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### Abstract

High-throughput screening (HTS) is the primary technique for new lead identification in drug discovery and chemical biology. Unfortunately, it is susceptible to false-positive hits. One common mechanism for such false-positives is the congregation of organic molecules into colloidal aggregates, which nonspecifically inhibit enzymes. To both evaluate the feasibility of large-scale identification of aggregate-based inhibition and quantify its prevalence among screening hits, we tested 70 563 molecules from the National Institutes of Health Chemical Genomics Center (NCGC) library for detergent-sensitive inhibition. Each molecule was screened in at least seven concentrations, such that dose–response curves were obtained for all molecules in the library. There were 1274 inhibitors identified in total, of which 1204 were unambiguously detergent-sensitive. We identified these as aggregate-based inhibitors. Thirty-one library molecules were independently purchased and retested in secondary low-throughput experiments; 29 of these were confirmed as either aggregators or nonaggregators, as appropriate. Finally, with the dose–response information collected for every compound, we could examine the correlation between aggregate-based inhibition and steep dose–response curves. Three key results emerge from this study: first, detergent-dependent identification of aggregate-based inhibition is feasible on the large scale. Second, 95% of the actives obtained in this screen are aggregate-based inhibitors. Third, aggregate-based inhibition is correlated with steep dose–response curves, although not absolutely. The results of this screen are being released publicly via the PubChem database.