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NOVEL 5-AMINO-6-METHYLQUINOLONE ANTIBACTERIALS: A NEW CLASS OF NON-6-FLUOROQUINOLONES#

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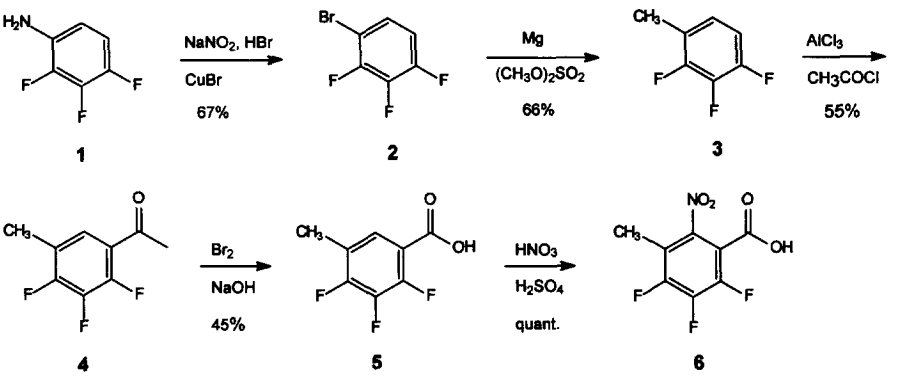
Abstract: A novel 5-amino-6-methylquinoline carboxylic acid was synthesized from 2,3,4-trifluoro aniline in 12 steps and coupled with various types of amines to furnish new quinolone antibacterial agents. Depending on the structure of amine, some of quinolones showed comparable activity to ciprofloxacin or better Gram positive activity than ciprofloxacin, demonstrating that the C6 fluorine atom is not a necessary requirement for good antibacterial potency. © 1997 Elsevier Science Ltd.

Quinolone antibacterials are known to be very effective theraputic agents for the treatment of various infectious diseases. Introduction of a fluorine atom into the C6 position of quinolone ring system brought to norfloxacin, the first broad spectrum antibacterial agent, which opened new era of fluoroquinolone antibacterials.[1] Therefore, so far almost all structural modifications of the quinolone nucleus have been made to the C6 fluorine substituted structure.[2,3] However, the exact role of C6 fluorine atom has never been demonstrated.

There have been two reports in the literature which lack a fluorine atom at the C6 position of quinolone nucleus. Ledoussal et al. reported a series of the non-C6-fluoroquinolones having antibacterial activities comparable to their C6-fluoro analogs.[4] More recently, scientists at Mediolanum also found that good activity could be still obtained by replacing the C6 fluorine atom with an amino group.[5] As part of our ongoing program to find potent, orally active antibacterial agents, we have been focusing on the modification of the C6 position of quinolone nucleus. These two reports on non-C6-fluoroquinolone compounds prompted us to disclose our preliminary results on the same subject.

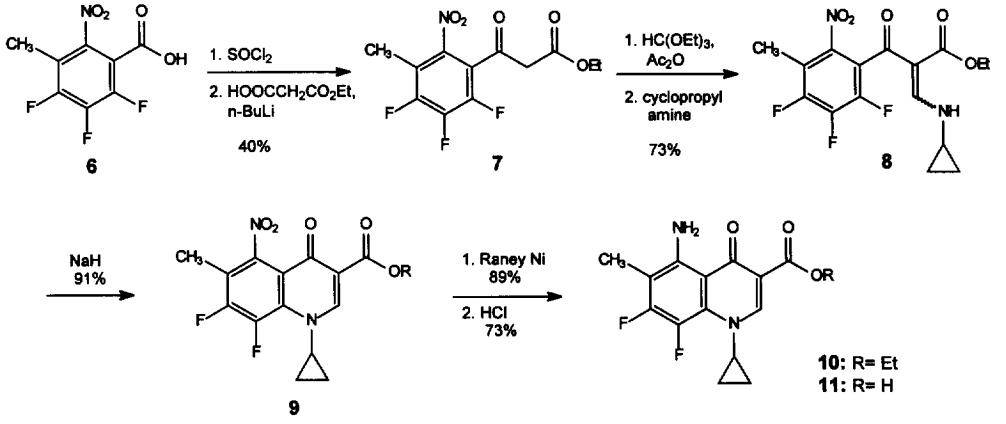
Scheme I: Synthesis of 5-nitro-6-methylquinoline carboxylic acid



Our idea was to introduce a methyl group into the C6 position of quinolone nucleus since we expected a methyl group could be the good replacement for a fluorine atom in terms of its size and lipophilicity. At the same time, we also decided to install an amino group at the C5 position with a hope that this combination would help to enhance antibacterial activity, especially against Gram positive strains.[6]

Synthesis of the new quinoline carboxylic acid is outlined in **Scheme I** and **Scheme II**. Thus, 2,3,4-trifluoro aniline (**1**) was reacted with sodium nitrite ($NaNO_2$) and hydrobromic acid to produce the diazonium salt, which was treated with cuprous bromide (CuBr) to yield 1-bromo-2,3,4-trifluorobenzene (**2**) in 67 % yield. The bromobenzene **2** was smoothly converted to the fluorotoluene **3** *via* Grignard reagent formation and sunsequent quenching with dimethyl sulfate. Friedel-Crafts acylation of **3** with acetyl chloride in the presence of aluminum chloride gave the acetylated compound **4** in 55 % yield. Transformation of the acetyl group in **4** into the acid **5** was done by classical bromoform reaction (Br_2/NaOH) in aqeous dioxane. Nitric acid and sulfuric acid mixture was used for the nitration of **5**, and the nitro compound **6** was isolated in quantitative yield. Two carbon homologation of **6** was accomplished by the two-step sequence (**Scheme II**). First, **6** was converted to the acid chloride in quantitative yield, which was subsequently reacted with the dianion of the monoethyl malonate to give rise to the β-keto ester **7** in 40 % overall yield. Reaction of the β-keto ester **7** with triethyl orthoformate and acetic anhydride under reflux gave the enol ether intermediate, which was transformed to the enamine **8** by the addition of cyclopropyl amine. This two-step procedure proceeded in 96 % overall yield. Cyclization of **8** through rapid *E, Z* isomerization of the enamine system was accomplished by treatment with sodium hydride in THF of the enamine **8** following the literature procedure.[7] By Raney-Ni reduction of the nitro group of **9** in ethanol, the 5-amino functionality was introduced, and the ester **10** was hydrolized to the acid **11** with 3N HCl in 73 % yield.

Scheme II: Synthesis of 5-amino-6-methylquinoline carboxylic acid



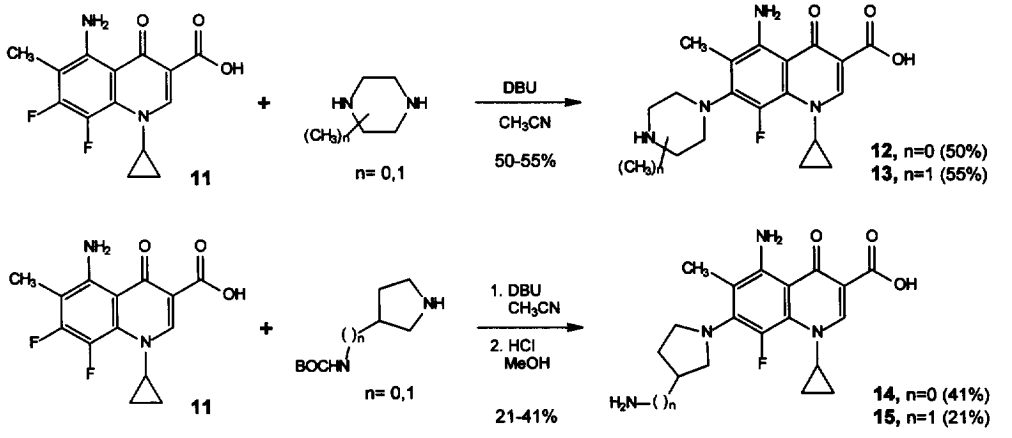
Coupling reactions of the 5-amino-6-methylquinoline carboxylic acid with typical piperazines or pyrrolidines followed the well established literature procedures (**Scheme III**).[8] When a mixture of 6-methylquinoline carboxylic acid and piperazine was heated at reflux in acetonitrile for 30 hours, the novel 6-methylquinolone **12** was produced in 50 % yield. In the case of pyrrolidine derivatives, the final compounds were obtained *via* two-step process. Thus, the BOC-protected aminomethylpyrrolidine was coupled with the

new quinolone nucleus, and subsequent treatment of the coupled compound with hydrochloric acid furnished the 7-pyrrolidino-6-methylquinolone **15**.

Most of the novel quinolones thus prepared maintained good antibacterial activities against both Gram negative and positive strains. (**Table I**). Compound **12** containing the same piperazine moiety as ciprofloxacin displayed comparable potency profile to ciprofloxacin, and definitely better than ofloxacin. More lipophilic 2-methylpiperazine gave us the novel quinolone **13** of similar but somewhat decreased Gram negative activity. These data demonstrated that 5-amino-6-methyl structure with 8-fluorine atom could be a very good surrogate for the prototypical 6-fluoroquinolone nucleus. On the other hand, pyrrolidine type amines yielded the novel compounds which have a different spectrum of potency. For example, compound **15** showed a strong activity against Gram positive bacteria (6 to 8 times better than ciprofloxacin) without significant sacrifice of Gram negative activity. Such a good Gram positive activity has not been observed for other non-C6-fluoroquinolones.[3,4] It is also worthwhile to note that novel quinolones generally showed improved potency against methicillin resistant *Staphylococcus aureus* (MRSA), which currently causes major problems because of its resistance to various antibacterial agents. Therefore, while compound **12** and **15** were advanced for further evaluations, modifications of these amine structures are currently under investigation.

In conclusion, this work has clearly demonstrated that the C6-fluoroquinolone nucleus could be replaced by a 5-amino-6-methyl-8-fluoro substituted structure. Especially, a piperazine substituted compound exhibited comparable activity to ciprofloxacin, and an aminomethyl pyrrolidine derived quinolone showed strong activity against Gram positive strains while retaining good Gram negative activity.

Scheme III: Synthesis of novel 5-amino-6-methylquinolone antibacterials



References and footnotes

This paper is dedicated to professor Yoshito Kishi at Harvard university on the occasion of his 60th birthday.

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Table I. *In vitro* antimicrobial activities of 5-amino-6-methylquinolones

		12	**13**	**14**	**15**	**OFLX**[a]	**CPFX**[a]
C7 amine							
Strains		Minimum Inhibitory Concentration (ug/ml)					
Staphylococcus aureus	6538p	0.25	0.5	0.25	0.031	0.5	0.13
Staphylococcus aureus	giorgio	0.25	0.25	0.25	0.031	0.5	0.25
Staphylococcus aureus	77	0.5	0.5	0.5	0.063	0.25	0.25
Staphylococcus aureus	241	16	16	8	8	64	128
Staphylococcus epidermis	887E	0.13	0.25	0.25	0.031	0.25	0.13
Staphylococcus epidermis	178	16	16	16	16	32	128
Streptococcus faecalis	29212	4	2	8	0.25	2	0.5
Bacillus subtilis	ATCC 6633	0.031	0.063	0.063	0.016	0.063	0.031
Micrococus luteus	ATCC 9341	4	8	8	4	2	4
Escherichia coli	10536	<=0.008	0.063	0.031	0.031	0.031	<=0.008
Escherichia coli	3190Y	<=0.008	0.016	0.031	0.016	0.016	<=0.008
Escherichia coli	851E	0.031	0.063	0.13	0.063	0.063	0.016
Escherichia coli	TEM5 3739E	0.5	0.5	1	0.5	0.5	0.13
Escherichia coli	TEM9 2639E	0.031	0.063	0.13	0.13	0.063	0.016
Pseudomonas aeruginosa	1012E	1	2	1	1	1	0.13
Pseudomonas aeruginosa	10145	2	2	4	2	2	0.25
Acinetobacter calcoaceticus	15473	0.13	0.13	0.5	0.13	0.25	0.25
Citrobacter diversus	2046E	0.063	0.063	0.13	0.13	0.13	0.016
Enterobacter cloacae	1194E	0.063	0.13	0.25	0.031	0.13	0.031
Enterobacter cloacae	p99	<=0.008	0.016	0.031	0.031	0.031	<=0.008
Klebsiella aerogenes	1076E	0.25	0.25	0.5	0.25	0.25	0.13
Klebsiella aerogenes	1082E	0.031	0.13	0.13	0.13	0.13	<=0.008
Salmonella typhimurium	14028	0.063	0.13	0.25	0.13	0.13	0.031

[a] OFLX: ofloxacin, CFLX: ciprofloxacin

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