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Synthesis, biological evaluation and docking study of sulfonates and sulfonamides of Resveratrol as aromatase inhibitors

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ABSTRACT

Resveratrol (trans-3,4',5-trihydroxystilbene, RSV) is a polyphenolic phytoalexin found in grapes, peanuts, and mulberry with documented beneficial physiological effects.[1] RSV has been also identified as a potent cancer chemo-preventive agent, acting on multiple molecular targets.[2] Breast cancer is one of the most common cancer types. Many tumors occur through estrogen-dependent mechanisms in which Aromatase (CYP19), a member of cytochrome P450 family, responsible for a key step in the biosynthesis of estrogens from androgens by aromatization,[3] plays a crucial role. Several Aromatase inhibitors (AIs) have been developed so far. RSV has relatively weak activity against Aromatase, but its analogues displayed much greater inhibition.[4] As a continuation of our research in novel Aromatase inhibitors,[5] in the current study, a library of analogues of RSV containing sulfonamide and sulfonate group was developed with the aim to inhibiting the active site of CYP19A1. At this scope, we prepared 22 trans-stilbene analogues of RSV in which the stilbene core is joined to aromatic or aliphatic core by a sulfonate or sulfonamide bridge (Figure). These RSV derivatives have been screened for their Aromatase inhibition through an in vitro fluorescence-based assay, using Letrozole as a reference compound. The compounds that showed good inhibitory activity in the low micromolar range were evaluated on a breast cancer cell line (MCF7) in terms of cell viability and cytotoxicity, using the MTT test and the LDH release assay. The selected compounds showed good cytotoxic activity, also confirmed by the haematoxylin/eosin staining. In agreement with the biological investigations, docking studies disclosed at a molecular level the rationale behind the observed Aromatase inhibition. These results open new insight into Aromatase inhibition field.

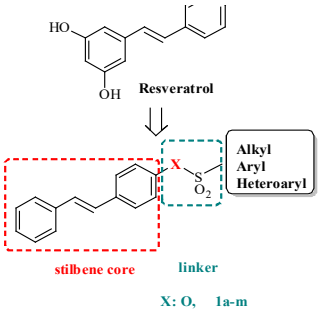

Figure: General stucture of sulfonate and sulfonamide derivatives of RSV

BIOGRAPHY

Barbara De Filippis has a degree in pharmaceutical chemistry and technology and earned her PhD in medicinal chemistry sciences at the University of Chieti (Italy), where she is currently an assistant professor of medicinal chemistry. Her main research topics are related to metabolic diseases and cancer fields. Her current research interests have shifted toward the design and the synthesis of natural polyphenol derivatives with multiple potential biological activities as anticancer, antioxidant and antimicrobial..

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