Supporting Information

Repurposing the Antihistamine Terfenadine for Antimicrobial Activity against *Staphylococcus aureus*

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**Contents:**

| Description                                      | Page   |
|--------------------------------------------------|--------|
| Experimental and analytical details for intermediates | S3-S15 |
| Transcription Profiling Gene Profile             | S16    |
| Scatter plot of LogP vs. MIC                     | S17    |
| Eurofin Panlabs hERG profiling data              | S18-S21|
| References                                       | S22    |
General Information:

Purity of all final compounds was confirmed by HPLC/MS analysis. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker AM 400 spectrometer (operating at 400 and 101 MHz respectively) or a Bruker AVIII spectrometer (operating at 500 and 126 MHz respectively) in CDCl$_3$ with 0.03% TMS as an internal standard or DMSO-$d_6$. The chemical shifts (δ) reported are given in parts per million (ppm) and the coupling constants (J) are in Hertz (Hz). The spin multiplicities are reported as s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet and m = multiplet. The LCMS analysis was performed on an Agilent 1200 RRL chromatograph with photodiode array UV detection and an Agilent 6224 TOF mass spectrometer. The chromatographic method utilized the following parameters: a Waters Acquity BEH C-18 2.1 x 50 mm, 1.7 μm column; UV detection wavelength = 214 nm; flow rate = 0.4ml/min; gradient = 5 - 100% acetonitrile over 3 minutes with a hold of 0.8 minutes at 100% acetonitrile; the aqueous mobile phase contained 0.15% ammonium hydroxide (v/v). The mass spectrometer utilized the following parameters: an Agilent multimode source which simultaneously acquires ESI+/APCI+; a reference mass solution consisting of purine and hexakis(1H, 1H, 3H-tetrafluoropropoxy) phosphazine; and a make-up solvent of 90:10:0.1 MeOH:Water:Formic Acid which was introduced to the LC flow prior to the source to assist ionization. The acronym MPLC is defined as medium performance liquid chromatography and refers to the automated Combiflash chromatography system (Teledyne, Lincoln, NE).

Scheme S1. Synthetic scheme for intermediate 8i.$^1$

![Scheme S1](image)

**Methyl 4-(1,3-dithian-2-yl)benzoate (13).** A flame dried vial was evacuated three times with argon and methyl 4-formylbenzoate (0.50 g, 3.05 mmol) was added with anhydrous CH$_2$Cl$_2$ (8.70 mL) followed by 1,3-propanedithiol (0.34 mL, 3.35 mmol). The reaction began to stir at rt for 1.5 h. The reaction was then cooled to 0 °C and the BF$_3$·OEt$_2$ (0.43 mL, 3.35 mmol) was added dropwise. The reaction was then warmed slowly to rt and stirred overnight. The reaction was then diluted with CH$_2$Cl$_2$ (15 mL) and quenched with saturated NaHCO$_3$ (15 mL) and the organic layer was dried with MgSO$_4$, filtered and adsorbed to silica and purified by MPLC (0 - 35% EtOAc:hexanes) to produce 13 (0.67 g, 2.63 mmol, 86% yield). $^1$H NMR (400 MHz, CDCl$_3$): δ 8.01 (d, $J$ = 8.4 Hz, 2H), 7.54 (d, $J$ = 8.3 Hz, 2H), 5.20 (s, 1H), 3.91 (s, 3H), 3.12 – 3.03 (m, 2H), 2.96 – 2.90 (m, 2H), 2.23 – 2.16 (m, 1H), 2.01 – 1.89 (m, 1H).
Methyl 4-(2-(3-chloropropyl)-1,3-dithian-2-yl)benzoate (14). To an oven-dried vial was added 13 (0.26 g, 1.01 mmol) and the vial was evacuated with argon 3 times. The dry THF (7 mL) was added and the reaction was cooled to -78 °C at and the NaHMDS (1.26 mL, 1.26 mmol) was added. After 30 minutes 1-chloro-3-iodopropane (0.53 mL, 5.03 mmol) was added. The reaction was then allowed to warm to rt and stirred for 18 h. The mixture was quenched with the addition of saturated NH₄Cl (10 mL) and extracted with EtOAc (3 x 15 mL). The organic layers were collected, dried with MgSO₄, filtered and adsorbed to silica and purified by MPLC (0 - 25% EtOAc:hexanes) to produce 14 (0.10 g, 0.31 mmol, 31% yield). "H NMR (400 MHz, CDCl₃): δ 8.07 – 8.03 (m, 2H), 8.01 – 7.98 (m, 2H), 3.93 (s, 3H), 3.41 (t, J = 6.4 Hz, 2H), 2.74 – 2.62 (m, 4H), 2.19 – 2.13 (m, 2H), 1.99 – 1.92 (m, 2H), 1.78 – 1.70 (m, 2H).

Methyl 4-(4-chlorobutanoyl)benzoate (8i). To a vial was added 14 (0.10 g, 0.31 mmol) and acetonitrile (1.5 mL) with water (0.2 mL). The bis(trifluoroacetoxy)iodobenzene (0.20 g, 0.46 mmol) was then added and the reaction stirred at rt for 1 h. The reaction was quenched with saturated NaHCO₃ (7 mL) then extracted with EtOAc (2 x 10 mL). The organic layers were collected and washed with water (2 x 8 mL) and then dried with MgSO₄, filtered and adsorbed to silica and purified by MPLC (0 - 25% EtOAc:hexanes) to produce 8i (0.051 g, 0.21 mmol, 69% yield). "H NMR (400 MHz, CDCl₃): δ 8.11 (d, J = 8.00 Hz, 2H), 8.00 (d, J = 8.6 Hz, 2H), 3.93 (s, 3H), 3.67 (t, J = 6.1 Hz, 2H), 2.22 (quintet, J = 6.3 Hz, 2H).

Scheme S2. Synthesis of intermediates to analogs 1o and 1p.

Methyl 2-(4-(4-hydroxybut-1-yn-1-yl)phenyl)-2-methylpropanoate (15). To a vial was added the methyl 2-(4-bromophenyl)-2-methylpropanoate (0.72 g, 2.78 mmol) and water (15 mL). The but-3-yn-1-ol (0.20 g, 0.21 mL, 2.78 mmol), copper(I) iodide (5.3 mg, 0.028 mmol), tetrakis(triphenylphosphine)palladium (0.16 g, 0.14 mmol) and pyrrolidine (0.30 g, 0.35 mL, 4.17 mmol) were all added and the vial was purged with argon for 20 min. The reaction then stirred at 70 °C for 30 minutes then allowed to cool to rt. The reaction was then extracted with diethyl ether (2 x 12 mL). The organic layers were combined and washed with water (20 mL) and brine (20 mL) then dried with MgSO₄, filtered and adsorbed to silica then purified by MPLC (0 - 35% EtOAc:hexanes) to produce the 15 (0.54 g, 2.21 mmol, 79% yield). "H NMR (500 MHz, CDCl₃): δ 7.37 (d, J = 8.6 Hz, 2H), 7.26 (d, J = 8.6 Hz, 2H), 3.81 (t, J = 6.2 Hz, 2H), 3.64 (s, 3H), 2.69 (t, J = 6.2 Hz, 2H), 1.79 (br s, 1H), 1.56 (s, 6H).
Methyl 2-methyl-2-(4-(4-((methylsulfonyl)oxy)but-1-yn-1-yl)phenyl)propanoate (16). To a vial was added the 17 (0.51 g, 2.06 mmol) and dry CH$_2$Cl$_2$ (15 mL). The methanesulfonyl chloride (0.47 g, 3.21 mL, 4.12 mmol) and pyridine (1.49 g, 2.04 mL, 25.0 mmol) were each added to the vial and the reaction stirred at rt for 16 h. The reaction was then diluted with CH$_2$Cl$_2$ (15 mL) and washed with 1% w/v sulfuric acid in water (3 x 25 mL), saturated NaHCO$_3$ (25 mL) and brine (25 mL). The organic layer was dried with MgSO$_4$, filtered and concentrated to produce 16 (0.60 g, 1.86 mmol, 90% yield). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.35 (d, $J$ = 8.6 Hz, 2H), 7.26 (d, $J$ = 8.6 Hz, 2H), 4.38 (t, $J$ = 6.8 Hz, 2H), 3.64 (s, 3H), 3.06 (s, 3H), 2.87 (t, $J$ = 6.8 Hz, 2H), 1.56 (s, 6H).

Methyl 2-(4-(4-(hydroxypyrrolophenyl)piperidin-1-yl)but-1-yn-1-yl)phenyl)-2-methyl propanoate (17). To a vial was added the 7 (0.53 g, 1.97 mmol), 16 (0.58 g, 1.79 mmol) and potassium carbonate (0.74 g, 5.38 mmol) with acetonitrile (10 mL). The reaction stirred at 70 °C for 18 h and cooled to rt and filtered to remove the potassium carbonate. The filtrate was adsorbed to silica gel and purified by reverse-phase MPLC (10 - 100% CH$_3$CN:water) to produce 17 (0.43 g, 0.88 mmol, 49% yield). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.49 – 7.46 (m, 4H), 7.34 – 7.27 (m, 6H), 7.25 – 7.15 (m, 4H), 3.64 (s, 3H), 3.03 – 2.97 (m, 2H), 2.68 – 2.63 (m, 2H), 2.59 – 2.54 (m, 2H), 2.48 – 2.40 (m, 1H), 2.14 – 2.06 (m, 2H), 1.63 (br s, 1H), 1.55 (s, 6H), 1.55 – 1.45 (m, 4H).

Methyl 2-(4-(4-(hydroxypyrrolophenyl)piperidin-1-yl)butanoyl)phenyl)-2-methyl propanoate (18). Followed procedure from Kawai et al. To a vial was added the 17 (0.074 g, 0.15 mmol). The mercuric oxide (1.49 mL, 0.045 mmol) was made into a 0.03 M solution in 4% w/v sulfuric acid and added to the starting material then heated to 55 °C and stirred for 3.5 h. The reaction turned a milky white color upon addition of the mercuric oxide solution. The reaction was removed from heat and diluted with saturated NaHCO$_3$ (10 mL) and extracted with CH$_2$Cl$_2$ (3 x 10 mL). The organic layers were combined and dried with MgSO$_4$, filtered and concentrated by reverse-phase MPLC (10 - 100% CH$_3$CN:water) to produce 18 (0.022 g, 0.042 mmol, 28% yield). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.93 – 7.91 (m, 2H), 7.48 – 7.45 (m, 4H), 7.42 – 7.39 (m, 2H), 7.30 – 7.26 (m, 4H), 7.19 – 7.14 (m, 2H), 3.63 (s, 3H), 2.96 – 2.88 (m, 4H), 2.44 – 2.34 (m, 3H), 2.08 (br s, 1H), 1.60 (s, 6H), 1.62 – 1.56 (m, 4H), 1.46 – 1.30 (m, 4H).

1-(Tert-butyl)-4-(4-chlorobutyl)benzene (10a). To a vial was added the 8a (0.27 g, 1.11 mmol) and triethylsilane (0.52 g, 0.71 mL, 4.46 mmol) with TFA (4 mL). The reaction stirred at 75 °C for 18 h then was cooled to rt and concentrated in vacuo. The residue was then dissolved in CH$_2$Cl$_2$ (5 mL) and washed with water (4 mL). The organic layer was collected and washed with water (5 mL), dried with MgSO$_4$, filtered and adsorbed to silica and purified by MPLC (0 - 40% EtOAc:hexanes) and fractions 4 and 5 were collected to produce 10a (0.16 g, 0.69 mmol, 62% yield) as an oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.32 (d, $J$ = 7.6 Hz, 2H), 7.12 (d, $J$ = 7.6 Hz, 2H), 3.56 (t, $J$ = 6.5 Hz, 2H), 2.62 (t, $J$ = 7.5 Hz, 2H), 1.87 – 1.74 (m, 4H), 1.32 (s, 9H).
1-(Tert-butyl)-4-(3-chloropropyl)benzene (10b). Same procedure as 21 using 8k (0.16 g, 0.71 mmol) and triethylsilane (0.33 g, 0.46 mL, 2.85 mmol) with TFA (4 mL). Purified by MPLC (0-40% EtOAc:hexanes) and fractions 4 and 5 were collected to produce 10b (0.13 g, 0.64 mmol, 89% yield) as an oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.32 (d, $J = 8.3$ Hz, 2H), 7.14 (d, $J = 8.2$ Hz, 2H), 3.54 (t, $J = 6.5$ Hz, 2H), 2.81–2.70 (m, 2H), 2.16–2.01 (m, 2H), 1.32 (s, 9H).

Synthesis of intermediates for analogs 2h and 2i.$^3$

(S)-1-(4-(Tert-butyl)phenyl)-4-chlorobutan-1-ol (19). Prepared according to a previously published procedure.$^3$ To a flame-dried vial was added dry THF (2 mL) and then cooled to 0 °C. The 1.0 M R-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborlidine (0.11 mL, 0.11 mmol) in THF was added followed by the 2.0 M borane-methyl sulfide complex (0.65 mL, 1.31 mmol) in THF. The reaction began to stir at 0 °C for 30 minutes. To another flame-dried vial was added the 1-(4-(tert-butyl)phenyl)-4-chlorobutan-1-one (0.25 g, 1.05 mmol) and this vial was evacuated with argon 3 times then dissolved in dry THF (5 mL) and the oxazaborlidine solution was added dropwise at 0 °C and the reaction was allowed to warm to rt stirred for 2 h. The reaction was quenched with MeOH (10 mL) extracted with EtOAc (20 mL) then was washed with 1.0 M HCl (3 x 25 mL). The EtOAc layer was dried with MgSO$_4$, filtered and concentrated to produce 19 (0.25 g, 1.03 mmol, 98% yield). $[\alpha]_D^{25}$ -24.0, (c 10, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.38 (d, $J = 8.4$ Hz, 2H), 7.28 (d, $J = 8.4$, 2H), 4.71–4.67 (m, 1H), 3.61–3.53 (m, 2H), 1.98–1.79 (m, 4H), 1.60 (br s, 1H), 1.32 (s, 9H).

(R)-1-(4-(tert-butyl)phenyl)-4-chlorobutan-1-ol (20). Prepared the same 19 with 1.0 M (S)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborlidine (0.11 mL, 0.11 mmol), 2.0 M borane-methyl sulfide complex (0.65 mL, 1.31 mmol) and 1-(4-(tert-butyl)phenyl)-4-chlorobutan-1-one (0.25 g, 1.05 mmol) to produce 20 (0.216 g, 0.897 mmol, 86% yield). $[\alpha]_D^{25}$ +23.1 (c 10, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.38 (d, $J = 8.4$ Hz, 2H), 7.28 (d, $J = 8.4$, 2H), 4.71–4.67 (m, 1H), 3.61–3.53 (m, 2H), 1.98–1.79 (m, 4H), 1.60 (br s, 1H), 1.32 (s, 9H).
(S)-1-(4-(tert-butyl)phenyl)-4-chlorobutyl acetate (21). To a vial was added the 19 (0.25 g, 1.03 mmol) and diethyl ether (5 mL). The triethylamine (0.22 mL, 1.55 mmol) was added followed by the acetyl chloride (0.073 mL, 1.03 mmol) and the reaction began to stir at rt. A white precipitate formed immediately and water (5 mL) was added to the reaction after 2 h and the ether layer was extracted. The aqueous was extracted again with diethyl ether (2 x 5 mL) and the combined organics were dried with MgSO₄, filtered and concentrated to produce 21 (0.25 g, 0.88 mmol, 86% yield). [α]D²⁵ -42.11, (c 10, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃): δ 7.36 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 5.78 – 5.73 (m, 1H), 3.53 (t, J = 6.4 Hz, 2H), 2.06 (s, 3H), 2.02 – 1.68 (m, 4H), 1.31 (s, 9H).

(R)-1-(4-(tert-butyl)phenyl)-4-chlorobutyl acetate (22). Prepared the same as 21 with 20 (0.22 g, 0.90 mmol) and diethyl ether (4.5 mL), triethylamine (0.19 mL, 1.35 mmol) and acetyl chloride (0.064 mL, 0.90 mmol) to produce 22 (0.25 g, 0.88 mmol, 98% yield). [α]D²⁵ +54.57, (c 10, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃): δ 7.36 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 5.78 – 5.73 (m, 1H), 3.53 (t, J = 6.4 Hz, 2H), 2.06 (s, 3H), 2.02 – 1.68 (m, 4H), 1.31 (s, 9H).

(S)-1-(4-(Tert-butyl)phenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butyl acetate (23). To a vial was added the 7 (0.15 g, 0.58 mmol), 21 (0.20 g, 0.69 mmol) and potassium carbonate (0.32 g, 2.31 mmol) in acetonitrile (10 mL). The reaction stirred at 70 °C for 18 h and was then cooled to rt and filtered. The filtrate was then diluted with CH₂Cl₂ (10 mL) and washed with water (10 mL) and brine (10 mL). The organic layers were combined, dried with MgSO₄, filtered and purified by reverse-phase MPLC (10 - 100% CH₂CN:water) to produce 23 (0.14 g, 0.26 mmol, 46% yield) as a brown oil. ¹H NMR (400 MHz, CDCl₃): δ 7.48 – 7.45 (m, 4H), 7.35 – 7.14 (m, 10H), 5.73 – 5.68 (m, 1H), 2.93 – 2.87 (m, 2H), 2.46 – 2.37 (m, 1H), 2.87 (t, J = 7.7
Hz, 2H), 2.11 (br s, 1H), 2.04 (s, 3H), 1.95 – 1.84 (m, 3H), 1.80 – 1.72 (m, 1H), 1.53 – 1.38 (m, 6H), 1.29 (s, 9H).

(R)-1-(4-(Tert-butyl)phenyl)-4-(4-(hydroxydiphenylmethyl)piperid-1-yl)butyl acetate (24). Prepared using the same procedure as 23 with 7 (0.20 g, 0.73 mmol), 22 (0.25 g, 0.88 mmol) and potassium carbonate (0.41 g, 2.93 mmol) in acetonitrile (10 mL) to 24 (0.24 g, 0.46 mmol, 63% yield) as a brown oil. 1H NMR (400 MHz, CDCl3): δ 7.48 – 7.45 (m, 4H), 7.35 – 7.14 (m, 10H), 5.73 – 5.68 (m, 1H), 2.93 – 2.87 (m, 2H), 2.46 – 2.37 (m, 1H), 2.87 (t, J = 7.7 Hz, 2H), 2.11 (br s, 1H), 2.04 (s, 3H), 1.95 – 1.84 (m, 3H), 1.80 – 1.72 (m, 1H), 1.53 – 1.38 (m, 6H), 1.29 (s, 9H).

2-(3-(Tert-butyl)phenyl)ethanol (25). To a vial was added the 1-bromo-3-(tert-butyl)benzene (0.11 g, 0.50 mmol) and dry THF (7 mL). The reaction was then cooled to -78 °C and the 2.5 M BuLi in hexanes (0.22 mL, 0.55 mmol) was added dropwise and the reaction stirred for 30 minutes at -78 °C. The ethylene oxide (0.50 mL, 1.26 mmol) (2.5 - 3.3M solution in THF) was added dropwise and the reaction stirred for 10 minutes at -78 °C then was allowed to warmed to rt and stirred for 1 h. The reaction was then quenched with 1.0 M aqueous HCl (2 mL) and extracted with EtOAc (3 x 5 mL). The EtOAc layers were combined, concentrated and purified by reverse-phase MPLC (10 - 100% CH3CN:water) to produce 25 (0.035 g, 0.20 mmol, 39% yield). 1H NMR (400 MHz, CDCl3): δ 7.31 – 7.27 (m, 3H), 7.10 - 7.07 (m, 1H), 3.90 (t, J = 6.6 Hz, 2H), 2.91 (t, J = 6.5 Hz, 2H), 1.52 (br s, 1H), 1.36 (s, 9H).

3-(Tert-butyl)phenethyl-4-methylbenzenesulfonate (10e). To a vial was added 25 (0.035 g, 0.20 mmol), triethylamine (0.082 mL, 0.59 mmol) and CH2Cl2 (2 mL) followed by p-toluene sulfonyl chloride (0.056 g, 0.29 mmol). The reaction began to stir at rt for 20 h and was then diluted with saturated NaHCO3 (5 mL) and extracted with EtOAc (3 x 5 mL). The organic layers were combined then dried with MgSO4, filtered and concentrated then purified by reverse-phase MPLC (10 - 100% CH3CN:water) to provide 10e (0.060 g, 0.18 mmol, 92% yield). 1H NMR
(400 MHz, CDCl₃): δ 7.70 (d, J = 8.4 Hz, 2H), 7.30 – 7.01 (m, 5H), 6.92 (m, 1H) 4.22 (t, J = 7.2 Hz, 2H), 2.96 (t, J = 7.2 Hz, 2H), 2.43 (s, 3H), 1.29 (s, 9H).

2-(Tert-butyl)phenyl trifluoromethanesulfonate (26). To a vial was added the 2-(tert-butyl)phenol (1.0 mL, 6.51 mmol) and CH₂Cl₂ (4 mL) followed by pyridine (1.05 mL, 13.02 mmol). The reaction was then cooled to 0 °C and the triflic anhydride (1.32 mL, 7.81 mmol) was added dropwise and the reaction stirred for 2 h. The reaction was then allowed to warm to rt and was diluted with CH₂Cl₂ (20 mL) and quenched with 1.0 M HCl (20 mL). The organic layer was collected and washed with saturated NaHCO₃ (20 mL) and brine (20 mL). The organic layer was then dried (MgSO₄), filtered and adsorbed to silica and purified by MPLC (0 - 25% EtOAc:hexanes) to produce 26 (1.66 g, 5.88 mmol, 90% yield). ¹H NMR (400 MHz, CDCl₃): δ 7.49 – 7.46 (m, 1H), 7.37 – 7.34 (m, 1H), 7.31 – 7.27 (m, 2H), 1.43 (s, 9H).

2-(2-(Tert-butyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (27). To a flame-dried vial was added activated molecular sieves and 26 (0.48 g, 1.68 mmol) and 1,1'-bis(diphenyl phosphino)ferrocenedichloropalladium(II) (0.042 g, 0.050 mmol). The vial was evacuated with argon three times and then anhydrous dioxane (1 mL), triethylamine (0.70 mL, 5.1 mmol) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.73 mL, 5.1 mmol) were added via syringe. The reaction stirred at reflux for 2 h and was then removed from heat and diluted with water (5 mL) then extracted with CH₂Cl₂ (3 x 5 mL). The organic layers were combined then washed again with water (3 x 10 mL). The organic layers were combined and dried with MgSO₄, filtered and concentrated. The hexanes layer was then concentrated to produce 27 (0.093 g, 0.36 mmol, 86% yield). ¹H NMR (400 MHz, CDCl₃): δ 7.45 (dd, J = 7.2 Hz, 1.2 Hz, 1H), 7.41 – 7.39 (m, 1H), 7.29 (td, J = 7.6 Hz, 2.0 Hz, 1H), 7.14 (td, J = 7.6 Hz, 2.0 Hz, 1H), 1.41 (s, 9H), 1.38 (s, 12H).

1-Bromo-2-(tert-butyl)benzene (28). To a vial was added the 27 (0.18 g, 0.69 mmol) and MeOH (5 mL). The copper (II) bromide (0.46 g, 2.08 mmol) was then dissolved in water (5 mL) and added to the reaction then stirred at 80 °C for 24 h. The reaction was then removed from heat and diluted with water (5 mL) and extracted with EtOAc (3 x 10 mL). The EtOAc layers were combined and dried with MgSO₄, filtered and concentrated to produce 28 (0.10 g, 0.48
mmol, 70% yield) as a brown liquid. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.59 (dd, $J = 8.0$ Hz, 1.6 Hz, 1H), 7.44 (dd, $J = 8.0$ Hz, 1.6 Hz, 1H), 7.24 (td, $J = 7.6$ Hz, 2.0 Hz, 1H), 7.02 (td, $J = 7.6$ Hz, 2.0 Hz, 1H), 1.51 (s, 9H).

![28](image) → ![29](image)

2-(2-(Tert-butyl)phenyl)ethanol (29). Prepared by same method as 25 using 28 (0.15 g, 0.69 mmol), dry THF, 2.5 M BuLi in hexanes (0.30 mL, 0.76 mmol) and then ethylene oxide (0.69 mL, 1.72 mmol) (2.5 - 3.3M solution in THF) to produce 29 (0.018 g, 0.10 mmol, 15% yield) as a clear oil. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.43 - 7.37 (m, 1H), 7.23 - 7.19 (m, 1H), 7.18 - 7.14 (m, 2H), 3.90 (t, $J = 7.6$ Hz, 2H), 3.19 (t, $J = 7.6$ Hz, 2H), 1.52 (br s, 1H), 1.44 (s, 9H).

![29](image) → ![10f](image)

2-(Tert-butyl)phenethyl-4-methylbenzenesulfonate (10f). Prepared according to same procedure as 10e using 29 (0.018 g, 0.10 mmol), triethylamine (0.042 mL, 0.30 mmol) and CH$_2$Cl$_2$ (2 mL) followed by p-toluenesulfonyl chloride (0.029 g, 0.15 mmol) to provide 10f (0.022 g, 0.066 mmol, 66% yield) and a clear oil. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.76 (d, $J = 8.0$ Hz, 2H), 7.37 - 7.31 (m, 3H), 7.17 - 7.04 (m, 3H), 4.19 (t, $J = 7.6$ Hz, 2H), 3.25 (t, $J = 7.6$ Hz, 2H), 2.44 (s, 3H), 1.33 (s, 9H).

![35](image) → ![30](image)

2-(6-(Tert-butyl)pyridin-3-yl)ethanol (30). Prepared by same method as 25 with 5-bromo-2-(tert-butyl)pyridine (0.30 g, 1.42 mmol), dry THF (10 mL), 2.5 M BuLi in hexanes (0.623 mL, 1.557 mmol) and ethylene oxide (1.415 mL, 3.54 mmol) (2.5 - 3.3M solution in THF) to produce 30 (0.21 g, 1.18 mmol, 83% yield). $^1$H NMR (400 MHz, CDCl$_3$): δ 8.40 (br d, $J = 2.4$ Hz, 1H), 7.48 (dd, $J = 8.2$ Hz, 2.4 Hz, 1H), 7.26 (dd, $J = 8.2$ Hz, 0.8 Hz, 1H), 3.85 (br t, $J = 6.0$ Hz, 2H), 2.82 (t, $J = 6.5$ Hz, 2H), 2.29 (br s, 1H), 1.33 (s, 9H).

![30](image) → ![10l](image)

2-(6-(Tert-butyl)pyridin-3-yl)ethyl-4-methylbenzenesulfonate (10l). Prepared by same method as 10e using 30 (0.21 g, 1.18 mmol), triethylamine (0.49 mL, 3.53 mmol) and CH$_2$Cl$_2$ (2 mL)
followed by p-toluenesulfonyl chloride (0.34 g, 1.77 mmol) to provide 10l (0.26 g, 0.78 mmol, 66 % yield). $^1$H NMR (400 MHz, CDCl$_3$; δ 8.29 (br d, $J = 2.4$ Hz, 1H), 7.69 (d, $J = 8.3$ Hz, 2H), 7.40 (dd, $J = 8.2$ Hz, 2.4 Hz, 1H), 7.30 – 7.27 (m, 2H), 7.23 (dd, $J = 8.2$ Hz, 0.8 Hz, 1H), 4.19 (t, $J = 6.9$ Hz, 2H), 2.92 (t, $J = 6.8$ Hz, 2H), 2.43 (s, 3H), 1.34 (s, 9H).

Synthesis of intermediates for analog 3o.$^4$

3-((Phenylsulfonyl)methylene)oxetane (31). Method adapted from Wuitschuk et al.$^4$. To an oven-dried vial was added (methylsulfonyl) benzene (0.57 g, 3.65 mmol) and the vial was evacuated with argon three times. The dry THF (17 mL) was added to the vial under argon and the reaction was cooled to 0 °C. The 2.5 M BuLi in hexanes (3.21 mL, 8.03 mmol) was added dropwise at 0 °C and the reaction stirred for 45 minutes. The diethyl chlorophosphate (0.53 mL, 3.65 mmol) was then added at 0 °C and the reaction stirred for an additional 30 minutes. The reaction was then cooled to -78 °C and the oxetan-3-one (0.33 mL, 5.15 mmol) was then added dropwise and the reaction stirred for an additional 2 h. The reaction was then allowed to warmed to rt and filtered through a silica plug and concentrated onto silica then purified by MPLC (0 - 40% EtOAc:hexanes) to provide 31 (0.58 g, 2.75 mmol, 75% yield). $^1$H NMR (400 MHz, CDCl$_3$; δ 7.91 – 7.87 (m, 2H), 7.69 – 7.64 (m, 1H), 7.60 – 7.55 (m, 2H), 6.12 (quintet, $J = 2.3$ Hz, 1H), 5.66 – 5.63 (m, 2H), 5.30 – 5.27 (m, 2H).

2-(4-(3-((Phenylsulfonyl)methyl)oxetan-3-y1)phenyl)ethanol (32). Method adapted from Wuitschuk et al.$^4$. To a microwave vial was added the chloro(1,5-cyclooctadiene)rhodium(I) dimer (0.012 g, 0.025 mmol) and 1,4-dioxane (10 mL). The 1.5 M aqueous KOH (0.50 mL, 0.75 mmol) was then added and the reaction stirred for 1 minute at rt. Then the 4-(2-hydroxyethyl) phenylboronic acid (0.10 g, 0.62 mmol) and 31 (0.052 g, 0.25 mmol) in 1 mL dioxane was added then the reaction stirred for 30 minutes at 100 °C in the microwave reactor. The reaction was then cooled to rt and diluted with EtOAc (20 mL) and washed with 1.0 M HCl (20 mL). The aqueous layer was further extracted with EtOAc (3 x 15 mL) and the organic layers were combined, dried with MgSO$_4$, filtered, concentrated then purified by reverse-phase MPLC (10 - 100% CH$_3$CN:water) to produce 32 (0.063 g, 0.19 mmol, 76% yield). $^1$H NMR (400 MHz,
CDCl$_3$; $\delta$ 7.55–7.52 (m, 2H), 7.50–7.46 (m, 1H), 7.36–7.31 (m, 2H), 7.09 (d, $J = 8.4$ Hz, 2H), 7.01 (d, $J = 8.3$ Hz, 2H), 5.03 (d, $J = 6.4$ Hz, 2H), 4.93 (d, $J = 6.4$ Hz, 2H), 4.03 (s, 2H), 3.82 (t, $J = 7.3$ Hz, 2H), 2.80 (t, $J = 7.3$ Hz, 2H).

4-(3-((Phenylsulfonyl)methyl)oxetan-3-yl)phenethyl-4-methylbenzenesulfonate (33). Prepared by the same method as 10e using 32 (0.10 g, 0.31 mmol), triethylamine (0.13 mL, 0.94 mmol) and CH$_2$Cl$_2$ (2 mL) followed by p-toluenesulfonyl chloride (0.089 g, 0.47 mmol) to produce 33 (0.041 g, 0.084 mmol, 27% yield). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.75 (d, $J = 8.3$ Hz, 2H), 7.57–7.46 (m, 4H), 7.36–7.32 (m, 4H), 7.02–6.96 (m, 3H), 5.00 (d, $J = 6.4$ Hz, 2H), 4.93 (d, $J = 6.4$ Hz, 2H), 4.17 (t, $J = 7.0$ Hz, 2H), 4.01 (s, 2H), 2.90 (t, $J = 7.0$ Hz, 2H), 2.45 (s, 3H).

(1-(4-(3-((Phenylsulfonyl)methyl)oxetan-3-yl)phenethyl)piperidin-4-yl)diphenylmethanol (34). Method C: 33 (0.041 g, 0.084 mmol) and 7 (0.025 g, 0.093 mmol), triethylamine (0.018 mL, 0.13 mmol) and acetonitrile (1.5 mL). Purified by reverse-phase MPLC (10 - 100% CH$_3$CN:water) to produce 34 (0.024 g, 0.041 mmol, 49% yield). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.53–7.43 (m, 6H), 7.33–7.27 (m, 7H), 7.21–7.16 (m, 2H), 7.04 (d, $J = 8.2$ Hz, 2H), 6.96 (d, $J = 8.2$ Hz, 2H), 5.02 (d, $J = 6.4$ Hz, 2H), 4.92 (d, $J = 6.4$ Hz, 2H), 4.01 (s, 2H), 3.08–3.02 (m, 2H), 2.74–2.69 (m, 2H), 2.56–2.44 (m, 3H), 2.10–2.02 (m, 2H), 1.60–1.50 (m, 5H).

4-(4-Benzoylpiperidin-1-yl)-1-(4-(tert-butyl)phenyl)butan-1-one (35). To a vial was added the 8a (0.060 g, 0.25 mmol) and potassium iodide (0.063 g, 0.38 mmol) with acetonitrile (2 mL). The reaction stirred at 85 °C for 1 h then the phenyl(piperidin-4-yl)methane (0.050 g, 0.26 mmol) along with potassium carbonate (0.052 g, 0.38 mmol) was added. The reaction was then
heated back to 85 °C for 48 h. The reaction was cooled to rt and diluted with water (15 mL) then extracted with EtOAc (3 x 15 mL). The EtOAc layers were combined, dried with MgSO₄, filtered and adsorbed to silica then purified by reverse-phase MPLC (10 - 100% CH₃CN:water) to produce 35 (0.026 g, 0.066 mmol, 26% yield). ^1H NMR (400 MHz, CDCl₃): δ 7.95 – 7.90 (m, 4H), 7.57 – 7.53 (m, 1H), 7.49 – 7.44 (m, 4H), 3.27 – 3.18 (m, 1H), 3.03 – 2.96 (m, 4H), 2.44 (t, J = 7.04 Hz, 2H), 2.13 – 2.06 (m, 2H), 1.98 – 1.91 (m, 2H), 1.85 – 1.76 (m, 4H), 1.34 (s, 9H).

4-(4-Benzylpiperidin-1-yl)-1-(4-(tert-butyl)phenyl)butan-1-one (36). Method C: 4-benzylpiperidine (0.25 mL, 1.42 mmol), 8a (0.41 g, 1.71 mmol), acetonitrile (15 mL) and triethylamine (0.30 mL, 2.13 mmol). Purified by reverse-phase MPLC (10 - 100% CH₃CN:water) to produce 36 (0.29 g, 0.77 mmol, 54% yield). ^1H NMR (400 MHz, CDCl₃): δ 7.91 (d, J = 8.6 Hz, 2H), 7.47 (d, J = 8.5 Hz, 2H), 7.29 – 7.24 (m, 2H), 7.20 – 7.16 (m, 1H), 7.14 – 7.11 (m, 2H), 2.96 (t, J = 7.2 Hz, 2H), 2.90 – 2.84 (m, 2H), 2.50 (d, J = 7.0 Hz, 2H), 2.36 (t, J = 7.3 Hz, 2H), 1.96 – 1.82 (m, 4H), 1.63 – 1.56 (m, 2H), 1.53 – 1.46 (m, 1H), 1.34 (s, 9H), 1.28 – 1.18 (m, 2H).

1-Benzhydrylpiperazine (37). Followed previously published procedure.⁵ To a vial was added the diphenylmethanol (0.32 g, 1.73 mmol) and CH₂Cl₂ (2 mL). The thionyl chloride (0.15 mL, 2.08 mmol) was added dropwise the reaction stirred at rt for 4.5 h then was concentrated. The residue was dissolved in acetonitrile (2 mL) and piperazine (0.75 g, 8.66 mmol). The reaction was stirred at 70 °C for 16 h and was allowed to cool to rt then concentrated. The residue was diluted with CH₂Cl₂ (15 mL) and washed with 1.0 N NaOH in water (15 mL). The organic layer was dried with MgSO₄, filtered and concentrated to produce 37 (0.43 g, 1.73 mmol, 98% yield) as a yellow solid. ^1H NMR (400 MHz, CDCl₃) δ 7.44 - 7.38 (m, 4H), 7.31 - 7.24 (m, 4H), 7.21 - 7.14 (m, 2H), 4.21 (s, 1H), 2.88 (t, J = 4.9 Hz, 4H), 2.35 (s, 4H).
4-(4-Benzhydrylpiperezin-1-yl)-1-(4-(tert-butyl)phenyl)butan-1-one (38). Method A: 37 (0.086 g, 0.34 mmol), 8a (0.077 g, 0.33 mmol), sodium bicarbonate (0.033 g, 0.39 mmol) with water:2-butanone (5 mL, 1:5). The reaction was purified by reverse-phase MPLC (10 - 100% CH$_3$CN:water) to produce 38 (0.084 g, 0.19 mmol, 57% yield) as a colorless oil. $^1$H NMR (500 MHz, CDCl$_3$): δ 7.94 - 7.84 (m, 2H), 7.49 - 7.43 (m, 2H), 7.43 - 7.35 (m, 4H), 7.30 - 7.20 (m, 4H), 7.20 - 7.12 (m, 2H), 4.19 (s, 1H), 2.96 (t, J = 7.2 Hz, 2H), 2.53 - 2.31 (m, 9H), 1.97 - 1.83 (m, 3H), 1.34 (s, 9H).

4-(Diphenylmethylene)piperidine (39). To a vial was added the 7 (0.51 g, 1.92 mmol) and TFA (4 mL). The reaction stirred at 75 °C for 24 h and was then cooled to rt and concentrated in vacuo. The residue was stirred in aqueous 1.0 M NaOH (15 mL) then extracted with CH$_2$Cl$_2$ (3 x 15 mL). The organic layers were combined and washed with water (15 mL), dried with MgSO$_4$, filtered and concentrated then purified by reverse-phase MPLC (10 - 100% CH$_3$CN:water) to produce 39 (0.30 g, 1.19 mmol, 62% yield). $^1$H NMR (400 MHz, CDCl$_3$): δ 7.34 – 7.28 (m, 4H), 7.25 – 7.20 (m, 2H), 7.18 – 7.14 (m, 4H), 2.96 – 2.92 (m, 4H), 2.37 – 2.33 (m, 4H), 1.75 (br s, 1H).

1-(4-(Tert-butyl)phenyl)-4-(4-(diphenylmethylene)piperidin-1-yl)butan-1-one (40). Method C: 39 (0.048 g, 0.193 mmol), 8a (0.055 g, 0.23 mmol), acetonitrile (5 mL) and triethylamine (0.29 mL, 0.289 mmol). Purified by reverse-phase MPLC (10 - 100% CH$_3$CN:water) to produce 40 (0.040 g, 0.089 mmol, 46% yield). $^1$H NMR (400 MHz, CDCl$_3$): δ 7.96 – 7.82 (m, 2H), 7.54 – 7.41 (m, 2H), 7.31 – 7.22 (m, 4H), 7.22 – 7.15 (m, 2H), 7.14 – 7.05 (m, 4H), 2.98 (t, J = 7.2 Hz, 2H), 2.58 – 2.45 (m, 3H), 2.45 – 2.36 (m, 2H), 2.36 – 2.30 (m, 3H), 1.99 – 1.85 (m, 4H), 1.34 (s, 9H).
4-Benzhydrylpiperidine (41). Followed the reported procedure from Edgar et al. To a vial was added the 7 (0.025 g, 0.094 mmol) and sodium borohydride (0.035 g, 0.94 mmol) and the solids were mixed homogenously. A vial containing TFA (1 mL) was then cooled to 0 °C. The solid mixture was added slowly portionwise to the TFA. After 45 min the reaction was concentrated and the residue was dissolved in CH$_2$Cl$_2$ (10 mL) and washed with 1.0 M NaOH (10 mL). The organic layer was then dried with MgSO$_4$, filtered and concentrated to produce pure 41 (0.022 g, 0.089 mmol, 95% yield) as a white solid. 1H NMR (400 MHz, CDCl$_3$) δ 7.32 - 7.22 (m, 7H), 7.20 - 7.13 (m, 3H), 3.53 (d, J = 11.1 Hz, 1H), 3.25 (m, 2H), 2.76 (td, J = 12.9, 2.8 Hz, 2H), 2.29 (m, 1H), 1.74 - 1.61 (m, 2H), 1.47 - 1.26 (m, 2H).

4-(4-Benzhydrylpiperidin-1-yl)-1-(4-(tert-butyl)phenyl)butan-1-one (42). To a vial was added the 41 (0.10 g, 0.40 mmol) and potassium carbonate (0.22 g, 1.59 mmol) in acetonitrile (10 mL). 8a (0.11 g, 0.48 mmol) was then added and the reaction stirred at 85 °C for 20 h. The reaction was then concentrated and diluted with EtOAc (10 mL) and washed with NaHCO$_3$ (10 mL). The organic layer was dried with MgSO$_4$, filtered and concentrated then purified by RP MPLC (10 - 100% CH$_3$CN:water) to produce 42 (0.037 g, 0.081 mmol, 20% yield). 1H NMR (400 MHz, CDCl$_3$) δ 7.77 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H), 7.17 - 7.08 (m, 8H), 7.07 - 6.96 (m, 2H), 3.35 (d, J = 10.9 Hz, 1H), 2.83 (t, J = 7.1 Hz, 2H), 2.76 (br s, 2H), 2.28 (br s, 2H), 2.04 - 1.89 (m, 1H), 1.88 - 1.71 (m, 4H), 1.51 - 1.33 (m, 2H), 1.21 (s, 9H), 1.16 - 1.03 (m, 2H).
Figure S1. Gene expression profile for terfenadine and other common antimicrobial conditions.
Chart S1. Scatter plot of LogP vs. MIC values.
Analog Key

4g = KSC-381-073

6 = KSC-381-082

### Experimental Results

| Cat # | Assay Name     | Batch | Spec. Rep | Conc. | % Inh  | IC<sub>50</sub> | K<sub>i</sub> | nH | R   |
|-------|----------------|-------|-----------|-------|--------|----------------|--------------|----|-----|
|       | Potassium Channel hERG | 350355 | num 1     | 10 µM | 105    | 0.21 µM       | 0.17 µM     | 1.19|     |
|       |                |       | num 1     | 3 µM  | 96     |                |              |     |     |
|       |                |       | num 1     | 1 µM  | 69     |                |              |     |     |
|       |                |       | num 1     | 0.3 µM| 66     |                |              |     |     |
|       |                |       | num 1     | 0.1 µM| 32     |                |              |     |     |
|       |                |       | num 1     | 0.03 µM| 13     |                |              |     |     |
|       |                |       | num 1     | 10 nM | -7     |                |              |     |     |
|       |                |       | num 1     | 3 nM  | 12     |                |              |     |     |
|       |                |       | num 1     | 1 nM  | 6      |                |              |     |     |
|       |                |       | num 1     | 0.3 nM| 10     |                |              |     |     |

| Cat # | Assay Name     | Batch | Spec. Rep | Conc. | % Inh  | IC<sub>50</sub> | K<sub>i</sub> | nH | R   |
|-------|----------------|-------|-----------|-------|--------|----------------|--------------|----|-----|
|       | Potassium Channel hERG | 350355 | num 1     | 10 µM | 100    | 0.14 µM       | 0.11 µM     | 0.74|     |
|       |                |       | num 1     | 3 µM  | 96     |                |              |     |     |
|       |                |       | num 1     | 1 µM  | 75     |                |              |     |     |
|       |                |       | num 1     | 0.3 µM| 57     |                |              |     |     |
|       |                |       | num 1     | 0.1 µM| 54     |                |              |     |     |
|       |                |       | num 1     | 0.03 µM| 25     |                |              |     |     |
|       |                |       | num 1     | 10 nM | 0      |                |              |     |     |
|       |                |       | num 1     | 3 nM  | 2      |                |              |     |     |
|       |                |       | num 1     | 1 nM  | -1     |                |              |     |     |
|       |                |       | num 1     | 0.2 nM| 3      |                |              |     |     |
Response Curves

Assay: 265900 - 1 Potassium Channel hERG

| Compound Name       | IC_{50}   | K_{i}  | n_{H} |
|---------------------|-----------|--------|-------|
| KSC-381-073 (1179706) | 0.21 μM  | 0.17 μM | 1.19  |
| Atemizole           | 5.37 nM   | 4.40 nM | 0.70  |
Response Curves

Assay: 265600 - 1 Potassium Channel hERG

| Compound Name       | IC_{50}  | K_d  | n_H |
|---------------------|----------|------|-----|
| KSC-381-082 (1179707) | 0.14 μM  | 0.11 μM | 0.74 |
| Astemizole          | 5.37 nM  | 4.40 nM | 0.70 |
## Methods

**265900 Potassium Channel hERG**

| Source: | Human recombinant HEK-293 cells |
|---------|----------------------------------|
| Vehicle: | 1.00% DMSO                      |
| Incubation Time/Temp: | 60 minutes @ 25°C |
| Incubation Buffer: | 10 mM HEPES, pH 7.4, 0.1% BSA, 5 mM KCl, 0.8 mM MgCl₂, 130 mM NaCl, 1 mM EGTA, 10 mM Glucose |
| Kd: | 6.80 nM * |

| Ligand: | 1.50 nM [³H] Astemizole |
|---------|-------------------------|
| Non-Specific Ligand: | 10.0 μM Astemizole |
| Specific Binding: | 90% * |
| Quantitation Method: | Radioligand Binding |
| Significance Criteria: | ≥50% of max stimulation or inhibition |
| Bmax: | 6.30 pmole/mg Protein * |
References:

(1) DeMartino, J. K.; Hwang, I.; Connelly, S.; Wilson, I. A.; Boger, D. L. Asymmetric synthesis of inhibitors of glycinamide ribonucleotide transformylase. *J. Med. Chem.* 2008, 51, 5441-5448.

(2) Kawai, S. H.; Hambalek, R. J.; Just, G. A facile synthesis of an oxidation product of terfenadine. *J. Org. Chem.* 1994, 59, 2620-2622.

(3) Zhang, M. Q.; ter Laak, A. M.; Timmerman, H. Structure-activity relationships within a series of analogues of the histamine H1-antagonist terfenadine. *Eur. J. Med. Chem.* 1993, 28, 165-173.

(4) Wuitschik, G.; Carreira, E. M.; Wagner, B. R.; Fischer, H.; Parrilla, I.; Schuler, F.; Rogers-Evans, M.; Müller, K. Oxetanes in drug discovery: structural and synthetic insights. *J. Med. Chem.* 2010, 53, 3227-3246.

(5) Lee, J.; Kang, S.-U.; Lim, J.-O.; Choi, H.-K.; Jin, M.-k.; Toth, A.; Pearce, L. V.; Tran, R.; Wang, Y.; Szabo, T.; Blumberg, P. M. N-[4-(Methylsulfonylamino)benzyl]thiourea analogues as vanillloid receptor antagonists: analysis of structure-activity relationships for the 'C-Region'. *Bioorg. Med. Chem.* 2004, 12, 371-385.

(6) Edgar, D. M.; Hangauer, D. G.; Leighton, H. J.; Mignot, E. J. M.; PCT patent WO2003032912A2, 2003