CHAPTER-IV

SYNTHESIS OF PMP, MPMP DERIVATIVES OF
INDOLE-N-ACETIC ACID AND PHENYLOXALAMIC
ACID DERIVATIVES AS CASPASE-3 INHIBITORS
INTRODUCTION

Recently, a number of isatin-based inhibitors of caspase-3 and caspase-7 have been reported in literature\textsuperscript{33-36} indicating the importance of side chains I and II (Figure-1). 5-Pyrrolidinylsulfonyl isatins (III, $IC_{50} = 0.0025$ µM and IV, $IC_{50} = 0.03$ µM) represent a unique direction in the design of selective inhibitors for caspase-3 and -7. In contrast to previously reported inhibitors of caspase-3 and -7, these structures do not possess an acidic functionality which may bind in the primary aspartic acid binding pocket, $S_1$\textsuperscript{35-37}. In addition, previous studies have shown that binding within the $S_3$ and $S_4$ subsites was most important for deriving selectivity between caspases.

The selectivity can be achieved from an interaction between the pyrrolidinylsulfonyl group of the inhibitor and the hydrophobic $S_2$ pocket of caspase-3. Despite the fact that distinguishing the roles of caspases-3 and -7 had been difficult, there has been recent evidence for the differential activation\textsuperscript{38,39} and sub cellular distribution\textsuperscript{40} of these two proteases in cells. A compound whichselectively inhibits only caspase-3 or caspase-7 would aid in characterizing the role that each protease plays during apoptosis\textsuperscript{41,42}. Since the isatin sulfonamides derive their selectivity by binding in the $S_2$ subsite, caspase-3 or -7 selective inhibitors can be obtained through modification of the isatin sulfonamide core. The isatin sulfonamides block apoptosis in several cell-based systems, including human chondrocytes, which are used as a model for osteoarthritis. There was
an attenuation in cell-based activity relative to in vitro isolated caspase-3 activity for this class of inhibitors.

**Figure-1**

![Chemical structures](image)

On the basis of the above findings and available crystal structure of caspases, we have modified isatin core to indole and evaluated the inhibitory activity of caspase-3 in vitro. As expected, compound V (**Figure-1**) has shown an IC$_{50}$ = 20 μM, and this result encouraged for further optimization to have compound VI$_{43}$ (**Figure-1**) with an IC$_{50}$ = 2.4 μM. Accordingly designed and synthesized novel non peptidyl inhibitors derived from indole-N-acetic acid and oxalamic acid to study the role of pyrrolidine amides as caspase inhibitors.
PRESENT WORK

Since indolesulfonamides of phenoxyethyl pyrrolidine have shown good potency against caspase-3 activity, here in we have explored indole-N-acetamides of phenoxyethyl pyrrolidine (PMP) and 4-methoxy phenoxyethyl pyrrolidine (MPMP) derivatives. We also explored coupling of PMP and MPMP side chains with the oxalamic acids prepared in chapter-III (3a-h) and evaluated the caspase-3 activity. Overall 26 novel compounds were designed and synthesized in this series belong to two diversities as shown in Figure-2

Figure-2

4.1 Synthesis of Chiral phenoxyethylpyrrolidine and 4-methoxy phenoxyethylpyrrolidine

Synthesis of key intermediates 8 and 9 were carried out using commercially available L-proline using the synthetic procedures followed in literature\textsuperscript{33}. Boc protection of the amino acid was carried out using aqueous NaOH to get intermediate 2, which upon
esterification gave intermediate 3. Reduction of methyl ester 3 with LAH gave alcohol 4, which in turn protected with tosyl chloride to obtain intermediate 5. Displacement of tosyl group with different phenols provided intermediates 6 and 7, which on hydrolysis with trifluoroacetic acid yielded corresponding phenoxyethyl pyrrolidines 8 and 9.

**Scheme-1**

Reagents and conditions: (i) Boc anhydride, aq NaOH, 0-25 °C, 4 h; (ii) CH₃I, K₂CO₃, DMF, 0-25 °C, 2 h; (iii) LAH, THF, -30 °C, 2 h; (iv) tosyl chloride, C₆H₆, rt, 15 h; (v) NaH, phenol (or 4-methoxy phenol), DMF, 90 °C, 4 h; (vi) CF₃COOH, anisole, CH₂Cl₂, rt, 2 h.

**4.2 SYNTHESIS OF DIVERSITY-I**

Synthesis of (S)-2-Oxo-2-(2-substituted phenoxyethyl pyrrolidin-1-yl)-N-substituted phenyl-acetamide

The novel oxalamides 10a-h and 11a-h were prepared by coupling of key intermediate 8 or 9 with different oxalamic acids (chapter-III, 3a-h) in presence of EDCI and HOBt with N, N-diisopropylethylamine as base.
Scheme-2

II-3a-h + \( \text{HN} \text{O} \text{R' a, R = 5-F} \)
\( \text{HN} \text{O} \text{R' b, R = 5-Br} \)
\( \text{HN} \text{O} \text{R' c, R = 5-Cl} \)
\( \text{HN} \text{O} \text{R' d, R = 5-OCH}_3 \)
\( \text{HN} \text{O} \text{R' e, R = 2-CH}_3 \)
\( \text{HN} \text{O} \text{R' f, R = 2-CH}_3 \)
\( \text{HN} \text{O} \text{R' g, R = 2-OCH}_3 \)
\( \text{HN} \text{O} \text{R' h, R = 2-F} \)
\( \text{HN} \text{O} \text{R' i, R = 2-F} \)

Reagent and conditions: (i) EDCI, HOBr, DIPEA, DMF, rt, 15 h.

4.3 SYNTHESIS OF DIVERSITY-II

Synthesis of 2-(substituted-indol-1-yl)-1-(2-substituted phenoxy)methyl pyrrolidin-1-yl)-ethanone

The novel indole acetamides 12a-e and 13a-e were prepared by coupling of key intermediate 8 or 9 with different indole-N-acetic acids (chapter-II 7a-e) in presence of EDCI and HOBr with N, N-diisopropylethylamine as base.

Scheme-3

II-7a-e + \( \text{HN} \text{O} \text{R' a, R = 5-F} \)
\( \text{HN} \text{O} \text{R' b, R = 5-Br} \)
\( \text{HN} \text{O} \text{R' c, R = 5-Cl} \)
\( \text{HN} \text{O} \text{R' d, R = 5-OCH}_3 \)
\( \text{HN} \text{O} \text{R' e, R = 2-CH}_3 \)
\( \text{HN} \text{O} \text{R' f, R = 2-CH}_3 \)
\( \text{HN} \text{O} \text{R' g, R = 2-OCH}_3 \)
\( \text{HN} \text{O} \text{R' h, R = 2-F} \)

Reagent and conditions: (i) EDCI, HOBr, DIPEA, DMF, rt, 15 h.
4.4 SPECTRAL DATA DISCUSSION

The compounds 10a-h, 11a-h, 12a-e and 13a-e obtained as pure single isomers and were characterized by \(^1\)H NMR spectrum, HPLC and LCMS analysis. For compounds 10a-h and 11a-h the \(^1\)H NMR spectrum can be explained as follows: \(\delta\) 9.4 (s, 1H, -NH), 7.65-7.50 (m, 2H, Aromatic), 7.15-7.0 (t, 2H, Aromatic), 6.90-6.75 (m, 4H, Aromatic), 5.45-4.50 (m, 1H, multiplet of chiral proton splitting into two halves may be because of rotomers), 4.25-3.90 (m, 4H, two protons of pyrrolidine ring and two protons of -CHCH\(_2\)O), 3.75 (s, 3H, 4-methoxy of MPMP and this peak will be absent in compounds 10a-h), 2.35-1.90 (m, 4H, pyrrolidine protons). The mass spectrum for major peak have shown mass in the form of m/z (M\(^+\)+1) for all compounds and the HPLC purity of all the compounds are between 96-99%.

For compounds 12a-e and 13a-e the \(^1\)H NMR spectrum can be explained as follows: \(\delta\) 7.30 (m, Aromatic protons), 6.55 (d, 1H, indolic proton), 4.8 (s, 2H, -NCH\(_2\)CO), 4.50 (m, 1H, chiral proton), 4.25-4.10 (m, 2H, protons of pyrrolidine ring CHCH\(_2\)O), 3.85 (s, 3H, 4-methoxy of MPMP and this peak will be absent in compounds 12a-e), 3.55 (m, 2H, pyrrolidine ring protons), 2.35-1.90 (m, 4H, pyrrolidine protons). The mass spectrum for major peak have shown mass in the form of m/z (M\(^+\)+1) for all compounds and the HPLC purity of all the compounds are between 96-98%. 
4.5 BIOLOGICAL ACTIVITY

The assay was carried out as mentioned in chapter-II (2.5) and the reference compound for this assay was IDN-6556 and the values are denoted in table-I. Most of the compounds showed no inhibition at 10 µM in this series except following compounds.

**Table-1**: Evaluation of caspase-3 activity of synthesized compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>% inhibition @ 10 µM</th>
</tr>
</thead>
<tbody>
<tr>
<td>13a</td>
<td>58% (IC$_{50}$=9.9 µM)</td>
</tr>
<tr>
<td>13b</td>
<td>24% (IC$_{50}$&lt;25 µM)</td>
</tr>
<tr>
<td>13c</td>
<td>14%</td>
</tr>
<tr>
<td>13d</td>
<td>7%</td>
</tr>
<tr>
<td>IDUN-6556</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Values are IC$_{50}$ (µM) expressed as the mean of two replicate determinations.

The novel phenoxyethyl pyrrolidine oxalamides, indole acetamides and 4-methoxy phenoxyethyl pyrrolidine oxalamides as well as indole acetamides have been synthesized and evaluated the caspase-3 inhibitory activity. Unfortunately most of the synthesized compounds have shown no inhibition at 10 µM except compound 13a which have shown 58% inhibition at 10 µM (IC$_{50}$ = 9.9 µM) followed by compound 13b with inhibitory activity of 24% at 10 µM (IC$_{50}$ = <25 µM). This indicates that pyrrolidinylsulfonyl group is playing a major role in activity of caspase-3 rather than pyrrolidinyl amide group.
CONCLUSION

The novel phenoxy methyl pyrrolidine and 4-methoxy phenoxy methyl pyrrolidine derivatives of oxalamic acid and indole-N-acetic acid have been synthesized and found that all the phenoxy methyl derivatives are inactive against caspase-3 enzyme at tested concentration. In terms of 4-methoxy phenoxy methyl pyrrolidine, all the oxalamic acid derivatives are inactive while some of the indole-N-acetic acid derivatives 13a and 13b have shown moderate activity against caspase-3.
4.6 EXPERIMENTALS

4.1 Pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (2): To a stirred solution of L-proline (8 g, 69.5 mmol) in 10% NaOH solution (80 mL) at 15 °C was added Boc anhydride (16.7 g, 76 mmol) and the mixture was stirred at room temperature for 4 h until TLC indicated completion of the reaction. The reaction mixture pH was adjusted to 5-7 with citric acid and extracted with ethyl acetate (2×100 mL). The combined organic layers was washed with saturated brine (100 mL) dried over Na$_2$SO$_4$ and evaporated in vacuum to afford 2 as white solid (14 g, 94%). Molecular formula: C$_{10}$H$_{17}$NO$_4$ (m/z = 215); LCMS: m/z = 216.1 (M$^+$+1).

Pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (3): To a stirred solution of 2 (14 g, 65 mmol) in dry DMF (30 mL) at 0 °C was added K$_2$CO$_3$ (27 g, 195 mmol) followed by methyl iodide (6.1 mL, 97 mmol) and stirred at room temperature for 2 h until TLC indicated completion of the reaction. The reaction mixture was diluted with cold water and extracted with ethyl acetate (2×100 mL). The combined organic layers were washed with saturated brine (100 mL) dried over Na$_2$SO$_4$ and evaporated in vacuum to afford 3 as pale yellow liquid (14.5 g, 97%). Molecular formula: C$_{11}$H$_{19}$NO$_4$ (m/z = 229); LCMS: m/z = 230.1 (M$^+$+1).

2-Hydroxymethyl pyrrolidine-1-carboxylic acid tert-butyl ester (4): To a stirred solution of LAH (3.6 g, 94.9 mmol) in dry THF (30 mL) at -30 °C was added 3 (14.5 g, 63 mmol) and stirred at same temperature
until TLC indicated that reaction was complete. The reaction mixture was quenched with 10% NaOH solution (10 mL) and filtered the solid and washed with ethyl acetate (100 mL). The combined filtrates were dried over Na$_2$SO$_4$ and evaporated in vacuum to afford 4 as colourless thick liquid (12.5 g, 98%). Molecular formula: C$_{10}$H$_{19}$NO$_3$ (m/z = 201); LCMS: m/z = 202.3 (M$^+$+1).

2-(Toluene-4-sulfonyloxymethyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (5): The compound 4 (12.5 g, 62 mmol) dissolved in dry DCM (100 mL) and added pyridine (37.5 mL) followed by p-toluene sulfonyl chloride (16.6 g, 87 mmol) and stirred at room temperature for 15 h until TLC indicated that reaction was complete. The reaction mixture was carefully acidified with 1N HCl and extracted with DCM (2×50 mL). The combined organic layers were dried over Na$_2$SO$_4$ and evaporated in vacuum and purified by column chromatography (15% EtOAc-hexane) to afford 5 as white crystals (20 g, 91%). Molecular formula: C$_{17}$H$_{25}$NO$_5$S (m/z = 355); LCMS: m/z = 356.1 (M$^+$+1).

2-(Phenoxy)methyl pyrrolidine-1-carboxylic acid tert-butyl ester (6): To a solution of NaH (2.3 g, 47.6 mmol) in dry DMF (25 mL) at 0 °C was added phenol (3.17 g, 33.8 mmol) and stirred for 30 min followed by addition of 5 (10 g, 28 mmol) in DMF (75 mL) and stirred at 100 °C for 3 h. The reaction monitored with TLC when it indicated the reaction was completed the reaction mixture was poured in ice water and extracted with ethyl acetate (2×50 mL). The combined organic layers were dried over Na$_2$SO$_4$ and evaporated in vacuum to
afford 6 as yellow oil (7 g, 91%). Molecular formula: C_{16}H_{23}NO_{3} (m/z = 277); LCMS: m/z = 278.2 (M^{+}+1).

\textbf{(S)-2-(Phenoxy)methyl pyrrolidine (8):} The compound 6 (7 g, 25 mmol) dissolved in dry DCM (70 mL) and added TFA (21 mL, 3 vol) and stirred at room temperature for 1 h until TLC indicated that reaction was complete. The reaction mixture was carefully basified with 10% NaOH solution and then extracted with DCM (2×100 mL). The combined organic layers were dried over Na_{2}SO_{4} and evaporated in vacuum to afford 8 as yellow oil (4 g, 91%). Molecular formula: C_{11}H_{15}NO (m/z = 177); LCMS: m/z = 178.1 (M^{+}+1); ¹H NMR (CDCl₃, 300 MHz): δ 7.27 (m, 2H), 6.91 (m, 3H), 3.88 (m, 2H), 3.55-3.45 (m, 1H), 3.05-2.94 (m, 2H), 2.36 (brs, 1H), 1.95-1.55 (m, 4H).

\textbf{2-(4-Methoxy phenoxy)methyl-pyrrolidine-1-carboxylic acid tert-butyl ester (7):} To a solution of NaH (2.3 g, 47.6 mmol) in dry DMF (25 mL) at 0 °C was added 4-methoxy phenol (4.2 g, 33.8 mmol) and stirred for 30 min followed by addition of 5 (10 g, 28 mmol) in DMF (75 mL) and stirred at 100 °C for 3 h. The reaction monitored with TLC when it indicated the reaction was completed the reaction mixture was poured in ice water and extracted with ethyl acetate (2×50 mL). The combined organic layers were dried over Na_{2}SO_{4} and evaporated in vacuum to afford 7 as yellow oil (8 g, 93%). Molecular formula: C_{17}H_{25}NO_{4} (m/z = 307); LCMS: m/z = 308.1 (M^{+}+1).
(S)-2-(4-Methoxy phenoxy methyl)-pyrrolidine (9): The compound 7 (8 g, 26 mmol) dissolved in dry DCM (70 mL) and added TFA (24 mL, 3 vol) and stirred at room temperature for 1 h until TLC indicated that reaction was complete. The reaction mixture was carefully basified with 10% NaOH solution and then extracted with DCM (2×100 mL). The combined organic layers were dried over Na₂SO₄ and evaporated in vacuum to afford 9 as pale brown oil (5 g, 92%). Molecular formula: C₁₂H₁₇NO₂ (m/z = 207); LCMS: m/z = 208.1 (M⁺+1); ¹H NMR (CDCl₃, 300 MHz): δ 6.90-6.75 (m, 4H), 3.95-3.75 (m, 5H), 3.55-3.45 (m, 1H), 3.10-2.90 (m, 2H), 2.26 (brs, 1H), 2.0-1.65 (m, 4H).

4.2 (S)-N-(4-Fluoro phenyl)-2-oxo-2-(2-phenoxy methyl pyrrolidin-1-yl)-acetamide (10a): To a stirred solution of N-(4-fluoro phenyl)-oxalamic acid (183 mg, 1 mmol) in DMF (5 mL) was added DIPEA (0.52 mL, 3 mmol), HOBt (135 mg, 1 mmol), 8 (177 mg, 1 mmol) and cooled to 0 °C. Then added EDCI (191 mg, 1 mmol) and stirred at room temperature until TLC indicated that reaction was complete. The reaction mixture was poured in ice water and extracted with ethyl acetate (2×25 mL). The combined organic layers were dried over Na₂SO₄ and evaporated in vacuum and purified by column chromatography (20% EtOAc-hexane) to afford 10a as colourless liquid (207 mg, 60%). Molecular formula: C₁₉H₁₉FN₂O₃ (m/z = 342); LCMS: m/z = 343.1 (M⁺+1); ¹H NMR (CDCl₃, 300 MHz): δ 9.45 (s, 1H), 7.65-7.55 (m, 2H), 7.35-7.20 (m, 3H), 7.10-6.85 (m, 4H), 5.45-4.55 (m,
(S)-2-Oxo-2-(2-phenoxyethyl pyrrolidin-1-yl)-N-p-tolyl-acetamide (10b): The compound 10b has been prepared according to the method described for the compound 10a employing the compound N-p-tolyl oxalamic acid (179 mg, 1 mmol) and 8 (177 mg, 1 mmol) to afford the crude product 10b which was purified by column chromatography (20% EtOAc-hexane) to afford desired compound as colourless liquid (125 mg, 37%). Molecular formula: C$_{20}$H$_{22}$N$_2$O$_3$ (m/z = 338); LCMS: m/z = 339.1 (M$^+$+1); $^1$H NMR (DMSO-d$_6$, 300 MHz): δ 10.60 (brs, 1H, -NH), 7.65-7.55 (m, 2H), 7.35-7.1 (m, 4H), 7.05-6.80 (m, 3H), 4.90-4.80-4.35 (m, 1H), 4.20-3.90 (m, 2H), 3.80-3.70 (m, 1H), 3.60-3.50 (m, 1H), 2.30 (s, 3H), 2.15-1.85 (m, 4H); HPLC purity: 99%.

(S)-N-(4-Methoxy phenyl)-2-oxo-2-(2-phenoxyethyl pyrrolidin-1-yl)-acetamide (10c): The compound 10c has been prepared according to the method described for the compound 10a employing the compound N-(4-methoxy phenyl)-oxalamic acid (195 mg, 1 mmol) and 8 (177 mg, 1 mmol) to afford the crude product 10c which was purified by column chromatography (20% EtOAc-hexane) to afford desired compound as pale brown liquid (278 mg, 78%). Molecular formula: C$_{20}$H$_{22}$N$_2$O$_4$ (m/z = 354); LCMS: m/z = 355.1 (M$^+$+1); $^1$H NMR (CDCl$_3$, 300 MHz): δ 9.40 (s, 1H), 7.60-7.50 (d, J = 8.2 Hz, 2H), 7.35-7.20 (m, 2H), 7.0-6.85 (m, 5H), 5.45-4.55 (m, 1H), 4.30-4.0 (m, 3H), 3.80 (s, 3H), 3.80-3.70 (t, 1H), 2.30-1.95 (m, 4H); HPLC purity: 97%.
**S**-2-Oxo-2-(2-phenoxyethyl pyrrolidin-1-yl)-N-m-tolyl acetamide (10d): The compound 10d has been prepared according to the method described for the compound 10a employing the compound N-m-tolyl oxalamic acid (179 mg, 1 mmol) and 8 (177 mg, 1 mmol) to afford the crude product 10d which was purified by column chromatography (20% EtOAc-hexane) to afford desired compound as colourless liquid (68 mg, 20%). Molecular formula: C_{20}H_{22}N_{2}O_{3} (m/z = 338); LCMS: m/z = 339.1 (M+1); ^{1}H NMR (CDCl_{3}, 300 MHz): δ 9.40 (s, 1H), 7.50-7.20 (m, 6H), 7.05-6.85 (m, 3H), 5.45-4.55 (m, 1H), 4.30-4.0 (m, 3H), 3.80-3.70 (t, 1H), 2.40 (s, 3H), 2.30-1.90 (m, 4H); HPLC purity: 98%.

**S**-N-(3-Methoxy phenyl)-2-oxo-2-(2-phenoxyethyl pyrrolidin-1-yl)-acetamide (10e): The compound 10e has been prepared according to the method described for the compound 10a employing the compound N-(3-methoxy phenyl)-oxalamic acid (195 mg, 1 mmol) and 8 (177 mg, 1 mmol) to afford the crude product 10e which was purified by column chromatography (20% EtOAc-hexane) to afford desired compound as pale yellow liquid (260 mg, 73%). Molecular formula: C_{20}H_{22}N_{2}O_{4} (m/z = 354); LCMS: m/z = 355.1 (M+1); ^{1}H NMR (CDCl_{3}, 300 MHz): δ 9.45 (s, 1H), 7.40-7.05 (m, 5H), 7.0-6.85 (m, 3H), 6.70 (d, J = 8.4 Hz, 1H), 5.45-4.55 (m, 1H), 4.30-4.0 (m, 3H), 3.85-3.70 (m, 4H), 2.30-1.95 (m, 4H); HPLC purity: 99%.

**S**-2-Oxo-2-(2-phenoxyethyl pyrrolidin-1-yl)-N-o-tolyl acetamide (10f): The compound 10f has been prepared according to the method described for the compound 10a employing the compound N-o-tolyl
oxalamic acid (179 mg, 1 mmol) and 8 (177 mg, 1 mmol) to afford the crude product 10f which was purified by column chromatography (20% EtOAc-hexane) to afford desired compound as low melting solid (125 mg, 37%). Molecular formula: C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub> (m/z = 338); LCMS: m/z = 339.1 (M<sup>+</sup> +1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 9.55-9.40 (brd, 1H), 8.02 (d, J = 8.1 Hz, 1H), 7.35-6.85 (m, 8H), 5.45-4.55 (m, 1H), 4.30-4.0 (m, 3H), 3.80-3.70 (t, 1H), 2.35 (s, 3H), 2.30-1.95 (m, 4H); HPLC purity: 98%.

(S)-N-(2-Methoxy phenyl)-2-oxo-2-(2-phenoxyethyl pyrrolidin-1-yl)-acetamide (10g): The compound 10g has been prepared according to the method described for the compound 10a employing the compound N-(2-methoxy phenyl)-oxalamic acid (195 mg, 1 mmol) and 8 (177 mg, 1 mmol) to afford the crude product 10g which was purified by column chromatography (20% EtOAc-hexane) to afford desired compound as pale yellow liquid (136 mg, 38%). Molecular formula: C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub> (m/z = 354); LCMS: m/z = 355.1 (M<sup>+</sup> +1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 10.00 (s, 1H), 8.40 (d, J = 3.0 Hz, 1H), 7.40-7.20 (m, 2H), 7.20-6.85 (m, 6H), 5.45-4.55 (m, 1H), 4.30-3.90 (m, 6H), 3.80-3.70 (t, 1H), 2.30-1.95 (m, 4H); HPLC purity: 99%.

(S)-N-(2-Fluoro phenyl)-2-oxo-2-(2-phenoxyethyl pyrrolidin-1-yl)-acetamide (10h): The compound 10h has been prepared according to the method described for the compound 10a employing the compound N-(2-fluoro phenyl)-oxalamic acid (183 mg, 1 mmol) and 8 (177 mg, 1 mmol) to afford the crude product 10h which was purified by column
chromatography (20% EtOAc-hexane) to afford desired compound as pale yellow liquid (135 mg, 39%). Molecular formula: C_{19}H_{19}FN_{2}O_{3} (m/z = 342); LCMS: m/z = 343.2 (M^+1); ^1H NMR (CDCl_{3}, 300 MHz): δ 9.70 (s, 1H), 8.35 (t, 1H), 7.35-7.05 (m, 5H), 7.0-6.85 (m, 3H), 5.45-4.55 (m, 1H), 4.30-4.0 (m, 3H), 3.80-3.70 (t, 1H), 2.30-1.95 (m, 4H); HPLC purity: 96%.

4.3 (S)-2-(5-Fluoro indol-1-yl)-1-(2-phenoxyethyl pyrrolidin-1-yl)-ethanone (12a): The compound 12a has been prepared according to the method described for the compound 10a employing the compound (5-fluoro indol-1-yl)-acetic acid (193 mg, 1 mmol) and 8 (177 mg, 1 mmol) to afford the crude product 12a which was purified by column chromatography (40% EtOAc-hexane) to afford desired compound as cream colour solid (199 mg, 56%). Molecular formula: C_{21}H_{21}FN_{2}O_{2} (m/z = 352); LCMS: m/z = 353.1 (M^+1); mp: 122-124 °C; ^1H NMR (CDCl_{3}, 300 MHz): δ 7.40-7.10 (m, 5H), 7.0-6.85 (m, 4H), 6.50 (d, J = 8.2 Hz, 1H), 4.80 (s, 2H), 4.50 (m, 1H), 4.20-4.10 (m, 2H), 3.55-3.40 (m, 2H), 2.30-1.95 (m, 4H); HPLC purity: 98%.

(S)-2-(5-Bromo indol-1-yl)-1-(2-phenoxyethyl pyrrolidin-1-yl)-ethanone (12b): The compound 12b has been prepared according to the method described for the compound 10a employing the compound (5-bromo indol-1-yl)-acetic acid (254 mg, 1 mmol) and 8 (177 mg, 1 mmol) to afford the crude product 12b which was purified by column chromatography (50% EtOAc-hexane) to afford desired compound as pale yellow solid (246 mg, 59%). Molecular formula: C_{21}H_{21}BrN_{2}O_{2}
(m/z = 413); LCMS: m/z = 413.0 (M⁺+1); mp: 109-111 °C; ¹H NMR (CDCl₃, 300 MHz): δ 7.75 (s, 1H), 7.35-7.20 (m, 3H), 7.15-7.05 (m, 2H), 7.0-6.85 (m, 3H), 6.50 (d, J = 8.1 Hz, 1H), 4.80 (s, 2H), 4.50 (m, 1H), 4.20-4.10 (m, 2H), 3.55-3.40 (m, 2H), 2.30-1.95 (m, 4H); HPLC purity: 98%.

(S)-2-(5-Chloro indol-1-yl)-1-(2-phenoxy methyl pyrrolidin-1-yl)-ethanone (12c): The compound 12c has been prepared according to the method described for the compound 10a employing the compound (5-chloro indol-1-yl)-acetic acid (209 mg, 1 mmol) and 8 (177 mg, 1 mmol) to afford the crude product 12c which was purified by column chromatography (40% EtOAc-hexane) to afford desired compound as white solid (234 mg, 63%). Molecular formula: C₂₁H₂₁ClN₂O₂ (m/z = 368); LCMS: m/z = 369.0 (M⁺+1); mp: 129-131 °C; ¹H NMR (CDCl₃, 300 MHz): δ 7.60 (s, 1H), 7.40-7.20 (m, 2H), 7.20-7.0 (m, 3H), 7.0-6.85 (m, 3H), 6.50 (d, J = 8.3 Hz, 1H), 4.80 (s, 2H), 4.50 (m, 1H), 4.20-4.10 (m, 2H), 3.55-3.40 (m, 2H), 2.30-1.95 (m, 4H); HPLC purity: 96%.

(S)-2-(5-Methoxy indol-1-yl)-1-(2-phenoxy methyl pyrrolidin-1-yl)-ethanone (12d): The compound 12d has been prepared according to the method described for the compound 10a employing the compound (5-methoxy indol-1-yl)-acetic acid (205 mg, 1 mmol) and 8 (177 mg, 1 mmol) to afford the crude product 12d which was purified by column chromatography (40% EtOAc-hexane) to afford desired compound as pale yellow liquid (276 mg, 76%). Molecular formula: C₂₂H₂₄N₂O₃ (m/z
= 364); LCMS: m/z = 365.1 (M⁺+1); ¹H NMR (DMSO-d₆, 300 MHz): δ 7.40-7.20 (m, 4H), 7.10-6.90 (m, 4H), 6.70 (d, J = 8.1 Hz, 1H), 6.35 (d, J = 3.1 Hz, 1H), 5.05 (s, 2H), 4.30-4.20 (m, 1H), 4.15-4.05 (m, 1H), 3.95 (m, 1H), 3.80 (s, 3H), 3.70-3.60 (m, 2H) 2.20-1.95 (m, 4H); HPLC purity: 97%.

(S)-2-(2-Methyl indol-1-yl)-1-(2-phenoxymethyl pyrrolidin-1-yl)-ethanone (12e): The compound 12e has been prepared according to the method described for the compound 10a employing the compound (5-methyl indol-1-yl)-acetic acid (189 mg, 1 mmol) and 8 (177 mg, 1 mmol) to afford the crude product 12e which was purified by column chromatography (40% EtOAc-hexane) to afford desired compound as cream colour solid (169 mg, 48%). Molecular formula: C₂₂H₂₄N₂O₂ (m/z = 348); LCMS: m/z = 349.1 (M⁺+1); mp : 67-70 °C; ¹H NMR (DMSO-d₆, 300 MHz): δ 7.45-7.25 (m, 4H), 7.10-6.90 (m, 5H), 6.20 (s, 1H), 5.0 (s, 2H), 4.30-4.20 (m, 1H), 4.15-4.05 (m, 1H), 3.95 (m, 1H), 3.80-3.65 (m, 2H), 2.30 (s, 3H), 2.20-1.95 (m, 4H); HPLC purity: 97%.

4.2 (S)-N-(4-Fluoro phenyl)-2-[2-(4-methoxy phenoxymethyl)pyrrolidin-1-yl]-2-oxo acetamide (11a): The compound 11a has been prepared according to the method described for the compound 10a employing the compound N-(4-fluoro phenyl)-oxalamic acid (183 mg, 1 mmol) and 9 (207 mg, 1 mmol) to afford the crude product 11a which was purified by column chromatography (20% EtOAc-hexane) to afford desired compound as colourless liquid (250 mg, 67%). Molecular formula: C₂₀H₂₁FN₂O₄ (m/z = 372); LCMS: m/z = 373.1 (M⁺+1); ¹H
NMR (CDCl₃, 300 MHz): δ 9.40 (s, 1H), 7.65-7.50 (m, 2H), 7.10-7.0 (t, 2H), 6.90-6.75 (m, 4H), 5.40-4.50 (m, 1H), 4.25-3.95 (m, 3H), 3.80-3.70 (m, 4H), 2.30-1.95 (m, 4H); HPLC purity: 97%.

(S)-2-[(4-Methoxy phenoxymethyl)-pyrrolidin-1-yl]-2-oxo-N-p-tolyl acetamide (11b): The compound 11b has been prepared according to the method described for the compound 10a employing the compound N-p-tolyl oxalamic acid (179 mg, 1 mmol) and 9 (207 mg, 1 mmol) to afford the crude product 11b which was purified by column chromatography (20% EtOAc-hexane) to afford desired compound as colourless liquid (150 mg, 41%). Molecular formula: C₂₁H₂₄N₂O₄ (m/z = 368); LCMS: m/z = 369.1 (M+1); ¹H NMR (CDCl₃, 300 MHz): δ 9.40 (s, 1H), 7.35-7.45 (d, J = 8.0 Hz, 2H), 7.20-7.10 (d, J = 8.2 Hz, 2H), 6.90-6.75 (m, 4H), 5.40-4.50 (m, 1H), 4.25-3.95 (m, 3H), 3.80-3.70 (m, 4H), 2.35 (s, 3H), 2.30-1.95 (m, 4H); HPLC purity: 97%.

(S)-2-[(4-Methoxy phenoxymethyl)-pyrrolidin-1-yl]-N-(4-methoxy phenyl)-2-oxo acetamide (11c): The compound 11c has been prepared according to the method described for the compound 10a employing the compound N-(4-methoxy phenyl)-oxalamic acid (195 mg, 1 mmol) and 9 (207 mg, 1 mmol) to afford the crude product 11c which was purified by column chromatography (20% EtOAc-hexane) to afford desired compound as white solid (240 mg, 62%). Molecular formula: C₂₁H₂₄N₂O₅ (m/z = 384); LCMS: m/z = 385.1 (M+1); mp: 126-128 °C; ¹H NMR (CDCl₃, 300 MHz): δ 9.35 (s, 1H), 7.60-7.50 (d, J
215

= 8.3 Hz, 2H), 6.95-6.75 (m, 6H), 5.40-4.50 (m, 1H), 4.25-3.95 (m, 3H), 3.85-3.70 (m, 7H), 2.30-1.95 (m, 4H); HPLC purity: 98%.

(S)-2-[2-(4-Methoxy phenoxymethyl)-pyrrolidin-1-yl]-2-oxo-N-m-toly1 acetamide (11d): The compound 11d has been prepared according to the method described for the compound 10a employing the compound N-m-tolyl oxalamic acid (179 mg, 1 mmol) and 9 (207 mg, 1 mmol) to afford the crude product 11d which was purified by column chromatography (20% EtOAc-hexane) to afford desired compound as colourless liquid (158 mg, 43%). Molecular formula: C21H24N2O4 (m/z = 368); LCMS: m/z = 369.0 (M+1); 1H NMR (CDCl3, 300 MHz): δ 9.40 (s, 1H), 7.50-7.35 (m, 2H), 7.30-7.20 (m, 1H), 7.0-6.80 (m, 5H), 5.40-4.50 (m, 1H), 4.25-3.95 (m, 3H), 3.80-3.70 (m, 4H), 2.35 (s, 3H), 2.30-1.95 (m, 4H); HPLC purity: 96%.

(S)-2-[2-(4-Methoxy phenoxymethyl)-pyrrolidin-1-yl]-N-(3-methoxy phenyl)-2-oxo-acetamide (11e): The compound 11e has been prepared according to the method described for the compound 10a employing the compound N-(3-methoxy phenyl)-oxalamic acid (195 mg, 1 mmol) and 9 (207 mg, 1 mmol) to afford the crude product 11e which was purified by column chromatography (20% EtOAc-hexane) to afford desired compound as colourless liquid (310 mg, 81%). Molecular formula: C21H24N2O5 (m/z = 384); LCMS: m/z = 385.1 (M+1); 1H NMR (CDCl3, 300 MHz): δ 9.45 (s, 1H), 7.40-7.30 (m, 2H), 7.10 (d, J = 8.1 Hz, 1H), 6.95-6.70 (m, 5H), 5.40-4.50 (m, 1H), 4.25-3.95 (m, 3H), 3.85-3.70 (m, 7H), 2.30-1.95 (m, 4H); HPLC purity: 97%.
(S)-2-[2-(4-Methoxy phenoxy)methyl]-2-oxo-N-o-tolyl acetamide (11f): The compound 11f has been prepared according to the method described for the compound 10a employing the compound N-o-tolyl oxalamic acid (179 mg, 1 mmol) and 9 (207 mg, 1 mmol) to afford the crude product 11f which was purified by column chromatography (20% EtOAc-hexane) to afford desired compound as colourless liquid (186 mg, 50%). Molecular formula: C_{21}H_{24}N_{2}O_{4} (m/z = 368); LCMS: m/z = 369.2 (M+1); $^1$H NMR (CDCl$_3$, 300 MHz): δ 9.45 (s, 1H), 8.0 (d, $J$ = 8.1 Hz, 1H), 7.30-7.05 (m, 3H), 6.95-6.75 (m, 4H), 5.40-4.50 (m, 1H), 4.25-3.95 (m, 3H), 3.80-3.70 (m, 4H), 2.35 (s, 3H), 2.30-1.95 (m, 4H); HPLC purity: 96%.

(S)-2-[2-(4-Methoxy phenoxy)methyl]-2-oxo-N-(2-methoxy phenyl)-acetamide (11g): The compound 11g has been prepared according to the method described for the compound 10a employing the compound N-(2-methoxy phenyl)-oxalamic acid (195 mg, 1 mmol) and 9 (207 mg, 1 mmol) to afford the crude product 11g which was purified by column chromatography (20% EtOAc-hexane) to afford desired compound as colourless liquid (135 mg, 35%). Molecular formula: C_{21}H_{24}N_{2}O_{5} (m/z = 384); LCMS: m/z = 385.1 (M+1); $^1$H NMR (CDCl$_3$, 300 MHz): δ 9.95 (s, 1H), 8.40-8.30 (m, 1H), 7.15-7.05 (t, 1H), 7.0-6.75 (m, 6H), 5.40-4.50 (m, 1H), 4.25-4.10 (m, 2H), 4.05-3.90 (m, 4H), 3.80-3.70 (m, 4H), 2.30-1.95 (m, 4H); HPLC purity: 97%.
(S)-N-(2-Fluoro phenyl)-2-[2-(4-methoxy phenoxy)methyl]-pyrrolidin-1-yl]-2-oxo acetamide (11h): The compound 11h has been prepared according to the method described for the compound 10a employing the compound N-(2-fluoro phenyl)-oxalamic acid (183 mg, 1 mmol) and 9 (207 mg, 1 mmol) to afford the crude product 11h which was purified by column chromatography (20% EtOAc-hexane) to afford desired compound as colourless liquid (250 mg, 67%). Molecular formula: C_{20}H_{21}FN_{2}O_{4} (m/z = 372); LCMS: m/z = 373.0 (M\(^{+}\)+1); \(^{1}\)H NMR (CDCl\(_{3}\), 300 MHz): δ 9.70 (s, 1H), 8.40-8.30 (m, 1H), 7.20-7.05 (m, 3H), 6.95-6.80 (m, 4H), 5.40-4.50 (m, 1H), 4.25-3.95 (m, 3H), 3.80-3.70 (m, 4H), 2.30-1.95 (m, 4H); HPLC purity: 96%.

4.3 (S)-2-(5-Fluoro indol-1-yl)-1-[2-(4-methoxy phenoxy)methyl]-pyrrolidin-1-yl]-ethanone (13a): The compound 13a has been prepared according to the method described for the compound 10a employing the compound (5-fluoro indol-1-yl)-acetic acid (193 mg, 1 mmol) and 9 (207 mg, 1 mmol) to afford the crude product 13a which was purified by column chromatography (40% EtOAc-hexane) to afford desired compound as pale yellow liquid (115 mg, 30%). Molecular formula: C_{22}H_{23}FN_{2}O_{3} (m/z = 382); LCMS: m/z = 383.1 (M\(^{+}\)+1); \(^{1}\)H NMR (CDCl\(_{3}\), 300 MHz): δ 7.30-7.10 (m, 3H), 6.95-6.75 (m, 5H), 6.50 (d, J = 8.1 Hz, 1H), 4.80 (s, 2H), 4.50-4.40 (m, 1H), 4.15-4.05 (m, 2H), 3.80 (s, 3H), 3.55-3.40 (m, 2H), 2.25-1.95 (m, 4H); HPLC purity: 97%.
(S)-2-(5-Bromo indol-1-yl)-1-[2-(4-methoxy phenoxymethyl)-pyrrolidin-1-yl]-ethanone (13b): The compound 13b has been prepared according to the method described for the compound 10a employing the compound (5-bromo indol-1-yl)-acetic acid (254 mg, 1 mmol) and 9 (207 mg, 1 mmol) to afford the crude product 13b which was purified by column chromatography (50% EtOAc-hexane) to afford desired compound as pale yellow liquid (80 mg, 18%). Molecular formula: C_{22}H_{23}BrN_{2}O_{3} (m/z = 443); LCMS: m/z = 444.8 (M^{+}+2); {\textsuperscript{1}}H NMR (CDCl_{3}, 300 MHz): δ 7.75 (s, 1H), 7.30-7.05 (m, 3H), 6.90-6.75 (m, 4H), 6.50 (d, J = 8.3 Hz, 1H), 4.80 (s, 2H), 4.50-4.40 (m, 1H), 4.15-4.05 (m, 2H), 3.80 (s, 3H), 3.55-3.40 (m, 2H), 2.25-1.95 (m, 4H); HPLC purity: 97%.

(S)-2-(5-Chloro indol-1-yl)-1-[2-(4-methoxy phenoxymethyl)-pyrrolidin-1-yl]-ethanone (13c): The compound 13c has been prepared according to the method described for the compound 10a employing the compound (5-chloro indol-1-yl)-acetic acid (209 mg, 1 mmol) and 9 (207 mg, 1 mmol) to afford the crude product 13c which was purified by column chromatography (40% EtOAc-hexane) to afford desired compound as pale yellow liquid (90 mg, 23%). Molecular formula: C_{22}H_{23}ClN_{2}O_{3} (m/z = 398); LCMS: m/z = 398.9 (M^{+}+1); {\textsuperscript{1}}H NMR (CDCl_{3}, 300 MHz): δ 7.60 (s, 1H), 7.20-7.05 (m, 3H), 6.90-6.75 (m, 4H), 6.50 (d, J = 8.0 Hz, 1H), 4.80 (s, 2H), 4.50-4.40 (m, 1H), 4.15-4.05 (m, 2H), 3.80 (s, 3H), 3.55-3.40 (m, 2H), 2.25-1.95 (m, 4H); HPLC purity: 96%.
(S)-2-(5-Methoxy indol-1-yl)-1-[2-(4-methoxy phenoxy)methyl]-pyrrolidin-1-yl]-ethanone (13d): The compound 13d has been prepared according to the method described for the compound 10a employing the compound (5-methoxy indol-1-yl)-acetic acid (205 mg, 1 mmol) and 9 (207 mg, 1 mmol) to afford the crude product 13d which was purified by column chromatography (40% EtOAc-hexane) to afford desired compound as pale brown liquid (95 mg, 24%). Molecular formula: C_{23}H_{26}N_{2}O_{4} (m/z = 394); LCMS: m/z = 395.1 (M^+1); ^1H NMR (CDCl_3, 300 MHz): δ 7.20-7.0 (m, 3H), 6.90-6.75 (m, 5H), 6.48 (d, J = 8.1 Hz, 1H), 4.80 (s, 2H), 4.50-4.40 (m, 1H), 4.15-4.05 (m, 2H), 3.90-3.70 (m, 6H), 3.50-3.40 (m, 2H), 2.25-1.95 (m, 4H); HPLC purity: 96%.

(S)-1-[2-(4-Methoxy phenoxy)methyl]-pyrrolidin-1-yl]-2-(2-methyl indol-1-yl)-ethanone (13e): The compound 13e has been prepared according to the method described for the compound 10a employing the compound (2-methyl indol-1-yl)-acetic acid (189 mg, 1 mmol) and 9 (207 mg, 1 mmol) to afford the crude product 13e which was purified by column chromatography (40% EtOAc-hexane) to afford desired compound as cream colour solid (66 mg, 17%). Molecular formula: C_{23}H_{26}N_{2}O_{3} (m/z = 378); LCMS: m/z = 379.1 (M^+1); mp : 107-109 °C; ^1H NMR (CDCl_3, 300 MHz): δ 7.50 (d, J = 7.8 Hz, 1H), 7.20-7.0 (m, 3H), 6.90-6.75 (m, 4H), 6.30 (s, 1H), 4.80 (s, 2H), 4.50-4.40 (m, 1H), 4.15-4.05 (m, 2H), 3.80 (s, 3H), 3.55-3.45 (m, 2H), 2.40 (s, 3H), 2.25-1.95 (m, 4H); HPLC purity: 97%.
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MASS spectrum of 11b
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**MASS spectrum of 11c**
1H NMR spectrum of 12c
**Sample ID: 13**

**Sample Name:** IN1958-075P

**Acq. File:** Data16040916.wiff

**Acq. Date:** Thursday, April 16, 2009

**Polarity/Scan Type:** Positive Q1 MS

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**TIC of +Q1 from Sample 1 ([IN1958-075P] of Data16040916.wiff (Turbo Spray))**

Max. 3.4e8 cps

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**+Q1 2.819 to 2.986 min from Sample 1 ([IN1958-075P] of Data16040916.wiff (Turbo Spray)), su...**

Max. 5.0e6 cps

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**TIC of DAD Spectral Data: from Sample 1 ([IN1958-075P] of Data16040916.wiff)**

Max. 5.9e4 mAU

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**Peak List for "TIC of DAD Spectral Data: from Sample 1 ([IN1958-075P] of Data16040916.wiff)"**

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**MASS spectrum of 12e**
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**Acq. File:** Data24040933.wiff  
**Acq. Date:** Friday, April 26, 2009

**TIC of +Q1 from Sample 1 (IN1958-087P) of Data24040933.wiff (Turbo Spray)**

Max 2.768 cps

**TIC of +Q1 2.184 to 2.552 min from Sample 1 (IN1958-087P) of Data24040933.wiff (Turbo Spray)**

Max 3.565 cps

**TIC of +Q2 from Sample 1 (IN1958-087P) of Data24040933.wiff (Turbo Spray)**

Max 4.904 mAU

**Peak List for TWC of DAD Spectral Data from Sample 1 (IN1958-087P) of Data24040933.wiff**

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**MASS spectrum of 13a**
$^{1} \text{H NMR spectrum of 13c}$
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Sample Name: IM1958-088P
Polarity/Scan Type: Positive Q1 MS
Acq. File: Data24Q040934.wiff
Acq. Date: Friday, April 24, 2009

TIC of +Q1 from Sample 1 (IN1958-088P) of Data24Q040934.wiff (Turbo Spray)
Max 3.068 cps

+Q1: 2.652 to 2.986 min from Sample 1 (IN1958-088P) of Data24Q040934.wiff (Turbo Spray), su...
Max 3.268 cps

TWC of DAD Spectral Data: from Sample 1 (IN1958-088P) of Data24Q040934.wiff
Max 5.164 mAU

Peak List for "TWC of DAD Spectral Data: from Sample 1 (IN1958-088P) of Data24Q040934.wiff"

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MASS spectrum of 13c