PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 251/18, 251/52, 251/70, A61K 31/53 | A1

(11) International Publication Number: **WO 99/01442**

(43) International Publication Date: 14 January 1999 (14.01.99)

(21) International Application Number: PCT/GB98/01884

(22) International Filing Date: 26 June 1998 (26.06.98)

(30) Priority Data:

9713908.3	2 July 1997 (02.07.97)	GB
9720840.9	2 October 1997 (02.10.97)	GB

(71) Applicant *(for all designated States except US)*: ZENECA LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: POYSER, Jeffrey, Philip [GB/GB]; Zeneca Pharmaceuticals, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). TELFORD, Berwick [GB/GB]; Zeneca Pharmaceuticals, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). TIMMS, David [GB/GB]; Zeneca Pharmaceuticals, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). BLOCK, Michael, Howard [GB/GB]; Zeneca Pharmaceuticals, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). HALES, Neil, James [GB/GB]; Zeneca Pharmaceuticals, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

(74) Agent: DENERLEY, Paul, Millington; Zeneca Pharmaceuticals, Intellectual Property Dept., Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

(81) Designated States: JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published

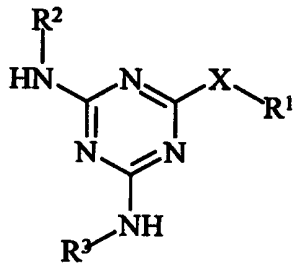
With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: TRIAZINE DERIVATIVES AND THEIR USE AS ANTIBACTERIAL AGENTS

(57) Abstract

Compounds of formula (I), pharmaceutically acceptable salts or *in vivo* hydrolysable esters thereof, wherein: X is O, NH, CH_2; R^1 is an optionally substituted aryl ring, optionally substituted heteroaryl ring, or such ring systems fused to an aryl or heteroaryl ring forming a bicyclic ring, or R^1 is carboxy–C_{1-6}alkyl or imidazolin–2–on–1–ylC_{1-6}alkyl; R^2 is an optionally substituted aryl ring or such ring system fused to a heteroaryl ring; R^3 is H, NHR^4, CHR^5R^6, where R^4, R^5 and R^6 are independently H or optionally substituted C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl or R^3 is an optionally substituted aryl ring; where any nitrogen containing heteroaryl ring in R^1 or R^2 may optionally be N oxidised or N alkylated; are useful as antibacterial compounds. Pharmaceutical compositions, methods and processes for preparation of compounds of formula (I) are described.



(I)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

TRIAZINE DERIVATIVES AND THEIR USE AS ANTIBACTERIAL AGENTS

The present invention relates to antibiotic compounds containing a 1,3,5-triazine ring. This invention further relates to processes for their preparation, to intermediates useful in their preparation, to their use as therapeutic agents and to pharmaceutical compositions containing them.

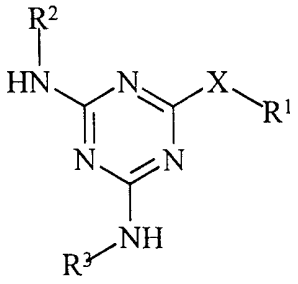
The ever increasing incidence of infection resulting from bacteria, in particular Gram Positive Bacteria, resistant to currently available therapy continues to drive the need to develop new and improved antibacterial agents. The compounds of the present invention in the main are believed to act via inhibition of DNA Gyrase. DNA Gyrase, the enzyme responsible for the process of supercoiling DNA in bacteria, represents an attractive antibacterial target because it is vital to bacteria and has no direct counterpart in mammals.

Structurally the enzyme has two discrete subunits (A and B) and it functions as an A_2B_2 tetramer in which the A subunits are responsible for the binding, breaking and recombination of the DNA and the B subunits which provide the energy for the process by the hydrolysis of ATP.

Two separate classes of clinically effective antibiotics are known to act at DNA Gyrase - the quinolones and the coumarins. The quinolones bind to the A subunits forming a stable ternary complex between DNA, enzyme and drug, which in turn is responsible for the subsequent cell death. The coumarins, typified by the natural product Novobiocin, bind to the B subunit of DNA Gyrase causing inhibition of the ATPase activity. The quinolones have found very widespread use as antibiotics but are gradually being compromised by problems of resistance. They are also limited in that they are not generally approved for use in paediatrics because of cartilage damage in animals. The coumarins have not been used widely because of a combination of problems including the rapid development of resistance, toxicity and poor physical properties. A third class of compounds, which also inhibit DNA Gyrase by competitive binding to the B subunit, are currently under investigation and include the natural product cyclothialidine, a variety of synthetic analogues and the closely related GR122222X.

The present inventors have discovered a class of antibiotic compounds containing a 1,3,5-triazine ring which has Gyrase inhibitory properties, in particular useful inhibitory activity against the Gyrase enzyme in Gram Positive Bacteria.

Accordingly the present invention provides a compound of the formula **(I)**, a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof:



(I)

wherein:

X is O, NH, CH_2;

R^1 is an optionally substituted aryl ring, optionally substituted heteroaryl ring, or such ring systems fused to an aryl or heteroaryl ring forming a bicyclic ring; or R^1 is carboxy-C_{1-6}alkyl or imidazolin-2-on-1-ylC_{1-6}alkyl;

R^2 is an optionally substituted aryl ring or such ring system fused to a heteroaryl ring;

R^3 is H, NHR^4, CHR^5R^6, where R^4, R^5 and R^6 are independently H or optionally substituted C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl or R^3 is an optionally substituted aryl ring;

wherein optional substituents for aryl, heteroaryl, such ring systems fused to an aryl ring (for example fused to a benzene ring) or fused to a heteroaryl ring, C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are:

C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkylC(O)-, C_{1-6}alkoxycarbonyl, aryl, aryloxy, heteroaryl, halo, cyano, nitro, hydroxy, carboxy, amino, C_{1-6}alkoxy, $(C_{1-6}alkoxy)_2CH$-, carboxyC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyl$S(O)_2NHC(O)$-, R^7R^8amino (including quaternary derivatives thereof such as $R^7R^8R^7N$-), $R^7NH(R^8N=)C$- (where R^7 and R^8 are independently H, C_{1-6}alkyl, arylC_{1-6}alkyl or R^7 and R^8 may together form an 4-8 membered heteroalkyl ring with 1 - 3 optionally substituted heteroatoms selected from O, S and N), $R^9R^{10}NC(O)$-, (where R^9 is OR^{10}, NHR^{10} or R^{10} and R^{10} is H, C_{1-6}alkyl, aryl, arylC_{1-6}alkyl or R^9 and R^{10} may together form an 4-8 membered heteroalkyl ring with 1 - 3 optionally substituted heteroatoms), $R^{11}S$-, $R^{11}S(O)$-, $R^{11}S(O)_2$-, $R^{11}C(O)NH$-, $R^{11}NHS(O)$-, $R^{11}NHS(O)_2$-, $R^{11}ON=CH$- (where R^{11} is H, C_{1-6}alkyl or arylC_{1-6}alkyl), or optionally substituted guanidine, and all C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, heteroalkyl rings and aryl groups referred to may themselves be optionally substituted as defined above;

where any nitrogen containing heteroaryl ring in R^1 or R^2 may optionally be N oxidised or N alkylated;

with the provisos

1) that on any optionally substituted phenyl or naphthyl ring the two positions on the ring ortho to the NH or X group linking to the 1,3,5-triazine ring must both be unsubstituted;

2) where R^3 is H, and X is NH, R^1 and R^2 are not both phenyl, 3-halophenyl, 4-halophenyl, 3-methylphenyl, 4-methylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 4-aminoquinolin-6-yl, 4-amino-2-methylquinolin-6-yl or 4-amino-2,3-dimethylquinolin-6-yl; and

3) excluding:

2,4-dianilino-6-(3'-phenylcoumarin-7'-ylamino)-1,3,5-triazine; 2,4-di(4'-amidinoaniline)-6-(4"-amino-2"-methylquinolin-6"-ylamino)-1,3,5-triazine; 2,4-di(4'-cyanoaniline)-6-(4"-amino-2"-methylquinolin-6"-ylamino)-1,3,5-triazine; 2,4,6-tri(N-acetyl-2'-methyl-3'-H-indol-5'-ylamino)-1,3,5-triazine; 2,4,6-tri(2'-methyl-3'-H-indol-5'-ylamino)-1,3,5-triazine; 2,4-di(4'-methoxyanilino)-6-[2"-(1"',3"'-dioxobenzoisobenzofuran-2"'-yl)-quinol-8"-ylamino]-1,3,5-triazine; 2,4-di(2',4'-dichloroanilino)-6-(2"-(1"',3"'-dioxobenzocyclopent-2-yl)-quinol-8"-ylamino)-1,3,5-triazine; 2,4,6-tri(2'-(1",3"-dioxo-4",5",6",7"-tetrachlorobenzocyclopent-2-yl)-quinol-8'-ylamino)-1,3,5-triazine; 2,4-dianilino-6-(2'-(1",3"-dioxo-4",5",6",7"-tetrachlorobenzocyclopent-2-yl)-quinol-8'-ylamino)-1,3,5-triazine and 2-amino-4-anilino-6-(3'-phenylcoumarin-7'-ylamino)-1,3,5-triazine.

Conveniently the present invention provides compounds of formula **(I)** or a pharmaceutically acceptable salt thereof.

In this specification the term 'alkyl' includes straight chained, branched structures and ring systems. For example, C_{1-6}alkyl includes propyl, isopropyl, *t*-butyl, cyclopropane and cyclohexane. However, references to individual alkyl groups such as 'propyl' are specific for the straight chained version only, references to individual branched chain alkyl groups such as 'isopropyl' are specific for the branched chain version only and references to the cyclo groups such as cyclohexane are specific to the cyclic groups only. A similar convention applies to other radicals, for example haloC_{1-6}alkyl includes 1-bromoethyl and 2-bromoethyl. The term halo refers to fluoro, chloro, bromo and iodo.

According to a further feature of this invention there is provided a compound of the formula **(I)** (as depicted above) or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof wherein:

X is O, NH, CH_2;

R^1 is an optionally substituted aryl ring, optionally substituted heteroaryl ring, or such ring systems fused to an aryl or heteroaryl ring forming a bicyclic ring;

R^2 is an optionally substituted aryl ring or such ring system fused to a heteroaryl ring;

R^3 is H, NHR^4, CHR^5R^6, where R^4, R^5 and R^6 are independently H or optionally substituted C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl or R^3 is an optionally substituted aryl ring;

wherein optional substituents are as defined above;

with the provisos

1) that on any optionally substituted phenyl or naphthyl ring the two positions on the ring ortho to the NH or X group linking to the 1,3,5-triazine ring must both be unsubstituted;

2) where R^3 is H, and X is NH, R^1 and R^2 are not both phenyl, 3-halophenyl, 4-halophenyl, 3-methylphenyl, 4-methylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 4-aminoquinolin-6-yl, 4-amino-2-methylquinolin-6-yl or 4-amino-2,3-dimethylquinolin-6-yl; and

3) excluding:

2,4-dianilino-6-(3'-phenylcoumarin-7'-ylamino)-1,3,5-triazine; 2,4-di(4'-amidinoaniline)-6-(4"-amino-2"-methylquinolin-6"-ylamino)-1,3,5-triazine; 2,4-di(4'-cyanoaniline)-6-(4"-amino-2"-methylquinolin-6"-ylamino)-1,3,5-triazine; 2,4,6-tri(N-acetyl-2'-methyl-3'-H-indol-5'-ylamino)-1,3,5-triazine; 2,4,6-tri(2'-methyl-3'-H-indol-5'-ylamino)-1,3,5-triazine; 2,4-di(4'-methoxyanilino)-6-[2"-(1"',3"'-dioxobenzoisobenzofuran-2"'-yl)-quinol-8"-ylamino]-1,3,5-triazine; 2,4-di(2',4'-dichloroanilino)-6-(2"-(1"',3"'-dioxobenzocyclopent-2-yl)-quinol-8"-ylamino)-1,3,5-triazine; 2,4,6-tri(2'-(1",3"-dioxo-4",5",6",7"-tetrachlorobenzocyclopent-2-yl)-quinol-8'-ylamino)-1,3,5-triazine; 2,4-dianilino-6-(2'-(1",3"-dioxo-4",5",6",7"-tetrachlorobenzocyclopent-2-yl)-quinol-8'-ylamino)-1,3,5-triazine and 2-amino-4-anilino-6-(3'-phenylcoumarin-7'-ylamino)-1,3,5-triazine.

X is O, NH, CH_2 preferably O and NH in particular O.

R^1 is an optionally substituted aryl, optionally substituted heteroaryl ring, or such ring systems fused to an aryl or heteroaryl ring forming a bicyclic ring. Suitable aryl and fused aryl rings include phenyl and naphthyl preferably phenyl. Suitable heteroaryl and fused

heteroaryl rings include pyridyl, pyrimidyl, triazinyl, imidazolyl, quinolyl, isoquinolyl, benzimidazolyl, coumarinyl, benzofuran-3-onyl preferably pyridyl, imidazolyl, coumarinyl and quinolyl and their N-oxides and N-alkyl derivatives. Where R^1 is heteroaryl with only one heteroatom preferably X is meta to the heteroatom. Preferred optional substituents are halo especially fluoro and chloro, $R^{11}S(O)$- or $R^{11}S(O)_2$- in particular where R^{11} is H, methyl or ethyl, $C_{1-6}C(O)NH$- (optionally substituted with di-C_{1-6}alkylamino or tri-C_{1-6}alkylamino), carboxy, C_{1-6}alkylcarbamoyl, carbamoyl, C_{1-6}alkyl in particular where C_{1-6}alkyl is methyl and ethyl, hydroxy, nitro and cyano. Particular values of R^1 are 3-fluorophenyl, 3,5-difluorophenyl, 3-chlorophenyl, 3,5-dichlorophenyl, 4-MeS(O)-phenyl, 4-$MeS(O)_2$-phenyl, 3-pyridyl, 3-pyridyl-N-oxy, 3-MeC(O)NH-phenyl, 4-MeC(O)NH-phenyl, 3-carboxyphenyl, 4-carboxyphenyl, 3-$H_2NC(O)$-phenyl, 4-$H_2NC(O)$-phenyl, 6-methyl-3-pyridyl-N-oxy, 4-hydroxycoumarinyl, 3-quinolyl-N-oxy, 8-nitroquinolyl, 8-cyano-quinolyl, 8-tetrazolyl-quinolyl or 8-carboxyquinolyl.

R^2 is an optionally substituted aryl ring. Suitable aryl rings include phenyl and naphthyl preferably phenyl. When R^2 is optionally substituted aryl fused to a heteroaryl ring, suitable ring systems are those listed above with respect to R^1. Preferred optional substituents for the ring systems of R^2 are halo especially fluoro and chloro, C_{1-6}alkyl especially methyl and ethyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $R^9R^{10}NC(O)$-, cyano, nitro, hydroxy, $R^{11}S$-, $R^{11}S(O)$-, $R^{11}S(O)_2$-, carboxy and C_{1-6}carboxy. Particular values of R^2 are 3-fluorophenyl, 3,5-difluorophenyl, 3-chlorophenyl, 3,5-dichlorophenyl 3-chloro-5-EtS-phenyl and 3-ethynyl-5-chlorophenyl.

R^3 is H, NHR^4, CHR^5R^6, where R^4, R^5 and R^6 are independently H or optionally substituted C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl or R^3 is an optionally substituted aryl ring Preferably R^3 is H, CR^5R^6 or an optionally substituted aryl ring. Where R^3 is CHR^5R^6 preferable values for R^5 and R^6 are H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl optionally substituted with cyano, halo, hydroxy, C_{1-6}alkoxy, carboxy, C_{1-6}alkylcarboxy, 1-imidazolidin-2-onyl, $NHCO_2R^{12}$ (R^{12} = optionally substituted C_{1-6}alkyl, optionally substituted aryl C_{1-6}alkyl) or R^5 and R^6 may together form a 3 - 8 membered ring optionally with 1 - 3 heteroatoms (optionally substituted). Where R^3 is an optionally substituted aryl ring preferably the aryl ring is phenyl and preferable optional substituents are halo in particular fluoro chloro and bromo, C_{1-6}alkyl in particular methyl and ethyl and C_{1-6}alkylS-. Particular values of R^3 are H, allyl, cyclopropyl,

cyanomethyl, 3-fluorophenyl, 3-chlorophenyl, 3-bromophenyl, 3-methylphenyl, 3-ethylphenyl, 3-MeS-phenyl and 3-ethynylphenyl.

Therefore a preferred class of compounds is that of formula **(I)** or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof wherein:

X is O;

R^1 is optionally substituted phenyl, 3-pyridyl-N-oxy, 3-quinolyl, 3-quinolyl-N-oxy, or coumarinyl, in particular 3-fluorophenyl, 3,5-difluorophenyl, 3-chlorophenyl, 3,5-dichlorophenyl, 4-MeS(O)-phenyl, 4-$MeS(O)_2$-phenyl, 3-pyridyl, 3-MeC(O)NH-phenyl, 4-MeC(O)NH-phenyl, 3-carboxyphenyl, 4-carboxyphenyl, 3-$H_2NC(O)$-phenyl, 4-$H_2NC(O)$-phenyl, 6-methyl-3-pyridyl-N-oxy, 4-hydroxycoumarinyl, 3-quinolyl-N-oxy, 8-nitroquinolyl, 8-cyano-quinolyl, 8-tetrazolyl-quinolyl or 8-carboxyquinolyl;

R^2 is optionally substituted phenyl, in particular 3-fluorophenyl, 3,5-difluorophenyl, 3-chlorophenyl, 3,5-dichlorophenyl or 3-ethynyl-5-chlorophenyl; and

R^3 is H, CHR^5R^6 or an optionally substituted aryl ring, in particular H, allyl, cyclopropyl, cyanomethyl, 3-fluorophenyl, 3-chlorophenyl, 3-bromophenyl, 3-methylphenyl, 3-ethylphenyl, 3-MeS-phenyl or 3-ethynylphenyl.

A further preferred class of compounds is that of Examples 1 - 43 or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

Suitable pharmaceutically acceptable salts include acid addition salts such as methanesulphonate, fumarate, hydrochloride, hydrobromide, citrate, maleate and salts formed with phosphoric and sulphuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example sodium, an alkaline earth metal salt for example calcium or magnesium, an organic amine salt for example triethylamine, morpholine, *N*-methylpiperidine, *N*-ethylpiperidine, procaine, dibenzylamine, *N*,*N*-dibenzylethylamine or amino acids for example lysine. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions. A preferred pharmaceutically acceptable salt is the sodium salt.

However, to facilitate isolation of the salt during preparation, salts which are less soluble in the chosen solvent may be preferred whether pharmaceutically acceptable or not.

In this specification an N-oxide refers to the N-oxides which may be formed on an available nitrogen atom on the R^1 ring where R^1 is heteroaryl or a heteroaryl fused to an aryl ring, for example where R^1 is pyridyl or quinolyl. Where R^2 is an aryl ring fused to a

heteroaryl ring which contains an available nitrogen atom, for example a quinolyl, N-oxides may also be formed here. An N-oxide may be optionally in the form of a pharmaceutically acceptable salt.

N-alkylation refers to an N-alkyl derivative that may be formed on R^1 where it is heteroaryl or a heteroaryl fused to an aryl ring, for example where R^1 is pyridyl or quinolyl. Where R^2 is an aryl ring fused to a heteroaryl ring which contains an available nitrogen atom, for example a quinolyl, N-alkyl derivatives may also be formed here. An N-alkyl derivative may be optionally in the form of a pharmaceutically acceptable salt. Preferred N-alkyl derivatives are N-methyl and N-ethyl derivatives, especially N-methyl derivatives.

Some compounds of formula **(I)** may possess chiral centres. It is to be understood that the invention encompasses all such optical isomers and diasteroisomers that possess Gyrase inhibitory activity.

The invention relates to all tautomeric forms of the compounds of formula **(I)** that possess Gyrase inhibitory activity.

It is also to be understood that certain compounds of the formula **(I)** can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess Gyrase inhibitory activity.

The compounds of the formula **(I)** may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the formula **(I)**. Examples of pro-drugs include *in vivo* hydrolysable esters of a compound of the formula **(I)**.

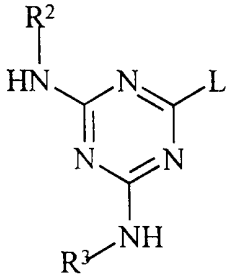
An *in vivo* hydrolysable ester of a compound of the formula **(I)** containing carboxy or hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol.

Suitable pharmaceutically acceptable esters for carboxy include C_{1-6}alkoxymethyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_{3-8}cycloalkoxycarbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

An *in vivo* hydrolysable ester of a compound of the formula **(I)** containing a hydroxy group includes inorganic esters such as phosphate esters and α-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl.

Another aspect of the present invention provides a process for preparing a compound of formula **(I)** or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof which process comprises of:

a) reacting a compound of formula **(II)**:



(II)

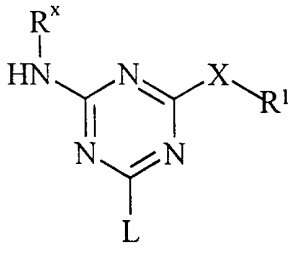
with a compound of formula **(III)**:

R^1XA

(III)

where R^1, R^2, R^3 and X are as defined for formula **(I)** and L is a leaving group and A is an atom or group capable of forming a cation; or

b) reacting a compound of formula **(IV)**:



(IV)

with a compound of formula **(V)**

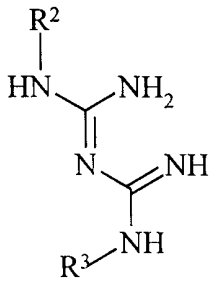
R^yNHA

(V)

where R^1 and X are as defined for formula **(I)**, L is a leaving group, A is as defined above and R^x is R^2 and R^y is R^3; or

R^x is R^3 and R^y is R^2;

c) for compounds where X is CH_2, reacting a compound of formula **(VI)**:



(VI)

where R^2 and R^3 are defined as for formula **(I)**;

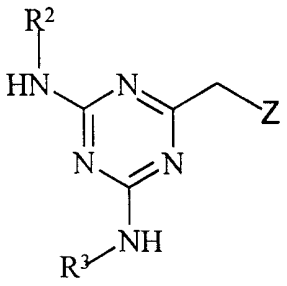
with a compound of formula **(VII)**:

R^1CH_2COY

(VII)

where Y is a leaving group, and R^1 is as defined for formula **(I)**; or

d) for compounds where X is CH_2 reacting a compound of formula **(VIII)**:



(VIII)

where Z is a leaving group with a compound of formula **(IX)**:

R^1A

(IX)

where R^1 is as defined for formula **(I)**, and A is as defined above;

and thereafter if necessary:

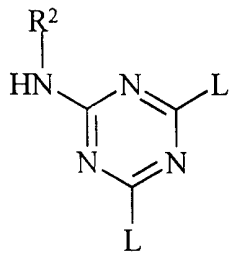
i) converting a compound of the formula **(I)** into another compound of the formula **(I)**;

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

a) Compounds of formula **(II)** and **(III)** may be reacted together in the presence of a base, either an inorganic base such as sodium hydride or sodium hydroxide or a tertiary organic base such as diisopropylamine or triethylamine or excess **(III)**, in an inert solvent such as dimethylsulphoxide, *N*,*N*-dimethylformamide or xylene at a temperature range of 85°C to 150°C, normally in the range 100 to 140°C.

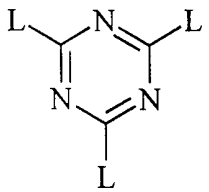
Compounds of formula **(II)** are conveniently prepared by reacting a compound of formula **(X)**:



(X)

with a compound of formula **(V)**. These may be reacted together in the presence of a base, either aqueous inorganic base such as sodium or potassium carbonate or sodium bicarbonate or a tertiary organic base such as diisopropylamine or triethylamine or excess **(V)**, in an inert solvent such as acetone or 1,4-dioxane at a temperature range of 10°C to 40°C, normally in the range 18 to 30°C.

Compounds of formula **(X)** are prepared by reacting a compound of formula **(XI)**:



(XI)

with a compound of formula **(XII)**:

R^2NHA

(XII)

Compounds of formula **(XI)** and **(XII)** may be reacted together in the presence of a base, either an aqueous inorganic base such as sodium or potassium carbonate or sodium bicarbonate or an organic base such as diisopropylamine or triethylamine, in an inert solvent such as acetone or chloroform at a temperature range of -10°C to ambient temperature, normally in the range -5 to 5°C.

b) Compounds of formula **(V)** and **(IV)** may be reacted together in the presence of a base for example a tertiary organic base such as diisopropylamine or triethylamine or excess **(IV)**, in an inert solvent such as dimethylsulphoxide, *N*,*N*-dimethylformamide or xylene at a temperature range of 85 to 150°C, normally in the range 100 to 140°C.

Compounds of formula **(IV)** are prepared by reacting compounds of formula **(X)** with compounds of formula **(III)**. These may be reacted together in the presence of a base, either aqueous inorganic base such as sodium or potassium carbonate or sodium hydroxide or a tertiary organic base such as diisopropylamine or triethylamine or excess **(III)**, in an inert solvent such as acetone or 1,4-dioxane at a temperature range of 10 to 40°C, normally in the range 18 to 30°C.

c) Compounds of formula **(VI)** and **(VII)** may be condensed together in the presence of a base, typically a tertiary organic base such as diisopropylamine or triethylamine in an inert solvent such as *N*,*N*-dimethylformamide at a temperature range of ambient temperature to 150°C, normally in the range 85-105°C.

d) Compounds of formula **(VIII)** and **(IX)** may be reacted together in the presence of a base, typically excess **(IX)** or a tertiary organic base such as diisopropylamine or triethylamine in an inert solvent such as *N*,*N*-dimethylformamide at a temperature range of ambient temperature to 150°C, normally in the range 85-105°C.

Compounds of formula **(VIII)** may be prepared by reacting a compound of formula **(VI)** with a compound of formula **(XIII)**:

$$ZCH_2CO_2Me$$

(XIII)

Compounds of formula **(IV)** and **(XIII)** may be condensed together in the presence of a strong base for example sodium methoxide in an alcoholic solvent such as methanol at a temperature range of -10°C to ambient temperature, normally in the range -5 to 5°C.

Compounds of the formula **(III)**, **(V)**, **(VI)**, **(VII)**, **(IX)**, **(XI)**, **(XII)** and **(XIII)** are commercially available or are prepared by processes known in the art by manipulation of commercially available materials.

A is a group capable of forming a cation, usually A is H or Na. L and Z are leaving groups. Preferable values for L and Z are halo for example chloro and aryloxy for example phenoxy.

These compounds of formula **(I)** produced by the above routes may optionally be further manipulated by processes known in the art such as oxidation e.g. of nitrogen or sulphur, removal of a protecting group e.g. an ester or quaternization e.g. of a nitrogen, forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester or other processes to give further compounds of formula **(I)**.

N-oxides of compounds of the formula **(I)** may be prepared directly from a compound of formula **(I)** (see example 21) or a compound of the formula **(XII)** (see example 9) using techniques well known to the ordinary skilled organic chemist, such as, for example, using a peracid (such as m-chloroperoxybenzoic acid) or perphthalic acid in a suitable solvent (such as 1,4-dioxane or a mixture of water and tetrahydrofuran) at a suitable temperature (such as ambient temperature).

N-alkyl derivatives of compounds of the formula **(I)** may be prepared directly from a compound of formula **(I)** or a compound of the formula **(XII)** using techniques well known to the ordinary skilled organic chemist, such as, for example, using a methylating agent (such as iodomethane) in a suitable solvent (such as 1,4-dioxane or dichloromethane) at a suitable temperature (such as ambient temperature).

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a

methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

It will also be appreciated that certain of the various optional substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or

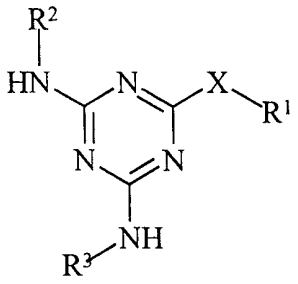
immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acylhalide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

When a pharmaceutically-acceptable salt of a compound of the formula **(I)** is required, it may be obtained, for example, by reaction of said compound with the appropriate acid (which affords a physiologically acceptable anion), or with the appropriate base (which affords a physiologically acceptable cation), or by any other conventional salt formation procedure.

When an optically active form of a compound of the formula **(I)** is required, it may be obtained, for example, by carrying out one of the aforesaid procedures using an optically active starting material or by resolution of a racemic form of said compound using a conventional procedure.

In order to use a compound of the formula **(I)** or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof for the therapeutic treatment of mammals including humans, in particular in treating infection, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Certain compounds excluded from the definition of formula **(I)** are known for non-pharmaceutical use. Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the formula **(IA)**:



(IA)

wherein:

X is O, NH, CH_2;

R^1 is an optionally substituted aryl ring, optionally substituted heteroaryl ring, or such ring systems fused to an aryl or heteroaryl ring forming a bicyclic ring; or R^1 is carboxy-C_{1-6}alkyl or imidazolin-2-on-1-ylC_{1-6}alkyl;

R^2 is an optionally substituted aryl ring or such ring system fused to a heteroaryl ring;

R^3 is H, NHR^4, CHR^5R^6, where R^4, R^5 and R^6 are independently H or optionally substituted C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl or R^3 is an optionally substituted aryl ring;

wherein optional substituents for aryl, heteroaryl, such ring systems fused to an aryl ring (for example fused to a benzene ring) or fused to a heteroaryl ring, C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are:

C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkylC(O)-, C_{1-6}alkoxycarbonyl, aryl, aryloxy, heteroaryl, halo, cyano, nitro, hydroxy, carboxy, amino, C_{1-6}alkoxy, $(C_{1-6}alkoxy)_2CH$-, carboxyC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyl$S(O)_2NHC(O)$-, R^7R^8amino (including quaternary derivatives thereof such as $R^7R^8R^7N$-), $R^7NH(R^8N=)C$- (where R^7 and R^8 are independently H, C_{1-6}alkyl, arylC_{1-6}alkyl or R^7 and R^8 may together form an 4-8 membered heteroalkyl ring with 1 - 3 optionally substituted heteroatoms selected from O, S and N), $R^9R^{10}NC(O)$-, (where R^9 is OR^{10}, NHR^{10} or R^{10} and R^{10} is H, C_{1-6}alkyl, aryl, arylC_{1-6}alkyl or R^9 and R^{10} may together form an 4-8 membered heteroalkyl ring with 1 - 3 optionally substituted heteroatoms), $R^{11}S$-, $R^{11}S(O)$-, $R^{11}S(O)_2$-, $R^{11}C(O)NH$-, $R^{11}NHS(O)$-, $R^{11}NHS(O)_2$-, $R^{11}ON=CH$- (where R^{11} is H, C_{1-6}alkyl or arylC_{1-6}alkyl), or optionally substituted guanidine, and all C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, heteroalkyl rings and aryl groups referred to may themselves be optionally substituted as defined above;

where any nitrogen containing heteroaryl ring in R^1 or R^2 may optionally be N oxidised or N alkylated;

with the provisos

1) that on any optionally substituted phenyl or naphthyl ring the two positions on the ring ortho to the NH or X group linking to the 1,3,5-triazine ring must both be unsubstituted;

2) where R^3 is H, and X is NH, R^1 and R^2 are not both 4-aminoquinolin-6-yl or 4-amino-2-methylquinolin-6-yl; and

3) excluding:

2,4-di(4'-amidinoaniline)-6-(4"-amino-2"-methylquinolin-6"-ylamino)-1,3,5-triazine and 2,4-di(4'-cyanoaniline)-6-(4"-amino-2"-methylquinolin-6"-ylamino)-1,3,5-triazine;

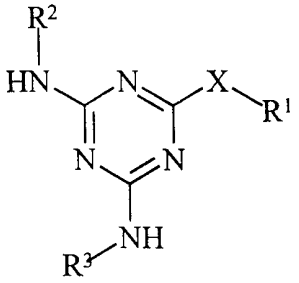
or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof and a pharmaceutically acceptable diluent or carrier.

According to a further feature of the invention there is provided a compound of the formula **(IA)**, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, for use in a method of treatment of the human or animal body by therapy.

According to a further feature of the present invention there is provided a method for producing an antibacterial effect, and in particular a Gyrase mediated antibacterial effect in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of formula **(IA)**, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

The invention also provides a compound of the formula **(IA)**, or a pharmaceutically acceptable salt, N-oxide or *in vivo* hydrolysable ester thereof, for use as a medicament.

This invention further provides the use of a compound of the formula **(IB)**:



(IB)

wherein:

X is O, NH, CH_2;

R^1 is an optionally substituted aryl ring, optionally substituted heteroaryl ring, or such ring systems fused to an aryl or heteroaryl ring forming a bicyclic ring; or R^1 is carboxy-

C_{1-6}alkyl or imidazolin-2-on-1-ylC_{1-6}alkyl;

R^2 is an optionally substituted aryl ring or such ring system fused to a heteroaryl ring;

R^3 is H, NHR^4, CHR^5R^6, where R^4, R^5 and R^6 are independently H or optionally substituted C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl or R^3 is an optionally substituted aryl ring;

wherein optional substituents for aryl, heteroaryl, such ring systems fused to an aryl ring (for example fused to a benzene ring) or fused to a heteroaryl ring, C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are:

C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkylC(O)-, C_{1-6}alkoxycarbonyl, aryl, aryloxy, heteroaryl, halo, cyano, nitro, hydroxy, carboxy, amino, C_{1-6}alkoxy, $(C_{1-6}alkoxy)_2CH$-, carboxyC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyl$S(O)_2NHC(O)$-, R^7R^8amino (including quaternary derivatives thereof such as $R^7R^8R^7N$-), $R^7NH(R^8N=)C$- (where R^7 and R^8 are independently H, C_{1-6}alkyl, arylC_{1-6}alkyl or R^7 and R^8 may together form an 4-8 membered heteroalkyl ring with 1 - 3 optionally substituted heteroatoms selected from O, S and N), $R^9R^{10}NC(O)$-, (where R^9 is OR^{10}, NHR^{10} or R^{10} and R^{10} is H, C_{1-6}alkyl, aryl, arylC_{1-6}alkyl or R^9 and R^{10} may together form an 4-8 membered heteroalkyl ring with 1 - 3 optionally substituted heteroatoms), $R^{11}S$-, $R^{11}S(O)$-, $R^{11}S(O)_2$-, $R^{11}C(O)NH$-, $R^{11}NHS(O)$-, $R^{11}NHS(O)_2$-, $R^{11}ON=CH$- (where R^{11} is H, C_{1-6}alkyl or arylC_{1-6}alkyl), or optionally substituted guanidine, and all C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, heteroalkyl rings and aryl groups referred to may themselves be optionally substituted as defined above;

where any nitrogen containing heteroaryl ring in R^1 or R^2 may optionally be N oxidised or N alkylated;

with the proviso that on any optionally substituted phenyl or naphthyl ring the two positions on the ring ortho to the NH or X group linking to the 1,3,5-triazine ring must both be unsubstituted;

or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof in the manufacture of a novel medicament for use in the production of an antibiotic effect, and in particular a Gyrase mediated antibacterial effect in a warm blooded animal, such as man.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by oral, rectal or parenteral administration. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous

or oily solutions or suspensions, (lipid) emulsions, dispersible powders, suppositories, ointments, creams, drops and sterile injectable aqueous or oily solutions or suspensions.

In addition to the compounds of the present invention the pharmaceutical composition of this invention may also contain or be co-administered with one or more known drugs selected from other clinically useful antibacterial agents (for example β-lactams or aminoglycosides). These may include penicillins, for example oxacillin or flucloxacillin and carbapenems, for example meropenem or imipenem, to broaden the therapeutic effectiveness against methicillin-resistant staphylococci. Compounds of this invention may also contain or be co-administered with bactericidal/permeability-increasing protein product (BPI) or efflux pump inhibitors to improve activity against gram negative bacteria and bacteria resistant to antimicrobial agents.

A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule which contains between 100mg and 1g of the compound of this invention.

In another aspect a pharmaceutical composition of the invention is one suitable for intravenous, subcutaneous or intramuscular injection.

Each patient may receive, for example, a daily intravenous, subcutaneous or intramuscular dose of 5 $mgkg^{-1}$ to 20 $mgkg^{-1}$ of the compound of this invention, the composition being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively the intravenous dose may be given by continuous infusion over a period of time. Alternatively each patient will receive a daily oral dose which is approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day.

Biological testing.

Synthetic products were tested for gyrase inhibitory activity in a standard supercoiling assay (M. Gellert, K. Mizuuchi, M. H. O'Dea and H. A. Nash, *Proc. Natl. Acad. Sci. USA*, 1976, **73**, 3872-76) and for antibacterial activity in a standard antimicrobial susceptibility assays (National Committee for Clinical Laboratory Standards,. (1993) Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically - 3rd ed; approved standard. Document M7-A3 13 (25), Villanova, PA.).

Antibacterial Activity.

The following results were obtained on a standard *in vitro* test system. The activity is described in terms of the minimum inhibitory concentration (MIC) determined by the agar-dilution technique with an inoculum size of 10^4 CFU/spot.

Staphylococci were tested on agar, using an inoculum of 10^4 CFU/spot and an incubation temperature of 37 °C for 24 hours - standard test conditions for the expression of methicillin resistance.

Streptococci and enterococci were tested on agar supplemented with 5% defibrinated horse blood, an inoculum of 10^4 CFU/spot and an incubation temperature of 37 °C in an atmosphere of 5% carbon dioxide for 48 hours - blood is required for the growth of some of the test organisms.

The following results were obtained for **Example 20**.

Organism		MIC (µg/ml)
Staphylococcus aureus:		
	Oxford	2.0
	Novb. Res	2.0
	MRQS	4.0
	MRQR	2.0
Coagulase Negative Staphylococcus:		
	MS	2.0
	MR	2.0
Streptococcus pyogenes:		
	C203	4.0
Enterococcus faecalis:		4.0
Bacillus subtilis:		4.0

Novb. Res = Novobiocin resistant

MRQS = methicillin resistant quinolone sensitive

MRQR = methicillin resistant quinolone resistant

MR. = methicillin resistant

MS.= methicillin sensitive

Gyrase Activity.

Assay Constituents:

Assay buffer

35mM	Tris pH7.0		48µg/ml	BSA
15mM	KCl		193µM	ATP
4mM	$MgCl_2$		2.7%	Glycerol
5mM	DTT		60µM	EDTA
1.62mM	Spermidine		~200 ng relaxed pUC18	

DNA gyrase subunits A and B quantities are adjusted such that 50% of relaxed pUC18 is supercoiled in 20min. Volumes vary depending upon the activity of a particular preparation.

Total assay volume including 1µl of test compound at a range of concentrations = 20µl. Incubation is at 37 °C for 20 mins..

The reaction is stopped by the addition of 4µl loading buffer (0.25% bromophenol blue, 0.25% xylene cymol, 15% Ficol tybe 400, 2% SDS).

The separation of relaxed from supercoiled pUC18 is by 0.7% agarose gel submarine electrophoresis visualised by ethidium bromide staining and UV illumination. The supercoiled plasmid having higher mobility than the relaxed.

The IC_{50} value is the concentration of compound which reduces the control 50% supercoiling by 50% and can be assessed visually or by densitometry. A typical dose response would exhibit the full range from total inhibition i.e. only relaxed plasmid visible, to no effect ie supercoiled and relaxed bands present at equal intensity.

Standard inhibitors of gyrase include Norfloxacin IC_{50} 1.0µg/ml and novobiocin IC_{50} 0.075µg/ml.

Typical active gyrase inhibitors have an $IC_{50} \leq 10$.

IC_{50} for **Example 31** = 0.55.

Examples.

The invention is further illustrated, but not limited by the following examples.

General Procedures.

All procedures were carried out at room temperature unless otherwise stated. N,N-Dimethylformamide (DMF) was dried over 4Å molecular sieves. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use. Other commercially available reagents and solvents were used without further purification unless otherwise stated. Organic solvent extracts were dried over anhydrous $MgSO_4$. ^1H, ^{13}C and ^{19}F NMR were recorded on Bruker WM200, WM250, WM300 or WM400 instruments using Me_2SO-d_6 with Me_4Si or CCl_3F as internal standard as appropriate, unless otherwise stated. Chemical shifts are in δ (ppm) and peak multiplicities are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; dt, doublet of triplets; q, quartet; m, multiplet; br, broad. Mass spectra were recorded on VG 12-12 quadrupole, VG 70-250 SE, VG ZAB 2-SE or a VG modified AEI/Kratos MS9 spectrometers. For TLC analysis, Merck precoated TLC plates (silica gel 60 F254, d = 0.25 mm) were used. Flash chromatography was performed on silica (Merck Kieselgel: Art.9385). Melting point determinations were performed on a Kofler block or with a Büchi melting point apparatus and are uncorrected.

Example 1.

Tris-3'-fluoroanilino-1,3,5-triazine.

2-Chloro-bis-4,6-(3'-fluoroanilino)-1,3,5-triazine (100 mg, 0.3 mM) was dissolved in THF (10 ml) and m-fluoroaniline (67 mg, 58 µl, 0.6 mM) was added. The solvent was evaporated and the residue was heated to melting point in a heating mantle for 10 mins.. After allowing to cool, isopropanol was added, the mixture was refluxed, allowed to cool and the resulting solid was collected by filtration. Yield 71 mg (58%); mp 213-214 °C; ^{1}H NMR δ 6.82 (dt, 3H), 7.32 (q, 3H), 7.52 (d, 3H), 7.86 (d, 3H), 9.59 (s, 3H); ^{13}C NMR δ 107.27 (d, J=25.2 Hz), 108.78 (d, J=18.9 Hz), 116.08 (s), 129.82 (d, J=9.4 Hz), 141.17 (d, J=11.3 Hz), 162.21 (d, J=239.0 Hz), 162.91 (s); MS (FAB) *m/z* 409 $[MH]^+$.

A sample (50 mg) was suspended in ethyl acetate and aqueous ammonia was added to give a clear two phase system. The organic phase was separated, washed with brine, dried and evaporated to dryness to give the free base, as a yellow oil which solidified to an off-white powder. Yield 43 mg (96%); mp 166-168 °C; NMR δ as above + 1.18 (t, 0.6H), 1.99 (s, 0.6H), 4.04 (q, 0.4H).

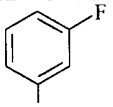
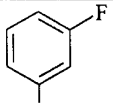
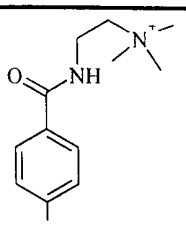
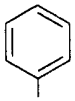
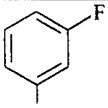
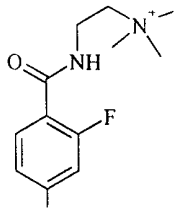
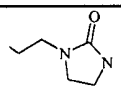
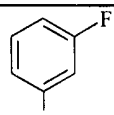
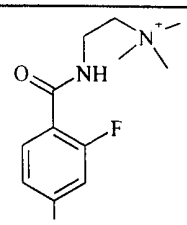
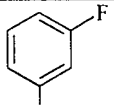
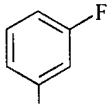
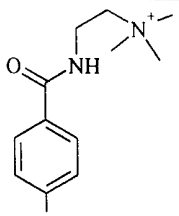
Example 2.

2-(4'-Trimethylammonioethylaminocarbonyl-3'-fluoroanilino)-bis-4,6-(3''-fluoroanilino)-1,3,5-triazine.

Iodomethane (21 mg, 9.3 µl, 0.15 mM) was added to 2-(4'-dimethylaminooethyl-aminocarbonyl-3'-fluoroanilino)-bis-4,6-(3''-fluoroanilino)-1,3,5-triazine (62 mg, 0.12 mM) in THF (400 µl). After standing overnight, evaporation gave a residue, which was triturated with diethyl ether (4 ml) and filtered to give Example 2. Yield 55 mg (69%); Mp 190-195 °C (decomp.); NMR δ 3.18 (s, 9H), 3.52 (t, 2H), 3.72 (q, 2H), 6.82 (dt, 2H), 7.35 (q, 2H), 7.52 (d, 2H), 7.61 (dd, 1H), 7.68 (q, 1H), 7.88 (d, 2H), 8.08 (d, 1H), 8.39 (q, 1H), 9.68 (s, 2H), 9.88 (s, 1H); MS (FAB) *m/z* 537 $[M]^+$.

Examples 3 - 6

The following compounds wherein X, R^1, R^2 and R^3 are as shown in formula **(I)**, were prepared using the appropriate starting materials, by a similar process to that described in Example 2:

Ex	X	R^3	R^2	R^1	NMR δ	MS, ES+
3[1]	NH				3.16 (s, 9H); 3.51 (t, 2H); 3.68 (q, 2H); 6.83 (td, 2H); 7.33 (q, 2H); 7.51 (d, 2H); 7.87 (brq, 6H); 8.67 (t, 1H); 9.57 (s, 2H); 9.66 (s, 1H)	519
4	NH				3.14 (s, 9H); 3.51 (t, 2H); 3.70 (q, 2H); 6.82 (td, 1H); 7.07 (t, 1H); 7.3-7.4 (m, 3H); 7.45-7.9 (m, 5H); 7.68 (s, 1H); 8.08 (s, 1H); 8.32 (q, 1H); 9.48 (s, 1H); 9.57 (s, 1H); 9.77 (s, 1H)	519
5[2]	NH				(373 K) 3.17 (s, 9H); 3.2-3.35 (m, 4H); 3.4-3.6 (m, 6H); 3.7-3.85 (q, 2H); 5.8 (s, 1H); 6.75 (td, 1H); 6.85 (t, 1H); 7.27 (q, 1H); 7.50 (dd, 1H); 7.6-7.8 (m, 3H); 7.87 (dd, 1H); 7.95 (q, 1H); 8.90 (s, 1H); 9.15 (s, 1H)	555
6	O				3.17 (s, 9H); 3.55 (t J=7Hz, 2H); 3.73 (m, 2H); 6.8 (m, 2H); 7.25 (m, 2H); 7.35 (m, 2H); 7.4 (d J=9Hz, 2H); 7.6 (brs, 2H); 7.97 (d J=9Hz, 2H); 8.8 (t J=5Hz, 1H); 10.0 (s, 2H)	-

[1] Precipitated directly from the reaction mixture.
[2] THF/MeOH solvent for the reaction.

Example 7.

2-Amino-4-(3,5-dichloroanilino)-6-(3-(N-oxidopyridyl)methyl)-1,3,5-triazine.

A mixture of 1-(3,5-dichlorophenyl)biguanidine hydrochloride (0.283g, 1 mmol), phenyl 3-pyridineacetate N-oxide (0.229g, 1mmol), diisopropylethylamine (5 ml) and DMF (5 ml) was heated at 100 °C for 70 mins. to give a precipitate. The precipitate was isolated by filtration and washed sequentially with DMF, methanol, acetone, and diethyl ether and then dried at 60 °C under vacuum over P_4O_{10} to give a white solid. Yield 0.179 g (49%); Mp >276 °C; NMR δ 3.8 (s, 2H), 7.08 (t, 1H), 7.1 -7.2 (m,4H), 7.81 (s, 2H), 8.08 (d, 1H), 8.18 (s, 1H), 9.79 (br. s, 1H); MS (ES+) *m/z* 230 $[MH]^+$.

Example 8.

2-Amino-4-(3,5-dichloroanilino)-6-(1-imidazolylmethyl)-1,3,5-triazine.

A mixture of 2-amino-4-(3,5-dichloroanilino)-6-chloromethyl-1,3,5-triazine (0.152 g, 0.5 mmol), imidazole (0.0374 g, 0.55 mmol), and dry DMF (3 ml) was heated at 100°C for 2.5 h. The mixture was cooled and filtered to give a first fraction of crude product. The filtrate was evaporated to dryness and the residue was triturated with acetone, filtered and the resulting solid was washed with acetone to give a second fraction of crude product. Both fractions of crude product were combined and methanol (5 ml) was added. The resulting suspension was filtered. The filtrate was concentrated and filtered. The filtrate was diluted with ethyl acetate/methanol; 3:1 and filtered through a column of silica. The purified filtrate was evaporated to dryness, taken into a small volume of methanol, filtered, diluted with ethyl acetate (3 volumes), and concentrated to give a purified product that was collected by filtration. Yield 0.027 g (16%); Mp 241-243 °C; NMR δ 5.03 (s, 2H), 6.90 (s, 1H), 7.10 (t, 1H), 7.17 (s, 1H), 7.32 (br. s, 2H), 7.66 (s, 1H), 7.82 (br. s, 2H), 9.82 (br. s, 1H); MS (ES^+) *m/z* 336 $[MH]^+$.

Example 9.

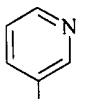
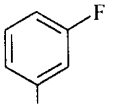
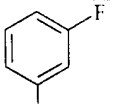
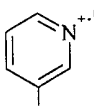
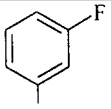
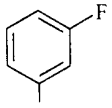
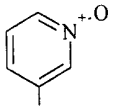
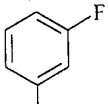
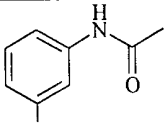
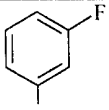
2,4-(Bis-3'-fluoroanilino)-6-(3''-fluorophenoxy)-1,3,5-triazine.

2-Chloro-bis-4,6-(3'-fluoroanilino)-1,3,5-triazine (207 mg, 0.62 mM) and 3-fluorophenol (77 mg, 0.68 mM) were dissolved in dimethyl sulphoxide (3ml). Aqueous sodium hydroxide (1M, 0.6 ml, 0.6 mM) was added and the resulting solution was heated at 90 °C for 18 h. The reaction mixture was cooled, diluted with water (15 ml) and extracted

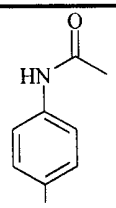
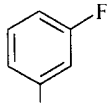
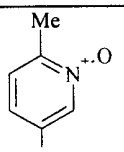
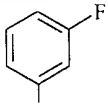
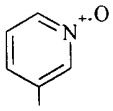
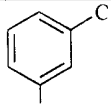
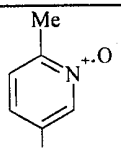
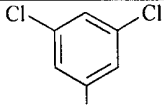
with ethyl acetate (2 x 20 ml). The combined organic layers were washed with brine (20 ml), dried, filtered and concentrated to give the 'crude product', which was chromatographed on silica eluting with dichloromethane/isohexane; 1:1 increasing to dichloromethane. The resulting oil was triturated with methanol (2 ml) and water (2 ml) and the resulting solid was collected by filtration and dried under vacuum at 50 °C. Yield 175 mg (89%); Mp 167-168 °C; NMR δ 6.82 (m, 2H), 7.1-7.7 (m, 10H), 10.04 (s, 2H); MS (ES^+) *m/z* 410 ($[MH]^+$, 100%).

Examples 10 - 21.

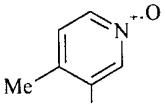
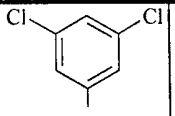
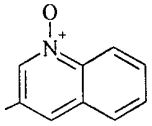
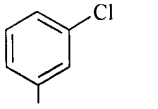
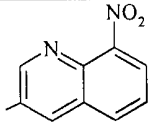
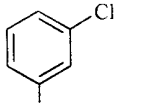
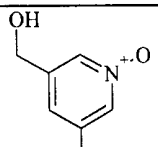
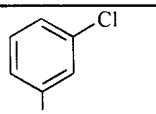
The following compounds wherein X, R^1, R^2 and R^3 are as shown in formula **(I)**, were prepared using the appropriate starting materials, by a similar process to that described in Example 9:

Ex	X	R^1	R^2	R^3	NMR δ	MS, ES+
10[3]	O				6.80 (m, 2H), 7.2-7.85 (m, 8H), 8.50 (m,1H), 8.60 (d J=3Hz, 1H), 10.00 (s, 2H)	393
11[4]	O				6.83 (m, 2H), 7.3-7.8 (m, 8H), 8.19 (m , 1H), 8.45 (m, 1H), 10.10 (s, 2H)	409
12[2]	O			H	6.75 (m, 1H), 7.17-7.5 (m, 6H), 7.7 (m, 1H), 8.13 (m, 1H), 8.35 (m, 1H), 9.78 (s, 1H)	315
13[5]	O			H	2.10 (s, 3H), 6.73 (dt J=2,8Hz, 1H), 6.86 (m, 1H), 7.24-7.50 (m, 7H), 7.68 (m, 1H), 9.75 (s, 1H), 10.0 (s, 1H)	355

[3] Product purified by crystallisation from ethyl acetate/isohexane.
[4] Product precipitated directly from the cooled reaction mixture by the addition of water and filtered.
[5] Product crystallised from dichloromethane.

Ex	X	R^1	R^2	R^3	NMR δ	MS, ES+
14[6]	O			H	2.05 (s, 3H), 6.72 (dt J=2,8Hz, 1H), 7.10 (d J=8Hz, 2H), 7.05-7.25 (m, 3H), 7.36 (brm, 1H), 7.57 (d J=8Hz, 2H), 7.69 (brm, 1H), 9.63 (s, 1H), 9.93 (s, 1H)	355
15[7]	O			H	(373 K) 2.40 (s, 3H), 6.72 (ddd J=3,8,8Hz, 1H), 6.85 (s, 2H), 7.16 (dd J=2,8Hz, 1H), 7.23 (dd J=7,8Hz, 1H), 7.42 (m, 2H), 7.61 (ddd J=2,2,10Hz, 1H), 8.25 (d J=2Hz, 1H), 9.40 (s, 1H)	327 $M-H^-$
16[8]	O			H	(373 K) 6.80 (s, 2H), 6.90 (m, 1H), 7.17 (m, 2H), 7.37 (dd J=7,8Hz, 1H), 7.55 (m, 1H), 7.74 (t J=2Hz, 1H), 8.09 (m, 1H), 8.18 (t J=2Hz, 1H), 9.29 (s, 1H)	331
17[9]	O			H	(373 K) 2.35 (s, 3H), 6.90 (brs, 2H), 7.0 (m, 1H), 7.14 (dd H=2,8Hz, 1H), 7.42 (d J=8Hz, 1H), 7.68 (m, 2H), 8.25 (m, 1H), 9.5 (brs, 1H)	379

[6] Product crystallised from acetonitrile.
[7] Product recrystallized from ethyl acetate.
[8] Product recrystallized from ethyl acetate.
[9] Reaction mixture diluted with water and the product was isolated by filtration. The precipitate was washed with water, THF, methanol and diethyl ether.

Ex	X	R^1	R^2	R^3	NMR δ	MS, ES+
18[10]	O			H	2.1 (s, 3H), 7.04 (s, 1H), 7.16 (brs, 2H), 7.3 (m, 1H), 7.7 (s, 2H), 8.01 (m, 1H), 8.19 (s, 1H)	379
19[11]	O			H	(373 K) 6.91 (dd, 1H), 7.12 (m, 3H), 7.54 (d, 1H), 7.75 (m, 3H), 7.84 (d, 1H), 8.04 (dd, 1H), 8.53 (dd, 1H), 8.68 (d, 1H), 9.56 (brs, 1H)	381
20[12]	O			H	(373 K) 2.5 (s), 6.92 (dd, 1H), 7.1-7.2 (m, 3H), 7.5 (dd, 1H), 7.7 (s, 1H), 7.79 (t, 1H), 8.22 (d, 1H), 8.27 (d, 1H), 8.46 (d, 1H), 9.02 (d, 1H), 9.57 (brs, 1H)	410
21[13]	O			H	4.5 (s, 2H); 5.1 (s, 1H); 6.85 (s, 2H); 6.98 (1H, m); 7.15 (m, 1H); 7.20 (t J=8Hz, 1H); 7.57 (m, 1H); 8.02 (s, 1H); 8.08 (s, 1H); 9.60 (s, 1H)	-

Examples 22 and 23.

2,4-(*Bis*-3'-fluoroanilino)-6-(4''-methylsulphoxidophenoxy)-1,3,5-triazine.

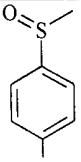
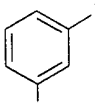
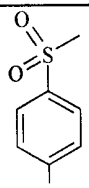
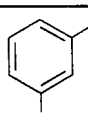
2,4-(*bis*-3'-fluoroanilino)-6-(4''-methylsulphonophenoxy)-1,3,5-triazine.

[10] Purified by crystallisation from methanol and ethyl acetate.
[11] Product precipitated directly from the cooled reaction mixture by the addition of water and filtered.
[12] Product precipitated directly from the cooled reaction mixture by the addition of water and filtered.
[13] Product recrystallized from ethyl acetate.

2,4-(*bis*-3'-fluoroanilino)-6-(4"-methylmercaptophenoxy)-1,3,5-triazine (223 mg, 0.5 mM) in dichloromethane (15 ml) m-chloroperoxybenzoic acid (50% aqu., 170 mg, 0.55 mM) was added and the reaction mixture was stirred for 20 mins. then concentrated. The solid was dissolved in ethyl acetate (10 ml) and silica (5 g) was added. The slurry was concentrated and then added to the top of a silica column and chromatographed eluting with ethyl acetate/hexane; 1:1 increasing to ethyl acetate to give the sulphoxide (Example 22) and sulphone (Example 23) as white solids. For Example 22: Yield 80 mg (35%); mp 203-205 °C; NMR δ 3.78 (s, 3H), 6.80 (m, 2H), 7.2-7.85 (m, 6H), 7.50 (d, 2H), 7.78 (d, 1H), 10.05 (s, 2H); MS (ES^+) *m/z* 454 ($[MH]^+$, 100%). For Example 23: Yield 88 mg (37%); mp 187-189 °C; NMR δ 3.55 (s,3H), 6.80 (m, 2H), 7.2-7.75 (m, 6H), 7.58 (d J=8Hz, 2H), 8.03 (d J=8Hz, 2H), 10.10 (s, 2H); MS (ES^+) *m/z* 470 ($[MH]^+$, 100%).

Example 24 and **Example 25.**

The following compounds wherein X, R^1, R^2 and R^3 are as shown in formula **(I)**, were prepared using the appropriate starting materials, by a similar process to that described in Examples 22 and 23:

Ex	X	R^1	R^2	R^3	NMR δ	MS, ES+
24	O			H	(373 K) δ 2.75 (s, 3H), 6.7 (m, 3H), 7.16 (dt J=6,8 Hz, 1H), 7.35 (m, 3H), 7.62 (dt J=3,12 Hz, 1H), 7.72 (d J=8 Hz, 2H), 9.50 (s, 1H)	360
25	O			H	(373 K) δ 3.15 (s, 3H), 6.69 (m, 1H), 6.78 (brs, 2H), 7.18 (dt J=6,8 Hz, 1H), 7.35-7.48 (m, 3H), 7.62 (dt J=3,12 Hz, 1H), 7.95 (d J=8 Hz, 2H), 9.25 (s, 1H)	376

Example 26.

2-Amino-4-(3'-fluoroanilino)-6-(3"-pyridyloxy)-1,3,5-triazine.

2-Chloro-4-(3'-fluoroanilino-6-(3"-pyridyloxy)-1,3,5-triazine (80 mg, 0.25 mM) was dissolved in acetone (10 ml) and conc. ammonia (1 ml) was added. After 30 mins., the solution was partitioned between ethyl acetate (30 ml) and water (30 ml). The organic layer

was washed with brine (30 ml), dried, filtered and concentrated and the residue was chromatographed over silica and eluted with ethyl acetate to give Example 26 as a white solid. Yield 20 mg (27%); NMR δ 6.75 (m, 1H), 7.15-7.4 (m, 4H), 7.5 (m, 1H), 7.7 (m, 2H), 8.45 (m, 1H), 8.5 (d J=3Hz, 1H), 9.7 (s, 1H); MS (ES^+) *m/z* 299 ($[MH]^+$, 100%).

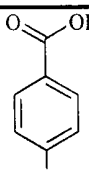
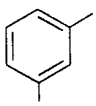
Example 27.

2-Amino-4-(3'-carboxyphenoxy)-6-(3"-fluoroanilino)-1,3,5-triazine.

Methyl 2-amino-4-(3'-carboxyphenoxy)-6-(3"-fluoroanilino)-1,3,5-triazine (15.2 g) was dissolved in methanol (250 ml) and aqueous sodium hydroxide (1M, 45 ml) was added. After stirring for 15 h., the reaction mixture was concentrated and diluted with water (200 ml, to pH12) and washed with ethyl acetate (50 ml). The aqueous layer was acidified with conc. hydrochloric acid to give Example 27 as a white precipitate which was collected by filtration. Yield 7.36 g (53%); NMR δ 6.13 (s, 2H), 6.32 (m, 1H), 6.82 (dd J=7,15Hz, 1H), 6.7-7.25 (m, 3H), 7.3 (brm, 1H), 7.48 (s, 1H), 7.58 (d J=7Hz, 1H), 8.73 (s, 1H); MS (ES^-) *m/z* 340 ($[M-H]^-$, 100%).

Example 28.

The following compound wherein X, R^1, R^2 and R^3 are as shown in formula **(I)**, were prepared using the appropriate starting materials, by a similar process to that described in Example 27:

Ex	X	R^1	R^2	R^3	NMR δ	MS, ES-
28	O			H	6.71 (dt J=3,8Hz, 1H), 7.1-7.4 (m, 4H), 7.32 (d J=9Hz, 2H), 7.64 (brm, 1H), 8.0 (d J=9Hz, 2H), 9.73 (s, 1H)	340

Example 29.

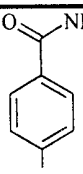
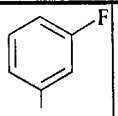
2-Amino-4-(3'-carboxamidophenoxy)-6-(3"-fluoroanilino)-1,3,5-triazine.

2-Amino-4-(3'-carboxyphenoxy)-6-(3"-fluoroanilino)-1,3,5-triazine (1.36 g, 4 mM) and carbonyl diimidazole (CDI) (650 mg, 4 mM) were dissolved in dimethylacetamide (16 ml) and stirred for 2 h.. A further quantity of CDI (300 mg, 1.8 mM) was added and the reaction mixture stirred for 1 h. A portion of the solution (2 ml, *ca.* 0.5 mM) was added to

conc. ammonia (0.1 ml) and stirred for 2 h. at 50 °C, then at room temperature for a further 15 h. The mixture was partitioned between ethyl acetate and water, the organic layer washed with water, dried, filtered and concentrated. The residue was dissolved in 30% ethyl acetate/isohexane (5 ml) and left for 15 h.. Example 29 had precipitated and was collected by filtration. Yield 36 mg (21%); NMR (373 K) δ 6.70 (m, 3H), 7.20 (m, 3H), 7.28-7.4 (m, 2H), 7.45 (t J=8Hz, 1H), 7.57 (dt J=3,12Hz, 1H), 7.67 (t J=2Hz, 1H), 7.74 (dt J=2,8Hz, 1H), 9.22 (s, 1H); MS (ES^-) *m/z* 339 ($[M-H]^-$, 100%).

Example 30.

The following compound wherein X, R^1, R^2 and R^3 are as shown in formula **(I)**, were prepared using the appropriate starting materials, by a similar process to that described in Example 29:

Ex	X	R^1	R^2	R^3	NMR δ	MS, ES-
30	O			H	6.71 (dt J=3,8Hz, 1H), 7.22 (d J=9Hz, 2H), 7.1-7.4 (m, 6H), 7.67 (brm, 1H), 7.92 (d J=9Hz, 2H), 9.67 (s,1H)	339

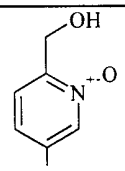
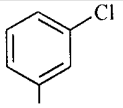
Example 31.

2-Amino-4-(3'-chloroanilino)-6-(1''-N-oxy-6''-methyl-3''pyridyloxy)-1,3,5-triazine.

2-amino-4-(3'chloroanilino)-6-(6''-methyl-3''-pyridyloxy)-1,3,5-triazine (0.5 g, 1.5 mM) was dissolved in acetone (10 ml) and m-chloroperoxybenzoic acid (50% aqu., 584 mg, 1.7 mM) was added. The mixture was stirred for 1 h. and a further portion of m-chloroperoxybenzoic acid (300 mg) was added and stirring continued for 2 h. The mixture was concentrated and slurried with acetone (5 ml) and diethyl ether (5 ml) and the product was filtered off as a white solid. Yield 311 mg (59%); Mp 214-215 °C; NMR (373 K) δ 2.38 (s, 3H), 6.80 (s, 2H), 6.96 (m, 1H), 7.13 (dd H=2,8Hz, 1H), 7.19 (dd J=3,8Hz, 1H), 7.42 (d J=8Hz, 1H), 7.54 (m, 1H), 7.76 (t J=2Hz, 1H), 8.26 (d J=2Hz, 1H), 9.32 (s, 1H); MS (ES^+) *m/z* 345 ($[MH]^+$, 100%).

Example 32

The following compound wherein X, R^1, R^2 and R^3 are as shown in formula **(I)**, were prepared using the appropriate starting materials, by a similar process to that described in Example 31:

Ex	X	R^1	R^2	R^3	NMR δ
31	O			H	4.66 (d J=5Hz, 2H); 5.60 (t J=5Hz, 1H); 6.98 (m, 1H); 7.24 (t J=8Hz,, 1H); 7.30 (m, 2H); 7.37 (m, 1H); 7.60 (m, 2H); 7.80 (s, 1H); 8.40 (d J=2Hz, 1H); 9.74 (s, 1H)

Example 33.

2-Amino-4-(3'-fluoroanilino)-6-(3''-[4'''-hydroxy-3'''-{3''''-methylbutyl}benzoyl]amino-4''-hydroxy-8''-methyl-7''-coumarinyloxy)-1,3,5-triazine.

Sodium hydride (55 mg, 60% in paraffin, 1.38 mM) was placed under an atmosphere of argon and washed with isohexane. DMF (2.5 ml) was added followed by 3-[4'-alloxy-3'-{3''-methylbutyl}benzoyl]amino-4,7-dihydroxy-8''-methylcoumarin (275 mg, 0.63 mM) in DMF (2 ml). The mixture was heated at 80 °C for 15 mins., cooled to 60 °C and 2-amino-4-chloro-6-(3'-fluoroanilino)-1,3,5-triazine (154 mg, 0.69 mM) was added with potassium iodide (10 mg) in DMF (3 ml). The mixture was stirred for 3 h. at 80 °C then left to stand for 15 h., diluted with water (25 ml) and acidified to pH1. A white solid was precipitated and collected by filtration. This material was recrystallized from acetone (8 ml) and water (2 ml) and chromatographed over silica using 50-100% THF/isohexane to give a white solid. Yield 220 mg (56%). A portion of this material (120 mg, 0.19 mM) was dissolved in THF (10 ml) and Meldrum's acid (50 mg). The mixture was placed under argon and a solution of $PdP(Ph_3)_4$ (50 mg) in THF (1 ml) was added. After stirring for 1 h. and standing for 15 h., the mixture was concentrated and partitioned between THF/ethyl acetate (1:1) and aqueous HCl (1M). The organic layer was washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The residue was chromatographed on silica and eluted with 50-100% THF/isohexane, to give Example 33 as a solid. Yield 35 mg (31%); NMR δ 0.94 (d J=7Hz, 6H), 1.4-1.7 (m, 3H), 2.2 (s, 3H), 2.6 (m, 2H), 6.7 (m, 1H), 6.87 (d J=9Hz, 1H), 7.1-7.4 (m, 3H), 7.5-7.85 (m, 7H), 9.27 (s, 1H), 9.69 (s, 1H), 9.94 (s, 1H); MS (ES^+) *m/z* 601 ($[MH]^+$, 70%).

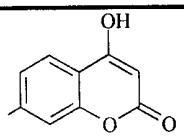
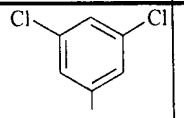
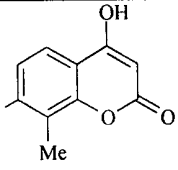
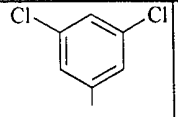
Example 34.

2-Amino-4-(3'-fluoroanilino)-6-(4''-hydroxy-7''-coumarinyloxy)-1,3,5-triazine.

Sodium hydride (80 mg, 60% in paraffin, 2 mM) was placed under an atmosphere of argon and washed with isohexane. 4,7-Dihydroxycoumarin[14] (178 mg, 1 mM) in DMF (5 ml) was added and the mixture heated at 50 °C for 30 mins.. 2-Amino-4-chloro-6-(3'-fluoroanilino)-1,3,5-triazine (239 mg, 1 mM) was added in DMF (7 ml) and the mixture was heated at 80 °C for 24 h., cooled and poured into water (100 ml). The mixture was adjusted to pH3 and extracted with ethyl acetate (3 x 100 ml). The combined organic layers were washed with brine, dried, filtered and concentrated. The residue was stirred with ethyl acetate (5 ml) and filtered to give Example 34 as a white solid. Yield 125 mg (33%); Mp 243-246 °C; NMR δ (300MHz) 5.56 (s, 1H), 6.70 (t, 1H), 7.1-7.4 (m, 6H), 7.6 (brs, 1H), 7.82 (d J=7Hz, 1H), 9.7 (s, 1H), 12.5 (brs, 1H); MS (ES^+) *m/z* 382 ($[MH]^+$, 100%).

Examples 35 -36.

The following compounds wherein X, R^1, R^2 and R^3 are as shown in formula **(I)**, were prepared using the appropriate starting materials, by a similar process to that described in Example 34:

Ex	X	R^1	R^2	R^3	NMR δ	MS, ES+
35	O			H	5.58 (s, 1H), 7.01 (s, 1H), 7.20 (m, 1H), 7.35 (m, 3H), 7.58 (brs, 2H), 7.84 (d J=7Hz, 1H), 9.86 (s, 1H), 12.5 (brs, 1H)	432
36	O			H	2.13 (s, 3H), 5.58 (s, 1H), 7.0 (s, 1H), 7.17 (d, 1H), 7.35 (m, 2H), 7.5 (brs, 2H), 7.75 (d, 1H), 10.0 (s, 1H)	446

[14] C. F. Spencer, C. H. Stammer, J. O. Rodin, E. Walton, F. W. Holly and K. Folkers, *J. Am. Chem. Soc.*, **1956**, *78*, 2655.

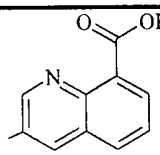
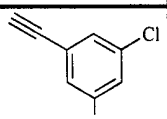
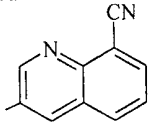
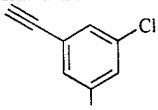
Example 37.

2-Amino-4-(3'-chloroanilino)-6-(8''-carboxyquinolin-3''-yloxy)-1,3,5-triazine.

A mixture of aqueous sodium hydroxide (1M, 6.8 ml, 6.8 mM) and ethyl 2-amino-4-(3'-chloroanilino)-6-quinolin-3''-yloxy)-1,3,5-triazine-8-carboxylate (2.8 g, 6.4 mM) in 1,4-dioxane (56 ml) was stirred at 80 °C for 3 h, cooled in ice and filtered, removing the sodium salt as a white solid (1.2 g). Additionally, the mother liquor was evaporated to dryness, triturated with 1,4-dioxane (5 ml), filtered and the resulting solid was heated in glacial acetic acid (30 ml), cooled and filtered to give Example 37 as a white solid. Yield 600 mg (25%); Mp 245-248 °C; NMR δ 6.95 (d, 1H), 7.10 (s, 1H), 7.20 (s, 2H), 7.40 (s,1H), 7.70 (s, 1H), 7.82 (t, 1H), 8.31 (d, 1H), 8.45 (d, 1H), 8.60 (d, 1H), 9.15 (d, 1H), 9.75 (s, 1H); MS (ES^-) *m/z* 407 $[M-H]^-$.

Examples 38 - 9.

The following compounds wherein X, R^1, R^2 and R^3 are as shown in formula **(I)**, were prepared using the appropriate starting materials, by a similar process to that described in Example 37:

Ex	X	R^1	R^2	R^3	NMR δ	MS, ES-
38	O			H	3.55 (s, 1.4H), 4.3 (s, 1H), 7.04 (s, 1H), 7.3-7.5 (m, 4H), 7.69-7.75 (m, 2H), 7.9 (brs, 1H), 8.1 (d, 1H), 8.75 (d, 1H), 9.88 (brs, 1H)	431
39[15]	O			H	4.14 (s, 1H), 7.00 (s, 1H), 7.66 (s, 2H), 7.57 (m, 1H), 7.80 (t, 2H), 8.14 (m, 2H), 8.46 (t, 1H), 9.09 (t, 1H), 9.83 (s, 1H)	412

[15] Product purified by chromatography on silica Mega Bond Elut, eluting with a gradient of ethyl acetate in isohexane (30-100%).

Example 40.

2-Allylamino-4-(3'-chloroanilino)-6-quinolin-3''-ylamino-1,3,5-triazine 1''-N-oxide.

Allylamine (50 mg, 0.9 mM), 2-chloro-4-(3'-chloroanilino)-6-quinolin-3''-ylamino-1,3,5-triazine-1''-N-oxide (50 mg, 0.13 mM) and 1M $NaHCO_3$ (0.2 ml, 0.2 mM) in 1,4-dioxane (1 ml) were heated at 90 °C for 20 h., poured into water (10 ml), filtered and the solid washed with ethanol to give Example 40. Yield 27 mg (52%); mp 135-140 °C; NMR δ 4.0 (s, 2H), 5.1 (d, 1H), 5.25 (d, 1H), 6.0 (m, 1H), 6.98 (d, 1H), 7.25 (t, 1H), 7.4 (m, 1H), 7.6 (m, 3H), 7.8-8.0 (m, 2H), 8.37 (s, 1H), 8.41 (d, 1H), 9.05 (s, 1H), 9.2 (s, 1H), 9.4 (s, 1H); MS (ES^-) *m/z* 418 $[M-H]^-$.

Example 41.

Diethyl-2-(bis-4,6-(3-fluoroanilino)-1,3,5-triazin-2-yl)hydrazino)methylenemalonate.

A stirred mixture of 2-hydrazino-bis-4,6-(3-fluoroanilino)-1,3,5-triazine (0.099g, 0.3mmol) and diethyl ethoxymethylenemalonate (0.0648g, 0.3mmol) and ethanol (1 ml) was heated (block temperature 90 °C) for 80 mins.. The warm reaction mixture was treated with aqueous sodium hydroxide (1M, 0.5 ml) to give a slurry. The slurry was treated with acetic acid (0.1 ml), diluted with ethanol-water (1:1, 5ml), and heated to reflux. The hot mixture was filtered and the resulting solid was washed with ethanol/water (1:1) and then dried under vacuum over P_4O_{10}. Yield 0.133g (87%); Mp 203-205 °C (decomp.); NMR δ 1.18 (t, 3H), 1.24 (t, 3H), 4.05 (q, 2H), 4.18 (q, 2H), 6.75 (td, 2H), 7.25 (br. q, 2H), 7.52 (br. d, 2H), 7.8 (br. d, 2H), 7.95 (d, 1H), 9.63 (br. s, 2H), 9.9 (brs, 1H), 10.23 (br. d, 1H); MS (CI+) *m/z* 454 $[MH]^+$.

Example 42

2-(5'-Carboxypentylamino)-4,6-bis-(3''-fluoroanilino)-1,3,5-triazine

A suspension of 2-chloro-bis-4,6-(3'-fluoroanilino)-1,3,5-triazine (200 mg, 0.6 mM) and 6-aminohexanoic acid (157 mg, 1.2 mM) in H_2O (1 ml), 3.2 M Na_2CO_3 (0.75 ml) and dioxan (0.75 ml) was vigorously stirred at reflux for 3 h, allowed to cool, added to H_2O (10 ml) and acidified to pH5 with 7% citric acid. The white precipitate was filtered, dried and chromatographed on SiO_2 (10 g) using 1 to 7.5% acetic acid in ethyl acetate, affording a solid: 135 mg (52%); Mp 179-181 °C; NMR δ 1.3-1.45 (m, 2H); 1.5-1.65 (sextet, 4H); 1.9 (s)

(CH_3COOH); 2.20 (t, 2H); 3.3-3.4 (partly obscured by HOD), 6.73 (td, 2H); 7.25 (pentuplet, 3H); 7.50 (d, 2H); 7.85 (d, 2H); 9.2 (s, 1H); 9.33 (s, 1H); MS (ES^+) *m/z* 429 $[MH]^+$.

Example 43.

2-Amino-4-(3',5'-dichloroanilino)-6-(5''-(3'''-carboxyethyl)-1''-N-oxypyrid-3''-yloxy)-1,3,5-triazine.

2-Amino-4-(3',5'-dichloroanilino)-6-(5''-(3'''-carboxyethyl)-1''-N-oxypyrid-3''-yloxy)-1,3,5-triazine, t-butyl ester (102 mg, 0.21 mM) was stirred in trifluoroacetic acid (3 ml) at room temperature for 4 h. Concentration *in vacuo* and azeotroping with toluene gave a brown solid: 138 mg (99%); NMR δ 2.58 (t, 2H); 2.78 (t, 2H); 7.10 (s, 1H); 7.24 (s, 2H); 7.28 (s, 1H); 7.62 (s, 2H); 8.10 (s, 1H); 8.24 (s, 1H); 9.92 (s, 1H); MS *m/z* 435/437 $[M-H]^-$.

Preparation of Starting Materials

The starting materials for the Examples above are either commercially available or are readily prepared by standard methods from known materials. Some of the starting materials also fall within the scope of the invention.

For example the following reactions (Methods A-Q) are illustrations but not limitations of the preparation of some of the starting materials used in the above reactions.

Method A.

2-chloro-bis-4,6-(3'-fluoroanilino)-1,3,5-triazine.

Cyanuric chloride (7.36 g, 40 mM) was dissolved in the minimum volume of acetone and added dropwise to rapidly stirred crushed ice to give a finely divided solid. 3-Fluoroaniline (8.89 g, 80 mM) was added dropwise, followed by sodium hydroxide (3.2 g, 80 mM) in water (50 ml) at a rate which maintained pH between 7 and 10. Towards the end of the addition, the reaction mixture was heated at 45-50 °C for 10 mins., cooled and filtered. The solid was washed with water, a small volume of ethanol and dried. Yield 10.76 g (81%); Mp 170-175 °C; NMR δ 6.85-6.95 (m, 2H), 7.28-7.6 (m, 4H), 7.55-7.75 (brs, 2H), 10.46 (brs, 2H); MS (FAB) *m/z* 334 $[MH]^+$.

Method B.

2-(4'-Dimethylaminoethylaminocarbonyl-3'-fluoroanilino)-bis-4,6-(3''-fluoroanilino)-1,3,5-triazine.

2-Chloro-bis-4,6-(3'-fluoroanilino)-1,3,5-triazine (6.66 g, 20 mM) and *t*-butyl-4-amino-2-fluorobenzoate[16] (3.8 g, 18 mM) were refluxed in xylene (100 ml) for 30 mins.. The resulting solid was filtered off and recrystallized from propan-2-ol to give a white solid. Yield 7.3 g (72%); Mp 103-106 °C; NMR (contains 7% propan-2-ol) δ 1.56 (s, 9H), 6.64 (dt, 2H), 7.33 (q, 2H), 7.4-7.65 (m, 3H), 7.7-7.9 (m, 3H), 8.02 (d, 1H), 9.66 (s, 2H), 9.89 (s, 1H); MS (CI^+) *m/z* 509 $[MH]^+$.

The *t*-butyl ester was stirred for 2 h. in trifluoroacetic acid (35 ml) containing water (3 ml), the white solid was filtered off and washed with diethyl ether to give the trifluoroacetic acid salt. Mp >250 °C; NMR δ 5.5-6.7 (brs), 6.83 (dt, 2H), 7.32 (q, 2H), 7.52 (d, 2H), 7.58 (dd, 1H), 7.75-7.9 (d + t, 3H), 8.05 (dd, 1H), 9.68 (s, 2H), 9.88 (s, 1H); MS (CI+) *m/z* 453. The salt was suspended in dichloromethane (150 ml) and ammonia (5M in methanol, 10 ml) was added, followed by methanol (50 ml) and water (100 ml). The aqueous phase was separated, adjusted to pH6 with 2M HCl, the solid filtered off and washed with water. Yield 5.3 g (87%); Mp 324-326 °C; NMR as for the trifluoroacetic acid salt except δ 7.15 (s, 1H).

The acid (13.8 g, 31 mM), pyridine (12 ml, 148 mM),and pentafluorophenyl trifluoroacetate (11.1 g, 6.8 ml, 40 mM) were stirred in DMF (100 ml) to give crude ester. Yield 14.8 g (79%). A sample (1.2 g) was chromatographed on silica. Mp 190-193 °C; NMR δ 6.85 (dt, 2H), 7.35 (q, 2H), 7.52 (brd, 2H), 7.7 (dd, 1H), 7.87 (brd, 2H), 8.06 (t, 1H), 8.3 (dd, 1H), 9.76 (brs, 2H), 10.16 (brs, 1H); MS (FAB) *m/z* 619 $[MH]^+$.

The pentafluorophenyl ester (309 mg, 0.5 mM) and N,N-dimethylethylenediamine (44 mg, 55 µl, 0.5 mM) were stirred in THF (3 ml) for 2 h. After distribution between ethyl acetate and water, the organic phase was separated and washed with aqueous sodium hydrogen carbonate solution and water, evaporated and chromatographed on an Isoelute column (5 g), eluting with ethyl acetate/methanol/triethylamine; 9:1:0, then 18:1:1 to give a white solid. Yield 169 mg (65%); Mp 197-198 °C; NMR δ (contains 1 ethyl acetate) 2.24 (s, 6H), 2.48 (obscured t), 3.4 (obscured m), 6.84 (dt, 2H), 7.35 (q, 2H), 7.53 (d, 2H), 7.6 (dd, 1H), 7.65 (q, 1H), 7.87 (m, 3H), 8.02 (d, 1H); MS (CI^+) *m/z* 523 $[MH]^+$.

Methods B1 -2.

Using the appropriate starting materials and a procedure similar to that above the following compound was prepared:

B1) 2-(4'-dimethylaminoethylaminocarbonyl-anilino)-bis-4,6-(3''-fluoroanilino)-1,3,5-triazine;

B2) 2-(4'-dimethylaminoethylaminocarbonyl-3'-fluoroanilino)-4-anilino-6-(3''-fluoroanilino)-1,3,5-triazine;

B3)[17] 2-(4'-dimethylaminoethylaminocarbonyl-3'-fluoroanilino)-4-(2''-(imidazolidin-2'''-on-1'''-ylethylamino-6-(3''-fluoroanilino)-1,3,5-triazine.

Method C.

Phenyl 3-pyridineacetate N-oxide.

Phenyl 3-pyridineacetate[18] (2.812 g, 13.2 mmol), 3-chloroperoxybenzoic acid (50% strength, 4.83 g, 14 mmol), and acetone (30 ml) were stirred at room temperature for 50 mins.. An additional portion of 3-chloroperoxybenzoic acid (50% strength, 0.23 g, 0.667 mmol) was added and the mixture was stirred for a further 10 mins.. The mixture was evaporated to dryness and the oily residue was triturated with diethyl ether (50 ml) until crystallisation occurred. The mixture was diluted with isohexane (50 ml) and filtered. The resulting solid was washed with isohexane/ether (1:1, 100 ml) and then dissolved in dichloromethane (200 ml). The solution was washed with saturated aqueous sodium bicarbonate (3 x 15 ml), dried, and evaporated to leave an oil that crystallised when triturated with diethyl ether/isohexane (1:1). The solid was collected by filtration and washed with diethyl ether/isohexane (1:1). Yield 2.259 g (75%); Mp 51.5-53 °C; NMR δ 4.01 (s, 2H), 8.13 (d, 2H), 8.23 (t, 1H), 8.31-8.45 (m, 4H), 8.13 (d, 1H), 8.29 (s, 1H); MS (ES+) *m/z* 230 $[MH]^+$.

Method D

2-amino-4-(3,5-dichloroanilino)-6-chloromethyl-1,3,5-triazine.

---

[16] A. L. Jackman, P. R. Marsham, T. J. Thornton, J. A. M. Bishop, B. M. O'Connor, L. R. Hughes, A. H. Calvert and T. R. Jones, *J. Med. Chem.*, **1990**, *33*, 3067.

[17] Procedure of Method B followed from ester cleavage. Preparation of starting materials to this poing as described below. 1,2-dimethoxyethane as a solvent for pentafluorophenyl ester reacion.

[18] C. Almansa et al, EP 488301A1 920603, CA 117: 130276

A stirred mixture of 1-(3,5-dichlorophenyl)biguanidine hydrochloride (0.283g, 1 mmol), sodium methoxide (0.5M in methanol, 40 ml, 2 mmol), and methanol (20 ml) was maintained at 0-2 °C and ethyl chloroacetate (1.225 g, 1 mmol) was added dropwise over 5 mins.. The mixture was allowed to warm to room temperature overnight. Conc. hydrochloric acid (0.84 ml, 1 mmol) was added and the mixture was evaporated to dryness. The residue was triturated with warm ethyl acetate and filtered to remove an undissolved solid. The filtrate was evaporated to dryness and a solution of the residue in a small volume of ethyl acetate was filtered through a column of silica-gel (Fluka 60741, 50 g) and eluted with ethyl acetate. The filtrate was evaporated to dryness, redissolved in a small volume of ethyl acetate and chromatographed on silica-gel (Fluka 60741, 50 g) and eluted with isohexane/ethyl acetate; 3:2 to give a crude product that was purified by trituration with isohexane/ether (trace of ether only). The purified residue was collected by filtration, washed with isohexane, and air-dried. Yield 0.943 g (31%); NMR δ 4.36 (s, 2H), 7.13 (t, 1H), 7.45 (br. s, 2H), 7.89 (d, 2H),10.0 (br. s, 1H); MS (ES^+) *m/z* 304 $[MH]^+$.

Method E - E3

Using the appropriate starting materials and a procedure similar to that of **Example 9** the following compounds were prepared:

E) 2,4-(*bis*-3'-fluoroanilino)-6-(4"-methylmercaptophenoxy)-1,3,5-triazine;

E1) Methyl 2-amino-4-(3'-carboxyphenoxy)-6-(3"-fluoroanilino)-1,3,5-triazine;

E2) 2-amino-4-(3'chloroanilino)-6-(6"-methyl-3"-pyridyloxy)-1,3,5-triazine;

E3)[19] 4-carboxyphenoxy-*bis*-m-fluoroanilino-1,3,5-triazine.

Method F.

2-Amino-4-chloro-6-(3'-fluoroanilino)-1,3,5-triazine.

Cyanuric chloride (36.8 g, 0.2 M) was dissolved in chloroform (500 ml) and cooled in an ice bath. m-Fluoroaniline (38.4 ml, 44.4 g, 0.4 M) in chloroform (100 ml) was added with vigorous stirring. The mixture was allowed to warm to room temperature and then filtered to give 2,4-dichloro-6-(3'-fluoroanilino)-1,3,5-triazine (30 g). A portion of this material (2.64 g, 10 mM) was dissolved in ethanol (20 ml) and ammonia (2M in ethanol, 10.5 ml, 21 mM) was added. After stirring for 1 h., conc. aqueous ammonia (2 ml) was added. After 1 h., water (10

ml) was added and a solid was collected by filtration. This material was dissolved in DMF (2 ml) and methanol (5 ml) and absorbed onto silica, dried and placed on the top of a silica column. The column was eluted with ethyl acetate/isohexane; 1:1 to give 2-amino-4-chloro-**6**-(3'-fluoroanilino)-1,3,5-triazine as a white solid. Yield 2.1 g (87%); NMR δ 6.82 (m, 1H), 7.3 (m, 1H), 7.45 (m, 1H), 7.65 (brs, 2H), 7.8 (m, 1H), 10.1 (s, 1H).

Methods F1 - 4.

Using the appropriate starting materials and a similar procedure to that described above the following compounds were also prepared:

F1) 2-Amino-4-chloro-6-(3'-chloroanilino)-1,3,5-triazine;

F2) 2-Amino-4-chloro-6-(3',5'-dichloroanilino)-1,3,5-triazine;

F3) 2-Amino-4-chloro-6-(3'-chloro-5'-ethynylanilino)-1,3,5-triazine;

F4) 2-chloro-4-anilino-6-(3'-fluoroanilino)-1,3,5-triazine.

Method G.

3-hydroxy-8-nitroquinoline.

3-Hydroxy-8-nitroquinoline was prepared by the method of T.Nakashima and I.Suzuki, *Chem. Pharm. Bull.(Japan)*, **1969**, 17, 2293.

Method H

5-Hydroxymethyl-3-hydroxypyridine N-oxide

Methyl 5-hydroxynicotinate[20] (2.5 g, 16.3 mM) was dissolved in DMSO (25 ml) and added to a cooled solution of sodium methoxide in methanol (375 mg sodium, 5 ml methanol). Benzyl bromide (2.79 g, 16.3 mM) was added dropwise and after 30 min the reaction was concentrated under vacuum and partitioned between ethyl acetate and water. The organic layer was dried, filtered and concentrated and the residue chromatographed on silica using 30% ethyl acetate in hexane as eluent to give methyl 5-benzyloxypyridine-3-carboxylate (1.5 g). A portion of this material (1.25 g, 5 mM) was dissolved in diethyl ether (20 ml) and added to a stirred slurry of lithium aluminium hydride (225 mg, 5.9 mM) in Et_2O (20 ml) under argon, whilst cooling in an ice bath. The mixture was then stirred at room temperature

[19] Hydrolysis of the resulting methyl ester was with aqueous NaOH in methanol

[20] R.Urban and O.Schnider, *Helv. Chim. Acta.*, 1964. **47**, 363

for 15 h. 'Wet' diethyl ether (10 ml) was added, followed by a solution of sodium hydroxide (360 mg in water (2 ml). After 30 min, the supernatant was decanted off and the precipitate washed with diethyl ether (10 ml) and decanted. The combined organic layers were dried, filtered and concentrated to a yellow solid (1.04g). A portion of this material (500 mg, 2.3 mM) was stirred in ethanol (20 ml) and 10% palladium on carbon (50 mg) under an atmosphere of hydrogen. After 18 h, the catalyst was filtered off and the filtrate concentrated to a solid. To a portion of this solid (266 mg, 2.1 mM) slurried in 10% methanol and dichloromethane was added 3-chloro-peroxybenzoic acid (50% aqueous, 734 mg). A clear solution was formed initially but after stirring for 18 h, the product, 5-hydroxymethyl-3-hydroxypyridine N-oxide, was precipitated and could be isolated by filtration: 204mg (22%).

Method I.

2-chloro-4-(3'-fluoroanilino-6-(3''-pyridyloxy)-1,3,5-triazine.

2,4-Dichloro-6-(3'-fluoroanilino)-1,3,5-triazine (1.0 g, 3.8 mM) was dissolved in acetone (30 ml) and cooled to 5-10 °C. 3-Hydroxypyridine (0.37 g, 3.8 mM) was added followed by aqueous sodium hydroxide (1M, 3.8 ml, 3.8 mM). The solution was stirred for 1.5 h. and then partitioned between ethyl acetate (100 ml) and water (100 ml). The organic layer was washed with 0.1M sodium hydroxide (50 ml), water (50 ml) and brine (50 ml), dried over Na_2SO_4, filtered and concentrated. The residue was chromatographed on silica and eluted with ethyl acetate/hexane; 1:1 to give 2-chloro-4-(3'-fluoroanilino-6-(3''-pyridyloxy)-1,3,5-triazine as a white solid. Yield 390 mg.

Method J

3-[4'-alloxy-3'-{3''-methylbutyl}-benzoyl]amino-4,7-dihydroxy-8''-methylcoumarin.

Sodium hydride (320 mg, 60% in paraffin, 8 mM) was placed under an atmosphere of argon and washed with isohexane. Dihydronovobiocin[21] (2.45 g, 4 mM) in DMF (10 ml) was added and the mixture stirred for 20 mins.. Allyl bromide (485 mg, 4 mM) in DMF (5 ml) was added and the reaction mixture was stirred at 60 °C for 2 h. and at room temperature for 15 h. The mixture was partitioned between ethyl acetate and HCl (0.5M) and the organic layer washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was

[21] J. Berger and A. D. Batcho, J. Chromatography, **1978**, *15*, 101-156.

dissolved in ethanol (100 ml) and acetyl chloride (1 ml) was added and the mixture was heated at reflux for 2 h., cooled and filtered to yield the 3-[4'-alloxy-3'-{3"-methylbutyl}-benzoyl] amino-4,7-dihydroxy-8"-methylcoumarin as a white solid. Yield 869 mg (51%).

Method K

Ethyl 2-amino-4-(3'-chloroanilino)-6-quinolin-3"-yloxy)-1,3,5-triazine-8-carboxylate.

2-amino-4-chloro-6-(3'-chloroanilino)-1,3,5-triazine (195 mg, 0.75 mM) and ethyl 3-hydroxyquinoline-8-carboxylate[22] (100 mg, 0.5 mM) were dissolved in anhydrous DMF (2 ml) and anhydrous potassium carbonate (83 mg, 0.6 mM) was added. The mixture was stirred at 90 °C for 2 h, cooled, added to water (50 ml) and the precipitate filtered off, washed with water (2 x 10 ml) and dried. Chromatography on a 5 g silica column, eluting with a gradient of ethyl acetate in isohexane, increasing from 10% to 90%, gave a white solid. Yield 160 mg (73%); Mp 217-218 °C; NMR δ 1.34 (t, 3H), 4.38 (q, 2H), 6.91 (d,1H), 7.15 (t, 1H), 7.30 (s, 2H), 7.52 (s, 1H), 7.68 (t, 1H), 7.72 (s, 1H), 7.88 (d, 1h), 8.13 (d, 1H), 8.30 (d, 1H), 8.91 (d, 1H), 9.71 (s, 1H); MS (ES^+) *m/z* 437 $[MH]^+$.

Method L.

3-chloro-5-ethynylaniline.

3-bromo-5-chloronitrobenzene (31.5 g, 133 mM) was dissolved in DMF (500 ml) under argon and bis-(triphenylphosphine)-palladium(II) chloride (1.87 g, 2.66 mM), $EtMe_2N$ (40 ml), copper(I) iodide (1.01 g, 5.32 mM) and trimethylsilylacetylene (36.8 g, 266 mM) were added. The reaction mixture was stirred at 40 °C for 16 h. After distribution between diethyl ether (500 ml) and water (500 ml), the aqueous layer was re-extracted with diethyl ether (500 ml), the organic layers combined and filtered through celite®. The organic phase was washed with water (3 x 500 ml), dried and evaporated to a brown oil which was dissolved in 2% ethyl acetate in isohexane (1000 ml) and filtered through silica. Evaporation gave 3-chloro-5-trimethylsilylethynylnitrobenzene as a brown solid. Yield 16.96 g (50%); NMR δ 0.22 (m, 9H), 7.76 (m, 1H), 8.16 (m, 1H), 8.18 (m, 1H); MS (ES^-) *m/z* 238 $[M\text{-}Me]^-$ and 240 $[M\text{-}Me]^-$.

---

[22] E. Ochiai, C. Kaneko, I. Shimada, Y. Murata, T. Kosuge, S. Miyashita and C. Kawasaki, *Chem. Pharm. Bull. (Japan)*, **1960**, 8, 126.

This brown solid (16.90 g, 66 mM) was dissolved in methanol (400 ml) and potassium carbonate (2.0 g) was added. After stirring for 5 mins. it was partitioned between diethyl ether (500 ml) and water (500 ml). The organic layer was separated and washed with water (2 x 500 ml), dried and evaporated to a brown solid. This was purified by dissolving in 50% ethyl acetate in isohexane and filtering through silica to give 3-chloro-5-ethynylnitrobenzene on evaporation as a pale brown solid. Yield 9.17 g (75.7%); NMR ($CDCl_3$) δ 3.28 (s, 1H), 7.77 (d, 1H), 8.21 (m, 2H); MS (ES^-) *m/z* 180 $[M-H]^-$.

The nitro compound (9.1 g, 50 mM) and iron powder (18.2 g, 0.33 g Atom) were refluxed in 1: 6 acetic acid/ethanol (350 ml) for 1 h., allowed to cool. poured into water (1 l). This was extracted with ethyl acetate (2 x 750 ml) and the organic phase was separated and washed with water (750 ml), $NaHCO_3$ (3 x 500 ml), brine (500 ml), dried and evaporated. The brown oil (7.05 g) was chromatographed on silica by MPLC, eluting with dichloromethane/hexane; 1:1 to give 3-chloro-5-ethynylaniline as a pale brown liquid. Yield 4.67 g (62%); NMR ($CDCl_3$) δ 3.04 (s, 1H), 3.76 (brs, 2H), 6.68 (m, 2H), 6.87 (d, 1H); MS (ES^-) *m/z* 150 $[M-H]^-$.

Method M.

8-cyano-3-hydroxyquinoline.

3-Hydroxy-8-nitroquinoline (2.68 g, 14.1 mM) was hydrogenated over 10% palladium on carbon (290 mg) in ethanol (100 ml) at 1 atmosphere pressure of hydrogen for 6 h. The reaction mixture was filtered through celite®, treated with decolourising charcoal, filtered through celite® again and concentrated *in vacuo* to yield 8-amino-3-hydroxyquinoline as a yellow solid. Yield 2.0 g (89%); NMR δ 5.72 (s, 2H), 6.61 (dd, 1H), 6.84 (d, 1H), 7.14 (t, 1H), 7.28 (d, 1H), 8.37 (d, 1H), 10.09 (s, 1H); MS (ES^+) *m/z* 159 $[MH]^+$.

Copper (I) cyanide (1.34 g, 15.0 mM) and potassium cyanide (1.95 g, 30.0 mM) were dissolved in water (7 ml) and heated to 60 °C. 8-amino-3-hydroxyquinoline (2.0 g, 12.5 mM) was dissolved in concentrated hydrochloric acid (5 ml) and water (5 ml) and cooled to 0 °C. Sodium nitrite (0.95 g, 13.75 mM) in water (5 ml) was added in 0.5 ml portions over 20 mins. keeping the temperature below 5 °C. The resulting brown solution was stirred at 0 °C for 10 mins. and sodium carbonate (1.1 g) added to adjust the pH to 7. The mixture was then added to the cyanide solution in 2 ml portions keeping the temperature below 70 °C. The resulting black mixture was stirred at 100 °C for 20 mins., allowed to cool and the reaction mixture

distributed between ethyl acetate (1000 ml) and water (1000 ml). The ethyl acetate layer was dried, filtered, concentrated *in vacuo* on to silica and chromatographed over silica, eluting with 50% and 60% methyl *t*-butylether in isohexane to give **8-cyano-3-hydroxyquinoline** as a yellow solid. Yield 270mg (13%); NMR δ 7.58-7.66 (m, 2H), 8.07 (dd, 1H), 8.15 (dd, 1H), 8.73 (d, 1H), 10.74 (s, 1H); MS (ES^+) *m/z* 171 $[MH]^+$.

Method N

2-chloro-4-(3'-chloroanilino)-6-quinolin-3''-ylamino-1,3,5-triazine 1''-N-oxide.

2,4-Dichloro-6-(3'-chloroanilino)-1,3,5-triazine (2.45 g, 9 mM), 3-aminoquinoline (1.44 g, 10 mM) and $NaHCO_3$ (0.5M, 24 ml, 12 mM) in 1,4-dioxane (40 ml) were stirred for 20 h.. Water (150 ml) was added, the slurry filtered, washed with water (30 ml) and crystallised from propan-2-ol (100 ml) to give 2-chloro-4-(3'-chloroanilino)-6-quinolin-3''-ylamino-1,3,5-triazine. Yield 2.4 g (69%); Mp >250 °C; NMR δ 7.15 (d, 1H), 7.35 (t, 1H), 7.6 (m, 3H), 7.74 (s, 1H), 7.8 (d, 1H), 8.0 (d, 1H), 8.6 (s, 1H), 9.05 (s, 1H), 10.2-10.3 (s, 1H), 10.5 (s, 1H); MS $(ES)^+$ *m/z* 383 $[MH]^+$.

Following the procedure of Example 22, but adding m-chloroperoxybenzoic acid as a solid to an acetone solution of the latter compound, gave, after filtration and ethanol digest, 2-chloro-4-(3'-chloroanilino)-6-quinolin-3''-ylamino-1,3,5-triazine 1''-N-oxide. Yield 950 mg (83%); Mp >265 °C; NMR δ 7.15 (d, 1H), 7.35 (t, 1H), 7.6-7.8 (m, 4H), 7.9 (s, 1H), 8.17 (s, 1H), 8.45 (m, 1H), 8.9 (s, 1H), 10.3 (s, 1H), 10.45 (s, 1H); MS (ES^-) *m/z* 397 $[M-H]^-$.

Method O.

2-Hydrazino-bis-4,6-(3'-fluoroanilino)-1,3,5-triazine.

A stirred mixture of 2-chloro-bis-4,6-(3-fluoroanilino)-1,3,5-triazine (see Example 1) (0.333 g, 1 mmol), hydrazine hydrate (0.46 g, 20 mmol), and 1,4-dioxane (5 ml) was heated at 100 °C for 1 h. The mixture was allowed to cool to room temperature and then poured into water (20 ml) to give a precipitate. The precipitated product was isolated by vacuum filtration and recrystallized from ethanol (5 ml). Yield 0.172g (52%); Mp 202-203 °C; NMR δ 4.29 (s, 2H), 6.72 (td, 2H), 7.23 (q, 2H), 7.48 (br. d, 2H), 7.86 (br. d, 2H), 8.31 (s, 1H), 9.38 (br. s, 1H); MS (CI+) *m/z* 330.1 $[MH]^+$.

Method P.

t-Butyl 2-(3'fluoro-4'-carboxyanilino)-4-(2''-(imidazolidin-2'''-on-1'''-ylethylamino-6-(3''''-fluoroanilino)-1,3,5-triazine.

A solution of cyanuric chloride (5.53 g, 29 mM) in acetone (55 ml) was dropped into water at 0-5 °C. 3-Fluoroaniline (3.33 g, 30 mM) was added, followed by 0.5 M Na_2CO_3 solution (30 ml). After 2 h at 0-5 °C, 2-(imidazolidin-2'-on-1'-yl)ethylamine[23] (3.87 g, 30.2 mM) was added and the mixture stirred at 40 °C during the portionwise addition of 0.5 M Na_2CO_3 (30 ml),such that the pH remained between 7 and 9. After 1 h, the solid was filtered, washed with H_2O and acetone, dissolved in hot DMF (70 ml), cooled to 50 °C and treated with 4:1 Et_2O/DMF (125 ml), with ice cooling. The solid was filtered and washed with Et_2O to give 2-chloro-4-(2'-(imidazolidin-2''-on-1''-ylethylamino-6-(3'''-fluoroanilino)-1,3,5-triazine: 5.84 g (55%); NMR (373 K) d 3.25 (m, 4H); 3.45 (m, 4H); 6.77 (m, 1H); 7.25 (q, 1H); 7.45 (d, 1H); 7.55-7.75 (m, 2H); 9.65 (s, 1H); MS (ES^+) *m/z* 352 $[MH]^+$.

The chloro-triazine (703 mg, 2 mM) and t-butyl 4-amino-2-fluorobenzoate (633 mg, 3 mM) were heated in DMSO (8 ml) at 80-85 °C for 5 h, the mixture poured into CH_2Cl_2 (200 ml), filtered and the solid washed with CH_2Cl_2 and chromatographed on SiO_2 (50 g), eluting with 2-10% methanol in methyl t-butyl ether to give a resin : 120 mg (10%); NMR δ 1.50 (s, 9H); 3.2 (partly obscured by HOD); 3.55 (t, 4H); 6.27 (s, 1H); 6.76 (brt); 7.2-8.1 (m, 7H); 9.42 (d, 1H); 9.65 (d, 1H); MS (ESP^+) *m/z* 527$[MH]^+$.

Method Q

2-Amino-4-(3',5'-dichloroanilino)-6-(5''-(3'''-carboxyethyl)-1''-N-oxypyrid-3''-yloxy)-1,3,5-triazine, t-butyl ester

5-benzyloxy-3-bromopyridine[24] (3.5 g, 13.3 mM), t-butyl acrylate (3.4 g, 26.7 mM), tetramethylethylenediamine (1.55 g, 13.3 mM), palladium acetate (0.12 g, 0.5 mM) and tri-*o*-tolylphosphine (0.324 mg, 1.06 mM) were stirred at 125 °C under argon for 48 h. After leaving at room temperature for 24 h, the mixture was partitioned between ethyl acetate and water. The organic layer was washed with water and brine, dried, filtered and concentrated. The residue was chromatographed on SiO_2 using 10-20% ethyl acetate in hexane as eluent to give a colourless gum: 2.65 g (65%). A portion of this material (1.27 g) was dissolved in

[23] . *Chem. Abs.*, 1954, 2782a. : USP 2613212

ethanol (20 ml) and methanol (10 ml) and hydrogenated over 10% palladium on charcoal (*ca.* 100 mg). The mixture was filtered through Celite, concentrated and chromatographed on SiO_2 using ethyl acetate as eluent giving the t-butyl ester as a gum: 650 mg (71%).

The t-butyl ester (0.64 g, 2.9 mM) and 3-chloroperoxybenzoic acid (1.09 g, 6.3 mM) were stirred O/N at room temperature in CH_2Cl_2 (50 ml). Concentration *in vacuo* and chromatography on SiO_2 using 5% MeOH/CH_2Cl_2 containing 0.1% acetic acid, gave a pale brown oil: 670 mg (98%); NMR δ 1.27 (s, 9H); 1.27ppm (t, 2H); 2.66 (t, 2H); 6.68 (s, 1H); 7.59 (s, 1H); 7.95 (s, 1H).

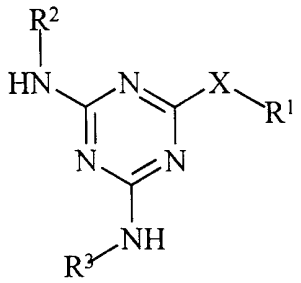
2-Amino-4-chloro-6-(3',5'-dichloroanilino)-1,3,5-triazine (0.81 g, 2.8 mM), the pyridine N-oxide (0.67 g, 2.8 mM) and K_2CO_3 (0.39 g, 5.6 mM) were heated in anhydrous DMF (20 ml) at 80 °C O/N. The mixture was added to ethyl acetate (200 ml) and H_2O (200 ml) and the precipitate filtered, washed and dried: 780 mg (57%); NMR δ 1.34 (s, 9H); 2.55 (t, 2H); 2.77 (t, 2H); 7.10 (s, 1H); 7.23 (s, 1H); 7.42 (s, 2H); 7.23 (s, 2H); 8.09 (s, 1H); 8.22 (s, 1H); 9.95 (s, 1H); MS *m/z* 493/495 $[MH]^+$, *m/z* 516/518.$[M+Na]^+$.

[24] G.C.Crawley, P.N.Edwards and J.M.Girodeau, 1990, EP 385662

CLAIMS

What is claimed is:

1. A compound of the formula **(I)**:



(I)

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof wherein:

X is O, NH, CH_2;

R^1 is an optionally substituted aryl ring, optionally substituted heteroaryl ring, or such ring systems fused to an aryl or heteroaryl ring forming a bicyclic ring; or R^1 is carboxy-C_{1-6}alkyl or imidazolin-2-on-1-ylC_{1-6}alkyl;

R^2 is an optionally substituted aryl ring or such ring system fused to a heteroaryl ring;

R^3 is H, NHR^4, CHR^5R^6, where R^4, R^5 and R^6 are independently H or optionally substituted C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl or R^3 is an optionally substituted aryl ring;

wherein optional substituents for aryl, heteroaryl, such ring systems fused to an aryl ring (for example fused to a benzene ring) or fused to a heteroaryl ring, C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are:

C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkylC(O)-, C_{1-6}alkoxycarbonyl, aryl, aryloxy, heteroaryl, halo, cyano, nitro, hydroxy, carboxy, amino, C_{1-6}alkoxy, $(C_{1-6}alkoxy)_2CH$-, carboxyC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyl$S(O)_2NHC(O)$-, R^7R^8amino (including quaternary derivatives thereof such as $R^7R^8R^7N$-), $R^7NH(R^8N=)C$- (where R^7 and R^8 are independently H, C_{1-6}alkyl, arylC_{1-6}alkyl or R^7 and R^8 may together form an 4-8 membered heteroalkyl ring with 1 - 3 optionally substituted heteroatoms selected from O, S and N), $R^9R^{10}NC(O)$-, (where R^9 is OR^{10}, NHR^{10} or R^{10} and R^{10} is H, C_{1-6}alkyl, aryl, arylC_{1-6}alkyl or R^9 and R^{10} may together form an 4-8 membered heteroalkyl ring with 1 - 3 optionally substituted heteroatoms), $R^{11}S$-, $R^{11}S(O)$-, $R^{11}S(O)_2$-, $R^{11}C(O)NH$-, $R^{11}NHS(O)$-, $R^{11}NHS(O)_2$-, $R^{11}ON=CH$- (where R^{11} is H, C_{1-6}alkyl or arylC_{1-6}alkyl), or optionally substituted guanidine,

and all C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, heteroalkyl rings and aryl groups referred to may themselves be optionally substituted as defined above;

where any nitrogen containing heteroaryl ring in R^1 or R^2 may optionally be N oxidised or N alkylated;

with the provisos

1) that on any optionally substituted phenyl or naphthyl ring the two positions on the ring ortho to the NH or X group linking to the 1,3,5-triazine ring must both be unsubstituted;

2) where R^3 is H, and X is NH, R^1 and R^2 are not both phenyl, 3-halophenyl, 4-halophenyl, 3-methylphenyl, 4-methylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 4-aminoquinolin-6-yl, 4-amino-2-methylquinolin-6-yl or 4-amino-2,3-dimethylquinolin-6-yl; and

3) excluding:

2,4-dianilino-6-(3'-phenylcoumarin-7'-ylamino)-1,3,5-triazine; 2,4-di(4'-amidinoaniline)-6-(4"-amino-2"-methylquinolin-6"-ylamino)-1,3,5-triazine; 2,4-di(4'-cyanoaniline)-6-(4"-amino-2"-methylquinolin-6"-ylamino)-1,3,5-triazine; 2,4,6-tri(N-acetyl-2'-methyl-3'-H-indol-5'-ylamino)-1,3,5-triazine; 2,4,6-tri(2'-methyl-3'-H-indol-5'-ylamino)-1,3,5-triazine; 2,4-di(4'-methoxyanilino)-6-[2"-(1"',3"'-dioxobenzoisobenzofuran-2"'-yl)-quinol-8"-ylamino]-1,3,5-triazine; 2,4-di(2',4'-dichloroanilino)-6-(2"-(1"',3"'-dioxobenzocyclopent-2-yl)-quinol-8"-ylamino)-1,3,5-triazine; 2,4,6-tri(2'-(1",3"-dioxo-4",5",6",7"-tetrachlorobenzocyclopent-2-yl)-quinol-8'-ylamino)-1,3,5-triazine; 2,4-dianilino-6-(2'-(1",3"-dioxo-4",5",6",7"-tetrachlorobenzocyclopent-2-yl)-quinol-8'-ylamino)-1,3,5-triazine and 2-amino-4-anilino-6-(3'-phenylcoumarin-7'-ylamino)-1,3,5-triazine.

2. A compound according to claim 1 wherein X is oxygen.

3. A compound according to either claim 1 or claim 2 wherein R^1 is phenyl or naphthyl or pyridyl, pyrimidyl, triazinyl, imidazolyl, quinolyl, isoquinolyl, benzimidazolyl or the N-oxides or N-alkyl derivatives thereof, or coumarinyl or benzofuran-3-onyl.

4. A compound according to any one of claims 1 to 3 wherein R^2 is 3-fluorophenyl, 3,5-difluorophenyl, 3-chlorophenyl, 3,5-dichlorophenyl 3-chloro-5-EtS-phenyl or 3-ethynyl-5-chlorophenyl.

5. A compound according to any one of claims 1 to 4 wherein R^3 is H, allyl, cyclopropyl, cyanomethyl, 3-fluorophenyl, 3-chlorophenyl, 3-bromophenyl, 3-methylphenyl, 3-ethylphenyl, 3-MeS-phenyl or 3-ethynylphenyl.

6. A compound according to claim 1 or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof wherein:

X is O;

R^1 is 3-fluorophenyl, 3,5-difluorophenyl, 3-chlorophenyl, 3,5-dichlorophenyl, 4-MeS(O)-phenyl, 4-$MeS(O)_2$-phenyl, 3-pyridyl, 3-MeC(O)NH-phenyl, 4-MeC(O)NH-phenyl, 3-carboxyphenyl, 4-carboxyphenyl, 3-$H_2NC(O)$-phenyl, 4-$H_2NC(O)$-phenyl, 6-methyl-3-pyridyl-N-oxy, 4-hydroxycoumarinyl, 3-quinolyl-N-oxy, 8-nitroquinolyl, 8-cyano-quinolyl, 8-tetrazolyl-quinolyl or 8-carboxyquinolyl;

R^2 is 3-fluorophenyl, 3,5-difluorophenyl, 3-chlorophenyl, 3,5-dichlorophenyl or 3-ethynyl-5-chlorophenyl; and

R^3 is H, allyl, cyclopropyl, cyanomethyl, 3-fluorophenyl, 3-chlorophenyl, 3-bromophenyl, 3-methylphenyl, 3-ethylphenyl, 3-MeS-phenyl or 3-ethynylphenyl.

7. A compound according to claim 1 which is chosen from:

Tris-3'-fluoroanilino-1,3,5-triazine;

2-(4'-Trimethylammonioethylaminocarbonyl-3'-fluoroanilino)-bis-4,6-(3"-fluoroanilino)-1,3,5-triazine;

2-Amino-4-(3,5-dichloroanilino)-6-(3-(N-oxidopyridyl)methyl)-1,3,5-triazine;

2-Amino-4-(3,5-dichloroanilino)-6-(1-imidazolylmethyl)-1,3,5-triazine;

2,4-(Bis-3'-fluoroanilino)-6-(3"-fluorophenoxy)-1,3,5-triazine;

2,4-(*Bis*-3'-fluoroanilino)-6-(4"-methylsulphoxidophenoxy)-1,3,5-triazine;

2,4-(*bis*-3'-fluoroanilino)-6-(4"-methylsulphonophenoxy)-1,3,5-triazine;

2,4-(*Bis*-3'-fluoroanilino)-6-(3"-pyridyloxy)-1,3,5-triazine;

2,4-(*Bis*-3'-fluoroanilino)-6-(1"-N-oxy-3"-pyridyloxy)-1,3,5-triazine;

2-Amino-4-(3'-fluoroanilino)-6-(4"-methylsulphoxidophenoxy)-1,3,5-triazine;

2-Amino-4-(3'-fluoroanilino)-6-(4"-methylsulphonophenoxy)-1,3,5-triazine;

2-Amino-4-(3'-fluoroanilino)-6-(3"-pyridyloxy)-1,3,5-triazine;

2-Amino-4-(3'-fluoroanilino)-6-(1"-N-oxy-3"-pyridyloxy)-1,3,5-triazine;

2-(3'-Acetylaminophenoxy)-4-amino-6-(3"-fluoroanilino)-1,3,5-triazine;

2-(4'-Acetylaminophenoxy)-4-amino-6-(3"-fluoroanilino)-1,3,5-triazine;

2-Amino-4-(3'-carboxyphenoxy)-6-(3"-fluoroanilino)-1,3,5-triazine;

2-Amino-4-(4'-carboxyphenoxy)-6-(3"-fluoroanilino)-1,3,5-triazine;

2-Amino-4-(3'-carboxamidophenoxy)-6-(3"-fluoroanilino)-1,3,5-triazine;

2-Amino-4-(4'-carboxamidophenoxy)-6-(3"-fluoroanilino)-1,3,5-triazine;

2-Amino-4-(3'-fluoroanilino)-6-(1"-N-oxy-6"-methyl-3"-pyridyloxy)-1,3,5-triazine;

2-Amino-4-(3'-chloroanilino)-6-(1"-N-oxy-3"-pyridyloxy)-1,3,5-triazine;

2-Amino-4-(3'-chloroanilino)-6-(1"-N-oxy-6"-methyl-3"pyridyloxy)-1,3,5-triazine;

2-Amino-4-(3',5'-dichloroanilino)-6-(1"-N-oxy-6"-methyl-3"-pyridyloxy)-1,3,5-triazine;

2-Amino-4-(3'-fluoroanilino)-6-(3"-[4"'-hydroxy-3"'-{3""-methylbutyl}benzoyl]amino-4"-hydroxy-8"-methyl-7"-coumarinyloxy)-1,3,5-triazine;

2-Amino-4-(3',5'-dichloroanilino)-6-(1"-N-oxy-4"-methyl-3"-pyridyloxy)-1,3,5-triazine;

2-Amino-4-(3'-fluoroanilino)-6-(4"-hydroxy-7"-coumarinyloxy)-1,3,5-triazine;

2-Amino-4-(3',5'-dichloroanilino)-6-(4"-hydroxy-7"-coumarinyloxy)-1,3,5-triazine;

2-Amino-4-(3',5'-dichloroanilino)-6-(4"-hydroxy-8"-methyl-7"-coumarinyloxy)-1,3,5-triazine;

2-Amino-4-(3'-chloroanilino)-6-quinolin-3"-yloxy-1,3,5-triazine 1"-N-oxide;

2-Amino-4-(3'-chloroanilino)-6-(8"-nitroquinolin-3"-yloxy)-1,3,5-triazine;

2-Amino-4-(3'-chloroanilino)-6-(8"-carboxyquinolin-3"-yloxy)-1,3,5-triazine;

2-Amino-4-(3'-chloro-5'-ethynylanilino)-6-(8"-carboxyquinolin-3"-yloxy)-1,3,5-triazine;

2-Amino-4-(3'-chloro-5'-ethynylanilino)-6-(8"-cyanoquinolin-3-yloxy)-1,3,5-triazine;

2-Allylamino-4-(3'-chloroanilino)-6-quinolin-3"-ylamino-1,3,5-triazine 1"-N-oxide;

Diethyl-2-(bis-4,6-(3-fluoroanilino)-1,3,5-triazin-2-yl)hydrazino)methylene-malonate;

2-(4'-Trimethylammonioethylaminocarbonylanilino)-bis-4,6-(3"-fluoroanilino)-1,3,5-triazine;

2-(4'-Trimethylammonioethylaminocarbonyl-3'-fluoroanilino)-4-anilino-6-(3"-fluoroanilino)-1,3,5-triazine;

2-(4'-Trimethylammonioethylaminocarbonyl-3'-fluoroanilino)-4-(2"-(imidazolidin-2"'-on-1"'-ylethylamino-6-(3""-fluoroanilino)-1,3,5-triazine;

2-(4'-Trimethylammonioethylaminocarbonylphenoxy)-bis-4,6-(3"-fluoroanilino)-1,3,5-triazine;

2-(5'-Carboxypentylamino)-4,6-bis-(3"-fluoroanilino)-1,3,5-triazine;

2-Amino-4-(3',5'-dichloroanilino)-6-(5"-(3"'-carboxyethyl)-1"-N-oxypyrid-3"-yloxy)-1,3,5-triazine;

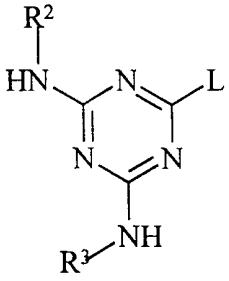
2-Amino-4-(3'-chloroanilino)-6-(1"-N-oxy-5"-hydroxymethylpyrid-3"-yloxy)-1,3,5-triazine;

2-Amino-4-(3'-chloroanilino)-6-(1"-N-oxy-6"-hydroxymethylpyrid-3"-yloxy)-1,3,5-triazine;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

8. A process for preparing a compound of formula **(I)** as defined in claim 1 or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, which process (wherein X, R^1, R^2 and R^3 are as defined in claim 1) comprises of:

a) reacting a compound of formula **(II)**:



(II)

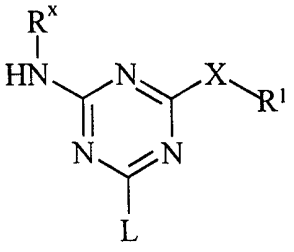
with a compound of formula **(III)**:

R^1XA

(III)

where L is a leaving group and A is an atom or group capable of forming a cation; or

b) reacting a compound of formula **(IV)**:



(IV)

with a compound of formula **(V)**

R^yNHA

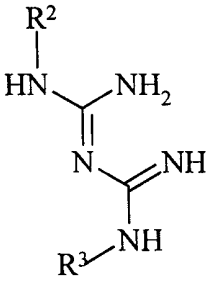
(V)

where L is a leaving group, A is as defined above and

R^x is R^2 and R^y is R^3; or

R^x is R^3 and R^y is R^2,

c) for compounds where X is CH_2, reacting a compound of formula **(VI)**:



(VI)

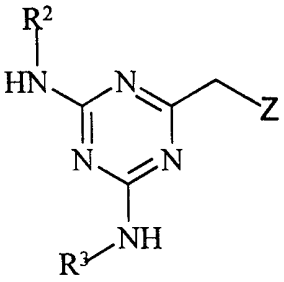
with a compound of formula **(VII)**:

R^1CH_2COY

(VII)

where Y is a leaving group; or

d) for compounds where X is CH_2 reacting a compound of formula **(VIII)**:



(VIII)

where Z is a leaving group with a compound of formula **(IX)**:

R^1A

(IX)

A is as defined above;

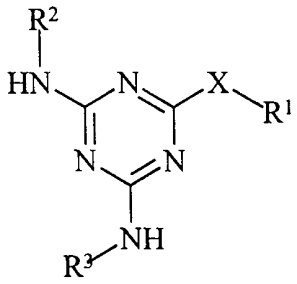
and thereafter if necessary:

i) converting a compound of the formula **(I)** into another compound of the formula **(I)**;

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

9. A pharmaceutical composition which comprises a compound of formula **(IA)**:



(IA)

wherein:

X is O, NH, CH_2;

R^1 is an optionally substituted aryl ring, optionally substituted heteroaryl ring, or such ring systems fused to an aryl or heteroaryl ring forming a bicyclic ring; or R^1 is carboxy-C_{1-6}alkyl or imidazolin-2-on-1-ylC_{1-6}alkyl;

R^2 is an optionally substituted aryl ring or such ring system fused to a heteroaryl ring;

R^3 is H, NHR^4, CHR^5R^6, where R^4, R^5 and R^6 are independently H or optionally substituted C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl or R^3 is an optionally substituted aryl ring;

wherein optional substituents for aryl, heteroaryl, such ring systems fused to an aryl ring (for example fused to a benzene ring) or fused to a heteroaryl ring, C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are:

C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkylC(O)-, C_{1-6}alkoxycarbonyl, aryl, aryloxy, heteroaryl, halo, cyano, nitro, hydroxy, carboxy, amino, C_{1-6}alkoxy, $(C_{1-6}alkoxy)_2CH$-, carboxyC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyl$S(O)_2NHC(O)$-, R^7R^8amino (including quaternary derivatives thereof such as $R^7R^8R^7N$-), $R^7NH(R^8N=)C$- (where R^7 and R^8 are independently H, C_{1-6}alkyl, arylC_{1-6}alkyl or R^7 and R^8 may together form an 4-8 membered heteroalkyl ring with 1 - 3 optionally substituted heteroatoms selected from O, S and N), $R^9R^{10}NC(O)$-, (where R^9 is OR^{10}, NHR^{10} or R^{10} and R^{10} is H, C_{1-6}alkyl, aryl, arylC_{1-6}alkyl or R^9 and R^{10} may together form an 4-8 membered heteroalkyl ring with 1 - 3 optionally substituted heteroatoms), $R^{11}S$-, $R^{11}S(O)$-, $R^{11}S(O)_2$-, $R^{11}C(O)NH$-, $R^{11}NHS(O)$-, $R^{11}NHS(O)_2$-, $R^{11}ON=CH$- (where R^{11} is H, C_{1-6}alkyl or arylC_{1-6}alkyl), or optionally substituted guanidine, and all C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, heteroalkyl rings and aryl groups referred to may themselves be optionally substituted as defined above;

where any nitrogen containing heteroaryl ring in R^1 or R^2 may optionally be N oxidised or N alkylated;

with the provisos

1) that on any optionally substituted phenyl or naphthyl ring the two positions on the ring ortho to the NH or X group linking to the 1,3,5-triazine ring must both be unsubstituted;

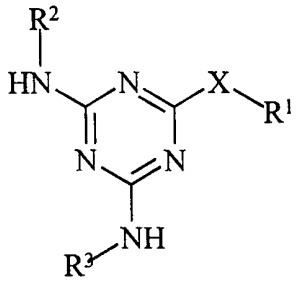
2) where R^3 is H, and X is NH, R^1 and R^2 are not both 4-aminoquinolin-6-yl or 4-amino-2-methylquinolin-6-yl; and

3) excluding:

2,4-di(4'-amidinoaniline)-6-(4"-amino-2"-methylquinolin-6"-ylamino)-1,3,5-triazine and 2,4-di(4'-cyanoaniline)-6-(4"-amino-2"-methylquinolin-6"-ylamino)-1,3,5-triazine;

or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof and a pharmaceutically acceptable diluent or carrier.

10. The use of a compound of the formula **(IB)**:



(IB)

wherein:

X is O, NH, CH_2;

R^1 is an optionally substituted aryl ring, optionally substituted heteroaryl ring, or such ring systems fused to an aryl or heteroaryl ring forming a bicyclic ring; or R^1 is carboxy-C_{1-6}alkyl or imidazolin-2-on-1-ylC_{1-6}alkyl;

R^2 is an optionally substituted aryl ring or such ring system fused to a heteroaryl ring;

R^3 is H, NHR^4, CHR^5R^6, where R^4, R^5 and R^6 are independently H or optionally substituted C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl or R^3 is an optionally substituted aryl ring;

wherein optional substituents for aryl, heteroaryl, such ring systems fused to an aryl ring (for example fused to a benzene ring) or fused to a heteroaryl ring, C_{1-6}alkyl, C_{2-6}alkenyl and C_{2-6}alkynyl are:

C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkylC(O)-, C_{1-6}alkoxycarbonyl, aryl, aryloxy, heteroaryl, halo, cyano, nitro, hydroxy, carboxy, amino, C_{1-6}alkoxy, $(C_{1-6}alkoxy)_2CH$-, carboxyC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkyl$S(O)_2NHC(O)$-, R^7R^8amino (including quaternary derivatives thereof such as $R^7R^8R^7N$-), $R^7NH(R^8N=)C$- (where R^7 and R^8 are independently H, C_{1-6}alkyl, arylC_{1-6}alkyl or R^7 and R^8 may together form an 4-8 membered heteroalkyl ring with 1 - 3 optionally substituted heteroatoms selected from O, S and N), $R^9R^{10}NC(O)$-, (where R^9 is OR^{10}, NHR^{10} or R^{10} and R^{10} is H, C_{1-6}alkyl, aryl, arylC_{1-6}alkyl or R^9 and R^{10} may together form an 4-8 membered heteroalkyl ring with 1 - 3 optionally substituted heteroatoms), $R^{11}S$-, $R^{11}S(O)$-, $R^{11}S(O)_2$-, $R^{11}C(O)NH$-, $R^{11}NHS(O)$-, $R^{11}NHS(O)_2$-, $R^{11}ON=CH$- (where R^{11} is H, C_{1-6}alkyl or arylC_{1-6}alkyl), or optionally substituted guanidine, and all C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, heteroalkyl rings and aryl groups referred to may themselves be optionally substituted as defined above;

where any nitrogen containing heteroaryl ring in R^1 or R^2 may optionally be N oxidised or N alkylated;

with the proviso that on any optionally substituted phenyl or naphthyl ring the two positions on the ring ortho to the NH or X group linking to the 1,3,5-triazine ring must both be unsubstituted;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof in the manufacture of a medicament for use in the production of an antibacterial effect in a warm-blooded animal such as a human being.

INTERNATIONAL SEARCH REPORT

Int ational Application No
PCT/GB 98/01884

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D251/18 C07D251/52 C07D251/70 A61K31/53

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 226 536 A (CIBA-GEIGY AG) 24 June 1987 see page 2 ---	1,9
A	GB 2 078 214 A (NIPPON SHINYAKU) 6 January 1982 see the whole document --- -/--	1,9

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 October 1998	12/11/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kyriakakou, G

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 121, no. 19, 7 November 1994 Columbus, Ohio, US; abstract no. 230747, DESAI, P. S. ET AL.: "Studies and Synthesis of coumarinyl-s-triazine derivatives as potential antibacterial agents" page 1088; column 2; XP002082773 see abstract & J. INDIAN CHEM. SOC., vol. 70, no. 9, 1993, pages 777-779, India	1,9
A	CHEMICAL ABSTRACTS, vol. 120, no. 25, 20 June 1994 Columbus, Ohio, US; abstract no. 323501e, DESAI, K. R. ET AL.: "2-(2'-chloroanilino)-4-(o-carbamoylphenoxy)-6-(arylureido)-s-triazines as antibacterials." page 911; column 2; XP002082774 see abstract & J. INST. CHEM., vol. 64, no. 6, 1992, pages 236-237, India	1,9
A	CHEMICAL ABSTRACTS, vol. 108, no. 5, 1 February 1988 Columbus, Ohio, US; abstract no. 37873m, page 644; column 2; XP002082775 see abstract & JP 62 178576 A (YOSHITOMI PHARMACEUTICALS) 5 August 1987	1,9
A	CHEMICAL ABSTRACTS, vol. 88, no. 5, 30 January 1978 Columbus, Ohio, US; abstract no. 37757v, RAJNANI, H. B. ET AL.: "Studies on thioureas. Part I: Preparation and antibacterial activity of '{2,4-bis(arylamino)-s-triazin-6-yl!aminoacyl!phenylthioureas" page 500; column 2; XP002082776 see abstract & J. INST CHEM., vol. 49, no. 4, 1977, pages 222-224, India	1,9

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte onal Application No
PCT/GB 98/01884

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 226536 A	24-06-1987	AU 583685 B	04-05-1989
		AU 6585786 A	04-06-1987
		CA 1262901 A	14-11-1989
		DD 258811 A	03-08-1988
		DK 576586 A	03-06-1987
		GB 2183646 A,B	10-06-1987
		JP 62138483 A	22-06-1987
		PT 83830 B	09-12-1988
		US 4732899 A	22-03-1988
GB 2078214 A	06-01-1982	JP 1457187 C	09-09-1988
		JP 57035587 A	26-02-1982
		JP 63002264 B	18-01-1988
		CH 648033 A	28-02-1985
		DE 3121922 A	25-02-1982
		FR 2483919 A	11-12-1981
		US 4333933 A	08-06-1982