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Synthesis and cytotoxic activity evaluation of 2,3-thiazolidin-4-one derivatives on human breast cancer cell lines

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ABSTRACT

It is well known that resveratrol (RSV) displayed cancer-preventing and anticancer properties but its clinical application is limited because of a low bioavailability and a rapid clearance from the circulation. Aim of this work was to synthesize pharmacologically active resveratrol analogs with an enhanced structural rigidity and bioavailability. In particular, we have synthesized a library of 2,3-thiazolidin-4-one derivatives in which a thiazolidinone nucleus connects two aromatic rings. Some of these compounds showed strong inhibitory effects on breast cancer cell growth. Our results indicate that some of thiazolidin-based resveratrol derivatives may become a new potent alternative tool for the treatment of human breast cancer.

Epidemiological and current laboratory studies suggest that consumption of certain types of fruits and vegetables, containing phytochemicals, is associated with reduced cancer risk.[1] Furthermore, it is postulated that dietary phytochemicals can function as chemopreventive and/or adjuvant chemotherapeutic agents. One such phytochemical is resveratrol (3,5,4′-trihydroxy-*trans*-stilbene) (RSV), (Fig. 1) a naturally occurring phytoalexin, readily available in the diet and a lot of health-promoting effects have been ascribed to it.

Resveratrol, first identified as a bioactive compound in 1992, is found in several plants, particularly in the skin of red grapes.[2]

This compound has elicited much attention in recent years, as a potential anticancer agent, since its inhibitory effect on carcinogenic processes (initiation, promotion, and progression) was first reported in 1997.[3] Thereafter extensive studies have verified the cancer-preventing and anticancer properties of resveratrol in various murine models of human cancer, including skin cancer (both chemically and ultraviolet B-induced), gastric and colorectal cancer, lung cancer, breast cancer, ovarian and prostate cancer, hepatoma, neuroblastoma, fibrosarcoma, pancreatic cancer, and leukemia.[4] Several studies, using both in vitro and in vivo model systems, have illustrated resveratrol's capacity to modulate a multitude of signaling pathways associated with cellular growth and division, apoptosis, angiogenesis, invasion, and metastasis.[5]

In particular, it exhibits an action in both hormone-sensitive and hormone-resistant breast cancer cells and shows cytostatic activity and determines cell growth arrest; these properties seem to be related to regulation of xenobiotic carcinogen metabolism and antiinflammatory, antiproliferative, and pro-apoptotic effects.[6] The phytoestrogenic character of RSV was confirmed by its capacity to bind and activate α- and β-estrogen receptors (ERs) regulating transcription of estrogen-responsive target genes. However,

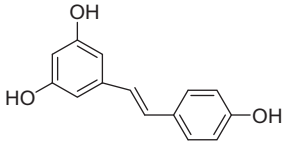

Figure 1. Resveratrol (3,5,4′-trihydroxy-*trans*-stilbene) (RSV).

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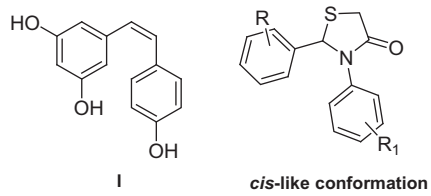
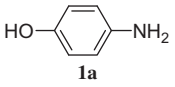
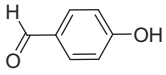
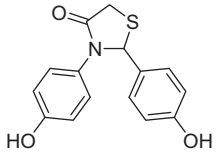
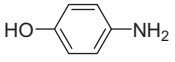
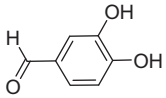
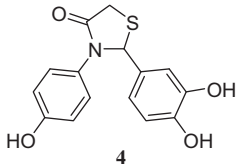
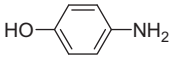
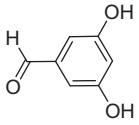
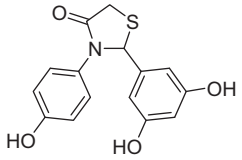
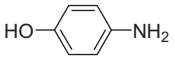
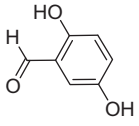
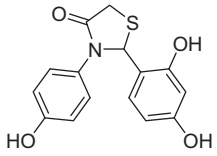
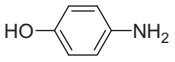
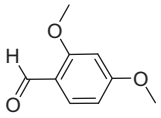
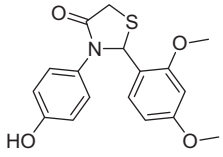
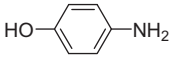
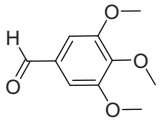
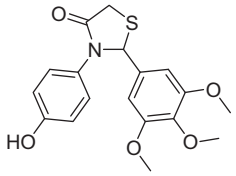
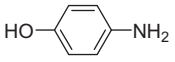
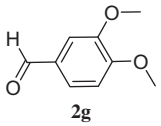
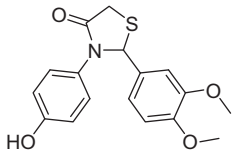


Figure 2. Structure of *cis*-resveratrol (**I**) and a *cis*-conformation mimetic of resveratrol containing an thiazolidin-4-one moiety.

although a number of studies have been conducted, the effects of RSV on ERs remain controversial. For example, with MCF-7 cells in culture, Gehm et al.[7] showed that RSV (3–10 μM) is a superagonist when combined with estradiol (E2), while Lu and Serrero[8] reported ER antagonism of RSV (5 μM) in the presence of E2 and partial agonism in its absence.[8] Bowers et al.[9] observed partial to full agonism in CHO-K1 cells transfected with ERα or ERβ and reporter genes based on various estrogen receptor element (EREs). The authors showed that RSV (100 μM) acts as a mixed agonist/antagonist in cells transiently transfected with ER and mediates higher transcriptional activity when bound to ERβ than to ERα. Moreover, RSV showed antagonist activity with ERα, but not with ERβ.[9] Based on these reports, it appears that the ability of RSV to act as an ER agonist varies between different cell types and dosage. Resveratrol acts as an estrogen-agonist or antagonist that depends

Table 1
Library of synthesized 2,3-thiazolidin-4-one (**3**–**14**)

Entry	Arylamine	Aryl-aldehyde	2,3-Thiazolidin-4-one derivative	Yield (%)
1	 **1a**	 **2a**	 **3**	93
2	 **1a**	 **2b**	 **4**	47
3	 **1a**	 **2c**	 **5**	63
4	 **1a**	 **2d**	 **6**	80
5	 **1a**	 **2e**	 **7**	85
6	 **1a**	 **2f**	 **8**	90
7	 **1a**	 **2g**	 **9**	90