REVIEW

by

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Corresponding member of Bulgarian Academy of Sciences

Member of the Academic Jury set to render a decision

on a procedure for the acquisition of Academic Degree

"Doctor" (PhD)

in the Professional Field 4.2. Chemical Sciences

according to the Classifier of the Areas of Higher Education and the Professional Fields

(Scientific Specialty "Organic Chemistry")

Dissertation:

CHIRAL AMINOBENZYL-NAPHTHOLS AND -QUINOLINOLS AND DIHYDRO-1,3-NAPHTHOXAZINES - SYNTHESIS AND CATALYTIC APPLICATIONS

Authored by

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1. Subject to review

The set of materials presented by Assist. Professor Maya Trifonova Tavlinova-Kirilova is in accordance with the Regulations for the Development of the Academic Staff of IOCCP-BAS, and meets the criteria of IOCCP-BAS for the acquisition of the scientific degree "Doctor".

Assist. Prof. Maya Tavlinova-Kirilova has attached a dissertation (in Bulgarian) and an abstract in Bulgarian and English, as well as copies of 3 publications in scientific journals on the subject of the dissertation 3 publications, a list of citations on the author's scientific works, a list of participation with poster-reports at 7 scientific conferences and a list in the collectives of 24 scientific projects. A separation protocol for the author's contribution in the scientific publications used in the dissertation is also presented.

Of the three scientific papers presented, all in journals with an impact factor (JCR on Web of Science), one is a publication in a journal with a rank of **Q2** (20 pts), and the other two are publications in a journal with a rank of **Q4** (24 pts). The total number of points under indicator D is 44 points, which exceeds the minimum threshold of 30 points required by the Regulations of the IOCCP-BAS.

2. Brief biographical information about the candidate

Maya Trifonova Tavlinova-Kirilova was born on February 3, 1977 in Pleven, Bulgaria. She completed her higher education as a master chemist with very good success in 2000 at the Faculty of Chemistry of the Sofia University "St. Kliment Ohridski" majoring in "Organic and Analytical Chemistry". In the fall of 2000, she started working as a chemist at the Institute of Organic Chemistry with the Center for Phytochemistry - BAS, since 2005 she has been a third-level research associate, and since 2011 she has been an assistant in the "Organic Synthesis and Stereochemistry" Laboratory. From 21.06.2021, she is enrolled as a PhD student in independent studies at the Institute of Organic Chemistry with a Center for Phytochemistry - BAS.

3. Actuality of the topic and expediency of the set goals and tasks

The dissertation is presented on 220 pages, includes 34 figures, 11 tables and 112 schemes. 187 literary sources were used.

The aim of the dissertation work is the synthesis of new chiral compounds that can be used as ligands in enantioselective nucleophilic addition reactions of nucleophilic reagents to carbonyl compounds in the preparation of chiral secondary alcohols.

The main emphasis is placed on the design and synthesis of new chiral dihydro-1,3-naphthoxazines, aminobenzylnaphthols and quinolinols using *Mannich* and *Betti* condensation reactions, as well as on the evaluation of their antimicrobial and antiviral activity and the possibilities of their application as catalysts in a model reaction for the enantioselective addition of diethylzinc to aldehydes.

The search for new drugs against resistance-developing pathogens is a major task of medicinal chemistry and is a serious challenge to the scientific community to search for new compounds with diverse structural characteristics. In this context, interest in multicomponent reactions has grown in recent years due to their high potential for obtaining enantiomerically (diastereoisomerically) pure products, due to the great influence of stereochemistry on the biological activity of substances. Therefore, the research of Assist. Professor Tavlinova-Kirilova can be defined as up-to-date and innovative with a fundamental and scientific-applied nature.

4. Knowledge of the problem

The review of the literature is presented informatively and corresponds directly to the set goal, focusing mainly on the potential and advantages of multicomponent reactions as an alternative to classical multistage syntheses, as well as on the possibilities of "Green Chemistry" for the ecologically friendly preparation of organic compounds with desired properties.

The characteristics, mechanism and potential reagents of the *Mannich* reaction in acidic and basic media as a classical method for aminoalkylation of CH-acidic compounds, as well as its variety – the *Betti* condensation, are analytically discussed. Particular attention is paid to the *Mannich* aminomethylation of phenols and naphthols, as well as the reaction using diamines and polyhydroxy aromatic systems. It has been extensively commented on the influence of reagents

and conditions of the *Mannich* and *Betti* reactions on the nature of the resulting condensation products such as dihydro-1,3-oxazines, bis-dihydro-1,3-benzoxazines, 1,3-naphthoxazines, bis-dihydro-1,3 -oxazinquinolines, aminobenzylquinolinols and isoquinolinols. The methods for the synthesis of dihydro-1,3-oxazines using various catalysts, "green" solvents, plant-based reagents and renewable sources are presented in all their diversity.

The accumulated experience in the use of condensation reactions for the synthesis of new chiral aminohydroxy compounds, in particular *Betti* bases such as aminobenzylnaphthols, which can be applied as ligands in the enantioselective addition of diethylzinc to aldehydes, is also thoroughly discussed.

The literature review unequivocally demonstrates the high competence of Assist. Professor Tavlinova-Kirilova in the field of asymmetric synthesis and catalysis, which are the starting point of her scientific research. 140 sources out of a total of 187 are cited in the dissertation.

5. Research methodology

The chosen research methodology in the Assist. Professor Tavlinova-Kirilova's dissertation is based on the design, synthesis under the conditions of the *Mannich* and *Betti* reactions and evaluation of the biological activity of a wide range of new chiral compounds as potential catalysts (ligands) in the model reaction for enantioselective addition of diethylzinc to aldehydes.

The chosen research methodology should be perceived as appropriate, which is evidenced by the encouraging results obtained in fulfilling the set goal and solving the tasks formulated in the dissertation.

6. Characterization and evaluation of the dissertation and its scientific contributions

The results achieved in the dissertation work, mainly related to the efforts to synthesize a large number of new chiral compounds with diverse structural composition and application as catalysts for enantioselective addition of diethylzinc to aldehydes, are clearly presented and critically commented. The synthesized compounds are fully characterized and proven with the best methods of structural analysis, incl. mass spectrometry, NMR spectroscopy in all its varieties, X-ray structural and elemental analysis.

The scientific achievements in the dissertation work and its scientific contributions can be grouped into the following main directions:

1. Synthesis of dihydro-1,3-naphthoxazines and corresponding aminohydroxyl compounds as new chiral ligands in enantioselective addition reactions.

- By *Mannich* condensation of naphthalene-2-ol with formaldehyde (formalin or paraformaldehyde) and the chiral amines ((S)-(+)-1,2,3,4-tetrahydronaphthalen-1-amine and (S)-(+) -3,3-dimethylbutan-2-amine) the corresponding dihydro-1,3-naphthoxazines are obtained in high yields. The synthesized new compounds are transformed to the corresponding aminomethylnaphthols after reduction with lithium aluminum hydride.

- The *Mannich* condensation of naphthalene-2-ol with paraformaldehyde and the chiral *α*-amino acid phenylglycine did not give a positive result, therefore it was successfully carried out with the chiral derivatives of phenylglycine – its methyl ester and 2-phenylglycinol. In the first case, the target dihydro-1,3-naphthoxazine is obtained in good yield, while in the second case, an isomeric mixture of two products is obtained. It has been proven that in both cases the reaction

proceeds with the preservation of the configuration of the starting chiral components. After reduction with lithium aluminum hydride of the resulting dihydro-1,3-naphthoxazine and the mixture of products, the same new chiral aminodiol is obtained in high yield.

- The possibility of obtaining bis-dihydro-1,3-naphthoxazines by *Mannich* and *Betti* condensations of naphthalene-2-ol, aldehydes and cyclohexane-1,2-diamine is investigated in detail. After large-scale optimization of the reaction conditions (molar ratios, solvents, reaction time and temperature), it is found that a mixture of unstable dihydro-1,3-naphthoxazine and imidazolidine bis-hydroxynaphthalene is obtained, which could not be separated each one individually in pure form. As a result, optimal conditions are found for preferential *Mannich* preparation of chiral, non-racemic imidazolidine bis-hydroxynaphthalene, whose absolute configuration is determined by single crystal X-ray structural analysis.

- In order to obtain ligands with two chiral coordination centers, a strategy for the synthesis of new chiral bis-dihydro-1,3-naphthoxazines by Mannich condensation of naphthalene-2,3 and -2,6 diols, formaldehyde and chiral 1-phenylethane -1-amine was developed. The new bis-naphthoxazines are obtained in high, near-quantitative yields. However, all attempts to synthesize *N*-substituted bis-aminomethylnaphthols, with a tertiary amino group, by reduction of the synthesized bis-naphthoxazines, regardless of varying the reaction conditions and the type of reducing agent, did not lead to the isolation of the desired products.

2. Synthesis of new dihydro-1,3-oxazinquinolines and corresponding aminoquinolinols as chiral ligands in enantioselective addition reactions.

- Two new dihydro-1,3-oxazinequinolines are synthesized in high, almost quantitative yields, after *Mannich* condensation of formaldehyde with different chiral amines ((S)-(−)-1-phenylethan-1-amine or (S)-(+)-1,2,3,4-tetrahydronaphthalen-1-amine) and quinolin-6-ol. To obtain chiral amino alcohols as ligands in addition reactions of diethylzinc to aldehydes, the new compounds after reduction with lithium aluminum hydride are transformed to the corresponding quinolinols containing a tertiary amine.

- Under the conditions of three-component *Betti* condensation of quinolin-6-ol with benz- or naphthaldehyde (3-methylbenzaldehyde or 1-naphthaldehyde) and the chiral amine (S)-(−)-1-phenylethan-1-amine, the corresponding aminobenzylquinolinols with a secondary nitrogen atom are obtained. In the condensation with 3-methylbenzaldehyde both diastereoisomers are isolated in pure form, while in the reaction with 1-naphthaldehyde only one of the isomers is isolated. It was shown that the obtained aminobenzylquinolinols after reduction with lithium aluminum hydride were successfully transformed with paraformaldehyde into the corresponding dihydro-1,3-oxazinquinolines. Reduction of the latter to obtain the more effective aminobenzylquinolinols possessing a tertiary nitrogen atom, however, did not give positive results.

- Through a combination of modern NMR techniques and X-ray structural analysis, the configuration of the newly formed stereogenic center in the synthesized by *Betti* condensation aminobenzylquinolinols with a secondary nitrogen atom is determined, which confirms the great potential of NMR spectroscopy for determining the configuration of this class of organic compounds.

- *Betti* condensation of quinolin-7-ol with benz- or naphthaldehyde (3-methylbenzaldehyde or 1-naphthaldehyde) and the chiral amine (S)-(−)-1-phenylethan-1-amine give the corresponding

aminobenzylquinolinols possessing a secondary nitrogen atom. With 3-methylbenzaldehyde, both diastereoisomers are isolated in pure form, while the reaction with 1-naphthaldehyde give a mixture of isomers in the ratio 87:13, which can not be separated.

3. Investigation of the catalytic capabilities of newly synthesized chiral, non-racemic amino alcohols (tertiary aminobenzylnaphthols, secondary aminobenzylquinolinols and imidazolidine bis-hydroxynaphthalenes) as ligands in the model reaction for the enantioselective addition of diethylzinc to aldehydes.

- Tertiary aminobenzylnaphthols obtained by *Manich* condensation of naphthalene-2-ol, formaldehyde and chiral amines are found to exhibit low enantioselectivity, while very high enantioselectivity (98% *ee*) are recorded for secondary aminobenzylquinolinols, which are typical *Betti* bases.

- The imidazolidine derivatives are shown to generate moderate asymmetric induction despite the presence of two coordination centers on the zinc atom.

4. Stereoselective functionalization of a diketopiperazine derived from L-proline and glycine.

- In order to obtain new chiral, enantiomerically pure compounds with potential biological activity, a stereoselective strategy for the preparation of differently substituted 2,5-diketopiperazines is developed. According to a methodology published in the literature, the basic derivative of 2,5-diketopiperazine is synthesized in 4 steps by cyclization of L-proline with the methyl ester of glycine. This known derivative is obtained with a good overall yield (59%), which is significantly higher than the one cited in the literature (38%).

- To protect the amide nitrogen atom from the diketopipiperazine cycle, the corresponding *N*-benzylated diketopiperazine was obtained as a starting structure for further synthetic stereoselective transformations by a significantly improved synthetic strategy of *N*-benzylation with benzyl bromide.

- After deprotonation of the mono-enol form of *N*-benzylated diketopiperazine in two variants, with lithium hexamethyldisilazide or lithium diisopropylamide, a lithium mono-enolate is obtained, which is further successfully alkylated with dimethoxybenzyl bromide to *N*-benzyl-6-dimethoxyphenyl-diketopiperazine in yields of 71% and 55%, respectively. In both cases, according to NMR data, the target product was isolated as a 95:5 (90% *de*) mixture of two diastereoisomers.

- In an analogous manner, *N*-benzylated diketopiperazine after deprotonation with lithium hexamethyldisilazide or lithium diisopropylamide is acylated with 3-methylbenzoyl chloride. In both cases, only one diastereoisomer is isolated, but in the second case, a small amount of the structural isomer is also obtained due to partial acylation proceeding at a different carbon atom of the piperazine ring.

5. Study of the biological activity of the synthesized compounds

- Some of the compounds synthesized according to the *Mannich* and *Betti* condensations are evaluated for their antimicrobial activity against gram-positive and gram-negative bacteria (*Bacillus cereus*, *Escherichia coli*, *Staphylococcus aureus* and yeast strain *Candida albicans*), as well as their antiviral activity against herpes simplex virus (HSV).

- Based on the obtained results, it was found that only two of the investigated derivatives of quinolin-6-ol (quinolinol containing tertiary amine and *Betti* dihydro-1,3-oxazinquinoline) exhibited antimicrobial activity against various pathogens. The first compound shows antibacterial activity against the test culture *Staphylococcus aureus*, and the second shows antimicrobial activity against the test pathogen *Bacillus cereus*.

- Only one of the dihydro-1,3-naphthoxazines synthesized by the *Mannich* three-component condensation of *β*-naphthol, formaldehyde and glycine methyl ester has shown antiviral activity, but it has not succeeded in accurately determining the potential of the substance as a possible antiviral agent in human medicine.

All the contributions of the dissertation work of Assist. Professor Maya Tavlinova-Kirilova can be defined as scientific and scientifically applied and to be related to the demonstration with new instruments of essential new aspects of already existing scientific areas and problems.

7. Assessment of dissertation publications

Assist. Professor Maya Tavlinova-Kirilova has included in her dissertation for the educational and scientific degree "Doctor" 3 scientific articles published between 2016 and 2023. There is no information about the use of these publications in other dissertations for obtaining the educational and scientific degree "Doctor", with the exception of the case for which is presented a separate protocol for the author's contribution in one of the scientific publications used in the dissertation work. Of the 3 scientific papers presented, all in journals with an impact factor (JCR on Web of Science), one is a publication in a journal with a rank of **Q2**, and the other two are publications in a journal with a rank of **Q4**. In addition, two citations are noted on one of the publications included in the dissertation.

A list of 7 participations in scientific conferences on the subject of the dissertation at home and abroad with poster reports is also presented.

Assist. Professor Maya Tavlinova-Kirilova has submitted a list of participation as a member of collectives of 24 scientific projects, which is probably her overall asset in terms of project subject-matter, but only a few of these projects, in my opinion, can be related to the content of the presented dissertation work.

8. Assessment of the personal contribution of the author

All publications of Assist. Professor Tavlinova-Kirilova included in the dissertation work are collective, with 6 to 8 co-authors. Regardless of the not small number of co-authors, the personal contribution of the doctoral student to the results obtained in the scientific works with her participation is indisputable, since in two of the publications (**Q2** and **Q4**) she is the first author.

9. Abstract

The extended abstract correctly reflects the main scientific contributions of the Assist. Professor Tavlinova-Kirilova's PhD dissertation.

10. Critical remarks and recommendations

Maya Tavlinova-Kirilova's dissertation was written at a high level in stylistic, grammatical, aesthetic and visual terms. Typographical errors, with few exceptions, are practically absent. I have no critical comments on the scientific content and technical design of the dissertation, except for some non-essential remarks and recommendations.

- The dissertation is presented in 220 pages, which I find unacceptable for the volume of a doctoral dissertation, even if it concerns a dissertation for the scientific degree "Doctor of Science".

- The title page of the dissertation lacks information about the area of higher education, the professional field and the scientific specialty. It should be added.

- Subheading “3.6 *Betti* Condensation” is omitted in the Contents section.

- It would be good if the literature review ends with a conclusion that better motivates the choice of the research topic and the formulation of the set tasks.

- It is not clear enough how the section on the synthesis of 2,5-diketopiperazine derivatives fits into the subject of the dissertation and its title.

- Some inaccuracies such as inconsistency of some yields, numerical values for selectivity and numbering of compounds in the abstract with those in the dissertation are admitted, which should be corrected.

- In the Author's abstract in Bulgarian, section Conclusions, item 11, the phrase "washed compounds" should be corrected to "selected compounds".

11. Personal impressions

I have no personal impressions of the PhD student outside of the current procedure.

12. Recommendations for future use of dissertation contributions and results

It would be good if future efforts were directed towards expanding the range of chiral products, including diketopiperazine derivatives, and more comprehensively investigating their biological activity.

CONCLUSION

The dissertation contains scientific and scientific-applied results, which represent an original contribution to science and meet all the requirements of the Law on the Development of the Academic Staff in the Republic of Bulgaria (LDASRB), the Regulations for the Implementation of the LDASRB and the Regulations for the Implementation of the LDASRB of the Bulgarian Academy of Sciences. The presented materials and dissertation results fully comply with the specific requirements of the Regulations of the Institute of Organic Chemistry with Centre of Phytochemistry – Bulgaria Academy of Sciences for the application of LDASRB.

The dissertation work shows that Assist. Professor Tavlinova-Kirilova possesses in-depth theoretical knowledge and professional skills in the scientific specialty “Organic Chemistry” by demonstrating qualities and skills for conducting research with obtaining original and significant scientific contributions.

Due to the above, I confidently give my ***positive assessment*** of the conducted research, presented by the above-reviewed dissertation work, abstract, achieved results and scientific contributions, and ***I recommend to the honorable Scientific Jury to award the educational and scientific degree “Doctor” (PhD)*** to Maya Trifonova Tavlinova-Kirilova in the field of higher

education: 4. Natural sciences, mathematics and informatics, Professional area 4.2. Chemical Sciences (Organic Chemistry).

20.02.2024 г. Reviewer: .....

Sofia, Bulgaria

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