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Short communication

Synthesis and pharmacological activity of *N*-(2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-4-yl)-4*H*-1,2,4-benzothiadiazine-3-carboxamides 1,1-dioxides on rat uterus, rat aorta and rat pancreatic β-cells

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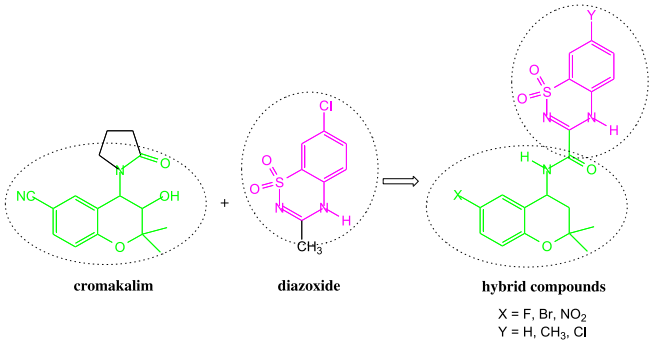
HIGHLIGHTS

- Hybrid compounds between diazoxide and cromakalim, two potassium channel openers, were synthesized.
- They were evaluated on three K_{ATP} channel-expressing tissues (pancreatic β-cells, aorta, uterus).
- Strong myorelaxant activity on uterus, but not on rat aorta, was found with 6-bromo-substituted dihydrobenzopyran hybrid compounds.
- None of these compounds were found to exert any inhibitory activity on insulin release.

GRAPHICAL ABSTRACT



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ABSTRACT

N-(2,2-Dimethyl-3,4-dihydro-2*H*-1-benzopyran-4-yl)-4*H*-1,2,4-benzothiadiazine-3-carboxamides 1,1-dioxides were prepared and evaluated on rat uterus, rat aortic rings and rat pancreatic β-cells. Pharmacological studies conducted on rat uterus indicated that several of these original hybrid compounds displayed a strong myorelaxant activity. The most active compounds hold a bromine atom at the 6-position of the dihydrobenzopyran ring. Moreover, the compounds failed to display a marked inhibitory effect on insulin secretion and vascular myogenic activity. These features suggest that the 6-bromo compounds could be relatively selective towards the uterine smooth muscle.

1. Introduction

Chemistry and pharmacology of benzo- or pyridothiadiazine dioxides, as well as of dihydrobenzopyrans, in the field of potassium channel openers, have raised great interest among chemists,

Abbreviations: K_{ATP} channel, ATP-sensitive potassium channel; NMR, nuclear magnetic resonance; DMSO, dimethylsulfoxide; HMDS, hexamethyldisiloxane.

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biologists and pharmacologists [1–8]. Compounds belonging to these classes of molecules are currently used as therapeutic drugs or pharmacological tools (i.e., diazoxide (**1**) and cromakalim (**2**); Fig. 1). The physiological interest of such compounds results from their interaction with a particular subtype of potassium channels, namely the ATP-sensitive potassium channel (K_{ATP} channel), onto which the two reference molecules diazoxide and cromakalim exert an opening activity [9,10]. According to such an effect, diazoxide has been reported to provoke an inhibitory activity on the insulin releasing process from pancreatic β-cells [11]. Moreover, this drug, as well as cromakalim, induces vasorelaxant effects as a result of their opening activity on smooth muscle K_{ATP} channels [9,10]. Lastly, cromakalim is also known to provoke the relaxation of other K_{ATP} channel-expressing smooth muscle tissues such as the airway and uterine smooth muscles [12,13].

Within the last decade, we have developed dihydrobenzopyrans and acyclic analogues structurally related to cromakalim, holding an arylsulfonylurea or an arylurea moiety at the 4-position of the heterocycle [14–18] (Fig. 2).

Biological data previously collected revealed that several compounds of general formula 3 (Z = CH_3) exhibited a marked myorelaxant activity on vascular smooth muscle (rat aorta) and reduced insulin secretion from rat pancreatic β-cells [15]. So far, no attempt was made to combine the 4*H*-1,2,4-benzothiadiazine 1,1-dioxide core structure (cfr diazoxide) with the dihydrobenzopyran nucleus (cfr cromakalim) in order to generate hybrid compounds between diazoxide and cromakalim. Thus, the present investigation describes the synthesis and the pharmacological evaluation of 4*H*-1,2,4-benzothiadiazine 1,1-dioxides bearing a 2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-4-yl moiety at the 3-position of the benzothiadiazine ring (Fig. 3). The different molecules have been tested on rat aortic and rat uterine smooth muscles to measure their myorelaxant properties, and on rat pancreatic islets to detect an effect on insulin secretion.

2. Results

2.1. Synthesis

Scheme 1 shows the synthetic route used to prepare novel *N*-(2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-4-yl)-4*H*-1,2,4-benzothiadiazine-3-carboxamides 1,1-dioxides (**7a**–**g**). Compound **9** was prepared according to a previously described method [19] from 4-substituted anilines **8** and chlorosulphonyl isocyanate in nitromethane. Such a procedure further comprised a ring closure reaction of a chlorosulphonylurea intermediate in the presence of aluminium chloride. Acidic hydrolysis of **9** yielded the *o*-aminobenzenesulfonamides **10** which reacted with ethyl oxalyl chloride to give compounds **11** [20]. Ring closure of compounds **11** with sodium ethanolate in anhydrous ethanol provided compounds **12** [20]. The latter compounds **12** yielded the target molecules (**7a**–**g**) after reaction with several 6-substituted 4-amino-*2H*-dihydrobenzopyrans, which were synthesized as previously described [14].

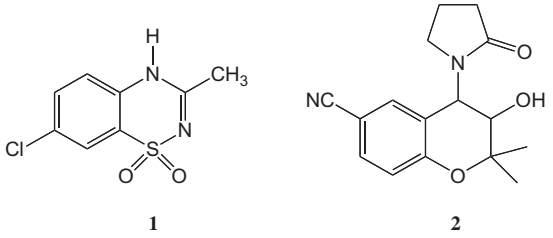

Fig. 1. Chemical structure of diazoxide (**1**) and cromakalim (**2**).

2.2. Biological assays

2.2.1. Inhibitory activity on insulin secretion from rat pancreatic islets

Compounds **7a**–**g** were evaluated as inhibitors of insulin secretion from rat pancreatic islets incubated in the presence of an insulinotropic glucose concentration (16.7 mM). As observed in Table 1, all compounds, tested at 50 μM, were less active than diazoxide [21] at inhibiting insulin release. Their effects were close to that of cromakalim or pinacidil.

2.2.2. Myorelaxant effect on rat aorta rings

Table 1 also reports the myorelaxant effects of compounds **7a**–**g** and of reference drugs [21] on rat aorta rings pre-contracted with a hyperpotassic 30 mM KCl solution. None of these new compounds exhibited a marked myorelaxant effect.

2.2.3. Myorelaxant effect on rat uterus

As shown in Table 2, at the concentration of 10 μM, compounds **7c** and **7d** were more active than diazoxide [22] but equi or slightly less potent than pinacidil [22] at relaxing rat uterus contracted by oxytocin. The other analogues (**7a**–**7b**, **7e**–**7g**), tested at the same concentration, failed to inhibit the oxytocin-induced contractile activity.

At a 50 μM concentration, four compounds elicited obvious activity. Compounds **7c** and **7d** were again markedly more potent than diazoxide, with both drugs being equipotent to pinacidil. Compounds **7e** and **7f** exhibited an inhibitory effect equivalent to that of diazoxide but were less potent than pinacidil.

At a 100 μM concentration, pinacidil expressed the same activity than at a 50 μM concentration, reflecting a "ceiling effect", while compounds **7c** and **7d** nearly completely suppressed the uterine contractile activity induced by oxytocin. Under the same experimental conditions, **7e** and **7f** were as potent as pinacidil in reducing the oxytocin-induced uterine contractions. Altogether, the data indicated that **7d** behaved as the most active uterine myorelaxant.

3. Discussion and conclusion

The data reported revealed that the introduction of a dihydrobenzopyranyl moiety at the 3-position of the benzothiadiazine dioxide core structure provided a new class of hybrid molecules (general formula **7**) expressing myorelaxant properties on rat uterus. Some of these new compounds, especially compounds bearing a bromine atom at the 6-position of the dihydrobenzopyran ring, were even more potent than the reference compound pinacidil. Moreover, the drugs were barely active as vascular myorelaxants and did not markedly affect the glucose-induced insulin releasing process. Such features highlight tissue selectivity towards the uterine smooth muscle.

In conclusion, we succeeded to develop novel compounds, hybrid structures between cromakalim and diazoxide, that were found to exert a myorelaxant activity on rat uterus and a marked uterine tissue selectivity. The development of this type of compounds needs to be pursued and the relationships between their biological activity and the modulation of K_{ATP} channels should be explored.

4. Experimental

Melting points were determined on a Büchi–Tottoli capillary apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Perkin–Elmer 1750 FT spectrophotometer. The ^{1}H NMR spectra were taken on a Bruker (500 MHz) instrument in DMSO-d_6 with tetramethylsilane (TMS) as an internal standard. Chemical