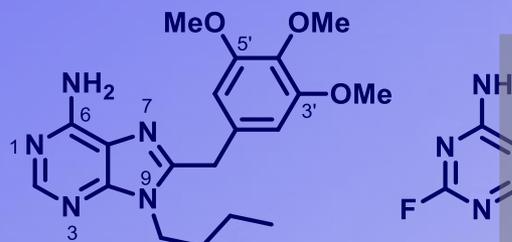
Aumento di attività

Esenziale

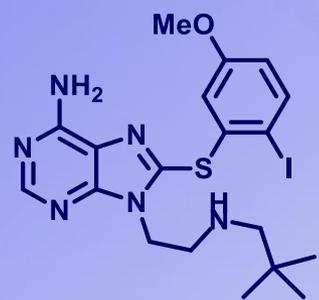


Inibitori N-terminali

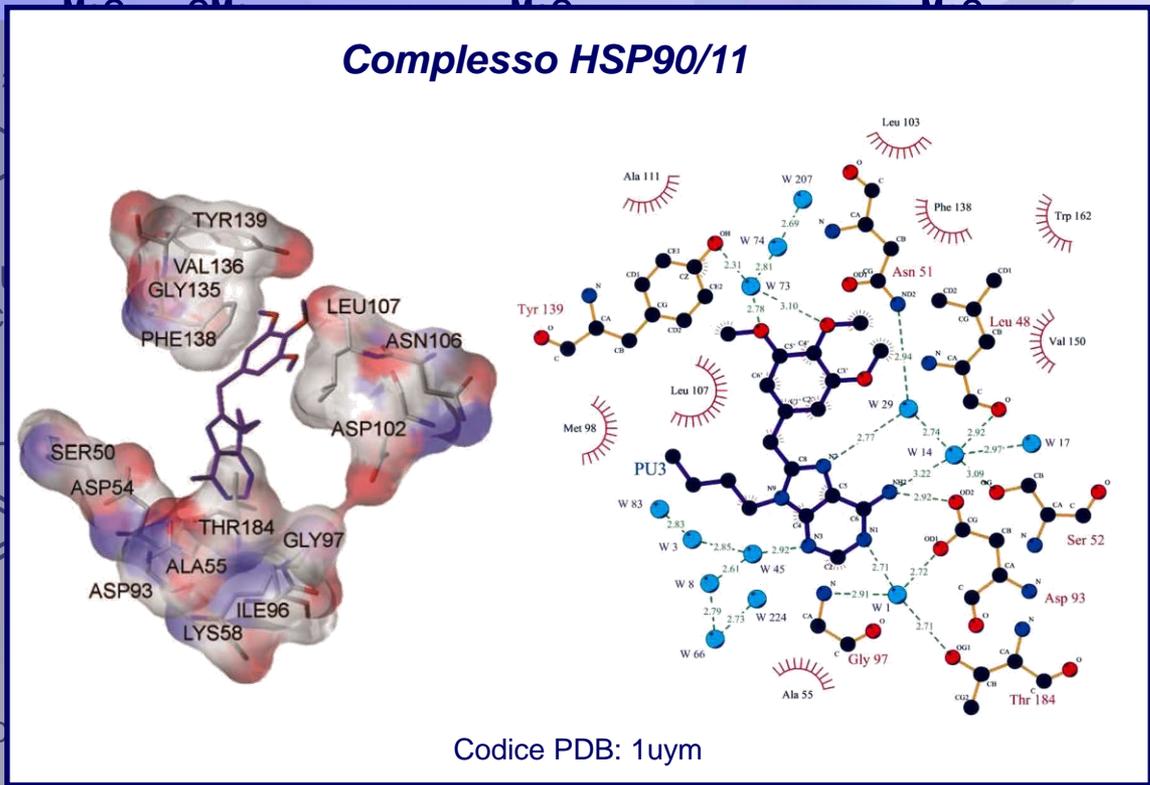
Derivati purinici



PU3¹ (11)
IC₅₀ = 50 μM



15⁵
IC₅₀ Her-2 = 140 nM



IC₅₀ HT29 = 0,9 μM

IC₅₀ HT29 = 0,1 μM

¹Chiosis et al. *Cancer Cells Chem. Biol.* **2001**, 8, 289-299. ²Chiosis et al. *Bioorg. Med. Chem.* **2002**, 10, 3555-3564. ³Kasibhatla et al. *PCT Int. Appl.* **2003**, WO3037860. ⁴Wright et al. *Chem. Biol.* **2004**, 6, 775-785. ⁵Biamonte et al. *J. Med. Chem.* **2006**, 49, 817-828. ⁶He et al. *J. Med. Chem.* **2006**, 49, 381-390. ⁷Kasibhatla et al. *J. Med. Chem.* **2007**, 50, 2767-2778.



Inibitori N-terminali

+ Derivati purinici: relazioni struttura-attività

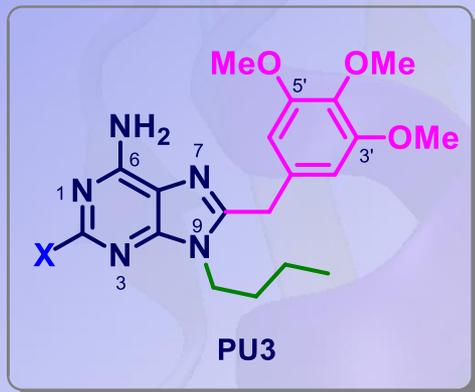
Aumento attività



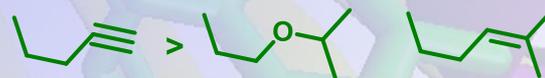
Aumento attività



F > H >> I, CN, NH₂,
alcossi, vinile



Aumento attività

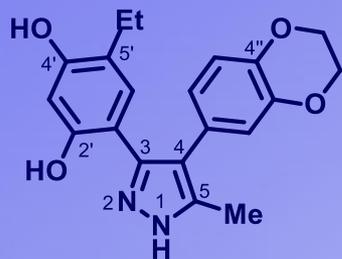


Aumento solubilità in acqua

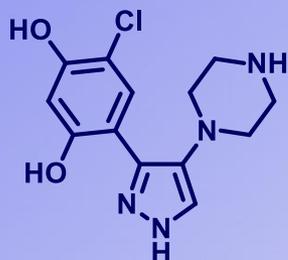


Inibitori N-terminali

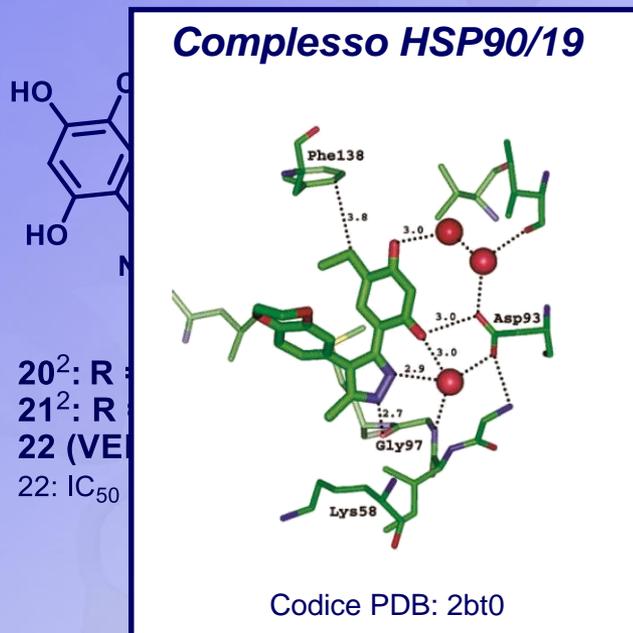
+ Derivati pirazolici



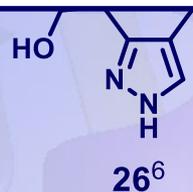
CCT018159¹ (19)
GI₅₀ HCT116 = 4 μM



25⁵
GI₅₀ HCT116 = 23,4 μM



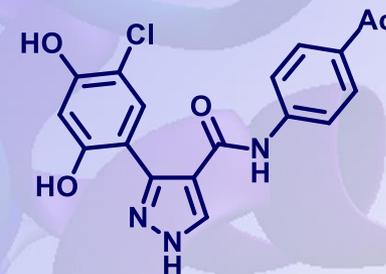
20²: R
21²: R
22 (VE)
22: IC₅₀



26⁶
 $K_d = 680 \text{ nM}$; IC₅₀ SK-BR-3 = 30 μM



27⁷
IC₅₀ = 1,4 μM; GI₅₀ MCF-7 = 10 μM



24⁴
IC₅₀ = 0,26 μM
GI₅₀ = 11,6 μM

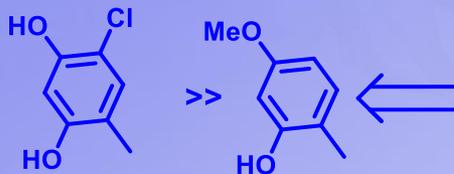
¹Cheung et al. *Bioorg. Med. Chem. Lett.* **2005**, 15, 3338-3343. ²Dymock et al. *J. Med. Chem.* **2005**, 48, 4212-4215. ³Brough et al. *J. Med. Chem.* **2008**, 51, 196-218. ⁴Brough et al. *Bioorg. Med. Chem. Lett.* **2005**, 15, 5197-5201. ⁵Barril et al. *Bioorg. Med. Chem. Lett.* **2006**, 16, 2543-2548. ⁶Kreusch et al. *Bioorg Med. Chem. Lett.* **2005**, 15, 1475-1478. ⁷Tomura et al. *JP Patent* **2005**, JP225,787.



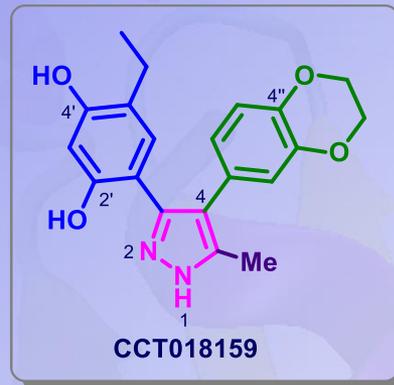
Inibitori N-terminali

Derivati pirazolici: relazioni struttura-attività

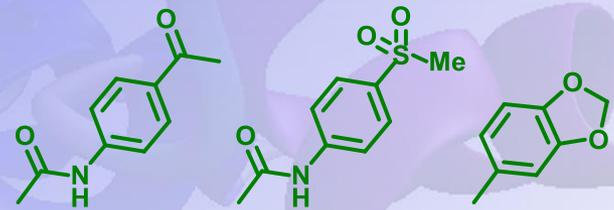
Aumento attività



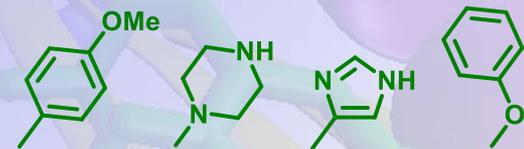
Aumento solubilità in acqua



Aumento attività



Mantenimento attività

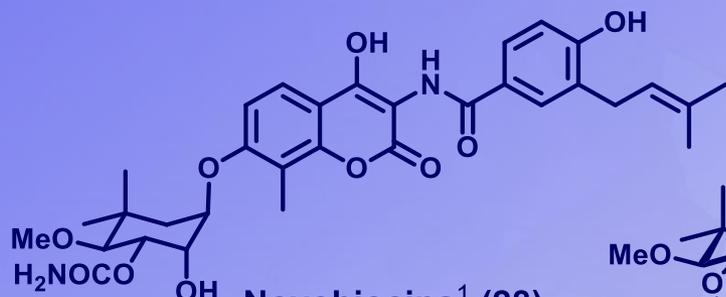


Aumento attività



Inibitori C-terminali

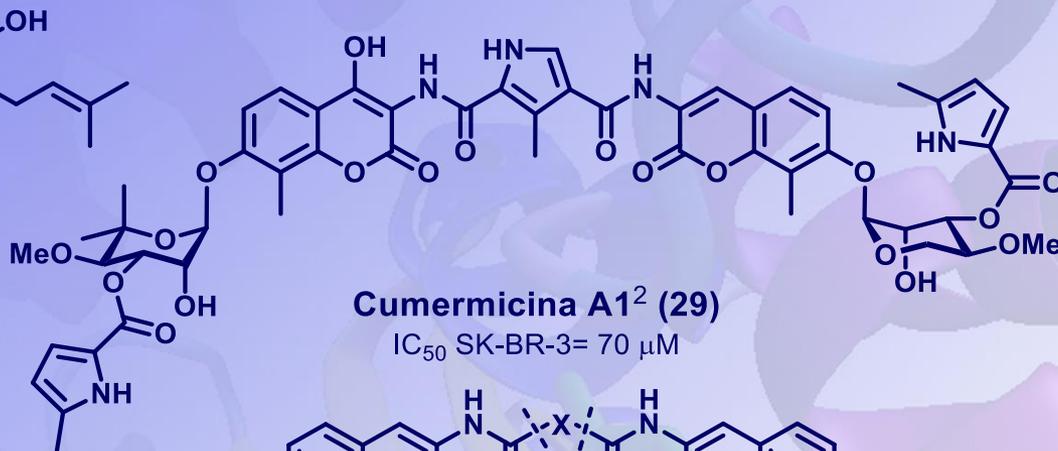
Novobiocina e derivati



Novobiocina¹ (28)

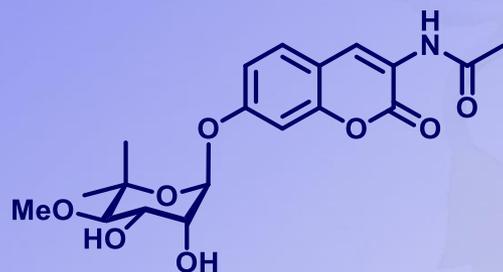
Streptomyces spheroides

IC₅₀ SK-BR-3= 700 μM

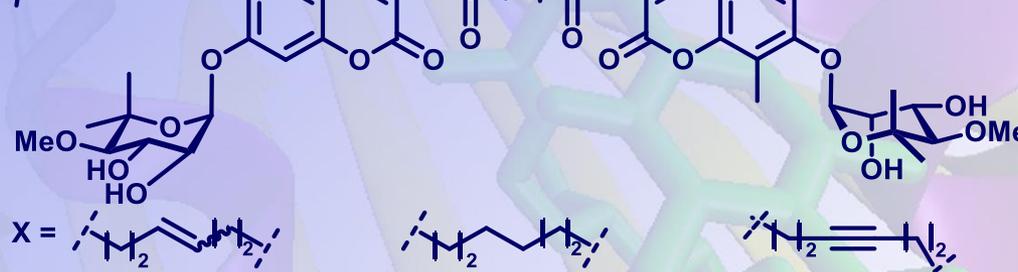


Cumermicina A1² (29)

IC₅₀ SK-BR-3= 70 μM



A4 (30)



31³ (cis)

IC₅₀ SK-BR-3= 23,9 μM

32³ (trans)

IC₅₀ SK-BR-3= 3,9 μM

33³

IC₅₀ SK-BR-3= 2,7 μM

34³

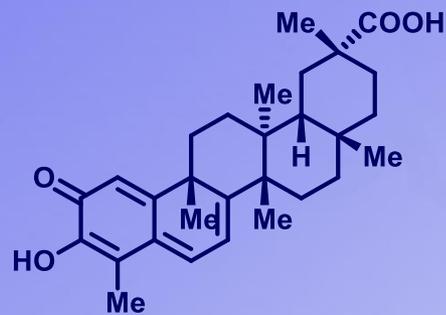
IC₅₀ SK-BR-3= 82,2 μM

¹Marcu et al. *J. Natl. Cancer Inst.* **2000**, 92, 242-248. ²Allan et al. *J. Biol. Chem.* **2006**, 281, 7161-7171. ³Burlison et al. *J. Am. Chem. Soc.* **2006**, 128, 15529-15536.

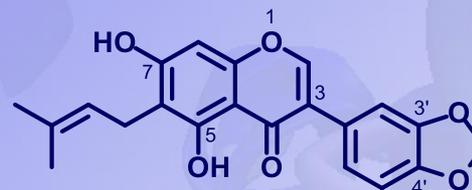


Altri inibitori

✚ Celastrolo e Derrubone



Celastrolo¹ (41)
Tripterygium wilfordii

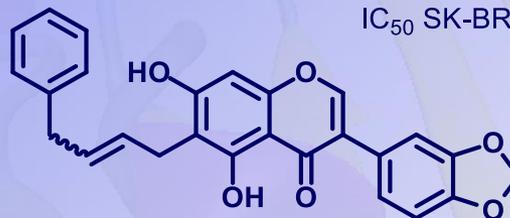


Derrubone² (42)

Derris robusta

IC₅₀ MCF-7 = 9 μM

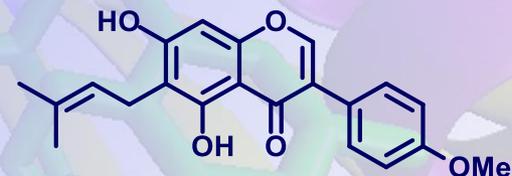
IC₅₀ SK-BR-3 = 12 μM



43³

IC₅₀ MCF-7 = 12,6 μM

IC₅₀ SK-BR-3 = 10,8 μM



44³

IC₅₀ MCF-7 = 5,5 μM

IC₅₀ SK-BR-3 = 7,3 μM

¹Zhang et al. *Mol. Cancer Ther.* **2008**, 7, 162-70. ²Hadden et al. *J. Nat. Prod.* **2007**, 70, 2014-2018. ³Hastings et al. *J. Org. Chem.* **2008**, 18, 369-373.



Conclusioni

- + L'inibizione farmacologica di HSP90 costituisce un recente approccio per la progettazione di nuovi agenti antitumorali.
- + Numerose ricerche sono stati rivolte alla progettazione di derivati semisintetici e sintetici. Due derivati semisintetici sono attualmente in fase I/II di sperimentazione clinica.
- + La modulazione chimica dei nuclei purinico e pirazolico ha consentito di ottenere eccellenti risultati.
- + La recente comprensione dei meccanismi di interazione fra HSP90 e clients e co-chaperones rappresenta un valido approccio alternativo per la progettazione di nuovi inibitori.

