

La familia PriA

PriA es una familia de enzimas de Actinobacteria homóloga a la familia HisA en Enterobacteria. Según las definiciones de este trabajo PriA es una familia promiscua. Se han caracterizado experimentalmente varios miembros de PriA con la capacidad de catalizar tanto la reacción correspondiente a HisA como la de TrpF. Es decir PriA participa a la vez en las rutas de síntesis de Histidina y Triptofano, al menos en varias Actinobacterias. Algunos de los primeros miembros caracterizados como promiscuos son *Streptomyces coelicolor* y XXXX. Dentro de la ruta de histidina HisA convierte ProFAR en PRFAR. Además de la isomerización de PROFAR también convierte PRA en CdRP actuando análogamente a la función TrpF en la ruta del triptófano. La mayoría de las actinobacterias han perdido el gen *trpF* en la ruta del triptofano, por lo que se cree que la promiscuidad de proFAR está extendida en un gran subconjunto de Actinobacteria.

Además, en Actinobacteria PriA ha mostrado un gradiente funcional. Esta variación divide esta familia en varias subfamilias según su funcionalidad. Por ejemplo, entre las subfamilias de PriA se encuentra PriB con presencia en el género *Streptomyces*. Esta familia muestra poca actividad *trpF* y un gen *trpF* fuera de contexto. Otra subfamilia es subHisA en *Corynebacteria* y *Actinomycetes* que ha perdido actividad *trpF*, y finalmente hay subTrpF en *Actinomycetes* que ha perdido su actividad de HisA.

En este capítulo se hace una exploración de PriA utilizando EvoMining y CORASON en diversos linajes genómicos. Como resultado se encuentran variantes en el número de copias según el linaje. En Actinobacteria PriA es promiscua a pesar de no tener copias extra con marcas de reclutamiento al metabolismo especializado. Otro resultado es el descubrimiento de que al analizar datos de cinéticas enzimáticas de PriA, no existe una trayectoria Darwiniana para ambos susstratos que lleve a la adquisición de promiscuidad. Es decir que al menos en este ejemplo, las mutaciones puntuales que llevan a una enzima monofuncional en la ruta para adquirir promiscuidad nunca incrementan la capacidad catalítica sobre ambas reacciones. Finalmente
||||[$M^{-1}s^{-1}$] ||[μM]|| [$M^{-1}s^{-1}$] ||[μM]|||

Tabla Datos Cinéticos de subfamilias de PriA

| Fuente | | HisA | TrpF | K_{cat}^{ProFAR} | K_m^{ProFAR} | HisA | K_{cat}^{PRA} | K_m^{PRA} | TrpF | |
|-----------------------------------|---------|----------------|----------------|--------------------|----------------|-----------------------|--------------------|-------------|-----------------------|--|
| | Familia | <i>in vivo</i> | <i>in vivo</i> | [$M^{-1}s^{-1}$] | [μM] | $\frac{K_{cat}}{K_m}$ | [$M^{-1}s^{-1}$] | [μM] | $\frac{K_{cat}}{K_m}$ | Referencia |
| <i>Escherichia coli</i> | HisA | - | - | 1.6 | 4.9 | 3.1 | - | - | 0 | Henn-Sax et al 2002 |
| <i>Escherichia coli</i> | TrpF | - | - | - | - | 0 | 12.2 | 34.5 | 2.82 | Sternner et al 1996 |
| <i>Mycobacterium smegmatis</i> | PriA | * | * | 2.6 ± 0.5 | 0.85 ± 0.04 | 0.33 | 7.9 ± 2.4 | 3.1 ± 0.43 | 0.39 | Verduzco [@verduzco-castro_co-occurrence_2016] |
| <i>Mycobacterium tuberculosis</i> | PriA | - | - | 19 | 0.23 | 12 | 21 | 3.6 | 0.17 | Due et al. (2011) |
| <i>Streptomyces globisporus</i> | PriA | * | * | 4.2 ± 0.8 | 0.74 ± 0.03 | 0.18 | 11 ± 1.0 | 3.8 ± 0.2 | 0.34 | Verduzco [@verduzco-castro_co-occurrence_2016] |
| <i>Streptomyces coelicolor</i> | PriA | - | - | 3.6 ± 0.7 | 1.3 ± 0.2 | 0.4 | 5.0 ± 0.08 | 3.4 ± 0.09 | 0.7 | Noda [@noda-garcia_identification_2010] |
| <i>Streptomyces coelicolor</i> | PriA | - | - | 3.6 ± 0.7 | 1.3 ± 0.2 | 0.4 | 5.0 ± 0.08 | 3.4 ± 0.09 | 0.7 | Noda [@noda-garcia_identification_2010] |
| <i>Streptomyces ipomoeae</i> | PriB | * | * | 3.8 ± 0.2 | 0.82 ± 0.02 | 0.21 | 60.8 ± 1.1 | 8.25 ± 0.4 | 0.14 | Verduzco [@verduzco-castro_co-occurrence_2016] |

| Fuente | Familia | HisA <i>in vivo</i> | TrpF <i>in vivo</i> | K_{cat}^{ProFAR} [M ⁻¹ s ⁻¹] | K_m^{ProFAR} [μM] | $\frac{K_{cat}}{K_m}$ | K_{cat}^{PRA} [M ⁻¹ s ⁻¹] | K_m^{PRA} [μM] | TrpF $\frac{K_{cat}}{K_m}$ | Referencia |
|---|---------|------------------------|------------------------|--|------------------------|-----------------------|---|---------------------|-------------------------------|---|
| <i>Streptomyces</i> Mg1 | PriB | * | * | 13.2 ± 3.4 | 0.92 ± 0.19 | 69 | 129.6 ± 34 | 0.29 ± 0.04 | 0.0022 | Verduzco [@verduzco- castro_co- occurrence_2016] |
| <i>Streptomyces</i> sp. C | PriB | * | * | 11.4 ± 3.4 | 2.53 ± 0.74 | 0.22 | 149. 9 ± 29 | 1.4 ± 0.12 | 9 | Verduzco [@verduzco- castro_co- occurrence_2016] |
| <i>Streptomyces</i> <i>sviceus</i> | PriB | * | * | 3.9 ± 0.89 | 0.69 ± 0.04 | 0.18 | 24.5 ± 4.0 | 1.6 ± 0.29 | 67 | Verduzco [@verduzco- castro_co- occurrence_2016] |
| <i>Corynebacterium</i> sub HisA- <i>diphtheriae</i> | | - | | 4.4 ± 0.5 | 2.6 ± 0.3 | 0.59 | | | 0 | Noda [@noda- garcia_evolution_2013] |
| <i>Corynebacterium</i> PriA <i>jeikeium</i> | | - | | 2.3 ± 0.2 | 0.9 ± 0.08 | 0.39 | 5.1 ± 1.0 | 1.6 ± 0.16 | 0.31 | Noda [@noda- garcia_evolution_2013] |
| <i>Corynebacterium</i> sub HisA- <i>striatum</i> | | - | | 6.9 ± 0.7 | 2.1 ± 0.5 | 0.3 | | | 0 | Noda [@noda- garcia_evolution_2013] |
| <i>Corynebacterium</i> sub HisA <i>diphtheriae</i> | | | | 4.5 ± 1.5 | 0.6 ± 0.08 | 0.13 | 133 ± 10 | 0.05 ± 0.01 | 0.0004 | Noda [@noda- garcia_evolution_2013] |
| L48I-F50L- T80S | | | | | | | | | | |
| <i>Actinomyces</i> <i>urogenitalis</i> DSM 15434 | PriB | * | * | 2.1 ± 0.5 | 1.8 ± 0.2 | 0.9 | 26.3 ± 6.3 | 0.37 ± 0.09 | 14 | Verduzco [@verduzco- castro_co- occurrence_2016] |
| <i>Actinomyces</i> <i>odontolyticus</i> ATCC 17982 | subTrpF | * | - | - | - | 0 | | | 0.02 | Juarez [@juarez- vazquez_evolution_2017] |
| <i>Actinomyces</i> <i>oris</i> K20 BABV01 | PriA | | | | | 0.02 | | | 0.01 | Juarez [@juarez- vazquez_evolution_2017] |
| <i>Actinomyces</i> sp. oral taxon 171 str. F0337 | PriA | | | | | 0.01 | | | 4 | Juarez [@juarez- vazquez_evolution_2017] |
| <i>Actinomyces</i> sp. oral taxon 848 str. F0332 | subTrpF | * | - | - | - | 0 | | | 0.0001 | Juarez [@juarez- vazquez_evolution_2017] |
| <i>Actinomyces</i> <i>urogenitalis</i> DSM 15434 | PriA | | | | | 0.01 | | | 0.02 | Juarez [@juarez- vazquez_evolution_2017] |
| <i>Bifidobacterium</i> <i>adolescentis</i> L2-32 | PriA | * | * | | | 0.2 | | | 0.1 | Juarez [@juarez- vazquez_evolution_2017] |

| Fuente | Familia | HisA <i>in vivo</i> | TrpF <i>in vivo</i> | K_{cat}^{ProFAR} [M ⁻¹ s ⁻¹] | K_m^{ProFAR} [μM] | $\frac{K_{cat}}{K_m}$ | HisA <i>in vivo</i> | K_{cat}^{PRA} [M ⁻¹ s ⁻¹] | K_m^{PRA} [μM] | TrpF <i>in vivo</i> | $\frac{K_{cat}}{K_m}$ | Referencia |
|---|------------|------------------------|------------------------|--|------------------------|-----------------------|------------------------|---|---------------------|------------------------|-----------------------|--|
| <i>Bifidobacterium gallicum</i> DSM 20093 | PriA | * | * | | | 0.1 | | | | 0.04 | | Juarez [@juarez-vazquez_evolution_2017] |
| <i>Bifidobacterium longum</i> ATCC 15697 | PriA | * | * | | | 0.1 | | | | 0.3 | | Juarez [@juarez-vazquez_evolution_2017] |
| Camera CAM1 | Metagenoma | | | 1.7 ± 0.1 | 0.3 ± 0.03 | 0.2 | 40 ± 7 | 3.5 ± 0.04 | | 0.09 | | Noda [@noda-garcia_insights_2015] |
| CAM1_A81G | Metagenoma | | | 1.7 ± 0.2 | 0.1 ± 0.01 | 0.06 | 32.2 ± 1.7 | 1.9 ± 0.1 | | 0.06 | | Noda [@noda-garcia_insights_2015] |
| CAM1_A81S | Metagenoma | | | 4.0 ± 0.9 | 0.2 ± 0.03 | 0.04 | 23.5 ± 6.5 | 0.5 ± 0.1 | | 0.02 | | Noda [@noda-garcia_insights_2015] |
| CAM2 | Metagenoma | n.d. | n.d. | 0 | | n.d. | n.d. | n.d. | 0 | | | Noda [@noda-garcia_insights_2015] |
| PriA_Ancestral | Ancestral | | | 9.4±1.6 | 0.3±0.009 | 0.03 | 4.3±0.4 | 0.6±0.02 | 0.13 | | | Verduzco-Castro Noda-García |
| PriA_SubHisA | Ancestral | | | 3.7±1.01 | 0.5±0.03 | 0.1 | - | - | 0 | | | Verduzco-Castro Noda-García |
| SubHisA_Ancest A Alcestral | Alcestral | | | 6.3±0.7 | 0.15±0.03 | 0.02 | - | - | 0 | | | Verduzco-Castro Noda-García |
| SubHisA_PriA | Ancestral | | | 27.7±3.4 | 0.05±0.002 | | 167.82 | 0.03±0.0020001 | | | | Verduzco-Castro Noda-García |
| <i>scabies</i> | 0 | 0 | 163.6 | 0.1 | | | | | | | | Ernesto |
| <i>Avisco</i> | | 46 | 1.37 | 36 | 3.4 | | | | | | | Ana |

En la tabla section se muestran los diferentes valores de PriA.

Algunas de estas enzimas se seleccionaron en busca de nuevas funciones promiscuas, las reacciones catalizadas por el candidato se investigaron mediante la exploración de sustratos químicamente similares a los nativos.

PriA como modelo de familia enzimática donde las expansiones no son condición necesaria para la promiscuidad.

PriA en EvoMining

Se investigaron las expansiones de la familia PriA en los linajes Actinobacteria, Cyanobacteria, Pseudomonas y Archaea. En Actinobacteria, donde se sabe que PriA es promiscua no se detectaron copias extra. EvoMining ha detectado un parólogo de PriA en Actinobacteria y una expansión conservada en un grupo de saxitoxinas en Cianobacteria [[@moustafa_origin_2009](#)].

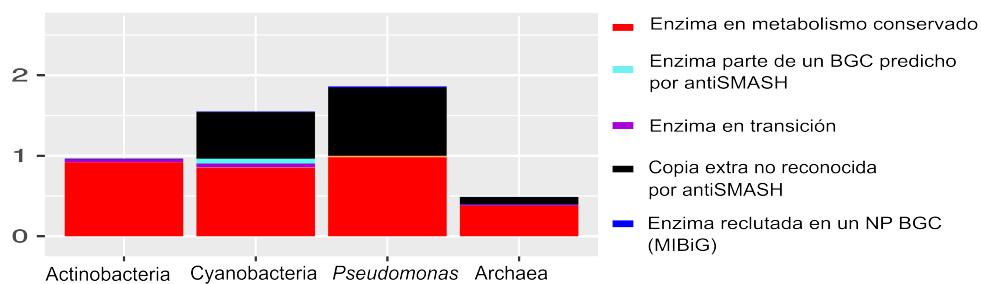


Figure 1:

Los reclutamientos que tuvieron estas expansiones son los siguientes

Table 2: Reclutamientos de expansiones de PriA en MIBiG

| Compuesto | Actinobacteria | Cyanobacteria | Pseudomonas | Archaea | BGC origen | Clase |
|------------------------------|----------------|---------------|-------------|---------|----------------|------------|
| saxitoxin | x | x | x | x | Cyanobacteria | Alkaloid |
| lipopoly saccharide | x | x | x | x | Proteobacteria | Saccharide |
| toxin | x | x | x | x | Cyanobacteria | Other T3 |
| 2'-chloro pentostatin | x | - | -x | - | Actinobacteria | Other |
| 2'-amino-2'- deoxy adenosine | | | | | | |

Finalmente, los árboles que se produjeron por EvoMining son:

Table 3: Árboles EvoMining de PriA en MicroReact

| Linaje | Link al árbol de EvoMining en Microreact |
|------------------|--|
| Actinobacteria | 7g2IGfkv9 |
| Cyanobacteria | qF6jWRMox |
| PriA_Pseudomonas | ydff6DWqs |
| Archaea | Ig-m9Cm6f |

PriA CORASON

Todos los Streptomyces tienen el cluster de PriA parcialmente conservado con respecto al BGC de *Streptomyces coelicolor*. El único *Streptomyces* con una copia extra es *Streptomyces CT34* cuyo mejor hit en NCBI proviene NCBI de una *Lentzea* con 50% de identidad y 98% de cobertura. No es el caso de Cyanobacteria.

TrpF1 TrpF1 queries gave hits with TrpC enzyme present on every Streptomyces, additionally *S. rimosus*, *S. coelicolor*, *S. venezuelae* and *S. NRRL S-1813* had an extra copy. *S rimosus* TrpC vicinity has PKS and

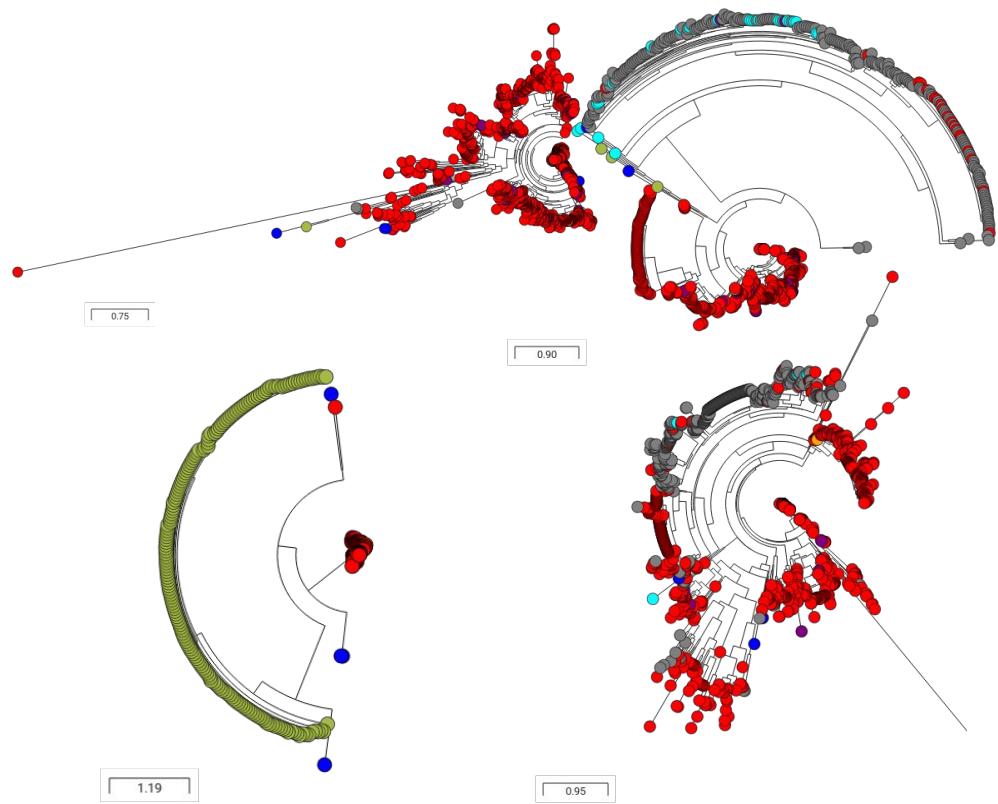


Figure 2:

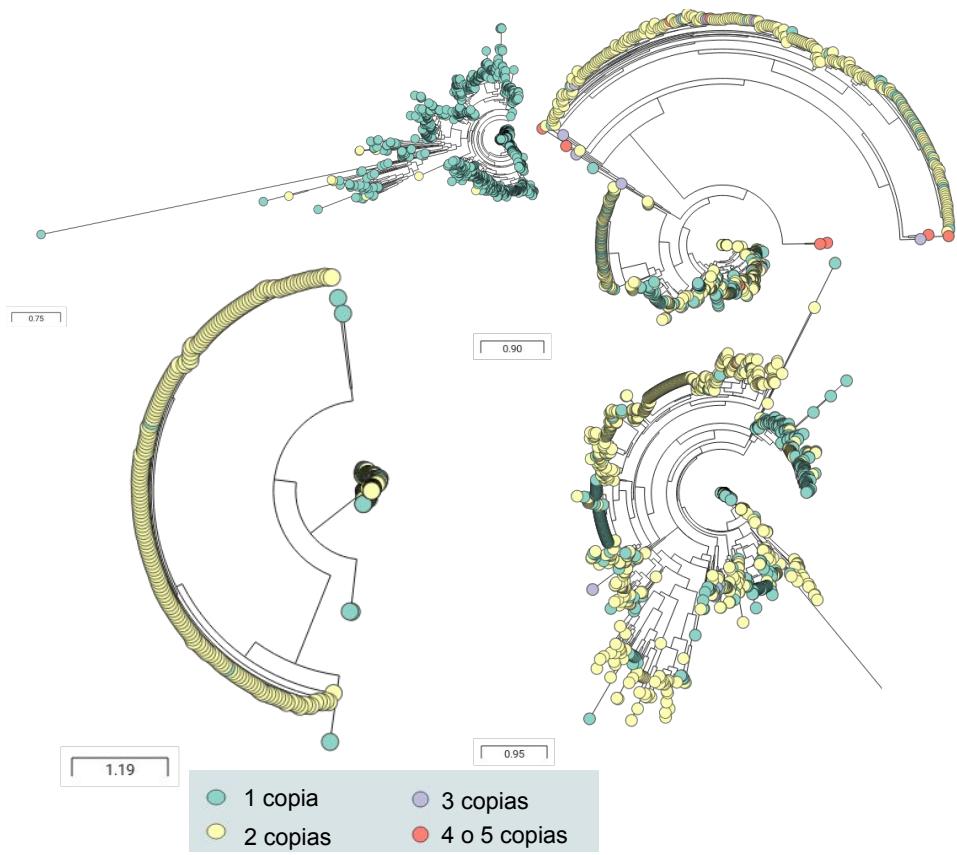


Figure 3:

siderophore genes.

TrpF2 Conserved cluster with NRPS sequences flanking TrpF2

TrpF3 Non conserved cluster

TrpF4 *purpeofuscus* and *S. bikiniensis*

Non darwinian trayectories

Resultado No existieron rutas darwinianas

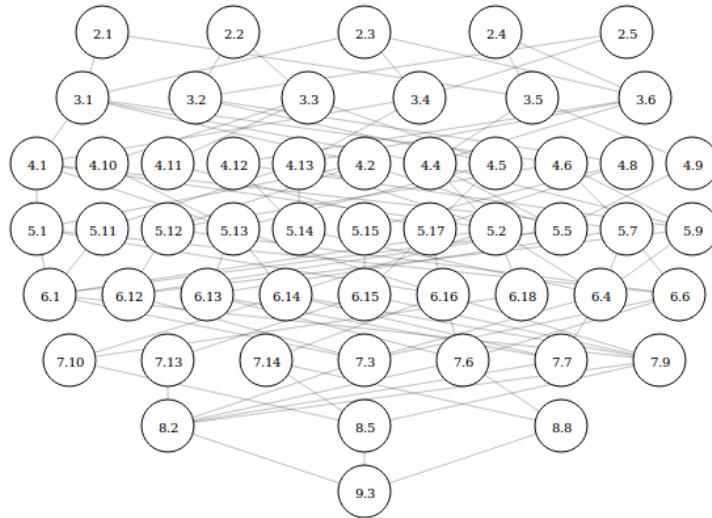


Figure 4:

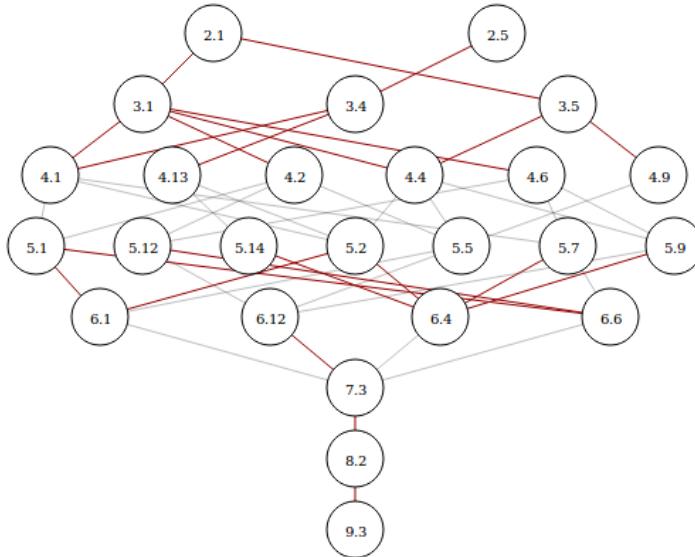


Figure 5:

Resultado se modelo PriA con evcouplings y los aminoácidos encontrados coinciden con los encontrados

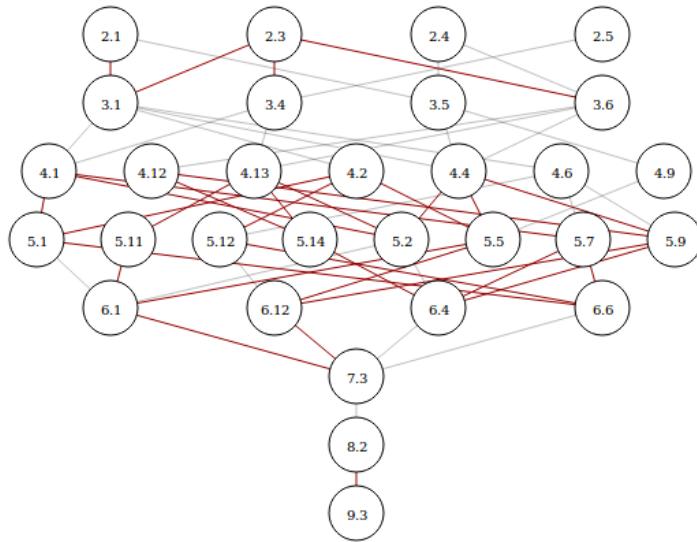


Figure 6:

experimentalmente.

La estructura reconstruida es parecida, pero para obtener mejor refinamiento se debe seleccionar mejor las secuencias del alineamiento

Estandarizacion de protocolos experimentales de PriA en sus sustratos tradicionales

Además de la exploración gen

Afinidad de enzimas selectas por sustratos químicamente parecidos a PRA y PROFAR

Dado que en *Streptomyces* se han encontrado representantes de las familias PriA y PriB, se seleccionaron 39 secuencias homólogas para realizar el análisis del sustrato de la enzima de acoplamiento. Estas secuencias seleccionadas de PriA / Prib pertenecen a *Streptomyces* uniformemente distribuidas en un árbol de especies RpoB con diferentes condiciones sobre la presencia / ausencia de TrpF. En este estudio se incluyeron otros homólogos de PriA Actinobacterial caracterizados químicamente, y finalmente se agregaron HisA de *Escherichia coli*, *Arthrobacter Aurescens*, *Salmonella enterica* y *Acidimicrobium ferrooxidans* y Actinobacterial TrpF como controles.

Cuando existían estructuras de cristal, de lo contrario, se generaban estructuras homólogas utilizando como plantilla la enzima más cercana disponible con estructura de cristal.

Controls

HisA Enterobacteria enzymes from *Salmonella enterica* (PDB:5AHE), *Escherichia coli* K12 *Acidimicrobium ferrooxydans* (PDB:4WD0)

TrpF Actinobacteria *Jonesia denitrificans* and *Streptomyces* sp Mg1 sequences.

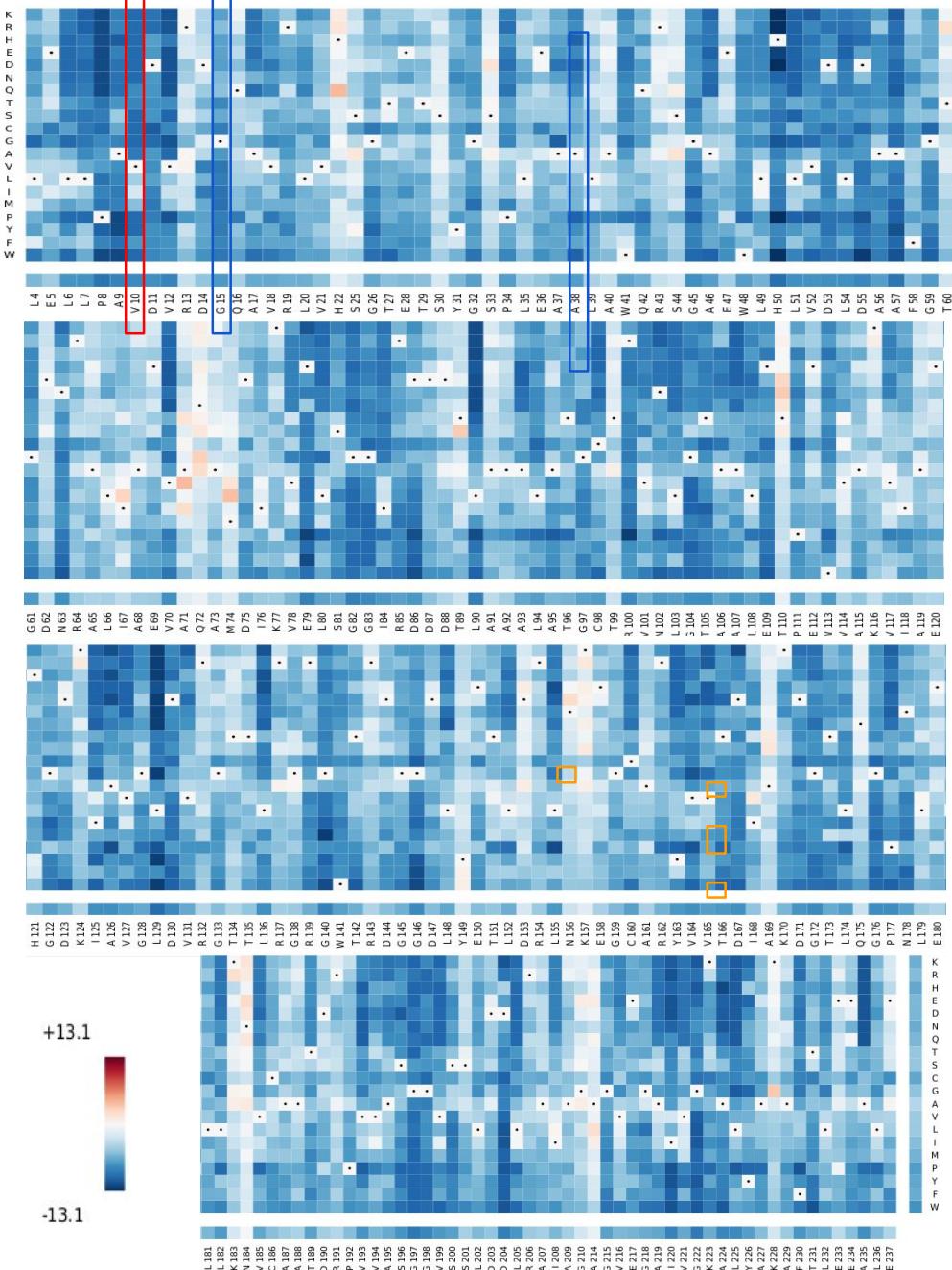


Figure 7:

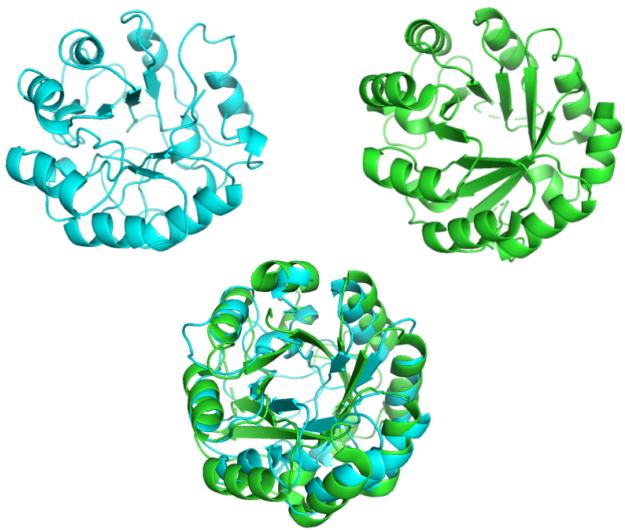


Figure 8:



Figure 9:

Chemically characterized Actinobacterial enzymes

PriA

Mycobacterium tuberculosis (Mtub PDB:2Y88,2Y89,2Y85,3ZS4) *Streptomyces coelicolor* (Scoe PDB:2VEP,2X30,1VZW),
Streptomyces globisporus, *Actinomyces urogenitalis* 4X2R *Corynebacterium jeikeum*

subHisA

Corynebacterium diphtheriae *Actinomyces car* (PDB:4X2R)

subTrpF

Arthrobacter aurescens (PDB:4WD0)

PriB

Streptomyces ipomoeae, *Streptomyces sviceus* (PDB:4U28,4TX9)

TrpF controls *Jonesia denitrificans* (PDB:4WUI) *Chlamidya trachomatis*, *Streptomyces sp. Mg1* TrpF and
Actinomyces odontolyticus were included

Es posible que PriA tenga actividad en GTP

Activity was measured fluorometrically in 96-well plates (Nuc 96-Well Optical Botto Plates) in a TECAN infinite M1000 plate reader (excitation at 286 nm and emission at 386 nm)

Preliminar activity essays were performed on an active PriA from *Streptomyces coelicolor* and an inactive mutant D11A.

Enzymes were cloned on coli V68 strains, overexpression were induced and protein were purified.

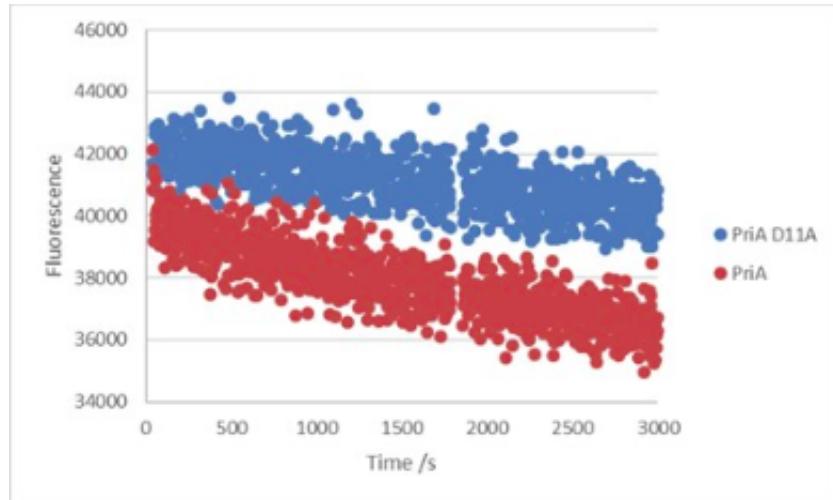


Figure 10:

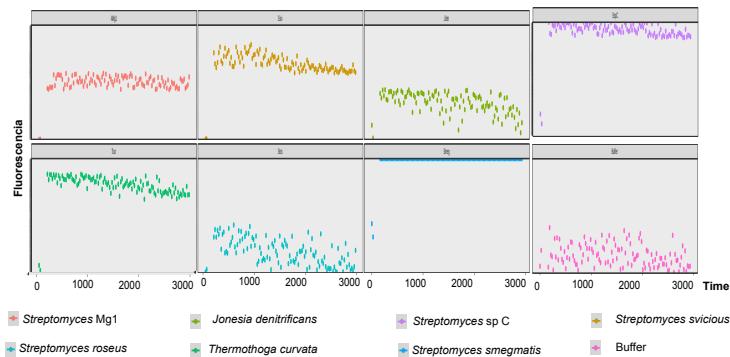


Figure 11:

the two enzymes with activity

Thermomonospora curvata thermophilic Actinobacteria from Thermomonosporaceae genus, it can be found in compost and participate in the active degradation of cellulose [@chertkov_complete_2011].

Jonesia trpF shows no activity *Jonesia denitrificans* is classified as a pathogenic organism for animals, reported genome was originally isolated from cooked ox blood [@pukall_complete_2009].

```
docking <- read.csv("chapter4/SmallHeat.data", header=TRUE, sep="\t")
kable(docking,
      caption = "Enzymes docking \\label{tab:docking}",
      caption.short = "Enzymes docking ")
```

Table 4: Enzymes docking

| Enzima | S13 | S15 | S14 | S16 | S10 | S12 | S9 | S18 | S5 | S4 | S8 | S17 | S7 | S6 | S11 | S1 |
|------------|------|-------|------|------|------|------|------|------|-------|-------|------|------|------|------|-------|-------|
| Srub_2VEP | -7.4 | -7.3 | -7.5 | -7.1 | -6.5 | -6.2 | -6.5 | -7.7 | -9.4 | -9.3 | -7.9 | -7.2 | -8.3 | -8.6 | -8.9 | -9.0 |
| Saver_2VEP | -7.4 | -7.2 | -7.0 | -6.5 | -7.3 | -6.4 | -7.0 | -7.5 | -9.6 | -8.5 | -7.9 | -7.6 | -8.4 | -8.7 | -9.8 | -8.3 |
| Scoe_2VEP | -7.5 | -7.5 | -7.9 | -7.0 | -7.0 | -6.2 | -6.5 | -7.8 | -8.8 | -9.2 | -7.8 | -7.9 | -8.0 | -8.9 | -10.3 | -9.2 |
| Scoe_2X30 | -8.1 | -7.4 | -7.6 | -6.9 | -6.7 | -6.8 | -7.1 | -7.9 | -9.1 | -9.0 | -8.3 | -8.6 | -8.5 | -9.0 | -10.6 | -10.0 |
| Scoe_1VZW | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Sfla_2VEP | -7.1 | -7.6 | -7.2 | -7.3 | -7.2 | -6.8 | -6.9 | -8.1 | -8.2 | -7.2 | -8.2 | -7.2 | -8.4 | -8.3 | -8.5 | -7.9 |
| Sgha_2VEP | -9.2 | -8.7 | -6.7 | -6.7 | -7.4 | -7.7 | -7.2 | -7.5 | -9.8 | -8.9 | -8.2 | -7.8 | -8.8 | -8.7 | -10.1 | -9.1 |
| Siak_2VEP | -6.6 | -7.3 | -7.0 | -7.1 | -7.1 | -7.1 | -6.8 | -8.0 | -9.2 | -8.7 | -7.8 | -7.6 | -8.3 | -8.4 | -9.1 | -5.8 |
| Sbic_2VEP | -7.2 | -6.7 | -6.8 | -6.5 | -6.2 | -6.6 | -5.9 | -7.8 | -8.5 | -7.8 | -7.8 | -7.2 | -8.2 | -8.0 | -9.6 | -8.2 |
| Sbot_2VEP | -9.6 | -10.9 | -8.9 | -7.1 | -6.0 | -6.2 | -6.7 | -8.1 | -9.1 | -8.8 | -8.3 | -7.9 | -8.9 | -9.3 | -9.4 | -9.8 |
| Sipo_2VEP | -6.6 | -6.6 | -7.3 | -6.9 | -6.5 | -6.3 | -6.5 | -8.1 | -8.6 | -9.1 | -8.0 | -7.9 | -8.0 | -8.4 | -8.5 | -7.2 |
| Ssvi | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Ssvi_4U28 | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Ssvi_4TX9 | -5.9 | -8.2 | -7.1 | -6.6 | -6.8 | -7.0 | -7.6 | -7.9 | -8.4 | -8.3 | -8.2 | -8.1 | -8.4 | -8.7 | -7.7 | -8.2 |
| Salb_2VEP | -6.3 | -7.1 | -7.4 | -6.8 | -7.7 | -6.9 | -6.6 | -8.0 | -9.6 | -8.9 | -8.6 | -7.9 | -8.6 | -8.4 | -9.1 | -7.4 |
| Sbik_2VEP | -7.4 | -6.7 | -7.4 | -7.3 | -7.7 | -6.5 | -6.8 | -8.5 | -9.9 | -9.8 | -8.3 | -7.8 | -8.2 | -8.4 | -10.5 | -7.1 |
| Stsu_2VEP | -6.9 | -7.5 | -7.9 | -7.8 | -7.5 | -7.3 | -7.7 | -8.1 | -10.0 | -9.7 | -8.7 | -7.8 | -8.8 | -8.8 | -10.6 | -7.8 |
| Sven_2VEP | -8.3 | -7.6 | -7.5 | -6.8 | -6.4 | -7.0 | -6.2 | -8.2 | -9.6 | -9.0 | -7.9 | -7.4 | -8.3 | -8.6 | -10.0 | -8.2 |
| Scal_2VEP | -7.3 | -8.8 | -7.5 | -6.7 | -7.0 | -6.5 | -6.5 | -8.7 | -10.0 | -9.7 | -8.8 | -7.7 | -8.2 | -8.6 | -10.5 | -8.1 |
| Sbaa_2VEP | -8.9 | -6.6 | -6.7 | -6.8 | -7.2 | -7.2 | -6.2 | -7.7 | -9.6 | -9.5 | -8.4 | -7.4 | -8.5 | -8.2 | -9.7 | -8.5 |
| Sglo_2VEP | -6.1 | -6.8 | -6.9 | -6.5 | -6.7 | -6.3 | -6.7 | -7.5 | -9.6 | -9.6 | -8.6 | -7.8 | -8.7 | -8.7 | -9.9 | -6.2 |
| Sful_2VEP | -9.0 | -6.9 | -7.1 | -6.8 | -6.3 | -7.2 | -6.6 | -8.1 | -9.8 | -9.3 | -7.7 | -8.0 | -8.7 | -8.8 | -10.5 | -7.6 |
| Sgri_2VEP | -6.6 | -8.2 | -7.1 | -6.4 | -7.1 | -7.4 | -7.1 | -7.4 | -9.4 | -8.5 | -8.6 | -7.5 | -8.8 | -8.4 | -9.6 | -8.8 |
| S34_2VEP | -7.8 | -7.2 | -7.6 | -7.3 | -6.2 | -6.5 | -6.9 | -8.0 | -8.8 | -8.6 | -7.7 | -7.1 | -7.7 | -7.9 | -7.2 | -7.1 |
| Srim_2VEP | -7.4 | -6.8 | -7.1 | -7.2 | -7.2 | -7.4 | -7.8 | -8.6 | -9.7 | -9.3 | -8.8 | -7.7 | -8.9 | -8.7 | -10.2 | -6.8 |
| Satr_2VEP | -7.6 | -7.1 | -7.5 | -7.4 | -6.2 | -6.5 | -6.9 | -8.0 | -8.9 | -8.7 | -7.7 | -7.4 | -7.7 | -7.8 | -6.5 | -7.0 |
| S1813_2VEP | -7.5 | -6.7 | -6.8 | -6.6 | -6.8 | -7.0 | -6.7 | -7.9 | -9.9 | -9.7 | -8.3 | -7.7 | -8.5 | -8.6 | -10.0 | -7.6 |
| Svar_2VEP | -6.3 | -6.8 | -7.0 | -6.3 | -6.9 | -6.9 | -6.6 | -7.8 | -9.3 | -7.4 | -8.5 | -7.3 | -8.0 | -8.7 | -7.4 | -8.5 |
| Sfra_2VEP | -7.3 | -7.0 | -6.8 | -6.6 | -6.5 | -7.3 | -6.6 | -8.6 | -9.1 | -8.7 | -8.9 | -7.7 | -8.9 | -9.0 | -8.7 | -6.0 |
| Smeg_2VEP | -8.0 | -7.3 | -6.9 | -6.6 | -7.2 | -6.7 | -6.1 | -7.6 | -9.2 | -9.1 | -7.8 | -7.4 | -8.2 | -8.5 | -9.6 | -9.2 |
| Ssul_2VEP | -7.5 | -7.0 | -6.9 | -6.6 | -6.6 | -6.7 | -6.9 | -7.7 | -8.4 | -8.2 | -8.2 | -7.5 | -8.1 | -7.7 | -8.2 | -6.7 |
| Slav_4X9S | -8.0 | -7.1 | -6.7 | -6.9 | -6.6 | -6.8 | -6.7 | -8.2 | -9.5 | -9.1 | -8.6 | -8.0 | -8.4 | -8.7 | -9.1 | -9.5 |
| Sery_4X9S | -7.8 | -7.2 | -7.6 | -7.2 | -7.4 | -6.9 | -7.4 | -8.5 | -9.4 | -9.4 | -8.6 | -7.6 | -8.4 | -8.6 | -9.1 | -10.0 |
| SspC_4X9S | -7.4 | -6.9 | -7.3 | -6.8 | -7.3 | -6.6 | -7.5 | -8.0 | -9.8 | -9.3 | -8.7 | -7.6 | -8.5 | -8.4 | -10.6 | -9.1 |
| Sxan_4X9S | -7.5 | -6.9 | -6.8 | -6.8 | -6.5 | -6.6 | -6.5 | -8.3 | -8.0 | -8.1 | -7.6 | -7.4 | -8.7 | -8.1 | -8.5 | -8.5 |
| Skat_4X9S | -6.4 | -7.0 | -7.1 | -6.7 | -7.7 | -6.3 | -6.2 | -8.1 | -8.5 | -9.2 | -8.3 | -7.6 | -9.0 | -8.5 | -9.7 | -9.5 |
| SMg1_4X9S | -6.5 | -6.9 | -7.2 | -7.1 | -6.5 | -6.9 | -6.4 | -7.3 | -7.8 | -7.7 | -8.3 | -7.5 | -7.9 | -8.4 | -9.5 | -7.6 |
| SMg1_W9T | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Sniv_2VEP | -6.2 | -6.8 | -7.4 | -6.5 | -7.8 | -6.8 | -6.7 | -9.5 | -9.6 | -9.4 | -8.7 | -8.2 | -8.6 | -9.1 | -9.9 | -5.4 |
| Scla_2VEP | -6.4 | -7.7 | -7.4 | -7.2 | -7.6 | -7.5 | -7.2 | -8.5 | -10.1 | -10.0 | -8.7 | -7.9 | -8.8 | -9.1 | -10.2 | -6.9 |

| Enzima | S13 | S15 | S14 | S16 | S10 | S12 | S9 | S18 | S5 | S4 | S8 | S17 | S7 | S6 | S11 | S1 |
|-----------|-------|-------|-------|------|------|------|------|------|-------|-------|------|------|------|------|-------|-------|
| Save_2VEP | -7.6 | -6.7 | -7.1 | -7.2 | -7.1 | -6.5 | -6.6 | -7.8 | -8.6 | -10.0 | -8.6 | -7.5 | -8.3 | -8.5 | -8.8 | -5.3 |
| Spur_2vEP | -6.8 | -7.3 | -6.9 | -6.7 | -8.0 | -7.9 | -7.7 | -8.5 | -9.5 | -9.8 | -8.1 | -7.8 | -8.7 | -9.7 | -10.0 | -5.3 |
| Scar_2Y89 | -6.9 | -6.8 | -7.5 | -7.1 | -7.8 | -7.3 | -7.2 | -8.3 | -9.2 | -8.3 | -8.9 | -8.4 | -8.9 | -9.3 | -9.4 | -5.3 |
| Mtub_2Y88 | -10.0 | -7.8 | -8.9 | -5.4 | -8.6 | -7.3 | -7.8 | -9.5 | -10.9 | -10.3 | -9.5 | -9.0 | -9.8 | -9.8 | -11.3 | -10.1 |
| Mtub_2Y89 | -8.7 | -8.6 | -9.6 | -9.4 | -6.4 | -5.9 | -5.6 | -7.1 | -7.0 | -7.5 | -7.3 | -6.8 | -7.4 | -8.4 | -7.5 | -8.1 |
| Mtub_2Y85 | -8.2 | -7.9 | -9.2 | -7.4 | -7.6 | -7.5 | -7.6 | -8.4 | -9.7 | -9.5 | -9.3 | -7.8 | -8.6 | -8.6 | -10.2 | -9.8 |
| Mtub_3ZS4 | -10.0 | -10.5 | -11.4 | -6.4 | -8.2 | -7.2 | -7.0 | -9.6 | -10.2 | -10.2 | -9.9 | -8.5 | -9.3 | -9.6 | -10.9 | -10.0 |
| S34_3ZS4 | -7.4 | -8.0 | -7.6 | -6.4 | -5.2 | -5.4 | -5.2 | -6.1 | -6.8 | -6.4 | -5.7 | -6.4 | -6.3 | -6.3 | -7.1 | -7.4 |
| Cdip_4AXK | -9.2 | -7.8 | -10.9 | -7.2 | -7.5 | -7.6 | -7.7 | -8.9 | -9.0 | -9.8 | -9.0 | -8.3 | -8.8 | -9.2 | -10.1 | -9.5 |
| Cjei_4AXK | -7.5 | -6.9 | -7.2 | -6.5 | -8.4 | -8.0 | -8.5 | -8.7 | -9.5 | -9.6 | -9.4 | -8.8 | -9.0 | -9.5 | -9.3 | -8.1 |
| Aaur | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Aaur_4WD0 | -8.2 | -8.5 | -8.1 | -7.9 | -5.7 | -5.5 | -5.9 | -7.0 | -7.5 | -7.2 | -7.1 | -6.7 | -7.1 | -7.4 | -8.4 | -7.2 |
| Acar_4X2R | -10.6 | -9.3 | -9.3 | -7.2 | -7.2 | -6.8 | -7.3 | -7.5 | -9.5 | -9.8 | -8.0 | -7.8 | -9.3 | -8.9 | -10.3 | -9.6 |
| Auro_4X2R | -9.9 | -9.1 | -9.8 | -8.1 | -7.4 | -7.1 | -7.4 | -7.8 | -9.2 | -9.8 | -8.3 | -7.8 | -9.3 | -9.0 | -9.9 | -9.0 |
| Afer_4WD0 | -5.7 | -5.8 | -6.0 | -5.7 | -6.7 | -6.2 | -5.8 | -7.6 | -9.2 | -8.8 | -7.8 | -7.4 | -8.3 | -8.4 | -9.3 | -6.7 |
| Sent_5AHE | -9.1 | -5.4 | -6.4 | -5.2 | -8.0 | -7.3 | -7.4 | -8.8 | -10.7 | -10.2 | -8.7 | -8.7 | -9.6 | -9.9 | -10.9 | -7.8 |
| Ecoli_K12 | -9.7 | -9.7 | -9.2 | -6.1 | -7.2 | -6.6 | -6.8 | -8.6 | -9.5 | -9.1 | -8.6 | -8.2 | -9.0 | -8.6 | -10.2 | -9.9 |
| Jden_4WUI | -8.3 | -8.8 | -8.2 | -6.8 | -6.2 | -6.1 | -6.0 | -6.8 | -7.4 | -7.6 | -7.5 | -6.9 | -7.6 | -7.5 | -7.7 | -7.5 |
| Ctra | -8.2 | -8.0 | -7.4 | -7.2 | -6.1 | -5.5 | -5.4 | -6.5 | -7.1 | -7.1 | -7.0 | -6.2 | -6.8 | -6.8 | -6.9 | -7.2 |
| SMg1_trpF | -7.2 | -8.8 | -8.2 | -7.3 | -6.2 | -5.7 | -5.7 | -6.9 | -6.6 | -6.7 | -7.3 | -6.7 | -7.6 | -6.9 | -7.5 | -7.1 |
| Aodo_4X2R | -8.5 | -8.6 | -8.8 | -7.3 | -7.1 | -7.1 | -7.1 | -7.5 | -9.7 | -9.4 | -7.8 | -7.6 | -9.6 | -8.8 | -10.1 | -8.4 |

| Enzima | S13 | S15 | S14 | S16 | S10 | S12 | S9 | S18 | S5 | S4 | S8 | S17 | S7 | S6 | S11 | S1 |
|--------|-----|-----|-----|-----|-----|-----|----|-----|----|----|----|-----|----|----|-----|----|
|--------|-----|-----|-----|-----|-----|-----|----|-----|----|----|----|-----|----|----|-----|----|

El análisis de PriA a nivel estructural sugiere que GTP es el sustrato más afín

```
table <- read.csv("chapter4/EstructurasPDB", row.names = 1, sep = "\t")
kable(table, caption = "Enzyme PDB \\label{tab:Enzyme PDB}", caption.short = "Enzyme PDB ")
```

Table 5: Enzyme PDB

| Organismo | Family | Observations | Resolution | Year | |
|-----------|----------------------------|--------------|----------------------------------|------|------|
| 4WUI | TrpF | | 1.09 | 2014 | |
| 4X9S | PriB | | 1.60 | 2014 | |
| 5DN1 | PriA | | 1.95 | 2015 | |
| 1DL3 | TrpF | | 2.70 | 1999 | |
| 1LBM | TrpF | RCDRP | 2.80 | 2002 | |
| 1NSJ | TrpF | | 2.00 | 1996 | |
| 1V5X | TrpF | | 2.00 | 2003 | |
| 1VZW | PriA | | 1.80 | 2004 | |
| 2VEP | PriA | | 1.80 | 2007 | |
| 2X30 | PriA | R139N | 1.95 | 2010 | |
| 2Y85 | PriA | RCDRP | 2.40 | 2011 | |
| 2Y88 | PriA | D11N PRFAR | 1.33 | 2011 | |
| 2Y89 | PriA | D11N | 2.50 | 2011 | |
| 3ZS4 | PriA | PRFAR | 1.90 | 2012 | |
| 4AAJ | TrpF | | 1.75 | 2012 | |
| 4TX9 | PriB | ProFAR | 1.60 | 2014 | |
| 4U28 | PriB | | 1.33 | 2014 | |
| 4W9T | PriB | | 1.57 | 2014 | |
| 4WD0 | PriB | | 1.50 | 2014 | |
| 4X2R | Actinomyces urogenitalis | | 1.05 | 2014 | |
| 4AXK | Corynebacterium efficiens | SubHisA | 2.25 | 2013 | |
| 5AHE | Salmonella enterica | HisA | 1.70 | 2015 | |
| 5AB3 | Salmonella enterica | HisA | D7N, D10G, dup13-15, Q24L, G102A | 1.80 | 2016 |
| 5ABT | Salmonella enterica | HisA | D7N, G102A, V106M, D176A | 1.65 | 2016 |
| 5AC7 | Salmonella enterica | HisA | D7N, D10G, dup13-15 | 1.90 | 2016 |
| 5AC8 | Salmonella enterica | HisA | D10G, dup13-15, G102A | 1.70 | 2016 |
| 5AC6 | Salmonella enterica | HisA | D7N, D10G, dup13-15, Q24L, G102A | 1.99 | 2016 |
| 5A5W | Salmonella enterica | HisA | HisA D7N D176A with ProFAR | NA | 2015 |
| 5AHF | Salmonella enterica | HisA | HisA D7N with ProFAR | NA | NA |
| 4GJ1 | Campylobacter jejuni | HisA | | 2.15 | 2012 |
| 2W79 | Thermotoga maritima | HisA | | 1.85 | 2008 |
| 1QO2 | Thermotoga maritima | HisA | | 1.85 | 2000 |
| 5LHE | Thermococcus kodakaraensis | TrpF | | 1.85 | 2016 |
| 5LHF | Thermococcus kodakaraensis | TrpF | | 1.75 | 2016 |

Similar substrates to PRA and PROFAR suggested by Tanimoto distance or previously tested

S1,S2,...S20 substrates were collected from literature and chemoinformatics predictions. S3 PRA and S7 PROFAR are native substrates, S13-S16 are light activated substrates, S17 PRAP, S18 Compound V, were found on literature, S6 GMP, S11 GTP and other were suggested by chemoinformatics.

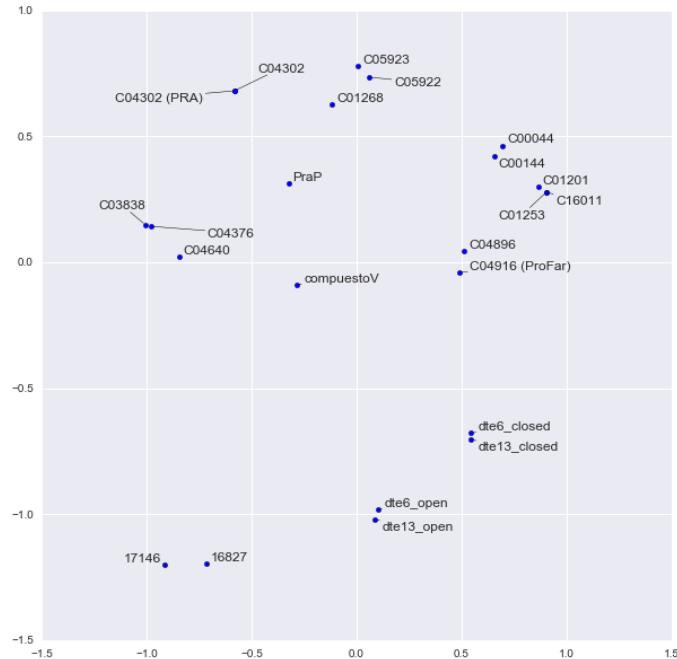
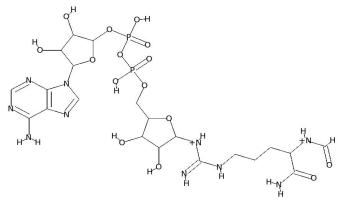
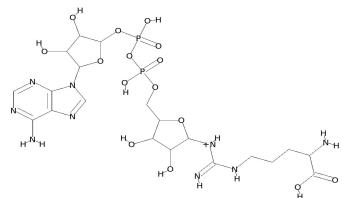


Figure 12:

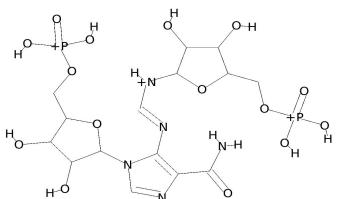
On next figure we can see their chemical structures.



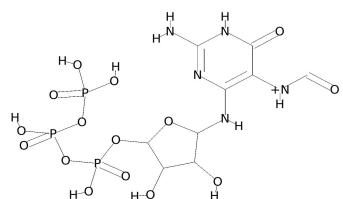
1
ADP-D-ribosyl-[dinitrogen reductase]



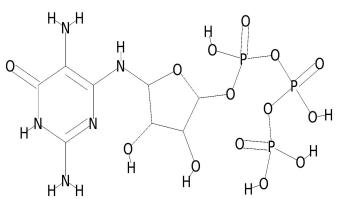
2
N(omega)-(ADP-D-ribosyl)-L-arginine



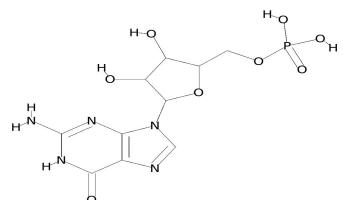
3
5-(5-Phospho-D-ribosylaminoformimino)-1-(5-phosphoribosyl)-imidazole-4-carboxamide



4
Formamidopyrimidine nucleoside triphosphate

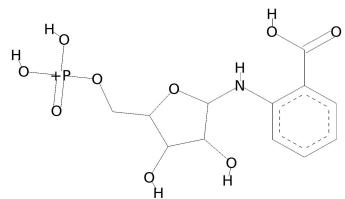


5
2,5-diaminopyrimidine nucleoside triphosphate

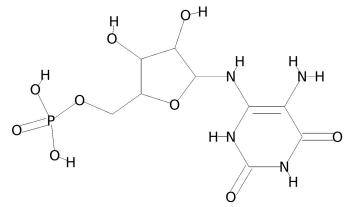


6
Guanosine monophosphate

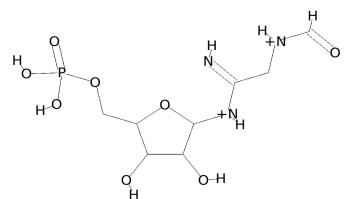
Figure 13: Substrates 1



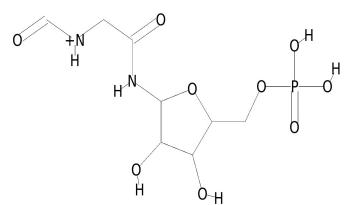
7
N-(5-phospho-D-ribosyl) anthranilate



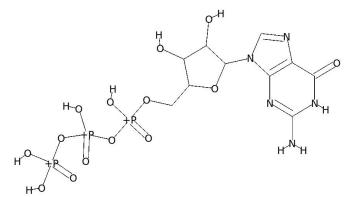
8
5-Amino-6-(5'-phosphoribosylamino)uracil



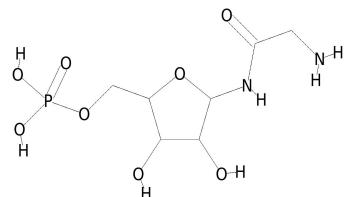
9
2-(Formido)-N1-(5'-phosphoribosyl)acetamidine



10
5'-Phosphoribosyl-N-formylglycinamide

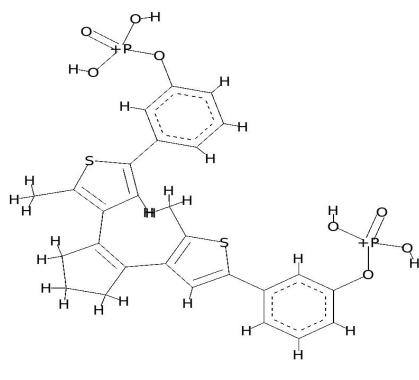


11
Guanosine 5'-triphosphate



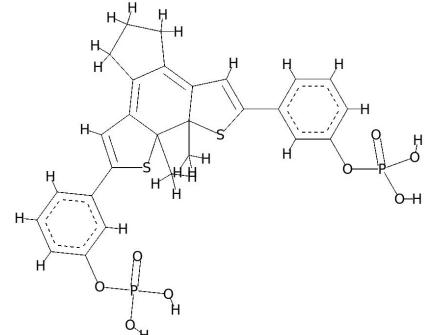
12
5'-Phosphoribosylglycinamide

Figure 14: Substrates 2



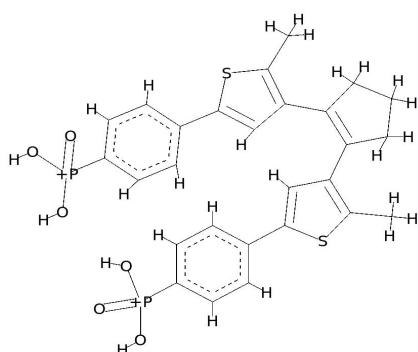
13

DTE-meta-phosphate(dte6_Open form)



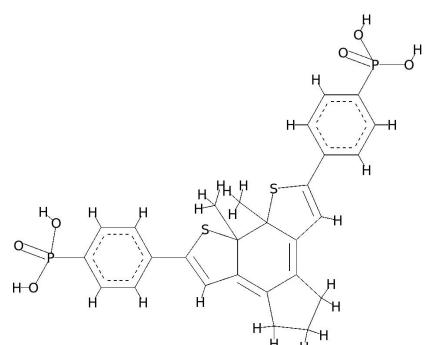
14

DTE-meta-phosphate(dte6_Closed form)



15

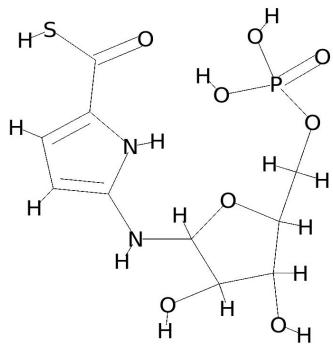
DTE-Para-Phosphonate(dte13_closed form)



16

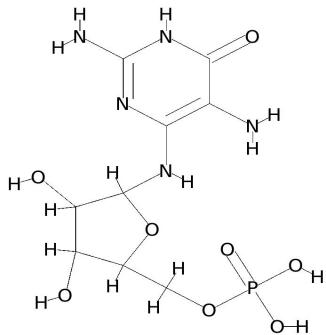
DTE-para-phosphonate(dte13_closed form)

Figure 15: Substrates 3



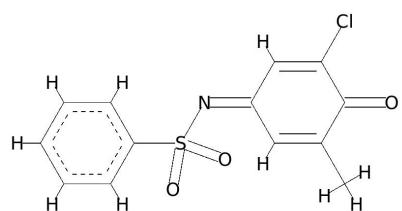
17

4N'-(5'-phosphoribosyl) 4-aminopyrrole-2-carboxilate



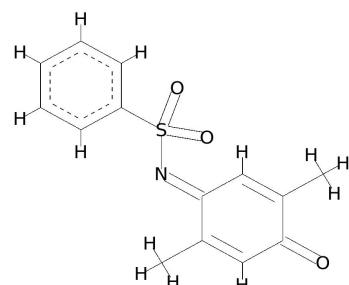
18

2,5-di-amino-6-ribosylamino-4(3H)-pyrimidinone 5'-phosphate



19

(E)-N-(3-chloro-5-methyl-4-oxocyclohexa-2,5-dienylidene)benzenesulfonamide



20

2,5 dimethyl-N-(4-oxocyclohexa-2,5-dienylidene)benzenesulfonamide

Figure 16: Substrates 4

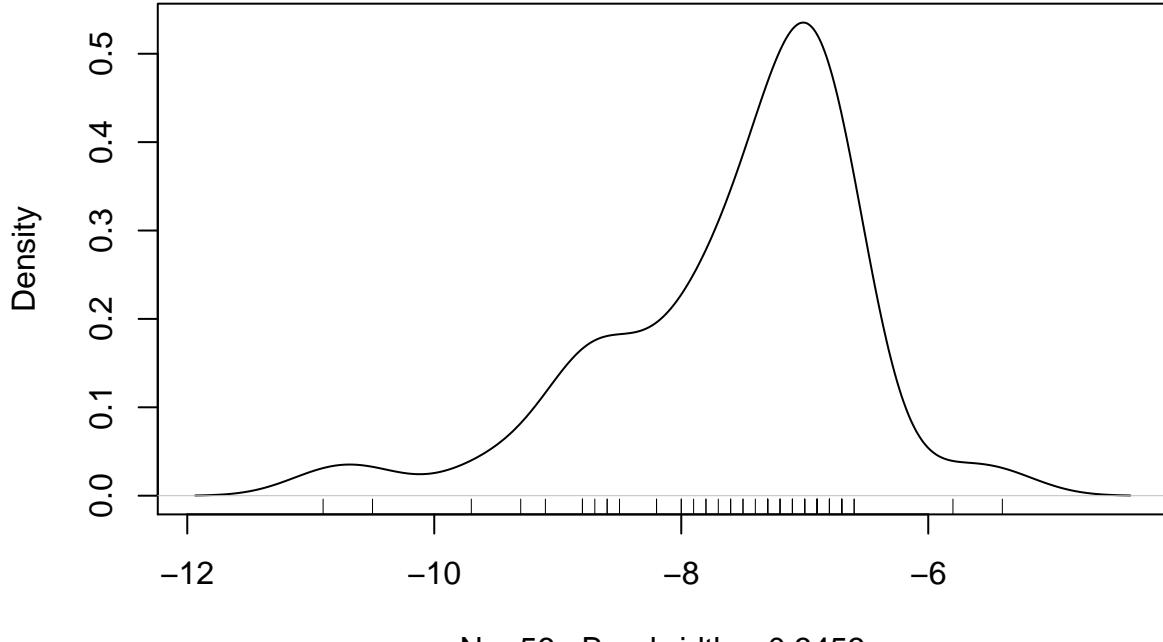
Docking between PriA enzymes and selected substrates

Docking simulation were calculated for PriA *Streptomyces* enzymes. TrpF enzymes from *Streptomyces Mg1*, *Jonesia denitrificans*, were added as controls

Procedures can be found at Docking Protocols

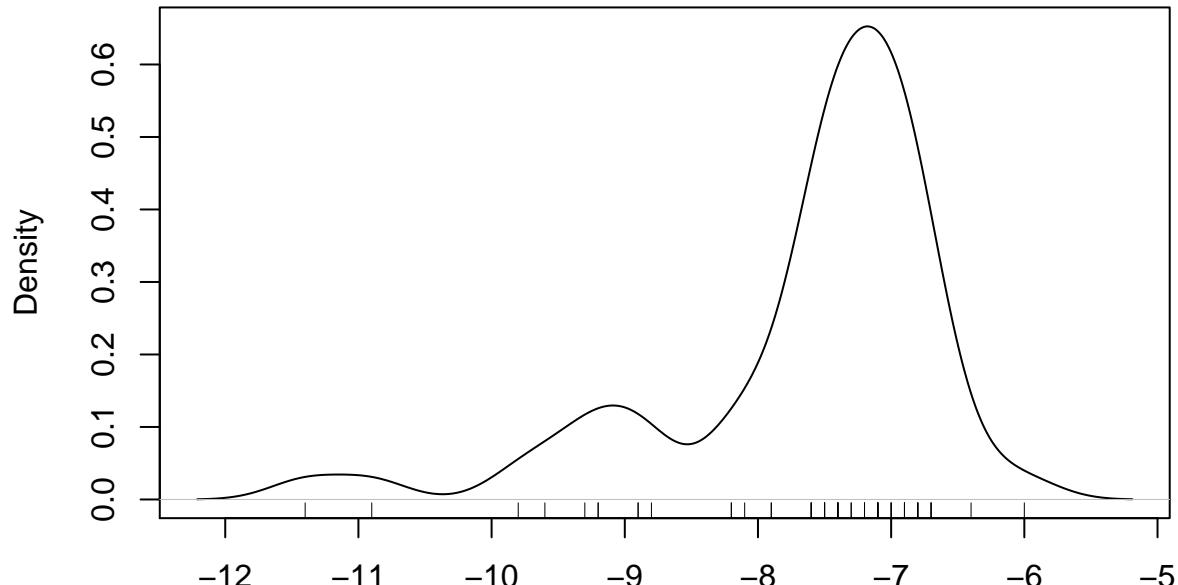
```
## Called from: eval(expr, envir, enclos)    ## debug en <text>#4: plot(density(docking[,  
i], na.rm = T))
```

```
density.default(x = docking[, i], na.rm = T)
```



```
## debug en <text>#4: rug(docking[, i])    ## debug en <text>#4: browser()    ## debug en  
<text>#4: plot(density(docking[, i], na.rm = T))
```

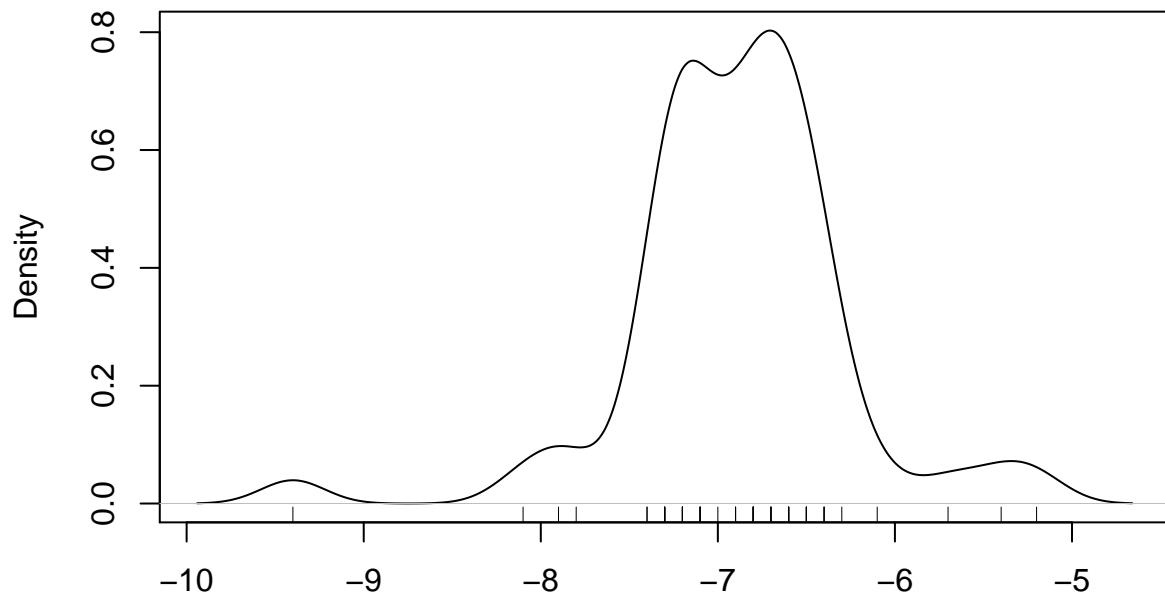
```
density.default(x = docking[, i], na.rm = T)
```



N = 56 Bandwidth = 0.2702

```
## debug en <text>#4: rug(docking[, i]) ## debug en <text>#4: browser() ## debug en
<text>#4: plot(density(docking[, i], na.rm = T))
```

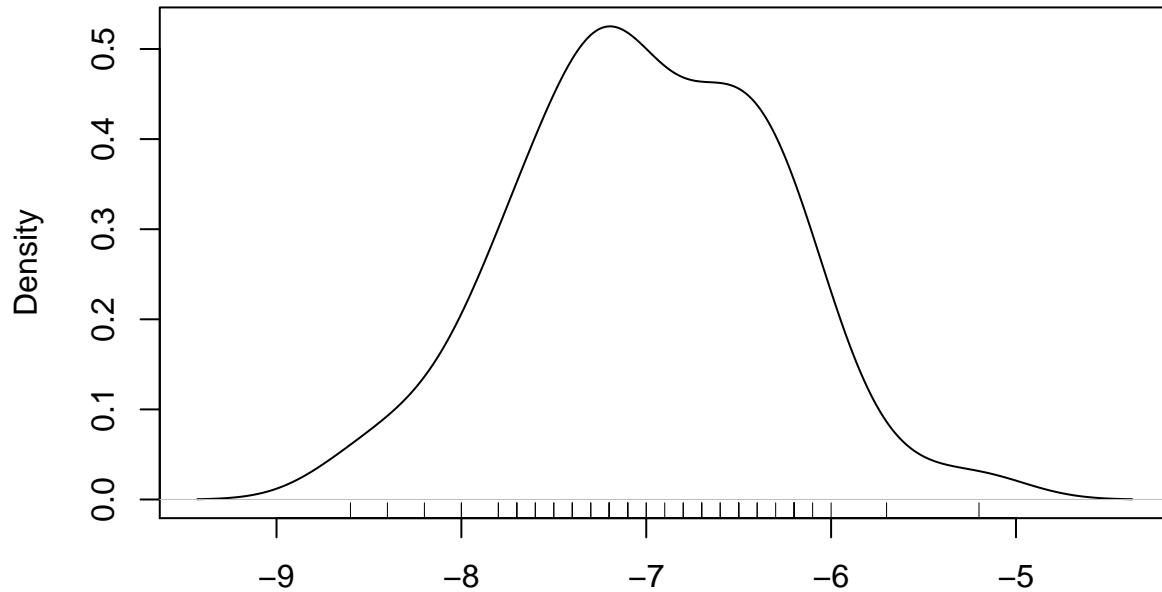
```
density.default(x = docking[, i], na.rm = T)
```



N = 56 Bandwidth = 0.1802

```
## debug en <text>#4: rug(docking[, i]) ## debug en <text>#4: browser() ## debug en
<text>#4: plot(density(docking[, i], na.rm = T))
```

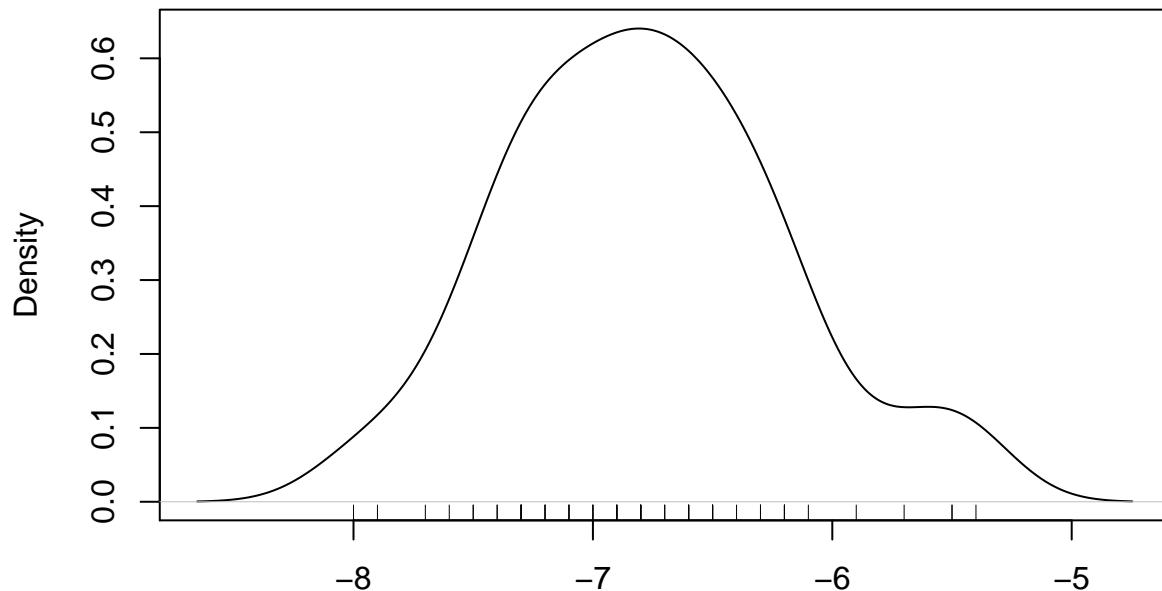
```
density.default(x = docking[, i], na.rm = T)
```



N = 56 Bandwidth = 0.2764

```
## debug en <text>#4: rug(docking[, i]) ## debug en <text>#4: browser() ## debug en
<text>#4: plot(density(docking[, i], na.rm = T))
```

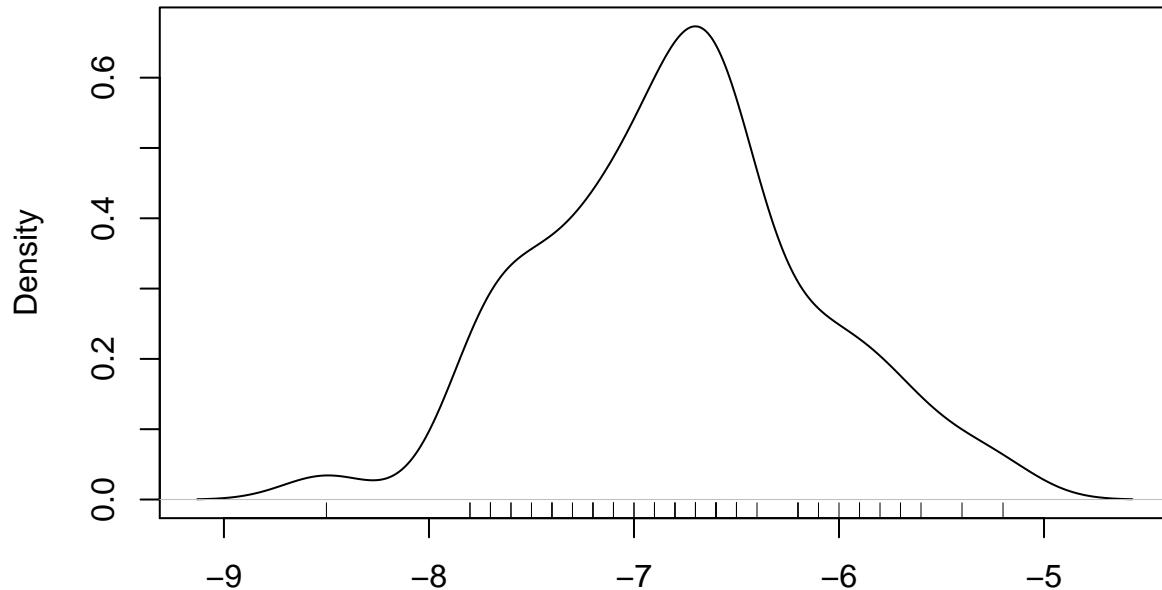
```
density.default(x = docking[, i], na.rm = T)
```



N = 56 Bandwidth = 0.2177

```
## debug en <text>#4: rug(docking[, i]) ## debug en <text>#4: browser() ## debug en
<text>#4: plot(density(docking[, i], na.rm = T))
```

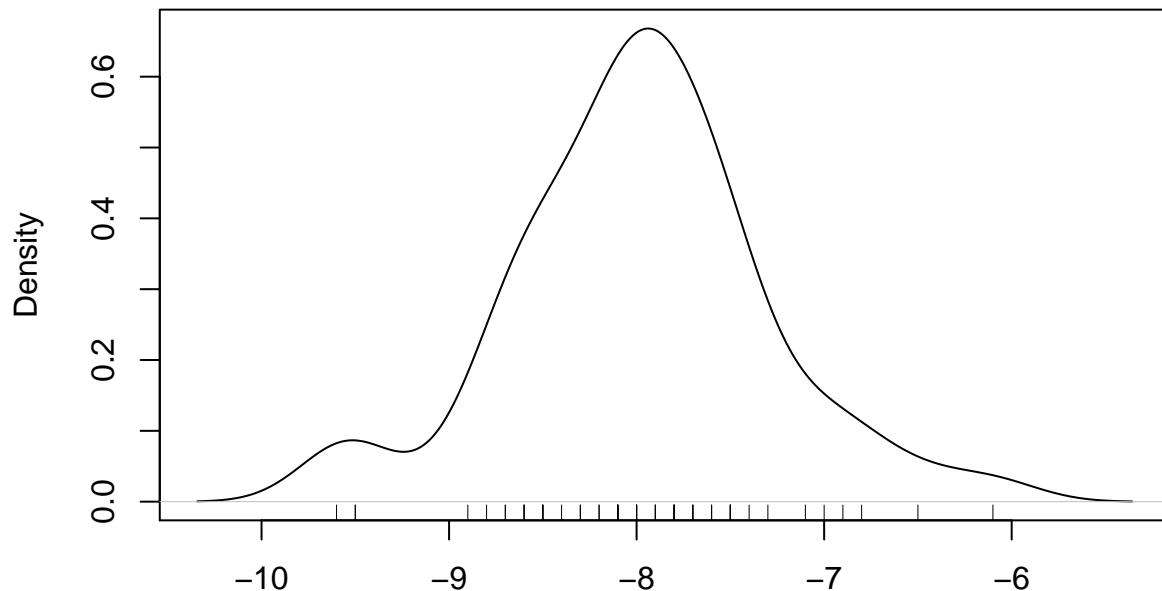
```
density.default(x = docking[, i], na.rm = T)
```



N = 56 Bandwidth = 0.2102

```
## debug en <text>#4: rug(docking[, i]) ## debug en <text>#4: browser() ## debug en
<text>#4: plot(density(docking[, i], na.rm = T))
```

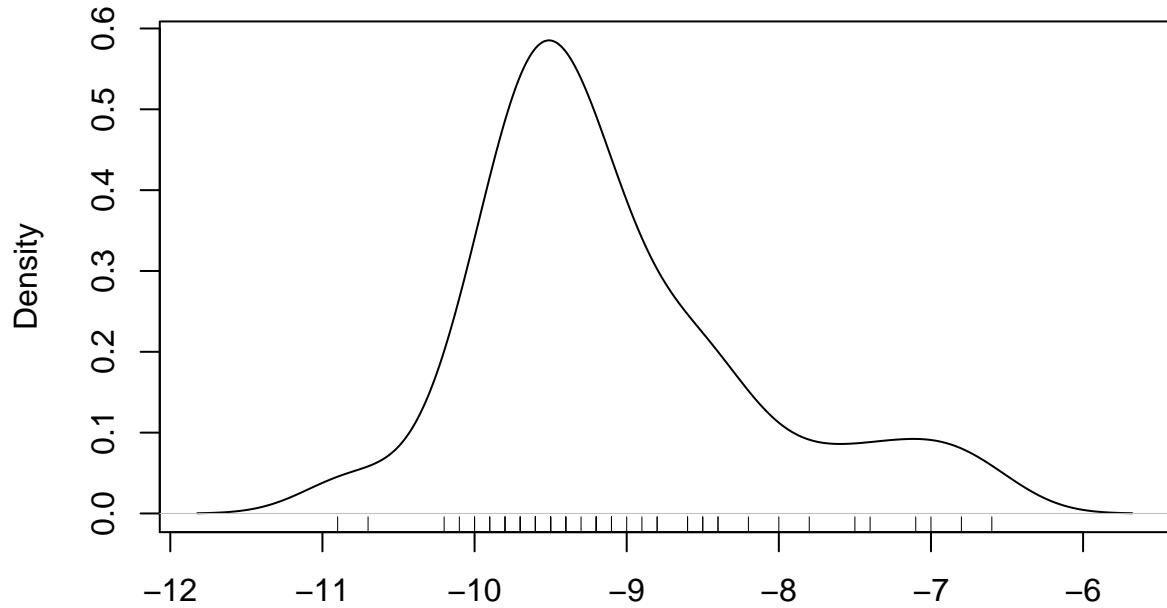
```
density.default(x = docking[, i], na.rm = T)
```



N = 56 Bandwidth = 0.2477

```
## debug en <text>#4: rug(docking[, i]) ## debug en <text>#4: browser() ## debug en
<text>#4: plot(density(docking[, i], na.rm = T))
```

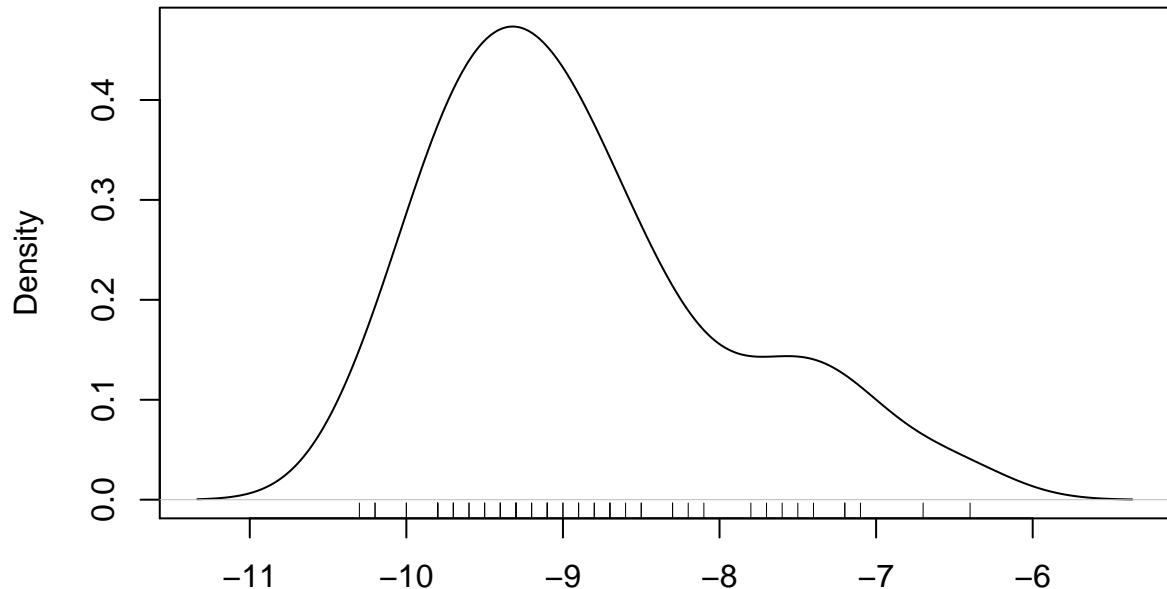
density.default(x = docking[, i], na.rm = T)



N = 56 Bandwidth = 0.3078

```
## debug en <text>#4: rug(docking[, i]) ## debug en <text>#4: browser() ## debug en
<text>#4: plot(density(docking[, i], na.rm = T))
```

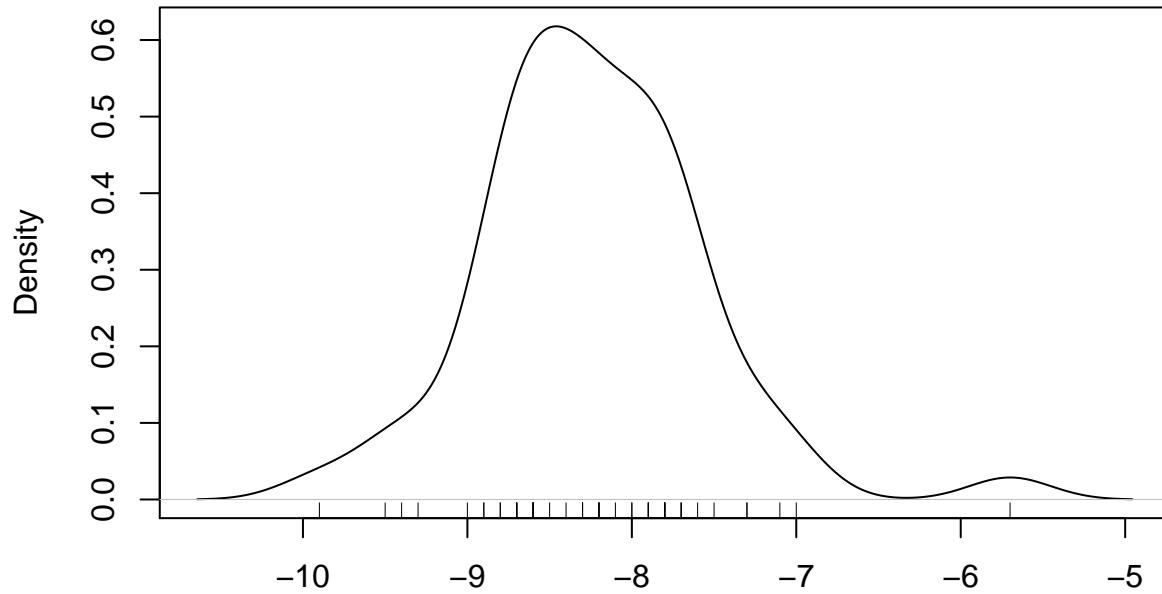
density.default(x = docking[, i], na.rm = T)



N = 56 Bandwidth = 0.3453

```
## debug en <text>#4: rug(docking[, i]) ## debug en <text>#4: browser() ## debug en
<text>#4: plot(density(docking[, i], na.rm = T))
```

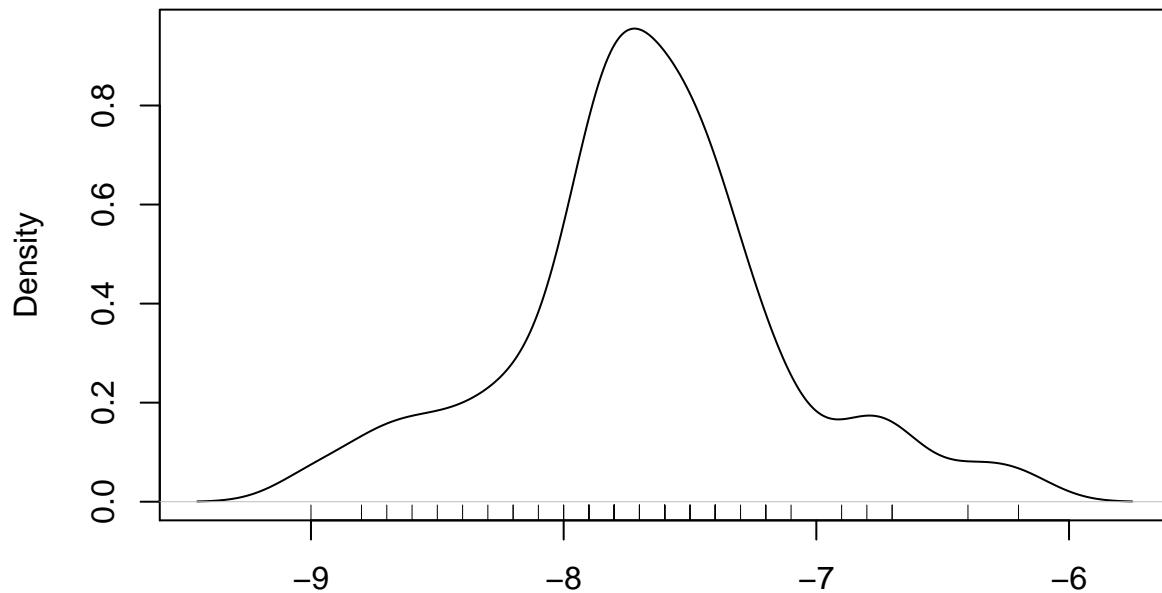
```
density.default(x = docking[, i], na.rm = T)
```



N = 56 Bandwidth = 0.2477

```
## debug en <text>#4: rug(docking[, i]) ## debug en <text>#4: browser() ## debug en
<text>#4: plot(density(docking[, i], na.rm = T))
```

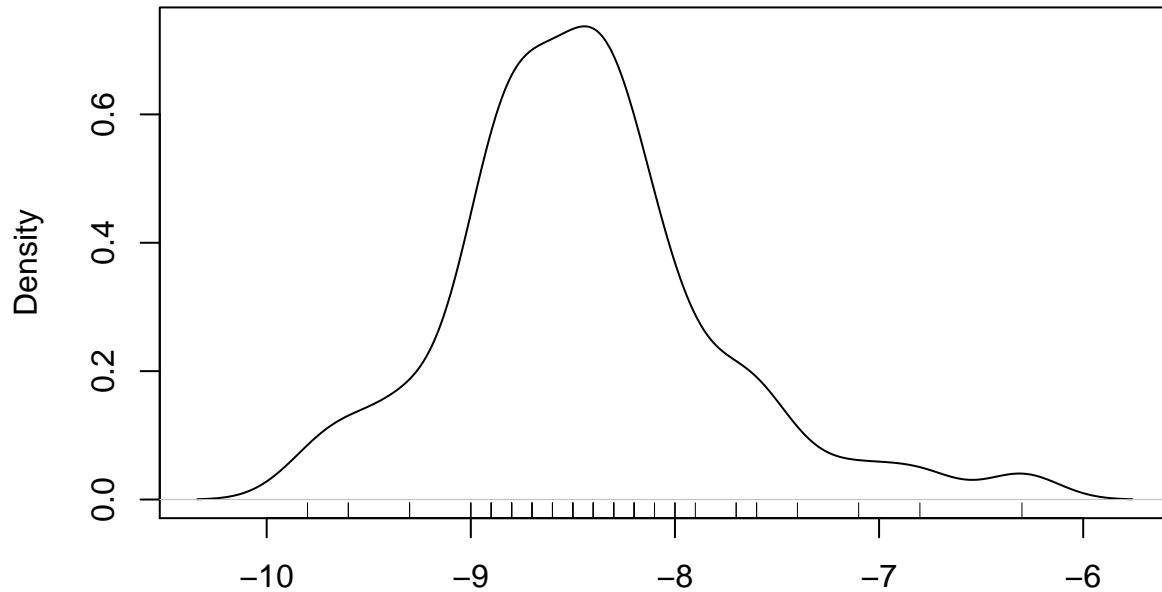
```
density.default(x = docking[, i], na.rm = T)
```



N = 56 Bandwidth = 0.1501

```
## debug en <text>#4: rug(docking[, i]) ## debug en <text>#4: browser() ## debug en
<text>#4: plot(density(docking[, i], na.rm = T))
```

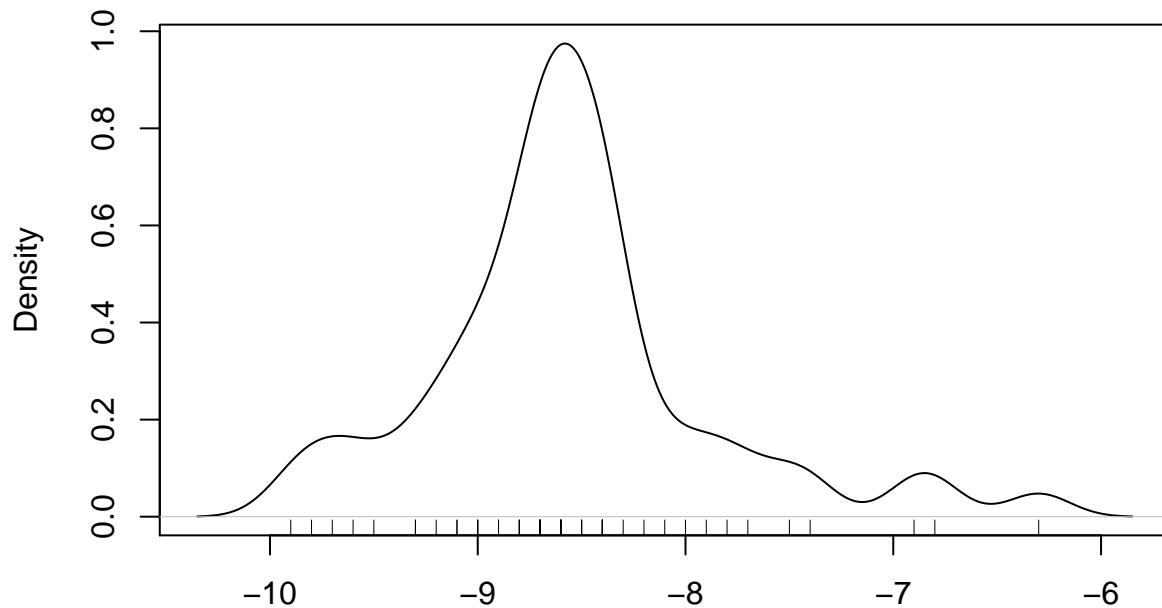
density.default(x = docking[, i], na.rm = T)



N = 56 Bandwidth = 0.1802

```
## debug en <text>#4: rug(docking[, i]) ## debug en <text>#4: browser() ## debug en
<text>#4: plot(density(docking[, i], na.rm = T))
```

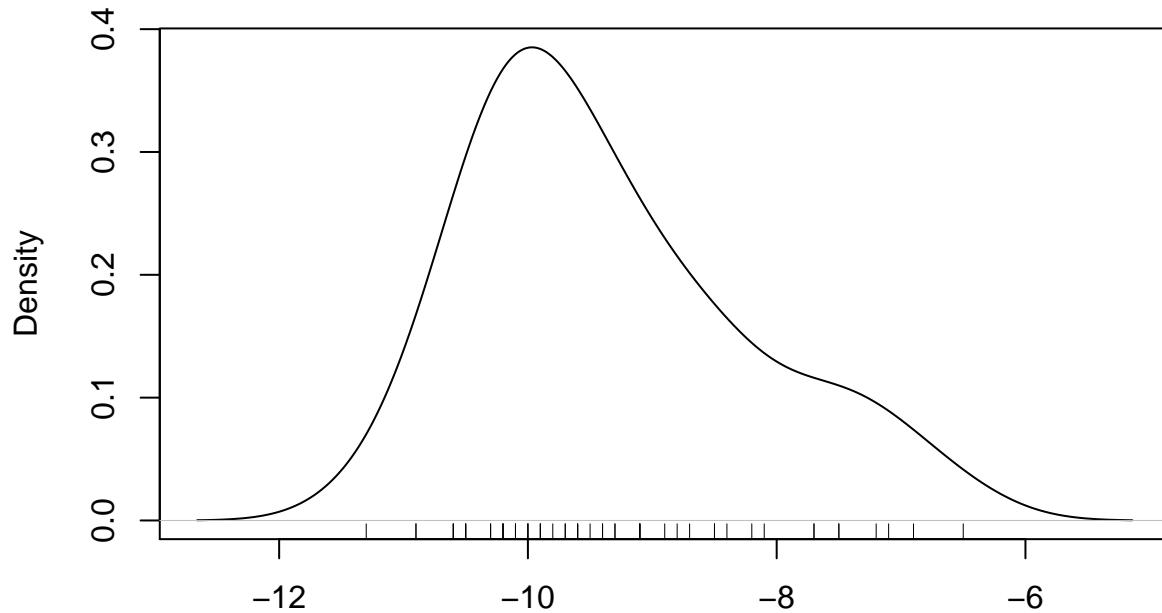
density.default(x = docking[, i], na.rm = T)



N = 56 Bandwidth = 0.1501

```
## debug en <text>#4: rug(docking[, i]) ## debug en <text>#4: browser() ## debug en
<text>#4: plot(density(docking[, i], na.rm = T))
```

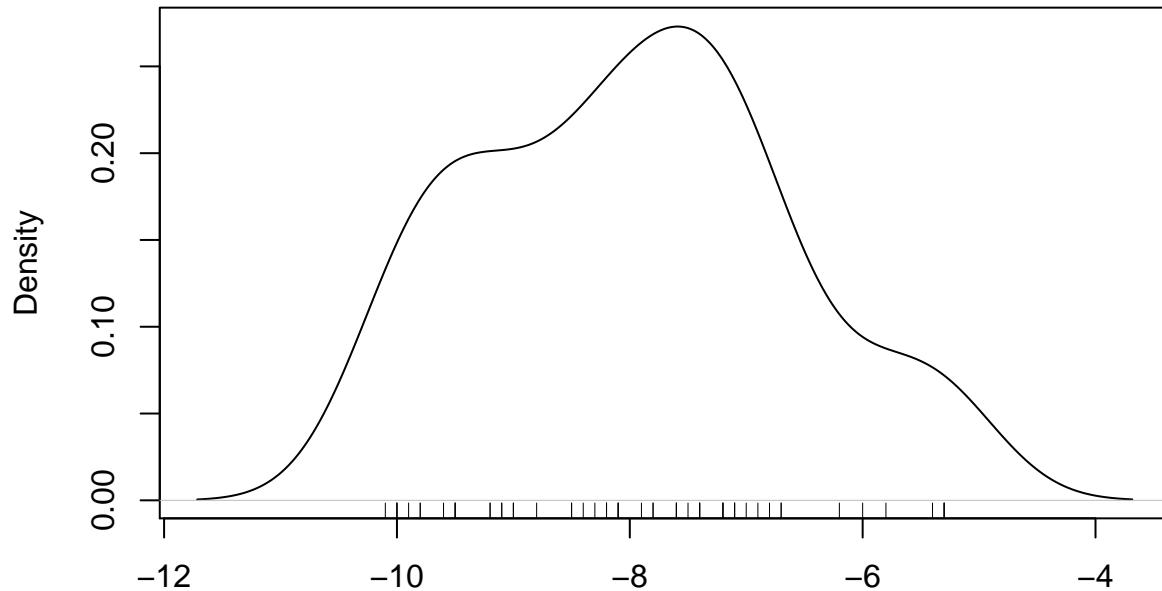
density.default(x = docking[, i], na.rm = T)



N = 56 Bandwidth = 0.453

```
## debug en <text>#4: rug(docking[, i]) ## debug en <text>#4: browser() ## debug en
<text>#4: plot(density(docking[, i], na.rm = T))
```

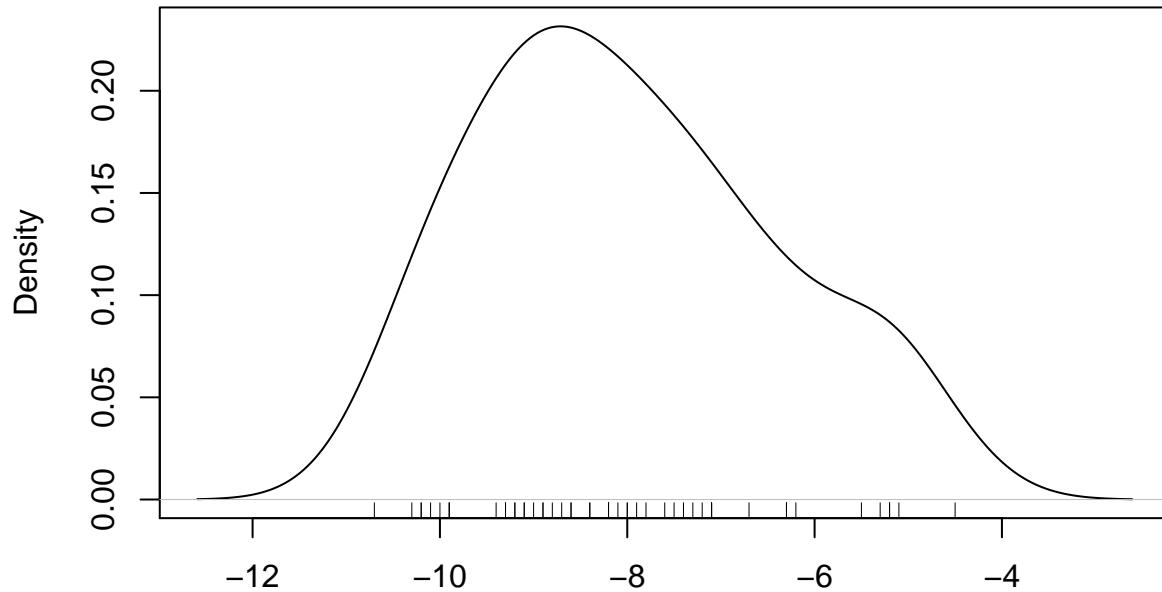
density.default(x = docking[, i], na.rm = T)



N = 56 Bandwidth = 0.5386

```
## debug en <text>#4: rug(docking[, i]) ## debug en <text>#4: browser() ## debug en
<text>#4: plot(density(docking[, i], na.rm = T))
```

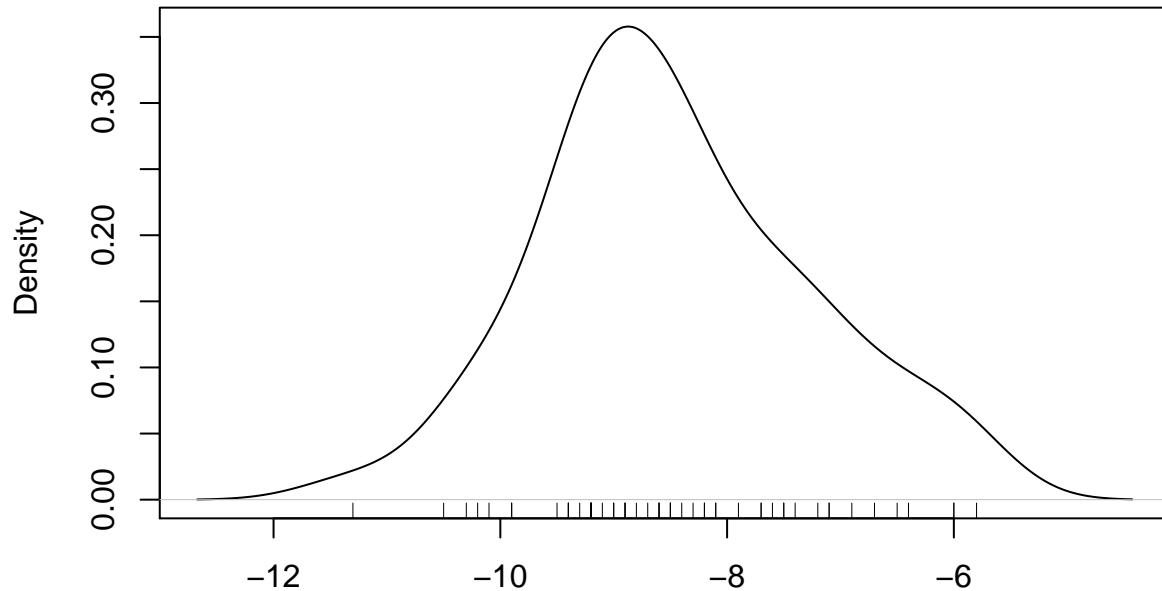
```
density.default(x = docking[, i], na.rm = T)
```



N = 56 Bandwidth = 0.6305

```
## debug en <text>#4: rug(docking[, i]) ## debug en <text>#4: browser() ## debug en
<text>#4: plot(density(docking[, i], na.rm = T))
```

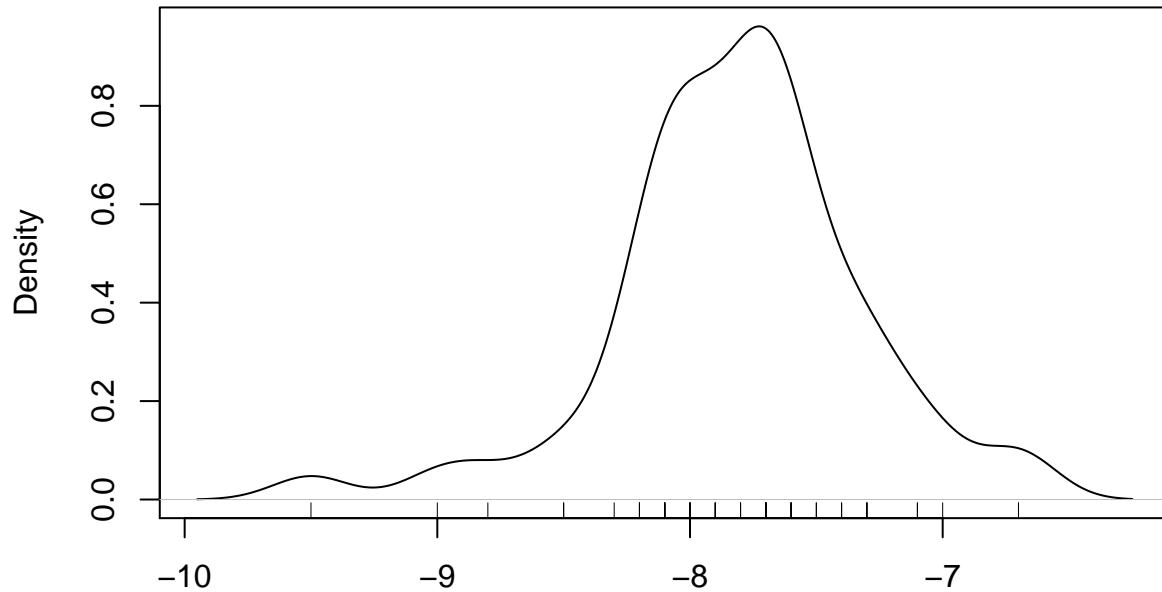
```
density.default(x = docking[, i], na.rm = T)
```



N = 56 Bandwidth = 0.4579

```
## debug en <text>#4: rug(docking[, i]) ## debug en <text>#4: browser() ## debug en
<text>#4: plot(density(docking[, i], na.rm = T))
```

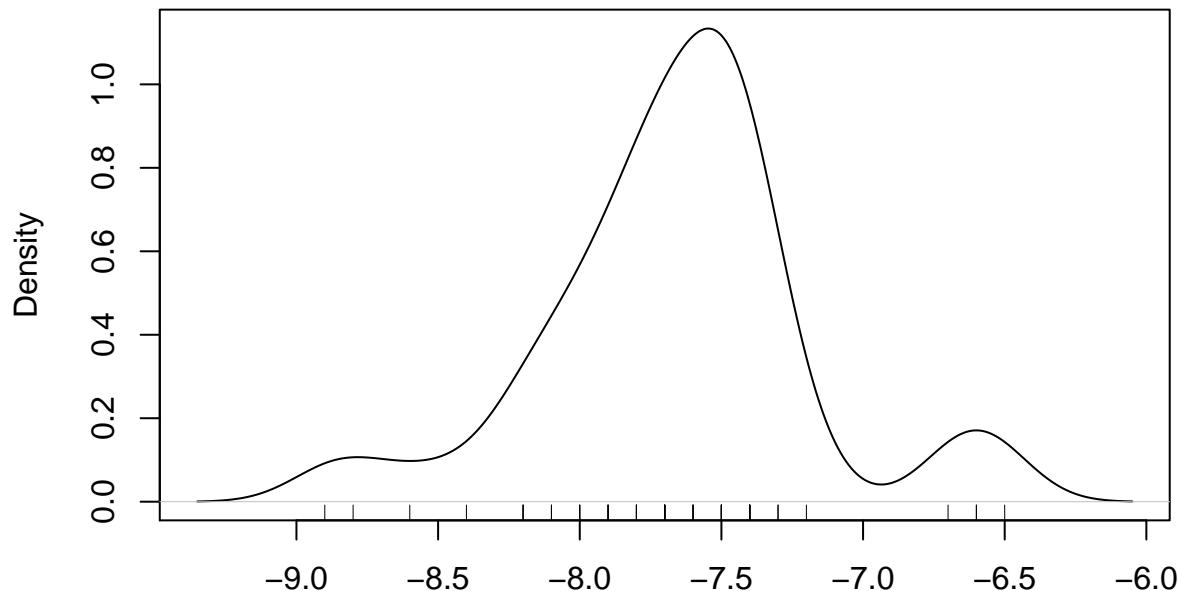
```
density.default(x = docking[, i], na.rm = T)
```



N = 56 Bandwidth = 0.1501

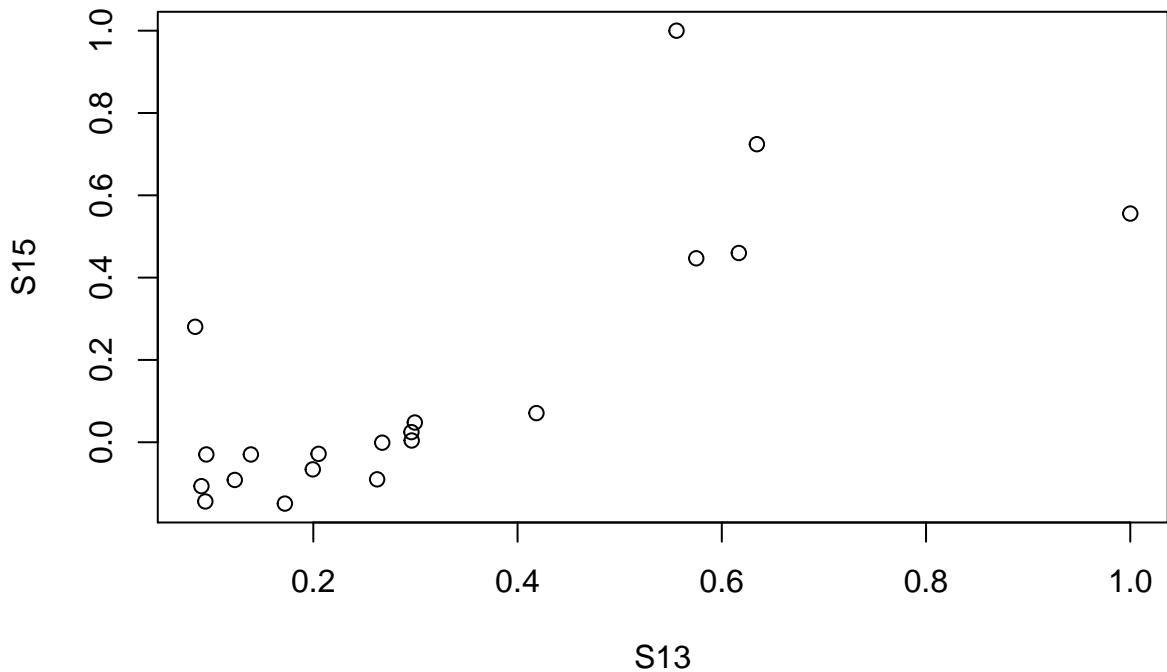
```
## debug en <text>#4: rug(docking[, i]) ## debug en <text>#4: browser() ## debug en
<text>#4: plot(density(docking[, i], na.rm = T))
```

```
density.default(x = docking[, i], na.rm = T)
```

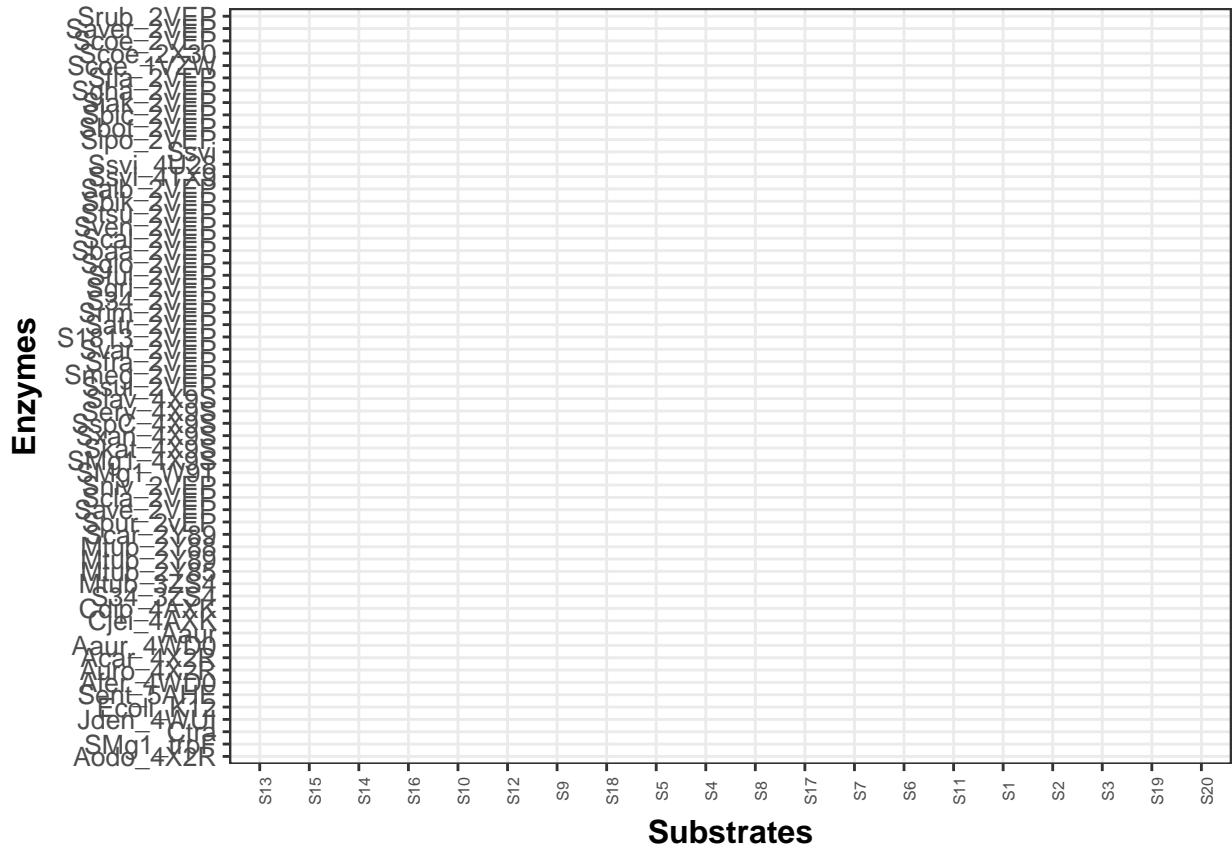


N = 56 Bandwidth = 0.1501

```
## debug en <text>#4: rug(docking[, i]) ## debug en <text>#4: browser()
r plot(cor(docking[-c(5,12,13,38,51),-1]))
```



```
r ## Leer sobre la incertidumbre del 2 y explicarla      ## Y leer el paper de Julian y  
el de mauricio sobre reportes de docking —>  
ggplot(docking.m, aes(x=variable, y=Enzima)) + labs(x = "Substrates", y = "Enzymes",text = element_text
```



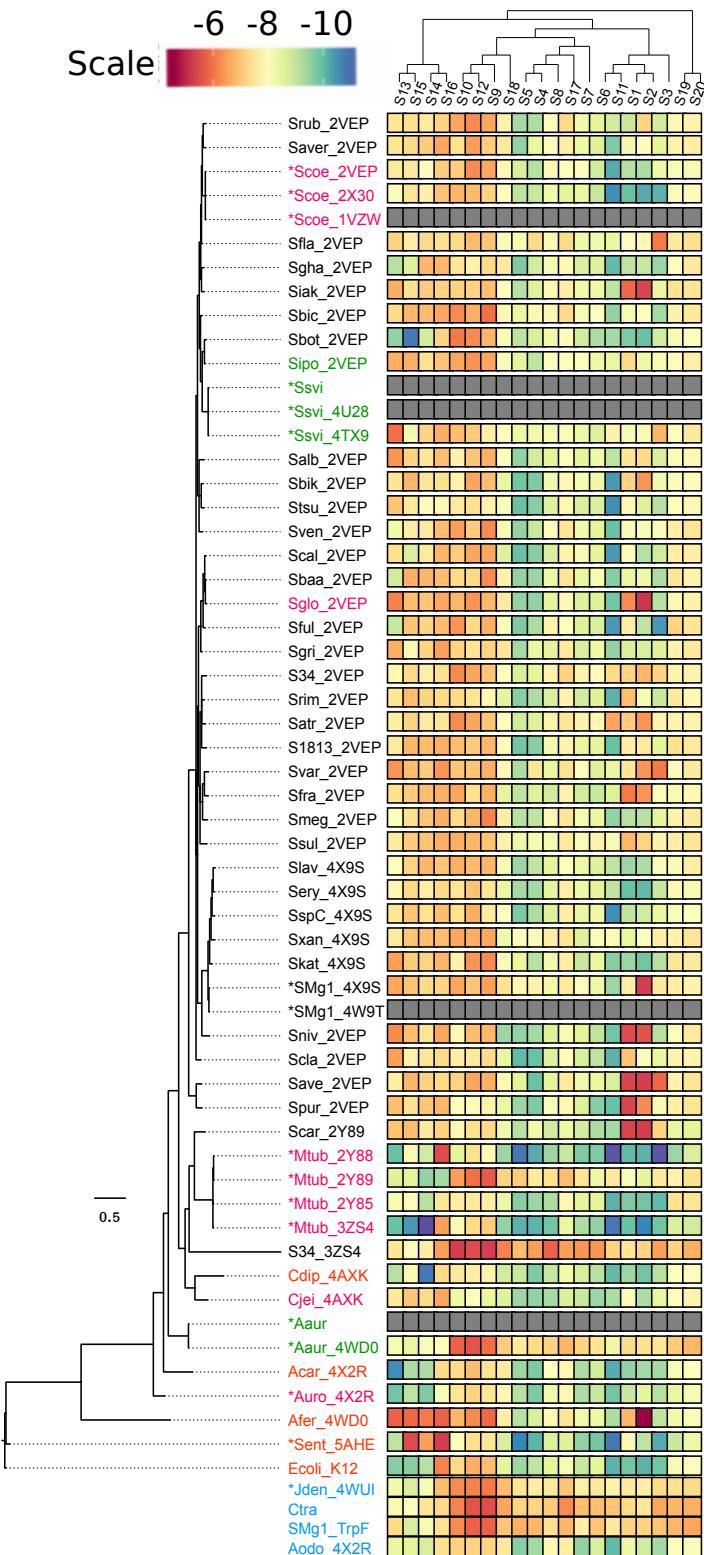


Figure 17:
33

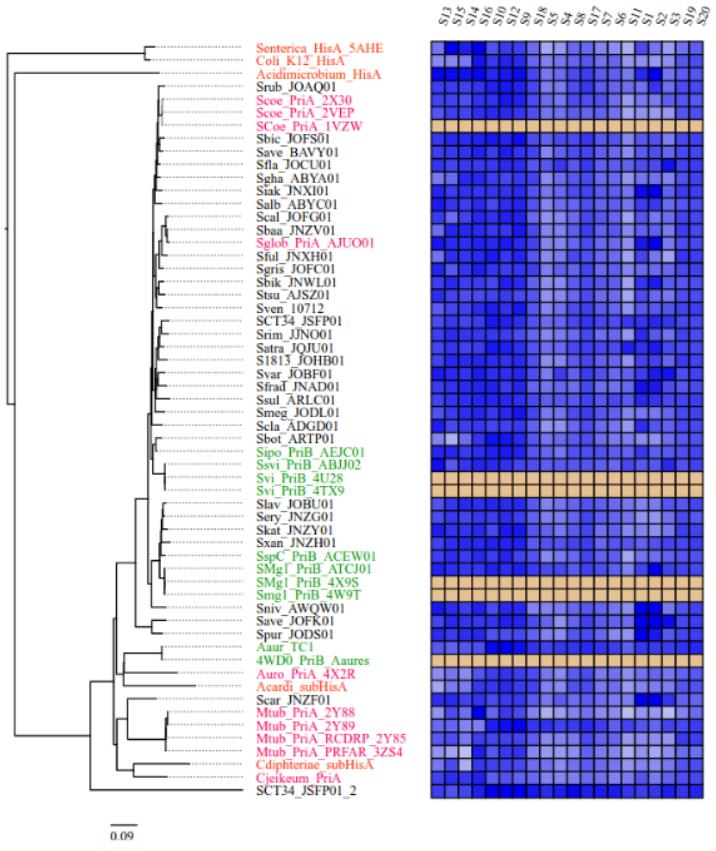
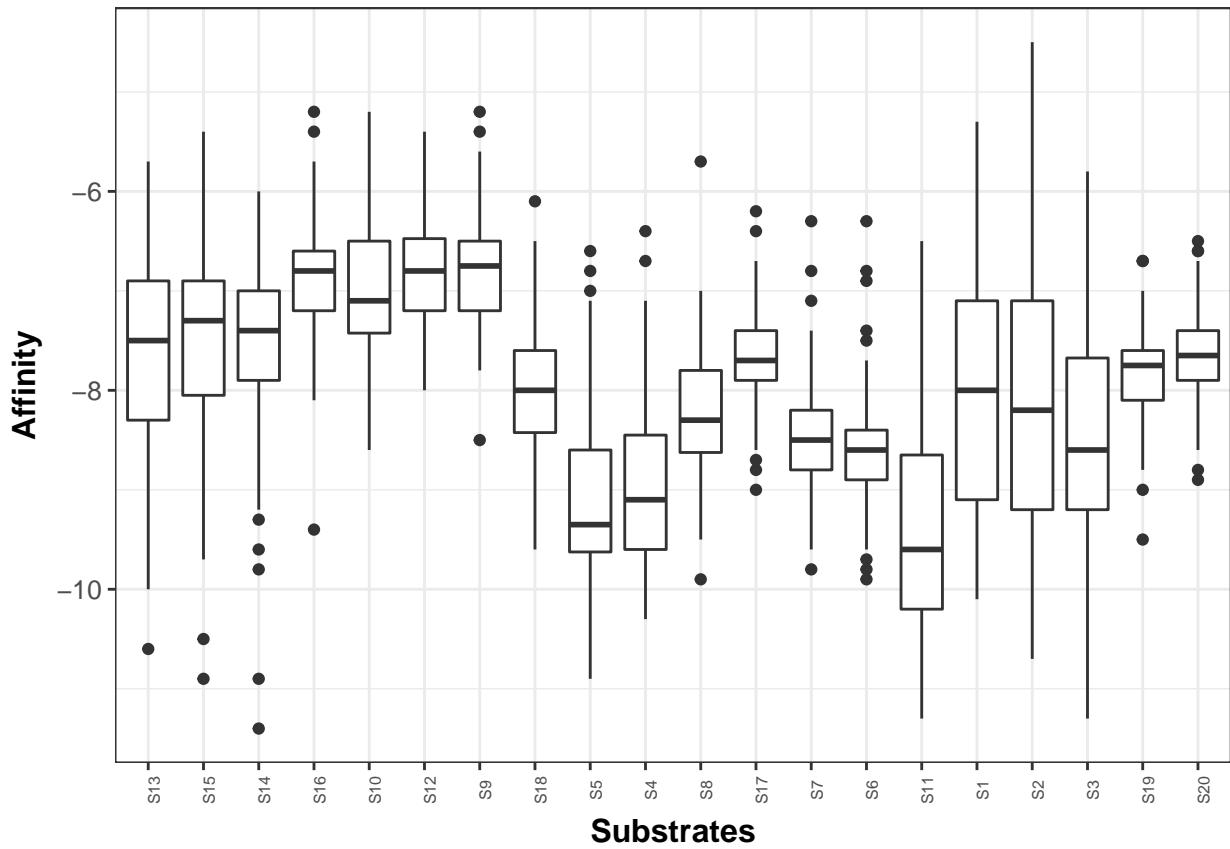


Figure 18:

GTP is the substrate with best PriA affinity

```
## boxplot de los sustratos
ggplot(docking.m, aes(x=variable, y=value)) + labs(x = "Substrates", y = "Affinity",text = element_text)
## Warning: Removed 100 rows containing non-finite values (stat_boxplot).
```



Molecular dynamics vs experimental data

PriA activity on S3 (PRA)

| organism | Family | K_M | k_{cat} | $\frac{k_{cat}}{K_M}$ | Pre MD | Pos MD | Reference |
|-----------|---------|----------------|------------------|-----------------------|--------|----------------|----------------------------------|
| Afer | HisA | 1.1 ± 0.2 | 0.05 ± 0.001 | 0.045 | -10.1 | -12.3 | Noda-García L et al 2015 |
| Ecoli | HisA | 1.6 | 4.9 | 3.1 | -9.9 | -16 | Henn-Sax et al. (2002) |
| Sent | HisA | 17.0 ± 0.1 | 7.8 ± 2.4 | 4.5×10^5 | -10.3 | -20.1 | Söderholm A et al (2015) |
| Aaur | PriB | 2.1 ± 0.5 | 1.8 ± 0.2 | 0.9 | -7.4 | | verduzco-castro 2016 |
| Sipo | PriB | 3.8 ± 0.2 | 0.82 ± 0.02 | 0.21 | -8.2 | -14.7 | verduzco-castro 2016 |
| SspC | PriB | 11.4 ± 3.4 | 2.53 ± 0.74 | 0.22 | -8.5 | -12.7 | verduzco-castro 2016 |
| SMg1 | PriB | 13.2 ± 3.4 | 0.92 ± 0.19 | 0.069 | -8 | -15.2 | verduzco-castro 2016 |
| Ssvi | PriB | 3.9 ± 0.89 | 0.69 ± 0.04 | 0.18 | -8.2 | -16.7 | verduzco-castro 2016 |
| ScOE | PriA | 3.6 ± 0.7 | 1.3 ± 0.2 | 0.4 | -8.4 | -15 | Noda-García et al (2010) |
| Sglob | PriA | 4.2 ± 0.8 | 0.74 ± 0.03 | 0.18 | -9.2 | -16.7 | verduzco-castro |
| Mtub 2Y85 | priA | 190.23 | 0.012 – 9.7 | | | | Due et al 2011 |
| Mtub 3ZS4 | priA | ? | -9.9 | | | | Due et al 2011 (To be published) |
| Auro | priA | 4.0 ± 0.9 | 0.2 ± 0.03 | 0.04 | -9.2 | | Vazquez-Juarez (2016) |
| Cjei | PriA | 2.3 ± 0.2 | 0.9 ± 0.08 | 0.39 | -8.5 | | Noda-García et al (2013) |
| Cdip | subHisA | 4.4 ± 0.5 | 2.6 ± 0.3 | 0.59 | -9.2 | | Noda-García et al (2013) |
| SMg1 TrpF | TrpF3 | - | - | - | -6.9 | -9.6 | verduzco-castro 2016 |
| Jden | TrpF3 | - | - | - -7.2 | -9.4 | 16.8 ± 3.3 | Verduzco-Castro E et al 2016 |
| Acar | SubHisA | 0.02 | | | | | |
| Aodo | SubTrpF | - | - | - | | | |

PriA activity on S7 (PROFAR) \$\$

| organism | Family | K_M | k_{cat} | $\frac{k_{cat}}{K_M}$ | Pre MD | Pos MD | Reference |
|-----------|---------|----------------|-----------------|-----------------------|--------|--------|----------------------------------|
| Afer | HisA | - | - | - | -9.2 | -9 | Noda-García L et al. (2015) |
| Ecoli | HisA | - | - | - | -9 | -11.1 | Henn-Sax et al. (2002) |
| Sent | HisA | - | - | - | -9.6 | -10.2 | Söderholm A et al (2015) |
| Aaur | PriB | 26.3 ± 6.3 | 0.37 ± 0.09 | 0.014 | -7.1 | - | verduzco-castro 2016 |
| Sipo | PriB | 60.8 ± 1.1 | 8.25 ± 0.4 | 0.14 | -8 | -8.5 | verduzco-castro 2016 |
| SspC | PriB | 149.9 ± 29 | 1.4 ± 0.12 | 0.009 | -8.5 | -10.8 | verduzco-castro 2016 |
| SMg1 | PriB | 129.6 ± 34 | 0.29 ± 0.04 | 0.0022 | -7.5 | -11 | verduzco-castro 2016 |
| Ssvi | PriB | 24.5 ± 4.0 | 1.6 ± 0.29 | 0.067 | -8 | -9.7 | verduzco-castro 2016 |
| Scoe | PriA | 5.0 ± 0.08 | 3.4 ± 0.09 | 0.7 | -8 | -9.4 | Noda-García et al (2010) |
| Sglob | PriA | 11 ± 1.0 | 3.8 ± 0.2 | 0.34 | -8.7 | -9.4 | verduzco-castro 2016 |
| Mtub2Y85 | priA | 21 | 3.6 | 0.17 | -8.6 | | Due et al 2011 |
| Mtub3ZS4 | priA | | | | -9.3 | | Due et al 2011 (To be published) |
| Auro | priA | 23 ± 6.5 | 0.5 ± 0.05 | 0.02 | -9.3 | | Vazquez-Juarez (2016) |
| Cjei | PriA | 5.1 ± 1.0 | 1.6 ± 0.16 | 0.31 | -9 | | Noda-García et al (2013) |
| Cdip | subHisA | - | - | - | -8.8 | | Noda-García et al (2013) |
| SMg1 TrpF | TrpF3 | 8.4 ± 1.7 | 10.5 ± 2.4 | 1.25 | -7.6 | -9 | verduzco-castro |
| Jden | TrpF3 | 16.8 ± 3.3 | 27 ± 1.6 | 1.6 | -7.6 | -7.7 | verduzco-castro |
| Acar | SubHisA | Na | Na | 0.02 | Na | Na | Na |
| Aodo | SubTrpF | - | - | - | - | Na | Na |

\$\$

Con actividad de FolE i.e activa para el compuesto V Adams et al (2014) Genome size vs Total antismash cluster coloured by order

```
#sessionInfo()
```