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Article

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Repurposing the antihistamine terfenadine for antimicrobial activity against *Staphylococcus aureus*

Jessamyn I. Perlmutter,[†] *Lauren T. Forbes,*[†] *Damian J. Krysan,*[‡] *Katherine Ebsworth-Mojica,*[‡,†] *Jennifer M. Colquhoun,*[†] *Jenna L. Wang,*[§] *Paul M. Dunman,*[†] *Daniel P. Flaherty**[§]

[†]University of Rochester Medical Center, Department of Microbiology and Immunology

601 Elmwood Ave., Rochester, NY 14642

[‡]University of Rochester Medical Center, Department of Pediatrics

601 Elmwood Ave., Rochester, NY 14642

[§]University of Kansas, Specialized Chemistry Center, Delbert M. Shankel Structural Biology Center, 2034 Becker Dr., Lawrence, KS 66047, United States

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ABSTRACT

Staphylococcus aureus is a rapidly growing health threat in the U.S. with resistance to several commonly prescribed treatments. A high-throughput screen identified the antihistamine terfenadine to possess, previously unreported, antimicrobial activity against *S. aureus* and other Gram-positive bacteria. In an effort to repurpose this drug, structure-activity relationship studies yielded 84 terfenadine-based analogs with several modifications providing increased activity versus *S. aureus* and other bacterial pathogens, including *Mycobacterium tuberculosis*. Mechanism of action studies revealed these compounds to exert their antibacterial effects, at

least in part, through inhibition of the bacterial type II topoisomerases. This scaffold suffers from hERG liabilities which were not remedied through this round of optimization; however, given the overall improvement in activity of the set, terfenadine-based analogs provide a novel structural class of antimicrobial compounds with potential for further characterization as part of the continuing process to meet the current need for new antibiotics.

INTRODUCTION

The ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) are responsible for 51% of all U.S. hospital-acquired infections (HAIs).[1] Among these, *S. aureus* accounts for 16% of HAIs and is responsible for more deaths in the U.S. annually than HIV/AIDS.[1-3] The organism's high morbidity and mortality rates are, in part, attributable to the fact that *S. aureus* has developed resistance to currently available antibiotics.[4] The quinolone class of antibiotics was once a predominant treatment option for *S. aureus* infections;[5] however, due to increasing quinolone resistance, these drugs continue to have diminishing efficacy.[6,7]

The antimicrobial activity of the quinolones and fluoroquinolones, such as ciprofloxacin (Figure 1) and levofloxacin, is thought to be mediated by their ability to inhibit the DNA re-ligation activity of the bacterial type II topoisomerases, DNA gyrase and topoisomerase IV. Resistance can arise from decreased access to these cellular targets or by mutations within the type II topoisomerases.[8,9] Despite the rise in resistance to quinolones, their previous success validates the type II topoisomerases as valuable targets in searching for novel antimicrobial scaffolds. Indeed, academic and industrial laboratories have devoted much effort toward developing novel bacterial type II topoisomerase inhibitors (NBTIs) featuring compound scaffolds chemically distinct from those of the quinolone class of antibiotics,[10-15] including the

N-linked piperidine 6-(methyloxy)-4-(2-{4-[([1,3]oxathiolo[5,4-*c*]pyridin-6-ylmethyl)amino]-1-piperidinyl}ethyl)-3-quinolinecarbonitrile dihydrochloride **43** (GSK299423).[16] However, despite NBTI development efforts, pharmaceutical pipelines are still severely lacking quality antibiotic candidates[17] and the loss of several antibiotic groups in the pharmaceutical industry only exacerbates the problem.[18,19] This, coupled with increasing prevalence of quinolone-resistant *S. aureus,* makes it paramount that novel small molecule inhibitors are discovered for type II topoisomerases for the therapeutic intervention of staphylococcal disease and possibly other bacterial pathogens.

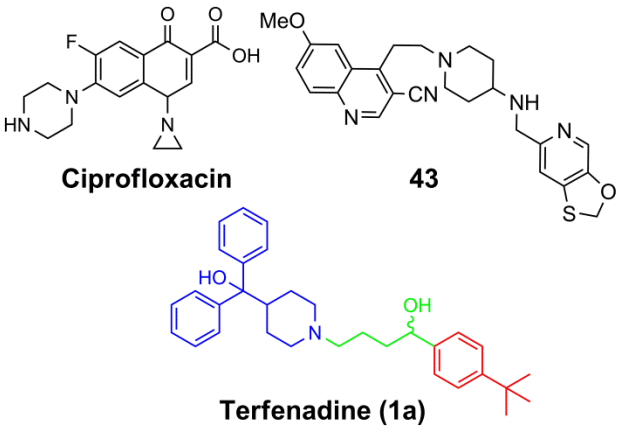


Figure 1. Structures of ciprofloxacin, NBTI **43** and terfenadine (**1a**)

The practice of drug repurposing, in which a drug previously developed to treat one disease is then identified for possibly treating a second disease, has emerged as an attractive alternative for drug discovery research.[20,21] The repurposed drug most likely has already been optimized for physicochemical and pharmacokinetic properties[22] providing a more attractive starting point as far as these factors are concerned. Recently the National Center for Advancing Translational Science (NCATS) has invested in this area with the formation of the NIH Chemical Genomic Center Pharmaceutical Collection as both an informatics and screening resource for

drug repurposing research,[23] lending credence to the potential and popularity of drug repurposing.

Given the need for novel antimicrobials and the attractive features of drug repurposing, we previously performed a high-throughput screen (HTS) to identify FDA approved drugs with bactericidal activity toward the ESKAPE pathogens.[24] Results identified a set of compounds that were developed for other indications but displayed previously unreported antimicrobial activity. One particular hit, the antihistamine terfenadine (Figure 1), was found to possess antimicrobial activity versus the planktonic, biofilm, and small-colony variant forms of *S. aureus*. Given the activity and relatively convenient synthetic route to analogs, terfenadine provided an attractive starting point for studying the structure-activity relationship (SAR) of *S. aureus* antimicrobial activity. However, terfenadine is not without its flaws. The clinical use of the drug was discontinued in favor of its active metabolite fexofenadine (Allegra®) because a segment of the patient population exhibited cardiac arrhythmia, attributed to prolonged QT interval,[25,26] due to inhibition of the human ether-á-go-go related gene (hERG) potassium channel.[27] Nonetheless, it has been shown previously that it is possible to reduce hERG liabilities via an SAR strategy[13] and given the encouraging results from the HTS, we decided it would be beneficial to embark on an SAR-optimization study of terfenadine (**1a**) and its analogs for inhibition of *S. aureus* and those results are reported herein.

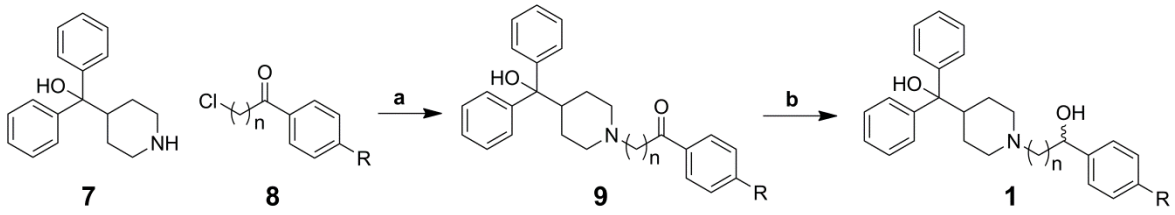
RESULTS AND DISCUSSION

Chemistry

A total of 84 terfenadine-based analogs were synthesized for optimization of antimicrobial activity against *S. aureus* strain UAMS-1,[14] a well-studied osteomyelitis clinical isolate, by standard CLSI methods.[28] The majority of analogs were synthesized by one of two

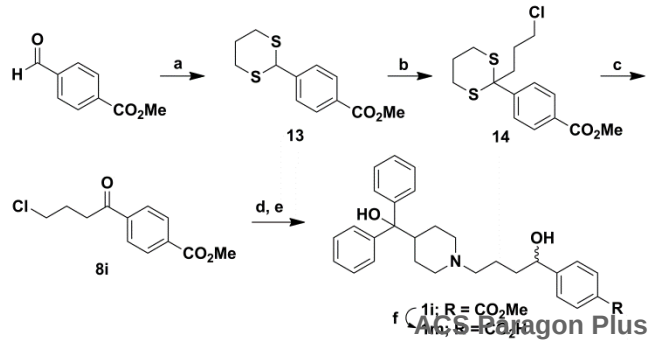
routes while several required alternate routes or further modification. The first route employs a substitution reaction with diphenyl(piperidin-4-yl)methanol (**7**) and corresponding substituted chloro-phenylbutanones (**8**) followed by subsequent reduction of the ketone intermediate (**9**) yielding analogs **1a-h** and **1j-l** (Scheme 1). An alternate pathway was used to synthesize analog **1i** in which the methyl 4-(4-chlorobutanoyl)benzoate **8i** was prepared according to a previously reported procedure,[29] reduced, and subjected to a Finkelstein reaction with **7** to yield the desired analog (Scheme 2). This ester was then hydrolyzed to the corresponding carboxylic acid **1m**. Compound **1n** was synthesized by Suzuki-Miyaura coupling using a procedure adapted from Moseley et al[30] (Scheme 3A). The final analog in this set, the known metabolite of terfenadine (**1p** also known as fexofenadine),[31] was generated according to a previously published procedure[32] (Scheme S2 in supporting information).

Scheme 1. General synthetic route for terfenadine (**1a**) and analogs series **1**.



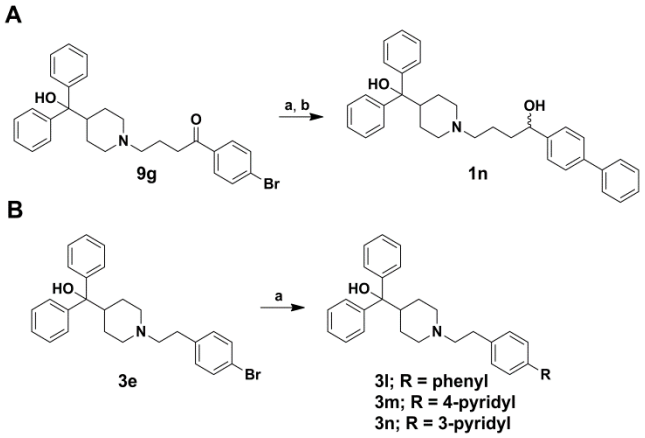
Reagents and conditions: (a) $NaHCO_3$, 2-butanone/water, 85 °C, 16 h, 23-95%; (b) $NaBH_4$, MeOH, rt, 3 h, 52-95%.

Scheme 2. Synthetic route for analogs **1i** and **1m**.



Reagents and conditions: (a) 1,3-propanedithiol, CH_2Cl_2, rt, 1.5 h then $BF_3 \cdot OEt_2$, 0 °C – rt, 18 h, 86%; (b) NaHMDS, THF, -78 °C then 1-chloro-3-iodopropane, rt, 18 h, 31%; (c) bis(trifluoroacetoxy)iodobenzene, CH_3CN/water, rt, 1 h, 69%; (d) $NaBH_4$, MeOH, rt, 3 h, 87%; (e) $NaHCO_3$, NaI, CH_3CN, reflux, 18 h, 37%; (g) LiOH, THF/water, rt, 3 h, 47%.

Scheme 3. Synthetic routes for analogs **1n** (A), **3l-3n** (B)**.**

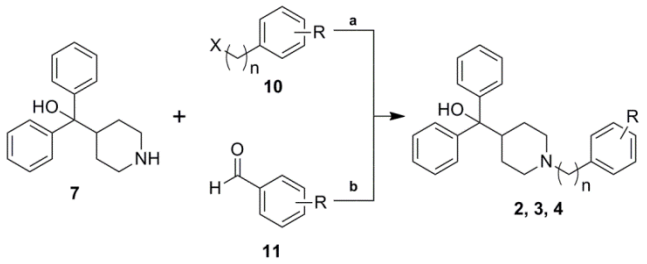


Reagents and conditions: (a) R-$B(OH)_2$, K_2CO_3, CH_3CN/water, 60 °C, 18 h, 30 – 88%; (b) $NaBH_4$, MeOH, rt, 3 h, 94%;

The second route to a majority of analogs was via nucleophilic substitution in which **7** was coupled with various substituted phenyl alkyl halides or tosylates (**10**) yielding analogs **2a-d**, **3a-i**, **4a-r**, **4t**, **4w** and **4y-bb** (Scheme 4). Benzyl bromides were not available for four desired analogs, thus reductive amination was employed for analogs **4s**, **4u**, **4v** and **4x** with the corresponding aldehydes **11a-d** (Scheme 4). A number of analogs required further modification such as reduction of the 4-nitro group of **3i** providing the 4-amino derivative **3j** followed subsequent di-methylation yielding the 4-dimethylamino analog **3k** (Scheme 5). Analogs **3l-3n** were synthesized from **3e** using the aforementioned Suzuki-Miyaura cross-coupling procedure (Scheme 3B). Saponification of methyl esters **4y-4aa** resulted in carboxylic acids **4cc-4ee**. A set of 5-membered heterocycles at the 4-position were synthesized in which the 4-iodo derivative **4bb** was subjected to Suzuki-Miyaura cross coupling with the corresponding boronic acids or

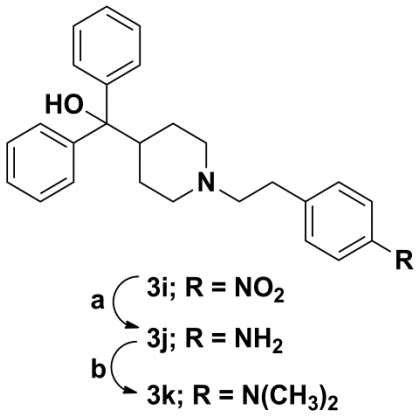
potassium trifluoroborate salts to provide **4ff-4ii** while a copper mediated Ullman type coupling of pyrrole[33] in acetonitrile afforded the pyrrole derivative **4jj** (Scheme 6).

Scheme 4. General synthetic route for analog series **2**, **3** and **4**.



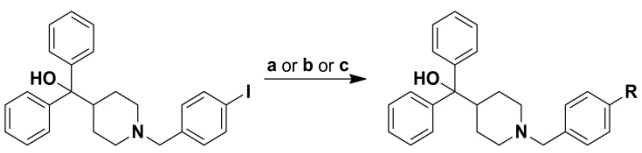
Reagents and conditions: (a) **7**, K_2CO_3 or Et_3N, acetonitrile, reflux,18 h, 20-94%; (b) For analogs **4s**, **4u**, **4v** and **4x**: **7**, $Na(OAc)_3BH$, THF, rt to 65 °C, 3 h, 16-29%.

Scheme 5. Synthetic route for analogs **3j** and **3k.**



Reagents and conditions: (a) Raney nickel, $NaBH_4$, CH_2Cl_2/MeOH, 0 °C – rt, 28 h, 61%; (b) paraformaldehyde, $NaBH_3CN$, AcOH, rt, 20 h, 84%.

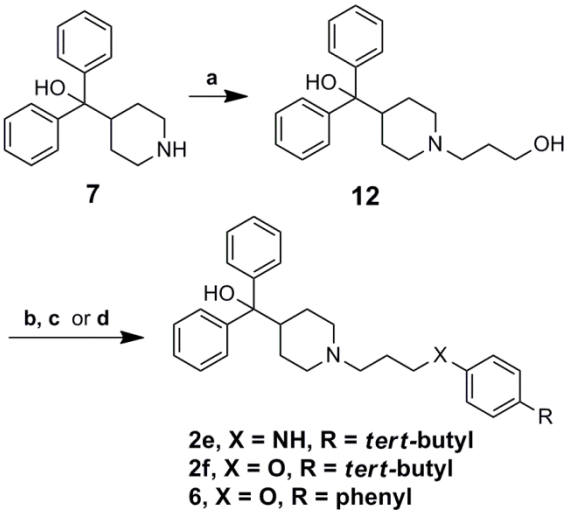
Scheme 6. Synthetic route for analogs **4ff-4jj**



Reagents and conditions: For **4ff** and **4hh** (a) R-$B(OH)_2$, K_2CO_3, CH_3CN/water, 60 °C, 18 h, 85 – 89%; For **4gg** and **4ii** (b) R-BF_3K, $Pd(OAc)_2$, RuPhos, $NaHCO_3$, 100 °C, μW, 60 min, 68 – 69%; For **4jj** (c) Cu, pyrrole, Cs_2CO_3, CH_3CN, 80 °C, 21 h, 47%.

Compounds **2e** and **2f** were prepared by alkylation of **7** with 3-bromopropan-1-ol providing the alcohol intermediate **12** which was subsequently tosylated and subjected to substitution conditions with 4-*tert*-butylaniline or 4-*tert*-butylphenol respectively (Scheme 7). Analog **2g** was synthesized via reductive amination of **9a** to arrive at the benzylic amine. Each enantiomer for terfenadine, **2h** and **2i**, were synthesized via a previously reported procedure (supporting information).[34]

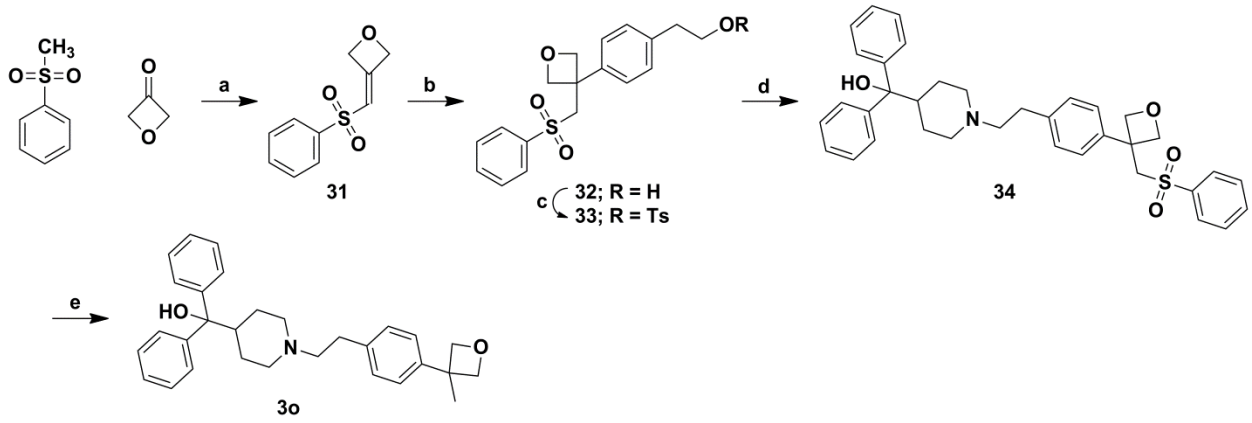
Scheme 7. Synthetic route to analogs **2e**, **2f** and **6**.



Reagents and conditions: 3-bromopropanol, Et_3N, acetonitrile, reflux, 3 h, 65%; (b) For **2e** and **2f**: TsCl, Et_3N, CH_2Cl_2, rt, 20 h, 33%; (c) For **2e**, 4-*tert*-butylaniline; for **2f**, 4-*tert*-butylphenol, Et_3N, acetonitrile, reflux, 18 h, 15-45%; (d) For **6**: 4-phenylphenol, triphenylphosphine, DIAD, THF, rt, 18 h, 77%.

A slightly more polar *tert*-butyl isostere, methyl oxetane,[35] was prepared using an adapted procedure from Wuitschik et al.[36] The key step being a rhodium catalyzed coupling of 4-(2-hydroxyethyl)phenylboronic acid with the Michael acceptor intermediate. Further modification resulted in analog **3o** (Scheme 8).

Scheme 8. Synthetic route for analog **3o**.



Reagents and conditions: (a) BuLi, THF, 0 °C, 45 min then diethyl chlorophosphate, 0 °C, 30 min then cool to -78 °C, oxetan-3-one, 2 h, 75%; (b) $[Rh(cod)Cl]_2$, KOH, 4-(2-hydroxyethyl) phenylboronic acid, 1,4-dioxane, 100 °C, μW, 30 min, 76%; (c) Et_3N, CH_2Cl_2, TsCl, rt, 20 h, 27%; (d) **7**, Et_3N, CH_3CN, reflux, 18 h, 49%; (e) Mg, MeOH, 50 °C, 4.5 h, 25%.

Analogs **5a** and **5b** (Figure 2) were created utilizing the same substitution and subsequent reduction conditions described for previous series. The diphenyl piperazine intermediate was synthesized using a previously reported procedure[37] followed by substitution with **8a** and reduction to arrive at **5c**. Finally, **5d** and **5e** were created by reducing the alcohol of **7** in either TFA alone or in the presence of sodium borohydride.[38] The reduced intermediates were then subjected to the same substitution/reduction procedure as described for previous series (supporting information).

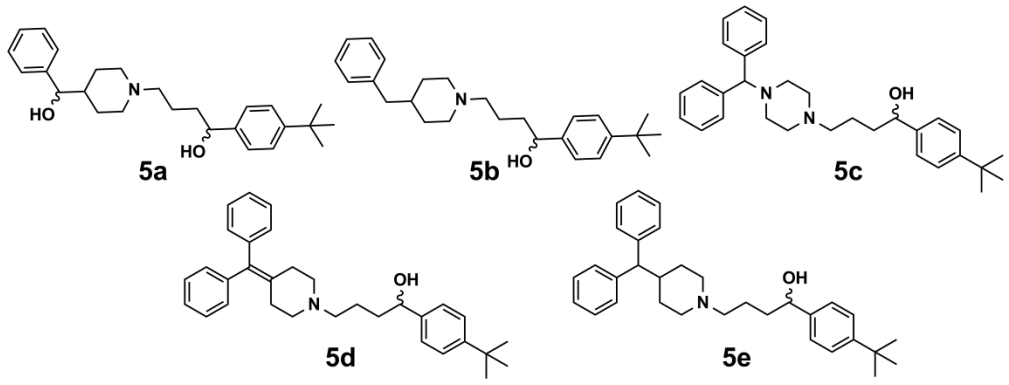


Figure 2. Analogs **5a-5e** displaying modifications to diphenyl piperidine region.

The final analog combined favorable changes to the linker and pendant phenyl in an attempt to further enhance potency. This compound was synthesized via Mitsunobu chemistry in which the intermediate **12** was coupled with 4-phenylphenol providing **6** (Scheme 7).[39]

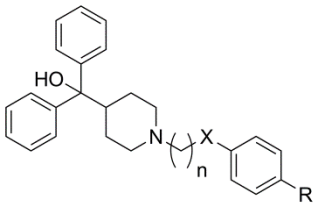
Design and SAR for Terfenadine Analogs

The SAR for all terfenadine analogs was studied using antimicrobial potency toward planktonic *S. aureus* UAMS-1 cells, as measured by minimum inhibitory concentration testing (MIC). Data from these assays helped drive iterative analog design and synthesis. Mechanism of action studies on terfenadine were performed in parallel. The most promising analogs were carried into MIC assays testing across a spectrum of Gram-positive and Gram-negative pathogens as well as *M. tuberculosis*. Furthermore, a common strategy for reducing hERG activity is to lower the logP of the compound[40,41] thus attempts at incorporating polar functional groups while optimizing for potency were undertaken with this goal in mind.

Series 1 compounds were designed to gain initial SAR information at the 4-position of the pendant phenyl (red region in Figure 1) of **1a** while preserving the linker (Table 1). A scan of lipophilic steric bulk showed that anti-*S. aureus* activity correlated with the size of the lipophilic groups (4-*tert*-butyl (**1a**) > 4-*iso*-propyl (**1b**) > 4-methyl (**1c**) > 4-H (**1d**)). A halogen

scan at the para-position also displayed a similar trend (4-bromo (**1g**) > 4-chloro (**1f**) > 4-fluoro (**1e**)). The 4-phenyl analog **1n** further supports this observation as it displayed a modest increase in potency (MIC to 8 μg/mL). Unfortunately the introduction of polarity at this position resulted in loss of antimicrobial activity as observed for the 4-methoxy (**1h**), 4-methyl carboxylate and its corresponding carboxylic acid (**1i** and **1m**) as well as for the primary metabolite of **1a,** carboxylic acid **1p** and the methyl ester precursor **1o** (Table 1). These results suggest lipophilicity and steric bulk at the 4-position of the pendant phenyl are optimal for anti-staphylococcal activity.

Table 1. MIC values for Series **1** and **2**.



Compound	n	X	R	*S. aureus* MIC (μg/mL)
1a	3	CH(OH)	*tert*-butyl	16
1b	3	CH(OH)	*iso*-propyl	32
1c	3	CH(OH)	CH_3	128
1d	3	CH(OH)	H	>256
1e	3	CH(OH)	F	128
1f	3	CH(OH)	Cl	64
1g	3	CH(OH)	Br	32
1h	3	CH(OH)	OMe	>256
1i	3	CH(OH)	CO_2Me	>256
1j	4	CH(OH)	*tert*-butyl	16
1k	2	CH(OH)	*tert*-butyl	8
1l	1	CH(OH)	*tert*-butyl	16
1m	3	CH(OH)	CO_2H	>256
1n	3	CH(OH)	phenyl	8
1o	3	CH(OH)	$C(CH_3)_2CO_2Me$	>256
1p	3	CH(OH)	$C(CH_3)_2CO_2H$	>256
2a	3	CH_2	*tert*-butyl	8
2b	2	CH_2	*tert*-butyl	8
2c	1	CH_2	*tert*-butyl	8
2d	0	CH_2	*tert*-butyl	8
2e	3	NH	*tert*-butyl	8
2f	3	O	*tert*-butyl	8
2g	3	$CH(NH_2)$	*tert*-butyl	16
2h	3	CH(OH) (*S*)	*tert*-butyl	16
2i	3	CH(OH) (R)	*tert*-butyl	16
9a	3	CO	*tert*-butyl	8
9k	2	CO	*tert*-butyl	32
9l	1	CO	*tert*-butyl	>256
9m	0	CO	*tert*-butyl	>256

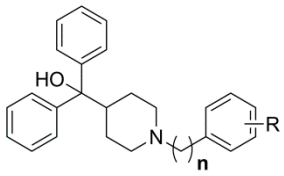
The second set of analogs was designed to study modifications to the linker (green region in Figure 1) while maintaining the 4-*tert*-butyl group on the pendant phenyl. Compounds **1j-1l** scanned linker length while maintaining the benzylic alcohol and showed that changes to the length were tolerated and did not reduce activity (MICs = 8 and 16 μg/mL). A study of linker length while altering the oxidation state on the benzylic carbon provided similar results. Analogs **2a-2d** all contained fully reduced benzylic carbons, scanning from four to one carbon linkers respectively, and provided MICs = 8 μg/mL. The ketone precursor to the hit (**9a**) maintained activity (MIC = 8 μg/mL) while the three-carbon derivative (**9l**) showed a slight reduction in activity compared to **1a** (MIC = 32 μg/mL). The ketone containing two-carbon and amide containing linkers resulted in a loss of activity possibly due to restriction of movement for the phenyl group, at least in terms of amide linker. Further exploration of the necessity of the alcohol led to a benzylic amino derivative (**2g**) and the *S*-OH (**2h**) and *R*-OH (**2i**) enantiomers, all of which exhibited no change in activity compared to the hit. The final two analogs in this set replaced the benzylic carbon with nitrogen (**2e**) and oxygen (**2f**) resulting in slight increases in activity to MICs = 8 μg/mL for each. The SAR of the linker region suggests the secondary alcohol is not necessary for *S. aureus* antimicrobial activity while shortening the linker in some cases led to a small, yet consistent, improvement in activity.

Given the modest success of the one and two carbon linkers from the previous set the next two series further studied SAR on the pendant phenyl while utilizing shorter, more accessible linkers. The two carbon linker set provided mixed results as far as potency but maintained the trend of favoring lipophilic bulk at the 4-position (Table 2). Moving the *tert*-butyl group around the pendent phenyl (**3a** and **3b**, MIC = 16 μg/mL for each) was tolerated and did not alter activity significantly compared to **2c**. The same was observed for bulkier derivatives as the 4-bromo (**3e**), 4-trifluoromethyl (**3f**) displayed MICs = 16 μg/mL for each, and

4-phenyl analog **3l** had an MIC = 8 μg/mL. Smaller and more polar substitutions in this set led to varying ranges of reduction in activity or a complete loss.

These trends continued in the one-carbon linker series as the 4-phenyl analog **4g** was the most active with an MIC = 4 μg/mL, a 4-fold increase in potency compared to the hit (Table 2). Unfortunately, all polar modifications at the 2-, 3-, or 4-positions led to a significant reduction or complete loss of *S. aureus* antimicrobial activity. A 4 to 8-fold reduction in activity was observed for heterocycles at the para-position as indicated by the 3- and 2-thiophene analogs **4ff** and **4gg**, 3- and 2-furan analogs **4hh** and **4ii** and the *N*-linked pyrrole **4jj**, compared to **4g** suggesting the slight increase in polarity for these common phenyl isosteres affect their activity.

Table 2. MIC values for Series **3** and **4**.



Compound	n	R	*S. aureus* MIC (μg/mL)	Compound	n	R	*S. aureus* MIC (μg/mL)
3a	2	3-*tert*-butyl	16	**4k**	1	3-CN	>256
3b	2	2-*tert*-butyl	16	**4l**	1	2-CN	>256
3c	2	4-F	128	**4m**	1	4-CF_3	>256
3d	2	4-Cl	32	**4n**	1	3-CF_3	>256
3e	2	4-Br	16	**4o**	1	2-CF_3	>256
3f	2	4-CF_3	16	**4p**	1	4-F	>256
3g	2	4-OMe	>256	**4q**	1	3-F	128
3h	2	3-pyridyl-4-*tert*-butyl[a]	64	**4r**	1	2-F	>256
3i	2	4-NO_2	64	**4s**	1	4-OMe	128
3j	2	4-NH_2	>256	**4t**	1	3-OMe	128
3k	2	4-$N(CH_3)_2$	>256	**4u**	1	2-OMe	128
3l	2	4-phenyl	8	**4v**	1	4-OH	128
3m	2	4-(4-pyridyl)	32	**4w**	1	3-OH	>256
3n	2	4-(3-pyridyl)	32	**4x**	1	2-OH	64
3o	2	4-$C(CH_2OCH_2)CH_3$	>256	**4y**	1	4-CO_2Me	>256
4a	1	3-*tert*-butyl	32	**4z**	1	3-CO_2Me	>256
4b	1	2-*tert*-butyl	>256	**4aa**	1	2-CO_2Me	>256
4c	1	4-*iso*-propyl	32	**4cc**	1	4-CO_2H	>256
4d	1	4-Me	128	**4dd**	1	3-CO_2H	>256
4e	1	3-Me	128	**4ee**	1	2-CO_2H	>256
4f	1	2-Me	128	**4ff**	1	4-(3-thiophene)	16
4g	1	4-phenyl	4	**4gg**	1	4-(2-thiophene)	32
4h	1	3-phenyl	64	**4hh**	1	4-(3-furan)	32
4i	1	2-phenyl	>256	**4ii**	1	4-(2-furan)	32
4j	1	4-CN	>256	**4jj**	1	4-(1-pyrrole)	32

[a]Analog **3h** employs a pendant 3-pyridine in place of the pendant phenyl

A small set of analogs were designed to explore more global changes to the piperidinyl diphenylmethanol (blue region in Figure 1) side of **1a** (Figure 2). Analogs **5a-5d** showed a complete loss of activity toward *S. aureus*; however, the removal of the alcohol while maintaining sp^3 character of the carbon (**5e**) was tolerated (Table 3). This provides some evidence, however small, that future work could establish SAR trends on this side of the molecule.

Table 3. MIC values for series 5

Compound	*S. aureus* MIC (μg/mL)
5a	>256
5b	>256
5c	>256
5d	>256
5e	8

In summary, there appears to be a trend in which lipophilicity may be driving the potency of this scaffold, at least in general. A scatter plot of logP vs MIC (Chart S1 in supporting information) displays this trend with the average logP generally decreasing as potency decreases. However, there are a few analogs that lie outside of the trend, such as **4g**, which has a lower calculated logP (estimated by ALOGPS)[42,43] than **1a** but displays a 4-fold increase in potency. Therefore, while the trend is general there are a few instances in which functional group identity or placement still might play a role in the potency. A strong relationship was noticed at the 4-position of the pendant phenyl with lipophilic bulk being beneficial for potency against *S. aureus*. Downsizing the *tert*-butyl group of the hit **1a** resulted in a reduction of potency, however slight, on all occasions while the addition of a phenyl group in this position was the lone substitution leading to a modest increase of potency.

The addition of hetercyclic isosteres (pyridinyl, thiophenyl and furyl moieties) are comparable in size to the phenyl, however, contain slightly larger polar surface areas. The

benefit of steric bulk in these cases may have been mostly negated due to increased polarity, however slight, ultimately resulting in an overall reduction of potency but not a complete loss. Modifications, either polar or non-polar, to other positions of the pendant phenyl were unfavorable leading to reduction or loss of potency. Therefore SAR on the pendant phenyl, while relatively steep for the ortho- and meta-positions, did offer some room for improvement at the para-position as far as potency against *S. aureus* is concerned. However, further optimization to the piperidinyl diphenylmethanol side of **1a** may be required for reduction of logP while maintaining or improving potency.

Several modifications to the linker region provided a slight increase in potency. The benzylic alcohol was not necessary for activity as indicated by the removal of the hydroxy group leading to moderately increased antimicrobial potency across the four different linker lengths (**2a-2d**). It was also shown that substituting an amine for the alcohol or resolving the enantiomers had no effect on activity. Furthermore, substituting the benzylic carbon for an amine or ether linkage resulted in a 2-fold increase in activity compared to the hit. Given these data, it was evident that modifications to the linker could lead to an analog with enhanced activity.

A final analog was designed to combine the favorable ether linker modification from **2f** and the 4-phenyl substitution on the pendant group to yield **6**. The combination of these modifications resulted in a synergistic boost in potency with an MIC = 1 μg/mL against *S. aureus* comparable to an MIC = 0.5 μg/mL for the widely prescribed fluoroquinoline, ciprofloxacin, in the same assay (Figure 3). The success of the combined modifications offers optimism that more potent analogs may be within reach with future SAR studies. However, compound properties such as solubility and logP remain an issue and will be addressed with future work.

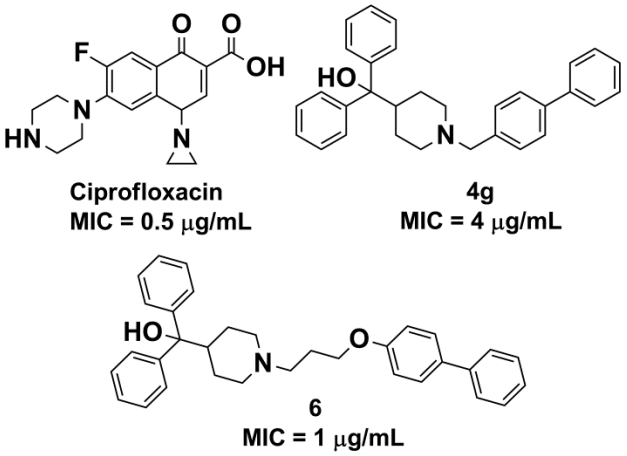


Figure 3. MIC values for ciprofloxacin, **4g** and **6**.

Mechanism of Action

Transcription profiling was used to compare the cellular response of *S. aureus* strain UAMS-1 following challenge with a sub-inhibitory concentration (0.5 x MIC) of terfenadine, with that of cells treated with 0.5 x MIC of the known topoisomerase II inhibitor, ciprofloxacin, or antibiotics with independent mechanisms of action. Results (Figure S1 in supporting information) revealed that terfenadine-treated cells elicit a cellular response most similar to that of ciprofloxacin and cells treated with the DNA damaging agent mitomycin C in comparison to cells treated with sub-inhibitory concentrations of cell wall active agents, RNA synthesis inhibitors, or general stress responses such as cold-shock conditions and metal depletion. For instance, 221 (43%) of the 509 genes that were differentially expressed within ciprofloxacin treated cells were also differentially expressed within terfenadine-treated cells. A total of 149 (67%) of these 221 genes were also differentially expressed within mitomycin treated cells, but none of the other stress conditions evaluated. Of direct relevance to this work, while the majority of these genes (55%) are annotated as hypothetical proteins two key components of the organism's SOS response, *lexA* and *umuC*, as well as twelve phage-associated replication

proteins were identified and known to be responsive to the topoisomerase inhibitor, ciprofloxacin.[44,45] The similarities between the cellular response of terfenadine-, ciprofloxacin-, and mitomycin-challenged cells, provided an initial indication that the scaffold's antimicrobial activity may be mediated via topoisomerase II inactivation.

As a direct test of whether the antimicrobial properties of terfenadine correlate with type II topoisomerase inhibition, *S. aureus* DNA gyrase and topoisomerase IV inhibition assays were used to measure each enzyme's activity in the absence and presence of various concentrations of terfenadine. As shown in Figure 4A (lanes 1 and 2), the addition of 0.5 units (U) of *S. aureus* DNA gyrase catalyzed supercoiling of relaxed circular plasmid pBR322 DNA, resulting in increased substrate mobility in an agarose gel, confirming that the assay conditions were appropriate to measure gyrase activity. Similar assays in the presence of increasing concentrations of terfenadine (62.5, 125, 250 and 500 μM), demonstrated that the compound was a relatively mild inhibitor of *S. aureus* gyrase with an apparent IC_{50} value of 190 μM. Similarly, terfenadine appeared to exhibit moderate topoisomerase IV inhibitory activity (Figure 5A).

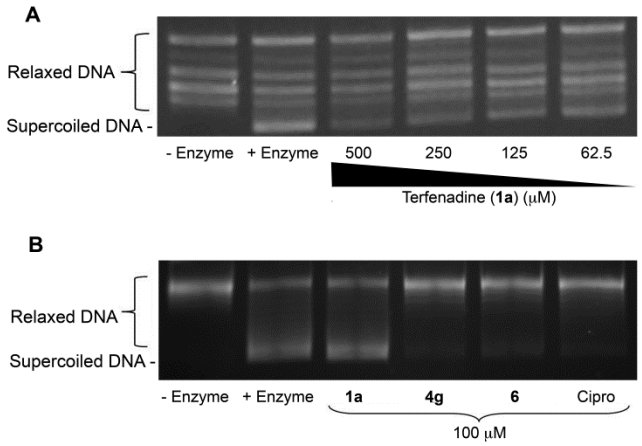


Figure 4. DNA gyrase supercoiling inhibition assays (A) dose-response gel for **1a**; (B) gel showing inhibition of DNA gyrase with analogs **1a**, **4g** and **6** with the positive control ciprofloxacin at 100 μM.

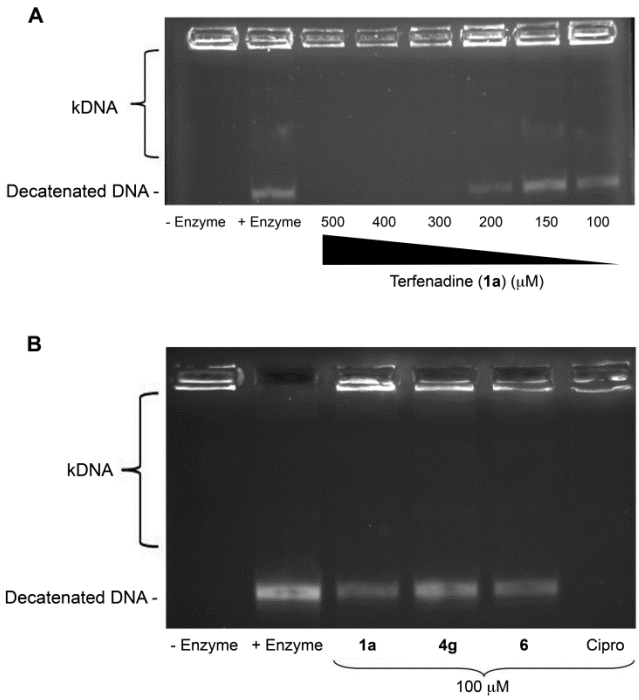


Figure 5. Topoisomerase IV inhibition assay (A) dose-response gel for **1a**; (B) gel showing inhibition of topoisomerase IV with analogs **1a**, **4g** and **6** with the positive control ciprofloxacin at 100 μM.

While these values are admittedly modest they are comparable to the topoisomerase II inhibitor, ciprofloxacin, in these assays, which displayed IC_{50} values of 110 and 4 μM for *S. aureus* DNA gyrase and topoisomerase IV, respectively (data not shown). This, combined with the fact that **1a** did not appear to affect the activity of other enzymes assessed (*S. aureus* RNase J2 and RnpA; data not shown), supports the hypothesis that the compound's antimicrobial activity may, in part, correspond to its topoisomerase II inhibitory activity.

Accordingly, IC_{50} values were measured for the first 48 analogs synthesized (Table 4) to determine whether improvements to the compound's antimicrobial activity tracked with enhanced enzyme inhibition. Results of those studies revealed two overarching features of the analog series. First, most compounds (11 of 12 in total) displaying modest improvement in

antimicrobial activity (MIC ≤ 8 μg/mL), in comparison to terfenadine, also exhibited at least modest improvement in potency toward *S. aureus* DNA gyrase and/or topoisomerase IV. Second, most compounds exhibiting reduced antimicrobial activity (MIC ≥ 32 μg/mL) displayed decreased potency toward the enzymes. Compounds **4g** and **6**, which exhibited the most improved antimicrobial properties toward *S. aureus* (MIC values of 4 μg/mL and 1 μg/mL, respectively) also displayed modest improvements toward *S. aureus* DNA gyrase inhibition (IC_{50}s = 130 and 50 μM, respectively) when compared to **1a**. Indeed, as shown in Figure 4B when tested at 100 μM, **4g**, **6** and ciprofloxacin, all displayed improved inhibition of *S. aureus* DNA gyrase supercoiling activity, in comparison to the parent molecule, terfenadine. This suggests that even if the gains in potency for **4g** and **6** over terfenadine are modest, they do appear to display a real improvement in DNA gyrase inhibition. Moreover, both derivatives maintained *S. aureus* topoisomerase IV inhibition activity that approximated the inhibitory activity of that of the parent molecule**, 1a** (Figure 5B).

Even though the terfenadine scaffold seems to be inhibiting the type II topoisomerases, it appears there may be other mechanisms contributing to the overall bactericidal effect. It is well noted that receptor promiscuity is correlated with lipophilicity.[46] Therefore, it is not out of the question that these compounds could be binding to multiple targets and the combined effect of these targets may be exerting the antibacterial effect. Analogs **2g**, **2i**, **3d**, **3e** and **3n** all are shown to have activity versus *S. aureus,* with MICs ranging from 16 – 32 μg/mL. However, these analogs possess reduced or no activity in the DNA gyrase and topoisomerase IV assays. Therefore, they must be exerting an antimicrobial effect via other means, supporting the multiple target hypothesis. Moreover, attempts to isolate resistant strains of *S. aureus* provided no stable resistant organisms also supporting a multiple target hypothesis. It should be noted that given the above correlations, expense and laborious nature of the enzyme assays, and fact that no

improvements in antimicrobial activity (≥ 32 μg/mL) were observed for the remaining compounds synthesized, their IC_{50} values were not measured.

Table 4. DNA Gyrase and Topoisomerase IV IC_{50} Measurements

Compound	DNA Gyrase IC_{50} (μM)	Topoisomerase IV IC_{50} (μM)	Compound	DNA Gyrase IC_{50} (μM)	Topoisomerase IV IC_{50} (μM)
Ciprofloxacin	110	4	**2h**	127	100
1a (terfenadine)	190	206	**2i**	410	110
1b	127	273	**9a**	93	110
1c	>500	>333	**9k**	90	133
1d	>500	>333	**9l**	73	247
1e	>500	>333	**9m**	93	>333
1f	133	>333	**3a**	93	>333
1g	>500	>333	**3c**	>333	>333
1h	>500	>333	**3d**	260	267
1i	440	>333	**3e**	247	260
1j	100	133	**3f**	17	>333
1k	133	333	**3g**	>333	>333
1l	73	100	**3h**	>333	>333
1m	>500	>333	**3i**	263	>333
1n	13	100	**3j**	93	>333
1o	>500	>333	**3k**	>333	>333
1p	>500	>333	**3l**	80	133
2a	93	320	**3m**	93	227
2b	93	100	**3n**	250	280
2c	93	147	**3o**	>333	>333
2d	90	213	**4g**	125	160
2e	193	250	**5a**	>333	>333
2f	100	>333	**5b**	>333	>333
2g	>500	>333	**6**	50	160

DNA Gyrase Modeling Studies

As was shown in the previous section, the terfenadine-based scaffolds are likely to, at least in part, exert their antibacterial effect via inhibition of the type II topoisomerases. Recently NBTIs, such as **43** have been reported.[16] These NBTIs also feature a piperidine with aromatic regions linked to the *N*- and 4-position. Therefore, we hypothesized that the terfenadine-based analogs may be binding in the same region as **43**. A docking study was carried out using the software Surflex module of SYBYL from Certara. The receptor protein (PDB ID 2XCS) was prepared by removing the ligand, **43**, and taking the corresponding ligand binding pocket defined as a 20 Å sphere around the GSK ligand. Out of 30 poses the best pose was selected on the basis

of Combined CScore (ChemScore, G_Score, D_Score and PMF_Score) and the scores were 8.85 for **43**, 7.65 for **6**, and 5.99 for **1a**, respectively. The scores generally correlated with the experimentally determined DNA gyrase activity (**43** = 14 nM, **6** = 50 μM and **1a** = 190 μM respectively).

To assess the potential of the terfenadine analogs for binding to other known sites on DNA gyrase, the same docking study was performed with a solved structure of ciprofloxacin (PDB ID 2XCT)[16] and the docking score of the best poses for **43** and **6** were 2.22 and 0.72 respectively. The same modeling was performed at the ATP site on the GyrB subunit, in which a pyrrolamide ligand was extracted from the ATP-binding site in a structure published by Eakin et al[47] (PDB ID 3U2K). Both **43** and **6** were docked and provided similar docking scores (5.05 and 5.23, respectively). These *in silico* results suggest a higher likelihood of the terfenadine-based analogs interacting in the same region as **43** than in the other two known inhibitor binding sites.

Information from the above modeling of binding site suggests that the aromatic character of the pendant bi-phenyl moiety intercalates between DNA basepairs similar to **43** (Figure 6A). However, due to the length of the linker, the diphenyl methanol portion may be able to interact with a section of the protein surface adjacent to the pocket in which the oxathiolo-pyridine group of **43** binds. The best pose of **6** suggests that hydrogen bonds may form between the alcohol with an acceptor phosphate group in the DNA backbone, and a donor Arg1122, respectively, with additional potential hydrophobic π-π stacking interactions (Figure 6B). While the modeling suggests a similar binding site, further work is needed to validate these results. Future plans include designing analogs to interrogate these possible interactions, competition assays with known inhibitors and solving a terfenadine-based ligand bound DNA gyrase structure aimed at providing more definitive evidence as to the binding site for this scaffold.

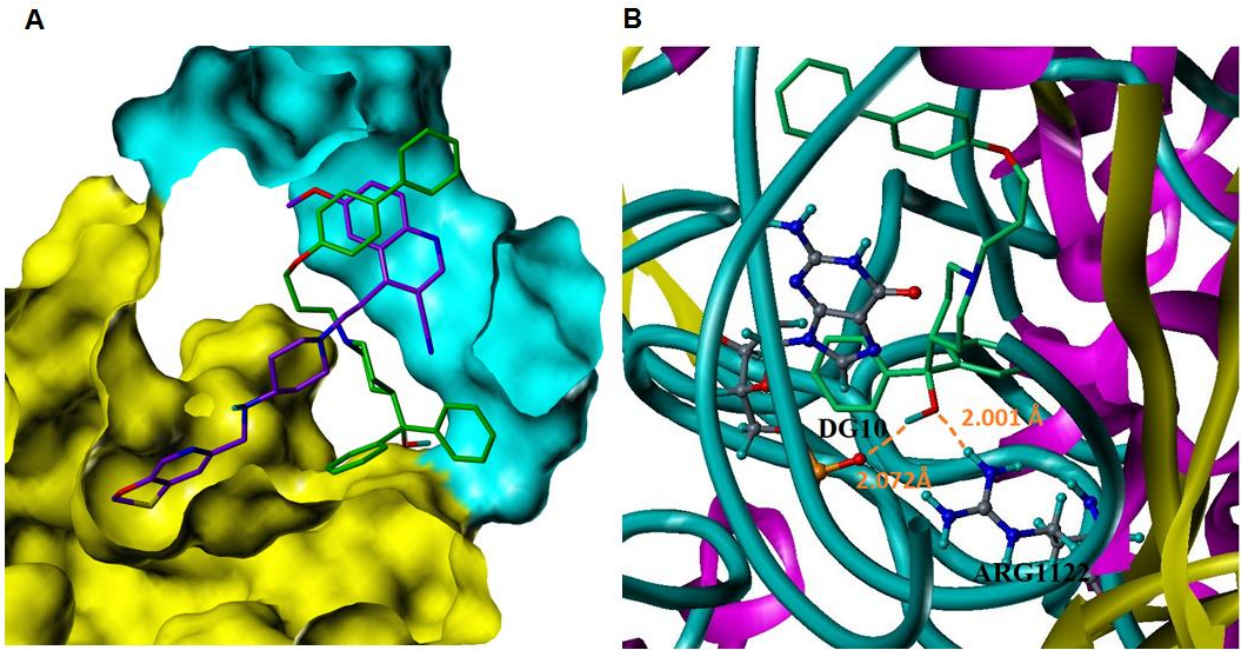


Figure 6. Docking studies utilizing the ligand-bound DNA gyrase structure PDB ID 2XCS (A) Overlay of solved ligand, **43** (purple ligand), and best docked pose for **6** (green ligand) within binding site. Protein surface shaded yellow and DNA surface shaded blue. (B) Potential interactions from the best docked pose of **6** (light blue ligand). Docking studies in two known alternative binding sites, the ATP and ciprofloxacin binding sites, were also performed using solved ligand-bound structures (PDB IDs 3U2K and 2XCT, respectively) and the binding score were inferior compared to the **43** binding site.

Antimicrobial Spectrum of Activity of Terfenadine, 4g and 6

As stated above, terfenadine (**1a**) was found to have anti-staphylococcal activity in a HTS campaign using the *S. aureus* strain UAMS-1, a methicillin-susceptible strain. In order to determine the spectrum of antimicrobial activity for **1a**, the activity of the scaffold toward genetically diverse *S. aureus* strains, other Gram-positive and Gram-negative bacterial species of immediate healthcare concern, and *Mycobacterium tuberculosis* was determined. As shown in

Table 5, each compound's antimicrobial activity was conserved across all Gram-positive strains evaluated. More specifically, the MIC values of **1a**, **4g**, and **6** were 16, 4, and approximately 2 μg/mL, respectively toward methicillin-resistant (MRSA), vancomycin-intermediate (VISA), vancomycin-resistant (VRSA) *S. aureus*, as well as flouroquinolone resistant strains. Likewise, they demonstrated corresponding antimicrobial activity toward *Enterococcus faecium, Enterococcus faecalis, and M. tuberculosis*. Neither **1a** nor its analogs were active against wild-type Gram-negative species tested thus far. The MIC is >256 μg/mL for both *K. pneumoniae* CKP4 and *E. coli* 8314. The MIC value for *A. baumannii* 98-37-09 is 256 μg/mL. However, when tested versus a membrane-compromised, efflux pump-deficient strain of *E. coli (tolC, imp)*, all three compounds did show activity. Therefore, the lack of efficacy versus Gram-negative species may be due to an inability of these compounds to traverse the outer membrane to gain entry to the cellular target and/or a result of expulsion via efflux pumps. Nonetheless, these results indicate that a terfenadine scaffold could potentially be optimized for use as an antimicrobial against Gram-positive organisms and potentially Gram-negative organisms if treated with an efflux pump inhibitor.

Table 5. Antimicrobial Spectrum for terfenadine, **4g** and **6**.

Strain (Relevant Resistance)	Terfenadine (1a) MIC (μg/mL)	4g MIC(μg/mL)	6 MIC (μg/mL)
S. aureus U1	16	4	1
S. aureus CRC61(Ciprofloxacin)	16	4	2
S. aureus CRC118 (Ciprofloxacin)	16	4	2
S. aureus USA300 NRS-384 (MRSA)	16	4	2
S. aureus USA 300-0114 (MRSA)	16	8	2
S. aureus Mu50 (VISA)	16	8	2
S. aureus VRSA-1 (VRSA)	16	8	2
E. faecium 824-05	16	8	2
E. faecalis OG1RF	16	4	2
M. tuberculosis mc^{2}6020	16	4	1
A. baumannii 983709	256	>256	>128
K. pneumoniae CKP4	>256	>256	>128
E. coli 8314	>256	>256	>128
E. coli (tolC, imp-)	8	2	4

hERG Activity of Terfenadine Analogs

Compounds **4g** and **6** emerged as the most promising analogs with MICs = 4 and 1 μg/mL, respectively, against *S. aureus*. Unfortunately, the SAR did not allow for addition of polar functionality and the predicted logP for each compound remains relatively high when compared to the hit. The predicted logP values for **1a**, **4g** and **6** are 5.89, 5.73 and 6.30, respectively (estimated by ALOGPS). Therefore, it appears no improvement was able to be gained in logP while optimizing for potency in this set of analogs. This observation carries over to the measured hERG activity for each compound. Terfenadine (**1a**) displayed a hERG IC_{50} = 130 nM while analogs **4g** and **6** display hERG IC_{50}s = 210 and 140 nM respectively. While hERG activity was not able to be reduced during this campaign, future SAR work on the piperdinyl diphenylmethanol side of the molecule may still provide opportunities for addition of polarity or reduction of the pK_a of the molecule, thus reducing logP and potentially reducing hERG activity.

Conclusions

The project commenced with a phenotypic whole-cell HTS against the ESKAPE pathogens using a library of off-patent FDA-approved drugs. The HTS identified the antihistamine, terfenadine (**1a**), as a hit possessing previously unreported antimicrobial activity versus *S. aureus* (MIC = 16 μg/mL). In an effort to repurpose **1a**, a total of 84 terfenadine-based analogs were designed and synthesized for optimized antimicrobial activity versus *S. aureus*. Analogs **4g** and **6** displayed improved activity (4 and 1 μg/mL respectively) compared to **1a** and promising activity toward other bacterial pathogens of immediate healthcare concern. The SAR study revealed bulky lipophilic substituents at the 4-position of the pendant phenyl, shortening the linker and/or replacing the benzylic carbon with oxygen enhance activity.

Mechanism of action studies suggest **1a**, **4g** and **6** are likely acting as bacterial type II topoisomerase inhibitors targeting both DNA gyrase and topoisomerase IV. However, there is evidence to suggest this scaffold may have multiple targets. Docking studies show these analogs may bind within the same site as the NBTI **43**. While antimicrobial activity versus *S. aureus* strains tested, including flouroquinolone, methicillin and vancomycin resistant isolates, and *M. tuberculosis* was improved, the hERG liability and physicochemical properties for this class of compounds still remains an issue. We believe **6**, and possibly **4g**, provide good starting points for further optimization to the piperidinyl diphenylmethanol side of the molecule. Furthemore, a strategy has been devised to improve antimicrobial activity while reducing hERG activity. In future work we also plan to confirm the possible DNA gyrase binding site for these analogs via competition assays and crystallography studies.

EXPERIMENTAL SECTION

Chemistry General Experimental

Purity of all final compounds was confirmed by HPLC/MS analysis and all compounds have a final purity of ≥ 95% purity. ^{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 = 0.4 mL/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.

General Method A:

1-(4-(*Tert*-butyl)phenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-one (9a). To a vial was added diphenyl(piperidin-4-yl)methanol **7** (1.19 g, 4.45 mmol), 1-(4-(*tert*-butyl)phenyl)-4-chlorobutan-1-one **8a** (1.01 g, 4.24 mmol), sodium bicarbonate (0.42 g, 5.09 mmol) with water and 2-butanone (18 mL, 1:5). The reaction stirred at 85 °C for 16 h and was then allowed to cooled to rt and diluted with water (50 mL). The reaction was diluted with water (20 mL) and extracted with EtOAc (3 x 50 mL). The organic layers were combined then dried with $MgSO_4$, filtered, concentrated and purified by MPLC (0 - 10% MeOH:CH_2Cl_2) to produce pure **9a** (1.37 g, 2.92 mmol, 69% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.4 Hz, 2H), 7.49 – 7.45 (m, 6H), 7.31 – 7.25 (m, 4H), 7.20 – 7.14 (m, 2H), 2.97 – 2.92 (m, 4H), 2.45 – 2.36 (m, 3H), 2.09 (br s, 1H), 2.00 – 1.87 (m, 4H), 1.49 – 1.32 (m, 4H), 1.34 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.7, 156.5, 146.0, 134.5, 128.1, 128.0, 126.4, 125.7, 125.4, 79.4, 57.9, 43.9, 43.4, 44.1, 36.2, 35.0, 31.0, 26.2, 21.9. LCMS Retention time: 4.207 min. LCMS purity 99.5%. HRMS (ESI): *m/z* calcd for $C_{32}H_{39}NO_2$ $[M+H]^+$ 470.3053, found 470.3076.

General Method B:

1-(4-(*Tert*-butyl)phenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-ol (1a). To a vial was added **9a** (0.20 g, 0.422 mmol) and MeOH (2 mL). The sodium borohydride (0.032 g,

0.844 mmol) was then added and the reaction stirred at rt for 3 h. The reaction was concentrated, water (5 mL) was added and a white precipitate formed. The precipitate was filtered out and then dissolved in CH_2Cl_2 (10 mL), dried with $MgSO_4$, filtered and concentrated to produce pure **1a** (0.15 g, 0.320 mmol, 76% yield) as on oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 – 7.46 (m, 4H), 7.33 – 7.25 (m, 8H), 7.21 – 7.15 (m, 2H), 4.61 – 4.56 (m, 1H), 3.16 – 3.11 (br m, 1H), 3.00 – 2.94 (m, 1H), 2.51 – 2.34 (m, 4H), 2.10 – 1.88 (m, 4H), 1.83 – 1.75 (m, 1H), 1.70 – 1.45 (m, 6H), 1.30 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.4, 146.1, 146.0, 142.7, 128.2, 128.1, 126.4, 126.3, 125.7, 125.6, 125.3, 125.0, 79.2, 73.4, 58.9, 54.7, 53.3, 44.2, 39.7, 34.4, 31.4, 26.0, 25.9, 24.1. LCMS Retention time: 4.137 min. LCMS purity 97.5%. HRMS (ESI): *m/z* calcd for $C_{32}H_{41}NO_2$ $[M+H]^+$ 472.3209, found 472.3219.

General Method C:

(1-([1,1'-Biphenyl]-4-ylmethyl)piperidin-4-yl)diphenylmethanol (4g). To a vial was added the 4-phenylbenzyl bromide **10t** (0.10 g, 0.40 mmol), **7** (0.098 g, 0.37 mmol) and acetonitrile (3 mL). The triethylamine (0.077 mL, 0.55 mmol) was added and the reaction stirred at 70 °C for 4 h. The reaction was cooled to rt and diluted with water then extracted with EtOAc. The EtOAc layer was concentrated and the crude product was purified by reverse-phase MPLC (10 - 100% MeCN:water) to produce the pure **4g** (0.12 g, 0.27 mmol, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 – 7.55 (m, 2H), 7.55 – 7.51 (m, 2H), 7.51 – 7.46 (m, 4H), 7.46 – 7.39 (m, 2H), 7.39 – 7.32 (m, 3H), 7.32 – 7.26 (m, 4H), 7.22 – 7.12 (m, 2H), 3.55 (s, 2H), 3.04 – 2.80 (m, 2H), 2.50 – 2.36 (m, 1H), 2.11 – 1.88 (m, 3H), 1.56 – 1.43 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.9, 140.9, 139.9, 137.1, 129.6, 128.7, 128.1, 127.1, 127.0, 126.8, 126.4, 125.7, 79.5, 62.8, 53.9, 44.1, 26.4. LCMS Retention time: 4.101 min. LCMS purity 98.5%. HRMS (ESI): *m/z* calcd for $C_{31}H_{31}NO$ $[M+H]^+$ 434.2478, found 434.2485.

1-(4-(*Iso*-propyl)phenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-one (9b). Method A: **7** (0.62 g, 2.32 mmol), 4-chloro-1-(4-*iso*-propylphenyl)butan-1-one (**8b**) (0.50 g, 2.21 mmol), sodium bicarbonate (0.22 g, 2.65 mmol) with water and 2-butanone (15 mL, 1:5) to produce pure **9b** (0.48 g, 1.06 mmol, 48% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8.3 Hz, 2H), 7.51 – 7.42 (m, 4H), 7.33 – 7.26 (m, 6H), 7.20 – 7.13 (m, 2H), 2.99 – 2.90 (m, 4H), 2.46 – 2.33 (m, 3H), 2.08 (s, 1H), 2.00 – 1.85 (m, 4H), 1.61 (s, 1H), 1.50 – 1.33 (m, 4H), 1.27 (d, *J* = 6.8 Hz, 6H).

1-(4-(Methyl)phenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-one (9c). Method A: **7** (0.50 g, 1.87 mmol), 4-chloro-1-(4-methylphenyl)butan-1-one (**8c**) (0.35 g, 1.78 mmol), sodium bicarbonate (0.18 g, 2.14 mmol) with water and 2-butanone (15 mL, 1:5) to produce pure **9c** (0.27 g, 0.64 mmol, 36% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86 (d, J = 8.2 Hz, 2H), 7.51 - 7.43 (m, 4H), 7.32 - 7.26 (m, 4H), 7.24 (d, J = 8.0 Hz, 2H), 7.18 (tt, 2H), 3.02 - 2.83 (m, 4H), 2.46 - 2.32 (m, 6H), 2.21 (s, 1H), 2.05 - 1.81 (m, 4H), 1.57 - 1.34 (m, 4H).

1-Phenyl-4-(4-(Hydroxydiphenylmethyl)piperidin-1-yl)butan-1-one (9d). Method A: **7** (0.52 g, 1.96 mmol), 4-chloro-1-phenylbutan-1-one **8d** (0.30 mL, 1.87 mmol), sodium bicarbonate (0.19 g, 2.24 mmol) with water:2-butanone (18 mL, 1:5) to produce pure **9d** (0.18 g, 0.43 mmol, 23% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 – 7.89 (m, 2H), 7.59 – 7.51 (m, 1H), 7.50 – 7.39 (m, 6H), 7.34 – 7.25 (m, 4H), 7.21 – 7.14 (m, 2H), 3.03 – 2.81 (m, 4H), 2.46 – 2.32 (m, 3H), 2.09 (br s, 1H), 2.01 – 1.86 (m, 4H), 1.53 – 1.29 (m, 4H).

1-(4-Fluorophenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-one (9e). Method A: **7** (0.39 g, 1.44 mmol), 4-chloro-1-(4-fluorophenyl)butan-1-one **8e** (0.28 g, 1.37 mmol), sodium bicarbonate (0.14 g, 1.64 mmol) with water (3 mL) and 2-butanone (15 mL) **9e** (0.17 g, 0.40 mmol, 29% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 – 7.96 (m, 2H),

7.48 – 7.44 (m, 4H), 7.31 – 7.26 (m, 4H), 7.20 – 7.15 (m, 2H), 7.14 – 7.08 (m, 2H), 2.97 – 2.94 (m, 4H), 2.46 – 2.36 (m, 3H), 2.15 (br s, 1H), 2.01 – 1.88 (m, 4H), 1.52 – 1.35 (m, 4H).

1-(4-Chlorophenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-one (9f). Method A: **7** (0.63 g, 2.34 mmol), 4-chloro-1-(4-chlorophenyl)butan-1-one **8f** (0.48 g, 2.23 mmol), sodium bicarbonate (0.23 g, 2.68 mmol) with water:2-butanone (18 mL, 1:5) to produce pure **9f** (0.39 g, 0.88 mmol, 39% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, J = 8.4 Hz, 2H), 7.48 – 7.44 (m, 4H), 7.42 (d, J = 8.6 Hz, 2H), 7.31 – 7.26 (m, 4H), 7.20 – 7.15 (m, 2H), 3.96 – 2.89 (m, 4H), 2.45 – 2.34 (m, 3H), 2.08 (br s, 1H), 1.99 – 1.87 (m, 4H), 1.50 – 1.30 (m, 4H).

1-(4-Bromophenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-one (9g). Method A: **7** (0.44 g, 1.64 mmol), 1-(4-bromophenyl)-4-chlorobutan-1-one (**8g**) (0.41 g, 1.56 mmol), sodium bicarbonate (0.16 g, 1.88 mmol) with water (3 mL) and 2-butanone (15 mL) to produce pure **9g** (0.25 g, 0.50 mmol, 32% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 – 7.79 (m, 2H), 7.60 – 7.56 (m, 2H), 7.48 – 7.45 (m, 4H), 7.31 – 7.26 (m, 4H), 7.20 – 7.15 (m, 2H), 2.95 – 2.90 (m, 4H), 2.45 – 2.35 (m, 3H), 2.17 (br s, 1H), 2.00 – 1.88 (m, 4H), 1.51 – 1.33 (m, 4H).

1-(4-Methoxyphenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-one (9h). Method A: **7** (0.49 g, 1.83 mmol), 4-chloro-1-(4-methoxyphenyl)butan-1-one (**8h**) (0.37 g, 1.74 mmol), sodium bicarbonate (0.18 g, 2.09 mmol) with water (3 mL) and 2-butanone (15 mL) to produce pure **9h** (0.28 g, 0.64 mmol, 36% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, J = 8.9 Hz, 2H), 7.51 – 7.44 (m, 4H), 7.32 – 7.26 (m, 4H), 7.21 – 7.12 (m, 2H), 6.92 (d, J = 8.9 Hz, 2H), 3.87 (s, 3H), 3.05 – 2.82 (m, 4H), 2.40 (q, J = 7.5, 6.6 Hz, 3H), 2.02 – 1.86 (m, 4H), 1.50 – 1.24 (m, 5H).

1-(4-(*Tert*-butyl)phenyl)-5-(4-(hydroxydiphenylmethyl)piperidin-1-yl)pentan-1-one (9j). Method A: **7** (0.54 g, 2.04 mmol), 1-(4-(*tert*-butyl)phenyl)-5-chloropentan-1-one (**8j**) (0.49 g, 1.94 mmol), sodium bicarbonate (0.20 g, 2.33 mmol) with water:2-butanone (18 mL, 1:5) to produce pure **9j** (0.60 g, 1.24 mmol, 64% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 – 7.84 (m, 2H), 7.51 – 7.42 (m, 6H), 7.34 – 7.27 (m, 4H), 7.21 – 7.12 (m, 2H), 3.02 – 2.91 (m, 4H), 2.43 (dd, *J* = 10.2, 4.6 Hz, 1H), 2.38 – 2.29 (m, 2H), 2.14 (s, 1H), 1.94 (td, *J* = 11.1, 4.0 Hz, 2H), 1.80 – 1.65 (m, 2H), 1.61 – 1.40 (m, 6H), 1.34 (s, 9H).

1-(4-(*Tert*-butyl)phenyl)-3-(4-(hydroxydiphenylmethyl)piperidin-1-yl)propan-1-one (9k). Method A: **7** (0.54 g, 2.03 mmol), 1-(4-(*tert*-butyl)phenyl)-3-chloropropan-1-one (**8k**) (0.44 g, 1.94 mmol), sodium bicarbonate (0.20 g, 2.32 mmol) with water:2-butanone (18 mL, 1:5) to produce pure **9k** (0.84 g, 1.84 mmol, 95% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.50 – 7.45 (m, 6H), 7.32 – 7.25 (m, 4H), 7.21 – 7.14 (m, 2H), 3.15 (t, *J* = 7.1 Hz, 2H), 3.01 – 2.96 (m, 2H), 2.81 (t, *J* = 7.1 Hz, 2H), 2.49 – 2.42 (m, 1H), 2.15 – 2.04 (m, 3H), 1.56 – 1.46 (m, 4H), 1.33 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.9, 171.1, 156.8, 145.8, 134.3, 128.2, 128.0, 126.5, 125.8, 125.5, 79.4, 60.4, 54.2, 53.4, 44.0, 36.3, 35.1, 31.1, 26.4, 21.1, 14.2. LCMS Retention time: 3.968 min. LCMS purity 98.1%. HRMS (ESI): *m/z* calcd for $C_{31}H_{37}NO_2$ $[M+H]^+$ 456.2896, found 456.2897.

1-(4-(*Tert*-butyl)phenyl)-2-(4-(hydroxydiphenylmethyl)piperidin-1-yl)ethanone (9l). Method A: **7** (0.40 g, 1.49 mmol), 1-(4-(*tert*-butyl)phenyl)-2-chloroethanone (**8l**) (0.30 g, 1.43 mmol), sodium bicarbonate (0.14 g, 1.71 mmol) with water (3 mL) and 2-butanone (15 mL) to produce pure **9l** (0.45 g, 1.02 mmol, 72% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (d, *J* = 8.6 Hz, 2H), 7.50 – 7.43 (m, 6H), 7.32 – 7.26 (m, 4H), 7.20 – 7.15 (m, 2H), 3.78 (s, 2H), 3.07 – 3.01 (m, 2H), 2.47 (tt, *J* = 11.8 Hz, 3.5 Hz, 1H), 2.26 – 2.18 (m, 2H), 1.66 – 1.45 (m, 5H), 1.33 (s, 9H).). ^{13}C NMR (125 MHz, $CDCl_3$): δ 196.1, 157.0, 145.8, 133.5, 129.8,

128.2, 128.0, 126.5, 125.8, 125.5, 125.1, 79.5, 64.2, 54.2, 43.8, 35.1, 31.2, 31.0, 26.2. LCMS Retention time: 3.987 min. LCMS purity 98.8%. HRMS (ESI): *m/z* calcd for $C_{30}H_{35}NO_2$ $[M+H]^+$ 442.2740, found 442.2743.

(4-(*Tert*-butyl)phenyl)(4-(hydroxydiphenylmethyl)piperidin-1-yl)methanone (9m). To a vial was added the **7** (0.23 g, 0.87 mmol), acetonitrile (3 mL) and triethylamine (0.18 mL, 1.30 mmol). The 4-(*tert*-butyl)benzoyl chloride (**8m**) (0.17 mL, 0.95 mmol) was added and the reaction stirred at 70 °C for 6 h and was then allowed to cool to rt and was diluted with EtOAc (15 mL) then washed with saturated $NaHCO_3$ (15 mL). The EtOAc was collected, dried with $MgSO_4$, filtered and adsorbed to silica and purified by MPLC (0 - 30 % EtOAc:hexanes) to produce pure **9m** (0.30 g, 0.71 mmol, 82% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 – 7.44 (m, 4H), 7.38 – 7.14 (m, 10H), 4.77 (br s, 1H), 3.84 (br s, 1H), 3.05 – 2.63 (m, 3H), 2.25 – 2.17 (m, 1H), 1.75 – 1.35 (m, 4H), 1.29 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 152.7, 145.4, 133.2, 128.3, 126.7, 125.7, 125.2, 79.5, 44.5, 34.7, 31.2. LCMS Retention time: 3.774 min. LCMS purity 100%. HRMS (ESI): *m/z* calcd for $C_{29}H_{33}NO_2$ $[M+H]^+$ 428.2583, found 428.2579.

1-(4-*Iso*-propylphenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-ol (1b). Method B: **9b** (0.15 g, 0.34 mmol) and MeOH (2 mL) sodium borohydride (0.026 g, 0.68 mmol) to produce pure **1b** (0.15 g, 0.32 mmol, 94% yield) as on oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 – 7.42 (m, 4H), 7.35 – 7.22 (m, 6H), 7.21 – 7.11 (m, 4H), 4.60 (dd, *J* = 8.1, 2.8 Hz, 1H), 3.14 (d, *J* = 11.0 Hz, 1H), 2.97 (d, *J* = 11.5 Hz, 1H), 2.87 (hept, *J* = 7.0 Hz, 1H), 2.51 – 2.33 (m, 3H), 2.29 (s, 1H), 2.11 – 1.87 (m, 3H), 1.85 – 1.42 (m, 8H), 1.22 (d, *J* = 6.9 Hz, 6H).^{13}C NMR (125 MHz, $CDCl_3$): δ 147.2, 146.1, 146.0, 128.2, 128.1, 126.5, 126.4, 126.1, 125.7, 125.7, 79.2, 73.5, 58.9, 54.7, 53.3, 44.2, 39.9, 33.7, 26.0, 25.9, 24.2, 24.1, 24.0. LCMS Retention time: 4.056

min. LCMS purity 98.6%. HRMS (ESI): *m/z* calcd for $C_{31}H_{39}NO_2$ $[M+H]^+$ 458.3053, found 458.3062.

1-(4-Methyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-ol (1c). Method B: **9c** (0.073 g, 0.17 mmol) and MeOH (2 mL) sodium borohydride (0.013 g, 0.34 mmol) to produce pure **1c** (0.070 g, 0.16 mmol, 94% yield) as on oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 – 7.43 (m, 4H), 7.34 – 7.13 (m, 8H), 7.13 – 7.06 (m, 2H), 4.59 (dd, *J* = 8.1, 2.9 Hz, 1H), 3.16 – 3.07 (m, 1H), 3.00 – 2.88 (m, 1H), 2.54 – 2.35 (m, 4H), 2.32 (s, 3H), 2.05 (td, *J* = 11.9, 2.7 Hz, 1H), 2.01 – 1.85 (m, 2H), 1.85 – 1.72 (m, 1H), 1.71 – 1.43 (m, 7H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.1, 146.0, 142.9, 136.0, 128.7, 128.1, 128.10, 128.07, 126.39, 126.37, 125.7, 125.64, 125.56, 79.2, 73.4, 58.9, 54.6, 53.4, 44.2, 39.9, 30.9, 26.0, 25.9, 24.0, 21.0. LCMS Retention time: 3.809 min. LCMS purity 98.6%. HRMS (ESI): *m/z* calcd for $C_{29}H_{35}NO_2$ $[M+H]^+$ 430.2740, found 430.2753.

1-Phenyl-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-ol (1d). Method B: **9d** (0.065 g, 0.16 mmol) and MeOH (2 mL) and sodium borohydride (0.012 g, 0.31 mmol) to produce pure **1d** (0.048 g, 0.12 mmol, 73% yield) as on oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 – 7.44 (m, 4H), 7.38 – 7.33 (m, 2H), 7.29 (td, *J* = 7.6, 4.0 Hz, 6H), 7.23 – 7.09 (m, 3H), 4.63 (dd, *J* = 8.2, 2.7 Hz, 1H), 3.24 – 3.07 (m, 1H), 3.02 – 2.90 (m, 1H), 2.54 – 2.26 (m, 4H), 2.13 – 1.88 (m, 3H), 1.87 – 1.71 (m, 2H), 1.71 – 1.42 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.0, 145.9, 145.8, 128.2, 128.1, 128.0, 126.6, 126.5, 126.4, 125.6, 125.6, 79.2, 73.6, 58.9, 54.7, 53.3, 44.2, 40.1, 26.0, 25.9, 24.1. LCMS Retention time: 3.711 min. LCMS purity 99.8%. HRMS (ESI): *m/z* calcd for $C_{28}H_{33}NO_2$ $[M+H]^+$ 416.2583, found 416.2592.

1-(4-Fluorophenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-ol (1e). Method B: **9e** (0.064 g, 0.15 mmol) and MeOH (2 mL) and sodium borohydride (0.011 g, 0.30 mmol) to produce pure **1e** (0.059 g, 0.14 mmol, 92% yield) as on oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 – 7.43 (m, 4H), 7.34 – 7.26 (m, 6H), 7.21 – 7.12 (m, 2H), 6.97 (t, *J* = 8.7 Hz, 2H), 4.65 – 4.53

(m, 1H), 3.20 – 3.08 (m, 1H), 3.00 – 2.84 (m, 1H), 2.51 – 2.29 (m, 4H), 2.09 (td, *J* = 11.9, 2.6 Hz, 1H), 2.01 – 1.82 (m, 2H), 1.80 – 1.41 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.6 (d, *J* = 243.8 Hz), 146.0 (d, *J* = 14.9 Hz), 141.7 (d, *J* = 3.1 Hz), 128.2, 128.1, 127.2, 127.1, 126.5, 126.4, 125.6, 125.5, 114.77 (d, *J* = 21.2 Hz), 79.2, 73.0, 58.8, 54.8, 53.1, 44.2, 40.3, 30.9, 26.0, 25.9, 24.1. LCMS Retention time: 3.691 min. LCMS purity 98.5%. HRMS (ESI): *m/z* calcd for $C_{28}H_{32}FNO_2$ $[M+H]^+$ 434.2489, found 434.2482.

1-(4-Chlorophenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-ol (1f). Method B: **9f** (0.16 g, 0.35 mmol) and MeOH (2 mL) sodium borohydride (0.026 g, 0.70 mmol) to produce pure **1f** (0.12 g, 0.26 mmol, 75% yield) as on oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 – 7.42 (m, 4H), 7.34 – 7.23 (m, 8H), 7.21 – 7.11 (m, 2H), 4.59 (dd, *J* = 8.0, 2.5 Hz, 1H), 3.19 – 3.10 (m, 1H), 3.03 – 2.80 (m, 1H), 2.52 – 2.41 (m, 1H), 2.41 – 2.31 (m, 3H), 2.08 (td, *J* = 12.0, 2.8 Hz, 1H), 2.03 – 1.84 (m, 2H), 1.83 – 1.35 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.0, 145.9, 144.5, 139.1, 128.19, 128.18, 128.1, 127.1, 126.49, 126.45, 125.62, 125.57, 79.2, 72.9, 58.8, 54.7, 53.2, 44.2, 40.2, 26.0, 25.9, 24.1. LCMS Retention time: 3.845 min. LCMS purity 98.4%. HRMS (ESI): *m/z* calcd for $C_{28}H_{32}ClNO_2$ $[M+H]^+$ 450.2194, found 450.2203.

1-(4-Bromophenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-ol (1g). Method B: **9g** (0.083 g, 0.17 mmol) and MeOH (2 mL) and sodium borohydride (0.013 g, 0.34 mmol) to produce pure **1g** (0.053 g, 0.11 mmol, 64% yield) as on oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 – 7.43 (m, 4H), 7.43 – 7.36 (m, 2H), 7.33 – 7.26 (m, 4H), 7.24 – 7.20 (m, 2H), 7.20 – 7.14 (m, 2H), 4.58 (dd, *J* = 8.2, 2.4 Hz, 1H), 3.19 – 3.07 (m, 1H), 3.00 – 2.86 (m, 1H), 2.46 (tt, *J* = 11.9, 3.4 Hz, 1H), 2.41 – 2.34 (m, 3H), 2.08 (td, *J* = 11.9, 2.7 Hz, 1H), 1.98 (td, *J* = 11.9, 2.7 Hz, 1H), 1.95 – 1.86 (m, 1H), 1.78 – 1.45 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.0, 145.9, 145.1, 131.1, 128.2, 128.1, 127.5, 126.5, 126.4, 125.6, 125.6, 120.2, 79.2, 72.9, 58.8, 54.7, 53.2, 44.1,

40.1, 26.0, 25.9, 24.1. LCMS Retention time: 3.902 min. LCMS purity 99.1%. HRMS (ESI): *m/z* calcd for $C_{28}H_{32}BrNO_2$ $[M+H]^+$ 494.1685, found 494.1673.

1-(4-Methoxyphenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-ol (1h). Method B: **9h** (0.11 g, 0.26 mmol) and MeOH (2 mL) and sodium borohydride (0.019 g, 0.51 mmol) to produce pure **1h** (0.062 g, 0.14 mmol, 55% yield) as on oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 – 7.44 (m, 4H), 7.32 – 7.23 (m, 6H), 7.20 – 7.11 (m, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 4.58 (dd, *J* = 8.3, 2.6 Hz, 1H), 3.78 (s, 3H), 3.19 – 3.06 (m, 1H), 3.01 – 2.87 (m, 1H), 2.52 – 2.29 (m, 4H), 2.06 (td, *J* = 11.9, 2.6 Hz, 1H), 2.00 – 1.84 (m, 2H), 1.84 – 1.70 (m, 1H), 1.70 – 1.39 (m, 7H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.3, 146.1, 146.0, 138.1, 128.1, 128.1, 126.7, 126.4, 126.4, 125.7, 125.6, 113.5, 79.2, 73.2, 58.9, 55.2, 54.7, 53.2, 44.2, 40.0, 26.0, 25.9, 24.1. LCMS Retention time: 3.620 min. LCMS purity 98.3%. HRMS (ESI): *m/z* calcd for $C_{29}H_{35}NO_3$ $[M+H]^+$ 446.2689, found 446.2728.

Methyl 4-(1-hydroxy-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butyl)benzoate (1i). Step 1: Method B: **8i** (0.042 g, 0.18 mmol) and MeOH with sodium borohydride (0.013 g, 0.35 mmol) to produce methyl 4-(4-chloro-1-hydroxybutyl)benzoate (0.037 g, 0.15 mmol, 87% yield) and was carried into the next reaction. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 4.8 – 4.6 (m, 1H), 3.90 (s, 3H), 3.58 – 3.52 (m, 2H), 2.19 (br s, 1H), 1.96 – 1.78 (m, 4H). Step 2: Methyl 4-(4-chloro-1-hydroxybutyl)benzoate (0.037 g, 0.15 mmol), **7** (0.12 g, 0.46 mmol), sodium bicarbonate (0.026 g, 0.31 mmol), sodium iodide (1.14 mg, 7.6 μmol) and the vial was evacuated with argon 3 times. Dry acetonitrile (2 mL) was added and the reaction stirred overnight at reflux and was then cooled to rt after 18 h and the solvent was concentrated. The residue was dissolved in CH_2Cl_2 (5 mL) and washed with 0.1 N HCl (5 mL), water (5 mL) and brine (5 mL). The product was purified by MPLC (0 - 10 % MeOH: CH_2Cl_2) to produce pure **1i** (0.027 g, 0.057 mmol, 37% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ

7.97 (d, *J* = 8.4 Hz, 2H), 7.52 – 7.47 (m, 4H), 7.42 (d, *J* = 7.9 Hz, 2H), 7.32 – 7.29 (m, 4H), 7.20 – 7.14 (m, 2H), 4.66 (m, 1H), 3.90 (s, 3H), 3.14 (m, 1H), 2.94 (m, 1H), 2.78 (br s, 1H), 2.52 – 2.43 (m, 1H), 2.39 (t, *J* = 4.8 Hz, 2H), 2.13 – 2.06 (m, 1H), 2.04 – 1.92 (m, 2H), 1.77 – 1.47 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.2, 151.4, 146.0, 145.9, 129.5, 128.4, 128.2, 128.2, 126.5, 126.5, 125.7, 125.6, 79.2, 73.2, 58.8, 54.7, 51.9, 44.2, 40.0, 26.0, 25.9, 24.0. LCMS Retention time: 3.652 min. LCMS purity 100%. HRMS (ESI): *m/z* calcd for $C_{30}H_{35}NO_4$ $[M+H]^+$ 474.2638, found 474.2646.

1-(4-(*Tert*-butyl)phenyl)-5-(4-(hydroxydiphenylmethyl)piperidin-1-yl)pentan-1-ol (1j). Method B: **9j** (0.20 g, 0.42 mmol) and MeOH (2 mL) and sodium borohydride (0.032 g, 0.84 mmol) to produce pure **1j** (0.16 g, 0.32 mmol, 76% yield) as on oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 – 7.45 (m, 4H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.31 – 7.24 (m, 6H), 7.19 – 7.14 (m, 2H), 4.65 – 4.60 (m, 1H), 2.98 – 2.90 (br m, 1H), 2.48 – 2.38 (m, 1H), 2.30 (t, *J* = 7.2 Hz, 2H), 2.23 (br s, 1H), 1.97 – 1.87 (m, 2H), 1.84 – 1.60 (m, 4H), 1.55 – 1.35 (m, 8H), 1.31 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.3, 146.0, 142.0, 128.1, 126.4, 125.8, 125.5, 125.3, 79.4, 74.1, 58.4, 54.1, 54.0, 44.2, 38.5, 34.5, 31.4, 31.3, 26.5, 26.3, 26.2, 23.7. LCMS Retention time: 4.254 min. LCMS purity 96.4%. HRMS (ESI): *m/z* calcd for $C_{33}H_{43}NO_2$ $[M+H]^+$ 486.3366, found 486.3370.

1-(4-(*Tert*-butyl)phenyl)-3-(4-(hydroxydiphenylmethyl)piperidin-1-yl)propan-1-ol (1k). Method B: **9k** (0.12 g, 0.26 mmol) and MeOH (2 mL) and sodium borohydride (0.019 g, 0.51 mmol) to produce pure **1k** (0.11 g, 0.23 mmol, 91% yield) as on oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 – 7.44 (m, 4H), 7.36 – 7.25 (m, 8H), 7.22 – 7.16 (m, 2H), 6.72 (br s, 1H), 4.90 – 4.85 (m, 1H), 3.21 – 3.15 (br m, 1H), 3.11 – 3.05 (br m, 1H), 2.70 – 2.62 (m, 1H), 2.57 – 2.40 (m, 2H), 2.14 – 2.06 (m, 2H), 1.91 – 1.79 (m, 3H), 1.57 – 1.45 (m, 4H), 1.31 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.6, 145.8, 145.7, 141.9, 128.2, 128.1, 126.6, 126.5, 125.8, 125.7, 125.2,

125.0, 79.4, 75.3, 57.3, 55.2, 53.2, 44.1, 34.4, 33.7, 31.4, 26.7, 26.4. LCMS Retention time: 4.006 min. LCMS purity 97.7%. HRMS (ESI): *m/z* calcd for $C_{31}H_{39}NO_2$ $[M+H]^+$ 458.3053, found 458.3066.

1-(4-(*Tert*-butyl)phenyl)-2-(4-(hydroxydiphenylmethyl)piperidin-1-yl)ethanol (1l). Method B: **9l** (0.11 g, 0.26 mmol) and MeOH (1 mL) and sodium borohydride (0.019 g, 0.51 mmol) to produce pure **1l** (0.11 g, 0.24 mmol, 93% yield) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 – 7.46 (m, 4H), 7.37 – 7.26 (m, 8H), 7.22 – 7.17 (M, 2H), 4.67 (m, 1H), 4.01 (br s, 1H), 3.20 (m, 1H), 2.86 (m, 1H), 2.50 – 2.45 (m, 3H), 2.37 – 2.30 (m, 1H), 2.10 – 2.02 (m, 1H), 1.60 – 1.45 (m, 5H), 1.31 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.3, 145.82, 145.78, 139.1, 128.20, 128.2, 126.6, 126.6, 125.7, 125.6, 125.2, 79.5, 68.6, 66.3, 55.8, 53.4, 52.2, 44.1, 34.5, 31.3, 26.8, 26.5. LCMS Retention time: 4.083 min. LCMS purity 100%. HRMS (ESI): *m/z* calcd for $C_{30}H_{37}NO_2$ $[M+H]^+$ 444.2896, found 444.2915.

4-(1-Hydroxy-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butyl)benzoic acid (1m). To a vial was added the **1i** (0.020 g, 0.041 mmol) and THF (1 mL). The LiOH (6.9 mg, 0.29 mmol) was dissolved in water (1 mL) and added to the reaction. The reaction stirred at rt for 18 h and was then acidified with 1.0 M HCl to pH 2 - 3 and extracted with CH_2Cl_2 (3 x 5 mL). The organic layer was concentrated and purified by reverse-phase MPLC (10 - 100 % CH_3CN:water) to produce pure **1m** (0.009 g, 0.020 mmol, 47% yield). ^{1}H NMR (400 MHz, CD_3OD): δ 7.85 (d, *J* = 8.2 Hz, 2H), 7.55 – 7.45 (m, 4H), 7.38 – 7.23 (m, 6H), 7.22 – 7.11 (m, 2H), 4.70 (t, *J* = 5.8 Hz, 1H), 3.53 – 3.42 (m, 2H), 2.99 (t, *J* = 7.1 Hz, 2H), 2.93 – 2.74 (m, 3H), 1.86 – 1.56 (m, 8H). ^{13}C NMR (125 MHz, CD_3OD): δ 174.7, 148.2, 147.2, 137.6, 130.4, 129.1, 127.6, 127.0, 126.4, 79.9, 74.0, 53.9, 36.9, 25.5, 21.8. LCMS Retention time: 2.490 min. LCMS purity 100%. HRMS (ESI): *m/z* calcd for $C_{29}H_{33}NO_4$ $[M+H]^+$ 460.2482, found 460.2483.

1-([1,1'-Biphenyl]-4-yl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-ol (1n). Step 1: to a vial was added the **9g** (0.098 g, 0.20 mmol), 1,1'-bis(di-*tert*-butylphosphino)ferrocene palladium dichloride, (2.7 mg, 4.0 μmol) and phenylboronic acid (0.029 g, 0.24 mmol) followed by acetonitrile (1.5 mL). The potassium carbonate (0.041 g, 0.30 mmol) was dissolved in water (1.5 mL) and added the reaction. The reaction stirred at 60 °C for 18 h. The reaction was stopped and the organic layer was diluted with saturated $NaHCO_3$ (10 mL) and extracted with EtOAc (2 x 15 mL). The organic layers were collected, dried with $MgSO_4$, filtered and purified by reverse-phase MPLC (10 - 100% CH_3CN:water) to produce the desired intermediate 1-([1,1'-biphenyl]-4-yl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-one (0.035 g, 0.071 mmol, 36% yield) and was carried into step 2. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, *J* = 8.6 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.64 – 7.61 (m, 2H), 7.50 – 7.45 (m, 6H), 7.42 – 7.38 (m, 1H), 7.31 – 7.26 (m, 4H), 7.19 – 7.14 (m, 2H), 3.02 – 2.91 (m, 4H), 2.46 – 2.37 (m, 3H), 2.10 (br s, 1H), 1.97 – 1.92 (m, 4H), 1.50 – 1.35 (m, 4H). Step 2: the intermediate from the previous reaction was carried into method B: 1-([1,1'-biphenyl]-4-yl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-one (0.035 g, 0.071 mmol) and MeOH (2 mL) and sodium borohydride (5.4 mg, 0.143 mmol) to produce pure **1n** (0.033 g, 0.067 mmol, 94% yield) as on oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 – 7.55 (m, 2H), 7.53 – 7.46 (m, 6H), 7.43 – 7.38 (m, 4H), 7.34 – 7.25 (m, 5H), 7.19 – 7.13 (m, 2H), 4.65 (dd, *J* = 8.2 Hz, 2.7 Hz, 1H), 3.16 – 3.10 (m, 1H), 2.99 – 2.93 (m, 1H), 2.56 (br s, 1H), 2.50 – 2.34 (m, 3H), 2.10 – 1.92 (m, 3H), 1.86 – 1.76 (m, 1H), 1.70 – 1.45 (m, 7H).). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.1, 146.0, 145.0, 141.1, 139.4, 128.6, 128.2, 128.1, 127.0, 126.9, 126.8, 126.4, 126.4, 126.1, 125.7, 125.6, 79.2, 73.3, 58.9, 54.7, 53.3, 44.2, 40.0, 26.0, 25.9, 24.1. LCMS Retention time: 4.049 min. LCMS purity 97.6%. HRMS (ESI): *m/z* calcd for $C_{34}H_{37}NO_2$ $[M+H]^+$ 492.2896, found 492.2893.

Methyl 2-(4-(1-hydroxy-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butyl)phenyl)-2-methylpropanoate (1o). Method B: **18** (0.148 g, 0.288 mmol) and MeOH (1 mL) and sodium borohydride (0.016 g, 0.432 mmol) to produce pure **1o** (0.11 g, 0.21 mmol, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 – 7.47 (m, 4H), 7.36 – 7.25 (m, 8H), 7.20 (m, 2H), 4.63 (dd, *J* = 8.2, 2.7 Hz, 1H), 3.65 (s, 3H), 3.25 – 3.09 (m, 1H), 3.07 – 2.90 (m, 1H), 2.55 – 2.36 (m, 3H), 2.29 (s, 1H), 2.10 (td, *J* = 11.9, 2.6 Hz, 1H), 2.02 – 1.86 (m, 2H), 1.87 – 1.44 (m, 14H). LCMS Retention time: 3.786 min. LCMS purity 98.2%. HRMS (ESI): *m/z* calcd for $C_{33}H_{41}NO_4$ $[M+H]^+$ 516.3108, found 516.3141.

2-(4-(1-hydroxy-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butyl)phenyl)-2-methyl propanoic acid (1p). To a vial was added the **1o** (0.094 g, 0.18 mmol) and THF (3 mL) to form a solution. The LiOH (0.022 g, 0.91 mmol) was dissolved in water (3 mL) and then added to the reaction and stirred at rt for 18 h. The reaction was acidified with 1.0 M HCl in water to pH 3. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL) and organic layers were combined and concentrated. The residue was purified by reverse-phase MPLC (10 - 100% CH_3CN:water) to produce 2-(4-(1-hydroxy-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butyl)phenyl)-2-methylpropanoic acid **1p** (0.038 g, 0.075 mmol, 41% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.22 (s, 1H), 7.55 – 7.45 (m, 4H), 7.31 – 7.19 (m, 8H), 7.17 – 7.07 (m, 2H), 5.28 (s, 1H), 4.47 (t, *J* = 5.9 Hz, 1H), 2.98 – 2.82 (m, 2H), 2.36 – 2.24 (m, 2H), 2.07 – 1.92 (m, 2H), 1.45 (s, 12H), 1.31 – 1.19 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.7, 163.7, 147.2, 144.4, 143.4, 127.8, 125.8, 125.7, 125.6, 125.1, 78.4, 71.8, 57.7, 53.4, 53.2, 45.5, 43.1, 37.3, 26.5, 25.6, 22.6. LCMS Retention time: 2.612 min. LCMS purity 100%. HRMS (ESI): *m/z* calcd for $C_{32}H_{39}NO_4$ $[M+H]^+$ 502.2951, found 502.2952.

(1-(4-(4-(*Tert*-butyl)phenyl)butyl)piperidin-4-yl)diphenylmethanol (2a). To a vial was added the **7** (0.15 g, 0.57 mmol), 1-(*tert*-butyl)-4-(4-chlorobutyl)benzene (**10a**) (0.15 g, 0.69 mmol) and

potassium carbonate (0.47 g, 3.43 mmol) in acetonitrile (5 mL). The reaction stirred overnight at 85 °C and for 18 h and was then cooled to rt and filtered. The filtrate was then diluted with brine and extracted with EtOAc (3 x 15 mL). The organic layers were combined, dried with $MgSO_4$, filtered and purified by reverse-phase MPLC (10 - 100% CH_3CN:water) to produce pure **2a** (0.18 g, 0.40 mmol, 69% yield) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.34 (m, 4H), 7.19 – 7.14 (m, 6H), 7.07 – 7.02 (m, 2H), 6.99 – 6.95 (m, 2H), 2.86 – 2.80 (m, 2H), 2.45 (t, *J* = 7.3 Hz, 2H), 2.35 – 2.26 (m, 1H), 2.22 – 2.17 (m, 2H), 1.84 – 1.76 (m, 3H), 1.52 – 1.30 (m, 8H), 1.18 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.4, 146.0, 139.4, 128.1, 128.0, 126.4, 125.8, 125.1, 79.5, 58.8, 54.1, 44.2, 35.2, 34.3, 31.4, 29.5, 26.8, 26.4. LCMS Retention time: 3.928 min. LCMS purity 98.5%. HRMS (ESI): *m/z* calcd for $C_{32}H_{41}NO$ $[M+H]^+$ 456.3260, found 456.3282.

(1-(3-(4-(*Tert*-butyl)phenyl)propyl)piperidin-4-yl)diphenylmethanol (2b). Same procedure as **2a** using **7** (0.14 g, 0.53 mmol), 1-(*tert*-butyl)-4-(3-chloropropyl)benzene (**10b**) (0.13 g, 0.64 mmol) and potassium carbonate (0.44 g, 3.18 mmol) in acetonitrile (5 mL). Purified by reverse-phase MPLC (10 - 100% CH_3CN:water) to produce pure **2b** (0.15 g, 0.34 mmol, 65% yield) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 – 7.45 (m, 4H), 7.31 – 7.24 (m, 6H), 7.19 – 7.14 (m, 2H), 7.11 – 7.08 (m, 2H), 2.96 (m, 2H), 2.57 (t, *J* = 7.7 Hz, 2H), 2.48 – 2.32 (m, 3H), 2.22 (br s, 1H), 1.97 – 1.90 (m, 2H), 1.83 – 1.75 (m, 2H), 1.53 – 1.45 (m, 4H), 1.29 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.5, 145.9, 138.8, 128.1, 127.9, 126.4, 125.7, 125.2, 79.4, 58.2, 53.9, 44.0, 40.9, 34.3, 33.2, 31.2, 28.4, 26.1. LCMS Retention time: 2.965 min. LCMS purity 97.2%. HRMS (ESI): *m/z* calcd for $C_{31}H_{39}NO$ $[M+H]^+$ 442.3104, found 442.3113.

(1-(4-(*Tert*-butyl)phenethyl)piperidin-4-yl)diphenylmethanol (2c). Same procedure as **2a** using **7** (0.15 g, 0.56 mmol), 1-(*tert*-butyl)-4-(2-chloroethyl)benzene (**10c**) (0.11 g, 0.56 mmol) and potassium carbonate (0.47 g, 3.37 mmol) in acetonitrile (5 mL). Purified by reverse-phase

MPLC (10 - 100% CH_3CN:water) to produce pure **2c** (0.18 g, 0.421 mmol, 75% yield) as an oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.53 – 7.45 (m, 4H), 7.35 – 7.27 (m, 6H), 7.22 – 7.15 (m, 2H), 7.15 – 7.08 (m, 2H), 3.09 – 3.00 (m, 2H), 2.81 – 2.72 (m, 2H), 2.60 – 2.53 (m, 2H), 2.51 – 2.40 (m, 1H), 2.28 (s, 1H), 2.11 – 2.00 (m, 2H), 1.63 – 1.44 (m, 4H), 1.30 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.8, 145.9, 137.3, 128.3, 128.1, 126.5, 125.8, 125.2, 79.5, 60.8, 54.0, 44.2, 40.9, 34.3, 33.1, 31.4, 26.4. LCMS Retention time: 4.384 min. LCMS purity 99.7%. HRMS (ESI): *m/z* calcd for $C_{30}H_{37}NO$ $[M+H]^+$ 428.2947, found 428.2955.

(1-(4-(*Tert*-butyl)benzyl)piperidin-4-yl)diphenylmethanol (2d). Method C: **7** (0.085 mL, 0.39 mmol), 4-tert-butylbenzyl bromide (**10d**) (0.098 g, 0.43 mmol), triethylamine (0.082 mL, 0.59 mmol) acetonitrile (2 mL) was then added and the reaction stirred at 70 °C and stirred for 5 h then diluted with EtOAc (15 mL) and washed with saturated $NaHCO_3$ (15 mL). The EtOAc was collected, dried with $MgSO_4$, filtered and adsorbed to silica and purified by reverse-phase MPLC (10 - 100 % CH_3CN:water) to produce pure **2d** (0.13 g, 0.32 mmol, 81% yield) as a brown oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.30 (m, 4H), 7.23 – 7.11 (m, 6H), 7.11 – 6.95 (m, 4H), 3.34 (s, 2H), 2.86 – 2.71 (m, 2H), 2.35 – 2.20 (m, 1H), 1.99 (s, 1H), 1.89 – 1.76 (m, 2H), 1.42 – 1.28 (m, 4H), 1.18 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.8, 146.0, 135.1, 128.9, 128.1, 126.4, 125.8, 125.0, 79.5, 62.8, 53.9, 44.2, 34.4, 31.4, 26.5. LCMS Retention time: 4.186 min. LCMS purity 99.7%. HRMS (ESI): *m/z* calcd for $C_{29}H_{35}NO$ $[M+H]^+$ 414.2767, found 414.2786.

4-(4-Benzylpiperidin-1-yl)-1-(4-(*tert*-butyl)phenyl)butan-1-ol (2e). Step 1: To a vial was added **12** (0.40 g, 1.21 mmol) and dry CH_2Cl_2 (15 mL). The methanesulfonyl chloride (0.024 g, 0.35 g, 1.82 mmol) and triethylamine (0.51 mL, 3.64 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 3-(4-(hydroxy

diphenylmethyl)piperidin-1-yl)propyl-4-methylbenzenesulfonate (0.19 g, 0.40 mmol, 33% yield) which a portion was carried into step 2. 1H NMR (400 MHz, $CDCl_3$): δ 7.69 – 7.66 (m, 2H), 7.46 – 7.41 (m, 4H), 7.24 – 7.19 (m, 4H), 7.15 – 7.05 (m, 4H), 4.26 – 4.12 (m, 4H), 3.73 – 3.65 (m, 2H), 3.27 – 3.18 (m, 2H), 2.68 – 2.60 (m, 1H), 2.47 – 2.37 (m, 2H), 2.30 (s, 3H), 1.88 – 1.76 (m, 3H), 1.52 – 1.43 (m, 2H). Step 2: To a vial was added the 3-(4-(hydroxydiphenyl methyl)piperidin-1-yl)propyl-4-methylbenzenesulfonate (0.088 g, 0.18 mmol), 4-(*tert*-butyl) aniline (0.035 mL, 0.22 mmol) and triethylamine (0.038 mL, 0.28 mmol) with acetonitrile (3 mL). The reaction began to stir at 85 °C for 18 h and was then cooled to rt and diluted with saturated $NaHCO_3$ (10 mL) then extracted with EtOAc (2 x 15 mL). The organic layers were combined and concentrated then purified by reverse-phase MPLC (10 - 100% CH_3CN:water) to produce pure **2e** (0.038 g, 0.083 mmol, 45% yield). 1H NMR (400 MHz, CDCl3): δ 7.50 – 7.46 (m, 4H), 7.33 – 7.28 (m, 4H), 7.21 – 7.16 (m, 4H), 6.51 (d, J = 8.7 Hz, 2H), 3.13 (t, J = 6.4 Hz, 2H), 3.02 – 2.96 (m, 2H), 2.49 – 2.41 (m, 3H), 2.15 (br s, 1H), 2.00 – 1.93 (m, 2H), 1.80 – 1.73 (m, 2H), 1.57 – 1.43 (m, 5H), 1.27 (s, 9H). 13C NMR (125 MHz, CDCl3): δ 146.4, 145.9, 139.7, 128.2, 126.5, 125.9, 125.8, 112.4, 79.6, 57.4, 54.2, 44.2, 43.7, 33.8, 31.5, 26.6, 26.2. LCMS Retention time: 4.208 min. LCMS purity 100%. HRMS (ESI): m/z calcd for C31H40N2O [M+H]+ 457.3213, found 457.3206.

(1-(3-(4-(*Tert*-butyl)phenoxy)propyl)piperidin-4-yl)diphenylmethanol (2f). To a vial was added the 3-(4-(hydroxydiphenyl methyl)piperidin-1-yl)propyl 4-methylbenzenesulfonate (0.11 g, 0.22 mmol) (from **2e** step 1), 4-(*tert*-butyl)phenol (0.039 g, 0.26 mmol) and triethylamine (0.046 mL, 0.33 mmol) with acetonitrile (3 mL). The reaction began to stir at 85 °C for 18 h and was then cooled to rt and diluted with saturated $NaHCO_3$ (10 mL) then extracted with EtOAc (2 x 15 mL). The organic layers were combined and concentrated then purified by reverse-phase MPLC (10 - 100% CH_3CN:water) to produce pure **2f** (0.015 g, 0.033 mmol, 15% yield). ^{1}H

NMR (400 MHz, $CDCl_3$): δ 7.49 – 7.46 (m, 4H), 7.31 – 7.26 (m, 6H), 7.19 – 7.14 (m, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 3.96 (t, *J* = 6.4 Hz, 2H), 3.01 – 2.94 (m, 2H), 2.51 – 2.40 (m, 3H), 1.99 – 1.89 (m, 5H), 1.52 – 1.45 (m, 4H), 1.28 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.7, 145.9, 143.2, 128.1, 126.5, 126.1, 125.7, 116.3, 113.9, 79.5, 66.3, 60.4, 55.4, 54.1, 44.1, 34.0, 31.5, 29.7, 27.0, 26.4. LCMS Retention time: 4.293 min. LCMS purity 95.2%. HRMS (ESI): *m/z* calcd for $C_{31}H_{39}NO_2$ $[M+H]^+$ 458.3053, found 458.3065.

(1-(4-Amino-4-(4-(*tert*-butyl)phenyl)butyl)piperidin-4-yl)diphenylmethanol (2g). To a vial was added the **9a** (0.20 g, 0.43 mmol), ammonium acetate (0.33 g, 4.26 mmol) and sodium cyanoborohydride (0.040 g, 0.64 mmol) with MeOH (5 mL). The reaction stirred at rt for 18 h then concentrated and diluted with aqueous ammonium hydroxide (10 mL) then extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, dried with $MgSO_4$, filtered and concentrated then purified by reverse-phase MPLC (10 - 100% CH_3CN:water). Fractions containing the desired product were further purified by MPLC (0 - 10% MeOH (5% NH_3OH): CH_2Cl_2) to produce pure **2g** (0.010 g, 0.021 mmol, 5% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.44 (m, 4H), 7.34 – 7.26 (m, 6H), 7.22 – 7.14 (m, 4H), 3.84 (t, *J* = 6.7 Hz, 1H), 2.95 – 2.87 (m, 2H), 2.46 – 2.37 (m, 1H), 2.28 (t, *J* = 7.6 Hz, 2H), 1.95 – 1.85 (m, 2H), 1.70 – 1.60 (m, 5H), 1.55 – 1.40 (m, 6H), 1.30 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.7, 146.0, 143.3, 128.1, 126.5, 125.9, 125.8, 125.3, 79.5, 58.7, 55.8, 54.2, 54.0, 44.2, 37.5, 34.4, 31.4, 26.4, 24.2. LCMS Retention time: 2.397 min. LCMS purity 100%. HRMS (ESI): *m/z* calcd for $C_{32}H_{42}N_2O$ $[M+H]^+$ 471.3369, found 471.3366.

(*S*)-1-(4-(*Tert*-butyl)phenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-ol (2h). To a vial was added **23** (0.14 g, 0.26 mmol) and the vial was evacuated with nitrogen three times. The dry THF (9 mL) was then added. The 1.0 M lithium aluminum hydride (0.26 mL, 0.26 mmol) in THF was added dropwise at rt and the reaction stirred for 5 h. The reaction was

quenched slowly with water (10 mL) and then extracted with diethyl ether (2 x 10 mL). The ether layer was dried with $MgSO_4$, filtered, concentrated and purified by reverse-phase MPLC (10 - 100% CH_3CN:water) to produce pure **2h** (0.10 g, 0.21 mmol, 81 % yield). $[\alpha]_D^{25}$ - 38.8 (*c* 1, CH_2Cl_2) ^1H NMR (400 MHz, $CDCl_3$): δ 7.52 – 7.46 (m, 4H), 7.33 – 7.25 (m, 8H), 7.21 – 7.15 (m, 2H), 4.61 – 4.56 (m, 1H), 3.16 – 3.11 (br m, 1H), 3.00 – 2.94 (m, 1H), 2.51 – 2.34 (m, 4H), 2.10 – 1.88 (m, 4H), 1.83 – 1.75 (m, 1H), 1.70 – 1.45 (m, 6H), 1.30 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 149.4, 146.1, 146.0, 142.7, 128.2, 128.1, 126.5, 126.4, 125.7, 125.6, 125.4, 125.0, 79.3, 73.4, 58.9, 54.7, 53.3, 44.2, 39.7, 34.4, 31.4, 26.1, 26.0, 24.1. LCMS Retention time: 4.159 min. LCMS purity 99.7%. HRMS (ESI): *m/z* calcd for $C_{32}H_{41}NO_2$ $[M+H]^+$ 472.3209, found 472.3234.

(*R*)-1-(4-(*Tert*-butyl)phenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-ol (2i). To a vial was added **24** (0.24 g, 0.46 mmol) and this vial was evacuated with nitrogen three times. The dry THF (4.5 mL) was added and then the 1.0 M lithium aluminum hydride (0.46 mL, 0.46 mmol) in THF was added portionwise at rt for 5 h. The reaction was quenched slowly with water (10 mL) and then extracted with diethyl ether (2 x 10 mL). The ether layer was dried with $MgSO_4$, filtered, concentrated and purified by reverse-phase MPLC (10 - 100% CH_3CN:water) to produce pure **2i** (0.12 g, 0.25 mmol, 53% yield). $[\alpha]_D^{25}$ + 38.6 (*c* 1, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.52 – 7.46 (m, 4H), 7.33 – 7.25 (m, 8H), 7.21 – 7.15 (m, 2H), 4.61 – 4.56 (m, 1H), 3.16 – 3.11 (br m, 1H), 3.00 – 2.94 (m, 1H), 2.51 – 2.34 (m, 4H), 2.10 – 1.88 (m, 4H), 1.83 – 1.75 (m, 1H), 1.70 – 1.45 (m, 6H), 1.30 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 149.4, 146.1, 146.0, 142.7, 128.2, 128.1, 126.5, 126.4, 125.7, 125.6, 125.4, 125.0, 79.3, 73.4, 58.9, 54.7, 53.3, 44.2, 39.7, 34.4, 31.4, 26.1, 26.0, 24.1. LCMS Retention time: 4.156 min. LCMS purity 97.8%. HRMS (ESI): *m/z* calcd for $C_{32}H_{41}NO_2$ $[M+H]^+$ 472.3209, found 472.3236.

(1-(3-(*Tert*-butyl)phenethyl)piperidin-4-yl)diphenylmethanol (3a). Method C: 1-(2-bromoethyl)-3-(*tert*-butyl)benzene **10e** (0.060 g, 0.18 mmol), **7** (0.048 g, 0.18 mmol), triethylamine (0.038 mL, 0.271 mmol) and acetonitrile (1 mL). Purified by reverse-phase MPLC (10 - 100% CH_3CN:water) to produce the pure **3a** (0.065 g, 0.15 mmol, 84% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.47 (m, 4H), 7.32 – 7.27 (m, 4H), 7.23 – 7.16 (m, 5H), 7.01 – 6.98 (m, 1H), 3.09 – 3.04 (m, 2H), 2.81 – 2.76 (m, 2H), 2.61 – 2.55 (m, 2H), 2.51 – 2.43 (m, 1H), 2.28 (br s, 1H), 2.10 – 2.02 (m, 2H), 1.30 (s, 9H), 1.32 – 1.26 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.2, 145.9, 140.0, 128.1, 128.0, 126.5, 125.8, 125.7, 125.7, 123.0, 79.5, 54.1, 44.2, 34.6, 34.0, 31.6, 31.4, 26.4, 22.6. LCMS Retention time: 4.214 min. LCMS purity 96.4%. HRMS (ESI): *m/z* calcd for $C_{30}H_{37}NO$ $[M+H]^+$ 428.2948, found 428.2970.

(1-(2-(*Tert*-butyl)phenethyl)piperidin-4-yl)diphenylmethanol (3b). Method C: 2-(*tert*-butyl)phenethyl 4-methylbenzenesulfonate **10f** (0.022 g, 0.066 mmol), **7** (0.018 g, 0.066 mmol), triethylamine (0.014 mL, 0.099 mmol) and acetonitrile (1 mL). Purified by reverse-phase MPLC (10 - 100% CH_3CN:water) to produce the pure **3b** (0.013 g, 0.030 mmol, 46% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.48 (m, 4H), 7.37 – 7.28 (m, 5H), 7.21 – 7.09 (m, 5H), 3.15 – 3.04 (m, 4H), 2.65 – 2.60 (m, 2H), 2.52 – 2.42 (m, 1H), 2.17 – 2.08 (m, 3H), 1.60 – 1.53 (m, 4H), 1.41 (s. 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.7, 145.9, 138.5, 132.1, 128.2, 126.5, 126.1, 125.9, 125.8, 125.8, 79.5, 61.7, 54.2, 44.2, 35.7, 31.7, 29.7, 26.4. LCMS Retention time: 4.200 min. LCMS purity 99.3%. HRMS (ESI): *m/z* calcd for $C_{30}H_{37}NO$ $[M+H]^+$ 428.2947, found 428.2948.

(1-(4-Fluorophenethyl)piperidin-4-yl)diphenylmethanol (3c). Method C: **7** (0.099 g, 0.37 mmol), 1-(2-bromoethyl)-4-fluorobenzene **10g** (0.047 mL, 0.34 mmol), triethylamine (0.070 mL, 0.51 mmol) and acetonitrile (10 mL). Purified by MPLC (0 - 10 % MeOH:CH_2Cl_2) to produce pure **3c** (0.12 g, 0.32 mmol, 94% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.47 (m, 4H),

7.32 – 7.27 (m, 4H), 7.21 – 7.11 (m, 4H), 6.98 – 6.92 (m, 2H), 3.06 – 3.00 (m, 2H), 2.78 – 2.72 (m, 2H), 2.56 – 2.51 (m, 2H), 2.50 – 2.42 (m, 1H), 2.21 (br s, 1H), 2.08 – 1.99 (m, 2H), 1.57 – 1.48 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.2 (d, J = 243.6 Hz), 145.9, 136.5 (d, J = 3.2 Hz), 129.9 (d, J = 7.9 Hz), 128.1, 126.5, 125.8, 115.0 (d, J = 21.2 Hz), 79.5, 60.8, 54.1, 44.2, 33.0, 26.4, 21.0. LCMS Retention time: 3.733 min. LCMS purity 96.8%. HRMS (ESI): *m/z* calcd for $C_{26}H_{28}FNO$ $[M+H]^+$ 390.2228, found 390.2227.

(1-(4-Chlorophenethyl)piperidin-4-yl)diphenylmethanol (3d). Method C: **7** (0.22 g, 0.83 mmol), 1-(2-bromoethyl)-4-chlorobenzene **10h** (0.17 g, 0.75 mmol), triethylamine (0.16 mL, 1.13 mmol) and acetonitrile (4 mL). Purified by reverse-phase MPLC (10 - 100% CH_3CN:water) to produce pure **3d** (0.22 g, 0.55 mmol, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.36 (m, 4H), 7.20 – 7.15 (m, 4H), 7.12 – 7.09 (m, 2H), 7.08 – 7.03 (m, 2H), 6.99 – 6.96 (m, 2H), 2.92 – 2.87 (m, 2H), 2.64 – 2.58 (m, 2H), 2.43 – 2.38 (m, 2H), 2.37 – 2.30 (m, 1H), 2.22 (br s, 1H), 1.95 – 1.88 (m, 2H), 1.44 – 1.35 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.9, 145.8, 138.9, 131.6, 129.9, 128.3, 128.0, 126.4, 125.7, 79.4, 79.3, 60.4, 57.0, 44.1, 33.0, 26.4. LCMS Retention time: 3.903 min. LCMS purity 99.6%. HRMS (ESI): *m/z* calcd for $C_{26}H_{28}ClNO$ $[M+H]^+$ 406.1931, found 406.1930.

(1-(4-Bromophenethyl)piperidin-4-yl)diphenylmethanol (3e). Method C: **7** (0.50 g, 1.86 mmol), 1-(2-bromoethyl)-4-bromobenzene **10i** (0.26 mL, 1.69 mmol), triethylamine (0.353 mL, 2.53 mmol) and acetonitrile (10 mL). Purified by MPLC (0 - 10 % MeOH:CH_2Cl_2) to produce pure **3e** (0.49 g, 1.08 mmol, 64% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 – 7.46 (m, 4H), 7.38 (d, J = 8.3 Hz, 2H), 7.34 – 7.27 (m, 4H), 7.18 (tt, J = 7.3 Hz, 1.8 Hz, 2H), 7.06 (d, J = 8.4 Hz, 2H), 3.06 – 3.00 (m, 2H), 2.77 – 2.72 (m, 2H), 2.58 – 2.52 (m, 2H), 2.50 – 2.41 (m, 1H), 2.15 – 2.00 (m, 3H), 1.56 – 1.49 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.8, 139.3, 131.4, 130.4, 128.2, 126.6, 125.8, 119.8, 79.5, 60.4, 54.0, 44.1, 33.1, 26.4, 21.1 LCMS Retention time:

3.969 min. LCMS purity 99.8%. HRMS (ESI): *m/z* calcd for $C_{26}H_{28}BrNO$ $[M+H]^+$ 450.1426, found 452.1403.

(1-(4-Trifluoromethylphenethyl)piperidin-4-yl)diphenylmethanol (3f). Method C: **7** (0.10 g, 0.37 mmol), 1-(2-bromoethyl)-4-trifluorobenzene **10j** (0.057 mL, 0.34 mmol), triethylamine (0.071 mL, 0.51 mmol) and acetonitrile (10 mL). Purified by MPLC (0 - 10 % MeOH:CH_2Cl_2) to produce pure **3f** (0.074 g, 0.17 mmol, 49% yield) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 – 7.47 (m, 6H), 7.33 – 7.27 (m, 6H), 7.19 (tt, *J* = 7.3 Hz, 1.8 Hz, 2H), 3.06 – 3.00 (m, 2H), 2.86 – 2.80 (m, 2H), 2.60 – 2.55 (m, 2H), 2.51 – 2.42 (m, 1H), 2.14 (br s, 1H), 2.10 – 2.03 (m, 2H), 1.57 – 1.47 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.9, 144.6, 129.0, 128.3 (q, *J* = 32 Hz), 128.2, 126.5, 125.8, 125.2 (q, 3.8 Hz), 124.2 (q, *J* = 271.8 Hz), 79.5, 60.2, 54.1, 44.1, 33.6, 26.4, 21.0. LCMS Retention time: 3.877 min. LCMS purity 99.1%. HRMS (ESI): *m/z* calcd for $C_{27}H_{28}F_3NO$ $[M+H]^+$ 440.2195, found 440.2204.

(1-(4-Methoxyphenethyl)piperidin-4-yl)diphenylmethanol (3g). Method C: **7** (0.38 g, 1.43 mmol), 1-(2-bromoethyl)-4-methoxybenzene **10k** (0.25 mL, 1.57 mmol), triethylamine (0.30 mL, 2.14 mmol) and acetonitrile (5 mL). Purified by MPLC (0 - 10% MeOH:CH_2Cl_2) to produce pure **3g** (0.29 g, 0.72 mmol, 50% yield) as a sticky solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 – 7.46 (m, 4H), 7.32 – 7.28 (m, 4H), 7.19 (tt, *J* = 7.3 Hz, 1.9 Hz, 2H), 7.12 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 3.77 (s, 3H), 3.29 – 3.24 (m, 2H), 2.95 – 2.90 (m, 2H), 2.80 – 2.75 (m, 2H), 2.58 – 2.50 (m, 1H), 2.42 – 2.30 (m, 3H), 1.90 – 1.77 (m, 2H), 1.65 – 1.57 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.3, 145.5, 129.6, 128.3, 126.7, 125.6, 114.0, 79.3, 55.3, 53.6, 53.4, 43.4, 31.5, 25.1. LCMS Retention time: 3.695 min. LCMS purity 100%. HRMS (ESI): *m/z* calcd for $C_{27}H_{31}NO_2$ $[M+H]^+$ 402.2426, found 402.2428.

(1-(2-(6-(*Tert*-butyl)pyridin-3-yl)ethyl)piperidin-4-yl)diphenylmethanol (3h). Method C: **7** (0.25 g, 0.94 mmol), 2-(6-(*tert*-butyl)pyridin-3-yl)ethyl-4-methylbenzenesulfonate **10l** (0.26 g,

0.78 mmol), triethylamine (0.16 mL, 1.17 mmol) and acetonitrile (5 mL). Purified by reverse-phase MPLC (10 - 100% CH_3CN:water) to produce pure **3h** (0.31 g, 0.72 mmol, 92% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 8.39 – 8.38 (m, 1H), 7.51 – 7.48 (m, 4H), 7.42 (dd, *J* = 8.1 Hz, 2.4 Hz, 1H), 7.32 – 7.27 (m, 4H), 7.25 – 7.22 (m, 1H), 7.20 – 7.15 (m, 2H), 3.07 – 3.01 (m, 2H), 2.76 – 2.71 (m, 2H), 2.57 – 2.52 (m, 2H), 2.50 – 2.42 (m, 1H), 2.31 (br s, 1H), 2.09 – 2.01 (m, 2H), 1.57 – 1.48 (m, 4H), 1.35 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.9, 148.7, 145.9, 136.3, 132.3, 128.1, 126.5, 125.8, 118.6, 79.4, 60.2, 54.0, 44.1, 37.0, 30.3, 30.2, 26.4. LCMS Retention time: 3.802 min. LCMS purity 99.5%. HRMS (ESI): *m/z* calcd for $C_{29}H_{36}N_2O$ $[M+H]^+$ 429.2900, found 429.2894.

(1-(4-Nitrophenethyl)piperidin-4-yl)diphenylmethanol (3i). Method C: **7** (0.51 g, 1.92 mmol), 1-(2-bromoethyl)-4-nitrobenzene **10m** (0.40 g, 1.74 mmol), triethylamine (0.37 mL, 2.62 mmol) and acetonitrile (10 mL). Purified by MPLC (0 - 10 % MeOH:CH_2Cl_2) to produce **3i** (0.15 g, 0.35 mmol, 20% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 8.7 Hz, 2H), 7.49 – 7.46 (m, 4H), 7.35 (d, *J* = 8.7 Hz, 2H), 7.32 – 7.27 (m, 4H), 7.21 – 7.16 (m, 2H), 3.11 – 3.05 (m, 2H), 2.97 – 2.91 (m, 2H), 2.69 – 2.63 (m, 2H), 2.52 – 2.43 (m, 1H), 2.25 (br s, 1H), 2.20 – 2.10 (m, 2H), 1.63 – 1.53 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.9, 146.5, 145.7, 129.5, 128.2, 126.6, 125.7, 123.7, 79.4, 59.4, 53.9, 43.9, 33.2, 26.1, 21.1. LCMS Retention time: 3.654 min. LCMS purity 98.8%. HRMS (ESI): *m/z* calcd for $C_{26}H_{28}N_2O_3$ $[M+H]^+$ 417.2172, found 417.2163.

(1-(4-Aminophenethyl)piperidin-4-yl)diphenylmethanol (3j). To a vial was added **3i** (0.14 g, 0.32 mmol) with MeOH (1 mL) and CH_2Cl_2 (1 mL). The reaction was cooled to 0 °C and the Raney Nickel (2 mg, 0.032 mmol) was added. The sodium borohydride (0.031 g, 0.81 mmol) was then added portionwise and the reaction stirred at rt for 28 h after which the Raney Nickel filtered through celite. The reaction was diluted with water (10 mL) and extracted with CH_2Cl_2

(3 x 10 mL) and the organic layers were combined and dried with $MgSO_4$, filtered and adsorbed to silica then purified by MPLC (0 - 15% MeOH:CH_2Cl_2) to produce **3j** (0.077 g, 0.20 mmol, 61% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.47 (m, 4H), 7.32 – 7.27 (m, 4H), 7.18 (tt, *J* = 7.3 Hz, 1.8 Hz, 2H), 6.97 (d, *J* = 8.3 Hz, 2H), 6.61 (d, *J* = 8.3 Hz, 2H), 3.52 (br s, 2H), 3.07 – 3.01 (m, 2H), 2.70 – 2.65 (m, 2H), 2.54 – 2.41 (m, 3H), 2.22 (br s, 1H), 2.07 – 1.98 (m, 2H), 1.56 – 1.49 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.9, 144.4, 130.4, 129.4, 128.1, 126.5, 125.8, 115.2, 79.5, 61.2, 54.1, 44.2, 32.8, 26.4, 21.0. LCMS Retention time: 3.328 min. LCMS purity 97.0%. HRMS (ESI): *m/z* calcd for $C_{26}H_{30}N_2O$ $[M+H]^+$ 387.2430, found 387.2412.

(1-(4-(Dimethylamino)phenethyl)piperidin-4-yl)diphenylmethanol (3k). To a vial was added **3j** (0.030 g, 0.078 mmol) and acetic acid (1 mL). The paraformaldehyde (0.058 mL, 0.78 mmol) solution in water followed by sodium cyanoborohydride (0.015 g, 0.23 mmol) was then added and the reaction stirred at rt for 20 h. The reaction was concentrated and diluted with saturated $NaHCO_3$ (10 mL) and extracted with EtOAc (3 x 10 mL). The organic layers were dried with $MgSO_4$, filtered and concentrated. The product was purified by reverse-phase MPLC (10 - 100% CH_3CN:water) to produce **3k** (0.027 g, 0.065 mmol, 84% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 – 7.46 (m, 4H), 7.31 – 7.26 (m, 4H), 7.17 (tt, *J* = 7.3 Hz, 1.8 Hz, 2H), 7.06 (d, *J* = 8.3 Hz, 2H), 6.68 (d, *J* = 8.3 Hz, 2H), 3.08 – 3.02 (m, 2H), 2.90 (s, 6H), 2.72 – 2.67 (m, 2H), 2.56 – 2.50 (m, 2H), 2.48 – 2.42 (m, 1H), 2.30 (br s, 1H), 2.07 – 2.00 (m, 2H), 1.56 – 1.51 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.1, 146.0, 129.2, 128.4, 128.1, 126.4, 125.8, 112.9, 79.4, 61.1, 54.0, 44.2, 41.0, 40.8, 32.6, 26.4. LCMS Retention time: 2.50 min. LCMS purity 96.1%. HRMS (ESI): *m/z* calcd for $C_{28}H_{34}N_2O$ $[M+H]^+$ 415.2744, found 415.2743.

(1-(2-([1,1'-Biphenyl]-4-yl)ethyl)piperidin-4-yl)diphenylmethanol (3l). To a vial was added the phenylboronic acid (0.019 g, 0.15 mmol), 1,1'-bis(di-*tert*-butylphosphino)ferrocene palladium dichloride (4.1 mg, 6.3 μmol), **3e** (0.057 g, 0.13 mmol) and potassium carbonate

(0.035 g, 0.253 mmol). The vial was then evacuated with argon three times and acetonitrile (1 mL) was added followed by water (1 mL). The reaction then stirred at 60 °C for 18 h then was diluted with saturated $NaHCO_3$ (5 mL) and extracted with EtOAc (3 x 5 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 pure **3l** (0.045 g, 0.10 mmol, 79% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 – 7.45 (m, 2H), 7.53 – 7.48 (m, 6H), 7.45 – 7.40 (m, 2H), 7.35 – 7.25 (m, 7H), 7.22 – 7.16 (m, 2H), 3.11 – 3.05 (m, 2H), 2.87 – 2.81 (m, 2H), 2.65 – 2.59 (m, 2H), 2.53 – 2.44 (m, 1H), 2.22 (br s, 1H), 2.12 – 2.04 (m, 2H), 1.59 – 1.52 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.9, 141.0, 139.5, 139.0, 129.1, 128.7, 128.2, 127.1, 127.0, 127.0, 126.5, 125.8, 79.5, 60.7, 54.0, 50.8, 44.2, 33.3, 26.4. LCMS Retention time: 4.086 min. LCMS purity 99%. HRMS (ESI): *m/z* calcd for $C_{32}H_{33}NO$ $[M+H]^+$ 448.2634, found 448.2648.

(1-(4-(Pyridin-4-yl)phenethyl)piperidin-4-yl)diphenylmethanol (3m). Same procedure as **3l** with **3e** (0.050 g, 0.11 mmol), pyridin-4-ylboronic acid (0.018 g, 0.13 mmol), 1,1'-bis(di-*tert*-butylphosphino)ferrocenepalladium dichloride (3.6 mg, 5.6 µmol) and potassium carbonate (0.031 g, 0.22 mmol). Purified by reverse-phase MPLC (10 - 100% CH_3CN:water) to produce **3m** (0.015 g, 0.033 mmol, 30% yield) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 – 8.62 (m, 2H), 7.60 (d, *J* = 8.2 Hz, 2H), 7.51 – 7.46 (m, 6H), 7.32 – 7.28 (m, 6H), 7.18 (tt, *J* = 7.3 Hz, 1.8 Hz, 2H), 3.10 – 3.04 (m, 2H), 2.88 – 2.82 (m, 2H), 2.65 – 2.58 (m, 2H), 2.51 – 2.43 (m, 1H), 2.19 (br s, 1H), 2.12 – 2.03 (m, 2H), 1.58 – 1.51 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.2, 148.1, 145.9, 141.7, 135.8, 129.5, 128.2, 127.0, 126.5, 125.8, 121.4, 79.5, 60.5, 54.1, 44.1, 41.0, 33.4, 26.4. LCMS Retention time: 3.585 min. LCMS purity 95.9%. HRMS (ESI): *m/z* calcd for $C_{31}H_{32}N_2O$ $[M+H]^+$ 449.2587, found 449.2559.

(1-(4-(Pyridin-3-yl)phenethyl)piperidin-4-yl)diphenylmethanol (3n). Same procedure as **3l** using **3e** (0.057 g, 0.13 mmol), pyridin-3-ylboronic acid (0.019 g, 0.15 mmol), 1,1'-bis(di-*tert*-

butylphosphino)ferrocenepalladium dichloride (4.1 mg, 6.3 μmol) and potassium carbonate (0.035 g, 0.253 mmol), acetonitrile (1 mL) and water (1 mL). Purified by reverse-phase MPLC (10 - 100% CH_3CN:water) to produce **3n** (0.05 g, 0.11 mmol, 88% yield) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.79 (dd, *J* = 2.4 Hz, 0.9 Hz, 1H), 8.53 (dd, *J* = 4.8 Hz, 1.6 Hz, 1H), 7.86 – 7.83 (m, 1H), 7.51 – 7.47 (m, 6H), 7.36 – 7.27 (m, 7H), 7.20 – 7.15 (m, 2H), 3.10 – 3.03 (m, 2H), 2.87 – 2.81 (m, 2H), 2.71 (br s, 1H), 2.63 – 2.58 (m, 2H), 2.51 – 2.43 (m, 1H), 2.11 – 2.03 (m, 2H), 1.58 – 1.52 (m, 4H).). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.04, 147.97, 146.0, 140.5, 136.5, 135.5, 134.3, 129.4, 128.1, 127.1, 126.4, 125.8, 123.5, 79.4, 60.5, 54.1, 44.1, 33.2, 26.2. LCMS Retention time: 3.582 min. LCMS purity 98.8%. HRMS (ESI): *m/z* calcd for $C_{31}H_{32}N_2O$ $[M+H]^+$ 449.2587, found 449.2595.

(1-(4-(3-Methyloxetan-3-yl)phenethyl)piperidin-4-yl)diphenylmethanol (3o). To a vial was added the **34** (0.024 g, 0.041 mmol) and MeOH (10 mL) and the reaction as heated to 50 °C. The magnesium was added in 3 additions (0.016 g, 0.066 mmol) 1.5 h apart. The reaction was removed from heat 1.5 h after the final magnesium addition, cooled to rt and poured into 1.0 M HCl (10 mL) with ice. The aqueous layer was then extracted with CH_2Cl_2 (3 x 15 mL) and the organic layers were combined and dried with $MgSO_4$, filtered and concentrated then purifed by reverse-phase MPLC (10 - 100% CH_3CN:water) to produce **3o** (0.005 g, 10 μmol, 25% yield) as a light brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 - 7.47 (m, 4H), 7.32 - 7.27 (m, 4H), 7.21 - 7.16 (m, 4H), 7.13 - 7.10 (m, 2H), 4.95 (d, *J* = 5.5 Hz, 2H), 4.61 (d, *J* = 5.5 Hz, 2H), 3.09 - 3.02 (m, 2H), 2.81 - 2.75 (m, 2H), 2.59 - 2.54 (m, 2H), 2.50 - 2.42 (m, 1H), 2.16 (br s, 1H), 2.09 - 2.00 (m, 2H), 1.71 (s, 3H), 1.56 - 1.48 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.9, 144.1, 138.4, 128.8, 128.2, 126.5, 125.8, 125.1, 83.8, 79.5, 60.7, 54.1, 44.1, 43.1, 33.3, 27.8, 26.4. LCMS Retention time: 3.652 min. LCMS purity 97.9%. HRMS (ESI): *m/z* calcd for $C_{30}H_{35}NO_2$ $[M+H]^+$ 442.2740, found 442.2749.

(1-(3-(*Tert*-butyl)benzyl)piperidin-4-yl)diphenylmethanol (4a). Method C: **7** (0.030 g, 0.11 mmol), 3-*tert*-butylbenzyl bromide **10n** (0.031 g, 0.14 mmol), triethylamine (0.023 mL, 0.17 mmol) in acetonitrile (2 mL). The reaction was purified by reverse-phase MPLC (10 – 100% CH_3CN:water) to produce **4a** (0.025 g, 0.060 mmol, 53% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 - 7.41 (m, 4H), 7.34 - 7.26 (m, 6H), 7.26 - 7.20 (m, 1H), 7.20 - 7.14 (m, 2H), 7.11 (dt, J = 7.1, 1.6 Hz, 1H), 3.52 (s, 2H), 3.01 - 2.85 (m, 2H), 2.53 - 2.34 (m, 1H), 2.34 (br s, 1H), 2.05 - 1.95 (m, 2H), 1.58 - 1.44 (m, 4H), 1.32 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.9, 146.0, 137.5, 128.1, 127.8, 126.4, 126.3, 126.2, 125.8, 123.8, 79.5, 63.4, 53.8, 44.1, 34.6, 31.4, 26.4. LCMS Retention time: 2.79 min. LCMS purity 99%. HRMS (ESI): *m/z* calcd for $C_{29}H_{35}NO$ $[M+H]^+$ 414.2767, found 414.2765.

(1-(2-(*Tert*-butyl)benzyl)piperidin-4-yl)diphenylmethanol (4b). Method C: **7** (0.023 g, 0.084 mmol), 2-*tert*-butylbenzyl bromide **10o** (0.023 g, 0.10 mmol) and triethylamine (0.018 mL, 0.13 mmol) in acetonitrile (2 mL). The reaction was purified by reverse-phase MPLC (10 – 100% CH_3CN:water) to produce **4b** (0.014 g, 0.035 mmol, 41% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (s, 1H), 7.53 - 7.44 (m, 4H), 7.41 - 7.34 (m, 1H), 7.32 - 7.23 (m, 4H), 7.22 - 7.06 (m, 4H), 3.73 (s, 2H), 2.96 (d, J = 11.2 Hz, 2H), 2.56 - 2.42 (m, 1H), 2.26 - 2.06 (m, 3H), 1.58 - 1.44 (m, 4H), 1.41 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.1, 146.0, 130.9, 128.1, 126.6, 126.5, 126.0, 125.8, 125.7, 79.5, 61.3, 54.1, 44.2, 35.9, 31.6, 26.5. LCMS Retention time: 2.93 min. LCMS purity 95.7%. HRMS (ESI): *m/z* calcd for $C_{29}H_{35}NO$ $[M+H]^+$ 414.2780, found 414.2829.

(1-(4-*Iso*-propylbenzyl)piperidin-4-yl)diphenylmethanol (4c). Method C: **7** (0.030 g, 0.11 mmol), 4-*iso*-propylbenzyl bromide **10p** (0.017 g, 0.023 mL, 0.14 mmol) and triethylamine (0.023 mL, 0.17 mmol) in acetonitrile (2 mL). The reaction was purified by reverse-phase MPLC (10 – 100% CH_3CN:water) to produce (**4c**) (0.030 g, 0.075 mmol, 67% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 - 7.43 (m, 4H), 7.31 - 7.26 (m, 4H), 7.23 - 7.07 (m, 6H), 3.48 (s, 2H), 2.98

- 2.91 (m, 2H), 2.91 - 2.83 (m, 1H), 2.54 - 2.18 (m, 2H), 2.05 - 1.92 (m, 2H), 1.53 - 1.42 (m, 4H), 1.25 (s, 3H), 1.23 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.6, 146.0, 135.2, 129.2, 128.1, 126.4, 126.1, 125.8, 79.5, 62.9, 53.8, 44.1, 33.7, 26.4, 24.0. LCMS Retention time: 4.094 min. LCMS purity 97.9%. HRMS (ESI): *m/z* calcd for $C_{28}H_{33}NO$ $[M+H]^+$ 400.2634, found 400.2670.

(1-(4-Methylbenzyl)piperidin-4-yl)diphenylmethanol (4d). Method C: **7** (0.030 g, 0.11 mmol), 4-methylbenzyl bromide **10q** (0.025 g, 0.14 mmol) and triethylamine (0.023 mL, 0.17 mmol) in acetonitrile (2 mL). The reaction was purified by reverse-phase MPLC (10 – 100% CH_3CN:water) to produce **4d** (0.025 g, 0.068 mmol, 61% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 - 7.41 (m, 4H), 7.33 - 7.24 (m, 4H), 7.21 - 7.14 (m, 4H), 7.11 (d, J = 7.8 Hz, 2H), 3.48 (s, 2H), 2.97 - 2.86 (m, 2H), 2.48 - 2.36 (m, 2H), 2.33 (s, 3H), 2.05 - 1.92 (m, 2H), 1.55 - 1.39 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.0, 136.5, 134.8, 129.2, 128.8, 128.1, 126.4, 125.8, 79.5, 62.8, 53.7, 44.1, 26.4. LCMS Retention time: 2.51 min. LCMS purity 97.7%. HRMS (ESI): *m/z* calcd for $C_{26}H_{29}NO$ $[M+H]^+$ 372.2321, found 372.2336.

(1-(3-Methylbenzyl)piperidin-4-yl)diphenylmethanol (4e). Method C: **7** (0.030 g, 0.11 mmol), 3-methylbenzyl bromide **10r** (0.025 g, 0.14 mmol) and triethylamine (0.023 mL, 0.17 mmol) in acetonitrile (2 mL). The reaction was purified by reverse-phase MPLC (10 – 100% CH_3CN:water) to produce **4e** (0.026 g, 0.070 mmol, 62% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 - 7.43 (m, 4H), 7.32 - 7.26 (m, 4H), 7.22 - 7.14 (m, 3H), 7.11 (br s, 1H), 7.07 (t, J = 7.9 Hz, 2H), 3.48 (s, 2H), 3.00 - 2.91 (m, 2H), 2.50 - 2.37 (m, 1H), 2.33 (s, 3H), 2.31 (br s, 1H), 2.05 - 1.94 (m, 2H), 1.57 - 1.41 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.0, 137.9, 137.7, 130.0, 128.1, 128.0, 127.7, 126.4, 126.3, 125.8, 79.5, 63.2, 53.9, 44.1, 26.4, 21.4. LCMS Retention time: 2.51 min. LCMS purity 97.7%. HRMS (ESI): *m/z* calcd for $C_{26}H_{29}NO$ $[M+H]^+$ 372.2321, found 372.2348.

(1-(2-Methylbenzyl)piperidin-4-yl)diphenylmethanol (4f). Method C: **7** (0.030 g, 0.11 mmol), 2-methylbenzyl bromide **10s** (0.024 g, 0.018 mL, 0.13 mmol) and triethylamine (0.023 mL, 0.17 mmol) in CH_3CN (2 mL). The reaction was purified by reverse-phase MPLC (10 – 100% CH_3CN:water) to produce **4f** (0.036 g, 0.097 mmol, 89% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 - 7.43 (m, 4H), 7.35 - 7.23 (m, 5H), 7.22 - 7.08 (m, 5H), 3.44 (s, 2H), 2.99 - 2.86 (m, 2H), 2.51 - 2.41 (m, 1H), 2.35 (s, 3H), 2.25 (s, 1H), 2.08 - 1.97 (m, 2H), 1.51 - 1.38 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.0, 137.3, 136.7, 130.1, 129.6, 128.1, 126.8, 126.4, 125.8, 125.9, 79.6, 60.8, 54.1, 44.2, 26.6, 19.2. LCMS Retention time: 3.987 min. LCMS purity 98.6%. HRMS (ESI): *m/z* calcd for $C_{26}H_{29}NO$ $[M+H]^+$ 372.2321, found 372.2327.

(1-([1,1'-Biphenyl]-4-ylmethyl)piperidin-4-yl)diphenylmethanol (4g). Reported as General Method C.

(1-([1,1'-Biphenyl]-3-ylmethyl)piperidin-4-yl)diphenylmethanol (4h). Method C: **7** (0.030 g, 0.11 mmol), 3-phenylbenzyl bromide **10u** (0.033 g, 0.14 mmol) and triethylamine (0.023 mL, 0.17 mmol) in acetonitrile (2 mL). The reaction was purified by reverse-phase MPLC (10 – 100% CH_3CN:water) to produce **4h** (0.041 g, 0.095 mmol, 84% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.63 - 7.57 (m, 2H), 7.54 - 7.50 (m, 1H), 7.50 - 7.40 (m, 7H), 7.40 - 7.32 (m, 2H), 7.32 - 7.25 (m, 5H), 7.21 - 7.13 (m, 2H), 3.58 (s, 2H), 3.03 - 2.86 (m, 2H), 2.50 - 2.22 (m, 2H), 2.10 - 1.96 (m, 2H), 1.51 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.0, 141.2, 141.1, 138.6, 128.7, 128.5, 128.1, 128.1, 128.0, 127.2, 127.2, 126.5, 125.8, 79.5, 63.2, 53.8, 44.1, 26.4. LCMS Retention time: 4.072 min. LCMS purity 99%. HRMS (ESI): *m/z* calcd for $C_{31}H_{31}NO$ $[M+H]^+$ 434.2478, found 434.2500.

(1-([1,1'-Biphenyl]-2-ylmethyl)piperidin-4-yl)diphenylmethanol (4i). Method C: **7** (0.030 g, 0.11 mmol), 2-phenylbenzyl bromide **10v** (0.025 mL, 0.14 mmol) and triethylamine (0.023 mL, 0.17 mmol) in CH_3CN (2 mL). The reaction was purified by reverse-phase MPLC (10 – 100%

CH_3CN:water) to produce **4i** (0.036 g, 0.083 mmol, 74% yield).^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 - 7.50 (m, 1H), 7.49 - 7.43 (m, 4H), 7.42 - 7.21 (m, 12H), 7.20 - 7.12 (m, 2H), 3.41 (s, 2H), 2.91 - 2.79 (m, 2H), 2.47 - 2.17 (m, 2H), 1.97 - 1.83 (m, 2H), 1.52 - 1.36 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.0, 142.5, 141.5, 130.0, 129.9, 129.5, 128.1, 127.8, 127.1, 126.7, 126.6, 126.4, 125.7, 79.5, 59.8, 53.7, 44.1, 26.5. LCMS Retention time: 4.136 min. LCMS purity 98.6%. HRMS (ESI): *m/z* calcd for $C_{31}H_{31}NO$ $[M+H]^+$ 434.2478, found 434.2499.

(1-(4-Cyanobenzyl)piperidin-4-yl)diphenylmethanol (4j). Method C: **7** (0.030 g, 0.11 mmol), 4-cyanobenzyl bromide **10w** (0.026 g, 0.14 mmol) and triethylamine (0.023 mL, 0.17 mmol) in acetonitrile (2 mL). The reaction was purified by reverse-phase MPLC (10 – 100% CH_3CN:water) to produce **4j** (0.031 g, 0.081 mmol, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 - 7.53 (m, 2H), 7.51 - 7.44 (m, 4H), 7.44 - 7.37 (m, 2H), 7.34 - 7.26 (m, 4H), 7.22 - 7.11 (m, 2H), 3.53 (s, 2H), 2.92 - 2.81 (m, 2H), 2.53 - 2.36 (m, 1H), 2.25 (s, 1H), 2.09 - 1.95 (m, 2H), 1.57 - 1.39 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.8, 144.4, 132.0, 129.4, 128.1, 126.5, 125.7, 119.0, 110.7, 79.5, 62.5, 54.0, 44.0, 26.4. LCMS Retention time: 2.26 min. LCMS purity 99%. HRMS (ESI): *m/z* calcd for $C_{26}H_{26}N_2O$ $[M+H]^+$ 383.2117, found 383.2116.

(1-(3-Cyanobenzyl)piperidin-4-yl)diphenylmethanol (4k). Method C: **7** (0.030 g, 0.11 mmol), 3-cyanobenzyl bromide **10x** (0.026 g, 0.14 mmol) and triethylamine (0.023 mL, 0.17 mmol) in acetonitrile (2 mL). The reaction was purified by reverse-phase MPLC (10 – 100% CH_3CN:water) to produce **4k** (0.035 g, 0.092 mmol, 82% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (s, 1H), 7.56 - 7.50 (m, 2H), 7.50 - 7.44 (m, 4H), 7.38 (t, J = 7.7 Hz, 1H), 7.34 - 7.26 (m, 4H), 7.23 - 7.13 (m, 2H), 3.50 (s, 2H), 2.91 - 2.77 (m, 2H), 2.56 - 2.33 (m, 1H), 2.22 (s, 1H), 2.07 - 1.95 (m, 2H), 1.57 - 1.40 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.8, 140.2, 133.3, 132.3, 130.6, 128.9, 128.1, 126.5, 125.8, 118.9, 112.2, 79.5, 62.2, 53.9, 44.0, 26.4. LCMS

Retention time: 2.26 min. LCMS purity 100%. HRMS (ESI): *m/z* calcd for $C_{26}H_{26}N_2O$ $[M+H]^+$ 383.2117, found 383.2116.

(1-(2-Cyanobenzyl)piperidin-4-yl)diphenylmethanol (4l). Method C: **7** (0.030 g, 0.11 mmol), 2-cyanobenzyl bromide **10y** (0.026 g, 0.135 mmol) and triethylamine (0.023 mL, 0.17 mmol) in acetonitrile (2 mL). The reaction was purified by reverse-phase MPLC (10 – 100% CH_3CN:water) to produce **4l** (0.027 g, 0.071 mmol, 63% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 - 7.58 (m, 1H), 7.58 - 7.51 (m, 2H), 7.51 - 7.43 (m, 4H), 7.35 - 7.26 (m, 5H), 7.22 - 7.11 (m, 2H), 3.69 (s, 2H), 2.97 - 2.84 (m, 2H), 2.52 - 2.40 (m, 1H), 2.37 - 2.07 (m, 3H), 1.57 - 1.37 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.9, 142.7, 132.7, 132.5, 129.9, 128.1, 127.4, 126.5, 125.7, 117.9, 112.8, 79.5, 60.5, 53.9, 44.0, 26.5. LCMS Retention time: 2.28 min. LCMS purity 100%. HRMS (ESI): *m/z* calcd for $C_{26}H_{26}N_2O$ $[M+H]^+$ 383.2117, found 383.2141.

(1-(4-(Trifluoromethyl)benzyl)piperidin-4-yl)diphenylmethanol (4m). Method C: **7** (0.030 g, 0.11 mmol), 4-trifluoromethylbenzyl bromide **10z** (0.032 g, 0.021 mL, 0.14 mmol) and triethylamine (0.023 mL, 0.17 mmol) in acetonitrile (2 mL). The reaction was purified by reverse-phase MPLC (10 – 100% CH_3CN:water) to produce **4m** (0.036 g, 0.085 mmol, 76% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, J = 7.7 Hz, 2H), 7.52 - 7.43 (m, 4H), 7.41 (d, J = 8.0 Hz, 2H), 7.35 - 7.25 (m, 4H), 7.23 - 7.12 (m, 2H), 3.54 (s, 2H), 2.97 - 2.78 (m, 2H), 2.44 (m, 1H), 2.28 (s, 1H), 2.11 - 1.95 (m, 2H), 1.50 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.9, 142.6, 129.2 (q, *J* = 32.0 Hz), 129.2, 128.1, 126.5, 125.8, 125.0 (q, *J* = 3.9 Hz), 124.2 (q, *J* = 270.3 Hz), 79.5, 62.5, 53.9, 44.0, 26.4. LCMS Retention time: 3.904 min. LCMS purity 98.9%. HRMS (ESI): *m/z* calcd for $C_{26}H_{26}F_3NO$ $[M+H]^+$ 426.2039, found 426.2070.

(1-(3-(Trifluoromethyl)benzyl)piperidin-4-yl)diphenylmethanol (4n). Method C: **7** (0.030 g, 0.11 mmol), 3-trifluoromethylbenzyl bromide **10aa** (0.032 g, 0.021 mL, 0.14 mmol) and triethylamine (0.023 mL, 0.17 mmol) in acetonitrile (2 mL). The reaction was purified by

reverse-phase MPLC (10 – 100% CH_3CN:water) to produce **4n** (0.034 g, 0.080 mmol, 71% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.56 (s, 1H), 7.53 - 7.45 (m, 6H), 7.44 - 7.37 (m, 1H), 7.35 - 7.26 (m, 4H), 7.22 - 7.12 (m, 2H), 3.54 (s, 2H), 2.95 - 2.84 (m, 2H), 2.50 - 2.38 (m, 1H), 2.24 (s, 1H), 2.08 - 1.96 (m, 2H), 1.55 - 1.45 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.9, 139.4, 132.3, 130.5 (q, J = 31.7 Hz), 128.6, 128.2, 126.5, 125.6 (q, J = 3.7 Hz), 124.2 (q, J = 270.7 Hz), 123.8 (q, J = 3.8 Hz), 79.5, 62.6, 53.9, 44.1, 26.4. LCMS Retention time: 3.897 min. LCMS purity 99.3%. HRMS (ESI): *m/z* calcd for $C_{26}H_{26}F_3NO$ $[M+H]^+$ 426.2039, found 426.2063.

(1-(2-(Trifluoromethyl)benzyl)piperidin-4-yl)diphenylmethanol (4o). Method C: **7** (0.030 g, 0.11 mmol), 2-trifluoromethylbenzyl bromide **10bb** (0.032 g, 0.020 mL, 0.14 mmol) and triethylamine (0.023 mL, 0.17 mmol) in acetonitrile(2 mL). The reaction was purified by reverse-phase MPLC (10 – 100% CH_3CN:water) to produce **4o** (0.045 g, 0.11 mmol, 95% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, J = 7.8 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.54 - 7.44 (m, 5H), 7.35 - 7.27 (m, 5H), 7.23 - 7.15 (m, 2H), 3.64 (d, J = 1.7 Hz, 2H), 2.94 - 2.82 (m, 2H), 2.55 - 2.42 (m, 1H), 2.27 - 2.06 (m, 3H), 1.58 - 1.43 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.0, 138.2, 131.7, 130.1, 128.2, 127.2 (q, J = 262.9 Hz), 126.5, 125.7, 125.5 (q, J = 5.8 Hz), 123.1, 79.6, 58.2 (q, J = 2.1 Hz), 54.2, 44.1, 26.6. LCMS Retention time: 4.054 min. LCMS purity 98.1%. HRMS (ESI): *m/z* calcd for $C_{26}H_{26}F_3NO$ $[M+H]^+$ 426.2039, found 426.2081.

(1-(4-Fluorobenzyl)piperidin-4-yl)diphenylmethanol (4p). Method C: **7** (0.030 g, 0.11 mmol), 4-fluoromethylbenzyl bromide **10cc** (0.017 mL, 0.14 mmol) and triethylamine (0.023 mL, 0.17 mmol) in acetonitrile (2 mL). The reaction was purified by reverse-phase MPLC (10 – 100% CH_3CN:water) to produce **4p** (0.028 g, 0.075 mmol, 67% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 - 7.40 (m, 4H), 7.32 - 7.22 (m, 6H), 7.20 - 7.13 (m, 2H), 7.02 - 6.92 (m, 2H), 3.47 (s, 2H), 2.98 - 2.85 (m, 2H), 2.49 - 2.37 (m, 1H), 2.29 (br s, 1H), 2.05 - 1.93 (m, 2H), 1.49 (td, J = 8.8,

7.8, 3.7 Hz, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.0 (d, *J* = 243.2 Hz), 145.9, 130.7 (d, *J* = 7.8 Hz), 128.1, 126.5, 125.8, 114.9 (d, *J* = 21.0 Hz), 79.5, 62.2, 53.7, 44.1, 26.3. LCMS Retention time: 3.734 min. LCMS purity 96.5%. HRMS (ESI): *m/z* calcd for $C_{25}H_{26}FNO$ $[M+H]^+$ 376.2070, found 376.2081.

(1-(3-Fluorobenzyl)piperidin-4-yl)diphenylmethanol (4q). Method C: **7** (0.030 g, 0.11 mmol), 3-fluorobenzyl bromide **10dd** (0.017 mL, 0.135 mmol) and triethylamine (0.023 mL, 0.17 mmol) in acetonitrile (2 mL). The reaction was purified by reverse-phase MPLC (10 – 100% CH_3CN:water) to produce **4q** (0.028 g, 0.074 mmol, 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 - 7.39 (m, 4H), 7.34 - 7.26 (m, 4H), 7.25 - 7.21 (m, 1H), 7.20 - 7.14 (m, 2H), 7.09 - 6.97 (m, 2H), 6.96 - 6.85 (m, 1H), 3.48 (s, 2H), 2.96 - 2.85 (m, 2H), 2.49 - 2.37 (m, 1H), 2.27 (s, 1H), 2.06 - 1.95 (m, 2H), 1.54 - 1.42 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.9 (d, *J* = 244.1 Hz), 145.9, 141.2 (d, *J* = 6.8 Hz), 129.5 (d, *J* = 8.1 Hz), 128.1, 126.5, 125.8, 124.5 (d, *J* = 2.7 Hz), 115.7 (d, *J* = 21.1 Hz), 113.7 (d, *J* = 21.1 Hz), 79.5, 62.6, 62.5, 53.9, 44.1, 26.5. LCMS Retention time: 2.41 min. LCMS purity 99%. HRMS (ESI): *m/z* calcd for $C_{25}H_{26}FNO$ $[M+H]^+$ 376.2070, found 376.2069.

(1-(2-Fluorobenzyl)piperidin-4-yl)diphenylmethanol (4r). Method C: **7** (0.030 g, 0.11 mmol), 2-fluorobenzyl bromide **10ee** (0.016 mL, 0.14 mmol) and triethylamine (0.023 mL, 0.17 mmol) in acetonitrile (2 mL). The reaction was purified by reverse-phase MPLC (10 – 100% CH_3CN:water) to produce **4r** (0.038 g, 0.10 mmol, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 - 7.44 (m, 4H), 7.35 (td, J = 7.5, 1.9 Hz, 1H), 7.31 - 7.26 (m, 4H), 7.26 - 7.20 (m, 1H), 7.20 - 7.14 (m, 2H), 7.09 (td, J = 7.5, 1.2 Hz, 1H), 7.06 - 6.96 (m, 1H), 3.60 (d, J = 1.5 Hz, 2H), 3.01 - 2.89 (m, 2H), 2.50 - 2.17 (m, 2H), 2.14 - 2.06 (m, 2H), 1.50 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.4 (d, *J* = 244.1 Hz), 145.9, 131.7 (d, *J* = 4.5 Hz), 128.7 (d, *J* = 8.2 Hz), 128.1, 126.5, 125.8, 124.5 (d, *J* = 14.8 Hz), 123.7 (d, *J* = 3.5 Hz), 115.2, 115.0, 79.5,

55.2, 55.2, 53.5, 44.0, 26.4. LCMS Retention time: 3.733 min. LCMS purity 98.6%. HRMS (ESI): *m/z* calcd for $C_{25}H_{26}FNO$ $[M+H]^+$ 376.2070, found 376.2074.

(1-(4-Methoxybenzyl)piperidin-4-yl)diphenylmethanol (4s). To a vial was added the **7** (0.030 g, 0.11 mmol) and 4-methoxybenzaldehyde **11a** (0.015 g, 0.013 mL, 0.11 mmol) in THF (0.5 mL) to form a solution. The reaction began to stir at rt and after 30 min then the sodium triacetoxyborohydride (0.026 g, 0.12 mmol) was added and the reaction continued to stir at rt. The reaction was then quenched with water (1.5 mL) and extracted with CH_2Cl_2 (1.5 mL). The organic layer was dried ($MgSO_4$), concentrated and purified by reverse-phase MPLC (10 - 100% CH_3CN:water) to produce **4s** (0.007 g, 0.018 mmol, 16% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 - 7.40 (m, 4H), 7.33 - 7.23 (m, 4H), 7.21 - 7.10 (m, 4H), 6.88 - 6.76 (m, 2H), 3.78 (s, 3H), 3.44 (s, 2H), 2.97 - 2.84 (m, 2H), 2.50 - 2.33 (m, 1H), 2.07 - 1.89 (m, 3H), 1.54 - 1.39 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.6, 146.0, 130.4, 130.0, 128.1, 126.4, 125.8, 113.4, 79.5, 62.5, 55.2, 53.7, 44.1, 26.4. LCMS Retention time: 2.35 min. LCMS purity 100%. HRMS (ESI): *m/z* calcd for $C_{26}H_{29}NO_2$ $[M+H]^+$ 388.2272, found 388.2295.

(1-(3-Methoxybenzyl)piperidin-4-yl)diphenylmethanol (4t). Method C: **7** (0.030 g, 0.11 mmol), 3-methoxybenzyl bromide **10ff** (0.016 mL, 0.14 mmol) and triethylamine (0.023 mL, 0.17 mmol) in acetonitrile (2 mL). The reaction was purified by reverse-phase MPLC (10 – 100% CH_3CN:water) to produce **4t** (0.034 g, 0.088 mmol, 79% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.53 - 7.38 (m, 4H), 7.35 - 7.24 (m, 4H), 7.24 - 7.11 (m, 3H), 6.91 - 6.84 (m, 2H), 6.82 - 6.73 (m, 1H), 3.79 (s, 3H), 3.49 (s, 2H), 3.04 - 2.83 (m, 2H), 2.51 - 2.23 (m, 2H), 2.05 - 1.96 (m, 2H), 1.56 - 1.38 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.5, 146.0, 139.8, 129.0, 128.1, 126.5, 125.8, 121.5, 114.6, 112.4, 79.5, 63.1, 55.2, 53.8, 44.1, 26.4. LCMS Retention time: 3.733 min. LCMS purity 97.3%. HRMS (ESI): *m/z* calcd for $C_{26}H_{29}NO_2$ $[M+H]^+$ 388.2272, found 388.2291.

(1-(2-Methoxybenzyl)piperidin-4-yl)diphenylmethanol (4u). To a vial was added the diphenyl(piperidin-4-yl)methanol (0.030 g, 0.11 mmol) and 2-methoxybenzaldehyde **11b** (0.015 g, 0.013 mL, 0.11 mmol) in THF (0.5 mL) to form a solution. The reaction began to stir at rt and after 30 min then the sodium triacetoxyborohydride (0.026 g, 0.12 mmol) was added and the reaction continued to stir at rt. The reaction was then quenched with water (1.5 mL) and extracted with CH_2Cl_2 (1.5 mL). The organic layer was dried ($MgSO_4$), concentrated and purified by reverse-phase MPLC (10 - 100% CH_3CN:water) to produce **4u** (0.011 g, 0.028 mmol, 25% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 - 7.40 (m, 4H), 7.34 - 7.25 (m, 5H), 7.22 (td, J = 8.1, 1.8 Hz, 1H), 7.19 - 7.13 (m, 2H), 6.91 (td, J = 7.4, 1.1 Hz, 1H), 6.85 (dd, J = 8.2, 1.1 Hz, 1H), 3.80 (s, 3H), 3.58 (s, 2H), 3.04 - 2.90 (m, 2H), 2.49 - 2.35 (m, 1H), 2.17 (s, 1H), 2.08 (td, J = 11.3, 3.6 Hz, 2H), 1.60 - 1.38 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.8, 146.0, 130.7, 128.1, 128.0, 126.4, 125.8, 120.2, 110.3, 79.5, 56.0, 55.4, 53.8, 44.1, 26.4. LCMS Retention time: 2.40 min. LCMS purity 97.7%. HRMS (ESI): *m/z* calcd for $C_{26}H_{29}NO_2$ $[M+H]^+$ 388.2270, found 388.2242.

(1-(4-Hydroxybenzyl)piperidin-4-yl)diphenylmethanol (4v). To a vial was added the **7** (0.030 g, 0.11 mmol) and 4-hydroxybenzaldehyde **11c** (0.013 g, 0.11 mmol) in THF (0.5 mL) to form a solution. The reaction began to stir at rt and after 30 min then the sodium triacetoxyborohydride (0.026 g, 0.12 mmol) was added and the reaction continued to stir at rt. The reaction was then quenched with water (1.5 mL) and extracted with CH_2Cl_2 (1.5 mL). The organic layer was dried with $MgSO_4$, filtered, concentrated and purified by reverse-phase MPLC (10 - 100% CH_3CN:water) to produce (**4v**) (0.012 g, 0.032 mmol, 29% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 - 7.40 (m, 4H), 7.32 - 7.21 (m, 4H), 7.20 - 7.11 (m, 2H), 7.11 - 7.01 (m, 2H), 6.73 - 6.65 (m, 2H), 3.45 (s, 2H), 2.98 (d, J = 11.4 Hz, 2H), 2.51 - 2.35 (m, 2H), 2.04 (m, 2H), 1.51 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.9, 145.9, 130.9, 128.1, 126.5, 125.7, 125.7, 115.4, 79.4,

62.3, 53.4, 43.9, 25.8. LCMS Retention time: 1.35 min. LCMS purity 95.8%. HRMS (ESI): *m/z* calcd for $C_{25}H_{27}NO_2$ $[M+H]^+$ 374.2114, found 374.2107.

(1-(3-Hydroxybenzyl)piperidin-4-yl)diphenylmethanol (4w). Method C: **7** (0.030 g, 0.11 mmol), 3-hydroxybenzyl bromide **10gg** (0.025 g, 0.14 mmol) and triethylamine (0.023 mL, 0.17 mmol) in acetonitrile (2 mL). The reaction was purified by reverse-phase MPLC (10 – 100% CH_3CN:water) to produce **4w** (0.029 g, 0.077 mmol, 69% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 - 7.40 (m, 4H), 7.31 - 7.22 (m, 4H), 7.18 - 7.11 (m, 2H), 7.08 (t, J = 7.8 Hz, 1H), 6.78 - 6.69 (m, 2H), 6.69 - 6.64 (m, 1H), 3.43 (s, 2H), 2.98 - 2.87 (m, 2H), 2.47 - 2.33 (m, 1H), 2.05 - 1.94 (m, 4H), 1.59 - 1.37 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.3, 145.9, 138.8, 129.2, 128.1, 126.4, 125.8, 125.7, 121.3, 116.8, 114.8, 79.4, 62.9, 53.7, 43.9, 25.9. LCMS Retention time: 1.28 min. LCMS purity 97.7%. HRMS (ESI): *m/z* calcd for $C_{25}H_{27}NO_2$ $[M+H]^+$ 374.2114, found 374.2129.

(1-(2-Hydroxybenzyl)piperidin-4-yl)diphenylmethanol (4x). To a vial was added the **7** (0.030 g, 0.11 mmol) and 2-hydroxybenzaldehyde **11d** (0.013 g, 0.011 mL, 0.11 mmol) in THF (0.5 mL) to form a solution. The reaction began to stir at rt and after 30 min then the sodium triacetoxyborohydride (0.026 g, 0.12 mmol) was added and the reaction continued to stir at rt. The reaction was then quenched with water (1.5 mL) and extracted with CH_2Cl_2 (1.5 mL). The organic layer was dried with $MgSO_4$, filtered, concentrated and purified by reverse-phase MPLC (10 - 100% CH_3CN:water) to produce **4x** (0.009 g, 0.024 mmol, 21 % yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 - 7.43 (m, 4H), 7.34 - 7.27 (m, 4H), 7.22 - 7.11 (m, 3H), 6.95 (dd, J = 7.5, 1.7 Hz, 1H), 6.79 (dd, J = 8.1, 1.2 Hz, 1H), 6.75 (td, J = 7.4, 1.2 Hz, 1H), 3.69 (s, 2H), 3.12 - 2.97 (m, 2H), 2.57 - 2.40 (m, 1H), 2.22 - 2.06 (m, 3H), 1.63 - 1.46 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.8, 145.6, 128.8, 128.6, 128.2, 126.7, 125.7, 119.0, 116.2, 79.3, 53.4, 43.8,

26.2. LCMS Retention time: 1.41 min. LCMS purity 100 %. HRMS (ESI): *m/z* calcd for $C_{25}H_{27}NO_2$ $[M+H]^+$ 374.2114, found 374.2108.

Methyl 4-((4-(hydroxydiphenylmethyl)piperidin-1-yl)methyl)benzoate (4y). Method C: **7** (0.15 g, 0.56 mmol), methyl 4-(bromomethyl)benzoate **10hh** (0.15 g, 0.67 mmol) and triethylamine (0.12 mL, 0.84 mmol) in acetonitrile (2 mL). The reaction was purified by reverse-phase MPLC (10 – 100% CH_3CN:water) to produce **4y** (0.21 g, 0.52 mmol, 92% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, J = 8.2 Hz, 2H), 7.51 - 7.42 (m, 4H), 7.37 (d, J = 8.1 Hz, 2H), 7.33 - 7.26 (m, 4H), 7.23 - 7.12 (m, 2H), 3.90 (s, 3H), 3.54 (s, 2H), 2.90 (d, J = 10.4 Hz, 2H), 2.43 (p, J = 8.6, 7.8 Hz, 1H), 2.14 (s, 1H), 2.04 (s, 2H), 1.55 - 1.42 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.0, 145.9, 129.5, 128.9, 128.1, 126.5, 125.8, 79.5, 62.8, 54.0, 52.0, 44.1, 26.4. LCMS Retention time: 3.697 min. LCMS purity 99.6%. HRMS (ESI): *m/z* calcd for $C_{27}H_{29}NO_3$ $[M+H]^+$ 416.2219, found 416.2225.

Methyl 3-((4-(hydroxydiphenylmethyl)piperidin-1-yl)methyl)benzoate (4z). Method C: **7** (0.030 g, 0.11 mmol), methyl 3-(bromomethyl)benzoate **10ii** (0.031 g, 0.14 mmol) and triethylamine (0.023 mL, 0.17 mmol) in acetonitrile (2 mL). The reaction was purified by reverse-phase MPLC (10 – 100% CH_3CN:water) to produce **4z** (0.028 g, 0.067 mmol, 60% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.97 - 7.87 (m, 2H), 7.53 - 7.43 (m, 5H), 7.40 - 7.33 (m, 1H), 7.31 - 7.24 (m, 4H), 7.20 - 7.14 (m, 2H), 3.90 (s, 3H), 3.54 (s, 2H), 2.97 - 2.83 (m, 2H), 2.50 - 2.37 (m, 1H), 2.29 (s, 1H), 2.07 - 1.95 (m, 2H), 1.49 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.2, 145.9, 138.7, 133.7, 130.2, 130.0, 128.3, 128.2, 128.1, 126.5, 125.8, 79.5, 62.7, 53.8, 52.1, 44.1, 26.4. LCMS Retention time: 3.695 min. LCMS purity 98.5%. HRMS (ESI): *m/z* calcd for $C_{27}H_{29}NO_3$ $[M+H]^+$ 416.2219, found 416.2227.

Methyl 2-((4-(hydroxydiphenylmethyl)piperidin-1-yl)methyl)benzoate (4aa). Method C: **7** (0.030 g, 0.11 mmol), methyl 2-(bromomethyl)benzoate **10jj** (0.031 g, 0.14 mmol) and

triethylamine (0.023 mL, 0.17 mmol) in acetonitrile (2 mL). The reaction was purified by reverse-phase MPLC (10 – 100% CH_3CN:water) to produce **4aa** (0.044 g, 0.10 mmol, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 - 7.87 (m, 2H), 7.53 - 7.43 (m, 5H), 7.40 - 7.33 (m, 1H), 7.31 - 7.24 (m, 4H), 7.20 - 7.14 (m, 2H), 3.90 (s, 3H), 3.54 (s, 2H), 2.97 - 2.83 (m, 2H), 2.50 - 2.37 (m, 1H), 2.29 (s, 1H), 2.07 - 1.95 (m, 2H), 1.49 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.2, 145.9, 138.7, 133.7, 130.2, 130.0, 128.3, 128.2, 128.1, 126.5, 125.8, 79.5, 62.7, 53.8, 52.1, 44.1, 26.4. LCMS Retention time: 3.695 min. LCMS purity 97.4%. HRMS (ESI): *m/z* calcd for $C_{27}H_{29}NO_3$ $[M+H]^+$ 416.2219, found 416.2248.

(1-(4-Iodobenzyl)piperidin-4-yl)diphenylmethanol (4bb). Method C: **7** (0.300 g, 1.12 mmol), 4-iodobenzyl bromide **10kk** (0.40 g, 1.35 mmol) and triethylamine (0.24 mL, 1.68 mmol) in acetonitrile (2 mL). The reaction was purified by reverse-phase MPLC (10 – 100% CH_3CN:water) to produce **4bb** (0.51 g, 1.06 mmol, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 - 7.57 (m, 2H), 7.49 - 7.40 (m, 4H), 7.33 - 7.26 (m, 4H), 7.22 - 7.11 (m, 2H), 7.06 (d, J = 7.9 Hz, 2H), 3.46 (s, 2H), 2.91 (d, J = 11.2 Hz, 2H), 2.50 - 2.34 (m, 1H), 2.13 (s, 1H), 2.05 (s, 2H), 1.50 (s, 4H).

4-((4-(Hydroxydiphenylmethyl)piperidin-1-yl)methyl)benzoic acid (4cc). To a vial was added the **4y** (0.18 g, 0.42 mmol) and THF (1 mL). The 2.0 M LiOH (1.48 mL, 2.96 mmol) in water was added and the reaction stirred at rt for 24 h. The reaction was acidified with 1.0 M HCl to pH 2 - 3 and then extracted with CH_2Cl_2 (3 x 15 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 (**4cc**) (0.011 g, 0.027 mmol, 6% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H), 7.99 (d, J = 8.2 Hz, 2H), 7.67 (d, J = 7.9 Hz, 2H), 7.58 - 7.42 (m, 4H), 7.28 (t, J = 7.8 Hz, 4H), 7.20 - 7.07 (m, 2H), 4.28 (s, 2H), 3.82 - 3.52 (m, 2H), 3.17 (s, 1H), 2.85 (d, J = 52.0 Hz, 3H), 1.88 - 1.69 (m, 4H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 167.4, 147.3,

143.7, 129.2, 128.6, 127.8, 125.8, 125.7, 78.5, 62.0, 53.5, 43.3, 26.0. LCMS Retention time: 1.250 min. LCMS purity 100%. HRMS (ESI): *m/z* calcd for $C_{26}H_{27}NO_3$ $[M+H]^+$ 402.2064, found 402.2062.

3-((4-(Hydroxydiphenylmethyl)piperidin-1-yl)methyl)benzoic acid (4dd). Same procedure as **4cc** using **4z** (0.012 g, 0.030 mmol), 2.0 M LiOH (0.10 mL, 0.21 mmol) in water and THF (1 mL). Purified by reverse-phase MPLC (10 - 100% CH_3CN:water) to produce **4dd** (0.005 g, 0.012 mmol, 42% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.00 (s, 1H), 8.11 (s, 1H), 8.00 (d, J = 7.7 Hz, 1H), 7.82 - 7.70 (m, 1H), 7.57 (t, J = 7.7 Hz, 1H), 7.49 (d, J = 7.8 Hz, 4H), 7.28 (t, J = 7.7 Hz, 4H), 7.18 - 7.10 (m, 2H), 4.37 - 4.12 (m, 2H), 3.76 - 3.53 (m, 2H), 3.21 - 3.14 (m, 1H), 3.03 - 2.68 (m, 3H), 1.91 - 1.56 (m, 4H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.9, 147.3, 138.7, 132.1, 129.5, 127.9, 127.8, 125.8, 125.7, 78.5, 62.1, 53.4, 43.3, 26.0. LCMS Retention time: 1.250 min. LCMS purity 100%. HRMS (ESI): *m/z* calcd for $C_{26}H_{27}NO_3$ $[M+H]^+$ 402.2064, found 402.2092.

2-((4-(Hydroxydiphenylmethyl)piperidin-1-yl)methyl)benzoic acid (4ee). Same procedure as **4cc** using **4ee** (0.043 g, 0.10 mmol), 2.0 M LiOH (0.36 mL, 0.72 mmol) in water and THF (1 mL). Purified by reverse-phase MPLC (10 - 100% CH_3CN:water) to produce **4ee** (0.007 g, 0.018 mmol, 17% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.05 (br s, 1H), 7.87 - 7.77 (m, 1H), 7.55 - 7.46 (m, 4H), 7.44 - 7.37 (m, 2H), 7.36 - 7.23 (m, 5H), 7.20 - 7.10 (m, 2H), 3.98 (s, 2H), 3.02 (d, J = 11.9 Hz, 2H), 2.83 - 2.72 (m, 1H), 2.72 - 2.58 (m, 2H), 2.47 (br s, 1H), 1.68 - 1.47 (m, 2H), 1.47 - 1.30 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.7, 146.7, 138.4, 131.8, 131.4, 131.3, 130.1, 128.7, 127.9, 126.1, 125.6, 78.2, 59.3, 50.2, 41.6, 24.4. LCMS Retention time: 1.50 min. LCMS purity 99%. HRMS (ESI): *m/z* calcd for $C_{26}H_{27}NO_3$ $[M+H]^+$ 402.2064, found 401.2059.

1-(4-(Thiophen-3-yl)benzyl)piperidin-4-yl)diphenylmethanol (4ff). Same procedure as **3l** using thiophen-3-ylboronic acid (0.011 g, 0.087 mmol), **4bb** (0.035 g, 0.072 mmol), 1,1'-bis(di-*tert*-butylphosphino)ferrocene palladium dichloride (2 mg, 3.6 μmol) and potassium carbonate (0.015 g, 0.11 mmol), acetonitrile (1 mL) and water (1 mL). Purified by reverse-phase MPLC (10 - 100% CH_3CN:water) to produce **4ff** (0.027 g, 0.062 mmol, 85% yield) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 - 7.51 (m, 2H), 7.51 - 7.45 (m, 4H), 7.45 - 7.42 (m, 1H), 7.40 - 7.35 (m, 2H), 7.35 - 7.26 (m, 6H), 7.21 - 7.13 (m, 2H), 3.53 (s, 2H), 3.02 - 2.87 (m, 2H), 2.52 - 2.37 (m, 1H), 2.18 (s, 1H), 2.10 - 1.95 (m, 2H), 1.62 - 1.41 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.0, 142.1, 137.0, 134.6, 129.7, 128.1, 126.5, 126.3, 126.2, 126.1, 125.8, 120.0, 79.5, 62.8, 53.9, 44.1, 26.4. LCMS Retention time: 2.65 min. LCMS purity 100%. HRMS (ESI): *m/z* calcd for $C_{29}H_{29}NOS$ $[M+H]^+$ 440.2042, found 440.2033.

(1-(4-(Thiophen-2-yl)benzyl)piperidin-4-yl)diphenylmethanol (4gg). To a microwave vial was added the **4bb** (0.035 g, 0.073 mmol), RuPhos (4 mg, 8.8 μmol), palladium (II) acetate (1.0 mg, 4.4 μmol), potassium trifluoro(thiophen-2-yl)borate (0.015 g, 0.077 mmol) and sodium bicarbonate (0.015 g, 0.15 mmol). The vial was evacuated with argon three times and then degassed ethanol (0.5 mL) was added. The reaction then stirred at 100 °C for 60 minutes in the microwave. The reaction was cooled to rt and diluted with saturated $NaHCO_3$ (10 mL) and extracted with EtOAc (3 x 15 mL). The organic layers were combined, dried with $MgSO_4$, filtered and concentrated. The reaction was purified by reverse-phase MPLC (10 - 100% CH_3CN:water) to produce (**4gg**) (0.022 g, 0.050 mmol, 69% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 - 7.51 (m, 2H), 7.50 - 7.44 (m, 4H), 7.32 - 7.22 (m, 8H), 7.21 - 7.15 (m, 2H), 7.11 - 7.05 (m, 1H), 3.48 (s, 2H), 3.00 - 2.87 (m, 2H), 2.50 - 2.37 (m, 1H), 2.17 (s, 1H), 2.10 - 1.95 (m, 2H), 1.56 - 1.38 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.9, 144.3, 133.2, 129.7, 128.1, 127.9, 126.5, 125.8, 125.7, 124.6, 122.9, 79.5, 62.8, 53.8, 44.1, 26.4. LCMS Retention time:

2.71 min. LCMS purity 99.3%. HRMS (ESI): *m/z* calcd for $C_{29}H_{29}NOS$ $[M+H]^+$ 440.2042, found 440.2056.

(1-(4-(Furan-3-yl)benzyl)piperidin-4-yl)diphenylmethanol (4hh). Same procedure as **3l** using furan-3-ylboronic acid (0.010 g, 0.091 mmol), **4bb** (0.037 g, 0.076 mmol), 1,1'-bis(di-*tert*-butylphosphino)ferrocene palladium dichloride (3 mg, 4 μmol) and potassium carbonate (0.016 g, 0.11 mmol). Purified by reverse-phase MPLC (10 - 100% CH_3CN:water) to produce **4hh** (0.028 g, 0.067 mmol, 89% yield) as an oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.71 (s, 1H), 7.51 - 7.45 (m, 5H), 7.45 - 7.37 (m, 2H), 7.34 - 7.24 (m, 6H), 7.23 - 7.09 (m, 2H), 6.69 (dd, J = 1.9, 0.9 Hz, 1H), 3.48 (s, 2H), 2.99 - 2.86 (m, 2H), 2.49 - 2.36 (m, 1H), 2.18 (s, 1H), 2.08 - 1.93 (m, 2H), 1.55 - 1.42 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.0, 143.6, 138.3, 136.9, 131.1, 129.7, 128.1, 126.5, 126.2, 125.8, 125.6, 108.8, 79.5, 62.9, 53.8, 44.1, 26.4. LCMS Retention time: 2.52 min. LCMS purity 99.3%. HRMS (ESI): *m/z* calcd for $C_{29}H_{29}NO_2$ $[M+H]^+$ 424.2270, found 424.2250.

(1-(4-(Furan-2-yl)benzyl)piperidin-4-yl)diphenylmethanol (4ii). Same procedure as **4gg** using **4bb** (0.036 g, 0.073 mmol), RuPhos (4 mg, 8.8 μmol), palladium (II) acetate (1 mg, 4.4 μmol), potassium trifluoro(furan-2-yl)borate (0.013 g, 0.077 mmol) and sodium carbonate (0.016 g, 0.15 mmol) and degassed ethanol (0.5 mL). Purified by reverse-phase MPLC (10 - 100% CH_3CN:water) to produce **4ii** (0.022 g, 0.050 mmol, 68% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.63 - 7.54 (m, 2H), 7.52 - 7.42 (m, 5H), 7.29 (m, 6H), 7.22 - 7.07 (m, 2H), 6.62 (dd, J = 3.4, 0.8 Hz, 1H), 6.46 (dd, J = 3.4, 1.8 Hz, 1H), 3.48 (s, 2H), 2.99 - 2.86 (m, 2H), 2.51 - 2.36 (m, 1H), 2.17 (s, 1H), 2.08 - 1.95 (m, 2H), 1.56 - 1.42 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.0, 146.0, 141.9, 137.3, 129.7, 129.5, 128.1, 126.5, 125.8, 123.6, 111.6, 104.7, 79.5, 62.9, 53.8, 44.1, 26.4. LCMS Retention time: 2.60 min. LCMS purity 97.4%. HRMS (ESI): *m/z* calcd for $C_{29}H_{29}NO_2$ $[M+H]^+$ 424.2270, found 424.2271.

(1-(4-(1H-pyrrol-1-yl)benzyl)piperidin-4-yl)diphenylmethanol (4jj). To a vial was added the **4bb** (0.030 g, 0.062 mmol), copper powder (0.8 mg, 0.012 mmol), pyrrole (7 µl, 0.093 mmol) and cesium carbonate (0.071 g, 0.22 mmol) in acetonitrile (1 mL). The vial was then purged with argon three times and then stirred at 80 °C for 21 h. The reaction was then diluted with EtOAc (10 mL) and filtered through Celite. The filtrate was concentrated then purified with reverse-phase MPLC (10 - 100% CH_3CN:water) to produce **4jj** (0.012 g, 0.029 mmol, 47% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 - 7.44 (m, 4H), 7.36 - 7.26 (m, 8H), 7.22 - 7.12 (m, 2H), 7.07 (t, J = 2.4 Hz, 2H), 6.33 (t, J = 2.2 Hz, 2H), 3.51 (s, 2H), 3.00 - 2.88 (m, 2H), 2.51 - 2.37 (m, 1H), 2.13 (s, 1H), 2.08 - 1.94 (m, 2H), 1.57 - 1.44 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.9, 139.7, 130.3, 128.1, 126.5, 125.8, 120.2, 119.3, 110.2, 79.5, 62.4, 53.8, 44.1, 26.4. LCMS Retention time: 2.60 min. LCMS purity 97.4%. HRMS (ESI): *m/z* calcd for $C_{29}H_{30}N_2O$ $[M+H]^+$ 423.2430, found 423.2441.

1-(4-(*Tert*-butyl)phenyl)-4-(4-(hydroxy(phenyl)methyl)piperidin-1-yl)butan-1-ol (5a). Method B: **35** (0.026 g, 0.066 mmol) and MeOH (2 mL) and sodium borohydride (10 mg, 0.27 mmol) to produce **5a** (0.019 g, 0.048 mmol, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.24 (m, 9H), 4.63 – 4.57 (m, 1H), 4.33 (d, *J* = 7.6 Hz, 1H), 3.23 – 2.83 (m, 2H), 2.42 – 2.35 (m, 2H), 2.13 – 1.89 (m, 3H), 1.86 – 1.52 (m, 6H), 1.46 – 1.16 (m, 4H), 1.31 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.4, 143.4, 142.8, 128.3, 127.63, 127.61, 126.6, 125.4, 125.0, 78.74, 78.67, 73.4, 58.9, 54.30, 54.26, 52.8, 52.7, 43.21, 43.2, 39.9, 34.4, 31.4, 28.4, 28.3, 28.2, 24.2, 24.1. LCMS Retention time: 3.707 min. LCMS purity 97.1%. HRMS (ESI): *m/z* calcd for $C_{26}H_{37}NO_2$ $[M+H]^+$ 396.2896, found 396.2891.

4-(4-Benzylpiperidin-1-yl)-1-(4-(*tert*-butyl)phenyl)butan-1-ol (5b). Method B: **36** (0.29 g, 0.77 mmol), MeOH (5 mL) and sodium borohydride (0.12 g, 3.08 mmol) to produce **5b** (0.23 g, 0.61 mmol, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.25 (m, 6H), 7.21 – 7.12 (m,

3H), 4.64 – 4.60 (m, 1H), 3.13 – 3.07 (m, 1H), 2.94 – 2.88 (m, 1H), 2.54 (d, *J* = 7.0 Hz, 2H), 2.44 – 2.34 (m, 2H), 2.03 – 1.93 (m, 2H), 1.90 – 1.38 (m, 10H), 1.31 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.4, 142.9, 140.7, 129.1, 128.2, 125.8, 125.4, 125.0, 73.5, 59.0, 54.6, 52.9, 42.9, 40.1, 38.0, 34.4, 31.8, 31.6, 31.4, 24.3. LCMS Retention time: 4.330 min. LCMS purity 99.1%. HRMS (ESI): *m/z* calcd for $C_{26}H_{37}NO$ $[M+H]^+$ 380.2948, found 380.2974.

4-(4-Benzhydrylpiperazin-1-yl)-1-(4-(*tert*-butyl)phenyl)butan-1-ol (5c). Method B: **38** (0.086 g, 0.19 mmol), MeOH (3 mL) and sodium borohydride (0.014 g, 0.39 mmol) to produce **5c** (0.232 g, 0.61 mmol, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 - 7.37 (m, 4H), 7.35 - 7.29 (m, 2H), 7.29 - 7.22 (m, 6H), 7.20 - 7.13 (m, 2H), 4.60 (dd, J = 8.3, 2.7 Hz, 1H), 4.22 (s, 1H), 2.86 - 2.16 (m, 10H), 1.94 (m, 1H), 1.87 - 1.75 (m, 1H), 1.72 - 1.55 (m, 2H), 1.29 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.5, 142.9, 142.8, 128.5, 128.3, 128.0, 127.9, 127.8, 126.9, 126.8, 125.3, 125.0, 77.3, 76.2, 73.4, 58.7, 53.3, 51.6, 39.7, 34.4, 31.4, 23.9. LCMS Retention time: 4.270 min. LCMS purity 97.3%. HRMS (ESI): *m/z* calcd for $C_{31}H_{40}N_2O$ $[M+H]^+$ 457.3213, found 457.3207.

1-(4-(*Tert*-butyl)phenyl)-4-(4-(diphenylmethylene)piperidin-1-yl)butan-1-ol (5d). Method B: **40** (0.019 g, 0.042 mmol), MeOH (3 mL) and sodium borohydride (6 mg, 0.17 mmol) to produce **5d** (0.010 g, 0.022 mmol, 52% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.26 (m, 8H), 7.23 – 7.18 (m, 2H), 7.13 – 7.10 (m, 4H), 4.68 – 4.65 (m, 1H), 2.66 – 2.60 (m, 2H), 2.55 – 2.42 (m, 8H), 2.00 – 1.94 (m, 1H), 1.90 – 1.81 (m, 1H), 1.73 – 1.63 (m, 3H), 1.30 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.5, 142.7, 142.3, 136.4, 134.6, 129.7, 128.0, 126.4, 125.3, 125.0, 73.3, 58.7, 55.0, 39.6, 34.4, 31.6, 31.4, 31.1, 24.0, 22.6. LCMS Retention time: 4.454 min. LCMS purity 97.1%. HRMS (ESI): *m/z* calcd for $C_{32}H_{39}NO$ $[M+H]^+$ 454.3104, found 454.3130.

4-(4-Benzhydrylpiperidin-1-yl)-1-(4-(*tert*-butyl)phenyl)butan-1-ol (5e). Method B: **42** (0.025 g, 0.056 mmol), sodium borohydride (4 mg, 0.11 mmol) and MeOH (2 mL) to produce **5e** (0.017

g, 0.036 mmol, 66% yield) as an oil. 1H NMR (400 MHz, Chloroform-d) δ 7.27 - 7.21 (m, 2H), 7.21 - 7.13 (m, 10H), 7.05 (m, 2H), 4.51 (dd, J = 8.4, 2.5 Hz, 1H), 3.44 (d, J = 11.1 Hz, 1H), 3.00 (d, J = 11.4 Hz, 1H), 2.82 (d, J = 11.3 Hz, 1H), 2.32 (s, 2H), 2.13 - 1.77 (m, 4H), 1.76 - 1.64 (m, 1H), 1.59 (m, 2H), 1.53 - 1.44 (m, 2H), 1.38 - 1.24 (m, 3H), 1.21 (s, 9H). ^{13}C NMR (101 MHz, CDCl3) δ 149.5, 143.7, 143.7, 142.9, 128.5, 128.5, 128.0, 128.0, 126.2, 125.4, 125.0, 73.5, 58.6, 53.0, 39.6, 34.4, 31.4, 29.7. LCMS Retention time: 1.76 min. LCMS purity 98.6%. HRMS (ESI): *m/z* calcd for $C_{32}H_{41}NO$ $[M+H]^+$ 456.3260, found 456.3245.

(1-(3-([1,1'-Biphenyl]-4-yloxy)propyl)piperidin-4-yl)diphenylmethanol (6). To a vial was added the **12** (0.050 g, 0.15 mmol) and THF (3 mL). The reaction was cooled to 0 °C and triphenylphosphine (0.060 g, 0.23 mmol), DIAD (0.045 mL, 0.23 mmol) and 4-phenylphenol (0.033 g, 0.19 mmol) were added and the reaction was allowed to warm to rt and stirred for 18 h. The reaction was then adsorbed to silica and purified by MPLC (0 - 10% MeOH:CH_2Cl_2) to produce the desired product **6** (0.057 g, 0.12 mmol, 77% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 - 7.44 (m, 8H), 7.44 - 7.37 (m, 2H), 7.30 (dd, J = 8.4, 7.1 Hz, 5H), 7.21 - 7.15 (m, 2H), 6.98 - 6.92 (m, 2H), 4.04 (t, J = 6.3 Hz, 2H), 3.09 - 2.95 (m, 2H), 2.57 - 2.51 (m, 2H), 2.51 - 2.41 (m, 1H), 2.17 (s, 1H), 2.08 - 1.93 (m, 4H), 1.59 - 1.45 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.5, 145.9, 140.8, 133.7, 128.7, 128.2, 128.1, 126.7, 126.6, 126.5, 125.8, 114.7, 79.5, 66.4, 55.4, 54.1, 44.1, 26.9, 26.3. LCMS Retention time: 4.155 min. LCMS purity 100%. HRMS (ESI): *m/z* calcd for $C_{33}H_{35}NO_2$ $[M+H]^+$ 478.2740, found 478.2737.

Strains and Conditions

S. aureus strain UAMS-1[14], a methicillin susceptible clinical osteomyelitis isolate, was used to evaluate the antimicrobial activity of terfenadine and corresponding structural derivatives. Where indicated antimicrobial activity measures were expanded to include: CRC61

and CRC118, which are spontaneous ciprofloxacin-resistant derivatives of UAMS-1 that were selected by growth on Mueller-Hinton agar (MHA) (Becton, Dickinson & Company, Franklin Lakes, NJ) at 1.5X MIC ciprofloxacin (0.75 μg/mL, Sigma-Aldrich, Saint Louis, MO); *S. aureus* strains USA 300-0114[49] (methicillin resistant), Mu50[50] (vancomycin intermediate resistant) and VRSA-1[51] (vancomycin resistant); *E. faecium* 824-05;[25] *E. faecalis* OG1RF;[52] *A. baumannii* 983709;[53] *K. pneumoniae* CKP4;[54] *E. coli* 8314 (URMC Clinical Isolate); and *M. tuberculosis* strain $mc^2$6020.[55] Terfenadine was purchased (Sigma-Aldrich) and its analogs were synthesized and provided by the Specialized Chemistry Center at the University of Kansas, Lawrence.

Minimum Inhibitory Concentration (MIC) Testing

Minimum Inhibitory Concentration (MIC) testing was performed to determine the minimum concentration of the indicated agent necessary to inhibit visible growth of bacteria according to Clinical and Laboratory Standards (CLSI) guidelines.[50] Briefly, with the exception of *M. tuberculosis*, overnight cultures of the indicated bacterial species/strain were subcultured 1:100 in fresh Mueller-Hinton broth (MHB) to early exponential phase (OD_{600nm} between 0.180 and 0.2). Then, 1×10^5 colony forming units (CFU)/mL bacteria were inoculated into the individual wells of a 96-well round-bottom microtiter plate containing 88 μl of MHB. To the first column, 2 μl of the test compound's corresponding solvent were also added to each well (negative control). To the next ten columns, 2 μl of the test compound (dissolved in DMSO for terfenadine and its derivatives or sterile water for ciprofloxacin) were added in increasing 2-fold increments of 0.5 μg/mL to 256 μg/mL (final concentration) to each successive well; each compound was evaluated in duplicate. Plates were incubated at 37°C incubator for 16 h at which point the minimum inhibitory concentration was determined to be the lowest concentration of test compound that inhibited bacterial growth, as judged by the unaided eye. For *M. tuberculosis*

MIC measures of the attenuated Biosafety Level 2 approved strain $mc^2$6020 was performed using alamar blue staining, as previously described.[51]

S. aureus DNA Gyrase Supercoiling Assay

S. aureus gyrase supercoiling assays were performed in the absence or presence of the indicated concentration of terfenadine and corresponding analogs using the *S. aureus* Gyrase Supercoiling Assay Kit, according to the manufacturer's recommendations (Inspiralis, Norwich, UK). Briefly, assays (30 μl) were performed in gyrase buffer (40 mM HEPES.KOH pH 7.6, 10 mM magnesium acetate, 10 mM DTT, 2 mM ATP, 500 mM potassium glutamate, 0.5 mg/mL albumin), containing relaxed plasmid pBR322 DNA (250 ng/μl), using 0.5 units (U) of *S. aureus* DNA gyrase. Where indicated, reactions were carried out in the presence of the indicated concentration (2 μl) of ciprofloxacin or test compounds; their vehicles, water and DMSO, served as negative controls, respectively. The reactions were incubated at 37°C for 30 min, followed by the addition of 30 μl of STEB (40% w/v sucrose, 100 mM pH 8 Tris-HCl, 1 mM EDTA, 0.5 mg/mL bromophenol blue) stop buffer and 30 μl of 24:1 chlorform:isoamyl alcohol (Amresco, Solon, OH) for a total volume of 90 μl. Reaction products were then loaded on 1% agarose TAE gels and allowed to sit for 40 min prior to electrophoresis, allowing for the salts to diffuse. Gels were stained with 0.5 μg/mL ethidium bromide and images were analyzed using densitometry (Image J, NIH). The IC_{50} values for each test compound were determined to be the compound concentration that inhibited *S. aureus* DNA gyrase activity by 50% (determined from densitometry values relative to positive and negative controls of reactions either with or without the enzyme, respectively).

S. aureus Topoisomerase IV Decatenation Assay

An *S. aureus* topoisomerase IV activity assay was performed according to the manufacturer's recommendations (Inspiralis) on terfenadine and corresponding analogs to determine if they inhibited the ability of *S. aureus* topoisomerase IV to decatenate kDNA. The assay was performed by incubating 0.25 U per reaction *S. aureus* topoisomerase IV enzyme with 200 ng kDNA (kinetoplast DNA isolated from *Crithidia fasciculate*) in kit-supplied assay buffer (50 mM Tris.HCl pH 7.5, 5 mM $MgCl_2$, 5 mM DTT, 1.5 mM ATP, 350 mM potassium glutamate, and 0.05 mg/mL albumin) with varying amounts of water, DMSO, or test compounds (2 μl total at the desired concentrations) for a total volume of 30 μl at 37°C for 30 min. Reactions were stopped by the addition of 30 μl of STEB buffer followed by the addition of 30 μl of 24:1 chlorform:isoamyl alcohol (total volume 90 μl). Reaction products were then loaded on 1% agarose TAE gels and allowed to sit for 40 min prior to electrophoresis, allowing for the salts to diffuse. Gels were stained with 0.5 μg/mL ethidium bromide and images were analyzed using densitometry (Image J, NIH). The IC_{50} values for each test compound were determined to be the compound concentration that inhibited *S. aureus* topoisomerase IV activity by 50% (determined from densitometry values relative to positive and negative controls of reactions either with or without the enzyme, respectively).

Transcription Profiling

To study the gene expression profile in response to treatment with terfenadine and ciprofloxacin, GeneChip studies were performed with *S. aureus* UAMS-1, as previously described.[48,49] Briefly, bacterial cells were grown in TSB to early exponential phase (OD_{600}= 0.250) and were treated with DMSO or 0.5X MIC of ciprofloxacin or terfenadine for 30 min, at which point RNA was extracted. Then, Superscript II Reverse Transcriptase (Invitrogen,

Carlsbad, CA) was used to reverse transcribe 7 μg of each of the three bacterial RNA samples. This was then purified with the QIAquick PCR Purification Kit (Qiagen, Gaithersburg, MD) and subsequently partially digested with DNase I (Ambion, Austin, TX). The Enzo Bioarray Terminal Labeling Kit (Enzo Life Sciences, Farmingdale, NY) was used to 3' biotinylate the fragmented DNA. This labeled cDNA (2 μg) was hybridized to an *S. aureus* Affymetrix GeneChip. The manufacturer's recommendations for the processing of prokaryotic arrays were then followed (Affymetrix; Santa Clara, CA). This was done in biological replicates a minimum of two times. In the data analysis, the control poly(A) cDNA signal intensity or the signals from the entire GeneChip were used to normalize each of the RNA species. These were then averaged with GeneSpring 7.2 software (Agilent Technologies, Redwood City, CA). Those isolates designated as differentially expressed were defined as the RNA species which had at least a 2-fold difference in signal compared to the mock-treated sample (*t*-test, P = 0.05).

Docking Studies

Using the Surflex module of the SYBYL 8.0 software package (Certara, St Louis, Mo), the receptor proteins (PDB ID 2XCS, 2XCT and 3U2K) were prepared by removing the bound solved ligand then defining a pocket as a 20 Å sphere around the original ligand site. The corresponding terfenadine-based ligands were then docked into the original ligand site. The compounds were sketched and protonated in SYBYL, and Gasteiger–Marsili charges were assigned. Default Surflex settings were utilized and the generated 30 docking poses per compound were visually inspected. The best pose was selected on the basis of Combined CScore (ChemScore, G_Score, D_Score and PMF_Score) from the SYBYL software.

hERG Inhibition Assay

This assay was performed off-site at Eurofins Panlabs (Taiwan) and was adapted from a previous procedure.[50] Human recombinant potassium channel hERG is expressed in human HEK-293 cells in HEPES buffer at pH 7.4, 0.1% BSA, 5 mM KCl, 0.8 mM $MgCl_2$, 130 mM NaCl, 1mM EGTA and 10 mM glucose. A 10 μg aliquot was incubated with [^{3}H] Astemizole and either compound **4g** or **6** in assay buffer containing 1% DMSO with ten increasing doses (0.3 nM – 10 μM). Binding was terminated by filtration onto glass filters followed by three washes with assay buffer. Radioactivity was determined by scintillation counting on each filter and specifically bound [^{3}H] Astemizole was determined. A dose-response curve was generated to provide the K_i and IC_{50} for the two compounds tested.

ASSOCIATED CONTENT

Supporting Information. Full synthetic experimentals for intermediates not shown in Schemes 1 – 8. Microarray data for terfenadine inhibition, LogP vs MIC data and hERG inhibition data. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*Phone: +1 (785) 864-1607. Fax: +1 (785) 864-8179. E-mail: dflaherty@ku.edu.

Author Contributions

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Notes

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ABBREVIATIONS

ESKAPE, *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species; NBTI, novel bacterial topoisomerase inhibitor; MPLC, medium performance liquid chromatography; HAI, hospital-acquired infection; MIC, minimum inhibitory concentration; SAR, structure-activity relationship; HTS, high-throughput screen; $IC_{50,}$ inhibitory concentration of 50%; TSB, tryptic soy broth; TSA, tryptic soy agar; MHB, Mueller-Hinton broth; MHA, Mueller-Hinton agar; VISA, vancomycin-intermediate *Staphylococcus aureus*; VRSA, vancomycin-resistant *Staphylococcus*

aureus; MRSA, methicillin-resistant *Staphylococcus aureus*; hERG, human Ether-à-go-go-Related Gene.

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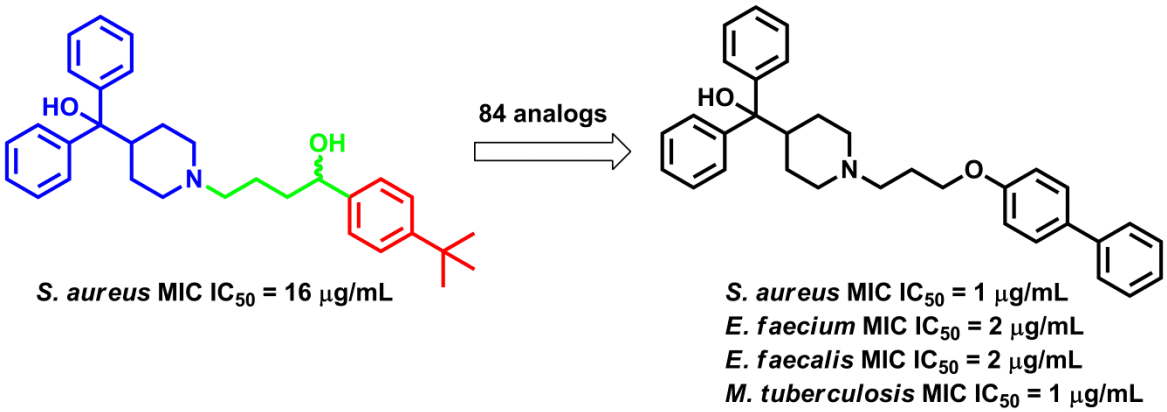
Table of Contents Graphic



S. aureus **MIC IC_{50} = 16 μg/mL**

S. aureus **MIC IC_{50} = 1 μg/mL**
E. faecium **MIC IC_{50} = 2 μg/mL**
E. faecalis **MIC IC_{50} = 2 μg/mL**
M. tuberculosis **MIC IC_{50} = 1 μg/mL**