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Triazolo and imidazo dihydropyrazolopyrimidine potassium channel antagonists

Heather J. Finlay [a,*], Ji Jiang [a], Yolanda Caringal [a], Alexander Kover [a], Mary Lee Conder [b], Dezhi Xing [b], Paul Levesque [b], Timothy Harper [c], Mei Mann Hsueh [c], Karnail Atwal [a], Michael Blanar [b], Ruth Wexler [a], John Lloyd [a]

[a] Department of Discovery Chemistry, Bristol-Myers Squibb, Research and Development, PO Box 5400, Princeton, NJ 08543-5400, United States
[b] Department of Discovery Biology, Bristol-Myers Squibb, Research and Development, PO Box 5400, Princeton, NJ 08543-5400, United States
[c] Department of Discovery Preclinical Candidate Optimization, Bristol-Myers Squibb, Research and Development, PO Box 5400, Princeton, NJ 08543-5400, United States

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ABSTRACT

Previously disclosed C6 amido and benzimidazole dihydropyrazolopyrimidines were potent and selective blockers of I_{Kur} current. Syntheses and SAR for C6 triazolo and imidazo dihydropyrazolopyrimidines series are described. Trifluoromethylcyclohexyl N(1) triazole, compound **51**, was identified as a potent and selective $K_v1.5$ inhibitor with an acceptable PK and liability profile.

Atrial fibrillation (AF) is the most common form of sustained cardiac arrhythmia.[1] AF is characterized by rapid and irregular sinus rhythm, which can lead to blood stasis and a significantly higher incidence of thromboembolism.[2] Reversion to normal sinus rhythm may be achieved through ablation,[3] pacemaker insertion[4] or the use of antiarrhythmic drugs.[5] Antiarrythmic drugs which target ion channels expressed in cardiac myocytes prolong the effective refractory period (ERP) and convert an atrial arrhythmia back to normal sinus rhythm.[6] Current clinically approved Class III agents target ion channels which are expressed in atrium and the ventricle, for example, D,L-sotalol, amiodarone, dofetilide and ibutilide and have the potential liability of fatal ventricular arrhythmias such as torsades de pointe.[7]

I_{Kur} is a delayed rectifier repolarization current which is functionally expressed in the human atrium and not in the ventricle.[8] Inhibition of I_{Kur} leads to prolongation of ERP and restoration of normal sinus rhythm.[9] The current body of data suggests that drugs which selectively target inhibition of I_{Kur} may be safer since they should prolong atrial ERP without being proarrhythmic in the ventricle.[10]

Selective inhibition of I_{Kur} with small molecule antagonists has been a long standing target with extensive effort to identify and advance potential drug candidates and demonstrate clinical proof of concept.[11–23] In a recent disclosure, the preclinical and clinical profile of MK-0448 was described.[24] In a small cohort of normal healthy volunteers, MK-0448 did not demonstrate atrial ERP increase at projected efficacious plasma exposures and further validation of the target is required.

In previous publications, we have described multiple chemical series[25–27] including the discovery and optimization of potent and selective dihydropyrazolopyrimidine based inhibitors of the I_{Kur} potassium current encoded by the $hK_v1.5$ gene in humans.[28] Early optimization of this series focused on C7 aryl substitution as well as C2, C3 and C5 substituents.[29] Additionally, the stereochemistry preference at position C7 was established.[28] C6 substituents were also explored and the C6 amide and

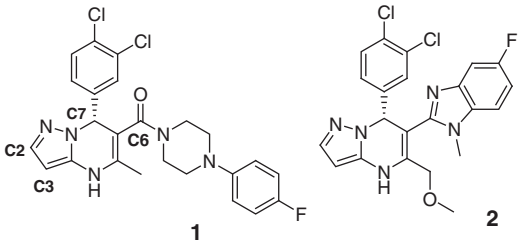

Figure 1. Previously disclosed C6 amido and benzimidazolo dihydropyrazolopyrimidines.

* Corresponding author.
E-mail address: heather.finlay@bms.com (H.J. Finlay).

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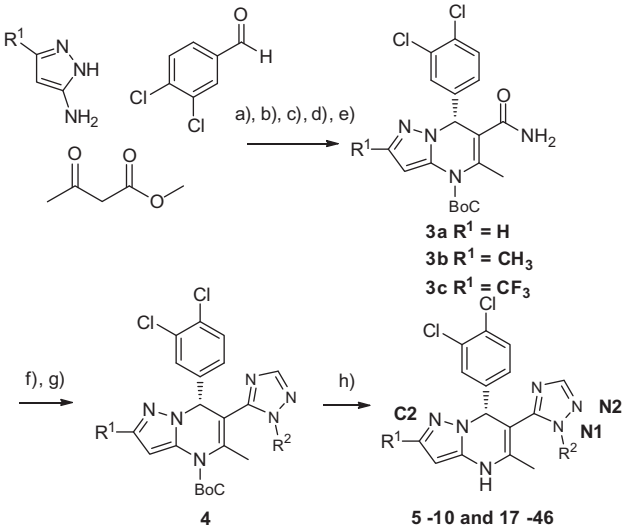


Scheme 1. Reagents and conditions for R^1 = H, R^1 = CH_3, R^1 = CF_3: (a) DMF, $NaHCO_3$, 75 °C, 24 h (R^1 = H, 55%) or heptane, THF catalytic piperidine, 75 °C, 24 h (R^1 = H, 50%, R^1 = CH_3, 76%, R_1 = CF_3, 52%); (b) di *t*-butyl carbonate, THF, DMAP, RT (R^1 = H, 89%, R^1 = CH_3, 100%, R^1 = CF_3, 100%); (c) chiral separation; (d) LiOH, THF; (e) EDCI, HOBt NH_4Cl, TEA, DCM (R^1 = H, 66%, R^1 = CH_3, 86%, R^1 = CF_3, 94%, 2 steps); (f) DMF, DMA, RT; (g) AcOH, R^2NHNH_2, 60 °C, 2 h; (h) 50% TFA, DCM (range in yield 13–70%, 3 steps).

benzimidazole series were optimized.[30] In an effort to improve the PK profile of our initial lead compounds, (Fig. 1, compounds **1** and **2**) additional amide isosteres at the C6 position were explored, leading to the identification of a potent series of substituted C6 triazoles and imidazoles described in this Letter.

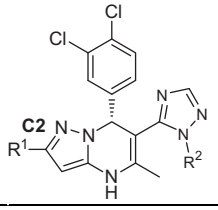
Initially we explored a series of N(1) aryl substituted triazoles which yielded our first potent K_v1.5 inhibitors in the triazole series. Using a general sequence which included a 3 component, 1 pot Biginelli reaction (Scheme 1), the core pyrazolo dihydropyrimidine C6 ester was synthesized as a racemate. The BoC protected racemate was separated under chiral HPLC conditions and the enantiomers taken on to the corresponding C6 amide (**3**).[31] The BoC protected N(1) aryl substituted triazoles were obtained from **3** by reaction with commercially available aryl hydrazines[32] as the single regioisomer at position N(1) (shown in Scheme 1). We have previously disclosed that in the C6 amide series, a substituent was required at either C2 or C3 to prevent the formation of reactive metabolites in vivo.[29] Intial examples were prepared without C2 or C3 substituents, but second generation compounds in all C6 triazoles included either a C2 methyl or trifluoromethyl group to address this potential issue. Compounds **5**–**10** and **17**–**46** (Table 1) were prepared in the N(1) aryl series.

N(2) aryl substituted triazoles were subsequently targeted and we utilized the Chan–Lam cross coupling conditions[33,34] (Scheme 2). Example compounds in this series **11**–**16** are included in Table 2.

Additional N(1) alkyl substituted triazoles and N(1) heterocycle triazoles were subsequently prepared as shown in Scheme 1 from the corresponding custom hydrazines. Due to the limited commercial availability of alkyl and heterocycle hydrazines, alkyl hydrazines were prepared conveniently from the corresponding aldehydes and ketones via reduction of the intermediate hydrazones[35] and pyridyl hydrazines from direct halide displacement with hydrazine.[36]

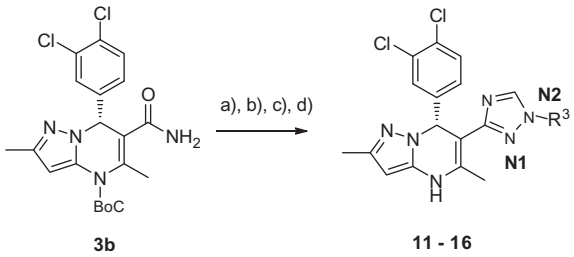
N(1) alkyl and cycloalkyl triazoles **17**–**37** are shown in Table 3. Using methyl hydrazine, a mixture of N(1) and N(2) methyl triazoles was obtained. The mixture was separated and the regiochemistry determined by NMR. Both N(1) and N(2) methyltriazoles demonstrated <10% K_v1.5 inhibition at 0.3 μM and we focused on

Table 1
C6 N(1) aryl triazolodihydropyrazolopyrimidines



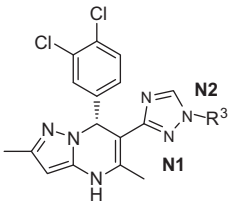
Compound	R^1	R^2	K_v1.5, L-929 cells (IC_{50}, μM)
5	H	4-Fluoro-phenyl	0.115
6	H	3-Fluoro-phenyl	0.097
7	H	2-Fluoro-phenyl	0.074
8	H	2-Methoxy-phenyl	0.116
9	H	4-Methyl-phenyl	0.080
10	CH_3	4-Methyl-phenyl	25%[b]

[a] Inhibition is measured in triplicate at 3 concentrations and the mean values used to calculate IC_{50} values.
[b] % Inhibition of current in L-929 cells at 0.3 μM, 2–4 point determinations.



Scheme 2. Reagents and conditions: (a) DMF/DMA, RT 2 h; (b) hydrazine, AcOH 60 °C, 2 h; 30%, 2 steps; (c) arylboronic acid, anhydrous pyridine, DCM, $Cu(OAc)_2$ RT, 24 h; (d) 50% TFA/DCM (range in yield 35–47%, 2 steps).

Table 2
C6 N(2) aryl triazolo dihydropyrimidines



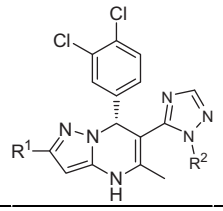
Compound	R^3	K_v 1.5, L-929 cells (IC_{50}, μM)
11	2-Fluoro-phenyl	23%[a]
12	4-Methyl-phenyl	14%[a]
13	2-Methyl-phenyl	0.722
14	2-Methoxy-phenyl	4%[a]
15	3-Methoxy-phenyl	14%[a]
16	4-Methoxy-phenyl	5%[a]

[a] % Inhibition of current in L-929 cells at 0.3 μM, 2–4 point determinations.

larger alkyl and cycloalkyl groups at N(1) to increase potency. All subsequent alkyl hydrazines explored yielded exclusively N(1) substituted triazoles under these conditions, the structures of which were also confirmed by NMR. Pyridyl triazoles **38**–**46** (Table 4) were also obtained as the single N(1) regioisomer.

To further extend the SAR in the N(1) alkyl and cycloalkyl C6 triazole series, C6 imidazo dihydropyrazolopyrimides were synthesized via the corresponding 1-(1-alkyl-1*H*-imidazol-2-yl)propan-2-one intermediate (e.g., **47**) as shown in Scheme 3 for the synthesis of compound **48**.[36] An alternate route to install the imidazole from common intermediate **3c** proved unsuccessful since we could

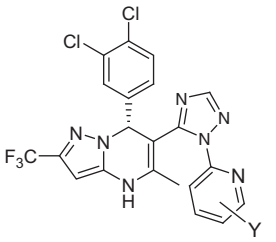
Table 3
C6 N(1) unsubstituted and alkyl triazolo dihydropyrimidines



Compound	R^1	R^2	K_v1.5, L-929 cells (IC_{50}, μM)	Inhibition of *h*ERG current
17	H	Benzyl	0.135	ND
18	H	H	8%[a]	ND
19	H	Ethyl	0.191	ND
20	H	*n*-Propyl	0.102	ND
21	H	*i*-Propyl	0.089	26% at 10 μM
22	H	Cyclohexyl	0.059	87% at 10 μM
23	H	*t*-Butyl	0.223	ND
24	H	Cyclopentyl	0.037	6.0 μM
25	H	Cyclobutyl	0.048	ND
26	H	Cyclopropyl methyl	0.229	ND
27	H	4-Cyclohexyl methyl	0.068	3.2 μM
28	H	CH_2CF_3	0.200	ND
29	H	Tetrahydro pyran	15%[a]	ND
30	H	$(CH_2)_2CF_3$	0.151	ND
31	H	$(CH_2)_3CF_3$	0.103	ND
32	H	$(CH_2)_2OH$	6%[a]	ND
33	CH_3	Cyclobutyl	0.094	40% at 10 μM
34	CH_3	Cyclohexyl	0.127	ND
35	*t*Bu	Cyclobutyl	0.283	ND
36	CF_3	Cyclobutyl	0.165	ND
37	CH_2OCH_3	Cyclobutyl	25%[a]	ND

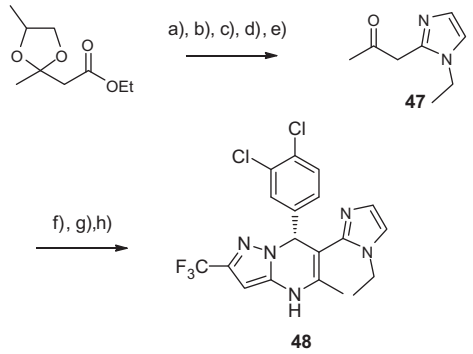
[a] % Inhibition of current in L-929 cells at 0.3 μM, 2–4 point determinations.

Table 4
C6 N(1) triazolo-2-pyridyl substituted dihydropyrimidines



Compound	Y	K_v1.5, L-929 cells IC_{50}, μM	PXR (EC_{20}, μM)
38	H	11%[a]	ND
39	6-F	0.256	0.07
40	6-CF_3	0.096	0.14
41	6-Cl	0.190	ND
42	4-CH_3	0.410	0.44
43	5-CH_3	0.389	ND
44	6-CH_3	0.211	0.44
45	6-OCH_3	0.087	0.96
46	6-O CH_2CH_3	0.223	1.1

[a] % Inhibition of current in L-929 cells at 0.3 μM, 2–4 point determinations.



Scheme 3. Reagents and conditions: (a) LAH, ether 0 °C–rt 2 h; (b) swern oxidation (74%, 2 steps); (c) glyoxal trimer, MeOH/7 N NH_3 rt 16 h; (d) EtI, NaH, DMF rt 4 h; (e) HCl aq, THF rt 16 h (29%, 3 steps); (f) dichlorobenzaldehyde, dioxane 160 °C microwave 10 min; (g) trifluoroaminopyrazole, dioxane 160 °C microwave 10 min (13%, 2 steps); (h) chiral HPLC OD separation.

not prepare the prerequisite C6 aldehyde directly and could not convert the intermediate C6 ester or primary amide into the aldehyde, without loss of the *N*-Boc protecting group. The sequence employed resulted in racemic imidazoles which were resolved using Chiral OD HPLC separation conditions. Example imidazoles **48**, **49** and **50** (Table 5) were prepared via this route.

All compounds synthesized by the methods described above were assayed for block of I_{Kur} current in patch clamped mammalian L929 cells expressing human K_v1.5 mRNA and stably express the I_{Kur} protein.[37] The initial N(1) aryl C6 triazolo dihydropyrazolopyrimidines compounds **5**–**9** were identified as potent inhibitors of K_v1.5 (Table 1). Compound **10** bearing a C2 methyl is significantly less potent than compound **9** which is unsubstituted at the C2 position.

Extending the SAR to N(2) aryl substituted triazoles, provided compounds **11**–**16**, which were significantly less potent than the corresponding N(1) analogs for K_v1.5 inhibition (Table 2). Therefore, further optimization of this series was focused on extending SAR in the N(1) triazole position.

To reduce lipophilicity in the N(1) aryl series, aliphatic and heterocyclic groups were subsequently targeted. These compounds were found to maintain potent K_v1.5 inhibition, (Tables 3 and 4).

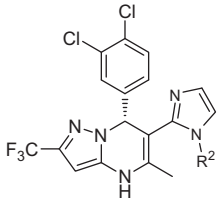
As shown in Table 3, cycloalkyl N(1) triazole derivatives were potent K_v1.5 inhibitors. These compounds also demonstrated significant selectivity with respect to *h*ERG channel inhibition, for example compound **33** showed only 40% inhibition of *h*ERG current at 10 μM. Substitution at position C2 to address the potential issue of reactive intermediate formation[29] led to a loss in potency consistent with previous work in the C6 amide series (e.g., **25** vs **33**, **36** and **22** vs **34**). Efforts to reduce lipophilicity further by incorporating polar groups resulted in reduced K_v1.5 activity, (e.g., **29** and **32**). Generally the C_3–C_6 cycloalkyl analogs were more potent compared to the corresponding linear alkyl analogs, (e.g., **22**, **24** and **25** vs **19**, **20**). Cyclobutyl triazole, **33**, had an acceptable in vitro liability profile and was progressed to a coarse rat PK study.[38] This compound, however, demonstrated rapid clearance in rats (Table 7).

As shown in Table 4, substituted pyridyl triazoles maintained K_v1.5 potency, but also demonstrated significant *h*ERG inhibition and PXR transactivation which was not attenuated by substitution on the pyridine. The most potent pyridine, compound **45**, demonstrated 98% inhibition of *h*ERG current at 10 μM[39] which precluded the compound from further in vivo evaluation.

Direct C6 imidazolo analogs were within two to threefold potency of the corresponding N(1) triazoles (e.g., **48** vs **19** and **49** vs **21**). However, the C2 substituted analogs also demonstrated potent in vitro PXR transactivation and rapid clearance in rats (e.g., **49** and **50** Tables 5 and 7).

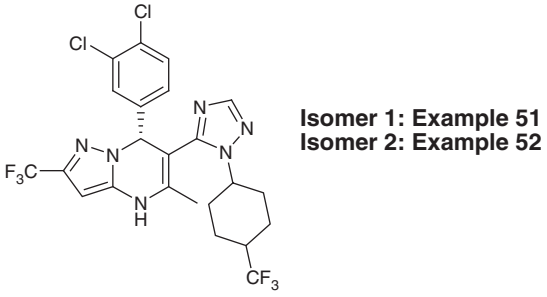
Lead N(1) cyclobutyl C6 triazolo **33** was further profiled in the in vitro microsomal incubation study. The principal sites of metabolism were identified as the C2 methyl group and oxidation of the pendant N(1) cyclobutyl group. To block both sites of metabolism, C2 trifluoromethyl and C4′ trifluoromethyl substituted cyclohexyl analogs compounds **51** (isomer 1) and **52** (isomer 2) were synthesized.

Table 5
Example C6 N substituted alkyl imidazo dihydropyrimidines



Compound	R^2	K_v1.5, L-929 cells (IC_{50}, μM)	PXR (EC_{20}, μM)
48	Ethyl	0.128	0.11
49	*i*-Propyl	0.204	0.11
50	$(CH_2)_2$ OCH_2CH_3	0.098	0.64

Table 6
Lead C6 N(1) triazolo dihydropyrimidine example **51**



Compound	Inhibition of current in L-929 cells (IC_{50}, μM[a])	CYP inhibition (μM; 1A2, 2C9, 2C19, 2D6, 3A4)	PXR (EC_{20}, μM)	% Inhibition of *h*ERG current 10 μM
51	0.133	40, 7, 6, 22, 40, 40	5	38
52	0.607	40, 8, 7, 27, 15, 25	3.6	ND

[a] % Inhibition of current in L-929 cells at 0.3 μM, 2–4 point determinations.

Table 7
Coarse IV rat PK profile for key C6 analogs (dosed 1 mpk in PEG/EtOH/water 1:1:1)

Compound	Half life (h)	Clearance (mL/min/kg)
1	0.6	134
33	0.6	101
49	0.9	63
50	0.6	45
51	1.2	29

Compound **51**, (*R*)-7-(3,4-dichlorophenyl)-5-methyl-2-(trifluoromethyl)-6-(1-(4-(trifluoromethyl)cyclohexyl)-1*H*-1,2,4-triazol-5-yl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine was identified as a potent and selective I_{Kur} inhibitor with an acceptable in vitro liability profile as shown in Table 6. Compound **51** demonstrated an improved rat PK profile as shown in Table 7 and was advanced to the rat PD model. Compound **51** was administered to rats at 0.3 mpk by IV infusion. A significant decrease in BP (−28 ± 7%), a compensatory increase in HR (6 ± 1%), a decrease in QT (−8 ± 4%) and a decrease in VERP (−25 ± 6%) were observed at plasma concentration 1.6 μM. Compound **51** did not have significant Na and L-type Ca channel inhibition in the flux assays, (IC_{50} 46 and 5.2 μM, respectively). The mechanism for observed hypotension in rats is not clearly understood at this time.

In summary, the first C6 triazolo and imidazolo substituted dihydropyrimidines have been synthesized and identified as potent inhibitors of K_v1.5. We focused on the C6 triazoles which had an improved in vitro and in vivo profile compared to the C6 imidazoles and optimized the N(1) substituent to improve the selectivity profile versus *h*ERG. We subsequently identified the sites of oxidative metabolism and improved the PK profile by blocking the N(1) cycloalkyl portion and at the C2 position of the dihydropyrimidine core. Compound **51**, (*R*)-7-(3,4-dichlorophenyl)-5-methyl-2-(trifluoromethyl)-6-(1-(4-(trifluoromethyl)cyclohexyl)-1*H*-1,2,4-triazol-5-yl)-4,7-dihydropyrazolo[1,5-*a*]pyrimidine was identified as a potent and selective inhibitor of I_{Kur} with an acceptable in vitro liability profile and an acceptable in vivo rat PK profile. However **51** demonstrated significant hypotension in the rat in vivo PD model precluding further evaluation of this compound.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2013.01.064.

References and notes

1. Go, A.; Hylek, E.; Phillips, K.; Chang, Y.; Henault, L.; Selby, J.; Singer, D. *J. Am. Med. Assoc.* **2001**, *285*, 2370.
2. Hart, R. G.; Halperin, J. L. *Stroke* **2001**, *32*, 803.
3. Cox, J. L.; Schuessler, R. B.; Lappas, D. G. *Ann. Surg.* **1996**, *224*, 267.
4. Williamson, B. D.; Man, K. C.; Daoud, E., et al *N. Engl. J. Med.* **1994**, *33*, 910.
5. Page, R. L.; Roden, D. M. *Nat. Rev. Drug Disc.* **2005**, *4*, 899.
6. Keating, M. T.; Sanguinetti, M. C. *Cell* **2001**, *104*, 569.
7. Synder, D. J. *Cardiovasc. Res.* **1999**, *42*, 377.
8. Marban, E. *Nature* **2002**, *415*, 213.
9. Li, G.-R.; Feng, J.; Wang, Z.; Fermini, B.; Nattel, S. *Circ. Res.* **1996**, *78*, 903.
10. Ford, J. W.; Milnes, J. T. *J. Cardiovasc. Pharmacol.* **2008**, *52*, 105.
11. Nanda, K. K.; Nolt, M. B.; Cato, M. J.; Kane, S. A.; Kiss, L.; Spencer, R. H.; Wang, J.; Lynch, J. J.; Regan, C. P.; Stump, G. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5897.
12. Trotter, B. W.; Nanda, K. K.; Kett, N. R.; Regan, C. P.; Lynch, J. J.; Stump, G. L.; Kiss, L.; Wang, J.; Spencer, R. H.; Kane, S. A. *J. Med. Chem.* **2006**, *49*, 6954.
13. Regan, C. P.; Kiss, L.; Stump, G. L.; McIntyre, C. J.; Beshore, D. C.; Liverton, N. J.; Dinsmore, C. J.; Lynch, J. J., Jr. *J. Pharmacol. Exp. Ther.* **2008**, *324*, 322.
14. Beshore, D. C.; Liverton, N. J.; McIntyre, C. J.; Claiborne, C. F.; Libby, B.; Culberson, J. C.; Salata, J. J.; Regan, C. P.; Lynch, J. J.; Kiss, L. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2493.
15. Janusz, J. M.; Wu, S.; Fairweather, N. T.; Lee, Wenlin; Blass, B. E.; Fluxe, A. J.; Hodson, S. J.; Ridgeway, J. M. PCT Int. Appl. WO2007149873, 2007.
16. Welmaker, G. S.; Wilson, M. A.; Mcfarlane, G. R.; Sabalski, J. E.; Butera, J. A.; Trybulski, E. J.; Herbst, D. R. U.S. 20080027049.
17. Blass, B. Eric; Janusz, J. M.; Wu, S.; Ridgeway, J. M., II; Coburn, K.; Lee, W.; Fluxe, A. J.; White, R. E.; Jackson, C. M.; Fairweather, N. PCT Appl. WO2009079624, 2009.
18. Blass, B. E.; Janusz, J. M.; Ridgeway, J. M.; Wu, S. PCT Int. Appl. WO2009079630, 2009.
19. John, D. E.; Mulla, M.; Hamlyn, R. J.; Garrett, S. L.; Hartzoulakis, B.; Madge, D.; Ford, J. PCT Int. Appl. WO2010023448, 2010.
20. Hamlyn, R. John; Madge, D.; Mulla, M. PCT Int. Appl. WO2010139953, 2010.
21. Madge, D.; Mulla, M. PCT Int. Appl. WO2010139967, 2010.
22. Hamlyn, R. J.; Mulla, M.; Madge, D. U.S. 20110136860 A1 20110609.
23. John, D. E.; Ford, J. PCT Int. Appl. WO2012131379, 2012.
24. Pavri, B. B.; Greenberg, H. E.; Kraft, W. K.; Lazarus, N.; Lynch, J. J.; Salata, J. J.; Bilodeau, M. T.; Regan, C. P.; Stump, G.; Fan, L. *Circ. Arrhythmia Electrophysiol.* **2012**, *5*, 1193.
25. Lloyd, J.; Atwal, K. A.; Finlay, H. J.; Nyman, M.; Huynh, T.; Bhandaru, R.; Kover, A.; Schmidt, J.; Vaccaro, W.; Conder, M.; West, T.; Levesque, P. *Biorg. Med. Chem. Lett.* **2007**, *17*, 3271.
26. Finlay, H. J.; Lloyd, J.; Atwal, K. A.; Nyman, M.; Levesque, P.; Conder, M.; Jenkins-West, T. *Biorg. Med. Chem. Lett.* **2008**, *18*, 2714.
27. Lloyd, J.; Finlay, H. J.; Vacarro, W.; Hyunh, T.; Kover, A.; Bhandaru, R.; Yan, L.; Atwal, K.; Conder, M.; Jenkins-West, T.; Shi, H.; Huang, C.; Li, D.; Sun, H.; Levesque, P. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1436.
28. Vaccaro, W.; Huynh, T.; Lloyd, J.; Atwal, K.; Finlay, H. J.; Levesque, P.; Conder, M.; Jenkins-West, T.; Shi, H.; Sun, L. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6381.
29. Finlay, H. J.; Lloyd, J.; Vaccaro, W.; Kover, A.; Yan, L.; Bhave, G.; Prol, J.; Huynh, T.; Bhandaru, R.; Caringal, Y.; DiMarco, J.; Gan, J.; Harper, T.; Huang, C.; Conder, M.; Sun, H.; Levesque, P.; Blanar, M.; Atwal, K.; Wexler, R. *J. Med. Chem.* **2012**, *55*, 3036.
30. Lloyd, J.; Finlay, H. J.; Atwal, K.; Kover, A.; Prol, J.; Yan, L.; Bhandaru, R.; Vaccaro, W.; Huynh, T.; Huang, C. S.; Conder, M.; Jenkins-West, T.; Sun, H.; Li, D.; Levesque, P. *Bioorg. Med. Chem. Lett.* **2009**, *18*, 6381.
31. Representative synthetic procedures and separation conditions are included in the Supplementary data.

32. Yang-I, Lin; Lang, S. A.; Lovell, M. F.; Perkinson, N. A. *J. Org. Chem.* **1979**, *44*, 4160.
33. Lam, P.; Clark, C. *Tetrahedron Lett.* **1998**, *39*, 2941.
34. Representative synthetic procedures and regiochemical assignments are included in the Supplementary data.
35. Ghali, N. I.; Venton, D. L.; Hung, S. C.; Le Breton, G. C. *J. Org. Chem.* **1981**, *46*, 5413.
36. Representative synthetic procedures are included in the Supplementary data.
37. Snyders, D. J.; Tamkun, M. N.; Bennett, P. B. *J. Gen. Physiol.* **1993**, *101*, 513.
38. Protocols for PK experiments are included in the Supplementary data.
39. Zhou, Z.; Vorperian, V. R.; Gong, Q.; Zhang, S.; January, C. T. *J. Cardiovasc. Electrophysiol.* **1999**, *10*, 836.