Bioorganic & Medicinal Chemistry 23 (2015) 1735–1746

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Design and synthesis of new potassium channel activators derived from the ring opening of diazoxide: Study of their vasodilatory effect, stimulation of elastin synthesis and inhibitory effect on insulin release

Nafila Bouider [a], Wassim Fhayli [b], Zeinab Ghandour [b], Marjorie Boyer [b], Kamel Harrouche [a], Xavier Florence [c], Bernard Pirotte [d,*], Philippe Lebrun [c], Gilles Faury [b], Smail Khelili [a]

[a] Laboratoire de Phytochimie et de Pharmacologie, Département de Chimie, Faculté des Sciences Exactes et informatique, Université de Jijel, B.P. 98 Ouled Aissa, 18000 Jijel, Algeria
[b] Laboratoire 'Hypoxie: Physiopathologie Cardiovasculaire et Respiratoire' (HP2), INSERM U1042-Université Grenoble Alpes, F-38042 La Tronche, France
[c] Laboratoire de Pharmacodynamie et de Thérapeutique, Université Libre de Bruxelles, Faculté de Médecine, 808, Route de Lennik, B-1070 Bruxelles, Belgium
[d] Laboratoire de Chimie Pharmaceutique, Center for Interdisciplinary Research on Medicines (CIRM), Université de Liège, 1, Avenue de l'Hôpital, B-4000 Liège, Belgium

ARTICLE INFO

Article history:
Received 19 December 2014
Revised 19 February 2015
Accepted 20 February 2015
Available online 27 February 2015

Keywords:
Potassium channel opener
Diazoxide
Benzenesulfonylurea
Benzenesulfonylthiourea
Benzenecarbonylurea
Benzenecarbonylthiourea
Elastin synthesis
Myorelaxant activity
Insulin secretion
Glycaemia

ABSTRACT

Benzenesulfonylureas and benzenesulfonylthioureas, as well as benzenecarbonylureas and benzenecarbonylthioureas, were prepared and evaluated as myorelaxants on 30 mM KCl-precontracted rat aortic rings. The most active compounds were further examined as stimulators of elastin synthesis by vascular smooth muscle cells and as inhibitors of insulin release from pancreaticβ-cells. The drugs were also characterized for their effects on glycaemia in rats. Benzenesulfonylureas and benzenesulfonylthioureas did not display any myorelaxant activity on precontracted rat aortic rings. Such an effect could be attributed to their ionization at physiological pH. By contrast, almost all benzenecarbonylureas and benzenecarbonylthioureas displayed a myorelaxant activity, in particular the benzenecarbonylureas with an oxybenzyl group linked to the *ortho* position of the phenyl ring. The vasodilatory activity of the most active compounds was reduced when measured in the presence of 80 mM KCl or in the presence of 30 mM KCl and 10 μM glibenclamide. Such results suggested the involvement, at least in part, of K_{ATP} channels. Preservation of a vasodilatory activity in rat aortic rings without endothelium indicated that the site of action of such molecules was located on the vascular smooth muscle cells and not on the endothelial cells. Some of the most active compounds also stimulated elastin synthesis by vascular smooth muscle cells. Lastly, most of the active vasorelaxant drugs, except **15k** and **15t** at high concentrations, did not exhibit marked inhibitory effects on the insulin releasing process and on glycaemia, suggesting a relative tissue selectivity of some of these compounds for the vascular smooth muscle.

1. Introduction

ATP-sensitive potassium (K_{ATP}) channels control insulin release,[1,2] vascular tone[3] and may protect heart,[4] kidney,[5] and brain under metabolic stress.[6] Channel inhibition by ATP and stimulation by nucleotide diphosphates allow the membrane potential and cell excitability to be regulated by the cellular metabolic state.

The K_{ATP} channel is an octameric complex of 4 Kir6.x and 4 SURx subunits.[7,8] The pore-forming Kir6.x subunit belongs to the inwardly rectifying family of potassium channels.[8–10] There are two isoforms: Kir6.1, which is found in vascular smooth muscle, and Kir6.2, which has a widespread tissue distribution. Binding of ATP to Kir6.x induces K_{ATP} channel closure. The sulfonylurea receptor (SUR) belongs to the ABC transporter family.[9] It functions as a regulatory subunit, which mediates, inter alia, channel inhibition by sulfonylurea drugs such as glibenclamide.[11,12] Differences in endogenous K_{ATP} channel properties and pharmacology[13] may

Abbreviations: K_{ATP} channel, ATP-sensitive potassium channel; Kir, inwardly rectifying potassium channel; SUR, sulfonylurea receptor; PCO, potassium channel opener; ABC transporter, ATP-binding cassette transporter; DMF, dimethylformamide; d_6-DMSO, deuterated dimethyl sulfoxide; TMS, tetramethylsilane; NMR, nuclear magnetic resonance; TLC, thin layer chromatography; DMEM, Dulbecco's modified Eagle medium; FCS, fetal calf serum; HRP, horseradish peroxidase; PBS, phosphate-buffered saline; BSA, bovine serum albumin; TMB, 3,3′,5,5′-tetramethylbenzidine.

* Corresponding author. Tel.: +32 4 366 43 65; fax: +32 4 366 43 62.
E-mail address: b.pirotte@ulg.ac.be (B. Pirotte).

http://dx.doi.org/10.1016/j.bmc.2015.02.043
0968-0896/

be accounted for by differences in subunit composition: Kir6.2 and SUR1 in pancreatic insulin-secreting cells, Kir6.2 and SUR2A in cardiac myocytes, Kir6.2/Kir6.1 and SUR2B in smooth muscle cells, and Kir6.2 and SUR1 in central neurons.[14]

Several drugs were found to activate the K_{ATP} channels. Such pharmacological or therapeutic agents, collectively termed potassium channel openers (PCOs), stabilize membrane excitability and preserve metabolic expenditure.[15] As a result, PCOs are able to inhibit insulin release from pancreatic β-cells[16] and exert a relaxant effect on different smooth muscles.[17]

Potassium channel openers constitute a family of chemically diverse compounds that belong to numerous structural classes. They include benzopyrans (cromakalim, **1**), cyanoguanidines (pinacidil, **2**), benzothiadiazines (diazoxide, **3**), nicotinamides (nicorandil, **4**), and pyrimidines (minoxidil, **5**) (Fig. 1).[16,18–20]

Cromakalim is a potent myorelaxant but a poor inhibitor of insulin secretion,[21–23] in contrast to diazoxide, which is active on both insulin-secreting cells (inhibitor) and vascular smooth muscle cells (vasodilator).[24] Optimization of the diazoxide structure provided compounds such as BPDZ 73 (**6**) and BPDZ 44 (**7**), which potently and selectively activated the K_{ATP} channels of pancreatic β-cells (Fig. 2).[25,26]

Modification of the benzothiadiazine core structure by ring opening has never been attempted so far. Thus, in order to develop new PCOs with improved pharmacological properties, we undertook the synthesis of some simplified compounds resulting both from the opening of the thiadiazine ring of 3-alkylamino-4*H*-1,2,4-benzothiadiazine 1,1-dioxides and the introduction of urea or thiourea moieties. The SO_2 group has also been replaced by its non-classical isoster C=O, while NH was replaced by an oxygen atom. Such structural modifications led to two new series of ring-opened analogues of diazoxide and 3-alkylamino-4*H*-1,2,4-benzothiadiazine 1,1-dioxides (series **A** and **B**), as illustrated in Figure 3.

This strategy was inspired by previous work consisting in the opening of the pyranic ring of cromakalim, a dihydrobenzopyran, and the introduction of urea and sulfonylurea groups, which provided simpler new molecules with substantial vasodilatory properties.[27]

It should be pointed out that the **A** and **B** series can also be virtually obtained by simplification of glibenclamide, a well-known K_{ATP} channel blocker (Fig. 4).[28] However, this observation is only fortuitous and did not direct our strategy for the development of new series of compounds expected to be potassium channel openers and not blockers.

The present work reports the synthesis and pharmacological testing of the vasodilatory activity of compounds belonging to series **A** and **B** on KCl-precontracted rat aorta rings. Some of the most potent compounds have also been tested as potential stimulators of elastin production by vascular smooth muscle cells.

Elastin is the main extracellular matrix protein composing the elastic fibers, which endow extensible tissues (including skin,

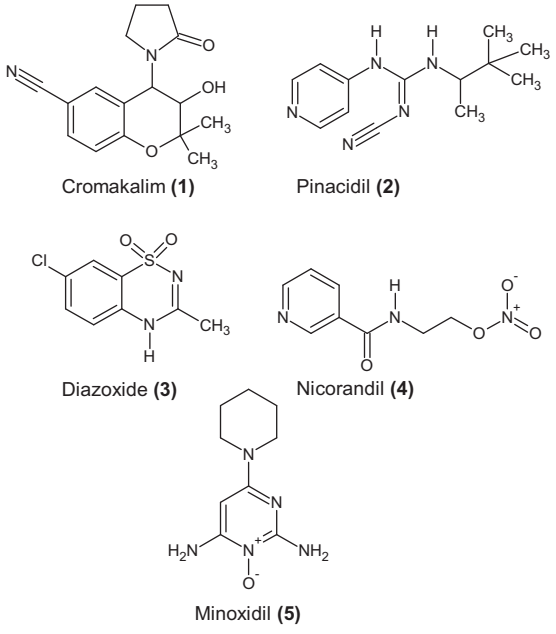

Figure 1. Chemical structure of some K_{ATP} channels openers.

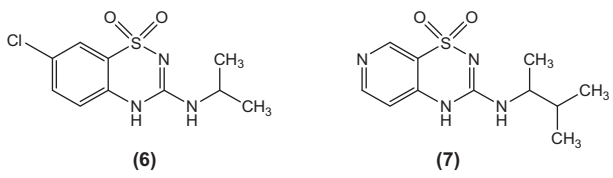

Figure 2. Examples of K_{ATP} channel openers resulting from structural modifications of diazoxide.

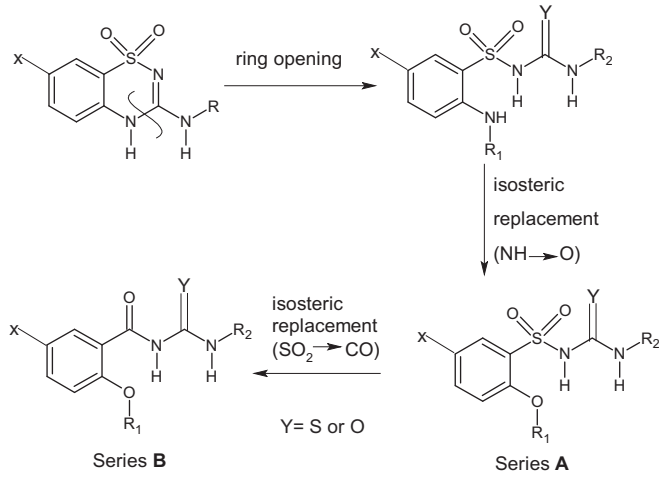

Figure 3. Simplification of 3-alkylamino-4*H*-1,2,4-benzothiadiazine 1,1-dioxides leading to two new series of compounds (**A** and **B**).

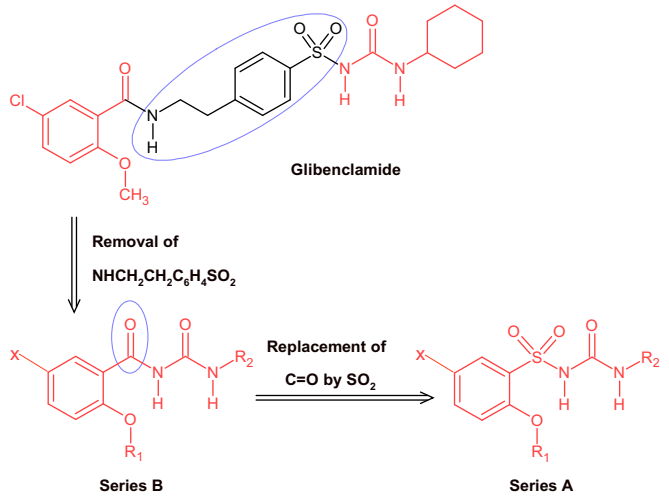

Figure 4. Structural modulation of glibenclamide leading to series **A** and **B**.