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Cardiovascular activity of the chiral xanthone derivatives

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ABSTRACT

A series of 6 derivatives of xanthone were synthesized and evaluated for cardiovascular activity. The following pharmacological experiments were conducted: the binding affinity for adrenoceptors, the influence on the normal electrocardiogram, the effect on the arterial blood pressure, the effect on blood pressor response and prophylactic antiarrhythmic activity in adrenaline induced model of arrhythmia (rats, iv). Two compounds revealed nanomolar affinity for α_1-adrenoceptor which was correlated with the strongest cardiovascular (antiarrhythmic and hypotensive) activity in animals' models. They were enantiomers of previously described (*R,S*)-4-(2-hydroxy-3-(4-(2-methoxyphenyl)piperazin-1-yl)propoxy)-9*H*-xanthen-9-one hydrochloride and revealed similar antiarrhythmic potential in adrenaline induced model of arrhythmia in rats after intravenous injection (ED_{50} = 0.53 mg/kg and 0.81 mg/kg, respectively). These values were lower than values obtained for reference drug urapidil. These compounds were more active in this experiment than urapidil (ED_{50} = 1.26 mg/kg). The compound **5** administered iv at doses of 0.62–2.5 mg/kg at the peak of arrhythmia prevented and/or reduced the number of premature ventricular beats in a statistically significant manner. The ED_{50} value was 1.20 mg/kg. The *S*-enantiomer (**6**) given at the same doses did not show therapeutic antiarrhythmic activity in this model.

These compounds significantly decreased the systolic and diastolic blood pressure throughout the whole observation period in anesthetized, normotensive rats. The studied enantiomers showed higher toxicity than urapidil, but imperceptibly higher that another cardiovascular drugs, that is, carvedilol or propranolol. They were also evaluated for mutagenic potential in the Ames (*Salmonella*) test. It was found that at the concentrations tested the compounds were non mutagenic when compared to solvent control.

Results were quite promising and suggested that in the group of xanthone derivatives new potential antiarrhythmics and hypotensives might be found.

1. Introduction

Cardiovascular diseases include broad spectrum of disorders, in especial: coronary heart disease, cerebrovascular disease, hypertension, peripheral artery disease, rheumatic heart disease, congenital heart disease and heart failure are caused by disorders of the heart and blood vessels. They remain number one cause of death worldwide, particularly among women (32% of all deaths). The Global Burden of Disease study estimated that in 2004, 12.9 million of almost 59 million total worldwide deaths were caused by them.[1]

One quarter of all cardiovascular-related deaths is caused by arrhythmias. What is important, their etiology is diversified and associated with many different conditions. The key role in the pathogenesis of abovementioned cardiac dysfunctions, plays activation of sympathetic nervous system. In that light, it is not surprising that adrenergic receptors antagonists are effective in the treatment of this disease and are widely used. Another important fact is proper interplay of ion channels, especially sodium, potassium, and calcium thus disturbances in their function may result in arrhythmia occurence.[2] Moreover, antiarrhythmic drugs are commonly affected with adverse effects such as bradykardia, tiredness, dizziness or thyroid dysfunction.[3] Taking into account the variety of arrhythmias' types, their diverse etiology and numerous side effects of antiarrhythmic drugs there is still a need to search

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for new agents that can improve heart function with minimal side effects.

The second, serious cardiovascular disorder is hypertension. Hypertension is one of the most common significant diseases, affecting approximately 1.4 billion people worldwide. The prevalence of essential hypertension steadily increases with age. As the world population ages, the prevalence of hypertension is expected to increase even further. Despite extensive translational and clinical research, concerted patient education with regard to vascular risk factors and lifestyle modifications, and a serious effort on the part of health care professionals over the last few decades, only one third of hypertensive patients have blood pressure (BP) controlled to recommended levels of: 140/90 mm Hg.[4]

Most cases of hypertension are so-called essential or primary hypertension, with unknown etiology. Only 5% of cases, named secondary hypertension, have known etiology and are associated with e.g. arteriosclerosis or hyperthyreosis. Nowadays, the number of patients suffering from hypertension is still increasing, partially due to current lifestyle: lack of physical activity, overweight or obesity, using tobacco, too much sodium and too little potassium in diet, too little vitamin D in diet, drinking too much alcohol and stress. Other risk factors are age and family predispositions. Taking into account the global scale of this disorder, searching for new potential hypotensive agents seems to be reasonable.[5]

Xanthone itself was proved to possess vasorelaxating properties in thoracic aorta isolated from rats.[6] These data suggested that xanthone-induced vasorelaxation was endothelium independent and the mechanism might involve an increase in intracellular cyclic adenosine 3′,5′-monophosphate (cAMP) and the blockade of Ca^{2+} channels. Other research on a series of aminoalkanolic xanthone derivatives confirmed hypotensive activity of all tested compounds. It was noticed that, an oxypropanolamine side chain substituted at the C-3 position of the xanthone nucleus significantly enhanced the hypotensive activity. The most potent seemed to be 3-(3*N*-*i*-propylamine-2-hydroxypropoxy)-9*H*-xanthen-9-one (xanthonolol), which lowered systolic blood pressure by about 32–7% in dependence of dosage (from 5 to 0.1 mg/kg). Its mechanism of action was calcium channel dependant and required the blockade of β-adrenergic receptors. Xanthonolol possess typical, β-blocker moiety (3-amine-2-hydroxypropan-1-yloxy) characteristic for cardiovascular drugs such as propranolol and carvedilol.[7]

The newest communications exhibited interesting properties of xanthone-amine derivatives without typical β-blocker structure and bearing relatively long (4–5 methylene groups) alkane linker connecting pharmacophore structures.[8]

Our Laboratory of Bioorganic Chemistry, Chair of Organic Chemistry (previously Department of Technology and Biotechnology of Drugs) has been conducting searching for new hypotensive and/or antiarrhythmic structures, especially in the group of xanthone derivatives.[9] The strongest hypotensive effects were observed for compounds containing piperazine moiety. These compounds showed both in vitro (via binding affinity evaluations) and in vivo activity.[10] Other researchers also confirmed pharmacophoric effect of piperazine moiety.[11]

Basing on literature survey, herein we report in vitro and in vivo cardiovascular activity of some new derivatives. Two of the mentioned structures were enantiomers of previously described active one.[12] Next four compounds were analogs of our reported aminoalkanolic structures, possessed typical β-blocker moiety (3-amine-2-hydroxypropan-1-yloxy), others were devoided of hydroxyl group analogously to structures described by Lin et al.[8] and were evaluated to estimate role of hydroxyl group. Piperazine like amines were also diversified. Most of them contained methoxyphenylpiperazine—structural element of urapidil (typical α_1-adrenoceptor antagonist), others contain benzylpiperazine, phenoxyethylpiperazine, cinnamylpiperazine to ascertain pharmacophoric effect of methoxyphenylpiperazine or piperazine itself. We also introduced chlor substituent into xanthone ring to enhance lipophilicity and examine its effect on cardiovascular system.

2. Chemistry

The synthetic route that was used to synthesize of starting materials is outlined in Scheme 1. The detailed description of the method and physico-chemical properties of 3-((oxiran-2-yl)methoxy)-9*H*-xanthen-9-one were described in Ref. 13, 4-((oxiran-2-yl)methoxy)-9*H*-xanthen-9-one in Ref. 14, 3-chloro-5-((oxiran-2-yl)methoxy)-9*H*-xanthen-9-one was published in Ref. 15, whereas characteristic of (*R*)-4-((oxiran-2-yl)methoxy)-9*H*-xanthen-9-one and (*S*)-4-((oxiran-2-yl)methoxy)-9*H*-xanthen-9-one is mentioned below. The crude products were recrystallized from *n*-hexane/toluene (1:4). These intermediates are characterized in Section 7.

Compounds **1**–**6** were obtained by amination of respective parent compounds with appropriate amines in *n*-propanol, as described previously.[13,16] The last step of the synthesis was amination of the respective parent compound with appropriate amines in *n*-propanol as described previously.[17] After aminolysis, *n*-propanol was distilled off. Resulted amines were dissolved in diluted HCl, cleaned with charcoal and precipitated using NaOH solution. All resulted bases were converted into hydrochloride salts using an excess of ethanol saturated with HCl. The crude products were recrystallized from acetone/ethanol (1:3).

3. Pharmacology

3.1. Animals and experimental conditions

The studies were carried out on normotensive male Wistar rats weighing 180–250 g and male Albino Swiss (CD-1) mice weighing 18–24 g (Source: Animal House, Faculty of Pharmacy, Jagiellonian University Medical College, Krakow, Poland, stocks name: KRF: WI(WU)). The animals were kept in plastic cages in a room at constant temperature of 20 ± 4 °C, under 12/12 h light/dark cycle (light on from 7 a.m. to 7 p.m.). They had free access to food (standard laboratory pellets) and water before experiments. The control and study groups consisted of six to eight animals each. The experiments were performed between 8 a.m. and 3 p.m. The animals were killed by cervical dislocation immediately after the assay. All the procedures were conducted according to the Animal Care and Use Committee guidelines, and approved by the Local Ethics Committee of the Jagiellonian University in Cracow (resolution No. 118/2012).

3.2. Drugs

The tested compounds **1**–**6** were synthesized at the Department of Bioorganic Chemistry UJ CM. The following drugs were used: adrenaline, noradrenaline (Polfa, Poland), methoxamine (Sigma–Aldrich, Germany), sodium heparin (Polfa, Poland), thiopental sodium (Biochemie GmbH, Austria), [^{3}H]CGP-12177 (NEN-Du Pont, Poland), [^{3}H]prazosin (NEN, Life Science Products, USA), [^{3}H]clonidine (NEN, Life Science Products, USA). Other chemicals used were obtained from POCH (Polish Chemical Reagents, Poland). The tested compounds were dissolved in saline and administered intravenously at a constant volume of 1 ml/kg (rats) or 10 ml/kg (mice). Urapidil (Sigma–Aldrich, Germany) was used as a reference drug.

3.3. Radioligand binding assay

The experiments were conducted on the rat cerebral cortex. [^{3}H]prazosin (19.5 Ci/mmol, α_1-adrenergic receptor), [^{3}H]clonidine