# Synthesis and EPIs activity of 5-arylhydantoin derivatives in *Enterobacter aerogenes*

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Efflux system in gram-negative bacteria contains tripartite protein pumps AcrAB-TolC, situated in outer membrane, periplasm and inner membrane of bacterial wall. One of the strategies to combat multidrug resistance is blocking the efflux capacity of bacterial cell by inhibitors. In our previous studies, a number of hydantoin derivatives, including simple structures modified at 5-position as well as various aminealkyl derivatives, were obtained and evaluated on their efflux pumps inhibition (EPIs) properties in two strains of *E. aerogenes* with(out) over-expression of AcrAB-TolC. Results indicated lack of intrinsic antibacterial activity for all tested compounds. Several compounds displayed moderate EPIs-activities. Among others, compound **GG-5k**, 1-(4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)-5,5-diphenylhydantoin-3-acetic acid, showed promising decrease of MIC for chloramphenicol, nalidixic acid and sparfloxacine. Treating the compound as a lead, further chemical modifications were carried out in the area of following structural factors: replacement of phenylpiperazine with "unaromatic" piperazine moieties, modifications of the length of alkyl linker ($C_3$-$C_8$), introduction of new substituents at N3-position of hydantoin (ester, acid, free NH) as well as the replacement of phenyl substituent at 5-hydantoin (pyridil, naphtyl, methyl). New compounds were tested on their EPIs-activity in microbiological assays (*E. aerogenes* strains: ATCC13048 and CM64). SAR-studies were performed. Results of microbiological tests indicated weak EPIs-activity for most of the tested compounds, lower than that of the lead **GG-5k**. An interesting activity was observed in case of N-unsubstituted 5-naphthyl hydantoin derivatives. These compounds caused 2-fold decrease of MIC of chloramphenicol in *E. aerogenes* strain with over-production of AcrAB- TolC efflux pump.