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# *IN VITRO* AND *IN SILICO* ASSESSMENT OF UREA/THIOUREA DERIVATIVES IN ANTIMICROBIAL THERAPY

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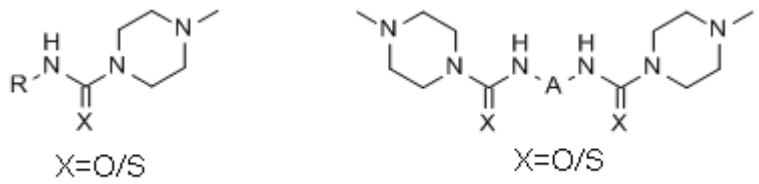
The emergence and spread of antimicrobial resistance, together with the lack of newly developed antimicrobial drugs present serious public health issues worldwide. Apart from bacteria that do not respond to antibiotics, therapy-resistant mutants of viruses and multidrug resistant fungal strains introduce additional difficulties to effective therapy.[1] Novel antimicrobial compounds containing chalcogenic elements (S, Se, Te) have attracted reasonable attention in the field of experimental chemotherapy.[2]

The aim of our study was to evaluate the potency of novel urea and thiourea derivatives (1-10) against various microorganisms (aerobic and anaerobic bacteria, fungi, Herpes Simplex Virus 1) *in vitro*, as well as their conformity to the attributes of successful drug candidates, using computational *in silico* methods.

**Figure 1.: General structure of the tested compounds**




The antimicrobial activities of the tested compounds against reference strains of aerobic or anaerobic bacteria and yeasts were evaluated using disk diffusion tests and when warranted, broth microdilution method, according to EUCAST standards.[3] A double-disk synergy test was used for the detection of synergism between the derivatives and antibiotics (ampicillin, cefuroxime, imipenem, vancomycin) against multiresistant bacterial strains.[4] A MIC reduction assay was performed to quantify the effects of the (thio)ureas on the minimal inhibitory concentrations of reference drugs. The anti-HSV activity of the tested compounds was evaluated using MTT assay on Vero cells.[5] The predicted physicochemical and pharmacokinetic properties of the tested compounds were determined *in silico*, using OSIRIS Molecular Property Explorer and PreADMET software.[6,7]

**Table 1.: Bacterial and fungal reference strains used in our experiments**

| **Bacteria** | | | **Fungi** |
|---|---|---|---|
| *Aerobic* | *Anaerobic* | *Multiresistant* | |
| *Staphylococcus aureus* ATCC 25923 | *Clostridium perfringens* ATCC 13124 | *Staphylococcus aureus* ATCC 43300 (MRSA) | *Candida albicans* ATCC 10231 |
| *Staphylococcus epidermidis* ATCC 12228 | *Propionibacterium acnes* ATCC 11827 | *Enterococcus faecium* QC/2008/12/03 (VRE) | *Candida krusei* ATCC 14243 |
| *Enterococcus faecalis* ATCC 29212 | *Bacteroides fragilis* ATCC 25285 | *Acinetobacter baumanii* clin. isol. no.: 59738 | *Candida glabrata* ATCC 2001 |
| *Escherichia coli* ATCC 25922 | | *Pseudomonas aeruginosa* ATCC 27863 | *Candida parapsilosis* ATCC 22019 |
| *Klebsiella pneumoniae* ATCC 49619 | | | *Candida tropicalis* ATCC 13803 |
| *Proteus mirabilis* PMI 60007 | | | *Cryptococcus diffluens* ATCC 32059 |
| *Salmonella Derby* HWCMB 10032 | | | |
| *Pseudomonas aeruginosa* PAE 170022 | | | |

The ureas/thioureas did not show antibacterial activity against the aerobic and anaerobic bacteria, nor did they inhibit the growth of the fungal strains included in our study (MICs of the tested compounds were >200 μM; inhibition zone diameters <10 mm in all experiments). Some of the tested compounds presented modest adjuvant properties, reducing the inhibitory concentrations of antibiotics by 25-50% against susceptible bacteria, however they did not influence the effects of reference drugs against resistant strains. Based on the percentages of maximum cell recovery and selectivity, a 4-nitrophenyl-derivative and a 1,4-phenylene-substituted compound showed potent anti-HSV properties. All tested compounds complied with Lipinsky's Rule of Five and the predicted percentages of intestinal absorption are excellent (≥ 95%) for all the respective compounds.[8,9]

The tested thio(ureas) lacked any antimicrobial activity against the bacterial and fungal strains, and their potential as antibiotic adjuvants is modest at best. On the other hand, their predicted ADME properties are of the highest standard and some of the compound showed promising antiviral activity. The synthesis and biological evaluation of novel derivatives in the future could introduce alternative antiviral drugs with selective activity.

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