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Synthesis of dimeric acridine derived antivirals

René Csuk,* Alexander Barthel, Torsten Brezesinski and Christian Raschke

Institut f. Organ. Chemie, Martin-Luther-Universität Halle-Wittenberg, Kurt-Mothes-Str. 2, D-06120 Halle (Saale), Germany

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Abstract—A series of antiviral compounds consisting of an intercalating acridine derived part, a spacer region and a reactive EDTA derived conjugate was synthesized in an easy sequence starting from 1,ω-alkyldiamines. As shown in model screenings, in the presence of ascorbic acid the Fe-complexes of these compounds reduced the phage-titer of MS2-phages by >8 logarithmic decades.

1. Introduction

Despite the great strides that have been made in blood screening over the past few decades to reduce the risk of pathogen transmission in the worldwide blood supply, transmission of pathogens via blood transfusion is still a risk. High-profile examples, such as HIV and Hepatitis B and C, demonstrate both the blood supply's vulnerability to previously unknown pathogens, as well as the inevitable lag time required to develop and implement suitable screening tests. Currently, blood products intended for transfusion are only screened for four viruses and one bacteria. The microbial challenge to the blood supply is significantly greater than just five pathogens. A recent example of a new virus entering the blood supply and bypassing all of the then existing safeguards was West Nile virus during the summer of 2002 in the United States.

Quite recently, a new type of pathogen inactivating agents (Fig. 1, type A) was introduced—consisting of an intercalator that binds to the nucleic acid of pathogens combined with a conjugate that destroys the nucleic acid subsequently via a *Fenton*[1,2] mechanism. The conjugate consisted of a metal-chelate complex wherein the metal can change between at least two levels of oxidation. These compounds preferentially showed an acridine as the intercalator possessing in addition a spacer group to an EDTA-Fe(II/III)[3–5] chelate acting as the conjugate. Damage to the DNA was accomplished by producing OH radicals by a Fe(II) catalyzed *Fenton* mechanism.[6–8] Furthermore, the addition of a reducing agent such as ascorbate[9–12] leads to a cycle, which increases the damage to the biological molecules.

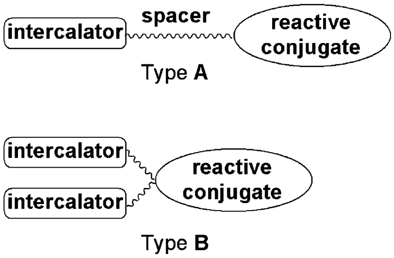

Figure 1. Basic structure of the pathogen inactivating compounds.

2. Results and discussion

From preliminary modeling studies we concluded that an improved antipathogenic performance could be expected from compounds exhibiting a stronger ability to interact with DNA or RNA. Thus, from a better intercalating action of the compounds a higher degree of viral inactivation should be expected. Therefore, the synthesis of dimeric structure (Fig. 1, type B) was planned. Retrosynthetic analysis revealed N-1-(9-acridinyl)-1,ω-alkanediamines **1**–**10** as ideal starting materials. Their reaction with EDTA dianhydride (**11**) gave the products **12**–**21** (Scheme 1) in good to fair yield.

For biological screening the well established system containing MS2 bacteriophages[13] (genus of the family Leviviridae; uncoated, containing ssRNA) was used. The target compounds were allowed to react with an

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* Corresponding author. Tel.: +49-345-5525660; fax: +49-345-5527030; e-mail: csuk@chemie.uni-halle.de

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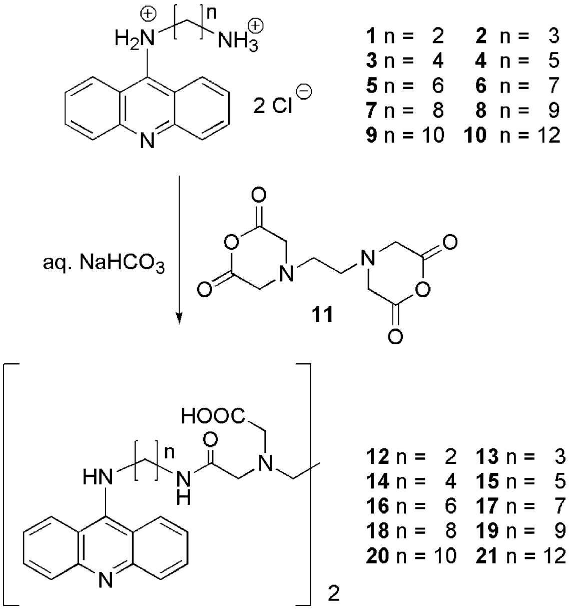

Scheme 1. Synthesis of the target compounds.

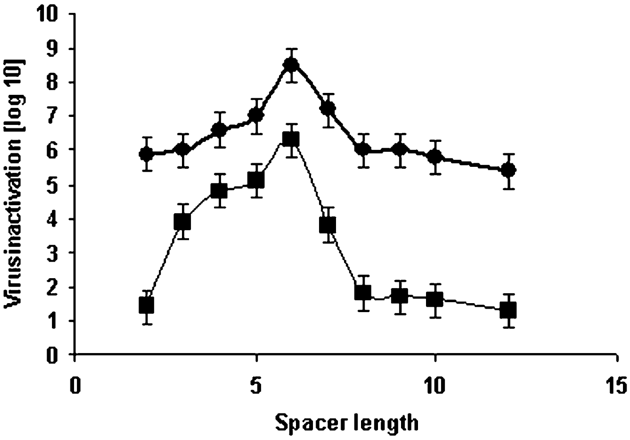

Figure 2. Inactivation of phage MS2 as a function of spacer length (20 °C, 5 mmol Na-ascorbate, 101 µmol of compounds **12**–**21**, Fe^{3+} loaded, 6 equiv, 4 h) as compared to the corresponding monomeric structures.

Table 1. Virus inactivation [VI, log 10][a] for compounds **12**–**21** and the corresponding monomers (Ref. 8)

Spacer length	VI [log 10] dimer	VI [log 10] monomer
2	5.9	1.4
3	6.0	3.9
4	6.6	4.8
5	7.0	5.1
6	8.5	6.3
7	7.2	3.8
8	6.0	1.8
9	6.0	1.7
10	5.8	1.6
12	5.4	1.3

[a] Values are means of three experiments; standard deviation ±0.5.

6 M excess of Fe^{3+}, then lyophilized and incubated with the phages in Tris-buffer in the presence of sodium ascorbate. As shown in Figure 2 the length of the spacer exhibits significant effects on the reduction of the phage-titer. Best results were obtained for a spacer length of $n = 6$ giving rise to a reduction of the phage-titer of MS2 phages by >8 logarithmic decades whereas for the corresponding compounds possessing only one intercalating moiety a ca. 100-fold decreased activity has been reported;[8] no significant virus inactivation has been found in a control experiment wherein the phages were incorporated with acridine and EDTA (100 µmol each, Fe^{3+} loaded, 5 mmol Na-ascorbate) Table 1.

Due to the unprecedented high activity of these compounds their biological screening against other viruses and bacteria is being investigated in our laboratories.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2004.07.015.

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