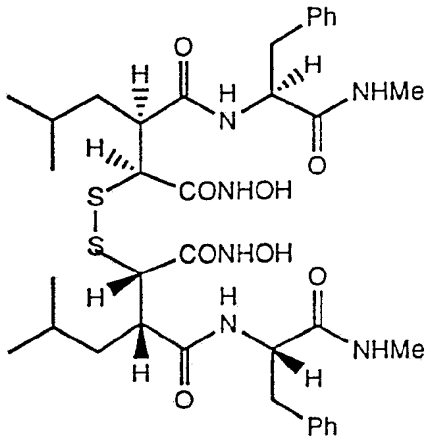
[4-Hydroxy-2R-isobutyl-3S-(2,4-dimethylphenylthiomethyl)succinyl]-L-phenylalanine-N-methylamide (1.8g, 3.7 mmol) and HOBT (0.67g, 12 mmol) were dissolved in 1:1 DCM/DMF and the mixture cooled to 0°C before adding WSDCI (0.86g, 4.5mmol) and NMM (0.45g, 4.5mmol). The mixture was stirred at 0°C for 1h to ensure complete formation of the activated ester. Hydroxylamine hydrochloride (0.39g, 5.6mmol) and NMM (0.56g, 5.6mmol) were dissolved in DMF then this mixture was added dropwise to the cooled solution of the activated ester. After 1h the reaction was poured into ether/water (1:1) whereupon the desired product precipitated as white crystals. These were collected by filtration, further washed with ether and water, then dried under vacuum at 50°C. This material was repeatedly recrystallised from methanol/water (1:1) to remove a trace of the minor diastereomer (1.08g, 2.2mmol, 58%).

m.p. 226°C (dec.)

Analysis calculated for $C_{27}H_{37}N_3O_4S$
Requires: C64.90 H7.46 N8.41
Found: C65.15 H7.48 N8.40

$delta_H$ (250MHz, D_6-DMSO) 8.83 (1H, s, NHOH), 8.32 (1H, d, J = 8Hz, CONH), 7.85 (1H, d, J = 6Hz, CONHMe), 7.30 - 6.71 (9H, m, aromatic H), 4.56 (1H, m, $CHCH_2Ph$), 2.91 (1H, dd, J = 14,4Hz, $CHCH_2Ph$), 2.76 (1H, dd, J = 14,10Hz, $CHCH_2Ph$), 2.57 (3H, d, J = 4.5Hz, $NHCH_3$), 2.53 - 2.38 (2H, m), 2.23 (3H, s, $C_6H_5(CH_3)2$), 2.13 (3H, s, $C_6H_5(CH_3)$), 1.30 (2H, m), 0.89 (1H, m, $CH_2CH(CH_3)_2$), 0.81 (3H, d, J = 6Hz, $CH(CH_3)_2$), and 0.74 (3H, d, J = 6Hz, $CH(CH_3)_2$).

Example 15

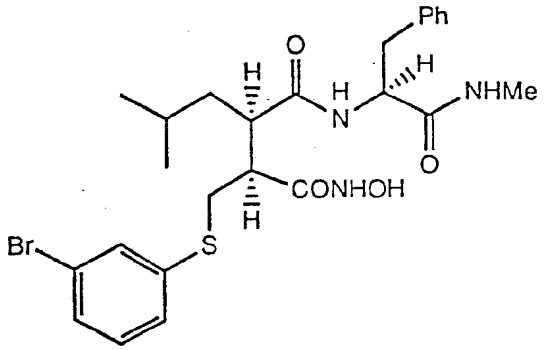


[4(N-Hydroxyamino-2R-isobutyl-3S-(acetylthiomethyl) succinyl]-L-phenylalanine-N-methylamide (1.0g, 2.4 mmol) was dissolved in 750ml methanol and 350ml pH 7 buffer added. Left to stand overnight and solvent removed in vacuo to 2/3 volume,left to crystallise for a further two hours. Filtered and dried to give 0.87g off-white crystals

Analysis calculated for $C_{38}H_{56}N_6O_8S_2.1.9H2O$
Requires: C55.34 H6.93 N9.88
Found: C55.44 H7.32 N10.21

Example 16

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-bromophenyl-thiomethyl) succinyl]-L-phenylalanine-N-methylamide



Prepared by the method described in example 1g to give material with the following characteristics.

m.p. 225 -229°C

$[alpha]_D$ = -164.8°

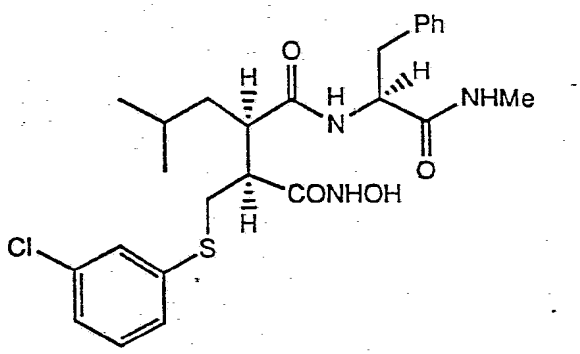
Analysis calculated for $C_{25}H_{32}BrN_3O_4S$
Requires: C54.40 H5.89 N7.40
Found: C54.54 H5.86 N7.63

$delta_H$ (250MHz, D_6-DMSO) 8.83 (1H, s, NHOH), 8.35 (1H, d, J = 8Hz, CONH), 7.90 (1H, q, J = 6Hz, CONHMe), 7.35 - 6.87 (9H, m, aromatic H), 4.64 (1H, m, $CHCH_2Ph$), 2.94 (1H, dd, J = 14,4Hz, $CHCH_2Ph$), 2.76 (1H, t, J = 13Hz, $CHCH_2Ph$) 2.60 (3H, d, J = 5Hz, $NHCH_3$), 2.55 - 2.35 (2H, m, CH_2S), 2.15 (1H, t, J = 10Hz, CHCO), 2.01 (1H, d, J = 11.5Hz, CHCO), 1.37 (2H, m), 0.88 (1H, m, $CH_2CH(CH_3)_2$), 0.81 (3H, d, J = 6Hz, $CH(CH_3)_2$), and 0.74 (3H, d,J = 6Hz,$CH(CH_3)_2$).

$delta_C$ (63.9MHz, D_6-DMSO) 173.0, 171.0, 168.8, 139.8, 138.0, 130.5, 129.0, 128.5, 127.5, 125.8, 125.5, 54.2, 46.0, 45.5, 38.0, 31.5, 25.5, 25.2, 24.7, and 21.0.

Example 17

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-chlorophenylthio-methyl) succinyl]-L-phenylalanine-N-methylamide



Prepared by the method described in example 1g to give material with the following characteristics.

m.p. 231-234°C

$[\alpha]_D = -96.5°$

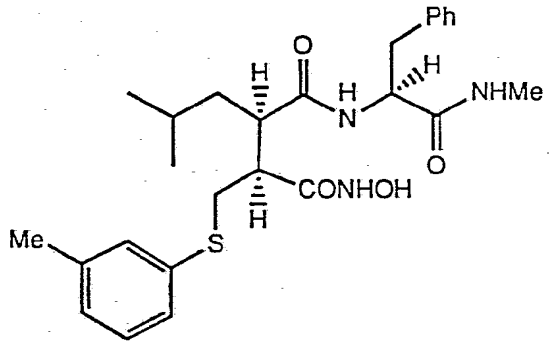
Analysis calculated for $C_{25}H_{32}ClN_3O_4S$
Requires: C59.34 H6.37 N8.30
Found: C59.51 H6.43 N8.24

δ_H (250MHz, D_6-DMSO) 8.85 (1H, s, NHOH), 8.37 (1H, d, J = 8.5Hz, CONH), 7.90 (1H, m, CONHMe), 7.30 - 6.88 (9H, m, aromatic H), 4.66 (1H, m, CHCH$_2$Ph), 2.96 (1H, bd, J = 14Hz, CHCH$_2$Ph), 2.76 (1H, bt, J = 13Hz, CHCH$_2$Ph) 2.60 (3H, d, J = 5Hz, NHCH$_3$), 2.55 - 2.40 (2H, m, CH$_2$S), 2.16 (1H, m, CHCO), 2.01 (1H, d, J = 14Hz, CHCO), 1.37 (2H, m), 0.91 (1H, m, CH$_2$CH(CH$_3$)$_2$), 0.81 (3H, d, J = 6Hz, CH(CH$_3$)$_2$), and 0.74 (3H, d, J = 6Hz,CH(CH$_3$)$_2$).

δ_C (63.9MHz, D_6-DMSO) 172.7, 171.6, 168.1, 139.2, 138.1, 130.3, 129.2, 127.9, 126.2, 125.9, 125.5, 125.0, 54.1, 46.3, 45.8, 37.8, 32.0, 25.7, 25.2, 24.2, and 21.7.

Example 18

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-methylphenylthiomethyl) succinyl]-L-phenylalanine-N-methylamide



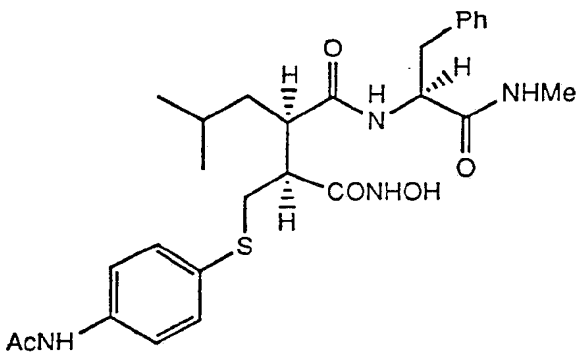
Prepared by the method described in example 1g to give material with the following characteristics.

Analysis calculated for $C_{26}H_{35}N_3O_4S$
Requires: C64.30 H7.26 N8.65
Found: C63.81 H7.21 N8.48

$delta_H$ (250MHz, D_6-DMSO) 8.83 (1H, s, NHOH), 8.35 (1H, d, J = 8.5Hz, CONH), 7.86 (1H, m, CONHMe), 7.28 - 6.77 (9H, m, aromatic H), 4.66 (1H, m, $CHCH_2Ph$), 2.96 (1H, dd, J = 14,4Hz, $CHCH_2Ph$), 2.80 (1H, bt, J = 13Hz, $CHCH_2Ph$) 2.59 (3H, d, J = 5Hz, $NHCH_3$), 2.55 - 2.37 (2H, m, CH_2S), 2.16 (2H, m, 2x$CHCO$), 1.38 (2H, m), 0.91 (1H, m, $CH_2CH(CH_3)_2$), 0.81 (3H, d, J = 6Hz, $CH(CH_3)_2$), and 0.74 (3H, d, J = 6Hz, $CH(CH_3)_2$).

Example 19

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(N-acetyl)-aminophenylthiomethyl)succinyl]-L-phenylalanine-N-methylamide.



A) [2R-isobutyl-3S-(4-aminophenylthiomethyl)succinyl]-L-phenylalanine -N-methylamide.

Prepared by the method described in example 1f to give material with the following characteristics.

delta$_H$ (250MHz, D_6-DMSO) 8.27 (1H, d, J = 8.5Hz, CONH), 7.81 (1H, m, CONHMe), 7.30 - 7.00 (5H, m, phenyl H), 6.86 (2H, d, J = 8.5Hz, aromatic H), 6.45 (2H, d, J = 8.5Hz, aromatic H), 5.25 (1H, bs, CO_2H), 4.48 (1H, m, $CHCH_2Ph$), 2.91 (1H, dd, J = 14,4Hz, $CHCH_2Ph$), 2.88 (1H, dd, J = 14,10Hz, $CHCH_2Ph$) 2.56 (3H, d, J = 5Hz, $NHCH_3$), 2.43 - 2.24 (3H, m, CH_2S and CHCO), 2.03 (1H, d, J = 10Hz, CHCO), 1.41 (1H, t, J = 11Hz, $CH_2CH(CH_3)_2$), 1.26 (1H, m, $CH_2CH(CH_3)_2$), 0.85 (1H, m, $CH_2CH(CH_3)_2$), 0.81 (3H, d, J = 6Hz, $CH(CH_3)_2$), and 0.74 (3H, d, J=6Hz, $CH(CH_3)_2$).

B) [2R-isobutyl-3S-(4-(N-acetyl)aminophenyl-thiomethyl)- succinyl]-Lphenylalanine-N-methylamide.

The product from above (350mg, 0.74 mmol) was dissolved in DCM (5 ml) cooled in an ice bath then triethylamine (75mg, 0.74 mmol), DMAP (91mg, 7.4 mmol) and finally acetic anhydride (83mg, 8.2 mmol) were added and the solution stirred at RT for 90 minutes. The mixture was partitioned between ethyl acetate and citric acid then the organic layer washed with water and finally dried over magnesium sulphate. Solvent removal gave the crude product as pale yellow crystals (160mg, 0.31 mmol, 42%).

$delta_H$ (250MHz, D_6-DMSO) 9.94 (1H, s, CO_2H), 8.34 (1H, d, J = 8.5Hz, CONH), 7.90 (1H, m, CONHMe), 7.46 (2H, d, J = 8.5Hz, aromatic H) 7.30 - 7.00 (5H, m, phenyl H), 6.96 (2H, d, J = 8.5Hz, aromatic H), 4.57 (1H, m, $CHCH_2Ph$), 2.91 (1H, dd, J = 14,4Hz, $CHCH_2Ph$), 2.88 (1H, bt, J = 13Hz, $CHCH_2Ph$), 2.58 (3H, d, J = 5Hz, $NHCH_3$), 2.43 - 2.16 (3H, m, CH_2S and CHCO), 2.10 (1H, d, J = 14Hz, CHCO), 1.35 (1H, t, J = 14Hz, $CH_2CH(CH_3)_2$), 1.26 (1H, m, $CH_2CH(CH_3)_2$), 0.86 (1H, m, $CH_2CH(CH_3)_2$), 0.81 (3H, d, J = 6Hz, $CH(CH_3)2$), and 0.74 (3H, d, J = 6Hz,$CH(CH_3)_2$).

C) [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(N-acetyl)-aminophenylthiomethyl)succinyl]-L-phenylalanine-N-methylamide.

Prepared by the method described in example 1g to give material with the following characteristics.

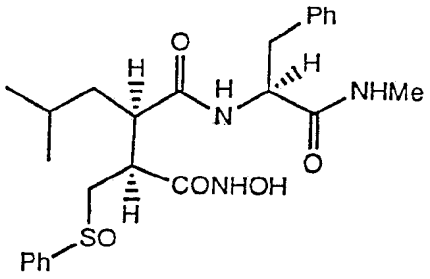
m.p. 201 -202°C (dec.)

$[alpha]_D$ = -7.5° (c=1.0, methanol)

$delta_H$ (250MHz, D_6-DMSO) 9.90 (1H, s, NHOH), 8.82 (1H, s, NHOH), 8.30 (1H, d, J = 8.5Hz, CONH), 7.85 (1H, m, CONHMe), 7.45 (2H, d, J = 8.5Hz, aromatic H), 7.28 - 6.94 (5H, m, phenyl H), 6.90 (2H, d, J = 8.5Hz, aromatic H), 4.66 (1H, m, $CHCH_2Ph$), 2.90 (1H, dd, J = 14,4Hz, $CHCH_2Ph$), 2.76 (1H, bt, J = 13Hz, $CHCH_2Ph$), 2.50 (3H, d, J = 5Hz, $NHCH_3$), 2.49 - 2.35 (2H, m, CH_2S), 2.14 (1H, m, CHCO), 2.03 (4H, s + m, $COCH_3$ and CHCO), 1.35 (2H, m), 0.86 (1H, m, $CH_2CH(CH_3)_2$), 0.81 (3H, d, J = 6Hz, $CH(CH_3)_2$), and 0.74 (3H, d, J = 6Hz, $CH(CH_3)_2$).

Example 20

[4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylsulfinyl-methylsuccinyl]-L-phenylalanine-N-methylamide.



[4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylthiomethyl-succinyl]-L-phenylalanine-N-methylamide (250mg, 0.53mmol) was dissolved in methanol (50 ml) and meta-

chloroperbenzoic acid (100mg, 0.58 mmol) was added. After stirring for 1h at room temperature ether was added and the mixture filtered. Solvent removal gave the crude white solid which was recrystallised from methanol / water then slurried in ether to remove final traces of meta-chlorobenzoic acid to give the desired material (70 mg, 0.014 mmol, 27%).

m.p. 186 -188°C

$[\alpha]_D$ = -13.6° (c=0.5, methanol)

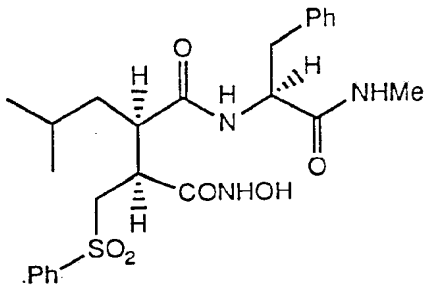
Analysis calculated for $C_{25}H_{33}N_3O_5S.0.5H_2O$
Requires: C60.46 H6.90 N8.46
Found: C60.58 H6.69 N8.29

δ_H (250MHz, D_6-DMSO, mixture of diastereomers) 9.04 + 8.93 (1H, 2xs, NHOH), 8.29 + 8.16 (1H, 2xd, J = 8.5 Hz, CONH), 7.79 (1H, m, CONHMe), 7.90 - 7.40 (8H, m, aromatic H), 7.06 + 6.82 (2H, 2xm, SO-Aromatic), 4.37 (1H, m, $CHCH_2Ph$), 2.93 - 2.58 (3H, m, containing $CHCH_2Ph$), 2.52 (3H, m, $NHCH_3$), 2.49 + 2.37 (1H, 2xm), 1.49 - 1.25 (2H, m, $CH_2CH(CH_3)_2$ and $CH2CH(CH_3)_2$), 0.95 (1H, m, $CH_2CH(CH_3)_2$), 0.81 (3H, d, J = 6Hz, $CH(CH_3)_2$), and 0.74 (3H, d, J=6Hz, $CH(CH_3)_2$).

δ_C (63.9MHz, D_6-DMSO, mixture of diastereomers) 172.2, 171.4, 171.3, 167.7, 144.5, 138.0, 137.9, 131.3, 130.9, 129.6, 129.3, 129.1, 128.8, 128.3, 127.8, 126.5, 126.2, 124.3, 123.6, 59.8, 58.1, 54.3, 54.0, 46.2, 45.8, 41.6, 40.9, 37.6, 37.4, 25.6, 25.0, 24.3, 24.2, 21.7, and 21.6.

Example 21

[4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylsulfonyl-methylsuccinyl]-L-phenylalanine-N-methylamide.



[4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylthiomethyl-succinyl]-L-phenylalanine-N-methylamide (50mg, 0.11mmol) was dissolved in methanol (12 ml) and meta-chloroperbenzoic acid (40mg, 0.23 mmol) was added. After stirring for 3h at room temperature ether was added and the mixture filtered. Solvent removal gave the crude white solid which was slurried in ether to remove final traces of meta-chlorobenzoic acid to give the desired material.

m.p. 228 - 231°C

$[\alpha]_D$ = 16.8° (c=0.5, methanol)

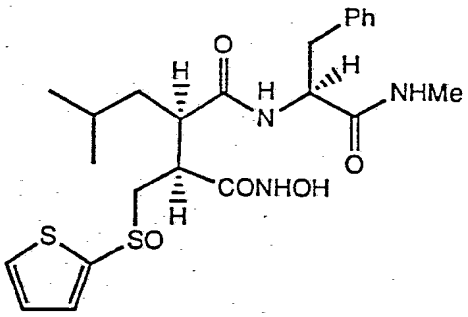
Analysis calculated for $C_{25}H_{33}N_3O_6S.0.3H_2O$
Requires: C58.99 H6.65 N8.25
Found: C58.92 H6.51 N8.05

δ_H (250MHz, D_6-DMSO) 8.66 (1H, s, NHOH), 8.25 (1H, d, J = 8.5 Hz, CONH), 7.83 (1H, m, CONHMe), 7.75 - 7.50 (5H, m, aromatic H), 7.30 7.05 (5H, m, aromatic H),

4.36 (1H, m, $C\underline{H}CH_2Ph$), 2.86 (1H, dd, J = 14,5 Hz, $CHC\underline{H}_2Ph$), 2.75 (1H, dd, J = 14,10 Hz, $CHC\underline{H}_2Ph$), 2.54 (3H, d, J = 4.5 Hz, $NHC\underline{H}_3$), 2.54 (2H, m), 1.30 (2H, m, $C\underline{H}_2CH(CH_3)_2$ and $CH_2C\underline{H}(CH_3)_2$), 0.86 (1H, m, $C\underline{H}_2CH(CH_3)_2$), 0.75 (3H, d, J = 6Hz, $CH(C\underline{H}_3)_2$), and 0.71 (3H, d, J = 6Hz,$CH(C\underline{H}_3)_2$).

Example 22

[4-(N-Hydroxyamino)-2R-isobutyl-3S-thiophenylsulphinylmethyl-succinyl] -L-phenylalanine-N-methylamide



[4-(N-Hydroxyamino)-2R-isobutyl-3S-thiophenylthio-methyl-succinyl]-L-phenylalanine-N-methylamide (50mg, 0.11mmol) was treated as described in example 21 to yield the title compound (16mg, 0.03 mmol, 29%) as a mixture of diastereomer with the following characteristics:

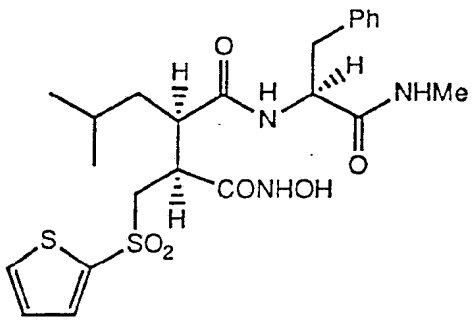
m.p. 195 -197°C (dec.)

Analysis calculated for $C_{23}H_{31}N_3O_5S_2.0.5H_2O$
Requires: C54.96 H6.42 N8.36
Found: C54.91 H6.23 N8.23

delta$_H$ (250MHz, D_6-DMSO, mixture of diastereomers) 9.04 + 8.96 (1H, 2xs, NHOH), 8.34 + 8.29 (1H, 2xd, J = 8.5 Hz, CONH), 8.02 + 7.98 (1H, 2xm, CONHMe), 7.81 (1H, bs, thiophene-H), 7.42 (1H, s, thiophene-H), 7.25 - 7.15 (5H, m, phenyl), 7.03 (1H, bs, thiophene-H), 4.43 (1H, m, $CHCH_2Ph$), 3.0 - 2.6 (4H, m, containing $CHCH_2Ph$), 2.52 (7H, m, containing $NHCH_3$), 2.05 (1H, m), 1.6 - 1.2 (2H, m, $CH_2CH(CH_3)_2$ and $CH_2CH(CH_3)_2$), 0.87 (1H, m, $CH_2CH(CH_3)_2$), and 0.85 - 0.71 (6H, m, $CH(CH_3)_2$).

Example 23

[4-(N-Hydroxyamino)-2R-isobutyl-3S-thiophenylsulphonylmethyl-succinyl] -L-phenylalanine-N-methylamide.



[4-(N-Hydroxyamino)-2R-isobutyl-3S-thiophenylthio-methyl-succinyl]-L-phenylalanine-N-methylamide (75mg, 0.16mmol) was treated as described in example 22 to yield the title compound (40mg, 0.08 mmol, 49%) with the following characteristics:

m.p. 215 - 216°C

Analysis calculated for $C_{23}H_{31}N_3O_6S_2$

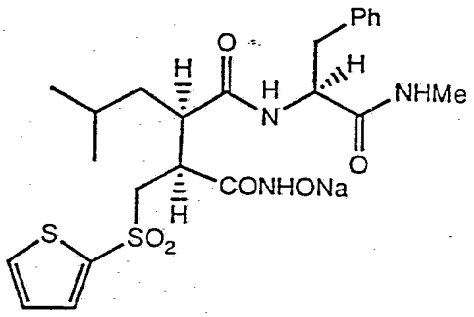
Requires: C54.21 H6.13 N8.24
Found: C54.07 H6.19 N8.04

delta$_H$ (250MHz, D_6-DMSO) 887 (1H, s, NHOH), 8.25 (1H, d, J = 8.5 Hz, CONH), 8.09 (1H, d, J = 4.7 Hz, thiophene-H), 7.83 (1H, m, CONHMe), 7.53 (1H, d, J = 3 Hz, thiophene H), 7.25 - 7.12 (6H, m, phenyl and thiophene-H), 4.36 (1H, m, $CHCH_2Ph$), 3.38 (1H, dd, J = 14,11 Hz, SCH_2), 2.87 (1H, dd, J = 14,5 Hz, $CHCH_2Ph$), 2.75 (1H, dd, J = 14,10 Hz, $CHCH_2Ph$), 2.70 - 2.36 (6H, m, containing $NHCH_3$), 1.20 (2H, m, $CH_2CH(CH_3)_2$ and $CH_2CH(CH_3)_2$), 0.89 (1H,m, $CH_2CH(CH_3)_2$), and 0.75 (6H, m, $CH(CH_3)_2$).

delta$_C$ (63.9MHz, D_6-DMSO) 172.0, 171.2, 166.5, 140.0, 138.0, 135.4, 134.6, 129.0, 128.4, 128.2, 126.6, 54.3, 45.6, 37.5, 25.6, 25.0, 24.2, and 21.7.

Example 24

[4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylsulfonyl-methylsuccinyl]-L-phenylalanine-N-methylamide sodium salt.



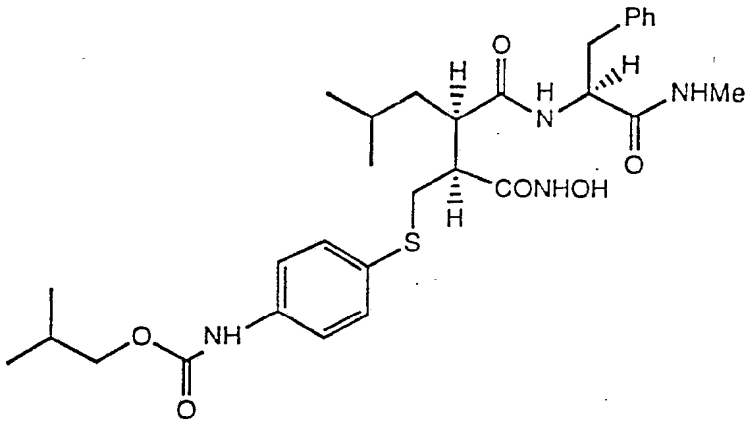
[4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylsulfonyl-

methylsuccinyl]-L-phenylalanine-N-methylamide (50mg, 0.1mmol) was dissolved in methanol (10ml) and sodium hydroxide solution (0.1M, 1.0ml) added to give a homogeneous solution. The methanol was removed under reduced pressure then the residual aqueous solution freeze dried to give the title compound (40mg).

delta$_H$ (250MHz, D_6-DMSO) 8.66 (1H, s, NHOH), 8.25 (1H, d, J = 8.5 Hz, CONH), 7.83 (1H, m, CONHMe), 7.75 - 7.50 (5H, m, aromatic H), 7.30 7.05 (5H, m, aromatic H), 4.36 (1H, m, $CHCH_2Ph$), 2.86 (1H, dd, J = 14,5 Hz, $CHCH_2Ph$), 2.75 (1H, dd, J = 14,10 Hz, $CHCH_2Ph$), 2.54 (3H, d, J=4.5 Hz, $NHCH_3$), 2.54 (2H, m), 1.30 (2H, m, $CH_2CH(CH_3)_2$ and $CH_2CH(CH_3)_2$), 0.86 (1H, m, $CH_2CH(CH_3)_2$), 0.75 (3H, d, J = 6Hz, $CH(CH_3)_2$), and 0.71 (3H, d, J = 6Hz, $CH(CH_3)_2$).

Example 25

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(isobutyloxy-carbonylamino)phenyl)thiomethyl-succinyl]-L-phenyl-alanine-N-methylamide



a) [4-Hydroxy-2R-isobutyl-3S-(4-aminophenyl)thio-

methylsuccinyl]-L-phenylalanine-N-methylamide was prepared by the method described in example 1f to give a compound with the following characteristics.

delta$_H$ (250MHz, D_6-DMSO) 8.26 (1H, d, J = 8.5 Hz, CONH), 7.81 (1H, m, CONHMe), 7.27 - 7.15 (5H, m, phenyl H), 6.85 (2H, d, J = 8.5Hz, aromatic H), 6.46 (2H, d, J = 8.5Hz, aromatic H), 5.2 (1H, bs, CO_2H), 4.48 (1H, m, $CHCH_2Ph$), 2.90 (1H, dd, J = 13.5,4.3 Hz, $CHCH_2Ph$), 2.75 (1H, dd, J = 13.6, 10 Hz, $CHCH_2Ph$), 2.56 (3H, d, J = 4.5 Hz, $NHCH_3$), 2.50 - 2.25 (3H, m), 2.03 (1H, d, J = 10 Hz), 1.41 (1H, m, $CH_2CH(CH_3)_2$), 1.26 (1H, m, $CH_2CH(CH_3)_2$), 0.86 (1H, m, $CH_2CH(CH_3)_2$), 0.75 (3H, d, J = 6Hz, $CH(CH_3)_2$), and 0.71 (3H, d, J = 6Hz,$CH(CH_3)_2$).

b) N,N-Dimethylglycine (100mg, 0.97 mmol) was stirred in dry THF (50ml) and triethylamine (108mg, 1.1mmol) and isobutylchloroformate (146mg, 1.1mmol) were added. After 1h the product from example 26a (500mg, 1.1mmol) was addedand the mixture stirred for a further 1h. The reaction was worked up by partitioning between citric acid and ethyl acetate, drying the organic layer and solvent removal to give the crude product (1g). Solution of the crude solid in ethyl acetate then precipitation with ether resulted in white crystals of the isobutylchloroformate derivative.

c) [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(isobutyloxy-carbonylamino) phenyl)thiomethyl-succinyl]-L-phenyl-alanine-N-methylamide

The product from example 26b was converted to the hydroxamic acid as described in example 1g. to give a compound with the following characteristics.

m.p. 198 - 200°C

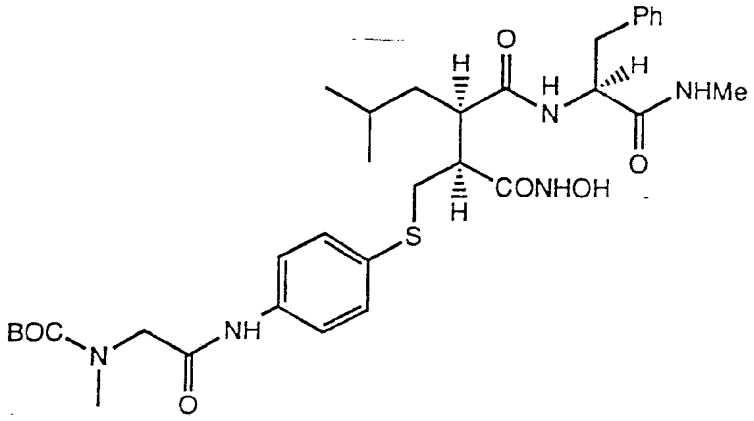
$[\alpha]_D$ = -8.5° (c=1, methanol)

Analysis calculated for $C_{30}H_{42}N_4O_6S$
Requires: C61.41 H7.22 N9.55
Found: C62.04 H7.32 N9.67

δ_H (250MHz, D_6-DMSO) 9.60 (1H, s, NHOH), 8.83 (1H, s, NHOH), 8.31 (1H, d, J = 8.5 Hz, CONH), 7.85 (1H, m, CONHMe), 7.36 - 7.25 (4H, m, aromatic H), 7.14 - 7.05 (3H, m, aromatic H), 6.91 (2H, d, J = 8.5Hz, aromatic H), 4.56 (1H, m, $CHCH_2Ph$), 3.87 (2H, d, J = 7Hz, $OCH_2CH(CH_3)_2$), 2.92 (1H, dd, J = 13.7,4.0 Hz, $CHCH_2Ph$), 2.76 (1H, dd, J = 13.6,10 Hz, $CHCH_2Ph$), 2.58 (3H, d, J = 4.5 Hz, $NHCH_3$), 2.50 - 2.34 (2H, m), 2.16 - 1.87 (3H, m), 1.35 (2H, m, $CH_2CH(CH_3)_2$ and $CH_2CH(CH_3)_2$), 0.93 (6H, d, J = 6.6Hz, $OCH_2CH(CH_3)_2$), 0.87 (1H,m, $CH_2CH(CH_3)_2$), 0.75 (3H, d, J = 6Hz, $CH(CH_3)_2$), and 0.71 (3H, d, J = 6Hz, $CH(CH_3)_2$).

Example 26

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(N-methyl-N-(tertbutoxycarbonyl)-glycylamino) phenyl)thiomethyl-succinyl]-Lphenylalanine-N-methylamide.



a) [4-Hydroxy-2R-isobutyl-3S-(4-(N-methyl-N-(tert-butoxycarbonyl)glycylamino) phenyl)thiomethyl-succinyl]-L-phenylalanine-N-methylamide was prepared as described in example 26b by substitution of N-BOC sarcosine for the acid component.

$delta_H$ (250MHz, D_6-DMSO) 9.97 (1H, s, $CO_2\underline{H}$), 8.36 (1H, d, J = 8.5 Hz, CON$\underline{H}$), 7.91 (1H, m, CON$\underline{H}$Me), 7.48 (2H, d, J = 8.5Hz, aromatic H), 7.40 - 7.05 (5H, m, aromatic H), 6.97 (2H, d, J = 8.5Hz, aromatic H), 4.58 (1H, m, C$\underline{H}CH_2$Ph), 3.95 (2H, d, J = 9Hz, NC$\underline{H}_2$CO), 2.92 (4H, m+d, CHC$\underline{H}_2$Ph and BOCNC$\underline{H}_3$), 2.76 (1H, dd, J = 13,10 Hz, CHC$\underline{H}_2$Ph), 2.58 (3H, d, J = 4.5 Hz, NHC$\underline{H}_3$), 2.50 - 2.09 (4H, m), 1.46 - 1.33 (11H, m + 2xs, (C$\underline{H}_3$)$_3$C, C$\underline{H}_2$CH(CH$_3$)$_2$ and CH$_2$C$\underline{H}$(CH$_3$)$_2$), 0.87 (1H, m, C$\underline{H}_2$CH(CH$_3$)$_2$), 0.75 (3H, d, J = 6Hz, CH(C$\underline{H}_3$)$_2$), and 0.71 (3H, d, J = 6Hz, CH(C$\underline{H}_3$)$_2$).

b) [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(N-methyl- N-(tertbutoxycarbonyl)-glycylamino)phenyl)- thiomethyl-succinyl]-Lphenylalanine-N-methylamide was prepared from the material produced in example 27a as described in example 1g.

$delta_H$ (250MHz, D_6-DMSO) 9.97 (1H, s, CONHO$\underline{H}$), 8.83 (1H, s, N$\underline{H}$OH), 8.32 (1H, d, J = 8.5 Hz, CON$\underline{H}$), 7.86 (1H, m, CON$\underline{H}$Me), 7.46 (2H, d, J = 8.5Hz, aromatic H), 7.28 - 7.00 (5H, m, aromatic H), 6.97 (2H, d, J = 8.5Hz, aromatic H), 4.56 (1H, m, C$\underline{H}CH_2$Ph), 3.94 (2H, d, J = 9Hz, NC$\underline{H}_2$CO), 2.87 (4H, m+d, CHC$\underline{H}_2$Ph and BOCNC$\underline{H}_3$), 2.76 (1H, m, CHC$\underline{H}_2$Ph), 2.57 (3H, d, J = 4.5 Hz, NHC$\underline{H}_3$), 2.25 - 1.91 (2H, m), 1.42 - 1.30 (11H, m + 2xs, (C$\underline{H}_3$)$_3$C, C$\underline{H}_2$CH(CH$_3$)$_2$ and CH$_2$C$\underline{H}$(CH$_3$)$_2$), 0.92 (1H, m, C$\underline{H}_2$CH(CH$_3$)$_2$), 0.80 (3H, d, J = 6Hz, CH(C$\underline{H}_3$)$_2$), and 0.73 (3H, d, J=6Hz, CH(C$\underline{H}_3$)$_2$).

Example 27

Collagenase inhibition activity

The potency of compounds of general formula I to act as inhibitors of collagenase (a metalloproteas involved in tissue degradation) was determined by the procedure of Cawston and Barrett, (Anal. Biochem., 99, 340-345, 1979), hereby incorporated by reference, whereby a 1mM solution of the inhibitor being tested or dilutions thereof was incubated at 37^{O} for 16 hours with collagen and collagenase (buffered with 25mM Hepes, pH 7.5 containing 5mM $CaCl_2$, 0.05% Brij 35 and 0.02% NaN_3). The collagen was acetylated ^{14}C collagen prepared by the method of Cawston and Murphy (Methods in Enzymology, 80, 711, 1981), hereby incorporated by reference. The samples were centrifuged to sediment undigested collagen and an aliquot of the radioactive supernatant removed for assay on a scintillation counter as a measure of hydrolysis. The collagenase activity in the presence of 1 mM inhibitor, or a dilution thereof, was compared to activity in a control devoid of inhibitor and the results reported below as that inhibitor concentration effecting 50% inhibition of the collagenase (IC_{50}).

Compound of Example No.	IC_{50}
1	20 nM
2	8 nM
5	3 nM
6	(50% @ 1 mcM)

Example 28

Stromelysin inhibition activity

The potency of compounds of general formula I to act as inhibitors of stromelysin was determined using the procedure of Cawston et al (Biochem. J., 195, 159-165 1981), hereby incorporated by reference, whereby a 1mM solution of the inhibitor being tested or dilutions thereof was incubated at 37°C for 16 hours with stromelysin and ^{14}C acetylate casein (buffered with 25mM Hepes, pH 7.5 containing 5mM $CaCl_2$, 0.05% Brij 35 and 0.02% NaN_3. The casein was ^{14}C acetylated according to the method described in Cawston et al (Biochem. J., 195, 159-165, 1981), hereby incorporated by reference. The stromelysin activity in the presence of 1mM, or a dilution thereof, was composed to activity in a control devoid of inhibitor and the results reported below as that inhibitor concentration effecting 50% inhibition of the stromelysin (IC_{50}).

Compound of Example No.	IC_{50}
1	10 nM
2	20 nM

Examples of unit dosage compositions are as follows:

Example 29

Capsules:

Ingredients	Per Capsule	Per 10,000 Capsules
1. Active ingredient Cpd. of Form. I	40.0 mg	400 g
2. Lactose	150.0 mg	1500 g
3. Magnesium stearate	4.0 mg	40 g
	194.0 mg	1940 g

Procedure for capsules:

Step 1. Blend ingredients No. 1 and No. 2 in a suitable blender.

Step 2. Pass blend from Step 1 through a No. 30 mesh (0.59 mm) screen.

Step 3. Place screened blend from Step 2 in a suitable blender with ingredient No. 3 and blend until the mixture is lubricated.

Step 4. Fill into No. 1 hard gelatin capsule shells on a capsule machine.

Example 30

Tablets:

Ingredients	Per Tablet	Per 10,000 Tablets
1. Active ingredient Cpd. of Form. I	40.0 mg	400 g
2. Corn Starch	20.0 mg	200 g
3. Alginic acid	20.0 mg	200 g
4. Sodium alginate	20.0 mg	200 g
5. Magnesium stearate	1.3 mg	13 g
	101.3 mg	1013 g

Procedure for tablets:

Step 1. Blend ingredients No. 1, No. 2, No. 3 and No. 4 in a suitable mixer/blender.

Step 2. Add sufficient water portionwise to the blend from Step 1 with careful mixing after each addition. Such additions of water and mixing until the mass is of a consistency to permit its conversion to wet granules.

Step 3. The wet mass is converted to granules by passing it through an oscillating granulator using a No. 8 mesh (2.38) screen.

Step 4. The wet granules are then dried in an oven at 140°F (60°C) until dry.

Step 5. The dry granules are lubricated with ingredient No. 5.

Step 6. The lubricated granules are compressed on a suitable tablet press.

Example 31

Intramuscular Injection:

Ingredient	Per ml.	Per liter
1. Compound of Formula I Active ingredient	10.0 mg	10 g
2. Istonic buffer solution pH 4.0.	q.s.	q.s.

Procedure:

Step 1. Dissolve the active ingredient in the buffer solution.

Step 2. Aseptically filter the solution from Step 1.

Step 3. The sterile solution is now aseptically filled into sterile ampoules.

Step 4. The ampoules are sealed under aspetic conditions.

Example 32

Suppositories:

Ingredients	Per Supp.	Per 1,000 Supp
1. Compound of Form. I Active ingredient	40.0 mg	40 g
2. Polyethylene Glycol 1000	1350.0 mg	1,350 g
3. Polyethylene Glycol 4000	450.0 mg	450 g
	1840.0 mg	1,840 g

Procedure:

Step 1. Melt ingredient No. 2 and No. 3 together and stir until uniform.

Step 2. Dissolve ingredient No. 1 in the molten mass from Step 1 and stir until uniform.

Step 3. Pour the molten mass from Step 2 into suppository moulds and chill.

Step 4. Remove the suppositories from moulds and wrap.

Example 33

Eye Ointment

An appropriate amount of a compound of general formula I is formulated into an eye ointment base having the following composition:

Liquid paraffin	10%
Wool fat	10%
Yellow soft paraffin	80%

Example 34

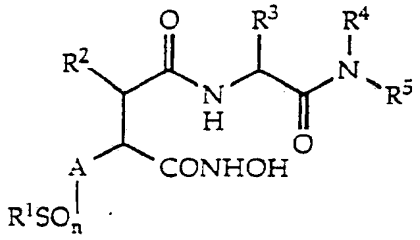
Topical skin ointment

An appropriate amount of a compound of general formula I is formulated into a topical skin ointment base having the following composition:

Emulsifying wax	30%
White soft paraffin	50%
Liquid paraffin	20%

CLAIMS

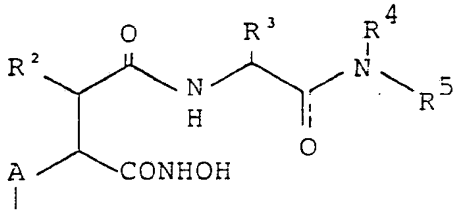
1. A compound of general formula I:



(I)

wherein:

R^1 represents a C_1-C_6 alkyl, phenyl, thiophenyl, substituted phenyl, phenyl(C_1-C_6)alkyl, heterocyclyl, (C_1-C_6)alkylcarbonyl or phenacyl or substituted phenacyl group; or when n = 0, R^1 represents SR^x, wherein R^x represents a group:



;

R^2 represents a hydrogen atom or a C_1-C_6 alkyl, C_1-C_6 alkenyl, phenyl(C_1-C_6)alkyl, cycloalkyl(C_1-C_6)alkyl or cycloalkenyl(C_1-C_6)alkyl group;

R^3 represents an amino acid side chain or a C_1-C_6 alkyl, benzyl, (C_1-C_6 alkoxy)benzyl or benzyloxy(C_1-C_6 alkyl) or benzyloxy benzyl group;

R^4 represents a hydrogen atom or a C_1-C_6 alkyl group;

R^5 represents a hydrogen atom or a methyl group;

n is an integer having the value 0, 1 or 2; and

A represents a C_1-C_6 hydrocarbon chain, optionaly substituted with one or more C_1-C_6 alkyl, phenyl or substituted phenyl groups;

or a salt thereof.

2. A compound as claimed in Claim 1, in which the chiral centre adjacent the substituent R^3 has S stereochemistry.

3. A compound as claimed in Claim 1 or 2, wherein the chiral centre adjacent the substituent R^2 has R stereochemistry.

4. A compound as claimed in Claim 1, 2 or 3, in which R^1 represents a hydrogen atom or a C_1-C_4 alkyl, phenyl, thiophenyl, benzyl, acetyl or phenacyl group.

5. A compound as claimed in any one of Claims 1 to 4, wherein R^2 represents a C_3-C_6 alkyl group.

6. A compound as claimed in any one of Claims 1 to 5, wherein R^3 represents a benzyl or 4-(C_1-C_6)alkoxyphenylmethyl or benzyloxybenzyl group.

7. A compound as claimed in any one of Claims 1 to 6, wherein R^4 represents a C_1-C_4 alkyl group.

8. A compound as claimed in any one of Claims 1 to 7, wherein R^5 represents a hydrogen atom.

9. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(phenylthiomethyl)-succinyl]-L-phenylalanine-N-methylamide,

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiophenylthiomethyl) succinyl]-L-phenylalanine-N-methylamide,

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(benzylthiomethyl) succinyl]-L-phenylalanine-N-methylamide,

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(acetylthiomethyl) succinyl]-L-phenylalanine-N-methylamide or

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiolmethyl) succinyl]-L-phenylalanine-N-methylamide

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(pivaloylthiomethyl) succinyl]-L-phenylalanine-N-methylamide

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(phenylthiomethyl) succinyl]-L-phenylalanine-N-methylamide sodium salt

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-methoxyphenylthiomethyl)succinyl]-L-phenylalanine-N-methylamide

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-hydroxyphenylthiomethyl)succinyl]-L-phenylalanine-N-methylamide

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thiophenethiomethyl)succinyl]-L-phenylalanine-N-methylamide sodium salt

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-methoxyphenyl-thiomethyl)succinyl]-L-phenylalanine-N-methylamide sodium salt

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-tertbutylphenyl-thiomethyl)succinyl]-L-phenylalanine-N-methylamide

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(2,4-dimethylphenyl-thiomethyl) succinyl]-L-phenylalanine-N-methylamide

bis-S,S'-{[4(N-Hydroxyamino-2R-isobutyl-3S-(thiomethyl) succinyl]-L-phenylalanine-N-methylamide) disulphide

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-bromophenylthio-methyl) succinyl]-L-phenylalanine-N-methylamide

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-chlorophenylthio-methyl) succinyl]-L-phenylalanine-N-methylamide

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(3-methylphenylthio-methyl) succinyl]-L-phenylalanine-N-methylamide

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(N-acetyl)-amino-phenylthiomethyl)succinyl]-L-phenylalanine-N-methyl-amide

[4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylsulphinyl-methylsuccinyl]-L-phenylalanine-N-methylamide

[4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylsulphonyl-methylsuccinyl]-L-phenylalanine-N-methylamide

[4-(N-Hydroxyamino)-2R-isobutyl-3S-thiophenylsulphinyl-methyl-succinyl]-L-phenylalanine-N-methylamide

[4-(N-Hydroxyamino)-2R-isobutyl-3S-thiophenylsulphonyl-methyl-succinyl]-L-phenylalanine-N-methylamide

[4-(N-Hydroxyamino)-2R-isobutyl-3S-phenylsulphonyl-methyl-succinyl]-L-phenylalanine-N-methylamide sodium salt

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(isobutyloxy-carbonylamino)phenyl)thiomethyl-succinyl]-L-phenyl-alanine-N-methylamide

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-(N-methyl-N-(tert-butoxycarbonyl)-glycylamino)phenyl)thiomethyl-succinyl]-L-phenylalanine-N-methylamide

or, where appropriate, a salt of such a compound.

10. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiophenyl-thiomethyl) succinyl]-L-phenylalanine-N-methylamide, or

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiolmethyl) succinyl]-L-phenylalanine-N-methylamide

or a salt thereof.

11. [4-(N-Hydroxyamino)-2R-isobutyl-3S-(thiophenyl-thiomethyl)succinyl]-L-phenylalanine-N-methylamide or a salt thereof.

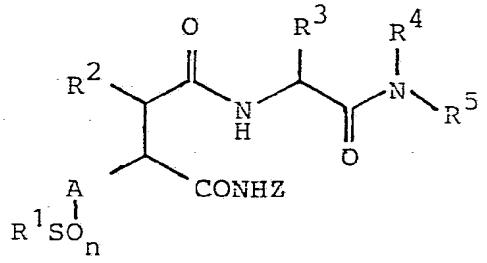
12. A compound as claimed in any one of claims 1 to 11 for use in human or veterinary medicine.

13. The use of a compound as claimed in any one of claims 1 to 11 in the preparation of an agent for use in the management of disease involving tissue degradation and/or in the promotion of wound healing.

14. A pharmaceutical or veterinary formulation comprising a compound as claimed in any one of claims 1 to 11 and a pharmaceutically and/or veterinarily acceptable carrier.

15. A process for preparing a compound of general formula I as defined in claim 1, the process comprising:

(a) deprotecting a compound of general formula II

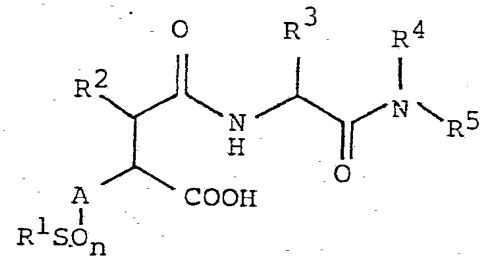


(II)

wherein:

R^1, R^2, R^3, R^4, R^5, A and n are as defined in general formula I and Bn represents a benzyloxycarbonyl group; or

(b) reacting a compound of general formula III



(III)

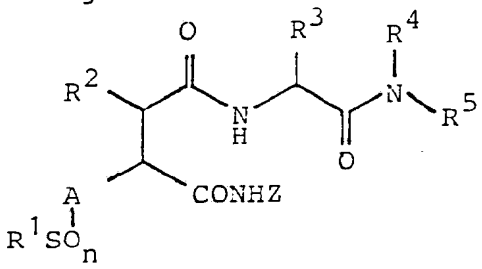
wherein:

R^1, R^2, R^3, R^4, R^5, A and n are as defined in general formula I,

with hydroxylamine or a salt thereof; and

(c) optionally after step (a) or step (b) converting a compound of general formula I into another compound of general formula I.

16. A compound of general formula II

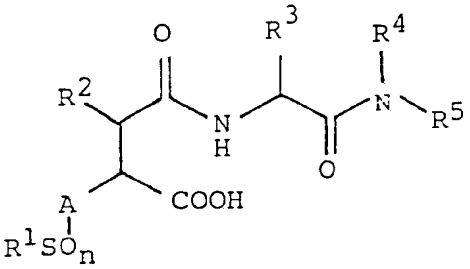


(II)

wherein:

R^1, R^2, R^3, R^4, R^5, A and n are as defined in general formula I and Z represents a protecting group.

17. A compound of general formula III



(III)

wherein:

R^1, R^2, R^3, R^4, R^5, A and n are as defined in general formula I.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 89/01399

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: C 07 C 323/62, 323/60, C 07 D 333/34, C 07 C 327/32, 317/50, 313/48, A 61 K 31/13, 31/38

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	C 07 C 259/00, 323/00, C 07 D 333/00, C 07 C 327/00, 317/00, 313/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	EP, A, 0236872 (F. HOFFMANN-LA ROCHE) 16 September 1987 see claim 1 cited in the application	1-17
A	EP, A, 0012401 (MERCK & CO. INC.) 25 June 1980 see claim 1 cited in the application	1-17
A	DE, A, 2720996 (E.R. SQUIBB & SONS) 24 November 1977 see claim 1 cited in the application & US, A, 4105789	1-17
A	EP, A, 0274453 (LABORATOIRE ROGER BELLON) 13 July 1988 see claim 1	1-17
A	EP, A, 0214639 (G.D. SEARLE) 18 March 1987 see claim 1	1-17

./.

* Special categories of cited documents: [10]

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

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

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

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

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

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

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

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

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
8th March 1990	17 AVR. 1990
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	MISS T. TAZELAAR

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
	cited in the application & US, A, 4599361 --	
A	Chemical Abstracts, volume 83, no. 7, 18 August 1975, (Columbus, Ohio, US), J.P. Devlin et al.: "Antibiotic actinonin. III. Synthesis of structural analogs of actinonin by the anhydride-imide method", see page 549, abstract 59249e, & J. Chem. Soc., Perkin Trans. I, 1975, (9), 830-41 --------	1-17

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 8901399 SA 33118

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 04/04/90
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0236872	16-09-87	AU-B- 588437	14-09-89
		AU-A- 6990287	17-09-87
		JP-A- 62230757	09-10-87
EP-A- 0012401	25-06-80	AT-T- E6503	15-03-84
		AU-B- 530380	14-07-83
		AU-A- 5346179	19-06-80
		CA-C- 1262684	07-11-89
		JP-A- 55081845	20-06-80
		US-A- 4374829	22-02-83
DE-A- 2720996	24-11-77	US-A- 4105789	08-08-78
		CA-A- 1103259	16-06-81
		FR-A,B 2421874	02-11-79
		GB-A- 1575850	01-10-80
		JP-A- 52136121	14-11-77
		US-A- 4146639	27-03-79
		US-A- 4228184	14-10-80
		US-A- 4153725	08-05-79
		US-A- 4192882	11-03-80
		US-A- 4146641	27-03-79
		US-A- 4207342	10-06-80
		US-A- 4200649	29-04-80
		US-A- 4206232	03-06-80
		US-A- 4192881	11-03-80
		US-A- 4207336	10-06-80
		US-A- 4207337	10-06-80
EP-A- 0274453	13-07-88	FR-A- 2609289	08-07-88
		JP-A- 63258449	25-10-88
EP-A- 0214639	18-03-87	US-A- 4599361	08-07-86
		US-A- 4743587	10-05-88
		AU-B- 588362	14-09-89
		AU-A- 6240886	12-03-87
		JP-A- 62103052	13-05-87

EPO FORM P0479

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07C 311/29, C07D 295/18, 213/56, A61K 31/535, 31/44, 31/495, 31/40, 31/18

A1

(11) International Publication Number: **WO 96/27583**

(43) International Publication Date: 12 September 1996 (12.09.96)

(21) International Application Number: PCT/US96/02679

(22) International Filing Date: 7 March 1996 (07.03.96)

(30) Priority Data:
08/401,049 8 March 1995 (08.03.95) US

(60) Parent Application or Grant
(63) Related by Continuation
US 08/401,049 (CON)
Filed on 8 March 1995 (08.03.95)

(71) Applicant *(for all designated States except US)*: PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017-5755 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: ROBINSON, Ralph, P. [US/US]; 30 Friartuck Drive, Gales Ferry, CT 06335 (US). RIZZI, James, P. [US/US]; 34 Devonshire Drive, Waterford, CT 06335 (US).

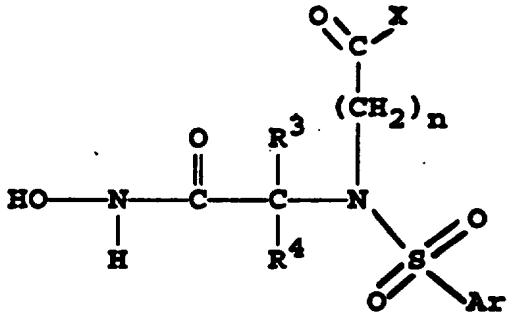
(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: ARYLSULFONYLAMINO HYDROXAMIC ACID DERIVATIVES

(57) Abstract

A compound of formula (I), wherein n, X, R^3, R^4 and Ar are as defined above, useful in the treatment of a condition selected from the group consisting of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of TNF.



(I)

FOR THE PURPOSES OF INFORMATION ONLY

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

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

ARYLSULFONYLAMINO HYDROXAMIC ACID DERIVATIVES

Background of the Invention

The present invention relates to arylsulfonylamino hydroxamic acid derivatives which are inhibitors of matrix metalloproteinases or the production of tumor necrosis factor (hereinafter also referred to as TNF) and as such are useful in the treatment of a condition selected from the group consisting of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of TNF.

This invention also relates to a method of using such compounds in the treatment of the above diseases in mammals, especially humans, and to the pharmaceutical compositions useful therefor.

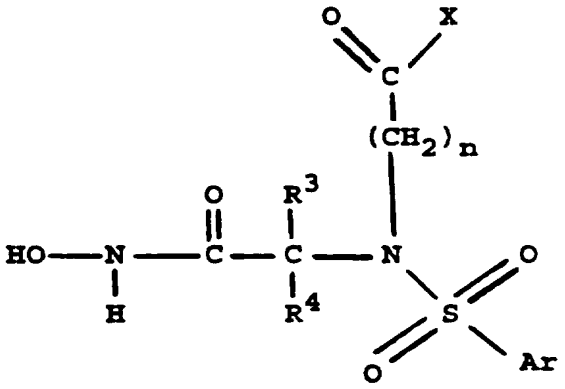
There are a number of enzymes which effect the breakdown of structural proteins and which are structurally related metalloproteases. Matrix-degrading metalloproteinases, such as gelatinase, stromelysin and collagenase, are involved in tissue matrix degradation (e.g. collagen collapse) and have been implicated in many pathological conditions involving abnormal connective tissue and basement membrane matrix metabolism, such as arthritis (e.g. osteoarthritis and rheumatoid arthritis), tissue ulceration (e.g. corneal, epidermal and gastric ulceration), abnormal wound healing, periodontal

disease, bone disease (e.g. Paget's disease and osteoporosis), tumor metastasis or invasion, as well as HIV-infection (J. Leuk. Biol., 52 (2):244-248, 1992).

Tumor necrosis factor is recognized to be involved in many infectious and auto-immune diseases (W. Friers, FEBS Letters, 1991, 285, 199). Furthermore, it has been shown that TNF is the prime mediator of the inflammatory response seen in sepsis and septic shock (C.E. Spooner et al., Clinical Immunology and Immunopathology, 1992, 62 S11).

Summary of the Invention

The present invention relates to a compound of the formula



I

or the pharmaceutically acceptable salts thereof, wherein

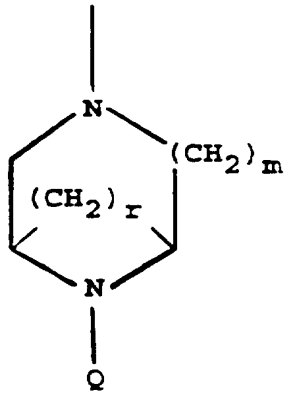
n is 1 to 6;

X is hydroxy, (C_1-C_6)alkoxy or NR^1R^2 wherein R^1 and R^2 are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_5-C_9)heteroarylpiperidyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperidyl, (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperidyl, (C_1-C_6)acylpiperidyl, (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_5-C_9)heteroaryl(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl(C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, $R^5(C_2-$

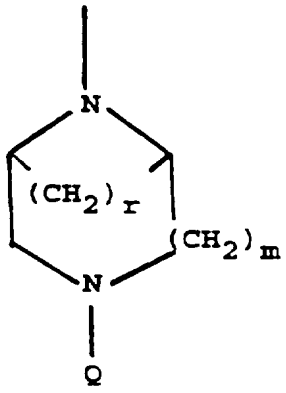
C_6)alkyl, (C_1-C_5)alkyl(CHR^5)(C_1-C_6)alkyl wherein R^5 is hydroxy, (C_1-C_6)acyloxy, (C_1-C_6)alkoxy, piperazino, (C_1-C_6)alkylamino, (C_1-C_6)alkylthio, (C_6-C_{10})arylthio, (C_1-C_6)alkylsulfinyl, (C_6-C_{10})arylsulfinyl, (C_1-C_6)alkylsulfoxyl, (C_6-C_{10})arylsulfoxyl, amino, (C_1-C_6)alkylamino, ((C_1-C_6)alkyl)$_2$amino, (C_1-C_6)acylpiperazino, (C_1-C_6)alkylpiperazino, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazino, (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperazino, morpholino, thiomorpholino, piperidino or pyrrolidino; R^6 (C_1-C_6)alkyl, (C_1-C_5)alkyl(CHR^6)(C_1-C_6)alkyl wherein R^6 is piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperidyl, (C_5-C_9)heteroarylpiperidyl or (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperidyl; and CH(R^7)COR^8 wherein R^7 is hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_5-C_9)heteroaryl(C_1-C_6)alkyl, (C_1-C_6)alkylthio(C_1-C_6)alkyl, (C_6-C_{10})arylthio(C_1-C_6)alkyl, (C_1-C_6)alkylsulfinyl(C_1-C_6)alkyl, (C_6-C_{10})arylsulfinyl(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonyl(C_1-C_6)alkyl, (C_6-C_{10})arylsulfonyl(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, ((C_1-C_6)alkylamino)$_2$(C_1-C_6)alkyl, R^{9}R^{10}NCO(C_1-C_6)alkyl or R^{9}OCO(C_1-C_6)alkyl wherein R^9 and R^{10} are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl and (C_5-C_9)heteroaryl(C_1-C_6)alkyl; and R^8 is R^{11}O or R^{11}R^{12}N wherein R^{11} and R^{12} are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl and (C_5-C_9)heteroaryl(C_1-C_6)alkyl;

or R^1 and R^2, or R^9 and R^{10}, or R^{11} and R^{12} may be taken together to form an azetidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, (C_1-C_6)acylpiperazinyl, (C_1-C_6)alkylpiperazinyl, (C_6-C_{10})arylpiperazinyl, (C_5-

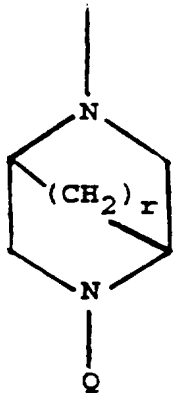
C_9)heteroarylpiperazinyl or a bridged diazabicycloalkyl ring selected from the group consisting of



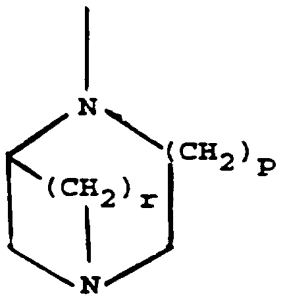
a



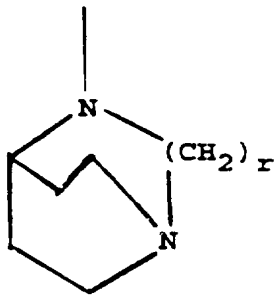
b



c



d



e

wherein r is 1, 2 or 3;

m is 1 or 2;

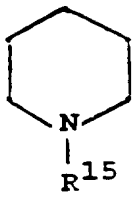
p is 0 or 1; and

Q is hydrogen, (C_1-C_3)alkyl or (C_1-C_6)acyl;

R^3 and R^4 are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, trifluoromethyl, trifluoromethyl(C_1-C_6)alkyl, (C_1-C_6)alkyl (difluoromethylene), (C_1-C_3)alkyl(difluoromethylene)(C_1-C_3)alkyl, (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_5-C_9)heteroaryl(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl(C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)acyloxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, piperazinyl(C_1-C_6)alkyl, (C_1-

C_6)acylamino(C_1-C_6)alkyl, piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_5-C_9)heteroaryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_1-C_6)alkylthio(C_1-C_6)alkyl, (C_6-C_{10})arylthio(C_1-C_6)alkyl, (C_1-C_6)alkylsulfinyl(C_1-C_6)alkyl, (C_6-C_{10})arylsulfinyl(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonyl(C_1-C_6)alkyl, (C_6-C_{10})arylsulfonyl(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, ((C_1-C_6)alkylamino)$_2$(C_1-C_6)alkyl, $R^{13}CO$(C_1-C_6)alkyl wherein R^{13} is $R^{20}O$ or $R^{20}R^{21}N$ wherein R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl or (C_5-C_9)heteroaryl(C_1-C_6)alkyl; or R^{14}(C_1-C_6)alkyl wherein R^{14} is (C_1-C_6)acylpiperazino, (C_6-C_{10})arylpiperazino, (C_5-C_9)heteroarylpiperazino, (C_1-C_6)alkylpiperazino, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazino, (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_5-C_9)heteroarylpiperidyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperidyl, (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperidyl or (C_1-C_6)acylpiperidyl;

or R^3 and R^4, or R^{20} and R^{21} may be taken together to form a (C_3-C_6)cycloalkyl, oxacyclohexyl, thiocyclohexyl, indanyl or tetralinyl ring or a group of the formula



wherein R^{15} is hydrogen, (C_1-C_6)acyl, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_5-C_9)heteroaryl(C_1-C_6)alkyl or (C_1-C_6)alkylsulfonyl; and

Ar is (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_1-C_6)alkyl(C_6-C_{10})aryl, (C_1-C_6)alkoxy(C_6-C_{10})aryl, ((C_1-

C_6)alkoxy)$_2$(C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_5-C_9)heteroaryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_5-C_9)heteroaryl, (C_1-C_6)alkoxy(C_5-C_9)heteroaryl, ((C_1-C_6)alkoxy)$_2$(C_5-C_9)heteroaryl, (C_6-C_{10})aryloxy(C_5-C_9)heteroaryl, (C_5-C_9)heteroaryloxy(C_5-C_9)heteroaryl;

with the proviso that when either R^1 or R^2 is $CH(R^7)COR^8$ wherein R^7 and R^8 are as defined above, the other of R^1 or R^2 is hydrogen, (C_1-C_6)alkyl or benzyl.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof.

The term "alkoxy", as used herein, includes O-alkyl groups wherein "alkyl" is defined above.

The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl or naphthyl, optionally substituted by 1 to 3 substituents selected from the group consisting of fluoro, chloro, trifluoromethyl, (C_1-C_6)alkoxy, (C_6-C_{10})aryloxy, trifluoromethoxy, difluoromethoxy and (C_1-C_6)alkyl.

The term "heteroaryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic heterocyclic compound by removal of one hydrogen, such as pyridyl, furyl, pyroyl, thienyl, isothiazolyl, imidazolyl, benzimidazolyl, terazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzofuryl, isobenzofuryl, benzothienyl, pyrazolyl, indolyl, isoindolyl, purinyl, carbazolyl, isoxazolyl, thiazolyl, oxazolyl, benzthiazolyl or benzoxazolyl, optionally substituted by 1 to 2 substituents selected from the group consisting of fluoro, chloro, trifluoromethyl, (C_1-C_6)alkoxy, (C_6-C_{10})aryloxy, trifluoromethoxy, difluoromethoxy and (C_1-C_6)alkyl.

The term "acyl", as used herein, unless

otherwise indicated, includes a radical of the general formula RCO wherein R is alkyl, alkoxy, aryl, arylalkyl or aryalkyloxy and the terms "alkyl" or "aryl" are as defined above.

The term "acyloxy", as used herein, includes O-acyl groups wherein "acyl" is defined above.

The compound of formula I may have chiral centers and therefore exist in different enantiomeric forms. This invention relates to all optical isomers and stereoisomers of the compounds of formula I and mixtures thereof.

Preferred compounds of formula I include those wherein n is 2.

Other preferred compounds of formula I include those wherein Ar is 4-methoxyphenyl or 4-phenoxyphenyl.

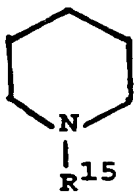
Other preferred compounds of formula I include those wherein either R^3 or R^4 is not hydrogen.

Other preferred compounds of formula I include those wherein n is 1 and either R^1 or R^2 is hydrogen.

Other preferred compounds of formula I include those wherein X is hydroxy, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and either R^3 or R^4 is not hydrogen.

Other preferred compounds of formula I include those wherein X is alkoxy, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and either R^3 or R^4 is not hydrogen.

Other preferred compounds of formula I include those wherein Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R^3 and R^4 are taken together to form (C_3-C_6)cycloalkanyl, oxacyclohexanyl, thiocyclohexanyl, indanyl or a group of the formula



wherein R^{15} is (C_1-C_6)acyl, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_5-C_9)heteroaryl(C_1-C_6)alkyl or (C_1-C_6)alkylsulfonyl.

More preferred compounds of formula I are those wherein n is 2, Ar is 4-methoxyphenyl or 4-phenoxyphenyl, R^1 and R^2 are taken together to form piperazinyl, (C_1-C_6)alkylpiperazinyl, (C_6-C_{10})aryl piperazinyl or (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperazinyl, and either R^3 or R^4 is not hydrogen or both R^3 and R^4 are not hydrogen.

More preferred compounds of formula I are those wherein n is 2, Ar is 4-methoxyphenyl or 4-phenoxyphenyl, R^1 is hydrogen or (C_1-C_6)alkyl, R^2 is 2-pyridylmethyl, 3-pyridylmethyl or 4-pyridylmethyl, and either R^3 or R^4 is not hydrogen or both R^3 and R^4 are not hydrogen.

More preferred compounds of formula I are those wherein n is 1, Ar is 4-methoxyphenyl or 4-phenoxyphenyl, R^1 is hydrogen, R^2 is 2-pyridylmethyl, 3-pyridylmethyl or 4-pyridylmethyl, and either R^3 or R^4 is not hydrogen or both R^3 and R^4 are not hydrogen.

More preferred compounds of formula I are those wherein n is 2, Ar is 4-methoxyphenyl, R^1 is hydrogen or (C_1-C_6)alkyl and R^2 is R^5 (C_2-C_6)alkyl wherein R^5 is morpholino, thiomorpholino, piperidino, pyrrolidino, (C_1-C_6)acylpiperazino, (C_1-C_6)alkylpiperazino, (C_6-C_{10})arylpiperazino, (C_5-C_9)heteroarylpiperazino, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazino or (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperazino and either R^3 or R^4 is not hydrogen or both R^3 and R^4 are not hydrogen.

More preferred compounds of formula I are

those wherein n is 1, Ar is 4-methoxyphenyl or 4-phenoxyphenyl, R^1 is hydrogen, R^2 is R^5 (C_2-C_6)alkyl wherein R^5 is morpholino, thiomorpholino, piperidino, pyrrolidino (C_1-C_6)acylpiperazino, (C_1-C_6)alkylpiperazino, (C_6-C_{10})arylpiperazino, (C_5-C_9)heteroarylpiperazino, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazino or (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperazino and either R^3 or R^4 is not hydrogen or both R^3 and R^4 are not hydrogen.

Specific preferred compounds of formula I include the following:

2-(R)-N-Hydroxy-2-[(4-methoxybenzenesulfonyl)(3-morpholin-4-yl-3-oxopropyl)amino]-3-methylbutyramide;

2-(R)-2-[(2-Benzylcarbamoylethyl)(4-methoxybenzenesulfonyl)amino]-N-hydroxy-3-methylbutyramide;

2-(R)-N-Hydroxy-2-((4-methoxybenzenesulfonyl)(2-[(pyridin-3-ylmethyl)-carbamoyl]ethyl)amino)-3-methylbutyramide;

2-(R)-N-Hydroxy-2-([4-methoxybenzenesulfonyl][2-(methylpyridin-3-ylmethylcarbamoyl)ethyl]amino)-3-methylbutyramide;

4-(3-[1-(R)-1-Hydroxycarbamoyl-2-methylpropyl)(4-methoxybenzenesulfonyl)amino]propionyl)piperazine-1-carboxylic acid, tert-butyl ester;

2-(R)-N-Hydroxy-2-[(4-methoxybenzenesulfonyl)(3-oxo-3-piperazin-1-ylpropyl)amino)-3-methylbutyramide hydrochloride;

2-(R)-2-[(Benzylcarbamoylmethyl)(4-methoxybenzenesulfonyl)amino]N-hydroxy-3-methylbutyramide;

2-(R)-N-Hydroxy-2-([4-methoxybenzenesulfonyl]-[(2-morpholin-4-ylethylcarbamoyl)methyl]amino)-3-methylbutyramide; and

2-(R)-N-Hydroxy-2-((4-

methoxybenzenesulfonyl)([(pyridin-3-ylmethyl)carbamoyl]methyl)amino)-3-methylbutyramide.

Other specific compounds of formula I include the following:

2-(R)-3,3,3-Trifluoro-N-hydroxy-2-[(methoxybenzenesulfonyl)(3-morpholin-4-yl-3-oxopropyl)amino]propionamide;

2-(R)-N-Hydroxy-2-((4-phenoxybenzenesulfonyl)[2-(methylpyridin-4-ylmethylcarbamoyl)ether]amino)-3-methylbutyramide;

4-[4-Methoxybenzenesulfonyl)(3-morpholin-4-yl-3-oxopropyl)amino]-1-methylpiperidene-4-carboxylic acid hydroxyamide;

2-(R)-N-Hydroxy-2-((4-methoxybenzenesulfonyl)-[3-(4-methylpiperazin-1-yl)-3-oxopropyl]amino)-3-methylbutyramide;

2-(R)-2-[(2-Carboxyethyl)(4-methoxybenzenesulfonyl)amino]-N-hydroxy-3-methylbutyramide;

[(2-Carboxyethyl)(3,4-dimethoxybenzenesulfonyl)amino]-N-hydroxy-acetamide;

2-(R)-2-[(2-Carbamoylethyl)(4-methoxybenzenesulfonyl)amino]-N-hydroxy-3-methylbutyramide;

2-(R),3-(R)-3,N-Dihydroxy-2-[(4-methoxybenzenesulfonyl)(3-oxo-3-piperidin-1-ylpropyl)amino]-butyramide;

2-(R)-N-Hydroxy-2-((4-methoxybenzenesulfonyl)[3-(methylpyridin-3-ylmethylcarbamoyl)propyl]amino)-3-methylbutyramide;

2-(R)-N-Hydroxy-2-((4-methoxybenzenesulfonyl)[2-(methylcarboxymethylcarbamoyl)ethyl]amino)-3-methylbutyramide;

2-(R)-N-Hydroxy-2-((4-methoxybenzenesulfonyl)-[(1-methylpiperidin-4-ylcarbamoyl)methyl]amino)-3-methylbutyramide;

2-(R)-2-Cyclohexyl-N-hydroxy-2-((4-methoxybenzenesulfonyl)-[3-(4-methylpiperazin-1-yl)-3-oxopropyl]amino)-acetamide;

2-(R)-N-Hydroxy-2-[(methoxybenzenesulfonyl)(3-morpholin-4-yl-3-oxopropyl)amino]-4-(morpholin-4-yl)butyramide.

The present invention also relates to a pharmaceutical composition for (a) the treatment of a condition selected from the group consisting of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) or (b) the inhibition of matrix metalloproteinases or the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising an amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, effective in such treatments and a pharmaceutically acceptable carrier.

The present invention also relates to a method for the inhibition of (a) matrix metalloproteinases or (b) the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof.

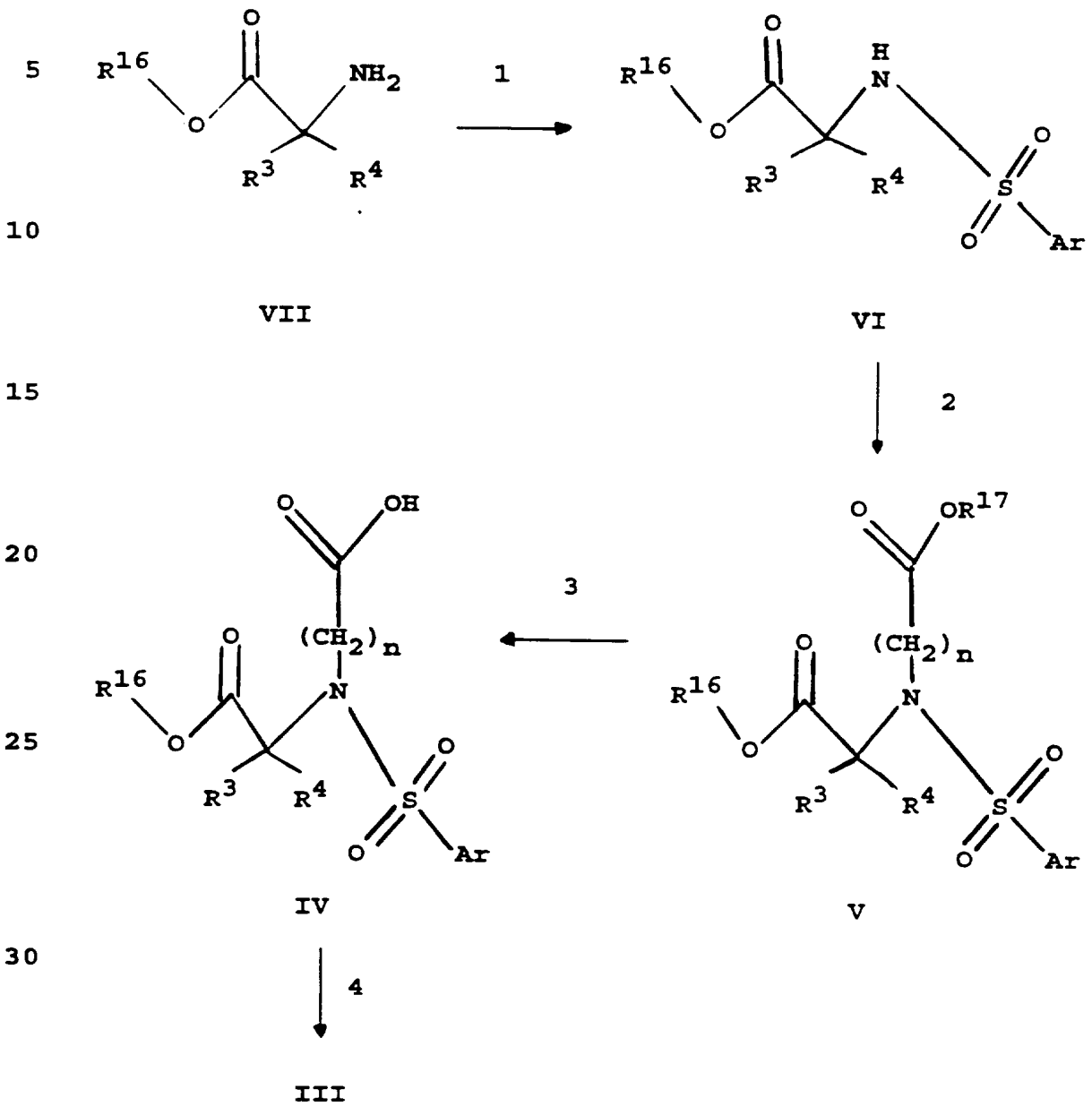
The present invention also relates to a method for treating a condition selected from the group consisting of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an amount of a

compound of claim 1 or a pharmaceutically acceptable salt thereof, effective in treating such a condition.

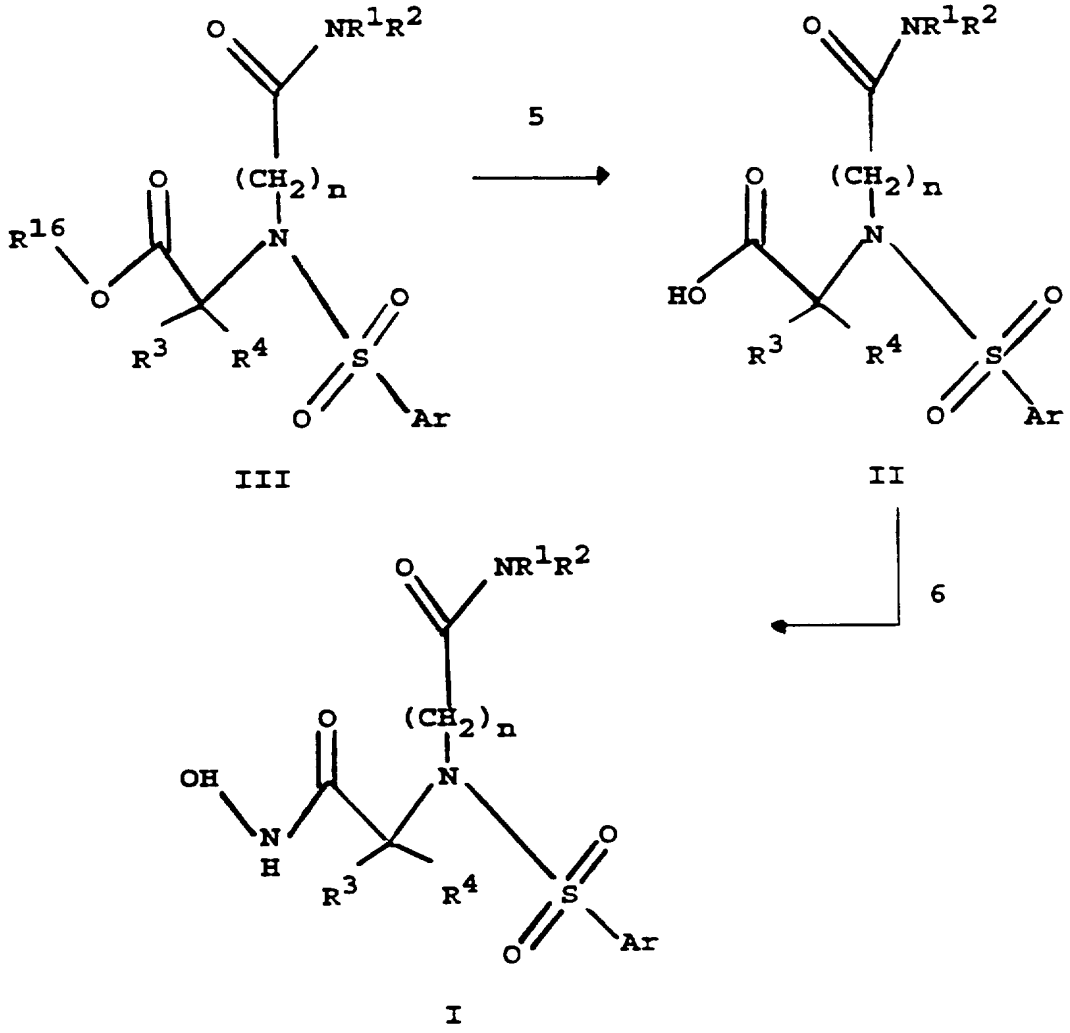
Detailed Description of the Invention

The following reaction Schemes illustrate the preparation of the compounds of the present invention. Unless otherwise indicated R^1, R^2, R^3, R^4, n and Ar in the reaction Schemes and the discussion that follow are defined as above.

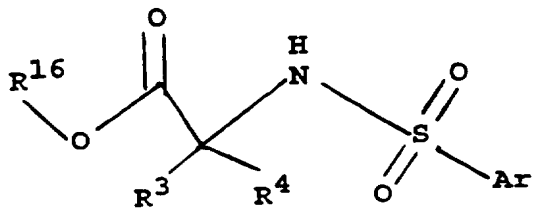
Scheme 1



Scheme 1 cont'd

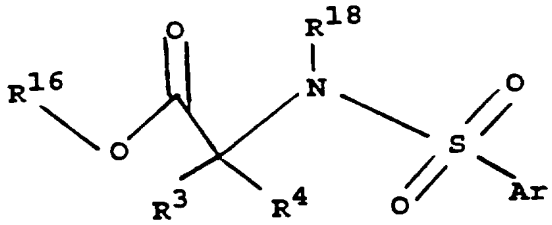


Scheme 2



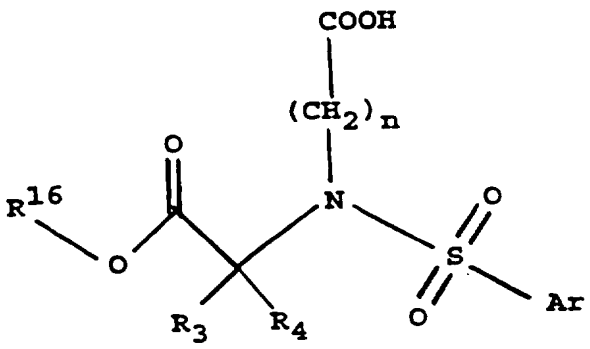
VI

1



VIII

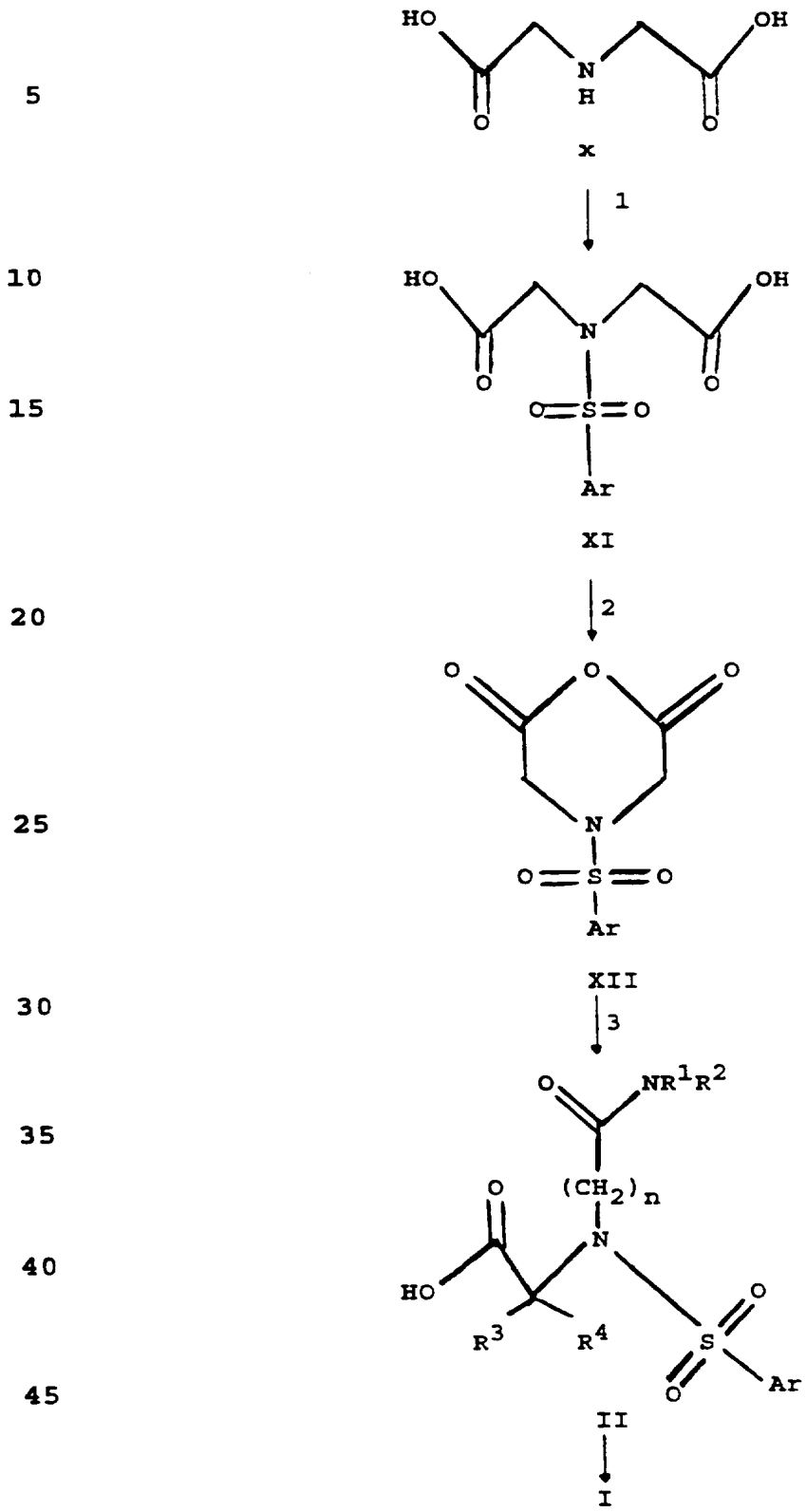
2



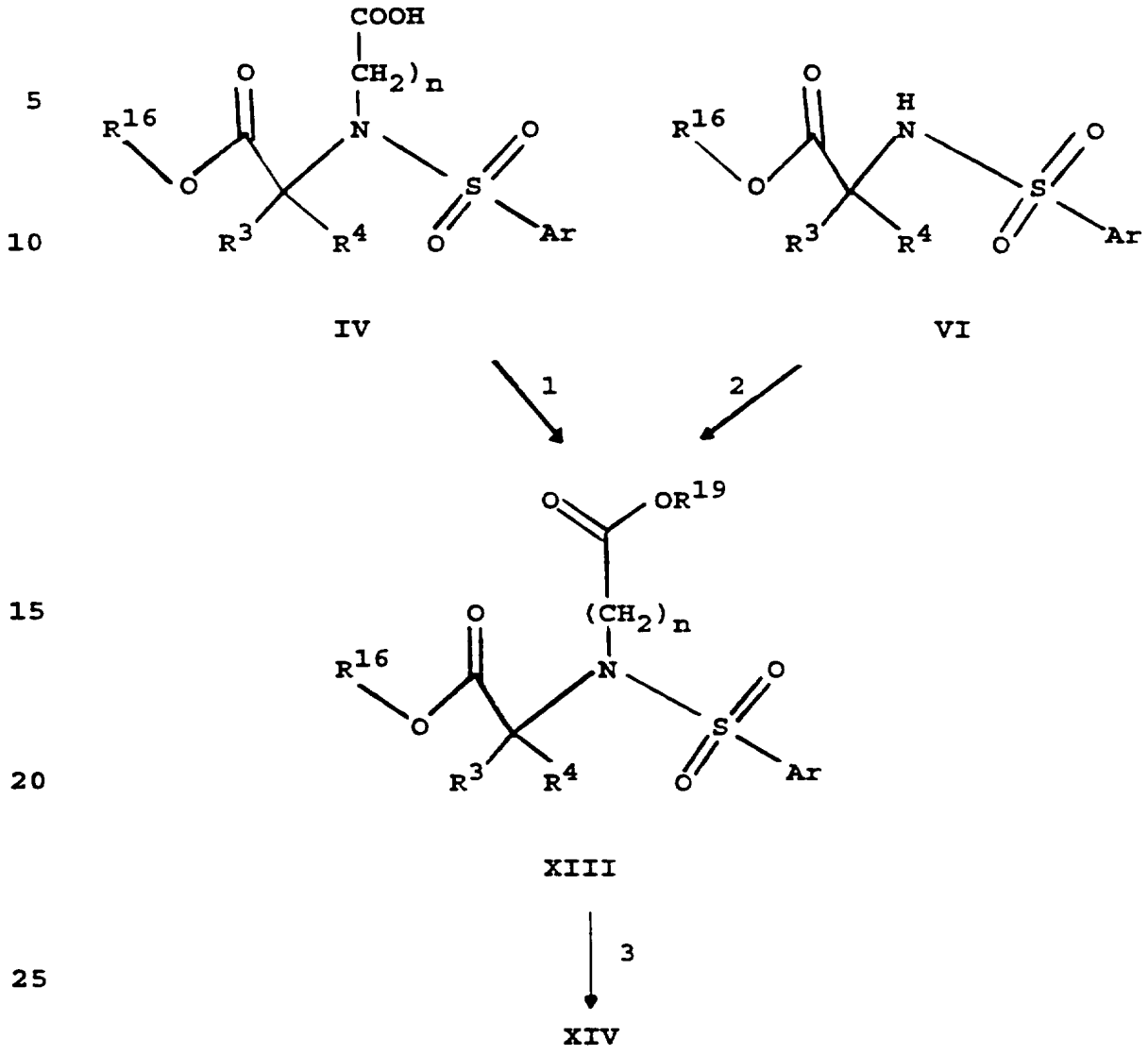
IV

I

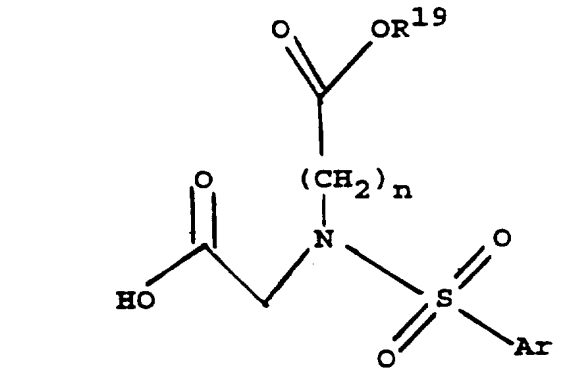
Scheme 3


HO
OH
N
H
O
O
x
1
HO
OH
N
O
O
O=S=O
Ar
XI
2
O
O
O
N
O=S=O
Ar
XII
3
O
NR1R2
(CH2)n
O
N
HO
R3
R4
S
O
O
Ar
II
I

Scheme 4

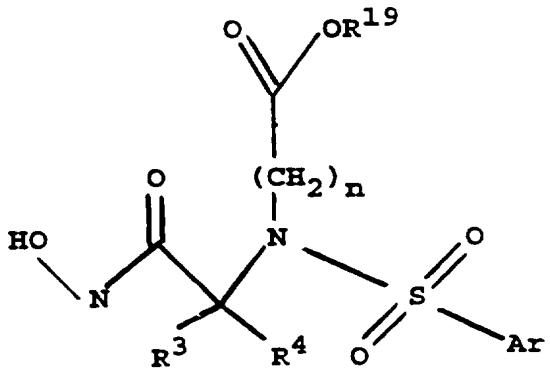


Scheme 4 cont'd



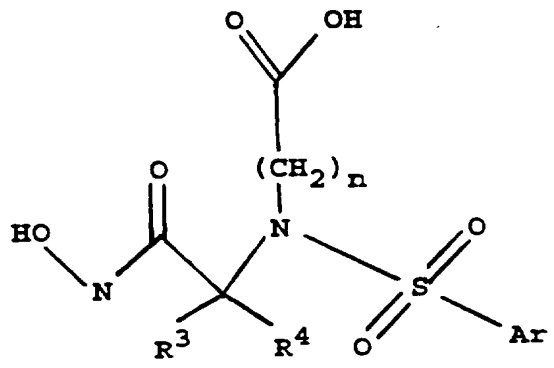
XIV

4



XV

5



XVI

In reaction 1 of Scheme 1, the amino acid compound of formula VII, wherein R^{16} is (C_1-C_6)alkyl, benzyl, allyl or tert-butyl, is converted to the corresponding compound of formula VI by reacting VII with a reactive functional derivative of an arylsulfonic acid compound, such as an arylsulfonyl chloride, in the presence of a base, such as triethylamine, and a polar solvent, such as tetrahydrofuran, dioxane, water or acetonitrile, preferably a mixture of dioxane and water. The reaction mixture is stirred, at room temperature, for time period between about 10 minutes to about 24 hours, preferably about 60 minutes.

In reaction 2 of Scheme 1, the arylsulfonyl amino compound of formula VI, wherein R^{16} is (C_1-C_6)alkyl, benzyl, allyl or tert-butyl, is converted to the corresponding compound of formula V, wherein n is 1, 3, 4, 5 or 6, by reacting VI with a reactive derivative of an alcohol of the formula

$$R^{17}\text{-O-}\overset{\overset{O}{\|}}{C}\text{-}(CH_2)_n\text{-OH}$$

such as the chloride, bromide or iodide derivative, preferably the bromide derivative, wherein the R^{17} protecting group is (C_1-C_6)alkyl, benzyl, allyl or tert-butyl, in the presence of a base such as potassium carbonate or sodium hydride, preferably sodium hydride, and a polar solvent, such as dimethylformamide. The reaction mixture is stirred, at room temperature, for a time period between about 60 minutes to about 48 hours, preferably about 18 hours. The R^{17} protecting group is chosen such that it may be selectively removed in the presence of and without loss of the R^{16} protecting group, therefore, R^{17} cannot be the same as R^{16}. Removal of the R^{17} protecting group from the compound of formula V to give the corresponding carboxylic acid of formula IV, in reaction 3 of Scheme 1, is carried out under conditions appropriate for that particular

R^{17} protecting group in use which will not affect the R^{16} protecting group. Such conditions include; (a) saponification where R^{17} is (C_1-C_6)alkyl and R^{16} is tert-butyl, (b) hydrogenolysis where R^{17} is benzyl and R^{16} is tert-butyl or (C_1-C_6)alkyl, (c) treatment with a strong acid such as trifluoroacetic acid or hydrochloric acid where R^{17} is tert-butyl and R^{16} is (C_1-C_6)alkyl, benzyl or allyl, or (d) treatment with tributyltinhydride and acetic acid in the presence of catalytic bis(triphenylphosphine) palladium (II) chloride where R^{17} is allyl and R^{16} is (C_1-C_6)alkyl, benzyl or tert-butyl.

In reaction 4 of Scheme 1, the carboxylic acid of formula IV is condensed with an amine, R^1R^2NH, or the salt thereof, to give the corresponding amide compound of formula III. The formation of amides from primary or secondary amines or ammonia and carboxylic acids is achieved by conversion of the carboxylic acid to an activated functional derivative which subsequently undergoes reaction with a primary or secondary amine or ammonia to form the amide. The activated functional derivative may be isolated prior to reaction with the primary or secondary amine or ammonia. Alternatively, the carboxylic acid may be treated with oxalyl chloride or thionyl chloride, neat or in an inert solvent, such as chloroform, at a temperature between about 25°C. to about 80°C., preferably about 50°C., to give the corresponding acid chloride functional derivative. The inert solvent and any remaining oxalyl chloride or thionyl chloride is then removed by evaporation under vacuum. The remaining acid chloride functional derivative is then reacted with the primary or secondary amine or ammonia in an inert solvent, such as methylene chloride, to form the amide. The preferred method for the condensation of the carboxylic acid of formula IV with an amine to provide the corresponding amide compound of

formula III is the treatment of IV with (benzotriazol-1-yloxy)tris(dimethylamino) phosphonium hexafluorophosphate in the presence of a base, such as triethylamine, to provide the benzotriazol-1-oxy ester in situ which, in turn, reacts with the amine, R^1R^2N, in an inert solvent, such as methylene chloride, at room temperature to give the amide compound of formula III.

Removal of the R^{16} protecting group from the compound of formula III to give the corresponding carboxylic acid of formula II, in reaction 5 of Scheme 1, is carried out under conditions appropriate for the particular R^{16} protecting group in use. Such conditions include; (a) saponification where R^{16} is lower alkyl, (b) hydrogenolysis where R^{16} is benzyl, (c) treatment with a strong acid, such as trifluoroacetic acid or hydrochloric acid, where R^{16} is tert-butyl, or (d) treatment with tributyltinhydride and acetic acid in the presence of catalytic bis(triphenylphosphine) palladium (II) chloride where R^{16} is allyl.

In reaction 6 of Scheme 1, the carboxylic acid compound of formula II is converted to the hydroxamic acid compound of formula I by treating II with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide and 1-hydroxybenztriazole in a polar solvent, such as dimethylformamide, followed by the addition of hydroxylamine to the reaction mixture after a time period between about 15 minutes to about 1 hour, preferably about 30 minutes. The hydroxylamine is preferably generated in situ from a salt form, such as hydroxylamine hydrochloride, in the presence of a base, such as N-methylmorpholine. Alternatively, a protected derivative of hydroxylamine or its salt form, where the hydroxyl group is protected as a tert-butyl, benzyl or allyl ether, may be used in the presence of (benzotriazol-1-yloxy)tris(dimethylamino) phosphonium

hexafluorophosphate and a base, such as N-methylmorpholine. Removal of the hydroxylamine protecting group is carried out by hydrogenolysis for a benzyl protecting group or treatment with a strong acid, such as trifluoroacetic acid, for a tert-butyl protecting group. The allyl protecting group may be removed by treatment with tributyltinhydride and acetic acid in the presence of catalytic bis(triphenylphosphine) palladium (II) chloride. N,O-bis(4-methoxybenzyl)hydroxylamine may also be used as the protected hydroxylamine derivative where deprotection is achieved using a mixture of methanesulfonic acid and trifluoroacetic acid.

In reaction 1 of Scheme 2, the arylsulfonylamino compound of formula VI, wherein R^{16} is (C_1-C_6)alkyl, benzyl or tert-butyl, is converted to the corresponding compound of formula VIII, wherein R^{18} is 2-propenyl or 3-butenyl, by reacting IX with a reactive functional derivative, such as the halide, preferably the iodide derivative, of 2-propen-1-ol when R^{18} is 2-propenyl or 3-buten-1-ol when R^{18} is 3-butenyl, in the presence of a base, such as potassium carbonate, cesium carbonate or sodium hydride, preferably sodium hydride when R^{18} is 2-propenyl or cesium carbonate when R^{18} is 3-butenyl. The reaction is stirred in a polar solvent, such as dimethylformamide, at room temperature, for a time period between about 2 hours to about 48 hours, preferably about 18 hours.

In reaction 2 of Scheme 2, the compound of formula VIII is converted to the carboxylic acid compound of formula IV, wherein n is 2. The compound of formula VIII, wherein R^{18} is 2-propenyl, is converted to the compound of formula IV, wherein n is 2, by reacting VIII with borane-dimethylsulfide complex, followed by immediate oxidation using chromium trioxide in aqueous acetic acid. The oxidative

cleavage of terminal olefins to carboxylic acids can be achieved by several methods known in the art. The preferred method for the oxidative cleavage of the compound of formula VIII, wherein R^{18} is 3-butenyl, to obtain the carboxylic acid compound of formula IV is to react VIII with sodium periodate in the presence of a catalytic amount of ruthenium (III) chloride in a mixture of carbon tetrachloride, acetonitrile and water.

The compound of formula IV, wherein n is 2, is further reacted to provide the hydroxamic acid compound of formula I, wherein n is 2, according to the procedure described above in reactions 4, 5 and 6 of Scheme 1.

An alternative method for the synthesis of the hydroxamic acid compound of formula I, wherein n is 1 and R^3 and R^4 are both hydrogen, is shown in reaction 1 of Scheme 3, beginning with reacting iminoacetic acid or a metal or ammonium salt of iminoacetic acid of formula X with a functional derivative of an arylsulfonic acid compound, such as an arylsulfonyl chloride, at room temperature, in the presence of a suitable base, such as triethylamine, and a polar solvent such as tetrahydrofuran, dioxane, water or acetonitrile, preferably a mixture of dioxane and water, to give the corresponding dicarboxylic acid compound of formula XI.

In reaction 2 of Scheme 3, the dicarboxylic acid compound of formula XI is dehydrated to give a cyclic anhydride compound of formula XII. The formation of cyclic anhydrides by dehydration of dicarboxylic acids may be achieved by a variety of means. The preferred method for the dehydration of the dicarboxylic acid compound of formula XI to give a cyclic anhydride compound of formula XII is to treat XI with an excess of acetic anhydride at a temperature between about 25°C. to about 80°C., preferably about

60°C. Excess acetic anhydride and acetic acid, a by-product of the reaction, are removed by evaporation under reduced pressure leaving the cyclic anhydride compound of formula XII.

In reaction 3 of Scheme 3, the cyclic anhydride compound of formula XII is reacted, at room temperature, with an amine, NR^1R^2, or a salt of the amine, such as the hydrochloride, in the presence of a base, such as triethylamine, to give the carboxylic acid of formula II, wherein n is 1 and R^3 and R^4 are both hydrogen. Suitable solvents for the reaction are those that will not react with the starting materials, which include chloroform, methylene chloride and dimethylformamide, preferably methylene chloride.

The compound of formula II is further reacted to give the hydroxamic acid compound of formula I, wherein n is 1 and R^3 and R^4 are both hydrogen, according to the procedure described above in reaction 6 of Scheme 1.

In reaction 1 of Scheme 4, the carboxylic acid compound of formula IV, wherein n is 2, is converted to the corresponding compound of formula V, wherein R^{19} is (C_1-C_6)alkyl or tert-butyl, by reacting IV with a compound of the formula

$$(R^{19}O)_2CHN(CH_3)_2$$

wherein R^{19} is (C_1-C_6)alkyl or tert-butyl, in an inert solvent, such as toluene, at a temperature between about 60°C. to about 100°C., preferably about 100°C., for a time period between about 1 hour to about 3 hours, preferably 2 hours. In reaction 2 of Scheme 4, the arylsulfonyl amino compound of formula VI wherein n is 1, 3, 4, 5 or 6 and R^{16} is (C_1-C_6)alkyl, benzyl, allyl or tert-butyl, is converted to the corresponding compound of formula XIII, wherein R^{19} is (C_1-C_6)alkyl or tert-butyl, by reacting VI with a reactive derivative of an alcohol of the formula

$$R^{19}\text{-O-}\overset{O}{\overset{\|}{C}}\text{-}(CH_2)_n\text{-OH}$$

such as the chloride, bromide or iodide derivative, preferably the bromide derivative, wherein R^{19} is (C_1-C_6)alkyl or tert-butyl, in the presence of a base such as potassium carbonate or sodium hydride, preferably sodium hydride, and a polar solvent, such as dimethylformamide. The reaction is stirred, at room temperature, for a time period between about 60 minutes to about 48 hours, preferably about 18 hours. The R^{16} protecting group, of the compounds of formulas IV and VI, is chosen such that it may be selectively removed in the presence of and without loss of the R^{19} (C_1-C_6)alkyl or tert-butyl group, therefore, R^{16} cannot be the same as R^{19}. Removal of the R^{16} protecting group from the compound of formula XIII to give the corresponding carboxylic acid of formula XIV, wherein n is 1 to 6, in reaction 3 of Scheme 4, is carried out under conditions appropriate for that particular R^{16} protecting group in use which will not affect the R^{19} (C_1-C_6)alkyl or tert-butyl group. Such conditions include; (a) saponification where R^{16} is (C_1-C_6)alkyl and R^{19} is tert-butyl, (b) hydrogenolysis where R^{16} is benzyl and R^{19} is tert-butyl or (C_1-C_6)alkyl, (c) treatment with a strong acid such as trifluoroacetic acid or hydrochloric acid where R^{16} is tert-butyl and R^{19} is (C_1-C_6)alkyl, or (d) treatment with tributyltinhydride and acetic acid in the presence of catalytic bis(triphenylphosphine) palladium (II) chloride where R^{16} is allyl and R^{19} is (C_1-C_6)alkyl or tert-butyl.

In reaction 4 of Scheme 4, the carboxylic acid of formula XIV is converted to the hydroxamic acid compound of formula XV, wherein n is 1 to 6, by treating XIV with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide and 1-hydroxybenztriazole in a polar solvent, such as dimethylformamide, followed by the

addition of hydroxylamine to the reaction mixture after a time period between about 15 minutes to about 1 hour, preferably about 30 minutes. The hydroxylamine is preferably generated in situ from a salt form, such as hydroxylamine hydrochloride, in the presence of a base, such as N-methylmorpholine. Alternatively, a protected derivative of hydroxylamine or its salt form, where the hydroxyl group is protected as a tert-butyl, benzyl or allyl ether, may be used in the presence of (benzotriazol-1-yloxy)tris(dimethylamino) phosphonium hexafluorophosphate and a base, such as N-methylmorpholine. Removal of the hydroxylamine protecting groups is carried out by hydrogenolysis for a benzyl protecting group or treatment with a strong acid, such as trifluoroacetic acid, for a tert-butyl protecting group. The allyl protecting group may be removed by treatment with tributyltinhydride and acetic acid in the presence of catalytic bis(triphenylphosphine) palladium (II) chloride. N,O-bis(4-methoxybenzyl)hydroxylamine may also be used, when R^{19} is (C_1-C_6)alkyl, as the protected hydroxylamine derivative where deprotection is achieved using a mixture of methanesulfonic acid and trifluoroacetic acid.

In reaction 5 of Scheme 4, the amide formula of formula XV is, if desired, converted to the corresponding carboxylic acid compound of formula XVI by (a) saponification where R^{19} is lower alkyl or (b) treatment with a strong acid, such as trifluoroacetic acid or hydrochloric acid, where R^{19} is tert-butyl.

Pharmaceutically acceptable salts of the acidic compounds of the invention are salts formed with bases, namely cationic salts such as alkali and alkaline earth metal salts, such as sodium, lithium, potassium, calcium, magnesium, as well as ammonium salts, such as ammonium, trimethyl-ammonium, diethylammonium, and tris-(hydroxymethyl)-

methylammonium salts.

Similarly acid addition salts, such as of mineral acids, organic carboxylic and organic sulfonic acids e.g. hydrochloric acid, methanesulfonic acid, maleic acid, are also possible provided a basic group, such as pyridyl, constitutes part of the structure.

The ability of the compounds of formula I or their pharmaceutically acceptable salts (hereinafter also referred to as the compounds of the present invention) to inhibit matrix metalloproteinases or the production of tumor necrosis factor (TNF) and, consequently, demonstrate their effectiveness for treating diseases characterized by matrix metalloproteinase or the production of tumor necrosis factor is shown by the following in vitro assay tests.

Biological Assay

Inhibition of Human Collagenase (MMP-1)

Human recombinant collagenase is activated with trypsin using the following ratio: 10 μg trypsin per 100 μg of collagenase. The trypsin and collagenase are incubated at room temperature for 10 minutes then a five fold excess (50 μg/10 μg trypsin) of soybean trypsin inhibitor is added.

10 mM stock solutions of inhibitors are made up in dimethyl sulfoxide and then diluted using the following Scheme:

10 mM ---> 120 μM ---> 12 μM ---> 1.2 μM ---> 0.12 μM

Twenty-five microliters of each concentration is then added in triplicate to appropriate wells of a 96 well microfluor plate. The final concentration of inhibitor will be a 1:4 dilution after addition of enzyme and substrate. Positive controls (enzyme, no inhibitor) are set up in wells D1-D6 and blanks (no enzyme, no inhibitors) are set in wells D7-D12.

Collagenase is diluted to 400 ng/ml and 25 μl is then added to appropriate wells of the microfluor plate. Final concentration of collagenase in the assay

is 100 ng/ml.

Substrate (DNP-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2) is made as a 5 mM stock in dimethyl sulfoxide and then diluted to 20 μM in assay buffer. The assay is initiated by the addition of 50 μl substrate per well of the microfluor plate to give a final concentration of 10 μM.

Fluorescence readings (360 nM excitation, 460 nm emission) were taken at time 0 and then at 20 minute intervals. The assay is conducted at room temperature with a typical assay time of 3 hours.

Fluorescence vs time is then plotted for both the blank and collagenase containing samples (data from triplicate determinations is averaged). A time point that provides a good signal (the blank) and that is on a linear part of the curve (usually around 120 minutes) is chosen to determine IC_{50} values. The zero time is used as a blank for each compound at each concentration and these values are subtracted from the 120 minute data. Data is plotted as inhibitor concentration vs % control (inhibitor fluorescence divided by fluorescence of collagenase alone x 100). IC_{50}'s are determined from the concentration of inhibitor that gives a signal that is 50% of the control.

If IC_{50}'s are reported to be <0.03 μM then the inhibitors are assayed at concentrations of 0.3 μM, 0.03 μM, 0.03 μM and 0.003 μM.

Inhibition of Gelatinase (MMP-2)

Inhibition of gelatinase activity is assayed using the Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2 substrate (10 μM) under the same conditions as inhibition of human collagenase (MMP-1).

72kD gelatinase is activated with 1 mM APMA (p-aminophenyl mercuric acetate) for 15 hours at 4°C. and is diluted to give a final concentration in the assay of 100 mg/ml. Inhibitors are diluted as for inhibition of human collagenase (MMP-1) to give final

concentrations in the assay of 30 μM, 3 μM, 0.3 μM and 0.03 μM. Each concentration is done in triplicate.

Fluorescence readings (360 nm excitation, 460 emission) are taken at time zero and then at 20 minutes intervals for 4 hours.

IC_{50}'s are determined as per inhibition of human collagenase (MMP-1). If IC_{50}'s are reported to be less than 0.03 μM, then the inhibitors are assayed at final concentrations of 0.3 μM, 0.03 μM, 0.003 μM and 0.003 μM.

Inhibition of Stromelysin Activity (MMP-3)

Inhibition of stromelysin activity is based on a modified spectrophotometric assay described by Weingarten and Feder (Weingarten, H. and Feder, J., Spectrophotometric Assay for Vertebrate Collagenase, Anal. Biochem. 147, 437-440 (1985)). Hydrolysis of the thio peptolide substrate [Ac-Pro-Leu-Gly-$SCH[CH_2CH(CH_3)_2]CO$-Leu-Gly-OC_2H_5] yields a mercaptan fragment that can be monitored in the presence of Ellman's reagent.

Human recombinant prostromelysin is activated with trypsin using a ratio of 1 μl of a 10 mg/ml trypsin stock per 26 μg of stromelysin. The trypsin and stromelysin are incubated at 37°C. for 15 minutes followed by 10 μl of 10 mg/ml soybean trypsin inhibitor for 10 minutes at 37°C. to quench trypsin activity.

Assays are conducted in a total volume of 250 μl of assay buffer (200 mM sodium chloride, 50 mM MES, and 10 mM calcium chloride, pH 6.0) in 96-well microliter plates. Activated stromelysin is diluted in assay buffer to 25 μg/ml. Ellman's reagent (3-Carboxy-4-nitrophenyl disulfide) is made as a 1M stock in dimethyl formamide and diluted to 5 mM in assay buffer with 50 μl per well yielding at 1 mM final concentration.

10 mM stock solutions of inhibitors are made in dimethyl sulfoxide and diluted serially in assay

buffer such that addition of 50 μL to the appropriate wells yields final concentrations of 3 μM, 0.3 μM, 0.003 μM, and 0.0003 μM. All conditions are completed in triplicate.

A 300 mM dimethyl sulfoxide stock solution of the peptide substrate is diluted to 15 mM in assay buffer and the assay is initiated by addition of 50 μl to each well to give a final concentration of 3 mM substrate. Blanks consist of the peptide substrate and Ellman's reagent without the enzyme. Product formation was monitored at 405 nm with a Molecular Devices UVmax plate reader.

IC_{50} values were determined in the same manner as for collagenase.

Inhibition of MMP-13

Human recombinant MMP-13 is activated with 2mM APMA (p-aminophenyl mercuric acetate) for 1.5 hours, at 37°C. and is diluted to 400 mg/ml in assay buffer (50 mM Tris, pH 7.5, 200 mM sodium chloride, 5mM calcium chloride, 20μM zinc chloride, 0.02% brij). Twenty-five microliters of diluted enzyme is added per well of a 96 well microfluor plate. The enzyme is then diluted in a 1:4 ratio in the assay by the addition of inhibitor and substrate to give a final concentration in the assay of 100 mg/ml.

10 mM stock solutions of inhibitors are made up in dimethyl sulfoxide and then diluted in assay buffer as per the inhibitor dilution scheme for inhibition of human collagenase (MMP-1): Twenty-five microliters of each concentration is added in triplicate to the microfluor plate. The final concentrations in the assay are 30 μM, 3 μM, 0.3 μM and 0.03 μM.

Substrate (Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2) is prepared as for inhibition of human collagenase (MMP-1) and 50 μl is added to each well to give a final assay concentration of 10 μM.

Fluorescence readings (360 nM excitation; 450 emission) are taken at time 0 and every 5 minutes for 1 hour.

Positive controls consist of enzyme and substrate with no inhibitor and blanks consist of substrate only.

IC_{50}'s are determined as per inhibition of human collagenase (MMP-1). If IC_{50}'s are reported to be less than 0.03 μM, inhibitors are then assayed at final concentrations of 0.3 μM, 0.03 μM, 0.003 μM and 0.0003 μM.

Inhibition of TNF Production

The ability of the compounds or the pharmaceutically acceptable salts thereof to inhibit the production of TNF and, consequently, demonstrate their effectiveness for treating diseases involving the production of TNF is shown by the following in vitro assay:

Human mononuclear cells were isolated from anti-coagulated human blood using a one-step Ficoll-hypaque separation technique. The mononuclear cells were washed three times in Hanks balanced salt solution (HBSS) with divalent cations and resuspended to a density of 2 x 10^6/ml in HBSS containing 1% BSA. Differential counts determined using the Abbott Cell Dyn 3500 analyzer indicated that monocytes ranged from 17 to 24% of the total cells in these preparations.

180μ of the cell suspension was aliquoted into flate bottom 96 well plates (Costar). Additions of compounds and LPS (100ng/ml final concentration) gave a final volume of 200μl. All conditions were performed in triplicate. After a four hour incubation at 37°C. in an humidified CO_2 incubator, plates were removed and centrifuged (10 minutes at approximately 250 x g) and the supernatants removed and assayed for TNFα using the R&D ELISA Kit.

For administration to humans for the inhibition of matrix metalloproteinases or the

production of tumor necrosis factor (TNF), a variety of conventional routes may be used including orally, parenterally and topically. In general, the active compound will be administered orally or parenterally at dosages between about 0.1 and 25 mg/kg body weight of the subject to be treated per day, preferably from about 0.3 to 5 mg/kg. However, some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

The compounds of the present invention can be administered in a wide variety of different dosage forms, in general, the therapeutically effective compounds of this invention are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelation and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired,

emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For parenteral administration (intramuscular, intraperitoneal, subcutaneous and intravenous use) a sterile injectable solution of the active ingredient is usually prepared. Solutions of a therapeutic compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably adjusted and buffered, preferably at a pH of greater than 8, if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

The present invention is illustrated by the following examples, but it is not limited to the details thereof.

EXAMPLE 1

2-(R)-N-Hydroxy-2-[(-methoxybenzenesulfonyl)(2-morpholin-4-yl-2-oxoethyl)amino]-3-methylbutyramide

To a solution of D-valine benzyl ester hydrochloride (2.4 grams, 10 mmol) and triethylamine (2.5 grams, 3.5 mL, 25 mmol) in water (50 mL) and 1,4-dioxane (50 mL) is added 4-methoxybenzenesulfonyl chloride (2.3 grams, 11 mmol). The mixture was stirred at room temperature for 1 hour and then most of the solvent was removed by evaporation under vacuum. The mixture was diluted with ethyl acetate and was washed successively with dilute hydrochloric acid solution, water and brine. The organic solution was dried over magnesium sulfate and concentrated to leave N-(4-methoxybenzenesulfonyl)-D-valine benzyl ester as a

white solid, 3.6 grams (97%); m.p. 92-94°C.

N-(4-Methoxybenzenesulfonyl)-D-valine benzyl ester (1.50 grams, 4.0 mmol) was added to a suspension of sodium hydride (0.1 grams, 4.2 mmol) in dry dimethylformamide (20 mL) and, after 30 minutes, tert-butyl bromoacetate (0.8 mL, 4.2 mmol) was added. The resulting mixture was stirred overnight at room temperature and was then quenched by addition of saturated ammonium chloride solution (3 mL). The dimethylformamide was removed by evaporation under vacuum. The residue was taken up in ethyl acetate and washed with water and brine. After drying over magnesium sulfate, ethyl acetate was evaporated to leave an oil from which 2-(R)-2-[tert-butoxycarbonylmethyl(4-methoxybenzenesulfonyl)amino]-3-methylbutyric acid benzyl ester, a clear oil (1.92 grams, 98%), was isolated using flash chromatography on silica gel eluting with 15% ethyl acetate in hexane.

To a cold (0°C.) solution of 2-(R)-2-[tert-butoxycarbonylmethyl(4-methoxybenzenesulfonyl)amino]-3-methylbutyric acid benzyl ester (1.92 grams, 3.9 mmol) in methylene chloride (28 mL) was added trifluoroacetic acid (7 mL). The resulting solution was allowed to warm to room temperature and was stirred overnight. The methylene chloride and trifluoroacetic acid were evaporated under vacuum leaving 2-(R)-2-[carboxymethyl(4-methoxybenzenesulfonyl)amino)]-3-methylbutyric acid benzyl ester as a clear oil, 1.70 grams (100%).

To a solution of 2-(R)-2-[carboxymethyl(4-methoxybenzenesulfonyl)amino]-3-methylbutyric acid benzyl ester (573 mg, 1.32 mmol) in methylene chloride (12 mL) were added sequentially triethylamine (0.46 mL, 3.28 mmol), morpholine (0.127 mL, 1.46 mmol) and (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (646 mg, 1.46 mmol). The mixture was stirred at room temperature overnight and then

diluted with ethyl acetate. The solution was washed with 0.5 N hydrochloric acid solution and brine, dried over magnesium sulfate and concentrated under vacuum. The residue was chromatographed on silica gel using 40% ethyl acetate in hexane affording 2-(R)-2-[(4-methoxybenzenesulfonyl)(2-morpholin-4-yl-oxoethyl)amino]-3-methylbutyric acid benzyl ester as a clear oil, 590 mg (89%).

To a solution of 2-(R)-2-[(4-methoxybenzenesulfonyl)(2-morpholin-4-yl-2-oxoethyl)amino]-3-methylbutyric acid benzyl ester (590 mg, 1.17 mmol) in ethanol (50 mL) was added 10% palladium on activated carbon (200 mg). The mixture was agitated under 3 atmospheres hydrogen in a Parr shaker for 2 hours. The catalyst was removed by filtration through nylon (pore size 0.45 μm) and the solvent was evaporated leaving 2-(R)-2-[(4-methoxybenzenesulfonyl)(2-morpholin-4-yl-2-oxoethyl)amino]-3-methylbutyric acid as a white foam, 485 mg (100%).

To a solution of 2-(R)-2-[(4-methoxybenzenesulfonyl)(2-morpholin-4-yl-2-oxoethyl)amino]-3-methylbutyric acid (485 mg, 1.17 mmol) in methylene chloride (12 mL) were added sequentially triethylamine (0.52 mL, 3.71 mmol), O-benzylhydroxylamine hydrochloride (205 mg, 1.28 mmol) and (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (570 mg, 1.29 mmol). The mixture was stirred at room temperature overnight and then diluted with ethyl acetate. The solution was washed sequentially with 0.5 N hydrochloric acid solution, water, saturated sodium hydrogen carbonate solution and brine, dried over magnesium sulfate and concentrated under vacuum. The residue was chromatographed on silica gel using 20% hexane in ethyl acetate to afford 2-(R)-N-benzyloxy-2-[(4-methoxybenzenesulfonyl)(2-

morpholin-4-yl-2-oxoethyl)amino]-3-methylbutyramide as a white foam, 510 mg (84%).

To a solution of 2-(R)-N-benzyloxy-2-[(4-methoxybenzenesulfonyl)(2-morpholin-4-yl-2-oxoethyl)amino]-3-methylbutyramide (510 mg, 0.98 mmol) in methanol (50 mL) was added 5% palladium on activated carbon (120 mg). The mixture was agitated under 2 atmospheres hydrogen in a Parr shaker for 2 hours. The catalyst was removed by filtration through nylon (pore size 0.45 μm) and the solvent was evaporated leaving 2-(R)-N-hydroxy-2-[(-methoxybenzenesulfonyl)(2-morpholin-4-yl-2-oxoethyl)amino]-3-methylbutyramide as a white solid, 418 mg (99%); ^{1}H NMR ($CDCl_3$): δ 10.3 (br s, 1H), 7.90 (br s, 1H, overlapped), 7.86 (d, J = 8.8 Hz, 2H, overlapped), 6.94 (d, J = 8.8 Hz, 2H), 4.39 (d, J = 17.1 Hz, 1H), 4.09 (d, J = 17.1, 1H), 3.84 (s, 3H), 3.80-3.48 (m, 9H), 2.20-1.95 (m, 1H), 0.82 (d, J = 6.5 Hz, 3H), 0.45 (d, J = 6.5 Hz, 3H); MS (LSIMS): m/z 430 (M+H).

EXAMPLE 2

2-(R)-N-Hydroxy-2-[(4-methoxybenzenesulfonyl)(3-morpholin-4-yl-3-oxopropyl)amino]-3-methylbutyramide

To a solution of N-(4-methoxybenzenesulfonyl)-D-valine benzyl ester (2.2 grams, 5.83 mmol) in dry dimethylformamide (40 mL) were added cesium carbonate (2.3 grams, 7.1 mmol) and 1-iodo-3-butene (1.3 grams, 7.1 mmol). The mixture was stirred at room temperature overnight and was then poured into water. The mixture was extracted twice with ether and the combined ether extracts were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was taken up in 20% ethyl acetate/hexane; starting material N-(4-methoxybenzenesulfonyl)-D-valine benzyl ester (1.5 g) crystallized from the mixture and was recovered by filtration. The filtrate was concentrated under vacuum and the residue was chromatographed on silica

gel using 20% ethyl acetate/hexane as eluent to provide 2-(R)-2-[but-3-enyl(4-methoxybenzenesulfonyl)amino]-3-methylbutyric acid benzyl ester as a clear oil, 404 mg (16%).

To a mixture of 2-(R)-2-[but-3-enyl(4-methoxybenzenesulfonyl)amino]-3-methylbutyric acid benzyl ester (780 mg, 1.81 mmol) and ruthenium (III) chloride hydrate (10 mg, 0.048 mmol) in acetonitrile (6 mL), carbon tetrachloride (6 mL) and water (8 mL) was added sodium periodate (1.7 grams, 7.9 mmol). After stirring at room temperature for 2 hours, the mixture was diluted with methylene chloride and filtered through diatomaceous earth. The organic layer was separated, washed with dilute hydrochloric acid solution and brine, dried over magnesium sulfate and concentrated to leave 2-(R)-2-[2-carboxyethyl(4-methoxybenzenesulfonyl)amino]-3-methylbutyric acid benzyl ester as an oil, 710 mg (87%).

Alternatively, the intermediate 2-(R)-2-[2-carboxyethyl(4-methoxybenzenesulfonyl)amino]-3-methylbutyric acid benzyl ester was prepared by the following higher yielding procedure:

N-(4-Methoxybenzenesulfonyl)-D-valine benzyl ester (18.8 grams, 49.8 mmol) was added to a suspension of sodium hydride (1.3 grams, 54 mmol) in dry dimethylformamide (200 mL) and, after 1.5 hours, a solution of allyl bromide (4.7 mL, 54 mmol) was added. The resulting mixture was stirred overnight at room temperature and was then quenched by addition of saturated ammonium chloride solution. The dimethylformamide was removed by evaporation under vacuum. The residue was taken up in ether and washed with water and brine. After drying over magnesium sulfate, ether was evaporated to leave an oil from which 2-(R)-2-[(4-methoxybenzenesulfonyl)prop-2-enylamino]-3-methylbutyric acid benzyl ester, a clear oil (18.1 grams, 87%), was isolated using flash

chromatography on silica gel eluting with 10% ethyl acetate in hexane and then 20% ethyl acetate in hexane.

To a 1 M solution of borane/disulfide complex in methylene chloride (1.45 mL, 2.9 mmol) was added a solution of 2-(R)-2-[(4-methoxybenzenesulfonyl)prop-2-enylamino]-3-methylbutyric acid benzyl ester (3.6 grams, 8.6 mmol) in methylene chloride (8 mL). The solution was stirred at room temperature for 4 hours at which time more 1 M solution of borane/disulfide complex in methylene chloride (2.0 mL, 4.0 mmol) was added. The mixture was stirred at room temperature overnight and was then added dropwise to a mechanically stirred solution of chromium trioxide (5.1 grams, 51.6 mole) in acetic acid (31 mL) and water (3.5 mL) while keeping the internal temperature between -5°C. and 10°C. After stirring at room temperature overnight, the mixture was diluted with water and extracted with methylene chloride. The extract was washed with brine, dried (magnesium sulfate) and concentrated. The residue was chromatographed on silica gel eluting successively with chloroform and 2% methanol in chloroform to afford 2-(R)-2-[2-carboxyethyl(4-methoxybenzenesulfonyl)amino]-3-methylbutyric acid benzyl as an oil (2.42 grams, 63%).

To a solution of 2-(R)-2-[2-carboxyethyl(4-methoxybenzenesulfonyl)amino]-3-methylbutyric acid benzyl ester (710 mg, 1.58 mmol) in methylene chloride (15 mL) were added sequentially triethylamine (0.47 mL, 3.35 mmol), morpholine (0.15 mL, 1.72 mmol) and (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (769 mg, 1.74 mmol). The mixture was stirred at room temperature overnight and then diluted with methylene chloride. The solution was washed with 0.5 N hydrochloric acid solution and brine, dried over magnesium sulfate and concentrated under vacuum. The solid residue was chromatographed on silica gel using 20% hexane in ethyl acetate affording

2-(R)-2-[(4-methoxybenzenesulfonyl)(3-morpholin-4-yl-3-oxopropyl)amino]-3-methylbutyric acid benzyl ester as a clear oil, 725 mg (88%).

To a solution of 2-(R)-2-[(4-methoxybenzenesulfonyl)(3-morpholin-4-yl-3-oxopropyl)amino]-3-methylbutyric acid benzyl ester (725 mg, 1.40 mmol) in ethanol (35 mL) was added 10% palladium on activated carbon (50 mg). The mixture was agitated under 3 atmospheres hydrogen in a Parr shaker for 3 hours. The catalyst was removed by filtration through nylon (pore size 0.45 μm) and the solvent was evaporated leaving 2-(R)-(2)-[(4-methoxybenzenesulfonyl)(3-morpholin-4-yl-3-oxopropyl)amino]-3-methyl-butyric acid as a white solid, 540 mg (90%).

To a solution of 2-(R)-2-[(4-methoxybenzenesulfonyl)(3-morpholin-4-yl-3-oxopropyl)amino]-3-methylbutyric acid (540 mg, 1.26 mmol) and 1-hydroxybenztriazole hydrate (205 mg, 1.33 mmol) in dry dimethylformamide (12 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (289 mg, 1.51 mmol). After stirring for 30 minutes, hydroxylamine hydrochloride (350 mg, 5.04 mmol) and then triethylamine (1.0 mL, 7.17 mmol) were added. The mixture was stirred at room temperature overnight and then diluted with ethyl acetate. The solution was washed sequentially with water, 0.5 N hydrochloric acid solution and brine. The solution was then dried over magnesium sulfate and concentrated under vacuum to leave a white foam. The material was dissolved in toluene, filtered and concentrated. The residue was triturated with ether to afford 2-(R)-N-hydroxy-2[(4-methoxybenzenesulfonyl)(3-morpholin-4-yl-3-oxopropyl)amino]-3-methylbutyramide as a solid, 200 mg (36%); ^{1}H NMR ($CDCl_3$): δ 9.35 (br s, 1H), 7.73 (d, J = 8.9 Hz, 2H), 6.95 (d, J = 8.9 Hz, 2H), 3.86 (s, 3H), 3.83-3.73 (m, 1H), 3.70-3.52 (m, 7H), 3.46-3.43 (m,

2H), 3.41-3.29 (m, 1H), 2.92-2.69 (m, 2H), 2.30-2.17 (m, 1H), 0.84 (d, J = 6.5 Hz, 3H), 0.41 (d, J = 6.5 Hz, 3H); MS (particle beam): m/z 444 (M+H), 428, 383, 329; HRMS calculated for $C_{19}H_{30}N_3O_7S$ (M+H): 444.1804, Found: 464.1818.

The title compounds of Examples 3-6 were prepared by a method analogous to that described in Example 2 using 2-(R)-2-[2-carboxyethyl(4-methoxybenzenesulfonyl)amino]-3-methylbutyric acid benzyl ester as the starting material which is coupled with the amine indicated.

EXAMPLE 3

2-(R)-2-[(2-Benzylcarbamoylethyl)(4-methoxybenzenesulfonyl)amino]-N-hydroxy-3-methylbutyramide

Coupled with benzylamine; ^1H NMR (DMSO-d_6): δ 10.72 (s, 1H), 8.89 (s, 1H), 8.39 (m, 1H), 7.74 (d, J = 9.0 Hz, 2H), 7.32-7.21 (m, 5H), 7.05 (d, J = 9.0 Hz, 2H), 4.21 (d, J = 5.9 Hz, 2H), 4.02-3.87 (m, 1H), 3.82 (s, 3H), 3.63 (d, J = 10.8 Hz, 1H), 3.29-3.17 (m, 1H), 2.71-2.57 (m, 1H), 2.52-2.40 (m, 1H), 2.06-1.94 (m, 1H), 0.77 (d, J = 6.6 Hz, 3H), 0.74 (d, J = 6.5 Hz, 3H); MS (LSIMS): m/z 464 (M+H); HRMS calculated for $C_{22}H_{30}N_3O_6S$ (M+H): 464.1855. Found: 464.1832.

EXAMPLE 4

2-(R)-N-Hydroxy-2-((4-methoxybenzenesulfonyl)(2-[(pyridin-3-ylmethyl)carbamoyl]ethyl)amino)-3-methylbutyramide

Coupled with 3-pyridylmethylamine: ^1H NMR (DMSO-d_6): δ 10.72 (s, 1H), 8.89 (s, 1H), 8.49-8.42 (m, 3H), 7.73 (d, J = 8.9 Hz, 2H), 7.63-7.60 (m, 1H), 7.32 (dd, J = 4.8, 7.8 Hz, 1H), 7.05 (d, J = 8.9 Hz, 2H), 4.23 (d, J = 5.8 Hz, 2H), 4.00-3.88 (m, 1H), 3.81 (s, 3H), 3.62 (d, J = 10.8 Hz, 1H), 3.27-3.17 (m, 1H), 2.69-2.58 (m, 1H), 2.52-2.41 (m, 1H), 2.07-1.94 (m, 1H), 0.76 (d, J = 6.5 Hz, 3H), 0.72 (d, J = 6.4 Hz, 3H); MS (LSIMS): m/z 465 (M+H).

EXAMPLE 5

2-(R)-N-Hydroxy-2-([4-methoxybenzenesulfonyl][2-(methylpyridin-3-ylmethylcarbamoyl)ethyl]amino)-3-methylbutyramide

Coupled with 3-(N-methylaminomethyl)pyridine: ^{1}H NMR (DMSO-d_6): δ 10.75 (br s, 1H), 8.92 (s, 1H), 8.52-8.29 (m, 2H), 7.75 (d, J = 8.8 Hz, 1.4 H), 7.67 (d, J = 8.8 Hz, 0.6 H), 7.62-7.58 (m, 1H), 7.42-7.32 (m, 1H), 7.06 (d, J = 8.8 Hz, 1.4 H), 7.01 (d, J = 8.8 Hz, 0.6 H), 4.55-4.41 (m, 2H), 3.94-3.82 (m, 1H), 3.81 (s, 2.1 H), 3.80 (s, 0.9 H), 3.68-3.60 (m, 1H), 3.33-3.19 (m, 1H), 2.90-2.50 (m, 2H), 2.88 (s, 2.1 H overlapped), 2.79 (s, 0.9 H), 2.05-1.80 (m, 1H), 0.79-0.63 (m, 6H): MS (thermospray): m/z 479 (M+H), 364.

EXAMPLE 6

4-(3-[(1-(R)-1-Hydroxycarbamoyl-2-methylpropyl)(4-methoxybenzenesulfonyl)amino]propionyl)piperazine-1-carboxylic acid, tert-butyl ester

Coupled with tert-butyl-1-piperazinecarboxylate: ^{1}H NMR (DMSO-d_6): δ 10.77 (br s, 1H), 8.93 (s, 1H), 7.74 (d, J = 8.9 Hz, 2H), 7.06 (d, J = 8.9 Hz, 2H), 3.90-3.80 (m, 1H), 3.82 (s, 3H, overlapped), 3.64 (d, J = 10.8 Hz, 1H), 3.60-3.16 (m, 9H), 2.80-2.71 (m, 1H), 2.59-2.47 (m, 1H), 2.03-1.91 (m, 1H), 1.39 (s, 9H), 0.77 (d, J = 6.5 Hz, 3H), 0.71 (d, J = 6.5, 3H); MS (thermospray): m/z 543 (M+H), 443, 382, 328.

EXAMPLE 7

2-(R)-N-Hydroxy-2-[(4-methoxybenzenesulfonyl)(3-oxo-3-piperazin-1-ylpropyl)amino]-3-methylbutyramide hydrocholoride

A solution of 4-(3-[(1-(R)-1-hydroxycarbamoyl-2-methylpropyl)(4-methoxybenzenesulfonyl)amino]propionyl)piperazine-1-carboxylic acid, tert-butylester [Example 6] (430 mg, 0.79 mmol) in methylene chloride (11 mL) was cooled to

0°C. Hydrogen chloride gas was then bubbled through the solution for about 0.5 minute. The solution was allowed to warm to room temperature with stirring over 1 hour. Volatiles were removed by evaporation and the residue was filtered washing with methylene chloride to collect solid 2-(R)-N-hydroxy-2-[(4-methoxybenzenesulfonyl)(3-oxo-3-piperazin-1-ylpropyl)amino]-3-methylbutyramide hydrochloride, 375 mg (99%). ^{1}H NMR (DMSO-d_6): δ 10.78 (br s, 1H), 9.16 (br s, 1H), 7.74 (d, J = 8.8 Hz, 2H), 7.07 (d, J = 8.9 Hz, 2H), 3.82 (s, 3H), 3.62 (br s, 4H), 3.38-3.18 (m, 1H), 3.16-3.07 (br s, 2H), 3.07-2.98 (br s, 2H), 2.83-2.73 (m, 1H), 2.65-2.53 (m, 1H), 2.06-1.90 (m, 1H), 0.76 (d, J = 6.5 Hz, 3H), 0.72 (d, J = 6.5 Hz, 3H). A broad water peak between δ 4.0 and 3.5 obscured some signals from this compound; MS (thermospray): m/z 443 (M+H), 382, 328.

EXAMPLE 8

2-(R)-2-[(Benzylcarbamoylmethyl)(4-methoxybenzenesulfonyl)amino]-N-hydroxy-3-methyl-butyramide

To a solution of 2-(R)-2-[carboxymethyl(4-methoxybenzenesulfonyl)amino]-3-methylbutyric acid benzyl ester (example 1) (905 mg, 2.08 mmol) in methylene chloride (18 mL) were added sequentially triethylamine (0.72 mL, 5.14 mmol), benzylamine (0.25 mL, 2.29 mmol) and (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluoro-phosphate (1.01 grams, 2.28 mmol). The mixture was stirred at room temperature overnight and then diluted with ethyl acetate. The solution was washed with 0.5 N hydrochloric acid solution and brine, dried over magnesium sulfate and concentrated under vacuum. The residue was chromatographed on silica gel using a 2:5:16 ratio of methylene chloride/ethyl acetate/hexane affording 2-(R)-2-[(benzylcarbamoylmethyl)(4-methoxybenzenesulfonyl)amino]-3-methylbutyric acid

benzyl ester as a clear oil, 933 mg (86%).

To a solution of 2-(R)-2-[(benzylcarbamoylmethyl)(4-methoxybenzenesulfonyl)-amino]-3-methylbutyric acid benzyl ester (933 mg, 1.17 mmol) in ethanol (50 mL) was added 10% palladium on activated carbon (85 mg). The mixture was agitated under 3 atmospheres hydrogen in a Parr shaker for 4 hours. The catalyst was removed by filtration through nylon (pore size 0.45 μm) and the solvent was evaporated leaving 2-(R)-2-[(benzylcarbamoylmethyl)(4-methoxybenzenesulfonyl)amino]-3-methylbutyric acid as a white foam, 755 mg (98%).

To a solution of 2-(R)-2-[(benzylcarbamoylmethyl)(4-methoxybenzenesulfonyl)amino]-3-methylbutyric acid (655 mg, 1.51 mmol) and 1-hydroxybenztriazole hydrate (224 mg, 1.46 mmol) in dry dimethylformamide (15 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (316 mg, 1.65 mmol). After stirring for 30 minutes, hydroxylamine hydrochloride (416 mg, 6.0 mmol) and then N-methylmorpholine (0.99 mL, 9.0 mmol) were added. The mixture was stirred at room temperature overnight and then diluted with ethyl acetate. The solution was washed sequentially with water, 0.5 N hydrochloric acid solution and brine. The solution was then dried over magnesium sulfate and concentrated under vacuum to leave a white foam which was chromatographed on silica gel eluting with ethyl acetate to afford 2-(R)-2-[(benzylcarbamoylmethyl)(4-methoxybenzene-sulfonyl)amino]-N-hydroxy-3-methylbutyramide as a white foam, 570 mg (84%); ^{1}H NMR (DMSO-d_6): δ 10.75 (br s, 1H), 8.90 (s, 1H), 8.47 (m, 1H), 7.85 (d, J = 8.9 Hz, 2H), 7.83-7.19 (m, 5H), 7.04 (d, J = 8.9 Hz, 2H), 4.37 (d, J = 11.4 Hz, 1H), 4.28 (d, J = 5.9 Hz, 2H), 3.89 (d, J = 11.4 Hz, 1H), 3.82 (s, 3H), 3.45 (d, J = 10.3 Hz, 1H), 1.90-1.79 (m, 1H), 0.73 (d, J = 6.3 Hz, 6H); MS (LSIMS): m/z 450 (M+H).

EXAMPLE 9

2-(R)-2-[(Benzylmethylcarbamoylmethyl)(4-methoxybenzenesulfonyl)amino]-N-hydroxy-3-methylbutyramide

To a solution of 2-(R)-2-[carboxymethyl(4-methoxybenzenesulfonyl)amino]-3-methylbutyric acid benzyl ester (Example 1) (1.05 grams, 2.41 mmol) in methylene chloride (20 mL) were added sequentially triethylamine (0.84 mL, 6.0 mmol), N-benzylmethylamine (0.34 mL, 2.63 mmol) and (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (1.17 grams, 2.69 mmol). The mixture was stirred at room temperature overnight and then diluted with ethyl acetate. The solution was washed with 0.5 N hydrochloric acid solution and brine, dried over magnesium sulfate and concentrated under vacuum. The residue was chromatographed on silica gel using 35% ethyl acetate in hexane (plus a small amount of methylene chloride to load the sample on the column) affording 2-(R)-2-[benzylmethylcarbamoylmethyl)(4-methoxybenzenesulfonyl)amino]-3-methylbutyric acid benzyl ester as a clear oil, 1.14 grams (88%).

To a solution of 2-(R)-2-[(benzylmethylcarbamoylmethyl)(4-methoxybenzenesulfonyl)amino]-3-methylbutyric acid benzyl ester (1.14 grams, 2.12 mmol) in ethanol (100 mL) was added 10% palladium on activated carbon (400 mg). The mixture was agitated under 3 atmospheres hydrogen in a Parr shaker for 3 hours. The catalyst was removed by filtration through nylon (pore size 0.45 μm) and the solvent was evaporated leaving 2-(R)-2-[(benzylmethylcarbamoylmethyl)(4-methoxybenzenesulfonyl)amino]-3-methylbutyric acid as a white foam, 902 mg (95%).

To a solution of 2-(R)-2-[(benzylmethylcarbamoylmethyl)(4-methoxybenzenesulfonyl)amino]-3-methylbutyric acid (902

mg, 2.01 mmol) in methylene chloride (20 mL) were added sequentially triethylamine (0.90 mL, 6.42 mmol), O-allylhydroxylamine hydrochloride (242 mg, 2.21 mmol) and (benzotriazol-1-yloxy)tris-(dimethylamino)phosphonium hexafluorophosphate (978 mg, 2.21 mmol). The mixture was stirred at room temperature overnight and then diluted with ethyl acetate. The solution was washed with 0.5 N hydrochloric acid solution and brine, dried over magnesium sulfate and concentrated under vacuum. The residue was chromatographed on silica gel using 40% hexane in ethyl acetate to afford 2-(R)-N-allyloxy-2-[(benzylmethylcarbamoylmethyl)(4-methoxy-benzenesulfonyl)amino]-3-methylbutyramide as an oil, 1.008 grams (100%).

To a solution of 2-(R)-N-allyloxy-2-[(benzylmethyl-carbamoylmethyl)(4-methoxybenzenesulfonyl)amino]-3-methylbutyramide (500 mg, 0.99 mmol) in methylene chloride (40 mL) was added bis(triphenylphosphine)palladium (II) chloride (280 mg, 0.4 mmol) and then, dropwise, tributyltinhydride (0.43 mL, 2.2 mmol). The solution was stirred at room temperature for 1 hour, diluted with methylene chloride, washed with 1 N hydrochloric acid solution, dried over magnesium sulfate and concentrated. The residue was taken up in ethyl acetate and filtered to remove a solid. After concentration, the filtrate was chromatographed on silica gel eluting with chloroform and then 2% methanol in chloroform to afford 2-(R)-2-[(benzylmethylcarbamoylmethyl)(4-methoxybenzene-sulfonyl)amino]-N-hydroxy-3-methylbutyramide as a white solid (340 mg, 74%). ^{1}H NMR (DMSO-d_6): δ 10.66 (br s, 1H), 8.87 (br s, 0.6 H), 8.84 (s, 0.4 H), 7.91 (d, J = 8.9 Hz, 1.2 H), 7.78 (d, J = 8.9 Hz, 0.8 H), 7.43-7.21 (m, 5H), 7.05 (d, J = 8.9 Hz, 1.2 H), 7.00 (d, J = 8.9 Hz, 0.8 H) 4.72 (d, J = 17.7 Hz, 0.4 H), 4.70 (d, J = 17.7 Hz, 0.6 H), 4.59-4.42 (m, 1H), 4.25 (d, J = 17.8

Hz, 0.6H), 4.07 (d, J = 17.7 Hz, 0.4H), 3.82 (s, 3H), 3.46-3.40 (m, 1H), 2.91 (s, 1.8H), 2.83 (s, 1.2 H), 1.92-1.70 (m, 1H), 0.75-0.69 (m, 6H); MS (thermospray): m/z 464 (M+H), 307, 239.

The title compounds of Examples 10-11 were prepared by a method analogous to that described in Example 9 using 2-(R)-2-[carboxymethyl(4-methoxybenzenesulfonyl)amino]-3-methylbutyric acid benzyl ester (Example 1) as the starting material which is coupled with the amine indicated.

EXAMPLE 10

2-(R)-N-Hydroxy-2-([4-methoxybenzenesulfonyl]-[(2-morpholin-4-ylethylcarbamoyl)methyl]amino)-3-methylbutyramide

Coupled with 4-(2-aminoethyl)morpholine: ^{1}H NMR (DMSO-d_6): δ 10.74 (br s, 1H), 8.90 (br s, 1H), 7.84 (br s, 1H, overlapped), 7.84 (d, J = 8.8 Hz, 2H), 7.06 (d, J = 8.8 Hz, 2H), 4.33 (d, J = 17.5 Hz, 1H), 3.83 (s, 3H), 3.78 (d, J = 17.5 Hz, 1H), 3.57-3.54 (m, 4H), 3.49 (d, J = 10.2 Hz, 1H), 3.28-3.06 (m, 2H), 2.34-2.30 (m, 6H), 1.93-1.77 (m, 1H), 0.77-0.74 (m, 6H).

EXAMPLE 11

2-(R)-N-Hydroxy-2-[(4-methoxybenzenesulfonyl)(2-oxo-2-pyrrolidin-1-ylethyl)amino]-3-methylbutyramide

Coupled with pyrrolidine: ^{1}H NMR (CD_3OD): δ 7.90 (d, J = 8.9 Hz, 2H), 7.04 (d, J = 8.9 Hz, 2H), 4.50 (d, J = 17.6 Hz, 1H), 4.15 (d, J = 17.6 Hz, 1H), 3.87 (s, 3H), 3.56-3.39 (m, 5H), 2.07-1.82 (m, 5H), 0.83 (d, J = 6.6 Hz, 3H), 0.73 (d, J = 6.6 Hz, 3H); MS (thermospray): m/z 414 (M+1); HRMS calculated for $C_{18}H_{28}N_3O_6S$ (M+H): 414.1699. Found 414.1703.

EXAMPLE 12

2-[Dimethylcarbamoylmethyl(4-methoxybenzenesulfonyl)amino]-N-hydroxy-3-methyl-butyramide

A solution of 2-(R)-2-[carboxymethyl(4-methoxybenzenesulfonyl)amino]-3-methylbutyric acid benzyl ester (Example 1) (1.89 grams, 4.34 mmol) in thionyl chloride (25 mL) was heated at reflux for 1 hour. After cooling, the excess thionyl chloride was evaporated. The residue was taken up in methylene chloride (50 mL) and the solution was cooled in an ice bath. Dimethylamine gas was slowly bubbled through the solution for 1 hour. After evaporation of the solvent, the residue was taken up in ethyl acetate, washed with 1 N hydrochloric acid solution, water and brine, dried over magnesium sulfate and concentrated to leave dimethylcarbamoylmethyl(4-methoxybenzenesulfonyl)amino-3-methylbutyric acid benzyl ester as an oil, 1.77 grams (88%).

To a solution of dimethylcarbamoylmethyl(4-methoxybenzenesulfonyl)amino-3-methylbutyric acid benzyl ester (1.77 grams, 3.83 mmol) in ethanol (100 mL) was added 10% palladium on activated carbon (644 mg). The mixture was agitated under 3 atmospheres hydrogen in a Parr shaker for 1.5 hours. The catalyst was removed by filtration through nylon (pore size 0.45 μm) and the solvent was evaporated leaving dimethylcarbamoylmethyl(4-methoxybenzenesulfonyl)amino-3-methylbutyric acid as a white foam, 1.42 grams (100%).

To a solution of dimethylcarbamoylmethyl(4-methoxybenzenesulfonyl)amino-3-methylbutyric acid (1.42 grams, 3.81 mmol) and 1-hydroxybenztriazole hydrate (687 mg, 4.48 mmol) in dry dimethylformamide (7 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (974 mg, 5.08 mmol). After stirring for 30 minutes, hydroxylamine hydrochloride (1.17 grams, 16.8 mmol) and then N-methylmorpholine (2.8 mL, 25.5

mmol) were added. The mixture was stirred at room temperature overnight and then concentrated under vacuum. The residue was taken up in ethyl acetate and the resulting solution was washed sequentially with water, 0.5 N hydrochloric acid solution and brine. The solution was then dried over magnesium sulfate and concentrated under vacuum to leave an oil which was chromatographed on silica gel eluting successively with ethyl acetate, 5% methanol in chloroform and 10% methanol in chloroform to afford 2-[dimethylcarbamoylmethyl(4-methoxybenzenesulfonyl)amino]-N-hydroxy-3-methylbutyramide as a white solid, 390 mg (26%). ^{1}H NMR (DMSO-d_6): δ 10.70 (br s, 1H), 8.89 (s, 1H), 7.80 (d, J = 8.9 Hz, 2H), 7.10 (d, J = 8.9 Hz, 2H), 4.62 (d, J = 17.7 Hz, 1H), 4.14 (d, J = 17.7 Hz, 1H), 3.84 (s, 3H), 3.40 (d, J = 10.4 Hz, 1H), 2.97 (s, 3H), 2.82 (s, 3H), 1.88-1.72 (m, 1H), 0.72 (d, J = 6.5 Hz, 6H); MS (thermospray): m/z 388 (M+1); HRMS calculated for $C_{16}H_{26}N_3O_6S$ (M+H): 388.1542 Found: 388.1592.

EXAMPLE 13

2-(R)-2-N-Hydroxy-2-((4-methoxybenzenesulfonyl)([(pyridin-3-ylmethyl)carbamoyl]methyl)amino)-3-methylbutyramide

2-(R)-N-Hydroxy-2-((4-methoxybenzenesulfonyl)([(pyridin-3-ylmethyl)carbamoyl]methyl)amino)-3-methylbutyramide was prepared by a procedure similar to that of Example 12 starting with 2-(R)-2-[carboxymethyl(4-methoxybenzenesulfonyl)amino]-3-methylbutyric acid benzyl ester (Example 1) and coupling this to 3-pyridylmethylamine via the acid chloride. ^{1}H NMR (CD_3OD): δ 8.55-8.53 (m, 1H), 8.43-8.40 (m, 1H), 7.90-7.82 (m, 1H, overlapped), 7.86 (d, J = 8.9 Hz, 2H), 7.40 (dd, J = 4.8, 7.8 Hz, 1H), 7.04 (d, J = 8.9 Hz, 2H), 4.50 (d, J = 17.5 Hz, 1H), 4.39 (d, J = 17.5 Hz, 1H), 4.32 (d, J = 17.7 Hz, 1H), 4.02 (d, J = 17.7 Hz,

1H), 3.87 (s, 3H), 3.60 (d, J = 10.3 Hz, 1H), 2.08-1.93 (m, 1H), 0.85 (d, J = 6.5 Hz, 3H), 0.70 (d, J = 6.5 Hz, 3H); MS (thermospray): m/z 451 (M+H), 336, 320.

EXAMPLE 14

N-Hydroxy-[(4-methoxybenzenesulfonyl)(2-morpholin-4-yl-2-oxoethyl)amino]acetamide

To a solution of iminoacetic acid disodium salt monohydrate (5.0 grams, 25.6 mmol) in dioxane (50 ml) and water (50 ml) was added triethylamine (5.3 ml, 38 mmol) followed by 4-methoxybenzenesulfonyl chloride (5.8 grams, 28.0 mmol). The mixture was stirred overnight at room temperature and diluted with methylene chloride. The solution was washed with 1 N hydrochloric acid solution, water and brine, dried over magnesium sulfate and concentrated under vacuum leaving [carboxymethyl(4-methoxybenzenesulfonyl)amino]acetic acid as a white solid, 3.83 grams (49%).

[Carboxymethyl(4-methoxybenzenesulfonyl)amino]acetic acid (0.5 grams, 1.65 mmol) in acetic anhydride (15 mL) was dissolved in acetic anhydride by gentle warming. The resulting solution was stirred at room temperature overnight. The acetic anhydride was removed by evaporation under vacuum; the residue was dissolved in methylene chloride and morpholine (0.16 mL, 1.82 mmol) was added. The mixture was stirred overnight at room temperature and then concentrated under vacuum. The residue was dissolved in ethyl acetate, washed with 1 N hydrochloric acid solution, water and brine, dried over magnesium sulfate and concentrated to afford [(4-methoxybenzenesulfonyl)(2-morpholin-4-yl-2-oxoethyl)amino]acetic acid as an oil, 0.33 grams (54%).

To a solution of [(4-methoxybenzenesulfonyl)(2-morpholin-4-yl-2-oxoethyl)-amino]acetic acid (0.33 grams, 0.89 mmol) in methylene chloride (10 mL) were added sequentially triethylamine (0.43 mL, 3.1 mmol), O-benzylhydroxylamine

hydrochloride (0.15 grams, 0.94 mmol) and (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (0.43 grams, 0.97 mmol). The mixture was stirred at room temperature overnight and then diluted with ethyl acetate. The solution was washed sequentially with 0.5 N hydrochloric acid solution, water and brine, dried over magnesium sulfate and concentrated under vacuum. The residue was chromatographed on silica gel using ethyl acetate to afford N-benzyloxy-[(4-methoxybenzenesulfonyl)(2-morpholin-4-yl-2-oxoethyl)amino]acetamide as a white solid, 0.33 grams (78%).

To a solution of N-benzyloxy-[(4-methoxybenzenesulfonyl)(2-morpholin-4-yl-2-oxoethyl)amino]acetamide (0.33 grams, 0.69 mmol) in methanol (35 mL) was added 5% palladium on activated carbon (85 mg). The mixture was agitated under 2 atmospheres hydrogen in a Parr shaker for 1.5 hours. The catalyst was removed by filtration through nylon (pore size 0.45 μm) and the solvent was evaporated. The residue was chromatographed on silica gel eluting with 5% methanol in methylene chloride to afford N-methoxy-[(4-methoxybenzenesulfonyl)(2-morpholin-4-yl-2-oxoethyl)amino]acetamide as a white solid, 65 mg (24%); ^{1}H NMR (CD_3OD): δ 7.82 (d, J = 9.0 Hz, 2H), 7.08 (d, J = 9.0 Hz, 2H), 4.24 (s, 2H), 3.88 (s, 3H), 3.84 (s, 2H), 3.68-3.64 (m, 4H), 3.58-3.50 (m, 4H); MS (thermospray): m/z 388 (M+1), 387 (M); HRMS calculated for $C_{16}H_{22}N_3O_7S$ (M+H): 388.1178, Found 338.1180.

The title compounds of Examples 15-16 were prepared by a method analogous to that described in Example 14 using [carboxymethyl(4-methoxybenzenesulfonyl)amino]acetic acid as the starting material which, after treatment with acetic anhydride, is coupled with the amine indicated.

EXAMPLE 15

N-Hydroxy-[(4-methoxybenzenesulfonyl)(2-oxo-2-pyrrolidin-1-ylethyl)amino]acetamide

Coupled with pyrrolidine: ^{1}H NMR (DMSO-d_6): δ 11.26 (br s, 1H), 8.89 (s, 1H), 7.81 (d, J = 8.9 Hz, 2H), 7.10 (d, J = 8.9 Hz, 2H), 4.09 (s, 2H), 3.85 (s, 3H), 3.74 (s, 2H), 3.45-3.25 (m, 4H), 1.93-1.72 (m, 4H); MS (thermospray): m/z 372 (M+1): Analysis calculated for $C_{15}H_{21}N_3O_6S$: C, 48.51; H, 5.70; N, 11.31. Found: C, 48.51; H, 5.82; N, 11.24.

EXAMPLE 16

2-[Dimethylcarbamoylmethyl(4-methoxybenzenesulfonyl)amino]-N-hydroxyacetamide

Coupled with dimethylamine: mp: 170°C. (dec.); ^{1}H NMR (DMSO-d_6): δ 10.69 (br s, 1H), 8.88 (s, 1H), 7.91 (d, J = 8.9 Hz, 2H), 7.06 (d, J = 8.9 Hz, 2H), 4.19 (s, 2H), 3.85 (s, 3H), 3.73 (s, 2H), 2.94 (s, 3H), 2.84 (s, 3H); MS (thermospray): m/z 346 (M+1); Analysis calculated for $C_{13}H_{19}N_3O_6S$: C, 45.21; H, 5.55 N, 12.17. Found: C, 44.93, H, 5.61; N, 12.03.

EXAMPLE 17

2-(R)-2-[(2-Carbamoylethyl)(4-methoxybenzenesulfonyl)amino]-N-hydroxy-3-methylbutyramide

To a solution of 2-(R)-2-[(2-carboxyethyl(4-methoxybenzenesulfonyl)amino]-3-methylbutyric acid benzyl ester (example 2) (900 mg., 2.0 mmol) in methylene chloride (10 mL) was added thionyl chloride (0.16 mL, 2.2 mmol). The reaction mixture was stirred for 1.5 hours at room temperature and then concentrated in vacuo. After dissolving the residue in methylene chloride (10 mL), ammonia gas was bubbled through the solution for 0.5 minutes. The solution was stirred at room temperature overnight and was concentrated under vacuum. Flash chromatography of the residue on silica gel eluting with 2% methanol in chloroform provided 2-(R)-2-[(2-carbamoylethyl)(4-

methoxybenzenesulfonyl)amino]-N-hydroxy-3-methylbutyric acid benzyl ester as a clear oil (275 mg, 31%).

To a solution of 2-(R)-2-[(2-carbamoylethyl)(4-methoxybenzenesulfonyl)amino]-N-hydroxy-3-methylbutyric acid benzyl ester (275 mg, 0.61 mmol) in ethanol (15 mL) was added 10% palladium on activated carbon (30 mg). The mixture was agitated under 3 atmospheres hydrogen in a Parr shaker for 5 hours. The catalyst was removed by filtration through diatomaceous earth and the solvent was evaporated leaving 2-(R)-2-[(2-carbamoylethyl)(4-methoxybenzenesulfonyl)amino]-N-hydroxy-3-methylbutyric acid as a white foam, 211 mg (96%).

To a solution of 2-(R)-2-[(2-carbamoylethyl)(4-methoxybenzenesulfonyl)amino]-N-hydroxy-3-methylbutyric acid (205 mg, 0.57 mmol) and 1-hydroxybenztriazole hydrate (85 mg, 0.55 mmol) in dry dimethylformamide (5 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (120 mg, 0.63 mmol). After stirring for 30 minutes, hydroxylamine hydrochloride (158 mg, 2.3 mmol) and then N-methylmorpholine (0.37 mL, 3.4 mmol) were added. The mixture was stirred at room temperature overnight and then diluted with ethyl acetate. The solution was washed with water and brine. The solution was then dried over magnesium sulfate and concentrated under vacuum to leave an oil which was chromatographed on silica gel eluting with 2% methanol in chloroform to afford 2-(R)-2-[(2-carbamoylethyl)(4-methoxybenzenesulfonyl)amino]-N-hydroxy-3-methylbutyramide as a white solid, 45 mg (21%); ^{1}H NMR (DMSO-d_6): δ 10.74 (br s, 1H), 8.91 (br s, 1H), 7.74 (d, J = 8.8 Hz, 2H), 7.33 (br s, 1H), 7.07 (d, J = 8.8 Hz, 2H), 6.79 (br s, 1H), 3.93-3.82 (m, 1H, overlapped), 3.83 (s, 3H), 3.64 (d, J = 10.7 Hz, 1H), 3.25-3.12 (m, 1H), 2.62-2.48 (m, 1H), 2.42-2.30 (m, 1H), 2.06-1.94 (m, 1H), 0.79 (d, J = 6.6 Hz, 3H), 0.76

(d, J = 6.6 Hz, 3H); MS (thermospray): m/z 374 (M+H).

EXAMPLE 18

2-(R)-2-[(2-tert-Butoxycarbonylethyl)(4-methoxybenzenesulfonyl)-amino]-N-hydroxy-3-methylbutyramide

A solution of N,N-dimethylformamide di-tert-butyl acetal (1.9 mL, 7.9 mmol) in toluene (15 mL) was added dropwise to a solution of 2-(R)-2-[(2-carboxyethyl(4-methoxybenzenesulfonyl)amino]-3-methylbutyric acid benzyl ester (example 2) 900 mg, 2.0 mmol) in toluene at 80°C. After heating for 2 hours at 80°C., the mixture was cooled and concentrated to leave an amber oil which was chromatographed on silica gel eluting with chloroform to afford (2-(R)-2-[(2-tert-butoxycarbonylethyl)(4-methoxybenzenesulfonyl)amino]-3-methylbutyric acid benzyl ester as an oil, 3.75 mg (37%).

To a solution of 2-(R)-2-[(2-tert-butoxycarbonylethyl)(4-methoxybenzenesulfonyl)amino]-3-methylbutyric acid benzyl ester (370 mg, 0.73 mmol) in ethanol (20 mL) was added 10% palladium on activated carbon (40 mg). The mixture was agitated under 3 atmospheres hydrogen in a Parr shaker for 5 hours. The catalyst was removed by filtration through diatomaceous earth and the solvent was evaporated leaving 2-(R)-2-[(2-tert-butoxycarbonylethyl)(4-methoxybenzenesulfonyl)amino]-3-methylbutyric acid as a white foam, 30 mg (100%).

To a solution of 2-(R)-2-[(2-tert-butoxycarbonylethyl)(4-methoxybenzenesulfonyl)amino]-3-methylbutyric acid (303 mg, 0.73 mmol) and 1-hydroxybenztriazole hydrate (108 mg, 0.70 mmol) in dry dimethylformamide (10 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (153 mg, 0.80 mmol). After stirring for 45 minutes, hydroxylamine hydrochloride (203 mg, 2.9 mmol) and then N-methylmorpholine (0.48 mL, 4.4 mmol) were added. The

mixture was stirred at room temperature overnight and then concentrated under vacuum. The residue was chromatographed on silica gel eluting with 2% methanol in chloroform and again with 10% ethyl acetate in hexane to afford 2-(R)-2-[(2-tert-butoxycarbonylethyl)(4-methoxybenzenesulfonyl)amino]-N-hydroxy-3-methylbutyramide as a white foam, 135 mg (43%); ^{1}H NMR (DMSO-d_6): δ 10.77 (br s 1H), 7.74 (d, J = 8.9 Hz, 2H), 7.08 (d, J = 8.9 Hz, 2H), 3.93-3.82 (m, 1H, overlapped), 3.83 (s, 3H), 3.64 (d, J = 10.8 Hz, 1H), 3.26-3.14 (m, 1H), 2.70-2.60 (m, 1H), 2.50-2.38 (m, 1H), 2.04-1.91 (m, 1H), 1.38 (s, 9H), 0.78 (d, J = 6.5 Hz, 3H), 0.72 (d, J = 6.5 Hz, 3H); MS (thermospray): m/z 431 (M+H), 375, 314.

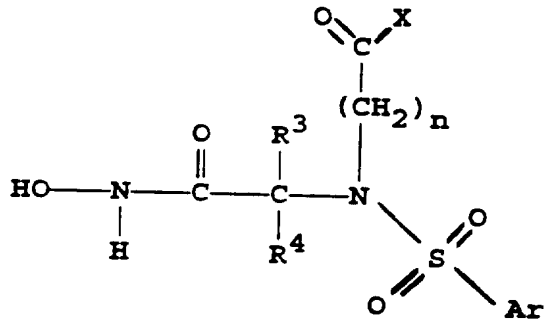
EXAMPLE 19

2-(R)-2-[2-Carboxyethyl)(4-methoxybenzenesulfonyl)amino]-N-hydroxy-3-methylbutyramide

To a solution of 2-(R)-2-[2-tert-butoxycarbonylethyl)(4-methoxybenzenesulfonyl)amino]-N-hydroxy-3-methylbutyramide (example 18) (100 mg, 0.23 mmol) in methylene chloride (1 mL) at 0°C. was added trifluoroacetic acid (1 mL). The mixture was allowed to warm to room temperature while stirring overnight. After evaporation of the trifluoroacetic acid and methylene chloride, the residue was chromatographed on silica gel eluting with 5% methanol in chloroform. Concentration of the appropriate fractions afforded 2-(R)-2-[2-carboxyethyl(4-methoxybenzenesulfonyl)amino]-N-hydroxy-3-methylbutyramide as a white solid, 35 mg (41%). ^{1}H NMR (DMSO-d_6): δ 10.79 (br s,1H), 8.97 (br s, 1H), 7.76 (d, J = 8.9 Hz, 2H), 7.09 (d, J = 8.9 Hz, 2H), 3.95-3.82 (m, 1H, overlapped), 3.84 (s, 3H), 3.66 (d, J = 10.8 Hz, 1H), 3.30-3.20 (m, 1H), 2.73-2.62 (m, 1H), 2.50-2.40 (m, 1H), 2.07-1.94 (m, 1H), 0.80 (d, J = 6.5 Hz, 3H), 0.74 (d, J = 6.5 Hz, 3H); MS (thermospray): m/z 375 (M+H), 314.

C L A I M S

1. A compound of the formula



I

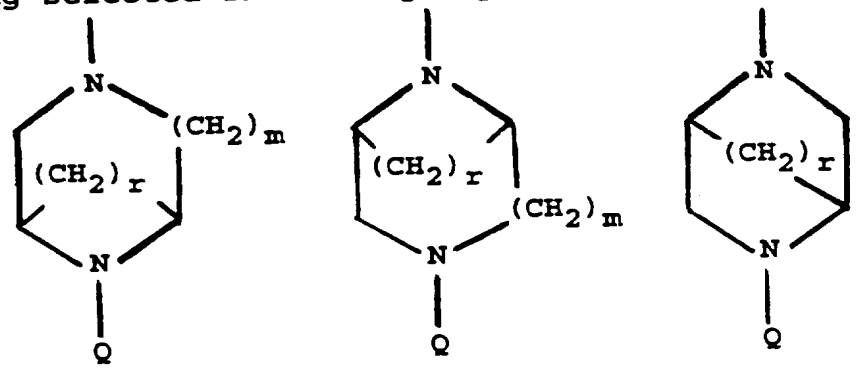
or the pharmaceutically acceptable salts thereof, wherein

n is 1 to 6;

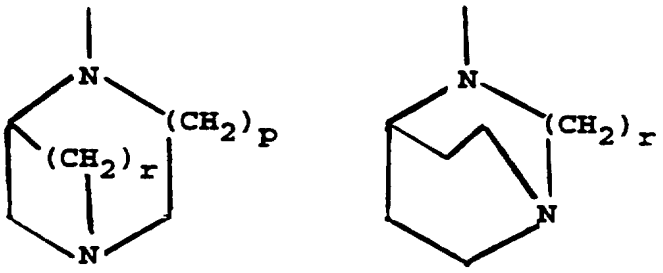
X is hydroxy, (C_1-C_6)alkoxy or NR^1R^2 wherein R^1 and R^2 are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_5-C_9)heteroarylpiperidyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperidyl, (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperidyl, (C_1-C_6)acylpiperidyl, (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_5-C_9)heteroaryl(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl(C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, $R^5(C_2-C_6)$alkyl, (C_1-C_5)alkyl$(CHR^5)(C_1-C_6)$alkyl wherein R^5 is hydroxy, (C_1-C_6)acyloxy, (C_1-C_6)alkoxy, piperazino, (C_1-C_6)acylamino, (C_1-C_6)alkylthio, (C_6-C_{10})arylthio, (C_1-C_6)alkylsulfinyl, (C_6-C_{10})arylsulfinyl, (C_1-C_6)alkylsulfoxyl, (C_6-C_{10})arylsulfoxyl, amino, (C_1-C_6)alkylamino, $((C_1-C_6)$alkyl$)_2$amino, (C_1-C_6)acylpiperazino, (C_1-C_6)alkylpiperazino, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazino, (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperazino, morpholino, thiomorpholino, piperidino or pyrrolidino; $R^6(C_1-C_6)$alkyl, (C_1-C_5)alkyl$(CHR^6)(C_1-C_6)$alkyl wherein R^6 is piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperidyl, $(C_5-$

C_9)heteroarylpiperidyl or (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperidyl; and CH(R^7)COR^8 wherein R^7 is hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_5-C_9)heteroaryl(C_1-C_6)alkyl, (C_1-C_6)alkylthio(C_1-C_6)alkyl, (C_6-C_{10})arylthio(C_1-C_6)alkyl, (C_1-C_6)alkylsulfinyl(C_1-C_6)alkyl, (C_6-C_{10})arylsulfinyl(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonyl(C_1-C_6)alkyl, (C_6-C_{10})arylsulfonyl(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, ((C_1-C_6)alkylamino)$_2$(C_1-C_6)alkyl, $R^9R^{10}NCO$(C_1-C_6)alkyl or R^9OCO(C_1-C_6)alkyl wherein R^9 and R^{10} are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl and (C_5-C_9)heteroaryl(C_1-C_6)alkyl; and R^8 is $R^{11}O$ or $R^{11}R^{12}N$ wherein R^{11} and R^{12} are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl and (C_5-C_9)heteroaryl(C_1-C_6)alkyl;

or R^1 and R^2, or R^9 and R^{10}, or R^{11} and R^{12} may be taken together to form an azetidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, (C_1-C_6)acylpiperazinyl, (C_1-C_6)alkylpiperazinyl, (C_6-C_{10})arylpiperazinyl, (C_5-C_9)heteroarylpiperazinyl or a bridged diazabicycloalkyl ring selected from the group consisting of



a b c



d e

wherein r is 1, 2 or 3;

m is 1 or 2;

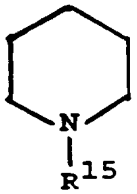
p is 0 or 1; and

Q is hydrogen, (C_1-C_3)alkyl or (C_1-C_6)acyl;

R^3 and R^4 are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, trifluoromethyl, trifluoromethyl(C_1-C_6)alkyl, (C_1-C_6)alkyl (difluoromethylene), (C_1-C_3)alkyl(difluoromethylene)(C_1-C_3)alkyl, (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_5-C_9)heteroaryl(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl(C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)acyloxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, piperazinyl(C_1-C_6)alkyl, (C_1-C_6)acylamino(C_1-C_6)alkyl, piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_5-C_9)heteroaryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_1-C_6)alkylthio(C_1-C_6)alkyl, (C_6-C_{10})arylthio(C_1-C_6)alkyl, (C_1-C_6)alkylsulfinyl(C_1-C_6)alkyl, (C_6-C_{10})arylsulfinyl(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonyl(C_1-C_6)alkyl, (C_6-C_{10})arylsulfonyl(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, $((C_1-C_6)$alkylamino$)_2(C_1-C_6)$alkyl, $R^{13}CO(C_1-C_6)$alkyl wherein R^{13} is $R^{20}O$ or $R^{20}R^{21}N$ wherein R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl or (C_5-C_9)heteroaryl(C_1-C_6)alkyl; or $R^{14}(C_1-C_6)$alkyl wherein R^{14} is (C_1-C_6)acylpiperazino, $(C_6-$

C_{10})arylpiperazino, (C_5-C_9)heteroarylpiperazino, (C_1-C_6)alkylpiperazino, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazino, (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_5-C_9)heteroarylpiperidyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperidyl, (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperidyl or (C_1-C_6)acylpiperidyl;

or R^3 and R^4, or R^{20} and R^{21} may be taken together to form a (C_3-C_6)cycloalkyl, oxacyclohexyl, thiocyclohexyl, indanyl or tetralinyl ring or a group of the formula



wherein R^{15} is hydrogen, (C_1-C_6)acyl, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_5-C_9)heteroaryl(C_1-C_6)alkyl or (C_1-C_6)alkylsulfonyl; and

Ar is (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_1-C_6)alkyl(C_6-C_{10})aryl, (C_1-C_6)alkoxy(C_6-C_{10})aryl, ((C_1-C_6)alkoxy)$_2$(C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_5-C_9)heteroaryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_5-C_9)heteroaryl, (C_1-C_6)alkoxy(C_5-C_9)heteroaryl, ((C_1-C_6)alkoxy)$_2$(C_5-C_9)heteroaryl, (C_6-C_{10})aryloxy(C_5-C_9)heteroaryl, (C_5-C_9)heteroaryloxy(C_5-C_9)heteroaryl;

with the proviso that when either R^1 or R^2 is $CH(R^7)COR^8$ wherein R^7 and R^8 are as defined above, the other of R^1 or R^2 is hydrogen, (C_1-C_6)alkyl or benzyl.

2. A compound according to claim 1, wherein n is 2.

3. A compound according to claim 1, wherein Ar is 4-methoxyphenyl or 4-phenoxyphenyl.

4. A compound according to claim 1, 2 or 3, wherein either R^3 or R^4 is not hydrogen.

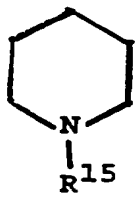
5. A compound according to claim 1, wherein n is

1 and either R^1 or R^2 is hydrogen.

6. A compound according to claim 4, wherein X is hydroxy, Ar is 4-methoxyphenyl or 4-phenoxyphenyl.

7. A compound according to claim 4, wherein X is alkoxy, Ar is 4-methoxyphenyl or 4-phenoxyphenyl.

8. A compound according to claim 1, wherein Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R^3 and R^4 are taken together to form (C_3-C_6)cycloalkanyl, oxacyclohexanyl, thiocyclohexanyl, indanyl or a group of the formula



wherein R^{15} is (C_1-C_6)acyl, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_5-C_9)heteroaryl(C_1-C_6)alkyl or (C_1-C_6)alkylsulfonyl.

9. A compound according to claim 1, wherein n is 2, Ar is 4-methoxyphenyl or 4-phenoxyphenyl, R^1 and R^2 are taken together to form piperazinyl, (C_1-C_6)alkylpiperazinyl, (C_6-C_{10})aryl piperazinyl or (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperazinyl, and either R^3 or R^4 is not hydrogen or both R^3 and R^4 are not hydrogen.

10. A compound according to claim 1, wherein n is 2, Ar is 4-methoxyphenyl or 4-phenoxyphenyl, R^1 is hydrogen or (C_1-C_6)alkyl, R^2 is 2-pyridylmethyl, 3-pyridylmethyl or 4-pyridylmethyl, and either R^3 or R^4 is not hydrogen or both R^3 and R^4 are not hydrogen.

11. A compound according to claim 1, wherein n is 1, Ar is 4-methoxyphenyl or 4-phenoxyphenyl, R^1 is hydrogen, R^2 is 2-pyridylmethyl, 3-pyridylmethyl or 4-pyridylmethyl, and either R^3 or R^4 is not hydrogen or both R^3 and R^4 are not hydrogen.

12. A compound according to claim 2, wherein Ar is 4-methoxyphenyl, R^1 is hydrogen or (C_1-C_6)alkyl and R^2 is $R^5(C_2-C_6)$alkyl wherein R^5 is morpholino,

thiomorpholino, piperidino, pyrrolidino, (C_1-C_6)acylpiperazino, (C_1-C_6)alkylpiperazino, (C_6-C_{10})arylpiperazino, (C_5-C_9)heteroarylpiperazino, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazino or (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperazino and either R^3 or R^4 is not hydrogen or both R^3 and R^4 are not hydrogen.

13. A compound according to claim 1, wherein n is 1, Ar is 4-methoxyphenyl or 4-phenoxyphenyl, R^1 is hydrogen, R^2 is R^5(C_2-C_6)alkyl wherein R^5 is morpholino, thiomorpholino, piperidino, pyrrolidino, (C_1-C_6)acylpiperazino, (C_1-C_6)alkylpiperazino, (C_6-C_{10})arylpiperazino, (C_5-C_9)heteroarylpiperazino, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazino or (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperazino and either R^3 or R^4 is not hydrogen or both R^3 and R^4 are not hydrogen.

14. A compound according to claim 1, wherein said compound is selected from:

2-(R)-N-Hydroxy-2-[(4-methoxybenzenesulfonyl)(3-morpholin-4-yl-3-oxopropyl)amino]-3-methylbutyramide;

2-(R)-2-[(2-Benzylcarbamoylethyl)(4-methoxybenzenesulfonyl)amino]-N-hydroxy-3-methylbutyramide;

2-(R)-N-Hydroxy-2-((4-methoxybenzenesulfonyl)(2-[(pyridin-3-ylmethyl)carbamoyl]ethyl)amino)-3-methylbutyramide;

2-(R)-N-Hydroxy-2-([4-methoxybenzenesulfonyl][2-(methylpyridin-3-ylmethylcarbamoyl)ethyl]amino)-3-methylbutyramide;

4-(3-[1-(R)-1-Hydroxycarbamoyl-2-methylpropyl)(4-methoxybenzenesulfonyl)amino]propionyl)piperazine-1-carboxylic acid, tert-butyl ester;

2-(R)-N-Hydroxy-2-[(4-methoxybenzenesulfonyl)(3-oxo-3-piperazin-1-ylpropyl)amino)-3-methylbutyramide hydrochloride;

2-(R)-2-[(Benzylcarbamoylmethyl)(4-

methoxybenzenesulfonyl)amino]N-hydroxy-3-methylbutyramide;

2-(R)-N-Hydroxy-2-[(4-methoxybenzenesulfonyl]-[(2-morpholin-4-ylethylcarbamoyl)methyl]amino)-3-methylbutyramide;

2-(R)-N-Hydroxy-2-((4-methoxybenzenesulfonyl)([(pyridin-3-ylmethyl)carbamoyl]methyl)amino)-3-methylbutyramide;

2-(R)-3,3,3-Trifluoro-N-hydroxy-2-[(methoxybenzenesulfonyl)(3-morpholin-4-yl-3-oxopropyl)amino]propionamide;

2-(R)-N-Hydroxy-2-((4-phenoxybenzenesulfonyl)[2-(methylpyridin-4-ylmethylcarbamoyl)ether]amino)-3-methylbutyramide;

4-[4-Methoxybenzenesulfonyl)(3-morpholin-4-yl-3-oxopropyl)amino]-1-methylpiperidene-4-carboxylic acid hydroxyamide;

2-(R)-N-Hydroxy-2-((4-methoxybenzenesulfonyl)-[3-(4-methylpiperazin-1-yl)-3-oxopropyl]amino)-3-methylbutyramide;

2-(R)-2-[(2-Carboxyethyl)(4-methoxybenzenesulfonyl)amino]-N-hydroxy-3-methylbutyramide;

[(2-Carboxyethyl)(3,4-dimethoxybenzenesulfonyl)amino]-N-hydroxy-acetamide;

2-(R)-2-[(2-Carbamoylethyl)(4-methoxybenzenesulfonyl)amino]-N-hydroxy-3-methylbutyramide;

2-(R),3-(R)-3,N-Dihydroxy-2-[(4-methoxybenzenesulfonyl)(3-oxo-3-piperidin-1-ylpropyl)amino]-butyramide;

2-(R)-N-Hydroxy-2-((4-methoxybenzenesulfonyl)[3-(methylpyridin-3-ylmethylcarbamoyl)propyl]amino)-3-methylbutyramide;

2-(R)-N-Hydroxy-2-((4-methoxybenzenesulfonyl)[2-(methylcarboxymethylcarbamoyl)ethyl]amino)-3-

methylbutyramide;

2-(R)-N-Hydroxy-2-((4-methoxybenzenesulfonyl)-[(1-methylpiperidin-4-ylcarbamoyl)methyl]amino)-3-methylbutyramide;

2-(R)-2-Clyclohexyl-N-hydroxy-2-((4-methoxybenzenesulfonyl)-[3-(4-methylpiperazin-1-yl)-3-oxopropyl]amino)-acetamide; and

2-(R)-N-Hydroxy-2-[(methoxybenzenesulfonyl)(3-morpholin-4-yl-3-oxopropyl)amino]-4-(morpholin-4-yl)butyramide.

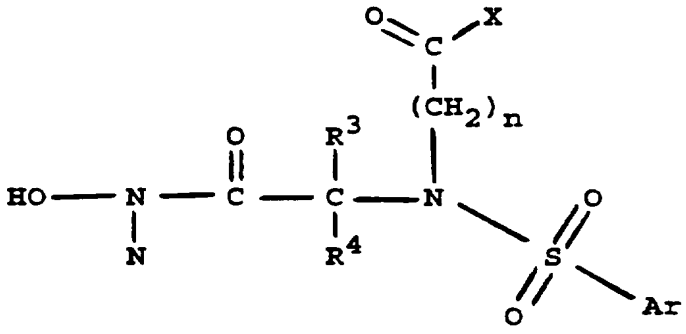
15. A pharmaceutical composition for (a) the treatment of a condition selected from the group consisting of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) or (b) the inhibition of matrix metalloproteinases or the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising an amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, effective in such treatments and a pharmaceutically acceptable carrier.

16. A method for the inhibition of (a) matrix metalloproteinases or (b) the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof.

17. A method for treating a condition selected from the group consisting of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) in a

mammal, including a human, comprising administering to said mammal an amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, effective in treating such a condition.

18. A method of preparing a compound of the formula



I

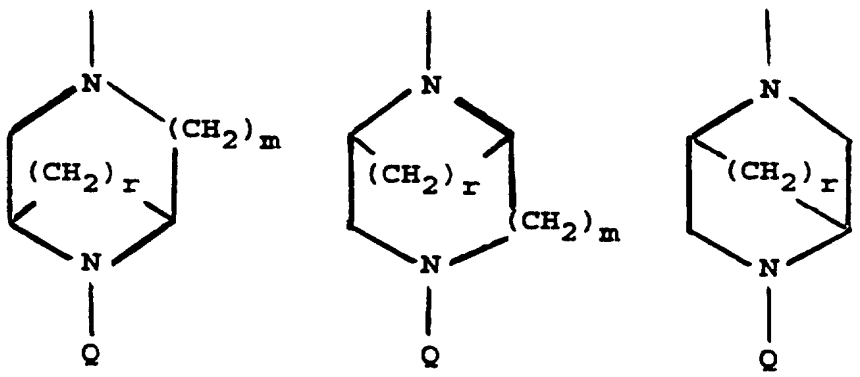
or the pharmaceutically acceptable salts thereof, wherein

n is 1 to 6;

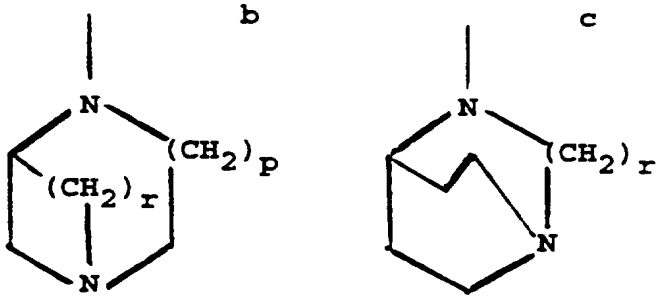
X is hydroxy, (C_1-C_6)alkoxy or NR^1R^2 wherein R^1 and R^2 are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_5-C_9)heteroarylpiperidyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperidyl, (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperidyl, (C_1-C_6)acylpiperidyl, (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_5-C_9)heteroaryl(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl(C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, $R^5(C_2-C_6)$alkyl, (C_1-C_5)alkyl$(CHR^5)(C_1-C_6)$alkyl wherein R^5 is hydroxy, (C_1-C_6)acyloxy, (C_1-C_6)alkoxy, piperazino, (C_1-C_6)acylamino, (C_1-C_6)alkylthio, (C_6-C_{10})arylthio, (C_1-C_6)alkylsulfinyl, (C_6-C_{10})arylsulfinyl, (C_1-C_6)alkylsulfoxyl, (C_6-C_{10})arylsulfoxyl, amino, (C_1-C_6)alkylamino, $((C_1-C_6)\text{alkyl})_2$amino, (C_1-C_6)acylpiperazino, (C_1-C_6)alkylpiperazino, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazino, (C_5-C_9)heteroaryl$(C_1-$

C_6)alkylpiperazino, morpholino, thiomorpholino, piperidino or pyrrolidino; R^6 (C_1-C_6)alkyl, (C_1-C_5)alkyl(CHR^6)(C_1-C_6)alkyl wherein R^6 is piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperidyl, (C_5-C_9)heteroarylpiperidyl or (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperidyl; and $CH(R^7)COR^8$ wherein R^7 is hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_5-C_9)heteroaryl(C_1-C_6)alkyl, (C_1-C_6)alkylthio(C_1-C_6)alkyl, (C_6-C_{10})arylthio(C_1-C_6)alkyl, (C_1-C_6)alkylsulfinyl(C_1-C_6)alkyl, (C_6-C_{10})arylsulfinyl(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonyl(C_1-C_6)alkyl, (C_6-C_{10})arylsulfonyl(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, ((C_1-C_6)alkylamino)$_2$(C_1-C_6)alkyl, $R^9R^{10}NCO(C_1$-C_6)alkyl or $R^9OCO(C_1$-C_6)alkyl wherein R^9 and R^{10} are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl and (C_5-C_9)heteroaryl(C_1-C_6)alkyl; and R^8 is $R^{11}O$ or $R^{11}R^{12}N$ wherein R^{11} and R^{12} are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl and (C_5-C_9)heteroaryl(C_1-C_6)alkyl;

or R^1 and R^2, or R^9 and R^{10}, or R^{11} and R^{12} may be taken together to form an azetidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, (C_1-C_6)acylpiperazinyl, (C_1-C_6)alkylpiperazinyl, (C_6-C_{10})arylpiperazinyl, (C_5-C_9)heteroarylpiperazinyl or a bridged diazabicycloalkyl ring selected from the group consisting of



a b c



d e

wherein r is 1, 2 or 3;

m is 1 or 2;

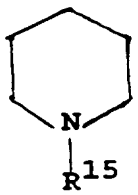
p is 0 or 1; and

Q is hydrogen, (C_1-C_3)alkyl or (C_1-C_6)acyl;

R^3 and R^4 are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, trifluoromethyl, trifluoromethyl(C_1-C_6)alkyl, (C_1-C_6)alkyl (difluoromethylene), (C_1-C_3)alkyl(difluoromethylene)(C_1-C_3)alkyl, (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_5-C_9)heteroaryl(C_1-C_6)alkyl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl(C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)acyloxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, piperazinyl(C_1-C_6)alkyl, (C_1-C_6)acylamino(C_1-C_6)alkyl, piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, $C_5-C_9)$heteroaryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_1-C_6)alkylthio(C_1-C_6)alkyl, (C_6-C_{10})arylthio$(C_1-$

C_6)alkyl, (C_1-C_6)alkylsulfinyl(C_1-C_6)alkyl, (C_6-C_{10})arylsulfinyl(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonyl(C_1-C_6)alkyl, (C_6-C_{10})arylsulfonyl(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, ((C_1-C_6)alkylamino)$_2$(C_1-C_6)alkyl, $R^{13}CO$(C_1-C_6)alkyl wherein R^{13} is $R^{20}O$ or $R^{20}R^{21}N$ wherein R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl or (C_5-C_9)heteroaryl(C_1-C_6)alkyl; or R^{14}(C_1-C_6)alkyl wherein R^{14} is (C_1-C_6)acylpiperazino, (C_6-C_{10})arylpiperazino, (C_5-C_9)heteroarylpiperazino, (C_1-C_6)alkylpiperazino, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazino, (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_5-C_9)heteroarylpiperidyl, (C_6-C_{10})aryl(C_1-C_6)alkylpiperidyl, (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperidyl or (C_1-C_6)acylpiperidyl;

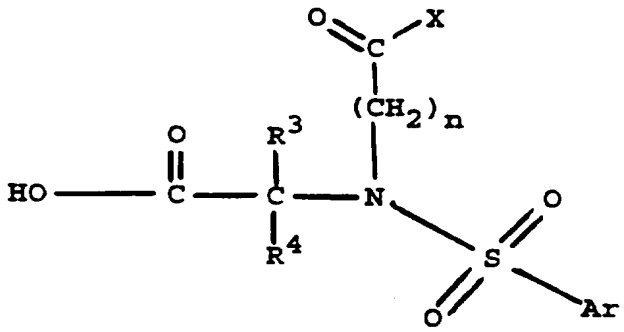
or R^3 and R^4, or R^{20} and R^{21} may be taken together to form a (C_3-C_6)cycloalkyl, oxacyclohexyl, thiocyclohexyl, indanyl or tetralinyl ring or a group of the formula



wherein R^{15} is hydrogen, (C_1-C_6)acyl, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_5-C_9)heteroaryl(C_1-C_6)alkyl or (C_1-C_6)alkylsulfonyl; and

Ar is (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_1-C_6)alkyl(C_6-C_{10})aryl, (C_1-C_6)alkoxy(C_6-C_{10})aryl, ((C_1-C_6)alkoxy)$_2$(C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_5-C_9)heteroaryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_5-C_9)heteroaryl, (C_1-C_6)alkoxy(C_5-C_9)heteroaryl, ((C_1-C_6)alkoxy)$_2$(C_5-C_9)heteroaryl, (C_6-C_{10})aryloxy(C_5-C_9)heteroaryl, (C_5-C_9)heteroaryloxy(C_5-C_9)heteroaryl;

with the proviso that when either R^1 or R^2 is $CH(R^7)COR^8$ wherein R^7 and R^8 are as defined above, the other of R^1 or R^2 is hydrogen, (C_1-C_6)alkyl or benzyl; comprising reacting a compound of the formula



wherein n, X, R^3, R^4 and Ar are as defined above with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, 1-hydroxybenztriazole and hydroxylamine.

INTERNATIONAL SEARCH REPORT

In onal Application No
PCT/US 96/02679

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C311/29 C07D295/18 C07D213/56 A61K31/535 A61K31/44
A61K31/495 A61K31/40 A61K31/18

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C C07D

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 606 046 (CIBA-GEIGY AG) 13 July 1994 see the whole document ---	1-15,18
A	WO,A,90 05719 (BRITISH BIOTECHNOLOGY LTD) 31 May 1990 see the whole document -----	1-15,18

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
15 May 1996	04.06.96

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

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

Ir ional Application No
PCT/US 96/02679

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-606046	13-07-94	US-A-	5455258	03-10-95
		AU-B-	5265593	04-05-95
		CA-A-	2112779	07-07-94
		FI-A-	940012	07-07-94
		HU-A-	70536	30-10-95
		JP-A-	6256293	13-09-94
		NO-A-	940038	07-07-94
		NZ-A-	250517	26-10-95
		US-A-	5506242	09-04-96
		ZA-A-	9400048	11-08-94
WO-A-9005719	31-05-90	AU-B-	644064	02-12-93
		AU-B-	4800390	12-06-90
		CA-A-	2003718	23-05-90
		DE-D-	68914687	19-05-94
		DE-T-	68914687	08-09-94
		EP-A-	0446267	18-09-91
		ES-T-	2055409	16-08-94
		JP-T-	4502008	09-04-92
		NO-B-	177701	31-07-95
		US-A-	5310763	10-05-94
		US-A-	5240958	31-08-93

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 211/96, A61K 31/445, C07D 241/04, 241/08

A1

(11) International Publication Number: **WO 96/33172**

(43) International Publication Date: 24 October 1996 (24.10.96)

(21) International Application Number: PCT/IB95/00279

(22) International Filing Date: 20 April 1995 (20.04.95)

(71) Applicant *(for all designated States except US)*: PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: PISCOPIO, Anthony, D. [US/US]; 196 Payer Lane, Mystic, CT 06355 (US). RIZZI, James, P. [US/US]; 34 Devonshire Drive, Waterford, CT 06385 (US).

(74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).

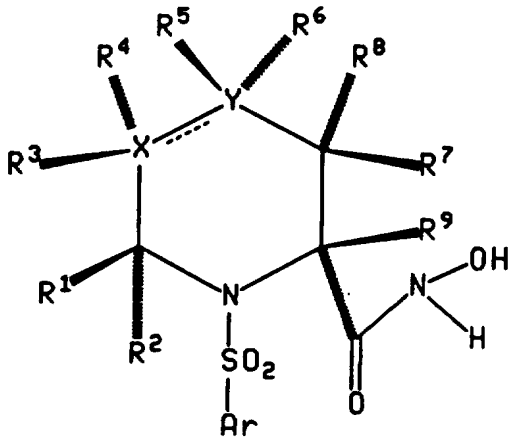
(81) Designated States: CA, FI, JP, MX, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: ARYLSULFONYL HYDROXAMIC ACID DERIVATIVES AS MMP AND TNF INHIBITORS

(57) Abstract

A compound of formula (I) wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9 and Ar are as defined above, useful in the treatment of a condition selected from the group consisting of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis and other diseases characterized by matrix metalloproteinase activity, as well as AIDS, sepsis, septic shock and other diseases involving the production of TNF.



(I)

FOR THE PURPOSES OF INFORMATION ONLY

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

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

ARYLSULFONYL HYDROXAMIC ACID DERIVATIVES AS MMP AND TNF INHIBITORS

Background of the Invention

The present invention relates to arylsulfonyl hydroxamic acid derivatives which are inhibitors of matrix metalloproteinases or the production of tumor necrosis factor (hereinafter also referred to as TNF) and as such are useful in the treatment of a condition selected from the group consisting of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis and other diseases characterized by matrix metalloproteinase activity, as well as AIDS, sepsis, septic shock and other diseases involving the production of TNF.

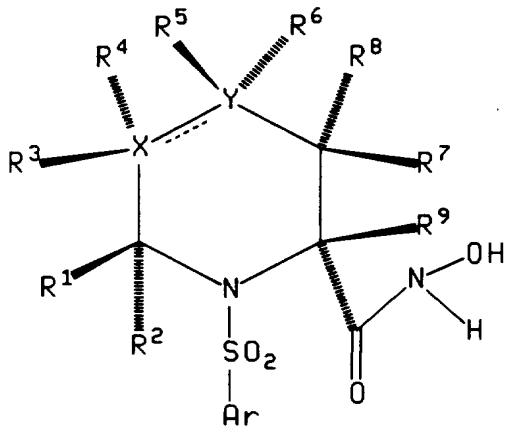
This invention also relates to a method of using such compounds in the treatment of the above diseases in mammals, especially humans, and to the pharmaceutical compositions useful therefor.

There are a number of enzymes which effect the breakdown of structural proteins and which are structurally related metalloproteases. Matrix-degrading metalloproteinases, such as gelatinase, stromelysin and collagenase, are involved in tissue matrix degradation (e.g. collagen collapse) and have been implicated in many pathological conditions involving abnormal connective tissue and basement membrane matrix metabolism, such as arthritis (e.g. osteoarthritis and rheumatoid arthritis), tissue ulceration (e.g. corneal, epidermal and gastric ulceration), abnormal wound healing, periodontal disease, bone disease (e.g. Paget's disease and osteoporosis), tumor metastasis or invasion, as well as HIV-infection (J. Leuk. Biol., 52 (2): 244-248, 1992).

Tumor necrosis factor is recognized to be involved in many infectious and auto-immune diseases (W. Friers, FEBS Letters, 1991, 285, 199). Furthermore, it has been shown that TNF is the prime mediator of the inflammatory response seen in sepsis and septic shock (C.E. Spooner et al., Clinical Immunology and Immunopathology, 1992, 62 S11).

Summary of the Invention

The present invention relates to a compound of the formula



I

or the pharmaceutically acceptable salt thereof, wherein the broken line represents an optional double bond;

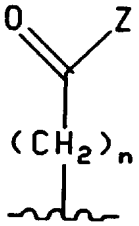
X is carbon, oxygen or sulfur;

Y is carbon, oxygen, sulfur, sulfoxide, sulfone or nitrogen;

R^1, R^2 R^3, R^4 R^5, R^6, R^7, R^8 and R^9 are selected from the group consisting of hydrogen, (C_1-C_6)alkyl optionally substituted by (C_1-C_6)alkylamino, (C_1-C_6)alkylthio, (C_1-C_6)alkoxy, trifluoromethyl, (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_6-C_{10})arylamino, (C_6-C_{10})arylthio, (C_6-C_{10})aryloxy, (C_5-C_9)heteroarylamino, (C_5-C_9)heteroarylthio, (C_5-C_9)heteroaryloxy, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_3-C_6)cycloalkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkyl(hydroxymethylene),piperazinyl,(C_6-C_{10})aryl(C_1-C_6)alkoxy,(C_5-C_9)heteroaryl(C_1-C_6)alkoxy, (C_1-C_6)acylamino, (C_1-C_6)acylthio, (C_1-C_6)acyloxy, (C_1-C_6)alkylsulfinyl, (C_6-C_{10})arylsulfinyl, (C_1-C_6)alkylsulfonyl, (C_6-C_{10})arylsulfonyl, amino, (C_1-C_6)alkylamino or ((C_1-C_6)alkylamino)$_2$; (C_2-C_6)alkenyl, (C_6-C_{10})aryl(C_2-C_6)alkenyl, (C_5-C_9)heteroaryl(C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_6-C_{10})aryl(C_2-C_6)alkynyl, (C_5-C_9)heteroaryl(C_2-C_6)alkynyl, (C_1-C_6)alkylamino, (C_1-C_6)alkylthio, (C_1-C_6)alkoxy, trifluoromethyl, (C_1-C_6)alkyl (difluoromethylene), (C_1-C_3)alkyl(difluoromethylene)(C_1-C_3)alkyl, (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_6-C_{10})arylamino, (C_6-C_{10})arylthio, (C_6-C_{10})aryloxy, (C_5-C_9)heteroarylamino, (C_5-C_9)heteroarylthio, (C_5-C_9)heteroaryloxy, (C_3-C_6)cycloalkyl, (C_1-C_6)alkyl(hydroxymethylene), piperidyl, (C_1-C_6)alkylpiperidyl, (C_1-C_6)acylamino, (C_1-

C_6)acylthio, (C_1-C_6)acyloxy, R^{13}(C_1-C_6)alkyl wherein R^{13} is (C_1-C_6)acylpiperazino, (C_6-C_{10})arylpiperazino, (C_5-C_9)heteroarylpiperazino, (C_1-C_6)alkylpiperazino, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazino,(C_5-C_9)heteroaryl(C_1-C_6)alkylpiperazino,morpholino,thiomorpholino, piperidino, pyrrolidino, piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_5-C_9)heteroarylpiperidyl,(C_1-C_6)alkylpiperidyl(C_1-C_6)alkyl,(C_6-C_{10})arylpiperidyl(C_1-C_6)alkyl, (C_5-C_9)heteroarylpiperidyl(C_1-C_6)alkyl or (C_1-C_6)acylpiperidyl;

or a group of the formula

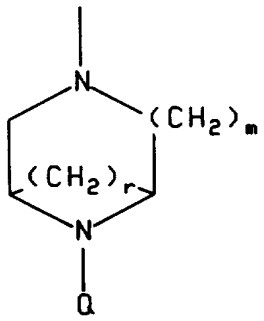


wherein n is 0 to 6;

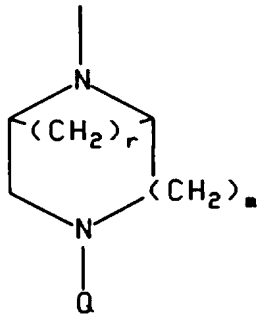
Z is hydroxy, (C_1-C_6)alkoxy or $NR^{14}R^{15}$ wherein R^{14} and R^{15} are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl optionally substituted by (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_5-C_9)heteroarylpiperidyl, (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_6-C_{10})aryl(C_6-C_{10})aryl or (C_3-C_6)cycloalkyl; piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_5-C_9)heteroarylpiperidyl, (C_1-C_6)acylpiperidyl, (C_6-C_{10})aryl,(C_5-C_9)heteroaryl,(C_6-C_{10})aryl(C_6-C_{10})aryl,(C_3-C_6)cycloalkyl,R^{16}(C_2-C_6)alkyl, (C_1-C_5)alkyl(CHR^{16})(C_1-C_6)alkyl wherein R^{16} is hydroxy, (C_1-C_6)acyloxy, (C_1-C_6)alkoxy, piperazino, (C_1-C_6)acylamino, (C_1-C_6)alkylthio, (C_6-C_{10})arylthio, (C_1-C_6)alkylsulfinyl, (C_6-C_{10})arylsulfinyl, (C_1-C_6)alkylsulfoxyl, (C_6-C_{10})arylsulfoxyl, amino, (C_1-C_6)alkylamino, ((C_1-C_6)alkyl)$_2$ amino, (C_1-C_6)acylpiperazino, (C_1-C_6)alkylpiperazino, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazino,(C_5-C_9)heteroaryl(C_1-C_6)alkylpiperazino,morpholino,thiomorpholino, piperidino or pyrrolidino; R^{17}(C_1-C_6)alkyl, (C_1-C_5)alkyl(CHR^{17})(C_1-C_6)alkyl wherein R^{17} is piperidyl or (C_1-C_6)alkylpiperidyl; and CH(R^{18})COR^{19} wherein R^{18} is hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_5-C_9)heteroaryl(C_1-C_6)alkyl, (C_1-C_6)alkylthio(C_1-C_6)alkyl, (C_6-C_{10})arylthio(C_1-C_6)alkyl, (C_1-C_6)alkylsulfinyl(C_1-C_6)alkyl, (C_6-C_{10})arylsulfinyl(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonyl(C_1-C_6)alkyl, (C_6-C_{10})arylsulfonyl(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, ((C_1-C_6)alkylamino)$_2$(C_1-C_6)alkyl, $R^{20}R^{21}$NCO(C_1-C_6)alkyl or R^{20}OCO(C_1-C_6)alkyl wherein R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, (C_1-

C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl and (C_5-C_9)heteroaryl(C_1-C_6)alkyl; and R^{19} is $R^{22}O$ or $R^{22}R^{23}N$ wherein R^{22} and R^{23} are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl and (C_5-C_9)heteroaryl(C_1-C_6)alkyl;

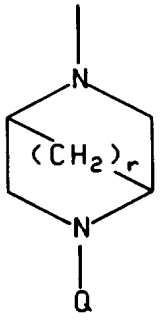
or R^{14} and R^{15}, or R^{20} and R^{21}, or R^{22} and R^{23} may be taken together to form an azetidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, (C_1-C_6)acylpiperazinyl, (C_1-C_6)alkylpiperazinyl, (C_6-C_{10})arylpiperazinyl, (C_5-C_9)heteroarylpiperazinyl or a bridged diazabicycloalkyl ring selected from the group consisting of



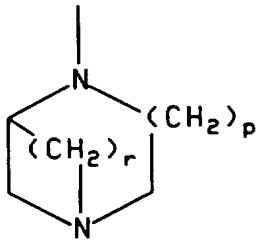
a



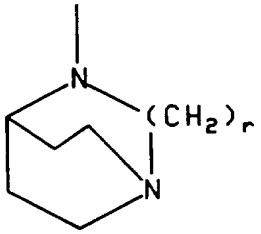
b



c



d



e

wherein r is 1, 2 or 3;

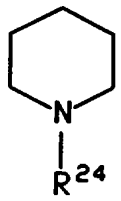
m is 1 or 2;

p is 0 or 1; and

Q is hydrogen, (C_1-C_3)alkyl, (C_1-C_6)acyl or (C_1-C_6)alkoxy carbamoyl;

or R^1 and R^2, or R^3 and R^4, or R^5 and R^6 may be taken together to form a carbonyl;

or R^1 and R^2, or R^3 and R^4, or R^5 and R^6, or R^7 and R^8 may be taken together to form a $(C_3$-$C_6)$cycloalkyl, oxacyclohexyl, thiocyclohexyl, indanyl or tetralinyl ring or a group of the formula



wherein R^{24} is hydrogen, $(C_1$-$C_6)$acyl, $(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkyl, $(C_5$-$C_9)$heteroaryl$(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$alkylsulfonyl; and

Ar is $(C_6$-$C_{10})$aryl or $(C_5$-$C_9)$heteroaryl, each of which may be optionally substituted by $(C_1$-$C_6)$alkyl, one or two $(C_1$-$C_6)$alkoxy, $(C_6$-$C_{10})$aryloxy or $(C_5$-$C_9)$heteroaryloxy;

with the proviso that R^7 is other than hydrogen only when R^8 is other than hydrogen;

with the proviso that R^6 is other than hydrogen only when R^5 is other than hydrogen;

with the proviso that R^3 is other than hydrogen only when R^4 is other than hydrogen;

with the proviso that R^2 is other than hydrogen only when R^1 is other than hydrogen;

with the provisio that when R^1, R^2 and R^9 are a substituent comprising a heteroatom, the heteroatom cannot be directly bonded to the 2- or 6- positions;

with the proviso that when X is nitrogen, R^4 is not present;

with the proviso that when X is oxygen, sulfur, sulfoxide, sulfone or nitrogen and when one or more of the group consisting of R^1, R^2, R^5 and R^6, is a substituent comprising a heteroatom, the heteroatom cannot be directly bonded to the 4- or 6- positions;

with the proviso that when Y is oxygen, sulfur, sulfoxide, sulfone or nitrogen and when one or more of the group consisting of R^3, R^4, R^7 and R^8, are independently a

substituent comprising a heteroatom, the heteroatom cannot be directly bonded to the 3- or 5- positions;

with the proviso that when X is oxygen, sulfur, sulfoxide or sulfone, R^3 and R^4 are not present;

with the proviso that when Y is nitrogen, R^4 is not present;

with the proviso that when Y is oxygen, sulfur, sulfoxide or sulfone, R^5 and R^6 are not present;

with the proviso that when Y is nitrogen, R^6 is not present;

with the proviso that when the broken line represents a double bond, R^4 and R^5 are not present;

with the proviso that when R^3 and R^5 are independently a substituent comprising a heteroatom when the broken line represents a double bond, the heteroatom cannot be directly bonded to positions X and Y;

with the proviso that when either the X or Y position is oxygen, sulfur, sulfoxide, sulfone or nitrogen, the other of X or Y is carbon;

with the proviso that when X or Y is defined by a heteroatom, the broken line does not represent a double bond;

with the proviso that when R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 are all defined by hydrogen or $(C_1\text{-}C_6)$alkyl, either X or Y is oxygen, sulfur, sulfoxide, sulfone or nitrogen, or the broken line represents a double bond.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof.

The term "alkoxy", as used herein, includes O-alkyl groups wherein "alkyl" is defined above.

The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl or naphthyl, optionally substituted by 1 to 3 substituents independently selected from the group consisting of fluoro, chloro, cyano, nitro, trifluoromethyl, $(C_1\text{-}C_6)$alkoxy, $(C_6\text{-}C_{10})$aryloxy, trifluoromethoxy, difluoromethoxy and $(C_1\text{-}C_6)$alkyl.

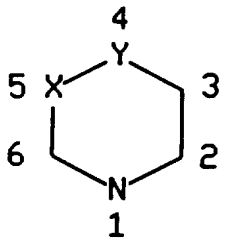
The term "heteroaryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic heterocyclic compound by removal of one hydrogen, such as pyridyl, furyl, pyroyl, thienyl, isothiazolyl, imidazolyl, benzimidazolyl,

tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzofuryl, isobenzofuryl, benzothienyl, pyrazolyl, indolyl, isoindolyl, purinyl, carbazolyl, isoxazolyl, thiazolyl, oxazolyl, benzthiazolyl or benzoxazolyl, optionally substituted by 1 to 2 substituents independently selected from the group consisting of fluoro, chloro, trifluoromethyl, (C_1-C_6)alkoxy, (C_6-C_{10})aryloxy, trifluoromethoxy, difluoromethoxy and (C_1-C_6)alkyl.

The term "acyl", as used herein, unless otherwise indicated, includes a radical of the general formula RCO wherein R is alkyl, alkoxy, aryl, arylalkyl or arylalkyloxy and the terms "alkyl" or "aryl" are as defined above.

The term "acyloxy", as used herein, includes O-acyl groups wherein "acyl" is defined above.

The positions on the ring of formula I, as used herein, are defined as follows:



The preferred conformation of the compound of formula I includes hydroxamic acid axially disposed in the 2-position.

The compound of formula I may have chiral centers and therefore exist in different enantiomeric forms. This invention relates to all optical isomers and stereoisomers of the compounds of formula I and mixtures thereof.

Preferred compounds of formula I include those wherein Y is oxygen, nitrogen or sulfur.

Other preferred compounds of formula I include those wherein Ar is 4-methoxyphenyl or 4-phenoxyphenyl.

Other preferred compounds of formula I include those wherein R^8 is (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_5-C_9)heteroaryl(C_1-C_6)alkyl, carboxylic acid or carboxylic acid (C_1-C_6)alkyl.

Other preferred compounds of formula I include those wherein R^2, R^3, R^6, R^7 and R^9 are hydrogen.

More preferred compounds of formula I include those wherein Y is carbon, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R^8 is (C_6-C_{10})arylalkynyl or (C_5-C_9)heteroarylalkynyl.

More preferred compounds of formula I include those wherein Y is oxygen, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R^8 is (C_6-C_{10})arylalkynyl or (C_5-C_9)heteroarylalkynyl.

More preferred compounds of formula I include those wherein Y is carbon, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R^8 is carboxylic acid or carboxylic acid (C_1-C_6)alkyl.

More preferred compounds of formula I include those wherein Y is oxygen, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R^8 is carboxylic acid or carboxylic acid (C_1-C_6)alkyl.

More preferred compounds of formula I include those wherein Y is carbon, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R^5 is (C_6-C_{10})arylalkynyl or (C_5-C_9)heteroarylalkynyl.

More preferred compounds of formula I include those wherein Y is oxygen, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R^5 is (C_6-C_{10})arylalkynyl or (C_5-C_9)heteroarylalkynyl.

More preferred compounds of formula I include those wherein Y is carbon, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R^5 is carboxylic acid or carboxylic acid (C_1-C_6)alkyl.

More preferred compounds of formula I include those wherein Y is oxygen, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R^5 is carboxylic acid or carboxylic acid (C_1-C_6)alkyl.

More preferred compounds of formula I include those wherein Y is carbon, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R^5 is (C_1-C_6)alkylamino.

More preferred compounds of formula I include those wherein Y is oxygen, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R^8 is (C_1-C_6)alkylamino.

Specific preferred compounds of formula I include the following:

(2R,3S)-N-hydroxy-3-ethynyl-1-(4-methoxybenzenesulfonyl)-piperidine-2-carboxamide;

(2R,3S)-N-hydroxy-l-(4-methoxybenzenesulfonyl)-3-(5-methoxythiophene-2-yl-ethynyl)-piperidine-2-carboxamide;

(2R,3R)-N-hydroxy-1-(4-methoxybenzenesulfonyl)-3-(3-pyridin-3-yl-prop-2-ynyl)-piperidine-2-carboxamide;

(2S,3R)-N-hydroxy-4-(4-methoxybenzenesulfonyl)-2-pyridine-3-yl-morpholine-3-carboxamide;

(2S,3R)-N-hydroxy-2-hydroxycarbamoyl-4-(4-methoxybenzenesulfonyl)-morpholine-3-carboxamide;

(2R,3R)-N-hydroxy-2-hydroxycarbamoyl-4-(4-methoxybenzenesulfonyl)-piperidine-2-carboxamide;

(2R,3S)-N-hydroxy-1-(4-methoxybenzenesulfonyl)-3-(4-phenylpyridine-2-yl)-piperidine-2-carboxamide;

(2S,3R)-N-hydroxy-1-(4-methoxybenzenesulfonyl)-2-(4-phenylpyridine-2-yl)-morpholine-2-carboxamide;

(2R,3S)-N-hydroxy-3-(2-chloro-4-fluorophenyl)-1-(4-methoxybenzenesulfonyl)-piperidine-2-carboxamide; and

(2S,3R)-N-hydroxy-2-(2-chloro-4-fluorophenyl)-1-(4-methoxybenzenesulfonyl)-piperidine-3-carboxamide.

The present invention also relates to a pharmaceutical composition for (a) the treatment of a condition selected from the group consisting of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) or (b) the inhibition of matrix metalloproteinases or the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising an amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, effective in such treatments or inhibition and a pharmaceutically acceptable carrier.

The present invention also relates to a method for the inhibition of (a) matrix metalloproteinases or (b) the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof.

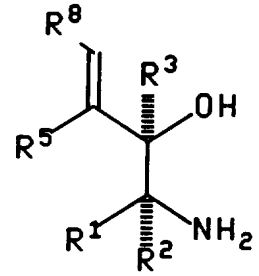
The present invention also relates to a method for treating a condition selected from the group consisting of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the

production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, effective in treating such a condition.

Detailed Description of the Invention

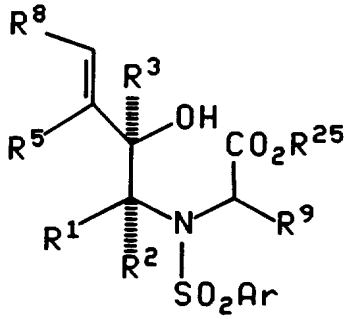
The following reaction Schemes illustrate the preparation of the compounds of the present invention. Unless otherwise indicated R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, n and Ar in the reaction Schemes and the discussion that follow are defined as above.

Preparation 1



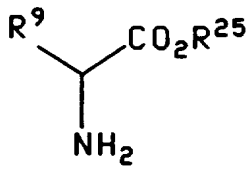
XVI

1



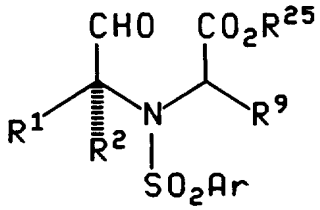
VI

Preparation 2



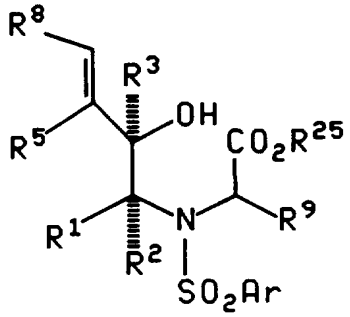
XVIII

1



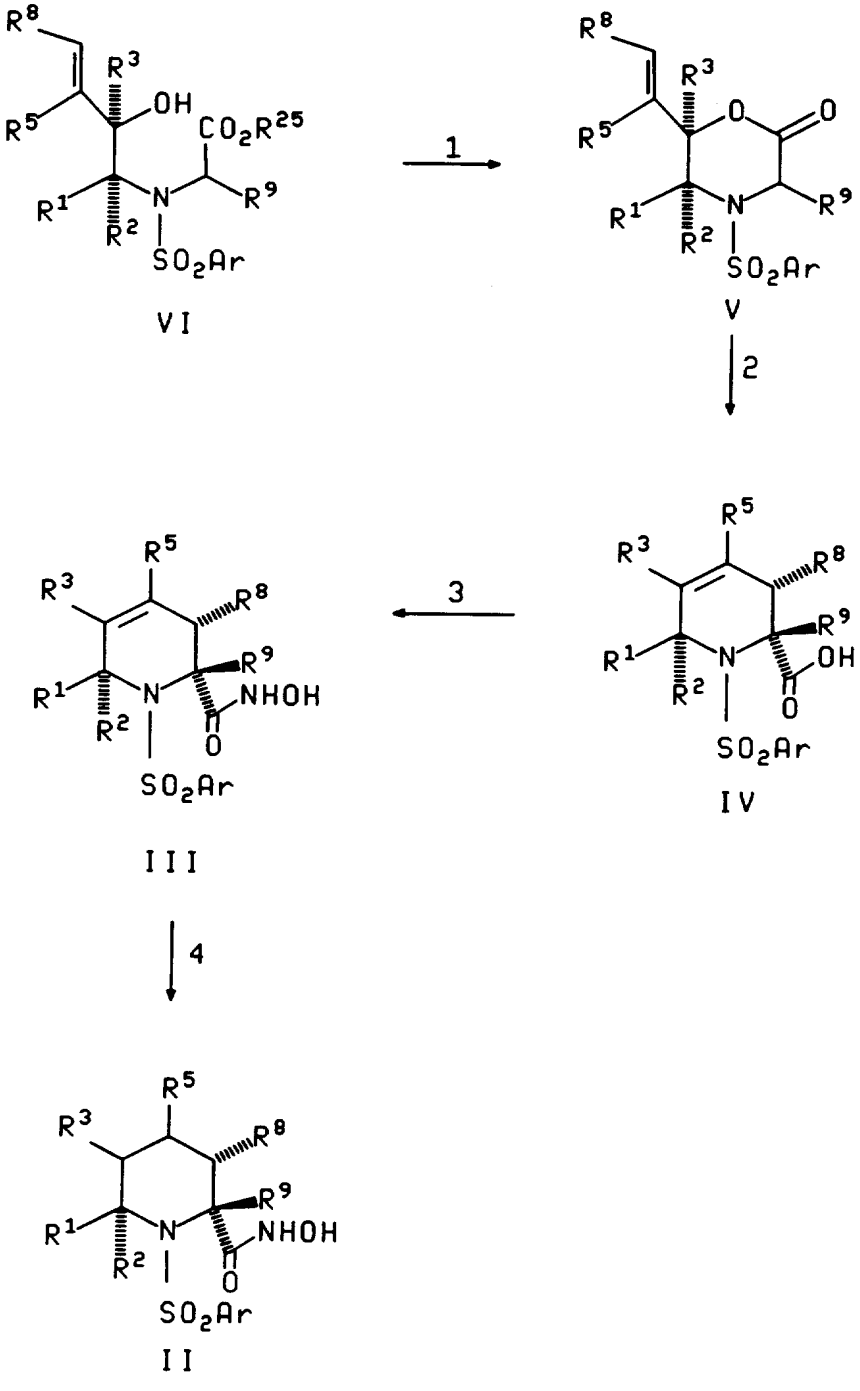
XVII

2

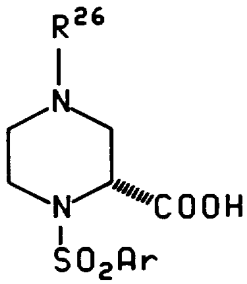


VI

Scheme 1

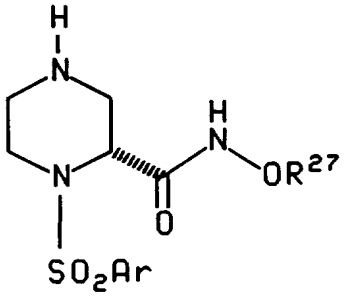


Scheme 2



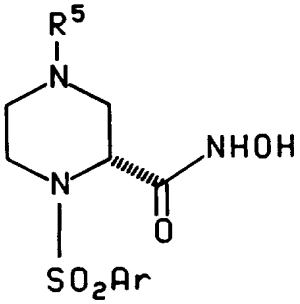
IX

1



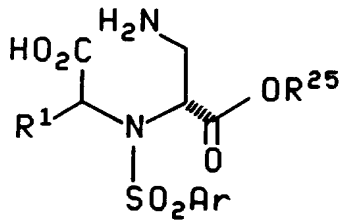
VIII

2



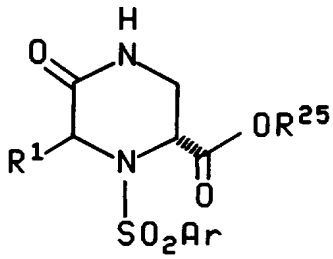
VII

Scheme 3



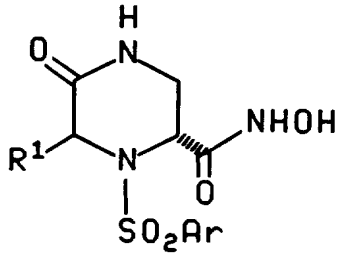
XII

1



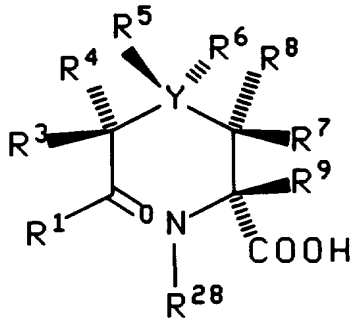
XI

2



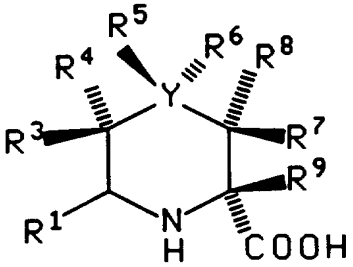
X

Scheme 4



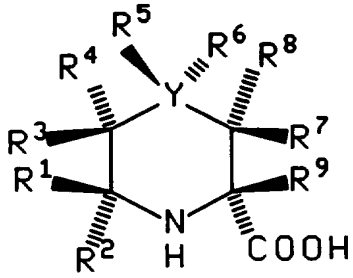
XXII

1



XXI

2

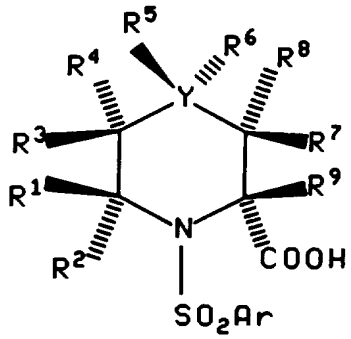


XX

Scheme 4 continued

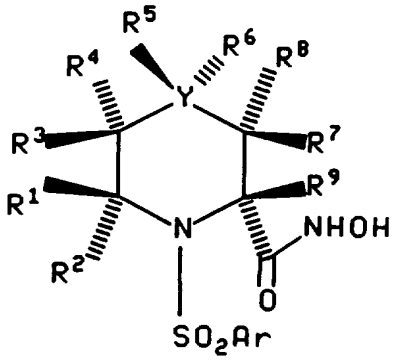
XX

3



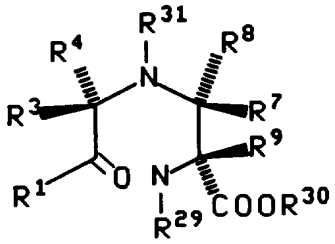
XIX

4



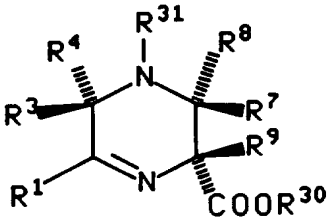
XIII

Scheme 5



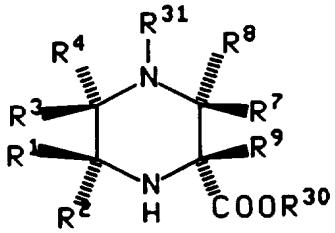
XXVI

1



XXV

2

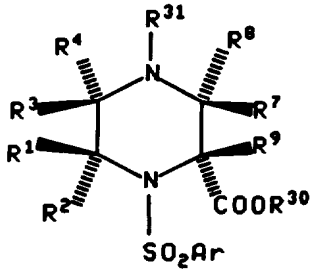


XXIV

Scheme 5 continued

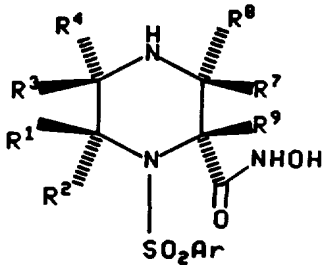
XXIV

3



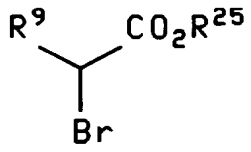
XXIII

4



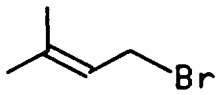
XIV

In reaction 1 of Preparation 1, the compound of formula **XVI** is converted to the corresponding hydroxy ester compound of formula **VI** by first reacting **XVI** with an arylsulfonylhalide in the presence of triethylamine and an aprotic solvent, such as methylene chloride, tetrahydrofuran or dioxane, at a temperature between about 20°C to about 30°C, preferably at room temperature. The compound so formed is further reacted with a compound of the formula

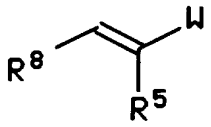


wherein R^{25} is carbobenzyloxy, (C_1-C_6)alkyl, benzyl, allyl or tert-butyl, in the presence of sodium hexamethyldisilazane and a tetrahydrofuran-dimethylformamide solvent mixture at a temperature between about -20°C to about 20°C, preferably about 0°C, to form the hydroxy ester compound of formula **VI**.

In reaction 1 of Preparation 2, the amine compound of formula **XVIII**, wherein R^{25} is as defined above, is converted to the corresponding arylsulfonyl amine compound of formula **XVII** by (1) reacting **XVIII** with an arylsulfonylhalide in the presence of triethylamine and an aprotic solvent, such as methylene chloride, tetrahydrofuran, or dioxane, at a temperature between about 20°C to about 30°C, preferably at room temperature, (2) reacting the compound so formed with a compound of the formula



in the presence of sodium hexamethyldisilazane and a tetrahydrofuran-dimethylformamide solvent mixture at a temperature between about -20°C to about 20°C, preferably about 0°C, and (3) further reacting the compound so formed with ozone in a methylene chloride-methanol solution at a temperature between about -90°C to about -70°C, preferably about -78°C. The unstable ozonide compound so formed is then reacted with triphenylphosphine to form the arylsulfonyl amine compound formula **XVII**. In Reaction 2 of Preparation 2, the arylsulfonyl amine compound of formula **XVII** is converted to the corresponding hydroxy ester compound of formula **VI** by reacting **XVII** with a compound of the formula



wherein W is lithium, magnesium, copper or chromium.

In reaction 1 of Scheme 1, the compound of formula VI, wherein the R^{25} protecting group is carbobenzyloxy, (C_1-C_6) alkyl, benzyl, allyl or tert-butyl, is converted to the corresponding morpholinone compound of formula V by lactonization and subsequent Claisen rearrangement of the compound of formula VI. The reaction is facilitated by the removal of the R^{25} protecting group from the compound of formula VI is carried out under conditions appropriate for that particular R^{25} protecting group in use. Such conditions include: (a) treatment with hydrogen and a hydrogenation catalyst, such as 10% palladium on carbon, where R^{25} is carbobenzyloxy, (b) saponification where R^{25} is lower alkyl, (c) hydrogenolysis where R^{25} is benzyl, (d) treatment with a strong acid, such as trifluoroacetic acid or hydrochloric acid, where R^{25} is tert-butyl, or (e) treatment with tributyltinhydride and acetic acid in the presence of catalytic bis(triphenylphosphine) palladium (II) chloride where R^{25} is allyl.

In reaction 2 of Scheme 1, the morpholinone compound of formula V is converted to the carboxylic acid compound of formula IV by reacting V with lithium hexamethyldisilazane in an aprotic solvent, such as tetrahydrofuran, at a temperature between about -90°C to about -70°C, preferably about -78°C. Trimethylsilyl chloride is then added to the reaction mixture and the solvent, tetrahydrofuran, is removed in vacuo and replaced with toluene. The resuling reaction mixture is heated to a temperature between about 100°C to about 120°C, preferably about 110°C, and treated with hydrochloric acid to form the carboxylic acid compound of formula IV.

In reaction 3 of Scheme 1, the carboxylic acid compound of formula IV is converted to the corresponding hydroxamic acid compound of formula III by treating IV with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide and 1-hydroxybenztriazole in a polar solvent, such as dimethylformamide, followed by the addition of hydroxylamine to the reaction mixture after a time period between about 15 minutes to about 1 hour, preferably about 30 minutes. The hydroxylamine is preferably generated in situ from a salt form, such as hydroxylamine hydrochloride, in the presence of a base, such as N-methylmorpholine. Alternatively, a protected derivative of hydroxylamine or its salt

form, where the hydroxyl group is protected as a tert-butyl, benzyl or allyl ether, may be used in the presence of (benzotriazol-1-yloxy)tris(dimethylamino) phosphonium hexafluorphosphate and a base, such as N-methylmorpholine. Removal of the hydroxylamine protecting group is carried out by hydrogenolysis for a benzyl protecting group or treatment with a strong acid, such as trifluoroacetic acid, for a tert-butyl protecting group. The allyl protecting group may be removed by treatment with tributyltinhydride and acetic acid in the presence of catalytic bis(triphenylphosphine) palladium (II) chloride. N,O-bis(4-methoxybenzyl)hydroxylamine may also be used as the protected hydroxylamine derivative where deprotection is achieved using a mixture of methanesulfonic acid and trifluoroacetic acid.

In reaction 4 of Scheme 1, the hydroxamic acid compound of formula III is converted, if desired, to the corresponding piperidine compound of formula II by treating III with hydrogen and a hydrogenation catayst, such a 10% palladium on carbon.

In reaction 1 of Scheme 2, the arylsulfonylpiperazine compound of formula IX, wherein R^{26} is carbobenzyloxy, benzyl or carbotertbutyloxy, is converted to the compound of formula VIII by reacting IX with a protected derivative of hydroxylamine of the formula

$$R^{27}ONH_2 \bullet HCl$$

wherein R^{27} is tertbutyl, benzyl or allyl, in the presence of dicyclohexylcarbodiimide, dimethylaminopyridine and an aprotic solvent, such as methylene chloride. The R^{26} protecting group is chosen such that it may be selectively removed in the presence of an without loss of the R^{27} protecting group, therefore, R^{26} cannot be the same as R^{27}. Removal of the R^{26} protecting group from the compound of formula IX is carried out under conditions appropriate for that particular R^{26} protecting group in use. Such conditions include; (a) treatment with a hydrogen and a hydrogenation catalyst, such as 10% palladium on carbon, where R^{26} is carbobenzyloxy, (b) hydrogenolysis where R^{26} is benzyl or (c) treatment with a strong acid, such as trifluoroacetic acid or hydrochloric acid where R^{26} is carbotertbutyloxy.

In reaction 2 of Scheme 2, the compound of formula VIII is converted to the corresponding hydroxamic acid compound of formula VII, wherein R^5 is hydrogen or $(C_1\text{-}C_6)$alkyl, by reacting, if desired, VIII with an alkylhalide when R^5 is $(C_1\text{-}C_6)$alkyl. Subsequent removal of the R^{27} hydroxylamine protecting group is carried out by

hydrogenolysis for a benzyl protecting group or treatment with a strong acid, such as trifluoroacetic acid, for a tert-butyl protecting group. The allyl protecting group may be removed by treatment with tributyltinhydride and acetic acid in the presence of catalytic bis(triphenylphosphine) palladium (II) chloride.

In reaction 1 of Scheme 3, the arylsulfonylamine compound of formula **XII**, wherein R^{25} is as defined above, is converted to the corresponding piperizine compound of formula **XI** by reacting **XII** with a carbodiimide and a base, such as triethylamine. The compound of formula **XI** is further reacted to give the hydroxamic acid compound of formula **X** according to the procedure described above in reaction 3 of Scheme 1.

In reaction 1 of Scheme 4, removal of the R^{28} protecting group and subsequent reductive amination of the compound of formula **XXII**, wherein Y is oxygen, sulfur or carbon, to give the corresponding imine compound of formula **XXI** is carried out under conditions appropriate for that particular R^{28} protecting group in use. Such conditions include those used above for removal of the R^{26} protecting group in reaction 1 of Scheme 2.

In reaction 2 of Scheme 4, the imine compound of formula **XXI** is converted to the corresponding piperidine compound of formula **XX** by reacting **XXI** with a nucleophile of the formula R^2M wherein M is lithium, magnesium halide or cerium halide. The reaction is carried out in ether solvents, such as diethyl ether or tetrahydrofuran, at a temperature between about -78°C to about 0°C, preferably about -70°C.

In reaction 3 of Scheme 4, the sulfonation of the piperidine compound of formula **XX** to given the corresponding arylsulfonylpiperidine compound of formula **XIX** is carried out by reacting **XX** with an arylsulfonylhalide in the presence of triethylamine and an aprotic solvent, such as metherone chloride, tetrahydrofuran or dioxane, at a temperature between about 20°C to about 30°C, preferably at room temperature.

In reaction 4 of Scheme 4, the arylsulfonylpiperidine compound of formula **XIX** is converted to the hydroxamic acid compound of formula **XIX** according to the procedure described above in reaction 3 of Scheme 1.

In reaction 1 of Scheme 5, the compound of formula **XXVI**, wherein the R^{29} and R^{31} protecting groups are each independently selected from the group consisting of carbobenzyloxy, benzyl and carbotertbutyloxy and R^{30} is carbobenzyloxy, $(C_1\text{-}C_6)$alkyl,

benzyl, allyl or tert-butyl, is converted to the corresponding imine compound of formula **XXV** by the removal of the R^{29} protecting group and subsequent reductive amination of the compound of formula **XXVI**. The R^{29} protecting group is chosen such that it may be selectively removed in the presence of and without loss of the R^{31} protecting group. Removal of the R^{29} protecting group from the compound of formula **XXVI** is carried out under conditions appropriate for that particular R^{29} protecting group in use which will not affect the R^{31} protecting group. Such conditions include; (a) treatment with hydrogen and a hydrogenation catalyst, such as 10% palladium on carbon, where R^{29} is carbobenzyloxy and R^{31} is tert-butyl, (b) saponification where R^{29} is $(C_1\text{-}C_6)$alkyl and R^{31} is tert-butyl, (c) hydrogenolysis where R^{29} is benzyl and R^{31} is $(C_1\text{-}C_6)$ alkyl or tert-butyl, (d) treatment with a strong acid such as trifluoroacetic acid or hydrochloric acid where R^{29} is tert-butyl and R^{31} is $(C_1\text{-}C_6)$alkyl, benzyl or allyl, or (e) treatment with tributyltinhydride and acetic acid in the presence of catalytic bis(triphenylphosphine) palladium (II) chloride where R^{29} is allyl and R^{31} is $(C_1\text{-}C_6)$alkyl, benzyl or tert-butyl. The R^{30} protective group may be selected such that it is removed in the same reaction step as the R^{29} protecting group.

In reaction 2 of Scheme 5, the imine compound of formula **XXV** is converted to the corresponding compound of formula **XXIV** by reacting **XXV** with a nucleophile of the formula R^2M wherein M is lithium, magnesium halide or calcium halide. The reaction is carried out in ether solvents, such as diethyl ether or tetrahydrofuran, at a temperature between about -78°C to about 0°C, preferably about -70°C.

In reaction 3 of Scheme 5, the sulfonation of the piperidine compound of formula **XXIV** to give the corresponding arylsulfonylpiperidine compound of formula **III** is carried out according to the procedure described above in reaction 3 of Scheme 4.

In reaction 4 of Scheme 5, the arylsulfonylpiperidine compound of formula **XXIII** is converted to the hydroxamic acid compound of formula **XIV** by (1) removing the R^{30}, if needed, and R^{31} protecting groups from **XXIII** followed by (2) reacting **XXIII** according to the procedure described above in reaction 3 of Scheme 1. Removal of the R^{30} and R^{31} protecting groups from the compound of formula **XXIII** is carried out under conditions appropriate for that particular R^{30} and R^{31} protecting group in use. Such conditions include those used above for removal of the R^{25} protecting group in reaction 1 of Scheme 1.

Pharmaceutically acceptable salts of the acidic compounds of the invention are salts formed with bases, namely cationic salts such as alkali and alkaline earth metal salts, such as sodium, lithium, potassium, calcium, magnesium, as well as ammonium slats, such as ammonium, trimethyl-ammonium, diethylammonium, and tris-(hydroxymethyl)-methylammonium slats.

Similarly acid addition salts, such as of mineral acids, organic carboxylic and organic sulfonic acids e.g. hydrochloric acid, methanesulfonic acid, maleic acid, are also possible provided a basic group, such as pyridyl, constitutes part of the structure.

The ability of the compounds of formula I or their pharmaceutically acceptable salts (hereinafter also referred to as the compounds of the present invention) to inhibit matrix metalloproteinases or the production of tumor necrosis factor (TNF) and, consequently, demonstrate their effectiveness for treating diseases characterized by matrix metalloproteinase or the production of tumor necrosis factor is shown by the following in vitro assay tests.

Biological Assay

Inhibition of Human Collagenase (MMP-1)

Human recombinant collagenase is activated with trypsin using the following ratio: 10 μg trypsin per 100 μg of collagenase. The trypsin and collagenase are incubated at room temperature for 10 minutes then a five fold excess (50 μg/10 μg trypsin) of soybean trypsin inhibitor is added.

10 mM stock solutions of inhibitors are made up in dimethyl sulfoxide and then diluted using the following Scheme:

10 mM ——> 120 μM ——> 12 μM ——> 1.2 μM ——> 0.12 μM

Twenty-five microliters of each concentration is then added in triplicate to appropriate wells of a 96 well microfluor plate. The final concentration of inhibitor will be a 1:4 dilution after addition of enzyme and substrate. Positive controls (enzyme, no inhibitor) are set up in wells D1-D6 and blanks (no enzyme, no inhibitors) are set in wells D7-D12.

Collagenase is diluted to 400 ng/ml and 25 μl is then added to appropriate wells of the microfluor plate. Final concentration of collagenase in the assay is 100 ng/ml.

Substrate (DNP-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2) is made as a 5 mM stock in dimethyl sulfoxide and then diluted to 20 μM in assay buffer. The assay is

initiated by the addition of 50 μl substrate per well of the microfluor plate to give a final concentration of 10 μM.

Fluorescence readings (360 nM excitation, 460 nm emission) were taken at time 0 and then at 20 minute intervals. The assay is conducted at room temperature with a typical assay time of 3 hours.

Fluorescence vs time is then plotted for both the blank and collagenase containing samples (data from triplicate determinations is averaged). A time point that provides a good signal (the blank) and that is on a linear part of the curve (usually around 120 minutes) is chosen to determine IC_{50} values. The zero time is used as a blank for each compound at each concentration and these values are subtracted from the 120 minute data. Data is plotted as inhibitor concentration vs % control (inhibitor fluorescence divided by fluorescence of collagenase alone x 100). IC_{50}'s are determined from the concentration of inhibitor that gives a signal that is 50% of the control.

If IC_{50}'s are reported to be <0.03 μM then the inhibitors are assayed at concentrations of 0.3 μM, 0.03 μM, 0.03 μM and 0.003 μM.

Inhibition of Gelatinase (MMP-2)

Inhibition of gelatinase activity is assayed using the Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2 substrate (10 μM) under the same conditions as inhibition of human collagenase (MMP-1).

72kD gelatinase is activated with 1 mM APMA (p-aminophenyl mercuric acetate) for 15 hours at 4°C and is diluted to give a final concentration in the assay of 100 mg/ml. Inhibitors are diluted as for inhibition of human collagenase (MMP-1) to give final concentrations in the assay of 30 μM, 3 μM, 0.3 μM and 0.03 μM. Each concentration is done in triplicate.

Fluorescence readings (360 nm excitation, 460 emission) are taken at time zero and then at 20 minutes intervals for 4 hours.

IC_{50}'s are determined as per inhibition of human collagenase (MMP-1). If IC_{50}'s are reported to be less than 0.03 μM, then the inhibitors are assayed at final concentrations of 0.3 μM, 0.03 μM, 0.003 μM and 0.003 μM.

Inhibition of Stromelysin Activity (MMP-3)

Inhibition of stromelysin activity is based on a modified spectrophotometric assay described by Weingarten and Feder (Weingarten, H. and Feder, J., Spectrophotometric Assay for Vertebrate Collagenase, Anal. Biochem. 147, 437-440 (1985)). Hydrolysis of the thio peptolide substrate [Ac-Pro-Leu-Gly-$SCH[CH_2CH(CH_3)_2]CO$-Leu-Gly-OC_2H_5] yields a mercaptan fragment that can be monitored in the presence of Ellman's reagent.

Human recombinant prostromelysin is activated with trypsin using a ratio of 1 μl of a 10 mg/ml trypsin stock per 26 μg of stromelysin. The trypsin and stromelysin are incubated at 37°C for 15 minutes followed by 10 μl of 10 mg/ml soybean trypsin inhibitor for 10 minutes at 37°C for 10 minutes at 37°C to quench trypsin activity.

Assays are conducted in a total volume of 250 μl of assay buffer (200 mM sodium chloride, 50 mM MES, and 10 mM calcium chloride, pH 6.0) in 96-well microliter plates. Activated stromelysin is diluted in assay buffer to 25 μg/ml. Ellman's reagent (3-Carboxy-4-nitrophenyl disulfide) is made as a 1M stock in dimethyl formamide and diluted to 5 mM in assay buffer with 50 μl per well yielding at 1 mM final concentration.

10 mM stock solutions of inhibitors are made in dimethyl sulfoxide and diluted serially in assay buffer such that addition of 50 μL to the appropriate wells yields final concentrations of 3 μM, 0.3 μM, 0.003 μM, and 0.0003 μM. All conditions are completed in triplicate.

A 300 mM dimethyl sulfoxide stock solution of the peptide substrate is diluted to 15 mM in assay buffer and the assay is initiated by addition of 50 μl to each well to give a final concentration of 3 mM substrate. Blanks consist of the peptide substrate and Ellman's reagent without the enzyme. Product formation was monitored at 405 nm with a Molecular Devices UVmax plate reader.

IC_{50} values were determined in the same manner as for collagenase.

Inhibition of MMP-13

Human recombinant MMP-13 is activated with 2mM APMA (p-aminophenyl mercuric acetate) for 1.5 hours, at 37°C and is diluted to 400 mg/ml in assay buffer (50 mM Tris, pH 7.5, 200 mM sodium chloride, 5mM calcium chloride, 20μM zinc chloride, 0.02% brij). Twenty-five microliters of diluted enzyme is added per well of a 96 well microfluor plate. The enzyme is then diluted in a 1:4 ratio in the assay by the addition of inhibitor and substrate to give a final concentration in the assay of 100 mg/ml.

10 mM stock solutions of inhibitors are made up in dimethyl sulfoxide and then diluted in assay buffer as per the inhibitor dilution scheme for inhibition of human collagenase (MMP-1): Twenty-five microliters of each concentration is added in triplicate to the microfluor plate. The final concentrations in the assay are 30 μM, 3μM, 0.3 μM, and 0.03 μM.

Substrate (Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2) is prepared as for inhibition of human collagenase (MMP-1) and 50 μl is added to each well to give a final assay concentration of 10 μM. Fluorescence readings (360 nM excitation; 450 emission) are taken at time 0 and every 5 minutes for 1 hour.

Positive controls consist of enzyme and substrate with no inhibitor and blanks consist of substrate only.

IC_{50}'s are determined as per inhibition of human collagenase (MMP-1). If IC_{50}'s are reported to be less than 0.03 μM, inhibitors are then assayed at final concentrations of 0.3 μM, 0.03 μM, 0.003 μM and 0.0003 μM.

Inhibition of TNF Production

The ability of the compounds or the pharmaceutically acceptable salts thereof to inhibit the production of TNF and, consequently, demonstrate their effectiveness for treating diseases involving the production of TNF is shown by the following in vitro assay:

Human mononuclear cells were isolated from anti-coagulated human blood using a one-step Ficoll-hypaque separation technique. (2) The mononuclear cells were washed three times in Hanks balanced salt solution (HBSS) with divalent cations and resuspended to a density of 2 x 10^6 /ml in HBSS containing 1% BSA. Differential counts determined using the Abbott Cell Dyn 3500 analyzer indicated that monocytes ranged from 17 to 24% of the total cells in these preparations.

180μ of the cell suspension was aliquoted into flate bottom 96 well plates (Costar). Additions of compounds and LPS (100ng/ml final concentration) gave a final volume of 200μl. All conditions were performed in triplicate. After a four hour incubation at 37°C in an humidified CO_2 incubator, plates were removed and centrifuged (10 minutes at approximately 250 x g) and the supernatants removed and assayed for TNFα using the R&D ELISA Kit.

For administration to humans for the inhibition of matrix metalloproteinases or the production of tumor necrosis factor (TNF), a variety of conventional routes may be

used including orally, parenterally and topically. In general, the active compound will be administered orally or parenterally at dosages between about 0.1 and 25 mg/kg body weight of the subject to be treated per day, preferably from about 0.3 to 5 mg/kg. However, some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

The compounds of the present invention can be administered in a wide variety of different dosage forms, in general, the therapeutically effective compounds of this invention are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelation and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For parenteral administration (intramuscular, intraperitoneal, subcutaneous and intravenous use) a sterile injectable solution of the active ingredient is usually prepared. Solutions of a therapeutic compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably adjusted and buffered, preferably at a pH of greater than 8, if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these

solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

Additionally, it is possible to administer the compounds of the present invention topically, e.g., when treating inflammatory conditions of the skin and this may be done by way of creams, jellies, gels, pastes, and ointments, in accordance with standard pharmaceutical practice.

The present invention is illustrated by the following examples, but it is not limited to the details thereof.

EXAMPLE 1

(+)-(2R*,3R*)-(N-hydroxy)-1-(4-methoxy-benzenesulfonyl)-3-methyl-1,2,3,6-tetrahydropyridine-2-carboxamide.

(a) To a solution of (E)-1-amino-3-pentent-2-ol (2.0 grams, 10.0 mmol) in methylene chloride (50 ml) is added triethylamine (160 μL, 11.0 mmol) followed by 4-methoxybenzenesulfonyl chloride (2.07 grams, 10.0 mmol). The mixture is stirred at room temperature for 12 hours and diluted with ethyl acetate. The mixture is washed with water, 10% citric acid, dried (sodium sulfate), filtered and concentrated. The crude product is purified by silica gel chromatography (elution with 2:1 ethyl acetate-hexanes) to provide (N-(2-hydroxy-pent-3-enyl)-4-methoxybenzenesulfonamide.

(b) To a solution of (±)-(E)-N-(2-hydroxy-pent-3-enyl)-4-methoxybenzenesulfonamide (1.2 grams, 4.42 mmol) in tetrahydrofuran-dimethylformamide (10 mL, ca. 3:1) at 0°C is added sodium bis(trimethylsilyl)amide (4.9 mL, 1.0 M solution in tetrahydrofuran). After 10 minutes, t-butylbromoacetate (786 mL, 4.83 mmol) is added. The mixture is warmed to room temperature, stirred for 1 hour and quenched with saturated ammonium chloride solution. The mixture is extracted with ethyl acetate and the combined extracts are dried (sodium sulfate), filtered and concentrated. The crude product is purified by silica gel chromatography (elution with 1:1 ethyl acetate-hexanes) to provide [(2-hydroxy-pent-3-enyl)-(4-methoxybenzenesulfonyl)-amino]-acetic acid t-butyl ester.

(c) To a solution of (±)-(E)-N-(2-hydroxy-pent-3-enyl)-4-methoxybenzenesulfonyl)-amino]-acetic acid t-butyl ester (900 mg, 2.43 mmol) in benzene (10 ml) is added trifluoroacetic acid (56 μL, 0.73 mmol). The solution is heated at 80°C for 3 hours, cooled to room temperature and concentrated to provide

(±)-(E)-4-(4-methoxybenzenesulfonyl)-6-propenylmorpholin-2-one which is used without further purification.

(d) To a solution of lithium bis(trimethylsilyl)amide (2.67 mmol, 1.0 M in tetrahydrofuran) in tetrahydrofuran (5.0 ml) at -78°C is added a solution of (±)-(E)-4-(4-methoxybenzenesulfonyl)-6-propenylmorpholine-2-one crude from the previous step. After 15 minutes, trimethylsilyl chloride (1.53 ml, 12.15 mmol) is added and the mixture warmed to room temperature. The solvent is removed (in vacuo) and replaced with toluene (10 ml). The resulting mixture is heated at 110°C for 3 hours, cooled to room temperature and treated with 1N hydrochloric acid solution. After stirring for 10 minutes, the mixture is extracted with ethyl acetate and the combined extracts are dried (sodium sulfate), filtered and concentrated. The crude product is purified by silica gel chromatography (elution with 2:1 ethyl acetate-hexanes with 1% acetic acid) to provide (±)-(2R*, 3R*)-1-(4-methoxy-benzenesulfonyl)-3-methyl-1,2,3,6-tetrahydropyridine-2-carboxylic acid.

(e) To a sodium of (±)-(2R*,3R*)-1-(4-methoxy-benzensulfonyl)-3-methyl-1,2,3,6-tetrahydropyridine-2-carboxylic acid (100 mg, 0.36 mmol) in dimethylformamide (5 ml.) is added hydroxybentriazole (53 mg, 0.39 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (75 mg, 0.39 mmol). After 1 hour, hydroxylamine hydrochloride (75 mg, 1.08 mmol) is added followed by triethylamine (150 μL, 1.08 mmol). After stirring overnight, the mixture is diluted with water and extracted with ethyl acetate. The combined extracts are dried, filtered and concentrated. The crude product is purified by silica gel chromatography (elution with 2:1 ethyl acetate-hexanes with 1% acetic acid) to provide (±)-(2R*,3R*)-(N-hydroxy)-1-(4-methoxy-benzenesulfonyl)-3-methyl-1,2,3,6-tetrahydropyridine-2-carboxamide as a white solid. Melting point 173°C (dec.). Mass spectrum (thermospray): m/Z 326 (m-C(O)N(H)OH, 100%, (m, 7%), (m+H, 30%), (m+NH_4, 10%). ^{1}H NMR ($CDCl_3$, 250 MHz, ppm): δ 7,72 (d, J = 8.9 Hz, 2H), 7.03 (d, J=8.9 Hz, 2H), 5.66 (dq, J=13.0, 2.7 Hz, 1H), 5.45 (dd, 13.0, 1.9 Hz), 4.37 (d, 7.0 Hz, 1H), 4.06-3.82 (m, 2H), 3.82 (s, 3H), 3.43-3.30 (m, 1H), 2.62-231 (m, 1H), 0.97 (d, 7.5 Hz, 3H).

EXAMPLE 2

N-hydroxy-1-(4-methoxybenzenesulfonyl)-3-phenyl-1,2,3,6-tetrahydropyridine-2-carboxamide

(a) To a solution of glycine t-butyl ester (5.0 grams, 29.82 mmol) in methylene chloride (50 ml) is added triethylamine (6.65 ml, 62.63 mmol) followed by 4-methoxybenzenesulfonyl chloride (29.82 mmol, 6.2 grams). The solution is stirred for 24 hours, diluted with water and extracted with ethyl acetate. The combined extracts are dried (sodium sulfate), filtered and concentrated. The crude product is purified by silica gel chromatography (elution with 6:1 hexane-ethyl acetate) to provide (4-methoxybenzenesulfonylamino) acetic acid t-butyl ester.

(b) To a solution of (4-methoxybenzenesulfonylamino) acetic acid t-butyl ester (3.0 grams, 10 mmol) in tetrahydrofuran-dimethylformamide (mL, ca. 3:1) at 0°C is added sodium bis(trimethylsilyl)amide (10.0 mL, 1.0 M solution in tetrahydrofuran). After 10 minutes, 4-bromo-2-methyl-2-butene (1.27 μL, 11.0 mmol) is added. The mixture is warmed to room temperature, stirred for 1 hour and quenched with saturated ammonium chloride solution. The mixture is extracted with ethyl acetate and the combined extracts are dried (sodium sulfate), filtered and concentrated. The crude product is purified by silica gel chromatography (elution with 1:1 ethyl acetate-hexanes) to provide [(4-methoxybenzenesulfonyl)-(3-methyl-but-2-enyl)-amino]-acetic acid t-butyl ester.

(c) Ozone is passed through a solution of [(4-methoxybenzenesulfonyl)-(3-methyl-but-2-enyl)-amino]-acetic acid t-butyl ester (2.0 grams, 5.4 mmol) in methylene chloride-methanol (50 mL, ca. 1:1) at -78°C until a blue color persisted. Triphenylphosphine (4.24 grams, 16.2 mmol) is added and the resulting solution is stirred at room temperature for 3 hours. Concentration provided the crude product which is purified by silica gel chromatography (elution with 1:1 ethyl acetate-hexanes) to provide [(4-methoxybenzenesulfonyl)-(2-oxo-ethyl)-amino]-acetic acid t-butyl ester.

(d) To a slurry of chromium (II) chloride (1.3 grams, 10.49 mmol) in dimethylformamide (20 ml) is added a suspension of nickel (II) chloride (0.026 mmol, 1 mg) in dimethylformamide (1 ml) followed by a mixture of (trans)-ß-iodostyrene (1.20 grams, 5.24 mmol) and [(4-methoxybenzenesulfonyl)-2-oxo-athyl)-amino]acetic acid t-butyl ester (900 mg, 2.62 mmol) in dimethylformamide (5 ml). The resulting solution is stirred for three hours, diluted with water and extracted with ethyl acetate. The

combined extracts are washed with brine, dried (sodium sulfate), filtered and concentrated. The crude product is purified by silica gel chromatography (elution with 3:2 hexane-ethyl acetate) to provide (±)-(E)-[(2-hydroxy-4-phenyl-but-3-enyl)-(4-methoxybenzenesulphonyl)-amino]-acetic acid t-butyl ester.

(e) (±)-(E)-[(2-hydroxy-4-phenyl-but-3-enyl)-(4-methoxybenzenesulphonyl)-amino]-acetic acid t-butyl ester is subjected to the conditions described in Example 1c. The crude product is recrystalized from chloroform to provide (±)-(E)-4-(4-methoxybenzenesulfonyl)-6-styryl-morpholin-2-one.

(f) (±)-(E)-4-(4-methoxybenzenesulfonyl)-6-styryl-morpholin-2-one is subjected to the conditions described in Example 1d. The crude product is purified by silica gel chromatography (elution with 2:1 hexane-ethyl acetate with 1% acetic acid) to provide (±)-(2R*-3R*)-1-(4-methoxybenzenesulfonyl)-3-phenyl-1,2,3,6-tetrahydropyridine-2-carboxylic acid.

(g) (±)-(2R*-3R*)-1-(4-methoxybenzenesulfonyl)-3-phenyl-1,2,3,6-tetrahydropyridine-2-carboxylic acid is subject to the conditions described in Example 1e. The crude product is purified by silica gel chromatography (elution with 1:1 hexane-ethyl acetate with 1% acetic acid) to provide N-hydroxy-1-(4-methoxybenzenesulfonyl)-3-phenyl-1,2,3,6-tetrahydropyridine-2-carboxamide as a white solid. Melting point 151-154°C (dec.). Mass spectrum [PBMS w/C.I. (NH_3)]: m/Z 388 (m+NH_4, 100%). ^{1}H NMR (CD_3OD) δ 7.75 (d, J = 8.5 Hz, 2H), 7.38-7.12 (m, 5H), 7.04 (d, J = 8.5 Hz, 2H), 5.91 (d, J = 8.9 Hz, 1H), 5.28 (d, J = 9.9 Hz, 1H), 4.89 (s, H_2O), 4.57 (d, 6.8 Hz, 1H), 4.07 (ABq, JAB = 18.0 Hz, $\Delta\nu$ AB = 39.1 Hz, 2H), 3.85 (o, 3H), 3.39 (bs, CD_3OD).

EXAMPLE 3

(+)-(2R*-3R*)-N-hydroxy-1-(4-methoxybenzenesulfonyl)-3-phenyl-piperidine-2-carboxamide

(a) To a solution of (±)-(2R*-3R*)-1-(4-methoxybenzenesulfonyl)-3-phenyl-1,2,3,6-tetrahydropyridine-2-carboxylic acid (65 mg, 0.17 mmol) (from Example 20), is added benzylhydroxylamine hydrochloride (32 mg, 0.20 mmol), dicyclohexylcarbodiimide (41 mg, 0.20 mmol) and dimethylaminopyridine (27 mg, 0.22 mmol). The resulting mixture is stirred overnight, diluted with ethyl acetate and filtered through Celite™ and evaporated. The crude product is purified by chromatography elution with 1:1 hexane-ethyl acetate to provide (±)-(2R*-3R*)-N-benzyloxy-1-(4-methoxybenzenesulfonyl)-3-phenyl-1,2,3,6-tetrahydropyridine-2-carboxamide.

(b) To a solution of (±)-(2R*-3R*)-N-benzyloxy-1-(4-methoxybenzenesulfonyl)-3-phenyl-1,2,3,6-tetrahydropyridine-2-carboxamide (35 mg, 0.073 mmol) in ethanol (5 ml) is added 10% palladium on carbon (10 mg, 5 mol) . The flask is evacuated and backfilled with hydrogen (repeated two times). The reaction mixture is then stirred for 1 hour at which time it is filtered through Celite™ and concentrated. The product (±)-2R*-3R*)-N-hydroxy-1-(4-methoxybenzenesulfonyl)-3-phenylpiperidine-2-carboxamide was collected as a white solid. Melting point 163°C (dec). Mass spectrum [PBMS w/C.I. (NH_3)]: m/Z 390 ($m+H_2$), ($m+NH_4$). ^{1}H NMR (CD_3OD) δ 7.73 (d, J = 8.9 Hz, 2H), 7.31-737 (m, 5H), 7.04 (d, 8.9 Hz, 2H0, 4.89 (s, H_2O), 4.34 (d, J = 5.4 Hz, 1H), 3.86 (s, 3H), 3.74-3.63 (m, 2H), 3.31 (bs, CD_3OD), 2.99-2.90 (m, 1H), 2.58-2.52 (m, 1H), 1.94-1.88 (m, 1H), 1.67-160 (m, 2H).

EXAMPLE 4

(+)-N-hydroxy-1-(4-methoxybenzenesulfonyl)-2-piperazinecarboxamide hydrochloride

(a) To a solution of (±)-4-benzyloxycarbonyl-2-piperazinecarboxylic acid (1.90 grams, 7.2 mmol) in dioxane-water (10 ml, ca. 1:1) is added 1N sodium hydroxide solution (15 ml, 15 mmol) followed by 4-methoxybenzenesulfonyl chloride. The solution is stirred for 1 hour, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The combined extracts are dried (sodium sulfate), filtered and concentrated. The crude product is purified by silica gel chromatography (elution with 2:1 ethyl acetate-hexanes with 1% acetic acid) to provide (±)-1-(4-methoxybenzenesulfonyl)-4-benzyloxycarbonyl-2-piperazinecarboxylic acid.

(b) To a solution of (±)-1-(4-methoxybenzenesulfonyl)-4-benzyloxycarbonyl-2-piperazinecarboxylic acid (100 mg, 0.23 mmol) in methylene chloride (5 ml) is added O-t-butylhydroxylamine hydrochloride (35 mg, 0.28 mmol), dimethylaminopyridine (37 mg, 0.30 mmol), and dicyclohexycarbodiimide (57 mg, 0.28 mmol). After stirring overnight, the reaction is diluted with hexanes and the precipitated solid filtered off. The solution is concentrated and the crude product is purified by silica gel chromatography (elution with 2:1 ethyl acetate-hexanes with 1% acetic acid) to provide (±)-N-(t-butyloxy)-1-(4-methoxybenzenesulfonyl)-4-benzyloxycarbonyl-2-piperazinecarboxamide.

(c) To a solution of (±)-N-(t-butyloxy)-1-(4-methoxybenzenesulfonyl)-4-benzyloxycarbonyl-2-piperazinecarboxamide (68 mg, 0.134 mmol), in methanol (6 ml)

is added 10% palladium on carbon (7 mg). The flask is evacuated and backfilled with hydrogen (repeated 2 times). The reaction mixture is then stirred for 1 hour at which time it is filtered through Celite™ and concentrated. The product (±)-N-(t-butyloxy)-1-(4-methoxybenzenesulfonyl)-2-piperazinecarboxamide is used without any further purification.

(d) To a solution of (±)-N-(t-butyloxy)-1-(4-methoxybenzenesulfonyl)-2-piperazinecarboxamide (30 mg, in dichloroethane is added ethanol (1 drop). The solution is cooled to -10°C and hydrogen chloride gase is bubbled through for 5 minutes. The reaction is then sealed and stirred for 24 hours at which time the volume is reduced to 1/3 by evaporation and the precipitated solids are filtered and dried (in vacuo) to give (±)-N-hydroxy-1-(4-methoxybenzenesulfonyl)-2-piperazinecarboxamide hydrochloride as a white solid. Melting point 167 °C. (dec.). Mass spectrum (thermospray): m/Z 343 (m + 1 100%). ^{1}H NMR (CD_3OD, 250 MHz, ppm): δ 7.76 (d, J = 8.9 Hz, 2H), 7.07 (d, J = 8.9 Hz, 2H), 3.87 (bs, H_2O), 4.19 (d, J = 3.3 Hz, 1H), 3.87 (s, 3H), 3.58 (bd, J = 6.2 Hz, 1H), 3.42 (bd, J = 6.1 Hz, 1H), 3.30 (bs, CD_3OD), 3.16 (d, J = 13.5 Hz, 1H), 2.87 (bd, J = 13.3 Hz, 1H), 2.69 (dd, J = 13.3, 3.0 Hz, 1H), 2.51 (dt, J = 12.5, 3.8 Hz, 1H).

EXAMPLE 5

N-hydroxy-1-(4-methoxybenzenesulfonyl)-5-oxo-piperazine-2-carboxamide

(a) To a solution of (±)-benzyloxycarbonylamino-2-t-butoxycarbonyl aminopropionate (2.8 grams, 7.9 mmol) in methylene chloride (25 ml) at 0°C is added a solution of hydrochloric acid (g) dissolved in dioxane (25 ml). The solution is stirred at O°C for 4 hours and then concentrated. The crude product 3-benzyloxycarbonylamino-2-amino-propionic acid methyl ester hydrochloride is used without further purification.

(b) 3-benzyloxycarbonylamino-2-amino-propionic acid methyl ester hydrochloride is subjected to the conditions described in Example 1a. The crude product is purified by silica gel chromatography (elution with 1:1 hexane-ethyl acetate) to provide (±)-3-benzyloxycarbonylamino-2-(4-methoxybenzenesulfonylamino)-propionic acid methyl ester.

(c) (±)-3-benzyloxycarbonylamino-2-(4-methoxybenzene sulfonylamino)-propionic acid methyl ester is subjected to the conditions described in Example 1. The crude product is purified by silica gel chromatography (elution with 3:2 ethyl acetate-

hexane) to provide (±)-3-benzyloxycarbonylamino-2-[t-butoxycarbonylmethyl-(4-methoxybenzenesulfonyl)-amino]-propionic acid methyl ester.

(d) (±)-3-benzyloxycarbonylamino-2-[t-butoxycarbonylmethyl-(4-methoxybenzenesulfonyl)-amino]-propionic acid methyl ester is subjected to the conditions described in Example 4c. The product 3-amino-2-[t-butoxycarbonylmethyl-(4-methoxybenzene-sulfonyl)-amino]-propionic acid methyl ester is used without further purification.

(e) To a solution of 3-amino-2-[t-butoxycarbonylmethyl-(4-methoxybenzenesulfonyl)-amino]-propionic acid methyl ester (2.46 grams, 6.1 mmol) in methylene chloride (20 ml) at 0°C is added trifluoroacetic acid (5 ml). The solution is stirred at 0°C for 12 hours and then concentrated. The crude product 3-amino-2-[carboxymethyl-(4-methoxybenzenesulfonyl)-amino]-propionic acid methyl ester trifluoroacetic acid salt is used without further purification.

(f) To a solution of 3-amino-2-[carboxymethyl-(4-methoxybenzenesulfonyl)-amino]-propionic acid methyl ester trifluoracetic acid salt (2.11 grams, 6.1 mmol) in methylene chloride (5 ml) is added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.76 grams, 9.2 mmol) and triethyamine (3.4 ml, 24.4 mmol). The resulting mixture is stirred overnight, diluted with ethyl acetate and washed with 1N hydrochlori acid. The organic layer is dried (sodium sulfate), filtered and concentrated. The crude product is purified by silica gel chromatography (elution with ethyl acetate) to provide 1-(4-methoxybenzenesulfonyl)-5-oxo-piperazine-2-carboxylic acid methyl ester.

(g) To a solution of 1-(4-methoxybenzenesulfonyl)-5-oxo-piperazine-2-carboxylic acid methyl ester. (200 mg, 0.61 mmol) in methanol-tetrahydrofuran-water (5 ml, ca. 6:2:1) at 0°C is added lithium hydroxide (64 mg, 1.53 mmol). The resulting mixture is stirred for 30 minutes, acidified with 1N hydrochloric acid and extracted with ethyl acetate. The combined extracts are dried (sodium sulfate), filtered and concentrated. The crude product 1-(4-methoxybenzenesulfonyl)-5-oxo-piperazine-2-carboxylic acid is used without furtehr purification.

(h) To a solution of 1-(4-methoxybenzenesulfonyl)-5-oxo-piperazine-2-carboxylic acid (166 mg, 0.53 mmol) in methylene chloride (5 ml) is added 0-benzyl hydroxylamine hydrochloride (255 mg, 1.6 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (153 mg, 0.8 mmol) and triethylamine (370 μL 2.65

mmol). The resulting mixture is stirred overnight, diluted with ethyl acetate and washed with 1N hydrocloric acid. The organic layer is dried (sodium sulfate), filtered and concentrated. The crude product is purified by silica gel chromatography (elution with 5% methanol in methylene chloride) to provide N-(benzyloxy)-1-(4-methoxybenzenesulfonyl)-5-oxo-piperazine-2-carboxamide.

(i) N-(benzyloxy)-1-(4-methocybenzenesulfonyl)-5-oxo-piperazine-2-carboxamide is subjected to the conditions described in Example 4c to give N-hydroxy-1-(4-methoxybenzenesulfonyl)-5-oxo-piperazine-2-carboxamide as a white solid. Mass spectrum (thermospray): m/Z 343 (m+H, 60%), (m+NH_4, 17%). ^{1}H NMR (CD_3OD), 250 MHz, ppm) δ7.79 (d, J = 8.9 Hz, 2H), 4.90 (s, H_2O), 4.47 (dd, J = 5.0, 3.2 Hz, 1H), (4.03, s, 2H), 3.88 (s, 3H), 3.47 (dd, J = 13.4, 3.2 Hz, 1H), 3.35-3.30 (m, 1H), 3.30 (s, CD_3OD)

EXAMPLE 6

N-hydroxy-1-(4-methoxybenzenesulfonyl)-morpholin-2-carboxamide

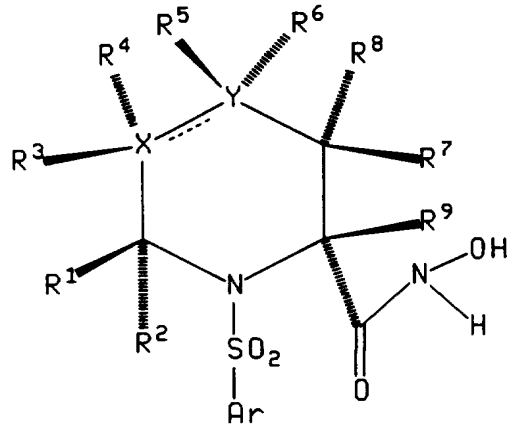
(a) morpholine-2-carboxylic acid is subjected to the conditions described in Example 4a to give 1-(4-methoxybenzenesulfonyl)-morpholin-2-carboxylic acid.

(b) 1-(4-methoxybenzenesulfonyl)-morpholin-2-carboxylic acid is subjected to the conditions described in example 5h to give N-benzyloxy-1-(4-methoxybenzenesulfonyl)-morpholin-2-carboxamide.

(c) N-benzyloxy-1-(4-methoxybenzenesulfonyl)-morpholin-2-carboxamide is subjected to the conditions described in Example 4c to give N-hydroxy-1-(4-methoxybenzenesulfonyl)-morpholin-2-carboxamide as a white foam. Mass spectrum (thermospray): m/Z 343 (m+H, 100%), $[\alpha]_D$: + 57° (c = 0.60, $CHCl_3$. ^{1}H NMR ($CDCL_3$), 250 MHz, ppm) δ7.78 (bd, J = 8.0 Hz, 2H), 7.38 (bs, 1H), 7.01 (bd, J = 8.0 Hz, 2H), (4.34 (bs, J = 2H), 3.87 (s, 3H), 3.85-3.30 (m, 3H), 3.30-3.15 (m, 2H).

CLAIMS

1. A compound of the formula



I

or the pharmaceutically acceptable salt thereof, wherein the broken line represents an optional double bond;

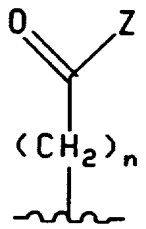
X is carbon, oxygen or sulfur;

Y is carbon, oxygen, sulfur, sulfoxide, sulfone or nitrogen;

R^1, R^2 R^3, R^4 R^5, R^6, R^7, R^8 and R^9 are selected from the group consisting of hydrogen, (C_1-C_6)alkyl optionally substituted by (C_1-C_6)alkylamino, (C_1-C_6)alkylthio, (C_1-C_6)alkoxy, trifluoromethyl, (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_6-C_{10})arylamino, (C_6-C_{10})arylthio, (C_6-C_{10})aryloxy, (C_5-C_9)heteroarylamino, (C_5-C_9)heteroarylthio, (C_5-C_9)heteroaryloxy, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_3-C_6)cycloalkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkyl(hydroxymethylene),piperazinyl,(C_6-C_{10})aryl(C_1-C_6)alkoxy,(C_5-C_9)heteroaryl(C_1-C_6)alkoxy, (C_1-C_6)acylamino, (C_1-C_6)acylthio, (C_1-C_6)acyloxy, (C_1-C_6)alkylsulfinyl, (C_6-C_{10})arylsulfinyl, (C_1-C_6)alkylsulfonyl, (C_6-C_{10})arylsulfonyl, amino, (C_1-C_6)alkylamino or ((C_1-C_6)alkylamino)$_2$; (C_2-C_6)alkenyl, (C_6-C_{10})aryl(C_2-C_6)alkenyl, (C_5-C_9)heteroaryl(C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_6-C_{10})aryl(C_2-C_6)alkynyl, (C_5-C_9)heteroaryl(C_2-C_6)alkynyl, (C_1-C_6)alkylamino, (C_1-C_6)alkylthio, (C_1-C_6)alkoxy, trifluoromethyl, (C_1-C_6)alkyl (difluoromethylene), (C_1-C_3)alkyl(difluoromethylene)(C_1-C_3)alkyl, (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_6-C_{10})arylamino, (C_6-C_{10})arylthio, (C_6-C_{10})aryloxy, (C_5-C_9)heteroarylamino, (C_5-C_9)heteroarylthio, (C_5-C_9)heteroaryloxy, (C_3-C_6)cycloalkyl, (C_1-C_6)alkyl(hydroxymethylene), piperidyl, (C_1-C_6)alkylpiperidyl, (C_1-C_6)acylamino, (C_1-

C_6)acylthio, (C_1-C_6)acyloxy, R^{13}(C_1-C_6)alkyl wherein R^{13} is (C_1-C_6)acylpiperazino, (C_6-C_{10})arylpiperazino, (C_5-C_9)heteroarylpiperazino, (C_1-C_6)alkylpiperazino, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazino,(C_5-C_9)heteroaryl(C_1-C_6)alkylpiperazino,morpholino,thiomorpholino, piperidino, pyrrolidino, piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_5-C_9)heteroarylpiperidyl,(C_1-C_6)alkylpiperidyl(C_1-C_6)alkyl,(C_6-C_{10})arylpiperidyl(C_1-C_6)alkyl, (C_5-C_9)heteroarylpiperidyl(C_1-C_6)alkyl or (C_1-C_6)acylpiperidyl;

or a group of the formula

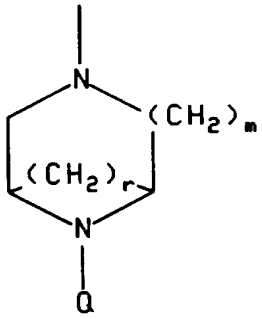


wherein n is 0 to 6;

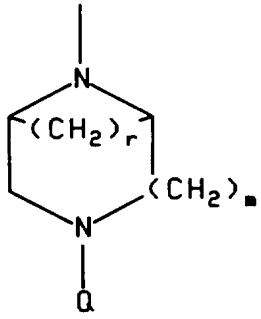
Z is hydroxy, (C_1-C_6)alkoxy or $NR^{14}R^{15}$ wherein R^{14} and R^{15} are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl optionally substituted by (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_5-C_9)heteroarylpiperidyl, (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_6-C_{10})aryl(C_6-C_{10})aryl or (C_3-C_6)cycloalkyl; piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_5-C_9)heteroarylpiperidyl, (C_1-C_6)acylpiperidyl, (C_6-C_{10})aryl,(C_5-C_9)heteroaryl,(C_6-C_{10})aryl(C_6-C_{10})aryl,(C_3-C_6)cycloalkyl,R^{16}(C_2-C_6)alkyl, (C_1-C_5)alkyl(CHR^{16})(C_1-C_6)alkyl wherein R^{16} is hydroxy, (C_1-C_6)acyloxy, (C_1-C_6)alkoxy, piperazino, (C_1-C_6)acylamino, (C_1-C_6)alkylthio, (C_6-C_{10})arylthio, (C_1-C_6)alkylsulfinyl, (C_6-C_{10})arylsulfinyl, (C_1-C_6)alkylsulfoxyl, (C_6-C_{10})arylsulfoxyl, amino, (C_1-C_6)alkylamino, ((C_1-C_6)alkyl)$_2$ amino, (C_1-C_6)acylpiperazino, (C_1-C_6)alkylpiperazino, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazino,(C_5-C_9)heteroaryl(C_1-C_6)alkylpiperazino,morpholino,thiomorpholino, piperidino or pyrrolidino; R^{17}(C_1-C_6)alkyl, (C_1-C_5)alkyl(CHR^{17})(C_1-C_6)alkyl wherein R^{17} is piperidyl or (C_1-C_6)alkylpiperidyl; and $CH(R^{18})COR^{19}$ wherein R^{18} is hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_5-C_9)heteroaryl(C_1-C_6)alkyl, (C_1-C_6)alkylthio(C_1-C_6)alkyl, (C_6-C_{10})arylthio(C_1-C_6)alkyl, (C_1-C_6)alkylsulfinyl(C_1-C_6)alkyl, (C_6-C_{10})arylsulfinyl(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonyl(C_1-C_6)alkyl, (C_6-C_{10})arylsulfonyl(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, ((C_1-C_6)alkylamino)$_2$(C_1-C_6)alkyl, $R^{20}R^{21}NCO$(C_1-C_6)alkyl or $R^{20}OCO$(C_1-C_6)alkyl wherein R^{20} and R^{21} are each independently selected from the group consisting of hydrogen, (C_1-

C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl and (C_5-C_9)heteroaryl(C_1-C_6)alkyl; and R^{19} is $R^{22}O$ or $R^{22}R^{23}N$ wherein R^{22} and R^{23} are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl and (C_5-C_9)heteroaryl(C_1-C_6)alkyl;

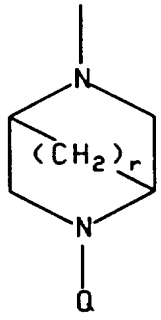
or R^{14} and R^{15}, or R^{20} and R^{21}, or R^{22} and R^{23} may be taken together to form an azetidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, (C_1-C_6)acylpiperazinyl, (C_1-C_6)alkylpiperazinyl, (C_6-C_{10})arylpiperazinyl, (C_5-C_9)heteroarylpiperazinyl or a bridged diazabicycloalkyl ring selected from the group consisting of



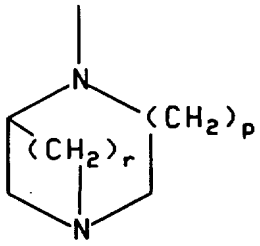
a



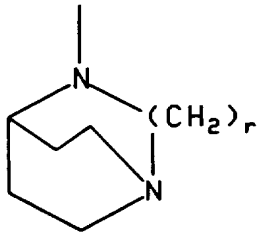
b



c



d



e

wherein r is 1, 2 or 3;

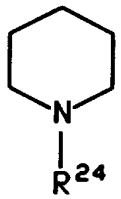
m is 1 or 2;

p is 0 or 1; and

Q is hydrogen, (C_1-C_3)alkyl, (C_1-C_6)acyl or (C_1-C_6)alkoxy carbamoyl;

or R^1 and R^2, or R^3 and R^4, or R^5 and R^6 may be taken together to form a carbonyl;

or R^1 and R^2, or R^3 and R^4, or R^5 and R^6, or R^7 and R^8 may be taken together to form a (C_3-C_6)cycloalkyl, oxacyclohexyl, thiocyclohexyl, indanyl or tetralinyl ring or a group of the formula



wherein R^{24} is hydrogen, (C_1-C_6)acyl, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_5-C_9)heteroaryl(C_1-C_6)alkyl or (C_1-C_6)alkylsulfonyl; and

Ar is (C_6-C_{10})aryl or (C_5-C_9)heteroaryl, each of which may be optionally substituted by (C_1-C_6)alkyl, one or two (C_1-C_6)alkoxy, (C_6-C_{10})aryloxy or (C_5-C_9)heteroaryloxy;

with the proviso that R^7 is other than hydrogen only when R^8 is other than hydrogen;

with the proviso that R^6 is other than hydrogen only when R^5 is other than hydrogen;

with the proviso that R^3 is other than hydrogen only when R^4 is other than hydrogen;

with the proviso that R^2 is other than hydrogen only when R^1 is other than hydrogen;

with the provisio that when R^1, R^2 and R^9 are a substituent comprising a heteroatom, the heteroatom cannot be directly bonded to the 2- or 6- positions;

with the proviso that when X is nitrogen, R^4 is not present;

with the proviso that when X is oxygen, sulfur, sulfoxide, sulfone or nitrogen and when one or more of the group consisting of R^1, R^2, R^5 and R^6, is a substituent comprising a heteroatom, the heteroatom cannot be directly bonded to the 4- or 6- positions;

with the proviso that when Y is oxygen, sulfur, sulfoxide, sulfone or nitrogen and when one or more of the group consisting of R^3, R^4, R^7 and R^8, are independently a

substituent comprising a heteroatom, the heteroatom cannot be directly bonded to the 3- or 5- positions;

with the proviso that when X is oxygen, sulfur, sulfoxide or sulfone, R^3 and R^4 are not present;

with the proviso that when Y is nitrogen, R^4 is not present;

with the proviso that when Y is oxygen, sulfur, sulfoxide or sulfone, R^5 and R^6 are not present;

with the proviso that when Y is nitrogen, R^6 is not present;

with the proviso that when the broken line represents a double bond, R^4 and R^5 are not present;

with the proviso that when R^3 and R^5 are independently a substituent comprising a heteroatom when the broken line represents a double bond, the heteroatom cannot be directly bonded to positions X and Y;

with the proviso that when either the X or Y position is oxygen, sulfur, sulfoxide, sulfone or nitrogen, the other of X or Y is carbon;

with the proviso that when X or Y is defined by a heteroatom, the broken line does not represent a double bond;

with the proviso that when R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 are all defined by hydrogen or $(C_1\text{-}C_6)$alkyl, either X or Y is oxygen, sulfur, sulfoxide, sulfone or nitrogen, or the broken line represents a double bond.

2. A compound according to claim 1, wherein Y is oxygen, nitrogen or sulfur.

3. A compound according to claim 1, wherein Ar is 4-methoxyphenyl or 4-phenoxyphenyl.

4. A compound according to claim 1, wherein R^8 is $(C_6\text{-}C_{10})$aryl, $(C_5\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_5\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkyl, carboxylic acid or carboxylic acid $(C_1\text{-}C_6)$alkyl.

5. A compound according to claim 1, wherein R^2, R^3, R^6, R^7 and R^9 are hydrogen.

6. A compound according to claim 1, wherein Y is carbon, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R^8 is $(C_6\text{-}C_{10})$arylalkynyl or $(C_5\text{-}C_9)$heteroarylalkynyl.

7. A compound according to claim 1, wherein Y is oxygen, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R^8 is (C_6-C_{10})arylalkynyl or (C_5-C_9)heteroarylalkynyl.

8. A compound according to claim 1, wherein Y is carbon, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R^8 is carboxylic acid or carboxylic acid (C_1-C_6)alkyl.

9. A compound according to claim 1, wherein Y is oxygen, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R^8 is carboxylic acid or carboxylic acid (C_1-C_6)alkyl.

10. A compound according to claim 1, wherein Y is carbon, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R^5 is (C_6-C_{10})arylalkynyl or (C_5-C_9)heteroarylalkynyl.

11. A compound according to claim 1, wherein Y is oxygen, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R^5 is (C_6-C_{10})arylalkynyl or (C_5-C_9)heteroarylalkynyl.

12. A compound according to claim 1, wherein Y is carbon, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R^5 is carboxylic acid or carboxylic acid (C_1-C_6)alkyl.

13. A compound according to claim 1, wherein Y is oxygen, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R^5 is carboxylic acid or carboxylic acid (C_1-C_6)alkyl.

14. A compound according to claim 1, wherein Y is carbon, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R^5 is (C_1-C_6)alkylamino.

15. A compound according to claim 1, wherein Y is oxygen, Ar is 4-methoxyphenyl or 4-phenoxyphenyl and R^8 is (C_1-C_6)alkylamino.

16. A compound according to claim 1, wherein said compound is selected from the group consisting of:

(2R,3S)-N-hydroxy-3-ethynyl-1-(4-methoxybenzenesulfonyl)-piperidine-2-carboxamide;

(2R,3S)-N-hydroxy-l-(4-methoxybenzenesulfonyl)-3-(5-methoxythiophene-2-yl-ethynyl)-piperidine-2-carboxamide;

(2R,3R)-N-hydroxy-1-(4-methoxybenzenesulfonyl)-3-(3-pyridin-3-yl-prop-2-ynyl)-piperidine-2-carboxamide;

(2S,3R)-N-hydroxy-4-(4-methoxybenzenesulfonyl)-2-pyridine-3-yl-morpholine-3-carboxamide;

(2S,3R)-N-hydroxy-2-hydroxycarbamoyl-4-(4-methoxybenzenesulfonyl)-morpholine-3-carboxamide;

(2R,3R)-N-hydroxy-2-hydroxycarbamoyl-4-(4-methoxybenzenesulfonyl)-piperidine-2-carboxamide;

(2R,3S)-N-hydroxy-1-(4-methoxybenzenesulfonyl)-3-(4-phenylpyridine-2-yl)-piperidine-2-carboxamide;

(2S,3R)-N-hydroxy-1-(4-methoxybenzenesulfonyl)-2-(4-phenylpyridine-2-yl)-morpholine-2-carboxamide;

(2R,3S)-N-hydroxy-3-(2-chloro-4-fluorophenyl)-1-(4-methoxybenzenesulfonyl)-piperidine-2-carboxamide; and

(2S,3R)-N-hydroxy-2-(2-chloro-4-fluorophenyl)-1-(4-methoxybenzenesulfonyl)-piperidine-3-carboxamide.

17. A pharmaceutical composition for (a) the treatment of a condition selected from the group consisting of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) or (b) the inhibition of matrix metalloproteinases or the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising an amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, effective in such treatments or inhibition and a pharmaceutically acceptable carrier.

18. A method for the inhibition of (a) matrix metalloproteinases or (b) the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof.

19. A method for treating a condition selected from the group consisting of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to

said mammal an amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof, effective in treating such a condition.

INTERNATIONAL SEARCH REPORT

Internat. Application No
PCT/IB 95/00279

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D211/96 A61K31/445 C07D241/04 C07D241/08

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 606 046 (CIBA GEIGY AG) 13 July 1994 see claims 1,2; example 6	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

2

Date of the actual completion of the international search	Date of mailing of the international search report
12 December 1995	20.12.95

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

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

INTERNATIONAL SEARCH REPORT

Int. ional application No.
PCT/IB 95/00279

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 18 and 19 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat Application No
PCT/IB 95/00279

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0606046	13-07-94	US-A-	5455258	03-10-95
		AU-B-	5265593	04-05-95
		CA-A-	2112779	07-07-94
		FI-A-	940012	07-07-94
		HU-A-	70536	30-10-95
		JP-A-	6256293	13-09-94
		NO-A-	940038	07-07-94
		NZ-A-	250517	26-10-95

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/14	A1	(11) International Publication Number: **WO 97/14407**
		(43) International Publication Date: 24 April 1997 (24.04.97)

(21) International Application Number: PCT/US96/16841

(22) International Filing Date: 17 October 1996 (17.10.96)

(30) Priority Data:
60/005,340 17 October 1995 (17.10.95) US

(71) Applicants *(for all designated States except US)*: RESEARCH TRIANGLE PHARMACEUTICALS [US/US]; Suite 201, 4364 Alston Avenue, Durham, NC 27713 (US). BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM [US/US]; 201 West 7th Street, Austin, TX 78701 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: HENRIKSEN, Inge, B. [NO/US]; Research Triangle Pharmaceuticals, Suite 201, 4364 Alston Avenue, Durham, NC 27713 (US). MISHRA, Awadesh, K. [IN/US]; Research Triangle Pharmaceuticals, Suite 201, 4364 Alston Avenue, Durham, NC 27713 (US). PACE, Gary, W. [US/US]; Research Triangle Pharmaceuticals, Suite 201, 4364 Alston Avenue, Durham, NC 27713 (US). JOHNSTON, Keith, P. [US/US]; University of Texas, Dept. Chemical Engineering, 26th and Speedway, Austin, TX 78712-1062 (US). MAWSON, Simon [US/US]; University of Texas, Dept. Chemical Engineering, 26th and Speedway, Austin, TX 78712-1062 (US).

(74) Agent: CRAWFORD, Arthur, R.; Nixon & Vanderhye P.C., 8th floor, 1100 North Glebe Road, Arlington, VA 22201-4714 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: INSOLUBLE DRUG DELIVERY

(57) Abstract

Particles of water insoluble biologically active compounds, particularly water-insoluble drugs, with an average size of 100 nm to about 300 nm, are prepared by dissolving the compound in a solution then spraying the solution into compressed gaz, liquid or supercritical fluid in the presence of appropriate surface modifiers.

FOR THE PURPOSES OF INFORMATION ONLY

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

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

INSOLUBLE DRUG DELIVERY

This invention provides a novel process for producing sub-micron sized particles of water insoluble compounds with biological uses, particularly water insoluble drugs.

BACKGROUND AND SUMMARY OF THE INVENTION

Approximately one-third of the drugs in the United States Pharmacopoeia are water-insoluble or poorly water-soluble. Many currently available injectable formulations of such drugs carry important adverse warnings on their labels that originate from detergents and other agents used for their solubilization. Oral formulations of water-insoluble drugs or compounds with biological uses frequently show poor and erratic bioavailability. In addition, water-solubility problems delay or completely block the development of many new drugs and other biologically useful compounds.

Two alternative approaches for insoluble drug delivery are microparticles which involves forming a phospholipid stabilized aqueous suspension of submicron sized particles of the drug (see U.S. 5,091,187; 5,091,188 and 5,246,707) and microdroplets which involves forming a phospholipid stabilized oil in water emulsion by dissolving the drug in a suitable bio-compatible hydrophobic carrier (see U.S. 4,622,219 and 4,725,442).

The pharmacokinetic properties of both oral and injectable microparticle formulations are dependent on both the particle size and phospholid surface modifier. However, with certain water insoluble compounds the current employed methods of particle size reduction are problematic. Thus, the overall objective of this invention is to develop a novel process based on the use of compressed fluids, including supercritical fluid technology, that yields surface modifier stabilized suspensions of water insoluble drugs with an average particle size of 100 nm to about 300 nm and a narrow size

distribution. The inventive process is robust, scalable and applicable to a wide range of water-insoluble compounds with biological uses.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is further explained with reference to the attached drawings in which

Figure 1 is a schematic representation of an apparatus for carrying out the present invention by precipitating the bioactive substance by rapid expansion from a supercritical solution;

Figure 2A is a more detailed representation of the preheater assembly of Figure 1;

Figure 2B is an enlarged perspective view of the expansion nozzle of Figure 1;

Figure 3 is a schematic representation of an apparatus for preparing sub-micronsized particles according to the invention by precipitating a bioactive substance, suitably solubilized, into a compressed gas, liquid or supercritical fluid;

Figure 4 is a graph showing the particle size distribution on a volume weighted basis of the cyclosporine particles produced in Example 1 expanded into a phospholipid containing 1 wt% stabilizer;

Figure 5 is a graph showing the particle size distribution on a volume weighted basis of the cyclosporine particles produced in Example 1 expanded into a phospholipid containing 2 wt% stabilizer;

Figure 6 is a graph showing the particle size distribution on a volume weighted basis of the indomethacin particles produced in Example 3 sprayed directly into carbon dioxide;

Figure 7 is a graph showing the particle size Gaussian distribution on a volume weighted basis of the indomethacin particles produced in Example 3 sprayed into a phospholipid containing 2 wt% stabilizer;

Figure 8 is a graph showing the particle size distribution on a volume weighted basis of the tetracaine hydrochloride particles produced in Example 4 sprayed into carbon dioxide and water;

Figure 9 is a graph showing the particle size distribution on a volume weighted basis of the tetracaine hydrochloride particles produced in Example 4 sprayed into carbon dioxide and water also containing 1 wt% of stabilizer; and

Figure 10 is a graph showing the particle size Gaussian distribution on a volume weighted basis of tetracaine hydrochloride particles produced in Example 4 sprayed into carbon dioxide, water and 2 wt% stabilizer.

DESCRIPTION OF THE INVENTION

This invention is a process using compressed fluids to produce submicron sized particles of industrially useful poorly soluble or insoluble compounds with biological uses by: (1) precipitating a compound by rapid expansion from a supercritical solution (Rapid expansion from supercritical solution) in which the compound is dissolved, or (2) precipitating a compound by spraying a solution, in which the compound is soluble, into compressed gas, liquid or supercritical fluid which is miscible with the solution but is antisolvent for the compound. In this manner precipitation with a compressed fluid antisolvent (Compressed fluid antisolvent) is achieved. Optionally, the process combines or integrates a phospholipid in water or other suitable surface modifiers such as surfactants, as may be required, into the processes. The surfactant is chosen to be active at the compound-water interface, but is not chosen to be active at the carbon dioxide-organic solvent or carbon dioxide- compound interface when carbon dioxide is used as the supercritical solution. A unique feature of this invention is the combination of either rapid expansion from supercritical solution or compressed fluid antisolvent with recovery of surface modified stable submicron particles in an aqueous phas-

By industrially useful insoluble or poorly soluble compounds we include biologically useful compounds, imaging agents, pharmaceutically useful compounds and in particular drugs for human and veterinary medicine. Water insoluble compounds are those having a poor solubility in water, that is less than 5 mg/ml at a physiological pH of 6.5 to 7.4, although the water solubility may be less than 1 mg/ml and even less than 0.1 mg/ml.

Examples of some preferred water-insoluble drugs include immunosuppressive and immunoactive agents, antiviral and antifungal agents, antineoplastic agents, analgesic and anti-inflammatory agents, antibiotics, anti-epileptics, anesthetics, hypnotics, sedatives, antipsychotic agents, neuroleptic agents, antidepressants, anxiolytics, anticonvulsant agents, antagonists, neuron blocking agents, anticholinergic and cholinomimetic agents, antimuscarinic and muscarinic agents, antiadrenergic and antarrhythmics, antihypertensive agents, antineoplastic agents, hormones, and nutrients. A detailed description of these and other suitable drugs may be found in *Remington's Pharmaceutical Sciences*, 18th edition, 1990, Mack Publishing Co. Philadelphia, PA.

Cyclosporine, a water insoluble immunosuppressive drug, is used as a model to illustrate the invention. This drug was chosen since it has not been possible by using conventional size reduction techniques to achieve the particle size and distribution believed necessary to reach the desired pharmacokinetic performance.

Cyclosporine is a water insoluble, lipophilic 11 amino acid polypeptide with unique immunosuppressive properties. Its major use is as an immunosuppressant in solid organ transplantation. The clinical utility of the currently available pharmaceutical dosage forms are severely limited by the drug's insolubility. That is, the bioavailability of the oral form is low and the intra and inter patient absorption is variable.

The phospholipid may be any natural or synthetic phospholipid, for example phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidylglycerol, phosphatidic acid, lysophospholipids, egg or soybean phospholipid or a combination thereof. The phospholipid may be salted or desalted, hydrogenated or partially hydrogenated or natural semisynthetic or synthetic.

Examples of some suitable second surface modifiers include: (a) natural surfactants such as casein, gelatin, tragacanth, waxes, enteric resins, paraffin, acacia, gelatin, cholesterol esters and triglycerides, (b) nonionic surfactants such as polyoxyethylene fatty alcohol ethers, sorbitan fatty acid esters, polyoxyethylene fatty acid esters, sorbitan esters, glycerol monostearate, polyethylene glycols, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, poloxamers, polaxamines, methylcellulose, hydroxycellulose, hydroxy propylcellulose, hydroxy propylmethylcellulose, noncrystalline cellulose, polyvinyl alcohol, polyvinylpyrrolidone, and synthetic phospholipids, (c) anionic surfactants such as potassium laurate, triethanolamine stearate, sodium lauryl sulfate, alkyl polyoxyethylene sulfates, sodium alginate, dioctyl sodium sulfosuccinate, negatively charged phospholipids (phosphatidyl glycerol, phosphatidyl inosite, phosphatidylserine, phosphatidic acid and their salts), and negatively charged glyceryl esters, sodium carboxymethylcellulose, and calcium carboxymethylcellulose, (d) cationic surfactants such as quaternary ammonium compounds, benzalkonium chloride, cetyltrimethylammonium bromide, chitosans and lauryldimethylbenzylammonium chloride, (e) colloidal clays such as bentonite and veegum. A detailed description of these surfactants may be found in *Remington's Pharmaceutical Sciences*, and Theory and Practice of Industrial Pharmacy, Lachman et al, 1986.

More specifically, examples of suitable second surface modifiers include one or combination of the following: polaxomers, such as Pluronic™ F68, F108

and F127, which are block copolymers of ethylene oxide and propylene oxide available from BASF, and poloxamines, such as Tetronic™ 908 (T908), which is a tetrafunctional block copolymer derived from sequential addition of ethylene oxide and propylene oxide to ethylene-diamine available from BASF, Triton™ X-200, which is an alkyl aryl polyether sulfonate, available from Rohm and Haas. Tween 20, 40, 60 and 80, which are polyoxyethylene sorbitan fatty acid esters, available from ICI Speciality Chemicals, Carbowax™ 3550 and 934, which are polyethylene glycols available from Union Carbide, hydroxy propylmethylcellulose, dimyristoyl phosphatidylglycerol sodium salt, sodium dodecylsulfate, sodium deoxycholate, and cetyltrimethylammonium bromide.

Particles produced by the process of this invention are generally at most 500 nm in size usually below 300 nm, desirably less than 200 nm, preferably less than about 100 nm and often in a range of 0.1 to 100 nm in size. These particles are narrowly distributed in that 99% of the particles are below 500 nm and preferably below 400 nm with peaks at half width at half height at about 200 nm and preferably below 100 nm. The particles may be recovered from suspension by any convenient means such as spray drying, lyophilization, diafiltration, dialysis or evaporation.

The solvent properties of supercritical fluids are strongly affected by their fluid density in the vicinity of the fluid's critical point. In rapid expansion from supercritical solutions, a non volatile solute is dissolved in a supercritical fluid. Nucleation and crystallization are triggered by reducing the solution density through rapid expansion of the supercritical fluid to atmospheric conditions. To achieve this the supercritical fluid is typically sprayed through 10-50 microns (internal diameter) nozzles with aspect ratios (L/D) of 5-100. The fluid approaches sonic terminal velocity at the nozzle tip and high levels of supersaturation result in rapid nucleation rates and limited crystal growth. The combination of a rapidly propagating mechanical perturbation and high

supersaturation is a distinguishing feature of rapid expansion from a supercritical solution. These conditions lead to the formation of very small particles with a narrow particle distribution.

The first comprehensive study of rapid expansion from a supercritical solution was reported by Krukonis (1984) [V.J.Krukonis: *AIChE Annual Meeting San Francisco* (1984), as cited in J.W.Tom *et al.*: *Supercritical Fluid Engineering Science*, Chapter 19, p238, (1993)] who formed micro-particles of an array of organic, inorganic, and biological materials. Most particle sizes reported for organic materials, such as lovastatin, polyhydroxyacids, and mevinolin, were in the 5-100 micron range. Nanoparticles of beta-carotene (300 nm) were formed by expansion of ethane into a viscous gelatin solution in order to inhibit post expansion particle aggregation.

Most rapid expansion from supercritical solution studies on organic materials utilize supercritical carbon dioxide. However, ethane was preferred to carbon dioxide for beta-carotene because of certain chemical interactions. Carbon dioxide is generally preferred, alone or in combination with a cosolvent. Minute additions of a cosolvent can increase the solubility of some solutes by orders of magnitude. When cosolvents are used in rapid expansion from a supercritical solution, care is required to prevent desolution of the particles due to solvent condensing in the nozzle. Normally, this is achieved by heating the supercritical fluid, prior to expansion, to a point where no condensate (mist) is visible at the nozzle tip.

A similar problem occurs when carbon dioxide is used alone. During adiabatic expansion (cooling), carbon dioxide will be in two phases unless sufficient heat is provided at the nozzle to maintain a gaseous state. Most investigators recognize this phenomenon and increase the pre-expansion temperature to prevent condensation and freezing in the nozzle. A significant heat input is required (40-50 kcal/kg) to maintain carbon dioxide in the gaseous

state. If this energy is supplied by increasing the pre-expansion temperature the density drops and consequently reduces the supercritical fluid's solvating power. This can lead to premature precipitation and clogging of the nozzle.

There are a number of advantages in utilizing compressed carbon dioxide in the liquid and supercritical fluid states, as a solvent or anti-solvent for the formation of materials with submicron particle features. Diffusion coefficients of organic solvents in supercritical fluid carbon dioxide are typically 1-2 orders of magnitude higher than in conventional liquid solvents. Furthermore, carbon dioxide is a small linear molecule that diffuses more rapidly in liquids than do other antisolvents. In the antisolvent precipitation process, the accelerated mass transfer in both directions can facilitate very rapid phase separation and hence the production of materials with sub-micron features. It is easy to recycle the supercritical fluid solvent at the end of the process by simply reducing pressure. Since supercritical fluids do not have a surface tension, they can be removed without collapse of structure due to capillary forces. Drying of the product is unusually rapid. No carbon dioxide residue is left in the product, and carbon dioxide has a number of other desirable characteristics, for example it is non-toxic, nonflammable, and inexpensive. Furthermore, solvent waste is greatly reduced since a typical ratio of antisolvent to solvent is 30:1.

As an antisolvent, carbon dioxide has broad applicability in that it lowers the cohesive energy of nearly all organic solvents. In 1992, D.J. Dixon, PhD. Dissertation, University of Texas at Austin, described a process in which liquid solutions of polymer in solvent are sprayed into compressed carbon dioxide to form microspheres and fibers. In this process, so called precipitation with a compressed fluid antisolvent, the polymer is insoluble in carbon dioxide, and the organic solvent is fully miscible with CO_2. This concept has been used to form biologically active insulin particles (4 microns) [Yeo, S. D., Lim, G.B. and Debenedetti, P.G. Formation of Microparticulate Protein Powders using a

Supercritical Fluid Anti-Solvent Biotechnol. and Bioeng. 1993, 341], several micron biodegradable L-poly(lactic acid) particles [Randolph, T. W. B., R.A.; Johnston, K.P. Micron Sized Biodegradeable Particles of Poly(L-lactic Acid) via the Gas Antisolvent Spray Precipitation Process. Biotechnology Progress. 1993, 9, 429] and methylprednisolone acetate particles (<5 microns) [W.J. Schmitt, M. C. S., G.G. Shook, S. M. Speaker. Finely-Divided Powders by Carrier Solution Injection into a Near or Supercritical Fluid. Am. Inst. Chem. Eng. J. 1995, 41, 2476-2486]. Somewhat surprisingly, the particle sizes have been as small as those made by rapid expansion from a supercritical solution, despite the potentially faster times for depressurization in rapid expansion from a supercritical solution versus two-way mass transfer in the Compressed fluid antisolvent process. Not only can the compressed fluid antisolvent process produce PS particles, but also solid and hollow fibers highly oriented microfibrils biocontinuous networks and 100 nm microballoons with porous shells.

To date, it has not been possible to make submicron particles by the compressed fluid antisolvent process without particle aggregation or flocculation. Our objective is to overcome this limitation with the use of surface modifiers, also termed surfactant stabilizers, such as phospholipids, salts of cholic and deoxycholic acids, Tweens (polyoxyethylene sorbitan esters), Pluronic F-68, Tetronic-908, hydroxypropylmethyl cellulose (HPMC), Triton X-100, cetyltrimethylammonium bromide, PEG-400 or combinations of these compounds as described in more detail above.

Considerable variations as to the identities and types of phospholipid and especially the surface active agent or agents should be expected depending upon the water-insoluble or poorly water-soluble biologically active substance selected as the surface properties of these small particles are different. The most advantageous surface active agent for the insoluble compound will be apparent following empirical tests to identify the surfactant or surfactant

system/combination resulting in the requisite particle size and particle size stability on storage over time.

Appropriate choice of stabilizers will prevent flocculation in the aqueous phase. The surfactant is chosen to be active at the compound water interface, but it is not chosen to be active at the carbon dioxide-organic solvent or carbon dioxide-drug interface. It is not necessary for the stabilizer to be soluble in CO_2; it can be soluble in the liquid to be sprayed, as it only needs to be active at the CO_2/solute interface.

This invention provides a supercritical fluid/compressed fluid based process to produce suspensions of water insoluble drugs with an average particle size of less than 100 nm and a narrow size distribution. An essential element is the use of phospholipids and other surfactants to modify the surface of the drug particles to prevent particle aggregation and thereby improve both their storage stability and pharmacokinetic properties.

DETAILED DESCRIPTION OF THE INVENTION

Materials and methods: Particle sizing was based on the principle of photon correlation spectroscopy using Submicron Particle Sizer-Autodilute Model 370 (NICOMP Particle Sizing Systems, Santa Barbara, CA). This instrument provides number weighted, intensity weighted, and volume weighted particle size distributions as well as multimodality of the particle size distribution, if present.

Separation and quantitation of cyclosporine was carried out with a Waters HPLC system utilizing reverse phase chromatography. The drug was extracted from the sample with methanol and injected for analysis on a C-18 analytical column at 60-80°C with a mobile phase consisting of acetonitrile, methanol, and water. Anylate was detected though its absorbance at 214nm. Operation of the chromatography system and data processing was conducted by Waters Millennium v2.1 software.

Carbon dioxide was used to prepare rapid expansion supercritical solutions since there is no literature reference to any chemical interaction with cyclosporine. Carbon dioxide has been used as a solvent for cyclosporine in fermentation recovery and in HPLC. The relative solubilities of cylclosporine dissolved in a solvent that is expanded with compressed carbon dioxide will be established.

A gas will approach sonic terminal velocity when expanded in a nozzle. Therefore it is important to determine the maximum nozzle diameter and aspect ratio (L/D) that will maintain these conditions in scaleup. Nozzle diameters of 10-50 microns are reported to be used in conjunction with aspect ratios ranging from 5 to 200.

The apparatus for rapid expansion from supercritical solution shown in Figure 1 included a high pressure vessel 1 for formulating the drug/CO_2 solution. Because the drug solution was isolated from the pressurizing fluid by the piston 2 and the valve 2a, the concentration of the drug was constant during the spray. The solution was mixed with a stir bar 14a and a magnetic stirrer 14. The temperature was controlled with heating tape 4. The pressure on the piston and hence the drug solution was controlled via line 3 by an automated syringe pump 5 (ISCO model 100DX) containing pure carbon dioxide.

The preheater as shown in Figure 2A consisted of a hole (0.030" i.d. and 4" long) 8a bored axially along the center of a 2" o.d. x 0.030" i.d. x 4" long copper rod to preheat the solution to a desired temperature before expansion. The preheater assembly 8 and the expansion valve 7 are connected to the high pressure vessel 1 via outlet tube 6. The assembly 8 and the expansion valve 7 were heated with high temperature heating tape 12 and were highly insulated. To monitor the temperature, a thermocouple 13 was placed directly into the preheater assembly close to the orifice.

The expansion nozzle as shown in more detail in Fig. 2B included a 0.254 mm thick, 30 micron diameter laser-drilled orifice 11 (length to diameter ratio ~8.5), which was placed between two copper gaskets 15 (10 mm o.d., 6 mm i.d. and 1 mm thick) and sealed in a 1/4" tubing assembly. The downstream end of the orifice was counterbored into a V-shape as shown in Fig. 2B to prevent the expanding jet from hitting the walls and distorting the morphology of the precipitating solute. To prevent plugging of the orifice, a 1/4" inch diameter, 0.5 micron metal filter 9 was inserted upstream of the nozzle preheater assembly (Figure 1). In addition, a bypass line 10 was used to pre-pressurize the preheater assembly with pure solvent (CO_2) before each spray, otherwise the initial pressure drop across the filter would precipitate the drug and plug the orifice 11. After displacing pure solvent from the preheater, the orifice was submerged into 25 mL aqueous solution in order to trap and stabilize the precipitating drug microparticles. The high kinetic energy of the jet forced the spray 2 cm below the surface of the aqueous phase.

The apparatus used to carry out the Compressed fluid antisolvent sprays is shown in Figure 3. A 300 mL high pressure vessel 16 equipped with a magnetically coupled agitator (Parr) depicted in outline above vessel 16 was used to precipitate the drug. Prior to spraying the drug solution, 50 mL of aqueous solution was added to this precipitator. The aqueous solutions were either pure water, 1.0 wt % Tween 80 in water 10 wt % phospholipid dispersion in water or 10 wt % phospholipid dispersion with 2.0 wt % Tween 80 in water Phospholipid and phospholipid plus Tween-80 dispersions were made by high shear homogenization of their aqueous suspension by passing through a microfluidizer (model M110EH, Microfluidics). Tween-80 was purchased from ICI and egg phospholipid was from Pfansthiel. Aqueous sodium hydroxide solution (1N) was used to adjust the pH of these dispersions to 7.5. Carbon dioxide was compressed with a Haskel air driven gas booster 17 (model AC-152), regulated with a Tescom

pressure regulator (model 26-1021) 18 and monitored by pressure gauge 19. The CO_2 pressure was monitored to within ±0.2 bar. A water bath with a recirculator 30 was used to control the precipitator temperature. The solution was sprayed through 50 micron i.d. fused silica capillary tubing 27 (Polymicro Technology) with a length/diameter ratio of 2800. To maintain a constant flow rate, the solution was pumped through the solution valve 28 to the capillary atomizer using an automated syringe pump 20 (ISCO model 100DX).

A 0.5 μm filter 21 was threaded into the CO_2 effluent line 22 to prevent loss of the water insoluble compound from the precipitation vessel. The filter assembly included an in-line sintered filter element (Swagelok "F" series) which was welded onto a 1/4" i.d. NPT fitting. The effluent vent valve 23 (Whitey, SS-21RS4) connected to rotameter 24 was heated in a water bath 29 to at least 50°C to prevent the expanding CO_2 from freezing. During precipitation, a known amount of aqueous solution 25 was agitated using a 45° pitched blade impeller 26. After precipitation, agitation was discontinued and the vessel was isolated to depressurize for 30-45 min. The aqueous solution was then recovered for particle size analysis.

Unless otherwise specified, all parts and percentages reported herein are weight per unit volume (w/v), in which the volume in the denominator represents the total volume of the system. Diameters of dimensions are given in millimeters (mm = 10^{-3} meters), micrometers (μm = 10^{-6} meters), nanometers (nm = 10^{-9} meters) or Angstrom units (= 0.1 nm). Volumes are given in liters (L), milliliters (mL = 10^{-3} L) and microliters (μL = 10^{-6}L). Dilutions are by volume. All temperatures are reported in degrees Celsius. The compositions of the invention can comprise, consist essentially of or consist of the materials set forth and the process or method can comprise, consist essentially of or consist of the steps set forth with such materials.

While the invention has been described in connection with what is presently considered to be the most practical and preferred embodiment, it is to be understood that the invention is not to be limited to the disclosed embodiment, but on the contrary, is intended to cover various modifications and equivalent arrangements included within the spirit and scope of the appended claims.

The following examples further explain and illustrate the invention:

Example 1

Cyclosporine Microparticle Formation by the Rapid Expansion from Supercritical Solution Process

A homogeneous solution of cyclosporine in supercritical CO_2 was expanded by rapid expansion from supercritical solution into various aqueous solutions to study microparticle stabilization. The aqueous solutions were pure water 1.0 wt % Tween 80, phospholipid dispersion or 2.0 wt % Tween 80 with phospholipid dispersion. An amount of 0.0480 g of cyclosporine was charged to a variable volume view cell and 20 mL of CO_2 were added to formulate a 0.25 wt % solution. After the solution came to thermal equilibrium (T=35°C) the cyclosporine/CO_2 solution at 3000 psia was sprayed through a 0.30 μm orifice (L/D of 8) into an aqueous solution for 25 seconds. The pre-expansion temperature was 40°C. The volume weighted particle size of the cyclosporine microparticles expanded into pure phospholipid was 153.7 nm (peak 2) as shown in Figure 4. Most of the mass that constitutes the peak 1 of 20-50 nm diameter may originate largely from the phospholipid; however, this population may also possess some particles that contain cyclosporine. The volume weighted mean particle size of the cyclosporine microparticles expanded into phospholipid dispersion with 2.0 wt % Tween 80 was 80.9 nm (peak 2) as shown in Figure 5. In this case again the smaller peak (26.8 nm) may originate largely from the phospholipid and Tween 80 dispersion and a small fraction of cyclosporine containing particulates. A control experiment was performed in which pure

carbon dioxide at 3000 psia was sprayed into the phospholipid dispersion. The mean diameter of the particulates in the dispersion was 9 nm. Therefore, the particles greater than 100 nm in Figures 4 and 5 were not originating from purely the phospholipids, but were drug microparticles. Similarly, for the phospholipid dispersion with 2 wt % Tween 80, the mean diameter of the was 28 nm.

Example 2

Water Insoluble Compound Phase Behavior in Compressed CO_2.

In order to assess whether a particular water insoluble compound should be processed by rapid expansion from supercritical solution or compressed fluid antisolvent, the solubility of the candidate drugs in carbon dioxide was measured. Cyclosporine, nifedipine, piroxicam, carbamazepine, indomethacin and tetracaine HI were studied. To prepare solutions with a constant molar composition, measured amounts of drug and CO_2 were charged to the variable volume view cell from Example 1. To increase the solubility, a cosolvent, i.e., acetone or ethanol, was added to the view cell. The temperature and pressure were varied from 25-45°C and 1200 to 4500 psia, respectively. The phase behavior was determined visually by noting when phase separation occurred as the pressure was slowly reduced at 1-2 psia/sec. Table 1 shows a summary of the solubility behavior in CO_2. Cyclosporine was soluble in CO_2 up to 0.5 wt %. Solutions containing 0.01 wt % carbamazepine, tetracaine HI, nifedipine and piroxicam were insoluble in CO_2. With the addition of 2.40 wt % acetone, 0.026 wt % piroxicam was soluble in CO_2 at 25°C for all pressures down to the vapor pressure of CO_2, which is 930 psia. A solution containing 0.028 wt % nifedipine and 2.26 wt % acetone cosolvent was insoluble in CO_2 at 25°C. At 45°C, the nifedipine was solvated with no visible phase separation down to 2000 psia.

SOLUTE	CONC. (wt%)	TEMP. (°C)	CLOUD POINT (psia)
Cyclosporine	0.25	25	soluble down to 1200
Cyclosporine	0.25	30	1850
Cyclosporine	0.25	35	2060
Piroxicam	0.069	25	insoluble up to 4500
Nifedipine	0.088	25	insoluble up to 4000
Nifedipine	0.029 (a)	25	insoluble up to 3500
Carbamazepine	0.0085	25, 40	insoluble up to 4500
Tetracaine HI	0.0097	25, 45	insoluble up to 4500
Indomethacin	0.0098	25	insoluble up to 4000

(a) with 2.0% ethanol as a co-solvent.

Example 3

Indomethacin Microparticle Formation by the Compressed fluid antisolvent Process

A 9.9 wt % solution of indomethacin in acetone was sprayed into carbon dioxide with the aqueous solution using the Compressed fluid antisolvent process. The duration of the spray was 30 s at 1 mL/min. The volume weighted mean particle size of the phospholipid dispersion was 26 nm (peak 1) as shown in Figure 6. A bimodal size distribution was observed for the indomethacin particles with mean diameters of 143.0 nm (peak 2) and 1088.9 nm (peak 3), respectively. Particles with such a size difference are easily separated by filtration. For the microparticles precipitated into phospholipid dispersion in the presence of 2.0 wt

% Tween 80, the volume weighted mean particle diameter was 126 nm as shown in Figure 7.

Example 4

Tetracaine HI Microparticle Formation by the Compressed fluid antisolvent Process

A 0.97 wt % solution of Tetracaine HI in acetone was sprayed into the precipitator containing carbon dioxide and pure water. The volume weighted mean particle sizes of the Tetracaine HI microparticles were 31.8, 193.4 and 2510.1 nm, respectively (Figure 8). This illustrates that the Compressed fluid antisolvent process can produce extremely small particles even without surfactant stabilizer. With 1.0 wt % Tween 80 added to the water, three peaks were observed with mean diameters of 9.5 nm, 38.3 nm and 169.1 nm (Figure 9). The particle size distribution for 1.0 wt % Tetracaine HI stabilized with phospholipid dispersion and 2.0 wt % Tween 80 is shown in Figure 10. A monomodal distribution is observed between 8-200 nm with a mean diameter of 27.3 nm. This peak includes both the surfactant aggregates and drug particles. No drug particles above 200 nm were observed.

WHAT IS CLAIMED IS:

1. A process of preparing microparticles up to 300 nm in size of water-insoluble or substantially water-insoluble biologically active compounds comprising the steps of :
(1) dissolving a water-insoluble or substantially water-insoluble biologically active compound in a solvent therefor to form a solution; and
(2) spraying the solution prepared in step (1) into a compressed gas, liquid or supercritical fluid in the presence of a surface modifier dispersed or dissolved in an aqueous phase.

2. A process of preparing microparticles up to 300 nm in size of a water-insoluble or substantially water-insoluble biologically active compound comprising the steps of:
(1) dissolving a water-insoluble or substantially water-insoluble biologically active compound in a compressed fluid;
(2) preparing an aqueous phase containing a surface modifier active at the compound-water interface; and
(3) spraying the compressed fluid of step (1) into the aqueous phase of step (2) to form microparticles of the compound.

3. The process according to claim 1 or 2, including the additional step of recovering the microparticles so produced.

4. The process according to claim 1 or 2, wherein the surface modifier is a phospholipid.

5. The process according to claim 1 or 2, wherein the surface modifier is a surfactant.

6. The process according to claim 1 or 2, wherein the surface modifier is a mixture of two or more surfactants.

7. The process according to claim 1 or 2, wherein the surface modifier is at least one surfactant devoid or substantially completely devoid of phospholipids.

8. The process of claim 1 or claim 2 wherein the surface modifier is a polyoxyethylene sorbitan fatty acid ester, a block copolymer of ethylene oxide and propylene oxide, a tetrafunctional block copolymer derived from sequential addition of ethylene oxide and propylene oxide to ethylenediamine, an alkyl aryl polyether sulfonate, polyethylene glycol, hydroxy propylmethylcellulose, sodium dodecylsulfate, sodium deoxycholate, cetyltrimethylammonium bromide or combinations thereof.

9. The process of claim 1 or 2 wherein the surface modifier is of egg or plant phospholipid or semisynthetic or synthetic in partly or fully hydrogenated or in a desalted or salt phospholipid such as phosphatidylcholine, phospholipon 90H or dimyristoyl phosphatidylglyerol sodium salt, phosphatidylethanolamine, phosphatidylserine, phosphatidic acid, lysophospholipids or combinations thereof.

10. The process of claim 1 or 2 wherein the compound is a cyclosporine, indomethacin, or tetracaine.

11. The process of claim 1 or 2 wherein the particles are less than 100 nm in size.

12. The process of claim 1 or 2 wherein the particles range from 5 up to about 50 nm in size.

13. The process of claim 1 or 2 wherein 99% of the particles produced are below 500 nm.

14. The process of claim 1 or 2 wherein 99% of the particles produced are below 400 nm with peaks at half width at half height at about 200 nm.

15. The process of claim 14 when the peaks are below 100 nm.

16. The process of claim 1 or 2 wherein the compressed gas or fluid is gas, liquid or supercritical carbon dioxide.

17. The process according to claim 2, wherein the compressed fluid sprayed in step (3) is sprayed through a capillary orifice.

Fig. 1

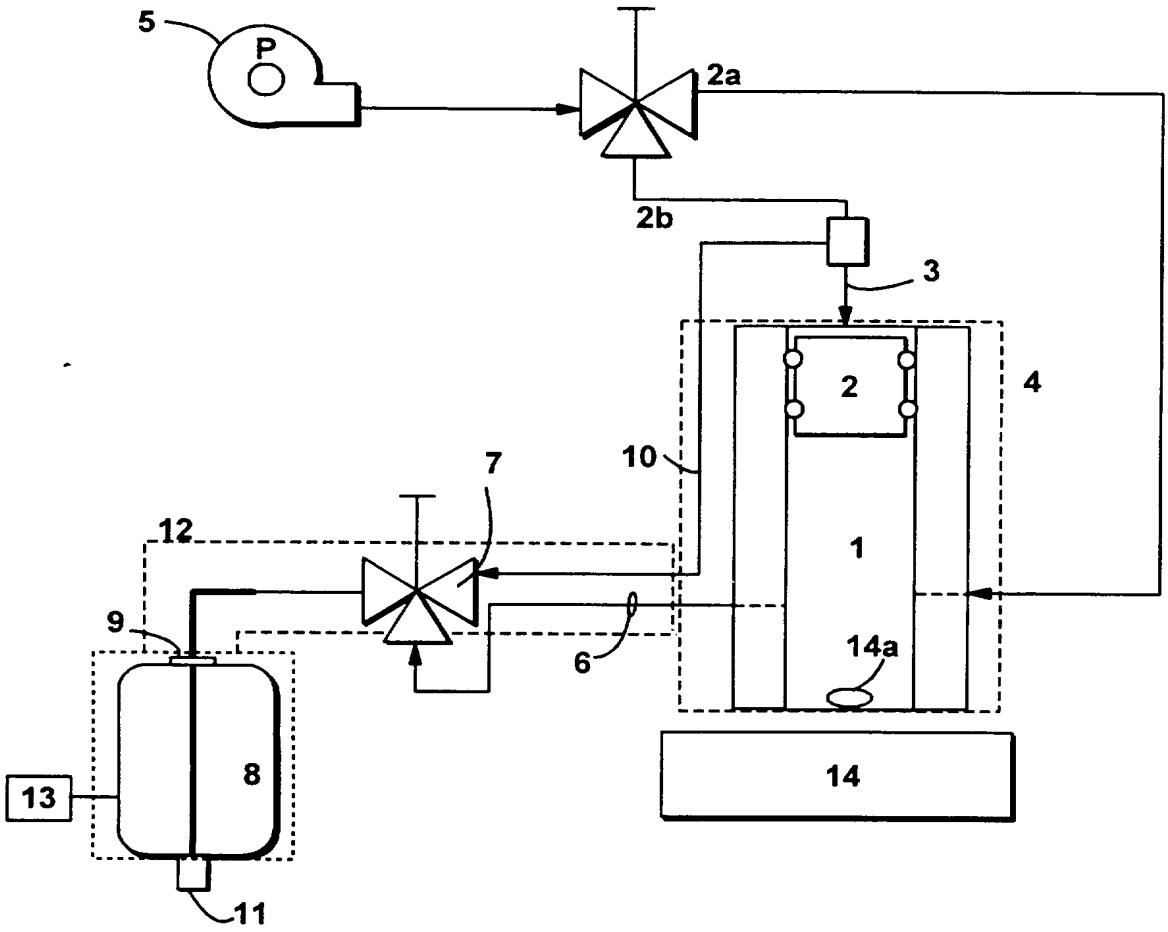


Fig. 2A

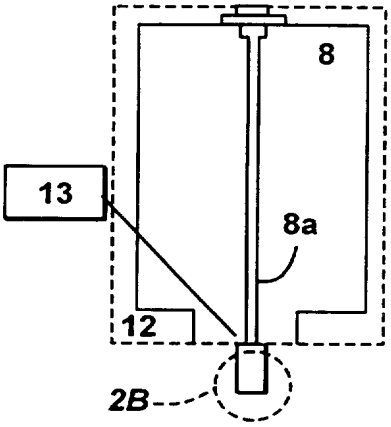


Fig. 2B

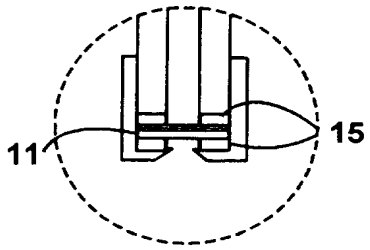
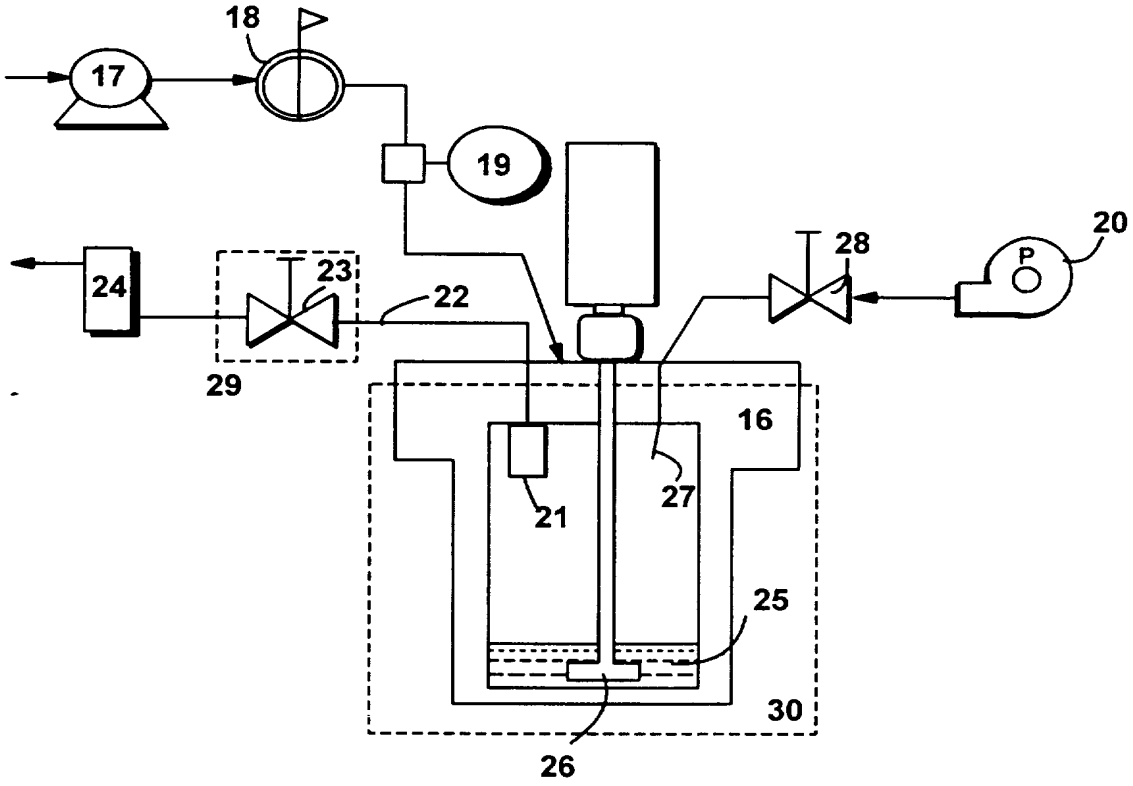


Fig. 3



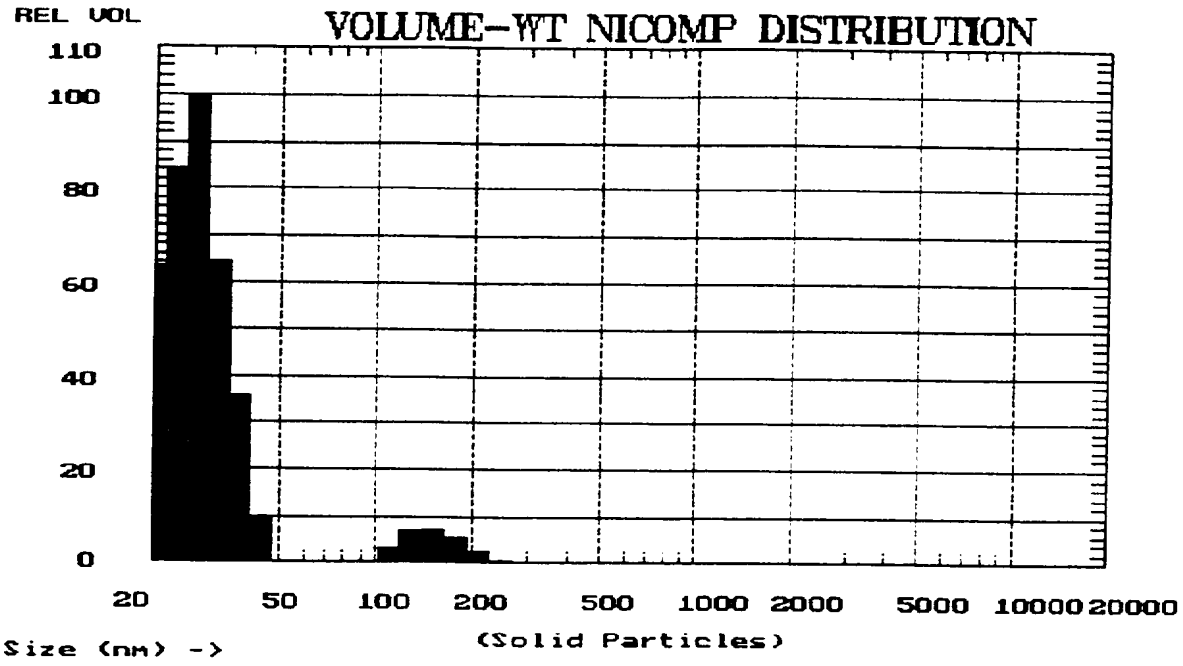

REL VOL
VOLUME-WT NICOMP DISTRIBUTION
110
100
80
60
40
20
0
20
50
100
200
500
1000
2000
5000
10000
20000
Size (nm) ->
(Solid Particles)

Fig. 4

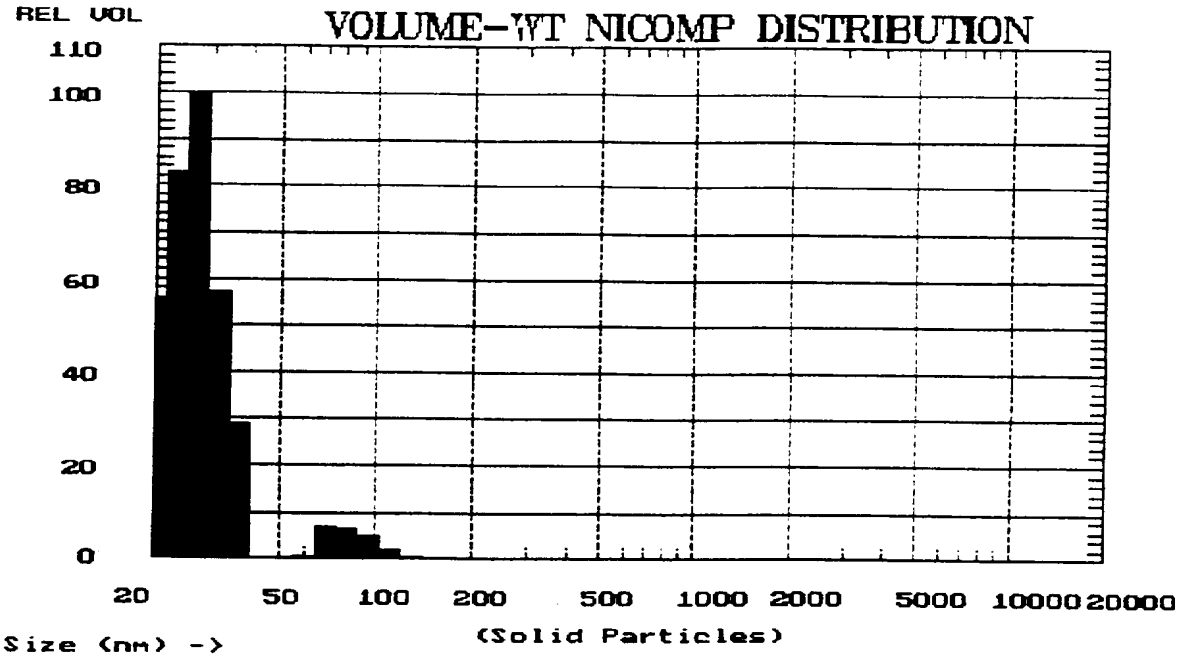

REL VOL
VOLUME-WT NICOMP DISTRIBUTION
110
100
80
60
40
20
0
20
50
100
200
500
1000
2000
5000
10000
20000
Size (nm) ->
(Solid Particles)

Fig. 5

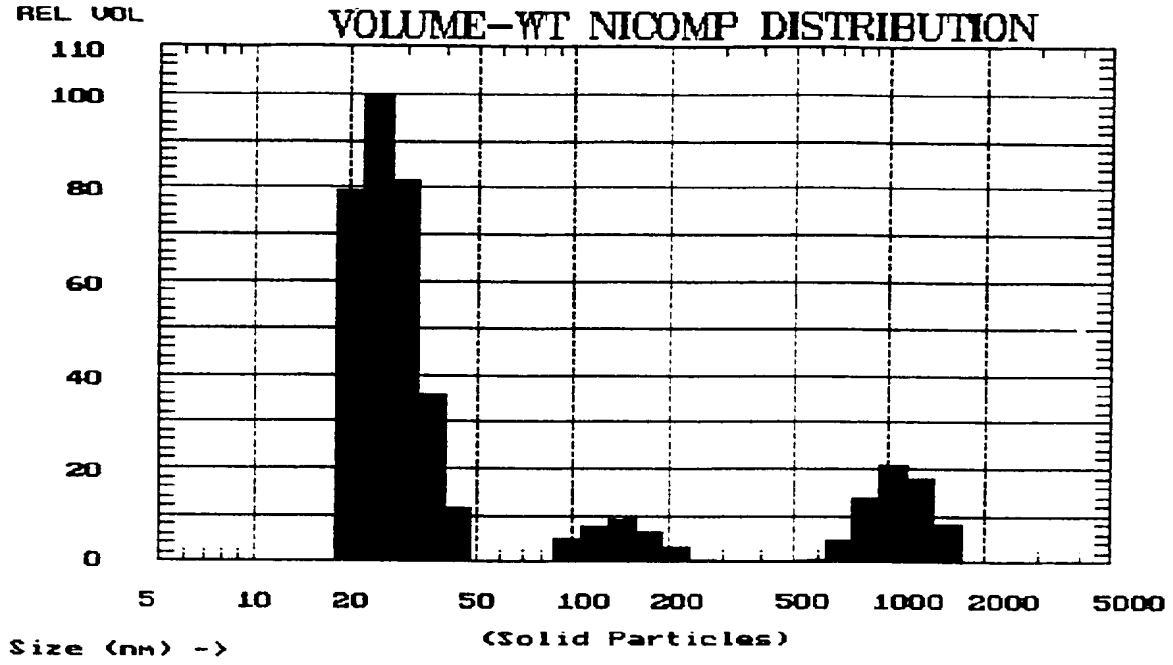

REL VOL
VOLUME-WT NICOMP DISTRIBUTION
110
100
80
60
40
20
0
5
10
20
50
100
200
500
1000
2000
5000
Size (nm) ->
(Solid Particles)

Fig. 6

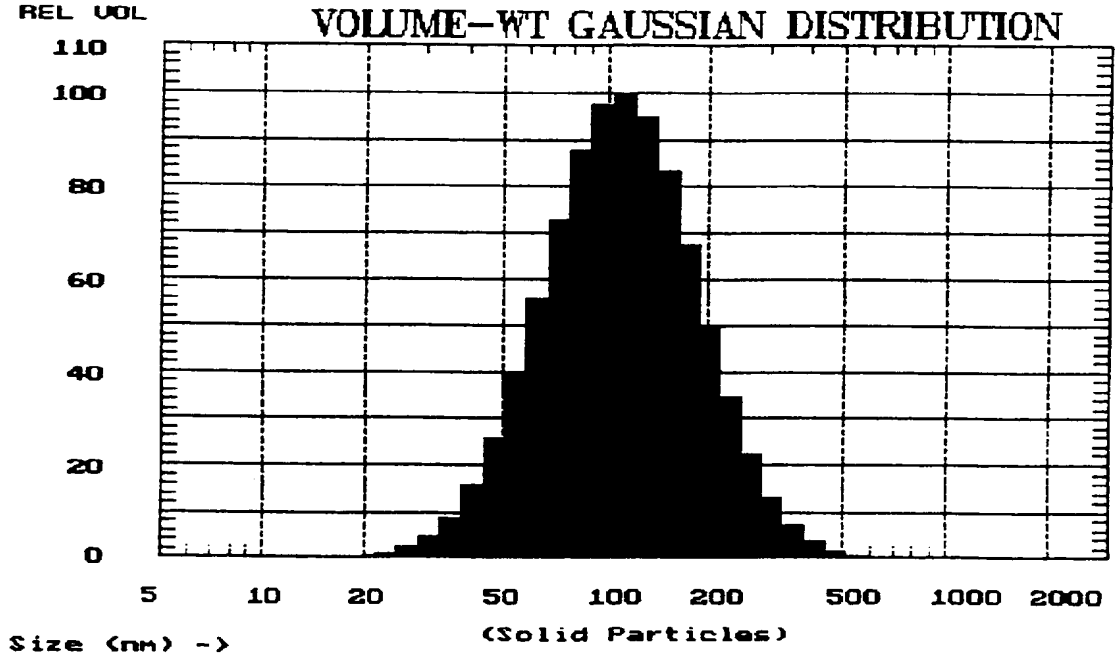

REL VOL
VOLUME-WT GAUSSIAN DISTRIBUTION
110
100
80
60
40
20
0
5
10
20
50
100
200
500
1000
2000
Size (nm) ->
(Solid Particles)

Fig. 7

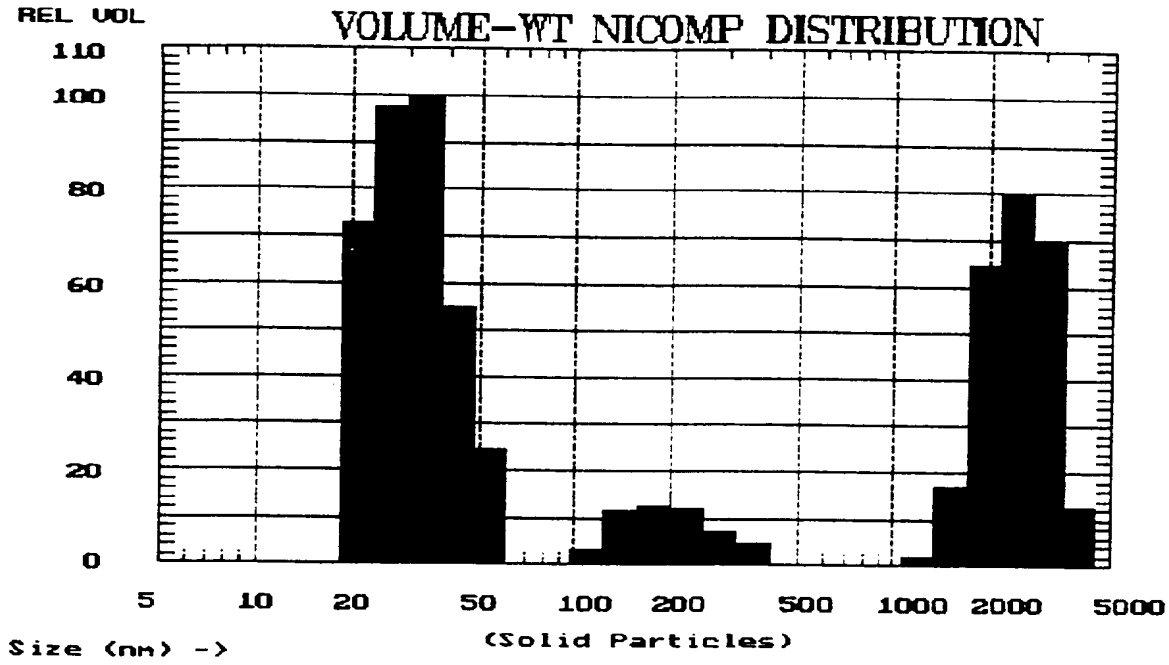

REL VOL
VOLUME-WT NICOMP DISTRIBUTION
110
100
80
60
40
20
0
5
10
20
50
100
200
500
1000
2000
5000
Size (nm) ->
(Solid Particles)

Fig. 8

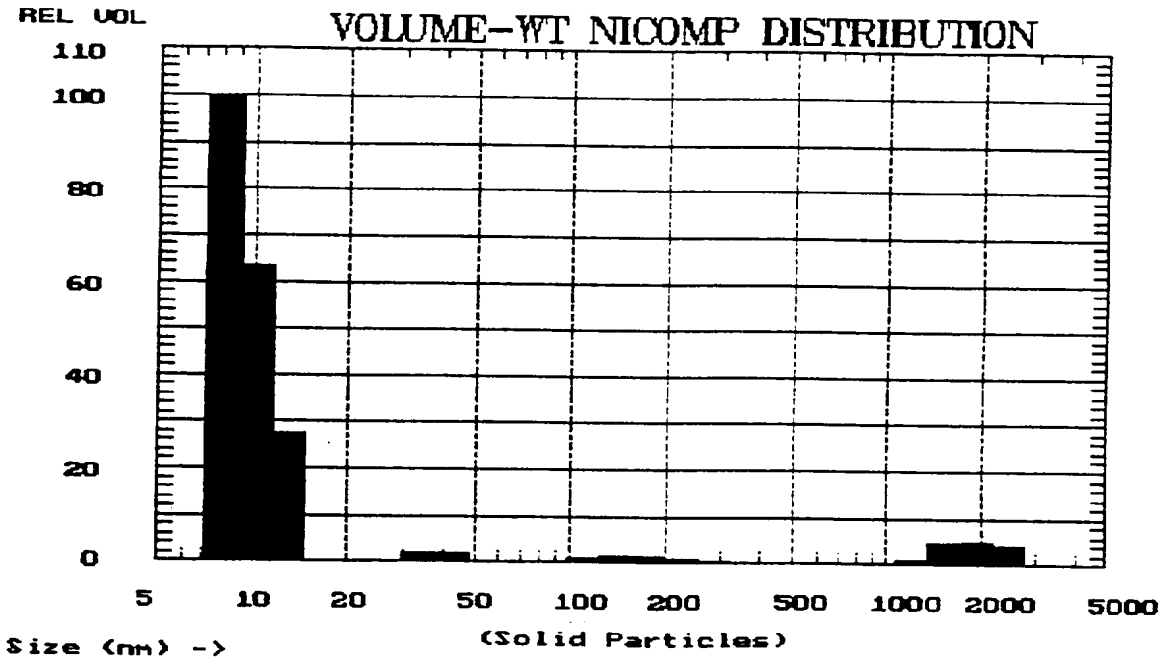
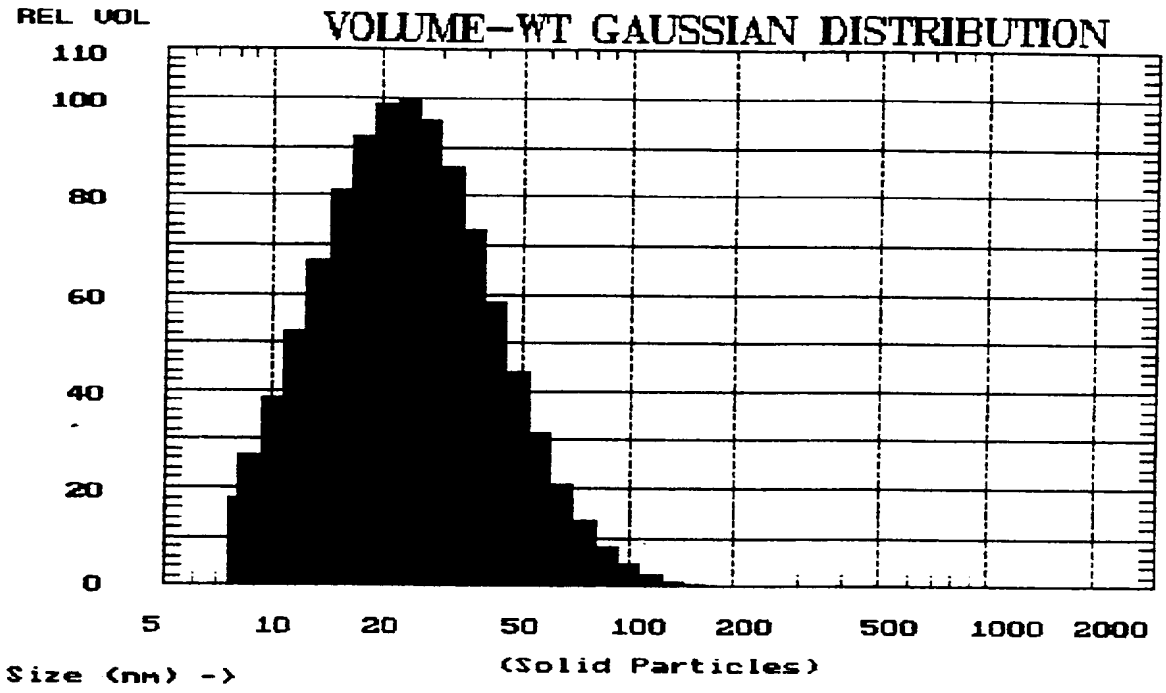

REL VOL
VOLUME-WT NICOMP DISTRIBUTION
110
100
80
60
40
20
0
5
10
20
50
100
200
500
1000
2000
5000
Size (nm) ->
(Solid Particles)

Fig. 9

Fig. 10


REL VOL
VOLUME-WT GAUSSIAN DISTRIBUTION
110
100
80
60
40
20
0
5
10
20
50
100
200
500
1000
2000
Size (nm) ->
(Solid Particles)

INTERNATIONAL SEARCH REPORT

Int. tional Application No
PCT/US 96/16841

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/14

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 542 314 A (UNIV PRINCETON) 19 May 1993 see column 1 - column 2; claims 1-12 ---	1-17
Y	EP 0 322 687 A (SANOL ARZNEI SCHWARZ GMBH) 5 July 1989 see claims 1-11 ---	1-17
Y	INTERNATIONAL JOURNAL OF PHARMACEUTICS, vol. 94, 1993, pages 1-10, XP002027507 PHILLIPS E.M. ET AL: "Rapid expansion from supercritical solutions: applications to pharmaceutical processes" see page 7 - page 8 --- -/--	1-17

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

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 March 1997	04.04.97

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

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

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/16841

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 601 618 A (STERLING WINTHROP INC) 15 June 1994 see page 2, line 6 - line 25; claims 1-18 ---	1-17
P,Y	EP 0 706 821 A (MICROENCAPSULATION CENTRE) 17 April 1996 see column 1, line 5 - line 18 see column 4, line 40 - line 42 -----	1-17

1

INTERNATIONAL SEARCH REPORT

Int. ational Application No
PCT/US 96/16841

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0542314 A	19-05-93	AU 668367 B	02-05-96
		AU 2831092 A	20-05-93
		CA 2083027 A	15-05-93
		JP 5293361 A	09-11-93
EP 0322687 A	05-07-89	DE 3744329 A	06-07-89
		DE 3880808 A	09-06-93
		ES 2056890 T	16-10-94
		JP 2004439 A	09-01-90
		US 5043280 A	27-08-91
EP 0601618 A	15-06-94	US 5336507 A	09-08-94
		AU 662453 B	31-08-95
		AU 5046893 A	23-06-94
		CA 2102267 A	12-06-94
		CZ 9302602 A	15-06-94
		FI 935305 A	12-06-94
		HU 65758 A	28-07-94
		JP 6211646 A	02-08-94
		NO 934204 A	13-06-94
		NZ 250062 A	27-04-95
		SK 139093 A	07-12-94
		US 5470583 A	28-11-95
EP 0706821 A	17-04-96	WO 9611055 A	18-04-96

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07F 9/30, A61K 31/66, C07F 9/58, 9/6553, 9/655

A1

(11) International Publication Number: **WO 98/03516**

(43) International Publication Date: 29 January 1998 (29.01.98)

(21) International Application Number: PCT/IB97/00800

(22) International Filing Date: 30 June 1997 (30.06.97)

(30) Priority Data:
60/021,959 18 July 1996 (18.07.96) US

(71) Applicant *(for all designated States except US)*: PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: REITER, Lawrence, Alan [US/US]; 32 West Mystic Avenue, Mystic, CT 06355 (US).

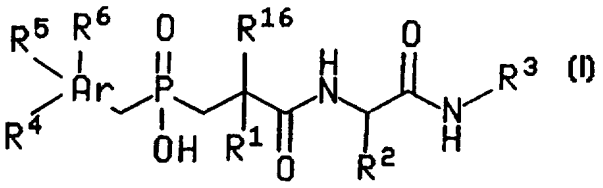
(74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., Patent Dept., 235 East 42nd Street, New York, NY 10017 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: PHOSPHINATE BASED INHIBITORS OF MATRIX METALLOPROTEASES

(57) **Abstract**



A compound of the formula (I) wherein R^1, R^2, R^3, R^4, R^5, R^6 and Ar are as defined above, useful in the treatment of a condition selected from the group consisting of arthritis, cancer, synergy with cytotoxic anticancer agents, tissue ulceration, macular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, in combination with standard NSAID'S and analgesics and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of TNF. In addition, the compounds of the present invention may be used in combination therapy with standard non-steroidal anti-inflammatory drugs (NSAID'S) and analgesics, and in combination with cytotoxic drugs such as adriamycin, daunomycin, cis-platinim, etoposide, taxol, taxotere and other alkaloids, such as vincristine, in the treatment of cancer.

FOR THE PURPOSES OF INFORMATION ONLY

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

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

PHOSPHINATE BASED INHIBITORS OF MATRIX METALLOPROTEASES

Background of the Invention

The present invention relates to phosphinate based derivatives which are inhibitors of matrix metalloproteinases or the production of tumor necrosis factor (TNF) and as such are useful in the treatment of a condition selected from the group consisting of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of TNF. In addition, the compounds of the present invention may be used in combination therapy with standard non-steroidal anti-inflammatory drugs (hereinafter NSAID'S) and analgesics, and in combination with cytotoxic drugs such as adriamycin, daunomycin, cis-platinim, etoposide, taxol, taxotere and other alkaloids, such as vincristine, in the treatment of cancer.

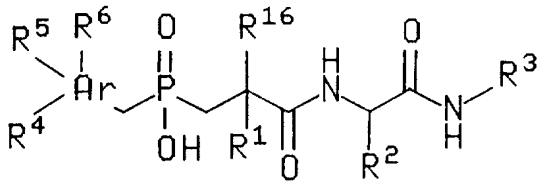
This invention also relates to a method of using such compounds in the treatment of the above diseases in mammals, especially humans, and to pharmaceutical compositions useful therefor.

There are a number of enzymes which effect the breakdown of structural proteins and which are structurally related metalloproteases. Matrix-degrading metalloproteinases, such as gelatinase, stromelysin and collagenase, are involved in tissue matrix degradation (e.g. collagen collapse) and have been implicated in many pathological conditions involving abnormal connective tissue and basement membrane matrix metabolism, such as arthritis (e.g. osteoarthritis and rheumatoid arthritis), tissue ulceration (e.g. corneal, epidermal and gastric ulceration), abnormal wound healing, periodontal disease, bone disease (e.g. Paget's disease and osteoporosis), tumor metastasis or invasion, as well as HIV-infection (J. Leuk. Biol., 52 (2): 244-248, 1992).

Tumor necrosis factor is recognized to be involved in many infectious and auto-immune diseases (W. Friers, FEBS Letters, 1991, 285, 199). Furthermore, it has been shown that TNF is the prime mediator of the inflammatory response seen in sepsis and septic shock (C.E. Spooner et al., Clinical Immunology and Immunopathology, 1992, 62 S11).

Summary of the Invention

The present invention relates to a compound of the formula



I

or a pharmaceutically acceptable salt thereof; wherein

Ar is phenyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl or imidazolyl;

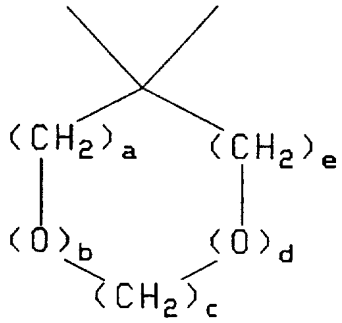
R^1 and R^{16} are each independently hydrogen, $(C_1\text{-}C_6)$alkyl, (trifluoromethyl)$_2$$(C_1\text{-}C_6)$alkyl, perfluoro$(C_1\text{-}C_6)$alkyl, perfluoro$(C_1\text{-}C_6)$alkyl$(C_1\text{-}C_6)$alkyl, difluoromethoxy, trifluoromethoxy, $(C_3\text{-}C_7)$cycloalkyl$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryloxy$(C_1\text{-}C_6)$alkyl or $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl;

R^2 is $(C_1\text{-}C_6)$alkyl or $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl optionally substituted by hydroxy, amino, halo, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, (trifluoromethyl)$_2$$(C_1\text{-}C_6)$alkyl, perfluoro$(C_1\text{-}C_6)$alkyl, perfluoro$(C_1\text{-}C_6)$alkyl$(C_1\text{-}C_6)$alkyl, difluoromethoxy, trifluoromethoxy, carboxy or carboxamoyl;

R^3 is $(C_1\text{-}C_6)$alkyl or $(C_6\text{-}C_{10})$aryl;

R^4 is hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_7)$cycloalkyl$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylsulfonyl, $(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryloxy, $(C_6\text{-}C_{10})$arylsulfonyl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl $(C_1\text{-}C_6)$alkoxy, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkylsulfonyl, N-phthalimido, $(C_6\text{-}C_{10})$arylNHCO, $(C_6\text{-}C_{10})$arylNHSO$_2$, R^7OOC, R^7R^8NCO, $R^7R^8NSO_2$ wherein R^7 and R^8 are each independently hydrogen, $(C_1\text{-}C_6)$alkyl or $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl; $(C_1\text{-}C_6)$alkyl CR^9R^{10}, $(C_6\text{-}C_{10})$aryl CR^9R^{10}, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkylCR^9R^{10} wherein R^9 and R^{10} are each independently fluoro, $(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$alkoxy;

or R^9 and R^{10} may be taken together with the carbon to which they are attached to form a group of the formula



wherein a is 0, 1 or 2;

b is 0 or 1;

c is 1, 2, or 3;

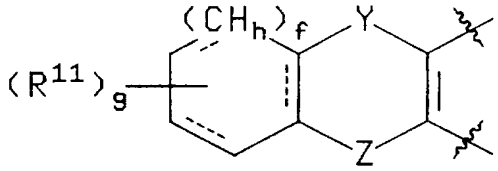
d is 0 or 1; and

e is 0, 1 or 2;

R^5 and R^6 are each independently hydrogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, halo, (trifluoromethyl)$_2(C_1$-$C_6)$alkyl, perfluoro$(C_1$-$C_6)$alkyl, perfluoro$(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, difluoromethoxy, trifluoromethoxy, $(C_1$-$C_6)$alkylthio, $(C_1$-$C_6)$alkylsulfinyl or $(C_1$-$C_6)$alkylsulfonyl;

or R^1 and R^{16} may be taken together with the carbon to which they are attached to form a $(C_3$-$C_7)$cycloalkyl group optionally substituted by $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkyl or $(C_6$-$C_{10})$aryloxy;

or R^5 and R^6, when attached to adjacent carbon positions, may be taken together to form a group of the formula



wherein the broken lines represent optional double bonds;

h is 1 or 2;

f and g are each independently 0, 1 or 2;

Y and Z are each independently CH_2, O, CO, SO_2, CH_2CH_2, CH_2O, CH_2S, CH_2NH, CH_2CO, CH_2SO_2, NHCO or $NHSO_2$; and

R^{11} is hydrogen, halo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (trifluoromethyl)$_2(C_1-C_6)$alkyl, perfluoro(C_1-C_6)alkyl, perfluoro(C_1-C_6)alkyl(C_1-C_6)alkyl, difluoromethoxy or trifluoromethoxy;

with the proviso that when either a or e is 0, the other must be 1;

with the proviso that when b and d are 1, the sum of a, c and e cannot be 5, 6 or 7;

with the proviso that when b and d are 0, the sum of a, c and e cannot be 7;

with the proviso that the methyene carbon attached to the phosphorus atom must be attached to a carbon atom of the Ar ring; and

with the proviso that R^5 and R^6 must be attached to carbon atoms of the Ar ring.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof.

The term "alkoxy", as used herein, includes O-alkyl groups wherein "alkyl" is defined above.

The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl or naphthyl, optionally substituted by 1 to 3 substituents selected from the group consisting of fluoro, chloro, trifluoromethyl, (C_1-C_6)alkoxy, (C_6-C_{10})aryloxy, trifluoromethoxy, difluoromethoxy and (C_1-C_6)alkyl.

The compound of formula I may have chiral centers and therefore exist in different enantiomeric forms. This invention relates to all optical isomers and stereoisomers of the compounds of formula I and mixtures thereof.

Preferred compounds of formula I include those wherein Ar is phenyl or thienyl.

Other preferred compounds of formula I include those wherein R^1 is 2-methylpropyl, trifluoromethylethyl, cyclopropylmethyl, cyclobutylmethyl, phenoxybutyl, cyclohexylmethyl, or phenylethyl.

Other preferred compounds of formula I include those wherein R^2 is (C_1-C_6)alkyl or 4-methoxybenzyl.

Other preferred compounds of formula I include those wherein R^3 is methyl.

Other preferred compounds of formula I include those wherein R^4 is benzyl, 2-chlorobenzyl, 2-fluorobenzyl, 3-fluorobenzyl or 4-fluorobenzyl.

More preferred compounds of formula I include those wherein Ar is phenyl or thienyl; R^1 is 2-methylpropyl, trifluoromethylethyl, cyclopropylmethyl, cyclobutylmethyl, phenoxybutyl, cyclohexylmethyl or phenylethyl; R^2 is (C_1-C_6)alkyl or 4-methoxybenzyl; R^3 is methyl and R^4 is benzyl, 2-chlorobenzyl, 2-fluorobenzyl, 3-fluorobenzyl or 4-fluorobenzyl.

Specific preferred compounds of formula I include the following:

(4-Benzylbenzyl)-[2-(2,2-dimethyl-1-methylcarbamoyl-propylcarbamoyl)-4-methyl-pentyl]-phosphinic acid;

(4-Benzylbenzyl-[2-(2,2-dimethyl-1-methylcarbamoyl-propylcarbamoyl)-5,5,5-trifluoropentyl]-phosphinic acid;

[2-(2,2-Dimethyl-1-methylcarbamoyl-propylcarbamoyl)-4-methylpentyl]-[4-(3-fluorobenzyl)-benzyl]-phosphinic acid;

Benzyl-{2-[2-(4-methoxyphenyl)-1-methylcarbamoyl-ethylcarbamoyl]-6-phenoxy-hexyl}-phosphinic acid;

(4-Benzylbenzyl)-{2-[2-(4-methoxyphenyl)-1-methylcarbamoyl-ethylcarbamoyl]-6-phenoxyhexyl}-phosphinic acid;

(4-Benzylbenzyl)-{3-cyclohexyl-2-[2-(4-methoxyphenyl)-1-methylcarbamoyl-ethylcarbamoyl]-propyl}-phosphinic acid;

(4-Benzylbenzyl)-[3-cyclohexyl-2-(2,2-dimethyl-1-methylcarbamoyl-propylcarbamoyl)-propyl]-phosphinic acid;

(4-Benzylbenzyl)-[2-(2,2-dimethyl-1-methylcarbamoyl-propylcarbamoyl)-4-phenyl-butyl]-phosphinic acid;

(4-Cyclohexylmethylbenzyl)-[2-(2,2-dimethyl-1-methylcarbamoyl-propylcarbamoyl)-4-methyl-pentyl]-phosphinic acid;

[2-(2,2-Dimethyl-1-methylcarbamoyl-propylcarbamoyl)-4-methylpentyl]-(4-isobutylbenzyl)-phosphinic acid;

[2-(2,2-Dimethyl-1-methylcarbamoyl-propylcarbamoyl)-4-methylpentyl]-[4-(4-fluoro-benzyl)-benzyl]-phosphinic acid;

[2-(2,2-Dimethyl-1-methylcarbamoyl-propylcarbamoyl)-4-methylpentyl]-[4-(2-fluoro-benzyl)-benzyl]phophinic acid;

(4-Benzylbenzyl)-{2-[2-(4-methoxyphenyl)-1-methylcarbamoyl-ethylcarbamoyl]-4-methyl-pentyl}-phosphinic acid;

[4-(2-Chlorobenzyl)benzyl]-[2-(2,2-dimethyl-1-methylcarbamoyl-1-propylcarbamoyl)-4-methylpentyl]phosphinic acid;

(5-Benzyl-pyridin-2-ylmethyl)-[2-(2,2-dimethyl-1-methylcarbamoyl-propylcarbamoyl)-4-methyl-pentyl]phosphinic acid;

[2-(2,2-Dimethyl-1-methylcarbamoyl-propylcarbamoyl)-5,5,5-trifluoro-pentyl]-[4-(2-fluoro-benzyl)-benzyl]phosphinic acid;

[3-Cyclopropyl-2-(2,2-dimethyl-1-methylcarbamoyl-propylcarbamoyl)-propyl]-[4-(2-fluoro-benzyl)-benzyl]phosphinic acid;

[3-Cyclobutyl-2-(2,2-dimethyl-1-methylcarbamoyl-propylcarbamoyl)-propyl]-[4-(2-fluoro-benzyl)-benzyl]-phosphinic acid; and

(5-Benzyl-thiophen-2-ylmethyl)-[2-(2,2-dimethyl-1-methylcarbamoyl-propylcarbamoyl)-4-methylpentyl]-phosphinic acid.

The present invention also relates to a pharmaceutical composition for (a) the treatment of a condition selected from the group consisting of arthritis, cancer, synergy with cytotoxic anticancer agents, tissue ulceration, macular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, in combination with standard NSAID'S and analgesics and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) or (b) the inhibition of matrix metalloproteinases or the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising an amount of a compound of formula I or a pharmaceutically acceptable salt thereof effective in such treatments and a pharmaceutically acceptable carrier.

The present invention also relates to a method for the inhibition of (a) matrix metalloproteinases or (b) the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

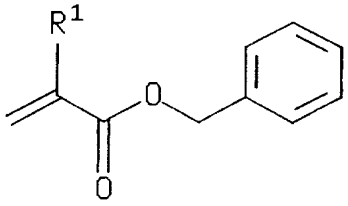
The present invention also relates to a method for treating a condition selected from the group consisting of arthritis, cancer, synergy with cytotoxic anticancer agents, tissue ulceration, macular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, in combination with standard NSAID'S and analgesics and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an amount of

a compound of formula I or a pharmaceutically acceptable salt thereof effective in treating such a condition.

Detailed Description of the Invention

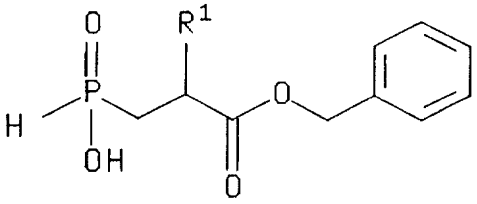
The following reaction Schemes illustrate the preparation of the compounds of the present invention. Unless otherwise indicated R^1, R^2, R^3, R^4, R^5, R^6 and Ar in the reaction Schemes and the discussion that follow are defined as above.

SCHEME 1



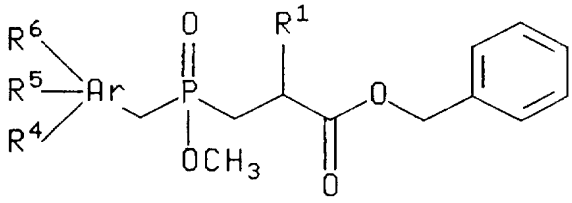
VI

1



V

2

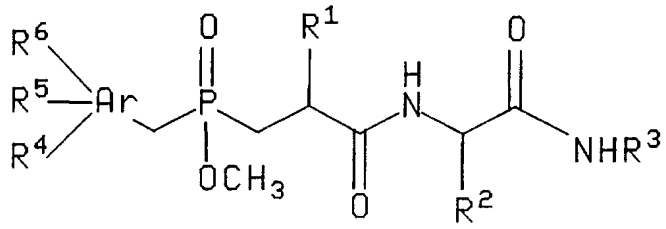


IV

3

III

SCHEME 1 (continued)

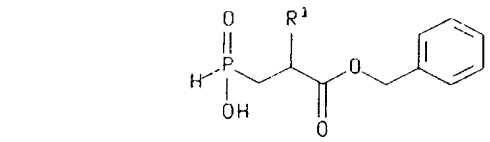


III

4

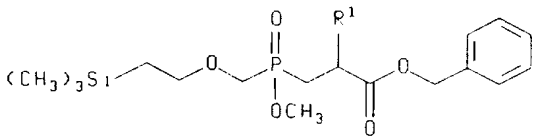
I

SCHEME 2



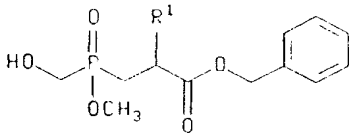
V

1



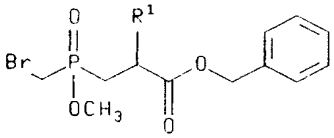
VIII

2



VII

3



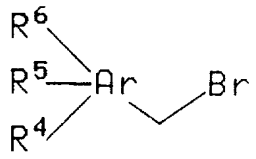
VI

4

IV

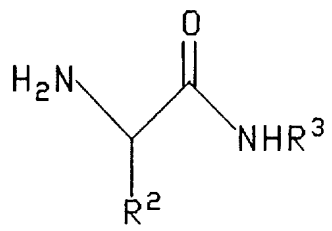
In reaction 1 of Scheme 1, the compound of formula VI is converted to the corresponding (2-benzyloxycarbonyl)phosphinic acid compound of formula **V** by reacting **VI** with bis-trimethylsilylphosphonite in an aprotic solvent, such as methylene chloride. The reaction mixture is stirred at room temperature for a time period between about 8 hours to about 48 hours, preferably about 18 hours.

In reaction 2 of Scheme 1, the compound of formula **V** is converted to the corresponding compound of formula **IV** by reacting **V** with an arylmethylhalide of the formula



and N,O-bis(trimethylsilyl)acetamide in an inert aprotic solvent, such a methylene chloride. The reaction mixture is stirred at room temperature or heated to reflux for a time period between about 18 hours to about 72 hours, preferably about 24 hours. An excess of trimethylsilyldiazomethane in a 7:3 ratio mixture of toluene and methanol is then added to the crude reaction product so formed for a time period between about 15 minutes to about 2 hours, preferably about 30 minutes.

In reaction 3 of Scheme 1, the compound of formula **IV** is converted to the corresponding compound of formula **III** by (1) hydrogenating **IV** in the presence of a catalyst, such 5% palladium on barium sulfate, and a protic solvent, such as methanol, under a pressure between about 30 psi to about 60 psi, preferably about 45 psi, for a time period between about 15 minutes to about 3 hours, preferably about 1 hour, (2) reacting the intermediate so formed with hydroxysuccinimide and 2-diethylaminoethyl propyl carbodiimide hydrochloride in a polar aprotic solvent, such as dimethylformamide, at room temperature, for a time period between about 8 hours to about 48 hours, preferably about 20 hours, and (3) reacting the 2,5-dioxo-pyrrolidin-1-yl intermediate so formed with an amine of the formula



In an aprotic solvent, such as methylene chloride, at room temperature, for a time period between about 16 hours to about 48 hours, preferably about 18 hours.

In reaction 4 of Scheme 1, the compound of formula **III** is converted to the corresponding compound of formula **I** by treating **III** with 10% aqueous trifluoroacetic acid. The reaction mixture is stirred, at room temperature, for a time period between about 30 minutes to about 24 hours, preferably about 2 hours.

Scheme 2 presents an alternative method for preparing a compound of formula **IV**.

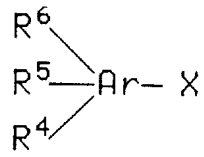
In reaction 1 of Scheme 2, the compound of formula **V** is converted to the corresponding compound of formula **VIII** by reacting **V** with 2-(trimethylsilyl) ethoxymethyl chloride and N,O-bis(trimethylsilyl)acetamide in an inert aprotic solvent, such as methylene chloride. The reaction mixture is stirred at a temperature between about 20°C to about 40°C, preferably about 25°C, for a time period between about 8 hours to about 48 hours, preferably about 18 hours. An excess of trimethylsilyl-diazomethane in a 7:3 ratio mixture of toluene and methanol is then added to the crude reaction product so formed for a time period between about 15 minutes to about 2 hours, preferably about 30 minutes.

In reaction 2 of Scheme 2, the compound of formula VIII is converted to the corresponding compound of formula **VII** by reacting **VIII** with boron trifluoride diethyl etherate in a inert aprotic solvent, such as methylene chloride. The reaction mixture is stirred at a temperature between about 0°C to about 40°C, preferably about 25°C, for a time period between about 1 hour to about 8 hours, preferably about 3 hours.

In reaction 3 of Scheme 2, the compound of formula **VII** is converted to the corresponding compound of formula **VI** by reacting **VII** with carbon tetrabromide in the presence of triphenylphosphine and diethyl azodicarboxylate in an inert aprotic solvent, such as methylene chloride. The reaction mixture is stirred at a temperature between

about 0°C to about 40°C, preferably about 25°C, for a time period between about 2 hours to about 24 hours, preferably about 4 hours.

In reaction 4 of Scheme 2, the compound of formula **VI** is converted to the corresponding compound of formula **IV** by reacting **VI** with an arylhalide of the formula



wherein X is bromo or iodo, in the presence of n-butyl lithium and copper (1) iodide in an inert aprotic solvent, such as tetrahydrofuran. The reaction mixture is stirred at a temperature between about -70°C to about 60°C, preferably about 0°C, for a time period between about 1 hour to about 48 hours, preferably about 18 hours.

Pharmaceutically acceptable salts of the acidic compounds of the invention are salts formed with bases, namely cationic salts such as alkali and alkaline earth metal salts, such as sodium, lithium, potassium, calcium, magnesium, as well as ammonium salts, such as ammonium, trimethyl-ammonium, diethylammonium, and tris-(hydroxymethyl)-methylammonium salts.

Similarly acid addition salts, such as of mineral acids, organic carboxylic and organic sulfonic acids e.g. hydrochloric acid, methanesulfonic acid, maleic acid, are also possible provided a basic group, such as pyridyl, constitutes part of the structure.

The ability of the compounds of formula **I** or their pharmaceutically acceptable salts (hereinafter also referred to as the compounds of the present invention) to inhibit matrix metalloproteinases or the production of tumor necrosis factor (TNF) and, consequently, demonstrate their effectiveness for treating diseases characterized by matrix metalloproteinase or the production of tumor necrosis factor is shown by the following in vitro assay tests.

Biological Assay

Inhibition of Human Collagenase (MMP-1)

Human recombinant collagenase is activated with trypsin using the following ratio: 10 μg trypsin per 100 μg of collagenase. The trypsin and collagenase are incubated at room temperature for 10 minutes then a five fold excess (50 μg/10 μg trypsin) of soybean trypsin inhibitor is added.

10 mM stock solutions of inhibitors are made up in dimethyl sulfoxide and then diluted using the following Scheme:

10 mM ------> 120 μM ------> 12 μM ------> 1.2 μM ------> 0.12 μM

Twenty-five microliters of each concentration is then added in triplicate to appropriate wells of a 96 well microfluor plate. The final concentration of inhibitor will be a 1:4 dilution after addition of enzyme and substrate. Positive controls (enzyme, no inhibitor) are set up in wells D1-D6 and blanks (no enzyme, no inhibitors) are set in wells D7-D12.

Collagenase is diluted to 400 ng/ml and 25 μl is then added to appropriate wells of the microfluor plate. Final concentration of collagenase in the assay is 100 ng/ml.

Substrate (DNP-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2) is made as a 5 mM stock in dimethyl sulfoxide and then diluted to 20 μM in assay buffer. The assay is initiated by the addition of 50 μl substrate per well of the microfluor plate to give a final concentration of 10 μM.

Fluorescence readings (360 nM excitation, 460 nm emission) were taken at time 0 and then at 20 minute intervals. The assay is conducted at room temperature with a typical assay time of 3 hours.

Fluorescence vs time is then plotted for both the blank and collagenase containing samples (data from triplicate determinations is averaged). A time point that provides a good signal (the blank) and that is on a linear part of the curve (usually around 120 minutes) is chosen to determine IC_{50} values. The zero time is used as a blank for each compound at each concentration and these values are subtracted from the 120 minute data. Data is plotted as inhibitor concentration vs % control (inhibitor fluorescence divided by fluorescence of collagenase alone x 100). IC_{50}'s are determined from the concentration of inhibitor that gives a signal that is 50% of the control.

If IC_{50}'s are reported to be <0.03 μM then the inhibitors are assayed at concentrations of 0.3 μM, 0.03 μM, 0.03 μM and 0.003 μM.

Inhibition of Gelatinase (MMP-2)

Inhibition of gelatinase activity is assayed using the Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2 substrate (10 μM) under the same conditions as inhibition of human collagenase (MMP-1).

72kD gelatinase is activated with 1 mM APMA (p-aminophenyl mercuric acetate) for 15 hours at 4°C and is diluted to give a final concentration in the assay of 100 ng/ml. Inhibitors are diluted as for inhibition of human collagenase (MMP-1) to give final concentrations in the assay of 30 μM, 3 μM, 0.3 μM and 0.03 μM. Each concentration is done in triplicate.

Fluorescence readings (360 nm excitation, 460 emission) are taken at time zero and then at 20 minutes intervals for 4 hours.

IC_{50}'s are determined as per inhibition of human collagenase (MMP-1). If IC_{50}'s are reported to be less than 0.03 μM, then the inhibitors are assayed at final concentrations of 0.3 μM, 0.03 μM, 0.003 μM and 0.003 μM.

Inhibition of Stromelysin Activity (MMP-3)

Inhibition of stromelysin activity is based on a modified spectrophotometric assay described by Weingarten and Feder (Weingarten, H. and Feder, J., Spectrophotometric Assay for Vertebrate Collagenase, Anal. Biochem. 147, 437-440 (1985)). Hydrolysis of the thio peptolide substrate [Ac-Pro-Leu-Gly-$SCH[CH_2CH(CH_3)_2]CO$-Leu-Gly-OC_2H_5] yields a mercaptan fragment that can be monitored in the presence of Ellman's reagent.

Human recombinant prostromelysin is activated with trypsin using a ratio of 1 μl of a 10 mg/ml trypsin stock per 26 μg of stromelysin. The trypsin and stromelysin are incubated at 37°C for 15 minutes followed by 10 μl of 10 mg/ml soybean trypsin inhibitor for 10 minutes at 37°C for 10 minutes at 37°C to quench trypsin activity.

Assays are conducted in a total volume of 250 μl of assay buffer (200 mM sodium chloride, 50 mM MES, and 10 mM calcium chloride, pH 6.0) in 96-well microliter plates. Activated stromelysin is diluted in assay buffer to 25 μg/ml. Ellman's reagent (3-Carboxy-4-nitrophenyl disulfide) is made as a 1M stock in dimethyl formamide and diluted to 5 mM in assay buffer with 50 μl per well yielding at 1 mM final concentration.

10 mM stock solutions of inhibitors are made in dimethyl sulfoxide and diluted serially in assay buffer such that addition of 50 μL to the appropriate wells yields final concentrations of 3 μM, 0.3 μM, 0.003 μM, and 0.0003 μM. All conditions are completed in triplicate.

A 300 mM dimethyl sulfoxide stock solution of the peptide substrate is diluted to 15 mM in assay buffer and the assay is initiated by addition of 50 μl to each well to give a final concentration of 3 mM substrate. Blanks consist of the peptide substrate and Ellman's reagent without the enzyme. Product formation was monitored at 405 nm with a Molecular Devices UVmax plate reader.

IC_{50} values were determined in the same manner as for collagenase.

Inhibition of MMP-13

Human recombinant MMP-13 is activated with 2mM APMA (p-aminophenyl mercuric acetate) for 1.5 hours, at 37°C and is diluted to 400 ng/ml in assay buffer (50 mM Tris, pH 7.5, 200 mM sodium chloride, 5mM calcium chloride, 20μM zinc chloride, 0.02% brij). Twenty-five microliters of diluted enzyme is added per well of a 96 well microfluor plate. The enzyme is then diluted in a 1:4 ratio in the assay by the addition of inhibitor and substrate to give a final concentration in the assay of 100 ng/ml.

10 mM stock solutions of inhibitors are made up in dimethyl sulfoxide and then diluted in assay buffer as per the inhibitor dilution scheme for inhibition of human collagenase (MMP-1): Twenty-five microliters of each concentration is added in triplicate to the microfluor plate. The final concentrations in the assay are 30 μM, 3μM, 0.3 μM, and 0.03 μM.

Substrate (Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2) is prepared as for inhibition of human collagenase (MMP-1) and 50 μl is added to each well to give a final assay concentration of 10 μM. Fluorescence readings (360 nM excitation; 450 emission) are taken at time 0 and every 5 minutes for 1 hour.

Positive controls consist of enzyme and substrate with no inhibitor and blanks consist of substrate only.

IC_{50}'s are determined as per inhibition of human collagenase (MMP-1). If IC_{50}'s are reported to be less than 0.03 μM, inhibitors are then assayed at final concentrations of 0.3 μM, 0.03 μM, 0.003 μM and 0.0003 μM.

Inhibition of TNF Production

The ability of the compounds or the pharmaceutically acceptable salts thereof to inhibit the production of TNF and, consequently, demonstrate their effectiveness for treating diseases involving the production of TNF is shown by the following in vitro assay:

Human mononuclear cells were isolated from anti-coagulated human blood using a one-step Ficoll-hypaque separation technique. (2) The mononuclear cells were washed three times in Hanks balanced salt solution (HBSS) with divalent cations and resuspended to a density of 2×10^6 /ml in HBSS containing 1% BSA. Differential counts determined using the Abbott Cell Dyn 3500 analyzer indicated that monocytes ranged from 17 to 24% of the total cells in these preparations.

180μl of the cell suspension was aliquoted into flate bottom 96 well plates (Costar). Additions of compounds and LPS (100ng/ml final concentration) gave a final volume of 200μl. All conditions were performed in triplicate. After a four hour incubation at 37°C in an humidified CO_2 incubator, plates were removed and centrifuged (10 minutes at approximately 250 x g) and the supernatants removed and assayed for TNFα using the R&D ELISA Kit.

For administration to mammals, including humans, for the inhibition of matrix metalloproteinases or the production of tumor necrosis factor (TNF), a variety of conventional routes may be used including orally, parenterally and topically. In general, the active compound will be administered orally or parenterally at dosages between about 0.1 and 25 mg/kg body weight of the subject to be treated per day, preferably from about 0.3 to 5 mg/kg. However, some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

The compounds of the present invention can be administered in a wide variety of different dosage forms. In general, the therapeutically effective compounds of this invention are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and

preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelation and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof. In the case of animals, they are advantageously contained in an animal feed or drinking water in a concentration of 5-5000 ppm, preferably 25 to 500 ppm.

For parenteral administration, e.g., for intramuscular, intraperitoneal, subcutaneous and intravenous use, a sterile injectable solution of the active ingredient is usually prepared. Solutions of a therapeutic compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably adjusted and buffered, preferably at a pH of greater than 8, if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art. In the case of animals, compounds can be administered intramuscularly or subcutaneously at dosage levels of about 0.1 to 50 mg/kg/day, advantageously 0.2 to 10 mg/kg/day given in a single dose or up to 3 divided doses.

The present invention is illustrated by the following examples, but it is not limited to the details thereof.

Example 1

S,S and R,S (4-Benzylbenzyl)[2-(2,2-dimethyl-1-methylcarbamoyl propylcarbamoyl)-4-methylpentyl]phosphinic acid

Step A: 4-Benzoylbenzyl bromide (2.75 grams, 10.0 mmole) and triethylsilane (2.33 grams, 20 mmole) in trifluoroacetic acid (4.56 grams, 40 mmole)

were warmed to 60°C for 18 hours. The cooled mixture was diluted with ethyl acetate (50 ml) and carefully washed with saturated sodium bicarbonate solution (2 x 50 ml). After drying with magnesium sulfate, the extract was filtered and concentrated. The residue was chromatographed (0.5:99.5 to 2:98 - ethyl acetate:hexane) to give 1.37 grams (52%) of 4-benzylbenzyl bromide as a colorless oil.

Step B: (2-Benzyloxycarbonyl-4 -methylpentyl)phosphinic acid (1.14 grams, 4.0 mmole), 4-benzylbenzyl bromide (1.31 grams, 5.0 mmole) and N,O-bis(trimethylsilyl) acetamide (2.44 grams, 12 mmole) were combined in dry methylene chloride (40 ml); the mixture was degassed with a stream of dry nitrogen, then stirred at room temperature for 18 hours and refluxed for 24 hours. The cooled solution was quenched with 1N hydrochloric acid (25 ml). The methylene chloride layer was separated and washed with 1N hydrochloric acid (2 x 25 ml), dried with magnesium sulfate, filtered and concentrated to a turbid oil. This was dissolved in methanol (10 ml) / toluene (40 ml) and treated with excess trimethylsilyldiazomethane (commercial hexane solution). After 30 minutes the excess trimethylsilyldiazo-methane was destroyed with acetic acid. The solution was concentrated to an oil which was chromatographed (75:25 - ethyl acetate:hexane) to give 1.18 grams (62%) of 2-[(4-benzylbenzyl)methoxyphosphinoylmethyl]-4-methylpentanoic acid benzyl ester as a colorless oil.

Step C: 2-[(4-Benzyl benzyl)methoxyphosphinoylmethyl]- 4-methylpentanoic acid benzyl ester (650 mg, 1.36 mmole) was hydrogenated at 45 psi at room temperature in methanol (50 ml) over 5% palladium on barium sulfate (650 mg) for 1 hour. The catalyst was filtered off and washed with methanol. The filtrate was concentrated and traces of methanol removed by twice diluting the sample with methylene chloride and reconcentrating. The intermediate 2-[(4-benzyl benzyl)methoxyphosphinoylmethyl]-4-methylpentanoic acid was dissolved in dry dimethylformamide (14 ml) and hydroxysuccinimide (235 mg, 2.04 mmole) and dimethylaminopropylethylcarbodiimide hydrochloride (391 mg, 2.04 mmol) added. After stirring at room temperature for 20 hours the solution was diluted with ether (50 ml) and washed with 1N hydrochloric acid (50 ml, 2 x 25 ml) and saturated sodium bicarbonate solution (25 ml) and dried with magnesium sulfate. After

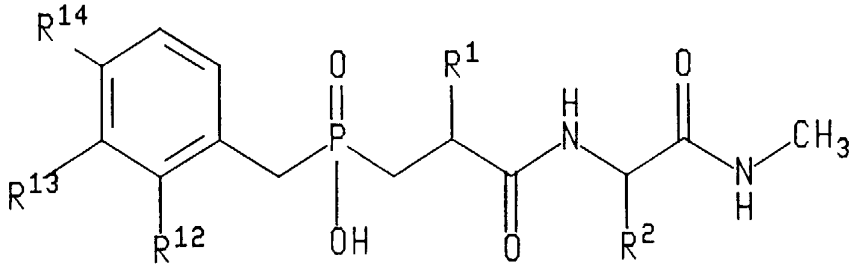
filtration and concentration 566 mg (86%) of 2-[(4-Benzylbenzyl) methoxyphosphinoylmethyl]-4- methyl-pentanoic acid 2,5-dioxo-pyrrolidin-1-yl ester was obtained as an oil.

Step D: 2-[(4-Benzylbenzyl)methoxyphosphinoylmethyl]-4-methylpentanoic acid 2,5-dioxo-pyrrolidin-1-yl ester (120 mg, 0.25 mmole), (S)-2-amino-3,3,N-trimethylbutyramide hydrochloride (25 mg, 0.30 mmole) and diisopropylethylamine (39 mg, 0.30 mmole) were combined and stirred together for 18 hours at room temperature in dry methylene chloride (10 ml). Additional (S)-2-amino-3,3,N-trimethylbutyramide hydrochloride (25 mg, 0.30 mmole) and diisopropylethylamine (39 mg, 0.30 mmole) were added to the reaction mixture. After four days the solution was washed with 1N hydrochloric acid (2 x 10 ml) and saturated sodium bicarbonate solution (2 x 10 ml) and dried with magnesium sulfate. After filtration and concentration the residue was chromatographed (3:97 - methanol:chloroform) to give 77 mg (60%) of (4-Benzylbenzyl)-[2-(2,2-dimethyl-1-methyl carbamoylpropylcarbamoyl)-4-methylpentyl]-phosphinic acid methyl ester.

Step E: (4-Benzylbenzyl)-[2-(2,2-dimethyl-1-methyl carbamoylpropylcarbamoyl)-4-methylpentyl]-phosphinic acid methyl ester (77 mg, 0.15 mmole) was dissolved in 10% aqueous trifluoroacetic acid (6 ml). After 4 hours at room temperature the reaction mixture was concentrated. Residual water was removed by twice diluting the sample with toluene and reconcentrating to give 75 mg (100%) of the title compound as a hard glass which was a 63:37 mixture of S,S and R,S isomers, respectively. Mass spectrum *m/e*: M^++1 501, M^++Na^+ 523, M^++K^+ 540, M^++2Na^+ 555. HPLC retention times: 13.00/15.90 minutes.

The compounds in Tables 1-4 were prepared by a method analogous to that described in in Example 1.

Table 1



EX	R^1	R^2	R^{12}	R^{13}	R^{14}	R^1 S/R	Ret. Time	MS
2	isobutyl	4-methoxybenzyl	H	phenyl	H	50/50	16.27/17.52	LSIMS: 551 M^++HP+
3	isobutyl	4-methoxybenzyl	phenyl	H	H	52/48	16.48/17.74	LSIMS: 551 M^++Na^+ 573 M^++Na^+ 589 M^++K^+
4	isobutyl	4-methoxybenzyl	H	H	phenyl	51/49	13.70/15.13	CI: 551 M^++H^+ 573 M^++Na^+
5	isobutyl	4-methoxybenzyl	H	H	methoxy	59/41	5.91/8.36	CI: 505 M^++H^+

EX	R^1	R^2	R^{12}	R^{13}	R^{14}	R^1 S/R	Ret. Time	MS
6	isobutyl	4-methoxybenzyl	H	H	H	49/51	7.03/9.42	LSIMS: 475 M^++H^+ 497 M^++Na^+
7	isobutyl	4-methoxybenzyl	H	H	benzyl	98/2	15.41/16.83	LSIMS: 565 M^++H^+
8	isobutyl	4-methoxybenzyl	H	H	benzyl	17/83	14.88/16.22	LSIMS: 565 M^++H^+
9	isobutyl	4-methoxybenzyl	H	1-phenyl-ethyl	H	51/49	16.45/17.64	LSIMS: 579 M^++H^+
10	phenoxybutyl	4-methoxybenzyl	H	H	H	49/51	13.10/14.34	LSIMS: 567 M^++H^+ 589 M^++Na+
11	phenoxybutyl	4-methoxybenzyl	H	H	benzyl	53/47	18.59/19.65	LSIMS: 657 M^++H^+
12	isobutyl	4-methoxybenzyl	H	H	benzyl	53/47	15.52/16.94	
13	isobutyl	4-methoxybenzyl	H	H	phenyl-sulfonyl	50/50	10.36/11.94	LSIMS: 615 M^++H^+
14	isobutyl	4-methoxybenzyl	H	H	phenoxy	50/50	14.58/15.98	LSIMS: 567 M^++H^+
15	isobutyl	methyl	H	H	benzyl	51/49	10.65/12.57	LSIMS: 459 M^++H^+ 481 M^++Na+

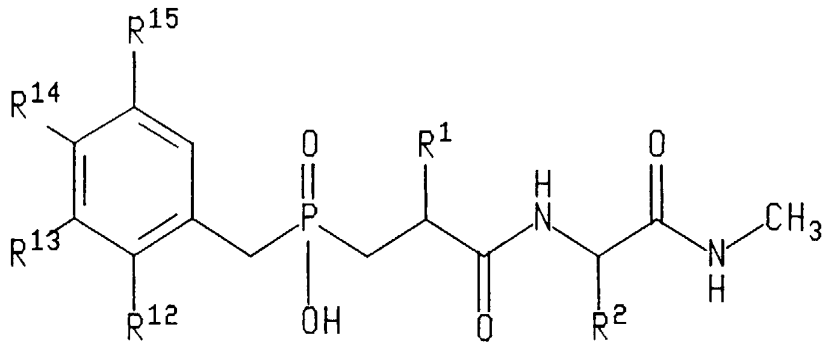
EX	R^1	R^2	R^{12}	R^{13}	R^{14}	R^1 S/R	Ret. Time	MS
16	cyclohexylmethyl	4-methoxybenzyl	H	H	benzyl	100:0	18.61/-	LSIMS: 605 M^++H^+ 627 M^++Na+
17	cyclohexylmethyl	4-methoxybenzyl	H	H	benzyl	19/81	18/55/19.92	LSIMS: 605 M^++H^+ 627 M^++H^+
18	isobutyl	tert-butyl	H	H	benzyl	63/37	13.00/15.90	LSIMS: 501 M^++H^+ 523 M^++Na+
19	cyclohexylmethyl	4-methoxybenzyl	H	H	H	50/50	12.00/13/59	LSIMS: 515 M^++H^+
20	cyclohexylmethyl	tert-butyl	H	H	benzyl	56/44	16.48/19.64	LSIMS: 541 M^++H^+ 563 M^++Na+
21	cyclohexylmethyl	tert-butyl	H	H	H	66/34	9.11/13/08	LSIMS: 451 M^++H^+
22	cyclohexylmethyl	4-methoxybenzyl	H	H	phenyl-sulfonyl	49/51	1395/15/21	LSIMS: 677 M^++Na+
23	cyclohexylmethyl	tert-butyl	H	H	phenyl-sulfonyl	52/48	11.63/14/71	LSIMS: 591 M^++H^+
24	cyclohexylmethyl	methyl	H	H	phenyl-sulfonyl	47/53	8.99/10.90	LSIMS: 549 M^++H^+ 571 M^++Na+

EX	R^1	R^2	R^{12}	R^{13}	R^{14}	R^1 S/R	Ret. Time	MS
25	isobutyl	methyl	H	H	H	48/52	2.22/3.10	Cl: 369 M^+ 370 M^++H^+
26	isobutyl	tert-butyl	H	H	H	51/49	10.05/11.63	Cl: 411 M^++H^+ 428 M^++NH_4^+
27	phenethyl	tert-butyl	H	H	H	62/38	6.91/10/51	Cl: 459 M^+ 460 M^++NH_4^+
28	trans 4-methyl-cyclohexylmethyl	tert-butyl	H	H	H	50/50	16.08/17.54	Cl: 465 M^++H^+ 466 M^++$2H_4^+$
29	trans 4-methyl cyclohexylmethyl	4-methoxybenzyl	H	H	H	50/50	14.54/15/91	Cl: 529 M^++H^+
30	trans 4-methyl-cyclohexylmethyl	methyl	H	H	H	100/0	11.59/-	Cl: 530 M^++$2H^+$
31	isobutyl	4-methoxybenzyl	H	H	isobutyl	50/50	15.85/17/45	LSIMS: 423 M^++H^+
32	isobutyl	tert-butyl	H	H	isobutyl	50/50	13/46/16.64	LSIMS: 531 M^++H^+
33	isobutyl	methyl	H	H	isobutyl	45/55	11.31/13.34	LSIMS: 425 M^++H^+ 447 M^++Na+

EX	R^1	R^2	R^{12}	R^{13}	R^{14}	R^1 S/R	Ret. Time	MS
34	isobutyl	tert-butyl	H	H	cyclohexyl methyl	52/48	18.36/21.46	LSIMS: 507 M^++H^+
35	isobutyl	4-methoxybenzyl	H	H	cyclohexyl methyl	42/58	20.24/21.81	LSIMS: 571 M^++H^+
36	phenethyl	tert-butyl	H	H	benzyl	50/50	15.30/17.53	CI: 549 M^++H^+ 550 M^++$2H^+$
37	phenethyl	4-methoxybenzyl	H	H	benzyl	62/38	16.00/17.86	CI: 613 M^++H^+ 614 M^++$2H^+$
38	phenethyl	methyl	H	H	benzyl	3/97	12.94/14.34	CI: 507 M^++H^+ 508 M^++$2H^+$
39	isopentyl	tert-butyl	H	H	benzyl	53/47	14.92/17.69	CI: 515 M^++H^+ 516 M^++$2H^+$
40	isopentyl	4-methoxybenzyl	H	H	benzyl	54/46	16.69/18.09	CI: 579 M^++H^+ 580 M^++$2H^+$
41	cyclohexylethyl	tert-butyl	H	H	benzyl	53/47	18.44/21.66	CI: 555 M^++H^+
42	cyclohexylethyl	4-methoxybenzyl	H	H	benzyl	53/47	20.28/21.55	CI: 619 M^++H^+

EX	R^1	R^2	R^{12}	R^{13}	R^{14}	R^1 S/R	Ret. Time	MS
43	3,3,3-trifluoropropyl	tert-butyl	H	H	benzyl	47/53	13.01/15.03	Cl: 540 M^+ 541 M^++H^+
44	isobutyl	tert-butyl	H	H	3-fluoro-benzyl	53/47	12.67/15.56	Cl: 519 M^++H^+
45	isobutyl	tert-butyl	H	H	phenyl-CO-	54/46	8.06/11.58	Cl: 515 M^++H^+ 516 M^++2H^+
46	propyl	tert-butyl	H	H	benzyl	50/50	10.13/13.15	Cl: 487 M^++H^+
47	isobutyl	tert-butyl	H	H	4-fluoro-benzyl	48/52	12.85/15.59	Cl: 519 M^++H^+
48	isobutyl	tert-butyl	H	H	2-fluoro-benzyl	43/57	12.95/15.85	Cl: 519 M^++H^+

Table 2



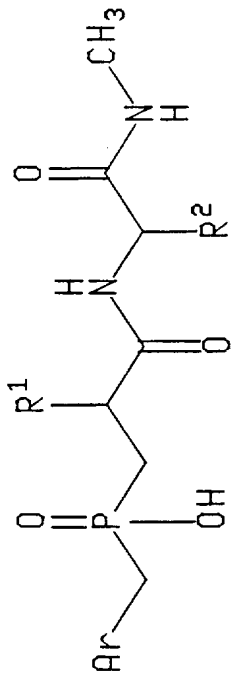
EX	R^1	R^2	R^{12}	R^{13}	R^{14}	R^{15}	R^1 S/R	Ret. Time	MS
49	isobutyl	4-methoxy-benzyl	H	H	benzylamino-carbonyl	H	57/43	9.24/10.76	LSIMS: 608 M^++H^+
50	isobutyl	4-methoxy-benzyl	H	H	methylamino-carbonyl	H	48/52	15.35/16.68	CI: 532 M^++H^+ 538 M^++Li^+
51	isobutyl	4-methoxy-benzyl	benzylamino-carbonyl	H	H	H	49/51	11.42/13.4	LSIMS: 608 M^++H^+ 630 M^++Na^+
52	isobutyl	4-methoxy-benzyl	H	benzylamino-carbonyl	H	H	47/53	09.74/11.44	LSIMS: 608 M^++H^+ 630 M^++Na^+

EX	R^1	R^2	R^{12}	R^{13}	R^{14}	R^{15}	R^1 S/R	Ret. Time	MS
53	isobutyl	4-methoxy-benzyl	H	H	dimethylamino-carbonyl	H	34/66	10.77/12.64	LSIMS: 546 M^++H^+
54	isobutyl	4-methoxy-benzyl	H	dimethylamino-carbonyl	H	H	47/53	11.66/13.49	LSIMS: 546 M^++H^+
55	isobutyl	4-methoxy-benzyl	H	H	benzyl(methyl) amino-carbonyl	H	45/55	10.64/12.16	LSIMS: 622 M^++H^+
56	isobutyl	4-methoxy-benzyl	H	benzyl(methyl) amino-carbonyl	H	H	50/50	11.55/13.20	LSIMS: 622 M^++H^+ 644 M^++Na^+
57	isobutyl	4-methoxy-benzyl	H	methoxy	benzylamino-carbonyl	CH_3O	42/58	9.63/11.15	LSIMS: 690 M^++Na^+ 712 M^++$2Na^+$
58	isobutyl	4-methoxy-benzyl	dimethylamino-carbonyl	H	H	H	45/55	13.54/15.44	LSIMS: 546 M^++H^+ 568 M^++$2Na^+$
59	isobutyl	4-methoxy-benzyl	benzyl(methyl) amino-carbonyl	H	H	H	53/47	13.11/14.83	LSIMS: 622 M^++H^+
60	isobutyl	4-methoxy-benzyl	H	methylamino-carbonyl	H	H	46/54	10.02/12.09	532 M^++H^+
61	isobutyl	tert-butyl	H	H	benzylamino-carbonyl	H	50/50	3.88/6.54	566 M^++$2Na^+$

Table 3

Ex	Y	Z	R^1	R^1 S/R	Ret. Time	MS
62	$-CH_2-$	$-CH_2CH_2-$	isobutyl	49/51	14.15/17.08	CI: 527 $M^+ + H^+$
63	$-CH_2-$	$-CH_2O-$	isobutyl	53/47	11.19/14.23	CI: 529 $M^+ + H^+$

Table 4



EX	R^1	R^2	Ar	R^1 S/R	Ret. Time	MS
64	isobutyl	4-methoxybenzyl	3-carbethoxy-2-pyridyl	50/50	3.36/4.30	LSIMS: 548 M^+H^+

Example 65

S,S and R,S (4-Benzoylaminobenzyl)-{2-[2-(4-methoxyphenyl)-1-methylcarbamoylethylcarbamoyl] -4-methylpentyl}phosphinic acid.

Step A: 2-[Methoxy(4-nitrobenzyl) phosphinoylmethyl]-4-methylpentanoic acid benzyl ester (prepared from 4-nitrobenzyl bromide and (2-benzyloxycarbonyl-4-methylpentyl)phosphinic acid by the procedure described in Example 1/Step B) (900 mg, 2.08 mmole) in a mixture of ethanol (25 ml) and water (6 ml) was treated with concentrated hydrochloric acid (3 drops) and iron powder (1.14 grams, 20 mmole) at reflux. After 2 hours the cooled mixture was filtered through diatomaceous earth. The filtrate was concentrated and the residue chromatographed (ethyl acetate) to give 444 mg (53%) of 2-[(4-Aminobenzyl) methoxyphosphinoylmethyl]-4-methylpentanoic acid benzyl ester as a yellow oil.

Step B: 2-[(4-Aminobenzyl)methoxyphosphinoylmethyl]-4-methylpentanoic acid benzyl ester (230 mg, 0.57 mmole), benzoyl chloride (96 mg, 0.68 mmole), and triethylamine (69 mg, 0.68 mmole) were combined in cold (ice bath) chloroform (10 ml). After stirring for 1 hour at ice bath temperature the reaction mixture was diluted with chloroform (150 ml) and washed with water (20 ml), 1N hydrochloric acid (2 x 20 ml) and saturated sodium bicarbonate solution (2 x 20 ml) and dried with magnesium sulfate. After filtration and concentration the yellow residue was chromatographed (ethyl acetate) to give 190 mg (66%) of 2-[(4-Benzoylamino-benzyl)methoxy phosphinoylmethyl]-4- methylpentanoic acid benzyl ester as a light yellow oil.

Step C: 2-[(4-Benzoylaminobenzyl)methoxy phosphinoylmethyl]-4-methylpentanoic acid benzyl ester (226 mg, 0.44 mmole) was hydrogenated hydrogenated at 50 psi at room temperature in methanol (20 ml) over 5% palladium on carbon (300 mg) for 2 hours. The catalyst was filtered off and washed with methanol. The filtrate was concentrated to give 154 mg (83%) of 2-[(4-benzoyl-aminobenzyl)methoxyphosphinoylmethyl]-4-methylpentanoic acid as an oil.

Step D: 2-[(4-Benzoylaminobenzyl)methoxyphosphinoyl methyl]-4-methylpentanoic acid (154 mg, 0.37 mmole), (S)-2-amino-3-(4-methoxyphenyl)-N- methylpropionamide (100 mg, 0.41 mmole), benzotriazol-1-yloxy -tris(dimethylamino)phosphonium hexafluorophosphate (180 mg, 0.41 mmole) and diisopropylethylamine (238 mg, 1.85 mmole) were stirred together in dry methylene chloride (10 ml) for 18 hours. The reaction mixture was

concentrated and diluted with ethyl acetate (100 ml). This solution was washed with 1N hydrochloric acid (20 ml) and saturated sodium bicarbonate solution (20 ml) and dried with magnesium sulfate. Filtration and concentration gave the crude product which was purified by chromatography (10:90 - methanol:methylene chloride) yielding 153 mg (68%) of (4-Benzoylamino benzyl){2-[2-(4-methoxyphenyl) -1-methylcarbamoylethylcarbamoyl]-4-methylpentyl} phosphinic acid methyl ester as a white solid.

Step E: By the procedure described in Example 1/Step E (4-Benzoylamino benzyl){2-[2-(4-methoxyphenyl) -1-methylcarbamoylethylcarbamoyl]-4-methylpentyl} phosphinic acid methyl ester (153 mg, 0.25 mmole) was converted to 100 mg (67%) the title compound, a white solid which was a 50:50 mixture of S,S and R,S isomers, respectively. Mass spectrum *m/e*: $M^+ + H^+$ 594, $M^+ + Na^+$ 616. HPLC retention times: 8.32/10.33 minutes.

The compounds in Table 5 were prepared by a method analogous to that described in Example 65.

Table 5

EX	R^1	R^{12}	R^{13}	R^{14}	R^1 S/R	Ret. Time	MS
66	isobutyl	H	H	benzamido	50/50	8.32/10.33	LSIMS 594 M^++H^+ 616 M^++Na^+
67	isobutyl	H	H	acetamido	45/55	9.93/11.81	532 M^++H^+ 554 M^++Na^+
68	isobutyl	H	benzamido	H	48/52	9.95/11.64	594 M^++H^+ 616 M^++Na^+
69	isobutyl	H	acetamido	H	43/57	11.16/12.96	532 M^++H^+ 554 M^++Na^+

EX	R^1	R^{12}	R^{13}	R^{14}	R^1 S/R	Ret. Time	MS
70	isobutyl	benzamido	H	H	66/34	8.80/11.30	594 M^++H^+ 616 M^++Na^+
71	isobutyl	acetamido	H	H	51/49	11.98/13.82	594 M^++H^+ 616 M^++Na^+
72	isobutyl	H	phenylsulfonyl-amino	H	51/49	16.38/17.35	652 M^++Na^+

Example 73

S,S and R,S [4-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)benzyl] {2-[2-(4-methoxyphenyl)-1-methyl carbamoylethylcarbamoyl]-4-methylpentyl} phosphinic acid

Step A: 2-[(4-Aminobenzyl)methoxyphosphinoylmethyl]-4-methylpentanoic acid benzyl ester (prepared as described in Example 2/Step A) (242 mg, 0.60 mmole) and phthalic anhydride (133 mg, 0.90 mmole) in acetic acid (10 ml) were refluxed for 1 hour. The cooled reaction mixture was concentrated and the residue dissolved in ethyl acetate (100 ml). This solution was washed with saturated sodium bicarbonate solution (3 x 20 ml) and dried with magnesium sulfate. Filtration and concentration gave a light yellow oil which was purified by chromatography (ethyl acetate) yielding 162 mg (51%) of 2-{[4-(1,3-dioxo-1,3-dihydroisoindol-2-yl)benzyl] methoxyphosphinoyl methyl}-4-methylpentanoic acid benzyl ester as a yellow solid. Step B: By the procedures described in Example 2/Steps C-E 2-{[4-(1,3-dioxo-1,3-dihydroisoindol-2-yl)benzyl] methoxyphosphinoyl methyl}-4-methylpentanoic acid benzyl ester (269 mg, 0.50 mmole) was converted to 61 mg (20% - 3 steps) of the title compound, a white solid which was a 50:50 mixture of S,S and R,S isomers, respectively. Mass spectrum *m/e*: $M^+ + H^+$ 620, $M^+ + Na^+$ 642. HPLC retention times: 10.12/11.92 minutes.

The compounds in Table 6 were prepared by a method analogous to that described in Example 73.

Table 6

EX	R^1	R^{12}	R^{13}	R^{14}	R^1 S/R	Ret. Time	MS
74	isobutyl	H	H	phthalimide	50/50	10.12/11.92	LSIMS: 620 M^++H^+ 642 M^++Na^+
75	isobutyl	H	phthalimide	H	46/54	10.58/12.65	LSIMS: 620 M^++H^+ 642 M^++Na^+
76	isobutyl	phthalimide	H	H	54/46	11.44/14.67	LSIMS: 620 M^++H^+ 642 M^++Na^+

Example 77

S,S and R,S (3-Aminobenzyl)-{2-[2-(4-methoxyphenyl)-1-methylcarbamoylethylcarbamoyl]-4-methylpentyl}phosphinic acid.

Step A: {2-[2-(4-Methoxyphenyl)-1-methylcarbamoylethylcarbamoyl]-4-methylpentyl}-[3-(2,2,2-trifluoroacetylamino)benzyl]phosphinic acid methyl ester (prepared from the appropriate starting materials using the procedures described in Example 2/Steps A-D) (105 mg, 0.18 mmole) was treated with potassium carbonate (242 mg, 1.75 mmole) in 10% aqueous methanol (10 ml) for 18 hours. 1N Sodium hydroxide (1 ml) was added and after 3 hours the reaction mixture was concentrated and ethyl acetate (25 ml) and water (5 ml) added. The ethyl acetate layer was removed and the water extracted with ethyl acetate (3 x 20 ml). The combined ethyl acetate extracts were dried with magnesium sulfate and filtered. The filtrate was concentrated to give 56 mg (64%) of (3-aminobenzyl){2-[2-(4-methoxy phenyl)-1-methylcarbamoylethyl carbamoyl]-4-methylpentyl}phosphinic acid methyl ester as a light yellow oil.

Step B: By the procedure described in Example 1/Step E (3-aminobenzyl){2-[2-(4-methoxy phenyl)-1-methylcarbamoylethyl carbamoyl]-4-methylpentyl}phosphinic acid methyl ester (56 mg, 0.11 mmole) was converted to 40 mg (74%) of the title compound, a white solid which was a 44:56 mixture of S,S and R,S isomers, respectively. Mass spectrum *m/e*: $M^+ + H^+$ 490. HPLC retention times (20% to 80% gradient): 6.17/8.94 minutes.

Example 78

S,S and R,S (3-Benzylaminobenzyl)-{2-[2- (4-methoxyphenyl)-1-methylcarbamoylethylcarbamoyl]-4-methylpentyl}phosphinic acid.

Step A: (3-Aminobenzyl){2-[2-(4-methoxyphenyl)-1-methylcarbamoyl ethylcarbamoyl]-4-methylpentyl}phosphinic acid methyl ester (prepared as described in Example 4/Step A) (150 mg, 0.30 mmole), benzaldehyde (38 mg, 0.36 mmole), sodium cyanoborohydride (23 mg, 0.357 mmole) and acetic acid (1 drop) in methanol were stirred at room temperature for 3 hours. The reaction was quenched with 1N hydrochloric acid (few ml's) and the reaction mixture concentrated. The residue was dissolved in ethyl acetate (20 ml) and washed with 1N hydrochloric acid (20 ml), saturated sodium bicarbonate solution (20 ml) and dried with magnesium sulfate. Filtration and concentration gave the crude product which was purified by chromatography (3:97 - methanol:methylene chloride) yielding 133 mg (75%) of

(3-Benzylamino benzyl)-{2-[2-(4-methoxyphenyl)-1- methylcarbamoylethylcarbamoyl] -4-methylpentyl} phosphinic acid methyl ester as an oil.

Step B: By the procedure described in Example 1/Step E (3-Benzylamino benzyl)-{2-[2-(4-methoxyphenyl)-1- methylcarbamoylethylcarbamoyl]-4-methylpentyl} phosphinic acid methyl ester (133 mg, 0.22 mmole) was converted to 100 mg (64%) of the title compound, a white solid which was a 67:33 mixture of S,S and R,S isomers, respectively. Mass spectrum *m/e*: M^++H^+ 580, M^++Na^+ 602. HPLC retention times: 7.29/9.61 minutes.

Example 79

Separation of S,S and R,S (4-benzylbenzyl)[2-(2,2-dimethyl -1-methylcarbamoylpropylcarbamoyl)-4- methylpentyl]phosphinic acid

A mixture of S,S and R,S (4-benzylbenzyl)[2-(2,2-dimethyl-1-methylcarbamoylpropylcarbamoyl)-4-methylpentyl]phosphinic acid (prepared as described in Example 1) (609 mg) was chromatographed on a preparative reverse phase (C-18) column eluting first with 40% aqueous acetonitrile containing 0.1% trifluoroacetic acid and then with 50% aqueous acetonitrile containing 0.1% trifluoroacetic acid. This gave nearly complete separation of the two diastereomers. Concentration of the fractions containing the two pure components gave 304 mg of S,S (4-benzylbenzyl)[2- (2,2-dimethyl-1-methylcarbamoyl propylcarbamoyl)-4-methylpentyl] phosphinic acid as a white solid: ^{1}HNMR (CD_3OD) d 0.83 (d,3H,J=6.9 Hz), 0.89 (d,3H,J=6.9 Hz), 1.02 (s,9H), 1.32 (m,1H), 1.42 (m,1H), 1.53 (m,1H), 1.67 (m,1H), 1.99 (m,1H), 2.69 (s,3H), 2.81 (m,1H), 3.10 (d,2H,J=17.1 Hz), 3.94 (s,2H), 4.08 (s,1H), 7.1-7.3 (m,9H); mass spectrum *m/e*: 501 M^++H^+; HPLC retention time: 12.96 minutes; and 208 mg of R,S (4-benzylbenzyl)[2-(2,2-dimethyl-1-methyl carbamoylpropylcarbamoyl)-4-methylpentyl]phosphinic acid as a white solid: ^{1}HNMR (CD_3OD) d 0.86 (d,3H,J=6.9 Hz), 0.91 (d,3H,J=6.9 Hz), 1.02 (s,9H), 1.22 (m,1H), 1.4-1.7 (m,3H), 2.00 (m,1H), 2.64 (s,3H), 2.85 (m,1H), 3.10 (d,2H,J=17.1 Hz), 3.94 (s,2H), 4.13 (s,1H), 7.1-7.3 (m,9H); mass spectrum *m/e*: 501 M^++H^+; HPLC retention time: 15.84 minutes.

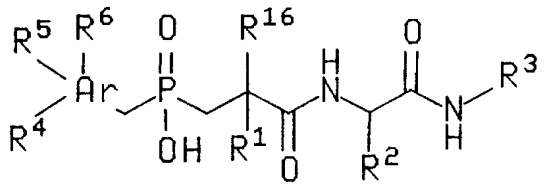
The compounds in Table 7 were separated by a method analogous to that described in Example 79.

Table 7

EX	R^1	R^2	R^{12}	R^{13}	R^{14}	R^1 S/R	Ret. Time	MS
80	isobutyl	tert-butyl	H	H	benzyl	0/100	-/15.84	CI: 501 M^++H^+
81	isobutyl	tert-butyl	H	H	benzyl	100/0	12.96/-	CI: 501 M^++H^+
82	isobutyl	tert-butyl	H	H	3-fluorobenzyl	100/0	13.54/-	CI: 519 M^++H^+
83	isobutyl	tert-butyl	H	H	3-fluorobenzyl	0/100	-/16.20	CI: 519 M^++H^+
84	3,3,3-trifluoropropyl	tert-butyl	H	H	benzyl	100/0	13.38/-	CI: 540 M^+ 541 M^++H^+
85	3,3,3-trifluoropropyl	tert-butyl	H	H	benzyl	0/100	-/15.16	CI: 540 M^+ 541 M^++H^+

CLAIMS

1. A compound of the formula



I

or a pharmaceutically acceptable salt thereof; wherein

Ar is phenyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl or imidazolyl;

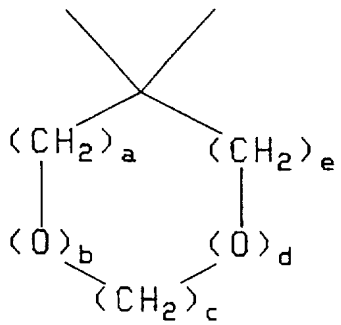
R^1 and R^{16} are each independently hydrogen, $(C_1\text{-}C_6)$alkyl, $(\text{trifluoromethyl})_2(C_1\text{-}C_6)$alkyl, perfluoro$(C_1\text{-}C_6)$alkyl, perfluoro$(C_1\text{-}C_6)$alkyl$(C_1\text{-}C_6)$alkyl, difluoromethoxy, trifluoromethoxy, $(C_3\text{-}C_7)$cycloalkyl$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryloxy$(C_1\text{-}C_6)$alkyl or $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl;

R^2 is $(C_1\text{-}C_6)$alkyl or $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl optionally substituted by hydroxy, amino, halo, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(\text{trifluoromethyl})_2(C_1\text{-}C_6)$alkyl, perfluoro$(C_1\text{-}C_6)$alkyl, perfluoro$(C_1\text{-}C_6)$alkyl$(C_1\text{-}C_6)$alkyl, difluoromethoxy, trifluoromethoxy, carboxy or carboxamoyl;

R^3 is $(C_1\text{-}C_6)$alkyl or $(C_6\text{-}C_{10})$aryl;

R^4 is hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_7)$cycloalkyl$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylsulfonyl, $(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryloxy, $(C_6\text{-}C_{10})$arylsulfonyl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl $(C_1\text{-}C_6)$alkoxy, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkylsulfonyl, N-phthalimido, $(C_6\text{-}C_{10})$arylNHCO, $(C_6\text{-}C_{10})$arylNHSO$_2$, R^7OOC, R^7R^8NCO, $R^7R^8NSO_2$ wherein R^7 and R^8 are each independently hydrogen, $(C_1\text{-}C_6)$alkyl or $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl; $(C_1\text{-}C_6)$alkyl CR^9R^{10}, $(C_6\text{-}C_{10})$aryl CR^9R^{10}, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkylCR^9R^{10} wherein R^9 and R^{10} are each independently fluoro, $(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$alkoxy;

or R^9 and R^{10} may be taken together with the carbon to which they are attached to form a group of the formula



wherein a is 0, 1 or 2;

b is 0 or 1;

c is 1, 2, or 3;

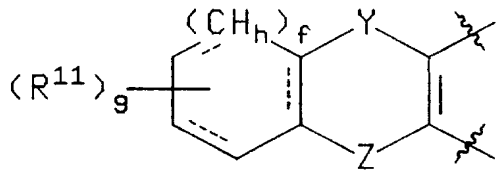
d is 0 or 1; and

e is 0, 1 or 2;

R^5 and R^6 are each independently hydrogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, halo, (trifluoromethyl)$_2(C_1$-$C_6)$alkyl, perfluoro$(C_1$-$C_6)$alkyl, perfluoro$(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, difluoromethoxy, trifluoromethoxy, $(C_1$-$C_6)$alkylthio, $(C_1$-$C_6)$alkylsulfinyl or $(C_1$-$C_6)$alkylsulfonyl;

or R^1 and R^{16} may be taken together with the carbon to which they are attached to form a $(C_3$-$C_7)$cycloalkyl group optionally substituted by $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkyl or $(C_6$-$C_{10})$aryloxy;

or R^5 and R^6, when attached to adjacent carbon positions, may be taken together to form a group of the formula



wherein the broken lines represent optional double bonds;

h is 1 or 2;

f and g are each independently 0, 1 or 2;

Y and Z are each independently CH_2, O, CO, SO_2, CH_2CH_2, CH_2O, CH_2S, CH_2NH, CH_2CO, CH_2SO_2, NHCO or $NHSO_2$; and

R^{11} is hydrogen, halo, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, (trifluoromethyl)$_2(C_1$-$C_6)$alkyl, perfluoro$(C_1$-$C_6)$alkyl, perfluoro$(C_1$-$C_6)$alkyl$(C_1$-$C_6)$alkyl, difluoromethoxy or trifluoromethoxy;

with the proviso that when either a or e is 0, the other must be 1;

with the proviso that when b and d are 1, the sum of a, c and e cannot be 5, 6 or 7;

with the proviso that when b and d are 0, the sum of a, c and e cannot be 7;

with the proviso that the methyene carbon attached to the phosphorus atom must be attached to a carbon atom of the Ar ring; and

with the proviso that R^5 and R^6 must be attached to carbon atoms of the Ar ring.

2. A compound according to claim 1, wherein Ar is phenyl or thienyl.

3. A compound according to claim 1, wherein R^1 is 2-methylpropyl, trifluoromethylethyl, cyclopropylmethyl, cyclobutylmethyl, phenoxybutyl, cyclohexylmethyl or phenylethyl.

4. A compound according to claim 1, wherein R^2 is (C_1-C_6)alkyl or 4-methoxybenzyl.

5. A compound according to claim 1, wherein R^3 is methyl.

6. A compound according to claim 1, wherein R^4 is hydrogen, benzyl, 2-chlorobenzyl, 2-fluorobenzyl, 3-fluorobenzyl or 4-fluorobenzyl.

7. A compound according to claim 1, wherein Ar is phenyl or thienyl; R^1 is 2-methylpropyl, trifluoromethylethyl, cyclopropylmethyl, cyclobutylmethyl, phenoxybutyl, cyclohexylmethyl or phenylethyl; R^2 is (C_1-C_6)alkyl or 4-methoxybenzyl; R^3 is methyl and R^4 is hydrogen, benzyl, 2-chlorobenzyl, 2-fluorobenzyl, 3-fluorobenzyl or 4-fluorobenzyl.

8. A compound according to claim 1, wherein said compound is selected from the group consisting of:

(4-Benzylbenzyl)-[2-(2,2-dimethyl-1-methylcarbamoyl-propylcarbamoyl)-4-methyl-pentyl]-phosphinic acid;

(4-Benzylbenzyl-[2-(2,2-dimethyl-1-methylcarbamoyl-propylcarbamoyl)-5,5,5-trifluoropentyl]-phosphinic acid;

[2-(2,2-Dimethyl-1-methylcarbamoyl-propylcarbamoyl)-4-methylpentyl]-[4-(3-fluorobenzyl)-benzyl]-phosphinic acid;

Benzyl-{2-[2-(4-methoxyphenyl)-1-methylcarbamoyl-ethylcarbamoyl]-6-phenoxy-hexyl}-phosphinic acid;

(4-Benzylbenzyl)-{2-[2-(4-methoxyphenyl)-1-methylcarbamoyl-ethylcarbamoyl]-6-phenoxyhexyl}-phosphinic acid;

(4-Benzylbenzyl)-{3-cyclohexyl-2-[2-(4-methoxyphenyl)-1-methylcarbamoyl-ethylcarbamoyl]-propyl}-phosphinic acid;

(4-Benzylbenzyl)-[3-cyclohexyl-2-(2,2-dimethyl-1-methylcarbamoyl-propylcarbamoyl)-propyl]-phosphinic acid;

(4-Benzylbenzyl)-[2-(2,2-dimethyl-1-methylcarbamoyl-propylcarbamoyl)-4-phenyl-butyl]-phosphinic acid;

(4-Cyclohexylmethylbenzyl)-[2-(2,2-dimethyl-1-methylcarbamoyl-propylcarbamoyl)-4-methyl-pentyl]-phosphinic acid;

[2-(2,2-Dimethyl-1-methylcarbamoyl-propylcarbamoyl)-4-methylpentyl]-(4-isobutylbenzyl)-phosphinic acid;

[2-(2,2-Dimethyl-1-methylcarbamoyl-propylcarbamoyl)-4-methylpentyl]-[4-(4-fluoro-benzyl)-benzyl]-phosphinic acid;

[2-(2,2-Dimethyl-1-methylcarbamoyl-propylcarbamoyl)-4-methylpentyl]-[4-(2-fluoro-benzyl)-benzyl]phophinic acid;

(4-Benzylbenzyl)-{2-[2-(4-methoxyphenyl)-1-methylcarbamoyl-ethylcarbamoyl]-4-methyl-pentyl}-phosphinic acid;

[4-(2-Chlorobenzyl)benzyl]-[2-(2,2-dimethyl-1-methylcarbamoyl-1-propylcarbamoyl)-4-methylpentyl]phosphinic acid;

(5-Benzyl-pyridin-2-ylmethyl)-[2-(2,2-dimethyl-1-methylcarbamoyl-propylcarbamoyl)-4-methyl-pentyl]phosphinic acid;

[2-(2,2-Dimethyl-1-methylcarbamoyl-propylcarbamoyl)-5,5,5-trifluoro-pentyl]-[4-(2-fluoro-benzyl)-benzyl]phosphinic acid;

[3-Cyclopropyl-2-(2,2-dimethyl-1-methylcarbamoyl-propylcarbamoyl)-propyl]-[4-(2-fluoro-benzyl)-benzyl]phosphinic acid;

[3-Cyclobutyl-2-(2,2-dimethyl-1-methylcarbamoyl-propylcarbamoyl)-propyl]-[4-(2-fluoro-benzyl)-benzyl]-phosphinic acid; and

(5-Benzyl-thiophen-2-ylmethyl)-[2-(2,2-dimethyl-1-methylcarbamoyl-propylcarbamoyl)-4-methylpentyl]-phosphinic acid.

9. A pharmaceutical composition for (a) the treatment of a condition selected from the group consisting of arthritis, cancer, synergy with cytotoxic anticancer agents, tissue ulceration, mucular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, in combination with standard NSAID'S and analgesics and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) or (b) the inhibition of matrix metalloproteinases or the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising an amount of a compound of claim 1 effective in such treatment and a pharmaceutically acceptable carrier.

10. A method for the inhibition of (a) matrix metalloproteinases or (b) the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of claim 1.

11. A method for treating a condition selected from the group consisting of arthritis, cancer, synergy with cytotoxic anticaner agents, tissue ulceration, macular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, in combination with standard NSAID'S and analgesics and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an amount of a compound of claim 1, effective in treating such a condition.

INTERNATIONAL SEARCH REPORT

In' ational Application No
PCT/IB 97/00800

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07F9/30 A61K31/66 C07F9/58 C07F9/6553 C07F9/655

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07F A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 93 14112 A (MERCK & CO.) 22 July 1993 see the whole document ---	1-11
Y	WO 95 12603 A (SYNTEX INC.) 11 May 1995 see the whole document -----	1-11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

1

Date of the actual completion of the international search
15 September 1997

Date of mailing of the international search report
30 -09- 1997

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

Authorized officer
Beslier, L

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

In' tional Application No
PCT/IB 97/00800

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9314112 A	22-07-93	AU 3475393 A	03-08-93
		CA 2126687 A	22-07-93
		EP 0623143 A	09-11-94
		JP 7503016 T	30-03-95
WO 9512603 A	11-05-95	AU 8089794 A	23-05-95
		BR 9407960 A	26-11-96
		CA 2175667 A	11-05-95
		CN 1134153 A	23-10-96
		CZ 9601260 A	13-11-96
		DE 69404324 D	21-08-97
		EP 0726903 A	21-08-96
		FI 961857 A	01-07-96
		HU 74730 A	28-02-97
		NO 961780 A	03-07-96
		NZ 275315 A	27-07-97
		PL 314134 A	19-08-96
		ZA 9408691 A	03-05-96

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 211/58, 211/46, 211/62, 295/18, 211/34, C07C 311/29, A61K 31/445, 31/495, 31/18

A1

(11) International Publication Number: **WO 98/07697**

(43) International Publication Date: 26 February 1998 (26.02.98)

(21) International Application Number: PCT/IB97/00924

(22) International Filing Date: 25 July 1997 (25.07.97)

(30) Priority Data:
60/024,675 23 August 1996 (23.08.96) US

(71) Applicant *(for all designated States except US)*: PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: BLUMENKOPF, Todd, A. [US/US]; 9 Fairway Lane, Old Lyme, CT 06371 (US). ROBINSON, Ralph, P. [US/US]; 30 Friar Tuck Drive, Gales Ferry, CT 06335 (US).

(74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).

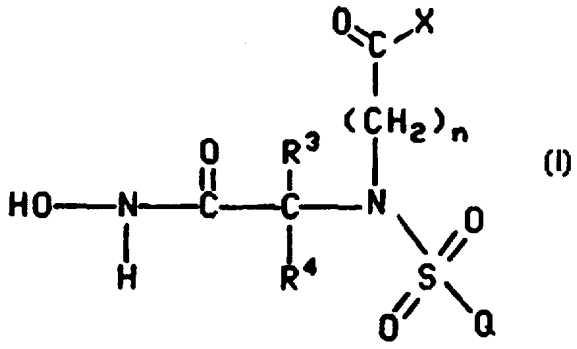
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: ARYLSULFONYLAMINO HYDROXAMIC ACID DERIVATIVES

(57) Abstract

A compound of formula (I) wherein n, X, R^3, R^4 and Q are as defined above, useful in the treatment of a condition selected from the group consisting of arthritis, cancer, tissue ulceration, macular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of TNF. In addition, the compounds of the present invention may be used in combination therapy with standard non-steroidal anti-inflammatory drugs (NSAID'S) and analgesics, and in combination with cytotoxic drugs such as adriamycin, daunomycin, cis-platinum, etoposide, taxol, taxotere and other alkaloids, such as vincristine, in the treatment of cancer.



(I)

FOR THE PURPOSES OF INFORMATION ONLY

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

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

ARYLSULFONYLAMINO HYDROXAMIC ACID DERIVATIVES

Background of the Invention

The present invention relates to arylsulfonylamino hydroxamic acid derivatives which are inhibitors of matrix metalloproteinases or the production of tumor necrosis factor (TNF) and as such are useful in the treatment of a condition selected from the group consisting of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of TNF. In addition, the compounds of the present invention may be used in combination therapy with standard non-steroidal anti-inflammatory drugs (hereinafter NSAID'S) and analgesics for the treatment of arthritis, and in combination with cytotoxic drugs such as adriamycin, daunomycin, cis-platinum, etoposide, taxol, taxotere and alkaloids, such as vincristine, in the treatment of cancer.

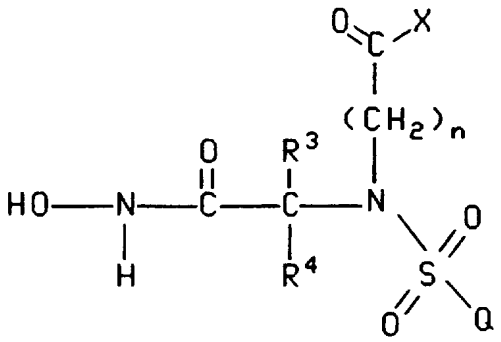
This invention also relates to a method of using such compounds in the treatment of the above diseases in mammals, especially humans, and to pharmaceutical compositions useful therefor.

There are a number of enzymes which effect the breakdown of structural proteins and which are structurally related metalloproteases. Matrix-degrading metalloproteinases, such as gelatinase, stromelysin and collagenase, are involved in tissue matrix degradation (e.g. collagen collapse) and have been implicated in many pathological conditions involving abnormal connective tissue and basement membrane matrix metabolism, such as arthritis (e.g. osteoarthritis and rheumatoid arthritis), tissue ulceration (e.g. corneal, epidermal and gastric ulceration), abnormal wound healing, periodontal disease, bone disease (e.g. Paget's disease and osteoporosis), tumor metastasis or invasion, as well as HIV-infection (J. Leuk. Biol., 52 (2): 244-248, 1992).

Tumor necrosis factor is recognized to be involved in many infectious and auto-immune diseases (W. Fiers, FEBS Letters, 1991, 285, 199). Furthermore, it has been shown that TNF is the prime mediator of the inflammatory response seen in sepsis and septic shock (C.E. Spooner et al., Clinical Immunology and Immunopathology, 1992, 62 S11).

Summary of the Invention

The present invention relates to a compound of the formula

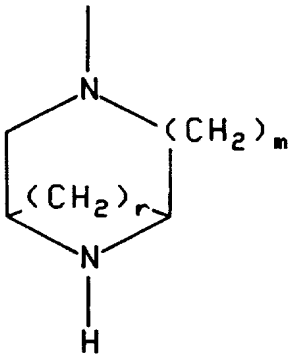


I

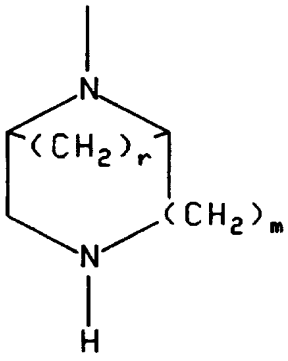
or the pharmaceutically acceptable salts thereof, wherein

n is 1 to 6;

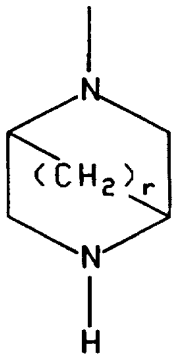
X is OR^1 wherein R^1 is as defined below; azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, piperazinyl or a bridged diazabicycloalkyl ring selected from the group consisting of



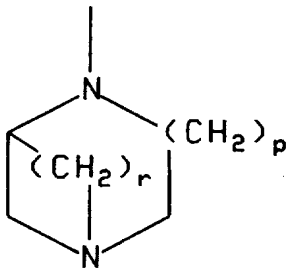
a



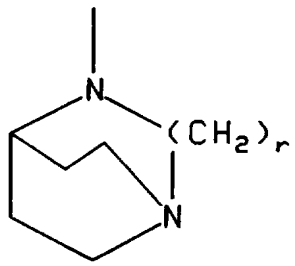
b



c



d



e

wherein r is 1, 2 or 3;

m is 1 or 2; and

p is 0 or 1;

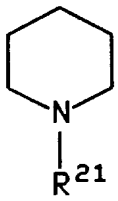
wherein each heterocyclic group may optionally be substituted by one or two groups selected from hydroxy, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_{10})acyl, (C_1-C_{10})acyloxy, (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_5-C_9)heteroaryl (C_1-C_6)alkyl, hydroxy (C_1-C_6)alkyl, (C_1-C_6)alkoxy (C_1-C_6)alkyl, (C_1-C_6)acyloxy(C_1-C_6)alkyl, (C_1-C_6)alkylthio, (C_1-C_6)alkylthio (C_1-C_6)alkyl, (C_6-C_{10})arylthio, (C_6-C_{10}) arylthio(C_1-C_6)alkyl, $R^9R^{10}N$, $R^9R^{10}NSO_2$, $R^9R^{10}NCO$, $R^9R^{10}NCO(C_1$-$C_6)$alkyl wherein R^9 and R^{10} are each independently hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_6-C_{10})aryl (C_1-C_6)alkyl or (C_5-C_9)heteroaryl (C_1-C_6)alkyl or R^9 and R^{10} may be taken together with the nitrogen to which they are attached to form an azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl or thiomorpolinyl ring; $R^{12}SO_2$, $R^{12}SO_2NH$ wherein R^{12} is trifluoromethyl, (C_1-C_6)alkyl, (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkyl or (C_5-C_9)heteroaryl (C_1-C_6)alkyl; $R^{13}CONR^9$ wherein R^9 is as defined above and R^{13} is hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_1-C_6)aryl(C_1-C_6)alkyl(C_6-C_{10})aryl(C_1-C_6)alkoxy or (C_5-C_9)heteroaryl(C_1-C_6)alkyl; $R^{14}OOC$, $R^{14}OOC(C_1$-$C_6)$alkyl wherein R^{14} is (C_1-C_6)alkyl, (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_6-C_{10})aryl (C_1-C_6)alkyl, 5-indanyl, CHR^5OCOR^6 wherein R^5 is hydrogen or (C_1-C_6)alkyl and R^6 is (C_1-C_6)alkyl, (C_1-C_6)alkoxy or (C_6-C_{10})aryl; $CH_2CONR^7R^8$ wherein R^7 and R^8 are each independently hydrogen or (C_1-C_6)alkyl or may be taken together with the nitrogen to which they are attached to form an azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl or thiomorpholinyl ring; or $R^{15}O$

(C_1C_6)alkyl wherein R^{15} is $H_2N(CHR^{16})CO$ wherein R^{16} is the side chain of a natural D- or L-amino acid;

R^1 is $(C_6$-$C_{10})$aryl, $(C_5$-$C_9)$heteroaryl, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkyl, 5-indanyl, CHR^5OCOR^6 or $CH_2CONR^7R^8$ wherein R^5, R^6, R^7 and R^8 are as defined above;

R^3 and R^4 are each independently selected from the group consisting of hydrogen, $(C_1$-$C_6)$alkyl, trifluoromethyl, trifluoromethyl$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkyl (difluoromethylene), $(C_1$-$C_3)$alkyl(difluoromethylene)$(C_1$-$C_3)$alkyl, $(C_6$-$C_{10})$aryl, $(C_5$-$C_9)$heteroaryl, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkyl, $(C_5$-$C_9)$heteroaryl$(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$aryl$(C_6$-$C_{10})$aryl, $(C_6$-$C_{10})$aryl$(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_3$-$C_6)$cycloalkyl$(C_1$-$C_6)$alkyl, hydroxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_{10})$acyloxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_{10})$acylamino$(C_1$-$C_6)$alkyl, piperidyl, $(C_1$-$C_6)$alkylpiperidyl, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl, $(C_5$-$C_9)$heteroaryl$(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylthio$(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$arylthio$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylsulfinyl$(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$arylsulfinyl$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylsulfonyl$(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$arylsulfonyl$(C_1$-$C_6)$alkyl, amino$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylamino$(C_1$-$C_6)$alkyl, $((C_1$-$C_6)$alkylamino$)_2(C_1$-$C_6)$alkyl, $R^{17}CO(C_1$-$C_6)$alkyl wherein R^{17} is $R^{14}O$ or R^7R^8N wherein R^7, R^8 and R^{14} are as defined above; or $R^{18}(C_1$-$C_6)$alkyl wherein R^{18} is piperazinyl, $(C_1$-$C_{10})$acylpiperazinyl, $(C_6$-$C_{10})$arylpiperazinyl, $(C_5$-$C_9)$heteroarylpiperazinyl, $(C_1$-$C_6)$alkylpiperazinyl, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkylpiperazinyl, $(C_5$-$C_9)$heteroaryl$(C_1$-$C_6)$alkylpiperazinyl, morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, piperidyl, $(C_1$-$C_6)$alkylpiperidyl, $(C_6$-$C_{10})$arylpiperidyl, $(C_5$-$C_9)$heteroarylpiperidyl, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkylpiperidyl, $(C_5$-$C_9)$heteroaryl$(C_1$-$C_6)$alkylpiperidyl or $(C_1$-$C_{10})$acylpiperidyl;

or R^3 and R^4 may be taken together to form a $(C_3$-$C_6)$cycloalkyl, oxacyclohexyl, thiocyclohexyl, indanyl or tetralinyl ring or a group of the formula



wherein R^{21} is hydrogen, $(C_1$-$C_{10})$acyl, $(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkyl, $(C_5$-$C_9)$heteroaryl$(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$alkylsulfonyl; and

Qis (C_1-C_6)alkyl, (C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl(C_1-C_6)alkyl, (C_6-C_{10})aryloxy(C_5-C_9)heteroaryl, (C_5-C_9)heteroaryl, (C_1-C_6)alkyl(C_6-C_{10})aryl, (C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_5-C_9)heteroaryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_5-C_9)heteroaryl, (C_1-C_6)alkoxy(C_5-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_5-C_9)heteroaryl, (C_5-C_9)heteroaryloxy(C_5-C_9)heteroaryl, (C_6-C_{10})aryloxy(C_1-C_6)alkyl, (C_5-C_9)heteroaryloxy(C_1-C_6)alkyl, (C_1-C_6)alkyl(C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_5-C_9)heteroaryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_6-C_{10})aryloxy(C_5-C_9)heteroaryl, (C_1-C_6)alkoxy(C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_1-C_6)alkoxy(C_5-C_9)heteroaryloxy(C_6-C_{10})aryl or (C_1-C_6)alkoxy(C_6-C_{10})aryloxy(C_5-C_9)heteroaryl wherein each aryl group is optionally substituted by fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or perfluoro(C_1-C_3)alkyl;

with the proviso that X must be substituted when defined as azetidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, piperazinyl, (C_1-C_{10})acylpiperazinyl, (C_1-C_6)alkylpiperazinyl, (C_6-C_{10})arylpiperazinyl, (C_5-C_9)heteroarylpiperazinyl or a bridged diazabicycloalkyl ring.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof.

The term "alkoxy", as used herein, includes O-alkyl groups wherein "alkyl" is defined above.

The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl or naphthyl, optionally substituted by 1 to 3 substituents selected from the group consisting of fluoro, chloro, trifluoromethyl, (C_1-C_6)alkoxy, (C_6-C_{10})aryloxy, trifluoromethoxy, difluoromethoxy and (C_1-C_6)alkyl.

The term "heteroaryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic heterocyclic compound by removal of one hydrogen, such as pyridyl, furyl, pyroyl, thienyl, isothiazolyl, imidazolyl, benzimidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzofuryl, isobenzofuryl, benzothienyl, pyrazolyl, indolyl, isoindolyl, purinyl, carbazolyl, isoxazolyl, thiazolyl, oxazolyl, benzthiazolyl or benzoxazolyl, optionally substituted by 1 to 2 substituents selected from the group consisting of fluoro, chloro, trifluoromethyl, (C_1-C_6)alkoxy, (C_6-C_{10})aryloxy, trifluoromethoxy, difluoromethoxy and (C_1-C_6)alkyl.

The term "acyl", as used herein, unless otherwise indicated, includes a radical of the general formula RCO wherein R is alkyl, alkoxy, aryl, arylalkyl or arylalkyloxy and the terms "alkyl" or "aryl" are as defined above.

The term "acyloxy", as used herein, includes O-acyl groups wherein "acyl" is defined above.

The term "D- or L-amino acid", as used herein, unless otherwise indicated, includes glycine, alanine, valine, leucine, isoleucine, phenylalanine, asparagine, glutamine, tryptophan, proline, serine, threonine, tyrosine, hydroxyproline, cysteine, cystine, methionine, aspartic acid, glutamic acid, lysine, arginine or histidine.

The compound of formula I may have chiral centers and therefore exist in different enantiomeric forms. This invention relates to all optical isomers and stereoisomers of the compounds of formula I and mixtures thereof.

Preferred compounds of formula I include those wherein n is 2.

Other preferred compounds of formula I include those wherein either R^3 or R^4 is not hydrogen.

Other preferred compounds of formula I include those wherein Ar is (C_1-C_6)alkoxy(C_6-C_{10})aryl,(C_6-C_{10})aryl(C_1-C_6)alkoxy(C_6-C_{10})aryl,4-fluorophenoxy(C_6-C_{10})aryl, 4-fluorobenzyloxy(C_6-C_{10})aryl or (C_1-C_6)alkyl(C_6-C_{10})aryloxy(C_6-C_{10})aryl.

Other preferred compounds of formula I include those wherein X is indolinyl or piperidinyl.

More preferred compounds of formula I include those wherein n is 2; either R^3 or R^4 is not hydrogen; Ar is (C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_6-C_{10})aryl, 4-fluorophenoxy(C_6-C_{10})aryl, 4-fluorobenzyloxy(C_6-C_{10})aryl or (C_1-C_6)alkyl(C_6-C_{10})aryloxy(C_6-C_{10})aryl; and X is indolinyl or piperidinyl.

Specific preferred compounds of formula I include the following:

3-[(Cyclohexylhydroxycarbamoylmethyl)-(4-methoxybenzenesulfonyl)-amino]-propionic acid indan-5-yl ester;

Acetic acid 1-{3-[(1-hydroxycarbamoyl-2-methylpropyl)-(4-methoxy-benzene-sulfonyl)-amino]propionyl}piperidin-4-yl ester;

2-Cyclohexyl-N-hydroxy-2-[[3-(4-hydroxypiperidin-1-yl)-3-oxo-propyl]-(4-methoxy-benzenesulfonyl)amino]acetamide;

Benzoic acid 1-{3-[(1-hydroxycarbamoyl-2-methylpropyl)-(4-methoxy-benzene-sulfonyl)amino]propionyl}piperidin-4-yl ester;

N-Hydroxy-2-[[3-(4-hydroxypiperidin-1-yl)-3-oxopropyl]-(4-methoxybenzenesulfonyl)amino]-3-methylbutyramide;

1-{3-[(Cyclohexylhydroxycarbamoylmethyl)-(4-methoxybenzenesulfonyl)-amino]propionyl}piperidine-4-carboxylic acid;

1-{3-[(Cyclohexylhydroxycarbamoylmethyl)-(4-methoxybenzenesulfonyl)-amino]propionyl}piperidine-4-carboxylic acid ethyl ester;

2-Cyclohexyl-N-hydroxy-2-{(4-methoxybenzenesulfonyl)-[3-(4-methylaminopiperidin-1-yl)-3-oxopropyl]amino}acetamide;

3-(4-Chlorophenyl)-N-hydroxy-2-{(4-methoxybenzenesulfonyl)-[3-(4-methylaminopiperidin-1-yl)-3-oxopropyl]amino}propionamide;

3-Cyclohexyl-N-hydroxy-2-{(4-methoxybenzenesulfonyl)-[3-(4-methylaminopiperidin-1-yl)-3-oxopropyl]amino}propionamide;

N-Hydroxy-2-[{3-[4-(2-hydroxy-2-methylpropyl)piperazin-1-yl]-3-oxopropyl}-(4-methoxy-benzenesulfonyl)amino]-3-methylbutyramide;

2,2-Dimethylpropionic acid 2-(4-{3-[(1-hydroxycarbamoyl-2-methylpropyl)-(4-methoxy-benzenesulfonyl)amino]propionyl}piperazin-1-yl)ethyl ester; and

Benzoicacid2-(4-{3-[(1-hydroxycarbamoyl-2-methylpropyl)-(4-methoxybenzenesulfonyl)-amino]propionyl}piperazin-1-yl)-ethyl ester.

Other specific compounds of formula I include the following:

2-Cyclohexyl-N-hydroxy-2-[{3-[4-(2-hydroxyethyl)piperazin-1-yl]-3-oxopropyl}-(4-methoxybenzenesulfonyl)amino]acetamide;

N-Hydroxy-2-[{3-[5-(2-hydroxyethyl)-2,5-diazabicyclo[2.2.1]-hept-2-yl]-3-oxopropyl}-(4-methoxybenzenesulfonyl)amino]-3-methylbutyramide;

2-{(4-Benzyloxybenzenesulfonyl)-[3-(4-hydroxypiperidin-1-yl)-3-oxopropyl]amino}-N-hydroxy-3-methylbutyramide;

2-Cyclohexyl-2-{[4-(4-fluorophenoxy)benzenesulfonyl]-[3-(4-hydroxypiperidin-1-yl)-3-oxopropyl]-amino}-N-hydroxyacetamide;

2-{[4-(4-Butylphenoxy)benzenesulfonyl]-[3-(4-hydroxypiperidin-1-yl)-3-oxopropyl]-amino}-N-hydroxy-3-methylbutyramide;

1-{(4-Methoxybenzenesulfonyl)-[3-(4-methylaminopiperidin-1-yl)-3-oxopropyl]amino}-cyclopentanecarboxylic acid hydroxyamide;

4-{3-[(1-Hydroxycarbamoyl-2-methylpropyl)-(4-methoxybenzenesulfonyl)amino]-propionyl}piperazine-2-carboxylic acid ethyl ester;

3-[(Cyclohexylhydroxycarbamoylmethyl)-(4-methoxybenzene-sulfonyl)amino]propionic acid ethoxycarbonyloxymethyl ester;

3-[(1-Hydroxycarbamoylpentyl)-(4-methoxybenzenesulfonyl)amino]propionic acid ethoxycarbonyloxymethyl ester;

3-[[4-(4-Fluorobenzyloxy)-benzenesulfonyl]-(1-hydroxy-carbamoyl-2-methyl-propyl)-amino]-propionic acid ethoxycarbonyloxymethyl ester; and

3-[[4-(4-Fluorophenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-2-methyl-propyl)-amino]-propionic acid ethoxycarbonyloxymethyl ester.

The present invention also relates to a pharmaceutical composition for (a) the treatment of a condition selected from the group consisting of arthritis, cancer, synergy with cytotoxic anticancer agents, tissue ulceration, macular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, in combination with standard NSAID'S and analgesics and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) or (b) the inhibition of matrix metalloproteinases or the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising an amount of a compound of formula I or a pharmaceutically acceptable salt thereof effective in such treatments and a pharmaceutically acceptable carrier.

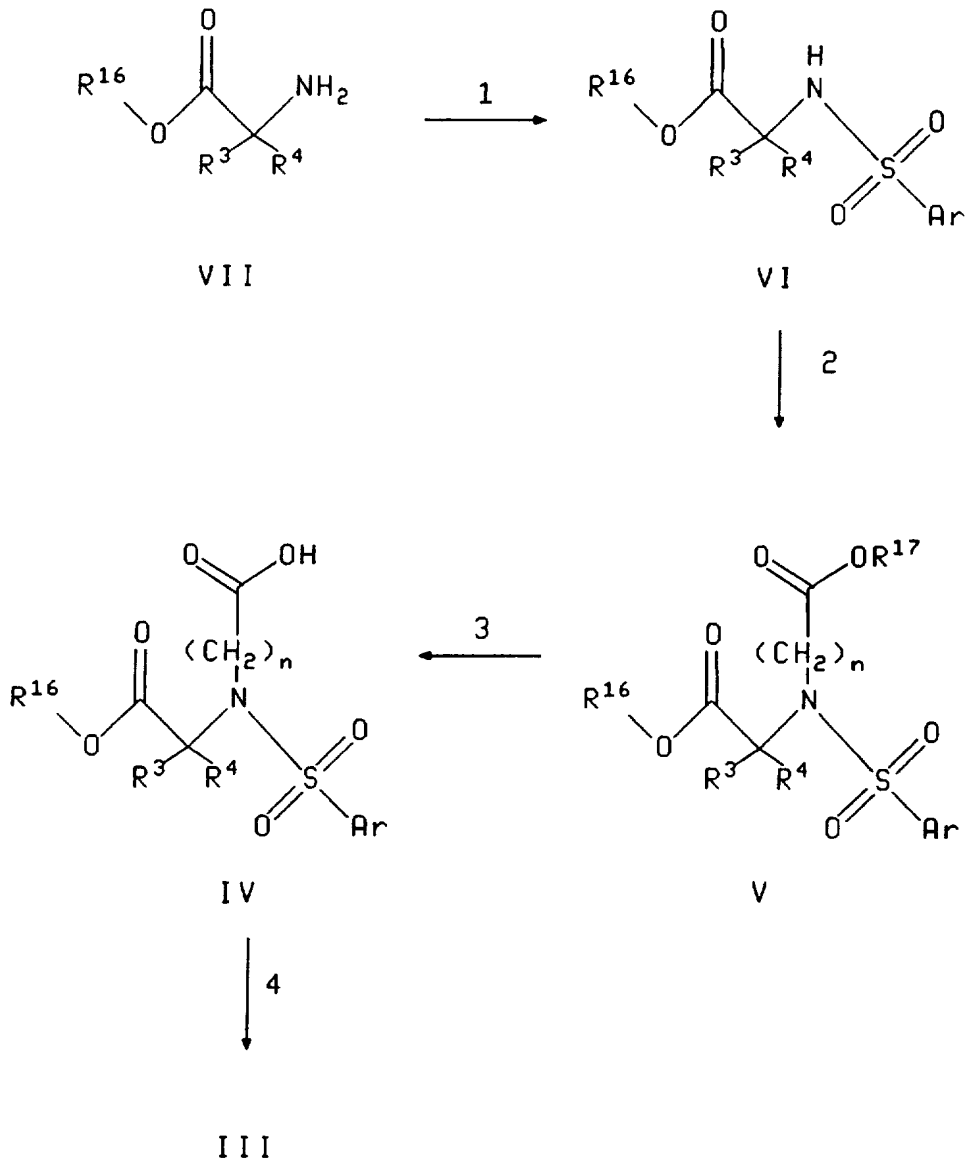
The present invention also relates to a method for the inhibition of (a) matrix metalloproteinases or (b) the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

The present invention also relates to a method for treating a condition selected from the group consisting of arthritis, cancer, tissue ulceration, macular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, compounds of formula I may be used in combination with standard NSAID'S and analgesics and in combination with cytotoxic anticancer agents, and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an amount of a compound of formula I or a pharmaceutically acceptable salt thereof effective in treating such a condition.

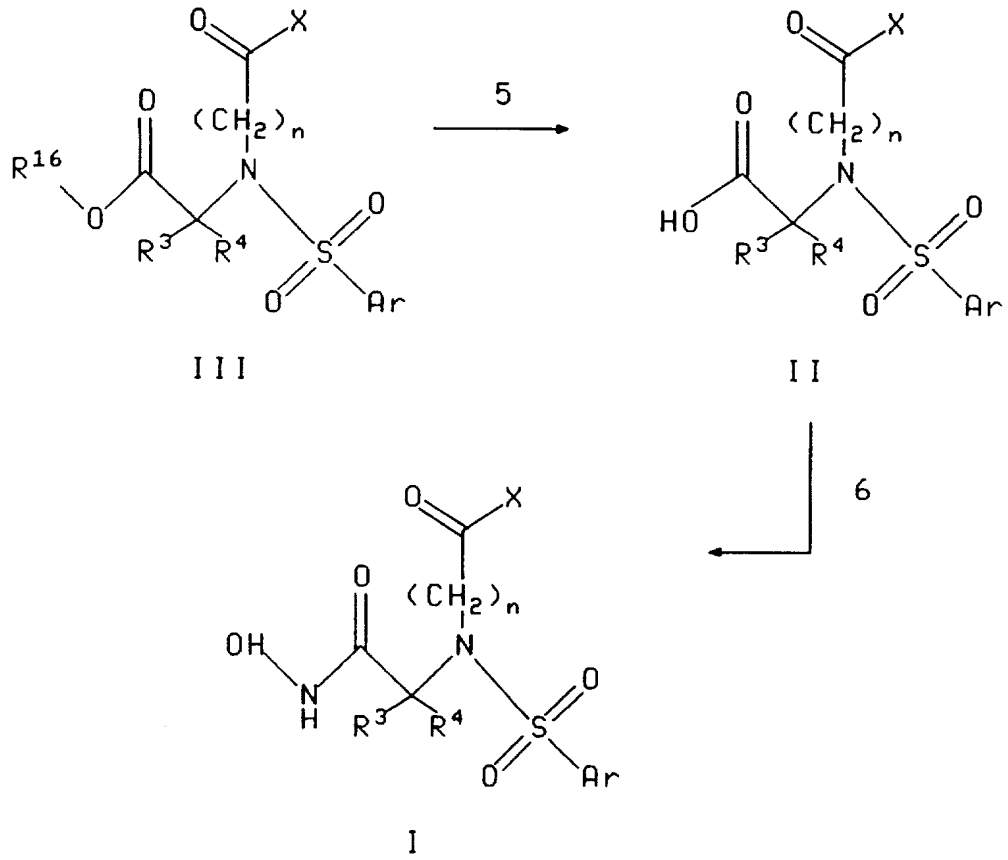
Detailed Description of the Invention

The following reaction Schemes illustrate the preparation of the compounds of the present invention. Unless otherwise indicated n, R^3, R^4, X and Ar in the reaction Schemes and the discussion that follow are defined as above.

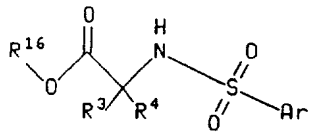
Scheme 1



Scheme 1 cont'd

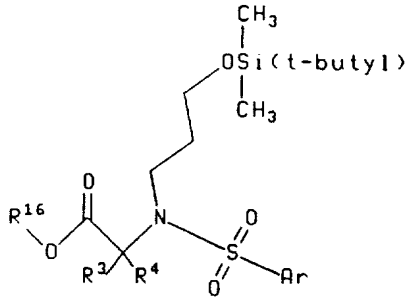


Scheme 2



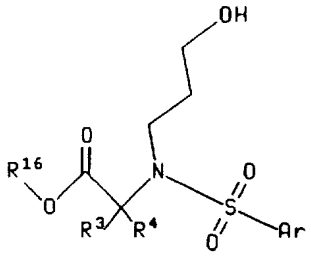
VI

1



VIII

2

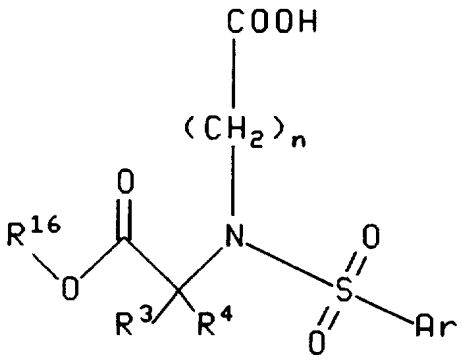


IX

3

IV

Scheme 2 (continued)



IV

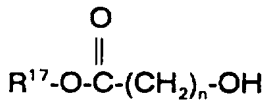
↓

↓

I

In reaction 1 of Scheme 1, the amino acid compound of formula **VII**, wherein R^{16} is $(C_1\text{-}C_6)$alkyl, benzyl, allyl or tert-butyl, is converted to the corresponding compound of formula **VI** by reacting **VII** with a reactive functional derivative of an arylsulfonic acid compound, such as an arylsulfonyl chloride, in the presence of a base, such as triethylamine, and a polar solvent, such as tetrahydrofuran, dioxane, water or acetonitrile, preferably a mixture of dioxane and water. The reaction mixture is stirred, at room temperature, for a time period between about 10 minutes to about 24 hours, preferably about 60 minutes.

In reaction 2 of Scheme 1, the arylsulfonyl amino compound of formula **VI**, wherein R^{16} is $(C_1\text{-}C_6)$alkyl, benzyl, allyl or tert-butyl, is converted to the corresponding compound of formula **V**, wherein n is 1, 3, 4, 5 or 6, by reacting **VI** with a reactive derivative of an alcohol of the formula



such as the chloride, bromide or iodide derivative, preferably the iodide derivative, wherein the R^{17} protecting group is $(C_1\text{-}C_6)$alkyl, benzyl, allyl or tert-butyl, in the presence of a base such as potassium carbonate or sodium hydride, preferably sodium hydride, and a polar solvent, such as dimethylformamide. The reaction mixture is stirred, at room temperature, for a time period between about 60 minutes to about 48 hours, preferably about 18 hours. The R^{17} protecting group is chosen such that it may be selectively removed in the presence of and without loss of the R^{16} protecting group, therefore, R^{17} cannot be the same as R^{16}. Removal of the R^{17} protecting group from the compound of formula **V** to give the corresponding carboxylic acid of formula **IV**, in reaction 3 of Scheme 1, is carried out under conditions appropriate for that particular R^{17} protecting group in use which will not affect the R^{16} protecting group. Such conditions include; (a) saponification where R^{17} is $(C_1\text{-}C_6)$alkyl and R^{16} is tert-butyl, (b) hydrogenolysis where R^{17} is benzyl and R^{16} is tert-butyl or $(C_1\text{-}C_6)$alkyl, (c) treatment with a strong acid, such as trifluoroacetic acid or hydrochloric acid where R^{17} is tert-butyl and R^{16} is $(C_1\text{-}C_6)$alkyl, benzyl or allyl, or (d) treatment with tributyltinhydride and acetic acid in the presence of catalytic bis(triphenylphosphine) palladium (II) chloride where R^{17} is allyl and R^{16} is $(C_1\text{-}C_6)$alkyl, benzyl or tert-butyl.

In reaction 4 of Scheme 1, the carboxylic acid of formula **IV** is condensed with a compound of the formula HX or the salt thereof, wherein X is as defined above, to

give the corresponding amide compound of formula III. The formation of amides from primary or secondary amines or ammonia and carboxylic acids is achieved by conversion of the carboxylic acid to an activated functional derivative which subsequently undergoes reaction with a primary or secondary amine or ammonia to form the amide. The activated functional derivative may be isolated prior to reaction with the primary or secondary amine or ammonia. Alternatively, the carboxylic acid may be treated with oxalyl chloride or thionyl chloride, neat or in an inert solvent, such as chloroform, at a temperature between about 25°C to about 80°C, preferably about 50°C, to give the corresponding acid chloride functional derivative. The inert solvent and any remaining oxalyl chloride or thionyl chloride is then removed by evaporation under vacuum. The remaining acid chloride functional derivative is then reacted with the primary or secondary amine or ammonia in an inert solvent, such as methylene chloride, to form the amide. The preferred method for the condensation of the carboxylic acid of formula IV with a compound of the formula HX, wherein X is as defined above, to provide the corresponding compound of formula III is the treatment of IV with (benzotriazol-1-yloxy)tris(dimethylamino) phosphonium hexafluorophosphate in the presence of a base, such as triethylamine, to provide the benzotriazol-1-oxy ester in situ which, in turn, reacts with the compound of the formula HX, in an inert solvent, such as methylene chloride, at room temperature to give the compound of formula III.

Removal of the R^{16} protecting group from the compound of formula III to give the corresponding carboxylic acid of formula II, in reaction 5 of Scheme 1, is carried out under conditions appropriate for the particular R^{16} protecting group in use. Such conditions include; (a) saponification where R^{16} is lower alkyl, (b) hydrogenolysis where R^{16} is benzyl, (c) treatment with a strong acid, such as trifluoroacetic acid or hydrochloric acid, where R^{16} is tert-butyl, or (d) treatment with tributyltinhydride and acetic acid in the presence of catalytic bis(triphenylphosphine) palladium (II) chloride where R^{16} is allyl.

In reaction 6 of Scheme 1, the carboxylic acid compound of formula II is converted to the hydroxamic acid compound of formula I by treating II with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide and 1-hydroxybenztriazole in a polar solvent, such as dimethylformamide, followed by the addition of hydroxylamine to the reaction mixture after a time period between about 15 minutes to about 1 hour, preferably about 30 minutes. The hydroxylamine is preferably generated in situ from a salt form, such

as hydroxylamine hydrochloride, in the presence of a base, such as N-methylmorpholine. Alternatively, a protected derivative of hydroxylamine or its salt form, where the hydroxyl group is protected as a tert-butyl, benzyl, allyl or trimethylsilylether, may be used in the presence of (benzotriazol-1-yloxy)tris-(dimethylamino) phosphonium hexafluorophosphate and a base, such as N-methylmorpholine. Removal of the hydroxylamine protecting group is carried out by hydrogenolysis for a benzyl protecting group or treatment with a strong acid, such as trifluoroacetic acid, for a tert-butyl protecting group. The allyl protecting group may be removed by treatment with tributyltinhydride and acetic acid in the presence of catalytic bis(triphenylphosphine) palladium (II) chloride. The 2-trimethylsilylethyl ether may be removed by reaction with a strong acid, such as trifluoroacetic acid or by reaction with a fluoride source such as boron trifluoride etherate. N,O-bis(4-methoxybenzyl)hydroxyl-amine may also be used as the protected hydroxylamine derivative where deprotection is achieved using a mixture of methanesulfonic acid and trifluoroacetic acid.

In reaction 1 of Scheme 2, the arylsulfonylamino compound of formula **VI**, wherein R^{16} is (C_1-C_6)alkyl, benzyl or tert-butyl, is converted to the corresponding compound of formula **VIII** by reacting **VI** with a reactive functional derivative, such as the halide, preferably the iodide derivative, of 3-(tert-butyldimethylsilyloxy)-1-propanol in the presence of a base, such as sodium hydride. The reaction is stirred in a polar solvent, such as dimethylformamide, at room temperature, for a time period between about 2 hours to about 48 hours, preferably about 18 hours.

In reaction 2 of Scheme 2, the compound of formula **VIII** is converted to the alcohol compound of formula **IX** by treatment of **VIII** with an excess of an acid, such as acetic acid, or an excess of a Lewis acid, such as boron trifluoride etherate. When using an acid, such as acetic acid, water is added and a water-soluble cosolvent, such as tetrahydrofuran, can be added to promote solubility. The reaction is stirred for a time period between about 18 hours to about 72 hours, preferably about 24 hours, at a temperature between about room temperature to about 60°C, preferably about 50°C. When using a Lewis acid, such as boron trifluoride etherate, the reaction is stirred in a solvent, such as methylene chloride, for a time period between about 10 minutes to about 6 hours, preferably about 20 minutes, at a temperature between about -20°C to about room temperature, preferably about room temperature.

In reaction 3 of Scheme 2, the alcohol compound of formula **IX** is oxidized to the carboxylic acid compound of formula **IV**, wherein n is 2, by reacting **IX** with an excess of sodium periodate and a catalytic amount of ruthenium trichloride in a solvent mixture consisting of acetonitrile, water and carbon tetrachloride, at room temperature, for a time period between about 1 hour to about 24 hours, preferably about 4 hours.

The compound of formula **IV**, wherein n is 2, is further reacted to provide the hydroxamic acid compound of formula **I**, wherein n is 2, according to the procedure described above in reactions 4, 5 and 6 of Scheme 1.

Pharmaceutically acceptable salts of the acidic compounds of the invention are salts formed with bases, namely cationic salts such as alkali and alkaline earth metal salts, such as sodium, lithium, potassium, calcium, magnesium, as well as ammonium salts, such as ammonium, trimethyl-ammonium, diethylammonium, and tris-(hydroxymethyl)-methylammonium slats.

Similarly acid addition salts, such as of mineral acids, organic carboxylic and organic sulfonic acids e.g. hydrochloric acid, methanesulfonic acid, maleic acid, are also possible provided a basic group, such as pyridyl, constitutes part of the structure.

The ability of the compounds of formula **I** or their pharmaceutically acceptable salts (hereinafter also referred to as the compounds of the present invention) to inhibit matrix metalloproteinases or the production of tumor necrosis factor (TNF) and, consequently, demonstrate their effectiveness for treating diseases characterized by matrix metalloproteinase or the production of tumor necrosis factor is shown by the following in vitro assay tests.

Biological Assay

Inhibition of Human Collagenase (MMP-1)

Human recombinant collagenase is activated with trypsin using the following ratio: 10 μg trypsin per 100 μg of collagenase. The trypsin and collagenase are incubated at room temperature for 10 minutes then a five fold excess (50 μg/10 μg trypsin) of soybean trypsin inhibitor is added.

10 mM stock solutions of inhibitors are made up in dimethyl sulfoxide and then diluted using the following Scheme:

10 mM ------> 120 μM ------> 12 μM ------> 1.2 μM ------> 0.12 μM

Twenty-five microliters of each concentration is then added in triplicate to appropriate wells of a 96 well microfluor plate. The final concentration of inhibitor will

be a 1:4 dilution after addition of enzyme and substrate. Positive controls (enzyme, no inhibitor) are set up in wells D1-D6 and blanks (no enzyme, no inhibitors) are set in wells D7-D12.

Collagenase is diluted to 400 ng/ml and 25 μl is then added to appropriate wells of the microfluor plate. Final concentration of collagenase in the assay is 100 ng/ml.

Substrate (DNP-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2) is made as a 5 mM stock in dimethyl sulfoxide and then diluted to 20 μM in assay buffer. The assay is initiated by the addition of 50 μl substrate per well of the microfluor plate to give a final concentration of 10 μM.

Fluorescence readings (360 nM excitation, 460 nm emission) were taken at time 0 and then at 20 minute intervals. The assay is conducted at room temperature with a typical assay time of 3 hours.

Fluorescence vs time is then plotted for both the blank and collagenase containing samples (data from triplicate determinations is averaged). A time point that provides a good signal (the blank) and that is on a linear part of the curve (usually around 120 minutes) is chosen to determine IC_{50} values. The zero time is used as a blank for each compound at each concentration and these values are subtracted from the 120 minute data. Data is plotted as inhibitor concentration vs % control (inhibitor fluorescence divided by fluorescence of collagenase alone x 100). IC_{50}'s are determined from the concentration of inhibitor that gives a signal that is 50% of the control.

If IC_{50}'s are reported to be <0.03 μM then the inhibitors are assayed at concentrations of 0.3 μM, 0.03 μM, 0.03 μM and 0.003 μM.

<u>Inhibition of Gelatinase (MMP-2)</u>

Inhibition of gelatinase activity is assayed using the Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2 substrate (10 μM) under the same conditions as inhibition of human collagenase (MMP-1).

72kD gelatinase is activated with 1 mM APMA (p-aminophenyl mercuric acetate) for 15 hours at 4°C and is diluted to give a final concentration in the assay of 100 mg/ml. Inhibitors are diluted as for inhibition of human collagenase (MMP-1) to give final concentrations in the assay of 30 μM, 3 μM, 0.3 μM and 0.03 μM. Each concentration is done in triplicate.

Fluorescence readings (360 nm excitation, 460 emission) are taken at time zero and then at 20 minutes intervals for 4 hours.

IC_{50}'s are determined as per inhibition of human collagenase (MMP-1). If IC_{50}'s are reported to be less than 0.03 μM, then the inhibitors are assayed at final concentrations of 0.3 μM, 0.03 μM, 0.003 μM and 0.003 μM.

Inhibition of Stromelysin Activity (MMP-3)

Inhibition of stromelysin activity is based on a modified spectrophotometric assay described by Weingarten and Feder (Weingarten, H. and Feder, J., Spectrophotometric Assay for Vertebrate Collagenase, Anal. Biochem. 147, 437-440 (1985)). Hydrolysis of the thio peptolide substrate [Ac-Pro-Leu-Gly-$SCH[CH_2CH(CH_3)_2]CO$-Leu-Gly-OC_2H_5] yields a mercaptan fragment that can be monitored in the presence of Ellman's reagent.

Human recombinant prostromelysin is activated with trypsin using a ratio of 1 μl of a 10 mg/ml trypsin stock per 26 μg of stromelysin. The trypsin and stromelysin are incubated at 37°C for 15 minutes followed by 10 μl of 10 mg/ml soybean trypsin inhibitor for 10 minutes at 37°C for 10 minutes at 37°C to quench trypsin activity.

Assays are conducted in a total volume of 250 μl of assay buffer (200 mM sodium chloride, 50 mM MES, and 10 mM calcium chloride, pH 6.0) in 96-well microliter plates. Activated stromelysin is diluted in assay buffer to 25 μg/ml. Ellman's reagent (3-Carboxy-4-nitrophenyl disulfide) is made as a 1M stock in dimethyl formamide and diluted to 5 mM in assay buffer with 50 μl per well yielding at 1 mM final concentration.

10 mM stock solutions of inhibitors are made in dimethyl sulfoxide and diluted serially in assay buffer such that addition of 50 μL to the appropriate wells yields final concentrations of 3 μM, 0.3 μM, 0.003 μM, and 0.0003 μM. All conditions are completed in triplicate.

A 300 mM dimethyl sulfoxide stock solution of the peptide substrate is diluted to 15 mM in assay buffer and the assay is initiated by addition of 50 μl to each well to give a final concentration of 3 mM substrate. Blanks consist of the peptide substrate and Ellman's reagent without the enzyme. Product formation was monitored at 405 nm with a Molecular Devices UVmax plate reader.

IC_{50} values were determined in the same manner as for collagenase.

Inhibition of MMP-13

Human recombinant MMP-13 is activated with 2mM APMA (p-aminophenyl mercuric acetate) for 1.5 hours, at 37°C and is diluted to 400 mg/ml in assay buffer (50 mM Tris, pH 7.5, 200 mM sodium chloride, 5mM calcium chloride, 20μM zinc chloride, 0.02% brij). Twenty-five microliters of diluted enzyme is added per well of a 96 well microfluor plate. The enzyme is then diluted in a 1:4 ratio in the assay by the addition of inhibitor and substrate to give a final concentration in the assay of 100 mg/ml.

10 mM stock solutions of inhibitors are made up in dimethyl sulfoxide and then diluted in assay buffer as per the inhibitor dilution scheme for inhibition of human collagenase (MMP-1): Twenty-five microliters of each concentration is added in triplicate to the microfluor plate. The final concentrations in the assay are 30 μM, 3μM, 0.3 μM, and 0.03 μM.

Substrate (Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2) is prepared as for inhibition of human collagenase (MMP-1) and 50 μl is added to each well to give a final assay concentration of 10 μM. Fluorescence readings (360 nM excitation; 450 emission) are taken at time 0 and every 5 minutes for 1 hour.

Positive controls consist of enzyme and substrate with no inhibitor and blanks consist of substrate only.

IC_{50}'s are determined as per inhibition of human collagenase (MMP-1). If IC_{50}'s are reported to be less than 0.03 μM, inhibitors are then assayed at final concentrations of 0.3 μM, 0.03 μM, 0.003 μM and 0.0003 μM.

Inhibition of TNF Production

The ability of the compounds or the pharmaceutically acceptable salts thereof to inhibit the production of TNF and, consequently, demonstrate their effectiveness for treating diseases involving the production of TNF is shown by the following in vitro assay:

Human mononuclear cells were isolated from anti-coagulated human blood using a one-step Ficoll-hypaque separation technique. (2) The mononuclear cells were washed three times in Hanks balanced salt solution (HBSS) with divalent cations and resuspended to a density of 2 x 10^6 /ml in HBSS containing 1% BSA. Differential counts determined using the Abbott Cell Dyn 3500 analyzer indicated that monocytes ranged from 17 to 24% of the total cells in these preparations.

180μ of the cell suspension was aliquoted into flate bottom 96 well plates (Costar). Additions of compounds and LPS (100ng/ml final concentration) gave a final volume of 200μl. All conditions were performed in triplicate. After a four hour incubation at 37°C in an humidified CO_2 incubator, plates were removed and centrifuged (10 minutes at approximately 250 x g) and the supernatants removed and assayed for TNFα using the R&D ELISA Kit.

For administration to mammals, including humans, for the inhibition of matrix metalloproteinases or the production of tumor necrosis factor (TNF), a variety of conventional routes may be used including orally, parenterally and topically. In general, the active compound will be administered orally or parenterally at dosages between about 0.1 and 25 mg/kg body weight of the subject to be treated per day, preferably from about 0.3 to 5 mg/kg. However, some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

The compounds of the present invention can be administered in a wide variety of different dosage forms, in general, the therapeutically effective compounds of this invention are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelation and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof. In the case of animals, they are

advantageously contained in an animal feed or drinking water in a concentration of 5-5000 ppm, preferably 25 to 500 ppm.

For parenteral administration (intramuscular, intraperitoneal, subcutaneous and intravenous use) a sterile injectable solution of the active ingredient is usually prepared. Solutions of a therapeutic compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably adjusted and buffered, preferably at a pH of greater than 8, if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art. In the case of animals, compounds can be administered intramuscularly or subcutaneously at dosage levels of about 0.1 to 50 mg/kg/day, advantageously 0.2 to 10 mg/kg/day given in a single dose or up to 3 divided doses.

The present invention is illustrated by the following examples, but it is not limited to the details thereof.

EXAMPLE 1

2-Cyclohexyl-N-hydroxy-2-{(4-methoxybenzenesulfonyl)-[3-(4-methyl-aminopiperidin-1-yl)-3-oxopropyl]amino}acetamide

(A) To a solution of D-cyclohexylgycine benzyl ester hydrochloride (17.0 grams, 59.9 mmol) and triethylamine (17.6 mL, 126.3 mmol) in water (60 mL) and 1,4-dioxane (100 mL) was added 4-methoxybenzenesulfonyl chloride (13.0 grams, 62.9 mmol). The mixture was stirred at room temperature for 16 hours and then most of the solvent was removed by evaporation under vacuum. The mixture was diluted with ethyl acetate and was washed successively with dilute hydrochloric acid solution, water, saturated sodium bicarbonate solution, and brine. The organic solution was dried over magnesium sulfate and concentrated to leave N-(4-methoxybenzenesulfonyl)-D-cyclohexylglycine benzyl ester as a white solid, 24.51 grams (99%).

(B) N-(4-Methoxybenzenesulfonyl)-D-cyclohexylglycine benzyl ester (12.0 grams, 29.16 mmol) was added to a suspension of sodium hydride (0.78 grams, 32.5 mmol) in dry N,N-dimethylformamide (100 ml) and, after 20 minutes, tert-butyl-(3-iodopropoxy)-dimethylsilane(9.2 grams, 30.6 mmol) was added. The resulting mixture was stirred at

room temperature for 16 hours and was then quenched by addition of saturated ammonium chloride solution. The N,N-dimethylformamide was then removed by evaporation under vacuum. The residue was taken up in diethyl ether and washed successively with dilute hydrochloric acid solution, water and brine. After drying over magnesium sulfate, the diethyl ether was evaporated under vacuum to afford a yellow oil from which [[3-(tert-butyldimethylsilanyloxy)propyl](4-methoxy-benzenesulfonyl)-amino]cyclohexylacetic acid benzyl ester, a clear oil (13.67 grams, 79%), was isolated by flash chromatography on silica gel eluting with 10% ethyl acetate in hexane.

(C) To a solution of [[3-(tert-butyldimethylsilanyloxy)propyl](4-methoxybenzene-sulfonyl)amino]cyclohexylacetic acid benzyl ester (13.67 grams, 23.2 mmol) in methylene chloride (60 mL) at room temperature was added boron trifluoride etherate (21 mL, 171 mmol). After 20 minutes, the reaction was quenched by addition of saturated ammonium chloride solution and subsequent addition of ethyl acetate and water. The organic phase was separated, washed with brine and dried over magnesium sulfate. Evaporation of the solvent under vacuum gave an oil from which cyclohexyl[(3-hydroxypropyl)(4-methoxy-benzenesulfonyl)amino]acetic acid benzyl ester, a clear oil (11.25 grams, 100%), was isolated by flash chromatography on silica gel eluting with 20% ethyl acetate in hexane and then 40% ethyl acetate in hexane.

(D) Cyclohexyl[(3-hydroxypropyl)(4-methoxybenzenesulfonyl)amino]acetic acid benzyl ester (45.8 grams, 96 mmol) and sodium periodate (92.6 grams, 433 mmol) were dissolved in a mixture of acetonitrile (345 mL), carbon tetrachloride (345 mL) and water (460 mL). While cooling in an ice bath, ruthenium trichloride monohydrate (4.4 grams, 21 mmol) was then added. The resulting mixture was mechanically stirred with ice bath cooling for 30 minutes. The bath was removed and stirring was continued at room temperature for 4 hours. The reaction mixture was diluted with ethyl acetate and filtered through diatomaceous earth. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water and saturated brine. After drying over magnesium sulfate, the solvents were evaporated to give a dark oil from which 3-[(benzyloxycarbonylcyclohexylmethyl)-(4-methoxybenzenesulfonyl)amino]propionic acid, a white foam (28.1 grams, 60%), was isolated by flash chromatography on silica gel eluting sequentially with chloroform and 1% methanol in chloroform.

(E) To a solution of 3-[(benzyloxycarbonylcyclohexylmethyl)(4-methoxybenzenesulfonyl)-amino]propionic acid (1.57 grams, 3.21 mmol) in methylene chloride (45 mL) were added sequentially triethylamine (1.12 mL, 8.04 mmol), methylpiperidin-4-ylcarbamic acid tert-butyl ester (0.89 grams, 4.15 mmol) and (benzotriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluoroborate (1.56 grams, 3.53 mmol). The resulting mixture was stirred for 16 hours at room temperature and then diluted with methylene chloride. The solution was washed successively with 0.5 M hydrochloric acid solution, saturated sodium bicarbonate solution and brine. The solution was dried over magnesium sulfate and concentrated to yield an oil which was chromatographed on silica gel eluting with 50% ethyl acetate in hexane to afford [{3-[4-(tert-butoxycarbonylmethylamino)piperidin-1-yl]-3-oxopropyl}(4-methoxybenzenesulfonyl)amino]cyclohexylacetic acid benzyl ester as an oil (1.89 grams, 86%).

(F) To a solution of [{3-[4-(tert-butoxycarbonylmethylamino)piperidin-1-yl]-3-oxopropyl}(4-methoxybenzenesulfonyl)amino]cyclohexylacetic acid benzyl ester (1.89 grams, 2.76 mmol) in ethanol (90 mL) was added 10% palladium on activated carbon (0.32 grams). The mixture was agitated under 3 atmospheres hydrogen in a Parr shaker for 2 hours. The catalyst was removed by filtration through nylon (pore size 0.45 μm) and the solvent was evaporated leaving [{3-[4-(tert-butoxycarbonylmethylamino)piperidin-1-yl]-3-oxo-propyl}(4-methoxybenzenesulfonyl)amino]cyclohexylacetic acid as a white foam (1.65 grams, 100%).

(G) To a solution of [{3-[4-(tert-butoxycarbonylmethylamino)piperidin-1-yl]-3-oxopropyl}(4-methoxybenzenesulfonyl)amino]cyclohexylacetic acid (1.65 grams, 2.76 mmol) in methylene chloride (30 mL) were added sequentially O-benzylhydroxylamine hydrochloride (0.47 grams, 2.94 mmol), triethylamine (1.25 mL, 9.0 mmol) and (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluoroborate (1.36 grams, 3.07 mmol). The resulting mixture was stirred for 24 hours at room temperature and then concentrated in vacuo. The residue was taken up in ethyl acetate and washed successively with 0.5 M hydrochloric acid solution, water, saturated sodium bicarbonate solution and brine. The solution was dried over magnesium sulfate and concentrated to yield an oil which was chromatographed on silica gel eluting with 40% hexane in ethylacetatetoafford(1-{3-[(benzyloxycarbamoylcyclohexylmethyl)(4-methoxybenzenesulfonyl)amino]-propionyl}piperidin-4-yl)methylcarbamic acid tert-butyl esteras a clear oil (1.86 grams, 96%).

(H) To a solution of (1-{3-[(benzyloxycarbamoylcyclohexylmethyl)(4-methoxy-benzenesulfonyl)amino]propionyl}piperidin-4-yl)methylcarbamic acid tert-butyl ester (1.86 grams, 2.65 mmol) in methanol (80 mL) was added 5% palladium on barium sulfate (0.85 grams). The mixture was agitated under 3 atmospheres hydrogen in a Parr shaker for 2.5 hours. The catalyst was removed by filtration through nylon (pore size 0.45 μm) and the solvent was evaporated leaving (1-{3-[(cyclohexylhydroxycarbamoylmethyl)(4-methoxybenzene-sulfonyl)amino]propionyl}piperidin-4-yl)methylcarbamic acid tert-butyl esteras a white foam (1.53 grams, 95%).

The title compounds of examples 2-8 were prepared analogously to that described in Example 1 using D-valine benzyl ester as the starting material in step A and the indicated amine in step E.

EXAMPLE 2

Acetic acid 1-{3-[(1-hydroxycarbamoyl-2-methylpropyl)(4-methoxybenzene-sulfonyl)-amino]propionyl}piperidin-4-yl ester

Coupled with acetic acid piperidin-4-yl ester. MS: 500 (M+1).

EXAMPLE 3

Butyric acid 1-{3-[(1-hydroxycarbamoyl-2-methylpropyl)-(4-methoxy-benzenesulfonyl)-amino]propionyl}piperidin-4-yl ester

Coupled with butyric acid piperidin-4-yl ester. MS: 528 (M+1).

EXAMPLE 4

Benzoic acid 1-{3-[(1-hydroxycarbamoyl-2-methylpropyl)(4-methoxy-benzene-sulfonyl)amino]propionyl}piperidin-4-yl ester

Coupled with benzoic acid piperidin-4-yl ester. MS: 562 (M+1). Analysis Calculated for $C_{27}H_{35}N_3O_8S \cdot 1.75\ H_2O$: C, 54.67; H, 6.54; N, 7.08. Found: C, 54.52, H, 6.14; N, 7.85.

Example 5

N-Hydroxy-2-[[3-(4-hydroxypiperidin-1-yl)-3-oxopropyl]-(4-methoxy-benzene-sulfonyl)amino]-3-methylbutyramide

Coupled with 4-hydroxypiperidine. MS: 458 (M+1). Analysis calculated for $C_{20}H_{31}N_3O_7S \cdot H_2O$: C, 50.51; H, 6.99; N, 8.84. Found: C, 50.04; H, 6.84; N, 9.14.

EXAMPLE 6

(1-{3-[(1-Hydroxycarbamoyl-2-methylpropyl)(4-methoxybenzenesulfonyl)-amino]-propionyl}piperidin-4-yl)-methylcarbamic acid tert-butyl ester

Coupled with methyl-piperidin-4-ylcarbamic acid tert-butyl ester.

EXAMPLE 7

1-{3-[(1-Hydroxycarbamoyl-2-methylpropyl)(4-methoxybenzenesulfonyl)-amino]-propionyl}piperidine-4-carboxylic acid ethyl ester

Coupled with piperidine-4-carboxylic acid ethyl ester. MS: 513 (M+1).

EXAMPLE 8

(4-{3-[(1-Hydroxycarbamoyl-2-methylpropyl)(4-methoxybenzenesulfonyl)-amino]-propionyl}piperazin-1-yl)-acetic acid ethyl ester

Coupled with piperazin-1-ylacetic acid ethyl ester. HRMS calculated for $C_{23}H_{37}N_4O_8S$(M+1): 529.2332. Found: 529.2366.

The title compounds of Examples 9-10 were prepared analogously to that described in Example 1 using D-leucine benzyl ester as the starting material in step A and the indicated amine in step E.

EXAMPLE 9

(1-{3-[(1-Hydroxycarbamoyl-3-methylbutyl)(4-methoxybenzenesulfonyl)-amino]-propionyl}piperidin-4-yl)methylcarbamic acid tert-butyl ester

Coupled with methyl-piperidin-4-ylcarbamic acid tert-butyl ester. MS: 585 (M+1).

EXAMPLE 10

1-{3-[(1-Hydroxycarbamoyl-3-methylbutyl)-(4-methoxybenzenesulfonyl)-amino]-propionyl}piperidine-4-carboxylic acid ethyl ester

Coupled with piperidine-4-carboxylic acid ethyl ester. Melting pont 78-80°C. MS: 528 (M+1).

The title compounds of Examples 11-13 were prepared analogously to that described in Example 1 using D-norleucine benzyl ester as the starting material in step A and the indicated amine or alcohol in step E.

EXAMPLE 11

(1-{3-[(1-Hydroxycarbamoylpentyl)(4-methoxybenzenesulfonyl)amino]-propionyl}piperidin-4-yl)methylcarbamic acid tert-butyl ester

Coupled with methyl-piperidin-4-ylcarbamic acid tert-butyl ester.

EXAMPLE 12

1-{3-[(1-Hydroxycarbamoylpentyl)(4-methoxybenzenesulfonyl)amino]-propionyl}piperidine-4-carboxylic acid ethyl ester

Coupled with piperidine-4-carboxylic acid ethyl ester. MS: 528 (M+1).

EXAMPLE 13

3-[(1-Hydroxycarbamoylpentyl)(4-methoxybenzenesulfonyl)amino]-propionic acid indan-5-yl ester

Coupled with 5-indanol. MS: 505 (M+1).

The title compounds of Examples 14-15 were prepared analogously to that described in Example 1 using D-tert-butylalanine benzyl ester as the starting material in step A and the indicated amine in step E.

EXAMPLE 14

(1-{3-[(1-Hydroxycarbamoyl-3,3-dimethylbutyl)-(4-methoxybenzene-sulfonyl)-amino]propionyl}piperidin-4-yl)methylcarbamic acid tert-butyl ester

Coupled with methyl-piperidin-4-ylcarbamic acid tert-butyl ester. MS: 599 (M+1).

EXAMPLE 15

1-{3-[(1-Hydroxycarbamoyl-3,3-dimethylbutyl)(4-methoxy-benzenesulfonyl)-amino]propionyl}piperidine-4-carboxylic acid ethyl ester

Coupled with piperidine-4-carboxylic acid ethyl ester. MS: 542 (M+1).

The title compounds of Examples 16-18 were prepared analogously to that described in Example 1 using D-cyclohexylglycine benzyl ester as the starting material in step A and the indicated amine or alcohol in step E.

EXAMPLE 16

2-Cyclohexyl-N-hydroxy-2-[[3-(4-hydroxypiperidin-1-yl)-3-oxopropyl]-(4-methoxy-benzenesulfonyl)amino]acetamide

Coupled with 4-hydroxypiperidine. MS: 498 (M+1). Analysis calculated for $C_{23}H_{35}N_3O_7S \bullet 0.5H_2O$: C, 54.53; H, 7.16; N, 8.29. Found: C, 54.21; H, 6.98; N, 8.21.

EXAMPLE 17

1-{3-[(Cyclohexylhydroxycarbamoylmethyl)(4-methoxybenzenesulfonyl)-amino]propionyl}piperidine-4-carboxylic acid ethyl ester

Coupled with piperidine-4-carboxylic acid ethyl ester. MS: 554 (M+1). Analysis calculated for $C_{26}H_{39}N_3O_8S \bullet 0.5H_2O$: C, 55.59; H, 7.16; N, 7.47. Found: C, 55.53; H, 7.18; N, 7.57.

EXAMPLE 18

3-[(Cyclohexylhydroxycarbamoylmethyl)-(4-methoxybenzenesulfonyl)-amino]-propionic acid indan-5-yl ester

Coupled with 5-indanol. MS: 531 (M+1). Analysis calculated for $C_{27}H_{34}N_2O_7S \bullet H_2O$: C, 59.11; H, 6.61; N, 5.10. Found: C, 59.40; H, 6.17; N, 5.06.

The title compounds of Examples 19-20 were prepared analogously to that described in Example 1 using D-phenylalanine benzyl ester as the starting material in step A and the indicated amine in step E.

EXAMPLE 19

(1-{3-[(1-Hydroxycarbamoyl-2-phenylethyl)(4-methoxybenzenesulfonyl)-amino]-propionyl}piperidin-4-yl)methylcarbamic acid tert-butyl ester

Coupled with methyl-piperidin-4-ylcarbamic acid tert-butyl ester. MS: 619 (M+1).

EXAMPLE 20

1-{3-[(1-Hydroxycarbamoyl-2-phenylethyl)-(4-methoxybenzenesulfonyl)-amino]-propionyl}piperidine-4-carboxylic acid ethyl ester

Coupled with piperidine-4-carboxylic acid ethyl ester. MS: 561 (M+1).

The title compounds of Examples 21-22 were prepared analogously to that described in Example 1 using D-4-fluorophenylalanine benzyl ester as the starting material in step A and the indicated amine in step E.

EXAMPLE 21

(1-{3-[[2-(4-Fluorophenyl)-1-hydroxycarbamoylethyl]-(4-methoxy-benzene-sulfonyl)amino]propionyl}piperidin-4-yl)methylcarbamic acid tert-butyl ester

Coupled with methyl-piperidin-4-ylcarbamic acid tert-butyl ester.

EXAMPLE 22

1-{3-[[2-(4-Fluorophenyl)-1-hydroxycarbamoylethyl](4-methoxy-benzenesulfonyl) amino]propionyl}piperidine-4-carboxylic acid ethyl ester

Coupled with piperidine-4-carboxylic acid ethyl ester. MS: 580 (M+1). Analysis calculated for $C_{27}H_{34}FN_3O_8S$: C, 55.95; H, 5.91; N, 7.25. Found: C, 55.72; H, 5.79; N, 7.08.

The title compounds of Examples 23-24 were prepared analogously to that described in Example 1 using D-4-homophenylalanine benzyl ester as the starting material in step A and the indicated amine in step E.

EXAMPLE 23

(1-{3-[(1-Hydroxycarbamoyl-3-phenylpropyl)-(4-methoxybenzene-sulfonyl)-amino]propionyl}piperidin-4-yl)methylcarbamic acid tert-butyl ester

Coupled with tert-butyl ester using methyl-piperidin-4-ylcarbamic acid tert-butyl ester. MS: 633 (M+1).

EXAMPLE 24

1-{3-[(1-Hydroxycarbamoyl-3-phenylpropyl)-(4-methoxybenzene-sulfonyl)amino]-propionyl}piperidine-4-carboxylic acid ethyl ester

Coupled with piperidine-4-carboxylic acid ethyl ester. MS: 576 (M+1).

The title compounds of Examples 27-28 were prepared analogously to that described in Example 1 using D-O-tert-butylserine benzyl ester as the starting material in step A and the indicated amine in step E.

EXAMPLE 25

(1-{3-[(2-tert-Butoxy-1-hydroxycarbamoylethyl)(4-methoxybenzene-sulfonyl)-amino]propionyl}piperidin-4-yl)methylcarbamic acid tert-butyl ester

Coupled with methyl-piperidin-4-ylcarbamic acid tert-butyl ester. MS: 615 (M+1).

EXAMPLE 26

1-{3-[(2-tert-Butoxy-1-hydroxycarbamoylethyl)(4-methoxy-benzenesulfonyl)-amino]propionyl}piperidine-4-carboxylic acid ethyl ester

Coupled with piperidine-4-carboxylic acid ethyl ester. MS: 558 (M+1).

The title compounds of Examples 27-28 were prepared analogously to that described in Example 1 using D-cyclohexylalanine benzyl ester as the starting material in step A and the indicated amine in step E.

EXAMPLE 27

(1-{3-[(2-Cyclohexyl-1-hydroxycarbamoylethyl)-(4-methoxy-benzene-sulfonyl)-amino]propionyl}piperidin-4-yl)methylcarbamic acid tert-butyl ester

Coupled with methyl-piperidin-4-ylcarbamic acid tert-butyl ester. MS: 625 (M+1).

EXAMPLE 28

1-{3-[(2-Cyclohexyl-1-hydroxycarbamoylethyl)(4-methoxy-benzenesulfonyl)-amino]propionyl}piperidine-4-carboxylic acid ethyl ester

Coupled with piperidine-4-carboxylic acid ethyl ester. MS: 568 (M+1).

The title compounds of Examples 29-30 were prepared analogously to that described in Example 1 using D-1-naphthylalanine benzyl ester as the starting material in step A and the indicated amine in step E.

EXAMPLE 29

(1-{3-[(1-Hydroxycarbamoyl-2-naphthalen-1-ylethyl)-(4-methoxy-benzenesulfonyl)amino]propionyl}piperidin-4-yl)methylcarbamic acid tert-butyl ester

Coupled with methylpiperidin-4-ylcarbamic acid tert-butyl ester.

EXAMPLE 30

1-{3-[(1-Hydroxycarbamoyl-2-naphthalen-1-ylethyl)(4-methoxybenzene-sulfonyl)amino]propionyl}piperidine-4-carboxylic acidethyl ester

Coupled with piperidine-4-carboxylic acid ethyl ester. MS: 611 (M+1).

EXAMPLE 31

2-Cyclohexyl-N-hydroxy-2-{(4-methoxybenzenesulfonyl)-[3-(4-methyl-amino-piperidin-1-yl)-3-oxopropyl]-amino}acetamide

A solution of 1-{3-[(cyclohexylhydroxycarbamoylmethyl)(4-methoxybenzene-sulfonyl)-amino]-propionyl}piperidin-4-yl)methylcarbamic acid tert-butyl ester (1.53 grams, 2.50 mmol) in methylene chloride (70 mL) was bubbled with hydrochloric acid gas for 2 minutes. The ice bath was removed and the reaction mixture was allowed to stir at room temperature for 1 hour. The solvent was evaporated and twice methanol was added to the residue and evaporated leaving 2-cyclohexyl-N-hydroxy-2-{(4-methoxybenzenesulfonyl)-[3-(4-methylaminopiperidin-1-yl)-3-oxopropyl]-amino}acetamide hydrochloride dihydrate as a white solid (1.22 grams, 90%). MS: 511 (M+1). Analysis calculated for $C_{24}H_{39}ClN_4O_6S \cdot 2H_2O$: C, 49.43; H, 7.43; N, 9.61. Found: C, 49.86; H, 7.23; N, 9.69.

The title compounds of Examples 32-41 were prepared analogously to that described in Example 33 using the starting material indicated.

EXAMPLE 32

N-Hydroxy-2-{(4-methoxybenzenesulfonyl)[3-(4-methylaminopiperidin-1-yl)-3-oxopropyl]amino}-3-methylbutyramide hydrochloride

Starting material: (1-{3-[(1-hydroxycarbamoyl-2-methylpropyl)(4-methoxybenzene-sulfonyl)-amino]propionyl}piperidin-4-yl)-methylcarbamic acid tert-butyl ester using methyl-piperidin-4-ylcarbamic acid tert-butyl. MS: 471 (M+1).

EXAMPLE 33

2-{(4-Methoxybenzenesulfonyl)-[3-(4-methylaminopiperidin-1-yl)-3-oxo-propyl]-amino}4-methylpentanoic acid hydroxyamide hydrochloride

Starting material: (1-{3-[(1-hydroxycarbamoyl-3-methylbutyl)(4-methoxybenzene-sulfonyl)amino]propionyl}piperidin-4-yl)methylcarbamic acid tert-butyl ester. Melting Point 170-173°C. MS: 485 (M+1).

EXAMPLE 34

2-{(4-Methoxybenzenesulfonyl)-[3-(4-methylaminopiperidin-1-yl)-3-oxo-propyl] amino}hexanoic acid hydroxyamide hydrochloride

Starting material: (1-{3-[(1-hydroxycarbamoylpentyl)-(4-methoxybenzenesulfonyl)-amino]-propionyl}piperidin-4-yl)methyl-carbamic acid tert-butyl ester. MS: 485 (M+1). Analysis calculated for $C_{21}H_{34}N_4O_6S \bullet HCl \bullet 4H_2O$: C, 43.5; H, 7.48; N, 9.67. Found: C, 43.65; H, 7.03; N, 9.79.

EXAMPLE 35

2-{(4-Methoxybenzenesulfonyl)-[3-(4-methylaminopiperidin-1-yl)-3-oxo-propyl] amino}-4,4-dimethylpentanoic acid hydroxyamide hydrochloride

Starting material: (1-{3-[(1-hydroxy-carbamoyl-3,3-dimethylbutyl)(4-methoxy-benzenesulfonyl)amino]propionyl}piperidin-4-yl)methylcarbamic acid tert-butyl ester. MS: 499 (M+1).

EXAMPLE 36

N-Hydroxy-2-{(4-methoxybenzenesulfonyl)-[3-(4-methylaminopiperidin-1-yl)-3-oxopropyllamino}-3-phenylpropionamide hydrochloride

Starting material: (1-{3-[(1-hydroxycarbamoyl-2-phenylethyl)(4-methoxybenzene-sulfonyl)-amino]propionyl}piperidin-4-yl)methylcarbamic acid tert-butyl ester. MS: 519 (M+1).

EXAMPLE 37

3-(4-Fluorophenyl)-N-hydroxy-2-{(4-methoxybenzenesulfonyl)-[3-(4-methylamino piperidin-1-yl)-3-oxo-propyllamino}propionamide hydrochloride

Starting material: (1-{3-[[2-(4-fluorophenyl)-1-hydroxycarbamoylethyl]-(4-methoxy-benzenesulfonyl)amino]propionyl}-piperidin-4-yl)methylcarbamic acid tert-butyl ester (Example 21). MS: 537 (M+1). Analysis calculated for

$C_{25}H_{33}FN_4O_6S \bullet HCl \bullet 2H_2O$: C, 49.30; H, 6.29; N, 9.20. Found: C, 49.14; H, 5.82; N, 9.24.

EXAMPLE 38

N-Hydroxy-2-{(4-methoxybenzenesulfonyl)-[3-(4-methylaminopiperidin-1-yl)-3-oxopropyllamino}-4-phenylbutyramide hydrochloride

Starting material: (1-{3-[(1-hydroxycarbamoyl-3-phenylpropyl)(4-methoxy-benzenesulfonyl)amino]propionyl}piperidin-4-yl)methylcarbamic acid tert-butyl ester. Melting Point 160-170°C. MS: 533 (M+1). Analysis calculated for $C_{26}H_{36}N_4O_6S \bullet HCl \bullet 1.5H_2O$: C, 52.38; H, 6.76; N, 9.40. Found: C, 52.25; H, 6.40; N, 9.00.

EXAMPLE 39

3-tert-Butoxy-N-hydroxy-2-{(4-methoxybenzenesulfonyl)-[3-(4-methyl-amino-piperidin-1-yl)-3-oxopropyl]-amino}propionamide hydrochloride

Starting material: (1-{3-[(2-tert-butoxy-1-hydroxycarbamoylethyl)(4-methoxy-benzenesulfonyl)amino]propionyl}piperidin-4-yl)methylcarbamic acid tert-butyl ester. MS: 515 (M+1).

EXAMPLE 40

3-Cyclohexyl-N-hydroxy-2-{(4-methoxybenzenesulfonyl)-[3-(4-methyl-amino-piperidin-1-yl)-3-oxopropyllamino}propionamide hydrochloride

Starting material: (1-{3-[(2-cyclohexyl-1-hydroxycarbamoylethyl)-(4-methoxy-benzenesulfonyl)amino]propionyl}piperidin-4-yl)methylcarbamic acid tert-butyl ester. MS: 525 (M+1).

EXAMPLE 41

N-Hydroxy-2-{(4-methoxybenzenesulfonyl)-[3-(4-methylaminopiperidin-1-yl)-3-oxopropyllamino}-3-naphthalen-1-ylpropionamide hydrochloride

Starting material: (1-{3-[(1-hydroxy-carbamoyl-2-naphthalen-1-ylethyl)-(4-methoxy-benzenesulfonyl)amino]propionyl}-piperidin-4-yl)methylcarbamic acid tert-butyl ester. MS: 569 (M+1).

EXAMPLE 42

1-{3-[(Cyclohexylhydroxycarbamoylmethyl)-(4-methoxybenzenesulfonyl)-amino]-propionyl}piperidine-4-carboxylic acid

To a solution of 1-{3-[(cyclohexylhydroxycarbamoylmethyl)(4-methoxy-benzenesulfonyl)amino]propionyl}piperidine-4-carboxylic acid ethyl ester (0.62 grams, 1.16 mmol) (Example 17) in ethanol (45 mL) and water (5 mL) was added lithium hydroxide monohydrate (0.24 grams, 5.72 mmol). After stirring for 3 hours at room temperature ethanol-washed Amberlite IR-120 plus ion exchange resin (6 grams) was added. Stirring was continued for 15 minutes and then the mixture was filtered. The filtrate was concentrated in vacuo to give 1-{3-[(cyclohexylhydroxycarbamoylmethyl)-(4-methoxy-benzenesulfonyl)amino]propionyl}-piperidine-4-carboxylic acid monohydrate as a white solid (0.52 grams, 88%). MS: 526 (M+1). Analysis calculated for $C_{24}H_{35}N_3O_8S \bullet H_2O$: C, 53.03; H, 6.86; N, 7.73. Found: C, 53.53; H, 7.15; N, 7.70.

The title compounds of Examples 43-53 were prepared analogously to that described in Example 45 using the starting material indicated.

EXAMPLE 43

1-{3-[(1-Hydroxycarbamoyl-2-methylpropyl)(4-methoxybenzene-sulfonyl)amino]propionyl}piperidine-4-carboxylic acid

Starting material: 1-{3-[(1-hydroxycarbamoyl-2-methylpropyl)(4-methoxybenzene-sulfonyl)amino]propionyl}piperidine-4-carboxylic acid ethyl ester. MS: 486 (M+1).

EXAMPLE 44

(4-{3-[(1-Hydroxycarbamoyl-2-methylpropyl)(4-methoxybenzene-sulfonyl)amino]propionyl}piperazin-1-yl)acetic acid

Starting material: (4-{3-[(1-hydroxycarbamoyl-2-methylpropyl)(4-methoxybenzene-sulfonyl)amino]-propionyl}piperazin-1-yl)acetic acid ethyl ester (Example 8). MS: 500 (M+1).

EXAMPLE 45

1-{3-[(1-Hydroxycarbamoyl-3-methylbutyl)-(4-methoxybenzenesulfonyl)-amino]-propionyl}piperidine-4-carboxylic acid

Starting material: 1-{3-[(1-hydroxycarbamoyl-3-methylbutyl)(4-methoxybenzene-sulfonyl)-amino]propionyl}piperidine-4-carboxylic acid ethyl ester. Melting Point 118-120°C. MS: 500 (M+1).

EXAMPLE 46

1-{3-[(1-Hydroxycarbamoylpentyl)(4-methoxybenzenesulfonyl)amino]-propionyl}piperidine-4-carboxylic acid

Starting material: 1-{3-[(1-hydroxycarbamoylpentyl)(4-methoxybenzenesulfonyl)-amino]propionyl}piperidine-4-carboxylic acid ethyl ester. MS: 500 (M+1).

EXAMPLE 47

1-{3-[(1-Hydroxycarbamoyl-3,3-dimethylbutyl)(4-methoxy-benzene-sulfonyl)-amino]propionyl}piperidine-4-carboxylic acid

Starting material: 1-{3-[(1-hydroxycarbamoyl-3,3-dimethylbutyl)(4-methoxybenzene-sulfonyl)-amino]propionyl}piperidine-4-carboxylic acid ethyl ester. MS: 514 (M+1).

EXAMPLE 48

1-{3-[(1-Hydroxycarbamoyl-2-phenylethyl)-(4-methoxybenzenesulfonyl)-amino]-propionyl}piperidine-4-carboxylic acid

Starting material: 1-{3-[(1-hydroxycarbamoyl-2-phenyl-ethyl)(4-methoxybenzene-sulfonyl)-amino]propionyl}piperidine-4-carboxylic acid ethyl ester. MS: 534 (M+1).

EXAMPLE 49

1-{3-[[2-(4-Fluorophenyl)-1-hydroxycarbamoylethyl](4-methoxybenzene-sulfonyl)amino]propionyl}piperidine-4-carboxylic acid

Starting material: 1-{3-[[2-(4-fluorophenyl)-1-hydroxycarbamoylethyl](4-methoxy-benzenesulfonyl)amino]propionyl}piperidine-4-carboxylic acid ethyl ester.
MS: 552 (M+1). Analysis calculated form $C_{25}H_{30}FN_3O_8S \cdot 0.5H_2O$: C, 53.56; H, 5.57; N, 7.50. Found: C, 53.53; H, 5.39; N, 7.28.

EXAMPLE 50

1-{3-[(1-Hydroxycarbamoyl-3-phenylpropyl)(4-methoxybenzenesulfonyl)-amino]-propionyl}piperidine-4-carboxylic acid

Starting material: 1-{3-[(1-hydroxycarbamoyl-3-phenyl-propyl)-(4-methoxybenzene-sulfonyl)-amino]propionyl}piperidine-4-carboxylic acid ethyl ester. Melting Point 85-92°C. MS: 598 (M+1).

EXAMPLE 51

1-{3-[(2-tert-Butoxy-1-hydroxycarbamoylethyl)(4-methoxybenzene-sulfonyl)-amino]propionyl}piperidine-4-carboxylic acid

Starting material: 1-{3-[(2-tert-butoxy-1-hydroxycarbamoylethyl)(4-methoxy-benzenesulfonyl)-amino]propionyl}piperidine-4-carboxylic acid ethyl ester.
MS: 529 (M+1).

EXAMPLE 52

1-{3-[(2-Cyclohexyl-1-hydroxycarbamoylethyl)(4-methoxybenzene-sulfonyl)-amino]propionyl}piperidine-4-carboxylic acid

Starting material: 1-{3-[(2-cyclohexyl-1-hydroxycarbamoylethyl)(4-methoxy-benzenesulfonyl)amino]propionyl}piperidine-4-carboxylic acid ethyl ester.
MS: 540 (M+1).

EXAMPLE 53

1-{3-[(1-Hydroxycarbamoyl-2-naphthalen-1-ylethyl)(4-methoxybenzene-sulfonyl) amino]propionyl}piperidine-4-carboxylic acid

Starting material: 1-{3-[(1-hydroxycarbamoyl-2-naphthalen-1-ylethyl)(4-methoxy-benzenesulfonyl)amino]propionyl}piperidine-4-carboxylic acidethyl ester.
MS: 584 (M+1).

EXAMPLE 54

N-Hydroxy-2-[{3-[4-(2-hydroxyethyl)piperazin-1-yl]-3-oxopropyl}-(4-methoxyben zenesulfonyl)amino]-3-methylbutyramide

(A) To a solution of 2-[(2-carboxyethyl)-(4-methoxybenzenesulfonyl)amino]-3-methylbutyric acid benzyl ester(prepared staring from D-valine benzyl ester according to the procedure of Example 1, steps A to D) (1.35 grams, 3.0 mmol) in methylene chloride (45 mL) were added sequentially triethylamine (0.92 mL, 6.9 mmol),

2-piperazin-1-ylethanol (0.43 grams, 3.3 mmol) and (benzotriazol-1-yloxy)tris-(dimethylamino)-phosphonium hexafluoroborate (1.53 grams, 3.45 mmol). The resulting mixture was stirred for 16 hours at room temperature and then concentrated in vacuo. The residue was taken up in ethyl acetate and washed with saturated sodium bicarbonate solution and brine. The solution was dried over magnesium sulfate and concentrated to yield an oil which was chromatographed on silica gel eluting with 5% methanol in chloroform to afford 2-[{3-[4-(2-hydroxyethyl)piperazin-1-yl]-3-oxo-propyl}(4-methoxybenzenesulfonyl)amino]-3-methylbutyric acid benzyl esteras an oil (1.40 grams, 83%). Conversion to the hydrochloride salt was subsequently carried out using anhydrous hydrochloric acid in cold (0°C) methylene chloride.

(B) To a solution of 2-[{3-[4-(2-hydroxyethyl)piperazin-1-yl]-3-oxopropyl}-(4-methoxy-benzenesulfonyl)amino]-3-methylbutyric acid benzyl ester hydrochloride (1.49 grams, 2.49 mmol) in ethanol (80 mL) was added 10% palladium on activated carbon (0.11 grams). The mixture was agitated under 3 atmospheres hydrogen in a Parr shaker for 16 hours. The catalyst was removed by filtration through nylon (pore size 0.45 μm) and the solvent was evaporated leaving 2-[{3-[4-(2-hydroxyethyl)piperazin-1-yl]-3-oxo-propyl}(4-methoxybenzenesulfonyl)amino]-3-methylbutyric acid hydrochloride as a white solid (1.16 grams, 92%).

(C) To a solution of 2-[{3-[4-(2-hydroxyethyl)piperazin-1-yl]-3-oxo-propyl}(4-methoxy-benzenesulfonyl)amino]-3-methylbutyric acid hydrochloride (1.10 grams, 2.17 mmol) in methylene chloride (50 mL) and N,N-dimethylformamide (0.5 mL) were added sequentially O-benzylhydroxylamine hydrochloride (0.41 grams, 2.60 mmol), triethylamine (0.91 mL, 6.5 mmol) and (benzotriazol-1-yloxy)tris-(dimethylamino)-phosphonium hexafluoroborate (1.20 grams, 2.71 mmol). The resulting mixture was stirred for 16 hours at room temperature and then concentrated in vacuo. The residue was taken up in ethyl acetate and washed successively with saturated sodium bicarbonate solution, water and brine. The solution was dried over magnesium sulfate and concentrated to yield an oil which was chromatographed on silica gel eluting with 3% methanol in chloroform to afford N-benzyloxy-2-[{3-[4-(2-hydroxyethyl)piperazin-1-yl]-3-oxopropyl}(4-methoxybenzenesulfonyl)am

ino]-3-methylbutyramide as a clear oil (0.85 grams, 68%). Conversion to the hydrochloride salt was subsequently carried out using anhydrous hydrochloric acid in cold (0°C) methylene chloride.

(D) To a solution of N-benzyloxy-2-[{3-[4-(2-hydroxyethyl)piperazin-1-yl]-3-oxopropyl}-(4-methoxybenzenesulfonyl)amino]-3-methylbutyramide hydrochloride (0.39 grams, 0.63 mmol) in methanol (30 mL) was added 5% palladium on barium sulfate (0.19 grams). The mixture was agitated under 3 atmospheres hydrogen in a Parr shaker for 2.25 hours. The catalyst was removed by filtration through nylon (pore size 0.45 μm) and the solvent was evaporated to a tan foam which was chromatographed on silica gel eluting with 15% methanol in chloroform containing 0.5% ammonium hydroxide. Clean fractions containing the desired product were taken up in saturated sodium bicarbonate solution. The resulting mixture was extracted several times with ethyl acetate and the combined extracts were concentrated to afford N-hydroxy-2-[{3-[4-(2-hydroxyethyl)piperazin-1-yl]-3-oxopropyl}-(4-methoxybenzenesulfonyl)amino]-3-methyl-butyramide as an oil. The hydrochloride salt (0.20 grams, 61%) was formed using anhydrous hydrochloric acid in cold (0°C) methanol. MS: 487 (M+1). Analysis calculated for $C_{21}H_{34}N_4O_7S \cdot HCl \cdot 0.5H_2O$: C, 47.41; H, 6.82; N, 10.53. Found: C, 47.41; H, 7.11; N, 9.91.

The title compounds of Examples 55-57 were prepared analogously to that described in Example 58 using the indicated amine in step A.

EXAMPLE 55

2-[[3-(4-Dimethylaminopiperidin-1-yl)-3-oxopropyl](4-methoxybenzene-sulfonyl)amino]-N-hydroxy-3-methylbutyramide

Coupled with dimethylpiperidin-4-ylamine. MS: 485 (M+1).

EXAMPLE 56

N-Hydroxy-2-[{3-[4-(3-hydroxypropyl)piperazin-1-yl]-3-oxopropyl}-(4-methoxybenzenesulfonyl)amino]-3-methylbutyramide

Coupled with 3-piperazin-1-ylpropan-1-ol. MS: 500 (M+1).

EXAMPLE 57

2-[(3-[1,4']Bipiperidinyl-1'-yl-3-oxopropyl)-(4-methoxybenzenesulfonyl)-amino]-N-hydroxy-3-methylbutyramide

Coupled with using [1,4']bipiperidinyl. MS: 525 (M+1). Analysis calculated for $C_{25}H_{40}N_4O_6S \bullet HCl \bullet 1.5H_2O$: C, 51.05; H, 7.54; N, 9.52. Found: C, 50.80; H, 7.45; N, 9.36.

EXAMPLE 58

1-{3-[(1-Hydroxycarbamoyl-2-methylpropyl)-(4-phenoxybenzenesulfonyl) amino] propionyl] piperidine-4-carboxylic acid ethyl ester

The title compound was prepared analogously to that described in Example 1 using D-valine benzyl ester and 4-phenoxybenzenesulfonyl chloride as the starting materials in step A and piperidine-4-carboxylic acid ethyl ester in step E. Analysis calculated for $C_{28}H_{37}N_3O_8S$. $0.1CH_2Cl_2$: C, 57.78; H, 6.42; N, 7.19. Found: C, 57.46; H, 6.41; N, 7.11.

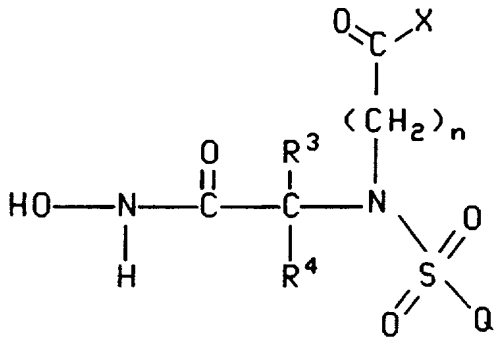
EXAMPLE 59

1-{3-[(1-Hydroxycarbamoyl-2-methylpropyl)-(4-phenoxybenzenesulfonyl) amino] propionyl]piperidine-4-carboxylic acid

The title compound was prepared analogously to that described in Example 42 using 1-{3-[(1-hydroxycarbamoyl-2-methylpropyl)-(4-phenoxybenzenesulfonyl)amino] propionyl]piperidine-4-carboxylic acid ethyl ester (Example 58) as the starting material. MS: 548 (M+1). Analysis calculated for $C_{26}H_{33}N_3O_8S$. $0.5H_2O$: C, 56.10; H, 6.16; N, 7.75. Found: C, 55.99; H, 6.06; N, 7.43.

CLAIMS

1. A compound of the formula

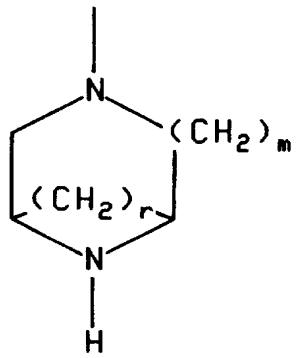


I

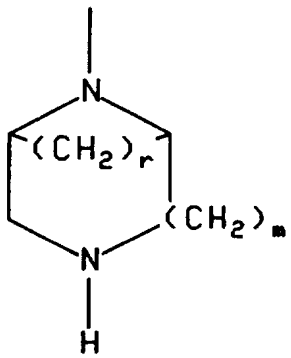
or the pharmaceutically acceptable salts thereof, wherein

n is 1 to 6;

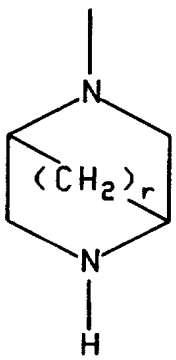
X is OR^1 wherein R^1 is as defined below; azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, piperazinyl or a bridged diazabicycloalkyl ring selected from the group consisting of



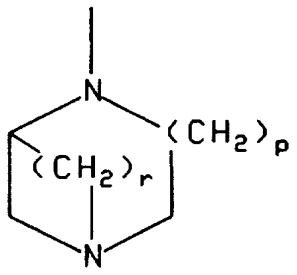
a



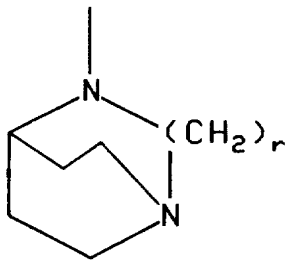
b



c



d



e

wherein r is 1, 2 or 3;

m is 1 or 2; and

p is 0 or 1;

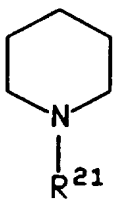
wherein each heterocyclic group may optionally be substituted by one or two groups selected from hydroxy, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $(C_1$-$C_{10})$acyl, $(C_1$-$C_{10})$acyloxy, $(C_6$-$C_{10})$aryl, $(C_5$-$C_9)$heteroaryl, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkyl, $(C_5$-$C_9)$heteroaryl $(C_1$-$C_6)$alkyl, hydroxy $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$acyloxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylthio, $(C_1$-$C_6)$alkylthio $(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$arylthio, $(C_6$-$C_{10})$ arylthio$(C_1$-$C_6)$alkyl, $R^9R^{10}N$, $R^9R^{10}NSO_2$, $R^9R^{10}NCO$, $R^9R^{10}NCO(C_1$-$C_6)$alkyl wherein R^9 and R^{10} are each independently hydrogen, $(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$aryl, $(C_5$-$C_9)$heteroaryl, $(C_6$-$C_{10})$aryl $(C_1$-$C_6)$alkyl or $(C_5$-$C_9)$heteroaryl $(C_1$-$C_6)$alkyl or R^9 and R^{10} may be taken together with the nitrogen to which they are attached to form an azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl or thiomorpolinyl ring; $R^{12}SO_2$, $R^{12}SO_2NH$ wherein R^{12} is trifluoromethyl, $(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$aryl, $(C_5$-$C_9)$heteroaryl, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkyl or $(C_5$-$C_9)$heteroaryl $(C_1$-$C_6)$alkyl; $R^{13}CONR^9$ wherein R^9 is as defined above and R^{13} is hydrogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $(C_6$-$C_{10})$aryl, $(C_5$-$C_9)$heteroaryl, $(C_1$-$C_6)$aryl$(C_1$-$C_6)$alkyl$(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkoxy or $(C_5$-$C_9)$heteroaryl$(C_1$-$C_6)$alkyl; $R^{14}OOC$, $R^{14}OOC(C_1$-$C_6)$alkyl wherein R^{14} is $(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$aryl, $(C_5$-$C_9)$heteroaryl, $(C_6$-$C_{10})$aryl $(C_1$-$C_6)$alkyl, 5-indanyl, CHR^5OCOR^6 wherein R^5 is hydrogen or $(C_1$-$C_6)$alkyl and R^6 is $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy or $(C_6$-$C_{10})$aryl; $CH_2CONR^7R^8$ wherein R^7 and R^8 are each independently hydrogen or $(C_1$-$C_6)$alkyl or may be taken together with the nitrogen to which they are attached to form an

azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl or thiomorpholinyl ring; or $R^{15}O(C_1C_6)$alkyl wherein R^{15} is $H_2N(CHR^{16})CO$ wherein R^{16} is the side chain of a natural D- or L-amino acid;

R^1 is $(C_6\text{-}C_{10})$aryl, $(C_5\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, 5-indanyl, CHR^5OCOR^6 or $CH_2CONR^7R^8$ wherein R^5, R^6, R^7 and R^8 are as defined above;

R^3 and R^4 are each independently selected from the group consisting of hydrogen, $(C_1\text{-}C_6)$alkyl, trifluoromethyl, trifluoromethyl$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl (difluoromethylene), $(C_1\text{-}C_3)$alkyl(difluoromethylene)$(C_1\text{-}C_3)$alkyl, $(C_6\text{-}C_{10})$aryl, $(C_5\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_5\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_{10})$acyloxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_{10})$acylamino$(C_1\text{-}C_6)$alkyl, piperidyl, $(C_1\text{-}C_6)$alkylpiperidyl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, $(C_5\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylthio$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$arylthio$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylsulfinyl$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$arylsulfinyl$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylsulfonyl$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$arylsulfonyl$(C_1\text{-}C_6)$alkyl, amino$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylamino$(C_1\text{-}C_6)$alkyl, $((C_1\text{-}C_6)\text{alkylamino})_2(C_1\text{-}C_6)$alkyl, $R^{17}CO(C_1\text{-}C_6)$alkyl wherein R^{17} is $R^{14}O$ or R^7R^8N wherein R^7, R^8 and R^{14} are as defined above; or $R^{18}(C_1\text{-}C_6)$alkyl wherein R^{18} is piperazinyl, $(C_1\text{-}C_{10})$acylpiperazinyl, $(C_6\text{-}C_{10})$arylpiperazinyl, $(C_5\text{-}C_9)$heteroarylpiperazinyl, $(C_1\text{-}C_6)$alkylpiperazinyl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkylpiperazinyl, $(C_5\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkylpiperazinyl, morpholinyl, thiomorpholinyl, piperidinyl, pyrrolidinyl, piperidyl, $(C_1\text{-}C_6)$alkylpiperidyl, $(C_6\text{-}C_{10})$arylpiperidyl, $(C_5\text{-}C_9)$heteroarylpiperidyl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkylpiperidyl, $(C_5\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkylpiperidyl or $(C_1\text{-}C_{10})$acylpiperidyl;

or R^3 and R^4 may be taken together to form a $(C_3\text{-}C_6)$cycloalkyl, oxacyclohexyl, thiocyclohexyl, indanyl or tetralinyl ring or a group of the formula



wherein R^{21} is hydrogen, (C_1-C_{10})acyl, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_5-C_9)heteroaryl(C_1-C_6)alkyl or (C_1-C_6)alkylsulfonyl; and

Q is (C_1-C_6)alkyl, (C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl(C_1-C_6)alkyl, (C_6-C_{10})aryloxy(C_5-C_9)heteroaryl, (C_5-C_9)heteroaryl, (C_1-C_6)alkyl(C_6-C_{10})aryl, (C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_6-C_{10})aryl,(C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl,(C_5-C_9)heteroaryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_5-C_9)heteroaryl, (C_1-C_6)alkoxy(C_5-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_5-C_9)heteroaryl, (C_5-C_9)heteroaryloxy(C_5-C_9)heteroaryl, (C_6-C_{10})aryloxy(C_1-C_6)alkyl, (C_5-C_9)heteroaryloxy(C_1-C_6)alkyl, (C_1-C_6)alkyl(C_6-C_{10})aryloxy(C_6-C_{10})aryl,(C_1-C_6)alkyl(C_5-C_9)heteroaryloxy(C_6-C_{10})aryl,(C_1-C_6)alkyl(C_6-C_{10})aryloxy(C_5-C_9)heteroaryl, (C_1-C_6)alkoxy(C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_1-C_6)alkoxy(C_5-C_9)heteroaryloxy(C_6-C_{10})aryl or (C_1-C_6)alkoxy(C_6-C_{10})aryloxy(C_5-C_9)heteroaryl wherein each aryl group is optionally substituted by fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or perfluoro(C_1-C_3)alkyl;

with the proviso that X must be substituted when defined as azetidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, indolinyl, isoindolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, piperazinyl, (C_1-C_{10})acylpiperazinyl, (C_1-C_6)alkylpiperazinyl, (C_6-C_{10})arylpiperazinyl, (C_5-C_9)heteroarylpiperazinyl or a bridged diazabicycloalkyl ring.

2. A compound according to claim 1, wherein n is 2.

3. A compound according to claim 1, wherein either R^3 or R^4 is not hydrogen.

4. A compound according to claim 1, wherein Q is (C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_6-C_{10})aryl, phenoxy(C_6-C_{10})aryl, 4-fluorophenoxy(C_6-C_{10})aryl, 4-fluorobenzyloxy(C_6-C_{10})aryl or (C_1-C_6)alkyl(C_6-C_{10})aryloxy(C_6-C_{10})aryl.

5. A compound according to claim 1, wherein X is indolinyl or piperidinyl.

6. A compound according to claim 1, wherein n is 2; either R^3 or R^4 is not hydrogen; Q is (C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_6-C_{10})aryl, 4-fluorophenoxy(C_6-C_{10})aryl, phenoxy(C_6-C_{10})aryl, 4-fluorobenzyloxy(C_6-C_{10})aryl or (C_1-C_6)alkyl(C_6-C_{10})aryloxy(C_6-C_{10})aryl; and X is indolinyl or piperidinyl.

7. A compound according to claim 1, wherein said compound is selected from the group consisting of:

3-[(Cyclohexylhydroxycarbamoylmethyl)-(4-methoxybenzenesulfonyl)-amino]-propionic acid indan-5-yl ester;

Acetic acid 1-{3-[(1-hydroxycarbamoyl-2-methylpropyl)-(4-methoxy-benzenesulfonyl)-amino]propionyl}piperidin-4-yl ester;

2-Cyclohexyl-N-hydroxy-2-[[3-(4-hydroxypiperidin-1-yl)-3-oxopropyl]-(4-methoxy-benzenesulfonyl)amino]acetamide;

Benzoic acid 1-{3-[(1-hydroxycarbamoyl-2-methylpropyl)-(4-methoxy-benzenesulfonyl)amino]propionyl}piperidin-4-yl ester;

N-Hydroxy-2-[[3-(4-hydroxypiperidin-1-yl)-3-oxopropyl]-(4-methoxybenzenesulfonyl)amino]-3-methylbutyramide;

1-{3-[(Cyclohexylhydroxycarbamoylmethyl)-(4-methoxybenzenesulfonyl)-amino]propionyl}piperidine-4-carboxylic acid;

1-{3-[(Cyclohexylhydroxycarbamoylmethyl)-(4-methoxybenzenesulfonyl)-amino]propionyl}piperidine-4-carboxylic acid ethyl ester;

2-Cyclohexyl-N-hydroxy-2-{(4-methoxybenzenesulfonyl)-[3-(4-methylaminopiperidin-1-yl)-3-oxopropyl]amino}acetamide;

3-(4-Chlorophenyl)-N-hydroxy-2-{(4-methoxybenzenesulfonyl)-[3-(4-methylaminopiperidin-1-yl)-3-oxopropyl]amino}propionamide;

3-Cyclohexyl-N-hydroxy-2-{(4-methoxybenzenesulfonyl)-[3-(4-methylaminopiperidin-1-yl)-3-oxopropyl]amino}propionamide;

N-Hydroxy-2-[{3-[4-(2-hydroxy-2-methylpropyl)piperazin-1-yl]-3-oxopropyl}-(4-methoxy-benzenesulfonyl)amino]-3-methylbutyramide;

2,2-Dimethylpropionic acid 2-(4-{3-[(1-hydroxycarbamoyl-2-methylpropyl)-(4-methoxy-benzenesulfonyl)amino]propionyl}piperazin-1-yl)ethyl ester;

Benzoic acid 2-(4-{3-[(1-hydroxycarbamoyl-2-methylpropyl)-(4-methoxybenzenesulfonyl)-amino]propionyl}piperazin-1-yl)-ethyl ester;

2-Cyclohexyl-N-hydroxy-2-[{3-[4-(2-hydroxyethyl)piperazin-1-yl]-3-oxopropyl}-(4-methoxybenzenesulfonyl)amino]acetamide;

2-Hydroxy-2-[{3-[5-(2-hydroxyethyl)-2,5-diazabicyclo[2.2.1]-hept-2-yl]-3-oxopropyl}-(4-methoxybenzenesulfonyl)amino]-3-methylbutyramide;

2-{(4-Benzyloxybenzenesulfonyl)-[3-(4-hydroxypiperidin-1-yl)-3-oxopropyl]amino}-N-hydroxy-3-methylbutyramide;

2-Cyclohexyl-2-{[4-(4-fluorophenoxy)benzenesulfonyl]-[3-(4-hydroxy-piperidin-1-yl)-3-oxopropyl]-amino}-N-hydroxyacetamide;

2-{[4-(4-Butylphenoxy)benzenesulfonyl]-[3-(4-hydroxypiperidin-1-yl)-3-oxopropyl]-amino}-N-hydroxy-3-methylbutyramide;

1-{(4-Methoxybenzenesulfonyl)-[3-(4-methylaminopiperidin-1-yl)-3-oxo-propyl]amino}-cyclopentanecarboxylic acid hydroxyamide;

4-{3-[(1-Hydroxycarbamoyl-2-methylpropyl)-(4-methoxybenzene-sulfonyl)amino]-propionyl}piperazine-2-carboxylic acid ethyl ester;

3-[(Cyclohexylhydroxycarbamoylmethyl)-(4-methoxybenzene-sulfonyl)amino]propionic acid ethoxycarbonyloxymethyl ester;

3-[(1-Hydroxycarbamoylpentyl)-(4-methoxybenzenesulfonyl)amino]propionic acid ethoxycarbonyloxymethyl ester;

1-{3-[(1-Hydroxycarbamoyl-2-methylpropyl)-(4-phenoxybenzenesulfonyl)amino] propionyl] piperidine-4-carboxylic acid.

3-[[4-(4-Fluorobenzyloxy)-benzenesulfonyl]-(1-hydroxy-carbamoyl-2-methyl-propyl)-amino]-propionic acid ethoxycarbonyloxymethyl ester; and

3-[[4-(4-Fluorophenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-2-methyl-propyl)-amino]-propionic acid ethoxycarbonyloxymethyl ester.

8. A pharmaceutical composition for (a) the treatment of a condition selected from the group consisting of arthritis, cancer, tissue ulceration, mucular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, in combination with standard NSAID'S and analgesics and in combination with cytotoxic anticancer agents, and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) or (b) the inhibition of matrix metalloproteinases or the production of tumor necrosis factor (TNF) in a mammal, including a human,

comprising an amount of a compound of claim 1 effective in such treatment and a pharmaceutically acceptable carrier.

9. A method for the inhibition of (a) matrix metalloproteinases or (b) the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of claim 1.

10. A method for treating a condition selected from the group consisting of arthritis, cancer, tissue ulceration, macular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, compounds of formula I may be used in combination with standard NSAID'S and analgesics and in combination with cytotoxic anticancer agents, and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an amount of a compound of claim 1, effective in treating such a condition.

INTERNATIONAL SEARCH REPORT

Interi. ..nal Application No
PCT/IB 97/00924

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D211/58 C07D211/46 C07D211/62 C07D295/18 C07D211/34
C07C311/29 A61K31/445 A61K31/495 A61K31/18

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07C A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 00214 A (CIBA-GEIGY AG) 4 January 1996 see claims	1-10
Y	EP 0 606 046 A (CIBA-GEIGY AG) 13 July 1994 see claims	1-10
Y	WO 95 35275 A (BRITISH BIOTECH PHARMACEUTICALS LIMITED) 28 December 1995 see claims	1-10
P,X	WO 96 27583 A (PFIZER INC.) 12 September 1996 see the whole document	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
14 October 1997	23. 10. 97
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Chouly, J

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

INTERNATIONAL SEARCH REPORT

In..ational application No.
PCT/IB 97/00924

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

Claims Nos.: claims 1-10 have been searched incompletely (see attached sheet)

because they relate to subject matter not required to be searched by this Authority, namely:

The claims encompasse such a large number and variety of compounds that a complete search is not possible on economic grounds (Guidelines for examination in the EPO, Part B, Chapter III,3.7).Thus the search was directed powards (but not limited to) compounds having variables as represented in the examples.

Remark : Although claims 9,10
are directed to a method of treatment of
the human/animal body , the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern ..al Application No
PCT/IB 97/00924

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9600214 A	04-01-96	US 5506242 A	09-04-96
		AU 2536995 A	19-01-96
		CA 2192092 A	04-01-96
		EP 0766672 A	09-04-97
		FI 965156 A	20-12-96
		NO 965568 A	17-02-97
		US 5552419 A	03-09-96
		US 5646167 A	08-07-97
		US 5672615 A	30-09-97
		ZA 9505206 A	27-12-95
EP 606046 A	13-07-94	US 5455258 A	03-10-95
		AU 5265593 A	04-05-95
		CA 2112779 A	07-07-94
		FI 940012 A	07-07-94
		HU 70536 A	30-10-95
		JP 6256293 A	13-09-94
		MX 9400276 A	29-07-94
		NO 940038 A,B,	07-07-94
		NZ 250517 A	26-10-95
		US 5506242 A	09-04-96
		US 5552419 A	03-09-96
		US 5646167 A	08-07-97
		US 5672615 A	30-09-97
		ZA 9400048 A	11-08-94
WO 9535275 A	28-12-95	AU 2746595 A	15-01-96
		AU 2746695 A	15-01-96
		CA 2193691 A	28-12-95
		CA 2193692 A	28-12-95
		EP 0766664 A	09-04-97
		EP 0766665 A	09-04-97
		FI 965153 A	20-12-96
		WO 9535276 A	28-12-95
		GB 2303850 A	05-03-97
		GB 2303629 A	26-02-97
		NO 965515 A	20-02-97
WO 9627583 A	12-09-96	AU 5029396 A	23-09-96

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 493/08, A61K 31/34 | **A1**

(11) International Publication Number: **WO 98/30566**

(43) International Publication Date: 16 July 1998 (16.07.98)

(21) International Application Number: PCT/IB97/01582

(22) International Filing Date: 18 December 1997 (18.12.97)

(30) Priority Data:
60/034,535 6 January 1997 (06.01.97) US

(71) Applicant *(for all designated States except US)*: PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: BURGESS, Laurence, Edward [US/US]; 5617 Slick Rock Court, Boulder, CO 80301 (US). RIZZI, James, Patrick [US/US]; 7180 Longview Drive, Niwot, CO 80503 (US).

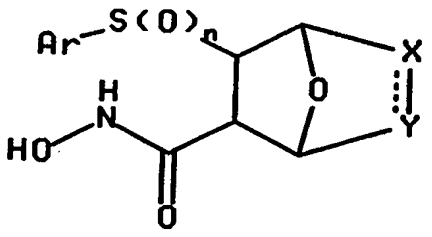
(74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: CYCLIC SULFONE DERIVATIVES

(57) Abstract



(I)

A compound of formula (I), wherein n, X, Y and Ar are as defined herein, useful in the treatment of a condition selected from the group consisting of arthritis, cancer, tissue ulceration, macular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of TNF. In addition, the compounds of the present invention may be used in combination therapy with standard non–steroidal anti–inflammatory drugs (NSAID'S) and analgesics, and in combination with cytotoxic drugs such as adriamycin, daunomycin, cis–platinum, etoposide, taxol, taxotere and other alkaloids, such as vincristine, in the treatment of cancer.

FOR THE PURPOSES OF INFORMATION ONLY

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

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

CYCLIC SULFONE DERIVATIVES

Background of the Invention

The present invention relates to cyclic sulfone derivatives which are inhibitors of matrix metalloproteinases or the production of tumor necrosis factor (TNF) and as such are useful in the treatment of a condition selected from the group consisting of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of TNF. In addition, the compounds of the present invention may be used in combination therapy with standard non-steroidal anti-inflammatory drugs (hereinafter NSAID'S) and analgesics for the treatment of arthritis, and in combination with cytotoxic drugs such as adriamycin, daunomycin, cis-platinum, etoposide, taxol, taxotere and alkaloids, such as vincristine, in the treatment of cancer.

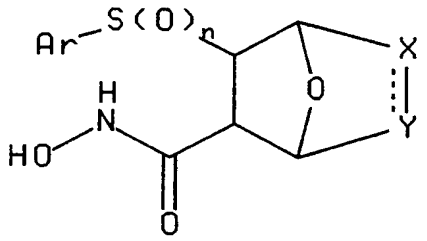
This invention also relates to a method of using such compounds in the treatment of the above diseases in mammals, especially humans, and to pharmaceutical compositions useful therefor.

There are a number of enzymes which effect the breakdown of structural proteins and which are structurally related metalloproteases. Matrix-degrading metalloproteinases, such as gelatinase, stromelysin and collagenase, are involved in tissue matrix degradation (e.g. collagen collapse) and have been implicated in many pathological conditions involving abnormal connective tissue and basement membrane matrix metabolism, such as arthritis (e.g. osteoarthritis and rheumatoid arthritis), tissue ulceration (e.g. corneal, epidermal and gastric ulceration), abnormal wound healing, periodontal disease, bone disease (e.g. Paget's disease and osteoporosis), tumor metastasis or invasion, as well as HIV-infection (J. Leuk. Biol., 52 (2): 244-248, 1992).

Tumor necrosis factor is recognized to be involved in many infectious and auto-immune diseases (W. Fiers, FEBS Letters, 1991, 285, 199). Furthermore, it has been shown that TNF is the prime mediator of the inflammatory response seen in sepsis and septic shock (C.E. Spooner et al., Clinical Immunology and Immunopathology, 1992, 62 S11).

Summary of the Invention

The present invention relates to a compound of the formula



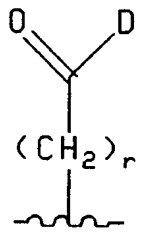
I

or a pharmaceutically acceptable salt thereof, wherein the broken line represents an optional double bond;

n is 0, 1 or 2;

X and Y are each independently CR^1 wherein R^1 is hydrogen, (C_1-C_6)alkyl optionally substituted by (C_1-C_6)alkylamino, (C_1-C_6)alkylthio, (C_1-C_6)alkoxy, trifluoromethyl, (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_6-C_{10})arylamino, (C_6-C_{10})arylthio, (C_6-C_{10})aryloxy, (C_5-C_9)heteroarylamino, (C_5-C_9)heteroarylthio, (C_5-C_9)heteroaryloxy, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_3-C_6)cycloalkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkyl(hydroxymethylene),piperazinyl,(C_6-C_{10})aryl(C_1-C_6)alkoxy,(C_5-C_9)heteroaryl(C_1-C_6)alkoxy, (C_1-C_6)acylamino, (C_1-C_6)acylthio, (C_1-C_6)acyloxy, (C_1-C_6)alkylsulfinyl, (C_6-C_{10})arylsulfinyl, (C_1-C_6)alkylsulfonyl, (C_6-C_{10})arylsulfonyl, amino, (C_1-C_6)alkylamino or ((C_1-C_6)alkyl)$_2$amino; trifluoromethyl, (C_1-C_6)alkyl (difluoromethylene), (C_1C_3)alkyl(difluoromethylene)(C_1-C_3)alkyl, (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_3-C_6)cycloalkyl, (C_1-C_6)alkyl-(hydroxymethylene), R^3(C_1-C_6)alkyl wherein R^3 is (C_1-C_6)acylpiperazino, (C_6-C_{10})arylpiperazino, (C_5-C_9)heteroarylpiperazino, (C_1-C_6)alkylpiperazino, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazino, (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_5-C_9)heteroarylpiperidyl, (C_1-C_6)alkylpiperidyl(C_1-C_6)alkyl, (C_6-C_{10})arylpiperidyl(C_1-C_6)alkyl, (C_5-C_9)heteroarylpiperidyl(C_1-C_6)alkyl or (C_1-C_6)acylpiperidyl;

or a group of the formula



wherein r is 0 to 6;

D is hydroxy, (C_1-C_6)alkoxy, piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_5-C_9)heteroarylpiperidyl, (C_1-C_6)acylpiperidyl or NR^4R^5 wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl optionally substituted by (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_5-C_9)heteroarylpiperidyl, (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_6-C_{10})aryl(C_6-C_{10})aryl or (C_3-C_6)cycloalkyl; (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_3-C_6)cycloalkyl, $R^6(C_2-C_6)$alkyl, (C_1-C_5)alkyl$(CHR^6)(C_1-C_6)$alkyl wherein R^6 is hydroxy, (C_1-C_6)acyloxy, (C_1-C_6)alkoxy, piperazino, (C_1-C_6)acylamino, (C_1-C_6)alkylthio, (C_6-C_{10})arylthio, (C_1-C_6)alkylsulfinyl, (C_6-C_{10})arylsulfinyl, (C_1-C_6)alkylsulfoxyl, (C_6-C_{10})arylsulfoxyl, amino, (C_1-C_6)alkylamino, $((C_1-C_6)$alkyl$)_2$amino, (C_1-C_6)acylpiperazino, (C_1-C_6)alkylpiperazino, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazino,(C_5-C_9)heteroaryl(C_1-C_6)alkylpiperazino,morpholino,thiomorpholino, piperidino or pyrrolidino; $R^7(C_1-C_6)$alkyl, (C_1-C_5)alkyl$(CHR^7)(C_1-C_6)$alkyl wherein R^7 is piperidyl or (C_1-C_6)alkylpiperidyl; and $CH(R^8)COR^9$ wherein R^8 is hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_5-C_9)heteroaryl(C_1-C_6)alkyl, (C_1-C_6)alkylthio(C_1-C_6)alkyl, (C_6-C_{10})arylthio(C_1-C_6)alkyl, (C_1-C_6)alkylsulfinyl(C_1-C_6)alkyl, (C_6-C_{10})arylsulfinyl(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonyl(C_1-C_6)alkyl, (C_6-C_{10})arylsulfonyl(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, $((C_1-C_6)$alkylamino$)_2(C_1-C_6)$alkyl, $R^{10}R^{11}NCO(C_1-C_6)$alkyl or $R^{10}OCO(C_1-C_6)$alkyl wherein R^{10} and R^{11} are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl and (C_5-C_9)heteroaryl(C_1-C_6)alkyl; and R^9 is $R^{12}O$ or $R^{12}R^{13}N$ wherein R^{12} and R^{13} are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl and (C_5-C_9)heteroaryl(C_1-C_6)alkyl; and

Ar is (C_1-C_6)alkyl, (C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_5-C_{10})aryl(C_1-C_6)alkyl, (C_6-C_{10})aryloxy(C_5-C_9)heteroaryl, (C_5-C_9)heteroaryl, (C_1-C_6)alkyl(C_6-C_{10})aryl, (C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_5-C_9)heteroaryloxy$(C_6-$

C_{10})aryl, (C_1-C_6)alkyl(C_5-C_9)heteroaryl, (C_1-C_6)alkoxy(C_5-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_5-C_9)heteroaryl, (C_5-C_9)heteroaryloxy(C_5-C_9)heteroaryl, (C_6-C_{10})aryloxy(C_1-C_6)alkyl, (C_5-C_9)heteroaryloxy(C_1-C_6)alkyl, (C_1-C_6)alkyl(C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_5-C_9)heteroaryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_6-C_{10})aryloxy(C_5-C_9)heteroaryl, (C_1-C_6)alkoxy(C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_1-C_6)alkoxy(C_5-C_9)heteroaryloxy(C_6-C_{10})aryl or (C_1-C_6)alkoxy(C_6-C_{10})aryloxy(C_5-C_9)heteroaryl wherein each aryl group is optionally substituted by fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or perfluoro(C_1-C_3)alkyl.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof.

The term "alkoxy", as used herein, includes alkyl-O groups wherein "alkyl" is defined above.

The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl or naphthyl, optionally substituted by 1 to 3 substituents independently selected from the group consisting of fluoro, chloro, cyano, nitro, trifluoromethyl, (C_1-C_6)alkoxy, (C_6-C_{10})aryloxy, trifluoromethoxy, difluoromethoxy and (C_1-C_6)alkyl.

The term "heteroaryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic heterocyclic compound by removal of one hydrogen, such as pyridyl, furyl, pyrroyl, thienyl, isothiazolyl, imidazolyl, benzimidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzofuryl, isobenzofuryl, benzothienyl, pyrazolyl, indolyl, isoindolyl, purinyl, carbazolyl, isoxazolyl, thiazolyl, oxazolyl, benzthiazolyl or benzoxazolyl, optionally substituted by 1 to 2 substituents independently selected from the group consisting of fluoro, chloro, trifluoromethyl, (C_1-C_6)alkoxy, (C_6-C_{10})aryloxy, trifluoromethoxy, difluoromethoxy and (C_1-C_6)alkyl.

The term "acyl", as used herein, unless otherwise indicated, includes a radical of the general formula RCO wherein R is alkyl, alkoxy, aryl, arylalkyl or arylalkyloxy and the terms "alkyl" or "aryl" are as defined above.

The term "acyloxy", as used herein, includes acyl-O groups wherein "acyl" is defined above.

Preferred compounds of formula I include those wherein n is 2.

Other preferred compounds of formula I include those wherein X and Y are both CR^1 wherein R^1 is hydrogen.

Other preferred compounds of formula I include those wherein Ar is (C_1-C_6)alkoxy(C_6-C_{10})aryl,(C_6-C_{10})aryl(C_1-C_6)alkoxy(C_6-C_{10})aryl,4-fluorophenoxy(C_6-C_{10})aryl, 4-fluorobenzyloxy(C_6-C_{10})aryl or (C_1-C_6)alkyl(C_6-C_{10})aryloxy(C_6-C_{10})aryl.

More preferred compounds of formula I include those wherein n is 2, X and Y are both CR^1 wherein R^1 is hydrogen and Ar is (C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_6-C_{10})aryl, 4-fluorophenoxy(C_6-C_{10})aryl, 4-fluorobenzyloxy(C_6-C_{10})aryl or (C_1-C_6)alkyl(C_6-C_{10})aryloxy(C_6-C_{10})aryl.

The present invention also relates to a pharmaceutical composition for (a) the treatment of a condition selected from the group consisting of arthritis, cancer, synergy with cytotoxic anticancer agents, tissue ulceration, macular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, in combination with standard NSAID'S and analgesics and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) or (b) the inhibition of matrix metalloproteinases or the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising an amount of a compound of formula I or a pharmaceutically acceptable salt thereof effective in such treatments and a pharmaceutically acceptable carrier.

The present invention also relates to a method for the inhibition of (a) matrix metalloproteinases or (b) the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

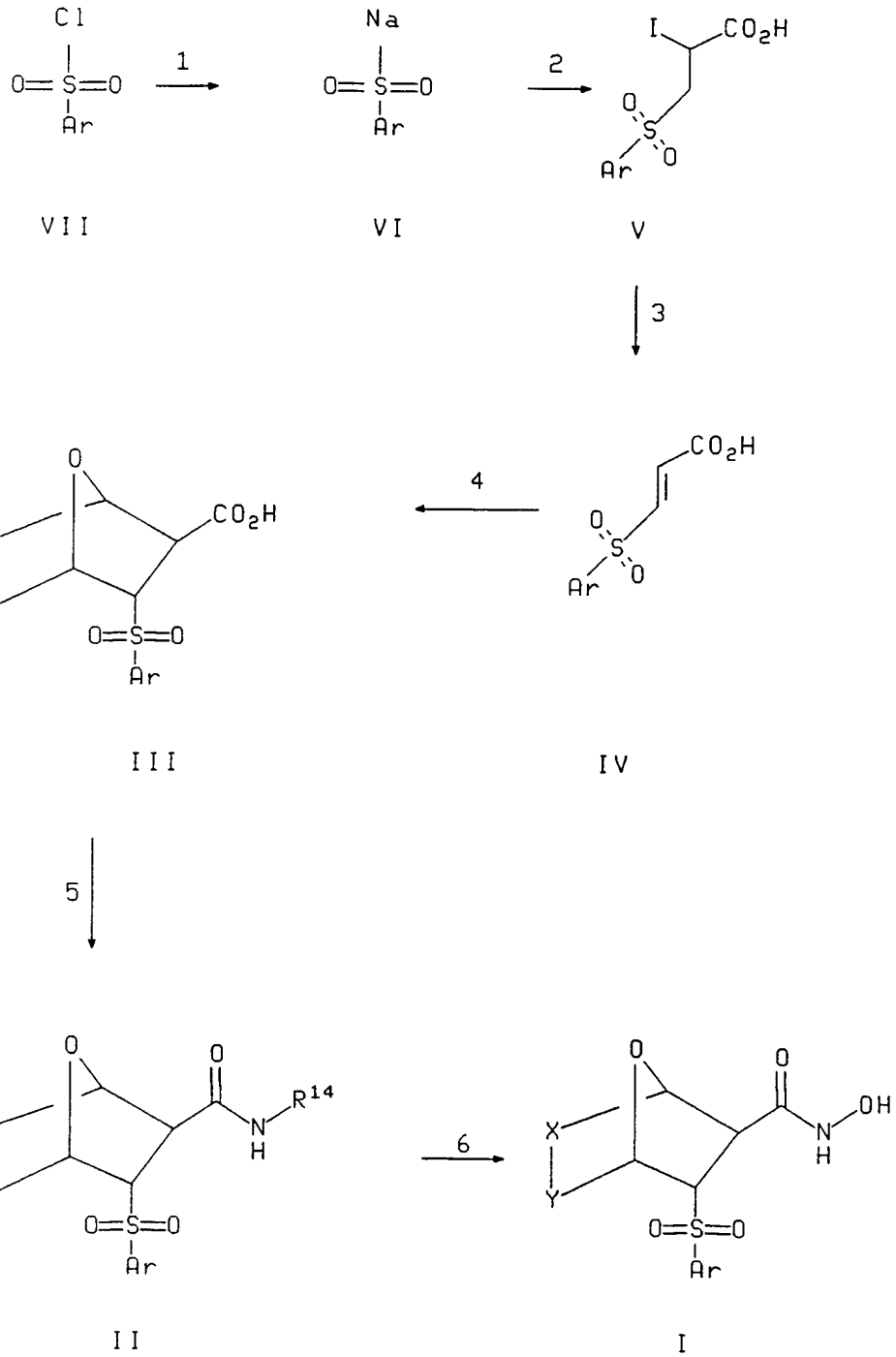
The present invention also relates to a method for treating a condition selected from the group consisting of arthritis, cancer, tissue ulceration, macular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, compounds of formula I may be used in combination with standard NSAID'S and analgesics and in combination with cytotoxic anticancer agents, and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an amount of a compound of formula I or a pharmaceutically acceptable salt thereof effective in treating such a condition.

Detailed Description of the Invention

The following reaction Schemes illustrate the preparation of the compounds of the present invention. Unless otherwise indicated X, Y and Ar in the reaction Schemes and the discussion that follow are defined as above.

5

SCHEME 1

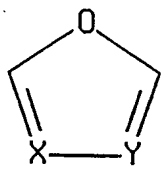


In reaction 1 of Scheme 1, the aryl sulfonyl chloride compound of formula **VII** is converted to the corresponding sodium aryl sulfonate compound of formula **VI** by reacting **VII** with sodium iodine in the presence of a polar aprotic solvent, such as acetone, under inert atmosphere. The reaction mixture is stirred, at room temperature, for a time period between about 12 hours to about 18 hours, preferably about 15 hours.

In reaction 2 of Scheme 1, the compound of formula **VI** is converted to the corresponding 2-iodo-3-(aryl) sulfonyl propionic acid compound of formula **V** by reacting **VI** with acrylic acid and iodine in the presence of a polar aprotic solvent, such as methylene chloride. The reaction mixture is stirred under inert atmosphere, at room temperature, for a time period between about 12 hours to about 3.5 days, preferably about 3 days.

In reaction 3 of Scheme 1, the compound of formula **V** is converted to the corresponding (E)-3-(aryl)sulfonyl-prop-2-enoic acid compound of formula **IV** by treating **V** with a base, such as triethylamine, in a polar aprotic solvent, such as methylene chloride, under inert atmosphere. The reaction is stirred, at room temperature, for a time period between about 10 hours to about 24 hours, preferably about 12 hours.

In reaction 4 of Scheme 1, the compound of formula **IV** is converted to the corresponding carboxylic acid compound of formula **III** by heating **IV** with an excess amount of a compound of the formula



to reflux in the presence of a polar aprotic solvent, such as toluene, for a time period between about 24 hours to about 56 hours, preferably about 48 hours.

In reaction 5 of Scheme 1, the compound of formula **III** is converted to the corresponding N-(R^{14})-carboxamide compound of formula **II**, wherein R^{14} is O-substituted oxy, such as O-benzylhydroxy or trimethylsilyl ethylhydroxy by reacting **III** with an activating agent, such as dimethylaminopyridine/dicyclohexylcarbodiimide, and an O-substituted hydroxylamine, such as benzylhydroxylamine hydrochloride or O-trimethyl-silylethylhydroxylamine, in the presence of a polar aprotic solvent, such as methylene chloride, under inert atmosphere. The reaction mixture is stirred, at room

temperature, for a time period between about 15 hours to about 25 hours, preferably about 20 hours.

In reaction 6 of Scheme 1, the compound of formula II is converted to the corresponding hydroxamic acid compound of formula I by (1) treating II with hydrogen in the presence of a catalyst, such as 5% palladium on barium sulfate, and a polar aprotic solvent, such as methanol, (2) treating II with trifluoroacetic acid or boron trifluoride diethyl etherate in a polar aprotic solvent, such as methylene chloride, or (3) treating II with tetrabutyl ammonium fluoride in a polar aprotic solution, such as tetrahydrofuran. The reaction mixture is stirred for a time period between about 2 hours to about 4 hours, preferably about 3 hours.

Pharmaceutically acceptable salts of the acidic compounds of the invention are salts formed with bases, namely cationic salts such as alkali and alkaline earth metal salts, such as sodium, lithium, potassium, calcium, magnesium, as well as ammonium slats, such as ammonium, trimethyl-ammonium, diethylammonium, and tris-(hydroxymethyl)-methylammonium slats.

Similarly acid addition salts, such as of mineral acids, organic carboxylic and organic sulfonic acids e.g. hydrochloric acid, methanesulfonic acid, maleic acid, are also possible provided a basic group, such as pyridyl, constitutes part of the structure.

The ability of the compounds of formula I or their pharmaceutically acceptable salts (hereinafter also referred to as the compounds of the present invention) to inhibit matrix metalloproteinases or the production of tumor necrosis factor (TNF) and, consequently, demonstrate their effectiveness for treating diseases characterized by matrix metalloproteinase or the production of tumor necrosis factor is shown by the following in vitro assay tests.

Biological Assay

Inhibition of Human Collagenase (MMP-1)

Human recombinant collagenase is activated with trypsin using the following ratio: 10 μg trypsin per 100 μg of collagenase. The trypsin and collagenase are incubated at room temperature for 10 minutes then a five fold excess (50 μg/10 μg trypsin) of soybean trypsin inhibitor is added.

10 mM stock solutions of inhibitors are made up in dimethyl sulfoxide and then diluted using the following Scheme:

10 mM ------> 120 μM -----> 12 μM -----> 1.2 μM ------> 0.12 μM

Twenty-five microliters of each concentration is then added in triplicate to appropriate wells of a 96 well microfluor plate. The final concentration of inhibitor will be a 1:4 dilution after addition of enzyme and substrate. Positive controls (enzyme, no inhibitor) are set up in wells D1-D6 and blanks (no enzyme, no inhibitors) are set in wells D7-D12.

Collagenase is diluted to 400 ng/ml and 25 μl is then added to appropriate wells of the microfluor plate. Final concentration of collagenase in the assay is 100 ng/ml.

Substrate (DNP-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2) is made as a 5 mM stock in dimethyl sulfoxide and then diluted to 20 μM in assay buffer. The assay is initiated by the addition of 50 μl substrate per well of the microfluor plate to give a final concentration of 10 μM.

Fluorescence readings (360 nM excitation, 460 nm emission) were taken at time 0 and then at 20 minute intervals. The assay is conducted at room temperature with a typical assay time of 3 hours.

Fluorescence vs time is then plotted for both the blank and collagenase containing samples (data from triplicate determinations is averaged). A time point that provides a good signal (the blank) and that is on a linear part of the curve (usually around 120 minutes) is chosen to determine IC_{50} values. The zero time is used as a blank for each compound at each concentration and these values are subtracted from the 120 minute data. Data is plotted as inhibitor concentration vs % control (inhibitor fluorescence divided by fluorescence of collagenase alone x 100). IC_{50}'s are determined from the concentration of inhibitor that gives a signal that is 50% of the control.

If IC_{50}'s are reported to be <0.03 μM then the inhibitors are assayed at concentrations of 0.3 μM, 0.03 μM, 0.03 μM and 0.003 μM.

Inhibition of Gelatinase (MMP-2)

Inhibition of gelatinase activity is assayed using the Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2 substrate (10 μM) under the same conditions as inhibition of human collagenase (MMP-1).

72kD gelatinase is activated with 1 mM APMA (p-aminophenyl mercuric acetate) for 15 hours at 4°C and is diluted to give a final concentration in the assay of 100 mg/ml. Inhibitors are diluted as for inhibition of human collagenase (MMP-1) to give

final concentrations in the assay of 30 μM, 3 μM, 0.3 μM and 0.03 μM. Each concentration is done in triplicate.

Fluorescence readings (360 nm excitation, 460 emission) are taken at time zero and then at 20 minutes intervals for 4 hours.

IC_{50}'s are determined as per inhibition of human collagenase (MMP-1). If IC_{50}'s are reported to be less than 0.03 μM, then the inhibitors are assayed at final concentrations of 0.3 μM, 0.03 μM, 0.003 μM and 0.003 μM.

Inhibition of Stromelysin Activity (MMP-3)

Inhibition of stromelysin activity is based on a modified spectrophotometric assay described by Weingarten and Feder (Weingarten, H. and Feder, J., Spectrophotometric Assay for Vertebrate Collagenase, Anal. Biochem. 147, 437-440 (1985)). Hydrolysis of the thio peptolide substrate [Ac-Pro-Leu-Gly-$SCH[CH_2CH(CH_3)_2]CO$-Leu-Gly-OC_2H_5] yields a mercaptan fragment that can be monitored in the presence of Ellman's reagent.

Human recombinant prostromelysin is activated with trypsin using a ratio of 1 μl of a 10 mg/ml trypsin stock per 26 μg of stromelysin. The trypsin and stromelysin are incubated at 37°C for 15 minutes followed by 10 μl of 10 mg/ml soybean trypsin inhibitor for 10 minutes at 37°C for 10 minutes at 37°C to quench trypsin activity.

Assays are conducted in a total volume of 250 μl of assay buffer (200 mM sodium chloride, 50 mM MES, and 10 mM calcium chloride, pH 6.0) in 96-well microliter plates. Activated stromelysin is diluted in assay buffer to 25 μg/ml. Ellman's reagent (3-Carboxy-4-nitrophenyl disulfide) is made as a 1M stock in dimethyl formamide and diluted to 5 mM in assay buffer with 50 μl per well yielding at 1 mM final concentration.

10 mM stock solutions of inhibitors are made in dimethyl sulfoxide and diluted serially in assay buffer such that addition of 50 μL to the appropriate wells yields final concentrations of 3 μM, 0.3 μM, 0.003 μM, and 0.0003 μM. All conditions are completed in triplicate.

A 300 mM dimethyl sulfoxide stock solution of the peptide substrate is diluted to 15 mM in assay buffer and the assay is initiated by addition of 50 μl to each well to give a final concentration of 3 mM substrate. Blanks consist of the peptide substrate and Ellman's reagent without the enzyme. Product formation was monitored at 405 nm with a Molecular Devices UVmax plate reader.

IC_{50} values were determined in the same manner as for collagenase.

Inhibition of MMP-13

Human recombinant MMP-13 is activated with 2mM APMA (p-aminophenyl mercuric acetate) for 1.5 hours, at 37°C and is diluted to 400 mg/ml in assay buffer (50 mM Tris, pH 7.5, 200 mM sodium chloride, 5mM calcium chloride, 20μM zinc chloride, 0.02% brij). Twenty-five microliters of diluted enzyme is added per well of a 96 well microfluor plate. The enzyme is then diluted in a 1:4 ratio in the assay by the addition of inhibitor and substrate to give a final concentration in the assay of 100 mg/ml.

10 mM stock solutions of inhibitors are made up in dimethyl sulfoxide and then diluted in assay buffer as per the inhibitor dilution scheme for inhibition of human collagenase (MMP-1): Twenty-five microliters of each concentration is added in triplicate to the microfluor plate. The final concentrations in the assay are 30 μM, 3μM, 0.3 μM, and 0.03 μM.

Substrate (Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2) is prepared as for inhibition of human collagenase (MMP-1) and 50 μl is added to each well to give a final assay concentration of 10 μM. Fluorescence readings (360 nM excitation; 450 emission) are taken at time 0 and every 5 minutes for 1 hour.

Positive controls consist of enzyme and substrate with no inhibitor and blanks consist of substrate only.

IC_{50}'s are determined as per inhibition of human collagenase (MMP-1). If IC_{50}'s are reported to be less than 0.03 μM, inhibitors are then assayed at final concentrations of 0.3 μM, 0.03 μM, 0.003 μM and 0.0003 μM.

Inhibition of TNF Production

The ability of the compounds or the pharmaceutically acceptable salts thereof to inhibit the production of TNF and, consequently, demonstrate their effectiveness for treating diseases involving the production of TNF is shown by the following in vitro assay:

Human mononuclear cells were isolated from anti-coagulated human blood using a one-step Ficoll-hypaque separation technique. (2) The mononuclear cells were washed three times in Hanks balanced salt solution (HBSS) with divalent cations and resuspended to a density of 2 x 10^6 /ml in HBSS containing 1% BSA. Differential counts determined using the Abbott Cell Dyn 3500 analyzer indicated that monocytes ranged from 17 to 24% of the total cells in these preparations.

180μ of the cell suspension was aliquoted into flate bottom 96 well plates (Costar). Additions of compounds and LPS (100ng/ml final concentration) gave a final volume of 200μl. All conditions were performed in triplicate. After a four hour incubation at 37°C in an humidified CO_2 incubator, plates were removed and centrifuged (10 minutes at approximately 250 x g) and the supernatants removed and assayed for TNFα using the R&D ELISA Kit.

For administration to humans for the inhibition of matrix metalloproteinases or the production of tumor necrosis factor, a variety of conventional routes may be used including orally, parenterally and topically. In general, the active compound will be administered orally or parenterally at dosages between about 0.1 and 25 mg/kg body weight of the subject to be treated per day, preferably from about 0.3 to 5 mg/kg. However, some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

The compounds of the present invention can be administered in a wide variety of different dosage forms, in general, the compounds of this invention are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelation and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof. In the case of animals, they are advantageously

contained in an animal feed or drinking water in a concentration of 5-5000 ppm, preferably 25 to 500 ppm.

For parenteral administration (intramuscular, intraperitoneal, subcutaneous and intravenous use) a sterile injectable solution of the active ingredient is usually prepared. Solutions of a therapeutic compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably adjusted and buffered, preferably at a pH of greater than 8, if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art. In the case of animals, compounds can be administered intramuscularly or subcutaneously at dosage levels of about 0.1 to 50 mg/kg/day, advantageously 0.2 to 10 mg/kg/day given in a single dose or up to 3 divided doses.

Additionally, it is possible to administer the compounds of the present invention topically, e.g., when treating inflammatory conditions of the skin and this may be done by way of creams, jellies, gels, pastes, and ointments, in accordance with standard pharmaceutical practice.

The present invention is illustrated by the following examples, but is not limited to the details thereof.

Example 1

3-(4-Methoxyphenylsufonyl-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid hydroxyamide

(a) Sodium iodide (21.76 grams, 145.2 mmol) and 4-methoxybenzenesulfonyl chloride (10.0 grams, 48.39 mmol) were combined in dry acetone (dried over $MgSO_4$ and filtered) (200 ml) and stirred at room temperature overnight. Collected fine white solids via suction filtration. Dried on high vacuum giving 9.11 grams of sodium 4-methoxybenzenesulfinate as a pale yellow fine powder (97% yield).

(b) Added water (0.85 grams, .85 ml) followed by the acrylic acid (3.42 grams, 3.25 ml), then I_2 (12.04 grams, 47.41 mmol) to a slurry of sodium 4-methoxybenzenesulfinate (9.11 grams, 46.94 mmol) in methylene chloride (150 ml). Added more methylene chloride (100 ml) so slurry could stir. Stirred at room

temperature for weekend. Washed reaction solution with 1N $Na_2S_2O_3$ (aq) (3 x 150 ml) until organic layer was colorless. Washed organic layer with brine. Dried ($MgSO_4$), filtered and concentrated in vacuo, to give 4.23 grams (25%) of crude 2-iodo-3-(4-methoxyphenylsulfonyl)propionic acid.

(c) 2-Iodo-3-(4-methoxyphenylsulfonyl)propionic acid (4.23 grams, 11.43 mmol) and Et_3N (3.22 ml, 2.34 grams, 23.09 mmol) were combined in methylene chloride (150 ml) and stirred overnight at room temperature. The reaction mixture was diluted with 1N hydrochloric acid(aq) (100 ml). The separated aqueous layer was extracted with Et_2O (2x). The dried ($MgSO_4$) combined organics were then filtered and concentrated in vacuo to give 2.58 grams of crude product. This was filtered, the filtrate concentrated and the residue taken up in methanol, filtered and the filtrate concentrated to give 1.87 grams of crude product. This was taken up in hot methylene chloride. Fine crystals crashed out. Decanted filtrate. Washed crystals methylene chloride (2 x 1 ml) (decanted washings). Dried crystals on high vac to give .396 grams of 3-(4-Methoxyphenylsulfonyl)propenoic acid as a pale yellow solid (m.p.: 123° - 128.5°C). The filtrate was concentrated to give 1.42 grams of yellow solid which was flash chromatographed (60% EtOAc/hexane/2%/HOAc/.5% methanol) to give 1.42 grams of 3-(4-Methoxyphenylsulfonyl)propenoic acid. A second chromatography (40% EtOAc/hexane/2%/HOAc/.5% methanol) gave .568 grams of pure 3-(4-Methoxyphenylsulfonyl)propenoic acid.

(d) 3-(4-Methoxyphenylsulfonyl)propenoic acid (200 mgs), excess furan (5.0 ml), and dry toluene (5.0 ml) were combined and warmed to 55°C (at which time starting material went into solution) for overnight. The cooled reaction was concentrated in vacuo to a tan solid which was a mixture of starting material and product. The material was taken up in toluene (5 ml) and furan (10 ml) and heated to 69°C overnight. The cooled reaction mixture was concentrated in vacuo to give 251 mgs of crude 3-(4-Methoxyphenylsulfonyl)-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid as a dark tan solid.

(e) Added the O-benzylhydroxylamine•hydrochloric acid (.387 grams, 2.43 mmol) to a stirred solution of 3-(4-methoxy-phenylsulfonyl-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid in methylene chloride (5 ml). Added 4-dimethylaminopyridine (.306 grams, 2.51 mmol) and stirred approximately one-half hour (until solids dissolved), then added the 1,3-dicyclohexylcarbodiimide (.250 grams, 1.21 mmol) and stirred at

room temperature overnight. The reaction was filtered through a pad of Celite and the filtrate concentrated in vacuo to give 1.06 grams of 3-(4-Methoxyphenylsulfonyl-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid benzyloxyamide. Took this up in methanol and decanted filtrate from fine needle crystals. Concentration of filtrate gave .82 grams of 3-(4-Methoxyphenylsulfonyl-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid benzyloxyamide.

(f) Added 5% palladium/barium sulfate (.80 grams) to crude 3-(4-methoxyphenylsulfonyl-7-oxa-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid benzyloxy amide (0.82 grams) in 30 ml methanol and hydrogenated at 45 psi at room temperature on a Parr Shaker for 4 hours. Filtered the reaction through a pad of Celite and concentrated the filtrate in vacuo. ^{1}H-NMR of the residue shows only the double bond has been removed. The residue was flash chromatographed (50% EtOAc/hexane) to give .126 grams of intermediate. To this was added 5% palladium/barium sulfate (.126 grams) in methanol (30 ml) and hydrogenation was continued on a Parr Shaker at 45 psi at room temperature for 1 3/4 hours. Filtered the reaction through a pad of Celite and concentrated the filtrate to give .101 grams of crude 3-(4-Methoxyphenylsulfonyl-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid hydroxyamide. Flash chromatographed (70/30/8/1) (EtOAc/hexane/methanol/HOAc) to give 77.1 mg of 3-(4-Methoxyphenylsulfonyl-7-oxabicyclo[2.2.1]heptane-2-carboxylicacidhydroxyamide. ^{1}H-NMR (CD_3OD) δ 1.6 (2H, m), 1.8 (2H, m), 3.11 (1H, t), 3.82 (1H, d), 3.88 (3H, s), 4.63 (1H, t), 4.91 (1H, d), 7.12 (2H, d), 7.80 (2H, d); HRMS $M^+ + H^+$, Calc'd: 328.0855, Found: 328.0872.

Example 2

3-(4-Phenoxyphenylsulfonyl-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid hydroxyamide

(a) 3-(4-Phenoxyphenylsulfonyl)propenoic acid prepared from 4-phenoxyphenylsulfonyl chloride and acrylic acid as described in Example 1 steps A and B was flash chromatographed (60/40/1.5/.5 - EtOAc/hexane/HOAc/methanol) to give 1.12 grams of product as an off-white solid. This was crystallized from EtOAc/hexane (3:1) to give .61 grams of pure product as fine white crystals.

(b) To 3-(4-phenoxyphenylsulfonyl)propenoic acid (250 mgs, .82 mmol) in toluene (5.0 ml) (starting material insoluble in toluene at room temperature) was added furan (10 ml) and the mixture heated to gentle reflux approximately 70°C. After

approximately one-half hour the reaction mixture was a solution. After 18 hours of reflux TLC of the milky white solution shows starting material to be consumed. The reaction mixture was cooled and the white precipitate collected via suction filtration and washed with toluene (2 x 1 ml). Dissolved solids in hot methanol and concentrated in vacuo to give .267 grams of 2-(4-Phenoxyphenylsulfonyl-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid as a white crystalline solid.

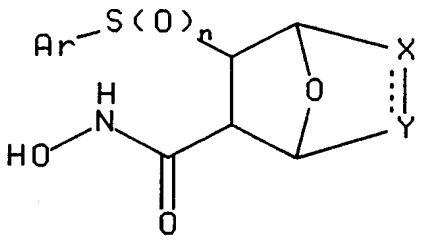
(c) 3-(4-Phenoxyphenylsulfonyl-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid (.243 grams, 0.65 mmol) was hydrogenated on a Parr Shaker over 5% palladium/barium sulfate (.125 grams) in methanol (30 ml) at room temperature at 45 psi for 3 hours. The reaction was filtered through a pad of Celite and the filtrate concentrated in vacuo to give .216 grams of 3-(4-Phenoxyphenylsulfonyl)-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid.

(d) Added the o-benzylhydroxylamine•hydrochloric acid (.28 grams, 1.73 mmol) to the 3-(4-phenoxyphenylsulfonyl)-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid (.216 grams, .58 mmol) dissolved in $CHCl_3$ with heating to dissolve it. Then the 4-dimethylaminopyridine (.22 grams, 1.79 mmol) was added and the mixture stirred until complete dissolution occurred approximately 5 minutes. Then the 1,3-dicyclohexylcarbodiimide (.18 grams, .87 mmol) was added. After 18 hours stirring at room temperature the reaction was concentrated in vacuo to give 1.05 grams of crude product. Flash chromatography (40% EtOAc/hexane/2%/HOAc/.5% methanol) gave .32 grams of impure product. Flash chromatography (40% EtOAc/hexane) gave .212 grams (75%) of pure 3-(4-Phenoxyphenylsulfonyl)-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid benzyloxy amide as a snow white foamy solid.

(e) Combined 3-(4-phenoxyphenylsulfonyl)-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid (.21 grams, .438 mmol) 5% palladium/barium sulfate (.11 grams) in methanol (20 ml) and hydrogenated on a Parr Shaker at room temperature at 45 psi for 1 3/4 hours. The reaction mixture was filtered and concentrated in vacuo to give .175 grams of 3-(4-Phenoxyphenylsulfonyl-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid hydroxyamide as a snow white foamy solid, m.p. 88.9° - 92.9°C. ^{1}H-NMR (CD_3OD) δ 2.5-2.7 (2H, m), 2.7-2.9 (2H, m), 3.11 (1H, t), 3.84 (1H, d), 4.64 (1H, t), 4.94 (1H, d), 7.10 (4H, d), 7.23 (1H, t), 7.44 (2, t), 7.82 (2H, d); mass spec $M^+ + NH_4^+$ 407. HRMS $M^+ + H^+$, Calc'd: 390.1011, Found: 390.1022.

PRODUCT CLAIMS

1. A compound of the formula



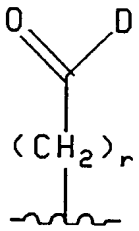
I

or a pharmaceutically acceptable salt thereof, wherein the broken line represents an optional double bond;

n is 0, 1 or 2;

X and Y are each independently CR^1 wherein R^1 is hydrogen, (C_1-C_6)alkyl optionally substituted by (C_1-C_6)alkylamino, (C_1-C_6)alkylthio, (C_1-C_6)alkoxy, trifluoromethyl, (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_6-C_{10})arylamino, (C_6-C_{10})arylthio, (C_6-C_{10})aryloxy, (C_5-C_9)heteroarylamino, (C_5-C_9)heteroarylthio, (C_5-C_9)heteroaryloxy, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_3-C_6)cycloalkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkyl(hydroxymethylene),piperazinyl,(C_6-C_{10})aryl(C_1-C_6)alkoxy,(C_5-C_9)heteroaryl(C_1-C_6)alkoxy, (C_1-C_6)acylamino, (C_1-C_6)acylthio, (C_1-C_6)acyloxy, (C_1-C_6)alkylsulfinyl, (C_6-C_{10})arylsulfinyl, (C_1-C_6)alkylsulfonyl, (C_6-C_{10})arylsulfonyl, amino, (C_1-C_6)alkylamino or ((C_1-C_6)alkyl)$_2$amino; trifluoromethyl, (C_1-C_6)alkyl (difluoromethylene), (C_1C_3)alkyl(difluoromethylene)(C_1-C_3)alkyl, (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_3-C_6)cycloalkyl, (C_1-C_6)alkyl-(hydroxymethylene), R^3(C_1-C_6)alkyl wherein R^3 is (C_1-C_6)acylpiperazino, (C_6-C_{10})arylpiperazino, (C_5-C_9)heteroarylpiperazino, (C_1-C_6)alkylpiperazino, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazino, (C_5-C_9)heteroaryl(C_1-C_6)alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_5-C_9)heteroarylpiperidyl, (C_1-C_6)alkylpiperidyl(C_1-C_6)alkyl, (C_6-C_{10})arylpiperidyl(C_1-C_6)alkyl, (C_5-C_9)heteroarylpiperidyl(C_1-C_6)alkyl or (C_1-C_6)acylpiperidyl;

or a group of the formula



wherein r is 0 to 6;

D is hydroxy, (C_1-C_6)alkoxy, piperidyl, (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_5-C_9)heteroarylpiperidyl, (C_1-C_6)acylpiperidyl or NR^4R^5 wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl optionally substituted by (C_1-C_6)alkylpiperidyl, (C_6-C_{10})arylpiperidyl, (C_5-C_9)heteroarylpiperidyl, (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_6-C_{10})aryl(C_6-C_{10})aryl or (C_3-C_6)cycloalkyl; (C_6-C_{10})aryl, (C_5-C_9)heteroaryl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_3-C_6)cycloalkyl, $R^6(C_2-C_6)$alkyl, (C_1-C_5)alkyl$(CHR^6)(C_1-C_6)$alkyl wherein R^6 is hydroxy, (C_1-C_6)acyloxy, (C_1-C_6)alkoxy, piperazino, (C_1-C_6)acylamino, (C_1-C_6)alkylthio, (C_6-C_{10})arylthio, (C_1-C_6)alkylsulfinyl, (C_6-C_{10})arylsulfinyl, (C_1-C_6)alkylsulfoxyl, (C_6-C_{10})arylsulfoxyl, amino, (C_1-C_6)alkylamino, $((C_1-C_6)$alkyl$)_2$amino, (C_1-C_6)acylpiperazino, (C_1-C_6)alkylpiperazino, (C_6-C_{10})aryl(C_1-C_6)alkylpiperazino,(C_5-C_9)heteroaryl(C_1-C_6)alkylpiperazino,morpholino,thiomorpholino, piperidino or pyrrolidino; $R^7(C_1-C_6)$alkyl, (C_1-C_5)alkyl$(CHR^7)(C_1-C_6)$alkyl wherein R^7 is piperidyl or (C_1-C_6)alkylpiperidyl; and $CH(R^8)COR^9$ wherein R^8 is hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl, (C_5-C_9)heteroaryl(C_1-C_6)alkyl, (C_1-C_6)alkylthio(C_1-C_6)alkyl, (C_6-C_{10})arylthio(C_1-C_6)alkyl, (C_1-C_6)alkylsulfinyl(C_1-C_6)alkyl, (C_6-C_{10})arylsulfinyl(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonyl(C_1-C_6)alkyl, (C_6-C_{10})arylsulfonyl(C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, (C_1-C_6)alkylamino(C_1-C_6)alkyl, $((C_1-C_6)$alkylamino$)_2(C_1-C_6)$alkyl, $R^{10}R^{11}NCO(C_1-C_6)$alkyl or $R^{10}OCO(C_1-C_6)$alkyl wherein R^{10} and R^{11} are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl and (C_5-C_9)heteroaryl(C_1-C_6)alkyl; and R^9 is $R^{12}O$ or $R^{12}R^{13}N$ wherein R^{12} and R^{13} are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_6-C_{10})aryl(C_1-C_6)alkyl and (C_5-C_9)heteroaryl(C_1-C_6)alkyl; and

Ar is (C_1-C_6)alkyl, (C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl(C_1-C_6)alkyl, (C_6-C_{10})aryloxy(C_5-C_9)heteroaryl, (C_5-C_9)heteroaryl, (C_1-C_6)alkyl(C_6-C_{10})aryl, (C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_1-C_6)alkyl, (C_5-C_9)heteroaryloxy$(C_6-$

C_{10})aryl, (C_1-C_6)alkyl(C_5-C_9)heteroaryl, (C_1-C_6)alkoxy(C_5-C_9)heteroaryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_5-C_9)heteroaryl, (C_5-C_9)heteroaryloxy(C_5-C_9)heteroaryl, (C_6-C_{10})aryloxy(C_1-C_6)alkyl, (C_5-C_9)heteroaryloxy(C_1-C_6)alkyl, (C_1-C_6)alkyl(C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_5-C_9)heteroaryloxy(C_6-C_{10})aryl, (C_1-C_6)alkyl(C_6-C_{10})aryloxy(C_5-C_9)heteroaryl, (C_1-C_6)alkoxy(C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_1-C_6)alkoxy(C_5-C_9)heteroaryloxy(C_6-C_{10})aryl or (C_1-C_6)alkoxy(C_6-C_{10})aryloxy(C_5-C_9)heteroaryl wherein each aryl group is optionally substituted by fluoro, chloro, bromo, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or perfluoro(C_1-C_3)alkyl.

2. A compound according to claim 1, wherein n is 2.

3. A compound according to claim 1, wherein X and Y are both CR^1 wherein R^1 is hydrogen.

4. A compound according to claim 1, wherein Ar is (C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_6-C_{10})aryl, 4-fluorophenoxy(C_6-C_{10})aryl, 4-fluorobenzyloxy(C_6-C_{10})aryl or (C_1-C_6)alkyl(C_6-C_{10})aryloxy(C_6-C_{10})aryl.

5. A compound according to claim 1, wherein n is 2, X and Y are both CR^1 wherein R^1 is hydrogen and Ar is (C_1-C_6)alkoxy(C_6-C_{10})aryl, (C_6-C_{10})aryl(C_1-C_6)alkoxy(C_6-C_{10})aryl, 4-fluorophenoxy(C_6-C_{10})aryl, 4-fluorobenzyloxy(C_6-C_{10})aryl or (C_1-C_6)alkyl(C_6-C_{10})aryloxy(C_6-C_{10})aryl.

6. A pharmaceutical composition for (a) the treatment of a condition selected from the group consisting of arthritis, cancer, tissue ulceration, mucular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, in combination with standard NSAID'S and analgesics and in combination with cytotoxic anticancer agents, and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) or (b) the inhibition of matrix metalloproteinases or the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising an amount of a compound of claim 1 effective in such treatment and a pharmaceutically acceptable carrier.

7. A method for the inhibition of (a) matrix metalloproteinases or (b) the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of claim 1.

8. A method for treating a condition selected from the group consisting of arthritis, cancer, tissue ulceration, macular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, compounds of formula I may be used in

combination with standard NSAID'S and analgesics and in combination with cytotoxic anticancer agents, and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an amount of a compound of claim 1, effective in treating such a condition.

INTERNATIONAL SEARCH REPORT

In ational Application No
PCT/IB 97/01582

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D493/08 A61K31/34

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 453 960 A (SHIONOGI & CO) 30 October 1991 see abstract; claims; example 3	1-8
A	EP 0 606 046 A (CIBA GEIGY AG) 13 July 1994 see abstract; claim 2; example 6	1-8
P,A	EP 0 780 386 A (HOFFMANN LA ROCHE ;AGOURON PHARMA (US)) 25 June 1997 see trans- N-hydroxy-2-'(4-methoxyphenyl)-sulfonyl!-cyclopentanecarboxamide see abstract; claims	1-8

-/--

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

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
17 March 1998	07. 04. 98

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

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

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 97/01582

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	M.A. STOLBERG ET AL.: "Synthesis of a Series of Vicinally Substituted Hydroxamic Acids" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 79, 20 May 1957, DC US, pages 2615-2617, XP002059123 see page 2615, column 2 see page 2617, column 2, paragraph 2	1-5

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 97/01582

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 7 and 8 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 97/01582

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0453960 A	30-10-91	AT 116650 T	15-01-95
		CA 2040319 A,C	20-10-91
		DE 69106425 D	16-02-95
		DE 69106425 T	04-05-95
		ES 2069112 T	01-05-95
		HU 210687 B	28-06-95
		JP 4211642 A	03-08-92
		KR 9702488 B	05-03-97
		US 5137914 A	11-08-92
EP 0606046 A	13-07-94	US 5455258 A	03-10-95
		AT 159012 T	15-10-97
		AU 684255 B	11-12-97
		AU 5265593 A	04-05-95
		CA 2112779 A	07-07-94
		DE 69314456 D	13-11-97
		DE 69314456 T	26-02-98
		FI 940012 A	07-07-94
		HU 70536 A	30-10-95
		JP 6256293 A	13-09-94
		MX 9400276 A	29-07-94
		NO 940038 A,B,	07-07-94
		NZ 250517 A	26-10-95
		US 5506242 A	09-04-96
		US 5552419 A	03-09-96
		US 5646167 A	08-07-97
		US 5672615 A	30-09-97
		ZA 9400048 A	11-08-94
EP 0780386 A	25-06-97	AU 7548296 A	31-07-97
		CA 2193178 A	21-06-97
		JP 9249638 A	22-09-97
		NO 965413 A	23-06-97
		PL 317604 A	23-06-97

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07C 311/29, 311/20, C07D 409/04, 205/04, 211/66, A61K 31/18, 31/44, 31/445

A1

(11) International Publication Number: **WO 98/33768**

(43) International Publication Date: 6 August 1998 (06.08.98)

(21) International Application Number: PCT/IB98/00023

(22) International Filing Date: 12 January 1998 (12.01.98)

(30) Priority Data:
60/036,857 3 February 1997 (03.02.97) US

(71) Applicant *(for all designated States except US)*: PFIZER PRODUCTS INC. [US/US]; Eastern Point Road, Groton, CT 06340 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: ROBINSON, Ralph, Pelton, Jr. [US/US]; 30 Friar Tuck Drive, Gales Ferry, CT 06335 (US). McCLURE, Kim, Francis [US/US]; Apartment #4, 6 School Street, Mystic, CT 06355 (US).

(74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).

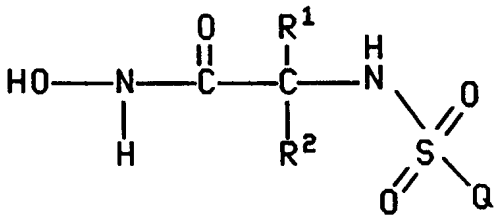
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: ARYLSULFONYLAMINO HYDROXAMIC ACID DERIVATIVES

(57) Abstract

A compound of formula (I) wherein R^1, R^2 and Q are as defined above, useful in the treatment of a condition selected from the group consisting of arthritis, cancer, tissue ulceration, macular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of TNF. In addition, the compounds of the present invention may be used in combination therapy with standard non–steroidal anti–inflammatory drugs (NSAID'S) and analgesics, and in combination with cytotoxic drugs such as adriamycin, daunomycin, cis–platinum, etoposide, taxol, taxotere and other alkaloids, such as vincristine, in the treatment of cancer.



(I)

FOR THE PURPOSES OF INFORMATION ONLY

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

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

ARYLSULFONYLAMINO HYDROXAMIC ACID DERIVATIVES

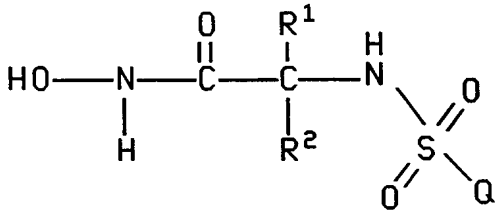
The present invention relates to arylsulfonylamino hydroxamic acid derivatives which are inhibitors of matrix metalloproteinases or the production of tumor necrosis factor (TNF) and as such are useful in the treatment of a condition selected from the group consisting of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of TNF. In addition, the compounds of the present invention may be used in combination therapy with standard non-steroidal anti-inflammatory drugs (hereinafter NSAID'S) and analgesics for the treatment of arthritis, and in combination with cytotoxic drugs such as adriamycin, daunomycin, cis-platinum, etoposide, taxol, taxotere and alkaloids, such as vincristine, in the treatment of cancer.

This invention also relates to a method of using such compounds in the treatment of the above diseases in mammals, especially humans, and to pharmaceutical compositions useful therefor.

There are a number of enzymes which effect the breakdown of structural proteins and which are structurally related metalloproteases. Matrix-degrading metalloproteinases, such as gelatinase, stromelysin and collagenase, are involved in tissue matrix degradation (e.g. collagen collapse) and have been implicated in many pathological conditions involving abnormal connective tissue and basement membrane matrix metabolism, such as arthritis (e.g. osteoarthritis and rheumatoid arthritis), tissue ulceration (e.g. corneal, epidermal and gastric ulceration), abnormal wound healing, periodontal disease, bone disease (e.g. Paget's disease and osteoporosis), tumor metastasis or invasion, as well as HIV-infection (J. Leuk. Biol., 52 (2): 244-248, 1992).

Tumor necrosis factor is recognized to be involved in many infectious and auto-immune diseases (W. Fiers, FEBS Letters, 1991, 285, 199). Furthermore, it has been shown that TNF is the prime mediator of the inflammatory response seen in sepsis and septic shock (C.E. Spooner et al., Clinical Immunology and Immunopathology, 1992, 62 S11).

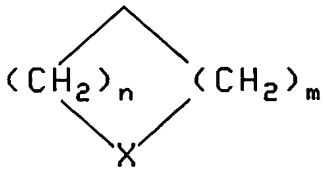
The present invention relates to a compound of the formula



I

or the pharmaceutically acceptable salts thereof, wherein

R^1 and R^2 are each independently selected from $(C_1\text{-}C_6)$alkyl, trifluoromethyl, trifluoromethyl$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl(difluoromethylene), $(C_1\text{-}C_3)$alkyl(difluoromethylene$(C_1\text{-}C_3)$alkyl, $(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkyl or R^1 and R^2 may be taken together to form a $(C_3\text{-}C_6)$cycloalkyl or benzo-fused $(C_3\text{-}C_6)$cycloalkyl ring or a group of the formula



wherein n and m are independently 1 or 2 and X is CF_2, S, O or NR^3 wherein R^3 is hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylsulfonyl, $(C_6\text{-}C_{10})$arylsulfonyl or acyl; and

Q is $(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryloxy$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl$(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryloxy$(C_2\text{-}C_9)$heteroaryl, $(C_2\text{-}C_9)$heteroaryl, $(C_2\text{-}C_9)$heteroaryl$(C_2\text{-}C_9)$heteroaryl, $(C_2\text{-}C_9)$heteroaryl$(C_6\text{-}C_{10})$aryl, $(C_1\text{-}C_6)$alkyl$(C_6\text{-}C_{10})$aryl, $(C_1\text{-}C_6)$alkoxy$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_9)$heteroaryloxy$(C_6\text{-}C_{10})$aryl, $(C_1\text{-}C_6)$alkyl$(C_2\text{-}C_9)$heteroaryl, $(C_1\text{-}C_6)$alkoxy$(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_2\text{-}C_9)$heteroaryl, $(C_2\text{-}C_9)$heteroaryloxy$(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryloxy$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_9)$heteroaryloxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl$(C_6\text{-}C_{10})$aryloxy$(C_6\text{-}C_{10})$aryl, $(C_1\text{-}C_6)$alkyl$(C_2\text{-}C_9)$heteroaryloxy$(C_6\text{-}C_{10})$aryl, $(C_1\text{-}C_6)$alkyl$(C_6\text{-}C_{10})$aryloxy$(C_2\text{-}C_9)$heteroaryl, $(C_1\text{-}C_6)$alkoxy$(C_6\text{-}C_{10})$aryloxy$(C_6\text{-}C_{10})$aryl, $(C_1\text{-}C_6)$alkoxy$(C_2\text{-}C_9)$heteroaryloxy$(C_6\text{-}C_{10})$aryl or $(C_1\text{-}C_6)$alkoxy$(C_6\text{-}C_{10})$aryloxy$(C_2\text{-}C_9)$heteroaryl wherein each aryl group is optionally substituted by fluoro, chloro, bromo, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy or perfluoro$(C_1\text{-}C_3)$alkyl.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof.

The term "alkoxy", as used herein, includes O-alkyl groups wherein "alkyl" is defined above.

The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl or naphthyl, optionally substituted by 1 to 3 substituents selected from the group consisting of fluoro, chloro, trifluoromethyl, $(C_1$-$C_6)$alkoxy, $(C_6$-$C_{10})$aryloxy, trifluoromethoxy, difluoromethoxy and $(C_1$-$C_6)$alkyl.

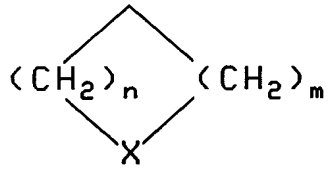
The term "heteroaryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic heterocyclic compound by removal of one hydrogen, such as pyridyl, furyl, pyroyl, thienyl, isothiazolyl, imidazolyl, benzimidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzofuryl, isobenzofuryl, benzothienyl, pyrazolyl, indolyl, isoindolyl, purinyl, carbazolyl, isoxazolyl, thiazolyl, oxazolyl, benzthiazolyl or benzoxazolyl, optionally substituted by 1 to 2 substituents selected from the group consisting of fluoro, chloro, trifluoromethyl, $(C_1$-$C_6)$alkoxy, $(C_6$-$C_{10})$aryloxy, trifluoromethoxy, difluoromethoxy and $(C_1$-$C_6)$alkyl.

The term "acyl", as used herein, unless otherwise indicated, includes a radical of the general formula RCO wherein R is alkyl, alkoxy, aryl, arylalkyl or arylalkyloxy and the terms "alkyl" or "aryl" are as defined above.

The term "acyloxy", as used herein, includes O-acyl groups wherein "acyl" is defined above.

The compound of formula I may have chiral centers and therefore exist in different enantiomeric forms. This invention relates to all optical isomers and stereoisomers of the compounds of formula I and mixtures thereof.

Preferred compounds of formula I include those wherein R^1 and R^2 are taken together to form a $(C_3$-$C_6)$cycloalkyl or benzo-fused $(C_3$-$C_6)$cycloalkyl ring or a group of the formula



wherein n and m are independently 1 or 2 and X is CF_2, S, O or NR^3 wherein R^3 is hydrogen, $(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$aryl, $(C_2$-$C_9)$heteroaryl, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkyl, $(C_2$-$C_9)$heteroaryl$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylsulfonyl, $(C_6$-$C_{10})$arylsulfonyl or acyl.

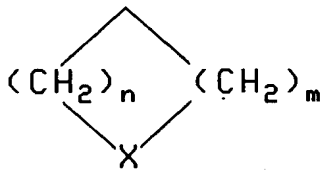
Other preferred compounds of formula I include those wherein R^1 and R^2 are taken together to form a $(C_3$-$C_6)$cycloalkyl or benzo-fused $(C_3$-$C_6)$cycloalkyl ring.

Other preferred compounds of formula I include those wherein Q is $(C_6$-$C_{10})$aryl, $(C_6$-$C_{10})$aryl$(C_6$-$C_{10})$aryl, $(C_6$-$C_{10})$aryloxy$(C_6$-$C_{10})$aryl, $(C_6$-$C_{10})$aryloxy$(C_2$-$C_9)$heteroaryl, $(C_2$-$C_9)$heteroaryl, $(C_2$-$C_9)$heteroaryl$(C_2$-$C_9)$heteroaryl, $(C_6$-$C_{10})$aryl$(C_2$-$C_9)$heteroaryl, $(C_2$-$C_9)$heteroaryl$(C_6$-$C_{10})$aryl or $(C_2$-$C_9)$heteroaryloxy$(C_6$-$C_{10})$aryl.

Other preferred compounds of formula I include those wherein Q is $(C_6$-$C_{10})$aryloxy$(C_6$-$C_{10})$aryl.

Other preferred compounds of formula I include those wherein R^1 and R^2 are each independently $(C_1$-$C_6)$alkyl.

More preferred compounds of formula I include those wherein R^1 and R^2 are taken together to form a $(C_3$-$C_6)$cycloalkyl or benzo-fused $(C_3$-$C_6)$cycloalkyl ring or a group of the formula



wherein n and m are independently 1 or 2 and X is CF_2, S, O or NR^3 wherein R^3 is hydrogen, $(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$aryl, $(C_2$-$C_9)$heteroaryl, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkyl, $(C_2$-$C_9)$heteroaryl$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylsulfonyl, $(C_6$-$C_{10})$arylsulfonyl or acyl; and Q is $(C_6$-$C_{10})$aryl, $(C_6$-$C_{10})$aryl$(C_6$-$C_{10})$aryl, $(C_6$-$C_{10})$aryloxy$(C_6$-$C_{10})$aryl, $(C_6$-$C_{10})$aryloxy-$(C_2$-$C_9)$heteroaryl, $(C_2$-$C_9)$heteroaryl, $(C_2$-$C_9)$heteroaryl$(C_2$-$C_9)$heteroaryl, $(C_6$-$C_{10})$aryl$(C_2$-$C_9)$heteroaryl, $(C_2$-$C_9)$heteroaryl$(C_6$-$C_{10})$aryl or $(C_2$-$C_9)$heteroaryloxy$(C_6$-$C_{10})$aryl.

More preferred compounds of formula I include those wherein R^1 and R^2 are taken together to form a (C_3-C_6)cycloalkyl or benzo-fused (C_3-C_6)cycloalkyl ring; and Q is (C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl(C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl(C_6-C_{10})aryl or (C_2-C_9)heteroaryloxy(C_6-C_{10})aryl.

More preferred compounds of formula I include those wherein R^1 and R^2 are each independently (C_1-C_6)alkyl; and Q is (C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl(C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl(C_6-C_{10})aryl or (C_2-C_9)heteroaryloxy(C_6-C_{10})aryl.

More preferred compounds of formula I include those wherein R^1 and R^2 are each independently (C_1-C_6)alkyl; and Q is (C_6-C_{10})aryloxy(C_6-C_{10})aryl.

Specific preferred compounds of formula I include the following:

3-[4-(4-Fluorophenoxy)benzenesulfonylamino]azetidine-3-carboxylic acid hydroxyamide;

4-[4-(4-Fluorophenoxy)benzenesulfonylamino]piperidine-4-carboxylic acid hydroxyamide;

1-[4-(4-Fluorophenoxy)benzenesulfonylamino]cyclopropane-1-carboxylic acid hydroxyamide;

1-[4-(4-Chlorophenoxy)benzenesulfonylamino]cyclopropane-1-carboxylic acid hydroxyamide;

1-[4-(4-Fluorophenoxy)benzenesulfonylamino]cyclobutane-1-carboxylic acid hydroxyamide;

1-[4-(4-Chlorophenoxy)benzenesulfonylamino]cyclobutane-1-carboxylic acid hydroxyamide;

1-[4-(4-Fluorophenoxy)benzenesulfonylamino]cyclopentane-1-carboxylic acid hydroxyamide;

1-[4-(4-Fluorophenoxy)benzenesulfonylamino]cyclohexane-1-carboxylic acid hydroxyamide;

2-[4-(4-Fluorophenoxy)benzenesulfonylamino]-N-hydroxy-2-methylpropionamide;

2-[4-(4-Chlorophenoxy)benzenesulfonylamino]-N-hydroxy-2-methyl-propionamide;

N-Hydroxy-2-methyl-2-(5-pyridin-2-ylthiophene-2-sulfonylamino)propionamide;

1-(5-Pyridin-2-yl-thiophene-2-sulfonylamino)cyclopentane-1-carboxylic acid hydroxyamide;

1-(4'-Fluorobiphenyl-4-sulfonylamino)cyclopropane-1-carboxylic acid hydroxyamide;

1-(4'-Fluorobiphenyl-4-sulfonylamino)cyclobutane-1-carboxylic acid hydroxyamide;

1-(4'-Fluorobiphenyl-4-sulfonylamino)cyclopentane-1-carboxylic acid hydroxyamide;

2-(4-Methoxybenzenesufonylamino)indan-2-carboxylic acid hydroxyamide; and

2-[4-(4-Fluorophenoxy)benzenesulfonylamino]-indan-2-carboxylic acid hydroxyamide.

The present invention also relates to a pharmaceutical composition for (a) the treatment of a condition selected from the group consisting of arthritis, cancer, synergy with cytotoxic anticancer agents, tissue ulceration, macular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, in combination with standard NSAID'S and analgesics and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) or (b) the inhibition of matrix metalloproteinases or the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising an amount of a compound of formula I or a pharmaceutically acceptable salt thereof effective in such treatments and a pharmaceutically acceptable carrier.

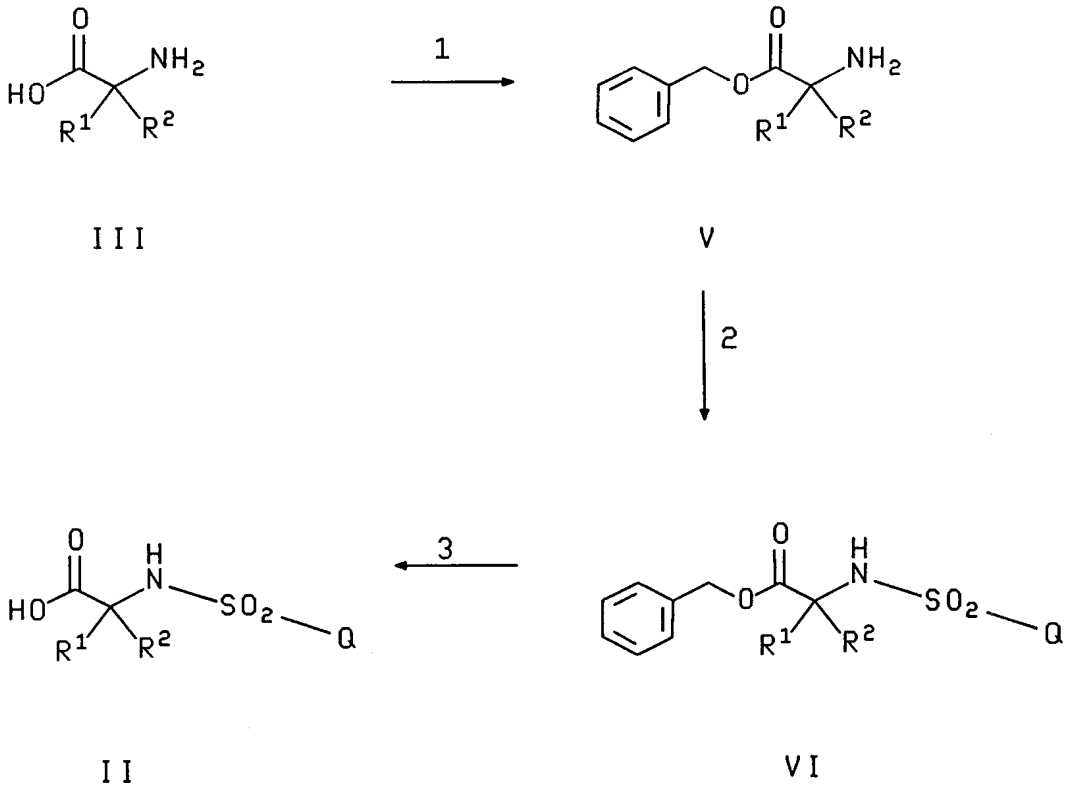
The present invention also relates to a method for the inhibition of (a) matrix metalloproteinases or (b) the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

The present invention also relates to a method for treating a condition selected from the group consisting of arthritis, cancer, tissue ulceration, macular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, compounds of formula I may be used in combination with standard NSAID'S and analgesics and in combination with cytotoxic anticancer agents, and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an amount of a compound of

formula I or a pharmaceutically acceptable salt thereof effective in treating such a condition.

The following reaction Schemes illustrate the preparation of the compounds of the present invention. Unless otherwise indicated R^1, R^2 and Q in the reaction Schemes and the discussion that follow are defined as above.

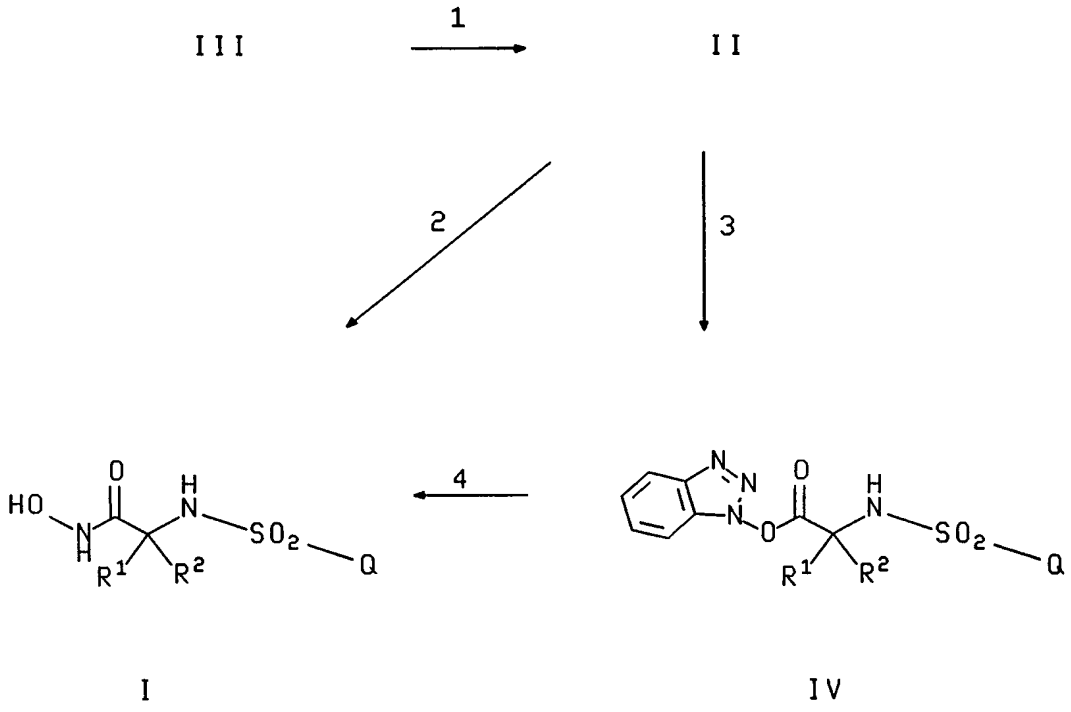
Preparation A



III V

II VI

Scheme 1



I IV

In Reaction 1 of Preparation A, an amino acid of formula **III** is treated with benzyl alcohol and an acid of the formula HX, wherein X is preferably 4-toluenesulfonate, in an inert solvent, such as benzene or toluene (toluene preferred) to obtain the corresponding benzyl ester acid salt of formula **V**. The reaction is normally carried out for a time period between about 1 hour to about 24 hours, at the boiling temperature of the solvent used. The water formed during the progress of the reaction is normally collected in a Dean-Stark trap.

In Reaction 2 of Preparation A, the compound of formula **V** is converted to the corresponding compound of formula **VI** by reacting **V** with a reactive functional derivative of a sulfonic acid (QSO_2OH), such as the sulfonyl chloride (QSO_2Cl), in the presence of a base, such as sodium hydroxide or triethylamine, and a solvent, such as methylene chloride, tetrahydrofuran, dioxane, water or acetonitrile, preferably a mixture of dioxane and water. The reaction mixture is stirred at a temperature between about 0°C to about 50°C, preferably at room temperature, for a time period between about 10 minutes to about 2 days, preferably about 60 minutes.

In Reaction 3 of Preparation A, the intermediate compound of formula **VI** is hydrogenolyzed to provide the intermediate of formula **II**. The reaction is carried out at in a solvent, such as ethanol, under an atmosphere of hydrogen (preferably at 3 atmospheres pressure) using a catalyst such as 10% palladium on activated carbon. The reaction mixture is normally agitated at room temperature for a time period between about 30 minutes to about 24 hours, preferably about 1.5 hours.

In reaction 1 of Scheme 1, the amino acid compound of formula **III** is converted to the corresponding compound of formula **II** by reacting **III** with a reactive functional derivative of a sulfonic acid of the formula QSO_2OH, wherein Q is as defined above, such as the sulfonyl chloride (QSO_2Cl), in the presence of a base, such as sodium hydroxide or triethylamine, and a polar solvent such as tetrahydrofuran, dioxane, water or acetonitrile, preferably a mixture of dioxane and water. The reaction mixture is stirred at a temperature between about 0°C to about 50°C, preferably at room temperature, for a time period between 10 minutes to about 2 days, preferably about 60 minutes.

In reaction 2 of Scheme 1, the carboxylic acid of formula **II** is converted to the hydroxamic acid compound of formula **I** by treating **II** with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide and 1-hydroxybenztriazole in a polar solvent, such as N,N-dimethylformamide, followed by the addition of hydroxylamine to the reaction mixture

after a time period between about 15 minutes to about 1 hour, preferably about 30 minutes. The hydroxylamine is preferably generated in situ from a salt form, such as hydroxylamine hydrochloride, in the presence of a base, such as triethylamine. Alternatively, a protected derivative of hydroxylamine or its salt form, where the hydroxyl group is protected as a tert-butyl, benzyl, allyl or 2-trimethylsilylethyl ether, may be used in place of hydroxylamine or a hydroxylamine salt. Removal of the hydroxyl protecting group is carried out by hydrogenolysis for a benzyl protecting group (5% palladium on barium sulfate is the preferred catalyst) or treatment with a strong acid, such as trifluoroacetic acid, for a tert-butyl protecting group. The allyl protecting group may be removed by treatment with tributyltinhydride and acetic acid in the presence of catalytic bis(triphenylphosphine) palladium(II)chloride. The 2-trimethylsilylethyl ether may be removed by reaction with a strong acid such as trifluoroacetic acid or by reaction with a fluoride source such as boron trifluoride etherate. The reaction of II with hydroxylamine, a salt of hydroxylamine, a protected derivative of hydroxylamine or a salt of a protected derivative of hydroxylamine may also be carried out the presence of (benztriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate and a base such as triethylamine in an inert solvent, such as methylene chloride. The reaction mixture is stirred at a temperature between about 0°C to about 50°C, preferably room temperature, for a time period between about 1 hour to about 3 days, preferably about 1 day. The preferred procedure for converting compound II to compound I is to react II with O-benzylhydroxylamine hydrochloride in the presence of (benztriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate and triethylamine using methylene chloride as solvent. Subsequent removal of the O-benzyl protecting group to afford a compound of formula I is then carried out by hydrogenolysis under 3 atmospheres hydrogen at room temperature using 5% palladium on barium sulfate as catalyst. The preferred solvent is methanol. The reaction time may vary from about 1 hour to about 5 hours (3.5 hours preferred).

In certain instances it is preferred to obtain the compound of formula I by reaction of hydroxylamine, a salt of hydroxylamine, a protected derivative of hydroxylamine or a salt of a protected derivative of hydroxylamine with an activated ester of formula IV, as shown in Reaction 3 of Scheme 1. The reaction is carried out in an inert solvent, such as N,N-dimethyl-formamide at a temperature ranging from about room temperature to about 80°C, preferably about 50°C for a time period of

about 1 hour to about 2 days. If a protected derivative of hydroxylamine or a salt of a protected derivative of hydroxylamine is used, removal of the protecting group is carried out as described above. The activated ester derivative of formula **IV** is obtained by treatment of the compound of formula **II** with (benztriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate and a base such as triethylamine in an inert solvent, such as methylene chloride (Reaction 4, Scheme 1). The reaction mixture is stirred at a temperature between about 0°C to about 50°C, preferably room temperature, for a time period between about 1 hour to about 3 days, preferably about 1 day.

Pharmaceutically acceptable salts of the acidic compounds of the invention are salts formed with bases, namely cationic salts such as alkali and alkaline earth metal salts, such as sodium, lithium, potassium, calcium, magnesium, as well as ammonium salts, such as ammonium, trimethyl-ammonium, diethylammonium, and tris-(hydroxymethyl)-methylammonium slats.

Similarly acid addition salts, such as of mineral acids, organic carboxylic and organic sulfonic acids e.g. hydrochloric acid, methanesulfonic acid, maleic acid, are also possible provided a basic group, such as pyridyl, constitutes part of the structure.

The ability of the compounds of formula **I** or their pharmaceutically acceptable salts (hereinafter also referred to as the compounds of the present invention) to inhibit matrix metalloproteinases or the production of tumor necrosis factor (TNF) and, consequently, demonstrate their effectiveness for treating diseases characterized by matrix metalloproteinase or the production of tumor necrosis factor is shown by the following in vitro assay tests.

Biological Assay

Inhibition of Human Collagenase (MMP-1)

Human recombinant collagenase is activated with trypsin using the following ratio: 10 μg trypsin per 100 μg of collagenase. The trypsin and collagenase are incubated at room temperature for 10 minutes then a five fold excess (50 μg/10 μg trypsin) of soybean trypsin inhibitor is added.

10 mM stock solutions of inhibitors are made up in dimethyl sulfoxide and then diluted using the following Scheme:

10 mM ------> 120 μM ------> 12 μM ------> 1.2 μM ------> 0.12 μM

Twenty-five microliters of each concentration is then added in triplicate to appropriate wells of a 96 well microfluor plate. The final concentration of inhibitor will be a 1:4 dilution after addition of enzyme and substrate. Positive controls (enzyme, no inhibitor) are set up in wells D1-D6 and blanks (no enzyme, no inhibitors) are set in wells D7-D12.

Collagenase is diluted to 400 ng/ml and 25 μl is then added to appropriate wells of the microfluor plate. Final concentration of collagenase in the assay is 100 ng/ml.

Substrate (DNP-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2) is made as a 5 mM stock in dimethyl sulfoxide and then diluted to 20 μM in assay buffer. The assay is initiated by the addition of 50 μl substrate per well of the microfluor plate to give a final concentration of 10 μM.

Fluorescence readings (360 nM excitation, 460 nm emission) were taken at time 0 and then at 20 minute intervals. The assay is conducted at room temperature with a typical assay time of 3 hours.

Fluorescence vs time is then plotted for both the blank and collagenase containing samples (data from triplicate determinations is averaged). A time point that provides a good signal (the blank) and that is on a linear part of the curve (usually around 120 minutes) is chosen to determine IC_{50} values. The zero time is used as a blank for each compound at each concentration and these values are subtracted from the 120 minute data. Data is plotted as inhibitor concentration vs % control (inhibitor fluorescence divided by fluorescence of collagenase alone x 100). IC_{50}'s are determined from the concentration of inhibitor that gives a signal that is 50% of the control.

If IC_{50}'s are reported to be <0.03 μM then the inhibitors are assayed at concentrations of 0.3 μM, 0.03 μM, 0.03 μM and 0.003 μM.

Inhibition of Gelatinase (MMP-2)

Inhibition of gelatinase activity is assayed using the Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2 substrate (10 μM) under the same conditions as inhibition of human collagenase (MMP-1).

72kD gelatinase is activated with 1 mM APMA (p-aminophenyl mercuric acetate) for 15 hours at 4°C and is diluted to give a final concentration in the assay of 100 mg/ml. Inhibitors are diluted as for inhibition of human collagenase (MMP-1) to give

final concentrations in the assay of 30 μM, 3 μM, 0.3 μM and 0.03 μM. Each concentration is done in triplicate.

Fluorescence readings (360 nm excitation, 460 emission) are taken at time zero and then at 20 minutes intervals for 4 hours.

IC_{50}'s are determined as per inhibition of human collagenase (MMP-1). If IC_{50}'s are reported to be less than 0.03 μM, then the inhibitors are assayed at final concentrations of 0.3 μM, 0.03 μM, 0.003 μM and 0.003 μM.

Inhibition of Stromelysin Activity (MMP-3)

Inhibition of stromelysin activity is based on a modified spectrophotometric assay described by Weingarten and Feder (Weingarten, H. and Feder, J., Spectrophotometric Assay for Vertebrate Collagenase, Anal. Biochem. 147, 437-440 (1985)). Hydrolysis of the thio peptolide substrate [Ac-Pro-Leu-Gly-$SCH[CH_2CH(CH_3)_2]CO$-Leu-Gly-OC_2H_5] yields a mercaptan fragment that can be monitored in the presence of Ellman's reagent.

Human recombinant prostromelysin is activated with trypsin using a ratio of 1 μl of a 10 mg/ml trypsin stock per 26 μg of stromelysin. The trypsin and stromelysin are incubated at 37°C for 15 minutes followed by 10 μl of 10 mg/ml soybean trypsin inhibitor for 10 minutes at 37°C for 10 minutes at 37°C to quench trypsin activity.

Assays are conducted in a total volume of 250 μl of assay buffer (200 mM sodium chloride, 50 mM MES, and 10 mM calcium chloride, pH 6.0) in 96-well microliter plates. Activated stromelysin is diluted in assay buffer to 25 μg/ml. Ellman's reagent (3-Carboxy-4-nitrophenyl disulfide) is made as a 1M stock in dimethyl formamide and diluted to 5 mM in assay buffer with 50 μl per well yielding at 1 mM final concentration.

10 mM stock solutions of inhibitors are made in dimethyl sulfoxide and diluted serially in assay buffer such that addition of 50 μL to the appropriate wells yields final concentrations of 3 μM, 0.3 μM, 0.003 μM, and 0.0003 μM. All conditions are completed in triplicate.

A 300 mM dimethyl sulfoxide stock solution of the peptide substrate is diluted to 15 mM in assay buffer and the assay is initiated by addition of 50 μl to each well to give a final concentration of 3 mM substrate. Blanks consist of the peptide substrate and Ellman's reagent without the enzyme. Product formation was monitored at 405 nm with a Molecular Devices UVmax plate reader.

IC_{50} values were determined in the same manner as for collagenase.

Inhibition of MMP-13

Human recombinant MMP-13 is activated with 2mM APMA (p-aminophenyl mercuric acetate) for 1.5 hours, at 37°C and is diluted to 400 mg/ml in assay buffer (50 mM Tris, pH 7.5, 200 mM sodium chloride, 5mM calcium chloride, 20μM zinc chloride, 0.02% brij). Twenty-five microliters of diluted enzyme is added per well of a 96 well microfluor plate. The enzyme is then diluted in a 1:4 ratio in the assay by the addition of inhibitor and substrate to give a final concentration in the assay of 100 mg/ml.

10 mM stock solutions of inhibitors are made up in dimethyl sulfoxide and then diluted in assay buffer as per the inhibitor dilution scheme for inhibition of human collagenase (MMP-1): Twenty-five microliters of each concentration is added in triplicate to the microfluor plate. The final concentrations in the assay are 30 μM, 3μM, 0.3 μM, and 0.03 μM.

Substrate (Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2) is prepared as for inhibition of human collagenase (MMP-1) and 50 μl is added to each well to give a final assay concentration of 10 μM. Fluorescence readings (360 nM excitation; 450 emission) are taken at time 0 and every 5 minutes for 1 hour.

Positive controls consist of enzyme and substrate with no inhibitor and blanks consist of substrate only.

IC_{50}'s are determined as per inhibition of human collagenase (MMP-1). If IC_{50}'s are reported to be less than 0.03 μM, inhibitors are then assayed at final concentrations of 0.3 μM, 0.03 μM, 0.003 μM and 0.0003 μM.

Inhibition of TNF Production

The ability of the compounds or the pharmaceutically acceptable salts thereof to inhibit the production of TNF and, consequently, demonstrate their effectiveness for treating diseases involving the production of TNF is shown by the following in vitro assay:

Human mononuclear cells were isolated from anti-coagulated human blood using a one-step Ficoll-hypaque separation technique. (2) The mononuclear cells were washed three times in Hanks balanced salt solution (HBSS) with divalent cations and resuspended to a density of 2 x 10^6 /ml in HBSS containing 1% BSA. Differential counts determined using the Abbott Cell Dyn 3500 analyzer indicated that monocytes ranged from 17 to 24% of the total cells in these preparations.

180μ of the cell suspension was aliquoted into flate bottom 96 well plates (Costar). Additions of compounds and LPS (100ng/ml final concentration) gave a final volume of 200μl. All conditions were performed in triplicate. After a four hour incubation at 37°C in an humidified CO_2 incubator, plates were removed and centrifuged (10 minutes at approximately 250 x g) and the supernatants removed and assayed for TNFα using the R&D ELISA Kit.

For administration to mammals, including humans, for the inhibition of matrix metalloproteinases or the production of tumor necrosis factor (TNF), a variety of conventional routes may be used including orally, parenterally and topically. In general, the active compound will be administered orally or parenterally at dosages between about 0.1 and 25 mg/kg body weight of the subject to be treated per day, preferably from about 0.3 to 5 mg/kg. However, some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

The compounds of the present invention can be administered in a wide variety of different dosage forms, in general, the therapeutically effective compounds of this invention are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelation and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof. In the case of animals, they are

advantageously contained in an animal feed or drinking water in a concentration of 5-5000 ppm, preferably 25 to 500 ppm.

For parenteral administration (intramuscular, intraperitoneal, subcutaneous and intravenous use) a sterile injectable solution of the active ingredient is usually prepared. Solutions of a therapeutic compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably adjusted and buffered, preferably at a pH of greater than 8, if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art. In the case of animals, compounds can be administered intramuscularly or subcutaneously at dosage levels of about 0.1 to 50 mg/kg/day, advantageously 0.2 to 10 mg/kg/day given in a single dose or up to 3 divided doses.

The present invention is illustrated by the following examples, but it is not limited to the details thereof.

Preparation A

4-(4-Fluorophenoxy)benzenesulfonyl chloride

Chlorosulfonic acid (26 mL, 0.392 mole) was added dropwise to ice-cooled 4-fluorophenoxybenzene (36.9 grams, 0.196 mole) with mechanical stirring. When addition was complete, the mixture was stirred at room temperature for 4 hours. The mixture was then poured into ice water. The product, 4-(4-fluorophenoxy)benzene-sulfonylchloride (18.6 grams, 33%) was collected by filtration and dried in the air.

Preparation B

Sodium 4-(3-methylbutoxy)benzenesulfonate

A solution of 4-hydroxybenzenesulfonic acid (10.0 grams, 43.1 mmole) and sodium hydroxide (3.3 grams, 83 mmole) in water (40 mL) was mixed with a solution of 1-iodo-3-methylbutane (11.3 mL, 86.4 mmole) in isopropanol (60 mL) and the resulting mixture was heated at reflux for 2 days. The isopropanol was removed by evaporation under vaccuum. The titled compound, 10.0 grams (87%), was collected by filtration washing with isopropanol.

Preparation C

4-(3-Methylbutoxy)benzenesulfonyl chloride

A mixture of sodium 4-(3-methylbutoxy)benzenesulfonate (2.5 grams, 9.4 mmole), thionyl chloride (10 mL), and 5 drops of N,N-dimethylformamide was heated at reflux for 5 hours. After cooling, the excess thionyl chloride was evaporated and the residue was taken up in ethyl acetate. The solution was cooled in an ice bath and water was added. The organic phase was separated and washed with water and brine. After drying over sodium sulfate, the solvent was evaporated to afford the titled compound as an oil, 2.34 grams (95%).

Preparation D

Sodium 4-(2-cyclopentylethoxy)benzenesulfonate

A solution of 4-hydroxybenzenesulfonic acid (6.5 grams, 28.2 mmole) and sodium hydroxide (2.2 grams, 55 mmole) in water (15 mL) was mixed with a solution of 2-(bromoethyl)cyclopentane (15.0 grams, 84.7 mmole) in isopropanol (40 mL) and the resulting mixture was heated at reflux for 2 days. The isopropanol was removed by evaporation under vaccuum. The titled compound, 4.7 grams (57%), was collected by filtration washing with isopropanol.

Preparation E

4-(3-Methylbutoxy)benzenesulfonyl chloride

A mixture of sodium 4-(2-cyclopentylethoxy)-benzenesulfonate (2.5 grams, 8.6 mmole), thionyl chloride (15 mL), and a few drops of N,N-dimethylformamide was heated at reflux for 5 hours. After cooling, the excess thionyl chloride was evaporated and the residue was taken up in ethyl acetate. The solution was cooled in an ice bath and water was added. The organic phase was separated and washed with water and brine. After drying over sodium sulfate, the solvent was evaporated to afford the titled compound as an oil, 2.24 grams (90%).

Preparation F

4'-Fluorobiphenylsulfonyl chloride

Chlorosulfonic acid (8.7 mL, 0.13 mole) was added dropwise to 4-fluorobiphenyl (10.2 grams, 59 mmol) while sirring in an ice bath. Stirring was continued with ice cooling for 0.5 hours and then the reaction mixture was poured onto ice. The resulting white precipitate was collected by filtration and dissolved in chloroform. The chloroform solution was washed with water and brine, dried over magnesium sulfate and

concentrated to afford a white solid. The desired product, 4'-fluorobiphenylsulfonyl chloride (4.3 grams, 27%), was separated from 4'-fluorobiphenylsulfonic acid (an unwanted side product) by crystallization of the latter from ethyl acetate and crystallization of the remaining material from hexane.

Preparation G

Sodium 4-(4-fluorobenzyloxy)benzenesulfonate

To a solution of 4-hydroxybenzenesulfonic acid (5.13 grams, 22.1 mmole) in 1N aqueous sodium hydroxide solution (23 mL) was added a solution of 4-fluorobenzylbromide (3.3 mL, 26.5 mmole) in ethanol (20 mL). The resulting mixture was heated at reflux for 2 days. Upon cooling and standing, a white solid precipitated. The precipitated product, sodium 4-(4-fluorobenzyloxy)benzenesulfonate, 4.95 grams (74%) was collected by filtration washing with ethyl acetate and diethyl ether.

Preparation H

4-(4-Fluorobenzyloxy)benzenesulfonyl chloride

To a slurry of sodium 4-(4-fluorobenzyloxy)benzenesulfonate (0.5 grams, 1.64 mmole), in methylene chloride (5 mL) was added phosphorus pentachloride (275 mg, 1.31 mmole). The resulting mixture was heated at reflux for 7 hours. After cooling in an ice bath and quenching with water (15 mL), the mixture was extracted with ethyl acetate. The organic phase was washed brine, dried over sodium sulfate, and concentrated to afford 4-(4-fluorobenzyloxy)benzenesulfonyl chloride a white solid (130 mg, 26%).

Preparation I

4-(4-Chlorophenoxy)benzenesulfonyl chloride

Chlorosulfonic acid (9.7 mL, 0.147 mole) was added dropwise to 4-chlorophenoxybenzene (12.6 mL, 73.4 mmole) at room temperature with stirring. When addition was complete, the mixture was stirred at room temperature for 1 hour and then poured into ice water. The solid was collected by filtration, dried in the air, and recrystallized from petroleum ether and ethyl acetate to give 4-(4-chlorophenoxy)benzenesulfonylchloride (7.43 grams, 33%).

Example 1

1-(4-Methoxybenzenesulfonylamino)cyclopentane-1-carboxylicacidhydroxyamide

(A) To a solution of 1-aminocyclopentane-1-carboxylic acid (6.0 grams, 46.5 mmole) and triethylamine (14 mL, 100 mmole) in dioxane (90 mL) and water (90 mL) was added 4-methoxybenzenesulfonyl chloride (10.6 grams, 51.3 mmole). The resulting mixture was stirred at room temperature for 4 hours, acidified with aqueous 1N hydrochloric acid solution, and extracted twice with ethyl acetate. The combined ethyl acetate extracts were washed with brine, dried over magnesium sulfate and concentrated to leave a tan solid which was triturated with chloroform to afford 1-(4-methoxybenzenesulfonylamino)-cyclopentane-1-carboxylic acid as a white solid, 5.42 grams (39%).

(B) To a solution of 1-(4-methoxybenzenesulfonylamino)cyclopentane-1-carboxylic acid (4.65 grams, 15.2 mmole) and triethylamine (2.5 mL, 17.9 mmole) in methylene chloride (120 mL) was added (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (7.4 grams, 16.3 mmole). The resulting mixture was stirred at room temperature for 2.5 days. The solvent was evaporated and the residue was taken up in ethyl acetate. The solution was washed successively with aqueous 0.5 N hydrochloric acid solution, water and brine. After drying over magnesium sulfate, the solvent was evaporated to afford 1-(4-methoxybenzenesulfonylamino)cyclopentane-carboxylic acid benzotriazol-1-yl ester as a yellow solid. This was dissolved in N,N-dimethylformamide (120 mL) and to the resulting solution was added diisopropylethylamine (5.3 mL, 30 mmole) and O-benzylhydroxylamine hydrochloride (3.2 grams, 20 mmole). The mixture was heated in an oil bath at 50°C for 20 hours. The solvent was evaporated and ethyl acetate was added. The mixture was filtered to collect a white solid. The filtrate was washed successively with aqueous 0.5 N hydrochloric acid solution, aqueous saturated sodium bicarbonate solution and brine. Upon evaporation of the solvent, a solid was obtained which was combined with that isolated by filtration and triturated with ethyl acetate to afford 1-(4-methoxybenzenesulfonylamino)cyclopentane-1-carboxylic acid benzyloxyamide as a white solid, 2.92 grams (47%).

(C) A solution of 1-(4-methoxybenzenesulfonylamino)cyclopentane-1-carboxylic acid benzyloxyamide (1.50 grams, 3.71 mmole) in methanol (200 mL) was treated with 5% palladium on barium sulfate (0.75 grams) and hydrogenated at 3 atmospheres

pressure for 3.5 hours in a Parr shaker. The catalyst was removed by passage through a 0.45 μm nylon filter and the filtrate was concentrated to afford 1-(4-methoxybenzenesulfonylamino)-cyclopentane-1-carboxylic acid hydroxyamide as a white solid, 1.13 grams (97%). MS: 313 (M-1).

The titled compounds of Examples 2-8 were prepared by a method analogous to that described in Example 1 using the reagents indicated.

Example 2

1-(4-Methoxybenzenesulfonylamino)cyclohexane-1-carboxylic acid hydroxyamide.

1-Aminocyclohexane-1-carboxylic acid; 4-methoxybenzenesulfonyl chloride. MS: 327 (M-1).

Example 3

1-[4-(4-Fluorophenoxy)benzenesulfonylamino]cyclopentane-1-carboxylic acid hydroxyamide

1-Aminocyclopentane-1-carboxylic acid; 4-(4-fluorophenoxy)benzenesulfonyl chloride. MS: 393 (M-1). Analysis calculated for $C_{18}H_{19}FN_2O_5S.0.25\ H_2O$: C 54.19, H 4.93, N 7.02. Found: C 54.20, H 5.13, N 7.08.

Example 4

1-[4-(4-Fluorophenoxy)benzenesulfonylamino]cyclohexane-1-carboxylic acid hydroxyamide

1-Aminocyclohexane-1-carboxylic acid; 4-(4-fluorophenoxy)benzenesulfonyl chloride. Recrystallized from chloroform. MP: 174°C; MS: 407 (M-1).

Example 5

1-[4-(4-Fluorophenoxy)benzenesulfonylamino]cyclopropane-1-carboxylic acid hydroxyamide

1-Aminocyclopropane-1-carboxylic acid; 4-(4-fluorophenoxy)benzenesulfonyl chloride. MP: 184°C; MS 365 (M-1); Analysis calculated for $C_{16}H_{15}FN_2O_5S$: C 52.45, H 4.13, N 7.65. Found: C 52.20, H 4.34, N 7.44.

Example 6

1-(4'-Fluorobiphenyl-4-sulfonylamino)cyclopentane-1-carboxylic acid hydroxyamide

1-Aminocyclopentane-1-carboxylic acid; 4'-fluorobiphenylsulfonyl chloride. Recrystallized from chloroform. MP 159 °C; MS: 377 (M-1).

Example 7

1-[4-(4-Fluorophenoxy)benzenesulfonylamino]cyclobutane-1-carboxylic acid hydroxyamide

1-Aminocyclobutane-1-carboxylic acid; 4-(fluorophenoxy)benzenesulfonyl chloride. MS: 379 (M-1).

Example 8

1-[4-(4-Fluorobenzyloxy)benzenesulfonylamino]cyclopropanecarboxylic acid hydroxyamide

1-Aminocyclopropane-1-carboxylic acid; 4-(4-fluorobenzyloxy)benzenesulfonyl chloride. MS: 379 (M-1).

Example 9

N-Hydroxy-2-(4-methoxybenzenesulfonylamino)-2-methylpropionamide

(A) A solution of 2-amino-2-methylpropionic acid benzyl ester hydrochloride (12.0 grams, 52.2 mmole) and 4-methoxybenzenesulfonylchloride (11.9 grams, 57.6 mmole) in dioxane (100 mL) and water (100 mL) was cooled in an ice bath. Triethylamine (18.2 mL, 0.13 mole) was then added. The ice bath was removed and the reaction mixture was allowed to stir at room temperature for 2 days. The solvents were removed under vacuum and the residue was taken up in ethyl acetate and water. The aqueous layer was separated and extracted twice with ethyl acetate. The combined organic layers were washed with aqueous saturated sodium bicarbonate solution, aqueous 1 N hydrochloric acid solution, and brine. After drying over sodium sulfate, the solvent was evaporated to leave a yellow oil (19.3 grams) a portion of which (10 grams) was chromatographed on silica gel eluting with 3:7 ethyl acetate/hexane to afford, after recrystallization from ethyl acetate/hexane, 2-(4-methoxybenzenesulfonylamino)-2-methylpropionic acid benzyl ester as a white solid, 6.59 grams (67%).

(B) A solution of 2-(4-methoxybenzenesulfonylamino)-2-methylpropionic acid benzyl ester (1.5 grams, 4.13 mmole) in ethanol (80 mL) was treated with 10% palladium on carbon (0.17 grams) and hydrogenated at 3 atmospheres pressure for 1.5 hours in a Parr shaker. The catalyst was removed by passage through a 0.45 μm nylon filter and the filtrate was concentrated to afford 2-(4-methoxybenzenesulfonylamino)-2-methylpropionic acid as a white solid, 1.09 grams (96%).

(C) A solution of 2-(4-methoxybenzenesulfonylamino)-2-methylpropionic acid (1.08 grams, 3.95 mmole) in methylene chloride (120 mL) was cooled in an ice bath. Triethylamine (2.2 mL, 15.8 mmole), (benzotriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate (2.6 grams, 5.88 mmole) and O-benzylhydroxylamine hydrochloride (0.95 grams, 5.95 mmole) were subsequently added. The resulting mixture was stirred at room temperature for 16 hours. The solvent was evaporated and the residue was taken up in ethyl acetate. The solution was washed successively with aqueous 1 N hydrochloric acid solution, aqueous saturated sodium bicarbonate solution, water and brine. After drying over sodium sulfate, the solvent was evaporated to afford an oil from which the desired product, N-benzyloxy-2-(4-methoxybenzenesulfonylamino)-2-methyl-propionamide (1.41 grams, 95%), a white solid, was obtained by chromatography on silica gel eluting with 1:2 ethyl acetate/hexanes.

(D) A solution of N-benzyloxy-2-(4-methoxybenzenesulfonylamino)-2-methyl-propionamide (1.40 grams, 3.70 mmole) in methanol (80 mL) was treated with 5% palladium on barium sulfate (0.75 grams) and hydrogenated at 3 atmospheres pressure for 1.5 hours in a Parr shaker. The catalyst was removed by passage through a 0.45 μm nylon filter and the filtrate was concentrated to afford N-hydroxy-2-(4-methoxy-benzenesulfonylamino)-2-methylpropionamide as a white solid, 1.06 grams (100%). MP: 122-125°C. MS: 289 (M+1): Analysis calculated for $C_{11}H_{16}N_2O_5S$: C, 45.82; H, 5.59; N, 9.72; Found: C, 45.88; H, 5.60; N, 9.69.

The titled compounds of Examples 10-12 were prepared by a method analogous to that described in Example 9 using the reagents indicated.

Example 10

2-[4-(4-Fluorophenoxy)benzenesulfonylamino]-N-hydroxy-2-methyl-propionamide

2-Amino-2-methylpropionic acid benzyl ester hydrochloride; 4-(4-fluorophenoxy)-benzenesulfonyl chloride. MP: 133-134°C. MS: 369 (M+1), Analysis calculated for $C_{16}H_{17}FN_2O_5S$: C, 52.17; H, 4.65; N, 7.60; Found: C, 52.21; H, 4.83; N, 7.80.

Example 11

N-Hydroxy-2-methyl-2-[4-(3-methylbutoxy)benzenesulfonylamino]-propionamide 2 Amino-2-methylpropionic acid benzyl ester hydrochloride; 4-(3-methylbutoxy)-benzenesulfonyl chloride. Recrystallized from ethyl acetate/hexane. MP 126.5-128°C.

MS: 343 (M-1), Analysis calculated for $C_{15}H_{24}N_2O_5S$: C, 52.31; H, 7.02; N, 8.13; Found: C, 52.30; H, 7.07; N, 8.16.

Example 12

2-[4-(2-Cyclopentylethoxy)benzenesulfonylamino]-N-hydroxy-2-methyl-propionamide

2-Amino-2-methylpropionic acid benzyl ester hydrochloride; 4-(2-cyclopentylethoxy) benzenesulfonyl chloride. Recrystallized from ethyl acetate/hexane. MP 126-127°C. MS: 369 (M-1). Analysis calculated for $C_{17}H_{26}N_2O_5S$: C 55.12, H 7.07, N 7.56. Found: C 55.46, H 7.09, N 7.38.

Example 13

N-Hydroxy-2-methyl-2-(5-pyridin-2-ylthiophene-2-sulfonylamino)propionamide

(A) To a solution of 2-amino-2-methylpropionic acid (2.0 grams, 19.4 mmole) in 1 N aqueous sodium hydroxide solution (45 mL) and dioxane (45 mL) was added 5-pyridin-2-ylthiophene-2-sulfonyl chloride (8.41 grams, 32.4 mmole). The resulting mixture was stirred at room temperature for 16 hours. Additional 1 N aqueous sodium hydroxide solution (45 mL) was added to the reaction mixture which was then extracted with diethyl ether. The organic extracts were discarded. The aqueous layer was acidified with 1 N hydrochloric acid solution and extracted with ethyl acetate. The ethyl acetate fractions were washed with brine, dried over magnesium sulfate and concentrated to afford 2-methyl-2-(5-pyridin-2-ylthiophene-2-sulfonylamino)propionic acid as a white solid (2.18 grams, 34%).

(B) To a solution of 2-methyl-2-(5-pyridin-2-ylthiophene-2-sulfonylamino)-propionic acid (1.60 grams, 4.91 mmole) in methylene chloride (160 mL) was added triethylamine (2.3 mL, 16.5 mmole), (benzotriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate (2.4 grams, 5.41 mmole) and O-(2-trimethylsilylethyl)hydroxylamine hydrochloride (0.92 grams, 5.41 mmole). The resulting mixture was stirred at room temperature for 16 hours. The solvent was evaporated and the residue was taken up in ethyl acetate. The solution was washed with water, aqueous saturated sodium bicarbonate solution, and brine. After drying over magnesium sulfate, the solvent was evaporated to afford a white foam from which the desired product, 2-methyl-2-(5-pyridin-2-ylthiophene-2-sulfonylamino)-N-(2-trimethylsilanylethoxy)-propionamide (220 mg, 10%), a white solid, was isolated by chromatography on silica gel eluting with 3:2 ethyl acetate/hexanes.

(C) 2-Methyl-2-(5-pyridin-2-ylthiophene-2-sulfonylamino)-N-(2-trimethylsilanyl-ethoxy)propionamide (80 mg, 0.18 mmole) was dissolved in trifluoroacetic acid and the resulting solution was stirred at room temperature for 16 hours. The trifluoroacetic acid was evaporated under vacuum, chasing with methanol, to afford N-hydroxy-2-methyl-2-(5-pyridin-2-ylthiophene-2-sulfonylamino)propionamide, a yellow oil (60 mg, 97%) which was crystallized from ethanol. MP 165-166°C. MS: 342 (M+1).

The titled compounds of Examples 14-15 were prepared by a method analogous to that described in Example 13 using the reagent indicated.

Example 14

1-(5-Pyridin-2-yl-thiophene-2-sulfonylamino)cyclopentane-1-carboxylic acid hydroxyamide

1-Aminocyclopentane-1-carboxylic acid; 5-pyridin-2-ylthiophene-2-sulfonyl chloride. MS: 368 (M+1).

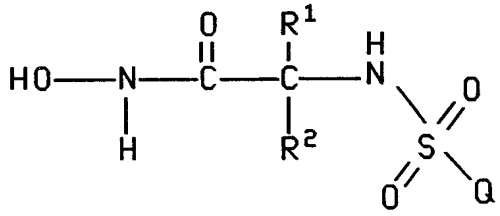
Example 15

1-[4-(4-Chlorophenoxy)benzenesulfonylamino]cyclopropane-1-carboxylic acid hydroxyamide

1-Aminocyclopropane-1-carboxylic acid; 4-(4-chlorophenoxy)benzenesulfonyl chloride. MS: 381 (M-1).

CLAIMS

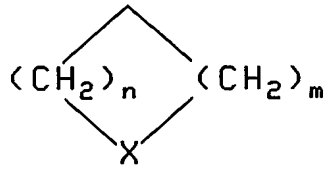
1. A compound of the formula



I

or the pharmaceutically acceptable salts thereof, wherein

R^1 and R^2 are each independently selected from $(C_1\text{-}C_6)$alkyl, trifluoromethyl, trifluoromethyl$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl(difluoromethylene), $(C_1\text{-}C_3)$alkyl(difluoromethylene$(C_1\text{-}C_3)$alkyl, $(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkyl or R^1 and R^2 may be taken together to form a $(C_3\text{-}C_6)$cycloalkyl or benzo-fused $(C_3\text{-}C_6)$cycloalkyl ring or a group of the formula

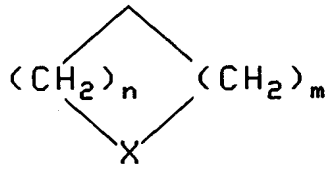


wherein n and m are independently 1 or 2 and X is CF_2, S, O or NR^3 wherein R^3 is hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylsulfonyl, $(C_6\text{-}C_{10})$arylsulfonyl or acyl; and

Qis$(C_1\text{-}C_6)$alkyl,$(C_6\text{-}C_{10})$aryl,$(C_6\text{-}C_{10})$aryloxy$(C_6\text{-}C_{10})$aryl,$(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl$(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryloxy$(C_2\text{-}C_9)$heteroaryl, $(C_2\text{-}C_9)$heteroaryl, $(C_2\text{-}C_9)$heteroaryl$(C_2\text{-}C_9)$heteroaryl, $(C_2\text{-}C_9)$heteroaryl$(C_6\text{-}C_{10})$aryl,$(C_1\text{-}C_6)$alkyl$(C_6\text{-}C_{10})$aryl,$(C_1\text{-}C_6)$alkoxy$(C_6\text{-}C_{10})$aryl,$(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_9)$heteroaryloxy$(C_6\text{-}C_{10})$aryl, $(C_1\text{-}C_6)$alkyl$(C_2\text{-}C_9)$heteroaryl, $(C_1\text{-}C_6)$alkoxy$(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_2\text{-}C_9)$heteroaryl, $(C_2\text{-}C_9)$heteroaryloxy$(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryloxy$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_9)$heteroaryloxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl$(C_6\text{-}C_{10})$aryloxy$(C_6\text{-}C_{10})$aryl, $(C_1\text{-}C_6)$alkyl$(C_2\text{-}C_9)$heteroaryloxy$(C_6\text{-}C_{10})$aryl, $(C_1\text{-}C_6)$alkyl$(C_6\text{-}C_{10})$aryloxy$(C_2\text{-}C_9)$heteroaryl, $(C_1\text{-}C_6)$alkoxy$(C_6\text{-}C_{10})$aryloxy$(C_6\text{-}C_{10})$aryl, $(C_1\text{-}C_6)$alkoxy$(C_2\text{-}C_9)$heteroaryloxy$(C_6\text{-}C_{10})$aryl or

$(C_1$-$C_6)$alkoxy$(C_6$-$C_{10})$aryloxy$(C_2$-$C_9)$heteroaryl wherein each aryl group is optionally substituted by fluoro, chloro, bromo, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy or perfluoro$(C_1$-$C_3)$alkyl.

2. A compound according to claim 1, wherein R^1 and R^2 are taken together to form a $(C_3$-$C_6)$cycloalkyl or benzo-fused $(C_3$-$C_6)$cycloalkyl ring or a group of the formula



wherein n and m are independently 1 or 2 and X is CF_2, S, O or NR^3 wherein R^3 is hydrogen, $(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$aryl, $(C_2$-$C_9)$heteroaryl, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkyl, $(C_2$-$C_9)$heteroaryl$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylsulfonyl, $(C_6$-$C_{10})$arylsulfonyl or acyl.

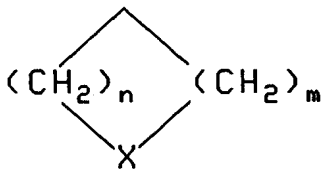
3. A compound according to claim 2, wherein R^1 and R^2 are taken together to form a $(C_3$-$C_6)$cycloalkyl or benzo-fused $(C_3$-$C_6)$cycloalkyl ring.

4. A compound according to claim 1, wherein Q is $(C_6$-$C_{10})$aryl, $(C_6$-$C_{10})$aryl$(C_6$-$C_{10})$aryl, $(C_6$-$C_{10})$aryloxy$(C_6$-$C_{10})$aryl, $(C_6$-$C_{10})$aryloxy$(C_2$-$C_9)$heteroaryl, $(C_2$-$C_9)$heteroaryl, $(C_2$-$C_9)$heteroaryl$(C_2$-$C_9)$heteroaryl, $(C_6$-$C_{10})$aryl$(C_2$-$C_9)$heteroaryl, $(C_2$-$C_9)$heteroaryl$(C_6$-$C_{10})$aryl or $(C_2$-$C_9)$heteroaryloxy$(C_6$-$C_{10})$aryl.

5. A compound according to claim 4, wherein Q is $(C_6$-$C_{10})$aryloxy$(C_6$-$C_{10})$aryl.

6. A compound according to claim 1, wherein R^1 and R^2 are each independently $(C_1$-$C_6)$alkyl.

7. A compound according to claim 1, wherein R^1 and R^2 are taken together to form a $(C_3$-$C_6)$cycloalkyl or benzo-fused $(C_3$-$C_6)$cycloalkyl ring or a group of the formula



wherein n and m are independently 1 or 2 and X is CF_2, S, O or NR^3 wherein R^3 is hydrogen, $(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$aryl, $(C_2$-$C_9)$heteroaryl, $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkyl, $(C_2$-

C_9)heteroaryl(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonyl, (C_6-C_{10})arylsulfonyl or acyl; and Q is (C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_6-C_{10})aryloxy-(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl(C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl(C_6-C_{10})aryl or (C_2-C_9)heteroaryloxy(C_6-C_{10})aryl.

8. A compound according to claim 1, wherein R^1 and R^2 are taken together to form a (C_3-C_6)cycloalkyl or benzo-fused (C_3-C_6)cycloalkyl ring; and Q is (C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl(C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl(C_6-C_{10})aryl or (C_2-C_9)heteroaryloxy(C_6-C_{10})aryl.

9. A compound according to claim 1, wherein R^1 and R^2 are each independently (C_1-C_6)alkyl; and Q is (C_6-C_{10})aryl, (C_6-C_{10})aryl(C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_6-C_{10})aryl, (C_6-C_{10})aryloxy(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl(C_2-C_9)heteroaryl, (C_6-C_{10})aryl(C_2-C_9)heteroaryl, (C_2-C_9)heteroaryl(C_6-C_{10})aryl or (C_2-C_9)heteroaryloxy(C_6-C_{10})aryl.

10. A compound according to claim 1, wherein R^1 and R^2 are each independently (C_1-C_6)alkyl; and Q is (C_6-C_{10})aryloxy(C_6-C_{10})aryl.

11. A compound according to claim 1, wherein said compound is selected from the group consisting of:

3-[4-(4-Fluorophenoxy)benzenesulfonylamino]azetidine-3-carboxylic acid hydroxyamide;

4-[4-(4-Fluorophenoxy)benzenesulfonylamino]piperidine-4-carboxylic acid hydroxyamide;

1-[4-(4-Fluorophenoxy)benzenesulfonylamino]cyclopropane-1-carboxylic acid hydroxyamide;

1-[4-(4-Chlorophenoxy)benzenesulfonylamino]cyclopropane-1-carboxylic acid hydroxyamide;

1-[4-(4-Fluorophenoxy)benzenesulfonylamino]cyclobutane-1-carboxylic acid hydroxyamide;

1-[4-(4-Chlorophenoxy)benzenesulfonylamino]cyclobutane-1-carboxylic acid hydroxyamide;

1-[4-(4-Fluorophenoxy)benzenesulfonylamino]cyclopentane-1-carboxylic acid hydroxyamide;

1-[4-(4-Fluorophenoxy)benzenesulfonylamino]cyclohexane-1-carboxylic acid hydroxyamide;

2-[4-(4-Fluorophenoxy)benzenesulfonylamino]-N-hydroxy-2-methylpropionamide;

2-[4-(4-Chlorophenoxy)benzenesulfonylamino]-N-hydroxy-2-methyl-propionamide;

N-Hydroxy-2-methyl-2-(5-pyridin-2-ylthiophene-2-sulfonylamino)propionamide;

1-(5-Pyridin-2-yl-thiophene-2-sulfonylamino)cyclopentane-1-carboxylic acid hydroxyamide;

1-(4'-Fluorobiphenyl-4-sulfonylamino)cyclopropane-1-carboxylic acid hydroxyamide;

1-(4'-Fluorobiphenyl-4-sulfonylamino)cyclobutane-1-carboxylic acid hydroxyamide;

1-(4'-Fluorobiphenyl-4-sulfonylamino)cyclopentane-1-carboxylic acid hydroxyamide;

2-(4-Methoxybenzenesufonylamino)indan-2-carboxylic acid hydroxyamide; and

2-[4-(4-Fluorophenoxy)benzenesulfonylamino]-indan-2-carboxylic acid hydroxyamide.

12. A pharmaceutical composition for (a) the treatment of a condition selected from the group consisting of arthritis, cancer, tissue ulceration, mucular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, in combination with standard NSAID'S and analgesics and in combination with cytotoxic anticancer agents, and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) or (b) the inhibition of matrix metalloproteinases or the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising an amount of a compound of claim 1 effective in such treatment and a pharmaceutically acceptable carrier.

13. A method for the inhibition of (a) matrix metalloproteinases or (b) the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of claim 1.

14. A method for treating a condition selected from the group consisting of arthritis, cancer, tissue ulceration, macular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, compounds of formula I may be used in combination with standard NSAID'S and analgesics and in combination with cytotoxic

anticancer agents, and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an amount of a compound of claim 1, effective in treating such a condition.

INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/IB 98/00023

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C311/29 C07C311/20 C07D409/04 C07D205/04 C07D211/66
A61K31/18 A61K31/44 A61K31/445

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C C07D A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 27583 A (PFIZER) 12 September 1996 see page 2 - page 6; claims 1,15-17	1,12-14
A	WO 96 00214 A (CIBA-GEIGY) 4 January 1996 see page 1 - page 2; claims 1,12-15	1,12-14
A	EP 0 606 046 A (CIBA-GEIGY) 13 July 1994 see page 2 see page 8	1,12-14

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 April 1998	14.04.98

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

1

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 98/00023

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 13, 14
are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 98/00023

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9627583 A	12-09-1996	AU 5029396 A	23-09-1996
		CA 2214720 A	12-09-1996
		EP 0813520 A	29-12-1997
		FI 973613 A	05-11-1997
		NO 974103 A	05-11-1997
		PL 322131 A	05-01-1998
WO 9600214 A	04-01-1996	US 5506242 A	09-04-1996
		AU 2536995 A	19-01-1996
		CA 2192092 A	04-01-1996
		EP 0766672 A	09-04-1997
		FI 965156 A	20-12-1996
		HU 76548 A	29-09-1997
		NO 965568 A	17-02-1997
		US 5552419 A	03-09-1996
		US 5646167 A	08-07-1997
		US 5672615 A	30-09-1997
		ZA 9505206 A	27-12-1995
EP 0606046 A	13-07-1994	US 5455258 A	03-10-1995
		AT 159012 T	15-10-1997
		AU 684255 B	11-12-1997
		AU 5265593 A	04-05-1995
		CA 2112779 A	07-07-1994
		DE 69314456 D	13-11-1997
		DE 69314456 T	26-02-1998
		FI 940012 A	07-07-1994
		HU 70536 A	30-10-1995
		JP 6256293 A	13-09-1994
		MX 9400276 A	29-07-1994
		NO 940038 A,B,	07-07-1994
		NZ 250517 A	26-10-1995
		US 5506242 A	09-04-1996
		US 5552419 A	03-09-1996
		US 5646167 A	08-07-1997
		US 5672615 A	30-09-1997
		ZA 9400048 A	11-08-1994

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07C 317/44, 317/46, A61K 31/16

A1

(11) International Publication Number: **WO 98/34915**

(43) International Publication Date: 13 August 1998 (13.08.98)

(21) International Application Number: PCT/IB98/00101

(22) International Filing Date: 27 January 1998 (27.01.98)

(30) Priority Data:
60/037,402 7 February 1997 (07.02.97) US

(71) Applicant *(for all designated States except US)*: PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: ROBINSON, Ralph, Pelton [US/US]; 30 Friar Tuck Drive, Gales Ferry, CT 06335 (US).

(74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., Patent Dept., 235 East 42nd Street, New York, NY 10017 (US).

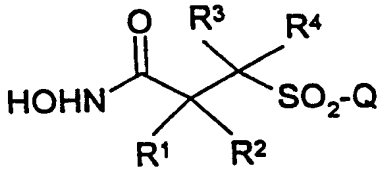
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: N–HYDROXY–BETA–SULFONYL–PROPIONAMIDE DERIVATIVES AND THEIR USE AS INHIBITORS OF MATRIX METALLOPROTEINASES

(57) Abstract

A compound of formula (I) wherein R^1, R^2, R^3, R^4 and Q are as defined in the specification, to pharmaceutical compositions containing them and to their medicinal use as matrix metalloproteinases inhibitors and for the production of tumor necrosis factor (TNF).



(I)

FOR THE PURPOSES OF INFORMATION ONLY

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

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

N-HYDROXY-BETA-SULFONYL-PROPIONAMIDE DERIVATIVES AND THEIR USE AS INHIBITORS OF MATRIX METALLOPROTEINASES

Background of the Invention

The present invention relates to arylsulfonylamino hydroxamic acid derivatives which are inhibitors of matrix metalloproteinases or the production of tumor necrosis factor (TNF) and as such are useful in the treatment of a condition selected from the group consisting of arthritis, osteoporosis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis and other diseases characterized by matrix metalloproteinase activity, such as AIDS, sepsis, or septic shock and other diseases involving the production of TNF. In addition, the compounds of the present invention may be used in combination therapy with standard non-steroidal anti-inflammatory drugs (hereinafter NSAID'S) and analgesics for the treatment of arthritis, and in combination with cytotoxic drugs such as adriamycin, daunomycin, cis-platinum, etoposide, taxol, taxotere and alkaloids, such as vincristine, in the treatment of cancer.

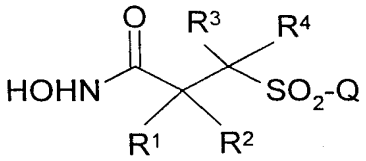
This invention also relates to a method of using such compounds in the treatment of the above diseases in mammals, especially humans, and to pharmaceutical compositions useful therefor.

There are a number of enzymes which effect the breakdown of structural proteins and which are structurally related metalloproteases. Matrix-degrading metalloproteinases, such as gelatinase, stromelysin and collagenase, are involved in tissue matrix degradation (e.g. collagen collapse) and have been implicated in many pathological conditions involving abnormal connective tissue and basement membrane matrix metabolism, such as arthritis (e.g., osteoarthritis and rheumatoid arthritis), tissue ulceration (e.g., corneal, epidermal and gastric ulceration), abnormal wound healing, periodontal disease, bone disease (e.g., Paget's disease and osteoporosis), tumor metastasis or invasion, as well as HIV-infection (J. Leuk. Biol., 52 (2): 244-248, 1992).

Tumor necrosis factor is recognized to be involved in many infectious and auto-immune diseases (W. Fiers, FEBS Letters, 1991, 285, 199). Furthermore, it has been shown that TNF is the prime mediator of the inflammatory response seen in sepsis and septic shock (C.E. Spooner et al., Clinical Immunology and Immunopathology, 1992, 62 S11).

Summary of the Invention

The present invention relates to a compound of the formula



wherein R^1 is hydrogen, hydroxy, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkyl$(C=O)O$-, $(C_1\text{-}C_6)$alkoxy$(C=O)O$-, $(C_6\text{-}C_{10})$aryl$(C=O)O$-, $(C_6\text{-}C_{10})$aryloxy$(C=O)O$-, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl$(C=O)O$- or $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C=O)O$-; wherein said aryl moiety of said $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy, $(C_6\text{-}C_{10})$aryl$(C=O)O$-, $(C_6\text{-}C_{10})$aryloxy$(C=O)O$-, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl$(C=O)O$- or $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C=O)O$- groups is optionally substituted by one or more substituents (preferably one to three substituents) independently selected from fluoro, chloro, bromo, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, perfluoro$(C_1\text{-}C_3)$alkyl, perfluoro$(C_1\text{-}C_3)$alkoxy and $(C_6\text{-}C_{10})$aryloxy;

R^2 is hydrogen or $(C_1\text{-}C_6)$alkyl;

R^3 and R^4 are independently selected from the group consisting of hydrogen, $(C_1\text{-}C_6)$alkyl, trifluoromethyl, trifluoromethyl$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl(difluoromethylene), $(C_1\text{-}C_3)$alkyl(difluoromethylene)$(C_1\text{-}C_3)$alkyl, $(C_6\text{-}C_{10})$aryl, $(C_2\text{-}C_9)$heteroaryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryl$(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl$(C=O)O$-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy$(C=O)O$-$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl$(C=O)O$-$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryloxy$(C=O)O$-$(C_1\text{-}C_6)$alkyl , $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl$(C=O)O$-$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C=O)O$-$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryloxy$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_9)$heteroaryl$(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, amino$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylamino$(C_1\text{-}C_6)$alkyl, $[(C_1\text{-}C_6)\text{alkyl}]_2$amino$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl$(C=O)NH(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy$(C=O)NH(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl$(C=O)NH(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryloxy$(C=O)NH(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl$(C=O)NH(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C=O)NH(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylsulfonyl$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$arylsulfonyl$(C_1\text{-}C_6)$alkyl, $R^5CO(C_1\text{-}C_6)$alkyl or $R^8(C_1\text{-}C_6)$alkyl; or R^3 and R^4 may be taken together with the carbon atom to which they are attached to form a $(C_3\text{-}C_6)$cycloalkyl or benzo-fused$(C_3\text{-}C_6)$cycloalkyl ring or a group of the formula