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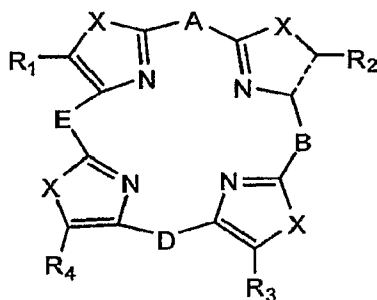
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(54) Title: THERAPEUTIC COMPOUNDS



(I)

(57) Abstract: The invention provides compounds of formula I: wherein A, B, D, E, R₁, R₂, R₃, R₄, R₅, X, and ----- have any values defined herein, as well as salts thereof. The compounds have activity as G-quadruplex DNA stabilizers and as anti-proliferative agents.

THERAPEUTIC COMPOUNDS

Priority of Invention

5 This application claims priority from U.S. Provisional Application Number 60/794,525, filed 25 April 2006, which application is incorporated by reference.

Background of the Invention

10 A diverse array of compounds, including anthraquinones, acridines, cationic porphyrins, perylenes, thidium derivatives, fluorenes, pentacyclic acridinium salts, fluoroquinophenoxazines, and other specific miscellaneous polycyclic compounds, have been reported to stabilize G-quadruplex DNA. Most of these compounds have little or no selectivity for G-quadruplex vs. duplex DNA.

15 Telomestatin is a natural product isolated from *Streptomyces anulatus* 3533-SV4 (Shin-ya *et al.*, *J. Am. Chem. Soc.*, **2001**, *123*, 1262-1263). At the time of its discovery, telomestatin was viewed as the most potent inhibitor of telomerase. *In vitro*, telomestatin stabilizes G-quadruplex vs. duplex DNA in a 70:1 ratio (Kim *et al.*, *Cancer Res.*, **2003**, *63*, 3247-3256). It has been suggested
20 that telomestatin also inhibits telomerase function *in vivo*, since cells treated with the natural product exhibit a cellular senescence phenotype. Like telomere dysfunction, telomestatin activates the ATM signaling pathway. While the precise mechanism by which telomestatin interacts with a G-quadruplex has not been definitively elucidated, telomestatin does suppress the plating efficiency of
25 K62 leukemia cells but has a much lesser effect on burst-forming units - erythrocyte (BFU-E) and colony-forming units - granulocyte/macrophage (CFU-GM) from natural bone marrow CD34-positive cells (Tauchi *et al.*, *Oncogene*, **2003**, *22*, 5338-5347).

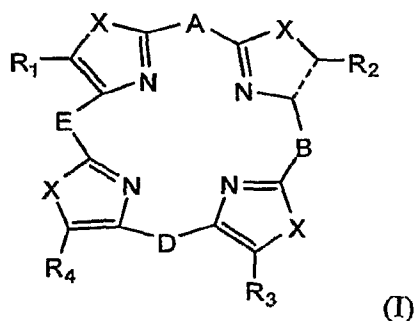
 The anticancer potential of telomestatin resides in its telomerase
30 inhibitory activity (IC₅₀ 5 nM) and in its ability to enhance apoptosis. Telomestatin has been evaluated for cytotoxicity in the human neuroblastoma cell lines SK-N-AS, LAN5, WAC2, and LAN1 with IC₅₀ values of 0.8, 2.5, 3.2,

and 4.0 μM respectively (Binz *et al.*, *Eur. J. Cancer*, **2005**, 41, 2873-2881) and in the human pancreatic carcinoma MiaPaCa with an IC_{50} value of 0.5 μM (Liu *et al.*, *Nucleosides, Nucleotides, and Nucleic Acids*, **2005**, 24, 1801-1815).

Currently, there is a need for novel therapeutic agents and therapeutic methods that are useful for treating diseases such as cancer. Such agents may have improved binding affinity for G-quadruplex DNA and/or they may have advantageous drug-like properties.

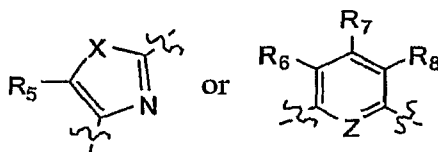
Summary of the Invention

The present invention provides compounds that stabilize G-quadruplex DNA and that possess anti-cancer properties. Accordingly there is provided a compound of the invention which is compound of formula I:



wherein:

each A, B, D, and E is independently $-\text{C}(=\text{O})\text{NH}-\text{CH}(\text{R}_a)-$, $-\text{C}(=\text{O})-\text{NH}-\text{C}(=\text{O})-$, or a group of the formula:



each R_1 , R_2 , R_3 , R_4 , and R_5 is independently H, $(\text{C}_1-\text{C}_6)\text{alkyl}$, or $(\text{C}_1-\text{C}_6)\text{alkoxy}$, wherein each $(\text{C}_1-\text{C}_6)\text{alkyl}$ and $(\text{C}_1-\text{C}_6)\text{alkoxy}$ is optionally substituted with OH, $(\text{C}_1-\text{C}_6)\text{alkoxy}$, $(\text{C}_1-\text{C}_6)\text{alkylthio}$, aryl, NR_cR_d , or $-\text{C}(=\text{O})\text{NR}_c\text{R}_d$;

each R_6 , R_7 , and R_8 is independently H; or each R_6 and R_7 together with the atoms to which they are attached form a benzo ring and R_8 is H; or R_6 is H

and R₇ and R₈ together with the atoms to which they are attached form a benzo ring;

each X is independently NH, S, or O;

each Z is independently N or CH;

5 the bond represented by ----- is a single or a double bond;

each R_a is independently H, aryl, or (C₁-C₆)alkyl that is optionally substituted with OH, (C₁-C₆)alkoxy, (C₁-C₆)alkylthio, aryl, NR_eR_f, or -C(=O)NR_eR_f;

each R_c and R_d is independently H or (C₁-C₆)alkyl; or R_c and R_d together with the nitrogen to which they are attached form a pyrrolidino, piperidino, piperazino, morpholino, thiomorpholino, or azepino ring; and
each R_e and R_f is independently H or (C₁-C₆)alkyl; or R_e and R_f together with the nitrogen to which they are attached form a pyrrolidino, piperidino, piperazino, morpholino, thiomorpholino, or azepino ring;

15 or a salt thereof;

provided the compound of formula I is not telomestatin or dehydrotelomestatin.

The invention also provides a pharmaceutical composition comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, in
20 combination with a pharmaceutically acceptable diluent or carrier.

Additionally, the invention provides a therapeutic method for treating cancer comprising administering to a mammal (*e.g.*, a human male or female) in need of such therapy, an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof.

25 The invention provides a compound of formula I or a pharmaceutically acceptable salt thereof for use in medical therapy (*e.g.*, for use in treating cancer), as well as the use of a compound of formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament useful for the treatment of cancer in a mammal, such as a human.

30 The invention also provides processes and intermediated disclosed herein (*e.g.*, novel intermediate compounds included in compounds 100-177) that are useful for preparing compounds of formula (I) or salts thereof.

Detailed Description

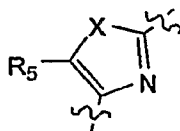
The following definitions are used, unless otherwise described: halo is fluoro, chloro, bromo, or iodo. Alkyl, alkoxy, *etc.* denote both straight and branched groups; but reference to an individual radical such as propyl embraces
5 only the straight chain radical, a branched chain isomer such as isopropyl being specifically referred to. Aryl denotes a phenyl radical or an ortho-fused bicyclic carbocyclic radical having about nine to ten ring atoms in which at least one ring is aromatic.

It will be appreciated by those skilled in the art that compounds of the
10 invention having a chiral center may exist in and be isolated in optically active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic, or stereoisomeric form, or mixtures thereof, of a compound of the invention, which possess the useful properties described herein, it being well
15 known in the art how to prepare optically active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase).

Specific values listed below for radicals, substituents, and ranges, are for
20 illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

Specifically, (C₁-C₆)alkyl can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-butyl, pentyl, 3-pentyl, or hexyl; (C₁-C₆)alkoxy can be methoxy, ethoxy, propoxy, isopropoxy, butoxy, iso-butoxy, sec-butoxy, pentoxy, 3-
25 pentoxy, or hexyloxy; and aryl can be phenyl, indenyl, or naphthyl.

A specific group of compounds are compounds wherein A and D are each independently a group of the following formula:



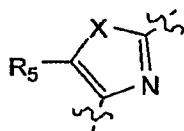
A specific value for X is O.

A specific value for the bond represented by ----- is a double bond.

A specific group of compounds are compounds wherein B and E are each independently $-C(=O)NH-CH(R_a)-$.

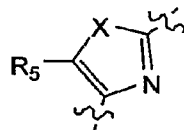
A specific value for R_a is H, methyl, isopropyl, 2-methylpropyl, benzyl, 3-
5 (N,N-dimethylamino)propyl, or 4-(N,N-dimethylamino)butyl.

A specific group of compounds are compounds wherein A, B, and D are each independently a group of the following formula:



A specific value for E is $-C(=O)NH-CH(R_a)-$.

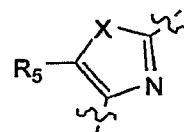
10 A specific group of compounds are compounds wherein A, B, D, and E are each independently a group of the following formula:



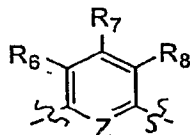
A specific value for each $R_1, R_2, R_3, R_4,$ and R_5 is independently H or (C₁-C₆)alkyl that is substituted with OH, (C₁-C₆)alkoxy, (C₁-C₆)alkylthio, aryl, NR_cR_d,
15 or $-C(=O)NR_cR_d$.

A specific value for each $R_1, R_2, R_3, R_4,$ and R_5 is independently H or (C₂-C₆)alkyl that is optionally substituted with OH, (C₁-C₆)alkoxy, (C₁-C₆)alkylthio, aryl, NR_cR_d, or $-C(=O)NR_cR_d$.

A specific group of compounds are compounds wherein each B and E is
20 independently a group of the formula:



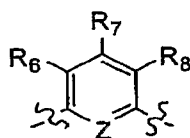
and each A and D is independently group of the formula:



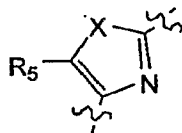
A specific value for Z is N.

A specific value for Z is CH.

A specific group of compounds are compounds wherein each A, B, D,
5 and E is independently a group of the formula:



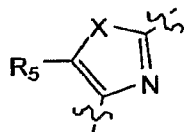
A specific group of compounds are compounds wherein A and D are each
independently a group of the following formula:



10 B is -C(=O)-NH-C(=O)-; and

E is -C(=O)NH-CH(R_a)-.

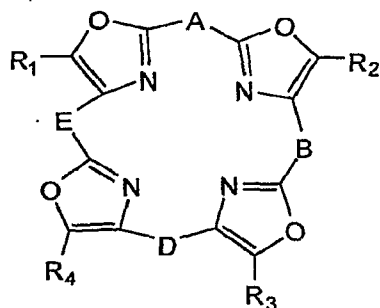
A specific group of compounds are compounds wherein A and D are each
independently a group of the following formula:



; and

15 B and E are each independently -C(=O)NH-CH(R_a)-.

A specific compound of the invention is a compound of formula (II):



(II);

or a pharmaceutically acceptable salt thereof.

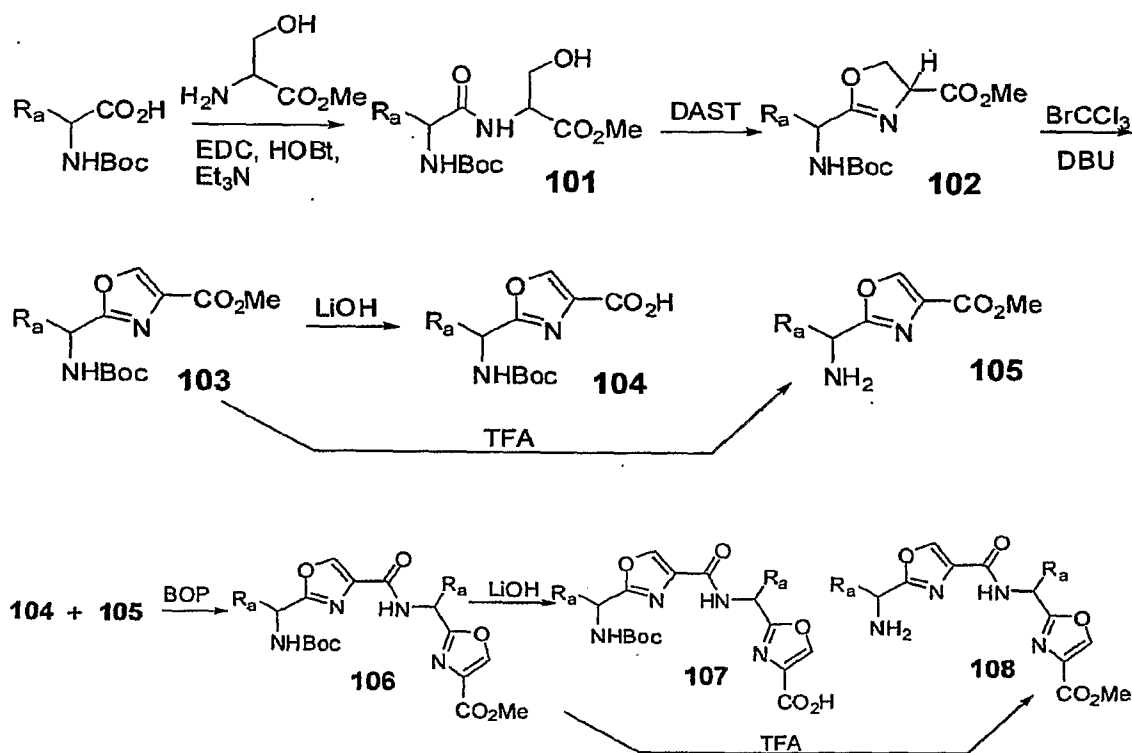
Processes for preparing compounds of formula I are provided as further embodiments of the invention and are illustrated by the following procedures in which the meanings of the generic radicals are as given above unless otherwise qualified.

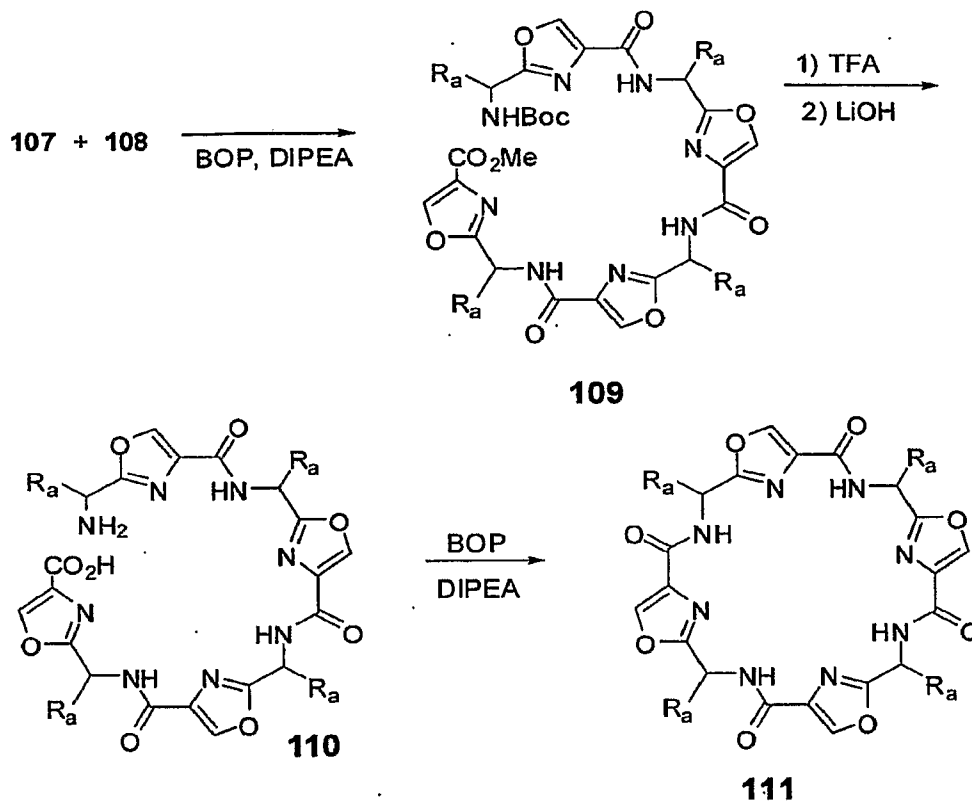
METHODS OF PREPARATION

Hexa-Oxazoles

This series of compounds can be prepared by using intermediates comprised of alternating oxazole and amino acid units as outlined in Scheme 1. Initially, cyclic tetraoxazole intermediates are synthesized from which further interconnected oxazole rings can be generated. Such intermediates can be prepared by condensation of the N-Boc derivatives of amino acids such as valine, leucine, alanine or an appropriately substituted α -amino acid (assuming that appropriate protecting groups are employed) and an O-protected serine methyl ester employing either 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) in the presence of 1-hydroxybenzotriazole (HOBt) and base, or benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) with triethylamine. In this manner, the resulting amides **101** can be prepared in good yield. Cyclodehydration can be achieved using (diethylamino)sulfur trifluoride (DAST) giving the corresponding oxazolines **102**. Dehydrogenation to the oxazole derivatives **103** can be performed using bromotrichloromethane in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). One portion of each of the oxazoles can then be hydrolyzed to carboxylic acids **104** using lithium hydroxide in aqueous

methanol or THF. Another portion can be treated with equal amounts of trifluoroacetic acid (TFA) in methylene chloride to afford the deprotected amines **105**. Oxazoles having a free amino group, such as **105**, can be coupled with others having a 4-carboxylic acid moiety, such as **104**, using BOP to provide the key structural intermediate **106** possessing two oxazole rings separated by an α -amino acid residue. Again, portions of these intermediates can be treated with either LiOH to give the 4'-carboxylic acid derivatives **107** or with TFA to give the unprotected amino derivatives **108**. Coupling of **107** and **108** with BOP will provide **109**, which can be deprotected sequentially with TFA, and then LiOH to provide **110**. Macrocyclization of **110** can be achieved using BOP in the presence of diisopropylethylamine (DIPEA) in DMF/acetonitrile (7:1) under high dilution (0.007M) conditions to yield the appropriately substituted tetra-oxazole, **111**.

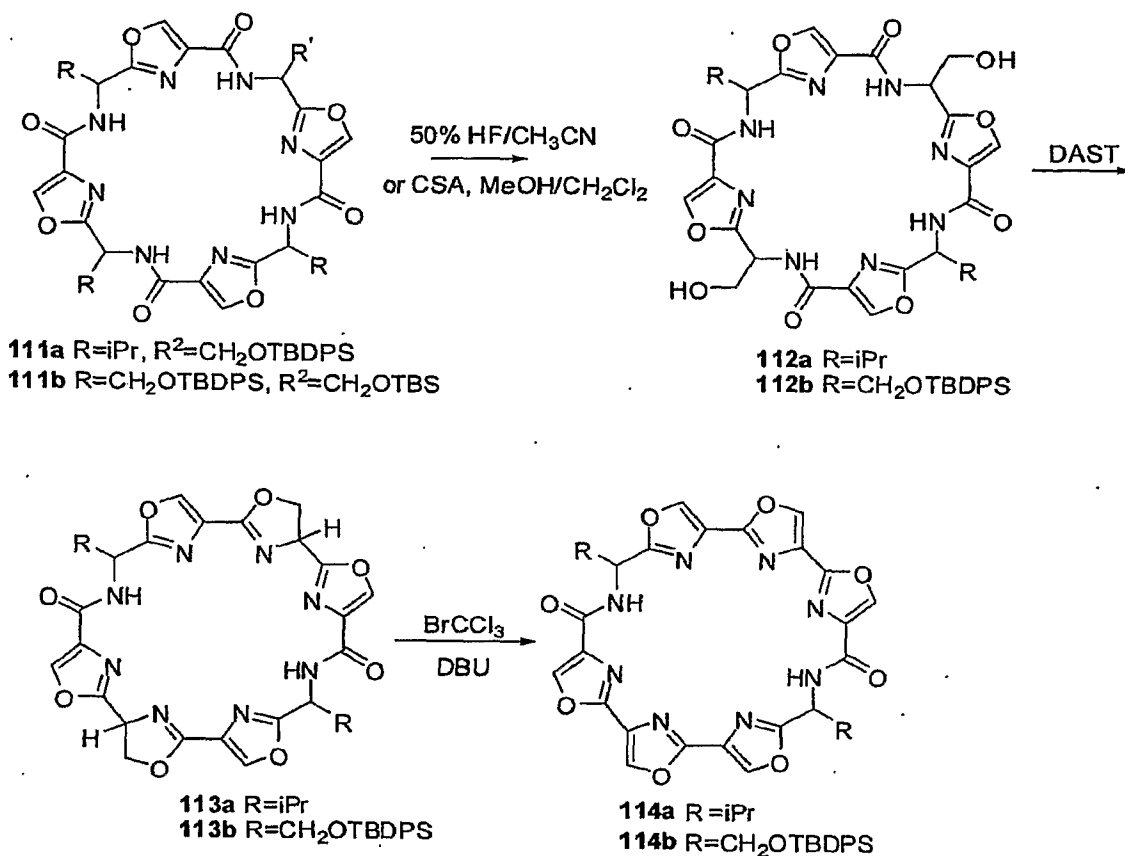




Scheme 1.

- 5 Hexa-oxazole compounds can be prepared from tetra-oxazoles where two of the R-substituents consist of a hydroxymethyl group as outlined in Scheme 2.
- The hydroxyl group in such instances can be protected by the formation of *tert*-butyldiphenylsilyl (TBDPS) ethers as represented by the specific intermediate
- 10 **111a**. Methods for the preparation of **114a** and **114b** illustrate the general method by which one can convert such tetra-oxazoles intermediates into hexa-oxazoles. Treatment of **111a** with HF will efficiently remove the *tert*-butyldiphenylsilyl (TBDPS) ethers. The resulting diol **112a** can then be cyclodehydrated using DAST to give the resulting bis-oxazoline **113a**, which can be aromatized to **114a** upon treatment with bromotrichloromethane and
- 15 **DBU**. The macrocycle **111b**, which is illustrated with two different silyl ether protecting groups on the hydroxymethyl groups designated as R₁ and R₂ can be treated with camphorsulfonic acid (CSA) in methanol and methylene chloride to selectively remove the *tert*-butyldimethylsilyl (TBS) groups to give diol **112b**.

Treatment of **112b** with DAST can provide **113b**. Aromatization of the two oxazoline rings would yield **114b**.



5

Scheme 2.

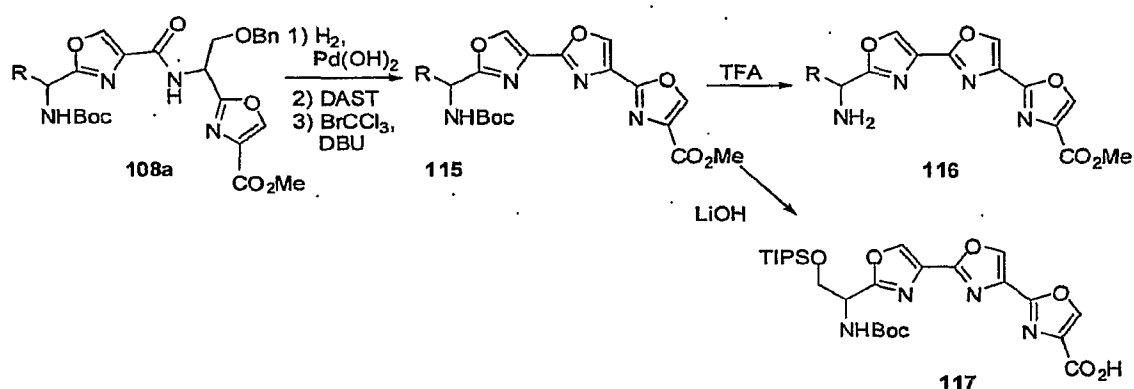
Hepta-oxazoles

10

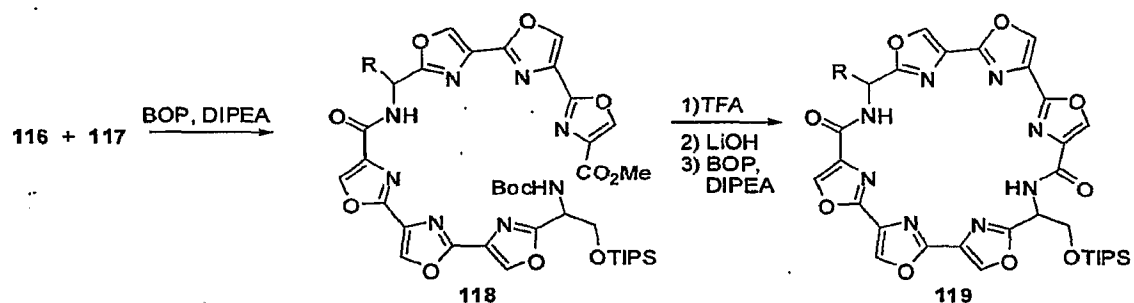
Macrocyclic dihydrohepta-oxazoles **120** and hepta-oxazoles **121** containing varied R substituents can be prepared as illustrated in Scheme 3. When R⁴ is a benzyl ether on intermediate **108** (whose synthesis was described in Scheme 1) one has intermediate **108a**, which can be hydrogenolyzed over palladium hydroxide to give its corresponding alcohol derivative. Such hydroxymethyl groups upon treatment with DAST will cyclize to a dihydrooxazole which can be dehydrogenated with bromotrichloromethane to give the teroxazole **115**, where R is a number of varied alpha-substituents, which have standard protecting groups as required. Treatment of **115** with TFA will remove the Boc-protecting group and

15

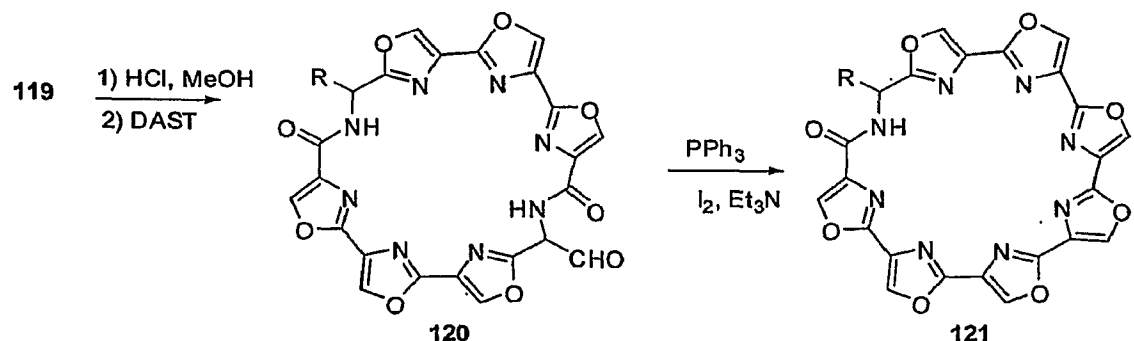
provide the amine **116**. Hydrolysis of **115**, where R = *tert*-butyldiphenylsilyl (TBDPS) with LiOH will provide **117**. Treatment of a mixture of **116** and **117** with BOP provides the amide **118**. The Boc group can then be removed with TFA, the ester hydrolyzed and the resulting compound macrocyclized using BOP to give lactam **119**. The TIPS group can be removed by treatment with concentrated HCl in methanol and methylene chloride to give the alcohol. The alcohol can be oxidized to an aldehyde using Dess-Martin periodinate and cyclized to hepatoxazole **121** using triphenylphosphine and iodine with triethylamine.



10

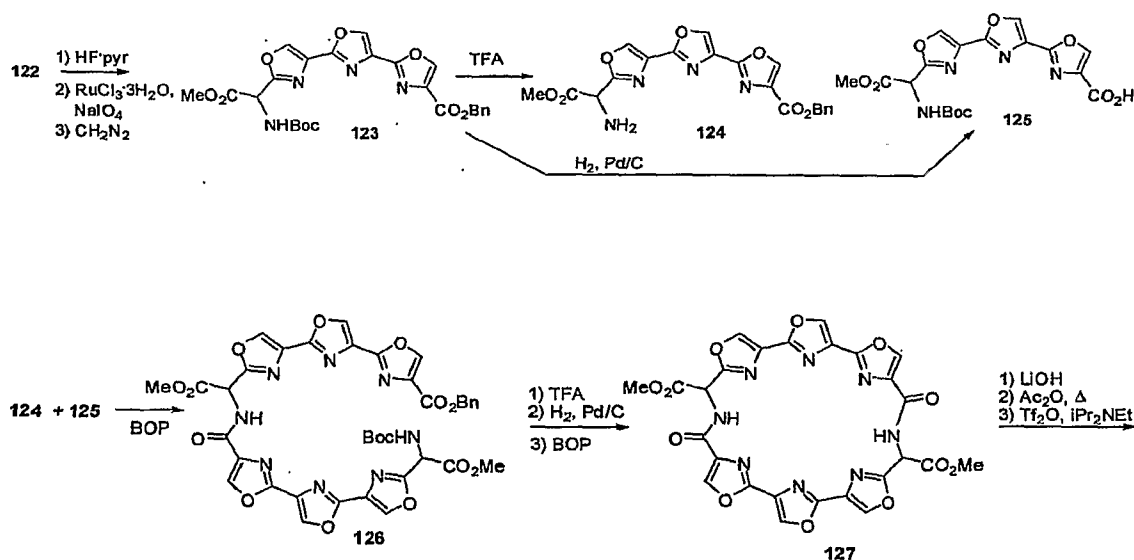


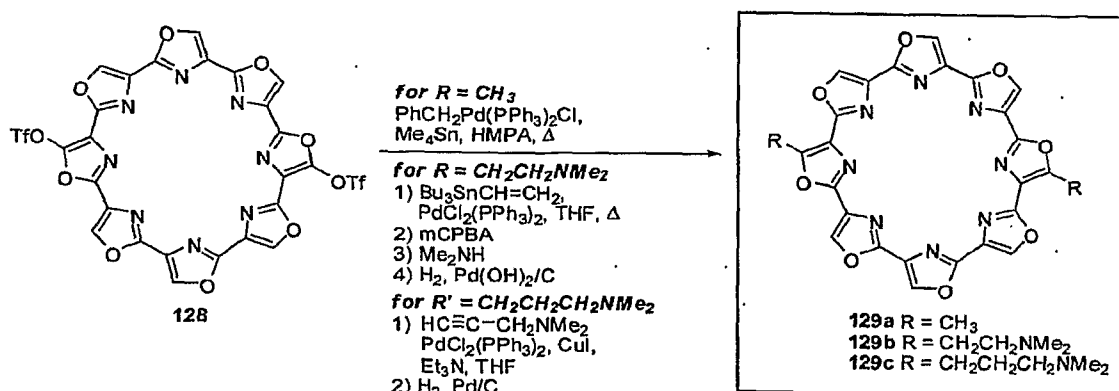
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Scheme 3.**Octa-Oxazoles**

- A convergent approach to the synthesis of octa-oxazoles can be employed as outlined in Scheme 4. Teroxazole **122** (which was prepared by forming the benzyl ester from acid **117**) will be treated with HF·pyridine complex to remove the TIPS group. The resulting alcohol will be oxidized with $\text{RuCl}_3/\text{NaIO}_4$ to give a carboxylic acid that will then be converted into methyl ester **123**. A portion of **123** will be treated with TFA to remove the Boc group to give amine **124**. Another portion of **123** will be converted into carboxylic acid **125** by selective hydrogenolysis of the benzyl ester. Coupling of **124** and **125** will give amide **126**. Treatment with TFA followed by hydrogenolytic removal of the remaining benzyl ester, and macrocyclization with BOP will form bislactam **127**. After ester hydrolysis, warming with acetic anhydride and then treatment with triflic anhydride will give the bis(triflate) derivative **128**. The same series of reactions employed above for heptaoxazoles herein will be used to prepare disubstituted octaoxazole torands **129a-c**.





Scheme 4.

Synthesis of Hexa-, Hepta, and Octa-oxazole Analogs Having Basic Side Chains.

The presence of alkyl side chains possessing basic functional groups may stabilize the interaction between the substrate and the G-quadruplex structure by providing for hydrogen bonding with the phosphate backbone. The presence of these substituents should also improve water solubility by providing a handle for salt formation. Two such groups on non-adjacent oxazole rings may magnify the binding affinity for G-quadruplex relative to duplex DNA. Methods have been outlined for the synthesis of hexa-, hepta, and oct-oxazoles having a single 2-(N,N-dimethylamino)ethyl chain on rings B, C, or D of a hexa-oxazole (see Figure A), and B, C, E or G of hepta- and octa-oxazoles. Several analogs having two 2-(N,N-dimethylamino)ethyl chains on rings B & G and C & G, or in the case of hepta and octa-oxazoles C & E or E & G. Similar methodology can be used to prepare macrocyclic hexa-, hepta- or octa-oxazoles having one or two ω -aminoalkyl chains in which the amine is substituted with H, alkyl, acetyl, or Boc groups.

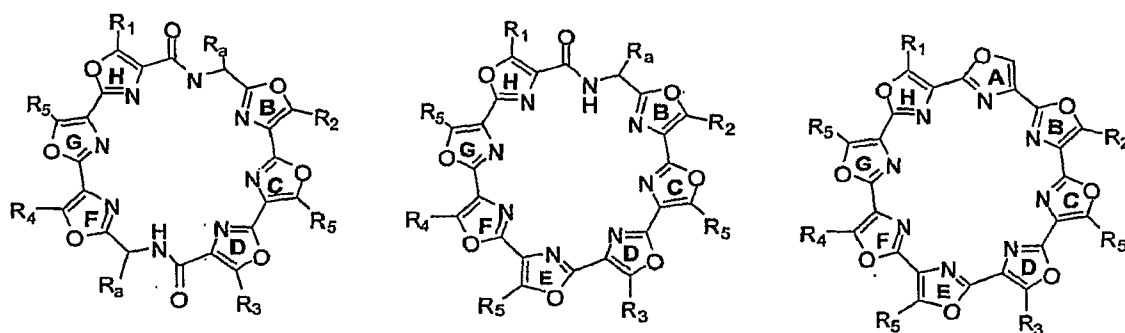


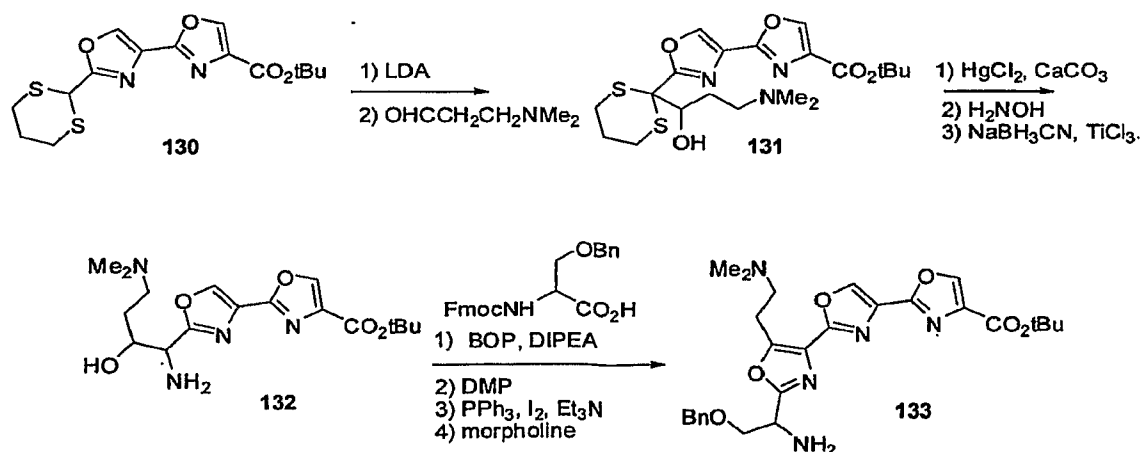
Figure A.

While the overall strategies for the synthesis of these analogs are the same to that used for hexa-, hepta- and octa-oxazoles and their intermediates, the presence of such aminoalkyl substituents at these various sites require the preparation of appropriately substituted teroxazoles. While there are various suitable methods available for the preparation of such teroxazole, representative methods are illustrated below for several such key intermediates (*see* Section A). In addition, one can generate an aminoalkyl oxazole from an appropriately substituted oxazole with a cyclic hexa- or hepta oxazole (*see* Section B). These methods are also illustrated below.

Section A. Synthesis of Teroxazole Intermediates:

Synthesis of the 4-[2-(N,N-dimethylamino)ethyl] teroxazole, Compound 133.

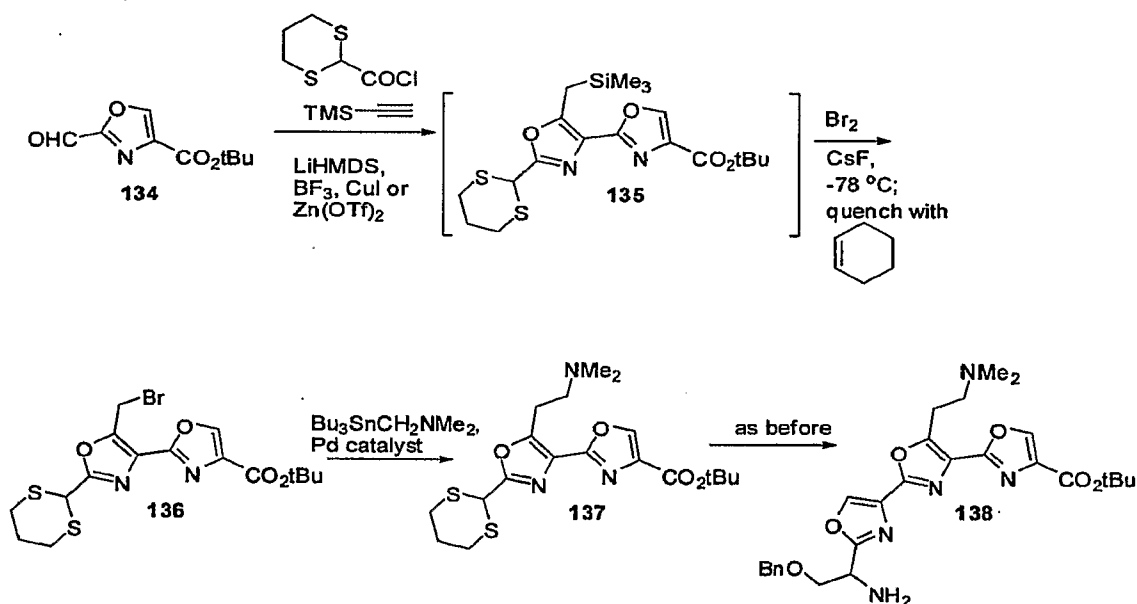
Lithiation of **130** followed by reaction with 3-(dimethylamino)propionaldehyde will give alcohol **131**. Mercury catalyzed hydrolysis of the dithiane to a ketone, followed by oxime formation and then reduction will lead to amino alcohol **132**. Amidation with O-benzyl-NH(Fmoc)-L-serine, followed by Dess-Martin oxidation, oxazole formation, and removal of the Fmoc group will yield substituted teroxazole **133**.



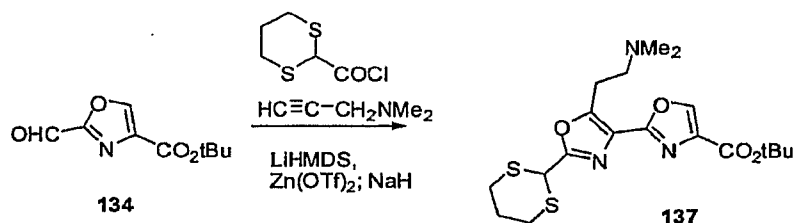
Synthesis of 4-[2-(N,N-dimethylamino)ethyl] teroxazole, Compound 138.

There are at least two methods for the formation of a teroxazole which has an 2-N,N-dimethylaminoethyl intermediate on the central oxazole unit. The first seeks to expand the utility of a multi-functionalized central oxazole similar

to that described in the synthesis above. To that end, the immediate product of reaction of aldehyde **134** with trimethylsilylacetylene, LiHMDS, and the acid chloride of 1,3-dithiane-2-carboxylic acid, after treatment with sodium hydride should be 5-(trimethylsilyl)methyl derivative **135**. Treatment with bromine and CsF at low temperature, followed by a quench with excess cyclohexene to prevent ring bromination is expected to give bromomethyl derivative **136** directly. An alternative preparation of **136** from methyl derivative **130** is possible by treatment with N-bromosuccinimide and a free-radical initiator in a non-protic solvent, conditions under which the dithiane is stable. Stille coupling of **136** with 1-(N,N-dimethylamino)methyltributylstannane will lead to bisoxazole **137**. This will be elaborated into teroxazole **138**.



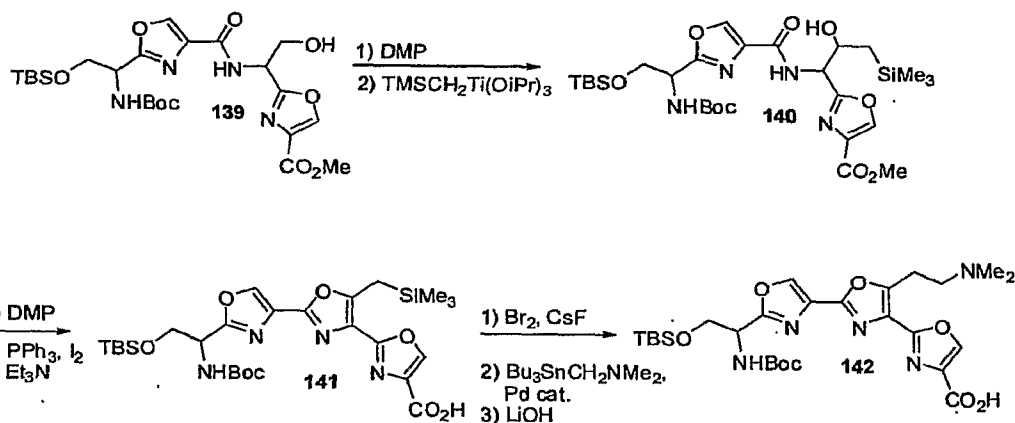
An alternate approach to **137** employs 3-dimethylamino-1-propyne as the acetylene in the multi-component coupling reaction, which should yield **137** directly upon workup of the reaction. Zinc triflate has been employed previously in Lewis acid catalyzed reactions in the presence of tertiary amines.



Synthesis of 4-[2-(N,N-dimethylamino)ethyl] teroxazole, Compound 143.

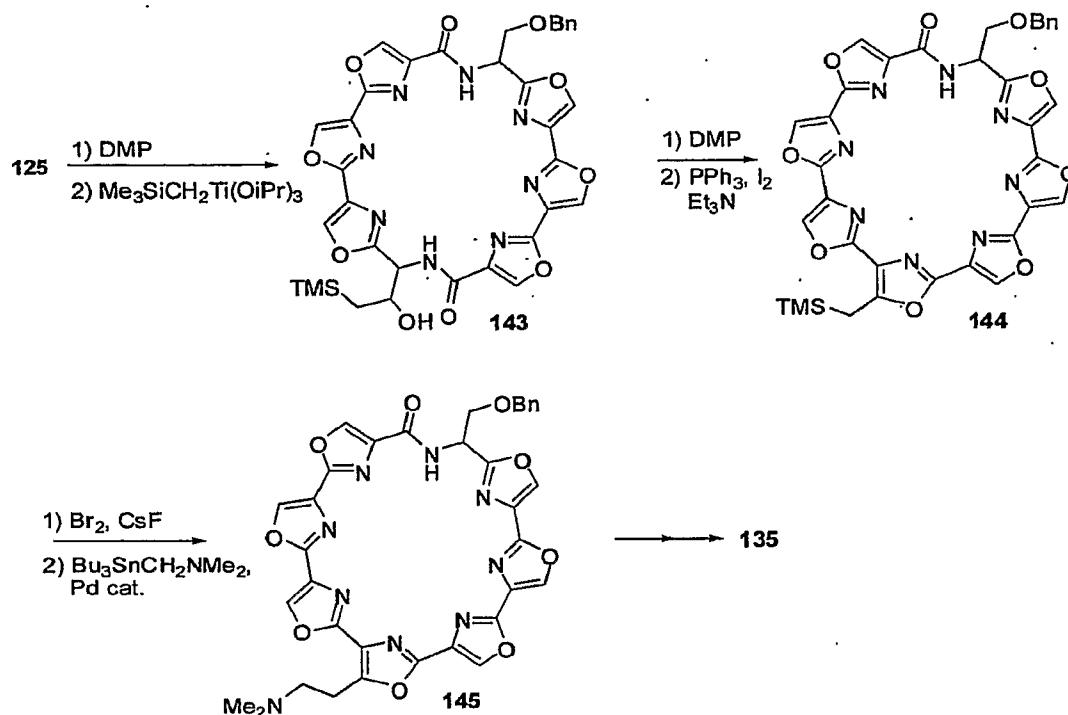
Amide **139** will be oxidized to an aldehyde and converted into β -hydroxysilane **140** as described above. Oxidation to the ketone and cyclodehydration using Wipf's procedure will furnish teroxazole **141**.

- 5 Bromodesilylation and Stille coupling, as detailed previously, followed by ester hydrolysis will give **142**.



Section B. Methods to Convert a Hexa- or Hepta- Oxazole Macrolide into a Hepta- or Octa Oxazole, which Possesses a 4-[2-(N,N-Dimethylamino)ethyl] Substituent within the Newly Generated Oxazole

Macrocycle **125** will be oxidized with Dess-Martin periodinane (DMP) and the resulting aldehyde reacted chemoselectively with (trimethylsilyl)methyl-titaniumtriisopropoxide to give alcohol **143**. A second Dess-Martin oxidation followed by treatment with triphenylphosphine and iodine will form heptaoxazole **144**. Replacement of the silane with bromine, and Stille coupling with 1-(N,N-dimethylamino)methyltributylstannane will furnish key intermediate **145** which will then be converted as described.



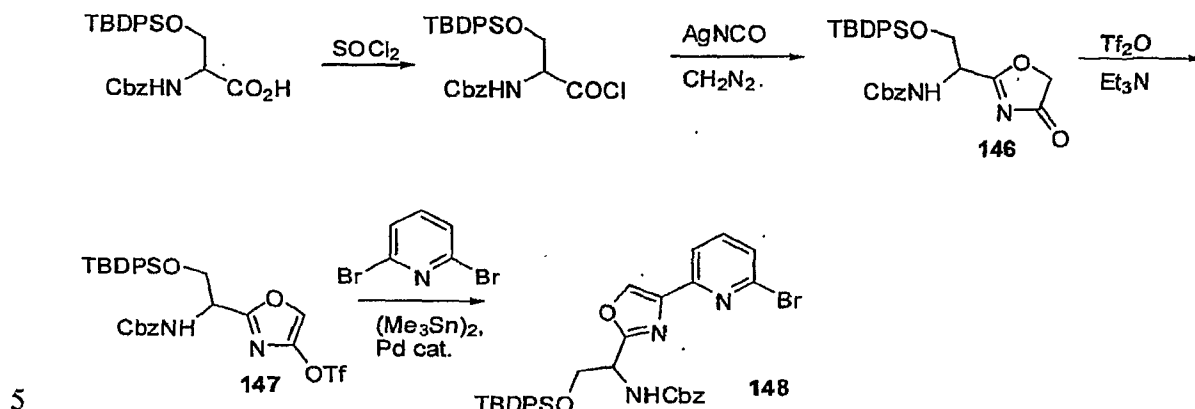
Synthesis of Hexa-, Hepta- and Octa-oxazoles with Two Basic Side Chains.

- 5 Analogues having two side chains can be prepared from the appropriate teroxazoles. Some specific examples can be assembled from teroxazoles **138** and **142**. Joining of teroxazoles **122** and **138** provides a suitable intermediate for the formation of a 4-substituted oxazole that will permit the formation of aminoalkyl substituents on the rings of either a hepta- or octa-oxazole. Similar
- 10 compounds can also be prepared from teroxazoles **123** and **142**.

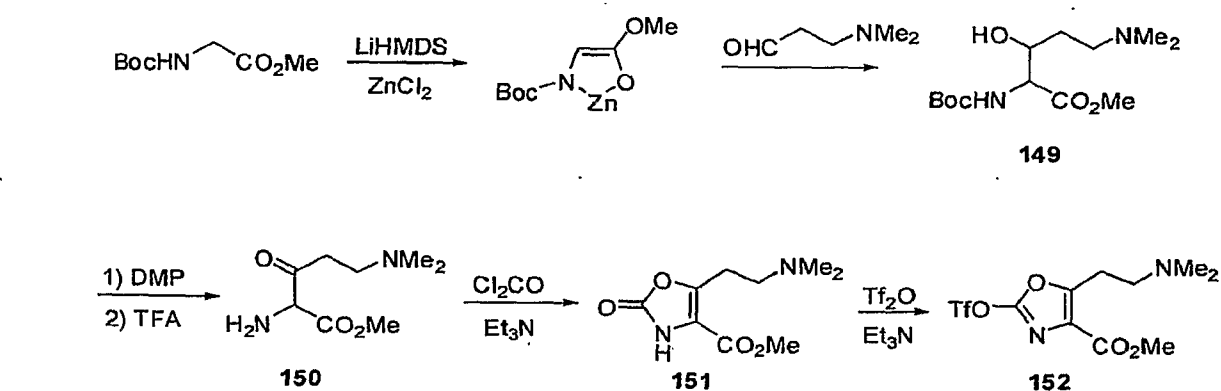
Mixed Torands Series A

- 15 Representative macrocyclic torands **160-162** can be prepared as illustrated below. The synthesis of torands consisting of two pyridine rings are detailed. N-Cbz-O-TBDPS serine will be converted into an acid chloride and then reacted with silver isocyanate followed by treatment with diazomethane to give oxazolone **146**. This will be treated immediately with triflic anhydride and base to form oxazole
- 20 triflate **147**. This will be joined with 2,6-dibromopyridine *via* a Stille coupling to give intermediate **148**. In the event that both bromines on the pyridine undergo facile Stille coupling to give a 2,6-di(oxazolyl)pyridine derivative, Suzuki coupling

of triflate **147** with 6-bromo-2-pyridylboronic acid will give **148** selectively. One could replace the pyridine in intermediate **148** with phenyl by using either 3-bromophenyl boronic acid in place of 6-bromo-2-pyridylboronic acid in the Suzuki coupling reaction.



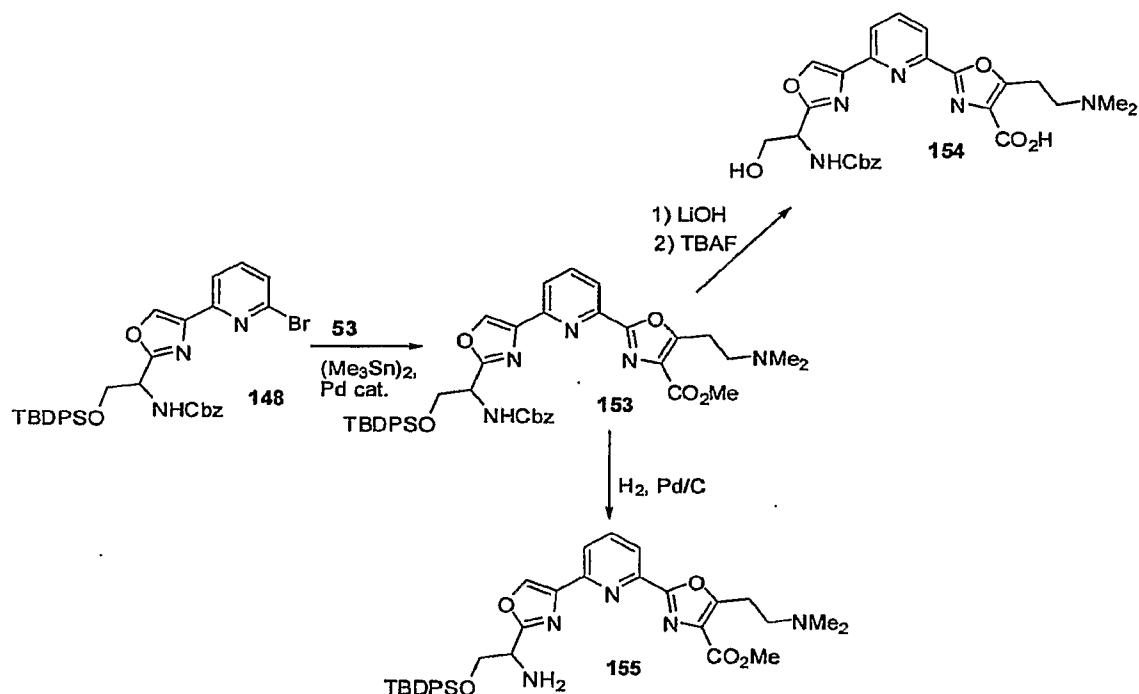
The second oxazole coupling partner will be prepared by reaction of the zinc enolate of methyl N-Boc glycinate with 3-(N,N-dimethylamino)propionaldehyde. Alcohol **149** will be oxidized with Dess Martin periodinane and the Boc group removed with TFA to give ketone **150**. Condensation with phosgene in the presence of base will give oxazolone **151**, which will be converted into triflate **152** using the procedure of Panek.



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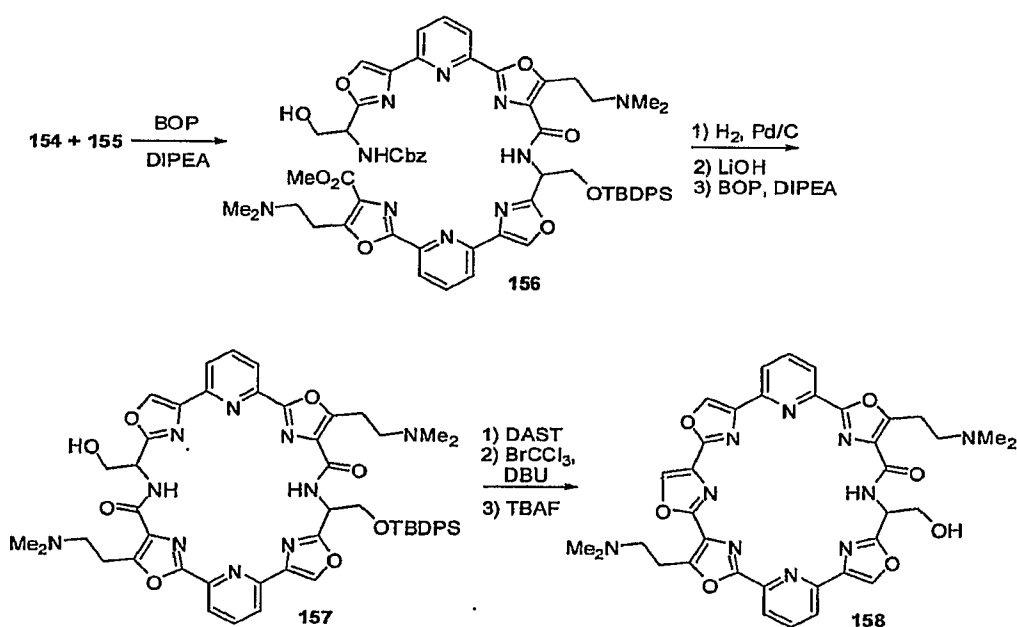
Stille coupling of triflate **152** with bromopyridine **148** in the presence of hexamethylditin will give bis(oxazolyl)pyridine **153**. A portion of this will be hydrolyzed with LiOH and the TBDPS group will then be removed with tetrabutylammonium fluoride (TBAF) to give acid **154**. The remainder of **153** will

be converted into amine **155** by hydrogenolysis of the Cbz group.

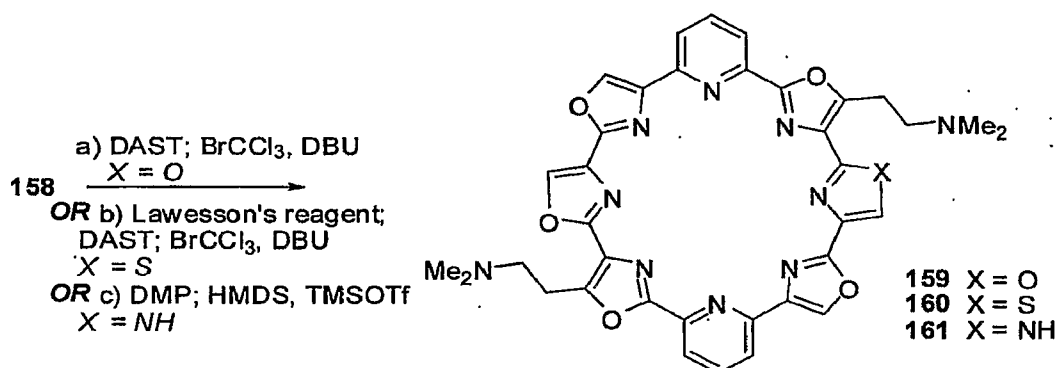


BOP-mediated coupling of **154** and **155** will give amide **156**.

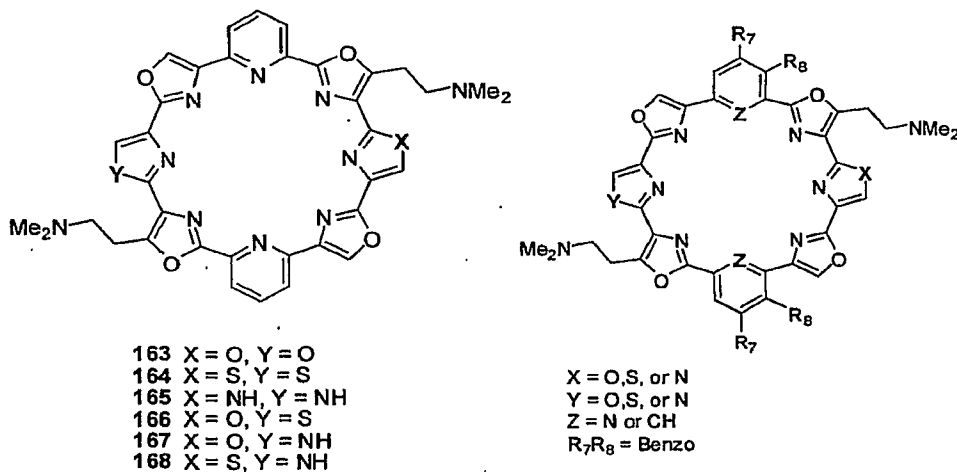
- 5 Hydrogenolysis of the Cbz group, hydrolysis of the ester and macrolactamization with BOP will give **157**. Macrocyclic pentaoxazole **158** will be formed by cyclodehydration of the primary alcohol with DAST, dehydrogenation with bromotrichloromethane, and removal of the silyl group with TBAF.



Series A analogs **159**, **160**, and **161** are prepared from common intermediate **158**. Treatment with DAST and then bromotrichloromethane and DBU will give oxazole **159**. Thiazole **160** will result from treatment of **158** with Lawesson's reagent, followed by DAST and BrCCl₃/DBU. Dess Martin oxidation of **158** and then reaction with HMDS in the presence of TMSOTf will give imidazole **161**.



Macrocycle **157** will serve as common intermediate to several Series A analogs such as **159**, **162**, and **163**. Treatment of **157** with TBDPSCl and then Lawesson's reagent will give a bis(thiolactam). Removal of the silyl protecting groups with TBAF followed by treatment with DAST and then bromotrichloromethane and DBU will give symmetrical bis(thiazole) analog **162** (X,Y = S). For the symmetrical imidazole analog **163** (X,Y = NH) treatment of **158** with TBAF and then Dess-Martin oxidation will form an aldehyde intermediate that will be converted into an imidazole via the N-trimethylsilylimine using HMDS and TMSOTf. Unsymmetrical analog **166** (X = S, Y = NH) will be prepared from **157** by Dess-Martin oxidation of the primary alcohol and conversion into the imidazole with HMDS and TMSOTf. Treatment with Lawesson's reagent will then give a thiolactam. The silyl group (TBDPS) will be removed with TBAF and the thiazole will then be formed upon cyclodehydration with DAST followed by dehydrogenation with bromotrichloromethane and DBU.

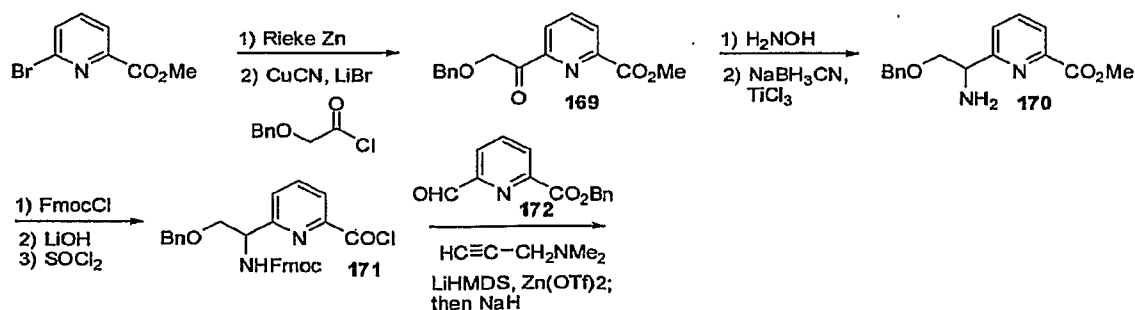


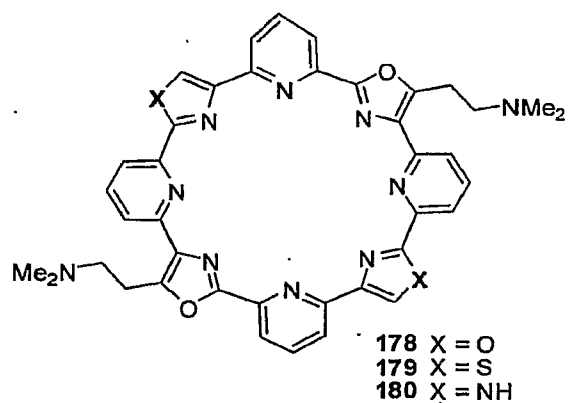
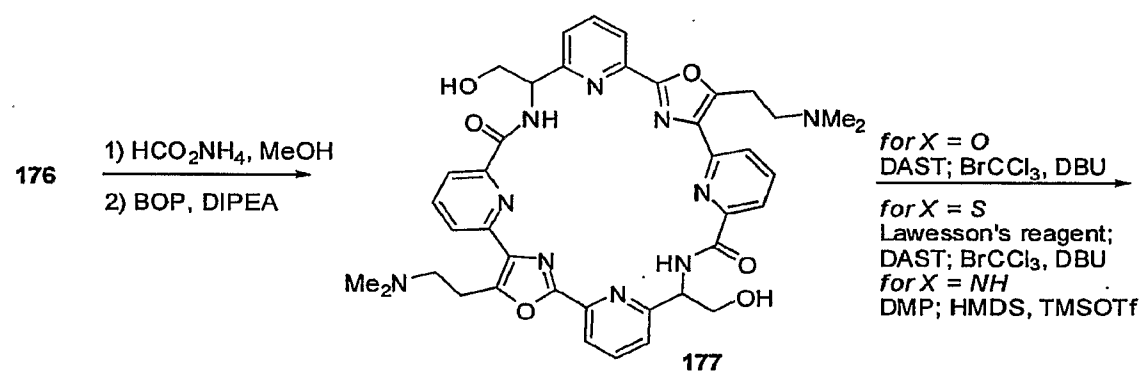
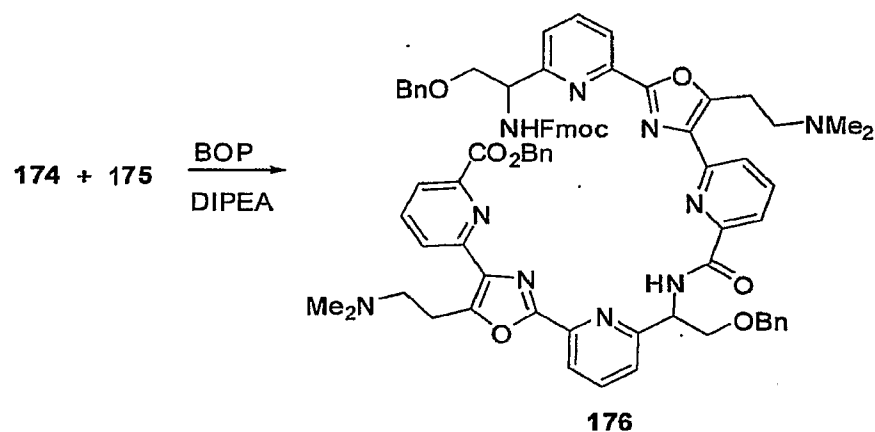
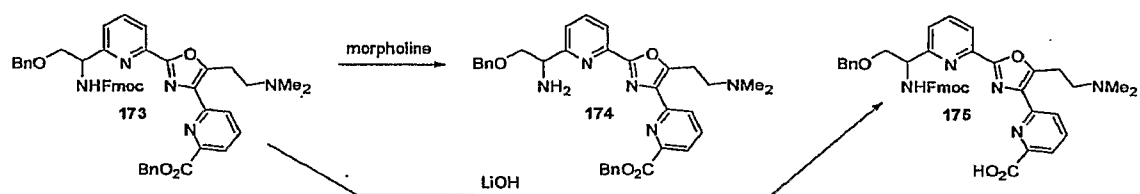
Mixed Torands Series B

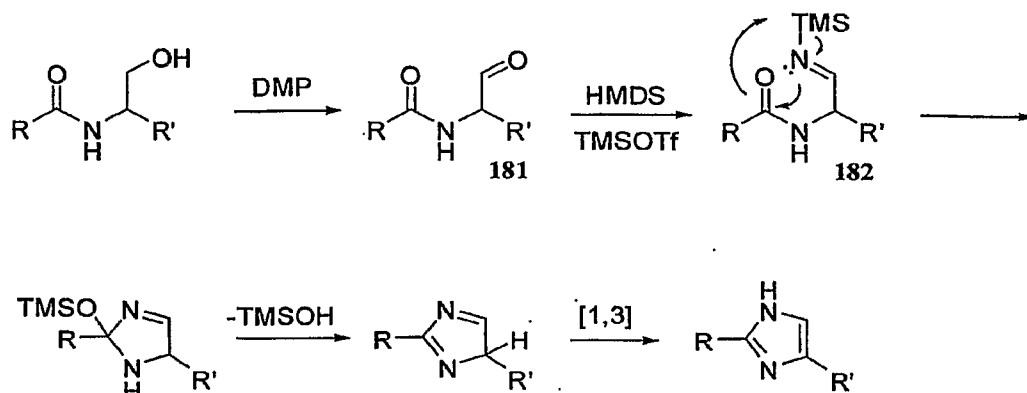
5

Commercially-available methyl 6-bromopyridine-2-carboxylate can be converted into an organozinc derivative using Rieke zinc. This can be coupled with benzyloxyacetyl chloride in the presence of copper cyanide to give ketone **169**. Conversion into an oxime followed by reduction will give amine **170**. One can then protect the amine as a 9-fluorenylmethyl carbamate (Fmoc) followed by hydrolysis of the ester with ultimate conversion of the hydrolysis product into acid chloride **171**. This can be subjected to multi-component coupling with pyridyl aldehyde **172**, 3-dimethylamino-1-propyne, and LiHMDS in the presence of zinc triflate, followed by treatment, *in situ*, with catalytic sodium hydride to provide oxazole **173**. Benzyl 6-formyl-2-pyridinecarboxylate **172** can be prepared from 2,6-pyridinedicarboxylic acid by a known three-step procedure. A portion of **173** will be treated briefly with morpholine to remove the Fmoc group, to give amine **174**. A second portion of **173** will be hydrolyzed to acid **175**. Coupling of **174** and **175** with BOP will give amide **176**. Hydrogenolysis of the remaining Fmoc group, the benzyl ester, and the benzyl alcohols with ammonium formate in dioxane-methanol, followed by macrocyclization with BOP will give bislactam **177** as a common intermediate for analogs **178-181**. Compound **178** (X = O) can be prepared from **177** by treatment with DAST followed by bromotrichloromethane and DBU. Thiazole analogs **179** (X = S) can be prepared from **177** by treatment with Lawesson's reagent to form a

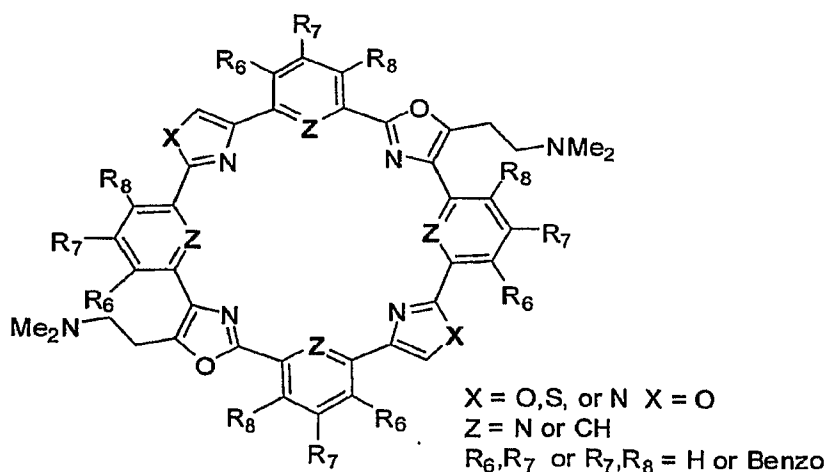
bis(thiolactam). Cyclization with DAST and dehydrogenation with bromotrichloromethane and DBU will furnish macrocycle **179**. For analog **180** a 2,4-disubstituted imidazoles, alcohol **177** will be oxidized to the corresponding aldehyde with Dess-Martin periodinane. Reaction with hexamethyldisilazane (HMDS) the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) should furnish macrocyclic bis(imidazole) **180** *via* the N-trimethylsilylimine. While β -amido ketones can be converted into 5-substituted imidazoles in the presence of ammonia and an acid catalysis, the analogous reaction of aldehydes to 5-unsubstituted imidazoles is not as well known. Evans reported in his synthesis of Diphthamide conversion of a serine derivative, *via* Swern oxidation to the aldehyde and imine formation with benzylamine. The N-benzylimidazole was then formed by cyclization using triphenylphosphine and hexachloroethane. Hydrogenolysis over palladium black then removed the benzyl group to give the 1H-imidazole. The reaction of HMDS with aldehydes in the presence of a Lewis acid results in the formation of N-trimethylsilylimines. These species behave as nucleophiles and can attack other carbonyl groups. It is proposed that the N-silylimine **182** derived from aldehyde **181** will attack the amide carbonyl in the presence of TMSOTf or another Lewis acid, and after N- to O- transfer of the silyl group, the electron pair from the amide nitrogen will eliminate the O-TMS group. A [1,3] sigmatropic hydrogen shift will complete the imidazole synthesis, with the driving force being establishment of aromaticity in the ring.







As noted in Series A, one can develop torands wherein two alternating phenyls can replace the pyridyl moiety by using commercially-available 3-bromobenzoic acid methyl ester in place of methyl 6-bromopyridine-2-carboxylate or by using 3-formylbenzoic acid benzyl ester place of benzyl 6-formyl-2-pyridinecarboxylate. One can also replace all four pyridine moieties within these torands by using both commercially-available 3-bromobenzoic acid methyl ester in place of methyl 6-bromopyridine-2-carboxylate and 3-formylbenzoic acid benzyl ester place of benzyl 6-formyl-2-pyridinecarboxylate. Use of appropriately substituted naphthalene and isoquinoline derivatives provides a convenient route wherein R_6 and R_7 or R_7 and R_8 represent a benzo-fused ring in the general structure provided below for these mixed torands.

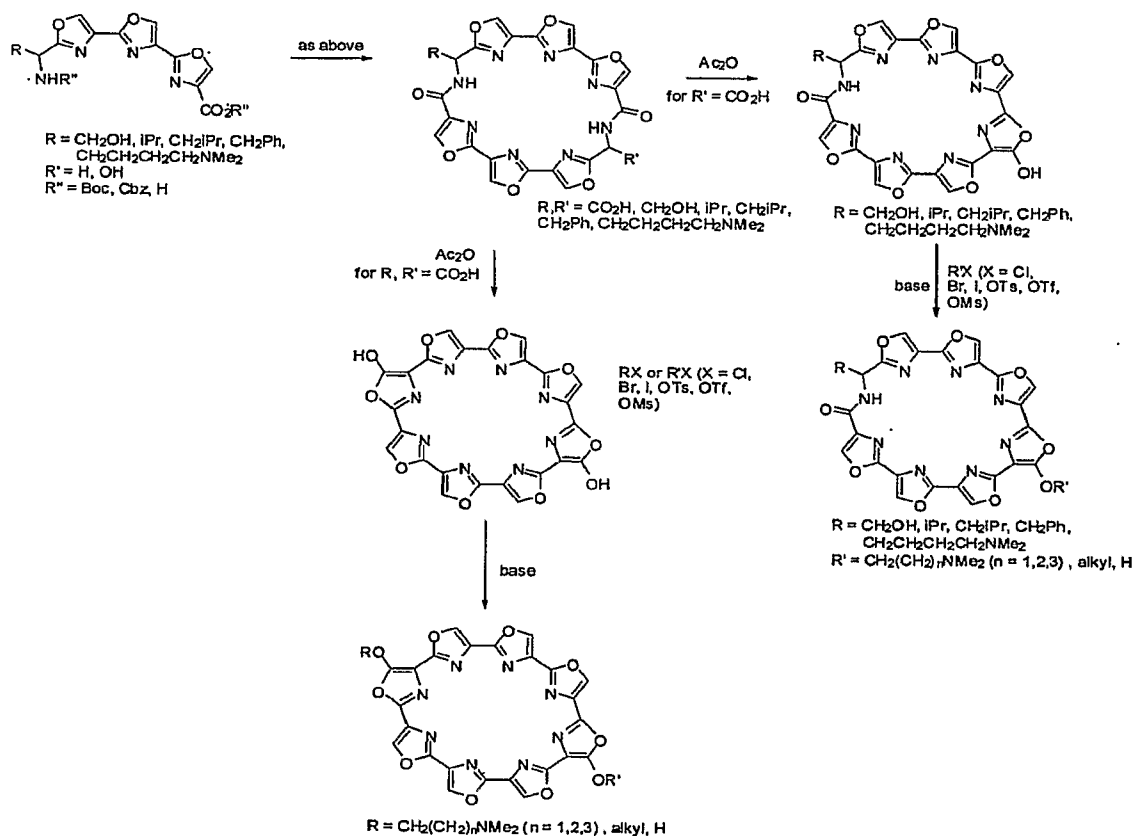


Hydroxyhepta-oxazoles and Hydroxyocta-oxazoles

These useful torands can be prepared by a modification in the cyclization conditions used to form one or more oxazoles within a preformed macrocycle.

A. Hydroxyhepta-oxazoles

Using the methods previously outlined, suitably substituted teroxazoles will be coupled using BOP or similar acylation catalyst. After protecting group removal, cyclization with BOP will give the macrocyclic hexaoxazole analogs. When group R' is a carboxylic acid group, treatment with acetic anhydride or similar dehydrating agent will provide the cyclic hydroxyhepta-oxazole or its 5-oxazolone tautomer. A substituent can be appended to the hydroxy group using a base such as triethylamine and an alkyl halide or alkyl sulfonate.



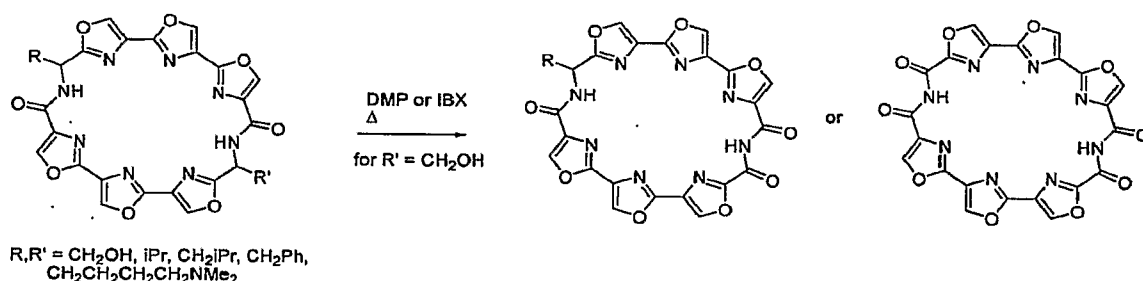
B. Hydroxyocta-oxazoles

Starting from a teroxazole in which group R is a protected carboxyl group, a cyclic hexaoxazole having identical groups R and R' will be prepared using methods described previously. Removal of the protecting groups will lead to the bis(carboxylic acid) derivative which will be treated with acetic anhydride or similar dehydrating agent to give the symmetrical dihydroxyocta-oxazole

compound or the bis(5-oxazolone) tautomers. Substituents can be appended to the hydroxy groups using a base such as triethylamine and an alkyl halide or alkyl sulfonate. Unsymmetrical analogs can be prepared starting from teroxazoles having differently protected carboxyl groups. Following the same synthetic pathway the differentially protected dihydroxyoctaoxazole can be prepared. Selective removal of one protecting group followed by attachment of a substituent to the hydroxy group will give the monoderivatized analog. Removal of the second protecting group and attachment of a different substituent will give the unsymmetrical octaoxazole derivative.

Macrocyclic Imido-polyoxazoles

Starting from a macrocyclic hexaoxazole, prepared as described above, having at least one serine residue (R or $R' = \text{CH}_2\text{OH}$) treatment with an oxidizing agent such as Dess Martin periodinane (DMP) or iodoxybenzoic acid (IBX) at reflux in a solvent such as methylene chloride, chloroform, benzene, or toluene results in oxidative cleavage to form an imide. If R and R' are both CH_2OH similar treatment will form the macrocyclic bis(imide)



In cases where compounds are sufficiently basic or acidic, a salt of a compound of formula I can be useful as an intermediate for isolating or purifying a compound of formula I. Additionally, administration of a compound of formula I as a pharmaceutically acceptable acid or base salt may be appropriate. Examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids which form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, α -ketoglutarate, and α -glycerophosphate. Suitable inorganic

salts may also be formed, including hydrochloride, sulfate, nitrate, bicarbonate, and carbonate salts.

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic
5 compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example calcium) salts of carboxylic acids can also be made.

The compounds of formula I can be formulated as pharmaceutical
10 compositions and administered to a mammalian host, such as a human patient in a variety of forms adapted to the chosen route of administration, *e.g.*, orally or parenterally, by intravenous, intramuscular, topical or subcutaneous routes.

Thus, the present compounds may be systemically administered, *e.g.*, orally, in combination with a pharmaceutically acceptable vehicle such as an
15 inert diluent or an assimilable edible carrier. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches,
20 capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful
25 compositions is such that an effective dosage level will be obtained.

The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium
30 stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in

addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

The active compound may also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the active compound or its salts can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form should be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), a vegetable oil, a nontoxic glyceryl ester, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for

example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

5 Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional
10 desired ingredient present in the previously sterile-filtered solutions.

For topical administration, the present compounds may be applied in pure form, *e.g.*, when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

15 Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and
20 additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers.

Thickeners such as synthetic polymers, fatty acids, fatty acid salts and
25 esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

Examples of useful dermatological compositions which can be used to deliver the compounds of formula I to the skin are known to the art; for example,
30 see Jacquet *et al.* (U.S. Pat. No. 4,608,392), Geria (U.S. Pat. No. 4,992,478), Smith *et al.* (U.S. Pat. No. 4,559,157) and Wortzman (U.S. Pat. No. 4,820,508).

Useful dosages of the compounds of formula I can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949.

5 Generally, the concentration of the compound(s) of formula I in a liquid composition, such as a lotion, will be from about 0.1-25 wt-%, preferably from about 0.5-10 wt-%. The concentration in a semi-solid or solid composition such as a gel or a powder will be about 0.1-5 wt-%, preferably about 0.5-2.5 wt-%.

10 The amount of the compound, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.

15 In general, however, a suitable dose will be in the range of from about 0.5 to about 100 mg/kg, *e.g.*, from about 10 to about 75 mg/kg of body weight per day, such as 3 to about 50 mg per kilogram body weight of the recipient per day, preferably in the range of 6 to 90 mg/kg/day, most preferably in the range of 15 to 60 mg/kg/day.

20 The compound is conveniently administered in unit dosage form; for example, containing 5 to 1000 mg, conveniently 10 to 750 mg, most conveniently, 50 to 500 mg of active ingredient per unit dosage form.

25 Ideally, the active ingredient should be administered to achieve peak plasma concentrations of the active compound of from about 0.5 to about 75 μ M, preferably, about 1 to 50 μ M, most preferably, about 2 to about 30 μ M. This may be achieved, for example, by the intravenous injection of a 0.05 to 5% solution of the active ingredient, optionally in saline, or orally administered as a bolus containing about 1-100 mg of the active ingredient. Desirable blood levels may be maintained by continuous infusion to provide about 0.01-5.0 mg/kg/hr or by intermittent infusions containing about 0.4-15 mg/kg of the active
30 ingredient(s).

 The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three,

four or more sub-doses per day. The sub-dose itself may be further divided, *e.g.*, into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator or by application of a plurality of drops into the eye.

5 Compounds of the invention can also be administered in combination with other therapeutic agents, for example, other agents that are useful for the treatment of cancer. Accordingly, in one embodiment the invention also provides a composition comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, at least one other therapeutic agent, and
10 a pharmaceutically acceptable diluent or carrier. The invention also provides a kit comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, at least one other therapeutic agent, packaging material, and instructions for administering the compound of formula I or the pharmaceutically acceptable salt thereof and the other therapeutic agent or agents to an animal to treat cancer.

15 The ability of a compound of the invention to stabilize G-quadruplex DNA may be determined using pharmacological models which are well known to the art, or using Test A described below.

Test A. Stabilization of G-quadruplex DNA

20 Analyses can be performed to determine the ability of the agents to bind and thermally stabilize the duplex, triplex, and quadruplex forms of nucleic acids. Toward this end, the UV absorbances of the nucleic acids as a function of temperature in the absence and presence of HXDV was monitored. The melting of duplex and triplex nucleic acids is generally associated with a hyperchromic
25 shift at 260 nm (76,77), while the melting of quadruplex nucleic acids is associated with a hypochromic shift at 295 nm (26,78). Thus, the temperature-dependent absorbances of duplexes and triplexes were monitored at 260 nm, with corresponding quadruplex absorbances being monitored at 295 nm. ST DNA, p(rA)•p(rU), p(rA)•p(dT), p(dA)•2p(dT), p(rA)•2p(rU), d(T₂AG₃)₄, and
30 r(UG₄U) were used as representative models of a DNA duplex, an RNA duplex, a hybrid DNA•RNA duplex, a DNA triplex, an RNA triplex, a DNA quadruplex,

and an RNA quadruplex, respectively. All the UV melting studies were conducted at pH 7.5 in the presence of potassium ions. Representative compounds of Formula I were evaluated and were found to stabilize G-quadruplex DNA.

- 5 The ability of compounds (*e.g.*, **219**) to stabilize G-quadruplex DNA may also be determined using Test B described below.

Test B. Temperature-dependent spectrophotometry

- 10 Temperature-dependent absorption experiments were conducted on an AVIV Model 14DS Spectrophotometer (Aviv Biomedical, Lakewood, NJ) equipped with a thermoelectrically controlled cell holder. Quartz cells with a pathlength of 1.0 cm were used for all the absorbance studies. Temperature-dependent absorption profiles were acquired at either 260 (for duplex and
- 15 triplex) or 295 (for quadruplex) nm with a 5 sec averaging time. The temperature was raised in 0.5 °C increments, and the samples were allowed to equilibrate for 1.5 min at each temperature setting. In the quadruplex melting studies, the concentrations of $d(T_2AG_3)_4$, 9AP, 15AP, and 21AP were 5 μ M in strand (120 μ M in nucleotide), while the concentration of $r(UG_4U)$ was 20 μ M in strand (120
- 20 μ M in nucleotide). When present in these quadruplex studies, compound **219** concentration was 20 μ M. In the duplex and triplex melting studies, the nucleic acid concentration was 15 μ M in base pair (30 μ M in nucleotide) or 15 μ M in base triple (45 μ M in nucleotide) and the HXDV concentration, when present, was 15 μ M. The buffer for all the UV melting experiments contained 10 mM
- 25 EPPS (pH 7.5). In addition, sufficient KCl was added to each solution to bring the total K^+ concentration to either 150 mM for $d(T_2AG_3)_4$ and $p(rA) \cdot p(dT)$, 2 mM for $r(UG_4U)$, 50 mM for ST DNA, 250 mM for $p(dA) \cdot 2p(dT)$, or 20 mM for $p(rA) \cdot 2p(rU)$. Prior to their use in UV melting experiments, all nucleic acid solutions are preheated at 90 °C for 5 min and slowly cooled to room
- 30 temperature over a period of 4 hr.

The anti-proliferative activity of a compound of the invention may be determined using pharmacological models which are well known to the art, or using Test C described below.

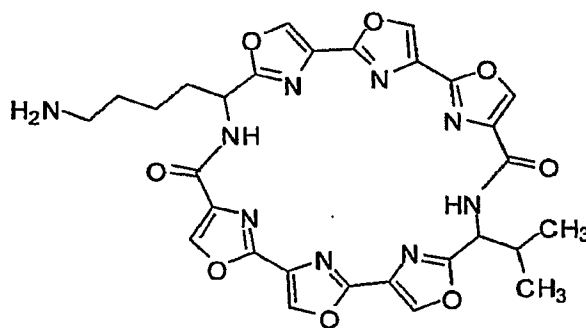
5 Test C. **Evaluation of G-quadruplex stabilizers using the MTT assay.**

Cell lines were selected based upon one or more factors including data on their relative telomerase activity, varied organ sites, available comparative data, and their ability to form solid tumors in athymic nude mice. The advantage of an
10 MTT assay is that the cytotoxic/cytostatic activities can be readily determined. Cells were cultured for 4 days at 37 °C followed by addition of MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (Sigma) (0.1 mg/ml). Cells were treated with MTT for 3 hrs and then dissolved in 100 µl 100% DMSO. Absorbance was measured at OD₅₇₀ using a microplate reader (Model
15 3550 UV from BIO-RAD). The MTT value was normalized to OD₅₇₀ of cells treated with Cellfectin alone. Stock solutions of each compound were prepared. MTT assays were performed using spectrometric analysis and 96 well plates. Representative compounds of Formula I were evaluated and were found to demonstrate anti-proliferative activity in Test C.

20 The invention will now be illustrated by the following non-limiting Examples.

Examples

Example 1. Synthesis of compound 15.

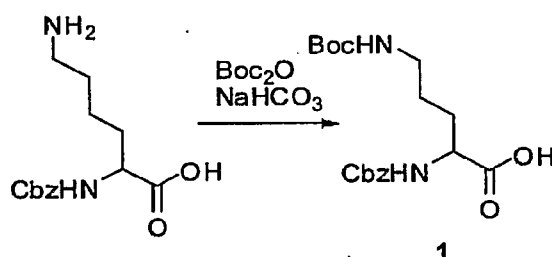


15

A representative compound of the invention (Compound 15) was prepared as illustrated and described below.

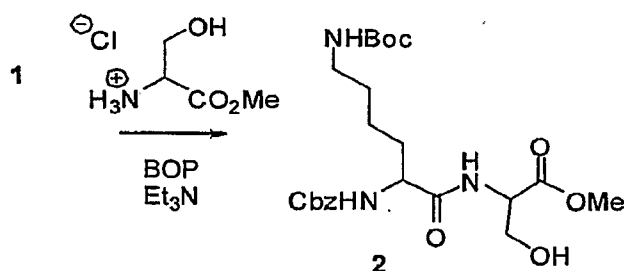
a. **Synthesis of Compound 1 (NBoc-Cbz Lysine)**

5



N- α -Cbz-(S)-Lysine (5g, 17.85mmol) was dissolved in a mixture of THF (50mL) and water (50mL). To this sodium bicarbonate (3g, 35.5mmol, 2eq) and a solution of Boc₂O (9g, 41mmol, 2.3eq) in THF (50mL). After stirring at room temperature overnight, the THF was removed under reduced pressure and the resulting aqueous solution was neutralized with 2N HCl. This was extracted with ethyl acetate and the combined organic layers were washed with brine. The organic layer was dried with sodium sulfate and concentrated to a clear oil. Removal of excess Boc₂O by Kugelrohr distillation resulted in a thick clear oil weighing 6.8g, 100%. ¹H NMR (CDCl₃) δ 11.6 (s, 1H), 7.32 (s, 5H), 6.36 (s, 1H), 5.75 (d, 1H, J=8), 5.09 (s, 2H), 4.37(m, 1H), 3.06 (m, 2H), 1.78 (m, 2H), 1.53 (s, 4H), 1.42 (s, 9H). ¹³C NMR (CDCl₃) δ 174.8, 155.4, 135.4, 127.6, 127.3, 127.2, 78.6, 66.1, 52.9, 39.2, 31.0, 28.6, 27.5, 26.6, 21.4

20 b. **Synthesis of Compound 2**

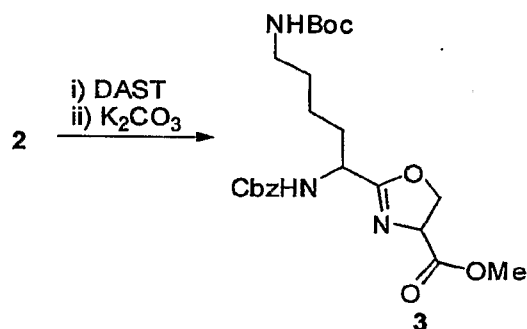


(DL)-serine methyl ester hydrochloride (2.78g, 17.85mmol 1eq), BOP

(7.9g, 17.85mmol, 1eq) and **1** (6.8g, 17.85mmol) were dissolved in dry CH₃CN (100mL). To this triethylamine (6.2mL, 44.6mmol, 2.5eq) was added and the reaction stirred at room temperature overnight. The solvent was then removed *in vacuo* and the residue was taken up in ethyl acetate. This was washed

5 successively with brine, 2N HCl, 0.5N NaHCO₃, water and brine. The organic layer was dried with sodium sulfate and concentrated to a clear oil weighing 8.6g, 100%. ¹H NMR (CDCl₃) δ 7.50 (m, 1H), 7.31 (s, 5H), 6.12 (m, 1H), 5.06 (m, 3H), 4.63 (m, 1H), 4.30 (m, 1H), 3.94 (m, 2H), 3.71 (s, 3H), 3.07 (m, 2H), 1.63 (m, 2H), 1.43 (m, 11H). ¹³C NMR (CDCl₃) δ 171.6, 170.3, 170.0, 155.7, 10
135.3, 127.6, 127.2, 127.1, 78.3, 66.1, 61.6, 53.8, 51.7, 51.7, 39.0, 31.4, 31.2, 28.5, 27.5, 21.5. IR (thin film, NaCl) 3336, 3068, 3014, 2981, 2937, 2866, 1693, 1525, 1455, 1392, 1366, 1250, 1170, 1061, 912, 849, 755, 698, 666 cm⁻¹

c. Synthesis of Compound 3 (Lysine oxazoline)



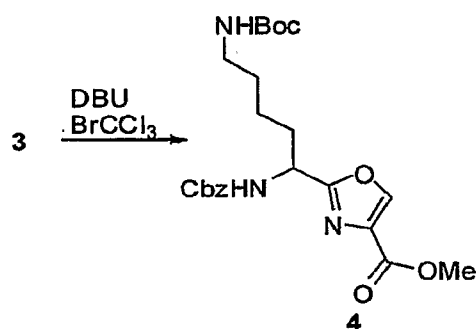
15

Compound **2** (8.6g, 17.85mmol) was dissolved in dry CH₂Cl₂ (40mL) and placed under argon. After cooling to -78°C, DAST (3.5mL, 26.8mmol, 1.5eq) was added. After stirring at low temperature for 4 hours, solid K₂CO₃ (3.7g, 26.8mmol, 1.5eq) was added and the reaction warmed to room temperature. The reaction mixture was poured into saturated NaHCO₃ and the layers were separated. The aqueous layer was further extracted with CH₂Cl₂ and the combined organic layers were dried with sodium sulfate. Removal of solvent under reduced pressure afforded the oxazoline as an orange oil weighing 8.3g, 99%. ¹H NMR (CDCl₃) δ 7.34 (s, 5H), 5.67 (t, 1H, J=9), 5.10 (s, 2H), 4.73 (m, 2H) 4.46 (m, 3H), 3.77 (s, 3H), 3.00 (m, 2H), 1.75 (m, 2H), 1.42 (s, 13H). ¹³C NMR (CDCl₃) δ 170.4, 170.3, 169.2, 168.8, 155.2, 154.9, 135.4, 127.6, 127.2,

78.1, 69.4, 69.2, 66.9, 66.8, 66.0, 51.8, 48.2, 39.3, 31.9, 31.8, 28.6, 27.5, 21.3, 21.1. IR (thin film, NaCl) 3349, 3069, 3034, 2981, 2953, 2866, 2249, 1705, 1666, 1519, 1455, 1439, 1392, 1366, 1337, 1249, 1174, 1060, 988, 912, 848, 777, 733, 698, 647 cm^{-1}

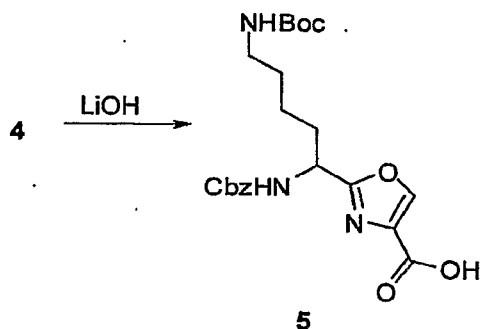
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d. Synthesis of Compound 4 (Lysine oxazole)



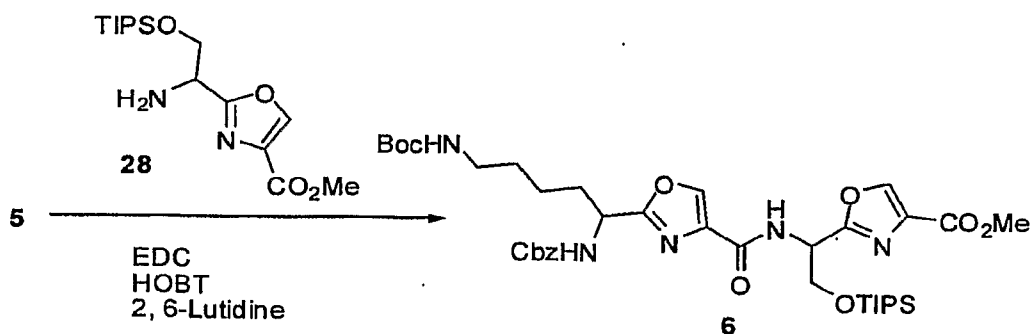
Compound 3 (8.3g, 17.85mmol) was dissolved in dry CH₂Cl₂ (40mL) and placed under argon. This was cooled to 0°C and treated dropwise with DBU (5.3mL, 35.7mmol, 2eq) and BrCCl₃ (4.2mL, 42.8mmol, 2.4eq) successively. The reaction mixture turned from orange to dark brown in color and was allowed to warm to room temperature overnight. It was then poured into a solution of saturated ammonium chloride and extracted with CH₂Cl₂. The organic layers were dried with sodium sulfate and concentrated to a brown oil. This was flash chromatographed on SiO₂ with 1-5% methanol/chloroform which gave the product as an amber oil weighing 7.0g, 85%. ¹H NMR (CDCl₃) δ 8.18 (s, 1H), 7.31 (m, 6H), 5.71 (d, 1H, J=8), 5.10 (s, 2H), 5.00 (m, 1H), 4.61 (M, 1H), 3.90 (s, 3H), 3.08 (m, 2H), 1.90 (m, 2H), 1.41 (m, 12H). ¹³C NMR (CDCl₃) δ 164.1, 160.5, 155.2, 154.9, 143.1, 135.3, 132.4, 127.6, 127.3, 127.2, 78.3, 76.4, 66.3, 51.3, 48.5, 39.1, 32.7, 28.6, 27.5, 21.5. IR (thin film, NaCl) 3337, 3167, 3069, 3034, 2975, 2952, 2866, 2250, 1705, 1585, 1523, 1455, 1439, 1392, 1366, 1325, 1249, 1170, 1111, 1044, 1002, 912, 863, 805, 733, 698, 647 cm^{-1}

e. Synthesis of Compound 5 (Lysine oxazole acid)



Compound **4** (7.0g, 15.23mmol) was dissolved in a 3:1 mixture of THF and water (40mL) and cooled to 0°C. To this LiOH (767mg, 18.3mmol, 1.2eq) was added and the reaction warmed to room temperature overnight. After removing the solvent under vacuum, 1N HCl (22mL) was added until the pH was slightly acidic. This was extracted with ethyl acetate and the combined organic layers were washed with brine. After drying with sodium sulfate, the organic phase was concentrated to a pale yellow, sticky solid weighing 5.9g, 87%. Melting point 65-67°C. ¹H NMR (CDCl₃) δ 12.39 (s, 1H), 8.17 (s, 1H), 7.25 (m, 6H), 6.52 (m, 1H), 5.08 (m, 3H), 4.69 (m, 1H), 3.09 (m, 2H), 1.92 (m, 2H), 1.42 (s, 12H). ¹³C NMR (CDCl₃) δ 165.1, 162.7, 155.3, 143.7, 135.3, 132.5, 128.2, 127.6, 127.3, 127.2, 124.4, 78.5, 66.2, 48.5, 39.1, 32.7, 28.5, 27.5, 21.6. IR (thin film, NaCl) 3321, 2934, 2551, 2250, 1701, 1527, 1455, 1367, 1251, 1164, 1111, 1045, 982, 911, 860, 732, 697, 947 cm⁻¹. HRMS (FAB) *m/z* calcd for C₂₂H₂₉N₃O₇Li (M + Li) 455.2194; found, 455.2179

f. Synthesis of Compound 6 (TIPS bisoxazole)



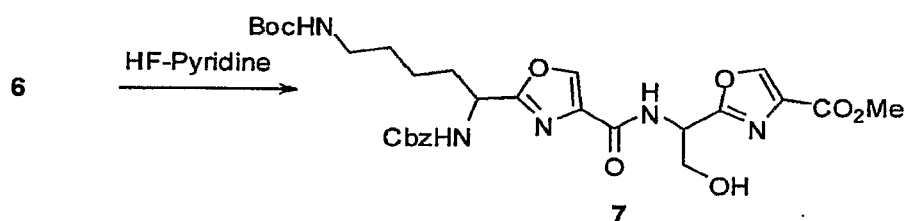
The TIPS oxazole **28** (3.58g, 10.47mmol) was dissolved in dry CH₂Cl₂

(20mL) and placed under argon. To this was added freshly distilled 2, 6-lutidine (6.1mL, 52.4mmol, 5eq) and the flask was cooled to 0°C. Then a solution of 5 (4.68g, 10.47mmol, 1eq), EDC (4.02g, 20.94mmol, 1.2eq) and HOBT (2.83g, 20.94mmol, 1.2eq) in CH₂Cl₂ (40mL) was added. The reaction warmed to room temperature overnight and then the solvent was removed under reduced pressure.

The residue was taken up in ethyl acetate and washed successively with saturated NaHCO₃, 5% HCl, water and brine. The organic phase was dried over sodium sulfate and concentrated to an orange oil weighing 7.04g, 87%. ¹H NMR (CDCl₃) δ 8.20 (s, 1H), 8.10 (s, 1H), 7.39 (d, 1H, J=8), 7.35(s, 6H), 5.66 (d, 1H, J=8), 5.46 (dt, 1H, J = 5, 8), 5.11 (s, 2H), 4.97 (dt, 1H J = 7, 7), 4.67 (dd, 1H J = 4, 10), 4.20 (m, 3H), 3.79 (s, 3H), 3.90 (m, 2H), 1.90 (m, 2H), 1.42 (m, 11H), 1.02 (m, 21H)

¹³C NMR (CDCl₃) δ 163.0, 162.5, 160.6, 159.2, 155.2, 154.9, 143.2, 140.6, 135.3, 134.7, 132.6, 127.6, 127.3, 127.3, 97.4, 78.5, 66.3, 63.9, 51.2, 48.4, 39.2, 32.5, 28.7, 27.5, 21.5, 17.2, 16.9, 12.1, 11.5, 10.9. IR (thin film, NaCl) 3295, 3034, 2944, 2866, 2250, 1712, 1599, 1520, 1461, 1391, 1366, 1324, 1249, 1204, 1171, 1115, 1045, 998, 912, 883, 843, 803, 733, 684, 647 cm⁻¹. HRMS (FAB) *m/z* calcd for C₃₈H₅₇N₅O₁₀SiLi (M + Li) 778.4029; found 778.4053

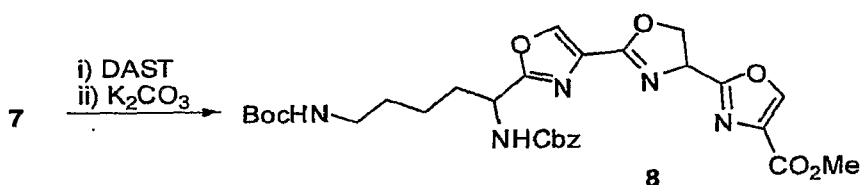
g. **Synthesis of Compound 7 (Lysine bisoxazole)**



Compound 6 (7.2g, 9.3mmol) was dissolved in THF (50mL) and pyridine (10mL). This was treated dropwise with HF-pyridine complex (3mL) during which a gas was evolved. The reaction stirred at room temperature for 18 hours and then slowly poured into saturated NaHCO₃. This was extracted with chloroform and dried with sodium sulfate. After concentrating and azeotropeing with toluene, the product was obtained as an orange oil weighing 5.76g, 100%. ¹H NMR (CDCl₃) δ 9.09 (d, 1H, J=7), 8.26 (s, 1H), 8.21 (s, 1H), 7.30 (m, 6H),

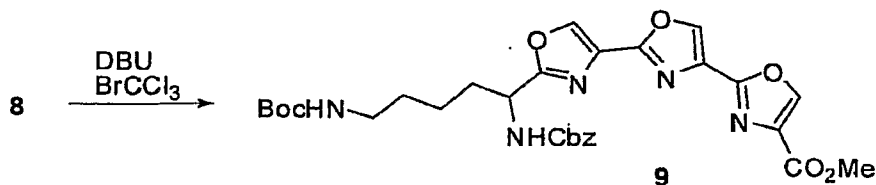
6.63 (d, 1H, J=9), 5.46 (m, 1H), 5.08 (s, 2H), 4.68 (m, 2H), 4.26 (m, 2H), 3.86 (s, 3H), 3.07 (m, 2H), 1.43 (s, 12H). ^{13}C NMR (CDCl_3) δ 162.9, 162.8, 160.8, 155.2, 143.4, 143.2, 135.4, 134.4, 132.1, 128.2, 127.7, 127.3, 127.2, 124.4, 78.3, 66.2, 63.8, 61.9, 51.5, 51.3, 49.4, 47.5, 39.3, 32.2, 31.2, 28.5, 27.5, 21.7. IR (thin film, NaCl) 3307, 3034, 2945, 2867, 2250, 1712, 1599, 1519, 1456, 1392, 1367, 1324, 1249, 1170, 1113, 1001, 911, 863, 805, 732, 697, 647 cm^{-1}

h. Synthesis of Compound 8



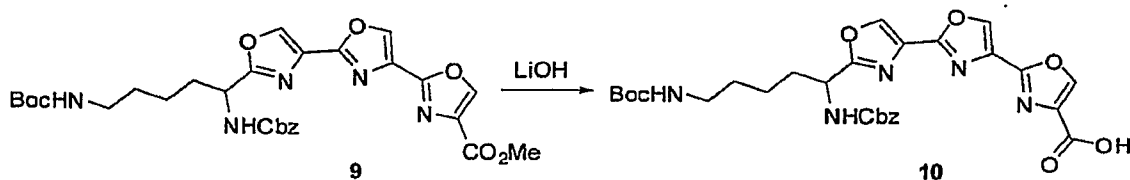
Compound 7 (2.76g, 9.3mmol) was dissolved in dry CH_2Cl_2 (40mL) and placed under argon. After cooling to -78°C , DAST (1.8mL, 13.95mmol, 1.5eq) was added and the reaction stirred at low temperature for 4 hours. This was followed by addition of solid K_2CO_3 (1.9g, 13.95mmol, 1.5eq) and the mixture warmed to room temperature. The solution was poured into saturated NaHCO_3 and extracted with CH_2Cl_2 . The combined organic layers were dried with sodium sulfate and concentrated to afford an orange oil weighing 5.58g, 100%. ^1H NMR (CDCl_3) δ 8.25 (s, 1H), 8.20 (s, 1H), 8.11 (d, 1H, J=3), 7.91 (d, 1H, J = 10), 7.33 (s, 5H), 5.71 (d, 1H, J=9), 5.53 (m, 1H), 5.10 (s, 2H), 4.87 (m, 2H), 4.62 (m, 1H), 3.91 (s, 3H), 3.07 (m, 2H), 1.85 (m, 2H), 1.41 (s, 14H). ^{13}C NMR (CDCl_3) δ 164.5, 163.0, 162.5, 162.1, 160.4, 159.3, 155.2, 144.0, 143.2, 140.9, 135.3, 134.7, 132.4, 129.1, 127.6, 127.3, 127.2, 78.3, 69.8, 66.2, 63.8, 62.8, 51.3, 48.4, 39.2, 35.5, 32.9, 28.7, 27.5, 21.5, 12.8. IR (thin film, NaCl) 3323, 3155, 3034, 2944, 2867, 2248, 1713, 1584, 1522, 1456, 1391, 1366, 1322, 1249, 1171, 1111, 1044, 995, 914, 885, 804, 775, 733, 698, 646 cm^{-1} .

i. Synthesis of Compound 9 (Lysine teroxazole)



- Compound **8** (5.58g, 9.3mmol) was dissolved in dry CH_2Cl_2 (40mL) and placed under argon. The flask was cooled to 0°C and DBU (2.8mL, 18.6mmol, 2eq) and BrCCl_3 (2.2mL, 22.3mmol, 2.4eq) were both added dropwise. This
- 5 warmed to room temperature overnight and was then poured into saturated ammonium chloride solution. The layers were separated and the aqueous extracted with CH_2Cl_2 . The combined organic layers were dried with sodium sulfate and concentrated to a brown oil. Flash chromatography on SiO_2 with 1-2% methanol/chloroform afforded a thick yellow oil. The product obtained from
- 10 the column was recrystallized from benzene to give white sand like crystals weighing 2.52g, 46%. Melting point $135\text{--}137^\circ\text{C}$; Optical rotation $[\alpha]_{\text{D}}^{22} = -37^\circ$ ($c = 1\text{g}/100\text{mL}$ in CHCl_3). ^1H NMR (CDCl_3) δ 8.44 (s, 1H), 8.34 (s, 1H), 8.31 (s, 1H), 7.35 (m, 5H), 5.68 (d, 1H, $J=8$), 5.12 (s, 2H), 5.04 (m, 1H), 4.61 (m, 1H), 3.95 (s, 3H), 3.10 (m, 2H), 1.98 (m, 2H), 1.41 (s, 14H)
- 15 ^{13}C NMR (CDCl_3) δ 164.7, 160.4, 155.2, 155.1, 155.0, 154.5, 143.4, 143.0, 139.8, 138.7, 138.5, 135.2, 133.6, 130.0, 128.9, 127.6, 127.4, 127.3, 127.3, 78.3, 66.3, 57.6, 51.4, 48.6, 39.1, 32.7, 28.7, 27.5, 21.5. IR (nujol) 3325, 3156, 3117, 1721, 1689, 1644, 1578, 1518, 1377, 1327, 1247, 1116, 999, 976, 816, 805, 775, 725 cm^{-1}
- 20 HRMS (FAB) m/z calcd for $\text{C}_{29}\text{H}_{33}\text{N}_5\text{O}_9\text{Li}$ ($\text{M}^+ \text{Li}$) 602.2433; found 602.2436

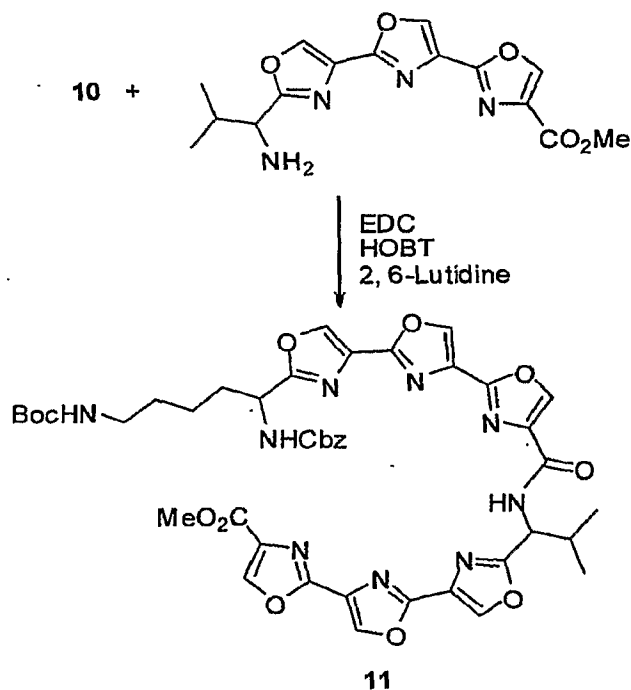
j. Synthesis of Compound 10 (Lysine teroxazole acid)



- 25 Compound **9** (1.9g, 3.2mmol) was dissolved in a 3:1 mixture of THF and water (60mL) and cooled to 0°C . Then LiOH (161mg, 3.83mmol, 1.2eq) was

added and the reaction warmed to room temperature overnight. The solvent was removed under vacuum and the residue was taken up in water. The pH was acidified with 1N HCl (15mL) and a white solid precipitated. The precipitate was filtered and the filtrate was extracted with ethyl acetate. The organic phase was washed with brine and dried with sodium sulfate. The solvent was removed to give a white solid weighing 1.90g, 100 %. Melting point 164-166°C. ¹H NMR (DMSO) δ 9.14 (s, 1H), 9.11 (s, 1H), 8.45 (s, 1H), 8.28 (d, 1H, J=8), 7.56 (s, 5H), 6.99 (m, 1H), 5.25 (s, 2H), 4.96 (m, 1H), 3.08 (m, 2H), 2.06 (m, 2H), 1.55 (s, 14H). ¹³C NMR (DMSO) δ 165.5, 155.9, 155.4, 140.6, 140.4, 139.8, 136.8, 128.8, 128.3, 128.1, 127.7, 125.2, 77.3, 65.6, 49.0, 31.8, 29.0, 28.2, 22.5, 21.0, 17.6. IR (nujol) 3337, 2367, 2334, 1681, 1523, 1381, 1364, 1255, 1167, 1109 cm⁻¹

k. Synthesis of Compound 11 (Protected linear hexaoxazole lysine-valine)

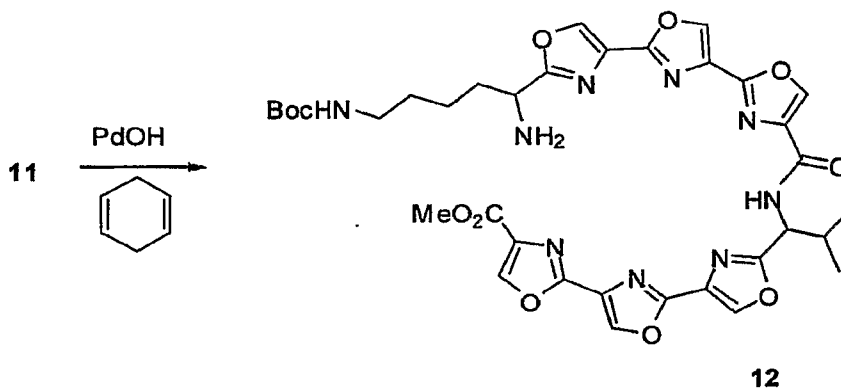


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The valine teroxazole (200mg, 0.6mmol), lysine teroxazole 10 (350mg, 0.6mmol), EDC (230mg, 1.2mmol, 2eq), HOBT (162mg, 1.2mmol, 2eq) and 2,6-lutidine (0.1mL, 0.6mmol, 10eq) were dissolved in dry DMF (100mL) and placed under argon. The reaction stirred at room temperature overnight. The

solvent was then removed under vacuum and the resulting residue was dissolved in ethyl acetate. This was washed successively with saturated NaHCO₃, 5% HCl, water and brine. The organic phase was dried with sodium sulfate and concentrated to give an orange solid weighing 456mg, 85%. Melting point 240-243°C; Optical rotation $[\alpha]_D^{23} = +14.9^\circ$ ($c = 1\text{g}/100\text{mL}$ in CHCl₃). ¹H NMR (CDCl₃) δ 8.44 (s, 1H), 8.33 (m, 5H), 7.61 (d, 1H, J=10), 7.35 (s, 5H), 5.65 (d, 1H, J=8), 5.36 (m, 1H), 5.13 (s, 2H), 5.05 (m, 1H), 4.60 (m, 1H), 3.95 (s, 3H), 3.11 (m, 2H), 2.43 (m, 1H), 2.01 (m, 2H), 1.42 (s, 13H), 1.09 (d, 3H, J=7), 1.02 (d, 3H, J=7). ¹³C NMR (CDCl₃) δ 164.7, 163.8, 160.4, 159.0, 155.2, 143.0, 140.8, 138.7, 138.6, 138.5, 138.3, 136.0, 133.6, 130.1, 130.0, 129.0, 128.9, 127.6, 127.3, 127.3, 78.3, 66.3, 51.6, 51.4, 48.6, 39.1, 32.8, 31.9, 28.7, 27.5, 21.5, 18.1, 17.6. IR (nujol) 3392, 3367, 3148, 1720, 1683, 1649, 1594, 1571, 1519, 1377, 1310, 1284, 1247, 1171, 1114, 1000, 914, 874, 808, 775, 723, 696 cm⁻¹. HRMS (FAB) m/z calcd for C₄₃H₄₅N₉O₁₃Li (M + Li) 902.3291; found, 902.3264.

I. Synthesis of Compound 12 (Linear hexaoxazole amine lysine-valine)



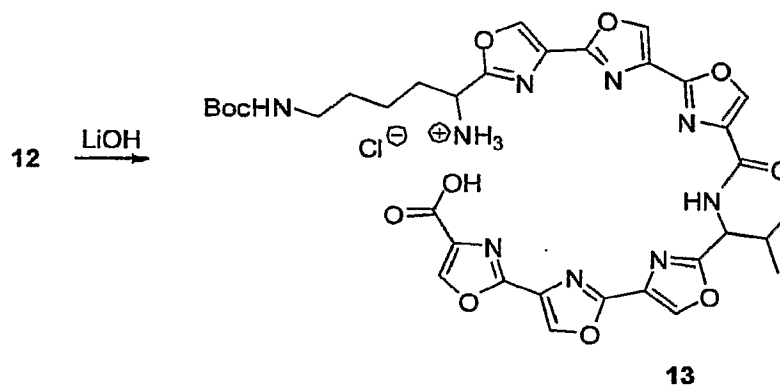
Compound 11 (450mg, 0.5mmol) was dissolved in a 10% mixture of ethanol in THF (75mL) and refluxed with 20% PdOH on carbon (150mg) and 1,4-cyclohexadiene (2mL) for 3 days. The reaction was cooled to room temperature and filtered through Celite, washing with 10% methanol/CH₂Cl₂ (200mL). This was concentrated to a cream colored solid weighing 380mg, 100%.

Melting point 157-160°C. ^1H NMR (CDCl_3) δ 8.45 (s, 1H), 8.33 (m, 5H), 7.65 (d, 1H, $J=10$), 5.36 (m, 1H), 5.03 (m, 1H), 4.65 (m, 1H), 9.95 (s, 3H), 3.11 (m, 2H), 2.43 (m, 1H), 2.01 (m, 2H), 1.43 (s, 13H), 1.09 (d, 3H, $J=7$), 1.03 (d, 3H, $J=6$)

5 ^{13}C NMR (CDCl_3) δ 163.8, 160.4, 159.0, 155.2, 150.6, 143.0, 140.8, 138.6, 138.5, 136.0, 135.0, 133.6, 130.0, 129.0, 127.4, 124.6, 78.2, 51.6, 51.4, 39.5, 33.3, 31.9, 29.4, 27.5, 20.3, 18.1, 17.6. IR (nujol) 3647, 3356, 3178, 3144, 3118, 1721, 1657, 1600, 1571, 1518, 1377, 1364, 1282, 1167, 1113, 999, 973, 914, 860, 775, 724 cm^{-1}

10

m. Synthesis of Compound 13 (Liner hexaoxazole de-esterified lysine-valine)

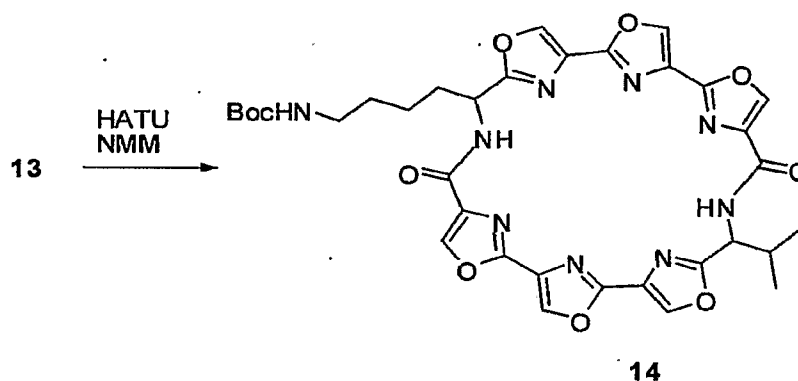


Compound 12 (380mg, 0.5mmol) was dissolved in a 3:1 mixture of THF and water (28mL) and cooled to 0°C. Then LiOH (25mg, 0.6mmol, 1.2eq) was added and the reaction warmed to room temperature overnight. The solvent was removed and the residue was dissolved in water. The pH was acidified with 1N HCl and a white solid precipitated. This was filtered and the filtrate was concentrated. After azeotroping the aqueous layer and triturating with ethanol, the product was obtained as a white solid weighing 378mg, 100%. Melting point 265°C

^1H NMR (DMSO) δ 9.02 (m, 3H), 8.88 (m, 3H), 6.76 (m, 1H), 5.06 (m, 1H), 4.33 (m, 1H), 2.87 (m, 2H), 1.86 (m, 2H), 1.33 (s, 13H), 1.02 (d, 3H, $J=7$), 0.92 (d, 3H, $J=7$). ^{13}C NMR ($\text{CDCl}_3 + \text{CD}_3\text{OD}$) 163.8, 142.8, 128.1, 127.3, 124.5, 124.3, 33.3, 29.4, 28.4, 27.2, 23.4, 20.1. IR (nujol) 3359, 3178, 3142, 1688,

1658, 1519, 1377, 1281, 1170, 1115, 974, 915, 725 cm^{-1}

n. Synthesis of Compound 14 (Boc protected cyclic hexaoxazole lysine-valine)



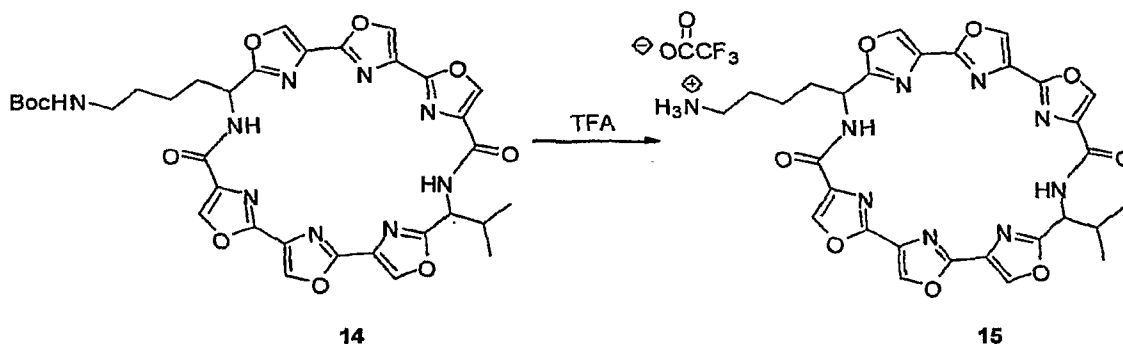
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Compound **13** (20mg, 0.0255mmol) was dissolved in a mixture of dry DMF (10mL) and dry CH_2Cl_2 (20mL) and placed under argon. The flask was cooled to 0°C and N-methylmorpholine (6 μL , 0.056mmol, 2.2eq) and a solution of HATU (12mg, 0.031mmol, 1.2eq) in DMF (1mL) were added. This stirred at 0°C for 4 hours then warmed to room temperature overnight. The solvent was removed under reduced pressure and the residue was chromatographed with 1% methanol/chloroform on SiO_2 which afforded 10mg of product as a white solid, 54%. Melting point $207\text{--}210^\circ\text{C}$ Optical rotation $[\alpha]_{\text{D}}^{24} = -22.8^\circ$ ($c = 0.25\text{g}/100\text{mL}$ in CHCl_3). ^1H NMR (CDCl_3) δ 8.56 (d, 1H, $J=8$), 8.84 (d, 1H, $J=8$), 8.22 (m, 6H), 5.42 (dt, 1H $J = 6, 8$), 5.33 (dd, 1H, $J = 5, 8$) 4.57 (m, 1H), 3.08 (m, 2H), 2.38 (m, 1H), 2.04 (m, 2H), 1.46 (m, 13H), 1.06 (d, 3H, $J=7$), 0.98 (d, 3H, $J=7$)

^{13}C NMR (CDCl_3) δ 164.0, 163.6, 159.0, 155.1, 153.9, 140.0, 138.2, 138.0, 137.4, 136.3, 130.2, 128.9, 52.2, 47.0, 44.8, 39.8, 33.9, 33.1, 28.7, 27.5, 21.2, 17.6, 17.3

IR (thin film, NaCl) 3380, 3146, 2966, 2937, 2866, 1678, 1594, 1509, 1366, 1249, 1169, 1106, 972, 916, 723 cm^{-1} . HRMS (FAB) m/z calcd for $\text{C}_{34}\text{H}_{35}\text{N}_9\text{O}_{10}\text{Li}$ ($M + \text{Li}$) 736.2662; found, 736.2665

o. Synthesis of Compound 15 (Cyclic lysine-valine amine TFA salt)

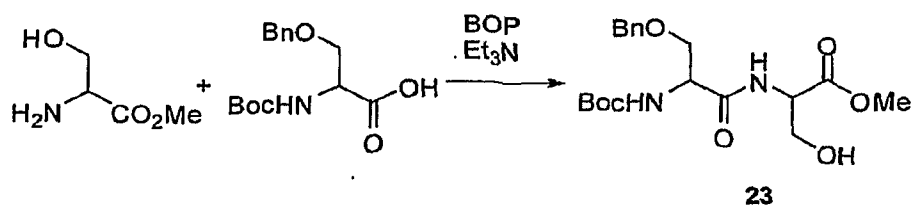


Compound **14** (21mg, 0.029mmol) was dissolved in CH_2Cl_2 (2mL) and cooled to 0°C . Then TFA (2mL) was added and this stirred at low temperature for 1.5 hours. The solvent was then removed *in vacuo* and the residue was azeotroped with benzene twice. The residue was then taken up in chloroform and 1 drop of methanol and the product was precipitated by adding hexane. After removal of the organic solvent via pipette, the product was obtained as a white solid weighing 21mg, 100%. Melting point $297\text{--}300^\circ\text{C}$; Optical rotation $[\alpha]_D^{24} = -20.6$ ($c = 0.18\text{g}/100\text{mL}$ in 10% MeOH/ CHCl_3). ^1H NMR (CDCl_3) δ 8.31 (m, 8H), 5.37 (m, 2H), 2.44 (m, 1H), 1.93 (m, 2H), 1.29 (m, 2H), 0.98 (m, 8H)

^{13}C NMR ($\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ 164.9, 164.0, 159.3, 155.6, 153.8, 140.4, 139.8, 139.2, 138.5, 138.3, 136.0, 135.6, 129.5, 128.2, 128.1, 63.0 52.6, 39.3, 32.5, 32.0, 26.2, 20.1, 17.5, 17.3. IR (thin film, NaCl) 3389, 2360, 2340, 1666, 1589, 1458, 1104 cm^{-1} . HRMS (FAB) m/z calcd for $\text{C}_{29}\text{H}_{27}\text{N}_9\text{O}_8\text{Li}$ (free base) ($\text{M} + \text{Li}$) 636.2137; found, 636.2139

The intermediate Compound **28** used in step f above was prepared as follows.

p. Synthesis of Compound 23

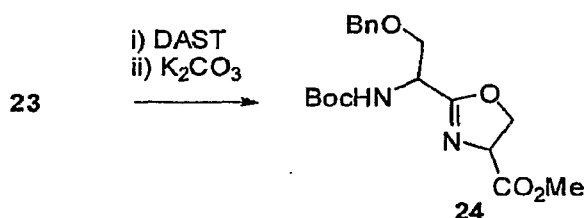


Boc-O-benzyl-L-serine (4.13g, 14mmol), serine methyl ester (2.18g,

14mmol) and BOP (6.19 g, 14mmol) were dissolved in CH₃CN (40 mL). Then triethylamine (4.2mL, 30.8mmol, 2.2eq) was added. The reaction stirred overnight at room temperature. The solvent was removed and the residue was dissolved in CH₂Cl₂ and washed successively with brine, 2N HCl, 0.5N NaHCO₃, water and brine. The organic extract was dried over Na₂SO₄ and concentrated to a clear oil weighing 5.54g, 100%.

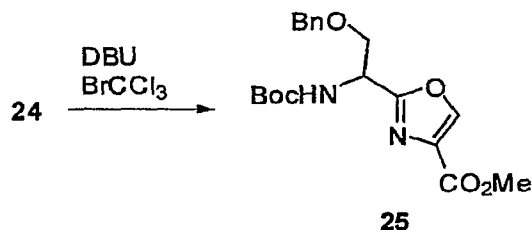
¹H NMR (CDCl₃) δ 7.31 (s, 6H), 5.49 (d, 1H, J = 6), 4.64 (m, 1H), 4.55 (s, 2H), 4.31 (m, 1H), 3.88 (dd, 1H J = 5, 10), 3.75 (s, 3H), 3.63 (dd, 1H J = 6, 10), 2.96 (br s, 1H), 1.44 (s, 9H). ¹³C NMR (CDCl₃) δ 170.5, 170.3, 155.5, 137.2, 128.3, 127.8, 127.8, 127.7, 80.5, 73.3, 69.8, 69.4, 62.6, 62.4, 60.3, 54.8, 52.5, 28.1. IR (thin film NaCl) 3419, 3065, 3032, 2979, 2954, 2871, 2251, 1670, 1498, 1455, 1439, 1392, 1368, 1248, 1167, 1105, 1027 cm⁻¹. HRMS (FAB) *m/z* calcd for C₁₉H₂₈N₂O₇Li (M + Li) 403.2057; found, 403.2052.

15 **q. Synthesis of Compound 24 (serine oxazoline)**



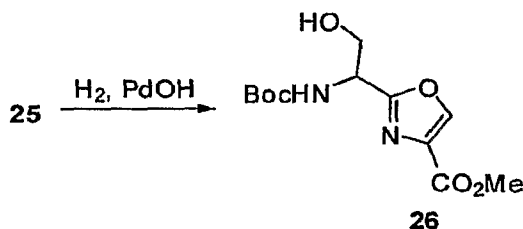
Compound **23** (5.54g, 14 mmol) was dissolved in CH₂Cl₂ (20mL) and placed under argon. After cooling to -78 °C, DAST (2.8mL 21.4mmol, 1.5eq) was added and the reaction stirred at low temperature for 2.5 hours. Then K₂CO₃ 2.9 g, 21.4 mmol, 1.5eq) was added and the reaction warmed to room temperature. This was poured into saturated NaHCO₃. The layers were separated and the aqueous was extracted with CH₂Cl₂. The organic extracts were dried over Na₂SO₄ and concentrated to an orange oil weighing 5.28g, 99%. ¹H NMR (CDCl₃) δ 7.50 (m, 5H), 5.66 (m, 1H), 4.99 (dd, 1H, J = 8, 10), 4.71 (m, 5H), 3.96 (m, 5H), 1.64 (s, 9H). ¹³C NMR (CDCl₃) δ 170.2, 167.4, 154.3, 136.9, 134.2, 127.5, 126.8, 126.6, 79.0, 72.2, 69.2, 69.0, 67.2, 67.1, 52.5, 51.7, 48.5, 24.7. IR (neat NaCl) 3384, 3063, 3030, 2977, 2870, 1709, 1666, 1506, 1454, 1367, 1322, 1166, 1109, 1051 cm⁻¹.

r. Synthesis of Compound 25 (Boc-O-benzyl serine oxazole)



Oxazoline **24** (5.28g, 14mmol) in CH_2Cl_2 (20mL) was placed under argon and cooled to 0 °C. DBU (3.2 mL, 2mmol, 1.6eq) was added dropwise and the solution turned yellow. Then BrCCl_3 (2.2mL, 22.4mmol) was added dropwise and the solution became brown. This warmed to room temperature overnight and then poured into saturated ammonium chloride. The aqueous layer was extracted with CH_2Cl_2 . The organic layers were dried over Na_2SO_4 and concentrated to a brown oil. This was flash chromatographed on SiO_2 with 15-50% EtOAc/hexane. The product was obtained as a clear oil 3.10g, 59%. $[\alpha]^{25}_{\text{D}} -33.35$ ($c = 2\text{g}/100\text{mL}$ in EtOH). ^1H NMR (CDCl_3) δ 8.36 (s, 1H) 7.41 (m, 5H), 5.76 (d, 1H, $J = 8$), 5.30 (m, 1H), 4.66 (s, 2H), 4.07 (m, 3H), 3.97 (m, 2H), 1.61 (s, 9H). ^{13}C NMR (CDCl_3) δ 163.4, 161.3, 154.9, 144.0, 137.2, 133.3, 128.2, 127.7, 127.4, 80.1, 73.1, 70.3, 52.0, 49.2, 28.1. IR (thin film NaCl) 3351, 3163, 3064, 3031, 2978, 2953, 2870, 2251, 1717, 1585, 1499, 1454, 1439, 1392, 13677, 1324, 1251, 1202, 1168, 1112, 1047, 1001 cm^{-1} .

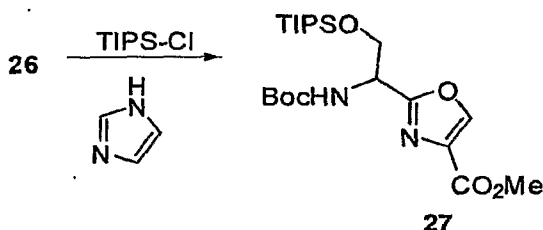
s. Synthesis of Compound 26 (Boc serine oxazole alcohol)



Compound **25** (3.10g, 8.24mmol) was dissolved in methanol (50mL) and 20% palladium hydroxide on carbon (500mg) was added to the reaction vessel. This was hydrogenated in a Parr hydrogenator at 40 psi for 72 hours. The reaction mixture was filtered through Celite while washing with methanol. The

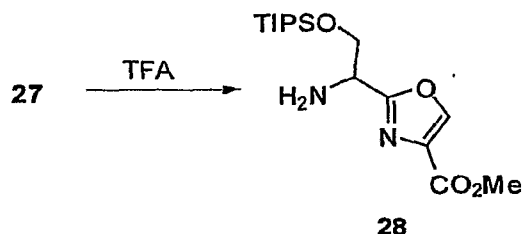
filtrate concentrated to a clear oil weighing 1.71g, 75% (some material lost in hydrogenator). ^1H NMR (CDCl_3) δ 8.21 (s, 1H), 5.67 (s, 1H), 5.02 (s, 1H), 3.96 (m, 5H), 1.45 (s, 9H). ^{13}C NMR (CDCl_3) δ 143.5, 79.7, 62.8, 51.4, 49.8, 27.4 IR (thin film, NaCl) 3364, 2979, 2251, 1716, 1585, 1519, 1456, 1440, 1393, 1368, 1324, 1252, 1168, 1112, 1061, 1001, 915, 861, 804, 774, 733 cm^{-1}

t. Synthesis of Compound 27 (Boc-O-TIPS serine oxazole)



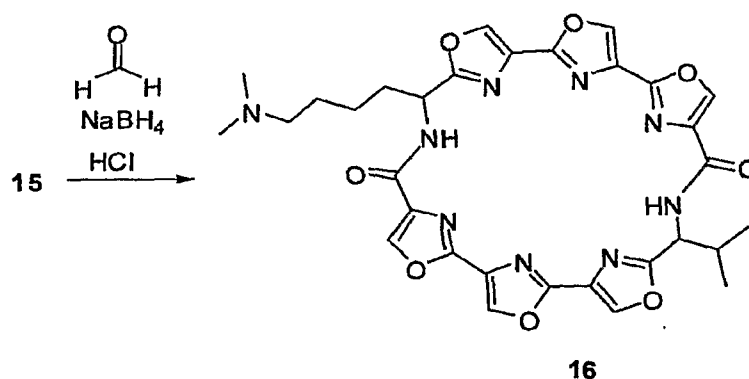
Compound 26 (1.71g, 6mmol) was dissolved in dry DMF (15mL) and imidazole (1.02g, 15mmol, 2.5eq) was added to the flask. This was placed under argon and treated with TIPS-Cl (1.52mL, 7.2mmol, 1.2eq). The reaction stirred at room temperature overnight and then poured into water. This was extracted with ethyl acetate and the combined organic layers were washed with brine and dried with sodium sulfate. Concentration afforded yellow oil that was flash chromatographed on SiO_2 with 5-15% ethyl acetate/hexane. This was concentrated to a clear oil weighing 1.9g, 72%. ^1H NMR (CDCl_3) δ 8.20 (s, 1H), 5.58 (d, 1H, $J = 8$), 5.03 (m, 1H), 4.09 (dq, 2H, $J = 3, 19$), 3.92 (s, 3H), 1.17 (m, 3H), 1.07 (s, 9H), 1.02 (m, 18H). ^{13}C NMR (CDCl_3) δ 169.3, 169.1, 163.0, 160.7, 143.1, 132.5, 79.3, 64.1, 51.3, 50.4, 27.4, 17.0, 11.5. IR (thin film NaCl) 3447, 3353, 3159, 3112, 2944, 2892, 2867, 2756, 2723, 2251, 1720, 1585, 1500, 1463, 1391, 1367, 1324, 1250, 1171, 1113, 1068, 998, 920, 882, 804, 766, 733, 684, 660 cm^{-1}

u. Synthesis of Compound 28 (TIPS serine oxazole amine)



Compound **27** (1.9g, 4.3mmol) was dissolved in CH_2Cl_2 (5mL) and cooled to 0°C . Then TFA (5 mL) was added and the reaction stirred under a drying tube for 2hours. The reaction mixture was concentrated and azeotroped with benzene twice. The residue was dissolved in CH_2Cl_2 and poured into saturated NaHCO_3 . The layers were separated and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were dried with sodium sulfate and concentrated to a pale yellow oil weighing 1.43g, 97%. ^1H NMR (CDCl_3) δ 8.21 (s, 1H), 4.21 (t, 1H, $J = 5$), 4.04 (d, 1H, $J = 5$), 3.92 (s, 3H), 3.74 (d, 1H, $J = 3$), 2.23 (s, 2H), 1.02 (m, 21H). ^{13}C NMR (CDCl_3) δ 165.7, 160.8, 143.1, 132.3, 65.5, 55.6, 51.5, 16.9, 10.9. IR (thin film, NaCl) 3376, 3315, 3168, 2944, 2893, 2866, 2762, 2726, 2625, 2247, 1744, 1673, 1583; 1514, 1463, 1439, 1384, 1367, 1345, 1323, 1203, 1110, 1069, 998, 918, 883, 841, 803, 769, 733, 683, 660, 647 cm^{-1}

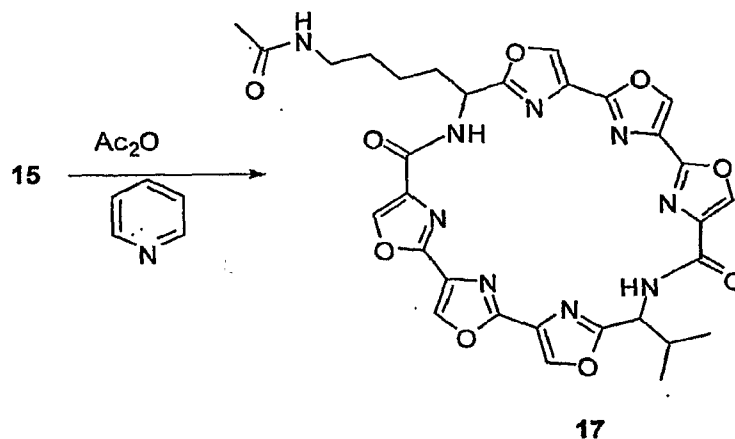
Example 2 Synthesis of Compound 16 (Cyclic lysine-valine dimethyl amine)



Compound **15** (21mg, 0.029mmol) was dissolved in methanol (1mL) and water (1mL) with 1 drop of HCl. This was cooled to 0°C and 37% aqueous

formaldehyde (30 μ L, 0.3mmol, 10eq) was added. After stirring for 5 minutes, sodium borohydride (11mg, 0.29mmol, 10eq) was slowly added to avoid excessive foaming. Then additional formaldehyde (30 μ L, 0.3mmol, 10eq) was added and the pH was adjusted to 3 with concentrated HCl. After stirring at 0°C for 8 hours, the pH was neutralized with 3N NaOH and the reaction mixture was concentrated. The residue was triturated with ethanol and filtered to remove precipitated NaCl. The residue was dissolved in 10mL of methanol and half of the solution was stirred with Amberlyst A-15 resin. After stirring for 1 hour the solvent was removed and the resin was washed with methanol. The resin was then stirred with a solution of methanolic ammonia to release the product from the resin. After stirring for 2 hours the resin was filtered and the filtrate was concentrated to give 2mg of product. The other half of the methanol solution was concentrated and triturated with 30% hexane/chloroform. The organic solvent was removed by pipette to give the product as a white solid weighing 10mg. Total product obtained was 12mg, 67%.
Melting point 308-310°C (decomposed). Optical rotation $[\alpha]_D^{24} = +19^\circ$ (c = 0.5g/100mL in 20%CHCl₃/MeOH). ¹H NMR (CDCl₃) δ 8.76 (d, 1H, J = 8), 8.41 (d, 1H, J = 8), 8.23 (m, 6H), 5.48 (dt, 1H, J = 6, 7), 5.34 (dd, 1H, J = 5, 8), 2.96 (m, 2H), 2.88 (s, 3H), 2.11 (m, 3H), 1.90 (m, 5H), 0.99 (m, 8H). ¹³C NMR (CDCl₃ + CD₃OD) δ 164.9, 140.2, 139.0, 138.5, 138.2, 128.2, 52.3, 39.7, 32.3, 17.8, 17.5
IR (thin film, NaCl) 3388, 2959, 2926, 1660, 1595, 1458, 1107 cm⁻¹. HRMS (FAB) *m/z* calcd for C₃₁H₃₁N₉O₈Li (M + Li) 658.2368; found, 658.2373

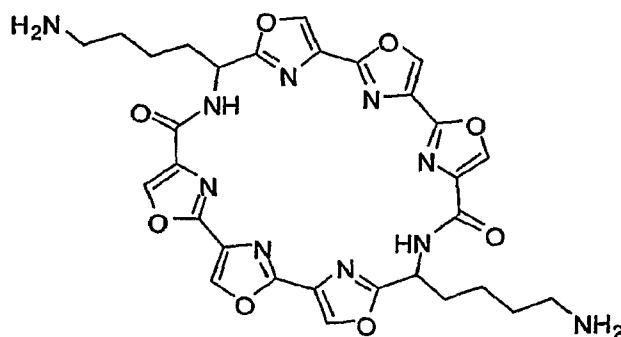
Example 3 Synthesis of Compound 17 (Cyclic lysine-valine acetyl amide)



Compound **15** (12.8mg, 0.017mmol) was treated with a mixture of acetic anhydride (1mL) and dry pyridine (1mL). This stirred at room temperature under a drying tube for 6 hours. The solvent was then removed by azeotrope with toluene twice. The residue was chromatographed on SiO₂ with 1% MeOH/CHCl₃ to afford 8mg of white solid, 72%.

Melting point 222-224°C; Optical rotation $[\alpha]_D^{24} = -37.4^\circ$ ($c = 0.605\text{g}/100\text{mL}$ in 10% MeOH/CHCl₃). ¹H NMR (CDCl₃) δ 8.60 (d, 1H, $J = 8$), 8.48 (d, 1H, $J = 8$), 8.23 (m, 6H), 5.78 (br s, 1H), 5.43 (dt, 1H, $J = 6, 7$), 5.33 (dd, 1H, $J = 5, 8$), 3.22 (m, 2H), 2.40 (m, 1H), 1.75 (m, 5H), 1.44 (m, 4H), 1.05 (d, 3H, $J = 7$), 0.99 (d, 3H, $J = 7$). IR (thin film, NaCl) 3368, 3153, 3047, 2964, 2930, 2871, 2359, 2340, 1660, 1597, 1510, 1468, 1441, 1372, 1359, 1269, 1190, 1105, 974, 915, 878, 810, 774, 722, 695 cm⁻¹.

15 Example 4 Synthesis of compound 50

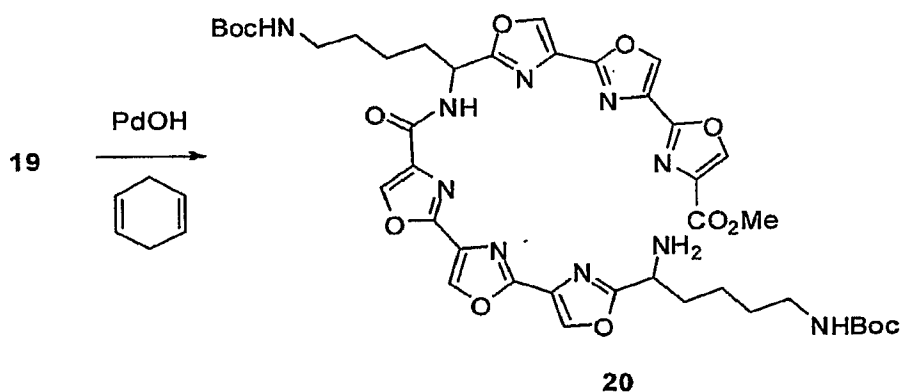


50

Compound **10** (327mg, 0.56mmol), Compound **18** (260mg, 0.56mmol), EDC (216mg, 1.13mmol, 2eq) and HOBT (152mg, 1.13mmol, 2eq) were dissolved in dry DMF (100mL) and placed under argon. This was cooled to 0°C and 2,6-lutidine (0.33mL, 2.8mmol, 5eq) was added. This warmed to room temperature overnight after which the solvent was removed under reduced pressure. The residue was dissolved in CH₂Cl₂ and washed successively with saturated NaHCO₃, 5% HCl and brine. The aqueous layers were all back extracted with ethyl acetate. The combined organic layers were dried with sodium sulfate and concentrated to an orange solid. This was recrystallized from benzene to give 133mg of product, 23%.

Melting point 186-189°C; Optical rotation $[\alpha]_D^{23} = -3.15^\circ$ (c = 1.65g/100mL in CHCl₃). ¹H NMR (CDCl₃) δ 8.44 (m, 2H), 8.32 (m, 4H), 7.54 (d, 1H, J = 9), 7.35 (m, 5H), 5.51 (m, 2H), 5.13 (s, 2H), 5.04 (m, 1H), 4.58 (m, 2H), 3.95 (s, 3H), 3.10 (m, 4H), 2.05 (m, 4H), 1.46 (m, 26H). ¹³C NMR (CDCl₃) δ 164.7, 164.0, 158.9, 155.1, 143.0, 140.8, 138.8, 138.5, 135, 130.0, 127.6, 127.3, 78.3, 66.4, 51.4, 48.6, 46.0, 39.1, 32.8, 28.7, 27.5, 21.9, 21.5. IR (nujol) 3408, 3364, 3159, 1715, 1690, 1644, 1600, 1574, 1522, 1377, 1364, 1282, 1170, 1114, 1001, 976, 915, 725 cm⁻¹.

c. Synthesis of Compound 20 (Linear dilysine hexaoxazole amine)



Compound **19** (130mg, 0.13mmol) was dissolved in 30% ethyl acetate in methanol (130mL) and refluxed with 20% palladium hydroxide (25mg) and 1,4-cyclohexadiene (2mL) overnight. Then additional palladium hydroxide (40mg)

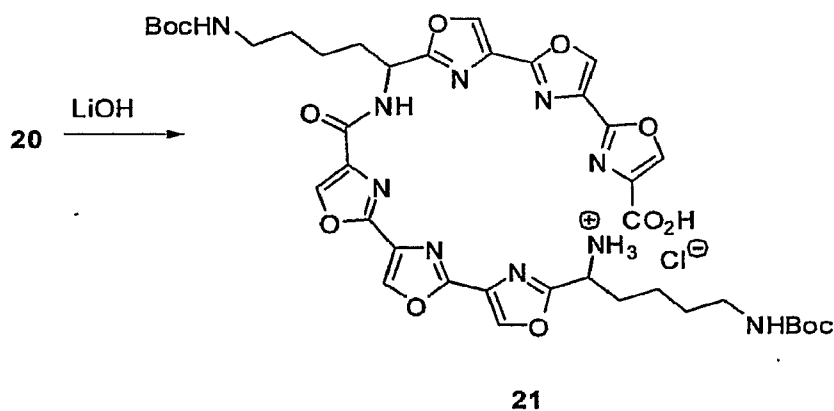
and 1,4-cyclohexadiene (1mL) were added and refluxed for 48 hours. After adding more palladium hydroxide (50mg) and refluxing overnight the reaction was cooled and filtered through Celite washing with 20% methanol/CH₂Cl₂. This was concentrated to a white solid weighing 111mg, 98%. Melting point 170-

5 173°C

¹H NMR (CDCl₃ + CD₃OD) δ 8.65 (m, 3H), 8.56 (m, 2H), 8.50 (s, 1H), 5.45 (dt, 1H, J = 1, 8), 4.56 (m, 1H), 3.95 (s, 3H), 3.08 (m, 4H), 2.14 (m, 6H), 1.48 (m, 28H)

¹³C NMR (CDCl₃ + CD₃OD) δ 165.2, 161.5, 160.8, 144.6, 142.2, 141.1, 140.5, 10 140.2, 133.9, 130.6, 129.6, 129.5, 125.1, 78.9, 51.9, 39.9, 32.7, 35.5, 29.9, 29.2, 27.9, 22.8, 22.2. IR (nujol) 3360, 3151, 2362, 2334, 1715, 1682, 1660, 1519, 1455, 1365, 1282, 1251, 1167, 115, 973, 914, 725 cm⁻¹.

d. **Synthesis of Compound 21** (Linear dilysine hexaoxazole fully
15 deprotected)



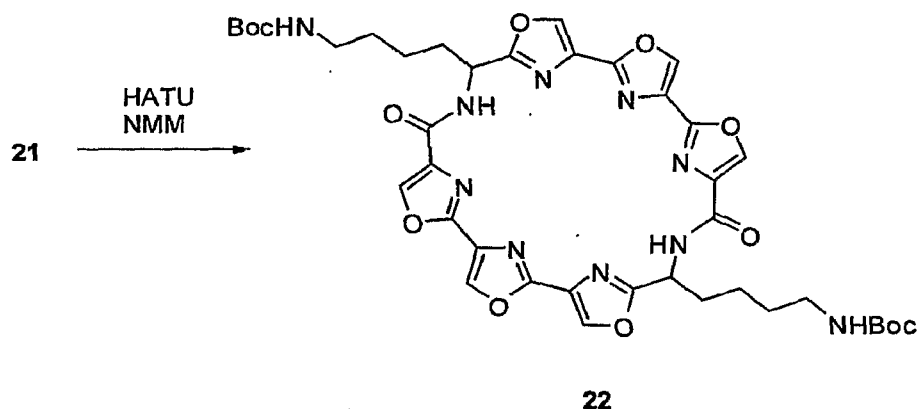
Compound **20** (111mg, 0.12mmol) was dissolved in a 3:1 mixture of THF and water (13mL) and cooled to 0°C. Then LiOH (10mg, 0.24mmol, 2eq) was added and the reaction warmed to room temperature overnight. The solvent was then removed and the aqueous solution was acidified with 1N HCl (1mL). This was concentrated and azeotroped with toluene to give 110mg of the hydrochloride salt as a white solid, 99%. Melting point 265-269°C. ¹H NMR (DMSO) δ 9.06 (m, 3H), 8.97 (m, 2H), 8.90 (s, 1H), 8.75 (br s, 2H), 6.79 (m, 1H), 5.25 (m, 1H), 4.46 (m, 2H), 2.82 (m, 8H), 1.99 (m, 6H), 1.60 (m, 6H), 1.34

(m, 18H)

^{13}C NMR ($\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ 168.6, 164.2, 159.5, 155.3, 155.2, 155.1 153.6, 142.3, 139.3, 135.4, 129.5, 129.5, 128.7, 128.4, 127.5, 124.5, 78.4, 39.1, 33.4, 32.1, 30.3, 29.3, 28.4, 27.3, 25.9, 21.8, 21.2. IR (nujol) 3396, 2367, 2360, 1633,

5 1375, 1260, 1105 cm^{-1}

e. **Synthesis of Compound 22 (Cyclic Boc-dilysine hexaoxazole)**



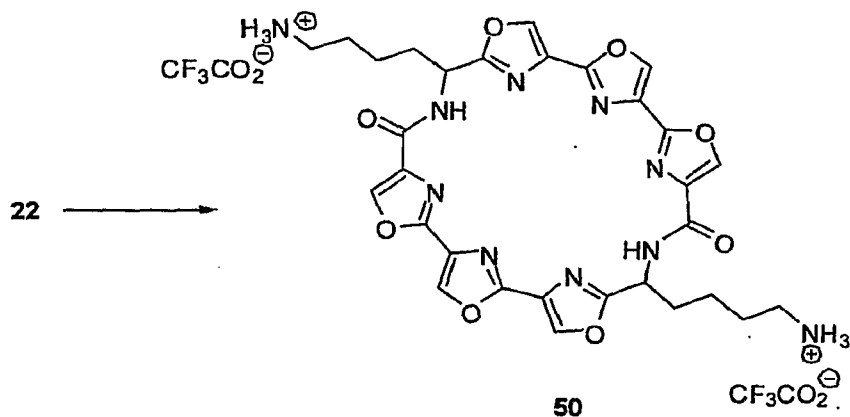
Compound **21** (100mg, 0.12mmol) was dissolved in dry DMF (60mL) and CH_2Cl_2 (120mL) and placed under argon. After cooling to 0°C , N-methylmorpholine (30 μL , 0.26mmol, 2.2eq) and a solution of HATU (55mg, 0.14mmol, 1.2eq) in DMF (1mL) were added. This warmed to room temperature overnight and the solvent was then removed. This was chromatographed with 1-2% MeOH/ CHCl_3 on SiO_2 to give 7mg of product as a white solid, 7%. Melting point 168°C ; Optical rotation $[\alpha]_{\text{D}}^{24} = -6.0^\circ$ ($c = 0.25\text{g}/100\text{mL}$ in 10% MeOH/ CHCl_3)

^1H NMR (CDCl_3) δ 8.54 (d, 1H, $J = 7$), 8.30 (d, 1H, $J = 8$), 8.22 (m, 6H), 7.35 (s, 1H), 5.46 (m, 2H), 4.55 (s, 1H), 3.07 (m, 4H), 1.99 (m, 6H), 1.29 (m, 24H)

^{13}C NMR (CDCl_3) δ 153.8, 142.5, 140.4, 138.3, 137.5, 46.9, 39.5, 34.2, 28.7, 27.5,

IR (thin film, NaCl) 3383, 3326, 3145, 2929, 2866, 1673, 1595, 1510, 1455, 1366, 1271, 1251, 1170, 1107, 973, 916, 724 cm^{-1}

f. **Synthesis of Compound 50**

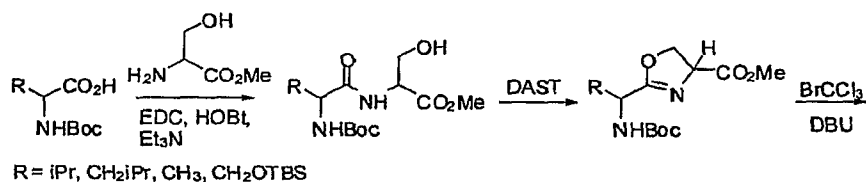


Compound 22 will be converted to Compound 50 by removing the protecting groups.

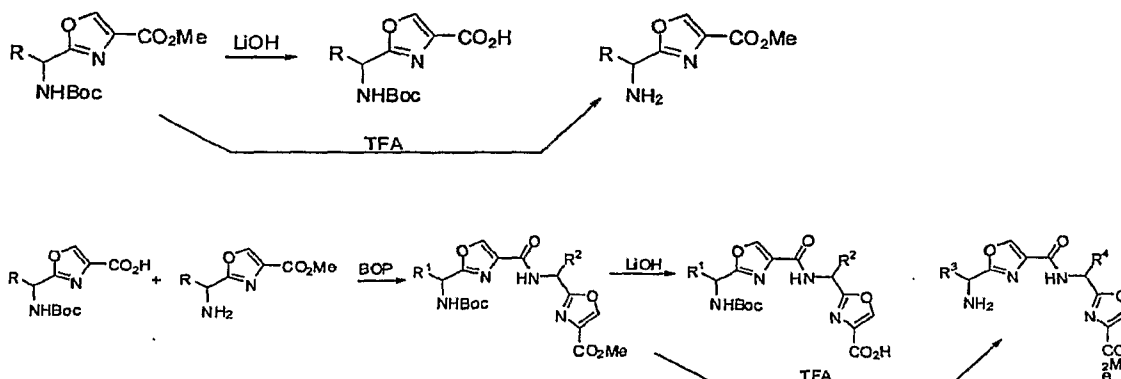
5

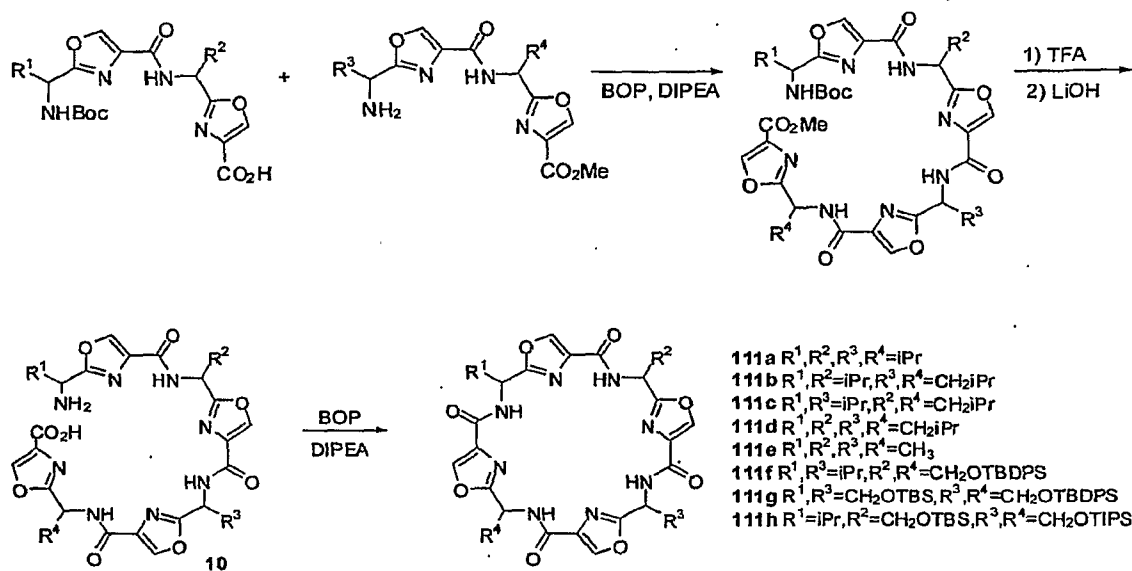
Example 5 Synthesis of Compounds 111a-111e

Compounds 111a-111e were prepared as illustrated below.

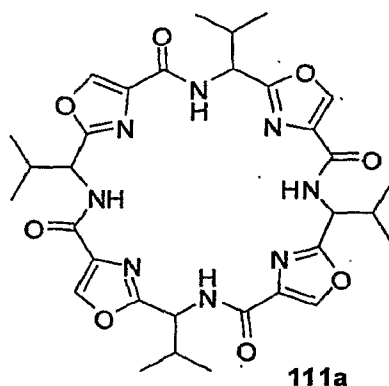


10



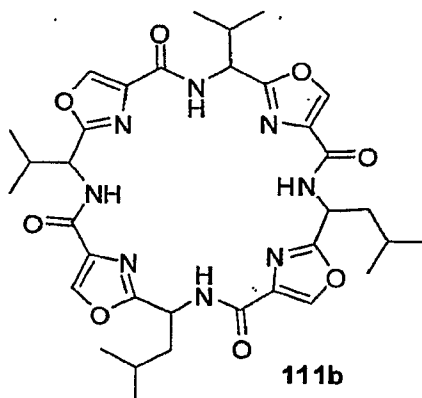


5 Compound **111a**:



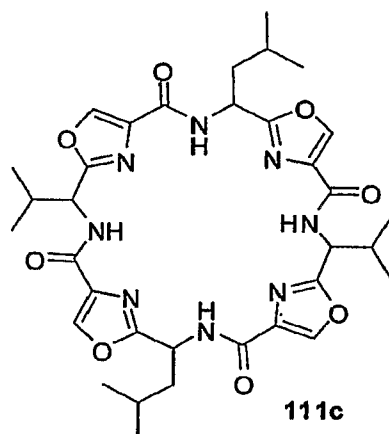
Yellow solid; mp. 122 -128 °C; ^1H NMR δ 8.15 (s, 4H), 7.27 (d, 4H, $J=9.4$), 5.26 (m, 4H), 2.34 (m, 4H), 1.08 (d, 12H, $J=6.6$), 0.98 (d, 12H, $J=6.6$); ^{13}C NMR δ 163.8, 159.8, 141.6, 135.8, 51.7, 32.9, 19.0, 18.7; HRMS ($M+Li^+$) Calcd for $C_{32}H_{40}N_8O_8(Li)$: 671.3129; Found: 671.3148.

Compound **111b**:

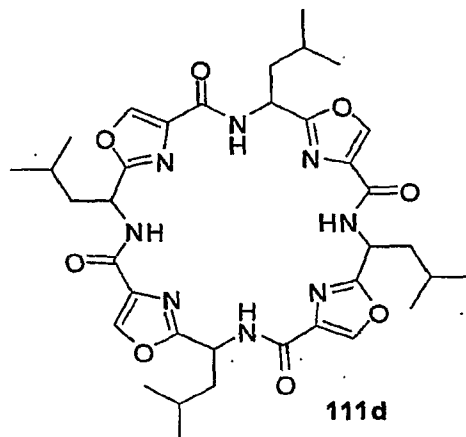


Yellowish white solid; mp. 132 °C-134 °C; ^1H NMR δ 8.14 (s, 2H), 8.11 (s, 2H), 7.31 (d, 2H, $J=9.6$), 7.14 (d, 2H, $J=9.6$), 5.51 (m, 2H), 5.23 (dd, 2H, $J=10,7$), 2.28 (m, 2H), 1.94 (m, 6H), 1.02 (d, 12H, $J=6.2$), 0.93 (d, 12H, $J=6.2$); ^{13}C NMR δ 164.4, 163.9, 160.2, 159.8, 159.5, 141.7, 141.6, 135.8, 135.6, 51.8, 45.5, 44.3, 42.9, 33.1, 32.4, 24.9, 24.8, 22.7, 22.6, 22.3, 22.1, 21.9, 19.0, 18.9, 18.5; HRMS (FAB) calcd for $\text{C}_{34}\text{H}_{44}\text{N}_8\text{O}_8(\text{Na})$: 715.3180; Found: 715.3174.

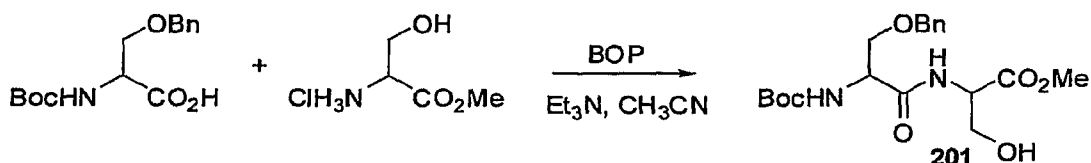
10 **Compound 111c:**



Yellowish white solid; mp. 124 -128 °C; ^1H NMR δ 8.12 (s, 4H), 7.21 (m, 4H), 5.25 (m, 4H), 2.30 (m, 2H), 1.86 (m, 6H), 0.96 (d, 12H, $J=6.6$), 0.94 (d, 12H, $J=6.6$); ^{13}C NMR δ 164.7, 164.6, 163.8, 163.7, 160.1, 159.8, 159.6, 141.7, 141.6, 135.7, 135.5, 52.5, 51.6, 45.4, 44.6, 44.5, 43.4, 42.4, 32.8, 32.4, 24.9, 24.7, 22.6, 22.5, 22.3, 22.2, 22.1, 21.9, 19.1, 18.6; HRMS (FAB) calcd for $\text{C}_{34}\text{H}_{44}\text{N}_8\text{O}_8(\text{Na})$: 715.3180; Found: 715.3148.

Compound **111d**:

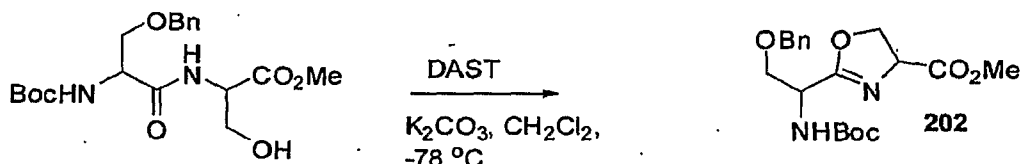
- 5 White solid; mp. 122 °C-128 °C; ^1H NMR (CDCl_3) δ 8.14 (s, 4H), 7.21 (d, 4H, $J=9.2$), 5.51 (m, 4H), 1.80 (m, 12H), 1.02 (d, 12H, $J=6.6$), 0.99 (d, 12H, $J=6.6$); ^{13}C NMR δ 164.6, 159.6, 141.6, 135.7, 44.6, 43.5, 24.9, 22.7, 22.3; HRMS (FAB) Calcd for $\text{C}_{36}\text{H}_{48}\text{N}_8\text{O}_8(\text{Li})$: 727.3755; Found: 727.3756.

10 **Example 6** Synthesis of Compound **219**a. **Synthesis of Compound 201 (N-Boc Serine Amide)**

- 15 Dry acetonitrile (200 mL) was added to a mixture of N-Boc-O-Benzyl serine (5.9 g, 20 mmol) and serine methyl ester hydrochloride (3.1 g, 20 mmol) and stirred for 5 min. BOP (8.84 g, 20 mmol) and triethylamine (6.2 mL, 44 mmol) were added and the mixture was stirred at room temperature for 12 h. The mixture was then evaporated under reduced pressure and diluted with EtOAc and brine. The phases were separated and then aqueous phase was extracted with EtOAc: The
- 20 combined organic phases were then washed successively with 1N HCl, saturated NaHCO_3 , and brine and then dried over Na_2SO_4 , filtered and evaporated to give the amide as a colorless oil, 7.92 g (100 %); ^1H NMR (CDCl_3) δ 7.56 (d, 1H, $J=7.6$),

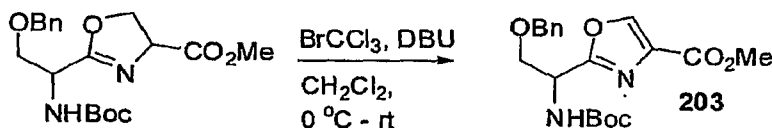
7.24 (m, 5H), 5.89 (d, 1H, $J=5.8$), 4.59 (m, 1H), 4.46 (s, 2H), 4.40 (m, 1H), 3.98 (m, 4H), 3.62 (s, 3H), 1.38 (s, 9H); ^{13}C -NMR δ 170.8, 155.9, 137.7, 128.4, 127.8, 80.3, 73.3, 70.2, 69.9, 62.5, 62.4, 60.4, 54.9, 54.6, 52.5, 28.3, 20.9, 14.2.

5 **b. Synthesis of Compound 202 (N-Boc Serine Oxazoline Methyl Ester)**



A solution of **201** (7.92 g, 20 mmol) in CH_2Cl_2 (40 mL) was cooled to -78°C under nitrogen and treated with DAST (4.34 mL, 33.1 mmol). After stirring for 1.5 h anhydrous K_2CO_3 was added and the mixture was then allowed to warm to room temperature. The mixture was poured into saturated NaHCO_3 and extracted several times with CH_2Cl_2 . The combined extracts were dried over Na_2SO_4 , filtered and concentrated to give oxazoline **202** as a red-yellow oil, 6.05 g (80%, crude); ^1H NMR (CDCl_3) δ 7.29 (m, 5H), 5.51 (d, 2H, $J=8.0$), 3.76 (s, 3H), 1.43 (s, 9H); ^{13}C -NMR δ 171.2, 168.4, 155.3, 137.9, 128.4, 127.7, 127.6, 80.0, 73.3, 73.2, 70.3, 68.1, 68.0, 52.7, 49.5, 28.4.

c. Synthesis of Compound 203 (N-Boc Serine Oxazole Methyl Ester)



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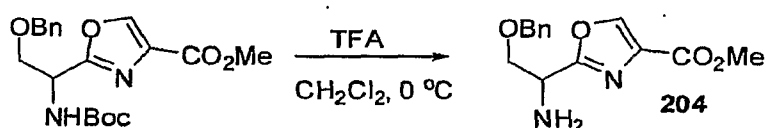
A solution of the crude oxazoline (6.05 g, 16 mmol) in dry CH_2Cl_2 (50 mL) was stirred under nitrogen at 0°C as dry DBU (3.7 mL, 25.6 mmol) was added over 2 min followed by BrCCl_3 (2.6 mL, 25.6 mmol) which was then added over 5 min. the reaction was stirred at 0°C for 5 h and was then poured into saturated NH_4Cl . The mixture was extracted with CH_2Cl_2 and the combined extracts were dried over Na_2SO_4 , filtered, and evaporated. The product was purified by flash chromatography on silica gel eluting with 2:3 EtOAc/hexane to give the oxazole as

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a colorless oil, 4.51 g (75%); ^1H NMR (CDCl_3) δ 8.14 (s, 1H), 7.42 (m, 5H), 5.66 (d, 1H, $J=8.8$), 5.08 (m, 1H), 4.43 (s, 2H), 3.82 (s, 3H), 3.71 (m, 2H), 1.38 (s, 9H); ^{13}C NMR δ 163.6, 161.5, 155.2, 144.3, 137.4, 133.4, 128.4, 127.8, 127.6, 80.2, 73.2, 70.4, 52.1, 49.4, 28.3.

5

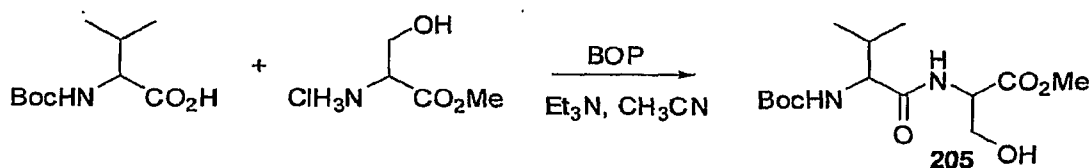
d. Synthesis of Compound 204 (Amino Oxazole)



A solution of the Boc derivative (4.51 g, 12 mmol) in CH_2Cl_2 (10 mL) was cooled to 0°C under protection from moisture by a drying tube. TFA (10 mL) was added and the solution was stirred for 1.5 h. Solvents were evaporated under reduced pressure and residual TFA was removed as an azeotrope with benzene. The residue was taken up in CH_2Cl_2 and washed with saturated NaHCO_3 and was then dried over Na_2SO_4 , filtered, and evaporated to give the amine as a yellow-red oil, 3.24 g (98%); ^1H NMR (CDCl_3) δ 8.19 (s, 1H), 7.29 (m, 5H), 4.54 (s, 2H), 4.31 (dd, 1H, $J=5.9, 4.8$), 3.90 (s, 3H), 3.81 (m, 2H), 1.98 (s, 2H); ^{13}C -NMR δ 166.6, 162.1, 144.6, 138.2, 133.7, 128.9, 128.3, 128.1, 73.8, 72.9, 52.7, 50.9.

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e. Synthesis of Compound 205 (N-Boc Valine Amide)



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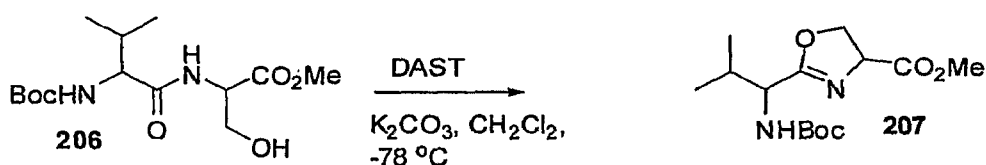
Dry acetonitrile (100 mL) was added to a mixture of N-Boc-L-valine (2.17 g, 10 mmol) and serine methyl ester hydrochloride (1.86 g, 12 mmol) and stirred for 5 min. BOP (4.42 g, 10 mmol) and triethylamine (3.1 mL, 22 mmol) were added and the mixture was stirred at room temperature for 12 h. The mixture was then evaporated under reduced pressure and diluted with EtOAc and brine. The phases were separated and then aqueous phase was extracted with EtOAc. The combined organic phases were then washed successively with 1N HCl, saturated NaHCO_3 , and brine and then dried over Na_2SO_4 , filtered and evaporated to give the amide as a

25

colorless oil, 3.18 g (100%); ^1H NMR (CDCl_3) δ 7.45 (dd, 1H, $J=1.4$), 5.58 (d, 1H, $J=8.8$), 4.45 (m, 1H), 4.37 (m, 1H), 3.79 (m, 2H), 3.54 (s, 3H), 1.88 (m, 1H), 1.23 (s, 9H), 0.74 (d, 6H, $J=6.6$); ^{13}C -NMR δ 172.3, 171.0, 162.9, 156.0, 79.4, 62.3, 54.6, 52.3, 31.3, 28.2, 17.7, 17.4.

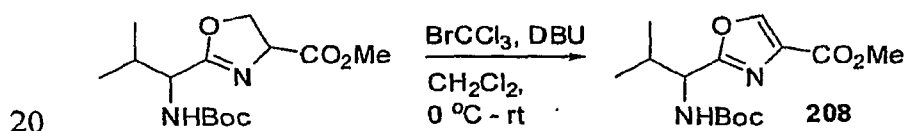
5

f. Synthesis of Compound 207 (N-Boc Valine Oxazoline)



A solution of **206** (2.54 g, 8 mmol) in CH_2Cl_2 (16 mL) was cooled to $-78\text{ }^\circ\text{C}$ under nitrogen and treated with DAST (1.7 mL, 13.2 mmol). After stirring for 1.5 h anhydrous K_2CO_3 (1.32 g) was added and the mixture was then allowed to warm to room temperature. The mixture was poured into saturated NaHCO_3 and extracted several times with CH_2Cl_2 . The combined extracts were dried over Na_2SO_4 , filtered and concentrated to give oxazoline **207** as a red-yellow oil, 2.36 g (98%, crude); ^1H NMR (CDCl_3) δ 5.12 (d, 1H, $J=8.4$), 4.70 (m, 1H), 4.41 (m, 3H), 3.74 (s, 3H), 2.02 (m, 1H), 1.24 (s, 9H), 0.74 (d, 6H, $J=6.6$); ^{13}C -NMR δ 171.3, 169.5, 155.5, 79.6, 69.8, 67.8, 54.1, 52.6, 31.8, 28.3, 17.7, 17.3.

g. Synthesis of Compound 208 (N-Boc Valine Oxazole)

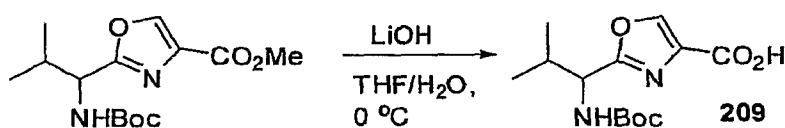


A solution of the crude oxazoline (2.36 g, 7.9 mmol) in dry CH_2Cl_2 (24 mL) was stirred under nitrogen at $0\text{ }^\circ\text{C}$ as dry DBU (1.8 mL, 12.5 mmol) was added over 2 min followed by BrCCl_3 (1.2 mL, 12.5 mmol) which was then added over 5 min. The reaction was stirred at $0\text{ }^\circ\text{C}$ for 5 h and was then poured into saturated NH_4Cl . The mixture was extracted with CH_2Cl_2 and the combined extracts were dried over Na_2SO_4 , filtered, and evaporated. The product was purified by flash chromatography on silica gel eluting with 2:3 EtOAc/hexane to give the oxazole as

a white solid, 2.36 g (75%); mp 125-129 °C; ¹H NMR (CDCl₃) δ 8.1 (s, 1H), 5.31 (d, 1H, J=9.2), 4.63 (dd, 1H, J=9,6), 3.73 (s, 3H), 2.04 (m, 1H), 1.25 (s, 9H), 0.74 (d, 6H, J=6.6); ¹³C NMR δ 165.0, 161.5, 155.3, 143.9, 133.0, 79.7, 54.2, 52.0, 32.8, 28.2, 18.6, 17.9.

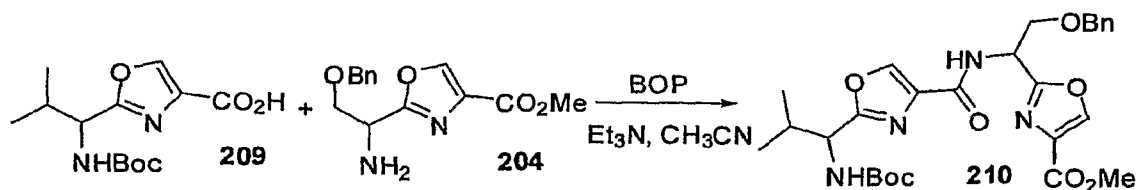
5

h. Synthesis of Compound 209 (N-Boc Valine Oxazole Carboxylic Acid)



A solution of the ester (0.8 g, 2.68 mmol) in 3:1 THF/H₂O (32 mL) was stirred at 0 °C as LiOH (134 mg, 3.19 mmol) was added in one portion. The reaction mixture was stirred for 10 h and was then evaporated under reduced pressure to remove THF. The aqueous solution was brought to pH 3 with 1N HCl and was then extracted with EtOAc. The organic phase was washed with brine and dried over Na₂SO₄, filtered and evaporated to give the carboxylic acid as a white solid, 0.67 g (88%); mp 157-160 °C; ¹H NMR (CDCl₃) δ 8.2 (s, 1H), 6.34 (d, 1H, J=8.4), 4.78 (t, 1H, J=8.3), 2.16 (m, 1H), 1.33 (s, 9H), 0.87 (dd, 6H, J=14,7); ¹³C NMR δ 166.4, 163.9, 155.9, 144.3, 133.8, 79.9, 54.6, 32.8, 28.3, 18.8, 18.3.

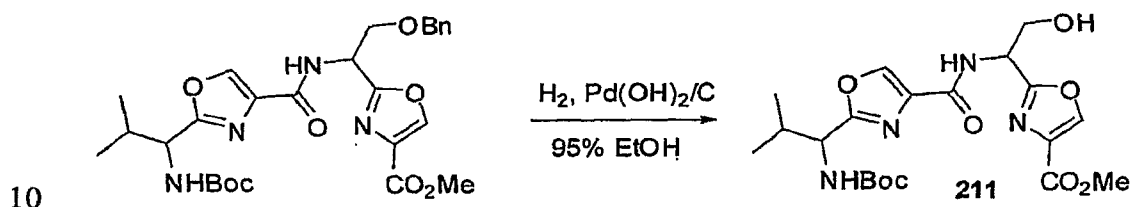
i. Synthesis of Compound 210 (N-Boc Valine O-Benzyl Bisoxazole Amide)



Dry acetonitrile (100 mL) was added to a mixture of amine **204** (3.24 g, 11.7 mmol) and acid **209** (3.33 g, 11.7 mmol) and stirred for 5 min. BOP (5.17 g, 11.7 mmol) and triethylamine (3.6 mL, 25.7 mmol) were added and the mixture was stirred at room temperature for 12 h. The mixture was then evaporated under reduced pressure and diluted with EtOAc and brine. The phases were separated and then aqueous phase was extracted with EtOAc. The combined organic phases were

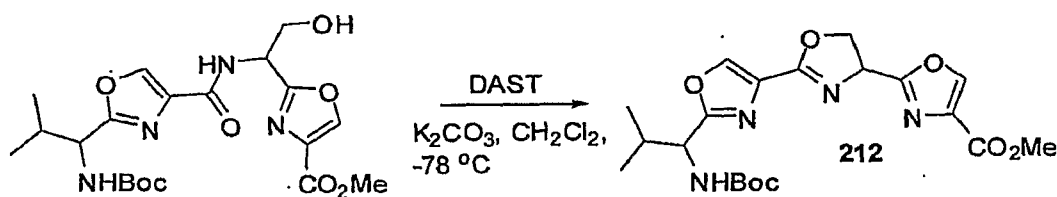
then washed successively with 1N HCl, saturated NaHCO₃, and brine and then dried over Na₂SO₄, filtered and evaporated to give the amide as a colorless oil, 4.76 g (90%); ¹H NMR (CDCl₃) δ 8.34 (s, 1H), 8.22 (s, 1H), 7.91 (d, 1H, J=8.4), 7.42 (m, 5H), 5.73 (m, 1H), 5.53 (m, 1H), 4.87 (m, 1H), 4.68 (s, 2H), 4.18 (m, 2H), 4.01 (s, 3H), 2.28 (m, 1H), 1.58 (s, 9H), 1.08 (d, 3H, J=6.6), 1.04 (d, 3H, J=7.0); ¹³C-NMR δ 163.2, 161.9, 161.8, 160.5, 159.5, 154.5, 143.4, 140.6, 136.4, 134.4, 132.5, 127.5, 126.9, 126.7, 79.1, 72.2, 68.9, 53.4, 51.2, 46.4, 31.7, 27.4, 17.9, 17.2.

j. **Synthesis of Compound 211 (N-Boc Valine Serine Amide)**



A solution of benzyl ether 9 (5.72 g, 10.6 mmol) in 95% EtOH (75 mL) was treated with 20% Pd(OH)₂/C (572 mg) and shaken in a Parr apparatus under 35 psi H₂ for 30 h at room temperature. The catalyst was filtered through a pad of Celite and the solvent was evaporated to give the alcohol as a colorless oil, 4.54 g (95%); ¹H NMR (CDCl₃) δ 8.69 (d, 1H, J=8.2), 8.36 (s, 1H), 8.29 (s, 1H), 6.19 (d, 1H, J=6.2), 5.66 (m, 1H), 4.77 (m, 1H), 4.33 (m, 2H), 3.97 (s, 3H), 2.25 (m, 1H), 1.55 (s, 9H), 1.04 (d, 3H, J=6.6), 0.89 (d, 3H, J=6.6); ¹³C-NMR δ 163.2, 162.9, 161.9, 160.7, 160.5, 160.4, 154.7, 143.5, 140.9, 140.5, 134.2, 132.1, 127.4, 79.2, 61.7, 53.4, 51.4, 49.1, 48.3, 31.7, 30.8, 27.4, 18.2, 17.9, 17.3, 17.1.

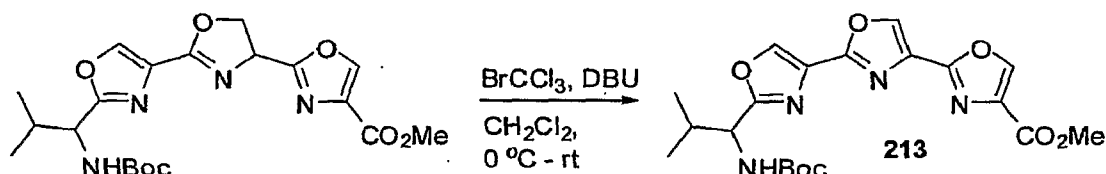
k. Synthesis of Compound 212 (N-Boc Valine Dihydroteroxazole)



25 A solution of **211** (4.54 g, 10 mmol) in CH₂Cl₂ (20 mL) was cooled to -78 °C under nitrogen and treated with DAST (2.17 mL, 16.6 mmol). After

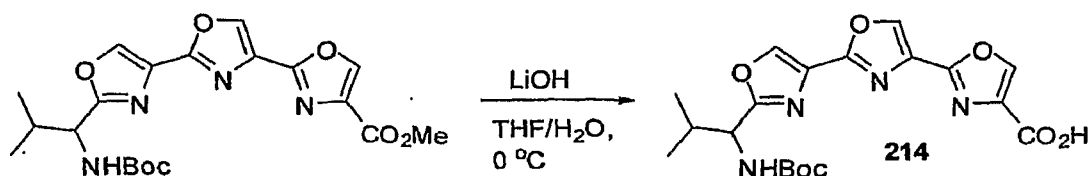
stirring for 1.5 h anhydrous K_2CO_3 was added and the mixture was then allowed to warm to room temperature. The mixture was poured into saturated $NaHCO_3$ and extracted several times with CH_2Cl_2 . The combined extracts were dried over Na_2SO_4 , filtered and concentrated to give crude oxazoline **212** as a red-yellow foam, 3.44 g (79%, crude); ^1H NMR ($CDCl_3$) δ 8.30 (s, 1H), 8.18 (s, 1H), 5.59 (m, 2H), 4.84 (m, 3H), 3.91 (s, 3H), 2.19 (m, 1H), 1.42 (s, 9H), 0.91 (d, 6H, $J=6.8$); ^{13}C -NMR δ 164.4, 162.1, 162.0, 160.3, 159.2, 154.3, 143.9, 140.7, 132.3, 128.7, 78.7, 69.7, 53.2, 51.2, 31.9, 27.2, 17.7, 16.9.

10 **l. Synthesis of Compound 213 (N-Boc Valine Teroxazole Ester)**



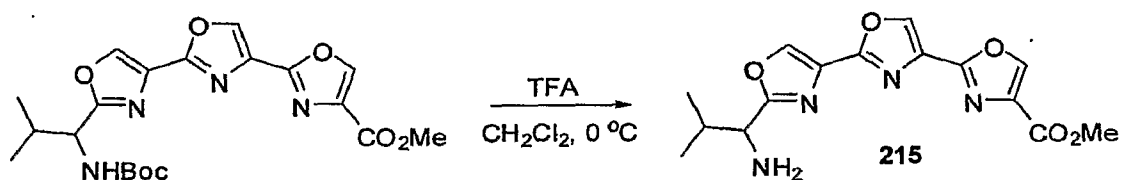
A solution of the crude oxazoline (3.44 g, 7.9 mmol) in dry CH_2Cl_2 (24 mL) was stirred under nitrogen at 0 °C as dry DBU (1.8 mL, 12.5 mmol) was added over 2 min followed by $BrCCl_3$ (1.2 mL, 12.5 mmol) which was then added over 5 min. The reaction was stirred at 0 °C for 5 h and was then poured into saturated NH_4Cl . The mixture was extracted with CH_2Cl_2 and the combined extracts were dried over Na_2SO_4 , filtered, and evaporated. The product was purified by flash chromatography on silica gel eluting with 2:3 EtOAc/hexane to give the oxazole as a white solid, 1.64 g (48%); mp 214-224 °C; ^1H NMR ($CDCl_3$) δ 8.58 (s, 1H), 8.48 (s, 1H), 8.46 (s, 1H), 5.53 (d, 1H, $J=9.0$), 4.95 (m, 1H), 4.08 (s, 3H), 2.35 (m, 1H), 1.56 (s, 9H), 1.07 (d, 6H, $J=6.6$); ^{13}C NMR δ 164.8, 160.4, 154.5, 143.1, 138.5, 133.4, 129.9, 128.7, 79.1, 53.4, 51.4, 31.9, 27.4, 17.8, 17.1.

25 **m. Synthesis of Compound 214 (N-Boc Valine Teroxazole Carboxylic Acid)**



A solution of the ester (0.82 g, 1.9 mmol) in 3:1 THF/H₂O (32 mL) was stirred at 0 °C as LiOH (126 mg, 3 mmol) was added in one portion. The reaction mixture was stirred for 10 h and was then evaporated under reduced pressure to remove THF. The aqueous solution was brought to pH 3 with 1N HCl and was then extracted with EtOAc. The organic phase was washed with brine and dried over Na₂SO₄, filtered and evaporated to give the carboxylic acid as a white solid, 0.77 g (98%); mp 225 °C (dec.); ¹H NMR (CDCl₃) δ 8.44 (s, 1H), 8.39 (s, 1H), 8.32 (s, 1H), 5.39 (d, 1H, J=8.4), 4.85 (m, 1H), 2.25 (m, 1H), 1.44 (s, 9H), 0.95 (d, 6H, J=6.0); ¹³C NMR δ 164.8, 160.4, 154.5, 143.1, 138.5, 133.4, 129.9, 128.7, 80.1, 51.4, 31.9, 27.4, 17.8, 17.1.

n. Synthesis of Compound 215 (Amino Valine Teroxazole Ester)

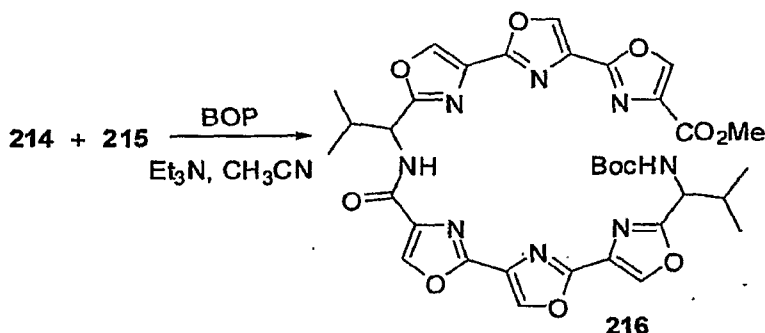


15

A solution of the N-Boc derivative (0.82 g, 1.9 mmol) in CH₂Cl₂ (10 mL) was cooled to 0 °C under protection from moisture by a drying tube. TFA (10 mL) was added and the solution was stirred for 1.5 h. Solvents were evaporated under reduced pressure and residual TFA was removed as an azeotrope with benzene. The residue was taken up in CH₂Cl₂ and washed with saturated NaHCO₃ and was then dried over Na₂SO₄, filtered, and evaporated to give the amine as a yellow-white solid, 0.62 g (98%); ¹H NMR (CDCl₃) δ 8.52 (s, 1H), 8.42 (s, 2H), 3.98 (s, 3H), 3.90 (m, 1H), 2.34 (m, 1H), 0.97 (d, 6H, J=6.6); ¹³C-NMR δ 163.5, 160.2, 155.1, 154.4, 154.1, 142.9, 138.6, 138.4, 133.4, 129.8, 128.8, 55.8, 51.9, 33.4, 18.9, 17.8.

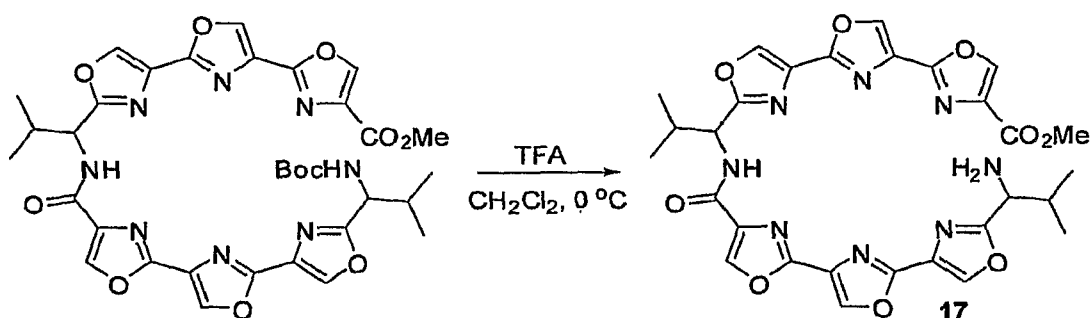
25

o. Synthesis of Compound 216 (N-Boc Divaline Hexaoxazole Ester)



Dry DMF (100 mL) was added to a mixture of amine **215** (0.61 g, 1.84 mmol) and acid **214** (0.77 g, 1.84 mmol) and stirred for 5 min. BOP (0.81 g, 1.84 mmol) and triethylamine (0.6 mL, 4.3 mmol) were added and the mixture was stirred at room temperature for 12 h. The mixture was then evaporated under reduced pressure and diluted with EtOAc and brine. The phases were separated and then aqueous phase was extracted with EtOAc. The combined organic phases were then washed successively with 1N HCl, saturated NaHCO₃, and brine and then dried over Na₂SO₄, filtered and evaporated to give the amide as a white solid, 0.72 g (53 %); mp 216-220 °C; ¹H NMR (CDCl₃) δ 8.39 (s, 1H), 8.30 (s, 1H), 8.29 (s, 4H), 7.55 (d, 1H, J=9.4), 5.32 (m, 2H), 4.76 (m, 2H), 3.88 (s, 3H), 2.28 (m, 2H), 1.38 (s, 9H), 0.99 (d, 6H, J=6.6), 0.89 (d, 6H, J=6.6); ¹³C-NMR δ 165.1, 164.8, 163.7, 160.4, 158.9, 155.1, 143.9, 143.0, 140.8, 138.5, 135.8, 133.4, 129.8, 128.9, 79.2, 69.7, 62.6, 53.4, 51.4, 31.9, 27.4, 18.0, 17.8, 17.5, 17.1.

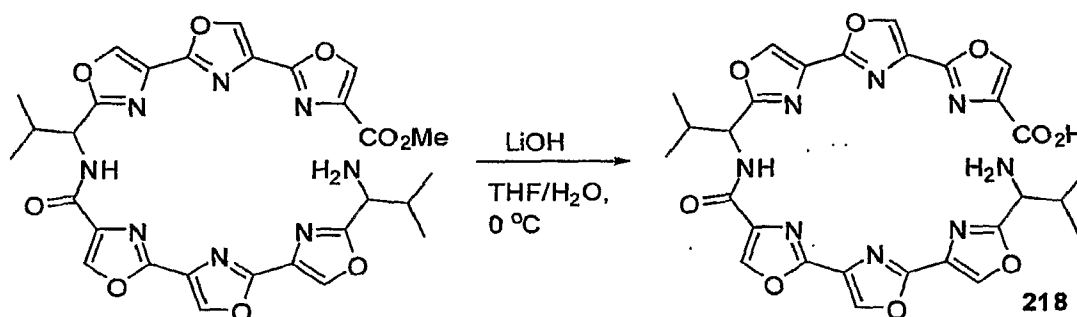
p. Synthesis of Compound 217 (Amino Divaline Hexaoxazole Ester)



A solution of the N-Boc derivative (0.715 g, 0.97 mmol) in CH₂Cl₂ (10 mL) was cooled to 0 °C under protection from moisture by a drying tube. TFA (10 mL) was added and the solution was stirred for 1.5 h. Solvents were evaporated under

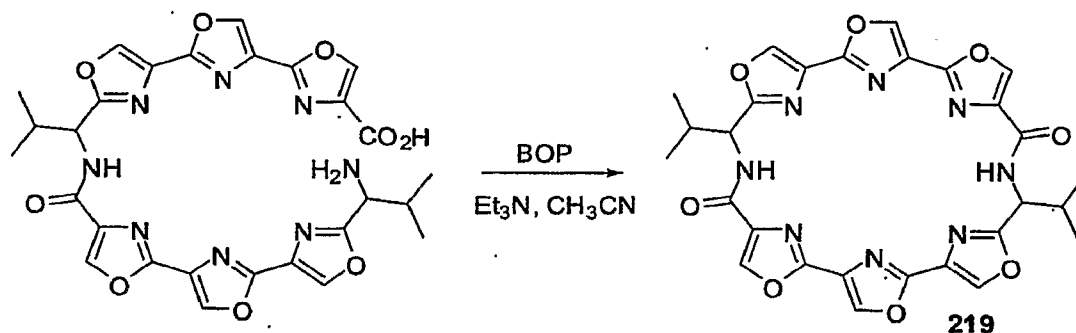
reduced pressure and residual TFA was removed as an azeotrope with benzene. The residue was taken up in CH_2Cl_2 and washed with saturated NaHCO_3 and was then dried over Na_2SO_4 , filtered, and evaporated to give the amine as a yellow-white solid, 0.55 g (90%); mp 267-268 °C; ^1H NMR (CDCl_3) δ 8.39 (s, 2H), 8.33 (s, 1H), 8.32 (s, 1H), 8.29 (s, 2H), 7.61 (d, 1H, $J=9.6$), 5.29 (m, 1H), 4.59 (m, 1H), 3.89 (s, 3H), 2.21 (m, 2H), 1.03 (d, 6H, $J=7.0$), 0.95 (d, 6H, $J=7.0$); ^{13}C -NMR δ 167.4, 163.8, 160.4, 159.0, 155.5, 154.5, 153.8, 143.6, 143.1, 140.8, 138.5, 138.3, 135.9, 133.5, 129.9, 128.9, 128.5, 54.9, 51.5, 32.5, 31.8, 18.0, 17.6, 17.1.

10 **q. Synthesis of Compound 218 (Amino Divaline Hexaoxazole Carboxylic Acid)**



A solution of the ester (0.55 g, 0.87 mmol) in 3:1 $\text{THF}/\text{H}_2\text{O}$ (32 mL) was stirred at $0\text{ }^\circ\text{C}$ as LiOH (126 mg, 3 mmol) was added in one portion. The reaction mixture was stirred for 10 h and was then evaporated under reduced pressure to remove THF . The aqueous solution was brought to pH 3 with 1N HCl and was then extracted with EtOAc . The organic phase was washed with brine and dried over Na_2SO_4 , filtered and evaporated to give the carboxylic acid as a pale yellow solid, 0.51 g (95%); mp 252-255 °C (dec.); ^1H NMR (CD_3OD) δ 9.01 (s, 1H), 8.98 (s, 1H), 8.92 (s, 1H), 8.90 (s, 1H), 8.82 (s, 1H), 8.78 (s, 1H), 4.87 (m, 2H), 2.66 (m, 2H), 1.36 (d, 6H, $J=7.0$), 1.28 (d, 6H, $J=7.0$); ^{13}C NMR δ 165.6, 162.3, 160.9, 160.8, 156.1, 144.7, 142.3, 141.7, 140.6, 140.4, 136.4, 134.3, 130.4, 130.3, 129.7, 129.3, 124.7, 53.9, 53.5, 53.0, 31.7, 29.5, 18.2, 17.7, 17.5, 16.7.

r. Synthesis of Compound 219



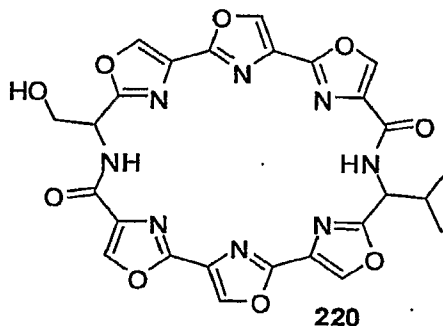
Amino acid **218** (0.51 g, 0.82 mmol) was dissolved in dry DMF (130 mL, 0.006 M solution) and stirred for 5 min. BOP (0.365 g, 0.82 mmol) and

5 triethylamine (0.38 mL, 2.72 mmol) was added and the mixture was stirred at room temperature for 12 h. The solvent was evaporated under reduced pressure and the residue was diluted with EtOAc (75 mL) and brine (20 mL). The phases were separated and the aqueous was extracted with EtOAc. The combined organic layers were washed successively with 1N HCl, saturated NaHCO₃, and

10 then brine. The solution was dried over Na₂SO₄, filtered, and evaporated to give compound **219** as a white solid, 0.22 g (45%); mp 246 °C (dec.); ¹H NMR (CDCl₃) δ 8.51 (d, 2H, J=8), 8.20 (m, 6H), 5.30 (dd, 2H, J=8,5), 2.40 (m, 2H), 1.04 (d, 6H, J=7), 0.98 (d, 6H, J=7); ¹³C NMR δ 163.7, 159.1, 155.3, 153.8, 140.0, 138.2, 137.6, 136.2, 130.2, 128.8, 52.3, 33.2, 17.7, 17.5; HRMS (FAB)

15 Calcd for C₂₈H₂₄N₈O₈(H⁺): 601.1795; Found: 601.1808.

Example 7 Synthesis of Compound **220**



20 Using procedures similar to those described herein above, compound **220** was prepared: Off-white solid; mp. 108 – 110 °C; ¹H NMR (CDCl₃) δ 8.47 (t, 1H,

$J=7.9$), 8.21 (s, 3H), 8.17 (s, 3H), 5.28 (m, 2H), 4.23 (m, 1H), 3.99 (m, 1H), 2.34 (m, 1H), 0.99 (m, 27H); ^{13}C NMR δ 163.5, 163.3, 159.0, 155.3, 153.8, 140.0, 138.3, 138.2, 137.6, 136.1, 135.9, 130.1, 128.9, 128.7, 64.1, 52.2, 51.6, 49.3, 33.0, 17.6, 17.3, 16.9, 10.9; HRMS (FAB) calcd. for $\text{C}_{35}\text{H}_{40}\text{N}_8\text{O}_9\text{Si}(\text{Li})$: 751.2848; Found: 751.2852.

Example 8. The following illustrate representative pharmaceutical dosage forms, containing a compound of formula I ('Compound X'), for therapeutic or prophylactic use in humans.

10

<u>(i) Tablet 1</u>		<u>mg/tablet</u>
Compound X=		100.0
Lactose		77.5
Povidone		15.0
15 Croscarmellose sodium		12.0
Microcrystalline cellulose		92.5
Magnesium stearate		<u>3.0</u>
		300.0

20

<u>(ii) Tablet 2</u>		<u>mg/tablet</u>
Compound X=		20.0
Microcrystalline cellulose		410.0
Starch		50.0
Sodium starch glycolate		15.0
25 Magnesium stearate		<u>5.0</u>
		500.0

30

<u>(iii) Capsule</u>		<u>mg/capsule</u>
Compound X=		10.0
30 Colloidal silicon dioxide		1.5
Lactose		465.5
Pregelatinized starch		120.0
Magnesium stearate		<u>3.0</u>
		600.0

35

<u>(iv) Injection 1 (1 mg/ml)</u>		<u>mg/ml</u>
Compound X= (free acid form)		1.0
Dibasic sodium phosphate		12.0
Monobasic sodium phosphate		0.7
40 Sodium chloride		4.5
1.0 N Sodium hydroxide solution		
(pH adjustment to 7.0-7.5)		q.s.

	Water for injection	q.s. ad 1 mL
	(v) <u>Injection 2 (10 mg/ml)</u>	<u>mg/ml</u>
	Compound X= (free acid form)	10.0
5	Monobasic sodium phosphate	0.3
	Dibasic sodium phosphate	1.1
	Polyethylene glycol 400	200.0
	01 N Sodium hydroxide solution (pH adjustment to 7.0-7.5)	q.s.
10	Water for injection	q.s. ad 1 mL
	(vi) <u>Aerosol</u>	<u>mg/can</u>
	Compound X=	20.0
	Oleic acid	10.0
15	Trichloromonofluoromethane	5,000.0
	Dichlorodifluoromethane	10,000.0
	Dichlorotetrafluoroethane	5,000.0

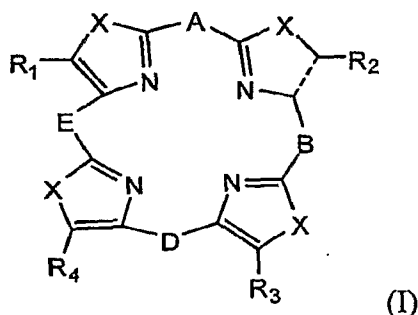
The above formulations may be obtained by conventional procedures well
 20 known in the pharmaceutical art.

All publications, patents, and patent documents are incorporated by
 reference herein, as though individually incorporated by reference. The
 invention has been described with reference to various specific and preferred
 25 embodiments and techniques. However, it should be understood that many
 variations and modifications may be made while remaining within the spirit and
 scope of the invention.

CLAIMS

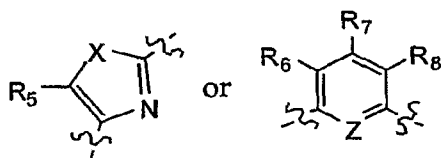
What is claimed is:

1. A compound of formula I:



wherein:

each A, B, D, and E is independently $-C(=O)NH-CH(R_a)-$, $-C(=O)-NH-C(=O)-$, or a group of the formula:



each R_1 , R_2 , R_3 , R_4 , and R_5 is independently H, (C_1-C_6) alkyl, or (C_1-C_6) alkoxy, wherein each (C_1-C_6) alkyl and (C_1-C_6) alkoxy is optionally substituted with OH, (C_1-C_6) alkoxy, (C_1-C_6) alkylthio, aryl, NR_cR_d , or $-C(=O)NR_cR_d$;

each R_6 , R_7 , and R_8 is independently H; or each R_6 and R_7 together with the atoms to which they are attached form a benzo ring and R_8 is H; or R_6 is H and R_7 and R_8 together with the atoms to which they are attached form a benzo ring;

each X is independently NH, S, or O;

each Z is independently N or CH;

the bond represented by ----- is a single or a double bond;

each R_a is independently H, aryl, or (C_1-C_6) alkyl that is optionally substituted with OH, (C_1-C_6) alkoxy, (C_1-C_6) alkylthio, aryl, NR_eR_f , or $-C(=O)NR_eR_f$;

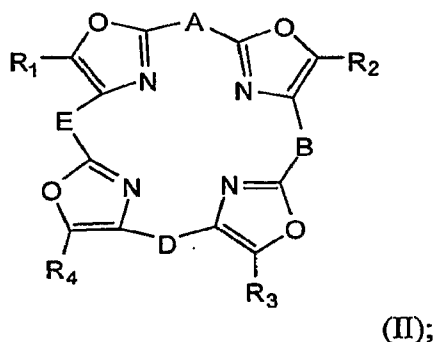
each R_c and R_d is independently H or (C_1-C_6) alkyl; or R_c and R_d together with the nitrogen to which they are attached form a pyrrolidino, piperidino, piperazino, morpholino, thiomorpholino, or azepino ring; and

each R_e and R_f is independently H or (C_1-C_6) alkyl; or R_e and R_f together with the nitrogen to which they are attached form a pyrrolidino, piperidino, piperazino, morpholino, thiomorpholino, or azepino ring;

or a salt thereof;

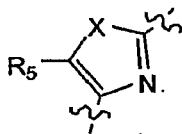
provided the compound of formula I is not telomestatin or dehydrotelomestatin.

2. The compound of claim 1 which is a compound of formula (II):



or a pharmaceutically acceptable salt thereof.

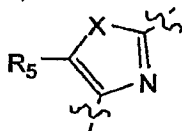
3. The compound of claim 1 wherein A and D are each independently a group of the following formula:



4. The compound of claim 3 wherein each X is O; and the bond represented by ----- is a double bond.
5. The compound of claim 4 wherein B and E are each independently $-C(=O)NH-CH(R_a)-$.

6. The compound of claim 5 wherein each R_a is H, methyl, isopropyl, 2-methylpropyl, benzyl, 3-(*N,N*-dimethylamino)propyl, or 4-(*N,N*-dimethylamino)butyl.

7. The compound of claim 1 wherein A, B, and D are each independently a group of the following formula:

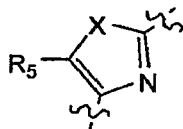


8. The compound of claim 7 wherein each X is O; and the bond represented by ----- is a double bond.

9. The compound of claim 8 wherein E is $-C(=O)NH-CH(R_a)-$.

10. The compound of claim 9 wherein each R_a is H, methyl, isopropyl, 2-methylpropyl, benzyl, 3-(*N,N*-dimethylamino)propyl, or 4-(*N,N*-dimethylamino)butyl.

11. The compound of claim 1 wherein A, B, D, and E are each independently a group of the following formula:



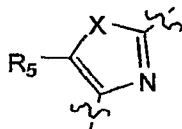
12. The compound of claim 11 wherein each X is O; and the bond represented by ----- is a single bond.

13. The compound of claim 11 wherein each X is O; and the bond represented by ----- is a double bond.

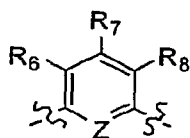
14. The compound of any one of claims 11-13 wherein each R_1 , R_2 , R_3 , R_4 , and R_5 is independently H or (C₁-C₆)alkyl that is substituted with OH, (C₁-C₆)alkoxy, (C₁-C₆)alkylthio, aryl, NR_cR_d , or $-C(=O)NR_cR_d$.

15. The compound of any one of claims 11-13 wherein each R_1 , R_2 , R_3 , R_4 , and R_5 is independently H or (C₂-C₆)alkyl that is optionally substituted with OH, (C₁-C₆)alkoxy, (C₁-C₆)alkylthio, aryl, NR_cR_d , or $-C(=O)NR_cR_d$.

16. The compound of claim 1 wherein each B and E is independently a group of the formula:



and each A and D is independently group of the formula:



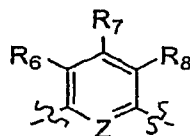
17. The compound of claim 16 wherein the X in formula B is NH, S, or O; the X in formula E is NH, S, or O; each other X in formula I is O; and the bond represented by ----- is a double bond.

18. The compound of claim 16 wherein each X is O; and the bond represented by ----- is a double bond.

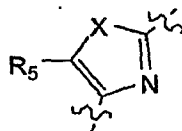
19. The compound of any one of claims 16-18 wherein each Z is N.

20. The compound of any one of claims 16-18 wherein each Z is CH.

21. The compound of claim 1 wherein each A, B, D, and E is independently a group of the formula:



22. The compound of claim 21 wherein the bond represented by ----- is a double bond.
23. The compound of claim 22 wherein each X is O.
24. The compound of any one of claims 21-23 wherein each Z is N.
25. The compound of any one of claims 21-23 wherein each Z is CH.
26. The compound of any one of claims 7-10 wherein R₅ in B is (C₁-C₆)alkoxy that is optionally substituted with OH, (C₁-C₆)alkoxy, (C₁-C₆)alkylthio, aryl, NR_cR_d, or -C(=O)NR_cR_d.
27. The compound of any one of claims 11-15 wherein R₅ in A is (C₁-C₆)alkoxy that is optionally substituted with OH, (C₁-C₆)alkoxy, (C₁-C₆)alkylthio, aryl, NR_cR_d, or -C(=O)NR_cR_d; and R₅ in D is (C₁-C₆)alkoxy that is optionally substituted with OH, (C₁-C₆)alkoxy, (C₁-C₆)alkylthio, aryl, NR_cR_d, or -C(=O)NR_cR_d.
28. The compound of claim 1 wherein A and D are each independently a group of the following formula:



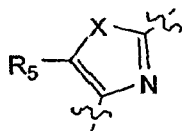
B is -C(=O)-NH-C(=O)-; and

E is -C(=O)NH-CH(R_a)-.

29. The compound of claim 28 wherein each X is O; and the bond represented by ----- is a double bond.

30. The compound of claim 29 wherein each R_a is H, methyl, isopropyl, 2-methylpropyl, benzyl, 3-(*N,N*-dimethylamino)propyl, or 4-(*N,N*-dimethylamino)butyl.

31. The compound of claim 1 wherein A and D are each independently a group of the following formula:



; and

B and E are each independently $-C(=O)NH-CH(R_a)-$.

32. The compound of claim 31 wherein each X is O; and the bond represented by ----- is a double bond.

33. The compound of claim 31 or 32 wherein each R_a is H, hydroxymethyl, phenyl, or (C_1-C_6)alkyl that is optionally substituted with NR_eR_f .

34. The compound of claim 31 or 32 wherein each R_a is H, methyl, isopropyl, 2-methylpropyl, benzyl, 3-(*N,N*-dimethylamino)propyl, or 4-(*N,N*-dimethylamino)butyl.

35. A pharmaceutical composition comprising a compound of formula I as described in any one of claims 1-34; or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

36. A therapeutic method for treating cancer comprising administering to a mammal in need of such therapy, an effective amount of a compound of

formula I as described in any one of claims 1-34, or a pharmaceutically acceptable salt thereof.

37. A method to stabilize G-quadruplex DNA comprising contacting the G-quadruplex DNA with a compound of formula I as described in any one of claims 1-34, or a salt thereof.

38. A compound as described in any one of claims 1-34, or a pharmaceutically acceptable salt thereof for use in medical therapy.

39. The use of a compound as described in any one of claims 1-34, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament useful for the treatment of cancer in a mammal.