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PREDICTING MOLECULAR PROPERTIES AND BIOACTIVITY SCORE OF SIMILAR COMPOUNDS OF TAZAROTENE

Assoc. Prof. Yana Koleva, PhD
Department of Chemistry,
University 'Prof. Assen Zlatarov'-Burgas, Bulgaria
E-mail: yanuriana@abv.bg

Abstract: *The purpose of present work was to define with a Tanimoto similarity metric of 0.8 similar compounds of tazarotene and to predict and analyze theirs molecular physicochemical properties and bioactivity score by the CompTox Chemistry Dashboard and Molinspiration software. The data analysis for the three similar compounds of tazarotene were found to have close molecular properties and structural features and their bioactivity score is active.*

Keywords: *tazarotene, similar compounds, predict, bioactivity score, molecular properties.*

INTRODUCTION

Retinoids regulate cell proliferation, differentiation and apoptosis in development and adult life (Altucci, L., & Gronemeyer, H., 2001). They also have anticancer activity in preclinical studies, acting topromote differentiation and/or apoptosis in tumour cells and nowhave an established role in the treatment of several malignancies,including acute promyelocytic leukaemia (APL), cutaneous T-cell lymphoma and neuroblastoma (Altucci, L., & Gronemeyer, H., 2001, Smith, M.A., & Anderson, B., 2001).

Retinoids act via two families of nuclear transcription factors, the retinoid (RARα, β, γ) and rexinoid (RXRα, β, γ) receptors (Altucci, L., & Gronemeyer, H., 2001). These receptors act mainly as RAR–RXR heterodimers, which regulate the transcription of downstream target genes after binding to retinoic acid response elements in their promoters (Kastner, P., et al, 1997). Gene targeting studies in mice indicate that the six retinoid receptors have distinct functions; this has encouraged the development of synthetic ligands that bind selectively to different retinoid receptors (Chen, J.Y., et al, 1996).

Tazarotene (ethyl 6-[2-(4,4-dimethylthiocroman-6-yl)-ethynyl]nicotinate) and tazarotenic acid, the free acid metabolite of tazarotene, belong to a novel class of retinoids called acetylenic retinoids (Chandraratna, R.A., 1996). Tazarotene itself does not bind to retinoid receptors, but tazarotenic acid is a retinoid agonist that binds with high affinity to the receptors RARβ and RARγ (Chandraratna, R.A., 1996). RARβ expression is decreased in breast and lung cancer compared with normal tissues suggesting that regulation of RARβ expression has a role in malignant progression (Xu, X.C., et al., 1997, Picard, E., et al., 1999). In vitro studies reveal that expression of RARβ correlates with sensitivity to retinoid-induced growth inhibition and apoptosis in tumour cell lines, suggesting that this receptor has a key role in retinoid-mediated antitumour effects (Liu, Y., et al., 1996).

The purpose of present work was to define with a Tanimoto similarity metric of 0.8 similar compounds of tazarotene and to predict and analyze theirs molecular physicochemical properties and bioactivity score by the CompTox Chemistry Dashboard and Molinspiration software. The data analysis for the three similar compounds of tazarotene were found to have close molecular properties and structural features and their bioactivity score is active.

MATERIAL AND METHODS

Compound Data. Tazarotene (ChemIDplus Advanced) is a third-generation retinoid with CAS number 118292-40-3. The chemical name is 3-pyridinecarboxylic acid, 6-((3,4-dihydro-4,4-dimethyl-2H-1-benzothiopyran-6-yl)ethynyl)-, ethyl ester, and the structural formula is as follows (Figure 1):

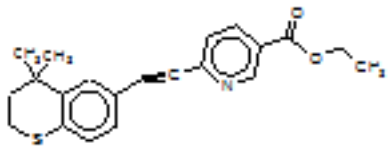


Fig. 1 Structure of tazarotene.

CompTox Chemistry Dashboard. The Dashboard is a freely accessible web-based application and data hub providing access to data associated with chemical substances. It accesses data from nine component databases housing generic data types. The Dashboard also integrates data from other platforms (specifically PubChem and PubMed) via web services and visualization widgets. The Dashboard represents a first step in building a comprehensive chemical substance- centric informatics architecture to provide flexible access to data, models and analysis tools in support of EPA's research programs (USA EPA, CompTox Chemistry Dashboard, Williams, A.J., et al. 2017).

Similar molecules. The similar molecules tab shows the results of a structural similarity search, underpinned by a Tanimoto similarity calculated using the Bingo Molecular Search Cartridge (with the associated Indigo fingerprints) ("Epam" Bingo PostGreSQL cartridge). The search displays up to 50 of the top-most similar molecules above a Tanimoto similarity metric of 0.8. The view also displays a selection of experimental and predicted chemical properties to help illustrate the consistency and concordance of these attributes within the identified set of structurally related molecules (USA EPA, CompTox Chemistry Dashboard, Williams, A.J., et al. 2017).

Molinspiration software. The Molinspiration software was used 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) (Molinspiration Chemoinformatic Software).

LogP (octanol/water partition coefficient). LogP is calculated by the methodology developed by the Molinspiration software 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 (Molinspiration Chemoinformatic Software).

Molecular Polar Surface Area TPSA. Molecular Polar Surface Area is calculated based on the methodology published by Ertl, P., et al., 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 (Molinspiration Chemoinformatic Software).

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 twelve thousand, mostly drug-like molecules. 3D molecular geometries for a training set were fully optimized by the semiempirical AM1 method (Molinspiration Chemoinformatic Software).

"Rule of 5" Properties is a set of simple molecular descriptors used by Lipinski in formulating his "Rule of 5" (Lipinski, C.A., 1997). 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 (Molinspiration Chemoinformatic Software).

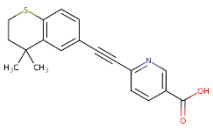
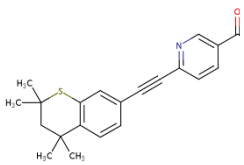
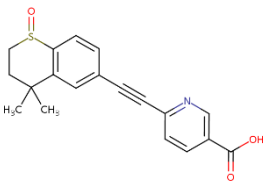
The number of Rotatable Bonds – nrotb. This simple topological parameter is a measure of molecular flexibility. It has been shown to be a very good descriptor of oral bioavailability of drugs (Veber, D.F., et al., 2000). Rotatable bond is defined as any single non-ring bond, bounded to nonterminal heavy (i.e., non-hydrogen) atom. Amide C-N bonds are not considered because of their high rotational energy barrier (Molinspiration Chemoinformatic Software).

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 (Molinspiration Chemoinformatic Software).

RESULTS AND DISCUSSIONS

Three similar tazarotene structures with a Tanimoto similarity metric of 0.8 (from 0.92 to 0.84) by the CompTox Chemistry Dashboard were found. The similar tazarotene compounds are presented in Table 1.

Table 1. Results of similar tazarotene structures

	CAS number	Name of compound	Structure of compound	Similarity
1	118292-41-4	6-((3,4-dihydro-4,4-dimethyl-2H-1-benzothiopyran-6-yl)ethynyl)- 3-pyridinecarboxylic acid		0.92
2	145352-11-0	6-[(2,2,4,4-Tetramethyl-3,4-dihydro-2H-1-benzothiopyran-7-yl)ethynyl]pyridine-3-carboxylic acid		0.88
3	603952-64-3	6-[(4,4-Dimethyl-1-oxo-1,2,3,4-tetrahydro-1-benzothiopyran-6-yl)ethynyl]pyridine-3-carboxylic acid		0.84

The Molinspiration software has been used for predicting parameters - molecular physicochemical properties (Table 2) and bioactivity score (Table 3) of three similar compounds of tazarotene. Data of the calculation of molecular physicochemical properties of the three similar compounds of tazarotene are presented in Table 2.

Table 2. Calculated data for molecular physicochemical properties of similar compounds of tazarotene.

Name of compound	A_1	A_2	A_3	A_4	A_5	A_6	A_7	A_8	A_9
6-((3,4-dihydro-4,4-dimethyl-2H-1-benzothiopyran-6-yl)ethynyl)- 3-pyridinecarboxylic acid	3.42	50.19	23	323.42	3	1	0	1	290.96
6-[(2,2,4,4-Tetramethyl-3,4-dihydro-2h-1-benzothiopyran-7-yl)ethynyl]pyridine-3-carboxylic acid	4.23	50.19	25	351.47	3	1	0	1	323.78
6-[(4,4-Dimethyl-1-oxo-1,2,3,4-tetrahydro-1-benzothiopyran-6-yl)ethynyl]pyridine-3-carboxylic acid	1.82	67.26	24	339.42	4	1	0	1	298.50

*The following properties are available:

A_1: LogP - octanol-water partition coefficient; A_2: TPSA - 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 2 shows that:

a) the three similar compounds of tazarotene have values less than five (log P has to be <=5); b) Molecular weight has to be <= 500; molecular weight for all three compounds are less than 500; c) The parameter Polar Surface Area is from 50.19 to 67.26 for the three compounds, 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 the three compounds; e) Number of Rule of 5 violations – the value of compounds is 0; f) The topological parameter (number of rotatable bonds) is a measure of molecular flexibility. The value of the compounds is 1; g) Molecular volume. The values of the molecular volume of the three compounds are from 290.96 to 323.78.

Calculated data of bioactivity score of the three similar compounds of tazarotene are present in table 3.

Table 3. Calculated data for bioactivity score of the three compounds of tazarotene

Name of compound	A_1	A_2	A_3	A_4	A_5	A_6
6-((3,4-dihydro-4,4-dimethyl-2H-1-benzothiopyran-6-yl)ethynyl)- 3-pyridinecarboxylic acid	0.41	0.01	0.16	0.84	0.22	0.60
6-[(2,2,4,4-Tetramethyl-3,4-dihydro-2h-1-benzothiopyran-7-yl)ethynyl]pyridine-3-carboxylic acid	0.41	-0.03	0.13	0.98	0.29	0.71
6-[(4,4-Dimethyl-1-oxo-1,2,3,4-tetrahydro-1-benzothiopyran-6-yl)ethynyl]pyridine-3-carboxylic acid	0.64	0.16	0.47	0.77	0.29	0.78

*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.

All three similar compounds of tazarotene are active against the GPCR ligand (values are from 0.41 to 0.64). Two of the three similar compounds of tazarotene are active against the Ion channel modular (values are from 0.01 to 0.16) and one compound is with moderately active (value is -0.03). The values of Kinase inhibitor are from 0.13 to 0.47, i.e. the three similar compounds are active. The three similar compounds of tazarotene are active against the Nuclear receptor ligand (values are from 0.77 to 0.98). Three compounds are active against the Protease inhibitor (values are from 0.22 to 0.29). The values of the three similar compounds of tazarotene are from 0.60 to 0.78 against the Enzyme inhibitor.

CONCLUSION

Three similar compounds of tazarotene with a Tanimoto similarity metric of 0.8 by the CompTox Chemistry Dashboard were found and their molecular properties and bioactivity score were predicted by In Silico methods (Molinspiration software). Analysis of the data showed that the similar chemical structures of tazarotene suggest close molecular properties and biological activity (mostly active).

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