Supplementary Data

Physical Stability Enhancement and antimicrobial properties of a Sodium Ionic Cocrystal with theophylline

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Antimicrobial tests

In vitro antimicrobial susceptibility tests similar to those reported by Pan et al[1] was carried out with few modifications. Furthermore, standardized protocols recommended by the Clinical and Laboratory Standards Institute (CLSI) using the broth microdilution technique described in the documents M07-A9 (for bacterial assays)[2] and M27-A3 (for fungal assays) was also employed.[3] The test compounds (Theo hydrate , Theo-Phen.$2H_2O$ and Na-$(theo)_2ClO.2H_2O$) were solubilised at 50 mg/mL and used in a range from 4 to 0.125 mg/mL. Standard antimicrobials used by CLSI are as follows: ceftazidime (32 - 0.062 µg/mL), ciprofloxacin (4 - 0.007 µg/mL) and voriconazole (16 - 0.0313 µg/mL). The lowest concentration of each compound that inhibited microbial growth, as ascertained by the absence of visible turbidity in each well, was considered the minimum inhibitory concentration (MIC). The minimum bactericidal concentration (MBC) and minimum fungicidal concentration (MFC) were also evaluated. After determination of MIC, each well was homogenized and 10 µL were transferred onto drug-free solid medium. The plates were incubated at 35 ± 2°C for 24 h. The MBC/MFC was determined as the lowest concentration without visual growth of microbial colonies.

1. Pan, X.; Zheng, Y.; Chen, R.; Qiu, S.; Chen, Z.; Rao, W.; Chen, S.; You, Y.; Lü, J.; Xu, L.; Guan, X. Cocrystal of sulfamethazine and p-aminobenzoic acid: Structural establishment and enhanced antibacterial properties. Cryst. Growth Des. 2019, 19, 2455−2460..
2. Clinical and Laboratory Standards Institute. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically: M07-A9. CLSI, Wayne, PA, USA, **2012**.
3. Clinical and Laboratory Standards Institute. Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts: Third Informational Supplement M27-S3. CLSI, Wayne, PA, USA, **2008**.

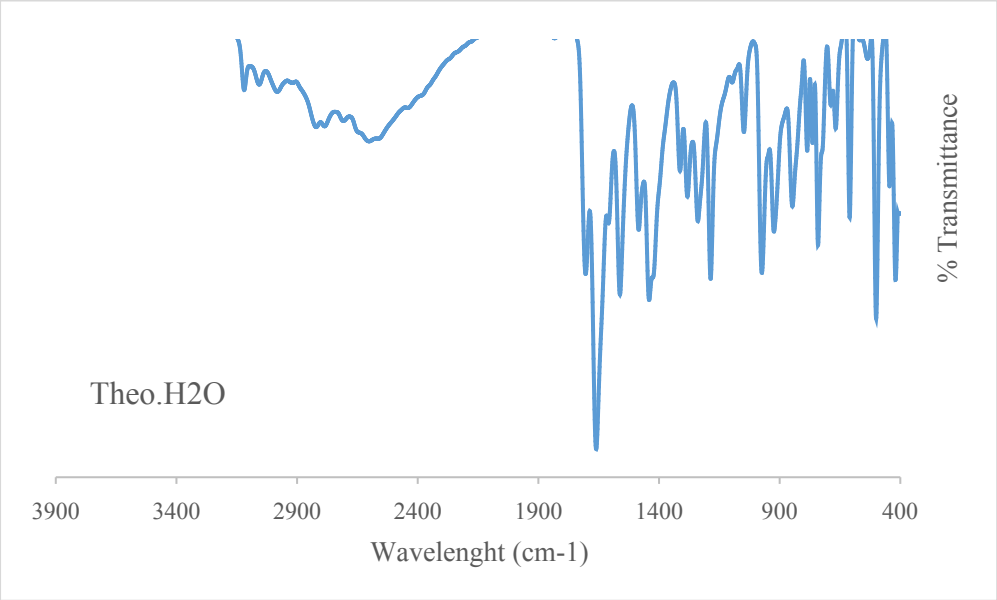


Fig. S1: FT-IR of Theo hydrate

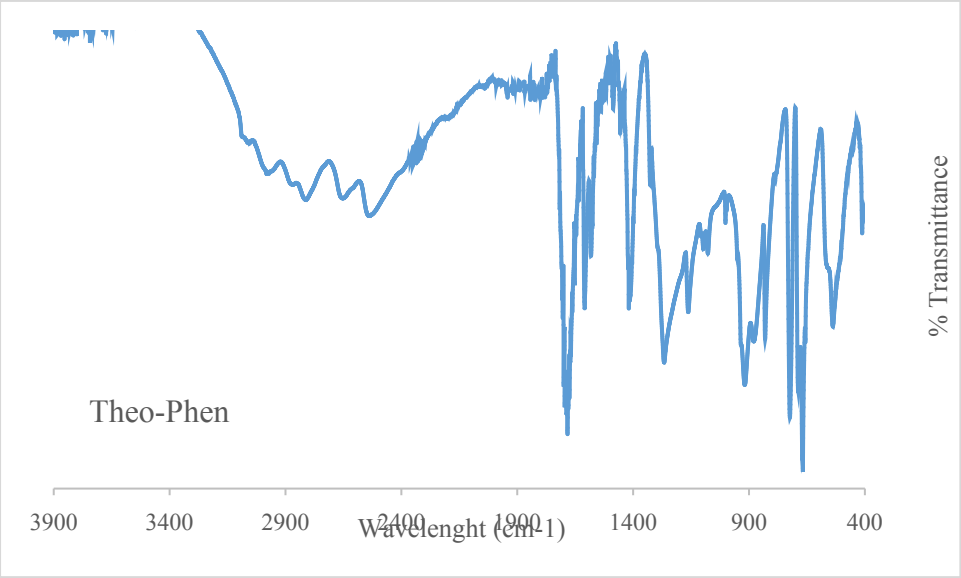


Fig. S2: FT-IR of Theo-Phen

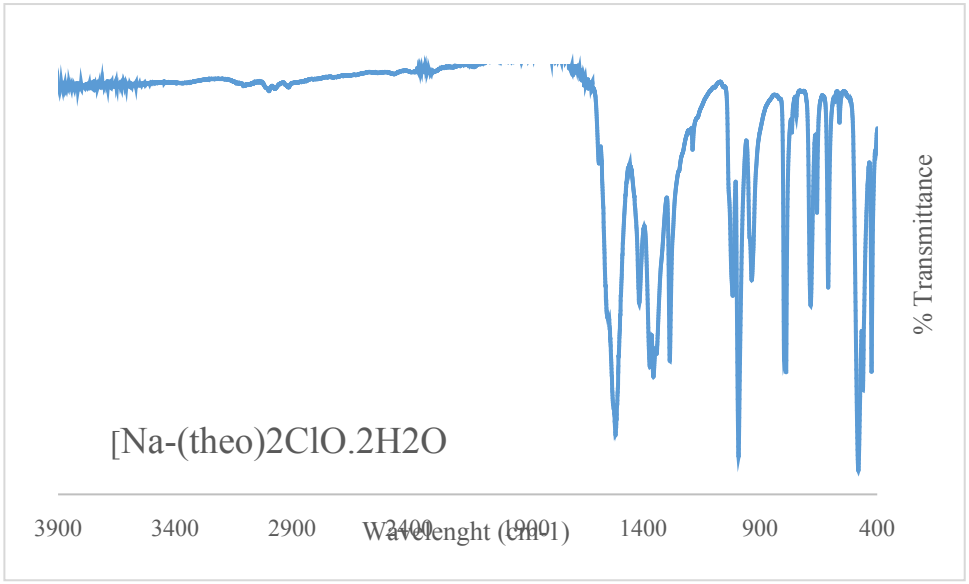


Fig. S3:. FT-IR of Na-(theo)$_2$ClO.2H$_2$O

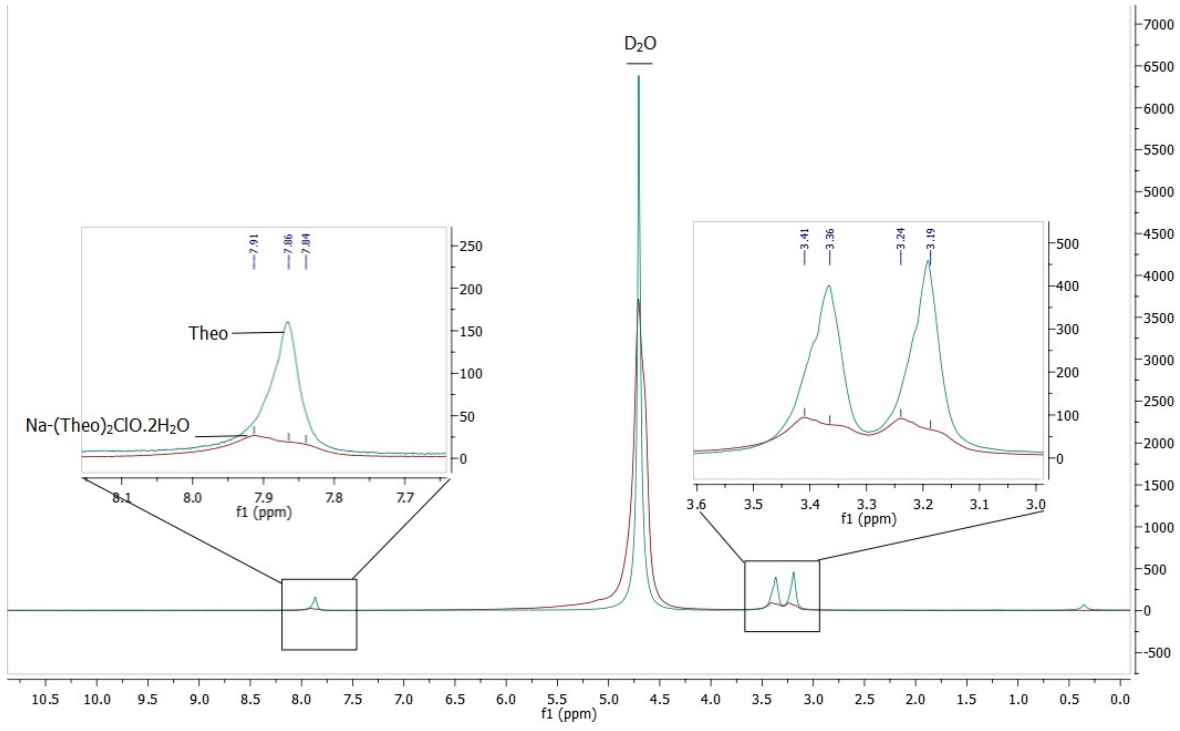


Fig. S4 NMR spectra of Theo (Blue) and Na-(theo)$_2$ClO.2H$_2$O (Brown)

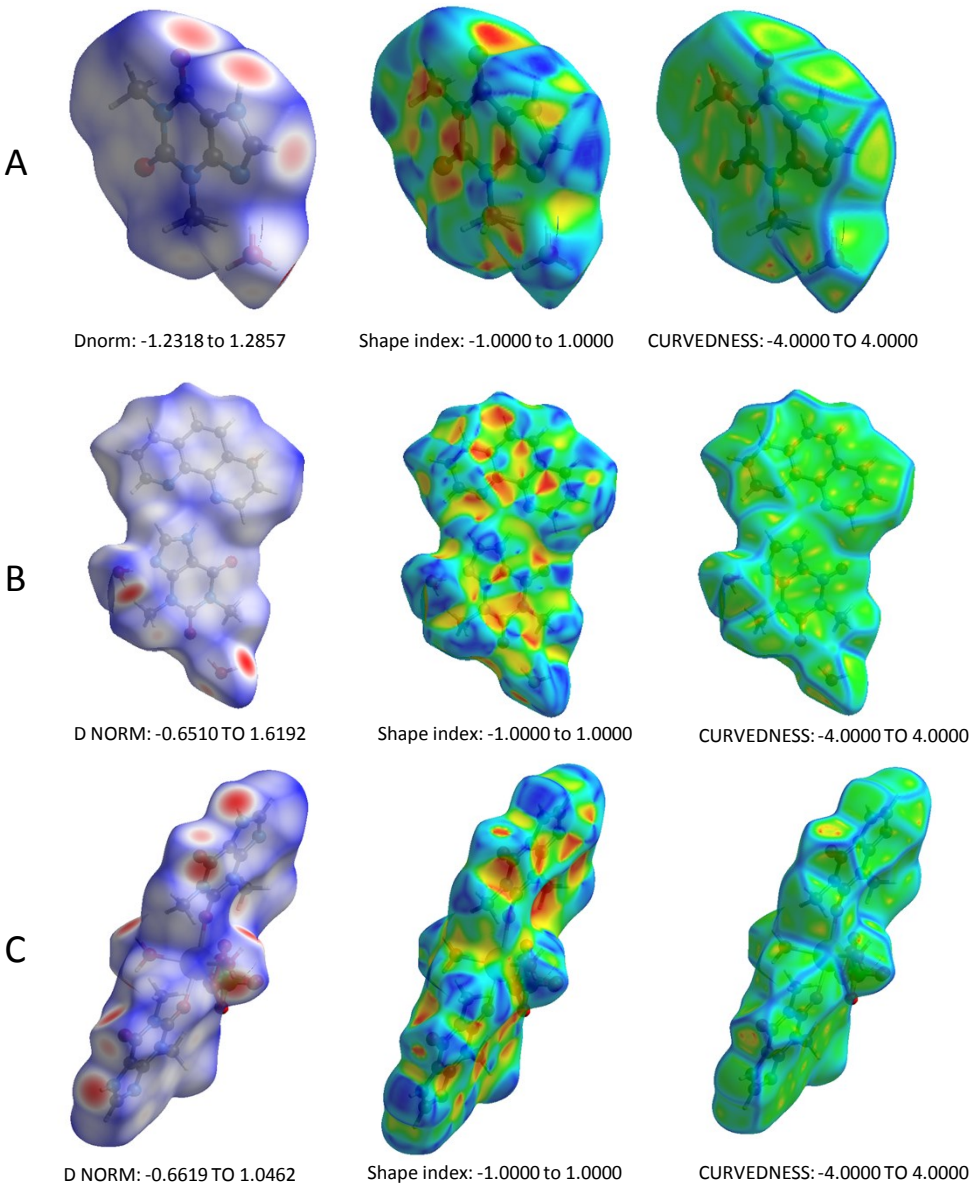


Fig. S5: Molecular Hirshfeld surface such as d_{norm}, shape index and curvedness for (A) Theo hydrate, (B) Theo-Phen.$2H_2O$ and (C) Na-$(theo)_2ClO.2H_2O$

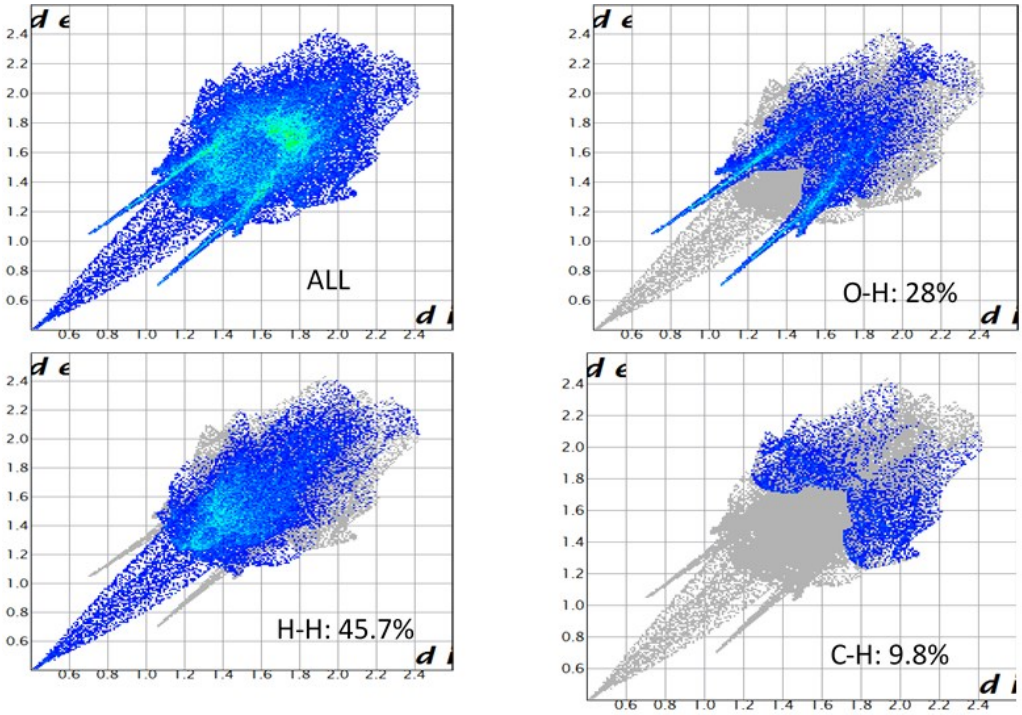


Fig. S6. Fingerprint plot of Theo hydrate full and resolved into (B) H···O (C) H···H, and (D) H···C contacts showing the percentages of contacts contributed to the total Hirshfeld surface area.

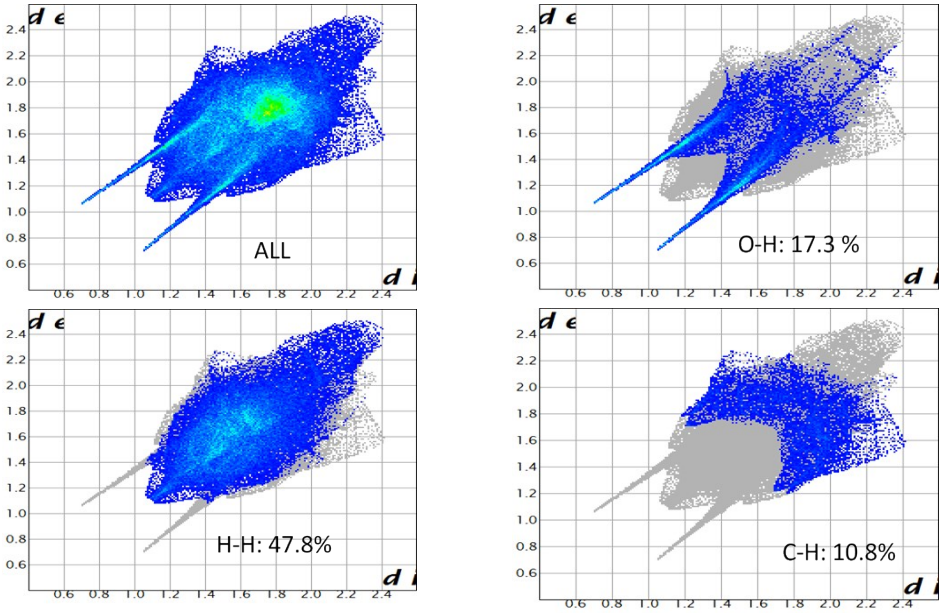


Fig. S7. Fingerprint plot of Theo-Phen.2H_2O: (A) full and resolved into (B) H···O (C) H···H, and (D) H···C contacts showing the percentages of contacts contributed to the total Hirshfeld surface area.

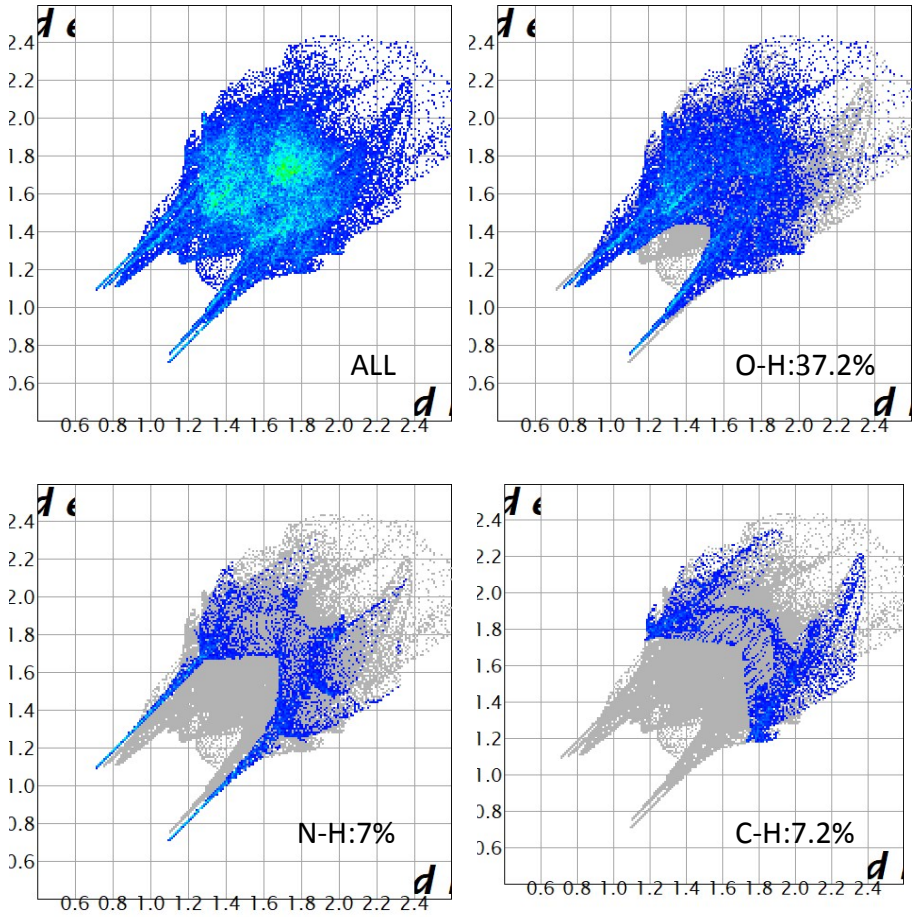


Fig S8: Fingerprint plot of [Na-(theo)$_2$ClO.2H$_2$O]: (A) full and resolved into (B) H···O (C) H···H, and (D) H···C contacts showing the percentages of contacts contributed to the total Hirshfeld surface area.

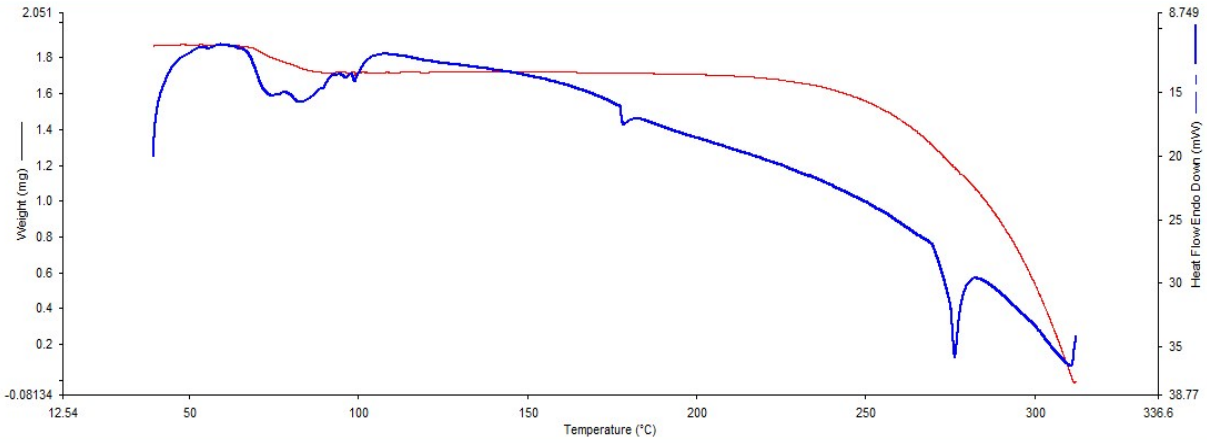


Fig. S9: TGA-DSC of Theo hydrate.

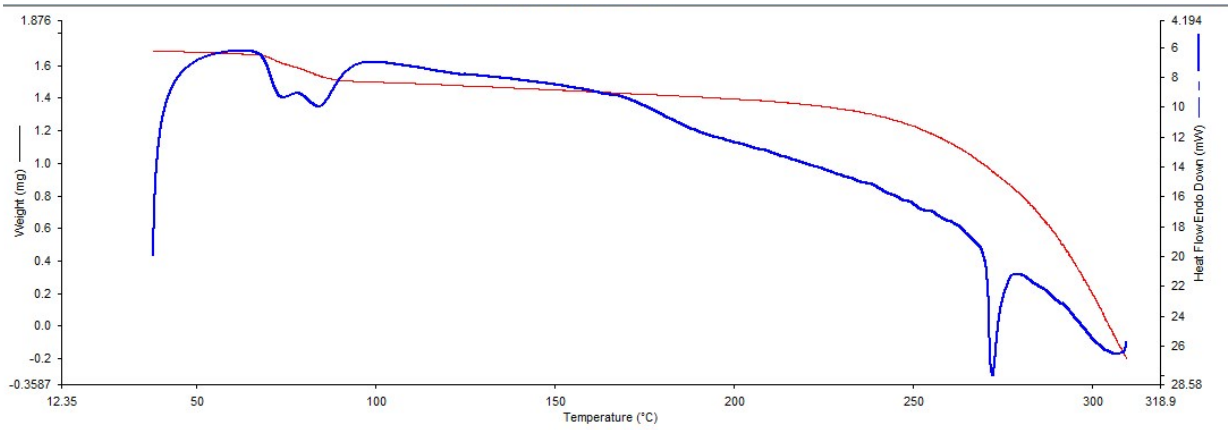


Fig. S10: TGA-DSC of Theo-Phen.$2H_2O$.

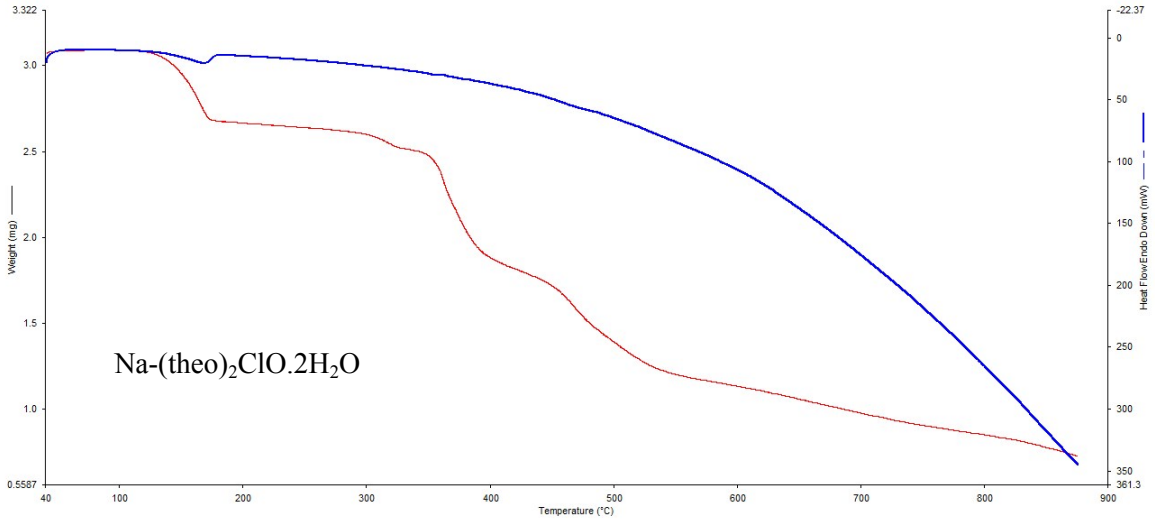


Fig S11: TGA-DSC of Na-$(theo)_2ClO.2H_2O$.

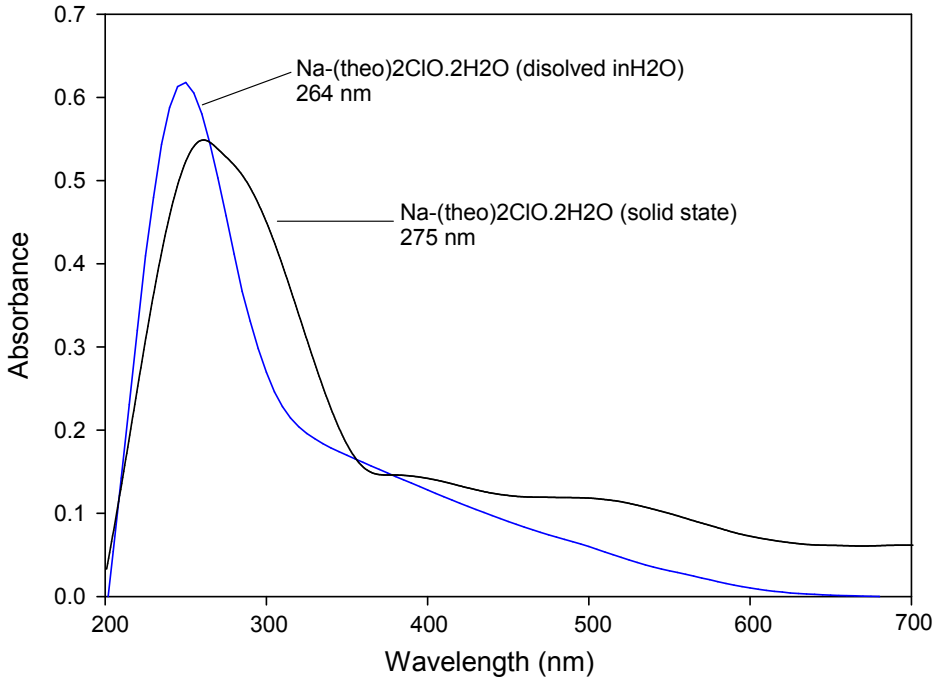


Fig S12**:** UV-Vis of Na-(theo)$_2$ClO.2H$_2$O (solid and when dissolved)

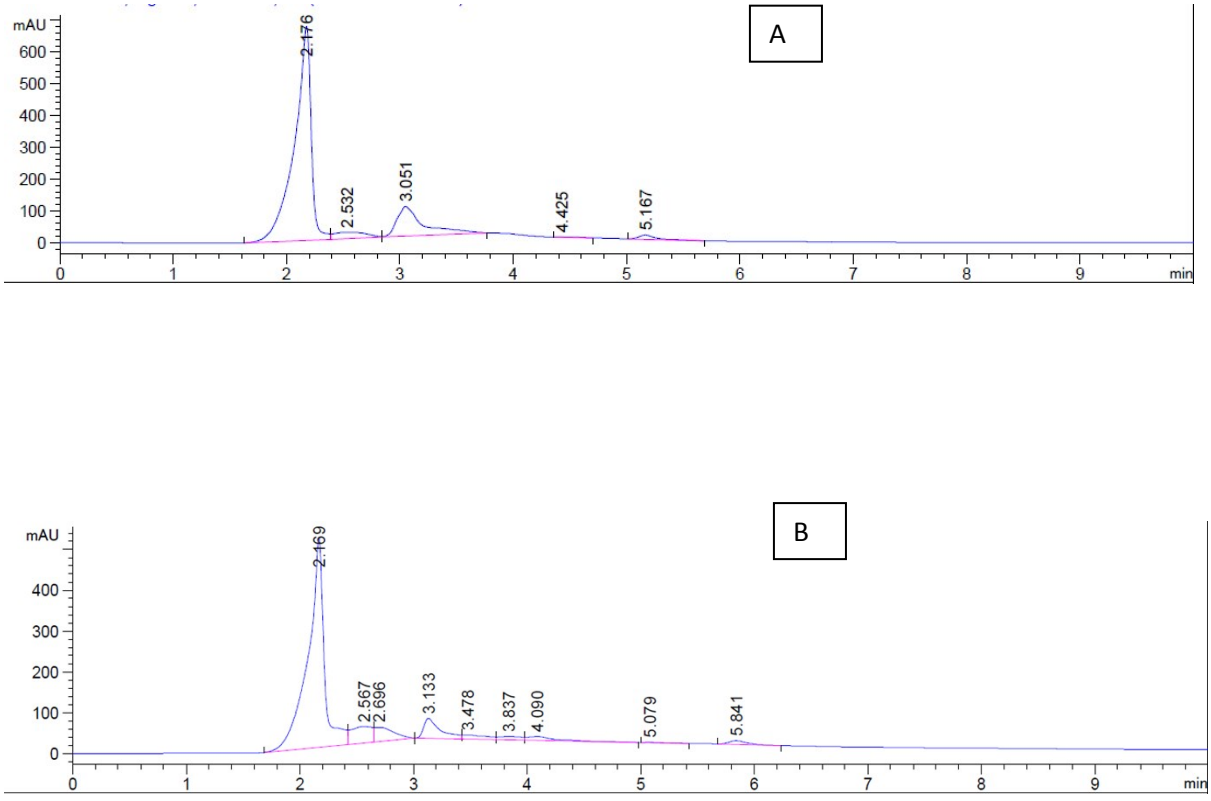


Fig S13**:** HPLC chromatogram of (A) Theo-Phen.2H$_2$O and (B) Na-(theo)$_2$ClO.2H$_2$O

Table S1: MIC of Salts

Compounds	*P. aeruginosa* ATCC 27853	*E. coli* ATCC 25922	*A. baumannii* ATCC 19606	*K. pneumonia* ATCC13883	*C. albicans ATCC 90028*	*C. tropicalis ATCC 750*
NaCl	>4 mg/ml	>4 mg/ml	>4 mg/ml	>4 mg/ml	>4 mg/ml	>4 mg/ml
$KClO_4$	>4 mg/ml	>4 mg/ml	>4 mg/ml	>4 mg/ml	>4 mg/ml	>4 mg/ml
LiCl	>4 mg/ml	>4 mg/ml	>4 mg/ml	>4 mg/ml	>4 mg/ml	>4 mg/ml

Minimum Bactericidal Concentration

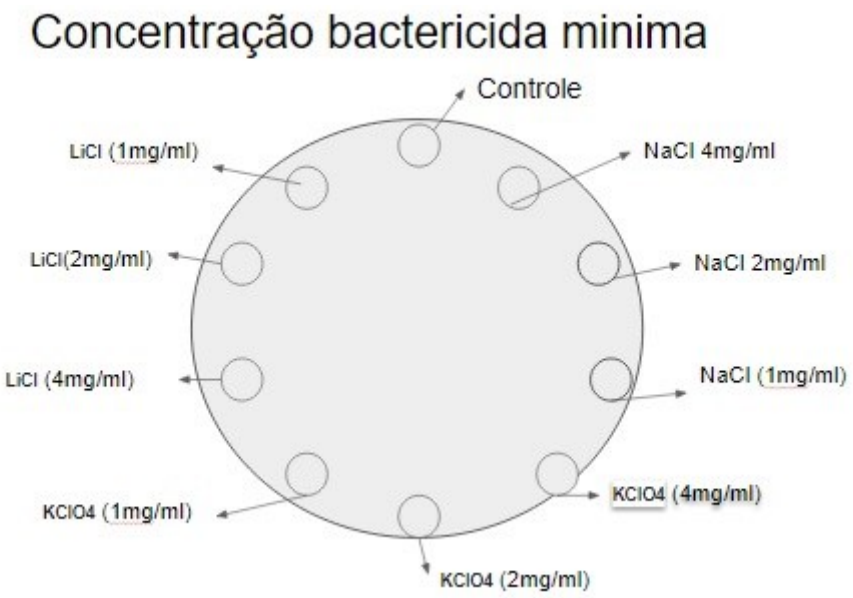
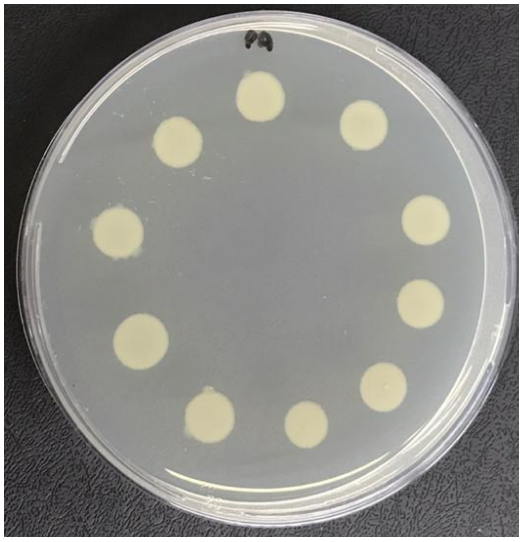
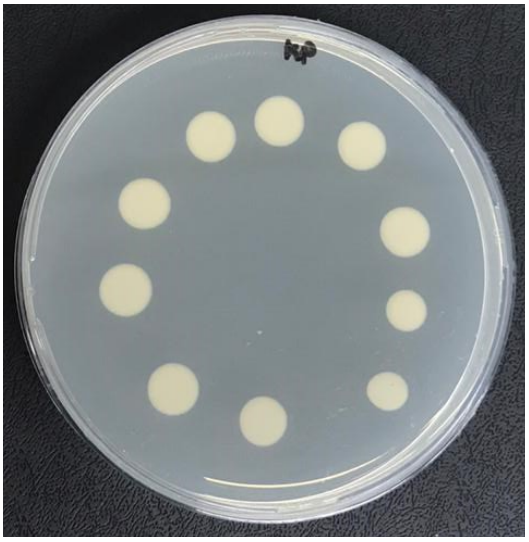


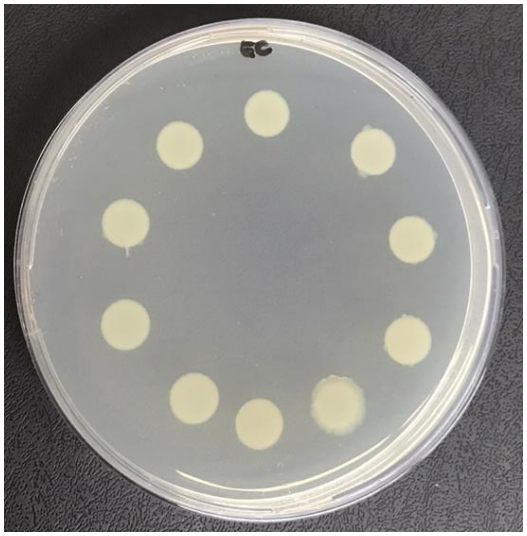
Fig S14. The representative plate shows the place of each system as follows: control, microbial growth in the presence of different concentrations of the tested salts.



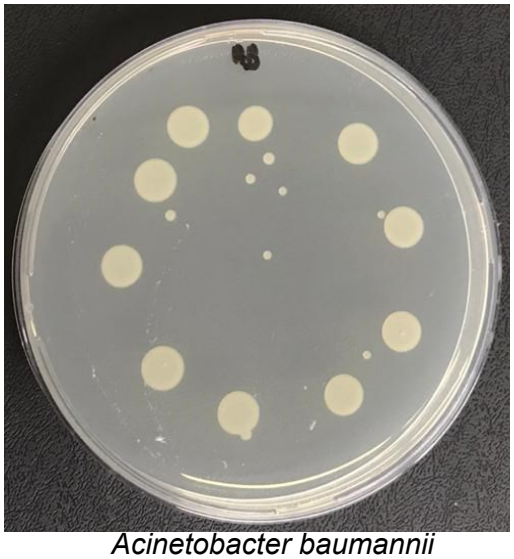
Pseudomonas aeruginosa



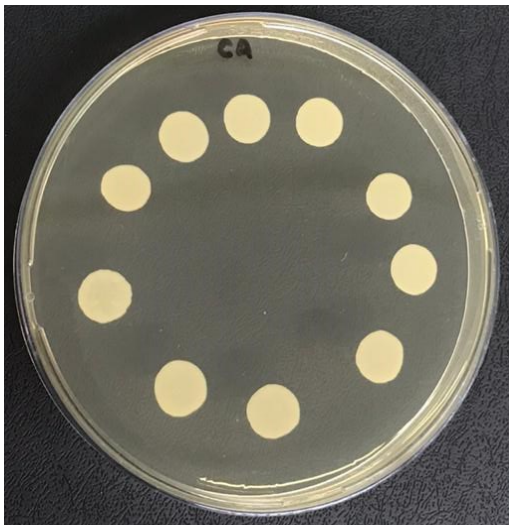
Klebsiella pneumoniae



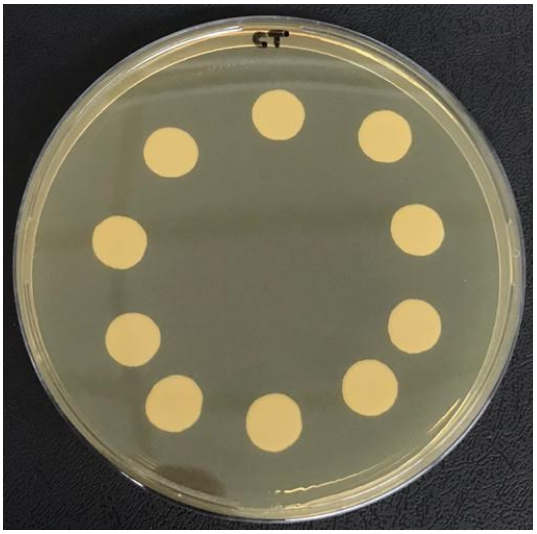
Escherichia coli



Acinetobacter baumannii



Candida albincas



Candida tropicalis

Fig S15. The representative plate shows the place of each system as follows: control, microbial growth in the presence of different concentrations of the tested salts.