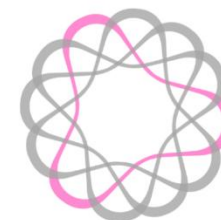


Inhibitory kináz příbuzných fosfatidylinositol-3-kináze jako možná protinádorová léčiva

Inhibice ATR

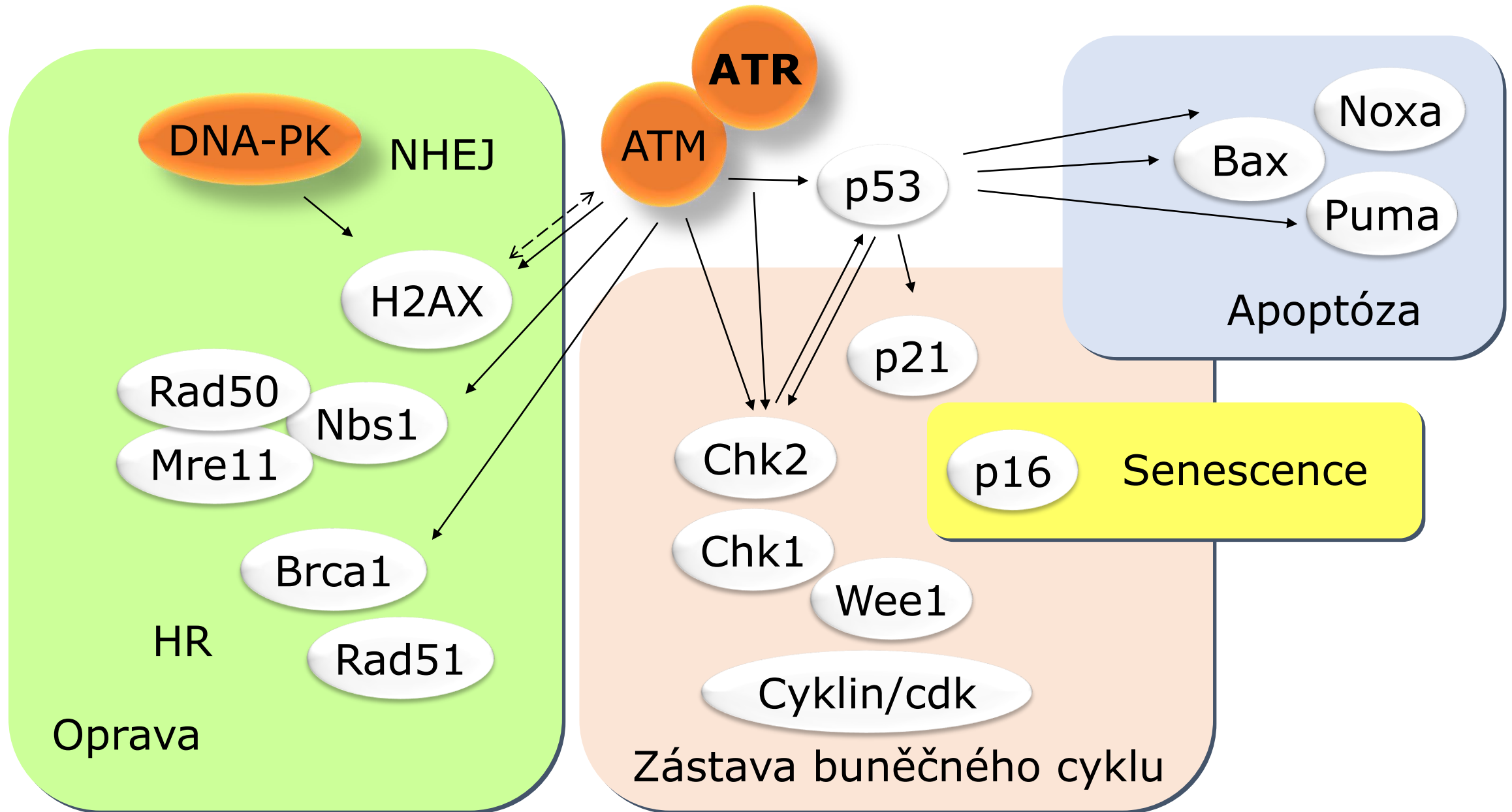


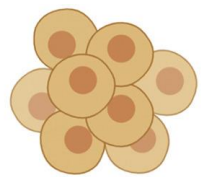
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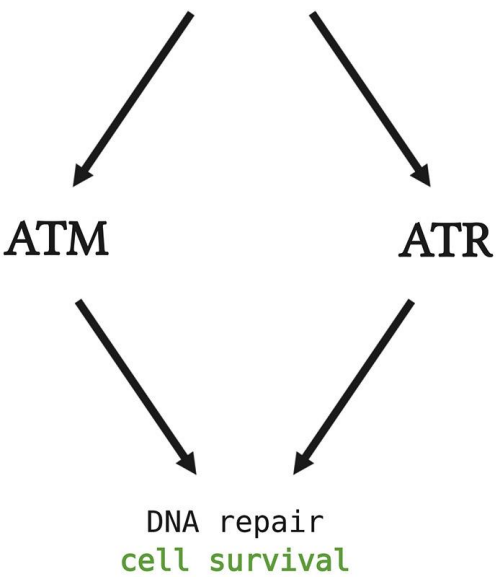
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Signální dráhy odpovědi na poškození DNA - DSB





normal cells



ELSEVIER

Discovery of ATR kinase inhibitor berzosertib (VX-970, M6620): Clinical candidate for cancer therapy

Lukas Gorecki ^a, Martin Andrs ^{a,b}, Martina Rezacova ^c, Jan Korabecny ^{a,*}

^a Biomedical Research Center, University Hospital Hradec Kralove, Sokolka 581, 500 05 Hradec Kralove, Czech Republic

^b Laboratory of Cancer Cell Biology, Institute of Molecular Genetics of the Czech Academy of Sciences, Videnska 1083, 142 20 Prague, Czech Republic

^c Department of Medical Biochemistry, Faculty of Medicine in Hradec Kralove, Charles University, Sirkova 870, 500 38 Hradec Kralove, Czech Republic



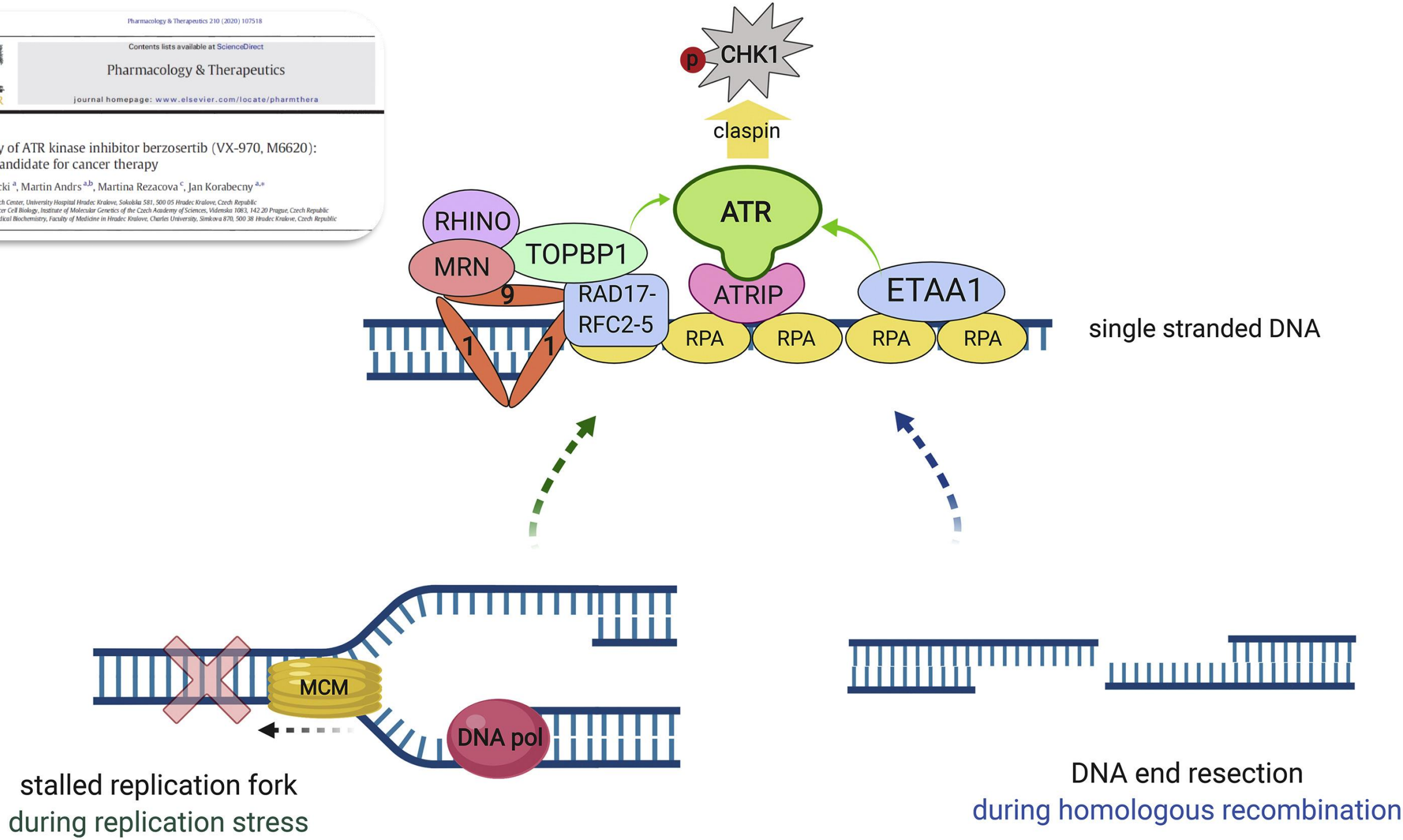
Discovery of ATR kinase inhibitor berzosertib (VX-970, M6620):
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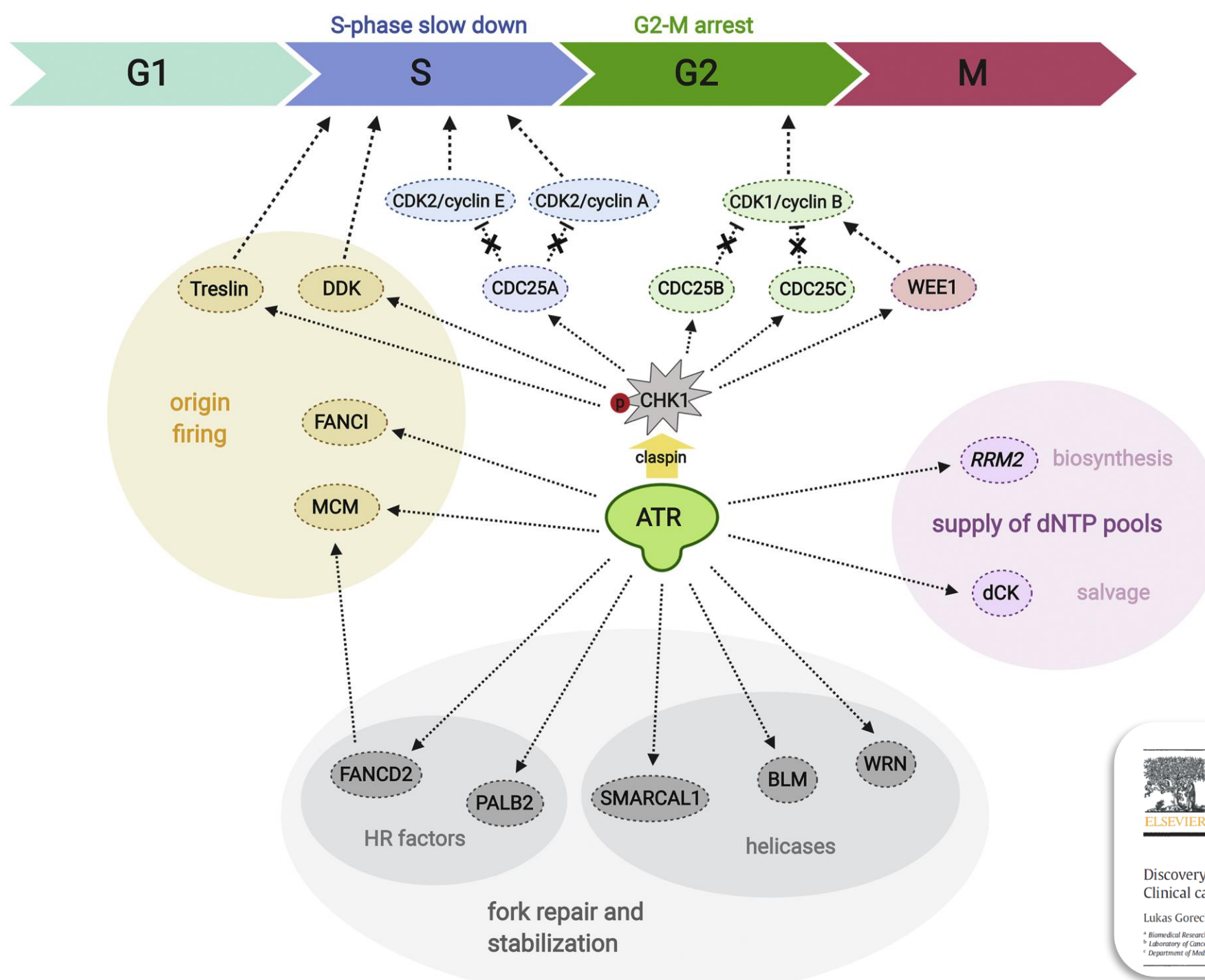
^b Laboratory of Cancer Cell Biology, Institute of Molecular Genetics of the Czech Academy of Sciences, Videnska 1083, 142 20 Prague, Czech Republic

^c Department of Medical Biochemistry, Faculty of Medicine in Hradec Kralove, Charles University, Simkova 870, 500 38 Hradec Kralove, Czech Republic



stalled replication fork
during replication stress

DNA end resection
during homologous recombination

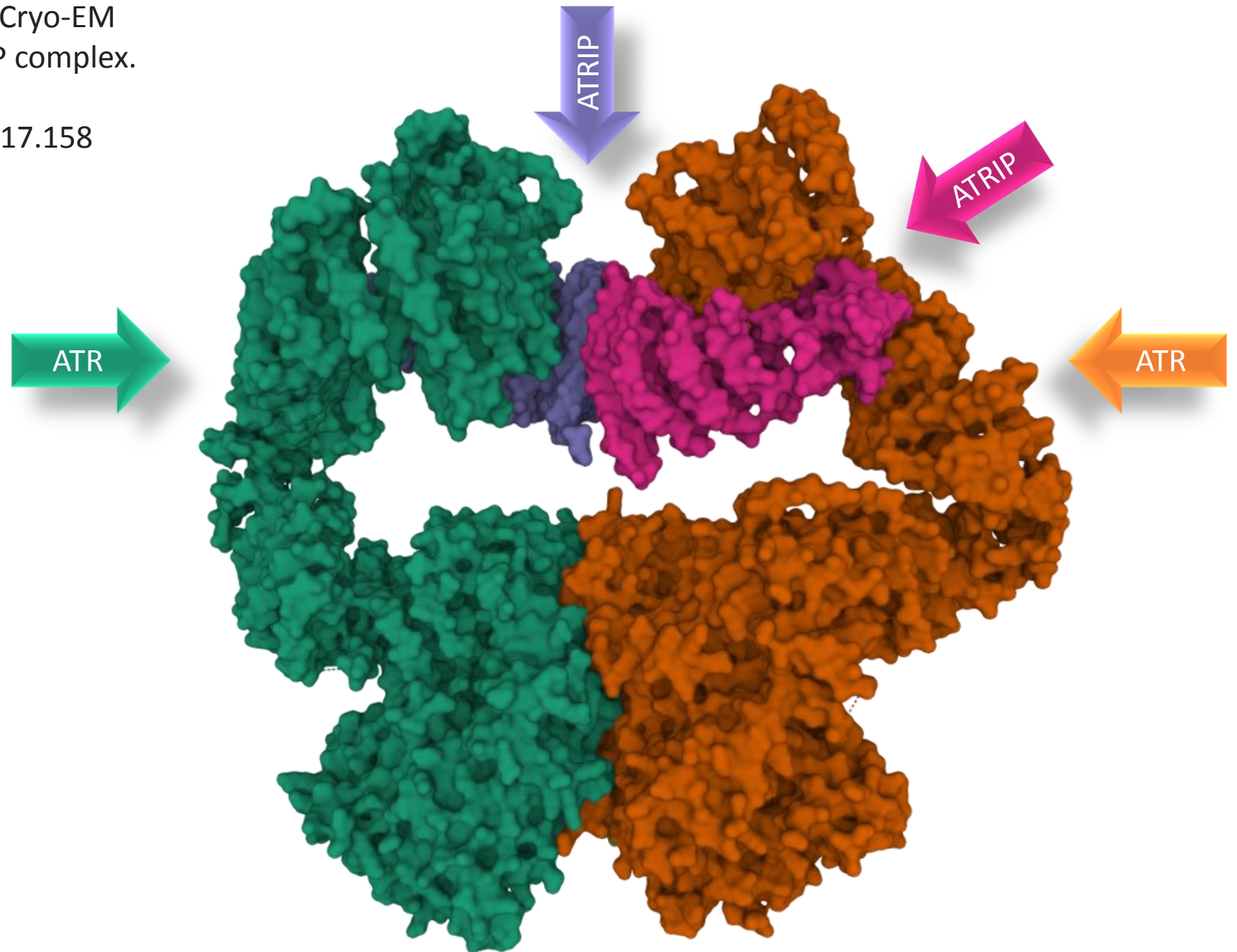


**Discovery of ATR kinase inhibitor berzosertib (VX-970, M6620):
Clinical candidate for cancer therapy**

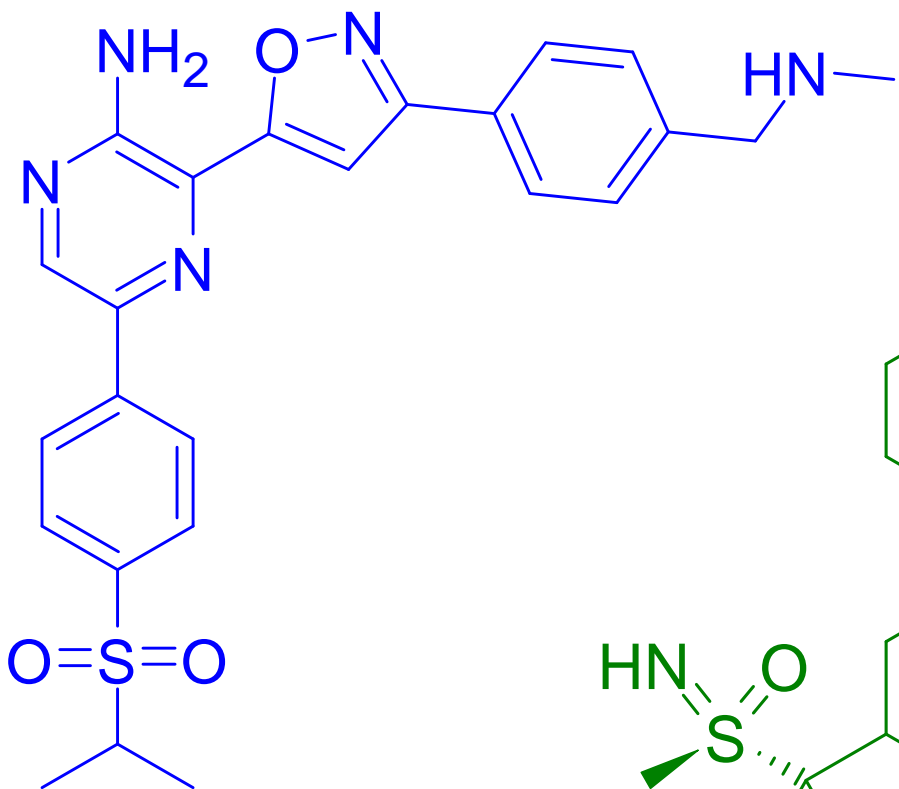
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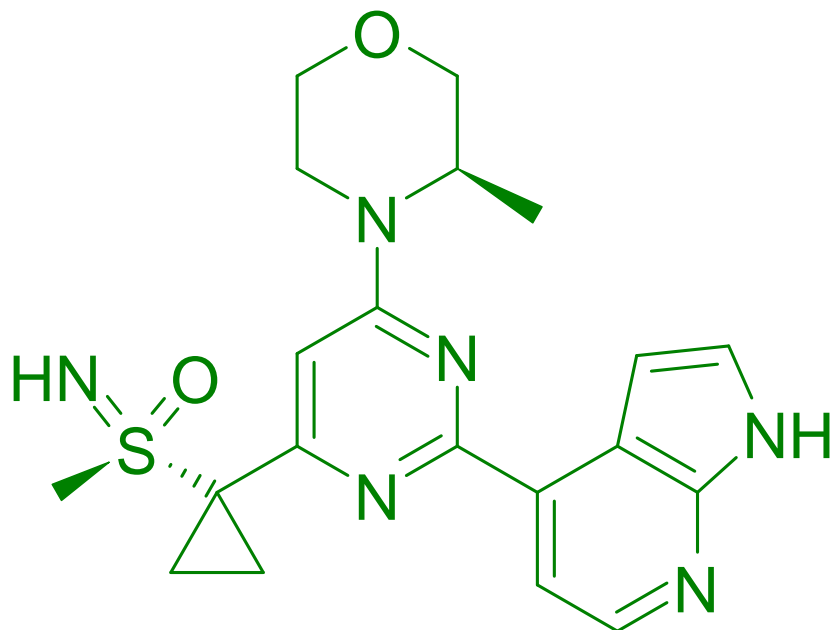
Rao, Q., Liu, M., Tian, Y. *et al.* Cryo-EM structure of human ATR-ATRIP complex. *Cell Res* **28**, 143–156 (2018).
<https://doi.org/10.1038/cr.2017.158>



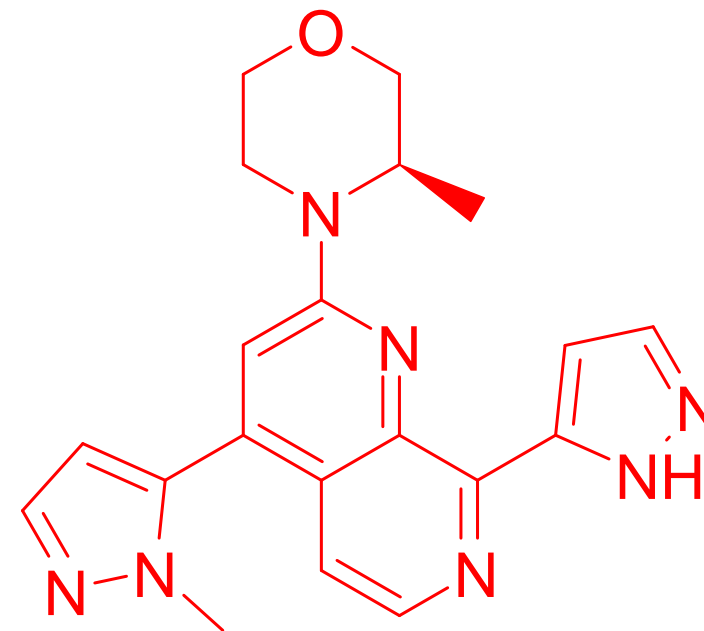
PDB entry 5YZ0



Berzosertib
VX-970
Merck



Ceralasertib
AZD6738
Astra-Zeneca



Elimusertib
BAY1895244
Bayer

> 100 mil
sloučenin

Databáze sloučenin ZINC

6570
sloučenin

Farmakofor:

- Databáze sloučenin ZincPharmer
- Na základě PDB: 5UK8, 5UKJ, 5UL1
- MW < 450

295
sloučenin

Semiflexibilní doking:

- PDB: 5YZ0
- Autodock Vina

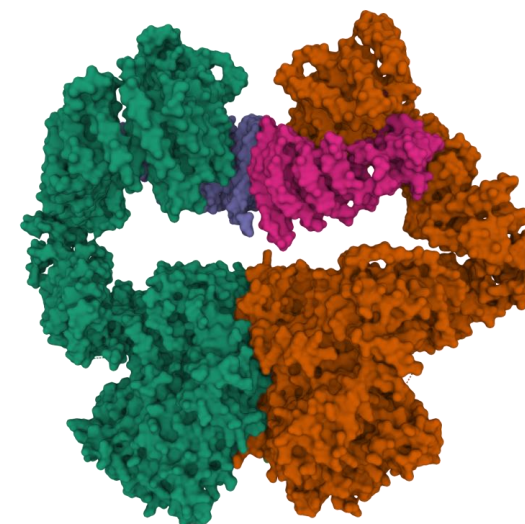
25
sloučenin

Flexibilní doking:

- PDB ID 5YZ0, 10 flexibilních residuí
- Autodock Vina

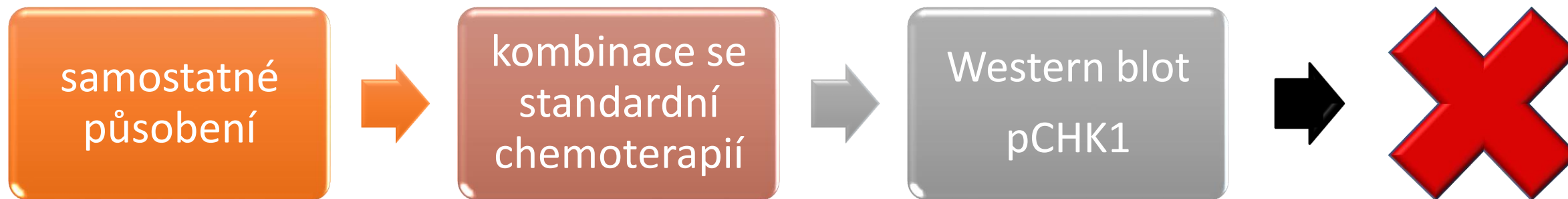
17
sloučenin

Dostupnost



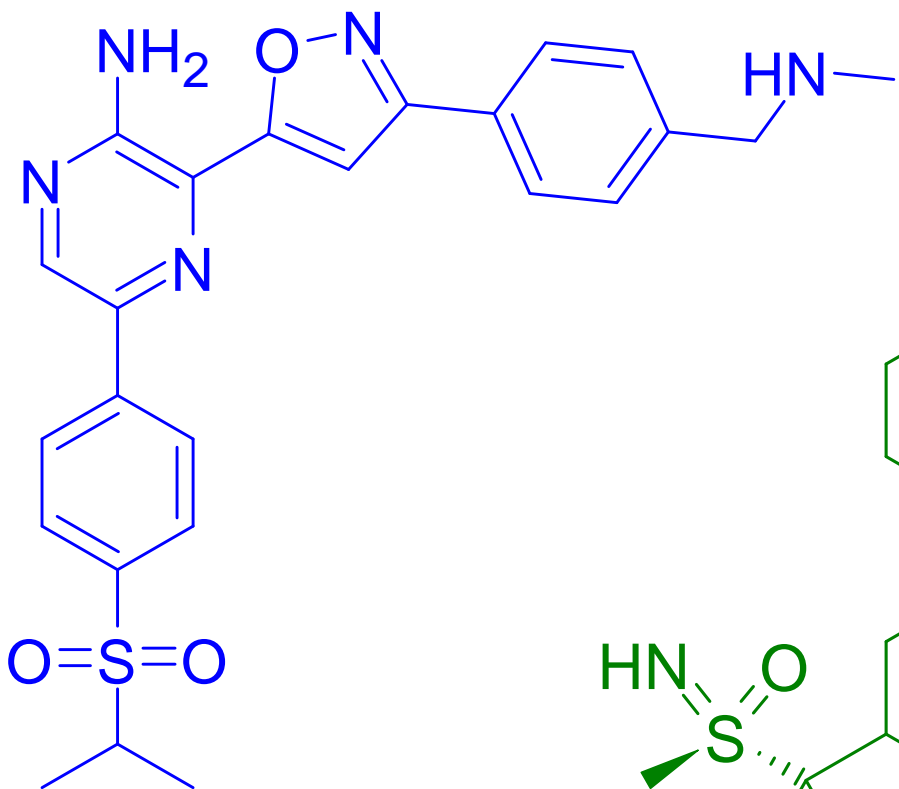
PDB 5YZ0
ATR-ATRIP complex

Virtuální screening

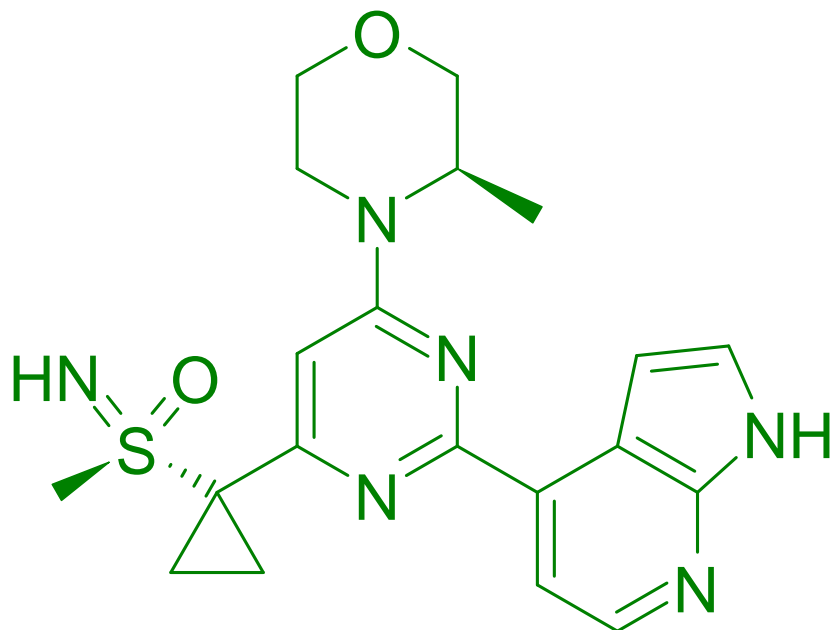


Nádorové buněčné linie: Jurkat, MOLT-4, A549, HT-29, PANC-1, A2780, HeLa, MCF-7, SAOS-2, MRC-5

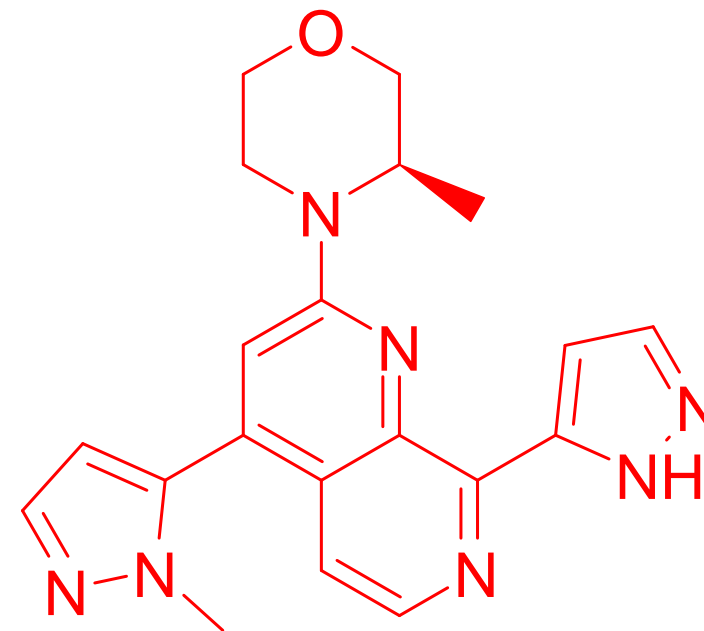




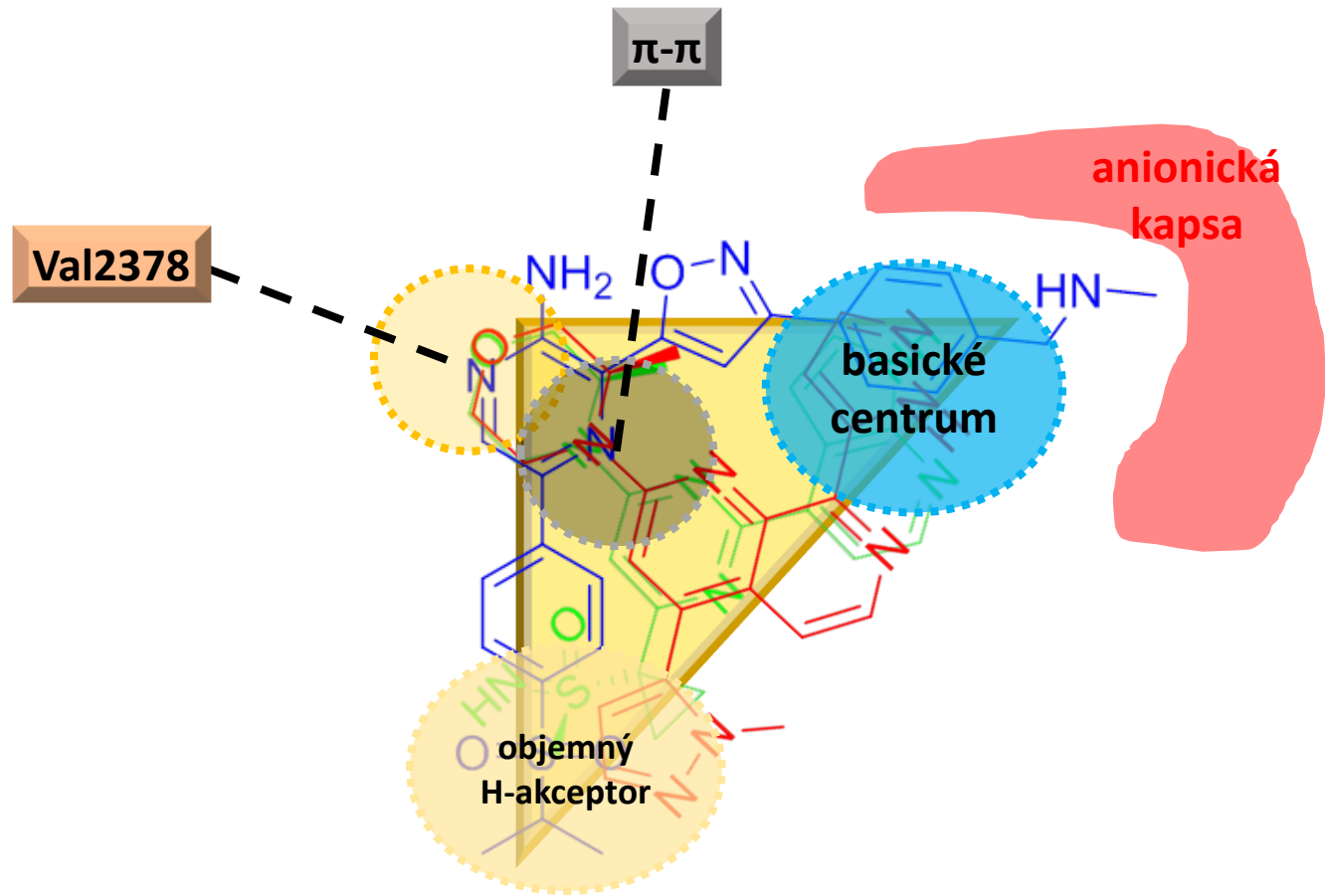
Berzosertib
VX-970
Merck



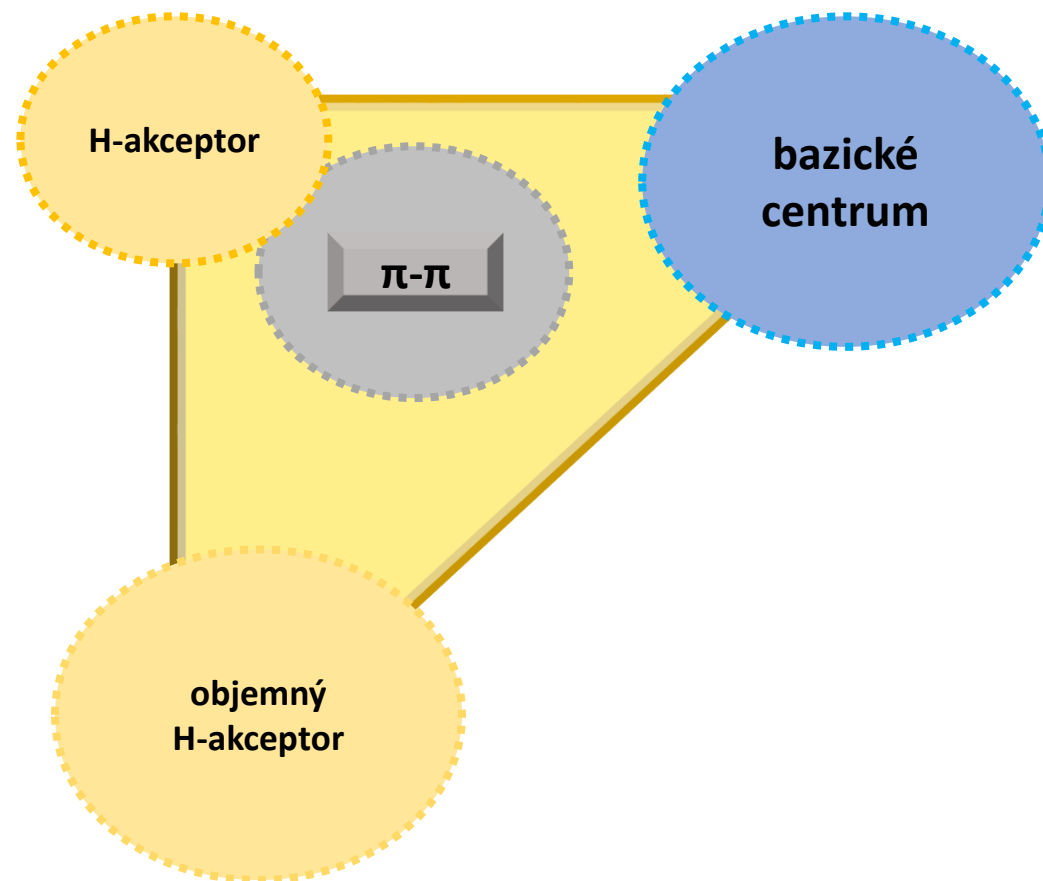
Ceralasertib
AZD6738
Astra-Zeneca



Elimusertib
BAY1895244
Bayer



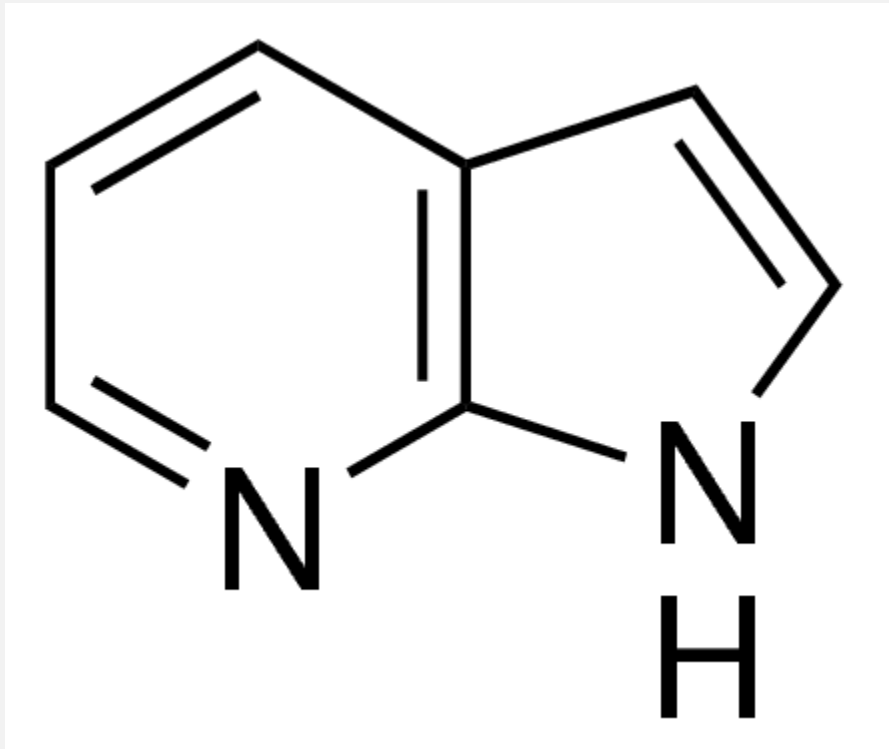
40 nových potenciálních inhibitorů ATR



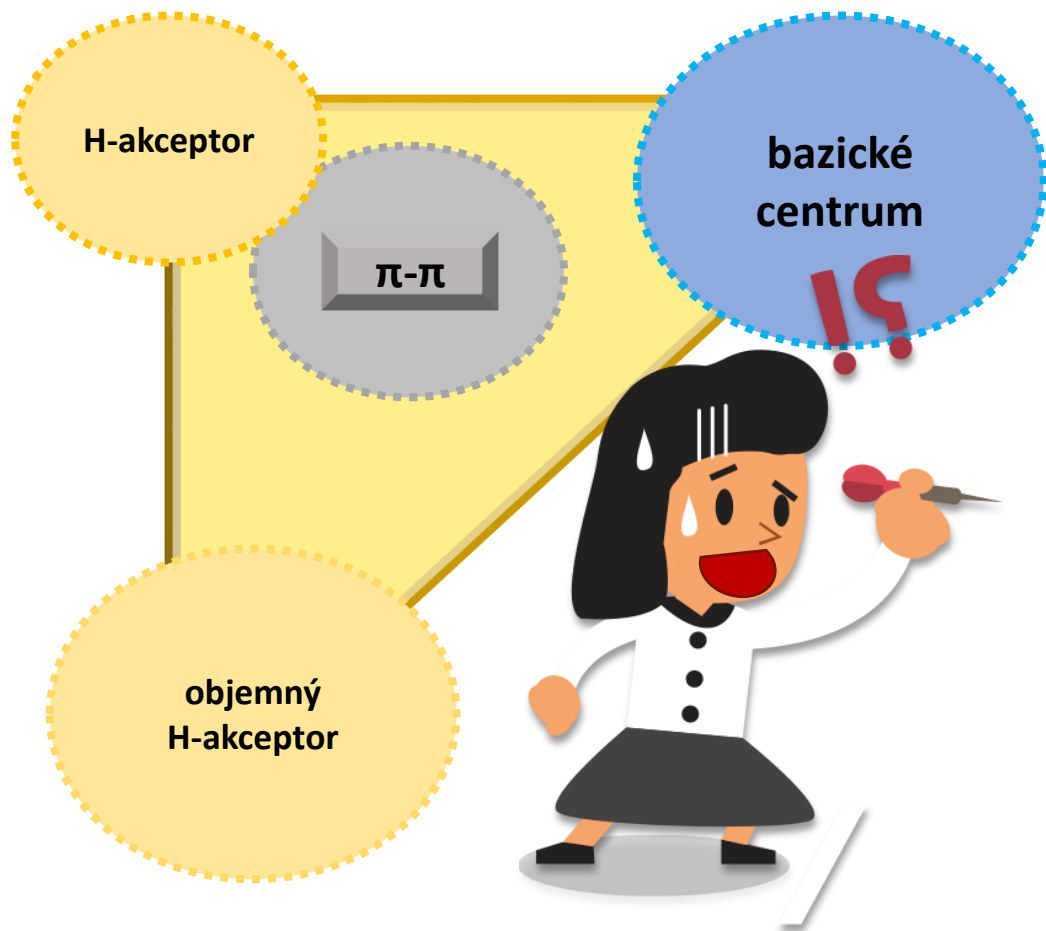
Koncentrace 10 μ M

Eurofins – broad oncology panel

	azaindol	di azaindol
kináza	sloučenina 22	sloučenina 29
ATR/ATRIP(h)	91	59



Číslo odpovídá reziduální aktivitě kinázy



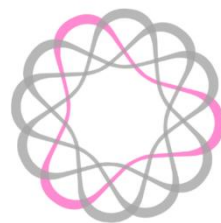
29: nová molekula s inhibičním účinkem vůči ATR, která má další potenciál pro derivatizaci a tím další zvýšení efektu.





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Univerzita Karlova

PharmDr. Darina Muthná, PhD.
RNDr. Radim Havelek, PhD.
Naděžda Mazánková



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Doc. PharmDr. Jan Korábečný, PhD.
PharmDr. Lukáš Górecki, PhD.

InoMed CZ.02.1.01/0.0/0.0/18_069/0010046



EVROPSKÁ UNIE
Evropské strukturální a investiční fondy
Operační program Výzkum, vývoj a vzdělávání

