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Evaluation report of the thesis untitled « Synthetic transformations of natural products » by M^r Ivaylo Momchilov SLAVCHEV.

This PhD thesis, submitted by M^r Ivaylo Momchilov SLAVCHEV, was achieved in the context of a collaborative research work, involving the Institute of Organic Chemistry with Centre of Phytochemistry of the Bulgarian Academy of Sciences (Sophia, Bulgaria), and the Faculté de Pharmacie de Paris of the University of Paris Descartes (Paris, France), under the supervision of Prof. Vladimir DIMITROV (Laboratory of Organic synthesis and stereochemistry), and Prof. Brigitte DEGUIN (Laboratory of Pharmacognosie - Chimie des Substances Naturelles).

This work deals with the use of natural chemical products as sources of starting material for hemisynthesis of bioactive compounds. Plants for example, can synthesise chiral natural products during their biogenetic pathway. These molecules can be extracted, purified, and their structure analysed, to give material for the organic chemistry. This chiral pool can be isolated in an enantiomerically pure form which represents an invaluable source of bioactive products. In this thesis, the molecules were chosen among the terpene family, more precisely three monoterpenes: Acubin, fenchone, and camphor. The antitubercular and cytotoxicity activities of their derivatives were evaluated.

The report is articulated around four main chapters, with a general introduction and conclusion. Each chapter is subdivided into four parts, with the previous works, the personal ones, the experimental part, and the bibliography. This is very well organized, well documented, and affords more clarity to the manuscript. A conclusion and a link between the different parts might be added.

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1. After a general introduction which presents the subject in its general context, the chapter one deals about generalities on the terpenes as material for synthetic transformation. In this chapter, some mistakes appeared about the name of the plants. Nowadays, it is more appropriate to use the phylogenetic classification, especially for the identification of the botanical family, which can be very different in comparison with the traditional classification. Among the monoterpenes, the difference between the iridoids (aucubin) and the bicyclic monoterpenes (camphor and fenchone) is described. The data about their activity/toxicity appear very important to understand before the hemisynthesis.

2. The second chapter is the core of the thesis. The previous works about each selected terpene on their catalytic application are discussed. Moreover, a paragraph about the selective functional modifications of the aucubin shows its interest to obtain non toxic, chiral scaffold for the hemisynthesis of biological active molecules. A synthetic scheme with the key positions of the modification of the molecules should be added in conclusion.

The next part explains the personal work. First, the author underlines the use of aucubin as a natural source of new stable chiral semisynthetic compounds. Halogenolactones are obtained and subjected to selective ring contraction in basic conditions yielding a mixture of diastereomeric cyclopentanofurans, inseparable by column chromatography, according to an Oxy-Favorskii rearrangement. The influence of the experimental conditions on the content of the isomer mixture, and the research to optimize the synthesis, are described. Then after the synthesis of iodo-, bromo-, chlorolactones from aucubin, yielding a mixture of endo-, exo-halogenolactones, an investigation of the influence of the conditions on the content of the isomers during the ring-contraction is discussed. An impressive work was performed and the author proposes in conclusion conditions for the selective synthesis of isomers.

After an interesting discussion about the epimerization of halogenolactones, and a modification of the functional groups of the skeleton, cyclopentanofuran derivatives were synthesised and tested as catalytic agents. Then, the last part is dedicated to the experimental data, very complete, and perfectly realised.

3. The third chapter reports and discusses the antitubercular activity of two types of natural products, terpenes and arylacrylic acids as cinnamic acid. After an updated bibliographic study of the biological interest of these molecules, a synthesis of chiral (*E*)-arylacrylic acid was achieved. Then, we understand that the fenchone is used to obtain a fenchane aminoalcohol, to combine later with the cinnamic acid derivatives, to yield the target

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amide. At the beginning of the paragraph of the personal work, the aim of the study is not clear and a small explanation might be useful for a better understanding. Five amides reveal a good activity against a strain of *Mycobacterium tuberculosis*, and the cytotoxicity of the most active ones is evaluated too. This chapter underlines the interest of these molecules with a structure / activity relationships discussion.

4. To continue with the biological activity, the last chapter is dedicated to the anticancer activity of terpenoids and ferrocenes. This time, the aim of the study is clearly announced: the coupling between a ferrocene moiety and camphor. Unfortunately, the problems of solubility and reproducibility led to a lack of conclusion on the cytotoxic activity.

A short and synthetic conclusion suggests, and confirms, the serious work of the author.

In conclusion, each part of the thesis is properly prepared, very well written, and very interesting to discover. The work of Mr Ivaylo Momchilov SLAVCHEV indicated high technical skills, subject-matter knowledge, and a great commitment. Each chapter is well structured, with an updated bibliography, and the results are discussed with rigor with all the quality requirements. The quantity and quality of synthesised compounds show the perseverance and work capacities of the author. His excellent results will be useful for the next researchers.

Therefore, based on these conclusions, I give a very positive opinion for the PhD thesis of Mr Ivaylo Momchilov SLAVCHEV.

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