

Article

A Bis(Acridino)-Crown Ether for Recognizing Oligoamines in Spermine Biosynthesis

Péter Kisfaludi ¹, Sára Spátay ^{1,2}, Marcell Krekó ^{2,3}, Panna Vezse ¹, Tünde Tóth ^{1,4}, Péter Huszthy ^{1,*}  and Ádám Golcs ^{1,2,3,*}

¹ Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, Szent Gellért Square 4, 1111 Budapest, Hungary; kisfaludi.peti@edu.bme.hu (P.K.); spatay.sara@edu.bme.hu (S.S.); panna.vezse@edu.bme.hu (P.V.); toth.tunde@vbk.bme.hu (T.T.)

² Department of Pharmaceutical Chemistry, Semmelweis University, Hőgyes Endre Street 9, 1092 Budapest, Hungary; kreko.marcell@semmelweis.hu

³ Center for Pharmacology and Drug Research & Development, Department of Pharmaceutical Chemistry, Semmelweis University, Üllői Street 26, 1085 Budapest, Hungary

⁴ HUN-REN Centre for Energy Research, Konkoly-Thege Miklós Street 29-33, 1121 Budapest, Hungary

* Correspondence: huszthy.peter@vbk.bme.hu (P.H.); golcs.adam@semmelweis.hu (Á.G.)

Abstract: Oligoamines in cellular metabolism carry extremely diverse biological functions (i.e., regulating Ca^{2+} -influx, neuronal nitric oxide synthase, membrane potential, Na^+ , K^+ -ATPase activity in synaptosomes, etc.). Furthermore, they also act as longevity agents and have a determinative role in autophagy, cell growth, proliferation, and death, while oligoamines dysregulation is a key in a variety of cancers. However, many of their mechanisms of actions have just begun to be understood. In addition to the numerous biosensing methods, only a very few simple small molecule-based tests are available for their selective but reversible tracking or fluorescent labeling. Motivated by this, we present herein a new fluorescent bis(acridino)-crown ether as a sensor molecule for biogenic oligoamines. The sensor molecule can selectively distinguish oligoamines from aliphatic mono- and diamino-analogues, while showing a reversible 1:2 (host:guest) complexation with a stepwise binding process accompanied by a turn-on fluorescence response. Both computational simulations on molecular docking and regression methods on titration experiments were carried out to reveal the oligoamine-recognition properties of the sensor molecule. The new fluorescent chemosensor molecule has a high potential for molecular-level functional studies on the oligoamine systems in cell processes (cellular uptake, transport, progression in cancers, etc.).

Keywords: biogenic oligoamines; spermine; spermidine; fluorescence; chemosensor; crown ether



Citation: Kisfaludi, P.; Spátay, S.; Krekó, M.; Vezse, P.; Tóth, T.; Huszthy, P.; Golcs, Á. A Bis(Acridino)-Crown Ether for Recognizing Oligoamines in Spermine Biosynthesis. *Molecules* **2024**, *29*, 4390. <https://doi.org/10.3390/molecules29184390>

Academic Editor: Alexander F. Khlebnikov

Received: 2 August 2024

Revised: 5 September 2024

Accepted: 11 September 2024

Published: 15 September 2024



Copyright: © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

A great number of biologically active molecules contain at least one or more amino functional groups. Biogenic amines are found in various organisms, cells, foods, and beverages and can be classified as monoamines, oligoamines, and polyamines depending on the number of amine functions they contain. They are typically synthesized by living organisms through enzymatic decarboxylation of amino acids [1–3]. Biogenic aliphatic oligoamines such as spermine (4), spermidine (3), putrescine (1), and cadaverine (2) (Figure 1) are among the most important ones, which can be found in almost all living organisms. They exist within cells in protonated forms and play important roles in diverse biological processes, such as cell growth, gene regulation, nucleic acid stabilization, and cell proliferation [4–6].

In vertebrates, two oligoamines, spermidine (3) and spermine (4), are present along with their precursor, the diamine putrescine (1). The absence of a normal oligoamine content can have a significant impact on cell functions including differentiation, apoptosis, motility, and resistance to oxidative and other stresses [7,8]. The importance of these oligoamines is shown not only in the effects of their absence but also in their extensive