**OPINION**

**by Dr. Plamen Angelov Angelov, associate professor at Paisii Hilendarski University of Plovdiv**

on the Thesis for awarding the educational and scientific degree "doctor" in higher education field 4 "Natural Sciences, Mathematics and Informatics", professional classification 4.2. "Chemical Sciences", scientific specialty "Organic Chemistry"

**Author**: Maya Trifonova Tavlinova-Kirilova

**Title**: Chiral aminobenzyl-naphtols and -quinolinols and dihydro-1,3-naphthoxazines - synthesis and catalytic applications

**Scientific advisors**: assoc. prof. Dr. Kalina Kostova and assist. prof. Dr. Mariana Kamenova-Nacheva, IOCCP-BAS

**1. General description of the procedure and the doctoral candidate**

According to administrative act № РД-09-06/19.01.2024 by the Director of IOCCP-BAS I have been appointed as a member of the scientific jury in a doctoral thesis defense procedure. The thesis submitted for evaluation in this procedure is authored by Maya Trifonova Tavlinova-Kirilova and contains original research results from her work at the laboratory of organic synthesis and stereochemistry at the IOCCP-BAS, where she currently holds a position of assistant professor. The title of the thesis is "Chiral aminobenzyl-naphtols and -quinolinols and dihydro-1,3-naphthoxazines - synthesis and catalytic applications ". The submitted thesis and all accompanying documents are in complete accordance with the requirements of the Law for the Development of the Academic Staff in the Republic of Bulgaria and the internal regulations of IOCCP-BAS.

**2. Relevance of the topic**

The presented doctoral thesis is in the field of organic chemistry, and more specifically – asymmetric organic synthesis and catalysis. The described research includes a large volume of experimental work, aimed at the development of novel chiral compounds with possible application as ligands in the asymmetric catalysis of organozinc additions to aldehydes. Some of the newly obtained compounds have also been assayed for antibacterial and antiviral activity. Considering the general importance of asymmetric catalytic methods in organic synthesis and the current need for new and more effective antiinfective drugs, this research is topical and of significant interest.

**3. Knowledge of the problem**

The author of the thesis has demonstrated detailed knowledge and deep understanding of the chosen research theme. The literature related to the research problem has been thoroughly reviewed in a dedicated chapter of the thesis, comprising 93 pages and including 187 references.

The skillful application of relevant methodological approaches in the pursuit of the chosen research goals is another indication of the authors' knowledge of the investigated problems.

**4. Research methodology**

The main objective of the presented doctoral thesis is the synthesis of new chiral, non-racemic dihydro-1,3-naphthoxazines and aminobenzyl-naphthols and -quinolinols, as well as their application as ligands in enantioselective reactions. This objective and the related research tasks in the field of organic synthesis require the application of classical and development of novel synthetic methodologies in conjunction with appropriate contemporary methods of the molecular spectroscopy. In this regard, all methodological aspects of the thesis are excellently implemented.

**5. Characteristics and evaluation of the thesis and its contributions**

The presented thesis includes a total of 220 pages and begins with a short introduction and description of the goals and objectives. This is followed by a large and well-structured review of the various aspects and implementations of the Mannich aminoalkylation – a reaction of central importance to the doctoral candidate's own research. The review also includes recent publications on the enantioselective additions of organozinc compounds to aldehydes, catalyzed by chiral aminobenzylnaphthols. The original results obtained by the doctoral candidate are presented and discussed in depth in a separate 62-page chapter "Results and discussion". This is followed by another 39-page chapter "Experimental", containing detailed experimental procedures and spectral data for all novel compounds.

By Mannich condensation of naphthalen-2-ol, formaldehyde and various chiral amines are synthesized dihydro-1,3-naphthoxazines, which are then reduced to tertiary *N*-substituted amino alcohols. As a source of chirality are used also (R)-(–)-2-phenylglycinol and the methyl ester of (R)-(–)-2-phenylglycine, the condensation of which with formaldehyde and naphthalene-2-ol is found to proceed with preservation of the configuration of the starting chiral components. Bis-dihydro-1,3-naphthoxazines are synthesized in high yield by three-component Mannich condensation of 2,3- or 2,6-dihydroxynaphthalenes with formaldehyde and (S)-(−)-1-phenylethan-1-amine. In a similar way, from naphthalene-2-ol, formaldehyde и (R,R)- or (S,S)-cyclohexane-1,2-diamine is obtained chiral, non-racemic imidazolidine bis-hydroxynaphthalene. Thoroughly investigated is the stereochemical outcome of three-component Betti-type condensations of quinoline analogues of naphthalen-2-ol (quinolin-6- or 7-ol) with aromatic aldehydes (3-methyl-benzaldehyde and 1-naphthaldehyde) and S-(−)-1-phenylethan-1-amine. The chiral products obtained in the above mentioned experiments are then investigated as catalysts (ligands) in a model reaction of enantioselective addition of diethylzinc to aldehydes. High enantioselectivity is achieved only with ligands obtained from quinoline-6- or 7-ol, aldehydes and (S)-(−)-1-phenylethan-1-amine.

All newly synthesized chiral compounds are fully characterized by NMR spectroscopy, mass spectrometry, specific rotation angle and elemental analysis. Some of the obtained products have also been assayed for antimicrobial activity. Moderate antibacterial activity is reported for three of the studied compounds and also antiviral activity for one compound.

**6. Assessment of the publications and personal participation of the doctoral candidate**

Until now, the results obtained in this thesis have been published in three separate research articles in specialized international journals. One of the publications is accompanied by a protocol delineating the sharing of contributions with another doctoral candidate. In two of the publications Maya Tavlinova-Kirilova is the leading author, which is indicative of significant personal participation and contribution.

**7. Abstract**

The submitted abstract is in complete accordance with the thesis and presents all important results with the relevant discussion in a short form. The summary and all conclusions are in full agreement with the research results presented in the thesis.

**CONCLUSION**

This doctoral thesis contains original research results which contribute to the development of the scientific field and satisfy the requirements for quality and novelty imposed by the Law for the Development of the Academic Staff in the Republic of Bulgaria. The thesis clearly shows that its author, Maya Trifonova Tavlinova-Kirilova, has sufficient theoretical knowledge and professional skill in the field of Organic Chemistry. The author demonstrates abilities for independent research. In view of the above, I kindly recommend the scientific jury **to award the educational and scientific degree "Doctor"** to Maya Trifonova Tavlinova-Kirilova.

05.03.2024 г. **Reviewer**: .....

Assoc. prof. Plamen Angelov, PhD