

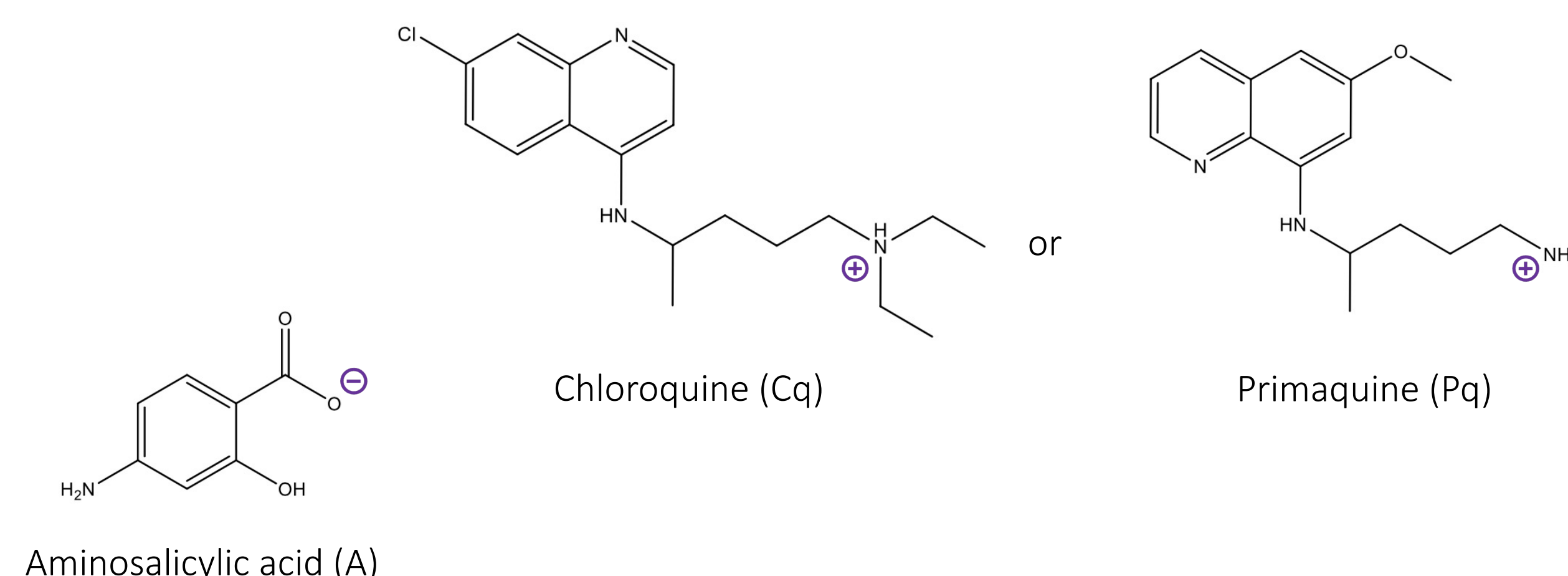
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Nontuberculous mycobacteria, namely the species belonging to the *Mycobacterium avium* complex, are highly infectious opportunistic pathogens, which incidence is increasing worldwide. Treating these infections is challenging, due to long duration, high toxicity, and low effectiveness of available drugs. It is therefore urgent to find new therapeutic strategies, including the repurposing of old drugs. Ionic liquids (ILs) are organic salts made by the combination of two molecules with opposite polarities, which are gaining attention in drug development. Combining the right ions, it is possible to create ILs that could avoid polymorphism and solubility issues presented by solid conventional drugs, improving their absorption and desired dissolution rate. Besides increasing the bioavailability, the main goals when formulating a new IL is keeping or improving the bioactivity and cytotoxicity properties of the parental drug(s). The aim of our work is to evaluate the ability of ILs based on conventional antimycobacterial drugs, like clofazimine, aminosalicylic acid, and fluoroquinolones, to inhibit the viability and growth of *M. avium* in axenic culture and inside macrophages.



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Direct activity against mycobacteria

Concentration (μM)	Clofazimine (C)	Ofloxacin (Of)	Norfloxacin (Nf)	OfC	NfC
0.00	100	100	100	100	100
0.04	100	100	100	100	100
0.15	100	100	100	100	100
0.30	100	100	100	100	100
0.40	100	100	100	100	100
0.80	100	100	100	100	100
1.60	100	100	100	100	100
3.20	100	100	100	100	100
6.40	100	100	100	100	100
25.00	100	100	100	100	100
50.00	100	100	100	100	100
100.00	100	100	100	100	100

The ILs maintain the same activity presented by the parental compounds

Toxicity against host cell

Concentration (μM)	Clofazimine (C)	Ofloxacin (Of)	Norfloxacin (Nf)	OfC	NfC
0.0	100	100	100	100	100
0.4	100	100	100	100	100
0.8	100	100	100	100	100
1.6	100	100	100	100	100
3.2	100	100	100	100	100
6.4	100	100	100	100	100
25.0	100	100	100	100	100
50.0	100	100	100	100	100
100.0	100	100	100	100	100

The ILs are not more toxic than the parental compounds

Activity against intracellular mycobacteria

Concentration (μM)	Clofazimine (C)	Ofloxacin (Of)	Norfloxacin (Nf)	OfC	NfC
NT	100	100	100	100	100
0.1	100	100	100	100	100
0.3	100	100	100	100	100
1.0	100	100	100	100	100
3.0	100	100	100	100	100
5.0	100	100	100	100	100
10.0	100	100	100	100	100
30.0	100	100	100	100	100
50.0	100	100	100	100	100
100.0	100	100	100	100	100

The ILs are more active than the parental compounds individually and are equivalent to their combined administration

Concentration (μM)	Aminos. acid (A)	Cloroquine (Cq)	Primaquine (Pq)	ACq	APq
0.00	100	100	100	100	100
0.04	100	100	100	100	100
0.15	100	100	100	100	100
0.30	100	100	100	100	100
0.40	100	100	100	100	100
0.80	100	100	100	100	100
1.60	100	100	100	100	100
3.20	100	100	100	100	100
6.40	100	100	100	100	100
25.00	100	100	100	100	100
50.00	100	100	100	100	100
100.00	100	100	100	100	100

Concentration (μM)	Aminos. acid (A)	Cloroquine (Cq)	Primaquine (Pq)	ACq	APq
0.0	100	100	100	100	100
0.4	100	100	100	100	100

Our results show that the ILs are like their parental compounds, both in terms of direct antimycobacterial activity and toxicity to the host cells. Moreover, against intracellular bacteria, the ILs are more active than their parental compounds when administered individually and equivalent to the combined administration of the parental compounds. Confirmation on better solubility and thermal stability profiles of the ILs will corroborate the potential of these new formulations as alternatives to conventional antimycobacterial drugs.

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