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Does structural similarity reflect biological activity?

A general medicinal chemistry principle usually applied in drug discovery is that molecules with a similar structure have similar biological activity. Nowadays, the availability of large databases of compounds systematically tested in a high number of biological assays offers an opportunity to re-examine this principle from a larger perspective, and to quantify the relationship between chemical structure and biological activity.

Wallqvist and co-workers [1] have recently analyzed data from the National Cancer Institute (NCI) repository, concerning ~16,000 compounds screened in a panel of 60 *in vitro* tumour cell assays, measuring 50% growth inhibition concentrations (GI_{50}s). On one hand, all compounds were characterized by 2D descriptors, and the structural similarity for each pair of compounds was established by Tanimoto coefficient calculations. On the other hand, the GI_{50} data for each of the 60 cell lines was used to construct a data vector for each compound tested, and growth inhibition pattern similarity for each pair of compounds was determined by Pearson correlation coefficient calculations.

Surprisingly, only 12% of pairs with a Tanimoto coefficient of 0.8 or higher (that is, compounds with a high structural similarity) had a GI_{50} correlation coefficient of 0.8 or higher, thus demonstrating that structural similarity did not imply the same biological pattern for most pairs. Also, 63% of pairs with a GI_{50} correlation of 0.8 (that is, compounds with a highly similar growth inhibition pattern) had a Tanimoto coefficient <0.4, thus confirming that most of the selected pairs with the same biological mechanisms of action had poor structural similarity. These results illustrate the limitations of the similarity principle – at least at the level of the 2D chemical description of the compounds.

In addition, the authors show several examples about how the correlation of GI_{50} patterns can be used to establish more operational SAR for the purpose of medicinal chemistry work. These analyses were performed with the NCI's tumour screening panel, but the approach can be generalized to other screening panels in order to use biospectra analysis [2,3] to perform chemical design.

1 Wallqvist, A. *et al.* (2006) Evaluating chemical structure similarity as an indicator of cellular growth inhibition. *J. Chem. Inf. Model.* 46, 430–437

2 Fliri, A.F. *et al.* (2005) Biological spectra analysis: linking biological activity profiles to molecular structure. *Proc. Natl. Acad. Sci.* 102, 261–266

3 Fliri, A.F. *et al.* (2005) Biospectra analysis: model proteome characterizations for linking molecular structure and biological response. *J. Med. Chem.* 48, 6918–6925

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