

Synteza i właściwości fizykochemiczne funkcjonalizowanych 1,2,4,5-tetraoksanów o spodziewanej aktywności przeciwnowotworowej

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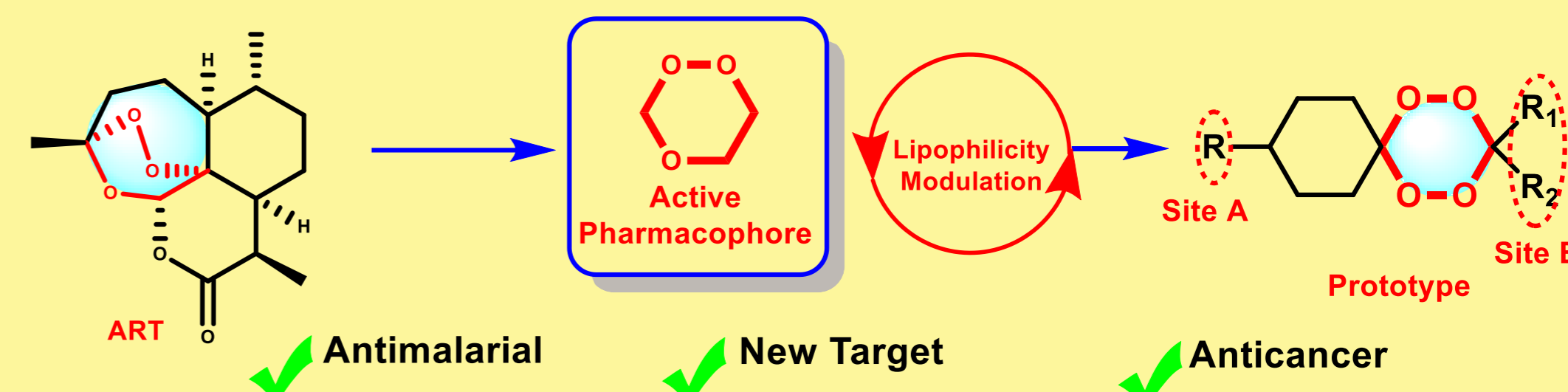
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Abstract

A novel library of diversely substituted non-symmetric 1,2,4,5-tetraoxanes (**4**) has been prepared using a key two-step methodology in the significant 26-78% yield range. In the preliminary *in vitro* microtox assessment, 1,2,4,5-tetraoxanes (**4**) exhibited a reduction of emitted bioluminescence at a 10⁻⁶ M concentration range against *Allivibrio fischeri* and have proven endowed with potent acute toxicity.



Introduction

The International Agency for Research on Cancer (IARC) has defined cancer as a global health issue, liable for 9.7 million mortalities in 2022 in 115 countries [1]. Chemotherapy is the most frequently used, easily accessible and efficient treatment protocol for fighting against cancer. However, fast-emerging drug resistance and severe immunity-related toxicity of classical drugs have imposed a demand for novel therapeutics [2]. Currently, researchers have relied on repurposing or reprofiling defined older drugs to overcome the challenge of the failure of traditional anticancer drugs [3]. Tetraoxanes are potent anticancer drug development candidates from the endoperoxide family with a higher therapeutic index [5]. Recently, it was confirmed that the core peroxide bridge is the active pharmacophore responsible for the key anticancer activities [6]. Hence, a series of novel functionalized 1,2,4,5-tetraoxanes have been developed and their physicochemical and biological potential has also been assessed.

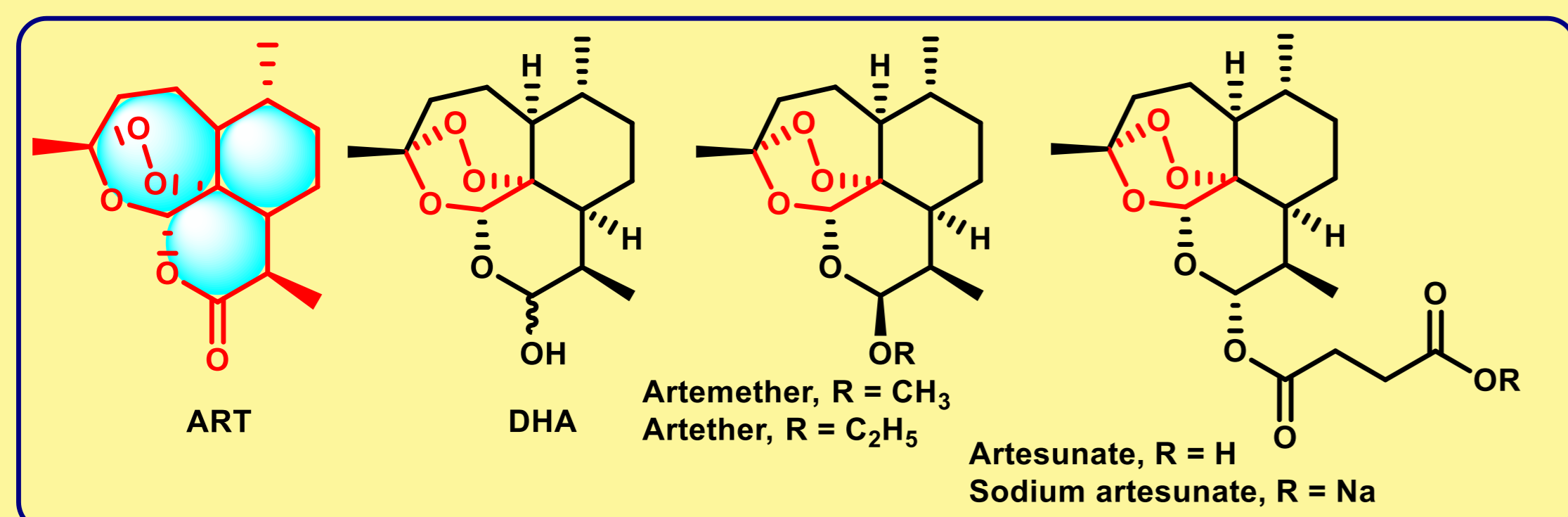
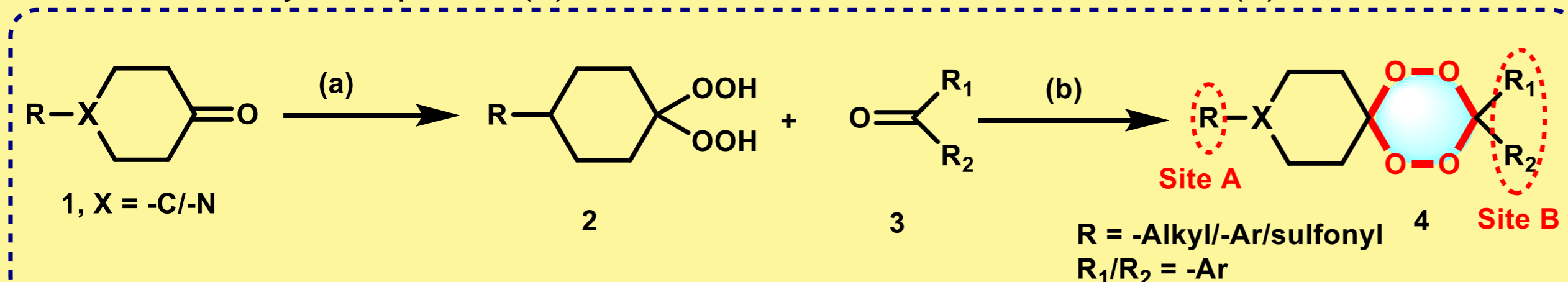


Figure 1: Artemisinin and derived semisynthetic analogues [4].

Results and Discussion

In the quest for more potent 1,2,4,5-tetraoxane motifs, the classical Methyltrioxorhenium(VII) complex (MTO)-catalysed two-step approach has been applied [7-8]. The critical steps of the protocol contain the following:

- MTO-catalysed *in-situ* generation of dihydroperoxides (DHP, **2**) from a range of substituted cyclohexanones (**1**), and
- Acid-catalysed condensation of highly reactive dihydroperoxides (DHP) with a suitable aromatic carbonyl compound (**3**) to afford desired 1,2,4,5-tetraoxanes (**4**).



Scheme 1: Reagents and Conditions: (a) **1** (1 equiv.), 35% H₂O₂ (2-4 equiv.), MTO (trace), HFIP/TFE (2-4 mL), r.t. 2h; (b) **3** (1-2 equiv.), HBF₄.OEt₂ (50-55% soln., 0.5 equiv.), r.t., 1 h.

This approach is quick and safe compared to other reported protocols and has been successfully applied for synthesising non-symmetric 1,2,4,5-tetraoxanes (**4**).

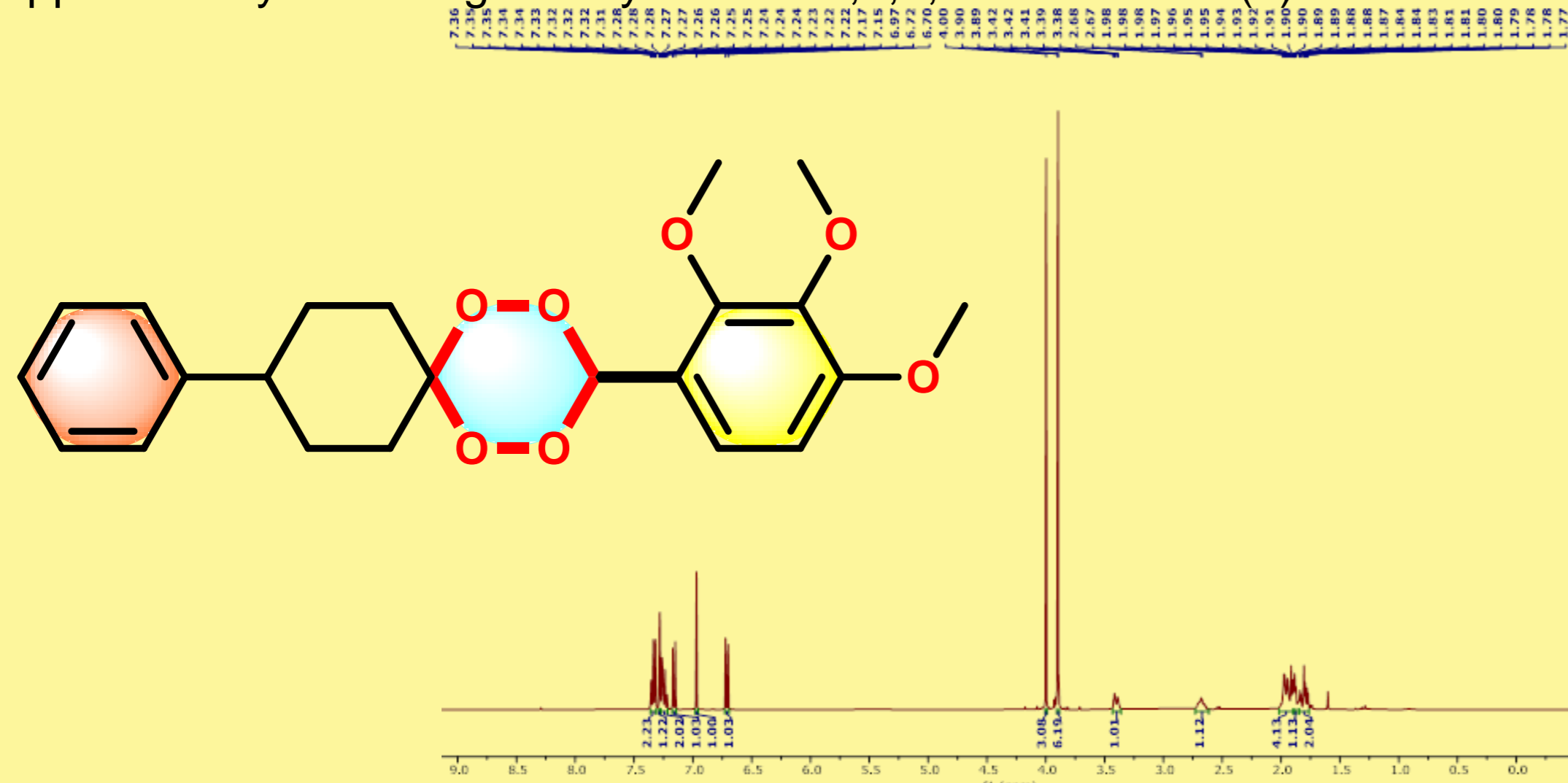


Figure 2: ¹H NMR of representative tetraoxane analogue.

Microtox Assessment

The novel non-symmetric 1,2,4,5-tetraoxanes (**4**) series was subjected to the Microtox acute toxicity test. The test is based on recording the changes in bioluminescence of a Gram-negative bacterium, *Allivibrio fischeri*, upon contact with a toxic substance.

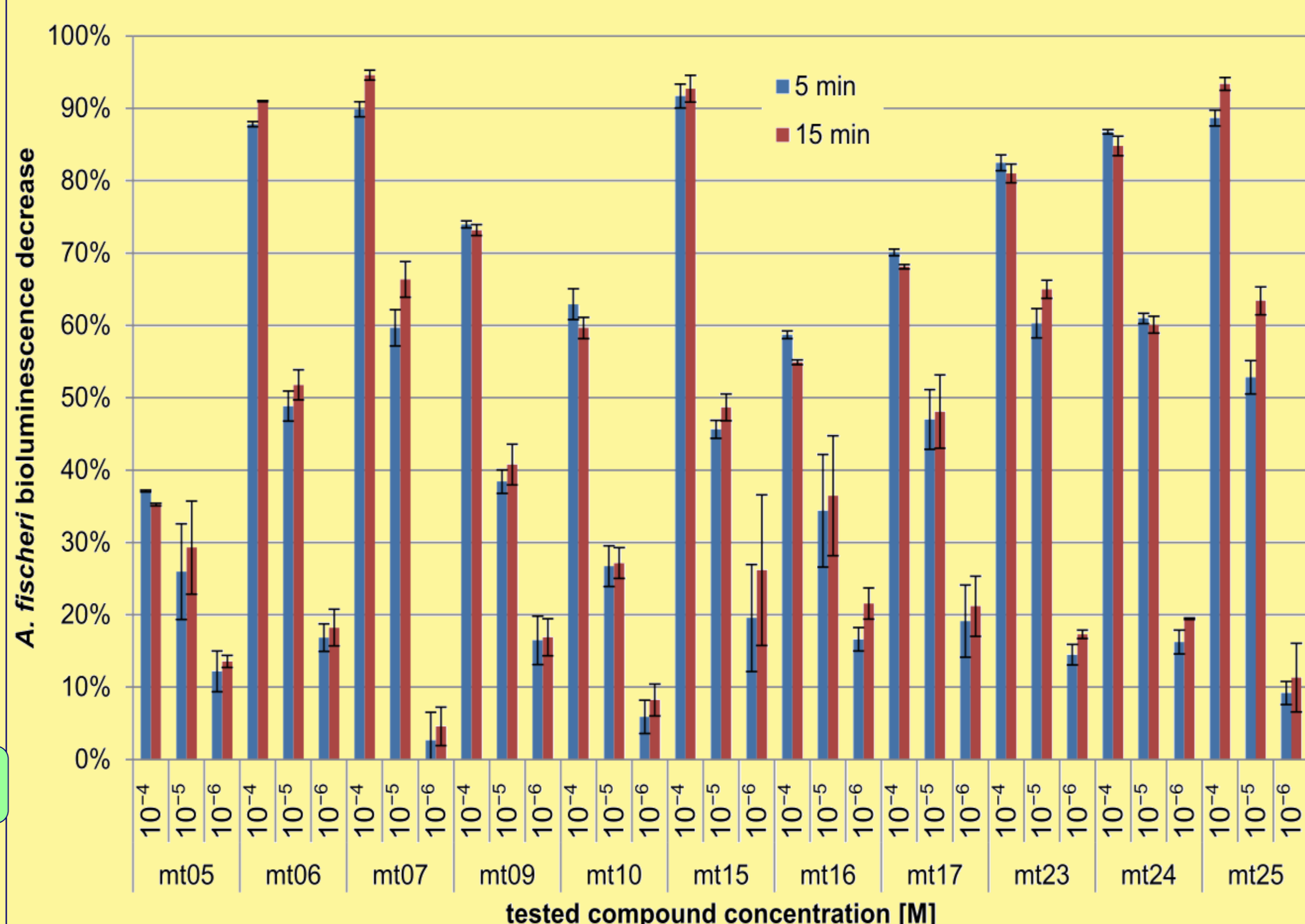


Figure 3: Changes in *Allivibrio fischeri* bioluminescence upon contact with the tested compounds. The experiments were performed in duplicate.

- The bioluminescence is correlated with the metabolism of this species – the presence of the toxicant results in decreased metabolism and emitted light. The arbitrary value of 20% is regarded as the toxicity threshold.
- The experiments were performed using the 81.9% Screening test protocol. Due to the limited solubility of 1,2,4,5-tetraoxanes, ≤1% of dimethylsulfoxide addition as the solubilizer was necessary.
- The obtained results are summarized in Figure 3.
- All of the tested compounds show toxic effects at 10⁻⁴ and 10⁻⁵ M concentrations. At the lowest tested concentration, 10⁻⁶ M, only three derivatives (mt15, mt16, mt17) still reduce the emitted bioluminescence of *A. fischeri* by over 20%, indicating them as toxic at this concentration.

Conclusions

- A novel series of non-symmetric 1,2,4,5-tetraoxanes (**4**) was developed in the 26-78% yield range.
- In vitro* acute toxicity of 1,2,4,5-tetraoxanes (**4**) was assessed against the Gram-negative bacterium, *Allivibrio fischeri*.
- Di- and tri-OMe substituted derivatives exhibited a reduction of emitted bioluminescence at a 10⁻⁶ M concentration range.
- 1,2,4,5-Tetraoxanes (**4**) showed profound *in vitro* cytotoxicity in preliminary examination.
- A detailed *in vitro* evaluation of antitumor potential against different drug-sensitive and multidrug-resistant cancer cells is currently under investigation.

References

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