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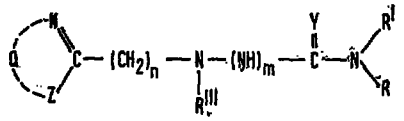
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(54) ANTI-VIRAL AND IMMUNE SUPPRESSANT COMPOSITIONS

(71) We, ELI LILLY AND COMPANY, a Corporation of the State of Indiana, United States of America, of 307 East McCarty Street, City of Indianapolis, State of Indiana, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention provides anti-viral and immune suppressant compositions comprising at least one N-heterocyclic urea-type compound of the formula:



wherein

R is α-naphthyl, C_5—C_8 cycloalkyl, 1-adamtyl, phenyl or substituted phenyl wherein said substituents can be one or more of halo, C_1—C_3 alkoxy, C_1—C_3 alkyl, amino, C_1—C_3 alkylamino, di-(C_1—C_3 alkyl)amino, nitro, or substituted by from 1 to 3 fluorine atoms;

R′ is hydrogen or phenyl;

R‴ is hydrogen or methyl;

n is 0, 1, 2 or 3;

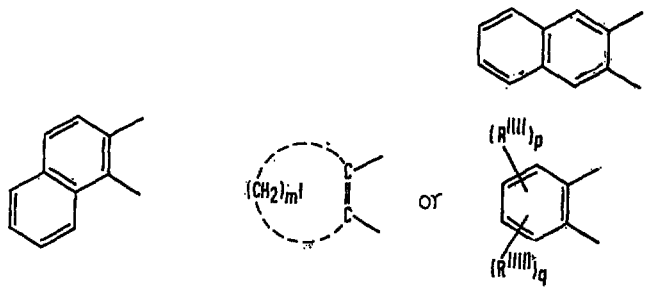
m is 0 or 1;

Y is S or 0;

Z is S, 0 or N—R″

[*Price 25p*]

wherein R'' is H, C_1—C_3 alkyl, or phenyl; and
Q is



wherein m' is 3,4,5 or 6;
R'''' is C_1—C_3 alkyl or halo;
R''''' is nitro, methyl substituted by from 1 to 3 fluorine atoms, C_1—C_3 alkoxy, carbo-(C_1—C_3)alkoxy, or C_1—C_3 alkylsulfonyl; and when R'''' and R''''' are taken together, they are methylene dioxy;
p is 0,1,2,3 or 4; and
q is 0,1 or 2.

The method of combatting the viral infection or suppressing the immune reaction in non-human mammals comprises administering to said mammals an effective non-toxic dose within the range of 0.01 to 1000 mgs of at least one of the N-heterocyclic ureas defined above. Accordingly, in a preferred aspect the anti-viral or immune suppressant compositions of the present invention are in non-toxic dosage form containing 0.01 to 1000 mgs of at least one of the N-heterocyclic ureas defined above.

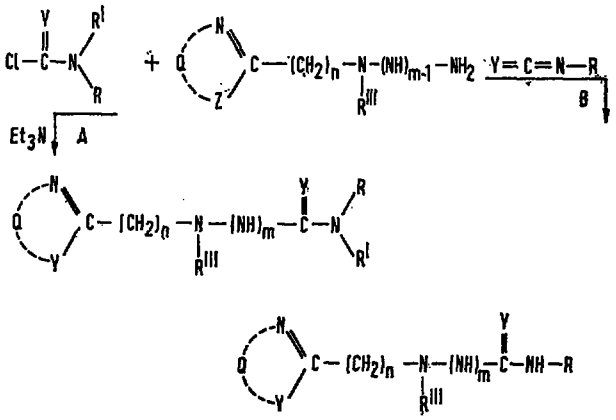
In the above formula, when R'' and R'''' represent C_1—C_3 alkyl, they can be methyl, ethyl, isopropyl or n-propyl. When R is C_5—C_8 cycloalkyl, permissible groupings include cyclopentyl, cyclohexyl, cycloheptyl and cyclo-octyl. When R is substituted phenyl, the substituent can be halo which hereinafter means fluorine, chlorine or bromine; C_1—C_3 alkoxy, such as methoxy, ethoxy, isopropoxy or *n*-propoxy; C_1—C_3 alkyl, the scope of which grouping is illustrated above for R'' and R''''; C_1—C_3 alkylamino such as methylamino, ethylamino, isopropylamino or *n*-propylamino; di-(C_1—C_3 alkyl)amino such as dimethylamino, diethylamino, methylethylamino, di-*n*-propylamino, methylisopropylamino and the like; or monofluoromethyl, difluoromethyl or trifluoromethyl.

When R'''' is halo, and R''''' is methyl substituted by from 1 to 3 fluorine atoms or C_1—C_3 alkoxy, their scope is the same as that defined above for R. When both R'''' and R''''' are taken together, they can be methylenedioxy. When R'''' is carbo-(C_1—C_3)alkoxy, groups which it represents include carbomethoxy, carboethoxy, carbo-*n*-propoxy and carboisopropoxy.

When R''''' is C_1—C_3 alkylsulfonyl, it can be illustratively, methyl-, ethyl-, isopropyl- or *n*-propylsulfonyl.

Illustrative compounds coming within the scope of the above formulas include:
N-(2-benzoxazolylmethyl)-N'-cyclopentyl urea,
N-(2-benzthiazolyl)-N'-(3,4-dichlorophenyl) urea,
N-[2-(5-fluoro)benzimidazolyl]-N'-(*p*-tolyl) urea,
N^1-[2-(4-nitro)benzimidazolyl]-N^4-(*o*-anisyl)semicarbazide,
N-[1-(*n*-propyl)-4-bromo-2-benzimidazolyl]-N'-cyclo-octyl urea,
N-(5-ethylsulfonyl-2-benzthiazolyl)-N'-(4-difluoromethyl)phenyl urea,
N^1-(5-carboethoxy-2-benzoxazolyl)-N^4-(*p*-dimethylaminophenyl)-semicarbazide,
N'-(4-isopropoxy-2-benzthiazolylmethyl)—
N^4-[(*p*-ethylamino)phenyl] semicarbazide.

Compounds represented by the above formulas useful in the therapeutic processes of this invention are prepared by reacting a 2-aminobenzimidazole, 2-aminobenzthiazole, or 2-aminobenzoxazole or a 2-hydrazinoheterocycle with an appropriately substituted isocyanate, thioisocyanate, thiocarbamoyl chloride or carbamoyl chloride according to the following reactions:



wherein Q, Z, Y, R, R′, R‴, n and m have the same meaning as hereinabove. In the above reaction scheme, reaction A must be employed when R′ is phenyl, but either reaction A or B can be used when R′ is hydrogen.

A typical preparation of a benzimidazolyl urea in which R′ is hydrogen follows:

Example 1

N-(2-Benzimidazolyl)-N′-cyclohexyl Urea

A reaction mixture was prepared contained 6.7 g. of 2-aminobenzimidazole and 6.3 g. of cyclohexylisocyanate and 200 ml. of tetrahydrofuran. A white precipitate formed immediately from the mixed substituents. The mixture was heated to refluxing temperature for about 8 hours. About 1 hour after heating had begun, the white precipitate redissolved, but appeared again toward the end of the heating period. The reaction mixture was cooled and the white precipitate separated by filtration. N-(2-benzimidazolyl)-N′-cyclohexyl urea thus prepared melted at about 335—336° C. after recrystallization from acetone-*n*-hexane.

N-cyclohexylcarbamoyl chloride can be used in place of cyclohexylisocyanate in the above reaction.

A typical preparation involving a carbamoyl chloride for compounds in which R′ is phenyl, is as follows.

Example 2

N-(2-Benzimidazolyl)-N′,N′-diphenyl Urea

A reaction mixture was prepared containing 2-amino-benzimidazole, diphenyl carbamoyl chloride and triethylamine in tetrahydrofuran. The reaction was carried out as in Example 1, but the compound was isolated by removing volatile materials by evaporation in dryness. The solid residue remaining in suspension was separated by filtration and the filter cake washed with water. N-(2-benzimidazolyl)-N′,N′-diphenyl urea thus prepared and purified melted at about 178°—180° C. after recrystallization from acetone-*n*-hexane solvent mixture.

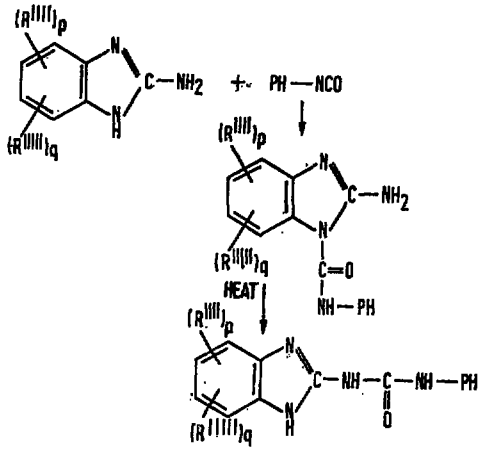
Tables 1—18 which follow contain analytical data and melting points for illustrative compounds for use with this invention prepared as indicated above.

Starting materials useful in the above process from which compounds in which R‴ is hydrogen and n is 0 can be produced are either available from commercial sources or are prepared by reacting the appropriately substituted *o*-phenylene or *o*-naphthalene diamine with cyanogen bromide according to the method of Leonard et al., *J. Am. Chem. Soc. 69,* 2459 (1947). Those starting materials in which R‴ is methyl are prepared by autoclaving a suitably substituted 2-chlorobenzimidazole, 2-chlorobenzthiazole or 2-chlorobenzoxazole with methylamine. Compounds in which m is 1 are prepared by autoclaving the 2-chloroheterocycle with hydrazine or a substituted hydrazine.

Novel starting materials prepared by the above procedure include the following:

2-amino-5(6)-chlorobenzimidazole
M.P.=158—161° C.
2-amino-5 (6)-methanesufonylbenzimidazole
M.P.=233—238° C.
2-amino-5(6)-trifluoromethylbenzimidazole
M.P.=152—155° C.
2-amino-5(6)-methylbenzimidazole
M.P.=192—199° C.

In the reaction scheme I above when a 2-aminobenzomidazole is used as one of the reactants, the first step of the reaction is the formation of a 1-carboxanilide or carboamide, which rearranges upon heating to the desired 2-benzimidazolyl urea. This reaction is illustrated in reaction scheme II below, wherein R', R'''' and R''''', p, and q have the same meaning as hereinabove, and in which PH is α-naphthyl, phenyl or substituted phenyl, wherein said substituents are one or more members of the group consisting of halo, C_1—C_3 alkoxy, C_1—C_3 alkyl, amino, C_1—C_3 alkylamino, C_1—C_3 dialkylamino, nitro, or methyl substituted by from 1 to 3 fluorine atoms. The scope of the phenyl substituents has been fully illustrated above in illustrating the scope of the term R, substituted phenyl being one of the permissible groupings for R.



Reaction Scheme II

The 1-substituted derivatives can be isolated when the reaction is carried out below 15° C. and preferably at about 0° C. The rearrangement of the 1-substituted compound to the benzimidazolyl urea itself is readily accomplished by heating the 1-substituted derivative to about 50° C. The same type of intermediate formation of a 2-amino-4-benzimidazolyl carboxanilide or carboxamide followed by rearrangement to a 2-benzimidazolyl urea occurs when a carbamoyl chloride is reacted with a 2-aminobenzimidazole as illustrated in route B, reaction scheme I above.

As previously stated, the compositions of this invention are employed in suppressing the immune reaction in mammals. Thus, the compound can be classed as " immune suppressant agents " by which is meant an agent which can suppress the formation of antibodies to foreign protein. This activity can thus also be characterized as anti-allergic in that the allergic reaction is part of the defense mechanism of the body (the immune mechanism) against foreign antigens. (This activity is quite different from an anti-histamine activity.) Although immune suppressant activity was determined in mice using sheep erythrocytes as the antigen, it should be understood that the same type of activity would be shown against any foreign protein (antigen) in any mammal. The compounds of this invention can be used in the same way as azathiaprene and in similar dosage forms.

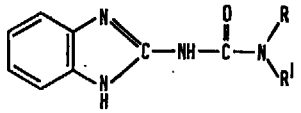
The ability of compounds according to the above formulae to suppress immune mechanisms in a host animal was measured by their activity as anti-allergic agents according to the following test. Groups of five 20-gram Swiss mice were injected intraperitoneally with standardized suspensions of an antigen—in this instance sheep blood cells. The active compounds were also injected by the intraperitoneal route at various times before and/or after the injection of the red blood cells. Eight days after injection of the antigen, the mice were bled and the sera from each group pooled. Anti-body determinations were made on the serum pools by a hemaglutination pattern procedure and comparisons made between treated and control animals. In Tables 1—18 which follow, the activity of the compounds listed therein as anti-allergics is given in therms of the minimum dose of drug necessary to suppress the hemaglutination titer by a 4-fold factor in the treated mice as compared with control titers.

The use of compositions according to this invention in combatting viral infections is illustrated by their ability to cure mice infected with Coxsackie A21 (Coe) virus. This virus was isolated by Lanette et al., *Am. J. Hyg. 68*, 2727 (1959), from human patients with mild respiratory illness. In mice, the virus produces muscle degeneration and

flaccid paralysis as well as respiratory involvement. Tables 1—18 which follow, give for the compounds listed therein, ED_{50} (effective dose for protecting 50 percent of the animals from the effects of administered virus at levels which produce lethal infections in 90—100 percent of the mice) when the drug is given intraperitoneally in unit dosage form to mice 3 hours before injection of the virus. The mouse-adapted Coxsackie A21 virus employed is usually in the form of a 1 : 10 dilution of the supernate of a 10 percent mouse gluteal muscle (obtained from infected mice) suspension. The LD_{50} of the suspension was determined in each case by titration in mice. The compounds were administered to the mice as suspensions in 0.25 ml. of a sterile water permissibly containing up to 3 percent of a non-ionic surfactant) at a series of dose levels from which the ED_{50} could be determined. The mice employed were SPF white Swiss mice weighing 11—13 grams. Ten mice were used for each drug level, and 3—5 groups of 10 mice each were used as controls. In this procedure, the control mice usually die on the fifth to eighth day after infection, and animals alive through the tenth day are considered survivors if free of paralysis. The ED_{50} given in the tables was calculated by the method of Reed and Muench, *Am. J. Hyg. 27,* 493, (1938).

In Tables 1—18, a blank space indicates that the compound listed has not yet been tested as an anti-viral agent or as an immune suppressant in mammals, and a dash indicates that the compound was not active at the highest dose tested, usually 128 mg./kg. in the anti-viral test or 100 mg./kg. in the immune suppressant test, but presumably would be active at higher dose levels.

TABLE 1

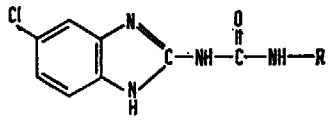


R	R′	Melting Point °C.	Analysis Calculated			Analysis Found			Antiviral ED_{50} mg,/kg.	Immuno-Suppressant ED_4-Fold mg./kg. × 3
			C	H	N	C	H	N		
phenyl	H	329—30	66.65	4.79	22.21	66.36	4.96	21.95	128	12.5
phenyl	phenyl	178—180	73.15	4.91	17.06	72.90	5.30	17.09	85	100
α-naphthyl	H	327—8	71.51	4.67	18.53	71.55	3.53	18.13	23	3.1
p-chlorophenyl	H	349—51	58.64	3.86	19.54	58.93	4.06	19.37	47	12.5
m-chlorophenyl	H	344—5	58.64	3.86	19.54	58.72	3.74	19.29	69	3.1
o-chlorophenyl	H	331—3	58.64	3.86	19.54	58.68	3.65	19.30	32	12.5
p-fluorophenyl	H	338—9	62.21	4.10	20.73	62.00	4.26	20.68	26	6.2
o-fluorophenyl	H	347—8	62.21	4.10	20.73	62.41	4.30	20.67	38	1.6
p-nitrophenyl	H	301—2	56.56	3.73	23.56	56.70	3.85	23.60	78	—
m-nitrophenyl	H	317—8	56.56	3.73	23.56	56.83	4.02	23.92	84	—
o-nitrophenyl	H	324—5	56.56	3.73	23.56	56.83	4.00	23.60	32	—

TABLE 1 (Continued)

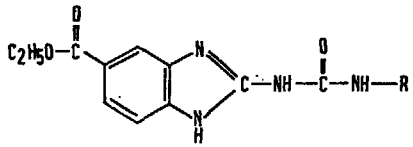
R	R′	Melting Point °C.	Analysis Calculated			Analysis Found			Antiviral ED_{50} mg./kg.	Immuno-Suppressant ED_4-Fold mg./kg. × 3
			C	H	N	C	H	N		
m-aminophenyl	H	330—1	62.91	4.90	26.20	63.02	5.16	26.44	84	—
m-trifluoro-methylphenyl	H	336—7	56.24	3.46	17.49	56.45	3.67	17.44	152	—
p-tolyl	H	342—3	67.65	5.30	21.04	67.64	5.54	20.84	32	—
o-tolyl	H	339—340	67.65	5.30	21.04	67.87	5.57	20.92	~100	25
p-bromophenyl	H	342—3	50.77	3.35	16.92	51.03	3.51	16.83	70	100
cyclohexyl	H	335—6	65.09	7.02	21.69	65.09	7.16	21.94	16	—
cycloheptyl	H	311—3	66.15	7.40	20.57	65.87	7.40	20.25	130	—
cylooctyl	H	322—4	67.10	7.74	19.57	66.99	7.76	19.43	182	100
1-adamantyl	H	327—8	69.65	7.14	18.05	69.69	7.14	18.29	26	—
3,4-dichlorophenyl	H	337—8	52.35	3.13	17.44	52.64	3.32	17.64	46	0.8

TABLE 2



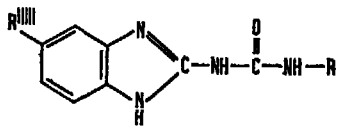
R	Melting Point °C.	Analysis Calculated			Analysis Found			Antiviral ED_{50} mg,/kg.	Immuno-Suppressant ED_4-Fold mg./kg × 3
		C	H	N	C	H	N		
phenyl	339—40	58.65	3.87	19.54	58.65	4.02	19.64	72	25
α-naphthyl	342—3	64.19	3.89	16.64	63.97	4.13	16.88		6.2
p-chlorophenyl	329—30	52.36	3.14	17.45	52.24	3.40	17.07	64	—
o-chlorophenyl	340	52.36	3.14	17.45	51.99	3.12	17.05	>128	100
p-fluorophenyl	348—50	55.18	3.30	18.38	55.04	3.27	18.45	<16	<12.5
o-fluorophenyl	339—40	55.18	3.30	18.38	55.45	3.56	18.38	36	—
m-nitrophenyl	294—6	50.68	3.03	21.11	50.95	3.19	20.60	30	—
p-nitrophenyl	296—8	50.68	3.03	21.11	50.68	3.04	21.41	28	<100
o-nitrophenyl	289—91	50.68	3.03	21.29	50.38	3.18	21.27	>128	<100
p-tolyl	319—20	59.90	4.35	19.04	59.85	4.62	18.90	34	—
o-tolyl	307—8	59.90	4.35	18.63	59.81	4.63	18.48	28	—
cyclohexyl	319—20	57.62	5.52	19.20	57.80	5.80	18.95	>128	—
m-tolyl	315—16	59.90	4.35	18.63	59.88	4.15	18.36	28	—
o-anisyl	340—2	56.87	4.13	17.68	56.69	4.09	17.48	96	<6.2

TABLE 3



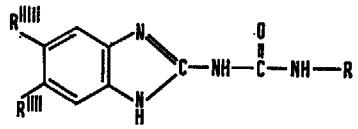
R	Melting Point °C.	Analysis Calculated C	H	N	Analysis Found C	H	N	Antiviral ED_{50} mg./kg	Immuno-Suppressant ED_4-Fold mg./kg.
phenyl	327—8	62.95	4.97	17.28	63.12	4.99	17.49	30	<25
α-naphthyl	315—6	67.37	4.85	14.97	67.28	4.94	14.94	27	6.2
p-chlorophenyl	309—11	56.90	4.21	15.62	56.61	4.30	15.82	26	—
m-chlorophenyl	308—310	56.90	4.21	15.62	56.85	4.50	15.67	22	50
o-chlorophenyl	308—9	56.90	4.21	15.62	56.69	5.79	15.32	32	—
p-fluorophenyl	310—11	59.64	4.41	16.36	59.82	4.62	16.33	46	25
o-fluorophenyl	315—16	59.64	4.41	16.36	59.75	4.67	16.65	64	<6.2
p-nitrophenyl	279—80	55.28	4.09	18.96	55.13	4.01	18.81	16	3.1
m-nitrophenyl	309—310	55.28	4.09	18.96	55.58	4.05	18.95	17	25
o-nitrophenyl	326—7	55.28	4.09	18.96	55.37	4.23	18.96	25	1.6
m-aminophenyl	277—8	60.17	5.05	20.64	59.97	4.95	20.48	81	<50
m-trifluoromethyl-phenyl	328—9	55.1	3.85	14.28	54.82	4.02	14.37	59	—
p-tolyl	305—7	63.89	5.36	16.56	63.71	5.39	16.30	83	100
m-tolyl	321—3	63.89	5.36	16.56	63.91	6.58	16.51	32	<12.5
o-tolyl	304—5	63.89	5.36	16.56	64.03	5.39	16.74	19	25
cyclohexyl	310—11	61.80	6.71	16.96	61.54	6.69	16.67		100

TABLE 4



R	R'''''	Melting Point °C.	Analysis Calculated			Analysis Found			Antiviral ED_{50} mg./kg	Immuno-Suppressant ED_4-Fold mg./kg. × 3
			C	H	N	C	H	N		
phenyl	CF_3	309—310	56.25	3.46	17.49	56.44	3.46	17.78	>128	12.5
α-naphthyl	CF_3	307—8	61.61	3.53	15.13	61.89	3.78	14.99	21	<50
m-chlorophenyl	CF_3	320—2	50.78	2.84	15.79	51.01	2.97	15.84	30	—
cyclohexyl	CF_3	308—9	55.20	5.25	17.17	55.49	4.96	16.88	59	100
phenyl	CH_3	327—8	67.65	5.30	21.04	67.41	5.42	20.85	>128	100
α-naphthyl	CH_3	315—6	72.13	5.10	17.71	71.96	5.25	17.62	<16	<0.4
cyclohexyl	CH_3	320—1	66.15	7.40	20.57	66.44	7.45	20.32	174	—
α-naphthyl	$CH_3—SO_2—$	309—10	59.98	4.24	14.72	59.83	4.53	14.59	17	—
cyclohexyl	$CH_3—SO_2—$	310—12	53.56	5.99	16.66	53.34	6.20	16.59	106	—
phenyl	$CH_3—SO_2—$	326—7	54.54	4.27	16.96	54.25	4.55	16.74	106	—

TABLE 5

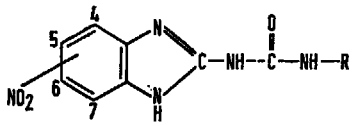


R	R'''''	R''''	Melting Point °C.	Analysis Calculated C	H	N	Analysis Found C	H	N	Antiviral ED_{50} mg./kg.	Immuno-Suppressant ED_4-Fold mg./kg. × 3
phenyl	CH_3	CH_3	336—7	68.55	5.75	19.99	68.62	5.72	19.81	30	12.5
α-naphthyl	CH_3	CH_3	298—300	71.70	5.40	16.76	71.43	5.04	16.42	17	50
p-chlorophenyl	CH_3	CH_3	351—2	61.04	4.80	17.80	61.07	4.78	17.77	26	12.5
m-chlorophenyl	CH_3	CH_3	342—3	61.04	4.80	17.80	60.99	5.08	17.99	87	—
3,4-dichloro-phenyl	CH_3	CH_3	342—5	55.02	4.04	16.04	54.91	4.20	15.99	20	100
2,5-dichloro-phenyl	CH_3	CH_3	336—7	55.02	4.04	16.04	54.81	4.19	16.19	>128	<25
2,4-difluoro-phenyl	CH_3	CH_3	327—8	64.41	5.06	18.78	64.22	5.10	18.92	43	0.4
o-fluorophenyl	CH_3	CH_3	321—2	64.41	5.06	18.78	64.52	5.33	18.79	44	100

TABLE 5 (Continued)

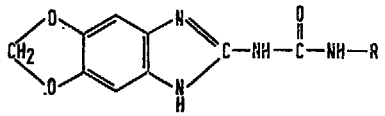
R	R'''''	R''''	Melting Point °C	Analysis Calculated			Analysis Found			Antiviral ED_{50} mg./kg.	Immuno-Suppressant ER_4-Fold mg./kg. × 3
				C	H	N	C	H	N		
p-nitrophenyl	CH_3	CH_3	297—9	59.07	4.65	21.53	58.82	4.50	21.38	53	25
γ_l-nitrophenyl	CN_3	CH_3	349—50	59.07	4.65	21.53	58.93	4.93	21.76	22	—
o-nitrophenyl	CH_3	CH_3	327—9	59.07	4.65	21.53	59.07	4.93	21.52	74	<100
p-tolyl	CH_3	CH_3	344—5	69.37	6.16	19.04	69.24	6.10	19.26	119	—
m-tolyl	CH_3	CH_3	329—30	69.37	6.16	19.04	69.19	6.25	19.01	45	—
o-tolyl	CH_3	CH_3	342—5	69.37	6.16	19.04	69.47	6.30	19.28	80	12.5
p-bromophenyl	CH_3	CH_3	335—6	53.49	4.20	16.59	53.81	4.42	15.23	22	12.5
p-anisyl	CH_3	CH_3	343—5	65.79	5.85	18.05	65.51	6.06	18.28	72	12.5
cyclohexyl	CH_3	CH_3	325—6	67.10	7.74	19.57	66.92	7.66	19.47	90	50
phenyl	Cl	Cl	364—5	52.35	3.13	17.44	52.10	3.29	17.54	88	12.5
cyclohexyl	Cl	Cl	363—4	51.38	4.92	17.12	51.17	5.18	17.12	>128	<50
α-naphthyl	Cl	Cl	339—40	58.23	3.25	15.09	58.30	3.50	15.20	>128	>12.5

TABLE 6



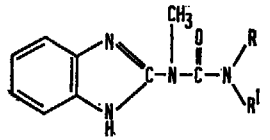
Position of NO_2	R	Melting Point °C	Analysis Calculated			Analysis Found			Antiviral ED_{50} mg./kg.	Immuno-Suppressant ED_4-Fold mg./kg. × 3
			C	H	N	C	H	N		
4(7)	phenyl	361—2	56.56	3.73	23.56	56.78	3.84	23.82	101	25
4(7)	cyclohexyl	335	55.43	5.68	23.09	55.10	5.51	23.15	<16	6.2
5(6)	cyclohexyl	318—9	55.43	5.65	23.09	55.14	5.50	22.89	67	—
4(7)	*o*-fluoro-phenyl	355—6	53.33	3.20	22.22	53.38	3.33	22.11		3.1

TABLE 7



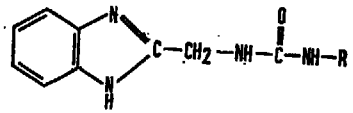
R	Melting Point °C.	Analysis Calculated			Analysis Found			Antiviral ED_{50} mg./kg.	Immuno-Suppressant ED_4-Fold mg./kg. × 3
		C	H	N	C	H	N		
phenyl	350	60.80	4.08	18.91	60.92	4.25	18.73	51	100
α-naphthyl	300	65.89	4.07	16.18	65.66	4.04	16.36	30	50
cyclohexyl	300	59.59	6.00	18.53	59.51	6.11	18.28	55	—

TABLE 8



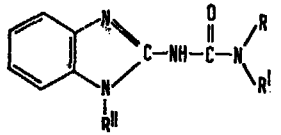
R	R′	Melting Point °C.	Analysis Calculated C	H	N	Analysis Found C	H	N	Antiviral ED_{50} mg./kg.	Immuno-Suppressant ED_4-Fold mg./kg. × 3
phenyl	H	189—190	67.65	5.30	21.04	67.52	5.39	21.02	>128	50
phenyl	phenyl	174—5	73.66	5.30	16.36	73.56	5.44	16.30	86	50
m-chlorophenyl	H	158—9	59.90	4.36	18.63	59.98	4.44	18.67	52	—
α-naphthyl	H	205—6	72.13	5.10	17.71	72.41	5.25	17.63	57	25
cyclohexyl	H	176—7	66.15	7.40	20.57	66.42	7.21	20.83	>64	—
p-chlorophenyl	H	195—6	59.90	4.36	18.63	59.86	4.62	18.35	78	50

TABLE 9



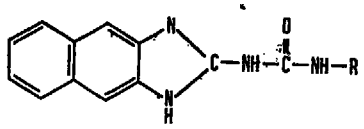
R	Melting Point °C.	Analysis Calculated C	H	N	Analysis Found C	H	N	Antiviral ED_{50} mg./kg.	Immuno-Suppressant ED_4-Fold mg./kg. × 3
phenyl	205—6	67.65	5.30	21.04	67.36	5.41	20.95	25	—
α-naphthyl	246—7	72.13	5.10	17.71	72.10	5.22	17.43	50	—
cyclohexyl	248—9	66.15	7.40	20.57	66.33	7.58	20.49	32	—

TABLE 10



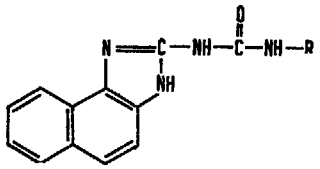
R	R′	R″	Melting Point °C.	Analysis Calculated C	H	N	Analysis Found C	H	N	Antiviral ED_{50} mg./kg.	Immuno-Suppressant ED_4-Fold mg./kg. × 3
phenyl	H	phenyl	170—1	73.15	4.91	17.06	73.19	5.11	17.35	41	50
α-naphthyl	H	phenyl	166—7	76.17	4.79	14.81	75.97	4.82	14.75	84	—
cyclohexyl	H	phenyl	166—7	71.83	6.63	16.76	71.60	6.87	16.59	>128	12.5
phenyl	H	methyl	181—2	67.65	5.30	21.04	67.92	5.58	21.20		3.1
α-naphthyl	H	methyl	238—9	72.13	5.10	17.71	71.88	5.04	17.73	>128	>50
m-chloro phenyl	H	methyl	190—1	59.90	4.36	18.63	60.13	4.31	18.75	18	6.2
p-chloro-phenyl	H	methyl	199—200	59.90	4.36	18.63	59.91	4.38	18.86	64	>50

TABLE 11



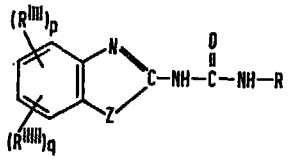
R	Melting Point °C.	Analysis Calculated			Analysis Found			Antiviral ED_{50} mg..kg.	Immuno-Suppressant ED_4-Fold mg./kg. × 3
		C	H	N	C	H	N		
phenyl	362—4	71.51	4.67	18.53	71.54	4.93	18.79	31	—
α-naphthyl	330	74.98	4.58	15.90	74.77	4.80	15.61	12	50
cyclohexyl	252—4	70.10	6.54	18.17	70.29	6.27	18.37	53	—
p-fluorophenyl	364—5	67.48	4.09	17.49	67.62	4.38	17.28	110	>25

TABLE 12



R	Melting Point °C.	Analysis Calculated			Analysis Found			Antiviral ED_{50} mg./kg.	Immuno-Suppressant ED_4-Fold mg./kg. × 3
		C	H	N	C	H	N		
phenyl	348—9	71.51	4.67	18.53	71.75	4.87	18.29	108	50
α-naphthyl	331—2	74.98	4.58	15.90	75.09	4.78	15.98	76	>6.2
m-chlorophenyl	354—5	64.18	3.88	16.62	64.19	3.91	16.41	22	.05
p-fluorophenyl	349—50	67.49	4.09	17.49	67.27	4.28	17.72	25	25

TABLE 13



R	$(R'''')_p$ and $(R''''')_q$	Z	Melting Point °C.	Analysis Calculated C	H	N	Analysis Found C	H	N	Antiviral ED_{50} mg./kg.	Immuno-Suppressant ED_4-Fold mg./kg. × 3
phenyl	H	S	333—5	62.44	4.12	15.61	62.23	4.33	15.82	>128	6.2
α-naphthyl	H	S	278—280	67.70	4.11	13.16	67.97	4.21	13.31	28	<50
p-chlorophenyl	H	S	315—16	55.35	3.32	13.83	55.47	3.60	13.59	>100	<6.2
m-chloro-phenyl	H	S	329—30	55.35	3.32	13.83	55.61	3.57	13.79	60	1.6
o-chlorophenyl	H	S	335—6	55.35	3.32	13.83	55.17	3.42	14.03		<50
3,4-dichloro-phenyl	H	S	316—7	49.71	2.68	12.42	49.85	2.77	12.19	49	12.5
p-fluorophenyl	H	S	341—2	58.52	3.51	14.63	58.33	3.62	14.67	83	<25
o-fluorophenyl	H	S	333—333.5	58.52	3.51	14.63	58.74	3.67	14.93	38	<6.2
2,5-dichloro-phenyl	H	S	327—8	49.71	2.68	12.42	49.83	2.55	12.56	16	12.5
p-nitrophenyl	H	S	290—1	53.51	3.27	17.83	53.24	3.32	18.11	19	—
m-nitrophenyl	H	S	309—310	53.51	3.27	17.83	53.71	3.49	18.07	32	<50
o-nitrophenyl	H	S	400	53.51	3.27	17.83	53.67	3.41	18.10	120	6.2
α-naphthyl	4-Cl	S	256—8	59.73	3.53	12.29	59.94	3.30	12.04	<16	<12.5

TABLE 13 (Continued)

R	$(R'''')_p$ and $(R''''')_q$	Z	Melting Point °C.	Analysis Calculated			Analysis Found			Antiviral ED_{50} mg./kg.	Immuno-Suppressant ED_4-Fold mg./kg. × 3
				C	H	N	C	H	N		
m-chlorophenyl	4-Cl	S	266—8	49.71	2.68	12.42	49.60	2.96	12.19	71	<50
cyclohexyl	4-Cl	S	219—20	54.27	5.20	13.56	54.05	5.39	13.33	128	1.6
phenyl	H	O	192—3	66.39	4.38	16.59	66.31	4.63	16.89	31	50
α-naphthyl	H	O	232—5	71.27	4.32	13.86	71.00	4.59	13.65	20	—
cyclohexyl	H	O	162—3	65.85	6.88	16.33	65.82	7.12	16.48	95	—
phenyl	5-Cl	O	202—3	58.44	3.50	14.61	58.59	3.68	14.53		200
α-naphthyl	5-Cl	O	234—5	64.00	3.58	12.44	63.97	3.78	12.37	32	—
m-chlorophenyl	5-Cl	O	233—5	52.19	2.81	13.04	52.10	2.94	12.79	74	400
cyclohexyl	5-Cl	O	181—2	57.23	5.49	14.30	57.42	5.79	14.36	>128	<50
m-trifluoromethylphenyl	H	S	328—9	53.41	2.99	12.46	53.61	3.22	12.29	52	<50
o-tolyl	H	S	335—6	63.59	4.63	14.83	63.86	4.54	14.80	45	<50
p-tolyl	H	S	327—8	63.59	4.63	14.83	63.80	4.72	14.73	64	100
p-bromophenyl	H	S	298—300	48.28	2.89	12.06	48.18	2.92	12.13		—
p-anisyl	H	S	325—6	60.19	4.38	14.04	60.03	4.44	13.83	22	50
o-ethoxyphenyl	H	S	336—7	61.32	4.82	13.40	61.05	4.70	13.50	45	<50
o-anisyl	H	S	339—40	60.19	4.38	14.04	60.19	4.58	13.75	89	

TABLE 13 (Continued)

R	$(R'''')_p$ and $(R''''')_q$	Z	Melting Point °C.	Analysis Calculated			Analysis Found			Antiviral ED_{50} mg./kg.	Immuno-Suppressant ED_4-Fold mg./kg. × 3
				C	H	N	C	H	N		
p-cyanophenyl	H	S	219—20	61.22	3.43	19.04	61.21	3.46	18.95	44	<100
cyclohexyl	H	S	319—20	61.08	6.22	15.26	61.03	6.16	15.27	159	<100
phenyl	4-Cl	S	268—70	55.35	3.31	13.83	55.62	3.60	13.66	87	<12.5
phenyl	5,6-dimethyl	S	370—2	64.62	5.09	14.14	64.91	5.41	14.48		100
α-naphthyl	5,6-dimethyl	S	355—6	69.15	4.93	12.10	69.18	5.18	12.05	19	—
p-chlorophenyl	5,6-dimethyl	S	359—60	57.92	4.25	12.66	58.00	4.24	12.42	60	—
m-chlorophenyl	5,6-dimethyl	S	345—6	57.92	4.25	12.66	58.42	4.46	13.06	27	100
o-chlorophenyl	5,6-dimethyl	S	353—4	57.92	4.25	12.66	58.14	4.26	12.49	88	<100
3,4-dichlorophenyl	5,6-dimethyl	S	331—2	52.46	3.58	11.47	52.76	3.74	11.56	81	50
p-fluorophenyl	5,6-dimethyl	S	353—4	60.93	4.47	13.32	60.89	4.50	13.03		—
o-fluorophenyl	5,6-dimethyl	S	355—6	60.93	4.47	13.32	60.69	4.73	13.22	28	<1.6
p-nitrophenyl	5,6-dimethyl	S	324—5	56.14	4.12	16.37	56.42	4.36	16.19	27	<100

19 1,296,561 19

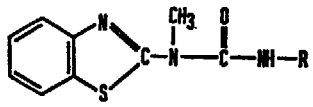
TABLE 13 (Continued)

R	$(R'''')_p$ and $(R'''')_q$	Z	Melting Point °C.	Analysis Calculated			Analysis Found			Antiviral ED_{50} mg./kg.	Immuno-Suppressant ED_4-Fold mg./kg. × 3
				C	H	N	C	H	N		
o-nitrophenyl	5,6-dimethyl	S	328—9	56.14	4.12	16.37	56.38	4.27	16.64	64	<1.6
m-trifluorophenyl	5,6-dimethyl	S	348—9	55.88	3.86	11.50	56.01	4.00	11.28	26	25
p-tolyl	5,6-dimethyl	S	349—50	65.58	5.50	13.50	65.35	5.42	13.51	36	100
m-tolyl	5,6-dimethyl	S	349—50	65.58	5.50	13.50	65.62	5.65	13.39	22	25
o-tolyl	5,6-dimethyl	S	340—1	6.58	5.50	13.50	65.60	5.65	12.37		<25
2,5-dichlorophenyl	5,6-dimethyl	S	360—1	52.46	3.57	11.47	52.36	3.49	11.71	17	<12.5
cyclohexyl	5,6-dimethyl	S	351—2	63.35	6.98	13.85	63.07	6.95	13.55	193	—
p-bromophenyl	5,6-dimethyl	S	340—1	51.06	3.74	11.16	51.31	3.92	11.00		
phenyl	6—CH_3O	S	321—2	60.19	4.38	14.04	59.95	4.42	14.03	>128	<25
α-naphthyl	6—CH_3O	S	297—8	65.32	4.33	12.03	65.21	4.56	12.26	20	<50
p-chlorophenyl	6—CH_3O	S	310—11	53.96	3.62	12.58	54.20	3.82	12.31	23	<50
m-chlorophenyl	6—CH_3O	S	306—7	53.96	3.62	12.58	54.06	4.06	12.50	<16	12.5

TABLE 13 (Continued)

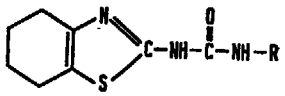
R	$(R'''')_p$ and $(R''''')_q$	Z	Melting Point °C.	Analysis Calculated			Analysis Found			Antiviral ED_{50} mg./kg.	Immuno-Suppressant ED_3-Fold mg./kg. × 3
				C	H	N	C	H	N		
o-chlorophenyl	6—CH_3O	S	314—5	53.97	3.62	12.59	53.84	3.90	12.34	28	<50
o-fluorophenyl	6—CH_3O	S	313—4	56.76	3.81	13.24	56.87	4.01	13.06	26	<3.1
m-nitrophenyl	6—CH_3O	S	270—2	52.30	3.51	16.27	52.34	3.61	16.17	22	<6.2
o-nitrophenyl	6—CH_3O	S	299—301	52.30	3.51	16.27	51.30	3.69	16.22	73	6.2
m-trifluoromethylphenyl	6—CH_3O	S	313—4	52.30	3.29	11.43	52.58	3.57	11.59	<16	12.5
p-tolyl	6—CH_3O	S	297—8	61.33	4.83	13.41	61.24	5.04	13.14	108	<100
o-tolyl	6—CH_3O	S	309—10	61.33	4.83	13.41	60.81	4.87	13.79	56	<50
m-tolyl	6—CH_3O	S	311—2	61.33	4.83	13.41	61.45	4.99	13.49	19	<25
cyclohexyl	6—CH_3O	S	304—6	59.00	6.27	13.76	58.97	6.13	13.28	82	—
p-bromophenyl	6—CH_3O	S	295	47.62	3.19	11.10	47.34	3.21	11.02		—
p-nitrophenyl	6—CH_3O	S	278—9	52.30	3.51	16.27	51.99	3.81	15.97		12.5

TABLE 14



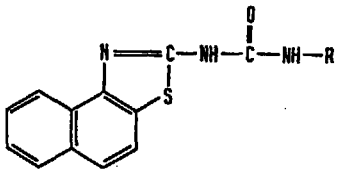
R	Melting Point °C.	Analysis Calculated			Analysis Found			Antiviral ED_{50} mg./kg.	Immuno-Suppressant ED_4-Fold mg./kg.
		C	H	N	C	H	N		
phenyl	95	63.59	4.63	14.83	63.72	4.74	14.89	>128	50
α-naphthyl	174—5	68.46	4.54	12.61	68.70	4.65	12.55	>128	—
p-chlorophenyl	140—1	56.68	3.80	3.22	56.93	3.93	13.25	85	<50
cyclohexyl	188—9	62.26	6.62	14.52	62.17	6.67	14.43	>128	—

TABLE 15



R	Melting Point °C.	Analysis Calculated			Analysis Found			Antiviral ED_{50} mg./kg.	Immuno-Suppressant ED_4-Fold mg./kg.
		A	H	N	C	H	N		
phenyl	318—9			15.37			15.52	>128	—
α-naphthyl	257—8	66.86	5.30	13.00	66.90	5.35	12.82	32	<50
cyclohexyl	218—9	60.42	7.60	15.00	60.81	7.90	14.85	>128	50

TABLE 16

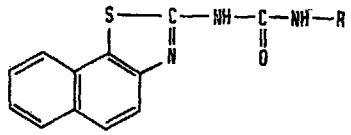


R	Melting Point °C.	Analysis Calculated			Analysis Found			Antiviral ED_{50} mg./kg.	Immuno-Suppressant ED_4-Fold mg./kg. × 3
		C	H	N	C	H	N		
phenyl	320—2	67.70	4.11	13.16	67.89	4.20	12.99		<12.5
α-naphthyl	269—270	71.53	4.09	11.38	71.53	4.09	11.68	42	3.1
p-chlorophenyl	310—11	61.09	3.41	11.87	60.88	3.39	11.80		<100
m-chlorophenyl	314—5	61.09	3.41	11.87	61.27	3.57	11.81	21	<1.6
o-chlorophenyl	321—2	61.09	3.41	11.87	61.25	3.50	11.84	49	6.2
2,5-dichlorophenyl	315—6	55.67	2.85	10.82	55.78	2.78	10.58	55	100
p-fluorophenyl	308—9	64.07	3.58	12.45	64.01	3.68	12.28	16	12.5
o-fluorophenyl	318—9	64.07	3.58	12.45	63.94	3.90	12.30	<16	3.1
p-nitrophenyl	293—4	59.32	3.32	15.37	59.40	3.36	15.14	16	<50
m-nitrophenyl	264—5	59.32	3.32	15.37	59.17	3.36	15.60		3.1

TABLE 16 (Continued)

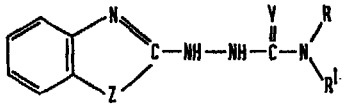
R	Melting Point -C.	Analysis Calculated			Analysis Found			Antiviral ED_{50} mg./kg.	Immuno-Suppressant ED_4-Fold mg./kg. × 3
		C	H	N	C	H	N		
o-nitrophenyl	303—4	59.32	3.32	15.37	59.60	3.32	5.11	<16	3.1
3,4-dichlorophenyl	305—6	55.68	2.85	10.82	55.88	2.79	10.56	16	3.1
m-trifluoromethylphenyl	316—7	59.90	3.12	10.85	60.15	3.39	10.59	89	<6.2
p-tolyl	307—8	68.46	4.54	12.61	68.53	4.82	12.33	17	6.2
m-tolyl	317—8	68.46	4.54	12.61	68.68	4.59	12.38	23	3.1
o-tolyl	319—20	68.46	4.54	12.61	68.52	4.69	12.32	22	<1.6
p-bromophenyl	316—7	54.27	3.03	10.55	54.23	3.17	10.60	25	<50
cyclohexyl	245—6	66.43	5.88	12.91	66.67	5.82	12.75	34	3.1
1-adamantyl	242—3	70.01	6.14	11.13	69.91	6.10	11.13	18	3.1

TABLE 17



R	Melting Point °C.	Analysis Calculated			Analysis Found			Antiviral ED_{50} mg./kg.	Immuno-Suppressant ED_4-Fold mg./kg. × 3
		C	H	N	C	H	M		
phenyl	353—4	67.70	4.11	13.16	67.98	4.04	13.22	23	0.8
α-naphthyl	346—7	71.53	4.09	11.38	71.36	4.14	11.50	<16	0.4
p-tolyl	369—70	68.46	4.54	12.61	68.21	4.59	12.76	<16	>25
p-bromophenyl	357—8	54.28	3.03	10.55	54.18	3.13	10.42	<16	—
cyclohexyl	354—5	66.44	5.89	12.92	66.59	5.79	13.09	27	

TABLE 18



Z	R	R'	Y	Melting Point °C.	Analysis Calculated			Analysis Found			Antiviral ED_{50} mg./kg.	Immuno-Suppressant ED_4-Fold mg./kg. × 3
					C	H	N	C	H	N		
S	phenyl	H	O	207—9	59.15	4.26	19.71	59.06	4.45	19.42	100	—
NH	cyclohexyl	H	O	182—3	61.52	7.07	—	61.29	7.27	—	60	76.2
S	cyclohexyl	H	S	200—1	54.89	5.92	18.29	54.91	5.75	18.36	51	—
NH	α-naphthyl	H	S	208—10	64.85	4.54	21.51	64.35	4.72	21.91	95	—
S	α-naphthyl	H	S	165	61.71	4.03	—	61.01	4.06	—	16	3.1
S	phenyl	H	S	237—8	56.00	4.03	18.66	56.19	4.11	18.80		50

While the use of compositions of this invention to protect mammals against viral injection has been specifically demonstrated with Coxsackie virus, a virus which particularly affects weanling mice, the compositions can also be used to combat infections caused by other mammalian viruses including polio type II, vaccinia and influenza.

Other routes in addition to the intraperitoneal route may be utilized to administer the anti-viral compounds represented by the above formula. For example, the compound can be mixed with a surfactant and then suspended in water by subjecting the mixture to the action of a high-speed blender and the resulting suspension administered by the intravenous route.

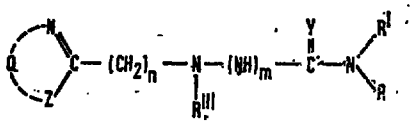
The active anti-viral agents represented by the above formulae whose activity against Coe virus is illustrated in the above tables have a broad spectrum of antiviral activity, being effective against both RNA and DNA containing viruses. Specifically, the compounds are capable of combatting mammalian infections caused by injection of the following viruses: Influenza, Polio, and Vaccinia.

In addition to their use in organ transplant operations, immune suppressant agents

are also useful in various diseases of little-understood etiology, denominated generically as " auto-immune " diseases. These diseases include: auto-immune hemolytic anemia, idiopathic thrombocytopenic purpura, lupus erythematosus, lupoid hepatitis, lupus nephritis, glomerulonephritis, the nephrotic syndrome, Goodpasture's syndrome, Wegener's granulomatosis, schleroderma, Sezary's disease, psoriasis, uveitis, rheumatoid arthritis, ulcerative colitis, thyroiditis and mumps orchitis. Auto-immune suppressant agents, such as azathiaprene, generally may be more or less useful in the treatment of the above diseases depending upon the degree to which the disease is dependent upon an auto-immune mechanism.

WHAT WE CLAIM IS: —

1. Anti-viral and immune suppressant compositions comprising a pharmaceutically acceptable carrier and at least one N-heterocyclic urea type compound of the formula:



wherein

R is a-naphthyl, C_5—C_8 cycloalkyl, 1-adamantyl, phenyl or substituted phenyl wherein said substituents can be one or more of; halo, C_1—C_3 alkoxy, C_1—C_3 alkyl, amino, C_1—C_3 alkylamino, di-(C_1—C_3 alkyl)-amino, nitro, or methyl substituted by from 1 to 3 fluorine atoms;

R′ is hydrogen or phenyl;

R‴ is hydrogen or methyl;

n is 0, 1, 2, or 3;

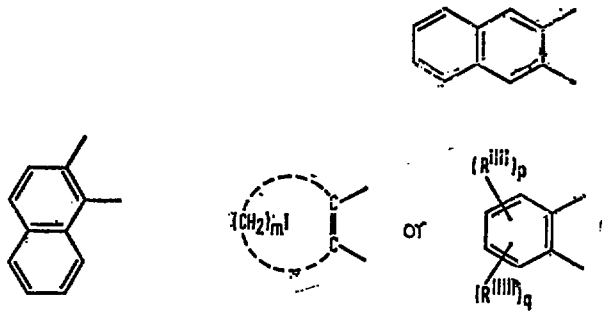
m is 0 or 1;

Y is S or 0;

Z is S, 0 or N—R″

wherein R″ is H, C_1—C_3 alkyl, or phenyl; and

Q is



wherein m′ is 3, 4, 5 or 6;

R⁗ is C_1—C_3 alkyl or halo;

R⁗′ is nitro, methyl substituted by from 1 to 3 fluorine atoms, C_1—C_3 alkoxy, carbo-(C_1—C_3)-alkoxy, or C_1—C_3 alkylsulfonyl, and when R⁗ and R⁗′ are taken together, they are methylene dioxy;

p is 0, 1, 2, 3 or 4; and

q is 0, 1 or 2.

2. The antiviral composition of claim 1 wherein the N-heterocyclic urea is N-5 (6) chloro-2-benzimidazolyl-N′-4-fluorophenyl urea, N-5 (6)-carboethoxy-2-benzimidazolyl-N′-4-nitrophenyl urea, N-5 (6)-methyl-2-benzimidazolyl-N′-a-naphthyl urea, N-4 (7)-nitro-2-benzimidazolyl-N′-cyclohexyl urea or N-(1H-naphth (2,3-*d*) imidazolyl-2)-N′-a-naphthyl urea.

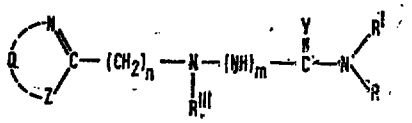
3. The immune suppressant composition of claim 1 wherein the N-heterocyclic urea is N-5 (6) methyl-2-benzimidazolyl-N′-a-naphthyl urea, N-(1H-naphth(2,3-*d*) imidazolyl-2)-N′-3-chlorophenyl urea, N-(1H-naphth(2,3-*d*) thiazolyl-2-)N′-a-naphthyl urea, N-(1H-naphth(2,3-*d*) thiazolyl-2)-N′-3-chlorophenyl urea or N-4(7)nitro-2-benzimidazolyl-N′-isopropyl urea.

4. The anti-viral or immune suppressant conpositions of any one of claims 1

are also useful in various diseases of little-understood etiology, denominated generically as "auto-immune" diseases. These diseases include: auto-immune hemolytic anemia, idiopathic thrombocytopenic purpura, lupus erythematosus, lupoid hepatitis, lupus nephritis, glomerulonephritis, the nephrotic syndrome, Goodpasture's syndrome, Wegener's granulomatosis, schleroderma, Sezary's disease, psoriasis, uveitis, rheumatoid arthritis, ulcerative colitis, thyroiditis and mumps orchitis. Auto-immune suppressant agents, such as azathiaprene, generally may be more or less useful in the treatment of the above diseases depending upon the degree to which the disease is dependent upon an auto-immune mechanism.

WHAT WE CLAIM IS:—

1. Anti-viral and immune suppressant compositions comprising a pharmaceutically acceptable carrier and at least one N-heterocyclic urea type compound of the formula:



wherein

R is a-naphthyl, C_5—C_8 cycloalkyl, 1-adamantyl, phenyl or substituted phenyl wherein said substituents can be one or more of; halo, C_1—C_3 alkoxy, C_1—C_3 alkyl, amino, C_1—C_3 alkylamino, di-(C_1—C_3 alkyl)-amino, nitro, or methyl substituted by from 1 to 3 fluorine atoms;

R′ is hydrogen or phenyl;

R″′ is hydrogen or methyl;

n is 0, 1, 2, or 3;

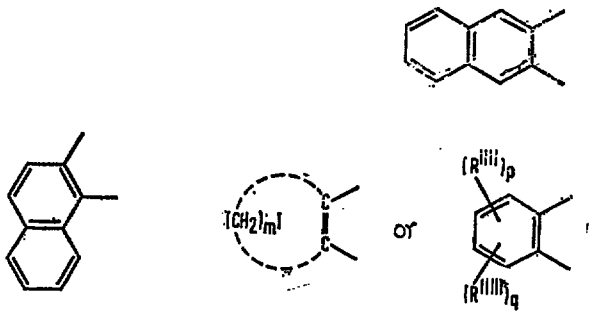
m is 0 or 1;

Y is S or 0;

Z is S, 0 or N—R″

wherein R″ is H, C_1—C_3 alkyl, or phenyl; and

Q is



wherein m′ is 3, 4, 5 or 6;

R″″ is C_1—C_3 alkyl or halo;

R″″′ is nitro, methyl substituted by from 1 to 3 fluorine atoms, C_1—C_3 alkoxy, carbo-(C_1—C_3)-alkoxy, or C_1—C_3 alkylsulfonyl, and when R″″ and R″″′ are taken together, they are methylene dioxy;

p is 0, 1, 2, 3 or 4; and

q is 0, 1 or 2.

2. The antiviral composition of claim 1 wherein the N-heterocyclic urea is N-5 (6) chloro-2-benzimidazolyl-N′-4-fluorophenyl urea, N-5 (6)-carboethoxy-2-benzimidazolyl-N′-4-nitrophenyl urea, N-5 (6)-methyl-2-benzimidazolyl-N′-a-naphthyl urea, N-4 (7)-nitro-2-benzimidazolyl-N′-cyclohexyl urea or N-(1H-naphth (2,3-*d*) imidazolyl-2)-N′-a-naphthyl urea.

3. The immune suppressant composition of claim 1 wherein the N-heterocyclic urea is N-5 (6) methyl-2-benzimidazolyl-N′-a-naphthyl urea, N-(1H-naphth(2,3-*d*) imidazolyl-2)-N′-3-chlorophenyl urea, N-(1H-naphth(2,3-*d*) thiazolyl-2-)N′-a-naphthyl urea, N-(1H-naphth(2,3-*d*) thiazolyl-2)-N′-3-chlorophenyl urea or N-4(7)nitro-2-benzimidazolyl-N′-isopropyl urea.

4. The anti-viral or immune suppressant conpositions of any one of claims 1

to 3, wherein they are in non-toxic dosage form containing 0.01 to 1000 mgs.

5. A method for combating viral infections in mammals other than human beings, comprising administering to said mammals an effective non-toxic dose within the range 0.01 to 1000 mgs. of at least one N-heterocyclic urea type compound of the formula as defined in claim 1.

6. A method for suppressing the immune reaction in mammals other than human beings, comprising administering to said mammals an effective non-toxic dose within the range 0.01 to 1000 mgs of at least one N-heterocyclic urea type compound of the formula as defined in claim 1.

7. The method according to claim 5 for combating viral infections comprising administering one of the compositions of claim 2.

8. The method according to claim 6 for suppressing the immune reaction comprising administering one of the compositions of claim 3.

9. Anti-viral and immune suppressant compositions according to claim 1 substantially as herein described.

10. The method of claim 5 substantially as herein described.

11. The method of claim 6 substantially as hereinbefore described.

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