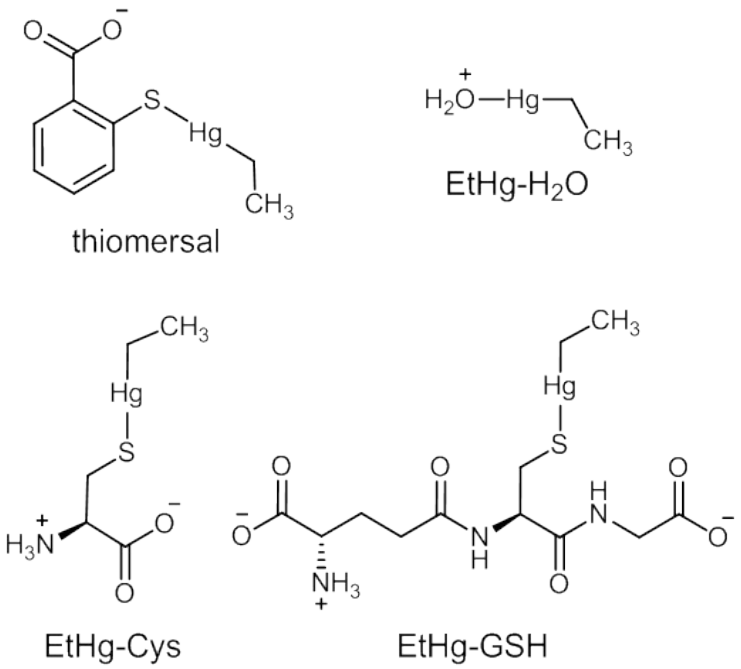
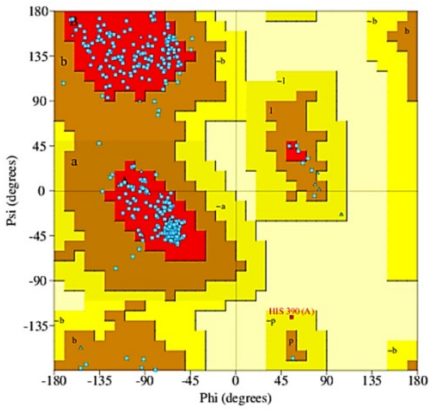
Supplementary Data

The identification of key residues that interact with a ligand in the binding cavity of protein can provide important information about molecular mechanism of inhibition. In this study we simulated the interactions of EtHg species with the *Dm*TyrH, by molecular docking. The EtHg species are represented by the Thiomersal (THIM), the EtHg complexed with one molecule of water (EtHg-H_2O), and with the low-mass thiols (*i.e.* Cys or GSH), leading to the respective adducts EtHg-Cys and EtHg-GSH (Supplementary Figure S1).

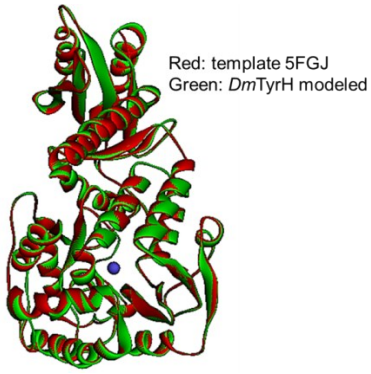


Supplementary Figure S1: ***Mercury forms and Hg adducts.***

Three dimensional structure of *Dm*TyrH modeled demonstrated that 92.0% of residues are in the most favored regions, and the overlapped structures (the template and the modeled) are very similar, with the residues from active site preserved (Supplementary Figures S2, S3, S4 and S5).



Supplementary Figure S2: Ramachandran plot for *Dm*TyrH from Swiss Model and PDBsum. Most favored regions present 92.0% of residues.



Supplementary Figure S3: Overlapping between the modeled *Dm*TyrH structure (in green) and the template rat tyrosine hydroxylase - 5FGJ (in red). The proteins present high structural similarities.

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DmTyrH   GLLTARDFLASLAFRIFQSTQYVRHVNSPYHTPEPDSIHELLGHMPLLADPSFAQFSQEI 359
5FGJ     GLLSSRDFLGGLAFRVFHCTQYIRHGSKPMYTPEPDICHELLGHVPLFSDRSFAQFSQEI 306
         ***::****..****:*:.***:** ..* :*****  ******:**::* *********

DmTyrH   GLASLGASDEEIEKLSTVYWFTVEFGLCKEHGQIKAYGAGLLSSYGELLHAISDKCEHRA 419
5FGJ     GLASLGAPDEYIEKLATIYWFTVEFGLCKEGDSIKAYGAGLLSSFGELQYCLSDKPKLLP 366
         ******* ** ****:*:************ ..***********:*** :.:*** :
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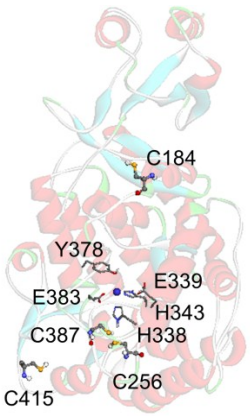
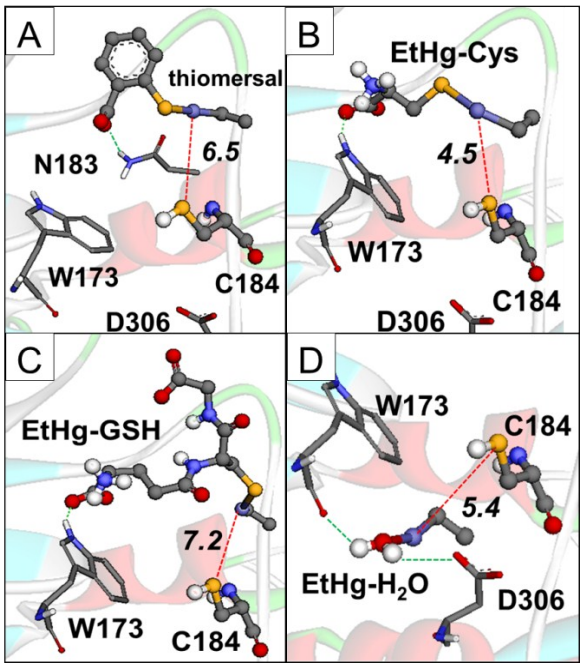
Supplementary Figure S4: Fragment of the alignment of residues from *Dm*TyrH and phenylalanine hydroxylase (5FGJ), obtained by ClustalOmega (http://www.ebi.ac.uk/Tools/msa/clustalo/). The residues from active site are highlight in colors: blue histidine; yellow glutamate and in green tyrosine.



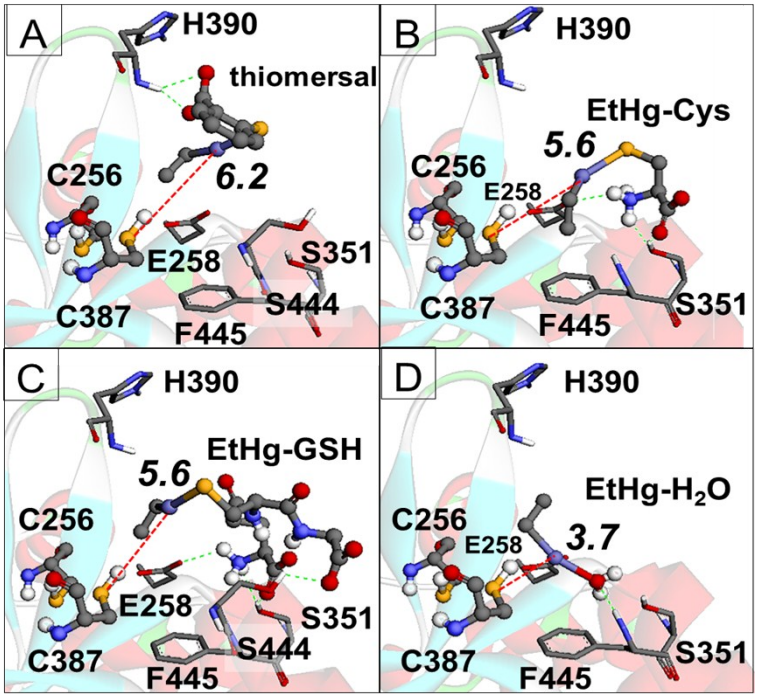
Supplementary Figure S5: Structure of *Dm*TyrH. The residues of the active site and the cysteines are highlight.

Based in the fact that the EtHg could binding in cysteinyl residues in proteins and low-mass thiol molecules [1, 2, 3], we performed two local docking (Supplementary Figure S6; S7 and Table S1). The first with the coordinates centered on the sulfur atom from C184, and the second with the gridbox that involve the C256, C387 and C415 (Supplementary Figure S6). The docking simulations on the C184 demonstrated that all EtHg species can interact with the thiol group of C184. Accordingly, THIM showed H-bonds with the N183 (Figure S6 A), while EtHg-Cys and EtHg-GSH presented H-bonds with W173 (Figure S6 B and C). The EtHg-H_2O complex showed H-bonds with the carboxyl moiety of D306 and the backbone of W173 (Figure S6 D). The (C184)S…Hg distances order were: EtHg-Cys < EtHg-H_2O < EtHg-GSH < THIM.



Supplementary Figure S6: Interactions between the EtHg species and C184 from local docking. The H-bonds are represented by green dot lines (2.0 – 2.5 Å) and S–Hg interactions is showed in red dot lines (distance in Å).

On the other hand, the second local docking showed the C387 residue could be a target to the EtHg species (Supplementary Figure S7). THIM interact with the backbone of H390 by H-bonds, while the EtHg-Cys and EtHg-GSH complexes made H-bonds with E258, S351 and S444. The EtHg-H_2O adduct showed a H-bond with the backbone of F445 and present the shorter S...Hg interaction (3.7 Å) when compared to the other EtHg species (5.6 – 6.2 Å) (Figure S7).



Supplementary Figure S7: Interactions between the EtHg species and *Dm*TyrH from local docking. Results from the gridbox that involve the C256, C387 and C415. The H-bonds are represented by green dot lines (2.0 – 2.5 Å) and S–Hg interactions is showed in red dot lines (distance in Å).

Table S1: Predicted ΔG_{bind} for EtHg species and *Dm*TyrH in the local docking.

ΔG (kcal/mol)	**THIM**	**EtHg-Cys**	**EtHg-GSH**	**EtHg-H_2O**
On C184	-4.7	-5.0	-6.1	-3.2
On C387*	-3.8	-3.7	-4.9	-2.6

* Represent the gridbox that involve the C256, C387 and C415.

Supplementary References

1. J. G. Dorea, M. Farina and J. B. Rocha, Toxicity of ethylmercury (and Thimerosal): a comparison with methylmercury, *Journal of applied toxicology : JAT*, 2013, **33**, 700-711.

2. J. F. Risher and P. Tucker, Alkyl Mercury-Induced Toxicity: Multiple Mechanisms of Action, *Reviews of environmental contamination and toxicology*, 2017, **240**, 105-149.

3. S. Trumpler, B. Meermann, S. Nowak, W. Buscher, U. Karst and M. Sperling, In vitro study of thimerosal reactions in human whole blood and plasma surrogate samples, *Journal of trace elements in medicine and biology : organ of the Society for Minerals and Trace Elements*, 2014, **28**, 125-130.