Discovery of (3*S*)-Amino-(4*R*)-ethylpiperidinyl Quinolones as Potent Antibacterial Agents with a Broad Spectrum of Activity and Activity against Resistant Pathogens

X. Eric Hu,* Nick K. Kim, Jeffrey L. Gray, Ji-In K. Almstead, William L. Seibel, and Benoit Ledoussal

Procter & Gamble Pharmaceuticals, 8700 Mason-Montgomery Road, Mason, Ohio 45040

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Novel quinolone antibacterial agents bearing (3*S*)-amino-(4*R*)-ethylpiperidines were designed by using low energy conformation analysis and synthesized by applying a conventional coupling reaction of the quinolone nuclei with new piperidine side chains. These compounds were tested in MIC assays and found to be highly potent against Gram-positive and Gram-negative organisms. In particular, the new compounds exhibited high activity against the resistant pathogens *Staphylococcus aureus* (MRCR) and *Streptococcus pneumoniae* (PR). Importantly, when the (3*S*)-amino-(4*R*)-ethylpiperidinyl quinolones were compared with marketed quinolones sharing the same quinolone nuclei but different side chains at the C-7 position, the new quinolones showed superior activity against Gram-positive organisms, including resistant pathogens.

Introduction

Because of increasing threats of bacterial infections, particularly those such as the clinically important pathogenic bacteria, methicillin resistant *Staphylococcus aureus* (MRSA) and methicillin resistant ciprofloxacin resistant *S. aureus* (MRCRSA),[1] drug discovery efforts have been significantly intensified in the past years to search for more effective quinolone antibacterial agents with a broader spectrum of activity and especially activity against resistant pathogens to fight infectious diseases.[2,3] In our ongoing antiinfective research program, we have recently developed new quinolone antibacterial agents derived from a quinolone nucleus lacking the typical 6-fluoro substituent[4] (nonfluorinated quinolones or NFQs), a similar approach also reported by others.[5] These agents exhibited not only improved potency, a broad spectrum of activity, and activity against resistant pathogens but also excellent in vivo efficacy.[6] More importantly, they have demonstrated ameliorated toxicity profiles, which may warrant further investigation.[7] During the course of this work, efforts were made to improve these NFQs by generating new types of side chains.[8] Here, we report a finding, the application of which goes beyond the scope of the NFQs.

The majority of quinolone C7 substituents can be arranged into three main categories: the piperazinyl, pyrrolidinyl, and piperidinyl type side chains. Additionally, three subfamilies of side chains were generated using the pyrrolidine backbone. Table 1 shows these various families of quinolones, a qualitative descriptor of their antibacterial spectrum, and some representatives of each family.

Piperazinyl type quinolones such as ciprofloxacin and levofloxacin display good Gram-negative coverage but a quite average Gram-positive spectrum. On the other hand, 3-amino-pyrrolidinyl-based quinolones such as clinafloxacin and moxifloxacin display a more balanced spectrum while 3-aminomethyl-pyrrolidinyl-based quinolones display good Gram-positive coverage but a relatively weaker Gram-negative spectrum. A very significant improvement in both spectrum and potency was reported upon introduction of a methyl group on the aminomethyl-pyrrolidine, resulting in aminoethyl-pyrrolidinyl side chains.[9] The corresponding quinolones were among the most potent quinolones described to date. Finally, 3-amino-piperidinyl type side chains led to quinolones with a spectrum of action quite compa-

Table 1. Comparison of Relative Antibacterial Activity of Quinolones Using Qualitative Descriptors

Type of side chain		Gram-positive	Gram-negative	Examples
Piperazinyl		+/-	++	Ciprofloxacin, Levofloxacin
Pyrrolidinyl	3-amino-	+	+	Clinafloxacin, Moxifloxacin
	3-aminomethyl-	+	+/-	NA
	3-aminoethyl-	++	+	Premafloxacin
3-Aminopiperidinyl		+	+	Balofloxacin (Q-35)

* To whom correspondence should be addressed. Tel: (513)622-3859. Fax: (513)622-1195. E-mail: hu.xe@pg.com.

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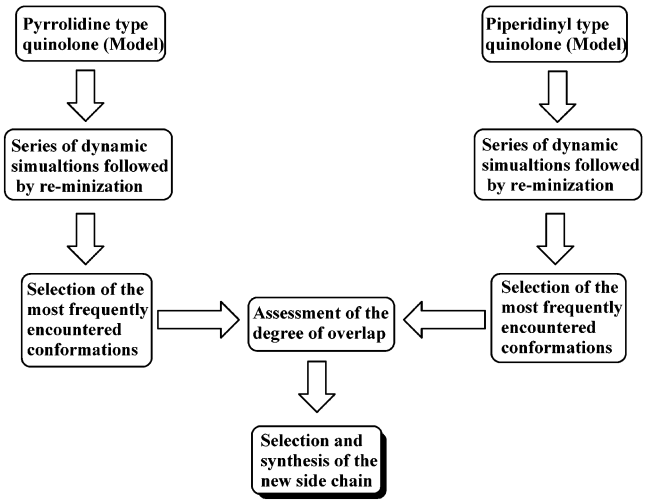


Figure 1. Energy minimization algorithm of pyrrolidine and piperidine quinolones.

rable to their 3-amino-pyrrolidinyl equivalent.[10] It is worth noting that the number of piperidinyl-based quinolones reported in the literature is very significantly lower than that of piperazinyl- and pyrrolidinyl-based analogues.

During the investigations on quinolones lacking fluorine mentioned above, we noticed that the only two types of C7 side chains leading to potent analogues were the 3-aminoalkyl pyrrolidinyl (aminomethyl and aminoethyl) as well as the 3-amino-piperidinyl type side chains.[11] Small molecule modeling investigations showed that these two types of side chains had low energy conformations positioning the distal nitrogen in the same area. As mentioned above, the addition of a methyl on the amino-methyl pyrrolidine side chains boosted significantly the activity of the resulting quinolone. Associating this earlier finding with the similar behavior of aminomethyl and piperidinyl type side chains in our NFQs, we hypothesized that we could obtain the same positive effects by properly substituting the piperidine ring with hydrophobic groups that would mimic the additional methyl of the aminoethyl-pyrrolidine type side chain.

To identify the most promising substitutions, we used the algorithm outlined in Figure 1. In the first step, using the aminoethyl-pyrrolidine side chain as the model to mimic, we identified the most frequently encountered low energy conformation of this side chain by using a series of dynamic simulations followed by reminimizations. Then, we proceeded similarly with a series of hypothetical substituted (3*S*)-amino-piperidine side chains. The (3*S*)-amino-(4*R*)-ethylpiperidinyl side chain was identified as the hypothetical side chain,[12] most likely to be able to position a methyl group at the same position as the beneficial methyl of the aminoethyl-pyrrolidine as seen in Figure 2. Three-dimensional superimposition of the 3-aminoethyl-pyrrolidine and 3-amino-4-ethyl-piperidine side chains illustrates our working hypothesis. The nitrogen atoms are in blue, the distal methyl of the 3-amino-4-ethyl-piperidine side chain is in red, and the corresponding methyl of the 3-aminoethyl-pyrrolidine is in orange. We then embarked upon synthesis and testing of quinolones bearing this type of side chain. Below, we report our findings.

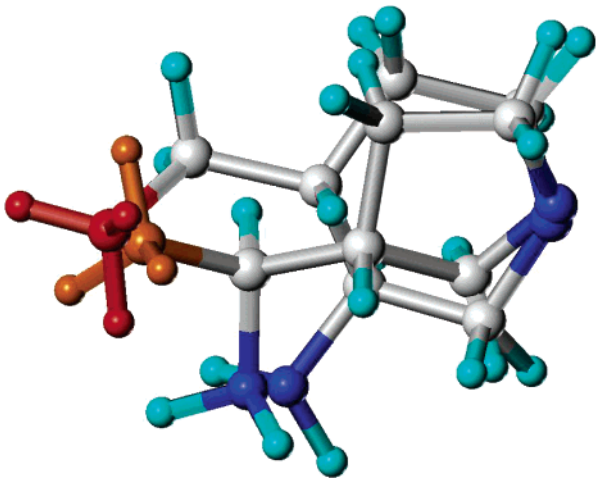


Figure 2. Three-dimensional superimposition of 3-aminoethyl-pyrrolidine and 3-amino-4-ethyl-piperidine side chains.

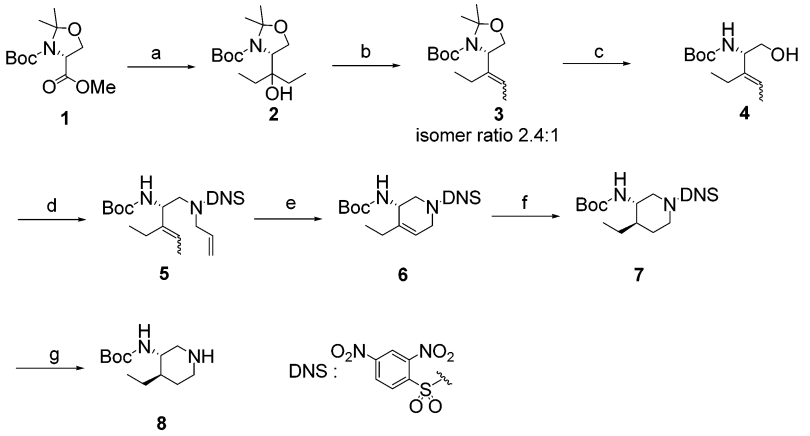
Chemistry

Substituted piperidines comprise one of the broadest subjects of synthetic chemistry due not only to their application as synthetic building blocks but also to their unique structural features as important bioactive components in pharmaceutical research.[13] However, to our surprise, the 4-alkyl-substituted 3-aminopiperidines were found to be a much less explored subclass among piperidine chemistry. Especially rare were asymmetric synthetic methods for the construction of such relatively simple piperidine structures. Very recently, the first asymmetric synthetic method of *trans*-(3*S*)-amino-4-alkyl- and aryl-piperidines was reported by our group.[14] Herein, we report a modified procedure based on the previous method,[15] which was utilized in the synthesis of (3*S*)-amino-(4*R*)-ethylpiperidine as outlined in Scheme 1. This synthesis represents a more efficient pathway with fewer steps, and more importantly, this new method significantly minimizes potential racemization of the α-carbon in the amino acid during functional group transformation.

The synthesis started from commercially available fully protected (D)-serine ester **1**. The methyl ester underwent double addition with ethyl Grignard reagent to give a tertiary alcohol (**2**), which was treated with methanesulfonyl chloride to afford an elimination intermediate (**3**) in a ratio of 2.4:1 stereoisomers. The mixed olefin was selectively deprotected, and the primary alcohol (**4**) was converted to the diene (**5**), a precursor for the ring closure metathesis reaction, via modified Mitsunobu conditions.[16,17] By using a standard cyclization procedure,[18] 3-Boc-NH-4-Et-1,2,3,6-tetrahydropyridine (**6**) was obtained in good yield.[19a] Stereoselective reduction of the double bond resulted in a trans:cis mixture in a 3:1 ratio, which was separated by flash chromatography. Desulfonylation of the piperidine (**7**) completed asymmetric synthesis of the side chain (**8**)[19b] in 30% overall yield.

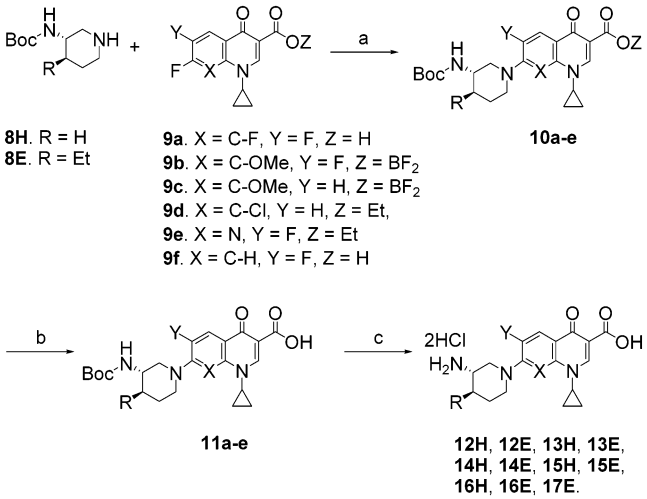
The piperidine side chains (**8H**,**E**) were connected to the substituted quinolone nuclei **9a**−**d**[20] and naphthyridine nucleus **9e**[21] using conventional coupling conditions shown in Scheme 2. In the case of the 8-MeO-substituted quinolones (**9b**,**c**), activation of the nuclei was necessary and accomplished by activating the carboxyl function with BF_3.[22] The coupled intermediates **10a**−**e**

Scheme 1[a]



[a] Reagents and conditions: (a) 3 equiv of EtMgBr, Et_2O, 0 °C, 15 min, 84%. (b) MsCl, Et_3N, CH_2Cl_2, −15 °C room temperature, 1 h, 86%. (c) *p*-TsOH (0.1 equiv), MeOH, 55 °C, 20 h, 91%. (d) *N*-Allyl-2,4-dinitro-benzenesulfonamide, Ph_3P, DEAD, benzene, <30 °C, 1 h, 66%. (e) $Cl_2Ru(=CHPh)[(P\text{-}(c\text{-}Hex)_3)]_2$, CH_2Cl_2, reflux, 12 h, 86%. (f) H_2, 5% Pd/C, MeOH, 86%. (g) *i*-$PrNH_2$, CH_2Cl_2, room temperature, 10 min, 93%.

Scheme 2[a]



[a] Reagents and conditions: (a) Et_3N, DMF, room temperature, 1−3 days. (b) When Z = BF_2, 20 equiv of Et_3N, EtOH, reflux, 1−2 h or when Z = Et, 5 equiv of NaOH, water, EtOH, room temperature, 2−3 h. (c) Concentrated HCl, room temperature, 20 min, overall yield > 65%.

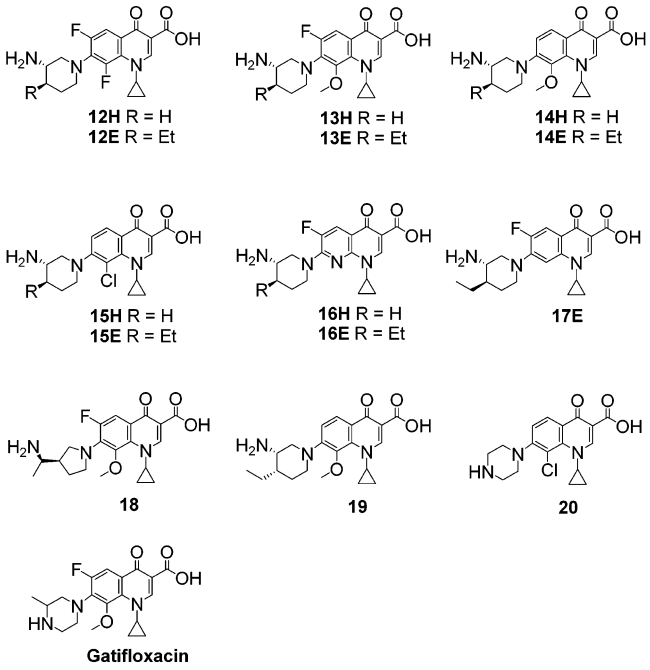


Figure 3. Newly synthesized (3*S*)-amino- and (3*S*)-amino-(4*R*)-piperidinyl quinolones.

underwent sequential deprotections: saponification followed by removal of the Boc group. The final quinolone products **12**−**17** were collected by crystallization.

Results and Discussion

Five (3*S*)-aminopiperidinyl quinolones (**12H**−**16H**) and five (3*S*)-amino-(4*R*)-ethylpiperidinyl quinolones (**12E**−**16E**) (Figure 3) were synthesized. Their antibacterial activity (MIC) is summarized in Table 2 in pairs in order to compare the in vitro activity of the nonsubstituted piperidinyl quinolones with the ethyl-substituted piperidinyl quinolones. Only representative in vitro antibacterial data are presented, including four key Gram-positive organisms of *S. aureus* (*S. a*) MRCS, *S. aureus* (*S. a*) MRCR, *Streptococcus pneumoniae* (*S. p*) PS, and *S. pneumoniae* (*S. p*) PR, and two key Gram-negative organisms, *Escherichia coli* and *Pseudomonas aeruginosa* (*P. a*). The effect of (4*R*)-ethyl substituted over the unsubstituted (3*S*)-aminopiperidinyl quinolones in enhancing antibacterial activity was clearly seen in most cases that we studied. The antibacterial activity of these new agents is more pronounced for the Gram-positive organisms as exemplified with **12E**−**15E** vs **12H**−**15H** and found to be 2−15-fold more active against *S. aureus* (MRCS); 3−21-fold more active against *S. aureus* (MRCR); 3−10-fold more active against *S. pneumoniae* (PS); and 2−11-fold more active against *S. pneumoniae* (PR). Enhanced activity against Gram-negative organism *E. coli* was observed to be 2−7-fold, but only comparable activity was observed against *P. aeruginosa*. Both substituted and unsubstituted piperidinyl quinolone consistently exhibited high potency and a broad spectrum of activity. Unlike quinolones, the naphthyridines (**16H**,**E**) showed not only modest antibacterial activity but also comparable activity between nonsubstituted and substituted piperidinyl naphthyridines across the spectrum. This suggests that the piperidine side chains may elevate antibacterial activity and a broad spectrum of activity only in certain nuclei.

Table 2. MICs of (3*S*)-Aminopiperidinyl Quinolones vs (3*S*)-Amino-(4*R*)-Ethylpiperidinyl Quinolones

	MIC (μg/mL)[a]					
	Gram-positive organism				Gram-negative organism	
compd	*S.a* (MRCS)	*S.a* (MRCR)	*S. p* (PS)	*S. p* (PR)	*E. coli*	*P. a*
12H	0.13	4	0.06	0.13	0.03	0.5
12E	0.006	0.188	0.023	0.012	0.006	0.75
13H	0.031	0.5	0.125	0.063	0.031	1
13E	0.008	0.125	0.031	0.008	0.016	1
14H	≤0.06	1	0.03	≤0.008	0.03	0.5
14E	≤0.004	0.25	≤0.003	0.008	0.006	1
15H	0.016	1	0.12	≤0.008	0.03	0.5
15E	≤0.004	0.31	≤0.004	≤0.004	≤0.004	0.125
16H	2	>4	4	4	0.125	1
16E	0.25	>4	4	2	0.03	4
18	0.008	0.016	0.008	0.008	0.008	0.25
19	0.25	4	1	0.5	0.125	4

[a] *S.a* (MRCS), strain MI300; *S.a* (MRCR), strain MI339; *S. p* (PS), strain STP64; *S. p* (PR), strain STP51; *E. coli*, strain ES142; *P. a*, strain PS96; MRCS, methicillin resistant ciprofloxacin sensitive; MRCR, methicillin resistant ciprofloxacin resistant; PS, penicillin sensitive; PR, penicillin resistant.

From the energy minimization algorithm, the inspiration of incorporating the ethyl group to the 3-aminopiperidinyl side chain led us to discover a very powerful side chain to enhance the quinolone in vitro potency significantly. In addition to the interesting structure−activity relationship (SAR) results for the side chain modification, we also noticed that the substitution at the C-6 position did not impose much influence to the antibacterial activity of the new quinolones. This observation was evidenced by comparing pairs of **13H**,**E** with **14H**,**E**, respectively, and they showed identical MIC activity against most of the pathogens. The substitution impact at the C-8 position to the MICs varies depending on the quinolone nuclei. For example, **13H** containing the amino-piperidine exhibited great enhancement in antibacterial activity against most of the Gram-positive pathogens when the 8-F in **12H** was replaced with 8-MeO. On the other hand, **12E** and **13E** containing the amino-ethyl-piperidine showed only identical in vitro activity across the spectrum. It was also true for **14H**,**E** in comparison with **15H**,**E**, respectively, when 8-Cl was replaced with 8-MeO. The tolerance patterns of substitution at the C-6 and C-8 positions suggest a potential avenue to explore for new quinolone antibacterial agents with no halogens embedded in the quinolone nucleus structure, beneficial for reducing unwanted side effects, such as phototoxicity and genotoxicity.

Amino-ethyl pyrrolidinyl quinolone **18** was a model compound used in our design concept of low energy conformation minimization algorithm described earlier to identify new quinolone side chains. As seen in entry 11, this quinolone indeed exhibited remarkable in vitro antibacterial activity across the board, one of the most potent quinolone antibacterial agents reported to date in the literature.[4a,9] A powerful feature in superimposing the substituent of the amino piperidine side chain with that of the amino-ethyl pyrrolidine was further evident in the case of (3*S*)-amino-(4*S*)-ethylpiperidinyl quinolone (**19**), a cis stereoisomer of NFQ **14E**.[12] A great disadvantage for antibacterial activity against the key pathogens was shown in the cis isomer as compared to the trans counterpart. These data strongly support that the design concept of the energy minimization algorithm is indeed a useful tool in search for new and effective quinolone side chains. It is believed that the positioning effect of the terminal methyl group in the amino-ethyl piperidine in alignment with that of the amino-ethyl pyrrolidine plays a key role for the observed enhancement of the antibacterial activity.

Table 3. Inhibitory Effect on *E. coli* Wild-Type DNA Gyrase/ Quinolone Resistant Gyrase Supercoiling Activity

	IC_{50} (μg/mL)[a]	
compd	WT gyrase	QR gyrase
12H	3.2	25.6
13H	1.6	6.4
14H	6.4	12.8
15H	3.2	12.8
16H	1.6	>102.4
ciprofloxacin	1.6	102.4
12E	0.2	12.8
13E	3.2	6.4
14E	3.2	12.8
15E	1.6	3.2
16E	25.6	>102.4
clinafloxacin	0.2	1.0

[a] WT gyrase, wild-type DNA gyrase; QR gyrase, quinolone resistant gyrase (mutation from serine 83 to tryptophane).

In addition to the finding of the increased in vitro antibacterial activity in (3*S*)-amino-(4*R*)-ethylpiperidinyl quinolones as compared to the (3*S*)-amino-piperidinyl quinolones, we also evaluated the new piperidinyl quinolone antibacterial agents against wild-type *E. coli* DNA gyrase and quinolone resistant gyrase (Table 3). Unsubstituted piperidinyl quinolones **12H**−**15H** and ethyl-substituted quinolones **12E**−**15E** exhibited identical inhibitory activity against both gyrases, although slight improvement was seen in the latter cases. In contrast, naphthyridine **16H** was notably less active against quinolone resistant gyrase and **16E** against both wild-type and quinolone resistant gyrases. This observation correlates with the impaired MIC data against key Gram-positive and Gram-negative pathogens discussed above. On the other hand, the gyrase data of the new quinolones are comparable to those of the benchmark ciprofloxacin and clinafloxacin, which may suggest that the new quinolones take the same pathways to intervene in the bacterial infection processes as the known quinolones.

One of the interesting SAR findings we generated was the comparison of the side chain effects in the same quinolone subclasses. Table 4 below summarizes the antibacterial activity data of (3*S*)-amino-(4*R*)-ethylpiperidinyl quinolones vs the marketed and clinical quinolones. Ciprofloxacin and quinolone **17E** share the same quinolone core structure, and the variation exists only at the C-7 side chain, piperazine for the former and the substituted piperidine for the later. The new quinolone exhibits fairly comparable antibacterial activity to that of ciprofloxacin across the spectrum, except for activity against *P. aeruginosa* pathogen, about 12-fold less active for **17E**. However, in the new piperidinyl quinolones having C-8 substituted with a methoxy as in **13E** and a chloro group as in **15E**, much improved antibacterial activity is observed against Gram-positive organisms relative to their counterparts, gatifloxacin and clinafloxacin, respectively. For example, both new quinolones

Table 4. MICs of (3*S*)-Amino-(4*R*)-ethylpiperidinyl Quinolones vs Marketed/Clinical Quinolones

	MIC (μg/mL)[a]					
	Gram-positive organism				Gram-negative organism	
compd	*S.a* (MRCS)	*S.a* (MRCR)	*S. p* (PS)	*S. p* (PR)	E. coli	P. *a*
ciprofloxacin	0.25	16	0.25	0.5	0.008	0.12
17E	0.094	>3	0.75	0.375	0.012	1.5
gatifloxacin	0.06	4	0.12	ND[b]	0.015	0.12
13E	0.008	0.125	0.031	0.008	0.016	1
clinafloxacin	0.03	0.5	0.03	0.15	0.015	0.06
15E	≤0.004	0.31	≤0.004	≤0.004	≤0.004	0.125
20	0.25	8	4	ND	0.06	0.5

[a] *S.a* (MRCS), strain MI300; *S.a* (MRCR), strain MI339; *S. p* (PS), strain STP64; *S. p* (PR), strain STP51; *E. coli*, strain ES142; *P. a*, strain PS96. [b] Not determined.

show 7.5-fold greater activity against *S. aureus* (MRCS) than gatifloxacin and clinafloxacin; **13E** is 32-fold more active against *S. aureus* (MRCR) than gatifloxacin, while **15E** shows similar activity against *S. a* (MRCR) to clinafloxacin; the piperidinyl quinolones are about 7.5-fold more active against penicillin sensitive *S. pneumoniae* and 37-fold more active against penicillin resistant *S. pneumoniae*. However, again, the new quinolones are less potent than the marketed drugs against *P. aeruginosa* pathogens. In addition, the substituted piperidinyl quinolone **15E** is far more active than the piperazinyl counterpart **20** across the spectrum studied. The enhanced activity against Gram-positive pathogens in the (3*S*)-amino-(4*R*)-ethylpiperidinyl quinolones (**13E** and **15E**) in comparison to the marketed drugs and those in clinical studies is believed to be associated with the presence of both the C-7 and the C-8 groups in the molecules to exert a synergic effect for the observed antibacterial activity, whereas these components are missing in **16H**,**E** and **17E**, which show much less effect on potency.

In conclusion, a low energy conformational analysis approach has been used to effectively assist our design of new substituted 3-amino piperidinyl side chains and has led to the discovery of a series of novel (3*S*)-amino-(4*R*)-ethylpiperidinyl quinolones. An efficient method for the synthesis of *trans*-(3*S*)-amino-(4*R*)-ethylpiperidine has been developed, and the substituted and unsubstituted (3*S*)-piperidines were incorporated into various quinolone nuclei. The antibacterial activity of (3*S*)-amino-(4*R*)-ethylpiperidinyl quinolones and naphthyridines was evaluated in comparison to pairs with (3*S*)-aminopiperidinyl quinolones and naphthyridines. The data clearly show that the (3*S*)-amino-(4*R*)-ethylpiperidinyl quinolones are far superior to (3*S*)-aminopiperidinyl quinolones in potency, spectrum of activity, and activity against resistant organisms. These new ethyl-substituted 3-aminopiperidinyl quinolones exhibit only comparable potency to unsubstituted 3-aminopiperidinyl quinolones against *P. aeruginosa*. The new side chains did not provide significant enhancement of activity in the naphthyridine series. In addition, activity superiority of the new (3*S*)-amino-(4*R*)-ethylpiperidinyl quinolones against Gram-positive organisms was also illustrated when compared with the marketed and clinical quinolones in the same nucleus classes, again with only comparable activity against Gram-negative organisms.

Experimental Section

Chemistry. All reagents were commercial grade and were used as received without further purification, unless otherwise specified. Commercially available anhydrous solvents were used for reactions conducted under inert atmosphere. Reagent grade solvents were used in all other cases, unless otherwise specified. Flash chromatography was performed on E. Merck silica gel 60 (230−400 mesh). Thin-layer chromatography was performed on E. Merck 60 F-254 precoated silica plates (250 mm layer thickness). The ^{1}H NMR spectra were recorded at 300 MHz. Chemical shifts for ^{1}H NMR spectra are expressed in parts per million downfield from tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet; br, broad. Coupling constants are given in Hertz (Hz). The ^{13}C NMR spectra were recorded at 75 MHz. The ^{19}F NMR spectra were recorded at 282.7 MHz. Mass spectra were obtained by electrospray mass spectrometry utilizing an electrospray ionization (ESI) interface in flow injection analysis (FIA) mode equipped with an ESI interface. Melting points were taken on a capillary melting point apparatus. High-resolution mass spectra were obtained by fast atom bombardment (FAB) with a *p*-nitrobenzyl alcohol matrix. IR spectra were recorded using attenuated total reflectance spectroscopy with a germanium internal reflection element. Optical rotations were measured with the use of a 10 cm cell at 20 °C.

General Procedure for the Synthesis of Quinolone 14E. A solution of (3*S*)-Boc-amino-(4*R*)-ethyl piperidine (**8E**) (1.201 g, 5.268 mmol), 1-cyclopropyl-7-fluoro-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid BF_2 ester (**9c**) (1.712 g, 5.268 mmol), and triethylamine (1.47 mL, 10.54 mmol) in CH_3CN (25 mL) was stirred at room temperature for 36 h. The volatiles were evaporated under reduced pressure, and the residue was dissolved in EtOAc (50 mL) and then washed with 0.1 N HCl (20 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (20 mL). The combined organic phase was washed with brine once, dried over anhydrous $MgSO_4$, and evaporated on a rotary evaporator to give a yellow solid (2.85 g) as a crude product, which was used for the next step without purification.

A mixture of the coupled boron ester (**10c**, when R = Et) (2.85 g, 5.35 mmol) in triethylamine (15 mL, excess) and ethanol (50 mL) was heated at reflux for 1 h, and the solid was dissolved into the solution when refluxing started. After the solution was cooled, the volatiles were evaporated on a rotary evaporator. The residue was dissolved in EtOAc (50 mL) and washed with 0.1 N HCl twice (20 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, and evaporated on a rotary evaporator to give a yellow solid (2.599 g) as a crude product, which was used for the next step without purification.

To the *t*-Boc-protected quinolone (**11c**, when R = Et) (2.599 g, 5.359 mmol) in a flask was added concentrated HCl (10 mL), and the mixture was stirred at room temperature for 30 min. The solid was dissolved at the end of the reaction time, and MS analysis showed the complete reaction. The mixture was washed with CH_2Cl_2 four times (20 mL each). The aqueous layer was evaporated under a reduced pressure, and the residue was azeotroped with ethanol (10 mL) on a rotary evaporator to produce a yellow solid (2.295 g, 95% for three steps).

7-((3*S*)-Amino-piperidin-1-yl)-1-cyclopropyl-6,8-difluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic Acid (12H). ^{1}H NMR (300 MHz, CD_3OD): δ 8.87 (s, 1H), 7.93 (dd, J = 2.1, 11.7 Hz, 1H), 4.18 (m, 1H), 3.72 (m, 1H), 3.34−3.58 (m, 4H), 2.13−2.23 (m. 1H), 1.98−2.08 (m, 1H), 1.75−1.92 (m, 2H), 1.25−1.36 (m, 4H). ^{13}C NMR (75 MHz, CD_3OD): δ 178.9, 169.1, 151.3 (d, J = 124.0 Hz), 150.7 (d, J = 124.0 Hz), 142.5, 142.0, 136.3, 122.5, 118.7, 104.5, 60.4,53.3, 50.1, 41.2, 28.4, 23.4, 8.9. ^{19}F NMR (282.7 MHz, CD_3OD): δ 42.2 (t, J = 11.7 Hz, 1F), 37.9 (s, 1F). EIMS m/z: 364 (M + H). Anal. calcd for $C_{18}H_{19}FN_3O_3\cdot 1.9HCl$: C, 49.97; H, 4.87; N, 9.71. Found: C, 50.32; H, 4.95; N, 9.64. $[\alpha]_D^{20}$ +26.1°, c = 1.74 in CH_3OH.

7-((3*S*)-Amino-(4*R*)-ethyl-piperidin-1-yl)-1-cyclopropyl-6,8-difluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic Acid (12E). ^{1}H NMR (300 MHz, CD_3OD): δ 8.94 (s, 1H), 7.92 (d, J = 11.7 Hz, 1H), 4.22−4.33 (m, 1H), 3.84−3.93 (m, 1H), 3.59−3.70 (m, 1H), 3.26−3.44 (m, 3H), 2.08−2.18 (m. 1H), 1.71−1.90 (m, 2H), 1.58−1.69 (m, 1H), 1.30−1.52 (m, 5H), 1.08 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, CD_3OD): δ 177.8, 168.7, 156.7 (d, J = 124.0 Hz), 148.8 (s, J = 124.0 Hz), 148.0, 135.1, 130.3, 123.0, 108.4, 108.2, 53.8, 53.0, 51.3, 41.7, 41.6, 41.0, 29.3, 24.7, 10.8, 9.4. ^{19}F NMR (282.7 MHz, CD_3OD): δ 43.5 (t, J = 10.7 Hz, 1F), 38.2 (s, 1F). EIMS *m/z*: 392 (M + H). Anal. calcd for $C_{20}H_{23}F_2N_3O_3$·2HCl: C, 51.37; H, 5.43; N, 9.05. Found: C, 51.80; H, 5.82; N, 9.01. $[\alpha]_D^{20}$ +28.5°, c = 1.85 in CH_3OH.

7-((3*S*)-Amino-piperidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic Acid (13H). ^{1}H NMR (300 MHz, CD_3OD): δ 8.88 (s, 1H), 7.82 (d, J = 12.0 Hz, 1H), 4.12 (m, 1H), 3.83 (s, 3H), 3.72−3.79 (m, 1H), 3.42−3.60 (m, 2H), 3.21−3.38 (m, 2H), 2.18−2.27 (m. 1H), 1.63−2.07 (m, 3H), 1.02−1.24 (m, 4H). ^{13}C NMR (75 MHz, CD_3OD): δ 179.2, 168.8, 151.5 (d, J = 124.0 Hz), 146.6, 139.2, 123.1, 122.0, 107.2, 107.0, 106.9, 63.0, 53.7, 51.0, 41.1, 28.1, 23.4, 9.0, 8.8. ^{19}F NMR (282.7 MHz, CD_3OD): δ 45.6 (d, J = 11.7 Hz, 1F). EIMS *m/z*: 376 (M + H). Anal. calcd for $C_{19}H_{22}FN_3O_4$·2HCl: C, 50.79; H, 5.61; N, 9.35. Found: C, 50.42; H, 5.61; N, 9.38. $[\alpha]_D^{20}$ +30.6°, c = 3.01 in CH_3OH.

7-((3*S*)-Amino-(4*R*)-ethyl-piperidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic Acid (13E). ^{1}H NMR (300 MHz, CD_3OD): δ 8.82 (s, 1H), 7.62 (d, J = 9.3 Hz, 1H), 4.23 (m, 1H), 3.84−3.95 (m, 1H), 3.85 (s, 3H), 3.22−3.37 (m, 4H), 2.05−2.14 (m, 1H), 1.25−1.93 (m, 6H), 1.08−1.15 (m, 2H), 1.07 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, CD_3OD): δ 179.0, 167.9, 151.7 (d, J = 124.0 Hz), 145.6, 137.5, 124.5, 121.3, 107.8, 107.3, 106.8, 61.6, 53.5, 51.2, 48.7, 42.8, 39.7, 28.9, 24.4, 18.2, 9.3, 9.1. ^{19}F NMR (282.7 MHz, CD_3OD): δ 41.7 (d, J = 9.0 Hz, 1F). EIMS *m/z*: 404 (M + H). Anal. calcd for $C_{21}H_{26}NF_3O_4$·4HCl: C, 48.45; H, 6.20; N, 7.71. Found: C, 48.51; H, 6.11; N, 7.75. $[\alpha]_D^{20}$ +26.1°, c = 2.6 in CH_3OH.

7-((3*S*)-Amino-piperidin-1-yl)-1-cyclopropyl-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic Acid (14H). ^{1}H NMR (300 MHz, CD_3OD): δ 9.02 (s, 1H), 8.25 (d, J = 9.3 Hz, 1H), 7.48 (d, J = 9.3 Hz, 1H), 4.38 (m, 1H), 4.01−4.08 (m, 1H), 3.89 (s, 3H), 3.70−3.81 (m, 1H), 3.50−3.62 (m, 1H), 3.03−3.18 (m. 2H), 2.21−2.36 (m, 1H), 1.86−2.17 (m, 2H), 1.62−1.78 (m, 1H), 1.28−1.33 (m, 2H), 1.08−1.19 (m, 2H). ^{13}C NMR (75 MHz, CD_3OD): δ 178.3, 168.3, 151.3, 150.7, 142.5, 137.6, 122.5, 118.7, 117.8, 106.8, 60.4, 53.3, 50.1, 41.2, 28.3, 23.4, 8.9. EIMS *m/z*: 358 (M + H). Anal. calcd for $C_{19}H_{23}N_3O_4$·2.5HCl: C, 50.88; H, 5.73; N, 9.37. Found: C, 50.50; H, 6.01; N, 9.22. $[\alpha]_D^{20}$ +23.5°, c = 1.48 in CH_3OH.

7-((3*S*)-Amino-(4*S*)-ethyl-piperidin-1-yl)-1-cyclopropyl-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic Acid (14E). ^{1}H NMR (300 MHz, CD_3OD): δ 9.06 (s, 1H), 8.22 (d, J = 8.7 Hz, 1H), 7.53 (d, J = 8.7 Hz, 1H), 4.41, (m, 1H), 4.23 (dd, J = 3, 11.7 Hz, 1H), 3.90−3.96 (br, 1H), 3.89 (s, 3H), 3.32 (m, 1H), 3.07 (m, 2H), 2.19 (m, 1H), 1.88 (m, 1H), 1.54−1.74 (br, 2H), 1.42 (m, 1H), 1.32−1.38 (br, 2H), 1.12−1.19 (br, 2H), 1.09 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, CD_3OD): δ 175.6, 168.8, 151.7, 151.1, 142.0, 137.6, 122.4, 120.0, 119.9, 105.7, 60.4, 52.5, 52.2, 49.7, 42.2, 40.8, 28.6, 23.7, 17.2, 9.5, 9.0. EIMS *m/z* 386 (M + H), 408, (M + Na). Anal. calcd for $C_{21}H_{27}N_3O_4$·2HCl: C, 55.03; H, 6.38; N, 9.17. Found: C, 55.01; H, 6.45; N, 9.03. $[\alpha]_D^{20}$ +23.2°, c = 2.6 in CH_3OH.

7-((3*S*)-Amino-piperidin-1-yl)-8-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic Acid (15H). ^{1}H NMR (300 MHz, DMSO-d_6): δ 14.50 (s, 1H), 9.01 (s, 1H), 8.18 (d, J = 8.7 Hz, 1H), 7.50 (d, J = 8.7 Hz, 1H), 7.23 (br, 2H), 4.38, (m, 1H), 4.11−4.25 (m, 1H), 3.78−3.89 (m, 1H), 3.38−3.43 (m, 1H), 3.10−3.20 (m, 2H), 2.19−2.24 (m, 1H), 1.68−1.79 (m, 2H), 1.25−1.40 (m, 1H), 1.25−1.30 (m, 2H), 1.10−1.19 (m, 2H). ^{13}C NMR (75 MHz, CD_3OD): δ 174.4, 168.0, 155.9, 153.2, 150.6, 148.0, 140.2, 126.1, 121.6, 107.8, 51.9, 50.7, 41.7, 40.1, 23.6, 11.0, 10.9, 9.6. EIMS *m/z* 362 (M + H). Anal. calcd for $C_{18}H_{20}ClN_3O_4$·2HCl: C, 49.73; H, 5.10; N, 9.67. Found: C, 50.01; H, 5.22; N, 9.58. $[\alpha]_D^{20}$ +24.5°, c = 2.1 in CH_3OH.

7-((3*S*)-Amino-(4*R*)-ethyl-piperidin-1-yl)-8-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic Acid (15E). ^{1}H NMR (300 MHz, CD_3OD): δ 14.80 (s, 1H), 8.88 (s, 1H), 8.27 (d, J = 8.7 Hz, 1H), 8.23 (br, 2H), 7.45 (d, J = 8.7 Hz, 1H), 4.45 (m, 1H), 3.77−4.85 (m, 1H), 3.49−3.51 (m, 1H), 3.07−3.20 (br, 1H), 2.28−3.05 (m, 2H), 1.08−2.17 (m, 1H), 1.40−1.72 (m, 1H), 1.54−1.68 (m, 1H), 1.38−1.53 (m, 1H), 1.21−1.35 (m, 3H), 0.95−1.03 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, CD3OD): δ 177.9, 166.2, 156.1, 153.9, 141.9, 126.6, 123.6, 119.9, 115.8, 108.9, 54.3, 51.8, 51.5, 42.5, 40.9, 28.9, 24.1, 11.9, 11.7, 11.1. EIMS *m/z*: 390 (M + H). Anal. calcd for $C_{20}H_{24}ClN_3O_3$·2HCl: C, 51.90; H, 5.66; N, 9.08. Found: C, 52.15; H, 5.38; N, 9.18. $[\alpha]_D^{20}$ +22.5°, c = 1.20 in CH_3OH.

7-((3*S*)-Amino-piperidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid (16H). ^{1}H NMR (300 MHz, DMSO-d_6): δ 14.67 (s, 1H), 8.64 (s, 1H), 8.24 (br, 2H), 8.13 (d, J = 13.2 Hz, 1H), 4.51 (m, 1H), 4.21 (m, 1H), 3.79 (m, 1H), 3.36−3.51 (m, 3H), 2.04−2.13 (m, 1H), 1.82−1.92 (m, 1H), 1.62−1.74 (m, 2H), 1.22−1.29 (m, 2H), 1.08−1.13 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 177.0, 166.1, 147.5 (d, J = 124.0 Hz), 146.9, 145.6, 120.1, 119.8, 113.1, 108.0, 49.2, 47.2, 46.5, 35.4, 28.5, 22.9, 7.3, 7.1. ^{19}F NMR (282.7 MHz, DMSO-d_6): δ 35.8 (d, J = 12.2 Hz, 1F). EIMS *m/z*: 347 (M + H). Anal. calcd for $C_{17}H_{19}FN_4O_3$·1.9HCl: C, 49.13; H, 5.07; N, 13.48. Found: C, 49.18; H, 4.89; N, 13.09. $[\alpha]_D^{20}$ +25.4°, c = 1.57 in CH_3OH.

7-((3*S*)-Amino-(4*S*)-ethyl-piperidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic Acid (16E). ^{1}H NMR (300 MHz, CD_3OD): δ 8.70 (s, 1H), 8.01 (d, J = 12.9 Hz, 1H), 4.70−4.84 (m, 1H), 4.45−4.56 (m, 1H), 3.81 (br, 1H), 3.36−3.50 (m, 3H), 2.07−2.18 (m, 1H), 1.74−1.87 (m, 2H), 1.31−1.64 (m, 4H), 1.01−1.17 (m, 2H), 1.04 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, CD_3OD): δ 177.5, 167.8, 150.5, 150.4, 147.3 (d, J = 124.0 Hz), 147.1, 119.6, 119.4, 113.7, 107.7, 51.3, 46.6, 40.7, 35.1, 27.7, 25.2, 24.9 23.6, 9.6, 6.7. ^{19}F NMR (282.7 MHz, CD_3OD): δ 34.6 (d, J = 13.8 Hz, 1F). EIMS *m/z*: 375 (M + H). Anal. calcd for $C_{19}H_{23}FN_4O_3$·1.5HCl: C, 53.24; H, 5.76; N, 13.07. Found: C, 53.44; H, 5.91; N, 13.07. $[\alpha]_D^{20}$ +23.1°, c = 1.80 in CH_3OH.

7-((3*S*)-Amino-(4*S*)-ethyl-piperidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic Acid (17E). ^{1}H NMR (300 MHz, CD_3OD): δ 8.62 (s, 1H), 7.63 (d, J = 12.9 Hz, 1H), 7.60 (s, 1H), 3.71−4.06 (m, 2H), 3.10−3.52 (m, 4H), 2.13−2.28 (m, 1H), 1.77−1.92 (m, 2H), 1.60−1.77 (m, 1H), 1.42−1.60 (m, 3H), 1.08−1.33 (m, 2H), 1.06 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, CD_3OD): δ 176.6, 168.3, 148.1 (d, J = 124.0 Hz), 145.8, 139.4, 197.3, 111.2, 110.9, 106.9, 106.5, 57.3, 51.5, 51.3, 39.4, 36.1, 27.1, 23.5, 17.3, 9.9, 7.6. ^{19}F NMR (282.7 MHz, CD_3OD): δ 41.1 (s, 1F). EIMS *m/z*: 374 g (M + H). Anal. calcd for $C_{20}H_{24}FN_4O_3$·2HCl: C, 53.82; H, 5.88; N, 9.41. Found: C, 53.66; H, 6.48; N, 9.36.

7-((3*S*)-Amino-(4*S*)-ethyl-piperidin-1-yl)-1-cyclopropyl-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic Acid (19). ^{1}H NMR (300 MHz, CD_3OD): δ 8.89 (s, 1H), 8.12 (d, J = 8.7 Hz, 1H), 7.41 (d, J = 8.7 Hz, 1H), 4.27, (m, 1H), 3.82−3.94 (m, 2H), 3.86 (s, 3H), 3.70−3.76 (m, 1H), 3.26−3.36 (m, 1H), 2.96−3.06 (m, 1H), 1.82−2.02 (m, 3H), 1.47−1.60 (m, 2H), 1.20−0.37 (m, 2H), 1.10 (t, J = 7.5 Hz, 3H), 1.02−1.12 (2H). ^{13}C NMR (75 MHz, CD_3OD): δ178.1, 168.3, 151.4, 151.3, 143.1, 137.2, 122.7, 122.5, 119.1, 107.0, 61.4, 53.6, 50.7, 50.3, 40.9, 38.6, 25.7, 24.0, 10.4, 8.9, 8.8. EIMS *m/z* 386 (M + H), 408, (M + Na). Anal. calcd for $C_{21}H_{27}N_3O_4$·2HCl: C, 55.03; H, 6.38; N, 9.17. Found: C, 54.96; H, 6.23; N, 9.38. $[\alpha]_D^{20}$ +21.0°, c = 1.4 in CH_3OH.

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(19) (a) Characterization: $[\alpha]_D^{20}$ +149.6°, c = 2.1 in $CHCl_3$. (b) ^1H NMR (300 MHz, $CDCl_3$): δ 4.37−4.66 (m, 1H), 3.20−3.39 (m, 2H), 3.04 (d, J = 12.0 Hz, 1H), 2.72 (br, 1H), 2.56 (t, J = 9.3 Hz, 1H), 2.34 (t, J = 11.1 Hz, 1H), 1.80−1.92 (m, 1H), 1.62−1.77 (m, 1H), 1.45 (s, 9H), 1.16−1.30 (m, 2H), 0.90 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.8, 79.4, 52.4, 51.6, 45.8, 43.2, 30.6, 28.6, 24.9, 11.0. EIMS m/z 229 (M + H): 173, (M-Bu-t). $[\alpha]_D^{20}$ −11.6°, c = 2.2 in $CHCl_3$.

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