Article

Modulatory effects of caffeine and pentoxifylline on aromatic antibiotics: a role for hetero-complex formation

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Figure S1a

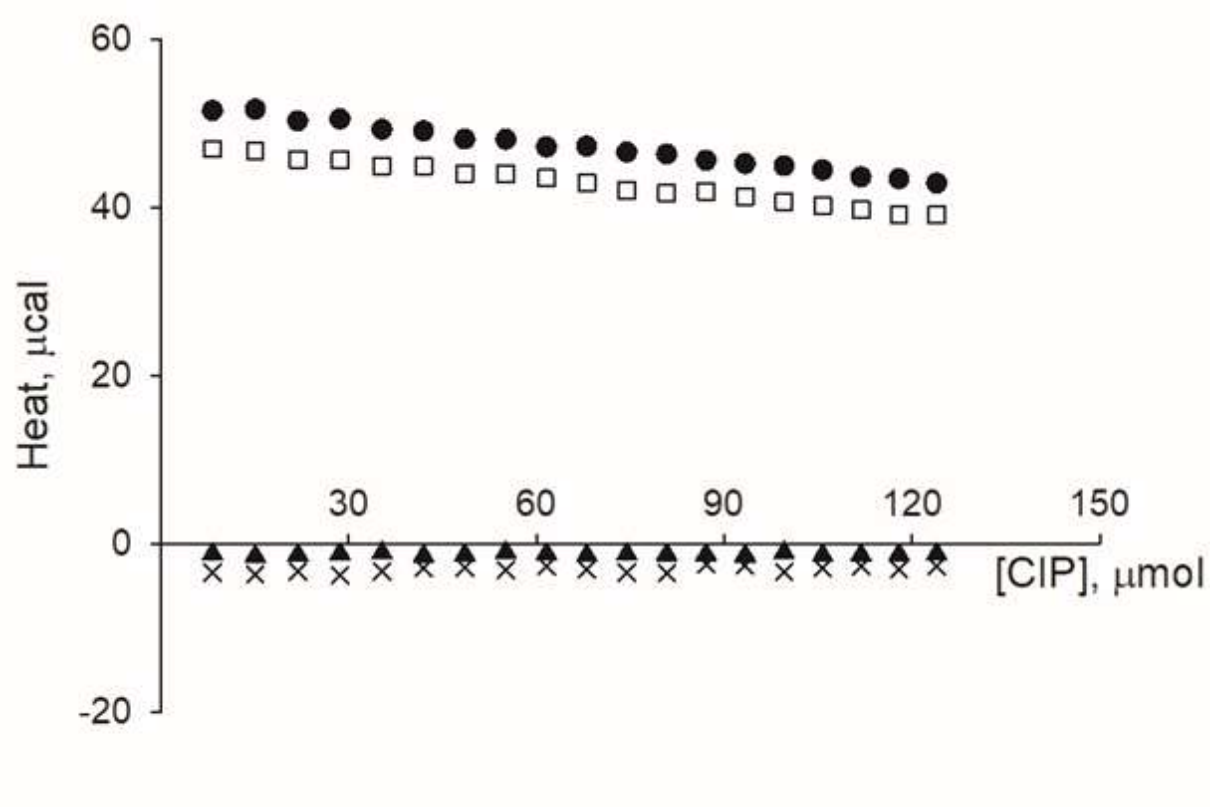
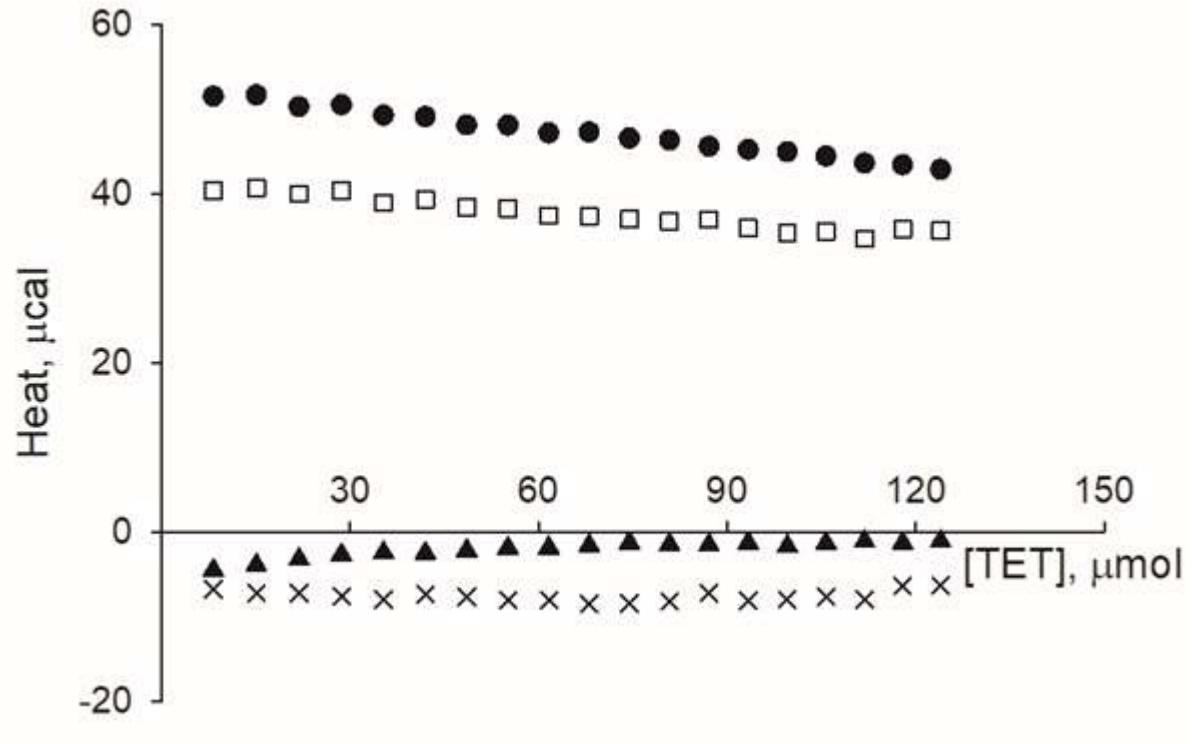


Figure S1b



Supplementary Figure S1. Thermal effects of ciprofloxacin-caffeine (a) and tetracycline-caffeine (b) interactions; circles, titration of caffeine with buffer; squares, titration of caffeine with antibiotic; triangles, titration of buffer with antibiotic. The net heat of antibiotic-caffeine interaction, calculated as the difference between heat of antibiotic-caffeine titration and control (buffer) titrations, is marked with crosses. CIP, ciprofloxacin. TET, tetracycline

Figure S2a

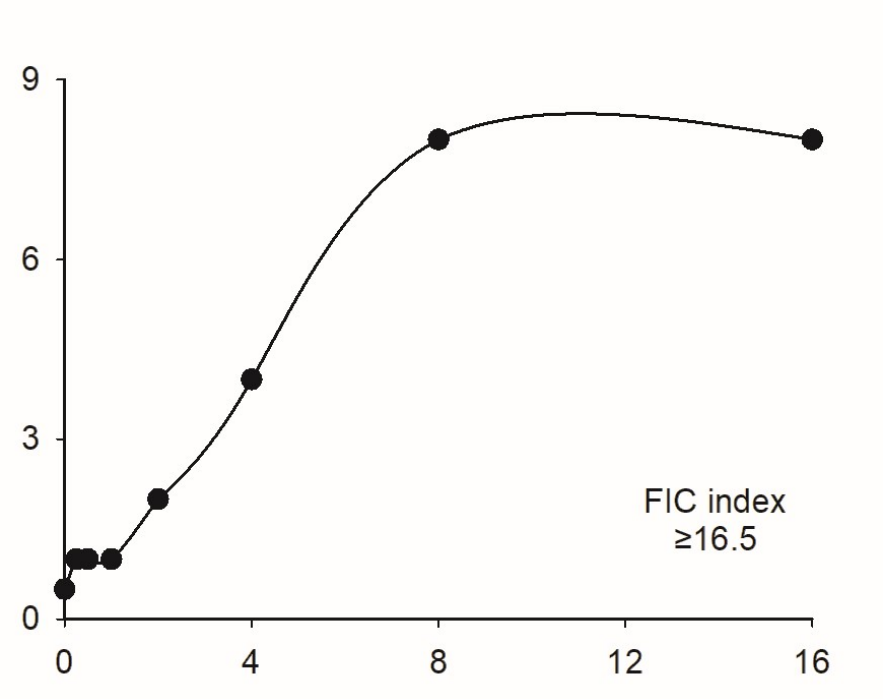


Figure S2b

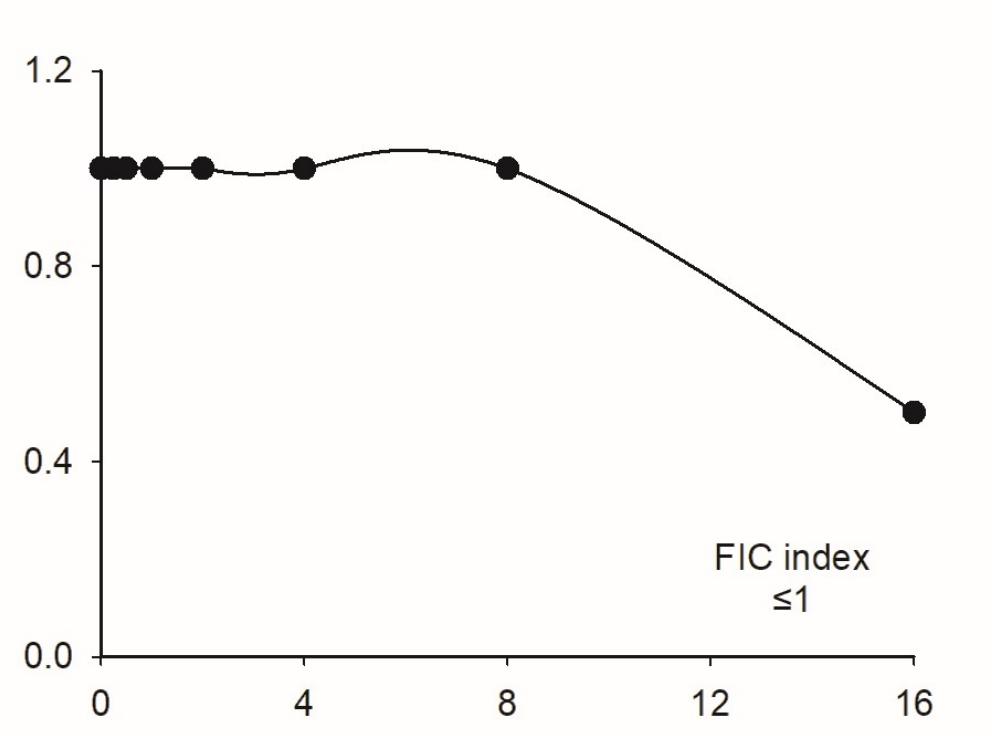


Figure S2c

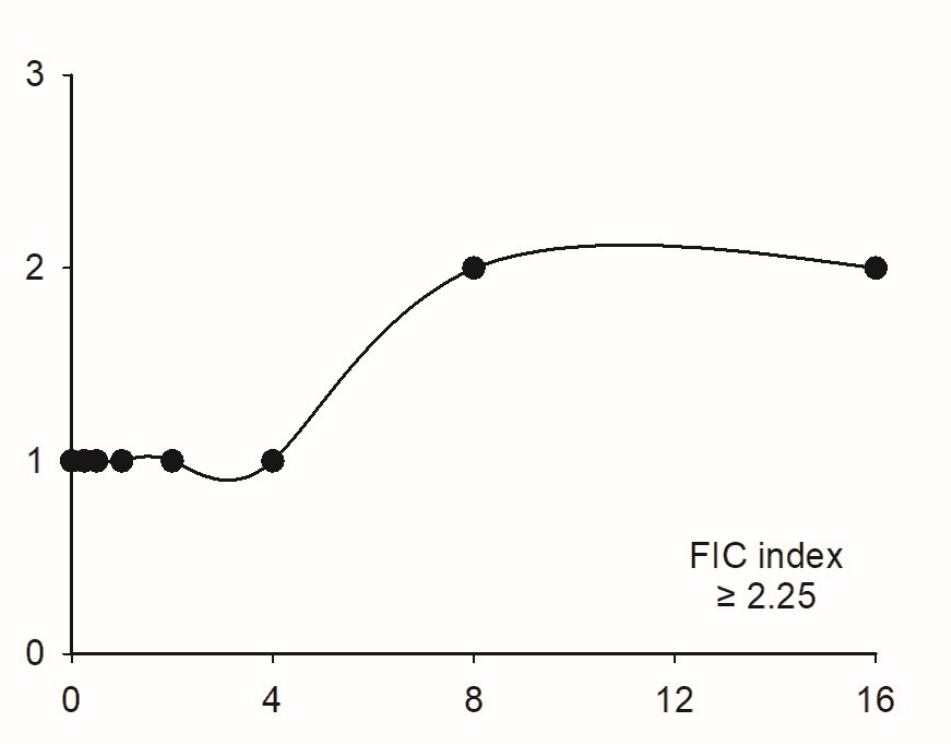
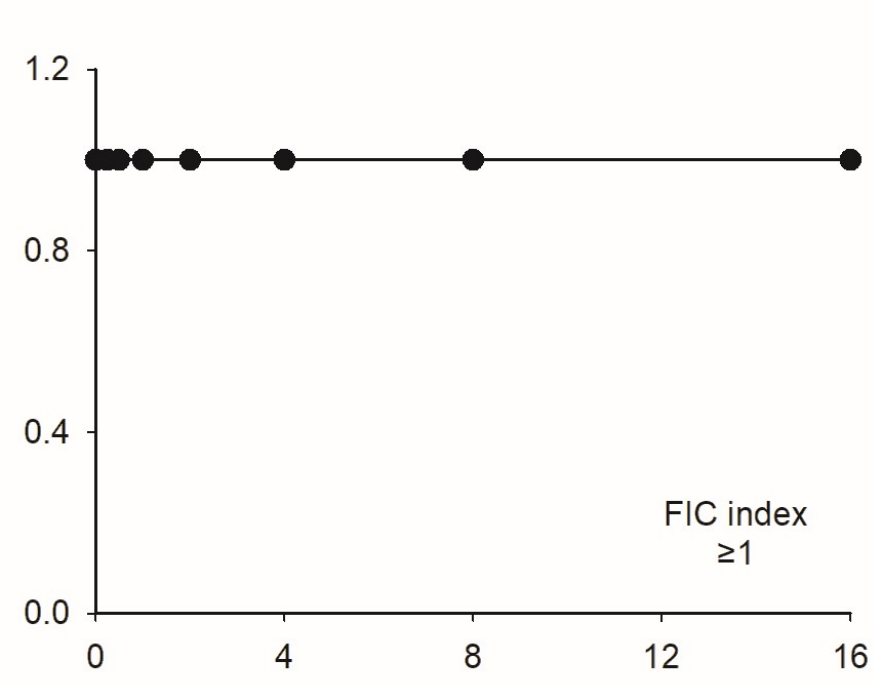


Figure S2d



Supplementary Figure S2. Modulation of ciprofloxacin and tetracycline antibacterial activity by xanthines (caffeine and pentoxifylline) in *Staphylococcus aureus* using microbroth dilution assay and checkerboard methodology. (**a**), ciprofloxacin-caffeine mixtures; (**b**), tetracycline-caffeine mixtures; (**c**), ciprofloxacin-pentoxifylline mixtures; (**d**), tetracycline-pentoxifylline mixtures. FIC, Fractional Inhibitory Concentration Index calculated for each tested antibiotic-xanthine combination according to Odds [33]

Figure S3a

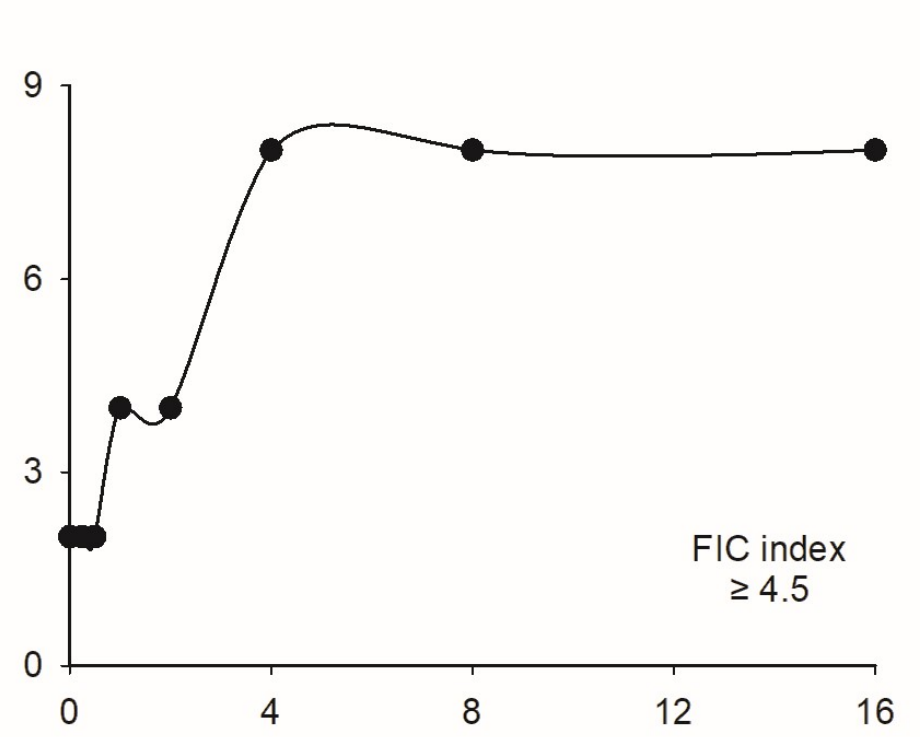
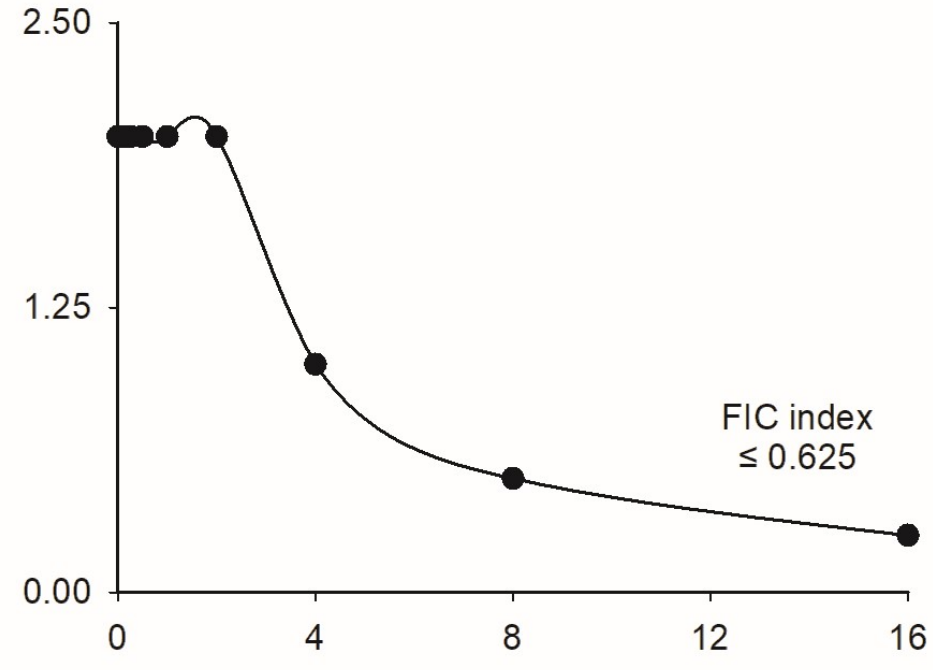


Figure S3b



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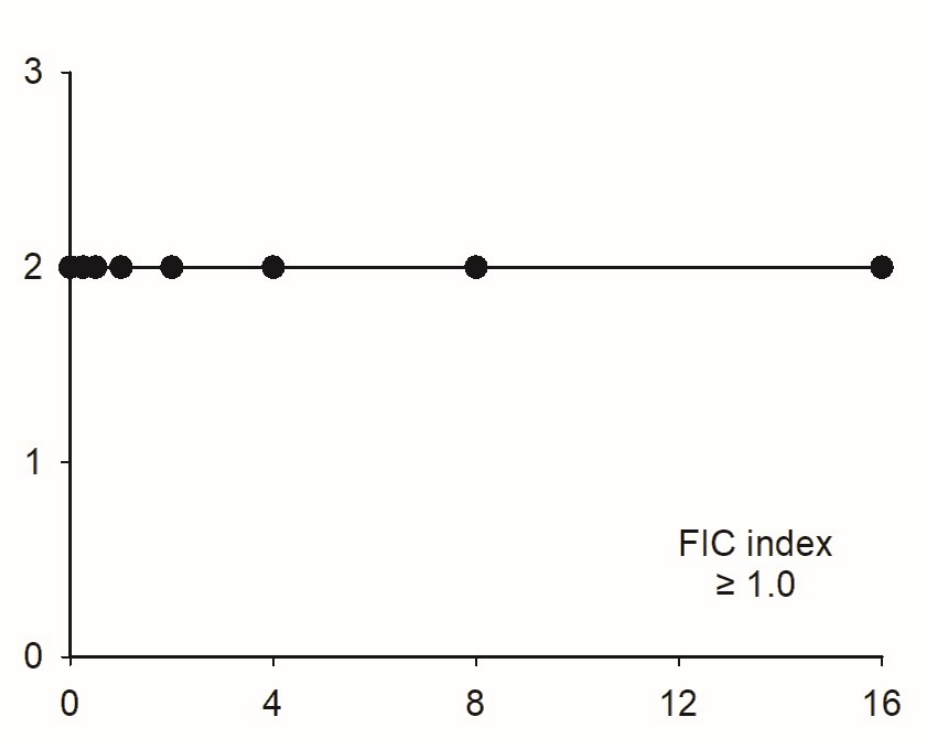

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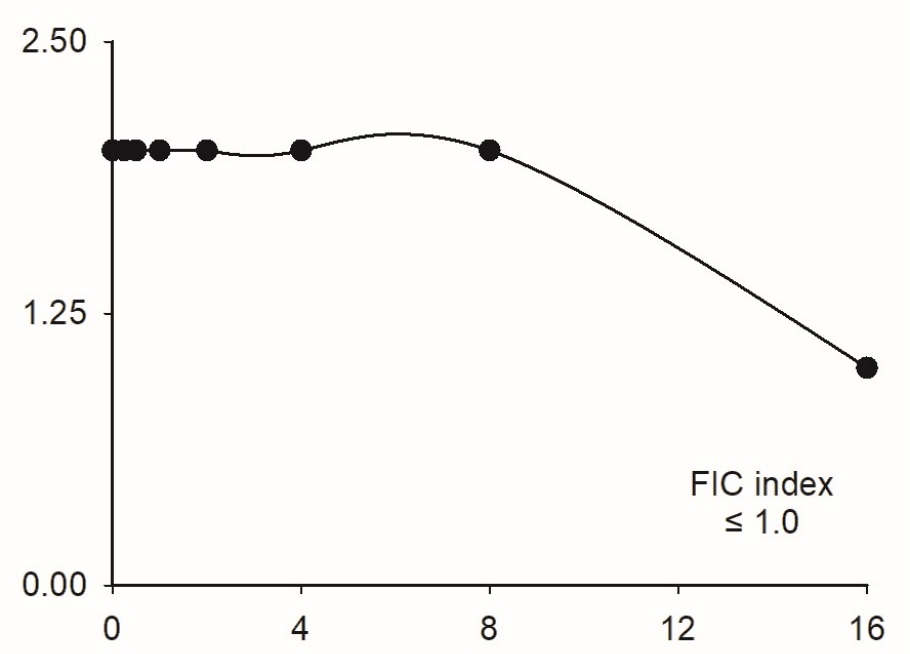
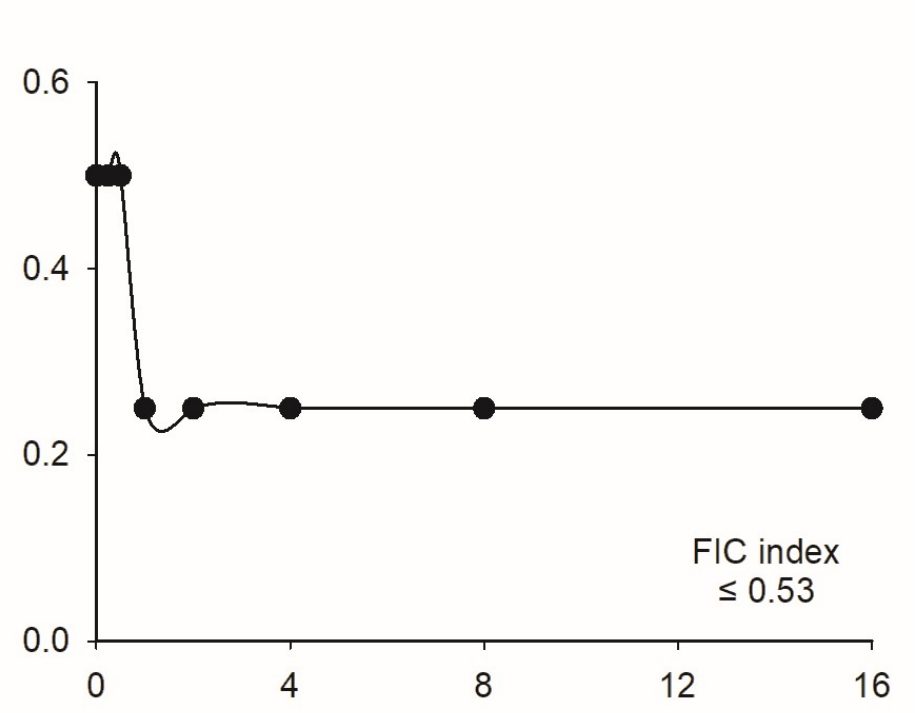


Supplementary Figure S3. Modulation of ciprofloxacin and tetracycline antibacterial activity by xanthines (caffeine and pentoxifylline) in *Enterococcus faecium* using microbroth dilution assay and checkerboard methodology. (**a**), ciprofloxacin-caffeine mixtures; (**b**), tetracycline-caffeine mixtures; (**c**), ciprofloxacin-pentoxifylline mixtures; (**d**), tetracycline-pentoxifylline mixtures. FIC, Fractional Inhibitory Concentration Index calculated for each tested antibiotic-xanthine combination according to Odds [33]

Figure S4a



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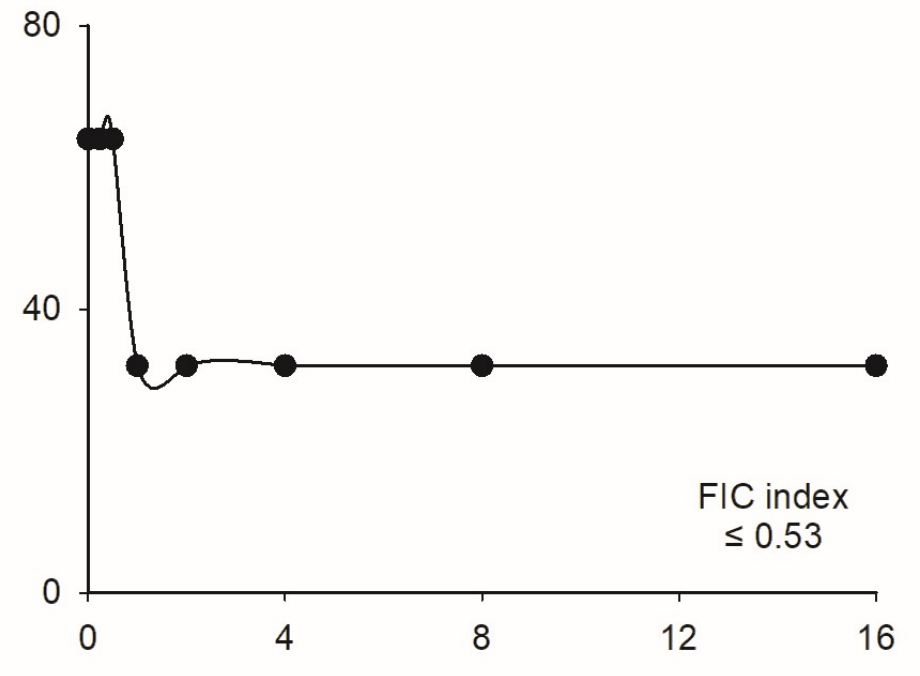

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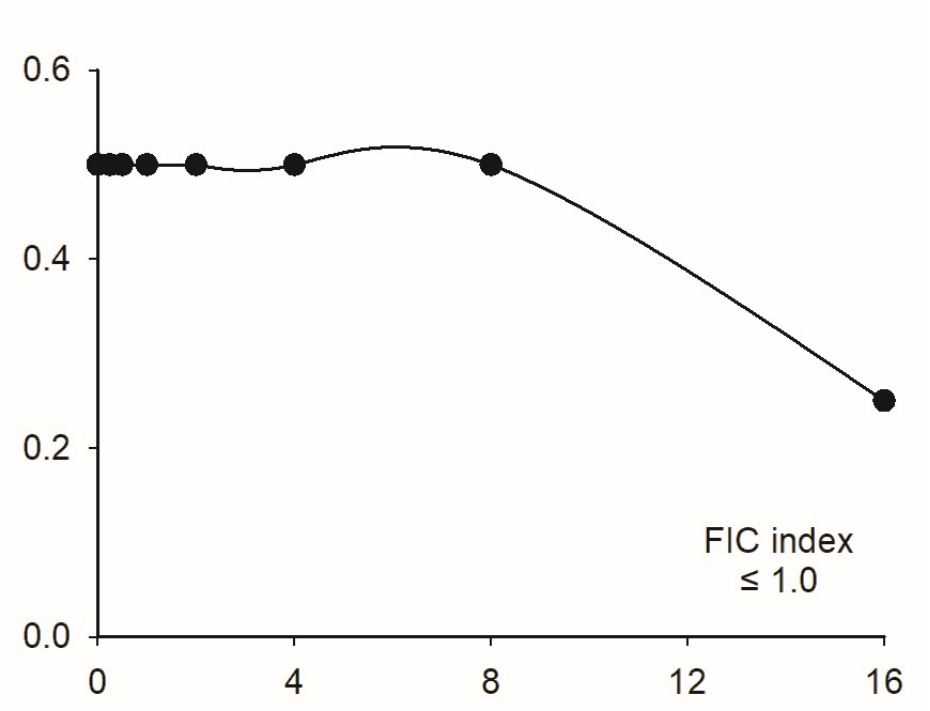

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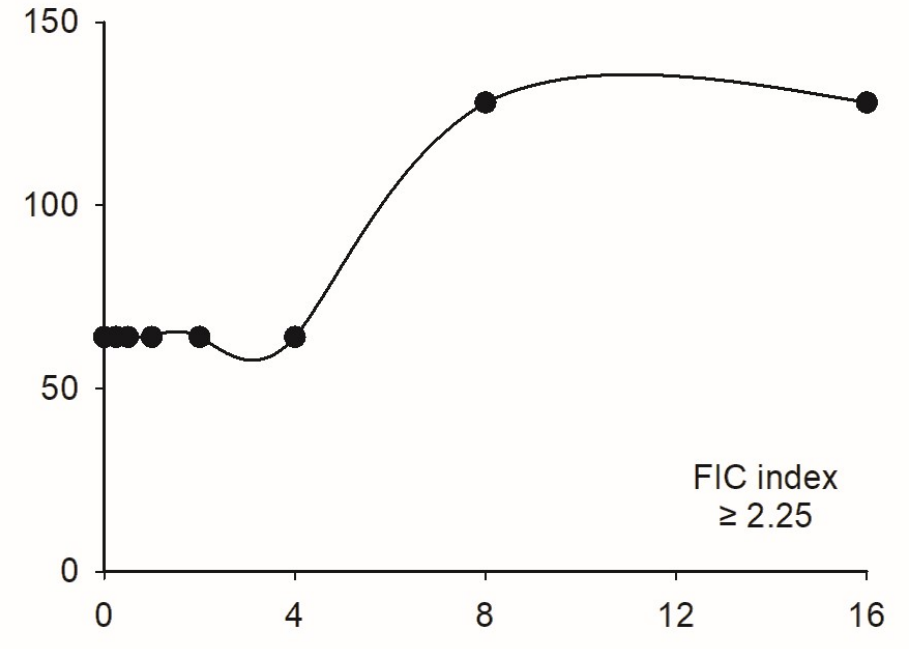


Supplementary Figure S4. Modulation of ciprofloxacin and tetracycline antibacterial activity by xanthines (caffeine and pentoxifylline) in *Pseudomonas aeruginosa* using microbroth dilution assay and checkerboard methodology. (**a**), ciprofloxacin-caffeine mixtures; (**b**), tetracycline-caffeine mixtures; (**c**), ciprofloxacin-pentoxifylline mixtures; (**d**), tetracycline-pentoxifylline mixtures. FIC, Fractional Inhibitory Concentration Index calculated for each tested antibiotic-xanthine combination according to Odds [33]

Figure S5a

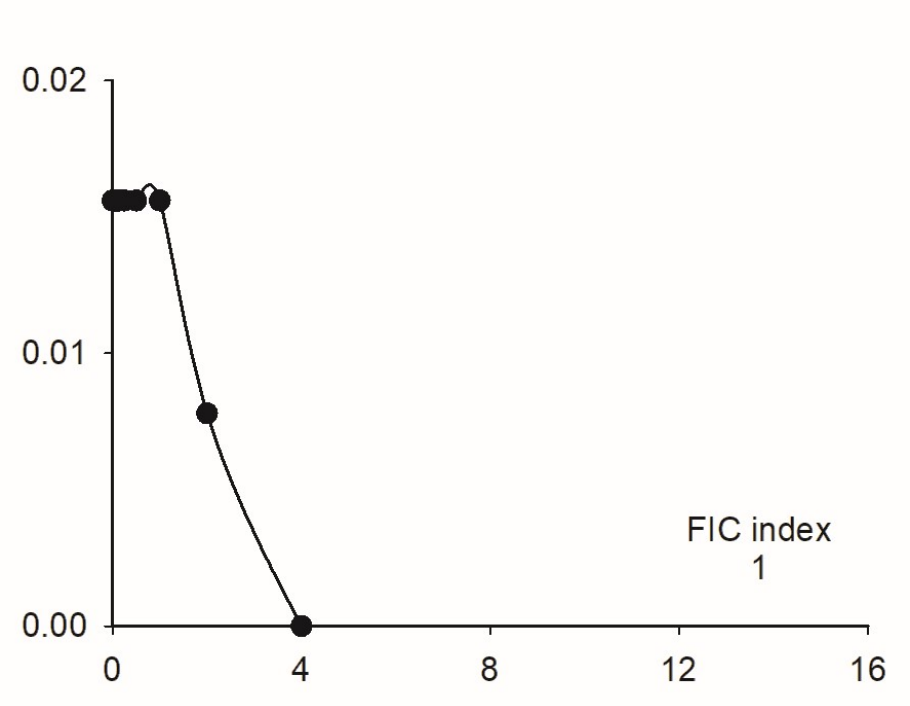
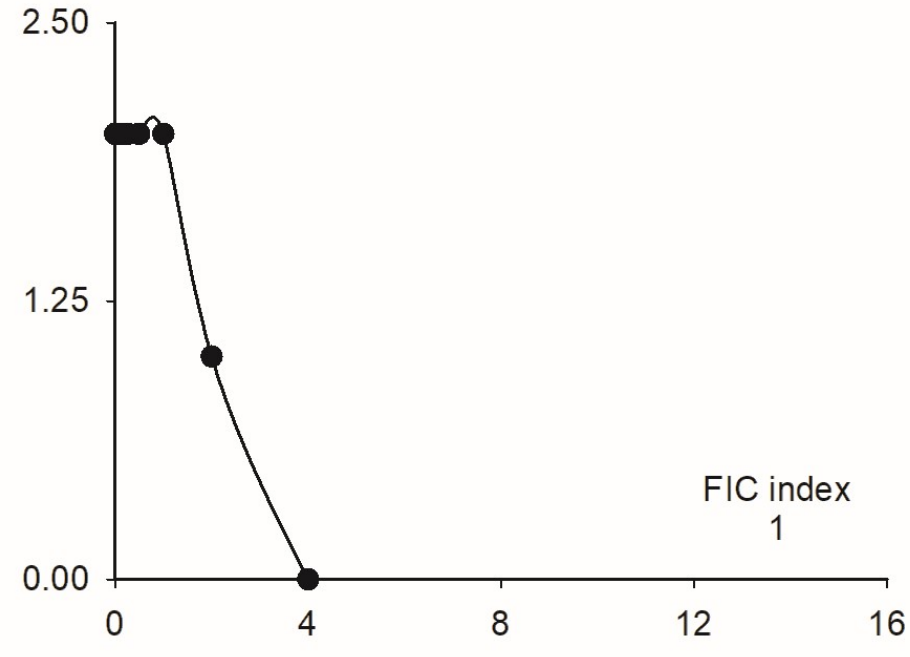


Figure S5b



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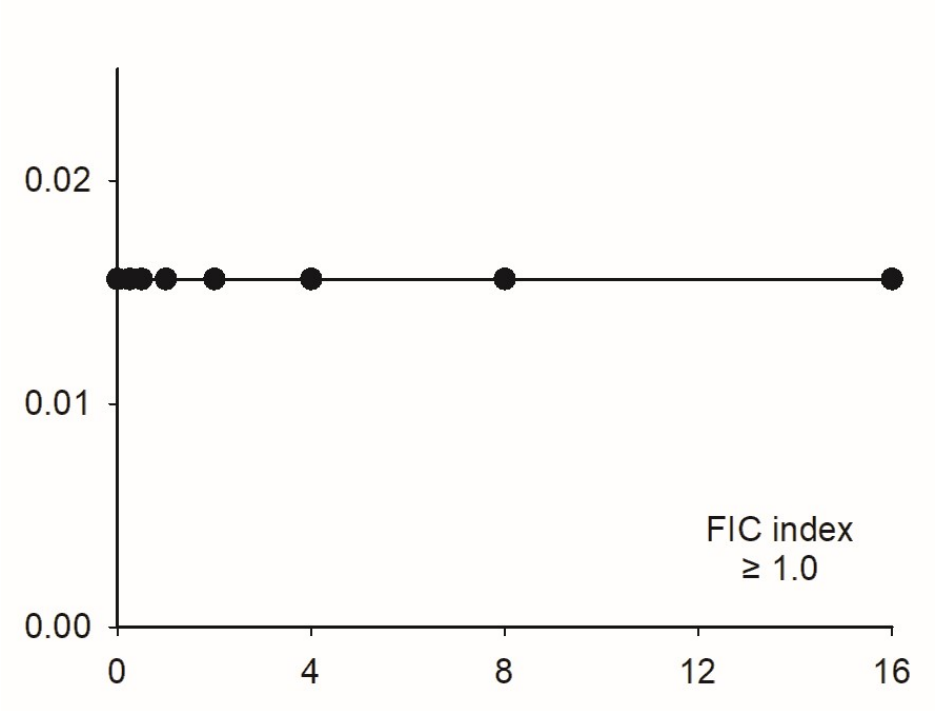

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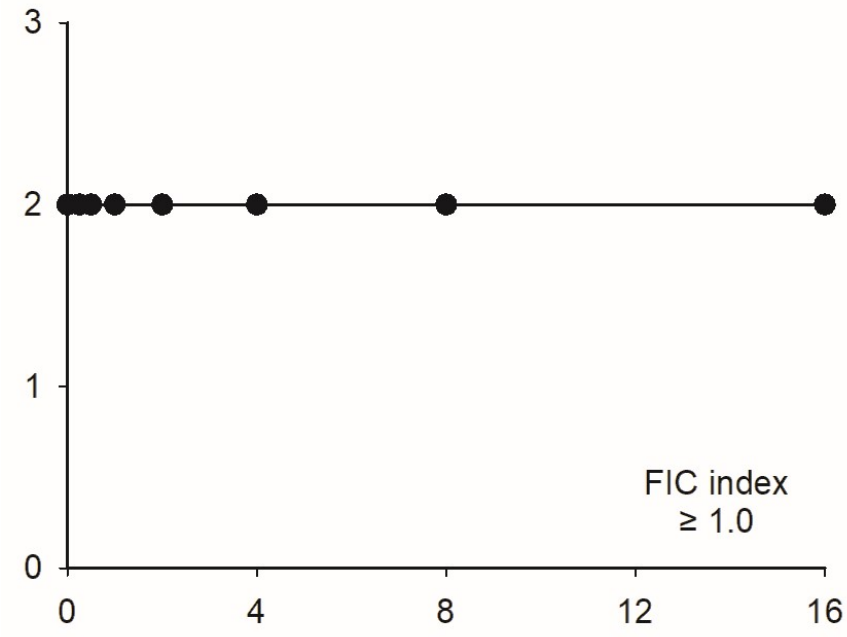
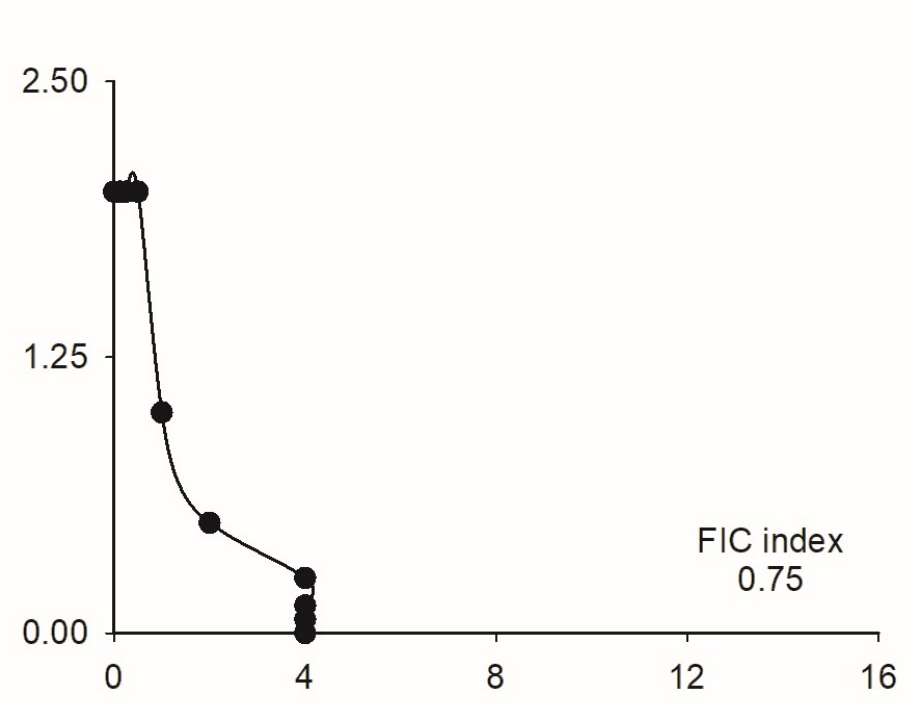


Supplementary Figure S5. Modulation of ciprofloxacin and tetracycline antibacterial activity by xanthines (caffeine and pentoxifylline) in *Escherichia coli* using microbroth dilution assay and checkerboard methodology. (**a**), ciprofloxacin-caffeine mixtures; (**b**), tetracycline-caffeine mixtures; (**c**), ciprofloxacin-pentoxifylline mixtures; (**d**), tetracycline-pentoxifylline mixtures. FIC, Fractional Inhibitory Concentration Index calculated for each tested antibiotic-xanthine combination according to Odds [33]

Figure S6a



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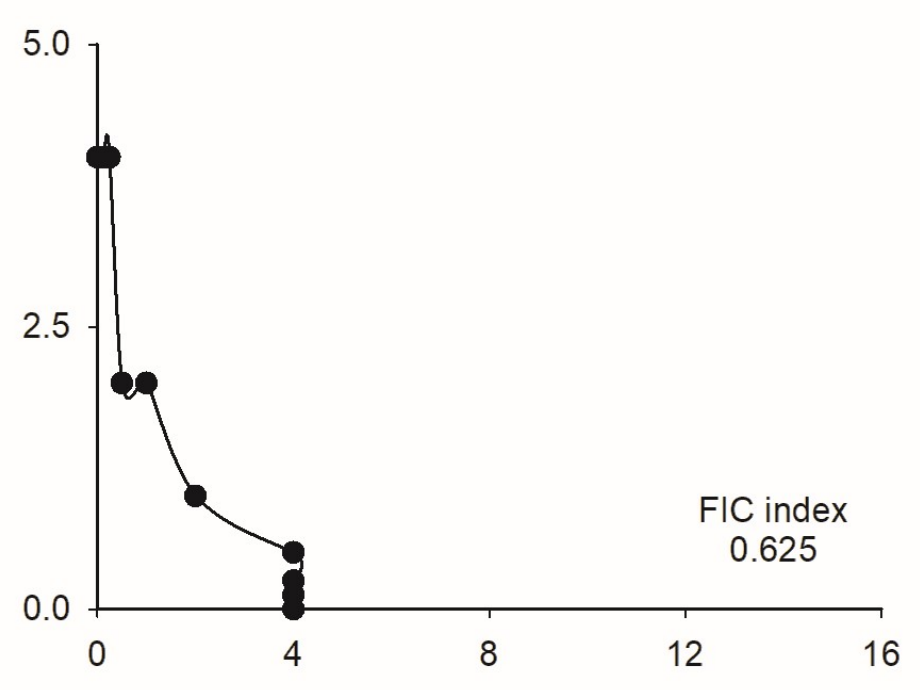
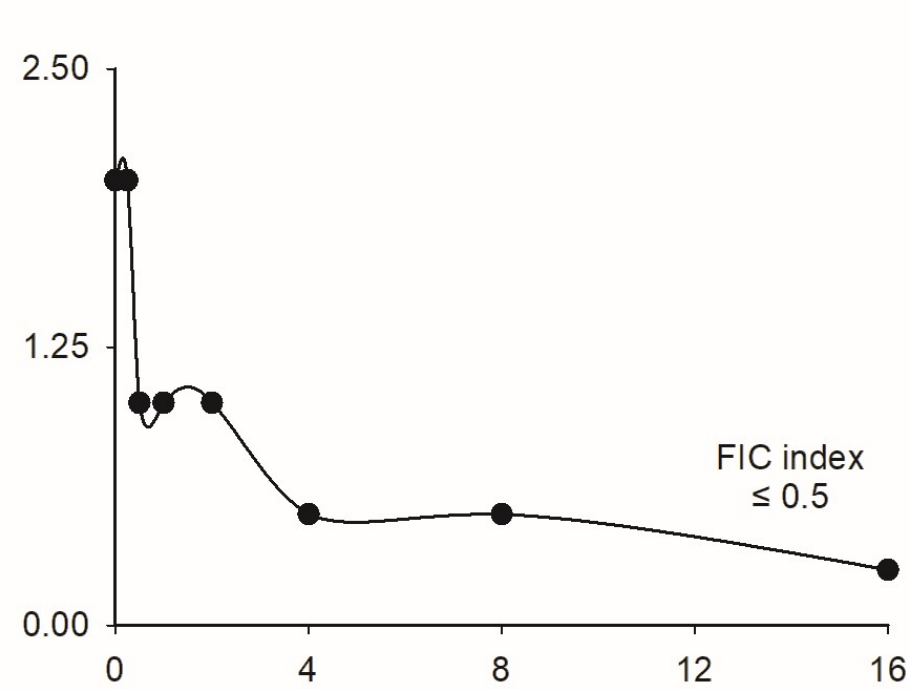


Figure S6c



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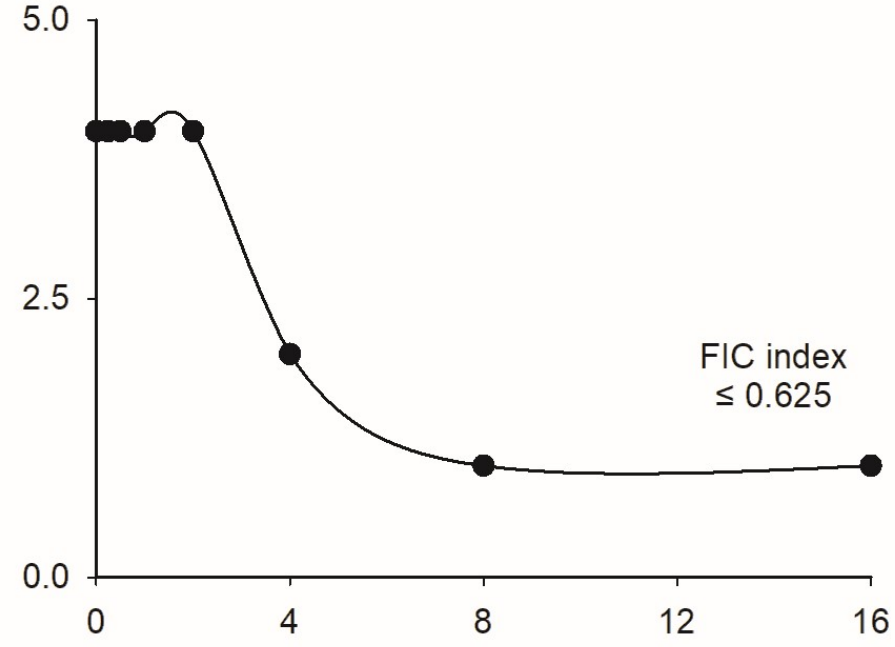
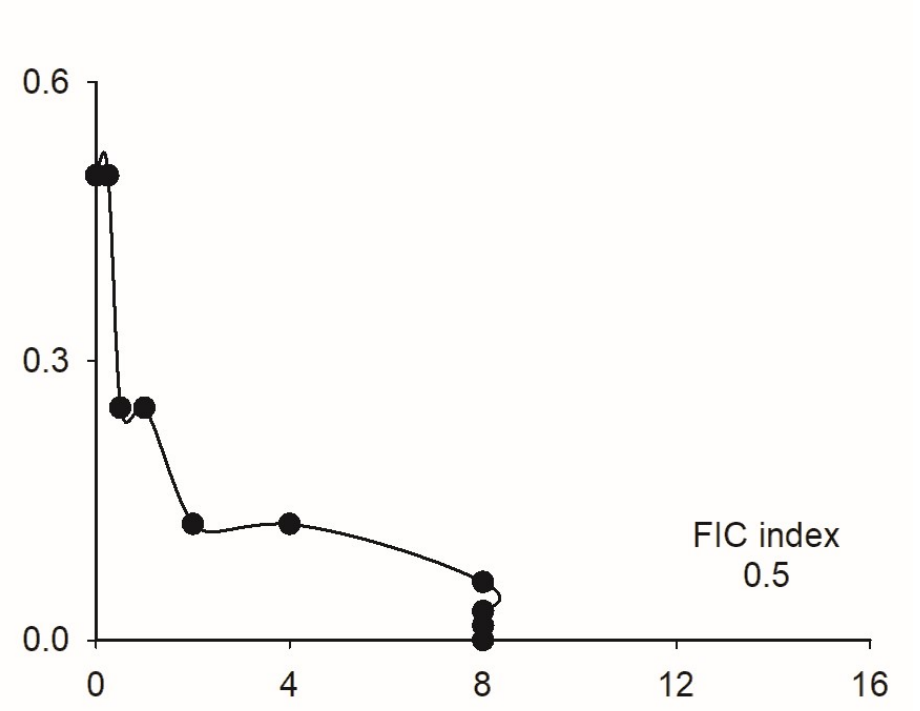


Supplementary Figure S6. Modulation of ciprofloxacin and tetracycline antibacterial activity by xanthines (caffeine and pentoxifylline) in *Acinetobacter baumannii* using microbroth dilution assay and checkerboard methodology. (**a**), ciprofloxacin-caffeine mixtures; (**b**), tetracycline-caffeine mixtures; (**c**), ciprofloxacin-pentoxifylline mixtures; (**d**), tetracycline-pentoxifylline mixtures. FIC, Fractional Inhibitory Concentration Index calculated for each tested antibiotic-xanthine combination according to Odds [33]

Figure S7a



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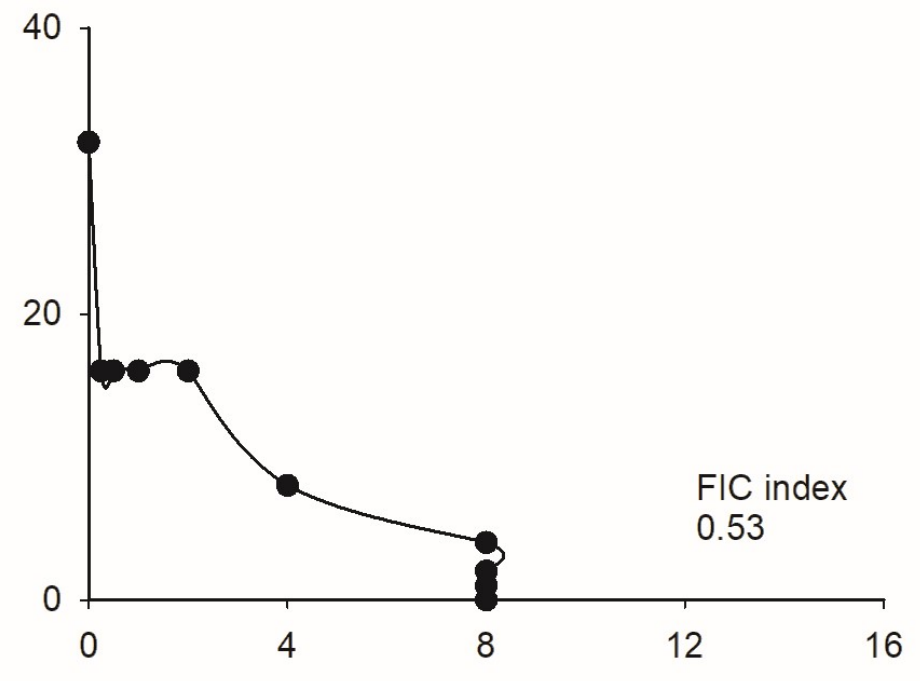

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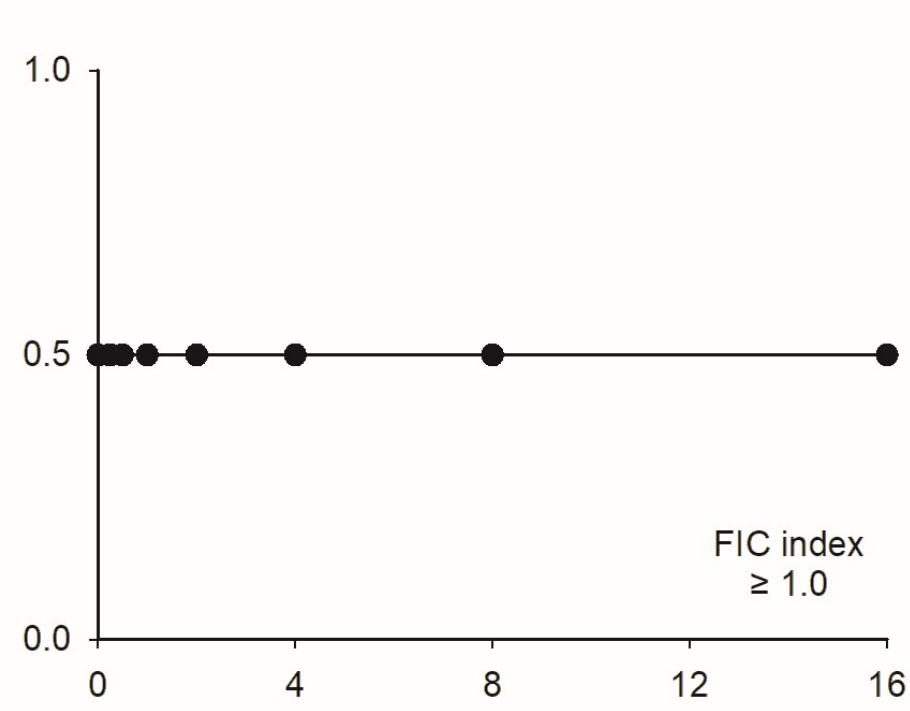

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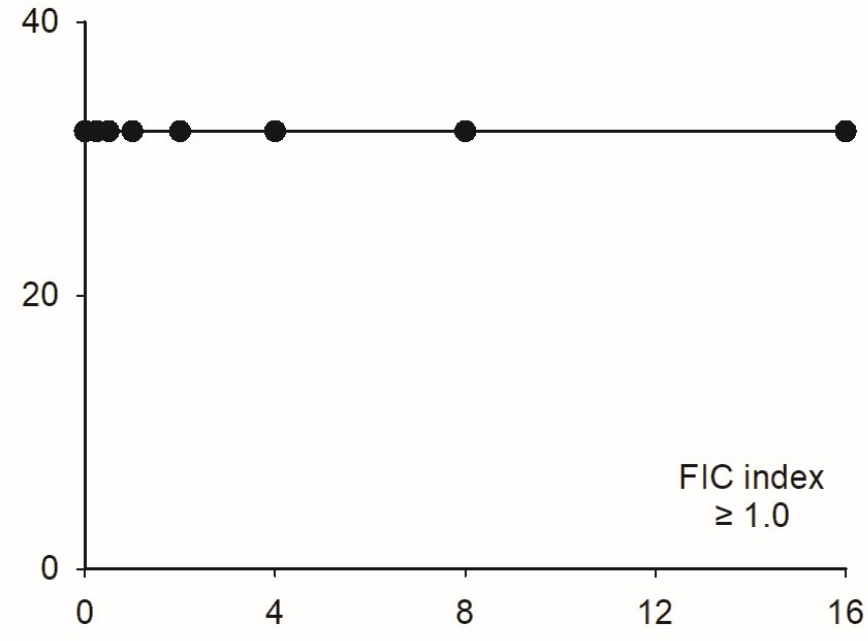


Supplementary Figure S7. Modulation of ciprofloxacin and tetracycline antibacterial activity by xanthines (caffeine and pentoxifylline) in *Klebsiella pneumoniae* using microbroth dilution assay and checkerboard methodology. (**a**), ciprofloxacin-caffeine mixtures; (**b**), tetracycline-caffeine mixtures; (**c**), ciprofloxacin-pentoxifylline mixtures; (**d**), tetracycline-pentoxifylline mixtures. FIC, Fractional Inhibitory Concentration Index calculated for each tested antibiotic-xanthine combination according to Odds [33]

Figure S8a

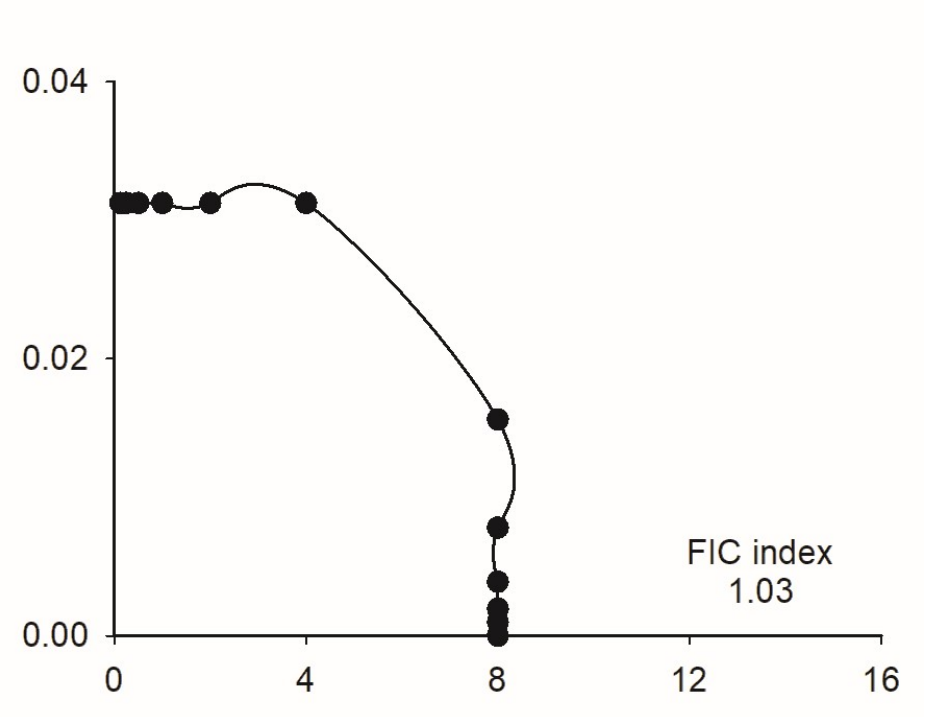


Figure S8b

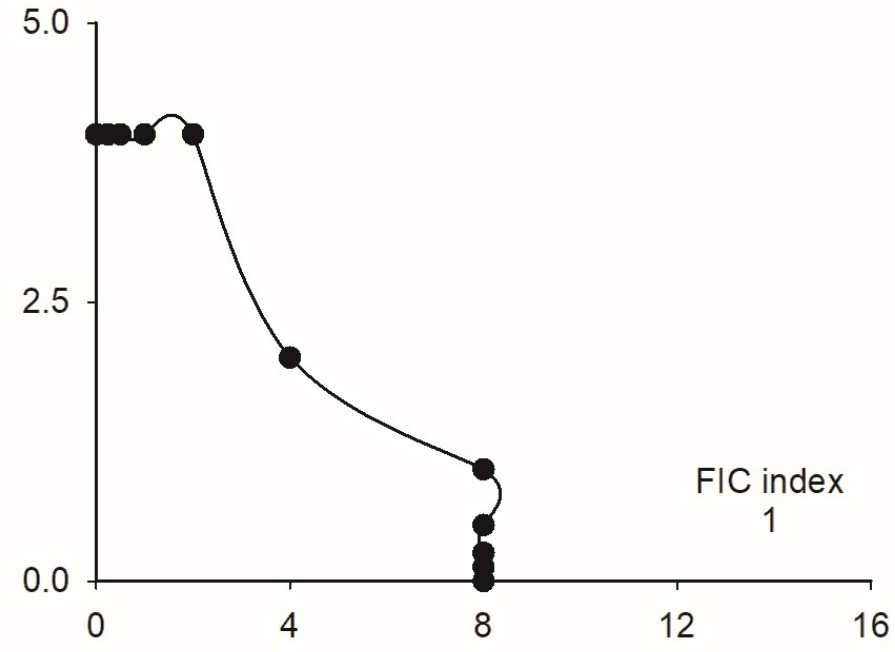


Figure S8c

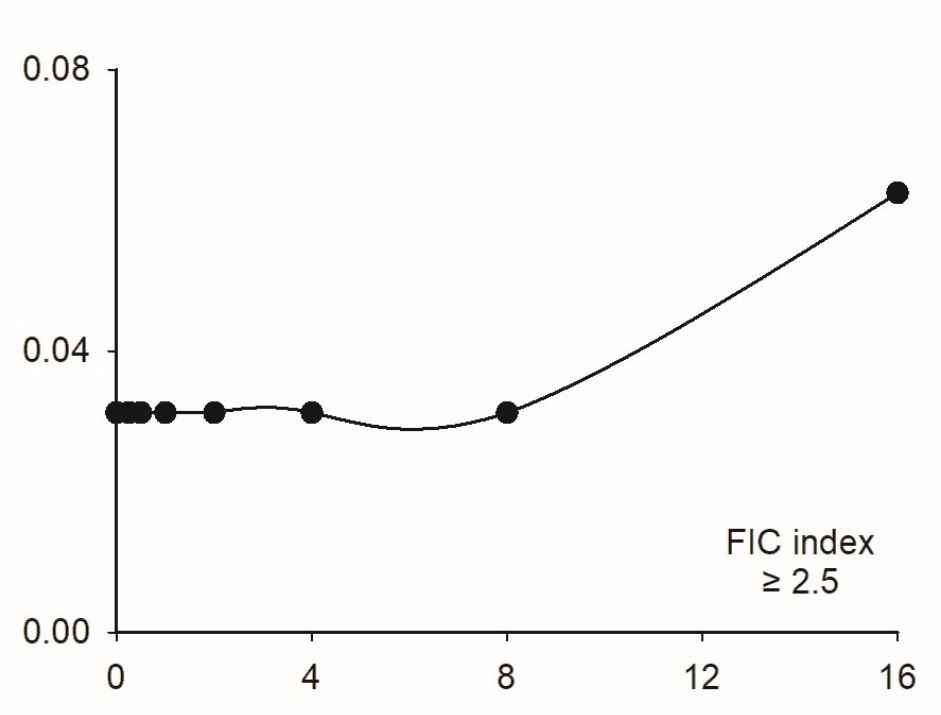
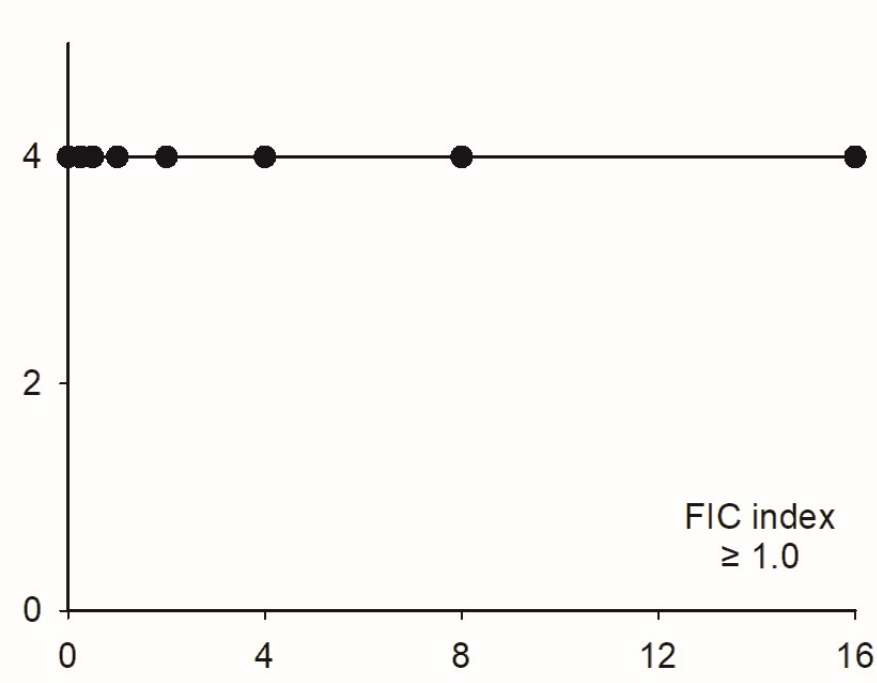


Figure S8d



Supplementary Figure S8. Modulation of ciprofloxacin and tetracycline antibacterial activity by xanthines (caffeine and pentoxifylline) in *Enterobacter cloacae* using microbroth dilution assay and checkerboard methodology. (**a**), ciprofloxacin-caffeine mixtures; (**b**), tetracycline-caffeine mixtures; (**c**), ciprofloxacin-pentoxifylline mixtures; (**d**), tetracycline-pentoxifylline mixtures. FIC, Fractional Inhibitory Concentration Index calculated for each tested antibiotic-xanthine combination according to Odds [33]