(HCMV) (McGuigan et al., 2004). Replacement of the sugar at N3 with the (2-hydroxyethoxy)methyl group (present in the antiherpes drug acyclovir) afforded compounds with weak activity against both VZV and HCMV (Janeba et al., 2005). Phosphorylation of the furo[2,3-d]pyrimidine nucleoside analogues by the VZV TK is a prerequisite for their anti-VZV activity, but it is apparently not sufficient (Balzarini and McGuigan, 2002). To further elucidate the mechanism of antiviral action of this group of compounds, novel series of phosphoryl methoxy ethyl (PME) furo[2,3-d]pyrimidines were synthesized. The target compounds were prepared by the Sonogashira coupling of various alkynes with protected 5-iodo PMEU, followed by Cu(I)-promoted intramolecular cyclization, and removal of the iPr ester groups. The antiviral activity against HIV, HSV, VZV and HCMV of these compounds will be reported.

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HIV-1 Gag Matrix Protein Fragments and Polyacid Conjugates Designed for the HIV Inhibition

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The HIV gag matrix protein (MA) plays an essential role in the HIV life cycle at earliest (viral uncoating, RNA delivery to nuclei) and latest (RNA re-transporting toward plasma membrane, virions assembly-maturation) steps. So, the MA, as promising anti-HIV therapeutic target, was included in priority of our anti-HIV inhibitors design strategy [Antivir. Res. 2003 57(3):50; 2006 70(1):85]. Here we report the recent experimental developments in frame of: (1) MA-derived peptides (MAP) design and synthesis; (2) a cooperation of the MA-interfere with an anti-RNA potency expected on macromolecular level of MAP grafted to specific polymers (NAM), mimicking furan- and acid-kind species alternation similar to polymeric backbone of nucleic acids. A number of MAP-imitators of MA helix 2–4 region fragments (responsible for MA–MA inter-self recognition-aggregation) were synthesized and modified to mono-amino group active reagents suitable for single-linked grafting to NAM, and the corresponding MAP-NAM conjugates were synthesized, purified and separated in soluble lyophilized forms too. The grafting link location within AA chain/N-terminus of MAP was regulated by regioselective variation of the active and protected –NH2 groups positions along the polypeptide chain. In parallel the fluorescent derivates of MAP and MAP-NAM were prepared. The newly synthesized candidates (Fig. 1) to therapeutic counter-intervention in HIV life cycle by MA-interfering and by cooperative RNA-antagonistic mechanisms are disposed to anti-HIV evaluation (particularly in A. Bukrinskaya Lab., Virol. Inst., Moscow), and current results will be discussed.

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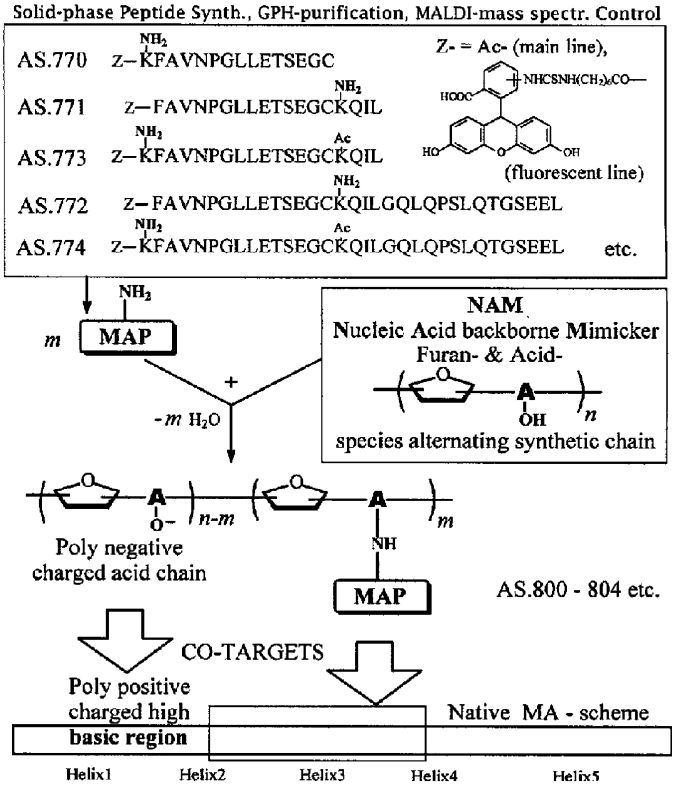

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CXCR4 Antagonists: A New Generation of Configurationally Restricted Bis-azamacrocyclic Compounds

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AMD3100 is a bis-azamacrocyclic compound that has been demonstrated to be a highly effective antagonist of the CXCR4 chemokine receptor. The two azamacrocyclic rings have been shown to interact with aspartate residues on the receptor via hydrogen bonding and electrostatic interactions. However, it is proposed that AMD3100 may bind metal ions in vivo and the active form may be a metal containing drug compound. This presents an issue as the metal complexes of AMD3100 exist in a configurational equilibrium some of which are better at binding to the receptor than others. The aim of this research is to design, synthesise and characterise new azamacrocyclic metal complexes with fixed configurations to provide optimised interactions with the CXCR4 receptor, increasing the potency and residence times of the new drugs relative to AMD3100. Informed design of a metal containing drug requires a comprehensive knowledge of coordination chemistry principles and must incorporate high kinetic stability of the complex to pre-