Bioorganic & Medicinal Chemistry Letters 19 (2009) 6424–6428

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Synthesis and biological activity of novel oxazolidinones

Biswajit Das [a,*], A. V. S. Rajarao [a], Sonali Rudra [a], Ajay Yadav [a], Abhijit Ray [a], Manisha Pandya [b], Ashok Rattan [b], Anita Mehta [a]

[a] Department of Medicinal Chemistry, New Drug Discovery Research, Ranbaxy Research Laboratories, Plot-20, Sector-18, Udyog Vihar, Gurgaon 122001, India
[b] Department of Infectious Diseases, New Drug Discovery Research, Ranbaxy Research Laboratories, Plot-20, Sector-18, Udyog Vihar, Gurgaon 122001, India

ARTICLE INFO

Article history:
Received 29 August 2008
Revised 7 January 2009
Accepted 14 September 2009
Available online 17 September 2009

Keywords:
Antibacterial
Oxazolidinone
Nitro-furan
Ranbezolid

ABSTRACT

A number of 5-substituted derivatives of Ranbezolid, a novel oxazolidinone were synthesized. Antibacterial activity of the compounds against a number of sensitive and resistant bacteria showed promising results.

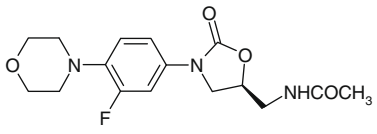
© 2009 Elsevier Ltd. All rights reserved.

Oxazolidinones were first discovered in the late 1970s at DuPont and were of great interest in view of their activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *Staphylococcus* epidermidis (MRSE). These strains were becoming increasingly problematic in clinical settings. As the scenario of infectious diseases changed in the 1990s, oxazolidinones were also found to exhibit potent activity against more recently problematic penicillin-resistant *Streptococcus pneumoniae* (PRSP) strains and the vancomycin-resistant *Enterococcus faecium* (VRE) and vancomycin-intermediate *Staphylococcus aureus* (VISA).[1,2] The oxazolidinone class also exhibits activity against multi-drug resistant mycobacterium tuberculosis strains. Oxazolidinones are orally active synthetic antibacterial agents that act by inhibiting protein synthesis at the ribosomal level. Their unique mode of action offers a potential for low cross resistance with existing antimicrobial protein synthesis inhibitors.[3,4]

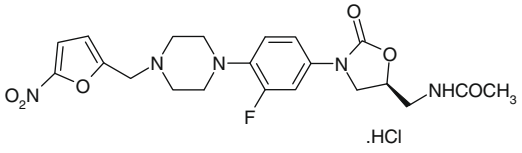
Linezolid,[5] the first member of the oxazolidinone class to be introduced by Pharmacia in 2000 was approved for the treatment of multi-drug resistant gram-positive infections such as nosocomial and community acquired pneumonia and skin infections.

Recently, linezolid-resistant isolates[6] have been reported and the development of resistance necessitates the urgent exploration of new oxazolidinone series with greater potency and a broader spectrum of activity.

The SAR of the oxazolidinone C-5 side chain has been extensively explored by the DuPont group in their early studies.[7] It



Linezolid



Ranbezolid

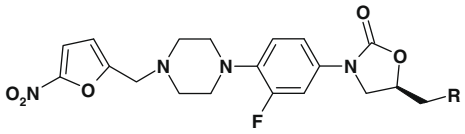
was found that minor variations in the acetamidomethyl group at C-5 position led to a decrease in activity. In other studies, Bayer and Versicor showed that sulfur isosteres of the acetamidomethyl side chain such as thioamides, thioureas or thiocarbamates could also give highly potent compounds, often better than the acetamido derivatives.[8] Phillips et al.[9,10] reported the synthesis and antibacterial activity of 5-substituted oxazolidinones with various substituents at the 5-position of the oxazolidinone ring. Gravestock et al. from AstraZeneca reported on a new class of antibacterial oxazolidinone with C-5 methylene O-linked and N-linked heterocyclic side chains.[11]

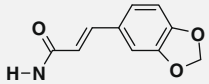
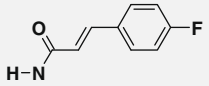
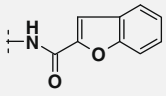
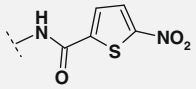
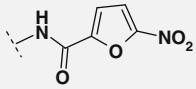
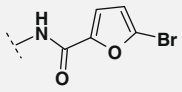
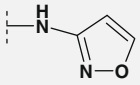
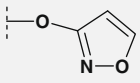
As part of the Ranbaxy oxazolidinone discovery program, RBx 7644 (Ranbezolid) was developed as a clinical candidate.[12] In the

* Corresponding author. Tel.: +91 124 2342001–10x5172; fax: +91 124 234544.
E-mail address: biswajit.das@ranbaxy.com (B. Das).

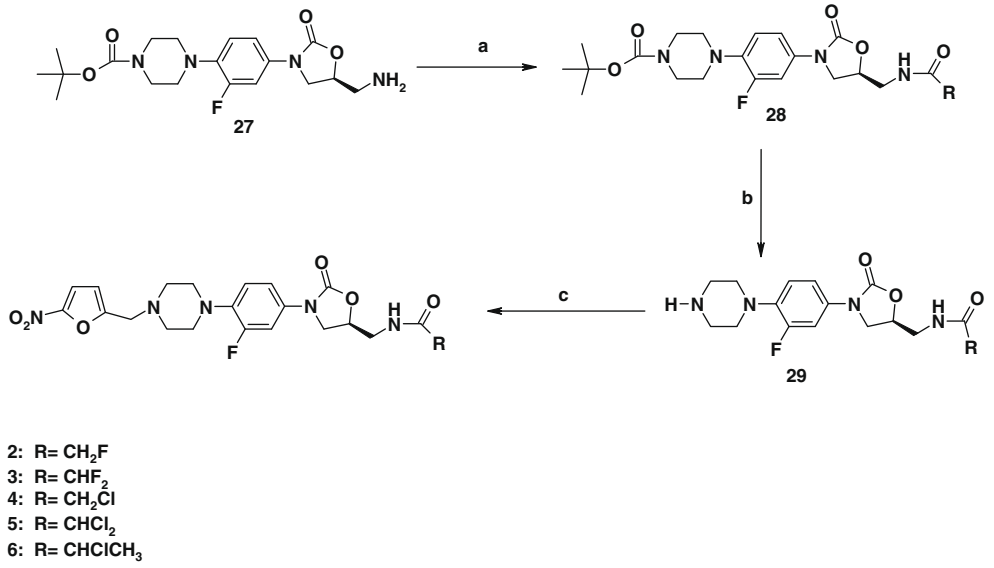
0960-894X/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2009.09.054

Table 1
Chemical yield and in-vitro activity of compounds **1–26**



Compd	R	% Yield[a]	MIC (μg/mL) (organisms)[b]							
			S.au 25923	*S.au* 15187	MRSA 562	MRSA 33	*E.fa* 29212	VRE 6A	*S.py* 19615	*S.pn* 6303
1	NH_2	61	>16	>16	>16	>16	>16	>16	>16	>16
2	$NHCOCH_2F$	50	4	2	2	4	4	4	0.5	1
3	$NHCOCHF_2$	22	2	1	2	2	2	2	0.5	0.5
4	$NHCOCH_2Cl$	38	2	2	2	2	2	2	0.5	0.5
5	$NHCOCHCl_2$	50	>16	>16	>16	>16	>16	>16	>16	>16
6	$NHCOCHClCH_3$	48	>16	>16	>16	>16	>16	>16	>16	>16
7	NCS	54	>16	>16	>16	>16	>16	>16	>16	>16
8	$NHCSSCH_3$	45	>16	>16	>16	>16	>16	>16	>16	>16
9	$NHCSCH_3$	20	1	1	1	1	1	1	0.5	0.25
10	$NHCSOCH_3$	24	2	2	2	2	1	1	1	0.5
11	$NHCSNH_2$	50	1	1	1	1	0.5	1	0.25	<0.06
12	$NHCSN(CH_3)_2$	53	>16	>16	>16	>16	>16	>16	>16	>16
13	$NHCOCH_2OCH_3$	50	>16	>16	>16	>16	>16	>16	>16	>16
14	NHCHO	56	4	2	2	2	2	4	0.5	1
15	$NHCOOCH_3$	25	8	8	2	8	8	8	1	1
16	$NHCOOC_2H_5$	23	>16	>16	>16	>16	>16	>16	>16	>16
17	NHCOCH=CHPh	50	>16	>16	>16	>16	>16	>16	>16	>16
18		50	>16	>16	>16	>16	>16	>16	>16	>16
19		18	>16	>16	>16	>16	>16	>16	>16	>16
20		25	>16	>16	>16	>16	>16	>16	>16	>16
21		12	>16	>16	>16	>16	>16	>16	>16	>16
22		14	8	2	1	2	4	>8	>8	8
23		17	>16	>16	>16	>16	>16	>16	>16	>16
24		50	2	2	2	2	2	2	1	1
25	OH	22	>16	>16	>16	>16	>16	>16	>16	>16
26		50	>16	>16	>16	>16	>16	>16	>16	>16
	Linezolid		2		2	2	2	2	2	2
	Ranbezolid		1		2	2	2	2	0.125	0.125

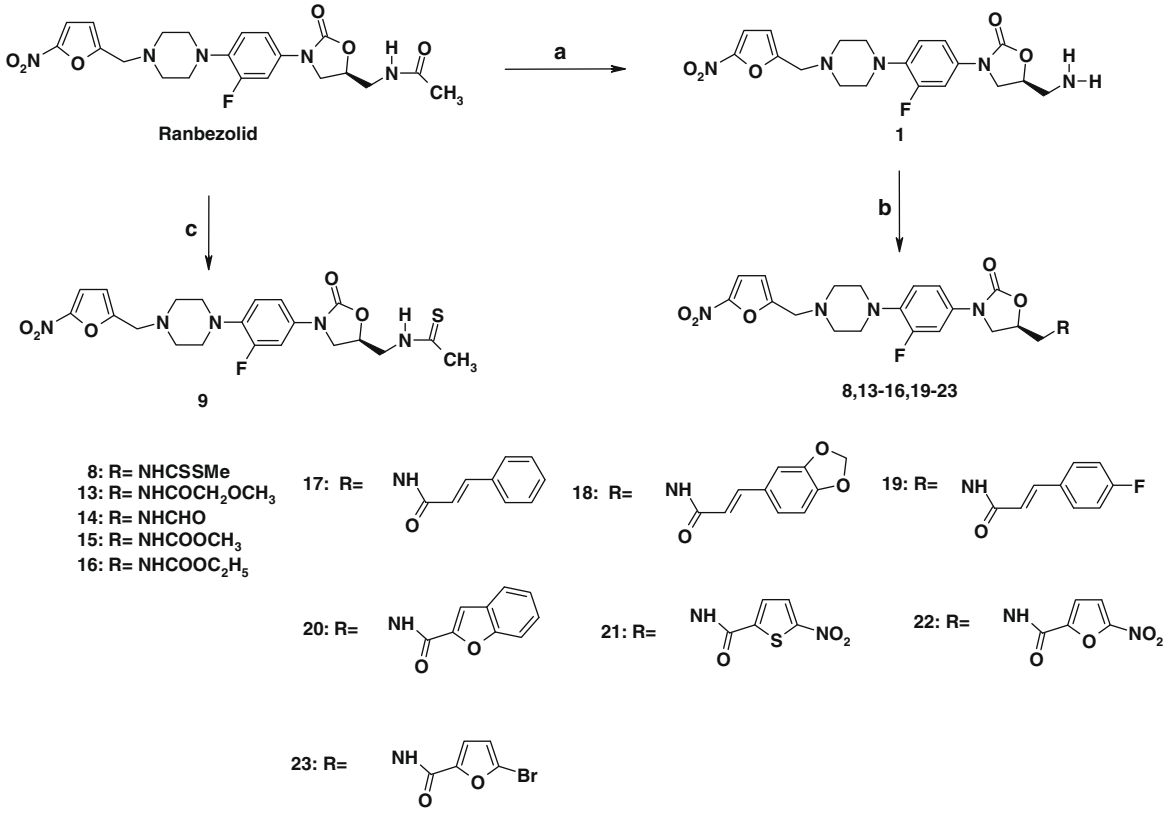
[a] % Yield: chemical yield in the final step of the synthetic sequence.
[b] Organisms: *S.au* 25923, *Staphylococcus aureus* ATCC 25923; *S.au* 15187, *Staphylococcus aureus* 15187; MRSA 562, methicillin-resistant *Staphylococcus aureus* 562; MRSA 33, methicillin-resistant *Staphylococcus aureus* 33; *E.fa* 29212, *Enterococcus faecalis* ATCC 29212; VRE 6A, vancomycin-resistant *Enterococcus faecium* 6A; *S.py* 19615, *Streptococcus pyogenes* ATCC 19615; *S.pn* 6303, *Streptococcus pneumoniae* ATCC 6303.



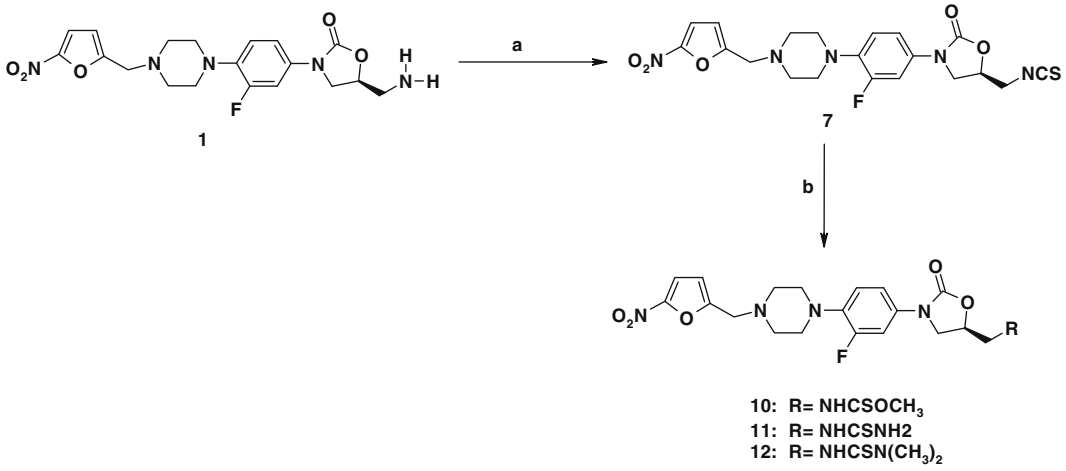
Scheme 1. Reagents and conditions: for compounds **2**–**6** (a) HOBT, NMM, EDC, DMF, carboxylic acid, 0 °C to rt for 24 h; (b) TFA, DCM, 0 °C to 10 °C, 2 h; (c) 5-nitrofuran-2-carboxaldehyde, sodium triacetoxyborohydride, THF, molecular sieve (4 Å), rt, 24 h.

present Letter we wish to report the synthesis and antibacterial activity of novel C-5 substituted derivatives of Ranbezolid. The different types of substituents that are incorporated are mentioned in Table 1 (compds **1**–**26**). Compounds **2**–**6** consist of derivatives wherein the acetamido methyl group was replaced by haloalkyl derivatives. Compounds bearing formamide (**14**), carbamate (**15**, **16**), thioamide (**9**), thiocyanide (**7**), thioester (**8**), thioketone (**9**), thiourea (**11**, **12**), methoxymethylacetamide (**13**) and cinnamoyl (**17**–**19**) groups were also synthesized. In another set of compounds, the heterocyclic derivatives (**20**–**22**, **24**, **26**) were synthesized.

A number of halomethyl and cinnamoyl derivatives of Ranbezolid were synthesized (Scheme 1). The amine **27**[13] on treatment



Scheme 2. Reagents and conditions: (a) 1 N HCl (aq), reflux, 8 h; (b) for **8**: TEA, dichloromethane, CS_2, 0 °C to rt, 7 h, then CH_3I, rt, 30 min; for **13**: TEA, dichloromethane, methoxyacetyl chloride, 0 °C to rt, 18 h; for **14**: ethyl formate, 80 °C, 18 h; for **15**, **16**: TEA, dichloromethane, then methyl chloroformate for or ethyl chloroformate, 0 °C to rt, 18 h; for **17**–**23**: HOBT, NMM, EDC, DMF, cinnamic acid, 3,4-methylenedioxycinnamic acid, 4-fluorocinnamic acid, benzofuran-2-carboxylic acid, 5-nitro-2-thiophene carboxylic acid, 5-nitro-2-furoic acid, 5-bromo-2-furoic acid respectively, at 0 °C to rt, 24 h; (c) Lawesson's reagent, toluene, 90 °C.

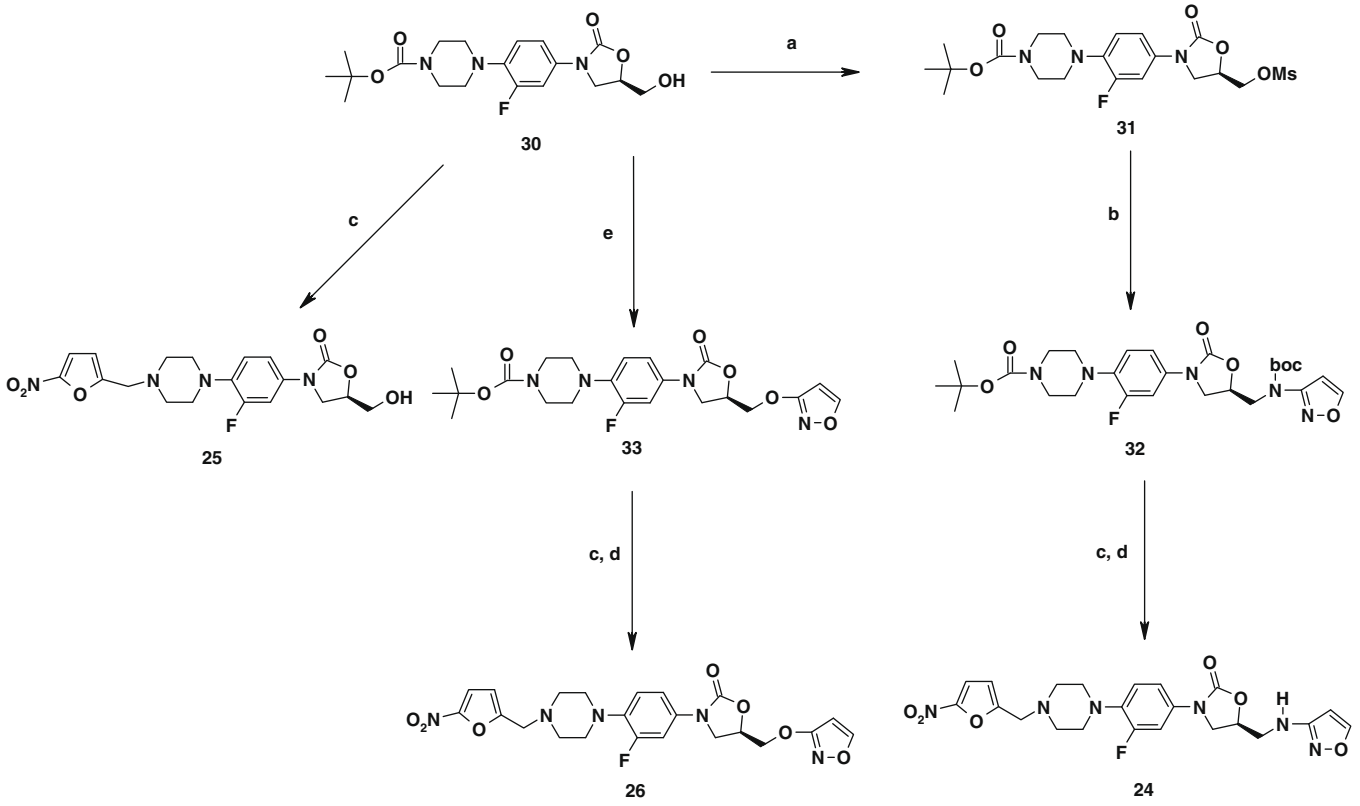


Scheme 3. Reagents and conditions: (a) CS_2, TEA, THF, rt, 5 h, 0 °C, ethylchloroformate, 2 h; (b) **10**: MeOH, TEA, diethylamine hydrochloride, rt, 2 h; for **11**: MeOH, methanolic ammonia, 0 °C, 3 h; for **12**: dimethylamine, MeOH, 0 °C to rt, 3 h.

with different carboxylic acids or acyl chlorides gave the respective amides (**28**). The Boc-group was removed under acidic conditions and the subsequent compounds subjected to a reductive amination reaction to give nitrofuran compounds (**2**–**6**, **17**, **18**).

A number of other amides in which the methyl group was replaced by different heteroaroyl groups is mentioned in Scheme 2. According to this procedure, the acetamido group of Ranbezolid was hydrolyzed by hydrochloric acid to give the corresponding amino compound (**1**). The desired amide derivatives (**8**, **13**–**16**, **19**–**23**) were made from amine **1** using alkyl and acyl chlorides in the presence of base in dichloromethane. Treatment of Ranbezolid with Lawesson's reagent produced the thioamide derivative **9**. In Scheme 3, a number of thiocarbamates **(10)**, and thioureas **(11**, **12)** were prepared from thiocyanide derivative (**7**) using methanol, ammoniacal methanol and dimethylamine. Compound (**7**) was synthesized from amine (**1**) using carbondisulphide and triethylamine.

In Scheme 4, the O-substituted derivative (**26**) and the N-substituted derivative (**24**) at the C-5 position were made from the hydroxyl methyl derivative (**30**). When this hydoxymethyl compound (**30**) was treated with 2-hydroxy isoxazole and DIAD compound **33** was formed. Compound **33** was treated with trifluo-



Scheme 4. Reagents and conditions: TEA, MsCl, DCM, 0 °C to rt, 4 h; (b) NaH, *N*-boc-2-aminoisoxazole, DMF, 80 °C, 2 h; (c) TFA, DCM, 0 °C, 2 h, THF, molecular sieves (4 Å); (d) 5-nitro-furan-2-carboxaldehyde, sodium triacetoxyborohydride, rt, 24 h; (e) 2-hydroxyisoxazole, diisopropylazadicarboxylate, PPh_3, THF, 5 °C to rt, 2 h.

roacetic acid in dichloromethane to remove Boc-group, this NH compound was then subjected to reductive amination to give compound **26**. By using similar method compound **25** was obtained from compound **30**. Similarly *N*-isoxazole derivative (**24**) was obtained from mesylderivative (**31**) by treatment with Boc protected aminoisoxazole followed by Boc deprotection in acidic condition.

Compounds were tested in-vitro against a panel of gram-positive bacteria. MIC values were determined using the NCCLS method and Ranbezolid and Linezolid were used as reference standards.

When the 5-acetamido methyl group of Ranbezolid was replaced by difluoromethyl and chloromethyl, the resulting compounds (**3**, **4**) showed comparable activity to Ranbezolid and Linezolid against S. au sensitive and resistant strains but their activity against *S. pyogenes* and *S. pneum* were four fold superior to Linezolid and four fold inferior to Ranbezolid. Compound **2**, in which the methyl group was replaced by fluoromethyl showed slightly inferior activity against different gram-positive strains compared to Ranbezolid. When the group was replaced by a dichloromethyl, chloromethyl or methoxymethyl group (**5**, **6**, **13**), a significant decrease in activity was observed. When the methyl group was replaced by aryl substituents (**20**–**23**), reasonable activity was only observed for nitrofuran compound **22**. Substituted cinnamoyl derivatives (**17**–**19**) uniformly led to weakly active compounds. Among the sulfur containing compounds (**7**–**12**) only the thioamide and thiourea derivatives (**9**, **11**) showed better activity than Ranbezolid. The methyl and ethyl carbamate derivatives (**15**, **16**) and the formamide showed inferior activity to Ranbezolid. When the acetamide group was replaced with an N-linked 3-substitued oxazole, the compound (**24**) showed comparable activity to Ranbezolid and Linezolid. The 5-hydroxymethyl derivative (**25**) and its O-linked oxazole derivative (**26**) showed weak activity against target pathogens.

In summary, only a very few 5-substituted derivatives were tolerated in the place of the acetamidomethyl group of Ranbezolid, and these were the thioamide, thiourea, and difluoromethyl derivatives (**9**, **11**, **3**). It appears therefore that with the exception of the reasonably potent nitrofuran (**22**), active compounds require a relatively small substituent at the C-5 position of the oxazolidinone ring (compare **4** with **5**, **6**, **13**; **9** with **8**; **11** with **12**; and **15** with **16b 17**, **18**, **19**).

Acknowledgments

We would like to thank Drs Pradip Bhatnagar, Ian A. Cliffe and Dharam Vir for their valuable comments; and the Analytical Dept. for the spectral data.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.09.054.

References and notes

1. Appelbaum, P. C. *Clin. Infect. Dis.* **1992**, *15*, 77.
2. Green, M.; Binezewski, B.; Pasculle, A. W.; Edmund, M.; Barvadova, K.; Kusne, S.; Shiles, D. M. *Antimicrob. Agents Chemother.* **1993**, *37*, 1238.
3. Swaney, S. M.; Aoki, H.; Ganoza, M. C.; Shinabarger, D. L. *Antimicrob. Agents Chemother.* **1998**, *42*, 3251.
4. Aoki, H.; Ke, L.; Poppe, S. M.; Poel, T. J.; Weaver, E. A.; Gadwood, R. C.; Thomas, R. C.; Shinabarger, D. L.; Ganoza, M. C. *Antimicrob. Agents Chemother.* **2002**, *46*, 1080.
5. Brickner, S. J.; Hutchinson, D. K.; Barbachyn, M. R.; Manninen, P. R.; Ulanowicz, D. A.; Garmon, S. A.; Grega, K. C.; Hendges, S. K.; Toops, D. S.; Ford, C. W.; Zurenko, G. E. *J. Med. Chem.* **1996**, *39*, 673.
6. Tsiodras, S.; Gold, H. S.; Sakoulas, G.; Eliopoulas, G. M.; Wennersten, C.; Venkataraman, L.; Moellering, R. C., Jr.; Ferraro, M. *Lancet* **2001**, *358*, 207.
7. Gregory, W. A.; Britelli, D. R.; Wang, C. L. J.; Wuonola, M. A.; McRipley, R. J.; Eustice, D. C.; Eberly, V. S.; Bartholomew, P. T.; Slee, A. M.; Forbes, M. *J. Med. Chem.* **1989**, *32*, 1673.
8. Hutchinson, D. K. *Curr. Top. Med. Chem.* **2003**, *3*, 1021.
9. Phillips, O. A.; Udo, E. E.; Ali, A. A. M.; Al-Hassawi, N. *Bioorg. Med. Chem.* **2003**, *11*, 35.
10. Phillips, O. A.; Udo, E. E.; Ali, A. A. M.; Samuel, S. M. *Bioorg. Med. Chem.* **2005**, *13*, 4113.
11. Gravestock, M. B.; Acton, D. G.; Betts, M. J.; Dennis, M.; Halter, G.; McGregor, A.; Swain, M. L.; Wilson, R. G.; Woods, L.; Wookey, A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4179.
12. Das, B.; Rudra, S.; Yadav, A. Y.; Ray, A.; Raja Rao, A. V. S.; Srinivas, A. S. S. V.; Soni, A.; Saini, S.; Shukla, S.; Pandya, M.; Bhateja, P.; Malhotra, S.; Mathur, T.; Arora, S. K.; Rattan, A.; Mehta, A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4261.
13. Hutchinson, D. K.; Brickner, S. J.; Gammill, R. V.; Patel, M. V. US 700799.