Cost Action CA21111

One Health drugs against parasitic vector borne diseases in Europe and beyond **OneHealth*drugs***

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Molecular docking study on antiparasitic nucleoside drugs

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Challenges in drug discovery targeting TriTryp diseases

- Tritryps diseases (*Leishmania* spp., *Trypanosoma cruzi* and *Trypanosoma brucei* subspecies) affect more than 30 million people worldwide; high mortality and morbidity.

- No vaccines available

- The treatment of infected people is one of the main strategies to control these diseases.
  Drugs in use present major drawbacks (high toxicity, relevant contraindications and complicated administration regimens)

- **Adenosine analogues inhibitors top Adenosine Kinase (AK)**

The objective for molecular Molecular docking study on antiparasitic nucleoside drugs

The tested hypothesis is whether nucleoside analogues are phosphorylated more easily by *Tb*ADK than by *Leishmania mexicana* (*Lmx*ADK).

Methodology:

Target site: Adenosine Kinase (AK) L. Mexicana (LmexAK) T. brucei AK (TbAK) Both, tested on cell toxicity.

No available experimentally resolved structure of TbAK and LmexAK

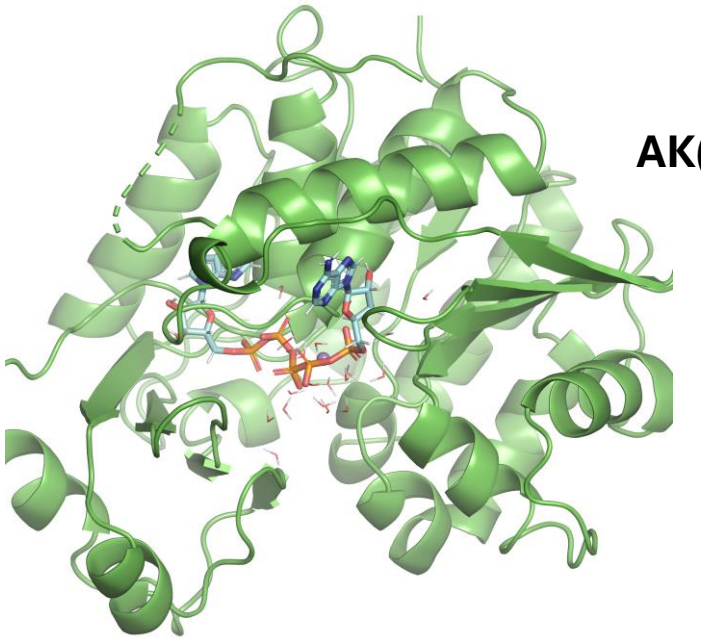
Leads, testing drugs: AK inhibitors (24 adenosine analogues drug class)

Utilizing amino acid sequences from genes of TbAK and LmexAK (TriTrypDB) https://tritrypdb.org/tritrypdb/app Generated structures for TbAK and LmexAK (amino acids sequences in software package) https://alphafold.ebi.ac.uk/

Optimizing the protein structures (PyMol software package) https://www.pymol.org/

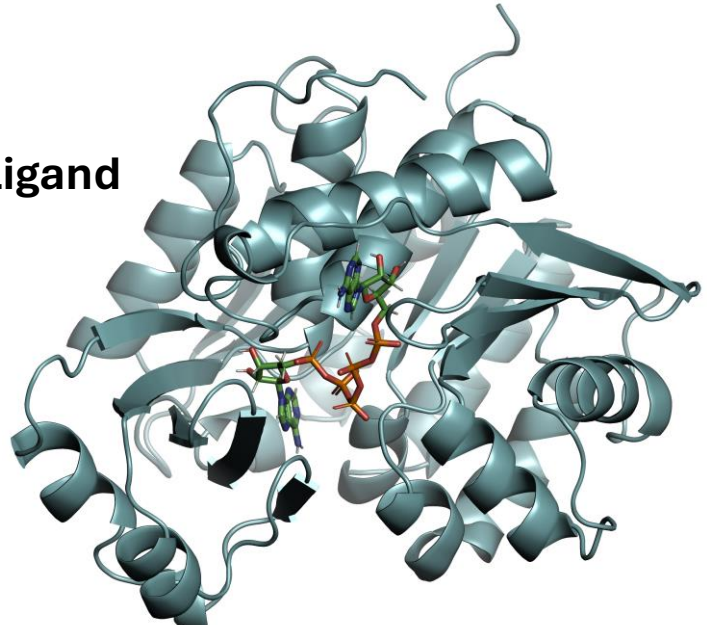
Docking testing: interaction AK with lead compounds (drugs): Software package https://www.schrodinger.com/platform/products/glide/

Measurement of bond distances (PyMol software package) https://www.pymol.org/)

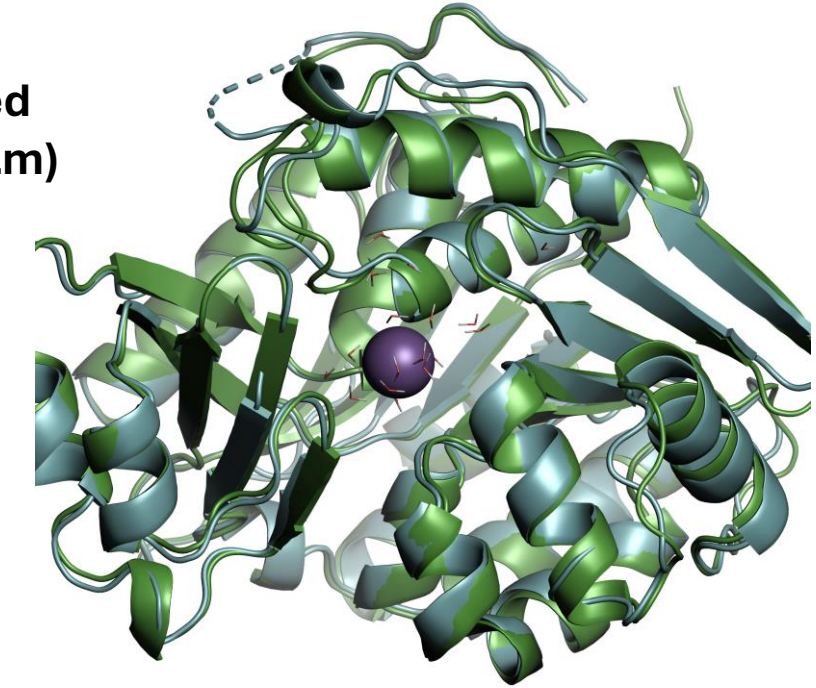


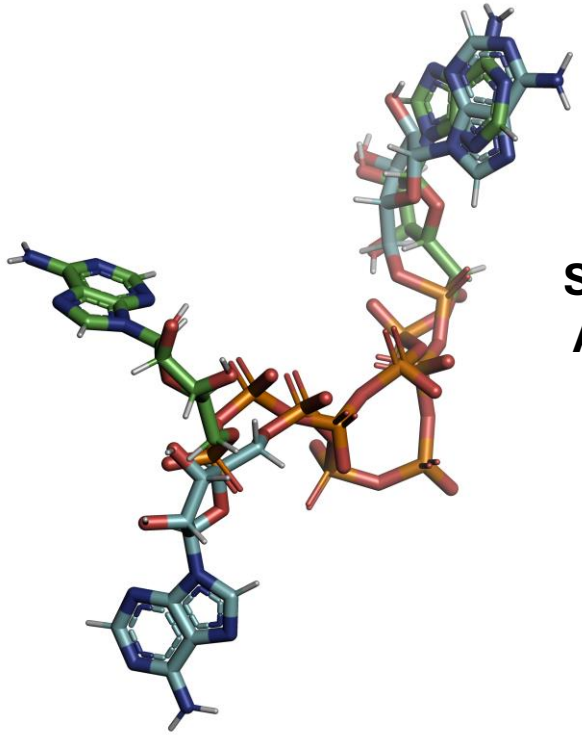
AK(Tb) with ligand

AK(Lm) with ligand



Superimposed
AK(Tb) & AK(Lm)





Superimposed ligands
AK(Tb) & AK(Lm)

Executive: RMSD = 1.316 (2283 to 2283 atoms)

AK (Tb) docked_3OTX-1_-_minimized / docked__lig3otx	Å
(N295)-NH···O(15)-P(13)	2.8
(N295) C=O ···O(46)(ring tetrahydrofuran/THF)	2.2
H2O··· N(56)(pyrimidine/purine ring)	2.6
(R132) guanidine/NH2+···O(44) – H (THF ring)	2.4
(N67)-NH2···O(19)-P(17) chain	2.2
(N67)-NH2···O(16)-P(13) chain	2.7
(R132)-NH2···O(39)-P(17)chain	1.9
(R132)-NH2···O(15)-P(13) chain	2.4
(R132)-NH2···O(10)-P(9) chain	1.8
(R132)-NH2···O(10)-P(9) chain	2.2
H2O···O(18)=P(19) chain	2.5
H2O···O(06)=P(5) chain	1.9
H2O···O(07)-P(5) chain	1.5
H2O···O(06)=P(5) chain	1.7
H2O···O(11)-P(9) chain	2.1
H2O···O(11)-P(9) chain	1.4
H2O···O(11)-P(9) chain	3.0
H2O···O(18)=P(17) chain	2.5
H2O···O(14)=P(13) chain	1.7
(D299)-NH···O(14)-P(13) chain	1.9
(A297)-NH···O(6)=P(5) chain	1.7
H2O···O(18)=P(17) chain	2.5
H2O···O(4)-P(1) chain	2.7
H2O···O(4)-P(1) chain	2.4
H2O···O(20)-P(1) chain	2.5
H2O···O(20)-P(1) chain	2.4
(T264)-O–H···O(20)-P(1) chain	2.7
(N222)_NH2···O(20)-P(1) chain	2.5
H2O···O(2)=P(1) chain	1.8
H2O···O(2)=P(1) chain	1.9
NA (Sodium)···O(1)–P(9) chain	3.0
NA (Sodium)···O(8)–P(9) chain	3.5
H2O··· O(23)– chain	2.7
Ligand: THF-O(25)···O(3)–P(1) chain	2.7, intra
Ligand: Purine/ imidazole (N31) – H ···O(27) THF ligand	2.0 intra

AK (Lm) nu_Lm_AK_AF_aligned_to_3otx/ docked_LMAK_lig3otx	Å
(R12)-NH2···(N54) pyrimidine	2.2
(G62)secNH···(N56) pyrimidine	2.0
(D16)C–O···H–(O46)/ Tetrahydrofuran THF ring	1.9
(D16)C–O···H–(O44)/ Tetrahydrofuran THF ring	1.8
(G296)N–H···(O19)–(P17)chain	1.8
(D299)N–H···(O18)=(P17)chain	2.6
(D298)N–H···(O18)=(P17)chain	2.3
(D298)N–H···(O6)=(P5)chain	2.5
(N221)N–H2···(O11)–(P9)chain	2.0
(N221)N–H2···(O8)–(P9)chain	2.4
(T263)O–H···(O3)–(P1)chain	2.0
(G265)N–H···(O3)–(P1)chain	2.1
(N323)C=O···H–(O25)/ Tetrahydrofuran THF ring	2.0
THF ring (O27)–H ···(N37)/ pyrimidine ring	2.2 intra

AK (Tb)

13 amino acids participate in H-bonds;

No one amino acid with Purine/pyrimidine or imidazole/ in Ligand

2 amino acids with THF ring in ligand (to this ring does not overlap highest ranked Tubricidin/C11H14N4O4

THF ring: 2 intramolecular bonds

17 H-bonds with water molecules

2 bonds with Na with Ligand chain in active site

AK (Lm)

13 amino acid participate in H-bonds;

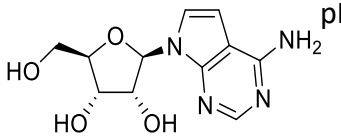
2 amino acids with purine ring/ to which do not attach highest DS C16H23N3O5

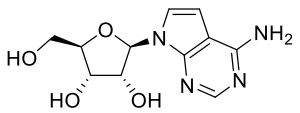
3 amino acids with THF ring in ligand/ N323 close to overlapping C16H23N3O5

THF ring in 2 bonds close to overlapping C16H23N3O5 (one bond is intramolecular)

No water molecules in active site of ligand

No Na in active site

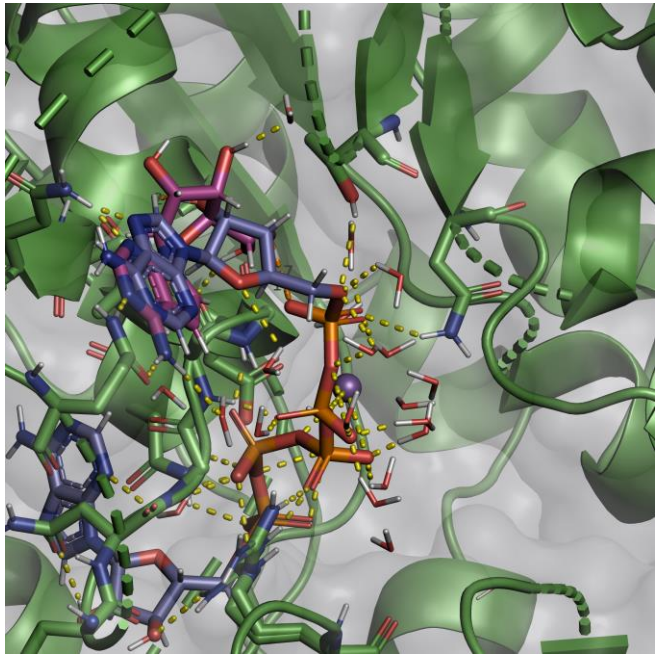


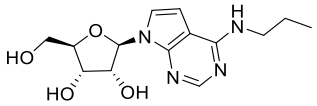


pIC50 158,5

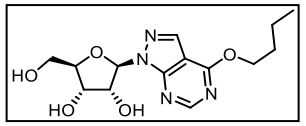
Docking score ranking -10,10

Tubercidin

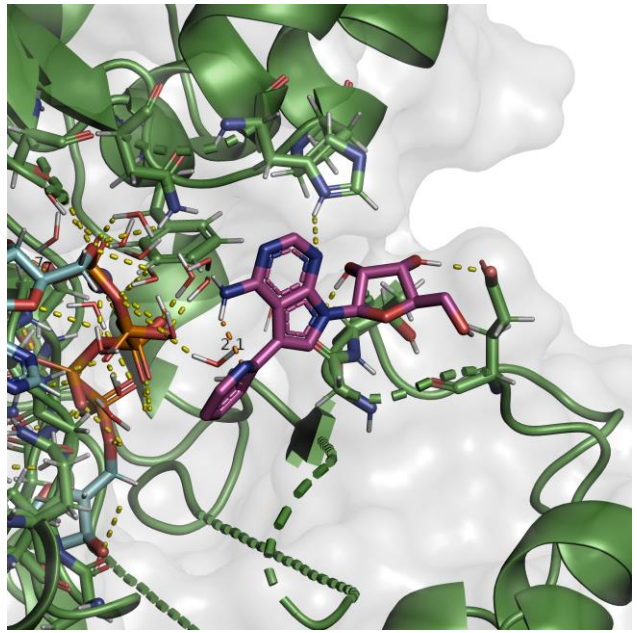




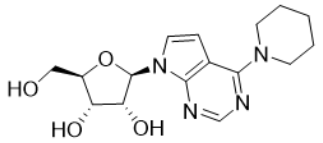
109,63 -7,39



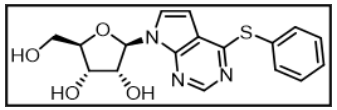
109,10 3,86



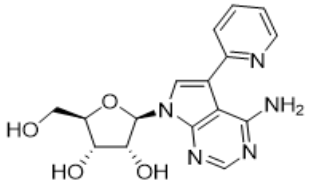
pIC50 Docking score ranking



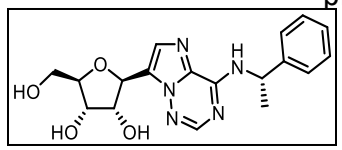
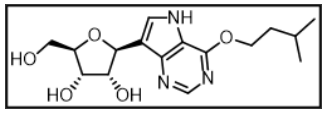
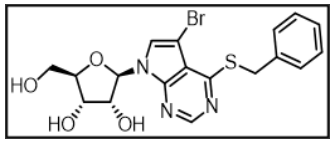
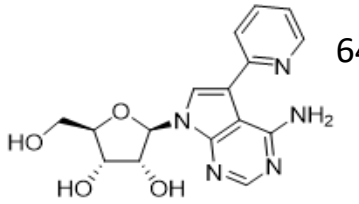
2,88 -,344

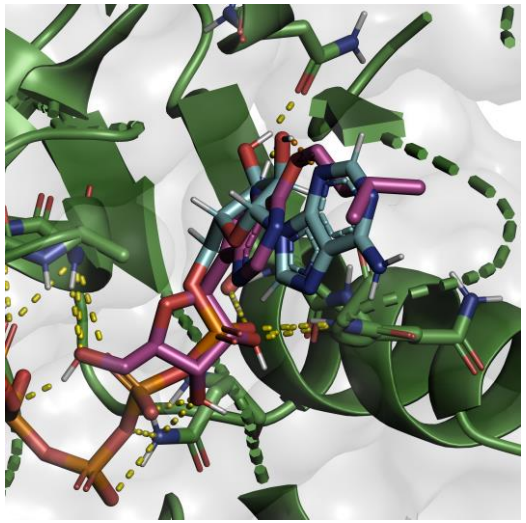


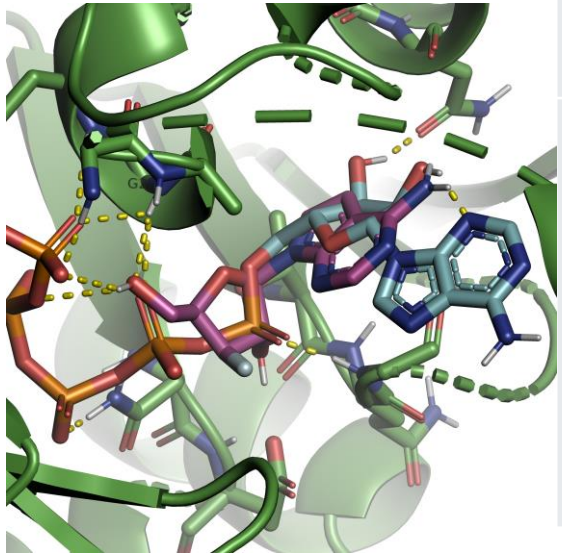
0,03 -3,19

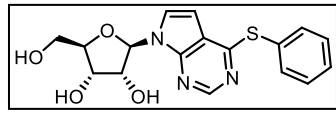
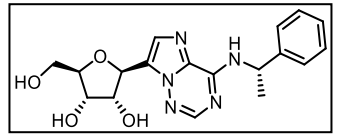
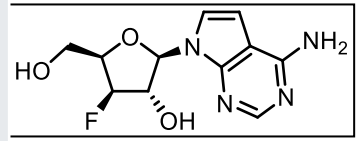


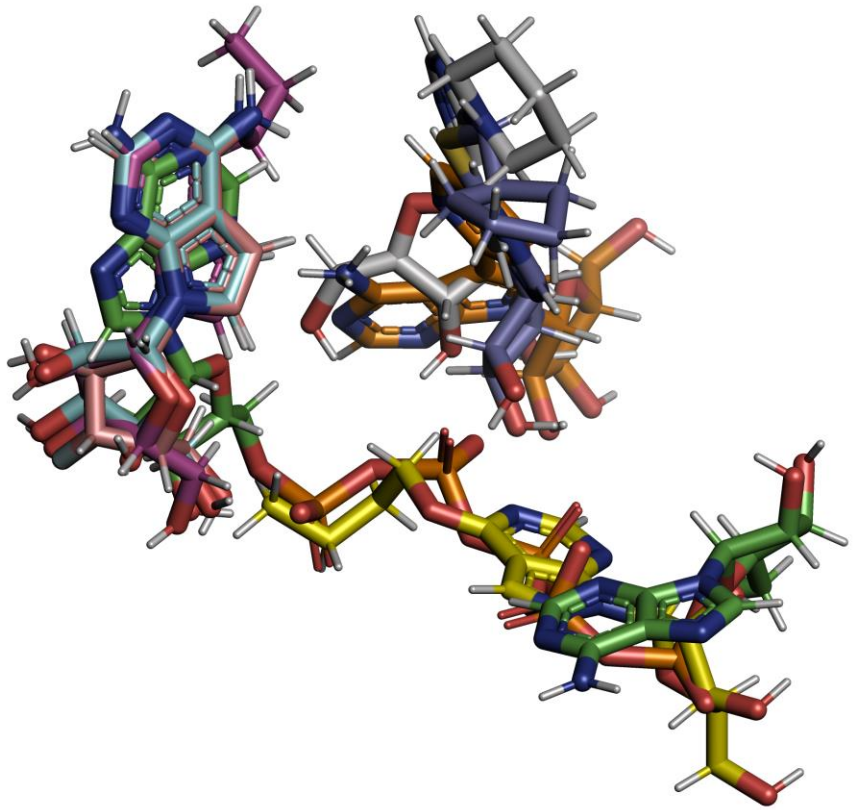
19,83 -3,18

	pIC50	Docking score ranking
		
	130,33	-9,2960
	64,00	-9,2840
	64,00	-8,7020

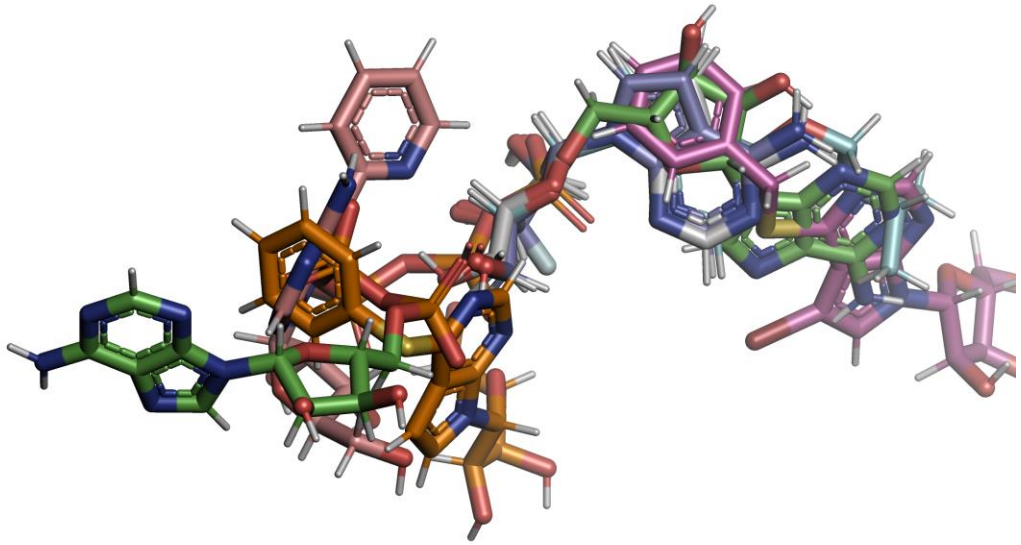




pIC50	Docking score ranking	
0,04	-6,7190	
0,04	-6,5340	
0,03	-5,8040	



Highest & lowest scored Drugs binding to ligand in AK (Tb)



Highest & lowest scored Drugs binding to ligand in AK (Lm)

Acknowledgment

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