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Spotlights on Recent *JACS* Publications

HALOGENS SHINE NEW LIGHT ON DRUG DISCOVERY

Halogens, which include the elements chlorine, bromine, and iodine, have unique properties that can favorably influence how molecules interact with one another. However, halogens are markedly under-represented in fragment-based lead discovery, an increasingly popular drug discovery strategy in which collections of small chemical fragments are screened against targets of interest to help identify compounds with desirable biological activity to serve as starting points in drug development.

Frank Boeckler and co-workers now describe the design of halogen-enriched fragment libraries, referred to as HEFLibs, to discover compounds that can activate a mutated form of the protein p53 (DOI: 10.1021/ja301056a). p53 normally works to prevent tumor formation, but mutations can destabilize and inactivate it, leading to the development of numerous types of cancer. Compounds that can reactivate the mutated protein have tremendous potential as anti-cancer agents. Using the HEFLibs, iodine-containing compounds were discovered that could bind to the p53 cancer mutant, facilitating its stabilization and reactivation. Indeed, when tested in cancer cells, the compounds induced cell death, supporting their ability to restore the function of p53.

The p53-targeting compounds identified in this study are exciting starting points for new anti-cancer drugs. Importantly, they also highlight the potential of HEFLibs as a general strategy for discovery of novel lead compounds for a wide variety of drug targets. **Eva J. Gordon, Ph.D.**

ELUSIVE TWO-COORDINATE, ACYCLIC SILYLENE IS CAPTURED

In two back-to-back papers, the research groups of Simon Aldridge and Philip Power describe the first examples of stable acyclic silylenes. Silylene, the silicon analogue of carbene, has eluded capture since chemists first observed it transiently decades ago. Scientists had previously managed to isolate silylenes in cyclic systems or with increased coordination numbers, but the two-coordinate, acyclic silylene, SiR_2, has not been isolated until now.

Aldridge and co-workers synthesized a silylene, Si{B-(NDippCH)$_2$}{N(SiMe$_3$)Dipp}, featuring bulky boryl and amido substituents, that is stable up to 130 °C as a solid (DOI: 10.1021/ja301042u). This silylene readily undergoes an oxidative addition reaction with dihydrogen below room temperature to produce a dihydrosilane. Mechanistically, the silylene appears to behave similarly to transition metal systems in reactions with dihydrogen. Power and co-workers isolated another monomeric, two-coordinate silylene (DOI: 10.1021/ja301091v). They synthesized silicon dithiolate, $Si(SAr^{Me_6})_2$, which has thermal stability up to 146 °C. This silylene is unreactive with dihydrogen under ambient conditions, but it does react with methyl iodide to produce iodomethyl bisthiolatosilane.

These two research groups have demonstrated that two-coordinate, acyclic silylenes can be stable and useful in chemical reactions leading to the activation of small molecules. Transition metal compounds are popularly used to react with small molecules, but silylenes may offer a metal-free alternative. Further work could expand the synthetic repertoire of silylenes. **Yun Xie, Ph.D.**

METHOD EXPLORES CATCH-AND-RELEASE PROPERTIES OF PROTEIN-CONJUGATED SMALL MOLECULES

A new method for reversibly attaching small molecules to serum proteins could lead to the development of improved drug delivery systems. With the goal of developing a method for attaching small molecules to proteins in a reversible manner, researchers led by M. G. Finn looked to an electrophilic class of compounds, known as oxanorbornadienes (DOI: 10.1021/ja301491h).

The compounds used in the study are reactive toward thiol and amine groups, such as those present in serum proteins that abound in the bloodstream. After forming a covalent attachment, the protein−small molecule conjugate is stable for a time until it undergoes reverse-Diels−Alder fragmentation to release the small molecule. By analyzing the properties of 30 model compounds under simulated physiological conditions, the team found that the release profile can be tuned by altering the composition of the electrophilic linker.

The results of this study may help inform the design of future protein-conjugated small-molecule therapeutics. Similar catch-and-release drug delivery systems have the potential to increase the efficacy of therapeutics by extending their lifetime in the bloodstream and enabling the compound to be released over time. **Christine Herman, Ph.D.**

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