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In vitro evaluation of novel azolylalkoxy heterocycles as potential anti-picornavirus agents.

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A novel series of azolylalkoxy heterocycles have been synthesized and reported in U.S. patent 5,026,848 (June 25, 1991). Syn numbers 65, 195, 217, 236 and 264 were the most active compounds of a number tested against twenty-one serotypes of rhinovirus. These compounds were re-tested against fifty-two serotypes of human rhinovirus (from a possible 100+) and representatives of other picornaviruses, namely coxsackie A9, A21, coxsackie B1,B4, ECHO7, 11 and Polio type 1. With respect to range of activity against various serotypes, Syn 195 was the best against rhinoviruses Syn217 against enteroviruses and Syn 65 against all picornaviruses. With respect to average MIC_{50} and therapeutic index (T.I.) Syn 236 was the best against all 52 serotypes of rhinovirus, Syn 217 the best against the first 21 tested and commonest 7. Syn 236 had the highest T.I. against enteroviruses. In summary, Syn numbers 65, 217 and 236 each had some merits and were tested in a more sensitive and accurate assay, namely HeLa cell plaque reduction assay using nine selected rhinoviruses. Syn 65 was active against most serotypes and Syn 217 had the lowest average MIC_{50} and highest T.I. The detailed results will be presented

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Novel Generation of Heteroarylthio, Sulfoxy, or Sulfonyl Alkyl Azoles as Antipicornavirus Agents.

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Heteroaryloxy alkyl azoles have been previously reported to exhibit strong antipicornavirus activity and specifically anti-rhinovirus activity*. In this article we wish to report the synthesis and antipicornavirus activity of the new thio, sulfoxy, and sulfonyl analogues of the above class of compounds. Namely, the title compounds were synthesized by the reaction of an appropriate mercapto heteroaryl derivative with ω-bromoalkyl azoles. Stepwise oxidation of the products with m-Chloroperbenzoic (MCPBA) resulted in the formation of the related sulfoxy and sulfonyl derivatives respectively. In the initial screening, majority of the compounds synthesized exhibited remarkable activity against rhinovirus - 1A and 39 comparable to that of Disoxaril. Two compounds, 5-[7-(benzimidazol-2-yl)thioheptyl]-methylisoxazole and 2-[6-(5-chlorobenzimidazol-2-yl)thiohexyl]-4-methyl thiazole, were further tested against twenty serotypes of rhinoviruses and exhibited strong activity. The latter compound also exhibited strong activity against coxsackie virus type 1B. The synthesis, screening, and structure-activity relationship will be discussed in detail.

*M. Daneshtalab et al. U.S. patent 5,026,848 (June 25, 1991)