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# Design of novel tazarotene derivatives as potential antipsoriatic drugs: physicochemical properties study and molecular docking analysis of their binding to retinoic acid receptor family (RAR-alpha, RAR-beta and RAR-gamma)

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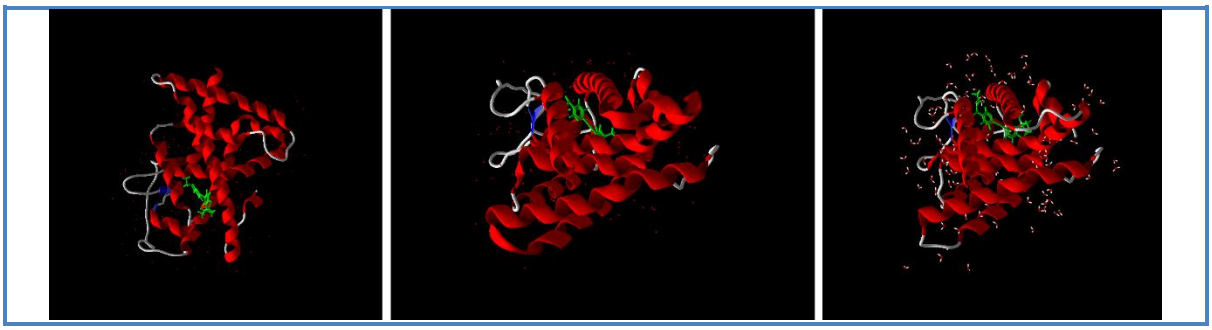
**ABSTRACT**

Design of novel antipsoriatic drugs based on the medicinal compound Tazarotene is the main purpose of the present study. Firstly, the molecular structures of Tazarotene and its derivatives (F, Cl, $CH_3$, $OCH_3$, COOH, OH, $NH_2$ and $CF_3$) were optimized using density functional theory (DFT) at B3LYP/6-311++G (d, p) computational method. Then, the optimized molecules were docked into the active site of the retinoic acid receptors. The molecular docking analyses revealed that, the Tazarotene derivatives with COOH, $CF_3$ and $OCH_3$ substituents can make strongest complexes with RAR-alpha, RAR-beta and RAR-gamma, respectively. Based on the physicochemical properties calculations, it was cleared that the $CF_3$ derivative of Tazarotene has better properties (receptor-ligand interaction efficiency, lipophilicity and skin permeation) compared with that of the Tazarotene.



## Graphical Abstract



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## Introduction

Psoriasis is a prevalent chronic inflammatory skin condition afflicting about 2-4% of patients all over the world. Psoriasis is mostly characterized by the skin covered with red, well-defined, hardened plaques with silver and micaceous scale [1]. Complications associated with psoriasis are including psoriatic arthritis, cardiovascular disease, eye diseases, depression and other health conditions. There are no known definitive cures for psoriasis; therefore, treatments for psoriasis mainly have focused on improving the patient's quality of life [2]. 70-80% of psoriasis cases suffer localized and limited versions of the disease that are classified as mild to moderate and are mostly treated with topical therapies. Furthermore, topical treatments could be used as adjuvant therapy in moderate to severe psoriasis alongside systemic and photo therapy. Therefore, topical treatments offer high efficacy while maintaining safety in psoriasis patients as they minimize dose consumption and adverse effects [3]. Topical treatment used for psoriasis are including corticosteroids, Anthralin and tars, topical vitamin D analogs, retinoids and miscellaneous therapies such as topical salicylic acid and 5-fluorouracil [4]. Although, the exact mechanism involved in psoriasis is not yet fully understood, various studies suggest alteration of vitamin A metabolism plays a significant role in the onset of this condition. Retinoids are vitamin A derivatives used both in systemic and topical treatment of psoriasis. Retinoids exert their effects by interaction with nuclear retinoid receptors, retinoid X receptor (RXR) and retinoic acid receptor (RAR) which both have three alpha, beta, and gamma subtypes [5, 6]. Retinoids are categorized into three generations based on their structure. Retinoid molecules are generally composed of 1) a cyclic end group, 2) a polyene side chain and 3) a polar end-group. The different substitution at each of these groups defines retinoid's generation. Tazarotene, is a third generation retinoid with polyaromatic structure which enhances its receptor specificity [7]. Tazarotene transforms into tazarotenic acid, its active form, which possesses high selectivity for RAR, specifically, beta and gamma subtypes [8]. Tazarotene attenuates psoriatic symptoms by regulating keratinocyte proliferation and differentiation. Furthermore, Tazarotene expresses a strong anti-inflammatory property which is of great importance in amelioration of psoriasis. Although Tazarotene is effective as monotherapy, it is mostly used in combination with corticosteroids or phototherapy [9]. The adjuvant therapy with topical corticosteroids in plaque psoriasis showed increased efficacy and a better skin tolerability [10]. Duobrii a corticosteroid and retinoid combination consisting of Halobetasol propionate plus Tazarotene received its FDA approval on 2019 for the topical treatment of plaque psoriasis [11].

A survey through previous studies determined several methods for the management of psoriasis. The use of Tazarotene as a retinoid, alone and in combination with corticosteroids, has been extensively investigated and explained. However, the exact molecular interactions of this drug with its known receptors is yet to be understood. This study was undertaken to comprehensively analyze the structural interactions of Tazarotene with three alpha, beta and gamma subtypes of RAR. Also, 8 different functional groups including F, Cl, CH3, OCH3, COOH, OH, NH2 and CF3 were placed in cyclic ring in Meta position relative to the polyene side chain, to determine the effect of each group on skin permeability and absorption and affinity towards RAR. For this purpose, molecular docking methods and computational

chemistry were utilized. The physiochemical and pharmacokinetic attributes of Tazarotene and its different derivatives were determined using Swiss ADME web tool.

## Methods and materials

The inventive process of finding novel drugs based on the biological target (protein, enzyme and receptor) knowledge is drug design or rational drug design [12-14]. A medicinal compound is most commonly an organic small molecular structure that activates or inhibits the biomolecule function [15]. A drug design process is made of four steps: theoretical drug design, synthesis, preclinical and clinical studies [16-19]. The theoretical drug design step consists to the quantum mechanical (QM) study of the candidate molecules and molecular docking analysis of their binding to the biological targets [20-22]. Here, the structural and electronic properties of Tazarotene and its derivatives are studied using density functional theory (DFT) computational method. Firstly, All molecular structures are optimized using B3LYP/6-311++G(d, p) level of theory in isolated form at room temperature. The QM computations were conducted using the Gaussian 03 software. Then, their stability and reactivity properties were discussed by frontier molecular orbitals (FMOs) calculations. Finally, all the optimized molecular structures were docked into the retinoid acid receptors (RAR-alpha, RAR-beta and RAR-gamma) and analyzed. The Molegro Virtual Docker (MVD) software was used for the molecular docking analysis. The physicochemical properties of the designed molecules were simulated using the online web tool *www.swissadme.ca*.

## Results and discussion

### *Tazarotene structural and electronic properties study*

The geometry of tazarotene molecular structure optimized using B3LYP/6-31+G(d, p) level of theory at room temperature using the Gaussian 03 software. Figure 1 indicates the theoretical geometric structure of the title compound. The ring A has been twisted but the rings B and C are planar. There are electron currents on the pi bonds of the benzene and pyridine rings. These unsaturated rings are connected together by a triple C-C bond. The pi bonds of benzene and pyridine rings and the triple carbon-carbon bond make resonance. So, this segment of the molecular structure is planar. Figure 2 indicates the dependence between the theoretical and experimental bond lengths of the tazarotene molecular structure. This dependence is shown by the equation y=0.9919x-0.0162. The higher correlation coefficient ($R^2$=0.9588) for this equation shows a great convergence. So, the B3LYP/6-311++G(d, p) basis set of theory is a good method to compute the electronic properties of the title compound.

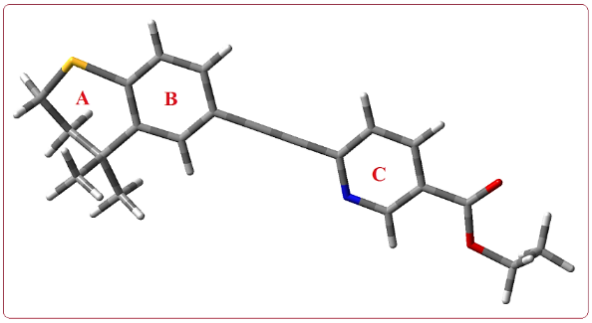



**Figure 1.** The optimized molecular structure of Tazarotene.

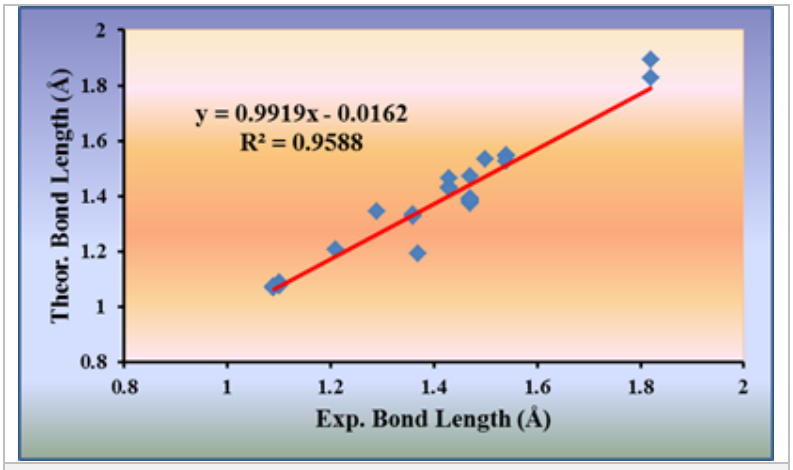



**Figure 2.** The experimental and theoretical bond lengths relationship of Tazarotene.

Stability and reactivity are two important parameters for each chemical compound which should be a medicinal substance. As mentioned in the computational methods section, these parameters can be discussed using FMOs theory. The frontier molecular orbitals are called to the highest occupied and lowest unoccupied molecular orbitals (HOMO and LUMO) [23-25]. Figure 3 depicts the frontier molecular orbitals of the Tazarotene. The HOMO is mainly constructed using the atomic orbitals of the rings A and B and acetylene atoms. In contrast, the LUMO relates to the participation of the atomic orbitals of the rings B and C and acetylene atoms. So, it can be predicted that the benzene ring and acetylene group will play main role in reaction with other chemical reagents. On the other hand, the pyridine ring will be participated in nucleophilic reactions on Tazarotene. For good discussion about the stability and reactivity properties of the said compound, the global reactivity descriptors like energy gap (Eg), ionization potential (IP), electron affinity (EA), chemical hardness (η), chemical softness (S), electronegativity (χ), electronic chemical potential (μ) and electrophilicity index (ω) will be computed from the energies of the frontier orbitals. These global reactivity indices are achieved by following formulas [26].

$$E_g = E_{LUMO} - E_{HOMO}$$

$$IP = -E_{HOMO}$$

$$EA = -E_{LUMO}$$

$$\eta = \frac{(\varepsilon_{LUMO} - \varepsilon_{HOMO})}{2}$$

$$\chi = \frac{-(\varepsilon_{LUMO} + \varepsilon_{HOMO})}{2}$$

$$\mu = \frac{(\varepsilon_{LUMO} + \varepsilon_{HOMO})}{2}$$

$$\omega = \frac{\mu^2}{2\eta}$$

$$S = \frac{1}{\eta}$$

Table 1 presents the global reactivity indices and frontier molecular orbitals energies of the active substance Tazarotene. The energy levels of HOMO and LUMO were -7.95 eV and 1.51 eV, respectively. These energy levels show the said molecule prefers the nucleophilic interactions. The low energy value of the electron affinity parameter proves the tendency of Tazarotene to the nucleophilic interactions. The density of states (DOS) graph (Figure 4) indicates the energy levels and density of the occupied and virtual orbitals of the title compound. It can be seen from this figure; the virtual orbitals have more density and high energy. So, this graph

indicates the high possibility of the nucleophilic interactions, as well. Also, the HOMO-LUMO energy levels gap was found to be 9.46 eV. This high frontier molecular orbitals energies gap shows the high stability of the substance under study. So, it can be concluded that the electronic transitions don't occur in the molecule. So, this molecule will show high resistance against redox agents and it will be stable into the cells. The chemical hardness (4.73 eV) and chemical softness (0.211 eV) parameters show Tazarotene has low tendency to interact with chemical reagents like biomolecules. This low interaction tendency also correlates with the low amount of electrophilicity index (1.096 eV). The molecular electrostatic potential (MEP) graph of Tazarotene can be shown in Figure 5. In this graph, the negative, zero and positive electrostatic potentials are indicated by red, green and blue colors, respectively. The nitrogen, oxygen and sulfur atoms of the said medicinal compound show negative potential. In contrast, other remaining atoms have zero potential. So, it can be predicted that the heteroatoms of Tazarotene will have more interaction with biomolecules like receptors within the cells.

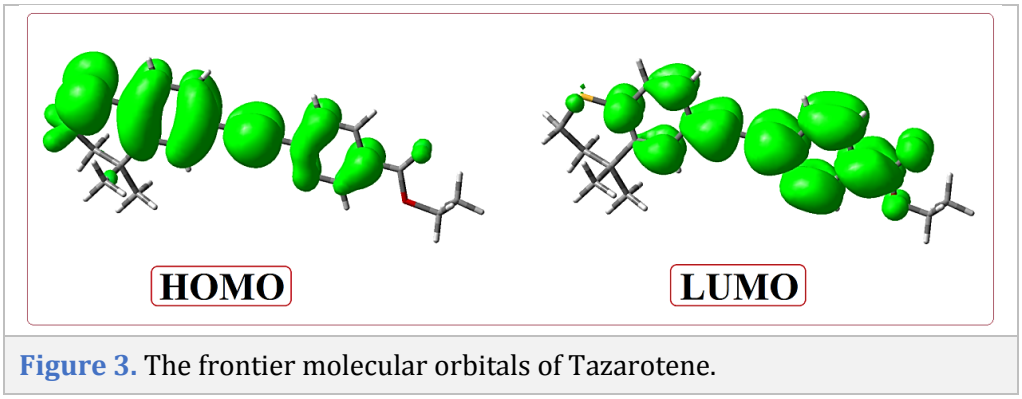



**Figure 3.** The frontier molecular orbitals of Tazarotene.

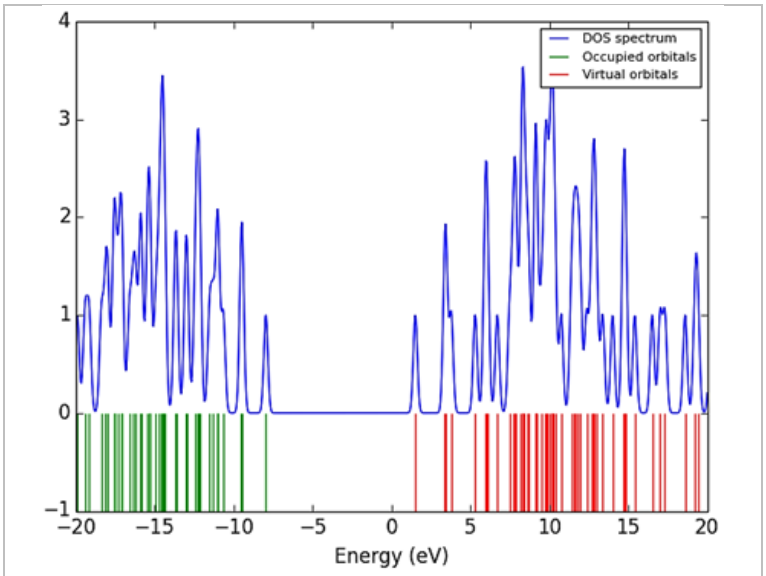



**Figure 4.** The density of states (DOS) graph of Tazarotene.

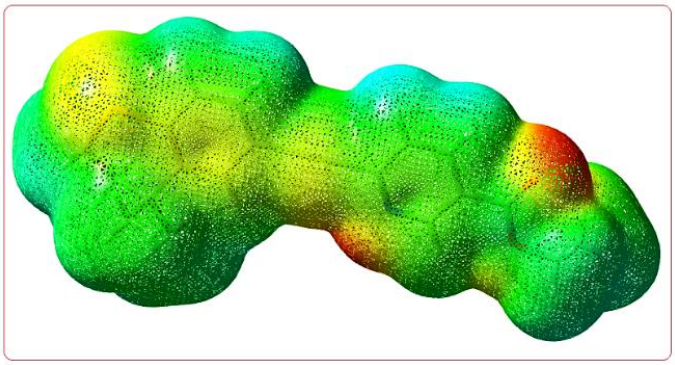


**Figure 5.** The molecular electrostatic potential (MEP) graph of Tazarotene.

**Table 1.** Global reactivity indices of Tazarotene.

| Parameter | Energy value (eV) |
|---|---|
| HOMO | -7.95 |
| LUMO | 1.51 |
| Ionization Potential (IP) | 7.95 |
| Electron Affinity (EA) | -1.51 |
| Energy Gap (Eg) | 9.46 |
| Electronegativity (χ) | 3.22 |
| Chemical Potential (μ) | -3.22 |
| Chemical Hardness (η) | 4.73 |
| Chemical Softness (S) | 0.211 |
| Electrophilicity index (ω) | 1.096 |

*Molecular docking analysis of Tazarotene binding to the retinoic acid receptors*

Molecular docking is a key tool in structural molecular biology and computer assisted drug design. This approach was utilized to analyze the binding modes of a medicinal compound with a biomolecule like receptor. Here, the binding modes of Tazarotene with the receptors RAR-alpha, RAR-beta and RAR-gamma were analyzed using the molecular docking technique. Figure 6 indicates that the medicinal compound Tazarotene embedded in the active site of the retinoic acid receptors.

Analyzing the Tazarotene-RARalpha complex shows the title active substance makes steric interactions with RAR-alpha using the residues Cys 235, Ile 273, Phe 199, Arg 272, Thr 285, Ser 287, Phe 286, Arg 276, Leu 269, Ser 232, Leu 231, Ile 270, Leu 305, Ala 392, Trp 225, Lys 390, Leu 398, Phe 228, Gly 391, Val 395, Leu 266, Phe 302, Arg 394 and Gly 301. The hydrogen bond interactions of the title complex were related to the binding of the Tazarotene to Ser 287 and two water molecules. The score of the steric and hydrogen bond interactions were -157.642 and -1.116, respectively. So, the steric interactions play a crucial role in binding of the molecule to the said receptor. On the other hand, the water-ligand interactions score was -7.473. In an overall survey, the main interactions of the said compound with the receptor were done using the residues Phe 302 (-25.5830), Leu 269 (-17.4083), Phe 286 (-17.1460), Phe 228 (-14.3883), Ile 273 (-13.5735), Leu 266 (-8.31716), Ser 232 (-7.73830), Leu 231 (-7.26270), Ser 287 (-6.57363), Cys 235 (-6.53151), Arg 394 (-6.21196), Ile 270 (-6.06548), Gly 301 (-4.13137), Leu 305 (-3.92618), Arg 272 (-3.60059), and Val 395 (-2.50303).

Tazarotene made complex with the receptor RAR-beta using hydrogen bond and steric intercations with the moldock scores -5.993 and -150.177, respectively. The hydrogen bond interactions are done using the residues Cys 228 and Ser 280 and two water molecules. On

the other hand, the residues Phe 192, Arg 269, Arg 265, Leu 262, Cys 228, Ser 280, Ile 266, Ala 225, Leu 224, Phe 279, Ile 263, Ile 380, Val 302, Lys 383, Leu 298, Arg 387, Leu 391, Gly 384, Leu 259, Phe 295, Gly 294 and Phe 221 make steric interactions with the said compound. In overall, Tazarotene mainly interacts with the residues of RAR-beta including Phe 295 (-27.8844), Phe 279 (-15.6343), Phe 221 (-12.9915), Leu 262 (-12.9121), Ile 266 (-11.9475), Ser 280 (-10.6141), Leu 224 (-9.93913), Cys 228 (-8.53459), Ile 263 (-6.38714), Arg 387 (-5.61605), Ala 225 (-5.47779), Arg 265 (-5.32511) and Leu 259 (-5.24493).

The Tazarotene-RAR-gamma complex analysis revealed two types of interactions between the ligand and the receptor: the hydrogen bond and steric interactions with scores -8.649 and -150.893, respectively. So, the steric interactions play main role in making complex between Tazarotene and RAR-gamma. The residues of the receptor containing Lys 236, Phe 288, Ser 289, Asp 290, Cys 237, Thr 287, Leu 233, Arg 278, Phe 201, Arg 274, Ile 275, Phe 304, Leu 268, Met 272, Arg 396, Ala 394, Leu 400, Ala 234, Met 415, Ile 412, Phe 230, Leu 271, Leu 416, Trp 227, Met 408, Gly 393 and Ala 39 make steric binds with the said medicinal compound. On the other hand, the residues Ser 289 and Arg 278 and one water molecule can make hydrogen bonds with the molecule. In overall, the main ligand-receptor interactions were related to the residues of the receptor containing Phe 288 (-18.3000), Leu 271 (-16.0302), Phe 230 (-13.4942), Leu 233 (-12.1891), Cys 237 (-11.0524), Ala 234 (-9.33727), Ile 275 (-9.28551), Phe 304 (-6.06224), Leu 268 (-5.67234) and Arg 278 (-4.185-455).

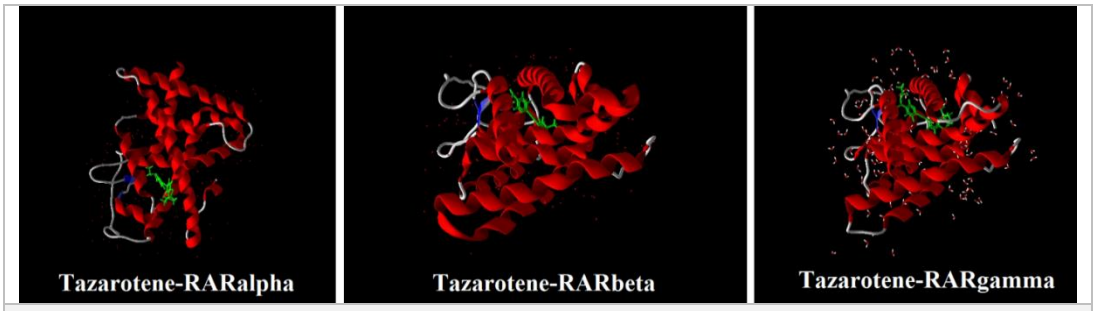
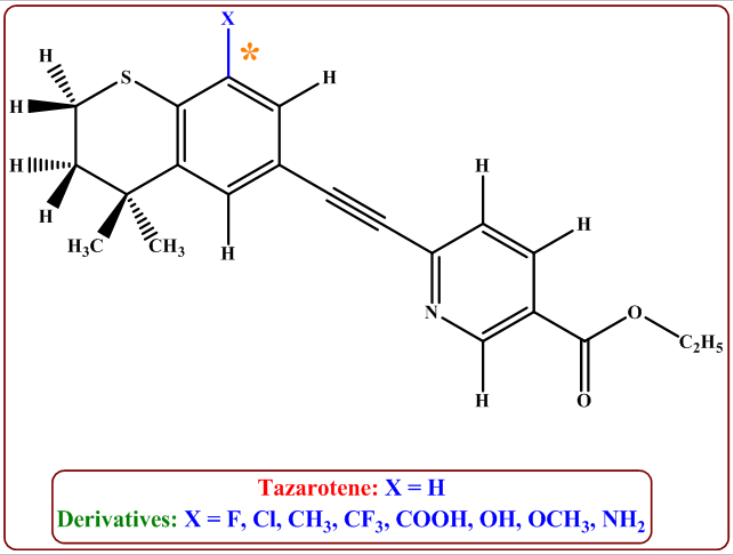



**Figure 6.** Ligand Tazarotene embedded in the active site of the retinoic acid receptors.

*Molecular docking analysis of Tazarotene derivatives binding to the retinoic acid receptors*

As described above, Tazarotene can make complex with the retinoic acid receptors (RAR-alpha, RAR-beta and RAR-gamma. Analyzing the ligand-receptors interactions shows all segments of Tazarotene except one C-H bond of the benzene ring participate in the said interactions. This bond is indicated by asterisk C-X bond in Scheme 1. For design of new drugs based on Tazarotene with high efficacy on psoriasis treatment, different substituents (X = F, Cl, $CH_3$, $CF_3$, COOH, OH, $OCH_3$ and $NH_2$) were considered. Firstly, all molecular structures were optimized theoretically and then their binding to the said receptors were analyzed using molecular docking study. Table 2 indicates the molecular structures-receptors docking analysis data. It can be seen from the data, the substituents efficacy order is: COOH (12.46 %) > $OCH_3$ (10.83 %) > $CF_3$ (9.78 %) > F (8.07 %) > Cl (7.67 %) > $NH_2$ (7.25 %) > $CH_3$ (5.99 %) > OH (1.27 %) > H. So, all Tazarotene derivatives have more efficacy than the

Tazarotene. Also, the electron-withdrawing substituents show high effect on binding of the related drugs to the receptors. Figure 7 shows the Tazarotene derivatives with COOH, $CF_3$ and $OCH_3$ substituents make the strongest complexes with RAR-alpha, RAR-beta and RAR-gamma, respectively.




**Scheme 1.** The molecular structure of Tazarotene and its dervatives.

**Table 2.** The molecular structures-receptors docking analysis data.

| Tazarotene Derivatives | MolDock Score | | | Efficiency |
|---|---|---|---|---|
| | RAR-alpha | RAR-beta | RAR-gamma | |
| X = H | -149.195 | -147.198 | -123.430 | 1.0000 |
| X = F | -154.366 | -146.086 | -143.590 | 1.0807 |
| X = Cl | -153.715 | -145.873 | -143.253 | 1.0767 |
| X = $CH_3$ | -153.834 | -144.972 | -143.813 | 1.0599 |
| X = $CF_3$ | -150.677 | -154.615 | -143.867 | 1.0978 |
| X = OH | -151.949 | -146.278 | -125.403 | 1.0127 |
| X = $OCH_3$ | -155.028 | -149.849 | -147.426 | 1.1083 |
| X = $NH_2$ | -152.865 | -144.983 | -143.735 | 1.0725 |
| X = COOH | -160.252 | -150.001 | -146.936 | 1.1246 |

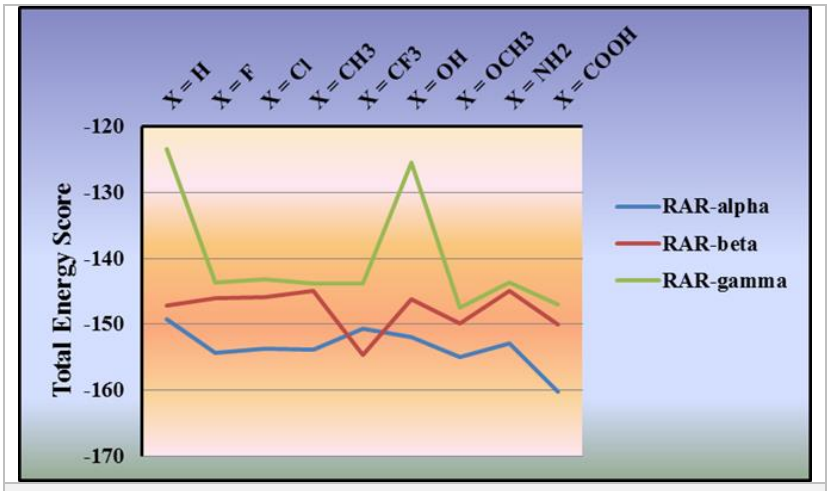



**Figure 7.** The effect of different substituents on Tazarotene efficacy.

*Physicochemical descriptors and ADME parameters of the designed compound*

Drug discovery and development relies heavily on analyzing the absorption, distribution, metabolism and excretion (ADME) and ADME-related physicochemical parameters to predict the bioavailability and drug likeness of molecular compounds [27-31]. In the present study, computational analysis of the physicochemical descriptors was done using the SwissADME web tool for prediction of ADME parameters and pharmacokinetic behavior of the investigated compound. Moreover, we analyzed the effect of 8 different functional groups (F, Cl, $CH_3$, $CF_3$, OH, $OCH_3$, $NH_2$ and COOH) on receptor affinity and physiochemical properties of the molecular structure. Based on molecular docking results presented in the previous section, addition of all functional groups improved drug's efficiency and receptor interaction. However, further analysis shows substitution with electron withdrawing functional groups results in greater scores of efficiency. In this regard, the most significant enhancement in efficiency belongs to COOH (12.46 %), $OCH_3$ (10.83 %) and $CF_3$ (9.78 %). In order to predict whether these functional groups also affect pharmacokinetic behavior as well as skin permeation and absorption, ADME parameters need to be analyzed. The ADME parameters of Tazarotene and all substitutions are presented in Table 3. To predict the compound's capacity to permeate through biological membranes, lipophilicity was determined by measuring the partition coefficient between n-octanol and water (log $P_{O/W}$). Among these three groups, $CF_3$ expresses greater lipophilic properties as witnessed by MLog P value which is 4.70 in $CF_3$, 3.08 in COOH and 3.95 in $OCH_3$ group, while the base-line group (H) had a MLog P of 3.81. Water solubility of the compound was determined using the ESOL model, a topical method to evaluate the Log S. The Log S scale was used to predict the water solubility. In this respect, the compounds were placed into six categories: Insoluble (Log S < -10), poorly soluble (-10 < Log S < -6), moderately soluble (-6 < Log S < -4), soluble (-4 < Log S < -2), very soluble (-4 < Log S < -2) and highly soluble (Log S > 0). As shown in Table 3, all the substitutions fall into moderately soluble category. The pharmacokinetic parameters predict individual ADME attributes of the compound under investigation. All of the three said substitutions

show mostly similar pharmacokinetic properties, except in BBB permeability and inhibitory properties of CYP2D6. The compound containing $OCH_3$ group is BBB permeant (similar to H), while $CF_3$ and COOH do not permeate through BBB and despite $CF_3$ and COOH, OCH3 adds CYP2D6 inhibitory properties to the compound. Furthermore, the skin permeation index (Log Kp) was related to lipophilicity and size of the molecule and the more negative values are indicative of less skin permeability. In this regard, $CF_3$ revealed greater skin permeability with Log Kp of -5.53 cm/s, compared with $OCH_3$ and COOH with values of -6.54 cm/s and -5.83 cm/s, respectively. Drug likeness is evaluated based on bioavailability score and adherence to Lipinski's rule (MW ≤ 500 Daltons, NH or OH (hydrogen bond donors)≤5, N or O (hydrogen bond acceptors)≤10 and MLog P≤4.15). The bioavailability score of the compounds with $CF_3$ and $OCH_3$ are 0.55 while substitution with COOH results in bioavailability score of 0.56. In all substitutions, compounds abide Lipinski's rule except $CF_3$ which shows 1 violation (MLOGP>4.15). Finally, the Synthetic accessibility score which ranges from 1 (very easy) to 10 (very difficult) was analyzed and presented in Table 3. In conclusion, based on molecular docking and ADME results, and considering the importance of lipophilicity and skin permeation in the delivery of Tazarotene, it could be surmised that amongst all of the investigated compounds, substitution with CF3 functional group not only increased efficiency and receptor interaction but also showed greater values of lipophilicity and skin permeation. Therefore, with respect to both parameters the compound with the optimum properties is the one containing $CF_3$ functional group.

**Table 3.** The physicochemical properties data of the designed drugs.

| | Tazarotene Derivatives | X = H | X = F | X = Cl | X = $CH_3$ | X = $CF_3$ | X = OH | X = $OCH_3$ | X = $NH_2$ | X = COOH |
|---|---|---|---|---|---|---|---|---|---|---|
| Physiochemical Properties | $M_W$ | 353.48 g/mol | 371.47 g/mol | 387.92 g/mol | 367.50 g/mol | 421.48 g/mol | 369.48 g/mol | 383.50 g/mol | 368.49 g/mol | 397.49 g/mol |
| | Num. Heavy Atoms | 25 | 26 | 26 | 26 | 29 | 26 | 27 | 26 | 28 |
| | Num. Arom. Heavy Atoms | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| | Fraction Csp3 | 0.43 | 0.43 | 0.43 | 0.45 | 0.45 | 0.43 | 0.45 | 0.43 | 0.41 |
| | Num. Rotatable bonds | 3 | 3 | 3 | 3 | 4 | 3 | 4 | 3 | 4 |
| | Num. H-bond acceptors | 3 | 4 | 3 | 3 | 6 | 4 | 4 | 3 | 5 |
| | Num. H-bond donors | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 1 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Lipophilicity | Molar Refractivity | 103.29 | 103.34 | 108.09 | 108.10 | 108.29 | 104.86 | 109.18 | 106.00 | 109.87 |
| | TPSA | 64.49 | 64.49 | 64.49 | 64.49 | 64.49 | 84.72 | 73.72 | 90.51 | 101.79 |
| | MLOGP | 3.81 | 3.92 | 4.03 | 4.70 | 4.70 | 3.95 | 3.95 | 2.96 | 3.08 |
| Water Solubility | ESOL | -4.69 | -4.69 | -5.12 | -4.03 | -4.03 | -2.96 | -2.96 | -4.18 | -4.40 |
| | Class of Solubility | Moderate | Moderate | Moderate | Moderate | Moderate | Moderate | Moderate | Moderate | Moderate |
| Pharmacokinetics | GI Absorption | High | High | High | High | High | High | High | High | High |
| | BBB permeant | Yes | Yes | Yes | Yes | No | No | Yes | No | No |
| | P-gp substrate | No | No | No | No | No | No | No | No | No |
| | CYP1A2 inhibitor | No | No | No | No | No | No | No | No | No |
| | CYP2C19 inhibitor | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| | CYP2C9 inhibitor | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| | CYP2D6 inhibitor | No | No | No | No | No | No | Yes | No | No |
| | CYP3A4 inhibitor | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| | Log Kp (skin permeation) | -5.43 cm/s | -5.67 cm/s | -5.39 cm/s | -5.57 cm/s | -5.53 cm/s | -5.98 cm/s | -5.83 cm/s | -6.20 cm/s | -6.54 cm/s |
| Drug-likeness | Lipinski | Yes; 0 violation | Yes; 0 violation | Yes; 0 violation | Yes; 0 violation | Yes; 1 violation: MLOGP >4.15 | Yes | Yes | Yes; 0 violation | Yes; 0 violation |
| | Bioavailability Score | 0.55 | 0.55 | 0.55 | 0.55 | 0.55 | 0.55 | 0.55 | 0.55 | 0.56 |
| Medicinal Chemistry | Synthetic accessibility | 4.68 | 4.72 | 4.73 | 4.79 | 4.78 | 4.74 | 4.89 | 4.70 | 4.84 |

As discussed above, based on both studied parameters (physicochemical properties and molecular docking analyses) the compound with the optimum properties was the Tazarotene derivative containing the $CF_3$ functional group.

Docking analysis of the compound-RARalpha complex indicates the title Tazarotene derivative makes steric interactions (moldock score = -164.820) with RAR-alpha using the residues Cys 235, Ile 273, Phe 199, Arg 272, Thr 285, Ser 287, Phe 286, Arg 276, Leu 269, Ser 232, Leu 231, Ile 270, Asp 267, Ser 388, Ala 392, Val 309, Ile 387, Leu 266, Lys 390, Arg 394, Leu 305, Phe 302, Ala 300, Trp 225, Gly 301, Leu 398, Phe 228, Val 395 and Gly 391. It should be said that the residues Asp 267, Ile 270, Ser 388, Ala 392, Val 309, Ile 387, Leu 266, Lys 390, Leu 305, Val 305, Val 395, Gly 391, Phe 302 and Leu 269 interact with the trifluoromethyl substituent. The hydrogen bond interactions (score = -2.783) of the title complex relate to the binding of the designed drug to Ser 287, Cys 235 and two water molecules. So, the steric interactions play main role in binding of the molecule to the said receptor. On the other hand, the water-ligand interactions score is -6.654. The total energy score of this ligand-receptor complex is -150.677. In an overall survey, the main interactions of the said compound with the receptor are done using the residues Phe 302 (-29.1145), Leu 269 (-17.4647), Phe 286 (-15.4758), Phe 228 (-12.6782), Leu 266 (-10.8069), Ile 273 (-10.7544), Cys 235 (-9.16829), Ser 232 (-8.40669), Leu 231 (-6.91745), Leu 305 (-5.52366), Ser 287 (-5.42726), Ser 388 (-5.16566), Gly 301 (-4.83939), Arg 394 (-4.62391), and Arg 272 (-4.47239).

This Tazarotene derivative makes complex with the receptor RAR-beta using hydrogen bond and steric intercations with the moldock scores -5.935 and -166.357, respectively. The total energy score of this complex is -154.615. The hydrogen bond interactions are done using the residues Arg 269 and Ser 280 and one water molecule. On the other hand, the residues Phe 192, Arg 269, Arg 265, Leu 262, Cys 228, Ser 280, Ile 266, Thr 278, Ala 225, Leu 224, Phe 279, Phe 295, Ser 381, Val 302, Leu 298, Ile 380, Ile 263, Arg 387, Leu 391, Ala 225, Trp 218, Phe 221, Ile 403, Leu 407, Gly 384, Leu 259, Met 406 and Val 388 make steric interactions with the title compound. It should be said that the fluorine atoms of the trifluoromethyl substituent interact with the residues Ile 266, Phe 295, Val 302, Leu 298, Ile 380, Ile 263, Arg 387, Gly 384 and Leu 259. In overall, the compound under study mainly interacts with the residues of RAR-beta including Phe 279 (-16.9686), Ile 266 (-14.9565), Leu 262 (-14.1678), Phe 221 (-12.8589), Leu 259 (-12.6333), Phe 295 (-12.2751), Ser 280 (-9.45751), Ile 263 (-7.55114), Arg 265 (-7.05556), Leu 224 (-6.34723), Cys 228 (-6.09950), Arg 269 (-5.54695), Ala 225 (-5.37581), Val 388 (-5.13745), Gly 384 (-4.64836) and Arg 387 (-4.21912).

The compound-RAR-gamma complex analysis shows two types of interactions between the ligand and the receptor: the hydrogen bond and steric interactions with scores -7.326 and -150.472, respectively. So, the steric interactions play main role in making complex between Tazarotene and RAR-gamma. The total energy score -143.867 is shown for this complex. The residues of the receptor containing Arg 274, Leu 271, Arg 278, Phe 201, Ser 289, Phe 288, Thr 287, Cys 237, Leu 233, Met 272, Leu 307, Arg 396, Phe 304, Ile 275, Ala 394, Gly 393, Leu 400, Leu 268, Met 415, Ser 231, Ile 412, Leu 416, Ala 397, Phe 230, Met 408, Ala 234 and Trp 227 make steric binds with the said medicinal compound. It should be said that the fluorine atoms of the trifluoromethyl substituent interact with the residues Met 272,

Leu 307, Arg 396, Phe 304, Ile 275, Gly 393, Leu 400, Ala 394, Leu 268 and Phe 230. On the other hand, the residues Ser 289 and Arg 278 and one water molecule can make hydrogen bonds with the molecule. In overall, the main ligand-receptor interactions relate to the residues of the receptor containing Phe 288 (-19.3931), Phe 230 (-16.8358), Leu 271 (-13.1421), Ser 289 (-11.0061), Ala 234 (-10.8177), Phe 304 (-9.34286), Ile 275 (-9.31625), Leu 233 (-8.64629), Cys 237 (-8.35112), Gly 393 (-5.56970), Leu 268 (-5.53051) and Trp 227 (-5.47213).

## Conclusions

There are several known topical formulations used in treatment of psoriasis, including the investigated compound in our study which has already been proven to be effective against this condition. The aim of this study was to utilize the functional groups most commonly observed in previous treatments to achieve a compound with improved physiochemical properties and enhanced efficiency. The procedure of substituting different functional groups in a pre-determined position of the base compound and comparison of the aforementioned properties provided us with a novel, convenient and cheap approach to reach our goal.

In this work we designed new derivatives of the medicinal compound Tazarotene as a psoriasis treatment. In first step, Tazarotene and its designed derivatives were optimized by quantum mechanical computations. Then, the molecular docking of all optimized molecular structures with retinoic acid receptors family was analyzed. Finally, the physicochemical properties of the designed compounds were studied by ADME calculations. Based on the studied parameters, it was cleared that the $CF_3$ derivative of Tazarotene can show the better properties than Tazarotene. We strongly believe that this method of Tazarotene-based compound screening and evaluation will be of great interest in future endeavors in drug design and drug delivery.

## Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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## Conflict of interest

We have no conflicts of interest to disclose.

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