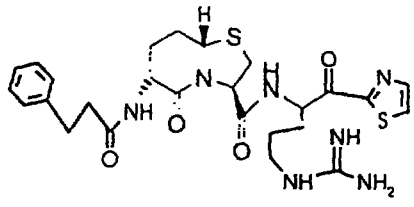
0315 5-Oxo-6-(3-phenyl-propionyl amino)-hexahydro thiazolo[3,2-a]pyridine-3-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



More preferred compounds according to formula (VII) include:

0085 6S-cyclohexylmethylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido(propylcarbo methoxyketoarginine);

0090 6S-cyclohexylmethylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido((propylketo)Arg-Phe-Arg-NH_2);

0095 6S-benzylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxamido((propanoic acid) ketoarginine);

0105 6S-cyclohexylmethylhexahydro-5-oxo-5H-thiazolo [3,2-a]pyridine-3R-carboxamido (α-benzothiozolo keto arginine);

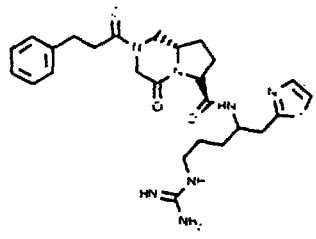
0210 6-Benzyl-5-oxo-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide;

0220 6-Benzyl-8a-methyl-5-oxo-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide; ~~0240 8a-Methyl-5-oxo-6-(2-trifluoromethyl-quinolin-6-ylmethyl)-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-amide;~~

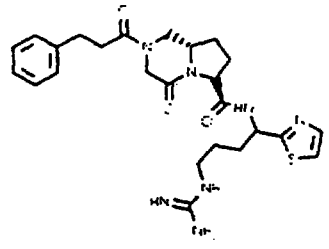
0245 6-Benzyl-5-oxo-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [4-guanidino-1-(thiazole-2-~~carbonyl)butyl]-amide;~~

0245 6-Benzyl-5-oxo-hexahydro-thiazolo[3,2-a]pyridine-3-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)butyl]-amide;

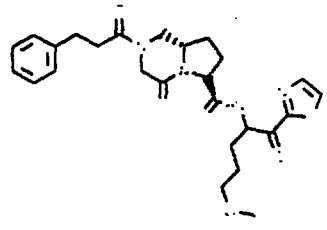
0830 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid (4-guanidino-1-thiazol-2-ylmethyl-butyl)-amide



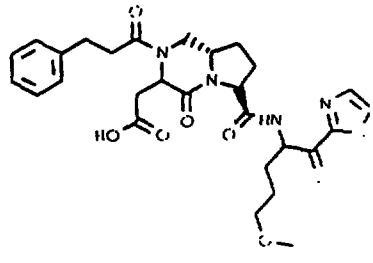
0835 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-thiazol-2-yl-butyl)-amide



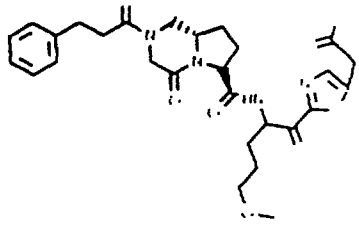
0840 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-methoxy-1-(thiazole-2-carbonyl)-butyl]-amide



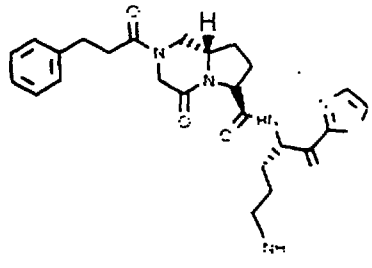
0845 [6-[4-Methoxy-1-(thiazole-2-carbonyl)-butylcarbamoyl]-4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazin-3-yl]-acetic acid



0850 [2-(5-Methoxy-2-([4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carbonyl]-amino)-pentanoyl)-thiazol-5-yl]-acetic acid



0855 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-amino-1-(thiazole-2-carbonyl)-butyl]-amide



0625 2-[2-(2-Methyl-benzylidene)-but-3-enoyl]-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide

0630 2-[2-(2-Methyl-benzylidene)-but-3-enoyl]-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(1-carbamimidoyl-piperidin-4-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide

0635 2-(2-Benzylidene-pent-3-enoyl)-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid (3-guanidino-propyl)-amide

~~0625 2-[2-(2-Methyl-benzylidene)-but-3-enoyl]-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide~~

~~0630 2-[2-(2-Methyl-benzylidene)-but-3-enoyl]-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [1-(1-carbamimidoyl-piperidin-4-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-amide~~

~~0635 2-(2-Benzylidene-pent-3-enoyl)-4-oxo-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid (3-guanidino-propyl)-amide~~

0645 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-imidazol-1-yl-1-(thiazole-2-carbonyl)-butyl]-amide

0840 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-methoxy-1-(thiazole-2-carbonyl)-butyl]-amide

0845 [6-[4-Methoxy-1-(thiazole-2-carbonyl)-butylcarbamoyl]-4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazin-3-yl]-acetic acid

0850 [2-(5-Methoxy-2-([4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carbonyl]-amino)-pentanoyl)-thiazol-5-yl]-acetic acid

0855 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-amino-1-(thiazole-2-carbonyl)-butyl]-amide

0860 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [5-amino-1-(thiazole-2-carbonyl)-pentyl]-amide

0865 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [5-guanidino-1-(thiazole-2-carbonyl)-pentyl]-amide

Most preferred compounds according to formula VIII include:

0345 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(5-methyl-thiazole-2-carbonyl)-butyl]-amide; and~~0340 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-~~

~~0840 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-methoxy-1-(thiazole-2-carbonyl)-butyl]-amide~~

0845 [6-[4-Methoxy-1-(thiazole-2-carbonyl)-butylcarbamoyl]-4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazin-3-yl]-acetic acid

0850 [2-(5-Methoxy-2-([4-oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carbonyl]-amino)-pentanoyl)-thiazol-5-yl]-acetic acid

0855 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-amino-1-(thiazole-2-carbonyl)-butyl]-amide

0860 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [5-amino-1-(thiazole-2-carbonyl)-pentyl]-amide

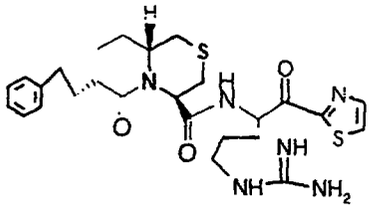
0865 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [5-guanidino-1-(thiazole-2-carbonyl)-pentyl]-amide

Most preferred compounds according to formula VIII include:

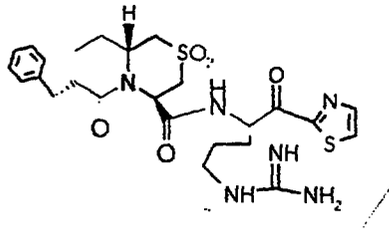
0345 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(5-methyl-~~thiazole-2-carbonyl)-butyl]-amide; and~~

0340 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-

0940 6-Oxo-7-phenethyl-octahydro-pyrido[2,1-c][1,4]thiazine-4-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



0950 7-Benzyl-2,2,6-trioxo-octahydro-21>6_pyrido[2,1-c][1,4]thiazine-4-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide

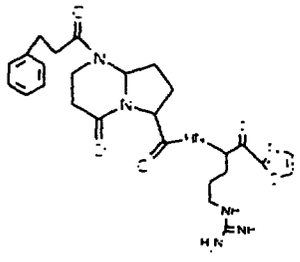


More preferred compounds according to formula X include:

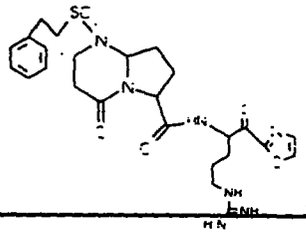
925 7-Benzyl-6-oxo-octahydro-pyrido[2,1-c][1,4]thiazine-4-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)butyl]-amide; and~~940 6-Oxo-7-phenethyl-octahydro-pyrido[2,1-c][1,4]thiazine-4-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide.~~

Preferred compounds according to formula III include:

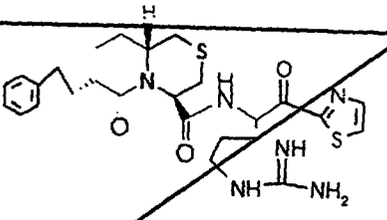
0960 4-oxo-1-(3-phenyl-propionyl)-octahydropyrrolo[1,2]pyrimidine-6-carboxylic acid[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



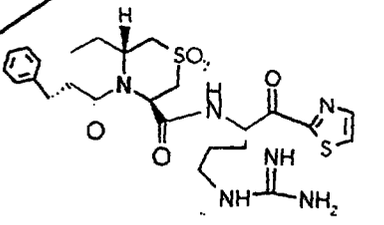
0965 4-oxo-1-(phenethylsulfonyl)-octahydropyrrolo[1,2]pyrimidine-6-carboxylic acid[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



~~0940 6-Oxo-7-phenethyl-octahydro-pyrido[2,1-c][1,4]thiazine-4-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide~~



~~0950 7-Benzyl-2,2,6-trioxo-octahydro-21>6_pyrido[2,1-c][1,4]thiazine-4-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide~~



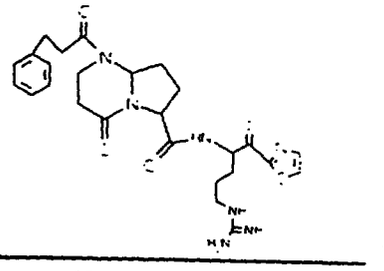
More preferred compounds according to formula X include:

925 7-Benzyl-6-oxo-octahydro-pyrido[2,1-c][1,4]thiazine-4-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)butyl]-amide; and

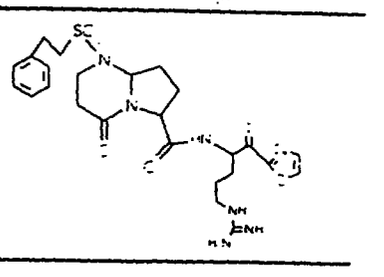
940 6-Oxo-7-phenethyl-octahydro-pyrido[2,1-c][1,4]thiazine-4-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide.

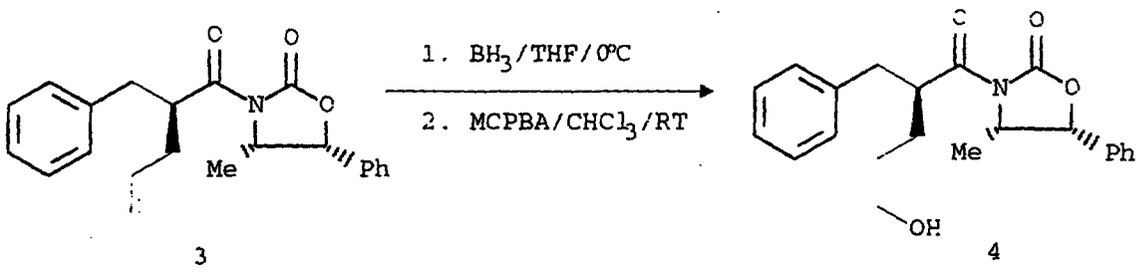
Preferred compounds according to formula III include:

0960 4-oxo-1-(3-phenyl-propionyl)-octahydropyrrolo[1,2]pyrimidine-6-carboxylic acid[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide



0965 4-oxo-1-(phenethylsulfonyl)-octahydropyrrolo[1,2]pyrimidine-6-carboxylic acid[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide





3 4

A sample of the allyl compound, **(3)**, (4.75 g, 13.6 mmol) in THF (100 mL) was treated with 13.6 mL (1.0 equiv., 13.6 mmol) of a 1.0 M solution of borane-tetrahydrofuran complex at 0°C and stirred for 2h. The solvent was evaporated and chloroform (100 mL) added via syringe. Oxidation of the organoborane was achieved by the addition of 4.7 g (2.0 equiv., 27.2 mmol) of 3-chloroperoxybenzoic acid at 0°C, with warming to ambient temperature and stirring for an additional hour. The organic phase was washed with 5% Na_2CO_3, , ddH_2O, and dried over sodium sulfate. Due to the instability of the alcohol, a quick column was performed to remove the extreme polar and nonpolar material which originated from the 3-chloroperoxybenzoic acid. The alcohol **(4)** was obtained in a yield of 65%.

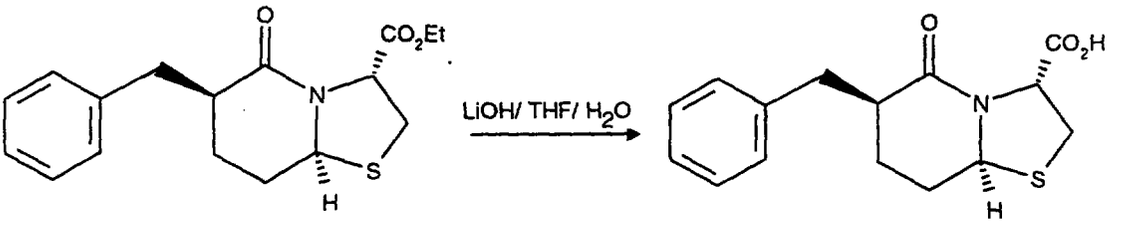
$[\alpha]_D$ 39.3 (c=1.038, CH_2Cl_2).

The Applicant submitted that this is an obvious error ⇒ omission of hyphen

^{1}HNMR ($CDCl_3$) δ 1.07 (d, 3H, CH_3-CH, J=6.5 Hz), 1.81-1.93 (m, 3H, CH_2-CH-H), 2.10-2.19 (m, 1H, CH_2-CH-H), 3.10-3.17 (m, 2H, Ph-CH_2), ~~3.873.90~~ 3.87-3.90 (m, 2H, CH_2OH), 4.43-4.49 (m, 1H, CH-CO), 4.70-4.75 (m, 1H, CH_3-CH), 5.36 (d, 1H, Ph-CH. J=7.1 Hz), 7.41-7.63 (m, 10H, ArH);

The mixture was quenched with excess methanol, then filtered on a short silica gel column (washing through with excess 10% methanol in ethylacetate. Evaporation gave 784 mg of crude material that was purified using 2:1 hexane:EtOAc on a silica gel column affording 258mg (0.81mmol being a 50% yield) of pure compound **(7)**, a 6S-benzylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-ethyl ester as a white/yellow solid.

^{1}H NMR ~~(CDCl3)~~ (CDCl$_3$) Applicant submitted that ③ → sld use in subscript → obvious d 1.28-1.31 (m, 3H), 1.72-1.81 (m, 3H), 2.10-2.13 (m, 1H), 2.66 (dd, 1H, J= 11.5 and 6.0 Hz), 3.29-3.34 (m, 2H), 4.19-4.29 (m, 2H), 4.88 (dd, 1H, J= 9.0 and 5.0 Hz), 5.22 (dd, 1H, J= 8.0 and 6.0 Hz), 7.18-7.23 (m, 3H), 7.28-7.31 (m, 2H).



7 **8**

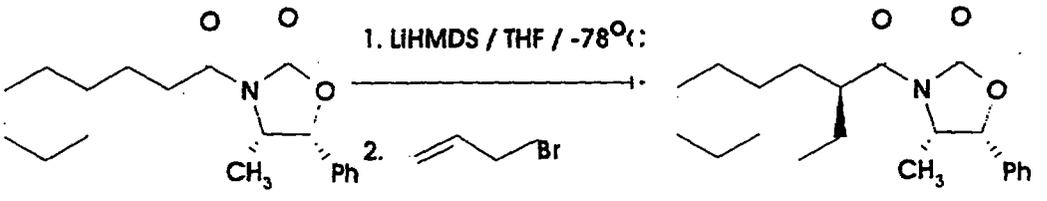
LiOH.H2O (48mg, 1.12mmol) in 10mL of water was added to starting material **(7)** (240mg, 0.76mmol) dissolved in 10mL of dioxane. After 1 hour, TLC in 1:1 Hexane:EtOAc showed no starting material. The reaction was quenched with 10% citric acid, then extracted twice with dichloromethane. Drying and evaporating the combined organic layers gave 354mg of crude product. This was redissolved in dichloromethane, then precipitated by adding excess hexane. The product was filtered to give 200mg (0.68mmol being a 90% yield)) of an off-white solid, **(8)**, also known as 6S-benzylhexahydro-5-oxo-5H-thiazolo[3,2-a]pyridine-3R-carboxylic acid.

^{1}H NMR (CD3OD) d 1.71-1.82 (m, 3H), 2.12-2.17 (m, 1H), 2.67 (dd, 1H, J= 14 and 11 Hz), 2.77-2.81 (m, 1H), 3.30-3.40

from ether and hexane to give the title compound in 78% yield.

[α]D=-20.1(c=1,EtOH); MP/BP mp=90.5-91.5oC

1H NMR (~~CDCl3~~) d 0.86-1.10 (m, 5H), 1.18-1.30 (m, 4H), 1.54-1.75 (m, 7H), 2.86-2.97 (m, 2H), 4.70-4.76 (m, 1H), 5.65 (d, 1H, J= 7.2 Hz), 7.28-7.42 (m, 5H).

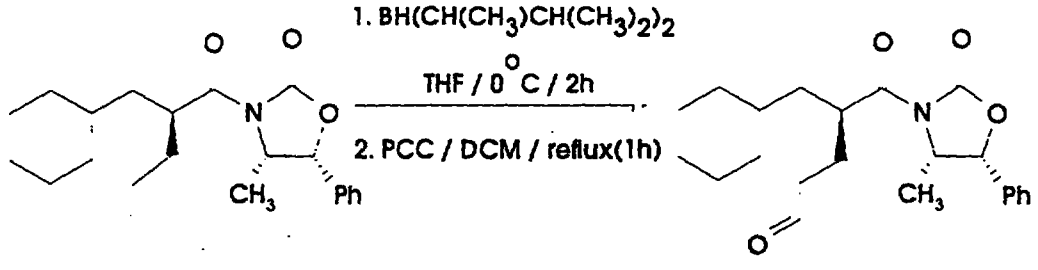


12 **13**

The starting material **(12)** (9.13g, 29 mmol, 1eq) was dissolved in dry THF and cooled to -78 C, after which LiHMDS (31.9 mL, 31.9 mmol, 1.1 eq) was added dropwise over 40 mins. Then, 30 minutes later, allyl bromide (7.5 mL, 86.9 mmol, 3 eq) was added slowly over 10 mins. The mixture was left to warm overnight. Work-up included quenching with sat. ammonium chloride, extraction with ethyl acetate, washing with 10% sodium thiosulphate, decolourising with charcoal, drying over sodium sulphate and concentration *in vacuo*. The product was obtained as a yellow oil **(13)** in 96% yield.

[α]D=+9.5(c=1.0,EtOH)

H NMR (~~CDCl3~~) d 0.92-1.10 (m, 5H), 1.10-1.39 (m, 5H), 1.63-1.75 (m, 6H), 2.27-2.42 (m, 2H), 4.01-4.14 (m, 1H), 4.76-4.85 (m, 1H), 5.00-5.07 (m, 2H), 5.65 (d, 1H, J= 7 Hz), 5.64-5.88 (m, 1H0, 7.27-7.46 (m, 5H).

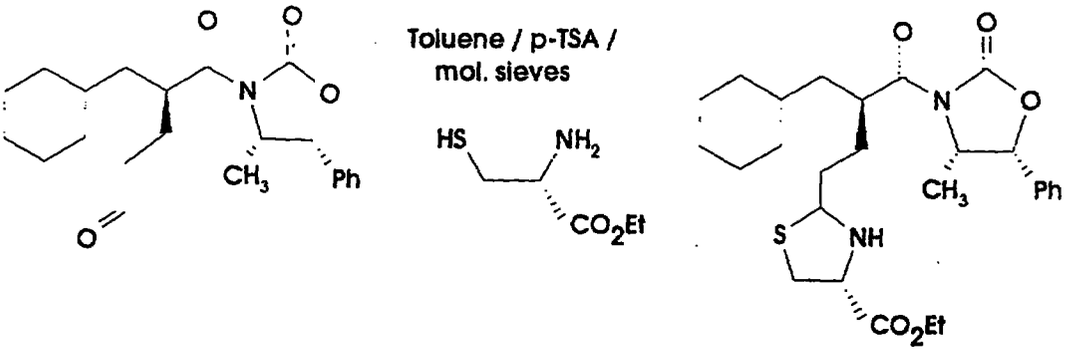


13 14

2-methyl-2-butene was added dropwise to borane dimethylsulphide complex at -12°C. The reaction was maintained at this temperature for 15 minutes and then it was warmed to 0°C, after which it was stirred for 2 hours. The disiamyl borane was then added to a mixture of the starting material **13** in THF using a double-ended needle at 0°C. The mixture was then stirred for 2 hours after which the solvents were removed and the residue dissolved in dichloromethane. It was carefully added to a suspension of pyridinium chlorochromate in dichloromethane contained in a flask equipped with a reflux condenser. After the initial exothermic reaction had subsided, the mixture was refluxed at 50°C for 1 hour. The dark brown liquid was dissolved in ethyl acetate and filtered through Florisil. The black residue of PCC was extracted with ethyl acetate and also filtered through the same Florisil pad. Concentration of the filtrates resulted in a 78% yield of a yellow gummy product **(14)**.

[α]D=-17.8(c=1.245,EtOH)

^{1}H NMR (CDCl$_3$) ~~(CDCl3)~~ d 0.89-1.18 (m, 5H), 1.20-1.47 (m, 8H), 1.60-1.74 (m, 6H), 1.83-2.00 (m, 1H), 2.48-2.53 (m, 2H), 3.90-4.10 (m, (1H) ~~1H0~~, 4.12-4.16 (m, 1H), 4.76-4.80 (m, 1H0, 5.67 (d, 1H, J= 7Hz), 7.27-7.46 (m, 5H), 9.77 (s, 1H).

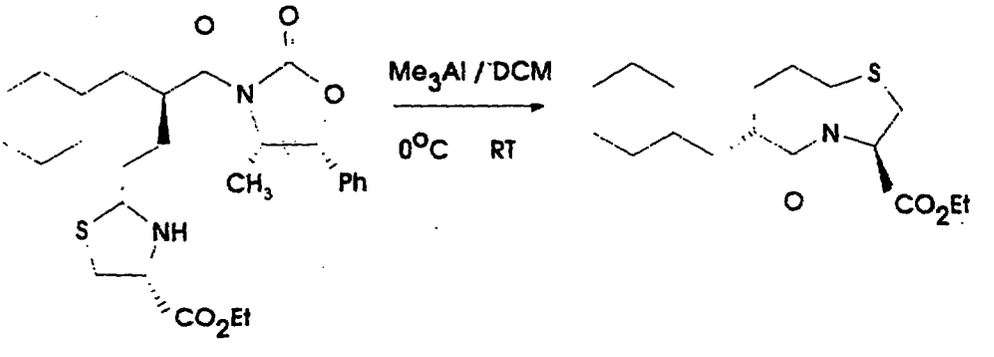


14 15

The resulting aldehyde **(14)** (7.7g crude, 20.8 mmol 1 equiv.) was dissolved in 75 mL of toluene. To the solution was added a catalytic amount of p-toluenesulphonic acid (50 mg), 10 g of 4Å molecular sieves, and L-cysteine ethyl ester (3.87 g, 20.8 mmol, 1 equiv.). The mixture was stirred overnight, filtered and concentrated. The residue was then purified by silica gel chromatography (6:1 hexane:ethyl acetate) afforded 6.36 g of the product **(15)** in 61% yield.

[α]D=-48.3(c=1.095,EtOH)

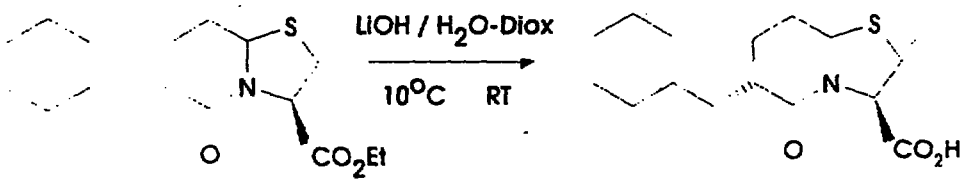
^{1}H NMR (CDCl$_3$) ~~(CDCl3)~~ d 0.84-0.98 (m, 4H), 1.11-1.38 (m, 7H), 1.50-1.90 (m, 10H), 2.80-2.99 (m, 1H), 3.24-3.34 (m, 1H), 3.77-4.29 (m, 4H), 4.46-4.81 (m, 2H), 5.66 (d, 1H, J= 7Hz), 7.27-7.46 (m, 5H).



15 16

The starting material **(15)** (1.97 g, 3.9 mmol, 1 equiv.) was dissolved in 20 mL of dry dichloromethane and cooled to 0 C. Trimethylaluminum (5.9 mL, 11.8 mmol, 3 equiv.), was added dropwise and the mixture was left stirring overnight. After complete reaction as evidenced by HPLC, methanol was added until a yellow solid mass was formed. Dichloromethane was added to dissolve the solid and the whole mixture was stirred for 15-30 minutes and then filtered. The residue after concentration *in vacuo* was run through a quick column (6:1 hexane:ethyl acetate), to remove auxilary and as many of the polar decomposition products as possible, affording in a 50% yield of a yellow oil **(16)**.

^{1}H NMR ~~(cdcl3)~~ ($CDCl_3$) d 0.83-0.98 (m, 2H), 1.09-1.38 (m, 10H), 1.57-2.00 (m, 11H), 2.12-2.18 (m, 1H), 2.49-2.54 (m, 1H), 3.10 (dd, 1H, J= 11 and 6 Hz), 3.27 (dd, 1H, J= 11.5 and 8.0 Hz), 4.11-4.25 (m, 2H), 4.88 (dd, 1H, J= 11.0 and 5.o Hz), 5.14 (dd, 1H, J= 10 and 6 Hz).

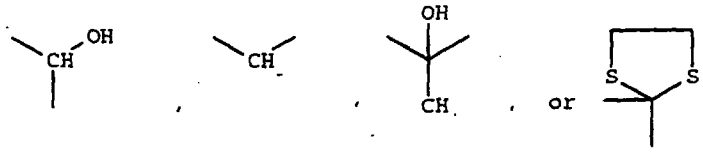


16 **17**

The starting material **(16)** (0.95 g, 2.9 mmol, 1 equiv.) was dissolved in 10 mL of dioxane. The solution was cooled to 10 C, and to it was added LiOH·H$_2$O (0.123 g, 2.9 mmol, 1 eq.) dissolved in 10 mL of water. The bath was removed and the mixture was stirred at room temperature for 1 hour. TLC showed complete reaction and the solvent was evaporated under vacuum. The remaining aqueous layer was washed with ether (2X), acidified with 10% citric acid, and extracted with dichloromethane (3X). The

(21) (1.03 g, 96%) which was used further without purification.

^{1}H NMR (~~CDCl3~~ $CDCl_3$) d 0.07-0.97 (m, 1H), 1.15-1.41 (m, 7H), 1.62-1.91 (m, 10H), 2.10-2.16 (m, 1H), 2.43-2.48 (m, 1H), 2.74-2.80 (m, 1H), 3.01-3.07 (m, 1H), 3.87-3.94 (m, 1H), 4.11-4.19 (m, 2H), 4.60-4.66 (m, 1H), 4.74-4.86 (m, 2H), 5.09-5.24 (m, 4H), 7.30-7.39 (m, 10H), 7.95 (d, 1H, J= 8 Hz), 9.4 (br s, 1H), 9.56 (br s, 1H).

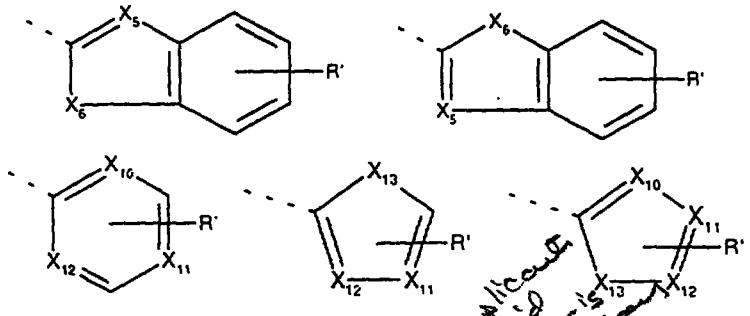


J is C_{1-3} alkylene optionally substituted with OH, NH_2 and C_{1-3} alkyl and optionally interrupted by a heteroatom selected from O, S and N;

n is 0 or 1; and

T is H, OH, amino, a peptide chain, C_{1-10} alkyl, C_{1-3} alkoxy, C_{7-9} aralkyl, or heterocycle optionally substituted.

3. A compound according to claim 2, wherein T is a heterocycle selected from the group consisting of:



wherein

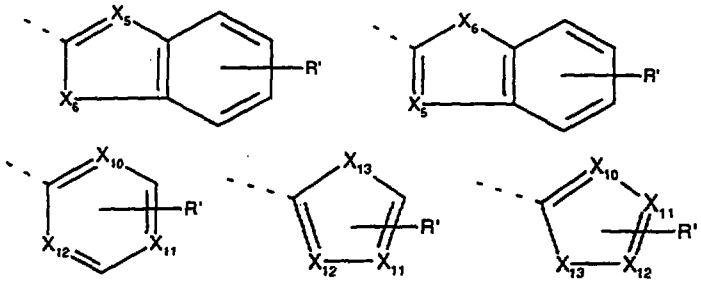
X_5, X_{10}, X_{11} and X_{12} are each independently selected from the group consisting of N, or C-X where X, is hydrogen, C_{1-3} alkyl, or C_{6-10} aryl;

X_6 and X_{13} are each independently selected from the group consisting of C, O, N, S, N-X, or CH-X; and

R' is hydrogen, C_{1-3} alkyl optionally carboxyl substituted, carboxyl, $-C_{1-3}$ alkyl-CO_2-C_{1-3} alkyl, C_{7-9} aralkyl, C_{3-7} cycloalkyl, aryl or an aromatic heterocycle.

4. A compound according to claim 3, wherein T is selected from the group consisting of:

12. A compound according to claim 11, wherein T is a heterocycle selected from the group consisting of:



wherein

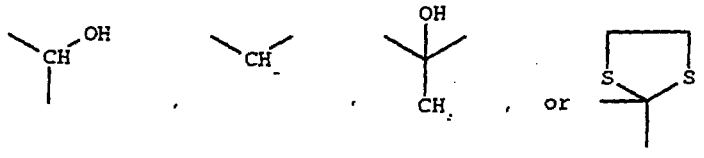
X_5, X_{10}, X_{11} and X_{12} are each independently selected from the group consisting of N, or C-X_7 where X_7 is hydrogen, C_{1-3} alkyl, or C_{6-10} aryl;

X_6 and X_{13} are each independently selected from the group consisting of C, O, N, S, N-X_7, or CH-X_7;

R' is hydrogen, C_{1-3} alkyl optionally carboxyl substituted, carboxyl, -C_{1-3} alkyl-CO-C_{1-3} alkyl, C_{7-9} aralkyl, C_{3-7} cycloalkyl, aryl or an aromatic heterocycle.

13. A compound according to claim 12, wherein T is selected from the group consisting of:

P is a bond, -C(O)- or a bivalent group:

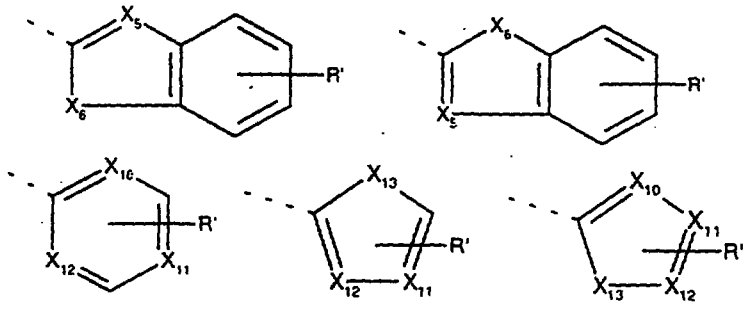


J is C_{1-6} alkylene optionally substituted with OH, NH_2 and C_{1-6} alkyl and optionally interrupted by a heteroatom selected from O, S and N;

n is 0 or 1; and

T is H, OH, amino, a peptide chain, C_{1-6} alkyl, C_{1-6} alkoxy, C_{7-12} aralkyl, or heterocycle optionally substituted.

22. A compound according to claim 21, wherein T is a heterocycle selected from the group consisting of:



wherein

X_5, X_{10}, X_{11} and X_{12} are each independently selected from the group consisting of N, or C-X_7 where X_7 is hydrogen, C_{1-6} alkyl, or C_{6-16} aryl;

X_6 and X_{13} are each independently selected from the group consisting of C, O, N, S, N-X_7, or CH-X_7;

R' is hydrogen, C_{1-6} alkyl optionally carboxyl substituted, carboxyl, -C_{1-6} alkyl-CO-C_{1-6} alkyl, C_{7-12} aralkyl, C_{3-7} cycloalkyl, aryl or an aromatic heterocycle.

23. A compound according to claim 22, wherein T is selected from the group consisting of:

26. A compound according to claim 20, wherein R_2 is H or C_{1-4} alkyl substituted with COOH.

27. A compound according to claim 20, wherein R_1, R_3 and R_4 are H and R_5 is C_{1-12} alkyl optionally interrupted by one or more heteroatom or carbonyl group and optionally substituted with OH, SH, NR_6R_7 or a C_{6-14} aryl, heterocycle or C_{3-7} cycloalkyl group optionally substituted with halogen, hydroxyl or C_{1-4} alkyl.

28. A compound according to claim 22, wherein:
R_1, R_3 and R_4 are H; and
R_5 is C_{1-12} alkyl optionally interrupted by one or more heteroatom or carbonyl group and optionally substituted with OH, SH, NR_6R_7 or a C_{6-14} aryl, heterocycle or C_{3-7} cycloalkyl group optionally substituted with halogen, hydroxyl or C_{1-4} alkyl.

29. A compound according to claim 20, selected from:
0345 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(5-methyl-thiazole-2-carbonyl)-butyl]-amide; and ~~0340 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide.~~ ψ para pushed down.

~~30. A compound according to claim 1, of formula (IX).~~

26. A compound according to claim 20, wherein R_4 is H or C_{1-6} alkyl substituted with COOH.

27. A compound according to claim 20, wherein R_1, R_3 and R_4 are H and R_2 is C_{1-6} alkyl optionally interrupted by one or more heteroatom or carbonyl group and optionally substituted with OH, SH, NR_7R_8 or a C_{6-10} aryl, heterocycle or C_{3-7} cycloalkyl group optionally substituted with halogen, hydroxyl or C_{1-6} alkyl.

28. A compound according to claim 22, wherein:
R_1, R_3 and R_4 are H; and
R_2 is C_{1-6} alkyl optionally interrupted by one or more heteroatom or carbonyl group and optionally substituted with OH, SH, NR_7R_8 or a C_{6-10} aryl, heterocycle or C_{3-7} cycloalkyl group optionally substituted with halogen, hydroxyl or C_{1-6} alkyl.

29. A compound according to claim 20, selected from:
0345 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(5-methyl-thiazole-2-carbonyl)-butyl]-amide; and

<u>0340 4-Oxo-2-(3-phenyl-propionyl)-octahydro-pyrrolo[1,2-a]pyrazine-6-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide.</u>

<u>30. A compound according to claim 1, of formula (IX):</u>

wherein:

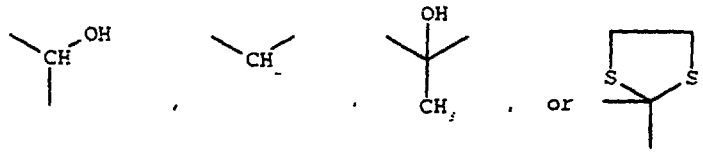
R_{11} is hydrogen or C_{1-4} alkyl;

K is a bond or -NH-;

G is C_{1-4} alkoxy; cyano; $-NH_2$; $-CH_2-NH_2$; $-C(NH)-NH_2$; $-NH-C(NH)-NH_2$; $-CH_2-NH-C(NH)-NH_2$; a C_5 cycloalkyl or aryl substituted with cyano, $-NH_2$, $-CH_2-NH_2$, $-C(NH)-NH_2$, $-NH-C(NH)-NH_2$ or $-CH_2-NH-C(NH)-NH_2$; or a 5 or 6 member, saturated or unsaturated heterocycle optionally substituted with cyano, $-NH_2$, $-CH_2-NH_2$, $-C(NH)-NH_2$, $-NH-C(NH)-NH_2$ or $-CH_2-NH-C(NH)-NH_2$;

U is cyano, $-NH_2$, $-C(NH)-NH_2$ or $-NH-C(NH)-NH_2$;

P is a bond, -C(O)- or a bivalent group:

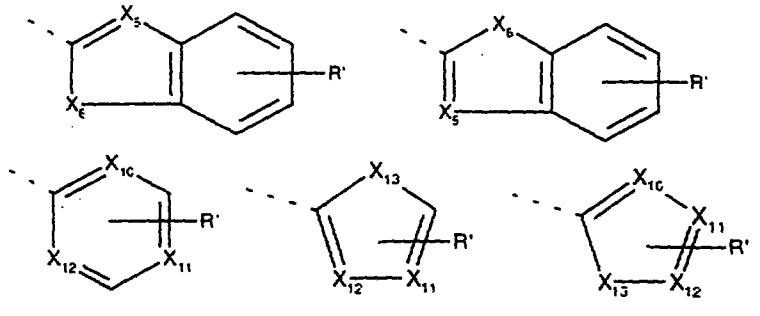


J is C_{1-6} alkylene optionally substituted with OH, NH_2 and C_{1-6} alkyl and optionally interrupted by a heteroatom selected from O, S and N;

n is 0 or 1; and

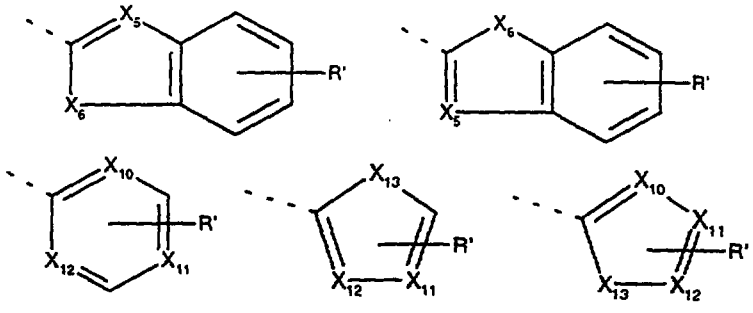
T is H, OH, amino, a peptide chain, C_{1-6} alkyl, C_{1-6} alkoxy, C_{7-12} aralkyl, or heterocycle optionally substituted.

32. A compound according to claim 31, wherein T is a heterocycle selected from the group consisting of:



wherein

X_5, X_{10}, X_{11} and X_{12} are each independently selected from the group consisting of N, or C-X_7 where X_7 is hydrogen, C_{1-4} alkyl, or C_{6-10} aryl;



wherein

X_5, X_{10}, X_{11} and X_{12} are each independently selected from the group consisting of N, or C-X_7 where X_7 is hydrogen, C_{1-3} alkyl, or C_{6-16} aryl;

X_6 and X_{13} are each independently selected from the group consisting of C, O, N, S, N-X_7, or CH-X_7;

R' is hydrogen, C_{1-3} alkyl optionally carboxyl substituted, carboxyl, $-C_{0-3}$ alkyl-CO_2-C_{1-3} alkyl, C_{1-20} aralkyl, C_{3-7} cycloalkyl, aryl or an aromatic heterocycle.

43. A compound according to claim 42, wherein T is selected from the group consisting of:

46. A compound according to claim 40, wherein R_5 is C_{1-3} alkyl substituted with C_{6-10} aryl optionally substituted with C_{1-3} alkyl.

47. A compound according to claim 40, wherein R_5 is H.

48. A compound according to claim 42, wherein
B is S;
R_2, R_3 and R_7 are H; and
R_5 is C_{1-3} alkyl substituted with C_{6-10} aryl optionally substituted with C_{1-3} alkyl.

49. A compound according to claim 40, selected from:
925 7-Benzyl-6-oxo-octahydro-pyrido[2,1-c][1,4]thiazine-4-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)butyl]-amide; and ~~940 6-Oxo-7-phenethyl-octahydro-pyrido[2,1-c][1,4]thiazine-4-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)-butyl]-amide.~~

Para pushed down

50. A method for the treatment or prophylaxis of thrombotic disorders in a mammal, comprising administering to said mammal an effective amount of a compound according to claim 1.

51. A method according to claim 50, wherein said thrombotic disorder is venous thrombosis.

52. A method according to claim 50, wherein said thrombotic disorder is a pulmonary embolism.

53. A method according to claim 50, wherein said ~~thrombotic disorder is arterial thrombosis.~~

46. A compound according to claim 40, wherein R_5 is C_{1-6} alkyl substituted with C_{1-10} aryl optionally substituted with C_{1-6} alkyl.

47. A compound according to claim 40, wherein R_5 is H.

48. A compound according to claim 42, wherein
B is S;
R_2, R_3 and R_4 are H; and
R_5 is C_{1-6} alkyl substituted with C_{1-10} aryl optionally substituted with C_{1-6} alkyl.

49. A compound according to claim 40, selected from:
925 7-Benzyl-6-oxo-octahydro-pyrido[2,1-c][1,4]thiazine-4-carboxylic acid [4-guanidino-1-(thiazole-2-carbonyl)butyl]-amide; and

940 6-Oxo-7-phenethyl-octahydro-pyrido[2,1-c][1,4]thiazine-4-carboxylic acid [4-guanidino-1-)thiazole-2-carbonyl)-butyl]-amide

50. A method for the treatment or prophylaxis of thrombotic disorders in a mammal, comprising administering to said mammal an effective amount of a compound according to claim 1.

51. A method according to claim 50, wherein said thrombotic disorder is venous thrombosis.

52. A method according to claim 50, wherein said thrombotic disorder is a pulmonary embolism.

53. A method according to claim 50, wherein said thrombotic disorder is arterial thrombosis.