Title: COORDINATION COMPLEXES, PHARMACEUTICAL SOLUTIONS COMPRISING COORDINATION COMPLEXES, AND METHODS OF TREATING PATIENTS

Abstract: A coordination complex having a physiologically acceptable pKa includes a metal and a biologically active agent. The pKa of the coordination complex is less than the pKa of the biologically active agent. A pharmaceutical solution for treating a patient includes a coordination complex and water, wherein the coordination complex is at least partially soluble in the water at physiological pH and in a therapeutically efficacious concentration. A method for treating a patient includes administering a pharmaceutical solution including a coordination complex and water to a patient in need of a biologically active agent.

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COORDINATION COMPLEXES, PHARMACEUTICAL SOLUTIONS COMPRISING COORDINATION COMPLEXES, AND METHODS OF TREATING PATIENTS

RELATED APPLICATIONS

[0001] This is a continuation-in-part of prior Application No. 11/824,411, filed June 29, 2007, which is a continuation-in-part of prior Application No. 11/257,504, filed October 24, 2005, which claims the benefit of U.S. Provisional Application No. 60/621,747, filed October 25, 2004. The entire contents of all of these documents are incorporated herein by reference, except that in the event of any inconsistent disclosure or definition from the present specification, the disclosure or definition herein shall be deemed to prevail.

TECHNICAL FIELD

[0002] The present teachings relate generally to metal coordination complexes and methods for their therapeutic use in the treatment of patients.

BACKGROUND

[0003] The therapeutic efficacy of pharmaceutical agents is oftentimes diminished as a result of their inadequate solubilities at physiological pH. In addition, the ability to administer some pharmaceutical agents in aqueous solution—for example, via intraperitoneal (I.P.) injection, intramuscular (I.M.) injection, intravenous (I.V.) injection, and the like—is oftentimes not practicable due to the inadequate solubilities of the pharmaceutical agents at the requisite concentrations and/or pH.

[0004] As a consequence of such inadequate solubilities, it is oftentimes necessary to restrict the formulation of pharmaceutical agents to peroral dosage forms. However, when oral administration is not feasible, practical or otherwise desirable (e.g., in the treatment of patients who are unable to swallow—such as neonates—as well as critically ill, paralysed, and/or comatose patients), the inability to administer the pharmaceutical agent in a parenteral dosage form is an acute problem.
A further limitation on the parenteral administration of pharmaceutical agents is observed in connection with compounds having high \( pK_a \) values. Since pharmaceutical agents having high \( pK_a \) values typically form solutions with \( pH \) values that are above the level at which one could safely or conveniently administer the drug, parenteral administration of such pharmaceutical agent is oftentimes not an option. Indeed, there are presently very few options available for formulating solutions of pharmaceutical agents with high \( pK_a \) values.

In short, it would be highly desirable to (a) enhance the aqueous solubilities of poorly soluble pharmaceutical agents in order to increase their utilities or availabilities at physiological \( pH \), and/or to (b) buffer the acidities of pharmaceutical agents to acceptable physiological levels without compromising their therapeutic efficacies.

**SUMMARY**

The scope of the present invention is defined solely by the appended claims and is not affected to any degree by the statements within this summary.

A first coordination complex includes a metal and a biologically active agent. The coordination complex has a \( pK_a \) that is less than a \( pK_a \) of the biologically active agent and the \( pK_a \) of the coordination complex is physiologically acceptable, with a proviso that when the biologically active agent is suberoylanilide hydroxamic acid, the metal is neither iron nor zinc.

A second coordination complex includes a metal other than iron or zinc and a biologically active agent. The coordination complex has a \( pK_a \) that is less than a \( pK_a \) of the biologically active agent, and the \( pK_a \) of the coordination complex is physiologically acceptable.

A third coordination complex includes a metal selected from the group consisting of magnesium, calcium, and nickel; and a biologically active agent. The coordination complex has a \( pK_a \) that is less than a \( pK_a \) of the biologically active agent, and the \( pK_a \) of the coordination complex is physiologically acceptable.
A fourth coordination complex includes a metal selected from the group consisting of magnesium, calcium, and nickel, and a biologically active agent selected from the group consisting of a sulfamate, a hydroxamic acid, and a dihydropyridine calcium channel blocker. The coordination complex has a pKa that is less than a pKg of the biologically active agent, and the pKa of the coordination complex is less than about 9.

A fifth coordination complex includes a metal and a biologically active agent, wherein water solubility of the coordination complex is greater than water solubility of the biologically active agent at physiological pH, and wherein the pKa of the coordination complex is physiologically acceptable. When the biologically active agent is suberoylanilide hydroxamic acid, then the metal is not a transition metal unless the coordination complex further comprises a buffering ligand.

A pharmaceutical solution for treating a patient includes a coordination complex of a type described herein and water. The coordination complex is at least partially soluble in the water at physiological pH in a therapeutically efficacious concentration.

A method for treating a patient includes administering a pharmaceutical solution of a type described herein to a patient in need of the biologically active agent thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the molecular structure and biopharmaceutical properties of suberoylanilide hydroxamic acid (SAHA).

FIG. 2 shows the enhancement of ligand polarization using topiramate (tpm) as a representative ligand.

FIG. 3 shows a magnesium-coordinated topiramate [Mg(tpm)₂] and a magnesium-coordinated topiramate with a histidine buffering ligand [Mg(tpm)(his)].

FIG. 4 shows molecular structures of representative buffering ligands.
FIG. 5 shows a plot of data from breast cancer cell proliferation assays.

DETAILED DESCRIPTION

As further described below, the inventors have discovered that coordinating a metal to a biologically active agent in a non-aqueous system favors the formation of a coordination complex—as opposed to a salt—and that the resultant coordination complex—unlike the corresponding salt—exhibits a surprising and unexpected buffering effect. It has been discovered that as a result of this buffering effect, the biologically active agent can remain soluble in water at physiological pH for a period of time sufficient for the preparation of a safe and convenient parenteral (e.g., I.V.) formulation and/or for delivering the biologically active agent to its target in the body. Thus, the coordination complexes described herein resolve the above-described problems associated with drugs having poor water solubilities that heretofore could not safely be converted to injectable forms or that exhibited diminished bioavailabilities due to their inabilitys to migrate to their target sites in the allotted time. The inventors have further discovered, surprisingly and unexpectedly, that the additional coordination of a buffering ligand or adjuvant to a metal complexed with a biologically active agent—in stark and dramatic contrast to what is observed in the case of salts—provides additional buffering capacity and further lowers the pH and/or increases the solubility of the entire metal coordination complex, as further described below.

Throughout this description and in the appended claims, the following definitions are to be understood:

The phrases "coordination complex," "metal coordination complex," and the like refer to a complex of an organic compound with a metal that can be empirically differentiated from a simple metal salt of the organic compound based on physiochemical and/or spectroscopic properties, with a coordination complex typically having enhanced covalency as compared to a salt. Without wishing to be bound by a particular theory or to in any way limit the scope of the appended claims or their equivalents, it is
presently believed that a "coordination complex" in the sense used herein involves a combination of coordinate covalent bonds and/or ionic bonds, whereas a metal salt is based on a purely electrostatic attraction between a cation (e.g., a metal) and an anion (e.g., an ionized form of a biologically active agent). As used herein, the phrase "coordination complex" also includes molecules that lack an ionic component (e.g., such as a neutral coordination complex prior to deprotonation, where \( pK_a \) of the coordination complex falls within a physiologically acceptable range).

The phrase "physiologically acceptable" and the like as used in reference to \( pK_a \) values refer to \( pK_a \) values of compounds that—when dissolved—result in solutions having a pH value in a range from about 5 to about 9. It is to be understood that the \( pK_a \) value per se of a compound may or may not lie in this range although the pH of the resultant solution does.

The phrase "physiological pH" refers to the pH of a patient's blood. Typically, this pH is slightly basic (e.g., approximately 7.4).

The phrase "biologically active agent" refers generally and without limitation to any compound that triggers—either directly or indirectly—a physiological response in a patient, desirably though not necessarily a therapeutically efficacious response. As used herein, the phrase "biologically active agent" is used interchangeably with the phrase "pharmaceutical agent" and the term "drug."

By way of general introduction, a coordination complex in accordance with the present teachings includes a metal and a biologically active agent. The coordination complex has a \( pK_a \) that is physiologically acceptable and less than a \( pK_a \) of the biologically active agent.

In some embodiments, the water solubility of the coordination complex is greater than that of the biologically active agent at physiological pH and/or is greater than that of a metal salt of the biologically active agent at physiological pH. In some embodiments, the biologically active agent exhibits therapeutic efficacy against one or more diseases, and at least a portion of the therapeutic efficacy is retained in the coordination complex. It is to be understood that liberation of the biologically active agent from the coordination
complex may or may not be a prerequisite to releasing a therapeutic efficacy of the drug (in other words, the free biologically active agent and the coordination complex that contains a metal-coordinated version of the biologically active agent may each exhibit its own therapeutic efficacy).

[0028] In some embodiments, the metal is a group IIA metal, a p-block metal, a transition metal, a lanthanide or an actinide. In some embodiments, the metal is a group IIA metal which, in some embodiments, is magnesium, calcium or strontium. In some embodiments, the p-block metal is a group MIA metal, a group IVA metal or a group VA metal. In other embodiments, the metal is a transition metal which, in some embodiments, is a group VIII transition metal, a group IB transition metal, a group IIb transition metal, a group IIIB transition metal, a group IVB transition metal, a group VB transition metal, a group VIB transition metal or a group VIIb transition metal. In some embodiments, the metal is a transition metal which, in some embodiments, is a group VIII transition metal. In some embodiments, the group VIII transition metal is nickel. In some embodiments, the metal is iron or zinc. In other embodiments, the metal is neither iron nor zinc.

[0029] All manner of biologically active agents are contemplated for use in accordance with the present teachings—preferably ones that have inadequate solubilities at physiological pH and/or pKₐ values that are physiologically unacceptable, and which could potentially benefit from metal-coordination in accordance with the present teachings. Representative agents contemplated for use include but are not limited to the following: medicaments for treating the gastrointestinal (Gl) tract (e.g., antacids; reflux suppressants; antiflatulents; antidopaminergics; proton pump inhibitors (PPIs); H₂-receptor antagonists; cytoprotectants; prostaglandin analogues; laxatives; antispasmodics; antiarrhythmics; nitrate antianginals; vasoconstrictors; vasodilators; peripheral activators; and the like); medicaments for treating the cardiovascular system (e.g., β-receptor blockers; calcium channel blockers; diuretics; cardiac glycosides; antiarrhythmics; nitrate antianginals; vasoconstrictors; vasodilators; peripheral activators; and the like); antihypertension agents (e.g., ACE inhibitors; angiotensin receptor blockers; a blockers; and the like); coagulation agents (e.g., anticoagulants;
heparin; antiplatelet drugs; fibrinolytics; anti-hemophilic factors; haemostatic
drugs; and the like); atherosclerosis/cholesterol inhibitors (e.g.,
hypolipidaemic agents; statins; and the like); medicaments that affect the
central nervous system (e.g., hypnotics; anesthetics; antipsychotics;
antidepressants including but not limited to tricyclic antidepressants,
monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, etc.;
and the like); antiemetics; anticonvulsants; antiepileptics; anxiolytics;
barbiturates; movement disorder drugs including but not limited to those for
treating Parkinson's disease, etc.; stimulants including but not limited to
amphetamines; benzodiazepines; cyclopyrrolones; dopamine antagonists;
antihistamines; cholinergics; anticholinergics; emetics; cannabinoids; 5-HT
serotonin antagonists; and the like); analgesics (e.g., nonsteroidal
antiinflammatory drugs or NSAIDs; opioids; various orphan drugs including
but not limited to paracetamol, tricyclic antidepressants, anticonvulsants, etc.;
and the like); medicaments for treating musculoskeletal disorders (e.g.,
NSAIDs including but not limited to COX-2 selective inhibitors, etc.; muscle
relaxants; neuromuscular drugs; anticholinesterases; and the like);
medicaments for treating the eye (e.g., adrenergic neurone blockers;
astringents; ocular lubricants; mydriatics; cycloplegics; anti-glaucoma agents
including but not limited to adrenergic agonists, beta-blockers, carbonic
anhydrase inhibitors/hyperosmotics, cholinergics, miotics,
parasympathomimetics, prostaglandin agonists/prostaglandin inhibitors,
nitroglycerin, etc.; and the like); topical anesthetics (e.g., benzocaine;
butamben; dibucaine; lidocaine; oxybuprocaine; pramoxine; proparacaine;
proxymetacaine; tetracaine; and the like); sympathomimetics;
parasympathomimetics; anti-bacterial agents (e.g., antibiotics; topical antibiotics;
sulfa drugs; aminoglycosides; fluoroquinolones; and the like); antiviral drugs;
medicaments for treatment of the ear, nose, and throat (e.g.,
sympathomimetics; antihistamines; anticholinergics; NSAIDs; steroids;
antiseptics; local anesthetics; antifungals; cerumenolyti; and the like);
medicaments for treating the respiratory system (e.g., bronchodilators;
NSAIDs; anti-allergics; antitussives; mucolytics; decongestants;
corticosteroids; β-2-adrenergic agonists; anticholinergics; steroids; and the like); medicaments for treating diseases of the endocrine system (e.g., androgens; antiandrogens; gonadotropin; corticosteroids; human growth hormone; insulin; antidiabetics including but not limited to sulfonylureas, biguanides/metformin, thiazolidinediones, insulin, etc.; thyroid hormones; antithyroid drugs; calcitonin; diphosponate; vasopressin analogues; and the like); medicaments for treating the reproductive system and urinary system (e.g., antifungals; alkalizing agents; quinolones; antibiotics; cholinergics; anticholinergics; anticholinesterases; antispasmodics; 5-a reductase inhibitor; selective α-1 blockers; sildenafil; fertility medications; and the like); contraceptives (e.g., hormonal contraceptives; and the like); medicaments for use in obstetrics and gynecology (e.g., NSAIDs; anticholinergics; haemostatic drugs; antifibrinolytics; hormone replacement therapy (HRT); bone regulators; β-receptor agonists; follicle stimulating hormone; luteinizing hormone; luteinizing-hormone-releasing hormone (LHRH); gonadotropin release inhibitor; progestogen; dopamine agonists; oestrogen; proglandins; gonadorelin; diethylstilbestrol; and the like); medicaments for treating the skin (e.g., emollients; anti-pruritics; antifungals; disinfectants; scabicides; pediculicides; tar products; vitamin A derivatives; vitamin D analogues; keratolyses; abrasives; systemic antibiotics; topical antibiotics; hormones; desloughing agents; exudate absorbents; fibrinolytics; proteolytics; sunscreens; antiperspirants; corticosteroids; and the like); medicaments for treating infections and infestations (e.g., antibiotics; antifungals including but not limited to imidazoles, polyenes, etc.; antileptotics; antituberculous drugs; antimalarials; antihelminthics; amoebicides; antivirals; antiprotozoals; antiparasitics; and the like); anti-inflammatory agents (e.g., NSAIDs; corticosteroids; and the like); medicaments for treating the immune system (e.g., vaccines; immunoglobulins; immunosuppressants; interferons; monoclonal antibodies; and the like); medicaments for treating allergies (e.g., anti-allergics; antihistamines; NSAIDs; mast cell inhibitors; and the like); nutritional agents (e.g., tonics; iron preparations; electrolytes; parenteral nutritional supplements; vitamins; anti-obesity drugs; anabolic drugs;
haematopoietic drugs; food product drugs; and the like); antineoplastic agents (e.g., cytotoxic drugs; therapeutic antibodies; sex hormones; aromatase inhibitors; somatostatin inhibitors; recombinant interleukins; G-CSF; erythropoietin; and the like); euthanaticum agents; and the like; and combinations thereof.

In some embodiments, the biologically active agent is selected from the group consisting of an anticonvulsant, an antineoplastic, and a calcium channel blocker. In some embodiments, the anticonvulsant is a sulfamate which, in some embodiments is topiramate (sold under the tradename TOPAMAX by Ortho-McNeil Neurologies). In some embodiments, the antineoplastic is a histone deacetylase (HDAC) inhibitor which, in some embodiments, is a hydroxamic acid. In some embodiments, the hydroxamic acid is suberoylanilide hydroxamic acid, which is also known by its generic name, vorinostat, and which is sold under the tradename ZOLINZA by Merck Sharp & Dohme Corp. In embodiments in which the biologically active agent is suberoylanilide hydroxamic acid, then the metal is neither iron nor zinc. In some embodiments, the calcium channel blocker is a dihydropyridine (DHP) calcium channel blocker which, in some embodiments, is nisoldipine (sold under the tradename SULAR), nifedipine (sold under the tradenames ADALAT, NIFEDICAL, and PROCARDIA), isradipine (sold under the tradenames DYNACIRC and PRESCAL) or amlodipine (sold under the tradename NORVASC).

In some embodiments, the pKa of the coordination complex is less than about 9, and in some embodiments the pKa of the coordination complex is in a range from about 5 to about 9. In some embodiments, the range is from about 6 to about 9. In some embodiments, the range is from about 6 to about 8.5.

In some embodiments, the coordination complex further includes a buffering ligand, as explained below. In some embodiments, the pKₐ of the coordination complex is lower when the coordination complex contains the buffering ligand than when the coordination complex does not. In some embodiments, the water solubility of the coordination complex is greater when
the coordination complex contains the buffering ligand than when the coordination complex does not. In some embodiments, the buffering ligand provides additional stability to the entire coordination complex that prevents the coordination complex from converting to a salt.

[0033] In some embodiments, the buffering ligand includes one or more hydrogen bonding sites and, in some embodiments, the buffering ligand is selected from the group consisting of an amino acid, a peptide, a carbohydrate, and a Good's buffer (e.g., MES, ADA, PIPES, ACES, cholamine chloride, BES, TES, HEPES, acetamidoglycine, tricine, glycinamide, and bicine). In some embodiments, the amino acid is arginine, lysine or histidine. In some embodiments, the buffering ligand is quinic acid, bicine, tricine, ascorbic acid or carnosine.

[0034] By way of further general introduction, a pharmaceutical solution for treating a patient includes a coordination complex of a type described above and water. The coordination complex is at least partially soluble in the water at physiological pH in a therapeutically efficacious concentration. In some embodiments, the coordination complex is soluble at least for a time sufficient to deliver the biologically active agent to a target site in the patient's body.

[0035] Finally, by way of further general introduction, a method for treating a patient includes administering a pharmaceutical solution of a type described above to a patient in need of the biologically active agent therein. In some embodiments, the pharmaceutical solution is administered to the patient by I.P. injection, I.M. injection or I.V. injection. In some embodiments, the method includes treating a neonatal seizure and the biologically active agent is topiramate. In some embodiments, the method includes treating a cancer and the biologically active agent is suberoylanilide hydroxamic acid.

[0036] Building upon the preceding general introduction to coordination complexes, pharmaceutical compositions, and methods in accordance with the present teachings, a more detailed description including specific examples is now provided solely for the purpose of illustration—not of limitation.
The present inventors have investigated the preparation of chelation compounds formed between a metal ion and polydentate drug ligands. Without wishing to be bound by a particular theory or to in any way limit the scope of the appended claims or their equivalents, it is presently believed that in these coordination complexes, the drug ligand at least partially neutralizes the positive charge of the metal ion through the formation of a combination of ionic and coordinate covalent bonds—as opposed to the purely electrostatic attraction observed in salts. While electrostatic attraction can also exist in coordination complexes, the complexes additionally have an inherently covalent coordination bond between the metal and drug ligand. It is presently believed that this enhanced covalency of the coordination complex is primarily responsible for reducing the $pK_a$ of its acidic protons, such that solutions of these coordination compounds are stable at physiological pH.

In a first series of embodiments, the biologically active agent coordinated to a metal is topiramate. Topiramate (2,3:4,5-bis-O-isopropylidene-p-D-fructopyranose sulfamate) is an anticonvulsant drug used to treat epilepsy in children and adults. It is also approved for the treatment of seizures associated with Lennox-Gastaut syndrome and for the prophylaxis of migraines. Topiramate has exhibited effective anticonvulsant and neuroprotective properties particularly after cerebral hypoxia ischemic events, and has been used experimentally in the treatment of bipolar disorders, obesity, alcoholism, post-traumatic stress disorder, bulimia, obsessive compulsive disorder, smoking addiction, and neuropathic pain. In some embodiments, when the biologically active agent is topiramate and the patient to be treated is a premature infant with an immature GI tract, the metal of the coordination complex is magnesium.

Autism symptoms often appear between the ages of 1 and 1½, which suggests that causes occur either prenatally or perinatally. Contributing factors at birth may include prematurity, lack of oxygen to the brain, prolonged labor or infections. In addition, low Apgar scores have been associated with autism, and this association is connected to pre-term births. Thus, in some embodiments, a metal coordinated topiramate in accordance with the present
teachings is delivered intravenously to a pre-term infant exhibiting low Apgar scores in order to help prevent the onset of autism.

Currently, topiramate is available only in an orally administered formulation, which limits its usefulness in situations where oral administration is not feasible or is otherwise undesirable. Solutions of the drug are impractical due to the hydrolytic lability of neutral topiramate in water. At present, one of the biggest limitations on the use of oral formulations of topiramate is in the treatment of neonates. Even if an I.V. solution could be formulated in an appropriately low volume for a 2-kg newborn baby, hydrolysis is likely to render the product too unstable to be practical. In addition to neonates, an I.V. formulation of topiramate would be useful for treating (a) patients who, like neonates, are unable to swallow; (b) patients with disturbed absorption from the GI tract; (c) patients who are undergoing GI surgery; and (d) patients in need of a rapid bolus of the drug. Therefore, it would be highly desirable to formulate an aqueous solution of some form of topiramate in a high enough concentration and a low enough pH to enable safe I.V. administration.

Alkaline solutions of topiramate stabilize the compound and prevent its hydrolysis. Alkaline salts of topiramate have shown promise in pre-clinical studies in neonatal pigs but no successful clinical trials have been reported. Although the solubility of topiramate salts is greatly increased relative to the neutral drug (3.59 M vs. 0.029 M), the pH of a 0.19 M solution of the salt is quite high (>10), making these salts unsuitable for many medical applications. In U.S. Patent No. 7,351,695 granted to Ortho-McNeil, Mg, Ca, and Zn compounds of topiramate are described but without mention of their detailed structures or aqueous solubilities. Investigation by the present inventors has revealed these compounds to be salts.

Although an I.V. formulation of topiramate has yet to be developed as a therapeutic option for patients, there has been a clinical trial in which a cyclodextrin (CD) has been used to enhance the solubility of neutral topiramate. However, the potential cost of a CD derivative together with ongoing regulatory and toxicology concerns over I.V. CD in neonates may
significantly limit CD's potential to address the need for an I.V. formulation of topiramate.

[0043] Topiramate has a pKₐ value of 8.7 due to its weakly acidic sulfamate group. The water solubility of topiramate is about 9.8 mg/mL (0.029 M) at 23 °C but increases to about 1300 mg/mL (3.59 M) for sodium topiramate trihydrate. It has been found that coordination of the topiramate anion with a suitable metal leads to increased aqueous solubility at lower physiological pH.

[0044] In accordance with the present teachings, a metal coordinated topiramate is used to formulate an aqueous solution of topiramate in a high enough concentration and a low enough pH to allow for safe I.V. administration. In some embodiments, the metal coordinated topiramate provides a heretofore unavailable treatment for neonatal seizures and related disease states.

[0045] In general, the preferred route of administration of most drugs is oral, with drug developers preferring to market oral dosage forms based on their cost, safety, and practicality. In most instances, the disadvantages of oral drug formulations (e.g., decreased and highly variable bioavailability) are mitigated by their advantages. One notable exception is that chemotherapy agents are traditionally administered parenterally in a physician's office or clinic. Taking oral doses outside such controlled settings increases risks and requires patients and caregivers to assume significantly greater responsibilities.

[0046] In a second series of embodiments, the biologically active agent coordinated to a metal is an antineoplastic agent which, in some embodiments, is suberoylanilide hydroxamic acid (SAHA). SAHA, which is shown in FIG. 1, was the first inhibitor of HDAC to be approved by the FDA and is presently indicated for the treatment of cutaneous manifestations of cutaneous T-cell lymphoma (CTCL) in patients with progressive, persistent or recurrent disease on or following two systemic therapies. Since its approval in October 2006, SAHA has also been found to be useful in the treatment of other cancers alone and in combination with other drugs or radiation therapy.
Although HDAC inhibitors show utility in the treatment of cancers, it is to be understood that HDAC inhibitors may also find use in non-cancer disease states.

[0047] The oral bioavailability of SAHA is less than 50% and highly variable. Nausea and vomiting—common symptoms of the disease and all too common adverse side effects of many antineoplastics—among patients exacerbates the variability in this drug's bioavailability and further complicates its oral administration. At present, however, SAHA is marketed by Merck only as an oral capsule (100 mg). An I.V. formulation would provide certain advantages over peroral formulations, especially with cancer and other patients that may suffer from GI upset.

[0048] SAHA is a relatively lipophilic molecule having limited water solubility of about 0.1 mg/mL. In a prior study aimed at increasing its solubility, the sodium salt of SAHA was prepared at Memorial Sloan Kettering Cancer Center but required solution pH values above 11—that is, two units above the maximum pH level (~9) usually observed for intravenous dosing—in order to stay in solution. In addition, the solution required slow administration over a two hour period in order to provide sufficient dilution to minimize irritation at the injection site.

[0049] In another study, workers used 2-hydroxypropyl-p-cyclodextrin (HOP-β-CD) at a molar concentration five times that of SAHA in an effort to enhance the latter's aqueous solubility and to enable administration of the drug in drinking water. However, cyclodextrins are expensive and not as biologically friendly as simple pH adjustment. In addition, there remains skepticism within regulatory agencies—particularly the FDA—concerning the intravenous use of cyclodextrins.

[0050] Hydroxamic acid HDAC inhibitors typically have a pKa value of about 9.2. In accordance with the present teachings, a metal coordinated SAHA is used to formulate an aqueous solution of SAHA in a high enough concentration and a low enough pH to allow for safe I.V. administration. As shown in an Example below, the solubility of SAHA in water at near physiological pH was increased ~19-fold for a Ca(SAHA)(quinic acid) analog.
Moreover, as further shown in the Examples below, it has been discovered that any change in the ability of several metal coordinated SAHA analogs to inhibit breast cancer cell growth as compared to SAHA itself is negligible. Thus, the ability to deliver a wide range of doses safely and comfortably resulting in more predictable blood levels while minimizing drug exposure over long periods makes an I.V. formulation of SAHA both clinically useful and commercially valuable.

[0051] In U.S. Patent Application Publication No. 2009/0239946 A1, Merck reports a chelate complex of iron or zinc and a SAHA ligand. However, the complexes described by Merck—in contrast to those prepared in accordance with the present teachings—were not designed to have a buffering effect or to have increased solubility at physiological pH relative to SAHA itself. Thus, the metals Merck used to complex with SAHA (viz., iron and zinc) bind to SAHA too tightly to provide the increased solubility desired in accordance with the present teachings. In fact, the present inventors have found that other transition metals—not just iron and zinc—appear to bind too tightly with SAHA and result in complexes that exhibit decreased solubility, as demonstrated in an Example described below involving nickel metal. In accordance with the present teachings, it has been found that s-block metals are better suited for binding SAHA than transition metals, and are better able to impart the desired dual properties of lipid and water solubility.

[0052] However, in some embodiments, a coordination complex contains SAHA, a transition metal, and a buffering ligand. In some embodiments, the additional coordination of the buffering ligand to the transition metal confers an additional buffering capacity on the complex and further increases the solubility of the entire metal coordination complex, thereby offsetting the overly tight binding of transition metals (e.g., iron, zinc, and nickel) to SAHA that—in the absence of the buffering ligand—can result in inadequate solubilities.

[0053] In a third series of embodiments, the biologically active agent coordinated to a metal is a DHP calcium channel blocker. DHP calcium channel blockers, which are considered BCS Class II drugs, are practically
insoluble in water (~ 1μg/mL). Their low bioavailability is also due to extensive oxidative metabolism by cytochrome P450 enzymes in the intestinal epithelia.

[0054] The pK_a of DHP calcium channel blockers typically ranges between about 9 and about 10, which means that the salts of these compounds will be soluble in water but only at a pH well above a physiologically relevant value. Lowering the pH of an aqueous solution of the salt of a DHP drug will result in its precipitation. Thus, there is a need for a formulation by which a DHP calcium channel blocker can be stabilized such that its migration from a drug delivery vehicle to a target site is facilitated sufficiently to enable maximum drug absorption.

[0055] In accordance with the present teachings, the solubility of a DHP calcium channel blocker, such as nisoldipine, is increased by forming a stable metal coordination complex thereof, which would facilitate the drug’s migration from a delivery vehicle (e.g., a GEOMATRIX tablet) to the microvillus lining, after which the metal coordination complex would revert back to its neutral form due to the lower pH of between about 5 and about 6 of the aqueous unstirred layer on the surface of the microvilli. The neutralized nisoldipine would now be associated with the epithelial cell membranes and absorption of the drug could ensue. Since DHP calcium channel blockers have very similar structures and pKa values, the mechanism of stable metal coordination complex migration described above can be applied to other DHP calcium channel blockers.

[0056] The present teachings are not to be construed as being limited to a single drug delivery technology. For example, any drug delivery technology that provides controlled release of a pharmaceutical and/or targeted delivery of a drug to a specific site is contemplated for use in accordance with the present teachings. Representative technologies include but are not limited to GEOMATRIX (U.S. Patent No. 5,422,123), cylindrical plug (U.S. Patent No. 7,195,778), OROS.RTM, and technologies described in U.S. Patent Nos. 6,375,978 B1; 6,368,626 B1; 6,342,249 B1; 6,333,050 B2; 6,287,295 B1; 6,283,953 B1; 6,270,787 B1; 6,245,357 B1; and 6,132,420. The entire
contents of each of the above-identified U.S. patents are incorporated herein by reference, except that in the event of any inconsistent disclosure or definition from the present specification, the disclosure or definition herein shall be deemed to prevail.

[0057] In a fourth series of embodiments, a coordination complex in accordance with the present teachings further includes a buffering ligand/adjuvant. It is to be understood that in any of the embodiments described herein—regardless of the metal and/or biologically active agent (e.g., topiramate, SAHA, DHP calcium channel blocker, etc.)—a buffering ligand is optionally included in the coordination complex. In such embodiments, the biologically active agent forms a stable complex with a metal having the capacity to bind more than one ligand with at least one of the additional ligands having a pH buffering capacity. In some embodiments, the buffering ligands formally donate electrons to the metal to form an electrostatic interaction or bond and/or donate electrons through a metal coordination bond. Traditionally, chelation compounds refer to a metallic ion bonded to one or more chelating ligands, wherein a chelating ligand is a polydentate ligand capable of two or more points of attachment to the metal ion (e.g., two or more donor atoms) to form a heterocyclic ring structure.

[0058] A sulfamate, HDAC inhibitor, or DHP calcium channel blocker used as the biologically active agent of a coordination complex in accordance with the present teachings can provide a ligand in which one atom is tightly bound to the metal while other atoms provide minor contributions to metal chelation. The bond between particular metals and biologically active agents imparts some covalency— as would be conferred in a coordination complex—in addition to some ionic character—as would be conferred in a salt. The combination of these properties confers onto the coordination complex an ability to retain solubility at relatively high concentrations at physiological pH.

[0059] The solubility of coordination complexes is influenced by various interacting factors that involve composition and structure including but not limited to the nature of the metal ion, the symmetry of the molecule, the redistribution of electron density in ligands upon complexation, and/or the
conformation of coordinated ligands. As a guideline, the higher the lipophilicity or hydrophilicity of the ligands involved in chelation, the higher the corresponding lipophilicity or hydrophilicity of a coordination complex.

[0060] Without wishing to be bound by a particular theory or to in any way limit the scope of the appended claims or their equivalents, it is presently believed that the lowering in pH of a coordination complex in accordance with the present teachings—whether or not the coordination complex contains a buffering ligand—involves ligand polarization enhancement.

[0061] According to the theory of ligand polarization enhancement, coordination of a ligand to a positively-charged metal center will result in development of a positive charge on the ligand donor atom or functional group, such that any group attached to the donor atom capable of leaving as a cation will have its leaving group capacity enhanced through metal coordination. Thus, the pK_a of protic acids will be typically lowered upon coordination (e.g., by ~2 pK_a units). For example, when the biologically active agent/ligand is topiramate (tpm), the donor atom is the N atom of the sulfamate group, and the leaving cation is a proton, thereby generating the tpm^- ligand as shown in FIG. 2. This phenomenon—combined with the fact that weaker bases can participate in chelate forming reactions—means that metal coordination complexes form molecules that are less basic than organic salts.

[0062] In embodiments in which a buffering ligand is included in the coordination complex of a metal and a biologically active agent, the metal is selected such that other ligands can be attached to the metal drug complex (i.e., the metal has more than 2 binding sites). In some embodiments, the metal is able to adopt a square planar or other 4-binding or 5-binding site geometry. In some embodiments, the metal is able to adopt octahedral geometry. In some embodiments, the metal is generally recognized as safe (GRAS) by the FDA. In some embodiments, the metal is magnesium, calcium, strontium or zinc.

[0063] In some embodiments, the buffering ligand is selected from a group of molecules that (a) form stable complexes or chelates with the metal
and (b) have a buffering capacity such that the entire complex has a $pK_a$ within a physiological acceptable range of about 5 to about 9 (in some embodiments from about 6 to about 8.5). In some embodiments, the buffering ligand is an amino acid which, in some embodiments, is arginine, lysine or histidine.

In some embodiments in which a buffering ligand is included in the coordination complex, the metal, the biologically active agent, and the buffering ligand are part of a single molecular entity, such that the entire coordination complex retains its structural integrity at physiological pH for a period of time sufficient to allow I.V. administration and/or migration from a drug delivery vehicle to target tissue. In addition to the stability provided to the coordination complex by its ionic and coordination bonds, other forces including but not limited to hydrogen bonding and/or Van der Waals attractions—especially between the buffering ligand and the biologically active agent—can also contribute to the overall stability of the coordination complex.

In some embodiments in which the coordination complex contains a buffering ligand and the biologically active agent is topiramate or an HDAC inhibitor, the coordination complex is stable in water at least long enough for it to be injected as a solution. Thus, sterile water is added to a powder of a coordination complex containing a buffering ligand, a solution formed, and the resultant solution injected into a patient before precipitation of the complex becomes problematic. Thus, through a combination of metal coordination, buffering to lower $pK_a$, and slowed kinetics of precipitation, a coordination complex in accordance with the present teachings provides a stable, water-soluble form of a drug that would otherwise have been exceedingly difficult and/or impossible to prepare.

FIG. 3 shows two coordination complexes embodying features of the present teachings in which the biologically active agent is topiramate, the metal is magnesium, and the coordination complex either lacks (i.e., the coordination complex on the left) or includes (i.e., the "mixed ligand" coordination complex on the right) a buffering ligand (e.g., the amino acid histidine). In the "mixed ligand" coordination complex shown on the right in
FIG. 3, a buffering ligand (i.e., histidine) replaces one of the topiramates of the coordination complex on the left. In some embodiments, the buffering ligand is an adjuvant capable of improving the solubility of a biologically active agent at low pH. One factor that enhances the aqueous solubility of a coordination complex is its ability to hydrogen bond with a solvent. Thus, a coordination complex that contains a buffering ligand capable of forming hydrogen bonds is generally more soluble in polar protic solvents because of the increased energy of solvation. Amino acids, peptides, and carbohydrates—including but not limited to those shown in FIG. 4—are three representative types of biocompatible buffering ligands that can be used in accordance with the present teachings.

[0067] In some embodiments, the buffering ligand is an amino acid. In general, amino acids have powerful chelating properties, are readily available, and exhibit diverse physicochemical properties. In some embodiments, the amino acids are protonated at physiological pH to increase water solubility and to act as intramolecular buffers. In some embodiments, the buffering ligand is a carbohydrate. Carbohydrates are configured for enhancing the water solubility of a coordination complex, and acidic carbohydrates (e.g., ascorbic acid) are configured to lower the pH of a coordination complex in solution. In some embodiments, the biologically active agent is topiramate and the buffering ligand is ascorbic acid. In some embodiments, a coordination complex in accordance with the present teachings includes a buffering ligand wherein the buffering ligand facilitates transport of a biologically active agent to a target site (e.g., a specific organ and/or tissue) in a patient.

[0068] The synthetic route by which a coordination complex in accordance with the present teachings—whether or not it further contains a buffering ligand—is prepared is not restricted. However, for purposes of illustration, some representative approaches, which are not to be construed as limiting and/or the only available routes, are now described.

[0069] First, the preparation of a coordination complex that does not necessarily contain a buffering ligand can be achieved by a synthetic route
including but not limited to the following: (1) reacting an acidic ligand having additional donor atoms with a strong base in water to form a salt, which is then reacted with a metal salt—usually in the form of a halide or an acetate—in an organic solvent; and (2) reacting an acidic ligand having additional donor atoms with a metallic base such as Mg(f-butoxide)$_2$, Ca(OMe)$_2$, or Zn(-propoxide)$_2$ in an organic solvent. As further shown in the examples below, a coordination complex containing topiramate and either magnesium or zinc metal has been prepared by method (1), while a coordination complex containing topiramate and calcium metal has been prepared by method (2). Moreover, it should be noted that a key principle in favoring the formation of a coordination complex of an organic compound and a metal as opposed to a salt is to prepare the complex in a non-aqueous system, such as shown in the following representative reaction in which the biologically active agent is topiramate:

\[
\text{tpmH} \xrightarrow{1. \text{KOH, THF}} \text{Ca(tpm)}_2 \xrightarrow{2. \text{Ca(OAc)}_2, \text{MeOH}}
\]

[0070] Second, in the preparation of a coordination complex that contains a buffering ligand, parameters such as stoichiometry, order of reagent addition, solvent, temperature, concentration, purity of solvents and/or reagents, and the like should be controlled. Within these parameters, the preparation of a coordination complex that contains a buffering ligand can be achieved by a synthetic route including but not limited to the following, as depicted schematically in the corresponding reactions (1) - (4) below: (1) simultaneous combination of the biologically active agent (L) and buffering ligand (U); (2) sequential combination of the ligands L and L'; (3) coproporportionation reaction between two binary bis-ligand (or homoleptic) complexes; and (4) substitution reaction in which a ligand in a metal complex is replaced by a second ligand (a reaction that depends on thermodynamic stability of the ligand binding with the metal ion and on the reaction mechanism).
In a solution containing a metal ion and ligands L and L', the formation of the mixed ligand complex MLL' is more favored on a statistical basis than the formation of the binary complexes ML₂ and ML'₂. The equilibrium constant for the formation of the mixed ligand complex is related to the equilibrium constant of the corresponding coproportionation reaction (reaction 3 above), K_coprop. If statistical factors alone were responsible for formation of the mixed ligand complex, then K_coprop would equal 4. However, since the experimental values of K_coprop differ from the statistical value, other factors are involved in the formation of mixed ligand complexes. These factors include electronic, electrostatic, and steric effects that can affect product formation by stabilizing or destabilizing the complexes.

As further shown in the examples below, a coordination complex that contains topiramate as its biologically active agent and an amino acid as a buffering ligand has been prepared using the coproportionation approach, shown in reaction (3) above. Other mixed ligand coordination complexes have also been prepared using the coproportionation approach as shown in the examples below:

\[
\begin{align*}
\text{Zn(tpm)}_2 + \text{Zn(arg)}_2 & \xrightarrow{\Delta \text{DMSO}} 2 \text{Zn(tpm)(arg)} \\
\text{Ca(saha)}_2 + \text{Ca(tricine)}_2 & \xrightarrow{\Delta \text{DMSO}} 2 \text{Ca(saha)(tricine)} \\
\text{Ca(saha)}_2 + \text{Ca(quinato)}_2 & \xrightarrow{\Delta \text{DMSO}} 2 \text{Ca(saha)(quinato)}
\end{align*}
\]

Of course, it is to be understood that the coproportionation reaction shown above is only one representative approach to preparing a
coordination complex containing a buffering ligand and that other synthetic approaches are also viable.

[0074] As explained above, a coordination complex in accordance with the present teachings is different than a simple metal salt. The differentiation of coordination complexes and simple salts can be achieved by various methods including but not limited to: \(^1\)H and \(^{13}\)C nuclear magnetic resonance (NMR) spectroscopy; two-dimensional NMR techniques, such as Diffusion Ordered Spectroscopy (DOSY) NMR; differentiating physiochemical properties (e.g., solubility and/or distribution coefficients); infrared (IR) spectroscopy; mass spectrometry; molar conductivity; magnetic measurements; and x-ray crystallography.

[0075] Structures can be determined using \(^1\)H and/or \(^{13}\)C NMR spectroscopy through a comparison of chemical shifts, coupling constants, and/or changes of relaxation parameters caused by coordinate covalent bond formation as compared to a reference drug ligand (e.g., topiramate). As shown in the examples below, the magnitude of the change in chemical shift in the \(^1\)H NMR spectra of a metal-coordinated topiramate is not similarly observed in the case of a simple salt.

[0076] Coordination complexes in accordance with the present teachings can be evaluated on the basis of solubility measurements, distribution coefficients, stability measurements, etc. A description of each of these types of measurement is given below.

[0077] Solubility: Intrinsic solubility (\(W_{i}\)) is defined as the number of moles per liter of solute that dissolves into solution. Equilibrium between solute and solution is maintained at a specific temperature (usually 25 °C). For a neutral compound, the total solubility equals the intrinsic solubility because only the neutral compound is involved. However, for a compound with ionizable groups, the solubility expression is more complex because multiple species with varying solubilities are present. Accordingly, it is necessary to use the term aqueous solubility (WS) to define the solubility of compounds having ionizable groups. Aqueous solubility is the sum of the individual solubilities for the neutral compound and all ionized species.
present. For compounds having ionizable groups, aqueous solubility is a function of pH. Given WSo (the solubility of the neutral compound) and the solubility of each ionized species (Ci), the equation for aqueous solubility becomes:

$$WS = WSo + \sum[Ci]_{aq}$$

[0078] A pH-solubility profile is a set of solubility values at specified pH values. The values given in a pH profile refer to solubility as a function of pH for all species of a compound (ionizable and neutral) in solution. Solubility profiles can be used to delineate solubility in complex situations where multiple ionizable species are present.

[0079] Distribution Coefficients: Due to the inherent covalency associated with coordination complexes, penetration of the blood-brain barrier (BBB) by the coordination complex after its administration into the bloodstream is facilitated. Indeed, in some embodiments, penetration of the BBB is particularly desirable, such as in treatments for brain cancer (e.g., using a biologically active agent such as topiramate or an HDAC inhibitor). The BBB permeability of coordination complexes in accordance with the present teachings can be predicted by measuring their distribution coefficients. The distribution coefficient (D) is the ratio of un-ionized compound in the lipid phase to the total in the aqueous phase as given by:

$$D = \frac{[\text{un-ionized}] (o)}{[\text{un-ionized}] (aq) + [\text{ionized}] (aq)}$$

[0080] The distribution coefficient is not a constant value and will vary according to the protogenic nature of the molecule. Log D (log10 of the distribution coefficient) at pH 7.4 is often reported to give an indication of the lipophilicity of a drug at the normal pH of blood plasma. A log D value of 2.0 is considered optimal for crossing the blood-brain barrier. For topiramate, for example, the log D value is -0.5. However, despite this relatively low value, topiramate appears to readily cross membranes.

[0081] Without wishing to be bound by a particular theory or to in any way limit the scope of the appended claims or their equivalents, it is presently believed that increasing log D by coordinating a ligand with a metal—although it may seem counterintuitive—is consistent with the formation of a coordinate
covalent bond between a metal and a ligand anion, and supports a contention that metal coordination leads to amphiphilic drugs. Without wishing to be bound by a particular theory or to in any way limit the scope of the appended claims or their equivalents, it is further believed that metal coordination in accordance with the present teachings will not significantly lower a drug's log D or adversely affect its ability to penetrate the BBB. Furthermore, for a coordination complex in which the biologically active agent is topiramate, it is expected that the bond between the metal and topiramate will dissociate prior to transport across the BBB due to circulating proteins and minerals in the bloodstream. Thus, coordination complexes in accordance with the present teachings—whether or not they contain a buffering ligand—should perform within the body at least as well as the reference drug itself.

[0082] Stability: In some embodiments, a coordination complex in accordance with the present teachings (e.g., one in which the biologically active agent is topiramate) does not revert back to the biologically active agent in aqueous solution before the solution is administered to the patient. However, once the coordination complex has been delivered to the blood, it is anticipated that that the coordination complex will dissociate (although, by that point, sufficient dilution will have occurred such that the biologically active agent will remain dissolved). In typical nursing/pharmacy operations, powders are reconstituted prior to use and administered within approximately 10 minutes of dilution. In some embodiments, integrity of the coordination complex is maintained at or above 90% for at least 30 minutes.

[0083] The following examples and representative procedures illustrate features in accordance with the present invention, and are provided solely by way of illustration. They are not intended to limit the scope of the appended claims or their equivalents.

EXAMPLES

[0084] Synthesis of Calcium(topiramate)?: To a 10-mL round-bottomed flask equipped with magnetic stirrer was added potassium topiramate (249.8 mg, 0.661 mmol). Anhydrous methanol (5 mL) was added via syringe and the
solid dissolved. Calcium acetate (52.9 mg, 0.330 mmol) was added and dissolved with stirring. The solution was stirred at room temperature for 16 hrs. Solvent was removed under reduced pressure affording a white solid in quantitative yield. $^1$H NMR (DMSO-d$_6$): $\delta$ 4.55 (dm; $J$ = 7.8 Hz; 1 H; H4), 4.29 (m; 1 H; H3), 4.21 (br. d; $J$ = 8.0 Hz; 1 H; H5); 3.75-3.66 (m; 3 H; H1a,b,6a), 3.55 (br. d; $J$ = 13.2 Hz; 1H; H6b), 1.43 (s; 3 H; CH$_3$); 1.35 (s; 3 H; CH$_3$), 1.34 (s; 3 H; CH$_3$), 1.27 (s; 3 H; CH$_3$). Ca 4.2% (theoretical 4.4%). This material (32 mg based on topiramate) was dissolved in H$_2$O (1 mL) and the pH adjusted to 7.0 by the addition of 1.0 N HCl. No precipitate was observed upon standing for 2 hours.

As a point of reference, the $^1$H NMR data for topiramate (DMSO-d$_6$) are as follows: $\delta$ 4.61 (dd; $J$ = 7.8, 2.4 Hz; 1 H; H4), 4.25 (br. d; $J$ = 8.0 Hz; 1 H; H3), 4.24 (d; $J$ = 2.0 Hz; 1 H; H5); 4.01 (d; $J$ = 10.0 Hz; 1 H; H1a), 3.96 (d; $J$ = 10.0 Hz; 1 H; H1b), 3.75 (d; $J$ = 12.8 Hz; 1H; H6a), 3.62 (d; $J$ = 12.8 Hz, 1H, H6b), 1.47 (s; 3 H; CH$_3$); 1.37 (s; 3 H; CH$_3$), 1.34 (s; 3 H; CH$_3$), 1.28 (s; 3 H; CH$_3$).

**Calcium Salt of Topiramate:** To a 10-mL beaker equipped with magnetic stirrer, topiramate (50 mg, 0.147 mmol) was suspended in 2 mL of water with stirring. KOH (147 µL, 147 µmol) was added as a 1.0 N aqueous solution. The topiramate mostly dissolved with gentle heating. Calcium acetate (11.63 mg, 0.0735 mmol) was added. The solution was stirred overnight. The slightly cloudy suspension was filtered to remove any unreacted topiramate. The water was removed from the filtrate under reduced pressure affording 43.7 mg of a white solid. $^1$H NMR (DMSO-d$_6$): $\delta$ 4.59 (dd; $J$ = 7.8, 2.4 Hz; 1 H; H4), 4.25 (d; $J$ = 2.0 Hz; 1 H; H3), 4.24 (br. m; 1 H; H5); 3.96 (d; $J$ = 10.0 Hz; 1 H; H1a), 3.91 (d; $J$ = 10.0 Hz; 1 H; H1b), 3.75 (d; $J$ = 12.8 Hz; 1H; H6a), 3.60 (d; $J$ = 12.8 Hz, 1H, H6b), 1.46 (s; 3 H; CH$_3$); 1.36 (s; 3 H; CH$_3$), 1.34 (s; 3 H; CH$_3$), 1.28 (s; 3 H; CH$_3$).

The compound obtained displayed a $^1$H NMR differing significantly from the coordination complex especially comparing the chemical shifts of protons 1a and 1b. A sample of this material (32 mg based on topiramate) was dissolved in H$_2$O (1 mL) and the pH adjusted to 7.0 as above. A
precipitate formed immediately which was identified after filtration as topiramate.

[0088] A comparison of the above results clearly shows a difference in physicochemical properties between a salt and a coordination complex.

[0089] Synthesis of Magnesium (topiramate)?: To a 5-mL conical vial equipped with magnetic stirrer was added potassium topiramate (120 mg, 0.317 mmol). Anhydrous methanol (2.5 mL) was added via syringe and the solid dissolved. Magnesium acetate (37.8 mg, 0.176 mmol) was added and dissolved with stirring. The solution was stirred at room temperature for 16 hrs. Solvent was removed from the solution under reduced pressure yielding white solid. $^1$H NMR (DMSO-d$_6$): δ 4.56 (dd; J = 8.0, 2.4 Hz; 1 H), 4.28 (d; J=2.4 Hz; 1 H), 4.22 (br. d; J=8.0 Hz; 1 H); 3.80 (d; J = 14.8 Hz; 1 H), 3.80 (d; J = 14.8 Hz; 1 H), 3.76 (d; J = 14.8 Hz; 1 H), 3.73 (d; J = 13.2 Hz; 1 H), 3.56 (d; J = 13.2 Hz; 1 H), 1.44 (s; 3 H); 1.35 (d; J= 5.2 Hz; 6 H), 1.27 (s; 3 H). $^{13}$C NMR (DMSO-de): δ 113.22, 113.02, 106.80, 75.33, 74.72, 72.27, 65.49, 53.73, 31.48, 30.95, 30.45, 29.23.

[0090] Synthesis of Magnesium(topiramate)(histidine): To a 1-mL ampoule were added magnesium topiramate (15.0 mg, 0.021 mmol), magnesium histidine (6.0 mg, 0.018 mmol), and water (1.0 mL) via pipette. The ampoule was sealed and heated at 100 °C for 16 hours. Solvent was removed under reduced pressure affording a white solid. $^1$H NMR; (D$_2$O): δ 7.74 (s; 1 H2), 7.04 (s; 1 H; H4), 4.48 (dd; J = 12.8 Hz, 4.8 Hz; 1 H; T4), 4.43 (d; J = 2.2 (av.); 1 H; T3), 4.21 (d; J = 5.2 Hz; 1 H; T5), 3.99 (d; J = 13.6 Hz; 1 H; T6a); 3.94 (d; J = 6.4; 1 H; T1a), 3.92 (d; J = 6.4 Hz; 1 H; T1b), 3.78 (d; J = 13.6; 1 H; T6b), 3.67 (dd; J = 26.4 Hz, 12.4 Hz; 1 H; H7), 3.19 (dd; J = 13.0 Hz (av.), 7.8 Hz (av.); 1 H; H6a); 3.08 (dd; J = 15.0 Hz (av.), 7.0 Hz (av.); 1 H; H6b), 1.59 (s, 3 H; T CH$_3$), 1.50 (s, 3 H; T CH$_3$), 1.45 (s, 3 H; T CH$_3$), 1.42 (s; 3 H; T CH$_3$).

[0091] Synthesis of Zinc(topiramate)(arginine): To a 5-mL vial equipped with magnetic stirrer were added zinc topiramate (25.4 mg, 0.034 mmol) and anhydrous dimethylacetamide (2.5 mL) via syringe. To this solution was added zinc arginate (14.1 mg, 0.034 mmol) and the mixture was stirred to
homogenize. An aliquot (1 ml) was syringed into an ampoule, which was sealed and heated at 102 °C for 6 hours. Solvent was removed under reduced pressure affording a white solid. ¹H NMR; (DMSO-d₆): δ 5.08 (m; 1 H; NH), 4.57 (br d; J = 8.0 Hz; 1 H; T4), 4.27 (s; 1 H; T3); 4.21 (d; J = 8.4; 1 H; T5), 3.73 (d; J = 12.8 Hz; 1 H; T6a), 3.54 (d; J = 11.6; 1 H; T6b), 3.45-3.30 (m; 3 H; T1a,b A2), 3.08 (m; 2 H; A5); 1.79-1.72 (m; 1 H; A3a), 1.60-1.48 (m, 3 H; A3b, A4a,b), 1.44 (s; 3 H; T CH3), 1.34 (s; 6 H; 2x T CH3), 1.27 (s; 3 H; T CH3).

[0092] As a point of reference, the ¹H NMR data for Zn(tpm)₂ (DMSO-d₆) are as follows: δ 4.56 (dd; J = 7.8, 2.0 Hz; 1 H; T4), 4.28 (d; J = 2.0 Hz; 1 H; T3), 4.22 (d; J = 8.0 Hz; 1 H; T5); 3.93 (d; J = 10.4 Hz; 1 H; T1a), 3.82 (d; J = 10.4 Hz; 1 H; T1b), 3.73 (d; J = 12.8 Hz; 1H; T6a), 3.57 (d; J = 12.8 Hz, 1H, T6b), 1.44 (s; 3 H; CH3); 1.37 (s; 3 H; CH3), 1.34 (s; 3 H; CH3), 1.27 (s; 3 H; CH3). As a point of reference, the ¹H NMR data for Zn(arg)₂ (DMSO) are as follows: δ 3.34 (br s; 1 H; A2), 3.12 (br s; 2 H; A5a,b), 1.78 (br s; 1H; A3a), 1.56 (br s; 3 H; A3b A4a,b).

[0093] Of particular significance are the observations in the ¹H NMR of the mixed ligand coordination complex that H3 of topiramate collapses from a doublet (J = 2.0 Hz) to a singlet, and that H4 collapses from a doublet of doublets to a doublet. Without wishing to be bound by a particular theory or to in any way limit the scope of the appended claims or their equivalents, it is presently believed that this is evidence of a ring conformational change caused by an intramolecular ligand-ligand interaction between topiramate and arginine in the ternary coordination complex, which is not observed for the Na, K or Ca salts or Zn coordination complex. A similar phenomenon with respect to the coupling of H3 in topiramate is observed for Ca(tpm)₂, the homoligated compound (binary complex), although the effect is not as large. In this case, the ligand-ligand interaction is influenced by the differential binding affinity of the metal.

[0094] Solubility/pH Studies of Topiramate-Containing Coordination Complexes: Initial screening of drug candidates was based on a qualitative determination of aqueous solubility using gravimetric methods. Briefly, a
known quantity of coordination compound (ca. 50 mg) was dissolved in a
known amount of water (1000 /L). The pH of the resulting mixture was
measured, and the solution/suspension was filtered and concentrated to
afford a minimal solubility value. Using this method, it was found that the
solubility of Ca(tpm)₂ is ≥34 mg/mL at pH 7.0 which—surprisingly and
unexpectedly—is at least three times the solubility of free topiramate (9.8
mg/mL).

[0095] Synthesis of Mg(saha)?: To a 25-mL round-bottomed flask
equipped with magnetic stirrer, heating mantle, and reflux condenser was
added saha (100 mg, 0.379 mmol). Anhydrous methanol (10 mL) was added
via syringe and the solid dissolved. Magnesium acetate (40.6 mg, 0.189
mmol) was added in one portion and immediately dissolved. The solution was
refluxed for 16 hrs. Solvent was removed from the clear solution under
reduced pressure yielding a colorless solid. The aqueous solubility was
determined by UV-VIS spectroscopy (242 nm in MeOH) to be 0.40 mg/mL at
pH 7.75. ¹³C NMR (DMSO-d₆): δ 171.7, 139.8, 136.6, 129.0, 123.3, 119.4,
36.8, 28.8, 25.4. Note: The ¹³C NMR chemical shifts for the carbonyl carbons
of SAHA are 171.7 and 169.5 ppm.

[0096] Synthesis of Cartricine)?: Tricine (250 mg, 1.40 mmol) and water
(7 mL) were added to a 10-mL vial. Barium hydroxide (133 mg, 0.70 mmol)
was added to this solution in one portion. The clear solution was stirred for 30
minutes at room temperature. CaSO₄ (121 mg, 0.70 mmol) was added in one
portion. A precipitate formed immediately. The suspension was stirred an
additional 1 hour. The mixture was vacuum filtered using medium porosity
filter paper. Solvent was removed under reduced pressure leaving 278 mg
(0.7 mmol, 100% yield) of Ca(tricine)₂ as a colorless solid.

[0097] Synthesis of Ca(saha)?: SAHA (50 mg, 0.19 mmol) and
anhydrous methanol (2 mL) were added to a 2-mL ampoule. Calcium acetate
(15 mg, 0.10 mmol) was added in one portion. The ampoule was sealed and
the solution was refluxed for 16 hrs. Solvent was removed under reduced
pressure leaving a colorless solid. The aqueous solubility was determined by
UV-VIS spectroscopy (242 nm in MeOH) to be 0.45 mg/mL at pH 8.60.
Synthesis of Ca(saha)(tricine). Ca(saha)$_2$ (25 mg, 0.04 mmol) and anhydrous DMSO (2 mL) were added to a 2-mL ampoule. Ca(tricine)$_2$ (18 mg, 0.04 mmol) was added in one portion. The ampoule was sealed and the solution was heated at 65 °C for 16 hrs. Solvent was removed under reduced pressure leaving a colorless solid. The aqueous solubility of this compound was determined by UV-VIS spectroscopy (242 nm in MeOH) to be 1.4 mg/mL at pH 8.75.

Synthesis of Ca(quinic acid): Quinic acid (150 mg, 0.781 mmol) and DMSO (5 mL) were added to a 25-mL round-bottomed flask. Calcium methoxide (39.8 mg, 0.391 mmol) was added in one portion. The clear solution was stirred for 16 hours at room temperature. Solvent was removed under reduced pressure leaving a colorless solid.

Synthesis of Ca(saha)(quinic acid): Ca(saha)$_2$ (20 mg, 0.035 mmol) and anhydrous DMSO (2 mL) were added to a 2-mL ampoule. Ca(quinic acid)$_2$ (15 mg, 0.035 mmol) was added in one portion. The ampoule was sealed and the solution was heated at 65 °C for 16 hrs. Solvent was removed under reduced pressure leaving a colorless solid. The aqueous solubility of this compound was determined by UV-VIS spectroscopy (242 nm in MeOH) to be 1.86 mg/mL at pH 8.25.

Synthesis of Nifsaha: To a 25-mL round-bottomed flask equipped with magnetic stirrer, heating mantle, and reflux condenser was added SAHA (100 mg, 0.379 mmol). Anhydrous methanol (10 mL) was added via syringe and the solid dissolved. Nickel acetate (47.2 mg, 0.189 mmol) was added in one portion and dissolved with stirring. The solution was refluxed for 16 hrs. Solvent was removed from the green solution under reduced pressure yielding green solid. The aqueous solubility was determined by UV-VIS spectroscopy (242 nm in MeOH) to be 0.04 mg/mL at pH 5.86.

Solubility and pH Testing: Table 1 below shows data for the solubility of SAHA, the sodium salt of SAHA, and five metal coordinated complexes of SAHA.
As shown in Table 1, the sodium salt of SAHA shows a nearly 7-fold increase in solubility over SAHA itself although the pH of the solution of this salt is 10—well above the acceptable range for an I.V. formulation. However, surprisingly and unexpectedly, metal coordination of SAHA with an s-block metal increased its solubility to approach that of the unusable sodium salt but at a much lower, physiologically acceptable pH. Moreover, incorporating adjuvants such as tricine and quinic acid into the coordination complex yields products that—surprisingly and unexpectedly—exhibit both a therapeutically relevant solubility and a therapeutically acceptable pH, thus providing effective and safe I.V. formulations for SAHA.

As noted in the description above and as evidenced by the solubility data for compound 3 shown in Table 1, a complex of SAHA coordinated with a transition metal (viz., Ni) as opposed to an s-block metal (e.g., Mg or Ca) results in a complex that is even less soluble than SAHA itself—a reduction in solubility that, based on present understanding, is attributable to the fact that transition metals bind SAHA too tightly (i.e., confer too much covalency to the complex).

As shown in Table 1, the pH of a solution of Ca(saha)$_2$ (compound 2) is actually slightly higher than the pH of a solution of SAHA itself. However,
this increase in pH is not to be automatically construed as reflecting a corresponding increase in pKₐ. The distinction can be explained as follows and is worth bearing in mind when evaluating the data in Table 1. First, references to pKₐ refer to the pKₐ of a proton attached to a neutral or fully protonated biologically active agent or a metal-coordinated biologically active agent. However, in the case of a metal-coordinated biologically active agent such as Ca(saha)₂, the SAHA moiety is deprotonated relative to SAHA itself. The pH of the deprotonated salt of SAHA is around 10 as revealed by Na(saha). Therefore, the pH of a solution of Ca(saha)₂ does not necessarily reflect the pKₐ of the corresponding protonated species.

[00106] Anticancer Activity Testing: To test whether the incorporation of SAHA into a coordination complex affects its anticancer activity, cell proliferation assays were conducted. In the experiment, MDA-MB-231 breast cancer cells were plated (500 cells/well) on a 96-well plate and grown in culture for 24 hours. Drug solution was added and the cells were incubated for 48 hours. The drug medium was removed and the number of cells determined using the MTS method. As shown in FIG. 5, the data demonstrate that SAHA-containing coordination complexes inhibit breast cancer cell growth at concentrations (2.5 - 5 mM) for which SAHA is active.

[00107] The foregoing detailed description and accompanying figures have been provided by way of explanation and illustration, and are not intended to limit the scope of the appended claims. Many variations in the presently preferred embodiments illustrated herein will be apparent to one of ordinary skill in the art, and remain within the scope of the appended claims and their equivalents.
CLAIMS

1. A coordination complex comprising:
   a metal; and
   a biologically active agent;
   wherein the coordination complex has a $pK_a$ that is less than a $pK_a$ of the biologically active agent; and
   wherein the $pK_g$ of the coordination complex is physiologically acceptable;
   with a proviso that when the biologically active agent is suberoylanilide hydroxamic acid, then the metal is neither iron nor zinc.

2. A coordination complex comprising:
   a metal other than iron or zinc; and
   a biologically active agent;
   wherein the coordination complex has a $pK_a$ that is less than a $pK_g$ of the biologically active agent; and
   wherein the $pK_a$ of the coordination complex is physiologically acceptable.

3. A coordination complex comprising:
   a metal selected from the group consisting of magnesium, calcium, and nickel; and
   a biologically active agent;
   wherein the coordination complex has a $pK_a$ that is less than a $pK_a$ of the biologically active agent; and
   wherein the $pK_a$ of the coordination complex is physiologically acceptable.

4. A coordination complex comprising:
   a metal selected from the group consisting of magnesium, calcium, and nickel; and
a biologically active agent selected from the group consisting of a
sulfamate, a hydroxamic acid, and a dihydropyridine calcium channel blocker;
wherein the coordination complex has a $pK_a$ that is less than a
$pK_g$ of the biologically active agent; and
wherein the $pK_a$ of the coordination complex is less than about
9.

5. The invention of claim 1, 2, 3 or 4 wherein water solubility of the
coordination complex is greater than that of the biologically active agent at
physiological pH.

6. The invention of claim 1, 2, 3 or 4 wherein water solubility of the
coordination complex is greater than that of a metal salt of the biologically
active agent at physiological pH.

7. The invention of claim 1, 2, 3 or 4 wherein the biologically active agent
exhibits therapeutic efficacy against one or a plurality of diseases, and
wherein at least a portion of the therapeutic efficacy is retained in the
coordination complex.

8. The invention of claim 1, 2, 3 or 4 wherein the coordination complex
further comprises a buffering ligand.

9. The invention of claim 8 wherein the $pK_a$ of the coordination complex is
lower when the coordination complex comprises the buffering ligand than
when the coordination complex does not.

10. The invention of claim 8 wherein water solubility of the coordination
complex is greater when the coordination complex comprises the buffering
ligand than when the coordination complex does not.
11. The invention of claim 8 wherein the buffering ligand comprises one or a plurality of hydrogen bonding sites.

12. The invention of claim 8 wherein the buffering ligand is selected from the group consisting of an amino acid, a peptide, a carbohydrate, and a Good's buffer.

13. The invention of claim 12 wherein the amino acid is selected from the group consisting of arginine, lysine, and histidine.

14. The invention of claim 8 wherein the buffering ligand is selected from the group consisting of quinic acid, bicine, tricine, ascorbic acid, and carnosine.

15. The invention of claim 1, 2 or 3 wherein the pKa of the coordination complex is less than about 9.

16. The invention of claim 1, 2 or 3 wherein the pKa of the coordination complex is between about 5 and about 9.

17. The invention of claim 1, 2, 3 or 4 wherein the biologically active agent comprises suberoylanilide hydroxamic acid.

18. The invention of claim 17 wherein the metal comprises calcium.

19. The invention of claim 8 wherein the buffering ligand is selected from the group consisting of tricine and quinic acid.

20. The invention of claim 1 or 2 wherein the metal is a group IIA metal, a transition metal or a p-block metal.
21. The invention of claim 1 or 2 wherein the metal is a group MA metal selected from the group consisting of magnesium, calcium, and strontium.

22. The invention of claim 20 wherein the transition metal is a group VIII transition metal or a group IIb transition metal.

23. The invention of claim 1 wherein the metal comprises iron.

24. The invention of claim 1 wherein the metal comprises zinc.

25. The invention of claim 1, 2 or 3 wherein the biologically active agent is selected from the group consisting of an anticonvulsant, an antineoplastic, and a calcium channel blocker.

26. The invention of claim 1, 2 or 3 wherein the biologically active agent is selected from the group consisting of a sulfamate, a hydroxamic acid, and a dihydropyridine calcium channel blocker.

27. The invention of claim 26 wherein the sulfamate comprises topiramate.

28. The invention of claim 27 wherein the metal comprises magnesium.

29. The invention of claim 26 wherein the hydroxamic acid comprises a histone deacetylase inhibitor.

30. The invention of claim 29 wherein the histone deacetylase inhibitor comprises suberoylanilide hydroxamic acid.

31. The invention of claim 26 wherein the dihydropyridine calcium channel blocker is selected from the group consisting of nisoldipine, nifedipine, isradipine, and amlodipine.
32. A pharmaceutical solution for treating a patient comprising the coordination complex of claim 1, 2, 3 or 4 and water, wherein the coordination complex is at least partially soluble in the water at physiological pH in a therapeutically efficacious concentration.

33. The invention of claim 32 wherein the coordination complex is soluble at least for a time sufficient to deliver the biologically active agent to a target site in the patient's body.

34. A method for treating a patient comprising administering the pharmaceutical solution of claim 33 to a patient in need of the biologically active agent thereof.

35. The invention of claim 34 wherein the pharmaceutical solution is administered to the patient by a route selected from the group consisting of intraperitoneal injection, intramuscular injection, and intravenous injection.

36. The invention of claim 35 wherein the method comprises treating a neonatal seizure and wherein the biologically active agent comprises topiramate.

37. The invention of claim 35 wherein the method comprises treating a cancer and wherein the biologically active agent comprises suberoylanilide hydroxamic acid.

38. A pharmaceutical solution for treating a patient comprising the coordination complex of claim 8 and water, wherein the coordination complex is at least partially soluble in the water at physiological pH in a therapeutically efficacious concentration.
39. The invention of claim 38 wherein the coordination complex is soluble at least for a time sufficient to deliver the biologically active agent to a target site in the patient's body.

40. A method for treating a patient comprising administering the pharmaceutical solution of claim 39 to a patient in need of the biologically active agent thereof.

41. A coordination complex comprising:
   a metal; and
   a biologically active agent;
   wherein water solubility of the coordination complex is greater than water solubility of the biologically active agent at physiological pH; and
   wherein the pKa of the coordination complex is physiologically acceptable;
   with a proviso that when the biologically active agent is suberoylanilide hydroxamic acid, then the metal is not a transition metal unless the coordination complex further comprises a buffering ligand.

42. The invention of claim 41 wherein the metal comprises a group IIA metal.

43. The invention of claim 41 wherein the coordination complex further comprises a buffering ligand.

44. The invention of claim 43 wherein the buffering ligand comprises one or a plurality of hydrogen bonding sites.
45. The invention of claim 43 wherein the buffering ligand is selected from the group consisting of an amino acid, a peptide, a carbohydrate, and a Good's buffer.

46. The invention of claim 45 wherein the amino acid is selected from the group consisting of arginine, lysine, and histidine.

47. The invention of claim 45 wherein the buffering ligand is selected from the group consisting of quinic acid, bicine, tricine, ascorbic acid, and carnosine.

48. The invention of claim 41 wherein the biologically active agent is suberoylanilide hydroxamic acid and the metal is calcium.

49. The invention of claim 48 wherein the coordination complex further comprises a buffering ligand.

50. The invention of claim 49 wherein the buffering ligand is selected from the group consisting of quinic acid, bicine, tricine, ascorbic acid, and carnosine.
FIG. 1

![Chemical structure diagram]

$\text{pK}_a = 9.2$

$\log D_{7.4} = 1.46$

oral bioavailability = 43%

BCS Class = IV

solubility = 0.1 mg/mL at 25 °C

FIG. 2

![Chemical structure diagram]
FIG. 5

**Diagram Description:**
- The graph shows the absorbance at 490 nm (×1000) for different concentrations of compounds.
- The x-axis represents the concentration of compound (μM) ranging from 0 to 5.0.
- The y-axis represents the absorbance values ranging from 0 to 400.
- Different patterns and colors are used to distinguish between SAHA and other compounds (#1 to #5).

**Key Points:**
- SAHA shows consistent absorbance across different concentrations.
- Compounds #1 to #5 exhibit variability in absorbance with some showing higher absorbance at certain concentrations.
- The absorbance values are indicated with error bars for each concentration point.
**INTERNATIONAL SEARCH REPORT**

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**A. CLASSIFICATION OF SUBJECT MATTER**

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**ADD.**

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

A61K C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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Further documents are listed in the continuation of Box C.

See patent family annex.

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* Special categories of cited documents:

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Date of the actual completion of the international search

23 August 2011

Date of mailing of the international search report

31/08/2011

Name and mailing address of the ISA

European Patent Office P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel: (+31-70) 340-2040, Fax: (+31-70) 340-3016

Authorized officer

Sproll, Susanne

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