МЕДИЦИНСКИ УНИВЕРСИТЕТ - ВАРНА
„Проф. д-р Параскев Стоянов“
Ул.“Марин Дринов“ 55, Варна 9002, България
Тел. : 052/ 65 00 57, Факс: 052/ 65 00 19
e-mail: uni@mu-varna.bg, www.mu-varna.bg

MEDICAL UNIVERSITY - VARNA
“Prof. Dr. Paraskev Stoyanov”
55, Marin Drinov Str., 9002 Varna, Bulgaria
Tel.: +359 52/ 65 00 57, Fax: + 359 52/ 65 00 19
e-mail: uni@mu-varna.bg, www.mu-varna.bg

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“Synthesis and characterization of a new generation of retinoids”

Project leader: Assoc. Prof. Svetlana Fotkova Georgieva, MScBiotech, PhD

Retinoid compounds, including both natural and synthetic retinol derivatives, are potent agents for controlling cellular differentiation and proliferation.

A major impetus for the development of synthetic retinoids is their great potential in the treatment and prevention of cancer processes. It stems from the ability to interact with different nuclear receptors, leading to the effect of cellular differentiation and proliferation, regulating many physiological processes in the body.

Modification of the structure of natural retinoids has resulted in the synthesis of atypical second-generation retinoids and third-generation retinoids with robust polyaromatic systems. These aromatic derivatives are more stable as well as more active and selective. Representatives of the third generation include the compounds adapalene, bexarotene, and tazarotene.

Bexarotene is an antineoplastic agent clinically used to treat cutaneous T-cell lymphoma and investigated for the possibility of using in treatment other different forms of cancer. Bexarotene selectively activates retinoid X receptors (RXRs).

Bexarotene is a remarkable compound because, in addition to its main application, there is a wealth of data to substantiate its mechanism of action in dementia, as well as in the field of dermatology and the response to the immune response. This determines his growing role in dermatology, neurology and especially in Alzheimer's disease therapy. In addition, the synergy between bexarotene and various cytokines as modulators of differentiation, which reveals the potential for the application of synthetic retinoids in oncology, is also relevant.

Awareness of the fact that retinoids are powerful agents for controlling cell proliferation and differentiation extends the sphere of knowledge about retinoids beyond their classical use in ophthalmology and dermatology.

This makes this class of compounds a valuable tool for studying one of the most important problems in medicine – the control of cell differentiation and the resulting disorders and diseases.

Continuous and intensive study of the role of retinoids in the complex of differentiation, cell proliferation, and cellular growth regulation determines the great potential for the application of retinoids (natural and synthetic) in the treatment of a number of

abnormalities arising from abnormal cell development. Of particular interest is the possibility of their use in the treatment of neoplastic processes in the body.

Based on the above data on the retinoid bexarotene, and in particular on its antineoplastic effects, as well as the fact that the preparation has been approved in the treatment of T-cell skin cancer, and the limited information in the literature concerning the possibility of altering the structure of bexarotene and synthesis of its new derivatives, the current research work was aimed at developing a methodology for the synthesis of bexarotene derivatives and their subsequent characterization.

The purpose of the present scientific work is to obtain, structurally characterize and investigate a group of new, non-described in the literature, bexarotene derivatives.

The following tasks are foreseen in connection with the achievement of the stated objective:

1. To develop an appropriate methodology for the synthesis of novel hydrazide-hydrazone derivatives of the antineoplastic preparation bexarotene.
2. To characterize newly obtained analogs structurally by instrumental methods of analysis, including:

- IR spectroscopy;
- NMR spectroscopy;
- Mass spectrometry.

3. Develop an HPLC method for the purity of the newly synthesized derivatives.

Hydrazones are a class of organic compounds that are condensation products of hydrazides with carbonyl compounds. As carbonyl reagents, different aldehydes and ketones may be incorporated into the reaction. They are characterized by a variety of pharmacological effects and act as reagents in various important reactions.

Hydrazones and their azomethine functional derivatives are an important class of compounds with a wide range of pharmacological effects.

For the synthesis of the target products, bexarotene hydrazide is reacted with aldehydes. The following aldehydes are involved in the reaction: 2,6-dichlorobenzaldehyde; 3-chlorobenzaldehyde; 4- (Trifluoromethyl) benzaldehyde; 4-bromobenzaldehyde; 4-chlorobenzaldehyde.

In order to prove the structure of the newly prepared compounds, a comparative ATR-FTIR analysis of the spectra of the parent compound - bexarotene, its methyl ester and the newly synthesized five derivatives in the range 4000-500 cm^{-1} was performed.

Investigation of the structure of organic compounds by the method of ^{1}H-NMR spectroscopy is based on the magnetic ratios of hydrogen atoms in the molecule. A detailed analysis of the data obtained by ^{1}H-NMR spectroscopy was performed.

Mass spectrometry is an analytical technique used to measure the mass-to-charge ratio (m/ z) of one or more molecules present in a sample. These measurements can often also be used to calculate the exact molecular weight of components in a sample. Typically, mass spectrometers can be used to identify unknown compounds by determining molecular weight, quantifying known compounds, and determining the structure and chemical properties of molecules.

HPLC is a versatile, reproducible chromatographic technique for drug evaluation. It has a wide scope of application in various fields concerning the quantitative and qualitative evaluation of the active substances.

Most methods for HPLC analysis of bexarotene, reported in the literature, have been developed to evaluate bexarotene in biological samples. Therefore, they are not suitable for routine analysis. Insufficient information on HPLC analysis of the substance bexarotene and its derivatives necessitates the search for appropriate chromatographic conditions for analysis.

For this purpose, chromatography of a standard substance bexarotene was first performed, which plays the role of a witness (standard) in determining the component composition of samples of newly synthesized bexarotene derivatives.

As a result of our research, the following conclusions can be drawn:

1. A three-step synthetic method for the preparation of hydrazide-hydrazone derivatives of the antineoplastic preparation bexarotene has been developed, with the aid of which one new hydrazide and five new hydrazones are obtained.
2. The novel compounds thus obtained are structurally characterized by IR spectroscopy, 1H-NMR analysis and mass spectrometry.
3. A rapid, and accurate HPLC method for identifying bexarotene and its derivatives alone and in mixtures has been developed and validated.