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(54) **HYDROLYTICALLY-RESISTANT BORON-CONTAINING THERAPEUTICS AND METHODS OF USE**

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C07F 9/02 (2006.01)

(52) **U.S. Cl.** **568/8**

(58) **Field of Classification Search** 568/8
See application file for complete search history.

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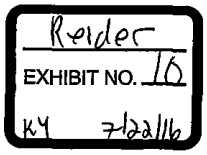
(57) **ABSTRACT**

Compositions and methods of use of borole derivatives, including benzoxaboroles, benzazaboroles and benzthiaboroles, as therapeutic agents for treatment of diseases caused by bacteria or viruses are disclosed, as well as methods for synthesis of said agents and compositions thereof.

30 Claims, No Drawings



HYDROLYTICALLY-RESISTANT BORON-CONTAINING THERAPEUTICS AND METHODS OF USE

This application claims priority of U.S. Provisional Application Ser. No. 60/478,921, filed 16 Jun. 2003, the disclosure of which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to novel compounds and compositions which have selective therapeutic activities, processes for making such compounds, synthetic intermediates employed in these processes and a method for treating human or other mammal in need of medical treatments.

BACKGROUND OF THE INVENTION

Many advances in medicine in the 20th century have been due to the discovery of new classes of small molecular weight effectors for various therapeutic needs. Herein we disclose the diverse, but selective pharmacologically active boron-containing entities.

One hallmark of the modern era of medicine has been the decline in morbidity and mortality associated with bacterial and fungal infections. However, misuse of conventional antibiotics and natural selection of the infectious bacterial population has resulted in the development of varying degrees of drug resistance by most bacterial infectious agents to most antibiotic agents. In severe cases, such as MRSA (Multidrug-Resistant StaphA), one or only a few antibiotics are currently effective. In addition, the existence of immunodeficiency syndromes results in additional incidences of opportunistic infections requiring intensive antibiotic treatment.

Viruses are implicated in a variety of animal and human disease. Numerous approaches have been proposed to combat these pathogens which include, but are not limited to herpesviruses 1 and 2 (HSV-1 and HSV-2), influenza viruses A, B and C, parainfluenza viruses 14, syncytial virus, Epstein-Barr virus, rhinoviruses, human immunodeficiency viruses (HIV), polioviruses, coxsackieviruses, echoviruses, rubella virus, varicella-zoster virus, neuroderma-tropic virus, variola virus, cytomegalovirus, hepatitis A, B and C viruses, papoviruses, rabies virus, yellow fever virus, dengue virus, West Nile virus and SARS virus.

One approach in the development of antiviral compounds has been to identify compounds which interfere with the normal viral metabolism and replication in infected host cells. During the screening of new borinic ester compounds, we have found that certain of these compounds show antiviral activity in cell culture assay systems. Many existing compounds currently in use for treating viral diseases are subject to resistance mechanisms, are expensive to make, do not adequately treat patients or have adverse side effects. Therefore, there is a continuing need for new compounds which act to kill viruses, to inhibit viral replication or to block the pathogenic action of viruses.

Virus Category	Pertinent Human Infections
	RNA Viruses
Picomaviridae	Polio
	Human hepatitis A
	Human rhinovirus
Togavindae and	Rubella - German measles

-continued

Virus Category	Pertinent Human Infections
Flaviviridae	Yellow fever
Coronaviridae	Human respiratory coronavirus (HCV)
	Severe acute respiratory syndrome (SAR)
Rhabdovindae	Lyssavirus - Rabies
Paramyxovindae	Paramyxovirus - Mumps
	Morbilivirus - measles
	Pneumovirus - respiratory syncytial virus
Orthomyxoviridae	Influenza A–C
Bunyaviridae	Bunyavirus - Bunyamwera (BUN)
	Hantavirus - Hantaan (HTN)
	Nairevirus - Crimean-Congo hemorrhagic fever (CCHF)
	Phlebovirus - Sandfly fever (SFN)
	Unkuvirus - Uukuniemi (UUK)
	Rift Valley Fever (RVFN)
Arenaviridae	Junin - Argentine hemorrhagic fever
	Machupo - Bolivian hemorrhagic fever
	Lassa - Lassa fever
	LCM - aseptic lymphocytic choriomeningitis
Reoviridae	Rotovirus
	Reovirus
	Orbivirus
Retroviridae	Human immunodeficiency virus 1 (HIV-1)
	Human immunodeficiency virus 2 (HIV-2)
	Simian immunodeficiency virus (SIV)
	DNA Viruses
Papovaviridae	Pediatric viruses that reside in kidney
Adenovindae	Human respiratory distress and some deep-seated eye infections
Parvovindae	Human gastro-intestinal distress (Norwalk Virus)
Herpesvindae	Herpes simplex virus 1 (HSV-1)
	Herpes simplex virus 2 (HSV-2)
	Human cytomegalovirus (HCMV)
	Varicella zoster virus (VZV)
	Epstein-Barr virus (EBV)
	Human herpes virus 6 (HHV6)
Poxvindae	Orthopoxvirus is sub-genus for smallpox
Hepadnaviridae	Hepatitis B virus (HBV)
	Hepatitis C virus (HCV)

Boron containing compounds have received increasing attention as therapeutic agents over the past few years as technology in organic synthesis has expanded to include this atom. [Boron Therapeutics on the horizon, Groziak, M. P.; American Journal of Therapeutics (2001) 8, 321-328] The most notable boron containing therapeutic is the boronic acid bortezomib which was recently launched for the treatment of multiple myeloma. This breakthrough demonstrates the feasibility of using boron containing compounds as pharmaceutical agents. Boron containing compounds have been shown to have various biological activities including herbicides [Organic boron compounds as herbicides. Barnsley, G. E.; Eaton, J. K.; Airs, R. S.; (1957), DE 1016978 19571003], boron neutron capture therapy [Molecular Design and Synthesis of B-10 Carriers for Neutron Capture Therapy. Yamamoto, Y.; Pure Appl. Chem., (1991) 63, 423-426], serine protease inhibition [Borinic acid inhibitors as probes of the factors involved in binding at the active sites of subtilisin Carlsberg and α-chymotrypsin. Simpelkamp, J.; Jones, J. B.; Bioorganic & Medicinal Chemistry Letters, (1992), 2(11), 1391-4], [Design, Synthesis and Biological Evaluation of Selective Boron-containing Thrombin Inhibitors. Weinand, A.; Ehrhardt, C.; Metternich, R.; Tapparelli, C.; Bioorganic and Medicinal Chemistry, (1999), 7, 1295-1307], acetylcholinesterase inhibition [New, specific and reversible bifunctional alkylborinic acid inhibitor of acetylcholinesterase. Koehler, K. A.; Hess, G. P.; Biochemistry (1974), 13, 5345-50] and as antibacterial agents [Boron-Containing Antibacterial Agents: Effects on Growth and Morphology of Bacteria

Under Various Culture Conditions. Bailey, P. J.; Cousins, G.; Snow, G. A.; and White, A. J.; Antimicrobial Agents and Chemotherapy, (1980), 17, 549-553]. The boron containing compounds with antibacterial activity can be sub-divided into two main classes, the diazaborinines, which have been known since the 1960's, and dithienylborinic acid complexes. This latter class has been expanded to include many different diarylborinic acid complexes with potent antibacterial activity [Preparation of diarylborinic acid esters as DNA methyl transferase inhibitors. Benkovic, S. J.; Shapiro, L.; Baker, S. J.; Wahnon, D. C.; Wall, M.; Shier, V. K.; Scott, C. P.; Baboval, J.; PCT Int. Appl. (2002), WO 2002044184]. Synthetic developments described in Benkovic et al. enabled creation of a much more diverse class of unsymmetrical disubstituted borinic acid complexes not possible before.

Thus, there continues to be a need in the medical arts for novel, more effective, antibiotic compounds, especially for treating infectious diseases, that are resistant to currently available therapies.

BRIEF SUMMARY OF THE INVENTION

In one aspect, the present invention relates to therapeutic compounds, which are boron-containing. These compounds include structures that encompass benzoxaboroles, benzazaboroles, benzthiaboroles and related analogs.

These compounds are also provided as pharmaceutical compositions that can be administered to an animal, most preferably a human, for treatment of a disease having either bacterial, fungal or viral etiology, most preferably a human, in an immunologically compromised or debilitated state of health.

In preferred embodiments, the compounds of the invention are those having the structures given by Formula 1, with preferred substituents as disclosed herein.

The invention also provides methods for preparing these therapeutic compounds and pharmaceutical compositions thereof, and methods of using said compounds therapeutically. Kits and packaged embodiments of these compounds and pharmaceutical compositions of the invention are also contemplated.

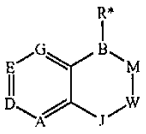
The invention also relates to methods of treating various medical conditions, using the compounds disclosed herein.

DETAILED DESCRIPTION OF THE INVENTION

This invention provides therapeutic agents, and specifically antibacterial, antifungal, or antiviral compounds, useful in treating and/or preventing conditions due to these pathogens.

The invention comprises a compound having the following structures

Formula 1



wherein B is boron, M is selected from oxygen, sulfur and NR**

wherein R* is selected from substituted or unsubstituted alkyl (C_1-C_4), substituted or unsubstituted cycloalkyl (C_3-C_7), substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl,

wherein R** is H, alkyl, alkyloxy, alkoxyalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,

and wherein A is CH, CR^1, or N

and wherein D is CH, CR^2, or N

and wherein E is CH, CR^3, or N

and wherein G is CH, CR^4, or N

and the combination of nitrogens (A+D+E+G) is 0-3

and wherein J is $(CH_2)_n$ (n=0 to 2) or CHR^5

and wherein W is $(CH_2)_m$ (m=0 to 1), C=O (carbonyl) or CHR^6

wherein R^1, R^2, R^3 and R^4 are each independently selected from the group consisting of hydrogen, haloalkyl, alkyl, cycloalkyl, $(CH_2)_pOH$ (p=1 to 3), halogen, CHO, CH=NOH, CO_2H, CO_2-alkyl, S-alkyl, SO_2-alkyl, S-aryl, $(CH^2)_qNR^{18}R^{19}$ (wherein R^{18} and R^{19} are independently selected from hydrogen, alkyl, and alkanoyl)(q=0 to 2), alkoxy, CF_3, SCF_3, NO_2, SO_3H, OH, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted heteroaryl, fused substituted or unsubstituted aryl, fused substituted or unsubstituted heteroaryl,

wherein R^5 is selected from substituted or unsubstituted alkyl (C_1-C_4), substituted or unsubstituted cycloalkyl (C_3-C_7), substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl,

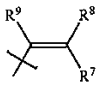
wherein R^6 is selected from substituted or unsubstituted alkyl (C_1-C_4), substituted or unsubstituted cycloalkyl (C_3-C_7), substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aralkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, including salts thereof, especially all pharmaceutically acceptable salts.

In preferred embodiments of Formula 1, M is oxygen, or M is sulfur, or M is NR**. Further preferred embodiments of any of these three are any of the following.

In a preferred embodiment of Formula 1, R* is a substituted or unsubstituted alkyl (C_1-C_4).

In a preferred embodiment of Formula 1, R* is a substituted or unsubstituted cycloalkyl (C_3-C_7).

In a preferred embodiment of Formula 1, R* is a substituted or unsubstituted alkenyl. In a further preferred embodiment thereof, the substituted alkenyl has the structure

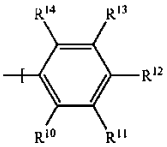


wherein R^7, R^8, and R^9 are each independently selected from the group consisting of hydrogen, alkyl, haloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, $(CH_2)_rOH$ (where r=1 to 3), $CH_2NR^{20}R^{21}$ (wherein R^{20} and R^{21} are independently selected from hydrogen and alkyl), CO_2H, CO_2alkyl, $CONH_2$, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3 and NO_2.

In a preferred embodiment of Formula 1, R* is a substituted or unsubstituted alkynyl. In a further preferred embodiment thereof the substituted alkynyl has the structure

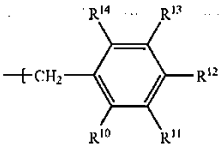
wherein R^7 is defined as before.

In a preferred embodiment of Formula 1, R* is a substituted or unsubstituted aryl. In a further preferred embodiment thereof the substituted aryl has the structure



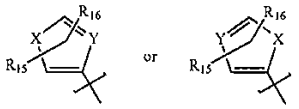
wherein R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are each independently selected from the group consisting of hydrogen, alkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, $(CH_2)_sOH$ (where s=1 to 3), CO_2H, CO_2alkyl, $CONH_2$, CONHalkyl, $CON(alkyl)_2$, OH, alkoxy, aryloxy, SH, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3, NO_2, $(CH_2)_tNR^{22}R^{23}$ (wherein R^{20} and R^{21} are independently selected from hydrogen, alkyl, and alkanoyl)(t=0 to 2), SO_2NH_2, $OCH_2CH_2NH_2$, OCH_2CH_2NHalkyl, $OCH_2CH_2N(alkyl)_2$, oxazolidin-2-yl, or alkyl substituted oxazolidin-2-yl.

In a preferred embodiment of Formula 1, R* is a substituted or unsubstituted aralkyl. In a further preferred embodiment thereof the substituted aralkyl has the structure



wherein R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are defined as before.

In a preferred embodiment of Formula 1, R* is a substituted or unsubstituted heteroaryl. In a further preferred embodiment thereof the heteroaryl has the structure



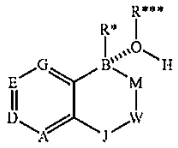
wherein X=CH=CH, N=CH, NR^{17} (wherein R^{17}=H, alkyl, aryl or benzyl), O, or S

and wherein Y=CH or N

and wherein R^{15} and R^{16} are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, haloalkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, $(CH_2)_uOH$ (where u=1, 2 or 3), $(CH_2)_vNR^{24}R^{25}$ (wherein R^{24} and R^{25} are independently selected from hydrogen, alkyl and alkanoyl)(v=0 to 3), CO_2H, CO_2alkyl, $CONH_2$, S-alkyl, S-aryl, SO_2alkyl, SO_3H, SCF_3, CN, halogen, CF_3 and NO_2.

The structures of the invention also permit solvent interactions that may afford structures (Formula 1B) that include atoms derived from the solvent encountered by the compounds of the invention during synthetic manipulations and therapeutic uses. Structures 1B arise from formation of a dative bond between the solvent(s) with the Lewis acidic boron center. Thus, such solvent complexes 1B could be stable entities with comparative bioactivities. Such structures are expressly contemplated by the present invention where R*** is H or alkyl.

Formula 1B



As used herein, the following terms have the stated meaning:

By "alkyl", "lower alkyl", and "C_1-C_6 alkyl" in the present invention is meant straight or branched chain alkyl groups having 1-6 carbon atoms, such as, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl.

By "alkanoyl" in the present invention is meant straight or branched chain alkanoyl groups having 1-6 carbon atoms, such as, acetyl, propanoyl, butanoyl, pentanoyl, hexanoyl, isobutanoyl, 3-methylbutanoyl, and 4-methylpentanoyl.

By "alkoxy", "lower alkoxy", and "C_1-C_6 alkoxy" in the present invention is meant straight or branched chain alkoxy groups having 1-6 carbon atoms, such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, 2-pentyl, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy.

By the term "halogen" in the present invention is meant fluorine, bromine, chlorine, and iodine.

By "cycloalkyl", e.g., C_3-C_7 cycloalkyl, in the present invention is meant cycloalkyl groups having 3-7 atoms such as, for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. In the C_3-C_7 cycloalkyl groups, preferably in the C_5-C_7 cycloalkyl groups, one or two of the carbon atoms forming the ring can optionally be replaced with a hetero atom, such as sulfur, oxygen or nitrogen. Examples of such groups are piperidinyl, piperazinyl, morpholinyl, pyrrolidinyl, imidazolidinyl, oxazolidinyl, perhydroazepinyl, perhydrooxazapinyl, oxepanyl, perhydrooxepanyl, tetrahydrofuranyl, and tetrahydropyranyl. C_3 and C_4 cycloalkyl groups having a member replaced by nitrogen or oxygen include aziridinyl, azetidinyl, oxetanyl, and oxiranyl.

By "aryl" is meant an aromatic carbocyclic group having a single ring (e.g., phenyl), multiple rings (e.g., biphenyl), or multiple condensed rings in which at least one is aromatic, (e.g., 1,2,3,4-tetrahydronaphthyl, naphthyl, anthryl, or phenanthryl), which is optionally mono-, di-, or trisubstituted with, e.g., halogen, lower alkyl, lower alkoxy, lower alkylthio, trifluoromethyl, lower acyloxy, aryl, heteroaryl, and hydroxy. Preferred aryl groups include phenyl and naphthyl, each of which is optionally substituted as defined herein.

By "heteroaryl" is meant one or more aromatic ring systems of 5-, 6-, or 7-membered rings containing at least one and up to four heteroatoms selected from nitrogen, oxygen, or sulfur. Such heteroaryl groups include, for example, thienyl, furanyl, thiazolyl, imidazolyl, (is)oxazolyl, pyridyl, pyrim-

idinyl, (iso)quinolinyl, napthyridinyl, benzimidazolyl, and benzoxazolyl. Preferred heteroaryls are thiazolyl, pyrimidinyl, preferably pyrimidin-2-yl, and pyridyl. Other preferred heteroaryl groups include 1-imidazolyl, 2-thienyl, 1-(or 2-)quinolinyl, 1-(or 2-)isoquinolinyl, 1-(or 2-)tetrahydroisoquinolinyl, and 2-(or 3-)furanyl.

The invention also provides embodiments of the compounds disclosed herein as pharmaceutical compositions. The pharmaceutical compositions of the present invention can be manufactured in a manner that is itself known, e.g., by means of a conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

Pharmaceutical compositions for use in accordance with the present invention thus can be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

Non-toxic pharmaceutical salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfinic, formic, toluenesulfonic, methanesulfonic, hydroxyethanesulfonic, nitric, benzoic, citric, tartaric, maleic, hydroiodic, alkanoic such as acetic, $HOOC—(CH_2)_n—CH_3$ where n is 0-4, and the like. Non-toxic pharmaceutical base addition salts include salts of bases such as sodium, potassium, calcium, ammonium, and functional equivalents. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

For injection, the compounds of the invention can be formulated in appropriate aqueous solutions, such as physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal and transcutaneous administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained with solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents can be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds can be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers can be added. All formulations for oral administration should be in dosages suitable for such administration. For buccal administration, the compositions can take the form of tablets or lozenges formulated in conventional manner.

For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetra-fluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g., gelatin for use in an inhaler, can be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds can be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection can be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions can take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds can be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions can contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension can also contain suitable stabilizers or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, the active ingredient can be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use. The compounds can also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds can also be formulated as a depot preparation. Such long acting formulations can be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds can be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

A pharmaceutical carrier for the hydrophobic compounds of the invention is a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. The cosolvent system can be the VPD co-solvent system. VPD is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant polysorbate 80, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. The VPD co-solvent system (VPD:5W) consists of VPD diluted 1:1 with a 5% dextrose in water solution. This co-solvent system dissolves hydrophobic compounds well, and itself produces low toxicity upon systemic administration. Naturally, the proportions of a co-solvent system can be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components can be varied: for example, other low-toxicity nonpolar surfactants can be used instead of polysorbate 80; the fraction size of polyethylene glycol can be varied; other biocompatible polymers can replace polyethyl-

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Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.