US005786361A

# United States Patent [19]

Müller et al.

[11] Patent Number: 5,786,361

[45] Date of Patent: Jul. 28, 1998

[54] **PYRIDAZINO-, PYRIMIDO-, PYRAZINO- AND TRIAZINOINDOLES, -PYRROLOCYCLOALKENES OR PYRROLOOXOCYCLOALKENES, OR PYRIDOPYRROLYLPYRIDO COMPOUNDS, COMPOSITIONS CONTAINING THEM, AND USE THEREOF TO TREAT ATHEROSCLEROSIS**

[75] Inventors: **Ulrich Müller**, Wuppertal; **Peter Eckenberg**, Erkrath; **Rudi Grützmann**, Solingen; **Hilmar Bischoff**, Wuppertal; **Dirk Denzer**, Wuppertal; **Ulrich Nielsch**, Wuppertal, all of Germany

[73] Assignee: **Bayer Aktiengesellschaft**, Leverkusen, Germany

[21] Appl. No.: **837,076**

[22] Filed: **Apr. 11, 1997**

[30] **Foreign Application Priority Data**

Apr. 11, 1997 [DE] Germany ..... 196 15 265.8

[51] **Int. Cl.**[6] ..... **A61K 31/505**; A61K 31/44; A61K 31/495; A61K 31/53; C07D 487/04; C07D 471/04; C07D 487/14

[52] **U.S. Cl.** ..... **514/267**; 514/243; 514/248; 514/250; 514/257; 514/292; 514/293; 544/183; 544/184; 544/233; 544/234; 544/246; 544/247; 544/250; 544/251; 544/343; 544/345; 546/82; 546/85

[58] **Field of Search** ..... 514/243, 248, 514/250, 257, 267, 292, 293; 544/183, 184, 233, 234, 246, 247, 250, 343, 345, 251; 546/82, 85

[56] **References Cited**

U.S. PATENT DOCUMENTS

| | | | |
|---|---|---|---|
| 5,238,248 | 8/1993 | Hubschwerlen et al. | 544/250 |
| 5,306,820 | 4/1994 | Decker et al. | 546/153 |
| 5,585,490 | 12/1996 | Thurkauf eta l. | 544/250 |

FOREIGN PATENT DOCUMENTS

| | | |
|---|---|---|
| 0313480 | 12/1989 | Japan . |
| 6220059 | 8/1994 | Japan . |

OTHER PUBLICATIONS

J. Clark und I. W. Souton, J. Chem. Soc. Perkin Trans. I, 1814 (1974).

T.D. Duffy und D.G. Wibberley, J. Chem. Soc., Perkin Trans. I, 1921 (1974).

Y. Kondo, R. Watanabe, T. Sakamoto und H. Yamanaka, Chem. Pharm. Bull., 37, 2933 (1989).

S. Senda, K. Hirota und G.N. Yang, Chem. Pharm. Bull. 20, 399 (1982).

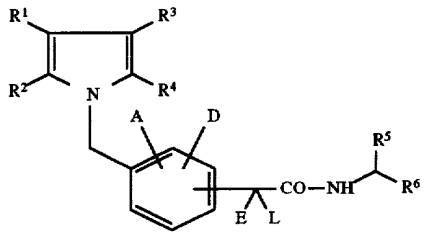
S. Senda, K. Hirota und M. Takahashi, J. Chem. Soc., Perkin Trans. I, 503 (1975).

*Primary Examiner*—Yogendra N. Gupta

*Attorney, Agent, or Firm*—Sprung Kramer Schaefer & Briscoe

[57] **ABSTRACT**

Compounds of the formula (I):




(I)

are prepared by reaction of the phenylacetic acid derivatives substituted by the appropriate heterocycles, optionally in an activated form, with phenylglycinols. The compounds are suitable as active compounds in medicaments, in particular in medicaments having antiatherosclerotic activity.

**7 Claims, No Drawings**

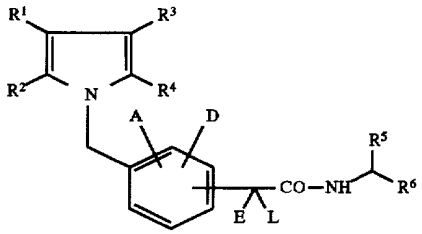
# PYRIDAZINO-, PYRIMIDO-, PYRAZINO- AND TRIAZINOINDOLES, -PYRROLOCYCLOALKENES OR PYRROLOOXOCYCLOALKENES, OR PYRIDOPYRROLYLPYRIDO COMPOUNDS, COMPOSITIONS CONTAINING THEM, AND USE THEREOF TO TREAT ATHEROSCLEROSIS

The present invention relates to new pyridazino-, pyrimido-, pyrazino- and triazino-indoles, processes for their preparation and their use as medicaments, in particular as antiatherosclerotic medicaments.

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

A distinctly increased risk of the development of coronary heart disorders moreover exists if these two risk factors occur in combination, which is in turn accompanied by an overproduction of apoliprotein B-100. There is therefore still a great need to make available effective medicaments for the control of atherosclerosis and of coronary heart diseases.

The present invention relates to pyridazino-, pyrimido-, pyrazino- and triazino-indoles of the general formula (I)



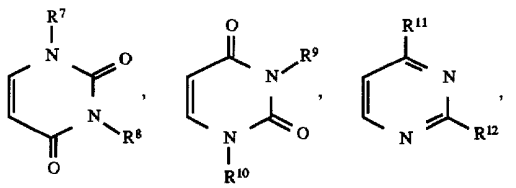
(I)

in which

$R^1$ and $R^2$, including the double bond connecting them, together form a phenyl ring or a 5- to 8-membered cycloalkene or oxocycloalkene ring,

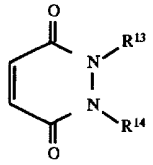
which is optionally substituted up to 3 times in an identical or different manner by halogen, trifluoromethyl, carboxyl, hydroxyl, by straight-chain or branched alkoxy or alkoxycarbonyl each having up to 6 carbon atoms or by straight-chain or branched alkyl having up to 6 carbon atoms, which for its part can be substituted by hydroxyl or by straight-chain or branched alkoxy having up to 4 carbon atoms,

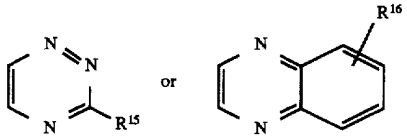
$R^3$ and $R^4$, including the double bond, together form a radical of the formula





-continued





in which

$R^7$, $R^8$, $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, $R^{13}$, $R^{14}$, $R^{15}$ and $R^{16}$ are identical or or different and denote hydrogen, carboxyl, straight-chain or branched alkoxy, alkylthio, acyl or alkoxycarbonyl each having up to 6 carbon atoms or straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by hydroxyl, or

$R^1$ and $R^2$, including the double bond, form a pyridyl ring, and

$R^3$ and $R^4$, likewise including the double bond, together form a pyridyl ring, both pyridyl rings optionally being substituted up to 3 times in an identical or different manner by halogen, trifluoromethyl, carboxyl, hydroxyl, 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 is substituted by hydroxyl or by straight-chain or branched alkoxy having up to 4 carbon atoms,

A and D are identical or different and represent hydrogen, halogen, trifluoromethyl, hydroxyl or straight-chain or branched alkyl or alkoxy each having up to 5 carbon atoms,

E and L are identical or different and represent hydrogen, cycloalkyl having 3 to 8 carbon atoms or straight-chain or branched alkyl having up to 10 carbon atoms, which is optionally substituted by cycloalkyl having 3 to 6 carbon atoms, or represent phenyl which is optionally substituted by halogen or trifluoromethyl, or

E and L, together with the carbon atom, form a 4-8-membered cycloalkyl ring,

$R^5$ represents phenyl or a 5- to 7-membered saturated or unsaturated heterocycle having up to 3 heteroatoms from the series S, N and/or O, the cycles optionally being substituted up to 3 times in an identical or different manner by nitro, carboxyl, halogen, cyano 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 group of the formula —$OR^{17}$ or —$NR^{18}R^{19}$,

in which

$R^{17}$ denotes hydrogen or straight-chain or branched alkyl or alkenyl each having up to 6 carbon atoms,

$R^{18}$ and $R^{19}$ are identical or different and denote phenyl, hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms or denote straight-chain or branched acyl having up to 8 carbon atoms,

which is optionally substituted by a group of the formula —$NR^{20}R^{21}$,

in which

$R^{20}$ and $R^{21}$ 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—$R^{22}$,

in which

$R^{22}$ denotes phenyl which is optionally substituted up to 3 times in an identical or different manner by halogen, hydroxyl or by straight-chain or branched alkyl having up to 5 carbon atoms,

or denotes 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 —$OR^{23}$,

in which

$R^{23}$ denotes hydrogen, benzyl, triphenylmethyl or straight-chain or branched acyl having up to 6 carbon atoms,

if appropriate in an isomeric form, and their salts.

The pyridazino-, pyrimido-, pyrazino- and triazino-indoles 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 salts of the substances according to the invention with mineral acids, carboxylic acids or sulphonic acids. Particularly 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. Those particularly preferred 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.

The cycloalkene radical ($R^1/R^2$), including the double bond of the parent structure, in the context of the invention in general represents a 5- to 8-membered, preferably 5- to 7-membered, hydrocarbon radical such as, for example, a cyclobutene, cyclopentene, cyclohexene or cycloheptene radical. The cyclopentene, cyclohexene, cyclooctene and cycloheptene radicals are preferred.

Heterocycle in the context of the invention in general represents a saturated or unsaturated 5- to 7-membered, preferably 5- to 6-membered, heterocycle which can contain up to 3 heteroatoms from the series 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.

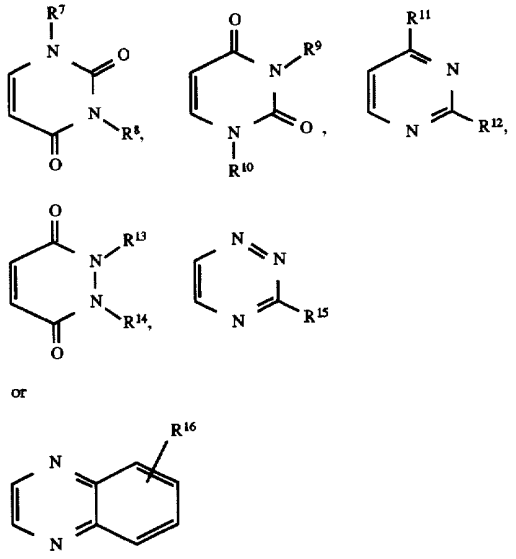
The compounds according to the invention can exist in stereoisomeric forms which either behave as image and mirror image (enantiomers), or which do not behave as image and mirror image (diastereomers). The invention relates both to the enantiomers and diastereomers or their respective mixtures. These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

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 ring or a cyclopentene, cyclohexene, cycloheptene, cyclooctene, oxocyclopentene, oxocyclohexene, oxocycloheptene or oxocyclooctene radical,

which is optionally substituted up to 2 times in an identical or different manner by fluorine, chlorine, bromine, trifluoromethyl, carboxyl, hydroxyl, by straight-chain or branched alkoxy or alkoxycarbonyl each having up to 4 carbon atoms or by straight-chain or branched alkyl having up to 4 carbon atoms, which for its part can be substituted by hydroxyl or by straight-chain or branched alkoxy having up to 3 carbon atoms,

$R^3$ and $R^4$, including the double bond, together form a radical of the formula



or



in which

$R^7$, $R^8$, $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, $R^{13}$, $R^{14}$, $R^{15}$ and $R^{16}$ are identical or different and

denote hydrogen, straight-chain or branched alkoxy, alkylthio, acyl or alkoxycarbonyl each having up to 4 carbon atoms or straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by hydroxyl,

or

$R^1$ and $R^2$, including the double bond, form a pyridyl ring, and

$R^3$ and $R^4$, likewise including the double bond, together form a pyridyl ring, both pyridyl rings optionally being substituted up to 2 times in an identical or different manner by fluorine, chlorine, bromine, trifluoromethyl, carboxyl, hydroxyl, by straight-chain or branched alkoxy or alkoxycarbonyl each having up to 4 carbon atoms or by straight-chain or branched alkyl having up to 4 carbon atoms, which for its part is substituted by hydroxyl or by straight-chain or branched alkoxy having up to 3 carbon atoms,

A and D are identical or different and

represent hydrogen, fluorine, chlorine, bromine, trifluoromethyl, hydroxyl or straight-chain or branched alkyl or alkoxy each having up to 4 carbon atoms,

E and L are identical or different and

represent hydrogen, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl or straight-chain or branched alkyl having up to 8 carbon atoms, which is optionally substituted by cyclopropyl, cyclopentyl or cyclohexyl, or represent phenyl which is optionally substituted by fluorine, chlorine or bromine, or

E and L, together with the carbon atom, form a 4-7-membered cycloalkyl ring,

$R^5$ represents phenyl, pyridyl, furyl, thienyl or imidazolyl, each of which is optionally substituted up to 2 times in an identical or different manner by nitro, carboxyl, fluorine, chlorine, bromine, cyano, by straight-chain or branched alkenyl or alkoxycarbonyl 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 $—OR^{17}$ or $—NR^{18}R^{19}$,

in which

$R^{17}$ denotes hydrogen or straight-chain or branched alkyl or alkenyl each having up to 4 carbon atoms,

$R^{18}$ and $R^{19}$ 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 $—NR^{20}R^{21}$,

in which

$R^{20}$ and $R^{21}$ 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 $—O—CO—R^{22}$,

in which

$R^{22}$ denotes phenyl which is optionally substituted up to 3 times in an identical or different marmer by fluorine, chlorine, bromine, hydroxyl or by straight-chain or branched alkyl having up to 4 carbon atoms, or denotes 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 $—OR^{23}$,

in which

$R^{23}$ denotes hydrogen, benzyl, triphenylmethyl or straight-chain or branched acyl having up to 5 carbon atoms,

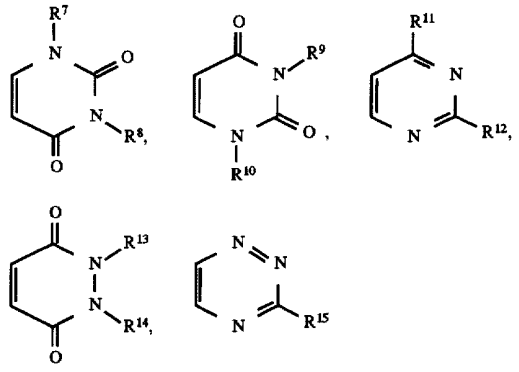
if appropriate in an isomeric form, and their salts.

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

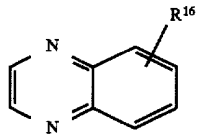
$R^1$ and $R^2$, including the double bond connecting them, together form a phenyl ring or a cyclopentene, cyclohexene, cycloheptene, cyclooctene, oxocyclopentene, oxocyclohexene, oxocycloheptene or oxocyclooctene radical,

which is optionally substituted up to 2 times in an identical or different manner by fluorine, chlorine, bromine, trifluoromethyl, carboxyl, hydroxyl, 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,

$R^3$ and $R^4$, including the double bond, together form a radical of the formula



or



in which

$R^7$, $R^8$, $R^9$, $R^{10}$, $R^{11}$, $R^{12}$, $R^{13}$, $R^{14}$, $R^{15}$ and $R^{16}$ are identical or different and denote hydrogen, straight-chain or branched alkoxy or alkylthio each having up to 3 carbon atoms or straight-chain or branched alkyl having up to 3 carbon atoms, which is optionally substituted by hydroxyl,

or

$R^1$ and $R^2$, including the double bond, form a pyridyl ring, and

$R^3$ and $R^4$, likewise including the double bond, together form a pyridyl ring, both pyridyl rings optionally being substituted up to 2 times in an identical or different manner by fluorine, chlorine, bromine, trifluoromethyl, carboxyl, hydroxyl, 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 is substituted by hydroxyl, methoxy or ethoxy,

A and D are identical or different and

represent hydrogen, fluorine, chlorine, bromine or trifluoromethyl,

E and L are identical or different and

represent hydrogen, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl or straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by cyclopentyl or cyclohexyl, or represent phenyl which is optionally substituted by fluorine, chlorine or bromine, or

E and L, together with the carbon atom, form a 5-7-membered cycloalkyl ring,

$R^5$ represents phenyl, pyridyl or thienyl, each of which is optionally substituted up to 2 times in an identical or

different manner by nitro, carboxyl, fluorine, chlorine, bromine, cyano, 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 $—OR^{17}$ or $—NR^{18}R^{19}$,

in which

$R^{17}$ denotes hydrogen or straight-chain or branched alkyl or alkenyl each having up to 3 carbon atoms,

$R^{18}$ and $R^{19}$ 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 $—NR^{20}R^{21}$,

in which

$R^{19}$ and $R^{20}$ 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 $—O—CO—R^{22}$,

in which

$R^{22}$ denotes phenyl which is optionally substituted up to 3 times in an identical or different manner by straight-chain or branched alkyl having up to 3 carbon atoms, 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 $—OR^{23}$,

in which

$R^{23}$ denotes hydrogen, benzyl, triphenylmethyl or straight-chain or branched acyl having up to 4 carbon atoms,

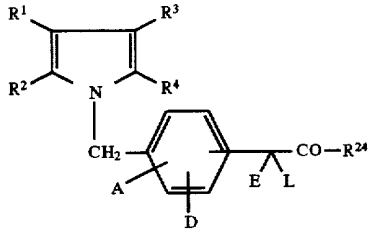
if appropriate in an isomeric form, and their salts.

Very particularly preferred compounds of the general formula (I) are those

in which

A and D represent hydrogen.

A process for the preparation of the compounds of the general formula (I) according to the invention has additionally been found, characterized in that racemic or alternatively already enantiomerically pure carboxylic acids or their activated derivatives of the general formula (II)

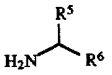


(II)

in which

A, D, E, L, $R^1$, $R^2$, $R^3$ and $R^4$ have the meaning indicated above, and

$R^{24}$ represents hydroxyl or an activating radical, preferably chloride, are amidated with compounds of the general formula (III)



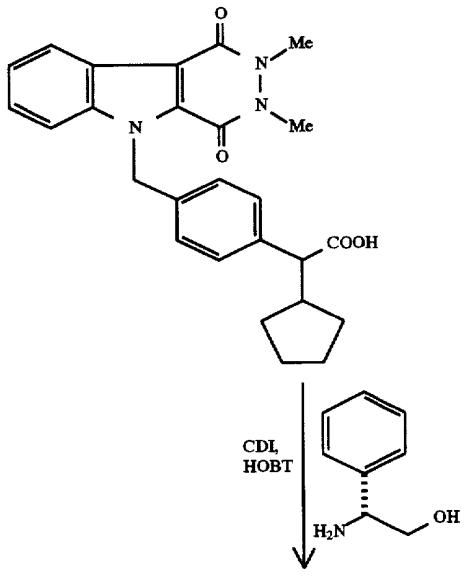
(III)

in which

$R^5$ and $R^6$ have the meaning indicated above,

in inert solvents, if appropriate in the presence of bases and/or auxiliaries.

The process according to the invention can be illustrated by way of example by the following equation:



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.