Antirhinovirus Activity of Purine Nucleoside Analogs

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A wide variety of purine nucleoside (mainly tubercidin and adenosine) analogs, which had previously been shown to inhibit the replication of a broad spectrum of RNA viruses, were evaluated for their antirhinovirus activity in human diploid (WI-38) fibroblasts. Tubercidin, 5-(1-hydroxyethyl)tubercidin, 5-(2-buten-1-yI)tubercidin, toycamycin, and sangivamycin emerged as the most potent inhibitors. These compounds inhibited the replication of rhinovirus types 1A, 1B, and 9 at an MIC well below 1 μg/ml. However, these compounds proved cytotoxic for the uninfected host cells at concentrations which were only slightly higher (3- to 10-fold, on the average) than those required for inhibition of rhinovirus replication. The most selective inhibitor of rhinovirus replication was 3-deazaguanine, with a selectivity index of 50. None of the carbocyclic and acyclic analogs of adenosine tested exhibited a potent or selective antirhinovirus activity.

The search for effective antiviral agents has yielded a wealth of compounds belonging to widely varying chemical classes: thiosemicarbazones (20), isoquinolines (35, 43), triazinoindoles (27), guanidines (a), benzoxazoles (30), furanyl (2), benzimidazoles (12), thiourea (18), diketones (14, 16, 17), flavans (3, 32), flavones (25), chalcones (24), nitrobenzenes (34, 41), and isoxazoles (15, 31). The most recently developed antirhinovirus compounds (3, 15, 24, 31) reach their MICs within the range of 0.001 to 0.01 μg/ml. Such low MICs are unusual for antiviral compounds and are only matched by the most potent antitherpesvirus compounds (11, 42).

From a structural viewpoint it is remarkable that, in contrast with the majority of the established antitherpesvirus compounds (idoxuridine, trifluridine, vidarabine, and acyclovir), none of the antirhinovirus compounds described so far (Table 1), except for ribavirin, is actually a nucleoside analog. Yet, to the extent that they interfere with viral RNA synthesis, nucleoside analogs may be expected to suppress the replicative cycle of rhinoviruses.

Recently, we have described a variety of nucleoside analogs with broad-spectrum antiviral properties. These compounds could be roughly divided in two classes: (i) tubercidin (7-deazaadenosine) analogs which are inhibitory to both (-)RNA viruses and (+)RNA viruses, including picornaviruses such as poliovirus and coxsackievirus B (4, 8); and (ii) acyclic and carbocyclic adenosine analogs, which are specifically inhibitory to (-)RNA viruses such as parainfluenza, measles, rables, and vesicular stomatitis viruses and to (+)RNA viruses such as reovirus and rotavirus (7, 8, 10; S. Kitaoka, T. Konno, and E. De Clercq, Antiviral Res., in press). Whereas the acyclic and carbocyclic analogs of adenosine appear to be targeted at S-adenosylhomocysteine hydrolase or other enzymes involved in transmethylation reactions (9) or both, the precise mode or site of antiviral action of these analogs has not been identified. In fact, the latter compounds do not exhibit much selectivity in their antiviral action, although it has proven possible to improve their selectivity by appropriate chemical modifications (4).

In view of the broad-spectrum antiviral properties of the tubercidin and adenosine analogs, it appeared important to examine whether the activity spectrum of these compounds also extended to rhinoviruses, and, if so, whether they were capable of inhibiting rhinovirus replication at concentrations that were not toxic for the host cells. For comparative purposes some other compounds which have previously been accredited with broad-spectrum antiviral activity, viz., ribavirin (23), 3-deazaguanine (1), pyrazofurin (13), and formycin A (19), were included in our assay systems.

MATERIALS AND METHODS

Compounds. According to their chemical structure, the compounds were divided into five classes (Fig. 1). The sources of the compounds were as follows. For the 5- and 6-substituted tubercidin analogs, see reference 4. The sugar-modified analogs of tubercidin, toycamycin, and sangivamycin, as well as toycamycin and sangivamycin themselves, were obtained from M. J. Robins. For the carbocyclic analogs of adenosine, 3-deazaadenosine and 7-deazaadenosine (tubercidin), see reference 8. Neplanocin A and neplanocin C were obtained from Toyo Jozo Co. (Mifuku Ohito-Cho, Tagata-Gun, Shizuoka-Ken, Japan). For the acyclic analogs of adenosine, see references 8, 10, and 22. Formycin A was obtained from M. J. Robins; pyrazofurin was purchased from Calbiochem-Behring Corp., Lucerne, Switzerland; and ribavirin was from ICN Nutritional Biochemi- cals, Cleveland, Ohio. 3-Deazaguanine was kindly provided by R. W. Sidwell (Department of Animal, Dairy and Veterinary Sciences, College of Agriculture, Utah State University, Logan, Utah) and R. K. Robins (Department of Chemistry, Cancer Research Center, Brigham Young University, Provo, Utah; present address: Nucleic Acid Research Institute, Costa Mesa, Calif.). 3,7-Dideazaguanine was kindly provided by S. W. Schneller (Department of Chemistry, University of South Florida, Tampa, Fla.) (see also reference 37). Finally, ara-adenine and ara-guanine were obtained from M. J. Robins.

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Cells. Human embryonic lung diploid fibroblasts (strain WI-38 [ATCC CCl 75]) were obtained from the American Type Culture Collection (Rockville, Md.). The cells were grown in Eagle minimum essential medium (EMEM) supplemented with 10% fetal calf serum (FCS) and 2 mM L-glutamine.

Viruses. Rhinovirus type 1A (ATCC VR-242), rhinovirus type 1B (ATCC VR-481), and rhinovirus type 9 (ATCC VR-489) were obtained from the American Type Culture Collection. Virus stocks were prepared in WI-38 cells, titrated at about 10^5 CCID_{50} units/ml (1 CCID_{50} unit being the infective dose for 50% of the cell cultures), and stored in aliquots at -70°C until used.

Inhibition of virus-induced cytopathogenicity. Confluent WI-38 cell monolayers in Falcon 96-well microtiter plates were inoculated with 100 CCID_{50} of rhinovirus type 1A, 1B, or 9. After 1 h of adsorption the virus was removed, and the cells were further incubated in EMEM containing 3% FCS and various concentrations of the test compounds (400, 200, 100, 40, 10, . . . , 0.04, 0.01, 0.004 μg/ml). Viral cytopathogenicity was recorded daily. In the control, virus-infected but untreated cell cultures, cytopathogenicity was generally completed at 2, 3, or 4 days after infection with rhinovirus type 1A, 1B, or 9, respectively. Antiviral activity is expressed as the MIC required to inhibit virus-induced cytopathogenicity by 50% (MIC_{50}) (within the microtiter well) when viral cytopathogenicity reached completion (100% cell destruction) in the control (virus-infected) cell cultures. The MIC_{50} values listed in Table 1 represent the average values for three separate experiments.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Antiviral activity (MIC_{50} [μg/ml])</th>
<th>Cytotoxicity</th>
<th>Selectivity index^b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>against rhinovirus:</td>
<td>MTC^c [μg/ml]</td>
<td>IC_{50}^d [μg/ml]</td>
</tr>
<tr>
<td></td>
<td>1A</td>
<td>1B</td>
<td>9</td>
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<tr>
<td>Tubercidin</td>
<td>0.03</td>
<td>0.03</td>
<td>0.025</td>
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<td>6-Bromotubercidin</td>
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<td>23</td>
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<td>0.25</td>
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<td>27</td>
<td>23</td>
<td>6</td>
</tr>
<tr>
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<td>25</td>
<td>15</td>
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<td>0.3</td>
<td>0.015</td>
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<td>5-Butyltubercidin</td>
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<td>Sangivamycin</td>
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<tr>
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<td>120</td>
<td>100</td>
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<td>6</td>
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<td>300</td>
<td>220</td>
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<td>ara analog of sangivamycin</td>
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<td>4</td>
<td>3</td>
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<td>xylO analog of tubercidin</td>
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<td>Neplanocin C</td>
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<tr>
<td>([(RS)-9-(2,3-dihydroxypropyl)adenine]</td>
<td>&gt;200</td>
<td>&gt;200</td>
<td>&gt;200</td>
</tr>
</tbody>
</table>

* MICs required to reduce the cytopathogenicity of rhinovirus type 1A, 1B, or 9 by 50%.

* Ratio of MTC to MIC_{50} for rhinovirus type 1A (selectivity index A) or ratio of IC_{50} to MIC_{50} for rhinovirus type 1A (selectivity index B).

* Concentration required to alter normal cell morphology as detectable by microscopic examination.

* Cytotoxicity Selectivity Index. All values listed in this column were obtained by microscopic examination of infected cells. Cytotoxicity Selectivity Index is defined as the ratio of the MIC_{50} to the Cytotoxic Concentration (MTC) of the compound.

* ND, Not determined.
FIG. 1. Structural formulas of selected purine nucleoside analogs. Class 1 (5- or 6-substituted tubercidin analogs):

\[
R_1 = H \quad R_2 = H: \text{tubercidin (7-deazaadenosine)} \\
R_1 = \text{CHOCH}_3 \quad R_2 = H: 5-(1-hydroxyethyl)tubercidin \\
R_1 = \text{CHOCH}_2\text{CH}_3 \quad R_2 = H: 5-(1-methoxyethyl)tubercidin \\
R_1 = \text{CH}_2\text{C}==\text{CHCH}_3 \quad R_2 = H: 5-(2-buten-1-yl)tubercidin \\
R_1 = \text{CONH}_2 \quad R_2 = H: \text{toyocamycin} \\
R_1 = \text{CN} \quad R_2 = H: 6\text{bromotubercidin} \\
R_1 = \text{H} \quad R_2 = \text{Br}: 6\text{bromotubercidin}
\]

5-(1-Hydroxyethyl)tubercidin, 5-(1-methoxyethyl)tubercidin, and 5-(2-buten-1-yl)tubercidin are each a pair of diastereomers. Class 2 (sugar-modified tubercidin analogs), in which \(R_1 = H, \text{CN}, \text{or CONH}_2\) and \(R_2 = H\) (2'-deoxy) or OH (ara). Class 3 (carbocyclic adenosine analogs), exemplified by neplanocin A. Class 4 (acyclic adenosine analogs), exemplified by (RS)-9-(2,3-dihydroxypropyl)adenine. Class 5 (miscellaneous), exemplified by 3-deazaguanine.

Cytotoxicity. Cytotoxicity measurements were based on two parameters: (i) alteration of normal cell morphology (morphological cytotoxicity) and (ii) inhibition of host-cell RNA synthesis (metabolic cytotoxicity). To evaluate (i) a change in cell morphology, confluent WI-38 cell monolayers which were not infected but were treated with various concentrations of the test compounds were incubated in parallel with the virus-infected cell cultures and examined microscopically at the same time as viral cytopathogenicity was recorded for the virus-infected cell cultures. Any change in cell morphology, e.g., rounding up, shrinking, or detachment of cells, was considered as evidence for cytotoxicity. The morphological cytotoxicity is expressed as the minimum toxic concentration (MTC) required to alter normal cell morphology. To measure (ii) inhibition of host-cell RNA synthesis, WI-38 cells were seeded in Linbro microtiter tray wells at 40,000 cells per well in EMEM containing 10% FCS, various concentrations of the test compounds (200, 100, 50, 25, . . . , 0.04, 0.02, 0.01 \(\mu\)g/ml), and 2.5 \(\mu\)Cl (0.125 \(\mu\)Ci/well) of \(^{3}H\)uridine (specific radioactivity, 29 Ci/mmol; The Radiochemical Centre, Amersham, United Kingdom) per ml. The cells were allowed to proliferate for 16 h at 37°C and then treated with 5% ice-cold trichloroacetic acid, washed five times with trichloroacetic acid, washed five times with 95% ethanol, air dried, and counted for radioactivity in 7.5 ml of Lipoloma scintillation fluid. The metabolic cytotoxicity is expressed as the inhibitory concentration required to inhibit \(^{3}H\)uridine incorporation by 50% (IC\(_{50}\)). The MTCs and IC\(_{50}\)s listed in Table 1 represent the average values for three separate experiments.

Selectivity. Based on the MIC\(_{50}\) required to inhibit virus-induced cytopathogenicity and the two cytotoxicity parameters (expressed as MTC and IC\(_{50}\), respectively), two selectivity indexes were calculated: index \(A = \text{MTC/MIC}_{50}\) and
index \( B = \text{IC}_{50}/\text{MIC}_{50} \). In almost all cases, index A was greater than index B, which reflects the sensitivity of the assay methods for detecting morphological and metabolic cytotoxicity.

**Virus yield reduction.** To determine the inhibitory effects of the compound on virus replication, confluent WI-38 cell monolayers in Nunclon macrowells (15-mm diameter) were inoculated with rhinovirus type 1A at a multiplicity of \( 10^{4.5} \) PFU/0.2 ml per well (about 0.3 PFU per cell). After 1 h of adsorption, virus was removed, and the cells were further incubated in 1 ml of EMEM containing 3% FCS and various concentrations (0, 0.1, 1, 10, or 100 \( \mu \text{g/ml} \)) of the test compounds for the indicated times (1, 8, 24, or 48 h). After freeze-thawing of the cell cultures (cells plus medium), cell debris was removed by centrifugation at 1,300 \( \times g \), and virus yield of the supernatants was determined by plaque formation in WI-38 cells (in Falcon petri dishes of 60-mm diameter).

**RESULTS**

Among the 5- or 6-substituted tubercidin analogs, several derivatives, i.e., tubercidin, sangivamycin, toyoacamycin, 5-(1-hydroxyethyl)tubercidin, and 5-(2-buten-1-yl)tubercidin (the latter being a mixture of \( E \) and \( Z \) isomers at a 2:1 ratio), inhibited the cytopathogenicity of rhinovirus types 1A, 1B, and 9 at concentrations well below 1 \( \mu \text{g/ml} \), the most potent being tubercidin itself with an MIC\(_{50}\) of 0.03 \( \mu \text{g/ml} \) (Table 1).

Of the sugar-modified tubercidin analogs, only 2'-deoxytoyoacamycin exhibited an MIC\(_{50}\) of \(<1 \mu \text{g/ml} \) (against rhinovirus types 1B and 9). Of the carbocyclic adenosine analogs, carbocyclic 7-deazaadenosine proved the most potent, with an MIC\(_{50}\) of 2 \( \mu \text{g/ml} \) (against rhinovirus types 1B and 9). Acyclic adenosine analogs were totally ineffective as antirhinovirus agents, and from the miscellaneous reference compounds formycin A, pyrazofurin, and 3-deazaguanine showed the lowest MIC\(_{50}\)s (within the range of 5 to 25 \( \mu \text{g/ml} \)) (Table 1).

From the results presented in Table 1, it is clear that, despite their high potency as antirhinovirus compounds, tubercidin, 5-(1-hydroxyethyl)tubercidin, 5-(2-buten-1-yl)tubercidin, sangivamycin, and toyoacamycin did not display much selectivity in their antirhinovirus action. Their selectivity indexes fell in the range of 3 to 30 (index A) and 1.3 to 4 (index B). Of the sugar-modified tubercidin analogs, only the \( ara \) analog of sangivamycin showed some selectivity (index A = 8.6; index B = 3.1). Of the carbocyclic and acyclic adenosine analogs, none proved to be a selective inhibitor of rhinovirus; and of the miscellaneous group of compounds, 3-deazaguanine showed the highest selectivity (index A = 50; index B = 33).

Ribavirin was negatively selective in that it inhibited the incorporation of \([5-\text{H}]\)uridine into host-cell RNA at a concentration far below the MIC for rhinovirus type 1A, 1B, or 9. It should be pointed out, however, that for ribavirin and pyrazofurin, the IC\(_{50}\) for \([5-\text{H}]\)uridine incorporation may not truly reflect inhibition of RNA synthesis; viz., the IC\(_{50}\) of ribavirin for \([5-\text{H}]\)uridine incorporation may be lower than expected because of an inhibitory effect on the salvage pathway of uridine secondary to an inhibition of the de novo biosynthesis of GMP (38), whereas the IC\(_{50}\) of pyrazofurin for \([5-\text{H}]\)uridine incorporation may be higher than expected because of a stimulatory effect on the salvage pathway of uridine (consequent to an inhibition of the de novo biosynthesis of UMP [6]).

With the compounds that proved most potent or selective, or both in inhibiting rhinovirus-induced cytopathogenicity, i.e., 5-(2-buten-1-yl)tubercidin, 5-(1-hydroxyethyl)tubercidin, sangivamycin, and 3-deazaguanine, further experiments were undertaken to determine their inhibitory effects on the production of rhinovirus type 1A progeny (yield). 5-(2-Buten-1-yl)tubercidin effected a 3 to 4 \( \log_{10} \) reduction in virus yield at a concentration as low as 1 \( \mu \text{g/ml} \) (Fig. 2). 3-Deazaguanine achieved a 1.5 to 2 \( \log_{10} \) reduction in virus yield, but only if added at a concentration of 100 \( \mu \text{g/ml} \), and, in contrast with the virus yield reductions obtained with 5-(2-buten-1-yl)tubercidin (Fig. 2A) and the two other compounds [5-(1-hydroxyethyl)tubercidin and sangivamycin (data not shown)], the virus yield reduction achieved by

![FIG. 2. Effects of 5-(2-buten-1-yl)tubercidin (A) and 3-deazaguanine (B) on the replication of rhinovirus type 1A in WI-38 cells. Concentration of the compounds: 100 \( \mu \text{g/ml} \) ( ), 10 \( \mu \text{g/ml} \) ( ), 1 \( \mu \text{g/ml} \) ( ), or control ( ).](image-url)
3-deazaguanine (Fig. 2B) was only transient. The reduction of rhinovirus type 1A yield by 5-(1-hydroxyethyl)tubercidin, 5-(2-buten-1-yl)tubercidin, sangivamycin, and 3-deazaguanine may be interpreted to mean that their inhibitory effects on rhinovirus cytopathogenicity probably result from an inhibition of virus replication.

DISCUSSION

A number of the purine nucleoside analogs tested, i.e., tubercidin, 5-(1-hydroxyethyl)tubercidin, 5-(2-buten-1-yl)tubercidin, sangivamycin, and 3-deazaguanine, proved to be quite potent or selective (or both) inhibitors of rhinovirus replication, but none of these nucleoside analogs appeared comparable in potency or selectivity to the recently described flavans (3), flavones (25), chalcones (24), or isoxazoles (15, 31). Most of the latter compounds bind directly to the rhinovirus particles and appear to inhibit virus replication by preventing uncoating of the virion and subsequent release of the viral RNA. Such a mode of action has been demonstrated for both 4',6-dichloroflavon (39) and 4'-ethoxy-2'-hydroxy-4,6-dimethoxychalcone (29) and suggested for several other compounds (15, 25, 29, 34, 41).

It is not yet known where the targets of the tubercidin analogs are. They may interact with one or, more probably, several sites; but it is, at present, impossible to conceive any particular target with which the compounds should interact to ensure a selective effect on rhinovirus replication. 3'-Adenosylmethylamine-dependent transmethylation reactions, and in particular the enzymes involved in the regulation of these reactions such as S-adenosylhomocysteine hydrolase, have been identified as likely targets for the activity of carbocyclic and acyclic adenosine analogs against (−)RNA viruses and (±)RNA viruses (9); but, since none of these nucleoside analogs has any substantial activity against rhinoviruses, S-adenosylhomocysteine hydrolase disqualifies as a useful target for the design of antirhinovirus agents.

Antirhinovirus compounds targeted at virus uncoating are apparently endowed with significant potency and selectivity (3, 15, 24, 25, 31). These compounds bind to specific sites of the viral capsid, which is thereby stabilized and prevented from releasing the RNA. The structural determinants of the viral capsid binding sites for antirhinovirus compounds remain to be elucidated. These structural determinants have to be rather subtle, considering the large variation in sensitivity of different rhinovirus types to the same antirhinovirus compound (3, 15, 43). Such highly specific binding sites may also be prone to mutations, which could, considering the easy transmission of rhinoviruses among humans, promptly lead to the circulation of drug-resistant rhinovirus mutants in a given population.

Despite their potent and selective antiviral activity in vitro, the rhinovirus inhibitors that have so far been the subject of clinical studies, viz., enviroxime (21, 26, 28, 33), 4',6-dichloroflavon (32), and some isoxazoline derivatives (40, 43), have proven of little, if any, value in the prophylaxis or therapy of rhinovirus infections in volunteers. No significant effects on rhinovirus clinical score, or virus excretion were noted whether the compounds were given intranasally (21, 26, 28, 33, 43) or orally (32, 40). It is not clear to what extent these failures are due to the formulation and route of administration and the ensuing bioavailability of the drug. But if lack of clinical effectiveness was to be found for all antirhinovirus compounds that are targeted at virus uncoating, it would certainly seem advisable to look for other targets and other approaches in the design of antirhinovirus agents.

Thus, an approach such as that used in the present study may well be worth pursuing. Although the present series of compounds did not yield any congener that came near in potency or selectivity to the rhinovirus uncoating inhibitors, the potency or selectivity of some compounds (i.e., tubercidin, 3-deazaguanine) was such that with the proper chemical modifications they may give rise to new derivatives with increased potency or selectivity or both. The synthesis of new analogs of tubercidin (4) and 3-deazaguanine (36) should be viewed in this perspective.

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LITERATURE CITED


