Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 525–528

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

NOVEL QUINOLONE DERIVATIVES AS POTENT ANTIBACTERIALS

Braj B. Lohray,*[a] S. Baskaran,[a] Bonthu Srinivasa Rao,[a] B. Mallesham,[a] K. S. N. Bharath,[a] B. Yadi Reddy[a]
S. Venkateswarlu,[a] Ashok K. Sadhukhan,[b] M. Sitaram Kumar,[b] Hemant M. Sarnaik[b]

[a] Department of Medicinal Chemistry and Drug Discovery, [b] Department of Biotechnology,
Dr. Reddy's Research Foundation, Bollaram Road, Miyapur, Hyderabad - 500 050, INDIA

Received 2 December 1997; accepted 27 January 1998

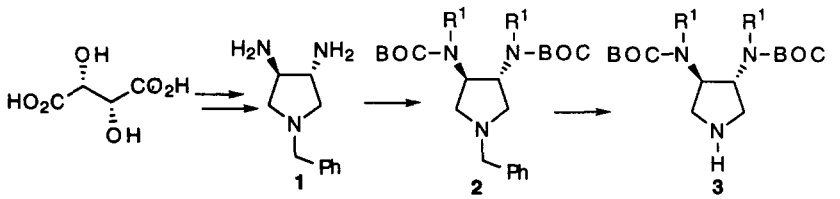
Abstract : Several 7-(3*R*,4*R*-N,N'-dialkyl diaminopyrrolidinyl)-substituted quinolones were synthesized and evaluated for antibacterial activities. 5-Amino-7-(3*R*,4*R*-N,N'-dimethyldiamino-6,8-difluoro-1,4-dihydro-1-cyclopropyl-4-oxoquinoline-3-carboxylic acid was found to have potent antibacterial activity against gram + ve organisms.

Since the discovery of Norfloxacin by Koga *et al.*,[1] many modifications have been reported with the aim of developing potent and wider spectrum antibacterials.[2] Some of the notable quinolone antibacterials in market are pefloxacin,[3] ciprofloxacin,[4] enoxacin,[5] ofloxacin[6] etc. These antibacterials have been shown to be selective inhibitors of bacterial DNA gyrase, an enzyme essential for DNA replication.[7] In general, medium sized heterocyclic rings (5- and 6-membered) at C-7 of the quinolone have contributed most significantly to their antibacterial activity. In addition, it is known that aminopyrrolidine derivatives have better *in vitro* activity than the corresponding piperazine analogs.[8] Since most of the quinolone antibacterials have excellent activity against gram (-) ve bacteria, our aim was to find a quinolone with improved gram (+) ve activity. Also, we wished to find compounds active against quinolone resistant organisms. Towards this goal, we synthesized some quinolones with a new 3,4-diaminosubstituted pyrrolidine derivative substituted at C-7 position of the quinolone frame. We report the results of these studies on novel quinolone derivatives, especially against gram (+) ve organisms. The strategy chosen for the synthesis of C_2-symmetric chiral 3,4-diaminopyrrolidine is shown in scheme-I. 3*R*, 4*R*-diaminopyrrolidine **1** was readily achieved in high yields, starting from naturally occuring *L*-tartaric acid.[9] Diamine **1**, upon treatment with 2 equiv. of di-tert-butyldicarbonate in dichloromethane at room temperature yielded **2a** in quantitative yield.

DRF Publication # 30 ; Dedicated to Prof. M. V. George on his 70th Birth Anniversary

0960-894X/98/$19.00
PII: S0960-894X(98)00063-8

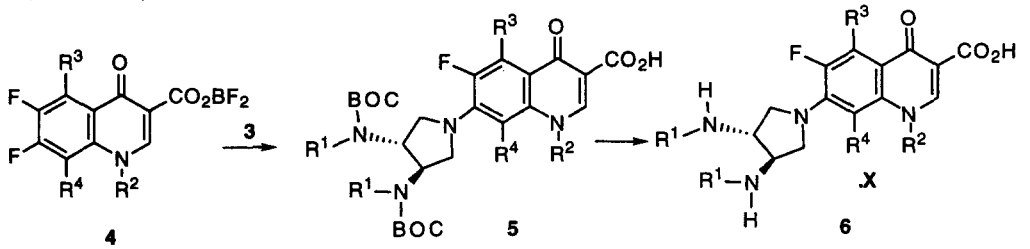
Our initial attempts to methylate **2a** with MeI/NaH was not encouraging. However, we could achieve this by simple two steps operation. The compound **2a** was reduced with LAH/THF at *ca.* 65 - 70 °C for 3h to furnish N, N'-dimethyl diaminopyrrolidine which was further treated with $(BOC)_2O/CH_2Cl_2$ overnight to give **2b** in 90 % overall yield. Similarly, 3*S*,4*S*-diaminopyrrolidine derivatives were prepared from the corresponding *D*(-) tartaric acid.



Scheme-1

a) $R^1 = H$; b) $R^1 = Me$

Debenzylation of **2a-b** was achieved with $Pd/C/HCO_2NH_4$ in methanol to furnish **3a-b** in excellent yields (95-100 %). Although, the reaction of **3** with quinolone-3-carboxylic acid ethyl ester was found to be very sluggish, the corresponding borate ester **4** reacted readily with **3** under mild conditions to yield **5** in very good yields (90 - 100 %).[10]



a) R^1=H; R^2=*C*-C_3H_7; R^3=R^4=H ; X=2.CF_3COOH
b) R^1=Me; R^2=*C*-C_3H_7; R^3=R^4=H ; X=2.HCl
c) R^1=H; R^2=*p*-F-C_6H_4; R^3=R^4=H ; X=2.HCl; L-isomer
d) R^1=H; R^2=*p*-F-C_6H_4; R^3=R^4=H ; X=2.HCl; D-isomer

Scheme-2

e) R^1=Me; R^2=*p*-F-C_6H_4; R^3=R^4=H ; X=2.HCl
f) R^1=Me; R^2=*O*-F-C_6H_4; R^3=R^4=H ; X=2.CF_3COOH
g) R^1=Me; R^2=Et; R^3=H; R^4=F; X=2.HCl
h) R^1=Me; R^2=*c*-C_3H_7; R^3=R^4=F ; X=2.HCl
i) R^1=Me; R^2=*c*-C_3H_7; R^3=NH_2; R^4=F ; X=3.HCl
j) R^1=H; R^2=Et; R^4=F ; X=2.HCl

Deprotection of BOC-group was achieved either in dil.HCl at *ca.* 25 °C or with trifluoroacetic acid in dichloromethane to provide the corresponding fluoroquinolone salts **6** in quantitative yields. Amino group was introduced at C-5 of **5h** in two steps to yield **6i** in good yields (86 %) using reported procedure[11] (scheme-2). A series of 7-(3,4-diaminopyrrolidinyl)fluoroquinolone derivatives **6** were tested against a variety of gram(+)ve and gram(-)ve organisms and the activity profile for some of the quinolone derivatives are shown in Table 1. The structure activity relationship (SAR) studies indicate that *in vitro* antibacterial potency is greatest when the substituent at N-1 position is either cyclopropyl (**6b**) or p-fluorophenyl (**6e**) and the substituent at C-7 is (3*R*, 4*R*)-3,4-N, N'-dimethyl diaminopyrrolidine. In contrast, if 3*R*, 4*R*- diaminopyrroline **6c** is the

Table 1 : *In vitro* Antibacterial Activities of Novel Quinolone Derivatives

Gram (-)ve Organisms	Minimum Inhibitory Concentration MIC (μg/mL)[a]									
	6a	**6b**	**6d**	**6e**	**6f**	**6g**	**6i**	**6j**	**Nor**	**Cipro**
Escherichia coli										
ATCC 25922	0.25	0.125	1.00	0.5	1.00	0.5	0.06	0.5	0.03	0.015
ATCC 35218	1.00	0.25	1.00	1.00	0.5	1.00	0.5	1.0	0.125	0.015
DRCC 091	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8
DRCC 133	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8
DRCC 134	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8
Klebsiella pneumoniae										
ATCC 10031	0.125	0.06	1.00	0.125	0.06	0.5	0.06	0.125	0.03	0.03
DRCC 132	>8	>8	>8	>8	>8	>8	>8	> 8	>8	>8
DRCC 136	4.0	0.5	>8	0.5	2.0	8.0	0.5	8	0.5	1.00
Pseudomonas fluorescens	-									
NCIMB 10586		>8	2.0	2.0	>8	-	>8	-	>8	>8
DRCC 008	1.00	4.0	8.0	4.0	4.0	4.0	4.0	4	0.25	0.5
Pseudomonas aeruginosa										
ATCC 27853	4.0	2.0	2.0	2.0	4.0	8.0	0.5	>8	4.0	0.5
MTCC 1688	0.5	2.0	1.00	0.25	0.5	1.00	1.00	1	0.125	0.06
DRCC 131	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8
DRCC 135	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8
DRCC 137	>8	1.00	4.0	1.00	1.00	8.0	0.25	>8	2.0	0.125
Salmonella abony										
NCIM 2257	2.0	0.5	>8	0.5	4.0	8.0	0.25	8	0.5	1.00
Salmonella typhi										
MTCC 531	1.00	0.5	1.00	0.25	1.00	1.00	0.125	1	0.25	0.25
Salmonella typhimurium										
MTCC 98	>8	-	-	-	0.5	1.00	-	0.5	0.5	0.25
Gram (+)ve Organisms	**6a**	**6b**	**6d**	**6e**	**6f**	**6g**	**6i**	**6j**	**Nor**	**Cipro**
Staphylococcus aureus										
ATCC 6538P	2.0	0.5	1.00	1.00	2.0	4.0	0.5	2	1.00	0.5
ATCC 29213	2.0	1.00	1.00	0.5	4.0	4.0	0.25	2	4.0	2.0
ATCC 33591	2.0	1.00	1.00	0.5	1.00	1.00	0.25	2	1.00	0.25
ATCC 33592	8.0	0.5	1.00	1.00	4.0	4.0	0.25	4	4.0	4.0
MTCC 737	2.0	1.00	1.00	0.25	4.0	4.0	0.25	2	4.0	0.25
Staphylococcus epidermidis										
ATCC 12228	2.0	0.5	1.00	0.5	2.0	2.0	1.00	2	1.00	1.00
Streptococcus faecalis										
ATCC 29212	2.0	2.0	2.0	1.00	4.0	4.0	1.00	4	1.00	0.125
ATCC 49384	4.0	4.0	1.00	0.5	4.0	8.0	1.00	4	4.0	4.0
ATCC 51299	1.0	0.25	1.00	0.25	2.0	2	0.25	2	2	1.00
Streptococcus pyogenes										
DRCC 092	1.00	0.06	0.5	1.00	0.03	4	0.03	2	2	0.0015

[a] MICs were determined by the agar dilution method as outlined by the National Committee for Clinical Laboratory Standards. Test strains were inoculated with multipoint inoculator. DRCC : Dr. Reddy's Culture Collection, India ; NCIM : National Collection of Industrial Microorganisms, India ; MTCC : Microbial Type Culture Collection, India ; NCIAB : National Collection of Industrial and Marine Bacteria, Scotland,; ATCC : American Type Culture Collection, USA. Nor : Norfloxacin ; Cipro : Ciprofloxacin.

substituent, the antibacterial activity is almost absent (not shown in the Table). Fluoroquinolones derived from (3*S*, 4*S*)-diaminopyrrolidine (**6d**) and *meso*-3,4-diaminopyrrolidine (not shown) at C-7 are found to be less active. Similar results were observed with 3*R*, 4*R*-diaminopyrroline derivative **6j**. Thus, it appears, 3,4-diaminopyrrodinyl substituted quinolones are not the drug of the choice. In contrast, 3-aminopyrrolidinyl substituted quinolones show excellent activities in various strains.[8] Variation of the C-5 substituent significantly influences the activity. Introduction of fluorine (**6h**) at C-5 position tends to cause a decrease in activity, however, when fluorine is replaced by amino group it resulted in one of the most active quinolones (**6i**), especially against gram +ve bacteria reported in the Table-1. The quinolone **6i** showed activity against gram + ve bacteria comparable to norfloxacin and ciprofloxacin and in some cases better than norfloxacin. Unfortunately, none of the quinolone derivatives reported in the Table-1 showed any significant activities against ciprofloxacin resistance clinical isolates (Table-1, DRCC 091, 131, 133, 134, 135), however, compounds **6b**, **6e** and **6i** showed excellent activity against methacillin resistant *Staphylococcus aureus* (MRSA) strains (ATCC 33591, 33592).

In summary, we have been able to improve the *in vitro* gram + ve activites of quinolone by substituting the 5-position with amino group especially for 7-(3*R*,4*R*-N,N'-dialkyl diaminopyrrolidinyl) derivative. Further studies for selecting the candidate for development are in progress and will be reported at a later date.

Acknowledgements

We are thankful to Dr. K. Anji Reddy, Chairman, Dr. A. Venkateswarlu, President, DRF for encouragement, Dr. Vidya Bhushan for helpful suggestions and analytical department for excellent service support.

References

1. Koga, H.; Itoh, A.; Murayama, S.; Suzue, S.; Irikura, T. *J. Med. Chem.* **1980**, *23*, 1358.
2. Gootz, T. D.; Brighty, K. E. *Med. Res. Rev.* **1996**, *16*, 433.
3. Goneffon, Y.; Montay, G.; Roquet, F.; Besson, M. C. R. *Hebd. Seance Acad. Sci.* **1981**, *292*, 37.
4. Wise, R. Anews, J. M.; Edwards, L. J. *Antimicrob. Agents. Chemother.* **1983**, *23*, 559.
5. Matsumoto, T.; Miyamoto, T.; Minamida, A. Nishimura, Y.; Egawa, H. *J. Med. Chem.* **1984**, *27*, 292.
6. Sato, K.; Matsuura, Y. Inone, M.; Une, T.; Osada, Y.; Ogawa, H.; Mitsuhashi, S. *Antimicrob. Agents. Chemother.* **1982**, *22*, 548.
7. Llorente, B.; Leclerc, F.; Cedergren, R. *Bioorg. Med. Chem.* **1996**, *4*, 61.
8. Sanchez, J. P.; Domagala, J. M.; Hagen, S. E.; Heifetz, C. L.; Hutt, M. P.; Nichols, J. B.; Trehan, A. K. *J. Med. Chem.* **1988**, *31*, 983.
9. Skarzewski, J.; Gupta, A. *Tetrahedron : Asymmetry*, **1997**, *8*, 1861.
10. Kimura, Y.; Atarashi, S.; Takahashi, M.; Hayakawa, I. *Chem. Pharm. Bull.* **1994**, *42*, 1442.
11. Miyamoto, T.; Matsumoto, J.; Chiba, K.; Egawa, H.; Shibamori, K.; Minamide,A.; Nishimura, Y.; Okada, H.; Kataoka, M.; Fujita, M.; Hirose, T.; Nakano, J. *J. Med. Chem.* **1990**, *33*, 1645.