European Journal of Medicinal Chemistry 115 (2016) 352–360

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Research paper

Synthesis, characterization and biological evaluation of benzothiazoles and tetrahydrobenzothiazoles bearing urea or thiourea moieties as vasorelaxants and inhibitors of the insulin releasing process

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ARTICLE INFO

Article history:
Received 20 November 2015
Received in revised form
7 March 2016
Accepted 10 March 2016
Available online 12 March 2016

Keywords:
Diazoxide
Pinacidil
Benzothiazole
Benzothiadiazine
K_{ATP} channel
Potassium channel openers

ABSTRACT

A series of 1,3-benzothiazoles (series **I**) and 4,5,6,7-tetrahydro-1,3-benzothiazoles (series **II**) bearing an urea or a thiourea moiety at the 2-position were synthesized and tested as myorelaxants and inhibitors of insulin secretion. Several compounds (i.e. **13u** and **13v**) from series **I** showed a marked myorelaxant activity. Benzothiazoles bearing a strong electron withdrawing group (NO_2, CN) at the 6-position and an alkyl group linked to the urea or the thiourea function at the 2-position were found to be the most potent compounds. The weak vasorelaxant activity of series **II** compounds evidenced the necessity of the presence of a complete aromatic heterocyclic system. The myorelaxant activity of some active compounds was reduced when measured on aorta rings precontracted by 80 mM KCl or by 30 mM KCl in the presence of 10 μM glibenclamide, suggesting the involvement of K_{ATP} channels in the vasorelaxant effect. Some compounds of series **I** tested on rat pancreatic islets provoked a marked inhibition of insulin secretion, among which **13a** exhibited a clear tissue selectivity for pancreatic β-cells.

1. Introduction

ATP-sensitive potassium channels, usually named K_{ATP} channels, are expressed in most excitable cells [1,2]. By tuning the membrane permeability to potassium ions as a function of intracellular ATP availability, they link membrane excitability to the metabolic state of the cell [3,4]. It is important to emphasize that K_{ATP} channels in different tissues display various biophysical and pharmacological properties. Such a diversity results from differences in the molecular composition of K_{ATP} channels. These channels are involved in the response to cerebral and cardiac ischemia, the regulation of insulin secretion by pancreatic β-cells, the control of vascular smooth muscle tone, the epithelial K^+ transport and the modulation of electrical activity in several types of neurons [5–7].

K_{ATP} channels are blocked by high concentrations of intracellular ATP and by several pharmacological substances, in particular by sulphonylurea drugs such as glibenclamide, which are used to treat non-insulin-dependent diabetes mellitus [8]. Conversely, K_{ATP} channels are activated by a variety of potassium channel openers (PCOs) such as cromakalim (**1**), pinacidil (**2**) and diazoxide (**3**) (Fig. 1) [9].

The main challenge in the development of new K_{ATP} channel modulators as therapeutic agents is the discovery of compounds exhibiting the highest selectivity for a single K_{ATP} channel subtype. The reference PCO diazoxide is known to be non-selective; being equipotent on both vascular smooth muscle cells (vasorelaxant effect) and on pancreatic β-cells (inhibition of insulin release).

Chemical optimizations of diazoxide resulted in compounds such as BPDZ 44 (**4**), BPDZ 73 (**5**), BPDZ 216 (**6**) and NN414 (**7**), which potently and selectively activate the K_{ATP} channels of pancreatic β-cells [10–13]. Recent work reported the apparent high selectivity of some benzothiazole derivatives bearing a thioamide

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http://dx.doi.org/10.1016/j.ejmech.2016.03.028
0223-5234/

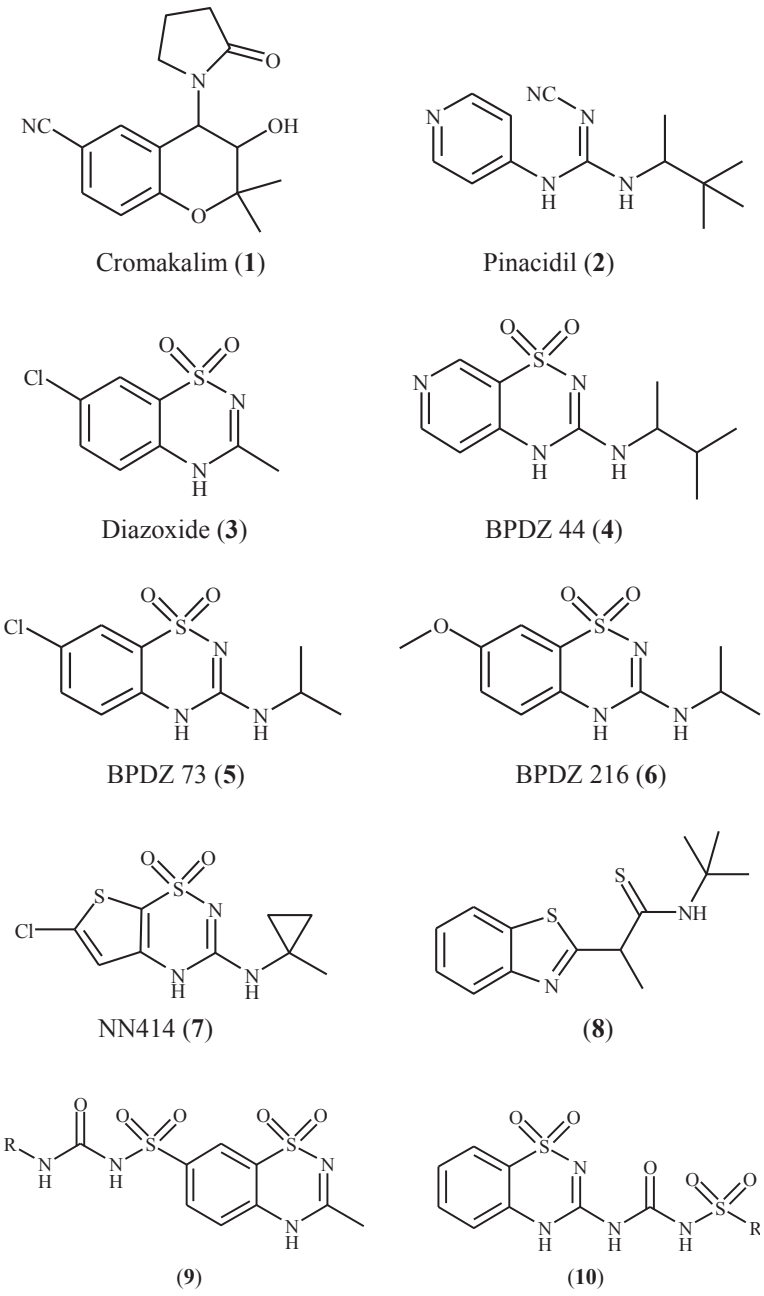

Fig. 1. Chemical structure of reference potassium channel openers.

group (**8**) for the vascular smooth muscle K_{ATP} channels (Fig. 1) [14]. Moreover, the introduction of sulfonylurea moieties on the diazoxide skeleton at the 7-position (**9**) or at the 3-position (**10**) of the benzothiadiazine ring gave rise to a series of compounds expressing a vasodilatory activity similar to that of diazoxide [15].

In order to develop new tissue selective K_{ATP} channel activators, we designed original compounds structurally related to compounds **8** and **10** (Fig. 1). Starting from compound **8**, our strategy first involved the replacement of the carbon atom linked at the 2-position of the thiazole ring by a nitrogen atom providing urea and thiourea analogues (Fig. 2). The second modification was the introduction of a substituent at the 6-position of the benzothiazole ring in order to better mimic benzothiadiazine dioxides such as diazoxide or compounds **5**, **6**, **9** bearing a substituent at the 7-position. The substituent on the second nitrogen atom of the urea or thiourea moiety was selected as a short branched alkyl chain (as found in **8**), an alicyclic nucleus or a diversely substituted phenyl ring (Fig. 2, series I). A second series was obtained from the former by formal saturation of the benzene ring of benzothiazole, in order to highlight the role of the presence of an aromatic cycle. This led to tetrahydrobenzothiazole derivatives (Fig. 2, series **II**).

The biological effects of the new compounds (series **I** and **II**) were characterized on rat pancreatic islets as well as on rat vascular smooth muscle in order to evaluate their potential inhibitory effects on insulin secretion and putative vasorelaxant activity. Further investigations were undertaken with a selection of compounds with the aim at determining the mechanism of action.