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(21) International Application Number: PCT/SE99/00732 (22) International Filing Date: 3 May 1999 (03.05.99) (30) Priority Data: 969/MAS/98 5 May 1998 (05.05.98) IN 9802118-1 15 June 1998 (15.06.98) SE ASTRAZENECA AB (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG (SE/SE); S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): BALGANESH, Meenakshi [IN/IN]; Astra Biochemicals Pvt Ltd., P.O. Box 8013, Malleswaram, Bangalore 560 080 (IN). ETHIRAJ, Kantharaj [IN/IN]; Astra Biochemicals Pvt Ltd., P.O. Box 8013, Malleswaram, Bangalore 560 080 (IN). GANGULY, Babita [IN/IN]; Astra Biochemicals Pvt Ltd., P.O. Box 8013, Malleswaram, Bangalore 560 080 (IN). JANAKI-RAMAN, Ramachandran [US/IN]; Astra Biochemicals Pvt Ltd., P.O. Box 8013, Malleswaram, Bangalore 560 080 (IN). KAUR, Parvinder [IN/IN]; Astra Biochemicals Pvt Ltd., P.O. Box 8013, Malleswaram, Bangalore 560 080 (IN). KAJIPAL, Rangarao [IN/IN]; Astra Biochemicals Pvt Ltd., P.O. Box 8013, Malleswaram, Bangalore 560 080 (IN). NANDAN, Santosh [IN/IN]; Astra Biochemicals		Pvt Ltd., P.O. Box 8013, Malleswaram, Bangalore 560 080 (IN). MURUGAPPAN, Ramanujulu [IN/IN]; Astra Biochemicals Pvt Ltd., P.O. Box 8013, Malleswaram, Bangalore 560 080 (IN). RAMACHANDRAN , Narayanan [IN/IN]; Astra Biochemicals Pvt Ltd., P.O. Box 8013, Malleswaram, Bangalore 560 080 (IN). VENKATARAMAN, Balasubramanian [IN/IN]; Astra Biochemicals Pvt Ltd., P.O. Box 8013, Malleswaram, Bangalore 560 080 (IN). RAMAMURTHY (74) Agent: ASTRA AKTIEBOLAG; Intellectual Property, Patents, S-151 85 Södertälje (SE). (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report.	
(54) Title: MYCOBACTERIAL INHIBITORS			
(I)			
(57) Abstract			
Use of a compound of general formula (I), wherein x is 0 or 1; R ¹ , R ² , R ³ and R ⁴ have the definitions given in the description, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for use in the treatment of a mycobacterial disease.			

MYCOBACTERIAL INHIBITORS

The present invention relates to compounds for use in the treatment of mycobacterial diseases, particularly those diseases caused by pathogenic mycobacteria such as
5 *Mycobacterium tuberculosis*, *M. bovis*, *M. avium* and *M. marinum*.

Tuberculosis is still a major public health problem affecting nearly all parts of the world. Based on skin test reactivity it has been estimated that about one-third of the world's population, i.e., 1.7 billion people, are infected with *Mycobacterium tuberculosis*.
10 Despite the availability of effective chemotherapies, it is responsible for three million deaths and from eight to ten million new cases annually and thus remains the leading cause of death world-wide due to a single infectious agent: 26% of all preventable deaths, 7% of all deaths. According to the World Health Organisation, 450,000 deaths per year due to tuberculosis in developing countries occur in children under fifteen years of age, and the
15 disease mostly affects the younger, more productive adults.

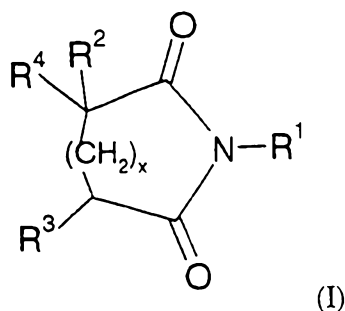
There are five front-line drugs known to be highly effective against *M. tuberculosis* and five second-line drugs that can be used when resistance to one or more of the front-line drugs is detected. The preferred mode of treatment for tuberculosis is the short course
20 chemotherapy in which there are two phases. The first phase consists of a daily regimen for two months with isoniazid (300 mg), rifampicin (600 mg), pyrazinamide (3 g) and ethambutol (1.5 g). The second phase or the continuation phase consists of a daily regimen for the next four months with isoniazid and rifampicin. Although infection with drug-sensitive strains of *M. tuberculosis* can be effectively cured with the short course
25 chemotherapy, the cure rate is very poor in most countries due to poor compliance which is reflective of the long duration of therapy.

The situation is further complicated by the rapid emergence of multi-drug resistant tuberculosis (MDR-TB) strains. For example, in certain populations, the incidence of
30 resistance to isoniazid is as high as 26% and the resistance to rifampicin is about 15%.

Prior to 1984, about 10% of tubercle bacilli isolated from patients in the United States were resistant to at least one single mycobacterial drug. By 1984, this figure had risen to 52%, of which over half (32%) were resistant to more than one drug (MDR-TB). Ten percent of the recorded MDR-TB cases have occurred in previously healthy people whose mortality rate - 70 to 90% - has been nearly the same as that of immunosuppressed individuals with MDR-TB. The number of cases of MDR-TB has doubled since 1984 and in many of them the tubercle bacilli are resistant to both isoniazid and rifampicin. The median interval between diagnosis of MDR-TB and death is only four weeks and therefore MDR-TB demands a shorter response time between diagnosis and appropriate commencement of treatment. However, MDR-TB is difficult to treat as such since most patients do not respond very well to the second-line drugs and the cost of alternate treatment procedures, including hospitalisation and possibly surgery, increases the cost to as much as ten times the cost of traditional treatment.

Thus, there is an urgent medical need to identify new drugs with significant therapeutic activity against single- or multiple-drug resistant strains of *M. tuberculosis* and with pharmacokinetic properties that permit reduced dosing which will in turn encourage better compliance.

In accordance with the present invention, there is therefore provided the use of a compound of general formula



wherein x is 0 or 1;

R¹ represents a hydrogen atom, or a C₁-C₂₀ alkyl or myrtanyl group, or a phenyl or benzyl group optionally substituted in the aromatic ring by one or more substituents selected from

amino, nitro, hydroxyl, carboxyl, halogen, trifluoromethyl, C₁-C₆ alkyl, C₁-C₆ alkoxy,

C₁-C₆ alkoxy carbonyl, piperidyl, piperazinyl and morpholinyl, or a group

(CH₂)_yCONH-R⁵ where y is an integer from 1 to 6 and R⁵ represents a phenyl group

optionally substituted by one or more substituents selected from amino, nitro, hydroxyl,

5 carboxyl, halogen, trifluoromethyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkoxy carbonyl,

piperidyl, piperazinyl and morpholinyl; and

either

R² represents a hydrogen atom or a C₁-C₆ alkyl group, or R² together with R³ represents a carbon-carbon single bond provided that x is 0, or R² together with R⁴ represents a group

10 =CH₂,

R³ represents a hydrogen atom or is linked to R² as defined above, and

R⁴ represents a hydrogen atom or a C₁-C₆ alkyl group; or a C₁-C₁₀ alkylamino group

optionally substituted by a di(C₁-C₆ alkyl)amino substituent group; or an anilino group

optionally substituted in the aromatic ring by one or more substituents selected from

15 amino, nitro, hydroxyl, carboxyl, halogen, trifluoromethyl, C₁-C₆ alkyl, C₁-C₆ alkoxy,

C₁-C₆ alkoxy carbonyl, piperidyl, piperazinyl and morpholinyl; or a group -SCH₂CH₂OH,

-SCH₂CH₂NH₂, -SCH₂CH₂(NH₂)CO₂H or -SCH₂CH₂NHCO-R⁶ where R⁶ represents a

C₁-C₁₀ alkyl or C₃-C₆ cycloalkyl group, or a phenyl group optionally substituted by one or

more substituents selected from amino, nitro, hydroxyl, carboxyl, halogen, trifluoromethyl,

20 C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkoxy carbonyl, piperidyl, piperazinyl and morpholinyl;

or R⁴ is linked to R² as defined above;

or

R², R³ and R⁴ together represent a phenyl group;

with the provisos that:

25 (i) R¹, R², R³ and R⁴ do not each simultaneously represent a hydrogen atom,

(ii) when x is 0, R¹ represents a 4-fluorophenyl group and R⁴ represents a hydrogen atom, then R² and R³ do not together represent a carbon-carbon single bond, and

(iii) when x is 0, R¹ represents a 4-fluorophenyl group and R² and R³ both represent a hydrogen atom, then R⁴ does not represent an anilino, 4-chloroanilino, 2,6-dichloroanilino,

30 3,4-dichloroanilino, 2,5-dichloroanilino, 3-chloro-4-fluoroanilino or 4-fluoroanilino group;

or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for use in the treatment of a mycobacterial disease, in particular tuberculosis.

In the context of the present specification, unless otherwise stated, an alkyl (substituent) group or an alkyl moiety in an alkoxy or alkoxycarbonyl substituent group may be linear or branched.

Preferably R^1 in formula (I) represents a hydrogen atom, or a C_1 - C_{15} , more preferably C_1 - C_{10} , alkyl or myrtanyl group, or a phenyl or benzyl group optionally substituted in the aromatic ring by one to four, particularly one or two, substituents selected from amino, nitro, hydroxyl, carboxyl, halogen (e.g. fluorine, chlorine or bromine), trifluoromethyl, C_1 - C_4 alkyl (e.g. methyl, ethyl, propyl, isopropyl or butyl), C_1 - C_4 alkoxy (e.g. methoxy, ethoxy, propoxy, or butoxy), C_1 - C_4 alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl or butoxycarbonyl), piperidyl, piperazinyl and morpholinyl, or a group $(CH_2)_yCONH-R^5$ where y is an integer 1, 2, 3 or 4 and R^5 represents a phenyl group optionally substituted by one to four, particularly one or two, substituents selected from amino, nitro, hydroxyl, carboxyl, halogen (e.g. fluorine, chlorine or bromine), trifluoromethyl, C_1 - C_4 alkyl (e.g. methyl, ethyl, propyl, isopropyl or butyl), C_1 - C_4 alkoxy (e.g. methoxy, ethoxy, propoxy, or butoxy), C_1 - C_4 alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl or butoxycarbonyl), piperidyl, piperazinyl and morpholinyl.

The group R^1 especially represents a hydrogen atom, or a C_4 - C_{10} alkyl (e.g. butyl, pentyl, hexyl, heptyl, octyl, nonyl or decyl) or myrtanyl group, or a phenyl group substituted by a piperidyl substituent group, or a group $(CH_2)_yCONH-R^5$ where y is 1 or 2 and R^5 represents a phenyl group substituted by a piperidyl substituent group.

Preferably R^2 represents a hydrogen atom or a C_1 - C_4 alkyl, particularly methyl, group, or R^2 together with R^3 represents a carbon-carbon single bond provided that x is 0, or R^2 together with R^4 represents a group $=CH_2$.

5 R^4 preferably represents a hydrogen atom or a C_1 - C_4 alkyl group (e.g. methyl, ethyl, propyl or butyl); or a C_2 - C_{10} alkylamino group optionally substituted by a di(C_1 - C_6 alkyl)amino, especially di(C_1 - C_4 alkyl)amino, substituent group; or an anilino group optionally substituted in the aromatic ring by one to four, particularly one or two, substituents selected from amino, nitro, hydroxyl, carboxyl, halogen (e.g. fluorine, chlorine
10 or bromine), trifluoromethyl, C_1 - C_4 alkyl (e.g. methyl, ethyl, propyl, isopropyl or butyl), C_1 - C_4 alkoxy (e.g. methoxy, ethoxy, propoxy, or butoxy), C_1 - C_4 alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl or butoxycarbonyl), piperidyl, piperazinyl and morpholinyl; or a group $-SCH_2CH_2OH$, $-SCH_2CH_2NH_2$, $-SCH_2CH_2(NH_2)CO_2H$ or $-SCH_2CH_2NHCO-R^6$ where R^6 represents a C_5 - C_{10} alkyl or
15 C_3 - C_6 cycloalkyl group, or a phenyl group optionally substituted by one or more substituents selected from amino, nitro, hydroxyl, carboxyl, halogen (e.g. fluorine, chlorine or bromine), trifluoromethyl, C_1 - C_4 alkyl (e.g. methyl, ethyl, propyl, isopropyl or butyl), C_3 - C_6 alkoxy (e.g. propoxy, butoxy, pentoxy or hexyloxy), C_1 - C_4 alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl or butoxycarbonyl), piperidyl,
20 piperazinyl and morpholinyl; or R^4 is linked to R^2 as defined above.

It is preferred that R^4 represents a hydrogen atom, a methyl or ethyl group, a C_2 - C_{10} alkylamino group optionally substituted by a di(C_2 - C_4 alkyl)amino substituent group, an anilino group substituted by a piperidyl substituent group, $-SCH_2CH_2OH$, $-SCH_2CH_2NH_2$,
25 $-SCH_2CH_2(NH_2)CO_2H$, $-SCH_2CH_2NHCO-R^6$ where R^6 represents a C_7 alkyl, cyclopropyl, cyclopentyl or cyclohexyl group or a phenyl group substituted by a nitro, C_1 - C_4 alkyl or C_3 - C_6 alkoxy substituent group, or R^4 is linked to R^2 as defined above.

Particularly preferred compounds of formula (I) include:

30 1-Decylpyrrolidine-2,5-dione,

- 1-Nonylpiperidine-2,6-dione,
2-((6,6-Dimethylbicyclo[3,1,1]hept-2-yl)methyl)isoindole-1,3-dione,
1-((6,6-Dimethylbicyclo[3,1,1]hept-3-yl)methyl)-3-methyl-3-pyrroline-2,5-dione,
3-Methyl-1-nonyl-3-pyrroline-2,5-dione,
5 3-Methylene-1-nonylpyrrolidine-2,5-dione,
3-Methyl-1-octyl-3-pyrroline-2,5-dione,
3-Methylene-1-octylpyrrolidine-2,5-dione,
(4-(3-methyl-2,5-dioxo-3-pyrrolinyl)phenyl)piperidine,
1-Octyl-3-pyrroline-2,5-dione,
10 1-Decyl-3-pyrroline-2,5-dione,
1-Nonyl-3-pyrroline-2,5-dione,
1-Butyl-3-pyrroline-2,5-dione,
1-Hexyl-3-pyrroline-2,5-dione,
1-(4-Piperidylphenyl)-3-pyrroline-2,5-dione,
15 1-(Octyl-3-(octylamino)-pyrrolidine-2,5-dione,
1-Decyl-3-(decylamino)pyrrolidine-2,5-dione,
3-(Octylamino)-3-pyrrolidine-2,5-dione,
3-(Heptylamino)-1-nonyl pyrrolidine-2,5-dione,
1-Nonyl-3-(nonylamino) pyrrolidine-2,5-dione,
20 1-Nonyl-3-(octylamino) pyrrolidine-2,5-dione,
2-Amino-3-(3-methyl-1-nonyl-2,5-dioxo-pyrrolidin-3-ylthio)propanoic acid,
2-Amino-3-(3-methyl-1-octyl-2,5-dioxo-pyrrolidin-3-ylthio)propanoic acid,
2-Amino-3-(1-octyl-2,5-dioxo-pyrrolidin-3-ylthio)propanoic acid,
3-Methyl-1-octylpyrrolidine-2,5-dione,
25 3-Methyl-1-nonylpyrrolidine-2,5-dione,
2-(2,5-Dioxopyrrolidinyl)-N-(4-piperidylphenyl)ethanamide,
2-(2,5-Dioxopyrrolidinyl)-N-(4-piperidylphenyl)propanamide,
3-Ethyl-1-nonylpyrrolidine-2,5-dione,
3-(2-Aminoethylthio)-1-nonylpyrrolidine-2,5-dione,
30 2-Ethyl-N-(2-(1-nonyl-2,5-dioxopyrrolidin-3-ylthio)ethyl)hexanamide,

Cyclopropyl-N-(2-(1-nonyl-2,5-dioxopyrrolidin-3-ylthio)ethyl)formamide,
 (4-Butylphenyl)-N-(2-(1-nonyl-2,5-dioxopyrrolidin-3-ylthio)ethyl)formamide,
 (4-Hexyloxyphenyl)-N-(2-(1-nonyl-2,5-dioxopyrrolidin-3-ylthio)ethyl)formamide,
 (4-Methylphenyl)-N-(2-(1-nonyl-2,5-dioxopyrrolidin-3-ylthio)ethyl)formamide,
 5 (4-(tert-Butyl)phenyl)-N-(2-(1-nonyl-2,5-dioxopyrrolidin-3-ylthio)ethyl)formamide,
 Cyclopentyl-N-(2-(1-nonyl-2,5-dioxopyrrolidin-3-ylthio)ethyl)formamide, ethane,
 Cyclohexyl-N-(2-(1-nonyl-2,5-dioxopyrrolidin-3-ylthio)ethyl)formamide,
 (4-Nitrophenyl)-N-(2-(1-nonyl-2,5-dioxopyrrolidin-3-ylthio)ethyl)formamide,
 3-((2-(Dibutylamino)ethyl)amino)-1-nonylpyrrolidine-2,5-dione,
 10 3-((2-(Diethylamino)ethyl)amino)-1-nonylpyrrolidine-2,5-dione,
 1-Nonyl-3-((4-piperidinylphenyl)amino)pyrrolidine-2,5-dione,
 3-(Hydroxyethylthio)-3-methyl-1-nonylpyrrolidine-2,5-dione,
 3-(2-Aminoethylthio)-3-methyl-1-nonylpyrrolidine-2,5-dione, and
 3-Methyl-1-octyl-3-(octylamino)pyrrolidine-2,5-dione.

15

The compounds of formula (I) are known compounds or may be prepared using
 techniques conventional in the art. The compounds of formula (I) may, if desired, be
 converted to a pharmaceutically-acceptable salt or solvate thereof, preferably an acid
 addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate,
 20 tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate, or an alkali metal salt
 such as a sodium or potassium salt.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It
 will be understood that the invention encompasses all geometric and optical isomers of the
 25 compounds of formula (I) and mixtures thereof including racemates. Tautomers and
 mixtures thereof also form an aspect of the present invention.

The compounds of formula (I) are advantageous in that they possess bactericidal
 activity against mycobacteria, particularly pathogenic mycobacteria such as *Mycobacterium*
 30 *tuberculosis*, *M. bovis*, *M. avium* and *M. marinum*.

Accordingly, in another aspect, the invention provides a method of treating a patient suffering from, or at risk of, a mycobacterial disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a

5 pharmaceutically-acceptable salt or solvate thereof, as defined above.

The compounds of formula (I) and pharmaceutically-acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active
10 ingredient) is in association with a pharmaceutically-acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.10 to 70 %w, of active ingredient, and, from 1 to 99.95 %w, more preferably from 30 to 99.90 %w, of a pharmaceutically-acceptable adjuvant, diluent or carrier, all percentages by weight being
15 based on total composition. The pharmaceutical composition may additionally contain another anti-tubercular agent and/or various other ingredients known in the art, for example, a lubricant, stabilising agent, buffering agent, emulsifying agent, viscosity-regulating agent, surfactant, preservative, flavouring or colorant.

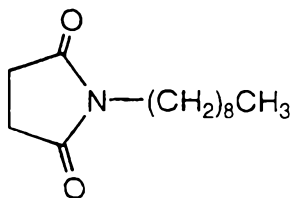
20 The daily dosage of formula (I) compound administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the mycobacterial disease indicated. However, in general, satisfactory results will be obtained when the compound of formula (I) is administered at a daily dosage not exceeding 1 g, e.g. in the range from 10 to 50 mg/kg body weight.

25 The compounds of formula (I) may be administered systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions.

The present invention will now be further explained with reference to the following illustrative examples.

Example 1

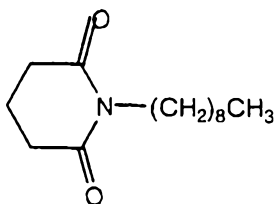
5 1-Decylpyrrolidine-2,5-dione



Succinimide (0.1 M) dissolved in dry dimethylformamide was treated with sodium hydride
10 (0.1 M) at a temperature of 0° C. Nonyl bromide (0.1 M) was then added and the reaction mixture was stirred at room temperature for three hours. The reaction mixture was concentrated *in vacuo* and the residue extracted into ethyl acetate. The ethyl acetate layer was washed with water, dried over sodium sulphate and concentrated *in vacuo*. The residue obtained was chromatographed over silica gel to afford the desired product.
15 ¹HNMR: δ 0.75 (3H, t), 1.10-1.20 (12H, m), 1.35-1.45 (2H, m), 2.55 (4H, s), 3.35 (2H, dd)

Example 2

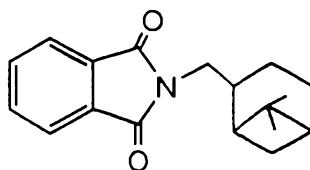
1-Nonylpiperidine-2,6-dione



20

The procedure of Example 1 was repeated except that glutarimide replaced the succinimide.

¹HNMR: δ 0.9 (3H, t), 1.2-1.3 (12H, m), 1.4-1.5 (2H, m), 1.9 (2H, p), 2.6 (4H, t),
25 3.7 (2H, dd)

Example 3**2-(((6,6-Dimethylbicyclo[3,1,1]hept-2-yl)methyl)isoindole-1,3-dione**

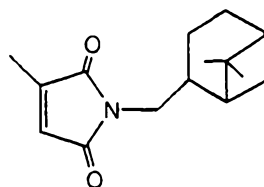
5

A solution of phthalic anhydride (0.1 M) in pyridine (20 ml) was treated with (-)-cis-myrtanylamine (0.1 M). The reaction mixture was heated to 90°C for six hours. The reaction mixture was then concentrated *in vacuo* and the residue was extracted into ethyl acetate. The ethyl acetate layer was washed with water and with cold aqueous hydrochloric acid, then dried over sodium sulphate and finally concentrated *in vacuo*. The residue

10

obtained was chromatographed over silica gel to afford the desired product.
¹HNMR: δ 0.85 (1H, d), 1.2 (6H, d), 1.5- 1.65 (2H, m), 1.80-2.05 (4H, m), 2.27-2.35 (1H, m), 2.45-2.60 (1H, m), 3.60-3.75 (2H, m), 7.65-7.70 (2H, m), 7.78-7.85 (2H, m)

15

Example 4**1-(((6,6-Dimethylbicyclo[3,1,1]hept-3-yl)methyl)-3-methyl-3-pyrroline-2,5-dione**

20

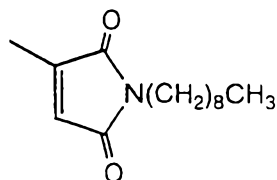
A solution of citraconic anhydride (0.1 M) in pyridine (20 ml) was treated with (-)-cis-myrtanylamine (0.1 M). The reaction mixture was heated to 90°C for six hours. The reaction mixture was then concentrated *in vacuo* and the residue was extracted into ethyl acetate. The ethyl acetate layer was washed with water and with cold aqueous hydrochloric acid, then dried over sodium sulphate and finally concentrated *in vacuo*. The residue

25

^1H NMR: δ 0.65(1H, d), 1.0 (6H, d), 1.25-1.37 (1H, m), 1.55-1.80 (5H, m), 1.9 (3H, s), 2.08-2.25 (2H, m), 3.15-3.40 (2H, m), 6.1 (1H, s)

Example 5

5 3-Methyl-1-nonyl-3-pyrroline-2,5-dione

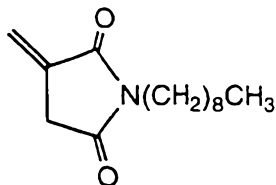


A solution of citraconic anhydride (0.1 M) in pyridine (20 ml) was treated with nonylamine
10 (0.1 M). The reaction mixture was heated to 90°C for six hours. The reaction mixture was then concentrated *in vacuo* and the residue was extracted into ethyl acetate. The ethyl acetate layer was washed with water and with cold aqueous hydrochloric acid, then dried over sodium sulphate and finally concentrated *in vacuo*. The residue obtained was chromatographed over silica gel to afford the desired product.

15 ^1H NMR: δ 0.8 (3H, t), 1.15-1.30 (12H, m), 1.4-1.55 (2H, m), 2.05 (3H, s), 3.4 (2H, dd), 6.25 (1H, s)

Example 6

20 3-Methylene-1-nonylpyrrolidine-2,5-dione

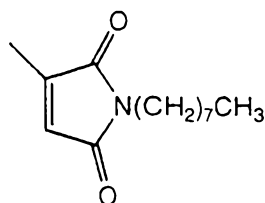


A solution of itaconic anhydride (0.1 M) in pyridine (20 ml) was treated with nonylamine
25 (0.1 M). The reaction mixture was heated to 90°C for six hours. The reaction mixture was then concentrated *in vacuo* and the residue was extracted into ethyl acetate. The ethyl

acetate layer was washed with water and with cold aqueous hydrochloric acid, then dried over sodium sulphate and finally concentrated *in vacuo*. The residue obtained was chromatographed over silica gel to afford the desired product.

5 **Example 7**

3-Methyl-1-octyl-3-pyrroline-2,5-dione

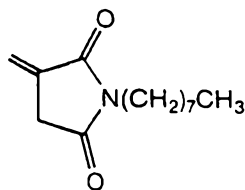


10 A solution of citraconic anhydride (0.1 M) in pyridine (20 ml) was treated with octylamine (0.1 M). The reaction mixture was heated to 90°C for six hours. The reaction mixture was then concentrated *in vacuo* and the residue was extracted into ethyl acetate. The ethyl acetate layer was washed with water and with cold aqueous hydrochloric acid, then dried over sodium sulphate and finally concentrated *in vacuo*. The residue obtained was
15 chromatographed over silica gel to afford the desired product.

¹HNMR: δ 0.85 (3H, t), 1.15-1.30 (12H, m), 1.45-1.60 (2H, m), 2.05 (2H, s),
3.45 (2H, dd), 6.27 (1H, s)

Example 8

20 **3-Methylene-1-octylpyrrolidine-2,5-dione**



A solution of itaconic anhydride (0.1 M) in pyridine (20 ml) was treated with octylamine
25 (0.1 M). The reaction mixture was heated to 90°C for six hours. The reaction mixture was

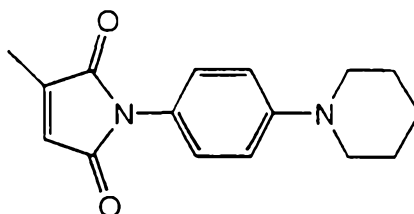
then concentrated *in vacuo* and the residue was extracted into ethyl acetate. The ethyl acetate layer was washed with water and with cold aqueous hydrochloric acid, then dried over sodium sulphate and finally concentrated *in vacuo*. The residue obtained was chromatographed over silica gel to afford the desired product.

5 $^1\text{H NMR}$: δ 0.85 (3H, t), 1.20-1.35 (10H, m), 1.50-1.65 (2H, m), 3.3 (2H, s), 3.55 (2H, dd), 5.6 (1H, s), 6.35 (1H, s)

Example 9

(4-(3-methyl-2,5-dioxo-3-pyrrolinyl)phenyl)piperidine

10



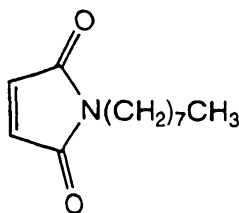
A solution of citraconic anhydride (0.1 M) in pyridine (20 ml) was treated with 4-(1-piperidyl)aniline (0.1 M). The reaction mixture was heated to 90°C for six hours. The reaction mixture was then concentrated *in vacuo* and the residue was extracted into ethyl acetate. The ethyl acetate layer was washed with water and with cold aqueous hydrochloric acid, then dried over sodium sulphate and finally concentrated *in vacuo*. The residue obtained was chromatographed over silica gel to afford the desired product.

15 $^1\text{H NMR}$: δ 1.5-1.75 (6H, m), 2.12 (3H, s), 3.18 (4H, t), 6.4 (1H, br s), 6.95 (2H, d), 7.1 (2H, d)

20

Example 10

1-Octyl-3-pyrroline-2,5-dione



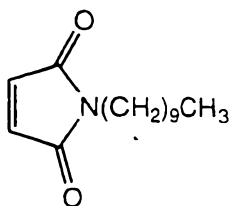
To a solution of maleic anhydride (0.1 M) in acetone (150 ml), maintained at 0 °C, was added octylamine (0.1 M) dropwise over a 15 minute period. The reaction mixture was stirred for an additional period of one hour, and the white crystalline N-octyl maleimic acid
5 that separated was filtered and dried.

A mixture of N-octyl maleimic acid (0.1 M) and sodium acetate (0.1 M) in acetic anhydride (150 ml) was heated on a steam bath for two hours. The acetic anhydride was removed under vacuum and the residual liquid product was taken up in ethyl acetate,
10 washed with water, dried with sodium sulfate and concentrated to give a viscous liquid. Purification by flash chromatography (10% ethyl acetate in petroleum ether) yielded the desired product.

¹HNMR: δ 0.82 (3H, t), 1.15-1.4 (10H, m), 1.48-1.6 (2H, m), 3.45 (2H, dd), 6.65 (2H, s)

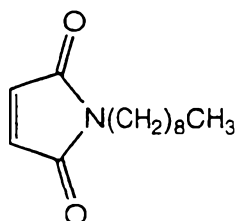
15 **Example 11**

1-Decyl-3-pyrroline-2,5-dione



20 The procedure of Example 10 was repeated using decylamine in place of octylamine.

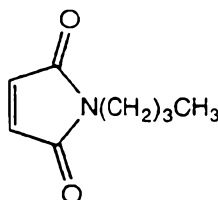
¹HNMR: δ 0.85 (3H, t), 1.15-1.30 (14H, m), 1.50-1.60 (2H, m), 3.47 (2H, dd), 6.65 (2H, s)

Example 12**1-Nonyl-3-pyrroline-2,5-dione**

5

The procedure of Example 10 was repeated using nonylamine in place of octylamine.

^1H NMR: δ 0.85 (3H, t), 1.15-1.35 (12H, m), 1.5-1.6 (2H, m), 3.45 (2H, t), 6.65 (1H, s)

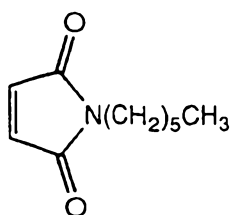
Example 13**1-Butyl-3-pyrroline-2,5-dione**

10

The procedure of Example 10 was repeated using butylamine in place of octylamine.

^1H NMR: δ 0.9 (3H, t), 1.25 (2H, m), 1.6 (2H, m), 3.5 (2H, dd), 6.65 (2H, s)

15

Example 14**1-Hexyl-3-pyrroline-2,5-dione**

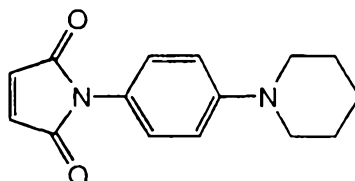
20

The procedure of Example 10 was repeated using hexylamine in place of octylamine.

^1H NMR: δ 0.85 (3H, t), 1.2-1.35 (6H, m), 1.45-1.60 (2H, m), 3.45 (2H, dd), 6.65 (2H, s)

Example 15

1-(4-Piperidylphenyl)-3-pyrrolone-2,5-dione

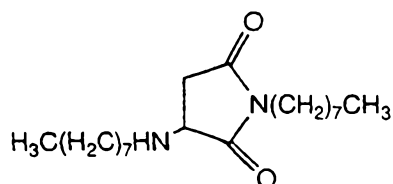


The procedure of Example 10 was repeated using 4-(piperidyl)aniline in place of octylamine.

^1H NMR: δ 1.5-1.65 (6H, m), 3.0-3.12 (4H, m), 6.80 (2H, s), 6.95 (2H, d), 7.1 (2H, d)

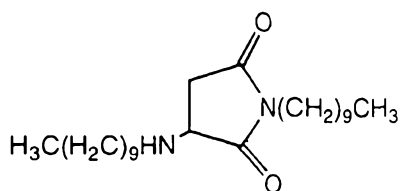
Example 16

1-(Octyl-3-(octylamino)-pyrrolidine-2,5-dione



A mixture of N-octyl maleimide (0.01 M) prepared as described in Example 10 above, octylamine (0.01 M), triethylamine [catalytic, 0.1 equivalent] in acetonitrile (25 ml) was stirred for 24 hours at room temperature. Acetonitrile was removed under vacuum to leave a residual liquid product which was flash chromatographed (25% ethyl acetate in petroleum ether) to yield a white solid as the desired product.

^1H NMR: δ 0.8 (6H, t), 1.15-1.35 (20H, m), 1.45-1.65 (4H, m), 1.7 (1H, s), 2.45-2.65 (3H, m), 2.88 (1H, dd), 3.25 (2H, dd), 3.7 (1H, dd)

Example 17**1-Decyl-3-(decylamino)pyrrolidine-2,5-dione**

5

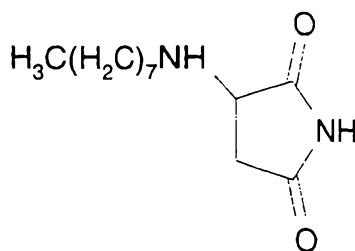
A mixture of N-decyl maleimide (0.01 M) prepared as described in Example 11 above, decylamine (0.01 M), triethylamine [catalytic, 0.1 equivalent] in acetonitrile (25 ml) was stirred for 24 hours at room temperature. Acetonitrile was removed under vacuum to leave a residual liquid product which was flash chromatographed (25% ethyl acetate in petroleum ether) to yield a white solid as the desired product.

10

^1H NMR: δ 0.8 (6H, t), 1.15-1.35 (24H, m), 1.45-1.65 (4H, m), 1.7 (1H, s), 2.45-2.65 (3H, m), 2.88 (1H, dd), 3.25 (2H, dd), 3.71 (1H, dd)

Example 18**3-(Octylamino)-3-pyrrolidine-2,5-dione**

15



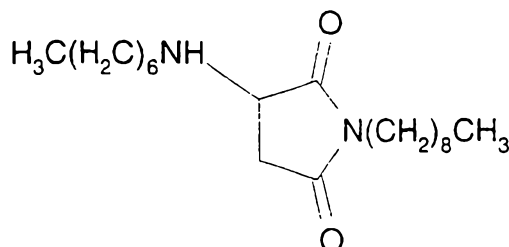
20

A mixture of maleimide (0.01 M), octylamine (0.01 M), triethylamine [catalytic, 0.1 equivalent] in acetonitrile (25 ml) was stirred for 24 hours at room temperature. Acetonitrile was removed under vacuum to leave a residual liquid product which was flash chromatographed (25% ethyl acetate in petroleum ether) to yield a white solid as the desired product.

¹HNMR: δ 0.85 (3H, t), 1.15-1.35 (10H, m), 1.42-1.55 (2H, m), 2.50-2.70 (3H, m), 2.90 (1H, dd), 2.80 (1H, dd)

Example 19

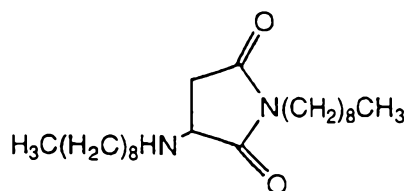
5 3-(Heptylamino)-1-nonylpyrrolidine-2,5-dione



A mixture of N-nonyl maleimide (0.01 M) prepared as described in Example 12 above,
10 heptylamine (0.01 M), triethylamine [catalytic, 0.1 equivalent] in acetonitrile (25 ml) was stirred for 24 hours at room temperature. Acetonitrile was removed under vacuum to leave a residual liquid product which was flash chromatographed (25% ethyl acetate in petroleum ether) to yield a white solid as the desired product.

15 Example 20

1-Nonyl-3-(nonylamino)pyrrolidine-2,5-dione

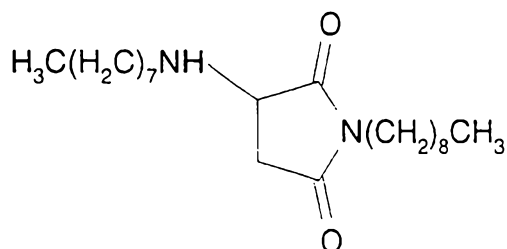


20 A mixture of N-nonyl maleimide (0.01 M) prepared as described in Example 12 above, nonylamine (0.01 M), triethylamine [catalytic, 0.1 equivalent] in acetonitrile (25 ml) was stirred for 24 hours at room temperature. Acetonitrile was removed under vacuum to leave a residual liquid product which was flash chromatographed (25% ethyl acetate in petroleum ether) to yield a white solid as the desired product.

^1H NMR: δ 0.85 (6H, t), 1.15-1.38 (24H, m), 1.40-1.55 (4H, m), 1.70 (1H, br s), 2.45-2.70 (3H, m), 2.85 (1H, dd), 3.45 (2H, dd), 3.70 (1H, dd)

Example 21

5 1-Nonyl-3-(octylamino)pyrrolidine-2,5-dione

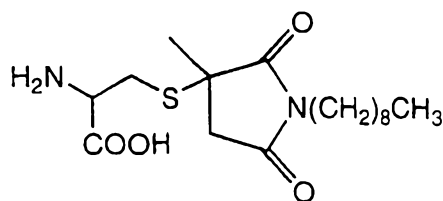


A mixture of N-nonyl maleimide (0.01 M) prepared as described in Example 12 above,
 10 octylamine (0.01 M), triethylamine [catalytic, 0.1 equivalent] in acetonitrile (25 ml) was stirred for 24 hours at room temperature. Acetonitrile was removed under vacuum to leave a residual liquid product which was flash chromatographed (25% ethyl acetate in petroleum ether) to yield a white solid as the desired product.

^1H NMR: δ 0.8-0.9 (6H, m), 1.18-1.30 (20H, m), 1.35-1.60 (4H, m), 2.5-2.6 (3H, m),
 15 2.7-3.0 (5H, m), 3.45 (2H, dd)

Example 22

2-Amino-3-(3-methyl-1-nonyl-2,5-dioxo-pyrrolidin-3-ylthio)propanoic acid

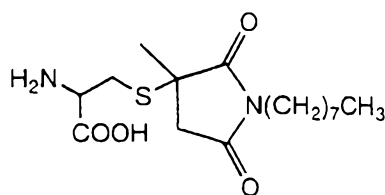


20

DL-Cysteine (0.0067 M) was dissolved in potassium acetate (50 mM) and the solution obtained was added slowly to N-nonyl itaconimide (0.004 M) prepared as described in Example 6 above. The reaction mixture was then dissolved in dimethylformamide with

gentle stirring and triethylamine was added. Stirring was continued for a further four hours at room temperature. The progress of the reaction was monitored by reverse phase thin layer chromatography using 75% methanol in water system. The formation of the desired product was detected by the ninhydrin reaction.

5

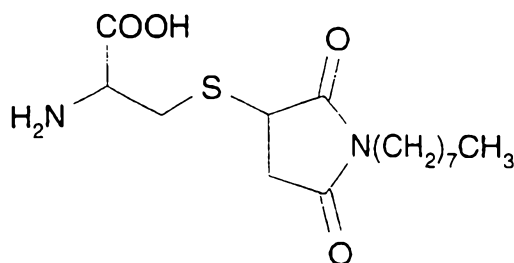
Example 23**2-Amino-3-(3-methyl-1-octyl-2,5-dioxo-pyrrolidin-3-ylthio)propanoic acid**

10

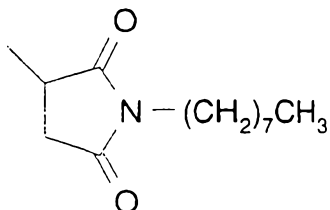
The procedure according to Example 22 was repeated using the imide of Example 8 above.

¹HNMR: δ 0.85 (3H, t), 1.15-1.32 (10H, m), 1.3 (3H, d), 1.4-1.52 (2H, m), 2.65-2.85 (2H, m), 3.00-3.30 (2H, m), 3.42 (2H, t), 3.85 (1H, dd)

15

Example 24**2-Amino-3-(1-octyl-2,5-dioxo-pyrrolidin-3-ylthio)propanoic acid**

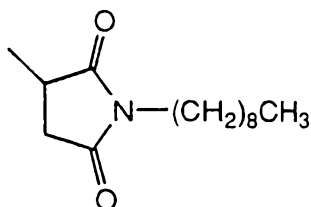
20 The procedure according to Example 22 was repeated using the imide of Example 10 above.

Example 25**3-Methyl-1-octylpyrrolidine-2,5-dione**

5

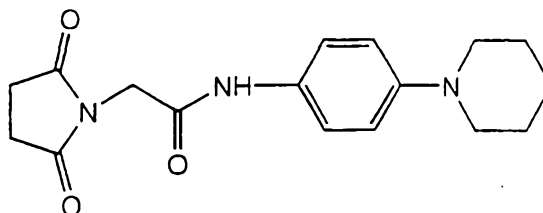
10% Palladium on carbon catalyst (5 wt%) was added to a stirred solution of N-nonyl citraconimide (0.02 M) prepared as described in Example 5 above in methanol (100 ml). Hydrogen gas was bubbled through this solution for three hours. The solution was then filtered over celite and concentrated *in vacuo*. Chromatography over silica gel gave the
10 desired product.

¹HNMR: δ 0.85 (3H, t), 1.15-1.3 (10H, m), 1.3 (3H, d), 1.47-1.60 (2H, m), 2.28 (1H, dd),
2.77-2.95 (2H, m), 3.45 (2H, dd)

Example 2615 **3-Methyl-1-nonylpyrrolidine-2,5-dione**

The procedure of Example 25 was repeated using instead N-octyl citraconimide prepared
20 as described in Example 7 above.

¹HNMR: δ 0.85 (3H, t), 1.15-1.3 (12H, m), 1.3 (3H, d), 1.47-1.60 (2H, m), 2.28 (1H, dd),
2.77-2.95 (2H, m), 3.45 (2H, dd)

Example 27**2-(2,5-Dioxopiperidinyl)-N-(4-piperidylphenyl)ethanamide**

5

A solution of glycine benzyl ester hydrochloride (0.1 mM) in diethyl ether was treated with triethylamine (0.11 mM) and then with succinic anhydride (0.11 mM). The reaction mixture was stirred at room temperature for two hours and then partitioned between 10% aqueous hydrochloric acid and ethyl acetate. The ethyl acetate layer was separated, dried over sodium sulphate and concentrated *in vacuo* to afford a yellow oil.

10

This oil was dissolved in acetic anhydride (20 ml) containing sodium acetate (0.1 mM) and heated to 90°C for three hours. The reaction mixture was cooled, poured into water and extracted thrice with ethyl acetate. The ethyl acetate layer was separated, dried over sodium sulphate and concentrated *in vacuo* to afford a yellow oil. Chromatography over silica gel gave the succinoyl glycine benzyl ester.

15

10% Palladium on carbon catalyst (5 wt%) was added to a stirred solution of the succinoyl benzyl ester (0.009 M) in methanol (50 ml). Hydrogen gas was bubbled through this solution for three hours. The solution was then filtered over celite and concentrated *in vacuo* to give the corresponding acid as a white solid.

20

A solution of the acid (0.1 mM) in dry dichloromethane was cooled to 0°C and treated with dimethylformamide (0.1 mM) followed by oxalyl chloride (0.1 mM). The cooling bath was removed and the reaction mixture was refluxed for one hour. 4-(piperidyl)aniline (0.1 mM) was then added to the reaction mixture and this solution was stirred for two hours at room temperature. The reaction was then diluted with dichloromethane, washed

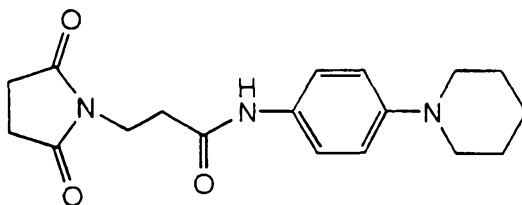
25

with saturated aqueous sodium bicarbonate and water. The organic layer was dried over sodium sulphate and concentrated *in vacuo*. The residue obtained was chromatographed to afford the desired product.

¹HNMR: δ 1.5-1.7 (6H, m), 2.8 (4H, s), 3.10 (4H, t), 4.3 (2H, s), 6.85 (2H, d),
5 7.30 (2H, d), 7.42 (1H, br s)

Example 28

2-(2,5-Dioxopyrrolidinyl)-N-(4-piperidinylphenyl)propanamide

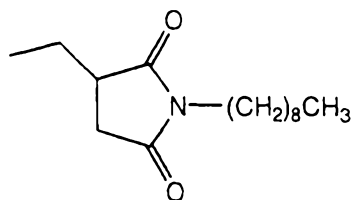


The procedure according to Example 27 was repeated using instead β-alanine benzyl ester hydrochloride.

¹HNMR: δ 1.50-1.85 (6H, m), 2.65-2.80 (6H, m), 3.05 (4H, t), 3.9 (2H, t), 6.85 (2H, d),
15 7.35 (2H, d), 7.4-7.5 (1H, br s)

Example 29

3-Ethyl-1-nonylpyrrolidine-2,5-dione



A solution of succinimide (15.15 mM) in tetrahydrofuran (15 ml) containing hexamethyl phosphorus triamide at -78 °C was treated with a solution of lithium diisopropylamide (30.30 mM) in tetrahydrofuran (25 ml). This solution was stirred at -78 °C for one hour
25 and then treated with ethyl iodide (15.90 mM). The reaction mixture was stirred at -78 °C

for 30 minutes, warmed up to room temperature and quenched with saturated aqueous ammonium chloride. The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 x 25 ml). The combined organic layers were washed with 10% aqueous sodium thiosulfate, brine, dried over sodium sulfate and concentrated *in vacuo*.

5 Chromatography over silica gel afforded pure 3-ethyl succinimide.

A solution of 3-ethyl succinimide (4.72 mM) in dimethylformamide (10 ml) was treated with sodium hydride (5.20 mM) and nonyl bromide (5.20 mM). The reaction mixture was stirred at room temperature for two hours and then quenched with saturated aqueous
10 ammonium chloride. The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 x 25 ml). The combined organic layers were washed with 10% aqueous sodium thiosulfate, brine, dried over sodium sulfate and concentrated *in vacuo*.

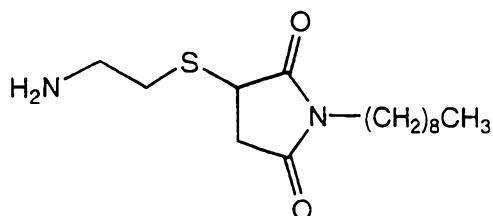
Chromatography over silica gel afforded the desired product, pure 3-ethyl *N*-nonyl succinimide.

15 ¹H NMR: δ 0.8 (3H, t), 0.9 (3H, t), 1.15-1.35 (12H, m), 1.45-1.65 (3H, m), 1.80-1.95 (1H, m), 2.35 (1H, dd), 2.6-2.95 (2H, m), 3.45 (2H, dd)

Example 30

3-(2-Aminoethylthio)-1-nonylpyrrolidine-2,5-dione

20



A mixture of *N*-nonyl maleimide (0.01 M) prepared as described in Example 12 above, mercapto ethylamine (0.01 M) and triethylamine (0.001 M) in acetonitrile (50 ml) was
25 stirred for 24 hours at room temperature. Acetonitrile was evaporated *in vacuo* and the residue obtained was triturated with ethyl acetate (25 ml). The resultant suspension was

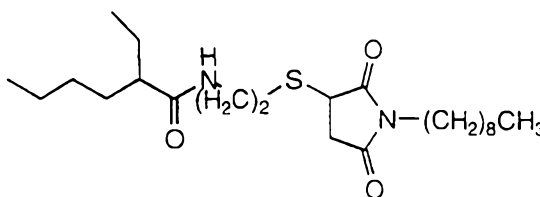
filtered and the solid washed with ethyl acetate. The solid was then dried and characterised as the desired product, N-nonyl,3-mercapto ethylamino maleimide.

^1H NMR: δ 0.85 (3H, t), 1.15-1.35 (12H, m), 1.45-1.55 (2H, m), 2.55 (2H, dd), 3.1-3.3 (2H, m), 3.35-3.50 (4H, m), 4.1 (1H, dd), 7.5-7.9 (2H, broad)

5

Example 31

2-Ethyl-N-(2-(1-nonyl-2,5-dioxopyrrolidin-3-ylthio)ethyl)hexanamide



10

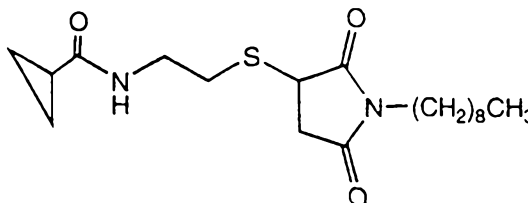
N-nonyl,3-mercapto ethylamino maleimide (0.5 mM) prepared as described in Example 30 above in 2ml of dichloromethane was treated with one equivalent of triethylamine and one equivalent of 2-ethylhexanoyl chloride. The reaction mixture was stirred for five hours. The dichloromethane was then evaporated to leave a residue to which a saturated sodium bicarbonate solution (2 ml) was added with stirring for 30 minutes, followed by ethyl acetate (2 ml) with stirring for a further 30 minutes. The ethyl acetate layer was then separated and concentrated to yield the desired product.

15

Example 32

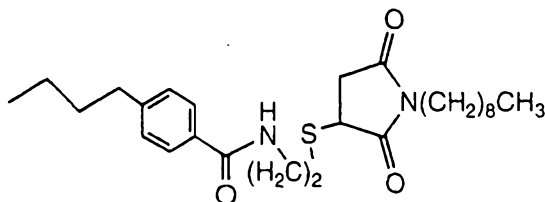
Cyclopropyl-N-(2-(1-nonyl-2,5-dioxopyrrolidin-3-ylthio)ethyl)formamide

20



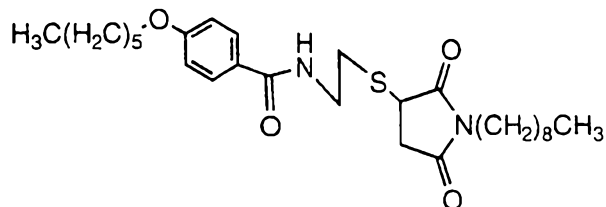
The procedure of Example 31 was repeated using instead cyclopropanecarbonyl chloride.

25

Example 33**(4-Butylphenyl)-N-(2-(1-nonyl-2,5-dioxopyrrolidin-3-ylthio)ethyl)formamide**

5

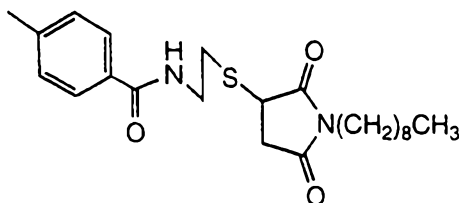
The procedure of Example 31 was repeated using instead 4-butylbenzoyl chloride.

Example 34**(4-Hexyloxyphenyl)-N-(2-(1-nonyl-2,5-dioxopyrrolidin-3-ylthio)ethyl)formamide**

10

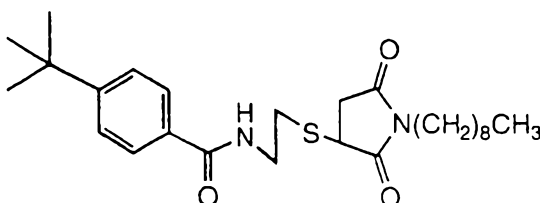
The procedure of Example 31 was repeated using instead 4-hexyloxybenzoyl chloride.

15

Example 35**(4-Methylphenyl)-N-(2-(1-nonyl-2,5-dioxopyrrolidin-3-ylthio)ethyl)formamide**

20

The procedure of Example 31 was repeated using instead 4-methylbenzoyl chloride.

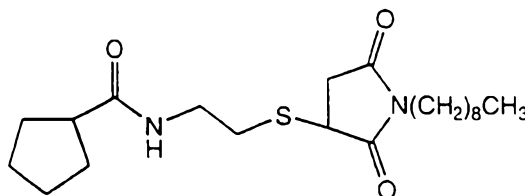
Example 36**(4-(tert-Butyl)phenyl-N-(2-(1-nonyl-2,5-dioxopyrrolidin-3-ylthio)ethyl)formamide**

5

The procedure of Example 31 was repeated using instead 4-*tert*-butylbenzoyl chloride.

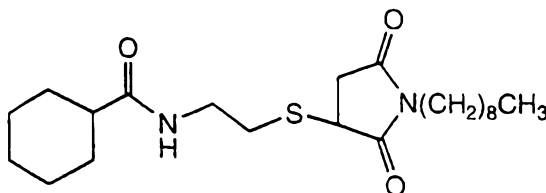
Example 37**Cyclopentyl-N-(2-(1-nonyl-2,5-dioxopyrrolidin-3-ylthio)ethyl)formamide, ethane**

10

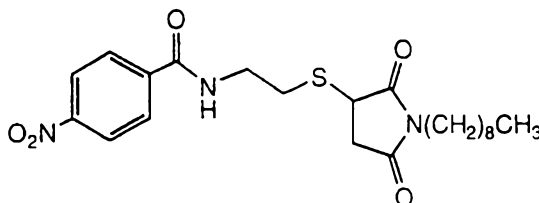


The procedure of Example 31 was repeated using instead cyclopentanecarbonyl chloride.

15

Example 38**Cyclohexyl-N-(2-(1-nonyl-2,5-dioxopyrrolidin-3-ylthio)ethyl)formamide**

20 The procedure of Example 31 was repeated using instead cyclohexanecarbonyl chloride.

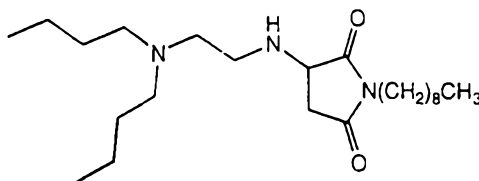
Example 39**(4-Nitrophenyl)-N-(2-(1-nonyl-2,5-dioxopyrrolidin-3-ylthio)ethyl)formamide**

5

The procedure of Example 31 was repeated using instead 4-nitrobenzoyl chloride.

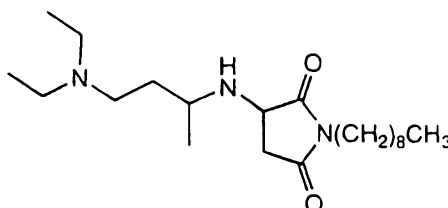
Example 40**3-((2-(Dibutylamino)ethyl)amino)-1-nonylpyrrolidine-2,5-dione**

10



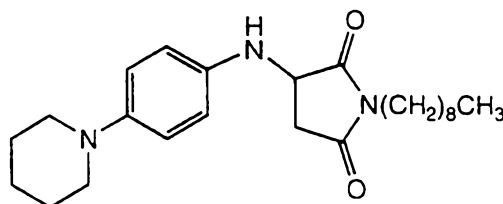
15

N-nonyl maleimide (0.02 mM) prepared as described in Example 12 above in 2 ml of acetonitrile was treated with one equivalent of triethylamine and one equivalent of N,N-dibutylethylenediamine. The reaction mixture was stirred for six hours and then the acetonitrile was evaporated. The residue obtained was treated with cold aqueous dilute hydrochloric acid solution and ethyl acetate, with stirring for one hour. The ethyl acetate layer was then separated and concentrated to give the desired product.

Example 41**3-((2-(Diethylamino)ethyl)amino)-1-nonylpyrrolidine-2,5-dione**

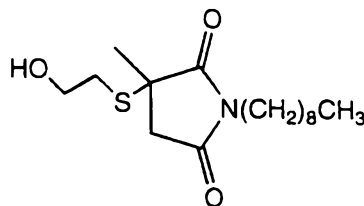
5

The procedure of Example 40 was repeated using instead 3-diethylamino-1-methylpropylamine.

Example 42**1-Nonyl-3-((4-piperidinylphenyl)amino)pyrrolidine-2,5-dione**

15

The procedure of Example 40 was repeated using instead 4-(piperidyl)aniline.

Example 43**3-(Hydroxyethylthio)-3-methyl-1-nonylpyrrolidine-2,5-dione**

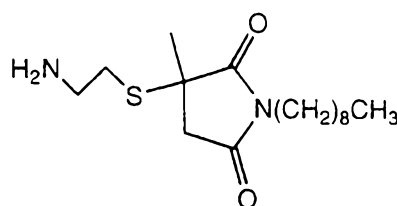
20

A solution of N-nonyl citraconimide (0.5 mM) prepared as described in Example 5 above in dimethylformamide (10 ml) was treated with triethylamine (0.5 mM) and then

2-mercaptoethanol (0.5 mM) was added dropwise. The progress of the reaction was monitored by thin layer chromatography and when the starting material could no longer be detected the reaction mixture was concentrated *in vacuo*. The residue obtained was dissolved in ethyl acetate, washed with water and dried over sodium sulfate. Purification by chromatography yielded the desired product.

Example 44

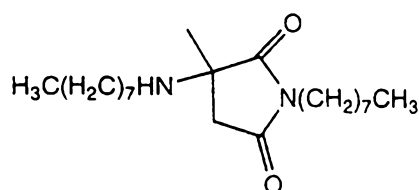
3-(2-Aminoethylthio)-3-methyl-1-nonylpyrrolidine-2,5-dione



The procedure of Example 43 was repeated using instead 2-mercaptoethylamine.

Example 45

3-Methyl-1-octyl-3-(octylamino)pyrrolidine-2,5-dione.



A solution of N-octyl citraconimide (0.223 g, 1 mM) prepared as described in Example 7 above in acetonitrile (2 ml) was treated with triethylamine (0.14 ml, 1 mM) and then octylamine (0.165 ml, 1 mM) was added dropwise. The progress of the reaction was monitored by thin layer chromatography and when the starting material could no longer be detected the reaction mixture was concentrated *in vacuo*. The residue obtained was dissolved in ethyl acetate, washed with water and dried over sodium sulfate. Purification by chromatography yielded the desired product.

¹HNMR: δ 0.8 (6H, t), 1.10-1.28 (20H, m), 1.3 (3H, s), 1.32-1.58 (4H, m), 2.25-2.48 (2H, m), 2.50 & 2.80 (2H, ABq), 3.42 (2H, dd)

Example 46

5

Each of the compounds of Examples 1 to 45 was assessed for bactericidal activity against *M. tuberculosis* by measuring its minimum inhibitory concentration (MIC) in the "BACTEC" (trade mark) system developed by Becton-Dickinson Diagnostic Instrument Systems, Sparks, U.S.A., which is based on a radiometric principle whereby carbon dioxide released by the catabolism of ¹⁴C-palmitate is spectrophotometrically detected and
10 quantitated in arbitrary units of measurement referred to as growth index (GI) units.

Thus, "BACTEC" vials were inoculated with 0.1 ml of *M. tuberculosis* (final bacterial concentration, 1×10^5 colony forming units per ml) and 0.1 ml of test compound in a range
15 of concentrations. GI values were monitored until a value of ≥ 30 was achieved for the 1:100 dilution control.

For the purpose of this test, MIC is defined as the minimum concentration of test compound that effects a >95% inhibition of the culture in comparison to the undiluted
20 control, when the control reaches a GI value of 999.

Endpoint determination (>99% inhibition) is based on a conventional 1% resistance cut-off, wherein the organism is considered resistant to a particular concentration of test compound if growth of greater than 1% of the bacterial population is observed. Thus, a
25 comparison is made between growth of the organism in the presence of a pre-determined concentration of test compound and growth of the same organism diluted 1:100 in the absence of any test compound. The change in the GI values (Δ GI) is used to determine the endpoint susceptibility of the organism to the test compound. If the Δ GI of the 1:100 control is greater than the Δ GI in the presence of the test compound, then the concentration
30 of test compound used is considered to be bactericidal (>99% inhibition) for the organism.

The MIC of the compounds of Examples 1 to 46 were determined for the following strains of *M. tuberculosis*:

H37Rv,

H37Ra,

- 5 1 clinical isolate susceptible to isoniazid, rifampicin, ethambutol and streptomycin [E:22/95; Estonia],

1 clinical isolate resistant to isoniazid [H:997/94; Honduras], 1 clinical isolate resistant to isoniazid and ethambutol [E:5/94; Estonia],

1 clinical isolate resistant to isoniazid and rifampicin [H:44/95; Honduras],

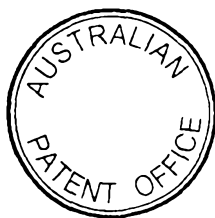
- 10 1 clinical isolate resistant to isoniazid and streptomycin [S:150/96; Sweden],

1 clinical isolate resistant to isoniazid, rifampicin and streptomycin [AA:063; Ethiopia],

3 clinical isolates resistant to isoniazid, rifampicin, streptomycin and ethambutol [P:24/95; Estonia, S:39/95; Nepal, S:42/95; China, H:1005/94; Honduras],

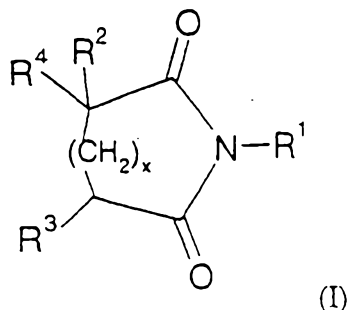
- 15 and were found in all cases to be less than or equal to 20 µg/ml. Therefore, the compounds of Examples 1 to 46 demonstrate effective bactericidal activity against the above strains of *M. tuberculosis* which include single- and multiple-drug resistant strains.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.



THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. Use of a compound of general formula



wherein x is 0 or 1;

R¹ represents a hydrogen atom, or a C₁-C₂₀ alkyl or myrtanyl group, or a phenyl or benzyl group optionally substituted in the aromatic ring by one or more substituents selected from amino, nitro, hydroxyl, carboxyl, halogen, trifluoromethyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkoxycarbonyl, piperidyl, piperazinyl and morpholinyl, or a group

(CH₂)ᵧCONH-R⁵ where y is an integer from 1 to 6 and R⁵ represents a phenyl group optionally substituted by one or more substituents selected from amino, nitro, hydroxyl, carboxyl, halogen, trifluoromethyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkoxycarbonyl, piperidyl, piperazinyl and morpholinyl; and

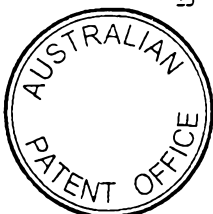
either

R² represents a hydrogen atom or a C₁-C₆ alkyl group, or R² together with R³ represents a carbon-carbon single bond provided that x is 0, or R² together with R⁴ represents a group =CH₂,

R³ represents a hydrogen atom or is linked to R² as defined above, and

R⁴ represents a hydrogen atom or a C₁-C₆ alkyl group; or a C₁-C₁₀ alkylamino group optionally substituted by a di(C₁-C₆ alkyl)amino substituent group; or an anilino group optionally substituted in the aromatic ring by one or more substituents selected from amino, nitro, hydroxyl, carboxyl, halogen, trifluoromethyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkoxycarbonyl, piperidyl, piperazinyl and morpholinyl; or a group -SCH₂CH₂OH,

25



-SCH₂CH₂NH₂, -SCH₂CH₂(NH₂)CO₂H or -SCH₂CH₂NHCO-R⁶ where R⁶ represents a C₁-C₁₀ alkyl or C₃-C₆ cycloalkyl group, or a phenyl group optionally substituted by one or more substituents selected from amino, nitro, hydroxyl, carboxyl, halogen, trifluoromethyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkoxycarbonyl, piperidyl, piperazinyl and morpholinyl; or R⁴ is linked to R² as defined above;

or

R², R³ and R⁴ together represent a phenyl group;

with the provisos that:

- (i) R¹, R², R³ and R⁴ do not each simultaneously represent a hydrogen atom,
 - (ii) when x is 0, R¹ represents a 4-fluorophenyl group and R⁴ represents a hydrogen atom, then R² and R³ do not together represent a carbon-carbon single bond, and
 - (iii) when x is 0, R¹ represents a 4-fluorophenyl group and R² and R³ both represent a hydrogen atom, then R⁴ does not represent an anilino, 4-chloroanilino, 2,6-dichloroanilino, 3,4-dichloroanilino, 2,5-dichloroanilino, 3-chloro-4-fluoroanilino or 4-fluoroanilino group;
- or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for use in the treatment of a mycobacterial disease.

2. Use according to claim 1, wherein R¹ represents a hydrogen atom, or a C₄-C₁₀ alkyl or myrtanyl group, or a phenyl group substituted by a piperidyl substituent group, or a group (CH₂)_yCONH-R⁵ where y is 1 or 2 and R⁵ represents a phenyl group substituted by a piperidyl substituent group.

3. Use according to claim 1 or claim 2, wherein R² represents a hydrogen atom or a methyl group, or R² together with R³ represents a carbon-carbon single bond provided that x is 0, or R² together with R⁴ represents a group =CH₂.

4. Use according to any one of claims 1 to 3, wherein R⁴ represents a hydrogen atom, a methyl or ethyl group, a C₂-C₁₀ alkylamino group optionally substituted by a di(C₂-C₄ alkyl)amino substituent group, an anilino group substituted by a piperidyl substituent group, -SCH₂CH₂OH, -SCH₂CH₂NH₂, -SCH₂CH₂(NH₂)CO₂H,

-SCH₂CH₂NHCO-R⁶ where R⁶ represents a C₇ alkyl, cyclopropyl, cyclopentyl or cyclohexyl group or a phenyl group substituted by a nitro, C₁-C₄ alkyl or C₃-C₆ alkoxy substituent group, or R⁴ is linked to R² as defined in claim 1.

5 5. Use according to claim 1 wherein the compound of formula (I) is selected from:

1-Decylpyrrolidine-2,5-dione,

1-Nonylpiperidine-2,6-dione,

2-((6,6-Dimethylbicyclo[3,1,1]hept-2-yl)methyl)isoindole-1,3-dione,

1-((6,6-Dimethylbicyclo[3,1,1]hept-3-yl)methyl)-3-methyl-3-pyrroline-2,5-dione,

10 3-Methyl-1-nonyl-3-pyrroline-2,5-dione,

3-Methylene-1-nonylpyrrolidine-2,5-dione,

3-Methyl-1-octyl-3-pyrroline-2,5-dione,

3-Methylene-1-octylpyrrolidine-2,5-dione,

(4-(3-methyl-2,5-dioxo-3-pyrrolinyl)phenyl)piperidine,

15 1-Octyl-3-pyrroline-2,5-dione,

1-Decyl-3-pyrroline-2,5-dione,

1-Nonyl-3-pyrroline-2,5-dione,

1-Butyl-3-pyrroline-2,5-dione,

1-Hexyl-3-pyrroline-2,5-dione,

20 1-(4-Piperidylphenyl)-3-pyrroline-2,5-dione,

1-(Octyl-3-(octylamino)-pyrrolidine-2,5-dione,

1-Decyl-3-(decylamino)pyrrolidine-2,5-dione,

3-(Octylamino)-3-pyrrolidine-2,5-dione,

3-(Heptylamino)-1-nonyl pyrrolidine-2,5-dione,

25 1-Nonyl-3-(nonylamino) pyrrolidine-2,5-dione,

1-Nonyl-3-(octylamino) pyrrolidine-2,5-dione,

2-Amino-3-(3-methyl-1-nonyl-2,5-dioxo-pyrrolidin-3-ylthio)propanoic acid,

2-Amino-3-(3-methyl-1-octyl-2,5-dioxo-pyrrolidin-3-ylthio)propanoic acid,

2-Amino-3-(1-octyl-2,5-dioxo-pyrrolidin-3-ylthio)propanoic acid,

30 3-Methyl-1-octylpyrrolidine-2,5-dione,

- 3-Methyl-1-nonylpyrrolidine-2,5-dione,
 2-(2,5-Dioxopyrrolidinyl)-N-(4-piperidylphenyl)ethanamide,
 2-(2,5-Dioxopyrrolidinyl)-N-(4-piperidylphenyl)propanamide,
 3-Ethyl-1-nonylpyrrolidine-2,5-dione,
 5 3-(2-Aminoethylthio)-1-nonylpyrrolidine-2,5-dione,
 2-Ethyl-N-(2-(1-nonyl-2,5-dioxopyrrolidin-3-ylthio)ethyl)hexanamide,
 Cyclopropyl-N-(2-(1-nonyl-2,5-dioxopyrrolidin-3-ylthio)ethyl)formamide,
 (4-Butylphenyl)-N-(2-(1-nonyl-2,5-dioxopyrrolidin-3-ylthio)ethyl)formamide,
 (4-Hexyloxyphenyl)-N-(2-(1-nonyl-2,5-dioxopyrrolidin-3-ylthio)ethyl)formamide,
 10 (4-Methylphenyl)-N-(2-(1-nonyl-2,5-dioxopyrrolidin-3-ylthio)ethyl)formamide,
 (4-(tert-Butyl)phenyl)-N-(2-(1-nonyl-2,5-dioxopyrrolidin-3-ylthio)ethyl)formamide,
 Cyclopentyl-N-(2-(1-nonyl-2,5-dioxopyrrolidin-3-ylthio)ethyl)formamide, ethane,
 Cyclohexyl-N-(2-(1-nonyl-2,5-dioxopyrrolidin-3-ylthio)ethyl)formamide,
 (4-Nitrophenyl)-N-(2-(1-nonyl-2,5-dioxopyrrolidin-3-ylthio)ethyl)formamide,
 15 3-((2-(Dibutylamino)ethyl)amino)-1-nonylpyrrolidine-2,5-dione,
 3-((2-(Diethylamino)ethyl)amino)-1-nonylpyrrolidine-2,5-dione,
 1-Nonyl-3-((4-piperidinylphenyl)amino)pyrrolidine-2,5-dione,
 3-(Hydroxyethylthio)-3-methyl-1-nonylpyrrolidine-2,5-dione,
 3-(2-Aminoethylthio)-3-methyl-1-nonylpyrrolidine-2,5-dione, and
 20 3-Methyl-1-octyl-3-(octylamino)pyrrolidine-2,5-dione.
6. Use according to any one of the preceding claims wherein the mycobacterial disease is tuberculosis.
- 25 7. A method of treating a patient suffering from, or at risk of, a mycobacterial disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as defined in claim 1.