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Original article

Influence of the alkylsulfonylamino substituent located at the 6-position of 2,2-dimethylchromans structurally related to cromakalim: From potassium channel openers to calcium entry blockers?

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ABSTRACT

The present study described the synthesis of original *R*/*S*-6-alkylsulfonylamino-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyrans bearing a 3- or 4-substituted phenylthiourea or phenylurea moiety at the 4-position. Their biological effects were evaluated both on insulin-secreting and smooth muscle cells and were compared to those of reference K_{ATP} channel activators such as (±)-cromakalim, diazoxide and previously synthesized cromakalim analogues. The study aimed at exploring the influence of the introduction of an alkylsulfonylamino substituent at the 6-position of 2,2-dimethylchromans in order to improve biological activity, tissue selectivity but also hydrophilicity of dihydrobenzopyran derivatives. Several compounds were found to be equipotent or even more potent than (±)-cromakalim and diazoxide at inhibiting the insulin releasing process. Most of the newly synthesized and more hydrophilic dihydrobenzopyrans also exhibited a marked vasorelaxant activity although they were less potent than (±)-cromakalim. Additional pharmacological and radioisotopic investigations suggested that *R*/*S*-*N*-3-chlorophenyl-*N'*-(3,4-dihydro-6-methylsulfonylamino-2,2-dimethyl-2*H*-1-benzopyran-4-yl)thiourea (**21**) did not act as a potassium channel opener but rather as a Ca^{2+} entry blocker.

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1. Introduction

Potassium channels represent a wide family of proteins involved in various cellular processes. Such channels are ubiquitously expressed and play a key role in the control of the membrane potential [1]. Among this family of ionic channels, ATP-sensitive potassium channels (K_{ATP} channels) have been shown to link cell metabolism to membrane excitability. Indeed, the activity of K_{ATP} channels is mainly coupled to the intracellular concentration ratio of adenosine triphosphate (ATP) to adenosine diphosphate (ADP). As the ratio increases, the K_{ATP} channel activity is reduced. At the opposite, a decrease of the ATP/ADP ratio activates the K_{ATP} channels [2–4].

K_{ATP} channels are distributed in many tissues where they play a large variety of physiological roles [5]. K_{ATP} channels are involved in the control of the insulin secretory process from pancreatic B-cells [6–8] and have also been depicted as participating in the control of the smooth muscle vascular tone [9].

K_{ATP} channels are octameric complexes comprising four Kir6.x subunits (Kir6.1 or Kir6.2), members of the inwardly rectifying K^+ channel family, and four sulfonylurea receptor (SUR) subunits (SUR1, SUR2A, or SUR2B). The Kir6.0 subunit forms the pore of the K_{ATP} channel complex whereas the SUR subunit acts as a regulator of K_{ATP} channel activity [5]. The combination of the different subunits leads to tissue-specific K_{ATP} channels, potential target sites for drugs. For example, four SUR1 subunits combine with four Kir6.2 subunits to form the SUR1/Kir6.2 K_{ATP} channel subtype as found in the endocrine pancreas and the brain tissue [10] whereas a SUR2A/Kir6.2 channel subtype is expressed in cardiac and skeletal muscle cells [11]. A SUR2B/Kir6.1 combination has been found in vascular smooth muscle cells while a SUR2B/Kir6.2 assembly has been characterized in various smooth muscle cells [11–13].

Abbreviations: Kir, inwardly rectifying potassium channel; SUR, sulfonylurea receptor; K_{ATP} channel, ATP-sensitive potassium channel.

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According to their wide physiological functions, K_{ATP} channels represent a promising target to develop new therapeutic agents. Such an objective can theoretically be reached through the synthesis of compounds exhibiting a marked specificity and a high selectivity for a single K_{ATP} channel subtype.

The potential and recognized therapeutic indications for ATP-sensitive potassium channel openers (PCOs) include, among others, the treatment of arterial hypertension [14,15], angina pectoris [14,16], cardiac arrhythmias [14,17], bronchial asthma [14,18], urinary incontinence [14,19] and androgenic alopecia [14,20]. PCOs have also been proposed for the prevention and/or management of type I, type II diabetes, obesity [14,15,21,22], nesidioblastosis [14], insulinomas [14] and polycystic ovary syndrome [21,23].

(±)-Cromakalim (**1**) and diazoxide (**2**) are well known PCOs belonging to different chemical families (Fig. 1). (±)-Cromakalim (**1**), leader of the dihydrobenzopyran-type PCOs, has been found to exert a marked myorelaxant activity [24,25] although the drug has also been reported to be slightly active as inhibitor of the insulin secretory process [26]. By contrast, diazoxide (**2**), leader of the benzothiadiazine 1,1-dioxide-type PCOs, has been reported to be equipotent on the vascular smooth muscle and the insulin secreting-cells [26,27].

We have previously identified original *R*/*S*-3,4-dihydro-2,2-dimethyl-6-halo-2*H*-1-benzopyrans structurally related to (±)-cromakalim, among which four derivatives exhibiting a modified tissue selectivity profile have been characterized [28,29]. These original 6-bromo-substituted *R*/*S*-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyrans bearing a 3- or 4-substituted phenylthiourea moiety at the 4-position (compounds **3**–**6**, Fig. 1) were found to be less effective as vasorelaxants but more potent as inhibitors of the insulin secretory process than the reference molecule (±)-cromakalim (**1**) [28]. Structure–activity relationships further indicated that the nature of the substituent at the 4-position of the benzopyran nucleus played a crucial role in the expression of an inhibitory effect on insulin release. Unfortunately, such compounds exhibited a weak solubility in the physiological medium. Thus, in another study, we kept identical substitutions at the 4-position and explored the influence of the nature of the substituent at the 6-position in order to develop 4,6-disubstituted *R*/*S*-2,2-dimethylchromans displaying improved hydrophilicity and selectivity towards insulin secreting cells. This approach allowed us to synthesize more hydrophilic 4-phenylthiourea-substituted *R*/*S*-6-acetamido-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyrans (compounds **7**–**10**, Fig. 1) but the latter compounds were less active on the endocrine pancreatic tissue than previously described derivatives [30].

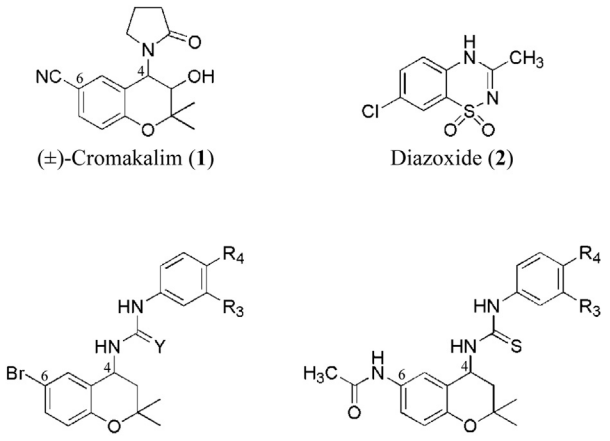

Fig. 1. Chemical structure of (±)-cromakalim (**1**), diazoxide (**2**) and previously described compounds **3**–**10** [30,32].

According to the structure–activity relationships deduced from our previous investigations, the present work aimed at further exploring the influence of the nature of the substituent at the 6-position in order to develop 4,6-disubstituted *R*/*S*-2,2-dimethylchromans displaying a marked inhibitory activity on the insulin secretory process but also an improved hydrophilicity. Therefore, the newly synthesized compounds were bearing, at the 6-position, a sulfonamide function as a bioisosteric group of the amide function characterizing previously described compounds (**7**–**10**) [31].

2. Chemistry

The common intermediate, *R*/*S*-6-amino-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-4-one (**15**), giving access to the target compounds (**19**–**34**) was synthesized as previously described [30] in four steps; starting from 4-methoxyaniline (Scheme 1).

Firstly, 4-methoxyaniline (**11**) was acetylated by acetic anhydride to provide *N*-(4-methoxyphenyl)acetamide (**12**). This reaction was followed by a Friedel–Crafts acylation to give *N*-(3-acetyl-4-hydroxyphenyl)acetamide (**13**). It should be noted that the reaction conditions led to the demethylation of the methoxy group located at the para-position of the acetamido moiety. Treatment of compound **13** with acetone, in the presence of pyrrolidine, led to chromanone intermediate **14**.

The acetamido group of intermediate **14** was hydrolyzed in an alcoholic solution of diluted hydrochloric acid.

The amine function of the resulting intermediate (**15**) was substituted by methanesulfonyl chloride or ethanesulfonyl chloride which provides compound **16a** or **16b**, respectively.

In order to obtain the key intermediates **18a**, **b**, the two ketonic compounds **16a** and **16b** were treated with hydroxylamine hydrochloride and potassium carbonate to give the corresponding oximes **17a**, **b**, which were further hydrogenated in the presence of Raney–Nickel.

R/*S*-*N*-(*m*/*p*-substituted)phenyl-*N*′-(6-methylsulfonylamino-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-4-yl)thioureas (**19**–**22**) or ureas (**23**–**26**) as well as *R*/*S*-*N*-(*m*/*p*-substituted)phenyl-*N*′-(6-ethylsulfonlamino-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-4-yl)thioureas (**27**–**30**) or ureas (**31**–**34**) were obtained from the reaction of the amines 18a–b with the appropriate *m*/*p*-cyano/chlorophenyl isothiocyanate (R–N=C=S) or isocyanate (R–N=C=O) (Scheme 1).

3. Results and discussion

3.1. Insulin secretion

The ability of the newly synthesized compounds (Table 1, compounds **19**–**34**) to inhibit the insulin releasing process was evaluated on isolated rat pancreatic islets incubated in the presence of an insulinotropic glucose concentration (16.7 mM).

(±)-Cromakalim and diazoxide were used as reference PCOs (Table 1). The biological activity of the original 2,2-dimethylchroman derivatives was also compared to that of previously described molecules (**7**–**10** and **3**–**6**) (Table 1) [28–30].

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