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Review Article

Selective pancreatic ATP-sensitive potassium channel openers for the treatment of glucose homeostasis disorders

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Abstract

Disorders of glucose homeostasis may be associated with severe pathologies such as type 1 and type 2 diabetes, insulinoma, persistent hyperinsulinemic hypoglycemia of infancy (PHHI), polycystic ovary syndrome (PCOS) and/or obesity. Specific activation of the Kir6.2/SUR1 K_{ATP} channel subtype has been shown to be beneficial for the treatment of these pathologies. Starting from diazoxide, a nonselective Kir6.2/SUR1 K_{ATP} channel activator, many research groups have conducted searches in an attempt to discover more potent and selective drugs. Several 3-alkylaminoarylthiadiazine 1,1-dioxides (BPDZ-44, BPDZ-73, BPDZ-415, NNC-55-0118, NN-414) have been described as potent Kir6.2/SUR1 K_{ATP} channel openers and are reported to inhibit insulin release without a pronounced effect on smooth muscle mechanical activity. NN-414 was the most extensively studied drug and had entered clinical trials, although its development was discontinued due to liver toxicity. Other chemical series have also been developed, but none has led to compounds as potent and/or as selective as the lead arylthiadiazine drugs. Based on the therapeutic interest of Kir6.2/SUR1 K_{ATP} channel activators, the discovery of new series with improved pharmacodynamic and/or pharmacokinetic properties remains a priority.

Glucose homeostasis disorders and related pathologies

The regulation of glucose homeostasis is a key process for maintaining a good metabolic state. Disorders of glucose homeostasis may lead to hypo- or hyperglycemic periods, which are generally associated with severe pathologies, such as type 1 and type 2 diabetes, insulinoma, persistent hyperinsulinemic hypoglycemia of infancy (PHHI), polycystic ovary syndrome (PCOS) and/or obesity. Such diseases are related to a disturbance in the pattern of insulin secretion (1).

The lifestyle of Western society (lack of exercise, increased food consumption, food imbalance and obesity) is the main determining factor for diabetes, which is expected to emerge as a global health problem, with an increasing number of patients affected by this disease (2-5).

Type 1 diabetes is an autoimmune pathology characterized by a rapid depletion of insulin production due to a destruction of pancreatic β-cells (6-9). This β-cell loss is attributable, at least in part, to the action of autoantibodies targeted against specific antigens expressed on the β-cell surface.

Type 2 diabetes is more common than type 1 diabetes and is expected to become a major health problem in the next few years (10, 11). It is characterized by dysfunctional insulin secretion coupled with a decrease in insulin receptor sensitivity, leading to glucose intolerance and high circulating glucose concentrations (12-14). These chronic hyperglycemic periods negatively affect β-cell functions and induce a progressive degeneration of insulin-secreting cells (15-17). Type 2 diabetes increases the risk for many serious complications, including cardiovascular diseases, retinopathy, neuropathy and nephropathy.

Obesity is generally associated with several metabolic disorders and constitutes an important risk factor for the development of type 2 diabetes. Indeed, obesity is frequently associated with abnormal insulin secretion and/or hyperinsulinemia (18-20).

Hyperinsulinism of infancy is the most frequent cause of PHHI (21, 22). The most severe forms arise from genetic defects in pancreatic β-cell ATP-sensitive potassium (K_{ATP}) channel subunits (23, 24). This leads to uncontrolled insulin release, which in turn induces chronic hypoglycemia, which is potentially lethal because of neurological complications associated with low circulating glucose levels (25).

PCOS is a severe hormonal disorder affecting females of reproductive age (26, 27). Symptoms of this pathology include hypersecretion of insulin, insulin resistance and obesity (28, 29). Similarly, insulinomas are also associated with a high level of insulin release, with a deleterious effect on the regulation of glucose homeostasis (30-32).

Glucose homeostasis disorders and K_{ATP} channels

The secretion of insulin from pancreatic β-cells is known to be controlled mainly by the activity of K_{ATP} channels (33-36). After a meal, glucose enters the insulin-secreting cells via the GLUT2 transporter and is phosphorylated to glucose-6-phosphate by glucokinase, an enzyme considered to be the "glucose sensor" (37). The result is an increase in the ratio of ATP to ADP, which in turn induces closure of β-cell K_{ATP} channels, depolarization of the cell membrane and subsequent activation of voltage-gated Ca^{2+} channels. The resulting Ca^{2+} entry and increase in $[Ca^{2+}]_i$ initiate the release of insulin from docked secretory vesicles. This insulin-secretory pulse will reduce glycemia, with a subsequent decrease in the ATP/ADP ratio leading to re-opening of β-cell K_{ATP} channels, hyperpolarization of the cell membrane below the threshold for activation of voltage-dependent Ca^{2+} channels, and ultimately a reduction in insulin secretion (38).

In PHHI, insulinoma and PCOS, several studies have demonstrated that a direct action on insulin secretion by activation of pancreatic K_{ATP} channels could reduce symptoms linked to these pathologies. Diazoxide, the first active pancreatic K_{ATP} channel opener described, is, along with somatostatin, currently the only therapeutic approach to treat PHHI and insulinoma syndrome (39-42). Reduction of insulin secretion with diazoxide also appears to be effective at reducing PCOS symptomatology (43, 44).

The case of diabetes is more complex because the disease is generally correlated with a deficit in insulin levels and/or in insulin receptor sensitivity. Therefore, the first approach to treat this pathology, and more specifically type 2 diabetes, consisted in enhancing insulin secretion by blocking pancreatic K_{ATP} channels. Hypoglycemic sulfonylureas such as tolbutamide, glibenclamide and glipizide, which are specific pancreatic K_{ATP} channel blockers, currently represent the most widely used drugs in the treatment of type 2 diabetes (45, 46). However, long-term treatment leads to a progressive decrease in the efficacy of sulfonylureas and may be associated with side effects such as weight gain or cardiovascular complications in patients at high risk (47).

More recently, several clinical studies have demonstrated that a reduction in endogenous insulin secretion using pancreatic K_{ATP} channel openers could be beneficial for preserving β-cell function. Indeed, when β-cell rest was induced by diazoxide, a delay in the progression of β-cell loss was seen in subjects with newly diagnosed type 1 diabetes (48, 49). *In vitro* and *in vivo* studies also provided evidence for the preservation of β-cell function upon treatment with diazoxide (50, 51). This beneficial effect of potassium channel openers could be related to modifications in autoantigen expression (48-52). Pancreatic potassium channel openers have further been shown to protect β-cells and preserve the function of human and rat islets, even in the presence of high concentrations of glucose, and to prevent or delay the progression of type 2 diabetes in animal models (53-60).

Obesity is often associated with type 2 diabetes and it has been postulated that a decrease in insulin release from pancreatic β-cells could restore the sensitivity, as well as the number, of insulin receptors, leading to recovery of glucose tolerance. In animal models, activation of pancreatic K_{ATP} channels has been shown to improve the glycemic profile and to induce weight loss (54, 61, 62).

In addition to pancreatic β-cell K_{ATP} channels which regulate insulin secretion and influence circulating blood glucose levels, hypothalamic K_{ATP} channels could also play an important role in the control of glucose homeostasis. Indeed, the medial hypothalamus is a major regulator of nutritional and hormonal signals and plays a crucial role in the modulation of liver glucose output. It has recently been suggested that activation of hypothalamic K_{ATP} channels could decrease glycemia through inhibition of hepatic gluconeogenesis (63-65). Thus, hypothalamic K_{ATP} channels could also be viewed as a target site for controlling glucose homeostasis.

The structure of pancreatic K_{ATP} channels

As previously noted, K_{ATP} channels are potassium-selective channels controlled by the intracellular ATP/ADP ratio. These channels play a crucial role in the control of membrane potential in a wide variety of excitable cells and are postulated to couple metabolism to the electrical activity of the cells (66, 67). K_{ATP} channels are octameric complexes of two different subunits: the ~160-kDa regulatory protein (termed SUR for sulfonylurea receptor) and a smaller ~40-kDa protein belonging to the inwardly rectifying potassium channel family (named Kir6.x) (68-70). Four Kir6.x subunits assemble themselves to form a K^+-selective pore, which is constitutively associated with four SUR subunits to form the active channel (Fig. 1) (71, 72). Kir6.x subunits have two transmembrane segments, M1 and M2, connected by a linker region that determines the potassium selectivity, and are endowed with an inhibitory site for ATP (Fig. 2). Two different isoforms have been identified: Kir6.1 and Kir6.2. The regulatory sulfonylurea receptor subunit (SUR) belongs to the ABCC protein gene family and is composed of 17 transmembrane segments arranged in 3

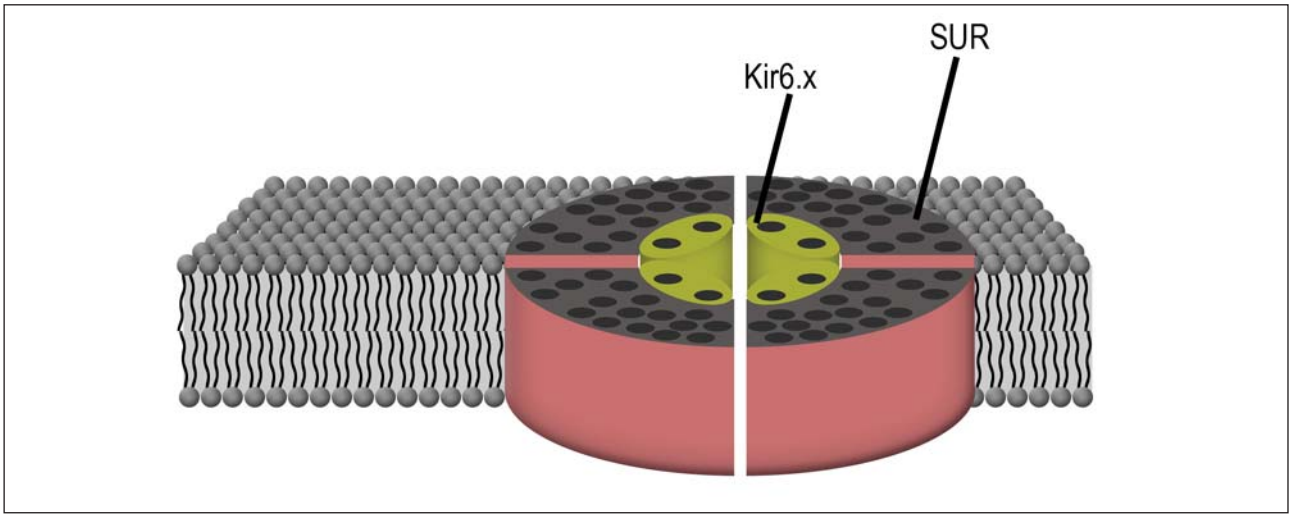


Fig. 1. SURx and Kir6.x subunit assembly into a K_{ATP} channel.

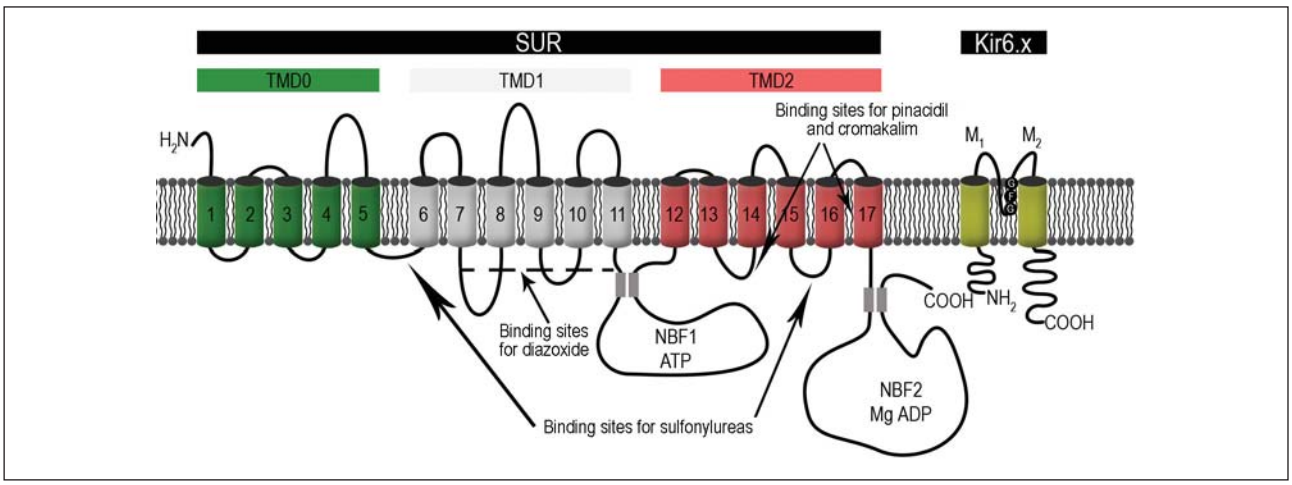


Fig. 2. Topology of Kir6.x and SURx subunits.

transmembrane domains (TMDs): TMD0 includes 5 segments and TMD1 and 2 each include 6 segments (Fig. 2). Two large intracellular loops contain the nucleotide binding domains (NBF1 and NBF2). Three isoforms of the SUR subunit have been identified: SUR1, SUR2A and SUR2B. SUR2A and SUR2B have 99% homology and differ only in the last 42 amino acids of the *C*-terminal part of NBF2, while SUR1 has 79% homology with the SUR2 isoforms (73, 74). Depending on their tissue localization, K_{ATP} channels are composed of different subunits. For example, SUR1 combined with Kir6.2 forms the pancreatic K_{ATP} channel. The combination of SUR2A and Kir6.2 subunits is found in cardiac and skeletal muscle, while the smooth muscle K_{ATP} channel is composed of SUR2B and Kir6.1 or Kir6.2 subunits. Although the binding sites for potassium channel openers have mainly been identified on the SUR subunits, several experimental studies have also demonstrated that these binding sites can be localized on different transmembrane segments (73). Thus, pinacidil and cromakalim, two reference potassium channel openers, have been shown to interact with TMD segments 12-17, whereas diazoxide preferentially binds to TMD segments 7-11 and NBF1 (Fig. 2).

Discovery of selective pancreatic K_{ATP} channel (Kir6.2/SUR1) openers

The search for selective Kir6.2/SUR1 potassium channel openers began in the sixties with the observation that certain sulfonamide diuretics, such as chlorothiazide (Fig. 3), elevated blood glucose in some susceptible individuals (75). Other research into the benzothiadiazine field led to the discovery of diazoxide (Fig. 3) (76). Initially developed for its antihypertensive properties, the drug was also found to increase blood glucose levels through inhibition of insulin release, and was proposed for the treatment of hyperinsulinemic states such as PHHI (77). In the following years, only one medicinal chemistry article reported derivatives of diazoxide with hyperglycemic activity (78).

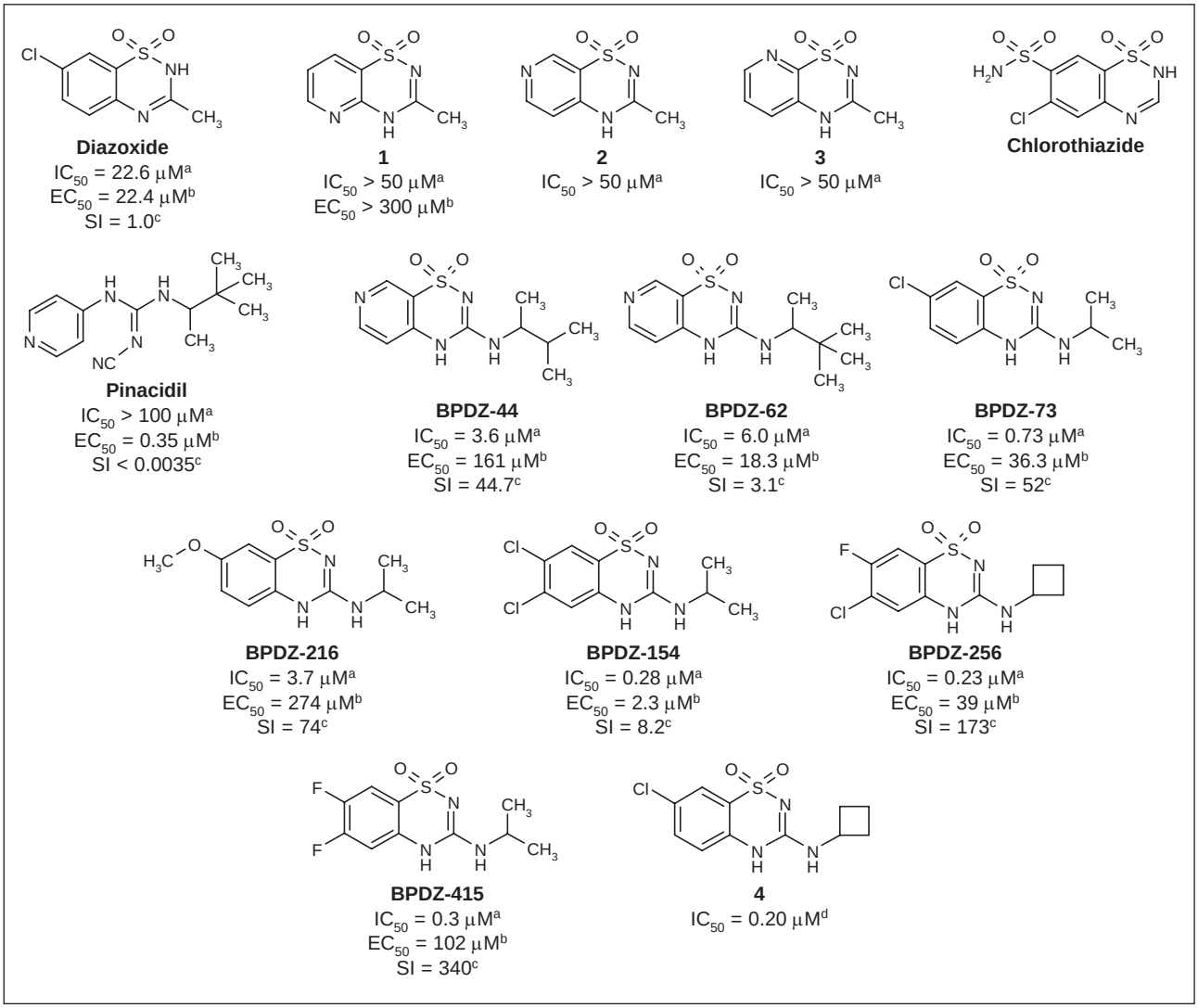


Fig. 3. Benzo- and pyridothiadiazine 1,1-dioxides. [a]Drug concentration giving 50% inhibition of glucose-induced insulin secretion from rat pancreatic islets. [b]Drug concentration giving 50% relaxation of KCl-induced contractions of rat aorta rings. [c]Selectivity index (SI) EC_{50}/IC_{50}. [d]Drug concentration eliciting 50% activation of K_{ATP} current in excised patches from *Xenopus* oocytes expressing human Kir6.2/SUR1 channels.

In the late 1980s, the target of diazoxide was identified as the K_{ATP} channels (79). Unfortunately, the drug appeared to be equipotent on both pancreatic and vascular tissues (Fig. 3). As a consequence of its lack of tissue selectivity, the clinical use of diazoxide was associated with many side effects, such as hypertrichosis, edema, headache and/or arterial hypotension (77, 80). However, in spite of these unwanted effects, diazoxide continues to be the compound of choice for the treatment of pathologies linked to insulin hypersecretion.

For a long time, most chemical developments linked to K_{ATP} channel openers have been focused on the enhancement of the antihypertensive properties of this pharmaceutical class. Until the nineties, few investigations were undertaken to discover new potent and selective pancreatic β-cell potassium channel openers. The first rational drug design approach was performed by our team and initially consisted of the synthesis of pyridine analogues of diazoxide (**1, 2, 3;** Fig. 3) (81). In contrast to diazoxide, none of the newly synthesized drugs markedly inhibited insulin release from rat pancreatic islets. This lack of inhibitory effect was probably due to the fact that, at physiological pH, the new pyridine derivatives were partially ionized.

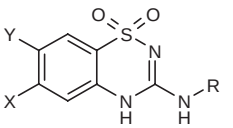
Wolleweber *et al*. demonstrated in 1981 that several 3-cycloalkylamino analogues of diazoxide exhibited a slight hyperglycemic effect (82). Based on these data, original 3-alkylamino-4*H*-pyridothiadiazine 1,1-dioxides were synthesized and evaluated on rat pancreatic islets and rat aorta rings (81, 83, 84). Such compounds should be regarded as hybrid structures between diazoxide and pinacidil (Fig. 3), a well-known K_{ATP} channel opener belonging to the cyanoguanidine family (83). From this series, compounds bearing a short and branched alkyl

side-chain at the 3-position, such as BPDZ-44 and BPDZ-62 (Fig. 3), were found to be more potent and more selective for pancreatic *versus* aortic tissue than diazoxide (81, 83, 84). BPDZ-44, shown to be 7 times more active than diazoxide *in vitro* at inhibiting insulin release and 40 times more selective for pancreatic *versus* aortic tissue, was the first potent and preferential/selective pancreatic K_{ATP} channel opener described. Additional studies indicated that BPDZ-44 acted through activation of pancreatic K_{ATP} channels (85, 86). As later reported for the related compound BPDZ-62, an increase in the size of the 3-alkylamino side-chain led to less selective derivatives. Moreover, modification of the position of the pyridine nitrogen atom caused changes in the pharmacological profile of the series, with a reduction in activity on insulin release and an enhancement of activity on aortic tissue (81, 87, 88).

Transposition of the structure-activity relationship (SAR) information on the pyridine series to the benzene series led, in several cases, to more potent and/or more selective compounds (89-91). BPDZ-73 (Fig. 3) was the first lead compound of this SUR1-selective class. Its IC_{50} value in an *in vitro* assay of insulin release was found to be < 1 μM, while the EC_{50} value in the 30 mM KCl-depolarized aorta was > 35 μM (89). BPDZ-73 was studied in different *in vitro* and *in vivo* models and its biological target was clearly identified as the K_{ATP} channel (92).

This lead compound was subjected to several modifications, starting with modulation of the 3-alkylamino chain and replacement of the chlorine atom at the 7-position by other halogen atoms or by electron-donating groups such as CH_3, OCH_3 and NH_2 and by electron-withdrawing groups such as CF_3, NO_2 and CN (89, 90). 6,7-Disubstituted derivatives were also prepared (91). All the compounds were tested as putative K_{ATP} channel openers on pancreatic endocrine and vascular tissue. The biological data were then analyzed using a CoMSIA QSAR approach, leading to the proposal of a pharmacophore model for activity and selectivity on pancreatic tissue (Fig. 4) (93). This model underlined the critical importance of the 3- and 7-positions for both activity and tissue selectivity. The best insulin-secreting cell activity and selectivity were obtained with compounds substituted at the 3-position by a small alkylamino or cycloalkylamino chain, and at the 6- and/or 7-position by a small halogen atom (F or Cl) or a small electron-donating group (CH_3 or OCH_3). Substitution at the 2- and 4-position appears to be unfavorable for inhibitory activity on insulin release.

Figure 3 shows the main lead compounds in the benzene series, along with their activity and selectivity index. Among these, BPDZ-154 was shown to activate K_{ATP} channels of rodent β-cells and islets isolated from young patients with hyperinsulinism (94), whereas BPDZ-216 proved to be a potent inhibitor of insulin release without marked vasorelaxant effects and to act mainly on the KIR6.2/SUR1 channel subtype (95). Other drugs, such as BPDZ-256 and BPDZ-415, were also reported to be very potent and selective for the pancreatic endocrine tissue (91).



X
- Less apparent steric constraints
- Hydrogen bond acceptor group favorable for activity
- Small lipophilic group increases tissue selectivity

R
- Short branched but also small cyclic chain favorable for activity and tissue selectivity
- Presence of a hydrogen bond acceptor not deleterious for activity

Y
- Small electronegative group increases activity and tissue selectivity
- Small lipophilic or hydrophilic group favorable for activity
- Large electronegative group deleterious for tissue selectivity
- Large lipophilic group unfavorable for activity and tissue selectivity
- Large hydrogen bond acceptor group impairs activity and tissue selectivity
- 7-Aza derivatives (C-Y = N) favorable for activity and tissue selectivity

Fig. 4. Pharmacophore model for activity and selectivity for pancreatic tissue of the benzo- and pyridothiadiazine series.

The recent discovery of the beneficial effect of pancreatic (Kir6.2/SUR1) K_{ATP} channel activation in the treatment of diabetes and obesity has broadened the interest for developing new pancreatic selective K_{ATP} channel openers. In 2002, Peat *et al*. prepared a small series of 3-cyclobutylamino derivatives (96). These compounds (*i.e*., **4**; Fig. 3), substituted at the 7-position by different groups, were also found to be potent activators of Kir6.2/SUR1 channels. However, no data on the effect of these derivatives on insulin release and smooth muscle mechanical activity were reported.

In parallel to the development of the benzene series, Novo Nordisk explored 3-alkylamino-4*H*-thieno[3,2-*e*]-1,2,4-thiadiazine 1,1-dioxide analogues (Fig. 5). Among the different drugs synthesized, several compounds, such as NNC-55-0118, the thiophene isostere of BPDZ-73, NNC-55-0462 and NN-414, were found to be potent K_{ATP} channel openers (97, 98). These compounds were tested in different pharmacological models and shown, like their benzene counterparts, to be potent and selective inhibitors of insulin release (97). Additional evaluation indicated that the key target for these drugs was the Kir6.2/SUR1 channel subtype (98). The most active compounds of this series have short alkylamino chains or small cycloalkylamino chains at the 3-position (Fig. 5). Increasing the size from cyclopropyl (NN-414) to cyclobutyl (NNC-55-0462) enhanced activity, while further ring expansions resulted in reduced potency (99). Introduction of a 1-methyl-1-phenethylamino group at the 3-position led to another potent and insulin-secreting cell-selective compound (**5**; Fig. 5). The chlorine atom at

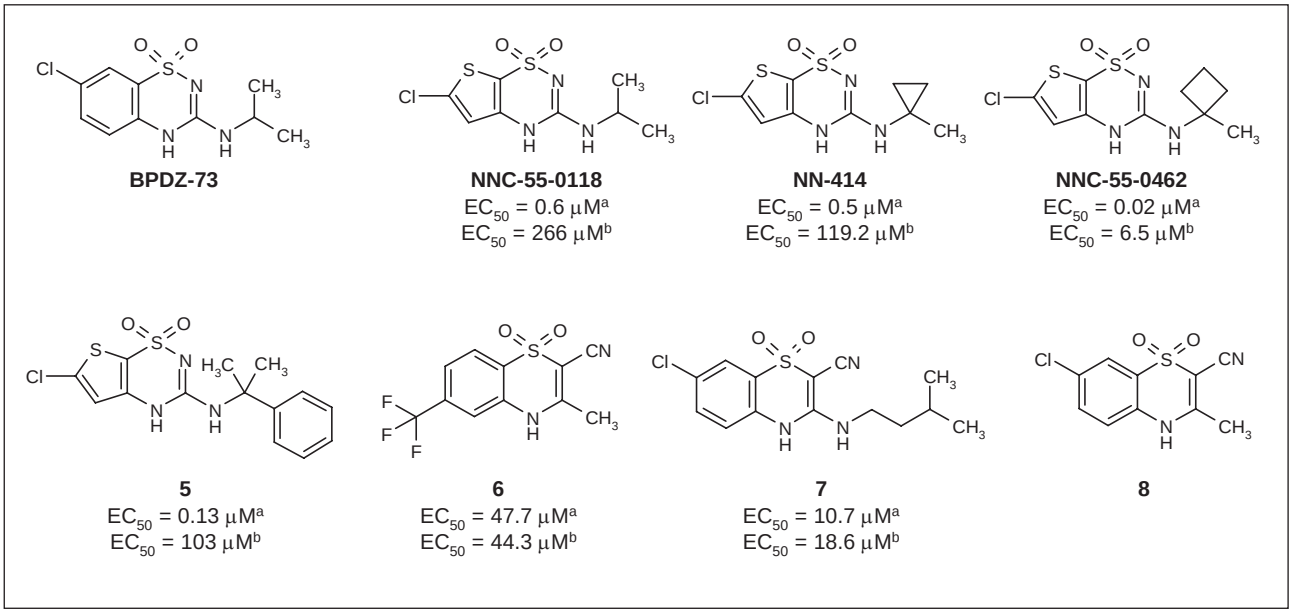


Fig. 5. Thienothiadiazine 1,1-dioxides and benzothiazine-2-carbonitriles. [a]Drug concentration giving 50% hyperpolarizing effect in TC3 β-cells. [b]Drug concentration giving 50% relaxation of phenylephrine- or KCl-induced contractions of rat aorta rings.

the 6-position can be replaced by a bromine atom without loss of activity, while modification of the position of this halogen resulted in a drastic decrease in activity (99).

High concentrations of NNC-55-0118 have been found to protect rat pancreatic islets from the toxic effects of streptozotocin, alloxan, sodium nitroprusside and IL-1β (100, 101). Moreover, *in vivo* data indicated that treatment with NN-414 improved pancreatic β-cell function and reduced insulitis in a type 1 diabetic rat model (102). Based on its pharmacological profile, NN-414 entered clinical trials and was shown to lower insulin levels in healthy male subjects (103). Unfortunately, the development of NN-414 was stopped in phase II clinical trials because of an unwanted increase in blood liver enzymes suggesting liver toxicity (104).

In the search for bioisosteres of the arylthiadiazine series, Novo Nordisk also explored a series of 1,4-benzothiazine-2-carbonitrile 1,1-dioxides (**6, 7, 8**; Fig. 5) (105). However, although the 2-cyanomethyl analogue of diazoxide (**8**) was found to activate Kir6.2/SUR1 K_{ATP} channels, none of the prepared compounds reached the potency of BPDZ-73, NNC-55-0118 or NN-414.

In terms of the tissue selectivity of pancreatic K_{ATP} channel openers, the arylthiadiazine dioxides are the most widely studied compounds. Other chemical series, however, have recently been developed. The first series was based on the structure of pinacidil (Fig. 6), which is a potent SUR2 K_{ATP} channels opener activating the SUR1 subtype only at high concentrations (106). Exploratory research indicated that replacement of the pyridyl group in pinacidil by a disubstituted phenyl group resulted in drugs activating pancreatic SUR1 K_{ATP} channels and exhibiting only a slight effect on smooth muscle SUR2 K_{ATP} channels (**9**; Fig. 6) (107).

Further modulation led to the discovery of compound **10** (Fig. 6), which was found to activate Kir6.2/SUR1 and inhibit Kir6.2/SUR2 K_{ATP} channel subtypes (108). Some 3,3-diaminosulfonylacrilonitriles (**11**; Fig. 6), which could be regarded as isostere structures of cyanoguanidines, were also reported to inhibit insulin secretion from β-cell lines and rat pancreatic islets, with minimal myorelaxant effects on vascular smooth muscle (109).

Levcromakalim (Fig. 7) is the lead compound in the benzopyran K_{ATP} channel opener family. Most drugs belonging to this family are known to activate the Kir6.2/SUR2 channel and to be poorly active as inhibitors of insulin release (110, 111). Nevertheless, several compounds, such as Y-26763 (Fig. 7), have been shown to exhibit modest activity on pancreatic-type Kir6.2/SUR1 channels, while maintaining effects on muscle-type Kir6.2/SUR2 channels (112). Several structural modifications introduced on the levcromakalim structure, such as replacement of the cyano group in the 6-position, elimination of the hydroxyl group in the 3-position and introduction of a phenylaminocarbonylamino group in the 4-position, led to the characterization of the first potent and selective pancreatic K_{ATP} channel openers belonging to the benzopyran chemical class (113, 114). SAR studies indicated that the most pronounced inhibitory activity on insulin release was obtained by introducing a *meta*- or a *para*-electron-withdrawing group (*i.e.*, a chlorine atom) at the C-4 position of the phenyl moiety and a halogen atom at the 6-position (*i.e.*, F, Cl, Br). The most promising compounds (**12**, **13**; Fig. 7) were more potent than diazoxide at 10 μM in a model of glucose-induced insulin release from rat pancreatic islets and failed to affect smooth muscle mechanical activity at up to 300 μM in a rat aorta ring model. Additional radioisotopic and electrophysiological experiments performed with compound **12** allowed us to define

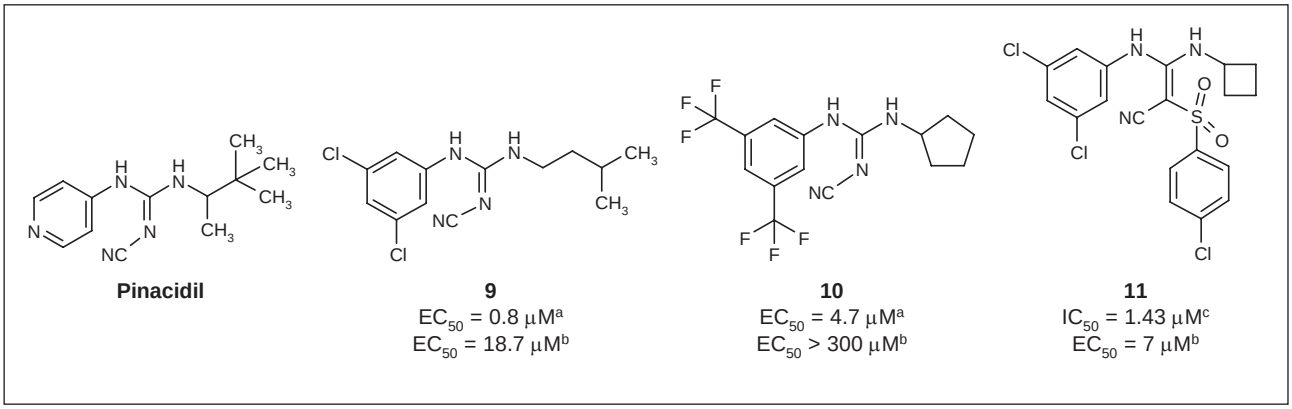


Fig. 6. Cyanoguanidines and sulfonylacrylonitriles. [a]Drug concentration giving 50% hyperpolarizing effect in TC3 β-cells. [b]Drug concentration giving 50% relaxation of phenylephrine- or KCl-induced contractions of rat aorta rings. [c]Drug concentration giving 50% inhibition of glucose-stimulated insulin release from TC6 β-cells.

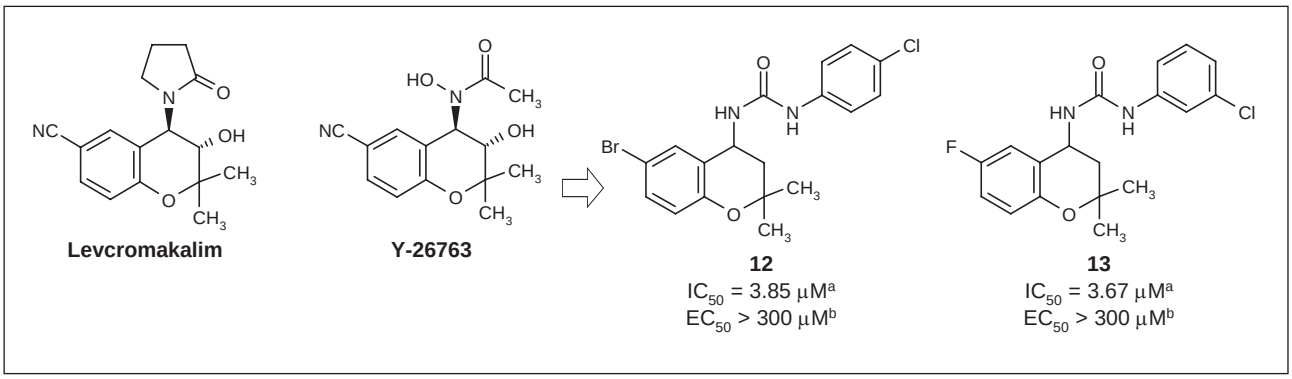


Fig. 7. Benzopyrans. [a]Drug concentration giving 50% inhibition of glucose-induced insulin secretion from rat pancreatic islets. [b]Drug concentration giving 50% relaxation of KCl-induced contractions of rat aorta rings.

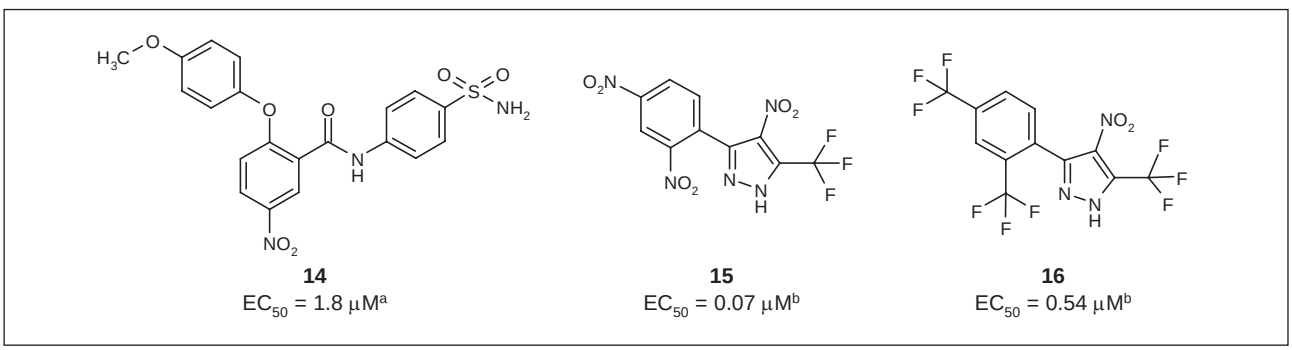


Fig. 8. Benzamides and pyrazoles. [a]Drug concentration giving 50% hyperpolarizing effect in TC3 β-cells. [b]Drug concentration giving 50% activation of K_{ATP} current in excised patches from *Xenopus* oocytes expressing human Kir6.2/SUR1 channels.

the pancreatic K_{ATP} channel as the main target for these drugs (114).

Recently, a series of 2-(4-methoxyphenoxy)-5-nitro-*N*-(4-sulfamoylphenyl)benzamides (**14**; Fig. 8) emerging from a compound library screening were found to activate Kir6.2/SUR1 K_{ATP} channels. However, no information about tissue selectivity was available for this series (115).

Using a high-throughput screening assay, and measurement of K_{ATP} current in inside-out patches, Peat *et al.* discovered the 3-trifluoromethyl-4-nitro-5-arylpyrazoles as another new scaffold for activation of Kir6.2/SUR1 channels (116). Several compounds of this series, such as **15** and **16** (Fig. 8), were shown to activate Kir6.2/SUR1 channels with only a minimal effect on Kir6.2/SUR2 channels.

Conclusions

Disorders of glucose homeostasis are generally associated with severe pathologies such as type 1 and type 2 diabetes, PHHI, PCOS, insulinoma and/or obesity. Such pathologies are related, directly or indirectly, to a defect in insulin secretion, a process tightly controlled by pancreatic K_{ATP} channels. Specific activation of these ionic channels has proved to be beneficial for most of these pathologies and to constitute a new therapeutic approach. Starting from diazoxide, a potent but poorly selective pancreatic K_{ATP} channel activator, numerous drugs belonging to the arylthiadiazine family have been designed. These pharmacochemical developments led to the discovery of potent and selective pancreatic K_{ATP} channel openers, such as BPDZ-44, BPDZ-73, BPDZ-415, NNC-55-0118 or NN-414. The latter compounds have proven therapeutic interest in the treatment of type 1 and type 2 diabetes and PHHI. Unfortunately, due to their poor pharmacokinetic properties or *in vivo* toxicity, none of these derivatives has passed initial clinical trials. Other chemical series have also been developed, but none of them has led to compounds as potent and/or as selective as the lead arylthiadiazine drugs. Thus, due to the great therapeutic interest in developing Kir6.2/SUR1-selective drugs, additional investigation needs to be conducted in order to optimize the existing leads or to find new lead compounds.

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