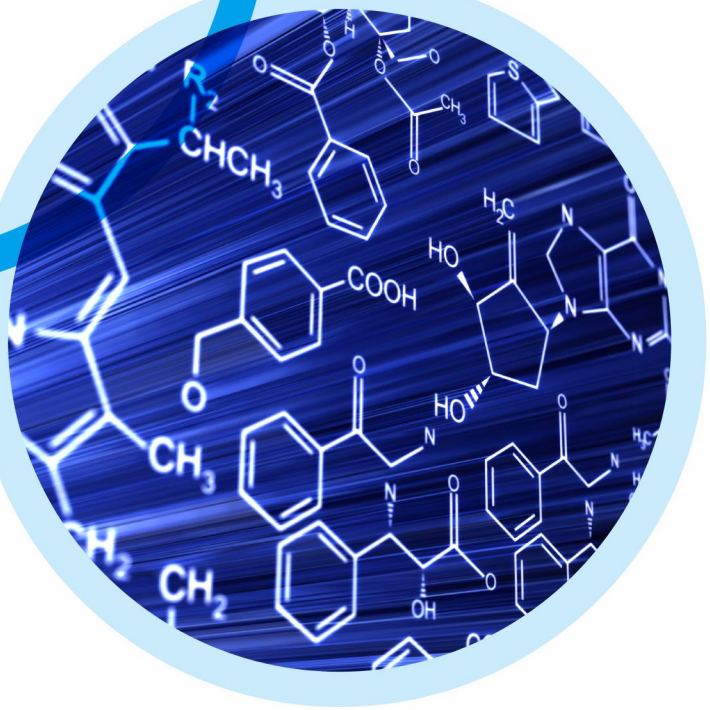

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Research Article
3D QSAR Studies of 3, 16 and 17 Position Modifications in Steroidal Derivatives for CNS Anticancer Activity

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Abstract

Background and Objective: The role of steroids in cancer is well established in reducing inflammation, immune response and sickness while undergoing chemotherapy and improving appetite. However, these steroidal agents have been seldom tested as direct inhibitors for the enzymes associated with cancer. This study was undertaken to establish a 3D QSAR model of 16-(substituted) dehydroepiandrosterone derivatives, which can help in designing novel compounds in the series. **Materials and Methods:** For this study, some novel steroidal derivatives exhibiting CNS anti-cancer activity were taken and tried to understand their SAR and quantify it using 3D QSAR to know the requirement for future development in the area. About 56 novels 16-(substituted) dehydroepiandrosterone derivatives which were previously synthesized in our lab and evaluated for CNS anticancer activity were taken for this study. After energy minimization, these compounds were aligned over each other to determine the pharmacophore and then subjected to CoMFA analysis. **Results:** Eight CoMFA models were generated, the most optimum model was the one with $r^2 = 0.892$, $q^2 = 0.02$ and the lowest STD deviation error correction. The introduction of electropositive groups at positions 11 and 14 and electro negative groups at positions 3 and 16 in the steroidal ring can lead to potentially active compounds. **Conclusion:** The 3D CoMFA model generated gave us an insight that the introduction of electropositive groups at positions 11 and 14 and electro-negative groups at positions 3 and 16 in the steroidal ring will give us compounds with better CNS anticancer activity.

Key words: 3D QSAR, 16-substituted dehydroepiandrosterone derivatives, CoMFA, steroidal derivatives

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Human bodies naturally produce modest levels of steroids. They aid in managing a variety of processes, such as the immune system, blood pressure and inflammation. A variety of ailments and disorders can be treated with synthetic steroids[1]. Some of these steroids are employed in the treatment of cancer. Typically, corticosteroids are the type of steroids used in the treatment of cancer. These hormones are synthesised versions of those made by the adrenal glands located above the kidneys. These corticosteroids are used to decrease pain, swelling and fever. They can be purchased as pills, lotions or injections[2].

Steroids like prednisolone, methylprednisolone, dexamethasone, hydrocortisone, etc., are used in the treatment of cancer. They can be prescribed in the treatment of cancer for a number of reasons treating cancer by themselves, lessening inflammation, lower immunological response in the body (for instance, following a bone marrow transplant), lessening nausea from chemotherapy and increasing appetite. For advanced cancer patients, steroids are utilised during the initial diagnosis, before and after surgery and radiotherapy, as well as before, during and after chemotherapy[3]. Candidates for the development of anti-cancer medications include steroid heterocyclic derivatives with 5- or 6-membered rings that have interesting therapeutic potential as cytotoxic agents and enzyme inhibitors[4]. Several thiazole, pyrido, pyrano and lactam steroid derivatives were obtained using 17β-hydroxy-5α-androstan-3-one (androstanolone) as starting steroid[5]. For this present study, we made our database of the steroidal derivatives evaluated for their anticancer activity by our team reported earlier. Performed 3D QSAR modelling of the data and chose best-fit 3D QSAR model and interpret and analyse the results. The key modifications required for designing new steroidal derivatives based on the 3D QSAR model were also proposed.

MATERIALS AND METHODS

Study area: The presented work was carried out at the College of Pharmaceutical Sciences, Dayananda Sagar University, Bangalore, India in August, 2021 to July, 2022.

The database was created for the 16-(substituted) dehydroepiandrosterone derivatives taken from the literature[6]. The 3D QSAR analysis was performed using 3D QSAR.com platform. The structure was shown in Fig. 1.

The structure was divided into a test set and a training set. The activity values were taken in log Inhibitory concentration for CNS anticancer activity. All the structures were analyzed for various possible confirmations and then aligned by Py-alignment (Fig. 2).

After that Py-CoMFA analysis was done and models were generated. The models were checked for their r^2 and q^2 values. The 3D QSAR contour maps were generated for visible representation and a better understanding of the results.

Statistical analysis: To interpret the 3D models generated in the study principal component analysis, regression analysis, regression coefficient (r^2) and cross validated r^2 (q^2) values, standard deviation error correction and standard deviation error prediction (represents the error committed by the model in predicting the data) were used.

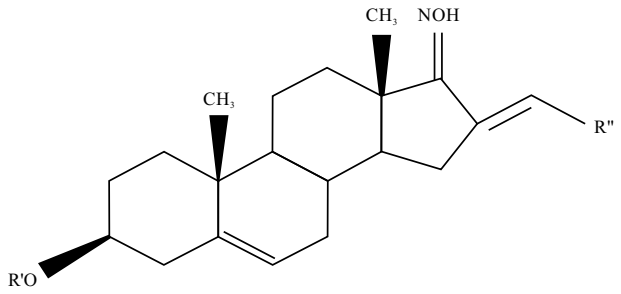

Fig. 1: A representative structure of various 16-substituted epiandrosterone derivatives chosen for the study

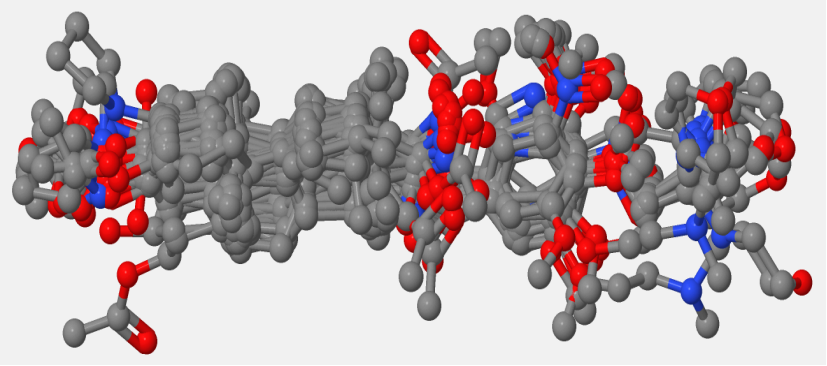

Fig. 2: Py-align model of 16-(substituted) dehydroepiandrosterone derivatives

RESULTS AND DISCUSSION

The selection of the CoMFA model is based on optimizing selection criteria based on the statistical results obtained. Hence, we selected the best fit CoMFA model PC-3 having r^2 = 0.892, SDEC = 0.002, SDEP = 0.017 and q^2 = 0.02 (Table 1 and Fig. 3-4). The 3D contour CoMFA model was depicted in Fig. 5. The green region represented the area that should be substituted by electropositive groups (E.g., CH_3, NH_2, CH_2CH_3 etc.) for better activity. Similarly, the yellow region represented the area that should be substituted by electronegative groups (E.g., CN^-, NO_2, OH^-, OCH_3 etc.) for better activity.

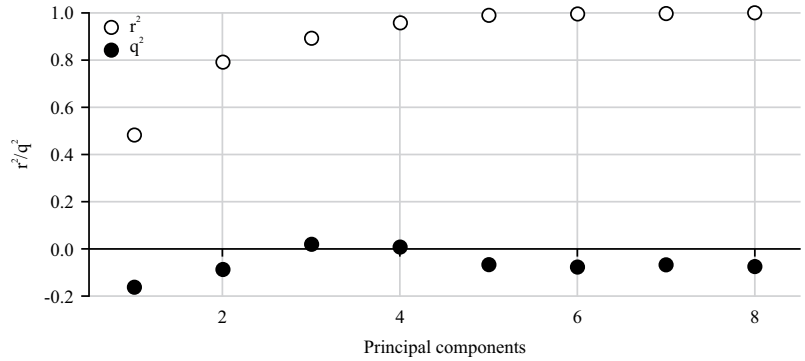

Fig. 3: Principal component analysis of the steroidal derivatives against r^2/q^2

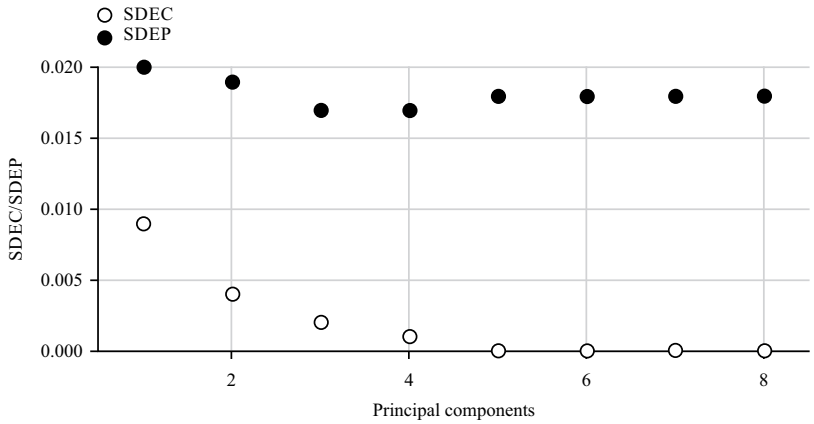

Fig. 4: Principal component analysis of the steroidal derivatives against SDEC/SDEP

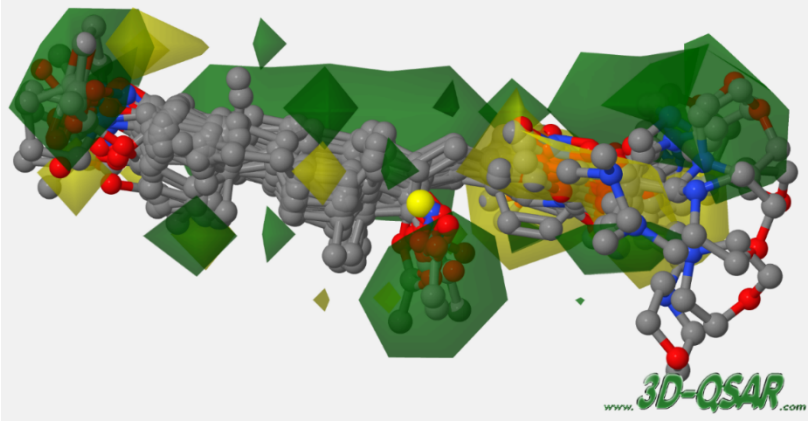

Fig. 5: 3D CoMFA model of 16-(substituted) dehydroepiandrosterone derivatives

Table 1: Statistical parameter of the CoMFA models

PC	Optimal PC	r^2	SDEC	q^2	SDEP
1		0.483	0.009	-0.16	0.02
2		0.79	0.004	-0.085	0.019
3	*	0.892	0.002	0.02	0.017
4		0.957	0.001	0.008	0.017
5		0.989	0.0	-0.066	0.018
6		0.995	0.0	-0.077	0.018
7		0.998	0.0	-0.066	0.018
8		1.0	0.0	-0.073	0.018

q^2: Parameter for strength and stability of the model, r^2: Regression co-efficient, PC: Principal component, SDEC: Standard deviation error correction, SDEP: Standard deviation error prediction-represents the error committed by the model in predicting the data

CONCLUSION

Steroidal derivatives are good molecules for designing anticancer molecules. Based on our CoMFA results obtained through the 3D QSAR platform. The introduction of electropositive groups at positions 11 and 14 and electro-negative groups at positions 3 and 16 in the steroidal ring were the recommendations of the study. This study can help in understanding the future directions for the various substitution to be made in steroidal rings to get more active molecules possessing CNS anti-cancer activity.

SIGNIFICANCE STATEMENT

This study signifies the possible potential of dehydroepiandrosterone derivatives as CNS anticancer agents This study was undertaken to correlate DHEA derivative's efficacy as CNS anticancer agents. With QSAR studies it was established that the substitution of electronegative groups at 16 positions is beneficial.

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