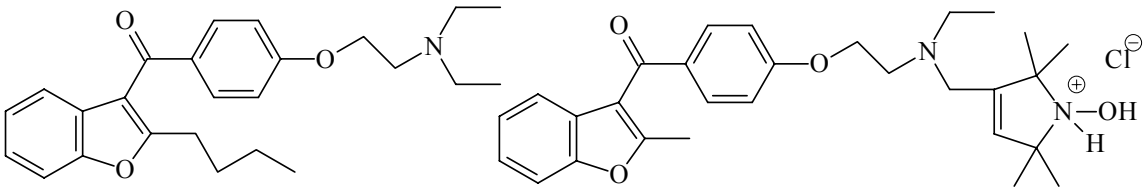
SYNTHESIS OF NEW AMIODARONE DERIVATIVES

Tamás Kálai[a], Zita Bognár[a], Gábor Várbiró[b], Balázs Bognár[a], Anita Pálfi[c], Katalin Hantó[c], Balázs Sümegi[b], and Kálmán Hideg[a]

[a]Institute of Organic and Medicinal Chemistry,
University of Pécs, Szigeti st. 12, H-7624 Pécs, Hungary
[b]Institute of Biochemistry and Medical Chemistry,
University of Pécs, Szigeti st. 12, H-7624 Pécs, Hungary
[c]Division of Cardiology, First Department of Medicine, Faculty of Medicine,
University of Pécs, Szigeti st. 12, H-7624 Pécs, Hungary

Amiodarone **1**, a widely used antiarrhythmic agent, has a mixed effect on the mitochondrial permeability transition (MPT) in low concentration, however induces mitochondrial swelling when administered in higher doses [1]. To eliminate the side-effects of amiodarone, several structural changes have been attempted [2]. In this work we report the butyl side-chain alteration for methyl and diethylamino side-chain modification with 2,2,5,5-tetramethylpyrroline nitroxide or its hydroxylamine or secondary amine precursor. The latter type of modification was proved to be advantageous previously in the case of class Ib antiarrhythmic agents: H-2545 [3], mexiletine [4]. This idea was confirmed again by the biological effect of compound **2** which inhibited MPT in isolated mitochondria in a concentration-dependent manner with an IC50 value of 4.9 ± 0.5 μM [5]. It also inhibited the release of mitochondrial pro-apoptotic proteins cyt c, AIF and endoG and exhibited antioxidant effect in cultured cell lines.



1 **2**

[1] Várbiró, G.; Tóth, A.; Tapodi, A.; Veres, B.; Sümegi, B.; Gallyas, F. *Biochem. Pharmacol.* **2003**, *65,* 1115.
[2] Carlsson, B.; Singh, B. N.; Temciuc, M.; Nilsson, S.; Li, Y-L.; Mellin, C.; Malm, J. *J. Med. Chem*. **2002**, *45*, 623.
[3] Hankovszky, H. O.; Hideg, K.; Bodi, I.; Frank, L. *J. Med. Chem*. **1986**, *29*, 1138.
[4] Li, H.; Xu, K. Y.; Zhou, L.; Kálai, T.; Zweier, J. L.; Hideg, K.; Kuppusamy, P. *J. Pharmacol. Exp. Ther.* **2000**, *295,* 563.
[5] Kálai, T.; Várbiró, G.; Bognár, Z.; Pálfi, A. Hantó, K.; Bognár, B.; Ősz, E.; Sümegi, B.; Hideg, K. *Bioorg. Med. Chem*. **2005** (in press)