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Isothiocyanates as H_2S-Releasing Agents and Their Cardioprotective Effects

Valentina Citi*, Angela Corvino, Ferdinando Fiorino, Francesco Frecentese, Elisa Magli, Elisa Perissutti, Vincenzo Santagada, Simone Brogi, Lorenzo Flori, Era Gorica, Lara Testai, Alma Martelli, Vincenzo Calderone, Giuseppe Caliendo and Beatrice Severino

Department of Pharmacy, University of Pisa, Italy.

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ABSTRACT

The endogenous gasotransmitter hydrogen sulfide (H_2S) is an important regulator of the cardiovascular system, particularly of myocardial function. Moreover, H_2S exhibits cardioprotective activity against ischemia/reperfusion (I/R) or hypoxic injury and is considered an important mediator of "ischemic preconditioning". In this work, a small library of isothiocyanates was evaluated for the H_2S releasing properties; the compound named ISOTHIA25 has been selected to further investigate its protective activity both *in vitro* and *in vivo* experimental procedures of ischemia/reperfusion injury.

All the isothiocyanates were able to release H_2S in a cell-free environment. The computational analysis lead to the selection of the compound named ISOTHIA25, which was able to release about 60 µM of H_2S when incubated at the concentration of 1 mM in the presence of L-Cysteine and which showed good solubility and a promising ADME profile. Furthermore, ISOTHIA25 was able to enter into the H9c2 cells and release H_2S in a concentration dependent manner. The protective effect was first evaluated using H9c2: the incubation of ISOTHIA25 before the treatment with H_2O_2, lead to a significant recovery in cell viability in a concentration dependent manner, with an almost complete recovery of the viability when incubated at the concentration of 1 µM.

The H_2S-donor ISOTHIA25 has been then tested in different experimental models of myocardial I/R: in Langendorff-perfused rat hearts subjected to I/R, ISOTHIA25 significantly improved the post-ischemic damage, limiting the tissue injury in a concentration dependent manner. Accordingly, also the LDH biomarker was reduced. This effect was antagonized by 5-hydroxydecanoic acid (a blocker of mitoKATP channels). Finally, in an in vivo model of acute myocardial infarction in rats, ISOTHIA25 significantly decreased I/R-induced tissue injury.

Isothiocyanate-based H_2S-releasing drugs like ISOTHIA25, can actually be considered a suitable pharmacological option in anti-ischemic therapy.

Isothia-25 exhibits H_2S-releasing properties both in a cell-free and in a cell-based assay, and due to this property, has cardioprotective effects *in vitro* and *in vivo*.

Keywords: Isothiocyanates, Cardioprotective Effects, Anti-ischemic therapy

Corresponding author: Valentina Citi, Department of Pharmacy, University of Pisa, Italy, E-mail: valentina.citi@unipi.it

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