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Electrophilic natural products: friends or foes in natural products drug discovery?

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Over the past years, the clinical relevance of covalent modification of druggable proteins by small molecules has been extensively debated within the medicinal chemistry community [1]. Covalent modification underlies the activity of successful drugs, as exemplified by aspirin, penicillin, and modern blockbusters like Pravacid, Nexium and Plavix. Nevertheless, there is still a rooted bias against covalent drugs, dismissed as "library polluters", irrespective of the mechanism by which they ultimately bind to biomolecules. Because of concerns over non-specific toxicity and lack of selectivity, the Michael acceptor motif is rarely introduced in drug leads by design. Paradoxically, our diet is instead rife with Michael acceptors, and food plants provide countless leads to investigate the biological role of Michael reactivity in a molecular context substantially devoid of toxicity, at least at dietary dosages, and therefore of potential pharmaceutical relevance. To capitalize on this opportunity, we have developed an NMR assay (the cysteamine assay) that can identify the reactive sites in electrophilic natural products, rank them in terms of reactivity, and distinguish between transient and non-transient thiol trapping properties [2]. The application of the cysteamine assay to various classes of bioactive natural products will be presented, critically evaluating the information provided by the assay.

References

[1] Newman DJ, Cragg GM. *J Nat Prod*. 2007; 70:461-77.
[2] Avonto C et al. *Angew. Chem. Int. Ed*. 2011; 50:467-471.