

QSAR MODELING OF DERMAL METABOLITES OF BEXAROTENE ANALOGS

Nadya Agova¹, Svetlana Georgieva¹, Sylvia Stamova¹, Yana Koleva²

¹*Department of Pharmaceutical Chemistry, Faculty of Pharmacy,
Medical University of Varna*

²*Department of Physical Chemistry and Organic Chemistry,
University "Prof. Assen Zlatarov", Burgas*

ABSTRACT

INTRODUCTION: Over the last decade, there has been a significant increase in the scientific knowledge about cancer, which has accordingly led to the development and increase of interest in new medicines and therapeutic approaches with potential applications in oncology. Activity research and the identification of potential therapeutic and toxic effects of bexarotene-like structures underpin the development of new approaches to the treatment of a number of untreated diseases.

This requires a further and in-depth study of the potential of newly synthesized compounds to produce active metabolites.

AIM: In view of the potential for dermal administration of bexarotene, the potential for toxic metabolism in the skin needs to be investigated.

MATERIALS AND METHODS: For the purpose the OECD (Q) SAR Application Toolbox was used. It is a software application for evaluating the properties of chemicals based on their molecular structure.

RESULTS: The application of the model for predicting metabolic changes makes it possible to assess the risk based on the chemical structure of the compounds.

CONCLUSION: The skin metabolic prediction of new hydrazones of third-generation retinoid bexarotene indicates that not one of them predicts binding to DNA or proteins.

Keywords: bexarotene analogs, metabolism, QSAR modeling, toxicity

Address for correspondence:

Nadya Agova
Faculty of Pharmacy
Medical University of Varna
84 Tzar Osvoboditel Blvd
9002 Varna
e-mail: nadya.agova@mu-varna.bg

Received: April 14, 2020

Accepted: June 16, 2020

INTRODUCTION

Retinoids are a large family of chemical compounds with polyisoprenoid lipid structure. They include vitamin A (retinol) and its both natural and synthetic analogs. Thus the compounds take part in different important physiological processes in the human body. Retinoids are part of the effective treatment for some precancerous conditions, the treat-

ment of acute promyelocytic leukemia (APL), cutaneous T-cell lymphoma (CTCL), and the prevention of malignancies in the high-risk cancer process (1-4).

CTCL is an uncommon type of cancer that begins with damage to white blood cells called T cells (T lymphocytes). These cells normally help your body's germ-fighting immune system. In CTCL, the T cells are changing and develop abnormalities that make them attack the skin (5-9).

Bexarotene is a third-generation retinoid that is used to treat early CTCL. This medication can stop or slow the growth of cancer cells. In treatment, bexarotene, 1% gel is used. The structure of bexarotene is presented on Fig. 1.

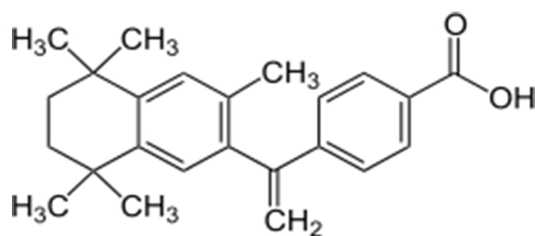


Fig. 1. Structure of bexarotene

The skin, like other organs in the human body, contains numerous enzymes that are capable of metabolizing endogenous substances and xenobiotics. In the past, the skin has been considered only as a physical barrier. Nowadays, it is well known that the skin also has the potential to metabolize substances with a different nature. Although the topical administration of drugs offers several advantages compared to traditional routes it is necessary to be well aware of the possibility of metabolism in the skin. The study of skin metabolism is of major importance not only in the field of transdermal drug delivery systems but also for the safe and efficient local skin treatment with topically applied substances (10).

Skin metabolism, in turn, can affect a number of processes, including skin toxicity, absorption, maintenance of homeostasis, delivery of dermal dosage forms, and efficacy. Due to the potentially wide-ranging effects that skin metabolism may affect, interest in it is increasing. This has led to the development of in vitro methods for predicting the potential of various substances to produce skin metabolites. Given the possibility of using bexarotene as a

gel, an analysis was conducted to determine its potential skin metabolism, as well as the ability of its analogs to metabolize in the skin (11-15).

Recently, the possibility of the metabolism of medicinal products in the skin has been the subject of numerous studies. The barrier functions, absorption, and distribution of chemicals into and through the skin have been studied long ago. Now it is known that skin metabolism plays a key role in toxicity processes.

To evaluate the risk of drug use, many factors have to be considered. Of these, the absorption and permeability of the skin to different molecules, as well as the possibility of metabolic changes, are of particular importance. The risk of dermal metabolite production should be thoroughly monitored in order to assess the safety and minimize the potential for toxic reactions.

AIM

The present study considers the possibility of dermal metabolism in some of the newly synthesized hydrazones of the antineoplastic drug bexarotene.

MATERIALS AND METHODS

The OECD (Q) SAR Application Toolbox is a software application for evaluating the properties of chemicals based on their molecular structure. The application has the potential to provide information on the dangers of various chemicals while reducing testing time, monetary costs, and testing on experimental animals. During the OECD (Q) SAR Application Toolbox analysis, an HP-Prodesck computer configuration using an Intel Core i3-8th Gen processor was used (16).

Experimental Process

Organisation for Economic Co-operation and Development (OECD) (Q)SAR Application Toolbox. (Quantitative) Structure-Activity Relationships [(Q)SARs] are methods for estimating the properties of a chemical from its molecular structure and have the potential to provide information on the hazards of chemicals, while reducing the time, monetary costs and animal testing currently needed. To facilitate practical application of (Q)SAR approaches in regulatory contexts by governments and industry and to improve their regulatory acceptance, the OECD (Q) SAR project has developed various outcomes such

as the principles for the validation of (Q)SAR models, guidance documents as well as the QSAR Toolbox (17).

In vivo and *in vitro* (predominantly, with liver microsomes as experimental systems) studies were used to analyze the metabolic fate of chemicals. Different sources, including monographs, scientific articles and public websites were used to compile the database (18-20).

In the present work, the dermal metabolites of bexarotene and two of its hydrazones have been modeled. Their structural formulas are presented on Fig. 2.

RESULTS AND DISCUSSION

The application of the model for predicting metabolic changes makes it possible to assess the risk based on the chemical structure of the compounds. In many cases, the parent chemical is not responsible for the development of an adverse reaction or toxic-

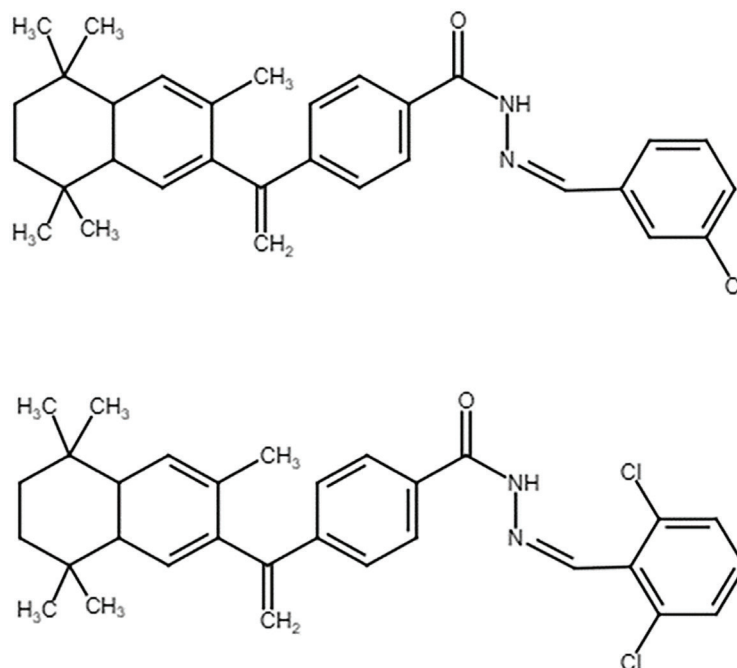


Fig. 2. Structures of bexarotene hydrazones

Table 1. Potential of bexarotene derivatives for the production of dermal metabolites

Structure	Protein Binding	Binding to DNA	Skin Metabolic Simulator
	No connection	No connection	No metabolites are predicted
	No connection	No connection	No metabolites are predicted

ty. They are the result of their transformation and activation (metabolic or chemical).

When a chemical changes as a result of metabolism, it is possible to form biologically active metabolites. Experimentally identifying metabolism opportunities is difficult, expensive, and often incomplete. Therefore, the use of mathematical models to predict metabolism opportunities is increasing.

For the purposes of this study, we have determined the potential for metabolism in the skin of bexarotene and two of its hydrazone analogs. The results are presented in Table 1.

However, metabolic transformation may be different for different species, organs, and even different cells.

The metabolic pathways documented in the database of our application include the metabolism of more than 200 organic substances in mammals. This allows easy computer access to information on different classes of compounds, with various functional groups including aliphatic carbons, alicyclic and furans rings, halogenated hydrocarbons, aromatic structures, and haloaromatic compounds, amines, nitro derivatives, etc., which can be used to predict the potential for toxicity in which metabolic activation leads to a toxic effect.

All organisms foreign to the body (xenobiotics) that enter the cell can react directly with the receptor proteins or undergo metabolic biotransformation into products that also interact with the receptors or bind to the nucleophilic centers of the macromolecules (DNA, proteins), or smaller molecules (endogenous molecules such as glutathione).

DNA-cohesive structures may have genotoxicity. When bound to proteins, the protein conjugates may have a direct effect on the cell by disrupting its basic functions or indirectly acting on the cell and again causing damage.

Active metabolites may interplay with a variety of biological macromolecules (such as proteins or DNA), resulting in an array of effects including skin or respiratory sensibilization, mitochondrial toxicity, or damage to DNA. The extent of injury elicited by a metabolite is a function of both the structure and derivation and the longevity of the metabolite, i.e. whether the metabolite persists for sufficient time

to cause a toxicological response or rapid clearance of the metabolite, to obviate the response.

CONCLUSION

The skin metabolic prediction of new hydrazones of third-generation retinoid bexarotene indicates that not one of them predicts binding to DNA or proteins. The data obtained does not show the possibility of potential adverse effects and the ability to induce skin injury.

The combination of all this knowledge will enable more robust models to be developed, and a deeper study and will engender greater confidence in risk assessments of medicinal substances following dermal exposure.

Acknowledgments

This work was supported by the Medical University of Varna through Project No. 17011 of the Science fund.

REFERENCES

1. Shen D, Yu X, Wu Y, Chen Y, Li G, Cheng F, et al. Emerging roles of bexarotene in the prevention, treatment and anti-drug resistance of cancers. *Expert Rev Anticancer Ther.* 2018;18(5):487-99. doi: 10.1080/14737140.2018.1449648.
2. Boehm MF, Zhang L, Badea BA, White SK, Mais DE, Berger E, et al. Synthesis and structure-activity relationships of novel retinoid X receptor-selective retinoids. *J Med Chem.* 1994;37(18):2930-41. doi: 10.1021/jm00044a014.
3. Alizadeh F, Bolhassani A, Khavari A, Bathaie SZ, Naji T, Bidgoli SA. Retinoids and their biological effects against cancer. *Int Immunopharmacol.* 2014;18(1):43-9. doi: 10.1016/j.intimp.2013.10.027
4. Robinson-Rechavi M, Escriva Garcia H, Laudet V. The nuclear receptor superfamily. *J Cell Sci.* 2003;116(Pt 4):585-6. doi: 10.1242/jcs.00247.
5. Appleby BS, Cummings JL. Discovering new treatments for Alzheimer's disease by repurposing approved medications. *Curr Top Med Chem.* 2013;13(18):2306-27. doi: 10.2174/15680266113136660162.
6. Bomben V, Holth J, Reed J, Cramer P, Landreth G, Noebels J. Bexarotene reduces network excitability in models of Alzheimer's disease and epilepsy. *Neurobiol Aging.* 2014;35(9):2091-5. doi: 10.1016/j.neurobiolaging.2014.03.029.

7. Njar VC, Gediya L, Purushottamachar P, Chopra P, Vasaitis TS, Khandelwal A, et al. Retinoic acid metabolism blocking agents (RAMBAs) for treatment of cancer and dermatological diseases. *Bioorg Med Chem*. 2006;14(13):4323-40. doi: 10.1016/j.bmc.2006.02.041.
8. Duvic M, Martin AG, Kim Y, Olsen E, Wood GS, Crowley CA, Yocum RC. Phase 2 and 3 clinical trial of oral bexarotene (Targretin capsules) for the treatment of refractory or persistent early-stage cutaneous T-cell lymphoma. *Arch Dermatol*. (2001);137(5):581-93.
9. Simeone AM, Tari AM. How retinoids regulate breast cancer cell proliferation and apoptosis. *Cell Mol Life Sci*. 2004;61(12):1475-84. doi:10.1007/s00018-004-4002-6
10. Magoulas GE, Bariamis SE, Athanassopoulos CM, Haskopoulos A, Dedes PG, Krokidis MG, et al. Syntheses, antiproliferative activity and theoretical characterization of acitretin-type retinoids with changes in the lipophilic part. *Eur J Med Chem*. 2011;46(2):721-37. doi: 10.1016/j.ejmech.2010.12.008.
11. Shirley MA, Wheelan P, Howell SR, Murphy RC. Oxidative metabolism of a retinoid and rapid phase II metabolite identification by mass spectrometry. *Drug Metab Dispos*. 1997;25(10):1144-9.
12. Howell SR, Shirley MA, Grese TA, Neel DA, Wells KE, Ulm EH. Bexarotene metabolism in rat, dog, and human, synthesis of oxidative metabolites, and in vitro activity at retinoid receptors. *Drug Metab Dispos*. 2001;29(7):990-8.
13. Pyo SM, Maibach HI. Skin metabolism: relevance of skin enzymes for rational drug design. *Skin Pharmacol Physiol*. 2019;32(5):283-94. doi: 10.1159/000501732.
14. Lee DS, Park J, Kay KA, Christakis NA, Oltvai ZN, Barabási AL. The implications of human metabolic network topology for disease comorbidity. *Proc Natl Acad Sci U S A*. 2008;105(29):9880-5. doi: 10.1073/pnas.0802208105.
15. Testa B, Krämer SD. The biochemistry of drug metabolism--an introduction: part 1. Principles and overview. *Chem Biodivers*. 2006;3(10):1053-101. doi: 10.1002/cbdv.200690111.
16. Mekenyan OG, Dimitrov SD, Pavlov TS, Veith GD. A systematic approach to simulating metabolism in computational toxicology. I. The TIMES heuristic modelling framework. *Curr Pharm Des*. 2004;10(11):1273-93. doi: 10.2174/1381612043452596.
17. OECD (Q)SARs Application Toolbox. Available from: http://www.oecd.org/document/23/0,3343,en_2649_34379_33957015_1_1_1_1,00.html.
18. Koleva Y, Georgieva SF, Agova N. Probable skin metabolic activity of third-generation retinoids and newly synthesized derivatives of bexarotene. *Bulg Chem Commun*. 2020; 52:80-6. doi: 10.34049/bcc.52.A.310.
19. Agova N, Koleva Y, Georgieva S. Probable metabolic activity of bexarotene in the liver. *Oxid Commun*. 2018; 41(4):526-32.
20. Marill J, Idres N, Capron CC, Nguyen E, Chabot GG. Retinoic acid metabolism and mechanism of action: a review. *Curr Drug Metab*. 2003;4(1):1-10. doi: 10.2174/1389200033336900.