**SAT–LCR-P-2-BFT(R)-01**

# MOLECULAR PROPERTIES AND BIOACTIVITY SCORE OF NEWLY SYNTHESIZED DERIVATIVES OF BEXAROTENE

**Assoc. Prof. Yana Koleva – PhD**
Department of Physical Chemistry and Organic Chemistry,
Bourgas "Prof. Assen Zlatarov" University
E-mail: yanuriana@abv.bg

**Assoc. Prof. Svetlana Georgieva– PhD**
Department of Pharmaceutical Sciences,
Faculty of Pharmacy,
Medical University-Varna "Prof.Dr.Paraskev Stoyanov"
E-mail: fotkova@abv.bg

**Assist. Prof. Nadya Agova - PhD Student**
Department of Pharmaceutical Sciences,
Faculty of Pharmacy,
Medical University-Varna "Prof.Dr.Paraskev Stoyanov"
E-mail: Nadya.Agova@mu-varna.bg

**Ivelin Iliev - Pharmacy Student**
Faculty of Pharmacy,
Medical University-Varna "Prof.Dr.Paraskev Stoyanov"
E-mail: i__iliev@abv.bg

***Abstract:*** *Bexarotene is a member of a subclass of third-generation synthetic retinoid. It is used as a treatment for cutaneous T cell lymphoma (CTCL). Bexarotene binds to and selectively activates retinoid X receptors (RXRs) which function as ligand-activated transcription factors that control gene expression, regulate cell differentiation and proliferation. The aim of this work is to calculate the probable molecular physicochemical properties and bioactivity scores of bexarotene and five newly synthesized derivatives of the bexarotene by software Molinspiration as potential drugs. The data analysis for all newly synthesized derivatives of bexarotene were found to haven't drug likeness property in some respects and their bioactivity scores are active for GPCR ligand and Nuclear receptor ligand and are moderately active for Ion channel modulator, Kinase inhibitor, Protease inhibitor and Enzyme inhibitor.*

***Keywords:*** *synthetic retinoids, bexarotene derivatives, predict, bioactivity score, molecular properties*

## INTRODUCTION

The term retinoids refer to vitamin A (retinol, ROL) and its natural and synthetic derivatives. Through interactions with specific cellular and nucleic acid receptors, this group of compounds influences many vital biological processes such as regulation of skin function and neuronal development (P. Berbis, 2010).

The pharmacologic effects of retinoids are extraordinarily multifarious. This is due to their mechanism of action related to the effect on nuclear receptors. The most data show the possibility for retinoid use in dermatology, but perhaps the antineoplastic use of retinoids outshines all others in clinical importance. There is evidence that topical retinoids had a beneficial effect on precancerous or cancerous neoplasms (A. M. Kligman, 1998). Synthetic retinoids are designed to restrict their toxicity and side effects of natural compounds. Mostly by increasing their selectivity toward each isotype of retinoic acids receptors (RARα,β, γ and RXRα, β, γ) (K. Babamiri, R. Nassab, 2010).

Recently, the concept of druggability has been widely used to postulate that the binding sites on biological molecules are complementary with their ligands in terms of volume, topology and physicochemical properties. In addition, the druggability concept evaluates the probability that small drug-like molecules can bind a given protein with sufficient potency to alter its activity (David J. Huggins, Woody Sherman, and Bruce Tidor 2012).

The aim of this work is to calculate the probable molecular physicochemical properties and bioactivity scores of bexarotene and five new synthesized derivatives of the bexarotene by software Molinspiration as potential drugs. The data analysis for all newly synthesized derivatives of bexarotene were found to haven't drug likeness property in some respects and their bioactivity scores are active for GPCR ligand and Nuclear receptor ligand and are moderately active for Ion channel modulator, Kinase inhibitor, Protease inhibitor and Enzyme inhibitor.

**Material and Methods**

*Compounds*. Retinoids, which were investigated in this work, are bexarotene and five newly synthesized derivatives of bexarotene with potential biological activity.

*Molinspiration*. Molinspiration supports internet chemistry community for calculation of important molecular properties (logP, polar surface area, number of hydrogen bond donors and acceptors and others), as well as prediction of bioactivity score for the most important drug targets (GPCR ligands, kinase inhibitors, ion channel modulators, nuclear receptors) (https://www.molinspiration.com/).

*LogP (octanol/water partition coefficient)*. LogP is calculated by the methodology developed by Molinspiration as a sum of fragment-based contributions and correction factors. The method is very robust and is able to process practically all organic and most organometallic molecules.

*Molecular Polar Surface Area TPSA*. Molecular Polar Surface Area is calculated based on the methodology published by Ertl et al. (P. Ertl, B. Rohde, P. Selzer, 2000) as a sum of fragment contributions. O- and N- centered polar fragments are considered. PSA has been shown to be a very good descriptor characterizing drug absorption, including intestinal absorption, bioavailability, Caco-2 permeability, and blood-brain barrier penetration.

*Molecular Volume*. Method for calculation of molecule volume developed at Molinspiration is based on group contributions. These have been obtained by the fitting sum of fragment contributions to "real" 3D volume for a training set of about twelv

e thousand, mostly drug-like molecules. 3D molecular geometries for a training set were fully optimized by the semiempirical AM1 method.

"Rule of 5" Properties is a set of simple molecular descriptors used by Lipinski in formulating his "Rule of 5" (Leslie Z. Benet,a,* Chelsea M. Hosey,a Oleg Ursu,b and Tudor I. Oprea 2016). The rule states, that most "drug-like" molecules have logP <= 5, molecular weight <= 500, number of hydrogen bond acceptors <= 10, and number of hydrogen bond donors <= 5. Molecules violating more than one of these rules may have problems with bioavailability. The rule is called "Rule of 5" because the border values are 5, 500, 2*5, and 5.

The number of Rotatable Bonds – nrotb. This simple topological parameter is a measure of molecular flexibility. It has been shown to be a very good descriptor of oral bioavailability of drugs. Rotatable bond is defined as any single non-ring bond, bounded to nonterminal heavy (i.e., non-hydrogen) atom. Amide C-N bonds are not considered because of their high rotational energy barrier.

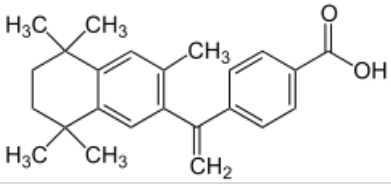
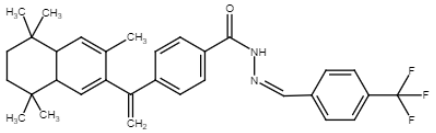
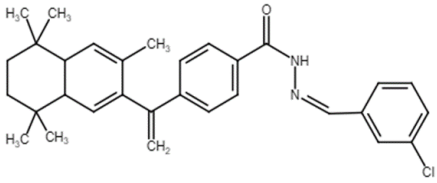
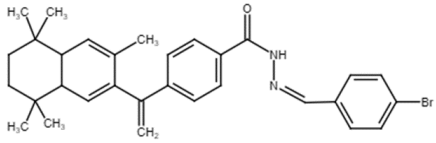
*Bioactivity score*. Bioactivity of the drug can be checked by calculating the activity score of GPCR ligand, ionchannel modulator, nuclear receptor legend, kinase inhibitor, protease inhibitor, enzyme inhibitor. Calculated drug likeness score of each compounds and compared with the specific activity of each compound,and the results were compared with standard drug. For organic molecules the probability is if the bioactivity scores (>0), then it is active, if (-5.0-0.0) then moderately active, if (<-5.0) then inactive (http://chem.sis.nlm.nih.gov/chemidplus/).

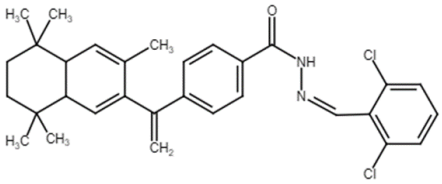
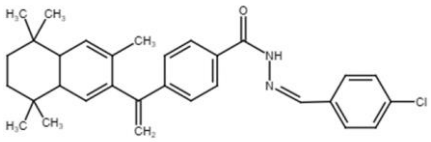
## EXPOSITION

In the present work, software Molinspiration has been used for identifying probable parameters - molecular physicochemical properties (Table 1) and bioactivity scores (Table 2) of newly synthesized derivatives of bexarotene.

Data of the calculation of molecular physicochemical properties of newly synthesized derivatives of bexarotene are presented in Table 1.

Table 1. Data about the calculation of molecular physicochemical properties of bexarotene and his newly synthesized analogues.

| Compound | $A_1$ | $A_2$ | $A_3$ | $A_4$ | $A_5$ | $A_6$ | $A_7$ | $A_8$ | $A_9$ |
|---|---|---|---|---|---|---|---|---|---|
| **Bexarotene**  | 6.81 | 37.30 | 26 | 348.49 | 2 | 1 | 1 | 3 | 348.76 |
| **1st derivative**<br>**4-[1-(3,5,5,8,8-pentamethyl-6,7-dihydronaphthalen-2 yl)ethenyl]-N'-[4-(trifluoromethyl)phenyl]methylidene]benzohydrazide**  | 8.67 | 41.46 | 38 | 518.62 | 3 | 1 | 2 | 6 | 479.11 |
| **2nd derivative**<br>**N'-[(3-chlorophenyl)methylidene]-4-[1-(3,5,5,8,8-pentamethyl-6,7-dihydronaphthalen-2-yl)ethenyl]benzohydrazide**  | 8.54 | 41.46 | 35 | 485.07 | 3 | 1 | 1 | 5 | 461.35 |
| **3rd derivative**<br>**N'-[(4-bromophenyl)methylidene]-4-[1-(3,5,5,8,8 pentamethyl 6,7-dihydronaphthalen-2-yl)ethenyl]benzohydrazide**  | 8.62 | 41.46 | 35 | 529.52 | 3 | 1 | 2 | 5 | 465.70 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **4th derivative**<br><br>**N'-[(2,6 - dichlorophenyl)methylidene]-4-[1-(3,5,5,8,8-pentamethyl-6,7-dihydronaphthalen-2-yl)ethenyl]benzohydrazide**<br>  | 8.84 | 41.46 | 36 | 519.52 | 3 | 1 | 2 | 5 | 474.88 |
| **5th derivative**<br>**N'-[(4-chlorophenyl)methylidene]-4-[1-(3,5,5,8,8-pentamethyl-6,7-dihydronaphthalen-2-yl)ethenyl]benzohydrazide**<br>  | 8.55 | 41.46 | 35 | 485.07 | 3 | 1 | 1 | 5 | 461.35 |

The following properties are available:

$A_1$: LogP - octanol-water partition coefficient; $A_2$: PSA - polar surface area; $A_3$: natoms - number of nonhydrogen atoms; $A_4$: MW - molecular weight; $A_5$: nON - number of hydrogen-bond acceptors (O and N atoms); $A_6$: Nohnh - number of hydrogen-bond donors (OH and NH groups); $A_7$: nviolations - number of Rule of 5 violations; $A_8$: nrotb - number of rotatable bonds; $A_9$: volume - molecular volume;

The data analysis in Table 1 shows that:

a) bexarotene and all five derivatives of bexarotene have larger values of five (log P has to be <=5); b) Molecular weight has to be <= 500; for bexarotene is in the range but for derivatives of bexarotene is from 485 to 529; c) The parameter Polar Surface Area is 41.46 for all derivatives of bexarotene, d) Number of hydrogen bond acceptors has to be <= 10 and has to be number of hydrogen bond donors <= 5; It's within limits for all derivatives; e) Number of Rule of 5 violations – the values of the derivatives of bexarotene are between 1 and 2. Molecules violating more than one of these rules may have problems with bioavailability; f) the topological parameter (number of rotatable bonds) is a measure of molecular flexibility. The value of all derivatives of bexarotene is five; g) Molecular volume. Most pharmaceuticals are small molecules. The values of the molecular volume of the derivatives of bexarotene are from 461.35 to 479.11.

Data about the calculation of bioactivity scores of bexarotene and newly synthesized derivatives of bexarotene are present in table 2.

Table 2. Calculation of bioactivity scores of new synthesized derivatives of bexarotene

| **Compound** | **$A_1$** | **$A_2$** | **$A_3$** | **$A_4$** | **$A_5$** | **$A_6$** |
|---|---|---|---|---|---|---|
| Bexarotene | 0.47 | 0.14 | 0.01 | 0.92 | 0.02 | 0.39 |
| 1st derivative of bexarotene | 0.15 | -0.36 | -0.14 | 0.33 | -0.25 | -0.01 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 2nd derivatives of bexarotene | 0.12 | -0.35 | -0.21 | 0.24 | -0.32 | -0.02 |
| 3rd derivatives of bexarotene | 0.05 | -0.41 | -0.23 | 0.18 | -0.37 | -0.05 |
| 4 th derivatives of bexarotene | 0.13 | -0.37 | -0.23 | 0.23 | -0.31 | -0.01 |
| 5th derivative of bexarotene | 0.12 | -0.35 | -0.21 | 0.25 | -0.32 | -0.02 |

The following properties are available:

$A_1$: GPCR ligand; $A_2$: Ion channel modular; $A_3$: Kinase inhibitor; $A_4$: Nuclear receptor ligand; $A_5$: Protease inhibitor; $A_6$: Enzyme inhibitor;

For all calculated bioactivity scores bexarotene is active because bioactivity values are greater than 0 and then bexarotene is active. All newly synthesized derivatives of bexarotene are active for the following bioactivity scores (GPCR ligand and nuclear receptor ligand) and are moderately active for Ion channel modulator, Kinase inhibitor, Protease inhibitor and Enzyme inhibitor.

Druglikeness may be defined as a complex balance of various molecular properties and structural features, which determine whether a particular molecule is similar to the known drugs. These properties, mainly hydrophobicity, electronic distribution, hydrogen bonding characteristics, molecule size and flexibility and of course presence of various pharmacophoric features influence the behaviour of molecule in a living organism, including bioavailability, transport properties, affinity to proteins, reactivity, toxicity, metabolic stability and many others.

The diversity of possible drug targets (of which each requires a different combination of matching molecular characteristics) is so enormous, that it is possible to find a common denominator for all of them and to express molecule drug-likeness by a single "magic number". Simple count criteria (like limits for molecular weight, log P, or a number of hydrogen bond donors or acceptors) have also relatively limited applicability and are useful only to discard obvious non-drugs (https://www.molinspiration.com/).

## CONCLUSION

Molecular properties of newly synthesized derivatives of bexarotene selected for in silico drug activity prediction by software molinespiration showed that there are derivatives in some properties. These facts indicated that all the five compounds were found to haven’t drug likeness property in some respects.

The bioactivity scores of the five compounds are active for GPCR ligand and nuclear receptor ligand and are moderately active for Ion channel modulator, Kinase inhibitor, Protease inhibitor and Enzyme inhibitor.

**Acknowledgements:** This study was financially supported by the Medical University – Varna through the Science Foundation – Project number 18018 and Burgas University through the Scientific Research Sector – Project number 434/2019.

## REFERENCES

A. M. Kligman (1998) - The growing importance of topical retinoids in clinical dermatology: a retrospective and prospective analysis - J. Am. Acad. Dermatol., 39 (2), S2. p. S2-S7

David J. Huggins, Woody Sherman, and Bruce Tidor (2012) - Rational Approaches to Improving Selectivity in Drug Design - J Med Chem. Feb 23; 55(4): 1424–1444.

K. Babamiri, R. Nassab (2010) - Cosmeceuticals: the evidence behind the retinoids.- Aesthet., 30(1) doi: 10.1177/1090820X09360704.

Leslie Z. Benet,a,* Chelsea M. Hosey,a Oleg Ursu,b and Tudor I. Oprea (2016) - BDDCS, the Rule of 5 and Drugability -Adv Drug Deliv Rev. Jun 1; 101: 89–98, doi: 10.1016/j.addr.2016.05.007

P. Berbis (2010) - Rétinoïdes: mécanismes d'action - Annales de dermatologie et de vénéréologiep. 97-S103 doi: 10.1016/S0151-9638(10)70036-3

P. Ertl, B. Rohde, P. Selzer (2000) - Fast calculation of molecular polar surface area as a sum of fragment-based contributions and its application to the prediction of drug transport properties. J.Med.Chem. 43, 3714-3717.

http://chem.sis.nlm.nih.gov/chemidplus/

https://www.molinspiration.com/