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Research Article

PHARMACOPHORE BASED 3D QSAR ANALYSIS OF A NEW CLASS OF HIGH-AFFINITY LIGANDS FOR ECDYSONE RECEPTORS FOR DEVELOPING POTENTIAL ANTI-CANCER AGENTS

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ABSTRACT

Ecdyson receptors are the members of a super family of nuclear hormone receptors and ecdyson-inducible mammalian expression system has been reported in human colon carcinoma cell line RKO. Ecdyson receptor ligand induce inhibition of non-contact inhibited cells, thus inhibiting growth of malignant tumor cells, which gives us enamel scope to use it as a therapeutic target against cancer. In our present study we have done ligand based pharmacophore modeling and 3D QSAR of 20 EcR receptor ligands using the Phase module of Schrödinger. We have also done the single point energy calculation of the molecules using the Jaguar module of Schrödinger. We have developed quite a statistically significant 3D QSAR model having r^2=0.82, q^2=0.53, Pearson r=0.84.This model will help us developing an antitumor agent and further docking study will help us to identify a potential lead with a novel mode of action. This present study indicates a new way to look at anticancer clinical research which may be successfully extrapolated in near future.

Keywords: Ecdyson receptor, 3D QSAR, PHASE, Pharmacophore Model.

INTRODUCTION

Ligand based 3D QSAR on the basis of pharmacophore alignment and molecular superimposition is an effective approach for optimizing molecules and for new drug targets insilico1. New antitumor agents with new protein targets are always very exciting for drug discovery scientists. It is possible, as we get to know more specific information about cancer biology through basic research on cell signaling, molecular genetics and proteomics.

Ecdyson receptor (EcR) is a member of a super family of nuclear hormone receptors. Its function is mainly to control growth, development and molting of the insects[2] and its ligands have been successfully used as effective insecticides against *L.cuprina,*and *B.ovis*[3, 4]. But most interestingly a property of this receptor made us think differently. The heterodimer of EcR is an ultra spiracle protein whose mammalian ortholog is retinoid X receptor(RXR),this property facilitated it to be used as gene expression controlling system based on GAL4 DNA binding domain,The expression was found to be very specific at nano dose levels[5, 6]. In contact inhibited cells like that of malignant tumor cell it has been reported to be connected to controlling the gene expression system related to apoptosis through contact inhibition. Also in another instance it has been reported to be controlling apoptotic behavior in human colon carcinoma cell line RKO, with reference to inhibition of Fas ligand- and TNF-related apoptosis-inducing ligand-induced apoptosis by muristerone A, which occurs at the level of caspase-8 activation[7].These information indicate that ecdyson receptor can be used as

an alternative therapeutic target for curing cancer.

In our present study, we have done 3D QSAR analysis of 20 c-methylene c-lactam ecdysone receptor ligands[4] to create a statistically significant PHASE model on the basis of their pharmacophore alignment which gives us an insight about a new way to think about a plausible answer to cure cancer, which still poses a threat to humans.

MATERIAL AND METHODS

The total experiment was carried out by using chemoffice 8.0 and Shordinger 9.1 molecular modeling software running over Windows OS. We have obtained a data set of 20 c-methylene c-lactam ecdyson receptor ligands from litarature[5]. The 2D structures were drawn using ChemDraw Ultra 8.0 software and then their 3D structure was produced using the Chem3D Ultra 8.0 software and biological activity data was taken as negative logarithmic format.

Using the Ligprep module of Schrödinger low energy conformation structure was generated and used to calculate the single point energy based on Density Field Theory and SCF calculations.

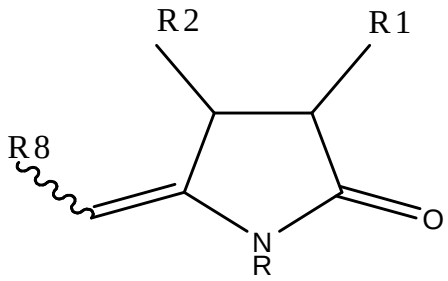
Energy calculated ligands were imported in PHASE[1] module for the development of Pharmacophore model. A large number of conformers were generated by Configen program and used to fiend and scoring of various sites like Hydrogen bond Acceptor (A) Hydrogen bond donor (D) Aromaticity (R) Hydrophobicity (H) etc. The best hypothesis AAHHR was selected on the basis of the fitness score and other relevant results like survival score, posthoc score and survival minus inactive score which ensure their feasibility.

On the basis of the pharmacophore hypothesis based alignment a 3D QSAR model was generated. By keeping 80% molecules of total set in training set (Table 1 and 2) and rest in test set (Table 2). The 3D QSAR model thus developed gave very statistically significant result when it was externally validated and crss validated using partial linear regression equations taking PLS factor 2.

RESULT AND DISCUSSION

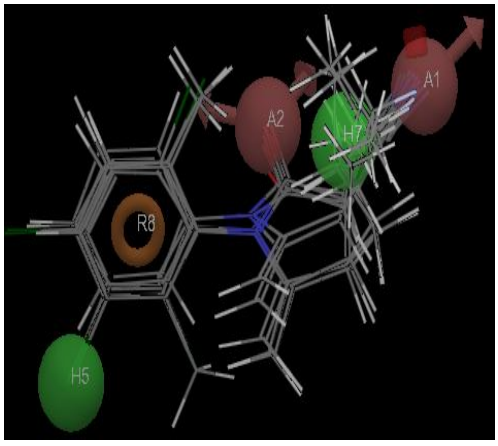
The PHASE pharmacophoric feature revealed the structural features of these compounds two acceptor site (A1 and A2), two hydrophobic site (H5 and H7) and one ring aromatic site (R) (fig 1) represent the crucial part for showing ECR binding affinity of highest active molecule. Among 87 hypotheses, AAHHR.65 hypothesis was selected and it can nicely describe the pharmacophoric features of all compounds (Table 3).

Fig. 1



This pharmacophoric features was used to align all the molecules (fig 2) for 3D QSAR analysis. The statistical result of the pharmacophore based 3D QSAR model was quite good and its external validation further proved it to be a statistically significant one (Table 4). The result at PLS factor 2 was SD = 0.13, R^2 = 0.94, Q^2 = 0.5, Pearson R = 0.78.Thus the developed model is a statistically relevant model which can add an edge to anticancer drug research for the development of potent anticancer agents.

Fig. 2



The QSAR result indicates electron withdrawing group and hydrophobic properties are important for ECR binding properties. The blue color indicates the positive effect and red colour indicate the negative effect and can be interpreated with the help of fig 1. In the highest active molecule 10 and 13 incorporation of strong electron withdrawing group at R^1 of position pyrrolidin-2-one (fig 3) will improve the activity. Substitution of hydrophobic group or bulky group at R^2 position may reduce the activity (fig 4).

Fig. 3

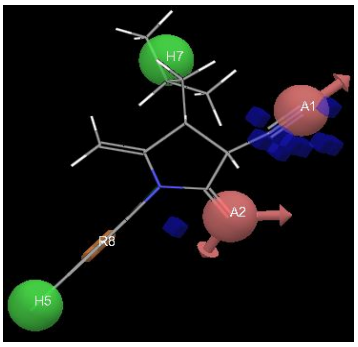
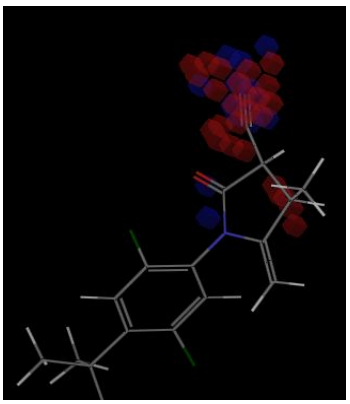


Fig. 4



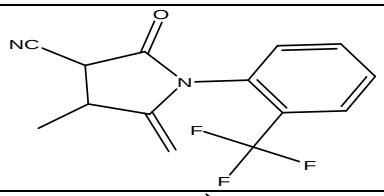
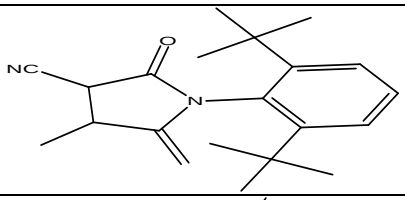
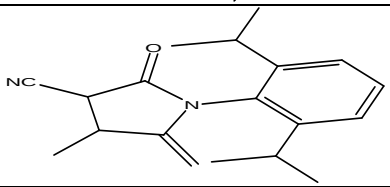
CONCLUSION

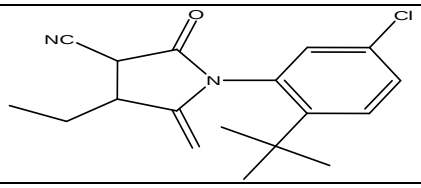
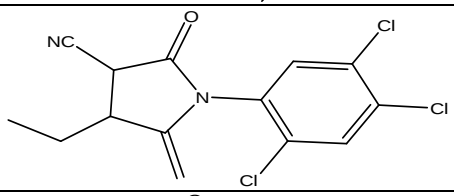
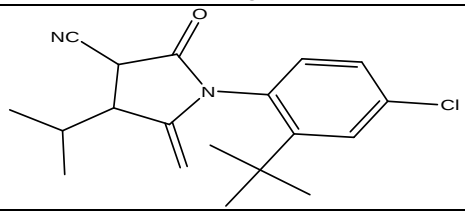
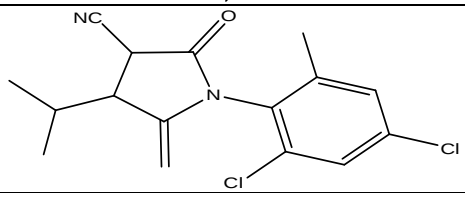
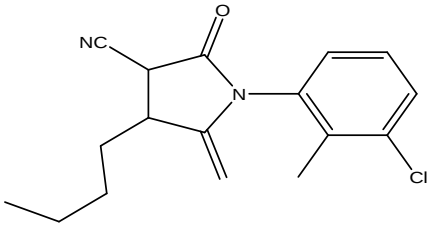
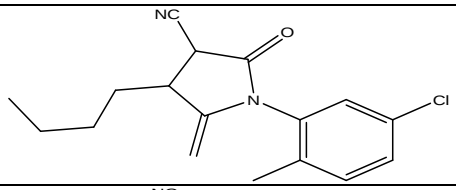
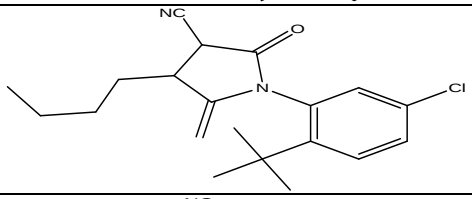
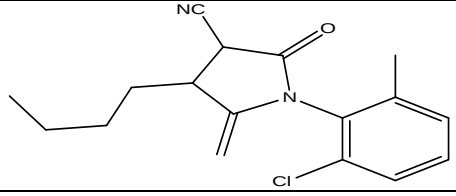
We have developed a statistically significant ligand based QSAR model. The model proven its superior predictive ability and can be use to develop more potent ECR binding ligands.

ACKNOWLEDGEMENT

We acknowledge Schrödinger LLC, Bangalore for providing there immense support to carry out the present work.

Table 1: Training set

S. No.	Compound ID	Compound Structure	Activity [pIC_{50}] *L.cuprina*	Predicted Activity
1	7		4.319	4.45
2	25		5.187	4.87
3	31		4.629	4.77

4	51		4.959	4.90
5	54		5.140	5.08
6	60		4.377	4.25
7	62		3.319	3.28
8	66		5.081	5.04
9	67		4.903	4.94
10	68		5.260	5.37
11	69		4.252	4.46

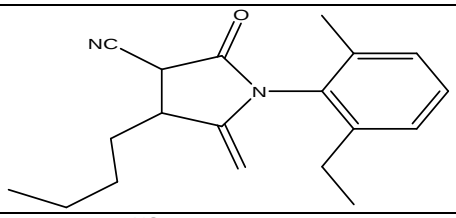
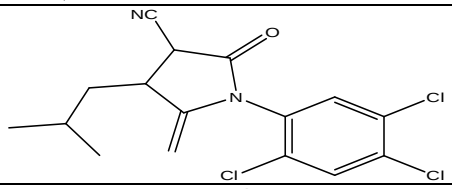
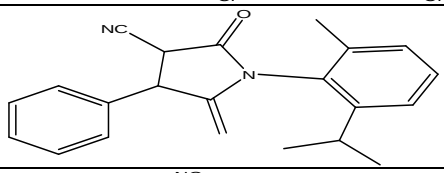
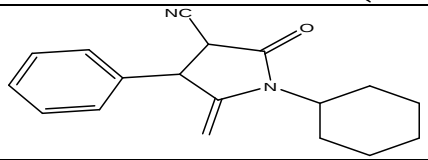
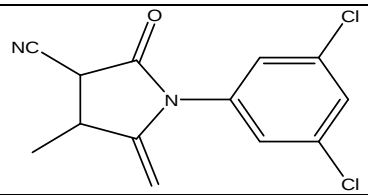
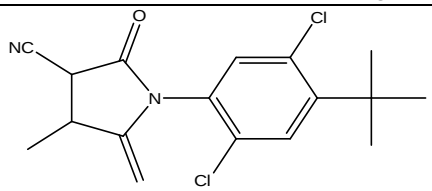
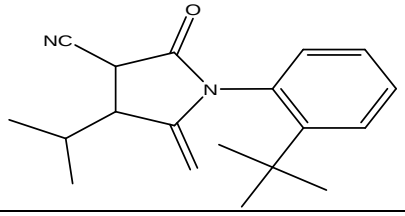
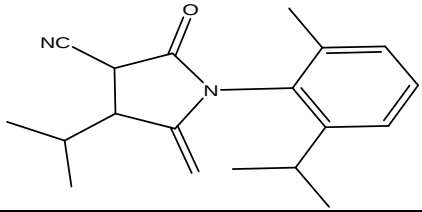
12	71		4.481	4.59
13	81		5.260	5.23
14	86		4.260	4.22
15	94		4.903	4.87

Table 2: Test Set

S. No.	Compound ID	Structure	Activity[pIC$_{50}$]	Predicted Activity
1	38		4.561	4.71
2	41		5.071	4.81
3	59		4.824	4.85
4	61		4.328	4.25

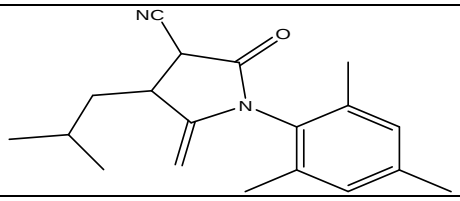
5	82		3.757	4.39

Table 3: Hypothesis Score

ID	Survival	Survival -inactive	Post-hoc	Site	Vector	Volume	Selectivity
AAHHR.11	3.123	1.337	3.123	0.51	0.952	0.665	1.79
AAHHR.59	3.094	1.476	3.094	0.55	0.959	0.59	1.815
AAHHR.62	3.029	1.318	3.029	0.52	0.928	0.585	1.801
AAHHR.61	2.991	1.235	2.991	0.44	0.922	0.63	1.773
AAHHR.65	2.99	1.546	2.99	0.46	0.957	0.57	1.825
AAHHR.64	2.973	0.481	2.973	0.37	0.933	0.669	1.817
AAHHR.66	2.925	0.64	2.925	0.43	0.935	0.559	1.827
AAHHR.63	2.822	1.109	2.822	0.37	0.929	0.522	1.81
AAHHR.9	2.807	1.198	2.807	0.4	0.923	0.487	1.841
AAHHR.10	2.807	1.198	2.807	0.4	0.923	0.487	1.841

Table 4: 3D QSAR Result

Hypothesis ID	PLS factor	SD	R-squared	Q-squared	Pearson-R
AAHHR.65	2	0.13	0.94	0.5	0.78

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