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BOOK OF ABSTRACT

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FLASH POSTER ABSTRACT

QR2 (putative MT3) Inhibitors in the Treatment of Glaucoma: Achievements and Prospects

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FP 12

Glaucoma is a neurodegenerative eye disease responsible for 15% of blindness worldwide. One of the crucial factors of this disease is the increased intraocular pressure (IOP). All available anti-glaucoma medications act only as IOP lowering agents. However, we have discovered that 2-oxindoles, being the ligands of the quinone reductase II (QR2, putative melatonin MT3 receptor), not only significantly reduce IOP, but also possess antioxidant neuroprotective properties[a-c]. We have developed effective synthetic method for the preparation of oxindole-based melatonin bioisosteres[e-d]. More than 75 new compounds were tested in vivo on normotensive rabbits. A group of compounds with high IOP reducing effect (>40%) at low concentrations (0.1 wt%) and prolonged action (up to 28 h) was identified[a]. The obtained lead compounds are even less toxic than melatonin (LD_{50} = 2400 mg/kg and 800 mg/kg, respectively)[a]. All tested compounds have great antioxidant properties – 100 times higher than melatonin. These results allow us to state that we are on the way to developing a new generation anti-glaucoma drug.

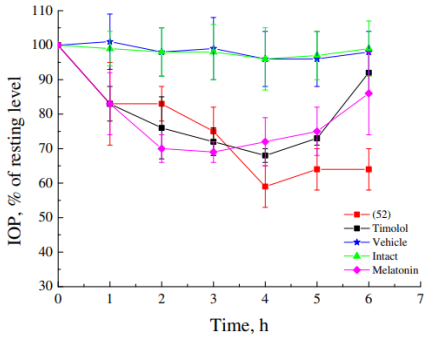
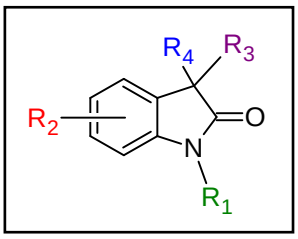


Fig. 1. Time-dependent study for (5-acetamido-2-oxindole-3-yl)acetic acid (52) [a]



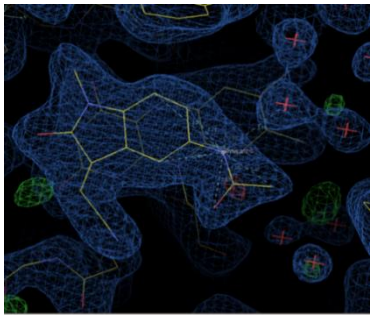


Fig. 2. X-ray crystal structures of (5-acetamido-2- oxoindolin-3-yl) acetonitrile in complex with QR2 (PDB ID: 4GQI, 4GR9) [a]

Bibliographic references:

(a) Bioorganic and Medicinal Chemistry Letters, 2017, Vol. 27, P. 3787-3793.

(b) Tetrahedron, 2017, Vol. 73, P. 6887-6893

(c) Biochemistry, Supplemental Series B, 2017, Vol. 11, no. 3, P. 272-278

(d) International Journal of Chemical and Biomedical Science, 2015, Vol. 1, no. 5, P. 109–118.

(e) Bioorganic and Medicinal Chemistry Letters, 2012, Vol. 22, no.5, P. 7578-7581

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