Pergamon

Bioorganic & Medicinal Chemistry Letters 11 (2001) 529–531

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Synthesis of Analogues of the *O*-β-D-Ribofuranosyl Nucleoside Moiety of Liposidomycins. Part 1: Contribution of the Amino Group and the Uracil Moiety upon the Inhibition of MraY

C. Dini,[a,*] N. Drochon,[a] S. Feteanu,[b] J. C. Guillot,[a] C. Peixoto[a] and J. Aszodi[a]

[a]*Medicinal Chemistry Department, Aventis Pharma, 102 route de Noisy, 93235 Romainville Cedex, France*
[b]*Infectious Disease Group, Aventis Pharma, 102 route de Noisy, 93235 Romainville Cedex, France*

Received 4 October 2000; revised 4 December 2000; accepted 7 December 2000

Abstract—The *O*-β-D-ribofuranosyl nucleoside **I** is the minimal structural entity of liposidomycins maintaining enzyme inhibitory activity. Modifications performed on both the primary amine and the uracil moieties clearly demonstrate their major contribution to the inhibition of the bacterial translocase (MraY).

Introduction

Translocase (MraY)[1] is involved in the biosynthesis of peptidoglycan, and has lately been shown to be essential for the survival of bacteria.[2] Consequently, it is a target of choice for the discovery of new antibacterial agents in view of bringing a solution to today's antibiotic resistance.[3] In a recent publication,[4] we have identified **I** and **II** (Fig. 1) as inhibitors of this enzyme. Compound **I** corresponds to the minimal active part of the liposidomycin (LPM) structure,[5] as predicted by SAR studies that compared this family of naturally occurring inhibitors of MraY and tunicamycins (TCMs).[6] Introduction of a specific chiral centre (**II**) further improved the activity.

In parallel to this study, we have undertaken a program for understanding the role played by the substituents present in **I**. In this paper, we wish to report our work to establish the importance of the primary amine, as well as the uracil moiety of **I** upon the inhibition of MraY.

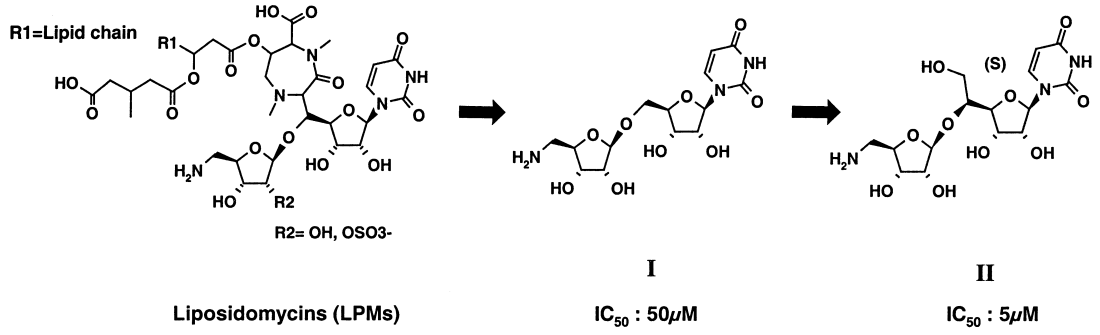
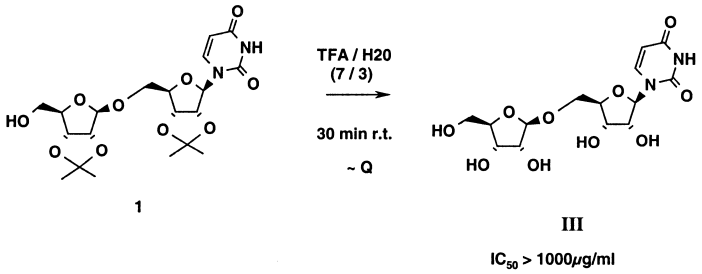


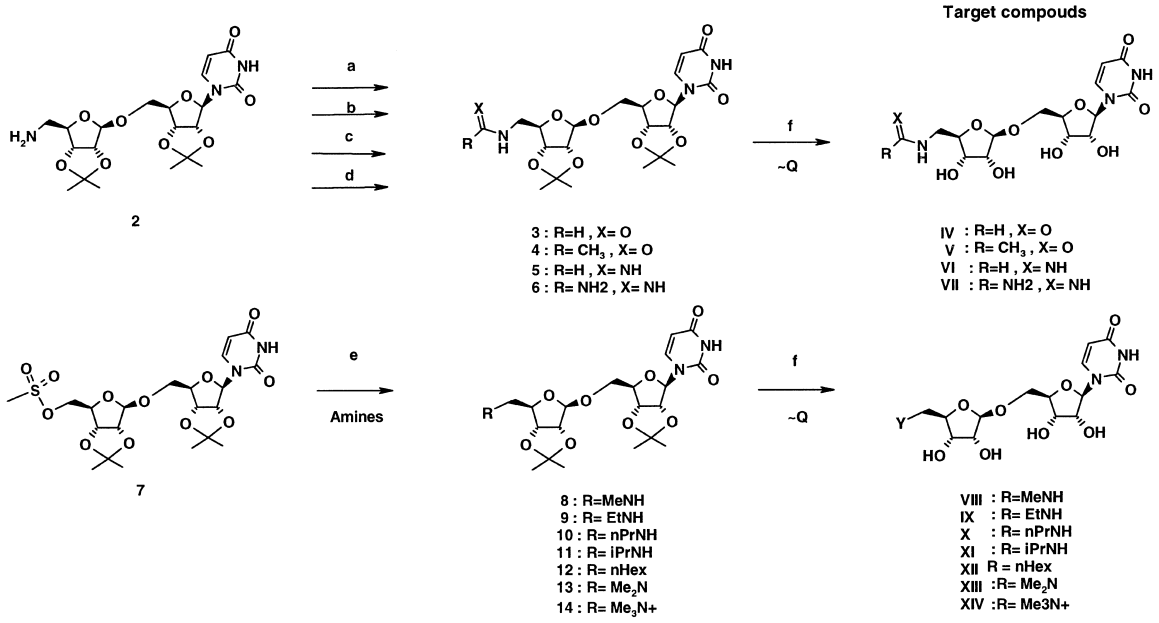
Figure 1.

*Corresponding author. Tel.: +33-(0)1-49-91-5480; +33-(0)1-49-91-5087; e-mail: christophe.dini@aventis.com

0960-894X/01/$ - see front matter
PII: S0960-894X(00)00715-0



Scheme 1.



Scheme 2. (a) HCO_2H, $(Im)_2CO$, CH_2Cl_2, rt, 2 h, 62%, (b) Ac_2O, pyridine, rt 1 h, 98%, (c) $H_2NCH{=}NH.HCl$, MeOH, 18 h, rt, 56%, (d) 1*H*-pyrazol-1-carboxamidine, hydrochloride, MeOH, 18 h, rt, 74%, (e) 'amine', H_2O, 4–18 h, 70 °C, (f) TFA/H_2O (7:3), 30 min, rt.

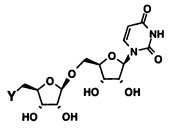
Chemistry and Biology

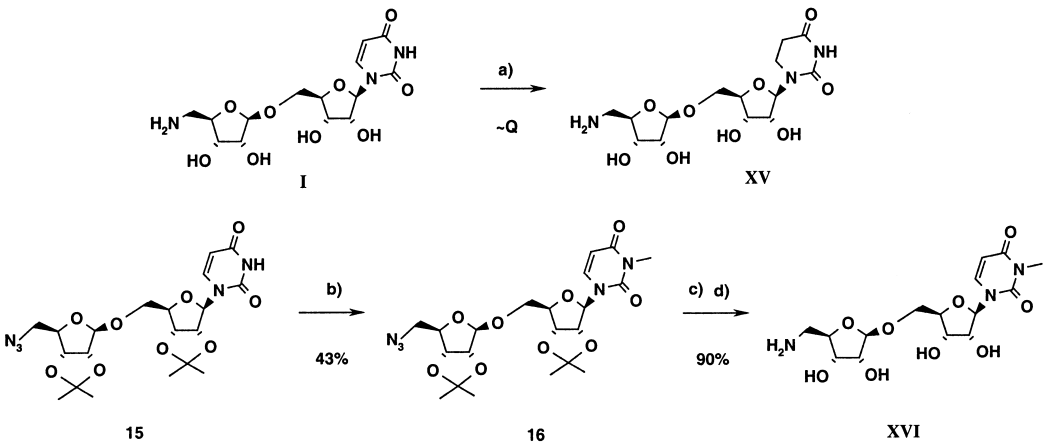
For a rapid insight into the importance of the amino group, we first synthesised **III** from **1**[4] by cleavage of both acetonide-protecting groups with 70% aqueous trifluoroacetic acid. Compound **III**, with a hydroxyl group in the 5″ position instead of a primary amine, is inactive in the translocase inhibitory assay[4] (Scheme 1).

For further SAR studies a set of differently substituted analogues of **I** in the 5″ position has been prepared by using available intermediates **2** and **7**[4] (Scheme 2). Formylation of **2** with formic acid and *N*,*N*′-carbonyldiimidazole led to **3**. Acetylation of **2** by acetic anhydride and pyridine provided **4**. The amidine **5** was prepared by condensation of **2** with formamidine hydrochloride. The guanidine analogue **6** was obtained by reaction of 1*H*-pyrazol-1-carboxamidine with **2**. Compounds **8**–**14** were prepared in parallel, using the same starting material **7**.[4] Intermediate **7** was added to different amine solutions contained in capped pressure resistant vials. The reaction mixtures were heated for 4–18 h (depending on the amine reactivity), at 70 °C. After evaporation of the solvents, the resulting crude compounds were purified through silica gel cartridges. Compounds **8**–**14** were recovered with yields varying from 36 to 80%. Finally, compounds **3**–**6** and **8**–**14** were deprotected using 70% aqueous trifluoroacetic acid giving rise to the expected products (**IV**–**XIV**) in almost quantitative yields.

The inhibitory activity (IC_{50}) of these compounds on translocase is summarised in Table 1.

Table 1.

	Y	Inhibitory activity on translocase IC_{50} (μM)
I (reference)	H_2N-	50
III	HO–	>1000
IV	HCONH–	>1000
V	CH_3CONH-	>1000
VI	$HC(NH)NH-$	30
VII	$H_2NC(NH)NH-$	25
VIII	MeNH–	45
IX	EtNH–	150
X	*n*PrNH–	140
XI	*i*PrNH–	180
XII	$CH_3(CH_2)_5NH-$	130
XIII	Me_2N-	>1000
XIV	Me_3N^+-	>1000



Scheme 3. (a) Pd/C, MeOH, 30 min, rt; (b) NaH, CH_3I, DMF, 4 h, rt; (c) PPh_3, H_2O, THF; (d) TFA/H_2O (7:3), 30 min, rt.

Analysis of the results suggests that a basic function is required in the 5″ position to get a good inhibitory activity. However, among basic groups, only secondary amines, amidine, and guanidine are tolerated (**VI**–**XII**). Tertiary and quaternary amines (**XIII** and **XIV**) as well as acylated derivatives (**IV** and **V**) are inactive. In the secondary amine series (**VIII**–**XII**), the length of the side chain has no (**VIII**) or a moderate effect (**IX**–**XII**) on the inhibitory potency. These latter derivatives being three to four times less active than **I**.

Other experiments were carried out on the uracil moiety in order to define further the pharmacophore (Scheme 3). Palladium catalysed reduction of the uracil double bond of **I** gave **XV**. Methylation of the imide group of **15**[4] with methyl iodide using NaH in DMF led to **16**. Subsequent reduction with PPh_3 and H_2O gave the corresponding amine, which was immediately converted to **XVI** by cleavage of both acetonide groups with 70% aqueous trifluoroacetic acid.

Compounds **XV** and **XVI** were tested on the translocase assay. No activity was detected at >1000 (μM).

Throughout this study, we have demonstrated that both the amino group and an intact uracil moiety are critical for the inhibition of the bacterial translocase and must be considered as a part of the pharmacophore of this family of inhibitors. The primary amine, however, can be replaced by isosteres (i.e., secondary amines or amidine or guanidine).

References

1. Struve, G. W.; Sinha, R. K.; Neuhaus, F. C. *Biochemistry* **1966**, *5*, 82.
2. Boyle, D. S.; Donachie, W. D. *J. Bacteriol.* **1998**, *180*, 6429.
3. Mitscher, L. A.; Pillai, S. P.; Gentry, E. J.; Shankel, D. M. *J. Med. Chem. Res. Rev.* **1999**, *19*, 477.
4. Aszodi, J.; Dini, C.; Collette, P.; Drochon, N.; Guillot, J. C.; Lemoine, G.; Mauvais, P. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1839.
5. Kimura, K.; Ikeda, Y.; Kagami, S.; Yoshihama, M.; Suzuki, K.; Osada, H.; Isono, K. *J. Antibiot.* **1998**, *51*, 1099 and references cited therein.
6. Takatsuki, A.; Kawamura, K.; Okina, M.; Kodama, Y.; Ito, T.; Tamura, G. *Agric. Biol. Chem.* **1977**, *41*, 2307.