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Mapping proteome-wide interactions of reactive chemicals using chemoproteomic platforms

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A large number of pharmaceuticals, endogenous metabolites, and environmental chemicals act through covalent mechanisms with protein targets. Yet, their specific interactions with the proteome still remain poorly defined for most of these reactive chemicals. Deciphering direct protein targets of reactive small-molecules is critical in understanding their biological action, off-target effects, potential toxicological liabilities, and development of safer and more selective agents. Chemoproteomic technologies have arisen as a powerful strategy that enable the assessment of proteome-wide interactions of these irreversible agents directly in complex biological systems. We review here several chemoproteomic strategies that have facilitated our understanding of specific protein interactions of irreversibly-acting pharmaceuticals, endogenous metabolites, and environmental electrophiles to reveal novel pharmacological, biological, and toxicological mechanisms.

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Introduction

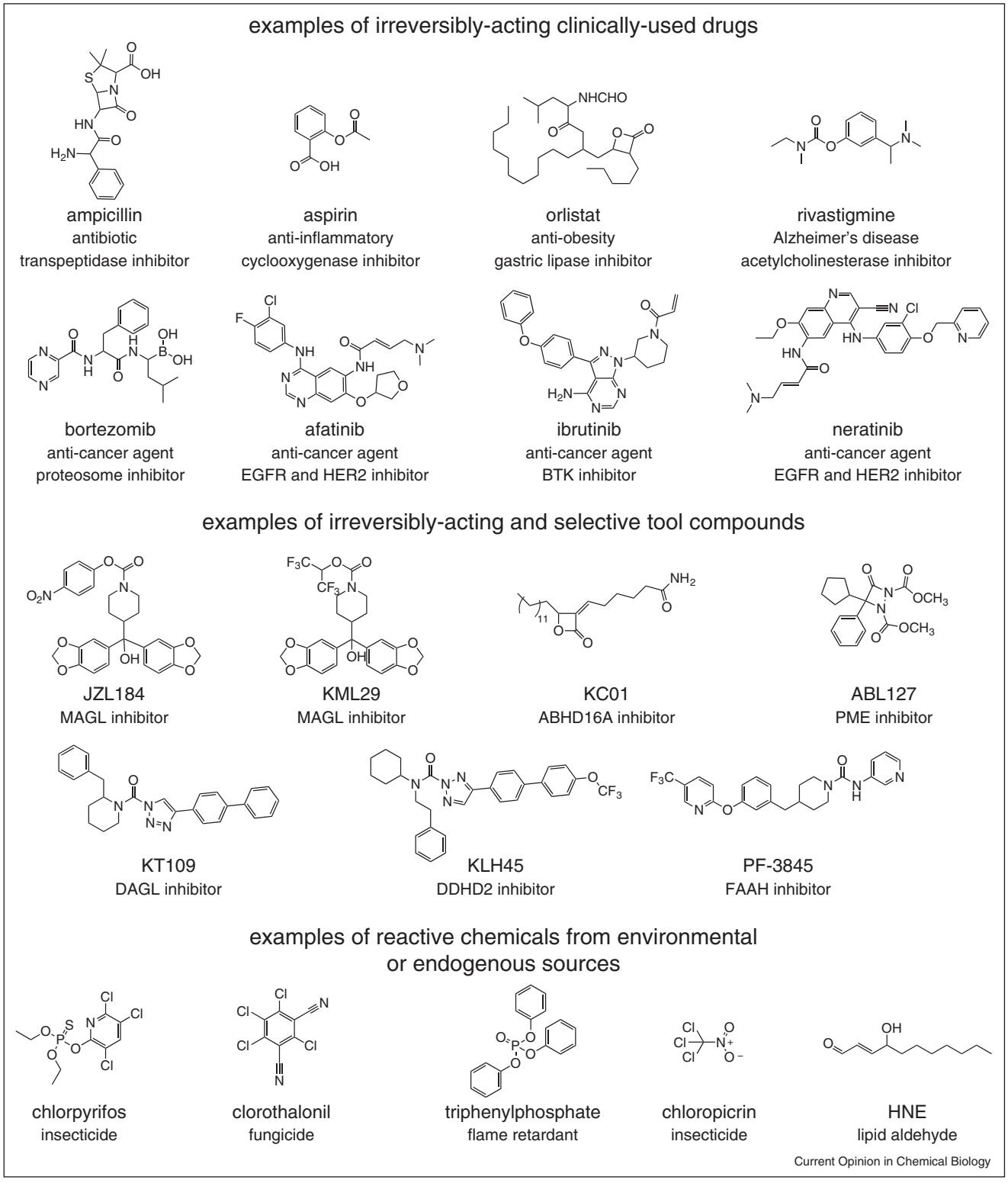
We are exposed to a large number of chemicals that act through covalent mechanisms. These chemicals include pharmaceutical agents that irreversibly inhibit their respective protein targets to treat human diseases, such as Alzheimer's disease, obesity, pain, and cancer [1–5]. Also included are reactive endogenous metabolites that are formed through metabolism, such as lipid aldehydes and various forms of reactive oxygen species or nitrogen stress. Many pesticides, environmental contaminants, and household chemicals also act through covalent mechanisms [6–9,10••]. While most of these chemicals have undergone standard toxicological testing, the reactivity of these chemicals across the proteome still remains poorly defined. Understanding the selectivity of these reactive agents is of paramount importance in comprehending the mechanisms underlying their biological or therapeutic action, identifying off-target effects that may lead to 'idiosyncratic' toxicities, and informing the development of safer and more selective agents (Figures 1–3).

Over the past several years, there have been major advancements in the development and use of chemoproteomic platforms to determine the proteome-wide interactions of irreversible small-molecule tool compounds, therapeutics, endogenous electrophiles, and environmental chemicals. In this review, we will describe how chemoproteomic technologies have been used to assess both the selectivity of therapeutic agents and the toxicological mechanisms of environmental chemicals.

Chemoproteomic profiling to assess selectivity of therapeutic irreversible small-molecule inhibitors

Pharmaceutical companies have historically shied away from pursuing covalent inhibitors due to risks of haptenization and immunologic reactions that may occur through non-specific covalent modification of small-molecules with protein targets [11]. Nonetheless, many irreversible or pseudo-irreversible inhibitors have been successfully developed as well-tolerated drugs in the clinic. Examples include the anti-inflammatory drug aspirin, the broad class of antibacterial beta-lactam antibiotics such as penicillin, drugs that require metabolic bioactivation including the proton pump inhibitor omeprazole, the Alzheimer's drug rivastigmine that inhibits acetylcholinesterase, the cancer therapy bortezomib (Velcade) that targets the proteosome, and the anti-obesity drug tetrahydrolipstatin (Orlistat) that inhibits gastric lipase [1–3,5]. In recent years, there has been resurgence in developing covalent and irreversible inhibitors, including several acrylamide-based inhibitors that act through Michael addition with a cysteine in the ATP binding pocket of oncogenic kinases for cancer therapy. Some examples include PCI-32765 (ibrutinib), a Bruton's tyrosine kinase (BTK) inhibitor now FDA approved for mantle cell lymphoma and chronic lymphoblastic leukemia; BIBW-2992 (afatinib) and HKI-272 (neratinib) that dually inhibit human epidermal growth factor receptor 2 (HER2) and epidermal growth factor receptor (EGFR), both of which are approved or in development for non-small cell lung cancer (NSCLC) and breast cancer, respectively; and CO1686 (Rociletinib) that specifically

Figure 1



Examples of irreversibly-acting drugs, tool compounds, environmental chemicals, and endogenous electrophiles.