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Antioxidant Potential of 6-(5-Mercapto-4-R-4H-1,2,4-triazol-3-yl)-pyrimidine-2,4(1H,3H)-dione Derivatives

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Oxidative stress is a key driver in the pathogenesis of inflammatory, neurodegenerative, and cardiovascular diseases. The 1,2,4-triazole scaffold is a suitable pharmacophore for designing multifunctional hybrid molecules with polypharmacological activity. Its incorporation into thiopyrimidine structures is expected to enhance interactions with oxidative-stress targets and may serve as a basis for "synthetic matrices" in the search for innovative antioxidants [1]. Uracil–triazole hybrids bearing thiol/thione functionality can operate through several antioxidant mechanisms, which makes 6-(5-mercapto-4-R-4H-1,2,4-triazol-3-yl)-pyrimidine-2,4(1H,3H)-dione derivatives promising multimodal antioxidants.

The target products were successfully synthesized and isolated in pure form, as confirmed by elemental analysis, $^{1}H/^{13}C$ NMR spectroscopy, and chromatography–mass spectrometry. A general structure of the series is shown in Fig. 1.

Antioxidant activity. A substantial number of compounds (15 derivatives) outperformed the reference—ascorbic acid, a natural antioxidant. The most active compound exhibited IC_{50} = 4.458 ± 1 μM, i.e., approximately 27-fold greater efficacy than ascorbic acid. Structural features were identified that can guide the creation of low-toxicity antioxidant adjuvants and cytoprotective agents for oxidative–inflammatory models and as stabilizers of lipid matrices or dosage forms.

Molecular docking. Many derivatives showed low binding energies (–8.7866 to –8.9324 kcal/mol) toward EC 1.11.1.5 Cytochrome c peroxidase (PDB: 2X08) and formed interactions with six key amino acids in the active site (LEU, MET, TRP, SER, HIS, ARG), consistent with their high antioxidant activity.

The developed synthetic methodologies are suitable for expanding the library of potential antioxidants. Incorporating the 1,2,4-triazole pharmacophore is expected to enhance activity and potentially reduce toxicity; the docking data support further *in vitro*/*in vivo* evaluation.

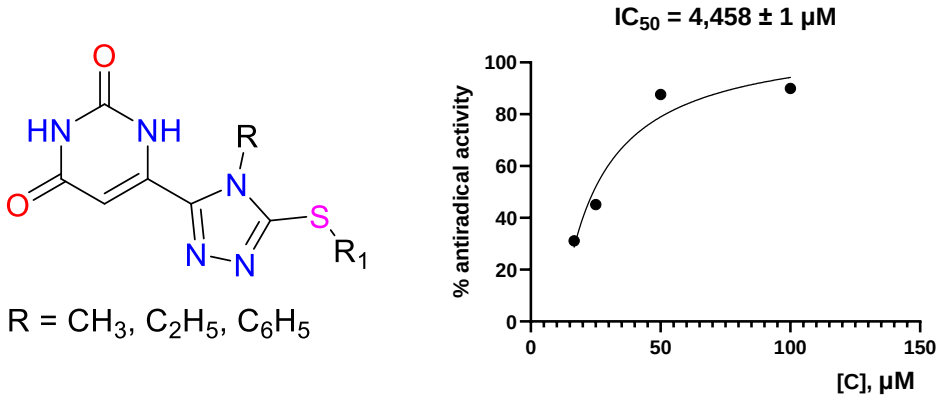

Fig. 1. Investigated compounds and IC_{50} calculation for the lead compound.

[1] Karpenko, Y.; Medvedeva, K.; Solomennyi, A.; Rudenko, O.; Panasenko, O.; Parchenko, V.; Vasyuk, S. Design, Synthesis, Molecular Docking, and Antioxidant Properties of a Series of New S-Derivatives of (1,2,4-Triazol-3(2H)-yl)methyl)thiopyrimidines. ScienceRise: Pharmaceutical Science 2025, 62-70.