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Synthesis and Biological Evaluation of Benzo[*b*]naphthyridones, a Series of New Topical Antibacterial Agents

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Abstract—We describe here the synthesis and biological evaluation of a series of benzo[*b*]naphthyridones, a new family of tricyclic antibacterial compounds that have a Gram-positive spectrum of activity. RP60556A, one of the most potent of these compounds, is bactericidal against multiresistant cocci, especially multiresistant *Staphylococcus aureus* strains. Its physico-chemical and biological properties make it particularly suitable for topical antibacterial use. © 2001 Elsevier Science Ltd. All rights reserved.

Introduction

In recent years, emergence of resistance to most common antimicrobial agents such as β-lactams, macrolides, vancomycin or quinolones has become a major worldwide health problem.[1,2] Therefore the search for new antibacterial drugs effective against bacteria resistant to multiple antibiotics is a key objective for many pharmaceutical companies.[3] The spread of resistant nosocomial pathogens, and especially methicillin-resistant *Staphylococcus aureus* (MRSA)[4,5] has created a specific need in hospital for prevention of nasal carriage[6] and topical treatment or prophylaxis of infections caused by these pathogens. Mupirocin[7] and fusidic acid[8] are used in these indications, but resistance to these agents[9,10] has become a concern. Therefore there is a need for alternative treatments.

We had previously described the synthesis[11] of a series of benzo[*b*]naphthyridones studied as systemic antibacterial agents.

We have found now that a modification of the substitution of the heterocycle led us to a new series of topical antibacterial agents particularly active against multiresistant Gram-positive pathogens, especially against MRSA. RP60556A is the most potent representative compound of this series (Fig. 1).

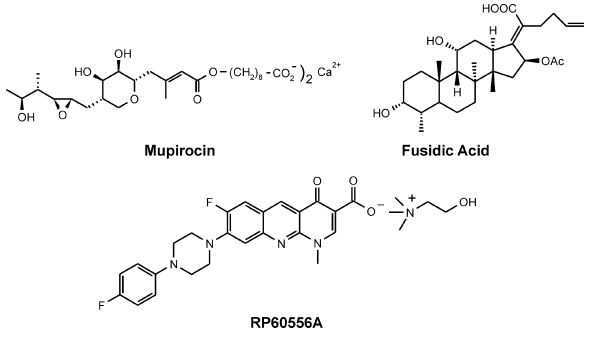

Figure 1.

Chemistry

RP60556A is obtained in a 10-step synthesis[12] (Scheme 1) with a global yield of 14%. The tricyclic structure of the benzo[*b*]naphthyridone is obtained by a Friedel–Craft cyclisation followed by a Grohe-type ring closure. Thus 3,4-difluoro aniline **1** is condensed on 3-chloropropionyl chloride to form the corresponding anilide **2** which is cyclised using aluminium chloride as Lewis acid catalyst. Compound **3** is formylated and chlorinated with the Vilsmeier reagent. The 1,4-dihydroquinoline **4** obtained is oxidized into quinoline **5** by potassium permanganate. Then the magnesium chelate of monomalonic ethyl ester[13] is condensed on the acid chloride of **5** to get β-keto ester **6** which is reacted with dimethyl formamide dimethyl acetal to obtain enamine **7**. The key step of the synthesis, i.e., the cyclization of quinoline **7**

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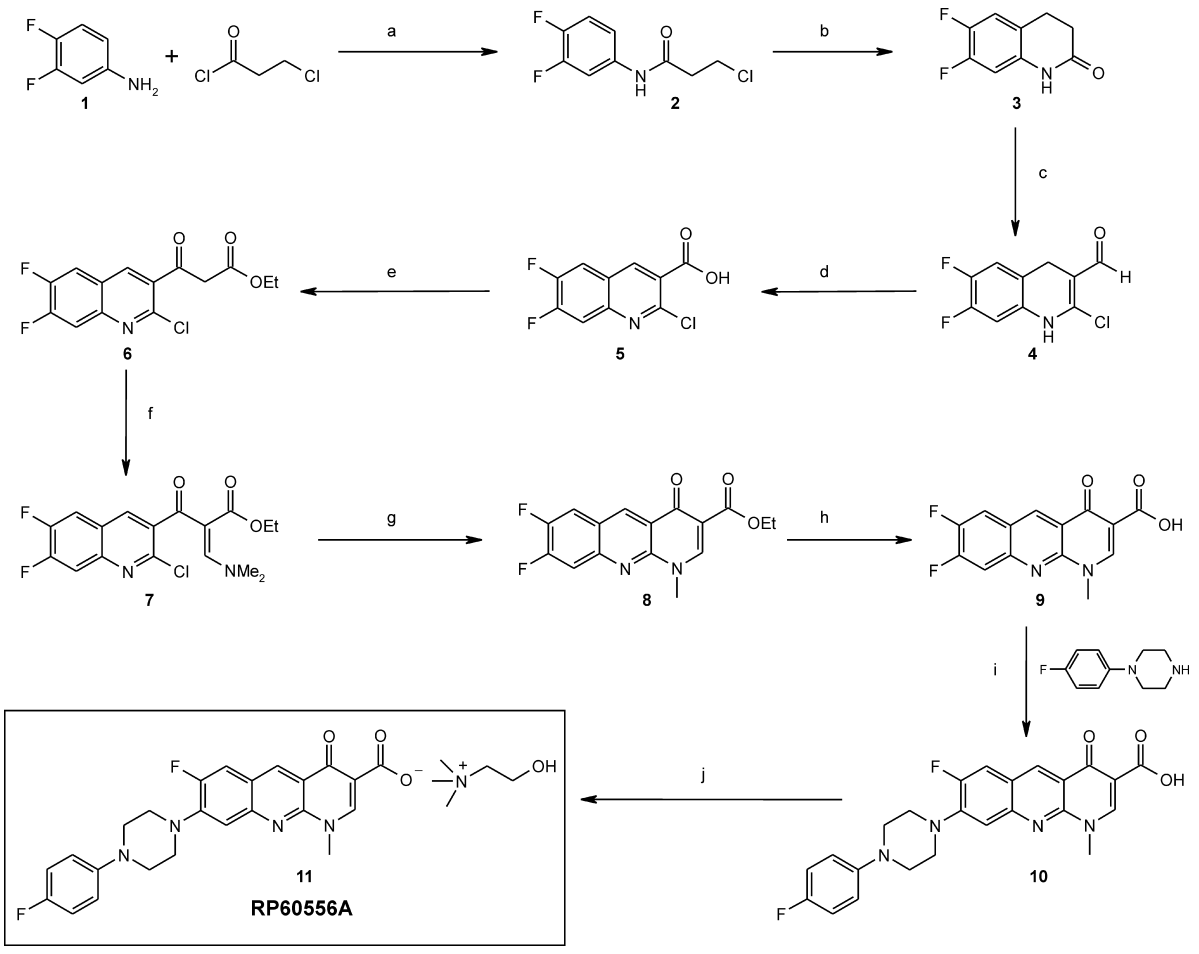
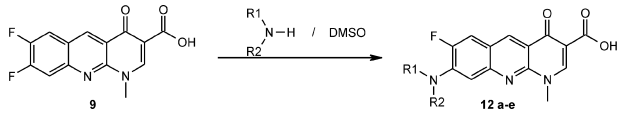


Scheme 1. (a) Pyridine, acetone, 55 °C, 3 h, 95%; (b) $AlCl_3$, 110 °C, 2 h, 78%; (c) DMF, $CHCl_3$, $POCl_3$, 60 °C, 2 h, 85%; (d) KOH, $KMnO_4$, H_2O, 10 °C, 1 h, 66%; (e) $CHCl_3$, $SOCl_2$ then magnesium chelate of monomalonic ethyl ester, THF, 65%; (f) DMFDMA, ethyl acetate, 75 °C, 1 h, 91%; (g) $MeNH_2$, EtOH, 25 °C, 16 h, 83%; (h) HCl 6 N, AcOH, 100 °C, 1.5 h, 89%; (i) DMSO, 90 °C, 4 h, 98%; (j) choline hydroxide 45% in MeOH, 2 h, 25 °C, 79%.

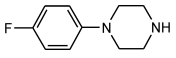
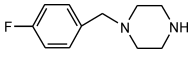
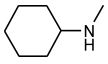
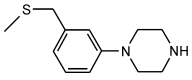
into tricyclic benzo[*b*]naphthyridone **8** is performed in good yield (83%) with methylamine in methanol. Ethyl ester **8** is hydrolyzed with a mixture of hydrochloric acid 6 N and acetic acid at 100 °C to obtain acid **9**. The nucleophillic aromatic substitution of the fluorine in position 8 of the benzo[*b*]naphthyridone **9** by a substituted piperazine is performed in DMSO in high yield (98%). It is interesting to note that the fluorine in position 7 of the tricycle is not substituted even in the presence of a large excess of nucleophile, just as in the quinolone chemistry. The obtained acid **10** is very insoluble in water and in most organic solvents, therefore it is transformed into its cholinate salt **11** with choline hydroxide in methanol. The cholinate salt **11**, RP60556A is readily soluble in water.

A series of benzo[*b*]naphthyridones was synthesized according to Scheme 2, in which fluorine in the position 8 of intermediate **9** was replaced by various amines.



Scheme 2.

Table 1.

Amine or ref cmpd	Cmpd no.	MIC G + QS[a]	MIC G + QR[b]
Pefloxacin	Pefloxacin	0.5	128
Muprirocin	Mupirocin	0.5	0.5
	**11** (RP60556A)	0.25	0.5
	**12a**	0.5	1
	**12b**	1	1
	**12c**	1	1
	**12d**	4	4

[a]G + QS = *Staphylococcus hominis* IP8203, quinolone sensitive, MIC in mg/L.
[b]G + QR = *Staphylococcus aureus* LF11C128B, quinolone resistant, MIC in mg/L.

Biological Evaluation

Minimal inhibitory concentrations (MICs) were determined on two Gram-positive strains, one quinolone sensitive, one quinolone resistant, for a set of compounds corresponding to representative amines. The results are summarized in Table 1.

The analysis of these results shows that MICs of derivatives tested are identical against quinolone-resistant and quinolone-sensitive strains: this suggests that these derivatives could have a mechanism of action in these strains different from that of quinolones.

Substituted piperazine is not mandatory for activity: secondary amines such as *N*-methyl *N*-cyclohexyl amine (**12b**) or aza-cyclooctane (**12c**) maintain a good level of activity.

The presence of a basic centre (**12a**) or not (**11**, **12b**, **12c**, **12d**) does not seem to have an influence on the spectrum of activity.

The best amine is 4-fluorophenyl piperazine (RP60556A). This compound is active against Gram-positive cocci (staphylococci, streptococci and enterococci, MIC range 0.25 to 2 mg/L) without cross-resistance with quinolones, β-lactams, MLS_B (macrolides, lincosamides, streptogramin B group), mupirocin and fusidic acid, and against anaerobes. RP60556A is generally bactericidal within 3–6 h at 4×MIC against Gram-positive strains tested. RP60556A is also active in vivo: in a guinea-pig model of *Staphylococcus aureus* cutaneous infection, a formulation containing 2% of active compound has shown in vivo activity close to that of mupirocin.

Conclusion

The RP60556A series is a unique family of antibacterial agents, developed only for topical, not systemic, use, which shows no cross-resistance with major classes of antibiotics, especially with quinolones. RP60556A is a very potent antibacterial agent with a Gram-positive spectrum of activity, it is bactericidal against multiresistant strains such as *Staphylococcus aureus*, and its in vivo activity in a cutaneous model of infection is close to that of mupirocin. RP60556A physico-chemical and biological properties make it particularly suitable for topical antibacterial use.

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