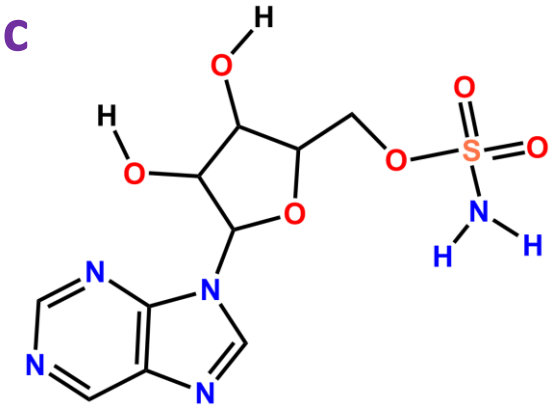
CIFHER

A Therapeutic Candidate for Pediatric Orphan Cancers



NSC 750854

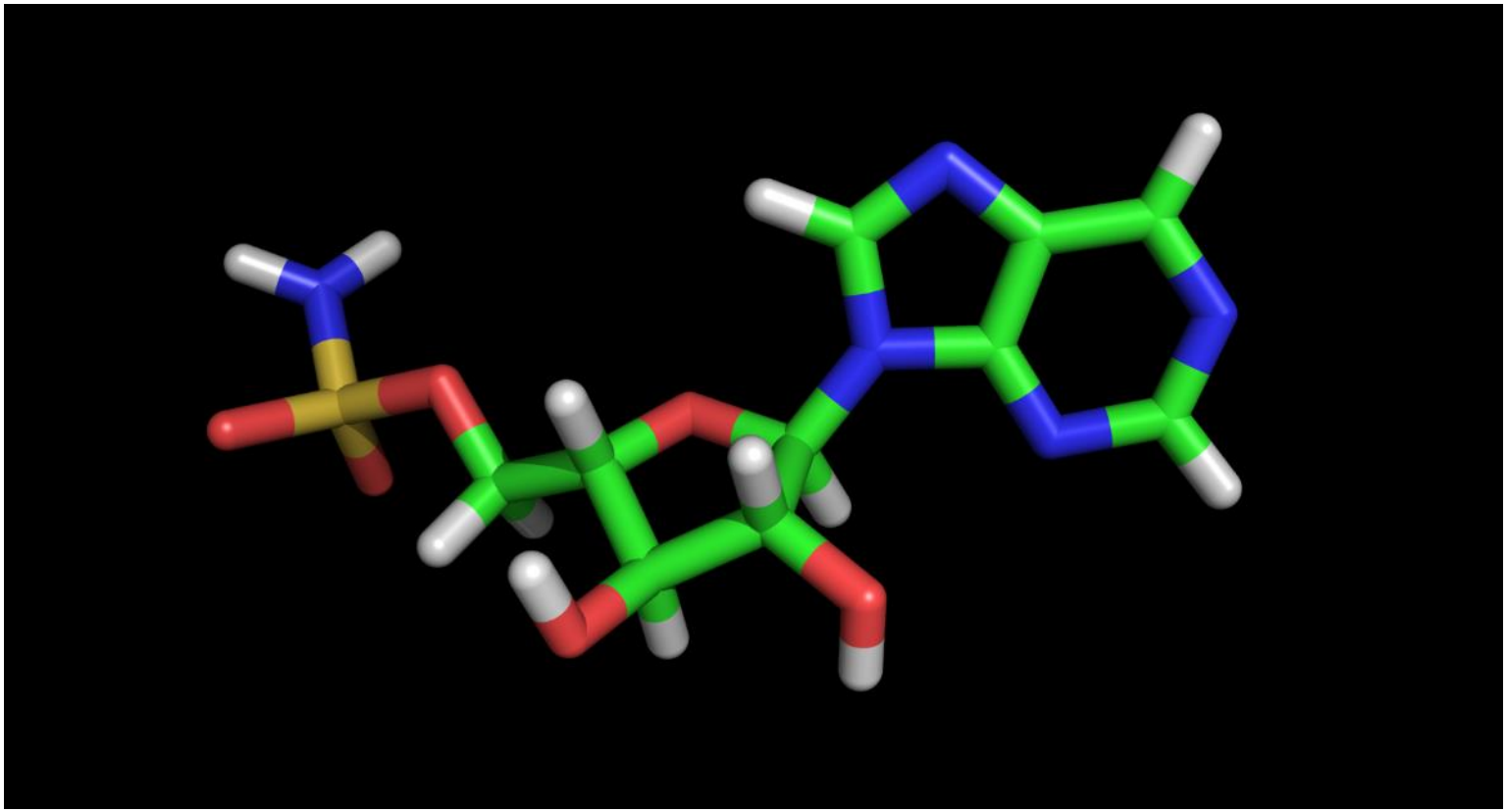
(3,4-dihydroxy-5-purin-9-yloxolan-2-yl)methyl sulfamate

CIFHER note: ***NCI developed 42 drugs before 2004. Since then, the drug development effort is practically non-existent. At the previous development rate, the tax-paying US Citizen is missing about 80 Investigational New Drugs that could be treating cancers. This Natural Product analog is one of them.***

CIFHER

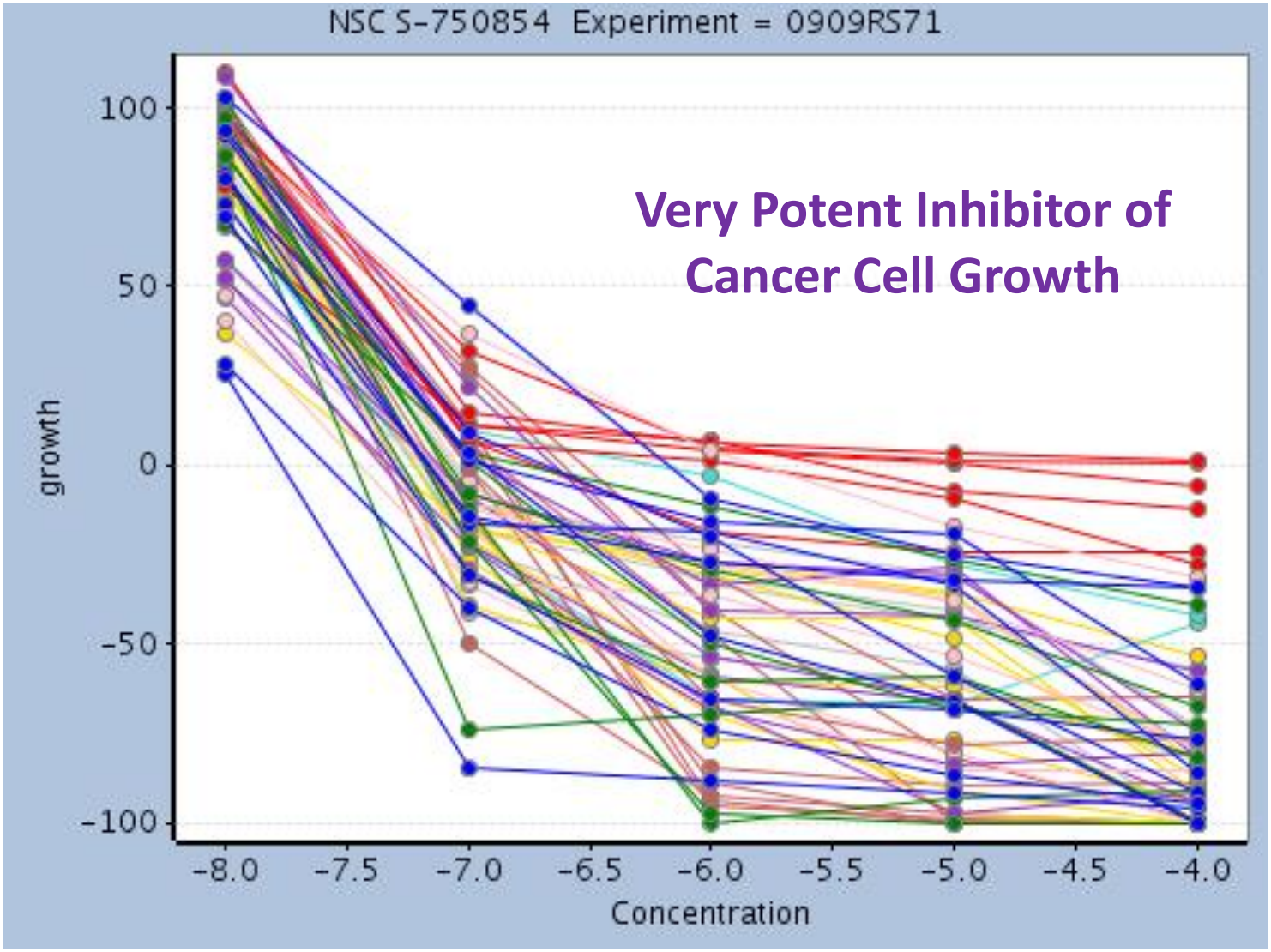
Computational Institute For Health and Environmental Research (formerly CDDG)

NSC 750854



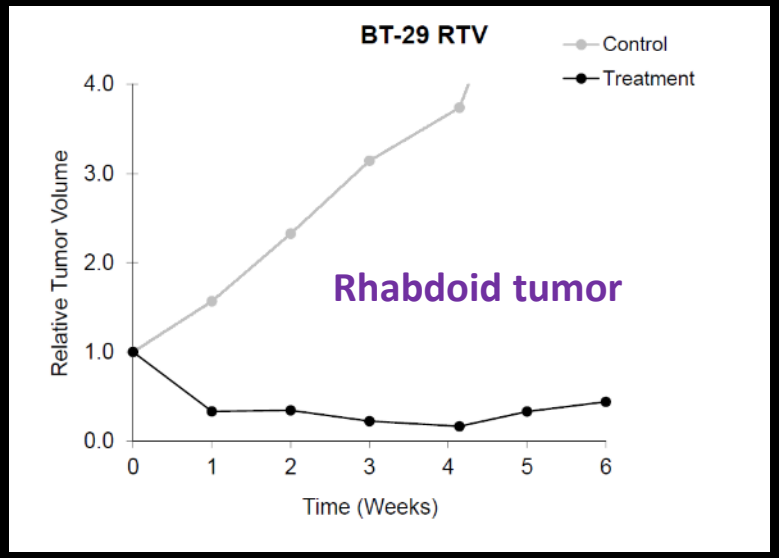
*This compound was discovered by **Dr. Jerry Collins** at the NCI*

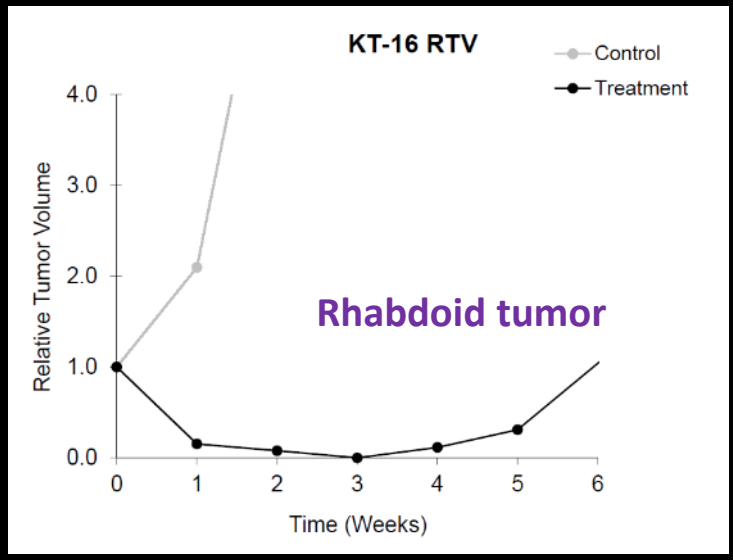
750854 NCI60 Results



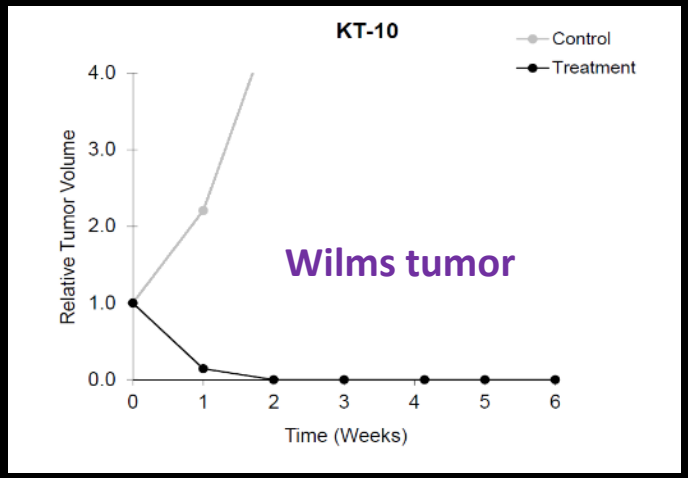
CIFHER

Selected Pediatric Xenografts





- Multiple pediatric xenografts respond to 750854
- 5 mg/kg IP QDx5, repeated at 2 wk
- Dose well-tolerated by mice
- **KT-10 *maintained complete remission***



CIFHER note: Even as a mechanistic toxin, the efficacy and potency of this compound can have a high therapeutic index in specific patient populations such as these pediatric cancers

Overview

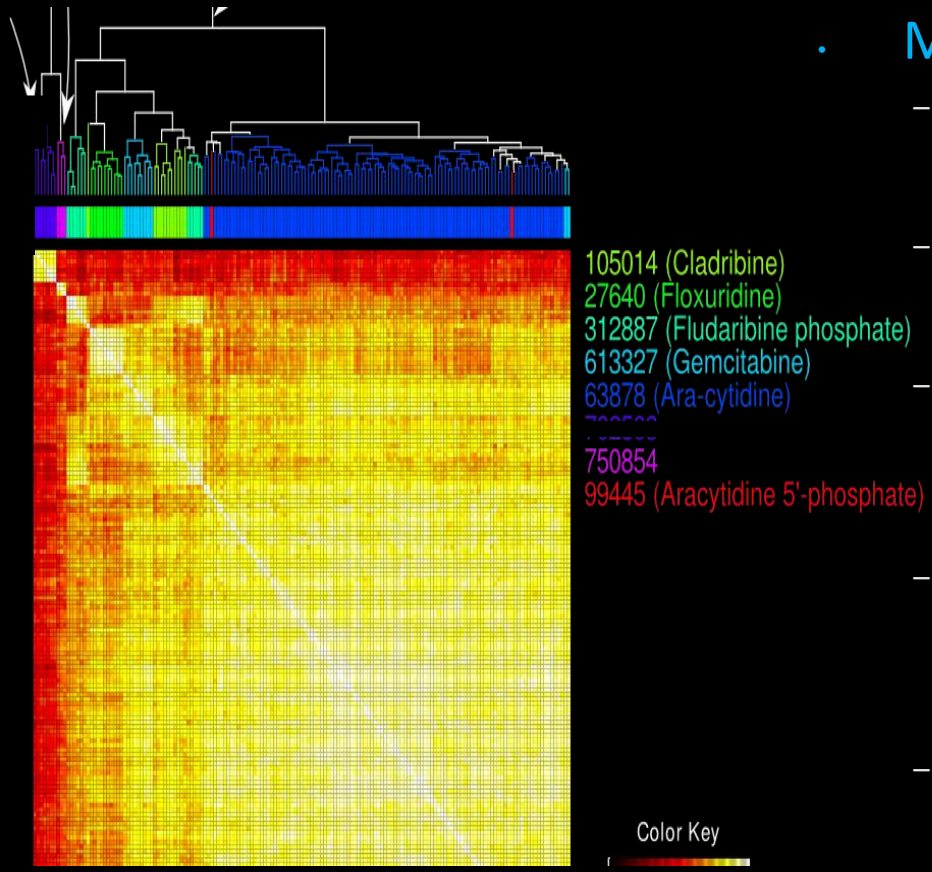
- 750854 is active in multiple xenografts models
- 750854 is distinct from approved nucleosides
- Mechanism is likely to be inhibition of amino-acyl tRNA synthetase, based on unpublished yeast data
- 750854 is active in 12 out of 20 Pediatric Cancer Efficacy Studies
- **Especially active in Pediatric Rhabdomyosarcoma, and other Pediatric Orphan Cancers**

CIFHER

Mechanistic Studies

CIFHER

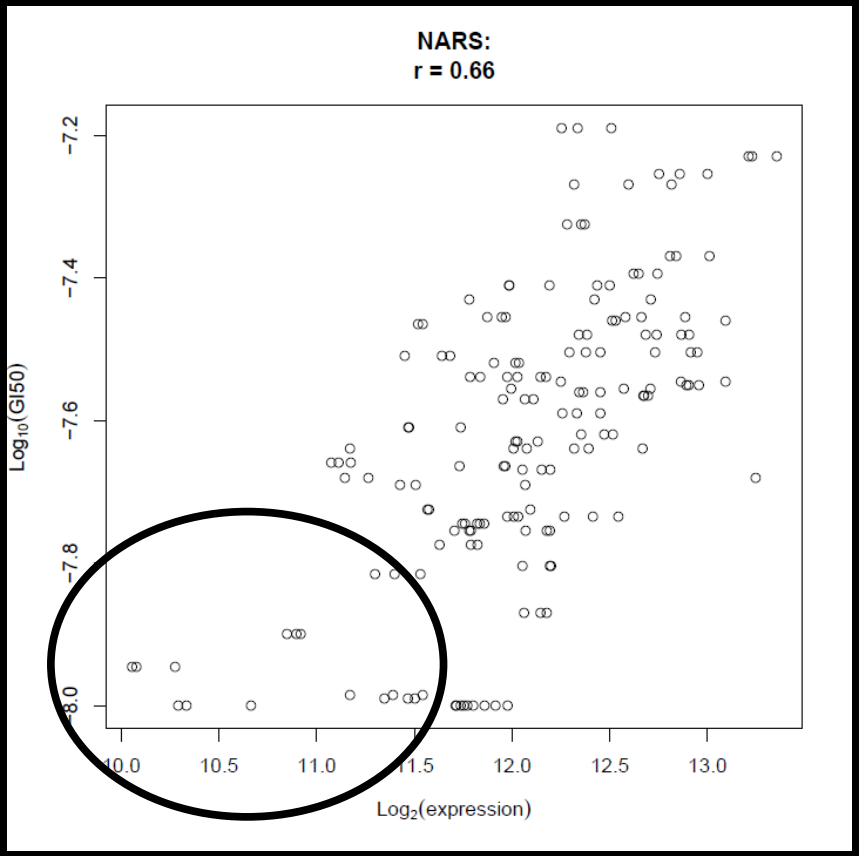
NSC 750854 is very distinct from other FDA-Approved Nucleoside Agents by GI_{50} Matrix COMPARE



- MATRIX COMPARE
  - Pairwise complete Pearson's product moment correlation
  - Each experiment yields ~60 GI50 values (one for each cell line)
  - Correlation of GI50 values for each experiment versus every other experiment is determined
  - Self-consistent experiments were retained (mean self:self correlation ≥ 0.6)
  - Vectors of correlation values were then hierarchically clustered

CIFHER

Susceptibility Correlates with mRNA Expression

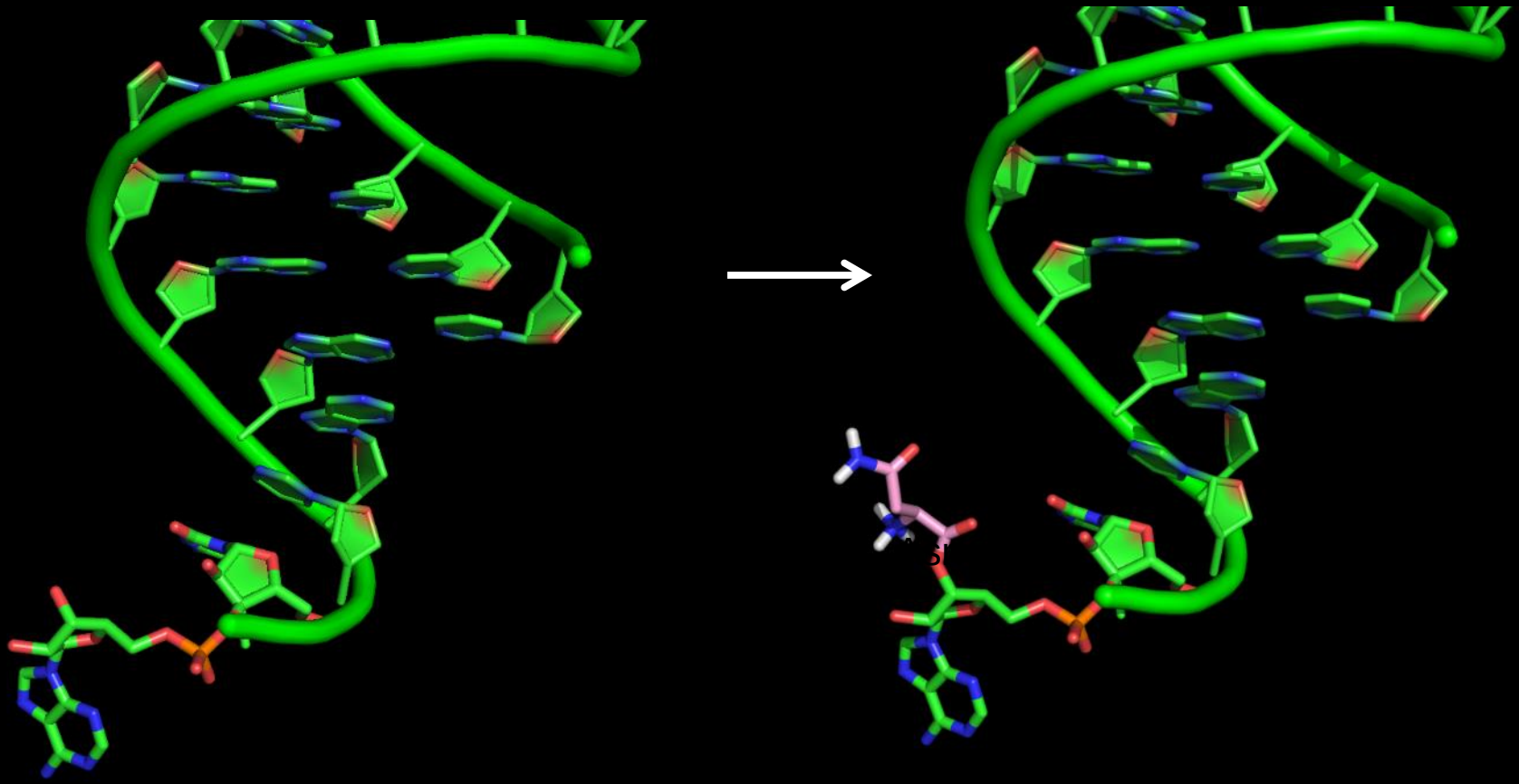


(NARS) mRNA expression is correlated with NCI-60 GI_{50}: r = 0.66

- Low NARS expression is associated with low GI_{50} (higher susceptibility)

CIFHER

aaRS Enzymes Charge tRNA

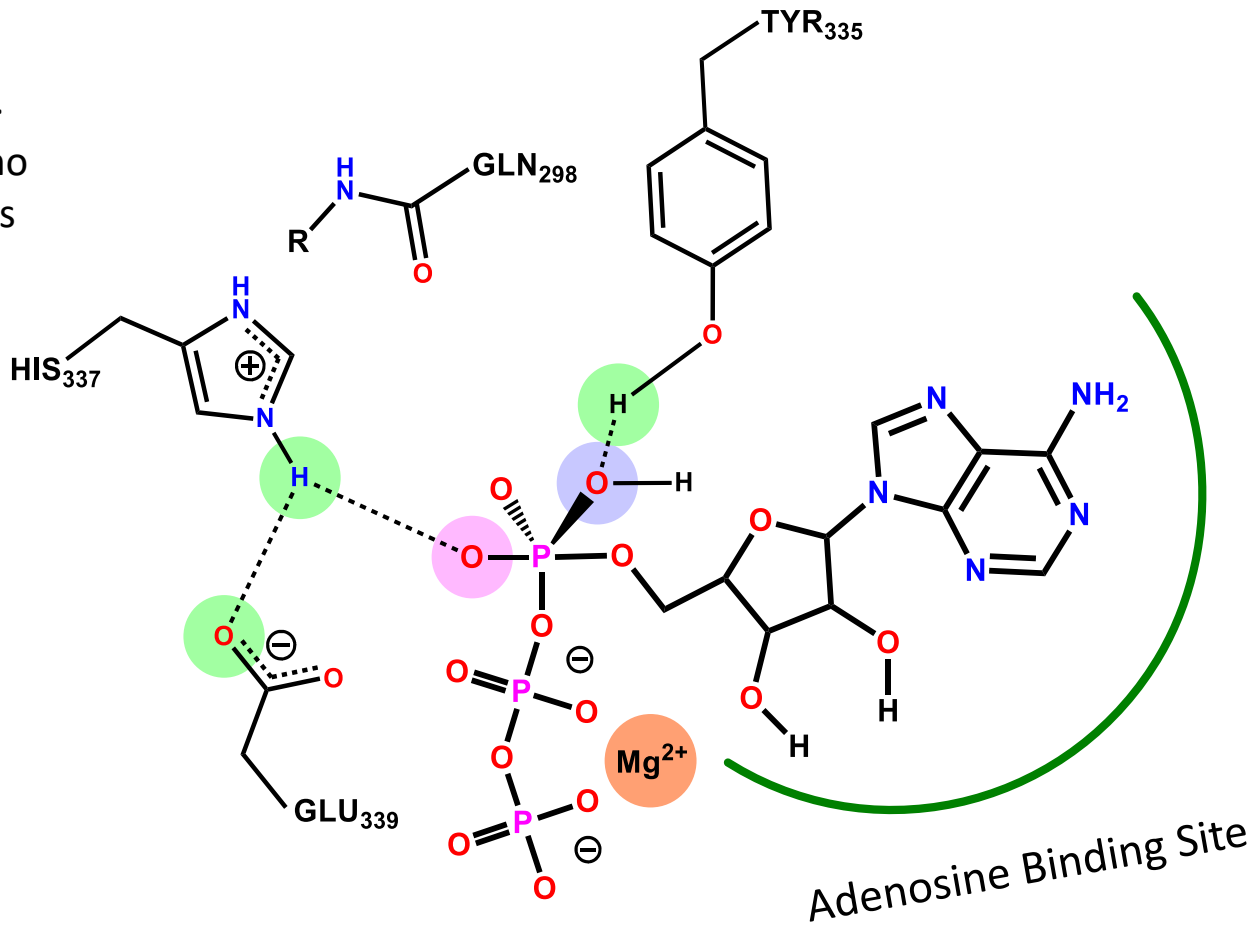


Binding Mode of 750854 in NARS

- Energy-refined all-atom protein model generated for human NARS based on archaebacterial crystal structure
- 750854 docked at AMP site of NARS

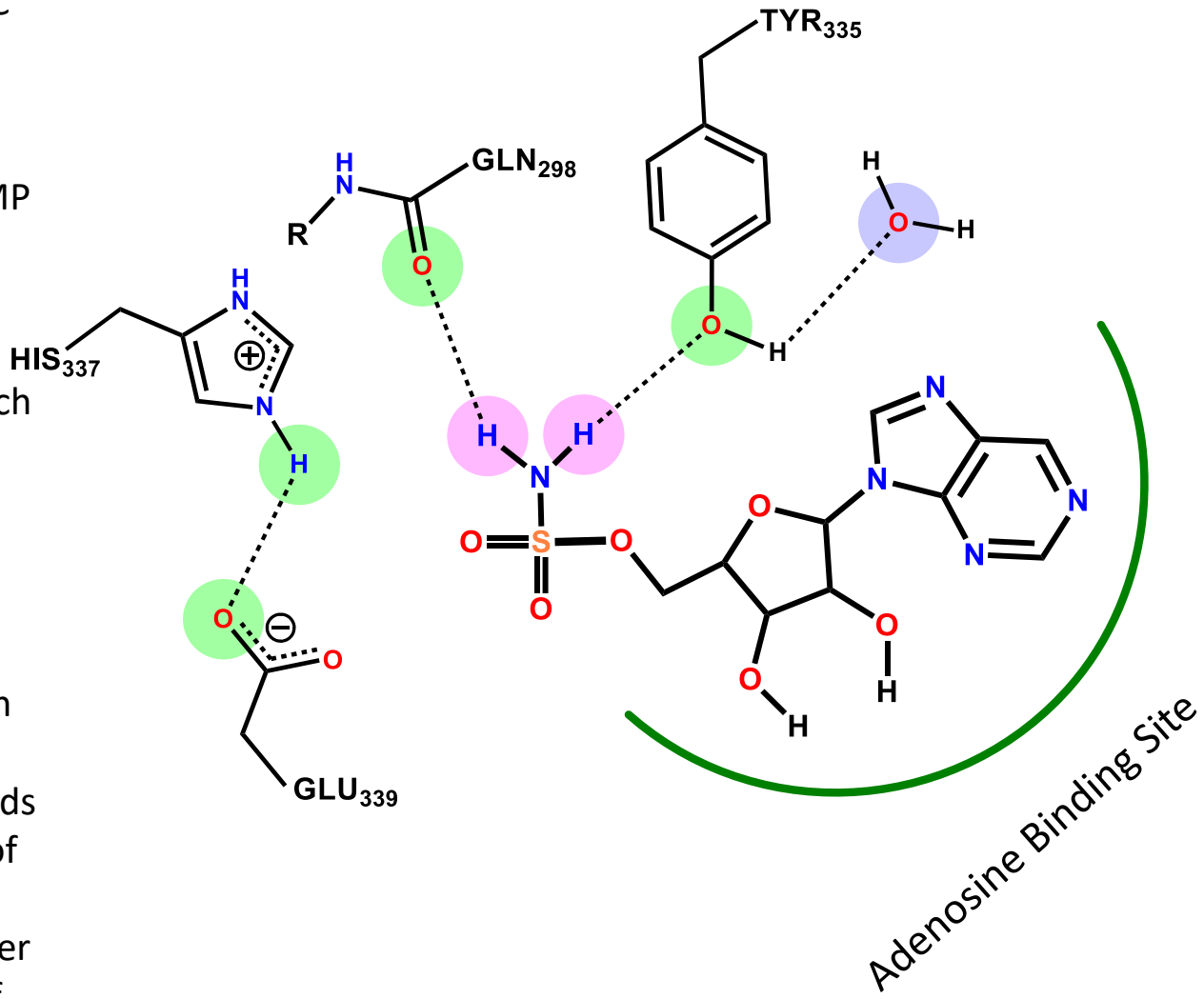
Native Binding Mode: ATP - Proton Relay Network

- ATP binds aaRS's and the first PO_4 is charged for nucleophilic attack via a proton relay network.
- A water serves as the ambident nucleophile.
- Subsequently, an amino acid: AMP conjugate is formed.



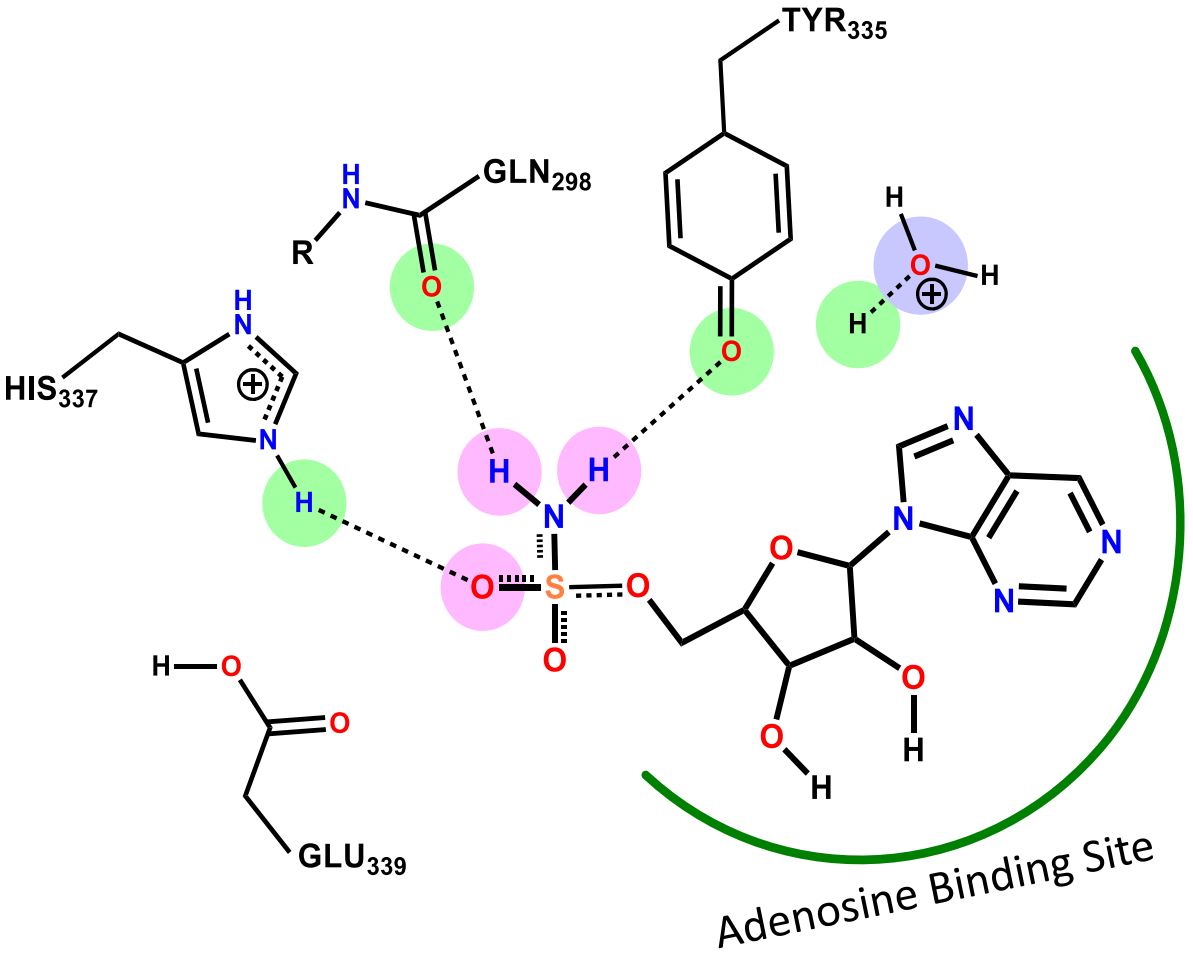
NSC 750854: Transition State Mimic – Stage I

- Upon binding, the sulfonamide moiety of NSC 750854 mimics the phosphate of AMP, while the purine and sugar components mimic the AMP adenosine.
- The sulfonamide proceeds to 'trap' the enzyme's proton relay network (which normally facilitates amino acid: AMP conjugation).
- Stage I: **a)** sulfonamide nitrogen proton forms a **unique** H-bond with the back-bone carbonyl oxygen of GLN_{298}, **b)** a second sulfonamide proton H-bonds with the hydroxyl oxygen of TYR_{335}, **c)** an H-bond forms between an ambident water and the hydroxyl proton of TYR_{335}, and **d)** GLU_{339}, exchanges a proton with HIS_{337}.



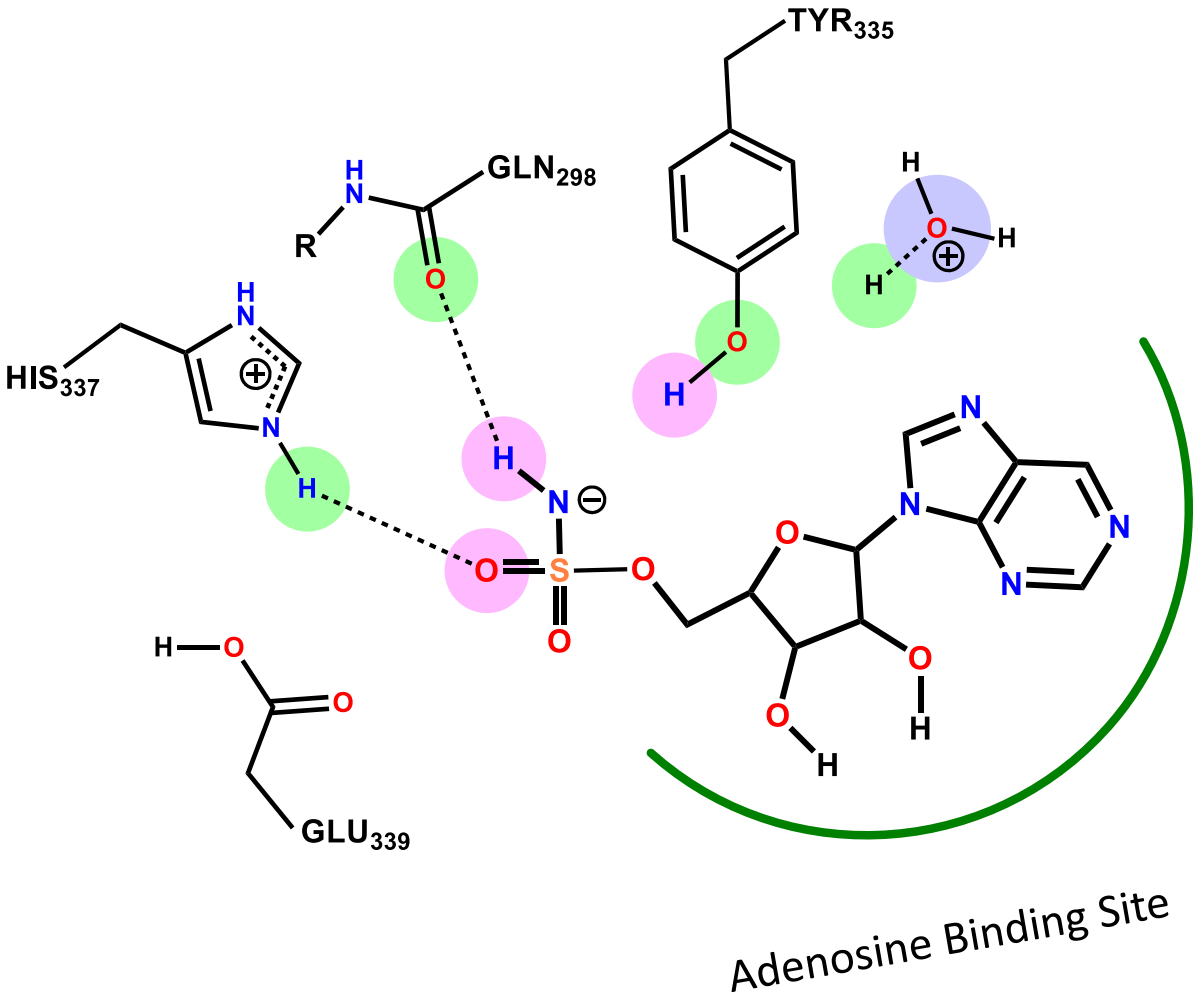
Transition State Mimic – Stage II

- The unique H-bond between one of the sulfonamide nitrogen protons and the backbone carbonyl oxygen of GLN_{298} is maintained during the entire mechanism.
- Stage II: **a)** the charged HIS_{337} H-bonds with one of the oxygens of the sulfonamide, this begins to further delocalize the sulfonamide π electon network, **b)** the second proton of the sulfonamide nitrogen H-bonds with oxygen of tautomerized TYR_{335}, which has lost its proton to an ambident water, and **c)** GLU_{339} is no longer ionized.



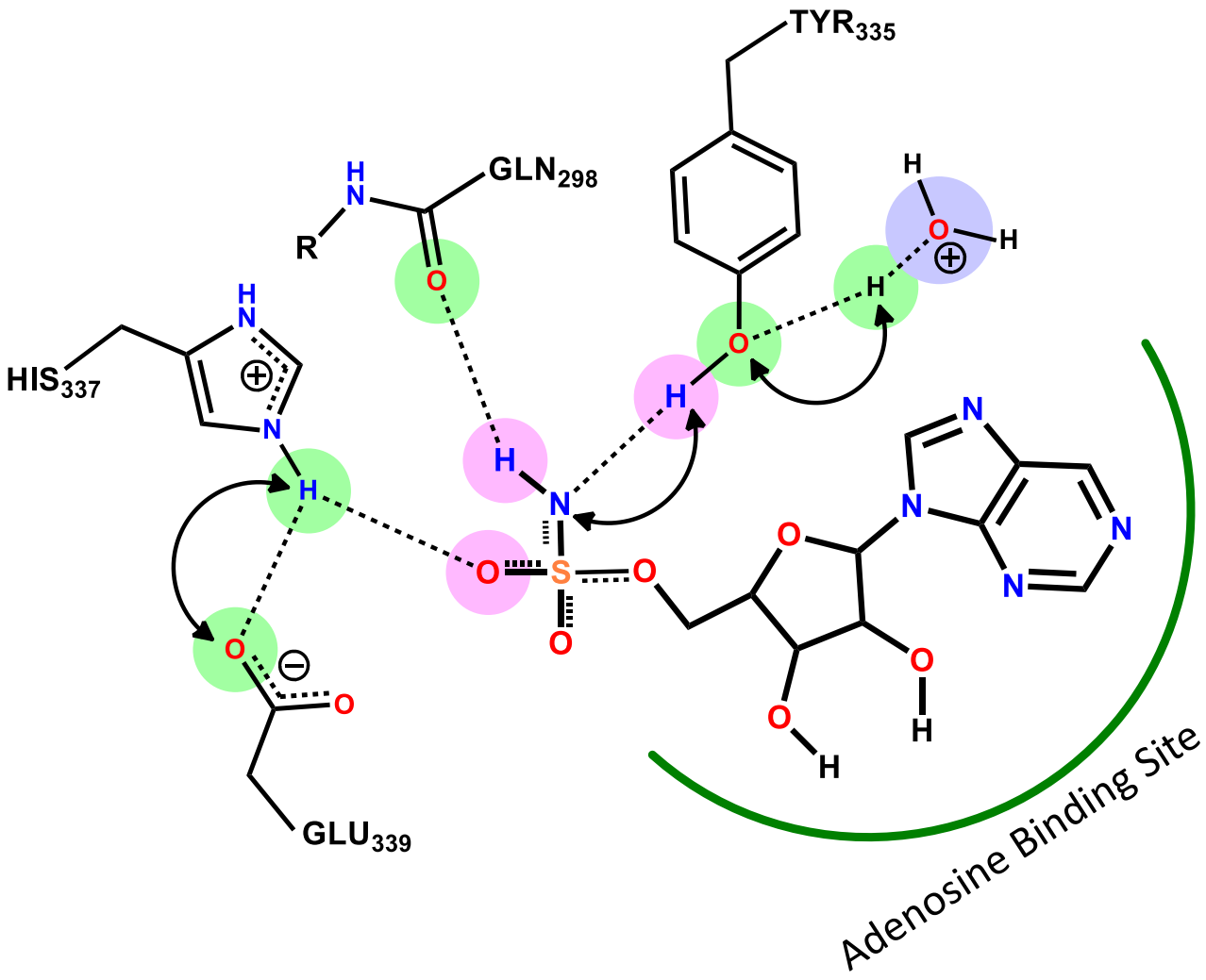
Transition State Mimic – Stage III

- Stage III: **a)** the acidic sulfonamide transfers a nitrogen proton to the oxygen of TYR_{335}, restoring the more stable tautomer, and **b)** the sulfonamide nitrogen becomes a fully ionized atom.



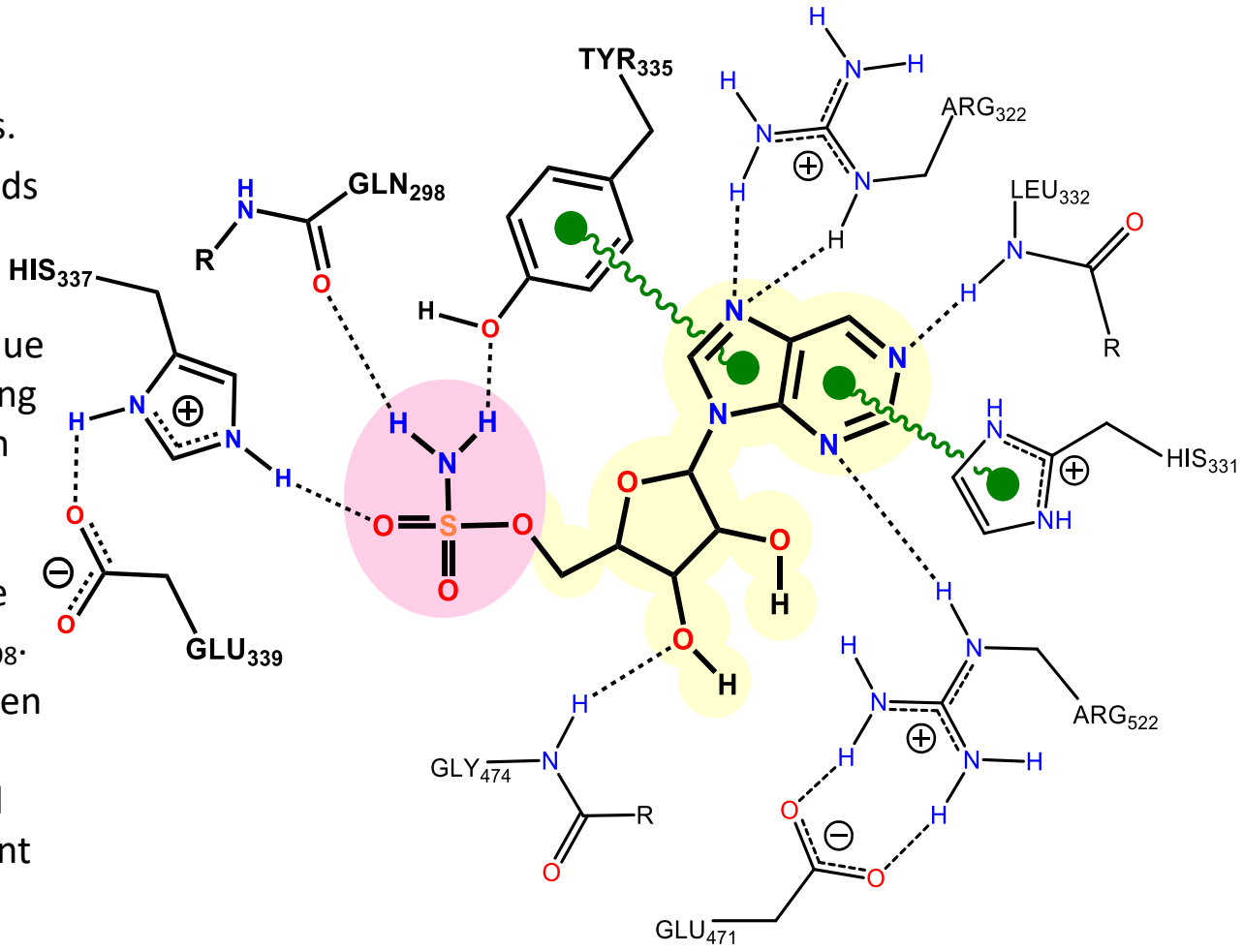
Culmination: Proton Relay Network Trapped

- Stages I – III are reversible. This results in a 'trapped' proton relay network.
- The continual shuffling back-and-forth of the proton relay network is hypothesized to contribute to the longevity of NSC 750854 binding site occupancy.



Full View: All Binding Site Contacts

- NSC 750854 possesses excellent chemical complementarity for the AMP binding site of NARs.
- Contacts include 7 H-bonds and 2 π stacking interactions.
- The binding mode is unique in that NSC 750854 binding results in a new hydrogen bond between the compound's sulfonamide moiety and the backbone carbonyl oxygen of GLN_{298}.
- The GLN_{298} carbonyl oxygen is engages in a water-mediated hydrogen bond with an unrelated segment of tRNA during normal biological function.
- Two other saltbridges: D463-K445, E279-R322, may help stabilize the pocket.



NSC 750854 Binding Mode to NARs