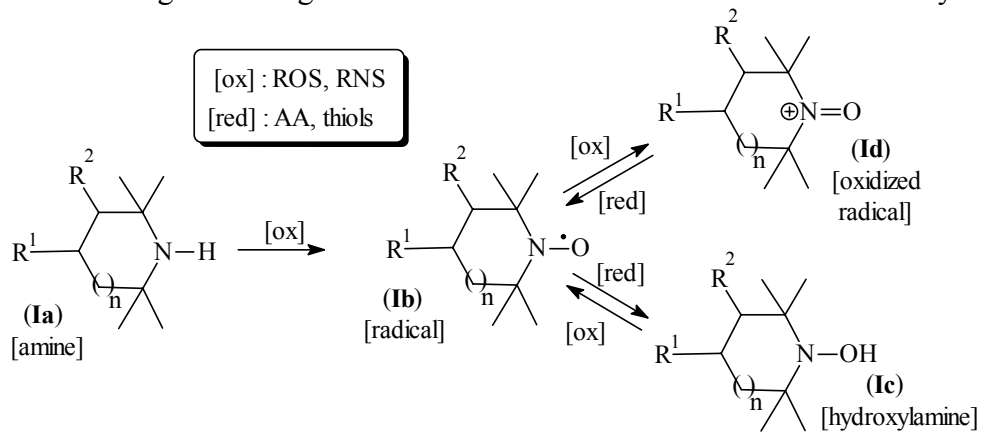
NEW PARP INHIBITORS

Kálmán Hideg

Institute of Organic and Medicinal Chemistry, University of Pécs, H-7602 Pécs, Hungary

Reactive oxygen and nitrogen species (ROS, RNS) contribute to the ischemia and reperfusion induced tissue injury, and initiate lipid peroxidation, protein oxidation and the formation of single-strand DNA breaks. Single-strand DNA breaks can activate the nuclear poly-ADP-ribose polymerase (PARP) ultimately resulting in depletion of NAD. The inhibition of PARP can improve the recovery of different cells from oxidative damages. PARP inhibitors abrogated the ischemia-reperfusion induced lipid peroxidation and protein oxidation, and significantly decreased ssDNA break formation.
Several PARP inhibitors were synthesized and have shown efficacies in several animal disease models of cancer, ischemia and inflammation. Various 2-substituted-4-carboxamidobenzi-midazoles, mono- and bicyclic carboxamides, bi-, tri- and tetracyclic lactams and some other heterocyclic molecules were proposed as PARP-inhibitors [1]. The sterically hindered amines and non-toxic radicals may offer the exceptional advantage that they can fulfil the function of multi-step protectors in an antioxidant cascade system. The sterically hindered pyrroli(di)ne or piperidine-*N*-oxyl derivatives (Ib) and their amine precursors (Ia) exhibit a protective effect against damages caused by H_2O_2 and other ROS; they also exhibit a cardioprotective effect [2]. Molecules I having R^1 heterocyclic substituent (e.g. 4-carboxamidobenzimidazolyl-, quinazolyl-group) R^2 e.g. alkyl, aryl) with proper affinity to nicotinamide binding pocket of PARP 1 protein make these compounds capable of inhibiting the damages of DNA *via* the inhibition of the PARP activity.



[1] Reviews: Virág, L.; Szabó, C. *Pharmacol. Rev.* **2002**. *54,* 804; Pellicciari, R. et al. *Progr. Med. Chem*. **2004,** *42***,** 125 (Eds. A. D. King, F. W. Oxford), Elsevier**.**
[2]. Hankovszky, H. O., et al. *J. Med. Chem*. **1986**, *29*, 1138; Krishna, M. C., et al. *J. Med. Chem.* **1998,** *41,* 3477; Twomey, P., et al. *Free Rad. Biol. Med*. **1997**, *22*, 909; Shankar, R. A. et al, *J. Pharmacol. Exp. Ther.* **2000**, *292*, 838. Li, H., et al *J. Pharmacol. Exp. Ther.* **2000**, *295*, 563; Alexy, T., et al. *J. Cardiovasc. Pharm*. **2004**, *43*, 423; Deres, P., et al. *J. Cardiovasc. Pharmacol*. **2005**. *45*, 36. Kulcsár, G. et al. *ARKIVOC* **2003***,* 121-131.