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# Synthesis and bladder smooth muscle relaxing properties of substituted 3-amino-4-aryl-(and aralkyl-)cyclobut-3-ene-1,2-diones

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**Abstract**—We have reported on the design, synthesis, and biological characterization of (*R*)-4-[3,4-dioxo-2-(1,2,2-trimethyl-propylamino)-cyclobut-1-enylamino]-3-ethyl-benzonitrile (**1**),[1] a novel, potent, and selective adenosine 5′-triphosphate-sensitive potassium ($K_{ATP}$) channel opener with potential utility for the treatment of urge urinary incontinence (UUI). Excising the aniline-derived nitrogen atom of **1** or replacing it with an aralkyl group, led to bladder smooth muscle relaxant chemotypes **3** and **4**, respectively. Prototype compounds in these series were found to produce significant increases in an iberiotoxin (IbTx)-sensitive hyperpolarizing current, thus suggesting that these relatively modest structural modifications resulted in a switch in the mechanism of action of these smooth muscle relaxants from $K_{ATP}$ channel openers to activators of the large-conductance $Ca^{2+}$-activated potassium channel ($BK_{Ca}$). We report herein the syntheses and biological evaluation of a series of substituted 3-amino-4-aryl-(and aralkyl-)cyclobut-3-ene-1,2-diones.


Transmembrane potassium channels, a diverse family of pore-forming proteins that allow for selective permeation of potassium ions across the cell membrane, continue to provide useful molecular targets for controlling the physiological function of excitable cells. Recent reviews have provided useful perspectives of potassium channel sub-type, structure, function and related medicinal chemistry, and SAR.[2–5] It has been shown that bladder smooth muscle may contain several sub-type families of potassium channels and that modulation of these channels with specific ligands produces significant detrusor muscle relaxation in vitro and in vivo.[6] Potassium channel openers (KCOs) with specificity towards bladder tissue may show promise as potential drugs to treat urge urinary incontinence (UUI), a condition characterized by spontaneously hyperactive bladder smooth muscle.

Subsequent to the discovery and characterization of diaminocyclobutenediones **1a** and **1b** (Fig. 1), two potent and bladder-selective $K_{ATP}$-channel openers possessing striking oral efficacy in a rat hypertrophied bladder model of UUI,[1,7] metabolic stability studies (in vitro and in vivo) on **1a** and **1b** suggested a rapid turnover to the primary metabolite, a 4-amino-benzonitrile derivative. Concern over potential long-term exposure to these compounds prompted us to focus our synthetic efforts on structural modifications of the aryl vinylogous amide bond. Numerous approaches were implemented and several have been reported: (i) homologation of the anilino-cyclobutenedione linker with concomitant re-optimization of SAR to afford development track compound **2** (KCO-616),[8,9] (ii) acylation of the anilino-nitrogen to afford acyl analogs **5**,[10] which slows but does not prevent formation of the aniline metabolite, and (iii) incorporation of the aryl amine and alkyl amine moieties onto numerous heterocyclic scaffolds (**6**) to circumvent the metabolic cleavage.[11] While approach (i) was successful and resulted in the identification, characterization, and development of a series of nonhydrolyzing benzylamino cyclobutenediones exemplified by KCO-616, concomitant strategies involved the excision of the labile vinylogous amide bond or its replacement with a carbon-based variant such as an olefin, methylene, or substituted methylene unit. Interestingly, preliminary cell-electrophysiological data suggest

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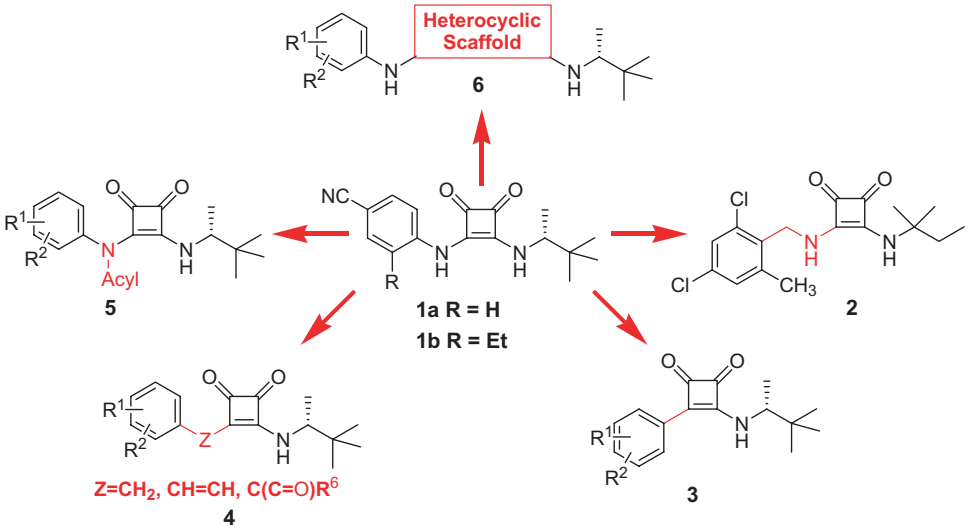



**Figure 1.** Attempts to modulate the metabolic fate of cyclobutenedione leads (**1a** and **1b**) via structural modification of the aryl vinylogous amide bond led to several novel chemotypes possessing in vitro and in vivo bladder smooth muscle relaxant properties.

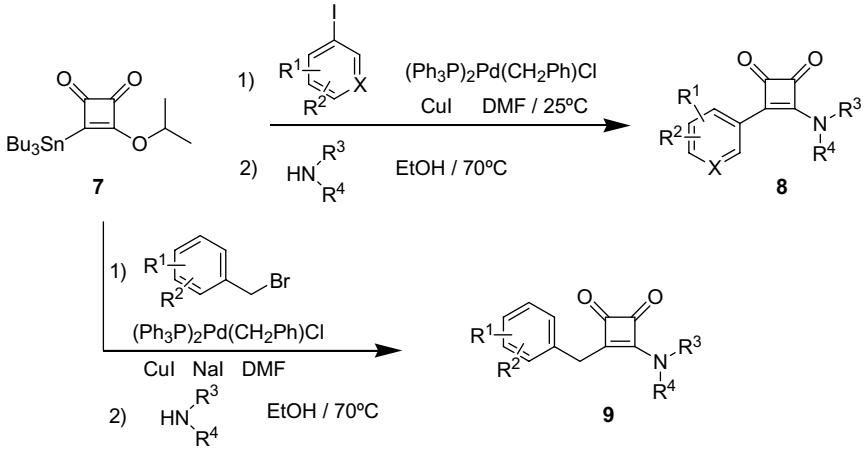
that these seemingly modest structural modifications resulted in a switch in the mechanism of action of these smooth muscle relaxants from $K_{ATP}$ channel openers to activators of the large-conductance $Ca^{2+}$-activated potassium channel ($BK_{Ca}$). This report will detail our efforts to synthesize a series of substituted 3-amino-4-aryl, 3-amino-4-aralkyl, and 3-amino-4-vinyl cyclobut-3-ene-1,2-diones, represented by templates **3** and **4**, and their biological evaluation as bladder smooth muscle relaxants.[12]

Cross-coupling reaction conditions (Scheme 1) using 3-isopropoxy-4-tri-*n*-butyl-stannyl)-3-cyclobutene-1,2-dione (**7**)[13] and an appropriate aryl halide (X = CH) or 3-pyridyl halide (X = N) in the presence of benzyl(chloro)bis-(triphenylphosphine)palladium(II) and cuprous iodide afforded the Stille product,[14] which was subsequently treated with a primary or secondary amine in ethanol to give the 3-amino-4-phenyl-(or pyridyl)-cyclobut-3-ene-1,2-dione (**8**).

Synthesis of benzyl analogs (**9**) was accomplished similarly by treating stannane **7** with an appropriate benzyl bromide in the presence of benzyl(chloro)bis-(triphenylphosphine)palladium(II), cuprous iodide, under *trans*-halogenation conditions using sodium iodide to afford the benzyl-substituted cyclobutenedione, which was converted to final product **9** by treatment with a primary or secondary amine in ethanol.

Compounds possessing an alkanoyl group appended from the benzylic carbon of chemotype **9** were prepared (Scheme 2) by inverse dropwise addition of the preformed enolate of the appropriate ketone **10** (potassium bis(trimethylsilyl)amide at −78 °C) into a cold solution of diethoxysquaric acid. Adduct **11** was then treated with one equivalent of amine in EtOH at 0 °C to afford compound **12**.

A third linker was explored where the aniline nitrogen of **1** was replaced with a C=C double bond. Thus, iodo-




**Scheme 1.** Synthesis of 3-amino-4-phenyl- and 3-amino-4-pyridyl-cyclobut-3-ene-1,2-diones **8** and benzyl analogs **9**.