The 24th International Electronic Conference on Synthetic Organic Chemistry
15 Nov - 15 Dec 2020

In silico evaluation of antimicrobial activity of some thiadiazoles using molecular docking approach

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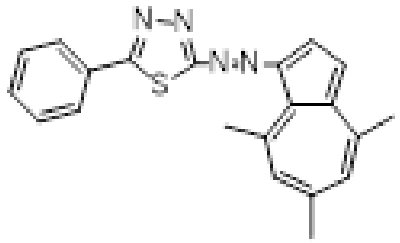
Structures of 1,3,4 - thiadiazoles under investigation



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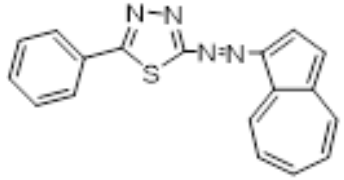
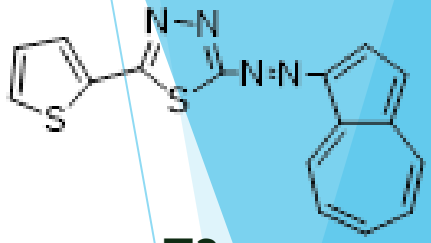
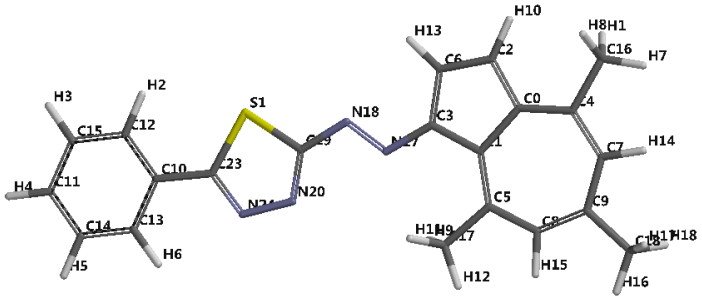
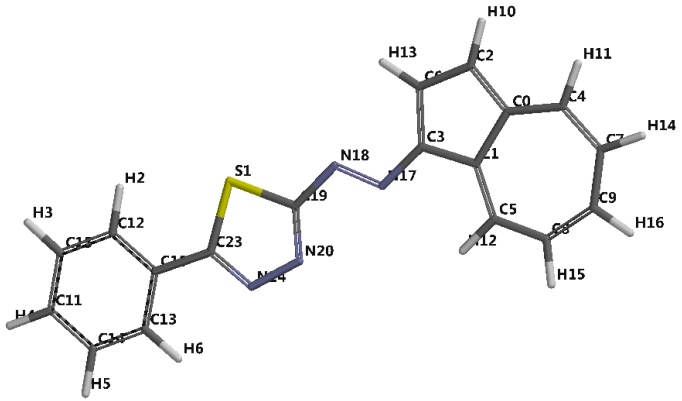


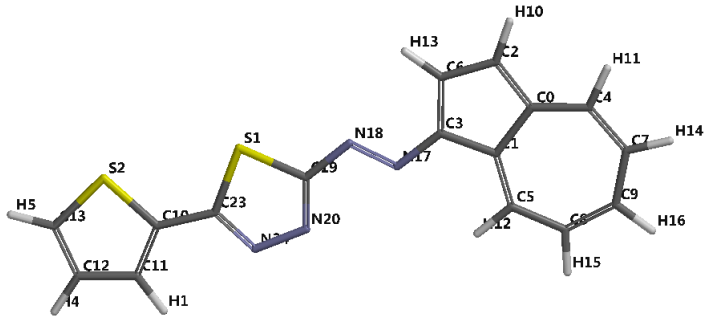
T2



T3





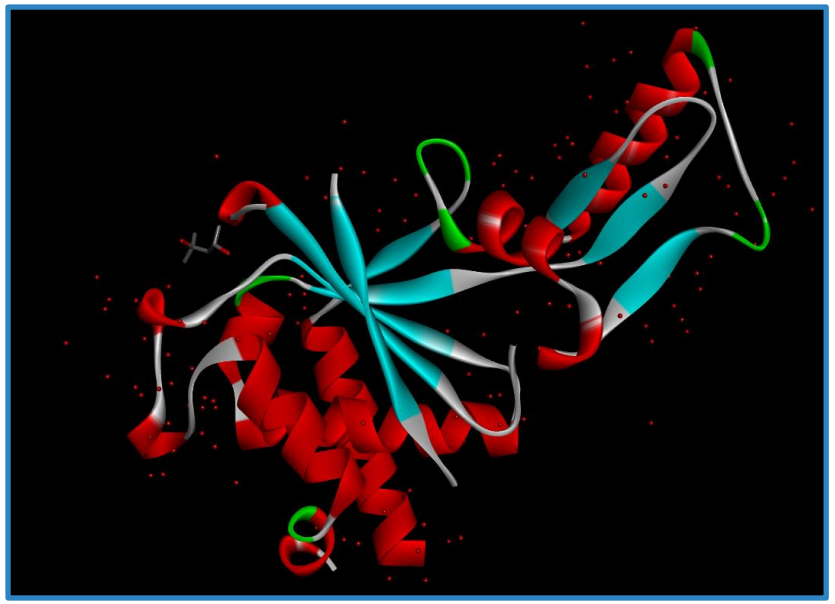


Geometry optimization: energy minimization, MMFF*, with Spartan Software, Wavefunction Inc, Irvine, USA**

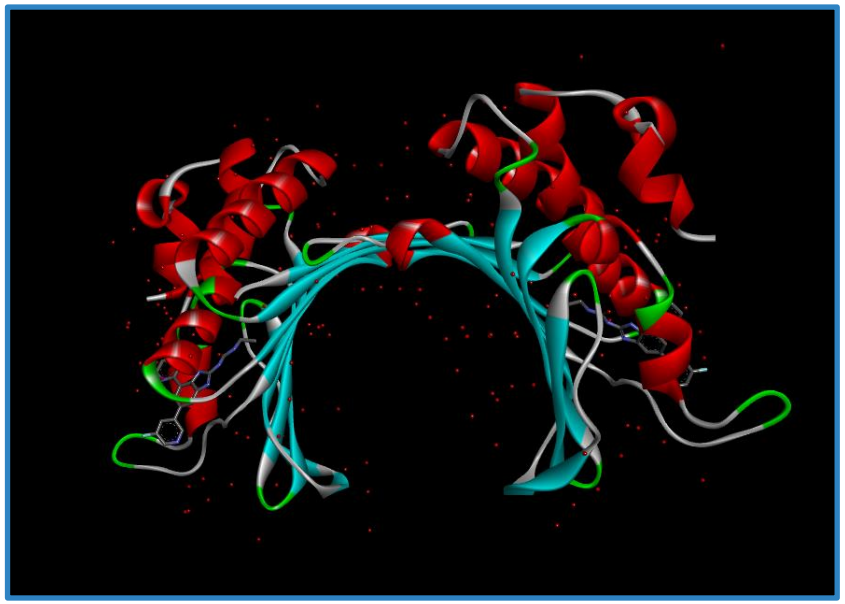
* W.J. Hehre, A Guide to Molecular Mechanics and Quantum Chemical Calculations, Wavefunction, Inc., Irvine, CA, 2003

** Y. Shao, L.F. Molnar, Y. Jung, et al., Advances in methods and algorithms in a modern quantum chemistry program package, Phys. Chem. Chem. Phys.2006, 8, 3172-3191

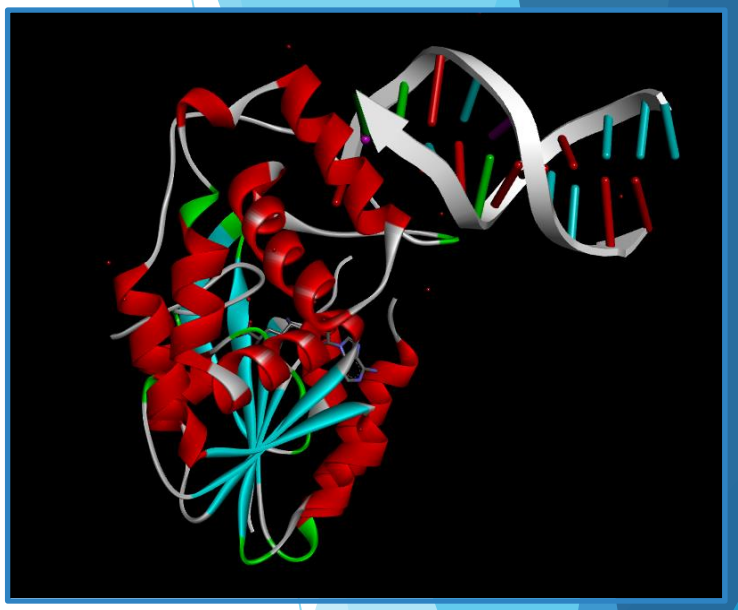
Biological targets from Protein Data Bank



PDB ID : 3M4I [1]
Crystal structure of the second part of the Mycobacterium tuberculosis DNA gyrase reaction core: the TOPRIM domain at 1.95 A resolution



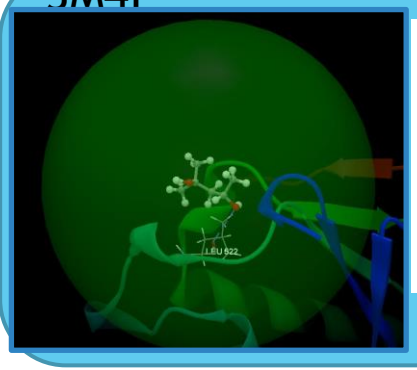
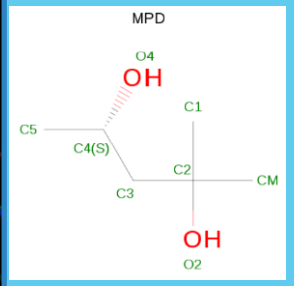
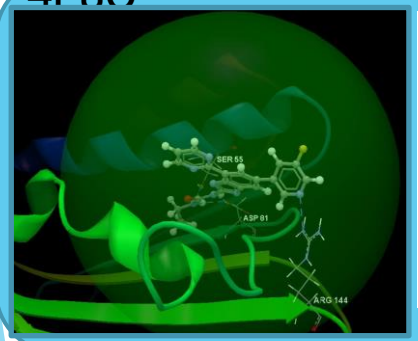
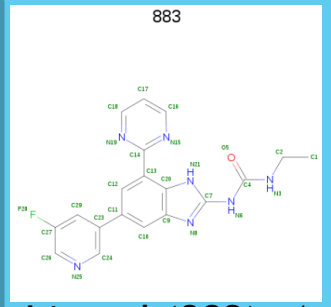
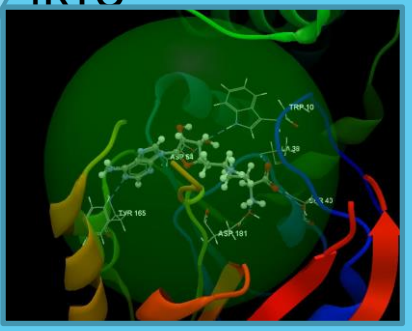
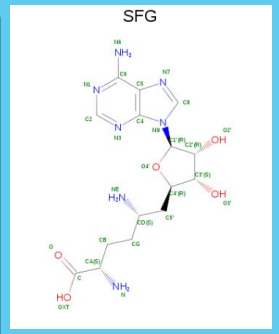
PDB ID : 4P8O [2]
S. aureus gyrase bound to an aminobenzimidazole urea inhibitor



PDB ID : 4RTO [3]
Complex of Escherichia coli DNA Adenine Methyltransferase (DAM) with Sinefungin and with DNA Containing Proximal Pap Regulon Sequence

[1] J. Piton, S. Petrella, M.Delarue, G. Andre-Leroux, V. Jarlier, A. Aubry, C. Mayer, *Structural insights into the quinolone resistance mechanism of Mycobacterium tuberculosis DNA gyrase*, PLoS One 2010 5, e12245-e12245.
[2] A.L. Grillot, A. Le Tiran, D.Shannon, E. Krueger, et al. *Second-Generation Antibacterial Benzimidazole Ureas: Discovery of a Preclinical Candidate with Reduced Metabolic Liability*, J. Med. Chem. 2014, 57, 21, 8792–8816.
[3] J.R. Horton, X. Zhang, R.M. Blumenthal, X.Cheng, *Structures of Escherichia coli DNA adenine methyltransferase (Dam) in complex with a non-GATC sequence: potential implications for methylation-independent transcriptional repression*, Nucleic Acids Research 2015, 43(8), 4296–4308.

Docking validation of co-crystallized ligands

		Interacting group	Ligand interactions (Å)	Score/ RMSD
3M4I	 	ARG451, HIS525, PRO450, TYR524, HIS560, GLY520, ILE519, LEU522, ARG523	O4(sp^3) - O (sp^2) LEU522:3.302	25.91 0.86
4P8O	 	ASN54, VAL52, ILE51, ILE102, VAL79, ILE175, VAL174, THR80, THR173, PRO87, GLY85, ASP81, ARG144, ARG84, GLY83, GLU58, SER55, ILE86	N25(sp^2) - N(sp^2) ARG144: 2.769 N6(sp^2) - O(sp^2) ASP81: 2.797 N3(sp^2) - O(sp^2) ASP81: 2.914 N3(sp^2) - O(sp^3) SER55: 3.081	70.22 0.08
4RTO	 	ASN56, ILE55, PHE201, GLU163, SER164, GLN205, TYR165, SER168, LEU59, ASP54, PRO183, PHE35, ALA53, PRO182, PRO34, ASP181, GLU33, TYR179, VAL36, TYR184, VAL41, LYS14, SER40, GLY39, GLY13, GLY12, GLY37, ALA38, ALA11, TRP10	N1(sp^2) - N(sp^2) TYR165: 3.129 O2'(sp^3) - O(sp^2) ASP54: 2.654 O3'(sp^3) - O(sp^3) ASP54: 2.567 O3'(sp^3) - N(sp^2) TRP10: 3.128 O(sp^2) - N(sp^2) ALA38: 2.834 OXT(sp^2) - O(sp^3) SER40: 2.980 N(sp^3) - O(sp^3) ASP181: 2.426	67.74 0.79

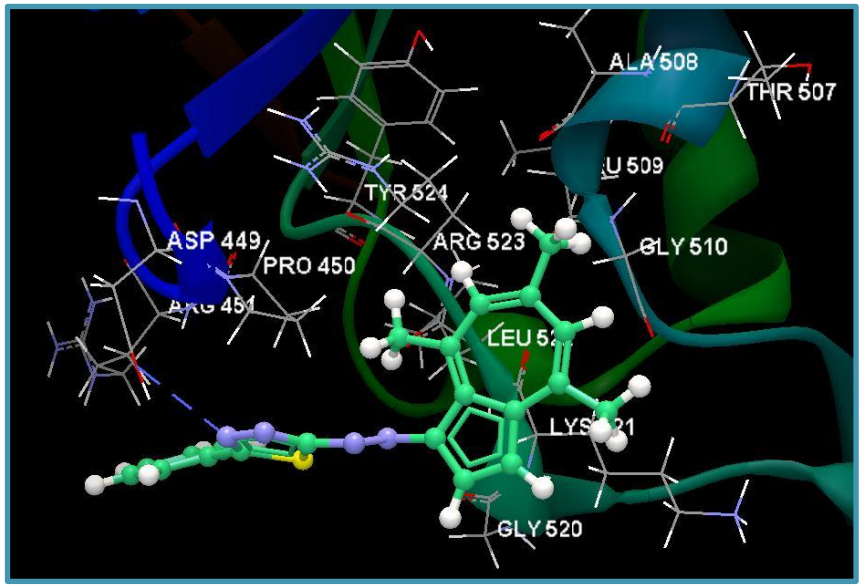
Ligand (MPD): (4S)-2-methyl-2,4-pentanediol

Ligand (883): 1-ethyl-3-[5-(5-fluoropyridin-3-yl)-7-(pyrimidin-2-yl)-1H-benzimidazol-2-yl]ure

Ligand (SFG): (2S,5S)-6-[(2R,3S,4R,5R)-5-(6-aminopurin-9-yl)-3,4-dihydroxy-oxolan-2-yl]-2,5-bis(azanyl)hexanoic acid

Docking results for 1,3,4 - thiadiazoles against 3M4I (Mycobacterium tuberculosis DNA gyrase)

T1



Interacting group

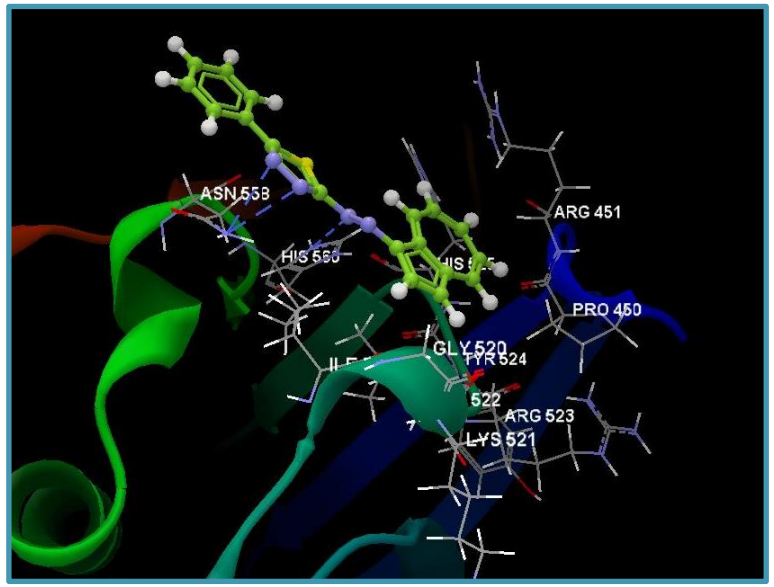
ASP449, ARG451, PRO450, TYR524, ARG523, LEU522, LYS521, GLY520, ALA508, LEU509, GLY510, THR507

Hydrogen bond:

N24(sp^2) – O (sp^3) ASP449: 3.247 Å

Score: 38.19, RMSD: 0.06

T2



Interacting group

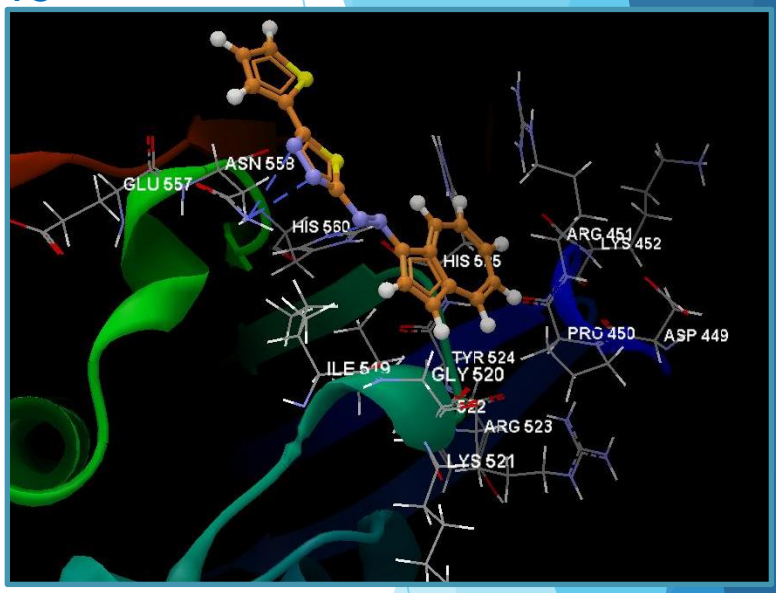
ASN558, HIS560, ILE519, HIS525, ARG451, PRO450, GLY520, TYR524, LEU522, ARG523, LYS521

Hydrogen bonds:

N18(sp^2) – N(sp^2) HIS560: 3.057 Å
N20(sp^2) - N(sp^2) ASN558: 3.126 Å
N24(sp^2) – N (sp^2) ASN558: 3.103 Å

Score:43.19, RMSD: 0.69

T3



Interacting group

GLU557, ASN558, HIS560, ILE519, HIS525, ARG451, LYS452, ASP449, PRO450, TYR524, GLY520, LEU522, ARG523, LYS521

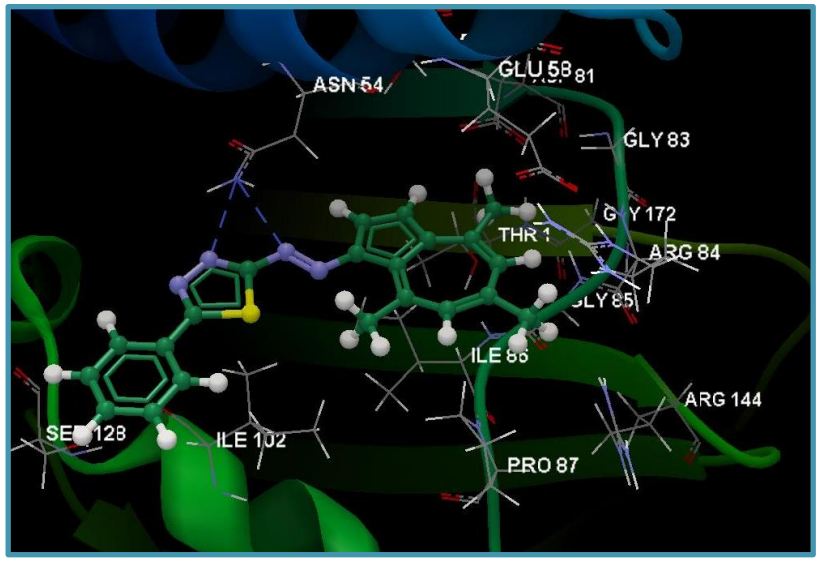
Hydrogen bonds:

N17(sp^2) – N (sp^2) HIS560: 3.187 Å
N20 (sp^2) – N(sp^2) ASN558: 2.914 Å
N24 (sp^2) – N (sp^2) ASN558: 3.135 Å

Score: 40.95, RMSD: 0.72

Docking results for 1,3,4 - thiadiazoles against 4P8O (Staphyloccocus aureus gyrase)

T1



Interacting group

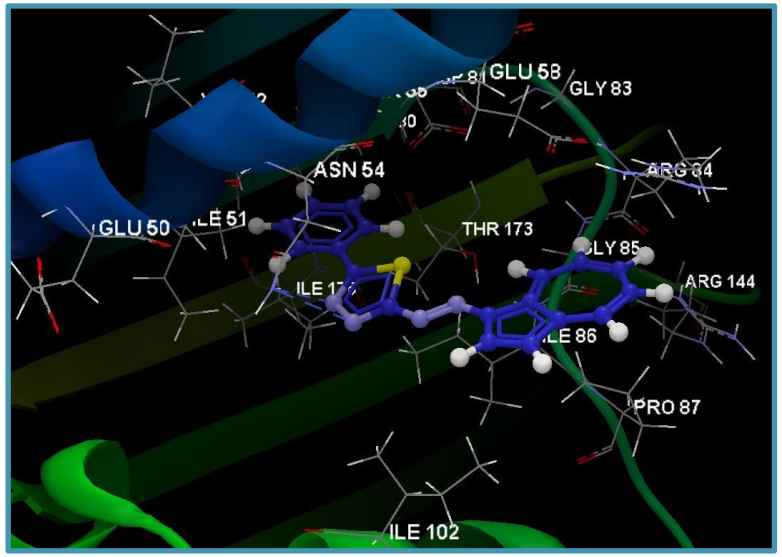
SER55, ASN54, GLU58, ASP81, GLY83, GLY172, ARG84, GLY85, ILE86, PRO87, ARG144, ILE102, SER128, THR173

Hydrogen bond:

N20(sp^2) – N(sp^2) ASN54: 3.062 Å
N18(sp^2) – N(sp^2) ASN54: 3.135 Å

Score: 58.08, RMSD: 0.10

T2



Interacting group

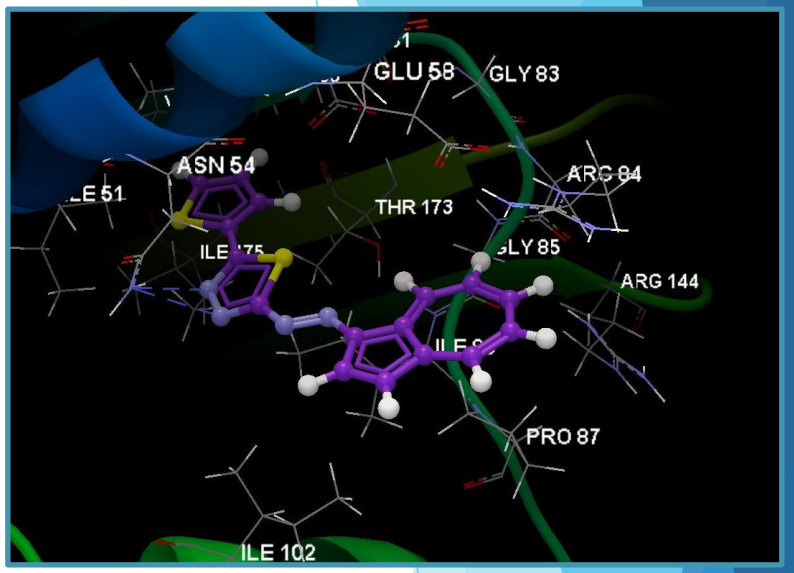
VAL52, VAL79, ASN54, ILE51, GLU50, SER55, THR80, ASP81, GLU88, GLY83, ARG84, THR173, VAL174, ILE175, GLY85, ARG144, ILE86, PRO87, ILE102

Hydrogen bonds:

N24(sp^2) – N(sp^2) ASN54: 2.790 Å
N20(sp^2) – N(sp^2) ASN54: 2.944 Å

Score: 56.49, RMSD: 0.18

T3



Interacting group

ASP81, GLU58, GLY83, THR80, SER55, VAL79, ASN54, ILE51, ILE175, VAL174, THR173, ARG84, GLY85, ARG144, ILE86, PRO87, ILE102

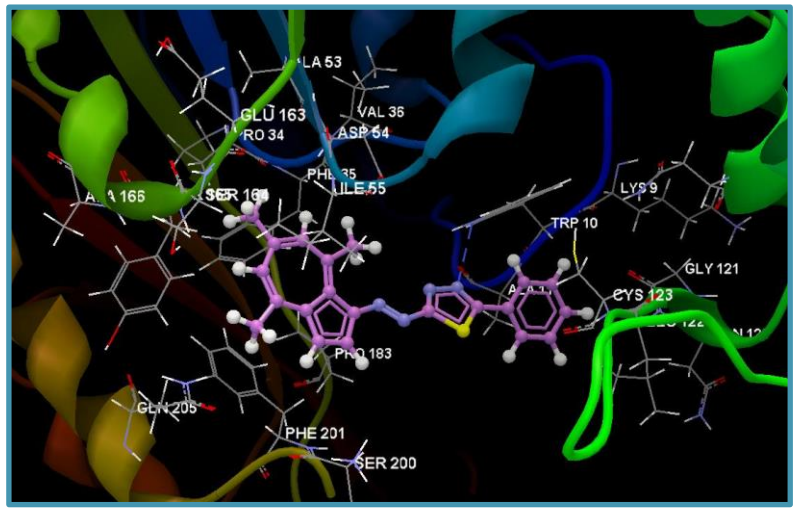
Hydrogen bonds:

N24(sp^2) – N(sp2) ASN54: 2.954 Å
N20(sp^2) – N(sp2) ASN54: 2.903 Å

Score: 53.61, RMSD: 0.19

Docking results for 1,3,4 - thiadiazoles against 4RTO (Escherichia coli DNA Adenine Methyltransferase)

T1



Interacting group

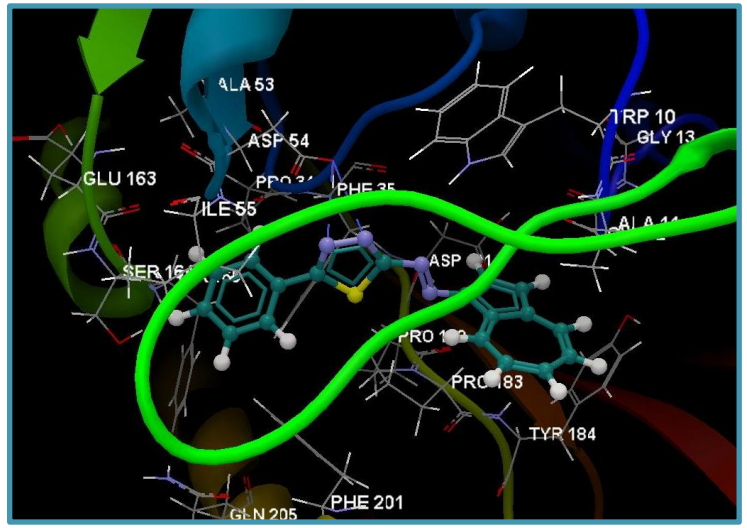
ALA53, VAL36, GLU163, PRO34, ASP54, PHE35, ILE55, SER164, TYR165, ALA166, GLN205, PHE201, SER200, PRO183, ASN120, LEU122, CYS123, ALA11, TRP10, LYS59, ASN115, GLY121

Hydrogen bond:

N24(sp^2) – N(sp^2) TRP10: 3.101 Å

Score: 72.21, RMSD: 0.07

T2



Interacting group

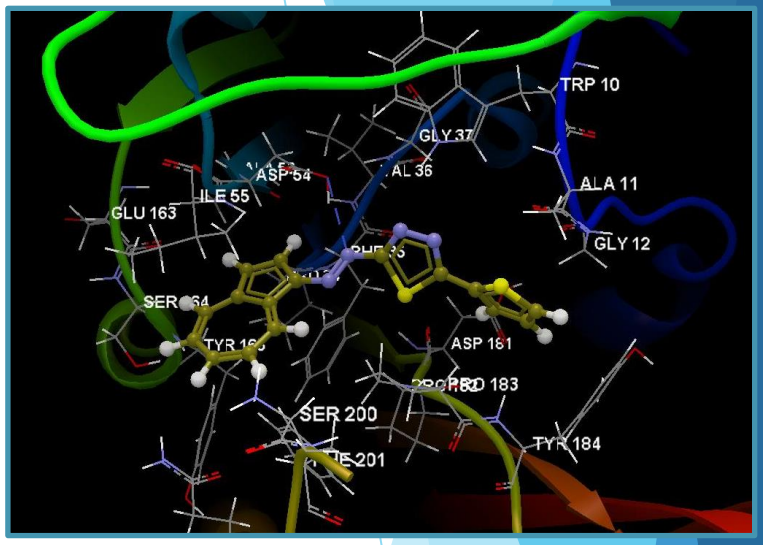
ALA53, ASP54, GLU163, PRO34, PHE35, ILE55, SER164, TYR165, GLN205, PHE201, TYR184, PRO183, PRO182, ASP181, ALA11, GLY12, TRP10, GLY13

Hydrogen bonds:

N24(sp^2) – O(sp^3) ASP54: 3.000 Å
N20(sp^2) – O(sp^3) ASP54: 2.982 Å

Score: 71.15, RMSD: 0.07

T3



Interacting group

TRP10, ALA11, GLY12, GLY37, VAL36, ASP54, ALA53, ILE55, GLU163, SER164, PHE35, PRO34, TYR165, ASP181, PRO183, PRO182, SER200, TYR184, PHE201, GLN205

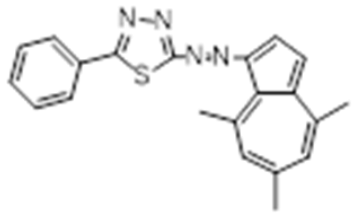
Hydrogen bond:

N18(sp^2) – O(sp^3) ASP54: 3.304 Å

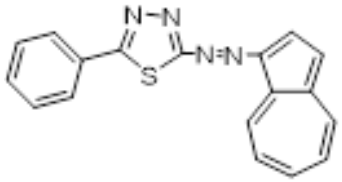
Score: 66.42, RMSD: 0.23

Assessment of oral bioavailability according Lipinski's rule of Five

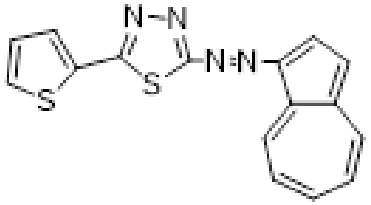
T1



T2



T3



Ligand/ protein/ strain	MW (g/mol)	HBD	HBA	LogP	Flexible bonds	Lipinski's violations
co-crystalized MPDA / 3M4I (M. tuberculosis)	118.17	2	2	0.27	2	0
co-crystalized 883 / 4P8O (S.aureus)	376.37	2	8	1.61	4	0
co-crystalized SFG / 4RTO (E. coli)	382.39	10	12	-3.22	7	2
M316 (T1)	358.46	0	4	5.24	3	1
M358 (T2)	326.46	0	4	5.49	3	1
L2548 (T3)	322.41	0	4	5.21	3	1

MW - molecular weight ; HBD - Hydrogen bond donor count; HBA - Hydrogen bond acceptor count; logP - water-octanol partition coefficient

Lipinski's rule of five [4]:
MW < 500 Da
LogP < 5
HBD < 5
HBA < 10

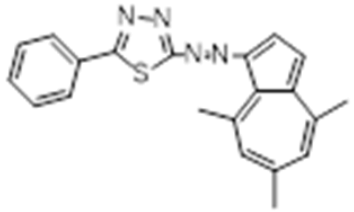
Conclusion:

Log P parameter is larger than 5 for all investigated 1,3,4 – thiadiazoles, these structures being highly lipophilic, with poor aqueous solubility. Values of LogP over 5 suggest poor absorption or permeation. Further optimization of such ligands containing together azulene and thiadiazole moieties, is required in order to increase the hydrophilicity and to favor hydrophilic interactions by means of NH/OH/N/O groups. Thus the propensity/probability to interact with proteins and the ability to become biologically active, can be successfully achieved.

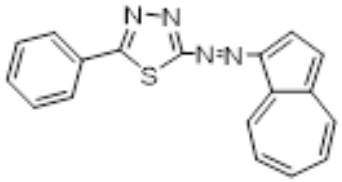
[4] C.A. Lipinski, *Lead-and drug-like compounds: the rule-of-five revolution*, Drug Discovery Today: Technologies 2004, 1(4), 337-341.

Conclusions and perspectives

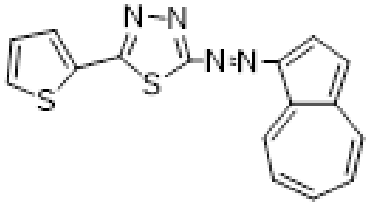
T1



T2



T3

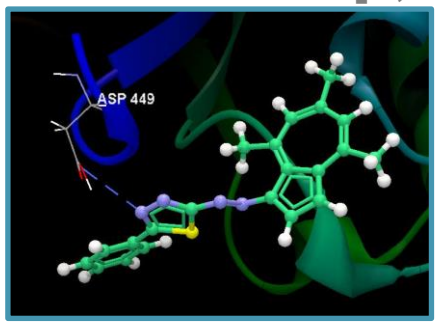


Docking conclusions:

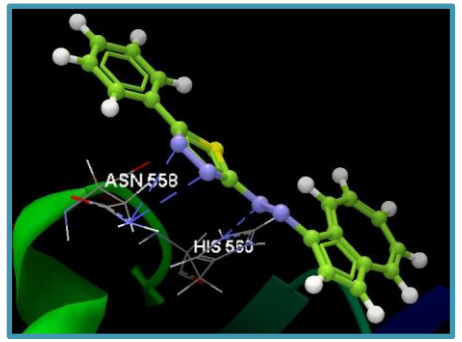
a) 3M4I (*Mycobacterium tuberculosis* DNA gyrase)

- All 1,3,4-thiadiazoles exhibit greater docking score than the natural ligand.
- T2 and T3 reveals similar scores, by forming 3 hydrogen bonds with the same amino acids residues, with N (sp^2) HIS560 and N (sp^2) ASN558, respectively, at the two nitrogen atoms of the thiadiazole aromatic ring, that is known as structural motif common in pharmacology [5] and one interaction by the diazo bond that link the thiadiazole with the azulene.
- The planar five-member thiadiazole ring acts as an acceptor in the H-bond formation, in the biological media. Some of thiadiazole based structures posses antimicrobial activities, e.g. oxazolidinone analogues possessing 1,3,4 – thiadiazole C-ring, designed as hybrids of linezolid [6, 7].

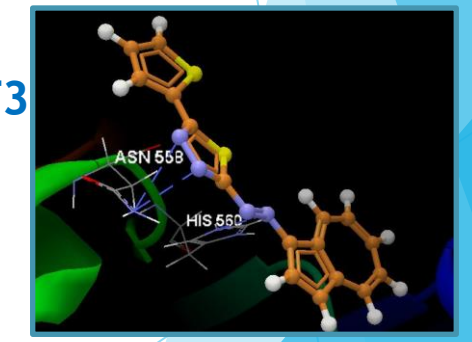
T1



T2



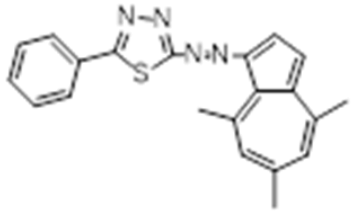
T3



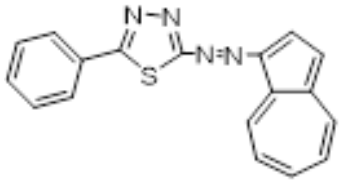
[5] Y. Hu, C.Y. Li, X.M. Wang, Y.H. Yang, H.L. Zhu, *1,3,4-Thiadiazole: Synthesis, Reactions, and Applications in Medicinal, Agricultural, and Materials Chemistry*, Chem. Rev. 2014, 114, 5572−5610.
[6] J. Matysiak, *Biological and Pharmacological Activities of 1,3,4-Thiadiazole Based Compounds*, Mini Reviews in Med. Chem. 15(9), 2012, 762-775.
[7] .M. Thomasco, R.C.Gadwood, E.A. Weaver, J.M. Ochoada, C.W. Ford, G.E. Zurenko, J.C. Hamel, D. Stapert, J.K. Moerman, R.D. Schaadt, B.H. Yagi, *The synthesis and antibacterial activity of 1,3,4-thiadiazole phenyl oxazolidinone analogues*, Bioorg. Med. Chem. Lett., 2003, 13, 4196-4196.

Conclusions and perspectives

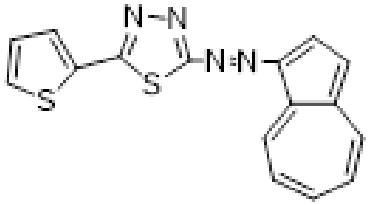
T1



T2



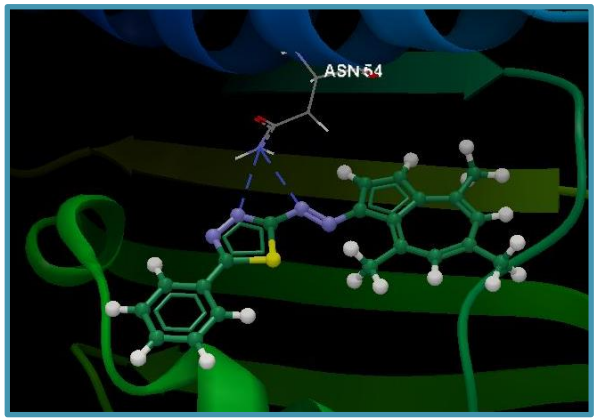
T3



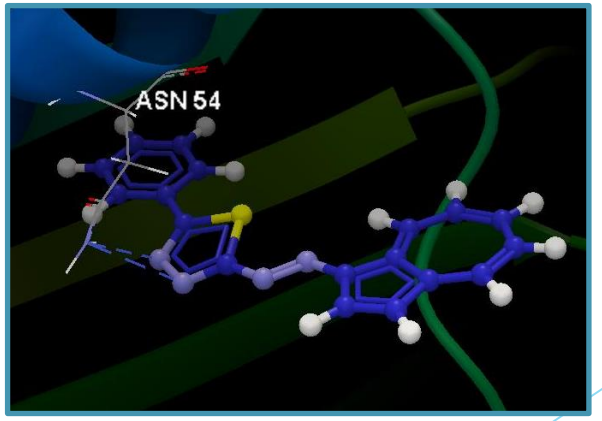
- **Docking conclusions:**

b). 4P8O (*S. aureus* gyrase)

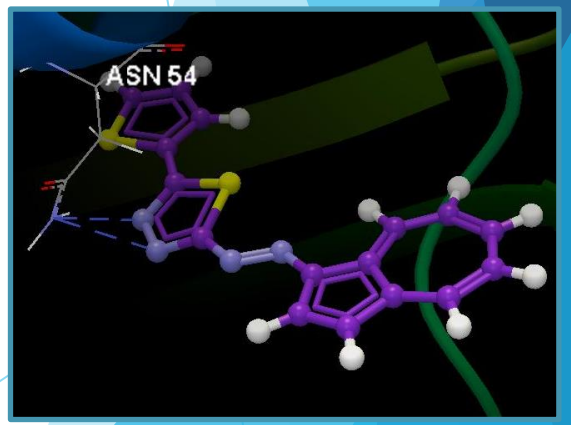
- All 1,3,4-thiadiazoles exhibit lower docking score than the natural ligand.
- ASN54 amino acid residue is involved by it's Nsp^2 in two H-bond forming with T1-T3 ligands. Although present in the interacting surrounding group of co-crystalized ligand and thiadizoles ligands, ASN54 don't interact by hydrogen bonding with the natural ligand. This compound reveals more interactions (4 H bonding and greater docking score). So, lower, maybe inefficient activity of investigated thiadiazoles against S. aureus gyrase is expected.



T1



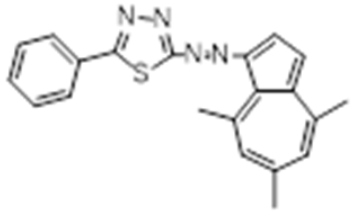
T2



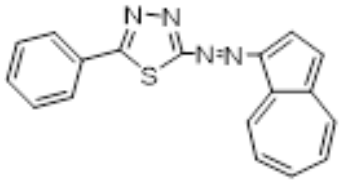
T3

Conclusions and perspectives

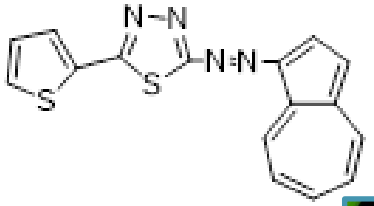
T1



T2



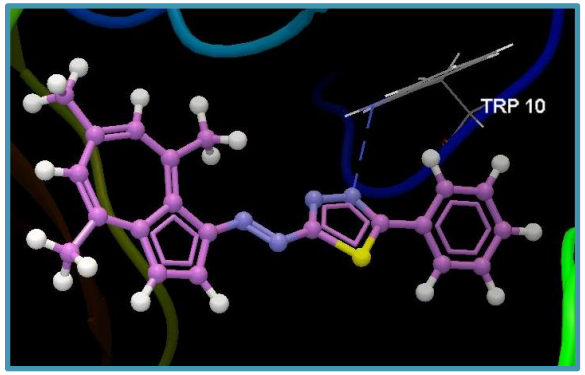
T3



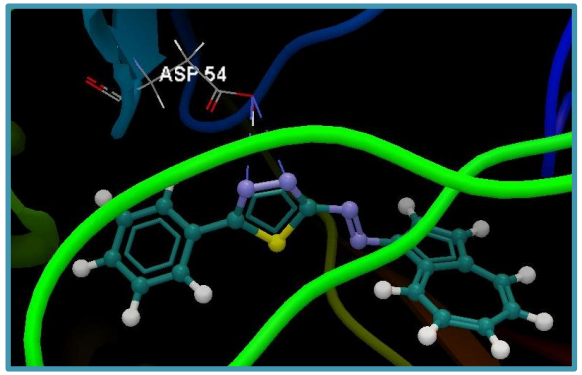
- **Docking conclusions:**

c). 4RTO (*Escherichia coli* DNA Adenine Methyltransferase)

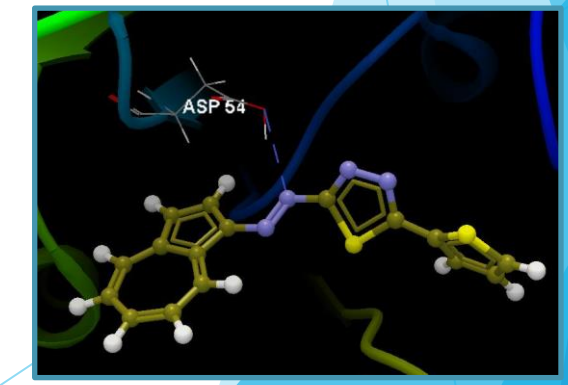
- Concerning T1 and T2, the thiadiazole ring is involved in H bonding with different amino acid residues (TRP10 and ASP54, respectively).T3 acts differently, by a nitrogen of the azo bond, that forms Hydrogen bond with ASP54.
- T1 and T2 reveals greater docking scores than the natural ligand. The obtained score for T3 is lower. The co-crystallized ligand presents interactions within the active binding site, whiles our investigated thiadiazoles are poorly interacting.
- Further analyses are required in order to establish certainly a possible inhibitory action against *E. coli* and other hybrid optimized structures containing thiadiazole and azulene scaffolds are considered.



T1



T2



T3