[P6] Extraction of structure-activity relationship information from activity cliff clusters via matching molecular series

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Activity cliffs (ACs) are defined as pairs or groups of structurally similar compounds having large differences in potency. The vast majority of ACs are formed in a coordinated manner involving multiple analogs with large potency fluctuations, as opposed to isolated cliffs formed by compounds without structural neighbors. In network representations, coordinated ACs emerge as clusters. Coordinated ACs have higher SAR information content than isolated cliffs. However, AC clusters are difficult to analyze. Consequently, computational approaches are highly desirable for the systematic assessment of SAR information associated with AC clusters.

For SAR analysis of AC clusters, a computational methodology is introduced that utilizes the concept of matching molecular series (MMSs). An MMS is defined as a series of compounds that share the same core and are only distinguished by a chemical modification at a single site. Computational analysis reveals that there is an abundance of MMSs in AC clusters and that many MMSs share compounds. MMSs with shared compounds typically contain closely related structural cores and alternative substitution sites that often reveal SAR determinants and preferred substituents.

Bibliography:

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