FT-IR SPECTRAL ANALYSIS FOR A NEWLY OBTAINED STRUCTURE ANALOG OF BEXAROTENE

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ABSTRACT

INTRODUCTION: Retinoids are natural and synthetic compounds part of the family of polyisoprenoid lipids. These compounds are involved in several important physiological processes in the human body because of their ability to bind to different nuclear receptors. Retinoids are used in the therapy of some precancerous lesions, the treatment of acute promyelocytic leukemia (APL), T-cell lymphoma, and the prevention of malignancies in high-risk cancer groups. In this work we discuss the possibilities for analysis of the newly synthesized hydrazone of the retinoid bexarotene.

AIM: The purpose of this study is to conduct FTIR spectral analysis of newly synthesized hydrazone of bexarotene.

MATERIALS AND METHODS: Infrared spectra 500-4000 cm^{-1} were taken on a Bruker FTIR spectrometer using ATR - a plug with Smart iTR adapter.

RESULTS: The infrared spectra of the newly synthesized compound were strikingly similar in the relative positions and intensities of the resulting peaks, confirming its close structural relationship with bexarotene. Despite the structural similarity, there were significant differences that point to the introduction of a substituent and the formation of a new hydrazone derivative.

CONCLUSION: In order to confirm the data obtained by FTIR spectroscopy, a further reversed-phase HPLC-UV analysis of the new hydrazone derivative should be performed.

Keywords: *retinoids, modification, hydrazone analogs, FTIR spectral analysis*

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INTRODUCTION

Retinoids are synthetic derivatives of natural vitamin A. Their structure includes lipophilic isoprenoids and a linear chain with a hydrophilic end group. Retinoids exert their effects by binding with a group of nuclear retinoic acid receptors (RARs) and retinoid X receptors (RXRs) which act as ligand-activated transcription regulators for specific genes (1,2).

The ligands of the nuclear receptors are small molecules that can be modified by drug design and in this way to achieve drugs for the treatment of underlying diseases, including oncological diseases, osteoporosis, and diabetes (3,4).

Studies investigating the therapeutic use of retinoids date back to the 1970s.

Retinoids have a very wide range of applications, which includes their use as cosmetic agents and effective pharmaceuticals for skin diseases. Furthermore, some retinoids are undergoing clinical trials for the treatment of breast, lung, and colon cancer and other diseases caused by uncontrolled cell proliferation (5). More recently, it has been shown that treatment with RXR agonists, such as bexarotene, leads to pathological and behavioral improvements in transgenic mouse models of Alzheimer's disease (6). However, retinoid use leads to many serious side effects. The most serious of these is that the family of retinoid compounds consists of the most potent teratogens known. Teratogens are compounds the use of which during the specific periods of pregnancy may cause severe birth defects. Other side effects result of retinoid use include irritation of the tissues treated, which can be so severe that patients cannot tolerate treatment.

The main structure of the retinoid compounds is shown in Fig. 1.

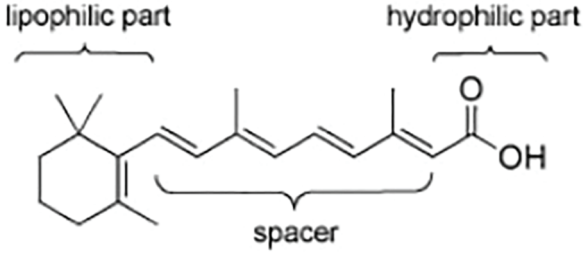

Fig. 1. The main structure of the retinoid compounds

Retinoids are subjected to clinical trials in cancer treatments both as monotherapy (7,8) and in combination with other drugs. Combination therapy allows a reduction in the effective concentration of retinoids, which reduces their toxicity and the process of retinoid resistance (9,10). Additionally, retinoid activity may increase neoplastic tissue sensitivity to other agents such as chemotherapy and epigenetic drugs.

There are many reasons to explore novel RXR agonists that may decrease or avoid the primary side effects to treatment with bexarotene, including hyperlipidemia, hypothyroidism, and cutaneous toxicity, as well as expand the range of therapy (11,12).

Bexarotene is synthetic retinoid compounds indicated for the treatment of cutaneous manifestations of cutaneous T-cell lymphoma. Nowadays the group of retinoids, including bexarotene, are of great interest due to the wide range of their application.

Infrared spectroscopy (IR spectroscopy or vibrational spectroscopy) involves the interaction of infrared radiation with matter. It is one of the most important analytic techniques and is mostly based on absorption spectroscopy (13). Infrared spectroscopy is an easy and reliable technique widely used for the qualitative characterization of newly obtained compounds.

Hydrazone derivate was synthesized and its structure was confirmed by his spectral data. To determine the newly obtained structure a detailed analysis of the FT-IR spectra was performed. We analyzed the starting compound for synthesis - bexarotene, its methyl ester, and the newly synthesized hydrazone analog. Analysis of the compounds was performed in the range 4000-500 cm^{-1}.

AIM

The present study considers determining the newly obtained structure of bexarotene hydrazone. In order to prove the structure of the newly obtained compound, a comparative ATR-FTIR analysis of the spectra of the starting compound - bexarotene, its methyl ester, and the newly synthesized Bexarotene derivative in the range 4000-500 cm^{-1} was performed.

MATERIALS AND METHODS

Bexarotene (99.99%, Fluorochem); methyl alcohol (99.99%, HPLC grade, Fisher Chemical), 4-isopropyl benzaldehyde (99.99%, HPLC grade, Fisher Chemical), water (HPLC grade, Fisher Chemical), formic acid (99-100% A.R., CHEM-LAB)

Infrared spectra 500-4000 cm^{-1} were taken on a Bruker FT-IR spectrometer using ATR - a plug with Smart iTR adapter.

RESULTS AND DISCUSSION

The newly obtained hydrazone of bexarotene and isopropylbenzaldehyde was synthesized according to the described methodology (14).

Infrared spectroscopy is one of the main instrumental methods for determining the identity and characterization of newly synthesized compounds. To perform analysis by infrared spectroscopy, a method of direct spectrum recording using an ATR with a Smart iTR adapter is used.

The newly obtained hydrazone of bexarotene and 4-isopropyl benzaldehyde is shown in Fig. 2.

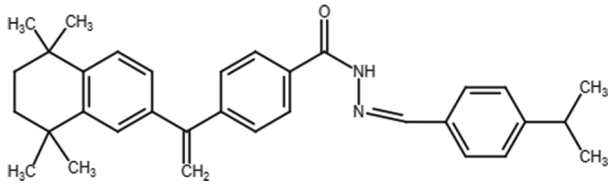

Fig. 2. Structure of 4-isopropyl-phenyl-methylidene-4-[1-(3,5,5,8,8-pentamethyl-6,7-dihydronaphthalen-2-yl) ethenyl] benzohydrazide - hydrazone of bexarotene and 4-isopropyl benzaldehyde

The spectra of the test compounds are similar in all analyzed regions of uptake, with several characteristic features resulting from the presence of structural similarities common to bexarotene and the newly obtained derivative.

ATR-FTIR spectra of the bexarotene, its methyl ester, and 4-isopropyl-phenyl-methylidene-4-[1-(3,5,5,8,8-pentamethyl-6,7-dihydronaphthalen-2-yl) ethenyl] benzohydrazide are presented in Fig. 3.

In the recorded spectra in the range from 3000 to 2800 cm^{-1}, the extremely high similarity in the absorption signals is observed. The obtained bands are close in location and intensity of the reported maxima. This is explained by the fact that in this area there are some characteristic oscillations of the benzene nuclei, as well as symmetrical and asymmetric vibrations of the CH bonds.

In the analysis, the slightly intensive bands in the interval 2000-1660 cm^{-1} were observed. They are characteristic of the presence of a benzene nucleus in the structure.

The most significant difference in the two considered spectra is observed in the range from 1620 to 1720 cm^{-1}, where the presence of a medium-intensity band is reported in the spectrum of the methyl ester. The presence of an ester functional and the deformation oscillations characteristic of the C=O bond are reported in the region of the spectrum between 1730 and 1715 cm^{-1}.

In the spectrum of the newly synthesized compound, the presence of a medium-intensity pronounced peak with a maximum at 1109 cm^{-1} is impressive. This assumption is further confirmed by the fact that such a band is not present in the spectra of bexarotene and its methyl ester.

CONCLUSION

Numerous studies have led to the development of a large number of methods for the synthesis of retinoids. More and more structurally diverse analogs of these natural compounds have emerged, making this aspect of retinoid chemistry difficult to summarize. The reason for this is precisely the constant demand for structures that target and selectively affect nuclear receptors, as well as to reduce the number of adverse reactions inherent in natural retinoids. In connection with the possibility of synthesis of novel derivatives, it is especially important to develop a fast, precise, and accurate method for quality analysis of the obtained products

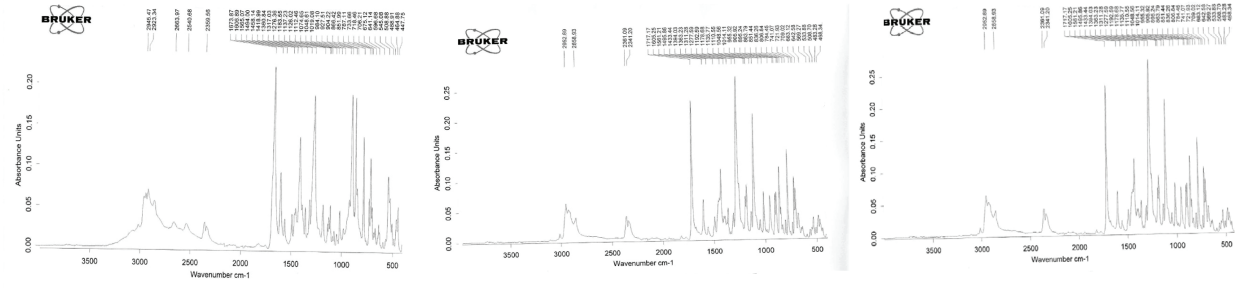

Fig. 3. ATR-FTIR spectra of the test compounds

The infrared spectrum of the newly synthesized compound is strikingly similar in the relative positions and intensities of the resulting peaks, confirming its close structural relationship with Bexarotene. This is mainly due to the present bexarotene skeleton containing three nuclei and the associated methyl radicals. Despite the structural similarity, there are significant differences that point to the introduction of a substituent and the formation of a new hydrazone derivative.

In order to confirm the data obtained by FT-IR spectroscopy, it is to be carried out to conduct a reversed-phase HPLC-UV analysis of the new bexarotene hydrazone derivative.

Acknowledgments

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