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Structure-Activity Relationship Studies for Various Oxathiin Carboxanilide Derivatives Modified in the Oxathiin Moiety Against Wild-Type and Mutant Human Immunodeficiency Virus Type 1 Strains.

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The HIV-1-specific reverse transcriptase (RT) inhibitor 1-methylethyl-2-chloro-5[[5,6-dihydro-2-methyl-1,4-oxathiin-3-yl-carbonyl]-amino]benzoate (NSC 615985), designated UC84, is a potent and selective inhibitor of HIV-1 in cell culture [50% effective concentration (EC_{50}): 0.015 μg/ml]. UC84 proved virtually inactive against mutant HIV-1 strains containing the 100 Leu → Ile, 106 Val → Ala, 138 Glu → Lys or 181 Tyr → Cys mutation in their RT. However, minor structural changes in the molecule such as replacing the carbonylamide moiety by thioxomethylamide, or the isopropyl ester moiety by cyclopentane or *sec*-butyl, or the methyl group of the oxathiin part by ethyl, resulted in test compounds that were markedly more inhibitory to one or several HIV-1 mutant strains. In particular, potent antiviral activity was found against the 181 Tyr → Cys mutant HIV-1 strain. Interestingly, more dramatic structural changes such as replacement of the oxathiin moiety by an isopropoxy group preserved the potent antiviral activity of the parent compound UC84 against wild-type HIV-1 but also resulted in molecules that were markedly inhibitory to mutant HIV-1 strains (EC_{50}: 0.06-0.75 μg/ml). In this respect, they proved superior to several other HIV-1-specific non-nucleoside RT inhibitors (NNRTIs) that are currently subject of clinical trials. The oxathiin carboxanilide derivatives predominantly selected for drug-resistant virus mutants with mutations at the amino acid positions 100 (Leu → Ile), 101 (Lys → Glu/Ile) and 103 (Lys → Asn/Thr) of the reverse transcriptase.

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Pyrryl-Aryl-sulphones: synthesis and anti-HIV Activity.

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Recently, diarylsulphones have emerged as a new class of non-nucleoside reverse transcriptase inhibitors. Only derivatives bearing a nitro group ortho to the position of the sulphur attachment have been found active, whereas the oxidation state of sulphur has been associated with the potency of antiviral activity.

Our interest in derivatives bearing a pyrrole ring as potential inhibitors of HIV-1 replication prompted us to synthesize and test for antiviral activity various pyrryl-nitro/amino-phenyl sulphones and some related derivatives.

Among them, various compounds were endowed with potent (nM range) anti-HIV-1 activity in vitro and were targeted at the reverse transcriptase. RS 980 was the compound endowed with the most potent and selective anti-HIV-1 activity. When the pyrryl-aryl-sulphones effective against HIV-1 were examined for inhibition of the HIV-2-induced cytopathogenicity, none was found active at doses up to 1000 μM. This indicated that these compounds discriminate between HIV-1 and HIV-2. Moreover, the above compounds were ineffective in reducing the HIV-1 yield in chronically infected $H9/III_B$ cells.

Combinations of RS 980 with AZT, ddI and ddC resulted in slightly synergistic anti-HIV-1 effects. Long-term treatments of HIV-1-infected cells with RS 980 alone or in combination with AZT resulted in complete protection from the virus-induced CPE for 30 days.

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