

QSAR model for the IC₅₀ of pyrazolo[1,5-a]pyridines

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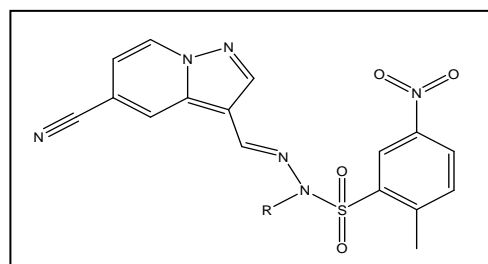
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Abstract: A part of the pyrazolo[1,5-a]pyridines as novel PI3K inhibitors. To build the quantitative structure activity relationships (QSAR) between the molecular structures and the inhibitory activities of 16 compounds, and to further discuss the structural factors that influence activity of compounds. The topological, constitutional, geometrical, electrostatic and quantum-chemical descriptors of 16 compounds were calculated by CODESSA, and these descriptors were preselected with the heuristic method (HM). As a result, the five descriptor linear model was developed to describe the relationship.

Keywords: Pyrazolo[1,5-a]pyridines as novel PI3K inhibitors; Heuristic method; Quantitative structure activity relationship

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1. Introduction

Phosphoinositide 3-kinases (PI3Ks) are a group of lipid kinases which can phosphorylate the 3 α -hydroxyl group of phosphatidylinositol diphosphate (PIP₂) to phosphatidylinositol triphosphate (PIP₃). PIP₃ then recruits protein kinase B (PKB, otherwise known as AKT) to the cell membrane where it is in turn phosphorylated and activated. PIP₃ leads leading to a cascade of cell signaling which controls a range of cellular processes like cell proliferation, growth and survival [1]. PI3Ks are often over-expressed, and the lipid phosphatase PTEN (which dephosphorylates PIP₃) is often deleted or inactivated in many cancer types, leading to increased levels of PIP₃ and increased tumor survival [2].

The PI3Ks are split into three sub-families (class I, II and III). Class I is further split into class Ia and Ib based upon their mechanism of activation. The class Ia PI3Ks are heterodimeric, consisting of a catalytic subunit 1PIK3CA, the gene encoding for p110 α , is often over-expressed and mutated in many cancer types. Two of the most common of these mutations (E545K and H1047R) have been commented as activating mutations and hence increase levels of PIP₃ [3]. Mutations of p110 β and p110 δ have not been reported [4, 5]. Inhibitors of PI3K, and in particular, selective inhibitors of p110 α could prove to be an important new strategy in cancer treatment.

We have shown previously that pyrazolo [1,5-a]pyridines such as 1 and 2 (Fig. 1) are potent and selective inhibitors of the p110 α isoform of PI3K. However, since the sulfonohydrazide central portion of the molecule is a known structural alert [6], we are interested in replacing this with an alternative linker group. This has been investigated to a limited extent by Hayakawa et al. [7]. with their related imidazo[1,2-a]pyridine series of compounds, however PI3K isoform selectivity data was not reported for all compounds.

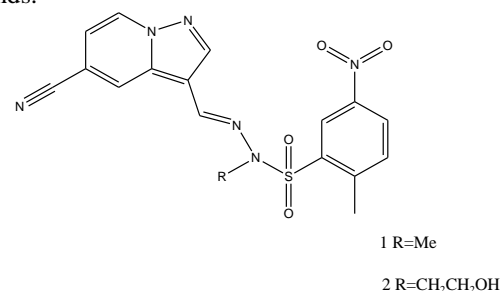


Figure 1. Structures of pyrazolo (1,5-a)pyridine PI3K inhibitors.

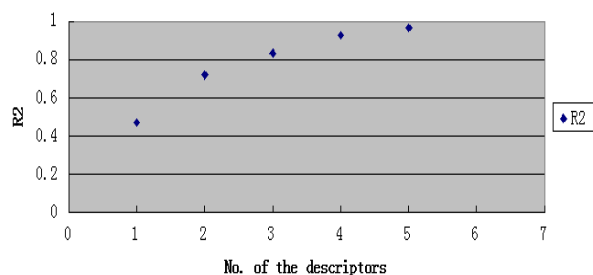


Figure 2. The Influence of the number of the descriptors on R2. Based on the Figure 1, it could be seen clearly that the best model included.

2. Methods

2.1. Data sets for Analysis.

In this study, According to the date of p110a and 60 of the 16 compounds was constructed using software chemoffice8.0. These 16 compounds have specific date. The 16 compounds: 1, 7, 16, 17, 40, 41, 48, 49, 51, 53, 54, 56, 57, 58, 59 and 60 separately. There data obtained from Codessa-2.63.

2.2. Molecular Modeling and Calculation of Molecular Descriptors.

In this work, all structures of 60 compounds were constructed using software chemoffice 8.0. According to the 60 compounds of IC_{50} (mM) nature, click from among the 60 compounds 16 respectively is saved as a SKC format. Open these 16 compounds by hyperchem 7. First, click Built-Add H & Model built. The compounds were added hydrogen and change configuration. Then, click Setup-Molecular Mechanics-MM+. Click Setup-Sema empirical-AM1 or PM3 (choosing PM3 when S and P in the compounds). Finally, choose Compute-Geometry Optimization. In the first time, RMS gradient of: 0.1 kcal or: several thousand maximum cycles, Click OK compound structure will change, to the lowest energy state changes. In the process, we need to constantly observe compounds to ensure that the compound key won't fracture. If the compound key has fracture, we need to solve the problem and play again. A few minutes late, when we say the Conv=Yes the Optimization of rough will finish. Then, Click Compute-Geometry Optimization again. RMS gradient of: 0.01 kcal or: several thousand maximum cycles. Repeat the above approach. When the Conv=Yes, Click File-Save As. Carried out in accordance with the compound number, 1-16 compounds was named, then keep the compound to ZMT and HIN format.

Open the document; there are three files in the document. Copy the MOPAC into this document. Open the file of ZMT In the first line of input AM1 VECTORS BONDS PIPOLAR PRECISE ENPART (If the compounds containing S, P elements) Open the MOPAC and input .ZMT. There will be three new files. Open the file of MNO. When MOPAC DONE is produced, then it calculate end. If not, the problem will

be found in this file. Creating a excel file, Fill in the table with the 16 compounds .hin and .mno save the path and name of the file (Save the path in the file name must be in English), willing excel file save as a text document. Using the HyperChem Release 8.0 software, all molecules were firstly optimized using the MM+ method, and then the final geometries of the minimum energy conformation were obtained using a more precise optimization. If there is "S" atom in the molecule, it was optimized with the PM3 method; if there is no, with the AM1 method [8]. After optimization, all structures were calculated by MOPAC program. Finally, the available data-exportation from HyperChem 8.0 (*.HIN files) and MOPAC (*.MNO files) to CODESSA 2.63 allowed us to account for a large set of molecular descriptors (constitutional, topological, geometrical, electrostatic, quantum-chemical and thermodynamic) for each of the compounds in this study [9].

2.3. The HM Linear Regression Model.

All descriptors of each compounds was calculated by CODESSA software. The best descriptors were screened by the heuristic method, which were used to build the linear regression model.

The heuristic method for descriptor selection proceeds with pre-selection of descriptors by eliminating those descriptors that are not available for each structure. Descriptors having a small variation in magnitude for all structures were founded according to the co linearity (one of any two descriptors with a correlation greater than 0.8 was removed to reduce redundant and useless information) [10]. Following the pre-selection of descriptors, the heuristic method was performed in a stepwise procedure. Thus, descriptors and correlations were ranked according to the values of the F-test and the correlation coefficient [11]. As the aforementioned method, we chose different number of descriptors for the model. With the number of descriptor increase, the correlation coefficient didn't change much (<0.2), we stopped [12]. Now, the best descriptor set was built by the descriptors.

3. Results and Discussion

3.1. Structures and Data Sets.

A total of 16 compounds and their active data were utilized from the text document. All of the Structures were constructed using software Chemoffice8.0. And their IC_{50} (mM)-p110a data.

3.2. The HM linear regression model.

The molecular descriptors for the given compounds were calculated using the software CODESSA. In CODESSA, a total of 526 different types of molecular descriptors were calculated to describe the structural diversity of the compounds, which include the topological, constitutional, geometrical, electrostatic and quantum-chemical descriptors. Then the best

descriptor sets were confirmed by the heuristic method (HM). To get the best descriptors, we measured the influence of the number of the descriptors on R2, and it is shown in Fig. 2.

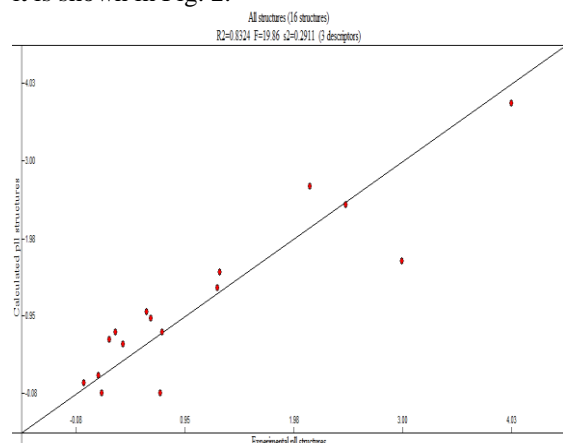


Figure 3. The calculated and the experiment values of IC50.

4. Conclusion

We built the regression model by the heuristic method, and get the molecular descriptors that mostly influence the activity of studied compound. The results showed that the most significant factors for activity of the compounds are geometrical and topological, including size and shape of the molecule. Our work will provide theoretical guide for the deep study of PI3K Inhibitors, and important model can be used in cancer drug research and development.

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