The 19th International Electronic Conference on Synthetic Organic Chemistry
Section: Computational Chemistry

Insight into the structural requirement for Anticancer Activity: Pharmacophore Generation and 3D QSAR Analysis

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Content

- Introduction
- Objective and Strategy
- Materials and Methods
- Results and Discussion
- Conclusion

INTRODUCTION

- **Cancer:**
  - Transforming growth factor β receptor-associated kinase 1 (TAK1) or mitogen activated-protein kinase kinase kinase 7 (MAP3K7)
  - It is serine/threonine kinase which forms a key part of canonical immune and inflammatory signaling pathways
  - Regulate expression of a large number of genes involved in immune and inflammatory responses, as well as in cell survival, proliferation, and differentiation
  - TAK1 inhibitors used in cancers with an inflammatory component, for example, ovarian and colorectal carcinomas, as well as in hematological malignancies

Computational Chemistry in Anticancer Drug Research

- Molecular modelling programs have been developed and widely used in the pharmaceutical and biological industry
- Pharmacophore modelling involves extracting common chemical features (hydrogen-bond acceptors, hydrogen bond donors, hydrophobic regions and positively or negatively charged groups) from 3D structures of a set of known ligands
- 3D QSAR analysis is performed for generating models which correlates biological activity with physico-chemical properties of the molecules
- A statistically significant 3D QSAR model helps in better understanding of structure activity relationship of a series of molecules and predicts the activity of yet to be synthesized compounds

OBJECTIVES AND STRATEGY

- Three-dimensional quantitative structure–activity relationships (3D-QSAR) models are used to analyze favorable and unfavorable pharmacophoric features of molecules which play a crucial role to mimic the interaction of ligands with a particular protein target
- The present paper reports 3D-QSAR analysis of set of 7-aminofuro [2,3-c]pyridine derivatives, reported by Hornberger K. R. *et al.* (2013) and intends to provide the platform to develop new compounds over existing substituted pyridines
- The calculated fields are correlated with experimental biological activity data
- Different color-coded contour maps surrounding the ligands give insights about favorable and unfavorable ligand–receptor interactions, and also used as guides for designing novel leads

MATERIAL AND METHODS

- The 3D-QSAR studies were performed using 54 molecules reported by Hornberger *et al.*
- Out of 54 molecules, **19** molecules were taken for the Test set and **35** molecules for Training set which was selected manually by considering activity variation present
- The dataset consists of both active and inactive molecules
- The study was performed using the PHASE 3.4 module of Schrodinger molecular modeling software for 3D-QSAR pharmacophore model developing

RESULTS AND DISCUSSION

- Different variant CPHs were generated by common pharmacophore identification process
- All CPHs were examined and scored to identify the pharmacophore that yields the best alignment of the active compounds (pIC_{50}> 6.2).
- All CPHs were validated by aligning and scoring the inactive compounds (pIC_{50}< 5.7).
- All top CPHs were used for atom-based 3D-QSAR model generation.
- The CPHs ADHRR.84 and ADHRR.651 yielded 3D-QSAR models with good PLS statistical values.

Table 1: Score of different parameters of the hypothesis ADHRR-84 and ADHRR-651

Parameter	Score	
	ADHRR-84	ADHRR-651
Survival	3.880	3.864
Survival-inactive	1.041	1.056
Post hoc	5.860	5.844
Site	0.97	0.95
Vector	1.000	0.999
Volume	0.908	0.911
Selectivity	1.869	1.971
Matches	17	17
Energy	0.00	17
Activity	6.602	6.602
Inactive	2.838	2.808

Table 2: 3D-QSAR statistical parameters for ADHRR-84 hypothesis

PLS factors	SD	r^2	F	P	RMSE	q^2	Pearson-R
1	0.4993	0.6342	57.2	1.059e-008	0.4367	0.5568	0.7895
2	0.3043	0.8682	105.4	8.297e-015	0.4071	0.6146	0.8027
3	0.2168	0.9352	149.1	1.679e-018	0.3423	0.7276	0.8684
4	**0.1705**	**0.9612**	**185.9**	**1.043e-020**	**0.297**	**0.7949**	**0.9093**

Table 3: 3D-QSAR statistical parameters for ADHRR-651 hypothesis

PLS factors	SD	r^2	F	P	RMSE	q^2	Pearson-R
1	0.5489	0.5578	41.6	2.569e-007	0.4776	0.4697	0.7878
2	0.3230	0.8515	91.8	5.566e-014	0.3918	0.6431	0.8247
3	0.2004	0.9446	176.3	1.463e-019	0.3436	0.7256	0.8884
4	**0.1431**	**0.9727**	**266.8**	**5.552e-023**	**0.2895**	**0.8051**	**0.9258**

- The training set correlation in both CPHs is characterized by PLS factors (R^2 = 0.9612, SD = 0.1705, F = 185.9, P = 1.043e-020, Q^2 = 0.7949 for CPH ADHRR.84 and R^2 = 0.9727, SD = 0.1431, F = 266.8, P = 5.552e-023, Q^2 = 0.8051 for CPH ADHRR.651).
- The CPH ADHRR.84 yielded a 3D-QSAR model with good value of regression coefficient, low standard deviation, and high variance ratio with good stability
- A pictorial representation of the cubes generated in the present 3D-QSAR is shown in Figs. 1 and 2
- In these generated cubes, the blue cubes indicate favorable features, while red cubes indicate unfavorable features for biological activity

Figure 1: Alignment of compounds using the 5-point pharmacophore hypothesis

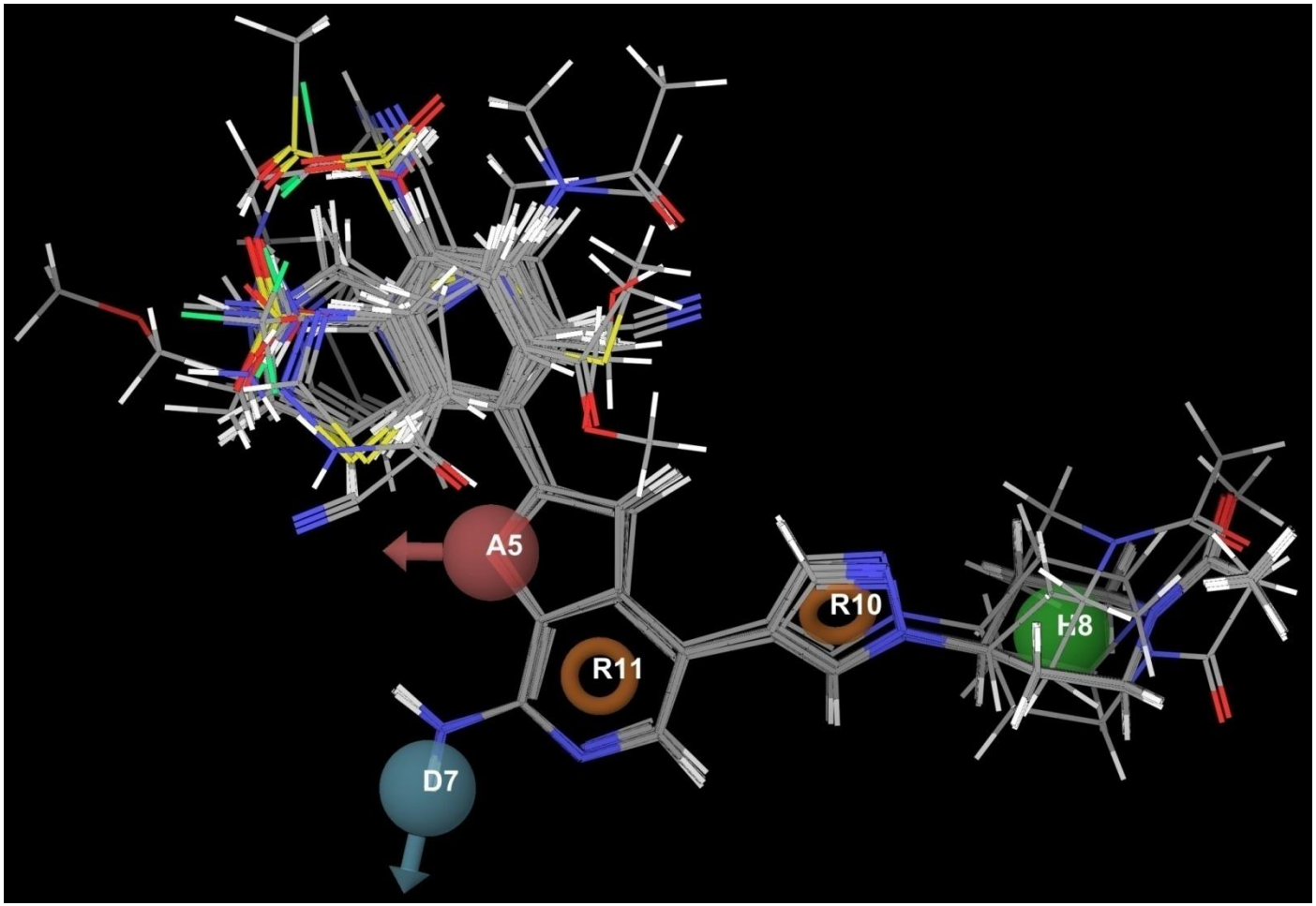


Figure 2: Alignment of active compounds using the CPH-651

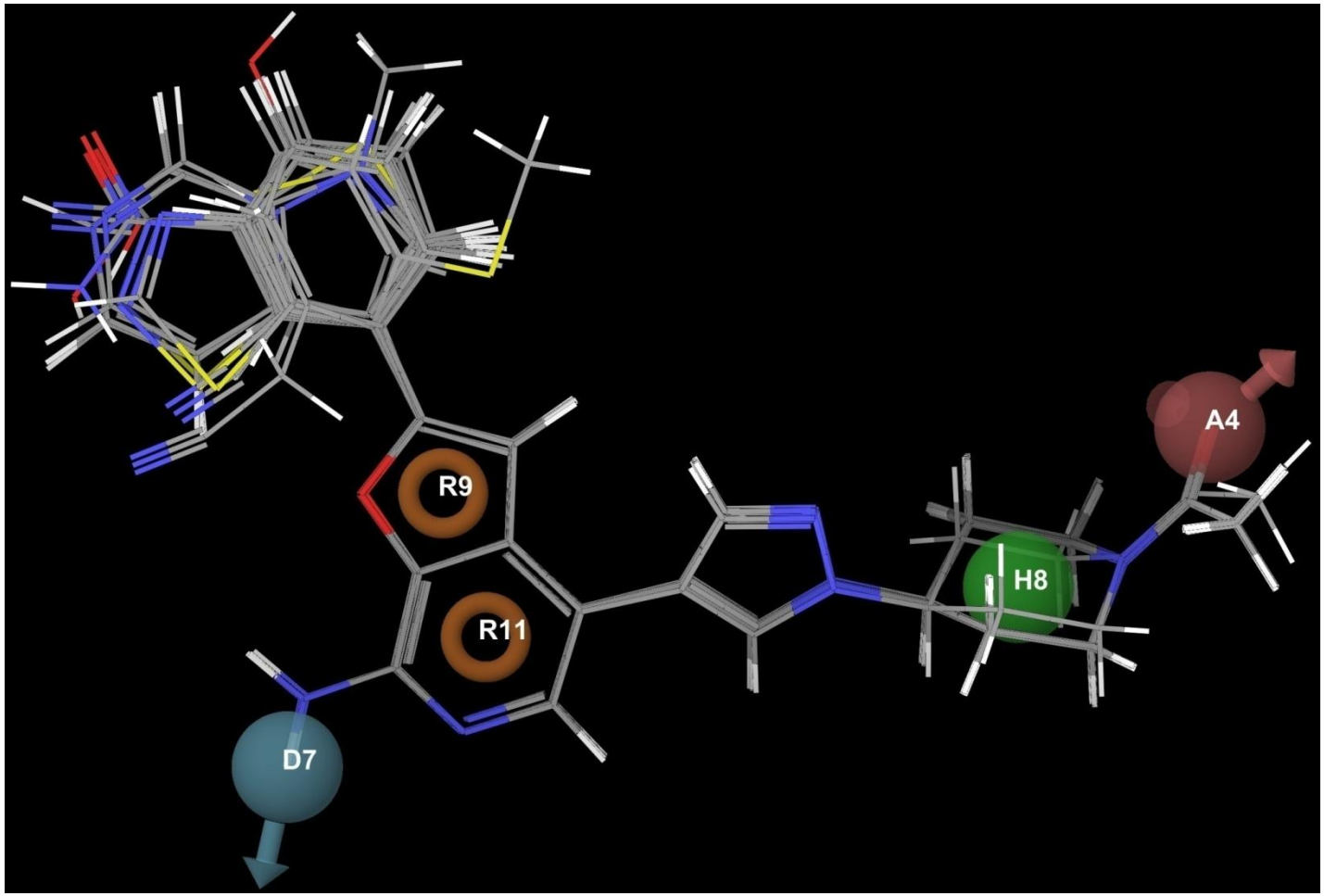


Figure 3: Plot of experimental versus predicted pIC_{50}values of compounds for A) CPH-84

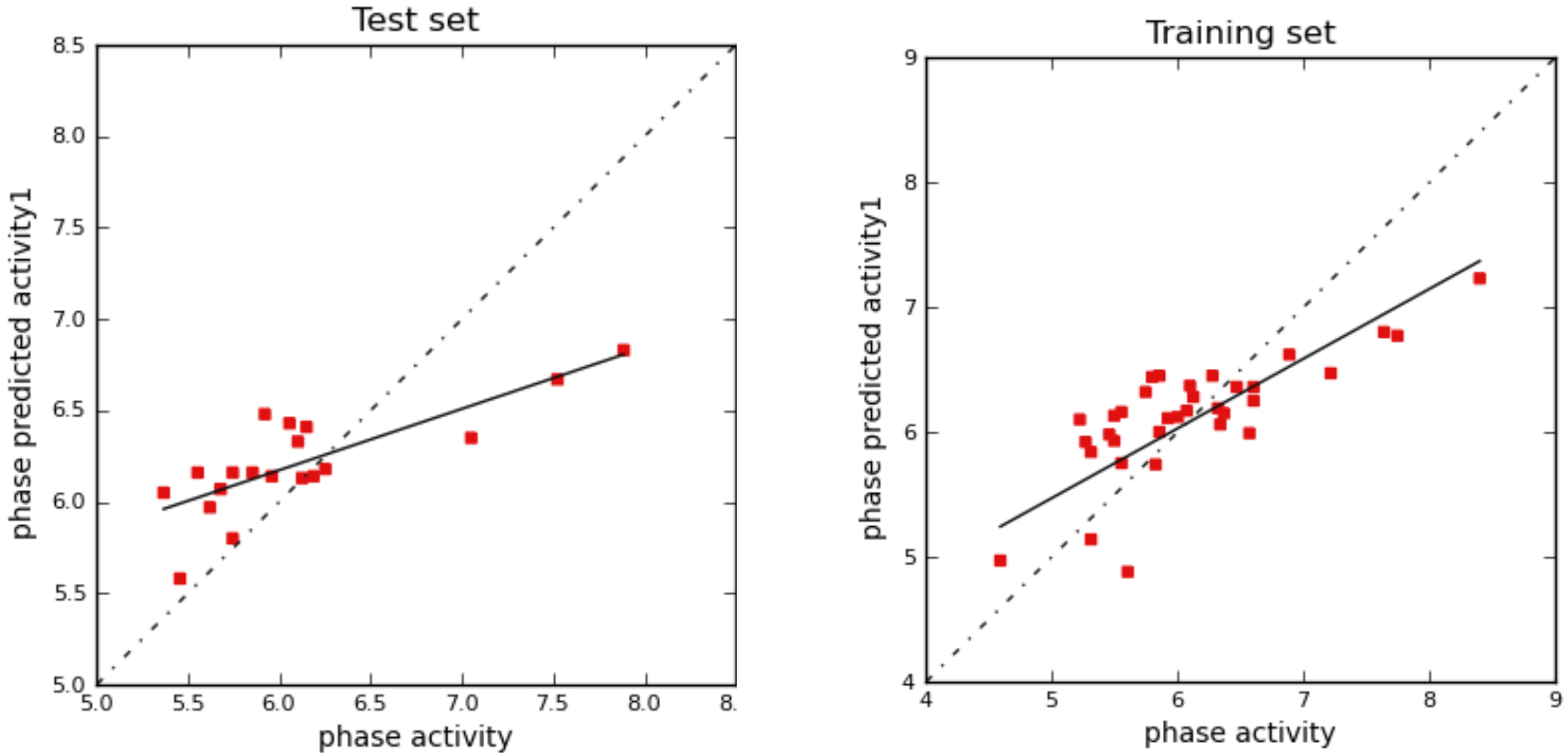
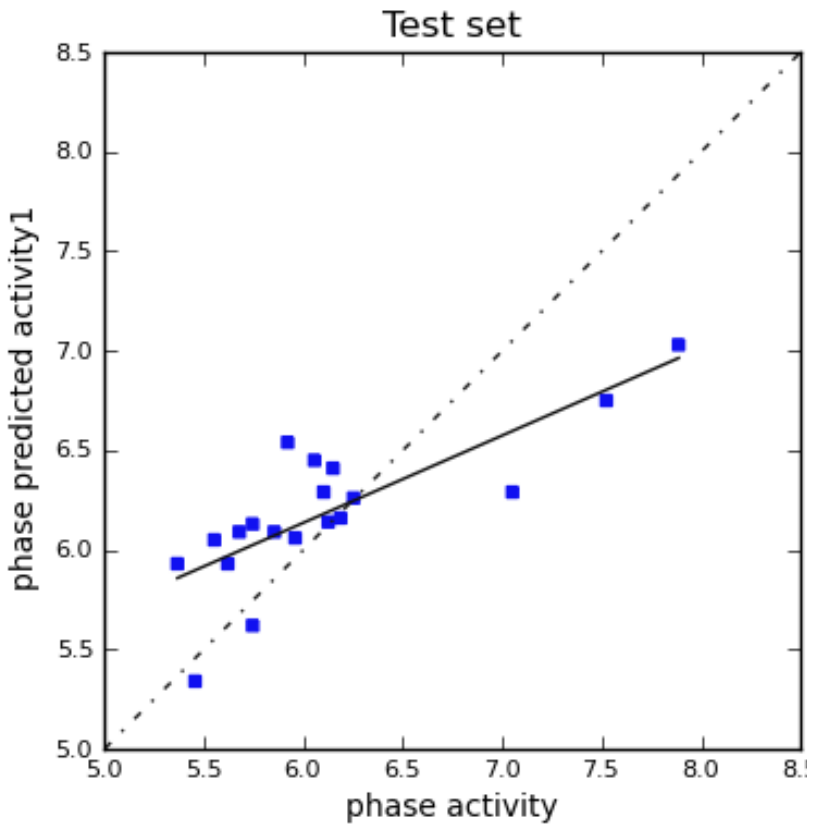


Figure 3: Plot of experimental versus predicted pIC_{50}values of compounds for B) CPH-651



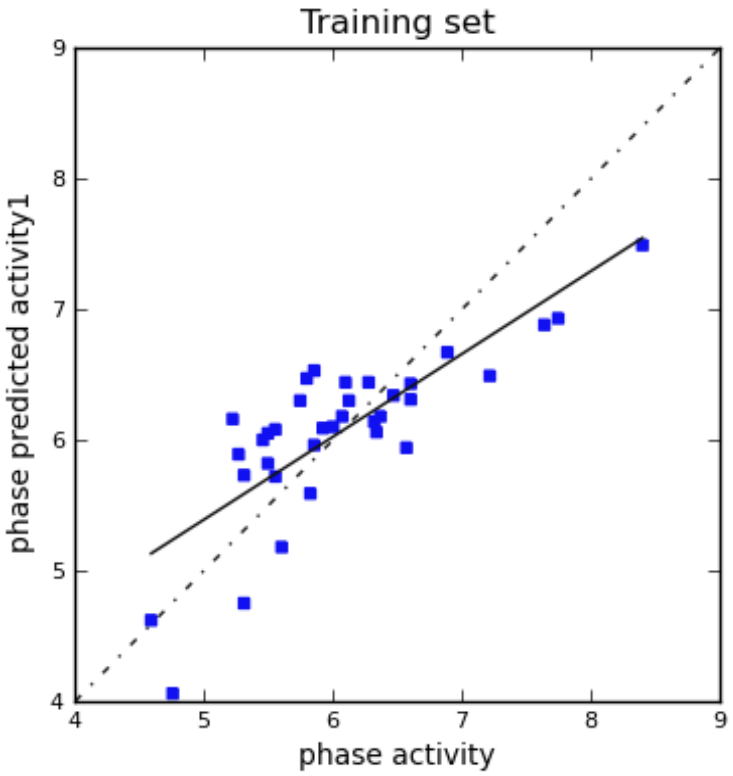
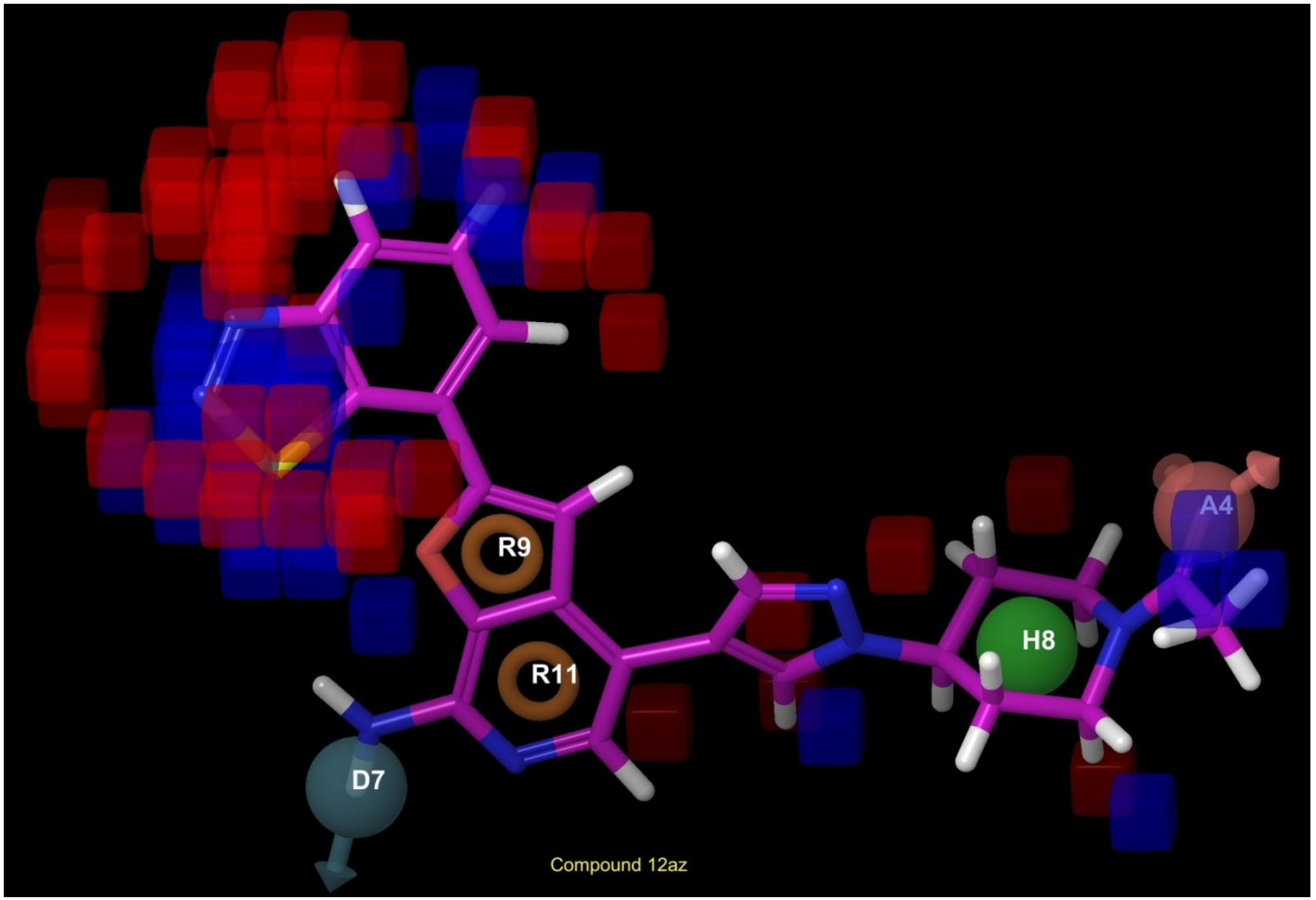
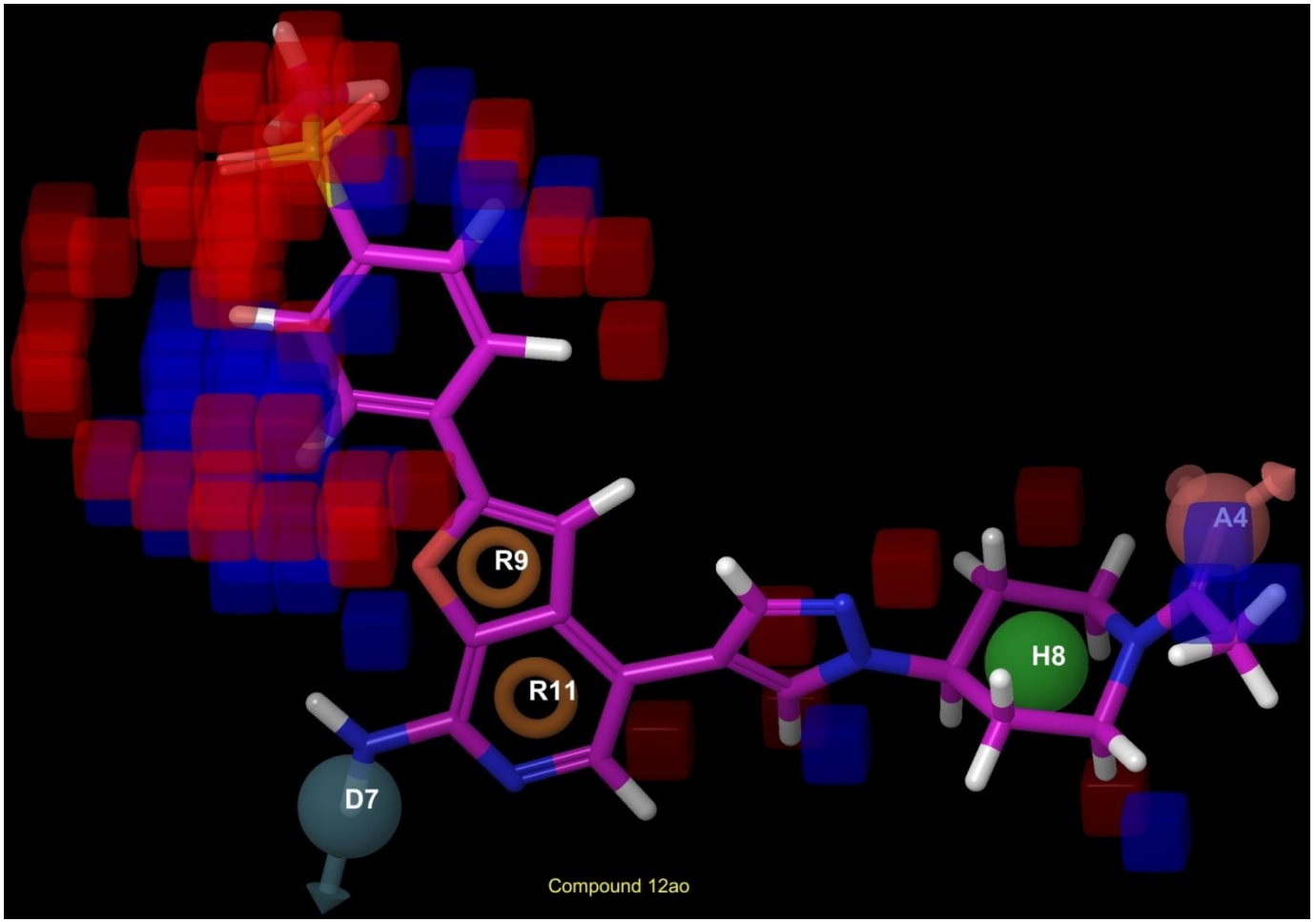


Figure 4: QSAR visualization of combined effect (blue cubes showing positive potential while red cubes showing negative potential of particular substitution) for CPH-651



Compound 12az

Figure 4: QSAR visualization of combined effect (blue cubes showing positive potential while red cubes showing negative potential of particular substitution) for CPH-651



Compound 12ao

CONCLUSIONS

- The goal of this study is to develop a model that facilitatesthe design of novel TAK1 inhibitors, for the treatment of cancer.
- Towards the end, a novel and unique pharmacophore is presented here based on 3D-QSAR modeling of pyrimidine derivatives, which is shown to have general applicability across several leads, clinical and pre-clinical candidates.
- The present study also explores the structure-activity relationships of TAK1 inhibitors using a pharmacophore based 3D-QSAR model and offers a rationale for their observed activities.
- Thus the proposed model offers a rationale for observed structure–activity relation-ships of this series of compounds, which can be incorporated for designing novel inhibitors of TAK1.

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