The work reported in this thesis comprises the synthesis, structural studies and biological evaluation of peptides containing conformationally constrained $\beta$- and $\gamma$-amino acids. The introduction of such amino acids into $\alpha$-peptide sequences is of great interest for the study of folded structures as well as biological activity. The thesis is divided into five chapters.

**Chapter 1: C$_{11}$/C$_{9}$ Helical folding in $\alpha\beta$ hybrid peptides containing 1-amino-cyclohexane acetic acid ($\beta$$^{3,3}$-Ac$_{6}$c)**

This chapter describes the synthesis and conformational studies of $\alpha\beta$ hybrid peptides containing $\beta$$,\beta$-disubstituted-$\beta$-amino acid, $\beta$$^{3,3}$-Ac$_{6}$c. The peptides are Boc-Leu-$\beta$$^{3,3}$-Ac$_{6}$c-OH, P$_1$; Boc-Leu-$\beta$$^{3,3}$-Ac$_{6}$c-Leu-$\beta$$^{3,3}$-Ac$_{6}$c-OMe, P$_2$; Boc-(Leu-$\beta$$^{3,3}$-Ac$_{6}$c)$_2$-Leu-OMe, P$_3$ and Boc-(Leu-$\beta$$^{3,3}$-Ac$_{6}$c)$_4$-OMe, P$_4$. The dipeptide P$_1$ adopts extended conformations while as tetrapeptide P$_2$ and peptapeptide P$_3$ favor helical conformation stabilized by C$_{11}$/C$_{9}$ intramolecular hydrogen bonds. Both amino groups of residues $\beta$$^{3,3}$-Ac$_{6}$c(2) and $\beta$$^{3,3}$-Ac$_{6}$c(4) in P$_3$ occupies axial orientations, while in P$_2$, it occupies axial and equatorial orientations for residues $\beta$$^{3,3}$-Ac$_{6}$c(2) and $\beta$$^{3,3}$-Ac$_{6}$c(4), respectively. The crystal packing of both the peptides demonstrates the presence of intramolecular as well as intermolecular hydrogen bonds together with hydrophobic interaction among the side chains In peptides P$_2$ and P$_3$, $\beta$$^{3,3}$-Ac$_{6}$c residue adopt gauche conformation, a feature which promotes local folding when incorporated into peptides. The peptide P$_4$ was studied by 2D-NMR.

**Chapter 2: Design, synthesis and conformational studies of proline containing $\alpha\gamma$ hybrid peptide**

This chapter describes the synthesis and crystallographic analysis of $\alpha\gamma$ hybrid peptides, Boc-Gpn-L-Pro-NHMe, P$_1$; Boc-Aib-Gpn-L-Pro-NHMe, P$_2$; Boc-L-Pro-Aib-Gpn-L-Pro-NHMe, P$_3$; Boc-Gpn-D-Pro-NHMe, P$_4$; Boc-Aib-Gpn-D-Pro-NHMe, P$_5$ and Boc-Gpn-
D-Pro-Aib-NHMe, P6. Peptides P1 and P2 adopt expanded twelve membered (C_{12}) helical turn over γα segment. Peptide P3 promote the ribbon structure stabilized by type ‘II’ β-turn (C_{10}) followed by the expanded C_{12} helical γα turn. Both right handed and left handed helical conformations for Aib residue are observed in peptides P2 and P3 respectively (Wani et al 2015). Peptides P4 and P5 adopt expanded twelve membered (C_{12}) helical left-handed turn over γα segment. Peptide P6 adopts folded conformation stabilized by three-centre, double hydrogen bond motif, seven membered (C_{7}) followed by type II' β-turn (C_{10}). Aib residue adopts left handed helical conformation in P5, while right handed helical conformation is observed for it in peptide P6, respectively (Wani et al 2016).

Chapter 3: Short hybrid peptides incorporating β- and γ-amino acids as antimicrobial agents

This chapter describes the synthesis, characterization and bioevaluation of hybrid peptides, P1-P8 containing β- and γ-amino acids against Gram-positive and Gram-negative bacteria. Among all, peptides P2, P3, P4, P5 and P6 displayed antimicrobial activity against all tested pathogens. Peptides P2, P3, P4 and P5 exhibited potent activity against S. aureus and P. aeruginosa. To understand the efficacy of peptides and mechanism of action, time kill kinetics and fluorescence microscopic studies were performed against S. aureus and P. aeruginosa for the peptide P2 and P4, which exhibited antimicrobial property against both the pathogens at 6.25μM. P4 was found more efficacious against P. aeruginosa and S. aureus in comparison to P2 as it took half time to show bactericidal effect. Fluorescence microscopic studies suggested that peptides P2 and P4 killed the bacteria via membrane disruption. Further, P4 showed lowest hemolytic activity among all the active peptides.

Chapter 4: Piperic acid (PA) & 4-ethylpiperic acid (EPA) amides with α-, β- and γ-amino acids as potent NorA efflux pump inhibitors

This chapter describes the synthesis, characterization and bioevaluation of piperic acid (PA) and 4-ethylpiperic acid (EPA) amides (1-20) with α-,β- and γ-amino acids for their efflux pump inhibitory activity against ciprofloxacin resistant Staphylococcus aureus.
The amides were screened against NorA overexpressing *S. aureus* SA-1199B and wild type *S. aureus* SA-1199 using ethidium bromide as NorA efflux pump substrate. Compounds 6, 10, 12, 13 & 20 were found to be the active compounds. EPI 12 was found to be the most potent and reduced the MIC of ciprofloxacin by 16 fold against NorA overexpressing strain of *S. aureus* (SA-1199B) followed by 20 which showed 4 fold reduction of MIC. Further, through ethidium bromide efflux inhibition and accumulation assays, these compounds have shown potent NorA inhibitors. From the above study it can be inferred that this study can be extended to develop the potent EPIs based on conjugation of piperic and 4-ethylpiperic acid with β,β-disubstituted-β- and γ-amino acids (Wani *et al* 2016).

**Chapter 5: Piperic acid (PA) & 4-ethylpiperic acid (EPA) amides with α-, β- and γ-amino acids as anticancer agents.**

This chapter describes the anticancer studies of the amides of piperic acid and 4-ethylpiperic acid. All the amides were bioevaluated by using MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay against a panel of three cancer cell lines i.e. human prostate cancer (PC-3), pancreatic cancer (Panc1) and colorectal carcinoma (HCT-116). Among all the tested amides, 5 and 20, a novel amides of PA and EPA, with β,β-disubstituted-β-amino acids, β3,3-Pip(Bzl)-OH 2-(4-amino-1-benzylpiperidin-4-yl) acetic acid and β3,3-Pip-OH 2-(4-aminopiperidin-4-yl)acetic acid) exhibited promising cytotoxicity against pancreatic cancer (Panc1) cell line with IC50 of 7.0 and 4.0µM, respectively. The amide 20 describes the anti-metastatic effect in human pancreatic carcinoma. The amide 20 inhibited invasion and migration of PANC-1 cells in wound healing, matrigel invasion and gelatin degradation assays. Apart from suppressing PI3K/Akt/NF-kB signaling, which is involved in the up-regulation of matrix metalloproteinases, our study also showed that dose dependent treatment of 20, results in the upregulation of TIMP-1 and E-cadherin expression. Further, 20 was found to be inhibiting the metastatic ability of PANC-1 cells by reducing MMP-2 and MMP-9 expression. These findings suggest that EPA amide with β3,3-Pip-OH, 20 may be used as an anti-metastatic agent against human pancreatic carcinoma (Wani *et al* 2015).
In addition, the cell growth inhibition and apoptopic induction by 5 was investigated in pancreatic cancer cells by using western-blot analysis, PARP-1 and caspase-3 cleavage along with DAPI staining and caspase glow assay. The compound arrested the Panc-1 cells in G2 phase of cell cycle. The mechanistic investigation revealed that 5 blocks the p-38-MAPK/ERK1/2, a strong prosurvival pathway. These results demonstrate that compound 5 has a potential antiproliferative and apoptosis inducing effects in Panc-1 cells (Wani et al 2016).