103475-82-7; **5a** (X = CPh_3), 103383-63-7; **5a** (X = CH_2Ph), 103476-86-4; **5c** (X = CH_2Ph), 90940-90-2; **6a**, 103475-81-6; **6b**, 103475-83-8; **6c**, 88929-32-2; **7a**, 103383-64-8; **7b**, 103383-65-9; **7c**, 103475-84-9; 8, 69467-87-4; **9a** (NH_3 salt), 103421-96-1; **9a**, 103383-66-0; **9b**, 103383-67-1; **9c**, 103383-68-2; (±)-1-*O*-hexadecylglycerol, 6145-69-3; (±)-3-*O*-benzylglycerol, 13071-59-5; 1-bromohexadecane, 112-82-3; palmitoyl chloride, 112-67-4; 1-bromooctadecane, 112-89-0; methyl iodide, 74-88-4.

Chiral DNA Gyrase Inhibitors. 1. Synthesis and Antimicrobial Activity of the Enantiomers of 6-Fluoro-7-(1-piperazinyl)-1-(2′-*trans*-phenyl-1′-cyclopropyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid

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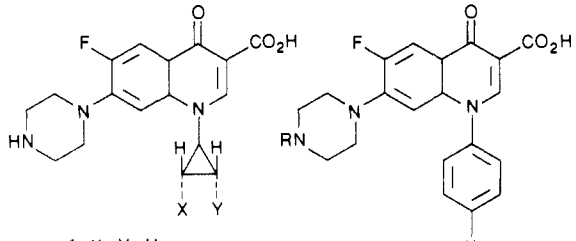
New quinolone antimicrobial agents (racemic, (1′*S*,2′*R*)- and (1′*R*,2′*S*)-6-fluoro-7-(1-piperazinyl)-1-(2′-*trans*-phenyl-1′-cyclopropyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acids) were synthesized, and their in vitro antimicrobial potencies and spectra were determined. As compared to their conceptual parents, these agents retained a considerable amount of the antimicrobial potency and spectra of ciprofloxacin and of 6-fluoro-1-phenyl-7-(1-piperazinyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid against Gram-positives. Gram-negatives were considerably less sensitive. The (−)-(1′*S*,2′*R*) analogue was the more potent of the enantiomers, but the degree of chiral discrimination by most bacteria was only 4-fold. The 4-fold chiral discrimination was observed also using purified DNA gyrase obtained from *Micrococcus luteus*, whereas the two enantiomers were essentially equiactive against the enzyme derived from *Escherichia coli*. These results confirm that there is a substantial degree of bulk tolerance available at N-1 of quinolone antimicrobial agents and suggest that electronic factors controlled by substitution at that site are of considerable importance. On the other hand, chiral recognition brought about by attachment of optically active groups to the N-1 position in these derivatives is relatively small.

Recently it has been shown that ciprofloxacin (**1**),[1] difloxacin (**2**),[2,3] and A-56620 (**3**)[3,4] possess attractive in vivo antimicrobial spectra and potencies. These compounds thus take their place among the substantial number of quinol-4-ones with clinical promise as antibacterial agents that have been prepared recently.[5] The attractive antimicrobial features of **1–3** led us to speculate whether incorporation of both of these features in a single molecule would be consistent with antimicrobial activity. Conventional wisdom in this field has held until recently that the optimal aliphatic group to attach to N-1 should be ethyl, vinyl, or a bioisostere of ethyl ($NHCH_3$, OCH_3, etc.).[3]

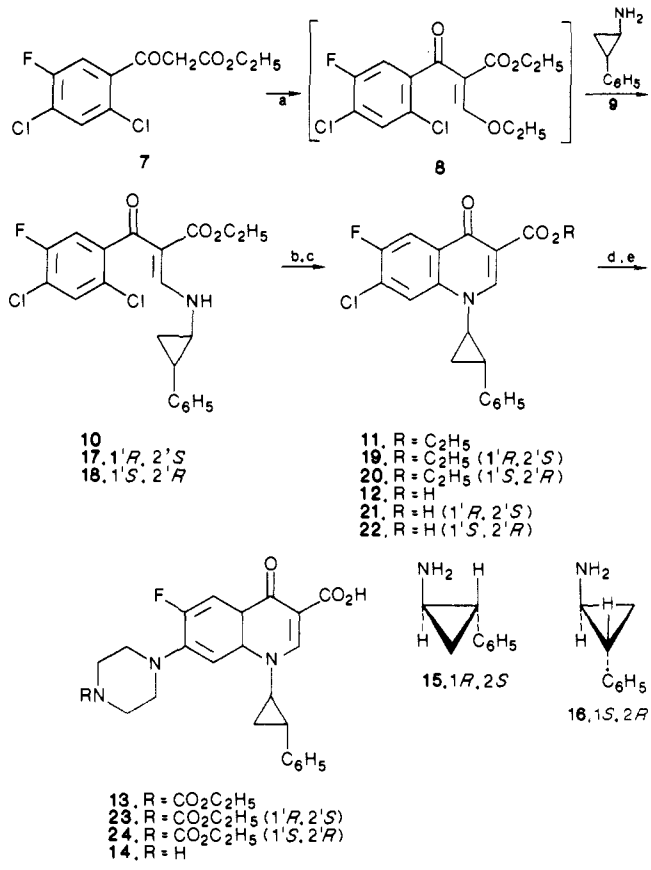


1, X = Y = H
5, X = H; Y = C_6H_5
6, X = C_6H_5; Y = H

2, R = CH_3; X = F
3, R = H; X = F
4, R = X = H

Recently several analogues have appeared whose potency casts doubt on the universality of this concept. Ciprofloxacin (*N*-cyclopropyl),[1] ofloxacin (tricyclic),[6] flumequine (tricyclic),[7] and A-56619 (*N*-aryl)[3] serve as examples. The excellent potency of **2**, **3**, and their congeners has been speculated to be due in part to electronic effects. The aryl group is clearly large compared to the aliphatic N-1 groups mentioned above. Attaching a benzene ring to the cyclopropyl ring of ciprofloxacin would not only preserve a considerable degree of electronic influence, through conjugative effects, but would provide an additional test of the bulk tolerance at N-1 for antimicrobial activity and would also allow the convenient preparation of antipodal

Scheme I



7

8

10
17, 1′*R*, 2′*S*
18, 1′*S*, 2′*R*

11, R = C_2H_5
19, R = C_2H_5 (1′*R*,2′*S*)
20, R = C_2H_5 (1′*S*,2′*R*)
12, R = H
21, R = H (1′*R*, 2′*S*)
22, R = H (1′*S*, 2′*R*)

15, 1*R*, 2*S*

16, 1*S*, 2*R*

13, R = $CO_2C_2H_5$
23, R = $CO_2C_2H_5$ (1′*R*,2′*S*)
24, R = $CO_2C_2H_5$ (1′*S*,2′*R*)
14, R = H

[a] a = $HC(OC_2H_5)_3$ + Ac_2O + Δ; b = NaH + Δ; c = KOH/H_2O + Δ; d = $HN[(CH_2)_2]_2NCO_2C_2H_5$; e = KOH + Δ

analogues. Chiral preferences of drug candidates is a subject of considerable contemporary interest[8-11] but one

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0022-2623/86/1829-2044$01.50/0

Table I. Antimicrobial Activities

compd	organism: MIC,[a] μg/mL											
	Sa(A)	Sa	Se	Sf	Sp	Ec	Ea	Kp	Pa(5)	Pa(K)	A	Ml
norfloxacin (17)	0.78	0.78	1.56	0.78	3.1	0.10	0.20	0.10	0.39	0.39	6.2	
ciprofloxacin (1)	0.20	0.20	0.20	0.39	0.39	0.01	0.05	0.01	0.10	0.05	3.1	1.56
4	0.39	0.39	1.56	12.5	1.56	0.20	0.39	0.10	0.78	1.56	0.78	
14	1.56	1.56	1.56	3.10	1.56	25	50	6.20	>100	100	25	0.39
5	3.10	3.10	3.10	6.20	3.10	50	50	12.5	>100	100	100	0.78
6	0.78	0.78	1.56	1.56	0.78	12.5	12.5	3.10	>50	100	6.20	0.39

[a] The MIC values were determined by the usual twofold agar dilution method using brain–heart infusion agar (ref 3). The microorganisms chosen for inclusion in the table are Sa(A), *Staphylococcus aureus* ATCC 6538P; Sa, *Staphylococcus aureus* CMX 68613; Se, *Staphylococcus epidermidis* 3519; Sf, *Streptococcus faecium* ATCC 8043; Sp, *Streptococcus pyogenes* 930; Ec, *Escherichia coli* Juhl; Ea, *Enterobacter aerogenes* ATCC 13048; Kp, *Klebsiella pneumoniae* 8045; Pa(5), *Pseudomonas aeruginosa* A5007; Pa(K), *Pseudomonas aeruginosa* K799/WT; A, *Acinetobacter sp.* CMX 669; Ml, *Micrococcus luteus*.

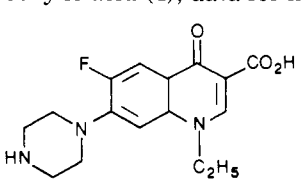
that has rarely been examined as yet amongst the quinolone antimicrobial agents.[12-14]

For convenience it was decided to prepare first a molecule that incorporated salient features of both ciprofloxacin and the unfluorinated analogue (**4**) of **3** (6-fluoro-1-phenyl-7-(1-piperazinyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid).[3] While not the most potent in its series, **4** has ample bioactivity for our purposes and essentially the same antimicrobial spectrum as its fluorinated analogue. Furthermore, a synthetic route could readily be devised to take advantage of the known absolute stereochemistry and availability of tranylcypromine and its enantiomer.[15]

Chemistry. The synthetic route (Scheme I) was adapted from that recently reported by Chu et al. for the preparation of 1-arylfluoroquinolone antibiotics.[3] Condensation of ethyl 2,4-dichloro-5-fluorobenzoylacetate (**7**) with triethyl orthoformate by refluxing in acetic anhydride produced ethyl 2-(2,4-dichloro-5-fluorobenzoyl)-3-ethoxyacrylate (**8**). Intermediate **8** was reacted without further purification with racemic *trans*-2-phenylcyclopropylamine (**9**)[15] in methylene chloride to afford ethyl 2-(2,4-dichloro-5-fluorobenzoyl)-3-(2′-*trans*-phenylcyclopropyl)-aminoacrylate (**10**). This was cyclized by heating with sodium hydride to give racemic 7-chloro-6-fluoro-1-(2′-*trans*-phenylcyclopropyl)-1,4-dihydro-3-ethoxycarbonyl-4-oxoquinoline (**11**) in 74% yield. Ester **11** was hydrolyzed by heating with aqueous KOH in tetrahydrofuran to give racemic 7-chloro-6-fluoro-1-(*trans*-2′-phenyl-cyclopropyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (**12**) in 93% yield. This, on condensation with ethyl 1-piperazinecarboxylate by heating in 1-methyl-2-pyrrolidinone, yielded racemic 7-[4-(ethoxycarbonyl)-piperazino]-6-fluoro-1-(*trans*-2′-phenylcyclopropyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid as its ethyl piperazinecarboxylate salt (**13**). The latter, on further hydrolysis with aqueous KOH in ethanol under 4 days reflux, afforded racemic 6-fluoro-7-piperazino-1-(*trans*-2′-phenylcyclopropyl)-1,4-dihydro-4-oxoquinoline (**14**) in 64% yield.

Repetition of this reaction sequence with (−)-(1*R*,2*S*)-2-*trans*-phenylcyclopropylamine (**15**) and then with (+)-(1*S*,2*R*)-2-*trans*-phenylcyclopropylamine (**16**)[16] afforded optically pure **5** and **6**, respectively, whose absolute configurations were assigned based upon the findings of Riley and Brier relating to **15**.[16]

Biological Evaluation. The antibacterial findings are collected in Table I.[3] In addition to ciprofloxacin (**1**) and 6-fluoro-1-phenyl-7-(1-piperazinyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (**4**), data for norfloxacin (**17**)



17

are included for comparison. As compared to norfloxacin,

Table II. Inhibition Constants (K_i)[a] against DNA Gyrase Isolated from *Micrococcus luteus* and from *Escherichia coli*

compd	K_i, μg/mL, from given source of DNA gyrase	
	M. luteus	*E. coli*
ciprofloxacin (1)	38	0.9
14	13.7	15.2
5	38	14.2
6	9.6	12.1
norfloxacin (17)	72	1.0

[a] K_i values were calculated from a Dixon plot of reciprocal velocity vs. inhibitor concentration (ref 17).

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(16) Riley, T. N.; Brier, C. G. *J. Med. Chem.* **1972**, *15*, 1187.

the racemic mixture (14), showed 0.25–0.50 as much activity against five Gram-positive species and only 0.10 or less the activity against six Gram-negatives. Both agents were less active across the board than ciprofloxacin. Experience with analogues where the aryl group is attached directly to N-1 suggests that preparation of a series of analogues wherein the para substituent was systematically varied could possibly raise the potency by as much as an order of magnitude.[3] Interestingly, choosing the appropriate enantiomer would also apparently contribute significantly to enhanced potency. The levorotatory enantiomer (1′*S*,2′*R*; **6**) made up part of the difference by being approximately twice as active as the racemate and 4 times as active as its enantiomer (1′*R*,2′*S*; **5**) against most of the microorganisms. Thus, while the organisms are sensitive to chirality attached to N-1, the difference between the more and the less active enantiomer is not gross. Interestingly, even the less active enantiomer retains considerable activity. That the differences are primarily a reflection of events at the receptor level is attested to by the finding that the enantiopreference is retained against DNA gyrase purified from *Micrococcus luteus*. In fact, **6** is the most active inhibitor presently known against this particular system. It is, for example, approximately 4 times more active than ciprofloxacin and 7 times more active than norfloxacin. These differences are roughly paralleled in intact cells. On the other hand, the enzyme purified from *Escherichia coli*[17] did not distinguish between the two enantiomers (Table II), and ciprofloxacin and norfloxacin are dramatically more potent than the new analogues against this enzyme. The difference in potency seen against *E. coli* cells may be due to (enantio)selectivity of uptake.

These compounds provide further examples indicating that there is rather substantial bulk tolerance available at N-1 in quinolones. The reason for optimization of activity at *N*-ethyl in purely aliphatic and noncyclic analogues must lie elsewhere.

These various considerations suggest strongly that this novel series of antibiotics is deserving of further study. Such work is now in progress.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Dr. Tho Nguyen at Kansas University and are in the range of ±0.4% of the theoretical values. Optical rotations were measured at 589 nm with a Perkin-Elmer Model 241 polarimeter using chloroform solvent unless otherwise stated. IR spectra were determined with a Beckman IR33 and a Perkin-Elmer FT instrument. ^{1}H NMR spectra were obtained with a Varian FT-80 spectrometer with Me_4Si as the internal standard. Electron impact mass spectra (EIMS) were determined at 70 eV with a Hitachi Perkin-Elmer RMS-4 mass spectrometer. Identical IR, NMR, and MS results were obtained for (±) and chiral analogues. Intermediate range pH strips (pH 0–6 and 5–10) from Aldrich Chemical Company, Inc., Milwaukee, WI, were used for pH determinations. Silica gel GF thin-layer chromatography plates for analytical purposes were purchased from Analtech, Inc., Newark, DE. The solvent systems used were as follows: A, CH_2Cl_2/EtOAc = 4:1 and B, CH_2Cl_2/EtOAc = 3:2.

(±)-Ethyl 2-(2,4-Dichloro-5-fluorobenzoyl)-3-[(2′-*trans*-phenylcyclopropyl)amino]acrylate (10). To a solution of ethyl 2,4-dichloro-5-fluorobenzoylacetate (**7**)[3] (670 mg, 2.41 mmol) in acetic anhydride (0.79 mL) was added triethyl *o*-formate (0.39 mL, 2.3 mmol), and the reaction mixture was heated at 110 °C for 2 h. The reaction mixture was concentrated under high vacuum to afford an oily residue, which was taken up in toluene and concentrated. This process was repeated 2–3 times to afford ethyl 2-(2,4-dichloro-5-fluorobenzoyl)-3-ethoxyacrylate (**8**) as a yellowish oily residue. This was dissolved in dry CH_2Cl_2 without further purification and added to a solution of (±)-tranylcypromine (**9**) (383 mg, 2.36 mmol) in CH_2Cl_2. The reaction mixture was stirred at room temperature for 30 min and then concentrated to afford a residue, which was crystallized from Et_2O to afford 750 mg (74%) of **10** as a white solid: mp 80 °C; IR ($CHCl_3$) 3450, 1700, 1620, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (3 H, t, CH_2CH_3), 1.50 (2 H, m, cyclopropyl-CH_2), 2.35 (1 H, m, J = 16 Hz, C*H*), 3.15 (1 H, m, J = 16 Hz, C*H*), 3.95 (3 H, m, CH_2CH_3 and C_2-*H*), 6.90–7.90 (6 H, m, 6 × Ar*H*), 8.25 (1 H, d, J = 14 Hz, C_5-*H*); EIMS, m/z 423 + 421 (M^+). Anal. C, H, N, F.

(±)-7-Chloro-6-fluoro-1-(2′-*trans*-phenylcyclopropyl)-1,4-dihydro-3-ethoxycarbonyl-4-oxoquinoline (11). To a stirred solution of **10** (628 mg, 1.49 mmol) in dry THF (5 mL) was added portionwise NaH (50% mineral oil suspension, 3.39 mmol), and the reaction mixture was stirred at room temperature until hydrogen evolution ceased (ca. 15 min) and then gently heated at 70 °C for 4 h at which time starting material was no longer detected by TLC in solvent system A. The reaction mixture was then evaporated under reduced pressure. The residue was taken up in water (3 mL) and extracted with EtOAc (4 × 10-mL portions). The combined organic layers were dried (Na_2SO_4) and concentrated to afford a solid, which turned to 465 mg (74%) of **11** as a pure white solid upon trituration with ether: mp 175 °C; IR ($CHCl_3$) 1730, 1690, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.40 (3 H, t, $COOCH_2CH_3$), 1.85 (2 H, m, cyclopropyl-CH_2), 2.50 (1 H, m, J = 16 Hz, C*H*), 3.45 (1 H, m, J = 16 Hz, C*H*), 4.35 (2 H, q, CH_2CH_3), 7.10–7.45 (5 H, m, 5 × Ar*H*), 7.70 (1 H, d, J = 8 Hz, C_8-*H*), 8.15 (1 H, d, J = 14 Hz, C_5-H), 8.55 (1 H, s, C_2-*H*); EIMS, m/z 387 + 385 (M^+). Anal. C, H, N, F.

(±)-7-Chloro-6-fluoro-1-(2′-*trans*-phenylcyclopropyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (12). To a stirred solution of **11** (450 mg, 1.16 mmol) in THF (3 mL) was added a solution of KOH (74 mg) in water (2 mL). The reaction mixture was heated at 65–70 °C for 1.5 h at which time starting material was no longer present according to TLC using system A. The reaction mixture was concentrated to remove THF, and the resulting basic aqueous layer was acidified (pH 4–5) by the addition of dilute HOAc and extracted several times with equal volumes of ethyl acetate. The combined organic layer was dried (Na_2SO_4) and concentrated to a solid, which, upon trituration with ether, produced 549 mg (93%) of **12** as a pure white powder: mp 180 °C; IR ($CHCl_3$) 3500, 1665, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.90 (2 H, m, cyclopropyl-CH_2), 2.50 (1 H, m, J = 16 Hz, C*H*), 3.60 (1 H, m, J = 16 Hz, C*H*), 7.10–7.45 (5 H, m, 5 × Ar*H*), 7.85 (1 H, d, J = 8 Hz, C_8-*H*), 8.15 (1 H, d, J = 14 Hz, C_5-*H*), 8.85 (1 H, s, C_2-H); EIMS, m/z 359 + 357 (M^+). Anal. C, H, N, F.

(±)-7-[4-(Ethoxycarbonyl)piperazino]-6-fluoro-1-(2′-*trans*-phenylcyclopropyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid Ethyl Piperazinecarboxylate Salt (13). To a stirred solution of **12** (335 mg, 0.94 mmol) in 1-methyl-2-pyrrolidinone (1.5 mL, clear solution effected upon heating) was added dropwise ethyl 1-piperazinecarboxylate (0.4 mL, 2.73 mmol), and the reaction mixture was heated at 100–110 °C for 18 h. The reaction mixture was evaporated under reduced pressure to give a yellowish solid, which, upon trituration with ether, afforded 322 mg (76%) of **13** as a pure yellowish solid: mp 230 °C; IR ($CHCl_3$) 3450, 1710, 1620, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (3 H, t, CH_2CH_3), 1.90 (2 H, m, cyclopropyl-CH_2), 2.35 (1 H, m, J = 16 Hz, C*H*), 2.95 (4 H, m, 2 × NCH_2), 3.50 (4 H, m, 2 × NCH_2), 3.65 (1 H, m, J = 16 Hz, C*H*), 4.15 (2 H, q, CH_2CH_3), 6.90–7.45 (6 H, m, 6 × Ar*H*), 7.95 (1 H, d, J = 15 Hz, C_5-*H*), 8.70 (1 H, s, C_2-*H*); EIMS, m/z 479.18563 (calcd for $C_{26}H_{26}FN_3O_5$, 479.18548) (M^+). Anal. C, H, N, F.

(±)-6-Fluoro-7-piperazino-1-(2′-*trans*-phenylcyclopropyl)-1,4-dihydro-4-oxoquinoline (14). A solution of **13** (275 mg, 0.57 mmol) in EtOH (3.5 mL) and 10% aqueous KOH (5 mL) was refluxed for 48 h (until **13** disappeared upon TLC examination using solvent system B). The reaction mixture was concentrated under reduced pressure to remove the EtOH, and the resulting basic aqueous layer was adjusted to pH 7 by the addition of dilute HCl. The white precipitate that formed was filtered and washed with water (2 × 1 mL). The solid was then dissolved in a minimum volume of DMF (0.5 mL), and the solid was precipitated by the

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addition of water (2 mL). After filtration, 112 mg (64%) of **14** was obtained as a white solid: mp 250 °C dec; IR (Nujol) 3450, 1720, 1620 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.10 (2 H, m, cyclopropyl-CH_2), 2.40 (1 H, m, J = 16 Hz, CH), 2.60–3.35 (8 H, m, 4 × NCH_2), 3.90 (1 H, m, J = 16 Hz, CH), 6.90–7.20 (6 H, m, 6 × ArH), 7.70 (1 H, d, J = 14 Hz, C_5-H), 8.55 (1 H, s, C_2-H); EIMS, m/z 407 (M^+), 363 ($M^+ - CO_2$); EIMS, 407.16497 (calcd for $C_{23}H_{22}FN_3O_3$, 407.16438).

Resolution of (±)-*trans*-2-Phenyl-1-cyclopropylamine (Tranylcypromine) (9). The racemic amine (**9**) was resolved by fractional crystallization from boiling 75% 2-propanol of its tartrate salts (using *d*- and then *l*-tartaric acids, respectively)[18] to afford the (1*S*,2*R*)-*trans*-2-phenyl-1-cyclopropylamine *d*-tartrate salt: mp 190 °C; $[\alpha]^{25}$ +32.5° (*c* 0.6, water). HCl salt (**16**·HCl): $[\alpha]^{25}$ +75° (*c* 0.7, water).[16] (1*R*,2*S*)-*trans*-2-phenylcyclopropylamine *l*-tartrate salt: mp 189 °C $[\alpha]^{25}$ −32° (*c* 0.5, water). On treatment with 17% aqueous HCl these tartrate salts afforded *d*-**16** and *l*-**15**, respectively.

(+)-Ethyl 2-(2,4-Dichloro-5-fluorobenzoyl)-3-[[(1′*S*,2′*R*)-2′-phenylcyclopropyl]amino]acrylate (18). This was prepared in 65% yield as described for **10** but using (+)-tranylcypromine (**16**) as a reactant: mp 95 °C; $[\alpha]^{25}$ + 273° (*c* 1.2); EIMS, m/z (M^+) 423 + 421. Anal. C, H, N, F.

(−)-Ethyl 2-(2,4-Dichloro-5-fluorobenzoyl)-3-[[(1′*R*,2′*S*)-2′-phenylcyclopropyl]amino]acrylate (17). This was prepared in 79% yield as described for **10** but using (−)-tranylcypromine (**15**) as reactant: mp 95 °C; $[\alpha]^{25}$ − 273° (*c* 0.3); EIMS, m/z (M^+) 423 + 421. Anal. C, H, N, F.

(+)-7-Chloro-6-fluoro-1-[(1′*S*,2′*R*)-2′-phenylcyclopropyl]-1,4-dihydro-3-ethoxycarbonyl-4-oxoquinoline (20). This was prepared in 68% yield from **18** as described for the conversion of **10** to **11**: mp 190 °C; $[\alpha]^{25}$ +40° (*c* 0.3); EIMS, m/z (M^+) 387 + 385. Anal. C, H, N, F.

(−)-7-Chloro-6-fluoro-1-[(1′*R*,2′*S*)-2′-phenylcyclopropyl]-1,4-dihydro-3-ethoxycarbonyl-4-oxoquinoline (19). This was prepared in 79% yield from **17** as described for the conversion of **10** to **11**: mp 189 °C; $[\alpha]^{25}$ −40.5° (*c* 0.4); EIMS, m/z (M^+) 387 + 385. Anal. C, H, N, F.

(+)-7-Chloro-6-fluoro-1-[(1′*S*,2′*R*)-2′-phenylcyclopropyl]-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (22). This was prepared in 92% yield from **20** as described for the conversion of **11** to **12**: mp 201 °C; $[\alpha]^{25}$ +31° (*c* 0.2); EIMS, m/z (M^+) 359 + 357. Anal. C, H, N, F.

(−)-7-Chloro-6-fluoro-1-[(1′*R*,2′*S*)-2′-phenylcyclopropyl]-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (21). This was prepared in 87% yield from **19** following the procedure given above for the conversion of **11** to **12**: mp 200 °C; $[\alpha]^{25}$ −30.5° (c 0.3); EIMS, m/z (M^+) 359 + 357. Anal. C, H, N, F.

(−)-7-[4-(Ethoxycarbonyl)piperazino]-6-fluoro-1-[(1′*S*,2′*R*)-2′-phenylcyclopropyl]-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid Ethyl Piperazinecarboxylate Salt (24). This was prepared in 97% yield from **22** using the procedure described for the conversion of **12** to **13**: mp 245 °C; $[\alpha]^{25}$ −57.5° (*c* 0.2); EIMS, m/z (M^+) 479.185 17. Calcd for $C_{26}H_{26}FN_3O_5$: 479.185 48.

(+)-7-[4-(Ethoxycarbonyl)piperazino]-6-fluoro-1-[(1′*R*,2′*S*)-2′-phenylcyclopropyl]-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid Ethyl Piperazinecarboxylate Salt (23). This was prepared in 90% yield from **23** using the method described for the conversion of **12** to **13**: mp 245 °C; $[\alpha]^{25}$ +57.5 (*c* 0.4); EIMS, m/z (M^+) 479.185 90. Calcd for $C_{26}H_{26}FN_3O_5$: 479.185 48.

(−)-6-Fluoro-1-[(1′*S*,2′*R*)-2′-phenylcyclopropyl]-7-piperazino-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (6). This was prepared in 56% yield from **24** as described for the conversion of **13** to **14**: mp 300 °C; $[\alpha]^{25}$ −107° (*c* 0.2, Me_2SO); EIMS, m/z (M^+) 407.164 97. Calcd for $C_{23}H_{22}FN_3O_3$: 407.164 38.

(+)-6-Fluoro-1-[(1′*R*,2′*S*)-2′-phenylcyclopropyl]-7-piperazino-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (5). This was prepared in 42% yield as described for the conversion of **13** to **14**: mp 300 °C; $[\alpha]^{25}$ +107.2° (*c* 0.3, Me_2SO); EIMS, m/z (M^+) 407.164 97. Calcd for $C_{23}H_{22}FN_3O_3$: 407.164 38.

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Registry No. **5**, 103531-48-2; **6**, 103531-47-1; **7**, 86483-51-4; **8**, 86483-52-5; (±)-**9**, 155-09-9; (±)-**10**, 103477-53-8; (±)-**11**, 103477-54-9; (±)-**12**, 103477-55-0; (±)-**13**, 103477-56-1; (±)-**14**, 103477-57-2; **15**, 3721-26-4; **15**·*l*-tartrate, 103531-38-0; **16**, 3721-28-6; **16**·HCl, 4548-34-9; **16**·*d*-tartrate, 103531-37-9; **17**, 103531-40-4; **18**, 103531-39-1; **19**, 103531-42-6; **20**, 103531-41-5; **21**, 103531-44-8; **22**, 103531-43-7; **23**, 103531-46-0; **24**, 103531-45-9; 1-piperazinecarboxylate, 120-43-4.

(18) Newman, P. *Optical Resolution Procedures for Chemical Compounds. Vol. 1. Amines and Related Compounds*; Optical Resolution and Information Center: Manhattan College, Riverdale, NY 1978; p 120.