CHAPTER 10

SUMMARY

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Isolation and identification of naphthoquinones from *Euclea natalensis* with activity against *Mycobacterium tuberculosis*, other pathogenic bacteria and herpes simplex virus

by

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Department of Botany

Doctor of Philosophiae

The antimycobacterial activity of twenty South African medicinal plants were investigated using two methods commonly used; the conventional agar plate method and the BACTEC radiometric method. Fourteen of the twenty acetone extracts of medicinal plants used to treat pulmonary diseases showed inhibitory activity at a concentration of 0.5 mg/ml against a sensitive strain of *Mycobacterium tuberculosis* using the conventional agar plate method. These fourteen extracts were also tested against *M. tuberculosis* by the BACTEC radiometric method against a sensitive as well as a strain resistant to the drugs isoniazid and rifampin. Eight plants showed activity against both the strains at a concentration of 1.0 mg/ml.

Susceptibility testing of *M. tuberculosis* by the agar plate method is reliable, economical, and reproducible whereas the BACTEC radiometric method is much faster and probably more accurate than the agar plate method.

A cytotoxicity assay of the fourteen plants on primary vervet monkey kidney cells showed that the crude acetone extracts of *E. natalensis* was the least cytotoxic extract with significant antimycobacterial properties. It was therefore, chosen for the isolation of active compound(s).

An antibacterial assay of the water and acetone extracts of the roots of *E. natalensis* showed that they inhibited the growth of Gram-positive bacteria at concentrations ranging between 0.1 and 6.0 mg/ml. The water extract did not exert any inhibitory action on Gram-negative bacteria while the acetone extract showed inhibitory activity at a concentration of 5.0 mg/ml.

The MIC of diospyrin, isolated from *E. natalensis,* was found to be 100 µg/ml for a drug-sensitive and a number of drug-resistant strains of *M. tuberculosis* and Gram-positive bacterial species.

An antiviral investigation of the crude extracts of *E. natalensis* showed that the water extract of the roots of the plant inhibited the replication of herpes simplex virus type 1 moderately at a concentration of 0.2 mg/ml whereas, acetone extract at concentrations ranging from 0.1 to 0.02 mg/ml. Diospyrin exhibited no inhibitory effect against the virus.

The MIC of 7-methyljuglone, isolated from *E. natalensis,* was found to be 50 µg/ml for both drug-sensitive and drug-resistant strains of *M. tuberculosis*. The compound inhibited the growth of Gram-positive bacterial species at concentrations ranging from 50 to 100 µg/ml. No inhibitory effect of the compound was observed on any Gram-negative bacteria at the highest concentration tested.

A significant synergistic effect of the two naphthoquinones was observed against *M. tuberculosis* and some of the bacterial species. MICs obtained were 10 µg/ml and 50 µg/ml for *M. tuberculosis* and the bacterial species respectively. No synergistic effect was observed on any Gram-negative bacterial species investigated.

In view of the encouraging results obtained from this study on the biological activity of the two naphthoquinones; diospyrin and 7-methyljuglone, it appears that the compounds deserve further investigation in order to explore its potential as antimycobacterial agents.

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CHAPTER 11

ACKNOWLEDGEMENTS

Chapter 11

ACKNOWLEDGEMENTS

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CHAPTER 12

APPENDICES

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APPENDIX 1 - Publications

12.1 Publications resulting from this thesis:

LALL, N. & MEYER, J.J.M. 1999. *In vitro* inhibition of drug-resistant and drug-sensitive strains of *Mycobacterium tuberculosis* by ethnobotanically selected South African Plants. *J Ethnopharmacol* 53: 51-54.

LALL, N. & MEYER, J.J.M. 2000. Antibacterial activity of water and acetone extracts of the roots of *Euclea natalensis. J Ethnopharmacol* 72: 313-316.

MEYER, J.J.M. & LALL, N. 2000. Inhibition of drug-sensitive and resistant strains of *Mycobacterium tuberculosis* and other bacterial species by diospyrin, isolated from *Euclea natalensis. Planta Med* (in press).

12.2 Articles in preparation:

LALL, N. & MEYER, J.J.M. 2000. Antiviral properties of the extracts of *Euclea natalensis* A. DC. against herpes simplex virus: *in vitro* studies on vervet cells.

LALL, N. & MEYER, J.J.M. 2000. Inhibition of drug-sensitive and resistant strains of *Mycobacterium tuberculosis* and other bacterial species by 7-methyljuglone, isolated from *Euclea natalensis*.

LALL, N. & MEYER, J.J.M. 2000. Synergistic effect of diospyrin and 7-methyljuglone on drug-sensitive and resistant strains of *Mycobacterium tuberculosis* and other bacterial species.

APPENDIX 2 - Provisional patent registered

SPOOR AND FISHER

JOHANNESBURG

PROVISIONAL PATENT SPECIFICATION

COUNTRY	**SOUTH AFRICA**
APPLICATION NUMBER	**99/4176**
DATE OF FILING	**24 JUNE 1999**
NAME OF APPLICANT	**UNIVERSITY OF PRETORIA**
NAMES OF INVENTORS	**JACOBUS JOHANNES MARION MEYER; NAMRITA LALL**
TITLE OF INVENTION	**TREATMENT AND CONTROL OF TUBERCULOSIS**
FILE REF	**JP/U 081/MK/acm**
DATE	**12 JULY 1999**

NAPHTHOQUINONE DERIVATIVES AND THEIR USE IN THE TREATMENT AND CONTROL OF TUBERCULOSIS

BACKGROUND OF THE INVENTION

THIS invention relates to the treatment and control of tuberculosis caused by *Mycobacterium tuberculosis* and in particular to the use of naphthoquinone derivatives in such treatment and control.

Tuberculosis (TB) remains a serious health problem in many regions of the world, especially in developing nations. It is a contagious disease and is becoming epidemic in some parts of the world. It is estimated that 30-60% of adults in developing countries are infected with *Mycobacterium tuberculosis*. Approximately 8-10 million individuals develop clinical TB and 3 million die of TB each year (WHO/IUATLD, 1989).

In South Africa, over 3 in every thousand people die of TB, the highest rate in the world, while one out of every 200 people suffers from active tuberculosis. Tuberculosis is the most commonly notified disease in South Africa and the fifth largest cause of death among the black population (South African Tuberculosis Association, 1998).

In the United States, the number of TB cases steadily decreased until 1986 when an increase was noted. Since then TB cases have continued to rise. Ten million individuals are infected in the U.S.A., with approximately 26000 new cases of active disease each year (National Jewish Medical and Research Center, 1994).

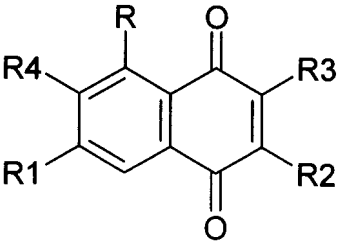
Individuals infected with Human Immunodeficiency Virus (HIV) are very susceptible to tuberculosis and often develop this disease before other manifestations of AIDS become

apparent (Grange and Davey, 1990). Control of the TB epidemic linked with HIV infection will depend largely on the adequate treatment of TB, and possibly of effective chemoprophylaxis, not just for HIV-infected persons but for communities as well (WHO/IUATLD, 1989).

TB therapy has been revolutionized and the present treatment regimes for TB are based on multidrug therapy with usually 3 or 4 antituberculosis drugs. However, the problem of multidrug resistant tubercle bacilli is emerging for various drugs such as isoniazid, ethambutol, rifampicin and streptomycin, for example (Girling, 1989; Grange and Davey, 1990). Drug-resistant TB is very difficult to treat requiring greater numbers and varieties of medications for a longer period of treatment. The need for new antituberculosis agents is urgent due to the increasing resistance of mycobacteria to these classic antituberculosis drugs. A recent WHO report states that, globally, 2% of all cases of tuberculosis are multidrug resistant - by definition, resistance to rifampicin plus isoniazid (plus/minus other resistances). Such cases can be treated in the USA and other high resource regions but at a great cost (> US$ 250,000 per case!) and using very long courses of rather toxic drugs, thereby raising serious problems of compliance (WHO, 1997). South Africa is witnessing an explosion in the number of cases of drug-resistant tuberculosis. In some parts of South Africa, 1 in 10 cases of TB is resistant to treatment (New Scientist, March 1997). It is essential to have new antituberculosis agents, preferably those that can readily and simply be produced from some local source.

SUMMARY OF THE INVENTION

According to a first aspect of the invention there is provided a naphthoquinone derivative of Formula 1:

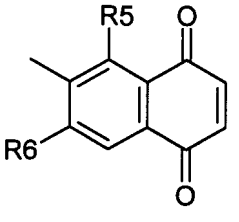


wherein,

R represents an OH group, methyl ether, ethyl ether or a similar ether;

R1 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

R2 and R3 each independently represent hydrogen or a group selected from:



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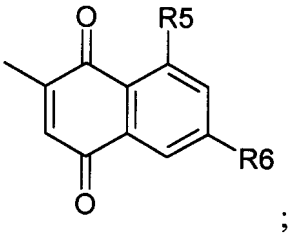

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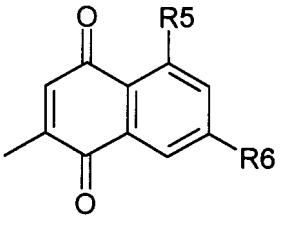
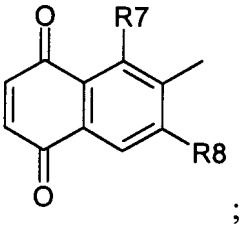


wherein,

R5 represents an OH group, methyl ether, ethyl ether or a similar ether and R6 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

R4 represents hydrogen or a group selected from:



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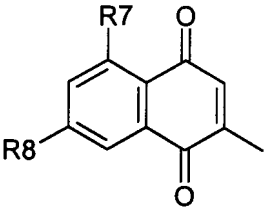

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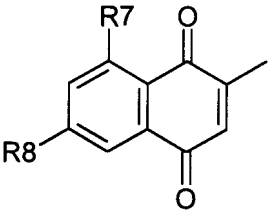
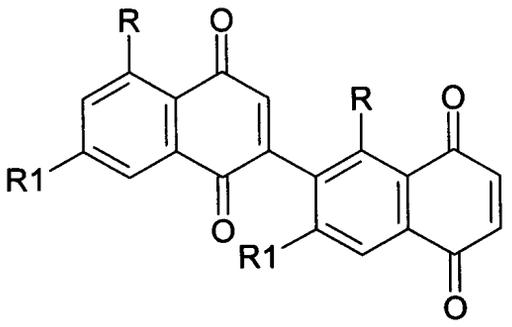


wherein R7 represents an OH group, methyl ether, ethyl ether or a similar ether and R8 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative; or Pharmaceutically acceptable salts thereof, for use in a method of treating and/or controlling tuberculosis in a patient caused by *Mycobacterium tuberculosis*.

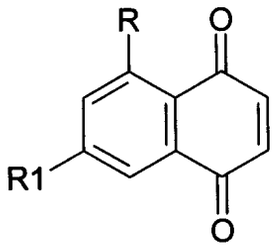
According to a second aspect of the invention there is provided the use of a naphthoquinone derivative having the Formula 1 as set out above in the manufacture of a medicament for use in a method of treating and/or controlling tuberculosis in a patient caused by *Mycobacterium tuberculosis*.

According to a third aspect of the invention there is provided a method of treating and/or controlling tuberculosis caused by *Mycobacterium tuberculosis* comprising administering to a patient in need thereof an effective amount of a naphthoquinone derivative having the Formula 1 as set out above.

The naphthoquinone derivative of Formula 1 is typically a compound of Formula 1a or Formula 1b:



Formula 1a



Formula 1b

wherein R and R1 are as defined for Formula 1 above.

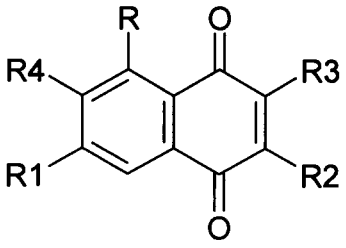
R in the compound of Formula 1a or 1b is preferably an OH group.

R1 in the compound of Formula 1a or 1b is preferably a CH_3 group.

In particular, the naphthoquinone derivative of Formula 1 is 5,5' dihydroxy 7,7' binaphthoquinone (diospyrin) or 5-hydroxy-7-methyl-1,4-naphtoquinone (methyljuglone).

DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention is directed at the use of naphthoquinone derivatives in the treatment and/or control of tuberculosis caused by *Mycobacterium tuberculosis*. In particular, naphthoquinone derivatives of the general Formula 1

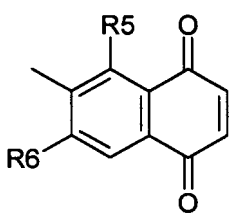


wherein,

R represents an OH group, methyl ether, ethyl ether or a similar ether;

R1 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

R2 and R3 each independently represent hydrogen or a group selected from:



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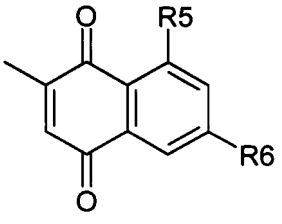

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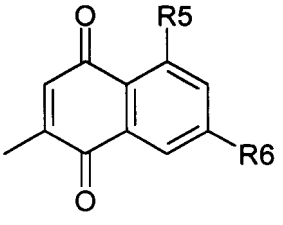
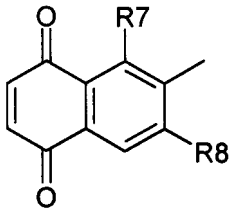


wherein R5 represents an OH group, methyl ether, ethyl ether or a similar ether and R6 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;
R4 represents hydrogen or a group selected from:



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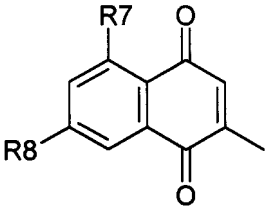

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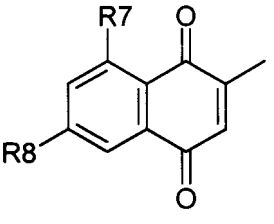
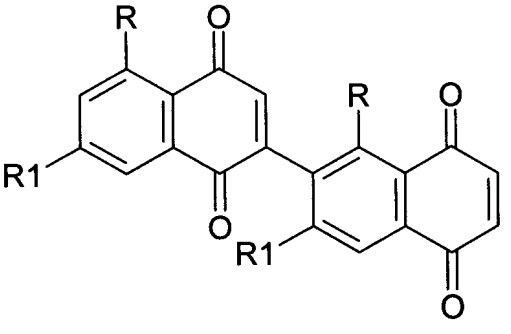
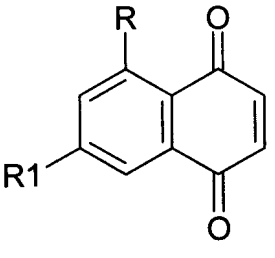


wherein R7 represents an OH group, methyl ether, ethyl ether or a similar ether and R8 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;
have been found to be effective against *Mycobacterium tuberculosis*.

Particular naphthoquinone derivatives of Formula 1a and 1b have been found to be particularly effective:



Formula 1a



Formula 1b

In particular diospyrin and methyljuglone, naphthoquinone derivatives of Formula 1a and Formula 1b, respectively, in which R is OH and R1 is a methyl group, have been found to inhibit several antibiotic resistant as well as antibiotic susceptible strains of *Mycobacterium tuberculosis*. Although diospyrin and methyljuglone are particularly preferred, naphthoquinone derivatives of Formula 1a and 1b in which R is a methyl ether, ethyl ether or similar ether and R1 is an ethyl or similar aliphatic hydrocarbon derivative are also provided.

An extensive research program was undertaken in order to identify anti-tuberculosis agents that can readily and simply be produced from local resources.

Twenty South African medicinal plants used to treat pulmonary diseases were screened for activity against drug-resistant and sensitive strains of *M. tuberculosis*. A preliminary screening of acetone and water plant extracts, against a drug-sensitive strain of *M. tuberculosis*; H37Rv, was carried out by the agar plate method. Fourteen of the 20 acetone extracts showed inhibitory activity at a concentration of 0.5 mg/ml against this strain. Acetone as well as water extracts of *Cryptocarya latifolia*, *Euclea natalensis*, *Helichrysum melanacme*, *Nidorella anomala* and *Thymus vulgaris* inhibited the growth of *M. tuberculosis*. Given the activity of 14 acetone extracts at 0.5 mg/ml against the drug-sensitive strain by the agar plate method a further study was carried out employing the rapid radiometric method to confirm the inhibitory activity. These active acetone extracts were screened against the H37Rv strain as well as a strain resistant to the drugs, isoniazid and rifampicin. The minimal inhibitory concentration of *Croton pseudopulchellus*, *Ekebergia capensis*, *Euclea natalensis*, *Nidorella anomala* and *Polygala myrtifolia* was 0.1 mg/ml against the H37Rv strain by the radiometric method. Extracts of *Chenopodium ambrosioides*, *Ekebergia capensis*, *Euclea natalensis*, *Helichrysum melanacme*, *Nidorella anomala* and *Polygala myrtifolia* were active against the resistant strain at 0.1 mg/ml. Eight plants showed activity against both the strains at a concentration of 1.0 mg/ml.

The following procedure was developed by the applicant for the isolation of diospyrin and methyljuglone from *E. natalensis* and other species in this genus, as well as any other plants that may synthesise diospyrin or methyljuglone or other quinone derivatives.

1. Identification of plant species

Roots and the aerial plant parts of *E. natalensis* were collected near Durban and identified at the HGWJ Schweickerdt Herbarium of the University of Pretoria and also at the herbarium of the National Botanical Institute, Pretoria.

2. Extraction

Dried roots of *E. natalensis* were ground to a powdery form with a dry mill and extracted over 48 hours with acetone. The extract was filtered and concentrated to dryness at reduced pressure on a rotary evaporator.

3. Thin layer chromatography

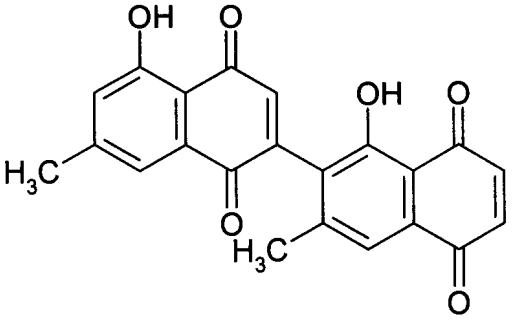
A direct antibacterial bioassay (Dilika & Meyer 1996) on TLC-plates was employed to speedup the activity guided isolation of the antituberculosis compounds. *M. tuberculosis* cannot be tested in this way because of its very slow growth rate. The direct antibacterial bioassays of the acetone extract were done on TLC plates (Merck) developed with chloroform-hexane (1:1). After development, the TLC plates were dried and sprayed with a 24 hr old *Staphylococcus aureus* culture in nutrient broth. After 24 hr incubation, the plates were sprayed with an aqueous solution of 2mg/ml p-iodonitrotetrazolium violet to visualise the bacterial cells. The plates were then reincubated at 37^0C for 2-3 hours. Bacterial growth inhibition could be seen on TLC plates sprayed with *S. aureus* and inhibitory activity was found to be prominent at R_f 0.30 and 0.54 zones (chloroform-hexane (1:1)). The fractions containing the active compounds of R_f 0.30 and R_f 0.54 were also found to be antimycobacterial in *in vitro* investigations.

4. Column chromatography

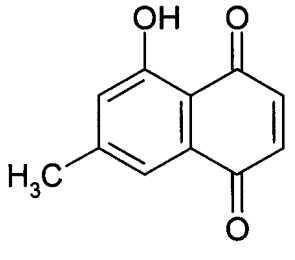
The crude extract of the plant was dried, its mass determined and resuspended in chloroform. Column chromatography was performed on silica gel 60 using chloroform as eluent. The antibacterial fractions collected were then subjected to a Sephadex LH-20 column chromatography using ethanol as eluent. The fractions collected were again tested for antibacterial activity on TLC to detect the fractions containing the active compounds of R_f 0.30 and R_f 0.54.

5. High performance liquid chromatography

The compounds were further purified by HPLC utilising an analytical Phenomenex reverse phase 250x4.60 mm column, at a flow rate of 1.0 ml/min, oven temp. 40^0C and a wavelength of 206nm. An ethanol-water (50:50) solution was employed as mobile phase. The pure compounds were once again subjected to a Sephadex LH-20 column chromatography and proved to be pure. The chemical structures were confirmed by ^{1}H and ^{13}C nmr and ms to be:



Diospyrin (5,5' dihydroxy 7,7' binaphthoquinone); $C_{22}H_{14}O_6$. Molecular weight: 374.35



7-methyljuglone (5-hydroxy-7-methyl-1,4-naphtoquinone); $C_{11}H_8O_3$ Molecular weight: 188.19

The effect of diospyrin and methyljuglone on the growth of the sensitive strain (H37Rv) and resistant strains of *Mycobacterium tuberculosis* as determined by the radiometric method are set out in Table 1 and Table 2.

TABLE 1

Effect of diospyrin on the growth of the sensitive strain (H37Rv) and resistant strains of *Mycobacterium tuberculosis* as determined by the radiometric method.

Mycobacterium tuberculosis strains	MIC (mg/ml)	ΔGI[a] values of plant extracts (mg/ml)	ΔGI values of the control vial (mg/ml)
H37 sensitive strain	0.1	-1 ± 1.41	20 ± 4.24
2 drug resistant strain (res. to Isoniazid and rifampicin).	0.1	3.5 ± 0.70	25 ± 7.07
3 drug resistant strain (res. to streptomycin, isoniazid and ethambutol),	0.1	4 ± 2.12	29 ± 1.41
4 drug resistant strain (res. to streptomycin, isoniazid, rifampicin and ethambutol).	0.1	5 ± 2.82	25 ± 2.82
5 drug resistant strain.(res to isoniazid, streptomycin, rifampicin, thiacetazone and cyclocerine).	0.1	10 ± 1.41	22.5 ± 3.53
6 drug resistant strain (res. to isoniazid, rifampicin, ethionamide, terizidone, thiacetazone and ofloxacin).	0.1	9 ± 2.82	30 ± 1.0
7 drug resistant strain.(res to isoniazid, thiacetazone, streptomycin, ethambutol, kanamycin, rifampicin, and ethionamide)	0.1	13.5 ±3.2	28 ± 3.1

[a] ΔGI values are means ± s.d.

TABLE 2

Effect of 7-methyljuglone as a single agent and in combination with diospyrin on the growth of the sensitive strain (H37Rv) and resistant strains of *Mycobacterium tuberculosis* as determined by the radiometric method.

Mycobacterium tuberculosis strains	Lab reference no.	Compound(s)	MIC[a] (µg/ml)	ΔGI[b] values of plant extracts	ΔGI values of the control vial
H37Rv sensitive strain	ATCC27294	7-methyljuglone	50	0 ± 1	15 ± 3.78
Two drug (isoniazid and rifampicin) resistant strain	CCKO28469V	7-methyljuglone	50	0 ± 0	30 ± 4.94
H37Rv sensitive strain	ATCC27294	Diospyrin + 7-methyljuglone	10	3 ± 1	15 ± 3.78
Two drug (Isoniazid and rifampicin resistant strain)	CCKO28469V	Diospyrin + 7-methyljuglone	10	3.33 ± 3.05	30 ± 4.94

[a]Minimal inhibitory concentration

[b]ΔGI values are means ± s.d.

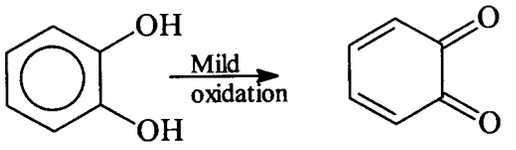
The results showed that diospyrin and methyljuglone control the *Mycobacterium tuberculosis* bacterium effectively. Oral administration of diospyrin or methyljuglone in an appropriate pharmaceutical composition with suitable diluents and carriers will typically be used to treat or control tuberculosis. This will be by way of tablet, liquid or similar oral dosage form, as diospyrin and methyljuglone are readily absorbed intestinally.

However, it is believed that diospyrin or methyljuglone administered intravenously or intramuscularly will also be absorbed effectively through blood vessels and the blood stream of a patient. Transdermal administration, via a plaster or similar transdermal administration vehicle, is also a possibility.

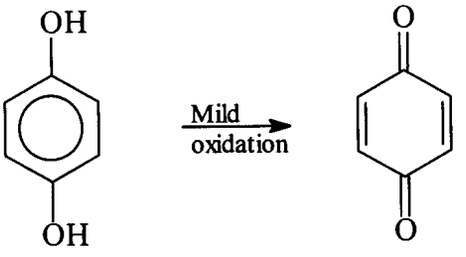
A combination treatment of diospyrin and methyljuglone, which may be more effective than singular treatments of the two naphthoquinones, is also envisaged.

The applicant believes that it may be possible to increase the concentration of diospyrin, methyljuglone and other quinones in *E. natalensis* or similar species by phytoalexic stimulation or by the biotechnological manipulation of tissue cultures and/or intact plants.

Quinones are generally synthesised from catechol (1,2-quinones) or hydroquinone (1,4-quinones) by mild oxidation.

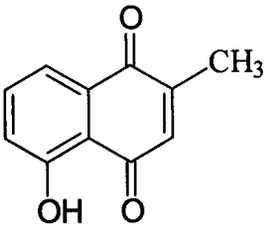


Catechol



Hydroquinone

As far as the applicant has been able to establish, diospyrin has been synthesised once in a laboratory (Yoshida, M and Mori, K. 2000. European Journal of Organic Chemistry pages 1313 – 1317). However, similar binapthoquinones can also be synthesised by the reaction of plumbagin (94mg in methanol, 10ml) and its hydroquinone (190mg in methanol, 14ml), buffered in phosphate to pH 6.8 at 30°C. (Sankaram et al. 1975; Kumari et al. 1982).

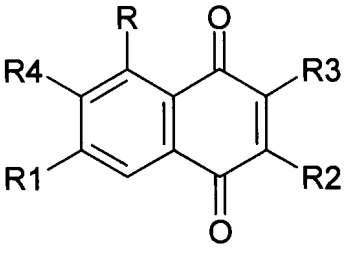


Plumbagin

It is believed that diospyrin, methyljuglone and related naphthoquinone derivatives are viable alternatives to conventional drugs in the treatment and control of tuberculosis in humans.

CLAIMS

1. A naphthoquinone derivative of Formula 1:

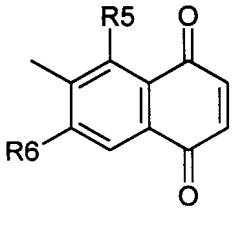


wherein,

R represents an OH group, methyl ether, ethyl ether or a similar ether;

R1 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

R2 and R3 each independently represent hydrogen or a group selected from:



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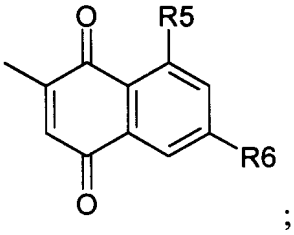
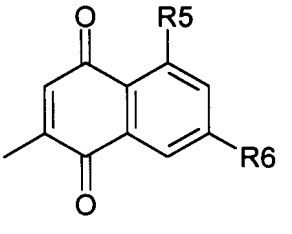
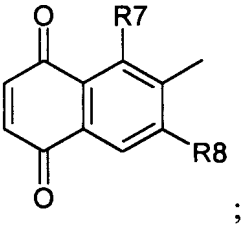


; or


wherein R5 represents an OH group, methyl ether, ethyl ether or a similar ether and R6 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

R4 represents hydrogen or a group selected from:



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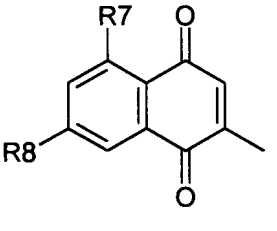
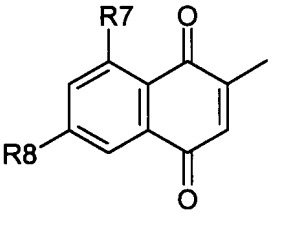
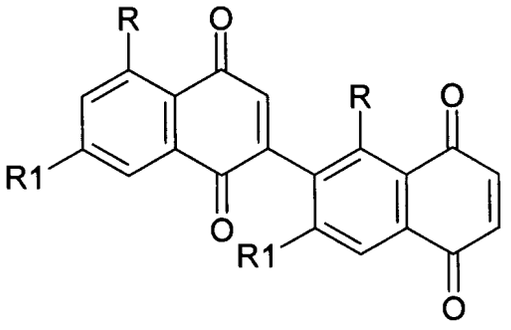


; or


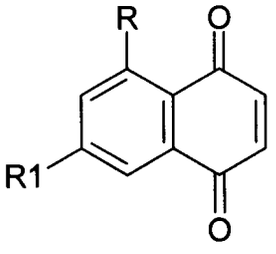
wherein R7 represents an OH group, methyl ether, ethyl ether or a similar ether and R8 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative; or

pharmaceutically acceptable salts thereof, for use in a method of treating and/or controlling tuberculosis in a patient caused by *Mycobacterium tuberculosis*.

2. A naphthoquinone derivative of Formula 1 according to claim 1 which is a compound of Formula 1a or Formula 1b:



Formula 1a



Formula 1b

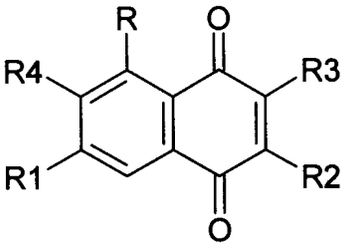
wherein R and R1 are as defined for Formula 1 in claim 1.

3. A naphthoquinone derivative according to claim 2 wherein R is an OH group.

4. A naphthoquinone derivative according to claim 2 or claim 3 wherein R1 is a CH_3 group.

5. A naphthoquinone derivative of Formula 1 according to claim 1 which is 5,5' dihydroxy 7,7' binaphthoquinone (diospyrin) or 5-hydroxy-7-methyl-1,4-naphtoquinone (methyljuglone), or a mixture thereof.

6. The use of a naphthoquinone derivative having the Formula 1:

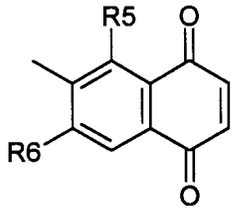


wherein,

R represents an OH group, methyl ether, ethyl ether or a similar ether;

R1 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

R2 and R3 each independently represent hydrogen or a group selected from:



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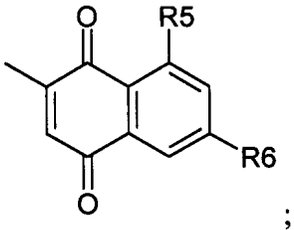
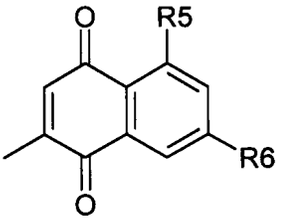
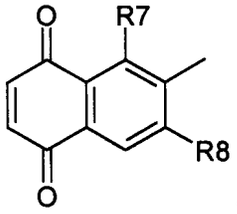


; or



wherein R5 represents an OH group, methyl ether, ethyl ether or a similar ether and R6 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

R4 represents hydrogen or a group selected from:



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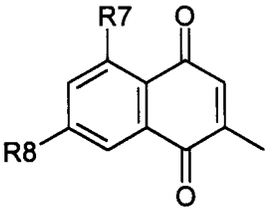

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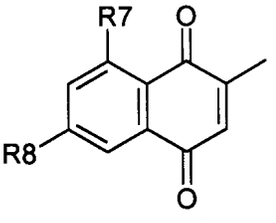
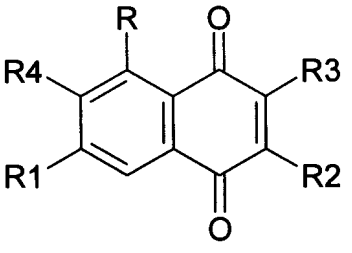


wherein R7 represents an OH group, methyl ether, ethyl ether or a similar ether and R8 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative; or pharmaceutically acceptable salts thereof, in the manufacture of a medicament for use

11. A method of treating and/or controlling tuberculosis caused by *Mycobacterium tuberculosis* comprising administering to a patient in need thereof an effective amount of a naphthoquinone derivative having the Formula 1:

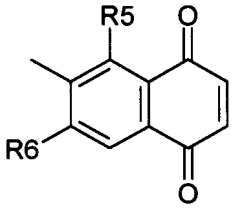


wherein,

R represents an OH group, methyl ether, ethyl ether or a similar ether;

R1 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

R2 and R3 each independently represent hydrogen or a group selected from:



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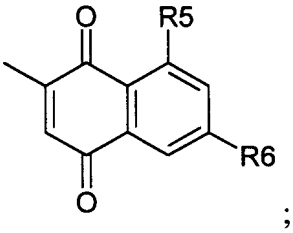
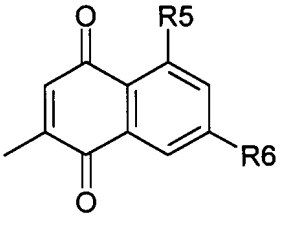
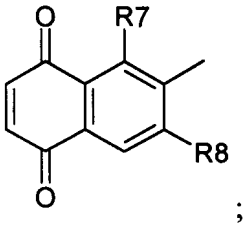


; or


wherein R5 represents an OH group, methyl ether, ethyl ether or a similar ether and R6 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

R4 represents hydrogen or a group selected from:



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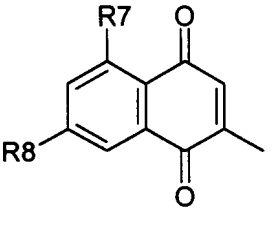
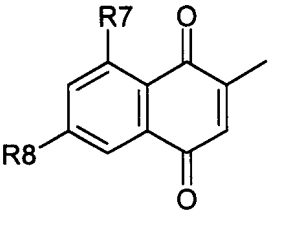
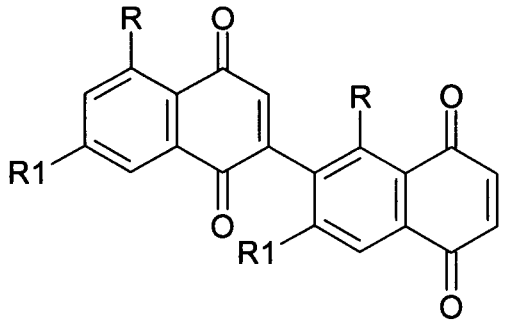


; or


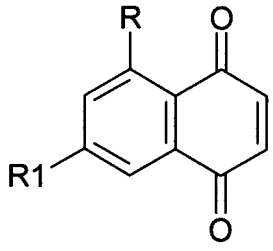
wherein R7 represents an OH group, methyl ether, ethyl ether or a similar ether and R8 represents a methyl, ethyl or similar aliphatic hydrocarbon derivative;

or pharmaceutically acceptable salts thereof.

12. A method according to claim 11 wherein the naphthoquinone derivative of Formula 1 is a compound of Formula 1a or Formula 1b:



Formula 1a



Formula 1b

wherein R and R1 are as defined for Formula 1 in claim 11.

13. A method according to claim 12 wherein R is an OH group.

14. A method according to claim 12 or claim 13 wherein R1 is a CH_3 group.

15. A method according to claim 11 wherein the naphthoquinone derivative of Formula 1 is 5,5' dihydroxy 7,7' binaphthoquinone (diospyrin) or 5-hydroxy-7-methyl-1,4-naphtoquinone (methyljuglone), or a mixture thereof.

16. A method according to claim 11 wherein the naphthoquinone derivative of Formula 1 is administered orally, intravenously, intramuscularly or transdermaly.

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