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Review article

Covalent inhibitors design and discovery

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ABSTRACT

In the history of therapeutics, covalent drugs occupy a very distinct category. While representing a significant fraction of the drugs on the market, very few have been deliberately designed to interact covalently with their biological target. In this review, the prevalence of covalent drugs will first be briefly covered, followed by an introduction to their mechanisms of action and more detailed discussions of their discovery and the development of safe and efficient covalent enzyme inhibitors. All stages of a drug discovery program will be covered, from target considerations to lead optimization, strategies to tune reactivity and computational methods. The goal of this article is to provide an overview of the field and to outline good practices that are needed for the proper assessment and development of covalent inhibitors as well as a good understanding of the potential and limitations of current computational methods for the design of covalent drugs.

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1. Introduction

1.1. Covalent drugs

Non-covalent interactions, including electrostatic interactions, hydrogen bonds, van der Waals interactions, and hydrophobic contacts, all contribute to the affinity and specificity of ligands for receptors, substrates for enzymes, and binders for ion channels to name a few, but also to the activity of drugs whether receptor antagonists or agonist, enzyme inhibitors or ion channels blockers. Consequently, the development of drugs has primarily relied on the optimization of non-bonded interactions to improve potency for a given (or a few) target(s) and to increase selectivity (i.e., relative to off-targets). However, this approach, which has been adopted by many pharmaceutical companies and academic groups, neglects a whole class of drugs: those which can form a covalent bond with their targeted enzyme or receptor.

While specificity has always been perceived as a major focus for a successful medicinal chemistry program, statistics reported years ago revealed that marketed drugs bind to an average of six targets [1]. In this quest for specificity, drugs featuring reactive groups had often been red-flagged. Fear of toxicity caused by non-specific modifications of proteins, nucleic acids and other key biomolecules as well as conjugation with glutathione has, for a long time, restrained the development of covalent drugs. However, although intentionally discarded by most medicinal chemistry research programs, various covalent drugs have found their way to the market, including blockbusters drugs (Fig. 1). This apparent paradox results from their mode of action being unraveled after their therapeutic application has been discovered, a famous example being aspirin, which irreversibly acetylates cyclooxygenase (COX) [2].

Recently, a boost in the development of covalent drugs has occurred (Fig. 2) [3,4]. It has been recognized that several properties of covalent drugs could be beneficial under certain circumstances compared to their non-covalent counterparts. For instance, the long-acting character of the covalent interaction opposes displacement of enzyme inhibitors by the natural substrates. This is particularly important when the biochemical pathway involves a build-up of the natural substrate upon inhibition, and when a covalent drug allows the same pharmacologic response to be achieved at a much lower concentration than a non-covalent drug for the same target.

In addition to toxicity concerns, inadequate characterization techniques for covalent inhibitors has impeded the development of covalent ligands. Indeed, with all the knowledge available in terms of enzymology, binding kinetics, pharmacokinetics and pharmacodynamics geared towards “conventional” non-covalent inhibitors, interpretation of data associated with covalent inhibition can be biased and erroneous. Often described as non-classical inhibitors, covalent inhibitors, when applied in a drug development project, also need non-classical treatments for their characterization.

1.2. This review

The objective of this review is to establish a framework for the development and optimization of covalent inhibitors and to illustrate how these concepts can contribute to the discovery of efficient

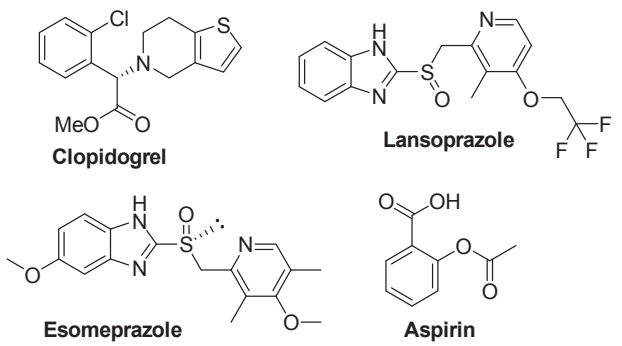

Fig. 1. Major drugs which act through covalent mechanisms.

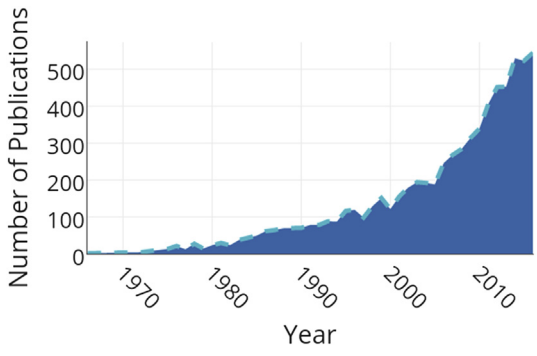

Fig. 2. Number of publications obtained from the search of the term “covalent drugs” in SciFinder®.