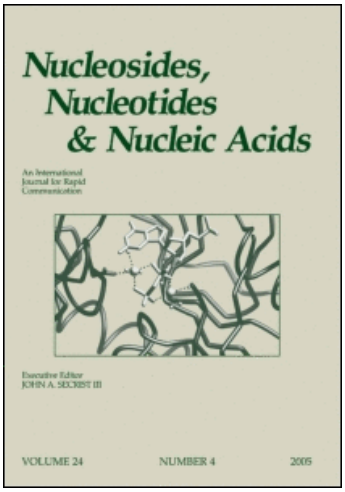

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Design of *Mycobacterium tuberculosis* Thymidine Monophosphate Kinase Inhibitors

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Design of *Mycobacterium tuberculosis* Thymidine Monophosphate Kinase Inhibitors

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M. tuberculosis is a major pathogen in the world and infects almost one third of the population. The current chemotherapy, which stands on a few molecules and involves long treatments of the patients, is challenged by emerging multiresistant strains. TMPK belongs to the family of nucleoside monophosphate kinase (NMPK): it catalyses the phophorylation of thymidine monophosphate (dTMP) to thymidine diphosphate (dTDP) utilizing ATP as its preferred phosphoryl donor. TMPK, essential for cell proliferation, was studied intensively the last years for its role in activation of antiviral drugs such AZT. Biochemical and physicochemical characterization of *M. tuberculosis* TMPK (TMPKmt) revealed distinct features when compared to its counterpart from yeast, human and *E. coli*, which renders this protein a good target for antituberculosis drugs.[1] Based on the 3D-structure of TMPKmt (Fig. 1,[2]), different positions on the natural substrate (dTMP) were

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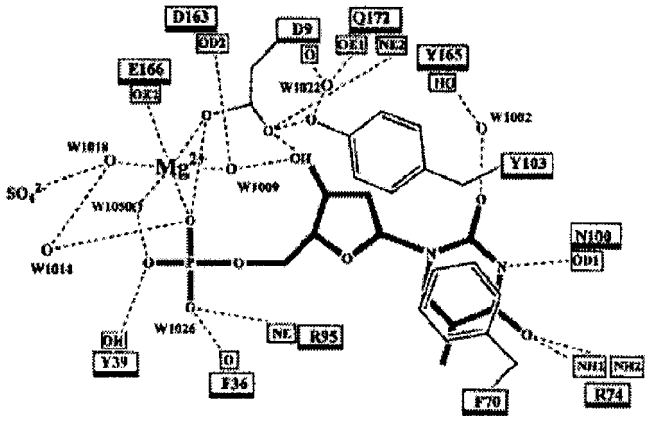


Figure 1. Schematic drawing of the TMP-binding site of TMPKmt.[2]

chosen to introduce modifications with the aim of obtaining specific inhibitors of the target.

Modifications at the 5- (Table 1) and 5′-positions (Table 2) of dTMP were first explored. The values given in Tables 1 and 2 (μM) correspond to the inhibitory constants of the different analogues and were determined using the coupled spectrophotometric assay at 334 nm.[3] The concentrations of ATP and dTMP were kept

Table 1. Modifications at the 5-position.

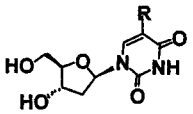
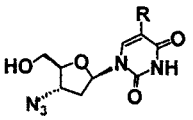
R				
CH_3	dT	27	AZT	28
H	dU	1020	AZdU	810
F	5FdU	212		
Cl	5CldU	10	5ClAZdU	16
Br	5BrdU	5	5BrAZdU	10,5
I	5IdU	33		
OH	5HOdU	270		
CF_3	5CF_3dU	97		
CH_2OH	5HOMedU	820		
CH_2CH_3	5EtdU	1140		
CH=CHBr (E)	BVDU	625		

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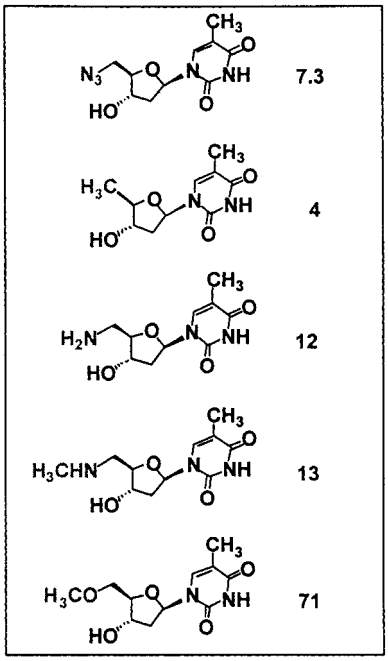
Table 2. Modifications at the 5′-position.



constant at 0.5 mM and 0.05 mM, respectively, whereas the concentration of nucleoside analogues was varied within 0.01 and 2 mM. Non phosphorylated thymidine analogues are as potent inhibitors as their monophosphate counterparts:[4] the 5′-phosphate group could be replaced by an amino or an azido function, or by a methyl group (Table 2). On the other hand, the 5-methyl group of dTMP could only be substituted by a bromine or a chlorine atom (Table 1).

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