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Quaternary Ammonium Salts inhibiting HIV replication *in vitro*

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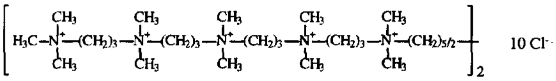
The discovery of the bicyclams, that are targeted at the CXCR4 coreceptor has opened new perspectives for the treatment of AIDS by preventing the entry of the HIV. A series of quaternary ammonium salts (QAS) are highly potent and selective inhibitors of the replication of different HIV-1 strains (NL4-3 and RF) *in vitro*. Selectivity indices higher than 2,000 were observed. The structure of QAS 1 is as follows:



$$\left[H_3C-\overset{CH_3}{\underset{CH_3}{N^+}}-(CH_2)_3-\overset{CH_3}{\underset{CH_3}{N^+}}-(CH_2)_3-\overset{CH_3}{\underset{CH_3}{N^+}}-(CH_2)_3-\overset{CH_3}{\underset{CH_3}{N^+}}-(CH_2)_3-\overset{CH_3}{\underset{CH_3}{N^+}}-(CH_2)_{5/2}- \right]_2 \quad 10\,Cl^-$$

From time of addition experiments QAS compounds appeared to act at the virus adsorption and/or virus-cell fusion process. The QAS are equipotent against wild-type NL4.3 strain and the bicyclam AMD2763-resistant NL4.3 strain, whereas no antiviral activity was observed against the AMD3100-and dextran sulfate-resistant NL4.3 strain. To further investigate the molecular target of QAS, we selected an NL4.3 strain for resistance against QAS 1. Over 500-fold reduced sensitivity towards QAS was observed. This QAS^{res} strain appeared to be 8-fold less sensitive to dextran sulfate, 10- to 25-fold less sensitive towards AMD2763 and 30-fold less sensitive towards AMD3100 than the wild type strain. Sequence analysis of gp120 revealed several mutations in the V2, V3 and V4 portion. The interaction of QAS with CXCR4 was evaluated by FACS analysis using the monoclonal antibodies (mAbs) 12G5, 2B11 and 171 that react specifically with different epitopes of CXCR4. We could not detect interference of different QAS congeners with the binding of these mAbs, even at QAS concentrations up to 100 µg/ml whereas the bicyclam AMD3100, a specific antagonist of CXCR4, inhibited the binding of mAb12G5 to CXCR4 for 80% at a concentration of 8 ng/ml. The precise mode of action of the QAS compounds remains to be elucidated.

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Total Synthesis of the Natural Products Inophyllum B, Cordatolide A, B and their Analogues 11-demethyl Cordatolide A and B. Non-Nucleoside Inhibitors of HIV-1 Reverse Transcriptase.

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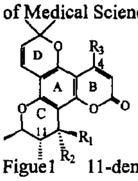

R_1=OH R_2=H R_3=n-C_3H_7 (±)-Calanolide A (1)
R_2=OH R_1=H R_3=n-C_3H_7 (±)-Calanolide B (2)
R_1=OH R_2=H R_3=CH_3 (±)-Cordatolide A (3)
R_2=OH R_1=H R_3=CH_3 (±)-Cordatolide B (4)
R_1= OH R_2=H R_3=C_6H_5 (±)-Inophyllum B (5)

Figue1 11-demethyl-cordatolide A (6) 11-demethyl-cordatolide B (7)

(+)-calanolide A isolated from tropical plants of the genus *Calophyllum* is active against strains of HIV-1. Calanolide A is undergoing for clinical trail. Cordatolide A, B (3,4) and Inophyllum B (5) are also natural products which isolate from *calophyllum Cordato-oblangum* and *C. Inophyllum*, respectively. According to the literature, (5) is a potent HIV-1 RT inhibitor and also have anti-HIV-1 activity but no anti-HIV activity data for Cordatolide A and B. The structure of (3), (4) and (5) are very similiar to (1) (Figue 1) which contain either a methyl or a phenyl group at the 4-position instead of the n-propyl group. However, up to now we haven't found any report for synthesis of (3), (4) and (5). Herein we present our study of total synthesis of (3), (4), (5) and analogues of (6) and (7) in order to evaluate their anti-HIV activity and also the structure-activity relationship study. The synthetic compounds (3~7) have been identified by ^{1}H-NMR, IR spectra and elemental analysis. Among them (2), (6), and (7) were evaluated for anti-HIV-1 RT activity in the primary screening assay. (2), (6), (7) were found to inhibit HIV-RT with IC_{50} 3.6, 118.2 and 3.8 µM, respectively.

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Electrostatic Potential Surfaces of Nucleosides and Nucleotides: Correlations with Inhibitors of HIV Reverse Transcriptase

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Examination of the anti-HIV data of some active dideoxynucleosides and their 3-D electron density patterns and their electrostatic potential surfaces (EPS) reveals some interesting correlations. Conversely, inactive compounds have different EPS to those in the same series that are active. The electrostatic potential distributions of active nucleoside triphosphates also show remarkable correlations. For example, (*S,S*)-isoddATP, AZTTP and oxetanocin A TP have similar 3D-electron density surface patterns and similar high and low regions of electrostatic potential, which suggest that these compounds proceed through related mechanisms in their interaction and inhibition of HIV reverse transcriptase. Docking of AZTTP, (*S,S*)-isoddATP and other active triphosphates into the active site of HIV RT and calculation of the EPS of both the nucleotide and active site show that there is excellent matching between inhibitor and enzyme binding site EPS data. The structure-activity profile discovered has contributed to the development of a first predictive QSAR analysis in the area. Our presentation will focus on this application of EPS data in the anti-HIV field.

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Synthesis of Aminoacids Derivatives as Rev-RRE Binding Inhibitors, using Solid Phase Combinatorial Chemistry.

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Solid phase combinatorial chemistry has made a huge impact on the pharmaceutical industry over the past few years and is an important tool for drug discovery. The aim of this project is the design and synthesis of potential anti-HIV compounds using combinatorial chemistry. HIV is still a major problem in the world despite recent advances in its therapy. The WHO estimates that 33.4 million people were living with HIV/AIDS by the end of 1998. Combination therapy using several different drugs has been a major breakthrough in the treatment of HIV. However this treatment only delays the progression of the disease and does not cure it. Therefore there is an urgent need for the development of new therapies. RNA-protein interactions are central features of many fundamental biological processes, including translation, mRNA processing, and transcription. The HIV-1 Rev and Tat protein are RNA-binding proteins that regulate viral gene transcription. The proteins work by binding to the RNA transcripts, stabilising them. Inhibition of the protein-RNA interaction has been shown to be a potential drug target. The area of research involves the design and synthesis of libraries for identification of compounds which inhibit tat-TAR and rev-RRE interaction by binding to the RNA. Our work concentrates on the synthesis of amino-acid derivatives with amide or guanidine groups on their side chain. Arginine and other amino acids show binding to RNA by interaction of their side chains in the RNA major/minor groove.