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Small molecule intercalation with double stranded DNA: Implications for normal gene regulation and for predicting the biological efficacy and genotoxicity of drugs and other chemicals

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Abstract

The binding of small molecules to double stranded DNA including intercalation between base pairs has been a topic of research for over 40 years. For the most part, however, intercalation has been of marginal interest given the prevailing notion that binding of small molecules to protein receptors is largely responsible for governing biological function. This picture is now changing with the discovery of nuclear enzymes, e.g. topoisomerases that modulate intercalation of various compounds including certain antitumor drugs and genotoxins. While intercalators are classically flat, aromatic structures that can easily insert between base pairs, our laboratories reported in 1977 that a number of biologically active compounds with greater molecular thickness, e.g. steroid hormones, could fit stereospecifically between base pairs. The hypothesis was advanced that intercalation was a salient feature of the action of gene regulatory molecules. Two parallel lines of research were pursued: (1) development of technology to employ intercalation in the design of safe and effective chemicals, e.g. pharmaceuticals, nutraceuticals, agricultural chemicals; (2) exploration of intercalation in the mode of action of nuclear receptor proteins. Computer modeling demonstrated that degree of fit of certain small molecules into DNA intercalation sites correlated with degree of biological activity but not with strength of receptor binding. These findings led to computational tools including pharmacophores and search engines to design new drug candidates by predicting desirable and undesirable activities. The specific sequences in DNA into which ligands best intercalated were later found in the consensus sequences of genes activated by nuclear receptors implying intercalation was central to their mode of action. Recently, the orientation of ligands bound to nuclear receptors was found to match closely the spatial locations of ligands derived from intercalation into unwound gene sequences suggesting that nuclear receptors may be guiding ligands to DNA with remarkable precision. Based upon multiple lines of experimental evidence, we suggest that intercalation in double stranded DNA is a ubiquitous, natural process and a salient feature of the regulation of genes. If double stranded DNA is proven to be the ultimate target of genomic drug action, intercalation will emerge as a cornerstone of the future discovery of safe and effective pharmaceuticals.

Keywords: Double stranded DNA; DNA intercalation; Drug discovery; Nuclear receptors; Gene regulation; Genotoxicity

1. Introduction

In 1953, Watson and Crick published the structure of double stranded DNA along with the hypothesis that the

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precise chemical properties of the base pairs suggested an obvious copying mechanism for genetic material [1]. Evidence that there may be other important features of DNA structure was reported 8 years later in 1961 by Lerman who demonstrated that acridine dye could insert or intercalate between DNA base pairs [2]. This observation led to the prevailing early thought that only small molecules with virtually flat, aromatic structures were capable of intercalation. Over the past 45 years, Lerman's salient observation has spawned a vast literature on intercalators which have a variety of molecular thicknesses including certain highly potent and effective drugs as well as certain carcinogenic compounds [3–5]. For simplicity, the well-characterized, flat molecules will be referred to as classical intercalators [6–10] (Fig. 1). Those molecules that are less studied including those with greater molecular thickness will be termed non-classical intercalators [11–24] (Fig. 2). Both types of intercalators will be referred to as ligands.

It should be noted the possibility that molecules other than flat, aromatic compounds might be capable of inserting between base pairs in DNA was originally considered by Huggins and Yang in 1962 [25]. He observed that space filling models of the mammalian hormonal

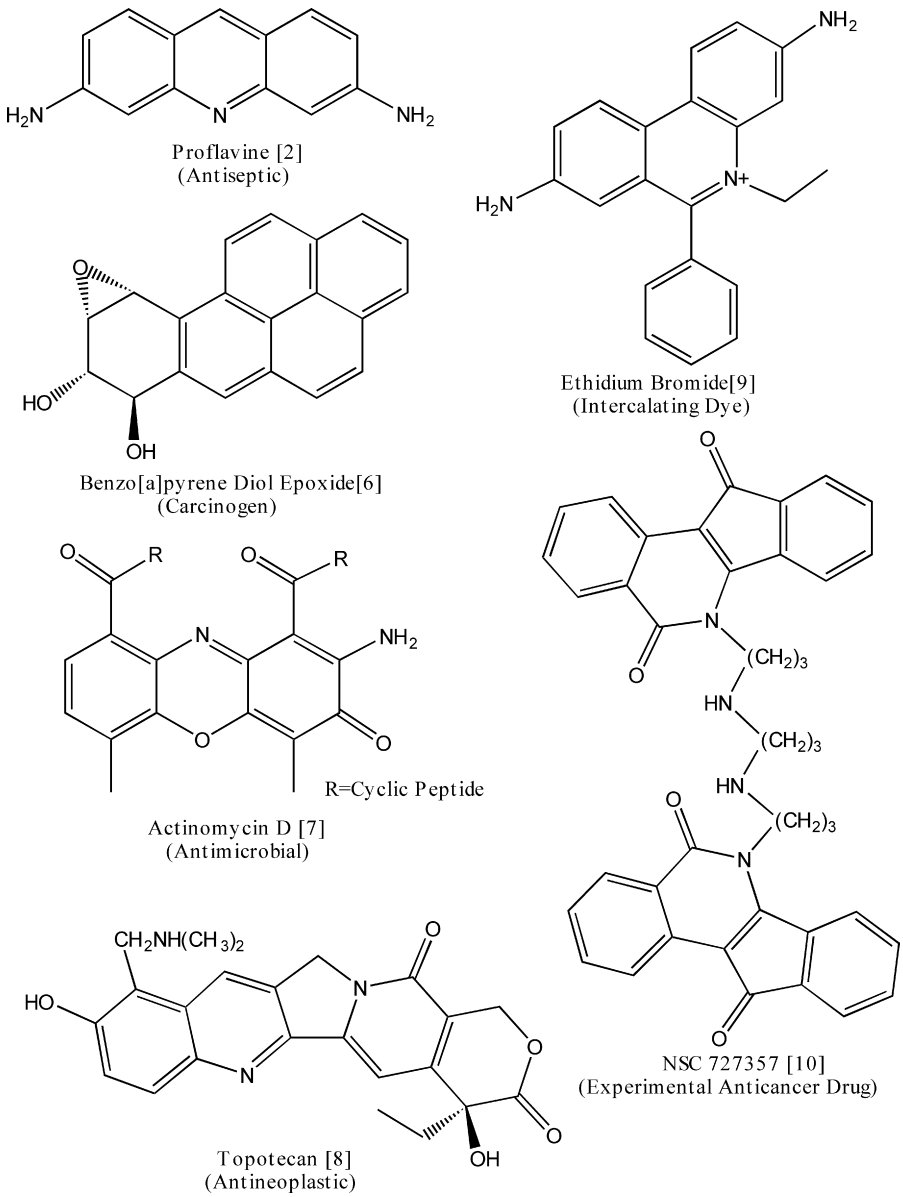

Fig. 1. Examples of classical intercalators: ligands with flat, aromatic structures demonstrated to fit between base pairs in double stranded DNA.