

# Absolute Binding Free Energy Calculations on a Riboswitch-like RNA-ligand complex from the Hepatitis C Virus Internal Ribosome Entry Site

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# Abstract

In this work we describe and leverage Qubit's advanced computational technics to compute the affinity of a class of small molecules for the HCV-IRES IIA subdomain. We have put in place a first tailored, state of the art approach, for absolute binding free energies (ABFE) of Riboswitch-like RNA using the dynamic lambda-ABF scheme combined with positional, orientational and conformational restraints. Calculations are done using AMOEBA, an advanced multipolar polarizable force field which accounts for quantum many-body effects, as well as polarization effects and the massively parallel molecular dynamics package Tinker-HP. Results show a solid reproduction of the binding mode, a prefect ranking with Ligands 12 and 13 as most potent and Ligand 2h as a non-binder, and a very good correlation with experiment ( $R^2 = 0.93$  - RMSE = 0.33 kcal/mol - MAE = 0.26 kcal/mol).

## Qubit's World leading Core technologies

Hybrid HPC-Quantum Computing  
Hyperion [1]

Next Generation Polarizable Force Fields –  
Quantum chemistry based  
AMOEBa [2,3]

Advanced Simulation Software  
Tinker-HP [4]

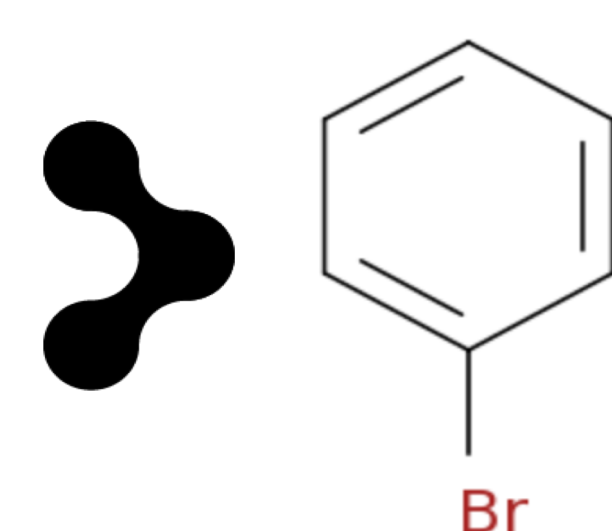
Advanced Simulation Algorithms  
Dynamic Lambda-ABF [5]

AI-ML assisted Medicinal Chemistry  
Hybrid Neural Network  
**FENNIX [6]**

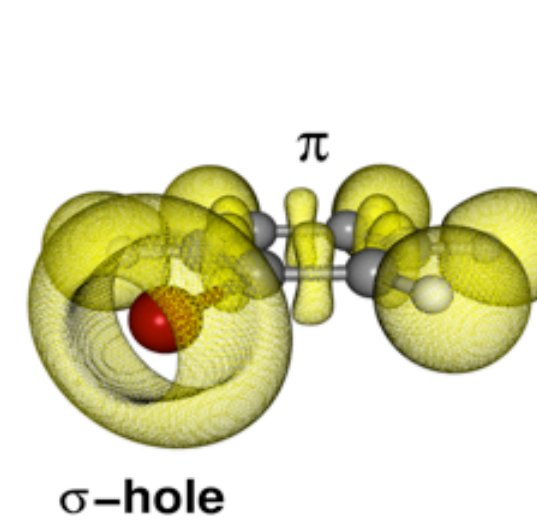
- AMOEBA polarizable force field uses atomic multipole moment through quadrupoles and induced dipole polarization to provide accurate electrostatic potentials.

- High-order atomic multipoles provide anisotropy critical to accurate description of hydrogen bonding.

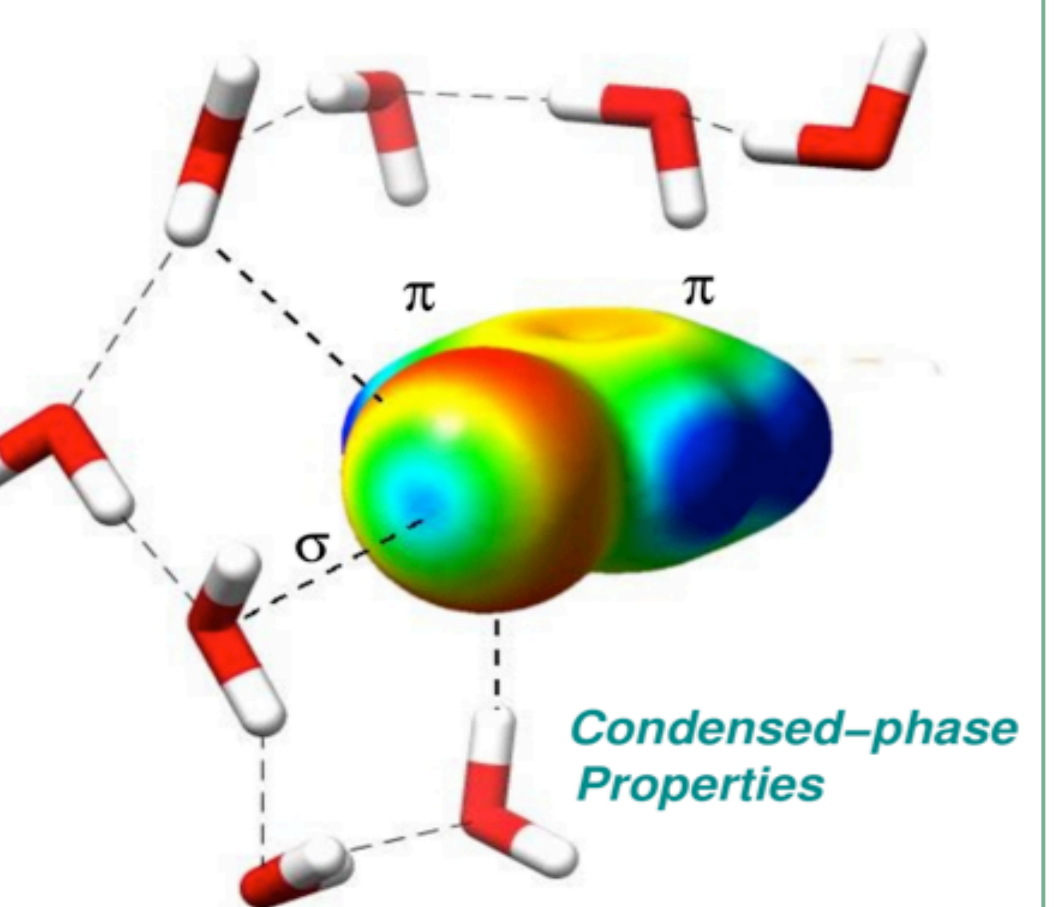
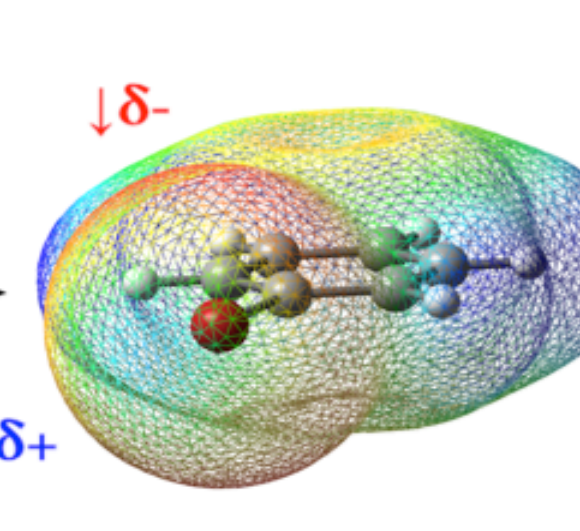
- Polarization effects are very important for modelling of simple ions, metals and highly charged species like nucleic acids and membrane head groups.



### Electronic Structure



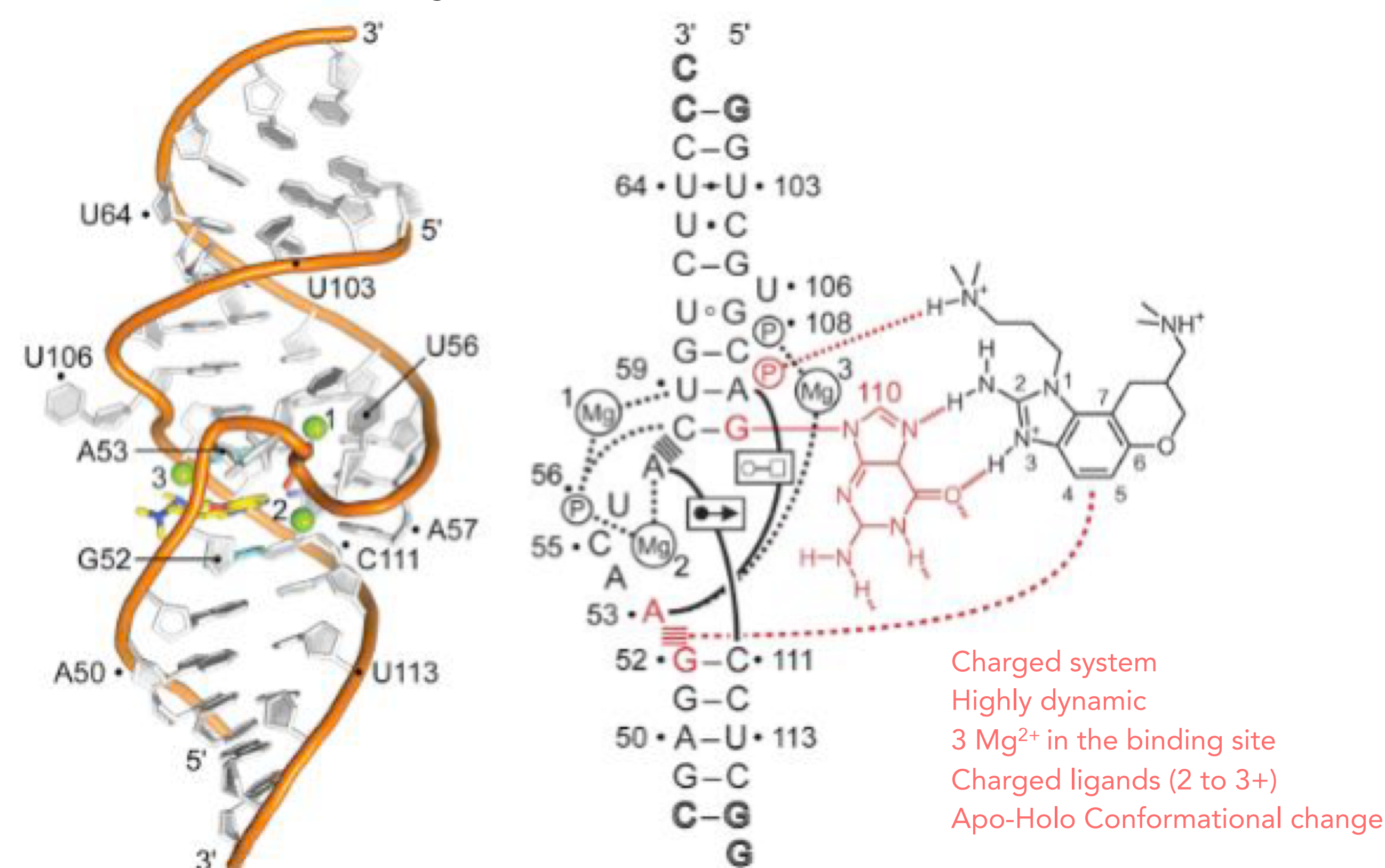
### Electrostatic Potential



- Inclusion of water polarization is mandatory to model the thermodynamics of desolvation.

## Application to Drug Discovery

## Riboswitch-like RNA-ligand complex from the Hepatitis C Virus Internal Ribosome Entry Site

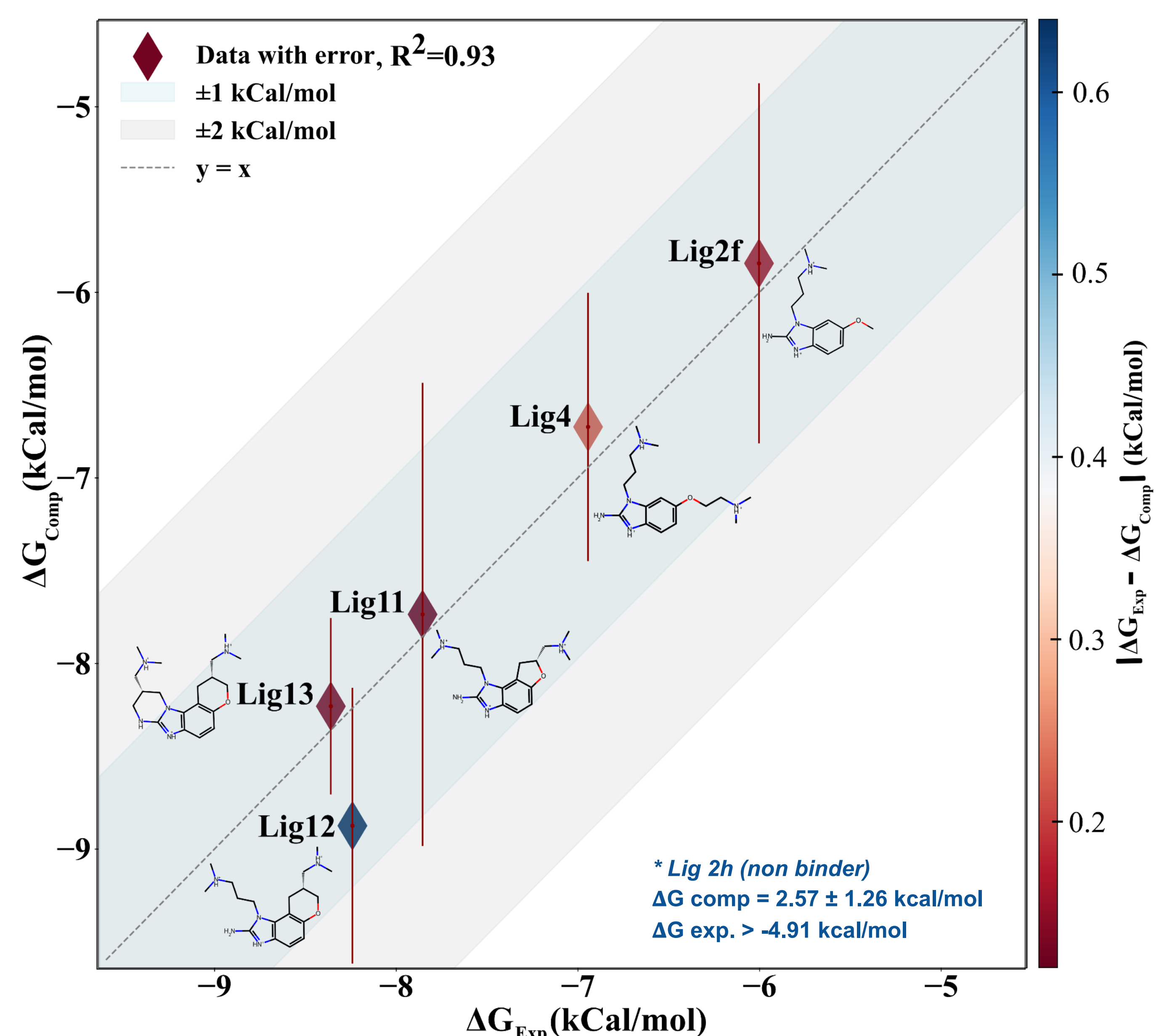


**First tailored and state of the art approach for absolute binding free energies of RNA-binding small molecules:**

- AMOEBA advanced polarizable force fields such encompassing distributed multipoles electrostatics.
- Tinker-HP, massively MPI parallel package dedicated to classical molecular dynamics (MD) and to multiscale simulations (CPU and GPU).
- Absolute binding free energies (ABFE) calculations overcome Relative Binding Free Energy's (RBFE) numerous limitations – ex. 5 RBFE steps compared to 1 ABFE are needed in order to go from Lig2f to Lig13.
- Dynamic Lambda-Adaptive Biasing Force scheme allowing orthogonal space sampling by random walk.
- Positional, orientational and conformational restraints during the alchemical path.

- Solid reproduction of the binding mode.
- Perfect ranking: Ligand 12 and 13 as most potent and Ligand 2h as non binder.
- Very good correlation with experiment:

$$R^2 = 0.986 - \text{RMSE} = 0.37 \text{ kcal/mol} - \text{MAE} = 0.35 \text{ kcal/mol}$$



**Experimental vs Computed  $\Delta G$  values.** Computed  $\Delta G$  and errors are the mean and standard error of the mean from three replicas for each ligand. The dark shaded region spans  $\pm 1$  kcal/mol; the lighter region spans  $\pm 2$  kcal/mol.

[1] C Fenjou, et al. (2023) arXiv preprint arXiv:2311.03347

[2] Yue Shi et al. (2013) JCTC pp. 4046–4063. doi: 10.1021/ct4003702

[3] Changsheng Zhang et al. (2018) JCTC, pp. 2084–2108. doi: 10.1021/acs.jctc.7b01169

[4] Olivier Adjoua, et al. (2021). *ICTC*, 17 (4), pp. 2034-2053

[5] Lagardere et al. (2023) [arXiv:2307.08006 \[physics.chem-ph\]](https://arxiv.org/abs/2307.08006)

[6] T Ple et al. (2023) *Chem. Sci.*, 14, 12554-12569