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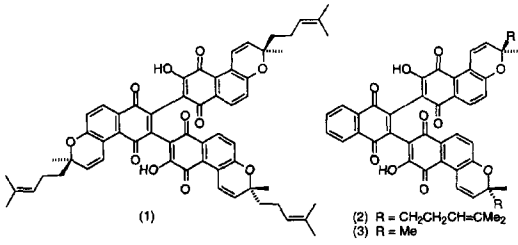
Naphthoquinones as Antiviral Agents

D G Bourke,[a] J A V Coates,[b] M P Collis,[b] I T Crosby,[a] P J de Bruyn,[a] P L C Keep,[b] M L Rose, and A D Robertson[b]
[a]Dept. of Medicinal Chemistry, Monash Uni, Parkville, Vic, Australia.
[b]AMRAD Operations Pty. Ltd. Richmond, Vic, Australia.

Conocurvone (1) is active in preventing the cytopathic effects and replication of HIV-1 in human T-lymphoblastic cells (CEM-SS) over a concentration range of 20 - 500 nM.[1] The difficulties inherent in isolating drugs from plant material together with the lipophilic characteristics of (1), and its analogue (2), provided an opportunity to design and synthesise a compound with improved physicochemical properties, such as solubility and bioavailability. The equipotency of conocurvone (1) and the synthetic "trimeric" analogue (2)[1] suggested that less complex compounds, such as (3), may still retain significant *anti*-HIV activity. Compounds based on (3) are less lipophilic than (1) or (2), and have the additional advantage of being stereochemically less complex. The synthesis, *anti*-HIV-1 activity and mode of action studies of (3) and a series of analogues will be presented.



(1)

(2) R = $CH_2CH_2CH{=}CMe_2$
(3) R = Me

1. Decosterd, L. A., et al., *J. Am. Chem. Soc.*, **1993**, *115*, 6673.

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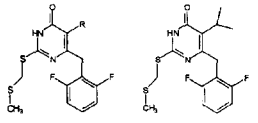
Does the 2-methylthiomethyl substituent really confer high anti-HIV-1 activity to S-DABOs? *°Marceddu T., *°Musiu C., *°Loi A.G., ^Mai A., ^Artico M., *Bryant M., +Sommadossi J.P. and °La Colla P.
*Novirio Pharmaceuticals Inc., USA °Dipartimento di Biologia Sperimentale, Università di Cagliari; ^Dipartimento di Studi Farmaceutici, Università "La Sapienza" di Roma; +University of Alabama at Birmingham, USA.

During the development of DABOs, we have introduced various substituents in either or both the pyrimidine and phenyl rings, modified the distance between them and varied the type of aryl moiety. We have been successfull in obtaining antiviral potency in the low nanomolar range, however, only after the introduction of a 2,6-difluorophenylmethyl moiety as a C-6 substituent. We now present the anti-HIV-1 activity of phenylmethyl- and 2,6-difluorophenylmethyl-S-DABOs carrying H, Me, Et or iPr at C-5 and a methyl-thio-methyl (MTM) substituent at C-2. When evaluated by MTT (EC_{50} values) or p24 assays (EC_{90} values), MTM-S-DABOs proved active at micromolar concentrations with potencies in the same range as those of 2-*sec*-butyl counterparts. Replacement of phenylmethyl with 2,6-difluorophenylmethyl moiety as a C-6 substituent increased the potency of both 2-*sec*-butyl and 2-MTM-S-DABO up to 58-fold. By increasing the size of the C-5 substituent from H to *iso*-propil, the potency of the 2-*sec*-butyl derivative diminished by 4.5-fold, whereas that of 2-MTM-thio derivative increased up to 12.5-fold. Thus, MTM-S-DABOs showed an SAR different from those of HEPTs and DABOs. For this reason, they were expected to possess a unique spectrum of antiviral activity against resistant mutants. Data on this aspect will be presented.

MTM-S-DABOs **MC 1145**



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DIFFERENT ADAMANTANE DERIVATIVES INHIBIT HIV-1 REPLICATION *IN VITRO*.

Marina Bourchteine[1], Alexandre Serbin[2],
Tatiana Khakhulina[3], Alissa Boukrinskaya[3]
[1]AIDS Prevention Center "ANTIVICH",
[2]Health Research and Development Foundation,
[3] D.I. Ivanovsky Institute of Virology;
Moscow, Russia

Newly developed anti-viral compounds consisting of adamantane derivate chemically linked to the water-soluble polyanionic matrix by different spacer groups inhibit HIV-1 infection in vitro. The absence of cytotoxic effect was shown by MTT test for estimating cytotoxic dose (CTD50). The antiviral effect of the compounds was shown in lymphoblastoid MT-4 cells and in HeLa CD4+/β-galactosidase cells («Magi» cells). The effect of the compounds was registered by immunoblotting of cell lysates and by measuring of β-galactosidase activity.

The strong inhibition of HIV-1 replication was observed when the compounds were added with the virus and was expressed even when the compounds added with the virus were removed 1 hour after infection. The anti HIV-1 effect of the compounds was gradually decreased if it was added 1 hour after infection, no inhibition was observed when the compounds were added 2 hours after infection.

The compounds do not impair the virion structure. The compounds effectivcly inhibit the replication of AZT-resistant strain of HIV-1. The compounds affect some early steps of virus replication following adsorption such as uncoating and /or nuclear transport of viral complex.

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Recognition and Inhibition of HIV Integrase by Novel Dinucleotides

V. Nair,[a] M. Taktakishvili,[a] N. Neamati,[b] and Y. Pommier.[b]
[a] Department of Chemistry, The University of Iowa, Iowa City, IA 52242, U.S.A. [b] Laboratory of Pharmacology, National Cancer Institute, Bethesda, MD 20892, U.S.A.

HIV integrase is involved in the integration of viral DNA into host cell DNA, a biochemical sequence of steps that involves DNA splicing (3′-processing) and coupling (integration). The enzyme apparently recognizes specific sequences (5′-ACTG...CAGT-3′) in the LTRs of viral DNA. In the first step (3′-processing), specific endo-nuclease activity removes two nucleotides from each end of the double helical viral DNA producing new 3′-hydroxyl ends (CAOH-3′). This truncated viral DNA is coupled in the next steps to host cell DNA (integration). Although studies on the search for clinically useful anti-integrase agents are relatively recent, the screening of inhibitors against purified recombinant integrase has contributed to the identification of some interesting lead compounds. In the quest for small DNA model systems with nuclease stability and critical structural features for recognition and inhibition of HIV integrase, we have discovered novel dinucleotides which are potent inhibitors of this key viral enzyme. This paper will focus on our discoveries in this area which will include synthesis, biophysical studies, enzymology and anti-integrase activity data.