HQSAR studies of LSD1 allosteric inhibitors for anticancer therapy

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Introduction

Lysine-specific demethylase-1 (LSD1), a nuclear protein belonging to the amine oxidase family[1,2], plays a pivotal role in epigenetic regulation of gene expression by removing methyl groups from methylated lysine 4 of histone H3 (H3K4) and lysine 9 of histone H3 (H3K9) using flavin adenine dinucleotide (FAD) as a cofactor[2,3]. Over-expression of LSD1 was observed in several types of tumors[1-4] and was shown to promote tumor cell proliferation, migration and invasion[4]. Pharmacological LSD1 inhibition was also shown to result in growth inhibition of cancer cells[2,3]. Hence, LSD1 and histone H3K4 methylation have recently been established as cancer-selective epigenetic targets in cancer cells with pluripotent stem cell properties[2]. Although many LSD1 inhibitors have been reported, no quantitative structure-activity relationship (QSAR) was established so far. Therefore, the objective of this study was to build and validate predictive hologram QSAR (HQSAR) models of allosteric LSD1 inhibitors to aid in lead optimization of new anticancer agents.

Results and Discussion

In this study, 93 1,2,3-triazole-dithiocarbamate derivatives, synthesized and tested by Zheng et al. [1] as LSD1 allosteric inhibitors, were grouped in training (74 compounds) and test (19 compounds) sets in order to build and validate HQSAR models. IC_{50} values of dataset were measured under same experimental conditions, ranging from 0.39 µm to >125 µm. The models were developed employing the built-in HQSAR module available in the SYBYL-X 2.1.1 platform (Tripos Inc., USA). Initially, we tested 24 models only varying fragment distinction (considering atom, bonds, connections, hydrogen atoms, chirality and H-bond donor/acceptor). From the 5 models with highest leave-one-out q^2 values, we also built models varying the fragment size (from 1-4 to 9-12 atoms). Hologram lengths ranged from 53 to 401 bins. The test set was used for external validation of the 5 most robust models. The 2 models with highest external validation coefficients are shown in Table 1, both showing a good predictive capacity (r^2_{pred}). Figure 1 shows the contribution map generated to aid in the interpretation of HQSAR analysis.

Figure 1. (A) Contribution map from model 29 for the most active inhibitor (IC_{50}= 0.39 µm) and (B) Predicted versus experimental pIC_{50} for training and test sets, obtained from model 29.

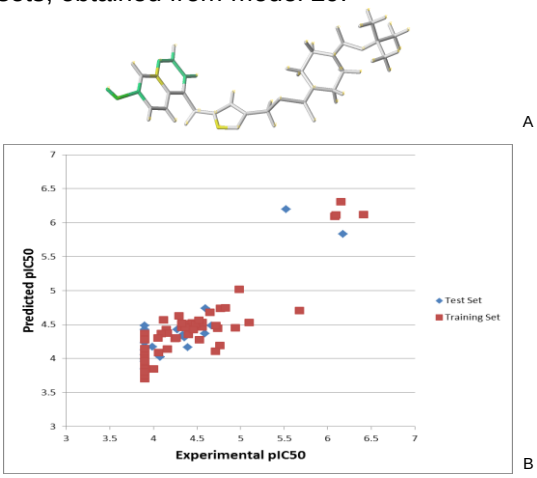

Table 1. Results from HQSAR analysis.

	Model 29	Model 42
Fragment Distinction	A/B	A/B/C
Fragment Size	5-8	9-12
q^2	0.690	0.699
Standard Error Validation	0.340	0.335
r^2	0.837	0.837
SEE	0.247	0.247
r^2_{pred}	0.801	0.718
Hologram Length	151	353

A: Atom, B: Bond, C: Connections

Conclusions

Contribution map for the best inhibitor shows substructures within the coumarin ring contribute positively for biological activity, with 7-OH being the best contributor. Results for model 29 showed optimal internal and external consistencies among the models studied, with high predictive capacity, being useful for lead optimization of LSD1 allosteric inhibitors.

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