Chapter 4.

Experimental

4 EXPERIMENTAL

4.1 CHEMICAL

All moisture-free operations were performed in oven-dried glassware under a positive pressure of nitrogen unless otherwise stated. Melting points (m.p.) were determined using a Toshniwals melting point apparatus (heating block type) and are uncorrected. Analytical TLC was performed on aluminium backed pre-coated silica gel plates with 0.25 mm thickness containing PF_{254} indicator (E. Merck). Visualization of spots was effected by exposure to either UV_{254nm} lamp or iodine vapours. IR was recorded on Shimadzu-8320 model using KBr pelletes/neat samples. Optical rotations were measured on Jasco-P1020 polarimeter using a quartz cell of 10 ml capacity and a 10 cm path length. PMR spectra were recorded with Bruker spectrometer (300/400 MHz), in deuterated chloroform ($CDCl_3$), unless specified. Chemical shifts are reported in parts per million (ppm, δ units) using TMS as an internal standard. Coupling constants (*J*) are reported in units of hertz (Hz). Mass spectral data was obtained on a QTRAP Applied Biosystem SCIEX spectrometer. Elemental analyses were performed on Perkin-Elmer/Carlo-Erba elemental analyzer.

Most of the starting materials and solvents were obtained from S. D. Fine chemicals, Spectrochem and Loba chemie, and used as such without further purification. THF was refluxed over sodium and stored on sodium wire. Some special chemicals like BOP, EDC, 4-morpholinecarbonyl chloride, thiophene-2-carboxylic acid, furane-2-carboxylic acid, α-methylcinnamic acid, 3-hydroxy-4-methoxyaniline, α-toluenesulfonyl chloride, ethyl 2-bromopropionate, 3,4,5-trimethoxyaniline, and 2-chloroethyl isocyanate were obtained from Aldrich or Lancaster. 5-Phenyl-1,3,4-thiadiazol-2-ylamine and 5-(4-methoxyphenyl)-1,3,4-thiadiazol-2-ylamine were obtained from Agimonto. p-Methoxycinnamic acid, α-phenylcinnamic acid, ferulic acid, 2-thiopheneacrylic acid and 2-furylacrylic acid were prepared by reported method[129]. All the amino acids used were of *L*-configurations and used as such.

4.1.1 Boc-*L*-Proline (44)

In a three-neck round-bottom flask (250 ml) equipped with an efficient stirrer, PEDF, thermometer and ice bath, *L*-Proline **(43)** (4.6 g, 0.04 mole) was suspended in a mixture of t-butanol (35 ml) and water (20 ml), and the mixture was cooled to 10-15 °C (internal temperature). A cold solution of sodium hydroxide (1.9 g, 0.048 mole in 20 ml water) was added dropwise to the above suspension to get a clear solution. Boc-carbonate (8.6 g, 0.04 mole) was added to the above solution through PEDF over a period of 30 min and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was washed with solvent ether (2x 40 ml), cooled to 10-15 °C and acidified with aq citric acid (0.5 M) to pH ~ 3 and extracted with chloroform (5 x 60 ml). The combined organic layer was washed with water (1x100 ml), dried and concentrated under vacuum to get a sticky mass which was scratched with spatula to get Boc-*L*-proline **(44)** as white solid, (8 g, 93 %), m.p. 132-35 °C (134-35 °C[133]).

Anal. :

TLC : R_f 0.36 (50 % EtOAc in MeOH)

4.1.2 Boc-*L*-Prolinamide (46)

In a three-neck round-bottom flask (250 ml) equipped with an efficient stirrer, PEDF, thermometer and ice bath, Boc-*L*-proline **(44)** (5 g, 0.023 mole) was dissolved in dichloromethane (80 ml) and the solution was cooled to 10-15 °C. NHS (2.67 g, 0.023 mole) was charged into the above solution followed by the addition of a solution of DCC (4.78 g, 0.023 mole in 25 ml of dichloromethane) through PEDF maintaining the same temperature. The reaction mixture was stirred at room temperature for 16 h, filtered to remove DCU as white solid (5.2 g) and the filtrate was concentrated under vacuum to get active ester of Boc-*L*-proline **(45)** (7 g). The ester so obtained was dissolved in THF (70 ml), cooled to a temperature below -10 °C and aq ammonia (7 ml, 30 %) added in portions at a temperature below 2 °C, stirred the reaction mixture at room temperature for 5 h and concentrated under vacuum. The sticky mass so obtained was diluted with

water (50 ml) and extracted with chloroform (5x 50 ml). The combined organic layer was washed with water, dried and concentrated under vacuum to get a semisolid mass. *n*-Hexane (150 ml) was added to this mass and it was left aside for 1 h. The solid so obtained was filtered, dried and crystallized from ethyl acetate to give the amide **46**, (4 g, 80 %), m.p. 108-10 °C.

Anal. :

TLC	: R_f 0.39 (EtOAc)
$[\alpha]_D^{25}$	: -41.78 (1 % in MeOH)
IR (KBr, cm^{-1})	: 3381, 3201, 1706, 1684, 1364 and 1164

4.1.3 *L*-Prolinamide TFA salt (47)

In a three-neck round-bottom flask (100 ml) equipped with an efficient stirrer, ice bath, thermometer and calcium chloride guard tube, Boc-*L*-prolinamide **(46)** (4.28 g, 0.02 mole) was dissolved in dichloromethane (40 ml) and the solution was cooled to 5-10 °C. Trifluoroacetic acid (8 ml) was added to the above solution in portions and the reaction mixture stirred at room temperature for 90 min and concentrated over water bath to get a yellow sticky mass **(47)**, which was dried in vacuum. The sticky mass so obtained was used as such without further purification and characterization. Yield of the product was almost quantitative.

4.1.4 Boc-*L*-Leucine monohydrate (49)

L-Leucine **(48)** (6 g, 0.0458 mole) was suspended in a mixture of t-butanol (60 ml) and water (30 ml), and the reaction mixture was cooled to 10-15 °C. A cold solution of sodium hydroxide (2.2 g, 0.055 mole in 30 ml water) was added dropwise to it to get a clear solution. Boc-carbonate (10 g, 0.045 mole) was added to the above solution through PEDF over a period of 30-40 min and the reaction mixture was stirred at room temperature for 16 h, washed with solvent ether (2×40 ml), cooled to 10-15 °C and acidified with aq citric acid (0.5 M) to pH ~ 3. The precipitated material was filtered and dried in vacuum to give compound **(49)**, (9.1 g, 80 %), m. p. 81-86 °C (85-87 °C[133]).

Anal. :

TLC	: R_f 0.63 (5 % MeOH in $CHCl_3$)
IR (KBr, cm^{-1})	: 3463, 3338, 1716, 1677, 1537, 1365 and 1248

4.1.5 *t*-Butyl *N*-{(*S*)3-methyl-1-[(*S*)2-carbamoyl-1-pyrrolidinocarbonyl]butyl} carbamate (50)

In a round-bottom flask (250 ml) equipped with an efficient stirrer, ice bath, thermometer and calcium chloride guard tube, Boc-*L*-leucine **(49)** (5 g, 0.02 mole) was dissolved in dichloromethane (90 ml) and the solution was cooled to 10-15 °C. 1-HOBT (2.7 g, 0.02 mole) and EDC (3.84 g, 0.02 mole) were charged into the solution and the reaction mixture was stirred for 45 min at 10-15 °C. The TFA salt **(47)** (4.28 g, 0.02 mole) was added into the above solution followed by the addition of TEA (7 ml) at 10-15 °C. This reaction mixture was stirred at room temperature for 15 h, washed with a solution of citric acid (0.5 M, 2 x 50 ml), aq sodium bicarbonate (5 %, 2 x 50 ml) and water (2 x 50 ml), sequentially. The organic layer was dried and concentrated under vacuum to get a sticky mass, which solidified on standing. The crude compound so obtained was purified by column chromatography using silica gel as adsorbent and ethyl acetate in *n*-hexane (30 %) as eluent to afford the desired compound **(50)**, (4.5 g, 69 %), 76-78 °C.

Anal. :

TLC	: R_f 0.54 (10 % MeOH in $CHCl_3$)
IR (KBr, cm^{-1})	: 3381, 3201, 1706, 1684, 1647, 1437, 1366 and 1170

4.1.6 α-Phenylcinnamic acid (52; R = b)

In a round-bottom flask (250 ml) benzaldehyde (4.25 g, 4 ml, 0.04 mole), phenylacetic acid (5.45 g, 0.04 mole), acetic anhydride (8 ml) and TEA (4 ml) were mixed together and the mixture so obtained was boiled gently for 5 h. The reaction mixture was steam distilled until the distillate passing over is no longer cloudy. The flask was cooled and water decanted off. The residue so obtained in the flask was dissolved in ethanol (50 ml) to get a clear solution and acidified

with HCl (10 %) to get a solid. The solid so obtained was filtered, dried and crystallized from 60 % ethanol to afford **(52)**, (3.2 g, 36 %), 171-73 °C (172-73 °C[129]).

4.1.7 p-Methoxycinnamic acid (54; R = d)

In a round-bottom flask (250 ml) anisaldehyde (13.7 g, 0.1 mole) and malonic acid (20.8 g, 0.2 mole) were dissolved in a mixture of pyridine (50 ml) and piperidine (1 ml). The solution so obtained was heated at 60 °C for 8 h. The reaction mixture was cooled to room temperature and poured over crushed ice containing hydrochloric acid. The solid so obtained was filtered, dried and crystallized from ethanol to give **(54)**, (12 g, 67 %), 171-72 °C (172 °C[129]).

4.1.8 (*S*)1-[(*S*)2-Benzamido-4-methylpentanoyl]pyrrolidine-2-carboxamide (55; R = a)

Compound **(50)** (3 g, 9.1 mmole) was dissolved in dichloromethane (40 ml) and the solution was cooled to 5-10 °C. Trifluoroacetic acid (5 ml) was added slowly into the above solution and the reaction mixture was stirred at room temperature for 90 min. The reaction mixture was concentrated on water bath to get a yellow sticky mass, which was dried in vacuum.

Benzoic acid **(51, R = a)** (1.1 g, 9.1 mmole) was dissolved in dichloromethane (35 ml) and the solution was cooled to 10-15 °C. 1-HOBT (1.23 g, 9.1 mmole) and EDC (1.74 g, 9.1 mmole) were charged to the above solution and the reaction mixture was stirred further for 45 min at 10-15 °C. The TFA salt prepared in the above described step was added to the above reaction mixture followed by addition of TEA (7 ml) at 10-15 °C. The resulting reaction mixture was stirred at room temperature for 15 h, washed with aq citric acid (0.5 M, 2x 50 ml), aq sodium bicarbonate (5 %, 2x 50 ml) and water (2x 50 ml), one after another. The organic layer was dried and concentrated under vacuum to get a sticky mass, which solidified on standing. The crude material so obtained was purified by column chromatography using silica gel as adsorbent and *n*-hexane

in ethyl acetate (20 to 30 %) as eluent to yield compound **(55)**, (1 g, 33 %), m.p. 120-22 °C.

Anal. :

TLC : R_f 0.54 (10 % MeOH in $CHCl_3$)

IR (KBr, cm^{-1}) : 3500, 3258, 1684, 1669, 1635, 1433, 1300 and 1158

4.1.9 (*S*)1-{(*S*)4-Methyl-2-[(*E*)-2,3-diphenylacryloylamino]pentanoyl}pyrrolidine -2-carboxamide (56; R = b)

Compound **(56)** was prepared by reacting compound **(50)** (1 g, 3 mmole) with α-phenylcinnamic acid **(52; R = b)** as described above for **55**. Work up of the reaction mixture followed by chromatographic purification using chloroform as eluent afforded compound **(56)**, (0.61 g, 47 %), m.p. 95-97 °C.

Anal. :

TLC : R_f 0.55 (10 % MeOH in $CHCl_3$)

IR (KBr, cm^{-1}) : 3408, 3300, 1686, 1646, 1615, 1433, 1301 and 1158

4.1.10 (*S*)1-{(*S*)4-Methyl-2-[(*E*)3-phenylacrylamido]pentanoyl}pyrrolidine-2-carboxamide (57; R = c)

Compound **(57)** was prepared by reacting compound **(50)** (3.5 g, 10.7 mmole) with *trans*-cinnamic acid **(53; R = c)** as described above for compound **(55)**. Work up of the reaction mixture followed by chromatographic purification with *n*-hexane in ethyl acetate (20 %) gave **57**, (1 g, 26 %), m.p. 118-20 °C.

Anal. :

TLC : R_f 0.59 (10 % MeOH in $CHCl_3$)

IR (KBr, cm^{-1}) :3381, 3258, 3176, 1686, 1666, 1632, 1608 and 1158

4.1.11 (*S*)1-{(*S*)2-[(*E*)3-(4-Methoxyphenyl)acryloylamino]-4-methylpentanoyl} pyrrolidine-2-carboxamide (58; R = d)

Compound **(58)** was prepared by reacting compound **(50)** (3.5 g, 10.7 mmole) with p-methoxycinnamic acid **(54; R = d)** as described above for compound **(55)**. Work up of the reaction mixture followed by chromatographic purification using *n*-hexane in ethyl acetate (20 %) yielded **58**, (1 g, 24 %), m.p. 140-42 °C.

Anal. :

TLC	: R_f 0.35 (10 % MeOH in $CHCl_3$)
IR (KBr, cm^{-1})	: 3463, 3368, 3171, 1686, 1663, 1632, 1599 and 1513

4.1.12 *N*-{(*S*)1-[(*S*)2-Cyanopyrrolidine-1-carbonyl]-3-methylbutyl}benzamide (59; R = a)

A solution of compound **(55)** (0.8 g, 2.4 mmole) in dry DMF (7 ml) was cooled to -10 to -12 °C. Cyanuric chloride (0.57 g, 3.1 mmole) was added to this solution in portions over a period of 10 min and the reaction mixture was stirred at this temperature for 1 hr. The reaction mixture was poured over crushed ice to get a white solid, which was filtered and dried. This dried material was purified by column chromatography on silica gel using ethyl acetate in *n*-hexane (20 to 30 %) to give compound **(59)**, (0.3 g, 40 %), m.p. 143-44 °C.

Anal. :

TLC	: R_f 0.51 (60 % EtOAc in *n*-hexane)
$[\alpha]_D^{25}$	: -102.14 (1 % in MeOH)
UV (λ_{max}, MeOH)	: 226.5 nm (log ε 4.57)
IR (KBr, cm^{-1})	: 3268, 2245, 1673, 1635, 1528, 1490 and 1293
PMR	: 0.98-1.00 (d, 3H, *J*= 4 Hz), 1.03-1.05 (d, 3H, *J*= 4 Hz), 1.61-1.65 (m, 1H), 1.70-1.81(m, 2H), 2.17-2.32 (m, 4H), 3.68-3.74 (m, 1H), 3.85-3.92 (m, 1H), 4.77-4.81 (m, 1H), 4.94-5.02 (m, 1H), 6.75-6.78 (d, 1H, *J*= 6 Hz), 7.49 (m, 3H) and 7.78 (d, 2H)
Mass (m/z)	: 314 (M+H), 218, 190 and 105

4.1.13 (*E*)*N*-{(*S*)1-[(*S*)2-Cyanopyrrolidine-1-carbonyl]-3-methylbutyl}-2,3-diphenylacrylamide (60; R = b)

Compound **(60)** was prepared by reacting compound **(56)**, (0.3 g, 0.7 mmole) with cyanuric chloride (0.13 g, 0.7 mmole) as described above for **59**. Work up of the reaction mixture followed by chromatographic purification of the crude product with ethyl acetate in *n*-hexane (30 %) yielded **60**, (0.11 g, 40 %), m.p. 160-62 °C.

Anal. :

TLC	: R_f 0.44 (50 % *n*-Hexane in EtOAc)
UV (λ_{max}, MeOH)	: 282 nm (log ε 4.66)
IR (KBr, cm^{-1})	: 3422, 2232, 1666, 1652, 1620, 1507, 1423 and 1192
PMR	: 0.90-0.92 (d, 3H), 0.97-0.98 (d, 3H), 1.25-1.48 (m, 1H), 1.52-1.65 (m, 2H), 2.19-3.00 (m, 4H), 3.45-3.68 (m, 1H), 3.84-3.92 (m, 1H), 4.75-4.78 (m, 1H), 4.81-4.88 (m, 1H), 6.00-6.04 (d, 1H), 6.96-6.99 (m, 2H), 7.10-7.20 (m, 3H), 7.24-7.27 (m, 2H), 7.43-7.49 (m, 3H) and 7.80 (s, 1H)

$C_{26}H_{29}N_3O_2$: Requires C, 75.15; H, 7.03; N, 10.11. Found C, 75.70; H, 7.25; N, 10.65 %

4.1.14 (*E*)*N*-{(*S*)1-[(*S*)2-Cyanopyrrolidine-1-carbonyl]-3-methylbutyl}-3-phenyl-acrylamide (61; R = c)

Compound **(61)** was prepared by reacting compound **(57)**, (0.5 g, 1.4 mmole) with cyanuric chloride (0.26 g, 1.4 mmole) as described above for compound **(59)**. Work up of the reaction mixture followed by chromatographic purification of the crude product with ethyl acetate in *n*-hexane (20-30 %) yielded compound **(60)**, (0.12 g, 25 %), m.p. 98-100 °C.

Anal. :

TLC	: R_f 0.56 (70 % EtOAc in *n*-hexane)
UV (λ_{max}, MeOH)	: 276.5 nm (log ε 3.46)
IR (KBr, cm^{-1})	: 3280, 2246, 1652, 1628, 1537 and 1423

$C_{20}H_{25}N_3O_2$: Requires C, 70.77; H, 7.42; N, 12.38. Found C, 70.80; H, 7.38; N, 12.43 %

4.1.15 (*E*)*N*-[(*S*)1-[(*S*)2-Cyanopyrrolidine-1-carbonyl]-3-methylbutyl]-3-(4-methoxyphenyl)acrylamide (62; R = d)

Compound **(62)** was prepared by reacting compound **(58)**, (0.8 g, 2 mmole) with cyanuric chloride (0.36 g, 2 mmole) as described above for compound **(59)**. Work up of the reaction mixture followed by chromatographic purification of the crude product with ethyl acetate in *n*-hexane (20 to 30 %) yielded **62**, (0.20 g, 27 %), m.p. 75-78 °C.

Anal. :

TLC	: R_f 0.47 (70 % EtOAc in *n*-hexane)
UV (λ_{max}, MeOH)	: 308 nm (log ε 4.51)
IR (KBr, cm^{-1})	: 3272, 2245, 1659, 1625, 1602, 1512, 1423 and 1173
PMR	: 0.97-0.99 (d, 3H, *J*= 4 Hz), 1.01-1.03 (d, 3H, *J*= 4 Hz), 1.26-1.81 (m, 3H), 2.18-2.31 (m, 4H), 3.66-3.71 (m, 1H), 3.83 (s, 3H), 3.85-3.93 (m, 1H), 4.78-4.80 (m, 1H), 4.86-4.94 (m, 1H), 6.26-6.41 (d, 1H, *J*= 15.6 Hz), 6.38-6.41 (d, 1H), 6.86-6.89 (d, 2H, *J*= 8.7 Hz), 7.39-7.43 (d, 2H, *J*= 8.7 Hz) and 7.51-7.56 (d, 1H, *J*= 15.6 Hz)

$C_{21}H_{27}N_3O_3$: Requires C, 68.27; H, 7.36; N, 11.37. Found C, 67.88; H, 7.10; N, 10.94 %

4.1.16 Boc-*L*-Methionine (64)

In a three-neck round-bottom flask (250 ml) equipped with an efficient stirrer, PEDF, thermometer and ice bath, *L*-methionine **(63)** (6.8 g, 45.8 mmole) was suspended in a mixture of t-butanol (50 ml) and water (25 ml), and the reaction mixture cooled to 10-15 °C. A cold solution of sodium hydroxide (2.1 g, 55 mmole in 25 ml water) was added to it dropwise to get a clear solution. Boc-carbonate (10 g, 45.8 mmole) was added to the above solution through PEDF over a period of 30-40 min at room temperature and the reaction mixture was stirred

for 16 h. The reaction mixture was washed with solvent ether (2×40 ml) and the aq layer cooled to 10-15 °C, acidified with aq citric acid (0.5 M) to pH ~ 3 and extracted with chloroform (5x50 ml). The combined organic layer was washed with water (2x100 ml), dried and concentrated under vacuum to get **64** as a sticky mass, (10 g, 88 %) which was used as such for the next step.

Anal. :

TLC	: R_f 0.76 (40 % MeOH in EtOAc)
IR (KBr, cm^{-1})	: 3450, 3326, 1710, 1686, 1597, 1523, 1366 and 1170

4.1.17 *t*-Butyl *N*-[(*S*)1-benzylcarbamoyl-3-methylmercaptopropyl]carbamate (65)

In a three-neck round-bottom flask (250 ml) equipped with an efficient stirrer, ice-bath, thermometer and calcium chloride guard tube, Boc-*L*-methionine **(64)** (11.0 g, 44 mmole) was dissolved in dichloromethane (125 ml) and the solution was cooled to 5-10 °C. Benzylamine (4.7 g, 4.8 ml, 44 mmole) was added to the above solution followed by the addition of TEA (7 ml) at 5-10 °C and 1-HOBT (6.0 g, 44 mmole). DCC (9.0 g, 44 mmole) was added in portions over a period of 30 min to it and the resulting reaction mixture was stirred at room temperature for 16 h. The reaction mixture was filtered to remove DCU (8.7 g) and the filtrate diluted with dichloromethane (100 ml). The organic layer was washed with aq citric acid (0.5 M, 3x50 ml), aq sodium bicarbonate (5 %, 3x50 ml) and water (2x100 ml) in the given sequence. The organic layer was dried and the solvent removed to afford a residue which was purified by column chromatography over silica gel using benzene as eluent to give compound **(65)**, (11 g, 74 %), m.p. 130-32 °C.

Anal. :

TLC	: R_f 0.85 (EtOAc)
IR (KBr, cm^{-1})	: 3337, 3317, 1680, 1656, 1522, 1331 and 1170
PMR	: 1.44 (s, 9H), 1.92-1.98 (m, 1H), 2.09 (s, 3H), 2.11-2.18 (m, 1H), 2.49-2.63 (m, 2H), 4.29-4.30 (m, 1H), 4.46-4.47 (d, 2H, *J*= 8 Hz), 5.21 (s, 1H), 6.61 (s, 1H) and 7.27-7.54 (m, 5H)

4.1.18 *t*-Butyl *N*-[(*S*)1-benzyl-2-oxo-3-pyrrolidinyl]carbamate (66)

In a round-bottom flask (100 ml) equipped with an efficient stirrer, water condenser and calcium chloride guard tube, compound **(65)** (5 g, 14.8 mmole) was dissolved in methyl iodide (15 ml). The solution was stirred at room temperature for 24 h during which time a gummy solid separated out. Methyl iodide was removed from this reaction mixture under vacuum to obtain sulfenium salt.

The salt was dissolved in a mixture of dichloromethane (75 ml) and dry DMF (15 ml), and the solution cooled to 0 °C. Sodium hydride (1.5 g, 31.5 mmole, 50 % in mineral oil dispersion) was charged into the above solution at 0 °C. The reaction mixture was stirred at 0 °C for 3 h followed by the addition of ethyl acetate (50 ml) and water (25 ml) maintaining the temperature at 0 °C and the mixture was left overnight, and concentrated under vacuum. The clear aq layer (pH ~ 8) was acidified to pH ~ 4 with aq citric acid (0.5 M) and the precipitated solid was filtered and dried. The crude material so obtained was crystallized from acetone-pet ether (60-80) to afford compound **(66)**, (2.7 g, 43%), m.p. 130-32 °C.

Anal. :

TLC	: R_f 0.76 (30 % *n*-Hexane in EtOAc)
$[\alpha]_D^{25}$	: -38.32 (1 % in MeOH)
UV (λ_{max}, MeOH)	: 258 nm (log ε 2.24)
IR (KBr, cm^{-1})	: 3287, 1710, 1671, 1534, 1365 and 1175
PMR	: 1.45 (s, 9H), 1.75-1.89 (m, 1H), 2.57-2.64 (m, 1H), 3.17-3.22 (dd, 2H), 4.20-4.22 (m, 1H), 4.46-4.53 (d, 2H, *J*= 4 Hz), 5.14 (s, 1H), 7.20-7.23 (m, 2H) and 7.28-7.36 (m, 3H)
Mass (m/z)	: 291.3 (M+H)

4.1.19 Ferulic acid (67; R = e)

Ferulic acid **(67)** was prepared by reacting vanillin (15.2 g, 0.1 mole) with malonic acid (20.8 g, 0.2 mole) in pyridine (40 ml) and piperidine (0.5 ml) as

described for **(54)**. The crude solid so obtained was crystallized from aq methanol to afford compound **(67)**, (10.5 g, 54 %), m.p. 229-231 °C (d), (230 °C[129, 134]), (d).

4.1.20 2-Thiopheneacrylic acid (68; R = f)

Compound **(68)** was prepared by reacting thiophene-2-carboxaldehyde (5 g, 44 mmole) with malonic acid (9.2 g, 88 mmole) in pyridine (10 ml) and piperidine (0.5 ml) as described for **(54)**. The crude solid so obtained was crystallized from methanol to afford **68**, (3.8 g, 55 %), m.p. 144-47 °C (145-48 °C[129, 134]).

4.1.21 2-Furylacrylic acid (69; R = g)

Compound **(69)** was prepared by reacting furfural (5 g, 52 mmole) with malonic acid (10.4 g, 0.1 mole) in pyridine (10 ml) and piperidine (0.5 ml) as described for **(54)**. The crude solid so obtained was crystallized from methanol to afford compound **(69)**, (3.5 g, 49 %), m.p. 138-39 °C, (138-39 °C[129]).

4.1.22 (*E*)*N*-[(*S*)1-Benzyl-2-oxo-3-pyrrolidino]-3-phenylacrylamide (75; R = c)

In a three-neck round-bottom flask (100 ml) equipped with an efficient stirrer, ice bath, thermometer and calcium chloride guard tube, compound **(66)** (0.8 g, 2.7 mmole) was dissolved in dichloromethane (25 ml) and the solution was cooled to 5-10 °C. Trifluoroacetic acid (1.5 ml) was added to the above solution in portions and the reaction mixture was stirred at room temperature for 90 min. The reaction mixture was concentrated to get yellow sticky mass, which was dried in vacuum.

In a separate round-bottom flask (100 ml) equipped with an efficient stirrer, ice bath, thermometer and calcium chloride guard tube, *trans*-cinnamic acid **(53; R = c)**, (0.4 g, 2.7 mmole) was dissolved in dichloromethane (40 ml). 1-HOBT (0.37 g, 2.7 mmole) and EDC (0.51 g, 2.7 mmole) were added into the above solution at 10-15 °C and the reaction mixture was stirred for 45 min. The TFA salt of compound **(66)** prepared in the above step was added into the above

reaction mixture followed by addition of TEA (5 ml) at -10 to 5 °C. The reaction mixture was stirred at room temperature for 15 h and diluted with dichloromethane (125 ml). The solution so obtained was washed with aq citric acid (0.5 M, 2 x 50 ml), aq sodium bicarbonate (5 %, 2 x 50 ml) and finally with water (2 x 50 ml). The organic layer was dried and concentrated under vacuum to get a solid mass which was purified by column chromatography using silica gel as adsorbent and ethyl acetate in *n*-hexane (30%) as eluent to afford compound **(75)** (0.47g, 54 %), m.p. 181-83 °C.

Anal. :

TLC	: R_f 0.65 (EtOAc)
UV (λ_{max}, MeOH)	: 275 nm (log ε 4.35)
IR (KBr, cm^{-1})	: 3279, 1683, 1646, 1615, 1538, 1295 and 1077
PMR	: 1.91-1.95 (m, 1H), 2.77-2.86 (m, 1H), 3.23-3.34 (m, 2H), 4.46-4.58 (m, 3H), 6.44 (s, 1H), 6.45-6.51 (d, 1H), 7.24-7.42 (m, 8H), 7.48-7.52 (m, 2H) and 7.62-7.67 (d, 1H)
Mass (m/z)	: 321.3 (M+H)

4.1.23 (*E*)*N*-[(*S*)1-Benzyl-2-oxo-3-pyrrolidino]-3-(4-methoxyphenyl)acrylamide (76; R = d)

Compound **(76)** was prepared by reacting compound **(66)** (0.4 g, 13.8 mmole) with p-methoxycinnamic acid **(54 R = d)** (0.25 g, 13.8 mmole) as described above for **75**. Work up of the reaction mixture followed by crystallization from acetone yielded compound **(76)**, (0.2 g, 42 %), m.p. 189-92 °C.

Anal. :

TLC	: R_f 0.6 (6 % MeOH in $CHCl_3$)
$[\alpha]_D^{25}$	: -37.22 (1 % in MeOH)
UV (λ_{max}, MeOH)	: 298 nm (log ε 3.38)
IR (KBr, cm^{-1})	: 3269, 1700, 1647, 1605, 1540, 1301, 1251 and 1024
PMR	: 1.82-1.95 (m, 1H), 2.76-2.85 (m, 1H), 3.25-3.32 (m, 2H), 3.82 (s, 3H), 4.46-4.58 (m, 3H), 6.32 (s, 1H), 6.32-

6.37 (d, 1H), 6.88-6.91 (d, 2H, *J*= 6Hz), 7.24-7.39 (m, 5H), 7.44-7.47 (d, 2H, *J*= 8 Hz) and 7.57-7.62 (d, 1H, *J*= 10 Hz)

Mass (m/z) : 351.3 (M+H)

4.1.24 (*E*)*N*-[(*S*)1-Benzyl-2-oxo-3-pyrrolidino]-3-(3-hydroxy-4-methoxyphenyl) acrylamide (77; R = e)

Compound (77) was prepared by reacting compound **(66)** (0.7 g, 2.4 mmole) with ferulic acid **(67; R = e)** (0.46 g, 2.4 mmole) as described above for compound **(75)**. Upon work up of the reaction mixture followed by chromatographic purification over silica gel using *n*-hexane in ethyl acetate (30 %) was obtained compound **(77)**, (0.27 g, 31 %), m.p. 185-87 °C.

Anal. :

TLC : R_f 0.52 (EtOAc)

UV (λ_{max}, MeOH) : 322 nm (log ε 4.62)

IR (KBr, cm^{-1}) : 3261, 3080, 1686, 1664, 1619, 1564, 1424 and 1191

PMR : 1.81-1.95 (m, 1H), 2.72-2.82 (m, 1H), 3.25-3.30 (m, 2H), 3.92 (s, 3H), 4.51-4.59 (m, 3H), 6.02 (s, 1H), 6.26-6.34 (d, 1H), 6.54-6.56 (d, 1H, *J*= 4 Hz), 6.87 -6.91 (d, 1H *J*= 4 Hz), 6.97 (s, 1H), 7.00-7.04 (d, 1H, *J*= 8 Hz), 7.23-7.38(m, 5H) and 7.50-7.55 (d, 1H)

Mass (m/z) : 367.3 (M+H)

4.1.25 (*E*)*N*-[(*S*)1-Benzyl-2-oxo-3-pyrrolidino]-3-(2-thiophenyl)acrylamide (78; R = f)

The compound **(78)** was obtained when compound **(66)** (0.32 g, 1.1 mmole) was reacted with 2-thiopheneacrylic acid **(68; R = f)** (0.17 g, 1.1 mmole) as described above for **75**. The crude material so obtained was purified by chromatographic purification over silica gel using ethyl acetate-*n*-hexane (30 %) as eluent to yield compound **(78)**, (0.2 g, 56 %), m.p. 176-78 °C.

Anal. :

TLC	: R_f 0.55 (20 % *n*-Hexane in EtOAc)
$[\alpha]_D^{25}$	: - 79.60 (1 % in MeOH)
UV (λ_{max}, MeOH)	: 308 nm (log ε 4.44)
IR (KBr, cm^{-1})	: 3279, 1680, 1648, 1609, 1534, 1431 and 954
PMR	: 1.78-1.92 (m, 1H), 2.73-2.82 (m, 1H), 3.24-3.29 (m, 2H), 4.44-4.56 (m, 3H), 6.26-6.31 (d, 1H, *J*= 10 Hz), 6.40-6.42 (d, 1H, *J*= 4 Hz), 7.01-7.38 (m, 8H) and 7.71-7.76 (d, 1H, *J*= 10 Hz)
Mass (m/z)	: 327.1 (M+H)

4.1.26 (*E*)*N*-[(*S*)1-Benzyl-2-oxo-3-pyrrolidino]-3-(2-furyl)acrylamide(79; R = g)

Compound **(79)** was prepared by reacting compound **(66)** (0.5 g, 1.7 mmole) with 2-furylacrylic acid **(69; R = g)** (0.23 g, 1.7 mmole) as described above for compound **(75)**. Work up of the reaction mixture followed by crystallization from acetone yielded compound **(79)**, (0.17 g, 32 %), m.p. 165-67 °C.

Anal. :

TLC	: R_f 0.6 (EtOAc)
UV (λ_{max}, MeOH)	: 302.6 nm (log ε 4.46)
IR (KBr, cm^{-1})	: 3300, 1696, 1652, 1610, 1539, 1437, 1327 and 1297
PMR	: 1.78-1.94 (m, 1H), 2.73-2.83 (m, 1H), 3.21-3.32 (m, 2H), 4.45-4.57 (m, 3H), 6.35-6.40 (d, 1H), 6.44-6.45 (m, 1H), 6.55-6.56 (d, 1H, *J*= 4 Hz) and 7.23-7.69 (m, 8H)

$C_{18}H_{18}N_2O_3$: Requires C, 69.66; H, 5.85; N, 9.02. Found C, 69.34; H, 5.60; N, 8.65 %

4.1.27 (*E*)*N*-[(*S*)1-Benzyl-2-oxo-3-pyrrolidino]-2-methyl-3-phenylacrylamide (80; R = h)

Compound **(80)** was prepared by reacting compound **(66)** (0.7 g, 2.4 mmole) with α-methylcinnamic acid **(70; R = h)** (0.38 g, 2.4 mmole) as described above for compound **(75)**. Work up of the reaction mixture followed by

crystallization from acetone-pet ether (60-80) yielded **80**, (0.3 g, 38 %), m.p. 135-38 °C.

Anal. :

TLC	: R_f 0.77 (20 % *n*-hexane in EtOAc)
$[\alpha]_D^{25}$	: - 63.75 (1 % in MeOH)
UV (λ_{max}, MeOH)	: 261 nm (log ε 4.42)
IR (KBr, cm^{-1})	: 3279, 1683, 1646,1615, 1538, 1433, 1295 and 1077
PMR	: 1.81-1.95 (m, 1H), 2.13 (s, 3H), 2.73-2.83 (m, 1H), 3.26-3.31 (m, 2H), 4.48-4.56 (m, 3H), 6.80-6.81 (d, 1H, *J*= 4 Hz), 7.24-7.35 (m, 10H) and 7.41-7.44 (d, 1H)
Mass (m/z)	: 335.5 (M+H)

4.1.28 (*S*)3-Methanesulfonamido-2-oxo-1-benzylpyrrolidine (81; R = i)

In a three-neck round-bottom flask (100 ml) equipped with an efficient stirrer, ice bath, thermometer and calcium chloride guard tube, compound **(66)** (0.4 g, 1.4 mmole) was dissolved in dichloromethane (20 ml) and it was cooled to 5-10 °C. Trifluoroacetic acid (1.3 ml) was added in portions into the above solutions and the reaction mixture was stirred at room temperature for 90 min, concentrated to get a yellow sticky mass, which was dried in vacuum.

This sticky mass was dissolved in dry THF (25 ml) and TEA (5 ml) was added to it in portions maintaining the temperature at 0 -5 °C. Mesyl chloride **(71; R = i)** (0.23 g, 0.16 ml, 2 mmole) dissolved in THF (5 ml) was added in portions into the above solution and the reaction mixture was stirred at room temperature for 15 h. The reaction mixture was concentrated to get a sticky mass which was diluted with ice-water (50 ml). The solid so obtained was filtered, dried (0.29 g) and crystallized from acetone-pet ether (60-80) to afford compound **(81)**, (0.19 g, 51%), m.p. 127 - 29 °C.

Anal. :

TLC	: R_f 0.73 (EtOAc)
UV (λ_{max}, MeOH)	: 258 nm (log ε 2.19)
IR (KBr, cm^{-1})	: 3163, 1680, 1493, 1452, 1320 and 1151

PMR : 1.89-2.00 (m, 1H), 2.51-2.61 (m, 1H), 3.15 (s, 3H), 3.20-3.25 (m, 2H), 4.14-4.22 (m, 1H), 4.46 (s, 2H), 5.28-5.30 (d, 1H, *J*= 4 Hz), 7.19-7.22 (m, 2H) and 7.26-7.37 (m, 3H)

Mass (m/z) : 269.5 (M+H)

4.1.29 (*S*)3-Phenylsulfonamido-2-oxo-1-benzylpyrrolidine (82; R = j)

Compound **(82)** was synthesized using compound **(66)** (0.5 g, 1.7 mmole) as described above for compound **(81)** except that benzenesulfonyl chloride **(72; R = j)** (0.45 g, 0.32 ml, 2.5 mmole) was used instead of mesyl chloride **(71)**. The crude solid so obtained was crystallized using acetone-pet ether (60-80) to afford compound **(82)**, (0.45 g, 80 %), m.p. 162-64 °C.

Anal. :

TLC : R_f 0.54 (5 % MeOH in $CHCl_3$)

$[\alpha]_D^{25}$: -9.35 (1 % in MeOH)

UV (λ_{max}, MeOH) : 265 nm (log ε 2.98)

IR (KBr, cm^{-1}) : 3166, 1675, 1448, 1329 and 1162

PMR : 1.96-2.10 (m, 1H), 2.49-2.59 (m, 1H), 3.11-3.24 (m, 2H), 3.69-3.76 (m, 1H), 4.36-4.48 (dd, 2H), 5.33 (s, 1H), 7.15-7.32 (m, 5H), 7.54-7.58 (m, 3H) and 7.90-7.94 (d, 2H)

Mass (m/z) : 331.4 (M+H)

4.1.30 (*S*)3-(4-Tolylsulfonamido)-2-oxo-1-benzylpyrrolidine (83; R = k)

Compound **(83)** was prepared by reacting compound **(66)** (0.35 g, 1.2 mmole) with tosyl chloride **(73 R = k)** (0.35 g, 1.8 mmole) as described above for **81.** The crude solid so obtained was crystallized using acetone-pet ether (60-80) to afford compound **(83)**, (0.3 g, 73 %), m.p. 173-75 °C.

Anal. :

TLC : R_f 0.73 (2 % MeOH in $CHCl_3$)

UV (λ_{max}, MeOH) : 263.5 nm (log ε 2.72)

IR (KBr, cm^{-1}) : 3171, 1675, 1490, 1448, 1330 and 1160

PMR : 1.96-2.10 (m, 1H), 2.43 (s, 3H), 2.48-2.58 (m, 1H), 3.11-3.23 (m, 2H), 3.65-3.72 (m, 1H), 4.36-4.48 (dd, 2H), 5.27 (s, 1H), 7.15-7.18 (dd, 2H), 7.26-7.35 (m, 5H) and 7.77-7.81 (m, 2H)

Mass (m/z) : 345.6 (M+H)

$C_{18}H_{20}N_2O_3S$: Requires C, 62.77; H, 5.85; N, 8.13. Found C, 62.66; H, 5.80; N, 7.95 %

4.1.31 (*S*)3-Benzylsulfonamido-2-oxo-1-benzylpyrrolidine (84; R = l)

Compound **(84)** was synthesized using compound **(66)** (0.5 g, 1.7 mmole) as described above for compound **(81)** except that α-toluenesulfonyl chloride **(74 R = l)** (0.48 g, 2.5 mmole) was used instead of mesyl chloride **(71)**. The crude solid so obtained was crystallized using acetone-pet ether (60-80) to afford compound **(84)**, (0.3 g, 51%), m.p. 176-78 °C.

Anal. :

TLC : Rf 0.68 (10 % MeOH in $CHCl_3$)

UV (λ_{max}, MeOH) : 258.4 nm (log ε 2.59)

IR (KBr, cm^{-1}) : 3215, 1684, 1491, 1320, 1155, 1128 and 694

PMR : 1.70-1.87 (m, 1H), 2.39-2.49 (m, 1H), 3.10-3.18 (m, 2H), 4.06-4.14 (m, 1H), 4.41-4.52 (m, 4H), 4.87-4.89 (d, 1H, *J*= 2 Hz) and 7.19-7.54 (m, 10H)

$C_{18}H_{20}N_2O_3S$: Requires C, 62.77; H, 5.85; N, 8.13. Found C, 62.50; H, 5.50; N, 7.90 %

4.1.32 *L*-Leucine methyl ester hydrochloride (85)

L-Leucine **(48)** (16 g 0.122 mole) was dissolved in methanol (160 ml) and the solution was cooled to below -10 °C. Thionyl chloride (16 ml) was added dropwise to this solution through PEDF at a temperature below 0 °C and the reaction mixture was stirred for 2 h, and concentrated under vacuum. The

residue so obtained was dried to give compound **(85)**, (22 g, 99 %), m.p. 145-48 °C (148-50 °C[134]).

4.1.33 Boc-Met-Leu-OMe (86)

In a three-neck round-bottom flask (100 ml) equipped with an efficient stirrer, thermometer and calcium chloride guard tube, Boc-*L*-Methionine **(64)** (3.6 g, 14.5 mmole) was dissolved in dichloromethane (30 ml). *L*-Leucine methyl ester hydrochloride **(85)** (2.7 g, 14.5 mmole) was suspended in this solution. TEA (2.3 ml) was charged to the above suspension in portions at -10 to -5 °C followed by the addition of 1-HOBT (1.95 g, 14.5 mmole). DCC (3.0 g, 14.5 mmole) was added to the above solution in portions over a period of 30 min. The reaction mixture was stirred at room temperature for 16 h. DCU formed in the reaction mixture was filtered off (3.2 g) and the filtrate was further diluted with dichloromethane (70 ml), washed with aq citric acid (0.5 M, 3x50 ml), aq sodium bicarbonate (5 %, 2x50 ml) and water (2x100 ml). The organic layer was dried and solvent removed under vacuum to get a solid mass. The solid mass so obtained was crystallized using ethyl acetate-*n*-hexane to afford **86**, (4.7 g, 86 %), m.p. 107-109 °C (108-09 °C[117]).

Anal. :

TLC	: R_f 0.59 (4 % MeOH in $CHCl_3$)
IR (KBr, cm^{-1})	: 3337, 3300, 1758, 1682, 1658, 1550, 1520 and 1157
PMR	: 0.92-0.94 (d, 6H, *J*= 4 Hz), 1.44 (s, 9H), 1.52-2.08 (m, 5H), 2.12 (s, 3H), 2.57-2.62 (t, 2H), 3.72 (s, 3H), 4.27-4.29 (m, 1H), 4.55-4.62 (m, 1H), 5.16-5.18 (d, 1H, *J*= 4 Hz) and 6.55-6.58 (d, 1H, *J*= 6 Hz)

4.1.34 (*S*)2-[(*S*)3-t-Butoxycarboxamido-2-oxo-1-pyrrolidino]-4-methyl--pentanoic acid (87)

In a single-neck round-bottom flask (250 ml) equipped with an efficient stirrer, water condenser and calcium chloride guard tube, compound **(86)** (25 g, 0.066 mole) was dissolved in methyl iodide (35 ml) and stirred at room

temperature for 48 h. The reaction mixture was concentrated *in vacuo* to afford methyl sulfenium iodide salt of compound **(86)**.

In a separate three-neck round-bottom flask (500 ml) the sulfenium salt was dissolved in a mixture of dichloromethane (180 ml) and DMF (20 ml), and the solution was cooled to 0 °C. Sodium hydride (6.33 g, 0.131 mole, 50 % mineral oil dispersion used as such) was added to the above solution at 0 °C (colour of reaction mixture changes from yellow to colourless). The reaction mixture was stirred at 0 °C for 3 h. Water (100 ml) was added to the reaction mixture at 0 °C and dichloromethane was removed under vacuum. The aq phase (pH ~ 8) was acidified to pH ~ 4 with aq citric acid (0.5 M) and extracted with chloroform (10x70 ml) by saturating the aq layer with sodium chloride. The combined organic layer was washed with water (10x500 ml) dried and concentrated to get a sticky mass, which solidified on standing. The solid so obtained was crystallized from ethyl acetate-*n*-hexane to give compound **(87)**, (13 g, 62 %), m.p. 152-54 °C (154-55 °C[117]).

Anal. :

TLC	: R_f 0.53 (5 % MeOH in $CHCl_3$, saturated with 1 drop of AcOH)
IR (KBr, cm^{-1})	: 3395, 1704, 1675, 1654, 1507 and 1181
PMR	: 0.83-0.85 (dd, 3H), 0.88-0.90 (dd, 3H), 1.38 (s, 9H), 1.49-1.82 (m, 4H), 2.17-2.25 (m, 1H), 3.14-3.20 (m, 2H), 4.17-4.20 (m, 1H), 4.46-4.51 (m, 1H) and 7.11-7.14 (d, 1H, J= 6 Hz)

4.1.35 *t*-Butyl *N*-[(*S*)1-[(*S*)1-((*S*)2-cyano-1-pyrrolidinecarbonyl)-3-methylbutyl]-2-oxo-3-pyrrolidino]carbamate (89)

In a three-neck round-bottom flask (250 ml) equipped with an efficient stirrer, ice bath, thermometer and calcium chloride guard tube, compound **(87)** (2.2 g, 7 mmole) was dissolved in dichloromethane (50 ml) and the solution was cooled to 10-15 °C. BOP (3.1 g, 7 mmole) was charged into the above solution and the reaction mixture was stirred for 45 min at 10-15 °C. Compound **(47)** (1.5 g, 7

mmole) was added into the above solution followed by the addition of TEA (3.5 ml) at -10 to 0 °C. The reaction mixture was stirred at room temperature for 15 h, washed with aq citric acid (0.5 M, 2 x 50 ml), aq sodium bicarbonate (5 %, 2 x 50 ml), and water (2 x 50 ml). The organic layer was dried and concentrated under vacuum to give **88**, (2 g) which was used as such without further purification and characterization.

A solution of compound **(88)** (1.9 g, 4.6 mmole, crude) in dry DMF (15 ml) was cooled to 0 °C. Cyanuric chloride (0.92 g, 5 mmole) was added to this solution in portions and the reaction mixture was stirred at room temperature for 2 h. During the course of the reaction a white precipitate was formed. The reaction mixture was poured over crushed ice and extracted with chloroform (5x 30 ml). The organic layer was washed extensively with water (5x200 ml), dried and the solvent removed. The yellow sticky mass so obtained was purified by column chromatography over silica gel eluting the desired compound **(89)** in ethyl acetate-*n*-hexane (30-45 %), (0.75 g, 41 %), m.p. 128-30 °C.

Anal. :

TLC	: R_f 0.7 (10 % MeOH in $CHCl_3$)
$[\alpha]_D^{25}$	: -180.37 (1 % in MeOH)
IR (KBr, cm^{-1})	: 3355, 2232, 1712, 1691, 1658, 1518, 1409 and 1367
PMR (DMSO-d_6)	: 0.84-0.92 (dd, 6H, J_1= 12 Hz, J_2= 12 Hz), 1.38 (s, 9H), 1.44-1.67 (m, 3H), 1.74-1.79 (m, 1H), 1.97-1.99 (m, 2H), 2.15-2.19 (m, 2H), 2.19-2.24 (m, 1H), 3.16-3.26 (m, 2H), 3.49-3.54 (m, 1H), 3.57-3.63 (m, 1H), 4.09-4.16 (m, 1H), 4.72-4.75 (t, 1H), 4.77-4.81 (m, 1H) and 7.16-7.18 (d, 1H)
Mass (m/z)	: 393.3 (M+H)

4.1.36 (*S*)1-{(*S*)2-[(*S*)3-Methanesulfonamido-2-oxo-1-pyrrolidino]- 4-methyl pentanoyl}pyrrolidine-2-carbonitrile (99; R= i)

Compound **(89)** (0.6 g, 1.5 mmole) was dissolved in dichloromethane (30 ml) and cooled to 5-10 °C. Trifluoroacetic acid (1.2 ml) was added to the above solution in portions, the reaction mixture stirred at room temperature for 90 min

and concentrated on water bath to get a yellow sticky mass which was dried in vacuum.

The TFA salt prepared in this way was dissolved in THF (40 ml), cooled to -10 to -5 °C and TEA (5 ml) was added to it in portions. Mesyl chloride **(71; R = i)** (0.35 g, 3 mmole) dissolved in THF (10 ml) was charged dropwise to the above solution and the reaction mixture was stirred for 16 h. The reaction mixture was concentrated to get a sticky mass to which crushed ice was added and the mixture was extracted with chloroform (4x25 ml). The combined organic layer was washed with water (100 ml), dried and concentrated. Chromatographic purification of the crude material over silica gel using ethyl acetate-*n*-hexane (30-40 %) as eluent yielded **99** as a sticky mass which could not be crystallized, (0.15 g, 27 %).

Anal. :

TLC	: R_f 0.6 (EtOAc)
IR (KBr, cm^{-1})	: 3176, 2232, 1699, 1645, 1343 and 1168

4.1.37 (*S*)1-[(*S*)2-[(*S*)3-Benzenesulfonamido-2-oxo-1-pyrrolidino]-4-methyl-pentanoyl]pyrrolidine-2-carbonitrile (100; R = j)

Compound **(100)** was prepared by reacting compound **(89)** (0.5 g, 1.3 mmole) with benzenesulfonyl chloride **(72; R = j)** (0.56 g, 0.4 ml, 3.17 mmole) as described above for compound **(99).** The crude material so obtained was crystallized from acetone-pet ether (60-80) to yield compound **(100)**, (0.37 g, 67 %), m.p. 169-71 °C.

Anal. :

TLC	: R_f 0.52 (30 % *n*-Hexane in EtOAc)
$[\alpha]_D^{25}$	: - 122.26 (1 % in MeOH)
UV (λ_{max}, MeOH)	: 233 nm (log ε 3.51)
IR (KBr, cm^{-1})	: 3258, 2232, 1694, 1650, 1428, 1334, 1173 and 748
PMR	: 0.87-0.94 (dd, 6H), 1.55-1.78 (m, 3H), 1.95-2.10 (m, 1H), 2.18-2.27 (m, 4H), 3.14-3.30 (m, 2H), 3.52-3.79 (m, 2H), 4.10-4.20 (m, 1H), 4.68-4.73 (m, 1H), 4.80-

4.84 (m, 1H), 5.34 (b, 1H), 7.52-7.61 (m, 3H) and 7.89-7.92 (m, 2H)

Mass (m/z) : 433.1 (M+H)

$C_{21}H_{28}N_4O_4S$: Requires C, 58.31; H, 6.52; N, 12.95. Found C, 58.70; H, 6.43; N, 12.53 %

4.1.38 (*S*)1-{(*S*)2-[(*S*)3-(4-Methylbenzenesulfonamido)-2-oxo-1-pyrrolidino]-4-methylpentanoyl}pyrrolidine-2-carbonitrile (101; R = k)

Compound **(89)** (0.3 g, 0.76 mmole) was reacted with tosyl chloride **(73; R = k)** (0.25 g, 1.3 mmole) as described above for **99**. Work up of the reaction mixture followed by crystallization of the crude solid from ethyl acetate-*n*-hexane afforded compound **(101)**, (0.23 g, 67 %), 110-12 °C.

Anal. :

TLC : R_f 0.53 (30 % *n*-Hexane in EtOAc)

UV (λ_{max}, MeOH) : 235 nm (log ε 3.51)

IR (KBr, cm^{-1}) : 3175, 2245, 1700, 1643, 1414, 1343 and 1167

PMR : 0.88-0.95 (dd, 6H), 1.56-1.77 (m, 3H), 1.97-2.08 (m, 1H), 2.12-2.30 (m, 4H), 2.44 (s, 3H), 2.48-2.56 (m, 1H), 3.14-3.28 (m, 2H), 3.71-3.80 (m, 2H), 4.10-4.15 (m, 1H), 4.68-4.73 (m, 1H), 4.81-4.84 (m, 1H), 5.30 (s, 1H), 7.26-7.36 (d, 2H) and 7.77-7.83 (d, 2H)

Mass (m/z) : 447.1 (M+H)

4.1.39 *N*-{(*S*)1-[(*S*)1-((*S*)2-Cyano-1-pyrrolidinocarbonyl)-3-methylbutyl]-2-oxo-3-pyrrolidino}-4-morpholinecarboxamide (102; R = m)

Compound **(102)** was prepared by reacting compound **(89)** (0.8 g, 2 mmole) with 4-morpholinecarbonyl chloride **(90; R = m)** (0.41 g, 0.31 ml, 3 mmole) as described above for **99**. Work up of the reaction mixture followed by crystallization from ethyl acetate gave **102**, (0.42 g, 51 %), 187-89 °C.

Anal. :

TLC	: R_f 0.57 (5 % MeOH in $CHCl_3$)
$[\alpha]_D^{25}$	: - 144.71 (1 % in MeOH)
IR (KBr, cm^{-1})	: 3341, 2232, 1698, 1656, 1638, 1534, 1411 and 1265
PMR	: 0.93-1.01 (dd, 6H), 1.32-1.63 (m, 3H), 1.82-1.85 (m, 1H), 1.90-2.10 (m, 2H), 2.15-2.20 (m, 2H), 2.26-2.33 (m, 1H), 2.60-2.75 (m, 2H), 3.20-3.31 (m, 2H), 3.33-3.39 (m, 1H), 3.59-3.63 (m, 1H), 3.81-3.85 (m, 2H), 4.30-4.40 (m, 1H), 4.73-4.75 (m, 1H), 4.84-4.90 (m, 1H), 4.92-4.97 (m, 2H), 5.00-5.05 (m, 2H) and 5.36-5.38 (d, 1H)

$C_{20}H_{31}N_5O_4$: Requires C, 59.24; H, 7.70; N, 17.27. Found C, 59.24; H, 7.91; N, 16.81 %

4.1.40 *N*-{(*S*)1-[(*S*)1-((*S*)2-Cyano-1-pyrrolidinocarbonyl)-3-methylbutyl]-2-oxo-3-pyrrolidino}benzamide (103; R = a)

In a three-neck round-bottom flask (100 ml) equipped with an efficient stirrer, ice bath, thermometer and calcium chloride guard tube, compound **(89)** (0.3 g, 0.76 mmole) was dissolved in dichloromethane (30 ml) and the solution was cooled to 5-10 °C. Trifluoroacetic acid (1.2 ml) was added to the above solution in portions. The reaction mixture was stirred at room temperature for 90 min and concentrated to get yellow sticky mass, which was dried in vacuum.

In a separate three-neck round-bottom flask (100 ml) equipped with an efficient stirrer, ice bath, thermometer and calcium chloride guard tube, benzoic acid **(51; R = a)** (0.1 g, 0.8 mmole) was dissolved in dichloromethane (25 ml) and cooled to 10-15 °C. BOP (0.35 g, 0.8 mmole) was added to the above clear solution and the reaction mixture was stirred for 45 min at 10-15 °C. The TFA salt prepared in the above step was dissolved in dichloromethane and charged to the above solution. TEA (4 ml) was added to it at 5-10 °C and the reaction mixture was stirred for 15 h. The reaction mixture was washed with aq citric acid (0.5 M, 2 x 50 ml), aq sodium bicarbonate (5 %, 2 x 50 ml) and finally with water (2 x 50

ml). The organic layer was dried and concentrated to get a sticky mass, which was purified by column chromatography using silica gel as adsorbent and ethyl acetate-*n*-hexane (30-45 %) as eluent to afford compound **(103)**, (0.1 g, 33 %), m.p. 78-80 °C.

Anal. :

TLC : R_f 0.62 (EtOAc)

IR (KBr, cm^{-1}) : 3365, 2232, 1700, 1659, 1647, 1545, 1412 and 1292

$C_{22}H_{28}N_4O_3$: Requires C, 66.64; H, 7.12; N, 14.13. Found C, 66.59; H, 7.08; N, 14.55 %

4.1.41 (*E*)*N*-{(*S*)1-[(*S*)1-((*S*)2-Cyano-1-pyrrolidinocarbonyl)-3-methylbutyl]-2-oxo-3-pyrrolidino}-3-phenylacrylamide (104; R = c)

Compound **(104)** was prepared by reacting compound **(89)** (0.65 g, 1.65 mmole) with *trans*-cinnamic acid **(53; R = c)** (0.24 g, 1.65 mmole) as described above for **103**. Work up of the reaction mixture followed by chromatographic purification with ethyl acetate-*n*-hexane (30-35 %) afforded **104**, (0.3 g, 43 %), m.p. 98-101 °C.

Anal. :

TLC : R_f 0.44 (EtOAc)

UV (λmax, MeOH) : 275 nm (log ε 4.42)

IR (KBr, cm^{-1}) : 3294, 2245, 1701, 1660, 1634 and 1419

Mass (m/z) : 423.2 (M+H), 422, 327.2, 299.2, 131.1 and 103.1

$C_{24}H_{30}N_4O_3$: Requires C, 68.22; H, 7.16; N, 13.26. Found C, 67.88; H, 6.82; N, 13.60 %

4.1.42 (*E*)*N*-{(*S*)1-[(*S*)1-((*S*)2-Cyano-1-pyrrolidinocarbonyl)-3-methylbutyl]-2-oxo-3-pyrrolidino}-3-(2-furyl)acrylamide (105; R = g)

Compound **(105)** was prepared by reacting compound **(89)** (0.65 g, 1.65 mmole) with 2-furylacrylic acid **(69; R = g)** (0.22 g, 1.65 mmole) as described above for compound **(103)**. Work up of the reaction mixture followed by

chromatographic purification with ethyl acetate-*n*-hexane (30-35 %) yielded **105**, (0.25 g, 38 %), m.p. 120-22 °C.

Anal. :

TLC : R_f 0.4 (EtOAc)

UV (λmax, MeOH) : 300 nm (log ε 3.35)

IR (KBr, cm^{-1}) : 3308, 2232, 1693, 1660 and 1630

$C_{24}H_{30}N_4O_3$: Requires C, 64.06; H, 6.84; N, 13.58. Found C, 63.80; H, 6.56; N, 13.06 %

4.1.43 *N*-{(*S*)1-[(*S*)1-((*S*)2-Cyano-1-pyrrolidinocarbonyl)-3-methylbutyl]-2-oxo-3-pyrrolidino}isonicotinamide (106; R = n)

Compound **(106)** was prepared by reacting compound **(89)** (0.5 g, 1.3 mmole) with isonicotinic acid **(91; R = n)** (0.16 g, 1.3 mmole) as described above for compound **(103)**. Work up of the reaction mixture followed by crystallization from ethyl acetate-*n*-hexane yielded compound **(106)**, (0.35 g, 70 %), m.p. 196-98 °C.

Anal. :

TLC : R_f 0.21 (10 % MeOH in EtOAc)

$[\alpha]_D^{25}$: - 146.45 (1 % MeOH)

UV (λmax, MeOH) : 263nm (log ε 3.78)

IR (KBr, cm^{-1}) : 3232, 2246, 1699, 1666 and 1655

PMR : 0.95-1.03 (dd, 6H), 1.25-1.55 (m, 3H), 1.85-1.88 (m, 1H), 2.23-2.37 (m, 4H), 2.65-2.80 (m, 1H), 3.29-3.38 (m, 2H), 3.63-3.72 (m, 2H), 4.10-4.18 (m, 1H), 4.92-5.03 (m, 2H), 7.18-7.20 (d, 1H), 7.62-7.66 (m, 2H) and 8.74-8.77 (m, 2H)

$C_{21}H_{27}N_5O_3$: Requires C, 63.46; H, 6.84; N, 17.62. Found C, 63.08; H, 6.66; N, 17.12 %

4.1.44 *N*-[(*S*)1-[(*S*)1-((*S*)2-Cyano-1-pyrrolidinocarbonyl)-3-methylbutyl]-2-oxo-3-pyrrolidino]nicotinamide (107; R = o)

Compound **(107)** was prepared by reacting compound **(89)** (0.5 g, 1.3 mmole) with nicotinic acid **(92; R = o)** (0.16 g, 1.3 mmole) as described above for **103**. Work up of the reaction mixture followed by crystallization from ethyl acetate-*n*-hexane yielded **107**, (0.35 g, 70 %), m.p. 165-68 °C.

Anal. :

TLC : R_f 0.27 (10 % MeOH in EtOAc)

$[\alpha]_D^{25}$: - 162.84 (1 % in MeOH)

UV (λmax, MeOH) : 255 nm (log ε 4.63)

IR (KBr, cm^{-1}) : 3354, 2232, 1700, 1653, 1631, 1545, 1419 and 736

PMR : 0.93-1.01 (dd, 6H), 1.45-1.66 (m, 3H), 1.85-1.90 (m, 1H), 2.11-2.37 (m, 4H), 2.68-2.81 (m, 1H), 3.33-3.45 (m, 2H), 3.59-3.64 (m, 1H), 3.65-3.71 (m, 1H), 3.81-3.90 (m, 1H), 4.90-5.00 (m, 1H), 5.08-5.18 (m, 1H), 7.09-7.11 (d, 1H), 7.35-7.39 (m, 1H), 8.09-8.12 (m, 1H), 8.72 (s, 1H) and 9.03-9.04 (d, 1H)

Mass (m/z) : 398.2 (M+H), 302, 274 and 256

$C_{21}H_{27}N_5O_3$: Requires C, 63.46; H, 6.84; N, 17.62. Found C, 63.05; H, 6.65; N, 17.28 %

4.1.45 *N*-[(*S*)1-[(*S*)1-((*S*)2-Cyano-1-pyrrolidinocarbonyl)-3-methylbutyl]-2-oxo-3-pyrrolidino]-2-thiophenecarboxamide (108; R = p)

The reaction between compound **(89)** (0.9 g, 2.3 mmole) with thiophene-2-carboxylic acid **(93; R = p)** (0.29 g, 2.3 mmole) as described above for compound **(103)** followed by crystallization from ethyl acetate yielded compound **(108)**, (0.55 g, 60 %), m.p. 205-07 °C.

Anal. :

TLC : R_f 0.7 (EtOAc)

$[\alpha]_D^{25}$: - 148.81 (1 % in MeOH)

UV (λmax, MeOH) : 250 nm (log ε 4.58)

IR (KBr, cm^{-1}) : 3354, 2245, 1700, 1652, 1630, 1545, 1294 and 1239

PMR : 0.92-1.00 (dd, 6H), 1.35-1.60 (m, 3H), 1.79-1.88 (m, 1H), 1.95-2.08 (m, 2H), 2.13-2.20 (m, 2H), 2.25-2.30 (m, 1H), 3.30-3.42 (m, 2H), 3.59-3.64 (m, 1H), 3.65-3.71 (m, 1H), 3.83-3.90 (m, 1H), 4.51-4.58 (m, 1H), 4.90-5.00 (m, 1H), 6.88-6.93 (d, 1H), 7.04-7.07 (m, 1H) and 7.47-7.52 (m, 2H)

Mass (m/z) : 403.5 (M+H), 307 and 279

$C_{20}H_{26}N_4O_3S$: Requires C, 59.67; H, 6.51; N, 13.91. Found C, 60.04; H, 6.52; N, 13.44 %

4.1.46 *N*-{(*S*)1-[(*S*)1-((*S*)2-Cyano-1-pyrrolidinocarbonyl)-3-methylbutyl]-2-oxo-3-pyrrolidino}-4-chlorobenzamide (109; R = q)

Compound **(109)** was prepared by reacting compound **(89)** (0.35 g, 0.9 mmole) with p-chlorobenzoic acid **(94; R = q)** (0.14 g, 0.9 mmole) as described above for **103**. Work up of the reaction mixture followed by chromatographic purification over silica gel with ethyl acetate in *n*-hexane (30-45 %) afforded **109**, (0.11 g, 29 %), m.p. 98-100 °C.

Anal. :

TLC : R_f 0.31 (30 % *n*-hexane in EtOAc)

UV (λ_{max}, MeOH) : 236.5 nm (log ε 4.12)

IR (KBr, cm^{-1}) : 3323, 2246, 1693, 1653, 1631, 1539, 1423 and 1091

$C_{22}H_{27}ClN_4O_3$: Requires C, 61.32; H, 6.31; N, 13.00. Found C, 59.90; H, 6.12; N, 12.62 %

4.1.47 *N*-{(*S*)1-[(*S*)1-((*S*)2-Cyano-1-pyrrolidinocarbonyl)-3-methylbutyl]-2-oxo-3-pyrrolidino}-2-furylcarboxamide (110; R = r)

Compound **(110)** was prepared by reacting compound **(89)** (0.6 g, 1.5 mmole) with 2-furoic acid **(95; R = r)** (0.17 g, 1.5 mmole) as described above for

compound **(103)**. Work up of the reaction mixture followed by crystallization from ethyl acetate yielded compound **(110)**, (0.3 g, 51 %), m.p. 175-77 °C.

Anal. :

TLC	: R_f 0.39 (EtOAc)
UV (λmax, MeOH)	: 252 nm (log ε 4.45)
IR (KBr, cm^{-1})	: 3341, 2232, 1698, 1655, 1638, 1534, 1411 and 1265
Mass (m/z)	: 387.3 (M+H), 291 and 263

$C_{20}H_{26}N_4O_4$: Requires C, 62.16; H, 6.78; N, 14.50. Found C, 62.49; H, 6.70; N, 14.04 %

4.1.48 *N*-[(*S*)1-[(*S*)1-((*S*)2-Cyano-1-pyrrolidinocarbonyl)-3-methylbutyl]-2-oxo-3-pyrrolidino]-4-nitrobenzamide (111; R = s)

Compound **(111)** was prepared by reacting compound **(89)** (0.4 g, 1 mmole) with p-nitrobenzoic acid **(96; R = s)** (0.17 g, 1 mmole) as described above for **103**. The crude compound so obtained was purified by chromatography over silica gel using ethyl acetate in *n*-hexane (30-45 %) as eluent to give compound **(111)**, (0.15 g, 33 %), m.p. 102-04 °C.

Anal. :

TLC	: R_f 0.27 (30 % *n*-Hexane in EtOAc)
UV (λmax, MeOH)	: 264nm (log ε 4.03)
IR (KBr, cm^{-1})	: 3323, 2246, 1701, 1666, 1647, 1525 and 1346
PMR	: 0.93-1.02 (dd, 6H), 1.25-1.58 (m, 3H), 1.83-1.87 (m, 1H), 2.10-2.35 (m, 4H), 2.68-2.73 (m, 1H), 3.28-3.60 (m, 3H), 3.44-3.65 (m, 1H), 4.58-4.64 (m, 1H), 4.89-5.02 (m, 2H), 7.14-7.16 (d, 1H), 7.94-7.98 (d, 2H) and 8.26-8.30 (d, 2H)
Mass (m/z)	: 442.1 (M+H), 346.1 and 318.1

4.1.49 *N*-{(*S*)1-[(*S*)1-((*S*)2-Cyano-1-pyrrolidinocarbonyl)-3-methylbutyl]-2-oxo-3-pyrrolidino}-2-pyridinecarboxamide (112; R = t)

Compound **(112)** was prepared by reacting compound **(89)** (0.5 g, 1.3 mmole) with 2-picolinic acid **(97; R = t)** (0.16 g, 1.3 mmole) as described above for compound **(103)**. Work up of the reaction mixture followed by chromatographic purification with ethyl acetate-*n*-hexane (25 %) over silica gel yielded **112**, (0.2 g, 39 %), m.p. 92-95 °C.

Anal. :

TLC : R_f 0.66 (10 % MeOH in $CHCl_3$)

UV (λmax, MeOH) : 260nm (log ε 3.76)

IR (KBr, cm^{-1}) : 3203, 2232, 1690, 1660, 1647, 1554 and 1429

$C_{21}H_{27}N_5O_3$: Requires C, 63.46; H, 6.84; N, 17.62. Found C, 63.00; H, 6.70; N, 17.48 %

4.1.50 *N*-{(*S*)1-[(*S*)1-((*S*)2-Cyano-1-pyrrolidinocarbonyl)-3-methylbutyl]-2-oxo-3-pyrrolidino}-4-fluorobenzamide (113; R = u)

Compound **(113)** was prepared by reacting compound **(89)** (0.3 g, 0.76 mmole) with p-flurobenzoic acid **(98; R = u)** (0.11 g, 0.76 mmole) as described above for **103**. Work up of the reaction mixture followed by chromatographic purification with ethyl acetate in *n*-hexane (30-45 %) yielded **113**, (0.13 g, 42 %), m.p. 79-81 °C.

Anal. :

TLC : R_f 0.31 (30 % *n*-Hexane in EtOAc)

IR (KBr, cm^{-1}) : 3354, 2245, 1700, 1659, 1648, 1545, 1502 and 1423

$C_{22}H_{27}FN_4O_3$: Requires C, 63.75; H, 6.56; N, 13.51. Found C, 63.48; H, 6.42; N, 13.70 %

4.1.51 *L*-Phenylalanine methyl ester hydrochloride (115)

L-Phenylalanine **(114)** (14 g 0.08 mole) was suspended in methanol (140 ml) and the mixture was cooled to below –10 °C. Thionyl chloride (14 ml) was added to the above suspension through PEDF at a temperature below 0 °C and

the clear reaction mixture was stirred at room temperature for 2 h, and the solvent removed. The solid so obtained was dried in vacuum to give **115**, (18 g, 98 %), m.p. 157-60 °C (158-62 °C[134]).

4.1.52 Boc-Met-Phe-OMe (116)

In a three-neck round-bottom flask (500 ml) equipped with an efficient stirrer, thermometer and calcium chloride guard tube, Boc-*L*-methionine **(64)** (30 g, 0.12 mole) was dissolved in dichloromethane (350 ml) and *L*-phenylalanine methyl ester hydrochloride **(115)** (25.9 g, 0.12 mole) was suspended in it. TEA (25 ml) was charged to the above suspension in fractions at a temperature -10 to -5 °C. 1-HOBT (16.2 g, 0.12 mole) was added to this reaction mixture followed by the addition of DCC (24.72 g, 0.12 mole) in small fractions over a period of 30 min. The reaction mixture was stirred at room temperature for 16 h and the DCU precipitated in the reaction mixture was filtered off. Dichloromethane (100 ml) was added to the filtrate and the combined filtrate was washed with aq citric acid (0.5 M, 3x50 ml), aq sodium bicarbonate (5 %, 2x50 ml) and water (2x100 ml). The organic layer was dried and the solvent removed under vacuum to get a solid. The crude solid so obtained was crystallized using ethyl acetate-*n*-hexane to afford **116**, (28 g, 57 %), m.p. 82-84 °C (83-85 °C[117]).

Anal. :

TLC	: R_f 0.31 (30 % EtOAc in *n*-hexane)
IR (KBr, cm^{-1})	: 3346, 3300, 1740, 1687, 1666, 1521 and 1173
PMR	: 1.43 (s, 9H), 1.80-2.03 (m, 2H), 2.04 (s, 3H), 2.50-2.54 (t, 2H, *J*= 8 Hz), 3.09-3.13 (m, 2H), 3.71 (s, 3H), 4.23-4.25 (m, 1H), 4.80-4.87 (m, 1H), 5.12-5.15 (d, 1H, *J*= 6 Hz), 6.58-6.60 (d, 1H, *J*= 4 Hz), 7.07-7.11 (m, 2H) and 7.20-7.30 (m, 3H)

4.1.53 (*S*)2-[(*S*)3-(t-Butoxycarboxamido)-2-oxo-1-pyrrolidino]-3-phenyl propanoic acid (117)

Compound **(116)** (25 g, 0.06 mole) was dissolved in methyl iodide (35 ml) and the solution was stirred for 48 h during which time a solid separated out.

Excess of methyl iodide was removed *in vacuo* to afford sulfenium salt as a white solid. The sulfenium salt was dissolved in dichloromethane (180 ml) and DMF (20 ml) and cooled to 0 °C. Sodium hydride (5.85 g, 0.12 mole, 50 % mineral oil dispersion used as such) was added to the above solution in portions at 0 °C and the reaction mixture was stirred at 0 °C for 3 h. Water (100 ml) was added to the above reaction mixture at 0 °C and the mixture concentrated under vacuum. The aq layer (pH ~ 8) was acidified to pH ~ 4 with aq citric acid (0.5 M) and extracted with chloroform (10x70 ml) by saturating the aqueous layer with sodium chloride. The combined organic layer was washed extensively with water (10x500 ml), dried and concentrated under vacuum to get a sticky mass of compound **(117)** that was used as such without further purification (7.2 g, 34 % crude[117]).

4.1.54 *t*-Butyl *N*-{(*S*)1-[(*S*)1-benzyl-2-((*S*)2-carbamoyl-1-pyrrolidino)-2-oxo-ethyl]-2-oxo-3-pyrrolidino}carbamate (118)

In a three-neck round-bottom flask (250 ml) equipped with an efficient stirrer, ice bath, thermometer and calcium chloride guard tube, compound **(117)** (7 g, 0.02 mole) was dissolved in dichloromethane (50 ml) and cooled to 10-15 °C. BOP (8.85 g, 0.02 mole) was added into this solution and the reaction mixture was stirred for 45 min at 10-15 °C. Compound **(47)** (4.28 g, 0.02 mole) was added into the above solution followed by the addition of TEA (25 ml) at –10 to 0 °C. The reaction mixture was stirred at room temperature for 15 h and washed with aq citric acid (0.5 M, 2 x 50 ml), aq sodium bicarbonate (5 %, 2 x 50 ml) and water (2 x 100 ml) in that order. The combined organic layer was dried and concentrated under vacuum. The crude solid so obtained was crystallized from ethyl acetate-*n*-hexane mixture to give **118**, (4.35 g, 48 %), m.p.175-77 °C.

Anal. :

TLC	: R_f 0.35 (5 % MeOH in $CHCl_3$)
IR (KBr, cm^{-1})	: 3382, 3300, 3200, 1705, 1680, 1652, 1624 and 1446

4.1.55 *t*-Butyl *N*-{(*S*)1-[(*S*)1-benzyl-2((*S*)2-cyano-1-pyrrolidino)-2-oxoethyl]-2-oxo-3-pyrrolidino}carbamate (119)

Compound **(118)** (4 g, 9 mmole) was dissolved in dry DMF (20 ml) and the solution was cooled to 0 °C. To this clear solution cyanuric chloride (1.65 g, 0.02

mole) was added in portions and the reaction mixture was stirred at room temperature for 2 h. During the course of the reaction a white precipitate separated out. The reaction mixture was poured over crushed ice and extracted with chloroform (5x 30 ml). The combined organic layer was washed extensively with water (5x200 ml), dried and concentrated under vacuum. The yellow sticky mass so obtained was purified by column chromatography using silica gel as adsorbent, and ethyl acetate in *n*-hexane (30-45 %) as eluent. Collected pure fractions were concentrated under vacuum to afford **119**, (2.4 g, 63 %), m.p.149-51 °C.

Anal. :

TLC	: R_f 0.54 (30 % *n*-Hexane in EtOAc)
$[\alpha]_D^{25}$	: -109.39 (1 % in MeOH)
UV (λ_{max}, MeOH)	: 258 nm (log ε 2.37)
IR (KBr, cm^{-1})	: 3436, 2232, 1722, 1692, 1646, 1511 and 1433
PMR	: 1.45 (s, 9H), 1.86-1.99 (m, 3H), 2.11-2.18 (m, 2H), 2.58-2.64 (m, 1H), 2.97-3.05 (m, 2H), 3.29-3.37 (m, 2H), 3.41-3.47 (m, 1H), 3.60-3.65 (m, 1H), 4.09-4.11 (m, 1H), 4.64-4.67 (m, 1H), 4.84-4.85 (d, 1H), 5.03-5.07 (m, 1H) and 7.25-7.37 (m, 5H)
Mass (m/z)	: 427 (M+H)

4.1.56 *N*-[1(*S*)-[(*S*)1-Benzyl-2((*S*)2-cyano-1-pyrrolidino)-2-oxoethyl]-2-oxo-3-pyrrolidino]benzenesulfonamide (120; R = j)

In a single-neck round-bottom flask (100 ml) compound **(119)** (0.8 g, 1.9 mmole) was dissolved in dichloromethane (30 ml) and the solution was cooled to 5-10 °C. Trifluoroacetic acid (1.6 ml) was added to the above solution and the reaction mixture was stirred at room temperature for 90 min. The reaction mixture was concentrated on water bath to get a yellow sticky mass that was dried in vacuum.

The TFA salt was dissolved in dry THF (40 ml) and the solution was cooled to -10 to -5 °C. TEA (5 ml) was added to the above reaction mixture in portions. Benzenesulfonyl chloride **(72; R = j)** (0.67 g, 3.8 mmole) dissolved in

THF (10 ml) was added in portions to the above solution and the reaction mixture was stirred at room temperature for 16 h, and concentrated to get a sticky mass. To this sticky mass crushed ice was added and the mixture was extracted with chloroform (4x25 ml). The organic layer was washed with aq citric acid (0.5 M, 2 x 50 ml), aq sodium bicarbonate (5 %, 2 x 50 ml) and water (2 x 50 ml) sequentially. The organic layer was dried and concentrated to get a solid. The solid material was purified by column chromatography. Required compound was eluted with ethyl acetate in *n*-hexane mixture (50 %) to offer compound **(120)**, (0.5 g, 57 %), m.p. 90-95 °C.

Anal. :

TLC	: R_f 0.45 (30 % *n*-Hexane in EtOAc)
UV (λ_{max}, MeOH)	: 265 nm (log ε 3.23)
IR (KBr, cm^{-1})	: 3258, 2232, 1700, 1651, 1423, 1330 and 1130
Mass (m/z)	: 467 (M+H)

4.1.57 *N*-{1(*S*)-[(*S*)1-Benzyl-2((*S*)2-cyano-1-pyrrolidino)-2-oxoethyl]-2-oxo-3-pyrrolidino}-4-methylbenzenesulfonamide (121; R = k)

Compound **(121)** was prepared by reacting compound **(119)** (0.7 g, 1.6 mmole) with tosyl chloride **(73; R = k)** (0.6 g, 3.2 mmole) as described above for compound **(120)**. Work up of the reaction mixture followed by chromatographic purification with EtOAc in *n*-hexane (30 %) afforded a sticky mass that was triturated in hexane with 2-3 drops of EtOAc to give compound **(121)**, (0.4 g, 51 %), m.p. 95-98 °C.

Anal. :

TLC	: R_f 0.38 (30 % *n*-Hexane in EtOAc)
$[\alpha]_D^{25}$	: -56.81 (1 % in MeOH)
UV (λ_{max}, MeOH)	: 257 nm (log ε 2.87)
IR (KBr, cm^{-1})	: 3218, 2232, 1700, 1657, 1423, 1335, 1163 and 1093
PMR	: 1.90-2.16 (m, 5H), 2.45 (s, 3H), 2.50-2.57 (m, 1H), 2.87-2.95 (m, 2H), 3.28-3.42 (m, 2H), 3.49-3.55 (m, 1H), 3.63-3.68 (m, 1H), 3.98-4.03 (m, 1H), 4.63-4.70

(m, 1H), 4.93-4.97 (m, 1H), 5.15-5.16 (d, 1H), 7.19-7.35 (m, 7H) and 7.70-7.91 (d, 2H)

$C_{25}H_{28}N_4O_4S$: Requires C, 62.47; H, 5.88; N, 11.66. Found C, 62.10; H, 5.50; N, 11.20 %

4.1.58 *N*-[1(*S*)-[(*S*)1-Benzyl-2((*S*)2-cyano-1-pyrrolidino)-2-oxoethyl]-2-oxo-3-pyrrolidino}-4-morpholinecarboxamide (122; R = m)

Compound **(122)** was prepared by reacting compound **(119)** (0.7 g, 1.6 mmole) with morpholine-4-carbonyl chloride **(90; R = m)** (0.45 ml, 3.2 mmole) as described above for compound **(120)**. Work up of the reaction mixture followed by chromatographic purification with EtOAc in *n*-hexane (70-80 %) afforded a sticky mass that was triturated in hexane with 2-3 drops of EtOAc to offer compound **(122)**, (0.29 g, 40 %), m.p. 95-97 °C.

Anal. :

TLC	: R_f 0.62 (10 % MeOH in $CHCl_3$)
UV (λ_{max}, MeOH)	: 258 nm (log ε 2.54)
IR (KBr, cm^{-1})	: 3218, 2245, 1700, 1666, 1653, 1545 and 1411
Mass (m/z)	: 440.1 (M+H), 353, 344, 316, 229 and 211

4.1.59 *N*-[1(*S*)-[(*S*)1-Benzyl-2((*S*)2-cyano-1-pyrrolidino)-2-oxoethyl]-2-oxo-3-pyrrolidino}isonicotinamide (123; R = n)

In a single neck round-bottom flask (100 ml) compound **(119)** (0.8 g, 1.9 mmole) was dissolved in dichloromethane (40 ml) and the solution was cooled to 5-10 °C. Trifluoroacetic acid (1.6 ml) was added in portions to the above solution and the reaction mixture was stirred at room temperature for 90 min and concentrated on water bath to get a yellow sticky mass, which was dried in vacuum.

Isonicotinic acid **(91; R = n)** (0.23 g, 1.9 mmole) was dissolved in dichloromethane (40 ml) and the solution was cooled to 10-15 °C. BOP (0.83 g, 1.9 mmole) was added to the above clear solution and the reaction mixture was stirred for 45 min at 10-15 °C. The TFA salt prepared as described above was

dissolved in dichloromethane and the solution was added to the above reaction mixture followed by the addition of TEA (8 ml) at -10 to 0 °C. The reaction mixture was stirred for 15 h, washed with aq citric acid (0.5 M, 2 x 50 ml), aq sodium bicarbonate (5 %, 2 x 50 ml) and water (2 x 50 ml). The organic layer was dried and concentrated under vacuum to get a crude yellow solid. The solid so obtained was crystallized with ethyl acetate-*n*-hexane to yield **123**, (0.38 g, 47 %), m.p. 100-02 °C.

Anal. :

TLC	: R_f 0.52 (10 % MeOH in $CHCl_3$)
IR (KBr, cm^{-1})	: 3364, 2232, 1700, 1659,1647 and 1545
Mass (m/z)	: 432.1 (M+H)

4.1.60 *N*-[1(*S*)-[(*S*)1-Benzyl-2((*S*)2-cyano-1-pyrrolidino)-2-oxoethyl]-2-oxo-3-pyrrolidino]nicotinamide (124; R = o)

Compound **(124)** was prepared by reacting compound **(119)** (0.8 g, 1.9 mmole) with nicotinic acid **(92; R = o)** (0.23 g, 1.9 mmole) as described above for compound **(123)**. Work up of the reaction mixture followed by crystallization with ethyl acetate yielded compound **(124)**, (0.4 g, 49 %), m.p. 220-22 °C.

Anal. :

TLC	: R_f 0.48 (10 % MeOH in $CHCl_3$)
$[\alpha]_D^{25}$	: - 69.37 (1 % in MeOH)
IR (KBr, cm^{-1})	: 3463, 2232, 1690, 1660, 1639, 1559, 1419 and 1290
PMR	: 1.88-2.09 (m, 3H), 2.15-2.21 (m, 2H), 2.82-2.89 (m, 1H), 3.06-3.11(m, 2H), 3.29-3.41 (m, 2H), 3.53-3.67 (m, 2H), 4.07-4.17 (m, 1H), 4.67-4.73 (m, 1H), 5.04-5.09 (m, 1H), 6.67-6.68 (d, 1H), 7.24-7.42 (m, 6H). 8.09-8.14 (m, 1H) 8.74-8.77 (d, 1H) and 9.00 (s, 1H)
Mass (m/z)	: 432.1 (M+H)

4.1.61 *N*-{1(*S*)-[(*S*)1-Benzyl-2((*S*)2-cyano-1-pyrrolidino)-2-oxoethyl]-2-oxo-3-pyrrolidino}-2-thiophenecarboxamide (125; R = p)

Compound **(125)** was prepared by reacting compound **(119)** (0.9 g, 2.1 mmole) with 2-thiophenecarboxylic acid **(93; R = p)** (0.27 g, 2.1 mmole) as described above for **123**. Work up of the reaction mixture followed by crystallization with ethyl acetate yielded **125**, (0.30 g, 32 %), m.p. 173-75 °C.

Anal. :

TLC	: R_f 0.50 (EtOAc)
UV (λ_{max}, MeOH)	: 250 nm (log ε 4.11)
$[\alpha]_D^{25}$	: - 95.21 (1 % in MeOH)
IR (KBr, cm^{-1})	: 3354, 2232, 1700, 1653, 1631, 1545, 1419 and 735
PMR	: 1.88-2.08 (m, 3H), 2.15-2.21 (m, 2H), 2.78-2.83 (m, 1H), 3.03-3.09 (m, 2H), 3.30-3.67 (m, 4H), 4.01-4.06 (m, 1H), 4.68-4.75 (m, 1H), 5.04-5.08 (m, 1H), 6.56-6.57 (d, 1H), 7.06-7.08 (m, 1H), 7.23-7.39 (m, 6H) and 7.49-7.53 (m, 1H)
Mass (m/z)	: 437.1 (M+H), 341, 313 and 111

4.1.62 1-(3-Bromophenyl)-3-(2-chloroethyl)urea (131; R = v)

In a single-neck round-bottom flask (100 ml) equipped with an efficient stirrer, ice bath, thermometer and calcium chloride guard tube, m-bromoaniline **(126; R = v)** (2.5 g, 14.5 mmole) was dissolved in dichloromethane (10 ml) and the solution was cooled to 5-10 °C. 2-Chloroethyl isocyanate (1.53 g, 14.5 mmole) was added dropwise to the above solution and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under vacuum to get a solid, which was dried in vacuum to afford compound **(131)**, (3.1 g, 77 %).

Anal. :

TLC	: R_f 0.40 (10 % MeOH in $CHCl_3$)
IR (KBr, cm^{-1})	: 3315, 1639, 1574, 1500, 1444 and 1244

4.1.63 1-(2-Chloroethyl)-3-(3-hydroxy-4-methoxyphenyl)urea (132; R = w)

Compound **(132)** was prepared by reacting compound **(127; R = w)** (1.5 g, 11 mmole) with 2-chloroethyl isocyanate (1.16 g, 11 mmole) as described above for compound **(131)**, (2.25 g, 85 %).

Anal. :

TLC : R_f 0.65 (10 % MeOH in $CHCl_3$)

4.1.64 1-(2-Chloroethyl)-3-(3,4,5-trimethoxyphenyl)urea (133; R = x)

Compound **(133)** was prepared by reacting compound **(128; R = x)** (1.5 g, 8.2 mmole) with 2-chloroethyl isocyanate (0.86 g, 8.2 mmole) as described above for compound **(131)**, (1.9 g, 80 %).

Anal. :

TLC : R_f 0.48 (10 % MeOH in EtOAc)

4.1.65 1-(2-Chloroethyl)-3-(5-phenyl-1,3,4-thiadiazol-2-yl)urea (134; R = y)

Compound **(134)** was prepared by reacting compound **(129; R = y)** (2.0 g, 11 mmole) with 2-chloroethyl isocyanate (1.16 g, 11 mmole) as described above for **131**, (2.5 g, 78 %).

Anal. :

TLC : R_f 0.25 (EtOAc)

4.1.66 1-(2-Chloroethyl)-3-[5-(4-methoxyphenyl)-1,3,4-thiadiazol-2-yl]urea (135; R = z)

Compound **(135)** was prepared by reacting compound **(130; R = z)** (2.2 g, 10 mmole) with 2-chloroethyl isocyanate (1.05 g, 10 mmole) as described above for compound **(131)**, (2.5 g, 75 %).

Anal. :

TLC : R_f 0.48 (10 % MeOH in $CHCl_3$)

4.1.67 1-(3-Bromophenyl)imidazolidin-2-one (136; R = v)

In a three-neck round-bottom flask (100 ml) a solution of compound **(131)** (2 g, 7.2 mmole) in dry DMF (10 ml) was cooled to 0-5 °C. Sodium hydride (0.5 g,

11 mmole, 50 % mineral oil dispersion used as such) was added in portions to the above solution at 0-5 °C and the reaction mixture was stirred for 1 h at 0-5 °C, and then at room temperature for 30 min. The reaction mixture was poured over crushed ice with stirring to get a solid mass of compound **(136)** which was filtered and dried, (1.2 g, 69 %), m.p. 127-30 °C.

Anal. :

TLC : R_f 0.48 (10 % MeOH in $CHCl_3$)

IR (KBr, cm^{-1}) : 3259, 1684, 1574, 1500, 1444, 1300 and 1244

4.1.68 1-(3-Hydroxy-4-methoxyphenyl)imidazolidin-2-one (137; R = w)

Compound **(137)** was obtained by reaction of compound **(132)** (2 g, 8.2 mmole) and sodium hydride (0.58 g, 12.3 mmole used as such without washing) as described above for compound **(136)**, (1.38 g, 81 %), m.p. 142-44 °C.

Anal. :

TLC : R_f 0.58 (10 % MeOH in $CHCl_3$)

4.1.69 1-(3,4,5-Trimethoxyphenyl)imidazolidin-2-one (138; R = x)

Compound **(138)** was obtained by reaction of compound **(133)** (1.5 g, 5.2 mmole) and sodium hydride (0.36 g, 7.8 mmole used as such without washing) as described above for compound **(136)**, (0.9 g, 68 %), m.p. 195-97 °C.

Anal. :

TLC : R_f 0.75 (EtOAc)

4.1.70 1-(5-Phenyl-1,3,4-thiadiazol-2-yl)imidazolidin-2-one (139; R = y)

Compound **(139)** was prepared by reacting compound **(134)** (2.1 g, 7.4 mmole) with sodium hydride (0.52 g, 11 mmole used as such without washing) as described above for **136**, (1.48 g, 81 %), m.p. 160-62 °C.

Anal. :

TLC : R_f 0.40 (5 % MeOH in EtOAc)

4.1.71 1-[5-(4-Methoxyphenyl)-1,3,4-thiadiazol-2-yl]imidazolidin-2-one (140; R = z)

Compound **(140)** was prepared by reacting compound **(135)** (2.3 g, 7.4 mmole) with sodium hydride (0.52 g, 11 mmole used as such without washing) as described above for compound **(136)**, (1.7 g, 83 %).

Anal. :

TLC : R_f 0.72 (10 % MeOH in $CHCl_3$)

4.1.72 Ethyl 2-[3-(3-bromophenyl)-2-oxo-1-imidazolidinyl]propionate (141; R = v)

In a three-neck round-bottom flask (100 ml) the imidazolidinone derivative **(136)** (2.1 g, 8.7 mmole) was dissolved in dry DMF (10 ml) and the solution was cooled to 0-5 °C. Sodium hydride (0.62 g, 13 mmole, used as such without washing) was added in portions to the above solution at 0-5 °C and the suspension was stirred for 1 h at 0-5 °C followed by stirring at room temperature for further 30 min. The reaction mixture was cooled again to 0-5 °C and ethyl 2-bromopropionate (2.36 g, 1.7 ml, 13 mmole) was added dropwise into it. The reaction mixture was stirred for 4 h at room temperature, poured over crushed ice with stirring and extracted with chloroform (3x 50 ml). The organic layer was washed extensively with water (10x 300 ml), dried and concentrated under vacuum. The sticky mass so obtained was purified by column chromatography using ethyl acetate in *n*-hexane (20-25 %) to obtain compound **(141)**, (1.85 g, 62 %), m.p. 179-81 °C.

Anal. :

TLC : R_f 0.50 (10 % MeOH in $CHCl_3$)

4.1.73 Ethyl 2-[3-(3-hydroxy-4-methoxyphenyl)-2-oxo-imidazolidinyl]-propionate (142; R = w)

Compound **(142)** was prepared by reacting compound **(137)** (1.5 g, 7.2 mmole) with ethyl 2-bromopropionate (2 g, 1.45 ml, 11 mmole) in presence of sodium hydride (0.52 g, 11 mmole, used as such without washing) as described above for compound **(141)**. The crude material so obtained was purified by

column chromatography using ethyl acetate in *n*-hexane (20-25 %) to yield compound **(142)**, (1.4 g, 63 %).

Anal. :

TLC : R_f 0.48 (10 % MeOH in $CHCl_3$)

IR (KBr, cm^{-1}) : 3176, 1736, 1665, 1493, 1445 and 1215

4.1.74 Ethyl 2-[2-oxo-3-(3,4,5-trimethoxyphenyl)-1-imidazolidinyl]propionate (143; R = x)

Compound **(143)** was prepared by reacting compound **(138)** (1.6 g, 6.3 mmole) with ethyl 2-bromopropionate (1.72 g, 1.24 ml, 9.5 mmole) in presence of sodium hydride (0.44 g, 9.5 mmole, used as such without washing) as described above for compound **(141)**. The crude material so obtained was purified by column chromatography using ethyl acetate in *n*-hexane (20-25 %) to yield compound **(143)**, (1.3 g, 58 %), m.p. 166-68 °C.

Anal. :

TLC : R_f 0.68 (10 % MeOH in $CHCl_3$)

4.1.75 Ethyl 2-[(2-oxo-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-1-imidazolidinyl] propionate (144; R = y)

Compound **(144)** was prepared by reacting compound **(139)** (2 g, 8.1 mmole) with ethyl 2-bromopropionate (2.17 g, 1.56 ml, 12 mmole) in presence of sodium hydride (1 g, 20 mmole, used as such without washing) as described above for **141**, (1.55 g, 55 %), m.p. 192-94 °C.

Anal. :

TLC : R_f 0.24 (10 % MeOH in $CHCl_3$)

4.1.76 Ethyl 2-[3-[(5-(4-methoxyphenyl)-1,3,4-thiadiazol-2-yl)-2-oxo-1-imidazolidinyl]]propionate (145; R = z)

Compound **(145)** was prepared by reacting compound **(140)** (1.5 g, 5.4 mmole) with ethyl 2-bromopropionate (1.46 g, 1.1 ml, 8.1 mmole) in presence of sodium hydride (0.38 g, 8.1 mmole, used as such without washing) as described above for compound **(141)**, (1.15 g, 56 %).

Anal. :

TLC : R_f 0.48 (EtOAc)

4.1.77 2-[3-(3-Bromophenyl)-2-oxo-1-imidazolidinyl]propionic acid (146; R = v)

The ester derivative **(141; R = v)** (1.6 g, 4.7 mmole) was suspended in water (10 ml) and lithium hydroxide (1.07 g, 25 mmole) was added to it. The reaction mixture was stirred at room temperature for 2 h. The aq layer was washed with ethyl acetate (2x 10 ml), cooled in ice bath and acidified to pH ~ 1 with conc. hydrochloric acid to get compound **(146)**, (0.95 g, 65 %) m.p. 100-02 °C.

Anal. :

TLC : R_f 0.30 (10 % MeOH in $CHCl_3$)

4.1.78 2-[3-(3-Hydroxy-4-methoxyphenyl)-2-oxo-1-imidazolidinyl]propionic acid (147; R = w)

Compound **(147)** was prepared by reacting compound **(142; R = w)** (1.4 g, 4.5 mmole) with lithium hydroxide (0.94 g, 22 mmole) as described above for **146** to get compound **(147)**, (0.65 g, 51 %), m.p. 150-52 °C.

Anal. :

TLC : R_f 0.3 (10 % MeOH in $CHCl_3$)

IR (KBr, cm^{-1}) : 3408, 1741, 1646, 1525 and 1480

4.1.79 2-[2-Oxo-3-(3,4,5-trimethoxyphenyl)-1-imidazolidinyl]propionic acid (148; R = x)

Compound **(148)** was prepared by reacting compound **(143; R = x)** (1.1 g, 3.1 mmole) with lithium hydroxide (0.64 g, 15 mmole) as described above for **146** to get compound **(148)**, (0.6 g, 56 %), m.p. 184-86 °C.

Anal. :

TLC : R_f 0.52 (10 % MeOH in $CHCl_3$)

IR (KBr, cm^{-1}) : 3423, 1753, 1654, 1585, 1511, 1426, 1275 and 1000

4.1.80 2-[2-Oxo-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-1-imidazolidinyl]propionic acid (149; R = y)

Compound **(149)** was prepared by reacting compound **(144; R = y)** (1.75 g, 5 mmole) with lithium hydroxide (1.07 g, 25 mmole) as described above for **146** to give compound **(149)**, (0.8 g, 50 %), m. p. 265-67 °C.

Anal. :

TLC : R_f 0.20 (10 % MeOH in $CHCl_3$)

IR (KBr, cm^{-1}) : 3436, 1755, 1668, 1490, 1445, 1280 and 1180

4.1.81 2-{3-[5-(4-Methoxyphenyl)-1,3,4-thiadiazol-2-yl]-2-oxo-1-imidazolidinyl} propionic acid (150; R = z)

Compound **(150)** was prepared by reacting compound **(145; R = z)** (1.8 g, 4.7 mmole) with lithium hydroxide (1 g, 23 mmole) as described above for compound **(146)** to yield compound **(150)**, (0.9 g, 54 %), 220-22 °C.

Anal. :

TLC : R_f 0.25 (10 % MeOH in $CHCl_3$)

4.1.82 (S)1-{2-[3-(3-Bromophenyl)-2-oxo-1-imidazolidinyl]propionyl} pyrrolidine-2-carboxamide (151; R = v)

In a three-neck round-bottom flask (100 ml) compound **(146; R = v)** (0.51 g, 2.4 mmole) was dissolved in dichloromethane (40 ml) and the solution was cooled to 10-15 °C. BOP (1.2 g, 2.7 mmole) was charged to the above solution and the reaction mixture was stirred for 45 min at 10-15 °C. The TFA salt **(47)** (0.51 g, 2.4 mmole) was added to this reaction mixture followed by addition of TEA (4 ml) at -10 to 5 °C. The reaction mixture was stirred at room temperature for 15 h, washed with aq citric acid (0.5 M, 2 x 50 ml), aq sodium bicarbonate (5 %, 2 x 50 ml) and finally with water (2 x 50 ml). The organic layer was dried and concentrated under vacuum to get crude solid. The solid on crystallization with ethyl acetate yielded compound **(151)**, (0.8 g, 78 %), m.p. 110-13 °C.

Anal. :

TLC : R_f 0.51 (10 % MeOH in $CHCl_3$)

IR (KBr, cm^{-1}) : 3395, 3204, 1693, 1666, 1646, 1419 and 1265

4.1.83 (S)1-{2-[3-(3-Hydroxy-4-methoxyphenyl)-2-oxo-1-imidazolidinyl]-propionyl}pyrrolidine-2-carboxamide (152; R = w)

Compound **(152)** was prepared by reacting compound **(47)** (0.57 g, 2.7 mmole) with compound **(147; R = w)** (0.75 g, 2.7 mmole) as described above

for **151**. Work up of the reaction mixture followed by crystallization in ethyl acetate gave compound **(152)**, (0.42 g, 42 %), m.p. 170-72 °C.

Anal. :

TLC : R_f 0.30 (10 % MeOH in $CHCl_3$)

IR (KBr, cm^{-1}) : 3367, 3280, 3203, 1706, 1674, 1642 and 1423

4.1.84 (S)1-{2-[2-Oxo-3-(3,4,5-trimethoxyphenyl)-1-imidazolidinyl]propionyl} pyrrolidine-2-carboxamide (153; R = x)

Compound **(153)** was prepared by reacting compound **(47)** (0.33 g, 1.54 mmole) with compound **(148; R = x)** (0.5 g, 1.54 mmole) as described above for **151**. Work up of the reaction mixture followed by crystallization in ethyl acetate afforded compound **(153)**, (0.24 g, 38 %), m.p. 220-22 °C.

Anal. :

TLC : R_f 0.63 (12 % MeOH in $CHCl_3$)

IR (KBr, cm^{-1}) : 3368, 3190, 1713, 1666, 1646, 1419 and 1270

4.1.85 (S)1-{2-[2-Oxo-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-1-imidazolidinyl]-propionyl}pyrrolidine-2-carboxamide (154; R = y)

Compound **(154)** was prepared by reacting compound **(47)** (0.13 g, 0.6 mmole) with compound **(149; R = y)** (0.2 g, 0.6 mmole) as described above for **151**. Work up of the reaction mixture followed by crystallization in ethyl acetate gave compound **(154)**, (0.18 g, 69 %), m.p. 209-13 °C.

Anal. :

TLC : R_f 0.44 (10 % MeOH in $CHCl_3$)

4.1.86 (S)1-{2-{3-[5-(4-Methoxyphenyl)-1,3,4-thiadiazol-2-yl]-2-oxo-1-imidazolidinyl}propionyl}pyrrolidine-2-carboxamide (155; R = z)

Compound **(155)** was prepared by reacting compound **(47)** (0.12 g, 0.57 mmole) with compound **(150; R = z)** (0.2 g, 0.57 mmole) as described above for compound **(151)**. Work up of the reaction mixture followed by crystallization with ethyl acetate -*n*-hexane yielded **155**, (0.21 g, 88 %), m.p. 256-59 °C.

Anal. :

TLC : R_f 0.28 (10 % MeOH in $CHCl_3$)

4.1.87 (*S*)1-{2-[3-(3-Bromophenyl)-2-oxo-1-imidazolidinyl]propionyl} pyrrolidine-2-carbonitrile (156; R = v)

In a three-neck round-bottom flask (100 ml), compound **(151; R = v)** (0.7 g, 1.7 mmole) was dissolved in dry DMF (5 ml) and the solution was cooled to -10 to -5 °C. Cyanuric chloride (0.37 g, 2 mmole) was added in portions to the above solution and the reaction mixture was stirred at room temperature for 90 min. During the course of reaction a white precipitate was formed. The reaction mixture was poured over crushed ice and extracted with chloroform (5x 50 ml). The organic layer was washed extensively with water (5x200 ml), dried and concentrated under vacuum. The sticky mass so obtained was purified by column chromatography with ethyl acetate in *n*-hexane (25-30 %) to give compound **(156)**, (0.21 g, 31 %), m.p. 138-40 °C.

Anal. :

TLC	: R_f 0.78 (10 % MeOH in $CHCl_3$)
UV (λ_{max}, MeOH)	: 253 nm (log ε 4.48)
IR (KBr, cm^{-1})	: 2232, 1694, 1653, 1594, 1489, 1412, 1269 and 792
PMR	: 1.39-1.41 (d, 1.5H, *J*= 6.8 Hz), 1.47-1.49 (d, 1.5H, *J*= 6.8 Hz), 2.11-2.36 (m, 4H), 3.59-3.93 (m, 6H), 4.73-4.78 (m, 1H), 4.87-4.96 (m, 1H), 7.17-7.25 (m, 2H), 7.43-7.50 (m, 1H) and 7.76-7.80 (d, 1H)
Mass (m/z)	: 391.5 (M+H), 296 and 268

4.1.88 (S)1-{2-[3-(3-Hydroxy-4-methoxyphenyl)-2-oxo-1-imidazolidinyl] propionyl}pyrrolidine-2-carbonitrile (157; R = w)

Compound **(157)** was prepared by reacting compound **(152; R = w)** (0.4 g, 1 mmole) with cyanuric chloride (0.22g, 1.2 mmole) as described above for **156**. Work up of the reaction mixture followed by chromatographic purification with ethyl acetate in *n*-hexane (30-35 %) afforded compound **(157)**, (0.18 g, 47 %), m.p. 115-18 °C.

Anal. :

TLC : R_f 0.52 (10 % MeOH in $CHCl_3$)

IR (KBr, cm^{-1}) : 3450, 2232, 1700, 1652, 1516, 1423 and 1155

$C_{18}H_{22}N_4O_4$: Requires C, 60.32; H, 6.18; N, 15.63. Found C, 59.96; H, 5.80; N, 15.30 %

4.1.89 (*S*)1-{2-[2-Oxo-3-(3,4,5-trimethoxyphenyl)-1-imidazolidinyl]propionyl} pyrrolidine-2-carbonitrile (158; R = x)

Compound **(158)** was prepared by reacting compound **(153; R = x)** (0.23 g, 0.54 mmole) with cyanuric chloride (0.1 g, 0.54 mmole) as described above for **156**. Work up of the reaction mixture followed by chromatographic purification with ethyl acetate in *n*-hexane (17-20 %) afforded compound **(158)** as sticky mass, which could not be crystallized out, (0.1 g, 46 %).

Anal. :

TLC : R_f 0.56 (10 % MeOH in $CHCl_3$)

IR (KBr, cm^{-1}) : 2232, 1700, 1651, 1588, 1418 and 1125

4.1.90 (*S*)1-{2-[2-Oxo-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-1-imidazolidinyl] propionyl}pyrrolidine-2-carbonitrile (159; R = y)

Compound **(159)** was prepared by reacting compound **(154; R = y)** (0.17 g, 0.41 mmole) with cyanuric chloride (0.075 g, 0.41 mmole) as described above for compound **(156)**. Work up of the reaction mixture followed by chromatographic purification with ethyl acetate in *n*-hexane (25-30 %) afforded compound **(159)**, (0.11 g, 68 %), m.p. 265-67 °C.

Anal. :

TLC : R_f 0.72 (10 % MeOH in $CHCl_3$)

UV (λ_{max}, MeOH) : 304.2 nm (log ε 4.24)

IR (KBr, cm^{-1}) : 2245, 1707, 1647, 1506, 1417 and 1271

$C_{19}H_{20}N_6O_2S$: Requires C, 57.56; H, 5.08; N, 21.20. Found C, 57.10; H, 4.76; N, 20.80 %

4.1.91 (*S*)1-{2-{3-[5-(4-Methoxyphenyl)-1,3,4-thiadiazol-2-yl]-2-oxo-1-imidazolidinyl}propionyl}pyrrolidine-2-carbonitrile (160; R = z)

Compound **(160)** was prepared by reacting compound **(155; R = z)** (0.17 g, 0.38 mmole) with cyanuric chloride (0.07 g, 0.38 mmole) as described above for compound **(156)**. Work up of the reaction mixture followed by chromatographic purification with ethyl acetate in *n*-hexane (25-30 %) afforded compound **(160)**, (0.09 g, 55 %), m.p. 170-73 °C.

Anal. :

TLC	: R_f 0.56 (10 % MeOH in $CHCl_3$)
UV (λ_{max}, MeOH)	: 306 nm (log ε 4.34)
IR (KBr, cm^{-1})	: 2245, 1705, 1655, 1606, 1417 and 1251
Mass (m/z)	: 427.5 (M+H), 303