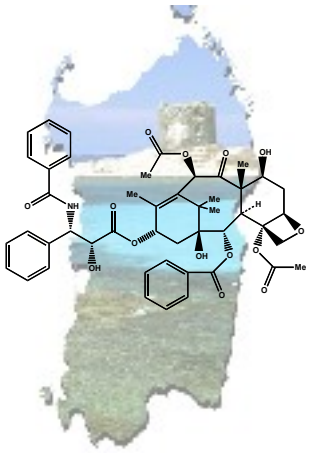
SardiniaChem2008

GIORNATA DI STUDIO DEDICATA ALLA CHIMICA ORGANICA DELLE MOLECOLE BIOLOGICAMENTE ATTIVE

30 Maggio 2008, Aula Magna della Facoltà di Scienze – Sassari



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INFLUENCE OF TETRATHIAFULVALENE (TTF) AND DERIVATIVES ON REDOX STATE AND CELL VIABILITY OF HUMAN ENDOTHELIAL CELLS

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TTF is still the most popular skeleton organic redox system (1) and it has attracted widespread attention ever since its synthesis (2) due to the unusual electric, magnetic and optical properties of its charge-transfer salts (3). The synthesis of a family of biphenyl-tetrathiafulvalene (TTF) derivatives incorporating a binding site has been carried out in good to moderate yields through functionalization of the biphenyl scaffold (4). This study was designed to investigate the potential effect of tetrathiafulvalene (TTF), tetrathiafulvalene-$(SMe)_4$ (TTF-S) and a biphenyl-tetrathiafulvalene-$(SMe)_4$ derivative (BIPH-TTF-S) on the vitality, proliferation and redox state of primary and transformed human endothelial cells. It is the first study of TTF and derivatives on the field.

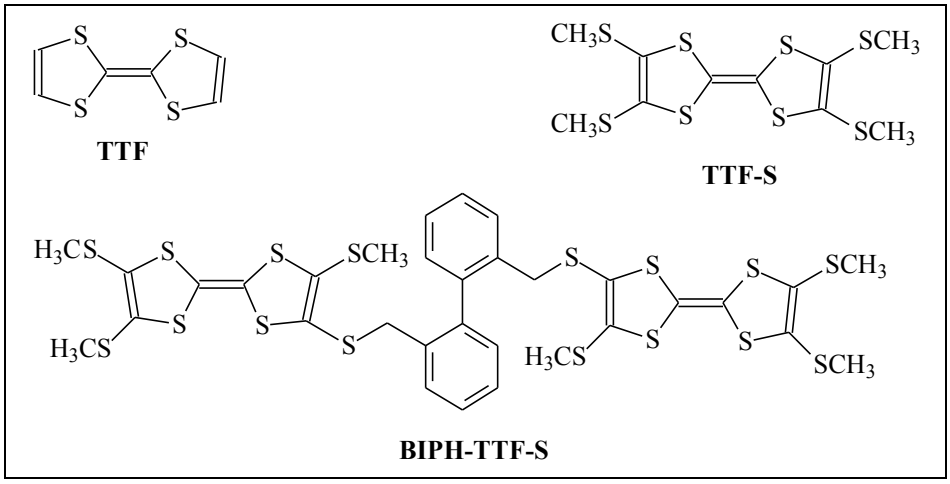
Reactive oxygen species (ROS) play central role as signal transduction intermediate in regulating a variety of cellular processes including death and survival, thus aberrant ROS signalling may lead to several pathological conditions such as cancer, aging and cardiovascular disorders. In this light ROS may be potential targets for therapeutic treatments.

Here we challenged different concentrations of the three aforementioned substances with two different types of cells, HUVEC (primary human umbilical vein endothelial cells) and ECV304 (a spontaneously transformed human endothelial cell line), and assessed their effect on cell proliferation, toxicity and ROS production,

Intracellular ROS generation was kinetically measured by using the molecular probe 2',7'-dichlorodihydrofluorescein diacetate (H_2DCF-DA). Within the cell, esterases cleave the acetate groups on H_2DCF-DA, thus trapping the reduced form of the probe (H_2DCF). Intracellular ROS oxidize H_2DCF, yielding the fluorescent product, DCF. In HUVEC, TTF was able to inhibit ROS production, on the contrary TTF-S induced a dose-dipendent proxidant effect.

The biphenyl-derivative, at the lower concentration did not significantly induce differences between treated and untreated cells, but at higher concentration it dropped ROS production in the treated cells. All the three compounds would seem to have a proxidant effect when applied to the ECV304 cell line. Cell vitality was evaluated by the monotetrazolium salt (MTT) assay. This test exclusively detects viable cells because tetrazolium salts are reduced to a colored formazan only by metabolically active cells. The current results showed that in HUVEC all the three compounds did not affect negatively cell vitality but rather, generally resulted effective in slightly stimulating it as compared to control cells. The same test in ECV 304 showed that lower concentrations of TTF and TTF-S lead to a stimulatory effect, while higher concentrations induced an inhibitory effect. The biphenyl-derivative showed an inhibitory effect at all the concentrations tested. Cell proliferation was evaluated by using the "CyQUANT NF Cell Proliferation assay kit" (Invitrogen), based on measurement of cellular DNA content via fluorescent dye binding.

All the three tested compounds did not significantly induce differences between treated and untreated HUVEC, while the results on ECV 304 highlighted an anti-proliferative effect for the used molecules on this transformed cell line.



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