

Ethambutol based Organic Salts and Ionic Liquids as Effective Drug Formulations against Tuberculosis

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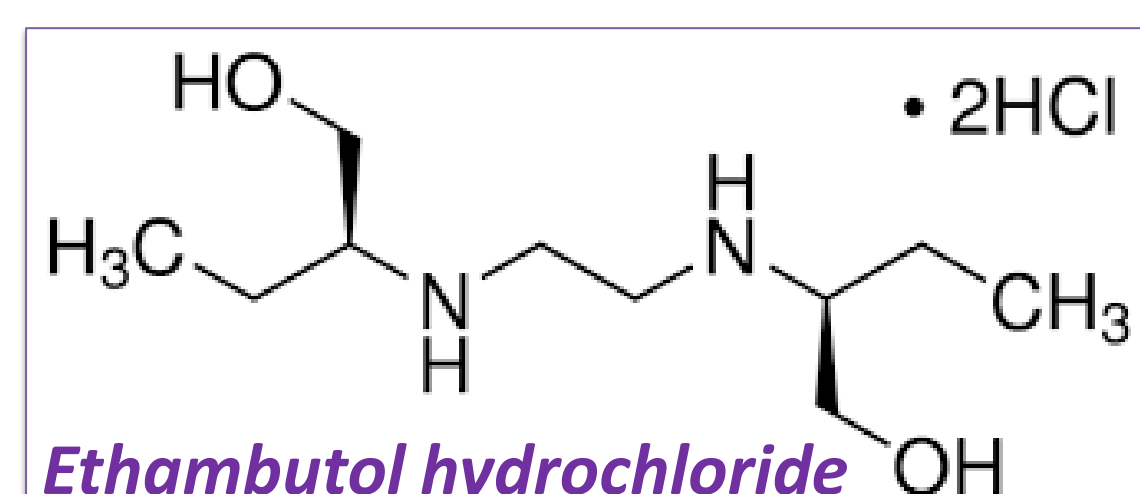
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Introduction

Tuberculosis (TB) remains the leading cause of death among adults worldwide. It has been primarily fought using drug combinatorial regimes including isoniazid, rifampicin and ethambutol. However, such first line therapies often fail to cure TB due the development of drug resistance. This can be related to low bioavailability and efficiency of the drugs, as well as polymorphism. Organic salts and ionic liquids (OSILs) containing active pharmaceutical ingredients (OSIL-APIs) have been showed as good drug delivery tools for APIs and drug modulations especially against resistant bacteria [1-6].



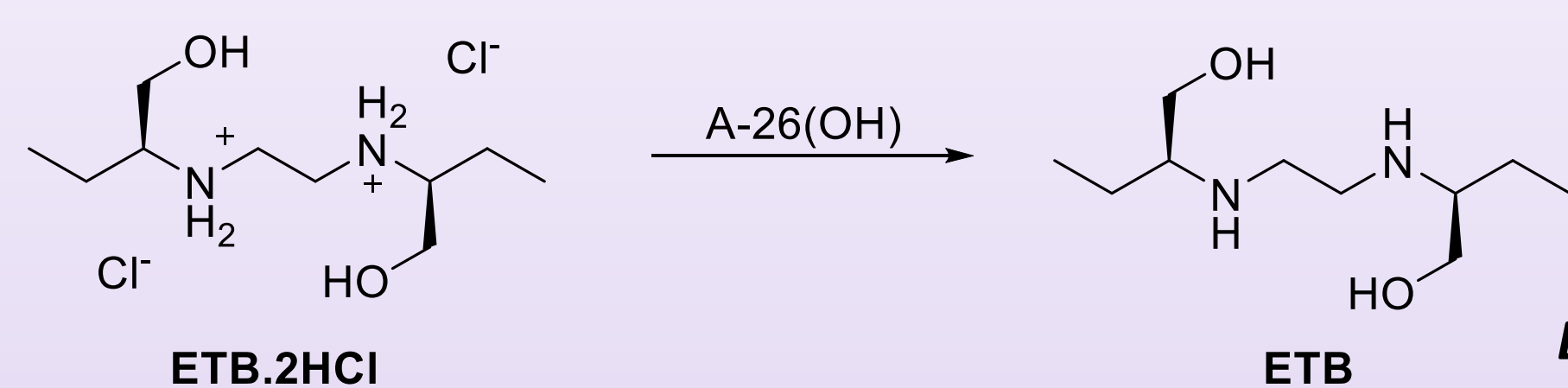
Objectives

In this work, we describe the suitable combination of a pharmaceutical drug, **ethambutol (ETB)** and **three suitable counter-ions** of different polarities as an innovative approach to improve the original compound's properties. This strategy is focused in the improvement of bioavailability as well as the elimination of polymorphism of ETB-OSILs comparing to original $[\text{ETBH}_2]\text{Cl}_2$. In order to evaluate the toxicity of prepared ETB-OSILs, three of the most promissory with the best solubility profile and containing biocompatible counteranions ($\text{X} = \text{TsO}, \text{MsO}, \text{GlucO}$) were selected for *in vivo* toxicity studies in zebrafish (*Danio rerio*).

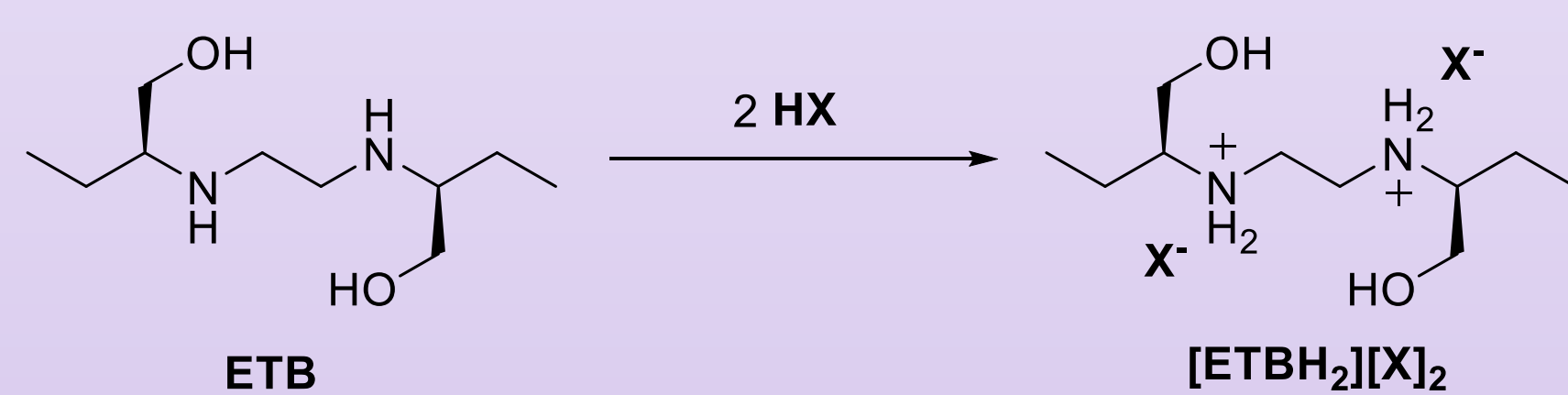


Results and discussion

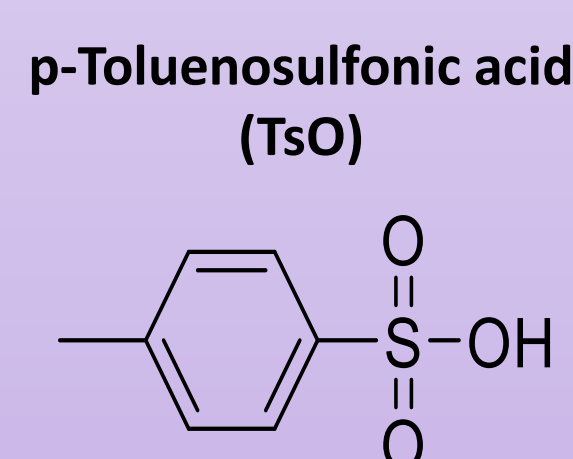
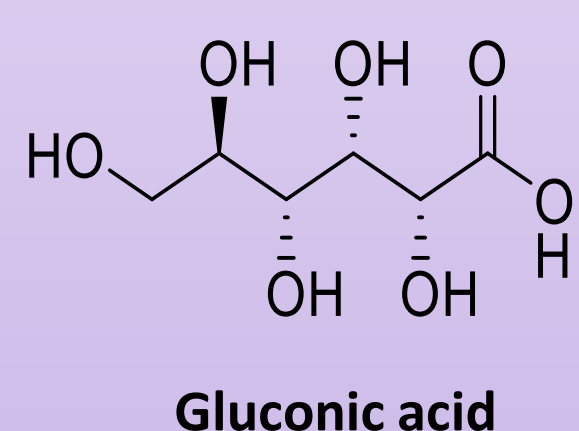
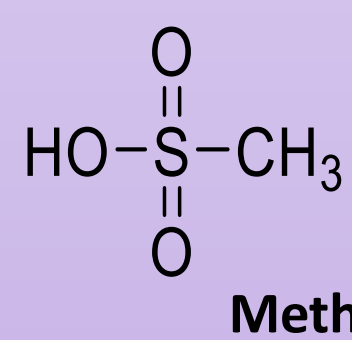
Preparation of different Ethambutol-OSILs



Synthesis of dicationic Ethambutol salts by direct protonation



HX (organic acids)



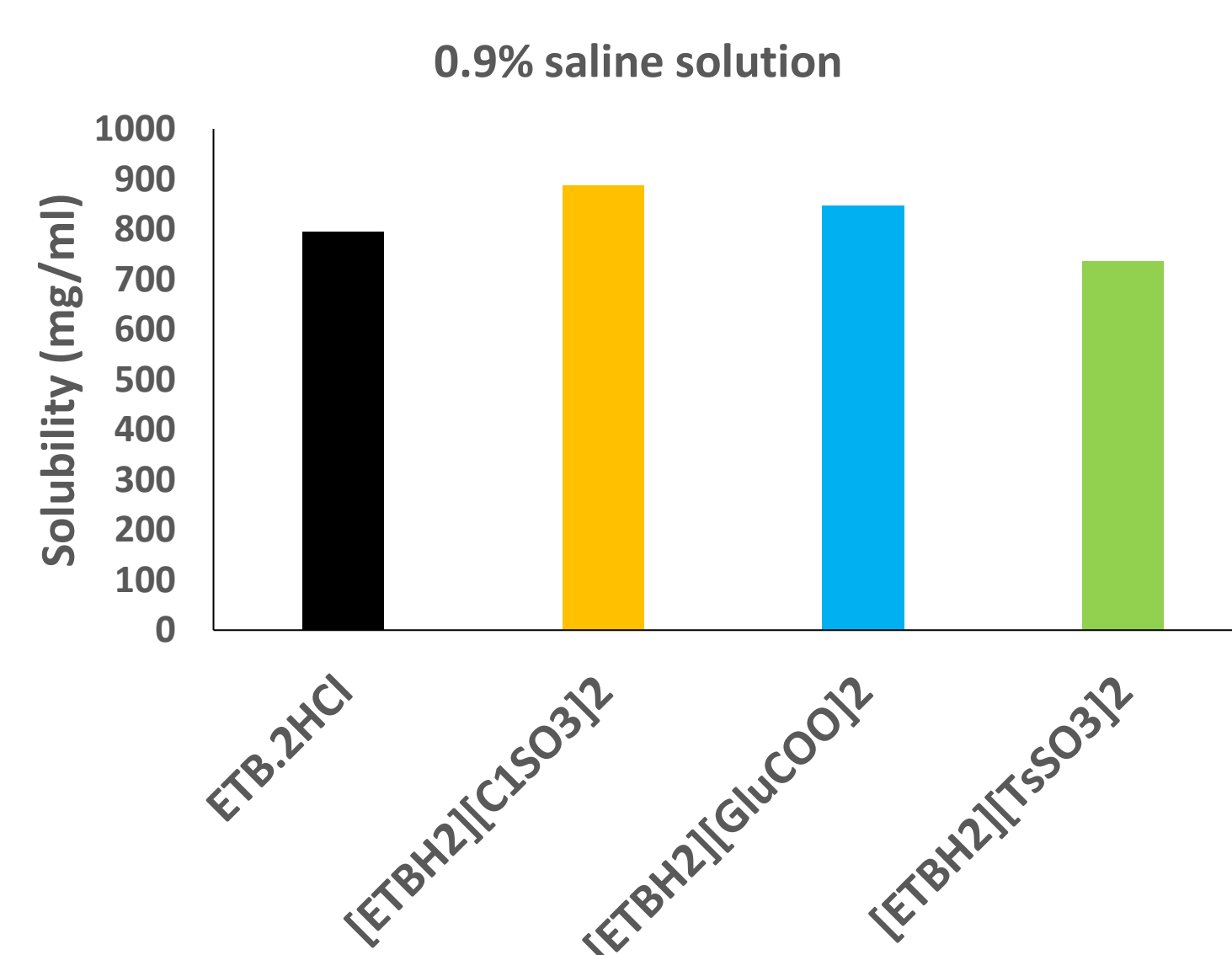
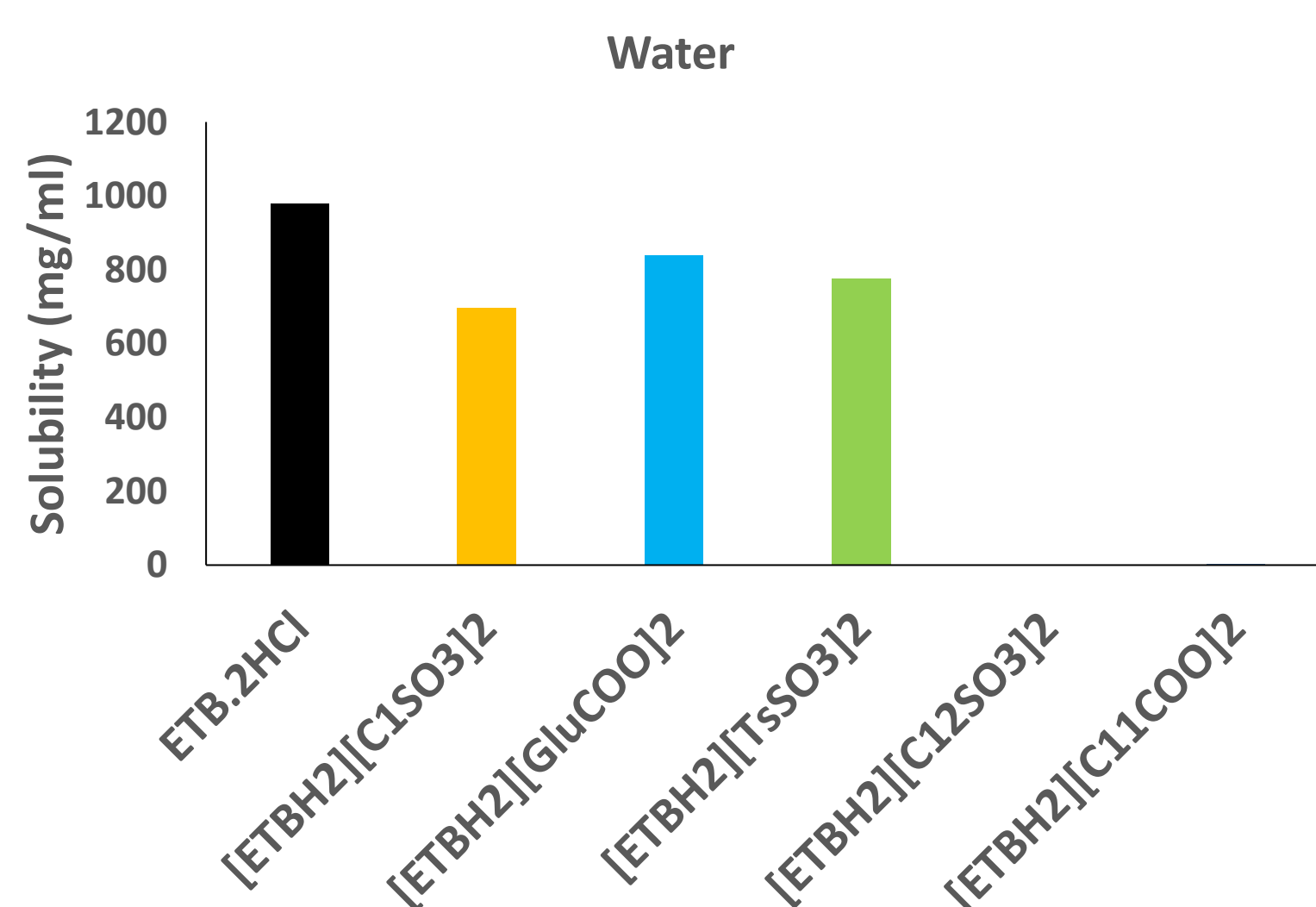
ETB based organic salts and ionic liquids (ETB-OSILs) were prepared in quantitative yields by neutralization reaction of ETB free base with biocompatible organic acids of different polarities.

The prepared ETB-OSILs were characterized by ¹H, ¹³C NMR, FTIR and elemental analysis.

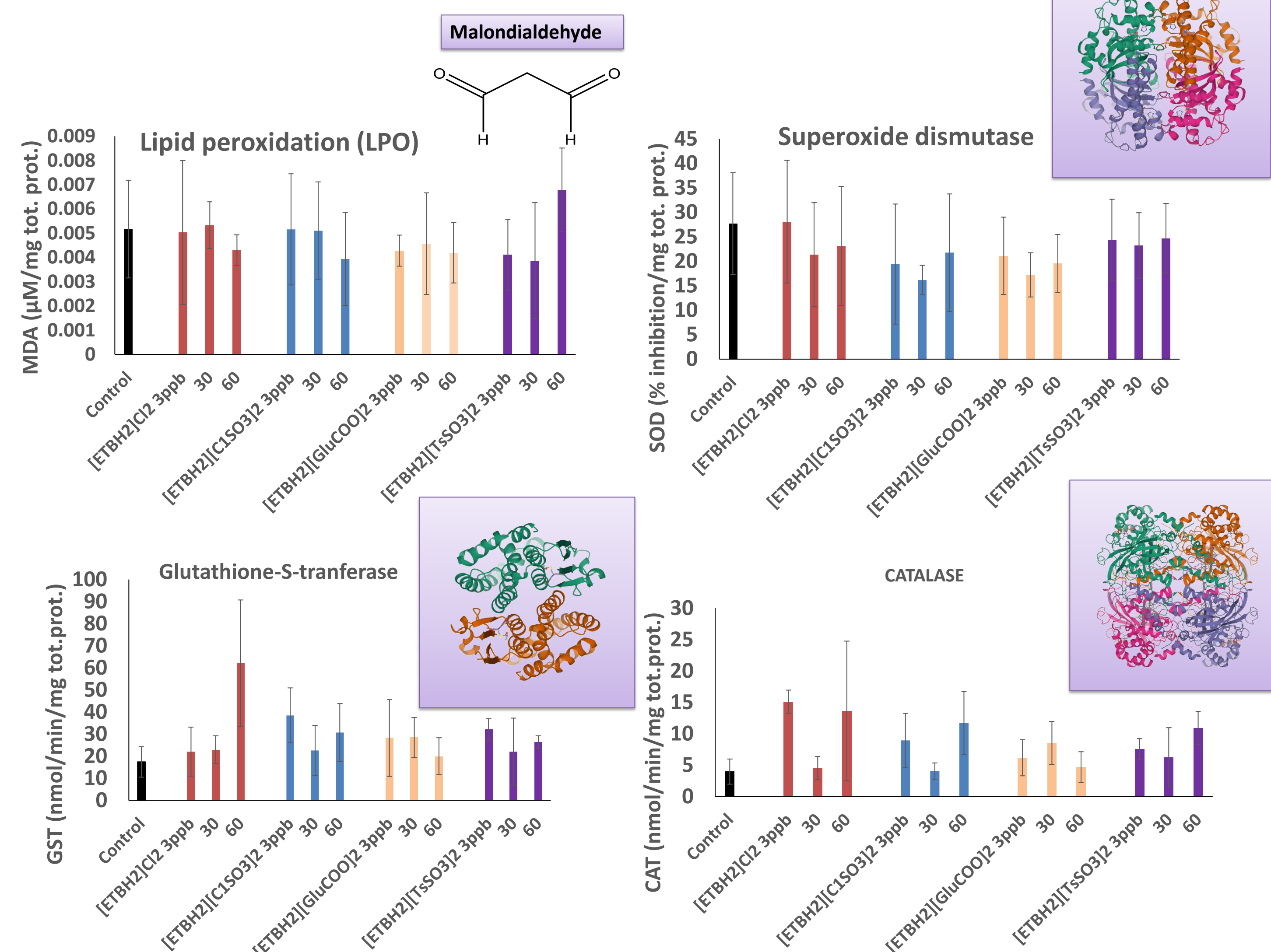
Solubility studies

$[\text{ETBH}_2]\text{X}_2$ solubility in saline sol. at 37 °C

$[\text{ETBH}_2]\text{X}_2$ solubility in water at 37 °C



Toxicity studies



For toxicological studies, 4 biomarkers were used to evaluate the levels of toxicity of the 3 selected compounds as well as ethambutol dihydrochloride as original drug. Through statistical analysis, we were able to conclude that no significant increase of the three oxidative stress enzymes (SOD, GST and CAT) of the prepared ETB-OSILs in respect to parent $[\text{ETBH}_2]\text{Cl}_2$ drug were observed.

Conclusions

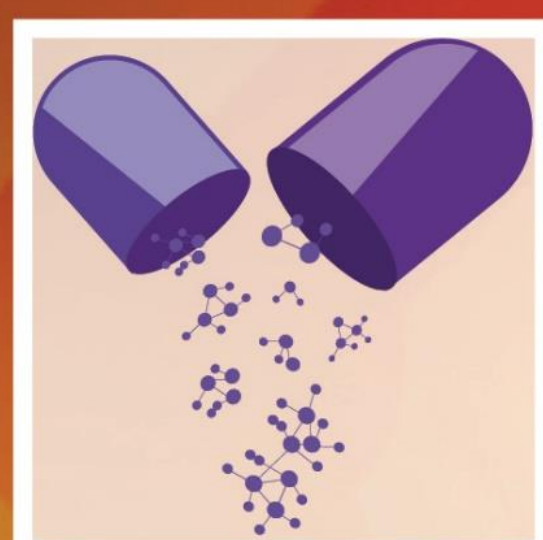
- Novel organic salts and ionic liquids based on ethambutol drug (ETB-OSILs) were prepared and characterized from commercial available $[\text{ETBH}_2]\text{Cl}_2$ drug;
- Solubility in water and saline solution of ETB OSILs is similar or even better comparing to $[\text{ETBH}_2]\text{Cl}_2$;
- ETB-OSILs showed no significant *in vivo* toxicity in zebrafish according to the evaluation of the three oxidative stress enzymes and lipoperoxidation comparing to original ethambutol hydrochloride ($[\text{ETBH}_2]\text{Cl}_2$);
- In the future, we are interested to test the most promissory ETB-OSILs against *Mycobacterium marinum* as well as sensitive and resistant *Mycobacterium tuberculosis*.

References

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Acknowledgment

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