Published in final edited form as:
Bioorg Med Chem Lett. 1993 ; 3(6): 1137–1140. doi:10.1016/S0960-894X(00)80302-9.

Pentamidine Congeners 1: Synthesis of *Cis*- and *Trans*-Butamidine Analogues As Anti-*Pneumocystis carinii* Pneumonia Agents

Isaac O. Donkor[+], **Susan K. Jones**[!], and **Richard R. Tidwell**[!]

[+]College of Pharmacy, Xavier University of Louisiana, New Orleans, LA 70125

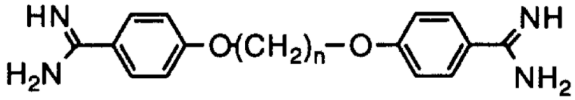
[!]Division of Cellular Biology and Biological Chemistry, Department of Pathology, School of Medicine, University of North Carolina at Chapel Hill, NC 27599

Abstract

Butamidine analogues possessing unsaturation in the ether bridge between the bisamidinophenyl or bisimidazolinophenyl functionalities have been synthesized as semirigid congeners of pentamidine. These compounds demonstrated good anti-*P. carinii* pueumonia activity in a rat model of the disease.

The incidence of *Pneumocystis carinii* pneumonia (PCP) has increased dramatically in the United States with the advent of acquired immunodeficiency syndrome (AIDS). Over 70% of AIDS patients develop PCP1. This opportunistic infection is the common cause of mortality of AIDS patients. The first line of therapy of PCP is either trimethoprim-sulfamethoxazole or pentamidine isethionate. These drugs precipitate serious adverse effects2،3 hence there is the need for new less toxic agents for treating PCP (eg. atovaquone, a hydroxy-1,4-naphthoquinone with limited side effects has recently been approved for treatment of mild to moderate PCP in AIDS patients).

At the molecular level pentamidine is known to interact with a number of macromolecules however the exact mechanism by which the drug achieves its anti-PCP activity is yet to be established.[4–8] This set-back coupled with the fact that the metabolic activity of *P. carinii* is poorly understood have limited anti-*P. carinii* drug discovery to an empirical approach.[9] Structure-activity relationship studies demonstrated that ether bridge contracted homologues of pentamidine (**1**), such as butamidine (**2**), and propamidine (**3**) are as active as pentamidine in treating experimental PCP in a rat model of the disease.[10]



1, n = 5; **2**, n = 4; **3**, n = 3

Pentamidine and its analogues such as butamidine are flexible molecules hence they can assume a variety of interconvertible conformations. The significance of reducing conformational flexibility of these compounds on biological activity is unknown. We have

Correspondence to: Isaac O. Donkor.

synthesized compounds **4–7** as conformationally restricted congeners of pentamidine. These compounds demonstrated good anti-PCP activity with no toxic side effects in a rat model of the disease (table 1).

The following scoring criteria were used to evaluate the compounds for toxicity *in vivo*: A score of 0 was assigned if no local, clinical, or histologic toxicity was observed; 1+, if all aminals survived with no observable distress, but some local toxicity; 2+, if most animals survived with severe distress and marked local toxicity as well as some clinical toxicity and histopathology; 3+, if an acute toxic effect occurred after a single dose and/or a sharp decrease in animals' health following multiple doses and resulted in loss of less than 50% of the animals; 4+, if more than 50% of the animals died at the test dose.

Synthesis of **4**[11] commenced with a Williamson ether synthesis between 4-cyanophenol and *cis* -1,4-dichloro-2-butene to give dicyano **10**. Subjection of **10** to Pinner reaction[12] followed by refluxing the resulting imidate **11** in methanolic ammonia gave bisamidino derivative **4**. Treatment of imidate **11** with a five fold excess of ethylenediamine in absolute methanol at reflux gave bisimidazolino derivative **6**. *Trans* isomers **5** and **7** were synthesized following the above procedures but using *trans* -1,4-dichloro-2-butene in place of the *cis* isomer.

Compounds **4–7** were evaluated for anti-PCP activity as well as toxicity in a rat model of the disease following standard procedures.[10,13,14] Pentamidine was used as positive control and saline as negative control. Table 1 shows the results of these studies. Efficacy of each compound is presented as number of cysts counted per gram of lung tissue expressed as a percentage of the number of cysts counted per gram of lung tissue for the saline treated animals. The number of cysts per gram of lung tissue in all treatment groups were significantly lower than that of the saline treated control. Pentamidine and its semi-rigid analogues **4–7** were effective in treating *P. carinii* infection in the rat model. All the test compounds were more potent than pentamidine as anti-PCP agents. *Trans* bisamidino derivative **5** was the most potent compound studied being over five times more effective than pentamidine. The test compounds precipitated no toxic side effects compared to the pentamidine which caused severe distress, marked local toxicity, some clinical toxicity and histopathology. No significant difference in anti-PCP activity or toxicity was observed between the *cis* and *trans* isomers especially for the bisimidazolino derivatives **6** and **7**.

This study supports our eailier finding that ether bridge contracted homologues of pentamidine are effective anti-PCP agents.[10] The study however did not demonstrate any significant difference between the geometric isomers in terms of anti-PCP efficacy or toxicity. Rigid analogues rather than semi-rigid derivatives are currently being developed in our laboratory for conformation biological activity relationship studies of diamidines and diimidazolines as anti-PCP agents.

Acknowledgments

The work was supported by an AIDS Consortium grant from NIH to the Association of Minority Professional Health Schools.

References and Notes

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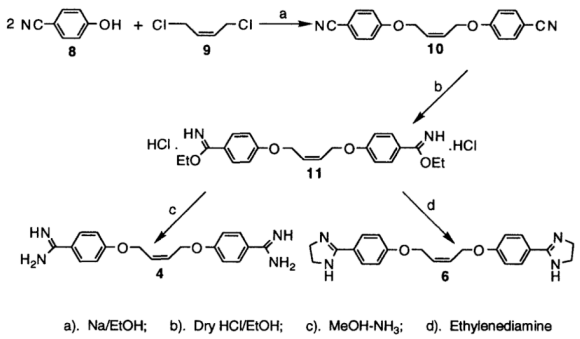
11. Scheme showing synthesis of *cis* isomers **4** and **6**. *Trans* isomers **5** and **7** were synthesized in a similar manner using *trans* -1,4-dichloro-2-butene in place of the *cis* isomer.



All new compounds showed consistent spectral data and gave satisfactory elemental analyses.

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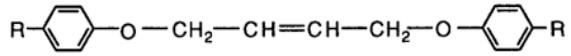
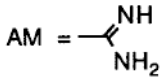
Bioorg Med Chem Lett. Author manuscript; available in PMC 2011 March 28.

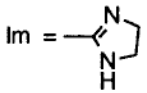
Table 1

Anti-*Pneumocystis carinii* Pneumonia Activity of Compounds **4**–**7**.



Compound	R	Double bond H	% of Control[a]	Toxicity
Saline	-	-	100.0	0
Pentamidine	-	-	4.5	2+
4	Am	Cis	1.3	0
5	Am	Trans	0.8	0
6	Im	Cis	1.4	0
7	Im	Trans	1.5	0





The compounds were tested as their hydrochloride salts for efficacy and toxicity at a dose of 10.0 mg/kg/day by iv injection.

[a]Saline control (100%) = 48.9×10^{-6} cysts per gram of lung tissue.