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Nelson et al.

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[54] **HETEROCYCLIC AMINOALKYL ESTERS OF MYCOPHENOLIC ACID AND DERIVATIVES THEREOF, COMPOSITIONS AND USE**

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[21] Appl. No.: **160,212**

[22] Filed: **Feb. 25, 1988**

Related U.S. Application Data

[62] Division of Ser. No. 99,950, Sep. 23, 1987, Pat. No. 4,748,173, which is a division of Ser. No. 8,909, Jan. 30, 1987, Pat. No. 4,727,069.

[51] **Int. Cl.**[4] **A61K 31/535**; A61K 31/54; C07D 413/12; C07D 417/12

[52] **U.S. Cl.** **514/233.5**; 514/211; 514/212; 514/218; 514/228.2; 514/253; 514/320; 514/367; 514/378; 514/385; 514/403; 514/422; 540/544; 540/553; 540/575; 540/596; 544/58.7; 544/153; 544/376; 546/196; 548/146; 548/240; 548/300; 548/356

[58] **Field of Search** 540/544, 575, 553, 596; 544/58.7, 153, 376; 546/196; 548/146, 240, 300, 356, 525; 514/211, 212, 218, 228.2, 233.5, 253, 320, 367, 378, 385, 403, 422

[56] **References Cited**

PUBLICATIONS

"Antitumor Activity of Derivatives of Mycophenolic Acid", Suzuki et al., J. Antibiotics, 29(3), 275–285, 1975.

Primary Examiner—Robert W. Ramsuer
Attorney, Agent, or Firm—David A. Lowin; Tom M. Moran

[57] **ABSTRACT**

Heterocyclic aminoalkyl esters of mycophenolic acid, and the derivatives and pharmaceutically acceptable salts thereof, are useful as immunosuppressive agents, anti-inflammatory agents, anti-tumor agents, anti-viral agents, and anti-psoriatic agents.

11 Claims, No Drawings

HETEROCYCLIC AMINOALKYL ESTERS OF MYCOPHENOLIC ACID AND DERIVATIVES THEREOF, COMPOSITIONS AND USE

This is a division of pending application Ser. No. 099,950, filed Sept. 23, 1987 now U.S. Pat. No. 4,748,173, which is a division of application Ser. No. 008,909, filed Jan. 30, 1987, now U.S. Pat. No. 4,727,069, issued Feb. 23, 1988.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to pharmaceutical compositions, particularly to aminoalkyl esters of mycophenolic acid and derivatives thereof, and to their use as immunosuppressive and anti-inflammatory agents. For example, they are useful for treating rheumatoid arthritis, in which there is an immunologically driven inflammatory process. Because of their effects on purine metabolism, the pharmaceutical compositions of the present invention also find use as anti-tumor, anti-viral and anti-psoriatic agents.

2. Cross-Reference to Related Applications

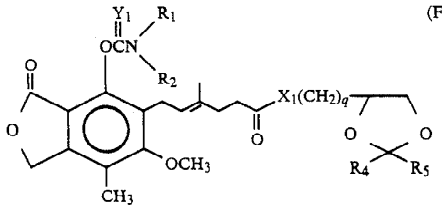
This application is related to Ser. No. 008,717 now U.S. Pat. No. 4,753,935, entitled "Morpholinoethylester of Mycophenolic Acid and Derivatives Thereof," filed contemporaneously herewith; to Ser. No. 803,041, filed Nov. 27, 1985 now U.S. Pat. No. 4,686,234; and to Ser. No. 821,633, filed Jan. 23, 1986 now U.S. Pat. No. 4,725,622.

BACKGROUND INFORMATION AND RELATED DISCLOSURES

Inflammatory diseases, in particular rheumatoid arthritis, have been treated with a variety of compounds representing several structural classes and biological activities, including, for example, anti-inflammatory agents (corticosteroids, aspirin, derivatives of arylacetic and arylpropionic acids, and oxicams), immunosuppressive agents and regimes (methotrexate, cyclophosphamide, cyclosporin, and total lymphoid irradiation), and long-acting anti-rheumatic drugs (gold salts, and penicillamine and its derivatives). However, no representative of any of these classes of compounds is regarded as ideal.

Mycophenolic acid is a weakly-active antibiotic found in the fermentation broth of *Penicillium brevicompactum*. Some compounds relating to mycophenolic acid, and their uses in the treatment of inflammatory diseases, such as rheumatoid arthritis, are disclosed in the following two prior related applications.

Ser. No. 803,041, filed Nov. 27, 1985, relates to compounds having the general structure of Formula 1:



(Formula 1)

and the pharmaceutically acceptable salts thereof, where:

R_1 is H or lower alkyl having 1 to 6 carbon atoms;

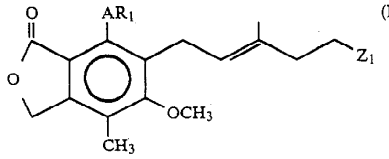
R_2 is H, lower alkyl having 1 to 6 carbon atoms or -phenyl-4-CO_2R_3, in which R_3 is H, lower alkyl having 1 to 6 carbon atoms or a pharmaceutically acceptable cation;

R_4 and R_5 are each independently H or lower alkyl having 1 to 6 carbon atoms;

X_1 and Y_1 are each independently O or S; and

q is an integer of 1–6.

Ser. No. 821,633, filed Jan. 23, 1986, relates to compounds having the general structure of Formula 2:

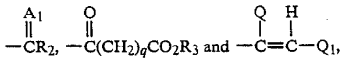


(Formula 2)

and the pharmaceutically acceptable salts thereof, where:

A is oxygen or sulfur;

R_1 is selected from the group consisting of: H,



in which:

A_1 is oxygen or sulfur;

q is an integer from 0–6;

R_2 is alkyl, haloalkyl or $—NR_4R_5$, where: R_4 and R_5 are independently H, alkyl, haloalkyl, cycloalkyl, phenyl optionally monosubstituted with halogen, hydroxy, carboxy, chlorocarbonyl, sulfonylamino, nitro, cyano, phenyl, alkyl, acyl, alkoxycarbonyl, acylamino, dialkylamino or dialkylaminoethoxycarbonyl, phenyl optionally disubstituted with hydroxy, carboxy, nitro or alkyl, or benzyl optionally substituted with dialkylamino;

R_3 is H, alkyl or a pharmaceutically acceptable cation;

Q and Q_1 are independently H or $—CO_2R_3$; and

Z_1 is selected from the group consisting of: 1H-tetrazolyl, $—CH_2OH$, —CHO, —CN, $—C(O)A_2R_6$ and $—C(O)NR_7R_8$, in which:

A_2 is oxygen or sulfur;

R_6 is H, alkyl, alkenyl, cycloalkyl, optionally substituted phenyl, optionally substituted benzyl or a pharmaceutically acceptable cation; and

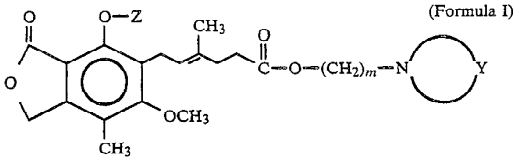
R_7 and R_8 are independently H, alkyl or cycloalkyl, or R_7 and R_8 taken together are $—(CH_2)_2O(CH_2)_2—$, $—(CH_2)_4—$, or $—(CH_2)_5—$;

with the proviso that R_1 and R_6 cannot both be H if A and A_2 are oxygen.

Compounds somewhat structurally similar to the compounds of Formulae 1 and 2 are described in U.S. Pat. Nos. 3,705,894; 3,853,919; 3,868,454; 3,880,995, in Japanese Pat. No. J 57024380, in *J. Antibiot.*, 29(3), 275–85, 286–91 (1976), and in *Cancer Research*, 36(8), 2923–7 (1976). The disclosed compounds are described as having anti-tumor, immunosuppressive, anti-viral, anti-arthritic and/or anti-psoriastic activities.

SUMMARY OF THE INVENTION

One aspect of the present invention concerns the heterocyclic aminoalkyl esters of mycophenolic acid and derivatives thereof, and the pharmaceutically acceptable salts thereof, i.e., the compounds of Formula I:



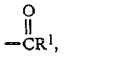
(Formula I)

wherein:

m is an integer from two to four;

Z is selected from Formulae (a) (b) (c) or (d), as follows:

(a)



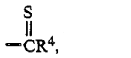
in which:

R^1 is hydrogen, alkyl having seven or more carbon atoms including cycloalkyl such as adamantyl, or $—NR^2R^3$,

where R^2 is hydrogen or lower alkyl, and

R^3 is hydrogen, lower alkyl, —phenyl-4-CO_2R^2 or a pharmaceutically acceptable cation;

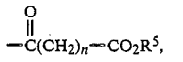
(b)



in which:

R^4 is hydrogen, alkyl, aryl, or $—NR^2R^3$;

(c)

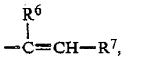


in which:

n is an integer from zero to six, and

R^5 is hydrogen, lower alkyl, or a pharmaceutically acceptable cation;

(d)



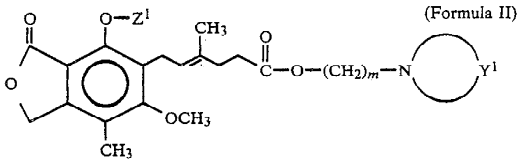
in which:

R^6 and R^7 are independently hydrogen or $—CO_2R^5$; and

Y is lower alkylene of four to six carbon atoms, or lower alkylene of three to five carbon atoms and one member that is —O—, —S—, or

where R^8 is hydrogen or alkyl of one to five carbon atoms.

Another aspect of the present invention concerns the heterocyclic aminoalkyl esters (excluding the morpholinoethyl ester) of mycophenolic acid and certain derivatives of mycophenolic acid, i.e, compounds having the structure of Formula II, which follows:



(Formula II)

wherein:

m is an integer from two to four;

Z^1 is hydrogen or $—C(O)R^9$,

where R^9 is lower alkyl or aryl; and

Y^1 is lower alkylene of four to six carbon atoms, or lower alkylene of three to five carbon atoms and one member that is —O—, —S—, or

where R^8 is hydrogen or alkyl of one to five carbon atoms; and the pharmaceutically acceptable salts thereof;

except that when m is two, Y^1 does not include $—(CH_2)_2—O—(CH_2)_2—$.

In yet another aspect, the invention relates to a pharmaceutical composition containing a therapeutically effective amount of a compound of Formula I or II admixed with at least one pharmaceutically acceptable excipient.

In still another aspect, the invention relates to a method of treating autoimmune disorders, psoriasis, inflammatory diseases including in particular rheumatoid arthritis, and for treating tumors and viruses in a mammal by administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Formula I or II.

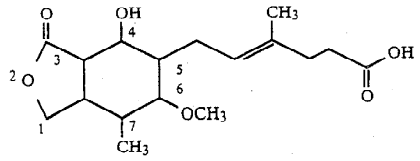
Compounds of Formulae I and II have advantageous pharmacokinetic properties, for example, solubility in the delivery environment (e.g., the stomach), peak plasma concentration, maximum plasma concentration, and improved activity, e.g., anti-inflammatory activity as compared to mycophenolic acid.

DETAILED DESCRIPTION OF THE INVENTION

Definitions and General Parameters

The following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

The numbering of the mycophenolic acid is as follows:



The compounds of the invention will be named using the above-shown numbering system as the morpholinoethyl esters of E-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoic acid and its derivatives. The compounds of the present invention are prepared as the E (or Entgegen) position isomer. Some representative compounds are named as follows:

the compound of Formula I where m is 2, Y is $-(CH_2)_2-O-(CH_2)_2-$, Z is $-C(O)R^1$ and wherein R^1 is 1-adamantyl, is named "morpholinoethyl E-6-[1,3-dihydro-4-(1-adamantoyloxy)-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl]-4-methyl-4-hexenoate";

the compound of Formula I where m is 4, Y is $-(CH_2)_3-$, Z is $-C(O)NR^2R^3$, R^2 is 4-carboxyphenyl and R^3 is hydrogen, is named "4-(pyrrolidin-1-yl)butyl E-6-{1,3-dihydro-4-[N-(4-carboxyphenyl)carbamoyloxy]-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl}-4-methyl-4-hexenoate";

the compound of Formula I where m is 2, Y is $-(CH_2)_2-S-(CH_2)_2-$, Z is $-C(S)NR^2R^3$, R^2 is methyl and R^3 is isobutyl, is named "2-(4-thiazin-1-yl)ethyl (E)-6-{1,3-dihydro-4-(N-methyl-N-isobutylthiocarbamoyloxy)-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl}-4-methyl-4-hexenoate";

the compound of Formula I where m is 2, Y is $-(CH_2)_2-N(CH_3)-(CH_2)_2-$, Z is $-(O)C(CH_2)_n-CO_2R^5$, n is 1, and R^5 is methyl, is named "2-(4-methylpiperazin-1-yl)ethyl (E)-6-[1,3-dihydro-4-(carbomethoxyethanoyloxy)-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl]-4-methyl-4-hexenoate";

the compound of Formula I where m is 2, Y is $-(CH_2)_2-O-(CH_2)_2-$, Z is $-(O)C(CH_2)_n-CO_2R^5$, n is 2, and R^5 is ethyl, is named "2-(morpholin-1-yl)ethyl (E)-6-[1,3-dihydro-4-(3-carboethoxypropanoyloxy)-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl]-4-methyl-4-hexenoate";

the compound of Formula I where m is 4, Y is $-(CH_2)_2-N[C-(CH_3)_3]-(CH_2)_3-$, Z is $-(R_6)C=CH-R^7$, R^6 is COOH, and R^7 is COOH, is named "4-(4-t-butyl-1,4-perhydroazepin-1-yl)butyl (E)-6-[1,3-dihydro-4-(1,2-dicarboxyeth-(E)-enyloxy)-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl]-4-methyl-4-hexenoate";

the compound of Formula I where m is 3, Y is $-(CH_2)_2-O-(CH_2)_2-$, Z is $-(R_6)C=CH-R^7$, R^6 is COOMe, and R^7 is COOEt, is named "3-(morpholin-1-yl)propyl (E)-6-[1,3-dihydro-4-(2-carboethoxy-1-carbomethoxy-eth-1-(E)-enyloxy)-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl]-4-methyl-4-hexenoate";

the compound of Formula II where m is 3, Y^1 is $-(CH_2)_4-$, and Z^1 is hydrogen is named "piperazinopropyl E-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate";

and

the compound of Formula II where m is 4, Y^1 is $-O-(CH_2)_5-$, and Z^1 is benzoyl is named "4-(perhydro-2-oxazepin-1-yl)butyl E-6-(1,3-dihydro-4-benzoyloxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate".

As used herein, the term "alkyl" refers to a fully saturated monovalent radical containing only carbon and hydrogen, and which may be a cyclic, branched or straight chain radical. This term is further exemplified by radicals such as methyl, ethyl, t-butyl, pentyl, pivalyl, heptyl and adamantyl.

The term "lower alkyl" refers to a monovalent alkyl radical of one to six carbon atoms. This term is further exemplified by such radicals as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, i-butyl (or 2-methylpropyl), isoamyl, pentyl, and i-pentyl.

The term "alkylene" refers to a fully saturated divalent radical containing only carbon and hydrogen, and which may be a branched or straight chain radical. This term is further exemplified by radicals such as methylene, ethylene, n-propylene, t-butylene, i-pentylene, and n-heptylene.

The term "lower alkylene" refers to a divalent alkyl radical of one to six carbon atoms. This term is further exemplified by such radicals as methylene, ethylene, n-propylene, i-propylene, n-butylene, t-butylene, i-butylene (or 2-methylpropylene), isoamylene, pentylene, and n-hexylene.

The term "aryl" refers to a substituted or unsubstituted monovalent unsaturated aromatic carbocyclic radical having a single ring (e.g., phenyl) or two condensed rings (e.g., naphthyl).

The term "acyl" refers to a radical based on an organic acid, e.g., —C(O)R where R is alkyl or aryl.

As used herein, the term "halo" refers to fluoro, bromo, chloro and iodo.

Isolation and purification of the compounds and intermediates described herein can be effected, if desired, by any suitable separation or purification procedure such as, for example, filtration, extraction, crystallization, column chromatography, thin-layer chromatography or thick-layer chromatography, or a combination of these procedures. Specific illustrations of suitable separation and isolation procedures can be found by reference to the examples hereinbelow. However, other equivalent separation or isolation procedures can, of course, also be used.

A "pharmaceutically acceptable salt" may be any salt derived from an inorganic or organic acid or base. The term "pharmaceutically acceptable anion" refers to the anion of such acid addition salts. "Pharmaceutically acceptable cation" refers to the cation of such base addition salts. The salt, the anion, and/or the cation are chosen not to be biologically or otherwise undesirable.

The anions are derived from inorganic acids, such as hydrochloric acid, hydrobromic acid, sulfuric acid (giving the sulfate and bisulfate salts), nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, salicylic acid, p-toluensulfonic acid and the like.

The cations derived from inorganic bases include sodium, potassium, lithium, ammonium, calcium, magnesium and the like. Cations derived from organic bases include those formed from primary, secondary and tertiary amines, such as isopropylamine, diethylamine, trimethylamine, pyridine, cyclohexylamine, ethylene

diamine, monoethanolamine, diethanolamine, triethanolamine and the like.

As used herein, the terms "inert organic solvent" or "inert solvent" mean a solvent inert under the conditions of the reaction being described in conjunction therewith (including, for example, benzene, toluene, acetonitrile, tetrahydrofuran, diethyl ether, chloroform, methylene chloride, pyridine and the like).

As used herein, the term "treatment" or "treating" means any treatment of a disease in a mammal, and includes:

(i) preventing the disease, that is, causing the clinical symptoms of the disease not to develop;

(ii) inhibiting the disease, that is, arresting the development of clinical symptoms; and/or

(iii) relieving the disease, that is, causing the regression of clinical symptoms.

Unless specified to the contrary, the reactions described herein take place at atmospheric pressure over a temperature range from about 10° C. to about 100° C., more preferably from about 10° C. to about 50° C., and most preferably at about room temperature.

Preparation of the Compounds of Formulae I and II

The compounds of Formulae I and II can be prepared according to several synthetic pathways, depending upon the substitution at Z or Z^1. Where Z or Z^1 is not hydrogen (hereinafter the "4-substituted derivatives"), the phenolic oxygen of mycophenolic acid can be substituted either before or after the esterification of the acid. Where Z or Z^1 is hydrogen, the starting material is typically mycophenolic acid, a commercially available compound.

Many of the synthetic routes and/or final synthetic steps for the starting materials of the 4-substituted derivatives are available from the published scientific and patent literature. For example, some such methods are described in U.S. Pat. Nos. 3.705,894, 3,777,020, and 3,868,454, Japanese Kokai Nos. 57/183776, 57/183777, and 48/86860, South African Application No. 68/4959, Great Britain Pat. No. 1261060, Belgian Pat. No. 815330, and West German Pat. No. 2237549, and in related the U.S. applications Ser. Nos. 803,041 and 821,633, the relevant portions of which are incorporated herein by reference.

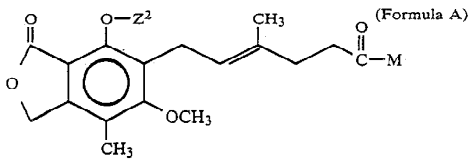
ESTERIFICATION OF MYCOPHENOLIC ACIDS

Many standard esterification procedures may be used, for example, as described in *Synthetic Organic Chemistry* by Wagner and Zook (Wiley, New York) 1956, see pages 479–532. Two presently preferred synthetic routes are described below for conversion of mycophenolic acid and its 4-substituted derivatives into the heterocyclic aminoalkylester compounds of Formulae I and II. The first route involves conversion into an acid halide, followed by condensation with a desired alcohol to form the end product. The second route involves conversion directly into the end product using a carbodiimide reaction.

As an example, a less preferred third route entails starting with an ester of mycophenolic acid (other than the desired heterocyclic aminoalkylester) in an ester exchange reaction, for conversion into the desired end product.

THE ACID HALIDE-CONDENSATION ROUTE

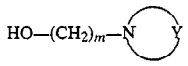
In the first synthetic route, mycophenolic acid or a 4-substituted derivative thereof (i.e., a compound of Formula A, in which Z^2 is the same as Z and Z^1 in the Summary of the Invention, and M is —OH)



(Formula A)

is dissolved or suspended in an inert organic solvent, preferably methylene chloride, and an excess (about 10 molar equivalents to 1) of a halogenating agent (e.g., thionyl chloride) is added, optionally together with a small amount of dimethylformamide. The reaction mixture is stirred for about 1–8 hours, preferably about 4 hours, to yield the corresponding acid halide.

The acid halide is dissolved in an inert solvent, as described above, and reacted by a condensation reaction with a cooled solution (e.g., maintained at about 4° C.) of a heterocyclic aminoalkanol, such as the compounds of Formula B



B

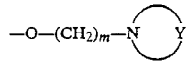
(in which m and Y are as previously defined in the Summary of the Invention and include, for example, 1-piperidineethanol, morpholinoethanol [also named 4-(2-hydroxyethyl)morpholine], and 4-methyl-piperazinylethanol), to which it is added slowly over a period of about 10 minutes to 2 hours, preferably about 90 minutes. The end product of Formula I or II is isolated and purified by conventional procedures.

THE CARBODIIMIDE ROUTE

In the second synthetic route, mycophenolic acid or an acylated derivative thereof (i.e., a compound according to Formula A as defined above) is dissolved in an inert solvent, preferably tetrahydrofuran ("THF"), and reacted with a heterocyclic aminoalkanol of Formula B in the presence of a carbodiimide, such as DCC ("dicyclohexylcarbodiimide") or di-p-tolylcarbodiimide. The molar ratio of alcohol to the starting acid is about 1:1. The reaction takes place at atmospheric pressure over a period of about 4–8 hours, preferably over 6 hours. A temperature range from about 10° C. to about reflux temperature, preferably about room temperature may be used. The end product of Formula I or II is isolated and purified in the usual manner.

FORMULA I WHERE Z IS —C(O)R^1 OR —C(S)R^4

The compounds of Formula I where Z is —C(O)R^1 or —C(S)R^4 (or of Formula II where Z^1 is —C(O)R^9) are prepared by dissolving mycophenolic acid or a heterocyclic aminoalkylester thereof, [i.e., a compound of Formula A wherein Z^2 is hydrogen, and M is hydrogen or a radical of Formula C,



C

in which m and Y are as defined in the Summary of the Invention] in an inert organic solvent, preferably pyridine, and reacting it with about 1 to 6 molar equivalents, preferably about 3 molar equivalents, of an appropriate acyl halide or anhydride or thiocarbonyl halide or anhydride (e.g., acetic anhydride, thioacetyl chloride, propionyl chloride, pivaloyl chloride or adamantoyl

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API

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

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Sync your system to PACER to automate legal marketing.