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Antimycobacterial effect of a new antitubercular drug candidate SQ109 against clinically relevant non-tuberculous mycobacteria

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Introduction

- Nontuberculous mycobacteria (NTMs) are a diverse group of mycobacterial species that can cause a wide range of infections, particularly in immunocompromised individuals or those with underlying lung conditions. (Griffith et al., 2007)

- Over the past few decades, the clinical isolation of NTMs and the prevalence of NTM-related diseases have increased globally. (Yang et al., 2020)

- In South Africa, where ~8 million people (12.7%) were living with HIV in 2024 and the WHO African Region recorded ~2.62 million TB cases including ~428,000 TB–HIV co-infections, the high burden of mycobacterial disease makes NTM infections an increasing concern. (Statistics South Africa, 2024; WHO, 2025)

- Current treatment are lengthy, toxic, and expensive, with cure rates ranging from 30–90% depending on the species. (Saxena et al., 2021). Therefore, new therapeutic options are urgently needed.

- One such drug candidate is SQ109, developed for TB which showed strong efficacy even against drug-resistant strains. (Imran et al., 2022)

- Its main primary mechanisms in *Mycobacterium tuberculosis* (*Mtb*) is the inhibition of the Mycobacterial membrane protein Large 3 (MmpL3), leading to increased cell wall permeability and bacterial lysis; while also impairing ATP synthesis through membrane disruption, ultimately reducing bacterial viability. (Imran et al., 2022)

Problem statement

- NTM are inherently resistant to the standard anti-tubercular drugs, and have further, shown resistance to antibacterial drugs. These complicate treatment options for NTM disease, highlighting the urgent need for new therapeutic drugs.

- SQ109, a new TB drug candidate that is currently in Phase IIb clinical trials for TB ,has shown strong activity against drug-resistant *Mtb* and a broad range of other pathogens.

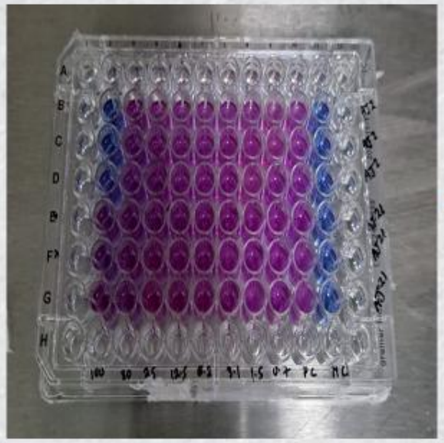
- However, the activity of SQ109 against clinically relevant NTMs such as *Mycobacterium abscessus, M. avium* complex *(*which include *M. avium* and *intracellulare) , M. kansasii,* and *M. fortuitum* remains unknown.

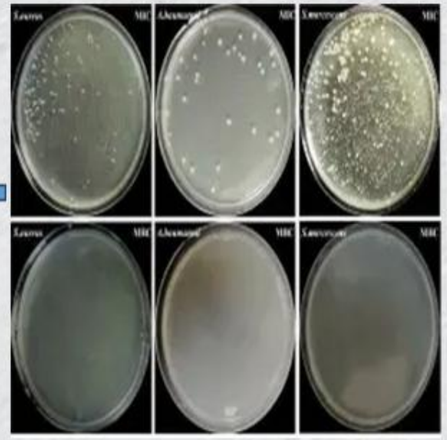
- Investigating its efficacy could help fill a critical knowledge gap and support new treatment strategies for NTM infections.

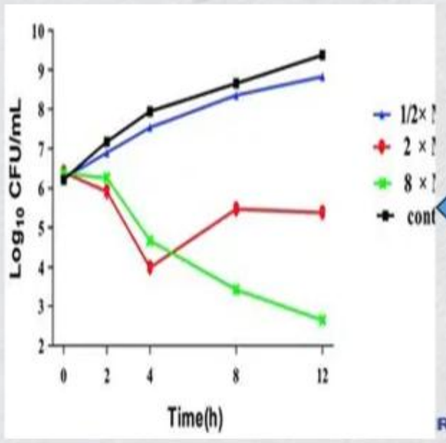
Objectives

- To determine the minimum inhibitory concentration of SQ109 on clinically relevant non-tuberculosis mycobacteria.
- To determine the minimum bactericidal concentration of SQ109 on clinically relevant non-tuberculosis mycobacteria.
- To determine the time-kill kinetics of SQ109 on clinically relevant non-tuberculosis mycobacteria.

Methods







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Results

Minimum inhibitory concentration (MIC) of SQ109 against clinically relevant NTMs at concentration ranging from 100 to 0.78 µM

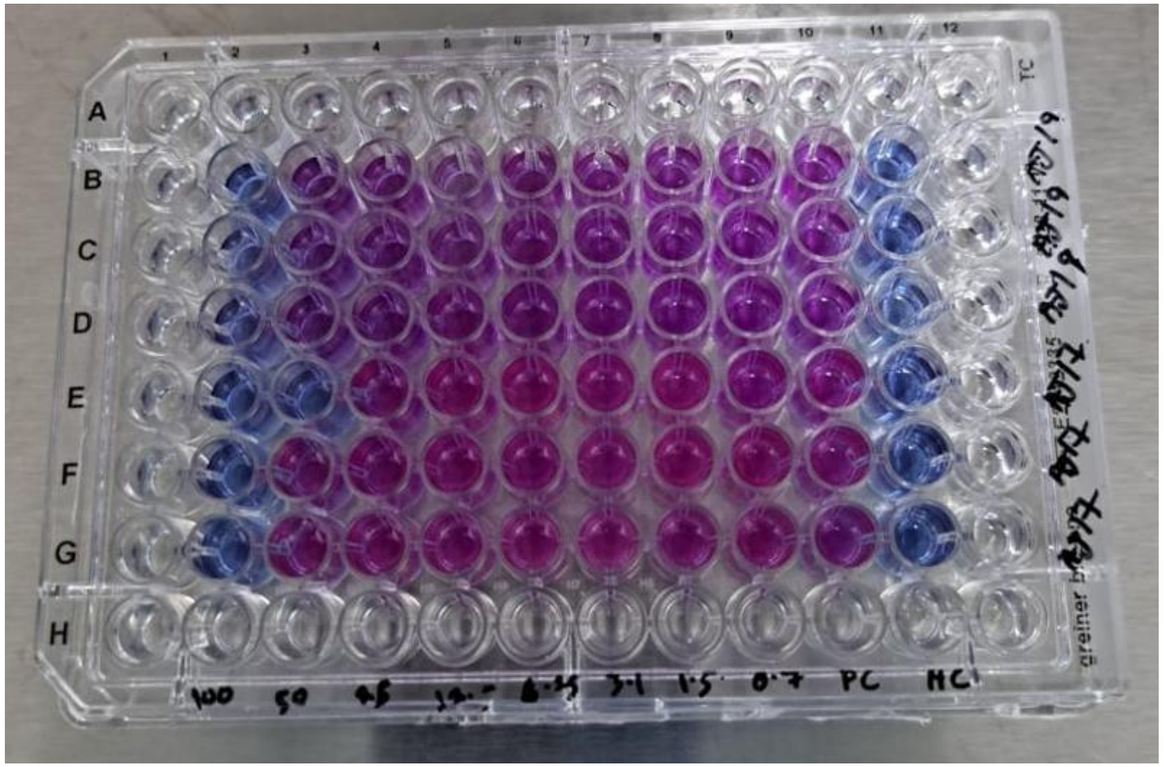

Figure 1: MIC of SQ109 against *M. kansasii* (AJ17) and *M. avium* (AJ19).

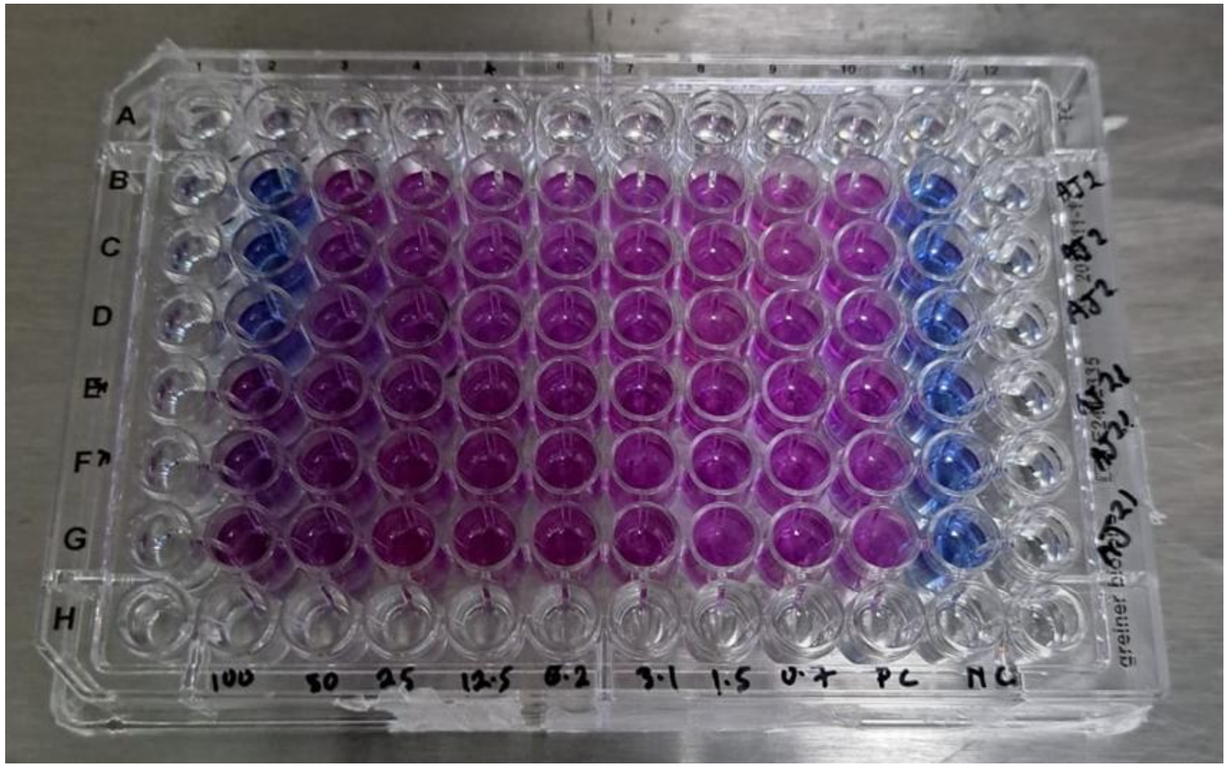

Figure 2: MIC of SQ109 against *M. abscessus* (AJ21) and *M. fortuitum* (AJ2).

Results cont..

Table 1: Minimum inhibitory concentration (MIC) and Minimum bactericidal concentration (MBC) (µM) of SQ109 against slow and fast-growing NTMs

Type of NTM	MIC 1 (µM)	MIC 2 (µM)	MIC 3 (µM)	Median MIC (µM)	Mean ± SD (MIC)	MBC 1 (µM)	MBC 2 (µM)	MBC 3 (µM)	Mean ± SD (MBC)
M. avium	50	100	100	100	83.3 ± 28.9	100	100	100	100 ± 0.0
M. kansasii	100	100	100	100	100 ± 0.0	100	100	100	100 ± 0.0
M. intracellulare	50	100	100	100	83.3 ± 28.9	50	100	100	83.3 ± 28.9
M. abscessus	>100	>100	>100	>100	>100	>100	>100	>100	>100
M. fortuitum	100	100	100	100	100 ± 0.0	>100	>100	>100	>100

Results cont…

Time kill kinetics of SQ109 against *M. fortuitum* and *M. avium*

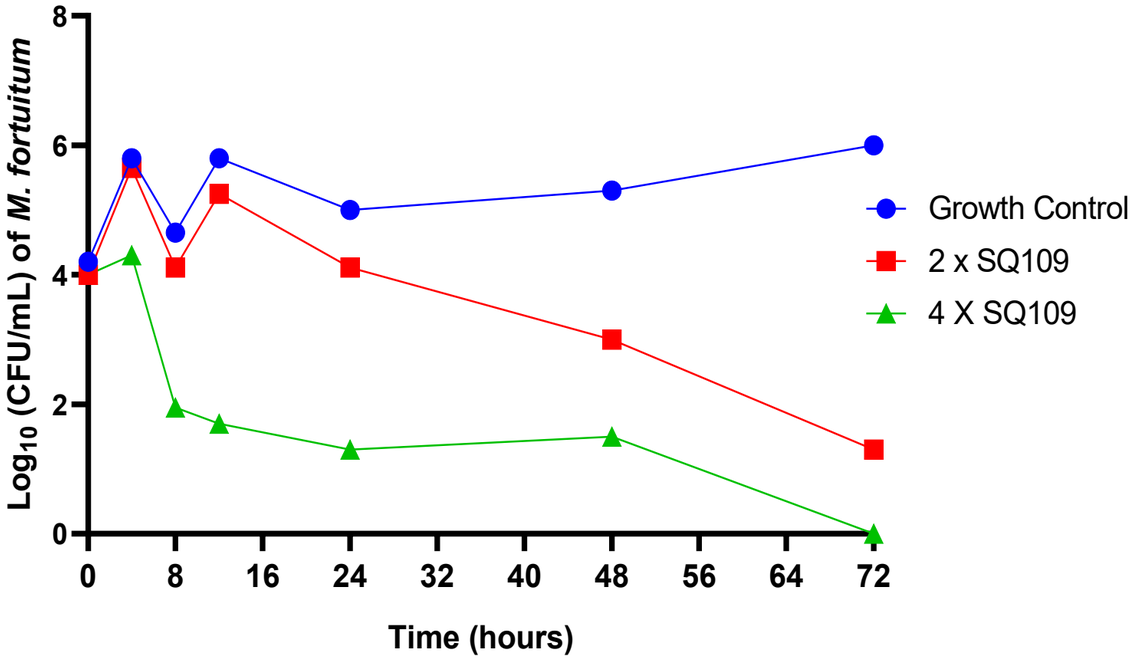

Figure 3: Time kill kinetics of SQ109 against *M. fortuitum*

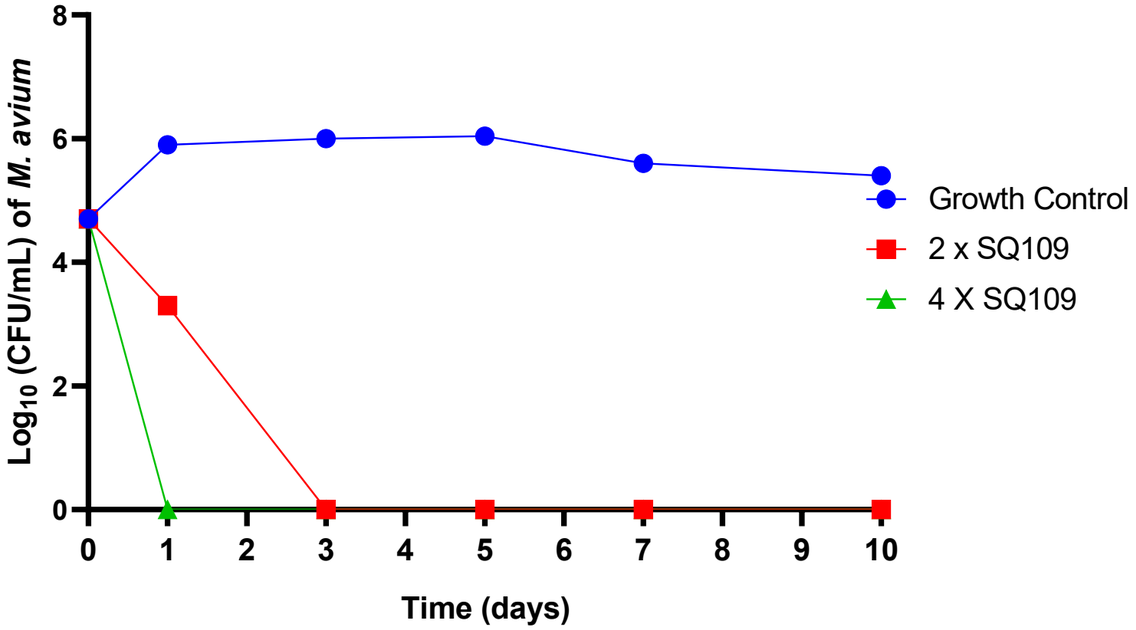

Figure 4 *:* Time kill kinetics of SQ109 against *M. avium*

Discussion

- SQ109 demonstrated species-specific variation and dose dependent activity against NTMs which is consistent with previous reports highlighting the fact that there is a substantial variation in sensitivity profile within the species. (Goswami et al., 2016)

- Slow-growing NTMs showed MIC and MBC values of 100 µM, whereas fast-growing NTMs were more resistant, with *M. abscessus* identified as the most resistant species to SQ109.

- The high MIC and MBC of SQ109 against treated naïve fast and slow growing NTMs may be due to their efficient efflux pumps and lipid-rich cell walls, contributing to higher drug tolerance. (Rodrigues et al., 2009)

- In contrast, Stampolaki et al., (2023) used newly developed SQ109 analogues to achieve substantially lower MIC values (20 - 44 µM) against *M. abscessus* due to their improved membrane penetration and enhanced inhibition of MmpL3.

- Previous studies in *Mtb* demonstrated that SQ109 enhances the activity of first-line drugs, remaining effective at sub-MIC levels (0.25–0.5× MIC) and reducing partner-drug MICs by approximately 4–16 fold, leading to synergistic bactericidal effects .(Sacksteder et al., 2012; Chen et al., 2012)

Discussion cont…

- Bactericidal activity was only observed at 4× MIC for *M. fortuitum*, the 2× MIC concentration did not reach a ≥3-$\log_{10}$ CFU reduction, suggesting that extended incubation time may have resulted in bactericidal activity at this lower dose.

- A previous study by Malwal et al., (2023) demonstrated that SQ109 only partially disrupted the proton-motive force and cell-wall biosynthesis at low concentrations, with these effects intensifying at higher doses.

- This aligns with our results, where increased SQ109 concentrations produced stronger bactericidal activity confirming a clear concentration-dependent effect *in vitro*.

Conclusion

- SQ109 demonstrated potent, species-specific variation and concentration-dependent activity against clinically relevant NTMs, with bactericidal effects observed for *M. avium* and *M. fortuitum* at higher MIC concentration.

- Although overall MIC and MBC values were high, these results indicate that SQ109 may not be a strong standalone agent against NTMs, but it shows clear promise as a valuable combination partner drug.

- Evaluating SQ109 with existing antimycobacterial agents, may enhance bacterial killing, improve treatment efficacy, and help shorten and optimize regimens for difficult NTM infections, especially in high TB/HIV burden settings.

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Thank you

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