OPINION

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regarding: competition for the academic position of "professor" in professional field 4.2 "Chemical Sciences", scientific specialty "Bioorganic Chemistry, Chemistry of Natural and Biologically Active Substances" for the needs of the section "Molecular Design and Biochemical Pharmacology", IMB-BAS, announced in the State Gazette, issue 114/24.12.2025.

With only one candidate who submitted documents: Assoc. Prof. Dr. Nikolay Tsvetkov Tsvetkov

By order of the Director of the Institute of Molecular Biology - BAS, I am appointed as a member of the scientific jury in the above-described competition.

At the first meeting of the scientific jury, we familiarized ourselves in detail with the materials provided by Assoc. Prof. Tsvetkov and established that they meet the requirements of the Law on the Development of the Academic Staff of the Republic of Bulgaria and the regulations of the IMB-BAS.

Assoc. Prof. Tsvetkov graduated from the Bulgarian Technical University of Medicine and Pharmacy in 1999 with a Master's degree in Chemical Technology with a professional qualification of "Chemical Engineer", acquired the scientific and educational degree "Doctor" in 2005, Doctor of Natural Sciences (Doctor rerum naturalium, Dr. rer. nat.) Faculty of Chemistry, Section Organic Chemistry I, University of Bielefeld, and since May 2018 he has held the academic position of "Associate Professor", scientific specialty "Bioorganic Chemistry, Chemistry of Natural and Biologically Active Substances" Section "Molecular Design and Biochemical Pharmacology" Institute of Molecular Biology "Acad. Rumen Tsanev", Bulgarian Academy of Sciences, Sofia, Bulgaria.

The materials submitted for participation in the competition show the distribution of Assoc. Prof. Tsvetkov's scientific contributions by points according to the minimum national requirements of the Bulgarian Academy of Sciences. The documents submitted show that the results achieved by Assoc. Prof. Tsvetkov not only cover, but also exceed, almost twice, the requirements set out in the law.

The scientific works submitted for participation in the competition under indicator group "B", indicator 4 include 5 publications in journals, referenced and indexed in world-renowned databases (Web of Science and Scopus), of which 4 are in quartile Q1 and 1 - in Q2, with a total impact factor of 25.00. The publications were realized in the period 2019–2023 and are thematically united around the development of new small molecules with potential application in neurodegenerative diseases, with a focus on Parkinson's disease.

The scientific research is distinguished by a clearly expressed interdisciplinary nature, combining approaches from the fields of medicinal chemistry, pharmacology and theoretical chemistry. The works have applied modern methodological approaches, including rational drug design, in silico modeling (molecular docking, molecular dynamics, QSAR analysis), organic

synthesis, spectral characterization (NMR, IR, MS), as well as complex in vitro and in vivo pharmacological studies.

The candidate has a leading contribution to the implementation of scientific research, which is evidenced by his participation as the first author and/or corresponding author in the submitted publications. The scientific results have received significant international response, with the publications being cited 153 times (Scopus), which testifies to their relevance and scientific significance.

The publications under indicator group "G", indicator 7 (15 in number), complement and expand the candidate's scientific profile. They have been published in prestigious international journals with a total impact factor of 90.00 and have been cited 245 times (Scopus). Thematically, they cover a wider spectrum of socially significant diseases and confirm the sustainability and consistency of the candidate's scientific research.

The scientific contributions in the publications, presented instead of a habilitation thesis, can be systematized in the following main directions:

1. Creation and development of a new class of selective and reversible MAO-B inhibitors

A new class of (pyrrolo-pyridin-5-yl)benzamide derivatives has been developed, characterized as selective and reversible inhibitors of monoamine oxidase B (MAO-B). Through rational molecular design and targeted introduction of an N-sp^2 atom into the structure, optimization of key pharmacokinetic parameters has been achieved, including solubility, lipophilicity and ability to pass through the blood-brain barrier.

A thorough analysis of the "structure-activity" relationships has been performed, and structural elements determining the selectivity and affinity for MAO-B have been identified. Leading compounds with nanomolar inhibitory activity, good selectivity towards MAO-A and a pronounced neuroprotective effect in cell models have been identified.

The obtained results have a contribution character both for the development of medicinal chemistry and for the creation of potential candidate drug molecules for the therapy of neurodegenerative diseases.

2. Development of new (indazol-5-yl)methanimine derivatives as MAO-B inhibitors

A new class of biologically active compounds has been created by structural transformation of the carboxamide spacer into an imine linker. This approach represents an original scientific solution aimed at modifying the electronic and spatial characteristics of molecules.

A comprehensive comparative analysis between carboxamide and methanimine derivatives was conducted, including experimental (synthesis, spectral characterization, biological activity) and theoretical (in silico modeling) studies. It was found that the new compounds exhibit high selectivity towards MAO-B, a favorable drug similarity profile and adequate chemical stability.

New “structure–activity” relationships were formulated, which expand the existing concepts of the interaction of MAO-B inhibitors with the enzyme system and have a methodological contribution to future developments.

3. Synthesis and biological evaluation of peptide mimetics of neurotensin

Short-chain peptide analogues of neurotensin(8–13) were developed, aimed at modulating the neurotensin receptors NTS1 and NTS2. For the first time, compounds with balanced affinity for both receptors have been created, which represents a significant contribution to the field of neuropharmacology.

A comprehensive evaluation of their pharmacological properties, including stability, bioavailability and ability to cross the blood-brain barrier, has been performed. Lead compounds demonstrate a significant therapeutic effect in an animal model of Parkinson's disease.

These results outline new prospects for the development of multitarget therapeutic strategies in neurodegenerative diseases.

Scientific contributions outside the habilitation thesis

Publications under indicator group "G", indicator 7 reflect the broad scientific profile of Assoc. Prof. Tsvetkov and his ability to apply the developed approaches in various fields of medicinal chemistry and pharmacology.

More significant contributions in this section include:

• research of natural bioactive compounds and plant extracts with antioxidant and neuroprotective activity;

• development and application of in silico methods for predicting biological activity and optimizing lead structures;

• creation of multitarget ligands with combined action on different biotargets;

• research aimed at identifying potential therapeutic agents for viral infections, including COVID-19;

• participation in interdisciplinary scientific collaborations leading to publications with high international visibility.

Assessment and summary of contributions

In summary, the candidate's scientific contributions are distinguished by a clearly expressed original and innovative character. They cover the full cycle of modern drug development - from conceptual design and synthesis to biological evaluation and theoretical modeling.

Particularly high praise deserves:

• the systematic approach to research;

• the formulation of new "structure-activity" relationships;

• the development of new classes of biologically active compounds;

• the combination of fundamental and applied scientific results.

The results obtained have significant scientific value, good international recognition and real potential for future application in pharmaceutical practice and the development of new therapeutic agents.

The candidate's overall scientific output is at a high international level and fully complies with the requirements for holding the academic position of "professor".

Conclusion

Based on the comprehensive analysis of the presented scientific works, their relevance, scientific significance and international visibility, as well as the volume and quality of the scientific research activity, I believe that the candidate is an established and recognizable scientist with a clear contribution to the field of medicinal chemistry and the development of biologically active compounds.

The scientific output is characterized by high quality, has been published in prestigious international journals and has received significant scientific response, which is an objective indicator of its value. The formulated scientific contributions are original, well-argued and have both fundamental and applied significance.

The interdisciplinary approach in research, the ability to develop new scientific directions and the sustainable development of the research topic deserve particularly high praise. The candidate demonstrates independence, scientific maturity and consistency in building his scientific profile.

The submitted materials fully meet, and in a number of indicators exceed, the minimum national requirements and the internal criteria of the Bulgarian Academy of Sciences for holding the academic position of "professor". Based on the above, I give a categorically positive opinion and I strongly recommend that the esteemed scientific jury propose to the scientific council of the Institute of Molecular Biology that Assoc. Prof. Dr. Nikolay Tsvetkov Tsvetkov be elected to the academic position of "professor" in the professional field 4.2 "Chemical Sciences", scientific specialty "Bioorganic Chemistry, Chemistry of Natural and Biologically Active Substances".

Sofia

14.04.2026

Signature:

prof. Biliana Nikolova