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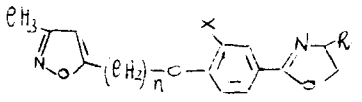
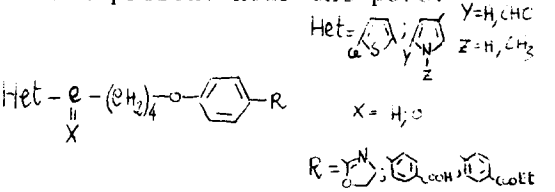
Synthesis and Antiviral Activity of New Disoxaril Analogues. P. La Colla^, F. Corelli*, S. Massa+, M. Artico+, P. Obino^, M.E. Marongiu^ and A. Pani^. Depts. of ^Biologia Sperimentale, Universitá di Cagliari, *Farmaco-Chimico Tecnologico, Universitá di Siena, +Studi Farmaceutici, Universitá di Roma. Italy.

Compounds of general formula **1** have been shown to prevent the uncoating of several entero and rhinovirus serotypes. X-Ray crystallographic studies performed on disoxaril bound to rhinovirus-14 have demonstrated that the isoxazole nucleus interacts with specific amino acids in a hydrophobic pocket within the viral capsid protein 1 (VP1), whereas the oxazolinyl moiety binds to the Asn 219 residue present near the pore.



1



2

To the best of our knowledge, no attempt has been made to ascertain whether heterocycles different from the isoxazole may also interact with aminoacids inside the VP1 pocket. Therefore, we prepared a series of disoxaril analogues of general structure **2** and tested them against a number of RNA and DNA viruses. The antiviral activity of these compounds will be discussed.

Supported by Cenci Bolognetti & Prog. AIDS 1990 Ist.Sup.Sanita'

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Anti-HIV Activity of iso-Trimethoprim Analogues. P. La Colla^, M. Botta+, M. Artico*, S. Massa*, L. Diliberto^, A.Pani^ and M.E. Marongiu^. Depts. of Biologia Sperimentale, Universitá di Cagliari, +Farmaco-Chimico Tecnologico, Universitá di Siena and *Studi Farmaceutici, Universitá di Roma. Italy.

In a search for new dihydrofolate reductase (DHFR) inhibitors we synthesized 2,4-diamino-6(3,4,5-trimethoxybenzyl) pyrimidine (1) (an isomer of trimethoprim (TMP)) and a series of analogues of (1) bearing substitutions in the benzylic -CH2 and/or in the pyrimidine moiety. Besides being congeners of TMP, the iso-TMP analogues are structurally related to 1-((2-hydroxyethoxy)methyl)pyrimidines bearing arylthio-substituents in the C6 position of the heterocycle, some of which are potent and selective inhibitors of HIV. Therefore, these compounds were tested in vitro for both antimicrobial and antiviral activity. Compounds bearing substitutions in the benzylic CH2 were the most cytotoxic (TD50 range: 0.1 - 3.0 ug/mL). While none of the compounds showed antimicotic activity, 4-chloro-2-methoxy-6(a,a-dichloro-4'-methoxy-benzyl) pyrimidine (6b) was more potent than SMZ and equipotent with TMP against Staphylococcus aureus. As was the case for TMP, the MIC of (6b) in combination with SMZ was reduced, suggesting that this compound is targeted at the DHFR. Interestingly, 4-amino-2-methoxy-6(4'-methoxybenzyl) pyrimidine (8b) and 2-butoxy-6(4'-methoxybenzyl)-4(3H)-pyrimidinone (14b), showed a selective anti-HIV-1 activity. (8b) was also active against HSV-1 and (14b) against ASFV.

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