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NOVEL QUINOLONE DERIVATIVES AS POTENT ANTIBACTERIALS

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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.

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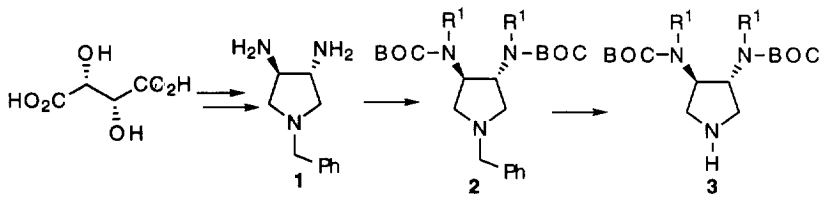
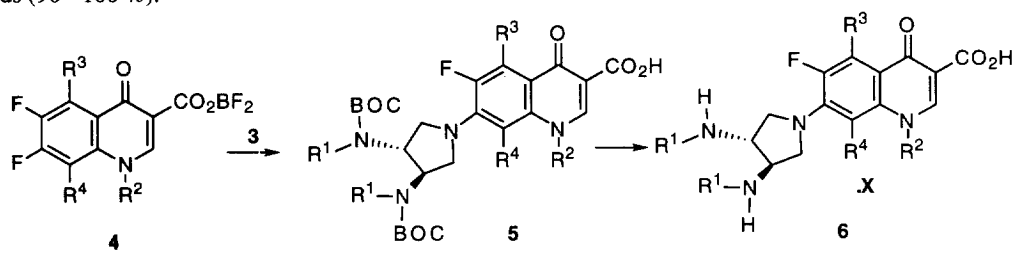
Our initial attempts to methylate **2a** with MeI/NaH was not encouraging. However, we could achieve this by simple two steps operation. The compound **2a** was reduced with LAH/THF at *ca.* 65 - 70 °C for 3h to furnish N, N'-dimethyl diaminopyrrolidine which was further treated with $(BOC)_2O/CH_2Cl_2$ 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
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

Scheme-2

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.

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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.