Second-Generation K_{ATP} Channel Openers

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Abstract: This review discusses structural aspects of second-generation K_{ATP} channel openers (KCOs), which exhibit improved tissue-selectivity. Their therapeutic profile is debated with main focus on cardiac ischemia, asthma, and urinary incontinence.

Keywords: K_{ATP} channel openers (KCOs), benzopyrans, cyclobutenediones, dihydropyridine related structures, tertiary carbinols, structure-activity relationships, therapeutic potential, myocardial ischemia, asthma, urinary incontinence.

1. INTRODUCTION

Given their many physiological functions, K_{ATP} channels represent promising drug targets [1-3]. Both blockers such as the antidiabetic sulfonylureas and openers of K_{ATP} channels (KCOs) have been described. KCOs add to existent pharmacotherapy with potential in promoting cellular protection under conditions of metabolic stress. Preclinical evidence indicates a broad therapeutic potential for KCOs [4-7] e.g. in hypertension, cardiac ischemia, asthma, or urinary incontinence; for an overview see Fig. (**1**).

The chemically heterogeneous KCOs comprise several structural classes such as the benzopyrans, cyanoguanidines, thioformamides, benzothiadiazines and pyridyl nitrates. Recently developed second generation KCOs include cyclobutenediones, dihydropyridi-nes, and tertiary carbinols. Prototypes for various KCO classes are shown in Fig. (**2**).

The therapeutic usefulness of KCOs ultimately depends on their tissue selectivity which was majorly not achieved with first generation compounds. Out of the broad spectrum of putative clinical utilities, we will focus on those therapeutic applications for which second generation KCOs were developed exhibiting at least *in vivo* tissue selectivity.

2. THERAPEUTIC PROFILE

2.1. Myocardial Ischemia

Cardioprotective properties of KCOs [8,9] were first suggested for nicorandil [10]. Later, Grover *et al*. [11] showed antiischemic effects of pinacidil and cromakalim in a model of ischemia and reperfusion in which vasodilator effects were avoided and thus direct cardio-protective activity could be verified. Cardioprotective properties of other KCOs were shown in similar models [12-14]. Beyond these *in vitro* data, several *in vivo* studies demonstrated the capability of KCOs to reduce infarct size; see e.g. Grover *et al*. [15].

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Molecular mechanisms of cardioprotection by KCOs are controversially debated. The APD hypothesis assumed a primacy of sarcolemmal K_{ATP} channels and postulated the following mechanism: K_{ATP} channel opening, induced by hypoxia, ischemia, or KCOs enhances shortening of the cardiac action potential duration (APD) by accelerating phase 3 repolarization. This diminishes Ca^{2+} entry into the cell, reduces Ca^{2+} overload during is-chemia and finally increases cell viability. However, KCOs exert cardioprotection without a significant cardiodepression. This questions the importance of APD shortening and consequently the importance of sarcolemmal K_{ATP} to mediate cardioprotection.

In contrast, the ROS (Reactive Oxygen Species) hypothesis [16,17] assumes a primacy of mitochondrial K_{ATP} channels and postulates this cellular mechanism: mitochondrial K_{ATP} opening leads to a K^+ influx into the mitochondrial inner matrix; this is the prerequisite for the generation and release of ROS from the respiratory chain; ROS then act as second messengers to activate protective kinases including PKC and probably p38 MAP kinase. Whereas many investigators exclude a significant role of sarcolemmal K_{ATP} channels in cardioprotection, some recent reports indicate cardioprotective roles for both sarcolemmal and mitochondrial K_{ATP} channels [18,19].

2.2. Asthma

Bronchial asthma is characterized by wide variations over short periods of time in the resistance to flow in intrapulmonary airways. Thus, this disease is commonly treated with bronchodilators. Nowadays asthma is no longer viewed simply as a reversible airways obstruction, but is considered as an inflammatory illness resulting in bronchial hyperreacti-vity and bronchospasm. Thus, pharmacological treatment of asthma deserves antiinflam-matory and bronchodilator drugs. Recent trends in the development of new antiasthmatics include inter alia KCOs [20]. Evidence for a bronchodilator potential of KCOs dates back to 1986, when Allen *et al*. [21] showed cromakalim to reduce spontaneous, and to a lesser extent, cholinergic and histaminergic tone in guinea-pig trachealis. Effective relaxation of tone by KCOs was also shown in bovine [22]

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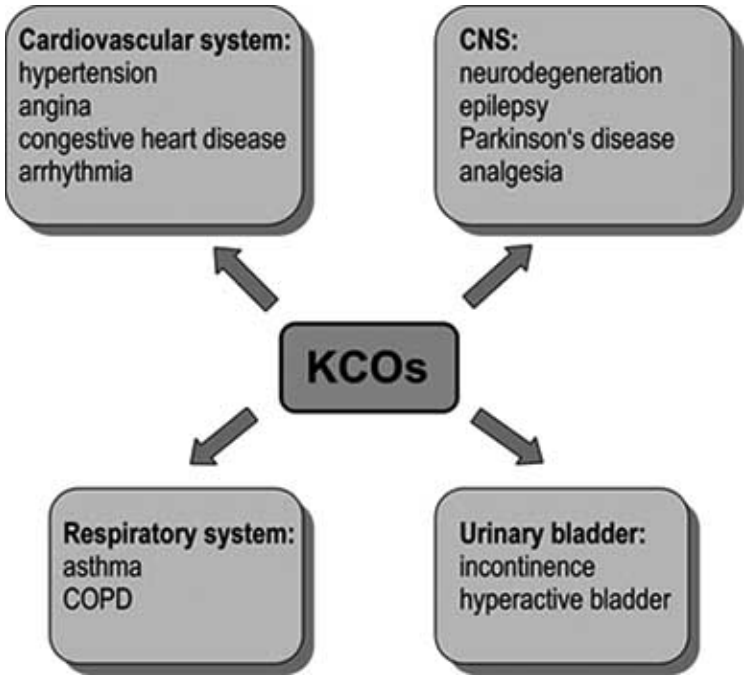

Fig. (1). *Therapeutic profile of KCOs*. This graph refers to a paper of Lawson,[4] where also the corresponding references can be found. The graph only lists main applicabilities. Additional organs and clinical targets e.g. include the reproductive system: dysmenorrhoea, impotence; the gastrointestinal tract: irritable bowel syndrome; the skeletal muscle: myotonic dystrophy, fatigue / paralysis; hair follicles: alopecia, and the eye: glaucoma.

and, more importantly, in human airways [23]. KCOs exhibit stronger spasmolytic rather than anti-spasmogenic activity which resembles other classes of smooth muscle relaxants [24].

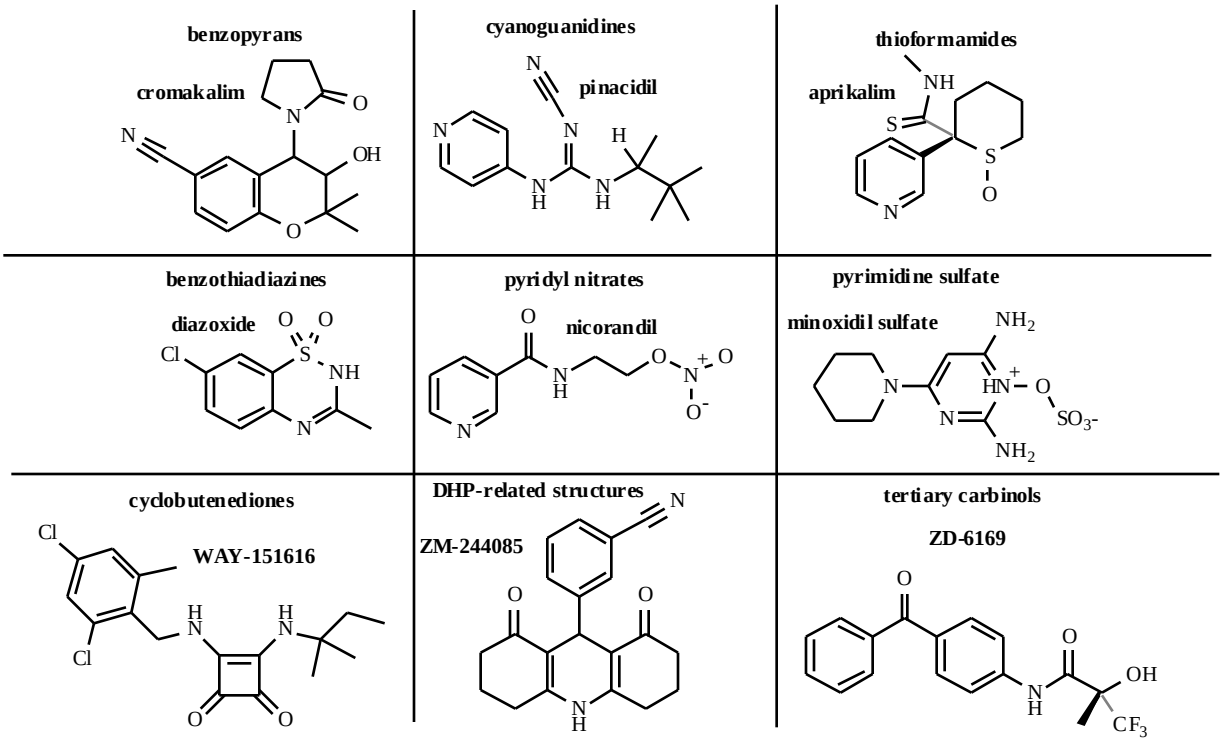

Fig. (2). *Structural classes of KCOs*. First generation KCOs comprise the chemical classes of benzopyrans (prototype cromakalim), cyanoguanidines (prototype pinacidil), thioformamides (prototype aprikalim), as well as the benzothiadiazine diazoxide, the pyridyl nitrate nicorandil, and the pyrimidine minoxidil sulfate. Second generation KCOs include structural variations of first generation KCOs (cyclobutenediones) or of Ca antagonists (DHP-related structures) as well as entirely new chemotypes such as the tertiary carbinols.

Bronchoconstriction often involves a reflex parasympathetic component. Thus, neural effects of KCOs might be relevant for their therapeutic utility in asthma. Several studies show KCOs to potently inhibit the neurotransmitter release from cholinergic and non-adrenergic, non-cholinergic (NANC) neurones. KCOs more effectively inhibit ACh- or NANC-mediated bronchoconstriction due to stimulated neurotransmitter release as compared to bronchoconstriction due to an exogenous supply of ACh or NANC neurotransmitters such as substance P or neurokinin A [25]. Inhibitory effects are probably mediated by hyper-polarization of sensory nerve endings *via* activation of prejunctional K-channels [26].

Beyond their effects on bronchoconstriction NANC neurotransmitters stimulate mucus secretion and the leakage of plasma from post-capillary venules, both of which are important in the pathology of asthma. These inflammatory effects of NANC neurotransmitters seem to be primarily due to substance P [27]. When studying the effects of KCOs on microvascular leakage and goblet cell secretion, it was found that they are only effective against stimuli that act by releasing neurotransmitters [24,28]. A final proof of the importance of the neural effects of KCOs for their antiasthmatic efficacy will demand direct studies of their effects on neurotransmitter release.

Airways hyperresponsiveness (AHR) to physiological and pharmacological stimuli is a commonly observed characteristic of asthmatic patients. KCOs acutely reverse AHR by a direct effect on airways smooth muscle and they are able to prevent the development of AHR [29]. Several KCOs, given at doses devoid of bronchodilator effects in control animals, inhibited AHR elicited by PAF, isoprenaline, or immune complexes [30]. Molecular mechanisms underlying the prevention of AHR by KCOs remain to be clarified.

2.3. Urinary Incontinence

Urinary incontinence is classified into following major types: stress incontinence, urge incontinence, reflex incontinence, and overflow incontinence [31]. Etiology of urinary incontinence is multivariant and includes neurogenic and myogenic instabilities. Most incontinence is due to failure to store urine (storage dysfunction), only overflow incontinence is due to failure to empty urine (emptying dysfunction).

Pharmacological treatment of storage dysfunction should be aimed at decreasing detrusor overactivity, increasing bladder capacity and/or increasing outlet resistance [31-33]. Pharmacological treatment of emptying dysfunction should be aimed at increasing detrusor contractility and/or decreasing outlet resistance. Most widely used in pharmacological treatment are antimuscarinic agents, which effectively inhibit bladder hyperreflexia, but suffer from main side effects such as the inhibition of normal bladder smooth muscle contractility and the blockade of muscarinic receptors in other organs.

As an alternative to antimuscarinics, KCOs should be able to achieve the goal of decreasing bladder overactivity. The existence of both Ca^{2+} dependent, large conductance potassium (BK_{Ca}) channels [34] as well as K_{ATP} channels [35] has been shown in guinea-pig bladder smooth muscle cells. Correspondingly, KCOs have attracted an early interest in investigating their potential utility in treating urinary incontinence [31-33]. Several KCOs were shown *in vitro* to relax bladder smooth muscle in various species including man [36,37]. KCOs also inhibit bladder overactivity *in vivo* in various animal models [37,38]. It is a complicating fact that *in vitro* data are often not predictive of *in vivo* results. In clinical studies, cromakalim showed beneficial effect against bladder instability in humans although full clinical efficacy was limited due to hypotension and tachycardia [39].

3. SECOND GENERATION KCOS EXHIBITING TISSUE-SELECTIVITY

3.1. Cardioselective Benzopyranyl Cyanoguanidines

Studies with cromakalim [40] showed cardioprotection *in vitro* and *in vivo*; but clinical efficacy was limited due to equipotent systemic vasodilation [41]. A benzopyran/cyano-guanidine hybrid (BMS-180448 **1** in Fig. (**3**)) was the first cardioselective KCO [42]. Starting from BMS-180448 Atwal *et al*. [43-47] performed detailed SAR studies (Fig. **4**). Among benzopyran ring modifications [43], an exchange of the oxygen in 1-position by CH_2 is tolerated; exchange by NH is detrimental. The geminal 2-methyl groups are essential. Presence of 3-OH is not mandatory, but, if present, trans-OH is superior to cis-OH. A 3, 4-double bond abolishes antiischemic activity indicating that an sp^3 carbon is preferred at C4. In contrast, chromenes exhibit increased vasodilator properties as compared to chromanols. Thus, different SAR exist for antiischemic and vasodilator properties. Regarding 6-variations, a significant bulk tolerance is observed; both small, electronegative (compound **2** in Fig. (**3**)) as well as larger sulfonamido substituents [47] as present in **3** significantly improve cardioprotective potency and selectivity relative to BMS-180448.

Modifications of the cyanoguanidine portion [44] show that a phenyl cyanoguanidine or phenyl urea moiety strongly favor cardioselectivity; modifying the distance between aniline nitrogen and the pendant aromatic ring attenuates potency and selectivity. Replacements of the aniline N by O, S, or CH_2 are detrimental as well. Exchange of phenyl by pyridyl is tolerated. In addition, an advantageous phenyl substitution by small, electronegative groups as well as small alkyl groups is found indicating favorable interactions of phenyl substituents. The impact of urea conformation on antiischemic activity and selectivity was evaluated *via* conformationally restrained analogs such as **4**. A moderate drop in anti-ischemic activity is coupled with a profound diminution of the vasodilator activity.

4-(N-aryl)-substituted benzopyrans were synthesized to further reduce the retaining vasodilator activity of BMS-180448 [46]. Within this series BMS-191095 **5** showed the highest antiischemic potency and selectivity; it is at least 30-fold more selective than BMS-180448. The antiischemic activity mainly resides in the 3S, 4R-enantiomer which is opposite to the enantioselectivity of BMS-180448. Reasons for the reversed stereoche-mical requirements are unknown, but may be related to different receptor binding modes.

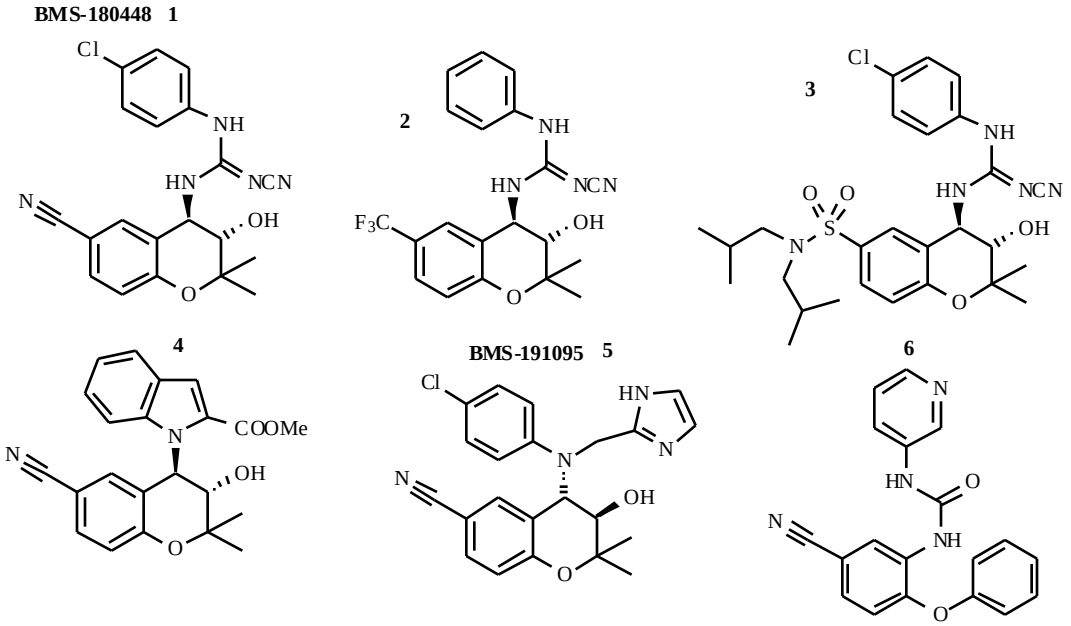

Fig. (3). ***Cardioselective benzopyranylcyanoguanidines and related structures***. BMS-180448 **1** was the first cardioselective KCO. 6-CF_3 **2** and larger 6-sulfonamido substituents **3** strongly improve the antiischemic potency. The impact of conformation was evaluated *via* conformationally restrained analogs **4**: a moderate drop in antiischemic activity is coupled with a profoundly reduced vasodilator activity. Attempts to further reduce the retaining vasodilator activity of BMS-180448 led to 4-(N-aryl)-substituted benzopyrans; in this series BMS-191095 **5** was most potent. Its antiischemic activity resides in the 3S, 4R-enantiomer which is opposite to findings with BMS-180448. Compound **6** demonstrates that the benzopyran portion is not mandatory for antiischemic activity; it exhibits a rather modest reduction in antiischemic activity and cardioselectivity as compared with their cyclic predecessors.

Finally it was shown that the benzopyran portion is not mandatory for antiischemic activity and cardioselectivity [45]; see compound **6** in Fig. (**3**).

3.2. Airways-Selective Benzopyrans and Dialkylnaphthalenones

Airways selective KCOs exclusively represent benzopyrans or closely related dialkyl-naphthalenones; their chemistry is given in Fig. (**5**). One of the rare examples for air-ways selectivity *in vitro* is KC-128 **7**, out of a series of benzopyran-4-(*N'*-cyano)-carbox-amidines [48,49]. Relaxant activities were quantified in isolated rat aorta and isolated guinea-pig trachea. Airways selectivity strongly depended on N-substitution within the carboxamidine moiety. KC-128, exhibiting N-dimethyl substitution, inhibited spontaneous tone in the trachealis preparation with a pIC_{50} of 7.3, but was inactive in the aortic preparation [48]. In contrast to classical KCOs, the relaxant activity of KC-128 was non-competitively blocked by glibenclamide, suggesting that KC-128 might target a binding site different from classical KCOs.

A further example for airways selectivity *in vitro* refers to dialkylnaphthalen-1-ones, in which the pyran oxygen is replaced by a keto group. Studying relaxant activities in isolated rat portal vein versus guinea-pig tracheal spirals, airways selectivity by a factor of roughly 12 was shown for compound **8** [50].

The 6-C_2F_5 substituted BRL 55834 **9** does not show absolute airways selectivity *in vitro*. In comparison to levcromakalim, BRL 55834 is 8- to 27-fold more potent in tracheal spirals, but only 3-fold more potent in rat portal vein. This comparison indicates a relative *in vitro* airways

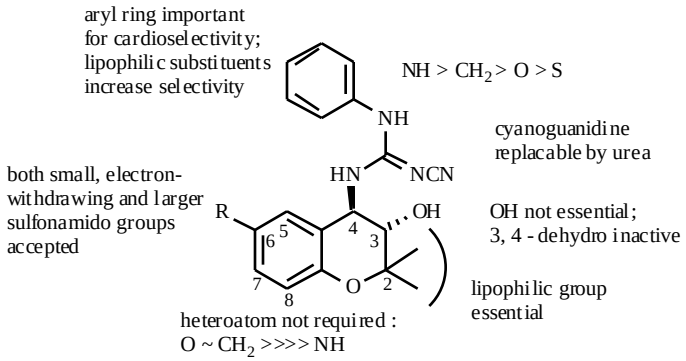

Fig. (4). ***SAR data for the antiischemic properties of benzopyranyl-cyanoguanidine KCOs***. For a detailed description see text. Adapted with some modifications from Atwal *et al*. [45].

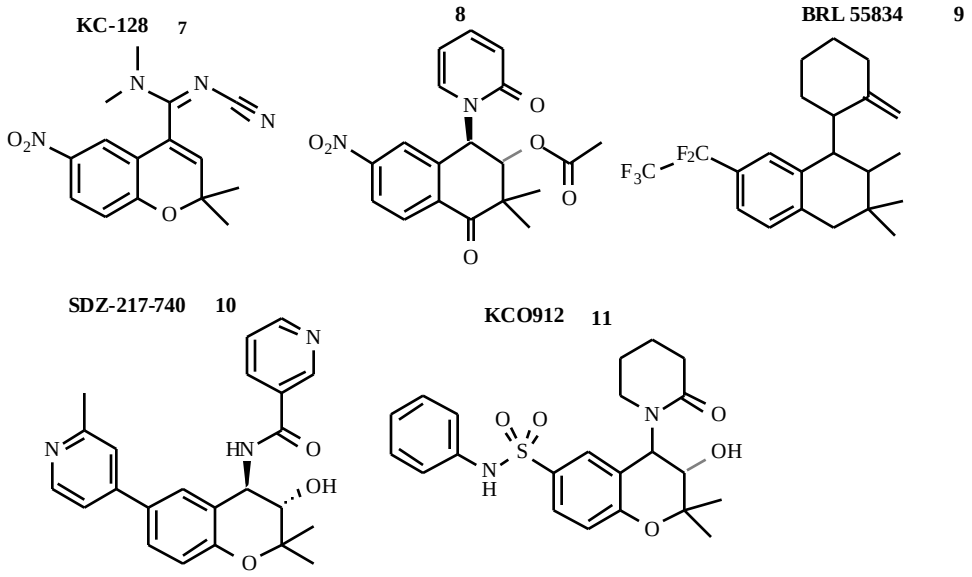

Fig. (5). ***Airways selective KCOs: benzopyrans and dialkylnaphthalenones***. Airways-selective KCOs exclusively represent benzopyrans **7**, **9**–**11** or closely related dialkyl-naphthalenones **8**. *In-vitro* selectivity is reported for **7** and **8**, whereas *in vivo* or clinical data are lacking. Both compounds represent interesting leads for further development. In contrast, **9**–**11** exhibit *in-vivo* selectivity. Structural inspection indicates the 4-piperidone moiety - present in **9** and **11** - and in particular the chromanol structure to favor tissue-selectivity.

selectivity. Comparison of BRL 55834 with levcromakalim in urethane-anaesthetized, freely respiring guinea-pigs and rats revealed *in vivo* selectivity [51].

SDZ-217-744 **10** has a 2-methyl-4-pyridyl group in 6-position and a 3-pyridinecarbox-amide moiety in C4-position. In guinea pigs, SDZ-217-744 exhibits improved selectivity for inhibition of AHR as compared to levcromakalim or bimakalim [29]. SDZ-217-744 inhibits immune complex-induced AHR with an ED_{50} value of 0.08 µg/kg, whereas the ED_{20} for reduction of mean arterial pressure is > 100 µg/kg upon intratracheal administration. Chronic administration of this compound also reversed the salbutamol-induced AHR.

KCO912 **11** is a most recent example of an airways selective benzopyran KCO [52]. It is chemically characterized by an N-sulfonamido substituent in 6-position and a 4-piperidone moiety. Because compounds with this 6-substituent [53] lack any airways selectivity, the 4-piperidone moiety (also present in BRL 55834) coupled with the chromanol structure might be responsible for this tissue-selective behaviour.

3.3. Bladder-Selective Benzopyran Related Structures

Bladder selective benzopyran-KCOs (Fig. **6**) are rather scarce. They exhibit pro-nounced chemical variations in comparison to first generation benzopyrans. Their 3- and 4-substituents are cis-oriented and connected *via* an ethylene bridge.

KCO activities were tested *in vitro* in spontaneously contracting rat portal vein and KCl-precontracted rat detrusor strips [54,55]. In a first study the (-)-enantiomer of **12** exhibited a modest 4-fold *in vitro* selectivity for rat detrusor versus rat portal vein [54]. Later the impact of benzamide substituents on potency and selectivity was investigated

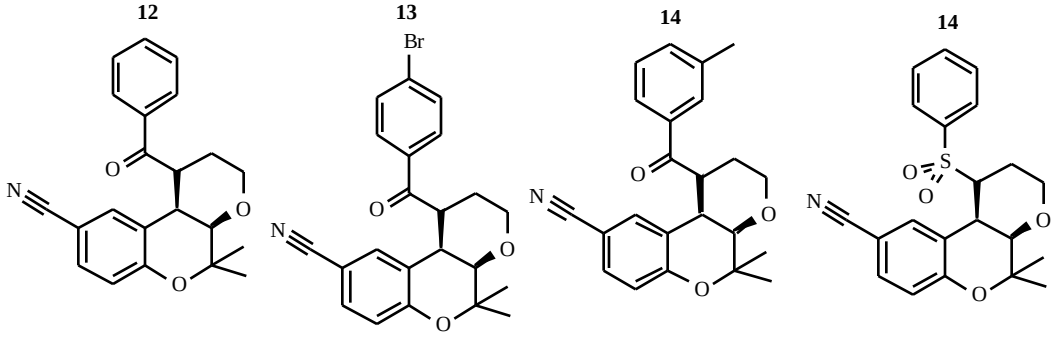

Fig. (6). *Bladder selective benzopyran related structures*. Chemistry of bladder selective benzopyran KCOs profoundly differs from first generation benzopyrans. Their 3- and 4-substituents are cis-oriented and connected *via* an ethylene bridge. Benzamide substituents significantly influence selectivity. 4-Bromo substitution 13 confers strong bladder activity, whereas 3-methyl substitution 14 confers strong selectivity for the rat portal vein. Bioisosteric replacement of the carbonyl in 12 by sulfonyl in 15 further improves *in vitro* bladder selectivity.

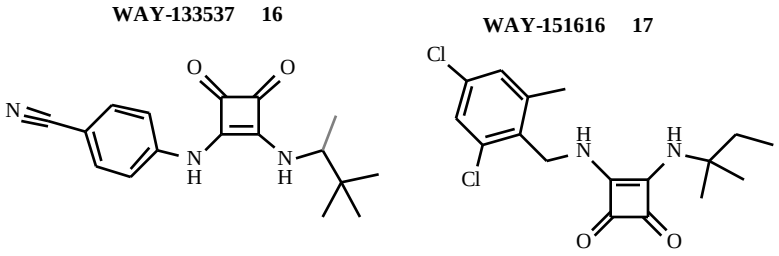

Fig. (7). ***Bladder selective diaminocyclobutenediones*.** This class was derived from the cyanoguanidine KCO by utilizing the 1,2-diaminocyclobutene-3,4-dione template as a bioisostere for the *N*-cyanoguanidine moiety.

[55]. The 4-Br derivative **13** exhibited the strongest bladder activity, whereas the 3-CH_3 derivative **14** showed strong selectivity for the rat portal vein. Bioisosteric replacement of CO by SO_2, as realized in **15**, resulted in a further improvement of *in vitro* selectivity. If this translates into improved *in vivo* selectivity remains unclear; corresponding studies are missing yet.

3.4. Bladder-Selective Diaminocyclobutenediones

Diaminocyclobutenediones, such as WAY-133537 **16** and WAY-151616 **17** (Fig. **7**) were developed at Wyeth-Ayerst [56,57]. The 1,2-diaminocyclobutene-3,4-dione template was utilized as bioisostere for the *N*-cyanoguanidine moiety known from the pinacidil class of KCOs. Relaxation of KCl-precontracted rat detrusor muscle strips served as assay for *in vitro* potency. To estimate *in vitro* selectivity, compounds were screened in similar assays using rat aortic rings. *In vivo* efficacy was evaluated in a rat model of bladder instability. Compounds that reduced the frequency of spontaneous bladder contractions *in vivo* were submitted to hemodynamic assessment; effects on mean arterial pressure and heart rate were recorded after oral drug administration. WAY-133537 and WAY-151616 exhibit i*n vivo* selectivity in conscious rats after oral application. WAY-133537 was 18-fold and WAY-151616 was 166-fold selective, when comparing the ED_{50} for inhibiting unstable bladder contractions and the ED_{20} for lowering mean arterial pressure.

Detailed SAR studies [56] on the central cyclobutenedione moiety and the arylamino and alkylamino side chains were reported (Fig. **8**). The central part proved to be essential. Replacing the squarate with other carbocyclic, heterocyclic or acyclic isosteres led to loss of activity. In the arylamino side chain, a phenyl group is preferred. Ortho-substituents enhance and meta-substituents reduce potency; 4-cyano is optimal. In the alkylamino side chain, voluminous, α-branched lipophilic groups are preferred; dilator potency resides in the R-enantiomers. Development candidate from these studies was WAY-133537. Efforts to improve the overall pharmacological profile of WAY-133537 were focused on metabolic stability and finally led to the design of WAY-151616 [57].

3.5. Bladder-Selective DHP-Related Structures

Dihydropyridines (DHPs) are known as L-type calcium channel blocking antihypertensive drugs. DHPs, however, also interact with other ion channels [58,59]. Thus, it is not surprising that DHP-like structures were shown to interact with K_{ATP} channels. Acridine-diones were identified as putative KCOs from screening of in-house databases at Zeneca.

A DHP-like KCO (Fig. **9**) is ZM-244085 **18** [60,61]. The effects on low and high KCl induced contractions, ^{86}Rb efflux, and [^{3}H]P1075 binding in guinea-pig bladder strips were used to characterize the *in vitro* KCO properties of ZM-244085 versus first-generation KCOs [60]. The typical profile of classical KCOs was also found for ZM-244085.

Replacing one of the cyclohexenone rings in ZM-244085 resulted in a further series of DHP-related KCOs including

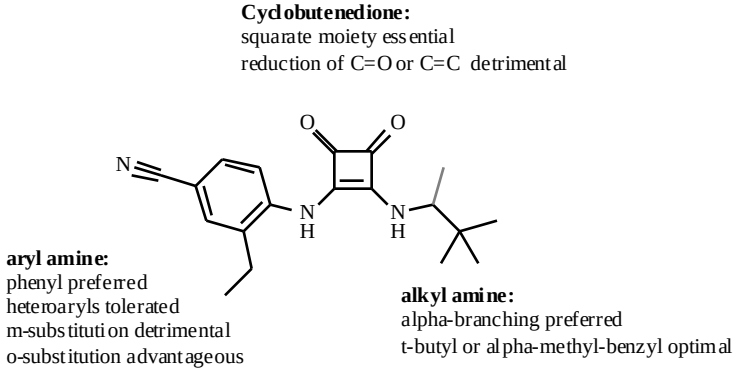

Fig. (8). ***SAR of diaminocyclobutenedione KCOs***. The central part proved to be essential. Attempts to replace the squarate with other carbocyclic, heterocyclic or acyclic isosteres led to loss of activity. In the arylamino side chain, a phenyl group is preferred. Ortho-substituents enhance and meta-substituents reduce potency; 4-cyano is optimal. In the alkylamino side chain, rather voluminous, α-branched lipophilic groups are preferred; dilator potency resides in the R-enantiomers. Adapted with some modifications from Butera *et al*. [56].

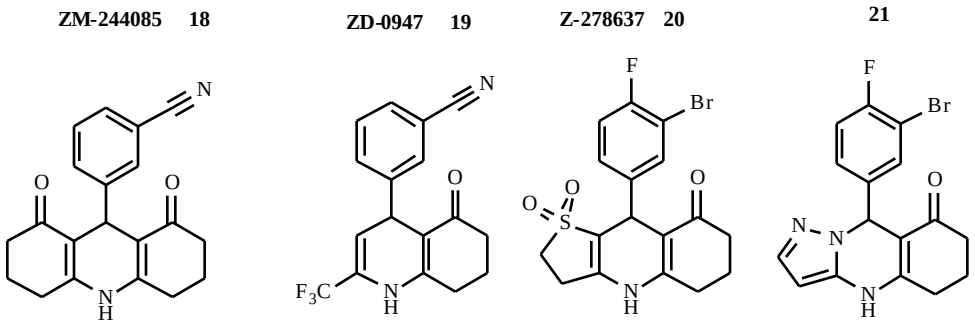

Fig. (9). *Bladder selective dihydropyridine related structures*. Prototype is ZM-244085 18. Replacement of one of the cyclohexenone rings in 18 resulted in ZD-0947 19, A-278637 20 and compound 21. In 20 a thiophene 1,1 dioxide replaces one of the cyclohexenone rings. 21 represents a novel series of tricyclic dihydropyrimidines.

ZD-0947 **19**, A-278637 **20** and compound **21** (Fig. **9**). ZD-0947 is reportedly undergoing clinical trials [62].

In A-278637 **20** a thiophene 1,1 dioxide replaces one of the cyclohexenone rings present in ZM-244085. A-278637 was comprehensive investigated both *in vitro* [63] and *in vivo* [64]. *In vitro* bladder selectivity of A-278637 versus vascular K_{ATP} channels was estimated in thoracic aorta and portal vein in comparison with WAY-133537 and ZD-6169. A-278637 showed modest bladder selectivity versus thoracic aorta, whereas WAY-133537 and ZD-6169 were somewhat more potent in relaxing aortic strips. All three compounds were more potent inhibitors of spontaneous phasic activity in portal vein as compared to bladder. A pig model of detrusor instability secondary to partial bladder outlet obstruction was used for characterization of A-278637 *in vivo* [64]. In comparison to WAY-133537 and ZD-6169, it was found to be approximately 5- to 6-fold more bladder selective.

A novel series of tricyclic dihydropyrimidines [65] is represented by **21** (Fig. **9**). Compounds were assayed in primary cultured guinea-pig urinary bladder cells by evaluating changes in membrane potential using the $DiBAC_4$ dye; most potent derivatives were afterwards tested in isolated bladder strips and found to exhibit activities comparable to cromakalim. It should be noted that any selectivity data are missing so far.

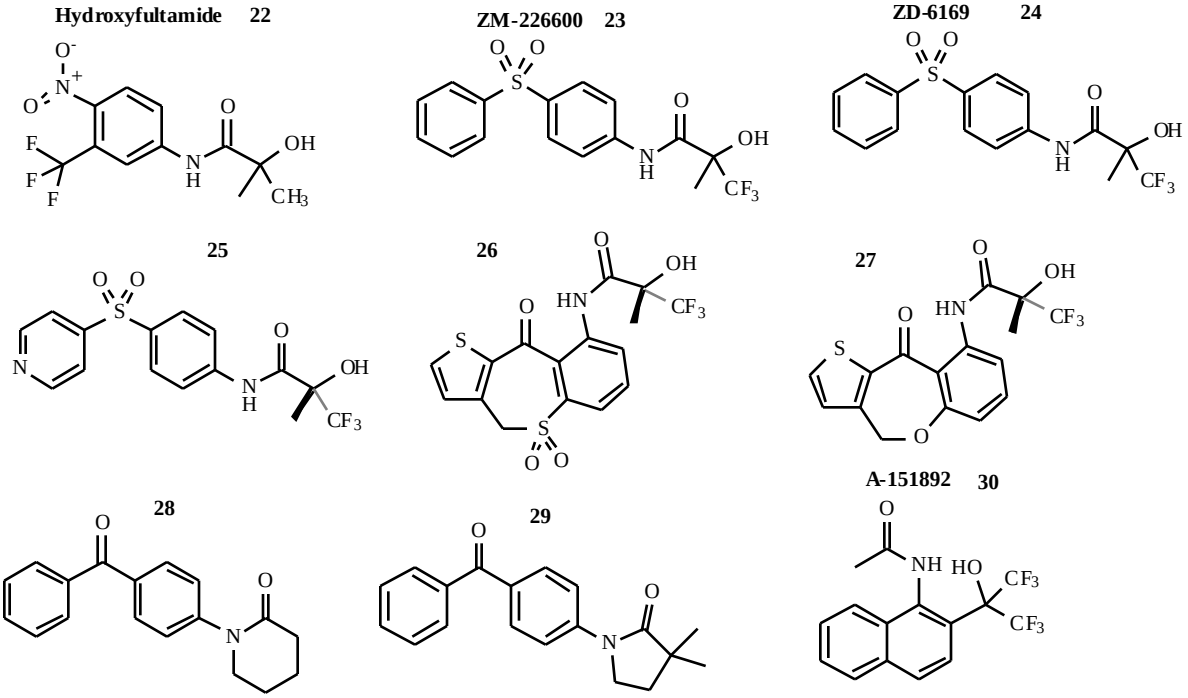

Fig. (10). ***Bladder selective tertiary carbinols***. Tertiary carbinol KCOs were derived from anti-androgens with hypotensive, KCO related side effects such as hydroxyflutamide **22**. More bulky substituents in the N-aryl and fluorination in the alkyl region increased KCO activity and selectivity. Thus, ZM-226600 **23** lacks anti-androgen activity. Compounds with large electron withdrawing 4-substituents (ZD-6169 **24** and **25**) exhibit rather high *in vivo* bladder selectivity, residing in the S-(-)-enantiomers. Variations of **24** include rigidization products in various parts of the molecule (compounds **26- 29**): in **26** and **27** the tertiary carbinol is ortho- instead of para-positioned relative to the carbonyl, and the flexible benzophenone moiety is transferred into a rigid tricyclic system. In structures like **28** and **29** the carbinol moiety itself is replaced more rigid rings. The most far-reaching modification of ZD-6169 was realized in A-151892 **30**, retaining only the carbinol moiety.

3.6. Bladder-Selective Tertiary Carbinols

In contrast to the above described KCOs, the tertiary carbinols (Fig. **10**) represent entirely new chemotypes. They were derived from a series of potent anti-androgenic propanamides such as hydroxyflutamide **22** [66]. Some of these anti-androgens exhibited unwanted hypotensive effects which were later attributed to KCO properties [67,68].

In a first step, the larger size tolerance for anti-androgen activity in the alkyl region and the larger size tolerance for KCO activity in the N-aryl region allowed to minimize the anti-androgen and to improve the KCO potency. Thus, ZM-226600 **23** is a representative of compounds with pronounced KCO, but lacking anti-androgen activity. Second step was dedicated to achieve *in vivo* bladder selectivity; the normotensive conscious rat bladder model was used as biological test system that allows the simultaneous measurement of cardiovascular and bladder effects [69,70]. Compounds with large electron withdrawing 4-substituents as present in **24** and **25** exhibit rather high *in vivo* bladder selectivity, residing in the S-(-)-enantiomers.

From these studies ZD-6169, was selected as a development candidate for treating urge urinary incontinence. KCO properties of ZD-6169 were intensively studied *in vitro* and *in vivo* [37,67-72] Recent studies on the mechanism of the bladder-selective actions of ZD-6169 suggest the involvement of an inhibitory effect on bladder C-fiber afferents in addition to KCOs properties. After intravesical infusion, ZD-6169 blocked acetic acid-induced bladder overactivity in a similar manner as the C-fiber afferent neurotoxin capsaicin [73].

Chemical variations of ZD-6169 include rigidization products in various parts of this lead; see compounds **26** - **29** (Figure **10**). The carbinols **26** and **27** differ in two ways from ZD-6169: i) the tertiary carbinol is ortho- instead of para-positioned relative to the carbonyl, and ii) the flexible benzophenone moiety is transferred into a rigid tricyclic ring *via* an interconnecting seven-membered heterocycle. *In vitro*, both compounds relax 15 mM KCl-stimulated guinea pig bladder strips with similar potency to ZD-6169. For compounds **26** and **27** *in vivo* bladder selectivity was reported [74,75]. In structures **28** and **29** the carbinol moiety itself is replaced by more rigid rings [76].

The most far-reaching modification of ZD-6169 was realized in A-151892 **30**, retaining only the carbinol moiety [77]. A-151892 is a potent KCO *in vitro* in guinea-pig bladder cells and pig bladder strips. Additionally, it was found to selectively inhibit unstable bladder contractions *in vivo* using an obstructed pig model of myogenic bladder function.

CONCLUDING REMARKS

The focus of medicinal chemistry efforts on K_{ATP} channels was pioneered by the discovery of first generation KCOs such as cromakalim, pinacidil and nicorandil. Treatment of hypertension was viewed as the main therapeutic potential of first generation KCOs. In general, however, these compounds failed to demonstrate clear advantages over established antihypertensive drugs such as calcium antagonists or ACE inhibitors.

Thus, in a second phase of research the therapeutic potential of KCOs in the treatment of disorders such as myocardial ischemia, airways hyperresponsiveness, and urinary incontinence was investigated in great detail. Second generation KCOs, which differ from their predecessors by significantly improved *in vitro* or *in vivo* selectivity, broaden the chemical diversity of K_{ATP} channel ligands including the cyclobutenediones, dihydro-pyridines, and as entirely new chemotypes within the KCO field the tertiary carbinols.

Despite this progress, a lot of work remains to be done to fully exploit the pharmaco-logical potential of KCOs. Methodological progress such as the availability of high-throughput screening against cloned subtypes and the application of structure-based drug design on the basis of a further refined information on K_{ATP} channel architecture should allow to develop third generation KCOs with a fine-tuned selectivity profile.

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