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# Tetrahydronaphthalene-derived amino alcohols and amino ketones as potent and selective inhibitors of the delayed rectifier potassium current $I_{Ks}$

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**Abstract**—Class III anti-arrhythmic drugs (e.g., dofetilide) prolong cardiac action potential duration (APD) by blocking the fast component of the delayed rectifier potassium current ($I_{Kr}$). The block of $I_{Kr}$ can result in life threatening ventricular arrhythmias (i.e., torsades de pointes). Unlike $I_{Kr}$, the role of the slow component of the delayed rectifier potassium current ($I_{Ks}$) becomes significant only at faster heart rate. Therefore selective blockers of $I_{Ks}$ could prolong APD with a reduced propensity to cause pro-arrhythmic side effects. This report describes structure–activity relationships (SARs) of a series of $I_{Ks}$ inhibitors derived from 6-alkoxytetralones with good in vitro activity ($IC_{50} \geq 30$ nM) and up to 40-fold $I_{Ks}/I_{Kr}$ selectivity.
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Potassium currents in cardiac myocytes play an important role in repolarization of the membrane potential after each contraction. Potassium channel blockers delay repolarization and prolong action potential duration (APD) thus producing a class III anti-arrhythmic effect.[1] The delayed rectifier potassium current ($I_K$) is conducted through potassium channels that exhibit slow ($I_{Ks}$), rapid ($I_{Kr}$) and ultra-rapid ($I_{Kur}$) activation–deactivation kinetics.[2–4] Current class III anti-arrhythmic therapies are based on prolonging action potential duration by blocking $I_{Kr}$ (dofetilide **1**, azimilide **2**) and thus have the potential to cause life-threatening ventricular arrhythmias (i.e., torsades de pointes).[5] Because of the slow activation kinetics of $I_{Ks}$, the contribution of this current is minimal at normal heart rates. However, at faster heart rates this current accumulates and plays a significant role in the repolarization of membrane potential. Therefore, selective blockade of this current can be an effective way of lengthening APD only at fast heart rate with no negative rate dependence and potentially reduced pro-arrhythmic risk relative to agents that block $I_{Kr}$.[6] Furthermore, several $I_{Ks}$ blockers have been evaluated in dogs and have shown efficacy in models of atrial and ventricular arrhythmias suggesting their potential utility for the treatment of these conditions.[7a,b]

Several groups have reported discovery of selective $I_{Ks}$ blockers and reviews describing their potential as anti-arrhythmic agents have been published.[8a–d] We had previously disclosed a novel benzamide series of highly potent and selective blockers of $I_{Ks}$.[9] This report describes synthesis and structure–activity relationship of a series of tetrahydronaphthalene derivatives based on the initial screening lead **3** ($IC_{50} = 5$ μM) (Fig. 1).[10,11]

Compounds **4b** and **4c** were prepared by reacting 6-methoxytetralone (**4a**) with refluxing 48% HBr to afford 6-hydroxytetralone (84% yield)[12] followed by treatment with respective alkyl bromides in the presence of potassium carbonate in dimethylformamide (55–65% yield). Compound **4d** was prepared in 41% yield by heating a mixture of 6-hydroxytetralone with bromobenzene in the presence of CuCl and $KHCO_3$ in a sealed tube at 200 °C. Treatment of 6-hydroxytetralone with trifluoromethanesulfonic anhydride in methylene chloride in the presence of pyridine afforded the corresponding

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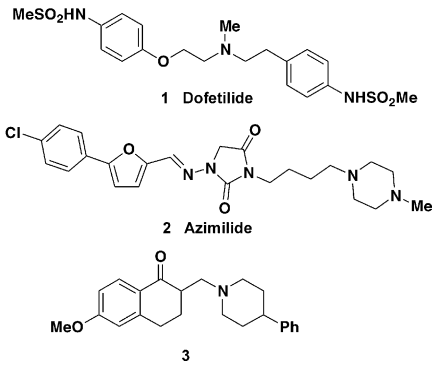


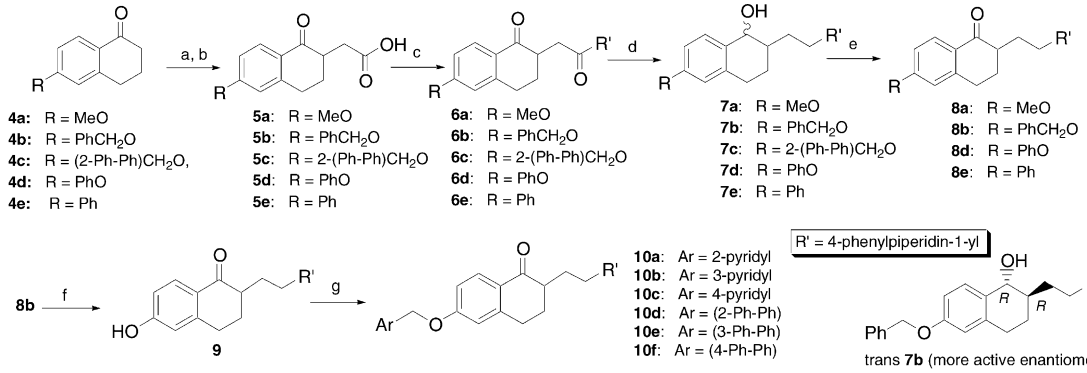

**Figure 1.**

triflate (99% yield). This was converted (98% yield) to the biaryl compound **4e** via Suzuki coupling with phenylboronic acid in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) and potassium carbonate in toluene at 80 °C.

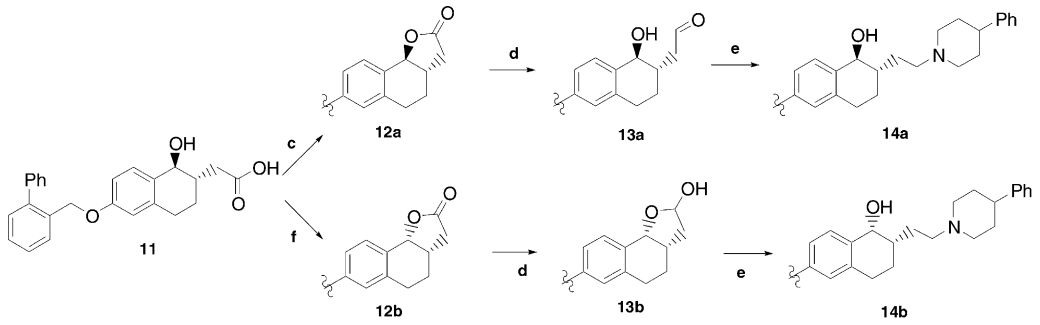
Treatment of tetralones **4a–e** with equimolar lithium bis(trimethylsilyl)amide and hexamethylphosphoramide (HMPA) at 0 °C in THF, followed by treatment with ethyl bromoacetate (3 equivalents) at rt afforded the corresponding keto esters which were hydrolyzed to give the keto acids **5a–e** in 60–70% yield (two steps). Coupling of **5a–e** with 4-phenylpiperidine was carried out in *N*,*N*-dimethylformamide (DMF) in the presence of BOP reagent and *N*-methylmorpholine (90–95% yield) to give the keto amides **6a–e**. Lithium aluminum hydride reduction of the keto amides gave amino alcohol **7a–e** (ca. 3:1 *trans*/*cis*, 80–90% yield). The amino ketones **8a**, **b**, **8d** and **8e** were prepared via oxidation of the corresponding alcohols with Dess–Martin's periodinane[13] or Jones reagent (75–85% yield). Compounds **10a–f** were conveniently prepared from **8b** via hydrogenolysis followed by alkylation of the resulting phenol **9** with various benzyl halides (Scheme 1).

The *trans* and *cis* amino-alcohols **14a** and **14b** were initially prepared by resolving a mixture of the two compounds (**7c**). Subsequently, a more efficient approach was developed. The key step in this route involves a stereoselective reduction of the keto acid **5c** to the hydroxy acid **11** which could be achieved with sodium borohydride in THF-diglyme at −78 °C to rt followed by a careful workup under weakly acidic (pH 4–4.5) conditions to afford **11** as 8:1 *trans*/*cis* mixture.[14] The crude hydroxy acid **11** was converted to the *trans* lactone **12a** by treatment with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) and *N*-methylmorpholine followed by silica gel chromatography (54% yield, two steps). DIBAL reduction of the lactone **12a** in toluene at −78 °C afforded the *trans* hydroxy aldehyde **13a** in 92% yield. The predominantly *trans* hydroxy acid **11** was also converted to the *cis* lactone **12b** by treatment with catalytic (1%, by wt) *p*-TsOH in refluxing toluene-diglyme (68% yield, 2 steps). DIBAL reduction of this compound afforded the *cis* lactol **13b** in 90% yield. The *trans* hydroxy aldehyde **13a** and the *cis* lactol **13b** were readily converted to the corresponding amino alcohols **14a** and **14b**, respectively, by reductive amination with 4-phenylpiperidine and $Na(OAc)_3BH$ in THF in 80–90% yield (Scheme 2).

While most compounds were tested for biological activity[10] as racemates, several key compounds were resolved by chiral chromatography and evaluated in enantiomerically pure form for activity.[16] The lead aminoketone **3** displayed only modest inhibition of $I_{Ks}$ ($IC_{50} = 5$ μM, see Table 1). However, this compound had a limited solution stability as it underwent a slow retro Mannich degradation. Efforts made to stabilize **3** without substantially sacrificing the $I_{Ks}$ inhibitory activity included homologation of the group linking the 4-phenylpiperidine moiety to the tetrahydronaphthalene group and reduction of the ketone group to an alcohol. Thus the homologous ethylene analogue **8a** was prepared and evaluated for biological activity. When compared to the parent lead **3** (racemic), compound **8a** (homochiral, $IC_{50} = 0.4$ μM) showed a ca. 12-fold increase in the $I_{Ks}$ inhibitory activity. The amide **6b** was inactive at 30 μM perhaps indicating a need for the presence of a charged interaction at the binding site. Efforts to optimize substituents at the 6-position of the tetralone group resulted in the discovery of the 6-benzyloxy compound **8b** ($IC_{50} = 69$ nM) with ca. 70-fold improvement in potency. Although more potent than the parent lead **3**, the phenoxy and phenyl analogues **8d** and **8e** were significantly less potent than the corresponding benzyloxy compound. Replacement of the




**Scheme 1.** (a) $(Me_3Si)_2NLi$/HMPA/THF at 0 °C then ethyl bromoacetate at rt; (b) aqueous KOH/dioxane/60–70% yield (two steps); (c) BOP reagent/4-phenylpiperidine/*N*-methylmorpholine/DMF/90–95% yield; (d) LAH/THF/80–90% yield; (e) Dess–Martin periodinane/*t*-BuOH/methylene chloride or Jones reagent, 75–85%; (f) $H_2$/10% Pd/C/EtOH–EtOAc/88% yield; (g) $ArCH_2Cl$ or $ArCH_2Br/K_2CO_3/n\text{-}Bu_4NI$/DMF 90–95% yield.




**Scheme 2.** (c) EDCI hydrochloride/*N*-methylmorpholine/methylene chloride-diglyme/0 °C/54% yield for two steps; (d) DIBAL/toluene/−78 °C/90–92% yield; (e) 4-phenylpiperidine/$Na(AcO)_3BH$/HOAc/THF/80–90% yield; (f) 1% (by wt) *p*-TsOH/toluene-diglyme/reflux/68% yield.

**Table 1.** $I_{Ks}$ and $I_{Kr}$ activity of the various tetrahydronaphthalene derived analogues[a]

| Compd # | $I_{Ks}$ $IC_{50}$ (μM) | $I_{Kr}$ $IC_{50}$ (μM) |
|---|---|---|
| **3** | 5 | 4 |
| **6b** | >30 | ND |
| **7b** | 0.15 (1.3)[b] | 0.17 (0.11)[b] |
| **8a** | 0.4 (1.7)[b] | 1.7 (ND)[b] |
| **8b** | 0.069 (2.2)[b] | 0.16 (0.22)[b] |
| **8d** | 1.5 | ND |
| **8e** | 2.4 | ND |
| **10a** | 1.3 | ND |
| **10b** | 0.38 | ND |
| **10c** | 0.2 | ND |
| **10d** | 0.03 (0.34)[b] | 0.26 (1.6)[b] |
| **10e** | 0.47 | ND |
| **10f** | 1 | ND |
| **14a** | 0.037 (1.0)[b] | 1.5 (ND)[b] |
| **14b** | 0.39 | ND |

[a] $I_{Ks}$ and $I_{Kr}$ activities were determined in guinea pig ventricular myocytes, $n \geq 2$.[9,10,15]

[b] Biological activity was determined for pure enantiomers, the $IC_{50}$ values in parentheses correspond to the enantiomers with weaker $I_{Ks}$ inhibitory activity.

benzyloxy group (compound **8b**) with pyridyl (**10a–c**) resulted in significant loss of activity perhaps indicating somewhat reduced hydrophobic interactions at the binding site. A study of the effect of substituents on the benzyloxy group resulted in the discovery of the 2-(phenyl)phenylmethoxy analogue **10d** ($IC_{50}$ = 30 nM) as the most potent compound prepared in this series.

The ketone functionality of several $I_{Ks}$ inhibitors described herein was replaced with a secondary alcohol. Thus, while the benzyloxy amino alcohol **7b** was ca. 2-fold less potent than the corresponding amino ketone **8b**, the 2(phenyl)phenylmethyl analogue **14a** exhibited potency comparable to the corresponding amino ketone **10d**. Furthermore, evaluation of the *trans* amino alcohol **14a** and the corresponding *cis* analogue **14b** revealed that the *trans* isomer was significantly more potent ($IC_{50}$ = 37 nM) than the *cis* compound ($IC_{50}$ = 390 nM).

Several key compounds were evaluated for selectivity for the $I_{Ks}$ current over $I_{Kr}$. While most amino ketones prepared in this series showed little to modest selectivity, the amino alcohol **14a** was ca. 40-fold selective. In conclusion, a novel series of potent $I_{Ks}$ inhibitors has been identified. The initial lead (compound **3**) with modest $I_{Ks}$ activity and no selectivity over $I_{Kr}$ was optimized to afford compounds with good potency and selectivity. Furthermore, a stereoselective synthetic approach based on utilizing a common intermediate (*trans* hydroxy acid **11**) to give either the *trans* or the *cis* amino alcohols (**14a** or **14b**) has been developed.

## Acknowledgements

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## References and notes

1. Colatsky, T. J.; Follmer, C. H.; Starmer, C. F. *Circulation* **1990**, *82*, 2235.
2. Sanguinetti, M. C.; Jurkiewicz, N. K. *J. Gen. Physiol* **1990**, *96*, 195.
3. Sanguinetti, M. C.; Jiang, C.; Curran, M. E.; Keating, M. T. *Cell* **1995**, *81*, 299.
4. (a) Barhanin, J.; Lesage, F.; Guillemare, E.; Fink, M.; Lazdunski, M.; Romey, G. *Nature* **1996**, *384*, 78. (b) Sanguinetti, M. C.; Curran, M. E.; Zou, A.; Shen, J.; Spector, P. S.; Atkinson, D. L.; Keating, M. T. *Nature* **1996**, *384*, 80.
5. Curran, M. E.; Splawski, I.; Timothy, K. W.; Vincent, G. M.; Green, E. D.; Keating, M. E. *Cell* **1995**, *80*, 795.
6. Jurkiewicz, N. K.; Sanguinetti, M. C. *Circ. Res.* **1993**, *72*, 75.
7. (a) Lynch, J. J.; Houle, M. S.; Stump, G. L.; Wallace, A. A.; Gilberto, D. B.; Jahansouz, H.; Smith, G. R.; Tebben, A. J.; Liverton, N. J.; Selnick, H. G.; Claremon, D. A.; Billman, G. E. *Circulation* **1999**, *100*, 1917. (b) Stump, G. L.; Smith, G. R.; Tebben, A. J.; Jahansouz, H.; Salata, J. J.; Selnick, H. G.; Claremon, D. A.; Lynch, J. J. *J. Cardio. Pharmac.* **2003**, *42*, 105.
8. (a) Butcher, J. W.; Liverton, N. J.; Claremon, D. A.; Freidinger, R. M.; Jurkiewicz, N. K.; Lynch, J. J.; Salata, J. J.; Wang, J.; Dieckhaus, C. M.; Slaughter, D. E.; Vyas, K. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1165. (b) Selnick, H. G.; Liverton, N. J.; Baldwin, J. J.; Butcher, J. W.; Claremon, D. A.; Elliot, J. M.; Freidinger, R. M.; King, S. A.; Libby, B. E.; McIntyre, C. J.; Pribush, D. A.; Remy, D. C.; Smith, G. R.; Tebben, A. J.; Jurkiewicz, N. K.; Lynch, J. J.; Salata, J. J.; Sanguinetti, M. A.; Siegl, P. K. S.; Slaughter, D. E.; Vyas, K. *J. Med. Chem.* **1997**, *40*, 3865. (c) Gerlach, U.; Brendel, J.; Lang, H.-J.; Paulus, E. F.; Weidmann, K.; Brueggemann, A.; Busch, A. E.; Suessbrich, H.; Bleich, M.; Greger, R. *J. Med. Chem.* **2001**, *44*, 3831. (d) Gerlach, U. *Drugs of the Future* **2001**, *26*, 473.

9. Lloyd, J.; Schmidt, J. B.; Rovnyak, G.; Ahmad, S.; Atwal, K. S.; Bisaha, S. N.; Doweyko, L. M.; Stein, P. D.; Traeger, S. C.; Mathur, A.; Conder, M. L.; DiMarco, J.; Harper, T. W.; Jenkins-West, T.; Levesque, P. C.; Normandin, D. E.; Russell, A. D.; Serafino, R. P.; Smith, M. A.; Lodge, N. J. *J. Med. Chem.* **2001**, *44*, 3764.
10. Screening of the internal compound database was carried out in guinea pig ventricular myocytes using voltage clamp techniques: Lodge, N. J.; Smith, M. A. *Naunyn-Schmiedeberg's Arch. Pharmaco.* **1996**, *354*, 444.
11. Ahmad, S., Stein, P. D., Ferrara, F. N., Atwal, K. S. WO 9836749.
12. Durden, J. A., Jr. *J. Agr. Food Chem.* **1971**, *19*, 432.
13. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
14. Workup under strongly acidic conditions affords an olefinic product derived from dehydration of **11**. Typically, the reaction is quenched by adding 0.1 N HCl, extracted with ethyl acetate and concentrated in vacuo at rt to afford a diglyme solution of **11** which is used as such in subsequent steps.
15. Lodge, N. J.; Normandin, D. E. *J. Mol. Cell. Cardiol.* **1997**, *29*, 3211.
16. Compounds **7b**, **8a**, **8b** and **10d** were obtained in enantiomerically pure form by subjecting the corresponding racemic mixtures to chromatography on a CHIRALCEL® OD column (hexane–isopropanol–triethylamine 90:10:0.2–80:20:0.2). The more potent enantiomers for compounds **7b** and **8b**, and the less potent enantiomers for **8a** and **10d**, are eluted first. The absolute stereochemistry of the more potent enantiomer for **7b** was determined to be *R,R* (see Scheme 1) by X-ray crystallography of 1:1 salt with R-mandelic acid. Compound **14a** was resolved by CHIRALPAK® AD column (hexane–isopropanol–triethylamine 80:20:0.2, the faster moving enantiomer is more active).