Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).
Description

[0001] This invention concerns improvements in chemical compounds, more especially it concerns compounds and pharmaceutical compositions. In particular it concerns compositions and compounds having activity in in vitro tests on Human Immunodeficiency Virus-infected cells.

[0002] The disease known as Acquired Immune Deficiency Syndrome (AIDS) caused by infection by HIV has attracted immense research effort because of the effects of the disease on infected individuals and the dangers of the disease spreading to a wider section of the population. In general, although various chemotherapeutic treatments have been advocated, and some compounds have emerged as a potential basis for treatment, there is still a need for effective alternatives. In particular, most treatments such as the compound known as AZT have a high toxicity to cells and it would be desirable to find compounds which are less toxic. In man, the development of resistance to AZT has been identified as an additional clinical problem.

[0003] We have found a group of compounds which show protective properties in in vitro screens of cells challenged with HIV-1 and/or HIV-2, and are therefore indicated as useful for the treatment of AIDS and AIDS Related Complex and other viral and especially retroviral infections. Accordingly, the present invention provides such compounds as defined below. The invention further provides pharmaceutical compositions comprising a said compound in combination or association with a pharmaceutically acceptable diluent or excipient, for the treatment of HIV-infected patients. The invention further provides a process for the production of one compounds as defined below. The compounds may be used for treatment that includes prophylactic treatment of patients at risk, in view of the protective properties observed. The compounds may also be used in a method of treating HIV-infected or HIV-challenged human cells to prevent or modulate the multiplication of the HIV, the method comprising administering to said cells an effective dose of a said compound.

[0004] A 2,2'-dimer of cyclam has been reported as being isolated as a 2% by-product in the synthesis of cyclam (1,4,8,11-tetraazacyclotetradecane) (Barefield et al, J C S Chem Comm (1981), 302). This compound was stated to be insoluble in water. We believe that the insoluble 2,2'-bicyclam is a mixture of the 2R, 2'R and 2S,2'S enantiomers; we have characterised a soluble dimer which we believe to be the meso 2R,2'S isomer. The 6,6'-bicyclam isomer has been reported by Fabbrizzi et al, Inorg Chem 25, 2671 (1986). Certain N,N'-linked bicyclic compounds have been reported by Ciampolini et al, Inorg Chem 26, 3527 (1987). No biological activity has been suggested for such compounds.

[0005] US Patent 4,156,683 discloses monocyclic and bicyclic macrocyclic compounds, which are said to have biological activity in regulating sodium, potassium and calcium levels in mammals. Additionally, a specific group of N-alkylated monocyclic compounds are said to possess activity against A2 influenza viruses in a modified Hermann test on chick fibroblast tissue. It is also said that the preferred compounds, which form complexes of greater stability, are those having three bridging chains between bridgehead nitrogen atoms, that is fused bicyclic compounds.

[0006] Our USP 5,021,409 and WO 93/12096 describe linked cyclic compounds as being active against HIV-1 and HIV-2 in in vitro tests. We have now discovered that certain linked cyclic compounds exhibit interesting physical chemical properties indicating that they possess potential oral activity against HIV. The present invention provides as active compounds linked polyamine cyclic compounds of the general formula I.

\[
V - R - A - R' - W
\]

in which each of V and W is independently a bicyclic or tricyclic fused ring system containing only carbon and nitrogen atoms in the ring and having from 10 to 20 ring members and from 3 to 6 amine nitrogens spaced by 2 or more carbon atoms from each other, and wherein one fused ring in the bicyclic system, and each of two fused rings in the tricyclic system, is independently phenylene or pyridinylene and which system may optionally be substituted by halogen, nitro, carboxyl, carboxamido, sulfonic acid, phosphate, oxo, hydroxy, alkoxyl, thio or alkylthio,

A is a 1,3- or 1,4-phenylene, and

each of R and R' is methylene which spaces the cyclic polyamines and the moiety A. The invention also encompasses acid addition salts and metal complexes of the compounds of formula I.

[0008] In the above formula, the cyclic polyamine moieties V and W are bicyclic or tricyclic polyamine systems which may be substituted or unsubstituted acarbon or nitrogen atoms, suitably by halogen, nitro, carboxyl, carboxamido, sulfonic acid, phosphate, oxo hydroxy alkoxyl, thio or alkylthio, ie by groups which do not adversely effect the activity or toxicity of the compounds but may reduce the basicity of the amines.

[0009] V and W may be identical or non-identical, although it is convenient that they are identical.

[0010] The aromatic or heteroaromatic moiety A in general formula I; tethers V and W through the linking groups R and R'. Moiety A may be 1,3- or 1,4-phenylene.
The invention also includes what may be termed "pro-drugs", that is protected forms of the linked cyclic compounds, which release the compound after administration to a patient. For example, the compound may carry a protective group which is split off by hydrolysis in body fluids, e.g. in the bloodstream, thus releasing active compound or are oxidised or reduced in body fluids to release the compound, for example pyridine N-oxides. A discussion of pro-drugs may be found in "Smith and Williams' Introduction to the Principles of Drug Design", H J Smith, Wright, 2nd Edition, London 1988.

The invention further provides a method for the production of the compounds of formula I, which method comprises nucleophilic attack by cyclic polyamines V' and W' each having a single unprotected ring amine nitrogen, all other ring amine nitrogens being protected, on a compound of formula III

\[ X - R - A - R' - X \]  (III)

wherein R, R' and A are as defined above, and each X is an active substituent which can be displaced by the unprotected nitrogens of polyamines V' and W' and is preferably selected from Br, Cl, I, methanesulphonate, 4-tolylsulphonate and trifluoromethane sulphonate, and subsequently de-protecting the ring amine nitrogens.

It is well within the capabilities and knowledge of the skilled synthetic chemist to protect the amine nitrogens of cyclic polyamines, and it is preferred to use substitution by methanesulphonyl and/or 4-tolylsulphonyl and/or diethylphosphoryl. The compounds of formula III are known or may be synthesised by generally known techniques.

The reaction is preferably carried out in a solvent, such as acetonitrile or dimethylformamide, tetrahydrofuran or dioxane and in the presence of a base, for example sodium carbonate or potassium carbonate. The reaction generally takes place readily at room temperature to elevated temperature, to give a linked molecule having protected amine nitrogen atoms. In general, a mixture of products will be obtained, and we have found that chromatography on silica gel is a particularly convenient method of separation.

The de-protection step is suitably carried out by refluxing the protected molecule in a mixture of aqueous HBr and acetic acid or concentrated sulphuric acid or in the case of diethylphosphoryl in the presence of hydrogen chloride (gas) in acetic acid.

It is convenient that V and W are identical, so that the compound of formula II is reacted with two equivalents of the protected polyamine.

In the case where V and W are not identical it is appropriate to modify the process described above using as reactant a compound of formula IIIa.

X is a halogen, preferably chlorine, bromine, iodine, tosyl or mesyl and each n, n' is 1 such as to yield methylene bridges in the product.

The protected polyamine V' is firstly reacted with a 5-10 fold excess of a compound of formula IIIa, then secondly reacting this product with a protected polyamine W'. Both stages are carried out using conditions described above, preferably using a solvent such as acetonitrile in the presence of a base such as sodium carbonate or potassium carbonate. Following chromatographic purification, the ring amine nitrogens are de-protected as described above.

The first stage reaction is conveniently carried out in a solvent, for example dichloromethane or chloroform with triethylamine, and the second stage reaction is conveniently carried out under the conditions described above, that is in a solvent and in the presence of a base. Before de-protection, which may be accomplished as described above, it is necessary to reduce the carbonyl group on the linking chain using a reducing agent such as borane or lithium aluminium hydride, in manner generally known. The skilled synthetic chemist will be able to carry into effect the process of the invention in its various stages and possible variants.

The compounds are indicated for the treatment of viral infections, especially retrovirus infections and particularly HIV infections, and the compounds of formula I are to be considered as active compounds for the pharmaceutical compositions, processes for making the same and methods of treatment mentioned above. In these aspects of the
invention, it is to be understood that meso forms, enantiomers and resolved optically active forms of the compounds of formula I are included. Also, it is to be considered within the invention, compounds of formula I diluted with non-toxic or other active substances.

[0022] Acid addition salts, for example hydrochlorides, and non-toxic labile metal complexes of the compounds of formula I are also active compounds according to the present invention. Non-toxic in the present context has to be considered with reference to the prognosis for the infected patient without treatment. Copper and zinc complexes are preferred although other metals such as nickel may be considered, whereas less labile metal atoms such as cobalt and rhodium are less preferred because of likely lower selectivity.

[0023] The present invention will now be illustrated by the following preparative Examples.

EXAMPLE 1

a) N-Diethoxyphosphoryl-3,3'-iminodipropionitrile

[0024] To a solution of 3,3'-iminodipropionitrile (2.0g, 16mmol) and triethylamine (2.7ml) in dichloromethane (50ml) was added dropwise with stirring, under Argon, a solution of diethylchlorophosphate (2.8g, 16mmol) in dichloromethane (20ml) over approximately 30 minutes and then allowed to stir overnight at room temperature. The mixture was washed with brine (50ml) then dried (Na$_2$SO$_4$) and evaporated in vacuo giving N-diethoxyphosphoryl-3,3'-iminodipropionitrile (2.7g, 64%) as a colourless oil.

b) N-Diethoxyphosphoryl-3,3'-iminobispropylamine

[0025] To a solution of N-diethoxyphosphoryl-3,3'-iminodipropionitrile (1.0g, 4mmol) in methanol (50ml, saturated with ammonia) was added Raney nickel (5.0g, excess) and the mixture was hydrogenated at 45psi and room temperature for 48 hours. The catalyst was filtered off and the solvent evaporated in vacuo to give N-diethoxyphosphoryl-3,3'-iminobispropylamine (0.95g, 92%) as a colourless viscous oil.

c) N-Diethoxyphosphoryl-N',N''-bis(p-toluenesulphonyl)-3,3'-iminobispropylamine

[0026] To a solution of N-diethoxyphosphoryl-3,3'-iminobispropylamine (1.0g, 4mmol) and triethylamine (1.2ml) in dichloromethane (50ml) was added dropwise with stirring a solution of p-toluenesulphonyl chloride (1.6g, 7mmol, 2.2 equiv.) in dichloromethane (25ml) over approximately 15 minutes and then allowed to stir at room temperature overnight. The mixture was washed with dilute hydrochloric acid (50ml), saturated aqueous sodium bicarbonate (50ml) and brine (50ml) then dried (Na$_2$SO$_4$) and evaporated in vacuo to give the crude product as a brown oil. The crude product was purified by column chromatography on silica gel using dichloromethane/methanol (97/3) as eluent, giving N-diethoxyphosphoryl-N',N''-bis(p-toluenesulphonyl)-3,3'-iminobispropylamine (0.9g, 43%) as a white solid.

d) 7-Diethoxyphosphoryl-3,11-bis(p-toluenesulphonyl)-3,7,11,17-tetraaza-bicyclo[13.3.1] heptadeca-1(17), 13,15-triene

General Procedure:

[0027] To a solution of N-diethoxyphosphoryl-N',N''-bis(p-toluenesulphonyl)-3,3'-iminobispropylamine (2.9g, 5mmol) in DMF (150ml) containing finely ground anhydrous cesium carbonate (4.1g, 13mmol, 2.5 equiv.) stirred at 55-60°C under argon added a solution of 2,6-bis-(dibromomethyl)pyridine hydrobromide [M E Haeg, B J Whitlock and H W Whitlock, Jr, J Am Chem Soc, 1989, 111, 692], (1.78g, 5mmol, 1.0 equiv.) in DMF (75ml) dropwise over a period of 3-4 hours. After a total of 25-30 hours at 55-60°C the mixture was allowed to cool to room temperature and evaporated to dryness under reduced pressure. The residue was partitioned between dichloromethane (150ml) and brine (150ml). The organic layer was separated and the aqueous phase was extracted with two further portions of dichloromethane. The combined organic extracts were dried (Na$_2$SO$_4$) and evaporated in vacuo to give the crude product as a light brown solid. Column chromatography on silica gel using dichloromethane/methanol (98/2) as eluent, gave 7-diethoxyphosphoryl-3,11-bis(p-toluenesulphonyl)-3,7,11,17-tetraaza-bicyclo[13.3.1]-heptadeca-1(17), 13,15-triene (2.1g, 60%) as a white solid.
e) 3,11-Bis-(p-toluenesulphonyl)-3,7,11,17-tetraaza-bicyclo[13.3.1]-heptadeca-1(17),13,15-triene

General Procedure:

To a solution of 7-diethoxyphosphoryl-3,11-bis(p-toluenesulphonyl)-3,7,11,17-tetraazabicyclo[13.3.1]-heptadeca-1(17),13,15-triene (500mg) in glacial acetic acid (2.5ml) was added 30% HBr / acetic acid (Aldrich, 1.5ml) and the reaction mixture stirred at room temperature for 2 hours. Ether (100ml) was added to precipitate the product. The white solid was allowed to settle to the bottom of the flask and the supernatant solution was decanted off. The solid was then washed by decantation with ether three times and the remaining traces of ether removed by evaporation under reduced pressure. The solid was partitioned between sodium hydroxide solution (10ml, 10N) and dichloromethane (150ml) and the organic layer was separated, dried (Na₂SO₄) and evaporated in vacua to give 3,11-bis(p-toluenesulphonyl)-3,7,11,17-tetraazabicyclo[13.3.1]-heptadeca-1(17),13,15-triene (290mg, 74%) as a white solid.

f) 7,7'-[1,4-Phenylenebis(methylene)]bis[3,11-bis(p-toluenesulphonyl)-3,7,11,17-tetraazabicyclo[13.3.1]-heptadeca-1(17),13,15-triene]

General Procedure

To a solution of 3,11-bis(p-toluenesulphonyl)-3,7,11,17-tetraazabicyclo[13.3.1]-heptadeca-1(17),13,15-triene (280mg, 0.52mmol) and potassium carbonate (108mg, 0.77mmol, 1.5 equiv.) in acetonitrile (30ml) was added α,α'-dibromo-p-xylene (68mg, 0.26mmol, 0.5 equiv.) and the mixture heated to reflux overnight with rapid stirring. The reaction mixture was allowed to cool to room temperature then evaporated and the residue was partitioned between dichloromethane (100ml) and brine (50ml). The organic layer was separated and the aqueous layer was extracted with two further portions of dichloromethane. The combined organic extracts were dried (Na₂SO₄) and evaporated to dryness under reduced pressure and the residue was purified by column chromatography on silica gel using methanol / dichloromethane (98/2) as eluant to give 7,7'-[1,4-phenylene-bis(methylene)]bis[3,11-bis(p-toluenesulphonyl)-3,7,11,17-tetraazabicyclo[13.3.1]-heptadeca-1(17),13,15-triene] (297mg, 97%) as a white solid.

Synthesis of Compound A

7,7'-[1,4-Phenylenebis(methylene)]bis[3,7,11,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene hexahydrobromide hexahydrate

To a solution of 7,7'-[1,4-phenylenebis(methylene)]bis[3,11-bis(p-toluenesulphonyl)-3,7,11,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene (150mg, 0.13mmol) in acetic acid (2.5ml) was added hydrobromic acid (Aldrich 48% aqueous, 1.5ml) and the mixture was heated to reflux with stirring for 18 hours. The mixture was allowed to cool and ether (50ml) was added to precipitate the product. The white solid was allowed to settle to the bottom of the flask and the supernatant solution was decanted off. The solid was then washed by decantation with ether three times and the remaining traces of ether removed by evaporation under reduced pressure giving 7,7'-[1,4-phenylenebis(methylene)]bis[3,7,11,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene hexahydrobromide hexahydrate (60 mg, 39%) as a white solid. ¹H NMR (D₂O) δ 2.22 (m, 8H), 3.03 (m, 8H), 3.27 (m, 8H), 4.35 (s, 4H), 4.43 (s, 8H), 7.44 (d, 4H, J=7.5 Hz), 7.49 (s, 4H), 7.85 (t, 2H, J=7.5 Hz). Mass spectrum (FAB); m/e (relative intensity); 653 (M+HBr, 13), 651 (M+HBr, 13), 571 (M+HBr, 13), 571 (M+HBr, 13), 439 (58), 235 (100). C₃₄H₆₈N₈Br₆O₆ requires: C, 35.07; H, 5.89; N, 9.62; Br, 41.17; found: C, 35.54; H, 5.53; N, 9.37; Br, 40.04.

EXAMPLE 2

4-Chloro-2,6-bis(hydroxymethyl)pyridine

To a stirred solution of dimethyl 4-chloropyridine-2,6-dicarboxylate (5g, 21.83mmol) (D G Markees and G W Kidder, J Am Chem Soc 1956, 78, 4130) in 200ml of anhydrous EtOH was added sodium borohydride (3.31g, 87.33mmol) and the mixture gently refluxed under an argon atmosphere for 16 hours. The solution was cooled to room temperature and concentrated to dryness. Ethyl acetate (50ml) and H₂O (50ml) was added to the residue and the aqueous phase was extracted with ethyl acetate (x3), dried over MgSO₄ and concentrated in vacuo thus affording a white solid which was identified by ¹H NMR as 4-chloro-2,6-bis(hydroxymethyl)pyridine (2.41g, 64%).
4-Chloro-2,6-bis(chloromethyl)pyridine

To a stirred solution of 4-chloro-2,6-bis(hydroxymethyl)pyridine (2.41g, 13.93mmol) and triethylamine (7.8ml, 55.72mmol) at 0°C in 100ml of anhydrous dichloromethane and 50ml of anhydrous chloroform under an argon atmosphere was added methanesulfonyl chloride (3.2ml, 41.79mmol). The solution was stirred at 0°C for 30 minutes, warmed to room temperature and stirred a further 36 hours. The reaction mixture was quenched with water (50ml), the aqueous phase extracted with dichloromethane, dried (MgSO4) and concentrated in vacuo to afford a red-orange oil. The residual oil was passed through a short plug of silica gel using dichloromethane as eluent thus affording after concentration a pale yellow solid which was identified by 1H NMR as 4-chloro-2,6-bis-(chloromethyl)pyridine (1.9g, 65%).

Using the general procedure in example 1d:

N-Diethoxyphosphoryl-N',N''-bis(p-toluenesulphonyl)-3,3'-iminobis-propylamine (1.8g, 3.13mmol) and 4-chloro-2,6-bis(chloromethyl)pyridine (660mg, 3.13mmol) gave 15-chloro-7-diethoxyphosphoryl-3,11-bis(p-toluenesulphonyl)-3,7,11,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene (640mg, 29%) as a fluffy white solid.

Using the general procedure in example 1e

15-Chloro-7-diethoxyphosphoryl-3,11-bis(p-toluenesulphonyl)-3,7,11,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene

Using the general procedure in example 1f


Using the general procedure in example 1f

15-Chloro-7-diethoxyphosphoryl-3,11-bis(p-toluenesulphonyl)-3,7,11,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene (640mg, 0.899mmol) gave 15-chloro-3,11-bis(p-toluenesulphonyl)-3,7,11,17-tetraazabicyclo[13.3.1]-heptadeca-1(17),13,15-triene (440mg, 85%) as a white solid.

7,7'-(1,4-Phenylenebis(methylene))bis[15-chloro-3,11-bis(p-toluenesulphonyl)-3,7,11,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene]

Using the general procedure in example 1f

15-Chloro-3,11-bis(p-toluenesulfonyl)-3,7,11,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene (430mg, 0.746mmol) and α,α'-dibromo-p-xylene (99mg, 0.373mmol) gave 7,7'-(1,4-phenylenebis(methylene))bis[15-chloro-3,11-bis(p-toluenesulfonyl)-3,7,11,17-hexaazabicyclo[13.3.1]heptadeca-1(17),13,15-triene] (280mg, 60%) as a white solid.

Synthesis of Compound B

7,7'-(1,4-Phenylenebis(methylene))bis[15-chloro-3,7,11,17-tetraazabicyclo[13.3.1] heptadeca-1(17), 13,15-triene] hexahydrobromide monoacetate

A solution of 7,7'-(1,4-phenylenebis(methylene))bis[15-chloro-3,11-bis(p-toluenesulphonyl)-3,7,11,17-hexaazabicyclo[13.3.1]heptadeca-1(17),13,15-triene] (270mg, 0.215mmol) in conc. H2SO4 (3ml) was stirred at 110°C for 2 hours. The dark brown solution was cooled to room temperature and the pH adjusted to 14 with 10N NaOH. The aqueous phase was extracted with CHCl3 (20ml, x 3), the combined organic phases were dried (MgSO4) and concentrated in vacuo affording a pale yellow oil. To a stirred solution of the oil in 5ml of anhydrous EtOH was passed HBr (g) resulting in a pale white precipitate. After stirring for 15 minutes at room temperature the solid was collected by filtration. The tan solid was dissolved in 5ml of H2O, activated charcoal was added (120mg) and the solution was heated for 30 minutes. The hot solution was eluted through celite and concentrated to approximately 2ml. Glacial acetic acid was added resulting in a white precipitate which was collected by filtration, washed with Et2O and dried in vacuo giving 7,7'-(1,4-phenylenebis(methylene))bis[15-chloro-3,11-bis(p-toluenesulphonyl)-3,7,11,17-hexaazabicyclo[13.3.1]heptadeca[17],13,15-triene]hexahydro-bromide monoacetate (90mg, 35%) as a white solid. 'H NMR (D2O) δ 2.10-2.24 (m, 8H), 3.00-3.12 (m, 8H), 3.12-3.24 (m, 8H), 4.21 (s, 4H), 4.40 (s, 8H), 7.39 (s, 4H), 7.53 (s, 4H). 13C NMR (D2O): 19.46, 43.22, 48.33, 48.75, 58.38, 125.09, 130.6, 132.1, 147.1, 151.6. Mass spectrum (FAB); m/e (relative intensity); 721 (M+HBr, 51), 719 (M+HBr, 38), 639 (M+1, 100), 372 (18). C36H58N8O2Cl2Br6 requires C, 36.48; H, 4.93; N, 9.45; Cl, 23.93; Br, 53.94. Found: C, 36.05; H, 4.97; N, 9.54; Cl, 23.85; Br, 53.75.
EXAMPLE 3

4-Methoxy-2,6-bis(hydroxymethyl)pyridine

To a stirred solution of dimethyl 4-methoxy-2,6-dicarboxylate (5g, 20.8mmol) (D G Markees and G W Kidder, J Am Chem Soc 1956, 78, 4130) in 200ml of anhydrous EtOH was added sodium borohydride (3.17g, 83.35mmol) and the mixture gently refluxed for 16 hours under an argon atmosphere. The solution was cooled to room temperature and concentrated to dryness. Ethyl acetate (100ml) and H₂O (50ml) was added to the residue and the aqueous phase was extracted with ethyl acetate (x3), dried over MgSO₄ and concentrated in vacuo thus affording a white solid which was identified by ¹H NMR as 4-methoxy-2,6-bis(hydroxymethyl)pyridine (2.89g, 82%).

4-Methoxy-2,6-bis(chloromethyl)pyridine

To a stirred solution of 4-methoxy-2,6-bis(hydroxymethyl)pyridine (2.89g, 17.10mmol) and triethylamine (9.6ml, 68.40mmol) at 0°C in 100ml of anhydrous dichloromethane and 50ml of chloroform under an argon atmosphere was added methanesulphonyl chloride (3.9ml, 51.30mmol). The solution was stirred at 0°C for 30 minutes, warmed to room temperature and stirred a further 24 hours. Additional methanesulphonyl chloride (1.5ml, 19.38mmol) was added and the mixture was stirred at 50°C for 24 hours. The reaction mixture was quenched with H₂O (50ml), the aqueous phase extracted with CH₂Cl₂, dried over MgSO₄ and concentrated to afford an orange oil. The residual oil was passed through a short plug of silica gel using dichloromethane as eluent thus affording after concentration a pale yellow solid which was identified by ¹H NMR as 4-methoxy-2,6-bis-(chloromethyl)pyridine (2.3 g, 66%).


Using the general procedure in example 1d

N-Diethoxyphosphoryl-N',N''-bis(p-toluenesulphonyl)-3,3'-iminobis-propylamine (1.8g, 3.13mmol) and 4-methoxy-2,6-bis(chloromethyl)pyridine (650mg, 3.13mmol) gave 7-diethoxyphosphoryl-15-methoxy-3,11-bis(p-toluenesulphonyl)-3,7,11,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene (810mg, 36%) as a fluffy white solid.

15-Methoxy-3,11-bis(p-toluenesulphonyl)-3,7,11,17-tetraazabicyclo-[13.3.1]-heptadeca-1(17),13,15-triene

Using the general procedure in example 1e

7-Diethoxyphosphoryl-15-methoxy-3,7,11,17-tetraazabicyclo-[13.3.1]-heptadeca-1(17),13,15-triene

Using the general procedure in example 1f

15-Methoxy-3,11-bis(p-toluenesulphonyl)-3,7,11,17-tetraazabicyclo-[13.3.1]-heptadeca-1(17),13,15-triene

Using the general procedure in example 1f

7,7''-[1,4-Phenylenebis(methylene)]bis[15-methoxy-3,11-(p-toluenesulphonyl)-3,7,11,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene]

Using the general procedure in example 1f

Synthesis of Compound C

7,7''-[1,4-Phenylenebis(methylene)]bis[15-methoxy-3,7,11,17-tetraazabicyclo-[13.3.1] heptadeca-1(17), 13,15-triene] hexahydrobromide dihydrate

A solution of 7,7''-[1,4-phenylenebis(methylene)]bis[15-methoxy-3,11-(p-toluenesulphonyl)-3,7,11,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene] (160mg, 0.128mmol) in conc. H₂SO₄ (2.5ml) was stirred at 105°C for 2 hours. The dark brown solution was cooled to room temperature and the pH adjusted to 14 with 10N NaOH. The aqueous phase was extracted with CHCl₃ (20ml, x3), the combined organic phases were dried
(MgSO₄) and concentrated in vacuo affording a pale yellow oil. To a stirred solution of the oil in 5ml of anhydrous EtOH was passed HBr (g) resulting in a tan precipitate. After stirring for 15 minutes at room temperature the solid was collected by filtration. The tan solid was dissolved in 5ml of H₂O, activated charcoal was added (100mg) and the solution was heated for 30 minutes. The hot solution was eluted through celite and concentrated to approximately 2ml. Glacial acetic acid was added resulting in a white precipitate which was collected by filtration, washed with Et₂O and dried in vacuo giving 7,7’-[1,4-phenylenebis(methylene)]bis[15-methoxy-3,7,11,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene] hexahydrobromide dihydrate (65mg, 44%) as a white solid. ‘H NMR (D₂O) δ 2.14-2.26 (m, 8H), 3.00-3.10 (m, 8H), 3.12-3.23 (m, 8H), 3.80 (s, 6H), 4.25 (s, 4H), 4.35 (s, 8H), 7.01 (s, 4H), 7.43 (s, 4H). 13C NMR (D₂O) δ 19.25, 42.98, 49.12, 55.99, 58.26, 110.80, 130.46, 132.16, 151.63, 167.99. Mass spectrum (FAB): m/e (relative intensity); 713 (M+HBr, 41), 711 (M+HBr, 40), 631 (M+1, 100), 617 (14), 416 (12), 368 (13). IR (KBr): 1607 cm⁻¹ (C=C-OMe).

Synthesis of Compound D

7,7’-[1,4-Phenylenebis(methylene)]bis-3,7,11,17-tetraazabicyclo[13.3.1]-heptadeca-13,16-triene-15-one octahydrobromide

[0043] To a stirred solution of 7,7’-[1,4-phenylenebis(methylene)]bis[15-methoxy-3,11-(p-toluenesulphonyl)-3,7,11,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene] (150mg, 0.12mmol) in acetic acid (6ml) was added 48% hydrobromic acid (4ml) and the solution was stirred at 115 °C for 46 hours resulting in a white precipitate. The solution was cooled to room temperature and diluted with Et₂O, the resulting white solid was collected by filtration, washed with glacial acetic acid and Et₂O giving 7,7’-[1,4-phenylenebis-(methylene)]bis-3,7,11,17-tetraazabicyclo[13.3.1]heptadeca-13,16-triene-15-one octahydrobromide (95mg, 64%) as a white solid. ‘H NMR (D₂O) δ 2.16-2.29 (m, 8H), 3.06 (t, 8H, J=7.6 Hz), 3.27 (t, 8H, J=7.6 Hz), 4.31 (s, 8H), 4.34 (s, 4H), 6.85 (s, 4H), 7.48 (s, 4H). 13C NMR (D₂O): δ 19.1, 42.94, 48.20, 49.03, 58.30, 112.19, 130.29, 132.24, 151.63, 165.71. Mass spectrum (FAB): m/e (relative intensity); 685 (M+HBr, 5), 683 (M+HBr, 5), 603 (M+1, 100), 460 (12), 329 (16). IR (KBr) 1629 cm⁻¹ (C=O).

EXAMPLE 4

a) N-Diethoxyphosphoryldiethanolamine

[0044] To a solution of diethanolamine (5.0g, 48mmol) and triethylamine (8.0ml) in dichloromethane (75ml) was added dropwise with stirring under Argon, a solution of diethylchlorophosphate (8.2g, 48mmol) in dichloromethane (25ml) over approximately 15 minutes and then allowed to stir at room temperature overnight. The mixture was washed with brine (50ml) then dried (Na₂SO₄) and evaporated in vacuo to give the crude product as a viscous oil. The oil was dissolved in ether (100ml) and the white solid which precipitated was filtered off (triethylamine hydrochloride). The ether solution was evaporated in vacuo giving N-diethoxyphosphoryldiethanolamine (6.2g, 54%) as a colourless oil.

b) N-Diethoxyphosphorylbis(2-methanesulphonyl)diethanolamine

[0045] To a solution of N-diethoxyphosphoryldiethanolamine (3.0g, 12mmol) and triethylamine (5.2ml) in dichloromethane (50ml), cooled to 0-5 °C, was added dropwise with stirring a solution of methanesulphonyl chloride (3.0g, 26mmol) in dichloromethane (25ml) over approximately 15 minutes and then allowed to stir at room temperature overnight. The mixture was washed with water (50ml) then dried (Na₂SO₄) and evaporated in vacuo to give N-diethoxyphosphorylbis(2-methanesulphonyl)diethanolamine (4.0g, 81%) as a light brown oil.

2,6-Bis(cyanomethyl)pyridine

[0046] A stirred solution of 2,6-bis(bromomethyl)pyridine hydrobromide (6.0g, 17mmol, sodium cyanide (5.1g, 104mmol) and cetyltrimethylammonium bromide (633mg, 1.7mmol) in benzene / water (50ml / 25ml) was heated to reflux for 4 hours. The reaction mixture was allowed to cool to room temperature and the organic layer separated. The aqueous layer was extracted with benzene (50ml) and dichloromethane (75ml). The combined organic extracts were dried (Na₂SO₄) and evaporated in vacuo to give a brown solid which was purified by filtration through basic alumina using dichloromethane (500ml) as eluent giving 2,6-bis(cyanomethyl)pyridine (2.4g, 86%) as a white solid.
2,6-Bis(2-aminoethyl)pyridine

[0047] To a solution of 2,6-bis(cyanomethyl)pyridine (4.3g, 27mmol) in methanol (75ml, saturated with ammonia) was added Raney nickel (10.0g, excess) and the mixture hydrogenated at 45psi and room temperature for 48 hours. The catalyst was filtered off and the solvent evaporated in vacuo to give 2,6-bis(2-aminoethyl)pyridine as a brown viscous oil (3.7g, 83%). This was used without further purification.

2,6-Bis(N,N'-p-toluenesulphonyl-2-aminoethyl)pyridine

[0048] To a stirred solution of 2,6-bis(2-aminoethyl)pyridine (3.8g, 23mmol) and triethylamine (7.0ml) in dichloromethane (75ml) was added dropwise with stirring a solution of p-toluenesulphonyl chloride (8.7g, 49mmol) in dichloromethane (25ml) over approximately 15 minutes and then allowed to stir at room temperature overnight. The mixture was washed with saturated aqueous sodium bicarbonate (50ml) and brine (50ml) then dried (Na₂SO₄) and evaporated in vacuo to give the crude product as a pale yellow viscous oil. The crude product was purified by column chromatography on silica gel using dichloromethane /methanol (98/2) as the eluent, whereby 2,6-bis(N,N'-p-toluenesulphonyl-2-aminoethyl)pyridine (8.0g, 75%) was obtained as a white solid.

7-Diethoxyphosphoryl-4,10-bis(p-toluenesulphonyl)-4,7,10,17-tetraazacyclo[13.3.1]heptadeca-1(17),13,15-triene

[0049] To a stirred solution of 2,6-bis(N,N'-p-toluenesulphonyl-2-aminoethyl)pyridine (5.7g, 12mmol) in DMF (550ml) containing cesium carbonate (13.7g, 42mmol) maintained at 55°C was added a solution of N-diethoxyphosphoryl-bis(2-methanesulphonyl)diethanolamine (4.8g, 12mmol) in DMF (55ml) dropwise over a period of 16-18 hours. The reaction mixture was stirred at 55°C for a total of 30 hours then allowed to cool to room temperature and evaporated in vacuo. The brown residue which was partitioned between dichloromethane (700ml) and brine (350ml). The organic layer was separated, dried (Na₂SO₄) and evaporated in vacuo to give the crude product as a light brown solid. Column chromatography on silica gel using ethyl acetate /hexane (70/30) as eluent gave 7-diethoxyphosphoryl-4,10-bis(p-toluenesulphonyl)-4,7,10,17-tetraazacyclo[13.3.1]heptadeca-1(17),13,15-triene (1.83g, 23%) as a white solid.

4,10-Bis(p-toluenesulphonyl)-4,7,10,17-tetraazabicyclo[13.3.1]-heptadeca-1(17),13,15-triene

Using the general procedure in example le

[0050] 7-Diethoxyphosphoryl-4,10-bis(p-toluenesulphonyl)-4,7,10,17-tetraazacyclo[13.3.1]heptadeca-1(17),13,15-triene (1.5g) gave 4,10-bis(p-toluene-sulphonyl)-4,7,10,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene (1.2g, 92%) as a white solid.

7,7’-[1,4-Phenylenebis(methylene)]bis[4,10-bis(p-toluene-sulphonyl)-4,7,10,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene]

Using the general procedure in example 1f

[0051] 4,10-Bis(p-toluenesulfonfonyl)-4,7,10,17-tetraazabicyclo[13.3.1]-heptadeca-1(17),13,15-triene (1.1g, 2mmol) and α,α’-dibromo-p-xylene (265mg, 1mmol) gave 7,7’-[1,4-phenylenebis (methylene)]bis[4,10-bis(p-toluenesulphonyl)-4,7,10,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene] (900mmg, 84%) as a white amorphous solid.

Synthesis of Compound E

7,7’-[1,4-Phenylenebis(methylene)]bis-4,7,10,17-tetraazabicyclo-[13.3.1]-heptadeca-1(17),13,15-triene octahydrobromide tetrahydrate

[0052] 7,7’-[1,4-Phenylenebis(methylene)]bis[4,10-bis(p-toluene-sulphonyl)-4,7,10,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene] (120mg) was dissolved in concentrated sulfuric acid (2.0ml) and stirred rapidly at 100°C for 3 hours. The resulting mixture was cooled and carefully made basic with sodium hydroxide solution (10ml, 10N). The solution was extracted with dichlormethane (2 x 100ml), dried (Na₂SO₄) and evaporated in vacuo giving the free base as a white solid. The solid was dissolved in acetic acid (5.0ml) and HBr / acetic acid (30%, Aldrich) (0.5ml) added and the reaction mixture stirred at room temperature for 5 minutes. Ether (50ml) was added to precipitate the product. The white solid was allowed to settle to the bottom of the flask and the supernatant solution was decanted off. The solid was washed by decantation with ether three times and the remaining traces of ether removed by evaporation under
reduced pressure giving 7,7’-[1,4-phenylenebis(methylene)]bis-4,7,10,17-tetraazabicyclo[13.3.1]heptadeca-1(17), 13,15-tetraene octahydrobromide tetrahydrate (88mg, 72%) as a white solid. 1H NMR (D$_2$O) δ 2.75 (m, 8H), 3.05-3.65 (m, 28H), 7.15 (d, 4H, J=7.5 Hz). 7.65 (t, 2H, J=7.5 Hz). Mass spectrum (FAB); m/e (relative intensity); 653 (M+HBr, 22), 651 (M+HBr, 22), 571 (M+1, 31), 339 (21), 235 (100). C$_{34}$H$_{66}$N$_8$Br$_8$O$_4$/0.5 acetic acid requires: C, 31.84; H, 5.19; N, 8.49; Br, 48.42; Found: C, 32.04; H, 5.14; N, 8.50; Br, 48.25.

EXAMPLE 5


8-Diethoxyphosphoryl-4,12-bis(p-toluenesulphonyl)-4,8,12,19-tetraazabicyclo[15.3.1] nonadeca-1(19), 15,17-tetraene

General procedure

[0054] To a stirred solution of 2,6-bis(N,N’-p-toluenesulphonyl-2-amino-ethyl)pyridine (2.2g, 5mmol) in DMF (200ml) containing finely ground anhydrous cesium carbonate (5.2g, 16mmol) maintained at 55°C under argon was added a solution of N-diethoxyphosphoryl-bis(3-methanesulphonyl)dipropanolamine (2.2g, 5mmol) in DMF (75ml) dropwise over a period of 16-18 hours. The reaction mixture was stirred at 55°C for a total of 30 hours then allowed to cool and evaporated in vacuo. The brown residue was partitioned in dichloromethane (250ml) and brine (150ml). The organic layer was separated and dried (Na$_2$SO$_4$) then evaporated in vacuo. The brown residue was chromatographed on silica gel using dichloromethane / methanol (97 / 3) as the eluent gave 8-diethoxyphosphoryl-4,12-bis(p-toluenesulphonyl)-4,8,12,19-tetraazacyclo[15.3.1]nonadeca-1(19),15,17-tetraene (1.5g, 48%) as a white solid.

4,12-Bis(p-toluenesulphonyl)-4,8,12,19-tetraazabicyclo[15.3.1]nonadeca-1(19),15,17-tetraene

Using the general procedure in example 1e

[0055] 8-Diethoxyphosphoryl-4,12-bis(p-toluenesulphonyl)-4,8,12,19-tetraazacyclo[15.3.1]nonadeca-1(19), 15,17-tetraene (780mg) gave 4,12-bis(p-toluenesulphonyl)-4,8,12,19-tetraazabicyclo[15.3.1]nonadeca-1(19), 15,17-tetraene (700mg, 97%) as a white solid.

8,8’-[1,4-Phenylenebis(methylene)]bis[4,12-bis(p-toluenesulphonyl)-4,8,12,19-tetraazabicyclo[15.3.1] nonadeca-1(19), 15,17-tetraene]

Using the general procedure in example 1f

[0056] 4,12-Bis(p-toluenesulphonyl)-4,8,12,19-tetraazabicyclo[15.3.1]-nonadeca-1(19),15,17-tetraene (534mg) and α,α’-dibromo-p-xylene (124mg) gave 8,8’-[1,4-phenylenebis(methylene)]bis[4,12-bis (p-toluenesulphonyl)]-4,8,12,19-tetraazabicyclo[15.3.1]nonadeca-1(19),15,17-tetraene (460mg, 83%) as a white solid.

Synthesis of Compound F

[0057] To a solution of 8,8’-[1,4-phenylenebis(methylene)]bis[4,12-bis(p-toluenesulphonyl)]-4,8,12,19-tetraazabicyclo[15.3.1]nonadeca-1(19),15,17-tetraene (150mg) in acetic acid (2.5ml) was added hydrobromic acid (Aldrich, 48% aqueous, 1.5ml) and the mixture heated to reflux with stirring for 18 hours. The mixture was cooled and ether (50ml) added to precipitate the product. The white solid was allowed to settle to the bottom of the flask and the supernatant solution was decanted off. The solid was then washed by decantation with ether three times and the remaining traces of ether removed by evaporation under reduced pressure and drying in vacuo overnight giving 8,8’-[1,4-Phenylenebis (methylene)]bis-4,8,12,19-tetraaza bicyclo[15.3.1]nonadeca-1(19),15,17-tetraene octahydrobromide heptahydrate as a white solid (100mg, 65%). 1H NMR (D$_2$O) δ 2.13 (m, 8H), 3.06-3.39 (M, 32H), 4.41 (s, 4H), 7.13 (d, 4H, J=7.5 Hz), 7.51 (s, 4H), 7.65 (t, 2H, J=7.5 Hz). Mass spectrum (FAB); m/e (relative intensity); 709 (M+HBr, 33), 707 (M+HBr, 33), 627 (M+1, 83), 367 (100). C$_{38}$H$_{80}$N$_8$Br$_8$O$_7$ requires: C, 32.59; H, 5.76; N, 8.00; Br, 45.65; Found: C, 32.44; H, 5.28; N,
EXAMPLE 6

N-Diethoxyphosphorylbis(2-azido)diethyamine

[0058] N-Diethoxyphosphorylbis(2-methanesulphonyl)diethanolamine (see Example 4b) (5.4g, 14mmol) was dissolved in DMF (25ml) containing sodium azide (3.9g, 35mmol) and stirred at 80°C under argon for 18 hours. The reaction mixture was cooled and concentrated in vacuo. The brown residue was partitioned between ethyl acetate (200ml) and water (200ml). The organic layer was separated, dried (Na₂SO₄) and evaporated under reduced pressure to give N-diethoxyphosphorylbis(2-azido)diethyamine (2.7g, 68%) as a colourless oil.

N-Diethoxyphosphoryl-2,2’-iminobisethylamine

[0059] To a solution of the above diazide (10.4g, 36mmol) in ethyl acetate (75ml) was added palladium on carbon (10%, 5.0g) and the mixture was hydrogenated at 45psi and room temperature for 18 hours. The catalyst was filtered off and the solvent evaporated in vacuo to give N-diethoxyphosphoryl-2,2’-iminobisethylamine (6.4g, 76%) as a colourless oil.

N-Diethoxyphosphoryl-N',N''-bis(p-toluenesulphonyl)-2,2’-iminobisethylamine

[0060] To a solution of N-diethoxyphosphoryl-2,2’-iminobisethylamine (4.7g, 20mmol) and triethylamine (5.8ml) in dichloromethane (100ml) was added dropwise with stirring a solution of p-toluene sulphonyl chloride (7.9g, 40mmol) in dichloromethane (25ml) over approximately 15 minutes and then allowed to stir at room temperature overnight. The mixture was washed with saturated aqueous sodium bicarbonate (50ml) and brine (50ml), then dried (Na₂SO₄) and evaporated in vacuo to give N-diethoxyphosphoryl-N',N''-bis(p-toluenesulphonyl)-2,2’-imino bisethylamine (10.2g, 95%) as a colourless oil.

6-Diethoxyphosphoryl-3,9-bis(p-toluenesulphonyl)-3,6,9,15-tetraazabicyclo[11.3.1]pentadeca-1(15),11,13-triene

Using the general procedure in example 1d

[0061] N-Diethoxyphosphoryl-N',N''-bis(p-toluenesulphonyl)-2,2’-iminobisethylamine (2.4g, 4.4mmol) and 2,6-bis-(dibromomethyl)pyridine hydrobromide (1.5g, 4.5mmol) gave 6-diethoxyphosphoryl-3,9-bis(p-toluenesulphonyl)-3,6,9,15-tetraazabicyclo[11.3.1]pentadeca-1(15),11,13-triene (2.0g, 68%) as a white solid.

3,9-Bis(p-toluenesulphonyl)-3,6,9,15-tetraazabicyclo[11.3.1]pentadeca-1(15),11,13-triene

Using the general procedure in example 1e


6,6’-[1,4’-Phenylenebis(methylene)]bis[3,9-bis(p-toluenesulphonyl)-3,6,9,15-tetraaza bicyclo[11.3.1]pentadeca-1(15),11,13-triene]

Using the general procedure in Example 1f

[0063] 3,9-Bis(p-toluenesulphonyl)-3,6,9,15-tetraazabicyclo[11.3.1]pentadeca-1(15),11,13-triene (540mg, 1.1mmol) and α,α’-dibromo-p-xylene (140mg, 0.53mmol) gave 6,6’-[1,4’-phenylenebis (methylene)]bis[3,9-bis(p-toluene-sulphonyl)-3,6,9,15-tetraazabicyclo[11.3.1]pentadeca-1(15),11,13-triene] (400mg, 67%) as a white solid.
Synthesis of Compound G

6,6’-[1,4’-Phenylenbis(methylene)]bis-3,6,9,15-tetraazabicyclo[11.3.1]pentadeca-1(15),11,13-triene hexahydmoridim trihydrate

[0064] 6,6’-[1,4’-Phenylenbis(methylene)]bis[3,9-bis(p-toluenesulphonyl)-3,6,9,15-tetraazabicyclo[11.3.1]pentadeca-1(15),11,13-triene] (90mg) was dissolved in concentrated sulfuric acid (2.0ml) and stirred rapidly at 100°C for 3 hours. The resulting mixture was cooled and carefully basified with sodium hydroxide solution (10ml, 10N). The solution was extracted with dichloromethane (2 x 100ml), dried (Na₂SO₄) and evaporated in vacuo giving the free base as a white solid. The solid was dissolved in acetic acid (5.0ml) and HBr / acetic acid (30%, Aldrich) (0.5ml) added and the reaction mixture stirred at room temperature for 5 minutes. Ether (50ml) was added to precipitate the product. The white solid was allowed to settle to the bottom of the flask and the supernatant solution was decanted off. The solid was washed by decantation with ether three times and the remaining traces of ether removed by evaporation under reduced pressure and drying in vacuo overnight, giving 6,6’-[1,4’-phenylenbis(methylene)]bis-3,6,9,15-tetraazabicyclo[11.3.1]pentadeca-1(15),11,13-triene hexahydromide trihydrate (25mg, 33%) as a white solid. ¹H NMR (D₂O) δ 2.65 (m, 8H), 3.05 (m, 8H), 3.75 (s, 4H), 4.45 (s, 8H), 7.20 (d, 4H, J=7.5 Hz), 7.26 (s, 4H), 7.85 (t, 2H, J=7.5 Hz). Mass spectrum (FAB); m/e (relative intensity); 595 (M+HBr, 9), 593 (M+HBr, 9), 515 (M+1, 57), 440 (48), 223 (100). C₃₀H₅₄N₈Br₆O₃ requires: C, 34.18; H, 5.16; N, 10.62; Br, 45.48; Found: C, 34.25; H, 5.17; N, 10.56; Br, 43.60.

EXAMPLE 7

6,6’-[1,3-Phenylenbis(methylene)]bis[3,9-bis(p-toluenesulphonyl)-3,6,9,15-tetraazabicyclo[11.3.1]pentadeca-1(15),11,13-triene]

Using the general procedure in example 1f

[0065] 3,9-Bis(p-toluenesulphonyl)-3.6.9.15-tetraaza[11.3.1]pentadeca-1(15),11,13-triene (514mg, 1mmol) and α, α’-dibromo-m-xylene (132mg, 0.55mmol) gave 6,6’-[1,3-phenylenebis (methylene)]bis[3,9-bis(p-toluenesulphonyl)-3.6.9.15-tetraazabicyclo[11.3.1]pentadeca-1(15),11,13-triene] (531 mg, 94%) as a white solid.

Synthesis of Compound H

6,6’-[1,3-Phenylenbis(methylene)]bis-3,6,9,15-tetraazabicyclo[11.3.1]pentadeca - 1(15),11,13-triene hexahydmoridim trihydrate

[0066] 6,6’-[1,3-Phenylene-bis(methylene)]bis[3,9-bis(p-toluenesulphonyl)-3,6,9,15-tetraazabicyclo[11.3.1]pentadeca-1(15),11,13-triene] (100mg) was de-protected with concentrated sulphuric acid using the procedure described in Example 6 (synthesis of G) giving 1,1’-[1,3-phenylenebis(methylene)]bis-3,6,9,15-tetraazabicyclo[11.3.1]pentadeca-1 (15),11,13-triene hexahydmoridim trihydrate (42mg, 45%) as a white solid. ¹H NMR (D₂O) δ 2.66 (m, 8H), 3.05 (m, 8H), 3.76 (s, 4H), 4.45 (s, 8H), 7.20-7.29 (m, 8H), 7.78 (t, 2H, J=7.5 Hz). Mass spectrum (FAB); m/e (relative intensity); 595 (M+HBr, 9), 593 (M+HBr, 9), 515 (M+1, 100); C₃₀H₅₄N₈Br₆O₃ requires: C, 34.18; H, 5.16; N, 10.63; found: C, 34.43; H, 5.28; N, 10.15.

EXAMPLE 8

8-Diethoxyphosphoryl-4,12-bis(p-toluenesulphonyl)-1-oxa-4,8,12-triazatetradecane

[0067] To a stirred solution of N-diethoxyphosphoryl-N',N"-bis(p-toluene-sulphonyl)-3,3’-iminobispropylamine (2.9g, 5mmol) in DMF (150ml) containing cesium carbonate (4.1g, 13mmol, 2.5 equiv.) maintained at 55°C under argon was added a solution of 2-bromoethyl ether (Aldrich, 1.16g, 5mmol) in DMF (75ml) dropwise over a period of 16-20 hours. The reaction mixture was stirred at 55°C for a total of 30 hours then allowed to cool to room temperature and evaporated to dryness under reduced pressure. The brown residue was partitioned in dichloromethane (150ml) and brine (150ml). The organic layer was separated then dried (Na₂SO₄) and evaporated in vacuo to give the crude product as a yellow oil. Column chromatography using dichloromethane / methanol (97 / 3) as the eluent, gave 8-diethoxyphosphoryl-4,12-bis(p-toluenesulphonyl)-1-oxa-4,8,12-triazatetradecane (1.1g, 79%) as a colourless oil.
4,12-Bis(p-toluenesulphonyl)-1-oxa-4,8,12-triazatetradecane

Using the general procedure in example 1e

[0068] 8-Diethoxyphosphoryl-4,12-bis(p-toluenesulphonyl)-1-oxa-4,8,12-triaza-tetradecane (750mg) gave 4,12-bis (p-toluenesulphonyl)-1-oxa-4,8,12-triazatetradecane (410mg, 69%) as a white solid.

8,8'-[1,4-Phenylenebis(methylene)]bis[4,12-bis-(p-toluenesulphonyl)-1-oxa-4,8,12-triazatetradecane]

Using the general procedure in example 1f

[0069] 4,12-Bis(p-toluenesulphonyl)-1-oxa-4,8,12-triazatetradecane (403 mg, 0.79mmol) and α,α'-dibromo-p-xylene (105mg, 0.40mmol) gave 8,8'-[1,4-phenylenebis(methylene)]bis[4,12-bis-(p-toluenesulphonyl)- 1-oxa-4,8,12-triazatetradecane] (393mg, 89%) as a white solid.

Synthesis of Compound J

8,8'-[1,4-Phenylenebis(methylene)]bis-1-oxa-4,8,12-triazatetradecanehexahydro bromide trihydrate

[0070] To a solution of 8,8'-[1,4-phenylenebis(methylene)]bis[4,12-bis-(p-toluenesulphonyl)-1-oxa-4,8,12-triazatetradecane] (250mg) in acetic acid (2.5ml) was added hydrobromic acid (Aldrich, 48% aqueous, 1.5ml) and the mixture was heated to reflux with stirring for 18 hours. The mixture was allowed to cool and ether (50ml) was added to precipitate the product. The white solid was allowed to settle to the bottom of the flask and the supernatant solution was decanted off. The solid was then washed by decantation with ether three times and the remaining traces of ether removed by evaporation under reduced pressure and drying in vacuo overnight giving 8,8'-[1,4-phenylenebis(methylene)]bis-1-oxa-4,8,12-triazatetradecanehexahydro bromide trihydrate as a white solid (221mg, 62%). 1 H NMR (D 2 O) δ 2.05 (m, 8H), 3.15-3.35 (m, 24H), 3.75 (m, 8H), 4.25 (s, 4H), 7.55 (s, 4H). Mass spectrum (FAB); m/e (relative intensity); 587 (M+HBr, 49), 585 (M+HBr, 49), 506 (M+1, 100), 307 (41). C28 H 64 N 6 Br 6 O 5 requires: C, 32.20; H, 6.18; N, 8.05; Br, 45.91. Found: C, 31.73; H, 5.86; N, 7.42; Br, 46.59.

[0071] The general reaction schemes are illustrated in the attached sheets 1 to 6.

[0072] The compounds of the invention were tested in a screen by the MTT method (J Virol Methods 120: 309-321 [1988]). MT-4 cells (2.5 x 10 4 /well) were challenged with HIV-1 (HTLV-IIIB) or HIV-2 (LAV-2 ROD) at a concentration of 100 CCID 50 and incubated in the presence of various concentrations of the test compounds, which were added immediately after challenge with the virus. After 5 days culture at 37 ° C in a CO 2 incubator, the number of viable cells was assessed by the MTT (tetrazolium) method. Antiviral activity and cytotoxicity of the compounds are expressed in the Table below as IC 50 (µg/ml) and CC 50 (µg/ml), respectively. The potential therapeutic usefulness was assessed by calculating a Selectivity Index (SI) corresponding to the ratio of CC 50 to IC 50. The results for the compounds of the invention are shown below in Table 1.

[0073] Compound K is 1,1'-[1,4-phenylenebis(methylene)]bis-1,4,8,11-tetraazacyclotetradecane octahydro bromide dihydrate, (see WO 93/12096).

| TABLE 1 |
|-------|-------|-------|-------|
| HIV-1 (IIIb) | HIV-2 (ROD) |
| CMPD | IC 50 µg/ml | CC 50 µg/ml | SI | IC 50 µg/ml | CC 50 µg/ml | SI |
| A | 0.719 | >250 | 348 | 3.51 | >250 | 71 |
| B | 0.89 | 12.52 | 14 | - | - | - |
| C | 3.57 | 229 | 64 | 9.74 | >250 | 26 |
| D | >218 | >218 | <1 | >250 | >250 | <1 |
| E | 0.0014 | >250 | 1.76x10 5 | 0.001 | >250 | 2.47x10 5 |
| F | 0.59 | 199 | 336 | 1.68 | 171 | 102 |
| G | 0.62 | 6.0 | 10 | 0.15 | 4.71 | 31 |
| H | 0.104 | 32.11 | 309 | 0.0027 | 30.70 | 1.12x10 4 |
| J | 4.62 | >250 | 54 | 2.15 | >250 | >116 |
The compounds were additionally studied to determine their partition coefficients as between octanol and water, in standard tests at various pH values. A partition coefficient greater than unity at pH 7-9 is generally considered to be a good indication that the compound will be absorbed through the upper gastrointestinal tract when dosed orally. Certain of the compounds of the invention demonstrate very significant activity against HIV combined with good partition coefficients, and thus are indicated for oral administration.

The compounds of Formula I may be administered in free base form or in pharmaceutically acceptable acid addition salt or metal complex form. Such salts and complexes may be prepared in conventional manner as described in the Examples, and exhibit the same order of activity as the free bases. Pharmaceutical compositions containing compounds of Formula I may be manufactured in conventional manner containing active ingredient in association with a pharmaceutically acceptable carrier or diluent. Unit dosages forms contain for example from about 0.5mg to about 100mg of a compound of Formula I in free base or pharmaceutically acceptable acid addition salt form. Pharmaceutical compositions for oral administration are well known and may be formulated in accordance with generally known principles. Such compositions may be in solid form as tablets, capsules or dragees or in liquid form as a syrup or suspension.

**Claims**

1. Linked polyamine cyclic compounds of general formula I,

   \[
   
   V-R-A-R'-W
   \]

   in which each of V and W is independently a bicyclic or tricyclic fused ring system containing only carbon and nitrogen atoms in the ring and having from 10 to 20 ring members and from 3 to 6 amine nitrogens spaced by 2 or more carbon atoms from each other, and wherein one fused ring in the bicyclic system, and each of two fused rings in the tricyclic system, is independently phenylene or pyridinylene and which system may optionally be substituted by halogen, nitro, carboxyl, carboxamido, sulfonic acid, phosphate, oxo, hydroxy, alkoxy, thio or alkylthio, A is 1,3- or 1,4-phenylene, and each of R and R’ is methylene which spaces the cyclic polyamines and the moiety A, and their acid addition salts and metal complexes.

2. The compound of claim 1 which is 7,7’-[1,4-phenylene-bis(methylene)]bis-3,7,11,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene.

3. The compound of claim 1 which is 7,7’-[1,4-phenylenebis(methylene)]-bis[15-chloro-3,7,11,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene].
4. The compound of claim 1 which is 7,7'-[1,4-phenylenebis(methylene)]-bis[15-methoxy-3,7,11,17-tetraazabicycl[88x753][13.3.1]heptadeca-1(17),13,15-triene].

5. The compound of claim 1 which is 7,7'-[1,4-phenylenebis(methylene)]-bis-3,7,11,17-tetraazabicyclo[13.3.1]heptadeca-13,16-tetra-ion.

6. The compound of claim 1 which is 7,7'-[1,4-phenylenebis(methylene)]-bis-4,7,10,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene.

7. The compound of claim 1 which is 8,8'-[1,4-phenylenebis(methylene)]-bis-4,8,12,19-tetraazabicyclo[15.3.1]nonadeca-1(19),15,17-triene.

8. The compound of claim 1 which is 6,6'-[1,4-phenylenebis(methylene)]-bis-3,6,9,15-tetraazabicyclo[11.3.1]pentadeca-1(15),11,13-triene.

9. The compound of claim 1 which is 6,6'-[1,3-phenylenebis(methylene)]-bis-3,6,9,15-tetraazabicyclo[11.3.1]pentadeca-1(15),11,13-triene.

10. The compound of claim 1 which is 17,17'-[1,4-phenylenebis(methylene)]bis-3,6,14,17,23,24-hexaazatricyclo[17.3.1.1 8.12]tetracos-1(23),8,10,12(24),19,21-hexaene.

11. A method for the production of compounds according to claim 1, which method comprises nucleophilic attack by cyclic polyamines V' and W' each having a single unprotected ring amine nitrogen, all other amine nitrogens being protected, on a compound of formula III

\[ X - R - A - R' - X \] (III)

wherein R, R' and A are as defined above, and each X is an active substituent which can be displaced by the unprotected nitrogens of polyamines V' and W' and is preferably selected from Br, Cl, I, methanesulphonate, 4-tolylsulphonate and trifluoromethane sulphonate, and subsequently de-protecting the ring amine nitrogens.

12. A pharmaceutical composition active against HIV, comprising as an active ingredient a compound according to any one of claims 1 to 10, in association or admixture with a pharmaceutically acceptable diluent or carrier.

13. A composition according to claim 12, in unit dosage form.

**Patentansprüche**

1. Verknüpfte cyclische Polyamin-Verbindungen der allgemeinen Formel I,

\[ V - R - A - R' - W \] (I)

worin jedes von V und W unabhängig ein bicyclisches oder tricyclisches verschmolzenes Ringsystem ist, das lediglich Kohlenstoff- und Stickstoffatome im Ring enthält und 10 bis 20 Ringglieder und 3 bis 6 Amin-Stickstoffe aufweist, die durch 2 oder mehr Kohlenstoffatome voneinander beabstandet sind, und wobei ein verschmolzener Ring im bicyclischen System, und jeder von zwei verschmolzenen Ringen im tricyclischen System unabhängig Phenyl en oder Pyridinylen ist, und welches System wahlweise substituiert sein kann durch Halogen, Nitro, Carboxyl, Carboxamido, Sulfonsäure, Phosphat, Oxo, Hydroxy, Alkoxy, Thio oder Alkylthio, A 1,3- oder 1,4-Phenylen ist, und jedes von R und R' Methylen ist, das den Abstand zwischen den cyclischen Polyaminen und der Komponente A besetzt, und deren Säureadditionssalze und Metallkomplexe.
2. Verbindung nach Anspruch 1, welche 7,7'-[1,4-Phenylenbis(methylen)]bis-3,7,11,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-trien ist.


5. Verbindung nach Anspruch 1, welche 7,7'-[1,4-Phenylenbis(methylen)]bis-3,7,11,17-tetraazabicyclo[13.3.1]heptadeca-13,16-trien-15-on ist.

6. Verbindung nach Anspruch 1, welche 7,7'-[1,4-Phenylenbis(methylen)]bis-4,7,10,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-trien ist.

7. Verbindung nach Anspruch 1, welche 8,8'-[1,4-Phenylenbis(methylen)]bis-4,8,12,19-tetraazabicyclo[15.3.1]nonadeca-1(19),15,17-trien ist.

8. Verbindung nach Anspruch 1, welche 6,6'-[1,4-Phenylenbis(methylen)]bis-3,6,9,15-tetraazabicyclo[11.3.1]pentadeca-1(15),11,13-trien ist.

9. Verbindung nach Anspruch 1, welche 6,6'-[1,3-Phenylenbis(methylen)]bis-3,6,9,15-tetraazabicyclo[11.3.1]pentadeca-1(15),11,13-trien ist.

10. Verbindung nach Anspruch 1, welche 17,17'-[1,4-Phenylenbis(methylen)]bis-3,6,14,17,23,24-hexaazatricyclo[17.3.1.1\(^8,12\)]tetracosa-1(23),8,10,12(24),19,21-hexan ist.

11. Verfahren zur Herstellung von Verbindungen nach Anspruch 1, welches Verfahren einen nukleophilen Angriff durch cyclische Polyamine V' und W' umfasst, die jeweils einen einzelnen ungeschützten Ringamin-Stickstoff, wobei alle anderen Amin-Stickstoffe geschützt sind, an einer Verbindung aufweisen der Formel III

\[ X - R - A - R' - X (\text{III}) \]

worin R, R' und A wie oben definiert sind, und jedes X ein aktiver Substituent ist, welcher durch die ungeschützten Stickstoffe der Polyamine V' und W' verdrängt werden kann und vorzugsweise gewählt ist aus Br, CI, I, Methansulfonat, 4-Tolylsulfonat und Trifluormethansulfonat, und anschließend Entschützen der Ringamin-Stickstoffe.


Rezensionen

1. Composés cycliques polyamino lié de formule générale I,

\[ V - R - A - R' - W \]

dans laquelle chacun parmi V et W est indépendamment un système cyclique condensé bicyclique ou tricyclique contenant seulement des atomes de carbone et d'azote dans le cycle et ayant de 10 à 20 chaîons de cycle et de 3 à 6 azotes d'amine espacés entre eux par 2 atomes de carbone ou plus, et dans laquelle un cycle condensé du système bicyclique, et chacun de deux cycles condensés dans le système tricyclique, est indépendamment un
groupe phénylène ou pyridinylène, et ce système pouvant éventuellement être substitué par un halogène, un
groupe nitro, carboxyle, carboxamido, acide sulfonique, phosphate, oxo, hydroxy, alcoxy, thio ou alkylthio,
A est un groupe 1,3- ou 1,4-phénylène, et
chacun parmi R et R’ est un groupe méthylène qui espace les polyamines cycliques et la fraction A,
et leurs sels d’addition avec un acide et complexes métalliques.

2. Composé selon la revendication 1, qui est le 7,7’-[1,4-phénylènebis(méthylène)]bis-3,7,11,17-tétraazabicy-
clo-[13.3.1]heptadéca-1(17),13,15-triène.

3. Composé selon la revendication 1, qui est le 7,7’-[1,4-phénylènebis(méthylène)]bis[15-chloro-3,7,11,17-tétraaza-
bicyclo[13.3.1]heptadéca-1(17),13,15-triène].

4. Composé selon la revendication 1, qui est le 7,7’-[1,4-phénylènebis(méthylène)]bis[15-méthoxy-3,7,11,17-tétraa-
zabicyclo[13.3.1]heptadéca-1(17),13,15-triène].

5. Composé selon la revendication 1, qui est la 7,7’-[1,4-phénylènebis(méthylène)]bis-3,7,11,17-tétraazabicy-

6. Composé selon la revendication 1, qui est le 7,7’-[1,4-phénylènebis(méthylène)]bis-4,7,10,17-tétraazabicy-
clo-[13.3.1]heptadéca-1(17),13,15-triène.

7. Composé selon la revendication 1, qui est le 8,8’-[1,4-phénylènebis(méthylène)]bis-4,8,12,19-tétraazabicy-
clo-[15.3.1]nonadéca-1(19),15,17-triène.

8. Composé selon la revendication 1, qui est le 6,6’-[1,4-phénylènebis(méthylène)]bis-3,6,9,15-tétraazabicy-
clo-[11.3.1]pentadéca-1(15),11,13-triène.

9. Composé selon la revendication 1, qui est le 6,6’-[1,3-phénylènebis(méthylène)]bis-3,6,9,15-tétraazabicy-
clo-[11.3.1]pentadéca-1(15),11,13-triène.

10. Composé selon la revendication 1, qui est le 17,17’-[1,4-phénylènebis(méthylène)]bis-3,6,14,17,23,24-hexaaza-
tricycl[17.3.1.1^8,12] tétracosa-1(23),8,10,12(24), 19,21-hexaène.

11. Procédé pour la production de composés selon la revendication 1, ce procédé comprenant l’attaque nucléophile
par des polyamines cycliques V’ et W’ ayant chacune un seul azote d’amine cyclique non protégé, tous les autres
azotes d’amine étant protégés, sur un composé de formule III

\[ X - R - A - R' - X \]  

(III)
dans laquelle R, R’ et A sont tels que définis ci-dessus, et
chaque X est un substituant actif qui peut être déplacé par les azotes non protégés des polyamines V’ et W’ et est
de préférence choisi parmi Br, Cl, I, méthanesulfonate, 4-tolylsulfonate et trifluorométhane sulfonate,
puis la déprotection des azotes d’amine cycliques.

12. Composition pharmaceutique active contre le VIH, comprenant en tant qu’ingrédient actif un composé selon l’une
quelconque des revendications 1 à 10, en association ou mélange avec un diluant ou support pharmaceutiquement
acceptable.

13. Composition selon la revendication 12, sous forme de dosage unitaire.
1. p-xylene dibromide
   \( \text{K}_2\text{CO}_3 / \text{Acetonitrile} \)

2. \( \text{H}_2\text{SO}_4 / 110^\circ\text{C} / 3\text{ h} \)
   Neutralise NaOH
   HBr/EtOH

\[ \begin{align*}
\text{C}_2\text{CO}_3 / \text{DMF} & \quad 55^\circ\text{C} / 30\text{ hours} \\
\text{HBr} / \text{AcOH} & \quad \text{Room temp} / 2.5\text{ h} \\
\end{align*} \]
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\[ \text{Dep N} \quad \text{NHTs} \quad \xrightarrow{\text{Cs}_2\text{CO}_3/\text{DMF}} \quad 50-70 \, ^\circ \text{C} \quad \text{NTs} \quad \text{O} \quad \xrightarrow{\text{HBr / AcOH}} \quad \text{NTs} \quad \text{O} \quad \xrightarrow{3 \, \text{hours}} \quad \text{Br} \quad \text{O} \quad \text{Br} \]

1. Dibromo-p-xylene
   \[ \text{K}_2\text{CO}_3 / \text{CH}_3\text{CN} \]
   2. 48 % HBr (aq)
      \[ \text{AcOH / reflux} \]
      or
      \[ \text{Na / Hg / Na}_2\text{HPO}_4 \]
      MeOH / THF / reflux

6 HBr   3 H_2O

\[ \text{J} \]