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Synthesis and evaluation of (2-phenethyl-2*H*-1,2,3-triazol-4-yl)(phenyl)methanones as Kv1.5 channel blockers for the treatment of atrial fibrillation

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Abstract—A series of novel (2-phenethyl-2*H*-1,2,3-triazol-4-yl)(phenyl)methanones were prepared and examined for utility as Kv1.5 channel blockers for the treatment of atrial fibrillation.

Atrial fibrillation (AF), a common cardiac arrhythmia that afflicts 2–3 million Americans, is associated with an increased risk of thromboembolism, stroke, and a two fold increase in mortality.[1] Available treatments are limited to implantable atrial defibrillators and class III anti-arrhythmic agents, such as dofetilide.[2] Class III anti-arrhythmic agents increase myocardial refractoriness by blocking ion channels responsible for repolarization, resulting in prolongation of the action potential duration (APD). These drugs, however, act on ion channels (e.g., IKr) that are found in both the atria and ventricles. Blockade of potassium ion channels in the ventricles (e.g., hERG) leads to a prolongation of the QT interval and an increased propensity for life-threatening ventricular arrhythmias (torsade de pointes). As part of our ongoing efforts to develop an effective therapy for AF, we have been exploring the utility of Kv1.5 blockade. This channel and its associated current (IKur) are found only in the atrial chambers of the heart, suggesting that selective blockade of this channel would provide relief from AF, without the associated risk of ion channel blockade in the ventricle.[3]

Herein, we wish to report the development of a series of functionalized 1,2,3-triazoles as blockers of the Kv1.5 channel. Members of this class of compounds have been identified as adenosine antagonists, oxalic acid antagonists, metalloprotease inhibitors, antibacterials, β-lactamase inhibitors, antivirals, and anticonvulsants.[4] We have recently found that this scaffold also has utility in the blockade of the Kv1.5 channel. Specifically, 2,4-disubstituted-1,2,3-triazoles (**1**) have been prepared and examined for their ability to block the Kv1.5 channel and increase the atrial effective refractory period (AERP) for the treatment of atrial fibrillation. The initial rationale for the design of this class of compounds was the Icagen benchmark ICA-32 (Fig. 1), a selective Kv1.5 blocker (IC_{50} = 132 nM) (Scheme 1).

A series of analogs was readily prepared in a two-step process from the appropriate phenyl-ketoacetylene (**2**).

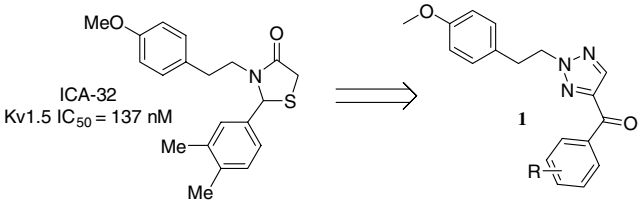

Figure 1. ICA-32 and a proposed 1,2,3-triazole lead structure.

Keywords: Atrial fibrillation; Kv1.5 ion channel; 1,2,3-Triazole.
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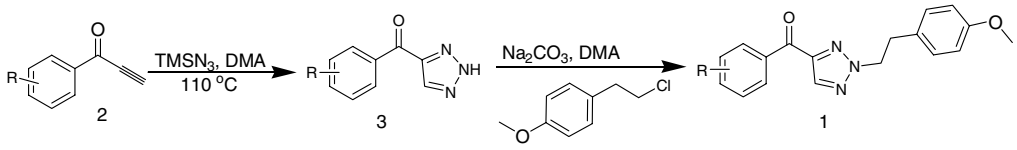
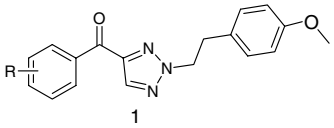


Scheme 1. Synthesis of 2,4-substituted-1,2,3-triazoles.

Thus, treatment of acetylene (**2**) with TMS azide in dimethylacetamide at 110 °C established the 1,2,3-triazole core (**3**) via a 2 + 3 cycloaddition reaction. Alkylation with 4-methoxyphenethyl chloride in the presence of sodium carbonate and dimethyl acetamide provided the desired products (**1**, see Table 1).[5]

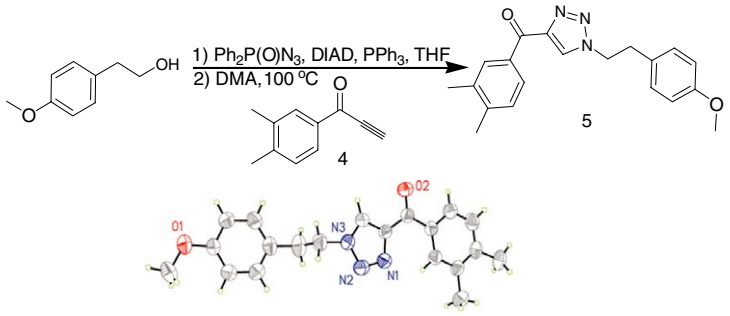
Table 1. Representative examples of the synthesis of (2-phenethyl-2*H*-1,2,3-triazol-4-yl)(phenyl)methanones and their blockade of Kv1.5



Entry	R	% Yield step 1	% Yield step 2	% blockade Kv1.5 @ 1 μM
1a	2-Cl	51	16	22
1b	4-OCH_3	79	53	84
1c	4-Cl	38	33	85
1d	4-Et	47	57	86
1e	3,4-Di-Cl	43	18	88
1f	3,4-Di-CH_3	68	52	90
1g	4-*i*-Pr	94	22	97
1h	4-NMe_2	33	87	99
1i	2-OMe-4-NMe_2	83	17	0

Since alkylation of the 1,2,3-triazole intermediate **3** could potentially occur at any of the three nitrogens, an independent synthesis of the 1,2,3-triazole core structure that did not require alkylation of the triazole was also examined (Scheme 2). Thus, conversion of 4-methoxyphenethyl alcohol to the azide with triphenyl phosphine, diphenyl phosphoryl azide, and diisopropylazodicarboxylate, followed by cycloaddition with acetylene **4**, provided **5**, an isomer of the previously described material.[6] The 1,4-orientation of this isomer was later confirmed by single crystal X-ray crystallography.[7]

While the synthesis of this alternative isomer does exclude the possibility that the Kv1.5 active compounds are 1,4-disubstituted triazoles, it still leaves open the two other possible isomers. Single crystal X-ray structures of several analogs from the alkylation series were obtained, all of which displayed the substituents about



Scheme 2. Synthesis of 1,4-disubstituted triazole and associated X-ray structure.

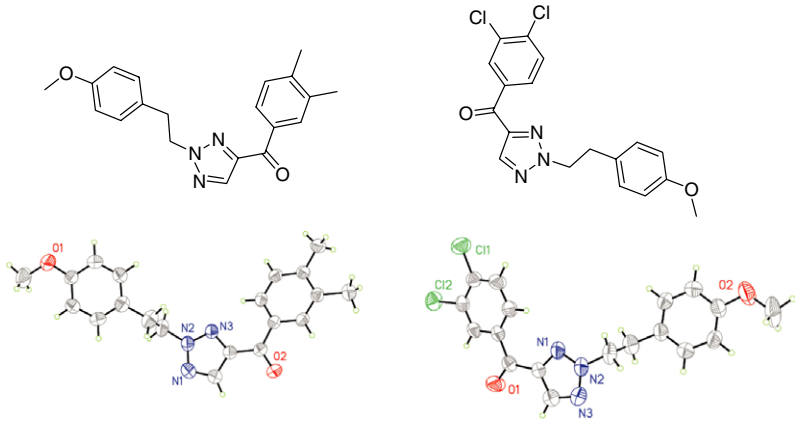


Figure 2. Selected X-ray structures of Kv1.5 blockers.

the triazole in a 2,4-orientation, verifying the structural assignment of the active series (Fig. 2).[8]

Initial screening of this class of compounds was accomplished by whole-cell patch-clamp electrophysiology to determine channel block in LTK cells expressing the Kv1.5 channel.[9] Results for some representative examples are shown in Table 1. From this data, one can conclude that substitution in the 4-position of the acetophenone-derived portion of the scaffold is highly favored. Increased lipophilicity is well tolerated (e.g., **1g** and **1h**), but the difference between electron donating and electron withdrawing is not substantial. Substitution in the 2-position of the same scaffold, however, appears to be detrimental to the desired activity. This is especially clear in the comparison of entries **1h** and **1i**, as the simple addition of a methoxy substituent in the 2-position eliminates all of the desired activity. Interestingly, 1,4-regioisomer **5** showed no activity.

Of this set, entry **1f** was selected for further progression based on its selectivity for Kv1.5 over other channels. The Kv1.5 blockade IC_{50} was 294 nM. Significantly decreased potency was observed at other related channels, such as hERG channel (>50 μM), Kv1.3 channel (10.1 μM), and the L-type calcium channel (26 μM). In vivo efficacy was demonstrated after a 15 min infusion of 30 mg/kg in an anesthetized pig model. An increase of 12% in the atrial effective refractory period (AERP) was observed, and the ventricular effective refractory period (VERP) remained unchanged. Control experiments showed no changes in AERP.

In summary, we have developed a new class of selective Kv1.5 channel blockers, which demonstrate atrial selective prolongation of the effective refractory period in a pig model of arrhythmic events.

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5. Typical Experimental Procedure: *Step 1:* 1,2,3-triazole ring formation: 1,2,3-triazole: 1-(3,4-dimethylphenyl) prop-2-yn-1-one (1.0 g, 6.3 mmol) was dissolved in 63 ml DMA and trimethylsilyl azide (0.874 ml, 7.59 mmol, 1.2 equiv) was added. The reaction mixture was then heated to 110 °C and monitored for loss of the alkyne. When the starting alkyne was consumed, the reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residual material was then purified via normal phase chromatography with a hexane and ethyl acetate gradient to yield 865 mg (68%) of the desired product. *Step 2:* Alkylation of the 1,2,3-triaozles: (3,4-dimethylphenyl)(2*H*-1,2,3-triazol-4-yl)methanone (1.0 g, 4.97 mmol) and sodium carbonate (1.05 g, 0.99 mmol, 2.0 equiv) were dissolved in 50 ml of DMA and stirred briefly. 4-Methoxyphenethylchloride (0.86 g, 763 μL, 5.47 mmol, 5.07 mmol, 1.02 equiv) was added and the reaction mixture was stirred at room temperature while monitoring for loss of the starting materials. When the reaction was complete, the solvent was removed under reduced pressure, and the residual material was purified by chromatography with a hexane and ethyl acetate gradient to yield 869 mg (52%) of the desired product. Data from Table 1: Entry **1** (^{1}H NMR, 300 MHz, CD_3OD): δ 3.22 (t, 2H, J = 6.8 Hz), 3.76 (s, 3H), 4.69 (t, 2H, J = 7.0 Hz), 6.80 (d, 2H, J = 6.6 Hz), 7.01 (d, 2H, J = 6.7 Hz), 7.40 (m, 2H), 7.51 (m, 2H), 8.18 (s, 1H). ($M+H^+$) 342. Entry **2** (^{1}H NMR, 300 MHz, CD_3OD): δ 3.26 (t, 2H, J = 6.9 Hz), 3.75 (s, 3H), 3.91 (s, 3H), 4.78 (t, 2H, J = 6.9 Hz), 6.83 (d, 2H, J = 6.6 Hz), 7.0 (d, 2H, J = 7.0 Hz), 7.06 (d, 2H, J = 8.6 Hz), 8.08 (d, 2H, J = 8.9 Hz), 8.17 (s, 1H). ($M+H^+$) 338. Entry **3** (^{1}H NMR, 300 MHz, CD_3OD): δ 3.27 (t, 2H, J = 6.8 Hz), 3.76 (s, 3H), 4.80 (t, 2H, J = 6.8 Hz), 6.85 (d, 2H, J = 6.6 Hz), 7.06 (d, 2H, J = 8.6 Hz), 7.50 (d, 2H, J = 6.7 Hz), 8.06 (d, 2H, J = 6.7 Hz), 8.24 (s, 1H). ($M+H^+$) 342. Entry **4** (^{1}H NMR, 300 MHz, CD_3OD): δ 1.29 (t, 3H, J = 7.2 Hz), 2.73, (q, 2H, J = 6.9 Hz), 3.24 (t, 2H, J = 6.5 Hz), 3.72 (s, 3H), 4.75 (t, 2H, J = 6.9 Hz), 6.81 (d, 2H, J = 8.5 Hz), 7.03 (d, 2H, J = 8.5 Hz), 7.31 (d, 2H, J = 8.2 Hz), 7.98 (d, 2H, 8.3 Hz), 8.19 (s, 1H). ($M+H^+$) 336. Entry **5** (^{1}H NMR, 300 MHz, CD_3OD): δ 3.29 (t, 2H, J = 6.8 Hz), 3.77 (s, 3H), 4.83 (t, 2H, J = 7.0 Hz), 6.86 (d, 2H, J = 6.5 Hz), 7.08 (d, 2H, J = 6.7 Hz), 7.68 (d, 1H, J = 8.4 Hz), 8.03 (dd, 1H, J = 1.9, 8.37 Hz), 8.29 (s, 1H), 8.32 (d, 1H, J = 2.0 Hz). ($M+H^+$) 376. Entry **6** (^{1}H NMR, 300 MHz, CD_3OD): δ 2.36 (s, 3H), 2.39, (s, 3H), 3.27 (t, 2H, J = 6.6 Hz), 3.77 (s, 3H), 4.78 (t, 2H, J = 6.9 Hz), 6.84 (d, 2H, J = 9.7 Hz), 7.07 (d, 2H, J = 8.4 Hz), 7.27 (d, 1H, J = 8.1 Hz), 7.83 (d, 1H, 8.3 Hz), 7.90 (s, 1H), 8.20 (s, 1H). ($M+H^+$) 336. Entry **7** (^{1}H NMR, 300 MHz, CD_3OD): δ 1.38 (d, 6H, J = 7.4 Hz), 3.07 (m, 1H, J = 7.2 Hz), 3.31 (t, 2H, J = 6.3 Hz), 3.81 (s, 3H), 4.82 (t, 2H, J = 6.5 Hz), 6.91 (d, 2H, J = 8.7 Hz), 7.12 (d, 2H, J = 8.1 Hz), 7.41 (d, 2H, J = 8.1 Hz), 8.04 (d, 2H, 7.9 Hz), 8.26 (s, 1H). ($M+H^+$) 350. Entry **8** (^{1}H NMR, 300 MHz, CD_3OD): δ 3.13 (s, 3H), 3.27 (t, 2H, J = 6.6 Hz), 3.77 (s, 3H), 4.78 (t, 2H, J = 6.9 Hz), 6.74 (d, 2H, J = 9.3 Hz), 6.85 (d, 2H, J = 8.7 Hz), 7.06 (d, 2H, J = 8.7 Hz), 8.02 (d, 2H, 9.3 Hz), 8.10 (s, 1H). ($M+H^+$) 351. Entry **9** (^{1}H NMR, 300 MHz, CD_3OD): δ 3.11 (s, 6H), 3.26 (t, 2H, J = 6.8 Hz), 3.76 (s, 3H), 3.79 (s, 3H), 4.70 (t, 2H, J = 7.0 Hz), 6.30 (s, 1H), 6.33 (d, 2H, J = 6.5 Hz), 6.82 (d, 2H, J = 6.6 Hz), 7.05 (d, 1H, J = 6.7 Hz), 7.45 (d, 1H, J = 8.8 Hz) 7.97 (s, 1H). ($M+H^+$) 381.
6. Experimental conditions: 1-(2-azidoethyl)-4-methoxy benzene: 4-methoxyphenethyl alcohol (2.65 g, 17.4 mmol, 1.0 equiv) and triphenyl phosphine (4.57 g, 17.4 mmol, 1.0 equiv) were dissolved in 100 ml of dry THF under a nitrogen atmosphere, the reaction mixture was stirred briefly, and then diisopropylazodicarboxylate (3.87 g, 3.78 ml, 19.2 mmol, 1.1 equiv) was added. The reaction mixture was stirred for 5 min,

diphenylphosphoryl azide (5.27 g, 19.2 mmol, 1.1 equiv) was added, and the reaction mixture was stirred for an additional 24 h. The solvents were then removed under reduced pressure, and the residual material was purified by chromatography with 7:1 hexane/ethyl acetate (2.22 g, 72%). (^{1}H NMR, 300 MHz, $CDCl_3$): δ 2.85 (t, 2H, J = 6.6 Hz), 3.47 (t, 2H, J = 6.9 Hz), 3.78 (s, 3H), 6.86 (d, 2H, J = 8.3 Hz), 7.15 (d, 2H, J = 8.7 Hz). ($M+H^+$) 178. (1-(4-Methoxyphenethyl)-1*H*-1,2,3-triazol-4-yl)(3,4-dimethylphenyl)methanone: 4-methoxyphenethyl azide (60 mg, 0.34 mmol) and 1-(3,4-dimethylphenyl)prop-2-yn-1-one (53.5 mg, 0.34 mmol) were dissolved in 1.0 ml of dimethylacetamide and the reaction mixture was heated to 100 °C. After 48 h, the reaction mixture was cooled, the solvent was removed under reduced pressure, and the residue was purified by reverse phase HPLC (0.5% TFA in acetonitrile/H2O) to yield 76 mg (67%) of a colorless oil. (^{1}H NMR, 300 MHz, CD_3OD): δ 2.37 (s, 3H), 2.40, (s, 3H), 3.20 (t, 2H, J = 6.1 Hz), 3.75 (s, 3H), 4.72 (t, 2H, J = 6.4 Hz), 6.88 (d, 2H, J = 8.7 Hz), 7.09 (d, 2H, J = 7.9 Hz), 7.30 (d, 1H, J = 8.4 Hz), 7.86 (d, 1H, 7.9 Hz), 7.88 (s, 1H), 8.29 (s, 1H). ($M+H^+$) 336.

7. Cambridge Crystallographic Data Centre reference number CCDC 609610.
8. Cambridge Crystallographic Data Centre reference numbers CCDC 608957 and CCDC 608958.
9. Whole-cell Kv1.5 current recordings were made at room temperature via the gigaseal patch clamp technique using Axopatch-1D and Axopatch 200B amplifiers (Axon Instruments, Foster City,CA). Ltk-cells overexpressing Kv1.5 channels were cultured for 24–72 h, induced to express Kv1.5 channels by 24 h incubation with 2 μM dexamethasone prior to use for patch clamp studies. Small, spherical cells approximately 10 μm in diameter were used for all patch recordings. Electrodes were made from TW-150F glass capillary tubes (World Precision Instruments, New Haven, CT) and had resistances of 1.5–3.0 MΩ when filled with internal solution containing: 110 mM KCl, 5 mM K2ATP, 5 mM K4BAPTA, 1 mM $MgCl_2$, and 10 mM Hepes, adjusted to pH 7.2 with KOH. The external solution contained: 130 mM NaCl, 4 mM KCl, 1.8 mM $CaCl_2$, 1 mM $MgCl_2$, 10 mM Hepes, and 10 mM glucose, adjusted to pH 7.4 with NaOH. Series resistance was compensated following rupture of the seal. Currents were sampled at 1 KHz and filtered at 500 Hz. Cells were pulsed (0.2 Hz) to +60 mV for 1 s, from a holding potential of −70 mV. After stable control currents were obtained, inhibitors were perfused onto the cells at increasing concentrations until maximal inhibition was obtained for a given concentration. Whole-cell patch-data were analyzed using Clampfit 8.0 in pCLAMP software (Axon Instruments). IC50 values for compounds were determined by nonlinear regression analysis using GraphPad Prism software (San Diego,CA). Single point screening determinations were determined by comparing control current amplitudes at the end of the depolarizing pulses to maximally inhibited current amplitudes at inhibitor concentrations of 1 μM.