IN BRIEF

LEAD IDENTIFICATION

Informative library design as an efficient strategy to identify and optimize leads: application to cyclin-dependent kinase 2 antagonists.

Bradley, E. K. *et al. J. Med. Chem.* **46**, 4360–4364 (2003).

The authors describe the application of a computational library-design strategy to the identification of cyclin-dependent kinase 2 (CDK2) antagonists, and show that it outperforms a lead-identification strategy commonly used in industry. Importantly, the dataset of 17,550 compounds and corresponding CDK2 activities used in this retrospective study has been freely released, which should facilitate further analysis to expand on these initial comparisons.

ANTIVIRAL DRUGS

PA-457: a potent HIV inhibitor that disrupts core condensation by targeting a late step in Gag processing.

Li, F. *et al. Proc. Natl Acad. Sci. USA* 22 Oct 2003 (doi:10.1073/pnas.2234683100).

Anti-HIV therapies with new mechanisms of action are desirable as they might be more likely to be active against the growing proportion of virus strains that are resistant to all the main classes of current drugs. Li *et al.* characterized the anti-HIV drug candidate PA-457, and showed that it inhibits HIV-1 replication by a previously unidentified mechanism — disrupting virus maturation — thereby providing further opportunities for anti-HIV drug discovery.

HIGH-THROUGHPUT SCREENING

A specific mechanism of non-specific inhibition.

McGovern, S. L. *et al. J. Med. Chem.* **46**, 4265–4272 (2003).

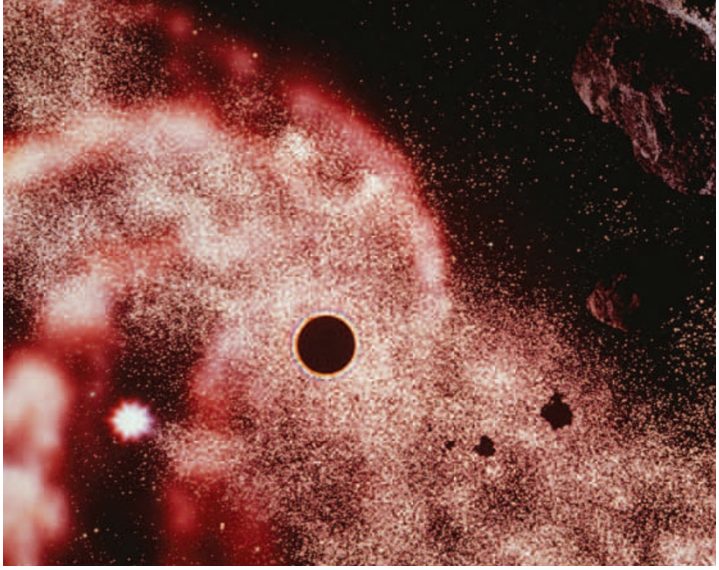
Previous research by McGovern, Shoichet and colleagues has shown that some 'promiscuous hitters' in high-throughput screening assays — compounds that inhibit many different enzymes and are therefore unlikely to be good starting points for drug discovery — form submicrometre aggregates. The authors now provide evidence that aggregates formed by promiscuous hitters reversibly sequester enzymes, resulting in apparent inhibition, and suggest a simple method involving the addition of detergent to identify or reverse the action of aggregate-based inhibitors.

ANTIBACTERIAL DRUGS

A new class of bacterial RNA polymerase inhibitor affects nucleotide addition.

Artsimovitch, I. *et al. Science* **302**, 650–654 (2003).

RNA polymerase (RNAP) is the central enzyme in gene expression. Artsimovitch and colleagues identified and characterized a new class of bacterial RNAP inhibitor that does not inhibit human RNAPII, which — in combination with available crystal structures of bacterial RNAPs — could form a promising basis for the rational design of drugs that specifically target the main classes of bacterial pathogens.



COMBINATORIAL CHEMISTRY

New directions in chemical space

Generating libraries of small molecules that possess a high degree of structural diversity is important for maximizing the chances of finding active compounds in screening programmes. A frequently used method for creating molecular diversity is to attach a large number of different building blocks to a common molecular skeleton, which can be efficiently achieved using established combinatorial chemistry approaches. But although these building blocks can be highly diverse, the way in which they are displayed in three-dimensional space — and therefore their potential to be complementary to the three-dimensional surface of a protein target — is limited by the fact that the molecules share the same skeleton. So, what is needed to address this issue are ways to efficiently generate diversity in molecular skeletons. Stuart Schreiber and colleagues now describe just such a strategy in the 24 October issue of *Science*.

The key to highly efficient generation of diversity in attached building blocks is a technique known as split–pool synthesis. This combinatorial chemistry approach, in which multiple substrates are transformed simultaneously under a common set of reaction conditions, can produce all possible combinations of a given set of building blocks attached to a common skeleton in the fewest steps. To achieve an analogous goal with molecular skeletons, the authors identified 'skeletal information elements' — sets of appendages on a special latently reactive common skeleton that react with the skeleton itself under a common set of conditions to give defined products with different skeletons.

The authors then demonstrated the potential of their combinatorial skeletal-diversity strategy in tandem with conventional combinatorial building-block variation using split–pool synthesis. A 1,260-compound library representing all possible combinations of six skeletons, derivatized at two separate sites with seven and fifteen different building blocks, respectively, in both enantiomeric and diastereomeric forms ($6 \times 7 \times 15 \times 2 = 1{,}260$) was produced in just five steps. The next step is systematic biological screening of this library to clarify the role of the three diversity elements — skeletal, building-block and stereochemical — in small-molecule–protein interactions. It will be interesting to see how the hit rate is influenced by the skeletal diversity in particular.

Peter Kirkpatrick

References and links

ORIGINAL RESEARCH PAPER Burke, M. D., Burger, E. M. & Schreiber, S. L. Generating diverse skeletons of small molecules combinatorially. *Science* **302**, 613–618 (2003)