Supporting Information

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

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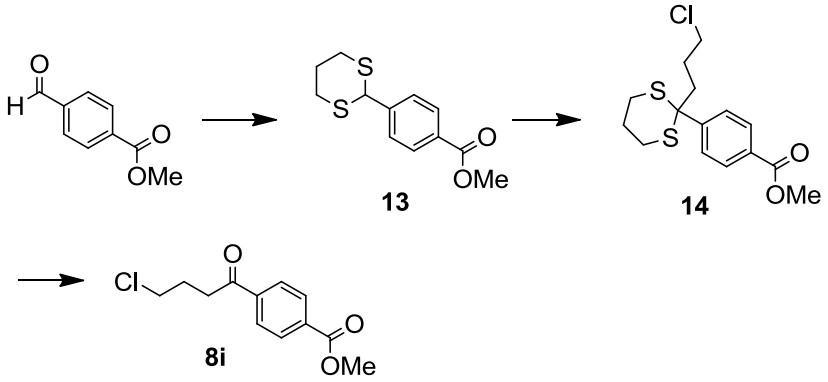
General Information:

Purity of all final compounds was confirmed by HPLC/MS analyis. ^{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]

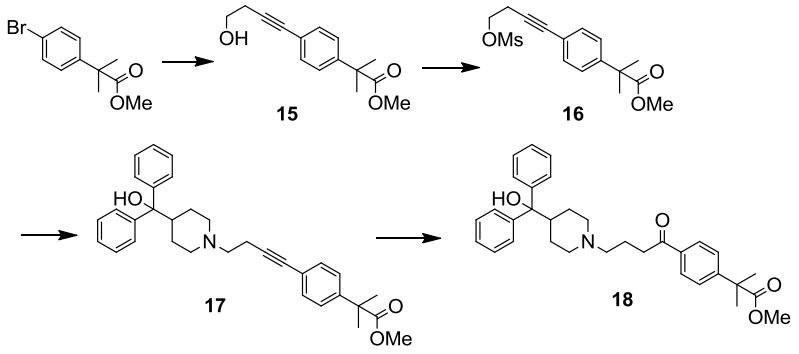


Methyl 4-(1,3-dithian-2-yl)benzoate (13). A flame dried vial was evacuated three times with argon and methyl 4-formylbenzoate (0.50 g, 3.05 mmol) was added with anhydrous CH_2Cl_2 (8.70 mL) followed by 1,3-propanedithiol (0.34 mL, 3.35 mmol). The reaction began to stir at rt for 1.5 h. The reaction was then cooled to 0 °C and the $BF_3{\cdot}OEt_2$ (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_2Cl_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 NH_4Cl (10 mL) and extracted with EtOAc (3 x 15 mL). The organic layers were collected, dried with $MgSO_4$, filtered and adsorbed to silica and purified by MPLC (0 - 25% EtOAc:hexanes) to produce **14** (0.10 g, 0.31 mmol, 31% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 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 $NaHCO_3$ (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 $MgSO_4$, filtered and adsorbed to silica and purified by MPLC (0 - 25% EtOAc:hexanes) to produce **8i** (0.051 g, 0.21 mmol, 69% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 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), 3.19 (t, *J* = 6.1 Hz, 2H), 2.22 (quintet, *J* = 6.3 Hz, 2H).

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

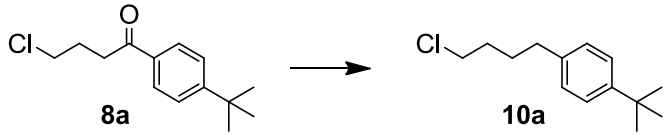


Methyl 2-(4-(4-hydroxybut-1-yn-1-yl)phenyl)-2-methylpropanoate (15). To a vial was added the methyl 2-(4-bromophenyl)-2-methylpropanoate (0.72 g, 2.78 mmol) and water (15 mL). The but-3-yn-1-ol (0.20 g, 0.21 mL, 2.78 mmol), copper(I) iodide (5.3 mg, 0.028 mmol), tetrakis (triphenylphosphine)palladium (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 $MgSO_4$, 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). ^{1}H NMR (500 MHz, $CDCl_3$): 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_2Cl_2 (15 mL). The methanesulfonyl chloride (0.47 g, 0.32 mL, 4.12 mmol) and pyridine (1.49 g, 1.50 mL, 18.5 mmol) were each added to the vial and the reaction stirred at rt for 16 h. The reaction was then diluted with CH_2Cl_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, 1.86mmol, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 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).

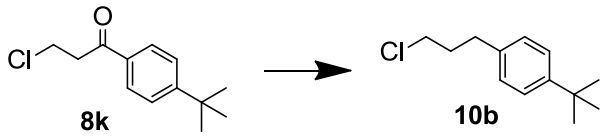
Methyl 2-(4-(4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)but-1-yn-1-yl)phenyl)-2-methyl propanoate (17). To a vial was added the **7** (0.53 g, 1.97 mmol), **16** (0.58 g, 1.79 mmol) and potassium carbonate (0.74 g, 5.38 mmol) with acetonitrile (10 mL). The reaction stirred at 70 °C for 18 h and cooled 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_3CN:water) to produce **17** (0.43 g, 0.88 mmol, 49% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 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-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butanoyl)phenyl)-2-methyl propanoate (18). Followed procedure from Kawai et al.[2] 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_2Cl_2 (3 x 10 mL). The organic layers were combined and dried with $MgSO_4$, filtered and concentrated then purified by reverse-phase MPLC (10 - 100% CH_3CN:water) to produce **18** (0.022 g, 0.042 mmol, 28% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 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).



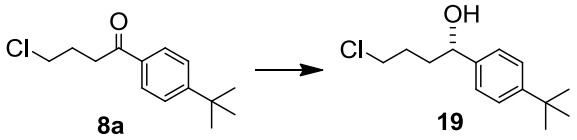
8a **10a**

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_2Cl_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, $CDCl_3$): δ 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).

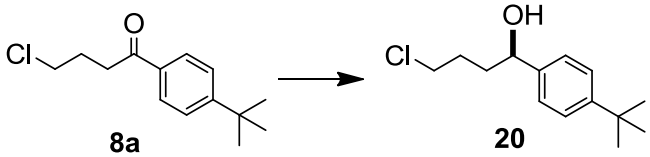


1-(*Tert*-butyl)-4-(3-chloropropyl)benzene (10b). Same procedure as **21** using **8k** (0.16 g, 0.71 mmol) and triethylsilane (0.33 g, 0.46 mL, 2.85 mmol) with TFA (4 mL). Purified by MPLC (0 - 40% EtOAc:hexanes) and fractions 4 and 5 were collected to produce **10b** (0.13 g, 0.64 mmol, 89% yield) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 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).

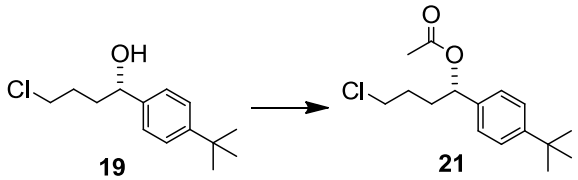
Synthesis of intermediates for analogs **2h** and **2i**.[3]



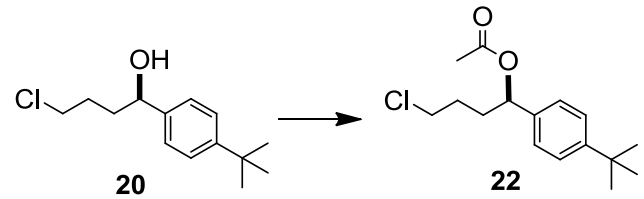
(*S*)-1-(4-(*Tert*-butyl)phenyl)-4-chlorobutan-1-ol (19). Prepared according to a previously published procedure[3]. To a flame-dried vial was added dry THF (2 mL) and then cooled to 0 °C. The 1.0 M *R*-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborlidine (0.11 mL, 0.11 mmol) in THF was added followed 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, $CDCl_3$): δ 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).



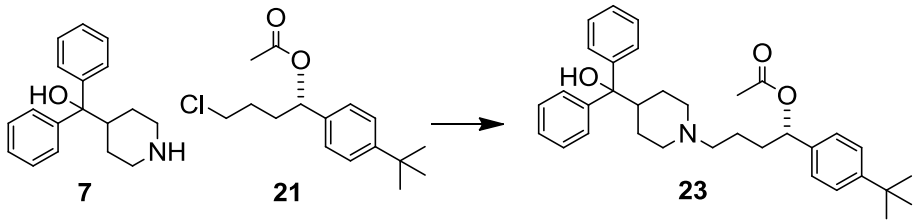
(*R*)-1-(4-(*tert*-butyl)phenyl)-4-chlorobutan-1-ol (20). Prepared the same **19** with 1.0 M (*S*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborlidine (0.11 mL, 0.11 mmol), 2.0 M borane-methyl sulfide complex (0.65 mL, 1.31 mmol) and 1-(4-(*tert*-butyl)phenyl)-4-chlorobutan-1-one (0.25 g, 1.05 mmol) 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, $CDCl_3$): δ 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 precipiate 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 $MgSO_4$, filtered and concentrated to produce **21** (0.25 g, 0.88 mmol, 86% yield). $[\alpha]_D^{25}$ -42.11, (*c* 10, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): 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).

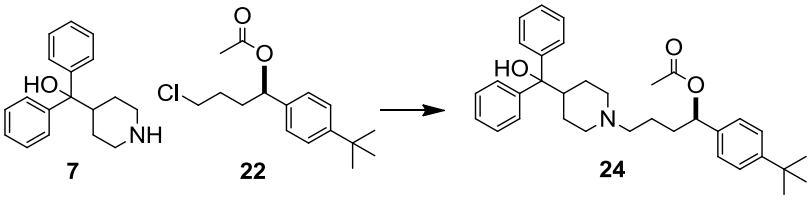


(*R*)-1-(4-(*tert*-butyl)phenyl)-4-chlorobutyl acetate (22). Prepared the same as **21** with **20** (0.22 g, 0.90 mmol) and diethyl ether (4.5 mL), triethylamine (0.19 mL, 1.35 mmol) and acetyl chloride (0.064 mL, 0.90 mmol) to produce **22** (0.25 g, 0.88 mmol, 98% yield). $[\alpha]_D^{25}$ +54.57, (*c* 10, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): 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).



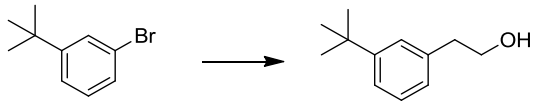
(*S*)-1-(4-(*Tert*-butyl)phenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butyl acetate (23). To a vial was added the **7** (0.15 g, 0.58 mmol), **21** (0.20 g, 0.69 mmol) and potassium carbonate (0.32 g, 2.31 mmol) in acetonitrile (10 mL). The reaction stirred at 70 °C for 18 h and was then cooled to rt and filtered. The filtrate was then diluted with CH_2Cl_2 (10 mL) and washed with water (10 mL) and brine (10 mL). The organic layers were combined, dried with $MgSO_4$, filtered and purified by reverse-phase MPLC (10 - 100% CH_3CN:water) to produce **23** (0.14 g, 0.26 mmol, 46% yield) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): 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).



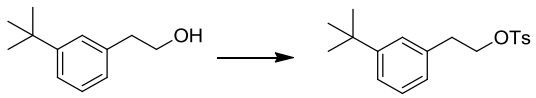
7 22 24

(*R*)-1-(4-(*Tert*-butyl)phenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-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. ^{1}H NMR (400 MHz, $CDCl_3$): 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).



25

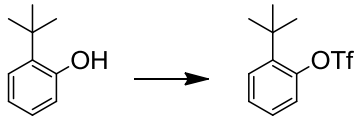
2-(3-(*Tert*-butyl)phenyl)ethanol (25). To a vial was added the 1-bromo-3-(*tert*-butyl)benzene (0.11 g, 0.50 mmol) and dry THF (7 mL). The reaction was then cooled to -78 °C and the 2.5 M BuLi in hexanes (0.22 mL, 0.55 mmol) was added dropwise and the reaction stirred for 30 minutes at -78 °C. The ethylene 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 % CH_3CN:water) to produce **25** (0.035 g, 0.20 mmol, 39% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 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).



25 10e

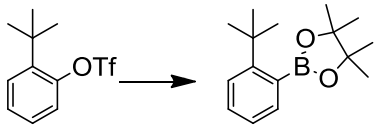
3-(*Tert*-butyl)phenethyl-4-methylbenzenesulfonate (10e). To a vial was added **25** (0.035 g, 0.20 mmol), triethylamine (0.082 mL, 0.59 mmol) and CH_2Cl_2 (2 mL) followed by p-toluene sulfonyl chloride (0.056 g, 0.29 mmol). The reaction began to stir at rt for 20 h and was then diluted with saturated $NaHCO_3$ (5 mL) and extracted with EtOAc (3 x 5 mL). The organic layers were combined then dried with $MgSO_4$, filtered and concentrated then purified by reverse-phase MPLC (10 - 100% CH_3CN:water) to provide **10e** (0.060 g, 0.18 mmol, 92% yield). ^{1}H NMR

(400 MHz, $CDCl_3$): 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).



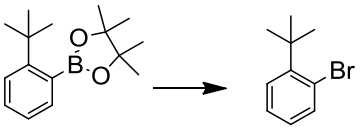
26

2-(*Tert*-butyl)phenyl trifluoromethanesulfonate (26). To a vial was added the 2-(*tert*-butyl)phenol (1.0 mL, 6.51 mmol) and CH_2Cl_2 (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 CH_2Cl_2 (20 mL) and quenched with 1.0 M HCl (20 mL). The organic layer was collected and washed with saturated $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was then dried ($MgSO_4$), filtered and adsorbed to silica and purified by MPLC (0 - 25% EtOAc:hexanes) to produce **26** (1.66 g, 5.88 mmol, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 – 7.46 (m, 1H), 7.37 – 7.34 (m, 1H), 7.31 – 7.27 (m, 2H), 1.43 (s, 9H).



26 **27**

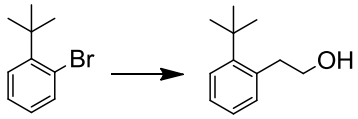
2-(2-(*Tert*-butyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (27). To a flame-dried vial was added activated molecular sieves and **26** (0.48 g, 1.68 mmol) and 1,1'-bis(diphenyl phosphino)ferrocenedichloropalladium(II) (0.042 g, 0.050 mmol). The vial was evacuated with argon three times and then 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 CH_2Cl_2 (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 $MgSO_4$, filtered and concentrated. The hexanes layer was then concentrated to produce **27** (0.093 g, 0.36 mmol, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 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).



27 **28**

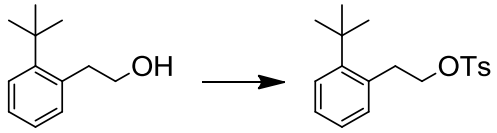
1-Bromo-2-(*tert*-butyl)benzene (28). To a vial was added the **27** (0.18 g, 0.69 mmol) and MeOH (5 mL). The copper (II) bromide (0.46 g, 2.08 mmol) was then dissolved in water (5 mL) and added to the reaction then stirred at 80 °C for 24 h. The reaction was then removed from heat and diluted with water (5 mL) and extracted with EtOAc (3 x 10 mL). The EtOAc layers were combined and dried with $MgSO_4$, 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).



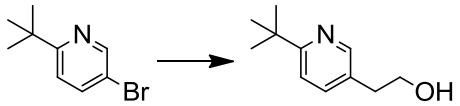
28 **29**

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).



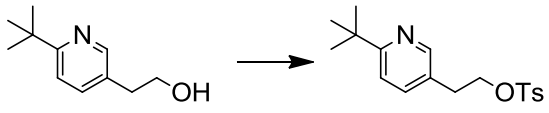
29 **10f**

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_2Cl_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

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).

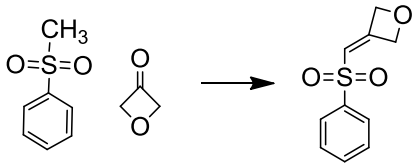


30 **10l**

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_2Cl_2 (2 mL)

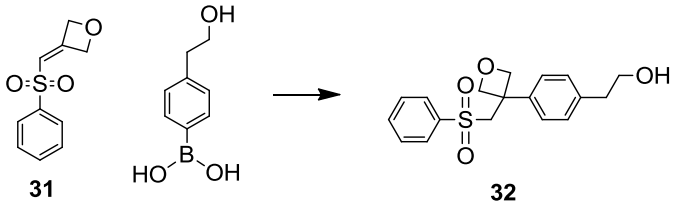
followed by p-toluenesulfonyl chloride (0.34 g, 1.77 mmol) to provide **10l** (0.26 g, 0.78 mmol, 66 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (br d, *J* = 2.4 Hz, 1H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.40 (dd, *J* = 8.2 Hz, 2.4 Hz, 1H), 7.30 – 7.27 (m, 2H), 7.23 (dd, *J* = 8.2 Hz, 0.8 Hz, 1H), 4.19 (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]



31

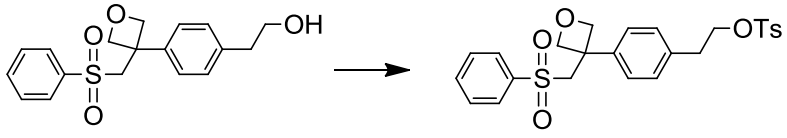
3-((Phenylsulfonyl)methylene)oxetane (31). Method adapted from Wuitschuk et al[4]. To an oven-dried vial was added (methylsulfonyl) benzene (0.57 g, 3.65 mmol) and the vial was evacuated with argon three times. The dry THF (17 mL) was added to the vial under argon and the reaction was cooled to 0 °C. 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).



31 **32**

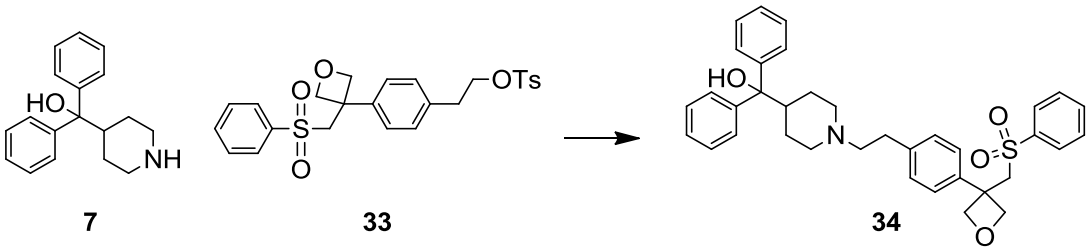
2-(4-(3-((Phenylsulfonyl)methyl)oxetan-3-yl)phenyl)ethanol (31). Method adapted from Wuitschuk et al[4]. To a microwave vial was added the chloro(1,5-cyclooctadiene)rhodium(I) dimer (0.012 g, 0.025 mmol) and 1,4-dioxane (10 mL). The 1.5 M aqueous KOH (0.50 mL, 0.75 mmol) was then added and the reaction 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_3CN:water) to produce **32** (0.063 g, 0.19 mmol, 76% yield). ^{1}H NMR (400 MHz,

$CDCl_3$): δ 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).



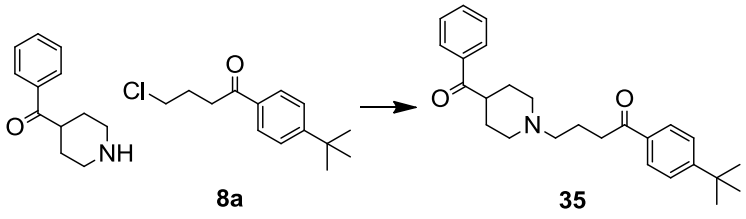
32 **33**

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_2Cl_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, $CDCl_3$): δ 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).



7 **33** **34**

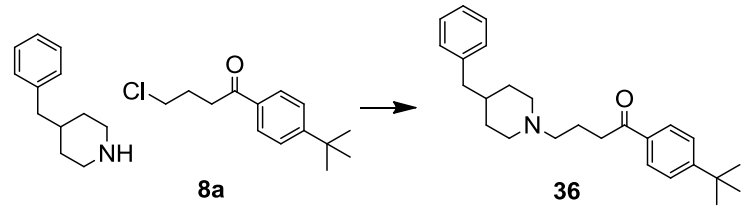
(1-(4-(3-((Phenylsulfonyl)methyl)oxetan-3-yl)phenethyl)piperidin-4-yl)diphenylmethanol (34). Method C: **33** (0.041 g, 0.084 mmol) and **7** (0.025 g, 0.093 mmol), triethylamine (0.018 mL, 0.13 mmol) and acetonitrile (1.5 mL). Purified by reverse-phase MPLC (10 - 100% CH_3CN:water) to produce **34** (0.024 g, 0.041 mmol, 49% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 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).



8a **35**

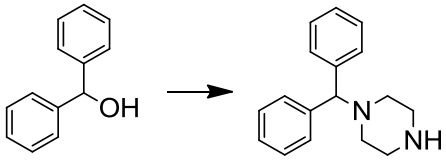
4-(4-Benzoylpiperidin-1-yl)-1-(4-(*tert*-butyl)phenyl)butan-1-one (35). To a vial was added the **8a** (0.060 g, 0.25 mmol) and potassium iodide (0.063 g, 0.38 mmol) with acetonitrile (2 mL). The reaction stirred at 85 °C for 1 h then the phenyl(piperidin-4-yl)methanone (0.050 g, 0.26 mmol) along with 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 $MgSO_4$, filtered and adsorbed to silica then purified by reverse-phase MPLC (10 - 100% CH_3CN:water) to produce **35** (0.026 g, 0.066 mmol, 26% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 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).



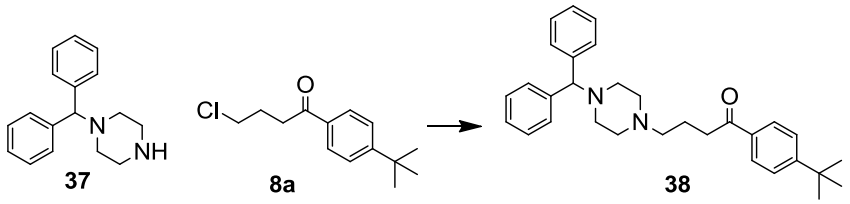
8a **36**

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% CH_3CN:water) to produce **36** (0.29 g, 0.77 mmol, 54% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 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).



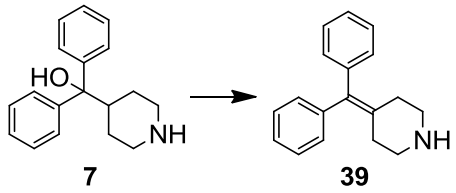
37

1-Benzhydrylpiperazine (37). Followed previously published procedure.[5] To a vial was added the diphenylmethanol (0.32 g, 1.73 mmol) and CH_2Cl_2 (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 CH_2Cl_2 (15 mL) and washed with 1.0 N NaOH in water (15 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated to produce **37** (0.43 g, 1.73 mmol, 98% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) 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).



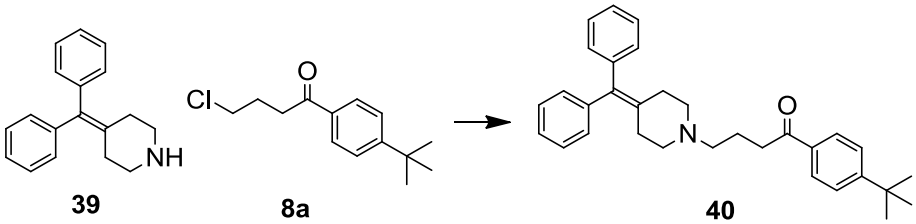
37 8a 38

4-(4-Benzhydrylpiperazin-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_3CN: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).



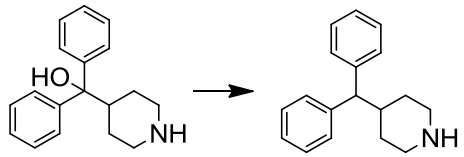
7 39

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_2Cl_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_3CN: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).



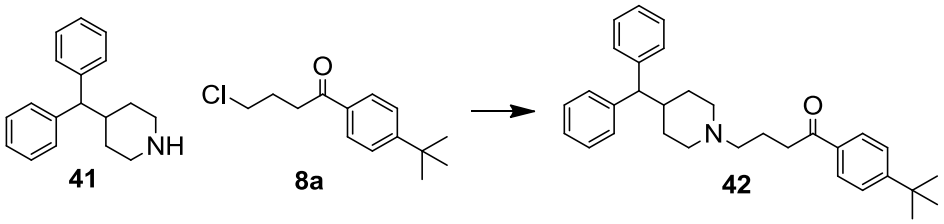
39 8a 40

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_3CN: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).



7 41

4-Benzhydrylpiperidine (41). Followed the reported procedure from Edgar et al.[6] 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_2Cl_2 (10 mL) and washed with 1.0 M NaOH (10 mL). The organic layer was then dried with $MgSO_4$, filtered and concetrated 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).



41 8a 42

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 m L). The organic layer was dried with $MgSO_4$, filtered and concentrated then purified by RP MPLC (10 - 100% CH_3CN:water) to produce **42** (0.037 g, 0.081 mmol, 20% yield). ^{1}H 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.

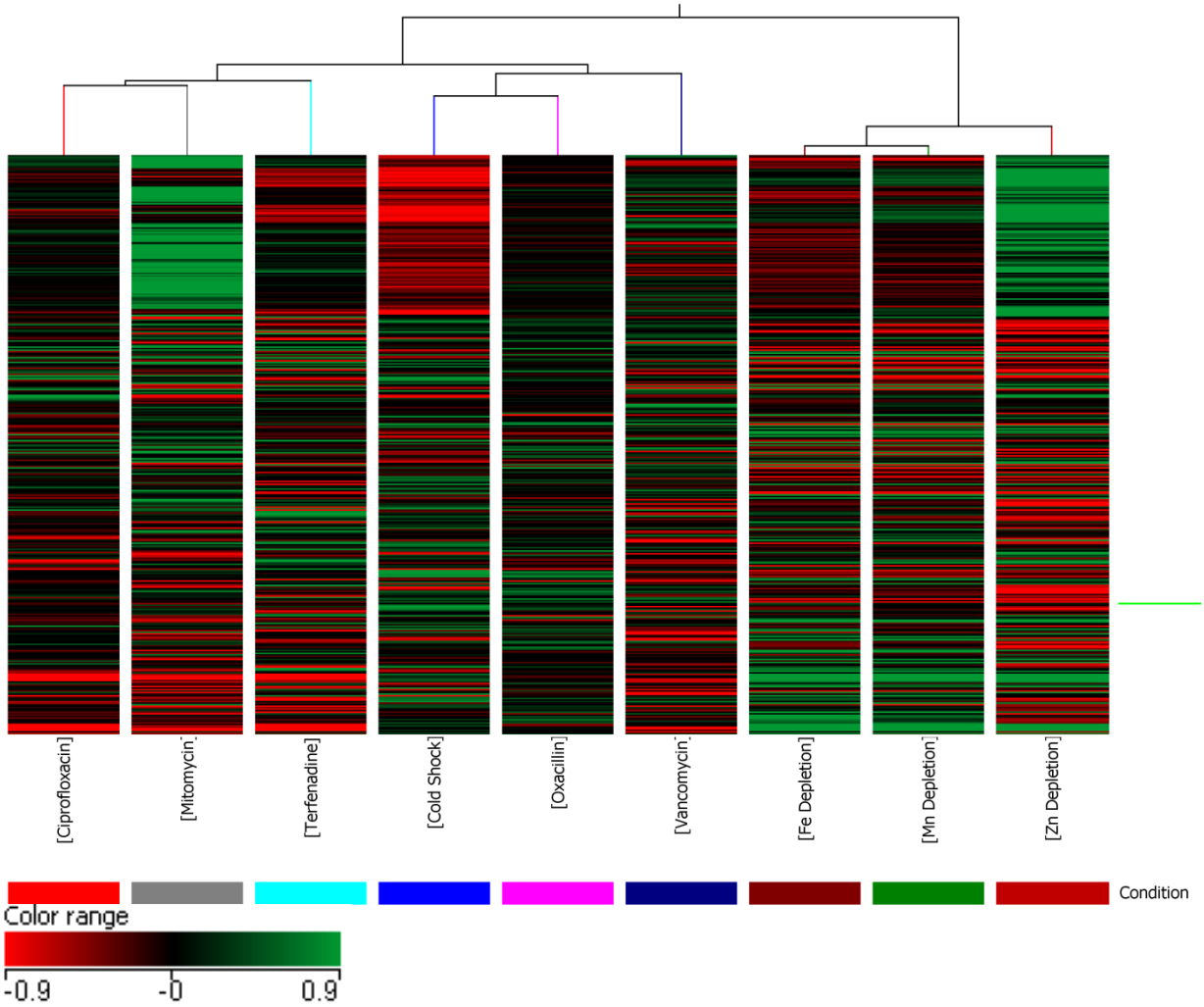
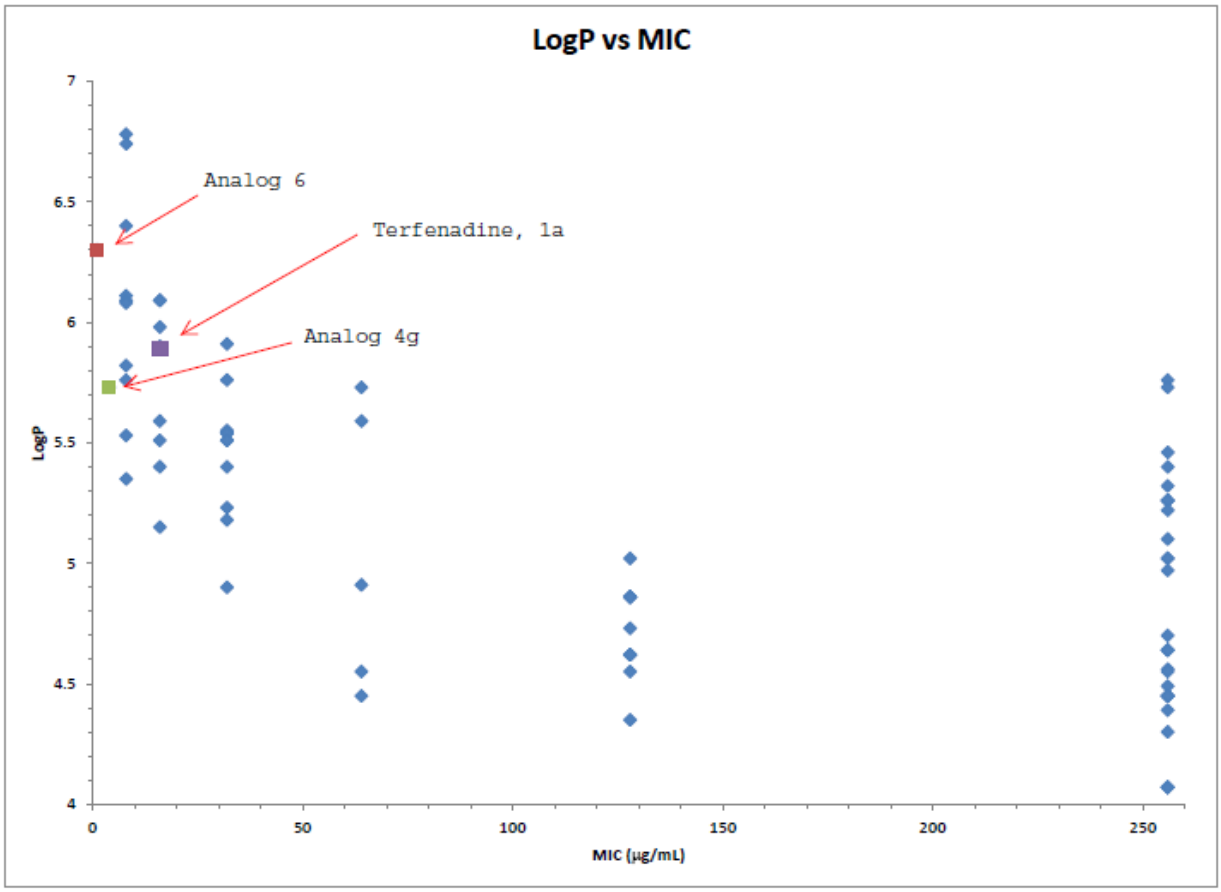


Chart S1. Scatter plot of LogP vs. MIC values.



Analog Key

4g = KSC-381-073

6 = KSC-381-082

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Experimental Results

Cat #	Assay Name	Batch*	Spec.	Rep.	Conc.	% Inh.	IC_{50}*	K_i	n_H	R
Compound: KSC-381-073, PT #: 1179706										
265900	Potassium Channel hERG	350355	hum	1	10 µM	105	0.21 µM	0.17 µM	1.19	
			hum	1	3 µM	98				
			hum	1	1 µM	89				
			hum	1	0.3 µM	56				
			hum	1	0.1 µM	32				
			hum	1	0.03 µM	13				
			hum	1	10 nM	-7				
			hum	1	3 nM	12				
			hum	1	1 nM	6				
			hum	1	0.3 nM	10				
Compound: KSC-381-082, PT #: 1179707										
265900	Potassium Channel hERG	350355	hum	1	10 µM	100	0.14 µM	0.11 µM	0.74	
			hum	1	3 µM	96				
			hum	1	1 µM	75				
			hum	1	0.3 µM	57				
			hum	1	0.1 µM	54				
			hum	1	0.03 µM	25				
			hum	1	10 nM	9				
			hum	1	3 nM	2				
			hum	1	1 nM	-1				
			hum	1	0.3 nM	3				

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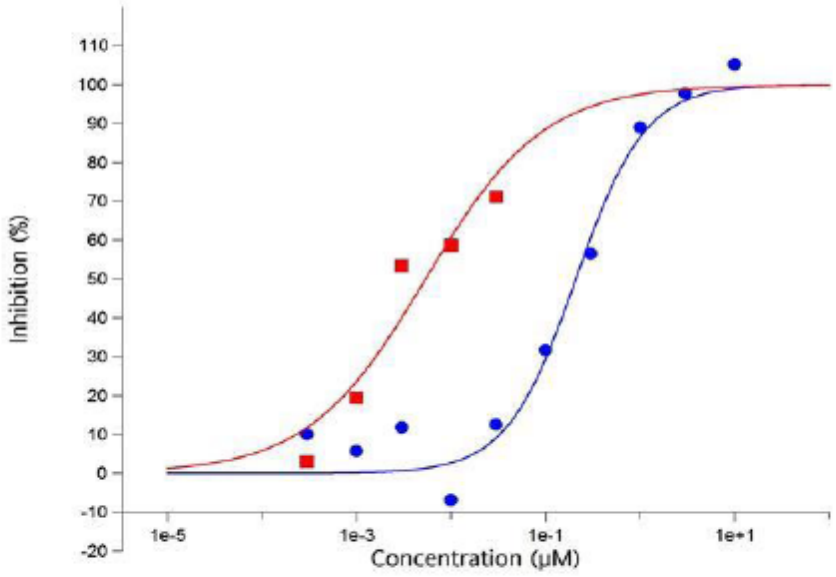
Response Curves

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
Astemizole	5.37 nM	4.40 nM	0.70

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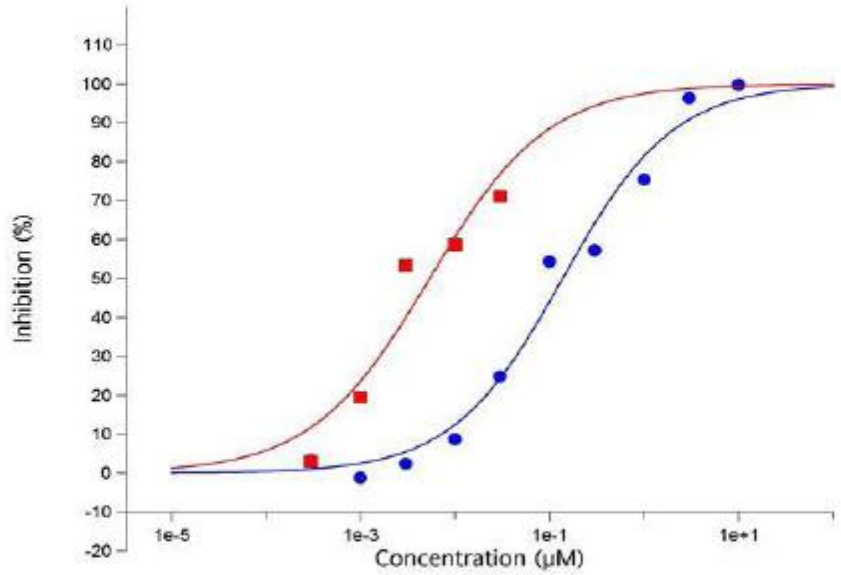
Response Curves

Assay: 265900 - 1 Potassium Channel hERG



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

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Methods

■ 265900 Potassium Channel hERG

Source:	Human recombinant HEK-293 cells	**Ligand:**	1.50 nM [^{3}H] Astemizole
Vehicle:	1.00% DMSO	**Non-Specific Ligand:**	10.0 µM Astemizole
Incubation Time/Temp:	60 minutes @ 25°C	**Specific Binding:**	90% *
Incubation Buffer:	10 mM HEPES, pH 7.4, 0.1% BSA, 5 mM KCl, 0.8 mM $MgCl_2$, 130 mM NaCl, 1 mM EGTA, 10 mM Glucose	**Quantitation Method:**	Radioligand Binding
Kd:	6.80 nM *	**Significance Criteria:**	≥50% of max stimulation or inhibition
		Bmax:	6.30 pmole/mg Protein *

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