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Bismuth(III) complexes as antibiotics adjuvant against multi-resistance bacteria

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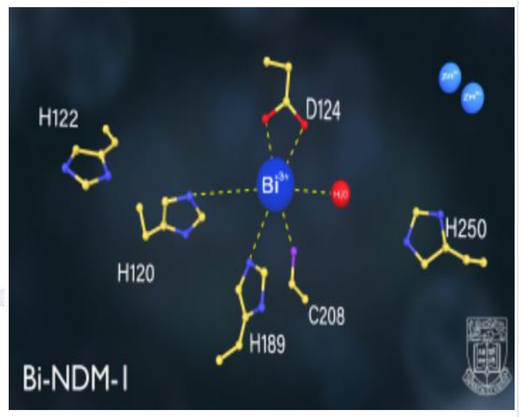
Background

- **According to WHO, it is estimated that people died from superbugs infections will be higher than cancers in 2050 [1] as more antibiotics failed even the last drug of resort like carbapenem and vancomycin.[2] FDA-approved antibiotics, cefiderocol (Fetroja®), had been reported in China before it approved in China market[3].**
- **As metal are more difficult to develop resistance, colloidal bismuth subcitrate which serves as a potent NDM-1 inhibitors together with meropenem which raise the survival rates of NDM-1 infected mice by 4-folds and slow down the resistance development [4] showing that metals is a good choice to slow down the development of resistance.**

CBS binding in NDM-1 active pocket

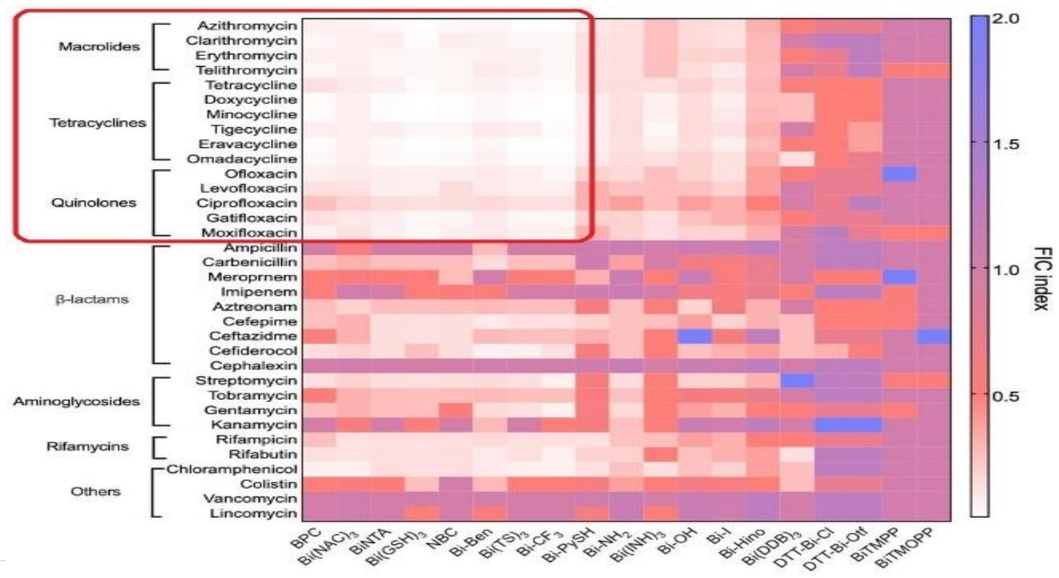


Bi(III) complexes exhibit good synergy with antibiotics against *P. aeruginosa*

- P. Aeruginosa is **intrinsically resistance to many antibiotics** including macrolides e.g. erythromycin, tetracyclines, rifamycins, chloramphenicol, auranofin, vancomycin, and some cephalosporins etc[5].
- More than 50 Bi(III) complexes with carboxylate, pyridine, thiolate, dithiocarbamate, α-hydroxy ketones and porphyrin ligands were synthesized and characterized by NMR and ESI.
- It is founded that Bi(III) thiolate and some thiocarbamate complexes showed **good synergy** (FIC index below 0.3) with macrolides, tetracyclines, quinolones against *P. aeruginosa PAO1* and are **non-toxic** even at above 256 μM in A549 cell suggested that they are good for adjuvant.
- With the use of these non-toxic Bi(III) complexes as antibiotics adjuvant, **tetracyclines and macrolides can become active drugs (MIC < 16 μM) against P. aeruginosa.**

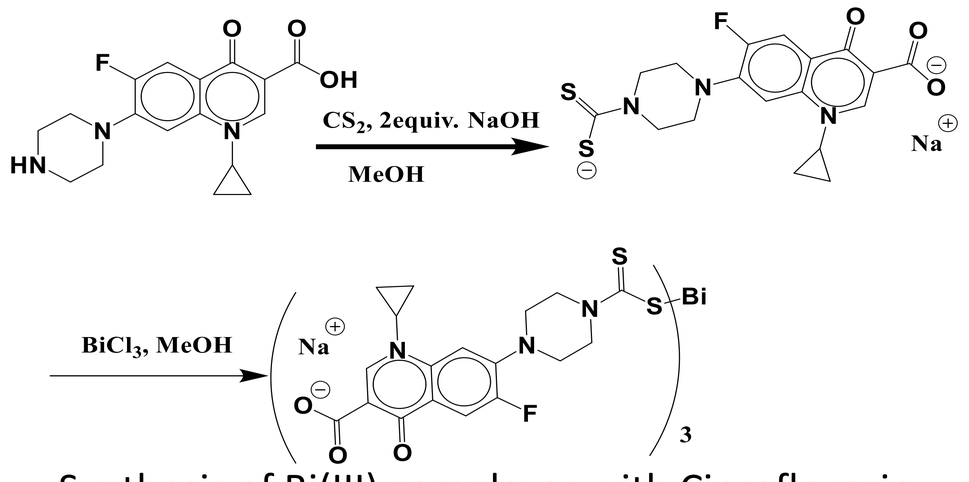
Synergy heat map

Figure 1. FIC index of various Bi(III) complexes with different antibiotics, **red circle part** suggested good synergy with some antibiotics. They are mainly **Bi(III) thiolate** complexes.



Synthesis of highly active Bi(III)-antibiotics complexes

- Based on the synergy data, we synthesized some Bi(III) antibiotics complexes with a CS_2 modification on the amine including ciprofloxacin, linezolid etc. Such modification not only **have synergy** with the mother antibiotics but also form **stable complexes** with Bi(III) as Bi(III) is a thiophilic soft metal.
- Ciprofloxacin are one of the limited antibiotics that work excellently against P. aeruginosa,
- The MIC value of ciprofloxacin and it complexes as shown in Table, as each Bi(III) complexes consist of 3 ciprofloxacin ligands, the **Bismuth complexes are around 3 times more active than the mother antibiotics**, which is in the **nanomolar range**, suggested that this complexes are **highly active against P. aeruginosa**.

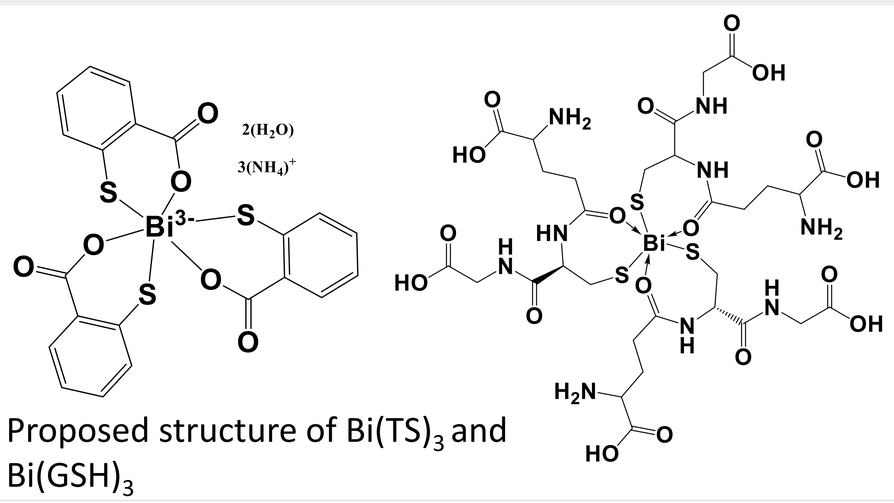


Synthesis of Bi(III) complexes with Ciprofloxacin

	$Bi(cip)_3Na_3$	Ciprofloxacin
PAO1 in M HB medium in uM	0.03125	0.25

Table 1. MIC values of Bi-ciprofloxacin complexes compare to it mother antibiotics

Structure of the active Bi(III) complexes



Proposed structure of $Bi(TS)_3$ and $Bi(GSH)_3$

Acknowledgements

References
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2) Davido, B., Moussiegt, A., Dinh, A. (2018). *Antimicrob Resist Infect Control*, 7, 100.
3) Pan P, Lu Y & Chen Z, et al. (2022). *Microbiol Spectr*. **10**, e0008422.
4) Wang, R., Lai, TP., Gao, P. & Sun, HZ. et al. (2018). *Nat Commun* 9, 439.
5) Mori, M., Ishii, Y., Tateda, K. et al. (2012) *J. Antimicrob. Chemother.* **67**(9), 2173-81

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