Novel organic salts and ionic liquids based on Mefloquine drug for application in Tuberculosis treatment

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Introduction

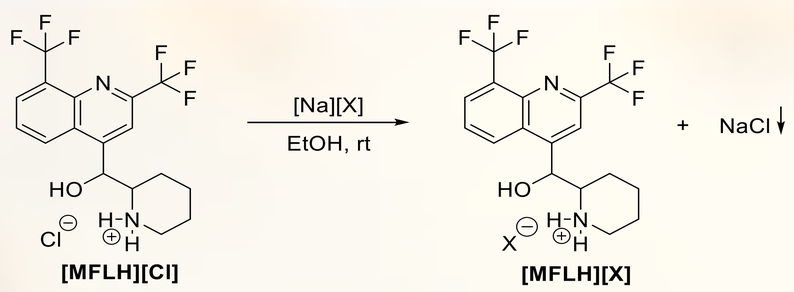
Tuberculosis (TB) remains a major public health concern and currently is the leading cause of human death by an infectious disease. According to the World Health Organization (WHO), around 10 million people were infected with the *Mycobacterium tuberculosis* in 2020 and 1.5 million died[1]. The emergence and spread of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains is particularly alarming.

During the last years, the use of organic salts and ionic liquids (OSILs) emerged as a topic of intense scientific interest. Due to the unique characteristics of these ionic systems, such as negligible vapor pressure, good thermal stability, high electric conductivity and miscibility with water and organic solvents, the applications in different fields have been described[2-4].

Hence, considering the potential of Mefloquine (MFL) for the development of new treatments against tuberculosis (TB) and the emergence of API-OSILs as an important strategy to achieve improved pharmaceutical properties of original drugs, herein we present our work on OSILs based on MFL as an improved formulation of this drug to tackle *M. tuberculosis*.

Synthesis of Mefloquine OSILs

The MFL salts were obtained through a metathesis reaction (Scheme 1), a straightforward and well described method for the preparation of this type of compounds.



Scheme 1.. Synthesis of MFL-OSILs and counter-ions used.

Thermal studies

All tested MFL salts presented lower melting temperatures than [MFLH][Cl], as expected (Figure 1). The latter, as well as [MFLH][HEPES], appeared to decompose upon melting. Moreover, [MFLH][MsO] was the only one to retain two distinct crystalline forms, analogously to [MFLH][Cl], given by the two endothermic signals observed in the first heating cycle.

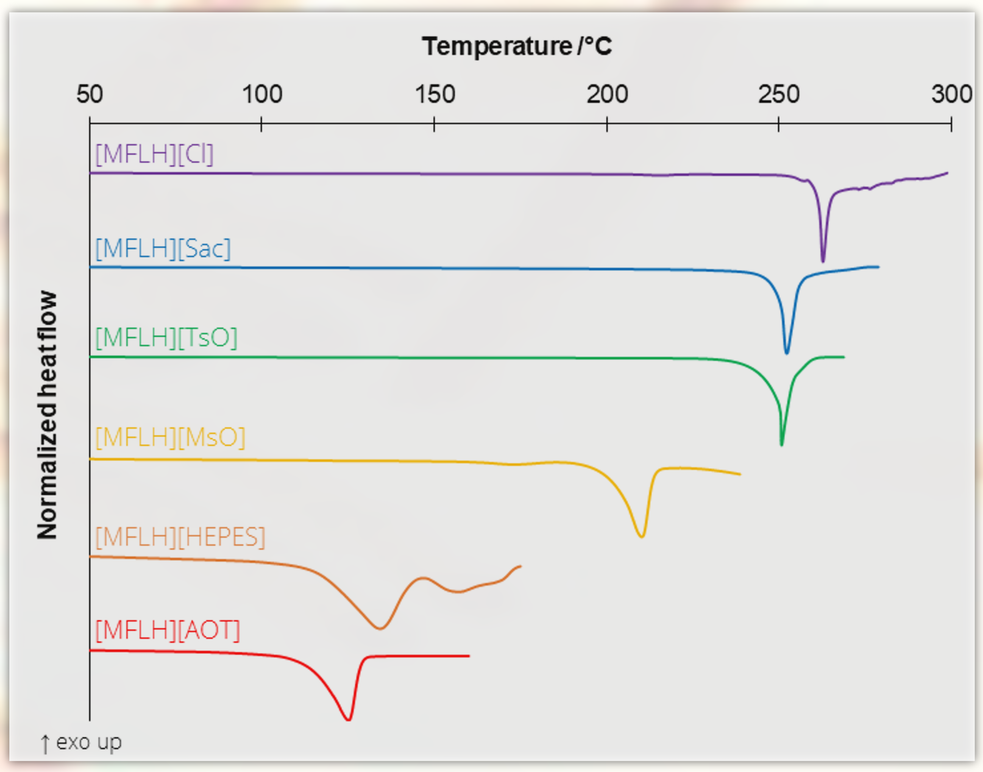


Figure 1. DSC first heating cycle of the tested MFL salts showing the salts' myriad of melting temperatures in comparison with [MFLH][Cl].

Bioavailability studies

Almost all MFL salts presented improved *in vitro* bioavailability in comparison with the original [MFLH][Cl]. In terms of solubility in water (24 hours shake-flask method), only [MFLH][MsO] showed improvement, probably due to the small size and solvability of the anion.

Table 1. Solubility, diffusion (D) and permeability (P) in water, and partition coefficients (K_d) of the MFL salts.

MFL salts	Solubility (mg/mL)	D ($\times10^{-6}$ cm^2/s)	P ($\times10^{-5}$ cm/s)	K_d
[MFLH][Cl]	4.37	0.16	0.17	0.16
[MFLH][AOT]	0.03	-	-	-
[MFLH][MsO]	7.71	0.62	0.79	0.19
[MFLH][(1R)-CSA]	0.59	1.67	1.95	0.18
[MFLH][(1S)-CSA]	0.77	0.22	0.36	0.25
[MFLH][Sac]	0.21	0.60	1.18	0.30
[MFLH][TsO]	0.09	1.21	4.23	0.52
[MFLH][HEPES]	0.64	1.75	1.13	0.10

Biological studies

With the exception of [MFLH][AOT], all salts presented a slightly improved antimycobacterial activity in comparison with the starting drug. The cellular viability of the MFL salts were determined by MTT assay at three different concentrations, 15, 30 and 60 µM, since these concentrations are in the range of the MIC values (20.27-38.80 µM).

Table 2. Minimum inhibitory concentrations (µM) and relative decrease in inhibitory concentrations (RDIC) of the MFL salts against the *M. tuberculosis* susceptible strain H37RV.

MFL salts	MIC (µM)	RDIC
[MFLH][Cl]	30.1	-
[MFLH][AOT]	31.2	0.96
[MFLH][MsO]	26.3	1.14
[MFLH][(1R)-CSA]	20.5	1.47
[MFLH][(1S)-CSA]	20.5	1.47
[MFLH][Sac]	22.4	1.35
[MFLH][TsO]	22.7	1.32
[MFLH][HEPES]	20.3	1.48

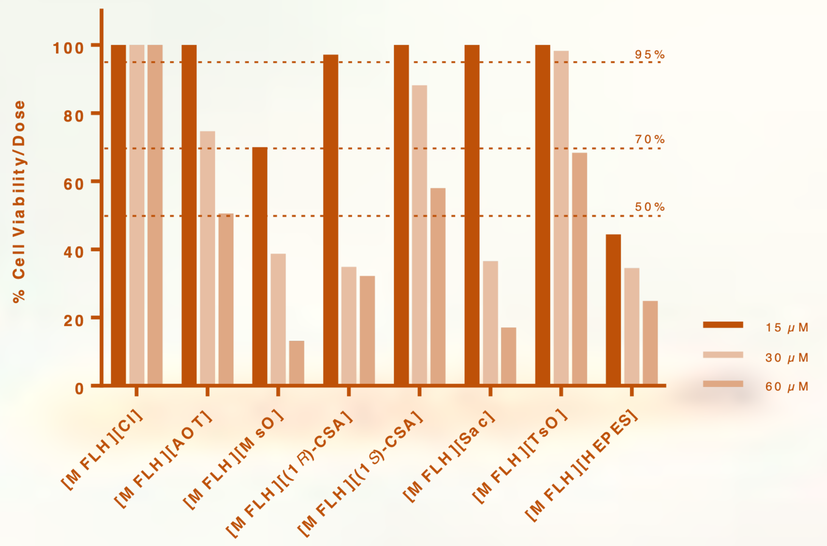


Figure 2. Plot of macrophages Raw 264.7 cellular viability by the MTT assay of [MFLH][Cl] and MFL salts.

Conclusion

In general, all developed MFL salts showed enhanced bioavailability in comparison with the original drug, [MFLH][(1*S*)-CSA] and [MFLH][(TsO)] are the most promising salts as they display the highest activities against the susceptible *Mycobacterium tuberculosis* H37RV strain at acceptable levels of cytotoxicity towards macrophages Raw 264.7.

References:

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