Uniwersytet Medyczny w Białymstoku

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***Synteza na podłożu stałym***

***i ocena aktywności przeciwnowotworowej***

***analogów netropsyny i bis-netropsyny***

Praca wykonana

na stopień doktora nauk farmaceutycznych

w Zakładzie Chemii Organicznej

Uniwersytetu Medycznego w Białymstoku

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Białystok 2015

**9. Summary.**

 Cancer is the second cause of death in Poland. Arduousness of side effect and insufficient efficiency chemotherapy is constantly current challenge for seeking new and safe anti-cancer drug.

 MGB's are a group of antiproliferative compounds, acting in non-intercalating manner in minor groove of DNA. Still looking forward representative in anticancer pharmacotherapy. Until now examined structures proved too high toxicity against healthy cells. Nevertheless, unique reaction mechanism this drug class, involving selective, no intercalative DNA binding with A-T regions of minor grove is still inspiration of many scientists in looking for newer active structures. Leading member above group is Netropsin, which helps as model structure of 24 analogues libraries.

The purpose of the study was solid state synthesis of 24 new oligopeptide analogues of netropsin and bis-netropsin, active in minoor groove and antiproliferative activity. Solid state synthesis accomplished by using SYNCORE reactore made by BÜCHI on Wang resin.

Recived analogs of netropsin and bis-netropsin with external rings where converted on pirol, pirydine, thiazole and benzens. Active tail of leading structure was changed on chloro-alkyl chain or α-bromoakrylamide fragmentem or chlorambucil. Bis-netropsine like in the place of active chain include linkers (CH2)n, where n=4 or 5.

New analogues affinity to DNA where confirm by FID. Aneksin-V-Fluos and propidium iodide test, examined antiproliferative abiliity, by using flow cytometry. As confirmation accomplished Fisher Leuko Stat Kit test microscopic method.

All new analogues prooved activity depending on the concentration, affirmed on standard human breast cancer cell line MCF-7, MDA-MB-231 and human breast basal epithelial cell line MCF-10A.

 Analogues where associaced with plazmid pBR322, some of them occured stronger than netropsin e.g. **A4**, **D4,** **B6**, **D6** i **D5**. Analogs inhibit proliferation standard human breast cancer cell line MCF-7, but none exceled netropsin IC50=5.40, the most active analog **A4** IC50=62.73 µM. All new structures also inhibit proliferation cell line MDA-MB-231 but all of them where stronger than model structure IC50=228,80 µM, among them most active **C3** z IC50=71.75 µM. Unfortunately all new structures inhibit proliferation human breast basal epithelial cell line MCF-10A, eight of them (**D4**, **D2**, **C6**, **D6**, **C5**, **D5**, **C4**, **C3**), where stronger than netropsin, the most active **C3** has IC50=94.52 µM.

 The most active structure was A4, belongs to most active group 4 with chlorambicil tail. Test on cell MDA-MB-231 showed 2 times higher activity than model structure and about 1/3 lower against MCF-10A.