Mgr Angelika KAMIZELA
Institute of Chemistry
Faculty of Natural Sciences
The Jan Kochanowski University
25-406 Kielce
Uniwersytecka St.7

Kielce, 26.02.2020r.

THE SYNTHESIS AND BIOLOGICAL ACTIVITY OF LACTONS WITH ARYL GROUP

Supervisors: dr hab. inż. Barbara Gawdzik, prof. UJK
dr hab. Alicja Wzorek, prof. UJK

ABSTRACT OF THE DISSERTATION

The main goal of the dissertation was to develop a new, efficient method for the synthesis of halolactones containing an aryl group in their structure. The structures of all received compounds were determined on the base of the following methods:

- infrared spectroscopy (FT-IR),
- nuclear magnetic resonance spectroscopy (^{1}H NMR and ^{13}C NMR),
- high resolution mass spectrometry (HR-MS),
- additionally X-ray structural analysis was carried out for lactones that were obtained in crystalline form.

Taking into account the unique biological properties exhibited by lactones, the examinations of cytotoxic, anti-cancer, bacteriostatic and deterrent properties of synthesized lactones were performed. An attempt was also made to find a correlation between the structure of the lactones and their biological activity.

In the theoretical part of the dissertation, selected methods for the synthesis of lactones with particular emphasis on the halogenolactonization reaction of γ, δ-unsaturated carboxylic acids were described. Overview of research results available in the literature on the biological activity of lactone derivatives, including anti-cancer, bacteriostatic and deterrent properties, from the last decade, were also presented.

In the experimental part of the work a new, four-step pathway for the synthesis of γ-halogen-δ-lactones and δ-halogen-γ-lactones was described. For the synthesis of these target compounds, simple and commercially available substrates were used. The first step of the planned lactone synthesis was the nucleophilic addition of Grignard reagents to the carbonyl carbon atom of *trans*-crotonaldehyde or 3-methyl-crotonaldehyde. As a result of the reaction, six allyl alcohols containing an aryl moiety in the structure were receive, which were subsequently used in the Johnson-Claisen rearrangement. The γ,δ-unsaturated ethyl esters obtained in this way were subjected to a hydrolysis under an alkaline conditions, to give the appropriate carboxylic acids. The key step of the synthesis was the halogenolactonization of γ,δ-unsaturated carboxylic acids. As a result of the reaction of the acids with NCS, nine new γ-chloro-δ-lactones were received. Similarly, nine new γ-bromo-δ-lactones were obtained in reaction with NBS. Iodolactonization, which were conducted under thermodynamic control conditions, provided seven γ-iodo-δ-lactones, two δ-iodo-γ-lactones and six δ-hydroxy-γ-lactones. All obtained lactone derivatives, except *trans*-6-phenyl-5--iodo-4,4-dimethyltetrahydro-2H-pyran-2-one, are new compounds, that have not been previously described in the literature. For selected lactonization products, several tests were carried out to verify their bacteriostatic, cytotoxic, anti-cancer and deterrent properties. Two bacterial strains were used as reference microorganisms in the tests of bacterial activity: *Escherichia coli* ATCC 8739 and *Staphylococcus ureus* ATCC 65389. The highest activity against Gram-negative bacteria was exhibited by following lactones: *cis,trans*-5-chloro-6-(p-fluorophenyl)-4-methyltetrahydro-2H-pyran-2-one, *trans,trans*-6-(p-fluorophenyl)-5-iodo-4-methyltetrahydro-2H-pyran-2-one and *cis,trans*-6-(p-fluorophenyl)-5-iodo-4-methyltetrahydro-2H-pyran-2-one, causing a reduction of living microorganisms from 70 to 78% as compared to the control sample. The most effective bacteriostatic agent against *S. aureus* turn out to be *trans,trans*-5-chloro-4-methyl-6-(α-naphthyl)tetrahydro-2H-pyran-2-one, reduced the number of CFU by 87% as compared to the control sample. Evaluation of cytotoxic and anti-tumor activity were performed using L929 cell line (mouse fibroblasts) and the AGS tumor cell line. The best potential anti-cancer drug was *trans*-6-phenyl-5-iodo-4,4-dimethyltetrahydro-2H-lactone-pyran-2-one, which showed low biological activity towards healthy, non-cancerous cells and high activity, compared to doxorubicin, for gastric adenocarcinoma AGS cells. The deterrent activity of synthesized lactone derivatives was tested against the peach-potato aphid *Myzus persicae*. The *trans,trans*--5-chloro-6-(p-fluorophenyl)-4-methyltetrahydro-2H-pyran-2-one and *cis,trans*-5-bromo-6--phenyl-4-methyltetrahydro-2H-pyran-2-one showed insect repellent effect after an hour

from the start of the experiment, while the detective properties of *cis,trans*-5-chloro-6-phenyl--4-methyltetrahydro-2Hpyran-2-one, *trans,trans*-6-phenyl-5-iodo-4-methyltetrahydro-2H--pyran-2-one and *cis,trans*-6-phenyl-5-iodo-4-methyltetrahydro-2H-pyran-2-one were revealed after 24 hours. Based on the results obtained, the correlations between the structural structure of the tested lactones and their biological activity were determined.

Angelika Hermiede