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Selenophene-Containing Inhibitors of Type IIA Bacterial Topoisomerases

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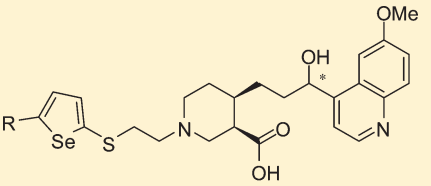
Supporting Information

ABSTRACT: We investigated compounds related to the previously reported antistaphyloccocal agent AVE6971 in an effort to attenuate inhibition of hERG potassium channel current that has been noted for this and related antibacterial drug classes. While most modifications of the original thiophene group compromised antibacterial activity, one selenophene analogue displayed (i) improved activity against the primary target enzyme DNA gyrase, (ii) similar activities against a panel of MRSA clinical isolates, and (iii) reduced hERG channel inhibition.



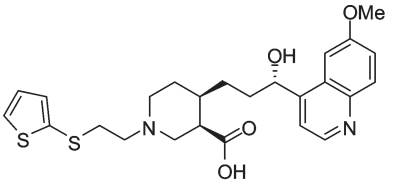
R = H, CHO, CF_2H, CN, COOH

INTRODUCTION

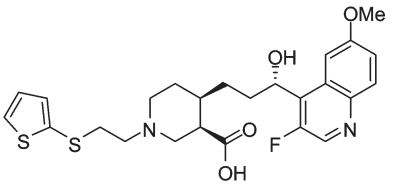
Topoisomerases are prominent drug targets in antibacterial research.[1,2] These enzymes catalyze the change in topological state of DNA during replication, transcription, recombination, and repair. Four main classes of bacterial topoisomerases have been identified, which are designated I–IV. Bacterial topoisomerases I and III are type IA topoisomerases, catalyzing transient breaking and rejoining of single-stranded regions of DNA, whereas bacterial topoisomerases II and IV are type IIA topoisomerases, breaking and rejoining duplex DNA.[3] These transient breaks, introduced in the phosphodiester backbone via formation of a covalent protein–DNA intermediate coupled through tyrosine and the 5′ phosphate termini, allow the DNA strands to pass through one another to effect interconversion of topoisomers.

Most antibacterial research efforts have focused on inhibitors of essential type IIA topoisomerases (topoisomerases II and IV) in the pursuit of developing new bactericidal agents with high bacterial specificity. Both topoisomerases II (DNA gyrase) and IV resolve issues incurred during DNA replication: DNA gyrase maintains helical tension and acts by introducing negative supercoils and eliminating positive supercoils that build up ahead of the replication fork (produced through the combined actions of helicase and DNA primase), whereas topoisomerase IV acts primarily by decatenating interlinked daughter DNA molecules before cell division. DNA gyrase has a heterodimeric A_2B_2 structure consisting of two GyrA and two GyrB subunits, with GyrA catalyzing the DNA breaking/rejoining cycle and GyrB catalyzing the required hydrolysis of ATP. Similarly, topoisomerase IV has a heterodimeric A_2B_2 structure consisting of two GrlA (ParC in *Escherichia coli*) and two GrlB (ParE in *E. coli*) subunits, with functions complementary to those of gyrase.

The most successful drug class that targets bacterial type IIA topoisomerases comprises the fluoroquinolones (FQs).[4,5] These drugs act as topoisomerase poisons that bind to the GyrA and GrlA/ParC subunits of DNA gyrase and topoisomerase IV, respectively.[6−8] Although this drug class continues to enjoy commercial success, resistance to FQs has developed.[9] There have been significant research efforts to develop non-FQ antibacterial agents that also target bacterial type IIA topoisomerases but do not share cross-resistance with the FQs. Two such novel bacterial topoisomerase inhibitors (NBTIs) were reported recently: the highly effective antistaphylococcal agents AVE6971[10] (**1**, Figure 1) and NXL101[11] (**2**). These piperidinyl quinolines demonstrated exquisite potency against FQ-sensitive and FQ-resistant (FQR) strains of *S. aureus* with MIC_{90} values of 1 and 0.5 μg/mL, respectively. They also inhibited DNA gyrase more



AVE6971 (**1**)



NXL101 (**2**)

Figure 1. Examples of piperidinyl quinoline antibacterial agents.

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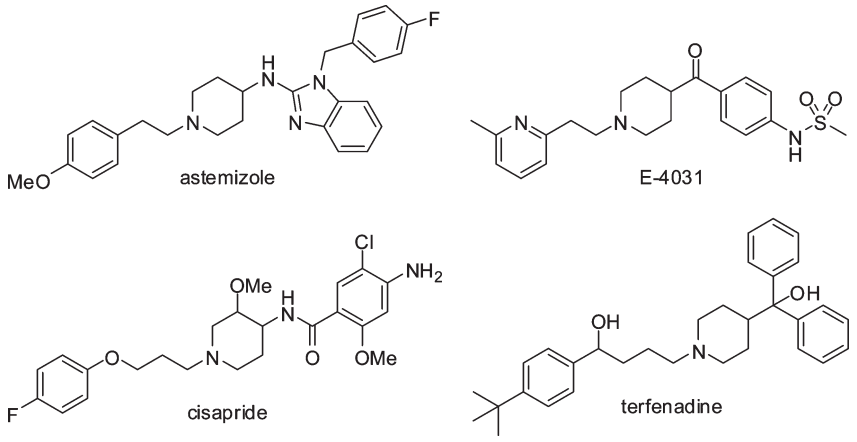


Figure 2. Chemical structures of nonantibacterial drugs that block the hERG potassium channel. These compounds, as well as the piperidinyl quinoline antibacterial agents shown in Figure 1, all share an *N*-(aryl-substituted alkyl)piperidine pharmacophore.

effectively than topoisomerase IV from *S. aureus*, which is opposite to the target preference associated with most FQs.[12] Although **2** demonstrated reduced inhibition of the human ether-a-go-go-related gene (hERG) potassium channel current when compared with its first-generation desfluoro analogue **1** (IC_{50} = 124 μM vs 21 μM),[13] phase I clinical development of **2** was halted because of observed QTc prolongation that was more severe than that noted in preclinical safety studies.[14,15] Poor cardiac safety has also compromised a number of other structurally related drug candidates that have an *N*-(aryl-substituted alkyl)piperidine pharmacophore (Figure 2).

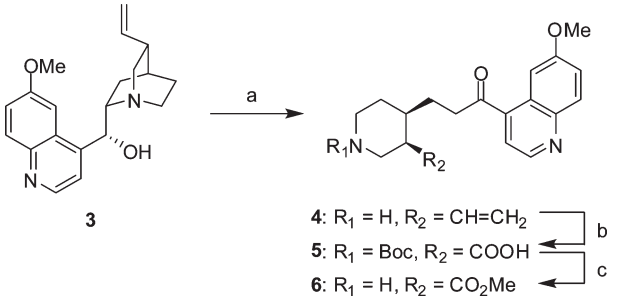
Despite potential cardiac safety issues, recently published work from AstraZeneca,[16] Daiichi Sankyo Co.,[17] GlaxoSmithKline,[18,19] Pfizer,[20] and Toyama Chemical Co./Taisho Pharmaceutical Co.[21] suggests that interest continues in piperidinyl quinolines and related NBTIs. This research activity, as well as the recent interest in selenium-containing therapeutics,[22−25] prompted us to explore the effect on antibacterial and hERG activities of exchanging the thiophene sulfur of **1** for selenium. While thiophene and selenophene are isosteric, these groups are not necessarily bioisosteric.[26,27] We herein report the syntheses and biological activities of selenophene-containing and related analogues of **1**.

CHEMISTRY

The synthetic routes to prepare piperidinyl quinoline analogues **15a**−**k** are shown in Schemes 1−3. Commercially available quinine (**3**, Aldrich, 90%) was heated in aqueous acetic acid to generate the rearrangement product *d*-quinotoxine (**4**, Scheme 1).[28] This acid-catalyzed process required prolonged heating (>3 days) under anaerobic conditions and generated a major byproduct (epiquinine, ∼30%, structure not shown). After purification by flash column chromatography (FCC), compound **4** was oxidized with potassium permanganate and Boc protected to give **5**, which was then treated with thionyl chloride in methanol to give Boc deprotected ester **6**.[29]

The chemical diversity in analogues **15a**−**k** was introduced via alkylation of intermediate **6** (Scheme 3, steps a−c). The synthetic routes to prepare the alkyl bromides **9** used in this step are illustrated in Scheme 2. Generation of lithium furan-2-thiolate (**8a**)[30] by addition of sulfur to furan-2-yllithium (generated in situ from furan, **7a**) followed by treatment with 1,2-dibromoethane

Scheme 1[a]



[a] Reagents and conditions: (a) AcOH/H_2O (2:1 v/v), Ar atmosphere, 80 °C, 10 days, 56%; (b) $KMnO_4$ (1.8 equiv), H_2SO_4, H_2O/acetone, 0−5 °C, 30 min, then to room temp, 4 h, then KOH (until pH ∼12), Boc_2O (1.0 equiv), room temp, 18 h; (c) $SOCl_2$ (2.4 equiv), MeOH, −40 °C, 30 min, then to room temp, 20 h, 14% (two steps).

provided the corresponding alkyl bromide **9a**. Thiophene and selenophene analogues **9b** and **9d** were prepared in a similar manner from lithium thiophene-2-thiolate (**8b**)[31] and lithium selenophene-2-thiolate (**8d**), respectively. Selenophene **9d** was then converted to aldehyde **9i** under Vilsmeier conditions.[32] This key step enabled further functionalization to generate strongly electron-withdrawing groups at the 5-position: aldehyde **9i** was treated with bis(2-methoxyethyl)aminosulfur trifluoride[33] to furnish the difluoromethyl derivative **9f** and was also treated with iodine in aqueous ammonia[34] to give nitrile **9g**. Oxidation of selenophene thioether **9d** was achieved with excess *m*-chloroperoxybenzoic acid (*m*-CPBA)[35] to generate sulfone **9e**. Phosphonate **8c** was prepared in situ as described earlier (via LDA-induced rearrangement of thiophosphate **11**)[36] and subsequently alkylated with 1,2-dibromoethane to give bromide **9c**. Amide **9h** was prepared from piperidine (**12**) and 3-bromopropanoyl chloride using standard conditions.

Alkylations of piperidine **6**, leading to derivatives **13**, were effected under conditions adapted from those described previously[29] (Scheme 3, step a−c). Alkylations employing bromides of selenophenes with electron-withdrawing groups (EWGs) at the 5-position (i.e., difluoromethyl analogue **9f** and nitrile **9g**) proved most difficult to accomplish and required extended heating (48−72 h). Alkylation of **6** with the highly

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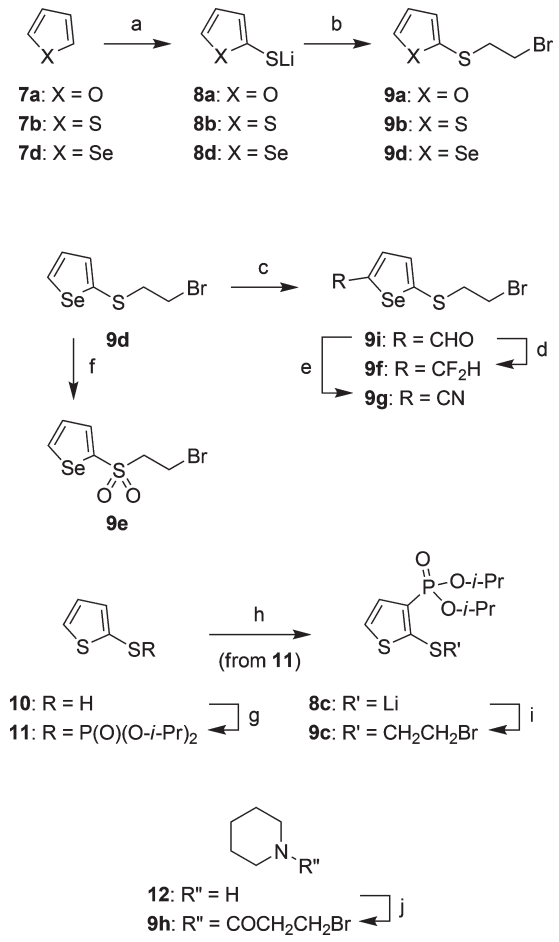
Scheme 2[a]



[a] Reagents and conditions: (a) *n*-BuLi (1 equiv, 1.6 M in hexanes), Et_2O, −10 → 0 °C (for **7a**), −40 °C (for **7b**), room temp (for **7d**), 1 h, S (1 equiv), 0 °C (for **7a**), −78 → 0 °C (for **7b** and **7d**), 1−3 h; (b) $BrCH_2CH_2Br$ (4 equiv), 0 °C → room temp, 18 h, 20−73%; (c) $POCl_3$ (1.2 equiv), DMF (1.2 equiv), 0 → 65 °C, 2 h, 72%; (d) $(CH_3OCH_2CH_2)_2NSF_3$ (1.7 equiv), EtOH (0.2 equiv), CH_2Cl_2, room temp, 18 h, 52%; (e) I_2 (1.2 equiv), 28% aq NH_4OH (excess), THF, 83%; (f) *m*-CPBA (3 equiv), CH_2Cl_2, 0 °C → reflux, 1 h, 79%; (g) NaH (1.3 equiv), THF, room temp, then $(i\text{-PrO})_2POCl$ (1 equiv), room temp, 24 h, 66%; (h, i) LDA (1.2 equiv), THF, −78 °C, 1 h, then 0 °C, 1 h, then $BrCH_2CH_2Br$ (4 equiv), 0 °C → room temp, 3 h, 11%; (j) $BrCH_2CH_2COCl$ (1 equiv), DIPEA (1.2 equiv), CH_2Cl_2, 0 °C → room temp, 18 h, 73%.

electrophilic β-sulfonyl bromide **9e**, however, was facile and required controlled slow addition of **9e** (limiting reagent) to **6** at room temperature to minimize undesired dialkylation (Scheme 3, step c). Compounds **13** were then sequentially reduced with sodium borohydride to the corresponding alcohols **14** and saponified with lithium hydroxide to give the target compounds **15a**−**h** as 50:50 mixtures of diastereomers. These mixtures were subjected to preparative thin-layer chromatography (PTLC) to furnish highly enriched mixtures of each diastereomer.[37] Aldehyde **15i** and acid **15j** were isolated as byproducts of hydrolysis from the desired difluoromethyl[38] and nitrile hydrolysis products **15f** and **15g**, respectively.[39] Phosphonic acid **15k** was derived from diisopropyl phosphonate **15c** by silylation with bromotrimethylsilane followed by hydrolysis with methanol.[40]

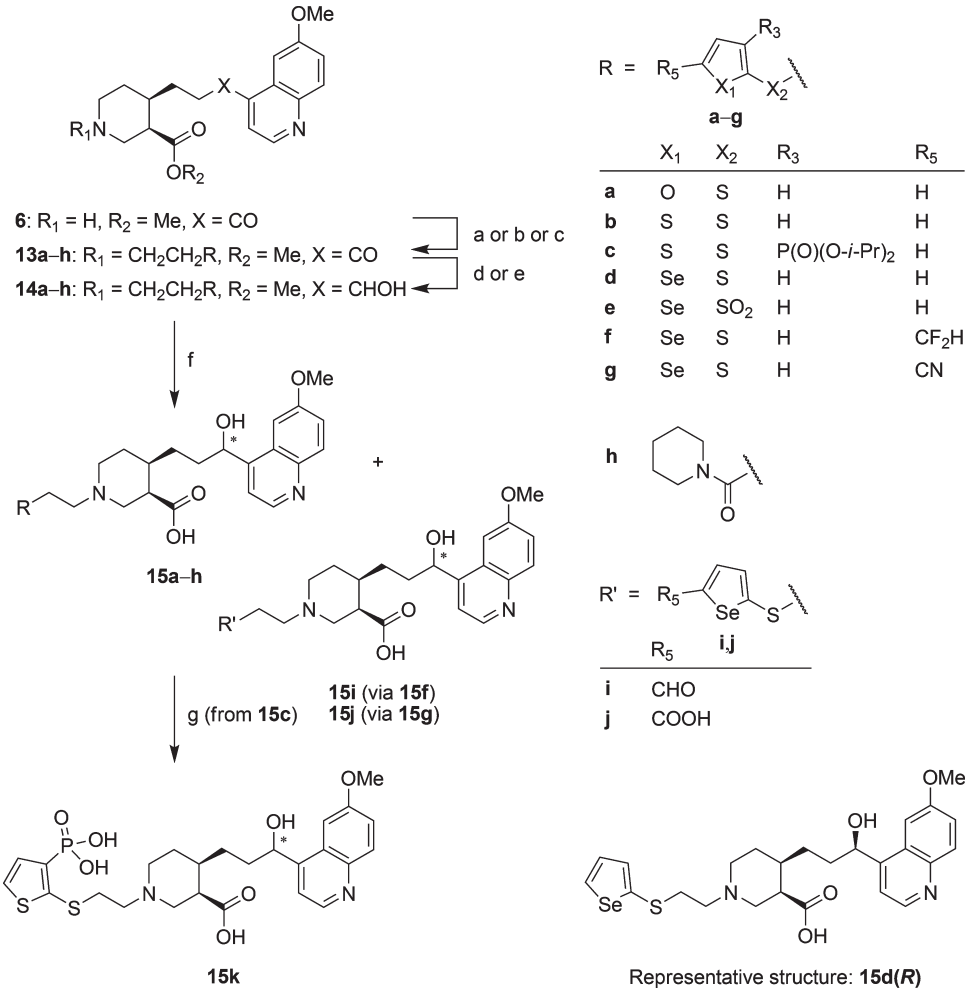
RESULTS AND DISCUSSION

The biological activities of compounds **15a**−**k** are shown in Tables 1 and 2. The chemical structures are also outlined in Scheme 3, where the letter designation for the *N*-alkyl substituent is listed in the included table and the stereochemical descriptor in parentheses designates the absolute configuration at C-3 of the propyl chain (see, for example, representative structure **15d**(*R*)). Several analogues of **15** demonstrated moderate to excellent activity against methicillin-sensitive *Staphylococcus aureus* (MSSA) and methicillin-resistant *Staphylococcus aureus* (MRSA) strains (Table 1). The antistaphyloccocal activities of analogues **15** tracked with the corresponding activities against the primary enzyme target DNA gyrase. All of these piperidinyl quinolines, however, were inactive (MIC > 64 μg/mL) against the Gram-negative pathogen *E. coli* (ATCC 25922, data not shown). Analogues **15** showed generally weak to moderate cytotoxicity against human laryngeal epidermoid carcinoma Hep2 cells. Analogues **15b** and **15d**, in particular, demonstrated minimal cytotoxicity (CC_{50} > 100 μM) as well as strong activities against MRSA (MIC of 0.13−0.5 μg/mL), indicating high bacterial specificities. Although several of the target compounds **15** were active against *S. aureus*, their corresponding synthetic precursors **13** and **14** were much less active (data not shown): the keto methyl esters **13** were all inactive (MRSA MIC ≥ 32 μg/mL), whereas the hydroxyl methyl esters **14** (50:50 diastereomeric mixtures) were typically less active (4- to 8-fold drop in MRSA activity) and also more cytotoxic (≥16-fold increase in activity) than their respective target analogues **15**.

We designed the target quinoline analogues of **1** (**15a**−**h**) with the ultimate goals of improving (or at least maintaining) antistaphyloccocal activity and reducing hERG channel inhibition. Following the general design principles reviewed previously for reduction in hERG channel inhibition,[41] we initially prepared an analogue that did not contain the peripheral aryl moiety (piperidinyl amide **15h**) and analogues that were of reduced and similar aromaticity[42] (furan **15a** and selenophene **15d**, respectively). The antistaphylococcal activity of furan **15a** and aliphatic amide **15h** (Table 1) was significantly lower than that of thiophene **1** (**15b**(*S*)), indicating that an aromatic substituent contributes to antibacterial activity. Selenophene and thiophene, however, proved to be bioisosteric, as **15d** and **15b** demonstrated comparable antibacterial activities against a panel of FQR MRSA clinical isolates (Table 2), with the *S* diastereomers consistently demonstrating greater activities than the *R* diastereomers. These analogues demonstrated excellent activities against all tested FQR strains, including those having up to four mutations in the quinolone resistance-determining regions (QRDRs) of the enzymes encoded by the *gyrA* and *grlA* genes.

We investigated hERG channel inhibition (Table 2) for each diastereomer of the series of congeners comprising furan (**15a**), thiophene (**15b**), and selenophene (**15d**). Unfortunately, the most potent antistaphyloccocal diastereomers (having *S* stereochemistry) consistently displayed stronger hERG channel inhibition (27−38% at 10 μM compound) than the corresponding less potent *R* diastereomers (12−22% inhibition). Selenophene analogues **15d**(*R*) and **15d**(*S*), however, showed the largest divergence in hERG channel inhibition and the greatest convergence of MRSA activity of the diastereomeric pairs investigated. Even though the antistaphyloccocal activity of selenophene **15d**(*R*) is 4-fold lower than that of the original thiophene **1** (but still comparable to that of the marketed drugs linezolid or vancomycin), this apparent liability is offset by its reduced hERG channel inhibition (12% at 10 μM for **15d**(*R*) compared with 29% for **1**).

Scheme 3[a]



[a] Reagents and conditions. (a) For **13a**, **13b**, **13f**, and **13g**: RCH_2CH_2Br (**9**, 2−3 equiv), KI (2−3 equiv), K_2CO_3 (2−3 equiv), DMF, 50 °C, 18−72 h, 32−41%. (b) For **13c**, **13d**, and **13h**: RCH_2CH_2Br (**9**, 2−3 equiv), K_2CO_3 (2−3 equiv), DMF, 50 °C, 2−4 h, 50−56%. (c) For **13e**: **9e** (1 equiv), K_2CO_3 (2 equiv), DMF, room temp, ∼1 h, 24%. (d) For **14a**−**c** and **14h**: $NaBH_4$ (3−3.5 equiv), MeOH, room temp, 1−2 h. (e) For **14d**−**g**: $NaBH_4$ (∼3 equiv), MeOH/THF (1:1 v/v), room temp, 1−2 h. (f) $LiOH·H_2O$ (5−6 equiv), MeOH/THF/H_2O (∼1:1:1 v/v/v), 60 °C, 1.5−7 h, PTLC purification, 27−42% (over two steps, sum of both diastereomers). (g) TMSBr (4 equiv), CH_2Cl_2, room temp, 18 h, then MeOH (excess), room temp, <1 h, quant.

After the successful bioisosteric exchange of thiophene for selenophene, we focused our efforts on additional modification of the heteroaryl ring to further reduce hERG channel inhibition and improve antistaphyloccocal activity. Unfortunately, introduction of EWGs (5-CF_2H, **15f**; 5-CN, **15g**) and negatively ionizable groups (3-PO_3H_3, **15k**; 5-COOH, **15j**) on the heteroaryl ring as well as possibly reducing the pK_a value of the piperidinyl amine via oxidation of the thioether linkage (SO_2, **15e**) (all known strategies to reduce hERG channel inhibition[43]) impacted the antistaphyloccocal activities of all the corresponding analogues negatively (MIC ≥ 8 μg/mL).

CONCLUSION

We have synthesized and evaluated a series of piperidinyl quinolines in an effort to attenuate the hERG channel inhibition that has been noted for this antibacterial drug class. Most modifications of the original thiophene portion of **1** significantly compromised antibacterial activities; however, selenophene analogues **15d** maintained similar (≤2-fold less) antistaphyloccocal activities to those of thiophenes **15b** against a panel of MRSA clinical isolates. Selenophene **15d**(***R***) also demonstrated the lowest potential hERG liability of the diastereomeric pairs of active compounds and did not display significant cytotoxicity against all four tested cell lines (CC_{50} > 100 μM). Although there is a historical association of supranutritional doses of selenium-containing compounds with toxicity,[44] this dogma has been challenged by the investigational drug ebselen (2-phenyl-1,2-benzisoselenazol-3(2*H*)-one), which is well tolerated and relatively nontoxic in vivo (rat oral LD_{50} ≥ 6810 mg/kg[45]). The low in vivo toxicity of ebselen has been attributed to the lack of extruded bioavailable selenium.[46−48] Similarly, preliminary in vitro human liver S9 microsomal stability assays of selenophene analogues **15d** did not indicate any apparent metabolic liabilities ($t_{1/2}$ > 60 min). The overall in vitro profile of **15d**(***R***) (good MRSA activity, limited hERG inhibition, low cytotoxicity, and high metabolic stability) supports further investigation of this compound for the treatment of infections caused by *S. aureus*.

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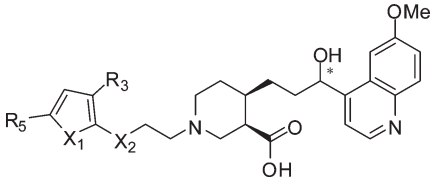
Table 1. Antibacterial, Antibacterial Target, Cytotoxic, and hERG Activities of Piperidinyl Quinolines 15a−k[a]



						MIC[b]		*S. aureus* enzyme inhib[c]		
compd	X_1	X_2	R_3	R_5	dr	MSSA	MRSA	Gyr	topo IV	cytotox[d]
15a(*R*)	O	S	H	H	96:4	4	4	10.2	>100	>100
15a(*S*)	O	S	H	H	90:10	2	2	4.7	>100	>100
15b(*R*)	S	S	H	H	96:4	1	0.5	3.3	23	>100
15b(*S*) (1)	S	S	H	H	98:2	0.25	0.13	1.4	45	>100
15c(*R*)	S	S	$P(O)(O\text{-}i\text{-}Pr)_2$	H	88:12	>64	>64	ND	ND	34
15c(*S*)	S	S	$P(O)(O\text{-}i\text{-}Pr)_2$	H	94:6	>64	>64	>100	ND	>98
15k(*R*)	S	S	PO_3H_2	H	88:12	>64	>64	>100	ND	>100
15k(*S*)	S	S	PO_3H_2	H	94:6	>64	>64	ND	ND	>94
15d(*R*)	Se	S	H	H	93:7	0.5	0.5	0.7	69	>100
15d(*S*)	Se	S	H	H	93:7	0.25	0.25	0.4	64	>100
15e(*R*)	Se	SO_2	H	H	91:9	>64	>64	ND	ND	>100
15e(*S*)	Se	SO_2	H	H	75:25	>64	>64	>100	ND	>100
15f(*S*)	Se	S	H	CF_2H	85:15	32	16	21.2	ND	39
15i(*R*)	Se	S	H	CHO	85:15	16	16	8.9	ND	>100
15g(*R*)	Se	S	H	CN	92:8	>64	>64	ND	ND	65
15g(*S*)	Se	S	H	CN	84:16	32	32	36.6	ND	48
15j(*RS*)	Se	S	H	COOH	50:50	>64	>64	>100	ND	>100
15h(*RS*)	NA	NA	NA	NA	50:50	32	32	10.6	ND	>100
CIP	NA	NA	NA	NA	NA	0.25	64	62	3.0	>100
GEM	NA	NA	NA	NA	NA	0.03	4	5.6	0.4	46
MXF	NA	NA	NA	NA	NA	0.06	4	18	1.0	>100

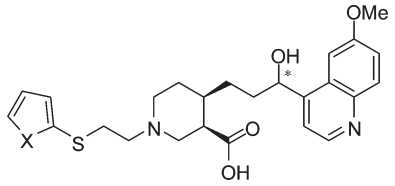
[a] Abbreviations: CIP, ciprofloxacin; dr, diastereomeric ratio; GEM, gemifloxacin; Gyr, wild-type DNA gyrase; MIC, minimum inhibitory concentration; MSSA, methicillin-sensitive *Staphylococcus aureus* ATCC 29213; MRSA, methicillin-resistant *Staphylococcus aureus* ATCC 700699; MXF, moxifloxacin; NA, not applicable; ND, not determined; topo IV, wild-type topoisomerase IV. [b] Minimum inhibitory concentration is expressed in μg/mL. [c] Inhibition (IC_{50}) of wild-type *S. aureus* DNA gyrase supercoiling and topoisomerase IV decatenation is expressed in μM. [d] 72 h cytotoxic activity (CC_{50}) against Hep2 cells is expressed in μM.

EXPERIMENTAL SECTION

General Chemical Methods. All nonaqueous reactions were performed under an atmosphere of dry argon gas using oven-dried glassware, commercially available anhydrous solvents, and standard Schlenk techniques. The progress of reactions was monitored using LC−MS or TLC on glass plates coated with silica gel 60 (F_{254}, EMD). Flash column chromatography (FCC) was performed on silica gel 60 (230−400 mesh, EMD). Preparative thin-layer chromatography (PTLC) was performed on glass plates coated with silica gel (20 cm × 20 cm × 2000 μm, Analtech). NMR spectra were recorded at room temperature using a Bruker Avance 300 spectrometer (^{1}H at 300.1 MHz, ^{13}C at 75.5 MHz, ^{19}F at 282.4 MHz, and ^{31}P at 121.5 MHz). All ^{13}C, ^{19}F, and ^{31}P NMR spectra were broadband ^{1}H decoupled. The chemical shifts for ^{1}H and ^{13}C are reported in parts per million (δ) relative to external tetramethylsilane and were referenced to signals of residual protons in the deuterated solvent. The chemical shifts for ^{19}F and ^{31}P are reported in parts per million (δ) relative to external $CFCl_3$ and 85% H_3PO_4, respectively. ^{1}H−^{1}H COSY, ^{1}H−^{13}C HMQC, ^{1}H−^{13}C HMBC, and ^{13}C APT spectra were used routinely for assignment of signals. The purity of target compounds **15a**−**k** (≥95%) was determined via analytical reverse-phase HPLC using a 3.5 min gradient elution of increasing concentrations of CH_3CN in H_2O (10−90%) containing 0.05% formic acid with a flow rate of 1.0 mL/min on a Waters AQUITY UPLC BEH C18 1.7 μm, 2.1 mm × 50 mm column with UV (PDA), ELS, and MS (SQ in APCI mode) detection.

General Procedure for the Preparation of 2-(2-Bromoethylthio)-Substituted Heterocycles. The procedure described below for (2-bromoethyl)(selenophen-2-yl)sulfane (**9d**) is representative. Subsequent chemical transformations of **9d** leading to sulfoxide[35] **9e**, difluoromethyl[33] derivative **9f**, nitrile[34] **9g**, and aldehyde[32] **9i** were performed using general synthetic methodologies outlined previously and are further detailed in the section Chemistry (Scheme 2). Modified conditions used for the syntheses of furan **9a** and thiophene **9b** are described as well in the section Chemistry (Scheme 2). *n*-BuLi (1.6 M in hexanes, 49.0 mL, 78.4 mmol) was added to a stirred solution of selenophene (**7d**, 10.3 g, 78.4 mmol) in Et_2O (200 mL) at room temperature. The resulting mixture was stirred at room temperature for 1 h and then cooled to −78 °C. To this cooled mixture was added powdered S (2.52 g, 78.6 mmol) in one portion; stirring continued at −78 °C for 3 h. The resulting thick yellow mixture was warmed to 0 °C to give a yellow solution of **8d**. Stirring continued at 0 °C for 30 min, and then $BrCH_2CH_2Br$ (59.0 g, 314 mmol) was added in one portion. The resulting opaque mixture was warmed to room temperature and stirred for 18 h. The reaction mixture was charged with H_2O (100 mL), and the aqueous layer was separated and extracted with Et_2O (2 × 150 mL). The combined organic phase was washed with H_2O (150 mL),

Table 2. Activities of Selected Piperidinyl Quinolines against Clinical Isolates of FQR MRSA, an Expanded Panel of Cell Lines, and hERG K^+ Channel[a]



		MRSA MIC[b]						
compd	X	1-FQR^{2M}	2-FQR^{2M}	3-FQR^{3M}	4-FQR^{3M}	5-FQR^{4M}	cytotox[c]	hERG[d]
15a(*R*)	O	8	8	4	16	32	>100	14
15a(*S*)	O	4	2	2	4	8	>100	27
15b(*R*)	S	1	1	0.5	1	4	>100	22
15b(*S*) (1)	S	0.25	0.25	0.13	0.25	0.5	>100	29
15d(*R*)	Se	1	1	0.5	1	2	>100	12
15d(*S*)	Se	0.25	0.5	0.25	0.5	1	>100	38
CIP	NA	64	256	64	256	128	ND	1
GEM	NA	1	32	4	32	64	ND	ND
MXF	NA	1	8	4	16	>64	ND	10
LZD	NA	ND	4	2	2	2	ND	ND
VAN	NA	0.5	ND	2	2	2	ND	ND

[a] Abbreviations: CIP, ciprofloxacin; FQR, fluoroquinolone-resistant; GEM, gemifloxacin; hERG, human ether-a-go-go-related gene; LZD, linezolid; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MXF, moxifloxacin; NA, not applicable; ND, not determined; VAN, vancomycin. [b] Minimum inhibitory concentration is expressed in μg/mL. 1-FQR^{2M}, BK2384 strain (double mutant, one in GyrA (Ser84Leu) and one in GrlA (Ser80Phe)). 2-FQR^{2M}, NY2746 strain (double mutant, one in GyrA (Ser84Leu) and one in GrlA (Ser80Phe)). 3-FQR^{3M}, ATCC 700699 strain (triple mutant, two in GyrA (Ser84Leu and Glu409Lys) and one in GrlA (Ser80Phe)). 4-FQR^{3M}, BSA643 strain (triple mutant, one in GyrA (Ser84Leu) and two in GrlA (Ser80Tyr and Glu84Gly)). 5-FQR^{4M}, BSA678 strain (quadruple mutant, two in GyrA (Ser84Leu and Ser85Pro) and two in GrlA (Ser80Phe and Glu84Lys)). [c] 72 h cytotoxic activities (CC_{50}) against CHO, HeLa, Hep2, and HepG2 cells are expressed in μM. [d] Inhibition (%) of human ether-a-go-go-related gene cardiac potassium channel current with 10 μM drug; 20% or greater inhibition correlated with lower IC_{50} (<30 μM), while 10% or less inhibition correlated with higher IC_{50} (30 to >100 μM) (unpublished data).

dried ($MgSO_4$), and evaporated under reduced pressure to give the crude product, which was purified by FCC (10% v/v EtOAc in CH_2Cl_2; R_f = 0.56) to give **9d** (15.5 g, 73% yield). ^{1}H NMR ($CDCl_3$): δ 3.17 (m, 2H, SCH_2), 3.52 (m, 2H, CH_2Br), 7.20 (dd, J = 6.0 Hz, 3.5 Hz, 1H, H-4), 7.34 (dd, J = 3.5 Hz, 1.0 Hz, 1H, H-3), 8.09 (dd, J = 6.0 Hz, 1.0 Hz, ^{1}H—^{77}Se satellites J = 44.0 Hz, 1H, H-5). ^{13}C NMR ($CDCl_3$): δ 29.8 (CH_2Br), 40.9 (SCH_2), 130.0 (C-4), 136.1 (^{13}C—^{77}Se satellites J = 118.5 Hz, C-5), 137.2 (C-3), 138.2 (C-2). MS m/z calcd for $C_6H_7{}^{79}BrSSe$ ($[M]^+$), 270; found, 271 ($[M + 1]^+$).

General Procedure for the Preparation of Alkylpiperidines 13. The procedure described below for (3*R*,4*R*)-methyl 4-(3-(6-methoxyquinolin-4-yl)-3-oxopropyl)-1-(2-(selenophen-2-ylthio)ethyl)piperidine-3-carboxylate (**13d**) is representative. Modified conditions used for the syntheses of **13a**—**c** and **13e**—**h** are described in the section Chemistry (Scheme 3). Bromide **9d** (2.0 g, 7.4 mmol) was added to a stirred mixture of piperidine **6** (1.2 g, 3.4 mmol) and finely ground K_2CO_3 (1.2 g, 8.7 mmol) in DMF (10 mL) at room temperature. The resulting mixture was heated at 50 °C for 4 h, allowed to cool to room temperature, and evaporated to dryness under reduced pressure. The remaining residue was treated with H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The extracts were combined, dried ($MgSO_4$), and evaporated to dryness under reduced pressure. This crude product was purified by FCC (200:10:1 v/v/v $CHCl_3$/MeOH/28% aqueous NH_4OH; R_f = 0.38) to give **13d** (0.9 g, 50% yield). Significant resonances for **13d**: ^{1}H NMR ($CDCl_3$): δ 3.66 (s, 3H, CO_2Me), 3.94 (s, 3H, quinoline OMe), 7.16 (dd, J = 6.0 Hz, 4.0 Hz, 1H, selenophene H-4), 7.26 (dd, J = 4.0 Hz, 1.0 Hz, 1H, selenophene H-3), 7.42 (dd, J = 9.0 Hz, 3.0 Hz, 1H, quinoline H-7), 7.58 (d, J = 4.5 Hz, 1H, quinoline H-3), 7.82 (d, J = 3.0 Hz, 1H, quinoline H-5), 8.01 (dd, J = 6.0 Hz, 1.0 Hz, ^{1}H—^{77}Se satellites J = 43.5 Hz, 1H, selenophene H-5), 8.04 (d, J = 9.0 Hz, 1H, quinoline H-8), 8.86 (d, J = 4.5 Hz, 1H, quinoline H-2). MS m/z calcd for $C_{26}H_{30}N_2O_4SSe$ ($[M]^+$), 546; found, 547 ($[M + 1]^+$).

General Procedure for the Preparation of Alcohols 14. The procedure described below for (3*R*,4*R*)-methyl 4-(3-hydroxy-3-(6-methoxyquinolin-4-yl)propyl)-1-(2-(selenophen-2-ylthio)ethyl)-piperidine-3-carboxylate (**14d**) is representative. $NaBH_4$ (0.11 g, 2.9 mmol) was added slowly to a stirred solution of alkylpiperidine **13d** (0.57 g, 1.0 mmol) in MeOH/THF (1:1 v/v, 8 mL) at room temperature. After the mixture was stirred 2 h, the reaction was quenched with H_2O (4 mL) and concentrated under reduced pressure to remove the organic solvent. The remaining oily mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with a saturated aqueous solution of NaCl (5 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The resulting crude foam (0.51 g of a 50:50 mixture of diastereomers) was used without further purification in the next synthetic step. Significant resonances for both diastereomers of **14d** are listed below. ^{1}H NMR ($CDCl_3$): δ 3.60 and 3.61 (2 × s, 3H), 3.92 and 3.93 (2 × s, 3H), 5.31 (m, 1H), 7.13—7.27 (m, 3H), 7.35 (m, 1H), 7.48 (apparent t, J = 4.5 Hz, 1H), 8.01 (m, 2H), 8.70 (d, J = 4.5 Hz, 1H). MS m/z calcd for $C_{26}H_{32}N_2O_4SSe$ ($[M]^+$), 548; found, 549 ($[M + 1]^+$).

General Procedure for the Preparation of Carboxylic Acids 15. The procedure described below for (3*R*,4*R*)-4-(3-hydroxy-3-(6-methoxyquinolin-4-yl)propyl)-1-(2-(selenophen-2-ylthio)ethyl)piperidine-3-carboxylic acid (**15d**) is representative. A solution of $LiOH \cdot H_2O$ (103.2 mg, 2.46 mmol) in H_2O (4 mL) was added to a solution of ester **14d** (239.1 mg, 0.44 mmol) in MeOH/THF (1:1 v/v, 8 mL). The resulting

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solution was heated at 60 °C for 1.5 h, allowed to cool to room temperature, and evaporated to dryness under reduced pressure. The remaining solid was dissolved in H_2O (10 mL), and to this solution was added slowly an aqueous solution of HCl (6 N) until a precipitate formed. The solid precipitate was collected by filtration, washed with H_2O (2 × 15 mL), dried in vacuo, and purified by PTLC (eluted with 50:10:1 v/v/v $CHCl_3$/MeOH/28% aqueous NH_4OH; R_f of 0.25 and 0.20) to yield 38.0 mg and 26.9 mg of diastereomerically enriched **15d(*R*)** and **15d(*S*)**, respectively, in 25% combined yield over two steps. The diastereomeric ratio (dr) for each isolated mixture of **15** (determined by ^{1}H NMR spectroscopy) is listed in Table 1. The least polar diastereomer of each pair was assigned as the (*S*)-hydroxy stereoisomer. These assignments are based on the stereochemical assignment of **1** (**15b(*S*)**) for which there are supporting chromatographic and X-ray crystallographic data.[49,50] Moreover, the resonances in the ^{1}H NMR spectra of the first-eluting diastereomers (assigned *S* configurations) attributed to OMe, C*H*OH, and H_3-quinoline were consistently downfield relative to those of the last-eluting diastereomers (assigned *R* configurations). See, for example, the ^{1}H NMR spectroscopic data for **15d** listed below.

15d(*R*): ^{1}H NMR ($CDCl_3$): δ 1.44−1.88 (m, 6H), 1.98 (m, 2H), 2.21 (m, 1H), 2.36 (m, 1H), 2.75 (m, 2H), 2.81 (m, 1H), 2.97 (m, 2H), 3.05 (m, 1H), 3.16 (m, 1H), 3.94 (s, 3H, CO_2Me), 5.31 (apparent t, J = 6.0 Hz, 1H, C*H*OH), 7.18 (dd, J = 6.0 Hz, 4.0 Hz, 1H, selenophene H-4), 7.24 (d, J = 3.0 Hz, 1H, quinoline H-5), 7.34 (dd, J = 4.0 Hz, 1.0 Hz, 1H, selenophene H-3), 7.36 (dd, J = 9.0 Hz, 3.0 Hz, 1H, quinoline H-7), 7.54 (d, J = 4.5 Hz, 1H, quinoline H-3), 8.03 (d, J = 9.0 Hz, 1H, quinoline H-8), 8.08 (dd, J = 6.0 Hz, 1.0 Hz, ^{1}H−^{77}Se satellites J = 44.0 Hz, 1H, selenophene H-5), 8.74 (d, J = 4.5 Hz, 1H, quinoline H-2). MS m/z calcd for $C_{25}H_{30}N_2O_4SSe$ ($[M]^+$), 534; found, 535 ($[M + 1]^+$). HPLC: t_R = 1.00 min.

15d(*S*): ^{1}H NMR ($CDCl_3$): δ 1.49−1.81 (m, 6H), 2.14−2.40 (m, 3H), 2.76 (m, 3H), 2.91−3.18 (m, 5H), 4.00 (s, 3H, OMe), 5.41 (m, 1H, C*H*OH), 7.18 (dd, J = 6.0 Hz, 4.0 Hz, 1H, selenophene H-4), 7.25 (d, J = 2.5 Hz, 1H, quinoline H-5), 7.33 (dd, J = 4.0 Hz, 1.0 Hz, 1H, selenophene H-3), 7.35 (dd, J = 9.0 Hz, 2.5 Hz, 1H, quinoline H-7), 7.62 (d, J = 4.5 Hz, 1H, quinoline H-3), 8.04 (d, J = 9.0 Hz, 1H, quinoline H-8), 8.07 (dd, J = 6.0 Hz, 1.0 Hz, ^{1}H−^{77}Se satellites J = 44.0 Hz, 1H, selenophene H-5), 8.70 (d, J = 4.5 Hz, 1H, quinoline H-2). MS m/z calcd for $C_{25}H_{30}N_2O_4SSe$ ($[M]^+$), 534; found, 535 ($[M + 1]^+$). HPLC: t_R = 1.00 min.

Biological Evaluation. Antimicrobial susceptibility, target enzyme (DNA gyrase and topoisomerase IV) activity, and cytotoxicity were measured as described previously using standard techniques.[51] Measurements of hERG potassium channel inhibition were performed at ChanTest (Cleveland, OH). The in vitro effects of test compounds on hERG potassium channel current (a surrogate for I_{Kr}, the rapidly activating, delayed rectifier cardiac potassium current) expressed in mammalian cells were evaluated at room temperature using the PatchXpress 700A (Molecular Devices) automatic parallel patch clamp system. Compounds **15a(*R*)**, **15a(*S*)**, **15b(*R*)**, **15b(*S*)**, **15d(*R*)**, and **15d(*S*)** were evaluated at 10 μM in two cells. The duration of exposure to each compound was 5 min. The positive control (E-4031, Figure 2) confirmed the sensitivity of the test system to hERG inhibition.

■ ASSOCIATED CONTENT

Supporting Information. Characterization data for intermediate and target compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ABBREVIATIONS USED

Boc, *tert*-butoxycarbonyl; *m*-CPBA, *m*-chloroperoxybenzoic acid; DIPEA, diisopropylethylamine; DMF, dimethylformamide; DNA, deoxyribonucleic acid; EWG, electron-withdrawing group; FCC, flash column chromatography; FQ, fluoroquinolone; FQR, fluoroquinolone resistant; hERG, human ether-a-go-go-related gene; LDA, lithium diisopropylamide; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; NBTI, novel bacterial topoisomerase inhibitor; PTLC, preparative thin-layer chromatography; QRDR, quinolone resistance-determining region; TMS, trimethylsilyl

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