US 20070149622A1

(19) United States

(12) Patent Application Publication (10) Pub. No.: US 2007/0149622 A1

Gant et al. (43) Pub. Date: Jun. 28, 2007

(54) SUBSTITUTED PHENETHYLAMINES WITH SEROTONINERGIC AND/OR NOREPINEPHRINERGIC ACTIVITY

(75) Inventors: **Thomas G. Gant**, Carlsbad, CA (US); **Sepehr Sarshar**, Cardiff by the Sea, CA (US)

Correspondence Address:
KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614 (US)

(73) Assignee: **AUSPEX Pharmaceuticals, Inc.**, Vista, CA (US)

(21) Appl. No.: **11/565,451**

(22) Filed: **Nov. 30, 2006**

Related U.S. Application Data

(60) Provisional application No. 60/741,315, filed on Dec. 1, 2005. Provisional application No. 60/841,366, filed on Aug. 30, 2006.

Publication Classification

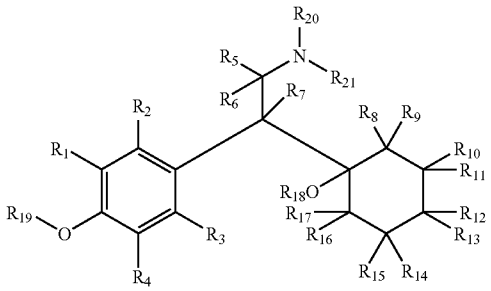
(51) **Int. Cl.**
A61K 31/137 (2006.01)

(52) **U.S. Cl.** **514/649**; 564/335

(57) **ABSTRACT**

Chemical syntheses and medical uses of novel inhibitors of the uptake of monoamine neurotransmitters and pharmaceutically acceptable salts and prodrugs thereof, for the treatment and/or management of psychotropic disorders, anxiety disorder, generalized anxiety disorder, depression, post-traumatic stress disorder, obsessive-compulsive disorder, panic disorder, hot flashes, senile dementia, migraine, hepatopulmonary syndrome, chronic pain, nociceptive pain, neuropathic pain, painful diabetic retinopathy, bipolar depression, obstructive sleep apnea, psychiatric disorders, premenstrual dysphoric disorder, social phobia, social anxiety disorder, urinary incontinence, anorexia, bulimia nervosa, obesity, ischemia, head injury, calcium overload in brain cells, drug dependence, and/or premature ejaculation are described.

Formula 1



SUBSTITUTED PHENETHYLAMINES WITH SEROTONINERGIC AND/OR NOREPINEPHRINERGIC ACTIVITY

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application Nos. 60/741,315, entitled "SUBSTITUTED PHENETHYLAMINES WITH SEROTONINERGIC AND/OR NOREPINEPHRINERGIC ACTIVITY", filed Dec. 1, 2005; and 60/841,366, entitled "SUBSTITUTED PHENETHYLAMINES WITH SEROTONINERGIC AND/OR NOREPINEPHRINERGIC ACTIVITY, filed Aug. 30, 2006, both of which are incorporated by reference in their entireties.

BACKGROUND OF THE INVENTION

[0002] 1. Field of the Invention

[0003] The present invention is directed to inhibitors of the uptake of monoamine neurotransmitters and pharmaceutically acceptable salts and prodrugs thereof, the chemical synthesis thereof, and the medical use of such compounds for the treatment and/or management of psychotropic disorders, anxiety disorder, generalized anxiety disorder, depression, post-traumatic stress disorder, obsessive-compulsive disorder, panic disorder, hot flashes, senile dementia, migraine, hepatopulmonary syndrome, chronic pain, nociceptive pain, neuropathic pain, painful diabetic retinopathy, bipolar depression, obstructive sleep apnea, psychiatric disorders, premenstrual dysphoric disorder, social phobia, social anxiety disorder, urinary incontinence, anorexia, bulimia nervosa, obesity, ischemia, head injury, calcium overload in brain cells, drug dependence, and/or premature ejaculation.

[0004] 2. Description of the Related Art

[0005] In an attempt to breakdown or to help solubilize chemicals and nutrients that have been absorbed into the blood, the human body expresses various enzymes (e.g. the cytochrome P_{450} enzymes or CYPs, esterases, proteases, reductases, dehydrogenases, and the like) that react with the chemicals and nutrients to produce novel intermediates or metabolites. Some of the most common metabolic reactions of pharmaceutical compounds involve the oxidation of a carbon-hydrogen (C—H) bond to either a carbon-oxygen (C—O) or carbon-carbon (C—C) π-bond. The resultant metabolites may be stable or unstable under physiological conditions, and can have substantially different pharmacokinetic, pharmacodynamic, acute and long-term toxicity profiles relative to the parent compounds. For most drugs, such oxidations are generally rapid and ultimately lead to administration of multiple or high daily doses. There is therefore an obvious and immediate need for improvements of such drugs.

[0006] Chemical kinetics is the study of reaction rates. The activation energy E_{act} in chemistry is the energy that must be supplied to a system in order to initiate a particular chemical process. In other words, this is the minimum energy required for a specific chemical reaction to take place. A reaction will occur between two properly oriented molecules if they repulsion. Overcoming this repulsion requires an input of energy (i.e. the activation energy), which results from the heat of the system; i.e. the translational, vibrational, and rotational energy of each molecule. If sufficient energy is available, the molecules may attain the proximity and orientation necessary to cause a rearrangement of bonds to form new substances.

[0007] The relationship between the activation energy and the rate of reaction may be quantified by the Arrhenius equation which states that the fraction of molecules that have enough energy to overcome an energy barrier—those with energy at least equal to the activation energy, E_{act}—depends exponentially on the ratio of the activation to thermal energy $k=Ae^{-Eact/RT}$. In this equation, RT is the average amount of thermal energy that molecules possess at a certain temperature T, where R is the molar gas constant, k is the rate constant for the reaction and A (the frequency factor) is a constant specific to each reaction that depends on the probability that the molecules will collide with the correct orientation.

[0008] The transition state in a reaction is a short lived state (on the order of 10^{-14} sec) along the reaction pathway during which the original bonds have stretched to their limit. By definition, the activation energy E_{act} for a reaction is the energy required to reach the transition state of that reaction. Reactions that involve multiple steps will necessarily have a number of transition states, and in these instances, the activation energy for the reaction is equal to the energy difference between the reactants and the most unstable transition state. Once the transition state is reached, the molecules can either revert, thus reforming the original reactants, or the new bonds form giving rise to the products. This dichotomy is possible because both pathways, forward and reverse, result in the release of energy. A catalyst facilitates a reaction process by lowering the activation energy leading to a transition state. Enzymes are examples of biological catalysts that reduce the energy necessary to achieve a particular transition state.

[0009] A carbon-hydrogen bond is by nature a covalent chemical bond. Such a bond forms when two atoms of similar electronegativity share some of their valence electrons, thereby creating a force that holds the atoms together. This force or bond strength can be quantified and is expressed in units of energy, and as such, covalent bonds between various atoms can be classified according to how much energy must be applied to the bond in order to break the bond or separate the two atoms.

[0010] The bond strength is directly proportional to the absolute value of the ground-state vibrational energy of the bond. This vibrational energy, which is also known as the zero-point vibrational energy, depends on the mass of the atoms that form the bond. The absolute value of the zero-point vibrational energy increases as the mass of one or both of the atoms making the bond increases. Since deuterium (D) is two-fold more massive than hydrogen (H), it follows that a C-D bond is stronger than the corresponding C—H bond. Compounds with C-D bonds are frequently indefinitely stable in H_2O, and have been widely used for isotopic studies. If a C—H bond is broken during a rate-determining step in a chemical reaction (i.e. the step with the highest

the process will slow down. This phenomenon is known as the Deuterium Kinetic Isotope Effect (DKIE) and can range from about 1 (no isotope effect) to very large numbers, such as 50 or more, meaning that the reaction can be fifty, or more, times slower when deuterium is substituted for hydrogen. High DKIE values may be due in part to a phenomenon known as tunneling, which is a consequence of the uncertainty principle. Tunneling is ascribed to the small size of a hydrogen atom, and occurs because transition states involving a proton can sometimes form in the absence of the required activation energy. A deuterium is larger and statistically has a much lower probability of undergoing this phenomenon. Substitution of tritium for hydrogen results in yet a stronger bond than deuterium and gives numerically larger isotope effects.

[0011] Discovered in 1932 by Urey, deuterium (D) is a stable and non-radioactive isotope of hydrogen. It was the first isotope to be separated from its element in pure form and is twice as massive as hydrogen, and makes up about 0.02% of the total mass of hydrogen (in this usage meaning all hydrogen isotopes) on earth. When two deuteriums bond with one oxygen, deuterium oxide (D_2O or "heavy water") is formed. D_2O looks and tastes like H_2O but it has different physical properties. It boils at 101.41° C. and freezes at 3.79° C. Its heat capacity, heat of fusion, heat of vaporization, and entropy are all higher than H_2O. It is also more viscous and is not as powerful a solvent as H_2O.

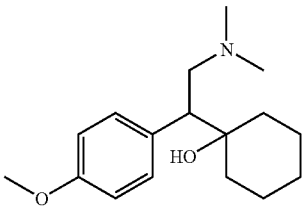
[0012] Tritium (T) is a radioactive isotope of hydrogen, used in research, fusion reactors, neutron generators and radiopharmaceuticals. Mixing tritium with a phosphor provides a continuous light source, a technique that is commonly used in wristwatches, compasses, rifle sights and exit signs. It was discovered by Rutherford, Oliphant and Harteck in 1934 and is produced naturally in the upper atmosphere when cosmic rays react with H_2 molecules. Tritium is a hydrogen atom that has 2 neutrons in the nucleus and has an atomic weight close to 3. It occurs naturally in the environment in very low concentrations, most commonly found as T_2O, a colorless and odorless liquid. Tritium decays slowly (half-life=12.3 years) and emits a low energy beta particle that cannot penetrate the outer layer of human skin. Internal exposure is the main hazard associated with this isotope, yet it must be ingested in large amounts to pose a significant health risk.

[0013] When pure D_2O is given to rodents, it is readily absorbed and reaches an equilibrium level that is usually about eighty percent of the concentration that is consumed by the animals. The quantity of deuterium required to induce toxicity is extremely high. When 0 to as much as 15% of the body water has been replaced by D_2O, animals are healthy but are unable to gain weight as fast as the control (untreated) group. Between 15 to 20% D_2O, the animals become excitable. At 20 to 25%, the animals are so excitable that they go into frequent convulsions when stimulated. Skin lesions, ulcers on the paws and muzzles, and necrosis of the tails appear. The animals also become very aggressive; males becoming almost unmanageable. At 30%, the animals refuse to eat and become comatose. Their body weight drops sharply and their metabolic rates drop far below normal, with death occurring at 30 to 35% replacement. The effects

shown that the use of D_2O can delay the growth of cancer cells and enhance the cytotoxicity of certain antineoplastic agents.

[0014] Deuteration of pharmaceuticals to improve pharmacokinetics (PK), pharmacodynamics (PD), and toxicity profiles, has been demonstrated previously with some classes of drugs. For example, DKIE was used to decrease the hepatotoxicity of halothane by presumably limiting the production of reactive species such as trifluoroacetyl chloride. However, this method may not be applicable to all drug classes. For example, deuterium incorporation can lead to metabolic switching which may even give rise to an oxidative intermediate with a faster off-rate from an activating Phase I enzyme (e.g. cytochrome P_{450} 3A4). The concept of metabolic switching asserts that xenogens, when sequestered by Phase I enzymes, may bind transiently and re-bind in a variety of conformations prior to the chemical reaction (e.g. oxidation). This claim is supported by the relatively vast size of binding pockets in many Phase I enzymes and the promiscuous nature of many metabolic reactions. Metabolic switching can potentially lead to different proportions of known metabolites as well as altogether new metabolites. This new metabolic profile may impart more or less toxicity. Such pitfalls are non-obvious and have not been heretofore sufficiently predictable a priori for any drug class.

[0015] It has been hypothesized that the efficacy of venlafaxine (Effexor®) is mainly due to its ability to inhibit serotonin reuptake and, potentially, norepinephrine reuptake in neuronal cells. The latter is purported to take effect only at high doses. The drug substance is sold as a 50/50 racemic mixture of R- and S-enantiomers. The mechanism of action of this drug has been extensively studied.



Venlafaxine

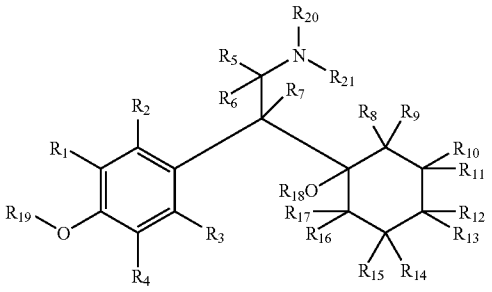
[0016] The benefits and shortcomings of this drug have been extensively reviewed as well. Some of these shortcomings can be traced to metabolism-related phenomena. Venlafaxine is converted in vivo by oxidative and conjugative degradation to multiple metabolites, at least 48 of which are documented. The major metabolites include much phase I metabolism leading to demethylation at the oxygen and/or nitrogen centers, and cyclohexyl ring hydroxylation, as well as significant phase II metabolism including glucuronidation of the hydroxylated metabolites. Because this drug is metabolized by polymorphically-expressed isozymes of cytochrome P_{450} including CYPs 2C19 and 2D6, and because it can act as an inhibitor of CYP2D6, its application in polypharmacy is necessarily complex and has potential for adverse events. These CYPs are involved in the metabolism of many medications that are typically prescribed

example of the critical need for improvement is the published interpatient variability observed in "poor metabolizers" having either defective CYP2D6 alleles or total lack of CYP2D6 expression. These patients fail to convert venlafaxine to its equipotent metabolite, O-desmethylvenlafaxine. Venlafaxine also suffers from a short half-life relative to the majority of serotonin reuptake inhibitors. The half-life of venlafaxine in humans is ~5 hours, while its active metabolite has a $T_{1/2}$ of ~11 hours. As a consequence of its 5-11 hour pharmacological half-life, those taking venlafaxine are at significant risk of SRI discontinuation symptoms if the drug is abruptly discontinued. Furthermore, in order to overcome its short half-life, the drug must be taken 2 (BID) or 3 (TID) times a day, which increases the probability of patient incompliance and discontinuance. Most other serotonin reuptake inhibitors (SRIs) have half-lives ≧24 hours. A 24-72 hour half-life is regarded as ideal for this class of compounds by most clinicians. There is therefore an obvious and immediate need for improvements in the development of monoamine reuptake inhibitors such as paroxetine.

SUMMARY OF THE INVENTION

[0017] Disclosed herein are compounds of Formula 1:

Formula 1



[0018] or a single enantiomer, a mixture of the (+)-enantiomer and the (−)-enantiomer, a mixture of about 90% or more by weight of the (−)-enantiomer and about 10% or less by weight of the (+)-enantiomer, a mixture of about 90% or more by weight of the (+)-enantiomer and about 10% or less by weight of the (−)-enantiomer, an individual diastereomer, a mixture of diastereomers, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein:

[0019] R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, and R_{18} are independently selected from the group consisting of hydrogen, and deuterium;

[0020] R_{19}, R_{20}, and R_{21} are independently selected from the group consisting of —CH_3, —CH_2D, —CHD_2, and —CD_3;

[0021] provided that compounds of Formula 1 contain at least one deuterium atom; and provided that deuterium enrichment in compounds of Formula 1 is at least about 1%.

[0022] Also disclosed herein are pharmaceutical compo-

(+)-enantiomer and the (−)-enantiomer, a mixture of about 90% or more by weight of the (−)-enantiomer and about 10% or less by weight of the (+)-enantiomer, a mixture of about 90% or more by weight of the (+)-enantiomer and about 10% or less by weight of the (−)-enantiomer, an individual diastereomer of a compound of Formula 1, a mixture of diastereomers, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, with a pharmaceutically acceptable carrier.

[0023] Further, disclosed herein are methods of eliciting, modulating and/or regulating the reuptake of monoamine neurotransmitters including serotonin and/or norepinephrine.

[0024] In addition, disclosed herein are methods of treating a mammalian subject having, suspected of having, or being prone to a disease or condition, such as a disease or condition selected from the group consisting of anxiety disorder, generalized anxiety disorder, depression, post-traumatic stress disorder, obsessive-compulsive disorder, panic disorder, a hot flash, senile dementia, migraine, hepatopulmonary syndrome, chronic pain, nociceptive pain, neuropathic pain, painful diabetic retinopathy, bipolar depression, obstructive sleep apnea, psychiatric disorders, premenstrual dysphoric disorder, social phobia, social anxiety disorder, urinary incontinence, anorexia, bulimia nervosa, obesity, ischemia, head injury, calcium overload in brain cells, drug dependence, and/or premature ejaculation.

DETAILED DESCRIPTION OF THE INVENTION

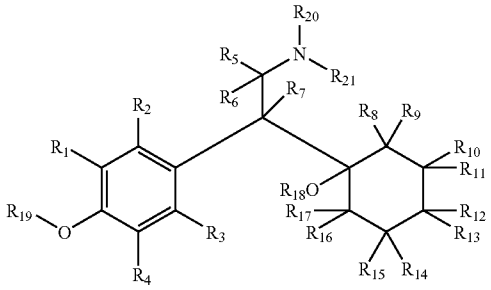
[0025] Certain monoamine reuptake inhibitors are known in the art and are shown herein. Venlafaxine (Effexor®) is one such compound. The carbon-hydrogen bonds of venlafaxine contain a naturally occurring distribution of hydrogen isotopes, namely ^1H or protium (about 99.9844%), ^2H or deuterium (about 0.0156%), and ^3H or tritium (in the range between about 0.5 and 67 tritium atoms per 10^{18} protium atoms). Increased levels of deuterium incorporation produce a detectable Kinetic Isotope Effect (KIE) that could affect the pharmacokinetic, pharmacologic and/or toxicologic parameters of such monoamine reuptake inhibitors relative to compounds having naturally occurring levels of deuterium. Aspects of the present invention disclosed herein describe a novel approach to designing and synthesizing new analogs of these monoamine reuptake inhibitors through chemical modifications and derivations of the carbon-hydrogen bonds of the modulators and/or of the chemical precursors used to synthesize said modulators. Suitable modifications of certain carbon-hydrogen bonds into carbon-deuterium bonds may generate novel monoamine reuptake inhibitors with unexpected and non-obvious improvements of pharmacological, pharmacokinetic and toxicological properties in comparison to the non-isotopically enriched monoamine reuptake inhibitors. This invention relies on the judicious and successful application of chemical kinetics to drug design. Deuterium incorporation levels in the compounds of the invention are significantly higher than the naturally-occurring levels and are sufficient to induce at least one substantial improvement as described herein.

tion, Distribution, Metabolism, Excretion, and Toxicological (ADMET) shortcomings for venlafaxine. For example, both N-methyl groups, the single O-methyl, and several sites on the cyclohexyl ring of venlafaxine are now known to be sites of cytochrome P_{450} metabolism. The toxicities of all resultant metabolites are not known. Furthermore, because polymorphically expressed CYPs such as 2C19 and 2D6 oxidize venlafaxine, and because venlafaxine inhibits the polymorphically expressed CYP2D6, the prevention of such interactions decreases interpatient variability, decreases drug-drug interactions, increases $T_{1/2}$, decreases the necessary C_{max}, and improves several other ADMET parameters. For example, the half-life of the parent drug of venlafaxine ranges from 3-7 hours. The equipotent metabolite, O-demethylated venlafaxine, has a half-life averaging 11 hours. Various deuteration patterns can be used to a) alter the ratio of active metabolites, b) reduce or eliminate unwanted metabolites, c) increase the half-life of the parent drug, and /or d) increase the half-life of active metabolites and create a more effective drug and a safer drug for polypharmacy, whether the polypharmacy be intentional or not. High doses of venlafaxine are often prescribed in order to reach levels capable of inhibiting norepinephrine reuptake. Unfortunately, high doses are also associated with hypertension. Since these phenomenon are linked by the pharmaceutical agent rather than the pharmacological target, the two phenomena are theoretically separable by increasing the half-life thus allowing dosing in a range that lowers the C_{max} and thus may avoid triggering the mechanism leading to hypertension. Further illustrating this point, venlafaxine is known to display linear kinetics at the low end of the dose range, 75 mg/day, but displays non-linear kinetics at the high end of the dose range, ~400 mg/day, as a result of the saturation of clearance mechanisms. This non-linearity produces an ascending, rather than a flat, dose-response curve for venlafaxine. The deuteration approach has strong potential to slow metabolism through the previously saturated mechanism allowing linear, more predictable ADMET responses throughout the dose range (which would also be lower via this invention). This leads to lesser interpatient variability of the type that can lead to the hypertensive effects.

[0027] The deuterated analogs of this invention have the potential to uniquely maintain the beneficial aspects of the non-isotopically enriched drugs while substantially increasing the half-life ($T_{1/2}$), lowering the maximum plasma concentration (C_{max}) of the minimum efficacious dose (MED), lowering the efficacious dose and thus decreasing the non-mechanism-related toxicity, and/or lowering the probability of drug-drug interactions. These drugs also have strong potential to reduce the cost-of-goods (COG) owing to the ready availability of inexpensive sources of deuterated reagents combined with previously mentioned potential for lowering the therapeutic dose. The present inventors have discovered that deuteration at the methylenedioxy moiety alone, and/or deuteration at the methylenedioxy moiety plus deuteration of additional sites found to be labile as a result

[0028] Thus, in one aspect, there are provided herein compounds having the structural Formula 1:

Formula 1



[0029] or a single enantiomer, a mixture of the (+)-enantiomer and the (−)-enantiomer, a mixture of about 90% or more by weight of the (−)-enantiomer and about 10% or less by weight of the (+)-enantiomer, a mixture of about 90% or more by weight of the (+)-enantiomer and about 10% or less by weight of the (−)-enantiomer, an individual diastereomer, a mixture of diastereomers, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein:

[0030] R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, and R_{18} are independently selected from the group consisting of hydrogen, and deuterium;

[0031] R_{19}, R_{20}, and R_{21} are independently selected from the group consisting of —CH_3, —CH_2D, —CHD_2, and —CD_3;

[0032] provided that compounds of Formula 1 contain at least one deuterium atom; and provided that deuterium enrichment in compounds of Formula 1 is at least about 1%.

[0033] Compounds of this invention have the potential to uniquely maintain the beneficial aspects of non-isotopically enriched monoamine reuptake inhibitors while substantially altering the half-life ($T_{1/2}$), lowering the maximum plasma concentration (C_{max}) of the minimum efficacious dose (MED), lowering the efficacious dose and thus decreasing non-mechanism-related toxicities and/or lowering the probability of drug-drug interactions. These drugs also have potential to reduce the cost-of-goods (COG) due to a potential for lowering the therapeutic dose when compared to the non-isotopically enriched monoamine reuptake inhibitors. In sum, many aspects of ADMET of the non-isotopically enriched monoamine reuptake inhibitors are substantially improved by this invention.

[0034] In some embodiments, agents in the present invention will expose patients to a maximum of about 0.000005% D_2O (can also be expressed as about 0.00001% DHO). This quantity is a small fraction of the naturally occurring background levels of D_2O (or DHO) in circulation. This maximum exposure limit is obtained if all of the C-D bonds of the deuterium-enriched drug are metabolized. However, because of the DKIE, most if not all, of the C-D bonds of the deuterium-enriched drug will not be metabolized prior to excretion of said deuterium-enriched drug from the subject.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

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