437m Solving the Inverse-Qsar Problem with Signature Using a Reduced System

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Quantitative structure-activity relationships (QSARs) are model equations that use descriptors to relate the structure of a molecule to a specific molecular property of interest. Plugging in the values of the descriptors for a given compound into the QSAR will give a prediction of the property for that compound. This process is recognized as the forward QSAR problem. [1] QSARs can be employed to refine the search for molecules matching a desired property in an existing database, but ideally one would like to examine potential compounds outside the database. Here we present a novel algorithm to do just that, which involves solving the inverse-QSAR (I-QSAR) problem [2] via a powerful molecular descriptor known as Signature. [3] Diophantine constraint equations are generated based on valence and consistency restrictions to solve the inverse problem. In our previous work with hydrofluoroethers (HFEs), the size of the compounds in the database was relatively small (10-30 atoms) and the inverse problem was easily solved. For larger compounds (50-100 atoms) and where the atom types vary, the number and complexity of the constraint equations increases greatly which makes solving those equations very challenging. In this work we present a method of reducing the Diophantine constraint equations and of generating linear combinations of the resulting basis vectors which is a key step in the arrival at a focused library of solutions. We explore this issue on a variety of problems we are working on including inhibitors for: γ-secretase, Dihydrofolate reductase, Candida Albicans and cyclo-oxygenase-II.