US006858622B2

(12) **United States Patent**
Müller et al.

(10) **Patent No.: US 6,858,622 B2**
(45) **Date of Patent: Feb. 22, 2005**

(54) **CYCLOALKANO-INDOLE AND -AZAINDOLE DERIVATIVES**

(75) Inventors: **Ulrich Müller**, Wuppertal (DE); **Richard Connell**, Trumbull, CT (US); **Siegfried Goldmann**, Wuppertal (DE); **Rudi Grützmann**, Solingen (DE); **Martin Beuck**, Nilford, CT (US); **Hilmar Bischoff**, Wuppertal (DE); **Dirk Denzer**, Wuppertal (DE); **Anke Domdey-Bette**, Hückeswagen (DE); **Stefan Wohlfeil**, Hilden (DE)

(73) Assignee: **Bayer Aktiengesellschaft**, Leverkusen (DE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/198,315**

(22) Filed: **Jul. 18, 2002**

(65) **Prior Publication Data**

US 2003/0149073 A1 Aug. 7, 2003

Related U.S. Application Data

(62) Division of application No. 09/814,263, filed on Mar. 21, 2001, now Pat. No. 6,479,503, which is a division of application No. 09/313,035, filed on May 17, 1999, now Pat. No. 6,265,431, which is a division of application No. 08/535,698, filed on Sep. 28, 1995, now Pat. No. 5,684,014.

(30) **Foreign Application Priority Data**

Oct. 4, 1994 (DE) ..... P 4435477

(51) **Int. Cl.**[7] **A61K 31/437**; C07D 471/06

(52) **U.S. Cl.** **514/292**; 546/85; 546/87

(58) **Field of Search** 514/292; 546/85, 546/87

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,632,807	A	1/1972	Maurer et al.	
4,775,680	A	10/1988	Gillard et al.	
5,521,206	A	5/1996	Müller et al.	
5,684,014	A	11/1997	Müller et al.	
5,776,964	A	7/1998	Müller et al.	
5,952,498	A *	9/1999	Lenfers et al.	544/252
6,194,424	B1 *	2/2001	Eckenberg et al.	514/292

FOREIGN PATENT DOCUMENTS

DE	4435477	*	11/1995
EP	0 234 708	A1	9/1987
EP	0 300 676	A2	1/1989
EP	0 310 179	A2	4/1989
EP	0 496 237	A2	7/1992
EP	0 509 359		10/1992
EP	0 617 035	A1	9/1994

* cited by examiner

Primary Examiner—Rita Desai
(74) *Attorney, Agent, or Firm*—Norris McLaughlin & Marcus P.A.

(57) **ABSTRACT**

Cycloalkano-indole and -azaindole derivatives are prepared by reaction of appropriately substituted carboxylic acids with amines. The cycloalkano-indole and -azaindole derivatives are suitable as active compounds for medicaments, preferably antiatherosclerotic medicaments.

5 Claims, No Drawings

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

CYCLOALKANO-INDOLE AND -AZAINDOLE DERIVATIVES

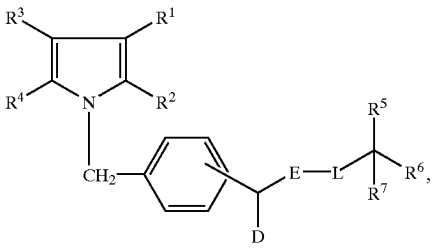
This application is a division of Ser. No. 09/814,263, filed on Mar. 21, 2001, now U.S. Pat. No. 6,479,503, which is a division of Ser. No. 09/313,035, filed on May 17, 1999, now U.S. Pat. No. 6,265,431, which is a division of Ser. No. 08/535,698, filed on Sep. 28, 1995, now U.S. Pat. No. 5,684,014.

The present invention relates to cycloalkano-indole and -azaindole derivatives, processes for their preparation and their use as medicaments, in particular as antiatherosclerotic medicaments.

It is known that increased blood levels of triglycerides (hypertriglyceridaemia) and cholesterol (hypercholesterolaemia) are associated with the genesis of atherosclerotic vessel wall changes and coronary heart diseases.

A distinctly increased risk of the development of coronary heart disease is moreover present if these two risk factors occur in combination, which is accompanied, in turn, with an overproduction of apolipoprotein B-100. There is therefore, as before, a great need to make available effective medicaments for the control of atherosclerosis and coronary heart diseases.

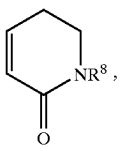
The present invention relates to cycloalkano-indole and -azaindole derivatives of the general formula (I)



(I)

in which

R^1 and R^2, including the double bond connecting them, together form a phenyl or pyridyl ring or a ring of the formula



wherein

R^8 denotes hydrogen or straight-chain or branched allot having up to 4 carbon atoms,

R^3 and R^4, including the double bond connecting them, together form a phenol ring or a 4- to 8-membered cycloalkene or oxocycloalkene radical,

all ring systems mentioned under R^1/R^2 and R^3/R^4 optionally being substituted up to 3 times by identical or different halogen, trifluoromethyl, carboxyl or hydroxyl substituents, by straight-chain or branched alkoxy or alkoxycarbonyl each having up to 6 carbon atoms or by straight-chain or branched alkyl having up to 6 carbon atoms, which, for its part, can be substituted by hydroxyl

D represents hydrogen, cycloalkyl having 4 to 12 carbon atoms or straight-chain or branched alkyl having up to 12 carbon atoms,

E represents the —CO— or —CS— group,

L represents an oxygen or sulphur atom or a group of the formula $—NR^9$,

wherein

R^9 denotes hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by hydroxyl or phenyl,

R^5 represents phenyl or a 5- to 7-membered saturated or unsaturated heterocycle having up to 3 heteroatoms from the series consisting of S, N and/or O,

the cycles optionally being substituted up to 3 times by identical or different nitro, carboxyl, halogen or cyano substituents or by straight-chain or branched alkenyl or alkoxycarbonyl each having up to 6 carbon atoms or by straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by hydroxyl, carboxyl or by straight-chain or branched alkoxy or alkoxycarbonyl each having up to 6 carbon atoms,

and/or the cycles optionally being substituted by a croup of the formula $—OR^{10}$ or $—NR^{11}R^{12}$,

wherein

R^{10} denotes hydrogen or straight-chain or branched alkyl or alkenyl each having up to 6 carbon atoms,

R^{11} and R^{12} are identical or different and denote phenyl, hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms

or straight-chain or branched acyl having up to 8 carbon atoms, which is optionally substituted by a group of the formula $—NR^{13}R^{14}$,

wherein

R^{13} and R^{14} are identical or different and denote hydrogen or straight-chain or branched acyl having up to 8 carbon atoms,

R^6 represents hydrogen, carboxyl or straight-chain or branched alkoxycarbonyl having up to 5 carbon atoms,

or represents straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by hydroxyl or by a group of the formula $—O—CO—R^{15}$,

wherein

R^{15} denotes phenyl which is optionally substituted up to 3 times by identical or different halogen or hydroxyl substituents or by straight-chain or branched alkyl having up to 5 carbon atoms,

or straight-chain or branched alkyl or alkenyl each having up to 22 carbon atoms, each of which is optionally substituted by a group of the formula $—OR^{16}$,

wherein

R^{16} is hydrogen, benzyl, triphenylmethyl or straight-chain or branched acyl having up to 6 carbon atoms,

R^7 represents hydrogen or

R^6 and R^7 together represent the group of the formula =O,

if appropriate in an isomeric form, and their salts.

The cycloalkano-indole and -azaindole derivatives according to the invention can also be present in the form of their salts. In general, salts with organic or inorganic bases or acids may be mentioned here.

In the context of the present invention, physiologically acceptable salts are preferred. Physiologically acceptable salts of the compounds according to the invention can be

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

larly preferred salts are, for example, those with hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, toluenesulphonic acid, benzenesulphonic acid, naphthalenedisulphonic acid, acetic acid, propionic acid, lactic acid, tartaric acid, citric acid, fumaric acid, maleic acid or benzoic acid.

Physiologically acceptable salts can also be metal or ammonium salts of the compounds according to the invention which have a free carboxyl group. Particularly preferred salts are, for example, sodium, potassium, magnesium or calcium salts, and also ammonium salts which are derived from ammonia, or organic amines, such as, for example ethylamine, di- or triethylamine, di- or triethanolamine, dicyclohexylamine, dimethylaminoethanol, arginine, lysine, ethylenediamine or 2-phenylethylamine.

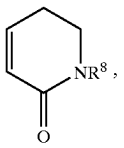
Including the double bond of parent structure, the cycloalkene radical (R^3/R^4) in the context of the invention in general represents a 4- to 8-membered hydrocarbon radical, preferably a 5- to 8-membered hydrocarbon radical, for example a cyclobutene, cyclopentene, cyclohexene, cycloheptene or cyclooctene radical. The cyclopentene, cyclohexene, cyclooctene or cycloheptene radicals are preferred.

Heterocycle (R^5) in the context of the invention in general represents a saturated or unsaturated 5- to 7-membered heterocycle, preferably a 5- to 6-membered heterocycle, which can contain up to 3 heteroatoms from the series consisting of S, N and/or O. Examples which may be mentioned are: pyridyl, thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, morpholinyl or piperidyl. Pyridyl and thienyl are preferred.

The compounds according to the invention can exist in stereoisomeric forms which either behave as image and mirror image (enantiomers), or do which do not behave as image and mirror image (diastereomers). The invention relates both to the enantiomers and diastereomers and their respective mixtures. These mixtures of the enantiomers and diastereomers can be separated in a known manner into the stereoisomerically uniform constituents.

Preferred compounds of the general formula (I) are those in which

R^1 and R^2, including the double bond connecting them, together form a phenyl or pyridyl ring or a ring of the formula



wherein

R^8 denotes hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms,

R^3 and R^4, including the double bond connecting them, together form a phenyl ring or a cyclopentene, cyclohexene, cycloheptene, cyclooctene, oxocyclopentene, oxocyclohexene, oxocycloheptene or oxocyclooctene radical,

all ring systems mentioned under R^1/R^2 and R^3/R^4 optionally being substituted up to 2 times by identical or different fluorine, chlorine, bromine, trifluoromethyl, carboxyl or hydroxyl substituents, by straight-chain or [illegible] having up to 4 carbon atoms, which, in turn, can be substituted by hydroxyl or by straight-chain or branched alkoxy having up to 3 carbon atoms.

D represents hydrogen, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl or straight-chain or branched alkyl having up to 10 carbon atoms,

E represents the —CO— or —CS— group,

L represents an oxygen or sulphur atom or represents a group of the formula $—NR^9$,

wherein

R^9 denotes hydrogen or straight-chain or branched alkyl having up to 5 carbon atoms, which is optionally substituted by hydroxyl or phenyl,

R^5 represents phenyl, pyridyl, furyl, thienyl or imidazolyl, each of which is optionally substituted up to 2 times by identical or different nitro, carboxyl, fluorine, chlorine, bromine or cyano substituents, by straight-chain or branched alkenyl or alkoxy carbonyl each having up to 4 carbon atoms or by straight-chain or branched alkyl having up to 5 carbon atoms, which is optionally substituted by hydroxyl, carboxyl or by straight-chain or branched alkoxy or alkoxycarbonyl each having up to 5 carbon atoms,

and/or the cycles are optionally substituted by a group of the formula $—OR^{10}$ or $—NR^{11}R^{12}$,

wherein

R^{10} denotes hydrogen or straight-chain or branched alkyl or alkenyl each having up to 4 carbon atoms,

R^{11} and R^{12} are identical or different and denote phenyl, hydrogen or straight-chain or branched alkyl having up to 5 carbon atoms

or denote straight-chain or branched acyl having up to 6 carbon atoms, which is optionally substituted by a group of the formula $—NR^{13}R^{14}$,

wherein

R^{13} and R^{14} are identical or different and denote hydrogen or straight-chain or branched acyl having up to 6 carbon atoms,

R^6 represents hydrogen, carboxyl or straight-chain or branched alkoxycarbonyl having up to 4 carbon atoms,

or represents straight-chain or branched alkyl having up to 5 carbon atoms, which is optionally substituted by hydroxyl or by a group of the formula $—O—CO—R^{15}$,

wherein

R^{15} denotes phenyl which is optionally substituted up to 3 times by identical or different fluorine, chlorine, bromine or hydroxyl substituents or by straight-chain or branched alkyl having up to 4 carbon atoms,

or straight-chain or branched alkyl or alkenyl each having up to 20 carbon atoms, each of which is optionally substituted by a group of the formula $—OR^{16}$,

wherein

R^{16} is hydrogen, benzyl, triphenylmethyl or straight-chain or branched acyl having up to 5 carbon atoms,

R^7 represents hydrogen or

R^6 and R^7 together represent the group of the formula =O,

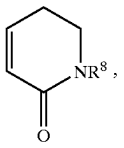
if appropriate in an isomeric form, and their salts.

Particularly preferred compounds of the general formula (I) are those

in which

R^1 and R^2, including the double bond connecting them,

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.



wherein

R^8 denotes hydrogen or methyl,

R^3 and R^4, including the double bond connecting them, together form a phenyl ring or a cyclopentene, cyclohexene, cycloheptene, cyclooctene, oxocyclopentene, oxocyclohexene, oxocycloheptene or oxocyclooctene radical,

all ring systems mentioned under R^1/R^2 and R^3/R^4 optionally being substituted up to 2 times by identical or different fluorine, chlorine, bromine, trifluoromethyl, carboxyl or hydroxyl substituents, by straight-chain or branched alkoxy or alkoxycarbonyl each having up to 3 carbon atoms or by straight-chain or branched alkyl having up to 3 carbon atoms, which, for its part, can be substituted by hydroxyl, methoxy or ethoxy,

D represents hydrogen, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl or straight-chain or branched alkyl having up to 6 carbon atoms,

E represents the —CO— or —CS— group,

L represents an oxygen or sulphur atom or represents a group of the formula $—NR^9$,

wherein

R^9 denotes hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by hydroxyl or phenyl,

R^5 represents phenyl, pyridyl or thienyl, each of which is optionally substituted up to 2 times by identical or different nitro, carboxyl, fluorine, chlorine, bromine or cyano substituents, by straight-chain or branched alkenyl or alkoxycarbonyl each having up to 3 carbon atoms or by straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by hydroxyl, carboxyl or by straight-chain or branched alkoxy or alkoxycarbonyl each having up to 4 carbon atoms,

and/or the cycles are optionally substituted by a group of the formula $—OR^{10}$ or $—NR^{11}R^{12}$,

wherein

R^{10} denotes hydrogen or straight-chain or branched alkyl or alkenyl each having up to 3 carbon atoms,

R^{11} and R^{12} are identical or different and denote phenyl, hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms

or denote straight-chain or branched acyl having up to 5 carbon atoms, which is optionally substituted by a group of the formula $—NR^{13}R^{14}$,

wherein

R^{13} and R^{14} are identical or different and denote hydrogen or straight-chain or branched acyl having up to 5 carbon atoms,

R^6 represents hydrogen, carboxyl or straight-chain or branched alkoxycarbonyl having up to 3 carbon atoms,

or represents straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by hydroxyl or by a group of the formula $—O—CO—R^{15}$,

wherein

R^{15} denotes phenyl which is optionally substituted up to [illegible]

or denotes straight-chain or branched alkyl or alkenyl each having up to 19 carbon atoms, each of which is optionally substituted by a group of the formula $—OR^{16}$,

wherein

R^{16} denotes hydrogen, benzyl, triphenylmethyl or straight-chain or branched acyl having up to 4 carbon atoms,

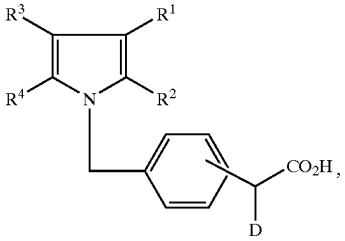
R^7 represents hydrogen or

R^6 and R^7 together represent the group of the formula =O,

if appropriate in an isomeric form and their salts.

A process for the preparation of the compounds of the general formula (I) according to the invention has additionally been found, characterized in that

carboxylic acids of the general formula (II)

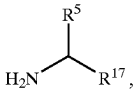


(II)

in which

R^1, R^2, R^3, R^4 and D have the meaning indicated,

are amidated using compounds of the general formula (III)



(III)

in which

R^5 has the meaning indicated

and

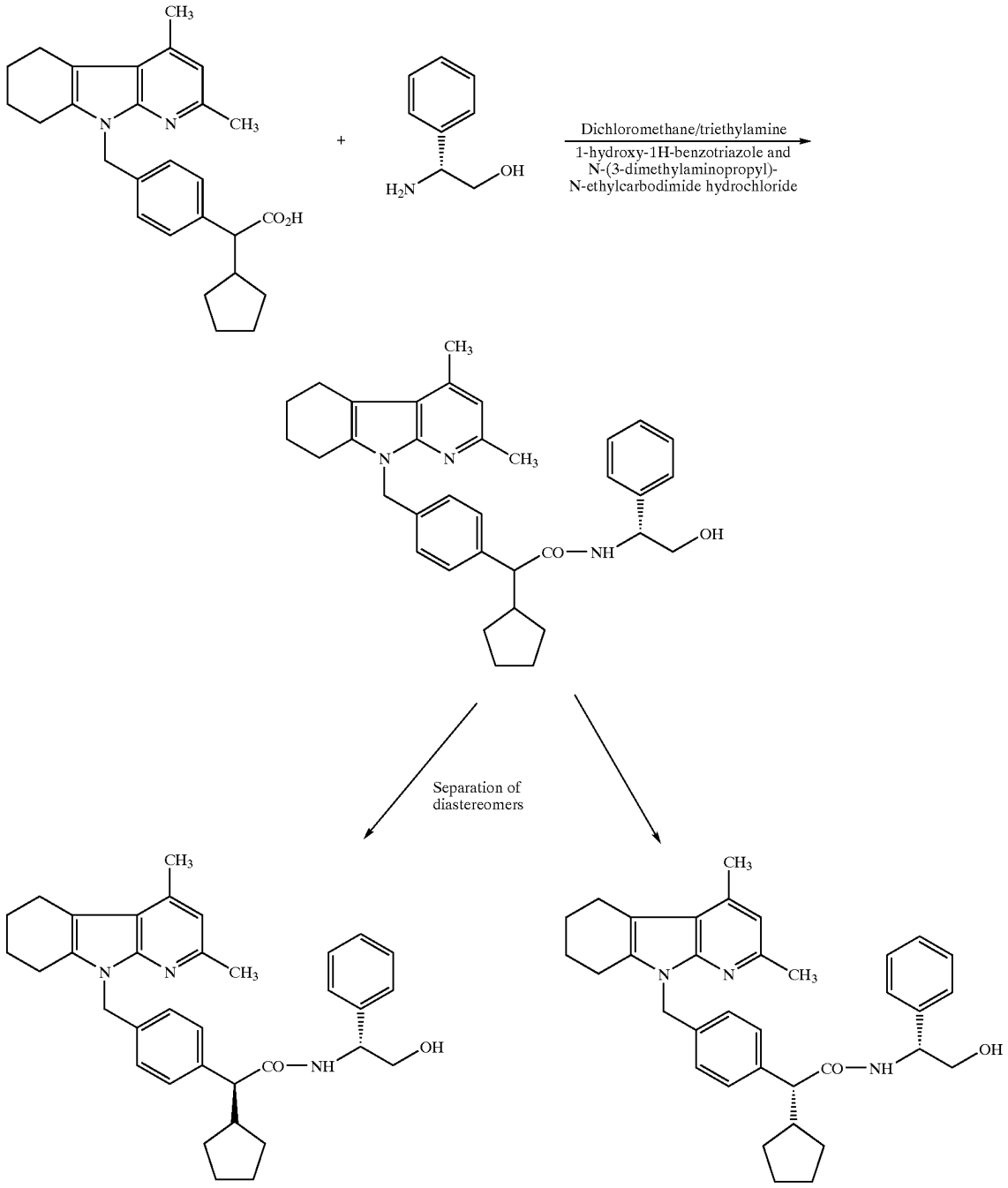
R^{17} has the indicated meaning of R^6, but does not represent carboxyl,

in an inert solvent and in the presence of bases and/or auxiliaries,

and, if appropriate, functional groups are varied by hydrolysis, esterification or reduction.

The process according to the invention can be illustrated

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.



Suitable solvents for the amidation are in this case inert organic solvents which do not change under the reaction conditions. These include ethers, such as diethyl ether or tetrahydrofuran, halogenohydrocarbons such as dichloromethane, trichloromethane, tetrachloromethane, trichloroethane, tetrachloroethane, 1,2-dichloroethane or trichloroethylene, hydrocarbons such as benzene, xylene, toluene, hexane, cyclohexane or petroleum fractions, nitromethane, dimethylformamide, acetone, acetonitrile or hexamethylphosphoramide. It is also possible to employ mixtures of the solvents. Dichloromethane, tetrahydrofuran, acetone and dimethylformamide are particularly preferred.

These preferably include alkali metal hydroxides such as, for example, sodium hydroxide or potassium hydroxide, alkaline earth metal hydroxides, such as, for example, barium hydroxide, alkali metal carbonates such as sodium carbonate or potassium carbonate, alkaline earth metal carbonates such as calcium carbonate, or alkali metal alkoxides such as sodium or potassium methoxide, sodium or potassium ethoxide or potassium tert-butoxide, or organic amines (trialkyl(C_1–C_6)amines) such as triethylamine, or heterocycles such as 1,4-diazabicyclo[2.2.2]octane (DABCO), 1.8-diazabicyclo[5.4.0]undec-7-ene (DBU), pyridine,

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

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.