QSAR for the characterization of drug resistance: Differential QSAR (DiffQSAR) using mathematical chemodescriptors

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The most fundamental and lasting objective of synthesis is not production of new compounds, but production of properties.

Norris Award Lecture, 1968
George S. Hammond
MAJOR PILLARS OF QSAR
Good quality data
Adequately large databases
Relevant descriptors
Proper statistical methods
Hierarchical QSAR

- Biodescriptors
  - Relativistic ab initio
  - Solvation state ab initio
    - In vacuo ab initio
    - In vacuo semi-empirical
  - Geometrical / Chirality Parameters
    - Topochemical Indices
      - Topostructural Indices

Complexity

Cost
Blood: Air Partition Coefficient Model (TC) Developed on 39 Diverse Chemicals

Normal Boiling Point for 1015 Diverse Chemicals

\[ n = 1015, \quad R^2 = 0.97, \quad s = 15.7, \quad F = 4014 \]

Differential QSAR

QSAR of molecules acting on related bio targets to illuminate the differences in chemical-biological interactions.
Differential QSAR

Cycloguanil analogs as PfDHFR inhibitors

➢ Wild type vs
➢ Mutant type

• TIs and APs
• RR, PCR, PLS
• Low overlap of significant descriptors
Regression Results

Dependent variable = binding affinity

<table>
<thead>
<tr>
<th>Model</th>
<th>N</th>
<th>Descriptors</th>
<th>$q^2$, wild type</th>
<th>$q^2$, mutant type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>RR</td>
<td>PCR</td>
</tr>
<tr>
<td>1a 1b</td>
<td>58</td>
<td>TI</td>
<td>-0.617</td>
<td>0.123</td>
</tr>
<tr>
<td>2a 2b</td>
<td>58</td>
<td>TI + AP</td>
<td>0.631</td>
<td>0.212</td>
</tr>
<tr>
<td>3a 3b</td>
<td>57a</td>
<td>TI</td>
<td>0.674</td>
<td>0.231</td>
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<tr>
<td>4a 4b</td>
<td>57a</td>
<td>TI + AP</td>
<td>0.790</td>
<td>0.292</td>
</tr>
</tbody>
</table>

* Compound #22 excluded
Of the 20 descriptors with the highest [t ] values only two are common between the wild and resistant strains of plasmodium DHFR
QSAR to gauge biology

Characterization of Dihydrofolate Reductases from Multiple Strains of Plasmodium falciparum using Mathematical Descriptors of their Inhibitors

Subhash C. Basak, Denise Mills, and Douglas M. Hawkins, Chemistry and Biodiversity, 8, 440-453, 2011
Five strains of DHFR
Wild, mut 1, mut 2, mut 3, and mut 4

Quantify their pairwise differences based on the set of significant descriptors needed for QSARs of inhibitors
Conclusions

The subsets of influential descriptors needed for the various strains may be looked upon as high-dimensional pharmacophores based on a set of calculated descriptors which capture the distinct, but essential, chemical-biological interactions involving the inhibitors and various DHFR enzymes, one from the wild type Pf and the others from resistant varieties of the organism.
Conclusions

Alterations in the genetic makeup of organisms, including the malaria parasite Pf, various multi-drug resistant bacteria such as mycobacterium tuberculosis (MTb), viruses such as Hepatitis C virus [46], human immunodeficiency virus influenza virus are occurring continuously in nature because of their exposure to drugs, adverse conditions, and other evolutionary pressures.
Conclusions

The pair-wise kappa values in conjunction with macromolecules (enzyme or receptors) and structurally broad set of ligands for the respective biotarget(s) may be a useful tool in gauging the evolving mutual similarities/ dissimilarities of mutating organisms from a computational chemistry point of view.