Università di Torino

Università di Padova

Università di Roma

Società Italiana di Biochimica
e Biologia Molecolare

Società Italiana di Biochimica e Biologia Molecolare

Gruppo Amine Biogene

International Congress:

Biogenic Amines 2011

Biochemical, Physiological and Clinical Perspectives

September 21 – 25, 2011

Alberè di Tenna (Trento), ITALY

A KINETIC STUDY OF NEW POLYAMINE ANALOGS OXIDIZED BY BOVINE SERUM AMINE OXIDASE

[1]Stefania Saccoccio, [2]Anna Minarini, [2]Andrea Milelli, [2]Vincenzo Tumiatti, [1]Giampiero Tempera, [1]Nikenza Viceconte, [3]Roberto Stevanato and [1]Enzo Agostinelli

[1]Department of Biochemical Sciences 'A. Rossi Fanelli', SAPIENZA University of Rome and CNR, Biology and Molecular Pathology Institutes, Piazzale Aldo Moro 5, 00185 Rome; [2]Department of Pharmaceutical Sciences, Alma Mater Studiorum, University of Bologna, Via Belmeloro 6, 40126 Bologna and [3]Department of Physical Chemistry, University of Venice "Ca' Foscari", Dorsoduro 2137, 30123 Venice, Italy

E-mail: enzo.agostinelli@uniroma1.it

The low efficacy of drugs currently used in anticancer therapeutic applications and the development of multidrug-resistance prompted us to study the polyamine pathway as a possible target for the development of new anti-proliferative pharmacological agents.

In order to develop new amino oxidase (AO) spermine-based ligands, several spermine analogs were synthesized with the aim to improve their enzymatic oxidative deamination. Kinetic observations were carried out in buffer phosphate 0.01M, at pH 7.4-7.6, in order to perform cytotoxic studies using BSAO enzyme (Bovine Serum Amine Oxidase) in the presence of polyamine analogs on cancer cells. BSAO catalyzes, in the presence of O_2, the oxidative deamination of spermine, spermidine and their analogs, providing the formation of H_2O_2, aldehyde(s) and NH_3. The kinetic assays were performed using the new synthesized compounds in the range between 0.05-1 mM in the presence of BSAO. As shown in Table 1 the insertion of thiophene on one of terminal amines and substitution of the inner nitrogen atoms of spermine with oxygens, led to improved kinetic parameters (Table 1).

The improvement of the kinetic parameters obtained at pH 7.6, in comparison with that observed at pH 7.4 (1) , is probably due to a better interaction between amine-oxidase with the substrates, constituted by polyamine analogs, that leads to the formation of the Schiff base (2,3).

As future perspective, these molecules will be assayed alone or in combination with BSAO on several cancer cells, with the aim to evaluate their cytotoxic effect, that could be taken into consideration as new approach in anti-cancer therapy.

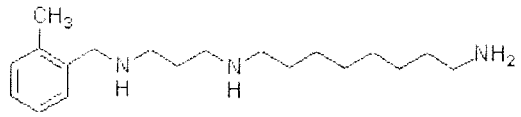
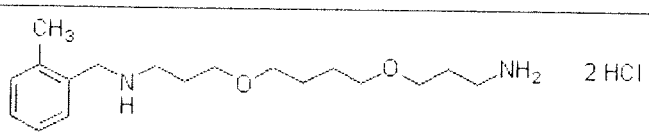
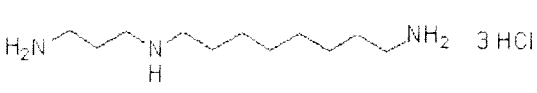
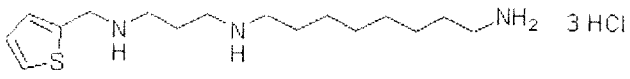
References:

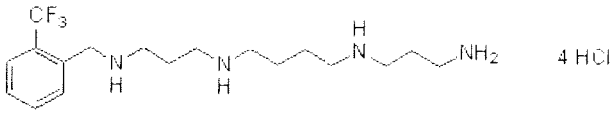
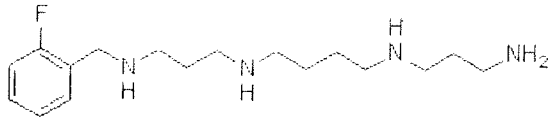
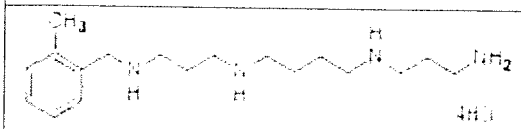
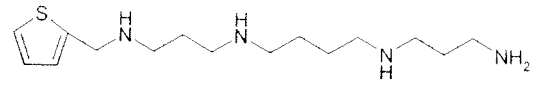
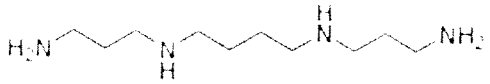
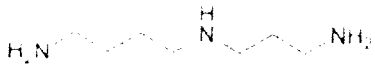
1. S. Saccoccio, A. Minarini, A. Milelli, V. Tumiatti, G. Tempera, N. Viceconte, R.o Stevanato and E. Agostinelli (2010) Oxidative deamination of new polyamine analogs by bovine serum amine oxidase: a kinetic study.2nd International Conference on the Role of Polyamines and their Analogs in Cancer and other Diseases Tivoli (Rome, Italy) December 1-6;

2. R. Stevanato, B. Mondovi, O. Befani, M. Scarpa and A. Rigo (1994) Electrostatic control of oxidative deamination catalysed by bovine serum amine oxidase.Biochem J 299: 317-320;

3. E. Agostinelli, A.Toninello, F. Vianello, R.Stevanato. (2011) Do mammalian amine oxidases and the mitochondrial polyamine transporter have similar protein structures? AminoAcids, doi: 10.1007/s00726-011-0988-x.

Table 1. Kinetic parameters of some polyamine analogs determined in buffer phosphate 0.01 M at pH 7.6

	Polyamines analogs	**Vmax** μM/s	K_M (μM) in BP 7,6 0,01M	K_C (s^{-1})in BP 7,6 0,01 M
	EB 20	0.33	97	0,04
	EB 22	0.36	3,78	0,47
	EB 23	0.24	10	0,31
	EB 26	0.36	7	0,462
	EB 27	0.36	8,37	0,46

 4 HCl	BD 32	0.47	17	0,61
 4 HCl	BD 33	0.40	38	0,52
	BD 9	0,13	7,2	0,25
 4HCl	BD 28	0.289	6	0.59
	Physiolog. polyamines	**Vmax** µM/s	K_M (µM) in TP 7.6 0.01M	K_C (s^{-1})in TP 7.6 0.01 M
	Spm	0.65	3.15	1,5
	Spd	0.56	51,5	1,13