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Benzo[*f*]naphtyridones: A New Family of Topical Antibacterial Agents Active on Multi-Resistant Gram-Positive Pathogens

Michel Tabart,* Guy Picaut, Marc Lavergne, Sylvie Wentzler, Jean-Luc Malleron, Sylvie Dutka-Malen and Nadine Berthaud

Aventis Pharma, Centre de Recherche de Vitry Alfortville, 13 Quai Jules Guesde, 94403 Vitry sur Seine, France

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Abstract—The synthesis and antibacterial activity of benzo[*f*][1,7]naphtyridone derivatives are reported. These compounds are potent antibacterial agents with a Gram-positive spectrum of activity. They are active against multi-resistant cocci, especially *Staphylococcus aureus* strains. Their physico-chemical and biological properties make them particularly suitable for topical antibacterial use.

Introduction

The introduction and increasing use of antibacterial agents such as β-lactams, macrolides, vancomycin or quinolones for antibacterial therapy has resulted in the emergence of multi-resistant pathogens, especially in Gram-positive bacteria.[1,2]

During the last decade, Gram-positive infections have become a major problem, particularly in the hospital setting, creating a need for new antibacterial drugs effective against bacteria resistant to multiple antibiotics,[3] especially methicillin-resistant *Staphylococcus aureus* (MRSA)[4,5] which are endemic in many hospitals.

The prevention of nasal carriage[6] and topical treatment or prophylaxis of infections caused by these pathogens in hospitals are important aspects of the battle against bacterial resistance. Mupirocin[7] and fusidic acid[8] are used in these indications, but resistance to these agents has become a concern.[9,10]

We had previously described[11,12] the synthesis and antibacterial activity of RP60556A, a representative compound of benzo[*b*]naphtyridone series which is active against multi-resistant strains (especially resistant to mupirocin) and could be used in these indications.

We describe now the synthesis and the biological evaluation of RPR203246 (Fig. 1), a new topical antibacterial agent active against multi-resistant Gram-positive pathogens, representative of the benzo[*f*][1,7]naphtyridone series. Some representative compounds of this series were first described by Lesher[13] but with no activity against resistant strains.

Chemistry

RPR203246 is obtained in a 10-step synthesis[14] (Scheme 1): nitro benzene **1** is reduced by tin chloride into the corresponding aniline **2**. Bromination of this aniline is performed with *N*-bromosuccinimide, which leads to compound **3**, which is then treated by *n*-butyllithium and formylated with DMF. The amino benzal-

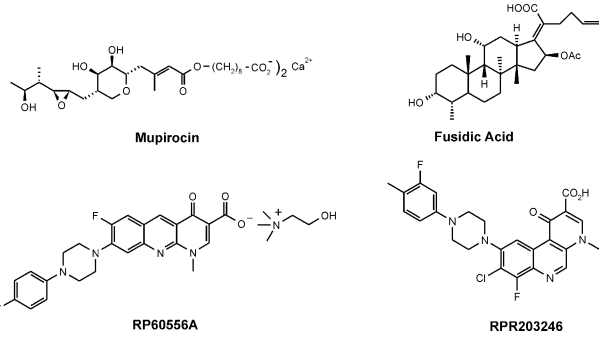

Figure 1.

*Corresponding author. Tel.: +33-1-5571-87709; fax: +33-1-5573-8770; e-mail: michel.tabart@aventis.com

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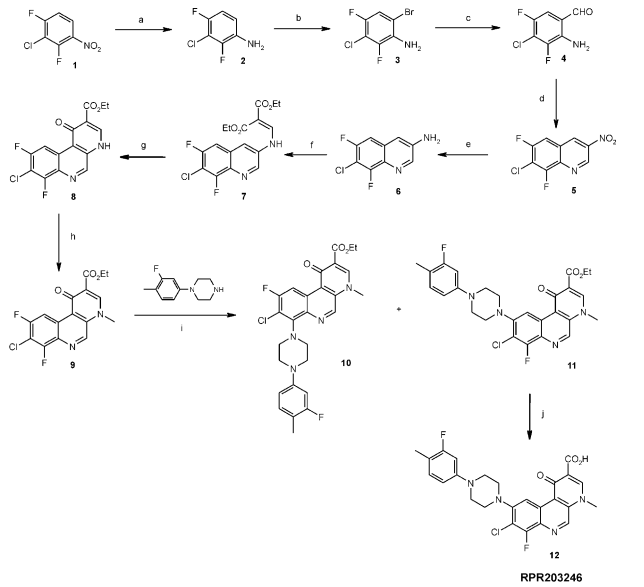


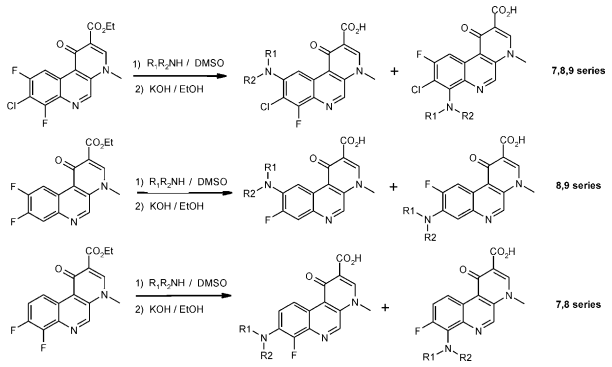
Scheme 1. (a) HCl 12 N, Et_2O, $SnCl_2$, 40 °C, O.5 h, 90%; (b) NBS, DMF, −2 °C, 1 h, 74%; (c) BuLi, THF, −75 °C, then DMF, −70 °C, 3 h, 59%; (d) EtOH, metazonic acid, HCl 12 N, 20 °C, 16 h, 73%; (e) EtOH, Ni Raney, H_2 1 atm, 20 °C, 1 h, 85%; (f) diethyl ethoxymethylenemalonate, 120 °C, 1 h, 89%; (g) diphenyl ether, 240 °C, 0.5 h, 90%; (h) DMF, K_2CO_3, MeI, 110 °C, 1 H, 85%; (i) DMSO, 80 °C, 28 h, separation of regioisomers by flash chromatography, compd **10**: 7%, compd **11**: 46%; (j) EtOH, KOH 1 N, 11 h, 100 °C, then aqueous AcOH 1 N, 69%.

dehyde **4** obtained is condensed on metazonic acid (nitroacetaldehyde oxime, freshly prepared by reacting nitromethane with aqueous sodium hydroxide, then quenching with concentrated aqueous hydrochloric acid and filtrating the precipitate) to get nitro quinoline **5** which is reduced into amino quinoline **6** using hydrogen and Raney–Nickel as catalyst. Compound **6** is reacted with diethyl ethoxymethylenemalonate to obtain enamine **7**. The key step of this synthesis, formation of the tricyclic structure benzo[*f*][1,7]naphtyridine is a Gould–Jacob cyclisation of **7** in diphenyl ether at 240 °C with a good yield (90%). The *N*-alkylation of compound **8** is performed with methyl iodide, and the benzo[*f*]naphtyridone **9** obtained is reacted with 4-(3-fluoro-4-methyl-phenyl) piperazine in DMSO. Only the fluorine atoms are substituted by the *N*-aryl piperazine in this nucleophilic aromatic substitution, leading to a mixture of regioisomers **10** and **11** in a 1:6 ratio. This mixture is separated by flash chromatography, and ethyl ester **11** is subjected to saponification with potassium hydroxide in ethanol to obtain compound **12**, RPR203246.

A series of benzo[*f*]naphtyridones has been synthesized according to Scheme 2, in which a fluorine atom of a polyhalogenated benzo[*f*]naphtyridine is substituted by various cyclic amines, leading to a mixture of regioisomers which is separated by flash chromatography before saponification.

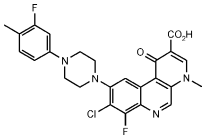
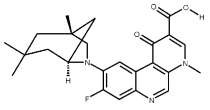
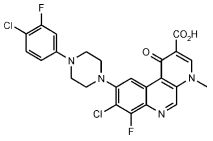
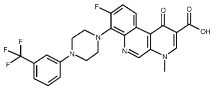
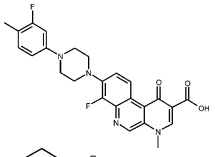
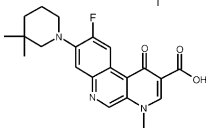
Biological Evaluation

Minimal inhibitory concentrations (MICs) of a set of compounds were determined against a range of Gram-positive strains. *Enterococcus* species, which are not relevant strains to study for a topical antibacterial use, were not tested. The results are summarized in Table 1 for a selection of three representative Gram-positive strains, one *S. aureus* quinolone sensitive, one *S. aureus* quinolone and methicillin resistant, and one *Streptococcus Pyogenes* quinolone sensitive.



Scheme 2.

Table 1.

Compd	Compd no	MIC *S.A.*S[a]	MIC *S.A.*R[b]	MIC *S.P.*S[c]
Pefloxacin		0.5	64	8
Muprirocin		0.5	1	0.12
RP60556A		0.25	2	0.5
	**12**	1	1	2
	**13**	2	2	4
	**14**	2	1	16
	**15**	2	4	16
	**16**	4	2	16
	**17**	4	4	4

[a]*S.A.*S, *Staphylococcus aureus RN4220*, quinolone sensitive, MIC in mg/L.
[b]*S.A.*R, *Staphylococcus aureus* AS5155, MRSA and resistant to quinolone, MIC in mg/L.
[c]*S.P.*S, *Streptococcus pyogenes Dig 7*, quinolone sensitive, MIC in mg/L.

The characteristic of this series of benzo[*f*][1,7]naphtyridones, just like in benzo[*b*]naphtyridone previous series, is that the MICs of the compounds tested are identical against quinolone-resistant and quinolone-sensitive *S. aureus* strains. This result suggests that the mechanism of action of these derivatives in the Gram-positive strains tested is different from that of quinolones.

Structure–activity relationship analysis in this series shows that a combination of a lipophilic cyclic amine and a fluorine (or a fluorine and a chlorine) as substituants in positions 7, 8 and 9 of the tricycle gives rise to the desired property, that is antibacterial activity on quinolone-resistant strains. A non-basic *N*-phenyl substituted piperazine such as in compounds **12**, **14**, **15**3 and **16** gives good results (like in RP60556A, benzo[*b*]-naphtyridone series), but a piperazine is not mandatory for the activity against resistant strains since lipophilic cyclic amines such as 3,3-dimethylpiperidine in compound **17** or 1,3,3-trimethyl-6-azabicyclo[3.2.1]octane (commercially available from Aldrich) in compound **13** give similar results.

The compounds from Table 1 are active against Gram-positive cocci (staphylococci and steptococci, MIC range 1–16 mg/L) without cross-resistance with quinolones, β-lactams, MLS_B (macrolides, lincosamides, streptogramin B group), mupirocin and fusidic acid, and are active against anaerobes.

Conclusion

This new series of benzo[*f*][1,7] derivatives shows many similarities with the benzo[*b*]naphtyridone series previously described: the compounds are interesting new antibacterial agents with a Gram positive spectrum of activity that could be developed for topical use. They show no cross resistance with major classes of antibiotics, especially with quinolones. Their antibacterial and physico-chemical properties make them particularly suitable for topical antibacterial use.

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