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Spotlights on Recent *JACS* Publications

A TWISTED APPROACH TO SCREENING DRUG CANDIDATES

Molecular rotors are best known for their utility as viscosity sensor probes, owing to their inherent sensitivity to changes in their environment. Although previously unexplored, these same properties also enable this class of fluorophores to assist in drug discovery, according to a new report from Yin Nah Teo, Farid Ghadessy, and co-workers. (DOI: 10.1021/ja413031h).

The team has designed a molecular rotor-based probe, JP1-R, which in free solution relaxes via the rotational relaxation pathway, not fluorescence. However, when JP1-R is bound to its protein target, Mdm2, the molecule's conformation is constrained, which prevents rotation, resulting in a turn-on in fluorescence signal. Using an assay based on this system, the researchers have screened 352 molecules and have identified 15 small-molecule inhibitors that potentially disrupt interactions between Mdm2 and p53, a well-studied tumor suppressor protein. Importantly, seven of these candidates would have been missed had they been screened using the more traditional fluorescence anisotropy technique. This report is the first to demonstrate the utility of molecular rotors in drug-screening applications.

Christine Herman, Ph.D.

FAST, FAIR, AND ALL-NATURAL

Bioorthogonal functional groups, like the azides and alkynes that mediate "click" chemistry, are powerful tools for organic chemists and biochemists alike. But most such combinations either require a large excess of one reaction partner or generate "unnatural" chemical linkages. Now Jeffrey Bode and colleagues describe an alternative strategy that addresses those limitations (DOI: 10.1021/ja5018442).

The new approach generates a natural amide bond between equal amounts of a hydroxylamine and a potassium acyltrifluoroborate (KAT). Broad functional group tolerance means that both of these compounds can be linked to a wide range of molecules of interest. For example, mixing a hydroxylamine-containing drug compound with a fluorophore-functionalized KAT in the presence of oxalic acid in aqueous solution results in a tagged molecule that could be used in bioimaging studies.

The authors identify a hydroxylamine group that is stable during peptide synthesis. It reacts with KATs rapidly and specifically in equimolar amounts in the presence of unprotected amino acid side chains. The researchers use the reaction to couple a lipid, biotin, PEG, and a fluorescent dye to a 31-amino acid peptide containing a hydroxylamine-modified alanine residue, yielding >90% product at 1 mM in 10 min at room temperature.

"The KAT ligation offers a natural-bond forming ligation fast enough (20 M^{-1} s^{-1}) for synthetic approaches to protein engineering, biomolecule conjugates, functional polymers, and the formation of oligomers of complex molecules," the authors conclude.

Jeffrey M. Perkel

A "SWEET" TARGET IN FOUR STEPS

Pentoses, a class of saccharides containing five carbons, are essential building units found in a wide variety of biomolecules, especially as nucleosides in DNA, RNA, and ATP. This extensive biological relevance renders pentose derivatives as highly sought-after targets for synthetic chemists. Despite the vast natural abundance of pentoses, their selective modification remains a challenge due to similar reactivity among the four hydroxyl groups.

David MacMillan and co-workers build on their earlier convenient approach to readily modifiable protected hexoses with a counterpart reaction applicable to pentoses (DOI: 10.1021/ja502205q). The strategy starts with two stereoselective reactions that furnish all chiral centers, followed by a cyclization and reduction sequence.

This protocol allows for installation of desired substituents and protecting groups before constructing the pentose cores from these functionalized fragments, instead of often tedious and inefficient direct modification of natural sugars. As a powerful and concise way to prepare pentose-based molecules, this method represents a promising toolbox for constructing large and diverse collections of interesting pentose-derived intermediates, such as α- and β-*C*-nucleosides, with well-defined stereochemistry and modularity.

Xin Su, Ph.D.

ENVISIONING AN IDEAL SPINTRONIC MATERIAL

An electron is more than a negative charge. Electrons also have spin, and while we thank electron spin for magnetism, the electron's magnetic moment is not always exploited in electronic devices. Spintronic devices aim to utilize both electron charge and spin for applications that include high-density memory, logic devices, and lasers.

In the world of spintronics, materials called half-metal ferromagnets are ideal. In these materials, only electrons that spin a certain way are free to conduct. These materials act like a conductor to electrons of one spin direction, but as semiconductors to those of the opposite spin direction.

Jinlong Yang and colleagues predict what kind of material would make an ideal half-metallic ferromagnet (DOI: 10.1021/ja412317s). Electron spin in such a material would not be easily perturbed by thermal jostling, would be strongly magnetic, and would maintain the separation between conductive and nonconductive electrons. No material candidate has yet fulfilled all requirements.

The team proposes a theoretical alloy that contains lanthanum, arsenic, manganese, zinc, and oxygen, but with atomic substitutions to increase or decrease conductive electrons. The researchers note that other similar compounds could also possess such attractive electronic and magnetic properties in parallel, which together could generate a new class of materials for spintronic and electronic devices.

Jenny Morber, Ph.D.

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STACKING UP TO UV LIGHT

Nucleobases—the basic building blocks of DNA—strongly absorb UV light and in turn form excitons, which have the potential to damage DNA and lead to skin cancer. A thorough understanding of how DNA dissipates the excess energy from absorption of UV light is needed to gain insight into the initial mutagenic events. Jinquan Chen and Bern Kohler use the femtosecond transient absorption (TA) technique to reveal how base stacking influences UV-excited states in single strands (DOI: 10.1021/ja501342b).

Adenosine dimer is a simplified model for a single strand with strong $\pi-\pi$ stacking between bases. The researchers show that five adenosine dimers with different backbones adopt stacked conformations that retard the dissipation of unwanted energy to a similar degree. The slow decay channel arises when the bases are in orbital−orbital overlap regardless of the precise stacking conformation.

The authors also note that femtosecond TA can accurately diagnose base stacking even when the bases fail to show a preference for right- vs left-handed arrangements. The knowledge obtained in this study reveals opportunities for improvements to molecular dynamics simulations in this area, and helps to shape the experimental methodology and mechanistic understanding behind DNA photochemistry.

Hui Jin, Ph.D.

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