

REVIEW

from prof. Plamen Peikov, PhD

for the acquisition of the educational and scientific degree "Doctor" of MPharm Tania Nedelcheva Dimova, PhD student in full-time study, doctorate program "Pharmaceutical Chemistry", field of higher education 7. "Health and Sport" and professional field 7.3. "Pharmacy", "New aromatic iodo-derivatives - synthesis, structure, properties", Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Medical University (MU) – Varna.

MPharm Tania Dimova was born in 1982. Her education and training is remarkable: 2006 - bachelor, professional qualification "Biologist" at Sofia University, Faculty of Biology, specialty "Biology"; 2010 - acquired the educational and qualification degree "Master of Pharmacy" at the Faculty of Pharmacy, MU - Sofia and bachelor's degree, specialty "Organic Chemical Technologies", professional qualification "Engineer - Chemist" at the University of Chemical Technology and Metallurgy - Sofia, Faculty of Chemical Technologies; 2019 - acquired educational and scientific degree "Doctor" in scientific specialty 5.10. Chemical technologies (Technology of composite materials); 2020 - specialty in Drug Technology with Biopharmacy, MU-Varna; 2020 – enrolled as a PhD student. The professional realization of MPharm Tania Dimova is associated with MU-Varna, as an assistant (2011-2019) and chief assistant (2019 and ongoing).

The dissertation thesis includes 101 pages, 10 tables, 29 figures and 75 diagrams. 213 literature sources are cited.

The structure of the PhD thesis involves the organic synthesis and characterization of halogen derivatives (iodo- and bromo-) of 3,4,5-trimethoxybenzoic acid, 3,4,5-trimethoxybenzaldehyde and 3,4,5-trimethoxyphenylacetic acid. The topic is trendy, useful, and dissertationable. It focuses on the chemistry of aromatic halogen derivatives and their potential applicability in diagnostics. The main hypothesis and scope of the study are the synthesis of chemical structures, application and optimization of synthetic methods known in the literature, isolation, structure analysis of the compounds, their characterization with a focus on crystallization and photoinduced toxicity and potential application in diagnostics. Halogenated

derivatives in organic synthesis are important precursors for the preparation of various derivatives with diverse biological activities.

The literature review is comprehensive and substantiates the scope and objectives of the PhD thesis, which are set very precisely and clearly.

The focus of the synthetic part of the PhD thesis is the optimization of the preparation of halogenoarenes. After varying the reaction conditions and reagents, the preparation of 2-iodo-3,4,5-trimethoxybenzoic acid (ITMBA) (quantitative yield and $^1\text{H-NMR}$ analysis, the crystal structure was established by SC-XRD analysis.), 2,6-diiodo-3,4,5-trimethoxybenzoic acid (DITMBA) (quantitative yield, $^1\text{H-NMR}$ and ATR-FTIR analysis), 2-iodo-3,4,5-trimethoxybenzaldehyde (ITMBD) (85 to 92% yield and ATR-FTIR spectroscopy) the optimal synthetic conditions - iodination with I_2/AgNO_3 in methanol were established. These are contributions of fundamental and mainly scientific and applied nature. For the synthesis of 2,6-dibromo-3,4,5-trimethoxybenzoic acid (DBrTMBA) and 2-bromo-3,4,5-trimethoxybenzoic acid (BrTMBA), a classical procedure, bromination with KBrO_3 in sulfuric acid medium, was applied.

Two new halogenoarenes were synthesized: 2-bromo-6-iodo-3,4,5-trimethoxybenzoic acid (BrITMBA) and 2-(2-iodo-3,4,5-trimethoxyphenyl)acetic acid (ITMPhAA). The synthesis of BrITMBA was in two steps, the first involving the preparation of the bromine derivative with $\text{KBrO}_3/\text{H}_2\text{SO}_4$ and subsequent iodination with I_2/AgNO_3 in methanol. The resulting acid crystallizes in a hydrogen-bonded active, catenary system. The crystal structure of the compound was proved by SC-XRD (single crystal X-ray diffraction). The analysis suggests the arrangement of the molecules is related to spatial translation of individual catenary chains and the cage of the compound has different characteristics, volume, and size, compared to monosubstituted analogues. The behavior of the BrITMBA catamer in the IR spectrum has been analyzed in detail. The induction effect of halogens, position of carbonyl and mesomeric effect between aromatic system, halogen atoms and methoxy groups are reported. The synthesis of ITMPhAA is analogous to iodination with I_2/AgNO_3 in methanol. The structure was determined by ATR-FTIR analysis. A detailed study of the IR spectrum of the resulting product was carried out and compared with the starting acid.

The characterization of the obtained compounds is fundamental and mainly of scientific and applied nature. Of importance are the crystallization conditions and the crystal structures of DITMBA, DBrTMBA and BrTMBA. After recrystallization in boiling water, the resulting crystals were structurally (SC-XRD) and spectrally (Raman and UV) characterized. The crystal structure of the dihalogens is composed of molecules cathedrally bonded, via hydrogen bonds. Two methods have been established allowing the crystallization of DITMBA in the form of a toluene solvatomorph and of a non-solvated catheomer.

The *in vitro* cytotoxicity and phototoxicity of DITMBA, ITMBA and the parent acid were investigated using the 3T3 NRU assay. The results determined them to be safe for topical application. The studies proved that DITMBA did not exhibit photo-induced toxicity towards the test cell line BALB/3T3 clone A31.

The research also has a practical focus related to the potential application of the sodium salt of DITMBA in contrast-enhanced mammography. The extensive research is based on comparison with Omnipaque used in practice. This primary study showed prospectivity as the performance of the halogenarene was similar to that of the contrast agent.

There are some inaccuracies, omissions, and errors in the doctoral thesis. There is inconsistency in the structure of the presentation. References are not listed correctly. Inappropriate terms and words are noted in some texts. These observations do not detract from the work done by the PhD student.

Scientific research work

There are four scientific publications related to the PhD thesis. Two of them are published in scientific journals, refereed, and indexed in world-known databases of scientific information. The remaining two publications are in the category of publications and reports published in non-refereed peer-reviewed journals or published in edited collective volumes. The PhD student participates in a scientific project on the topic of the PhD thesis at the Science Fund of MU-Varna.

The Abstract book covers the thesis.

The thesis of MPharm Tanya Dimova fully meets the requirements of the Regulations for the Development of the Academic Staff at MU-Varna and the Minimum Scientific and Metric Requirements of MU-Varna and meets the requirements of the PhD program in Pharmaceutical Chemistry. The scientific hypothesis and scope are fulfilled, the experiment is sufficient in scope, the conclusions are accurate and the contributions are of fundamental and mainly scientific and applied nature.

Conclusion

This is a serious scientific work in the field of organic synthesis of aromatic halogen derivatives, analysis of their structure and properties. The PhD student has carried out serious experimental work by mastering and applying a variety of methodologies to realize this scientific research.

I propose to award the educational and scientific degree "Doctor" to MPharm of MPharm Tania Nedelcheva Dimova.

My assessment is convincingly POSITIVE.

15.01.2024

Reviewer:

Заличено на основание чл. 5, §1, б. „В“ от Регламент (ЕС) 2016/679
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(prof. Peikov, PhD)