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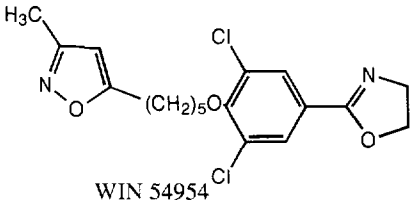
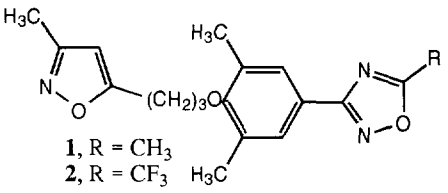
WIN 63843, A Metabolically Stable Broad Spectrum Antipicornaviral Compound. G.D. Diana, P. Rudewicz, D.C. Pevear, T.J. Nitz, D.J. Aldous, D.T. Robinson, F.J. Dutko, C. Aldi, M. Reuman, T.R. Bailey, R. Czerniak, T. Block and R. Roland. Sterling Winthrop Pharmaceuticals Research Division, Collegeville, Pennsylvania USA

Several modifications of the oxazoline ring of WIN 54954, a broad spectrum antipicornavirus compound have been prepared in order to address the acid lability and metabolic instability of this compound. We have previously shown that the oxadiazole analogue **1** displayed comparable activity against a variety of human rhinovirus serotypes and appeared to be stable to acid. A monkey liver microsomal assay was developed to examine the metabolic stability in vitro of both compounds and it was determined that WIN 54954 displayed 18 metabolic products in this assay while **1** was comverted to 8 products. Two major products of **1** were identified by LC-MS/MS to be monohydroxylated at each of the terminal methyl groups. Replacement of the methyl on the isoxazole ring with a trifluoromethyl group, while preventing metabolism at this position, did not reduce the overall number of metaboilc products. However, the trifluoromethyl oxadiazole **2** not only prevented hydroxylation at this position but also provided protection at the isoxazole end of the molecule, resulting in 2 minor products to the extent of 4%. Compound **2** exhibited activity comparable to WIN 54954 in vitro while displaying improved pharmacokinetics in dogs.



WIN 54954



1, R = CH_3
2, R = CF_3

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Antipicornavirus Activity of SCH 47802: In Vitro and In Vivo Studies. S. Cox, P. Buontempo, J. Wright-Minogue, A. Skelton, J. DeMartino, E. Rozhon, C. Linn, V. Girijavallablan, J. Schwartz, and J. O'Connell. Schering-Plough Research Institute, Kenilworth, NJ.

SCH 47802 and its derivatives are potent inhibitors of picornaviruses in vitro. The IC_{50} for SCH 47802 ranges from 0.03 to 10 ug/ml when tested against a broad spectrum of enteroviruses in plaque reduction assays. The LC_{50} for the compounds is > 50 ug/ml based on pre-mix MTT cytotoxicity. The addition of compound at various times after infection indicates that SCH 47802 acts early in viral infection. The in vitro activity of SCH 47802 translates into in vivo activity in the murine model of poliovirus encephalitis. In an oral dosing regimen, SCH 47802 protects mice at doses as low as 60 mg/kg/day. Pharmacokinetic analyses after oral dosing with SCH 47802 demonstrate serum levels of the compound above the in vitro IC_{50} values for the majority of enteroviruses tested. This class of molecules represents potential candidates for the treatment of human enterovirus infections.