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Oxindole-based intraocular pressure reducing agents

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ABSTRACT

The study represents the new findings at the crossroads of chemistry and medicine, particularly between medicinal and organic chemistry and ophthalmology. In this work we describe how the chemical reactivity of indolinone scaffold may be used to create small molecule ligands with strong biological response comparable with and larger than that of endogenous hormone. The synthesis of oxindole-based melatonin and 5-methoxycarbonylamino-N-acetyltryptamine (5-MCA-NAT) analogues was proposed and their ability to influence intraocular pressure (IOP) was studied *in vivo*. Time-dependent study revealed the prolonged effect (more than 6 h) of the lead-compound. This effect in combination with high IOP reducing effect (41 ± 6%) in low concentrations of the active compound (0.1 wt%) and with high water solubility represents a great potential of low-cost oxindole derivatives as potent antiglaucoma agents.

Introduction

According to the World Health Organization, about 65% of all people who are visually impaired are aged 50 and older, while this age group comprises about 20% of the world's population. The major causes of blindness are uncorrected refractive errors (myopia, hyperopia or astigmatism), unoperated cataract, and glaucoma. The most disruptive symptom of glaucoma is increased intraocular pressure (IOP). It leads to disorders of the visual system and optic atrophy.[1] The most common treatment for glaucoma is the application of IOP-lowering drugs. There are a lot of types of agents, which can reduce the intraocular pressure, such as miotics, prostaglandin analogues and carbonic anhydrase inhibitors[1,2] and their different formulations, including solutions and nanoparticles.[2] Nowadays the drug combination therapy is also applied.[2] The mechanisms of IOP reduction are different for different drug types; the value of biological effect varies from 15 to 35%. Moreover, side effects often come along with the desired one, thus the lack of selective and effective drug for glaucoma treatment is the reason for further research.

Meanwhile, new targets for the treatment of glaucoma have been recently found. Melatonin is known to reduce IOP and also to exhibit antioxidative and neuroprotective properties, which are most likely to associate with the MT3-subtype receptor (quinone reductase 2, QR2, NQO2) inhibition.[3–5]

There are several available MT3-selective ligands, including the potent antidepressant agent 5-methoxycarbonylamino-N-acetyltryptamine (MCA-NAT), which has a high affinity (Ki = 65 nM, IC50 = 58 nM[2]) for the MT3 receptor.[6,7] MCA-NAT is also known to significantly decrease IOP in a dose-dependent manner (max 45%).[8,9] Despite effective lowering of IOP, 5-MCA-NAT is not used as an antiglaucoma agent due probably to its low solubility in water.[5]

The oxindole nucleus was selected as a scaffold because of its planar structure close to indole ring of melatonin, greater metabolic resistance, stability during synthetic experiments allowing the modification of such a central fragment in different ways and cost effectiveness of the synthetic procedures and starting materials. Moreover our research group previously demonstrated that indolinone-based melatonin and MCA-NAT analogues have a good affinity for quinone reductase 2.[6] According to the data of X-ray diffraction, these compounds can be strongly bound to QR2 (Fig. 1, Table 1).

Taking into account a great potential of ligands for melatonin-binding sites, the development of a general approach to the synthesis of such ligands is an important problem. Recently, we described the synthesis of melatonin receptor ligands and demonstrated their high affinity for MT3 melatonin receptors.[6] On the basis of the analysis of X-ray crystal structures of MT3 receptor/

Abbreviations: IOP, intraocular pressure; QR2, NQO2, quinone reductase 2; MCA-NAT, 5-MCA-NAT - 5-methoxycarbonylamino-N-acetyltryptamine.

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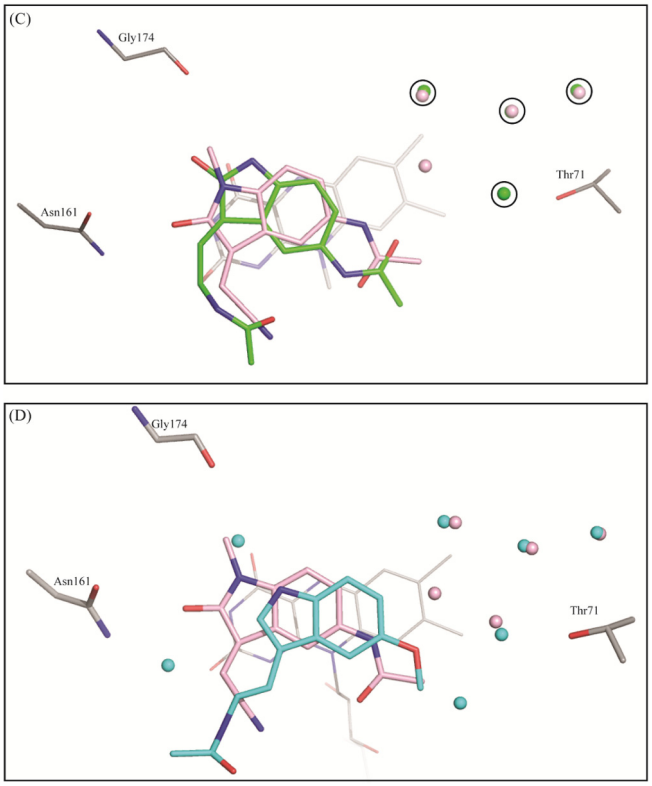


Fig. 1. X-ray crystal structures of superposition of melatonin (green/blue) with N-acetyl-(5-acetamido-2-oxoindolin-3-yl)ethylamine (C, pink) and (5-acetamido-2-oxoindolin-3-yl)acetonitrile (D, pink) in complex with QR2 (PDB ID: 4GQJ, 4GR9). Ligands are shown in stick and ball representation and are colored according to atom type (red for oxygen, blue for nitrogen). Water molecules in the active site are shown in solid spheres, and are colored according to the colour of the compound to which they refer; water molecules, present in each complex, are circled in black.[6]

ligand complexes, we proposed some new ways of modification of the oxindole core to improve the affinity and biological activity of agents. The results supported the feasibility of the new general approach to the synthesis of novel melatonin analogues, and this method was used for preparation of new indolinones. The biological activity was also measured *in vivo*. These data suggest a great potential of synthesized compounds for treating ophthalmological diseases.

Based on the results of the previous research of enzymatic activity,[6] several other compounds were examined as inhibitors of the QR2, IC50 values were estimated (Table 1).

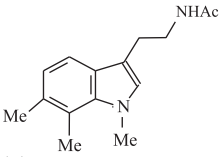
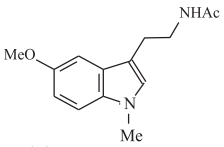
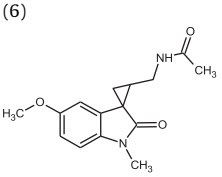
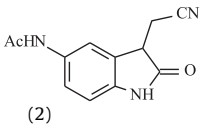
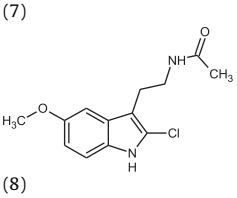
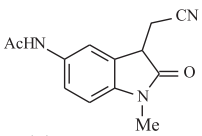
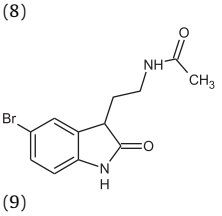
It was shown that the IC50 values for indolinones and spiroindolinones are similar to the value for melatonin (6.6 μM[6]). So, it may be suggested that the introduction of carbonyl group at the 2nd position of oxindole does not change the planarity of the system, and can also participate in the formation of additional hydrogen bonds in the active site of the receptor. The modification of the 3-position of indole proved important. Thus, the addition of hydroxyl group (5) improves the affinity, whereas the conformational restriction has no effect on this parameter (7). Moreover, an increase in the cycle size of the cyclic substituent leads to a decrease of the affinity (10). It was demonstrated that the 2-acetamidoethyl substituent is not required for MT3 receptor affinity (1, 4–10) because IC50 values for (2-oxindol-3-yl)acetonitriles (2, 3) are in the same range.

However, the role of the ring substituents in selective binding is unclear. Therefore, it is interesting to vary the substituents at 4–7-positions and perform isosteric or bioisosteric replacements of the nitro-group.

We performed the synthesis, as described below, taking into account the structure-activity relationships observed in enzymatic activity assay.

A variety of approaches have been developed to modify the oxindole core. The general approach for the synthesis of the indolinones based drug candidates is presented in Scheme 1.

Table 1
IC50 values and inhibition activity of indolinones derivatives.

Ligand	IC50 (μM)	% max inhibition	Ligand	IC50 (μM)	% max inhibition
Melatonin	6.6 ± 0.7	85.2 ± 2.3	 (6)	4.5 ± 1.1	97.4 ± 0.4
 (1)	5.7 ± 1.0	101.9 ± 1.1	 (7)	5.1 ± 1.1	93.9 ± 0.4
 (2)	14.1 ± 0.8	100 ± 2	 (8)	13.0 ± 1.8	91 ± 2
 (3)	7.0 ± 0.5	99 ± 2	 (9)	19.0 ± 2.4	29.9 ± 0.4