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Mini-Review

A comparative test of fifteen compounds against all known human rhinovirus serotypes as a basis for a more rational screening program

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Summary

A systematic evaluation of 15 rhinovirus capsid-binding agents against all 100 serotyped human rhinoviruses revealed the existence of two virus groups, based upon differential susceptibility to antiviral compounds. Elongated and short-chained compounds preferentially inhibited groups A and B. The positions of the rhinoviruses within a map derived from a multivariate analysis allow for the selection of a panel of 17 rhinoviruses, for which the median antiviral inhibitory value against them will accurately predict the median value against 100 serotypes. This rationalizes the search for broad-spectrum capsid-binding antirhinovirus drugs, or combinations of drugs with complementary spectra that may be necessary to effectively inhibit both type A and type B viruses.

Rational screening program; Rhinovirus; Screening, antiviral

Human rhinoviruses (HRV) represent a large genus within the class of the picornaviridae, containing 100 antigenically different serotypes (Hamparian et al., 1987). The three-dimensional structures of HRV14 (Rossmann et al., 1985) and HRV1A (Kim et al., 1989) have recently been studied in atomic detail. The three larger structural proteins (VP1, VP2 and VP3) of both viruses form the exterior of the viral capsid, while VP4 is at the interface between the capsid and the RNA. Neutralizing antibody binding sites were found on the extreme surface of the virus, surrounding a 25 Å deep 'canyon' on the viral surface. The

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canyon structure has been proposed to be the site of receptor binding (Colonno et al., 1988). The floor of the canyon is formed by relatively conserved sequences (Rossmann et al., 1985). By use of X-ray diffraction, WIN 51711, an antipicornavirus agent was shown to bind into a hydrophobic pocket beneath this canyon floor in HRV14 (Smith et al., 1986).

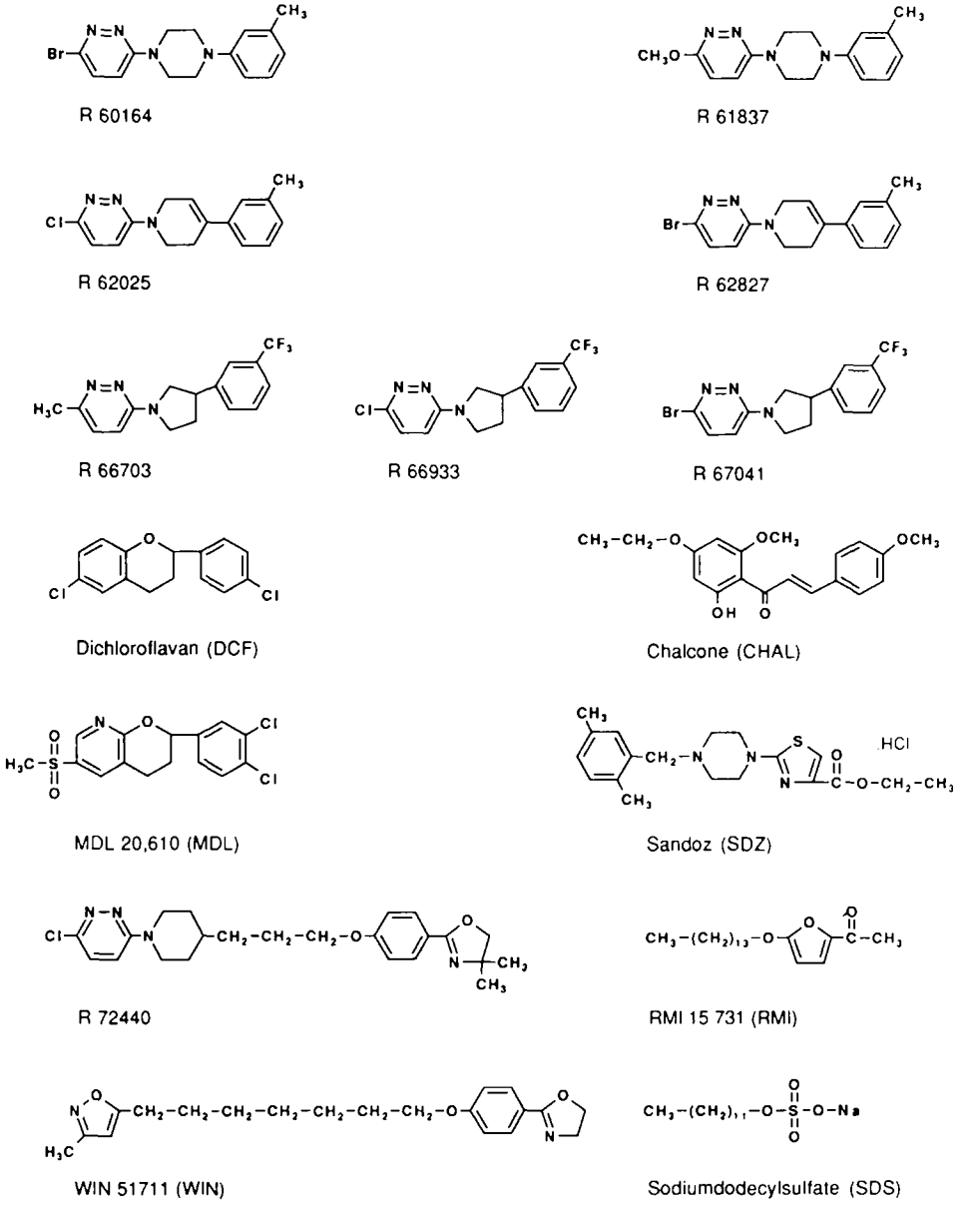

Fig. 1. Panel of antiviral compounds known to inhibit rhinovirus replication by binding to the capsid proteins.

TABLE I

Minimal inhibitory concentrations (in ng/ml) of 15 capsid-binding compounds as tested against 100 typed rhinoviruses

HRV	AVG	Antiviral compound															Median MIC per virus
		CHAL	DCF	MDL	RMI	SDS	SDZ	WIN	60164	61837	62025	62827	66703	66933	67041	72440	
1A	B	313	33	362	1200	4600	275	3350	300	312	44	50	31	48	78	32000	300
1B	B	400	18	100	2050	5200	20	4600	337	726	63	55	9	5	6	32000	100
2	B	10	163	1.4	43	1600	300	658	16	39	19	3	18	16	6	925	19
3	A	255	16000	32000	1600	32000	1325	228	1250	5600	6000	2500	10000	32000	16000	285	5600
4	A	4500	16000	32000	558	32000	16000	110	32000	22000	3300	1400	5700	32000	32000	63	16000
5	A	16000	13000	32000	250	32000	16000	203	32000	5500	3500	1600	5000	32000	5000	44	5500
6	A	16000	16000	32000	419	32000	16000	39	32000	32000	32000	32000	16000	32000	32000	75	32000
7	B	16	1250	250	104	12600	1500	2700	5600	4800	1300	1050	250	725	39	2200	1250
8	A	16000	16000	32000	16000	24000	15000	20000	32000	32000	9600	13600	13600	32000	7000	32000	16000
9	B	97	125	31	338	638	3500	3500	8	6	3	2	11	5	13	32000	31
10	B	219	89	500	250	21000	2800	1500	32000	6000	1025	1057	175	51	78	8000	1025
11	B	16	23	2	157	1200	157	1125	16	16	2	2	2	1.0	2	194	16
12	B	310	275	50	32000	2600	11400	3400	2400	2500	883	288	88	16	16	32000	883
13	A	624	16000	32000	32000	32000	16000	1400	32000	32000	24000	32000	16000	32000	32000	32000	32000
14	A	600	16000	32000	1750	32000	2400	175	20000	11700	11200	6016	16000	17000	32000	700	11700
15	B	100	175	135	575	3200	5800	1176	194	310	60	47	59	30	36	32000	175
16	B	82	104	23	645	7200	1925	800	20	67	22	16	78	16	16	32000	78
17	A	16000	16000	32000	2500	25200	10000	312	32000	29000	32000	16000	16000	32000	32000	32000	25200
18	B	27	250	45	144	9400	78	3150	426	657	44	56	94	63	27	11200	94
19	B	188	250	35	575	3000	1600	20000	228	180	52	41	47	85	42	19200	188
20	B	16	125	117	1875	4150	11	479	325	1300	22	30	55	13	10	32000	117
21	B	16	350	47	91	6600	808	2800	16	16	16	0.5	1.4	0.8	1.0	32000	16
22	B	25	1500	25	250	19000	16000	1050	800	1600	250	266	175	356	141	32000	356
23	B	9	17	0.2	105	407	103	166	0.4	16	2.4	1.3	5	1.6	1.7	1675	9
24	B	27	500	46	125	18000	175	750	163	175	109	63	16	13	16	16000	125
25	B	20	6	2	2496	20000	83	4800	244	1000	110	41	19	11	13	32000	83
26	A	16000	16000	32000	463	2800	16000	58	32000	16000	3750	4000	8000	32000	4000	15	8000
27	A	500	16000	32000	32000	32000	16000	1000	32000	32000	32000	24000	16000	32000	32000	32000	32000
28	B	156	4200	700	32000	3200	1000	3200	3000	5000	313	615	482	125	106	8000	1000
29	B	130	2	7	77	11200	85	1650	24	47	21	16	0.9	0.4	0.5	22400	24
30	B	26	29	1.2	44	1400	700	294	15	22	23	8	3	1.3	1.0	857	23
31	B	190	23	250	38	14000	1301	22000	3000	14000	526	375	100	100	70	32000	375
32	A	238	16000	32000	32000	32000	16000	688	32000	32000	32000	32000	16000	32000	32000	32000	32000
33	B	21	31	12	154	9100	538	600	16	19	16	3	16	16	6	1600	19

TABLE 1 *(continued)*

HRV	AVG	Antiviral compound															Median MIC per virus
		CHAL	DCF	MDL	RMI	SDS	SDZ	WIN	60164	61837	62025	62827	66703	66933	67041	72440	
34	B	24	36	6	49	5300	100	1450	29	74	14	7	52	36	21	838	36
35	A	28	16000	32000	90	32000	251	9	122	975	9600	32000	10000	19200	19200	78	9600
36	B	16	219	41	41	11400	1675	1075	7400	5600	2000	800	232	132	57	1752	800
37	A	253	16000	32000	645	25000	406	85	2500	8096	6400	32000	12800	5000	5600	54	5600
38	B	16	20	22	182	850	350	750	24	117	10	11	21	14	16	17000	22
39	B	36	213	1050	188	21000	5200	2475	244	375	75	22	282	250	156	32000	250
40	B	39	33	175	182	9900	7800	900	172	313	56	44	53	32	40	11750	172
41	B	775	188	2700	2450	10100	2275	32000	1500	5800	1100	876	1075	876	600	32000	1500
42	A	16000	16000	29500	32000	32000	16000	3600	32000	32000	32000	32000	16000	32000	32000	32000	32000
43	A	652	16000	32000	32000	32000	16000	852	32000	32000	32000	32000	16000	32000	32000	32000	32000
44	B	99	16	16	50	22000	438	2375	458	1300	85	44	7	3	3	32000	85
45	A	1250	16000	32000	32000	32000	16000	1504	32000	32000	32000	32000	16000	32000	32000	32000	32000
46	B	150	1727	651	500	32000	12800	147	1012	2266	370	141	29	30	27	3200	500
47	B	144	3	3	24	9000	36	3100	375	3000	52	72	12	6	7	32000	52
48	A	16000	16000	32000	32000	25800	16000	6000	32000	21000	6200	1248	12800	11590	32000	5600	16000
49	B	18	150	1.5	43	2000	1625	1475	24	25	16	13	16	14	13	32000	24
50	B	55	13	6	18	1240	79	500	12	33	6	3	20	18	20	1400	20
51	B	40	5600	125	150	11000	88	2300	250	6000	33	40	63	5	4	312	125
52	A	16000	16000	32000	350	32000	16000	94	32000	11200	5600	32000	12000	32000	32000	500	16000
53	B	188	1950	257	4800	12800	8000	10000	12000	4000	1425	483	375	219	175	5600	1950
54	A	1625	3900	32000	32000	30000	16000	32000	32000	32000	6000	3200	8000	25600	28000	32000	30000
55	B	1600	20	3	2000	8400	63	4950	22	63	50	24	10	6	9	32000	50
56	B	85	85	600	20	6800	2800	2225	1350	2700	395	188	306	332	287	32000	395
57	B	619	2000	500	863	19000	1050	32000	16000	15000	1875	1238	1400	32000	838	32000	1875
58	B	16	800	63	16	16000	2850	1000	17400	5600	700	700	595	313	125	2000	700
59	B	300	1950	6000	900	10600	7200	32000	1500	4000	375	338	1400	32000	32000	32000	4000
60	B	298	2000	2600	32000	24200	16000	24000	1700	2250	375	338	1550	888	563	32000	2000
61	B	31	184	16	400	16000	876	5150	26	78	16	16	75	156	132	32000	132
62	B	46	16	16	9600	32000	176	32000	1400	5200	490	200	42	94	30	32000	200
63	B	269	1300	733	355	5100	2200	3400	3000	6000	313	94	550	200	475	3600	733
64	B	21	74	16	1675	7200	14500	2150	138	106	16	16	41	8	16	26000	74
65	B	145	6900	985	1150	11600	3050	2650	615	7000	66	39	88	87	47	1900	985
66	B	250	156	172	775	23000	4800	3500	1900	3000	263	169	88	31	88	32000	263
67	B	107	188	22	200	438	3500	3000	16	16	0.8	1.2	16	16	16	32000	22
68	B	16	14000	32000	32000	22000	500	21000	32000	32000	1438	850	1650	79	110	32000	14000
69	A	16000	16000	32000	2600	32000	16000	213	32000	28000	3475	6400	16000	32000	16000	550	16000

TABLE 1 *(continued)*

HRV	AVG	Antiviral compound															Median MIC per virus
		CHAL	DCF	MDL	RMI	SDS	SDZ	WIN	60164	61837	62025	62827	66703	66933	67041	72440	
70	A	32000	16000	32000	188	27000	5000	16	9000	12000	6400	1000	2750	32000	6000	29	6400
71	B	17	192	13	24	750	58	273	23	350	6	3	9	0.5	0.5	20	20
72	A	1350	16000	32000	32000	32000	5200	1000	32000	32000	5000	16000	16000	16000	32000	2300	16000
73	B	77	313	125	75	11200	1000	11200	116	177	63	23	288	156	117	32000	156
74	B	71	107	52	156	1400	7800	2275	102	203	16	16	92	31	34	5200	102
75	B	215	3000	925	150	25000	1000	6400	32000	32000	1400	752	6000	32000	3000	18000	3000
76	B	16	12	6	47	407	54	425	2	4	1.0	0.7	3	4	2	275	6
77	B	94	149	675	3000	26000	5000	16000	5000	4000	776	512	100	328	138	4000	776
78	B	22	16	0.2	2800	1600	219	425	800	2800	256	125	22	10	69	32000	219
79	A	38	16000	32000	750	32000	300	16	750	8000	5000	8000	10800	32000	32000	16	8000
80	B	106	16	5	400	22000	269	105	55	155	5	4	10	5	5	20000	55
81	B	82	24	24	408	1600	950	1227	11	22	7	6	6	6	6	32000	24
82	B	90	163	150	300	500	2400	2000	16	36	8	7	8	6	12	8000	90
83	A	16	16000	32000	119	32000	250	11	325	1100	2600	1500	3400	7000	1750	28	1500
84	A	2700	16000	32000	1250	32000	16000	357	32000	32000	5600	6000	16000	16000	32000	1673	16000
85	B	36	250	250	310	9200	10000	1500	700	1400	86	79	30	25	22	32000	250
86	A	16000	16000	32000	16000	32000	16000	1000	32000	32000	5600	32000	7000	32000	32000	800	16000
87	A	119	10000	32000	2800	23800	8000	9000	10000	9600	1500	1000	5700	3000	2500	4000	5700
88	B	38	185	13	45	5780	1300	670	725	796	171	200	53	12	88	32000	185
89	B	33	500	64	50	9600	125	1575	3500	8000	1100	1126	60	31	20	32000	500
90	B	43	14	3	310	4000	200	440	6	6	3	2	2	2	2	1450	6
91	A	32000	13600	4000	800	32000	21600	100	30000	21700	3400	5400	16000	24000	32000	880	16000
92	A	110	32000	32000	3200	32000	700	125	425	2800	20800	24000	12400	21600	21600	875	12400
93	A	32000	32000	32000	500	32000	11000	140	5000	2500	250	375	12000	32000	32000	400	11000
94	B	220	125	100	2000	700	22000	5250	63	125	12	16	63	50	63	32000	125
95	A	32000	32000	32000	32000	32000	32000	32000	32000	32000	32000	32000	32000	32000	32000	32000	32000
96	B	63	175	13	150	10500	1250	3200	88	156	31	31	78	100	39	32000	100
97	A	32000	6600	4000	400	21600	6500	63	1500	1250	175	175	4600	32000	32000	350	4000
98	B	700	752	4000	1600	22800	7000	22000	32000	11200	1250	2000	2400	3000	3200	3200	3200
99	A	32000	32000	32000	2400	27200	32000	1000	32000	21600	4000	8000	11500	18800	32000	11200	21600
100	B	188	1400	4000	150	22400	11800	2500	32000	21400	1500	1750	2000	1250	750	32000	2000
Median MIC per compound			130	500	257	463	16000	2400	1475	1250	2800	370	266	175	132	106	18000

HRV = human rhinovirus serotype; AVG = antiviral group (see text and Fig. 2). For abbreviations of antiviral compounds, see Fig. 1. Median MIC per virus = MIC needed for inhibition by 8 of the 15 compounds. Median MIC per compound = MIC needed to inhibit 51 of the 100 serotypes.

In addition to WIN 51711, several structurally unrelated antiviral compounds, such as SDS (Lonberg-Holm et al., 1973), dichloroflavan (Bauer et al., 1981), R 61837 (Andries et al., 1988), chalcone (Ishitsuka et al., 1982), MDL 20610 (Kenny et al., 1986), RMI 15731 (Ash et al., 1979) a Sandoz antirhinovirus compound (Fig. 1, SDZ; EP 187618) and chalcone amides (Ninomiya et al., 1990) have also been found to inhibit rhinoviral replication by binding to the viral capsid proteins (see Fig. 1 for structures).

Resistant mutants raised against one of these compounds are usually cross-resistant to the other capsid-binding compounds (Andries et al., 1989; Ninomiya et al., 1990), suggesting that all these molecules bind to a place corresponding to the hydrophobic pocket in HRV14, although not necessarily binding to the same amino acids.

The first generation capsid-binding compounds were typically active against only a limited number of rhinovirus serotypes. Interestingly, when we compared the antiviral spectra of these molecules, it was found that most of the capsid-binding compounds were active against almost the same serotypes in each case, while being inactive against a group of other serotypes. However, the antiviral spectrum of one of these compounds, WIN 51711, was very different from the consensus spectrum that we had identified for the other capsid-binding compounds. This finding implied that a combination of two compounds with complimentary antiviral spectra could result in the inhibition of a broader spectrum of rhinoviruses. In order to exploit this possibility, more comparative data were needed on the spectra of the different compounds, which were all tested by slightly different methods, and more importantly, against only a limited number of serotypes.

We selected a panel of 15 capsid-binding compounds belonging to structurally different chemical classes (see Fig. 1) but all sharing the binding site of WIN 51711 (Andries et al., 1989), and evaluated their antiviral potency and spectrum in an MIC (Minimal Inhibitory Concentration) test (Andries et al., 1990), using all 100 typed rhinoviruses. Results of these MIC tests (Table 1) allow a comparison of the potencies of the compounds and the sensitivities of the viruses. Median MIC values can be calculated for each compound (Table 1; median MIC per compound = MIC needed to inhibit 51 of the 100 serotypes) and for each virus (Table 1; median MIC per virus = MIC needed for inhibition by 8 of the 15 compounds). The most potent compounds were R 67041 (median MIC 106 ng/ml), followed by chalcone (130 ng/ml), R 66933 (132 ng/ml), R 66703 (175 ng/ml), MDL 20610 (257 ng/ml) and so on (see last row of Table 1). Nine serotypes (serotypes 76, 90, 23, 11, 21, 2, 33, 50, and 71) displayed a very high sensitivity to capsid-binding compounds with median MICs below 20 ng/ml (see last column of Table 1).

The overall potencies of the compounds and the sensitivities of the viruses do not take into account the specificity of the interaction between an antiviral compound and a virus. Indeed, the MIC values shown in Table 1 are a result of the potency and the specificity of the compound on the one hand, and the sensitivity and specificity of the viral target on the other hand. Irrespective of

having a low potency, a compound can be either specifically active against one or more serotypes or exhibit a broader spectrum of antiviral activity. SDS is an example of a compound with a low, but broad-spectrum activity. Some serotypes are more susceptible to SDS than others, but these same serotypes tend to be the most sensitive for other compounds as well. On the other hand, a compound with a low potency can be specifically active against one or more serotypes. WIN 51711 and R 72440 have an overall potency lower than that of the other compounds studied here, but they tend to be specifically active against those serotypes that are not susceptible to the more potent compounds. The same reasoning can be followed in case of the serotypes. A given serotype, irrespective of having a low sensitivity, can be either specifically sensitive for one or more compounds, or exhibit a broad sensitivity for most antivirals. For instance, serotypes such as HRV 3, 4, 5, and 6 have a low overall sensitivity for most compounds, but are at the same time sensitive to WIN 51711 and R 72440.

In order to analyse and represent the specificity of an interaction in a highly visual way, and irrespective of potencies of compounds and sensitivities of viruses, we used the spectral map analysis technique, a variation of principal component analysis (Lewi, 1989). A virus is positioned in a multi-dimensional plot based on its specific sensitivity for each of the fifteen antivirals. An antiviral is positioned in the same plot based on its specific activity against each of the 100 rhinoviruses. When a virus has an above average sensitivity to a given compound, it is attracted by that compound and vice versa. When a virus has a below average sensitivity to a given compound, it is repelled from that compound. All these interactions and positions are computed automatically, based on the MIC data, and the resulting map, also called a spectral map, is a multi-dimensional plot of which the two most important dimensions are shown (Fig. 2). More details about the methods used to determine compound and virus locations using the spectral map analysis technique can be found elsewhere (Andries et al., 1990).

Two groups of rhinoviruses, designated antiviral group A and antiviral group B, were identified by use of cluster analysis (Andries et al., 1990). Antiviral group A contains twice as many (67) serotypes as antiviral group B (33 serotypes). The possible implications of the antiviral groups hypothesis to the understanding of evolutionary relationships between rhinoviruses and of rhinovirus epidemiology has been discussed elsewhere (Andries et al., 1990). We would now like to explain how this model can be used to rationalize drug screening.

The analysis places similar viruses, that is viruses with similar susceptibilities to antiviral compounds, into clusters. Antiviral group A consists of viruses having a more than average susceptibility to elongated compounds such as WIN 51711 and R 72440. Antiviral group B consists of viruses susceptible to structurally shorter antivirals such as R 61837, chalcone and dichloroflavan. Viruses which are computed to lie closely to each other on the spectral map, tend to have the same MICs when tested against the same antivirals, if their

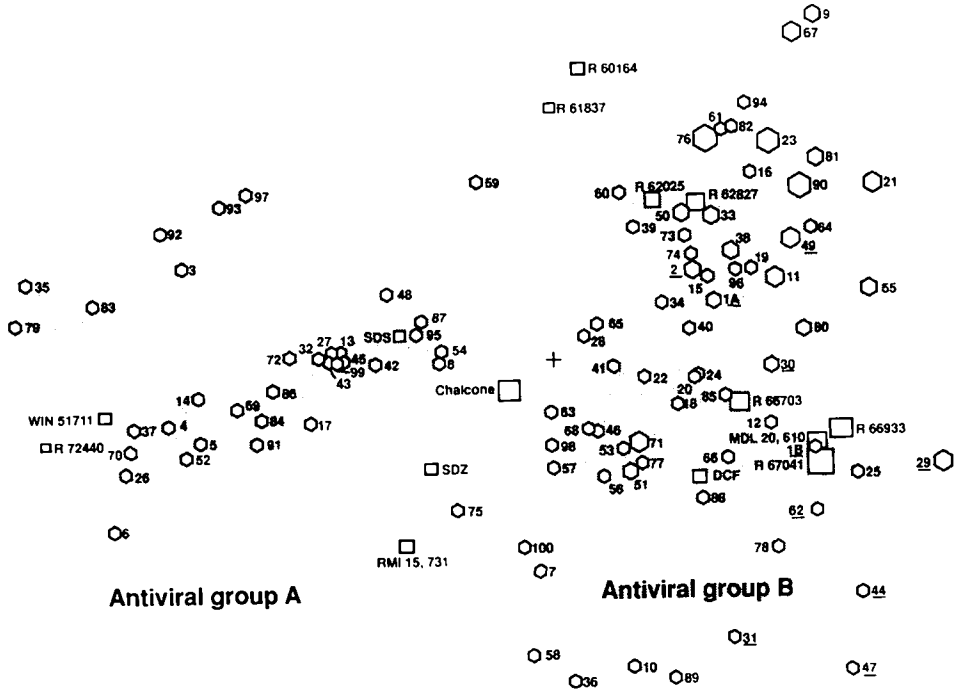

Fig. 2. Spectral map obtained by multivariate analysis of antiviral tests. A panel of 15 antiviral compounds (see Fig. 1) was tested against all rhinovirus serotypes. The origin of viruses and compounds has already been described (Andries et al., 1990). The positions of compounds are computed according to their specificities for the 100 rhinovirus serotypes, and irrespective of their potencies (potency is defined here as the median reciprocal MIC of a compound against the various viruses). Viruses are located on the same map according to their specificities for the 15 compounds and irrespective of their sensitivities (sensitivity is defined here as the median reciprocal MIC of a virus for the various compounds). Median potencies of compounds and median sensitivities of serotypes (see Table 1) are reflected by the sizes of hexagons and squares, respectively. The three-dimensional arrangement of compounds and serotypes has been rotated in order to show optimum separation of the two groups of serotypes.

overall sensitivities are similar (e.g. HRV 9 and 67, HRV 58 and 36).

Antiviral compounds with a similar chemical structure usually have similar antiviral specificities and are therefore computed to lie closely to each other (compare Figs. 1 and 2). Shorter compounds are positioned at the right hand side of Fig. 2, while longer compounds are usually located in the left hand side. Some antiviral compounds are particularly active against one subset of rhinoviruses while being inactive or less than averagely active against another subset of serotypes. According to calculation, compounds specifically active against serotypes from antiviral group A appear to lie on the left-hand side of Fig. 2, while compounds specifically active against serotypes from antiviral group B appear on the right-hand side. It is interesting to see that two groups of compounds seem to exist: a large group clearly more active against serotypes of antiviral group B and a small group with activity largely restricted to rhinoviruses of antiviral group A. None of the compounds studied seems to be

endowed with a real broad spectrum of activity. On the other hand, the combination of a compound, highly active against serotypes of antiviral group B and another one with high activity against serotypes of group A could result in the inhibition of a broader spectrum of rhinoviruses. Our own data suggest that neither antagonism nor synergism occurs when such a combination is tested against a particular serotype (results not shown). However, new compounds with a high activity against antiviral group A viruses are needed to make such a combination possible.

To explain how antiviral compounds that belong to different chemical classes draw a distinction between two groups of viruses, we assume that the hydrophobic pocket, which is the putative binding site for all these compounds, is dimorphic in shape and/or composition. A crystallographic study of HRV14 showed that the WIN compounds bind into a long and narrow hydrophobic pocket. The other rhinoviruses from antiviral group A probably have a similar long and narrow drug-binding pocket. On the other hand, the viruses from antiviral group B seem to have a pocket which is different in amino acid composition (Andries et al., 1990) and shape (Kim et al., 1989) to accept the generally shorter molecules active against these serotypes. The higher activity of shorter compounds against viruses of antiviral group B, is consistent with the finding that WIN compounds with short (5-carbon) aliphatic chains have a greater activity in HRV1A (antiviral group B) than compounds with a 7-carbon aliphatic chain (Kim et al., 1989).

It is obvious that the model can be used to rationalize the search for new or more potent antirhinovirus compounds. From the MICs shown in Table 1 and the spectral map analysis it can be deduced that screening new compounds against only one or two serotypes can be very misleading if the serotype is not carefully selected. For instance, we initially used RV9 for screening in our laboratory. It is probably not a coincidence that we initially found a compound (R 61837), highly active against HRV9 and some other serotypes with a susceptibility profile similar to that of HRV9, but inactive against others. By using screening viruses located at the edges of the antiviral groups, such as RV9, 89 or 35, chances to select compounds with activity against only a few serotypes are relatively high.

For general screening, it is obviously necessary to select at least one serotype from each antiviral group. Serotypes located close to the centre of the antiviral groups are preferable because it can be anticipated that many other serotypes will have a similar antiviral susceptibility. The selection of serotypes with a high overall sensitivity for antiviral compounds and favourable culturing properties (e.g. HRV14 from antiviral group A and HRV2 from antiviral group B) further increases the chance of detecting weak but specific antiviral activity.

Once a new lead compound has been identified, it becomes increasingly important to discriminate between narrow-spectrum and broad-spectrum compounds. In order to do that, a panel of 17 viruses was selected from the spectral map (Fig. 3). As selection criteria we took into account what was known about the serotypes (for instance the sequence) and, more importantly,

the overall sensitivity and the position of that serotype in our model. Several serotypes with a low overall sensitivity for antiviral compounds were included in this panel to enable the assessment of antiviral activities for more resistant serotypes. When the spectrum of a variant of a lead compound is to be evaluated, the compound is tested against the panel of 17 serotypes. The calculation of a median MIC from the MICs obtained for the serotypes of each antiviral group allows for a very simple but accurate comparison of a compound's potency and antiviral spectrum.

The validity of this screening strategy is illustrated in Table 2. The MICs needed to inhibit 18% (3 of 17), 53% (9 of 17) or 71% (12 of 17) of the 17 screening viruses were compared with the MICs needed to inhibit the same percentage of all 100 serotypes. It can be seen that the values obtained with the panel of 17 are highly predictive for those obtained from the testing of all 100. In only 9% of the cases did the final MIC differ by a factor of more than three from the predicted one. The final MICs were usually somewhat lower than the predicted ones. This is probably a consequence of the inclusion of some fairly resistant viruses in the screening panel.

The data shown in Table 1 not only provide a rational basis for screening new capsid-binding compounds and improving existing ones, they also can be used for comparison with spectra of new compounds. Even when only a few MICs are published, it is now very easy to check whether the serotypes used

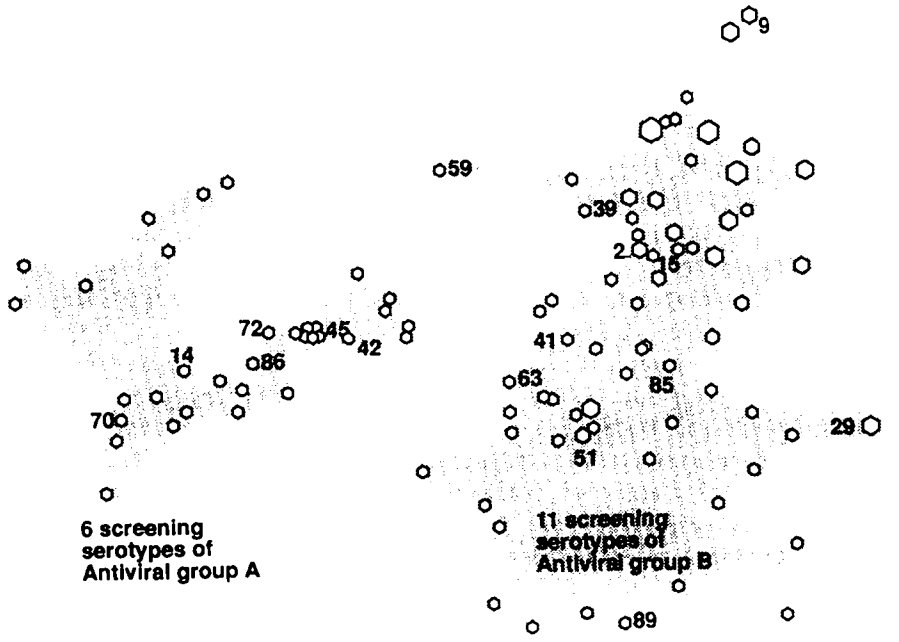

Fig. 3.Panel of screening viruses, selected from Fig. 2, and used to estimate a compounds activity against all 100 serotypes.

TABLE 2

Predictions of minimal inhibitory concentrations (in ng/ml) needed to inhibit 18, 53, and 71% of the 17 screening viruses (upper part), and MICs found upon testing all 100 rhinovirus serotypes

	SDS	DCF	60164	61837	62025	CHAL	62827	RMI	66703	66933	67041	72440	SDZ	WIN	MDL
18% of 17	3200	163	24	47	21	36	16	77	18	5	6	700	125	658	31
53% of 17	11000	1300	1500	6000	375	269	338	355	550	250	475	32000	5000	1575	1050
71% of 17	27000	16000	9000	11700	5000	775	1126	1750	2750	17000	32000	32000	5800	2475	29500
18% of 100	2800	29	24	74	16	22	13	91	16	8	10	550	200	203	13
53% of 100	18000	752	1400	3000	375	145	338	500	250	156	117	20000	2800	1500	500
71% of 100	25800	13600	16000	9600	2600	400	1400	2000	5700	17000	5600	32000	10000	3200	32000

have a high or low overall sensitivity, thus providing a more accurate idea of a compound's real potency.

The present study does not address whether the proposed model is applicable to compounds that do not share the same mechanism of action, i.e., binding to the hydrophobic pocket. However, as the antiviral grouping seems to be highly correlated to differences in amino acid sequences of several serotypes (Andries et al., 1990), it is possible that the model is indeed applicable to non capsid-binding compounds as well. Additional studies using such compounds are needed to evaluate the potential of this approach.

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