Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters 17 (2007) 3271–3275
Bioorganic & Medicinal Chemistry Letters

Benzopyran sulfonamides as $K_V1.5$ potassium channel blockers

John Lloyd,* Karnail S. Atwal, Heather J. Finlay, Michael Nyman, Tram Huynh, Rao Bhandaru, Alexander Kover, Joan Schmidt, Wayne Vaccaro, Mary Lee Conder, Tonya Jenkins-West and Paul Levesque

Bristol-Myers Squibb Pharmaceutical Research Institute, PO Box 5400, Princeton, NJ 08543-5400, USA

Received 2 February 2007; revised 2 April 2007; accepted 4 April 2007
Available online 10 April 2007

Abstract—$K_V1.5$ blockers have the potential to be atrium-selective agents for treatment of atrial fibrillation. The benzopyrans provide a template for the synthesis of potent and selective $K_V1.5$ blockers.
© 2007 Elsevier Ltd. All rights reserved.

Atrial fibrillation (AF) is a cardiac arrhythmia that affects a large and growing population. Over 2 million cases were reported in the US in 1999 and that number has increased 2- to 3-fold over that last 15 years.[1] Incidence of AF increases with age so that the number of cases will likely increase in the future.[2] Although AF is not a fatal condition, the inefficient emptying of the atrium can lead to thrombus formation. The primary mortality risk in AF is from stroke.[3]

Cardiac rhythm is regulated by the cyclic changes in membrane potential of the cardiac myocytes. Changes in membrane potential are regulated by the opening and closing of ion channels. Together, ionic currents contribute to the shape of the membrane potential versus time relationship known as the action potential. After excitation and depolarization caused by the influx of sodium and then calcium ions, the myocytes return to their resting potential following the efflux of potassium ions. This final repolarization phase is necessary for another excitation and contraction to occur. The net potassium current is conducted through several different potassium channels, including the rapid (I_{Kr}) and slow (I_{Ks}) delayed rectifier potassium currents. Block of the I_{Kr} with class III antiarrhythmic drugs (e.g., dofetilide) results in delayed repolarization and has been shown to effectively treat both atrial and ventricular arrhythmias.[4] Unfortunately, prolongation of repolarization in the ventricle at normal heart rates has been shown to also cause arrhythmia. The polymorphic ventricular tachycardia torsades de pointes can be caused by block of repolarization in the ventricle and can lead to fatal ventricular fibrillation.[5]

The ultrarapid potassium current (I_{Kur}) is an important repolarizing current that in humans is expressed in the atrium but not ventricle.[6] Therefore, selective block of this current may lead to a method of treating atrial arrhythmia without the risk of ventricular effects. I_{Kur} is conducted by the voltage gated potassium channel encoded by $K_V1.5$.[7] Drugs that block this channel have the potential to increase atrial action potential duration and prevent and/or terminate atrial fibrillation with increased safety.

Researchers at Icagen discovered an indane compound (**1**) that blocked $K_V1.5$ (Fig. 1).[8] We proposed that the indane template could be replaced by the benzopyran template and we wished to test this hypothesis with the synthesis of $K_V1.5$ blockers based on a benzopyran.

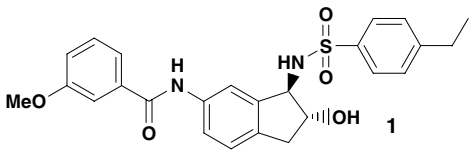
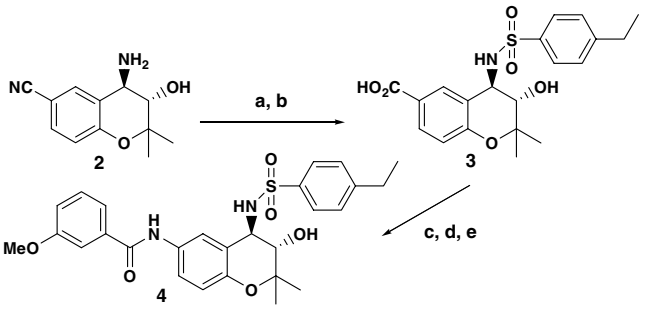


Figure 1. Indane $K_V1.5$ blocker.

Keywords: $K_V1.5$; I_{Kur}; Ultra rapid potassium current; Potassium ion channel; Ion channel blocker; Antiarrhythmic; Atrial arrhythmia; Atrial fibrillation.
* Corresponding author. Tel.: +1 609 818 5327; fax: +1 609 818 3331; e-mail: john.lloyd@bms.com

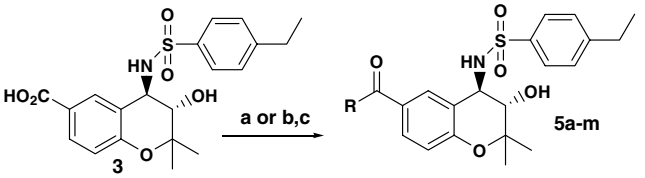
0960-894X/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2007.04.020

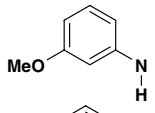
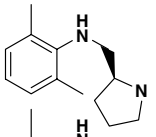
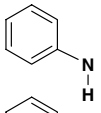
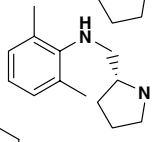
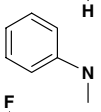
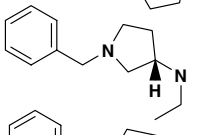
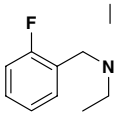
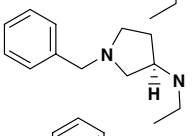
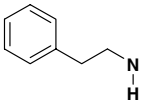
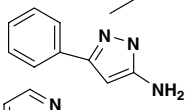
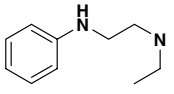
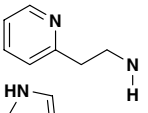
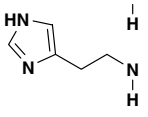


Scheme 1. Reagents and condition: (a) HCl, H_2O, 100 °C (99%); (b) 4-EtPhSO$_2$Cl, NaOH (1 M aq), THF (27%); (c) Ph_2PON_3, *t*-BuOH, dioxane, Et_3N (46%); (d) TFA, CH_2Cl_2 (65%); (e) 3-MeO–Ph–COCl, Et_3N, CH_2Cl_2 (75%).

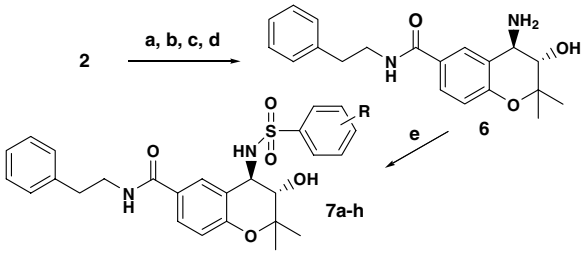
The benzopyran template was available from the known 3*S*,4*R*-aminoalcohol (**2**).[9] Hydrolysis of the nitrile followed by sulfonylation of the amine provided the acid **3** (Scheme 1). The 6-aminobenzopyran analog of the indane was synthesized from the acid using the Arndt–Eistert synthesis to form the amine which was coupled with 3-methoxybenzoyl chloride to provide the amide **4**.

The reversed amide analog (**5a**) of amide **4** and additional amide analogs **5b**–**m** were synthesized from acid **3** using standard coupling procedures (Scheme 2).



compd	R	compd	R
5a		5g	
5b		5h	
5c		5i	
5d		5j	
5e		5k	
5f		5l	
		5m	

Scheme 2. Reagents: (a) amine, EDC, HOAt, CH_2Cl_2 (40–90%); (b) TFFH, Et_3N, CH_2Cl_2 (90%); (c) amine, Et_3N, MeCN (30–85%).



compd	R	compd	R
7a	H	7e	2-OCF_3
7b	4-CF_3	7f	4-F
7c	4-CH_3	7g	4-OCH_3
7d	3-CH_3	7h	4-NO_2

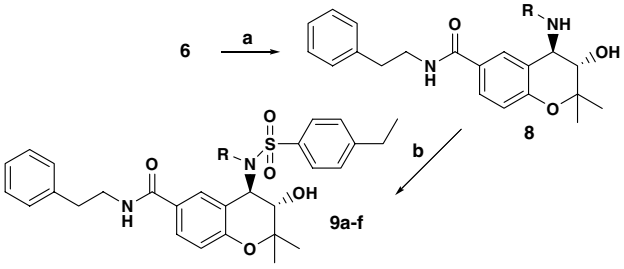
Scheme 3. Reagents and condition: (a) HCl, H_2O, 100 °C (99%); (b) BOC_2O, NaOH (1 M aq), THF (24%); (c) $PhCH_2CH_2NH_2$, EDC, HOBt, NMM, CH_2Cl_2, (99%); (d) TFA, CH_2Cl_2 (77%); (e) R-PhSO$_2$Cl, Et_3N, CH_2Cl_2 (60–84%).

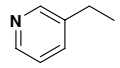
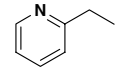
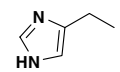
Analogs with variation in the sulfonamide fragment were synthesized from **2** by hydrolysis of the nitrile and BOC protection of the amine followed by amide formation with phenethylamine. Deprotection and subsequent sulfonylation provided the analogs **7a**–**h** (Scheme 3).

The tertiary sulfonamides **9a**–**f** were synthesized from the amine **6** by reductive amination followed by sulfonylation (Scheme 4).

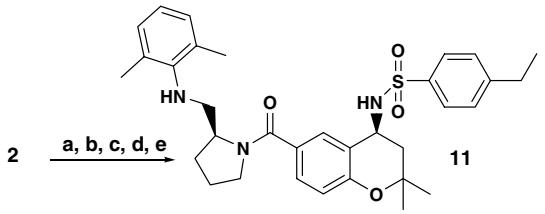
Compounds with the opposite stereochemistry of the amino alcohol were synthesized from the known 3*R*,4*S*-benzopyran[10] by methods described (Schemes 1 and 2). Thus we synthesized analogs of **5e** and **5g**–**j** with 3*R*,4*S*-configuration (**10a**–**e**).

The des-hydroxy compound **11** was synthesized from the amino alcohol **2** by sulfonylation followed by thio-



compd	R	compd	R
9a	*n*-Bu	9d	
9b		9e	
9c		9f	

Scheme 4. Reagents: (a) R-CHO, $NaBH(OAc)_3$, HOAc (22–58%); (b) 4-EtPhSO$_2$Cl, Et_3N, CH_2Cl_2 (9–71%).

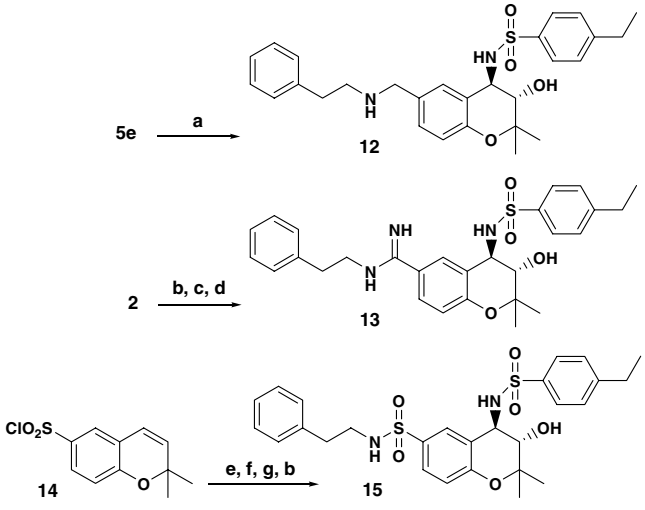


Scheme 5. Reagents: (a) 4-EtPhSO$_2$Cl, Et$_3$N, CH$_2$Cl$_2$ (85%); (b) Im$_2$CS, C$_2$H$_4$Cl$_2$ (85%); (c) *n*-Bu$_3$SnH, AIBN, MePh; (d) KOH, HOC$_2$H$_4$OH; (e) pyrrolidine, EDC, HOAt, DMF (31% 3 steps).

carbonylimidazolide formation then reduction.[10] Hydrolysis of the nitrile to the acid followed by amide formation provided **11** (Scheme 5).

The analog with replacement of the amide functionality at the 6-position with an isosteric amine **12** was synthesized by reduction of the amide **5e**. The amidine **13** was synthesized by sulfonylation of the nitrile **2** followed by formation of the imidate and reaction with phenethylamine. The sulfonamide **15** was made from the sulfonylchloride **14**[11] by formation of the sulfonamide followed by epoxide formation, ring opening with ammonia, and sulfonylation (Scheme 6).

All the compounds were tested for block of potassium current in mouse fibroblast L929 cells expressing human $K_V1.5$.[12] The initial compounds were direct analogs of **1** where we retained the 4-ethylphenylsulfonamide but modified the substituent at the 6-position of the benzopyran (Table 1). The direct benzopyran analog **4** showed a 10-fold decrease in potency from the indane, however, it still retained significant potency. Although the reversed amide analog **5a** lost additional potency, we felt we could re-optimize this chemotype using automated synthesis. This proved to be the case and we quickly identified alternate substituents that significantly improved potency over **5a**. In many cases, these



Scheme 6. Reagents and condition: (a) LiAlH$_4$, THF, 67 °C (13%); (b) 4-EtPhSO$_2$Cl, Et$_2$N, CH$_2$Cl$_2$ (80%); (c) HCl, EtOH; (d) PhCH$_2$CH$_2$NH$_2$ (47% 2 steps); (e) PhCH$_2$CH$_2$NH$_2$, Et$_3$N, CH$_2$Cl$_2$ (87%); (f) mCPBA, CH$_2$Cl$_2$; (g) NH$_4$OH, THF, EtOH (71% 2 steps).

Table 1. Indane and benzopyran anaolgs

Compound	$K_V1.5$ inhibition IC_{50}[a](μM)
1	0.033
4	0.29
5a	>10
5b	>1.0
5c	0.28
5d	0.17
5e	0.26
5f	0.077
5g	0.12
5h	0.13
5i	0.17
5j	0.21
5k	0.079
5l	>1.0
5m	>10

[a] Values are means of 2–4 experiments.

contained combinations of aryl and alkyl substituents (**5b–e**).

We were interested in the tolerance for basic functionality. Amides with both anilines (**5f–h**) and alkyl amines (**5i–j**) showed potency in the range of 0.08–0.2 μM (Table 1). The amide of 5-phenyl-3-aminopyrazole (**5k**) was among the most potent compounds we discovered. However, not all basic functionality was tolerated. Pyridine and imidazole replacements of the phenyl ring in **5e** resulted in compounds (**5l** and **5m**) that showed little $K_V1.5$ block.

Our investigation then turned to the sulfonamide substituent. We first modified substituents on the benzenesulfonamide while the 6-position substituent was held as the 2-phenylethylamide. The unsubstituted benzenesulfonamide (**7a**) was much less potent than the 4-ethyl compound (**5e**). The compounds containing either 4-trifluoromethyl (**7b**), 4-methyl (**7c**), 3-methyl (**7d**) or 2-trifluoromethoxy (**7e**) groups had about the same potency as the 4-ethylbenzenesulfonamide (**5e**). However, the 4-fluoro (**7f**), 4-methoxy (**7g**), and 4-nitro (**7h**) substituents were significantly less potent (Table 2).

Additional substitution on the sulfonamide nitrogen appeared to be well tolerated and enhanced potency in some cases (Table 3). The simple butyl substituent provided one of our most potent compounds (**9a**). Compounds **9b** and **9c** with branched alkyl groups were

Table 2. Sulfonamide substituents

Compound	$K_V1.5$ inhibition IC_{50}[a](μM)
5b	0.26
7a	>1.0
7b	0.20
7c	0.40
7d	0.34
7e	0.15
7f	>1.0
7g	>1.0
7h	>1.0

[a] Values are means of 2–4 experiments.

Table 3. Amide benzopyran analogs

Compound	$K_V1.5$ inhibition IC_{50}[a](μM)
9a	0.057
9b	0.32
9c	0.12
9d	0.13
9e	0.12
9f	0.28

[a] Values are means of 2–4 experiments.

Table 4. Amino alcohol modifications

Compound	$K_V1.5$ inhibition IC_{50}[a](μM)
5e	0.26
5g	0.12
5h	0.13
5i	0.17
5j	0.21
5g	0.19
10a	>1
10b	0.26
10c	0.089
10d	0.20
10e	0.22
11	0.11

[a] Values are means of 2–4 experiments.

less potent than **9a**. Some basic substituents were tolerated. The pyridylmethyl compounds **9d** and **9e** were about 2-fold less potent than the *n*-butyl compound **9a**, however, the imidazomethyl compound **9f** suffered significant loss of potency.

We were also interested in investigating some modifications of the amino alcohol template. We reversed the stereochemistry of the amino alcohol in **5e** and **5g–i** to give the 3*R*,4*S* analogs **10a–e**. This modification was not well tolerated in the neutral phenethyl compound **10a** but was tolerated in the analogs containing a basic amine (**10b–e**). Among these basic analogs, stereochemistry of either the amide or the benzopyran makes little difference in blocking potency. This suggests that the compounds that contain an amine may bind differently from the neutral compounds. The des-hydroxy compound (**11**) was as potent as the hydroxy compound (**5g**) indicating that the alcohol is not important for interaction with the channel protein (Table 4).

We have also attempted to replace the amide at the 6-position. Reduction of the amide at the 6-position to the amine (**12**) was a successful replacement with little loss of potency, however, the amidine replacement of the amide (**13**) was inactive. Replacement of the amide with a sulfonamide gave a compound (**15**) with about 2-fold less potency (Table 5).

Several of the most potent compounds (**4**, **5d**, **5f**, **5g**, **5k**, **9a**, **9d**, **10d**, and **11**) were tested for block of the human ether-a-go-go-related gene (*h*ERG) expressed in human embryonic kidney cells.[13] Most of these compounds have less than 50% block at 10 μM (Table 6).

Table 5. Amide replacements

Compound	$K_V1.5$ inhibition IC_{50}[a](μM)
5e	0.26
13	>10
12	0.24
15	0.51

[a] Values are means of 2–4 experiments.

Table 6. Block of *h*ERG

Compound	% Inhibition at 10 μM[a]
1	21%
4	40%
5d	7%
5f	39%
5g	9%
5k	47%
9a	35%
9d	61%
10d	80%
11	51%

[a] Values are means of 2–4 experiments.

In conclusion, we have established that the benzopyran core is an acceptable scaffold for potent I_{Kur} blockers. We have explored modifications of this scaffold including the amide at the 6-position, the substituent on the phenyl ring of the benzenesulfonamide, and modifications of the amino alcohol template. We have discovered several compounds with good potency for block of I_{Kur} and good selectivity over block of *h*ERG. In subsequent publications we will discuss further modification of the benzopyran core structure.

Acknowledgment

This paper is dedicated to the memory of Karnail S. Atwal.

References and notes

1. Wattigney, W. A.; Mensah, G. A.; Croft, J. B. *Circulation* **2003**, *108*, 711.
2. Feinberg, W. M.; Blackshear, J. L.; Laupacais, A.; Kronmal, R.; Hart, R. G. *Arch. Intern. Med.* **1995**, *155*, 469.
3. Wolf, P. A.; Mitchell, J. B.; Baker, C. S.; Kannel, W. B.; D'Agostino, R. B. *Arch. Intern. Med.* **1998**, *158*, 229.
4. Falk, R.; DeCara, J. M. *Am. Heart J.* **2000**, *140*, 697.
5. Yang, T.; Snyders, D.; Roden, D. *J. Cardiovasc. Pharmacol.* **2001**, *38*, 737.
6. Amos, G. J.; Wettwer, E.; Li, Q.; Himmel, H. M.; Ravens, U. *J. Physiol.* **1996**, *491*, 30; Li, G. R.; Feng, J.; Yue, L.; Carrier, M.; Nattel, S. *Circ. Res.* **1996**, *78*, 689.
7. Wang, Z.; Fermini, B.; Nattel, S. *Circ. Res.* **1993**, *73*, 1061; Feng, J.; Wible, B.; Li, G. R.; Wang, Z.; Nattel, S. *Circ. Res.* **1997**, *80*, 572.
8. Gross, M. F. et al. *Bioorg. Med. Chem. Lett.* **2007**. doi:10.1016/j.bmcl.2007.02.52.

9. Atwal, K. S.; Grover, G. J.; Ahmed, S. Z.; Ferrera, F. N.; Harper, T. W.; Kim, K. S.; Sleph, P. G.; Dzwonczyk, S.; Russel, A. D.; Moreland, S.; McCullough, J. R.; Mormandin, D. E. *J. Med. Chem.* **1993**, *36*, 3971.
10. Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.
11. Ding, C. Z.; Rovnyak, G. C.; Misra, R. N.; Grover, G. J.; Miller, A. V.; Ahmed, S. Z.; Kelly, Y.; Normandin, D. E.; Sleph, P. G.; Atwal, K. S. *J. Med. Chem.* **1999**, *42*, 3711.
12. Snyders, D. J.; Tamkun, M. M.; Bennet, P. B. *J. Gen. Physiol.* **1993**, *101*, 513.
13. Mohammad, S.; Zhou, Z.; Gong, Q.; January, C. T. *Am. J. Physiol.* **1997**, *273*, H2534.