Nonnatural Glycosyl Anthraquinones as DNA Binding and Photocleaving Agents

Kazunobu Toshima

Department of Applied Chemistry, Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan
toshima@applc.keio.ac.jp

1 Introduction ........................................ 285
2 Design, Synthesis, and Evaluation of Nonnatural Glycosyl Anthraquinones as DNA Binders ............ 286
3 Design, Synthesis, and Evaluation of Nonnatural Glycosyl Anthraquinones as DNA Photocleavers ...... 290
   3.1 First Generation .................................... 290
   3.2 Second Generation .................................. 292
4 Concluding Remarks .................................. 297

Abstract Several artificial anthraquinone–carbohydrate hybrids were designed and synthesized. A selected number of hybrids did bind to DNA via intercalation in a sequence-selective manner, leading to inhibition of DNA cleavage by DNase I, whereas other hybrids cleaved DNA with base selectivity upon photoirradiation. This hybrid system was found to be very important for both DNA binding and photocleaving.

Keywords Anthraquinone · Carbohydrate · DNA · Intercalation · Photocleavage

Abbreviations
Bz Benzoyl
CAN Ceric ammonium nitrate
DNA Deoxyribonucleic acid
MS Molecular sieve
rt Room temperature
Tf Trifluoromethanesulfonyl
THF Tetrahydrofuran
TMS Trimethylsilyl

1 Introduction

Novel DNA binding or cleaving molecules, particularly those with high efficiency and sequence specificity, are very interesting from the chemical and
biological standpoint and offer considerable potential in medicine [1, 2]. The design and synthesis of artificial molecules that exhibit such interactions with DNA is therefore an important goal in contemporary chemistry. Certain clinically important antitumor antibiotics, such as anthracyclines [3, 4] and pluramycins [5], which strongly bind to DNA in a sequence-selective manner, have been found in nature (Fig. 1) [6]. Although these various agents have been regarded as belonging to distinct classes of antibiotics from a chemical standpoint, they are commonly found to contain aromatic and carbohydrate domains. In their DNA binding modes, the aromatic moieties function as DNA intercalators, whereas the carbohydrate residues bind to the DNA minor groove. Even enediyne antibiotics, which effectively cleave DNA via cycloaromatization reactions, can be viewed as aromatic–carbohydrate hybrids [7, 8]. These facts concerning DNA binding compounds of natural origin led us to consider the possibility of creating artificial DNA binding or cleaving molecules that consist of aromatic and carbohydrate domains [9–17]. In this study, anthraquinone, which is the key structure in anthracycline antibiotics, was selected as the DNA intercalating and photocleaving aromatic [9–11]. This chapter describes the molecular design, chemical synthesis, DNA binding, and DNA photocleaving properties, as well as the cytotoxic profiles, of several novel and artificial anthraquinone–carbohydrate hybrids.

2 Design, Synthesis, and Evaluation of Nonnatural Glycosyl Anthraquinones as DNA Binders

In our approach to DNA binding hybrids, the anthraquinone molecule was selected as the aromatic building block because it is the aromatic skeleton...