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Design and synthesis of 8-hydroxyquinoline-based radioprotective agents

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ABSTRACT

In radiation therapy, adverse side effects are often induced due to the excessive cell death that occurs in radiosensitive normal cells. The radiation-induced cell death of normal cells is caused, at least in part, by apoptosis, which undergoes via activation of p53 and increase in the p53 protein, a zinc-containing transcriptional factor, in response to cellular damage. Therefore, radioprotective drugs that can protect normal cells from radiation and thus suppress adverse side effects would be highly desirable. We report herein on the radioprotective activity of 8-hydroxyquinoline (8HQ) derivatives that were initially designed so as to interact with the Zn^{2+} in p53. Indeed, the 5,7-bis(methylaminosulfonyl)-8HQ and 8-methoxyquinoline derivatives considerably protected MOLT-4 cells against γ-ray radiation (10 Gy), accompanied by a low cytotoxicity. However, mechanistic studies revealed that the interaction of these drugs with p53 is weak and the mechanism for inhibiting apoptosis appears to be different from that of previously reported radioprotectors such as bispicen, which inhibits apoptosis via the denaturation of p53 as well as by blocking both transcription-dependent and -independent apoptotic pathways.

1. Introduction

Radiation therapy is a major form of cancer therapy,[1] in which tumor cells are forced to undergo cell death by strong and spatially controlled radiation. Generally, this therapy is thought to be less invasive than surgery. However, adverse side effects such as death of bone marrow or intestinal cells are sometimes induced, due to the apoptosis of radiosensitive normal cells that are in close proximity to the tumor tissue.[2] Therefore, the development of radioprotective drugs that can protect normal cells against radiation and thus suppress adverse side effects are urgently needed.

The radiation-induced cell death of normal cells is caused, at least in part, by the induction of apoptosis by the p53 protein (Fig. 1),[3] which is a zinc-containing transcription factor. The p53 protein is known as a tumor-suppressor factor and is frequently mutated or inactivated in various cancer cells.[4] In the case of critical DNA-damage in radiosensitive normal cells by radiation, the activation of p53 proteins induce apoptosis as a result of an acute

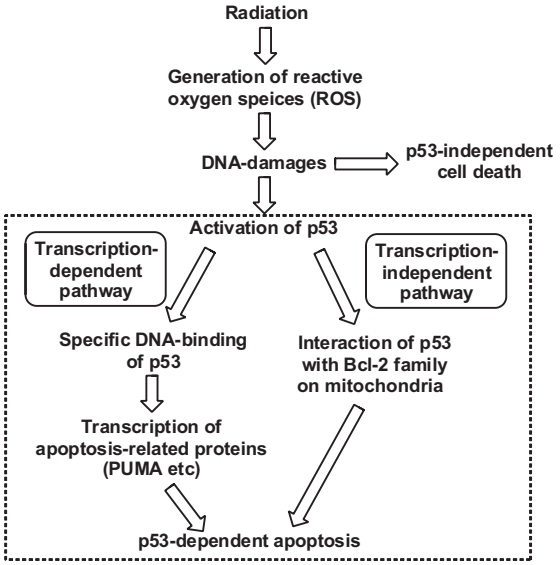

Figure 1. Possible radiation-induced apoptosis pathways.

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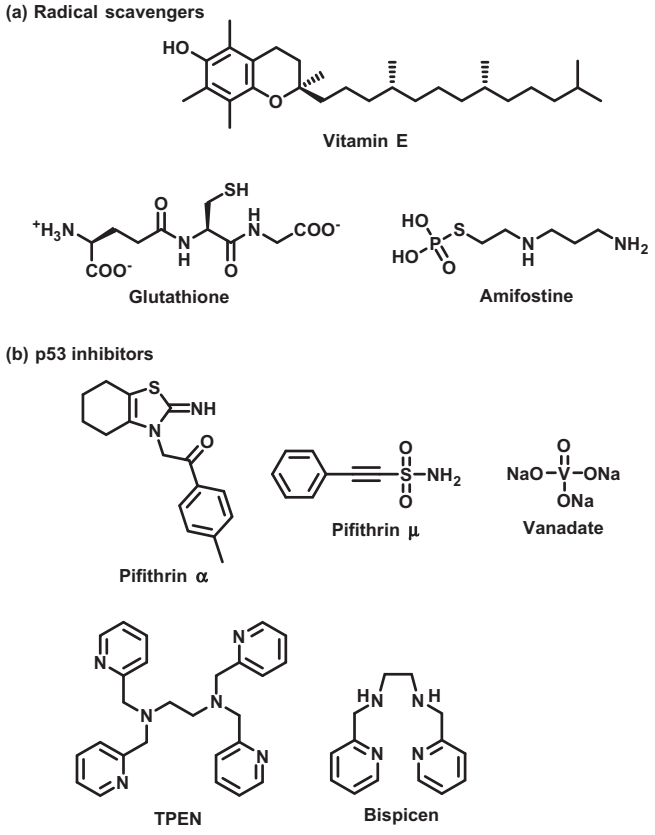


Figure 2. Chemical structures of reported radioprotectors and related compounds, (a) radical scavengers and (b) p53 inhibitors.

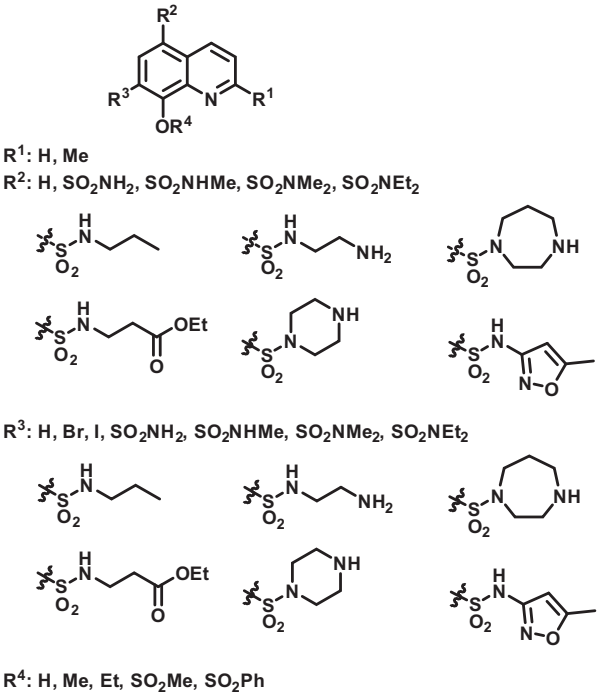
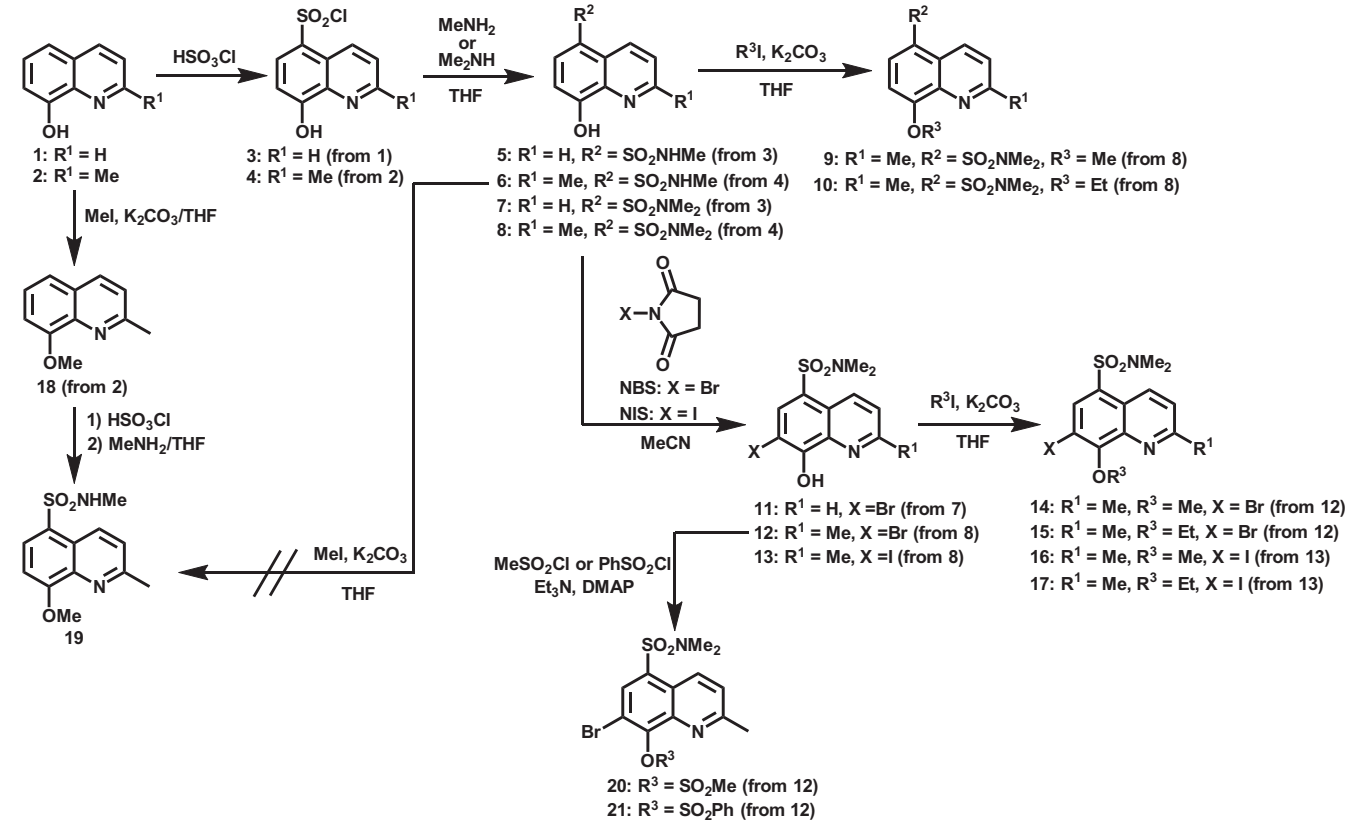


Figure 3. General structure of 8HQ derivatives in this work.

radiation reaction.[5] The mechanisms responsible for p53-induced apoptosis are classified into a transcription-dependent pathway and a transcription-independent pathway, as indicated in Figure 1.[6] In the transcription-dependent pathway, p53 binds to DNA and induces apoptosis. In the transcription-independent pathway, on



Scheme 1. Synthesis of 5-aminosulfonyl-8HQ derivatives.