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Molecular recognition of naphthoquinone-containing compounds against human DNA topoisomerase IIα ATPase domain: A molecular modeling study

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ABSTRACT

Several quinone-based metabolites of anticancer drugs and naturally occurring quinone-containing compounds have been characterized as potent inhibitors toward topoisomerase IIα (TopoIIα), an essential enzyme involved in maintaining genomic integrity during DNA replication and mitotic division. Mansonone G (MG), a naphthoquinone-containing compound extracted from the heartwood of *Mansonia gagei*, exhibits various biological activities including antitumor potential. In the present study, MG and its semi-synthetic derivatives were selected to study the preferential binding site and dynamics behavior as well as to predict the inhibitory activity against TopoIIα using molecular modeling approaches. The molecular docking results revealed that the entire series of MG preferentially target to the ATPase domain. Among all studied MGs, the ester derivative MG14 containing C-10 length exhibited the highest binding affinity against TopoIIα and greater than that of the ATP-competitive inhibitor salvicine as well as 1,4-benzoquinone. Interestingly, the MG14 binding could induce the closed form of the turn region (residues 147–151) inside ATP-binding pocket, implying that this event might be one of the crucial mechanisms underlying TopoIIα inhibition. The obtained theoretical information is useful as rational guide for further development of new anticancer agents containing naphthoquinone moiety against TopoIIα.

1. Introduction

DNA topoisomerase II (TopoII, Fig. 1A) is a nuclear enzyme that plays an important role in a number of DNA-related processes such as replication, transcription, recombination, and mitosis [1–3]. To maintain genomic integrity during such events, TopoII alleviates the topological constraints of the genetic material by breaking and rejoining the phosphodiester backbone of undesirable regions (i.e., superhelical twists, tangles, and knots) using double-stranded break mechanism [4]. TopoII is a homodimeric enzyme with two catalytically important domains: (*i*) the N-terminal ATPase domain, which catalyses the hydrolysis of ATP molecules, providing the energy for catalytic processes and (*ii*) the central domain, which is located at the center of cleavage/religation domain, comprising the important catalytic residues (TOPRIM sequence and Tyr805) for DNA breaking and resealing (Fig. 1D) [5]. Mammals have two closely related TopoII isoforms, TopoIIα and TopoIIβ, that share 93% of similarity and 81% of identity for their ATPase and cleavage/religation domains [2]. The expression level of TopoIIβ remains constant throughout the cell cycle, whereas TopoIIα is expressed at high levels and dramatically increased during G2/M phase of the cancer cell cycle, making it an ideal protein target for molecularly targeted therapy [2,6,7]. There are two classes of TopoII-targeting compounds: (*i*) TopoII poisons (i.e., etoposide (VP-16), teniposide (VM-26), doxorubicin, amsacrine and mitoxanthrone) [8], which can target the catalytic core domain or stabilize the enzyme-DNA complex (known as cleavage complex) [9–11], resulting in DNA strand breaks and (*ii*) TopoII catalytic inhibitors (i.e., ICRF-193 [12], novobiocin [13], sobuzoxane (MST-16) [14],

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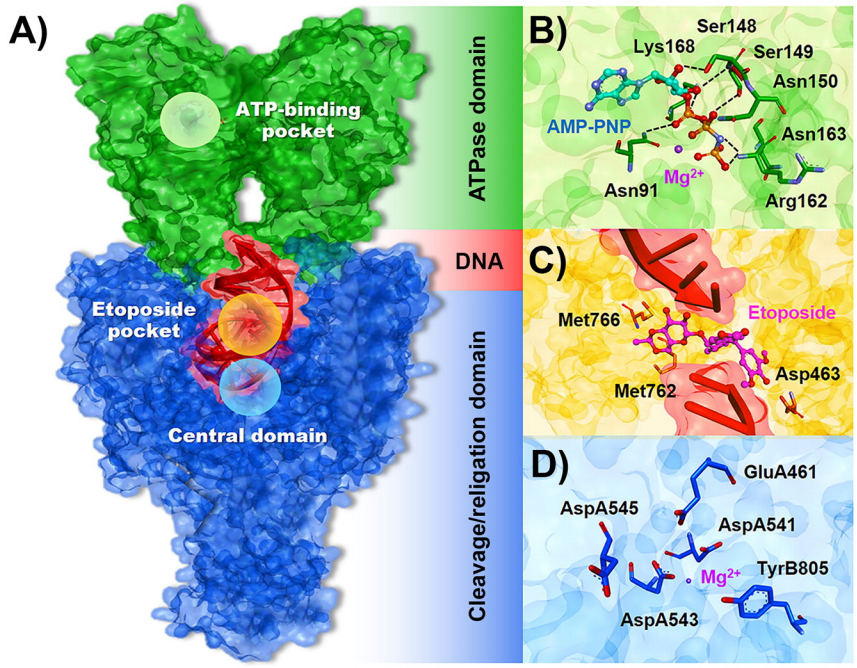

Fig. 1. (A) The 3D structure of DNA topoisomerase IIα, in which the ATPase and the cleavage/religation domains are shaded by green and dark blue colors. The ATP-binding pocket, etoposide pocket, and central domain are represented by light green, orange, and blue circles, respectively. The close-up regions for (B) ATP-binding pocket, (C) etoposide pocket, and (D) central domain. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

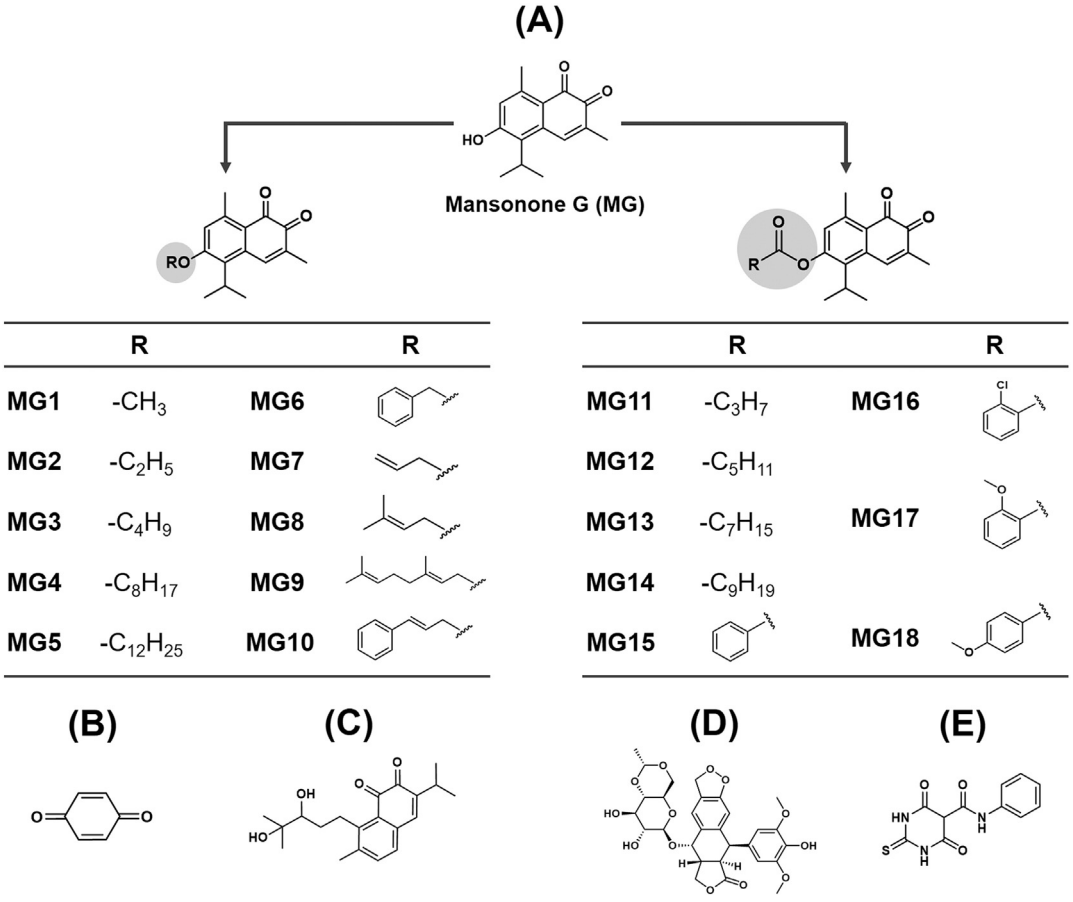

Fig. 2. Chemical structures of (A) MG and its synthesized derivatives, which are ether derivatives (left panel) and ester derivatives (right panel), (B) 1,4-BQ, (C) salvicine, (D) etoposide, and (E) merbarone.