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Naphthazarin Derivatives: Synthesis, Inhibition of DNA Topoisomerase-I and Antitumor Activity

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Inhibitory effect on DNA topoisomerase-I, rate of glutathione conjugation and cytotoxicity of naphthoquinone derivatives were correlated. During 5 min exposure of the derivatives to glutathione (GSH), it was found that 14% of 5,8-dimethoxy-1,4-naphthoquinone(DMNQ) was converted into a GSH-conjugate, whereas 5,8-dihydroxy-1,4-naphthoquinone(DHNQ) did not interact with GSH, implying that DMNQ exerted higher electrophilicity than DHNQ. However, DHNQ (IC_{50}, 0.15 μM) showed stronger cytotoxicity in L1210 cells than DMNQ(IC_{50}, 0.45 μM). The stronger cytotoxicity of DHNQ, compared to DMNQ, could be ascribed to more rapid redox cycling. Both naphthoquinones (IC_{50}, 60-65 μM) exhibiting about the same inhibitory effect on DNA topoisomerase-I were more potent than 1,4-naphthoquinone(1,4-NQ, IC_{50}, 134 μM). Thus, 5,8-oxy groups in the structure seem to be important for the inhibition of the enzyme. DMNQ showed a broader dose range while maintaining a good antitumor activity against S-180 fluid tumor. For these reasons, DMNQ was taken as useful pharmacophore for structural modification. Introduction of 1-hydroxyalkyl groups at C-2 of DMNQ lowered all of the activities mentioned above, while acetylation of 1-hydroxyalkyl moiety enhanced the activities by 4-5 times. Introduction of the same side chains at C-6 exhibited stronger activities than 2-substituted ones. Based on these results it was suggested that the quinonoid moiety in 6-substituted DMNQ was more exposed to cellular nucleophiles such as DNA, thiols of enzymes and so on. The synthesis of DHNQ or DMNQ derivatives are going on, and the corelationship between structure - activity will be discussed.