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esperimenti"

Sintesi di composti organici naturali e non: antivirali, antitumorali e altro

Maria Funicello e Lucia Chiummiento

Orientatesi, 21 dicembre 2022

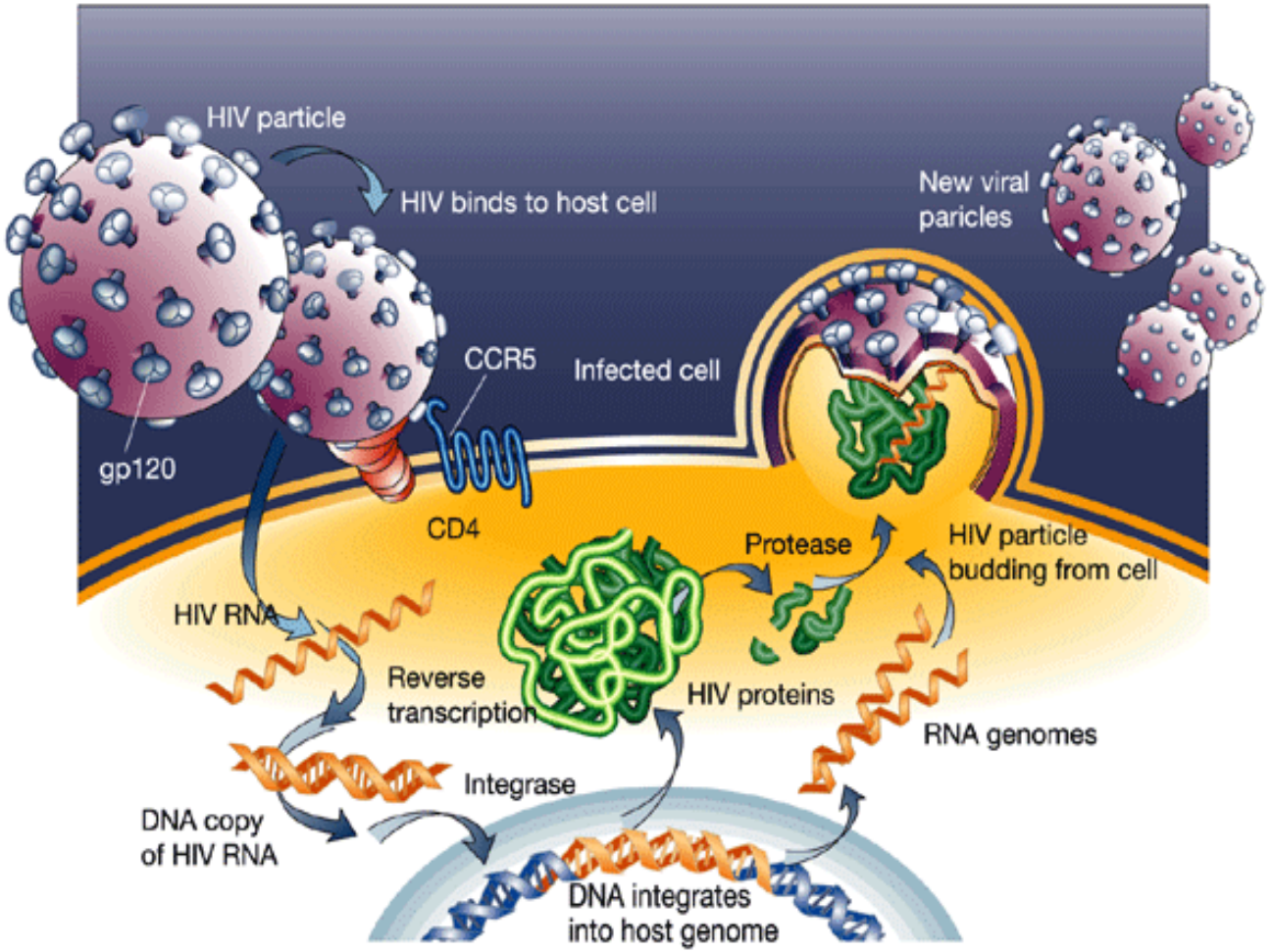
Introduzione

HIV-1: virus responsabile della Sindrome di Immunodeficienza Umana (AIDS)

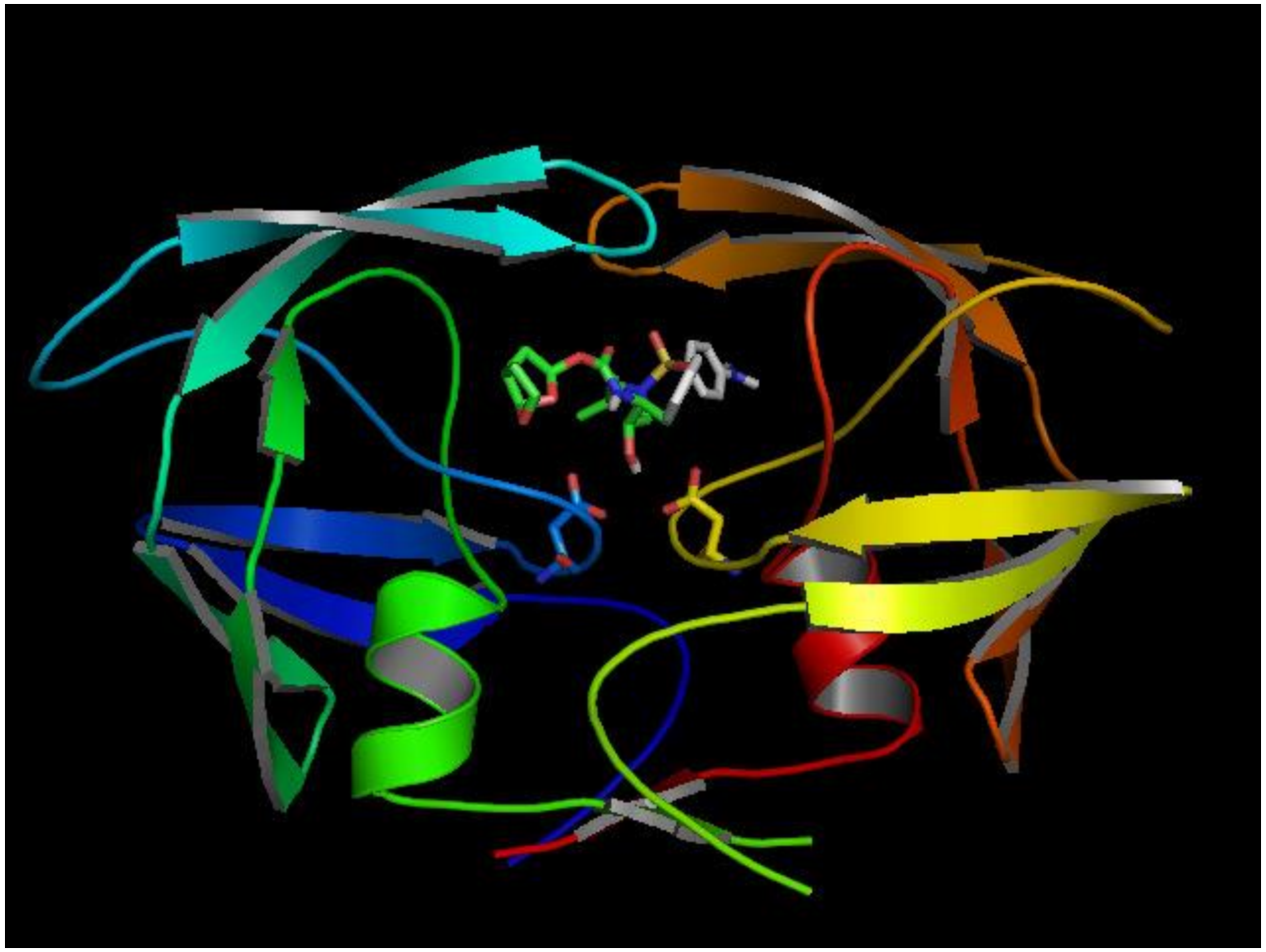
La terapia attualmente in uso (ART) è mirata a bloccare i tre enzimi cruciali per la sua riproduzione.

Obiettivo: sintesi di nuovi inibitori dell'HIV Proteasi.

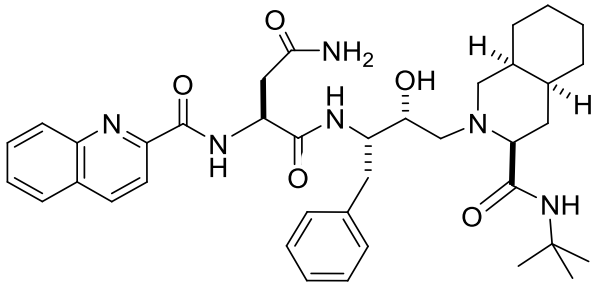
Ciclo vitale del virus HIV



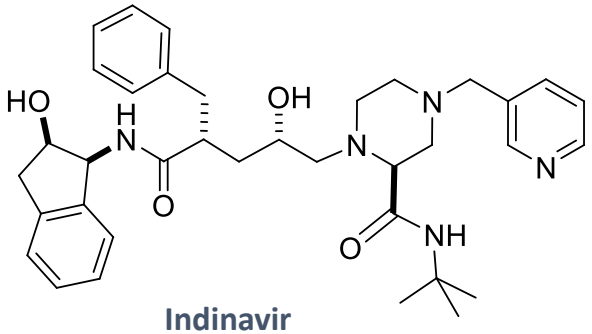
Struttura Proteasi con Darunavir nel sito attivo



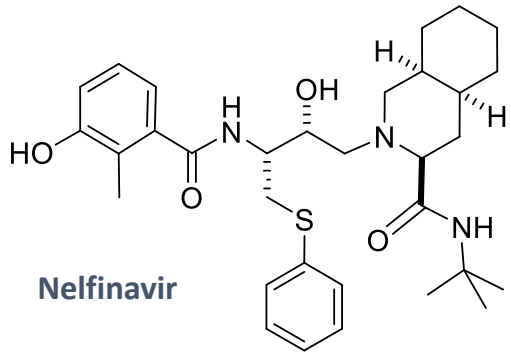
Principali inibitori dell'HIV Proteasi



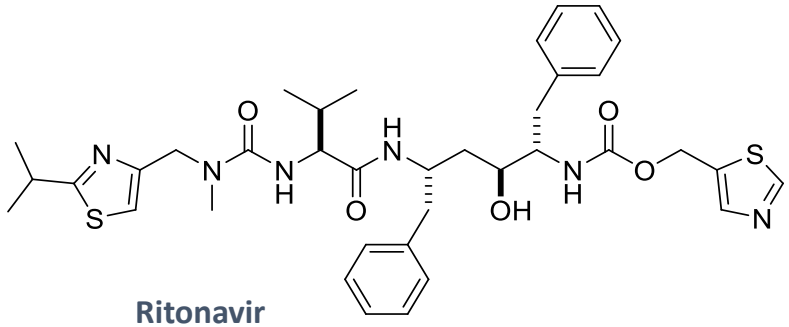
Saquinavir



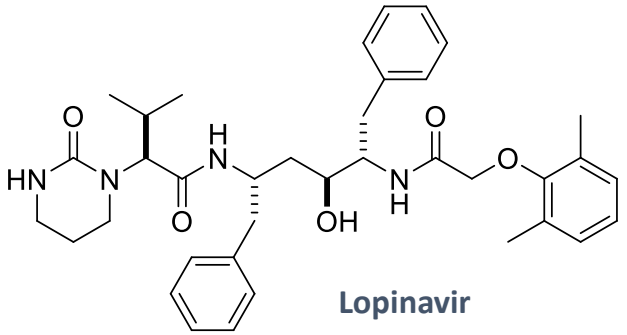
Indinavir



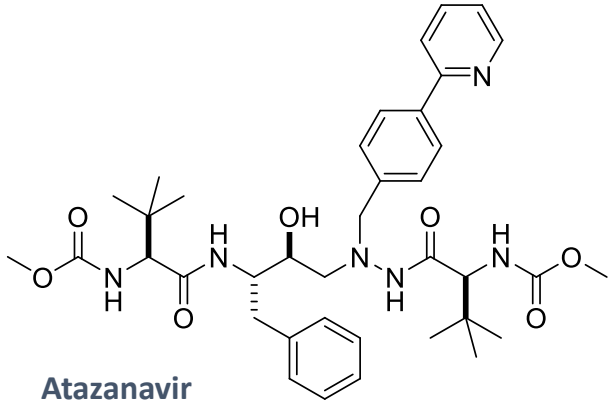
Nelfinavir



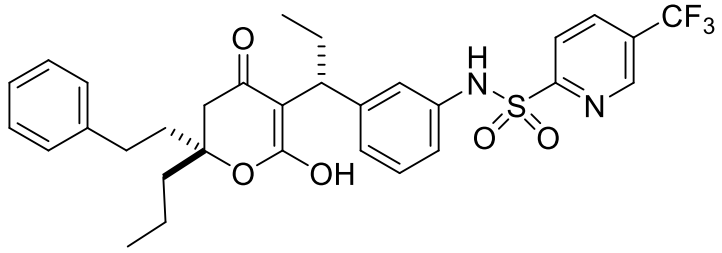
Ritonavir



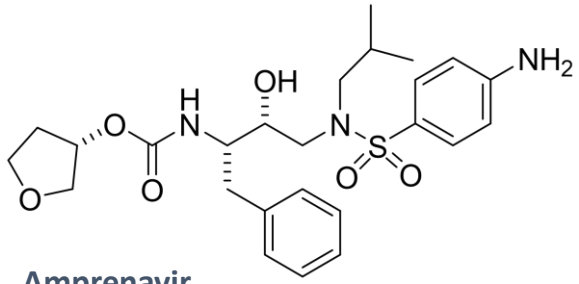
Lopinavir



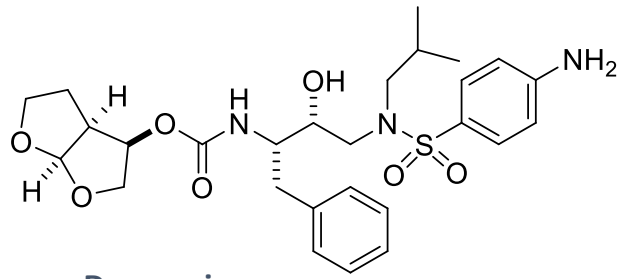
Atazanavir



Tripanavir



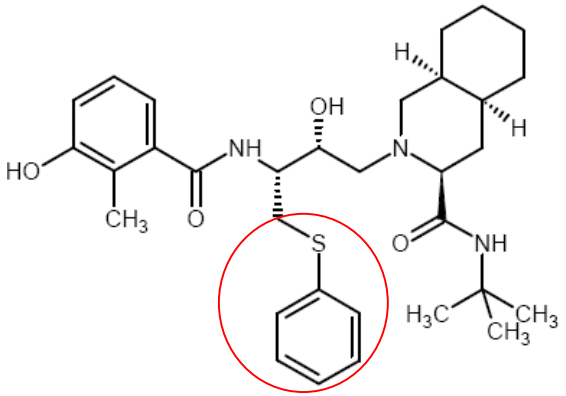
Amprenavir



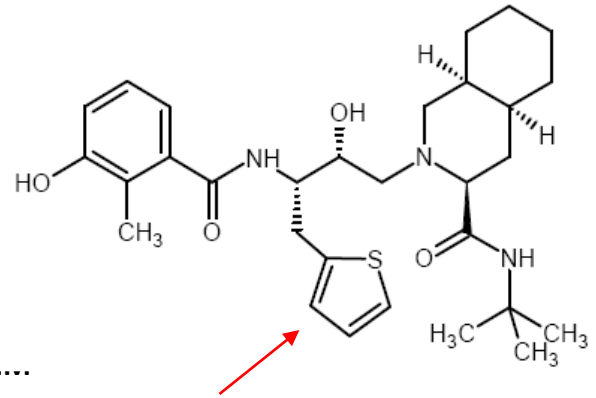
Darunavir

Ghosh, A. K.; Anderson, D. D. *Future Med. Chem.* **2011**, *3*, 1181

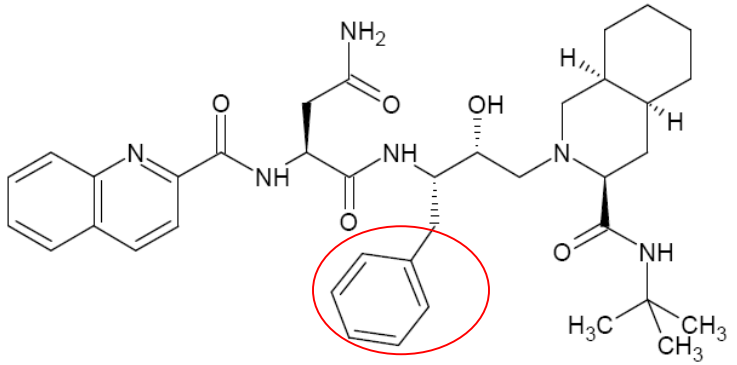
Strutture e attività



IC_{50}= 1.9 nM

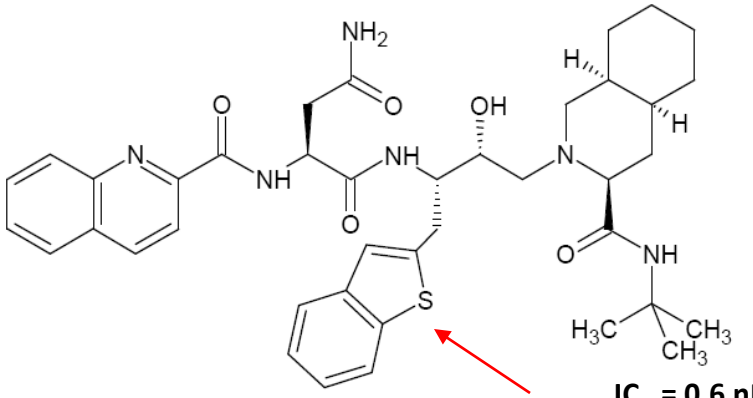


IC_{50}= 2.9 n....



Saquinavir

IC_{50}= 0.4 nM



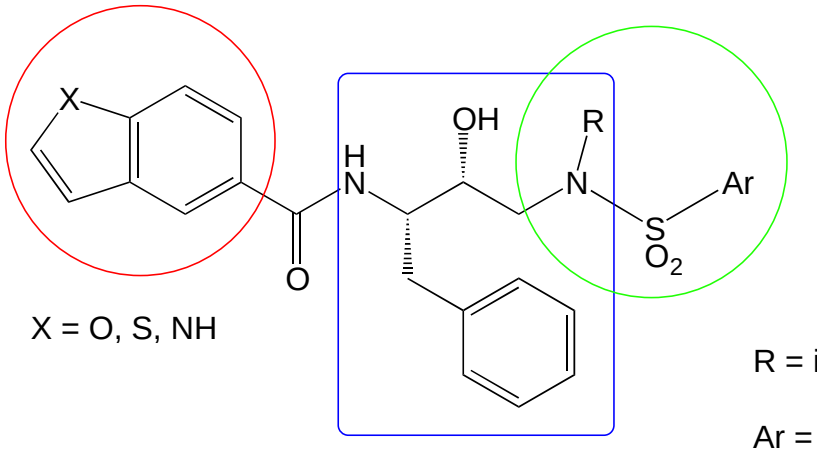
IC_{50}= 0.6 nM

	Attività enzimatica residua (%)	
	V32I	V82A
1 nM	97	60
10 nM	32	

	Attività enzimatica residua (%)	
	V32I	V82A
1 nM	54	37

Bonini, C.; Chiummiento, L.; De Bonis, M.; Di Blasio, N.; Funicello, M.; Lupattelli, P.; Pandolfo, R.; Tramutola, F.; Berti, F. *J. Med. Chem.* **2010**, *53*, 1451.

Struttura generale target



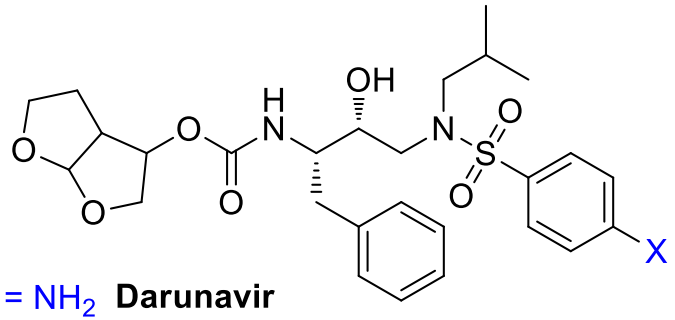
X = O, S, NH

R = isobutile, Ph

Ar = Ph-OMe, Ph-NO_2

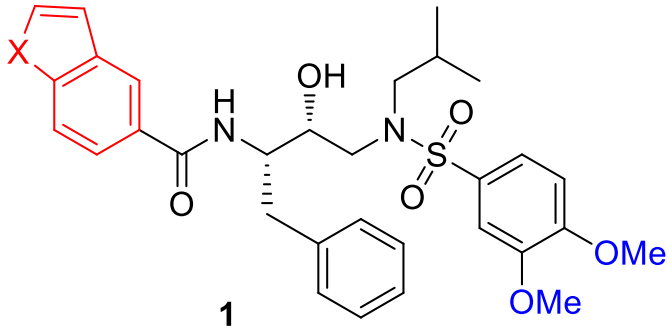
Het = Th, BHT

Darunavir e analoghi



X = NH_2 **Darunavir**
X = OMe **TMC-126**

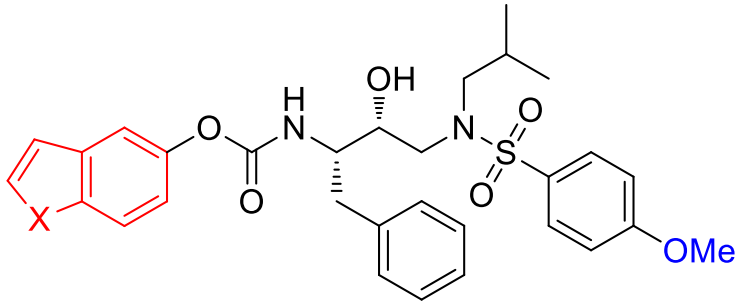
- Struttura Darunavir: anello bis tetraidrofuranico in P2, core idrossietilamminico e solfonile in P2'



1

X = S, O, NH

(IC_{50} = 1-13 nM)



2

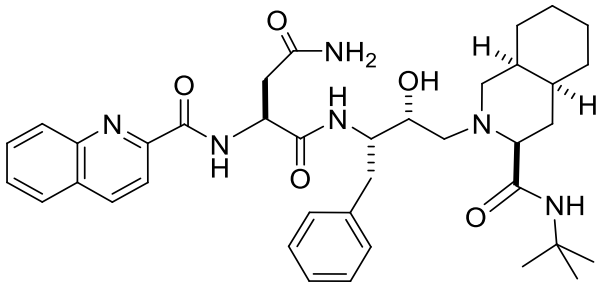
X = S, O, NH

(IC_{50} < 0.6-11 nM)

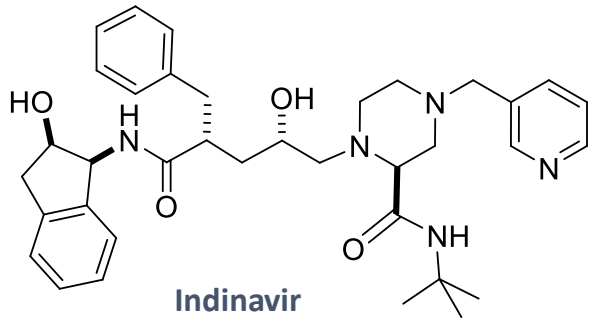
- Sintesi di due serie di analoghi a struttura 1 e 2 con proprietà inibitorie simili ai commerciali

a) Funicello, M. Chiummiento, L. Tramutola, F. et al. *Bioorg Med Chem.* **2017**, *25*, 4715-4722; b) T;ramutola, F.; Armentano, M. F.; Berti, F.; Chiummiento, L.; Lupattelli, P.; D'Orsi, R.; Miglionico, R.; Milella, L.; Bisaccia, F.; Funicello, M. *Bioorg. Med. Chem.* **2019**, *27*, 1863-1870.

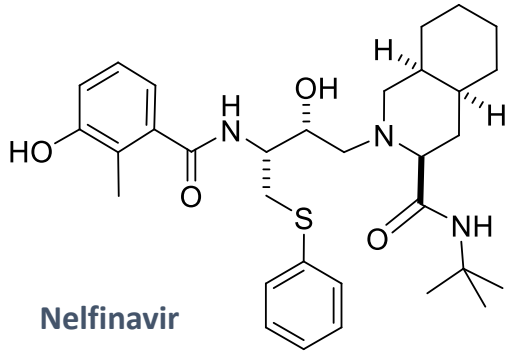
Principali inibitori dell'HIV Proteasi



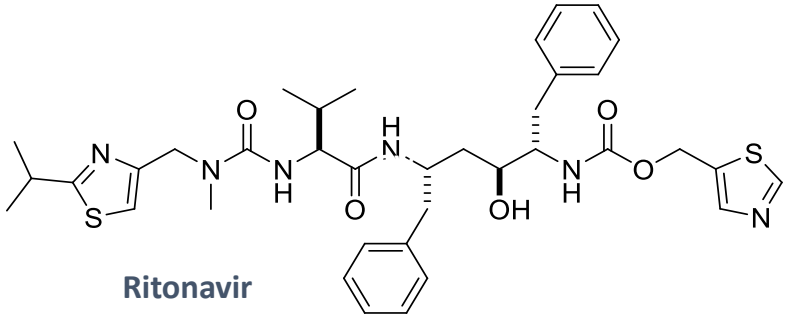
Saquinavir



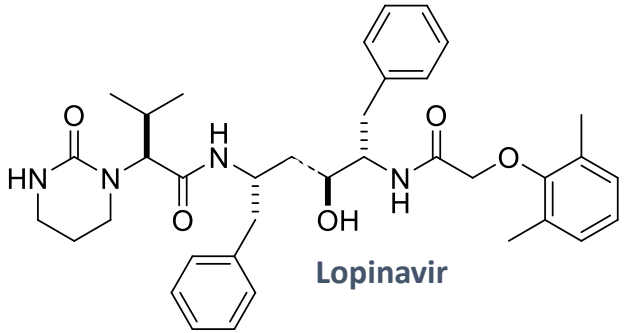
Indinavir



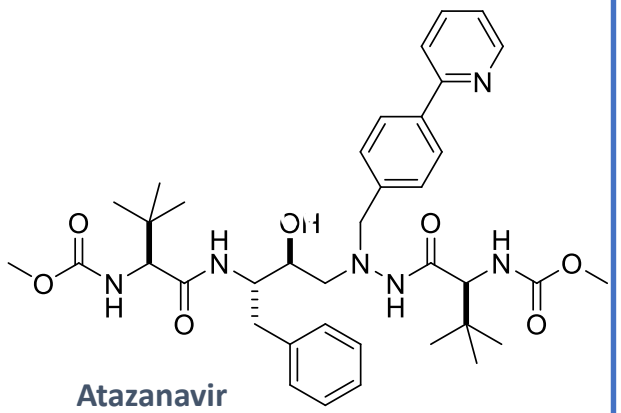
Nelfinavir



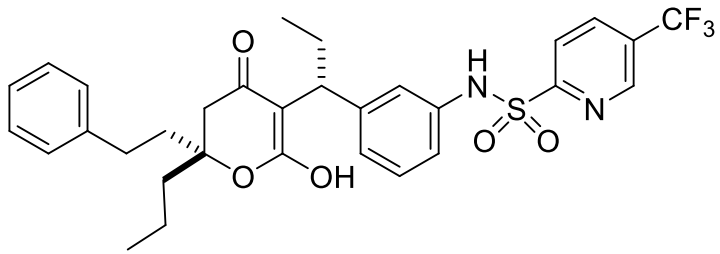
Ritonavir



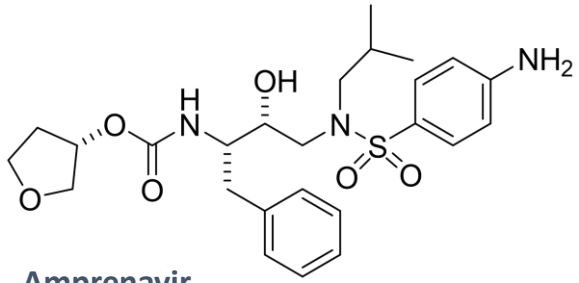
Lopinavir



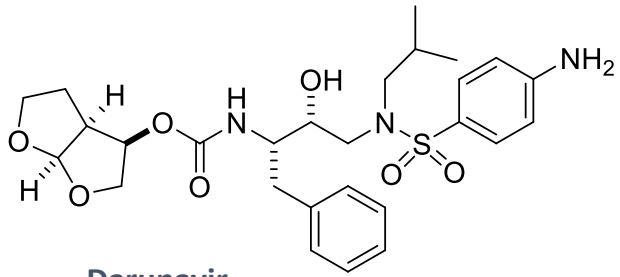
Atazanavir



Tripanavir



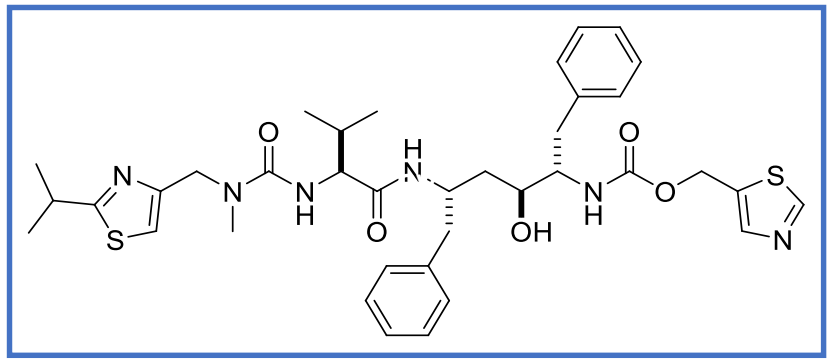
Amprenavir



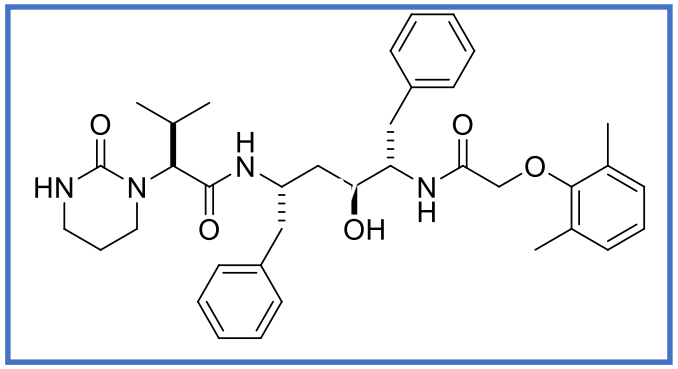
Darunavir

Ghosh, A. K.; Anderson, D. D. *Future Med. Chem.* **2011**, *3*, 1181

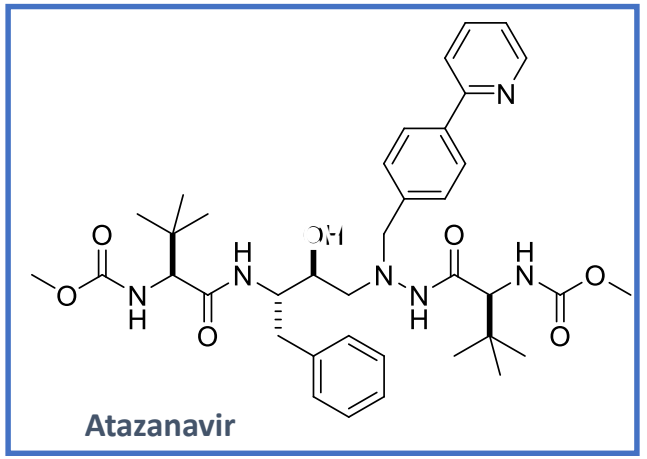
Inibitori a core pseudosimmetrico



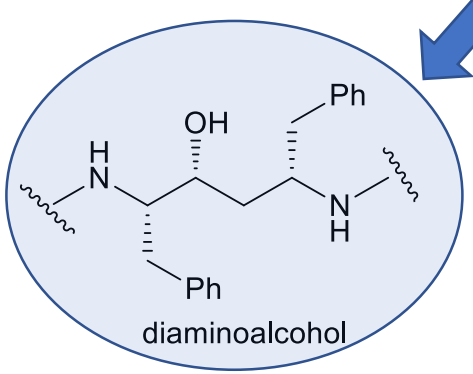
Ritonavir

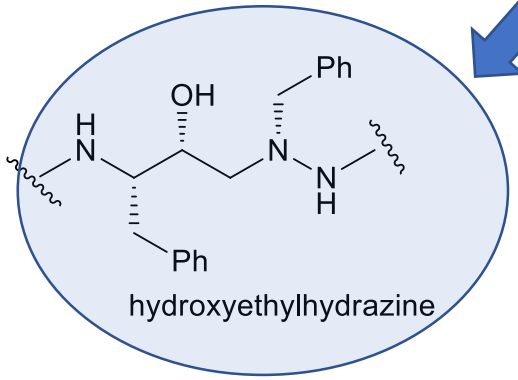


Lopinavir

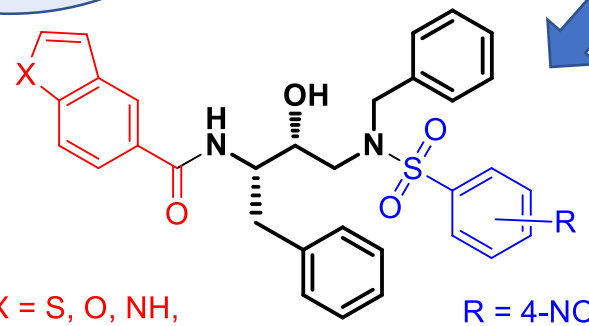


Atazanavir





A

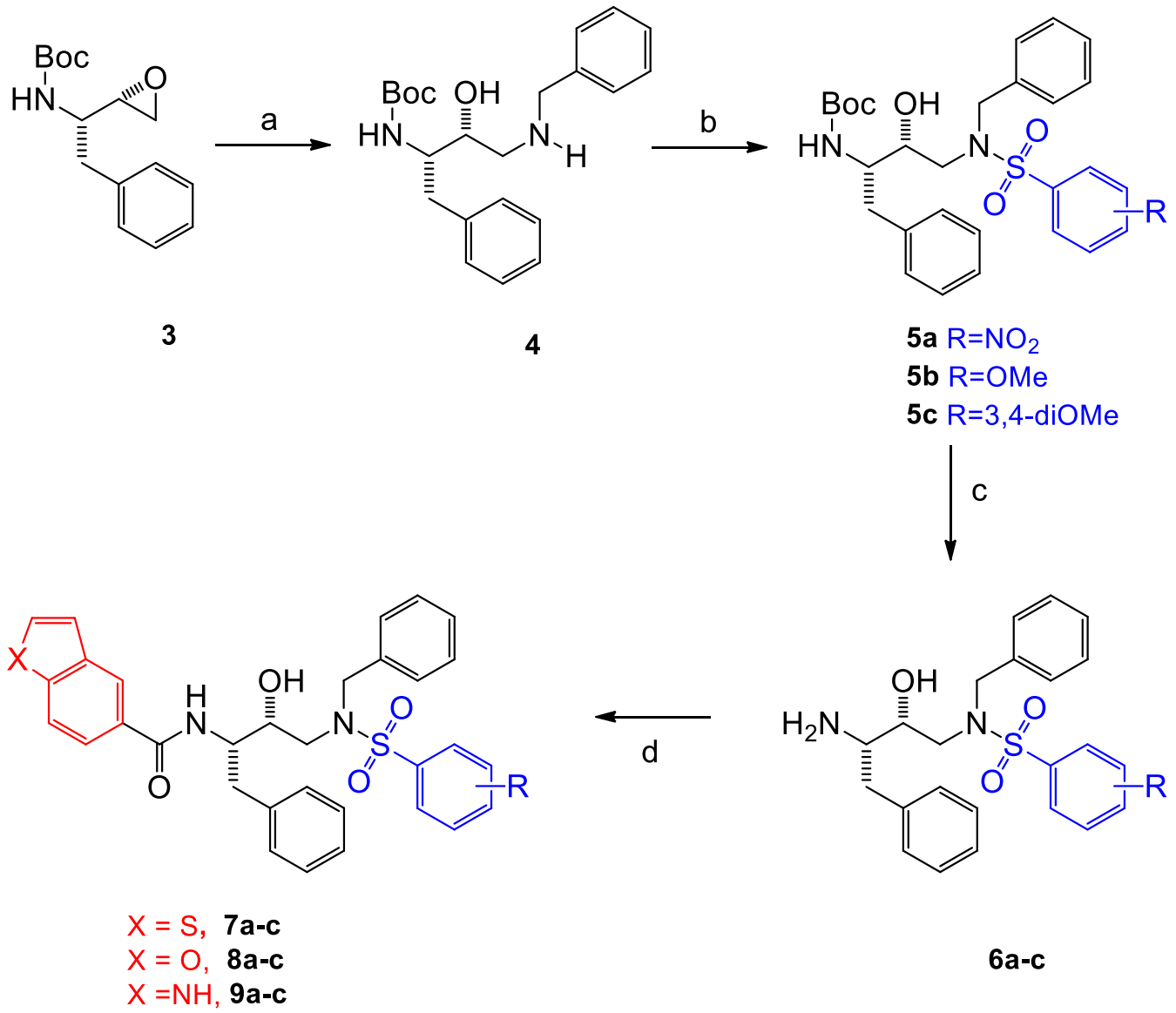


X = S, O, NH,

R = 4-NO_2, 4-OMe, 3,4-diOMe

Funicello, M. et al., *Biomolecules*, **2021**.

Sequenza sintetica



Reagenti e condizioni:

(a) $BnNH_2$, *i*-PrOH, 60°C, 4h (Resa: 88%);

(b) arylsulfonyl chloride, Et_3N, CH_2Cl_2, rt, 24h (Rese: **5a** 94%; **5b** 85%; **5c** 90%);

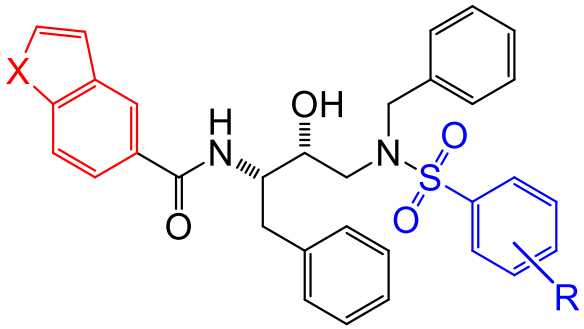
(c) TFA/CH_2Cl_2 30%, rt, 1 h, Et_3N;

(d) 5-heteroarylcarboxylic acid, EDC, HOBt, Successivamente **6a-c**, *i*Pr_2NEt, CH_2Cl_2, 24h, rt (Rese: **7a**, 50%; **7b** 57%; **7c** 55%; **8a** 53%; **8b** 54%; **8c** 56%; **9a** 33%; **9b** 43%; **9c** 44%).

Attività inibitoria

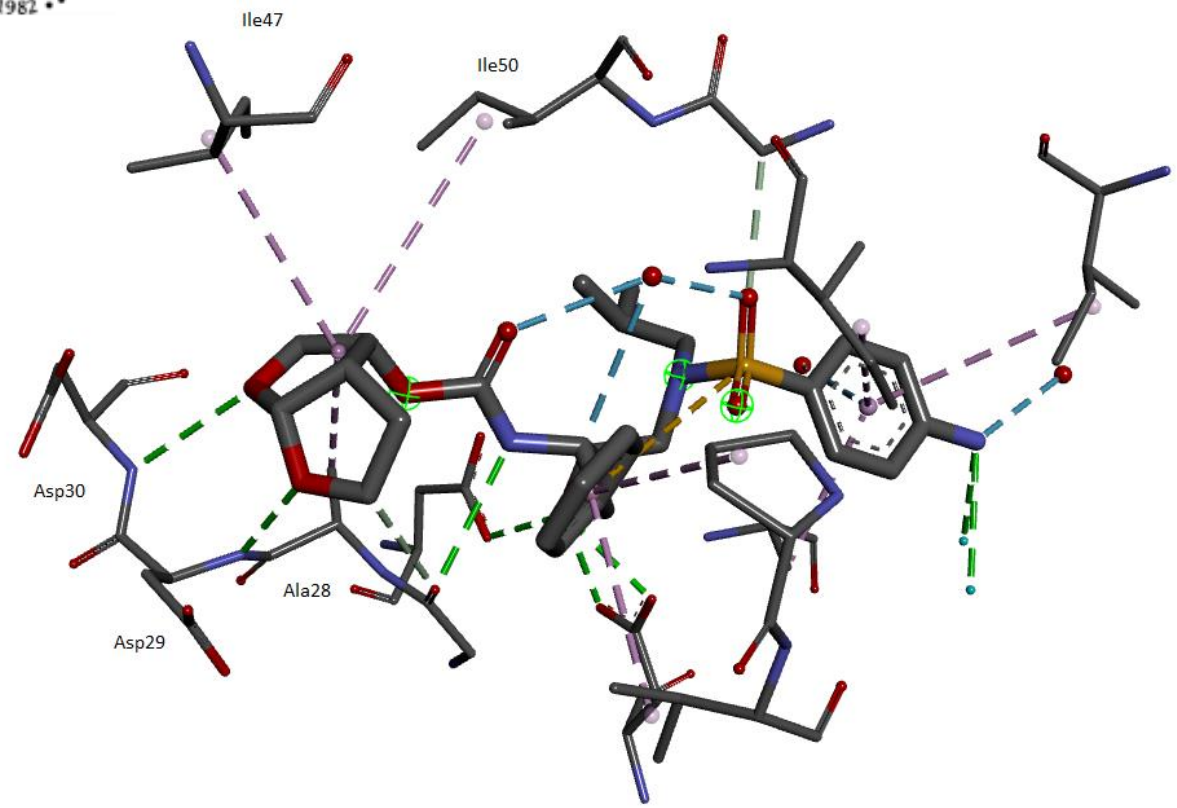
Table 1. *In vitro* inhibition activity of compounds **7-9**.

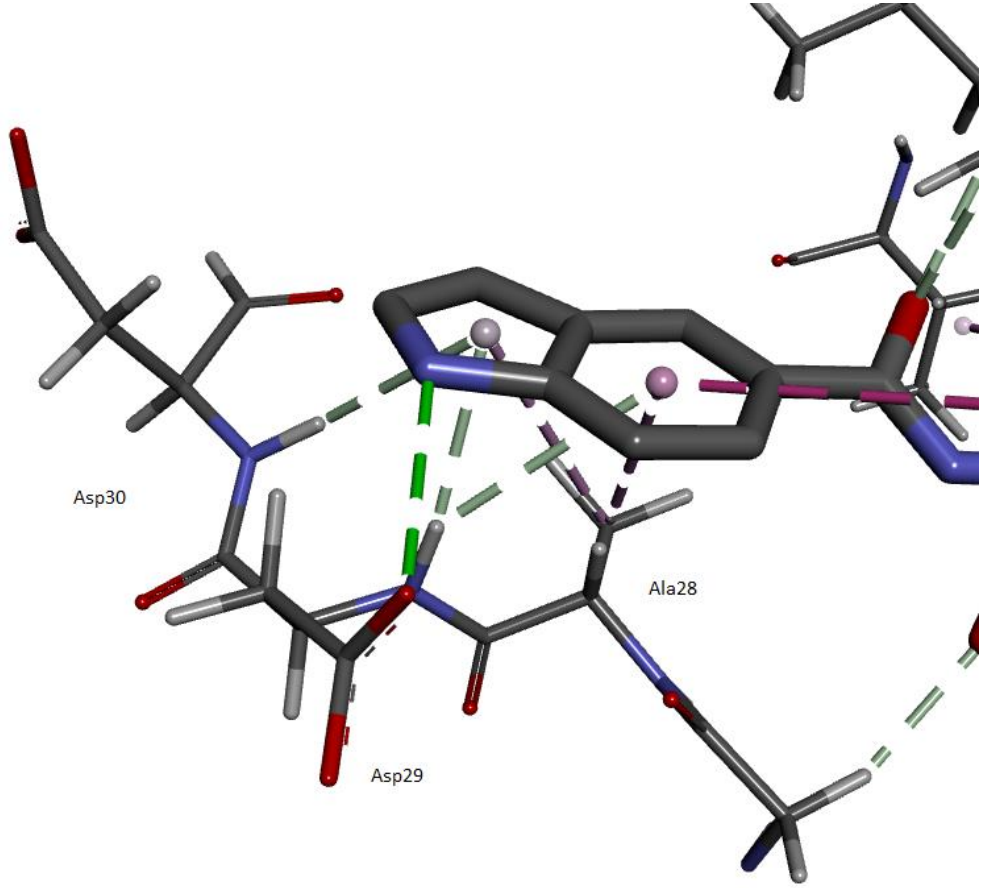
entry	Compound	X	R	IC_{50} (nM)	Std. error (nM)
1	7a	S	4-NO_2	4.2	0.6
2	7b	S	4-OMe	2.3	0.4
3	7c	S	3,4-diOMe	6.2	2.1
4	8a	O	4-NO_2	47.0	6.0
5	8b	O	4-OMe	9.6	0.1
6	8c	O	3,4-diOMe	82.0	7.0
7	9a	NH	4-NO_2	27.7%*	3.5%
8	9b	NH	4-OMe	36.3%*	5.1%
9	9c	NH	3,4-diOMe	10.2%*	2.4%
10	Darunavir			1.8	0.3



*residual activity at 500 pM

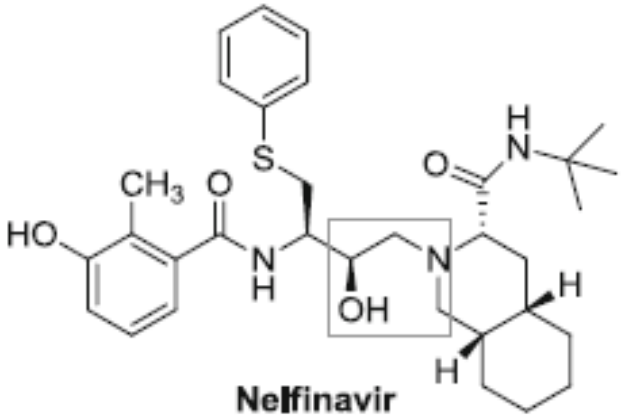
Darunavir e nostri inibitori: interazioni



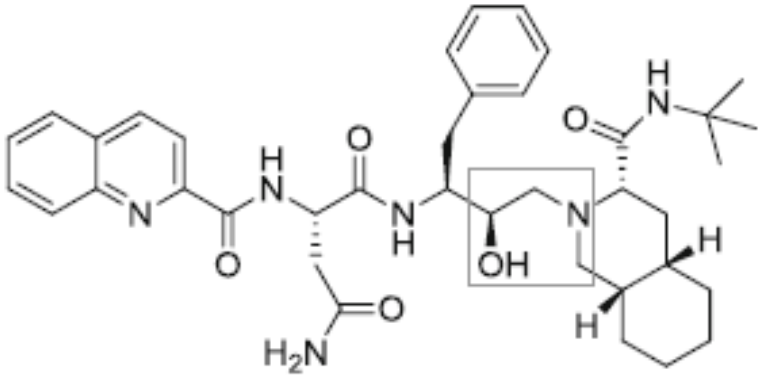


Interazioni principali: legame idrogeno tra asp29 e NH (verde), interazione π-metile con Ala28 (linee marroni) e due legami idrogeno π-accettore con gli NH di backbone di asp29 e asp30 (verde chiaro).

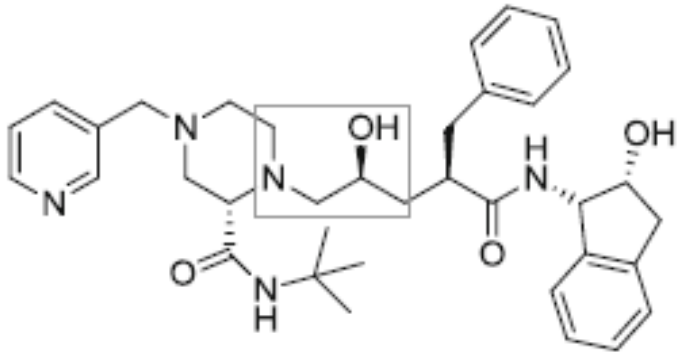
Attività antitumorale di alcuni inibitori dell'HIV Proteasi



Nelfinavir



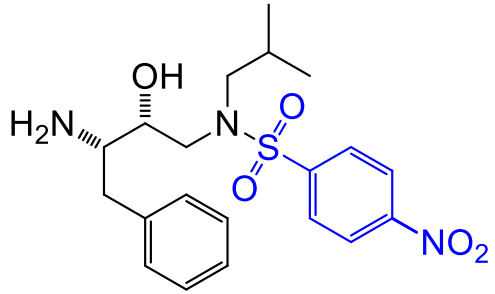
Saquinavir

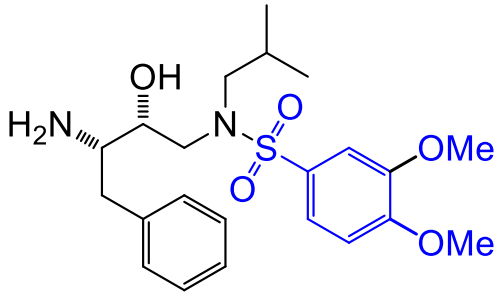


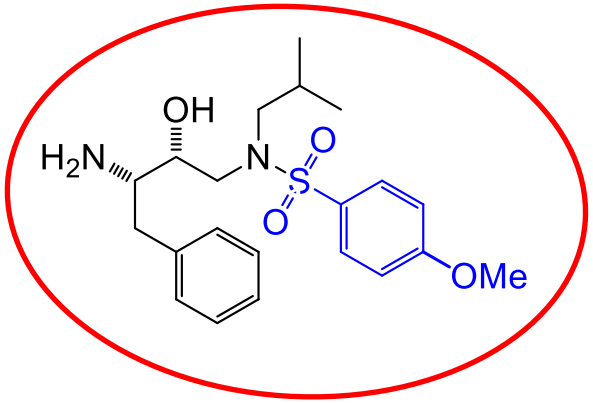
Indinavir

a) Esposito V, Palescandolo E, Spugnini EP, et al. *Clin Cancer Res.* **2006**, *12*, 2634–2639;
b) Facchinetti, V.; Moreth, M.; Gomes, C. R. B. et al. *Med. Chem. Res.* **2015**, *24*, 533-542.

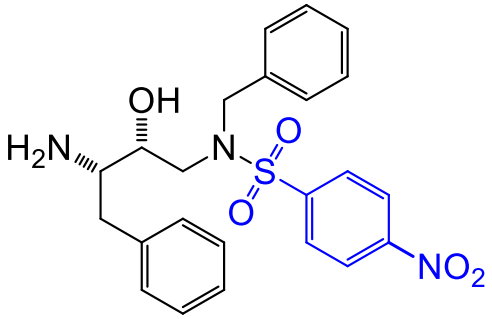
Attività antitumorale

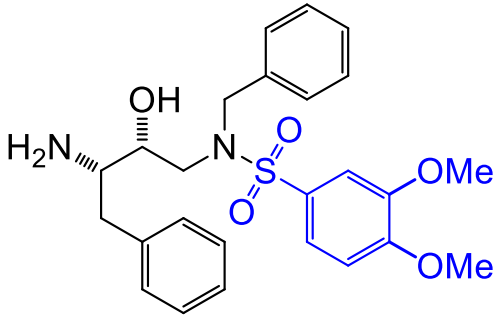


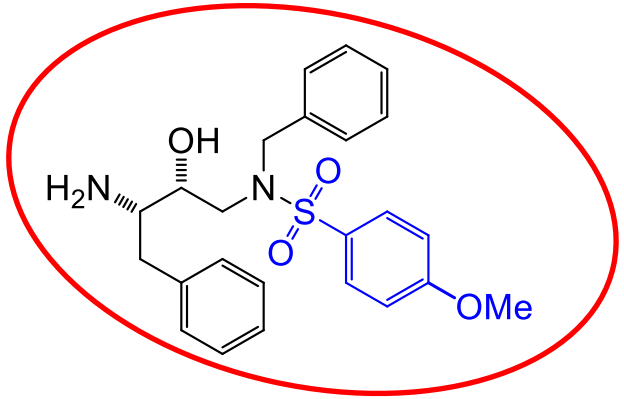




RDD-19







RDD-142

Cell line	IC50 (μM)		
	RDD-19	RDD-142	Darunavir
IHH	106,9	99,02	-
JHH6	96,61	95,04	-
HuH7	55,52	75,10	-
HepG2	57,05	67,96	> 200

Armentano, M. F. et al., *Cell*, **2021**

Ulteriori sviluppi

1. Studi di attività anti Covid-19 in collaborazione con Università di Messina

2. Studi di «Drug Delivery» tramite liposomi per le strutture con attività antitumorale in collaborazione con gruppo prof. Bisaccia, prof. Vassallo e gruppo Università di Cagliari

3. Nuova classe di inibitori HIV-Pr attivi verso virus mutati in collaborazione con Università di Trieste e laboratorio di Biologia Cellulare in Unibas

4. Studi metodologici per ottenere nuovi core in modalità ecosostenibile