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Antitubercular activity of α,ω-diaminoalkanes, $H_2N(CH_2)_nNH_2$

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ABSTRACT

A series of 11 α,ω-diaminoalkanes, ($H_2N(CH_2)_nNH_2$, $n = 2–12$) have been evaluated for their in vitro antibacterial activity against *Mycobacterium tuberculosis* H37Rv. Compounds, ($H_2N(CH_2)_nNH_2$, $n = 9–12$), exhibited a very good activities in the range 2.50–3.12 μg/mL, which can be compared with that of the first line drug, ethambutol (3.12 μg/mL). These results and a preliminary QSAR study can be considered an important start point for the rational design of new leads for anti-TB compounds.

Diamines constitute a very important and versatile class of compound with important applications and roles in many fields. As a particular example in medicinal chemistry, 1,2-ethylenediamine is a pharmacophore of ethambutol, a front-line drug used to treat tuberculosis (TB).[1,2] TB is responsible for more than 1.7 million people deaths each year and it is estimated that there are around 1 billion people infected with this disease worldwide.[3,4] Of particular current concern is the enormous problem resulting from extensively drug-resistant tuberculosis, XDR-TB, which is commonly defined as strains resistance to all the current first line drugs, fluoroquinolones and at least to one of the three injectable second-line drugs (capreomycin, kanamycin or amikacin). In 2006, XDR was detected in all regions of the world and has been classified as an urgent public health worldwide problem by WHO. Due to the importance of this disease, various actions have been undertaken by academic institutions, government research laboratories, non-governmental organizations, the pharmaceutical industry and contract research houses with the goal of developing new drugs and strategies. One of the many valuable contributions has been the library of 63.238 compounds based on the pharmacophore of ethambutol, 1,2-ethylenediamine, developed by Sequella Inc., in collaboration with NIH/NIAID. From this library, it was possible to develop the compound named SQ-109, currently under clinical phase I. (Fig. 1)[5] Due to the promise of SQ-109, several compounds containing the group ethylenediamine as a pharmacophore have been synthesized and evaluated, also with promising perspectives.[6–8] So far, there have been no reported studies with other diamines, and this compound has motivated us to evaluate commercial α,ω-diaminoalkanes, ($H_2N(CH_2)_nNH_2$, $n = 2–12$) compounds.

Table 1 showed that α,ω-diaminoalkanes, ($H_2N(CH_2)_nNH_2$, $n = 9–12$) have good activity with MIC between 3.12 and 2.5 μg/mL compared to that of the first line drug ethambutol 3.12 μg/mL (Fig. 1).[11] The good activities of the longer chain compounds and non-activity of the shorter chain compounds clearly point to the importance of the lipophilicity of the compounds: as indicated in Table 1 the Log *P* values of the active compounds are in the range 0.99–2.50.

Table 1
The in vitro activity of compounds **1**–**12** against *M. tuberculosis* $H_{37}Rv$ strain

$NH_2(CH_2)_nNH_2$	MIC (μg/mL)	*C* Log *P*
($n = 12$)	2.50	2.50
($n = 11$)	3.12	2.00
($n = 10$)	3.12	1.49
($n = 9$)	3.12	0.99
($n = 8$)	–	0.48
($n = 7$)	–	−0.02
($n = 6$)	–	−0.53
($n = 5$)	–	−1.03
($n = 4$)	–	−1.54
($n = 3$)	–	−1.81
($n = 2$)	–	−2.08

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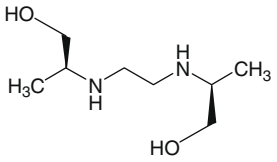
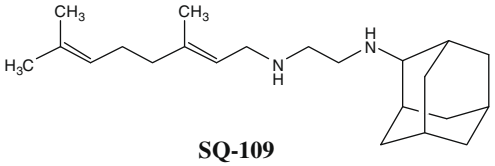


***S,S*-Ethambutol**

First line drug against TB



SQ-109

Figure 1. Structure of the first line drug ethambutol and SQ-109.

Table 2
Cytotoxic effects of test compounds on non-infected J774 macrophage

Diamines	1.0 μg/mL	10 μg/mL	100 μg/mL
Medium	100	100	100
Tween	0	0	0
(n = 10)	100	100	94
(n = 8)	100	100	95
(n = 2-7, 9,11 and 12)	100	100	100
Ethambutol	100	93	82

Results presented in percentage of cell viability (%).

The compounds, ($H_2N(CH_2)_nNH_2$, $n = 9–12$) are all non-cytotoxic at all concentrations tested, thus are less cytotoxic towards normal cells than the first line drug ethambutol,[16] see Table 2. In cells infected with BCG only ($H_2N(CH_2)_nNH_2$, $n = 5$) was non-cytotoxic: results for all compounds ($H_2N(CH_2)_nNH_2$, $n = 2–12$) are listed in Table 3.[16] Preliminary QSAR study suggested that in as well as the importance of lipophilicity, free bis amine functions are crucial for the biological activity. This can be observed by the lost of anti-TB activity when the diamines $n = 9–12$ are mono or disubstituted with Ac, Boc, Bz, Bn, Cbz, Me and by the fact that monoamines ($CH_3(CH_2)_nNH_2$, $n = 8–11$) are ineffective.

In conclusion, among the compounds evaluated, ($H_2N(CH_2)_n$-NH_2, $n = 12$) exhibited the best anti-TB activity (2.5 μg/mL), when compared with first line drugs such ethambutol (MIC = 3.12 μg/mL). This suggested that this diamine may be selectively targeted to *Mycobacterium tuberculosis* growth. This compound is also not cytotoxic to host cells at the concentrations effective in inhibiting *M. tuberculosis*. Preliminary QSAR information also indicated that the length of the alkyl chain and the free base diamine are crucial for the biological activity. More information regarding QSAR, the mechanism of action and in vivo antibacterial activity are currently under way in our laboratory.

Table 3
Cytotoxic effects of test compounds on BCG -infected J774 macrophage

Diamines	1.0 μg/mL	10 μg/mL	100 μg/mL
Medium	100	100	100
Tween	0	0	0
(*n* = 12)	56	49	38
(*n* = 11)	58	53	40
(*n* = 10)	56	34	42
(*n* = 9)	100	100	71
(*n* = 8)	68	64	64
(*n* = 7)	79	78	70
(*n* = 6)	98	92	76
(*n* = 5)	100	100	98
(*n* = 4)	100	90	82
(*n* = 3)	100	94	89
(*n* = 2)	35	23	29
Ethambutol	92	88	85

Results presented in percentage of cell viability (%).

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