

## Synthesis, cytotoxic and genotoxic activity of new chlorine-containing chlorophyll *a* derivatives

© Yana I. Pylina,<sup>1+</sup> Irina S. Khudyaeva,<sup>2</sup> Ekaterina A. Osipova,<sup>2</sup> Dmitry M. Shadrin,<sup>1</sup> Iliia O. Velegzhaninov,<sup>1</sup> Elena S. Belykh,<sup>1</sup> and Dmitry V. Belykh<sup>2\*</sup>

<sup>1</sup> Institute of Biology of Komi Science Centre of Ural Branch of RAS. Kommunisticheskaya St., 28. Syktyvkar, 167982. Republic of Komi. Russia. Phone: +7 (88212)31-25-23. E-mail: yanapylina@yandex.ru

<sup>2</sup> Institute of Chemistry of Komi Science Centre of Ural Branch of RAS. Pervomaiskaya St., 48. Syktyvkar, 167000. Republic of Komi. Russia. Phone: +7 (8212)21-99-47. E-mail: belykh-dv@mail.ru

\*Supervising author; <sup>+</sup>Corresponding author

**Keywords:** methylpheophorbide *a*, chlorin *e*<sub>6</sub>, chlorine-substituted porphyrins, *in vitro*, cytotoxic activity, photosensitizer.

### Abstract

On the basis of methylpheophorbide *a* new *a*-series chlorins with chlorine-containing substituents on the periphery of the macrocycle were synthesized. The dark and photoinduced cytotoxic activity of these compounds on HeLa cells was studied. It was shown that chlorins containing in their structure an exocycle have low dark and high photoinduced cytotoxic activity. By "DNA-comet assay" it was established that under photoinduced exposure of chlorins with an exocycle to HeLa cells, DNA damage does not occur.

### References

- [1] R.L. Lipson, E.J. Baldes, A.M. Olsen. The Use of a Derivative of Hematoporphyrin In Tumor Detection. *J. of the National Cancer Institute*. **1961**. Vol.26. No.1. P.1-11.
- [2] J. Moan, K. Berg. Photochemotherapy of cancer: experimental research. *Photochem. Photobiol.* **1992**. Vol.55. P.931-948.
- [3] B.W. Henderson, T.J. Dougherty. How does photodynamic therapy work? *Photochem. Photobiol.* **1992**. Vol.55. No.1. P.145-157.
- [4] G. Jori. Tumour photosensitizers: approaches to enhance the selectivity and efficiency of photodynamic therapy. *J. of Photochem. and Photobiol. B: Biology*. **1996**. Vol.36. P.87-93.
- [5] S.P. Songca. In-vitro activity and tissue distribution of new fluorinated meso-tetrahydroxyphenylporphyrin photosensitizers. *J. of Pharmacy and Pharmacology*. **2001**. Vol.53. P.1469-1476.
- [6] A.L. Gryshuk, Y. Chen, W. Potter, T. Ohulchansky, A. Oseroff, R.K. Pandey. In Vivo Stability and Photodynamic Efficacy of Fluorinated Bacterioporpurinimides Derived from Bacteriochlorophyll-*a*. *J. Med. Chem.* **2006**. Vol.49. P.1874-1881.
- [7] A.C. Serra, M. Pineiro, A.M. d'A. Rocha Gonsalves, M. Abrantes, M. Laranjo, A.C. Santos, M.F. Botelho. Halogen atom effect on photophysical and photodynamic characteristics of derivatives of 5,10,15,20-tetrakis(3-hydroxyphenyl)porphyrin. *J. of Photochem. and Photobiol. B: Biology*. **2008**. Vol.92. P.59-65.
- [8] X. Chen, L. Hui, D.A. Foster, C.M. Drain. Efficient Synthesis and Photodynamic Activity of Porphyrin-Saccharide Conjugates: Targeting and Incapacitating Cancer Cells. *Biochemistry*. **2004**. Vol.43. P.10918-10929.
- [9] Y.-J. Ko, K.-J. Yun, M.-S. Kang, J. Park, K.-T. Lee, S.B. Park, J.-H. Shin. Synthesis and in vitro photodynamic activities of water-soluble fluorinated tetrapyrrolylporphyrins as tumor photosensitizers. *Bioorganic & Medicinal Chemistry Letters*. **2007**. Vol.17(10). P.2789-2794.
- [10] A. Serra, M. Pineiro, C.I. Santos, A.M. d'A.R. Gonsalves, M. Abrantes, M. Laranjo, M.F. Botelho. In Vitro Photodynamic Activity of 5,15-bis(3-Hydroxyphenyl)porphyrin and Its Halogenated Derivatives Against Cancer Cells. *Photochem. Photobiol.* **2010**. Vol.86. P.206-212.
- [11] E.G. Azenha, A.C. Serra, M. Pineiro, M.M. Pereira, Melo J.S. de, L.G. Arnaut, S.J. Formosinho, A.M. d'A. R. Gonsalves. Heavy-atom effects on metalloporphyrins and polyhalogenated porphyrins. *Chemical Physics*. **2002**. Vol.280. P.177-190.
- [12] D.V. Belykh, E.V. Ashikhmina. Hydroxymethylation of Methylpheophorbide *a* Exocyclic Ring. *Macrocyclics*. **2014**. Vol.7. No.1. P.88-90.

- [13] D.V. Belykh, L.P. Karmanova, L.V. Spirikhin, A.V. Kuchin. Synthesis of amide derivatives of chlorin e6. *Journal of Organic Chemistry*. **2007**. Vol.43. Iss.1. P.120-128. (russian)
- [14] Y.I. Pylina, D.M. Shadrin, O.G. Shevchenko, O.M. Startseva, I.O. Velegzhaninov, D.V. Belykh, I.O. Velegzhaninov. Dark and Photoinduced Cytotoxic Activity of the New Chlorophyll-a Derivatives with Oligoethylene Glycol Substituents on the Periphery of Their Macrocycles. *Int. J. Mol. Sci.* **2017**. Vol.18. P.103.
- [15] L. Lindhagen, P. Nygren, R. Larsson. The fluorometric microculture cytotoxicity assay. *Nature protocols*. **2008**. Vol.3. No.8. P.1364-1369.
- [16] R.R. Tice, E. Agurell, D. Anderson, B. Burlinson, A. Hartmann, H. Kobayashi, Y. Miyamae, E. Rojas, J.-C. Ryu, Y.F. Sasaki. Single Cell Gel/Comet Assay: Guidelines for In Vitro and In Vivo Genetic Toxicology Testing. *Environmental and Molecular Mutagenesis*. **2000**. Vol.35. P.206-221.
- [17] R. Appel. Tertiary Phosphane/Tetrachloromethane, a Versatile Reagent for Chlorination, Dehydration, and P-N Linkage. *Angew. Chem. Internat. Edit.* **1975**. Vol.14. No.12. P.801-811.
- [18] D.V. Belykh, O.M. Startseva, Patov S.A. Novel pH-Independent Amphiphilic Chlorophyll a Derivatives with Oligoethyleneglycol Substituents as a Hydrophilic Part: Synthesis and Hydrophilicity Estimation. *Macroheterocycles*. **2014**. Vol.7. No.4. P.401-413.