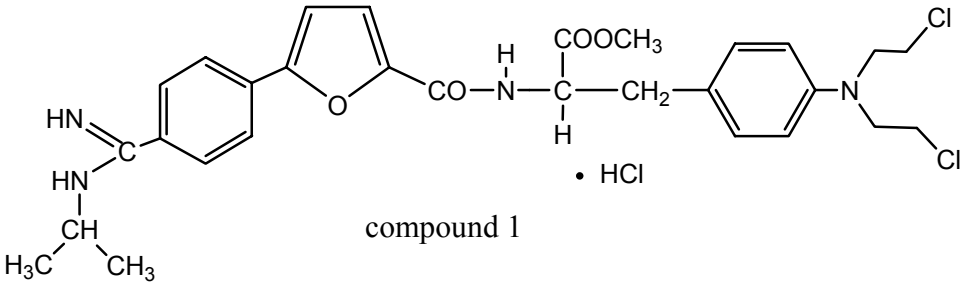
STRUCTURE – ACTIVITY STUDIES OF NOVEL AMIDINE ANALOGUES OF MELPHALAN

Anna Bielawska[a], Krzysztof Bielawski[a], Katarzyna Sosnowska[b], Wojciech Miltyk[a], Tomasz Anchim[c]

[a]Department of Medicinal Chemistry and Drug Technology, Medical University of Białystok, Mickiewicza 2, 15-089 Białystok, Poland
[b]Department of Pharmaceutical Technology, Medical University of Białystok, Mickiewicza 2c, 15-422 Białystok, Poland
[c]Department of Gynecological Endocrinology, Medical University of Białystok, Skłodowskiej 24A, 15-276 Białystok, Poland
kbiel@amb.edu.pl

A number of novel amidine analogues of melphalan were synthesized and examined for cytotoxicity in breast cancer cell cultures. Evaluation of the cytotoxicity of these compounds employing a MTT assay and inhibition of [^{3}H]thymidine incorporation into DNA in both MDA-MB-231 and MCF-7 breast cancer cells demonstrated that these compounds were more active than melphalan. Data from the ethidium displacement assay indicated that these compounds bind in the minor groove of DNA and show moderate specificity for AT base pairs. To test whether cytotoxic properties were related to topoisomerase action, the most potent compound **1** was evaluated in a cell-free system. Compound **1** inhibited the catalytic activity of both topoisomerases I and II at a concentration of 120 and 20 μM, respectively. This suggests that DNA binding may be implicated in the cytotoxicity of these bisamidines, possibly by inhibiting interactions between topoisomerase II and their DNA targets.



compound 1

Molecular mechanic studies were carried out using the AM1 method, in order to generate a set of representative low-energy conformations for one representative amidine analogue of melphalan, i.e., compound **1**. Molecular dynamics approach was used to examine the structure of complexes formed between the d(CGCGAATTCGCG)$_2$ and compound **1**. The resulting structures of the ligand-DNA model complexes and their energetics were been examined. It was predicted that the compound **1** should have a decreased affinity for the minor groove of AT-rich regions in comparison to furamidine, netropsin and distamycin. From the energetic analysis it appears that van der Waals and electrostatic interactions are more important than specific hydrogen bonds in stabilizing the compound **1** - duplex complexes.