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Probable skin metabolic activity of third-generation retinoids and newly synthesized derivatives of bexarotene

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Synthetic third-generation retinoids (bexarotene, adapalene, tazarotene, temarotene and mofarotene) can activate retinoid X receptors (RXR), which determines their various effects in the body. However, safety profile of both structures of the third-generation retinoids and their metabolites are not yet fully understood. The aim of this work is to examine the probable skin metabolic activity of third-generation retinoids (bexarotene, adapalene, tazarotene, temarotene and mofarotene) and of five newly synthesized derivatives of bexarotene, as well as to predict the protein and DNA binding of their metabolites by OECD (Q)SAR Application Toolbox. The data analysis of skin metabolic prediction of some retinoids of third generation shows that only adapalene and tazarotene have metabolic activation in the skin (adapalene – 2 metabolites and tazarotene – 4 metabolites). They have no DNA binding but two of them have the ability to bind to proteins by Michael-type nucleophilic addition. The five newly synthesized derivatives of bexarotene have no metabolic activation in the skin.

Keywords: synthetic retinoids, bexarotene derivatives, metabolism, OECD (Q)SAR Application Toolbox.

INTRODUCTION

Bexarotene is a synthetic compound that exerts its biological action through selective binding and activation of the three RXRs: α, β, and γ. Once activated, these receptors function as transcription factors that regulate processes such as cellular differentiation and proliferation, apoptosis, and insulin sensitization. The ability of the RXRs to form heterodimers with various receptor partners that are important in cellular function and in physiology indicates that the biological activities of bexarotene are more diverse than those of compounds that activate the RARs [1].

The pharmacologic effects of retinoids are extraordinarily multifarious. This is due to their mechanism of action related to the effect on nuclear receptors. 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 [2]. With respect to their skin action, retinoids can be divided into three categories, i.e. topically administered retinoids registered as drugs (e.g. tretinoin, isotretinoin, alitretinoin, tazarotene and adapalene); systemic retinoids that are not available for topical treatment (e.g. acitretin and etretinate); and compounds incorporated into skin products (e.g. ROL, retinaldehyde (RAL) and retinyl esters (REs)) [3].

The term retinoids refers to vitamin A (retinol, OL) 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 [4]. A hallmark of endogenous retinoid signaling in the skin is its local, paracrine, homeostatic regulation, in which local retinoic acid (RA) metabolism plays an essential role [5]. It was previously demonstrated that retinoids antagonize reduced cell growth and increase collagen degrading matrix metalloproteinases in naturally aged human skin and regulate the keratinization process [6]. Additionally, retinoids abolish sun-induced skin hyperpigmentation and are effective in treatment of the sun-damaged skin [7]. This is achieved through transformation of less active fibroblasts into cells that produce large amounts of collagen [8]. The increase in the number and activity of fibroblasts improves skin firmness, elasticity and hydration. Additionally, retinoids may be also classified as anti-inflammatory agents, inhibiting, e.g., microglial activation [4]. Retinoids are divided into four categories based on their chemical structure. First generation includes the natural, nonaromatic compounds. Retinoids belonging to this group such as ROL, RA and isotretinoin are used in the treatment of acne.

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The second generation of retinoids consists of monoaromatic compounds that are synthetic vitamin A analogues. This group of compounds is useful in the pharmacotherapy of severe forms of psoriasis and keratinization disorders [9]. In this category there are acitretin and etretinate. The third generation, such as adapalene, bexarotene and tazarotene are polyaromatic retinoid derivatives and are used in the therapy of plaque psoriasis. Finally, fourth generation of retinoids comprises pyranones such as seletinoid G [10, 11]. Seletinoid G is a novel synthetic retinoid that was found to repair altered connective tissue and to inhibit UV-induced collagen deficiency when tested in aged human skin *in vivo* [12]. As the skin is the active site of retinoid metabolism, the aim of this study was to predict probable skin metabolic activity of retinoids of third generation (adapalene, tazarotene, temarotene, mofarotene, bexarotene) and of five newly synthesized derivatives of bexarotene in the skin, by using the Organisation for Economic Co-operation and Development (OECD) (Q)SAR Application Toolbox. Subsequently, the results obtained were compared to experimental observations in order to evaluate the utility of (OECD) (Q)SAR Application Toolbox in drug discovery metabolite identification studies.

MATERIALS AND METHODS

Compounds. Retinoids, which were investigated in this work, are adapalene, tazarotene, temarotene, mofarotene, bexarotene [13] and five newly synthesized derivatives of bexarotene as potential drugs.

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 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 [14].

Metabolic pathways documented for 200 organic chemicals in different mammals are stored in a database format that allows easy computer-aided access to the metabolism information. The collection includes chemicals of different classes, with a variety of functionalities such as aliphatic hydrocarbons, alicyclic rings, furans, halogenated hydrocarbons, aromatic hydrocarbons and haloaromatics, amines, nitro-derivatives, and multifunctional compounds. *In vivo* and *in vitro* (predominantly, with liver microsomes as experimental systems) studies were used to analyse the metabolic fate of chemicals. Different sources, including monographs, scientific articles and public websites were used to compile the database [14, 15].

RESULTS AND DISCUSSION

In the present work, OECD (Q)SAR Application Toolbox has been used for identifying the probable metabolic activity of some retinoids of third generation and of five newly synthesized derivatives of bexarotene in the skin and their protein and DNA binding.

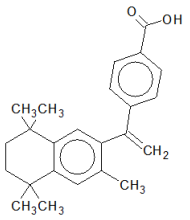
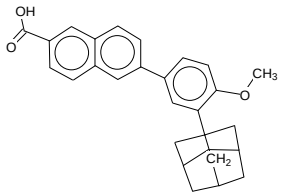
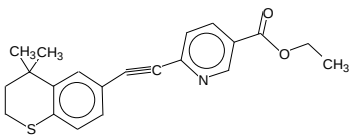
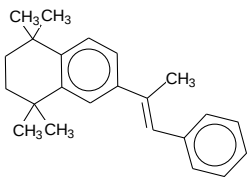
Data of metabolic activation of some retinoids in the skin and their protein and DNA binding are presented in Table 1. The data analysis in Table 1 shows that all five retinoids of third generation cannot bind to proteins and DNA (parent structure). Metabolic activation was observed for adapalene and tazarotene in the skin. Two metabolites were predicted for adapalene and four metabolites for tazarotene.

The two metabolites of adapalene are not active. They have no DNA and protein binding (Table 2).

Four metabolites of tazarotene were predicted in the skin with metabolic activation. All four metabolites have no DNA binding and only two of them have protein binding – Michael-type nucleophilic addition (Table 3).

Data for the metabolic activation of five newly synthesized derivatives of bexarotene in the skin and its protein and DNA binding are presented in Table 4. The data analysis in Table 4 shows that all five derivatives of bexarotene, similar to bexarotene, cannot bind to proteins and DNA. No metabolic activation was observed for the derivatives of bexarotene in the skin.

Table 1. Probable skin metabolism of some retinoids of third generation

Name and 2D Structure (Parent structure)	Protein binding (Parent structure)	DNA binding (Parent structure)	Skin metabolism simulator
4-[1-(3,5,5,8,8-pentamethyl-6,7-dihydronaphthalen-2 yl)ethenyl]benzoic acid (Bexarotene) 	No binding	No binding	0 metabolite; No DNA binding; No protein binding
Adapalene 	No binding	No binding	2 metabolites; No DNA binding; No protein binding
Tazarotene 	No binding	No binding	4 metabolites; No DNA binding; Protein binding – 2 metabolites
Temarotene 	No binding	No binding	0 metabolite; No DNA binding; No protein binding

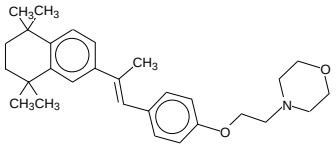
Name and 2D Structure (Parent structure)	Protein binding (Parent structure)	DNA binding (Parent structure)	Skin metabolism simulator
Mofarotene 	No binding	No binding	0 metabolite; No DNA binding; No protein binding

Table 2. Probable skin metabolites of adapalene and their protein and DNA binding.

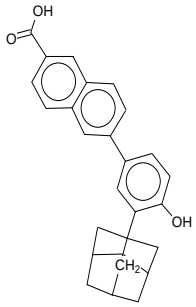
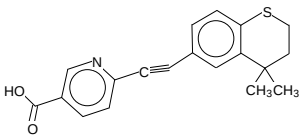
Metabolite No	Metabolite structure	Protein binding	DNA binding
1		No binding	No binding
2	$H_2C=O$	No binding	No binding

Table 3. Probable skin metabolites of tazarotene and their protein and DNA binding.

Metabolite No	Metabolite structure	Protein binding	DNA binding
1		No binding	No binding

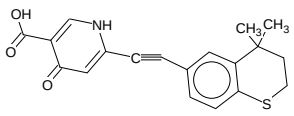
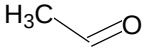
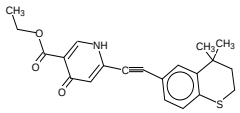
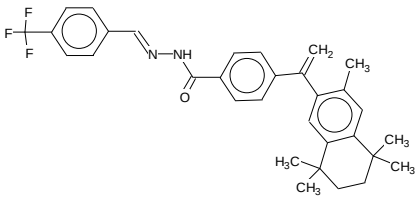
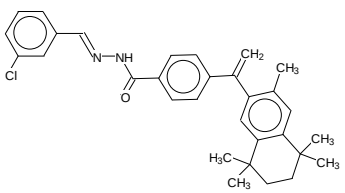
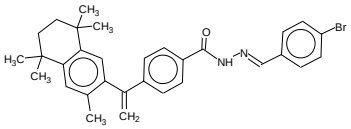
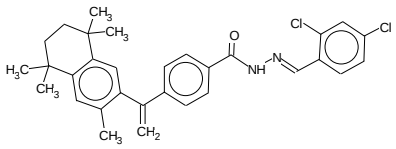
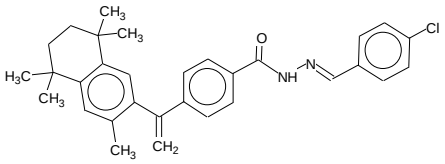
2		Michael-type nucleophilic addition	No binding
3		No binding	No binding
4		Michael-type nucleophilic addition	No binding

Table 4. Probable skin metabolites newly synthesized derivatives of bexarotene and their protein and DNA binding.

Name and 2D Structure (Parent structure)	Protein binding (Parent structure)	DNA binding (Parent structure)	Skin metabolism simulator
1st derivative of bexarotene: 4-[1-(3,5,5,8,8-pentamethyl-6,7-dihydronaphthalen-2-yl)ethenyl]-N'-[(E)-[4-(trifluoromethyl)phenyl]methylidene]benzohydrazide			
	No binding	No binding	0 metabolite; No DNA binding; No protein binding

2nd derivatives of bexarotene: N'-[(E)-(3-chlorophenyl)methylidene]-4-[1-(3,5,5,8,8-pentamethyl-6,7-dihydronaphthalen-2-yl)ethenyl]benzohydrazide			
			0 metabolite; No DNA binding; No protein binding
3rd derivatives of bexarotene: N'-[(E)-(4-bromophenyl)methylidene]-4-[1-(3,5,5,8,8-pentamethyl-6,7-dihydronaphthalen-2-yl)ethenyl]benzohydrazide			
	No binding	No binding	0 metabolite
4th derivatives of bexarotene: N'-[(E)-(2,4-dichlorophenyl)methylidene]-4-[1-(3,5,5,8,8-pentamethyl-6,7-dihydronaphthalen-2-yl)ethenyl]benzohydrazide			
	No binding	No binding	0 metabolite

5th derivative of bexarotene: N'-[(E)-(4-chlorophenyl)methylidene]-4-[1-(3,5,5,8,8-pentamethyl-6,7-dihydronaphthalen-2-yl)ethenyl]benzohydrazide		No binding	No binding 0 metabolite

Tazarotene is a chemical substance whose metabolites after metabolic activation in the skin can cause skin sensitization effect as a result of protein conjugation *via* Michael-type nucleophilic addition. Michael-type addition provides a means of covalent adduct formation at an electrophilic center, without any leaving group. Direct addition of a nucleophile can take place across a double or triple carbon-carbon bond if it is attached to a highly polarized substituent that permits the resultant negatively charged transition state to be stabilized.

CONCLUSIONS

Results of this work for skin metabolic prediction of some retinoids of third generation shows that only adapalene and tazarotene have metabolic activation in skin (adapalene – 2 metabolites, which are not active and tazarotene – 4 metabolites (two of them are active)). They have no DNA binding but two of them have the ability to bind to proteins by Michael-type nucleophilic addition. The five newly synthesized derivatives of bexarotene have no metabolic activation in the skin. Metabolites with electrophilic character may react with nucleophilic sites in DNA and also bind to proteins. The data obtained show the possibility of potential adverse effects and ability to induce skin injury on tazarotene metabolites (two of four) by the mechanism of Michael-type nucleophilic addition.

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