Bioorganic & Medicinal Chemistry Letters, Vol.3, No.4, pp. 671-676, 1993
Printed in Great Britain

0960-894X/93 \$6.00 + .00

U-87947E, A POTENT QUINOLONE ANTIBACTERIAL AGENT INCORPORATING A BICYCLO[1.1.1]PENT-1-YL *(BCP)* SUBUNIT

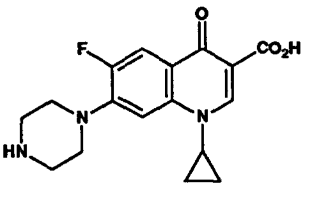
Michael R. Barbachyn,[*,†] Douglas K. Hutchinson,[†] Dana S. Toops,[†] Raymond J. Reid,[†]
Gary E. Zurenko,[‡] Betty H. Yagi,[‡] Ronda D. Schaadt[‡] and John W. Allison[‡]

Medicinal Chemistry Research,[†] *Cancer and Infectious Diseases Research*[‡]
The Upjohn Company, Kalamazoo, MI 49001, USA

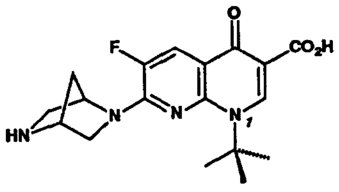
(*Received in USA* 21 *December* 1992)

Abstract: Incorporation of a bicyclo[1.1.1]pent-1-yl group at the N-1 position of quinolone antibacterial agents affords compounds with potent activity. One of these analogs, U-87947E, exhibits enhanced activity relative to that of ciprofloxacin against gram-positive aerobic bacteria and anaerobic organisms. Time-kill kinetic studies reveal that U-87947E is exquisitely bactericidal against ciprofloxacin-resistant *Staphylococcus aureus*.

The fluoroquinolones, exemplified by ciprofloxacin, continue to receive a great deal of attention from the medicinal chemistry community.[1] Their potent and broad spectrum activity, unique mechanism of action involving inhibition of bacterial DNA gyrase, and the availability of oral and parenteral dosing forms, appears to justify the intense scrutiny. However, despite the noted advantages, resistance development occurs relatively frequently in infections caused by *Pseudomonas aeruginosa*, *Staphyloccocus aureus*, and *Streptococcus pneumoniae*.[2,3] We were therefore intrigued by the recent disclosure of potent quinolone analogs characterized by a *tert*-butyl group at the N-1 position, exemplified by the clinical lead BMY-40062.[4] This compound was reported to have improved activity relative to that of ciprofloxacin against staphylococci, streptococci and anaerobes. BMY-40062's *tert*-butyl residue also represented a significant SAR revelation, in that the old dogma had concluded that optimal antibacterial activity was achieved when the N-1 substituent was ethyl or a bioisostere of ethyl.[5] A consideration of other successful contemporary N-1 substituents indicates that steric bulk alone cannot account for observed activity, and that electronic and spatial orientation factors also play an important role.[6] Optimal activity in the *tert*-butyl series was realized with a naphthyridine ring system.



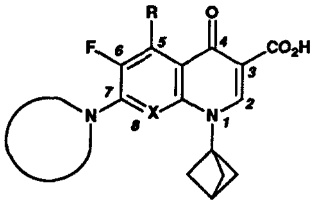
ciprofloxacin



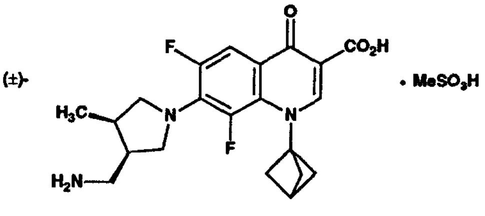
BMY-40062

Corresponding analogs with a quinoline nucleus, especially the 8-fluoro congeners, were significantly less potent.[7] Presumably, this reflects more pronounced steric interactions between the C-8 substituent and the *tert*-butyl residue at N-1.

In contemplating sterically less demanding tertiary alkyl surrogates for the *tert*-butyl group, we wondered whether the bicyclo[1.1.1]pent-1-yl *(BCP)* moiety would be a suitable replacement (see generic structure **1**). Modeling studies indicated that the highly condensed *BCP* group would be significantly more tolerant of substitution at the 8-position than the *tert*-butyl appendage, perhaps allowing analogs with a quinoline skeleton to attain a potency comparable to their naphthyridine counterparts. The ability to utilize the quinoline ring system would also allow more latitude in appending other known potentiating groups at C-5 and C-8. In addition, the *BCP* group was expected to exert a unique electronic effect in light of the increased electronegativity of its bridgehead carbon atom.[8] A detailed summary of structure-activity relationships in the *BCP* quinolone series will be presented elsewhere.[9] In this paper we focus primarily on the synthesis of U-87947E, a *BCP* quinolone whose preparation can be viewed as representative for this subclass, and report on the remarkable antibacterial activity which it manifests.



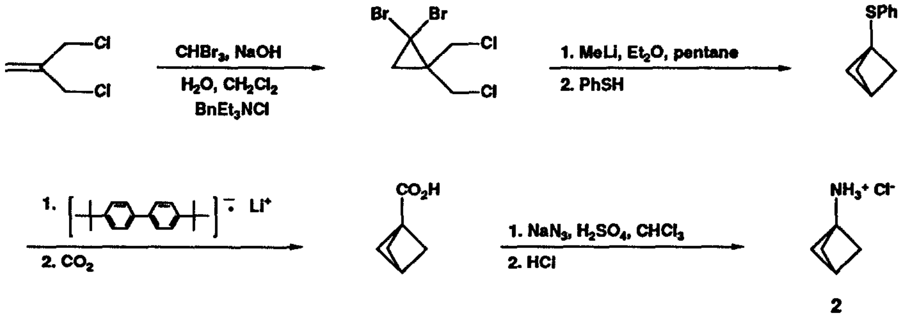
1



U-87947E

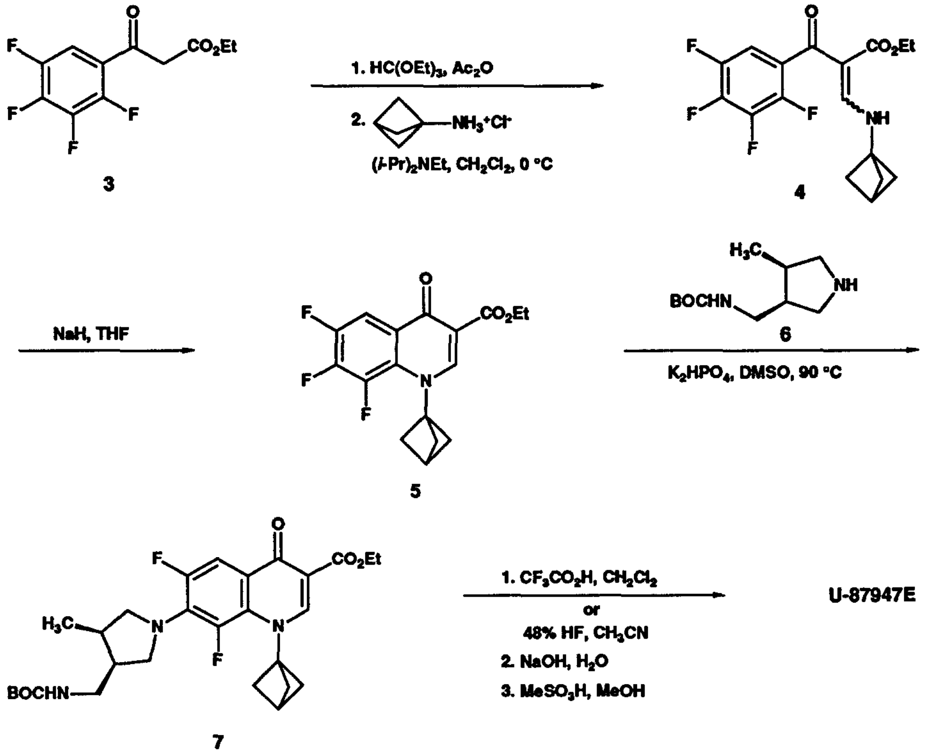
Chemistry

The pivotal intermediate for preparing U-87947E, 1-bicyclo[1.1.1]pentylamine hydrochloride (**2**), is readily prepared from commercially available methallyl dichloride by a sequence of well precedented steps as shown in the scheme.[10,11,12]

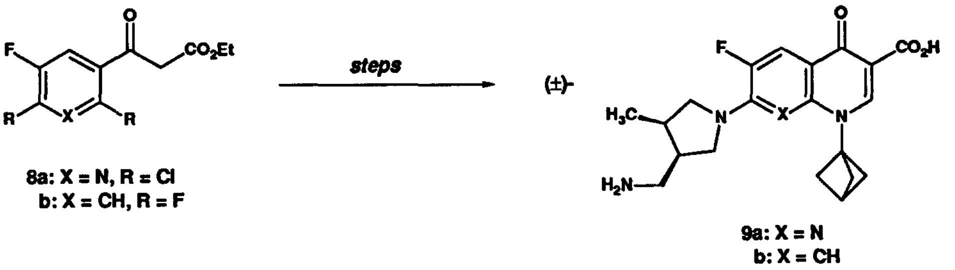


2

The remaining steps involved in the preparation of U-87947E are detailed below.[13] Reaction of tetrafluorobenzoylacetate 3 with triethyl orthoformate in acetic anhydride led to an intermediate ethoxymethylene derivative[14] which was then treated with 1-bicyclo[1.1.1]pentylamine hydrochloride (2) in the presence of Hünig's base to give the enamine 4. Cyclization of 4 under basic conditions proceeded smoothly to provide the key quinolone ester 5 (mp 176-178 °C) in 93% overall yield from 3. Displacement of the C-7 fluorine substituent of quinolone ester 5 with (±)-*cis*-3-(*tert*-butoxycarbonylaminomethyl)-4-methylpyrrolidine (6)[15] furnished the adduct 7 in high yield (85%). Removal of the BOC group was accomplished in 94% yield by the action of trifluoroacetic acid/dichloromethane or aqueous HF/acetonitrile. Subsequent hydrolysis of the ester and treatment with methanesulfonic acid then afforded a 70% yield of the targeted quinolone U-87947E.[16]



Employing essentially identical procedures, but starting with the nicotinoylacetate 8a[17] and benzoylacetate 8b,[18] the *BCP* quinolone analogs 9a and 9b, respectively, were prepared.



Biological Evaluation and Discussion

The *in vitro* antibacterial activity of U-87947E and ciprofloxacin was assessed by determination of minimal inhibitory concentration (MIC) values, and by the measurement of bactericidal activity in time-kill kinetic studies, using methods previously described.[20,21,22] The basic spectrum of U-87947E activity was obtained with a battery of 24 stock and reference strains, while a more extensive evaluation was conducted against multiple clinical isolates, including strains resistant to ciprofloxacin.

U-87947E displayed broad spectrum activity against gram-positive and gram-negative aerobic bacteria, and also anaerobic organisms (data not shown).[9] Interestingly, a comparison of the activity of U-87947E to that of the congeners **9a** and **9b** revealed that U-87947E was slightly more active than the other two *BCP* analogs. This finding confirmed our supposition that, unlike their *tert*-butyl-substituted progenitors,[4] the *BCP* quinolones are significantly more tolerant of substitution at C-8.[19] Against clinical isolates (Table 1), the activity of U-87947E against gram-negative aerobic bacteria was less than that of ciprofloxacin, while its activity against gram-positive aerobic bacteria and anaerobes was significantly enhanced. In a gratifying result, U-87947E was found to be greater than 32-fold more active than ciprofloxacin against ciprofloxacin-resistant *Staphylococcus aureus*, thus adding coverage where ciprofloxacin has a liability.

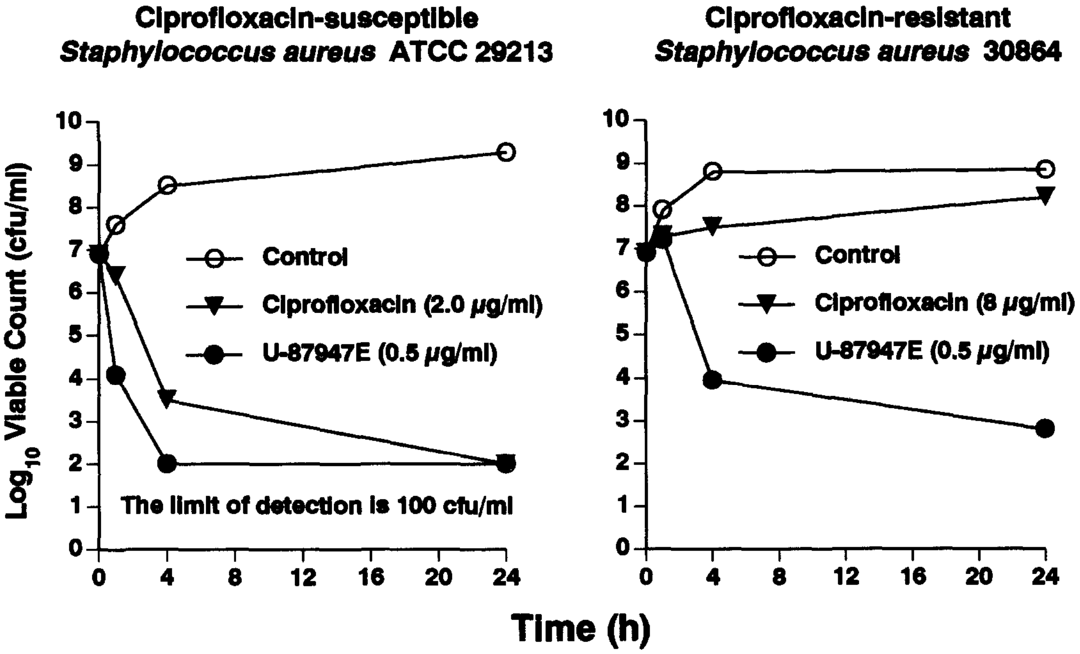
Table 1. Activity of U-87947E and Ciprofloxacin Against Bacterial Clinical Isolates

Organism (No. Strains)	MIC_{90}[1]	
	U-87947E	ciprofloxacin
Enterococcus faecalis (10)	0.25	2
Staphylococcus aureus (12)	0.125	1
Staphylococcus aureus, cip-R[2] (14)	0.50	>16
Streptococcus pyogenes (10)	0.125	0.50
Streptococcus pneumoniae (10)	0.125	1
Escherichia coli (21)	0.125	0.03
Haemophilus influenzae (10)	0.06	0.015
Pseudomonas aeruginosa (20)	8	2
Bacteroides fragilis (12)	1	8

[1] Minimal Inhibitory Concentration (μg/mL) of the drug for 90% of the isolates tested
[2] ciprofloxacin-resistant strains

The bactericidal activity of U-87947E and ciprofloxacin is shown in Figure 1 [time-kill kinetics expressed as $\log_{10}$ viable count in colony-forming units/mL (cfu/mL)]. Both compounds were bactericidal at a drug concentration which was 4-fold the respective MIC against an antibiotic-sensitive strain of *S. aureus* (ATCC® 29213). However, when the drugs were tested against a ciprofloxacin-resistant strain of *S. aureus* (30864), U-87947E exhibited a profound bactericidal effect, even at a concentration equivalent to its MIC. The *in vitro* data reported herein have correlated well with the efficacy of U-87947E in experimental animal models of human infection.[9] Details of these studies and the structural features of U-87947E responsible for its exemplary anti-staphyloccocal activity will be presented in due course. The exquisite activity of this *BCP* quinolone warrants further developmental studies.

Figure 1. Time-Kill Curves for U-87947E and Ciprofloxacin



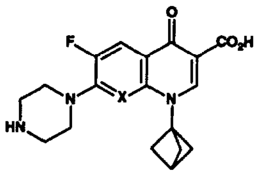
Ciprofloxacin-susceptible *Staphylococcus aureus* ATCC 29213

Ciprofloxacin-resistant *Staphylococcus aureus* 30864

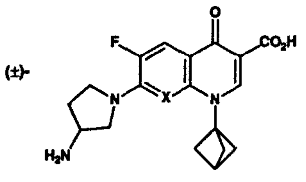
References and Notes

1. Chu, D. T. W.; Fernandes, P. B. *Antimicrob. Agents Chemother.* **1989**, *33*, 131. *International Telesymposium on Quinolones*; Fernandes, P. B., Ed,; J. R. Prous Science: Barcelona, 1990.
2. Fung-Tomc, J. C. *Antimicrob. Newsl.* **1990**, *7*, 17, and references cited therein.
3. Lewin, C. S.; Allen, R. A.; Amyes, S. G. B. *J. Med. Microbiol.* **1990**, *31*, 153, and cited references.
4. Bouzard, D.; Di Cesare, P.; Essiz, M.; Jacquet, J. P.; Kiechel, J. R.; Remuzon, P.; Weber, A.; Oki, T.; Masuyoshi, M.; Kessler, R. E.; Fung-Tomc, J.; Desiderio, J. *J. Med. Chem.* **1990**, *33*, 1344 and references cited therein.
5. Albrecht, R. *Prog. Drug Res.* **1977**, *21*, 9. Fujita, T. *Drug Design: Fact or Fantasy?*; Jolles, G.; Wooldridge, K. R. H., Eds.; Academic Press: New York, 1984; pp 19-33.
6. Chu, D. T. W.; Fernandes, P. B. *Antimicrob. Agents Chemother.* **1989**, *33*, 131.
7. Bouzard, D.; Di Cesare, P.; Essiz, M.; Jacquet, J. P.; Remuzon, P.; Weber, A.; Oki, T.; Masuyoshi, M. *J. Med. Chem.* **1989**, *32*, 537.
8. Wiberg, K. B.; Bader, R. F. W.; Lau, C. D. H. *J. Am. Chem. Soc.* **1987**, *109*, 1001.

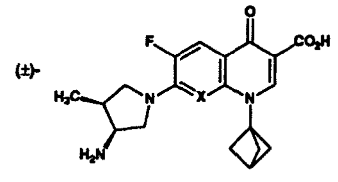
9. A poster preliminarily reporting the SAR of *BCP* quinolones has been presented: Barbachyn, M. R.; Hutchinson, D. K. H.; Reid, R. J.; Toops, D. S. Abstract No. 1456, 31st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, October 2, 1991. A portion of this work was presented at the Symposium on Synthetic Organic Chemistry at Hope College, Holland, MI, September 24, 1991. A full paper on the *BCP* quinolones is under preparation.
10. Semmler, K. S.; Szeimies, G.; Belzner, J. *J. Am Chem. Soc.* **1985**, *107*, 6410. Kaszynski, P.; Michl, J. *J. Org. Chem.* **1988**, *53*, 4593.
11. Wiberg, K. B.; Waddell, S. T. *Tetrahedron Lett.* **1988**, *29*, 289.
12. Wiberg, K. B.; Williams, Van Zandt, Jr. *J. Org. Chem.* **1970**, *35*, 369.
13. Satisfactory analytical and spectral data were obtained for all new compounds.
14. Chu, D. T. W.; Fernandes, P. B.; Maleczka, R. E.; Nordeen, C. W.; Pernet, A. G. *J. Med. Chem.* **1987**, *30*, 504.
15. **6** (Matsumoto, J.; Miyamoto, K.; Egawa, H.; Minamida, A.; Nakamura, S. Japanese Patent 62 30 776, 1987) and related 3,4-disubstituted pyrrolidines have been reported in the quinolone patent literature. However, we have found the reported relative stereochemistry of some of these pyrrolidines to be in error (e.g. Masuzawa, K.; Suzue, S.; Hirai, K.; Ishizaki, T. U.S. Patent 4 753 953, 1988). An unambiguous synthesis of **6** and related *cis*- and *trans*-3,4-disubstituted pyrrolidines from a common precursor, with stereochemical assignments rigorously addressed by NOE experiments and x-ray crystallographic methods, will be described in a subsequent publication.
16. The following characteristics were noted for U-87947 (free base): mp 230-233 °C; IR (mull) 3409, 1728, 1637, 1618, 1579, 1551, 1504, 1404, 1362, 1346, 1250, 1222, 1204, 1177, 1157, 1110, 821 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.75 (d, J = 13.8 Hz, 1H), 3.89 (m, 1H), 3.69 (m, 2H), 3.39 (m, 1H), 2.85 (dd, J = 12.0, 6.7 Hz, 1H), 2.72 (m, 1H), 2.68 (s, 1H), 2.41 (d, J = 3.1 Hz, 6H), 2.41 (om, 3H), 2.25 (m, 1H), 0.98 (d, J = 7.0 Hz, 3H); MS, *m/z* (rel intensity) 403 (M^+, 26), 386 (60), 371 (10), 359 (12), 342 (35), 327 (33), 300 (38), 41 (100); exact mass (FAB) calcd for $C_{21}H_{24}F_2N_3O_3$ (M + H^+) 404.1786, found 404.1781. Anal. Calcd for $C_{21}H_{23}F_2N_3O_3 \cdot H_2O$: C, 59.85; H, 5.98; N, 9.97. Found: C, 60.16; H, 5.87; N, 9.70. U-87947E (mesylate salt): mp 212-214 °C. Anal. Calcd for $C_{22}H_{27}F_2N_3O_6S$: C, 52.90; H, 5.45; N, 8.41. Found: C, 52.59; H, 5.86; N, 8.15.
17. Chu, D. T. W.; Fernandes, P. B.; Claiborne, A. K.; Gracey, E. H.; Pernet, A. G. *J. Med. Chem.* **1986**, *29*, 2363.
18. Chu, D. T. W.; Nordeen, C. W.; Hardy, D. J.; Swanson, R. N.; Giardina, W. J.; Pernet, A. G.; Plattner, J. J. *J. Med. Chem.* **1991**, *34*, 168, and references cited therein.
19. This approximate equivalency of the various C-8 substituted ring systems has also been seen for other *BCP* quinolone analogs, such as **10**, **11** and **12** (X = CF, CH, N):



10



11



12

20. A preliminary disclosure of this data was presented in a poster: Zurenko, G. E.; Yagi, B. H.; Schaadt, R. D.; Allison, J. W. Abstract No. 1457, 31st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, October 2, 1991.
21. National Committee for Clinical Laboratory Standards. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically-second edition; Approved Standard; NCCLS Document M7-A2; NCCLS: Villanova, PA, 1990.
22. National Committee for Clinical Laboratory Standards. Methods for antimicrobial susceptibility testing of anaerobic bacteria-second edition; Approved Standard; NCCLS Document M11-A2; NCCLS: Villanova, PA, 1990.