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Bioorganic & Medicinal Chemistry Letters 18 (2008) 2714–2718
Bioorganic & Medicinal Chemistry Letters

Pyrano-[2,3*b*]-pyridines as potassium channel antagonists

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Received 8 November 2007; revised 4 March 2008; accepted 6 March 2008
Available online 14 March 2008

Abstract—The design and synthesis of a series of highly functionalized pyrano-[2,3*b*]-pyridines is described. These compounds were assayed for their ability to block the I_{Kur} channel encoded by the gene hKV1.5 in patch-clamped L-929 cells. Six of the compounds in this series showed sub-micromolar activity, the most potent being 4-(4-ethyl-benzenesulfonylamino)-3-hydroxy-2,2-dimethyl-3,4-dihydro-2H-pyrano[2,3*b*]-pyridine-6-carboxylic acid ethyl-phenyl-amide with an IC_{50} of 378 nM.

Ventricular and atrial cardiac arrhythmias[1,2] affect a significant proportion of the general population. The most common form of sustained cardiac arrhythmia is atrial fibrillation (AF) which affects approximately 2.2 million adults in the US.[3] The incidence of AF increases significantly with age; <1% of 50–59 years old were diagnosed with AF compared with 7–13% of the octogenarian population.[4] Concomitant with an aging population, the prevalence of AF is increasing.[5] Atrial fibrillation is characterized by the rapid and irregular contraction of the atria, which can lead to a higher incidence of stroke[6,7] via blood stasis and higher mortality in patients with congestive heart failure.[8] Conversion to normal sinus rhythm may be achieved through invasive AV node ablation and pacemaker insertion,[9] catheter based ablation[10] or administration of antiarrhythmic drugs.[11,12]

Potassium channels are transmembrane protein channels which selectively allow potassium ions across the plasma membrane.[13] The movement of ions across cell membranes mediates many biological processes including regulation of action potential duration in cardiac cells.[14] Potassium currents are essential for cardiac cell repolarization and blocking of these outward currents results in an increase in action potential duration.[15] Three of the most important outward potassium currents are I_{Ks}[16] (slowly activating) I_{Kr}[17] (rapidly activating) and I_{Kur}[17] (ultra rapidly activating). I_{Ks} and I_{Kr} are present in the human atrium and ventricle, but I_{Kur} is atrial-specific.[18]

Currently approved class III agents, for example, D,L-sotalol, amiodarone, dofetilide and ibutilide inhibit I_{Kr} and have the potential liability of being proarrhythmic in the ventricle.[19,20] Ventricular arrhythmias, such as torsades de pointe, are potentially fatal and limit initial administration of several of these drugs to an in-patient environment.[21] Drugs which selectively target inhibition of I_{Kur} may be safer since they prolong action potential duration in the atrium, without delaying ventricular repolarization and, therefore, should be without the subsequent risk of ventricular arrhythmia.[22,23]

Early efforts in our program had identified a series of potent and selective indane and tetraline[24] based I_{Kur} inhibitors. These series had low oral bioavailability and lacked metabolic stability (e.g., **1**, **2**, Fig. 1). Our goal was to investigate alternate related chemotypes and determine the viability of those series showing potency for I_{Kur}. A series of benzopyrans[25] (e.g., **3**, Fig. 1) were investigated which led to synthesis and evaluation of a series of pyrano-[2,3*b*]-pyridine[26] based inhibitors which are described in this letter.

The substitution at position 4 on the benzopyran moiety had been optimized as the 4-ethyl-phenyl-sulfonamide.[25]

Keywords: Atrial fibrillation; Potassium channel; KV1.5; Pyrano-[2,3-*b*]-pyridine.
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doi:10.1016/j.bmcl.2008.03.026

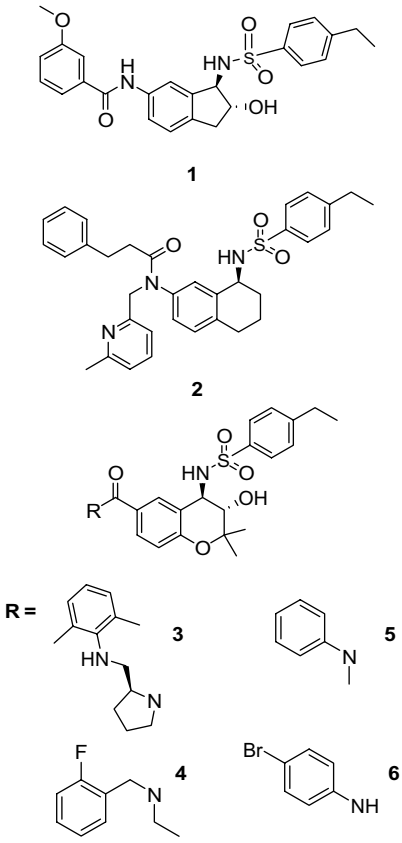
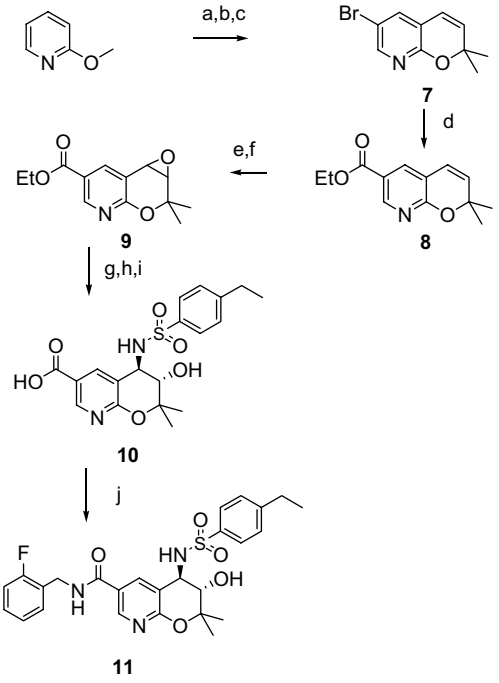


Figure 1. Examples of early chemotypes.



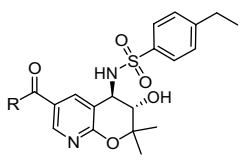
Scheme 1. Reagents and conditions: (a) Br_2, acetic acid, 80 °C, 50% yield; (b) *n*-BuLi, −78 °C, 2-butenal, 52% yield; (c) HBr (48% aqueous), acetic acid, 100 °C, 53% yield; (d) *t*-BuLi, −78 °C, ethylchloroformate, 54% yield; (e) NBS, DMSO aqueous, 100% yield; (f) KOH, THF, 100% yield; (g) NH_4OH, EtOH, 80 °C, 75% yield; (h) 4-ethyl-phenylsulfonyl chloride, TEA, DCM, 73% yield; (i) LiOH, aqueous acetone, 65 °C, 59% yield; (j) EDCI, HOAt, 2-fluoro benzylamine, 43% yield.

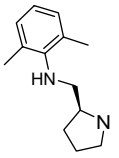
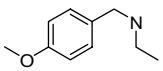
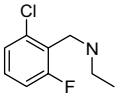
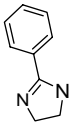
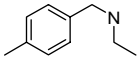
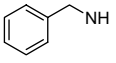
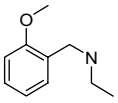
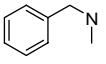
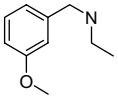
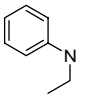
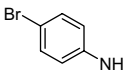
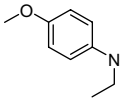
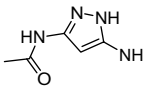
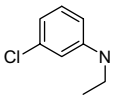
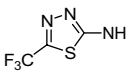
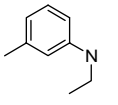
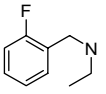
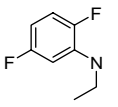
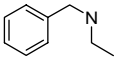
Thus, this moiety was initially incorporated into the pyrano-[2,3*b*]-pyridine series. The 2*H*-pyrano-[2,3*b*]-pyridine core was synthesized as described previously.[27] The resulting 6-bromo-2,2-dimethyl-2*H*-pyrano-[2,3*b*]-pyridine (**7**) was converted to the corresponding ethyl ester (**8**) by halogen metal exchange and quench with ethylchloroformate (Scheme 1).[28] Epoxidation was accomplished via the bromohydrin.[29,30] Closure of the bromohydrin to the epoxide was unsuccessful using the standard NaH/DMF conditions, due to difficulty in extracting the epoxide from the DMF solution. Alternatively, the epoxide (**9**) was formed in quantitative yield by treatment of the bromohydrin with KOH in THF and subsequently converted to the racemic *trans* amino alcohol using ammonium hydroxide in ethanol (Scheme 1).[29] We had demonstrated previously that the absolute stereochemistry at positions 3 and 4 was not critical for potency in the benzopyran analogs[25] and thus, racemic *trans* amino alcohol was used throughout this study. Standard sulfonylation conditions, followed by hydrolysis yielded the 6-carboxylic acid (**10**).[31] For the benzopyran series, we were able to utilize fluoro-*N,*tetramethylformamidinium hexafluorophosphate[32] for coupling example amines to the 6-carboxylic acid, (**10**) but this reagent was not successful for coupling in the pyrano-[2,3*b*]-pyridine series. Individual compounds were coupled using standard EDCI/HOAt conditions[33] (e.g., **11**,[34] Scheme 1) in yields from 30% to 93%. Product amides with additional basic amines (e.g., **19**) were purified by retention on an SCX cartridge followed by elution with ammonia/MeOH solution. Non-basic products were purified by reverse phase preparative HPLC.

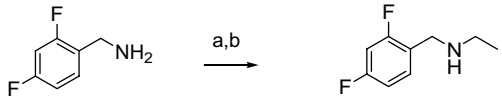
To flush out SAR at the 6-position, synthesis of a parallel solution phase amidation library furnished 42 diverse amides, examples of which are shown in Table 1. From this first library, it was clear that initial SAR for this series was divergent to that observed for the benzopyran series. Compound **21** was identified as a weak inhibitor from this library and a second 2-step solution phase library was prepared to determine SAR around the *N*-ethylated benzylamine and aniline amides. *N*-Ethylated benzylamines and anilines were synthesized in parallel by acylation of the corresponding amine with acetyl chloride and subsequent reduction with LAH at 70 °C (Scheme 2). The crude *N*-ethylamines were cautiously quenched with MeOH and purified using automated C18 chromatography. *N*-Ethyl benzylamines were coupled to acid (**10**) using standard EDCI/HOAt conditions[33] and *N*-ethyl anilines were coupled to acid (**10**) using PyBrOP, triethylamine in acetonitrile at 80 °C.[35]

Product amides were purified by reverse-phase preparative HPLC. Additional 34 *N*-ethyl amide analogs were synthesized in parallel via this route and examples are included in Table 1.

Table 1. Examples of amides from parallel solution phase coupling



	**12**		**23**
	**13**		**24**
	**14**		**25**
	**15**		**26**
	**16**		**27**
	**17**		**28**
	**18**		**29**
	**19**		**30**
	**20**		**31**
	**21**		**32**
	**22**		



Scheme 2. Reagents and conditions: (a) acetyl chloride, TEA, rt, 100% yield; (b) LAH, THF, 70 °C, 52% yield.

All compounds synthesized were characterized in L-929 cells that stably expressed human $K_V1.5$. Compounds were initially tested at 1 μM concentration using voltage clamp techniques.[36,37] The % inhibition was measured and is reported as an average value from testing in triplicate. For those compounds with >50% inhibition at 1 μM, the IC_{50} for block of $K_V1.5$ current was subsequently measured. Compounds with % inhibition at 1 μM and subsequent IC_{50} determinants are shown in Table 2.

In the benzopyran series, amides **3**–**6** were among the most potent compounds. However, in the pyrano-[2,3*b*]-pyridines series, the corresponding analogs **12**, **21**, **17**, and **18**, respectively, were significantly less potent. Overall, the most potent pyrano-[2,3*b*]-pyridine identified in this study was *N*-ethyl amide **28** with an IC_{50} value of 378 nM.

In continued efforts to improve the aqueous solubility of this series, basic amines, hydroxyl groups and heterocycles were incorporated into the amide functionality (e.g., **14**, **19**, and **20**), but polar groups and heterocycles were not tolerated at the amide position.

The most potent compound identified from the first library synthesis was benzylamide **21**. The des-fluoro benzylamide direct analog, **22** and the corresponding *N*-methyl benzylamide **16** were less potent. Direct *N*-ethyl benzylamide analogs of **21** showed some improvement in potency (e.g., **23** and **24**), with incorporation of aryl group substituents. However, the SAR at this position was narrow, for example, methoxy substitution was tolerated at the para position, but not at the ortho or meta positions (**23** vs **26** and **27**). Additionally, para methoxy substitution was tolerated, but not para methyl substitution (**23** vs **25**). In the aniline series, *N*-ethyl substitution was also required for potency (**28** vs **17** and **13**). Additional efforts to explore the substitution on the aryl moiety did not result in improved potency and SAR proved to be divergent from that observed with the benzylamides (e.g., **29** vs **23**). The most potent aryl substituted anilines had meta substituents (**30** and **31**) but these analogs were 2-fold less potent than unsubstituted *N*-ethyl aniline lead compound **28**.

Some compounds in this series demonstrated significantly improved equilibrium solubility in aqueous buffer over the corresponding benzopyran amide direct analogs (e.g., **4** had aqueous solubility in pH 6.5 buffer of 0.010 mg/mL compared to **21** with solubility 0.067 mg/mL).[38] The most potent pyrano-[2,3*b*]-pyridine, **28** had an aqueous solubility of 0.108 mg/mL. However, due to the generally reduced potency compared to the benzopyran series, the potential metabolic liabilities of the

Table 2. IC_{50} inhibition results for compounds

Compound	Inhibition of current in L-929 cells % inhibition at 1 μM	Inhibition of current in L-929 cells IC_{50}[a] (μM)	Compound	Inhibition of current in L-929 cells % inhibition at 1 μM	Inhibition of current in L-929 cells IC_{50}[a] (μM)
1	—	0.050	**19**	31	—
2	—	0.046	**20**	3	—
3	—	0.060	**21**	38	—
4	—	0.172	**22**	20	—
5	87	0.281	**23**	70	0.605
6	73	0.316	**24**	54	0.615
11	4	—	**25**	15	1.56
12	15	—	**26**	35	2.09
13	30	—	**27**	23	—
14	2	—	**28**	89	0.378
15	17	—	**29**	22	—
16	12	—	**30**	64	0.649
17	12	—	**31**	58	0.776
18	8	—	**32**	52	0.912

[a] Inhibition is measured in duplicate at 9 concentrations and the mean values were used to calculate IC_{50} values.

aniline functionality[39] and the lack of clear SAR, further efforts were focused on investigation of alternate chemotypes.

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35. Coste, J.; Frerot, E.; Jouin, P. *J. Org. Chem.* **1994**, *59*, 2437.
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40. Example data for **11**, Scheme 1: 1H NMR (400 MHz, $CDCl_3$) 8.66 (1H, s), 8.42 (1H, s), 7.76 (2H, d, $J = 8.2$ Hz),

7.62 (1H, br s), 7.29 (2H, d, J = 8.1 Hz), 7.23 (2H, m), 7.06 (1H, dd, J = 7.6 Hz), 7.03 (1H, dd, J = 7.6 Hz), 4.56 (2H, d, J = 5.2 Hz), 4.29 (1H, d, J = 9.1 Hz), 3.71 (1H, d, J = 9.7 Hz), 2.68 (2H, q, J = 7.6 Hz), 1.48 (3H, s), 1.25 (3H, s), 1.23 (3H, t, J = 7.6 Hz). 19F NMR (376 MHz, $CDCl_3$) −76.25 (s). LC–MS retention time: 3.58 min (100%) YMC ODS S5 4.6 × 50 mm, 4 min gradient 10% MeOH/90% H_2O −0.1% TFA to 90% MeOH/10% H_2O −0.1% TFA. 4 mL/min flow rate, λ = 220 nM. [M+1] 514.20.