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(54) Title: COMPOSITIONS AND METHODS FOR TREATMENT OF VIRAL DISEASES

(57) Abstract: The present invention features compositions, methods, and kits useful in the treatment of viral diseases. In certain embodiments, the viral disease is caused by a single stranded RNA virus, a flaviviridae virus, or a hepatic virus. In particular embodiments, the viral disease is viral hepatitis (e.g., hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E). Also featured are screening methods for identification of novel compounds that may be used to treat a viral disease.

COMPOSITIONS AND METHODS FOR TREATMENT OF VIRAL DISEASES

Background of the Invention

The invention relates to the treatment of diseases caused by a virus.

Diseases caused by viruses are major health problems worldwide, and include many potentially fatal or disabilitating illnesses. Viral diseases include diseases caused by single stranded RNA viruses, flaviviridae viruses, and hepatic viruses. In one example, viral hepatitis (e.g., hepatitis A, hepatitis B, hepatitis C, hepatitis D, and hepatitis E) can result in chronic or acute hepatitis. While vaccines protective against hepatitis A and hepatitis B exist, no cures for many viruses, including hepatitis B, C, D, or E, are available.

With regard to the hepatitis C virus (HCV), the Center for Disease Control estimates that 4.1 million Americans (1.6%) have been infected with this virus. Of those infected, 3.2 million are chronically infected, and HCV is the leading cause of death from liver disease in the United States. Hepatitis C is a major risk factor for developing liver cirrhosis and hepatocellular carcinoma, and the World Health Organization indicates that hepatitis C is responsible for two thirds of liver transplants. Worldwide, an estimated 180 million people, or about 3% of the world's population, are infected with HCV. No vaccine for hepatitis C is presently available, and the currently recommended therapy, a combination of pegylated interferon and ribavirin, is effective in only about 50% of those infected with HCV genotype 1. Further, both interferon and ribavirin have potentially serious side effects, which include seizures, acute heart or kidney failure, and anemia.

Given the lack of safe, efficacious treatments for many viral diseases, there exists a need for improved therapies.

Summary of the Invention

Based on the results of our screen identifying compounds and combinations of compounds having antiviral activity, the present invention features compositions, methods, and kits for the treatment of viral disease (e.g., caused by the viruses described herein). In certain embodiments, the viral disease may be caused by a virus which is a member of one or more of the following groups: single stranded RNA viruses, flaviviridae viruses (e.g., a hepacivirus such as HCV, flavivirus, pestivirus, or hepatitis G virus), and hepatic viruses. HCV, for example, is a single stranded RNA virus, a flaviviridae virus, and a hepatic virus. In certain embodiments, the viral disease is caused by the hepatitis C virus. Additional exemplary viruses are described herein.

Accordingly in a first aspect, the invention features a composition including a first agent selected from the agents of Table 1, Table 2, and Table 3; and a second agent selected from the agents of Table 1, Table 2, Table 3, Table 4, and Table 5 (e.g., Table 4 and Table 5, or excluding the combinations of Table 6).

Table 1

Compound	IC50*	Compound	IC50*
1,2-Bis-(2-aminophenoxy)ethane N,N,N,N,-tetreacetic acid	14.50	Isosulfan Blue	24.86
1,5-Isoquinolinediol	25.88	JSH-23	2.55
10-Deacetylbaccatine Iii	10.34	Levothyroxine (e.g., sodium)	3.79
2',2''-(Pentamethylenedioxy)diacetanilide	3.14	Loratadine	8.16
2-Hydroxyflavanone	2.48	Manganese gluconate	24.71
2-Methoxyestradiol	7.91	Maprotiline (e.g., hydrochloride)	7.18
3,3'-(Pentamethylenedioxy)dianiline	1.63	Mebeverine (e.g., hydrochloride)	14.88
6-Nitroquipazine	16.41	Mechlorethamine (e.g., hydrochloride)	4.15
AG-490	5.03	Meclizine	14.62
AG-494	3.45	Mecobalamin	0.179
Albendazole	0.324	Melphalan	5.94
Amitraz	26.4*	Mequinol	18.65
Amitrole	14.62	Mesoridazine (e.g., Besylate)	19.00

Amorolfine (e.g., hydrochloride)	1.62	Mesterolone	5.18
Anisomycin	0.608	Methylglyoxal bis(guanylhydrazone) dihydrochloride hydrate	10.80
Auranofin	1.07	Methyltestosterone	19.11
Azelastine	6.22	Mianserin (e.g., hydrochloride)	13.72
Bay 11-7082	15.01	Mitotane	28.1*
Bay 41-2272	0.754	ML 9	4.44
Benoxinate (e.g., hydrochloride)	3.02	Mofebutazone	14.60
Benzamil (e.g., HCl)	4.73	Mometasone (e.g., furoate)	11.35
Benzocaine	13.91	Monobenzone	1.59
Benztropine (e.g., mesylate)	5.70	Mosapride (e.g., citrate)	10.91
Benzydamine (e.g., hydrochloride)	9.00	Narasin	0.176
Beta Escin	4.27	Noscapine	15.83
Beta-Carotene	18.50	NSC 663284	0.614
Beta-Ionol	21.00	N-Tosyl-L-phenylalanine chloromethyl ketone	16.67
Betaxolol (e.g., hydrochloride)	29.4*	Octyl Methoxycinnamate	1.24
BHQ	23.28	Oxeladin	8.72
Bifonazole	6.15	Oxfendazole	7.30
Bismuth subsalicylate	18.09	Oxibendazole	0.300
Bromhexine	14.25	Oxyphenbutazone (e.g., hydrate)	4.17
Bromocriptine (e.g., mesylate)	3.38	Paclitaxel	0.0092
Budesonide	15.66	Padimate O	5.44
Bufexamac	8.29	P-Aminosalicylic acid	13.16
Camptothecin	0.026	Parthenolide	2.69
Capsaicin	11.72	Perospirone	3.60
Carbaryl	9.65	Phenazopyridine (e.g., hydrochloride)	7.85
CAY10433	7.88	Piceatannol	5.47
Celastrol	0.449	Picotamide	28.7*
Cerulenin	16.21	PKR inhibitor	1.75
Chlorophyllin	1.30	Pramoxine (e.g., hydrochloride)	5.17*
Chlorphenoxamine (e.g., hydrochloride)	16.20	Promazine (e.g., hydrochloride)	16.12
Citalopram (e.g., hydrobromide)	27.30	Propidium (e.g., iodide)	9.38
Cladribine	0.112	Quinacrine	4.17
Clomiphene (e.g., citrate)	1.19	Quinestrol	5.43
Cobamamide	0.410	R(+)-Verapamil (e.g., hydrochloride)	15.67
Cyclocytidine (e.g., hydrochloride)	0.183	Raloxifene (e.g., hydrochloride)	3.74
Cycloheximide	0.184	Repaglinide	12.21
Cyproheptadine (e.g., hydrochloride)	17.97	Rescinnamine	7.88
Dehydroepiandrosterone	11.19	Reserpine	25.29
Deptropine (e.g., citrate)	11.14	Rifabutin	17.25
Desloratadine	6.07	Rifaximin	19.36
Desoxycorticosterone (e.g., acetate)	14.65	Saponin	361.62
Dextrothyroxine (e.g., sodium)	5.00	Satraplatin	4.80
Dibucaine (e.g., hydrochloride)	6.68	SB-202190	5.18
Dicyclomine (e.g., hydrochloride)	25.01	Sertraline (e.g., hydrochloride)	5.39

Dienestrol	16.49	Shikonin	26.4*
Diethylstilbestrol	12.18	Siguazodan	2.20
Dihydroergotamine (e.g., mesylate)	22.75	Silver sulfadiazine	2.20
Dilazep (e.g., dihydrochloride)	13.87	Sirolimus	0.005*
Diphenidol (e.g., hydrochloride)	25.45	Fusidic acid (e.g., sodium fusidate)	7.72
Disulfiram	5.50	Spiperone	7.21
DNA-PK inhibitor II	6.52	Stanozolol	15.18
Donepezil (e.g., hydrochloride)	29.29	Suberohydroxamic acid	4.02
Doxepin (e.g., hydrochloride)	14.88	Tamoxifen (e.g., citrate)	3.13
Dydrogesterone	2.75	Terconazole	2.55
Erbstatin	7.63	Testosterone	8.11
Ergoloid Mesylates	15.25	Thapsigargin	0.0113
Evans Blue	1.94	Thiostrepton	3.84
Exemestane	29.04	Thiram	3.64
Ezetimibe	4.20	Tioxolone	16.24
Fascaplysin	0.444	Tirapazamine	1.83
Fenbendazole	0.419	Tiratricol	15.56
Fenretinide	2.26	Tolterodine (e.g., tartrate)	27.23
Fenvalerate	18.95	Topotecan (e.g., hydrochloride)	0.095
Flubendazole	0.173	Toremifene	15.86
Fludarabine	4.47	Trequinsin (e.g., hydrochloride)	2.93
Fluorouracil	18.66	Trifluoperazine (e.g., hydrochloride)	4.97
Flupentixol (e.g., dihydrochloride)	3.60	Trifluperidol	7.80
Fluphenazine (e.g., hydrochloride)	3.35	Trimipramine (e.g., maleate)	15.62
Fluvoxamine (e.g., maleate)	23.79	Tyrphostin 23	14.61
FR122047	23.01	Tyrphostin 25	16.01
Fulvestrant	3.05	Tyrphostin 46	21.22
Gefitinib (Base)	3.17	Tyrphostin 47	18.3*
Gramicidin	0.017	Tyrphostin Ag 1478	3.41
Griseofulvin (e.g., microcrystalline)	11.53	U18666A	0.020
GW 5074	2.36	UCH-L1 inhibitor	17.18
Halcinonide	17.40	UCH-L3 inhibitor	19.7*
Hydroquinone	13.99	Vanillin (e.g., acetate)	3.73
Hydroxocobalamin	1.33	Vinorelbine	0.081
Hydroxyzine (e.g., hydrochloride)	10.93	Vitamin B12	8.28
Ifenprodil (e.g., tartrate)	4.68	Vitamin K5	19.59
Imipramine (e.g., hydrochloride)	16.93	Wedelolactone	4.66
Indocyanine Green	8.13	Wortmannin	3.16
Iophenoxic acid	10.63	Zafirlukast	18.49
LY 294002	3.40	Zimelidine (e.g., dihydrochloride)	15.14
(S,S)-N-Desmethyl sertraline (e.g., hydrochloride)	4.94	3',3''-(Pentamethylenedioxy)diacetanilide	9.35*
1,5-Bis(4-aminophenoxy)pentane	1.70	rac-cis-N-Desmethyl Sertraline, (e.g., hydrochloride)	6.03
Emetine (e.g., dihydrochloride hydrate)	0.03	2,2'-(Pentamethylenedioxy)dianiline	0.27
Irinotecan (e.g., hydrochloride)	1.56		

*Values noted with an asterisk (*) are IC25 values

Table 2

Compound	IC50	Compound	IC50
Efavirenz	15.45	Cytarabine	0.117
Nelfinavir (e.g., mesylate)	4.25	Floxuridine	0.0045
Vidarabine	26.71	Edoxudine	1.95
Ritonavir	14.91	Cepharanthine	19.48
Aphidicolin	1.71	Tunicamycin	0.107
Andrographis	8.39	Triciribine	2.14
Saquinavir (e.g., mesylate)	10.04	Curcumin	8.68
Trifluridine	0.380	Vincristine (e.g., sulfate)	0.02
Arbidol	12.20		

Table 3

Compound	IC50*	Compound	IC50*
Lovastatin	1.41	Artemisinin	4.45
Artemether		Dihydroartemisinin	3.87
Artesunate	3.73	Nitazoxanide	14.04
Cyclosporine	0.379	Chloroquine (e.g., phosphate)	4.78
Ribavirin	42.95	Mevastatin	3.45
Simvastatin hydroxy acid, ammonium salt	13.40	TOFA	5.53
Mycophenolic Acid	0.751	2'-C-Methylcytidine	1.63
Atorvastatin	35.60	Adefovir (e.g., dipivoxil)	0.319
Fluvastatin (e.g., sodium)	22.20	Telaprevir (VX-950)	0.529
Celgosivir	6.25*	Valopicitabine (NM-283)	11.2
Merimepodib (VX-497)	0.475	HCV-796	0.0192
Boceprevir (SCH 503034)	0.259	Gemcitabine (e.g., hydrochloride)	0.06
Interferon Alfa-2a	2.35	Simvastatin	21.34

*Values noted with an asterisk (*) are IC25 values

In another aspect, the invention features a composition including sertraline and an HMG-CoA reductase inhibitor. The HMG-CoA reductase inhibitor may be fluvastatin, simvastatin, lovastatin, or rosuvastatin.

In another aspect, the invention features a composition including sertraline and an antihistamine. The antihistamine may be hydroxyzine.

In yet another aspect, the invention features a composition including a pair of agents selected from the group consisting of amorolfine and sertraline; fluvastatin and sertraline; rosuvastatin and sertraline; fulvestrant and satraplatin; amorolfine and mebeverine; amorolfine and satraplatin; ifenprodil and sertraline; amorolfine and tolterodine; atorvastatin and sertraline; amorolfine and irinotecan; lovastatin and sertraline; cytarabine and triciribine; artesunate and wortmannin; sertraline and simvastatin hydroxy acid, ammonium salt; amorolfine and cytarabine; sertraline and simvastatin; octyl methoxycinnamate and suberohydroxamic acid; 1,5-bis(4-aminophenoxy)pentane and amorolfine; (S,S)-N-desmethyl sertraline and simvastatin; artemisinin and SB-202190; interferon alfa-2a and sirolimus; amorolfine and indocyanine green; TOFA and triciribine; 3,3'-(pentamethylenedioxy)dianiline and artemisinin; artemisinin and wortmannin; 3,3''-(pentamethylenedioxy)diacetanilide and artemisinin; amorolfine and benzamil; artemisinin and triciribine; 2,2'-(pentamethylenedioxy)dianiline and amorolfine; (s,s)-n-desmethyl sertraline and simvastatin; levothyroxine and wedelolactone; 1,5-bis(4-aminophenoxy)pentane and artemisinin; benzamil and dextrothyroxine; amorolfine and trifluperidol; artemisinin and indocyanine green; dihydroartemisinin and wortmannin; flupentixol and sertraline; benzamil and levothyroxine; amorolfine and meclizine; pravastatin and sertraline; 1,5-bis(4-aminophenoxy)pentane and indocyanine green; 2-hydroxyflavanone and amorolfine; ritonavir and vinorelbine; benoxinate and dehydroepiandrosterone;

ifenprodil and indocyanine green; amorolfine and arbidol; 3,3'-(pentamethylenedioxy)dianiline and indocyanine green; fulvestrant and vinorelbine; amorolfine and ezetimibe; amorolfine and Evans blue; amorolfine and gefitinib; amorolfine and topotecan; 2',2''-(pentamethylenedioxy)diacetanilide and artemisinin; amorolfine and wedelolactone; 3,3'-(pentamethylenedioxy)dianiline and amorolfine; simvastatin and rac-cis-n-desmethyl sertraline; adefovir dipivoxil and triciribine; cytarabine and Evans blue; artemisinin and Evans blue; fluphenazine and sertraline; benzamil and SB-202190; artemisinin and rifabutin; fluphenazine and tolterodine; interferon alfa-2a and melphalan; amorolfine and melphalan; artemisinin and fulvestrant; ifenprodil and quinacrine; simvastatin and rac-cis-n-desmethyl sertraline; flupentixol and tolterodine; triciribine and wortmannin; loratadine and vinorelbine; meclizine and sertraline; budesonide and vinorelbine; 2-hydroxyflavanone and indocyanine green; hydroxyzine and sertraline; 2,2'-(pentamethylenedioxy)dianiline and artemisinin; amorolfine and flupentixol; artemisinin and chlorophyllin; ezetimibe and fluphenazine; benzamil and fluphenazine; artemisinin and wedelolactone; cytarabine and dydrogesterone; artemisinin and benzamil; 3,3'-(pentamethylenedioxy)dianiline and artemether; tolterodine and trifluperidol; artesunate and fluvastatin; artemisinin and trifluridine; adefovir dipivoxil and amorolfine; interferon alfa-2a and trifluridine; fulvestrant and triciribine; artesunate and dydrogesterone; artesunate and LY 294002; mosapride citrate and TOFA; bromocriptine and wedelolactone; artemisinin and sodium fusidate; celgosivir and interferon alfa-2a; amorolfine and dextrothyroxine; andrographis and fulvestrant; 2'-c-methylcytidine and artemisinin; amorolfine and gemcitabine; oxeladin and sertraline; artemisinin and parthenolide; artemisinin and ribavirin; dehydroepiandrosterone and tyrphostin AG 1478; sertraline and toremifene;

dihydroartemisinin and fulvestrant; 2-hydroxyflavanone and TOFA; artesunate and repaglinide; mofebutazone and wedelolactone; artesunate and simvastatin; 2,2'-(pentamethylenedioxy)dianiline and artesunate; artemisinin and gemcitabine; dihydroartemisinin and ezetimibe; chlorophyllin and cytarabine; interferon alfa-2a and sirolimus; suberohydroxamic acid and VX-497; artemisinin and VX-497; artesunate and VX-497; tolterodine and VX-950; artemisinin and HCV-796; artemisinin and NM-283; NM-283 and wedelolactone; artemisinin and SCH 503034; cytarabine and SCH 503034; SCH 503034 and triciribine; interferon alfa-2a and melphalan; benoxinate and VX-950; HCV-796 and sirolimus; benoxinate and SCH 503034; melphalan and VX-950; ritonavir and VX-950; VX-950 and VX-497; artemisinin and VX-950; triciribine and VX-950; suberohydroxamic acid and VX-950; HCV-796 and suberohydroxamic acid; sirolimus and VX-950; melphalan and SCH 503034; SCH 503034 and wortmannin; SCH 503034 and tolterodine; ritonavir and SCH 503034; ezetimibe and VX-950; HCV-796 and VX-497; chlorophyllin and VX-497; HCV-796 and melphalan; capsaicin and NM-283; SCH 503034 and sirolimus; LY 294002 and SCH 503034; adefovir dipivoxil and SCH 503034; interferon alfa-2a and trifluridine; HCV-796 and trifluridine; GW 5074 and NM-283; mosapride and VX-950; interferon alfa-2a and VX-497; NM-283 and trequinsin; cytarabine and HCV-796; adefovir dipivoxil and VX-950; cytarabine and VX-950; SCH 503034 and saquinavir; VX-950 and wortmannin; capsaicin and VX-950; 2-hydroxyflavanone and NM-283; bromhexine and VX-950; HCV-796 and wortmannin; artemisinin and ribavirin; VX-950 and verapamil; SCH 503034 and verapamil; SCH 503034 and topotecan; HCV-796 and topotecan; trifluperidol and VX-950; irinotecan and SCH 503034; artesunate and SCH 503034; repaglinide and SCH 503034; topotecan and VX-950; tepaglinide and VX-950; arbidol and VX-950; chlorophyllin and HCV-

796; benzydamine and VX-950; NM-283 and trifluperidol; capsaicin and HCV-796; NM-283 and phenazopyridine; NM-283 and trifluridine; and adefovir dipivoxil and HCV-796.

In certain embodiments, the combination is selected from group consisting of simvastatin and sertraline; fluvastatin and sertraline; fluphenazine and sertraline; artesunate and simvastatin; artesunate and wortmannin; artemisinin and chlorophyllin; artemisinin and 3,3'-(pentamethylenedioxy)dianiline; amorolfine and meclizine; amorolfine and sertraline; amorolfine and trifluridine; amorolfine and 2-hydroxyflavanone; amorolfine and ezetimibe; amorolfine and benzamil; amorolfine and trifluperidol; and octyl methoxycinnamate and suberohydroxamic acid.

In any of the above aspects, the two agents may be present in amounts that, when administered to a patient having a viral disease (e.g., any viral disease described herein), are effective to treat the patient. The composition may further include one or more (e.g., two, three, four, five, or six) additional agents selected from the agents of Table 1, Table 2, Table 3, Table 4, and Table 5 (e.g., where the agents are not a combination of agents selected from Table 7). The composition may be formulated, for example, for oral, systemic, parenteral, topical (e.g., ophthalmic, dermatologic), intravenous, or intramuscular administration.

In another aspect, the invention features a method for treating a patient having a viral disease. The method includes administering to the patient an agent selected from the agents of Table 1 in an amount effective to treat the patient.

In another aspect, the invention features a method for treating a patient having hepatitis C. The method includes administering to the patient an agent

selected from the agents of Table 1 and Table 2 in an amount effective to treat the patient.

In another aspect, the invention features a method for treating a patient having a viral disease. The method includes administering to the patient a plurality of agents where the first agent is selected from the agents of Table 1, Table 2, and Table 3 and the second agent is selected from the agents of Table 1, Table 2, Table 3, Table 4, and Table 5 (e.g., Table 4 and Table 5), where the agents are administered within 28 days (e.g., within 21, 14, 10, 7, 5, 4, 3, 2, or 1 days) or within 24 hours (e.g., 12, 6, 3, 2, or 1 hours; or concomitantly) of each other in amounts that together are effective to treat the patient.

In another aspect, the invention features a method for treating a patient having a viral disease. The method includes administering to the patient sertraline and an HMG-CoA reductase inhibitor, where the two agents are administered within 28 days of each other in amounts that together are effective to treat the patient. The HMG-CoA reductase inhibitor may be fluvastatin, simvastatin, lovastatin, or rosuvastatin.

In another aspect, the invention features a method for treating a patient having a viral disease. The method includes administering to the patient sertraline and an antihistamine where the two agents are administered within 28 days of each other in amounts that together are effective to treat the patient. The antihistamine may be hydroxyzine.

In yet another aspect, the invention features a method for treating a patient having a viral disease. The method includes administering to the patient a pair of agents selected from the group consisting of amorolfine and sertraline; fluvastatin and sertraline; rosuvastatin and sertraline; fulvestrant and satraplatin; amorolfine and mebeverine; amorolfine and satraplatin; ifenprodil and sertraline; amorolfine and tolterodine; atorvastatin and sertraline;

amorolfine and irinotecan; lovastatin and sertraline; cytarabine and triciribine; artesunate and wortmannin; sertraline and simvastatin hydroxy acid, ammonium salt; amorolfine and cytarabine; sertraline and simvastatin; octyl methoxycinnamate and suberohydroxamic acid; 1,5-bis(4-aminophenoxy)pentane and amorolfine; (S,S)-N-desmethyl sertraline and simvastatin; artemisinin and SB-202190; interferon alfa-2a and sirolimus; amorolfine and indocyanine green; TOFA and triciribine; 3,3'-(pentamethylenedioxy)dianiline and artemisinin; artemisinin and wortmannin; 3,3''-(pentamethylenedioxy)diacetanilide and artemisinin; amorolfine and benzamil; artemisinin and triciribine; 2,2'-(pentamethylenedioxy)dianiline and amorolfine; (s,s)-n-desmethyl sertraline and simvastatin; levothyroxine and wedelolactone; 1,5-bis(4-aminophenoxy)pentane and artemisinin; benzamil and dextrothyroxine; amorolfine and trifluperidol; artemisinin and indocyanine green; dihydroartemisinin and wortmannin; flupentixol and sertraline; benzamil and levothyroxine; amorolfine and meclizine; pravastatin and sertraline; 1,5-bis(4-aminophenoxy)pentane and indocyanine green; 2-hydroxyflavanone and amorolfine; ritonavir and vinorelbine; benoxinate and dehydroepiandrosterone; ifenprodil and indocyanine green; amorolfine and arbidol; 3,3'-(pentamethylenedioxy)dianiline and indocyanine green; fulvestrant and vinorelbine; amorolfine and ezetimibe; amorolfine and Evans blue; amorolfine and gefitinib; amorolfine and topotecan; 2',2''-(pentamethylenedioxy)diacetanilide and artemisinin; amorolfine and wedelolactone; 3,3'-(pentamethylenedioxy)dianiline and amorolfine; simvastatin and rac-cis-n-desmethyl sertraline; adefovir dipivoxil and triciribine; cytarabine and Evans blue; artemisinin and Evans blue; fluphenazine and sertraline; benzamil and SB-202190; artemisinin and rifabutin; fluphenazine and tolterodine; interferon alfa-2a and melphalan; amorolfine and

melphalan; artemisinin and fulvestrant; ifenprodil and quinacrine; simvastatin and rac-cis-n-desmethyl sertraline; flupentixol and tolterodine; triciribine and wortmannin; loratadine and vinorelbine; meclizine and sertraline; budesonide and vinorelbine; 2-hydroxyflavanone and indocyanine green; hydroxyzine and sertraline; 2,2'-(pentamethylenedioxy)dianiline and artemisinin; amorolfine and flupentixol; artemisinin and chlorophyllin; ezetimibe and fluphenazine; benzamil and fluphenazine; artemisinin and wedelolactone; cytarabine and dydrogesterone; artemisinin and benzamil; 3,3'-(pentamethylenedioxy)dianiline and artemether; tolterodine and trifluperidol; artesunate and fluvastatin; artemisinin and trifluridine; adefovir dipivoxil and amorolfine; interferon alfa-2a and trifluridine; fulvestrant and triciribine; artesunate and dydrogesterone; artesunate and LY 294002; mosapride citrate and TOFA; bromocriptine and wedelolactone; artemisinin and sodium fusidate; celgosivir and interferon alfa-2a; amorolfine and dextrothyroxine; andrographis and fulvestrant; 2'-c-methylcytidine and artemisinin; amorolfine and gemcitabine; oxeladin and sertraline; artemisinin and parthenolide; artemisinin and ribavirin; dehydroepiandrosterone and tyrphostin AG 1478; sertraline and toremifene; dihydroartemisinin and fulvestrant; 2-hydroxyflavanone and TOFA; artesunate and repaglinide; mofebutazone and wedelolactone; artesunate and simvastatin; 2,2'-(pentamethylenedioxy)dianiline and artesunate; artemisinin and gemcitabine; dihydroartemisinin and ezetimibe; chlorophyllin and cytarabine; interferon alfa-2a and sirolimus; suberohydroxamic acid and VX-497; artemisinin and VX-497; artesunate and VX-497; tolterodine and VX-950; artemisinin and HCV-796; artemisinin and NM-283; NM-283 and wedelolactone; artemisinin and SCH 503034; cytarabine and SCH 503034; SCH 503034 and triciribine; interferon alfa-2a and melphalan; benoxinate and VX-950; HCV-796 and sirolimus; benoxinate and SCH 503034; melphalan and

VX-950; ritonavir and VX-950; VX-950 and VX-497; artemisinin and VX-950; triciribine and VX-950; suberohydroxamic acid and VX-950; HCV-796 and suberohydroxamic acid; sirolimus and VX-950; melphalan and SCH 503034; SCH 503034 and wortmannin; SCH 503034 and tolterodine; ritonavir and SCH 503034; ezetimibe and VX-950; HCV-796 and VX-497; chlorophyllin and VX-497; HCV-796 and melphalan; capsaicin and NM-283; SCH 503034 and sirolimus; LY 294002 and SCH 503034; adefovir dipivoxil and SCH 503034; interferon alfa-2a and trifluridine; HCV-796 and trifluridine; GW 5074 and NM-283; mosapride and VX-950; interferon alfa-2a and VX-497; NM-283 and trequinsin; cytarabine and HCV-796; adefovir dipivoxil and VX-950; cytarabine and VX-950; SCH 503034 and saquinavir; VX-950 and wortmannin; capsaicin and VX-950; 2-hydroxyflavanone and NM-283; bromhexine and VX-950; HCV-796 and wortmannin; artemisinin and ribavirin; VX-950 and verapamil; SCH 503034 and verapamil; SCH 503034 and topotecan; HCV-796 and topotecan; trifluperidol and VX-950; irinotecan and SCH 503034; artesunate and SCH 503034; repaglinide and SCH 503034; topotecan and VX-950; tepaglinide and VX-950; arbidol and VX-950; chlorophyllin and HCV-796; benzydamine and VX-950; NM-283 and trifluperidol; capsaicin and HCV-796; NM-283 and phenazopyridine; NM-283 and trifluridine; and adefovir dipivoxil and HCV-796, where the agents are administered within 28 days of each other in amounts that together are effective to treat the patient.

In another aspect, the invention features a method for treating a patient having a viral disease. The method includes administering to the patient a pair of agents selected from the group consisting of simvastatin and sertraline; fluvastatin and sertraline; fluphenazine and sertraline; artesunate and simvastatin; artesunate and wortmannin; artemisinin and chlorophyllin; artemisinin and 3,3'-(pentamethylenedioxy)dianiline; amorolfine and

meclizine; amorolfine and sertraline; amorolfine and trifluridine; amorolfine and 2-hydroxyflavanone; amorolfine and ezetimibe; amorolfine and benzamil; amorolfine and trifluperidol; and octyl methoxycinnamate and suberohydroxamic acid, where the two agents are administered within 28 days of each other in amounts that together are effective to treat the patient.

The methods of any of the above aspects may be performed in conjunction with administering to the patient an additional treatment (e.g., an antiviral therapy such as those agents listed in Table 4 and Table 5) for a viral disease, where the method and the additional treatment (e.g., not a combination of agents selected from Table 6 and Table 7) are administered within 6 months (e.g., within 3, 2, or 1 months; within 28, 21, 14, 10, 7, 5, 4, 3, 2, or 1 days; within 24, 12, 6, 3, 2, or 1 hours; or concomitantly) of each other. The agents may be administered to the patient by intravenous, intramuscular, inhalation, topical (e.g., ophthalmic, determatologic), or oral administration.

In another aspect, the invention features a kit including an agent selected from any of the agents of Table 1; and instructions for administering the agent to a patient having a viral disease.

In another aspect, the invention features a kit including an agent selected from any of the agents of Table 1 and Table 2; and instructions for administering the agent to a patient having hepatitis C.

In another aspect, the invention features a kit including a composition including two or more (e.g., 3, 4, 5, 6, or 7) agents selected from any of the agents of Table 1, Table 2, and Table 3; and instructions for administering the composition to a patient having a viral disease.

In another aspect, the invention features a kit including a first agent selected from any of the agents of Table 1, Table 2, and Table 3; a second, different agent selected from any of the agents of Table 1, Table 2, and Table 3;

and instructions for administering the first and second agents to a patient having a viral disease.

In another aspect, the invention features a kit including an agent selected from any one of the agents of Table 1, Table 2, and Table 3; and instructions for administering the agent with a second, different agent selected from any of the agents of Table 1, Table 2, and Table 3 to a patient having a viral disease.

In another aspect, the invention features a kit including a composition including (i) a first agent selected from any one of the agents of Table 1, Table 2, and Table 3, and (ii) one or more agents of Table 4 and Table 5; and instructions for administering the composition to a patient having a viral disease.

In another aspect, the invention features a kit including (a) a first agent selected from any of the agents of Table 1, Table 2, and Table 3; (b) one or more agents of Table 4 and Table 5; and (c) instructions for administering (a) and (b) to a patient having a viral disease.

In another aspect, the invention features a kit including an agent selected from any of the agents of Table 1; and instructions for administering the agent and one or more agents of Table 4 or Table 5 to a patient having a viral disease.

In another aspect, the invention features a kit including an agent selected from any of the agents of Table 1 and Table 2; and instructions for administering the agent and one or more agents of Table 4 or Table 5 to a patient having hepatitis C.

In another aspect, the invention features a kit including (a) one or more agents of Table 4 and Table 5; and (b) instructions for administering the agent from (a) with any agent of Table 1, Table 2, and Table 3 to a patient having a viral disease.

In another aspect, the invention features a kit including sertraline; an HMG-CoA reductase inhibitor (e.g., fluvastatin, simvastatin, lovastatin, or rosuvastatin); and instructions for administering the sertraline and the HMG-CoA reductase inhibitor to a patient having a viral disease.

In another aspect, the invention features a kit including a composition including sertraline and an HMG-CoA reductase inhibitor (e.g., fluvastatin, simvastatin, lovastatin, or rosuvastatin); and instructions for administering the composition to a patient having a viral disease.

In another aspect, the invention features a kit including sertraline; an antihistamine (e.g., hydroxyzine); and instructions for administering the sertraline and the antihistamine to a patient having a viral disease.

In another aspect, the invention features a kit including a composition including sertraline and an antihistamine (e.g., hydroxyzine); and instructions for administering the composition to a patient having a viral disease.

In another aspect, the invention features a kit including (a) a pair of agents selected from the group consisting of amorolfine and sertraline; fluvastatin and sertraline; rosuvastatin and sertraline; fulvestrant and satraplatin; amorolfine and mebeverine; amorolfine and satraplatin; ifenprodil and sertraline; amorolfine and tolterodine; atorvastatin and sertraline; amorolfine and irinotecan; lovastatin and sertraline; cytarabine and triciribine; artesunate and wortmannin; sertraline and simvastatin hydroxy acid, ammonium salt; amorolfine and cytarabine; sertraline and simvastatin; octyl methoxycinnamate and suberohydroxamic acid; 1,5-bis(4-aminophenoxy)pentane and amorolfine; (S,S)-N-desmethyl sertraline and simvastatin; artemisinin and SB-202190; interferon alfa-2a and sirolimus; amorolfine and indocyanine green; TOFA and triciribine; 3,3'-(pentamethylenedioxy)dianiline and artemisinin; artemisinin and wortmannin;

3,3''-(pentamethylenedioxy)diacetanilide and artemisinin; amorolfine and benzamil; artemisinin and triciribine; 2,2'-(pentamethylenedioxy)dianiline and amorolfine; (S,S)-n-desmethyl sertraline and simvastatin; levothyroxine and wedelolactone; 1,5-bis(4-aminophenoxy)pentane and artemisinin; benzamil and dextrothyroxine; amorolfine and trifluperidol; artemisinin and indocyanine green; dihydroartemisinin and wortmannin; flupentixol and sertraline; benzamil and levothyroxine; amorolfine and meclizine; pravastatin and sertraline; 1,5-bis(4-aminophenoxy)pentane and indocyanine green; 2-hydroxyflavanone and amorolfine; ritonavir and vinorelbine; benoxinate and dehydroepiandrosterone; ifenprodil and indocyanine green; amorolfine and arbidol; 3,3'-(pentamethylenedioxy)dianiline and indocyanine green; fulvestrant and vinorelbine; amorolfine and ezetimibe; amorolfine and Evans blue; amorolfine and gefitinib; amorolfine and topotecan; 2',2''-(pentamethylenedioxy)diacetanilide and artemisinin; amorolfine and wedelolactone; 3,3'-(pentamethylenedioxy)dianiline and amorolfine; simvastatin and rac-cis-n-desmethyl sertraline; adefovir dipivoxil and triciribine; cytarabine and Evans blue; artemisinin and Evans blue; fluphenazine and sertraline; benzamil and SB-202190; artemisinin and rifabutin; fluphenazine and tolterodine; interferon alfa-2a and melphalan; amorolfine and melphalan; artemisinin and fulvestrant; ifenprodil and quinacrine; simvastatin and rac-cis-n-desmethyl sertraline; flupentixol and tolterodine; triciribine and wortmannin; loratadine and vinorelbine; meclizine and sertraline; budesonide and vinorelbine; 2-hydroxyflavanone and indocyanine green; hydroxyzine and sertraline; 2,2'-(pentamethylenedioxy)dianiline and artemisinin; amorolfine and flupentixol; artemisinin and chlorophyllin; ezetimibe and fluphenazine; benzamil and fluphenazine; artemisinin and wedelolactone; cytarabine and dydrogesterone; artemisinin and benzamil; 3,3'-(pentamethylenedioxy)dianiline

and artemether; tolterodine and trifluperidol; artesunate and fluvastatin; artemisinin and trifluridine; adefovir dipivoxil and amorolfine; interferon alfa-2a and trifluridine; fulvestrant and triciribine; artesunate and dydrogesterone; artesunate and LY 294002; mosapride citrate and TOFA; bromocriptine and wedelolactone; artemisinin and sodium fusidate; celgosivir and interferon alfa-2a; amorolfine and dextrothyroxine; andrographis and fulvestrant; 2'-c-methylcytidine and artemisinin; amorolfine and gemcitabine; oxeladin and sertraline; artemisinin and parthenolide; artemisinin and ribavirin; dehydroepiandrosterone and tyrphostin ag 1478; sertraline and toremifene; dihydroartemisinin and fulvestrant; 2-hydroxyflavanone and TOFA; artesunate and repaglinide; mofebutazone and wedelolactone; artesunate and simvastatin; 2,2'-(pentamethylenedioxy)dianiline and artesunate; artemisinin and gemcitabine; dihydroartemisinin and ezetimibe; chlorophyllin and cytarabine; interferon alfa-2a and sirolimus; suberohydroxamic acid and VX-497; artemisinin and VX-497; artesunate and VX-497; tolterodine and VX-950; artemisinin and HCV-796; artemisinin and NM-283; NM-283 and wedelolactone; artemisinin and SCH 503034; cytarabine and SCH 503034; SCH 503034 and triciribine; interferon alfa-2a and melphalan; benoxinate and VX-950; HCV-796 and sirolimus; benoxinate and SCH 503034; melphalan and VX-950; ritonavir and VX-950; VX-950 and VX-497; artemisinin and VX-950; triciribine and VX-950; suberohydroxamic acid and VX-950; HCV-796 and suberohydroxamic acid; sirolimus and VX-950; melphalan and SCH 503034; SCH 503034 and wortmannin; SCH 503034 and tolterodine; ritonavir and SCH 503034; ezetimibe and VX-950; HCV-796 and VX-497; chlorophyllin and VX-497; HCV-796 and melphalan; capsaicin and NM-283; SCH 503034 and sirolimus; LY 294002 and SCH 503034; adefovir dipivoxil and SCH 503034; interferon alfa-2a and trifluridine; HCV-796 and trifluridine; GW 5074 and

NM-283; mosapride and VX-950; interferon alfa-2a and VX-497; NM-283 and trequinsin; cytarabine and HCV-796; adefovir dipivoxil and VX-950; cytarabine and VX-950; SCH 503034 and saquinavir; VX-950 and wortmannin; capsaicin and VX-950; 2-hydroxyflavanone and NM-283; bromhexine and VX-950; HCV-796 and wortmannin; artemisinin and ribavirin; VX-950 and verapamil; SCH 503034 and verapamil; SCH 503034 and topotecan; HCV-796 and topotecan; trifluperidol and VX-950; irinotecan and SCH 503034; artesunate and SCH 503034; repaglinide and SCH 503034; topotecan and VX-950; repaglinide and VX-950; arbidol and VX-950; chlorophyllin and HCV-796; benzydamine and VX-950; NM-283 and trifluperidol; capsaicin and HCV-796; NM-283 and phenazopyridine; NM-283 and trifluridine; and adefovir dipivoxil and HCV-796; and (b) instructions for administering the pair of agents to a patient having a viral disease. The kit may include a composition including the pair of agents.

In another aspect, the invention features a kit including (a) a pair of agents selected from the group consisting of simvastatin and sertraline; fluvastatin and sertraline; fluphenazine and sertraline; artesunate and simvastatin; artesunate and wortmannin; artemisinin and chlorophyllin; artemisinin and 3,3'-(pentamethylenedioxy)dianiline; amorolfine and meclizine; amorolfine and sertraline; amorolfine and trifluridine; amorolfine and 2-hydroxyflavanone; amorolfine and ezetimibe; amorolfine and benzamil; amorolfine and trifluperidol; and octyl methoxycinnamate and suberohydroxamic acid; and (b)instructions for administering the pair of agents to a patient having a viral disease. The kit may include a composition including the pair of agents.

In another aspect, the invention features a method of identifying a combination that may be useful for the treatment of a patient having a viral

disease, or the prevention or reduction of the viral disease. The method includes the steps of contacting cells including at least a portion of the genome of a virus with an agent selected from any one the agents of Table 1, Table 2, and Table 3 and a candidate compound, wherein the portion of the genome (e.g., of any virus described herein) is capable of replication in the cells; and determining whether the combination of the agent and the candidate compound inhibits the replication of the portion of the genome relative to cells contacted with the agent but not contacted with the candidate compound, where a reduction in replication identifies the combination as a combination useful for the treatment of a patient having a viral disease, or the prevention or reduction of a viral disease. The reduction in replication may be the result of a decreased rate of DNA or RNA replication, a decreased rate of RNA translation, or inhibition of a protein required for viral replication (e.g., a protein coded for by the viral genome or the host organism). If the at least portion of a genome is from the hepatitis C genome, the reduction in replication may also be due to a decreased rate of polyprotein processing. The cells may be mammalian cells (e.g., hepatic cells, for example, any of those described herein) such as human cells.

The viral disease referred to in any of the above aspects of the invention, including the methods of treatment of the invention, the compositions and kits of the invention, and methods of the invention for identifying combinations may be caused by a single stranded RNA virus, a flaviviridae virus (e.g., a hepacivirus such as HCV, flavivirus, pestivirus, or hepatitis G virus), or a hepatic virus (e.g., any hepatic virus described herein such as hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E, non-ABCDE hepatitis, or hepatitis G). In certain embodiments, the viral disease is caused by a flavivirus which include without limitation Absettarov, Alfuy, Apoi, Aroa, Bagaza, Banzi,

Bouboui, Bussuquara, Cacipacore, Carey Island, Dakar bat, Dengue 1, Dengue 2, Dengue 3, Dengue 4, Edge Hill, Entebbe bat, Gadgets Gully, Hanzalova, Hypr, Ilheus, Israel turkey meningoencephalitis, Japanese encephalitis, Jugra, Jutiapa, Kadam, Karshi, Kedougou, Kokobera, Koutango, Kumlinge, Kunjin, Kyasanur Forest disease, Langat, Louping ill, Meaban, Modoc, Montana myotis leukoencephalitis, Murray valley encephalitis, Naranjal, Negishi, Ntaya, Omsk hemorrhagic fever, Phnom-Penh bat, Powassan, Rio Bravo, Rocio, royal farm, Russian spring-summer encephalitis, Saboya, St. Louis encephalitis, Sal Vieja, San Perlita, Saumarez Reef, Sepik, Sokuluk, Spondweni, Stratford, Tembusu, Tyuleniy, Uganda S, Usutu, Wesselsbron, west Nile, Yaounde, yellow fever, and Zika viruses, or any of the viruses described in Chapter 31 of *Fields Virology*, Fields, B. N., Knipe, D. M., and Howley, P. M., eds. Lippincott-Raven Publishers, Philadelphia, Pa., 1996. In other embodiments, the viral disease is caused by a pestivirus, which include bovine viral diarrhea virus ("BVDV"), classical swine fever virus ("CSFV," also called hog cholera virus), border disease virus ("BDV") and any of those discussed in Chapter 33 of *Fields Virology*, supra. In other embodiments, the viral disease is caused by a virus such as hepatitis A, hepatitis B, hepatitis C (e.g., genotype 1 such as 1a or 1b; genotype 2 such as 2a, 2b, or 2c; genotype 3; genotype 4; genotype 5; genotype 6); hepatitis D; or hepatitis E. The viral hepatitis may further be a non-ABCDE viral hepatitis (e.g., hepatitis G).

Additional viral therapies are described in Table 4 and Table 5.

Table 4

(+)-Calanolide A	(+)-Dihydrocalanolide A	145U87	2-Nor-cyclic GMP
3;4-Dicaffeoylquinic acid	3-Hydroxymethyl dicamphanoyl khellactone	3-Hydroxyphthaloyl-beta-lactoglobulin	3-Nitrosobenzamide
4-Azidothymidine	4-Methyl dicamphanoyl khellactone	524C79	739W94
A 160621	A 315675	A 315677	A 5021
A 74259	A 74704	A 77003	A 80735
A 80987	A 91883A	A 98881	Abacavir
AC 2	Acemannan	Acetylcysteine - Zambon	ACH 126445

ACH 126447	Aciclovir (e.g., extended release, controlled release, topical patch)	Aciclovir-PMPA	ACP HIP
Actinohivin	AD 439	AD 519	Adamantylamide dipeptide
ADS J1	Afovirsen	AG 1284	AG 1350
AG 1478	AG 1859	AG 555	AG 6840
AG 6863	AGT-1	AHA 008	Aidfarel
AL 721	Alamifovir	Albumin/interferon-alpha	ALN RSV01
Alovudine	Alpha HGA	Alpha-1PDX	Alpha-antitrypsin
Alvircept sudotox	Alvocidib	ALX 0019	ALX 404C
AM 285	AM 365	Amantadine	AMD 070
AMD 3329	AMD 3465	AMD 8664	Amdoxovir
Amidinomycin	Aminopeptidase	Amitivir	Ampligen
Amprenavir	AMZ 0026	Ancriviroc	Anti-CCR5 monoclonal antibody
Anti-CCR5/CXCR4 sheep monoclonal antibody	Anti-CD3 monoclonal antibody CD4IgG conjugate	Anti-CD4 monoclonal antibody	Anti-CD7 monoclonal antibody
Anti-CD8 monoclonal antibody	Anti-CMV monoclonal antibody	Anti-hepatitis B ribozyme	Anti-HIV catalytic antibody
Anti-HIV immunotoxin (IVAX)	Anti-HIV-1 human monoclonal antibody 2F5	Anti-HIV-1 human monoclonal antibody 2G12	Anti-HIV-1 human monoclonal antibody 4E10
Antineoplaston AS2 1 (e.g., oral)	Anti-RSV antibody (Intracel, Corp.)	Antisense oligonucleotide PB2 AUG	Aop-RANTES
Aplaviroc	Apricitabine	AQ 148	AR 132
AR 177	ARB 95214	ARB 97265	ARB 97268
	ARQ 323	AS 101	AT 61
Atazanavir	Atevirdine	AV 1101	AV 2921
AV 2923	AV 2925	AV 2927	Avarol
AXD 455	Azidodideoxyguanosine	Azodicarbonamide	Bafilomycin A1
Baicalin	BAY 414109	BAY 439695	BAY 504798
BAY Z 4305	BB 10010	BB 2116	BCH 10652
BCH 371	BCH 527	BCTP	BCX 140
BCX 1591	BCX 1827	BCX 1898	BCX 1923
BEA	BEA 005	Bellenamine	Benanomicin A
Benzalkonium (e.g., chloride)	Benzalkonium chloride/octoxynol 9 (e.g., vaginal gel)	Beta-D-FDOC	Beta-L-ddC
Beta-L-FddC	Bevirimat	BG 777	BGP 15
BILA 2185 BS	BILR 355	BIRM ECA 10-142	BL 1743
BM 510836	BMS 181167-02	BMS 181184	BMS 182193
BMS 186318	BMS 187071	BMS 488043	BMS 806
BMY 27709	Brecanavir	Brefeldin A	Brequinar
Brivudine	BRL 47923DP	BSL 4	BST 5001
BTA 188	BTA 798	C 1605	C 2507
C31G	Calcium spirulan	Canventol	Capravirine
Carbendazim	Carbocyclic deazaadenosine	Carbopol polymer gel	Carbovir
CC 3052	CD4 fusion toxin	CD4 IgG	CD4-ricin chain A
Cellulose sulfate	CF 1743	CFY 196	CGA 137053
CGP 35269	CGP 49689	CGP 53437	CGP 53820
CGP 57813	CGP 61783	CGP 64222	CGP 70726
CGP 75136	CGP 75176	CGP 75355	CI 1012
CI 1013	Cidofovir	Civamide	CL 190038
CL 387626	Clevudine	CMV 423	CMX 001
CNBA-Na	CNJ I02	Cobra venom peptide	Conocurvone
Cosalane	Costatolide	CP 1018161	CP 38
CP 51	CPFDD	CRL 1072	Crofelemer
CS 8958	CS 92	CT 2576	CTC 96
Curdlan sulfate	Cyanovirin-N	CYT 99007	Cytomegalovirus immune globulin
DAB486interleukin-2	DABO 1220	Dacopafant	DAP 30
DAP 32	Dapivirine	Darunavir	D-aspartic-beta-hydroxamate
DB 340	DDCDP-DG	DDGA	Deazaadenosine
Deazaneplanocin A	DEB 025	Delavirdine	Delmitide
Denileukin diftitox	Deoxyfluoroguanosine	DES 6	Dexelvucitabine

Dextran sulfate	Dextrin 2-sulfate	DG 35	Didanosine
Dideoxyadenosine	Dideoxyguanosine	Dideoxythymidine	Didox
Dihydrocostatolide	Dinitrochlorobenzene	DL 110	DMP 323
DMP 850	DMP 851	DmTr-ODN12	Docosanol
DP 107	DPC 082	DPC 083	DPC 681
DPC 684	DPC 961	DPC 963	Droxinavir
DUP 925	DYE	E 913	EB-Foscarnet
E-EPSEU	EGS 21	EHT 899	Elvucitabine
EM 1421	EM 2487	Emivirine	Emtricitabine
Emtricitabine/tenofovir disoproxil fumarate	Enfuvirtide	Entecavir	Eosinophil-derived neutralizing agent
Episiastatin B	ET 007	Etanercept	Ether lipid analogue
Etoviram	Etravirine	F 105	F 36
F 50003	Famciclovir	Fasudil	Fattiviracin A1
FEAU	Feglymycin	Felvizumab	FGI 345
Fiacitabine	Fialuridine	FLG	Flutimide
Fomivirsen	Fosalvudine tidoxil	Fosamprenavir	Foscarnet Sodium
Fozivudine	FP 21399	F-PBT	FPMPA
FPMPDAP	FR 191512	FR 198248	Galactan sulfate
Ganciclovir	GAP 31	GCA 186	GCPK
GE 20372A	GE 20372B	GEM 122	GEM 132
GEM 144	GEM 92	GEM 93	Glamolec
Glutathionarsenoxide	Glycovir	GMDP	GO 6976
GO 7716	GO 7775	Gossypol	GPG-NH2
GPI 1485	GPI 2A	GPs 0193	GR 137615
GR 92938X	GS 2838	GS 2992	GS 3333
GS 3435	GS 4071	GS 438	GS 7340
GS 9005	GS 9160	GS 930	GW 275175
GW 5950X	HB 19	HBY 946	HE 317
Hepatitis B immune globulin	HEPT	HGS-H/A27	HI 236
HI 240	HI 244	HI 280	HI 346
HI 443	HI 445	HIV DNA vaccine (Antigen Express, Inc.)	Thiovir
HIV immune globulin	HIV immune plasma	HL 9	HOE BAY 793
HRG 214	HS 058	Hydroxycarbamide	Hydroxychloroquine
I 152	IAZT	Idoxuridine	IM28
ImmStat	ImmuDyn	Immunocal	Imreg 1
Incadronic acid	INCB 9471	Indinavir	Infliximab
Influenza matrix protein Zn2+ finger peptide	Ingenol Triacetate	Inophyllum B	Inosine pranobex
Interferon-tau	Interleukin-1 receptor type I	Interleukin-13	Interleukin-15
Interleukin-16	Interleukin-2 agonist	Interleukin-4	IPdR
Ipilimumab	ISIS 13312	Iso ddA	ITI 002
ITI 011	JBP 485	JCA 304	JE 2147
JM 1596	JM 2763	JTK 303	K 12
K 37	K 42	Kamizol	kethoxal
Kijimicin	Kistamicin	KKKI 538	KM 043
KNI 102	KNI 241	KNI 272	KNI 413
KNI 684	Kootikuppala	KP 1461	KPC 2
KRH 1120	L 689502	L 693549	L 696229
L 696474	L 696661	L 697639	L 697661
L 708906	L 731988	L 732801	L 734005
L 735882	L 738372	L 738684	L 738872
L 739594	L 748496	L 754394	L 756423
L 870810	L HSA ara AMP	Lamivudine/abacavir	Lamivudine/zidovudine
Lamivudine/zidovudine/abacavir	Lasinavir	LB 71116	LB 71148
LB 71262	LB 71350	LB 80380	L-chicoric acid
Lecithinized superoxide dismutase	Leflunomide	Lentinan	Leukocyte interleukin injection (CEL-SCI Corp.)
Leukotriene B4 - LTB4	Levcycloserine	Levofloxacin	Lexithromycin
Liposomal ODG-PFA-OMe	Lithium succinate	Lobucavir	Lodenosine
Lopinavir	Loviride	Lufironil	LY 180299
LY 214624	LY 253963	LY 289612	LY 296242
LY 296416	LY 309391	LY 309840	LY 311912

LY 314163	LY 314177	LY 316683	LY 326188
LY 326594	LY 326620	LY 338387	LY 343814
LY 354400	LY 355455	LY 366094	LY 366405
LY 368177	LY 73497	Lysozyme	M 40401
M4N	Madu	Mannan sulfate	MAP 30
Maraviroc	Maribavir	Masoprocol	MB-Foscarnet
MC 207044	MC 207685	MC 867	mCDS71
MDI-P	MDL 101028	MDL 20610	MDL 27393
MDL 73669	MDL 74428	MDL 74695	MDL 74968
MDX 240	ME 609	MEDI 488	MEN 10690
MEN 10979	MER N5075A	Met-enkephalin	Methisazone
MGN 3	Michellamine B	Miglustat	MIV 150
MIV 210	Mivotilate	MK 0518	MK 944A
MM 1	MMS 1	MOL 0275	Monoclonal antibody 1F7
Monoclonal antibody 2F5	Monoclonal antibody 3F12	Monoclonal antibody 447-52D	Monoclonal antibody 50-61A
Monoclonal antibody B4	Monoclonal antibody HNK20	Monoclonal antibody NM01	Mopyridone
Moroxydine	Motavizumab	Motexafin gadolinium	Mozenavir
MPC 531	MRK 1	MS 1060	MS 1126
MS 8209	MS 888	MSC 127	MSH 143
MTCH 24	MTP-PE	Murabutide	MV 026048
MX 1313	Mycophenolate mofetil	Navuridine	NB 001
Neomycin B-arginine conjugate	Neotripterifordin	Nevirapine	Nitric oxide (e.g., ProStrakan)
Nitrodeazauridine	NM 01	NM 49	NM 55
NNY-RANTES	Nonakine	NP 06	NP 77A
NPC 15437	NSC 158393	NSC 20625	NSC 287474
NSC 4493	NSC 615985	NSC 620055	NSC 624151
NSC 624321	NSC 627708	NSC 651016	NSC 667952
NSC 708199	NV 01	Octoxynol 9	OCX 0191
OH 1	OKU 40	OKU 41	Oltipraz
Omaciclovir	Opaviraline	OPT TL3	Oragen
ORI 9020	Oseltamivir	Oxetanocin	Oxothiazolidine carboxylate
PA 344 / PA 344B	Palinavir	Palivizumab	PAMBAEEG
Papuamide A	PBS 119	PC 1250	PC 515
PCL 016	PD 0084430	PD 144795	PD 153103
PD 157945	PD 169277	PD 171277	PD 171791
PD 173606	PD 173638	PD 177298	PD 178390
PD 178392	PD 190497	Pegaldesleukin	Peldesine
PEN 203	Penciclovir	Pentosan polysulfate	Pentoxifylline
Peptide T	Peramivir	PETT 4	PG 36
Phellodendrine	Phosphatidyllamivudine	Phosphatidylzalcitabine	Phosphatidylzidovudine
Phosphazid	Phosphinic cyclocreatine	Pinosylvin	Pirodavir
PL 2500	Pleconaril	Plerixafor	PM 104
PM 19	PM 523	PM 92131	PM 94116
PMEDAP	PMS 601	PMTG	PMTI
PN 355	PNU 103657	PNU 142721	podophyllotoxin
Poly ICLC	Polyadenylic polyuridylic acid	Polysaccharide K	PP 29
PPB 2	PPL 100	Pradefovir	Pradimicin A
Prasterone	PRO 140	PRO 2000	PRO 367
PRO 542	Probucol (Vyrex Corp.)	Propagermanium	Prostratin
Pseudohypericin	PSI 5004	PTPR	PTX 111
Pyriferone	Q 8045	QM 96521	QM 96639
QR 435	Quinobene	Quinoxapeptin A	Quinoxapeptin B
QYL 438	QYL 609	QYL 685	QYL 769
R 170591	R 18893	R 61837	R 71762
R 82150	R 82913	R 851	R 87366
R 91767	R 944	R 95288	Raluridine
Ramatroban	Ranpirnase	RB 2121	RBC CD4
RD 30028	RD 42024	RD 42138	RD 42217
RD 42227	RD 62198	RD 65071	RD6 Y664

Regavirumab	Resobene	Respiratory syncytial virus immune globulin	Retrogen
REV 123	RFI 641	Rilpivirine	Rimantadine
RKS 1443	RO 0334649	RO 247429	RO 250236
RO 316840	RO 53335	Robustaflavone	Rolipram
RP 70034	RP 71955	RPI 312	RPI 856
RPR 103611	RPR 106868	RPR 111423	RS 654
RS 980	RSV 604	Rubitecan	Rupintrivir
S 1360	S 2720	S 9a	SA 1042
SA 8443	SB 180922	SB 205700	SB 206343
SB 73	SC 49483	SC 55099	SCH 350634
SD 894	S-DABO	SDF 1	SDZ 282870
SDZ 283053	SDZ 283471	SDZ 89104	SDZ PRI 053
SE 063	Semapimod	Sevirumab	SF 950
SF 953	Siamycin 1	Siamycin 2	sICAM-1
Sifuvirtide	SIGA 246	Sizofiran	SJ 3366
SK 034	SKF 108922	SKI 1695	SO 324
Sodium laurilsulfate	Solutein	Sorivudine (e.g., topical)	SP 10
SP 1093V	Sparfosic acid	SPC 3	SPD 756
SpecifEx-Hep B	SPI 119	SPL 2992	SPL 7013
SPV 30	SR 10204	SR 10208	SR 11335
SR 3745A	SR 3773	SR 3775	SR 3784
SR 3785	SR 41476	SRL 172	SRR SB3
ST 135647	Stachyflin	stallimycin	Stampidine
Statolon	Stavudine	Stepronin	Suksdorfin
Sulfated maltoheptaose	Superoxide dismutase	Suramin (e.g., sodium)	Sy 801
T 1100	T 118	T 22	T 30695
T 611	T 705	T4GEN	Tacrine
TAK 220	TAK 652	TAK 779	Talviraline
TAP 29	TASP	Teceleukin	Tecogalan (e.g., sodium)
TEI 2306	Telbivudine	Telinavir	Temacrazine
Tenidap	Tenofovir	Tenofovir disoproxil fumarate	TGG II 23A
TH 9407	TH 9411	Thalidomide	Thiophosphonoformic acid
Thymoctonan	Thymosin fraction 5	Thymotrinan	tICAM-1
Tifuvirtide	Tilarginine	Tipranavir	Tiviciclovir
Tivirapine	TJ 41	TL 3024	TMC 126
TNF-alpha inhibitor	TNK 6123	TNX 355	Todoxin
Tomeglovir	Transforming growth factor-alpha	TraT	Trecovirsen
Tremacamra	Trichosanthin	Triconal	Trimidox
Trodusquemine	Tromantadine	Trovirdine	Tuvirumab
U 103017	U 75875	U 78036	U 80493
U 81749	U 88204E	U 96988	U 9843
UA 926	Ubenimex	UC 10	UC 16
UC 38	UC 42	UC 68	UC 70
UC 781	UC 81	UC 82	UIC 94003
Ukrain	UL36ANTI	UMJD 828	Valaciclovir
Valganciclovir	Valomaciclovir	Valtorcitabine	Varicella zoster immune globulin
VB 19038	Vesnarinone	VF 1634	VGV 1
Vicriviroc	VIR 101	Viraprexin	Virodene
Viscum album extract	VRX 496	VX 10166	VX 10217
VX 10493	VX 11106	WHI 05	WHI 07
WIN 49569	WIN 49611	WM 5	WR 151327
XK 216	XK 234	XN 482	XP 951
XQ 9302	XR 835	XU 348	XU 430
Y-ART-3	YHI 1	YK FH312	Z 100
Z 15	Zalcitabine	Zanamivir	Zidovudine (e.g., phosphate-didanosine dimer)
Zidovudine triphosphate mimics	ZX 0610	ZX 0620	ZX 0791
ZX 0792	ZX 0793	ZX 0851	ZY II

Additional hepatitis C therapies are described in Table 5.

Table 5

Albuferon		JTK 003	R7128
2'-C-methyl-7-deaza-adenosine	HCV AB 68	JTK 109	Resiquimod
A-837093	HCV-SM	KPE 00001113	Rosiglitazone
AG-021541	HE 2000	KPE 02003002	Sargramostim
Aldesleukin	Hepatitis C immune globulin	Lactoferrin	
ANA 971	Hepex C	Lamivudine	SCH 6
ANA 975	Heptazyme	LB 84451	Schisandra
AVI 4065	Histamine	Licorice root	SCV 07
AVR 118	Histamine dihydrochloride (e.g., injection, oral)	ME 3738	SCY-635
Bavituximab	HuMax-HepC	Medusa Interferon	Silipide
BILN 303 SE	Hypericin		Taribavirin
BIVN 401	ICN 17261	Milk thistle	
BLX 833 (e.g., controlled release)	IDN 6556	Mitoquinone	Thymalfasin (e.g., Zadaxin)
	Imiquimod	NIM 811	Thymus extract
CellCept	Interferon	N-nonyl-DNJ	TJ 9
Ceplene	Interferon alfa-2b (e.g., inhalation)	NOV 205	Tucaresol
Ciluprevir (BILN 2061)	Interferon alfacon-1	NV-08	Ursodeoxycholic acid
Civacir	Interferon alpha (e.g., sustained release, intranasal, Omniferon)	P 56	UT 231B
Colloidal silver		Peginterferon alfa-2a	Valopicitabine (NM 283)
CpG 10101	Interferon alpha-2b (e.g., controlled release or transdermal)	Peginterferon alfa-2b	VGX 410
DEBIO-025	Interferon alpha-2b gene therapy	PEGinterferon alfacon-1	Virostat
Edodekin alfa	Interferon alpha-n3	PEGylated interferon	VP 50406
EHC 18	Interferon beta-1a	Pegylated thymalfasin	VRT 21493
EMZ 702	Interferon beta-1b	PF-03491390	
Fas-ligand inhibitor	Interferon gamma-1b	PG 301029	WF 10
Ginseng	Interferon omega	PSI-6130	XTL 2125
Glycyrrhizin	Interleukin 10 (e.g., human recombinant)	R 1518	XTL 6865
GS 9132	Isatoribine	R 1626	
HCV 086	ISIS 14803	R 803	
HCV 371	ITMN-191	R-1626	

Table 6

Interferon alpha-2b/ribavirin
Lopinavir/ritonavir
Peginterferon alfa-2b/ribavirin

Table 7

Peginterferon-alpha/ribavirin/EMZ 702
Efavirenz/emtricitabine/tenofovir disoproxil fumarate

Analogs of any of the compounds listed in Tables 1, 2, or 3 may be used in any of the compositions, methods, and kits of the invention. Such analogs include any agent from the same therapeutic class, having the same or related molecular targets, or from the same mechanistic class as those listed in Table 8.

Table 8

Name	Therapeutic Classification	Molecular Target	Mechanism of Action	Misc Classification/Information
Mecobalamin	Vitamin (e.g., B12 analog)	Homocysteine Methionine synthetase	Coenzyme of methionine synthetase in the synthesis of methionine from homocysteine; role in transmethylation	Vitamin (hematopoietic) Vitamin B12 analog
Cobamamide	Vitamin Liver extracts and combinations with B12 Ophthalmological Alimentary tract product Systemic anabolics	Methionine synthetase	Cofactor of Methionine synthetase	Vitamine B12 analog Coenzymic form of vitamin B12
Curcumin	Alimentary tract product Anorectics Antacids/antiflatulants carminative Anti-atheroma preparation of natural origin Antidiarrheal Antiemetic Antifungal Antiviral Antineoplastic Antihemorrhoidal Antimigraine preparation Antirheumatic, non-steroidal (NSAID) Antiseptic and disinfectant Appetite stimulant Bile therapy and cholagogues Cytostatic Dermatological Digestives Hepatic Protector, Lipotropics Laxative Musculoskeletal product Prostatic disease product Stomach disorder prep Topical vasoprotective Wound healing agent		Transcription, activation Immunosuppressant Platelet aggregation antagonist Thromboxane synthase inhibitor NFκB inhibitor Anti-inflammatory activity Possible antineoplastic activity; antiproliferative effects; Induction of cell death in colon and melanoma tumor cells Induces apoptosis independently of p53 status	Antioxidant NSAID Enzyme inhibitor Dye

Name	Therapeutic Classification	Molecular Target	Mechanism of Action	Misc Classification/Information
			Anabolic	Commonly used as an ergogenic aid; banned substance in sports competition by International Association of Athletics Federations (IAAF).
	Systemic anabolic		Androgenic	
	Hematological agent		FSH antagonist	
	Anabolic steroid		Protein catabolism inhibitor	
Stanozolol			ICSH antagonist	Used in treatment of hereditary angioedema
			Testosterone release inhibitor	
	Cardiovascular product			
	Cerebral and peripheral vasotherapeutic			
	Anti-atheroma preparations of natural origin			
	Cholesterol and triglyceride reduction preparation			
	Anti-anemic product			
	Non-narcotic analgesic			
	Anti-inflammatory enzyme			
	Musculoskeletal product			
	Systemic muscle relaxant			
	Antirheumatic		Succinyl-CoA production	
	Systemic antihistamine		Activates folate coenzymes	
	Neurotonic		Synthetic Adrenergic	
	Antidepressant		Participates in DNA-synthesis	
	Stomatological		Participates in protein-synthesis	
	Blood coagulation		Hematopoiesis	
	Antifibrinolytic		Cell reproduction	
	Digestive		Essential for growth	Hematinic
	Antidiarrheal micro-organisms		Nucleoprotein synthesis	Vitamin (hematopoietic)
	Appetite stimulant		Physiological role associated with	Hematopoietic activity appears
	Anorectic		Methylation	identical to antianemia-factor in
Vitamin B12	Vitamin	Methionine synthase	Myelin synthesis	purified liver extract
			Cytoskeleton	Hematinic
	Cytostatics		Tubulin destabilizer	Vinca alkaloid
Vinorelbine	Antineoplastic	Tubulin	Mitotic inhibitor	Antineoplastic agent, phytogenic
				Radiation-sensitizing agent
	Immunosuppressive agent			
Sirolimus	Antifungal	mTOR	mTOR inhibitor	May inhibit human T- and B-
(rapamycin)	Antineoplastic	Immunophilins	Blocks cytokine transcription	lymphocyte proliferation
				Acaricide
				Fungicide, bactericide, wood
				preservative
	Alcohol deterrent		Aldehyde dehydrogenase inhibitor	Immunomodulator
Disulfiram	Drugs used In alcohol dependence	aldehyde dehydrogenase	Metabolism, energy	Enzyme inhibitors

Name	Therapeutic Classification	Molecular Target	Mechanism of Action	Misc Classification/Information
Hydroxocobalamin	Vitamin (e.g., B12) Anti-anemic product, including folic acid Ophthalmological Neurotonic Non-narcotic analgesic Musculoskeletal product Antirheumatic			Hematinics Vitamin (hematopoietic) Vitamin B12 analog
Testosterone	Hormone	FSH ICSH	FSH antagonist High dose: spermatogenesis-inhibitor Gonadotropin antagonist ICSH antagonist	Androgen Hormone Activity in many tissues may depend on reduction to dihydrotestosterone which binds to cytosolic-receptor-proteins Exogenous administration inhibits endogenous release via feedback inhibition of pituitary ICSH
Paclitaxel	Cytostatic Antineoplastic	Tubulin Microtubules	Microtubule Inhibitor Tubulin stabilizer Radiation sensitization	Antineoplastic agents, phytogenic Vinca Alkaloid
Fludarabine	Antineoplastic Cytostatic Antimetabolite Immunosuppressant	DNA polymerase alpha	Inhibition of DNA polymerase alpha by 2-fluora-ara-ATP (metabolite of fludarabine)	Nucleoside analog
Cycloheximide		Ribosomal peptidyl transferase 23S rRNA	Prostaglandin synthesis stimulant Ribosomal peptidyl transferase inhibitor Translation, ribosome	
Wedelolactone		IkB-α kinase IKKα Kinase IKKβ Kinase	IKKα and IKKβ Kinase inhibitor IkB-α kinase inhibitor	
Vidarabine	Antivirals (e.g., topical) Ophthalmological (e.g., antiviral agent) Antineoplastic	DNA polymerase	DNA polymerase inhibitor DNA synthesis inhibitor DNA synthesis	Antimetabolite Principal metabolite is hypoxanthine arabinoside possesses virucidal activity may interfere with early steps of viral DNA synthesis

Name	Therapeutic Classification	Molecular Target	Mechanism of Action	Misc Classification/Information
Wortmannin	Anti-inflammatory agents, steroidal Immunosuppressive Antibiotic Antifungal	PI3K phospholipase-d phospholipase-c	Phosphodiesterase inhibitor Phosphatidylinositol 3-kinase inhibitor. Insulin antagonist Phospholipase d inhibitor Phospholipase c inhibitor Serotonin antagonist	
Aphidicolin	Antiviral Antiherpetic Antiproliferative	DNA polymerase DNA polymerase II Viral-induced DNA polymerase DNA polymerase α	DNA polymerase inhibitor DNA synthesis inhibitor	May be of clinical use as an antiherpetic agent in AIDS patients resistant to aciclovir.
FR122047	NSAID	COX-1	Selective COX1 inhibitor Metabolism, hormone, prostaglandin	
Fluorouracil	Cytostatic Antimetabolite Antineoplastic Immunosuppressive	Thymidylate synthase	DNA synthesis inhibitor Pyrimidine antagonist DNA metabolism, pyrimidine Apparent deoxyuridylate methylation inhibitor Partial RNA synthesis inhibitor	
Evans Blue				Dye
SB-202190		p38 MAPK p38α and β isoforms	Eosinophil antagonist MAP kinase inhibitor (e.g., p38) TGF-beta stimulator	Apoptosis inducer
JSH-23			blocks nuclear translocation of NK-kB NFκB translocation inhibitor Transcription, activation	
N-Tosyl-L-phenylalanine chloromethyl ketone		NFκB	NFκB inhibitor serine protease inhibitor	
GW 5074		cRAF1	MAPK, cRAF1 inhibitor Raf-1 kinase inhibitor	
ML 9		MAP kinase	MAP kinase inhibitor Myosin light chain kinase inhibitor Catecholamine secretion inhibitor Protein kinase C (PKC) inhibitor Protein cAMP-dependent protein kinase (PKA) inhibitor	Enzyme inhibitors Azepine
Bay 11-7082	Apoptosis promoter	IkB-alpha kinase	I-kappa B-alpha kinase inhibitor. Kinase inhibitor Inhibits NFκB	
PKR inhibitor		RNA-dependent protein kinase	RNA-dependent protein kinase inhibitor	

Name	Therapeutic Classification	Molecular Target	Mechanism of Action	Misc Classification/Information
Vitamin K5	Antifungal Coagulation factor	Coagulation factor II, VII, IX, and X Protein C Protein S Protein Z	Required for conversion of prothrombin to thrombin Plays a role in coagulation factors II, VII, IX, and X, and Protein C, Protein S, and Protein Z	Insulin mimicking effect Antitumor activity
Saquinavir mesylate	Antiviral	HIV-1 Protease HIV-2 Protease	HIV-1 and HIV-2 protease inhibitor Protein processing	
Nelfinavir mesylate	Antiviral	Proteases	HIV protease inhibitor Peptide hydrolase inhibitor Protein processing	
Fenbendazole	Anthelmintic Antinematodal	Tubulin	Binds to tubulin and prevents microtubule formation	
Ritonavir	Antiviral	Proteases	HIV protease inhibitor Protein processing	
Dextrothyroxine sodium	Hypolipemics		Thyroid hormone Stimulates hepatic-cholesterol catabolism Reduces serum-cholesterol (e.g., LDL) May reduce elevated lipoprotein-beta and triglyceride fractions Stimulates biliary excretion of cholesterol and its degradation products	
Levothyroxine Sodium	Thyroid therapy Muscle relaxant Stimulant		Increases metabolic rate Protein, carbohydrate, and lipid metabolism stimulant	Thyroid-hormone
Reserpine	Antihypertensive Beta blocker Antipsychotic		Adrenergic uptake inhibitor Dopamine antagonist	Sympatholytics
Desloratadine	Antihistamine (e.g., systemic) Antioxidant	Histamine H1	Histamine receptor antagonist (e.g., H1) Calcium antagonist Eosinophil antagonist	Anti-allergic agent
Tamoxifen citrate	Antiesterogen Antineoplastic	Estrogen receptor PKC	PKC inhibitor Estrogen receptor inhibitor, modulator Estrogen agonist (e.g., in bone) Estrogen antagonist Receptor, hormone	Competes with estradiol and estrogen for receptor protein Selective estrogen receptor modulator
Raloxifene hydrochloride	Antineoplastic Anti-esterogenic	Estrogen receptor	Estrogen receptor modulator Estrogen agonist (e.g., in bone) Estrogen antagonist Receptor, hormone	Selective estrogen receptor modulator
Repaglinide	Antidiabetic		Stimulates Insulin release	Hypoglycemic agent
Loratadine	Antihistamine (e.g., systemic)		Histamine receptor antagonist (e.g., H1)	Antipruritic

Name	Therapeutic Classification	Molecular Target	Mechanism of Action	Misc Classification/Information
Fluvoxamine maleate	SSRI	Serotonin 5-HT transporter	Serotonin uptake inhibitor Receptor, neural	Antiobsessional agent little effect on noradrenaline uptake
Adefovir dipivoxil	Antiviral (e.g. HIV)	Reverse transcriptase	Reverse transcriptase inhibitor Viral replication	
Efavirenz	Antiviral (e.g., HIV)	Reverse transcriptase	Reverse transcriptase inhibitor Viral replication	Benzoxazinone Non-nucleoside reverse transcriptase Inhibitor
Doxepin hydrochloride	Sedative Antihistamine	Norepinephrine transporter Serotonin transporter	Histamine receptor antagonist (H1, H2) Inhibits noradrenaline and serotonin reuptake at presynaptic neuron Amine pump blocker Adrenergic innervation	Tricyclic Mild peripheral vasodilator Parasympatholytic Antidepressant
Maprotiline hydrochloride	Sedative Antihistamine Antidepressant	Norepinephrine transporter	Alpha2-adrenergic receptor antagonist Amine pump blocker Presynaptic serotonin and noradrenaline uptake inhibitor Mild peripheral vasodilator	Tetracylcic Parasympatholytic Related structurally and functionally to tricyclic antidepressants
Ezetimibe	Antihyperlipoproteinemic		Lipid transport inhibitor Cholesterol absorption inhibitors	
Albendazole sulfone	Antiparasitic Anthelmintic Non-steroidal respiratory antiinflammatory Amoebicide Antiprotozoal Anticestodal	Lanosterol 14-α-demethylase Microtubules	Metabolism, sterol Lanosterol 14-α-demethylase inhibitor Reported ATP-synthesis-inhibitor Reported to interact with microtubules Activity against *Giardia lamblia*	
Hydroxyzine (hydrochloride or pamoate)	Antihistamine Antiemetic	Histamine H1	Possible subcortical CNS-depressant Mild gastric secretion inhibitor Histamine (H1) blocker	Primary skeletal-muscle relaxant Spasmolytic activity Tranquilizer (minor)
Bromocriptine mesylate	Estrogens Other sex hormones Antiparkinson	Dopamine D2 receptor Prolactin	Dopaminergic; dopamine agonist Suppresses prolactin secretion Stimulates dopamine receptors Prolactin antagonist Dopamine D2 receptor agonist	Enzyme inhibitor (prolactin) Ergot alkyloid Ergotamine
Trifluoperazine Hydrochloride	Antipsychotic	Calmodulin inhibitor Eg5 inhibitor	Calmodulin antagonist Sympatholytic-alpha Dopamine antagonist, release inhibitor May depress reticular activating system Dopamine turnover stimulant	Parasympatholytic Phenothiazine Increases neuronal firing-rate in the midbrain Sedative hypnotic

Name	Therapeutic Classification	Molecular Target	Mechanism of Action	Misc Classification/Information
Benzydamine hydrochloride	Analgesic Anti-inflammatory NSAID		Blocks action of cyclo-oxygenase	Analgesic Antipyretic
Mebeverine	Digestive Antispasmodic and anticholinergic Antispasmodic,Ataractic combinations			Relaxant [smooth muscle] Reported to be a direct-acting smooth muscle relaxant
Chlorophyllin	Stomatological		May have antimutagenic and anticarcinogenic properties	Chlorophyll
Mosapride citrate	Gastroprokinetic Gastointestinal agent	5-HT4 receptor antagonist	Serotonin 4 receptor agonist Enhances gastric emptying and colonic motor activity Dopamine antagonists	
Flupentixol	Neuroleptic Antipsychotic		Dopamine receptor antagonist Prolactin release stimulant Dopamine turnover stimulant Ganglionplegic Heat regulating center inhibitor Membrane stabilizer Benzodiazepine agonist Sympatholytic-alpha Dopamine antagonist (e.g., D2)	Parasympatholytic
Rescinnamine	Antihypertensive		Probable mechanism: peripheral adrenaline-depletor peripheral noradrenaline-depletor angiotensin-converting enzyme inhibitor	Related structurally to reserpine and yohimbine
Dydrogesterone	Hormonal contraceptive Estrogen, progestogen combination Progestogen		Progestogen Tocolytic	Hormone Progestational hormones, synthetic Progestin
Rifabutin	Antibiotic Antitubercular, tuberculostatic Rifampicin/Rifamycin		RNA polymerase inhibitor Interferes with bacterial DNA-synthesis	
P-Aminosalicylic acid (e.g., sodium salt)	Antitubercular Bacteriostatic Antibiotic		Inhibits bacterial resistance to streptomycin and isoniazid. May inhibit folic acid synthesis without potentiation with antifolic compounds May inhibit synthesis of mycobactin, thus reducing iron uptake by *M. tuberculosis.*	Active only against mycobacteria (e.g., *Mycobacterium tuberculosis*).
Sertraline hydrochloride	SSRI		Inhibition of seratonin re-uptake	Antidepressant

Name	Therapeutic Classification	Molecular Target	Mechanism of Action	Misc Classification/Information
Benztropine mesylate	Antihistamine Antiparkinsonian		Muscarinic antagonist Dopamine uptake inhibitor Anticholinergic	Parasympatholytic Synthetic compound containing structural features of atropine and diphenhydramine.
Fluphenazine hydrochloride	Antipsychotic	Dopamine (D1, D2) receptor	Dopamine receptor antagonist (postsynaptic) Dopamine release inhibitor Sympatholytic alpha Dopamine antagonist Dopamine turnover stimulant Calmodulin antagonist	Parasympatholytic Similar to chlorpromazine
Andrographis	Hepatic protectors, lipotropics Antineoplastic Antiviral (e.g., HIV) Antipyretic		Arrest of cell growth caused by viruses Anticancer activity	Contains analgesic, antithrombotic, thrombolytic, hypoglycemic, and antipyretic compounds. Andrographolide is major labdane diterpenoidal constituent of *Andrographis paniculata*
Perospirone	Antipsychotic			
Meclizine	Antiemetic, antinauseant Antihistamine		Histamine (H1) agonist	Benzhydryl compounds Piperazines
Bufexamac	Antihemorrhoidal Antipruritic Anti-inflammatory (e.g., non-steriodal) Antirheumatic (e.g., topical, non-steroidal) Antipsoriasis Antifungal		Prostaglandin antagonist	Benzeneacetamides Analgesic antipyretic Anti-inflammatory agents, topical
Mesterolone	Steroid Androgen		Anabolic Androgen	
Trifluperidol	Antipsychotic		Benzodiazepine agonist Dopamine antagonist Ganglionplegic Membrane stabilizer Dopamine turnover stimulant Sympatholytic-alpha Heat regulating center inhibitor Prolactin release stimulant Dopamine-2 antagonist	Parasympatholytic Butyrophenone Similar properties to haloperidol

Name	Therapeutic Classification	Molecular Target	Mechanism of Action	Misc Classification/Information
Clomiphene citrate	Estrogen agonist Estrogen antagonist		Metabolism, sterol Ovary stimulant Squalene epoxidase inhibitor	Gonad-stimulating principle Hormone
Trimipramine Maleate	Antidepressant SSRI Sedative Antihistamine	Serotonin 5-HT transporter	Presynaptic serotonin reuptake inhibitor Presynaptic noradrenaline reuptake inhibitor Amine pump blocker Mild peripheral vasodilator	Parasympatholytic Dibenzazepines Tricyclic
Fenretinide	Retinoic acid receptor agonist Antineoplastic Retention of cyctotoxicity under hypoxia.	PPAR agonist	PPAR agonist Transcription, activation	Retinoid Inhibits the growth of prostate cancer in rats Decreases plasma retinol and retinol-binding protein levels in breast cancer patients Increases levels of ceramide.
Budesonide	Antiinflammatory (e.g., intestinal, steroidal) Corticosteroid (e.g., topical, systemic) Antiasthmatic (e.g., B2-stimulant, corticoid, xanthines) Bronchodilator	GC receptor	GC receptor activator Transcription, activation	Glucocorticoids, topical Hormone
Toremifene citrate	Cytostatic Antineoplastic	Estrogen receptor	Estrogen antagonist Estrogen agonist Estrogen receptor inhibitor	Hormone Anti-estrogen
Cladribine	Antimetabolite Cytostatic Antineoplastic Immunosuppressant	DNA polymerase Adenosine receptor DNA	Arrests cell division Incorporates into DNA DNA polymerase inhibitor Adenosine receptor agonist Immunosuppressive activity possibly mediated by triggering apoptosis in monocytes and lymphocytes Cytotoxic in lymphoid and myeloid neoplasms	May disrupt later stages of cell division Activity against low-grade lymphocytic malignancies; Inhibits T and B cell proliferation Prolongs the survival of skin and small bowel allografts in animals; Reduces hypodense lesions in patients with multiple sclerosis.
Cytarabine	Antimetabolite Antineoplastic Antiviral Cytostatic Immunosuppressive agent	DNA polymerase DNA polymerase-α DNA	Blocks progression from G_1-phase to S-phase Virucidal activity Primarily active in S-phase DNA polymerase inhibitor Damages DNA/chromosomes Incorporated into DNA and RNA	

Name	Therapeutic Classification	Molecular Target	Mechanism of Action	Misc Classification/Information
Melphalan	Antineoplastic Cytostatic Alkylating agent Immunosuppressant	DNA	Bifunctional alkylating-agent reported DNA-crosslinker DNA alkylator DNA damage	
Mechlorethamine hydrochloride	Alkylating agent Antineoplastic	DNA	DNA damage DNA alkylator	Destructive to mucous membranes
Trequinsin hydrochloride		Phosphodiesterase	Phosphodiesterase inhibitor	Platelet aggregation inhibitor
Auranofin	Antirheumatic			
Ergoloid mesylates	Antihypertensive (e.g., herbal) Peripheral vasodilator		Decreases vascular tone and slows the heart rate Blocks alpha-receptors. May increase oxygen uptake and cerebral metabolism, thereby normalizing depressed neurotransmitter levels.	Mixture of the mesylates (methane sulfonates) of dihydroergocornine, dihydroergocristine, and the α- and β-isomers of dihydroergocryptine. Used to treat decreasing mental capacity with age
Bismuth subsalicylate	Antibacterial Antidiarrheal		Inhibits growth of *Helicobacter pylori* in peptic ulcer Influences capsular polysaccharide production Possible prostaglandin synthesis inducer Possible enhancer of aminoglycoside production	Fungicide, bactericide, wood preservative
Bromhexine	Antiasthmatic, B2 stimulant Cough sedative Expectorant	Mucus glands Acid mucopolysaccharide fibers	Acts on mucus formation Disrupts structure of acid mucopolysaccharide fibers Produces less viscous mucus	Mucolytic Expectorant
Phenazopyridine hydrochloride	Anesthetic Analgesic		Mechanism of action unknown Produces prompt and effective local analgesia and relief of urinary symptoms by its rapid excretion in the urinary tract. Effects are confined to the genitourinary system and are not accompanied by generalized sedation or narcosis.	Exerts a topical analgesic effect on the urinary-tract mucosa during excretion
Diethylstilbestrol	Estrogens (nonsteroidal) Antineoplastic		inhibits luteinizing hormone secretion by the pituitary, thereby inhibiting testosterone secretion.	Hormone Contraceptives, postcoital, synthetic
Dicyclomine hydrochloride	Antispasmodic Anesthetic		Gastric secretion inhibitor	Anticholinergic Parasympatholytic

Name	Therapeutic Classification	Molecular Target	Mechanism of Action	Misc Classification/Information
Indocyanine Green	Ophthalmological diagnostic agent Imaging agent Diagnostic			Diagnostic aid (cardiac output and hepatic function) Dyes
Dibucaine hydrochloride	Anesthetic (e.g., local)		Calcium antagonist Nerve sodium permeability inhibitor Sensory nerve impulse inhibitor Calmodulin antagonist	primary site of action may be sodium transport proteins
Vanillin acetate				Scent
Flubendazole	Anthelmintic Antinematodal			Antiprotozoal
Oxfendazole	Anthelmintic			Antinematodal agents
Griseofulvin, microcrystalline	Antirheumatic nonsteroidal Antifungal	Phosphodiesterase Tubulin	Phosphodiesterase inhibitor Tubulin inhibitor	Fungicide, bactericide, wood preservative
Citalopram hydrobromide	SSRI Antidepressant	Serotonin 5-HT transporter	Serotonin-reuptake-inhibitor Serotonin 5-HT transporter	
Imipramine hydrochloride	Antihistamine Sedative Tricyclic antidepressant Antidepressant	Serotonin 5-HT transporter	Serotoninergic Mild peripheral vasodilator Presynaptic serotonin-reuptake-inhibitor Amine pump blocker Presynaptic noradrenaline reuptake inhibitor	
Azelastine	Antihistamine Preparations for non-specific conjuctivitis Non-Steroidal respiratory antiinflammatory Rhinologicals (topical, systemic) Bronchodilators and antiasthmatics NSAID	Histamine H1	Platelet aggregation inhibitor Histamine Receptor Antagonist (H1) May interfere with leukotriene-B4 synthesis and release May interfere with HETE-5-synthesis and release Interferes with activation/mobilization of Lipoxygenase-5 Lipoxygenase inhibitor May stabilize pulmonary epithelium May interfere with leukotriene-C4-synthesis/release May inhibit leukocyte migration Mast cell stabilizer	May interfere with calcium-dependent translocation
Cyproheptadine hydrochloride	Antihistamine	Histamine H1	Histamine receptor antagonist (H1) Serotonin antagonist	

Name	Therapeutic Classification	Molecular Target	Mechanism of Action	Misc Classification/Information
Mometasone furoate	Corticosteroid (topical) Topical rhinological Antiasthmatic, corticoid Steriodal anti-inflammatory Glucocorticoids, topical Anti-allergic	GC receptor Progesterone receptor	ACTH secretion inhibitor Causes protein catabolism Glycogen deposition inhibitor Calcium mobilizer GC receptor activator Transcription activator Immunomodulator Gluconeogenesis promoter Phosphorus mobilizer Inhibits production of reactive protein by inflammatory cells Inhibits migration of inflammatory cells	
Fulvestrant	Cytostatic hormone antagonist Antineoplastic	Estrogen receptor	Estrogen antagonist Estrogen receptor inhibitor	
Topotecan hydrochloride	Antineoplastic	DNA topoisomerase I	DNA topoisomerase I inhibitor DNA damage	
Irinotecan hydrochloride	Antineoplastic	DNA topoisomerase I	DNA topoisomerase I inhibitor DNA damage	
Amorolfine hydrochloride	Antifungal	C-14 sterol reductase	Metabolism, sterol C-14 sterol reductase inhibitor	Antimycotic
Exemestane	Cytostatic Hormone antagonist	Aromatase	Estrogen antagonist aromatase inhibitor Metabolism, hormone, estrogen	
Benzocaine	Anesthetic (e.g., local) Stomatological Ophthalmological,otological Antipruritic Wound healing agent Topical vasoprotective Antihemorrhoidal Anorectic Scabicides and ectoparasiticide Non-narcotic analgesic Antiemetic Antirheumatic		May block sodium channels Nerve sodium permeability inhibitor Sensory nerve impulse inhibitor	
Padimate O	Dermatological Emollients and protectives Sunscreen		Absorbs UVB, which forms excited species that inflict DNA damage	
R(+)-Verapamil hydrochloride	Antihypertensive Antiarrhythmic	Calcium channel	Calcium channel blocker Class IV anti-arrhythmia agent	
Terconazole	Antifungal Trichomonacide		Possible fungal-cell-membrane-permeabilizer	

Name	Therapeutic Classification	Molecular Target	Mechanism of Action	Misc Classification/Information
Halcinonide	Antiinflammatory Corticosteroid (e.g., topical)		ACTH antagonist Glycogen deposition inhibitor Calcium mobilizer ACTH secretion inhibitor Gluconeogenesis promoter Phosphorus mobilizer Immunosuppressive	Glucocorticoids, topical
Rifaximin	Antidiarrheal and oral electrolyte replacer Rifampicin/rifamycin Antibiotic	β-subunit of DNA-dependent RNA polymerase	Acts on the β-subunit DNA-dependent RNA polymerase of microorganisms to inhibit RNA synthesis.	
Quinestrol	Antineoplastic Estrogen	Estrogen receptor	Estrogen receptor agonist	
Zafirlukast	Antileukotriene Antiasthmatic		Leukotriene D4 and E4 antagonist	IC50 in our hands of 18.5 uM
Tolterodine tartrate	Antispasmodic Anti-Incontinence Genitourinary smooth muscle relaxant		Muscarinic receptor antagonist	
Diphenidol hydrochloride	Antiemetic Antivertigo agent			
Benoxinate hydrochloride	Local anesthetic		Na^+ channel binder Blocks sensory nerve endings near the site of application.	
Mesoridazine besylate	Tranquilizer Antipsychotic Phenothiazine Antihistamine		Dopamine antagonist Sympatholytic alpha Benzodiazepine agonist Heat regulating center inhibitor Membrane stabilizer Dopamine turnover stimulant Prolactin release stimulant Ganglionplegic Parasympatholytic Dopamine-2 antagonist	
Desoxycorticosterone acetate	Diuretic Anti-Addison agent		Binds mineralocorticoid receptor	Adrenocortical steroid (salt-regulating)
Oxeladin	Cough suppressant			
Manganese gluconate	Mineral supplement Antioxidant			
Oxibendazole	Antihelmintic		Reported ATP-synthesis-inhibitor	

Name	Therapeutic Classification	Molecular Target	Mechanism of Action	Misc Classification/Information
Sodium fusidate	Antibiotic		Protein synthesis inhibitor Chloramphenicol acetyltransferase inhibitor	
Noscapine	Non-narcotic analgesic Cough sedatives (antitussive) Antiasthmatic (e.g., xanthines) Expectorant cough preparation			
Narasin	Antibiotic Coccidiostat Growth stimulant	membranes	Increases ion transport through membranes	
Promazine hydrochloride	Antipsychotic Antiemetic Neuroleptic Phenothiazine		Neuron receptor blocker Dopamine receptor antagonist	
Zimelidine dihydrochloride	Antidepressant SSRI		Inhibition of serotonin uptake	
Benzamil HCL		Sodium, proton channel	Ion transport Sodium, proton channel inhibitor	
Thiostrepton	Antibiotic	Ribosome	Inhibits ribosome function Translation, ribosome	Cyclic peptide from *Streptomyces* active against gram-positive bacteria
Mianserin hydrochloride	Antihistamine Antidepressant	α-adrenergic receptor, Histamine H1 receptor Serotonin receptor Norepinephrine transporter	Antihistamine H1 Norepinephrine transporter Antiserotonin	Tetracylic compound
Quinacrine	Antiparasitic Antihelmintic Antiprotozoal (e.g., antimalarial) Antineoplastic Antinematodal Anticestodal	Monoamine oxygenase DNA	DNA replication inhibitor Binds DNA Transcription inhibitor Protein synthesis inhibitor Destroys ribosomes Monoamine oxygenase inhibitor Inhibits succinate oxidation Interferes with electron transport Destroys gametocytes of quartan malaria and vivax malaria Destroys trophozoites of quarta malaria, falciparum malaria, and vivax malaria	Probably active against Diphyllobothrium latum Giardia lamblia Hymenolepsis nana activity against: Taenia phospholipase inhibitor DNA incorporation

Name	Therapeutic Classification	Molecular Target	Mechanism of Action	Misc Classification/Information
Bifonazole	Antifungal	Lanosterol 14-alpha-demethylase	Reported carnitine acetyltransferase stimulator Interferes with sterol biosynthesis Lanosterol 14-alpha-demethylase inhibitor May enhance peroxisomal-β-oxidation system Reported carnitine-palmitoyl transferase-stimulator	Appears to increase permeability of fungal-cell-membrane, causing leakage of intracellular components
Bay 41-2272		Guanylate cyclase	NO-sensitive guanylate cyclase activator	
Erbstatin	Cytostatic Antineoplastic agent	EGFR	EGFR tyrosine kinase inhibitor Receptor, growth factor	Isolated from Actinomyces MH435-hF Enzyme inhibitor Growth inhibitor
Gefitinib (base)	Antineoplastic Protein kinase inhibitor	EGFR	Receptor, growth factor EGFR tyrosine kinase inhibitor	
Tyrphostin Ag 1478	Antineoplastic	EGFR	Receptor, growth factor EGFR tyrosine kinase inhibitor	Tyrphostin
Floxuridine	Antimetabolite Antineoplastic Cytostatic Analgesic Antiviral	DHFR DNA polymerase	DNA polymerase inhibitor DHFR inhibitor DNA metabolism, pyrimidine Apparent deoxyuridylate-methylation-inhibitor Inhibits thymydilate synthase Partial RNA-synthesis-inhibitor DNA-synthesis-inhibitor	
Spiperone	Antipsychotic	Aldosterone receptor Dopamine receptor	Dopamine receptor antagonist Receptor, renin-angiotensin Aldosterone receptor antagonist Dopamine antagonist	Butyrophenone
Donepezil hydrochloride	Nootropic Parasympathomimetic	Acetylcholinesterase	Acetylcholinesterase inhibitor	Cholinesterase inhibitors
Capsaicin	Stimulant Analgesic (e.g., narcotic) Musculoskeletal product Antigout preparation Topical antirheumatic Antipruritic	Vanilloid Nociceptin	Reported gastric-motility-inhibitor Probable mechanism: substance-P-depletor Nociceptin antagonist Vanilloid receptor agonist Prevents reaccumulation of substance-P in peripheral sensory neurons	

Name	Therapeutic Classification	Molecular Target	Mechanism of Action	Misc Classification/Information
Isosulfan Blue			Selectively picked up by lymphatic vessels delineating them from surrounding tissue possibly due to a protein-binding phenomenon May weakly bind serum-albumin	Rosaniline dye Imaging agent
Dienestrol	Estrogens (e.g., nonsteroidal)	Estrogen receptor	Estrogen receptor agonist	Hormone
Octyl methoxycinnamate	Antiacne Emollients and Protectives		Esterogenic Absorber of ultraviolet light	Sunscreen ingredient
Hydroquinone	Vitamin Topical nonsteroidal products for inflammatory skin disorders including psoriasis Antiacne Vitamin A and D		Desceases formation of melanin Melanin antagonist Tyrosine oxidation inhibitor	Depigmentor Reduces Skin Pigmentation By Inhibiting Enzymatic Oxidation Of Tyrosine Radiation-protective agents
Monobenzone	Depigmentor		Depigmenting agent; unknown mechanism	Depigmentor
Mitotane	Cytostatic Antineoplastic	Adrenal cortex	Antiadrenal cortex; adrenal-suppressant Reduces measurable 17-hydroxycorticosteroids Increases formation of hydroxycortisol-6-β Corticosteroid-antagonist Alters peripheral hydrocortisone metabolism	Can cause adrenal inhibition without cellular destruction Insecticide Dichlorodiphenyldichloroethane derivative
Trifluridine	Antiviral (e.g., ophthalmological) Ophthalmological Antimetabolite	Thymidine kinase (e.g., HSV, VSV) Viral DNA polymerase	Antimetabolite (pyrimidine) herpes-simplex-virus type-2 Thymidine phosphorylase inhibitor Activity against herpes simplex virus type-1 vaccinia-virus	In-vitro activity against adenovirus Interferes with DNA synthesis in cultured mammalian-cells
Gramicidin	Anti-infective Antibiotic (e.g., topical, peptide)	Membranes	Bacterial membrane disruptor	
2-Hydroxyflavanone	Antioxidant			Flavonoid Isolated from *Collinsonia canadensis*
10-Deacetylbaccatine III	Antineoplastic			extracted from the needles of the Yew tree, Taxus baccata L. Precursor to taxol drugs
Ifenprodil tartrate	Vascular dilator	NMDA receptor	5-HT3 receptor antagonist alpha1-adrenoceptor antagonist NMDA receptor antagonist Possible glutamate antagonist	Traxoprodil, an analog of ifenprodil, is highly selective for the NR2B subunit of the NMDA receptor.

Name	Therapeutic Classification	Molecular Target	Mechanism of Action	Misc Classification/Information
3,3'-(Pentamethylenedioxy)dianiline				
Tiratricol	Anorectic Thyroid therapy		Antioxidant Thyroid-hormone activity (metabolite of T3) Inhibits of TSH production and secretion by the pituitary gland.	
Oxyphenbutazone hydrate	Antiinflammatory NSAID Antirheumatic			
Siguazodan	Vasodilator	Cyclic nucleotide phosphodiesterase type III	Phosphodiesterase inhibition selective inhibition of cyclic nucleotide phosphodiesterase type III.	
Chlorphenoxamine hydrochloride	Antihistamine		Sedative Anticholinergic	Parasympatholytic
Edoxudine	Antiviral (e.g., topical)	Thymidine kinase	Thymidine kinase inhibitor	
Thiram	Antifungal Antiseptic		Aldehyde dehydrogenase inhibitor Glutathione reductase inactivator	Insect attractant, repellent and chemost Pesticide Fungicide, bactericide, wood preservative
Beta Escin	Systemic vasoprotective Systemic muscle relaxant		Inhibits edema formation Decreases vascular fragility	
Carbaryl	Insecticide (e.g., carbamate) Scabicide Ectoparasiticide Antiparasitic		Inhibits cholinesterase	Acaricide Growth regulator / Fertilizer Cholinesterase inhibitors
Iophenoxic Acid	Contrast agent	Bilirubin Human serum albumin	Increases fluorescence of bilirubin bound to human serum albumin at drug/albumin molar ratios lower then 1. The increase may result from a conformational change in the albumin, which in turn causes displacement of bilrubin	Contrast media
Piceatannol	Antineoplastic agent	Syk Lck Mitochondrial F1 ATPase	Tyrosine kinase inhibitor Protein kinase inhibitor Syk inhibitor Lck inhibitor mitochondrial F1 ATPase inhibitor	Platelet aggregation inhibitor

Name	Therapeutic Classification	Molecular Target	Mechanism of Action	Misc Classification/Information
U18666A		Seladin-1 D^8-sterol isomerase	2,3 oxidosqualene-lanosterol cyclase inhibitor D^8-sterol isomerase inhibitor Seladin-1 inhibitor Cholesterol synthesis inhibitor	
Methylglyoxal		S-adenosyl-L-methionine decarboxylase Lactoylglutathione lyase	S-adenosyl-L-methionine decarboxylase inhibitor Lactoylglutathione lyase inhibitor	Flavoring agent
Anisomycin	Antibiotic Antifungal	Ribosomal peptidyl transferase p38 JNK	Ribosomal peptidyl transferase inhibitor p38 activator JNK activator p54 activator MAP kinase activator Stress-activated protein kinases activator	
Celastrol	Antioxidant Anti-inflammatory	HSF1 DNA topoisomerase I Tyrosine kinase 20S proteasome	Suppresses LPS-induced pro-inflammatory cytokines release Suppresses LPS-induced NF-kB activation and NO production HSF1 inhibitor Transcription activator DNA topoisomerase I inhibitor Tyrosine kinase inhibitor Inhibits chymotrypsin-like activity of 20S proteasome	triterpenoid isolated from the root of a Chinese medicinal herb, Tripterygium regeli, is a DNA topoisomerase inhibitor
Cerulenin		HMG-CoA synthetase	Irreversible inhibitor of fatty acid synthase Metabolism, sterol HMG-CoA synthetase inhibitor	
Camptothecin	Antineoplastic	DNA topoisomerase I	DNA topoisomerase I inhibitor	
Tirapazamine	Antineoplastic Radiation-sensitizing agent	DNA strand breaker	DNA damage DNA strand breaker Kills hypoxic cells	
Fascaplysin	Antiangiogenic	Cdk4/Cyclin D1 Cdk6/D1	Cdk4/Cyclin D1 inhibitor Cdk6/D1 inhibitor ATP competitive inhibitor	
Triciribine	Antineoplastic Antiviral (e.g., HIV)	AKT1/2/3	Metabolite triciribine phosphate inhibits amidophosphoribosyl transferase and IMP-dehydrogenase Signaling, kinase, PKB AKT1/2/3 inhibitor Inhibits nuclear import of HIV	
Deptropine citrate	Antihistamine (H1)		Antiserotonin Anticholinergic	

Name	Therapeutic Classification	Molecular Target	Mechanism of Action	Misc Classification/Information
Mequinol	Antineoplastic Hypopigmenting agent			Antioxidant
Pramoxine hydrochloride	Anesthetic (e.g., topical)		Reduces sodium permeability of nerves	Inhibits generation and conduction of nerve impulses from sensory nerves
Betaxolol hydrochloride	Antihypertensive Sympatholytic		Cardioselective beta-1-adrenergic antagonist	Anti-adrenergic
Dihydroergotamine mesylate	Cardiac sympathomimetic Antimigraine preparation Peripheral vasodilator Systemic vasoprotective Vasoconstrictor		Antiserotonin Sympatholytic Dopamine agonist	Anti-adrenergic
Beta-Ionol	Antioxidant		Prevents toxic effect of thiophenol on rats . Increase o-demethylase activity of cytochrome P-450 Activates cytosol and microsomal glutathione-dependent enzymes. Protects erythrocytes from peroxide damage by thiophenol and simultaneously enhanced its prooxidant effect in the liver.	
Thapsigargin		Endoplasmic reticulum Ca^{2+}-ATPase	Histaminergic Ca^{2+} pump inhibitor Calcium ATPase pump inhibitor Calcium channel antagonist	Tumor promoter
Dilazep dihydrochloride	Vasodilator Antithrombotic		Calcium antagonist Adenosine uptake inhibitor coronary and cerebral vasodilator	Antiarrhythmic activity Antiplatelet
Cyclocytidine hydrochloride	Antimetabolite Antineoplastic		DNA synthesis inhibitor Cell proliferation inhibitor	Specific for S-phase of the cell-cycle
Saponin			Permeabilizes cell membranes hemolytic activity	Saponin is any glucosides that occur in plants and are characterized by the property of producing a soapy lather. A moisture absolving amorphous saponin mixture can be used as a foaming and emulsifying agent and detergent When it is digested, it yields a sugar and a sapogenin aglycone.
Mofebutazone	Anti-inflammatory agent Antirheumatic, non-steroidal NSAID			

Name	Therapeutic Classification	Molecular Target	Mechanism of Action	Misc Classification/Information
Dehydroepiandrosterone	Anabolic Androgen		Androgen	Adjuvants, immunologic Hormone
Amitrole (4)		Catalase	Catalase inhibitor	Herbicide Pesticide
Tioxolone	Antiacne			
6-Nitroquipazine	SSRI	5-HT transporter complex	Inhibits serotonin reuptake	Serotonin antagonists
Shikonin	Antibacterial Anti-inflammatory Antitumor	Caspase 3/8	Signaling, apoptosis, inducer Caspase 3/8 activator Angiogenesis inhibitor Blocks expression of integrin $\alpha_v\beta_3$	
Picotamide	Anticoagulants and platelet aggregation inhibitor	Thromboxane A2/prostaglandin endoperoxide H2 (TXA2/PGH2) receptor Thromboxane A2 (TXA2) synthase	Antiaggregant TXA2/PGH2 receptor inhibitor TXA2 synthase inhibitor	
Amitraz	Insecticide Antiparasitic		Alpha-adrenergic receptor agonist Monoamine oxidase inhibitor	Scabicide Insect repellent Acaricide
Cepharanthine	Antiallergic Antineoplastic NSAID Antiviral (e.g., Anti-HIV) Antiinflammatory Antiallergenic	PKC ODC	Interferes with release of histamine from mast cells May inhibit linkage of H1-histone with phospholipid vesicles Blocks IL-1 release PKC inhibitor Reported protein-kinase-C-inhibitor Suppresses NO production ODC inhibitor	Antineoplastic agents, phytogenic
UCH-L3 inhibitor (4,5,6,7-Tetrachloroindan-1,3-dione)		UCH-L3	UCH-L3 inhibitor Proteasome	
UCH-L1 inhibitor (LDN-57444)		UCH-L1	Protein processing UCH-L1 inhibitor	
2-Methoxyestradiol	Anti-angiogenic	PARP Tubulin HIF-1	Proliferation inhibitor Angiogenesis inhibitor Signaling, apoptosis PARP inhibitor Tubulin binder HIF-1 antagonist	Steroid Estrogen
1,5-Isoquinolinediol		PARP	PARP inhibitor Potent inhibitor of Poly(ADP-ribose) synthetase Blocks nitric oxide-induced neuronal toxicity	neuroprotective agent

Name	Therapeutic Classification	Molecular Target	Mechanism of Action	Misc Classification/Information
AG-490		JAK-2 JAK-3 STAT-3	Kinase inhibitor JAK-2 tyrosine kinase inhibitor Inhibits constitutive activation of STAT-3 DNA binding Inhibits IL-2-induced growth of MF tumor cells JAK-3 tyrosine kinase inhibitor	Tyrphostin possible antineoplastic
1,2-bis-(2 aminophenoxy)ethane N,N,N,N,-tetreacetic acid		Ca^{2+}	Calcium chelator	
CAY10433		Histone deacetylase	Transcription, chromatin HDAC inhibitor	
Suberohydroxamic Acid		Histone deacetylase	Transcription, chromatin HDAC inhibitor	
Tyrphostin 23	Antineoplastic	EGFR/PDGFR kinase	Tyrosine kinase inhibitor Aldosterone secretion inhibitor Suppresses MAPK kinase activation Receptor, growth factor EGFR/PDGFR kinase inhibitor	Tyrphostin Growth inhibitor Enzyme inhibitors
Tyrphostin 47	Antineoplastic	EGFR/PDGFR kinase	Receptor, growth factor EGFR/PDGFR kinase inhibitor	Tyrphostin Blocks HT-29 colon cancer cell proliferation
AG-494	Antineoplastic	EGFR JAK-2 tyrosine kinase HER1	JAK-2 tyrosine kinase inhibitor EGFR inhibitor Selective HER1 inhibitor (vs. HER1-2; IC50: HER1 1.1 µM; HER1-2 45 µM2.) Receptor, growth factor Blocks Cdk2 activation	Tyrphostin
Tyrphostin 25	Antineoplastic	EGFR Transducin	Inhibits substrate binding on protein tyrosine kinases Inhibits EGFR tyrosine kinase Inhibits GTPase activity of transducin Inhibits neuromedin B-induced phosphorylation of p125FAK Blocks induction of inducible nitric oxide synthase in glial cells. Induces apoptosis in human leukemic cell lines.	Tyrphostin Enzyme inhibitors

Name	Therapeutic Classification	Molecular Target	Mechanism of Action	Misc Classification/Information
Tyrphostin 46	Antineoplastic	EGFR ERK1 ERK2	Inhibits EGFR tyrosine kinase and EGFR phosphorylation Inhibits EGF-dependent cell proliferation Inhibits ERK1 and ERK2	Tyrphostin
DNA-PK inhibitor II		DNA-PK	DNA-PK inhibitor	
NSC 663284		CDC25 phosphatase	CDC25 phosphatase inhibitor Arrests cell cycle progression Inhibits Cdk dephosphorylation Delays tumor growth	
BHQ		Calcium ATPase Prostaglandin E_2	Mobilizes Ca^{2+} specifically from Ins(1,4,5)P_3-sensitive Ca^{2+} stores by inhibiting microsomal and sarcoplasmic reticulum Ca^{2+}-ATPase activity. Does not affect mitochondrial Ca2+ fluxes or plasma membrane Ca2+/Mg2+ ATPase activity Inhibits prostaglandin E_2 Calcium ATPase inhibitor	
Fenvalerate		Calcineurin	Calcineurin inhibitor Induces depolarization by keeping Na^+ channels open.	Insecticide
Satraplatin	Antineoplastic			Platinum agent
Parthenolide		NFκB	Interleukin-1 antagonist NFκB inhibitor Prostaglandin E2 antagonist Prostaglandin antagonist Interleukin antagonist Nitric oxide antagonist TNF-alpha antagonist MAP kinase activation inhibitor	
Silver sulfadiazine	Wound healing agent Antipruritic Antibiotic and/or sulphonamide (e.g., topical) Antiseptic and disinfectant	DHFS	DHFS inhibitor DNA metabolism, pyrimidine	Anti-infective agents, local Acts on cell-membrane and cell wall Silver is released slowly in concentrations toxic to bacteria
Beta-carotene	Vitamin Neurotonic Emollient and protective Anti-atheroma preparation (e.g., of natural origin) Preparations to prevent cataract, anticataractogenic Vitamin A		Vitamin A	Antioxidant Food coloring agent Ultraviolet screen

Name	Therapeutic Classification	Molecular Target	Mechanism of Action	Misc Classification/Information
Methyltestosterone	Androgen, female hormone combination Estrogen, progestogen combinations Androgen		ICSH antagonist Gonadotropin antagonist Testosterone release inhibitor Spermatogenesis inhibitor Protein catabolism inhibitor Predominant anabolic activity Anabolic High-dose: FSH antagonist Minor androgenic activity	increased pharmacologic activity compared with testosterone
Propidium iodide		DNA Cholinesterase	Reported to intercalate DNA Cholinesterase inhibitor	
Tunicamycin	Antibiotic Antifungal Antiviral	P-MurNAc penapeptide synthase; Glycosyltransferase	Protein modification P-MurNAc penapeptide synthase; Glycosyltransferase inhibitor Inhibits expression of thrombin receptors	Nucleoside
2',2''-(Pentamethylenedioxy)diacetanilide				
3',3''-(Pentamethylenedioxy)diacetanilide				
Lovastatin	Cardiovascular agent Hypolipemics/antiatheroma Cholesterol and triglyceride reduction	HMG-CoA reductase	HMG-CoA reductase Inhibitor Metabolism, sterol	
Cyclosporine	Immunosuppressive Cytostatic Immunosuppressant Immunomodulator Antirheumatic Antifungal	Calcineurin	Inhibits lymphokine production Suppresses humoral immunity Inhibits helper-T-cells preferentially T-suppressor-cells may be suppressed interleukin-2-release-inhibitor Calcineurin inhibitor Suppresses cell-mediated reactions including: allograft-rejection	Prolongs survival of allogeneic transplanted tissue Action may be due to specific and reversible inhibition of immunocompetent lymphocytes in the G_0-phase or G_1-phase of the cell-cycle
Ribavirin	Antivirals (e.g., HIV, topical) Antimetabolite	RNA polymerase Inosine phosphate dehydrogenase	RNA polymerase inhibitor Inosine phosphate dehydrogenase inhibitor Transcription, machinery	In-vitro activity against respiratory syncytial virus, influenza virus, herpes simplex virus

Name	Therapeutic Classification	Molecular Target	Mechanism of Action	Misc Classification/Information
Simvastatin	Hypolipemic Angiotensin II antagonist Cholesterol and triglyceride reduction Cardiovascular product Cardiac glycoside	HMG-CoA reductase	cholesterol-synthesis-inhibitor decreases LDL-cholesterol-levels, VLDL-cholesterol-levels and plasma-triglycerides increases HDL-cholesterol-levels HMG-CoA reductase inhibitor	Anticholesteremic agent Antihyperlipidemic Antilipemic agents
Mycophenolic acid	Antibiotic Immunosuppressant	INPDH (inosine phosphate dehydrogenase)	INPDH inhibitor Inhibits T- and B-lymphocyte proliferation	Antibiotics, antineoplastic Enzyme inhibitor Antineoplastic
Atorvastatin	Antilipemic/hypolipemic Cholesterol and triglyceride reduction Antidiabetic Anti-atheroma preparation (e.g., of natural origin)	HMG-CoA reductase	Metabolism, sterol HMG-CoA reductase inhibitor	
Fluvastatin Sodium	Hypolipemic Cardiac glycoside Cholesterol and triglyceride reduction	HMG-CoA reductase inhibitor	HMG-CoA reductase inhibitor Metabolism, sterol	
Artemisinin	Antimalarial Antiparasitic Antiprotozoal Antineoplastic	Iron	Interacts with iron to generate free radicals, toxicity to parasites	Toxicity specific to cells with high iron content
Nitazoxanide	Antiprotozoal Antiparasitic Anti-infective Anticestodal Antiviral	pyruvate:ferredoxin oxidoreductase (PFOR)	Interferes with the PFOR enzyme-dependent electron transfer reaction	
Chloroquine	Antiprotozoal Antimalarial	Heme polymerase	Inhibits heme polymerase Inhibits biosynthesis of nucleic acids	
Mevastatin	Antibiotic	HMG-CoA reductase	Inhibits protein geranylgeranylation HMG-CoA reductase inhibitor May induce bone morphogenic protein-2 (BMP-2) Causes cell cycle arrest in late G_1 phase	
TOFA		Acetyl-CoA carboxylase	Inhibitor of acetyl-CoA carboxylase (ACC), key enzyme involved in fatty acid biosynthesis	
2'-C-Methylcytidine	Antiviral Antimetabolite		Ribonucleoside analog	
LY 294002		Phosphoinositide 3-kinases	Inhibitor of phosphoinositide 3-kinase	

Name	Therapeutic Classification	Molecular Target	Mechanism of Action	Misc Classification/Information
Telaprevir (VX-950)	Antiviral Anti-HCV	NS3-4A serine protease	Inhibitor of NS3-4A serine protease	
Merimepodib (VX-497)	Antiviral Anti-HCV	Inosine monophosphate dehydrogenase (IMPDH)	Inhibitor of IMPDH	
Valopicitabine (NM-283)	Antiviral Anti-HCV	HCV RNA polymerase	Inhibitor of RNA polymerase Inhibitor of HCV RNA polymerase	
Boceprevir (SCH 503034)	Antiviral Anti-HCV	NS3 protease	Inhibitor of NS3 protease	
Celgosivir	Antiviral Anti-HCV	α-Glucosidase I	Inhibitor of α-glucosidase I	
HCV-796	Antiviral Anti-HCV	HCV RNA polymerase	Inhibitor of RNA polymerase Inhibitor HCV RNA polymerase	Benzofuran
Emetine	Antiamoebic Antiprotozoal Antiparasitic	40S ribosome	Inhibitor of eukaryotic protein synthesis Binds 40S ribosome Inhibits translocation	Can cause vomiting or diarrhea
Arbidol	Antiviral		Induces interferon production Inhibition of membrane fusion	
Gemcitabine	Pyrimadine analog Antineoplastic Nucleoside analog	DNA DNA polymerase	Inhibits DNA replication	
Vincristine	Antiviral Antineoplastic	Tubulin Tubilin dimers Microtubules	Inhibits mitosis by binding tubulin	Isolated from *Vinca Rosea*
Dihydroergotamine mesylate	Antimigraine Vasoconstrictor	Serotonin receptor 5-HT1_{Da} receptor 5-HT1_{Db} receptor 5-HT_{1A} receptor 5-HT_{2A} receptor 5-HT_{2C} receptor α-Adrenergic receptor Dopamine D2L receptor Dopamine D3 receptor	Partial agonist of α-adrenergic receptors Partial agonist of dopamine D2 and D3 receptors Binds to 5-HT1_{Da}, 5-HT1_{Db}, 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors Inhibits release of proinflammatory neuropeptides	
Interferon alfa-2a	Antiviral Antineoplastic Anti-HIV	IFN-α receptor	Inhibits viral replication Upregulation of MHC I protein expression	

Compounds useful in the invention include those described herein in any of their pharmaceutically acceptable forms, including isomers such as diastereomers and enantiomers, salts, solvates, and polymorphs thereof, as well as racemic mixtures. Compounds useful in the invention may also be isotopically labeled compounds. Useful isotopes include hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, (e.g., ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl). Isotopically-labeled compounds can be prepared by synthesizing a compound using a readily available isotopically-labeled reagent in place of a non-isotopically-labeled reagent.

By "patient" is meant any animal (e.g., a mammal such as a human). Any animal can be treated using the methods, compositions, and kits of the invention.

To "treat" is meant to administer one or more agents to measurably slow or stop the replication of a virus *in vitro* or *in vivo*, to measurably decrease the load of a virus (e.g., any virus described herein including a hepatitis virus such as hepatitis A, B, C, D, or E) in a cell *in vitro* or *in vivo*, or to reduce at least one symptom (e.g., those described herein) associated with having a viral disease in a patient. Desirably, the slowing in replication or the decrease in viral load is at least 20%, 30%, 50%, 70%, 80%, 90%, 95%, or 99%, as determined using a suitable assay (e.g., a replication assay described herein). Typically, a decrease in viral replication is accomplished by reducing the rate of DNA or RNA polymerization, RNA translation, polyprotein processing, or by reducing the activity of a protein involved in any step of viral replication (e.g., proteins coded by the genome of the virus or host protein important for viral replication).

By "an effective amount" is meant the amount of a compound, alone or in combination with another therapeutic regimen, required to treat a patient

with a viral disease (e.g., any virus described herein including a hepatitis virus such as hepatitis A, B, C, D, or E) in a clinically relevant manner. A sufficient amount of an active compound used to practice the present invention for therapeutic treatment of conditions caused by a virus varies depending upon the manner of administration, the age, body weight, and general health of the patient. Ultimately, the prescribers will decide the appropriate amount and dosage regimen. Additionally, an effective amount may be an amount of compound in the combination of the invention that is safe and efficacious in the treatment of a patient having a viral disease over each agent alone as determined and approved by a regulatory authority (such as the U.S. Food and Drug Administration).

By "more effective" is meant that a treatment exhibits greater efficacy, or is less toxic, safer, more convenient, or less expensive than another treatment with which it is being compared. Efficacy may be measured by a skilled practitioner using any standard method that is appropriate for a given indication.

By "hepatic virus" is meant a virus that can cause hepatitis. Such viruses include hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E, non-ABCDE hepatitis, and hepatitis G.

By a "low dosage" is meant at least 5% less (e.g., at least 10%, 20%, 50%, 80%, 90%, or even 95%) than the lowest standard recommended dosage of a particular compound formulated for a given route of administration for treatment of any human disease or condition. For example, a low dosage of an agent that inhibits viral replication and that is formulated for administration by intravenous injection will differ from a low dosage of the same agent formulated for oral administration.

By a "high dosage" is meant at least 5% (e.g., at least 10%, 20%, 50%, 100%, 200%, or even 300%) more than the highest standard recommended dosage of a particular compound for treatment of any human disease or condition.

By a "candidate compound" is meant a chemical, be it naturally-occurring or artificially-derived. Candidate compounds may include, for example, peptides, polypeptides, synthetic organic molecules, naturally occurring organic molecules, nucleic acid molecules, peptide nucleic acid molecules, and components or derivatives thereof.

In the generic descriptions of compounds of this invention, the number of atoms of a particular type in a substituent group is generally given as a range, e.g., an alkyl group containing from 1 to 4 carbon atoms or C_{1-4} alkyl. Reference to such a range is intended to include specific references to groups having each of the integer number of atoms within the specified range. For example, an alkyl group from 1 to 4 carbon atoms includes each of C_1, C_2, C_3, and C_4. A C_{1-12} heteroalkyl, for example, includes from 1 to 12 carbon atoms in addition to one or more heteroatoms. Other numbers of atoms and other types of atoms may be indicated in a similar manner.

As used herein, the terms "alkyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, i.e., cycloalkyl. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 12 ring carbon atoms, inclusive. Exemplary cyclic groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl groups.

By "C_{1-4} alkyl" is meant a branched or unbranched hydrocarbon group having from 1 to 4 carbon atoms. A C_{1-4} alkyl group may be substituted or unsubstituted. Exemplary substituents include alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halide, hydroxyl, fluoroalkyl, perfluoralkyl, amino,

aminoalkyl, disubstituted amino, quaternary amino, hydroxyalkyl, carboxyalkyl, and carboxyl groups. C_{1-4} alkyls include, without limitation, methyl, ethyl, n-propyl, isopropyl, cyclopropyl, cyclopropylmethyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, and cyclobutyl.

By "C_{2-4} alkenyl" is meant a branched or unbranched hydrocarbon group containing one or more double bonds and having from 2 to 4 carbon atoms. A C_{2-4} alkenyl may optionally include monocyclic or polycyclic rings, in which each ring desirably has from three to six members. The C_{2-4} alkenyl group may be substituted or unsubstituted. Exemplary substituents include alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halide, hydroxyl, fluoroalkyl, perfluoralkyl, amino, aminoalkyl, disubstituted amino, quaternary amino, hydroxyalkyl, carboxyalkyl, and carboxyl groups. C_{2-4} alkenyls include, without limitation, vinyl, allyl, 2-cyclopropyl-1-ethenyl, 1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, and 2-methyl-2-propenyl.

By "C_{2-4} alkynyl" is meant a branched or unbranched hydrocarbon group containing one or more triple bonds and having from 2 to 4 carbon atoms. A C_{2-4} alkynyl may optionally include monocyclic, bicyclic, or tricyclic rings, in which each ring desirably has five or six members. The C_{2-4} alkynyl group may be substituted or unsubstituted. Exemplary substituents include alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halide, hydroxy, fluoroalkyl, perfluoralkyl, amino, aminoalkyl, disubstituted amino, quaternary amino, hydroxyalkyl, carboxyalkyl, and carboxyl groups. C_{2-4} alkynyls include, without limitation, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, and 3-butynyl.

By "C_{2-6} heterocyclyl" is meant a stable 5- to 7-membered monocyclic or 7- to 14-membered bicyclic heterocyclic ring which is saturated, partially unsaturated, or unsaturated (aromatic), and which consists of 2 to 6 carbon

atoms and 1, 2, 3, or 4 heteroatoms independently selected from N, O, and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclyl group may be substituted or unsubstituted. Exemplary substituents include alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halide, hydroxy, fluoroalkyl, perfluoralkyl, amino, aminoalkyl, disubstituted amino, quaternary amino, hydroxyalkyl, carboxyalkyl, and carboxyl groups. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be covalently attached via any heteroatom or carbon atom which results in a stable structure, e.g., an imidazolinyl ring may be linked at either of the ring-carbon atom positions or at the nitrogen atom. A nitrogen atom in the heterocycle may optionally be quaternized. Preferably when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. Heterocycles include, without limitation, 1H-indazole, 2-pyrrolidonyl, 2H,6H-1,5,2-dithiazinyl, 2H-pyrrolyl, 3H-indolyl, 4-piperidonyl, 4aH-carbazole, 4H-quinolizinyl, 6H-1,2,5-thiadiazinyl, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalonyl, carbazolyl, 4aH-carbazolyl, b-carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinylperimidinyl, phenanthridinyl, phenanthrolinyl, phenarsazinyl,

phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, piperidonyl, 4-piperidonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, carbolinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl. Preferred 5 to 10 membered heterocycles include, but are not limited to, pyridinyl, pyrimidinyl, triazinyl, furanyl, thienyl, thiazolyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, tetrazolyl, benzofuranyl, benzothiofuranyl, indolyl, benzimidazolyl, 1H-indazolyl, oxazolidinyl, isoxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, quinolinyl, and isoquinolinyl. Preferred 5 to 6 membered heterocycles include, without limitation, pyridinyl, pyrimidinyl, triazinyl, furanyl, thienyl, thiazolyl, pyrrolyl, piperazinyl, piperidinyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, and tetrazolyl.

By "C_{6-12} aryl" is meant an aromatic group having a ring system comprised of carbon atoms with conjugated π electrons (e.g., phenyl). The aryl group has from 6 to 12 carbon atoms. Aryl groups may optionally include monocyclic, bicyclic, or tricyclic rings, in which each ring desirably has five or six members. The aryl group may be substituted or unsubstituted. Exemplary substituents include alkyl, hydroxy, alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halide, fluoroalkyl, carboxyl, hydroxyalkyl, carboxyalkyl, amino,

aminoalkyl, monosubstituted amino, disubstituted amino, and quaternary amino groups.

By "C_{7-14} alkaryl" is meant an alkyl substituted by an aryl group (e.g., benzyl, phenethyl, or 3,4-dichlorophenethyl) having from 7 to 14 carbon atoms.

By "C_{3-10} alkheterocyclyl" is meant an alkyl substituted heterocyclic group having from 3 to 10 carbon atoms in addition to one or more heteroatoms (e.g., 3-furanylmethyl, 2-furanylmethyl, 3-tetrahydrofuranylmethyl, or 2-tetrahydrofuranylmethyl).

By "C_{1-7} heteroalkyl" is meant a branched or unbranched alkyl, alkenyl, or alkynyl group having from 1 to 7 carbon atoms in addition to 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, O, S, and P. Heteroalkyls include, without limitation, tertiary amines, secondary amines, ethers, thioethers, amides, thioamides, carbamates, thiocarbamates, hydrazones, imines, phosphodiesters, phosphoramidates, sulfonamides, and disulfides. A heteroalkyl may optionally include monocyclic, bicyclic, or tricyclic rings, in which each ring desirably has three to six members. The heteroalkyl group may be substituted or unsubstituted. Exemplary substituents include alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halide, hydroxyl, fluoroalkyl, perfluoralkyl, amino, aminoalkyl, disubstituted amino, quaternary amino, hydroxyalkyl, hydroxyalkyl, carboxyalkyl, and carboxyl groups. Examples of C_{1-7} heteroalkyls include, without limitation, methoxymethyl and ethoxyethyl.

By "halide" or "halogen" is meant bromine, chlorine, iodine, or fluorine.

By "fluoroalkyl" is meant an alkyl group that is substituted with a fluorine atom.

By "perfluoroalkyl" is meant an alkyl group consisting of only carbon and fluorine atoms.

By "carboxyalkyl" is meant a chemical moiety with the formula -(R)-COOH, wherein R is selected from C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl.

By "hydroxyalkyl" is meant a chemical moiety with the formula -(R)-OH, wherein R is selected from C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl,
C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl.

By "alkoxy" is meant a chemical substituent of the formula -OR, wherein R is selected from C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl.

By "aryloxy" is meant a chemical substituent of the formula -OR, wherein R is a C_{6-12} aryl group.

By "alkylthio" is meant a chemical substituent of the formula -SR, wherein R is selected from C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl.

By "arylthio" is meant a chemical substituent of the formula -SR, wherein R is a C_{6-12} aryl group.

By "quaternary amino" is meant a chemical substituent of the formula -(R)-N(R')(R'')(R''')$^+$, wherein R, R', R'', and R''' are each independently an alkyl, alkenyl, alkynyl, or aryl group. R may be an alkyl group linking the quaternary amino nitrogen atom, as a substituent, to another moiety. The nitrogen atom, N, is covalently attached to four carbon atoms of alkyl, heteroalkyl, heteroaryl, and/or aryl groups, resulting in a positive charge at the nitrogen atom.

Other features and advantages of the invention will be apparent from the following Detailed Description and the claims.

Detailed Description

We have identified compounds that decrease replication of a hepatitis C (HCV) replicon in mammalian cells. Accordingly, the present invention provides compositions, methods, and kits useful in the treatment of viral diseases, which may be caused by a single stranded RNA virus, a flaviviridae virus, or a hepatic virus (e.g., described herein). In certain embodiments, the viral disease is viral hepatitis (e.g., hepatitis A, hepatitis B, hepatitis C, hepatitis D, and hepatitis E). The invention also features screening methods useful for the identification of novel compounds for the treatment of viral diseases. Compositions of the invention can include one or more agents selected from the agents of Table 1, Table 2, Table 3, Table 4, and Table 5. Treatment methods of the invention include administration of one or more agents selected from the agents of Table 1, Table 2, and Table 3, optionally along with an additional antiviral therapy (e.g., administration of one or more agents of Table 4 or Table 5) to a patient (e.g., a mammal such as a human). Optionally, functional or structural analogs (e.g., those described herein) of these agents or agents of the same therapeutic or mechanistic class as those described herein (see, e.g., Table 8) may be employed in the compositions, methods, and kits of the invention. The ability of a composition to reduce replication of a virus may be due to a decrease in RNA or DNA polymerization, RNA translation, RNA or DNA transcription, a decrease in posttranslational protein processing (e.g., polyprotein processing in hepatitis C), or a decrease in activity of a protein involved in viral replication (e.g., a protein coded for by the viral genome or a host protein required for viral replication). The compounds or combinations of compounds may also enhance the efficacy of the other therapeutic regimens such that the dosage, frequency, or duration of the other therapeutic regimen is

lowered to achieve the same therapeutic benefit, thereby moderating any unwanted side effects.

In one particular example, the patient being treated is administered two agents listed in Table 1, Table 2 and/or Table 3 within 28 days of each other in amounts that together are sufficient to treat a patient having a viral disease. The two agents can be administered within 14 days of each other, within seven days of each other, within twenty-four hours of each other, or even simultaneously (i.e., concomitantly). If desired, either one of the two agents may be administered in low dosage.

Viral diseases

The invention relates to the treatment of viral disease, which can be caused by any virus. Viruses include single stranded RNA viruses, flaviviridae viruses, and hepatic viruses. In particular, the flaviviridae family of viruses include hepacivirus (e.g., HCV); flaviviruses; pestiviruses, and hepatitis G virus.

Flaviviruses generally are discussed in Chapter 31 of *Fields Virology*, supra. Exemplary flaviviruses include Absettarov, Alfuy, Apoi, Aroa, Bagaza, Banzi, Bouboui, Bussuquara, Cacipacore, Carey Island, Dakar bat, Dengue 1, Dengue 2, Dengue 3, Dengue 4, Edge Hill, Entebbe bat, Gadgets Gully, Hanzalova, Hypr, Ilheus, Israel turkey meningoencephalitis, Japanese encephalitis, Jugra, Jutiapa, Kadam, Karshi, Kedougou, Kokobera, Koutango, Kumlinge, Kunjin, Kyasanur Forest disease, Langat, Louping ill, Meaban, Modoc, Montana myotis leukoencephalitis, Murray valley encephalitis, Naranjal, Negishi, Ntaya, Omsk hemorrhagic fever, Phnom-Penh bat, Powassan, Rio Bravo, Rocio, royal farm, Russian spring-summer encephalitis, Saboya, St. Louis encephalitis, Sal Vieja, San Perlita, Saumarez Reef, Sepik,

Sokuluk, Spondweni, Stratford, Tembusu, Tyuleniy, Uganda S, Usutu, Wesselsbron, west Nile, Yaounde, yellow fever, and Zika viruses.

Pestiviruses generally are discussed in Chapter 33 of *Fields Virology*, supra. Specific pestiviruses include, without limitation: bovine viral diarrhea virus, classical swine fever virus (also called hog cholera virus), and border disease virus.

Hepatitis viruses

Viruses that can cause viral hepatitis include hepatitis A, hepatitis B, hepatitis C, hepatitis D, and hepatitis E. In addition, non-ABCDE cases of viral hepatitis have also been reported (see, for example, Rochling et al., *Hepatology* 25:478-483, 1997). Within each type of viral hepatitis, several subgroupings have been identified. Hepatitis C, for example, has at least six distinct genotypes (1, 2, 3, 4, 5, and 6), which have been further categorized into subtypes (e.g., 1a, 1b, 2a, 2b, 2c, 3a, 4a) (Simmonds, *J. Gen. Virol.* 85:3173-3188, 2004).

In the case of hepatitis C, acute symptoms can include jaundice, abdominal pain, fatigue, loss of appetite, nausea, vomiting, low-grade fever, pale or clay-colored stools, dark urine, generalized itching, ascites, and bleeding varices (dilated veins in the esophagus). Hepatitis C can become a chronic infection, which can lead to liver infection and scarring of the liver, which can, in turn, require the patient to undergo a liver transplant.

Hepatitis C is an RNA virus taken up specifically by hepatic cells. Once inside the cells, the RNA is translated into a polyprotein of about 3,000 amino acids. The protein is then processed into three structural and several non-structural proteins necessary for viral replication. Accordingly, HCV may be treated by reducing the rate any of the steps required for its replication or

inhibiting any molecule involved in replication, including but not limited to, entry into a target cell, viral genome replication, translation of viral RNA, protolytic processing, and assembly and release from the target cell (e.g., using the agents described herein).

Compounds

Certain compounds that may be employed in the methods, compositions, and kits of the present invention are discussed in greater detail below. It will be understood that analogs of any compound of Table 1, Table 2, or Table 3 can be used instead of the compound of Table 1, Table 2, or Table 3 in the methods, compositions, and kits of the present invention.

HMG-CoA reductase inhibitors

In certain embodiments, an HMG-CoA reductase inhibitor can be used in the compositions, methods, and kits of the invention. By an "HMG-CoA reductase inhibitor" is a compound that inhibits the enzymatic activity of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase by at least about 10%. HMG-CoA reductase inhibitors include but are not limited to simvastatin, lovastatin, mevastatin, pravastatin, monacolin M, monacolin X, fluvastatin, atorvastatin, cerivastatin, rosuvastatin, fluindostatin, velostatin, compactin, dihydrocompactin, rivastatin, dalvastatin, pitavastatin, BAY102987, BAY X 2678, BB476, bervastatin, BMY21950, BMY22089, colestolone, CP83101, crilvastatin, DMP565, glenvastatin, L659699, L669262, P882222, P882284, PD134965, PD135022, RP61969, S2468, SC37111, SC45355, SQ33600, SR12813, SR45023A, U20685, and U88156, as well as pharmaceutically acceptable salts thereof (e.g., simvastatin sodium, lovastatin sodium, fluvastatin sodium, etc.). Additional HMG-CoA reductase inhibitors

and analogs thereof useful in the methods and compositions of the present invention are described in U.S. Pat. Nos. 3,983,140; 4,231,938; 4,282,155; 4,293,496; 4,294,926; 4,319,039; 4,343,814; 4,346,227; 4,351,844; 4,361,515; 4,376,863; 4,444,784; 4,448,784; 4,448,979; 4,450,171; 4,503,072; 4,517,373; 4,661,483; 4,668,699; 4,681,893; 4,719,229; 4,738,982; 4,739,073; 4,766,145; 4,782,084; 4,804,770; 4,841,074; 4,847,306; 4,857,546; 4,857,547; 4,940,727; 4,946,864; 5,001,148; 5,006,530; 5,075,311; 5,112,857; 5,116,870; 5,120,848; 5,166,364; 5,173,487; 5,177,080; 5,273,995; 5,276,021; 5,369,123; 5,385,932; 5,502,199; 5,763,414; 5,877,208; and 6,541,511; and U.S. Pat. Application Publication Nos. 2002/0013334 A1; 2002/0028826 A1; 2002/0061901 A1; and 2002/0094977 A1.

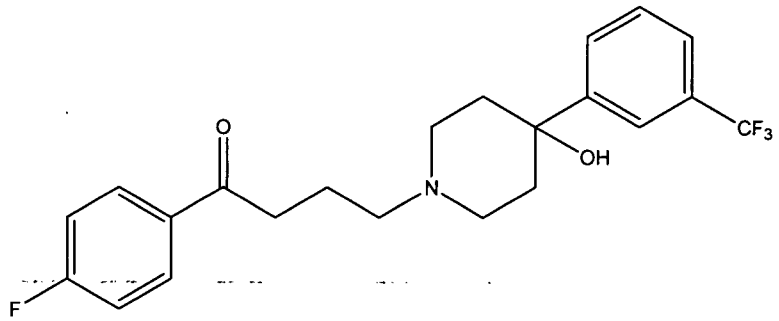
Clozapine

In certain embodiments, clozapine or a clozapine analog can be used in the compositions, methods, and kits of the invention. Suitable clozapine analogs include acetophenazine maleate, alentemol hydrobromide, alpertine, azaperone, batelapine maleate, benperidol, benzindopyrine hydrochloride, brofoxine, bromperidol, bromperidol decanoate, butaclamol hydrochloride, butaperazine, butaperazine maleate, carphenazine maleate, carvotroline hydrochloride, chlorpromazine, chlorpromazine hydrochloride, chlorprothixene, cinperene: cintriamide, clomacran phosphate, clopenthixol, clopimozide, clopipazan mesylate, cloroperone hydrochloride, clothiapine, clothixamide maleate, cyclophenazine hydrochloride, droperidol, etazolate hydrochloride, fenimide, flucindole, flumezapine, fluphenazine decanoate, fluphenazine enanthate, fluphenazine hydrochloride, fluspiperone, fluspirilene, flutroline, gevotroline hydrochloride, halopemide, haloperidol, haloperidol decanoate, iloperidone, imidoline hydrochloride, lenperone, mazapertine succinate, mesoridazine, mesoridazine besylate, metiapine, milenperone, milipertine,

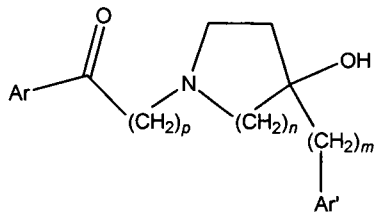
molindone hydrochloride, naranol hydrochloride, neflumozide hydrochloride, ocaperidone, olanzapine, oxiperomide, penfluridol, pentiapine maleate, perphenazine, pimozide, pinoxepin hydrochloride, pipamperone, piperacetazine, pipotiazine palmitate, piquindone hydrochloride, prochlorperazine edisylate, prochlorperazine maleate, promazine hydrochloride, remoxipride, remoxipride hydrochloride, rimcazole hydrochloride, seperidol hydrochloride, sertindole, setoperone, spiperone, thioridazine, thioridazine hydrochloride, thiothixene, thiothixene hydrochloride, tioperidone hydrochloride, tiospirone hydrochloride, trifluoperazine hydrochloride, trifluperidol, triflupromazine, triflupromazine hydrochloride, and ziprasidone hydrochloride. Additional clozapine analogs are described in U.S. Pat. Nos. 2,519,886; 2,921,069, 3,084,161, 3,155,669, 3,155,670, 3,438,991, 3,161,644, 4,045,445, 4,308,207, 4,459,232, 4,460,508, 4,460,587, 4,507,311, 4,595,535, 4,192,803, 5,955,459, and 6,197,764.

Trifluperidol

In certain embodiments, trifluperidol or an analog thereof can be used in the compositions, methods, and kits of the invention. The structure of trifluperidol is:



Analogs of trifluperidol are described for example in U.S. Pat. No. 3,438,991 and have the general structure:



where Ar and Ar' are monocyclic aryl rings, *p* is 2 to 4, *n* is 1 or 2, *m* is 0, 1, or 2, and X is a hydrogen or a methyl group. Ar and Ar' can represent halophenyls such as fluorophenyl, chlorophenyl, bromophenyl, and iodophenyl; alkoxyphenyls such as methoxyphenyl, ethoxyphenyl, dimethoxyphenyl, and trimethoxyphenyl; monocyclic aromatic hydrocarbon radicals such as phenyl, tolyl, xylyl, isopropylphenyl, and tertiary butyl phenyl; and a trifiuoromethylphenyl radical. $(CH_2)_p$ can represent a lower alkylene group, e.g., 2 to 4 carbon atoms such as ethylene, trimethylene, propylene, butylene, methylpropylene, and tetramethylene.

Paclitaxel

In certain embodiments, paclitaxel or a paclitaxel analog can be used in the compositions, methods, and kits of the invention. Paclitaxel is described in U.S. Pat. No. 4,814,470. Paclitaxel analogs include isoserine, taxol, taxotere, cephalomannine, 10-deacetylbaccatine III and those compounds described in U.S. Pat. Nos. 4,814,470, 4,857,653, 4,876,399, 4,924,011, 4,924,012, 4,942,184, 4,960,790, 5,015,744, 5,059,699, 5,136,060, 5,157,049, 5,192,796, 5,227,400, 5,243,045, 5,248,796, 5,250,683, 5,254,580, 5,271,268, 5,272,171, 5,283,253, 5,284,864, 5,290,957, 5,292,921, 5,294,637, 5,319,112, 5,336,684, 5,338,872, 5,350,866, 5,380,751, 5,380,916, 5,399,726, 5,430,160, 5,438,072, 5,470,866, 5,489,601, 5,508,447, 5,539,103, 5,547,981, 5,556,878, 5,574,156, 5,580,899, 5,580,998, 5,587,489, 5,587,493, 5,606,083, 5,622,986, 5,635,531, 5,646,176, 5,654,447, 5,677,470, 5,688,977, 5,693,666, 5,703,117, 5,710,287, 5,714,512, 5,714,513, 5,717,115, 5,721,268, 5,728,725, 5,728,850, 5,739,362,

5,750,562, 5,760,219, 5,773,464, 5,807,888, 5,821,363, 5,840,748, 5,840,929, 5,840,930, 5,854,278, 5,912,264, 5,919,815, 5,902,822, 5,965,739, 5,977,386, 5,990,325, 5,994,576, 5,998,656, 6,011,056, 6,017,935, 6,018,073, 6,028,205, 6,051,724, 6,066,747, 6,080,877, 6,107,332, 6,118,011, 6,124,481, 6,136,961, 6,147,234, 6,177,456, 6,307,064, 6,310,201, 6,350,886, 6,362,217, 6,455,575, 6,462,208, 6,482,963, 6,495,704, 6,515,151, 6,545,168, 6,710,191, 6,762,309, 6,794,523, 6,797,833, 6,878,834, 6,911,549, and 7,019,150.

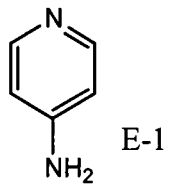
Estrogenic compounds

In certain embodiments, an estrogenic compound can be used in the compositions, methods, and kits of the invention. Estrogenic compounds include estradiol (e.g., estradiol valerate, estradiol cypionate), colpormon, 2-methyoxyestradiol, conjugated estrogenic hormones, equilenin, equilin, dienestrol, ethinyl estradiol, estriol, mestranol, moxestrol, quinestradiol, quinestrol, estrone, estrone sulfate, equilin, diethylstilbestrol, broparoestrol, chlorotrianisine, fosfestrol, hexestrol, methestrol, and genistein. Estrogenic compounds are also described in U.S. Pat. Nos. 2,096,744, 2,465,505, 2,464,203, 3,159,543.

Aminopyridines

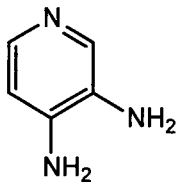
In certain embodiments, an aminopyridine can be used in the composition, methods, and kits of the invention. By "aminopyridine" is meant any pyridine ring-containing compound in which the pyridine has one, two, or three amino group substituents. Other substituents may optionally be present. Exemplary aminopyridines include phenazopyridine, 4-aminopyridine, 3,4-diaminopyridine, 2,5-diamino-4-methylpyridine, 2,3,6-triaminopyridine, 2,4,6-triaminopyridine, and 2,6-diaminopyridine, the structures of which are depicted below. Phenazopyridine and derivatives thereof have been disclosed in U.S.

Pat. Nos. 1,680,108 through 1,680,111. Modifications of di-amino(phenylazo)pyridines have been performed to improve solubility in water by reacting these compounds with alkylating agents (e.g., alkyl halides and alkyl sulphates) to produce quaternary pyridinium bases (see, e.g., U.S. Pat. No. 2,135,293). Heterocyclic azo derivatives and N-substituted diaminopyridines have also been described (U.S. Pat. Nos. 2,145,579 and 3,647,808).



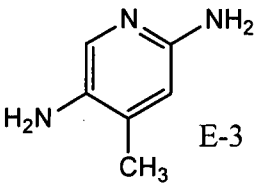
E-1

4-aminopyridine



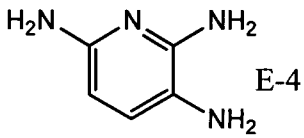
E-2

3,4-diaminopyridine



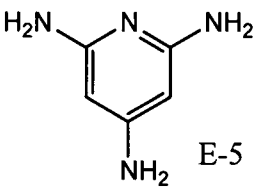
E-3

2,5-diamino-4-methylpyridine



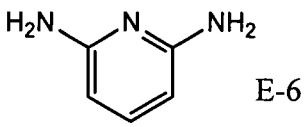
E-4

2,3,6-triaminopyridine



E-5

2,4,6-triaminopyridine



E-6

2,6-diaminopyridine

Antiestrogens

In certain embodiments, an antiestrogen can be used in the methods, compositions, and kits of the invention. Antiestrogens include tamoxifen, 4-hydroxy tamoxifen, clomifene, raloxifene, faslodex, nafoxidine, fulvestrant, CI-680, CI-628, CN-55,956-27, MER-25, U-11,555A, U-11,100A, ICI-46,669, ICI-46,474, diphenolhydrochrysene, erythro-MEA, Parke Davis CN-35,945,

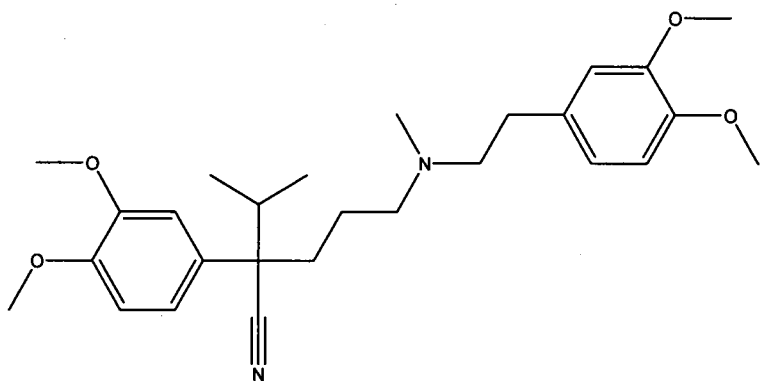
allenolic acid, cyclofenil, ethamoxytriphetol, and triparanol and those compounds described in U.S. Pat. Nos. 5,384,332, 4,894,373, 4,536,516, 4,418,068, and 2,914,563.

Calcium channel inhibitors

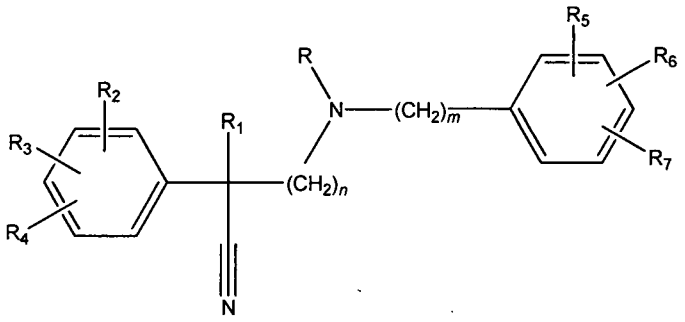
In certain embodiments, a calcium channel inhibitor can be used in the compositions, methods, and kits of the invention. Calcium channel inhibitors include thapsigargin, verapamil, anipamil, bepridil, gallopamil, devapamil, falipamil, tiapamil, nifedipine, amlodipine, dazodipine, felodipine, isradipine, lanicardipine, nicardipine, nimodipine, nisoldipine, nitrendipine, ryosidie, diltiazem, cinnarizine, flunarizine, BAY-m 4786, and diperdipine.

Verapamil

In certain embodiments, verapamil or an analog thereof can be used in the compositions, methods, and kits of the invention. The structure of verapamil is:



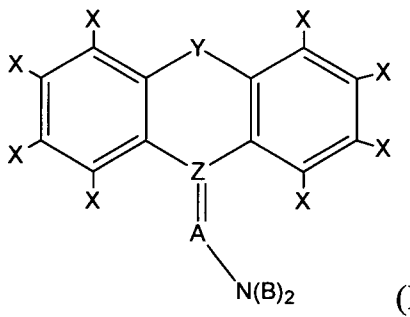
Verapamil analogs are described, for example, in U.S. Pat. No. 3,261,859 and have the general formula:



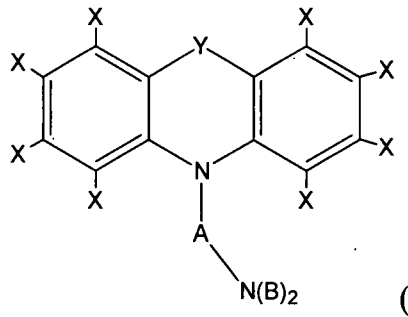
where R is a lower aliphatic hydrocarbon radical; R_1 is hydrogen, a lower alkyl radical, a saturated or unsaturated cyclic or bicyclic hydrocarbon radical, the benzyl radical, or the phenyl radical; R_2, R_3, R_4, R_5, R_6, and R_7 are hydrogen, halogen, lower alkyl radicals, lower alkoxy groups, or two of said substituents together forming the methylene dioxy group; *n* is an integer between 2 and 4; and *m* is an integer between 1 and 3.

Tricyclic compounds

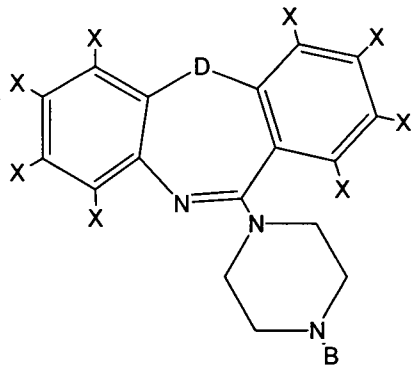
In certain embodiments, a tricyclic compound can be used in the compositions, methods, and kits of the invention. By "tricyclic compound" is meant a compound having one the formulas (I), (II), (III), or (IV):



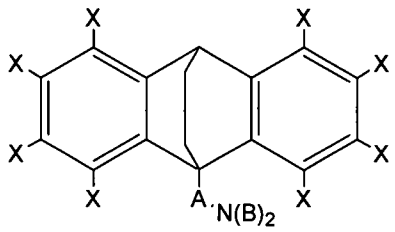
(I)



(II)



(III)



(IV)

wherein each X is, independently, H, Cl, F, Br, I, CH_3, CF_3, OH, OCH_3, CH_2CH_3, or OCH_2CH_3; Y is CH_2, O, NH, $S(O)_{0-2}$, $(CH_2)_3$, $(CH)_2$, CH_2O, CH_2NH, CHN, or CH_2S; Z is C or S; A is a branched or unbranched, saturated or monounsaturated hydrocarbon chain having between 3 and 6 carbons, inclusive; each B is, independently, H, Cl, F, Br, I, CX_3, CH_2CH_3, OCX_3, or OCX_2CX_3; and D is CH_2, O, NH, or $S(O)_{0-2}$. In preferred embodiments, each X is, independently, H, Cl, or F; Y is $(CH_2)_2$, Z is C; A is $(CH_2)_3$; and each B is, independently, H, Cl, or F. Other tricyclic compounds are described below.

Tricyclic compounds include tricyclic antidepressants such as amoxapine, 8-hydroxyamoxapine, 7-hydroxyamoxapine, loxapine (e.g., loxapine succinate, loxapine hydrochloride), 8-hydroxyloxapine, amitriptyline, clomipramine, doxepin, imipramine, trimipramine, desipramine, nortriptyline, and protriptyline, although compounds need not have antidepressant activities to be considered tricyclic compounds of the invention.

Tricyclic compounds that can be used in connection with the invention include amitriptyline, amoxapine, clomipramine, desipramine, dothiepin, doxepin, imipramine, lofepramine, maprotiline, mianserin, mirtazapine, nortriptyline, octriptyline, oxaprotiline, protriptyline, trimipramine, 10-(4-methylpiperazin-1-yl)pyrido(4,3-b)(1,4)benzothiazepine; 11-(4-methyl-1-piperazinyl)-5H-dibenzo(b,e)(1,4)diazepine; 5,10-dihydro-7-chloro-10-(2-(morpholino)ethyl)- 11H-dibenzo(b,e)(1,4)diazepin-11-one; 2-(2-(7-hydroxy-4-dibenzo(b,f)(1,4)thiazepine-11-yl-1-piperazinyl)ethoxy)ethanol; 2-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo(b,e)(1,4)diazepine; 4-(11H-dibenz(b,e)azepin-6-yl)piperazine; 8-chloro-11-(4-methyl-1-piperazinyl)- 5H-dibenzo(b,e)(1,4)diazepin-2-ol; 8-chloro-11-(4-methyl-1-piperazinyl)- 5H-dibenzo(b,e)(1,4)diazepine monohydrochloride; (Z)-2-butenedioate 5H-dibenzo(b,e)(1,4)diazepine; adinazolam; amineptine; amitriptylinoxide; butriptyline; clothiapine; clozapine; demexiptiline; 11-(4-methyl-1-piperazinyl)-dibenz(b,f)(1,4)oxazepine; 11-(4-methyl-1-piperazinyl)-2-nitro-dibenz(b,f)(1,4)oxazepine; 2-chloro-11-(4-methyl-1-piperazinyl)-dibenz(b,f)(1,4)oxazepine monohydrochloride; dibenzepin; 11-(4-methyl-1-piperazinyl)-dibenzo(b,f)(1,4)thiazepine; dimetacrine; fluacizine; fluperlapine; imipramine N-oxide; iprindole; lofepramine; melitracen; metapramine; metiapine; metralindole; mianserin; mirtazapine; 8-chloro-6-(4-methyl-1-piperazinyl)-morphanthridine; N-acetylamoxapine; nomifensine;

norclomipramine; norclozapine; noxiptilin; opipramol; oxaprotiline; perlapine; pizotyline; propizepine; quetiapine; quinupramine; tianeptine; tomoxetine; flupenthixol; clopenthixol; piflutixol; chlorprothixene; and thiothixene. Other tricyclic compounds are described in U.S. Pat. Nos. 2,554,736, 3,046,283, 3,058,979, 3,310,553, 3,177,209, 3,194,733, 3,205,264, 3,244,748, 3,271,451, 3,272,826, 3,282,930, 3,282,942, 3,299,139, 3,312,689, 3,389,139, 3,399,201, 3,409,640, 3,419,547, 3,438,981, 3,454,554, 3,467,650, 3,505,321, 3,527,766, 3,534,041, 3,539,573, 3,574,852, 3,622,565, 3,637,660, 3,663,696, 3,758,528, 3,922,305, 3,963,778, 3,978,121, 3,981,917, 4,017,542, 4,017,621, 4,020,096, 4,045,560, 4,045,580, 4,048,223, 4,062,848, 4,088,647, 4,128,641, 4,148,919, 4,153,629, 4,224,321, 4,224,344, 4,250,094, 4,284,559, 4,333,935, 4,358,620, 4,548,933, 4,691,040, 4,879,288, 5,238,959, 5,266,570, 5,399,568, 5,464,840, 5,455,246, 5,512,575, 5,550,136, 5,574,173, 5,681,840, 5,688,805, 5,916,889, 6,545,057, and 6,600,065, and phenothiazine compounds that fit Formula (I) of U.S. Pat. Application Nos. 10/617,424 (published as U.S. 2004/0116407) or 60/504,310.

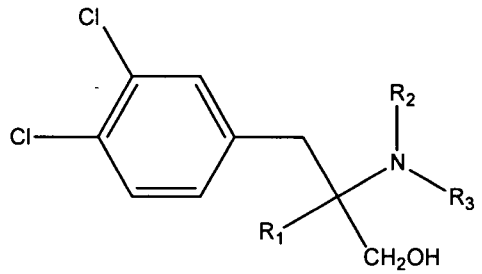
Selective serotonin reuptake inhibitors

In certain embodiments, a selective serotonin reuptake inhibitor can be used in the compositions, methods, and kits of the invention. By "selective serotonin reuptake inhibitor" or "SSRI" is meant any member of the class of compounds that (i) inhibit the uptake of serotonin by neurons of the central nervous system, (ii) have an inhibition constant (Ki) of 10 nM or less, and (iii) a selectivity for serotonin over norepinephrine (i.e., the ratio of K_i(norepinephrine) over K_i(serotonin)) of greater than 100.

SSRIs may be used in connection with the invention include cericlamine (e.g., cericlamine hydrochloride); citalopram (e.g., citalopram hydrobromide);

clovoxamine; cyanodothiepin; dapoxetine; escitalopram (escitalopram oxalate); femoxetine (e.g., femoxetine hydrochloride); fluoxetine (e.g., fluoxetine hydrochloride); fluvoxamine (e.g., fluvoxamine maleate); ifoxetine; indalpine (e.g., indalpine hydrochloride); indeloxazine (e.g., indeloxazine hydrochloride); litoxetine; milnacipran (e.g., minlacipran hydrochloride); 6-nitroquipazine; paroxetine (e.g., paroxetine hydrochloride hemihydrate; paroxetine maleate; paroxetine mesylate); sertraline (e.g., sertraline hydrochloride); tametraline hydrochloride; viqualine; and zimeldine (e.g., zimeldine hydrochloride).

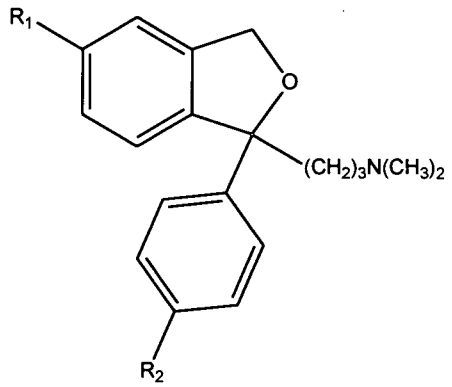
Structural analogs of cericlamine are those having the formula:



as well as pharmaceutically acceptable salts thereof, wherein R_1 is a C_1-C_4 alkyl and R_2 is H or C_{1-4} alkyl, R_3 is H, C_{1-4} alkyl, C_{2-4} alkenyl, phenylalkyl or cycloalkylalkyl with 3 to 6 cyclic carbon atoms, alkanoyl, phenylalkanoyl or cycloalkylcarbonyl having 3 to 6 cyclic carbon atoms, or R_2 and R_3 form, together with the nitrogen atom to which they are linked, a heterocycle saturated with 5 to 7 chain links which can have, as the second heteroatom not directly connected to the nitrogen atom, an oxygen, a sulphur or a nitrogen, the latter nitrogen heteroatom possibly carrying a C_{2-4} alkyl.

Exemplary cericlamine structural analogs are 2-methyl-2-amino-3-(3,4-dichlorophenyl)-propanol, 2-pentyl-2-amino-3-(3,4-dichlorophenyl)-propanol, 2-methyl-2-methylamino-3-(3,4-dichlorophenyl)-propanol, 2-methyl-2-dimethylamino-3-(3,4-dichlorophenyl)-propanol, and pharmaceutically acceptable salts of any thereof.

Structural analogs of citalopram are those having the formula:

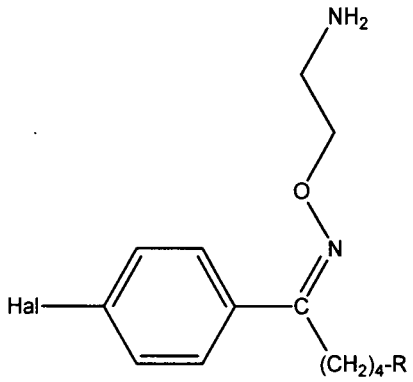


as well as pharmaceutically acceptable salts thereof, wherein each of R_1 and R_2 is independently selected from the group consisting of bromo, chloro, fluoro, trifluoromethyl, cyano and R-CO-, wherein R is C_{1-4} alkyl.

Exemplary citalopram structural analogs (which are thus SSRI structural analogs according to the invention) are 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-bromophthalane; 1-(4'-chlorophenyl)-1-(3-dimethylaminopropyl)-5-chlorophthalane; 1-(4'-bromophenyl)-1-(3-dimethylaminopropyl)-5-chlorophthalane; 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-chlorophthalane; 1-(4'-chlorophenyl)-1-(3-dimethylaminopropyl)-5-trifluoromethyl-phthalane; 1-(4'-bromophenyl)-1-(3-dimethylaminopropyl)-5-trifluoromethyl-phthalane; 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-trifluoromethyl-phthalane; 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-fluorophthalane; 1-(4'-chlorophenyl)-1-(3-dimethylaminopropyl)-5-fluorophthalane; 1-(4'-chlorophenyl)-1-(3-dimethylaminopropyl)-5-phthalancarbonitrile; 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-phthalancarbonitrile; 1-(4'-cyanophenyl)-1-(3-dimethylaminopropyl)-5-phthalancarbonitrile; 1-(4'-cyanophenyl)-1-(3-dimethylaminopropyl)-5-chlorophthalane; 1-(4'-cyanophenyl)-1-(3-dimethylaminopropyl)-5-trifluoromethylphthalane; 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-phthalancarbonitrile; 1-(4'-chlorophenyl)-1-(3-dimethylaminopropyl)-5-ionylphthalane; 1-(4-(chlorophenyl)-1-(3-

dimethylaminopropyl)-5-propionylphthalane; and pharmaceutically acceptable salts of any thereof. Citalopram analogs are also described in U.S. Pat. No. 4,136,193.

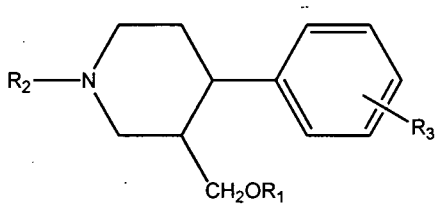
Structural analogs of clovoxamine are those having the formula:



as well as pharmaceutically acceptable salts thereof, wherein Hal is a chloro, bromo, or fluoro group and R is a cyano, methoxy, ethoxy, methoxymethyl, ethoxymethyl, methoxyethoxy, or cyanomethyl group.

Exemplary clovoxamine structural analogs are 4'-chloro-5-ethoxyvalerophenone O-(2-aminoethyl)oxime; 4'-chloro-5-(2-methoxyethoxy)valerophenone O-(2-aminoethyl)oxime; 4'-chloro-6-methoxycaprophenone O-(2-aminoethyl)oxime; 4'-chloro-6-ethoxycaprophenone O-(2-aminoethyl)oxime; 4'-bromo-5-(2-methoxyethoxy)valerophenone O-(2-aminoethyl)oxime; 4'-bromo-5-methoxyvalerophenone O-(2-aminoethyl)oxime; 4'-chloro-6-cyanocaprophenone O-(2-aminoethyl)oxime; 4'-chloro-5-cyanovalerophenone O-(2-aminoethyl)oxime; 4'-bromo-5-cyanovalerophenone O-(2-aminoethyl)oxime; and pharmaceutically acceptable salts of any thereof.

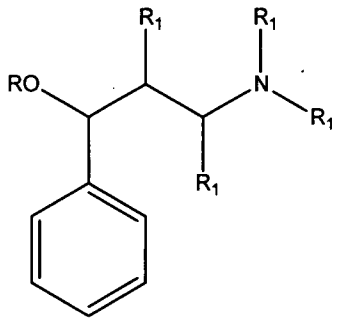
Structural analogs of femoxetine are those having the formula:



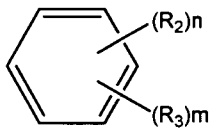
wherein R_1 represents a C_{1-4} alkyl or C_{2-4} alkynyl group, or a phenyl group optionally substituted by C_{1-4} alkyl, C_{1-4} alkylthio, C_{1-4} alkoxy, bromo, chloro, fluoro, nitro, acylamino, methylsulfonyl, methylenedioxy, or tetrahydronaphthyl, R_2 represents a C_{1-4} alkyl or C_{2-4} alkynyl group, and R_3 represents hydrogen, C_{1-4} alkyl, C_{1-4}alkoxy, trifluoroalkyl, hydroxy, bromo, chloro, fluoro, methylthio, or aralkyloxy.

Exemplary femoxetine structural analogs are disclosed in Examples 7-67 of U.S. Pat. No. 3,912,743, hereby incorporated by reference.

Structural analogs of fluoxetine are those compounds having the formula:



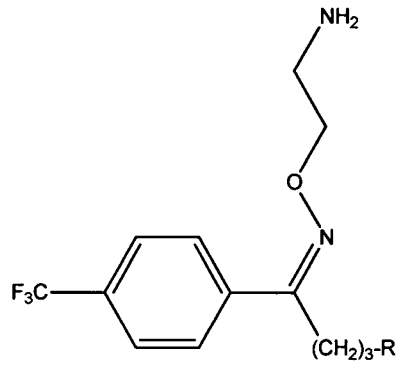
as well as pharmaceutically acceptable salts thereof, wherein each R_1 is independently hydrogen or methyl; R is naphthyl or



wherein each of R_2 and R_3 is, independently, bromo, chloro, fluoro, trifluoromethyl, C_{1-4} alkyl, C_{1-3} alkoxy or C_{3-4} alkenyl; and each of n and m is, independently, 0, 1 or 2. When R is naphthyl, it can be either α-naphthyl or β-naphthyl.

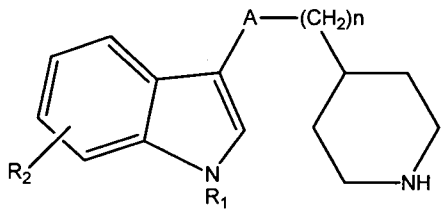
Exemplary fluoxetine structural analogs are 3-(p-isopropoxyphenoxy)-3-phenylpropylamine methanesulfonate, N,N-dimethyl 3-(3',4'-dimethoxyphenoxy)-3-phenylpropylamine p-hydroxybenzoate, N,N-dimethyl 3-(α-naphthoxy)-3-phenylpropylamine bromide, N,N-dimethyl 3-(β-naphthoxy)-3-phenyl-1-methylpropylamine iodide, 3-(2'-methyl-4',5'-dichlorophenoxy)-3-phenylpropylamine nitrate, 3-(p-t-butylphenoxy)-3-phenylpropylamine glutarate, N-methyl 3-(2'-chloro-p-tolyloxy)-3-phenyl-1-methylpropylamine lactate, 3-(2',4'-dichlorophenoxy)-3-phenyl-2-methylpropylamine citrate, N,N-dimethyl 3-(m-anisyloxy)-3-phenyl-1-methylpropylamine maleate, N-methyl 3-(p-tolyloxy)-3-phenylpropylamine sulfate, N,N-dimethyl 3-(2',4'-difluorophenoxy)-3-phenylpropylamine 2,4-dinitrobenzoate, 3-(o-ethylphenoxy)-3-phenylpropylamine dihydrogen phosphate, N-methyl 3-(2'-chloro-4'-isopropylphenoxy)-3-phenyl-2-methylpropylamine maleate, N,N-dimethyl 3-(2'-alkyl-4'-fluorophenoxy)-3-phenyl-propylamine succinate, N,N-dimethyl 3-(o-isopropoxyphenoxy)-3-phenyl-propylamine phenylacetate, N,N-dimethyl 3-(o-bromophenoxy)-3-phenyl-propylamine β-phenylpropionate, N-methyl 3-(p-iodophenoxy)-3-phenyl-propylamine propiolate, and N-methyl 3-(3-n-propylphenoxy)-3-phenyl-propylamine decanoate.

Structural analogs of fluvoxamine are those having the formula:



as well as pharmaceutically acceptable salts thereof, wherein R is cyano, cyanomethyl, methoxymethyl, or ethoxymethyl. Analogs of fluvoxamine are also described in U.S. Pat. No. 4,085,225.

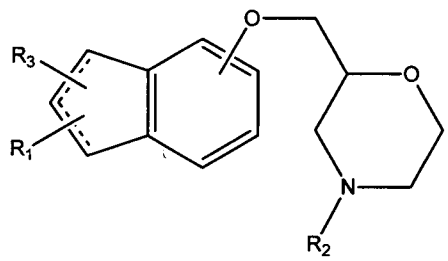
Structural analogs of indalpine are those having the formula:



or pharmaceutically acceptable salts thereof, wherein R_1 is a hydrogen atom, a C_1-C_4 alkyl group, or an aralkyl group of which the alkyl has 1 or 2 carbon atoms, R_2 is hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy or C_{1-4} alkylthio, chloro, bromo, fluoro, trifluoromethyl, nitro, hydroxy, or amino, the latter optionally substituted by one or two C_{1-4} alkyl groups, an acyl group or a C_{1-4}alkylsulfonyl group; A represents –CO or –CH_2- group; and n is 0, 1 or 2.

Exemplary indalpine structural analogs are indolyl-3 (piperidyl-4 methyl) ketone; (methoxy-5-indolyl-3) (piperidyl-4 methyl) ketone; (chloro-5-indolyl-3) (piperidyl-4 methyl) ketone; (indolyl-3)-1(piperidyl-4)-3 propanone, indolyl-3 piperidyl-4 ketone; (methyl-1 indolyl-3) (piperidyl-4 methyl) ketone, (benzyl-1 indolyl-3) (piperidyl-4 methyl) ketone; [(methoxy-5 indolyl-3)-2 ethyl]-piperidine, [(methyl-1 indolyl-3)-2 ethyl]-4-piperidine; [(indolyl-3)-2 ethyl]-4 piperidine; (indolyl-3 methyl)-4 piperidine, [(chloro-5 indolyl-3)-2 ethyl]-4 piperidine; [(indolyl-b 3)-3 propyl]-4 piperidine; [(benzyl-1 indolyl-3)-2 ethyl]-4 piperidine; and pharmaceutically acceptable salts of any thereof.

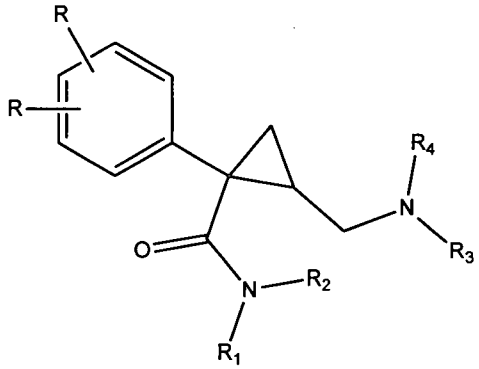
Structural analogs of indeloxazine are those having the formula:



and pharmaceutically acceptable salts thereof, wherein R_1 and R_3 each represents hydrogen, C_{1-4} alkyl, or phenyl; R_2 represents hydrogen, C_{1-4} alkyl, C_{4-7} cycloalkyl, phenyl, or benzyl; one of the dotted lines means a single bond and the other means a double bond, or the tautomeric mixtures thereof.

Exemplary indeloxazine structural analogs are 2-(7-indenyloxymethyl)-4-isopropylmorpholine; 4-butyl-2-(7-indenyloxymethyl)morpholine; 2-(7-indenyloxymethyl)-4-methylmorpholine; 4-ethyl-2-(7-indenyloxymethyl)morpholine, 2-(7-indenyloxymethyl)-morpholine; 2-(7-indenyloxymethyl)-4-propylmorpholine; 4-cyclohexyl-2-(7-indenyloxymethyl)morpholine; 4-benzyl-2-(7-indenyloxymethyl)-morpholine; 2-(7-indenyloxymethyl)-4-phenylmorpholine; 2-(4-indenyloxymethyl)morpholine; 2-(3-methyl-7-indenyloxymethyl)-morpholine; 4-isopropyl-2-(3-methyl-7-indenyloxymethyl)morpholine; 4-isopropyl-2-(3-methyl-4-indenyloxymethyl)morpholine; 4-isopropyl-2-(3-methyl-5-indenyloxymethyl)morpholine; 4-isopropyl-2-(1-methyl-3-phenyl-6-indenyloxymethyl)morpholine; 2-(5-indenyloxymethyl)-4-isopropyl-morpholine, 2-(6-indenyloxymethyl)-4-isopropylmorpholine; and 4-isopropyl-2-(3-phenyl-6-indenyloxymethyl)morpholine; as well as pharmaceutically acceptable salts of any thereof.

Structural analogs of milnacipram are those having the formula:

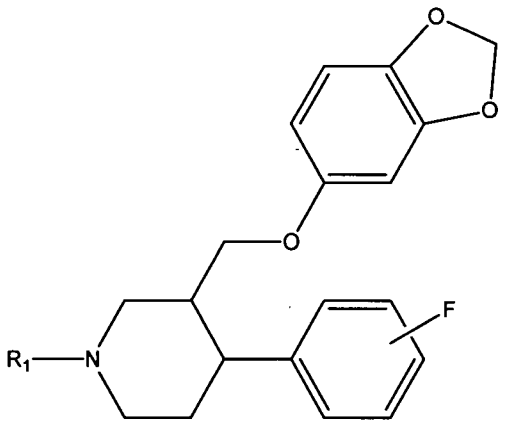


as well as pharmaceutically acceptable salts thereof, wherein each R, independently, represents hydrogen, bromo, chloro, fluoro, C_{1-4} alkyl, C_{1-4} alkoxy, hydroxy, nitro or amino; each of R_1 and R_2, independently, represents hydrogen, C_{1-4} alkyl, C_{6-12} aryl or C_{7-14} alkylaryl, optionally substituted, preferably in para position, by bromo, chloro, or fluoro, or R_1 and R_2 together form a heterocycle having 5 or 6 members with the adjacent nitrogen atoms; R_3 and R_4 represent hydrogen or a C_{1-4} alkyl group or R_3 and R_4 form with the adjacent nitrogen atom a heterocycle having 5 or 6 members, optionally containing an additional heteroatom selected from nitrogen, sulphur, and oxygen.

Exemplary milnacipram structural analogs are 1-phenyl 1-aminocarbonyl 2-dimethylaminomethyl cyclopropane; 1-phenyl 1-dimethylaminocarbonyl 2-dimethylaminomethyl cyclopropane; 1-phenyl 1-ethylaminocarbonyl 2-dimethylaminomethyl cyclopropane; 1-phenyl 1-diethylaminocarbonyl 2-aminomethyl cyclopropane; 1-phenyl 2-dimethylaminomethyl N-(4'-chlorophenyl)cyclopropane carboxamide; 1-phenyl 2-dimethylaminomethyl N-(4'-chlorobenzyl)cyclopropane carboxamide; 1-phenyl 2-dimethylaminomethyl N-(2-phenylethyl)cyclopropane carboxamide; (3,4-dichloro-1-phenyl) 2-dimethylaminomethyl N,N-dimethylcyclopropane carboxamide; 1-phenyl 1-pyrrolidinocarbonyl 2-morpholinomethyl cyclopropane; 1-p-chlorophenyl 1-aminocarbonyl 2-aminomethyl cyclopropane; 1-orthochlorophenyl 1-

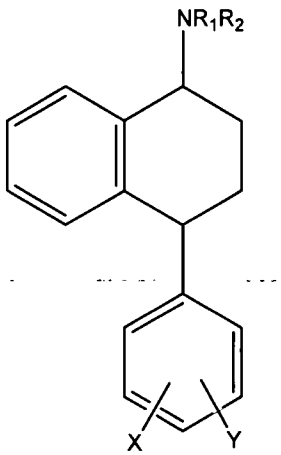
aminocarbonyl 2-dimethylaminomethyl cyclopropane; 1-p-hydroxyphenyl 1-aminocarbonyl 2-dimethylaminomethyl cyclopropane; 1-p-nitrophenyl 1-dimethylaminocarbonyl 2-dimethylaminomethyl cyclopropane; 1-p-aminophenyl 1-dimethylaminocarbonyl 2-dimethylaminomethyl cyclopropane; 1-p-tolyl 1-methylaminocarbonyl 2-dimethylaminomethyl cyclopropane; 1-p-methoxyphenyl 1-aminomethylcarbonyl 2-aminomethyl cyclopropane; and pharmaceutically acceptable salts of any thereof.

Structural analogs of paroxetine are those having the formula:



and pharmaceutically acceptable salts thereof, wherein R_1 represents hydrogen or a C_{1-4} alkyl group, and the fluorine atom may be in any of the available positions.

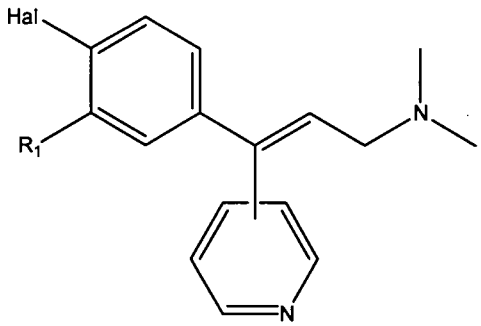
Structural analogs of sertraline are those having the formula:



wherein R_1 is selected from the group consisting of hydrogen and C_{1-4} alkyl; R_2 is hydrogen, or C_{1-4} alkyl; X and Y are each selected from the group consisting of hydrogen, fluoro, chloro, bromo, trifluoromethyl, C_{1-3} alkoxy, and cyano; and W is selected from the group consisting of hydrogen, fluoro, chloro, bromo, trifluoromethyl and C_{1-3} alkoxy. Preferred sertraline analogs are in the cis-isomeric configuration. The term "cis-isomeric" refers to the relative orientation of the NR_1R_2 and phenyl moieties on the cyclohexene ring (i.e. they are both oriented on the same side of the ring). Because both the 1- and 4-carbons are asymmetrically substituted, each cis- compound has two optically active enantiomeric forms denoted (with reference to the 1-carbon) as the cis-(1R) and cis-(1S) enantiomers. Sertraline analogs are also described in U.S. Pat. No. 4,536,518. Other related compounds include (S,S)-N-desmethylsetraline and rac-cis-N-desmethylsertraline.

Particularly useful are the following compounds, in either the (1S)-enantiomeric or (1S)(1R) racemic forms, and their pharmaceutically acceptable salts: cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine; cis-N-methyl-4-(4-bromophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine; cis-N-methyl-4-(4-chlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine; cis-N-methyl-4-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-1-naphthalenamine; cis-N-methyl-4-(3-trifluoromethyl-4-chlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine; cis-N,N-dimethyl-4-(4-chlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine; cis-N,N-dimethyl-4-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-1-naphthalenamine; and cis-N-methyl-4-(4-chlorophenyl)-7-chloro-1,2,3,4-tetrahydro-1-naphthalenamine. Of interest also is the (1R)-enantiomer of cis-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine.

Structural analogs of zimeldine are those compounds having the formula:



and pharmaceutically acceptable salts thereof, wherein the pyridine nucleus is bound in ortho-, meta- or para-position to the adjacent carbon atom and where R_1 is selected from the group consisting of H, chloro, fluoro, and bromo.

Exemplary zimeldine analogs are (e)- and (z)- 3-(4'-bromophenyl-3-(2"-pyridyl)-dimethylallylamine; 3-(4'-bromophenyl)-3-(3"-pyridyl)-dimethylallylamine; 3-(4'-bromophenyl)-3-(4"-pyridyl)-dimethylallylamine; and pharmaceutically acceptable salts of any thereof. Zimelidine analogs are also described in U.S. Pat. No. 3,928,369.

Structural analogs of any of the above SSRIs are considered herein to be SSRI analogs and thus may be employed in any of the methods, compositions, and kits of the invention.

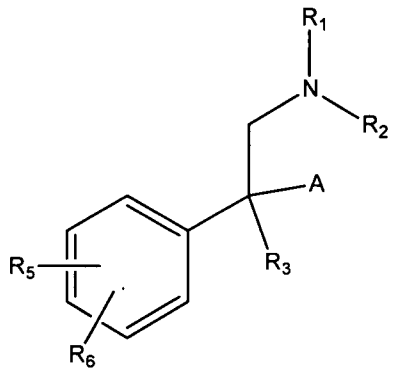
Metabolites

Pharmacologically active metabolites of any of the foregoing SSRIs can also be used in the methods, compositions, and kits of the invention. Exemplary metabolites are didesmethylcitalopram, desmethylcitalopram, desmethylsertraline, and norfluoxetine.

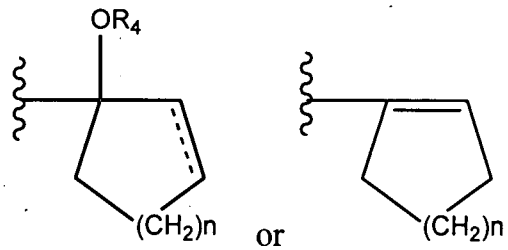
Analogs

Functional analogs of SSRIs can also be used in the methods, compositions, and kits of the invention. Exemplary SSRI functional analogs are provided below. One class of SSRI analogs includes SNRIs (selective serotonin norepinephrine reuptake inhibitors), which include venlafaxine, duloxetine, and 4-(2-fluorophenyl)-6-methyl-2-piperazinothieno [2,3-d] pyrimidine.

Structural analogs of venlafaxine are those compounds having the formula:



as well as pharmaceutically acceptable salts thereof, wherein A is a moiety of the formula:



where the dotted line represents optional unsaturation; R_1 is hydrogen or alkyl; R_2 is C_{1-4} alkyl; R_4 is hydrogen, C_{1-4} alkyl, formyl or alkanoyl; R_3 is hydrogen or C_{1-4} alkyl; R_5 and R_6 are, independently, hydrogen, hydroxyl, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkanoyloxy, cyano, nitro, alkylmercapto, amino, C_{1-4} alkylamino, dialkylamino, C_{1-4} alkanamido, halo, trifluoromethyl or, taken together, methylenedioxy; and n is 0, 1, 2, 3 or 4.

Structural analogs of duloxetine are those compounds described by the formula disclosed in U.S. Pat. No. 4,956,388, hereby incorporated by reference. Other SSRI analogs are 4-(2-fluorophenyl)-6-methyl-2-piperazinothieno [2,3-d] pyrimidine, 1,2,3,4-tetrahydro-N-methyl-4-phenyl-1-naphthylamine hydrochloride; 1,2,3,4-tetrahydro-N-methyl-4-phenyl-(E)-1-naphthylamine hydrochloride; N,N-dimethyl-1-phenyl-1-phthalanpropylamine hydrochloride; gamma-(4-(trifluoromethyl)phenoxy)-benzenepropanamine hydrochloride; BP 554; CP 53261; O-desmethylvenlafaxine; WY 45,818; WY 45,881; N-(3-fluoropropyl)paroxetine; Lu 19005; and SNRIs described in PCT Publication No. WO 04/004734.

Corticosteroids

In certain embodiments, a corticosteroid can be used in the compositions, methods, and kits of the invention. If desired, one or more corticosteroid may be administered in a method of the invention or may be formulated with a tricyclic compound in a composition of the invention. Suitable corticosteroids include 11-alpha,17-alpha,21-trihydroxypregn-4-ene-3,20-dione; 11-beta,16-alpha,17,21-tetrahydroxypregn-4-ene-3,20-dione; 11-beta,16-alpha,17,21-tetrahydroxypregn-1,4-diene-3,20-dione; 11-beta,17-alpha,21-trihydroxy-6-alpha-methylpregn-4-ene-3,20-dione; 11-dehydrocorticosterone; 11-deoxycortisol; 11-hydroxy-1,4-androstadiene-3,17-dione; 11-ketotestosterone; 14-hydroxyandrost-4-ene-3,6,17-trione; 15,17-dihydroxyprogesterone; 16-methylhydrocortisone; 17,21-dihydroxy-16-alpha-methylpregna-1,4,9(11)-triene-3,20-dione; 17-alpha-hydroxypregn-4-ene-3,20-dione; 17-alpha-hydroxypregnenolone; 17-hydroxy-16-beta-methyl-5-beta-pregn-9(11)-ene-3,20-dione; 17-hydroxy-4,6,8(14)-pregnatriene-3,20-dione; 17-hydroxypregna-4,9(11)-diene-3,20-dione; 18-hydroxycorticosterone; 18-

hydroxycortisone; 18-oxocortisol; 21-acetoxypregnenolone; 21-deoxyaldosterone; 21-deoxycortisone; 2-deoxyecdysone; 2-methylcortisone; 3-dehydroecdysone; 4-pregnene-17-alpha,20-beta, 21-triol-3,11-dione; 6,17,20-trihydroxypregn-4-ene-3-one; 6-alpha-hydroxycortisol; 6-alpha-fluoroprednisolone, 6-alpha-methylprednisolone, 6-alpha-methylprednisolone 21-acetate, 6-alpha-methylprednisolone 21-hemisuccinate sodium salt, 6-beta-hydroxycortisol, 6-alpha, 9-alpha-difluoroprednisolone 21-acetate 17-butyrate, 6-hydroxycorticosterone; 6-hydroxydexamethasone; 6-hydroxyprednisolone; 9-fluorocortisone; alclomethasone dipropionate; aldosterone; algestone; alphaderm; amadinone; amcinonide; anagestone; androstenedione; anecortave acetate; beclomethasone; beclomethasone dipropionate; betamethasone 17-valerate; betamethasone sodium acetate; betamethasone sodium phosphate; betamethasone valerate; bolasterone; budesonide (analogs described in U.S. Pat. No. 3,929,768); calusterone; chlormadinone; chloroprednisone; chloroprednisone acetate; cholesterol; ciclesonide; clobetasol; clobetasol propionate; clobetasone; clocortolone; clocortolone pivalate; clogestone; cloprednol; corticosterone; cortisol; cortisol acetate; cortisol butyrate; cortisol cypionate; cortisol octanoate; cortisol sodium phosphate; cortisol sodium succinate; cortisol valerate; cortisone; cortisone acetate; cortivazol; cortodoxone; daturaolone; deflazacort, 21-deoxycortisol, dehydroepiandrosterone; delmadinone; deoxycorticosterone; deprodone; descinolone; desonide; desoximethasone; dexafen; dexamethasone; dexamethasone 21-acetate; dexamethasone acetate; dexamethasone sodium phosphate; dichlorisone; diflorasone; diflorasone diacetate; diflucortolone; difluprednate; dihydroelatericin a; domoprednate; doxibetasol; ecdysone; ecdysterone; emoxolone; endrysone; enoxolone; fluazacort; flucinolone; flucloronide; fludrocortisone; fludrocortisone acetate; flugestone;

flumethasone; flumethasone pivalate; flumoxonide; flunisolide; fluocinolone; fluocinolone acetonide; fluocinonide; fluocortin butyl; 9-fluorocortisone; fluocortolone; fluorohydroxyandrostenedione; fluorometholone; fluorometholone acetate; fluoxymesterone; fluperolone acetate; fluprednidene; fluprednisolone; flurandrenolide; fluticasone; fluticasone propionate; formebolone; formestane; formocortal; gestonorone; glyderinine; halcinonide; halobetasol propionate; halometasone; halopredone; haloprogesterone; hydrocortamate; hydrocortiosone cypionate; hydrocortisone; hydrocortisone 21-butyrate; hydrocortisone aceponate; hydrocortisone acetate; hydrocortisone buteprate; hydrocortisone butyrate; hydrocortisone cypionate; hydrocortisone hemisuccinate; hydrocortisone probutate; hydrocortisone sodium phosphate; hydrocortisone sodium succinate; hydrocortisone valerate; hydroxyprogesterone; inokosterone; isoflupredone; isoflupredone acetate; isoprednidene; loteprednol etabonate; meclorisone; mecortolon; medrogestone; medroxyprogesterone; medrysone; megestrol; megestrol acetate; melengestrol; meprednisone; methandrostenolone; methylprednisolone; methylprednisolone aceponate; methylprednisolone acetate; methylprednisolone hemisuccinate; methylprednisolone sodium succinate; methyltestosterone; metribolone; mometasone (analogs described in 4,472,393); mometasone furoate; mometasone furoate monohydrate; nisone; nomegestrol; norgestomet; norvinisterone; oxymesterone; paramethasone; paramethasone acetate; ponasterone; prednicarbate; prednisolamate; prednisolone; prednisolone 21-diethylaminoacetate; prednisolone 21-hemisuccinate; prednisolone acetate; prednisolone farnesylate; prednisolone hemisuccinate; prednisolone-21(beta-D-glucuronide); prednisolone metasulphobenzoate; prednisolone sodium phosphate; prednisolone steaglate; prednisolone tebutate; prednisolone tetrahydrophthalate; prednisone; prednival; prednylidene; pregnenolone;

procinonide; tralonide; progesterone; promegestone; rhapontisterone; rimexolone; roxibolone; rubrosterone; stizophyllin; tixocortol; topterone; triamcinolone; triamcinolone acetonide; triamcinolone acetonide 21-palmitate; triamcinolone benetonide; triamcinolone diacetate; triamcinolone hexacetonide; trimegestone; turkesterone; and wortmannin or derivatives thereof (see, e.g., U.S. Pat. No. 7,081,475).

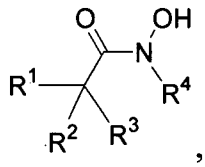
Steroid receptor modulators

Steroid receptor modulators (e.g., antagonists and agonists) may be used as a substitute for or in addition to a corticosteroid in the compositions, methods, and kits of the invention.

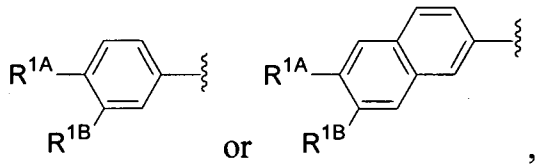
Glucocorticoid receptor modulators that may used in the compositions, methods, and kits of the invention include compounds described in U.S. Pat. Nos. 6,380,207, 6,380,223, 6,448,405, 6,506,766, and 6,570,020, U.S. Pat. Application Publication Nos. 2003/0176478, 2003/0171585, 2003/0120081, 2003/0073703, 2002/015631, 2002/0147336, 2002/0107235, 2002/0103217, and 2001/0041802, and PCT Publication No. WO00/66522, each of which is hereby incorporated by reference. Other steroid receptor modulators may also be used in the methods, compositions, and kits of the invention are described in U.S. Pat. Nos. 6,093,821, 6,121,450, 5,994,544, 5,696,133, 5,696,127, 5,693,647, 5,693,646, 5,688,810, 5,688,808, and 5,696,130, each of which is hereby incorporated by reference.

Bufexamac

In certain embodiments, bufexamac or a bufexamac analog can be used in the compositions, methods, and kits of the invention. By "bufexamac analog" is meant a compound having the formula (VI):



wherein R^1 is



wherein R^{1A} is and R^{1B} is H, halo, CF_3, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{1-6} alkoxy, or optionally substituted C_{1-6} thioalkoxy; each of R^2 and R^3 is, independently, H, C_{1-4} alkyl, or CF_3; and R^4 is optionally substituted C_{1-6} alkyl or optionally substituted C_{3-8} cycloalkyl.

Antiviral agents

In certain embodiments, an antiviral agent can be used in the compositions, methods, and kits of the invention. Suitable antiviral agents include, without limitation, abacavir, acemannan, acyclovir, adefovir, amantadine, amidinomycin, ampligen, amprenavir, aphidicolin, atevirdine, capravirine cidofovir, cytarabine, delavirdine, didanosine, dideoxyadenosine, *n*-docosanol, edoxudine, efavirenz, emtricitabine, famciclovir, floxuridine, fomivirsen, foscarnet sodium, ganciclovir, idoxuridine, imiquimod, indinavir, inosine pranobex, interferon-α, interferon-β, kethoxal, lamivudine, lopinavir, lysozyme, madu, methisazone, moroxydine, nelfinavir, nevirapine, nitazoxanide, oseltamivir, palivizumab, penciclovir, enfuvirtide, pleconaril, podophyllotoxin, ribavirin, rimantadine, ritonavir, saquinavir, sorivudine, stallimycin, statolon, stavudine, tenofovir, tremacamra, triciribine, trifluridine,

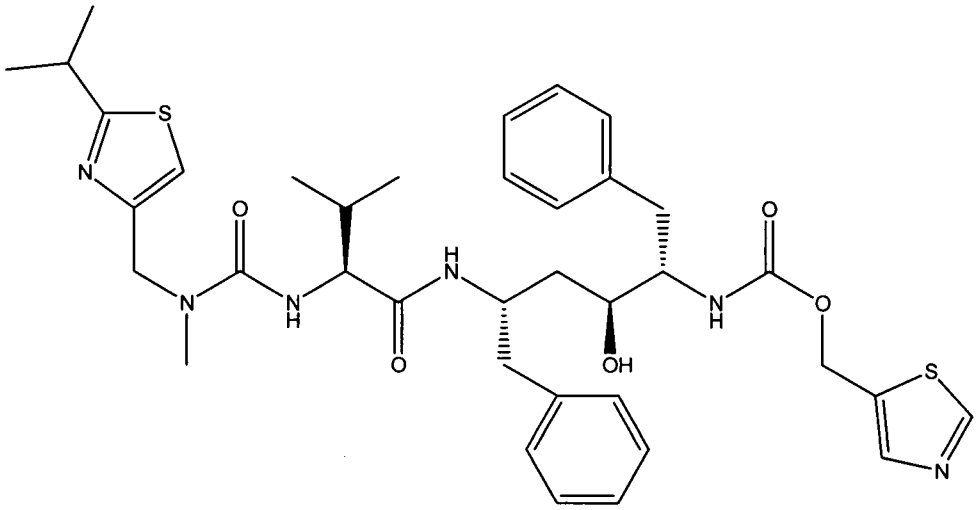
tromantadine, tunicamycin, valacyclovir, valganciclovir, vidarabine, zalcitabine, zanamivir, zidovudine, resiquimod, atazanavir, tipranavir, entecavir, fosamprenavir, merimepodib, docosanol, vx-950, and peg interferon. Additional antiviral agents are listed in Table 4 and Table 5.

Structural analogs of antiviral agents which may be used in the combinations of the invention include 9-((2-aminoethoxy)methyl)guanine, 8-hydroxyacyclovir, 2'-O-glycyl acyclovir, ganciclovir, PD 116124, valacyclovir, omaciclovir, valganciclovir, buciclovir, penciclovir, valmaciclovir, carbovir, theophylline, xanthine, 3-methylguanine, enprofylline, cafaminol, 7-methylxanthine, L 653180, BMS 181164, valomaciclovir stearate, deriphyllin, acyclovir monophosphate, acyclovir diphosphate dimyristoylglycerol, and etofylline.

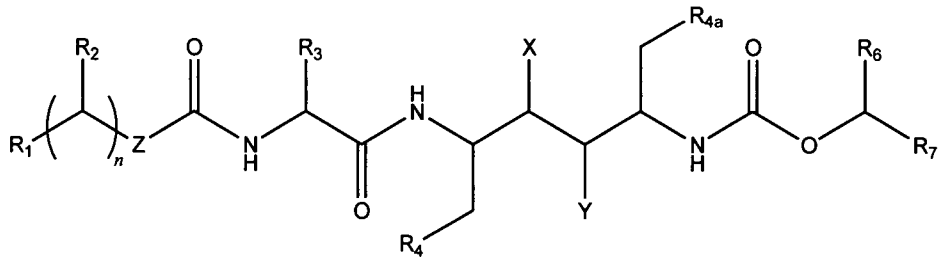
Edoxudine analogs are described in U.S. Pat. No. 3,553,192. Efavirenz analogs are described in European Patent 582,455 and U.S. Pat. No. 5,519,021. Floxuridine analogs are described in U.S. Pat. Nos. 2,970,139 and 2,949,451. Nelfinavir analogs are described in U.S. Pat. No. 5,484,926. Aphidicolin analogs are described in U.S. Pat. No. 3,761,512. Trifluridine analogs are described in U.S. Pat. No. 3,201,387. Cytarabine analogs are described in U.S. Pat. No. 3,116,282. Triciribine analogs, including triciribine 5'-phosphate and triciribine-dimethylformamide, are described in U.S. Pat. No. 5,633,235. Nitazoxanide analogs are described in U.S. Pat. No. 3,950,391.

Ritonavir

Ritonavir is an antiviral used in treatment of HIV and has the structure:



Ritonavir analogs are described, for example, in U.S. Pat. No. 5,541,206 and have the general structure:

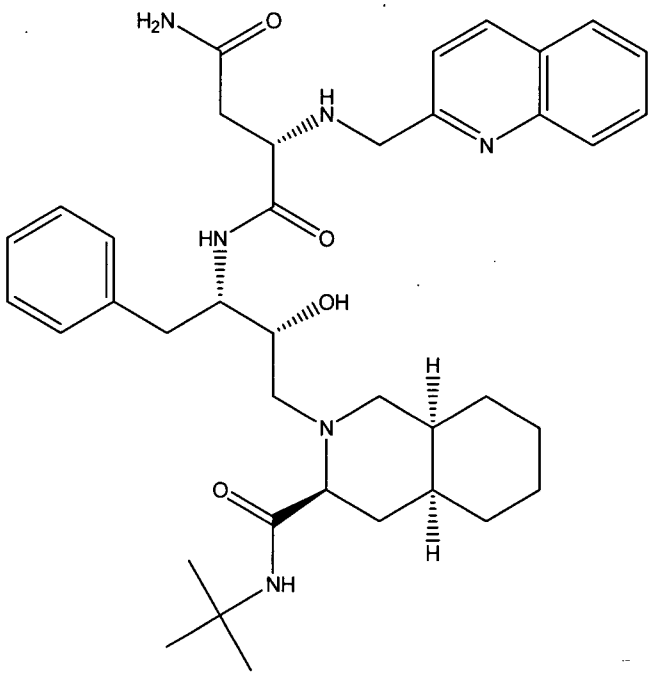


where R_1 is monosubstituted thiazolyl, monosubstituted oxazolyl, monosubstituted isoxazolyl or monosubstituted isothiazolyl wherein the substituent is selected from (i) loweralkyl, (ii) loweralkenyl, (iii) cycloalkyl, (iv) cycloalkylalkyl, (v) cycloalkenyl, (vi) cycloalkenylalkyl, (vii) heterocyclic wherein the heterocyclic is selected from aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyridazinyl and pyrazinyl and wherein the heterocyclic is unsubstituted or substituted with a substituent selected from halo, loweralkyl, hydroxy, alkoxy and thioalkoxy, (viii) (heterocyclic)alkyl wherein heterocyclic is defined as above, (ix) alkoxyalkyl,

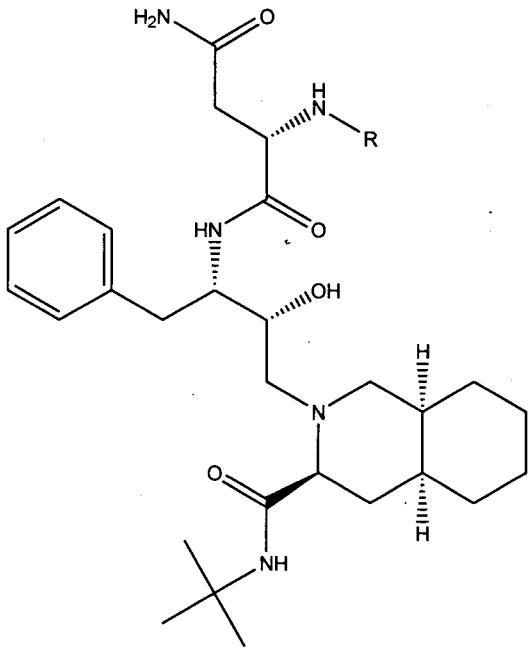
(x) thioalkoxyalkyl, (xi) alkylamino, (xii) dialkylamino, (xiii) phenyl wherein the phenyl ring is unsubstituted or substituted with a substituent selected from halo, loweralkyl, hydroxy, alkoxy and thioalkoxy, (xiv) phenylalkyl wherein the phenyl ring is unsubstituted or substituted as defined above, (xv) dialkylaminoalkyl, (xvi) alkoxy and (xvii) thioalkoxy; n is 1,2 or 3; R_2 is hydrogen or loweralkyl; R_3 is loweralkyl; R_4 and R_{4a} are independently selected from phenyl, thiazolyl and oxazolyl wherein the phenyl, thiazolyl or oxazolyl ring is unsubstituted or substituted with a substituent selected from (i) halo, (ii) loweralkyl, (iii) hydroxy, (iv) alkoxy and (v) thioalkoxy; R_6 is hydrogen or loweralkyl; R_7 is thiazolyl, oxazolyl, isoxazolyl or isothiazolyl wherein the thiazolyl, oxazolyl, isoxazolyl or isothiazolyl ring is unsubstituted or substituted with loweralkyl; X is hydrogen and Y is –OH or X is –OH and Y is hydrogen, with the proviso that X is hydrogen and Y is –OH when Z is $-N(R_8)-$ and R_7 is unsubstituted and with the proviso that X is hydrogen and Y is –OH when R_3 is methyl and R_7 is unsubstituted; and Z is absent, –O–, –S–, $-CH_2-$ or $-N(R_8)-$ wherein R_8 is loweralkyl, cycloalkyl, –OH or $-NHR_{8a}$ wherein R_{8a} is hydrogen, loweralkyl or an N-protecting group.

Saquinavir

In certain embodiments, saquinavir or its analogs can be used in the compositions, methods, and kits of the invention. Saquinavir is a protease inhibitor that is highly specific for the HIV-1 and HIV-2 proteases. The structure of saquinavir is:



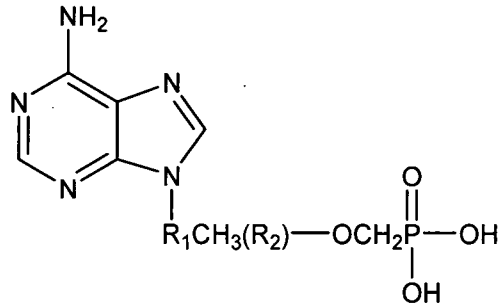
Saquinavir analogs are described, for example, in U.S. Pat. No. 5,196,438 and have the general structure:



where R is benzyloxycarbonyl or 2-quinolylcarbonyl, and pharmaceutically acceptable acid addition salts thereof.

Adefovir dipivoxil

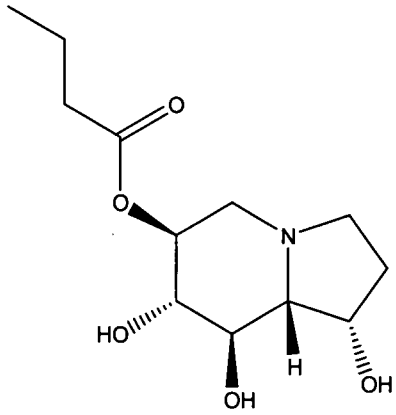
In certain embodiments, adefovir dipivoxil or its analogs can be used in the compositions, methods, and kits of the invention. Analogs of adefovir dipivoxil are described, for example, in U.S. Pat. No. 4,808,716 and include compounds with the general structure:



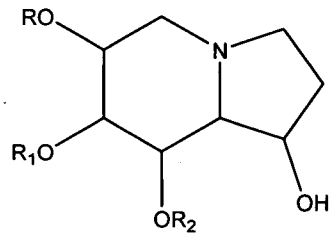
wherein R_1 is a hydrogen atom, an alkyl group containing one to three carbon atoms, or a hydroxymethyl group, and R_2 is a methylene, ethylene, propylene, ethylidene, methoxyethylene, benzyloxyethylene, tetrahydropyran-2-yloxyethylene, (1-ethoxyethoxy)ethylene, or 1,2-O-isopropylidene-1,2-dihydroxypropylene group.

Celgosivir

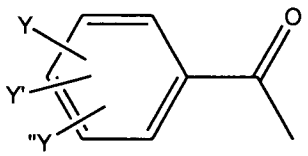
In certain embodiments, celgosivir or an analog thereof can be used in the compositions, methods, and kits of the invention. Celgosivir is a prodrug of castanospermine, a natural product derived from the Australian Black Bean chestnut tree. It has antiviral (e.g., anti-HCV) activity, and acts as an inhibitor of α- and β-glucosidase. The structure of celgosivir is:



Analogs of celgosivir are described, for example, in PCT Publication No. WO 2006/096285 and have the general structure:



where R, R_1 and R_2 are independently hydrogen, C_{1-14} alkanoyl, C_{2-14} alkenoyl, cyclohexanecarbonyl, C_{1-8} alkoxyacetyl,



naphthalenecarbonyl optionally substituted by methyl or halogen; phenyl(C_{2-6} alkanoyl) wherein the phenyl is optionally substituted by methyl or halogen; cinnamoyl; pyridinecarbonyl optionally substituted by methyl or halogen; dihydropyridine carbonyl optionally substituted by C_{1-10} alkyl; thiophenecarbonyl optionally substituted by methyl or halogen; or furancarbonyl optionally substituted by methyl or halogen; Y is hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, trifluoromethyl, C_{1-4} alkylsulphonyl, C_{1-4} alkylmercapto, cyano or dimethylamino; Y' is hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, halogen or it is combined with Y to give 3,4-methylenedioxy; Y" is hydrogen,

C_{1-4} alkyl, C_{1-4} alkoxy or halogen; and pharmaceutically acceptable salts thereof.

Nonsteroidal immunophilin-dependent immunosuppressants

In certain embodiments, a nonsteroidal immunophilin-dependent immunosuppressant can be used in the compositions, methods, and kits of the invention. Suitable NsIDIs include cyclosporine, tacrolimus, rapamycin (sirolimus), everolimus, and pimecrolimus.

Cyclosporines

The cyclosporines are fungal metabolites that comprise a class of cyclic oligopeptides that act as immunosuppressants. Cyclosporine A is a hydrophobic cyclic polypeptide consisting of eleven amino acids. It binds and forms a complex with the intracellular receptor cyclophilin. The cyclosporine/cyclophilin complex binds to and inhibits calcineurin, a Ca^{2+}-calmodulin-dependent serine-threonine-specific protein phosphatase. Calcineurin mediates signal transduction events required for T-cell activation (reviewed in Schreiber et al., Cell 70:365-368, 1991). Cyclosporines and their functional and structural analogs suppress the T cell-dependent immune response by inhibiting antigen-triggered signal transduction. This inhibition decreases the expression of proinflammatory cytokines, such as IL-2.

Many different cyclosporines (e.g., cyclosporine A, B, C, D, E, F, G, H, and I) are produced by fungi. Cyclosporine A is a commercially available under the trade name NEORAL from Novartis. Cyclosporine A structural and functional analogs include cyclosporines having one or more fluorinated amino acids (described, e.g., in U.S. Pat. No. 5,227,467); cyclosporines having modified amino acids (described, e.g., in U.S. Pat. Nos. 5,122,511 and

4,798,823); and deuterated cyclosporines, such as ISAtx247 (described in U.S. Pat. Application Publication No. 2002/0132763 A1). Additional cyclosporine analogs are described in U.S. Pat. Nos. 6,136,357, 4,384,996, 5,284,826, and 5,709,797. Cyclosporine analogs include, but are not limited to, D-Sar (α-SMe)^3 Val^2-DH-Cs (209-825), Allo-Thr-2-Cs, Norvaline-2-Cs, D-Ala(3-acetylamino)-8-Cs, Thr-2-Cs, and D-MeSer-3-Cs, D-Ser(O-CH_2CH_2-OH)-8-Cs, and D-Ser-8-Cs, which are described in Cruz et al. (Antimicrob. Agents Chemother. 44:143-149, 2000).

Tacrolimus

Tacrolimus and tacrolimus analogs are described by Tanaka et al., (J. Am. Chem. Soc., 109:5031, 1987) and in U.S. Pat. Nos. 4,894,366, 4,929,611, and 4,956,352. FK506-related compounds, including FR-900520, FR-900523, and FR-900525, are described in U.S. Pat. No. 5,254,562; O-aryl, O-alkyl, O-alkenyl, and O-alkynylmacrolides are described in U.S. Pat. Nos. 5,250,678, 532,248, 5,693,648; amino O-aryl macrolides are described in U.S. Pat. No. 5,262,533; alkylidene macrolides are described in U.S. Pat. No. 5,284,840; N-heteroaryl, N-alkylheteroaryl, N-alkenylheteroaryl, and N-alkynylheteroaryl macrolides are described in U.S. Pat. No. 5,208,241; aminomacrolides and derivatives thereof are described in U.S. Pat. No. 5,208,228; fluoromacrolides are described in U.S. Pat. No. 5,189,042; amino O-alkyl, O-alkenyl, and O-alkynylmacrolides are described in U.S. Pat. No. 5,162,334; and halomacrolides are described in U.S. Pat. No. 5,143,918.

Tacrolimus is extensively metabolized by the mixed-function oxidase system, in particular, by the cytochrome P-450 system. The primary mechanism of metabolism is demethylation and hydroxylation. While various tacrolimus metabolites are likely to exhibit immunosuppressive biological

activity, the 13-demethyl metabolite is reported to have the same activity as tacrolimus.

Pimecrolimus

Pimecrolimus is the 33-epi-chloro derivative of the macrolactam ascomyin. Pimecrolimus structural and functional analogs are described in U.S. Pat. No. 6,384,073.

Rapamycin

Rapamycin structural and functional analogs include mono- and diacylated rapamycin derivatives (U.S. Pat. No. 4,316,885); rapamycin water-soluble prodrugs (U.S. Pat. No. 4,650,803); carboxylic acid esters (PCT Publication No. WO 92/05179); carbamates (U.S. Pat. No. 5,118,678); amide esters (U.S. Pat. No. 5,118,678); biotin esters (U.S. Pat. No. 5,504,091); fluorinated esters (U.S. Pat. No. 5,100,883); acetals (U.S. Pat. No. 5,151,413); silyl ethers (U.S. Pat. No. 5,120,842); bicyclic derivatives (U.S. Pat. No. 5,120,725); rapamycin dimers (U.S. Pat. No. 5,120,727); O-aryl, O-alkyl, O-alkyenyl and O-alkynyl derivatives (U.S. Pat. No. 5,258,389); and deuterated rapamycin (U.S. Pat. No. 6,503,921). Additional rapamycin analogs are described in U.S. Pat. Nos. 5,202,332 and 5,169,851.

Peptide moieties

Peptides, peptide mimetics, peptide fragments, either natural, synthetic or chemically modified, that impair the calcineurin-mediated dephosphorylation and nuclear translocation of NFAT are suitable for use in practicing the invention. Examples of peptides that act as calcineurin inhibitors by inhibiting the NFAT activation and the NFAT transcription factor are described, e.g., by

Aramburu et al., *Science* 285:2129-2133, 1999) and Aramburu et al., Mol. Cell 1:627-637, 1998). As a class of calcineurin inhibitors, these agents are useful in the methods of the invention.

Antihistamines

In certain embodiments, an antihistamine or an antihistamine analog can be used in the compositions, methods, and kits of the invention. Antihistamines are compounds that block the action of histamine. Classes of antihistamines include:

(1) Ethanolamines (e.g., bromodiphenhydramine, carbinoxamine, clemastine, dimenhydrinate, diphenhydramine, diphenylpyraline, and doxylamine);

(2) Ethylenediamines (e.g., pheniramine, pyrilamine, tripelennamine, and triprolidine);

(3) Phenothiazines (e.g., diethazine, ethopropazine, methdilazine, promethazine, thiethylperazine, and trimeprazine);

(4) Alkylamines (e.g., acrivastine, brompheniramine, chlorpheniramine, desbrompheniramine, dexchlorpheniramine, pyrrobutamine, and triprolidine);

(5) Piperazines (e.g., buclizine, cetirizine, chlorcyclizine, cyclizine, meclizine, hydroxyzine);

(6) Piperidines (e.g., astemizole, azatadine, cyproheptadine, desloratadine, fexofenadine, loratadine, ketotifen, olopatadine, phenindamine, and terfenadine);

(7) Atypical antihistamines (e.g., azelastine, levocabastine, methapyrilene, and phenyltoxamine).

In the compositions, methods, and kits of the invention, both non-sedating and sedating antihistamines may be employed. Non-sedating

antihistamines include loratadine and desloratadine. Sedating antihistamines include azatadine, bromodiphenhydramine; chlorpheniramine; clemizole; cyproheptadine; dimenhydrinate; diphenhydramine; doxylamine; meclizine; promethazine; pyrilamine; thiethylperazine; and tripelennamine.

Other antihistamines suitable for use in the compositions, methods, and kits of the invention are acrivastine; ahistan; antazoline; astemizole; azelastine (e.g., azelsatine hydrochloride); bamipine; bepotastine; benztropine, bietanautine; brompheniramine (e.g., brompheniramine maleate); carbinoxamine (e.g., carbinoxamine maleate); cetirizine (e.g., cetirizine hydrochloride); cetoxime; chlorocyclizine; chloropyramine; chlorothen; chlorphenoxamine; cinnarizine; clemastine (e.g., clemastine fumarate); clobenzepam; clobenztropine; clocinizine; cyclizine (e.g., cyclizine hydrochloride; cyclizine lactate); deptropine; dexchlorpheniramine; dexchlorpheniramine maleate; diphenylpyraline; doxepin; ebastine; embramine; emedastine (e.g., emedastine difumarate); epinastine; etymemazine hydrochloride; fexofenadine (e.g., fexofenadine hydrochloride); histapyrrodine; hydroxyzine (e.g., hydroxyzine hydrochloride; hydroxyzine pamoate); isopromethazine; isothipendyl; levocabastine (e.g., levocabastine hydrochloride); mebhydroline; mequitazine; methafurylene; methapyrilene; metron; mizolastine; olapatadine (e.g., olopatadine hydrochloride); orphenadrine; phenindamine (e.g., phenindamine tartrate); pheniramine; phenyltoloxamine; p-methyldiphenhydramine; pyrrobutamine; setastine; talastine; terfenadine; thenyldiamine; thiazinamium (e.g., thiazinamium methylsulfate); thonzylamine hydrochloride; tolpropamine; triprolidine; and tritoqualine.

Antihistamine analogs may also be used in according to the invention. Antihistamine analogs include 10-piperazinylpropylphenothiazine; 4-(3-(2-

chlorophenothiazin-10-yl)propyl)-1-piperazineethanol dihydrochloride; 1-(10-(3-(4-methyl-1-piperazinyl)propyl)-10H-phenothiazin-2-yl)-(9CI) 1-propanone; 3-methoxycyproheptadine; 4-(3-(2-Chloro-10H-phenothiazin-10-yl)propyl)piperazine-1-ethanol hydrochloride; 10,11-dihydro-5-(3-(4-ethoxycarbonyl-4-phenylpiperidino)propylidene)-5H-dibenzo(a,d)cycloheptene; aceprometazine; acetophenazine; alimemazin (e.g., alimemazin hydrochloride); aminopromazine; benzimidazole; butaperazine; carfenazine; chlorfenethazine; chlormidazole; cinprazole; desmethylastemizole; desmethylcyproheptadine; diethazine (e.g., diethazine hydrochloride); ethopropazine (e.g., ethopropazine hydrochloride); 2-(p-bromophenyl-(p'-tolyl)methoxy)-N,N-dimethyl-ethylamine hydrochloride; N,N-dimethyl-2-(diphenylmethoxy)-ethylamine methylbromide; EX-10-542A; fenethazine; fuprazole; methyl 10-(3-(4-methyl-1-piperazinyl)propyl)phenothiazin-2-yl ketone; lerisetron; medrylamine; mesoridazine; methylpromazine; N-desmethylpromethazine; nilprazole; northioridazine; perphenazine (e.g., perphenazine enanthate); 10-(3-dimethylaminopropyl)-2-methylthio-phenothiazine; 4-(dibenzo(b,e)thiepin-6(11H)-ylidene)-1-methyl-piperidine hydrochloride; prochlorperazine; promazine; propiomazine (e.g., propiomazine hydrochloride); rotoxamine; rupatadine; SCH 37370; SCH 434; tecastemizole; thiazinamium; thiopropazate; thioridazine (e.g., thioridazine hydrochloride); and 3-(10,11-dihydro-5H-dibenzo(a,d)cyclohepten-5-ylidene)-tropane.

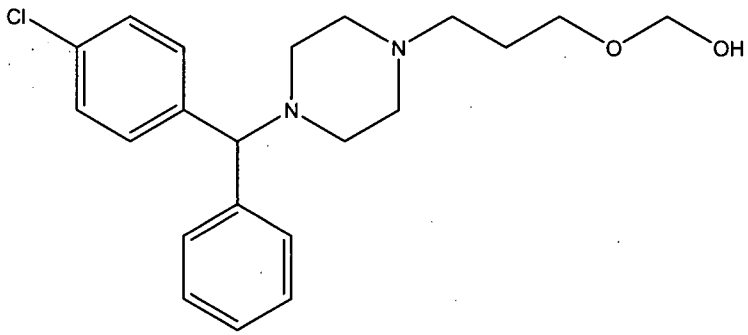
Other compounds that are suitable for use in the invention are AD-0261; AHR-5333; alinastine; arpromidine; ATI-19000; bermastine; bilastin; Bron-12; carebastine; chlorphenamine; clofurenadine; corsym; DF-1105501; DF-11062; DF-1111301; EL-301; elbanizine; F-7946T; F-9505; HE-90481; HE-90512; hivenyl; HSR-609; icotidine; KAA-276; KY-234; lamiakast; LAS-36509; LAS-36674; levocetirizine; levoprotiline; metoclopramide; NIP-531; noberastine;

oxatomide; PR-881-884A; quisultazine; rocastine; selenotifen; SK&F-94461; SODAS-HC; tagorizine; TAK-427; temelastine; UCB-34742; UCB-35440; VUF-K-8707; Wy-49051; and ZCR-2060.

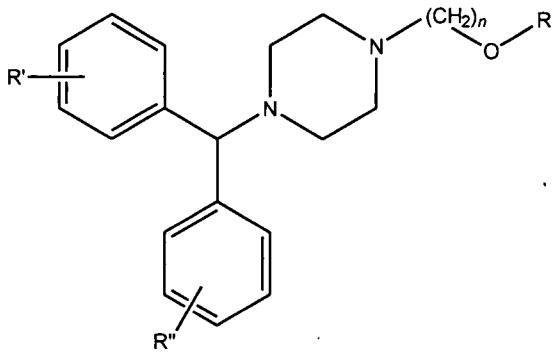
Still other compounds that are suitable for use in the invention are described in U.S. Pat. Nos. 2,595,405, 2,709,169, 2,785,202, 2,899,436, 3,014,911, 3,813,384, 3,956,296, 4,254,129, 4,254,130, 4,282,833, 4,283,408, 4,362,736, 4,394,508, 4,285,957, 4,285,958, 4,440,933, 4,510,309, 4,550,116, 4,659,716, 4,692,456, 4,742,175, 4,833,138, 4,908,372, 5,204,249, 5,375,693, 5,578,610, 5,581,011, 5,589,487, 5,663,412, 5,994,549, 6,201,124, and 6,458,958.

Hydroxyzine

In certain embodiments, hydroxyzine or an analog thereof can be used in the compositions, methods, and kits of the invention. The structure of hydroxyzine is:



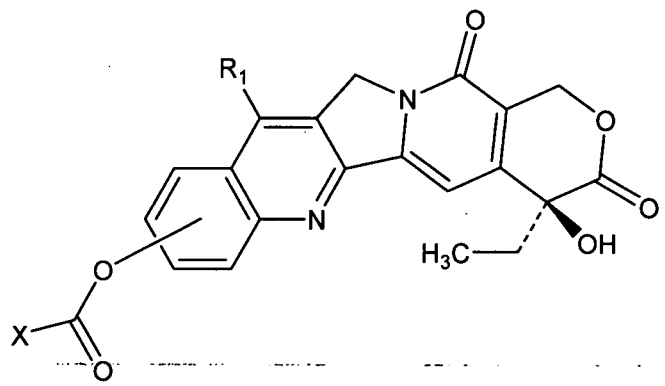
Analogs of hydroxyzine are described, for example, in U.S. Pat. No. 2,899,436 and have the general structure:



wherein R' and R" are a hydrogen atom, a halogen atom, an alkyl group, or an alkoxy group, R' and R" being in ortho, meta, or para positions; R contains 2 to 11 carbon atoms and is alkyl, phenyl, alkyl substituted phenyl, aralkyl, cycloalkyl, hydroxyalkyl, hydroxycycloalkyl or $-CH_2-CH_2-O-CH_2-CH_2-OH$, and *n* is an integer from 1 to 6, inclusive. The compound may be in the form of a mineral acid salt or an organic acid salt.

Irinotecan

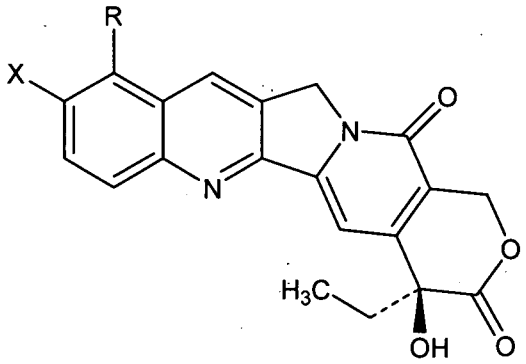
In certain embodiments, irinotecan, topotecan, or their analogs can be used in the compositions, methods, and kits of the invention. Analogs of irinotecan are described, for example, in U.S. Pat. No. 4,604,463 and have the general structure:



where R_1 is a hydrogen atom, a halogen atom, or a C_{1-4} alkyl, and X is a chlorine or $-NR_2R_3$, wherein R_2 and R_3 are the same or different and each represents a hydrogen atom, a C_{1-4} alkyl, or a substituted or unsubstituted

carbocyclic or heterocyclic group, with the proviso that when both R_2 and R_3 are the substituted or unsubstituted alkyl groups, they may be combined together with the nitrogen atom, to which they are bonded, to form a heterocyclic ring which may be interrupted with –O–, –S–, and/or >N–R_4 in which R_4 is a hydrogen atom, a substituted or unsubstituted C_{1-4} alkyl, or a substituted or unsubstituted phenyl group and where the grouping –O–CO–X is bonded to a carbon atom located in any of the 9-, 10-, and 11-positions in the ring A of camptothecin.

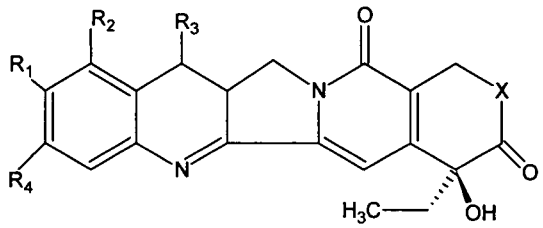
Analogs of topotecan are described, for example, in European Patent No. 321122 and include compounds with the general formula:



where X is hydroxy, hydrogen, cyano, -CH_2NH_2, or formyl; R is hydrogen when X is cyano, CH_2NH_2 or formyl or R is –CHO or –CH_2R_1 when X is hydrogen or hydroxy; R_1 is –O–R_2, -S-R_2, -N-$R_2(R_3)$; or –N^+-R_2-$(R_3)(R_4)$, R_2, R_3, and R_4 are the same or different and are selected from H, C_{1-6} alkyl, C_{2-6} hydroxyalkyl, C_{1-6} dialkyamino, C_{1-6}-dialkylaminoC_{2-6}alkyl, C_{1-6} alkyamino-C_{2-6} alkyl, C_{2-6} aminoalkyl, or a 3-7 member unsubstituted or substituted carbocyclic ring; and when R_1 is –N–$R_2(R_3)$, the R_2 and R_3 groups may be combined together to form a ring.

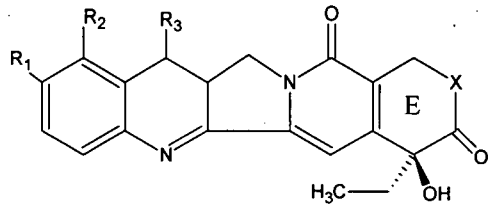
Camptothecins

In certain embodiments, the anti-infective therapeutic agent is camptothecin, or an analogue or derivative thereof. Camptothecins have the following general structure.



In this structure, X is typically O, but can be other groups, e.g., NH in the case of 21-lactam derivatives. R_1 is typically H or OH, but may be other groups, e.g., a terminally hydroxylated C_{1-3} alkane. R_2 is typically H or an amino containing group such as $(CH_3)_2NHCH_2$, but may be other groups e.g., NO_2, NH_2, halogen (as disclosed in, e.g., U.S. Pat. No. 5,552,156) or a short alkane containing these groups. R_3 is typically H or a short alkyl such as C_2H_5. R_4 is typically H but may be other groups, e.g., a methylenedioxy group with R_1.

Exemplary camptothecin compounds include topotecan, irinotecan (CPT-11), 9-aminocamptothecin, 21-lactam-20(S)-camptothecin, 10,11-methylenedioxycamptothecin, SN-38, 9-nitrocamptothecin, 10-hydroxycamptothecin. Exemplary compounds have the structures:



	R_1	R_2	R_3
Camptothecin:	H	H	H
Topotecan:	OH	$(CH_3)_2NHCH_2$	H
SN-38:	OH	H	C_2H_5

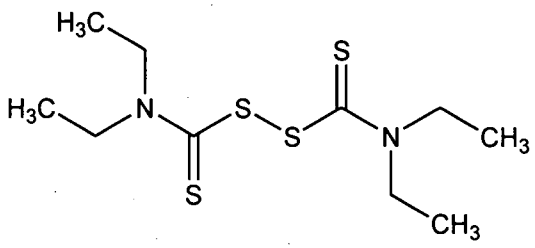
X: O for most analogs, NH for 21-lactam analogs

Camptothecins have the five rings shown here. The ring labeled E must be intact (the lactone rather than carboxylate form) for maximum activity and minimum toxicity.

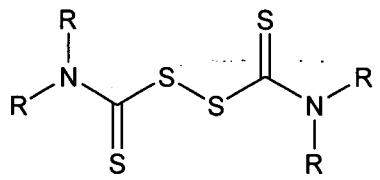
Camptothecins are believed to function as topoisomerase I inhibitors and/or DNA cleavage agents.

Disulfuram

Disulfiram is used in the treatment of alcoholism; its mechanism of action is inhibition of alcohol dehydrogenase. The structure of disulfiram is:



Analogs of disulfiram are described in, for example, U.S. Pat. No. 1,796,977 and have the general structure:

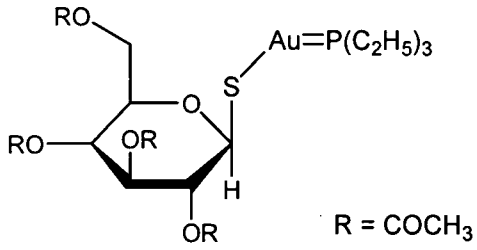


wherein the R groups represent same of dissimilar organic groups (e.g., C_{1-4} alkyls).

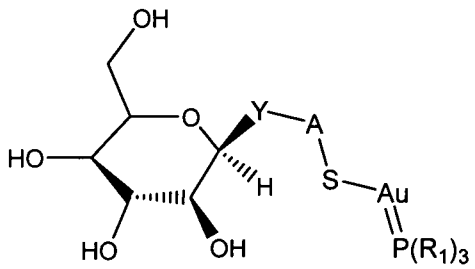
Analogs include thiram. Disulfiram is a crystal, barely soluble in water, and is soluble in solvents such as alcohol, ether, acetone, and benzene. Disulfiram is available in tablet form, and is typically administered orally.

Auranofin

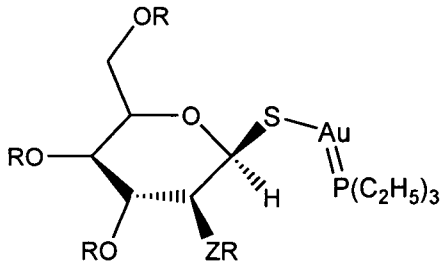
Auranofin is an anti-inflammatory agent and an antirheumatic. The structure of auranofin is:



Analogs of auranofin are described, for example, in U.S. Pat. No. 3,635,945, and can be represented by the general formulas:



and



where R represents acetyl or, when Z is oxygen, hydrogen; R_1 represents a C_{1-4} alkyl; A represents a C_{2-5} alkylene chain, straight or branched; Y represents oxygen or sulfur; and Z represents oxygen or –NH–.

Auronfin is a white, odorless, crystaline powder and is insoluble in water. It is administered orally in tablet form.

NSAIDs

In certain embodiments, an NSAID can be used in the compositions, methods, and kits of the invention. Suitable NSAIDs include A183827, ABT963, aceclofenac, acemetacin, acetyl salicylic acid, AHR10037, alclofenac, alminoprofen, ampiroxicam, amtolmetin guacil, apazone, aspirin, atliprofen methyl ester, AU8001, azelastine, benoxaprofen, benzydamine, benzydamine flufenamate, benzydamine hydrochloride, bermoprofen, bezpiperylon, BF388, BF389, BIRL790, BMS347070, bromfenac, bucloxic acid, butibufen, BW755C, C53, C73, C85, carprofen, CBS1108, celecoxib, CHF2003, chlorobiphenyl, choline magnesium trisalicylate, CHX108, cimicoxib, cinnoxicam, clidanac, CLX1205, CP331, CS502, CS706, D1367, curcumin, darbufelone, deracoxib, dexibuprofen, dexibuprofen lysine, dexketoprofen, DFP, DFU, diclofenac (e.g., diclofenac potassium, diclofenac sodium), diflunisal, DP155, DRF4367, E5110, E6087, eltenac, ER34122, esflurbiprofen, etoricoxib, F025, felbinac ethyl, fenbufen, fenclofenac, fenclozic acid, fenclozine, fenoprofen, fentiazac, feprazone, filenadol, flobufen, florifenine, flosulide, flubichin methanesulfonate, flufenamic acid, fluprofen, flurbiprofen, FPL62064, FR122047, FR123826, FR140423, FR188582, FS205397, furofenac, GR253035, GW406381, HAI105, HAI106, HCT2035, HCT6015, HGP12, HN3392, HP977, HX0835. HYAL AT2101, ibufenac, ibuprofen, ibuproxam-beta-cyclodextrin, icodulinum, IDEA070, iguratimod, imrecoxib, indomethacin, indoprofen, IP751, isoxepac, isoxicam, KC764, ketoprofen, L652343, L745337, L748731, L752860, L761066, L768277, L776967, L783003, L784520, L791456, L804600, L818571, LAS33815, LAS34475,

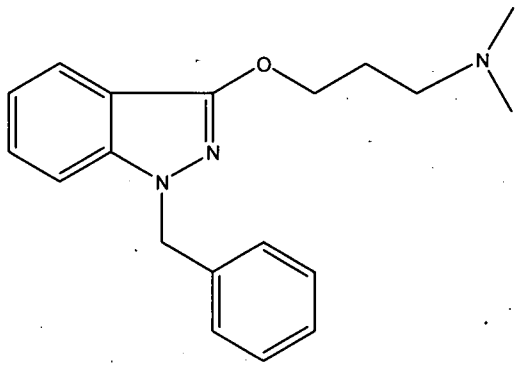
licofelone, LM 4108, lobuprofen, lornoxicam, lumiracoxib, mabuprofen, meclofenamic acid, meclofenamate sodium, mefenamic acid, meloxicam, mercaptoethylguanidine, mesoporphyrin, metoxibutropate, miroprofen, mofebutazone, mofezolac, MX1094, nabumetone, naproxen sodium, naproxen-sodium/metoclopramide, NCX1101, NCX284, NCX285, NCX4016, NCX4215, NCX530, niflumic acid, nitric oxide-based COX-2 inhibitors and NSAIDs (NitroMed), nitrofenac, nitroflurbiprofen, nitronaproxen, NS398, ocimum sanctum oil, ONO3144, orpanoxin, oxaprozin, oxindanac, oxpinac, oxycodone/ibuprofen, oxyphenbutazone, P10294, P54, P8892, pamicogrel, parcetasal, parecoxib, PD138387, PD145246, PD164387, pelubiprofen, pemedolac, phenylbutazone, pirazolac, piroxicam, piroxicam beta-cyclodextrin, piroxicam pivalate, pirprofen, pranoprofen, resveratrol, R-ketoprofen, R-ketorolac, rofecoxib, RP66364, RU43526, RU54808, RWJ63556, S19812, S2474, S33516, salicylsalicylic acid, satigrel, SC236, SC57666, SC58125, SC58451, SFPP, SKF105809, SKF86002, sodium salicylate, sudoxicam, sulfasalazine, sulindac, suprofen, SVT2016, T3788, TA60, talmetacin, talniflumate, tazofelone, tebufelone, tenidap, tenoxican, tepoxalin, tiaprofenic acid, tilmacoxib, tilnoprofen arbamel, tinoridine, tiopinac, tioxaprofen, tolfenamic acid, tolmetin, triflusal, tropesin, TY10222, TY10246, TY10474, UR8962, ursolic acid, valdecoxib, WAY120739, WY28342, WY41770, ximoprofen, YS134, zaltoprofen, zidometacin, and zomepirac.

Other NSAIDs are described in U.S. Pat. Nos. 2,745,783, 3,318,905, 5,344,991, 5,380,738, 5,393,790, 5,401,765, 5,418,254, 5,420,287, 5,434,178, 5,466,823, 5,475,018, 5,474,995, 5,486,534, 5,504,215, 5,508,426, 5,510,368, 5,510,496, 5,516,907, 5,521,193, 5,521,207, 5,534,521, 5,565,482, 5,596,008, 5,616,601, 5,633,272, 5,639,777, 5,663,180, 5,668,161, 5,670,510, 5,672,626, 5,672,627 5,736,579, 5,739,166, 5,760,068, 5,756,529, 5,859,257, 5,886,016,

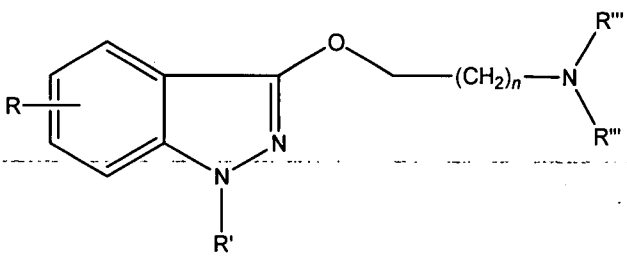
5,908,852, 5,916,905, 6,294,558, 6,476,042, 6,486,203, 6,492,411, 6,608,095, 6,649,645, 6,673,818, 6,689,805, 6,696,477, 6,727,268, 6,699,884, 6,727,238, 6,777,434, 6,846,818, 6,849,652, 6,949,536, 6,967,213, 7,019,144, and 7,041,694, PCT Publication Nos. WO94/13635, WO94/15932, WO94/20480, WO94/26731, WO96/03387, WO96/03388, WO96/09293, WO97/16435, WO98/03484, WO98/47890, WO96/06840, WO96/25405, WO95/15316, WO94/15932, WO94/27980, WO95/00501, and WO94/2673, and GB 839,057, GB 2,294,879, and EP 0745596.

Benzydamine

In certain embodiments, an NSAID such as benzydamine or an analog thereof can be used in the compositions, methods, and kits of the invention. The structure of benzydamine is:



Analogs of benzydamine are described, for example, in U.S. Pat. No. 3,318,905 and have the general structure:



wherein R is selected from the class consisting of hydrogen and chlorine; R' is selected from the class consisting of lower alkyl and phenyl groups which latter

may be substituted or not in their phenyl nucleus by halogen atoms or lower alkyl or lower alkoxy groups; R" is a member selected from the class consisting of hydrogen and lower alkyl groups; R"', which may be like or unlike, are lower alkyl residues; *n* is selected from the group consisting of 1 and 2.

Androgens

In certain embodiments, an androgen such as testerone or a testosterone analog can be used in the compositions, methods, and kits of the invention. Androgens such as androstenols include 14-hydroxyandrost-4-ene-3,6,17-trione, 16-acetoxy-17-acetoxymethyl-11,17-dihydroxy-D-homoandrosta-1,4-diene-3,17-dione, 17 beta-((1R)-1-hydroxy-2-propynyl)androst-4-en-3-one, 17 beta-amino-3 beta-methoxy-5-androstene, 17 beta-hydroxy-17-(2-methylallyl)-9 beta,10 alpha-androst-4-en-3-one, 17-(cyclopropylamino)androst-5-en-3-ol, 17-acetamido-5-androsten-3-ol-4-bis(2-chloroethyl)aminophenylacetate, 17-beta-hydroxy-7 alpha-methyl-androst-5-en-3-one, 17-ethynyl-(5a)-androst-2-ene-17-ol-17-nicotinate, 17-ethynylandrost-2-ene-17-ol-17-acetate, 17-hydroxy-17-methyl-3-oxospiro(androst-5-ene-4,1'-cyclopropane)-2-carbonitrile, 17-methyl-17-hydroxyandrosta-1,4,6-trien-3-one, 19-ethynyl-19-hydroxyandrost-4-en-17-one, 2,3,17,19-tetrahydroxyandrost-4-ene, 2-beta-hydroxy-19-oxo-4-androstene-3,17-dione, 3 beta-methoxy-5-androsten-17-one, 3'-azido-3'-deoxy-5'-O-((11-hydroxy-3-oxo-17-androst-4-enyl)carbonyl)thymidine, 3,15,17-trihydroxy-5-androstene, 3,16,19-trihydroxy-5-androsten-17-one, 3,17-dihydroxy-7-(4-methoxyphenyl)-androst-5-ene 3,17-diacetate, 3-hydroxy-17-methyl-18-norandrost-13(17)-ene-16-one, 3-methoxy-17-aza-homoandrost-5-ene-17-one, 5 alpha-androst-16-en-3 beta-ol, 5-androstene-3,16,17-triol, 9-fluoro-11,16,17-trihydroxy-17-hydroxymethyl-D-homoandrosta-1,4-diene-3,17-dione, 9-fluoro-16-methyl-6,11,16-trihydroxy-1,4-androstadiene-3,17-dione,

abiraterone, androst-16-en-3-ol, androst-16-en-3-ol sulfoconjugate, androst-5-en-3-ol, androst-5-ene-3,16,17-triol-3-sulfate, androsta-2,4-diene-17 beta-ol, androsta-5,16-dien-3 beta-ol, Androstenediols (e.g., 17-cyano-9,17-dihydroxyandrost-4-ene-3-one, 2-carbamoyl-4,5-epoxyandrost-2-ene-3,17-diol, 3 beta,17 beta-dihydroxyandrost-5-en-16-one, 3,16-dihydroxyandrost-5-ene-17,19-dione, 4-androstene-3,17-diol, 4a,17-dimethyl-A-homo-B,19-dinor-3,4-secoandrost-9-ene-3,17-diol, androst-4-ene-3 beta,17 beta-diol dicyclopentylpropionate, androst-4-ene-3 beta,17 beta-diol dienanthate, androstenediol, cortienic acid, delta (2,16)-5 alpha-androstadiene-3,17-diol-3,17-diacetate, Fluoxymesterone, formyldienolone, Methandriol, and viridiol), azastene, cyanoketone (e.g., Win 19578), Dehydroepiandrosterone (e.g., 1-hydroxydehydroepiandrosterone, 15 beta-carboxyethylmercaptodehydroepiandrosterone, 15-hydroxydehydroisoandrosterone, 16-hydroxydehydroepiandrosterone, 16-hydroxydehydroepiandrosterone sulfate, 7-hydroxydehydroepiandrosterone, 7-oxodehydroepiandrosterone, androst-5-en-17-one, dehydroepiandrosterone acetate, dehydroepiandrosterone enanthate, dehydroepiandrosterone sulfate, dehydroepiandrosterone-3-O-methylthiophosphonate, fluasterone, gonasterone, gynodian, OH 8356, and testosterone mustard), epostane, etiocholenic acid, methyl 14-hydroxy-1,7,17-trioxoandrost-8-ene-19-oate, mexrenoate potassium, nordinone, ratibol, RS 21314, RS 85095, stenbolone, stenbolone acetate, testosterone, and thiomesterone.

Testosterone derivatives include 11-ketotestosterone, 11-oxatestosterone, 15 beta-carboxyethylmercaptotestosterone, 15-carboxymethyltestosterone, 17 beta-aminocarbonyloxy-4-androsten-3-one, 17-bromoacetoxy-4-androsten-3-one, 17-ethinyl-11-oxa-testosterone, 19-O-carboxymethoxytestosterone, 4-(carboxymethylmercapto)testosterone, 6-

dehydrotestosterone, 6-methylenetestosterone acetate, ablacton, androsta-3,5-diene-3,17-diol diacetate, bolasterone, boldenone undecylenate, climacterone, clostebol, D-4-chloro-17 beta-hydroxy-3-oxo-17 alpha-methylandrosta-1,4-diene, dehydrotestosterone, deladumone, dimeric testosterone, epitestosterone, estandron prolongatum, ethynodiol testosterone ester, gonasterone, hydroxytestosterones, metharmon F, methenolone, methyltestosterone, nichlotest, synovex-H, testosterone 17 beta-carboxylic acid, testosterone 17 beta-cypionate, testosterone 17-cyclohexanecarboxylate, testosterone 17-enanthate 3-benzilic acid hydrazone, testosterone 3-(O-dimethylaminopropyl)oxime, testosterone 4-n-butylcyclohexylcarboxylic acid, testosterone acetate, testosterone decanoate, testosterone enanthate, testosterone formate, testosterone glucuronate, testosterone isobutyrate, testosterone isocaproate, testosterone palmitate, testosterone pivalate, testosterone propionate, testosterone undecanoate, testosterone-17-succinate, testosterone-17-sulfate, testosterone-19-hemisuccinate, testosterone-3-(n-hexyl)cyclobutane carboxylate, testosterone-3-oxime, testosterone-4-n-pentylcyclohexyl carboxylate, testosterone-cysteamine-DANS, testosterone-DAH-fluorescein, testosterone-DAP-fluorescein, testosteronyl 4-dimethylaminobutyrate, testoviron-depot, topterone, trofodermin, and turinabol.

Androstanols include 1,2-seco-A-bis(norandrostan-17-ol)acetate, 1,3,5,6-tetrahydroxyandrostan-17-one, 1,3-trimethylene-2',5-epoxyandrostane-3,17-diol 17-propionate, 11,17-dihydroxy-6-methyl-17-(1-propynyl)androsta-1,4,6-triene-3-one, 16,17-epoxyandrostan-3-ol, 17 beta-(3-furyl)-5 beta,14 beta-androstane-3 beta,14 beta-diol, 17-(3'-thiophenyl)androstane-3,14-diol 3-glucopyranoside, 17-acetamido-5-androstan-3-ol-4-bis(2-chloroethyl)aminophenylacetate, 17-ethyl-17-hydroxyandrostane, 17-hydroxy-2,3-cyclopropanoandrostane, 17-methyl-17a-chloro-D-homoandrostan-3-ol, 2-

(2-(3-hydroxy-12-(2-methyl-1-oxobutoxy)-5-androstan-17-yl)ethyl)tetrahydro-4-hydroxy-2H-pyran-6-one, 3 beta-acetoxy-5,6 beta-dichloromethylene-5 beta-androstan-17-one, 3,3-difluoroandrostane-17-ol acetate, 3-acetoxy-7,15-oxido-16-oxaandrostan-17-one, 3-hydroxy-17-(1H-1,2,3-triazol-1-yl)androsta-5,16-diene, 3-hydroxy-5-androstane-17-carbonitrile, 3-hydroxyetianic acid, 3-keto-5,10-epoxy-nor-19-methylandrostane-17-acetate, 4,5-epoxy-17-hydroxy-2-methylsulfonyl-3-androstanone, 5-bromo-3,6-dihydroxyandrostan-17-one-3-acetate, amafolone, androsol acetate, androstan-17-ol, androstan-3-ol, androstane-3,17-diol or derivatives thereof (e.g., 17-hydroxyandrostane-3-glucuronide, 17-methyl-D-homoandrostane-3,17-diol, 2,4-cycloandrostane-3,17-diol diacetate, 3-desacetylpipecuronium, 4-ethenylideneandrostane-3,17-diol, 4-ethenylideneandrostane-3,17-dione, androstane-2,3,17-triol, androstane-3,14-diol, androstane-3,16,17-triol, androstane-3,17-diol 17-sulfate, androstane-3,17-diol dipropionate, androstane-3,17-diol glucuronide, androstane-3,6,17-triol, androstane-3,7,17-triol, androstane-3,7-diol disulfate), androsterone or its derivatives (e.g., 11 beta-hydroxyandrosterone, 11-ketoandrosterone, 16 beta-hydroxyandrosterone, 16-bromoepiandrosterone, 17-hydroxy-6,6-ethylene-4-androsten-3-one, 19-hydroxy-4-androsten-17-one, 3-bromoacetoxyandrostan-17-one, 3-hydroxy-4-androsten-17-one, androsterone 3-benzoate, androsterone 3-palmitate, androsterone glucuronide, and androsterone sulfate), BOMT, CCI 22277, dihydrotestosterone or its derviatives (e.g., 11-fluoro-19-nor-dihydro-testosterone, 11-fluoro-dihydro-testosterone, 16-iodostanolone, 17-(2-iodoethenyl)androsta-4,6-dien-17-ol-3-one, 17-(2-iodoethynyl)androsta-4,6-dien-17-ol-3-one, 17-(2-iodovinyl)dihydrotestosterone, 17-hydroxyandrostan-19-ol-3-one, 17-hydroxyandrostan-3-one 17-sulfate, 17-ketotrilostane, 17-N,N-diethylcarbamoyl-4-methyl-4-azaandrostane-3-one, 17-N,N-diisopropylcarbamoyl-4-azaandrostan-3-one, 18-hydroxy-18-methyl-16,17-

methylene-D-homoandrostane-3-one, 2,17-dimethyldihydrotestosterone, 2-bromo-5-dihydrotestosterone, 2-chloroethylnitrosocarbamoylalanine 17-dihydrotestosterone ester, 3-hydroxyandrostan-16-one, 4,17-dimethyltrilostane, 4,5-secodihydrotestosterone, 5-dihydrotestosterone 3,17-bromoacetate, androstan-3,17-diol-11-one, androstan-3-one, demalon, dihydrotestosterone 17-bromoacetate, dihydrotestosterone glucuronide, dihydrotestosterone heptanoate, dihydrotestosterone propionate, dihydrotestosterone-17-N-bis(2-chloroethyl)carbamate, mestanolone, mesterolone, nitrostanolone, stanolone benzoate, testiphenon, and trilostane), dromostanolone, dromostanolone propionate, epitiostanol, etiocholanolone or its derivatives (e.g., 11-ketoetiocholanolone, 3,7-dihydroxyandrostan-17-one, 3-hydroxyandrostane-7,17-dione, and androstane-3,17-dione), furazabol, mebolazine, mepitiostane, N-cyano-2-aza-A-norandrostan-17-ol acetate, nisterime acetate, ORG 9943, ORG 9991, Org NA13, oxandrolone, oxymetholone or its derivatives (e.g., 17-hydroxy-2-(hydroxymethylene)androstan-3-one), Pancuronium or its derivative (e.g., (dideacetoxy)pancuronium, 2,16-dipiperidinoandrostane-3,17-diol dipivalate, 3 alpha,17 beta-dibutyryloxy-2 beta,16 beta-dipiperidino-5 alpha-androstane dimethobromide, 3-(deacetoxy)pancuronium, 3-desacetylpancuronium, dacuronium, and Org 6368), RU 26988, rubrosterone, samanine, spiro-3-oxiranylandrostan-17-ol, stanozolol or its derivatives (e.g., 16-hydroxystanozolol and 4,16-dihydroxystanozolol), vecuronium bromide or its derivatives (e.g., (dideacetoxy)vecuronium, 17-deacetylvecuronium, 3,17-bis-deacetylvecuronium, 3-(deacetoxy)vecuronium, 3-deacetylvecuronium, Org 7617, Org 7678, Org 7684, Org 9273, and Org 9616).

Stanozolol analogs are described in U.S. Pat. No. 3,030,358. Mesterolone analogs are described in U.S. Pat. No. 3,361,773. Methyltestosterone analogs are described in U.S. Pat. No. 2,374,370.

Tyrphostins

In certain embodiments, a tyrophostin can be used in the compositions, methods, and kits of the invention. The tyrphostins are family of synthetic kinase inhibitors . Exemplary tyrphostins include 6,7-dimethoxy-2-phenylquinoxaline, AG 127, AG 183, AG 30, AG 494, AG 556, AG 879, RG 13022, RG 14620, RG 50810, RG 50864, tyrphostin 11, tyrphostin 23, tyrphostin 25, tyrphostin 8, tyrophostin 47, tyrphostin A46, tyrphostin A51, tyrphostin A9, tyrphostin AG 1024, tyrphostin AG 1112, tyrphostin AG 1296, tyrphostin AG 1478, tyrphostin AG 555, tyrphostin AG 568, tyrphostin AG-490, tyrphostin AG17, tyrphostin AG879, and tyrphostin AG957. Tyrphostins are described in U.S. Pat. Nos. 5,728,868 and 5,854,285.

Vitiamin B_{12}

Vitamin B_{12} and B_{12} analogs can be used in the compositions, methods, and kits of the invention. Vitamin B_{12}, its derivatives, and its analogs are cofactors in folate enzymes and methionine synthase. 5-Deoxyadenosyl cobalamin is a cofactor required by the enzyme that converts L-methylmalonyl-CoA to succinyl-CoA. Other vitamin B_{12} analogs include 1,N(6)-ethenoadenosylcobalamin, 2',5'-dideoxyadenosylcobalamin, 2-methyl-2-aminopropanol-B_{12}, adeninylethylcobalamin, ambene, aminopropylcobalamin, aquacobalamin, biofer, Co-(carboxymethyl)cobalamin, cob(II)alamin, cobamides (e.g., (2-amino-5,6-dimethylbenzimidazolyl)cobamide, (2-hydroxy-5,6-dimethylbenzimidazolyl)cobamide, 2-methylsulfinyladenylcobamide, 2-methylsulfonyladenylcobamide, 4-cresolylcobamide, adenosylcobinamide methyl phosphate, coalpha-(alpha-5,6-dimethylbenzimidazolyl)-cobeta-cyanocobamide, cobamamide, cobamamide 5'-phosphate, cobinamide, phenolyl cobamide, thiobanzyme), cobyric acid, cobyrinic acid, cobyrinic acid

hexamethyl ester f-nitrile, compound 102804, cyanocobalamin-b-monocarboxylic acid, cyanocobalamin-e-monocarboxylic acid, cysteinylcobalamin, factor A, factor III, ferribalamin, formylmethylcobalamin, FV 82, glutathionylcobalamin, hepavis, hydroxocobalamin (e.g., nitrosocobalamin and acetatocobalamin), Jectofer compound, mecobalamin, methylcobalamine chlorpalladate, nitritocobalamin, nitrosylcobalamin, proheparum, pseudovitamin B_{12}, sulfitocobalamin, Transcobalamins, triredisol, and vitamin B_{12} factor B. Cobamamide analogs are described in U.S. Pat. No. 3,461,114.

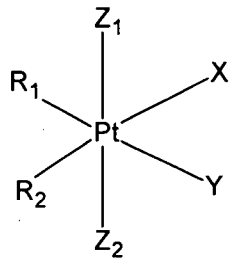
Histone deacetylase (HDAC) inhibitors

Histone deacetylase inhibitors and their analogs may be used in the compositions, methods, and kits of the invention. Exemplary HDACs include CAY10433 and suberohydroxamic acid. Histone deacetylase inhibitors are used, for example, in cancer therapy, and in the treatment of inflammation and are a group of compounds that include, for example, cyclic peptides (e.g., depsipeptides such as FK228), short chain fatty acids (e.g., phenylbutyrate and valproic acid), benzamides (e.g., CI-994 and MS-27-275), and hydroxamic acids (e.g., suberoylanilide hydroxamic acid (SAHA)) as described in Richon and O'Brien ((2002) *Clin. Canc. Res.* 8, 662-664). Cyclic peptides and analogs useful in the invention are described, for example, in U.S. Pat. No. 6,403,555. Short chain fatty acid HDAC inhibitors are described in, for example, U.S. Pat. Nos. 6,888,027 and 5,369,108. Benzamides analogs are described, for example, in U.S. Pat. No. 5,137,918. Analogs of SAHA are described, for example, in U.S. Pat. No. 6,511,990. Other HDACs include anacardic acid, apicidin, histone deacetylase inhibitor I, histone deacetylase inhibitor II, histone deacetylase inhibitor III, ITSA1, oxamflatin, SBHA, scriptaid, sirtinol,

splitomicin, trichostatin A, and valproic acid (e.g., sodium salt). Any of these compounds or other HDAC inhibitors may be used in the compositions, methods, or kits of the invention.

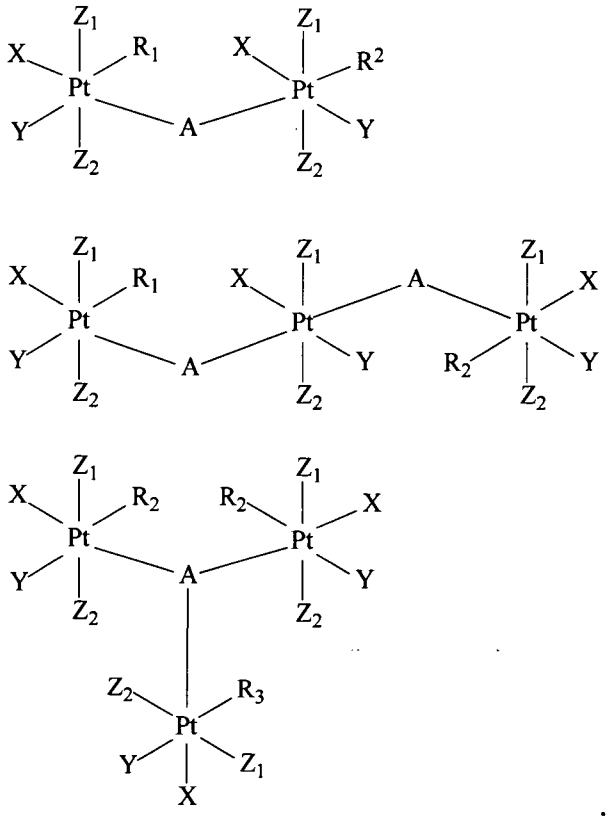
Platinum complexes

In certain embodiments, a platinum compound can be used in the compositions, methods, and kits of the invention. In general, suitable platinum complexes may be of Pt(II) or Pt(IV) and have this basic structure:

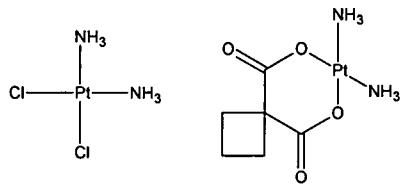


wherein X and Y are anionic leaving groups such as sulfate, phosphate, carboxylate, and halogen; R_1 and R_2 are alkyl, amine, amino alkyl any may be further substituted, and are basically inert or bridging groups. For Pt(II) complexes Z_1 and Z_2 are non-existent. For Pt(IV) Z_1 and Z_2 may be anionic groups such as halogen, hydroxy, carboxylate, ester, sulfate or phosphate. See, e.g., U.S. Pat. Nos. 4,588,831 and 4,250,189.

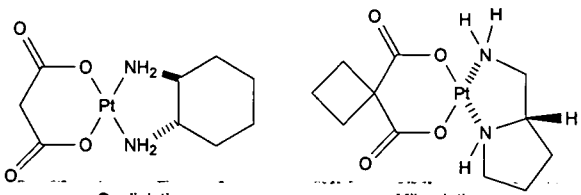
Suitable platinum complexes may contain multiple Pt atoms. See, e.g., U.S. Pat. Nos. 5,409,915 and 5,380,897. For example bisplatinum and triplatinum complexes of the type:



Exemplary platinum compounds are cisplatin, carboplatin, oxaliplatin, and miboplatin having the structures:



Cisplatin Carboplatin



Oxaliplatin Miboplatin

Other representative platinum compounds include $(CPA)_2Pt(DOLYM)$ and (DACH)Pt(DOLYM) cisplatin (Choi et al., *Arch. Pharmacal Res.* 22(2):151-156, 1999), Cis-($PtCl_2$(4,7-H-5-methyl-7-oxo)1,2,4(triazolo(1,5-

a)pyrimidine)$_2$) (Navarro et al., *J. Med. Chem.* 41(3):332-338, 1998), (Pt(cis-1,4-DACH)(trans-Cl$_2$)(CBDCA)) • ½MeOH cisplatin (Shamsuddin et al., *Inorg. Chem.* 36(25):5969-5971, 1997), 4-pyridoxate diammine hydroxy platinum (Tokunaga et al., *Pharm. Sci.* 3(7):353-356, 1997), Pt(II) •••Pt(II) (Pt$_2$(NHCHN(C(CH$_2$)(CH$_3$)))$_4$) (Navarro et al., *Inorg. Chem.* 35(26):7829-7835, 1996), 254-S cisplatin analogue (Koga et al., *Neurol. Res.* 18(3):244-247, 1996), o-phenylenediamine ligand bearing cisplatin analogues (Koeckerbauer & Bednarski, *J. Inorg. Biochem.* 62(4):281-298, 1996), trans, cis-(Pt(OAc)$_2$I$_2$(en)) (Kratochwil et al., *J. Med. Chem.* 39(13):2499-2507, 1996), estrogenic 1,2-diarylethylenediamine ligand (with sulfur-containing amino acids and glutathione) bearing cisplatin analogues (Bednarski, *J. Inorg. Biochem.* 62(1):75, 1996), cis-1,4-diaminocyclohexane cisplatin analogues (Shamsuddin et al., *J. Inorg. Biochem.* 61(4):291-301, 1996), 5' orientational isomer of cis-(Pt(NH$_3$)(4-aminoTEMP-O){d(GpG)}) (Dunham & Lippard, *J. Am. Chem. Soc.* 117(43):10702-12, 1995), chelating diamine-bearing cisplatin analogues (Koeckerbauer & Bednarski, J. Pharm. Sci. 84(7):819-23, 1995), 1,2-diarylethyleneamine ligand-bearing cisplatin analogues (Otto et al., *J. Cancer Res. Clin. Oncol.* 121(1):31-8, 1995), (ethylenediamine)platinum(II) complexes (Pasini et al., *J. Chem. Soc., Dalton Trans.* 4:579-85, 1995), CI-973 cisplatin analogue (Yang et al., *Int. J. Oncol.* 5(3):597-602, 1994), cis-diaminedichloroplatinum(II) and its analogues cis-1,1-cyclobutanedicarbosylato(2R)-2-methyl-1,4-butanediamineplatinum(II) and cis-diammine(glycolato)platinum (Claycamp & Zimbrick, *J. Inorg. Biochem.* 26(4):257-67, 1986; Fan et al., *Cancer Res.* 48(11):3135-9, 1988; Heiger-Bernays et al., *Biochemistry* 29(36):8461-6, 1990; Kikkawa et al., *J. Exp. Clin. Cancer Res.* 12(4):233-40, 1993; Murray et al., *Biochemistry* 31(47):11812-17, 1992; Takahashi et al., *Cancer Chemother. Pharmacol.* 33(1):31-5, 1993), cis-

amine-cyclohexylamine-dichloroplatinum(II) (Yoshida et al., *Biochem. Pharmacol.* 48(4):793-9, 1994), gem-diphosphonate cisplatin analogues (FR 2683529), (meso-1,2-bis(2,6-dichloro-4-hydroxyplenyl)ethylenediamine) dichloroplatinum(II) (Bednarski et al., *J. Med. Chem.* 35(23):4479-85, 1992), cisplatin analogues containing a tethered dansyl group (Hartwig et al., *J. Am. Chem. Soc.* 114(21):8292-3, 1992), platinum(II) polyamines (Siegmann et al., *Inorg. Met.-Containing Polym. Mater.*, (Proc. Am. Chem. Soc. Int. Symp.), 335-61, 1990), cis-(3H)dichloro(ethylenediamine)platinum(II) (Eastman, *Anal. Biochem.* 197(2):311-15, 1991), trans-diamminedichloroplatinum(II) and cis-($Pt(NH_3)_2(N_3$-cytosine)Cl) (Bellon & Lippard, *Biophys. Chem.* 35(2-3):179-88, 1990), 3H-cis-1,2-diaminocyclohexanedichloroplatinum(II) and 3H-cis-1,2-diaminocyclohexanemalonatoplatinum (II) (Oswald et al., *Res. Commun. Chem. Pathol. Pharmacol.* 64(1):41-58, 1989), diaminocarboxylatoplatinum (EPA 296321), trans-(D,1)-1,2-diaminocyclohexane carrier ligand-bearing platinum analogues (Wyrick & Chaney, *J. Labelled Compd. Radiopharm.* 25(4):349-57, 1988), aminoalkylaminoanthraquinone-derived cisplatin analogues (Kitov et al., *Eur. J. Med. Chem.* 23(4):381-3, 1988), spiroplatin, carboplatin, iproplatin and JM40 platinum analogues (Schroyen et al., *Eur. J. Cancer Clin. Oncol.* 24(8):1309-12, 1988), bidentate tertiary diamine-containing cisplatinum derivatives (Orbell et al., *Inorg. Chim. Acta* 152(2):125-34, 1988), platinum(II), platinum(IV) (Liu & Wang, *Shandong Yike Daxue Xuebao* 24(1):35-41, 1986), cis-diammine(1,1-cyclobutanedicarboxylato-)platinum(II) (carboplatin, JM8) and ethylenediammine-malonatoplatinum(II) (JM40) (Begg et al., *Radiother. Oncol.* 9(2):157-65, 1987), JM8 and JM9 cisplatin analogues (Harstrick et al., *Int. J. Androl.* 10(1); 139-45, 1987), $(NPr^n_4)_2((PtCL_4)\cdot cis\text{-}(PtCl_2\text{-}(NH_2Me)_2))$ (Brammer et al., *J. Chem. Soc., Chem. Commun.* 6:443-5, 1987), aliphatic tricarboxylic acid platinum complexes (EPA 185225), and cis-dichloro(amino

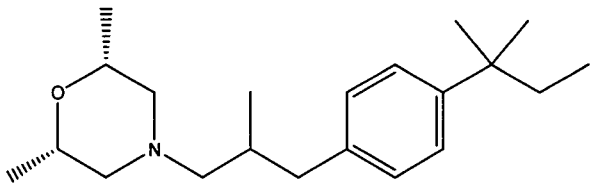
acid)(tert-butylamine)platinum(II) complexes (Pasini & *Bersanetti, Inorg. Chim. Acta* 107(4):259-67, 1985). Oxaliplatin analogs are described in U.S. Pat. Nos. 4,169,846, 5,290,961, 5,298,642, and 6,153,646. Satraplatin is described in Choy, *Expert Rev. Anticancer Ther.* 6(7):973-982, 2006). These compounds are thought to function by binding to DNA, i.e., acting as alkylating agents of DNA.

Flavanones

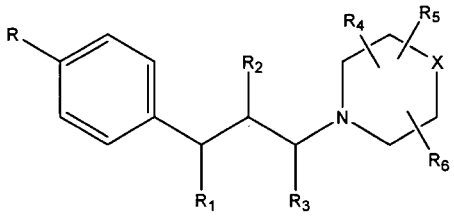
In certain embodiments, a flavanone can be used in the compositions, methods, and kits of the invention. Exemplary flavanones include 2-hydroxyflavanone, 137 L, 2',3,5,7-tetrahydroxyflavanone, 3'-prenylnaringenin, 6-(1,1-dimethylallyl)naringenin, 7-hydroxyflavanone, 7-O-methyleriodictyol, 8-prenylnaringenin, baicalein, BE 14348D, carthamidin, desmal, eriodictyol, eriodictyol 7-glucuronide, flavanone, flemiphilippinin D, Hesperidin (e.g., Cirkan N.D., dehydro-sanol-tri, essaven, fleboplex, hesperetin, hesperetin 5-O-glucoside, hesperetin 7-O-lauryl ether, hesperidin methylchalcone, methyl hesperidin, neohesperidin dihydrochalcone, and S 5682), liquiritigenin, naringenin, naringenin-6-C-glucoside, naringin, pinobanksin, pinocembrin, plantagoside, scuteamoenin, scuteamoenoside, shinflavanone, uralenin, vexibinol, wogonin, and WS 7528.

Amorolfine

In certain embodiments, amorolfine or an amorolfine derivative such as benzamil can be used in the compositions, methods, and kits of the invention. Amorolfine is an antifungal agent that is typically administered topically. The structure of amorolfine is:



Analogs of amorolfine are described, for example, in U.S. Pat. No. 4,202,894 and have the general structure:



wherein R is alkyl of 4 to 12 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, mono(lower alkyl)-substituted cycloalkyl of 4 to 7 carbon atoms, cycloalkylalkyl of 4 to 12 carbon atoms, phenyl or aryl-(lower alkyl) of 7 to 12 carbon atoms; R_1, R_2, and R_3, independently, are hydrogen or alkyl of 1 to 8 carbon atoms; R_4, R_5, and R_6, independently, are hydrogen or alkyl of 1 to 8 carbon atoms, and two of R_4, R_5, and R_6 can each be bonded to the same carbon atom or together can form a fused alicyclic or aromatic 6-membered ring; provided that when R is tert.-butyl, at least one of R_1 and R_3 is alkyl of 2 to 8 carbon atoms or R_2 is hydrogen or alkyl of 2 to 8 carbon atoms or at least one of R_4, R_5, and R_6 is alkyl of 5 to 8 carbon atoms; X is methylene or an oxygen atom; z is zero or 1 and the dotted bonds can be hydrogenated, and acid addition salts of those compounds of formula I which are basic, where the term "lower alkyl" denotes a straight-chain or branched-chain hydrocarbon group of 1 to 4 carbon atoms, such as, methyl, ethyl, propyl, isopropyl, butyl, isobutyl and tert.-butyl. Alkyl groups of 4 to 12 carbon atoms are straight-chain or branched-chain hydrocarbon groups, for example, butyl, isobutyl, tert.-butyl, neopentyl, 1,1-dimethylpropyl, 1,1-dimethylpentyl, 1,1-diethylpropyl, 1,1-dimethylbutyl, 1-isopropyl-3-methyl-but-1-yl, 1-ethyl-1-methylbutyl, dodecyl,

and the like. Cycloalkylalkyls include, in particular, those groups in which the alkyl moiety is branched. The term "aryl-(lower alkyl)" includes not only groups which are mono- or di(lower alkyl)-substituted in the aryl ring but also groups which are mono- or di(lower alkyl)-substituted in the lower alkyl moiety. Exemplary of aryl(lower alkyl) groups are benzyl, phenylethyl, (lower alkyl)-benzyl, for example, methylbenzyl and dimethylbenzyl, naphthylmethyl, 2-phenyl-propan-2-yl, 1 -phenyl-1-ethyl, or the like.

Amorolfine is a member of the morpholines, which include ((2-azido-4-benzyl)phenoxy)-N-ethylmorpholine, (+)-(S)-5,5-dimethylmorpholinyl-2-acetic acid, (morpholinyl-2-methoxy)-8-tetrahydro-1,2,3,4-quinoline, 1,1'-hexamethylenebis(3-cyclohexyl-3-((cyclohexylimino)(4-morpholinyl)methyl)urea), 1,4-bis(3'-morpholinopropyl-1'-yl-1')benzene, 1,4-thiomorpholine-3,5-dicarboxylic acid, 1,4-thiomorpholine-3-carboxylic acid, 1-(morpholinomethyl)-4-phthalimidopiperidine-2,6- dione, 1-deoxy-1-morpholino-psicose, 1-deoxy-1-morpholinofructose, 1-phenyl-2,3-dimethyl-4-naphthalanmorpholinomethylpyrazolin-5-one, 1-phenyl-2-palmitoylamino-3-morpholino-1-propanol, 2,6-bis(carboxymethyl)-4,4-dimethylmorpholinium, 2,6-dimethylmorpholine, 2,6-dioxo-N-(carboxymethyl)morpholine, 2-(((3-(morpholinylmethyl)-2H-chromen-8-yl)oxy)methyl)morpholine, 2-(3-trifluoromethyl)phenyltetrahydro-1,4- oxazine, 2-(4-morpholino)ethyl-1-phenylcyclohexane-1-carboxylate, 2-(4-morpholino-6-propyl-1,3,5-triazin-2-yl)aminoethanol, 2-(4-morpholinyl)-4H-1-benzopyran-4-one, 2-(4-morpholinyl)-8-phenyl-4H-1-benzopyran-4-one, 2-(4-nitrophenyl)-4-isopropylmorpholine, 2-(morpholin-4-yl)benzo(h)chromen-4-one, 2-(N-methylmorpholinium)ethyl acetate, 2-(N-morpholino)ethanesulfonic acid, 2-benzylmorpholine, 2-hydroxy-4,4-dimethyl-2-(4-tolyl)morpholinium, 2-methyl-3-(2-methyl-2,3-diphenyl-4-morpholinyl)-1-phenyl-1-propanone, 2-

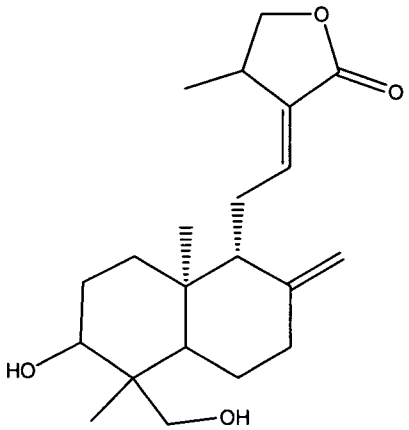
morpholinomethyl-2',3',4'-trimethoxyacrylophenone, 2-n-pentyloxy-2-phenyl-4-methylmorpholine, 2-phenyl-5,5-dimethyltetrahydro-1,4-oxazine, 2-thiomorpholinoethylacrylamide, 3,5,5-trimethyl-2-morpholinon-3-yl radical dimer, 3-((benzyloxy)methyl)morpholine, 3-(beta-morpholinoethoxy)-1H-indazole, 3-cyano-2-morpholino-5-(pyrid-4-yl)pyridine, 3-thiomorpholinopropylacrylamide, 4,4'-dithiodimorpholine, 4,4-methylenedimorpholine, 4-(2-morpholinoethoxy)benzophenone, 4-(3,7,11,15-tetramethyl-6,10,14-hexadecatrienoyl)morpholine, 4-amino-5-chloro-2-ethoxy-N-((2-morpholinyl)methyl)benzamide, 4-amino-N-((4-benzyl-2-morpholinyl)-methyl)-5-chloro-2-ethoxybenzamide, 4-amino-N-((4-benzyl-2-morpholinyl)methyl)-5-chloro-2-methoxybenzamide, 4-benzylphenoxy-N-ethylmorpholine, 4-cyclododecyl-2,6-dimethylmorpholine acetate, 4-methoxyphenyl-(5-methyl-6-(2-(4-morpholinyl)ethyl)-6H-thieno(2,3-b)pyrrol-4-yl)phenylmethanone, 4-methylmorpholine, 4-methylmorpholine N-oxide, 4-morpholinedithiocarbamate, 4-morpholinocarbonitrile, 5-pentyl-N-nitrosomorpholine, A 74273, AH 19437, aprepitant, AWD 140076, befol, BIBW 22, bis(3,5-dimethyl-5-hydroxymethyl-2-oxomorpholin-3-yl), BW 175, cetethyl morpholinium, CGP 53437, CI1033, ciclosidomine, CNK 6001, CNK 6004, CP 80794, CP 84364, CS 722, delmopinol, detensitral, Dextromoramide, di-beta-(morpholinoethyl)selenide, dimethomorph, dimethyl morpholinophosphoramidate, dimorpholamine, ES 6864, ES 8891, fenpropimorph, filenadol, FK 906, fominoben, FR 76830, Go 8288, GYKI 11679, indeloxazine, L 689502, L 742694, L 760735, landiolol, lateritin, M&B 16573, MDL 101146, MF 268, mofarotene, Molsidomine, morfolep, Moricizine, morlincain, moroxybrate, moroxydine, morpholine, morpholineoethylamino-3-benzocyclohepta(5,6-c)pyridazine, morpholinoamidine, morpholinophosphordichloridite, morpholinopropane

sulfonic acid, morpholinosulfonic acid, morpholinylethoxy-3-methyl-4-(2'-naphthyl)-6-pyridazine, mosapride, N,N'-dicyclohexyl-4-morpholinecarboxamidine, N-((4-benzyl-2-morpholinyl)methyl)-5-chloro-4-(dimethylamino)-2-methoxybenzamide, N-(3,N'-morpholinopropyl)-2-(3-nitropyrrolo-(2,3-b)pyridine-1-yl)ethanoic acid amide, N-(3-nitro-4-quinoline)morpholino-4-carboxamidine, N-dodecylmorpholine, N-ethylmorpholine, N-hexylmorpholine-2',5'-oligoadenylate, N-nitromorpholine, N-oxydiethylene-2-benzothiazole sulfenamide, O-(N-morpholinocarbonyl)-3-phenyllactic acid, oxaflozane, oxymorphindole, P 1487, P 34081, PD 132002, phendimetrazine, Phenmetrazine, phenyl 2-(2-N-morpholinoethoxy)phenyl ether, pholcodine, phosphorodiamidate morpholino oligomer, pinaverium, pramoxine, proctofoam-HC, promolate, RE 102, reboxetine, Ro 12-5637, Ro 12-8095, RS 1893, RV 538, S 12024, S 14001, S-anisylformamidino-4-(N-methylisothioamide)morpholine, S-phenethylformamidino-4-(N-ethylisothioamide)morpholine, SC 46944, Seda-Miroton, silatiemonium iodide, SIN 1C, SR 121463A, Stymulen, sufoxazine, teomorfolin, theniloxazine, thiamorpholine, tiemonium iodide, tiemonium methylsulfate, tridemorph, trifenmorph, trimetozine, trimorfamid, trithiozine, TVX 2656, U 37883A, U 84569, U 86983, UP 614-04, Viloxazine, Win 55212-2, and YM 21095.

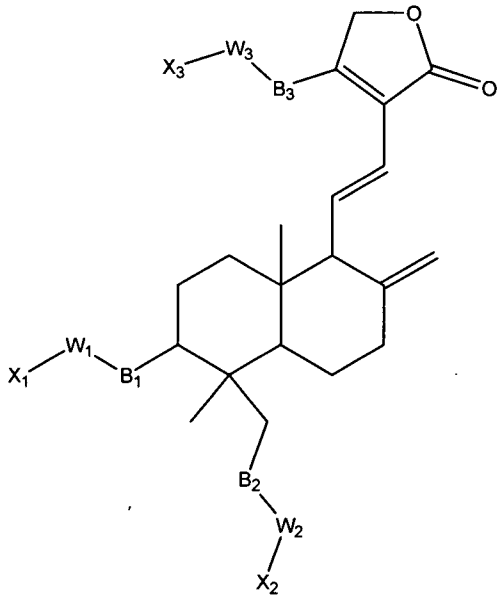
Andrographis

In certain embodiments, andrographis, or an extract or component thereof, can be used in the compositions, methods, and kits of the invention. *Andographis paniculata* is medicinal herb, which has been used as an antipyretic, an anti-inflammatory agent, and a liver protectant. It also is reported to have anticancer and antiviral (e.g., anti-HCV and anti-HIV)

properties. The primary active agent in andrographis is andrographolide. The structure of andrographolide is:



Andrographolide analogs are described, for example, in U.S. Pat. Application Publication No. 2006/0223785 and have the general structure:



or its cis isomer, or its pharmaceutically acceptable salt, ester, salt of an ester or prodrug, wherein: B_1, B_2 and B_3 are independently CR_1R_2, $C(Y_1)$, O, NR_4, PR_5, $P(=Y_2)R_6$, $P(=Y_3)_2$, $S(=Y_4)_k$, a spacer group or a covalent bond; and k can be 0, 1 or 2; and W_1, W_2 and W_3 are independently CR_7R_8, CR_9, C, $C(Y_5)$, O, NR_{10}, PR_{11}, $P(=Y_6)R_{12}$, $P(=Y_7)_2$, $S(=Y_8)_f$ or a covalent bond; and f can be 0, 1 or 2; or B_1–W_1, B_2–W_2, and/or B_3–W_3 are independently CR_3=CR_9 or C≡C; and X_1, X_2

and X_3 are independently hydrogen, $CR_{18}R_{19}R_{20}$, $C{=}R_{21}R_{22}$, $C{\equiv}R_{23}$, $C{\equiv}N$, $C(=Y_9)R_{24}$, OR_{25}, $NR_{26}R_{27}$, $N{=}NR_{28}$, $P(=Y_{10})_d(R_{29})V$, $S(=Y_{11})_d(R_{30})_i$ or NO_2; and d can be 0, 1 or 2; and v can be 0, 1 or 2; and i can be independently 0 or 1; and Y_1, Y_2, Y_3, Y_4, Y_5, Y_6, Y_7, Y_8, Y_9, Y_{10}, and Y_{11} are independently O, S, or NZ; and Z can be independently hydrogen, R_{13}, OR_{14}, SR_{15} or $NR_{16}R_{17}$; and R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, R_{29}, R_{30}, R_{31} and R_{32} are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, arylalkyl, heterocyclic, heteroaromatic, acyl, aldehyde, carbamide, alkoxy, amino, halogen, silyl, thiol, sulfoxy, sulfinyl, sulfamoyl, hydroxyl, ester, carboxylic acid, amide, nitro, cyano, phosphonyl, phosphinyl, phosphoryl, imide, thioester, ether, acid halide, oxime, carbamate, thioether, residue of a natural or synthetic amino acid or a carbohydrate, any of which can be optionally attached to the targeting moiety or oxygen radical through a spacer group; or alternatively, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, R_{29}, R_{30}, R_{31} and R_{32} can individually come together to form a bridged compound comprising of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, alkaryl, aryl alkyl, heterocyclic, heteroaromatic, acyl, carbamide, alkoxy, amino, halogen, silyl, thiol, sulfinyl, sulfamoyl, ester, amide, phosphonyl, phosphinyl, phosphoryl, imide, thioester, ether, oxime, carbamate, thioether, residue of a natural or synthetic amino acid or a carbohydrate, any of which can be optionally attached to the targeting moiety or oxygen radical through a spacer group; and each carbon atom cannot be covalently bound to more than two heteroatoms; and wherein each B, W and X cannot be all heteroatom moieties unless B, W and X are all nitrogen based or B and X are independently O or N and W is PR_{11}, POR_{12}, PO_2, $S(Y_4)_m$ and m is 1 or 2; and wherein each B

and W or W and X cannot both be of the general formula C(Y), POR_{12}, PO_2, $S(=Y_4)_t$ and t is 1 or 2.

In one subembodiment of formula I, B_1, B_2, and B_3 are independently CR_1R_2, $C(Y_1)$, O, or a covalent bond; W_1, W_2 and W_3 are independently CR_7R_8, CR_9, C, $C(Y_5)$, O, or a covalent bond; and X_1, X_2 and X_3 are independently hydrogen, $CR_{18}R_{19}R_{20}$, $C=R_{21}R_{22}$, $C\equiv R_{23}$. In one subembodiment of formula I, at least one of B_1, B_2, and B_3 and at least one W_1, W_2, and W_3 is a covalent bond and at least one X_1, X_2, and X_3 is hydrogen.

In another embodiment of the above formula, at least one R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, R_{29}, R_{30}, R_{31}, and R_{32} is selected from an aliphatic, saturated or unsaturated alkyl, alkenyl or alkynyl. In one subembodiment, the alkyl, alkenyl or alkynyl groups are substituted, and can be halogen substituted.

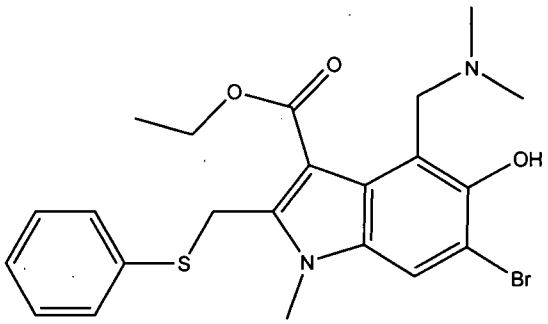
In one embodiment of the above formula, at least one R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, R_{29}, R_{30}, R_{31} and R_{32} is selected from a carbonyl containing groups, including, but not limited to, aldehyde, ketone, carboxylic acid, ester, amide, enone, acyl chloride or anhydride.

In one embodiment of the above formula, at least one R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, R_{29}, R_{30}, R_{31} and R_{32} is selected from an alkyl, aryl, heteroaryl or heteroaromatic ring.

In one embodiment of the above formula, at least one R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, R_{26}, R_{27}, R_{28}, R_{29}, R_{30}, R_{31} and R_{32} is independently selected from alkyl, nitro, a phosphate, a sulfate, a thiol, and an amine.

Arbidol

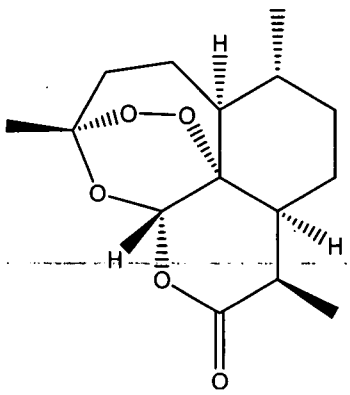
In certain embodiments, arbidol or an analog thereof can be used in the compositions, methods, and kits of the invention. Aribdol is an antiviral that has anti-influenza activity and functions by inhibition of the fusion of influenza A and B viruses within endosomes. The structure of arbidol is:



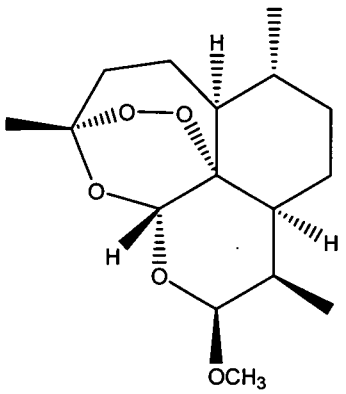
Arbidol is typically administered orally.

Artemisinins

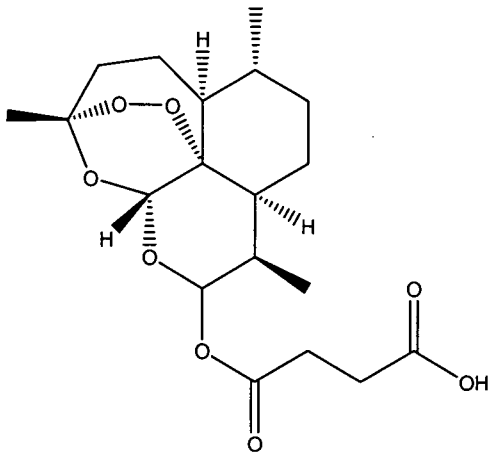
In certain embodiments, artemisinin or an analog thereof can be used in the compositions, methods, and kits of the invention. The artemeisins are a family of compounds that include antimalarials such as artemisinin and artemether, a semi-synthetic derivative of artemisinin. The structure of artemisinin is:



The structure of artemether is:



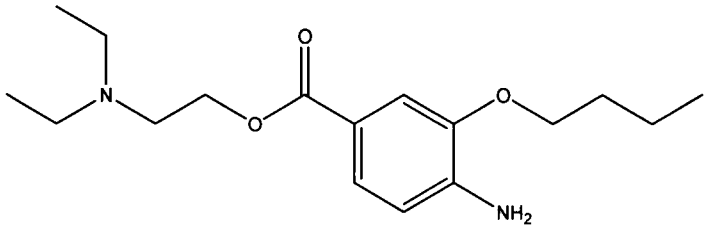
The structure of artesunate is:



Other artemisinins include 3-hydroxydeoxyartemisinin, α-propoxycarbonyldihydroartemisine, arteannuin B, arteether, arteflene, artelinic acid, artemether, artemisic acid, artemisin, artemisinin B, artemisinine, artemisitene, artesunate, artesunic acid, deoxoartemisinin, deoxyartemisinin, and dihydroquinghaosu. The active metabolite of artemisinins is dihydroartemisinin.

Benoxinate

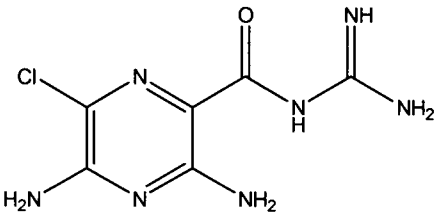
In certain embodiments, procaine or a derivative thereof such as benoxiante can be used in the compositions, methods, and kits of the invention. Benoxinate is an anesthetic agent. The structure of benoxinate is:



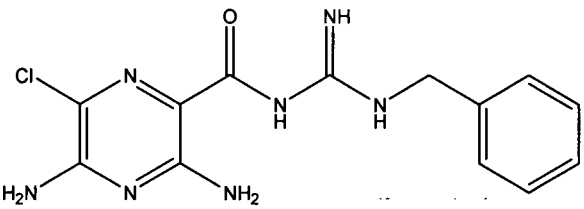
Benoxinate is a procaine derivative. Other procaine derivatives include 4-bromoacetamidoprocaine, analgesin, aslavital, benoxinate, bivelin, Cardioplegin, celnovocaine, chloroprocaine, efatin, Fluress, Impletol, impletol depot Bayer, N,N-diethylaminoethyl(2-N-methyl)benzoate, N-acetylprocaine, nicotinoylprocaine, novdimal, Penicillin G, Procaine, procaine acryloyl polymer, procaine azide, procaine isothiocyanate, Renovaine, sulfocamphocaine, Tardomyocel compound, and turigeran.

Amiloride

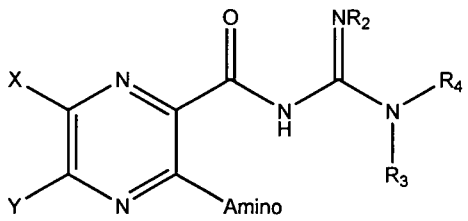
In certain embodiments, amiloride or an analog thereof such as benzamil can be used in the compositions, methods, and kits of the invention. Amiloride is a diuretic agent. The structure of amiloride is:



The structure of benzamil is:



Amiloride derivatives are described, for example, in U.S. Pat. No. 3,313,813 and can be represented by the following formula:



where X represents hydrogen, a halogen or halogen-like radical, such as, chloro, bromo, iodo or trifluoromethyl, or a lower-alkyl, lower-cycloalkyl, mononuclear aryl, either unsubstituted or substituted, advantageously with a halogen especially a chloro or bromo substituent, animo, Z-thio or Z-sulfonyl wherein Z is lower alkyl or phenyl-lower alkyl; Y represents hydrogen, hydroxyl or mercapto, lower alkoxy or lower alkyl-thio, halogen, especially chlorine, lower-alkyl, lower-cycloalkyl, mononuclear aryl, especially phenyl or amino, advantageously having the structure NRR_1, wherein R and R1 can be similar or dissimilar radicals and respectively represent hydrogen, amino or mono-or di-lower-alkylamino, (advantageously forming a hydrazino group at the 5-position carbon), lower alkoxy, Y represents substituted amino, $-NRR_1$, where R and R_1 represent lower alkyl either straight or branched chain or cyclic (3- to 6-membered rings) and either unsubstituted or containing one or more substituents such as hydroxyl, halogen (chlorine, bromine, fluorine and the like), a cycloalkyl substituent having 3 to 6 carbons in the cycloalkyl structure, an aryl substituent preferably phenyl or substituted phenyl such as lower-alkyl-phenyl and halophenyl as chlorophenyl, bromophenyl, fluorophenyl, and the like, or a heterocyclic substituent especially furyl, pyridyl, and $(CH_2)_nN-$ wherein n is one of the numerals 4 through 6, or an amino substituent as the unsubstituted amino, or mono- or di4ower-alkyl amino, and when R and R_1 each represents a lower alkyl, the lower alkyl groups can be linked together to form a cyclic structure with the nitrogen atom to which they are attached, particularly a 5- to 8-membered ring, advantageously forming with the nitrogen atom a 1-pyrrolidinyl, piperidino, hexahydro-1-azepinyl, or octahydro-1-

azocinyl radical and the like, Y represents substituted amino, $-NRR_1$, where R and R_1 represent lower alkenyl, aryl, advantageously an unsubstituted or substituted phenyl, wherein the substituent(s) are preferably halogen (chlorine, bromine, fluorine) or lower alkyl (methyl, ethyl, propyl, iso-propyl) and the like, amidino or substituted amidino, especially an N,N-di-lower alkyl-imidino, such as N,N-dimethylamidino; X and Y, in addition, can be linked together to form a 4-membered carbon chain that can be either unsaturated or saturated and that can be unsubstituted or substituted, and if substituted the substituent advantageously is a halogen, especially a chloro-atom. R_2 represents hydrogen and lower alkyl; R_3 represents hydrogen, lower alkyl, either saturated or unsaturated and substituted or unsubstituted, the substituent group(s) preferably being hydroxyl, aryl, either mono- or di-nuclear aryl, as phenyl or naphthyl, and either unsubstituted or containing one or more substituents, especially selected from lower alkyl, definition of substituents, continued substituents on aryl moiety of aryl-alkyl group halogen, lower alkyl, lower alkoxy, or any combination of these substituent groups, mono- or di-lower-alkylamino, wherein the alkyl groups may be linked to form a hetero structure with the aminonitrogen to which they are attached such as to form an azacycloalkyl group, heterocyclic, and especially the pyridyl group, halogen, aryl or substituted aryl, the substituent group(s) preferably being halogen, and lower alkyl, heterocyclic, advantageously a pyridyl radical, alkylideneamirio, and acyl; R_4 represents hydrogen, lower alkyl, either saturated or unsaturated and substituted or unsubstituted as described above for R_3 or R_3 and R_4 can be lower alkyl groups linked directly together or through a hetero atom, especially through oxygen or nitrogen to produce a 5 to 8 membered cyclic structure, thus forming with the nitrogen atom to which they are attached a 1-pyrrolidinyl, piperidino, 1-piperazinyl, especially a 4-lower alkyl-1-piperazinyl or

morpholino, and the like radicals; and when R_2 and R_3 (or R_4) each represents a lower alkyl, they can be linked together to form a cyclic structure with the nitrogen atoms to which they are attached, particularly to form a 2-(2-imidazolinyl) radical. The 3-position amino group can be an unsubstituted amino as well as mono- or di-substituted amino groups, the substituent(s) advantageously being lower alkyl and lower alkanoyl and also where the substituents are linked to form a heterocyclic structure with the amino nitrogen to which they are attached.

Amiloride derivatives include 2',4'-dichlorobenzamil amiloride, 2',4'-dimethylbenzamil, 2'-methoxy-5'-nitrobenzamil, 2-chlorobenzylamiloride, 3',4'-dichlorobenzamil, 3,5-diamino-6-fluoro-2-pyrazinoylguanidine, 3,5-diamino-N-(aminoiminomethyl)-6-bromopyrazine-N-methylcarboxamide, 4-(((((3,5-diamino-6-chloropyrazinyl)carbonyl)amino)iminomethyl)amino)-2,2,6,6-tetramethyl-1-piperidinyloxy, 5,6-dichloroamiloride, 5-(ethylpropyl)amiloride, 5-(N,N-hexamethylene)amiloride, 5-(N-2'-(4''-azidosalicylamidino)ethyl-N'-isopropyl)amiloride, 5-(N-2'-aminoethyl-N'-isopropyl)amiloride-N-(4''-azidosalicylamide), 5-(N-4-chlorobenzyl)-N-(2',4'-dimethyl)benzamil, 5-(N-butyl-N-methyl)amiloride, 5-(N-ethyl-(2'-methoxy-5'-nitrobenzyl))amiloride, 5-(N-methyl-N-isobutyl)amiloride, 5-(N-methyl-N-propyl)amiloride, 5-(N-propyl-N-butyl)-2',4'-dichlorobenzamil amiloride, 5-(N-tert-butyl)amiloride, 5-diethylamiloride, 5-dimethylamiloride, 5-N-(3-aminophenyl)amiloride, 5H-amiloride, 6-bromoamiloride, 6-bromobenzamil, 6-chloro-3,5-diaminopyrazine-3-carboxamide, 6-iodoamiloride, alpha',2'-benzobenzamil, amiloride caproate, benzamil, co-amilozide, Esmalorid, ethylisopropylamiloride, frumil, kalten, methylisopropylamiloride, moducrin, N(5)-piperazine-amiloride, N(5)-piperidine-amiloride, phenylamil, and uranidil A.

Ergotamine alkaloids

In certain embodiments, ergotamine alkaloids such as bromocriptine, can be used in the compositions, methods, and kits of the invention. Bromocriptin analogs are described, for example, in U.S. Pat. No. 4,145,549. Ergotamine alkaliods include 1-methylergotamine, 9,10-dihydroergosine, bellataminal, Bellergal, beta-ergoptine, Bromocriptine, dihydroergocornine, dihydroergocristine, dihydroergocryptine, dihydroergotamine, dihydroergotoxine, ergosine, ergotamine, ergovaline, and neo-secatropin.

Chlorophyllin

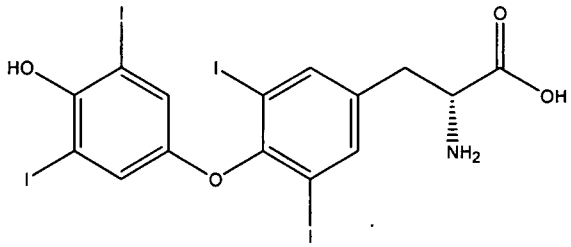
In certain embodiments, a chlorophyllide or an analog thereof can be used in the compositions, methods, and kits of the invention. Chlorophyllin is a derivative of chlorophyl, and a member of the chlorophyllides. Other chlorophyllides include chlorophyllide a, chlorophyllide b,methylchlorophyllide A, and methylchlorophyllide B.

Cytarabine

In certain embodiments, cytarabine or an analog thereof can be used in the compositions, methods, and kits of the invention. Cytarabine is an antimetabolic and an antiviral agent. Cytarabine analogs are described in U.S. Pat. No. 3,116,282.

Thyroxines

In certain embodiments, a thyroxine or derivative thereof can be used in the compositions, methods, and kits of the invention. Thyroxines are thyroid horomones and include levo thyroxine and dextrothyroxine, which has been used as antihyperlipidemic. The formula for dextrthyroxine is:



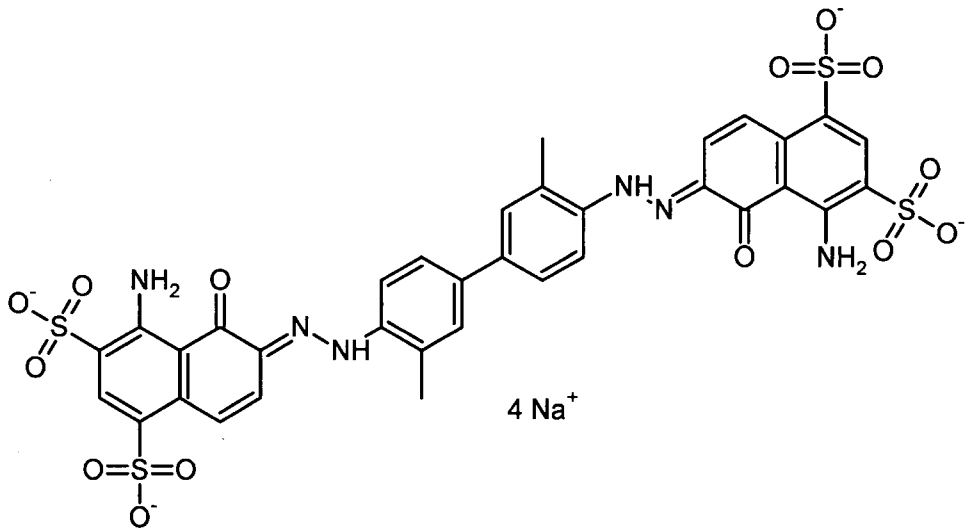
Dextrathyroxine can be administered orally and is typically provided in 2 mg or 4 mg tablets. Levothyroxine is used to increase the metabolic rate of cells.

Pregnadienes

In certain embodiments, a pregnadiene or an analog or derivative thereof such as dydrogesterone can be used in the compositions, methods, and kits of the invention. Dydrogesterone is a progesterone and used thus to treat progesterone deficiency. Pregnadienes include 12-hydroxy-3-oxo-1,4-pregnadiene-20-carboxylic acid, 17-benzoyloxy-11-hydroxy-3,20-dioxo-1,4-pregnadien-21-al hemiacetal, 20-carboxy-1,4-pregnadien-3-one, 20-succinamylpregna-1,4-dien-3-one, 21-hydroxypregna-1,4-diene-3,11,20-trione, 3 alpha-hydroxy-5 alpha-pregna-9(11),16-diene-20-one, 3-hydroxy-5,7-pregnadien-20-one, canrenoate potassium, canrenone, chlormadinone acetate, cymegesolate, cyproterone, danazol, domoprednate, fluocinolone acetonide, GR 2-1159, icometasone enbutate, medrogestone, megestrol, melengestrol acetate, nivazol, oxyma, pregnadienediols, pregnadienetriols, rimexolone, Ro 12-2503, Ro 14-9012, Ro 6-1963, and triamcinolone.

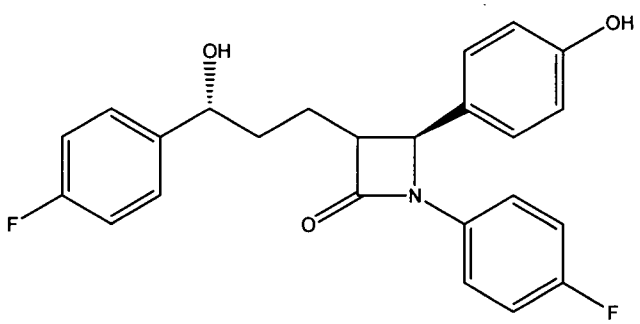
Evans blue

In certain embodiments, a azo dye such as Evans blue can be used in the compositions, methods, and kits of the invention. Evans blue is used in blood volume and cardiac output measurement by the dye dilution method. It is very soluble, strongly bound to plasma albumin. The structure of Evans blue is:

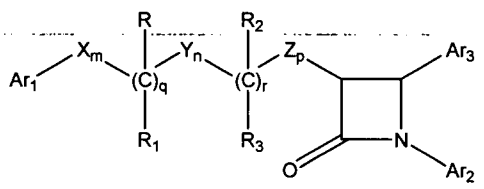


Azetidines

In certain embodiments, an azetidine or derivative thereof such as ezitamibe can be used in the compositions, methods, and kits of the invention. The structure of ezitamibe is:



Analogs of ezitamibe are described, for example, in U.S. Pat. No. 5,767,115 and are described by the formula:



where Ar_1 and Ar_2 are independently selected from the group consisting of aryl and R_4 -substituted aryl; Ar_3 is aryl or R_5-substituted aryl; X, Y and Z are independently selected from the group consisting of $-CH_2-$, –CH(lower alkyl)– and –C(dilower alkyl)–; R and R_2 are independently selected from the group consisting of $-OR_6$, $-O(CO)R_6$, $-O(CO)OR_9$ and $-O(CO)NR_6R_7$; R_1 and R_3 are independently selected from the group consisting of hydrogen, lower alkyl and aryl; q is 0 or 1; r is 0 or 1; m, n and p are independently 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1, 2, 3, 4, 5 or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is1, 2, 3, 4 or5; R_4 is 1-5 substituents independently selected from the group consisting of lower alkyl, $-OR_6$, $-O(CO)R_6$, $-O(CO)OR_9$, $-O(CH_2)_{1-5}OR_6$, $-O(CO)NR_6R_7$, $-NR_6R_7$, $-NR_6(CO)R_7$, $-NR_6(CO)OR_9$, $-NR_6(CO)NR_7R_8$, $-NR_6SO_2R_9$, $-COOR_6$, $-CONR_6R_7$, $-COR_6$, $-SO_2NR_6R_7$, $S(O)_{0-2}R_9$, $-O(CH_2)_{1-10}-COOR_6$, $-O(CH_2)_{1-10}CONR_6R_7$, –(lower alkylene)$COOR_6$, –CH=CH–$COOR_6$, $-CF_3$, $-CN$, $-NO_2$ and halogen; R_5 is 1-5 substituents independently selected from the group consisting of $-OR_6$, $-O(CO)R_6$, $-O(CO)OR_9$, $-O(CH_2)_{1-5}OR_6$, $-O(CO)NR_6R_7$, $-NR_6R_7$, $-NR_6(CO)R_7$, $-NR_6(CO)OR_9$, $-NR_6(CO)NR_7R_8$, $-NR_6SO_2R_9$, $-COOR_6$, $-CONR_6R_7$, $-COR_6$, $-SO_2NR_6R_7$, $S(O)_{0-2}R_9$, $-O(CH_2)_{1-10}-COOR_6$, $-O(CH_2)_{1-10}CONR_6R_7$, –(lower alkylene)$COOR_6$ and –CH=CH–$COOR_6$; R_6, R_7 and R_8 are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and R_9 is lower alkyl, aryl or aryl-substituted lower alkyl. R_4 is preferably 1-3 independently selected substituents, and R_5 is preferably 1-3 independently selected substituents. Preferred are compounds of formula I wherein Ar_1 is phenyl or R_4 -substituted phenyl, especially (4-R_4)-substituted phenyl. Ar_2 is preferably phenyl or R_4 -substituted phenyl, especially (4-R_4)-substituted phenyl. Ar_3 is preferably R_5 -substituted phenyl, especially (4-R_5)-substituted phenyl. When

Ar_1 is (4-R_4)-substituted phenyl, R_4 is preferably a halogen. When Ar_2 and Ar_3 are R_4 - and R_5 -substituted phenyl, respectively, R_4 is preferably halogen or –OR_6 and R_5 is preferably –OR_6, wherein R_6 is lower alkyl or hydrogen. Especially preferred are compounds wherein each of Ar_1 and Ar_2 is 4-fluorophenyl and Ar_3 is 4-hydroxyphenyl or 4-methoxyphenyl.

Other azetidines include 1,4-bis(4-methoxyphenyl)-3-(3-phenylpropyl)-2-azetidinone, 1-(N-(3-ammoniopropyl)-N-(n-propyl)amino)diazen-1-ium-1,2-diolate, 1-methyl-2-(3-pyridyl)azetidine, 2-oxo-3-phenyl-1,3-oxazetidine, 2-tetradecylglycidyl-coenzyme A, 3-(2-oxopropylidene)azetidin-2-one, 3-aminonocardicinic acid, 3-phenyl-2-methylazetidine-3-ol, 4-((4-carboxyphenyl)oxy)-3,3-diethyl-1-(((phenylmethyl)amino)carbonyl)-2-azetidinone, 4-(3-amino-2-oxoazetidinonyl-1)methylbenzoic acid, 4-(3-amino-2-oxoazetidinonyl-1)methylcyclohexanecarboxylic acid, AHR 11748, azetidine, azetidine platinum(II), azetidinecarboxylic acid, azetidyl-2-carboxylic acid, azetirelin, BDF 9148, BMS-262084, E 4695, fluzinamide, L 652117, L 684248, N-(2-chloromethylphenyl)-3,3-difluoroazetidin-2-one, SCH 60663, SF 2185, tabtoxinine beta-lactam, tazadolene succinate, and ximelagatran.

Thioxanthanes

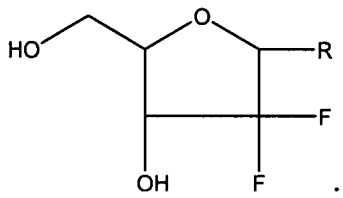
In certain embodiments, thioxanthanes such as flupentixol can be used in the compositions, methods, and kits of the invention. Flupentixol is a antipsychotic that acts as a dopamine (D2 receptor) antagonist. Thioxanthane analogs are described, for example, in U.S. Pat. No. 3,951,961. Thioxanthane analogs include 2-(beta-diethylaminoethylamino)-3,4-cyclohexenothiaxanthone, 2-chlorothioxanthen-9-one, 2-thioxanthene, 3-carboxy-thioxanthone-10,10-dioxide, 4-(beta-diethylaminoethylamino)-1,2-cyclohexenothiaxanthone, 4-(bis(2'-chloroethyl)amino)propylamino-1,2-cyclohexenothioxanthone, 7-oxo-

7-thiomethoxyxanthone-2-carboxylic acid, BW 616U76, chlorprothixene, clopenthixol, doxantrazole, flupenthixol, hycanthone, lucanthone, methixene, piflutixol, pimethixene, prothixene, quantacure QTX, spasmocanulase, teflutixol, thiothixene, and WIN 33377.

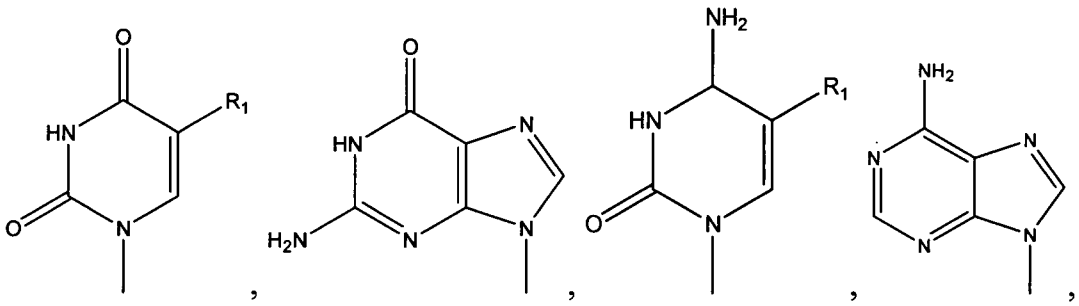
Gemcitabine

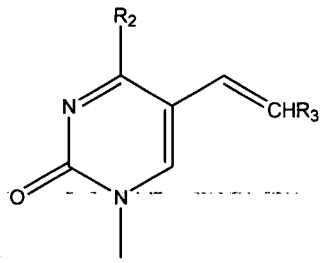
In certain embodiments, gemcitabine or an analog thereof can be used in the compositions, methods, and kits of the invention. Gemcitabine is a nucleoside with antineoplastic activity.

Analogs of gemcitabine are described, for example, in U.S. Pat. No. 4,808,614 and have the general structure:



wherein R is a base of one of the formulae:



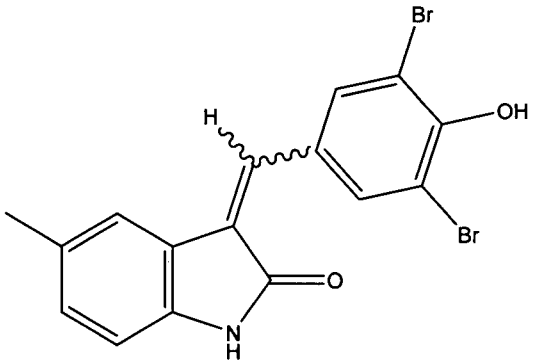


and

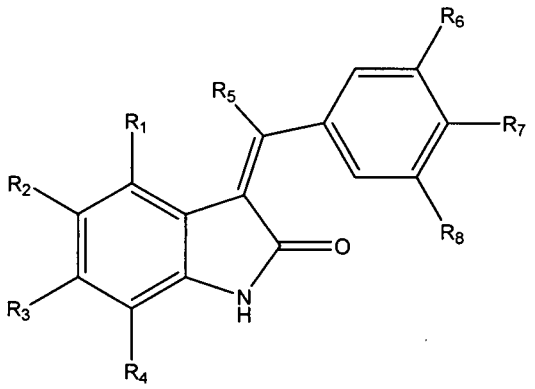
wherein R_1 is hydrogen, methyl, bromo, fluoro, chloro, or iodo; R_2 is hydroxy or amino; R_3 is hydrogen, bromo, chloro, or iodo.

GW 5074

In certain embodiments, GW 5074 or an analog thereof can be used in the compositions, methods, and kits of the invention. GW 5074 is a benzylidene-1,3-dihydro-indol-2-one derivative which acts as a receptor tyrosine kinase inhibitor (e.g., raf, such as cRaf1). The structure of GW 5074 is:



Analogs of GW 5074 are described, for example, in U.S. Pat. No. 6,268,391 and have the general structure:



wherein R_1 is H or optionally joined with R_2 to form a fused ring selected from the group consisting of five to ten membered aryl, heteroaryl or heterocyclyl rings, said heteroaryl or said heterocyclyl rings having one to three heteroatoms where zero to three of said heteroatoms are N and zero to 1 of said heteroatoms are O or S and where said fused ring is optionally substituted by one to three of R_9, where R_2 and R_9 are as defined below; R_2 and R_3 are independently H,

HET, aryl, C_{1-12} aliphatic, CN, NO_2, halogen, R_{10}, $-OR_{10}$, $-SR_{10}$, $-S(O)R_{10}$, $-SO_2R_{10}$, $-NR_{10}R_{11}$, $-NR_{11}R_{12}$, $-NR_{12}COR_{11}$, $-NR_{12}CO_2R_{11}$, $-NR_{12}CONR_{11}R_{12}$, $-NR_{12}SO_2R_{11}$, $-NR_{12}C(NR_{12})NHR_{11}$, $-COR_{11}$, $-CO_2R_{11}$, $-CONR_{12}R_{11}$, $-SO_2NR_{12}R_{11}$, $-OCONR_{12}R_{11}$, $C(NR_{12})NR_{12}R_{11}$ where said C_{1-12} aliphatic optionally bears one or two insertions of one to two groups selected from C(O), O, S, S(O), SO_2 or NR_{12}; with said HET, aryl or C_{1-12} aliphatic being optionally substituted by one to three of R_{10}; and where R_2 is optionally joined with R_3 to form a fused ring selected from the group consisting of five to ten membered aryl, heteroaryl or heterocyclyl rings, said heteroaryl or said heterocyclyl rings having zero to three heteroatoms where zero to three of said heteroatoms are N and zero to one of said heteroatoms are O or S and where said fused ring is optionally substituted by one to three of R_9, where HET, R_9, R_{10}, R_{11} and R_{12} are as defined below; R_4 is H, halogen, NO_2 or CN; R_5 is H or C_{1-12} aliphatic optionally substituted by one to three of halo, hydroxyl, heteroaryl, or aryl; R_6 and R_7 are independently halogen, CN, NO_2, $-CONR_{10}R_{11}$, $-SO_2NR_{10}R_{11}$, $-NR_{10}R_{11}$, or $-OR_{11}$, where R_{10} and R_{11} are as defined below; R_8 is OH, $NHSO_2R_{12}$ or $NHCOCF_3$; R_9 is each independently halogen, C_{1-12} aliphatic, CN, $-NO_2$, R_{10}, $-OR_{11}$, $-SR_{11}$, $-S(O)R_{10}$, $-SO_2R_{10}$, $-NR_{10}R_{11}$, $-N_{11}R_{12}$, $-NR_{12}COR_{11}$, $-NR_{12}CO_2R_{11}$, $-NR_{12}CONR_{11}R_{12}$, $-NR_{12}SO_2R_{11}$, $-NR_{12}C(NR_{12})NHR_{11}$, $-CO_2R_{11}$, $-CONR_{12}R_{11}$, $-SO_2NR_{12}R_{11}$, $-OCONR_{12}R_{11}$ or $C(NR_{12})NR_{12}R_{11}$, where R_{10}, R_{11} and R_{12} are as defined below; R_{10} is each independently H, halogen, C_{1-12} aliphatic, aryl or HET, where said C_{1-12} aliphatic optionally bears an inserted one to two groups selected from O, S, S(O), SO_2 or NR_{12}, where said C_{1-12} aliphatic, aryl or HET is optionally substituted by one to three of halo, another HET, aryl, CN, $-SR_{12}$, $-OR_{12}$, $-N(R_{12})_2$, $-S(O)R_{12}$, $-SO_2R_{12}$, $-SO_2N(R_{12})_2$, $-NR_{12}COR_{12}$, $-NR_{12}CO_2R_{12}$, $-NR_{12}CON(R_{12})_2$, $-NR_{12}(NR_{12})NHR_{12}$, $-CO_2R_{12}$, $-CON(R_{12})_2$, $-NR_{12}SO_2R_{12}$, $-$

$OCON(R_{12})_2$, where HET and R_{12} are as defined below; R_{11} is H or R_{10}; R_{12} is H, C_{1-12} aliphatic or HET, said C_{1-12} aliphatic optionally substituted by one to three of halogen or OH where HET is as defined below; and HET is a five to ten-membered saturated or unsaturated heterocyclic ring selected from the group consisting of benzofuran, benzoxazole, dioxin, dioxane, dioxolane, dithiane, dithiazine, dithiazoie, dithiolane, furan, imidazole, indole, indazole, morpholine, oxazole, oxadiazole, oxathiazole, oxathiazolidine, oxazine, oxiadiazine, piperazine, piperidine, pyran, pyrazine, pyrazole, pyridine, pyrimidine, pyrrole, pyrrolidine, quinoline, quinazoline, tetrahydrofuran, tetrazine, tetrazole, thiophene, thiadiazine, thiadiazole, thiatriazole, thiazine, thiazole, thiomorpholine, thianaphthalene, thiopyran, triazine, and triazole; and the pharmaceutically acceptable salts, biohydrolyzable esters, biohydolyzable amides, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, solvates, hydrates, or prodrugs of the as defined above.

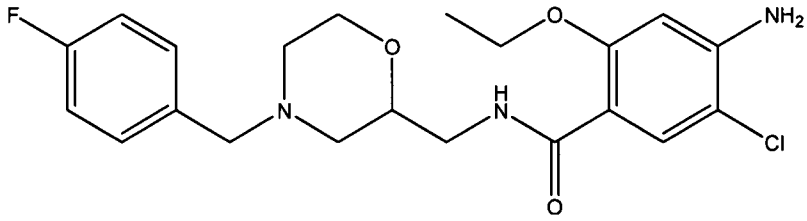
Melphalan

In certain embodiments, melphalan or an analog thereof can be used in the compositions, methods, and kits of the invention. Melphalan is an alkylating nitrogen mustard used as an antineoplastic in the form of the levo isomer, melphalan. The racemic mixture is merphalan, and the dextro isomer is medphalan. Melphalan analogs are described, for example, in U.S. Pat. No. 3,032,584.

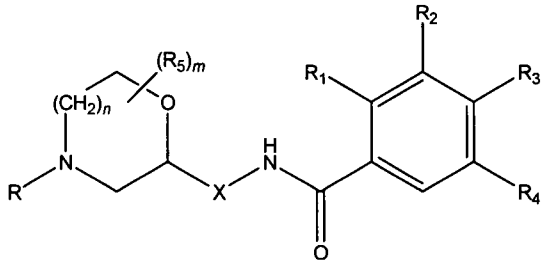
Mosapride

In certain embodiments, mosapride or an analog thereof can be used in the compositions, methods, and kits of the invention. Mosapride is a

benzamide that acts as a selective 5-HT_4 receptor agonist and is used as a gastroprokinetic. The structure of mosparide is:



Analogs of mosparide are described, for example, in U.S. Pat. No. 4,870,074 and have the general structure:



wherein R is hydrogen, a C_2-C_5 alkoxycarbonyl, benzyloxycarbonyl, a heteroaryl(C_1-C_3)alkyl in which the heteroaryl is furyl, thienyl, pyridyl, or 1,2-benzisoxazolyl, a phenyl(C_3-C_5)alkenyl, or –T–$(Y)_p$–R_6 (wherein T is a single bond or a C_1-C_6 alkylene, Y is oxygen, sulfur or carbonyl, R_6 is phenyl, a phenyl substituted by one to five members each independently selected from the group consisting of a halogen, a C_1-C_4 alkyl, trifluoromethyl, a C_1-C_4 alkoxy, nitro, cyano and amino, naphthyl, or diphenylmethyl, and p is 0 or 1, provided that when T is a single bond, p is 0), R_1 is a halogen, hydroxy, a C_1-C_{12} alkoxy, a C_3-C_6 cycloalkyloxy, a C_3-C_8 alkenyloxy, a C_3-C_8 alkynyloxy, a C_2-C_6 alkoxy interrupted by one or two oxygens or carbonyls, a C_1-C_4 alkylthio, amino, a monosubstituted amino in which the substituted is a C_1-C_8 alkyl, a phenyl(C_1-C_3)alkyl or a C_3-C_6 cycloalkyl, a C_2-C_6 alkoxy in which the carbon atom at any position other than the 1-position is substituted by one hydroxy or amino, or a substituted C_1-C_6 alkoxy in which the substituent is a halogen, cyano, a C_2-C_5 alkoxycarbonyl, phthalimido, a C_3-C_6 cycloalkyl, a phenyl optionally

substituted by one halogen, a phenoxy optionally substituted by one halogen, or a benzoyl optionally substituted by one halogen, R_2 is hydrogen, R_3 is hydrogen, a halogen, amino, a C_1-C_4 alkylamino, a di(C_1-C_4 alkyl)amino, a C_2-C_5 alkanoylamino, or nitro, R_4 is hydrogen, a halogen, nitro, sulfamoyl, a C_1-C_4 alkylsulfamoyl, or a di(C_1-C_4 alkyl)sulfamoyl, or any two adjacent groups of the R_1, R_2, R_3 and R_4 combine to form a C_1-C_3 alkylenedioxy, and the remaining two groups are each hydrogen, R_5 is hydrogen or a C_1-C_4 alkyl, X is a C_1-C_3 alkylene, and m and n are each 1 or 2, provided that at least one of the groups R_2, R_3 and R_4 is not hydrogen.

Mosapride is a benzamide. Other benzamides include 1-((4-fluorobenzoylamino)ethyl)-4-(7-methoxy-1-naphthyl)piperazine hydrochloride, 1-(3,4-dihydroxyphenyl)-2-(3-(4-carbamylphenyl)-1-methylpropylamino)ethanol, 1-nitrohydroxyphenyl-N-benzoylalanine, 2,2'-dithiobis(N-2-hydroxypropylbenzamide), 2,3-dimethoxy-5-iodo-N-((1-(4'-fluorobenzyl)-2-pyrrolidinyl)methyl)benzamide, 2,3-dimethoxy-N-(1-(4-fluorobenzyl)piperidin-4-yl)benzamide, 2,3-dimethoxy-N-(9-(4-fluorobenzyl)-9-azabicyclo(3.3.1)nonan-3-yl)benzamide, 2,4-dichloro-6-nitrophenolamide, 2,6-dichlorobenzamide, 2,6-difluorobenzamide, 2-(2-chloro-4-iodophenylamino)-N-cyclopropylmethoxy-3,4-difluoro-5-bromobenzamide, 2-chlorobenzamide, 2-hexyloxybenzamide, 2-methoxy-4-fluoro-3-amino-N-((2-methylcyclopropylamino)ethyl)benzamide, 264 CP, 3,4,5-trimethoxybenzamide, 3,4-dichloro-N,N-di-sec-butylbenzamide, 3-(3-(dimethylamino)propyl)-4-hydroxy-N-(4-(4-pyridinyl)phenyl)benzamide, 3-(cyclopentyloxy)-N-(3,5-dichloro-4-pyridyl)-4-methoxybenzamide, 3-(N-butyrylamino)benzamide, 3-acetamidobenzamide, 3-aminobenzamide, 3-carbamyl-(3'-picolyl)-4-methoxy-1-benzamide, 3-chloro-N-(4,6-dimethyl-2-pyridiny)benzamide, 3-iodo-2-hydroxy-6-methoxy-N-((1-ethyl-2-

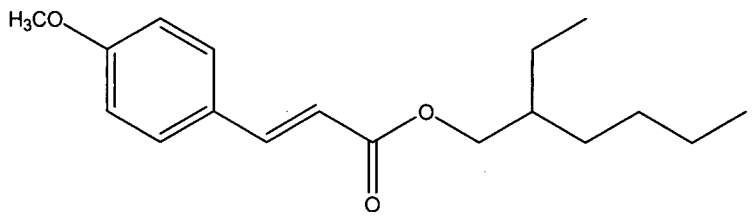
pyrrolidinyl)methyl)benzamide, 3-methoxybenzamide, 3-nitrosobenzamide, 4-((methylsulfonyl)amino)-N-((4-phenylpiperazin-2-yl)methyl)benzamide, 4-(1H-tetrazol-5-yl)-N-(4-(1H-tetrazol-5-yl)phenyl)benzamide, 4-(3-(2-hydroxy-2-phenyl)ethylamino-3-methylbutyl)benzamide, 4-(5-benzo(1,3)dioxol-5-yl-4-pyridin-2-yl-1H-imidazol-2-yl)benzamide, 4-(alpha-(4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl)-N,N-diethylbenzamide, 4-(trifluoromethyl)benzamide, 4-amino-5-chloro-2-ethoxy-N-((2-morpholinyl)methyl)benzamide, 4-amino-N-((4-benzyl-2-morpholinyl)-methyl)-5-chloro-2-ethoxybenzamide, 4-amino-N-((4-benzyl-2-morpholinyl)methyl)-5-chloro-2-methoxybenzamide, 4-aminobenzamidopyridine, 4-azido-5-iodoclebopride, 4-chloro-N-(hydroxymethyl)benzamide, 4-diethoxyphosphorylmethyl-N-(4-bromo-2-cyanophenyl)benzamide, 4-dimethylamino-N-(4-(2-hydroxycarbamoylvinyl)benzyl)benzamide, 4-fluorobenzamide, 4-fluorobenzylamine, 4-hydroxybenzamide, 4-iodo-N-(2-(4-morpholinyl)ethyl)benzamide, 4-iodo-N-piperidinoethylbenzamide, 5-(aziridin-1-yl)-2-nitro-4-nitrosobenzamide, 5-bromo-2,3-dimethoxy-N-((1-(4-fluorobenzyl)-2-pyrrolidinyl)methyl)benzamide, 5-bromo-2-ethoxybenzamide, 5-fluoropropylepidepride, 7-(3-(2-(cyclopropylmethyl)-3-methoxy-4-((methylamino)carbonyl)phenoxy)propoxy)-3,4-dihydro-8-propyl-2H-1-benzopyran-2-propanoic acid, A 22700, AH 7921, aklomide, alloclamide, ameltolide, azapride, BA 74, befol, benodanil, benzamide, benzamide adenine nucleotide, benzcoprine, benzotripte, bis(2-(N-phenylcarboxamido)phenyl)diselenide, BRL 24682, BRL 32872, BRL 34778, bromadoline, bromtianide, brovanexine, BW 373U86, BWA 466C, BWA 728C, Card-Instenon, cinitapride, Cisapride, clebopride, cloxacepride, dazopride, DEET, dehydroxymethylepoxyquinomicin, desbenzylclebopride,

Diethyltoluamide-20, dimetpramid, Dinitolmide, dobupride, ecabapide, EL 494, epidepride, ethamivan, ethyl 2-(4'-carboxybenzamido)-4-aminobenzoate, ethyl 2-(4'-carboxybenzamido)-4-propionamidobenzoate, FLA 981, flatoril, FLB 524, fluoroclebopride, fluphenacur, flurfamide, fomesafen, gentisamide, GGTI 297, GGTI 298, GRI 1665, GW 300, GW 532, GW 575, hexafluoron, Hippurates, HMR 1098, Indoramin, Instenon, iodopride, iofratol, isoxaben, itopride, L 1215, L 7063, LY 135114, LY 188544, LY 201409, meglitinide, Metoclopramide, Moclobemide, N(1)-(4-chlorobenzoyl)-N(2)-(1-(1-naphthyl)ethyl)-1,2-diaminocyclohexane, N,N-dimethylbenzamide, N-((4-benzyl-2-morpholinyl)methyl)-5-chloro-4-(dimethylamino)-2-methoxybenzamide, N-((4-methylphenyl)sulfonyl)-3-(2-quinolinylmethoxy)benzamide, N-(1'-benzyl-4'-piperidyl-N-oxide)-4-amino-5-chloro-2-methoxybenzamide, N-(2,6-dimethylphenyl)-4-(((diethylamino)acetyl)amino)benzamide, N-(2-(diethylamino)ethyl)-4-iodobenzamide, N-(2-(diethylamino)ethyl)benzamide, N-(2-aminocyclohexyl)-3,4-dichlorobenzamide, N-(2-aminoethyl)-2-anisamide, N-(2-aminophenyl)-4-(N-(pyridin-3-ylmethoxycarbonyl)aminomethyl)benzamide, N-(2-dimethylaminoethyl)-2-anisamide, N-(2-methylaminocyclohexyl)-3,4-dichlorobenzamide, N-(2-picolyl)-3,5-dimethylbenzamide, N-(3,4,5-trimethoxybenzoyloxy)-3,4,5-trimethoxybenzamide, N-(3-picolyl)-3,5-dimethylbenzamide, N-(4'-(delta-1'-piperidyl-N-oxide))-4-amino-5-chloro-2-methoxybenzamide, N-(4'-(N-hydroxypiperidyl))-4-amino-5-chloro-2-methoxybenzamide, N-(4,6-dimethyl-2-pyridinyl)benzamide, N-(4-(2-(dimethylamino)ethoxy)benzyl)-3,4-dimethoxybenzmide, N-(4-(5-bromo-2-pyrimidinyloxy)-3-chlorophenyl)-N'-(2-nitrobenzoyl)urea, N-(4-acetyl-1-piperazinyl) -4-fluorobenzamide monohydrate, N-(4-amino-1-butyl)-N-nitrosobenzamide, N-(4-chlorobenzoyl)-N-methyl-4-(4-

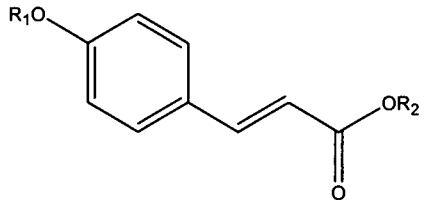
dimethylaminomethylphenyl)cyclohexylamine, N-(acetoxymethyl)-4-chlorobenzamide, N-(exo-(hexahydro-1H-pyrrolizine-1-yl)methyl)-2-methoxy-4-amino-5-chlorobenzamide, N-(N-benzylpiperidin-4-yl)-4-iodobenzamide, N-2-fluorenylbenzamide, N-acetylbenzamide, N-butyrylbenzamide, N-demethylbromadoline, N-didemethylbromadoline, N-ethylbenzamide, N-formylbenzamide, N-hydroxymethyl-N-methylbenzamide, N-hydroxymethylbenzamide, N-isopropyl-4-hydroxymethylbenzamide, N-methyl-2,3-dihydroxybenzamide, N-methylbenzamide, N-octyl-3-nitro-2,4,6-trihydroxybenzamide, N-propionylbenzamide, N-pyrimidinobenzamide-2-carboxylic acid, nemonapride, nitromide, norcisapride, NP 101A, pancopride, parsalmide, Pellit, penfluron, picobenzide, picobenzide N-oxide, Procainamide, Procarbazine, pronamide, Raclopride, rebemide, Remoxipride, renzapride, RG-4, RG-7, riparin, Ro 12-5637, Ro 12-8095, Ro 16-3177, Ro 16-6491, roflumilast, S 1688, SC 53116, sirtinol, SNC 121, spectramide, SR 48968, Sulpiride, T 0070907, teflubenzuron, tegalide, Tiapride, tonabersat, triflumuron, trimethobenzamide, WAY 100289, YM-08050, Z 338, and zacopride.

Octyl methoxycinnamate

In certain embodiments, telaprevir or an analog thereof can be used in the compositions, methods, and kits of the invention. Octyl methoxycinnamate absorbs ultraviolet (UV) light and is used in sunscreens and other topical applications where UV protection is desired. The structure of octyl methoxycinnamte is:



Cinnamic acid derivatives are described, for example, in U.S. Pat. No. 5,457,226 and have the general structure:



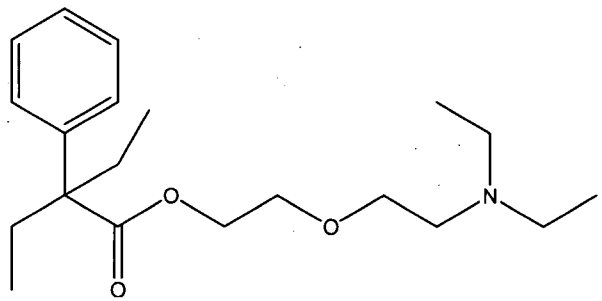
wherein R_1 signifies hydrogen or C_{1-8}-alkyl and R_2 signifies hydrogen, C_{1-10}-alkyl, C_{1-10}-hydroxyalkyl or C_{1-4}-alkoxy-C_{1-10}-alkyl. Cinnamic acid derivative include Other cinnmates include (4-(dimethylamino)cinnamoyl)imidazole, (N-(3,5-dimethoxy-4-n-octyloxycinnamoyl)-N'-(3,4-dimethylphenyl)piperazine), 1,1-dimethylallyl-3',4'-dihydroxycinnamic acid ester, 2,3-dihydroxycinnamic acid, 2-(4-amylcinnamoyl)amino-4-chlorobenzoic acid, 2-chlorocinnamic acid, 2-ethylhexyl-4-methoxycinnamate, 2-fluoro-p-hydroxycinnamate, 2-fluorocinnamic acid, 3,4,5-trimethoxycinnamic acid, 3,4-di(OH)-cinnamate, 3,4-dihydroxyhydrocinammic acid (l-aspartic acid dibenzyl ester) amide, 3,5-dihydroxycinnamic acid, 3,5-dimethoxycinnamic acid, 3,7-dimethyl-1,6-octadien-3-yl cinnamtae, 3-(3,4-dimethoxyphenyl)propenoic acid, 3-(4'-hydroxy-3'-adamantylbiphenyl-4-yl)acrylic acid, 3-(4-(1,2-diphenylbut-1-enyl)phenyl)acrylic acid, 3-(4-methoxyphenyl)-2-propenoic acid 3-methylbutyl ester, 3-(trifluoromethyl)cinnamide, 3-bromocinnamamide, 3-bromocinnamic acid, 3-fluorocinnamic acid, 4-(3,3-dimethyl-1-triazeno)cinnamic acid, 4-(3-(1-adamantyl)-4-hydroxyphenyl)-3-chlorocinnamic acid, 4-amidinophenyl 2-methylcinnamate, 4-amidinophenyl cinnamate, 4-amylcinnamoylanthranilic acid, 4-dimethylaminocinnamaldehyde, 4-fluorocinnamic acid, 4-hydroxy-3-methoxycinnamylpiperidine, 4-hydroxycinnamic acid (l-phenylalanine methyl ester) amide, 4-methoxycinnamate methyl ester, 4-methoxycinnamic acid, 5-(2-(methyl(2-phenethyl)amino)-2-oxoethyl)-2-(benzyloxy)cinnamic acid, A 25794, adamon, alpha-cyanocinnamate, alpha-methyl-2-hydroxy-4-

diethylaminocinnamic acid, alpha-phenylcinnamate, aminocinnamonitrile, antithiamine factor, asarumin C, BM 42304, caffeic acids (e.g., 1,1-dimethylallyl caffeic acid ester, 2-S-glutathionylcaffeic acid, 3,4-dihydroxyphenylpropionic acid, 7-caffeoylloganin, caffeic acid, caffeic acid phenethyl ester, calceolarioside A, chicoric acid, crenatoside, dehydrodicaffeic acid dilactone, ethyl caffeate, ethyl ferulate, eugenol, fukinolic acid, methyl caffeate, myriceron caffeoyl ester, N-(3,4-diacetoxycinnamoyl)-2-pyrrolidone, N-caffeoyl-4-aminobutyric acid, octyl caffeate, petasiphenol, phenylethyl 3-methylcaffeate, salvianolic acid A, suspensaside, and swertiamacroside), caracasanamide, chlorogenic acid, cinametic acid, cinanserin or derivatives thereof (e.g., SQ 10631 and SQ 11447), cinnamic acid, cinnamic anhydride, cinnamoyl chloride, cinnamyl isobutyrate, cinromide, CKA 1303, clocinnamox, coniferin, coumaric acids (e.g., (3,4-disinapoyl)fructofuranosyl-(6-sinapoyl)glucopyranoside, (3-sinapoyl)fructofuranosyl-(6-sinapoyl)glucopyranoside, 1-(4-coumaroyl)alpha-rhamnopyranose, 2-hydroxycinnamic acid, 3-coumaric acid, 4-coumaric acid, 4-coumaric acid methyl ester, 4-hydroxycinnamoylmethane, 5-hydroxyferulic acid, 5-O-feruloylarabinose, alpha-cyano-3-hydroxycinnamate, alpha-cyano-4-hydroxycinnamate, angoroside C, asprellic acid A, coniferyl ferulate, cycloartenol ferulic acid ester, dihydro-3-coumaric acid, ferulic acid, feruloylputrescine, feruloyltyramine, karenin, methyl 5-O-feruloylarabinofuranoside, and sinapinic acid), cyclamen aldehyde, cyclamen aldehyde methyl anthranilate, diacetylcymarol, dimethylaminoethyl-alpha-phenylcinnamate, Dolo-Adamon, ethyl 2,5-dihydroxycinnamate, ethyl cinnamate, fagaramide, gagaminine, hordatine M, hygromycin A, igmesine, isoferulic acid, kutkin, linusitamarin, maxafil, methyl 2,5-dihydroxycinnamate, methyl 3-phenyl-2,3-epoxypropanoate, methyl 4-(dimethylamino)cinnamate,

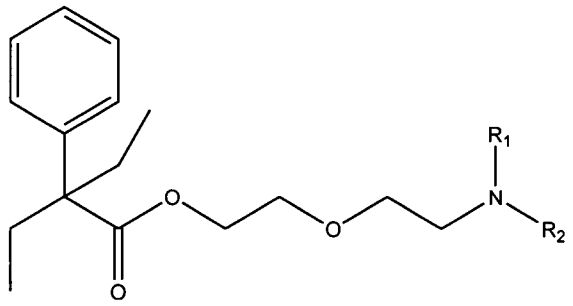
methyl cinnamate, N,N-dimethylhydrocinnamide, N-hydroxy-N-methyl-3-(2-(methylthio)phenyl)-2-propenamide, O-(alpha-(benzoylamino)-4-(phenylazo)cinnamoyl)-beta-phenyllactate, O-(alpha-(benzoylamino)cinnamoyl)-beta phenyllactate, octylmethoxycinnamate, ONO 8713, penupogenin, picroside I, picroside II, puromycin or derivative thereof (e.g., 2'-deoxypuromycin, 4-azidopuromycin, carbocyclic puromycin, cyclohexylpuromycin, cytidine-2'(3')-P-5'-puromycin, methionylpuromycin, N-(2-nitro-4-azidobenzoyl)puromycin, N-acetylphenylalanylpuromycin, N-iodoacetylpuromycin, O-demethylpuromycin, puromycin aminonucleoside, and sparsopuromycin), Ro 03-6037, rosmarinic acid, S 8932, SC 1001A, sibirate, SQ 10624, ST 638, SU 1498, tolibut, trans-3-(2'-methylphenyl)-2-propene-1-carboxamide, vanicoside A, and vanicoside B.

Oxeladin

In certain embodiments, oxeladin or an analog thereof can be used in the compositions, methods, and kits of the invention. Oxeladin is a used as an antitussive agent. The structure of oxeladin is:



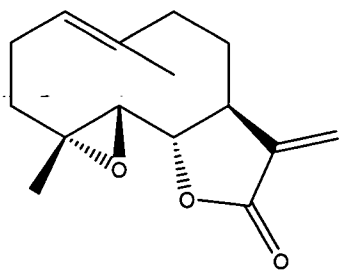
Oxeladin deriviativates are described, for example, in U.S. Pat. No. 2,885,404 and have the general structure:



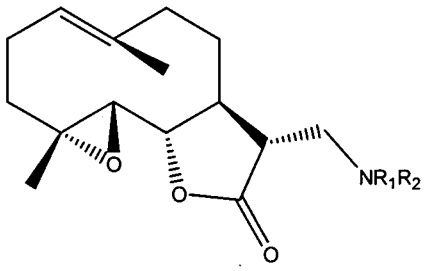
in which R_1 and R_2 are alkyl groups containing together not more than 12 carbon atoms, or together form a cyclic structure wherein $-NR_1R_2$ represents pyrrolidino, piperideino or piperidino. The groups R_1 and R_2 may be the same or different. Particular derivatives include 2-(β-diethylaminoethoxy)ethyl diethylphenylacetate, 2-(β-N-pyrrolidinoethoxy) ethyl diethylphenylacetate, 2-(β-N-piperidinoethoxy)ethyl diethylphenylacetate, 2-(β-N-Δ^3-piperideinoethoxy)ethyl diethylphenylacetate, 2-(β-N-ethylmethylaminoethoxy)ethyl diethylphenylacetate, 2-(β-N-ethylpropylaminoethoxy)ethyl diethylphenylacetate, 2-(β-N-di-n-butylaminoethoxy)ethyl diethylphenylacetate and 2-(β-di-n-hexylaminoethoxy)ethyl diethylphenylacetate.

Parthenolide

In certain embodiments, parthenolide or an analog thereof can be used in the compositions, methods, and kits of the invention. Parthenolide is a sesquiterpene lactone found in plants such as feverfew and *Chrysanthemum parthenium*. It has anti NFκB activity. The structure of parthenolide is:



Analogs of parthenolide are described, for example, in U.S. Pat. Application Publication No. 2005/0032886 and have the following structure.



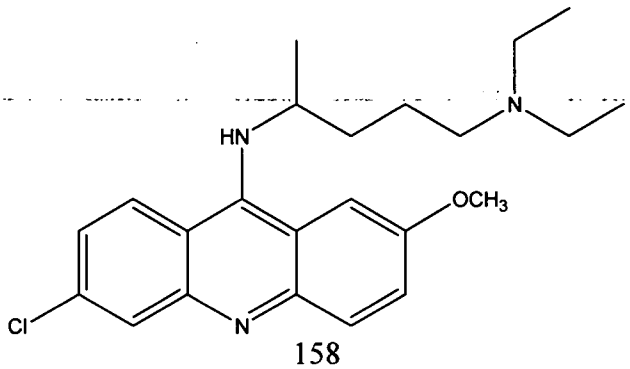
wherein R_1 and R_2 may be the same or different; R_1 is selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, hydroxyalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, heterocyclic, substituted heterocyclic, trifluoromethyl, perfluoroalkyl, cyano, cyanomethyl, carboxyl, carbamate, sulfonyl, sulfonamide and aryloxyalkyl, or OR_1, wherein, O is an oxygen;R_2 is selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, hydroxyalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, heterocyclic, substituted heterocyclic, trifluoromethyl, perfluoroalkyl, cyano, cyanomethyl, carboxyl, carbamate, sulfonyl, sulfonamide and aryloxyalkyl. In certain embodiments, R_1 is hydrogen or optionally substituted lower alkyl; and R_2 is optionally substituted lower alkyl. R_1 and R_2 can be each $-CH_3$, or each $-CH_2CH_3$. R_1 can be $-CH_2CH_3$ and R_2 can be $-CH_3$. R_1 can be $-CH_2CH_2CH_3$ and R_2 can be $-CH_3$. R_1 can be $-CH(CH_3)_2$, and R_2 can be $-CH_3$. R_1 and R_2 also can combine with N to form a ring system. Examples of such combination include $-CH_2(CH_2)_nCH_2-$; where n is selected from 0 to 5. These ring systems can also have one or more substituents selected from alkyl, substituted alkyl, cycloalkyl,

substituted cycloalkyl, hydroxyalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, heterocyclic, substituted heterocyclic, trifluoromethyl, perfluoroalkyl, cyano, cyanomethyl, carboxyl, carbamate, sulfonyl, sulfonamide, aryloxyalkyl and halogen as set forth above. This ring system can also be $-CH_2(CH_2)_nCH_2Z-$; where Z is O, S, Se, Si, P, –CO–, –SO–, $-SO_2-$, –PO–; and $-CH_2(CH_2)_nCH_2-$ are the groups as set forth above. Alternatively, this ring system can be $-(CH_2)_a-Z-(CH_2)_b-$; where a and b are the same or different and are from 1 to 4; and Z is O, N, S, Se, Si, P, –CO–, –SO–, $-SO_2-$ or –PO–. This ring system can also be a uracil ring and its derivatives with one or more substituents. These ring systems can also have one or more substituents connected to the carbon atom(s) and/or Z. The substituent is selected from alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, hydroxyalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, heterocyclic, substituted heterocyclic, trifluoromethyl, perfluoroalkyl, cyano, cyanomethyl, carboxyl, carbamate, sulfonyl, sulfonamide, aryloxyalkyl and halogen as set forth above. These ring systems can also be aromatic, such as pyrrole, imidazole, purine, and pyrazole and substituted derivative of these heterocyclics listed above with one or more substituents selected from alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, hydroxyalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, heterocyclic, substituted heterocyclic, trifluoromethyl, perfluoroalkyl, cyano, cyanomethyl, carboxyl,

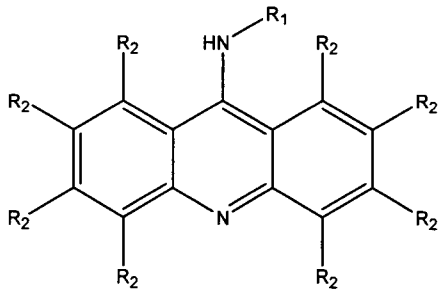
carboxylate, carboxaldehyde, carboxamide, carbamate, hydroxy, alkoxy, isocyanate, isothiocyanate, nitro, nitroso, nitrate, sulfate, sulfonyl, sulfonamide, thiol, thioalkyl, aryloxyalkyl and halogen as set forth above. Any of the above ring systems comprising NR_1R_2 may optionally be fused with another ring to form an optionally substituted bicyclic or tricyclic ring system, each of the rings optionally comprising one or more heteroatoms. Preferred ring systems include aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl, piperidin-1-yl, homopiperidyn-1-yl and heptamethyleneimin-1-yl, each being optionally substituted with one or more substituents as set forth above. Exemplary parthenolide derivatives include 11βH,13-Dimethylaminoparthenolide; 11βH,13-Diethylaminoparthenolide; 11βH,13-(tert-Butylamino)parthenolide; 11βH,13-(Pyrrolidin-1-yl)parthenolide; 11βH,13-(Piperidin-1-yl)parthenolide; 11βH,13-(Morpholin-1-yl)parthenolide; 11βH,13-(4-Methylpiperidin-1-yl)parthenolide; 11βH,13-(4-Methylpiperazin-1-yl)parthenolide; 11βH,13-(Homopiperidin-1-yl)parthenolide; 11βH,13-(Heptamethyleneimin-1-yl)parthenolide; 11βH,13-(Azetidin-1-yl)parthenolide; and 11βH,13-Diallylaminoparthenolide.

Quinacrine

In certain embodiments, quinacrine or an analog thereof can be used in the compositions, methods, and kits of the invention. Quinacrine is an antiparasitic and an antiprotozoal (e.g., antimalarial) agent. The structure of quinacrine is:



Analogs of quincrine are described, for example, in U.S. Pat. No 1,782,272 and have the following structure:



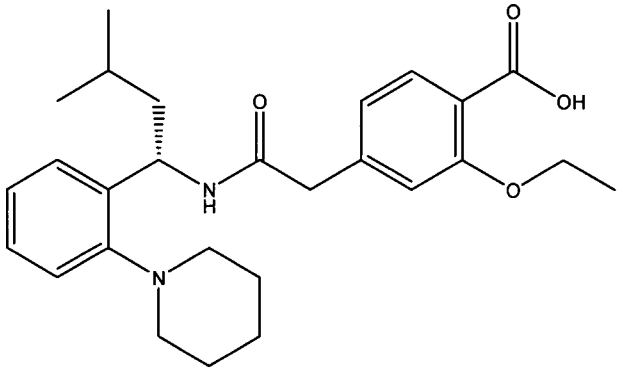
wherein R_1 stands for hydrogen or alkyl, at least one R_2 for the nitro group and another R_2 for a basic residue, the remaining R_2 representing hydrogen, halogen, or a nitro-, alkyl- or àlkoxy group, where a "basic residue" is By the term "basic residue" is to be understood in the sense of the foregoing formula such groups contain at least one aliphatically bound N-atom and which may be linked to the acridine ring for instance through the medium of oxygen (in the manner of an ether), of nitrogen (in the manner of an amine), or of carbon (in the manner of a C–C linkage). Derivatives of quinacrine include acrisuxine, collagenan, dimethylquinacrine, Preparation ABP, quinacrine half mustard, and quinacrine mustard.

Quinacrine is an aminoacridine. Other aminoacridines include (((amino-2-ethyl)-2-aminomethyl)-2-pyridine-6-carboxylhistidyl-gamma-(2-amino-2-deoxyglucosyl)glutamylglycylamino)-4-phenyl-1-aminoacridine, (N-(2-((4-((2-((4-(9-acridinylamino)phenyl)amino)-2-oxoethyl)amino)-4-oxobutyl)amino)-1-(1H-imidazol-4-ylmethyl)-1-oxoethyl)-6-(((-2-aminoethyl)amino)methyl)-2-pyridinecarboxamidato) iron(1+), 1,2,3,4-tetrahydro-N-(3-iodophenyl-methyl)-9-acridinamine, 1,2,3,4-tetrahydro-N-(phenyl-methyl)-9-acridinamine, 1-nitro-9-(dimethylamino)acridine, 10-N-nonylacridinium orange, 2-(3,6-bis(dimethylamino)-10-acridinyl)ethyl-(2,3-di-O-palmitoylglycero)phosphate, 2-aminoacridone, 3,6-diamino-10-methylacridinium, 3,6-diamino-9-(4-

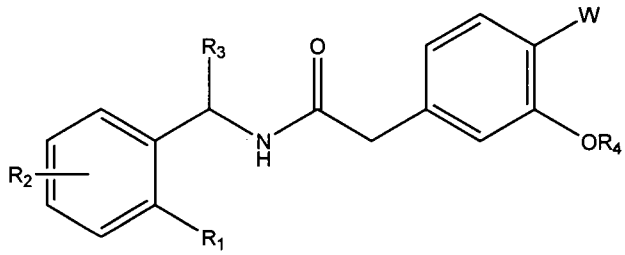
(methylsulfonyl)aminophenyl)aminoacridine, 3-amino-6-methoxy-9-(2-hydroxyethylamino)acridine, 3-amino-6-methoxyacridine, 3-amino-7-methoxyacridine, 3-amino-9-(diethylaminoethylthio)acridine, 3-aminothioacridone, 3-dimethylamino-6-methoxyacridine, 4-(9-acridinylamino)-N-(4-(((4-amino-1-methylpyrrol-2-yl)carbonyl)amino)-1-methylpyrrol-2-carbonyl)glycylaniline, 4-(9-acridinylamino)-N-(glycyl-histidyl-lysyl-glycyl)aniline, 9-((6-(4-nitrobenzoyloxy)hexyl)amino)acridine, 9-(2-(2-nitro-1-imidazolyl)ethylamino)acridine, 9-(5-carboxypentylamino)acridine, 9-(6-(2-diazocyclopentadienylcarbonyloxy)hexylamino)acridine, 9-(6-(4-azidobenzamido)hexylamino)acridine, 9-amino-2-hydroxyacridine, 9-amino-3-azido-7-methoxyacridine, 9-amino-6-chloro-2-methoxyacridine, 9-amino-6-chloroacridine-2-phosphate, 9-aminoacridine-4-carboxamide, acridine mustard, acridine orange, acridine yellow, acriflavine, aminacrine, Amsacrine, C 1310, C 1311, C 325, C 829, coriphosphine, ethacridine, euchrysine, fluoroquinacrine, N-((2-dimethylamino)ethyl)-9-aminoacridine-4-carboxamide, N-((4-dimethylamino)butyl)-9-aminoacridine-4-carboxamide, N-(6-azido-2-methoxy-9-acridinyl)-N'-(9-acridinyl)octane-1,8-diamine, N-(9-acridinyl)bromoacetamide, Nitracrine, NLA 1, NSC 210733, proflavine, pyracrine phosphate, SDM, suronacrine, and tacrine.

Repaglinide

In certain embodiments, repaglinide or an analog thereof can be used in the compositions, methods, and kits of the invention. Repaglinide is an antidiabetic agent which lowers glucose levels by closing potassium channels in the b-cell membrane. The structure of repaglinide is:



Analogs of repaglinide are described, for example, in U.S. Pat. No. 5,312,924 and can be represented as follows:

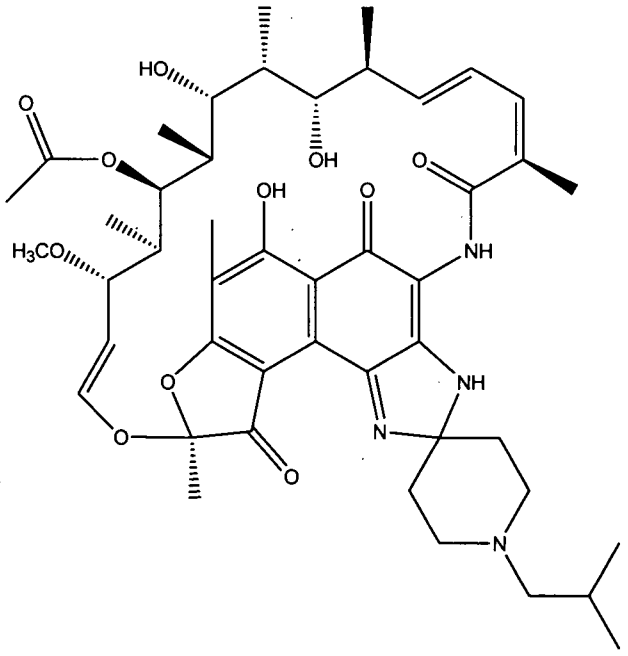


wherein R_1 represents an unbranched alkyleneimino group with 4 to 6 carbon atoms optionally mono- or di-(alkyl of 1 to 3 carbon atoms)-substituted; R_2 represents a hydrogen or halogen atom or a methyl or methoxy group; R_3 represents a hydrogen atom, an alkyl group with 1 to 7 carbon atoms, a phenyl group optionally substituted by a halogen atom or a methyl or methoxy group, an alkyl group with 1 or 2 carbon atoms substituted by a hydroxy, alkoxy, alkanoyloxy, tetrahydrofuranyl, tetrahydropyranyl, cycloalkyl or phenyl group, in which the alkoxy part can contain from 1 to 3 carbon atoms, the alkanoyloxy part can contain 2 to 3 carbon atoms and the cycloalkyl part can contain 3 to 7 carbon atoms, an alkenyl group with 3 to 6 carbon atoms, an alkynyl group with 3 to 5 carbon atoms, a carboxy group or an alkoxycarbonyl group with a total of 2 to 5 carbon atoms; R_4 represents a hydrogen atom, a methyl, ethyl or allyl group; and W represents a methyl, hydroxymethyl, formyl, carboxyl, alkoxycarbonyl, cyanomethyl, 2-cyano-ethyl, 2-cyano-ethenyl, carboxymethyl, 2-carboxyethyl, 2-carboxyethenyl, alkoxycarbonylmethyl, 2-alkoxycarbonyl-

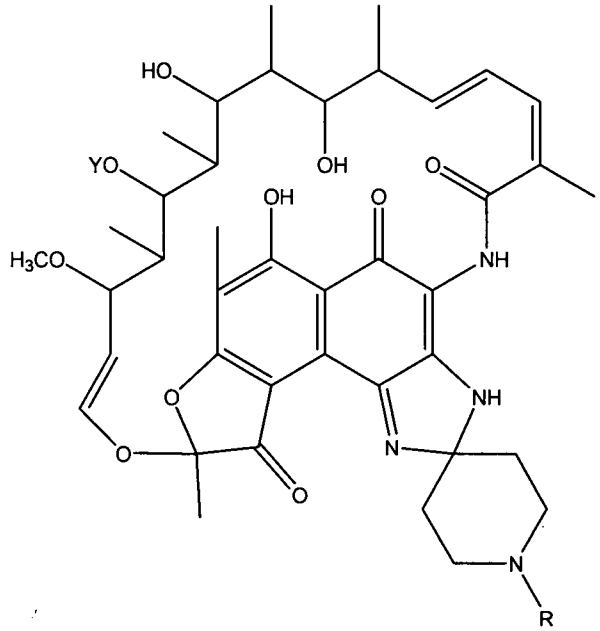
ethyl or 2-alkoxycarbonylethenyl group, in which each alkoxy part can contain from 1 to 4 carbon atoms and can be substituted by a phenyl group; and when R_3 is other then hydrogen and/or the radical R_1 contains an optically active carbon atom, the enantiomeres and the diastereomeres thereof or their mixtures; when W is carboxyl, a non-toxic salt thereof formed with an inorganic or organic base; or a non-toxic acid addition salt thereof formed by an inorganic or organic acid with the amino function in the R_1-position.

Rifamycins

In certain embodiments, a rifamycin such as rifabutin or an analog thereof can be used in the compositions, methods, and kits of the invention. Rifamycins are antibiotic compounds. The structure of rifabutin, an exemplary rifamycin, is:



Ribabutin analogs are described, for example, in U.S. Pat. No. 4,219,478, and have the general structure:

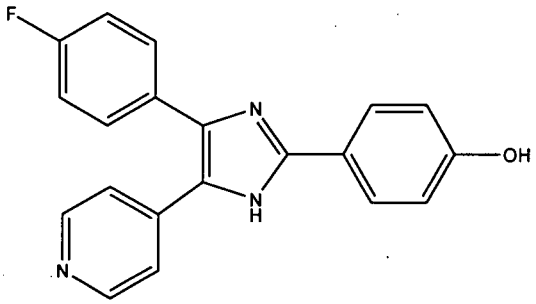


where R is selected from the group consisting of linear alkyl having 4 to 8 carbon atoms, branched alkyl having 4 to 8 carbon atoms, alkenyl having 3 or 4 carbon atoms, cycloalkyl having 3 to 6 carbon atoms, alkoxyalkyl having 3 to 7 carbon atoms, alkyl-furyl having 5 or 6 carbon atoms, alkyl tetrahydrofuryl having 5 or 6 carbon atoms, alkanoyl having 5 or 6 carbon atoms, and monohaloalkanoyl having 2 to 6 carbon atoms, and Y is –H or $–COCH_3$. Other rifamycins include 16,17-dihydro-17-hydroxyrifamycin S, 16,17-dihydrorifamycin S, 25-deacetoxy-25-hydroxyrifamycin S, 3-((dimethylhydrazono)methyl)rifamycin SV, 3-carbomethoxy rifamycin S, 3-formyl-25-desacetylrifamycin, 3-formylrifamycin SV, 31-homorifamycin W, 4-deoxy-3'-bromopyrido(1',2'-1,2)imidazo(5,4-c)rifamycin S, AF 013, benzothiazole-rifamycin, C 27, CGP 27557, CGP 29861, CGP 4832, CGP 7040, FCE 22250, FCE 22807, halomicin B, kanglemycin A, KRM 1648, KRM 1657, KRM 1668, KRM 1671, protorifamycin I, R 761, reprimun, rifabutin derivatives (e.g., 17-(allylamino)-17-demethoxygeldanamycin, 25-desacetylrifabutin, and streptovaricin), rifamdin, rifamexil, rifamide, Rifampin or derivatives thereof (e.g., 18,19-dihydrorifampicin, 25-deacetylrifampicin,

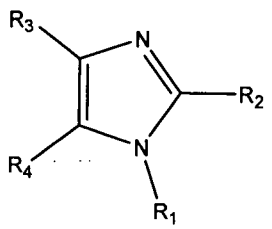
25-desacetylrifapentine, CGP 43371, CGS 24565, dehydrorifampicin, DMB-rifampicin, rifampicin N-oxide, rifapentine, Rifaprim, Rifater, and rivicycline), rifamycin B, rifamycin L, rifamycin O, rifamycin P, rifamycin Q, rifamycin S, rifamycin SV, rifamycin Verde, rifaximin, rifazone-82, SPA-S 565, streptovaricin derivatives (e.g., damavaricin C, damavaricin Fc pentyl ether, protostreptovaricin, streptoval C, streptovaricin C, and streptovarone), tolypomycin Y, and tolypomycinone.

SB-202190

In certain embodiments, SB-202190 or an analog thereof can be used in the compositions, methods, and kits of the invention. SB-202190 is a pyridyl substituted imidazole with selective p38 MAP Kinase (MAPK) inhibitory activity. SB-202190 binds to the ATP binding site on active p38 MAPK. The structure of SB-202190 is:



Analogs of SB-202190 are described, for example, in U.S. Pat. No. 6,008,235 and have the structure:



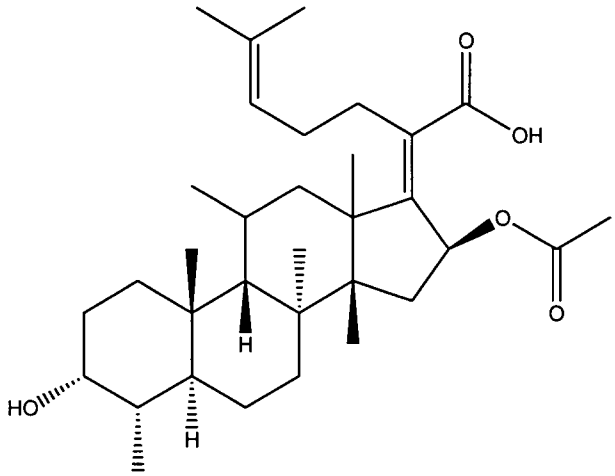
wherein R_1 is a mono- or di-substituted 4-quinolyl, 4-pyridyl, 1-imidazolyl, 1-benzimidazolyl, 4-pyrimidinyl wherein the substituent is independently selected

from the group consisting of hydrogen, C_{1-4} alkyl, halo, O–C_{1-4} alkyl, S–C_{1-4} alkyl, or $N(R_a)_2$; R_a is hydrogen, C_{1-6} alkyl, or R_a together with the nitrogen, may form a heterocyclic ring of 5 to 7 members, said ring optionally containing an additional heteroatom selected from the group consisting of oxygen, sulfur or nitrogen; R_2 is mono- or di-substituted phenyl wherein the substituents are independently selected from the group consisting of hydrogen, halo, $S(O)_mR_5$, OR_6, halo substituted C_{1-4} alkyl, C_{1-4} alkyl, or $N(R_{12})_2$; R_4 is hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{5-7} cycloalkenyl, heterocyclic, heterocyclicalkyl, aryl, aryl alkyl, heteroaryl, heteroaryl alkyl; R_3 is $(X)_r$–$(Q)_s$–$(Y)_t$; X is hydrogen, –$(C(R_{10})_2)_n$, –NR_{13}, –O–, or $S(O)_m$; r is a number having a value of 0 or 1; m is a number having a value of 0, 1 or 2; Q is alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclic, heterocyclicalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl; s is a number having a value of 0 or 1; Y is a substituent selected from the group consisting of hydrogen, C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, halogen, –$(C(R_{10})_2)_n$ OR_8, –$(C(R_{10})_2)_n$ NO_2, –$(C(R_{10})_2)_nS(O)_{m'}R_{11}$, –$(C(R_{10})_2)_nSR_8$, –$(C(R_{10})_2)_nS(O)_{m'}OR_8$, –$(C(R_{10})_2)_nS(O)_{m'}$ NR_8R_9, –X_a–$P(Z)$–$(X_aR_{13})_2$, –$(C(R_{10})_2)_n$ NR_8 R_9, –$(C(R_{10})_2)_nCO_2R_8$, –$(C(R_{10})_2)_nOC(O)$–R_8, –$(C(R_{10})_2)_nCN$, –$(C(R_{10})_2)_n$ $CONR_8$ R_9, –$(C(R_{10})_2)_nC(S)NR_8$ R_9, –$(C(R_{10})_2)_nNR_{10}$ $C(O)R_8$, –$(C(R_{10})_2)_nNR_{10}C(S)R_8$, –$(C(R_{10})_2)_nNR_{10}$ $C(Z)NR_8R_9$, –$(C(R_{10})_2)_nNR_{10}S(O)_mR_{11}$, –$(C(R_{10})_2)_nNR_{10}C(=NCN)$–S–$R_{11}$, –$(C(R_{10})_2)_nNR_{10}C(=NCN)$–$NR_8R_9$, –$(C(R_{10})_2)_nNR_{10}$ $C(O)C(O)$–NR_8R_9, –$(C(R_{10})_2)_n$ $NR_{10}C(O)C(O)$–OR_{10}, –$(C(R_{10})_2)_nC(=NR_{10})$–$NR_8R_9$, –$(C(R_{10})_2)_n$–$C(=NR_{10})$–$ZR_{11}$, –$(C(R_{10})_2)_n$–$OC(Z)$–$NR_8R_9$, –$(C(R_{10})_2)_nNR_{10}S(O)_mCF_3$, –$(C(R_{10})_2)_nNR_{10}C(O)OR_{10}$; t is an integer having a value of 0, 1, 2, or 3; Xa is independently –$(C(R_{10})_2)_n$, –NR_8–, –O– or –S–; Z is oxygen or sulfur, m' is an integer having a value of 1 or 2; n is an integer having a value of 0 to 10; R_5 is hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4}

alkynyl, C_{3-7} cycloalkyl, C_{5-7} cycloalkenyl, aryl, or $N(R_7)_2$; provided that when m is 1 or 2 then R_5 is not hydrogen. R_6 is hydrogen, C_{1-4} alkyl, halo substituted C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} cycloalkyl, C_{5-7} cycloalkenyl, or aryl; R_7 is hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, aryl, or may form a heterocyclic ring of 5 to 7 members together with the nitrogen, said ring optionally containing an additional heteroatom selected from the group consisting of oxygen, sulfur or nitrogen; provided that when R_5 is $N(R_7)_2$ then m is 1 or 2; R_8 is hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{5-7} cycloalkenyl, heterocyclic, heterocyclic alkyl, aryl, aryl alkyl, heteroaryl, heteroaryl alkyl; R_9 is hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{5-7} cycloalkenyl, aryl, aryl alkyl, heteroaryl, heteroaryl alkyl or R_8 and R_9 may together form a heterocyclic ring of 5 to 7 members together with the nitrogen, said ring optionally containing an additional heteroatom selected from the group consisting of oxygen, sulfur or nitrogen; R_{10} is hydrogen, or C_{1-4} alkyl; R_{11} is C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{5-7} cycloalkenyl, aryl, aryl alkyl, heteroaryl, heteroaryl alkyl; R_{12} is hydrogen, C_{1-4} alkyl, aryl, or may form a heterocyclic ring of 5 to 7 members together with the nitrogen; R_{13} is hydrogen, C_{1-10} alkyl, cycloalkyl, heterocylic, aryl, aryl alkyl, heteroaryl, or heteroaryl alkyl.

Fusidic acid

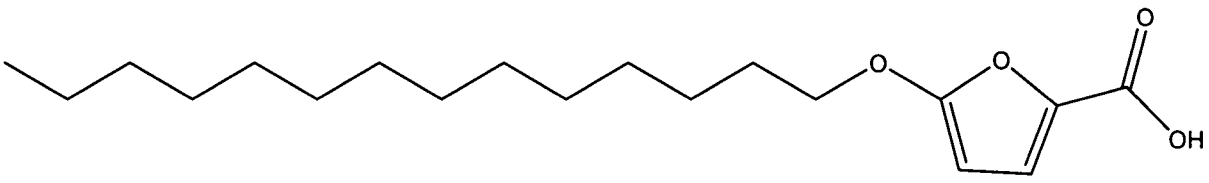
In certain embodiments, fusidic acid or a derivative thereof (e.g., sodium fusidate) can be used in the compositions, methods, and kits of the invention. The structure of fusidic acid is:



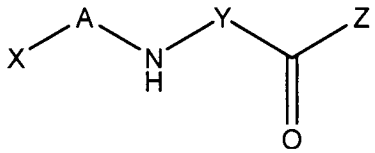
Fusidic acid derivatives are described in U.S. Pat. Nos. 3,352,854, 3,385,869, 3,376,324, 4,004,004, 4,060,606, 4,162,259, 4,315,004, 4,119,717, 6,103,884, and 6,593,319. Derivative include 11-monoketofusidic acid, 16-O-deacetylfusidic acid, 16-O-deacetylfusidic acid lactone, 3,11-diketofusidic acid, diethanolamine fusidate, helvolic acid, and tauro-24,25-dihydrofusidate.

TOFA

In certain embodiments, 5-(tetradecyloxy)-2-furancarboxylic acid (TOFA) or an analog thereof can be used in the compositions, methods, and kits of the invention. TOFA is an inhibitor of acetyl-CoA carboxylase. The structure of TOFA is:



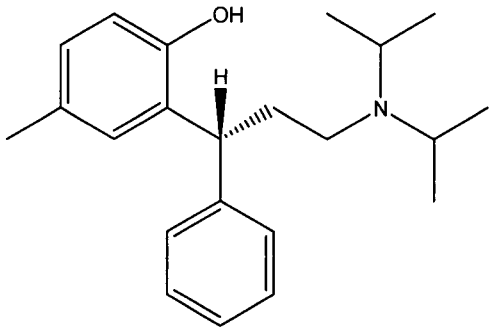
Analogs of TOFA are described, for example, in U.S. Patent 4,382,143 and have the general structure:



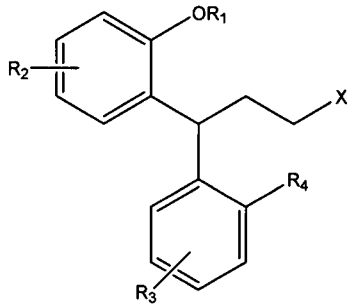
wherein X is selected from the group consisting of hydrogen, C_3-C_8 cycloalkyl, and substituted or unsubstituted aryl; A is a divalent radical selected from the group consisting of branched or unbranched C_6-C_{19} alkylene, alkenylene, and alkynylene; Y is a 5- or 6-membered heteroaryl ring containing one or more nitrogen, sulfur, or oxygen atoms and optionally unsubstituted or substituted with one fluoro; and Z is selected from the group consisting of hydrogen, hydroxy, loweralkoxy, loweralkoxyloweralkoxy, diloweralkylaminoloweralkoxy, (mono- or polyhydroxy)loweralkoxy, (mono- or polycarboxy)loweralkoxy, (mono- or polycarboxy)hydroxyloweralkoxy, allyloxy, 2,3-epoxypropoxy, substituted or unsubstituted-(phenoxy, benzyloxy, or 3-pyridyloxy), pyridylmethoxy, tetrahydropyranyloxy, (mono- or polyhydroxy)alkylamino, allylamino, propargylamino, 2-sulfoethylamino, (mono- or polycarboxyl)loweralkylamino, loweralkanoylamino, (substituted or unsubstituted)aroylamino, loweralkanesulfonylamino, (substituted or unsubstituted)arenesulfonylamino, loweralkanylhydrazino, hydroxylamino, polymethyleneimino, and (4-carboxy- or 4-carboethoxy)thiazolidino; and the pharmaceutically acceptable acid-addition and cationic salts thereof.

Tolterodine

In certain embodiments, tolterodine or an analog thereof can be used in the compositions, methods, and kits of the invention. Tolterodine is a competitive muscarinic receptor antagonist. The pharmacologically active agent is the 5-hydroxymethyl derivative. Cholinergic muscarinic receptors mediate urinary bladder contraction. Tolterodine is thus used to treat urinary incontinence. The structure of tolterodine is:



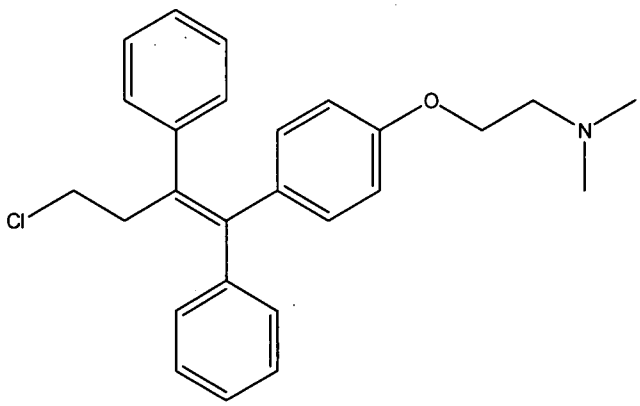
Analogs of tolterodine are described, for example, in U.S. Pat. No. 5,382,600 and have the general structure:



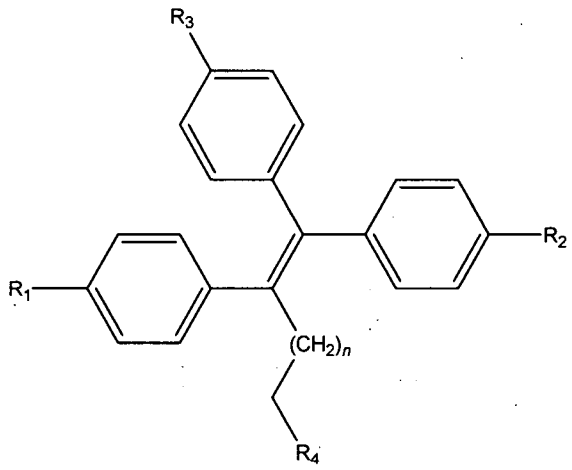
wherein R_1 signifies hydrogen or methyl, R_2, R_3, and R_4 independently signify hydrogen, methyl, methoxy, hydroxy, carbamoyl, sulphanoyl or halogen, and X represents a tertiary amino group ($-NR_5R_6$) wherein R_5 and R_6 signify non-aromatic hydrocarbol groups, which may be the same or different and which together contain at least three carbon atoms, preferably at least four or five carbon atoms, and where R_5 and R_6 may form a ring together with the amine nitrogen, said ring preferably having no other hetero atom that the amine nitrogen.

Toremifene

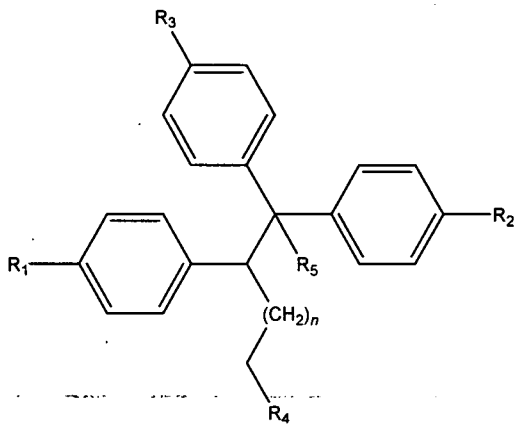
In certain embodiments, toremifene or an analog thereof can be used in the compositions, methods, and kits of the invention. Toremifene is antiestrogen and antineoplastic agent. The structure of toremifene is:



Analogs of toremifene are described, for example, in U.S. Pat. No. 4,696,949 have the general structure:



or the structure:

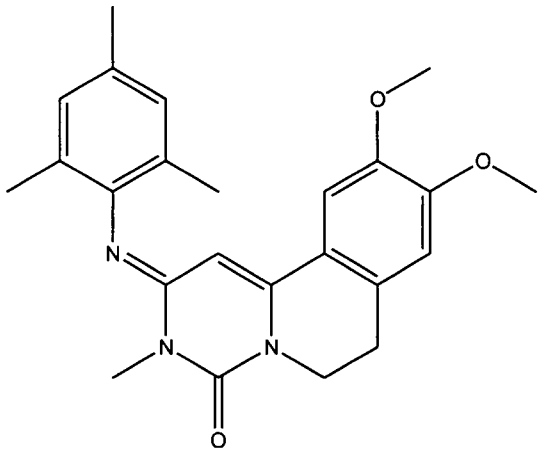


wherein n is 0 to 4, R_1 and R_2, which can be the same or different are H, OH, an alkoxy group of 1 to 4 carbon atoms, benzyloxy or methoxymethoxy; R_3 is H, OH, halogen, alkoxy of 1 to 4 carbon atoms, benzyloxy, methoxymethoxy, 2,3-

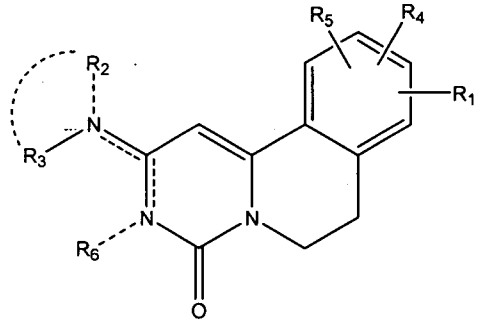
dihydroxypropoxy or $-O(CH_2)_mCH_2NR_6R_7$ wherein m is 1 or 2, R_6 and R_7, which can be the same or different, are H or an alkyl group of 1 to 4 carbon atoms, or $-NR_6R_7$ can form an N-containing three-, four-, five- or six-membered heterocyclic ring; R_4 is OH, F, Cl, Br, I, mesyloxy, tosyloxy, alkylcarbonyloxy of 1 to 4 carbon atoms, formyloxy or CH_2 R_4 is replaced by CHO; R_5 is H or OH; or R_4 and R_5 together form an –O– bridge between the carbon atoms to which they are attached.

Trequinsin

In certain embodiments, trequinsin or an analog thereof can be used in the compositions, methods, and kits of the invention. Trequinsin is a platelet aggreation inhibitor. The structure of trequinsin is:



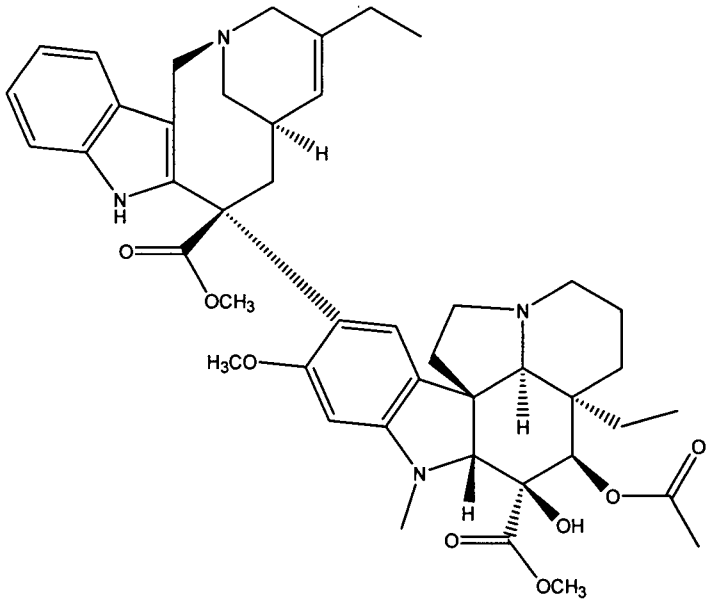
Trequinsin analogs are described, for example, in U.S. Pat. No. 5,141,936 and have the general structure:



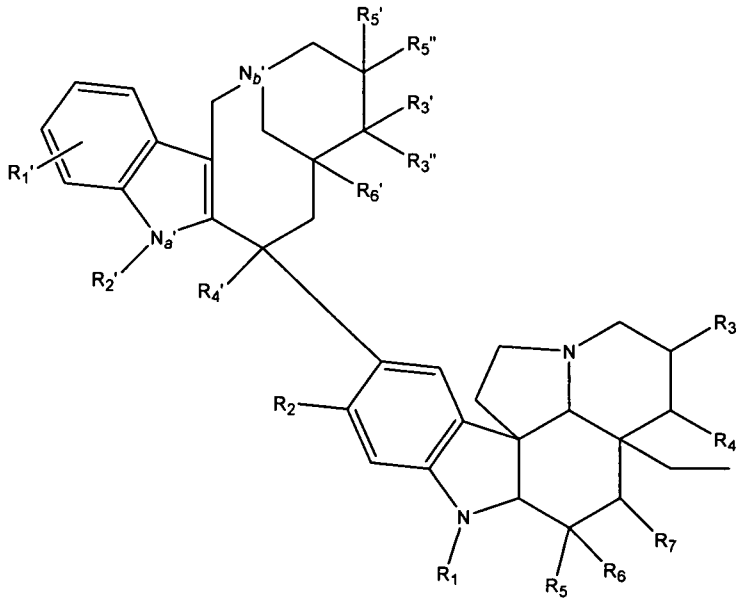
in which R_1, R_4 and R_5, which may be identical or different, may be hydrogen, hydroxyl, lower alkoxy, dialkylphosphinylalkoxy, acyloxy or halogen, where two adjacent groups together may denote a methylenedioxy or ethylenedioxy group, and R_2 and R_3, which may be identical or different, may be hydrogen, hydroxyl, lower alkoxy, amino, alkylamino, dialkylamino, arylamino, alkyl, amino or alkyl substituted by a 5- or 6-membered carbon ring which may contain up to 3 heteroatoms from the group comprising N, O or S, cycloalkyl, hydroxyalkyl, alkoxyalkyl, dialkoxyalkyl, haloalkyl, dialkylaminoalkyl, aralkyl, acyl and, optionally substituted, aryl, where aryl is in each case taken to mean an aromatic hydrocarbon having up to 10 carbon atoms, and R_2 denotes an electron pair if R_6 denotes one of the radicals indicated below and R_2 and R_3 together with the nitrogen atom to which they are bonded may denote a part of an optionally substituted nitrogen heterocycle which may contain a further nitrogen atom or an oxygen atom, and R_6 stands for hydrogen, alkyl, cycloalkyl, hydroxyalkyl, alkoxyalkyl, dialkoxyalkyl, haloalkyl, dialkylaminoalkyl, aralkyl, heterocyclic-substituted alkyl, dialkylphosphinylalkyl, acyl and optionally substituted aryl, and also stands for an electron pair if R_2 denotes one of the radicals indicated above, and their acid salts and quaternary ammonium salts.

Vinorelbine

In certain embodiments, vinorelbine or an analog thereof can be used in the compositions, methods, and kits of the invention. Vinorelbine is an antineoplastic agent that functions by binding microtubular proteins of the mitotic spindle, thereby inhibiting mitosis. The structure of vinorelbine is:



Analogs of vinorelbine are described, for example, in U.S. Pat. No. 4,307,100 and have the general structure:

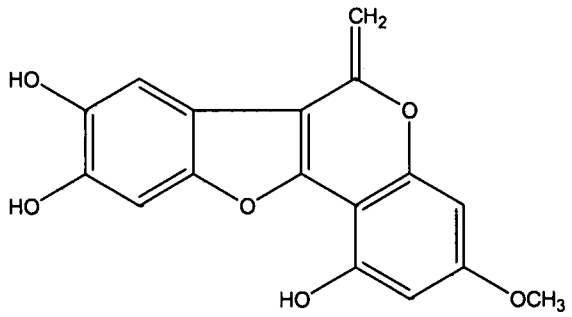


wherein R'$_1$ represents a hydrogen atom or an alkoxy, acyl, formyl or haloacyl radical; R'$_2$ represents a hydrogen atom or an alkyl radical; R'$_3$ and R"$_3$ which may be the same or different each represents a hydrogen atom or a hydroxyl radical or an alkanoyloxyl radical or together represent a carbonyl group, or R'$_3$ and R'$_5$ together represent an epoxy bridge or a double bond; R'$_4$ represent a hydrogen atom or an alkyloxycarbonyl, hydroxymethyl, alkanoyloxymethyl or

acetamido radical; R'$_5$ and R"$_5$ which may be the same or different each represents a hydrogen atom or a hydroxyl, alkanoyloxyl, ethyl or 2-hydroxyethyl radical; R'$_6$ represents a hydrogen atom or an ethyl, 2-hydroxyethyl or acetyl radical; R_1 represents a hydrogen atom or an alkyl, formyl, or acyl radical; R_2 represents a hydrogen atom or an alkoxy radical; R_3 represents a hydrogen atom or a hydroxyl or alkanoyloxyl radical, or R_3 and R_4 together represent an epoxy bridge or a double bond; R_4 represents a hydrogen atom or a hydroxyl or alkanoyloxyl radical, or R_4 and R_5 together represent an epoxy bridge; R_6 represents an alkyloxycarbonyl, hydrazido, acetamido, hydroxymethyl or alkanyloxymethyl radical; and R_5 and R_7 represent a hydrogen atom or a hydroxyl or alkanoyloxyl radical. Vinorelbine is a member of the vinblastine compounds, which include 16-O-acetylvindoline, 3',4'-anhydrovinblastine, 4'-deoxyvinblastine, 4-desacetylvinblastine, 4-desacetylvinblastine hydrazide, 4-O-deacetylvinblastine-3-oic acid, bis(N-ethylidene vindesine)disulfide, catharanthamine, catharinine, desacetylnavelbine, KAR 2, LY 266070, NAPAVIN, ViFuP protocol, vincathicine, vindoline, vindolinine, vinepidine, vinflunine, vinleucinol, vinorelbine, vintriptol, and vintriptol acid.

Wedelolactone

In certain embodiments, wedelolactone or an analog thereof can be used in the compositions, methods, and kits of the invention. Wedelolactone is IKKα and IKKβ kinase inhibitor and a IkB-α kinase inhibitor. The structure of wedelolactone is:



Wedelolactone is a member of the coumarins. Other coumarins include 11,12-dihydroxy-5-methylcoumestan, 11-desacetoxywortmannin, 2'',3''-dihydrogeiparvarin, 2-amino-3-(7-methoxy-4-coumaryl)propionic acid, 2-nitro-6H-dibenzo(b,d)pyran-6-one, 3'-angeloyloxy-4'-acetoxy-3',4'-dihydroseselin, 3,4-dichloroisocoumarin, 3,4-dihydro-3,4-dibromo-6-bromomethylcoumarin, 3,4-dihydro-3-benzyl-6-chloromethylcoumarin, 3,4-dihydrocoumarin, 3,8-dihydroxy-6H-dibenzo(b,d)pyran-6-one, 3-(2-(N,N-diethyl-N-methylammonium)ethyl)-7-methoxy-4-methylcoumarin, 3-acetylcoumarin, 3-carbethoxypyranocoumarin, 3-carboxylic acid-picumast, 3-cyano-7-ethoxycoumarin, 3-cyano-7-hydroxycoumarin, 3-hydroxy-(28-4-coumaroyloxy)lup-20(29)-en-27-oic acid, 3-hydroxymethyl-picumast, 3-nitro-6H-dibenzo(b,d)pyran-6-one, 3-phenyl-5,6-benzocoumarin, 3H-naphtho(2,1-b)pyran-3-one, 4'-hydroxyasperentin, 4-(diazomethyl)-7-(diethylamino)coumarin, 4-acetylisocoumarin, 4-bromomethyl-6,7-dimethoxycoumarin, 4-bromomethyl-6,7-methylenedioxycoumarin, 4-bromomethyl-7-acetoxycoumarin, 4-chloro-3-ethoxy-7-guanidinoisocoumarin, 4-methyl-7-diethylaminocoumarin, 4-methyl-7-ethoxycoumarin, 4-methyl-N-ethyl pyrrolo(3,2-g)coumarin, 4-nitro-6H-dibenzo(b,d)pyran-6-one, 4-phenyl-3-isocoumarinic acid, 4-phenyl-3-isocoumarinic acid allylamide, 4-trifluoromethylcoumarin phosphate, 5,6-benzocoumarin-3-carboxylic acid ethyl ester, 5,7-dihydroxy-4-imino-2-oxochroman, 5,7-dimethoxycoumarin, 5-iodo-6-amino-1,2-benzopyrone, 5-methyl-8-hydroxycoumarin, 5-methylcoumarin-4-

cellobioside, 5-methylcoumarin-4-gentiobioside, 5H-(2)benzopyrano(3,4-g)(1,4)benzodioxin-5-one, 6'-feruloylnodakenin, 6,7-(4-methyl)coumaro-(2.2.2)cryptand, 6,8-dimethoxy-3-methyl-3,4-dihydroisocoumarin, 6-(7-beta-galactosylcoumarin-3-carboxamido)hexylamine, 6-amino-1,2-benzopyrone, 6-amino-4,4,5,7,8-pentamethyldihydrocoumarin, 6-chloro-3,4-dihydroxy-2H-1-benzopyran-2-one, 6-cyano-7-hydroxy-4,8-dimethylcoumarin, 6-hydroxymellein, 6-methoxy-8-hydroxy-3-methyl-3,4-dihydroisocoumarin, 6-methylcoumarin, 6-methylthionecoumarin, 6-nitroso-1,2-benzopyrone, 7,8-dimethoxycoumarin, 7-((N-tosylphenylalanyl)amino)-4-chloro-3-methoxyisocoumarin, 7-(alpha-glutamyl)-4-methylcoumarylamide, 7-(gamma-glutamyl)-4-methylcoumarylamide, 7-(N-benzyloxycarbonyl-beta-benzylaspartyl-prolyl-leucyl)amino-4-methylcoumarin, 7-(N-benzyloxycarbonylglycyl-glycyl-leucyl)amino-4-methylcoumarin, 7-amino-3-(2-bromoethoxy)-4-chloroisocoumarin, 7-amino-4-chloro-3-(3-isothiureidopropoxy)isocoumarin, 7-amino-4-methylcoumarin, 7-amino-4-methylcoumarin-3-acetic acid, 7-amino-4-trifluoromethylcoumarin, 7-aminocoumarin, 7-aminocoumarin-4-methanesulfonic acid, 7-anilino-4-methylcoumarin-3-acetic acid, 7-anilinocoumarin-4-acetic acid, 7-benzylcysteinyl-4-methylcoumarinylamide, 7-benzyloxy-4-trifluoromethylcoumarin, 7-beta-galactopyranosyl-oxycoumarin-4-acetic acid methyl ester, 7-beta-galactopyranosyloxycoumarin-4-acetic acid, 7-diethylamino-3-(4'-isothiocyanatophenyl)-4-methylcoumarin, 7-diethylaminocoumarin-3-carbohydrazide, 7-diethylaminocoumarin-3-carboxylic acid, 7-dimethylamino-4-methylcoumarin, 7-ethenyloxycoumarin, 7-ethoxy-4-trifluoromethylcoumarin, 7-ethoxycoumarin, 7-glycidoxycoumarin, 7-hydroxy-4-phenyl-3-(4-hydroxyphenyl)coumarin, 7-hydroxy-4-trifluoromethylcoumarin, 7-hydroxycoumarin-4-acetic acid, 7-leucylamido-4-methylcoumarin, 7-

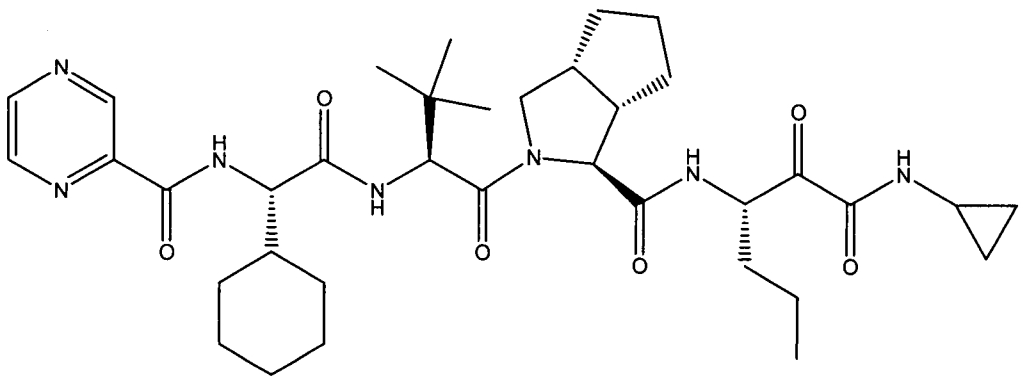
lysylalanyl-4-methylcoumarinamide, 7-succinylglycyl-prolyl-4-methylcoumaryl-7-amide, 8-(3-(4-phenyl-1-piperazinyl)propoxy)-7-methoxycoumarin, 8-hydroxy-4-methyl-3,4-dihydroxycoumarin, 8-hydroxycoumarin, 9-(3-diethylaminopropyloxy)-3H-naphtho(2,1-b)pyran-3-one, A 1062, Ac-aspartyl-glutamyl-valyl-aspartyl-aminomethylcoumarin, acetyl-aspartyl-glutamyl-valyl-aspartyl-amino-4-methylcoumarin, agrimonolide-6-O-glucopyranoside, AI 77B, alanyl-alanyl-phenylalanyl-7-amino-4-methylcoumarin, amicoumacin A, anomalin, arginine 4-methyl-7-coumarylamide, arnottin I, aspartyl-glutamyl-valyl-aspartyl-7-amino-4-trifluoromethylcoumarin, aurapten, baciphelacin, benzyloxycarbonyl-phenylalanylarginine-4-methylcoumaryl-7-amide, benzyloxycarbonylarginyl-arginine 4-methylcoumarin-7-ylamide, bergaptol-O-glucopyranoside, Boc-leucyl-seryl-threonyl-arginine-4-methylcoumaryl-7-amide, byakangelicol, calanolide A, calanolide B, calophyllolid, carbobenzoxycoumarin, Cassella 7657, CGP 13143, chlorobiocic acid, Chromonar, CI 923, cladosporin, clausarin, clausindine, clausmarin, columbianadin, cordatolide A, coumachlor, coumarin, coumarin 3,4-epoxide, coumarin-3-carboxylic acid, coumarin-3-carboxylic acid succinimidyl ester, coumermycins, coumestrol, coumetarol, crenulatin, cytogenin, daphnoretin, dehydroindicolactone, demethylwedelolactone, dicurin, erythrocentaurin, Esculin, esuprone, F 1375, ferujol, ferulenol, folescutol, fraxetin, fraxin, galbanic acid, geiparvarin, gerberinside, glaupadiol, glisoflavone, glutaryl-alanyl-alanyl-phenylalanyl-amidomethylcoumarin, glutaryl-glycyl-arginine-4-methylcoumaryl-7-amide, glycyl-7-amino-4-methylcoumarin-3-acetic acid, glycylprolyl-4-methylcoumaryl-7-amide, GU 7, GUT-70, 4-hydroxycoumarins, hymecromone O,O-diethyl phosphorothioate, iliparcil, inophyllum B, isobyakangelicin angelate, isofraxidin, isorhamnetin 3-O-beta-(4'''-4-coumaroyl-alpha-

rhamnosyl(1-6)galactoside), kaempferol-2,4-dicoumaroyl-3-O-glucoside, licopyranocoumarin, LL-N 313, mammein, mammeisin, maoyancaosu, marmesin, marmin, melilot, moellendorffiline, morocromen, moxicoumone, murayalactone, N-(2-(1-maleimidyl)ethyl)-7-(diethylamino)coumarin-3-carboxamide, N-(4-(7-(diethylamino)-4-methylcoumarin-3-yl))maleimide, N-(4-(7-diethylamino 4-methylcoumarin-3-yl)phenyl)iodoacetamide, N-(4-(7-diethylamino-4-methylcoumarin-3-yl)phenyl)maleimide, N-acetyl-alanyl-alanyl-prolyl-alanyl-amidomethylcoumarin, N-benzyloxycarbonylalanyl-arginyl-arginyl-4-trifluoromethyl-7-coumarylamide, N-benzyloxycarbonylglycyl-glycyl-arginine-4-methylcoumarinyl-7-amide, N-carbobenzoxyglycyl-prolyl-4-methylcoumarinyl amide, N-salicylidene-3-aminocoumarin, N-succinimidyl-7-dimethylaminocoumarin-4-acetate, necatorin, neoglycyrol, nitrofarin, nordentatin, notopterol, Ochratoxins, oosponol, oroselol, osthenol, osthol, oxamarine, pargyropyranone, PD 118717, peuarenine, peujaponiside, phebalosin, phellopterin, phyllodulcin, picumast, ponfolin, praeruptorin C, praeruptorin E, Psoralens, psoralidin, pterybinthinone, pteryxin, pyranocoumarins, qianhucoumarin A, qianhucoumarin B, qianhucoumarin C, reticulol, Ro7-AMCA, rubradiric acid A, rubradiric acid B, rubricauloside, sclerin, scoparone, scopolin, serine-7-amino-4-methylcoumarin carbamate, shijiaocaolactone A, soulattrolide, SP500263, succinyl-isoleucyl-isoleucyl-tryptophyl-methylcoumarinamide, succinyl-leucyl-leucyl-valyl-tyrosyl-methylcoumarinamide, succinyl-leucyl-tyrosyl-4-methyl-7-coumarylamide, succinylalanylalanyl-prolyl-phenylalanine-4-methylcoumaryl-7-amide, succinylglycyl-prolyl-leucyl-glycyl-prolyl-4-methylcoumaryl-7-amide, suksdorfin, sulfosuccinimidyl 7-amino-4-methylcoumarin-3-acetate, surangin B, tert-butyloxycarbonyl-leucyl-glycyl-arginine-4-trifluoromethylcoumarin-7-amide, tert-butyloxycarbonyl-norleucyl-glutaminyl-leucyl-glycyl-arginine-7-

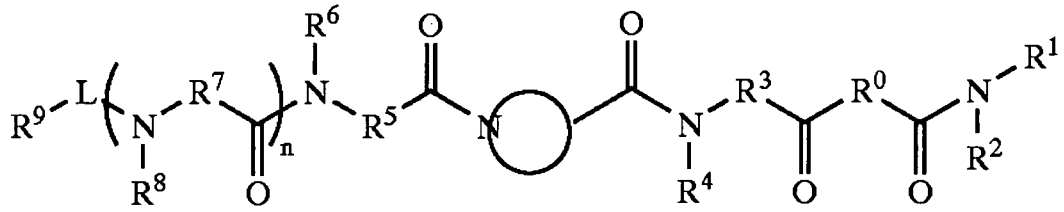
amino-4-methylcoumarin, tertiary butyloxycarbonylvalyl-leucyl-lysinyl-4-methylcoumarin-7-amide, tertiary-butyloxycarbonyl-isoleucyl-glutamyl-glycyl-arginyl-7-amino-4-methylcoumarin, tertiary-butyloxycarbonyl-phenylalanyl-seryl-arginyl-4-methylcoumarin-7-amide, tertiary-butyloxycarbonyl-valyl-prolyl-arginyl-7-amino-4-methylcoumarin, theo-esberiven, thunberginol A, thunberginol B, thunberginol D, tioclomarol, toddalolactone, tosyl-glycyl-prolyl-arginyl-4-methylcoumaryl-7-amide, ubiquitin C-terminal 7-amido-4-methylcoumarin, Umbelliferones, valyl-leucyl-lysyl-4-aminomethylcoumarin, valyl-leucyl-lysyl-7-amino-4-methylcoumarin, Venalot, W10294A, WS-5995 A, xanthalin, and xanthyletine.

Telaprevir

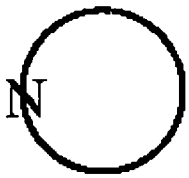
In certain embodiments, telaprevir or an analog thereof can be used in the compositions, methods, and kits of the invention. Telaprevir (VX-950) is a hepatitis C therapy. The structure of telaprevir is:



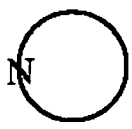
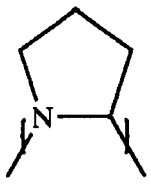
Analogs of telaprevir are described, for example, in U.S. Pat. Application Publication No. 2005/0197299 and can be represented as follows:



wherein R^0 is a bond or difluoromethylene; R^1 is hydrogen, optionally substituted aliphatic group, optionally substituted cyclic group or optionally substituted aromatic group; R^2 and R^9 are each independently optionally substituted aliphatic group, optionally substituted cyclic group or optionally substituted aromatic group; R^3, R^5, and R^7 are each independently (optionally substituted aliphatic group, optionally substituted cyclic group or optionally substituted aromatic group)(optionally substituted methylene or optionally substituted ethylene), optionally substituted (1,1- or 1,2-)cycloalkylene or optionally substituted (1,1- or 1,2-)heterocyclylene; R^4, R^6, R^8 and R^{10} are each independently hydrogen or optionally substituted aliphatic group;



is substituted monocyclic azaheterocyclyl or optionally substituted multicyclic azaheterocyclyl, or optionally substituted multicyclic azaheterocyclenyl wherein the unsaturatation is in the ring distal to the ring bearing the R^9-L-N(R^8)–R^7–C(O)–)$_n$N(R^6)–R^5–C(O)–N moiety and to which the –C(O)–N(R^4)–R^3–C(O)-C(O)NR^2R^1 moiety is attached; L is –C(O)–, –OC(O)–, –NR^{10}C(O)–, –S(O)$_2$–, or –NR^{10}S(O)$_2$–; and n is 0 or 1, or a pharmaceutically acceptable salt or prodrug thereof, or a solvate of such a compound, its salt or its prodrug, provided when

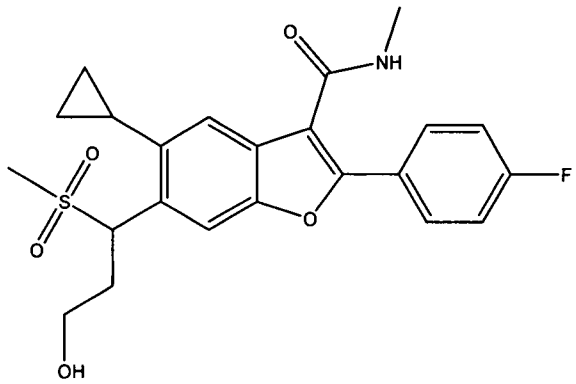
 is substituted  ,

then L is –OC(O)– and R^9 is optionally substituted aliphatic, or at least one of

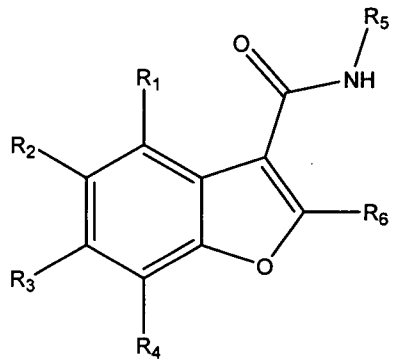
R^3, R^5 and R^7 is (optionally substituted aliphatic group, optionally substituted cyclic group or optionally substituted aromatic group)(optionally substituted ethanediyl), or $R^4$is optionally substituted aliphatic.

HCV-796

In certain embodiments, HCV-796 or an analog thereof can be used in the compositions, methods, and kits of the invention. HCV-796 is a non-nucleoside polymerase inhibitor. The structure of HCV-796 is:



Analogs of HCV-796 are described for example, in U.S. Pat. No. 7,265,152 and have the general structure:



wherein R_1 represents a radical selected from the group consisting of hydrogen, alkyl, halogen, and cyano; R_2 represents a radical selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl radical, a substituted or unsubstituted alkoxy group, hydroxy, cycloalkyl, cycloalkyloxy, polyfluoroalkyl, polyfluoroalkoxy, halogen, amino, monoalkylamino,

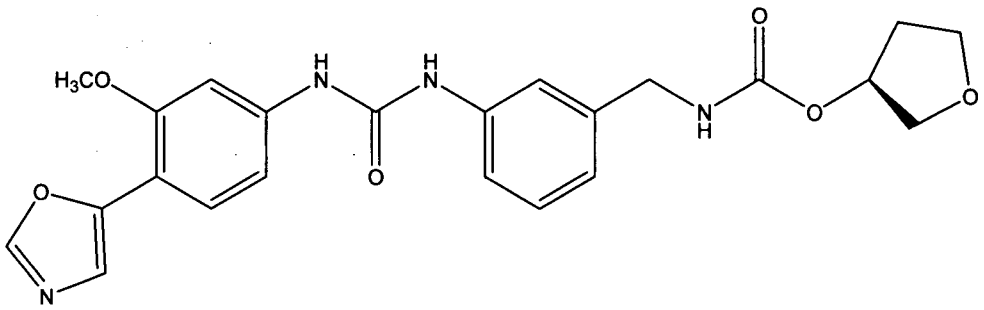
dialkylamino, cyano, a substituted or unsubstituted benzyloxy group, and a substituted or unsubstituted heterocyclic radical; R_3 represents a radical selected from the group consisting of hydrogen, a substituted or unsubstituted alkyl radical, a substituted or unsubstituted alkoxy group, alkenyl, halogen, hydroxy, polyfluoroalkyl, polyfluoroalkoxy, formyl, carboxyl, alkylcarbonyl, alkoxycarbonyl, hydroxyalkylcarbonyl, amino, a substituted or unsubstituted monoalkylamino, dialkylamino, cyano, amido, alkoxyamido, a substituted or unsubstituted heteroarylamino, acetylsulfonylamino, ureido, carboxamide, sulfonamide, a substituted sulfonamide, a substituted or unsubstituted heterocyclosulfonyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonic acid, a substituted or unsubstituted heterocyclic radical, and --$O(CH_2)$--$C(=O)$--R_7; R_4 represents a radical selected from the group consisting of hydrogen, alkyl, halogen, and alkoxy; R_5 represents a radical selected from the group consisting of an alkyl (C_1-C_6) group, cycloalkyl, and cycloalkylalkyl; R_6 represents a radical selected from the group consisting of a substituted or unsubstituted aryl group and a substituted or unsubstituted heteroaryl group; R_7 represents a radical selected from the group consisting of dialkylamino, a substituted or unsubstituted arylamino, a substituted or unsubstituted heteroarylamino, and a substituted or unsubstituted aryl group, said monoalkylamino substituents being one or more radical(s) independently selected from the group consisting of cycloalkyl, hydroxy, alkoxy, and a substituted or unsubstituted heterocyclic radical; said arylamino substituents and said heteroarylamino substituents being one or more radical(s) independently selected from an alkyl group and an alkoxycarbonyl; said sulfonamide substituents being one or more radical(s) independently selected from the group consisting of alkenyl, cycloalkyl, alkoxy, hydroxy, halogen, polyfluoroalkyl, polyfluoroalkoxy, carboxyl, alkylcarbonyl, alkoxycarbonyl, carboxamide, a substituted or unsubstituted aryl group, and a

substituted or unsubstituted heterocyclic radical; said heterocyclosulfonyl substituents being one or more radical(s) independently selected from the group consisting of alkoxy and hydroxy; said alkyl radical substituents and said alkoxy group substituents being one or more radical(s) independently selected from the group consisting of alkenyl, amino, monoalkylamino, dialkylamino, alkoxy, cycloalkyl, hydroxy, carboxyl, halogen, cyano, polyfluoroalkyl, polyfluoroalkoxy, sulfonamide, carboxamide, alkylsulfonyl, alkylcarbonyl, alkoxycarbonyl, mercapto, 2,2-dimethyl-4-oxo-4H-benzo[1,3]dioxinyl, a substituted or unsubstituted aryl group, and a substituted or unsubstituted heterocyclic radical; said heterocyclic radical substituents being one or more radical(s) independently selected from the group consisting of alkyl, amino, amido, monoalkylamino, cycloalkyl-alkylamino, dialkylamino, alkoxy, alkoxyalkyl, hydroxy, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, carboxyl, carboxamide, halogen, haloalkyl, cyano, polyfluoroalkyl, polyfluoroalkoxy, alkylsulfonyl, alkylcarbonyl, cycloalkylcarbonyl, alkoxycarbonyl, mercapto, oxo, a substituted or unsubstituted aryl group, arylalkyl, and a substituted or unsubstituted heteroaryl group; said heteroaryl group substituents being one or more radical(s) independently selected from the group consisting of alkyl, amino, alkoxy, alkoxyalkyl, hydroxy, hydroxyalkyl, cycloalkyl, carboxyl, carboxamide, halogen, polyfluoroalkyl, polyfluoroalkoxy, alkylsulfonyl, mercapto, and oxo; said benzyloxy group substituents being one or more radical(s) independently selected from the group consisting of alkyl, alkoxy, polyfluoroalkyl, polyfluoroalkoxy, hydroxy, carboxyl, alkoxycarbonyl, halogen, cyano, alkylsulfonyl, and phenyl; said aryl group substituents being one or more radical(s) independently selected from the group consisting of alkyl, acetylenyl, alkoxy, hydroxy, halogen, polyfluoroalkyl, polyfluoroalkoxy, cyano, amino, monoalkylamino, dialkylamino, aminoalkyl, alkoxyalkoxy, amido, amidoalkyl,

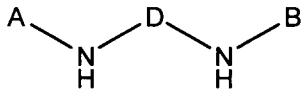
carboxyl, alkylsulfonyl, alkylcarbonyl, alkoxycarbonyl, mercapto, and a heterocyclic radical; and pharmaceutically acceptable salts thereof;

Merimepodib (VX-497)

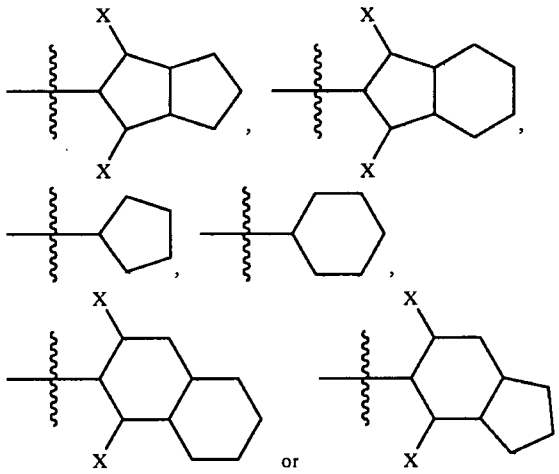
In certain embodiments, merimepodib or an analog thereof can be used in the compositions, methods, and kits of the invention. Merimepodib is an inhibitor of inosine-5'-monophosphate dehydrogenase (IMPDH) and is used to treat HCV. The structure of merimepodib is:



Analogs of merimepodib are described for example, in U.S. Pat. No. 6,541,496 and have the general structure:



wherein A is selected from (C_1-C_6)-straight or branched alkyl, or (C_2-C_6)-straight or branched alkenyl or alkynyl; and A optionally comprises up to 2 substituents, wherein the first of said substituents, if present, is selected from R^1 or R^3, and the second of said substituents, if present, is R^1; B is a saturated, unsaturated or partially saturated monocyclic or bicyclic ring system optionally comprising up to 4 heteroatoms selected from N, O, or S and selected from the formulae:



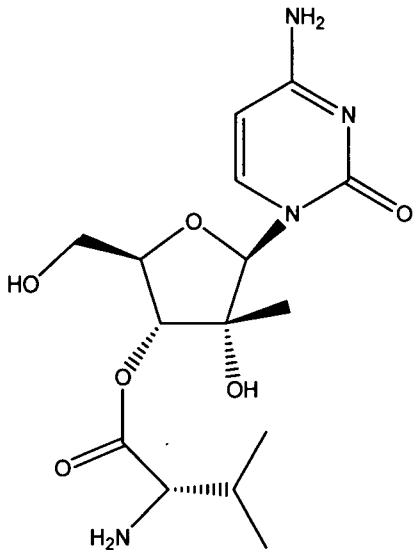
wherein each X is the number of hydrogen atoms necessary to complete proper valence; and B optionally comprises up to 3 substituents, wherein: the first of said substituents, if present, is selected from R^1, R^2, R^4 or R^5, the second of said substituents, if present, is selected from R^1 or R^4, and the third of said substituents, if present, is R^1; and D is selected from C(O), C(S), or $S(O)_2$; wherein each R^1 is independently selected from 1,2-methylenedioxy, 1,2-ethylenedioxy, R^6 or $(CH_2)_n$–Y; wherein n is 0, 1 or 2; and Y is selected from halogen, CN, NO_2, CF_3, OCF_3, OH, SR^6, $S(O)R^6$, SO_2R^6, NH_2, NHR^6, $N(R^6)_2$, NR^6R^8, COOH, $COOR^6$ or OR^6; each R^2 is independently selected from (C_1-C_4)-straight or branched alkyl, or (C_2-C_4)-straight or branched alkenyl or alkynyl; and each R^2 optionally comprises up to 2 substituents, wherein the first of said substituents, if present, is selected from R^1, R^4 and R^5, and the second of said substituents, if present, is R^1; R^3 is selected from a monocyclic or a bicyclic ring system consisting of 5 to 6 members per ring, wherein said ring system optionally comprises up to 4 heteroatoms selected from N, O, or S, and wherein a CH_2 adjacent to any of said N, O, or S heteroatoms is optionally substituted with C(O); and each R^3 optionally comprises up to 3 substituents, wherein the first of said substituents, if present, is selected from R^1, R^2, R^4 or

R^5, the second of said substituents, if present, is selected from R^1 or R^4, and the third of said substituents, if present, is R^1; each R^4 is independently selected from OR^5, $OC(O)R^6$, $OC(O)R^5$, $OC(O)OR^6$, $OC(O)OR^5$, $OC(O)N(R^6)_2$, $OP(O)(OR^6)_2$, SR^6, SR^5, $S(O)R^6$, $S(O)R^5$, SO_2R^6, SO_2R^5, $SO_2N(R^6)_2$, $SO_2NR^5R^6$, SO_3R^6, $C(O)R^5$, $C(O)OR^5$, $C(O)R^6$, $C(O)OR^6$, $NC(O)C(O)R^6$, $NC(O)C(O)R^5$, $NC(O)C(O)OR^6$, $NC(O)C(O)N(R^6)_2$, $C(O)N(R^6)_2$, $C(O)N(OR^6)R^6$, $C(O)N(OR^6)R^5$, $C(NOR^6)R^6$, $C(NOR^6)R^5$, $N(R^6)_2$, $NR^6C(O)R^1$, $NR^6C(O)R^6$, $NR^6C(O)R^5$, $NR^6C(O)OR^6$, $NR^6C(O)OR^5$, $NR^6C(O)N(R^6)_2$, $NR^6C(O)NR^5R^6$, $NR^6SO_2R^6$, $NR^6SO_2R^5$, $NR^6SO_2N(R^6)_2$, $NR^6SO_2NR^5R^6$, $N(OR^6)R^6$, $N(OR^6)R^5$, $P(O)(OR^6)N(R^6)_2$, and $P(O)(OR^6)_2$; each R^5 is a monocyclic or a bicyclic ring system consisting of 5 to 6 members per ring, wherein said ring system optionally comprises up to 4 heteroatoms selected from N, O, or S, and wherein a CH_2 adjacent to said N, O or S maybe substituted with C(O); and each R^5 optionally comprises up to 3 substituents, each of which, if present, is R^1; each R^6 is independently selected from H, (C_1-C_4)-straight or branched alkyl, or (C_2-C_4) straight or branched alkenyl; and each R^6 optionally comprises a substituent that is R^7; R^7 is a monocyclic or a bicyclic ring system consisting of 5 to 6 members per ring, wherein said ring system optionally comprises up to 4 heteroatoms selected from N, O, or S, and wherein a CH_2 adjacent to said N, O or S maybe substituted with C(O); and each R^7 optionally comprises up to 2 substituents independently chosen from H, (C_1-C_4)-straight or branched alkyl, (C_2-C_4) straight or branched alkenyl, 1,2-methylenedioxy, 1,2-ethylenedioxy, or $(CH_2)_n$–Z; wherein n is 0, 1 or 2; and Z is selected from halogen, CN, NO_2, CF_3, OCF_3, OH, S(C_1-C_4)-alkyl, SO(C_1-C_4)-alkyl, SO_2(C_1-C_4)-alkyl, NH_2, NH(C_1-C_4)-alkyl, N((C_1-C_4)-alkyl)$_2$, N((C_1-C_4)-alkyl)R^8, COOH, C(O)O(C_1-C_4)-alkyl or O(C_1-C_4)-alkyl; and R^8 is an

amino protecting group; and wherein any carbon atom in any A, R^2 or R^6 is optionally replaced by O, S, SO, SO_2, NH, or $N(C_1\text{-}C_4)$-alkyl.

Valopicitabine

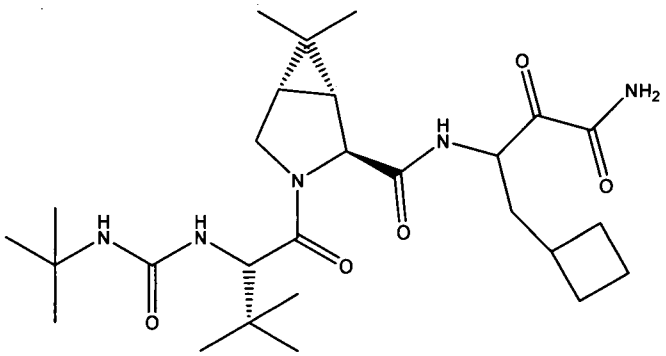
In certain embodiments, valopicitabine (NM-283) or an analog thereof can be used in the compositions, methods, and kits of the invention. Valopicitabine is a hepatitis C therapy that acts as a polymerase inhibitor. Valopicitabine is an orally available prodrug of 2'-*C*-methylcytidine. The structure of valopicitabine is:



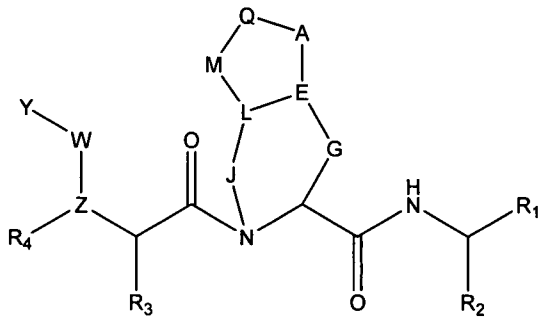
Analogs of valopicitabine are described, for example, in U.S. Pat. Application Publication No. 2007/0015905, which is hereby incorporated by reference.

Boceprevir (SCH 503034)

In certain embodiments, boceprevir (SCH 503034) or an analog thereof can be used in the compositions, methods, and kits of the invention. Boceprevir is a hepatitis C therapy that acts as a inhibitor of the NS3-serine protease. The structure of boceprevir is:



Analogs of boceprivir are described, for example, in U.S. Pat. Application Publication No. 2004/0254117 and have the general structure:



wherein Y is selected from the group consisting of the following moieties: alkyl, alkyl-aryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, cycloalkyloxy, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino and heterocycloalkylamino, with the proviso that Y may be optionally substituted with X_{11} or X_{12}; X_{11} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkylheteroaryl, or heteroarylalkyl, with the proviso that X_{11} may be additionally optionally substituted with X_{12}; X_{12} is hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, or nitro, with the proviso that said alkyl, alkoxy, and aryl may be additionally optionally substituted with moieties

independently selected from X_{12}; R_1 is COR_5 or $B(OR)_2$, wherein R_5 is H, OH, OR_8, NR_9R_{10}, CF_3, C_2F_5, C_3F_7, CF_2R_6, R_6, or COR_7 wherein R_7 is H, OH, OR_8, CHR_9R_{10}, or NR_9R_{10}, wherein R_6, R_8, R_9 and R_{10} are independently selected from the group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, cycloalkyl, arylalkyl, heteroarylalkyl, $[CH(R_1')]_pCOOR_{11}$, $[CH(R_1')]_pCONR_{12}R_{13}$, $[CH(R_1')]_pSO_2R_{11}$, $[CH(R_1')]_pCOR_{11}$, $[CH(R_1')]_pCH(OH)R_{11}$, $CH(R_1')CONHCH(R_2')COO\ R_{11}$, $CH(R_1')CONHCH(R_2')CON\text{-}\ R_{12}R_{13}$, $CH(R_1')CONHCH(R_2')R_{11}$, $CH(R_1')CONHCH(R_2')CONHCH(R_3')COO\ R_{11}$, $CH(R_1')CONHCH(R_2')CONHCH(R_3')CONR_{12}R_{13}$, $CH(R_1')CONHCH(R_2')CONHCH(R_3')CONHCH(R_4')COO\ R_{11}$, $CH(R_1')CONHCH(R_2')CONHCH(R_3')CONHCH(R_4')CONR_{12}R.\text{-}$ sup.13, $CH(R_1')CONHCH(R_2')CONHCH(R_3')CONHCH(R_4')CONHCH\text{-}\ (R_5')COO\ R_{11}$ and $CH(R_1')CONHCH(R_2')CONHCH(R_3')CON\text{-}HCH(R_4')CONHCH(R_5')\ CONR_{12}R_{13}$, wherein R_1', R_2', R_3', R_4', R_5', R_{11}, R_{12}, R_{13}, and R' are independently selected from the group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, alkyl-heteroaryl, aryl-alkyl and heteroaralkyl; Z is selected from O, N, CH or CR; W may be present or absent, and if W is present, W is selected from C=O, C=S, C(=N–CN), or SO_2; Q may be present or absent, and when Q is present, Q is CH, N, P, $(CH_2)_p$, $(CHR)_p$, $(CRR')_p$, O, NR, S, or SO_2; and when Q is absent, M may be present or absent; when Q and M are absent, A is directly linked to L; A is O, CH_2, $(CHR)_p$, $(CHR\text{–}CHR')_p$, $(CRR')_p$, NR, S, SO_2 or a bond; E is CH, N, CR, or a double bond towards A, L or G; G may be present or absent, and when G is present, G is $(CH_2)_p$, $(CHR)_p$, or $(CRR')_p$; and when G is absent, J is present and E is directly connected to the carbon atom in Formula I as G is linked to; J maybe present or absent, and when J is present, J is $(CH_2)_p$, $(CHR)_p$, or $(CRR')_p$, SO_2, NH, NR or O; and when J is absent, G is present and E is

directly linked to N shown in Formula I as linked to J; L may be present or absent, and when L is present, L is CH, CR, O, S or NR; and when L is absent, then M may be present or absent; and if M is present with L being absent, then M is directly and independently linked to E, and J is directly and independently linked to E; M may be present or absent, and when M is present, M is O, NR, S, SO_2, $(CH_2)_p$, $(CHR)_p(CHR–CHR')_p$, or $(CRR')_p$; p is a number from 0 to 6; and R, R', R_2, R_3 and R_4 are independently selected from the group consisting of H; C_1-C_{10} alkyl; C_2-C_{10} alkenyl; C_3-C_8 cycloalkyl; C_3-C_8 heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, halogen; (cycloalkyl)alkyl and (heterocycloalkyl)alkyl, wherein said cycloalkyl is made of three to eight carbon atoms, and zero to six oxygen, nitrogen, sulfur, or phosphorus atoms, and said alkyl is of one to six carbon atoms; aryl; heteroaryl; alkyl-aryl; and alkyl-heteroaryl; wherein said alkyl, heteroalkyl, alkenyl, heteroalkenyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl moieties may be optionally and chemically-suitably substituted, with said term "substituted" referring to optional and chemically-suitable substitution with one or more moieties selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, heterocyclic, halogen, hydroxy, thio, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, sulfonamido, sulfoxide, sulfone, sulfonyl urea, hydrazide, and hydroxamate; further wherein said unit N–C–G–E–L–J–N represents a five-membered or six-membered cyclic ring structure with the proviso that when said unit N–C–G–E–L–J–N represents a five-membered cyclic ring structure, or when the bicyclic ring structure in Formula I comprising N, C, G, E, L, J, N, A, Q, and M represents a five-membered cyclic

ring structure, then said five-membered cyclic ring structure lacks a carbonyl group as part of the cyclic ring.

Interferons

In certain embodiments, an interferon or an analog thereof can be used in the compositions, methods, and kits of the invention. Intefereons includes interferon-α, interferon alfa-2a, interferon alfa-2b, interfereon alfa-2c, interferon alfacon-1, interferon alfa-n1, interferon alfa-n3, intefereon-β, interferon β-1a, interferon β-1b, interferon-γ, interferon γ-1a, interferon γ-1b, and pegylated forms thereof.

Miscellaneous agents

Albendazole analogs are described in U.S. Pat. Nos. 5,468,765, 5,432,187, 4,299,837, 4,156,006, and 4,136,174. Amitraz analogs are described in U.S. Pat. No. 3,781,355. Betaxolol analogs are described in U.S. Pat. No. 4,252,984. Bromhexine analogs are described in U.S. Pat. Nos. 3,408,446 and 4,191,780 and Belgian patent BE625002. Bromocriptine analogs are described in U.S. Pat. No. 4,145,549. Capsaicin analogs are described in U.S. Pat. No. 4,812,446. Carbaryl analogs are described in U.S. Pat. No. 2,903,478. Chloroquine analogs are described in U.S. Pat. No. 2,233,970. Cladribine (2-chloro-2'-deoxyadenosine) analogs are described in U.S. Pat. Nos. 4,760,137, 5,208,327, 6,252,061, 6,596,858, and 6,884,880. Clomiphene analogs are described in U.S. Pat. No. 2,914,563. Cyclocytidine analogs are described in U.S. Pat. No. 3,463,850. Dibucaine analogs are described in U.S. Pat. No. 1,825,623. Dicyclomine analogs are described in U.S. Pat. No. 2,474,796. Dilazep analogs are described in U.S. Pat. No. 3,532,685. Diphenidol analogs are described in U.S. Pat. No. 2,411,664.

Donepezil analogs are described in U.S. Pat. No. 4,895,841. Emetine analogs are described in U.S. Pat. No. 3,102,118. Exemestane analogs are described in U.S. Pat. No. 4,808,616. Ezetimibe analogs are described in U.S. Pat. No. 5,767,115. Fenbendazole analogs are described in U.S. Pat. No. 3,954,791. Fenretinide analogs are described in U.S. Pat. No. 4,190,594. Fenvalerate analogs are described in U.S. Pat. No. 3,996,244. Flubendazole analogs are described in U.S. Pat. No. 3,657,267 and German patent DE2029637. Fludarabine analogs are described in U.S. Pat. No. 5,034,518. Fluorouracil analogs are described in U.S. Pat. No. 2,802,005, 2,885,396, 4,092,313, and 4,080,455. Ifenprodil analogs are described in U.S. Pat. No. 3,509,164. Indocyanine green analogs are described in U.S. Pat. No. 2,895,955. Iophenoxic acid analogs are described in British patent GB726987. Isosulfan blue analogs include sulfan blue. Mycophenolic acid analogs are described in U.S. Pat. Nos. 3,705,894, 3,903,071, 4,686,234, 4,725,622, 4,727,069, 4,753,935, 4,786,637, 4,808,592, 4,861,776, 4,868,153, 4,948,793, 4,952,579, 4,959,387, 4,992,467, 5.247,083, 5,380,879, 5,441,953, 5,444,072, 5,493,030, 5,538,969, 5,512,568, 5,525,602, 5,554,612, 5,633,279, 6,399,773, 6,420,403, 6,624,184, 6,916,809, 6,919,335, 7,053,111, and U.S. patent application Ser. No. 07/927,260. Narasin analogs are described in U.S. Pat. Nos. 4,035,481, 4,038,384, 4,141,907, 4,174,404, 4,204,039, and 5,541,224. Oxeladin analogs are described in U.S. Pat. No. 2,885,404. Oxfendazole analogs are described in U.S. Pat. No. 3,929,821. Oxibendazole analogs are described in U.S. Pat. No. 3,574,845. Perospirone analogs are described in U.S. Pat. No. 4,745,117. Picotamide analogs are described in French patent FR2100850. Pramoxine analogs are described in U.S. Pat. No. 2,870,151. Quinacrine analogs are described in U.S. Pat. Nos. 2,113,357, 1,782,727, and 1,889,704. Repaglinide analogs are described in International Application Publication No. WO

93/00337. Rifaximin analogs are described in U.S. Pat. No. 4,341,785. Silver sulfadiazine analogs are described in U.S. Pat. Nos. 2,407,966 2,410,793. Terconazole analogs are described in U.S. Pat. Nos. 4,144,346 and 4,223,036. Tioxolone analogs are described in U.S. Pat. Nos. 2,332,418 and 2,886,488. Tirapazamine analogs are described in U.S. Pat. No. 3,868,371. Tiratricol analogs are described in British patent Nos. GB803149 GB805761. Toremifene analogs are described in U.S. Pat. No. 4,696,949. Vincristine analogs are described in U.S. Pat. No. 4,144,237. Zafirlukast analogs are described in U.S. Pat. No. 4,859,692.

Conjugates

If desired, the agents used in any of the combinations described herein may be covalently attached to one another to form a conjugate of formula I.

(A)-(L)-(B) (I)

In formula I, (A) is a drug listed on Table 1, Table 2, or Table 3 covalently tethered via a linker (L) to (B), a second drug listed on Table 1, Table 2, Table 3, Table 4, or Table 5.

Conjugates of the invention can be administered to a subject by any route and for the treatment of viral hepatitis (e.g., those described herein).

The conjugates of the invention can be prodrugs, releasing drug (A) and drug (B) upon, for example, cleavage of the conjugate by intracellular and extracellular enzymes (e.g., amidases, esterases, and phosphatases). The conjugates of the invention can also be designed to largely remain intact in vivo, resisting cleavage by intracellular and extracellular enzymes. The degradation of the conjugate in vivo can be controlled by the design of linker

(L) and the covalent bonds formed with drug (A) and drug (B) during the synthesis of the conjugate.

Conjugates can be prepared using techniques familiar to those skilled in the art. For example, the conjugates can be prepared using the methods disclosed in G. Hermanson, *Bioconjugate Techniques*, Academic Press, Inc., 1996. The synthesis of conjugates may involve the selective protection and deprotection of alcohols, amines, ketones, sulfhydryls or carboxyl functional groups of drug (A), the linker, and/or drug (B). For example, commonly used protecting groups for amines include carbamates, such as *tert*-butyl, benzyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 9-fluorenylmethyl, allyl, and m-nitrophenyl. Other commonly used protecting groups for amines include amides, such as formamides, acetamides, trifluoroacetamides, sulfonamides, trifluoromethanesulfonyl amides, trimethylsilylethanesulfonamides, and *tert*-butylsulfonyl amides. Examples of commonly used protecting groups for carboxyls include esters, such as methyl, ethyl, *tert*-butyl, 9-fluorenylmethyl, 2-(trimethylsilyl)ethoxy methyl, benzyl, diphenylmethyl, O-nitrobenzyl, ortho-esters, and halo-esters. Examples of commonly used protecting groups for alcohols include ethers, such as methyl, methoxymethyl, methoxyethoxymethyl, methylthiomethyl, benzyloxymethyl, tetrahydropyranyl, ethoxyethyl, benzyl, 2-napthylmethyl, O-nitrobenzyl, P-nitrobenzyl, P-methoxybenzyl, 9-phenylxanthyl, trityl (including methoxy-trityls), and silyl ethers. Examples of commonly used protecting groups for sulfhydryls include many of the same protecting groups used for hydroxyls. In addition, sulfhydryls can be protected in a reduced form (e.g., as disulfides) or an oxidized form (e.g., as sulfonic acids, sulfonic esters, or sulfonic amides). Protecting groups can be chosen such that selective conditions (e.g., acidic conditions, basic conditions, catalysis by a nucleophile, catalysis by a lewis acid, or hydrogenation) are required to

remove each, exclusive of other protecting groups in a molecule. The conditions required for the addition of protecting groups to amine, alcohol, sulfhydryl, and carboxyl functionalities and the conditions required for their removal are provided in detail in T.W. Green and P.G.M. Wuts, *Protective Groups in Organic Synthesis* (2nd Ed.), John Wiley & Sons, 1991 and P.J. Kocienski, *Protecting Groups*, Georg Thieme Verlag, 1994. Additional synthetic details are provided below.

Linkers

The linker component of the invention is, at its simplest, a bond between drug (A) and drug (B), but typically provides a linear, cyclic, or branched molecular skeleton having pendant groups covalently linking drug (A) to drug (B).

Thus, linking of drug (A) to drug (B) is achieved by covalent means, involving bond formation with one or more functional groups located on drug (A) and drug (B). Examples of chemically reactive functional groups which may be employed for this purpose include, without limitation, amino, hydroxyl, sulfhydryl, carboxyl, carbonyl, carbohydrate groups, vicinal diols, thioethers, 2-aminoalcohols, 2-aminothiols, guanidinyl, imidazolyl, and phenolic groups.

The covalent linking of drug (A) and drug (B) may be effected using a linker which contains reactive moieties capable of reaction with such functional groups present in drug (A) and drug (B). For example, an amine group of drug (A) may react with a carboxyl group of the linker, or an activated derivative thereof, resulting in the formation of an amide linking the two.

Examples of moieties capable of reaction with sulfhydryl groups include α-haloacetyl compounds of the type XCH_2CO- (where X=Br, Cl, or I), which show particular reactivity for sulfhydryl groups, but which can also be used to

modify imidazolyl, thioether, phenol, and amino groups as described by Gurd, *Methods Enzymol.* 11:532 (1967). N-Maleimide derivatives are also considered selective towards sulfhydryl groups, but may additionally be useful in coupling to amino groups under certain conditions. Reagents such as 2-iminothiolane (Traut et al., *Biochemistry* 12:3266 (1973)), which introduce a thiol group through conversion of an amino group, may be considered as sulfhydryl reagents if linking occurs through the formation of disulfide bridges.

Examples of reactive moieties capable of reaction with amino groups include, for example, alkylating and acylating agents. Representative alkylating agents include:

(i) α-haloacetyl compounds, which show specificity towards amino groups in the absence of reactive thiol groups and are of the type XCH_2CO- (where X=Br, Cl, or I), for example, as described by Wong *Biochemistry* 24:5337 (1979);

(ii) N-maleimide derivatives, which may react with amino groups either through a Michael type reaction or through acylation by addition to the ring carbonyl group, for example, as described by Smyth et al., *J. Am. Chem. Soc.* 82:4600 (1960) and *Biochem. J.* 91:589 (1964);

(iii) aryl halides such as reactive nitrohaloaromatic compounds;

(iv) alkyl halides, as described, for example, by McKenzie et al., *J. Protein Chem.* 7:581 (1988);

(v) aldehydes and ketones capable of Schiff's base formation with amino groups, the adducts formed usually being stabilized through reduction to give a stable amine;

(vi) epoxide derivatives such as epichlorohydrin and bisoxiranes, which may react with amino, sulfhydryl, or phenolic hydroxyl groups;

(vii) chlorine-containing derivatives of s-triazines, which are very reactive towards nucleophiles such as amino, sufhydryl, and hydroxyl groups;

(viii) aziridines based on s-triazine compounds detailed above, e.g., as described by Ross, *J. Adv. Cancer Res.* 2:1 (1954), which react with nucleophiles such as amino groups by ring opening;

(ix) squaric acid diethyl esters as described by Tietze, *Chem. Ber.* 124:1215 (1991); and

(x) α-haloalkyl ethers, which are more reactive alkylating agents than normal alkyl halides because of the activation caused by the ether oxygen atom, as described by Benneche et al., *Eur. J. Med. Chem.* 28:463 (1993).

Representative amino-reactive acylating agents include:

(i) isocyanates and isothiocyanates, particularly aromatic derivatives, which form stable urea and thiourea derivatives respectively;

(ii) sulfonyl chlorides, which have been described by Herzig et al., *Biopolymers* 2:349 (1964);

(iii) acid halides;

(iv) active esters such as nitrophenylesters or N-hydroxysuccinimidyl esters;

(v) acid anhydrides such as mixed, symmetrical, or N-carboxyanhydrides;

(vi) other useful reagents for amide bond formation, for example, as described by M. Bodansky, *Principles of Peptide Synthesis*, Springer-Verlag, 1984;

(vii) acylazides, e.g., wherein the azide group is generated from a preformed hydrazide derivative using sodium nitrite, as described by Wetz et al., *Anal. Biochem.* 58:347 (1974); and

(viii) imidoesters, which form stable amidines on reaction with amino groups, for example, as described by Hunter and Ludwig, *J. Am. Chem. Soc.* 84:3491 (1962).

Aldehydes and ketones may be reacted with amines to form Schiff's bases, which may advantageously be stabilized through reductive amination. Alkoxylamino moieties readily react with ketones and aldehydes to produce stable alkoxamines, for example, as described by Webb et al., in *Bioconjugate Chem.* 1:96 (1990).

Examples of reactive moieties capable of reaction with carboxyl groups include diazo compounds such as diazoacetate esters and diazoacetamides, which react with high specificity to generate ester groups, for example, as described by Herriot, *Adv. Protein Chem.* 3:169 (1947). Carboxyl modifying reagents such as carbodiimides, which react through O-acylurea formation followed by amide bond formation, may also be employed.

It will be appreciated that functional groups in drug (A) and/or drug (B) may, if desired, be converted to other functional groups prior to reaction, for example, to confer additional reactivity or selectivity. Examples of methods useful for this purpose include conversion of amines to carboxyls using reagents such as dicarboxylic anhydrides; conversion of amines to thiols using reagents such as N-acetylhomocysteine thiolactone, S-acetylmercaptosuccinic anhydride, 2-iminothiolane, or thiol-containing succinimidyl derivatives; conversion of thiols to carboxyls using reagents such as α -haloacetates; conversion of thiols to amines using reagents such as ethylenimine or 2-bromoethylamine; conversion of carboxyls to amines using reagents such as carbodiimides followed by diamines; and conversion of alcohols to thiols using reagents such as tosyl chloride followed by transesterification with thioacetate and hydrolysis to the thiol with sodium acetate.

So-called zero-length linkers, involving direct covalent joining of a reactive chemical group of drug (A) with a reactive chemical group of drug (B) without introducing additional linking material may, if desired, be used in accordance with the invention.

More commonly, however, the linker will include two or more reactive moieties, as described above, connected by a spacer element. The presence of such a spacer permits bifunctional linkers to react with specific functional groups within drug (A) and drug (B), resulting in a covalent linkage between the two. The reactive moieties in a linker may be the same (homobifunctional linker) or different (heterobifunctional linker, or, where several dissimilar reactive moieties are present, heteromultifunctional linker), providing a diversity of potential reagents that may bring about covalent attachment between drug (A) and drug (B).

Spacer elements in the linker typically consist of linear or branched chains and may include a C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-10} heteroalkyl.

In some instances, the linker is described by formula (II):

$$G^1\text{-}(Z^1)_o\text{-}(Y^1)_u\text{-}(Z^2)_s\text{-}(R_{30})\text{-}(Z^3)_t\text{-}(Y^2)_v\text{-}(Z^4)_p\text{–}G^2 \quad \text{(II)}$$

In formula (II), G^1 is a bond between drug (A) and the linker; G^2 is a bond between the linker and drug (B); Z^1, Z^2, Z^3, and Z^4 each, independently, is selected from O, S, and NR_{31}; R_{31} is hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-7} heteroalkyl; Y^1 and Y^2 are each, independently, selected from carbonyl, thiocarbonyl, sulphonyl, or phosphoryl; o, p, s, t, u, and v are each, independently, 0 or 1; and R_{30} is a C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{2-6}

heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-10} heteroalkyl, or a chemical bond linking G^1-$(Z^1)_o$-$(Y^1)_u$-$(Z^2)_s$- to -$(Z^3)_t$-$(Y^2)_v$-$(Z^4)_p$–G^2.

Examples of homobifunctional linkers useful in the preparation of conjugates of the invention include, without limitation, diamines and diols selected from ethylenediamine, propylenediamine and hexamethylenediamine, ethylene glycol, diethylene glycol, propylene glycol, 1,4-butanediol, 1,6-hexanediol, cyclohexanediol, and polycaprolactone diol.

Formulation of pharmaceutical compositions

The compositions, methods, and kits of the invention can include formulation(s) of compound(s) that, upon administration to a subject, result in a concentration of the compound(s) that treats a viral hepatitis infection. The compound(s) may be contained in any appropriate amount in any suitable carrier substance, and are generally present in an amount of 1-95% by weight of the total weight of the composition. The composition may be provided in a dosage form that is suitable for the oral, parenteral (e.g., intravenously or intramuscularly), rectal, determatological, cutaneous, nasal, vaginal, inhalant, skin (patch), ocular, intrathecal, or intracranial administration route. Thus, the composition may be in the form of, e.g., tablets, capsules, pills, powders, granulates, suspensions, emulsions, solutions, gels including hydrogels, pastes, ointments, creams, plasters, drenches, osmotic delivery devices, suppositories, enemas, injectables, implants, sprays, or aerosols. The pharmaceutical compositions may be formulated according to conventional pharmaceutical practice (see, e.g., Remington: *The Science and Practice of Pharmacy*, 20th edition, 2000, ed. A.R. Gennaro, Lippincott Williams & Wilkins, Philadelphia, and *Encyclopedia of Pharmaceutical Technology*, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York).

Pharmaceutical compositions according to the invention or used in the methods of the invention may be formulated to release the active compound immediately upon administration or at any predetermined time or time period after administration. The latter types of compositions are generally known as controlled release formulations, which include (i) formulations that create substantially constant concentrations of the agent(s) of the invention within the body over an extended period of time; (ii) formulations that after a predetermined lag time create substantially constant concentrations of the agent(s) of the invention within the body over an extended period of time; (iii) formulations that sustain the agent(s) action during a predetermined time period by maintaining a relatively constant, effective level of the agent(s) in the body with concomitant minimization of undesirable side effects associated with fluctuations in the plasma level of the agent(s) (sawtooth kinetic pattern); (iv) formulations that localize action of agent(s), e.g., spatial placement of a controlled release composition adjacent to or in the diseased tissue or organ; (v) formulations that achieve convenience of dosing, e.g., administering the composition once per week or once every two weeks; and (vi) formulations that target the action of the agent(s) by using carriers or chemical derivatives to deliver the combination to a particular target cell type. Administration of compound(s) in the form of a controlled release formulation is especially preferred for compounds having a narrow absorption window in the gastro-intestinal tract or a relatively short biological half-life.

Any of a number of strategies can be pursued in order to obtain controlled release in which the rate of release outweighs the rate of metabolism of the compound in question. In one example, controlled release is obtained by appropriate selection of various formulation parameters and ingredients, including, e.g., various types of controlled release compositions and coatings.

Thus, the compound(s) are formulated with appropriate excipients into a pharmaceutical composition that, upon administration, releases the compound(s) in a controlled manner. Examples include single or multiple unit tablet or capsule compositions, oil solutions, suspensions, emulsions, microcapsules, molecular complexes, microspheres, nanoparticles, patches, and liposomes.

Delivery of compound(s)

It is not intended that administration of compounds be limited to a single formulation and delivery method for all compounds of a combination. The combination can be administered using separate formulations and/or delivery methods for each compound of the combination using, for example, any of the above-described formulations and methods. In one example, a first agent is delivered orally, and a second agent is delivered intravenously.

Dosages

The dosage of a compound or a combination of compounds depends on several factors, including: the administration method, the type of viral hepatitis to be treated, the severity of the infection, whether dosage is designed to treat or prevent a viral hepatitis infection, and the age, weight, and health of the patient to be treated.

For combinations that include an anti-viral agent in addition to a compound identified herein (e.g., a compound of Table 1, Table 2, or Table 3), the recommended dosage for the anti-viral agent is can be less than or equal to the recommended dose as given in the *Physician's Desk Reference*, 60th Edition (2006).

As described above, the compound in question may be administered orally in the form of tablets, capsules, elixirs or syrups, or rectally in the form of suppositories. Parenteral administration of a compound is suitably performed, for example, in the form of saline solutions or with the compound incorporated into liposomes. In cases where the compound in itself is not sufficiently soluble to be dissolved, a solubilizer such as ethanol can be applied. The correct dosage of a compound can be determined by examining the efficacy of the compound in viral replication assays, as well as its toxicity in humans.

An antiviral agent is usually given by the same route of administration that is known to be effective for delivering it as a monotherapy. For example, when used in combination therapy with a compound of Table 1, Table 2, or Table 3 according to the methods of this invention, an agent of Table 4 or Table 5 is dosed in amounts and frequencies equivalent to or less than those that result in its effective monotherapeutic use.

Additional applications

If desired, the compounds of the invention may be employed in mechanistic assays to determine whether other combinations, or single agents, are as effective as the combinations of the invention in inhibiting a viral disease (e.g., those described herein) using assays generally known in the art. For example, candidate compounds may be tested, alone or in combination (e.g., with an agent that inhibits viral replication, such as those described herein) and applied to cells (e.g., hepatic cells such as Huh7, Huh2, Huh 8, Sk-Hep-1, Huh7 lunet, HepG2, WRL-68, FCA-1, LX-1, and LX-2). After a suitable time, viral replication or load of these cells is examined. A decrease in viral replication or

viral load identifies a candidate compound or combination of agents as an effective agent for treating a viral disease.

The agents of the invention are also useful tools in elucidating mechanistic information about the biological pathways involved in viral diseases. Such information can lead to the development of new combinations or single agents for treating, preventing, or reducing a viral disease. Methods known in the art to determine biological pathways can be used to determine the pathway, or network of pathways affected by contacting cells (e.g., hepatic cells) infected with a virus with the compounds of the invention. Such methods can include, analyzing cellular constituents that are expressed or repressed after contact with the compounds of the invention as compared to untreated, positive or negative control compounds, and/or new single agents and combinations, or analyzing some other activity of the cell or virus such as an enzymatic activity, nutrient uptake, and proliferation. Cellular components analyzed can include gene transcripts, and protein expression. Suitable methods can include standard biochemistry techniques, radiolabeling the compounds of the invention (e.g., ^{14}C or ^{3}H labeling), and observing the compounds binding to proteins, e.g., using 2D gels, gene expression profiling. Once identified, such compounds can be used in *in vivo* models (e.g., knockout or transgenic mice) to further validate the tool or develop new agents or strategies to treat viral disease.

Exemplary candidate compounds

Peptide moieties

Peptides, peptide mimetics, and peptide fragments (whether natural, synthetic or chemically modified) are suitable for use in the methods of the invention. Exemplary inhibitors include compounds that reduce the amount of a target protein or RNA levels (e.g., antisense compounds, dsRNA, ribozymes)

and compounds that compete with viral reproduction machinery (e.g., dominant negative proteins or polynucleotides encoding the same).

Antisense compounds

The biological activity of any protein that increases viral replication, viral RNA or DNA replication, viral RNA translation, viral protein processing or activity, or viral packaging can be reduced through the use of an antisense compound directed to RNA encoding the target protein. Antisense compounds can be identified using standard techniques. For example, accessible regions of the target the mRNA of the target enzyme can be predicted using an RNA secondary structure folding program such as MFOLD (M. Zuker, D. H. Mathews & D. H. Turner, *Algorithms and Thermodynamics for RNA Secondary Structure Prediction: A Practical Guide*. In: *RNA Biochemistry and Biotechnology*, J. Barciszewski & B. F. C. Clark, eds., NATO ASI Series, Kluwer Academic Publishers, (1999)). Sub-optimal folds with a free energy value within 5% of the predicted most stable fold of the mRNA are predicted using a window of 200 bases within which a residue can find a complimentary base to form a base pair bond. Open regions that do not form a base pair are summed together with each suboptimal fold and areas that are predicted as open are considered more accessible to the binding to antisense nucleobase oligomers. Other methods for antisense design are described, for example, in U.S. Pat. No. 6,472,521, *Antisense Nucleic Acid Drug Dev.* 1997 7:439-444, *Nucleic Acids Res.* 28:2597-2604, 2000, and *Nucleic Acids Res.* 31:4989-4994, 2003.

RNA interference

The biological activity of a molecule involved in a viral infection or viral replication can be reduced through the use of RNA interference (RNAi), employing, e.g., a double stranded RNA (dsRNA) or small interfering RNA (siRNA) directed to the signaling molecule in question (see, e.g., Miyamoto et al., *Prog. Cell Cycle Res.* 5:349-360, 2003; U.S. Pat. Application Publication No. 20030157030). Methods for designing such interfering RNAs are known in the art. For example, software for designing interfering RNA is available from Oligoengine (Seattle, WA).

Dominant negative proteins

One skilled in the art would know how to make dominant negative proteins to the molecules involved in a viral infection or viral replication. Such dominant negative proteins are described, for example, in Gupta et al., *J. Exp. Med.*, 186:473-478, 1997; Maegawa et al., *J. Biol. Chem.* 274:30236-30243, 1999; Woodford-Thomas et al., *J. Cell Biol.* 117:401-414, 1992).

The following example is intended to illustrate rather than limit the invention.

Example

HCV replicon assay

The HCV replicon assay enables screening of compounds with antiviral activity against HCV viral RNA replication. Huh7 cells expressing a subgenomic RNA replicon of Con1 (genotype 1b) sequence origin and expressing the reporter enzyme luciferase were obtained from ReBLikon, GmBH. In order to perform the assay, seed replicon cells on a 384-well plate at

4,000 cells/well in a total volume of 30 uL/well. The plated cells are incubated at 37°C, 5% CO_2. Pre-diluted compounds are added at a 10X concentration to each well to achieve the desired final concentration. Plates are centrifuged at 900 x g, 1 minute following the addition of compounds. Incubate cells an additional 48 hours at 37°C, 5% CO_2. Remove plates from the incubator 30 minutes to 1 hour prior to the addition of 25 µL/well of SteadyLite luciferase assay reagent from Perkin Elmer in order to equilibrate plates to room temperature. Following the addition of SteadyLite reagent, allow cells to incubate for 10 minutes prior to collecting data with a luminometer. Antiviral activity is quantified by the inhibition of luciferase activity.

In order to confirm that a decrease in luciferase activity correlates with inhibition of HCV replicon replication and not an increase in cell death, a counter screen is run in tandem. Huh7 parental cells which do not express HCV replicon RNA are treated similarly to the above replicon cells; briefly, seed cells on a 384-well plate at 4,000 cells/well as described above. Compounds are added the following day and, after a subsequent 48-hour incubation at 37°C, 5% CO_2, 15 µl/well of ATPlite (Perkin Elmer) is added after plates have been equilibrated at room temperature. The ATPlite assay provides a quantitative measure of the levels of ATP in the cell cultures in each well, where higher levels of ATP correlate with greater cellular viability. Thus, a compound with antiviral activity is expected to inhibit the levels of luciferase measured by the SteadyLite assay without any or minimal effect on the ATP levels measured by the ATPlite assay.

Using the screen described above or a similar screen, we identified the agents listed in Tables 1, 2, and 3 and the combinations of agents listed in Table 9. For screens involving a combination of compounds, a synergy score was calculated by the formula $S = \log f_X \log f_Y \sum I_{data} (I_{data} - I_{Loewe})$, summed over all non-

single-agent concentration pairs, and where $\log f_{X,Y}$ are the natural logarithm of the dilution factors used for each single agent. This effectively calculates a volume between the measured and Loewe additive response surfaces, weighted towards high inhibition and corrected for varying dilution factors. The synergy score indicates that the combination of the two agents provides greater antiviral activity than would be expected based on the protection provided by each agent of the combination individually. The following ranges of concentrations of agents were used to generate the synergy scores in Table 9: sertraline (0.105-13 μM); simvastatin (0.175-22 μM); fluvastatin (0.22-28 μM); lovastatin (0.06-7.9 μM); rosuvastatin (0.19-24 μM); and hydroxyzine (0.21-27 μM).

Table 9: Combinations of compounds

Compound 1	Compound 2	Synergy Score
Sertraline hydrochloride	Fluvastatin	4.7305
Sertraline hydrochloride	Lovastatin	3.6093
Sertraline hydrochloride	Rosuvastatin calcium	4.4640
Sertraline hydrochloride	Simvastatin	3.0251
Sertraline hydrochloride	Hydroxyzine hydrochloride	1.4113

Synergy scores were also identified for the following combination of compounds (Tables 10 and 11).

Table 10

Compound A	Compound B	Synergy Score
Amorolfine Hydrochloride	Sertraline Hydrochloride	5.202
Fluvastatin	Sertraline Hydrochloride	4.729
Rosuvastatin calcium	Sertraline Hydrochloride	4.481
Fulvestrant	Satraplatin	3.562
Amorolfine Hydrochloride	Mebeverine Hydrochloride	3.527
Amorolfine Hydrochloride	Satraplatin	3.414
Ifenprodil tartrate	Sertraline Hydrochloride	3.344
Amorolfine Hydrochloride	Tolterodine Tartrate	3.156
Atorvastatin	Sertraline Hydrochloride	3.136

Amorolfine Hydrochloride	Irinotecan Hydrochloride	3.059
Lovastatin	Sertraline Hydrochloride	3.022
Cytarabine	Triciribine	2.970
Artesunate	Wortmannin	2.964
Sertraline Hydrochloride	Simvastatin Hydroxy Acid, Ammonium Salt	2.955
Amorolfine Hydrochloride	Cytarabine	2.944
Sertraline Hydrochloride	Simvastatin	2.930
Octyl Methoxycinnamate	Suberohydroxamic Acid	2.840
1,5-Bis(4-aminophenoxy)pentane	Amorolfine Hydrochloride	2.756
(S,S)-N-Desmethyl Sertraline, Hydrochloride	Simvastatin	2.737
Artemisinin	SB-202190	2.689
Interferon Alfa-2a	Sirolimus	2.678
Amorolfine Hydrochloride	Indocyanine Green	2.623
TOFA	Triciribine	2.606
3,3'-(Pentamethylenedioxy)dianiline	Artemisinin	2.602
Artemisinin	Wortmannin	2.599
3,3''-(Pentamethylenedioxy)diacetanilide	Artemisinin	2.554
Amorolfine Hydrochloride	Benzamil HCL	2.549
Artemisinin	Triciribine	2.495
2,2'-(Pentamethylenedioxy)dianiline	Amorolfine Hydrochloride	2.494
(S,S)-N-Desmethyl Sertraline, Hydrochloride	Simvastatin Hydroxy Acid, Ammonium Salt	2.475
Levothyroxine Sodium	Wedelolactone	2.417
1,5-Bis(4-aminophenoxy)pentane	Artemisinin	2.390
Benzamil HCL	Dextrothyroxine Sodium	2.353
Amorolfine Hydrochloride	Trifluperidol	2.321
Artemisinin	Indocyanine Green	2.311
Dihydroartemisinin	Wortmannin	2.243
Flupentixol Dihydrochloride	Sertraline Hydrochloride	2.185
Benzamil HCL	Levothyroxine Sodium	2.131
Amorolfine Hydrochloride	Meclizine	2.093
Pravastatin Sodium	Sertraline Hydrochloride	2.033
1,5-Bis(4-aminophenoxy)pentane	Indocyanine Green	2.030
2-Hydroxyflavanone	Amorolfine Hydrochloride	1.990
Ritonavir	Vinorelbine	1.989
Benoxinate Hydrochloride	Dehydroepiandrosterone	1.975
Ifenprodil tartrate	Indocyanine Green	1.930
Amorolfine Hydrochloride	Arbidol	1.911

3,3'-(Pentamethylenedioxy)dianiline	Indocyanine Green	1.905
Fulvestrant	Vinorelbine	1.902
Amorolfine Hydrochloride	Ezetimibe	1.890
Amorolfine Hydrochloride	Evans Blue	1.885
Amorolfine Hydrochloride	Gefitinib (Base)	1.838
Amorolfine Hydrochloride	Topotecan Hydrochloride	1.810
2',2''-(Pentamethylenedioxy)diacetanilide	Artemisinin	1.798
Amorolfine Hydrochloride	Wedelolactone	1.770
3,3'-(Pentamethylenedioxy)dianiline	Amorolfine Hydrochloride	1.746
Simvastatin	rac-cis-N-Desmethyl Sertraline, Hydrochloride	1.744
Adefovir Dipivoxil	Triciribine	1.741
Cytarabine	Evans Blue	1.714
Artemisinin	Evans Blue	1.664
Fluphenazine Hydrochloride	Sertraline Hydrochloride	1.647
Benzamil HCL	SB-202190	1.643
Artemisinin	Rifabutin	1.627
Fluphenazine Hydrochloride	Tolterodine Tartrate	1.603
Interferon Alfa-2a	Melphalan	1.537
Amorolfine Hydrochloride	Melphalan	1.535
Artemisinin	Fulvestrant	1.477
Ifenprodil tartrate	Quinacrine	1.466
Simvastatin Hydroxy Acid, Ammonium Salt	rac-cis-N-Desmethyl Sertraline, Hydrochloride	1.456
Flupentixol Dihydrochloride	Tolterodine Tartrate	1.440
Triciribine	Wortmannin	1.439
Loratadine	Vinorelbine	1.423
Meclizine	Sertraline Hydrochloride	1.358
Budesonide	Vinorelbine	1.356
2-Hydroxyflavanone	Indocyanine Green	1.308
Hydroxyzine Hydrochloride	Sertraline Hydrochloride	1.293
2,2'-(Pentamethylenedioxy)dianiline	Artemisinin	1.281
Amorolfine Hydrochloride	Flupentixol Dihydrochloride	1.259
Artemisinin	Chlorophyllin	1.256
Ezetimibe	Fluphenazine Hydrochloride	1.240
Benzamil HCL	Fluphenazine Hydrochloride	1.237
Artemisinin	Wedelolactone	1.228
Cytarabine	Dydrogesterone	1.215
Artemisinin	Benzamil HCL	1.205

3,3'-(Pentamethylenedioxy)dianiline	Artemether	1.169
Tolterodine Tartrate	Trifluperidol	1.146
Artesunate	Fluvastatin	1.102
Artemisinin	Trifluridine	1.095
Adefovir Dipivoxil	Amorolfine Hydrochloride	1.069
Interferon Alfa-2a	Trifluridine	1.066
Fulvestrant	Triciribine	1.032
Artesunate	Dydrogesterone	1.032
Artesunate	LY 294002	1.006
Mosapride Citrate	TOFA	0.986
Bromocriptine Mesylate	Wedelolactone	0.978
Artemisinin	Sodium Fusidate	0.968
Celgosivir	Interferon Alfa-2a	0.966
Amorolfine Hydrochloride	Dextrothyroxine Sodium	0.960
Andrographis	Fulvestrant	0.944
2'-C-Methylcytidine	Artemisinin	0.937
Amorolfine Hydrochloride	Gemcitabine Hydrochloride	0.923
Oxeladin	Sertraline Hydrochloride	0.909
Artemisinin	Parthenolide	0.903
Artemisinin	Ribavirin	0.899
Dehydroepiandrosterone	Tyrphostin Ag 1478	0.880
Sertraline Hydrochloride	Toremifene	0.879
Dihydroartemisinin	Fulvestrant	0.863
2-Hydroxyflavanone	TOFA	0.860
Artesunate	Repaglinide	0.854
Mofebutazone	Wedelolactone	0.842
Artesunate	Simvastatin	0.841
2,2'-(Pentamethylenedioxy)dianiline	Artesunate	0.821
Artemisinin	Gemcitabine Hydrochloride	0.820
Dihydroartemisinin	Ezetimibe	0.812
Chlorophyllin	Cytarabine	0.811

Table 11

Compound A	**Compound B**	**Synergy Score**
Interferon Alfa-2a	Sirolimus	2.678
Suberohydroxamic Acid	VX-497	2.113
Artemisinin	VX-497	2.103
Artesunate	VX-497	1.692

Tolterodine Tartrate	VX-950	1.689
Artemisinin	HCV-796	1.683
Artemisinin	NM-283	1.681
NM-283	Wedelolactone	1.667
Artemisinin	SCH 503034	1.654
Cytarabine	SCH 503034	1.562
SCH 503034	Triciribine	1.549
Interferon Alfa-2a	Melphalan	1.537
Benoxinate Hydrochloride	VX-950	1.432
HCV-796	Sirolimus	1.412
Benoxinate Hydrochloride	SCH 503034	1.401
Melphalan	VX-950	1.397
Ritonavir	VX-950	1.388
VX-950	VX-497	1.354
Artemisinin	VX-950	1.343
Triciribine	VX-950	1.305
Suberohydroxamic Acid	VX-950	1.277
HCV-796	Suberohydroxamic Acid	1.259
Sirolimus	VX-950	1.245
Melphalan	SCH 503034	1.224
SCH 503034	Wortmannin	1.212
SCH 503034	Tolterodine Tartrate	1.188
Ritonavir	SCH 503034	1.160
Ezetimibe	VX-950	1.160
HCV-796	VX-497	1.146
Chlorophyllin	VX-497	1.144
HCV-796	Melphalan	1.143
Capsaicin	NM-283	1.112
SCH 503034	Sirolimus	1.105
LY 294002	SCH 503034	1.073
Adefovir Dipivoxil	SCH 503034	1.072
Interferon Alfa-2a	Trifluridine	1.066
HCV-796	Trifluridine	1.065
GW 5074	NM-283	1.061
Mosapride Citrate	VX-950	1.057
Interferon Alfa-2a	VX-497	1.017
NM-283	Trequinsin Hydrochloride	0.990
Cytarabine	HCV-796	0.989
Adefovir Dipivoxil	VX-950	0.961
Cytarabine	VX-950	0.956
SCH 503034	Saquinavir Mesylate	0.948
VX-950	Wortmannin	0.941
Capsaicin	VX-950	0.938

2-Hydroxyflavanone	NM-283	0.935
Bromhexine	VX-950	0.935
HCV-796	Wortmannin	0.915
Artemisinin	Ribavirin	0.899
VX-950	Verapamil	0.895
SCH 503034	Verapamil	0.880
SCH 503034	Topotecan Hydrochloride	0.879
HCV-796	Topotecan Hydrochloride	0.875
Trifluperidol	VX-950	0.866
Irinotecan Hydrochloride	SCH 503034	0.864
Artesunate	SCH 503034	0.849
Repaglinide	SCH 503034	0.845
Topotecan Hydrochloride	VX-950	0.839
Repaglinide	VX-950	0.825
Arbidol	VX-950	0.821
Chlorophyllin	HCV-796	0.813
Benzydamine hydrochloride	VX-950	0.800
NM-283	Trifluperidol	0.798
Capsaicin	HCV-796	0.755
NM-283 Hydrochloride	Phenazopyridine	0.692
NM-283	Trifluridine	0.688
Adefovir Dipivoxil	HCV-796	0.672

Other Embodiments

All publications, patent applications including U.S. Provisional Application Nos. 60/844,463, filed September 14, 2006, and 60/874,061 filed December 11, 2006, and patents mentioned in this specification are herein incorporated by reference.

Various modifications and variations of the described method and system of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific desired embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention that are obvious to those skilled in the

fields of molecular biology, medicine, immunology, pharmacology, virology, or related fields are intended to be within the scope of the invention.

What is claimed is:

Claims

1. A composition comprising:

(a) a first agent selected from the agents of Table 1, Table 2, and Table 3; and

(b) a second agent selected from the agents of Table 4 and Table 5.

2. The composition of claim 1, wherein said first agent and said second agent are present in amounts that, when administered to a patient with a viral disease, are effective to treat said patient.

3. The composition of claim 2, wherein said viral disease is caused by a single stranded RNA virus, a flaviviridae virus, or a hepatic virus.

4. The composition of claim 3, wherein said flaviviridae virus is a hepacivirus, a flavivirus, a pestivirus, or a hepatitis G virus.

5. The composition of claim 4, wherein said flavivirus is selected from the group consisting of Absettarov, Alfuy, Apoi, Aroa, Bagaza, Banzi, Bouboui, Bussuquara, Cacipacore, Carey Island, Dakar bat, Dengue 1, Dengue 2, Dengue 3, Dengue 4, Edge Hill, Entebbe bat, Gadgets Gully, Hanzalova, Hypr, Ilheus, Israel turkey meningoencephalitis, Japanese encephalitis, Jugra, Jutiapa, Kadam, Karshi, Kedougou, Kokobera, Koutango, Kumlinge, Kunjin, Kyasanur Forest disease, Langat, Louping ill, Meaban, Modoc, Montana myotis leukoencephalitis, Murray valley encephalitis, Naranjal, Negishi, Ntaya, Omsk hemorrhagic fever, Phnom-Penh bat, Powassan, Rio Bravo, Rocio, royal farm, Russian spring-summer encephalitis, Saboya, St. Louis encephalitis, Sal Vieja, San Perlita, Saumarez Reef, Sepik, Sokuluk, Spondweni, Stratford, Tembusu,

Tyuleniy, Uganda S, Usutu, Wesselsbron, west Nile, Yaounde, yellow fever, and Zika.

6. The composition of claim 4, wherein said pestivirus is selected from the group consisting of bovine viral diarrhea virus, classical swine fever virus, and border disease virus.

7. The composition of claim 3, wherein said hepatic virus is hepatitis A, hepatitis B, hepatitis C, hepatitis D, or hepatitis E.

8. The composition of claim 2, wherein said viral disease is hepatitis A, hepatitis B, hepatitis C, hepatitis D, or hepatitis E.

9. The composition of claim 1, further comprising one or more additional agents selected the agents of Table 4 and Table 5.

10. The composition of claim 1, wherein said composition is formulated for oral administration.

11. The composition of claim 1, wherein said composition is formulated for systemic administration.

12. The composition of claim 1, wherein said composition is formulated for parenteral administration.

13. A composition comprising sertraline and an HMG-CoA reductase inhibitor.

14. The composition of claim 13, wherein said HMG-CoA reductase inhibitor is fluvastatin, simvastatin, lovastatin, or rosuvastatin.

15. A composition comprising sertraline and an antihistamine.

16. The composition of claim 15, wherein said antihistamine is hydroxyzine.

17. A composition comprising a pair of agents selected from the group consisting of amorolfine and sertraline; fluvastatin and sertraline; rosuvastatin and sertraline; fulvestrant and satraplatin; amorolfine and mebeverine; amorolfine and satraplatin; ifenprodil and sertraline; amorolfine and tolterodine; atorvastatin and sertraline; amorolfine and irinotecan; lovastatin and sertraline; cytarabine and triciribine; artesunate and wortmannin; sertraline and simvastatin hydroxy acid, ammonium salt; amorolfine and cytarabine; sertraline and simvastatin; octyl methoxycinnamate and suberohydroxamic acid; 1,5-bis(4-aminophenoxy)pentane and amorolfine; (S,S)-N-desmethyl sertraline and simvastatin; artemisinin and SB-202190; interferon alfa-2a and sirolimus; amorolfine and indocyanine green; TOFA and triciribine; 3,3'-(pentamethylenedioxy)dianiline and artemisinin; artemisinin and wortmannin; 3,3''-(pentamethylenedioxy)diacetanilide and artemisinin; amorolfine and benzamil; artemisinin and triciribine; 2,2'-(pentamethylenedioxy)dianiline and amorolfine; (s,s)-n-desmethyl sertraline and simvastatin; levothyroxine and wedelolactone; 1,5-bis(4-aminophenoxy)pentane and artemisinin; benzamil and dextrothyroxine; amorolfine and trifluperidol; artemisinin and indocyanine green; dihydroartemisinin and wortmannin; flupentixol and sertraline; benzamil and levothyroxine; amorolfine and meclizine; pravastatin and sertraline; 1,5-

bis(4-aminophenoxy)pentane and indocyanine green; 2-hydroxyflavanone and amorolfine; ritonavir and vinorelbine; benoxinate and dehydroepiandrosterone; ifenprodil and indocyanine green; amorolfine and arbidol; 3,3'-(pentamethylenedioxy)dianiline and indocyanine green; fulvestrant and vinorelbine; amorolfine and ezetimibe; amorolfine and Evans blue; amorolfine and gefitinib; amorolfine and topotecan; 2',2''-(pentamethylenedioxy)diacetanilide and artemisinin; amorolfine and wedelolactone; 3,3'-(pentamethylenedioxy)dianiline and amorolfine; simvastatin and rac-cis-n-desmethyl sertraline; adefovir dipivoxil and triciribine; cytarabine and Evans blue; artemisinin and Evans blue; fluphenazine and sertraline; benzamil and SB-202190; artemisinin and rifabutin; fluphenazine and tolterodine; interferon alfa-2a and melphalan; amorolfine and melphalan; artemisinin and fulvestrant; ifenprodil and quinacrine; simvastatin and rac-cis-n-desmethyl sertraline; flupentixol and tolterodine; triciribine and wortmannin; loratadine and vinorelbine; meclizine and sertraline; budesonide and vinorelbine; 2-hydroxyflavanone and indocyanine green; hydroxyzine and sertraline; 2,2'-(pentamethylenedioxy)dianiline and artemisinin; amorolfine and flupentixol; artemisinin and chlorophyllin; ezetimibe and fluphenazine; benzamil and fluphenazine; artemisinin and wedelolactone; cytarabine and dydrogesterone; artemisinin and benzamil; 3,3'-(pentamethylenedioxy)dianiline and artemether; tolterodine and trifluperidol; artesunate and fluvastatin; artemisinin and trifluridine; adefovir dipivoxil and amorolfine; interferon alfa-2a and trifluridine; fulvestrant and triciribine; artesunate and dydrogesterone; artesunate and LY 294002; mosapride citrate and TOFA; bromocriptine and wedelolactone; artemisinin and sodium fusidate; celgosivir and interferon alfa-2a; amorolfine and dextrothyroxine; andrographis and fulvestrant; 2'-c-methylcytidine and artemisinin; amorolfine and gemcitabine; oxeladin and

sertraline; artemisinin and parthenolide; artemisinin and ribavirin; dehydroepiandrosterone and tyrphostin AG 1478; sertraline and toremifene; dihydroartemisinin and fulvestrant; 2-hydroxyflavanone and TOFA; artesunate and repaglinide; mofebutazone and wedelolactone; artesunate and simvastatin; 2,2'-(pentamethylenedioxy)dianiline and artesunate; artemisinin and gemcitabine; dihydroartemisinin and ezetimibe; chlorophyllin and cytarabine; interferon alfa-2a and sirolimus; suberohydroxamic acid and VX-497; artemisinin and VX-497; artesunate and VX-497; tolterodine and VX-950; artemisinin and HCV-796; artemisinin and NM-283; NM-283 and wedelolactone; artemisinin and SCH 503034; cytarabine and SCH 503034; SCH 503034 and triciribine; interferon alfa-2a and melphalan; benoxinate and VX-950; HCV-796 and sirolimus; benoxinate and SCH 503034; melphalan and VX-950; ritonavir and VX-950; VX-950 and VX-497; artemisinin and VX-950; triciribine and VX-950; suberohydroxamic acid and VX-950; HCV-796 and suberohydroxamic acid; sirolimus and VX-950; melphalan and SCH 503034; SCH 503034 and wortmannin; SCH 503034 and tolterodine; ritonavir and SCH 503034; ezetimibe and VX-950; HCV-796 and VX-497; chlorophyllin and VX-497; HCV-796 and melphalan; capsaicin and NM-283; SCH 503034 and sirolimus; LY 294002 and SCH 503034; adefovir dipivoxil and SCH 503034; interferon alfa-2a and trifluridine; HCV-796 and trifluridine; GW 5074 and NM-283; mosapride and VX-950; interferon alfa-2a and VX-497; NM-283 and trequinsin; cytarabine and HCV-796; adefovir dipivoxil and VX-950; cytarabine and VX-950; SCH 503034 and saquinavir; VX-950 and wortmannin; capsaicin and VX-950; 2-hydroxyflavanone and NM-283; bromhexine and VX-950; HCV-796 and wortmannin; artemisinin and ribavirin; VX-950 and verapamil; SCH 503034 and verapamil; SCH 503034 and topotecan; HCV-796 and topotecan; trifluperidol and VX-950; irinotecan and SCH 503034;

artesunate and SCH 503034; repaglinide and SCH 503034; topotecan and VX-950; tepaglinide and VX-950; arbidol and VX-950; chlorophyllin and HCV-796; benzydamine and VX-950; NM-283 and trifluperidol; capsaicin and HCV-796; NM-283 and phenazopyridine; NM-283 and trifluridine; and adefovir dipivoxil and HCV-796.

18. A composition comprising a pair of agents selected from the group consisting of simvastatin and sertraline; fluvastatin and sertraline; fluphenazine and sertraline; artesunate and simvastatin; artesunate and wortmannin; artemisinin and chlorophyllin; artemisinin and 3,3'-(pentamethylenedioxy)dianiline; amorolfine and meclizine; amorolfine and sertraline; amorolfine and trifluridine; amorolfine and 2-hydroxyflavanone; amorolfine and ezetimibe; amorolfine and benzamil; amorolfine and trifluperidol; and octyl methoxycinnamate and suberohydroxamic acid.

19. A method for treating a patient having a viral disease, said method comprising administering to said patient an agent selected from the agents of Table 1 in an amount effective to treat said patient.

20. A method for treating a patient having hepatitis C, said method comprising administering to said patient an agent selected from the agents of Table 1 and Table 2 in an amount effective to treat said patient.

21. A method for treating a patient having a viral disease, said method comprising administering to said patient a plurality of agents where the first agent is selected from the agents of Table 1, Table 2, and Table 3 and the second agent is selected from the agents of Table 4 and Table 5, wherein said

agents are administered within 28 days of each other in amounts that together are effective to treat said patient, wherein said plurality is not a combination of agents listed in Table 6 or Table 7.

22. The method of claim 21, wherein said agents are administered within ten days of each other.

23. The method of claim 22, wherein said agents are administered within five days of each other.

24. The method of claim 23, wherein said agents are administered within twenty-four hours of each other.

25. The method of claim 19 or 21, wherein said viral disease is caused by a single stranded RNA virus, a flaviviridae virus, or a hepatic virus.

26. The method of claim 25, wherein said flaviviridae virus is a hepacivirus, a flavivirus, a pestivirus, or hepatitis G virus.

27. The method of claim 26, wherein said flavivirus is selected from the group consisting of Absettarov, Alfuy, Apoi, Aroa, Bagaza, Banzi, Bouboui, Bussuquara, Cacipacore, Carey Island, Dakar bat, Dengue 1, Dengue 2, Dengue 3, Dengue 4, Edge Hill, Entebbe bat, Gadgets Gully, Hanzalova, Hypr, Ilheus, Israel turkey meningoencephalitis, Japanese encephalitis, Jugra, Jutiapa, Kadam, Karshi, Kedougou, Kokobera, Koutango, Kumlinge, Kunjin, Kyasanur Forest disease, Langat, Louping ill, Meaban, Modoc, Montana myotis leukoencephalitis, Murray valley encephalitis, Naranjal, Negishi, Ntaya, Omsk

hemorrhagic fever, Phnom-Penh bat, Powassan, Rio Bravo, Rocio, royal farm, Russian spring-summer encephalitis, Saboya, St. Louis encephalitis, Sal Vieja, San Perlita, Saumarez Reef, Sepik, Sokuluk, Spondweni, Stratford, Tembusu, Tyuleniy, Uganda S, Usutu, Wesselsbron, west Nile, Yaounde, yellow fever, and Zika.

28. The method of claim 26, wherein said pestivirus is selected from the group consisting of bovine viral diarrhea virus, classical swine fever viru, and border disease virus.

29. The method of claim 19 or 21, wherein said viral disease is viral hepatitis.

30. The method of claim 29, wherein said viral hepatitis is caused by hepatitis A, hepatitis B, hepatitis C, hepatitis D, or hepatitis E.

31. The method of claim 25, wherein said hepatic virus is hepatitis A, hepatitis B, hepatitis C, hepatitis D, or hepatitis E.

32. The method of claim 31, wherein said hepatitis C is hepatitis C genotype 1, 2, 3, 4, 5, or 6.

33. The method of claim 32, wherein said hepatitis C genotype 1 is genotype 1a or 1b.

34. The method of claim 19, 20, or 21, wherein said method is performed in conjunction with administering to said patient an additional

antiviral treatment, wherein said method is performed and said additional treatment is administered within 6 months of each other.

35. The method of claim 34, wherein said additional antiviral treatment is administered and said method is performed within fourteen days of each other.

36. The method of claim 34, wherein said additional antiviral treatment is administered and said method is performed within five days of each other.

37. The method of claim 34, wherein said additional antiviral treatment is administered and said method is performed within twenty-four hours of each other.

38. The method of claim 34, said additional antiviral treatment comprising administration of one or more agents selected from Table 4 and Table 5.

39. The method of claim 19, 20, or 21, wherein said agent or agents are administered to said patient by intravenous, intramuscular, inhalation, topical, or oral administration.

40. A method for treating a patient having a viral disease, said method comprising administering to said patient sertraline and an HMG-CoA reductase inhibitor, wherein said two agents are administered within 28 days of each other in amounts that together are effective to treat said patient.

41. The method of claim 40, wherein said HMG-CoA reductase inhibitor is fluvastatin, simvastatin, lovastatin, or rosuvastatin.

42. A method for treating a patient having a viral disease, said method comprising administering to said patient sertraline and an antihistamine wherein said two agents are administered within 28 days of each other in amounts that together are effective to treat said patient.

43. The method of claim 42, wherein said antihistamine is hydroxyzine.

44. A method for treating a patient having a viral disease, said method comprising administering to said patient a pair of agents selected from the group consisting of amorolfine and sertraline; fluvastatin and sertraline; rosuvastatin and sertraline; fulvestrant and satraplatin; amorolfine and mebeverine; amorolfine and satraplatin; ifenprodil and sertraline; amorolfine and tolterodine; atorvastatin and sertraline; amorolfine and irinotecan; lovastatin and sertraline; cytarabine and triciribine; artesunate and wortmannin; sertraline and simvastatin hydroxy acid, ammonium salt; amorolfine and cytarabine; sertraline and simvastatin; octyl methoxycinnamate and suberohydroxamic acid; 1,5-bis(4-aminophenoxy)pentane and amorolfine; (S,S)-N-desmethyl sertraline and simvastatin; artemisinin and SB-202190; interferon alfa-2a and sirolimus; amorolfine and indocyanine green; TOFA and triciribine; 3,3'-(pentamethylenedioxy)dianiline and artemisinin; artemisinin and wortmannin; 3,3''-(pentamethylenedioxy)diacetanilide and artemisinin; amorolfine and benzamil; artemisinin and triciribine; 2,2'-(pentamethylenedioxy)dianiline and amorolfine; (s,s)-n-desmethyl sertraline

and simvastatin; levothyroxine and wedelolactone; 1,5-bis(4-aminophenoxy)pentane and artemisinin; benzamil and dextrothyroxine; amorolfine and trifluperidol; artemisinin and indocyanine green; dihydroartemisinin and wortmannin; flupentixol and sertraline; benzamil and levothyroxine; amorolfine and meclizine; pravastatin and sertraline; 1,5-bis(4-aminophenoxy)pentane and indocyanine green; 2-hydroxyflavanone and amorolfine; ritonavir and vinorelbine; benoxinate and dehydroepiandrosterone; ifenprodil and indocyanine green; amorolfine and arbidol; 3,3'-(pentamethylenedioxy)dianiline and indocyanine green; fulvestrant and vinorelbine; amorolfine and ezetimibe; amorolfine and Evans blue; amorolfine and gefitinib; amorolfine and topotecan; 2',2''-(pentamethylenedioxy)diacetanilide and artemisinin; amorolfine and wedelolactone; 3,3'-(pentamethylenedioxy)dianiline and amorolfine; simvastatin and rac-cis-n-desmethyl sertraline; adefovir dipivoxil and triciribine; cytarabine and Evans blue; artemisinin and Evans blue; fluphenazine and sertraline; benzamil and SB-202190; artemisinin and rifabutin; fluphenazine and tolterodine; interferon alfa-2a and melphalan; amorolfine and melphalan; artemisinin and fulvestrant; ifenprodil and quinacrine; simvastatin and rac-cis-n-desmethyl sertraline; flupentixol and tolterodine; triciribine and wortmannin; loratadine and vinorelbine; meclizine and sertraline; budesonide and vinorelbine; 2-hydroxyflavanone and indocyanine green; hydroxyzine and sertraline; 2,2'-(pentamethylenedioxy)dianiline and artemisinin; amorolfine and flupentixol; artemisinin and chlorophyllin; ezetimibe and fluphenazine; benzamil and fluphenazine; artemisinin and wedelolactone; cytarabine and dydrogesterone; artemisinin and benzamil; 3,3'-(pentamethylenedioxy)dianiline and artemether; tolterodine and trifluperidol; artesunate and fluvastatin; artemisinin and trifluridine; adefovir dipivoxil and amorolfine; interferon alfa-

2a and trifluridine; fulvestrant and triciribine; artesunate and dydrogesterone; artesunate and LY 294002; mosapride citrate and TOFA; bromocriptine and wedelolactone; artemisinin and sodium fusidate; celgosivir and interferon alfa-2a; amorolfine and dextrothyroxine; andrographis and fulvestrant; 2'-c-methylcytidine and artemisinin; amorolfine and gemcitabine; oxeladin and sertraline; artemisinin and parthenolide; artemisinin and ribavirin; dehydroepiandrosterone and tyrphostin AG 1478; sertraline and toremifene; dihydroartemisinin and fulvestrant; 2-hydroxyflavanone and TOFA; artesunate and repaglinide; mofebutazone and wedelolactone; artesunate and simvastatin; 2,2'-(pentamethylenedioxy)dianiline and artesunate; artemisinin and gemcitabine; dihydroartemisinin and ezetimibe; chlorophyllin and cytarabine; interferon alfa-2a and sirolimus; suberohydroxamic acid and VX-497; artemisinin and VX-497; artesunate and VX-497; tolterodine and VX-950; artemisinin and HCV-796; artemisinin and NM-283; NM-283 and wedelolactone; artemisinin and SCH 503034; cytarabine and SCH 503034; SCH 503034 and triciribine; interferon alfa-2a and melphalan; benoxinate and VX-950; HCV-796 and sirolimus; benoxinate and SCH 503034; melphalan and VX-950; ritonavir and VX-950; VX-950 and VX-497; artemisinin and VX-950; triciribine and VX-950; suberohydroxamic acid and VX-950; HCV-796 and suberohydroxamic acid; sirolimus and VX-950; melphalan and SCH 503034; SCH 503034 and wortmannin; SCH 503034 and tolterodine; ritonavir and SCH 503034; ezetimibe and VX-950; HCV-796 and VX-497; chlorophyllin and VX-497; HCV-796 and melphalan; capsaicin and NM-283; SCH 503034 and sirolimus; LY 294002 and SCH 503034; adefovir dipivoxil and SCH 503034; interferon alfa-2a and trifluridine; HCV-796 and trifluridine; GW 5074 and NM-283; mosapride and VX-950; interferon alfa-2a and VX-497; NM-283 and trequinsin; cytarabine and HCV-796; adefovir dipivoxil and VX-950;

cytarabine and VX-950; SCH 503034 and saquinavir; VX-950 and wortmannin; capsaicin and VX-950; 2-hydroxyflavanone and NM-283; bromhexine and VX-950; HCV-796 and wortmannin; artemisinin and ribavirin; VX-950 and verapamil; SCH 503034 and verapamil; SCH 503034 and topotecan; HCV-796 and topotecan; trifluperidol and VX-950; irinotecan and SCH 503034; artesunate and SCH 503034; repaglinide and SCH 503034; topotecan and VX-950; tepaglinide and VX-950; arbidol and VX-950; chlorophyllin and HCV-796; benzydamine and VX-950; NM-283 and trifluperidol; capsaicin and HCV-796; NM-283 and phenazopyridine; NM-283 and trifluridine; and adefovir dipivoxil and HCV-796, wherein said agents are administered within 28 days of each other in amounts that together are effective to treat said patient.

45. A method for treating a patient having a viral disease, said method comprising administering to said patient a pair of agents selected from the group consisting of simvastatin and sertraline; fluvastatin and sertraline; fluphenazine and sertraline; artesunate and simvastatin; artesunate and wortmannin; artemisinin and chlorophyllin; artemisinin and 3,3'-(pentamethylenedioxy)dianiline; amorolfine and meclizine; amorolfine and sertraline; amorolfine and trifluridine; amorolfine and 2-hydroxyflavanone; amorolfine and ezetimibe; amorolfine and benzamil; amorolfine and trifluperidol; and octyl methoxycinnamate and suberohydroxamic acid, wherein said two agents are administered within 28 days of each other in amounts that together are effective to treat said patient.

46. A kit comprising:

(a) an agent selected from any of the agents of Table 1; and

(b) instructions for administering said agent to a patient having a viral disease.

47. A kit comprising:

(a) an agent selected from any of the agents of Table 1 and Table 2; and

(b) instructions for administering said agent to a patient having hepatitis C.

48. A kit comprising:

(a) a composition comprising:

(i) a first agent selected from any one of the agents of Table 1, Table 2, and Table 3; and

(ii) one or more agents of Table 4 or Table 5; and

(b) instructions for administering said composition to a patient having a viral disease.

49. A kit comprising:

(a) a first agent selected from any of the agents of Table 1, Table 2, and Table 3;

(b) one or more agents of Table 4 or Table 5; and

(c) instructions for administering (a) and (b) to a patient having a viral disease.

50. A kit comprising:

(a) an agent selected from any one of the agents of Table 1; and

(b) instructions for administering said agent and one or more agents selected from any of the agents of Table 4 and Table 5 to a patient having a viral disease.

51. A kit comprising:

(a) an agent selected from any of the agents of Table 1 and Table 2; and

(b) instructions for administering the agent and one or more agents of Table 4 or Table 5 to a patient having hepatitis C.

52. A kit comprising:

(a) one or more agents selected from any of the agents of Table 4 and Table 5; and

(b) instructions for administering said agent from (a) with any agent of Table 1, Table 2, and Table 3 to a patient having a viral disease.

53. A kit comprising:

(a) sertraline;

(b) an HMG-CoA reductase inhibitor; and

(c) instructions for administering (a) and (b) to a patient having a viral disease.

54. A kit comprising:

(a) a composition comprising sertraline and an HMG-CoA reductase inhibitor; and

(b) instructions for administering said composition to a patient having a viral disease.

55. The kit of claim 53 or 54, wherein said HMG-CoA reductase inhibitor is fluvastatin, simvastatin, lovastatin, or rosuvastatin.

56. A kit comprising:

(a) sertraline;

(b) an antihistamine; and

(c) instructions for administering (a) and (b) to a patient having a viral disease.

57. A kit comprising:

(a) a composition comprising sertraline and an antihistamine; and

(b) instructions for administering said composition to a patient having a viral disease.

58. The kit of claim 56 or 57, wherein said antihistamine is hydroxyzine.

59. A kit comprising:

(a) a pair of agents selected from the group consisting of amorolfine and sertraline; fluvastatin and sertraline; rosuvastatin and sertraline; fulvestrant and satraplatin; amorolfine and mebeverine; amorolfine and satraplatin; ifenprodil and sertraline; amorolfine and tolterodine; atorvastatin and sertraline; amorolfine and irinotecan; lovastatin and sertraline; cytarabine and triciribine; artesunate and wortmannin; sertraline and simvastatin hydroxy acid, ammonium salt; amorolfine and cytarabine; sertraline and simvastatin; octyl methoxycinnamate and suberohydroxamic acid; 1,5-bis(4-

aminophenoxy)pentane and amorolfine; (S,S)-N-desmethyl sertraline and simvastatin; artemisinin and SB-202190; interferon alfa-2a and sirolimus; amorolfine and indocyanine green; TOFA and triciribine; 3,3'-(pentamethylenedioxy)dianiline and artemisinin; artemisinin and wortmannin; 3,3''-(pentamethylenedioxy)diacetanilide and artemisinin; amorolfine and benzamil; artemisinin and triciribine; 2,2'-(pentamethylenedioxy)dianiline and amorolfine; (s,s)-n-desmethyl sertraline and simvastatin; levothyroxine and wedelolactone; 1,5-bis(4-aminophenoxy)pentane and artemisinin; benzamil and dextrothyroxine; amorolfine and trifluperidol; artemisinin and indocyanine green; dihydroartemisinin and wortmannin; flupentixol and sertraline; benzamil and levothyroxine; amorolfine and meclizine; pravastatin and sertraline; 1,5-bis(4-aminophenoxy)pentane and indocyanine green; 2-hydroxyflavanone and amorolfine; ritonavir and vinorelbine; benoxinate and dehydroepiandrosterone; ifenprodil and indocyanine green; amorolfine and arbidol; 3,3'-(pentamethylenedioxy)dianiline and indocyanine green; fulvestrant and vinorelbine; amorolfine and ezetimibe; amorolfine and Evans blue; amorolfine and gefitinib; amorolfine and topotecan; 2',2''-(pentamethylenedioxy)diacetanilide and artemisinin; amorolfine and wedelolactone; 3,3'-(pentamethylenedioxy)dianiline and amorolfine; simvastatin and rac-cis-n-desmethyl sertraline; adefovir dipivoxil and triciribine; cytarabine and Evans blue; artemisinin and Evans blue; fluphenazine and sertraline; benzamil and SB-202190; artemisinin and rifabutin; fluphenazine and tolterodine; interferon alfa-2a and melphalan; amorolfine and melphalan; artemisinin and fulvestrant; ifenprodil and quinacrine; simvastatin and rac-cis-n-desmethyl sertraline; flupentixol and tolterodine; triciribine and wortmannin; loratadine and vinorelbine; meclizine and sertraline; budesonide and vinorelbine; 2-hydroxyflavanone and indocyanine green; hydroxyzine and

sertraline; 2,2'-(pentamethylenedioxy)dianiline and artemisinin; amorolfine and flupentixol; artemisinin and chlorophyllin; ezetimibe and fluphenazine; benzamil and fluphenazine; artemisinin and wedelolactone; cytarabine and dydrogesterone; artemisinin and benzamil; 3,3'-(pentamethylenedioxy)dianiline and artemether; tolterodine and trifluperidol; artesunate and fluvastatin; artemisinin and trifluridine; adefovir dipivoxil and amorolfine; interferon alfa-2a and trifluridine; fulvestrant and triciribine; artesunate and dydrogesterone; artesunate and LY 294002; mosapride citrate and TOFA; bromocriptine and wedelolactone; artemisinin and sodium fusidate; celgosivir and interferon alfa-2a; amorolfine and dextrothyroxine; andrographis and fulvestrant; 2'-c-methylcytidine and artemisinin; amorolfine and gemcitabine; oxeladin and sertraline; artemisinin and parthenolide; artemisinin and ribavirin; dehydroepiandrosterone and tyrphostin ag 1478; sertraline and toremifene; dihydroartemisinin and fulvestrant; 2-hydroxyflavanone and TOFA; artesunate and repaglinide; mofebutazone and wedelolactone; artesunate and simvastatin; 2,2'-(pentamethylenedioxy)dianiline and artesunate; artemisinin and gemcitabine; dihydroartemisinin and ezetimibe; chlorophyllin and cytarabine; interferon alfa-2a and sirolimus; suberohydroxamic acid and VX-497; artemisinin and VX-497; artesunate and VX-497; tolterodine and VX-950; artemisinin and HCV-796; artemisinin and NM-283; NM-283 and wedelolactone; artemisinin and SCH 503034; cytarabine and SCH 503034; SCH 503034 and triciribine; interferon alfa-2a and melphalan; benoxinate and VX-950; HCV-796 and sirolimus; benoxinate and SCH 503034; melphalan and VX-950; ritonavir and VX-950; VX-950 and VX-497; artemisinin and VX-950; triciribine and VX-950; suberohydroxamic acid and VX-950; HCV-796 and suberohydroxamic acid; sirolimus and VX-950; melphalan and SCH 503034; SCH 503034 and wortmannin; SCH 503034 and tolterodine; ritonavir and SCH

503034; ezetimibe and VX-950; HCV-796 and VX-497; chlorophyllin and VX-497; HCV-796 and melphalan; capsaicin and NM-283; SCH 503034 and sirolimus; LY 294002 and SCH 503034; adefovir dipivoxil and SCH 503034; interferon alfa-2a and trifluridine; HCV-796 and trifluridine; GW 5074 and NM-283; mosapride and VX-950; interferon alfa-2a and VX-497; NM-283 and trequinsin; cytarabine and HCV-796; adefovir dipivoxil and VX-950; cytarabine and VX-950; SCH 503034 and saquinavir; VX-950 and wortmannin; capsaicin and VX-950; 2-hydroxyflavanone and NM-283; bromhexine and VX-950; HCV-796 and wortmannin; artemisinin and ribavirin; VX-950 and verapamil; SCH 503034 and verapamil; SCH 503034 and topotecan; HCV-796 and topotecan; trifluperidol and VX-950; irinotecan and SCH 503034; artesunate and SCH 503034; repaglinide and SCH 503034; topotecan and VX-950; tepaglinide and VX-950; arbidol and VX-950; chlorophyllin and HCV-796; benzydamine and VX-950; NM-283 and trifluperidol; capsaicin and HCV-796; NM-283 and phenazopyridine; NM-283 and trifluridine; and adefovir dipivoxil and HCV-796; and

(b) instructions for administering said pair of agents to a patient having a viral disease.

60. The kit of claim 59, wherein said kit comprises a composition comprising said pair of agents.

61. A kit comprising:

(a) a pair of agents selected from the group consisting of simvastatin and sertraline; fluvastatin and sertraline; fluphenazine and sertraline; artesunate and simvastatin; artesunate and wortmannin; artemisinin and chlorophyllin; artemisinin and 3,3'-(pentamethylenedioxy)dianiline;

amorolfine and meclizine; amorolfine and sertraline; amorolfine and trifluridine; amorolfine and 2-hydroxyflavanone; amorolfine and ezetimibe; amorolfine and benzamil; amorolfine and trifluperidol; and octyl methoxycinnamate and suberohydroxamic acid; and

(b) instructions for administering said pair of agents to a patient having a viral disease.

62. The kit of claim 61, wherein said kit comprises a composition comprising said pair of agents.

63. A method for identifying a combination that may be useful for the treatment of a patient having a viral disease, or the prevention or reduction of said viral disease, said method comprising the steps of:

(a) contacting cells comprising at least a portion of the genome of a virus with an agent selected from any one the agents of Table 1, Table 2, and Table 3 and a candidate compound, wherein said portion of the genome is capable of replication in said cells; and

(b) determining whether the combination of said agent and said candidate compound inhibits the replication of said portion of the genome relative to cells contacted with said agent but not contacted with the candidate compound, wherein a reduction in replication identifies the combination as a combination useful for the treatment of a patient having a viral disease, or the prevention or reduction of a viral disease.

64. The method of claim 53, wherein said viral disease is caused by a single stranded RNA virus, a flaviviridae virus, or a hepatic virus.

65. The method of claim 64, wherein said flaviviridae virus is a hepacivirus, a flavivirus, a pestivirus, or a hepatitis G virus.

66. The method of claim 65, wherein said flavivirus is selected from the group consisting of Absettarov, Alfuy, Apoi, Aroa, Bagaza, Banzi, Bouboui, Bussuquara, Cacipacore, Carey Island, Dakar bat, Dengue 1, Dengue 2, Dengue 3, Dengue 4, Edge Hill, Entebbe bat, Gadgets Gully, Hanzalova, Hypr, Ilheus, Israel turkey meningoencephalitis, Japanese encephalitis, Jugra, Jutiapa, Kadam, Karshi, Kedougou, Kokobera, Koutango, Kumlinge, Kunjin, Kyasanur Forest disease, Langat, Louping ill, Meaban, Modoc, Montana myotis leukoencephalitis, Murray valley encephalitis, Naranjal, Negishi, Ntaya, Omsk hemorrhagic fever, Phnom-Penh bat, Powassan, Rio Bravo, Rocio, royal farm, Russian spring-summer encephalitis, Saboya, St. Louis encephalitis, Sal Vieja, San Perlita, Saumarez Reef, Sepik, Sokuluk, Spondweni, Stratford, Tembusu, Tyuleniy, Uganda S, Usutu, Wesselsbron, west Nile, Yaounde, yellow fever, and Zika.

67. The method of claim 65, wherein said pestivirus is selected from the group consisting of bovine viral diarrhea virus, classical swine fever virus, and border disease virus.

68. The method of claim 53, wherein said viral disease is hepatitis A, hepatitis B, hepatitis C, hepatitis D, or hepatitis E.

69. The method of claim 64, wherein said hepatic virus is hepatitis A, hepatitis B, hepatitis C, hepatitis D, or hepatitis E.

70. The method of claim 69, wherein said reduction in replication is due to decreased polyprotein processing, decreased RNA replication, decreased RNA transcription, decreased protein translation, or inhibition of a protein required for viral replication.

71. The method of claim 53, wherein said reduction in replication is the result of decreased DNA or RNA replication, decreased RNA transcription, decreased protein translation, or inhibition of a protein required for viral replication.

72. The method of claim 70 or 71, wherein said protein required for viral replication is a protein coded for by the viral genome or by the host cell.

73. The method of claim 53, wherein said cells are mammalian cells.

74. The method of claim 73, wherein said cells are human cells.

75. The method of claim 73, wherein said cells are hepatic cells.