Bioorganic & Medicinal Chemistry Letters 18 (2008) 3556–3561

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Pleuromutilin derivatives having a purine ring. Part 1: New compounds with promising antibacterial activity against resistant Gram-positive pathogens

Yoshimi Hirokawa [a,†], Hironori Kinoshita [a,*], Tomoyuki Tanaka [a], Takanori Nakamura [a], Koichi Fujimoto [b], Shigeki Kashimoto [b], Tsuyoshi Kojima [b], Shiro Kato [a]

[a] Chemistry Research Laboratories, Dainippon Sumitomo Pharma Co., Ltd, Enoki 33-94, Suita 564-0053, Japan
[b] Pharmacology Research Laboratories, Dainippon Sumitomo Pharma Co., Ltd, 3-1-98 Kasugade Naka, Konohana-ku, Osaka 554-0022, Japan

ARTICLE INFO

Article history:
Received 28 February 2008
Revised 27 April 2008
Accepted 2 May 2008
Available online 4 May 2008

Keywords:
Pleuromutilin
Gram-positive bacteria
MRSA
PRSP
VRE
Purine ring
Metabolic stability
MIC
Sulfide

ABSTRACT

In the course of our research aimed at the discovery of metabolic stable pleuromutilin derivatives with more potent antibacterial activity against Gram-positive pathogens than previous analogues, a series of compounds bearing a purine ring were prepared and evaluated. From SAR studies, we identified two promising compounds **85** and **87**, which have excellent in vitro activity against a number of Gram-positive pathogens, including existing drug-resistant strains, and potent in vivo efficacy.

The increasing use of antibacterial agents for infectious diseases has resulted in the emergence of resistant pathogens, especially Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae* (PRSP), and vancomycin-resistant *enterococci* (VRE).[1–3] To combat such drug-resistant bacterial strains, there is an increasing need to discover and develop novel classes of antibiotics, particularly agents with new mechanisms of action and consequently no cross-resistance to marketed antibacterial agents. In our search for promising lead structures that can be used as new antibiotics, we have focused our attention on the natural product pleuromutilin[4–7] (**1**), which has good antibacterial activity but insufficient in vivo potency.

The fused 5-6-8 tricyclic diterpenoid **1** was first isolated in 1951 from two basidiomycete species and was characterized as a crystalline antibiotic with modest in vitro activity against Gram-positive bacteria and mycoplasmas.[8] The antibiotic **1** selectively inhibits bacterial protein synthesis through interaction with prokaryotic ribosomes, but has no effect on eukaryotic protein synthesis and does not bind to mammalian ribosomes.[9] A Sandoz group prepared a number of semisynthetic pleuromutilin derivatives and reported initial SAR studies that focused on variations in the C14 glycolic acid side chain.[10–12] As a result, tiamulin (**2**) and valunemulin (**3**) were successfully developed as therapeutic agent for veterinary use.[13] Further chemical modifications of **1** aimed at producing an agent for human use that has sufficient antibacterial efficacy and is less prone to metabolic degradation than **1**. These efforts resulted in the 1980s in the development of azamulin (**4**).[14] Although **4** showed good in vitro antibacterial activity, its oral bioavailability was severely limited by atrocious solubility in water. Thus, **4** entered phase I clinical studies in volunteers but did not progress further. Recently, researchers at GlaxoSmithKline identified the novel pleuromutilin analogue retapamulin (**5**),[15] which shows excellent in vitro antibacterial activity and was therefore approved in 2007 as a topical antimicrobial agent for treatment of human skin infections. From previous SAR studies on **1**, analogues in which the hydroxyl of the C14 glycolic ester group in **1** was replaced with a substituent containing the sulfide linkage, show potent in vitro activity but suffer from being rapidly and extensively metabolized in vivo because of their strong hydrophobic nature. Quite recently, we reported the excellent in vitro and in

* Corresponding author. Tel.: +81 6 6337 5906; fax: +81 6 6337 6010.
E-mail address: hironori-kinoshita@ds-pharma.co.jp (H. Kinoshita).
† Present address: Faculty of Pharmacy, Osaka Ohtani University, 3-11-1 Nishikiori-kita, Tondabayashi, Osaka 584-8540, Japan.

0960-894X/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2008.05.011

vivo antibacterial activity of the structurally novel pleuromutilin analogue **6** having a purine ring as a polar and water solubilizing group.[16] The excellent in vivo efficacy of **6** showing good solubility in water may reflect good metabolic stability. In this communication we describe the synthesis and in vitro and in vivo antibacterial activities of these pleuromutilin derivatives having 4-piperidinethio moiety (see Fig. 1).

The purine-carboxylic esters **8a**–**11a**, **12b**, **13c**–**16c**, **17d**, **18e**, **19**–**37**, and **46**–**53** were prepared as shown in Scheme 1. Reaction of purine (**7a**) and 2-aminopurine (**7c**) with *tert*-butyl bromoacetate, *tert*-butyl 3-bromopropionate or *tert*-butyl acrylate, and *tert*-butyl propiolate gave a mixture of the corresponding 9- and 7-substituted purine esters **8a**, **10a**, **14c** and **9a**, **11a**, **15c**, respectively. After separation of the mixture by silica gel column chromatography, the less polar 9-substituted purine esters **8a** (51%), **10a** (19%), and **14c** (57%) and the more polar 7-substituted purine esters **9a** (32%), **11a** (4%), and **15c** (23%) were obtained.[17] Treatment of 6-amino-, 2-amino-, and 2,6-diaminopurine (**7b–d**) with *tert*-butyl 3-bromopropionate or *tert*-butyl acrylate and *tert*-butyl 4-bromobutyrate regioselectively furnished the 9-substituted purine esters **12b**, **13c**, **16c**, and **17d**. The 3-(2-amino-6-substituted purin-9-yl)propionic esters **19**–**26** were prepared by treatment of **18e**, which was obtained by reaction of 2-amino-6-chloropurine (**7e**) with *tert*-butyl acrylate, with methylamine, dimethylamine, and nitrogen-containing heteroalicycles, such as pyrrolidine, morpholine, piperazine, and piperidine rings. On the other hand, the 3-(2-amino-6-substituted purin-9-yl)propionic ethyl esters **28**–**37** having *N*-Boc substituent in the nitrogen-containing heteroalicycles were obtained by reaction of the corresponding ethyl ester **27**, which was prepared from **7e** and ethyl acrylate, with nitrogen-containing heteroalicycles bearing *N*-Boc substituent.

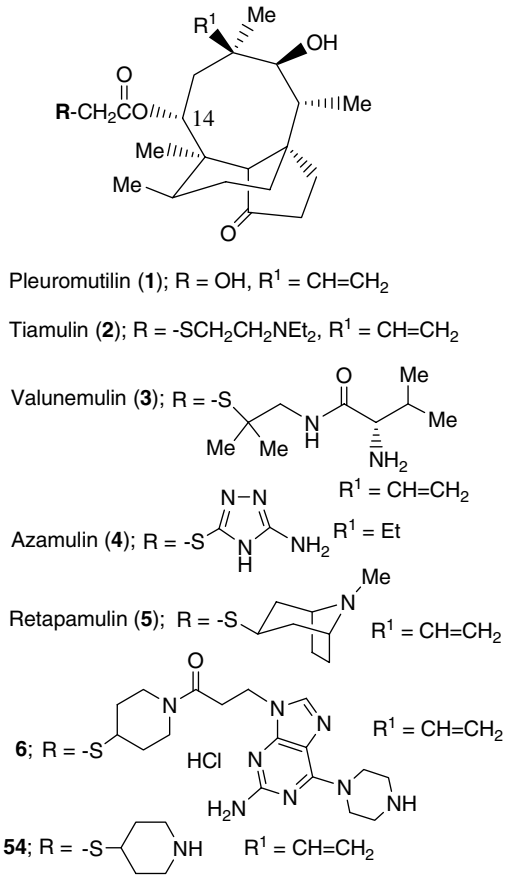


Figure 1. Structure of pleuromutilin derivatives.

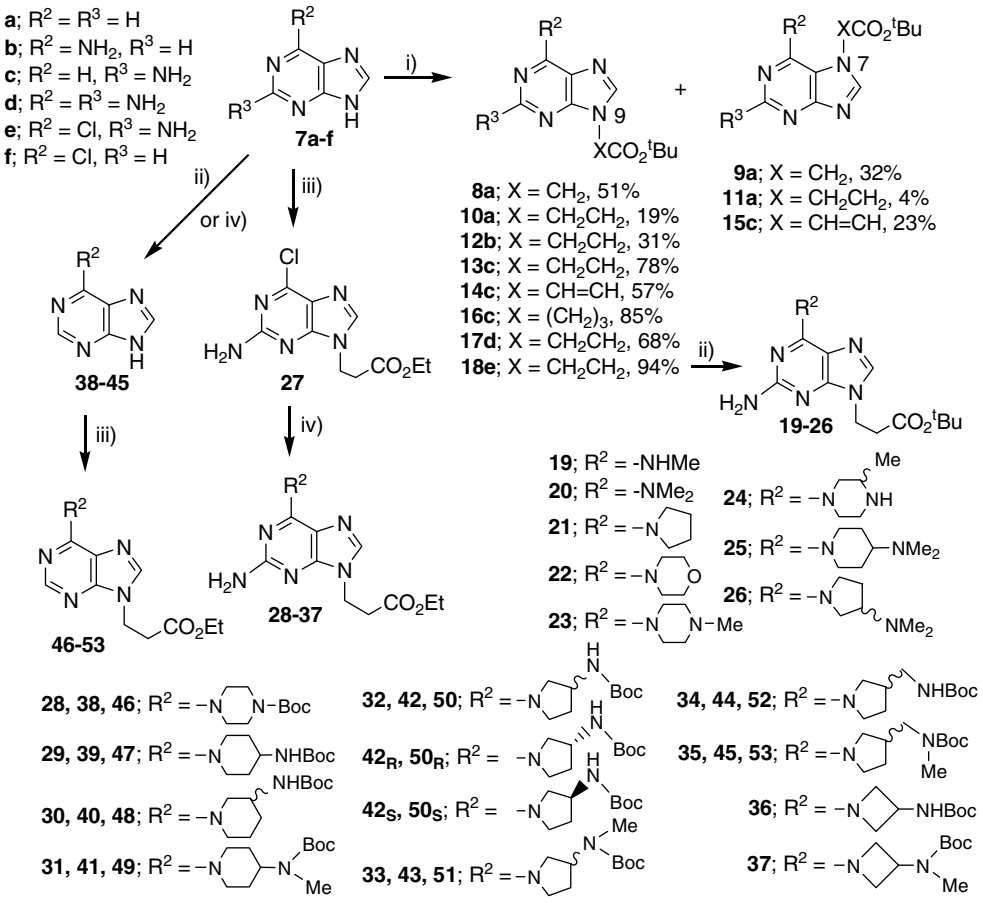
The 3-(6-substituted purin-9-yl)propionic ethyl esters **46**–**53** were prepared by the reverse method described for synthesis of **28**–**37**, that is, reaction of **7f** with nitrogen-containing heteroalicycles bearing *N*-Boc substituent, followed by alkylation of the resultants **38**–**45** with ethyl acrylate gave the desired esters **46**–**53**.

The pleuromutilin derivatives **55**–**89** shown in Tables 1–3 were prepared as illustrated in Scheme 2. Acid hydrolysis of the resultant *tert*-butyl esters **8a**, **10a**, **11a**, **12b**, **13c**, **14c**, **16c**, **17d**, and **19**–**26** using trifluoroacetic acid (TFA) afforded the corresponding (purin-7- or -9-yl)carboxylic acids. The 3-(purin-9-yl)propionic acids having *N*-Boc substituent in nitrogen-containing heteroalicycles were obtained by alkaline hydrolysis of the corresponding ethyl esters **28**–**37** and **46**–**53**. Condensation of the (purin-7- or -9-yl)carboxylic acids with **54**[10,11] in the presence of benzotriazole-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate as a coupling agent, and in the case of compounds having *N*-Boc substituent, successive acid hydrolysis gave **55**–**89** as a free base or a hydrochloride in moderate to good yields. The free base compounds **68**, **69**, **76**, and **83** having a basic nitrogen were treated with HCl in AcOEt to prepare the corresponding hydrochlorides. The chemical structures of all pleuromutilin derivatives obtained were confirmed by ^{1}H NMR and mass spectra and the purity was demonstrated by HPLC analysis. The pleuromutilin derivatives obtained as hydrochlorides showed good solubility in water (~50 mg/mL).

Initial screening for antibacterial activity[18] led to identification of the 3-(purin-9-yl)propionamide **55**, which showed potent in vitro activity against methicillin-susceptible *S. aureus* Smith (MSSA), *S. aureus* KMP9 (MRSA), penicillin-susceptible *S. pneumoniae* I (PSSP), and *Enterococcus faecium* KU1778 (VRE). Although **55** displayed similar activity against both susceptible (MSSA, PSSP) and resistant (MRSA, VRE) strains regardless of their susceptibility to other classes of antibiotics, its in vivo efficacy was characterized by a higher ED_{50} value (>3.13 mg/kg) against *S. aureus* Smith systemic infection model in mice. We therefore set out to investigate the influence of changes in the position and substituent, such as the amino group of the purine ring or the ethylene chain on the in vitro and in vivo antibacterial activities, while keeping the mutilin framework with its 4-piperidinylthio moiety as a spacer intact (Table 1). The 3-(purin-7-yl)propionamide **56** as a regioisomer of lead compound **55** showed slightly decreased in vitro activity. Shortening of the ethylene chain in **55** (giving **57**) caused a significant decrease in activity against all strains. Introduction of an amino group into the 6-position at the purine ring as in **58** led to poorer MIC values. On the other hand, the regioisomer **59** of **58**, that is, 3-(2-aminopurin-9-yl)propionamide was essentially equipotent to **55**. Quite surprisingly, **59** exhibited dramatic improvement of in vivo efficacy (ED_{50} = <3.13 mg/kg) compared with **55**, **56**, and **58**. Extension of the ethylene chain (giving **60**) and insertion of double bond (giving **61**) in the ethylene chain of **59** had no favorable influence on the in vitro or in vivo activity.

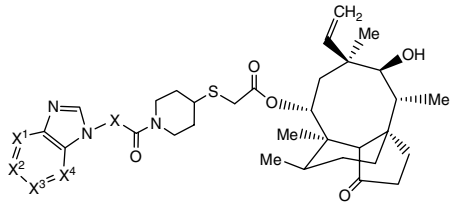
Influence of a change in the substituent at the 6-position in the 2-aminopurine ring of **59** was next examined (Table 2). Introduction of an amino group as in **62** substantially retained the in vitro activity against all strains compared with that of **59**, but the in vivo efficacy was not improved. Substitution by a methylamino or a dimethylamino group, or by a pyrrolidine or a morpholine ring (giving **63**–**66**, respectively) provided no favorable effect on the in vitro or in vivo activity. On the other hand, introduction of a piperazine ring (yielding **6**) improves in vivo efficacy.

In addition to MSSA, MRSA, PSSP, and VRE shown in Tables 1 and 2, MIC values of the pleuromutilin analogues **59**, **6**, and **67**–**89** against *S. pneumoniae* KT2524 (PRSP), *Streptococcus pyogenes*, *Moraxella catarrhalis*, and *Haemophilus influenzae*, all of which are common serious respiratory tract pathogen and their in vivo efficacy in mice are illustrated in Table 3, which also includes the



Scheme 1. Reagents and conditions: (i) $BrCH_2CO_2{}^tBu$, $Br(CH_2)_3CO_2{}^tBu$, $CH_2{=}CHCO_2{}^tBu$ ($Br(CH_2)_2CO_2{}^tBu$) or $CH{\equiv}CCO_2{}^tBu$, K_2CO_3 (Na_2CO_3), DMF (aq THF), 50–80 °C (reflux), 4–24 h; (ii) R^2H, K_2CO_3 (80 °C) or DBU (rt), DMF, 15 h; (iii) $CH_2{=}CHCO_2Et$, K_2CO_3, DMF, 80 °C, 24 h, 65%; (iv) R^2H, $^iPr_2NEt$, 2-PrOH, 20 h, >90%.

Table 1
In vitro and in vivo antibacterial activities of **55**–**61**

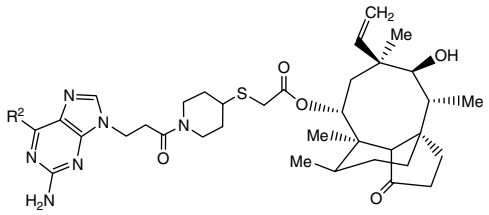


Compound	X^1	X^2	X^3	X^4	X	MIC[a] (μg/mL)				MSSA[b]
						MSSA[a]	MRSA[c]	PSSP[d]	VRE[e]	ED_{50}[f] (mg/kg, iv)
55	CH	N	CH	N	$(CH_2)_2$	0.05	0.05	0.1	0.05	>3.13
56	N	CH	N	CH	$(CH_2)_2$	0.1	0.1	0.1	0.1	>3.13
57	CH	N	CH	N	CH_2	0.2	0.2	1.56	0.2	NT[g]
58	C-NH_2	N	CH	N	$(CH_2)_2$	0.2	0.39	0.78	0.39	>3.13
59	CH	N	C-NH_2	N	$(CH_2)_2$	0.05	0.05	0.05	0.05	<3.13
60	CH	N	C-NH_2	N	$(CH_2)_3$	0.1	0.2	0.78	0.1	>3.13
61	CH	N	C-NH_2	N	CH=CH	0.1	0.2	0.39	0.2	>3.13

[a] Minimum inhibitory concentration (MIC): lowest concentration of compound that inhibits visible growth of the organism.
[b] MSSA, methicillin-susceptible *S. aureus* Smith.
[c] MRSA, *S. aureus* KMP9.
[d] PSSP, penicillin- susceptible *S. pneumoniae* I.
[e] VRE, *E. faecium* KU1778.
[f] The efficacy criterion, ED_{50}, was calculated as the dose at which mice survival rate was 50%. Mice were inoculated with each organism intraperitoneally. Medication was given intravenously once, 1 h after inoculation.
[g] NT, not tested.

activity of the earlier pleuromutilin analogue **4** and the marketed antibacterial agent vancomycin (VCM) for comparison. Compound **59**, which showed potent in vitro activity displayed strong in vivo efficacy with an ED_{50} value of 2.89 mg/kg. This value was much lower than that of **4** but approximately threefold higher than that of VCM. All compounds with the nitrogen-containing heteroalicy-

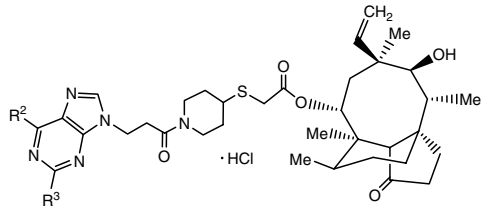
Table 2
In vitro and in vivo antibacterial activities of **6**, **59**, and **62**–**66**

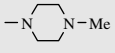
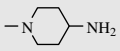
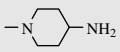
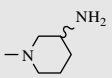
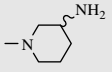
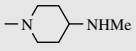
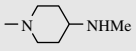
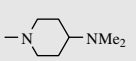


Compound	R^2	MIC[a] (μg/mL)				MSSA[b]
		MSSA[b]	MRSA[c]	PSSP[d]	VRE[e]	ED_{50}[f] (mg/kg, iv)
59	H	0.05	0.05	0.05	0.05	<3.13
62	NH_2	0.05	0.1	0.025	0.05	>3.13
63	NHMe	0.1	0.2	0.025	0.1	>3.13
64	NMe_2	0.1	0.1	0.05	0.1	>3.13
65		0.39	0.39	0.2	0.39	>3.13
66		0.2	0.2	0.1	0.2	NT[g]
6		0.25	0.5	0.063	0.25	<3.13

[a–g]See Table 1.

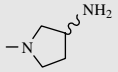
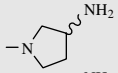
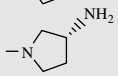
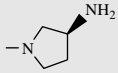
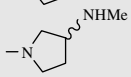
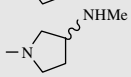
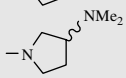
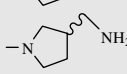
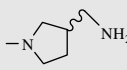
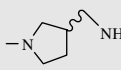
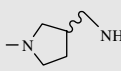
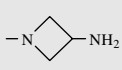
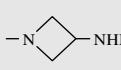
Table 3
In vitro and in vivo antibacterial activities of **6, 59**, and **67**–**89**



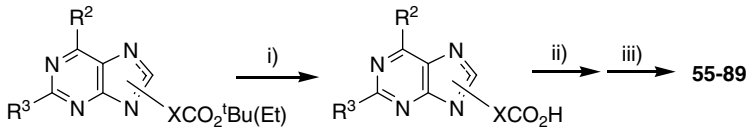
Compound	R^2	R^3	MIC[a] (μg/mL)								MSSA[b]
			MSSA[b]	MRSA[c]	PSSP[d]	PRSP[e]	*S. p.*[f]	VRE[g]	*M. c.*[h]	*H. i.*[i]	ED_{50}[j] (mg/kg, iv)
59	H	NH_2	0.05	0.05	0.125	0.063	0.063	0.05	0.25	2	2.89
6		NH_2	0.25	0.5	0.063	0.063	0.032	0.125	0.25	1	1.86 (1.51)[k]
67		H	0.063	0.063	0.032	0.032	0.016	0.032	0.032	1	2.94
68		NH_2	0.125	0.125	0.125	0.063	0.063	0.125	0.063	2	8.83
69		NH_2	0.25	0.25	0.063	0.063	0.032	0.125	0.063	2	2.21
70		NH_2	0.25	1	0.063	0.125	0.063	0.25	0.125	2	1.86
71		H	0.125	0.25	0.016	0.032	0.016	0.063	0.063	4	1.50
72		NH_2	0.25	1	0.063	0.063	0.032	0.25	0.125	2	2.21
73		H	0.125	0.125	0.016	0.032	0.016	0.032	0.032	1	2.21
74		NH_2	0.5	2	0.125	0.25	0.063	0.5	0.25	2	1.41
75		H	0.125	0.25	0.063	0.063	0.032	0.063	0.125	2	2.21
76		NH_2	0.25	0.25	0.063	0.063	0.032	0.125	0.063	2	1.72

(*continued on next page*)

Table 3 (*continued*)

Compound	R^2	R^3	MIC[a] (μg/mL)								MSSA[b]
			MSSA[b]	MRSA[c]	PSSP[d]	PRSP[e]	*S. p.*[f]	VRE[g]	*M. c.*[h]	*H. i.*[i]	ED_{50}[j] (mg/kg, iv)
77		NH_2	0.5	1	0.125	0.125	0.063	0.125	0.25	1	3.05
78		H	0.063	0.125	0.016	0.032	0.016	0.032	0.032	1	1.47
79		H	0.125	0.5	0.032	0.032	0.016	0.125	0.125	2	1.30
80		H	0.063	0.25	0.016	0.016	0.008	0.063	0.063	1	1.01
81		NH_2	0.25	1	0.063	0.063	0.032	0.25	0.125	1	1.72
82		H	0.063	0.25	0.016	0.032	0.016	0.032	0.063	2	1.61
83		NH_2	0.25	0.25	0.063	0.063	0.063	0.125	0.125	2	3.00
84		NH_2	0.5	2	0.063	0.125	0.032	0.5	0.125	4	2.84
85		H	0.125	0.5	0.016	0.032	0.008	0.125	0.063	1	0.59
86		NH_2	0.5	4	0.125	0.25	0.032	0.5	0.25	4	1.01
87		H	0.25	0.5	0.063	0.063	0.016	0.125	0.125	2	0.76
88		NH_2	0.5	1	0.063	0.125	0.063	0.25	0.25	1	3.04
89		NH_2	0.5	1	0.063	0.125	0.125	0.5	0.25	2	3.97
	4		0.5	2	0.5	0.5	0.25	0.25	0.032	0.5	(6.88)[k]
	VCM		1	0.5	0.25	0.5	0.5	>128	64	>128	0.88

[a–c, g, j] See Table 1a–c, e, f.
[d] *S. pneumoniae* ATCC49619.
[e] *S. pneumoniae* KT2524.
[f] *S. pyogenes* ATCC12344.
[h] *M. catarrhalis* K1209.
[i] *H. influenzae* TH13.
[k] Mice were inoculated with each organism and medication was given intravenously twice, 1 and 4 h after inoculation.



8a, 10a, 11a, 12b, 13c, 14c, 16c, 17d, 19-26, 28-37, 46-53

Scheme 2. Reagents and conditions: (i) TFA, CH_2Cl_2, rt, 2 h or 2 N NaOH/MeOH, reflux, 2 h; (ii) **54**, benzotriazole-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate, Et_3N, DMF, rt, 2 h; (iii) 30% HCl/EtOH, rt, 2 h or 4 M HCl/AcOEt.

cles at the 6-position in the purine ring were found to possess good to excellent in vitro activity against all strains compared with VCM. Furthermore, their in vivo efficacy was clearly superior to that of **4**.

As the 2-amino-6-piperazinylpurine analogue **6** shown in Table 2 displayed more potent in vivo efficacy than **59**, we decided to prepare its related piperazine derivatives. Removal of the 2-amino group from **6** (giving **67**) exhibited a higher in vitro activity against all strains, but the in vivo efficacy was less than that of **6**. Introduction of a methyl group into the piperazine ring of **6** (yielding **68** and **69**) did not improve the in vitro or in vivo activity. Replacement of the piperazine ring in **6** and **67** with a 4-aminopiperidine ring (giving **70** and **71**, respectively) generally had no favorable influence on the in vitro activity. However, **70** showed an in vivo efficacy comparable to that of **6** and the in vivo efficacy of **71** was almost twofold more potent than that of **67**. The 3-aminopiperidine derivatives **72** and **73** had an in vitro activity comparable to that of **70**

and **71**, respectively, but reduced in vivo efficacy. Introduction of a methyl group into the amino group on the 4-aminopiperidine ring of **70** and **71** (yielding **74**, **76**, and **75**, respectively) caused a slight decrease or increase in in vitro activity, while the in vivo efficacy of **74** was more potent than that of **70**. The in vivo efficacy of **75** and **76** did not improve. Furthermore, replacement of the piperazine ring in **6** with racemic 3-aminopyrrolidine (giving **77**) or 3-aminomethylpyrrolidine (giving **84**) ring led to a decrease in both the in vitro and in vivo antibacterial activities. On the other hand, the (±)-6-(3-aminopyrrolidin-1-yl)purine **78** and the (±)-6-(3-aminomethylpyrrolidine)purine **85** displayed excellent in vivo efficacy compared with **67** although their in vitro activity was comparable to that of **67**. In particular, **85** conferred the highest in vivo activity with an efficacy more potent than that of VCM (ED_{50} = 0.59 mg/kg). Next, the stereochemistry at the 3-position of the pyrrolidine ring of **78** was examined. Both compounds **79** and **80** with *R* and *S* configurations, respectively, as well as the racemic compound **78** showed excellent in vitro and in vivo activities. Introduction of a methyl group at the amino group of **77**, **78**, **84**, and **85** (giving **81**, **82**, **86**, and **87**, respectively) provided favorable influence on the in vivo efficacy, thus retaining (as in **82** and **87**) or slightly increasing the activity (as in **81** and **86**). Compound **87** showed excellent in vitro and in vivo antibacterial activities and was essentially equipotent to **85**. By contrast, the in vivo efficacy of the 3-dimethylaminopyrrolidine analogue **83** did not improve compared to that of **77**. Replacement of the piperidine ring of **6** by 3-amino- and 3-methylaminoazetizine rings (giving **88** and **89**, respectively) resulted in a significant decrease in in vivo efficacy.

As part of our research to develop novel pleuromutilin derivatives for human use, the polar and water solubilizing purine ring was introduced into the pleuromutilin C14 side chain. From SAR studies, we found that compounds **85** and **87** show not only excellent in vitro antibacterial activity against MRSA, PRSP, VRE, *S. pyogenes*, *M. catarrhalis*, and *H. influenzae* but also potent in vivo efficacy when compared to azamulin (**4**) and VCM. The excellent in vivo efficacy of these compounds, which also have good solubility in water, reflects good pharmacokinetics and ADME properties (data not shown). It is therefore believed that compounds **85** and **87** have potential as novel antibacterial agents for use in human. A more comprehensive study directed at optimization of these compounds will be reported in due course.

References and notes

1. Projan, S. J.; Youngman, P. J. *Curr. Opin. Microbiol.* **2002**, *5*, 463.
2. Livermore, D. M. *Clin. Infect. Dis.* **2003**, *36*, 1058.
3. Ohno, A. *Infect. Control* **2004**, *13*, 1012.
4. Hunt, E. *Drug Future* **2000**, *25*, 1163.
5. Anchel, M. *J. Biol. Chem.* **1952**, *199*, 133.
6. Arigoni, D. *Gazz. Chim. Ital.* **1962**, *92*, 884.
7. Birch, A. J.; Cameron, D. W.; Holzapfel, C. W.; Richards, R. W. *Chem. Ind.* **1963**, 374.
8. Drews, J.; Georgopoulos, G.; Laber, G.; Schutze, E.; Unger, J. *Antimicrob. Agents Chemother.* **1975**, *7*, 507.
9. Hogenauer, G. *Eur. J. Biochem.* **1975**, *52*, 93.
10. Riedl, K. *J. Antibiotics* **1976**, *29*, 132.
11. Egger, H.; Reinshagen, H. *J. Antibiotics* **1976**, *29*, 915.
12. Egger, H.; Reinshagen, H. *J. Antibiotics* **1976**, *29*, 923.
13. Hannan, P. C. T.; Windsor, H. M.; Ripley, P. H. *Res. Vet. Sci.* **1997**, *63*, 157.
14. (a) Berner, H.; Fischer, G.; Hildebrandt, J. F.; Laber, G.; Vyplel, H. *Curr. Chemother. Immunother.* **1982**, *1*, 345; (b) Hildebrandt, J. F.; Berner, H.; Laber, G.; Turnowsky, F.; Schütze, E. *Curr. Chemother. Immunother.* **1982**, *1*, 346; (c) Wenzel, A. F.; Baumgartner, R.; Georgopoulos, A.; Hildebrandt, J. F.; Laber, G.; Schütze, E.; Walzl, H. *Curr. Chemother. Immunother.* **1982**, *1*, 347.
15. Draghi, D.; Scangarella, N.; Shawar, R.; Sahm, D. *Abstract 1900*, Presented at the 45th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, Dec 16–19, 2005.
16. Hirokawa, Y.; Kinoshita, H.; Tanaka, T.; Nakata, K.; Kitadai, N.; Fujimoto, K.; Kashimoto, S.; Kojima, T.; Kato, S. *J. Med. Chem.* **2008**, *51*, 1991.
17. Green, G. R.; Grinter, T. J.; Kincey, P. M.; Jarvest, R. L. *Tetrahedron* **1990**, *46*, 6903.
18. *National Committee for Clinical Laboratory Standards 2000. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically,* 5th ed.; Approved Standard M7 A5; National Committee for Clinical Laboratory Standards: Wayne, PA, 2000.