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THIOPHENE SYSTEMS. 15. SYNTHESIS AND ANTIHYPERTENSIVE ACTIVITY OF 7-(SUBSTITUTED BENZAMIDO)-6-HYDROXYTHIENO[3,2-b]PYRANS AS NEW POTASSIUM CHANNEL ACTIVATORS

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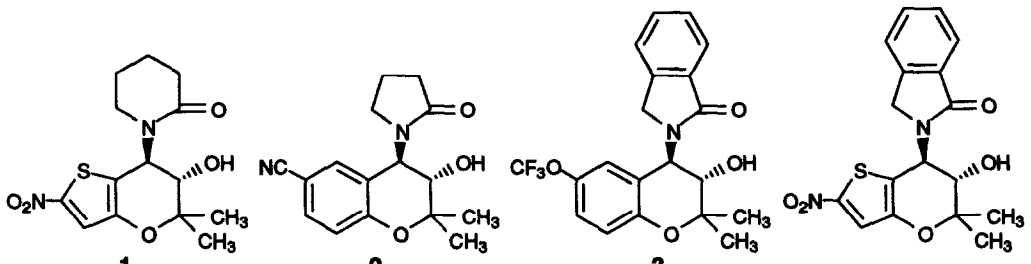
Abstract. The synthesis and antihypertensive activity of novel 7-(substituted benzamido)-6-hydroxy-5,5-dimethylthieno[3,2-b]pyrans are described. Acetyl substitution on the thiophene significantly increases potency of these benzamides in contrast to the nitro substitution which gives the best results in the 7-(cyclic amido)-6-hydroxythieno[3,2-b]pyran series. Compound **21** is 3-fold more potent than the benzopyran cromakalim (**2**).

Recently, we have described a novel series of 7-(cyclic amido)-6-hydroxythieno[3,2-b]pyrans as new potassium channel activators.[1] This work culminated in the characterization of *trans*-(±)-5,6-dihydro-6-hydroxy-5,5-dimethyl-2-nitro-7-(2-oxopiperidin-1-yl)-7*H*-thieno[3,2-b]pyran (**1**, RWJ 26629) with an ED_{30}=0.015 mg/kg in the spontaneously hypertensive rat (SHR). Compound **1** is ten-fold more potent in SHR than cromakalim (**2**), the prototype benzopyran potassium channel opener.[2] Replacement of the C-7 piperidinone with the bulky isoindolone group, a structural feature of celikalim (**3**),[3] produced **4** which is two-fold more potent than **3** in the SHR. However, **4** does not have the delayed onset or prolonged duration of action in SHR claimed for **3** (>24 hrs). As part of our continuing interest in the area of potassium channel activators, we began a study of the structure activity relationship (SAR) of 7-(substituted benzamido)-6-hydroxythieno[3,2-b]pyrans **5**.

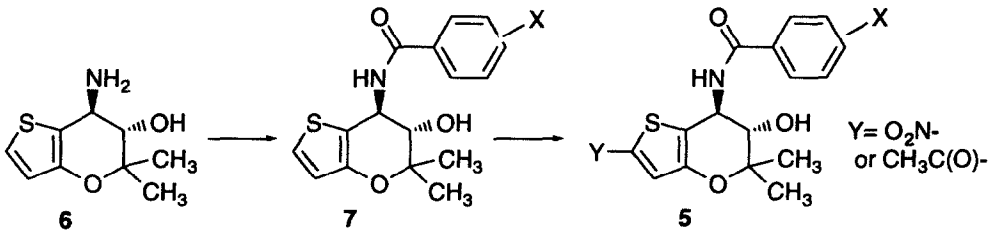


1 **(±)-RWJ 26629** **2** **(±)-Cromakalim** **3** **(-)-Celikalim** **(±)-4**

The 7-(substituted benzamido)-6-hydroxythieno[3,2-b]pyrans (**5**) were prepared by acylation of the amino-alcohol **6**[1] with the appropriate substituted benzoyl chloride (Scheme). As in the case for the cyclic amido analogues, **7** undergoes a variety of electrophilic substitution reactions to give the 2-substituted thiophene derivatives **5**. Nitration of **7** with 90% nitric acid in acetic acid produced the nitro compound **5** (Y = NO_2). Acylation of **7** with either acetyl chloride or acetic anhydride in the presence of a Lewis or protic acid catalyst

gives an acetyl acetate which can be saponified with methanolic potassium carbonate to yield the acetyl derivative **5** (Y=CH_3CO). The various 7-(substituted benzamido)-6-hydroxythieno[3,2-b]pyrans prepared for this report are listed in the Table.

SCHEME



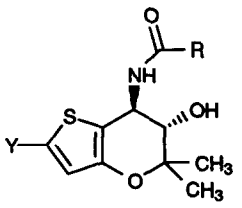
The compounds were evaluated for oral antihypertensive activity in the SHR.[1,4] As expected from our earlier studies, the unsubstituted benzoyl derivative **8** was marginally active at the screening dose of 20 mg/kg, lowering blood pressure by 35%. Surprisingly, introduction of a nitro substituent, a strong electron-withdrawing group (σ = +0.778), at the 2-position of thiophene **9** did not enhance activity. Such substitution gives superlative results in the 7-cyclic amido series.[1] However, acetyl substitution, a less powerful electron-withdrawing group (σ = +0.502), at the 2-position of thiophene **10** greatly enhances activity compared to the unsubstituted thienopyran **8**. Acetyl derivative **10** is equipotent to cromakalim (**2**).

The effects of substitution on the benzamide ring in the SHR were then studied. Electron-donating groups such as methyl (**11**) and methoxy (**12**) attentuate activity. Nitro substitution either in the *meta*- (**13**) or *para*- (**14**) position of the benzamide maintains or enhances activity. As predicted from the above discussion, the corresponding 2-nitrothieno[3,2-b]pyran **15** had only marginal activity. Although the *meta* compound **13** is equiactive to the *para* derivative **14** at the screening dose of 20 mg/kg, antihypertensive activity diminishes significantly at lower doses.

Pyridyl (**16**) or furanyl (**17**) isosteres of the benzamide diminish activity as compared to the unsubstituted phenyl (**10**). This is in contrast to what is observed in the benzopyran series with 4-substituted aroylamines, where these isosteric replacements are equiactive to the phenyl derivative.[5] A trifluoromethyl group (**18**) had marginal activity. However, halo substituents such as chloro (**19**, **20**), fluoro (**21**, **24**) or difluoro (**22**, **23**) were extremely active at the screening dose. Unlike the substituted benzamides in the benzopyran series, the 4-halo benzamides (**19**, **21**) were more potent than cromakalim (**2**).[5]

Compound **21** was found to increase the basal efflux rate of $^{86}Rb^+$, a radioactive K^+ surrogate,[6,7] in rabbit mesenteric artery by 34% at 10 μM. These data suggests that the mode of action of these novel thienopyrans is, at least in part, via potassium channel activation. In summary, compound **21** is three-fold more potent in SHR than cromakalim with an ED_{30} = 0.059 mg/kg and is the best compound in this study.

Table. Novel (±)-7-Substituted benzamido-5,6-dihydro-5,5-dimethyl-7*H*-thieno[3,2-b]pyrans.



no.	R	Y	mp,°C	formula	anal.[a]	% change MAP[b]	ED_{30}, mg/kg, po[c]
8	Ph	H	219-220	$C_{16}H_{17}NO_3S$	C,H,N	-35	
9	Ph	NO_2	205-207	$C_{16}H_{16}N_2O_5S$	C,H,N	-38	
10	Ph	Ac	210-216	$C_{18}H_{19}NO_4S$	C,H,N	-55	0.20 (0.10-0.32)
11	4-MePh	Ac	158-160	$C_{19}H_{21}NO_4S$	C,H,N	-10	
12	4-MeOPh	Ac	156-157	$C_{19}H_{21}NO_5S$	C,H,N	-20	
13	3-NO_2Ph	Ac	205-206	$C_{19}H_{18}N_2O_6S$	C,H,N,S	-63, -17[d]	
14	4-NO_2Ph	Ac	223-225	$C_{18}H_{18}N_2O_6S$	C,H,N,S	-63	0.89 (0.812-0.996)
15	4-NO_2Ph	NO_2	221-225	$C_{16}H_{15}N_3O_7S$	C,H,N	-29	
16		Ac	212-213	$C_{17}H_{17}N_2O_4S$	C,H,N	-29	
17		Ac	195-197	$C_{16}H_{17}NO_5S$	C,H,N	-38	
18	4-CF_3Ph	Ac	227-229	$C_{19}H_{18}F_3NO_4S$	C,H,N	-26	
19	4-ClPh	Ac	212-214	$C_{18}H_{18}ClNO_4S$	C,H,N	-60	0.11 (0.085-0.16)
20	3-ClPh	Ac	132-133	$C_{18}H_{18}ClNO_4S$	C,H,N	-59, -17[e]	
21	4-FPh	Ac	192-194	$C_{18}H_{18}FNO_4S$	C,H,N	-75	0.059 (0.037-0.082)
22	3,4-F_2Ph	Ac	225-227	$C_{18}H_{17}F_2NO_4S$	C,H,N	-62	0.099 (0.073-0.14)
23	2,4-F_2Ph	Ac	168-170	$C_{18}H_{17}F_2NO_4S$	C,H,N	-59, -16[f]	
24	2-FPh	Ac	210-212	$C_{18}H_{18}FNO_4S$	C,H,N	-59, -17[d]	
1 (RWJ 26629)						-63[f]	0.015 (0.003-0.021)[g]
2 (cromakalim)						-47[h]	0.19 (0.14-0.23)[g]
3 (celikalim)							0.50[i]
4							0.22 (0.18-0.26)[g]

[a]Analyses for the elements indicated were within ± 0.4% of the theoretical values. [b]Maximal change in mean arterial blood pressure (MAP) comparing MAP immediately prior to and up to 240 min after oral administration of 20 mg/kg of the test substance, except where noted; (N ≥ 3 rats). [c]Dose to produce 30% reduction in MAP. 95% Confidence limits in parentheses. [d]Test substance dose of 1 mg/kg. [e]Test substance dose of 0.3 mg/kg [f]Test substance dose of 0.1 mg/kg. [g]See reference 1. [h]See reference 2. [i]See reference 3.

EXPERIMENTAL

All compounds were homogenous by TLC analysis and had spectral properties consistent with their assigned structures. All new compounds had acceptable (±0.4%) combustion analysis for elements indicated in the Table.

Preparation of (±)-**21**

A solution of 4-fluorobenzoyl chloride (0.91 mL, 7.72 mmol) in CH_2Cl_2 (5 mL) was added slowly to a solution of 7-amino-5,6-dihydro-6-hydroxy-5,5-dimethyl-7*H*-thieno[3,2-b]pyran[1] (1.4 g, 7.03 mmol) and Et_3N(2.9 mL, 21.1 mmol) in CH_2Cl_2 (30 mL) at 0°C. The mixture was stirred an additional hour at 0°C, washed with 1N HCl, aqueous $NaHCO_3$ and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was recrystallized from CH_2Cl_2/hexanes to give 1.91 g (85%) of **7** (X=*p*-F); mp 162-4°C. IR (KBr): 3365, 1648, 1604, 1535 and 1500 cm^{-1}; MS: 322 (MH^+); ^1H NMR ($CDCl_3$): δ 1.35 (s, 3H), 1.50 (s, 3H), 3.76 (dd, J=2.0 Hz, 7.9 Hz, 1H), 4.72 (d, J=2.0 Hz, 1H), 5.14 (m, 1H), 6.45 (br d, 1H), 6.62 (d, J= 5.4 Hz, 1H), 7.15 (m, 3H), 7.82 (m, 2H). This product (2.5 g, 7.78 mmol) was suspended at 0°C in acetic anhydride (30 mL) containing perchloric acid (70%, 10 drops) and the mixture was stirred at rt for 7 h. The solution was poured into water, stirred (1 h) and extracted with CH_2Cl_2. The organic layer was washed with water (2x), aqueous $NaHCO_3$, and dried over $MgSO_4$. The solvent was evaporated in vacuo, and the residue was purified by flash chromatography (SiO_2, 1% MeOH in CH_2Cl_2) and crystallized from Et_2O to give 6-acetoxy-2-acetyl-7-(4-fluorobenzamido)-5,6-dihydro-5,5-dimethyl-7*H*-thieno[3,2-b]pyran, 2.26 g (71%) as a tan solid; mp 203-205°C. This material (1.41 g, 3.48 mmol) was dissolved in methanol (30 mL), treated with K_2CO_3 (0.529 g, 3.83 mmol) and stirred at rt for 16 h. After quenching with water (100 mL), the product was extracted into 5% isopropanol in CH_2Cl_2, washed with water and dried over $MgSO_4$. The solvent was evaporated in vacuo, and the residue was purified by flash chromatography (2% MeOH in CH_2Cl_2) to give (±)-**21**, 0.991 g (78%) as a colorless solid; mp 192-194°C. IR(KBr): 3356, 1651, 1641, 1533, 1501 cm^{-1}; MS: 364 (MH^+); ^1H NMR($CDCl_3$): δ 1.35 (s, 3H), 1.50 (s, 3H), 2.50 (s, 3H), 3.75 (m, 1H), 4.65 (br d, J=1.5 Hz, 1H, exchanges with D_2O), 5.17 (m, 1H, collapses to d, J=8.7 Hz, with D_2O), 6.54 (br d, J=6.5 Hz, 1H, exchanges with D_2O), 7.13-7.24 (m, 3H), 7.82-7.90 (m, 2H). Anal. calc'd for $C_{18}H_{18}FNO_4S$: C, 59.49; H, 4.99; N, 3.85. Found: C, 59.51; H, 5.08; N, 3.65.

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