United States Patent [19]
Seydel et al.

[11] **Patent Number: 4,829,058**
[45] **Date of Patent: May 9, 1989**

[54] **SUBSTITUTED BIS-(4-AMINOPHENYL)-SULFONES**

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[21] Appl. No.: **62,291**

[22] Filed: **Jun. 15, 1987**

Related U.S. Application Data

[63] Continuation of Ser. No. 732,024, May 8, 1985, abandoned.

[30] **Foreign Application Priority Data**

May 22, 1984 [DE] Fed. Rep. of Germany 3419009

[51] **Int. Cl.**[4] **C07C 103/22**
[52] **U.S. Cl.** **514/155**; 260/397.6
[58] **Field of Search** 260/397.6; 514/155

[56] **References Cited**

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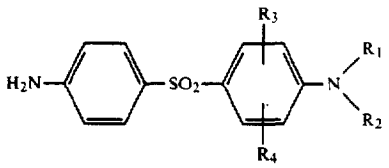
[57] **ABSTRACT**

Disclosed are substituted bis(4-aminophenyl)-sulfones of general formula


(I)

wherein
R_1 is hydrogen, alkyl or cycloalkyl; group,
R_2 is hydrogen or C_1–C_3 alkyl,
R_3 is nitrile, C_1–C_3 alkylaminocarbonyl, di C_1–C_3 alkylaminocarbonyl, C_3–C_7 N-cycloalkyl-C_1–C_3 alkylaminocarbonyl C_1–C_3 alkylamino, C_1–C_3, di alkylaminocarbonyl alkoxy, alkylaminosulfonyl, di C_1–C_3 alkylaminono, diC_1–C_3 alkylaminosulfonyl, hydroxy C_1–C_3 alkyl, C_1–C_3 alkylcarbonyl, amino C_1–C_3 alkyl or C_1–C_3 alkoxy C_1–C_3 alkyl group
or, when R_1 and R_2 are each hydrogen, R_3 can be hydroxy, hydroxycarbonyl C_1–C_3 alkoxy or di C_1–C_3 aminocarbonylalkoxy;
or, when R_1 is C_1–C_3 alkyl or C_1–C_3 cycloalkyl and R_2 is hydrogen or C_1–C_3 alkyl, R_3 can also be halogen, trifluoromethyl, nitro, amino, aminosulfonyl, aminocarbonyl, C_1–C_3 alkyl, carboxy or C_1–C_3 alkoxycarbonyl; and
R_4 is hydrogen or, when R_1 and R_2 are each hydrogen and R_3 is halogen or hydroxy, R_4 can also be halogen, hydroxy or C_1–C_3 alkoxy; or a nontoxic, pharmaceutically acceptable salt thereof. Also disclosed are pharmaceutical compositions comprising such compounds alone and in combination with dihydrofolic acid-reductase inhibitors. The compounds and compositions are useful for their inhibiting effect on bacteria, mycobacteria and plasmodia.

11 Claims, No Drawings

SUBSTITUTED BIS-(4-AMINOPHENYL)-SULFONES

This is a continuation of application Ser. No. 732,024, filed May 8, 1985 now abandoned.

BACKGROUND OF THE INVENTION

1. Field of the Invention

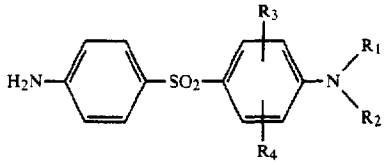
The present invention relates to the field of compounds useful for inhibiting bacteria, mycobacteria and plasmodia, particularly to sulfone compounds which are useful in this regard and in treating animals and humans suffering from infections of such organisms.

2. Brief Information Disclosure Statement

U.S. Pat. No. 2,385,899 describes the compound bis-(4-aminophenyl)-sulfone which has an inhibiting effect on the growth of bacteria, mycobacteria and plasmodia.

SUMMARY OF THE INVENTION

The present invention provides substituted bis-(4-aminophenyl)-sulfones of formula I



wherein

R_1 is hydrogen, C_1–C_7 alkyl or C_3–C_7 cycloalkyl;

R_2 is hydrogen or C_1–C_3 alkyl;

R_3 is nitrile, C_1–C_3 alkylaminocarbonyl, di C_1–C_3 alkylaminocarbonyl, C_3–C_7 N-cycloalkyl C_1–C_3 alkylaminocarbonyl, C_1–C_3 alkylamino, di C_1–C_3 alkylamino, di C_1–C_3 alkylaminocarbonyl, C_1–C_3 alkoxy, C_1–C_3 alkylaminosulfonyl, di C_1–C_3 alkylaminosulfonyl, hydroxy C_1–C_3 alkyl, C_1–C_3 alkylcarbonyl, amino C_1–C_3 alkyl or C_1–C_3 alkoxy C_1–C_3 alkyl

or, when R_1 and R_2 are each hydrogen, R_3 can be hydroxy or hydroxycarbonyl C_1–C_3 alkoxy

or, when R_1 is C_1–C_3 alkyl or C_3–C_7 cycloalkyl and R_2 is hydrogen or C_1–C_3 alkyl, R_3 can also be halogen, trifluoromethyl, nitro, amino, aminosulfonyl, aminocarbonyl, C_1–C_3 alkyl, carboxy or C_1–C_3 alkoxycarbonyl; and

R_4 is hydrogen, or when R_1 and R_2 are each hydrogen and R_3 is halogen or hydroxy in the 2-position, R_4 can also be halogen, hydroxy or C_1–C_3 alkoxy, or a nontoxic, pharmaceutically acceptable salt thereof.

One subgeneric aspect includes compounds of formula I wherein:

R_1 is hydrogen, C_1–C_7 alkyl or a C_4–C_7 cycloalkyl;

R_2 is hydrogen or methyl;

R_3 is nitrile, methylaminocarbonyl, N-cyclohexylmethylaminocarbonyl, methylamino, dimethylamino, dimethylaminocarbonylmethoxy, hydroxymethyl, hydroxyethyl, methylcarbonyl, aminocarbonyl or methoxymethyl;

or when, R_1 and R_2 are each hydrogen, R_3 can also be hydroxy or hydroxycarbonylmethoxy

or, when R_1 is alkyl or cycloalkyl and R_2 is hydrogen or methyl, R_3 can also be chlorine, bromine, methyl, trifluoromethyl, nitro, amino or aminocarbonyl; and

R_4 is hydrogen or, when R_1 and R_2 are each hydrogen and R_3 is hydroxy, chlorine or bromine in the 2-position, R_4 can also be chlorine, bromine, hydroxy or methoxy, or a nontoxic, pharmaceutically acceptable salts thereof.

A further subgeneric aspect includes compounds of formula I wherein:

R_1 is hydrogen, C_1–C_3 alkyl or C_4–C_7 cycloalkyl;

R_2 is hydrogen or, when R_1 is methyl, R_2 can also be methyl;

R_3 is chlorine, bromine, methyl, trifluoromethyl, hydroxymethyl, hydroxyethyl, methylamino, dimethylamino, cyano or methylcarbonyl in the 2-position; and

R_4 is hydrogen; or a nontoxic, pharmaceutically acceptable addition salt thereof.

The present invention thus relates to the compounds of formula I above, the addition salts thereof, particularly the acid addition salts thereof with pharmaceutically acceptable inorganic or organic acids, pharmaceutical compositions containing these compounds including their addition salts, their preparation and the use thereof for inhibiting bacteria, mycobacteria and plasmodia and for treating animals and humans suffering from infections of such organisms.

This invention further relates to combinations of the substituted bis(4-aminophenyl)-sulfones of formula I including their nontoxic, pharmaceutically acceptable addition salts with a dihydrofolic acid-reductase inhibitor such as pyrimethamine, trimethoprim or trimethoprim derivatives.

DETAILED DESCRIPTION OF THE INVENTION

Examples of groups R_1 to R_4 include the following.

R_1 can be hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, n-pentyl, isoamyl, n-hexyl, n-heptyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

R_2 can be hydrogen, methyl, ethyl, n-propyl or isopropyl.

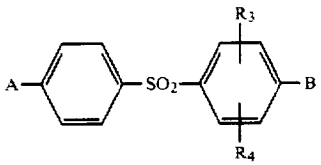
R_3 can be cyano, methylaminocarbonyl, ethylaminocarbonyl, isopropylaminocarbonyl, dimethylaminocarbonyl, diethylaminocarbonyl, di-n-propylaminocarbonyl, N-methylethylaminocarbonyl, N-methyl-cyclopentylaminocarbonyl, N-methyl-cyclohexylaminocarbonyl, N-methyl-cycloheptylaminocarbonyl, N-ethyl-cyclohexylaminocarbonyl, methylamino, ethylamino, n-propylamino, isopropylamino, dimethylamino, diethylamino, diisopropylamino, N-methyl-ethylamino, N-ethyl-n-propylamino, dimethylaminocarbonylmethoxy, diethylaminocarbonylmethoxy, 2-dimethylaminocarbonylethoxy, 2-diethylaminocarbonylethoxy, methylaminosulfonyl, ethylaminosulfonyl, isopropylaminosulfonyl, dimethylaminosulfonyl, diethylaminosulfonyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1-hydroxypropyl, 3-hydroxypropyl, methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, aminomethyl, 2-aminoethyl, 3-aminopropyl, methoxymethyl, 2-methoxyethyl, ethoxymethyl, 2-ethoxyethyl, n-propoxymethyl, 2-n-propoxyethyl, hydroxy, hydroxycarbonylmethoxy, 2-hydroxycarbonylethoxy, 3-hydroxycarbonylpropoxy, 2-dimethylaminoethoxy, 2-diethylaminoethoxy, trifluoromethyl, nitro, amino, aminosulfonyl, aminocarbonyl, methyl, ethyl, n-propyl, isopropyl, carboxy, methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, fluorine, chlorine, bromine or iodine.

R_4 can be hydrogen, fluorine, chlorine, bromine, iodine, hydroxy, methoxy, ethoxy or n-propoxy.

According to the invention the compounds of formula I can be obtained by the following processes.

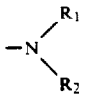
Method A

In one method, compounds of formula I are made by reduction of a compound of formula II



(II)

wherein R_3 and R_4 are as previously defined, one of A and B is nitro and the other is

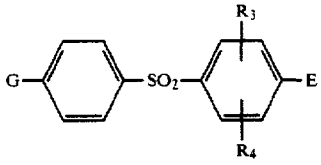


wherein R_1 and R_2 are as previously defined, or is also nitro.

The reduction is conveniently carried out in a solvent or mixture of solvents such as water, methanol, ethanol, glacial acetic acid, ethyl acetate, dimethylformamide, water/ethanol or water/tetrahydrofuran in the presence of a reduction agent, e.g. with hydrogen in the presence of an hydrogenation catalyst such as Raney nickel, platinum or palladium/charcoal, with metals such as iron, tin or zinc in the presence of an acid such as hydrochloric or acetic acid, with salts such as iron-(II)sulphate, tin(II)chloride/hydrochloric acid or sodium dithionite in the presence of a base such as sodium hydroxide solution or pyridine or with hydrazine in the presence of Raney nickel, at temperatures of 0° to 50° C., preferably at ambient temperature.

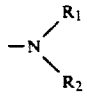
Method B

In another method, one or two protecting groups are cleaved from a compound of formula III



(III)

wherein R_3 and R_4 are as previously defined, E is amino, C_1–C_7 alkylamino or C_3–C_7 cycloalkylamino protected by a protecting group, or is



wherein

R_1 and R_2 are as previously defined; and

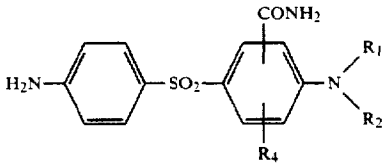
G is an amino group optionally protected by a protecting group. At least one of E and G must be one of the above-mentioned groups protected by a protecting group.

Suitable protecting groups are the protecting groups conventionally used for amino groups, e.g. hydrolytically removable protecting groups such as acetyl, propionyl; benzoyl, p-toluenesulfonyl, methanesulfonyl or ethoxycarbonyl, or hydrogenolytically removable groups such as benzyl.

Any protecting group used is preferably split off by hydrolysis, e.g. with an acid such as hydrochloric, sulphuric or phosphoric acid or with a base such as sodium hydroxide or potassium hydroxide in a suitable solvent or a mixture of solvents such as water, water/methanol, ethanol, water/ethanol, water/isopropanol or water/dioxan at temperatures of −10° to 120° C., preferably ambient temperature to the boiling temperature of the reaction mixture, or by hydrogenolysis, e.g. with hydrogen in the presence of a hydrogenation catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, glacial acetic acid, ethyl acetate, dioxan or dimethylformamide at temperatures of 0° to 50° C., preferably at ambient temperature.

Method C

Compounds of formula I wherein R_3 is cyano are prepared by dehydration of a compound of formula IV



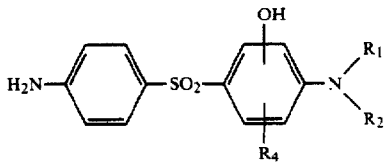
(IV)

wherein R_1, R_2 and R_4 are as previously defined.

The dehydration is conveniently carried out with a dehydrating agent such as phosphorus pentoxide, concetrated sulphuric acid, p-toluenesulphonic acid, thionylchloride, phosphorus oxychloride, sulfurylchloride, phosphoric acid or dicyclohexylcarbodiimide, optionally in a solvent such as methylene chloride, phyridine or chlorobenzene or in an excess of the dehydrating agent used such as thionyl chloride, phosphorus oxychloride, sulfurylchloride, or phosphoric acid at temperatures of 0° to 100°, preferably 20° to 80° C. However, the reaction can also be carried out without a solvent.

Method D

Compounds of formula wherein R_3 is hydroxycarbonylalkoxy or dialkylaminocarbonyl-alkoxy can be prepared by alkylation of a compound of formula V



(V)

wherein R_1, R_2 and R_4 are as previously defined with a compound of formula VI

(VI)

wherein

Alk is a C_1–C_3 alkylene;

R_5 is hydroxy, C_1–C_3 alkoxy or di C_1–C_3alkylamino; and

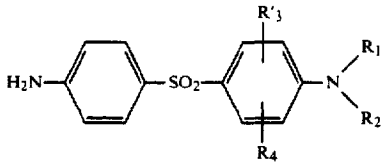
X is a nucleophilically exchangeable group such as chlorine or bromine, optionally with subsequent hydrolysis.

The reaction is preferably carried out in a solvent such as diethylether, tetrahydrofuran, dioxan, methanol, ethanol, pyridine or dimethylformamide, optionally with a base such as sodium hydride, potassium hydride, potassium carbonate or potassium tert.butoxide at temperatures of 0° to 75° C. preferably at ambient temperature.

The optional subsequent hydrolysis is preferably carried out either with an acid such as hydrochloric, sulphuric, phosphoric or trichloroacetic acid or with a base such as sodium hydroxide or potassium hydroxide in a suitable solvent such as water, water/methanol, ethanol, water/ethanol, water/isopropanol or water/dioxan at temperatures of −10° C. to 120° C., e.g. ambient temperature to the boiling temperature of the reaction mixture.

Method E

Compounds of formula I wherein R_3 is aminocarbonyl, alkylamino-carbonyl, dialkylaminocarbonyl or dialkylaminocarbonylalkoxy can be prepared by reaction of a compound of formula VII.



(VII)

wherein

R_1, R_2 and R_4 are as hereinbefore defined; and

R_3' is hydroxycarbonyl, hydroxycarbonyl-alkoxy or a reactive derivative thereof, with an amine of formula VIII

(VIII)

wherein

R_6 is hydrogen atom or C_1–C_3 alkyl; and

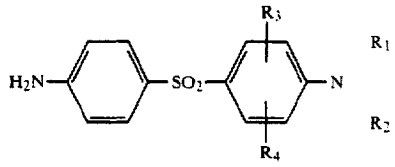
R_7 is hydrogen or C_1–C_3 alkyl, or reactive derivatives thereof.

The reaction is conveniently carried out in a solvent such as methylene chloride, chloroform, carbon tetrachloride, ether, tetrahydrofuran, dioxan, benzene, toluene, acetronitrile or dimethylformamide, optionally in the presence of an acid-activating agent or a dehydrating agent, e.g. in the presence of ethylchloroformate, thionylchloride, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxy succinimide, N,N'-carbonyldiimidazole or N,N'-thionyldiimidazole or triphenylphosphine/carbon tetrachloride, or an agent which activates the amino group, e.g. phosphorus trichloride, and optionally in the presence of an inorganic base such as sodium carbonate or a tertiary organic base such as triethylamine or pyridine, which can simultaneously serve as solvent, at temperatures of −25° C. to 250° C., preferably −10° C. to the boiling temperature of the solvent used. The reaction can also be carried out without a solvent and furthermore any water formed during the reaction can be removed by azeotropic distillation, e.g. by heating with toluene using a water separator or by adding a drying agent such as magnesium sulphate or molecular sieve.

In this reaction it can also be advantageous to prepare an activated derivative of a compound of formula VII or VIII in the reaction mixture initially and then react this derivative with a compound of formula VIII or VII.

Method F

Compounds of formula I wherein R_3 is hydroxymethyl, aminomethyl or 1-hydroxyalkyl can be prepared by reduction of a compound of formula IX



(IX)

wherein

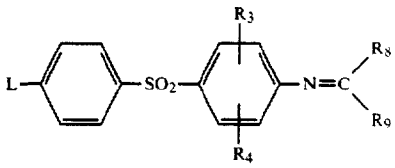
R_1 and R_2 and R_4 are as previously defined; and

R_3'' is hydroxycarbonyl, alkoxycarbonyl, aminocarbonyl or C_2–C_4 alkylcarbonyl.

The reaction is preferably carried out with a metal hydride such as sodium borohydride, lithium aluminium hydride or diborane in a solvent such as water, methanol, water/methanol, diethyl ether, tetrahydrofuran or dioxan at temperatures of 0° to 80° C., preferably ambient temperature to 70° C.

Method G

Compounds of formula I wherein R_1 is alkyl or cycloalkyl and R_2 is hydrogen can be prepared by reduction of a compound of formula X



(X)

wherein

R_3 and R_4 are as previously defined;

L is amino or nitro; and

R_8 and R_9 together with the carbon atom between them are a C_1–C_7 alkylidene or a C_3–C_7 cycloalkylidene.

The reduction is preferably carried out in a suitable solvent such as methanol, ethanol, methanol/water, ethyl acetate, tetrahydrofuran or dioxan with nascent or catalytically activated hydrogen or with a hydride such as diborane, sodium borohydride or lithium aluminium hydride at temperatures of 0° to 50° C., preferably at ambient temperature.

If L is nitro, the reduction is particularly advantageously carried out in a solvent such as methanol or ethyl acetate with hydrogen in the presence of a hydrogenation catalyst such as platinum or palladium/charcoal and under a hydrogen pressure of 0 to 5 bar or with a complex metal hydride such as lithium aluminium hydride or diborane at temperatures of 0° to 50° C., preferably at ambient temperature.

If L in a compund of formula X is amino, the reduction is carried out particularly advantageously in a solvent such as methanol, methanol/water, tetrahydrofuran or dioxan with a complex metal hydride such as sodium borohydride or lithium aluminium hydride at

temperatures of 0° to 50° C., preferably at ambient temperature.

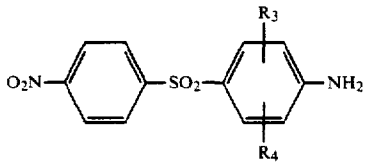
If a compound of formula I is obtained wherein R_3 is alkoxycarbonyl or alkoxycarbonylalkoxy, it can be converted by hydrolysis into a corresponding compound of formula I wherein R_3 is hydroxycarbonyl or hydroxycarbonylalkoxy. If a compound of formula I is obtained hwerein R_3 and/or R_4 is chlorine or bromine, it can be converted by hydrolysis or alcoholysis into a corresponding compound of formula I wherein R_3 is hydroxy or alkoxy in the 2 position and R_4 is chlorine or bromine.

This hydrolysis is conveniently carried out either with an acid such as hydrochloric or sulphuric acid or with a base such as sodium hydroxide or potassium hydroxide in a suitable solvent such as water, water/-methanol, ethanol, water/ethanol, water/isopropanol or water/dioxan at temperatures of −10° C. to 120° C., e.g. at temperatures of ambient temperature to the boiling temperature of the reaction mixture.

The alcoholysis is conveniently carried out in a corresponding alcohol as the solvent such as methanol, ethanol or propanol, optionally in a pressure vessel, preferably with a base such as sodium hydroxide or potassium hydroxide at temperatures of 20° C. to 200° C., preferably 50° to 180° C.

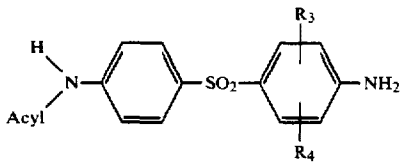
The compounds of general formulae II to X used as starting materials are known from the literature or can be obtained by methods known from the literature.

Thus, for example, a compound of formula II or III can be obtained by reacting an alkali metal salt of a corresponding acylaminophenyl-sulfinic acid with a corresponding p-halonitrobenzene. A compound of formula XI

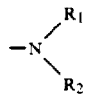

(XI)

optionally obtained after splitting off an acyl protecting group, wherein R_3 and R_4 are as previously defined, can subsequently be converted by reductive amination into a compound of formula II or after tosylation, subsequent alkylation and reduction of the nitro group and optionally subsequent acylation into a compound of formula III.

Moreover, a compound of formula XII

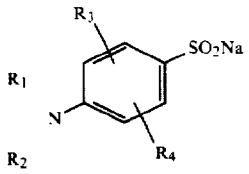

(XII)

prepared by methods known from the literature, wherein R_3 and R_4 are as previously defined and Acyl is an organic acyl group, can be converted by reductive amination or by reduction of a Schiff's base obtained after reaction with a corresponding carbonyl compound into a compound of formula III wherein D is an aminoacyl group and E is



wherein, R_1 and R_2 are as previously defined.

Moreover a compound of formula XIII


(XIII)

wherein R_1 to R_4 are as previously defined and Na is a sodium ion, can be reacted with a 4-halonitrobenzene to form a corresponding diphenylsulfone of formula III.

A cycloalkylamino compound of formula II, however, is preferably obtained by reductive amination of a corresponding amino compound with a cycloalkanone in the presence of sodium cyanoborohydride or by reduction of the corresponding Schiff's base with a complex metal hydride.

A compound of formula X used as starting material is obtained by reacting a corresponding compound of formula XI with a corresponding carbonyl drivative, optionally in the presence of titanium(IV) chloride and optional subsequent reduction of the nitro group, for example with catalytically activated hydrogen.

As already mentioned hereinbefore, the new compounds of formula I including their nontoxic, pharmaceutically acceptable addition salts having an inhibiting effect on the growth of bacteria and parasites such as plasmodia and mycobacteria which is believed to be due to their inhibiting effect on 7,8-dihydropteroic acid-synthetase.

For example, the following compounds

A = 4-Ethylamino-4′-amino-2-chloro-diphenylsulfone,
B = 4′-Amino-2-chloro-4-isopropylamino-diphenylsulfone,
C = 4-Ethylamino-4′-amino-2-methyl-diphenylsulfone,
D = 4-Ethylamino-4′-amino-2-trifluoromethyl-diphenyl-sulfone,
E = 4,4′-Diamino-2-hydroxymethyl-diphenylsulfone,
F = 4,4′-Diamino-2-(1-hydroxyethyl)-diphenylsulfone,
G = 4,4′-Diamino-2-(N,N-dimethylamino)-diphenylsulfone,
H = 4,4′-Diamino-2-(N-methylamino)-diphenylsulfone,
I = 4,4′-Diamino-2-cyano-diphenylsulfone,
K = 4,4′-Diamino-2-methylcarbonyl-diphenylsulfone,
L = 4′-Amino-2-methyl-4-methylamino-diphenylsulfone and
M = 4′-Amino-2-methyl-4-propylamino-diphenylsulfone were tested for their biological activity in cell-free enzyme extract of Plasmodiumberghei as follows.

1. Preparation of the enzyme extract

Plasmodia are isolated from mouse blood infected with *Plasmodium berghei* in accordance with the following reference (Heidrich, H.-G. et al., Z. Parasitenkd. 59: 151 (1979). The plasmodia were opened by ultrasound. Proteins with 7,8-hydropteroic acid synthetase activity are concentrated by gel filtration.

2. Biological test system

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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.

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

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API

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LAW FIRMS
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.