Design, Synthesis and Characterization of Unnatural Neurotransmitter Amino Acid-based Peptides

M.Sc. Thesis

By

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Design, Synthesis and Characterization of Unnatural Neurotransmitter Amino Acid-based Peptides

A Thesis

Sumbitted in partial fulfilment

of requirements for the

awards of the degree

of

Master of Science

by

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CANDIDATE DECLARATION

I hereby certify that the work is shown in the thesis entitled **"Design, synthesis and characterization of unnatural neurotransmitter amino acid-based peptides"** in the partial fulfillment of the requirements for the award of the degree of **Master of Science** and submitted in the Department of Chemistry, IIT Indore, is an authentic record of my own work carried out during the time period 31/01/2020 to 31/05/2021 under the supervision of **Dr. Apurba K. Das**, Associate Professor, **Department of Chemistry, Indian Institute of Technology Indore.**

The matter presented in thesis has not been submitted by me for the award of any other degree by this or any other institute.

Arati Samal
03/06/21

Arati Samal

This is to certify that the above statement made by the candidate is correct to the best of my/our knowledge.

03.06.2021

Dr. Apurba K. Das

Arati Samal has successfully given his M.Sc. oral examination held on date 08/06/2021

03.06.2021

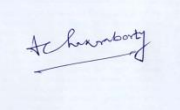
Tushar Kanti Mukherjee

Signature of supervisor of M.Sc. thesis

Date:03.06.2021

Convener, DPGC

Date: 10.06.2021



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Date: 4.6.2021

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Date: 10.06.2021

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Dedicated to
My
Family

ABSTRACT

Gababutin, an unnatural γ-amino acid, is protected with Boc-group (Boc-Gbn-OH) that shows different kind of conformation. To synthesize the unnatural γ-amino acid, I have started with cyclopentanone which is the precursor compound for synthesis of my target compound that is "gababutin". The precursor compound, cyclopentanone reacts with triethyl phosphonoacetate generally by modified Wittig reaction (Horner Emmons modification) to give exclusively *E*-alkene product. Here it gives an ester, which undergoes Michael addition on reaction with nitromethane to give nitro compound. Then the nitro compound is reduced using hydrogen gas over activated palladium charcoal and at the final stage the reduced product gives spiro lactam and hydrolysis results into the formation of gababutin. The target compound, gababutin is followed by Boc protection to form ultimate Boc-protected gababutin based unnatural amino acid (Boc-Gbn-OH). All synthesized compounds have been purified by using column chromatography method and characterized by the mass spectrometry and nuclear magnetic resonance (NMR) spectroscopic techniques.

NOMENCLATURES

δ	Delta (chemical shift)
nm	Nanometer
mL	Milliliter
ppm	Parts per million
Hz	Hertz
g	Gram
mg	Milligram
K	Kelvin
˚C	Degree Celsius
α	Alpha
γ	Gamma

ACRONYMS

GABA	γ-amino-butyric acid
Gpn	Gabapentin
Gbn	Gababutin
THF	Tetrahydrofuran
Aib	α-amino-isobutyric acid
Na_2SO_4	Sodium sulfate
DMSO	Dimethyl sulfoxide
DCC	Dicyclohexyldicarbodiimide
HOBt	1-Hydroxybenzotriazole
NaOH	Sodium hydroxide
K_2CO_3	Potassium carbonate
KO^tBu	Potassium *tert*-butoxide
$PO(OEt)_2CH_2COOEt$	Triethyl phosphonoacetate
Boc	*tert*-butoxycarbonyl
CH_3NO_2	Nitromethane
$(Boc)_2O$	Di-*tert*-butyl dicarbonate
DMF	*N*,*N*-dimethylformamide
NMR	Nuclear Magnetic Resonance
ESI	Electron spray ionization
TLC	Thin Layer Chromatography
MeOH	Methanol
EtOAc	Ethyl acetate
s	Singlet
d	Doublet
m	Multiplet
J	Coupling constant

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Chapter 1

1.1 INTRODUCTION

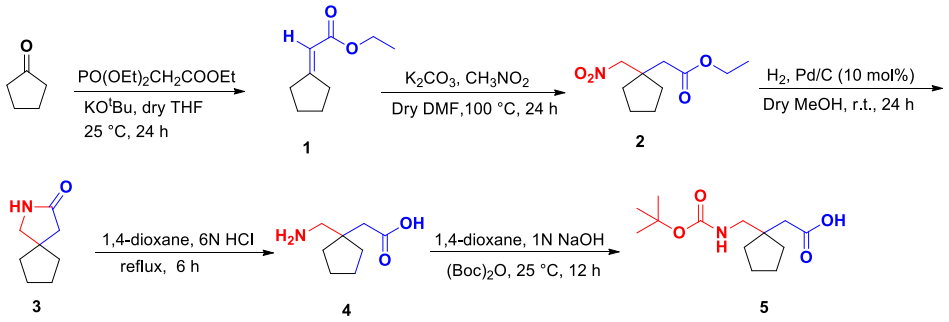
Recently, the self-assembly and self-aggregation have been charming the hobby of many researchers. Self-assembly of small organic molecules at molecular level has captivated substantial interests in current years because of its packages in biology and fabric sciences.[1] Bio-molecular self-aggregation is quite convertible and spontaneous that's ruled via way by means of the mixture of diverse covalent and non-covalent interactions. Bio-organic and medicinal chemistry are the emerging fields in which biomolecules are imitate by synthesis of artificial building blocks and scaffolds.[2-3] The intermixing-frameworks of biopolymers is best layout by researchers inspired by the discovery of DNA double helix.[4] Due to the numerous tendencies like folding, turns, helices, sheets and reverse turns, proteins and deoxyribonucleic acid (DNA) shows diverse features. These protein structures are nicely stabilized with the aid of using non-covalent interactions.[5-6] Peptide self-meeting gives full-size benefits because of its organic affinity, ease of synthesis, low level of toxicity and diverse-features.[7] The compact folding structures of proteins/peptides shows wide range of biological event. Natural and artificial scaffolds shows distinct folded susceptibility in foldamers.[5] Turn nucleation is the basic characteristic properties of proteins, in which peptides of α-amino acid adopt 7-membered H-bonded γ-turn or 10-membered H-bonded conformations.[7-12] Features like recognition of molecules, interaction of proteins, drug discovery and the function of protein inhibition, are the key role in bio-medicinal chemistry. [13-18] The various interactions such as ionic, van der Waals, π-π stacking, H-bonding, results into self-combination of various peptides and gives nanostructures. Peptide-based molecules have wide range of applications in solvent chemistry and have tremendous role in the fields of nanoscience and wastewater treatment.[19]

Protein structure mainly stabilized through non-covalent interactions and the supra molecular like helices, sheets and reverse turns are the important part of protein conformation.[20-21] Biological balance may be done by imparting small changes in the secondary structure of peptides by incorporating artificial amino acids.[22] The action of protease enzyme mainly depends upon the β and γ-peptides conformation, have quite adorable significance in medicinal chemistry.[23] The incorporation of –$(CH2)_n$– unit in the peptide backbone of β, and γ-amino acids provides chance to better understand properties of the hybrid peptide systems.[24-25] Various folding styles is observed with the inclusion of small synthetic peptides providing different H-bonded conformation.[26]

The existence of polypeptide into double helical structure is quite uncommon, compare to gramicidin A, obtaining left-handed anti-parallel mode and plays important role in the transportation of ions (monovalent) across the cell membrane.[27-29] Presently researchers are working on synthetic oligomers to understand the formation of helicity from single to multiple strands.[30-32] But the concepts of non-DNA dual helical structure or unconventional incorporated based H-bonding is quite not that much known. The interactions between the electrophilic and nucleophilic centers resulting from electronic dispersion, in the complementary stacking stabilized the double helical structures.[34] Now a days, numerous supramolecular frameworks are obtained by incorporating GABA operated peptides.[34-36] GABA, γ-aminobutyric acid is a neurotransmitter, when incorporated in the peptide backbone, consequently affect the folding features and functionality on the microscopic levels.[37] Supramolecular double helix structure is shown by dipeptides containing Gababutin both in solid and solution state, due to the substitution at C-terminal of Boc-Gbn-OH. Recently, it's miles stated that the structural and morphological research of Gpn-primarily incorporated hybrid tetrapeptides (Boc-Gpn-Aib-Aaa-Aib-OMe), which followed C_{12}/C_{10} H-bonded double helical systems and confirms numerous supramolecular

features both in solution and solid phase.[1] So, our principal goal is to substitute gabapentin (Gpn) with gababutin (Gbn) in various hybrid tetrapeptides and observe the numerous conformational changes occurring at the supramolecular level both in crystal and solution phase. I also expect to get double helical like conformation for these gababutin incorporated hybrid peptides same like that of DNA both in crystal and solution state.

1.2 Reaction Scheme



Scheme 1: Overall synthetic scheme of Boc-Gbn-OH (**5**).

Chapter 2

2.1: Experimental Section

2.1.1 Materials

The used solvents and reagents were purchased from commercially available source like Alfa Aesar, Sigma Aldrich-India (Merck) and Spectro-chem. Triethyl phosphonoacetate, nitromethane, and potassium carbonate (K_2CO_3) were obtained from Alfa Aesar. Sodium hydroxide and diethyl ether were purchased from Spectro-chem whereas DMF, THF, methanol, 1,4-dioxane, cyclopentanone and Pd/C (10%) were purchased from Sigma-Aldrich. For moisture sensitive reactions dry solvent has been used in the presence of N_2 or Ar gas. After completion of the reaction, column chromatography using silica (100-200 mesh) as immobile phase and hexane, ethyl acetate or toluene as a mobile phase was done for further purification.

2.1.2 General

The course of reactions was monitored by TLC. All ^{1}H and ^{13}C NMR spectra were set down on Bruker (400 MHz) instrument at 25 °C. Mass spectra were set down on Bruker instrument by using ESI positive mode. The NMR spectra of all intermediates and final compounds were analyzed by using ACD NMR software. The NMR samples were prepared in DMSO and $CDCl_3$. solvent. Chemical shift was expressed in the form of ppm (δ) relative to surplus solvents protons as internal standards ($CHCl_3$: δ 7.26, DMSO: δ = 2.50 For ^{1}H NMR; and $CHCl_3$: δ 77.00, DMSO: δ 39.50 for ^{13}C NMR).

Chapter 3

3: Synthesis of Compounds

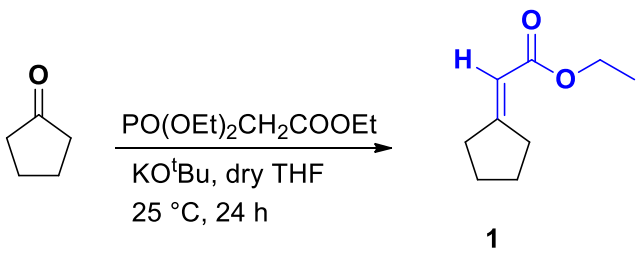
3.1. Synthesis of Compound **1**

In a clean and dry 100 mL R.B. flask, 2.93 g (26.14 mmol) of KO^{t}Bu was taken and 40 mL of dry THF was added and agitated for 10-15 min. Nitrogen gas was purged to provide an inert atmosphere. After 15-20 min, to the stirred reaction mixture, 2 mL of cyclopentanone was added dropwise and it was ice-cooled and 7.07 mL (35.65 mmol) of triethyl phosphonoacetate was added dropwise to the reaction solution for 5-10 min and the entire reaction solution was stirred overnight at 25 ℃. Once the reaction was completed, the reaction mixture was washed with water (30 mL) and the crude product was obtained with hexane (3×80 mL). The organic layer was washed with brine solution (2×30 mL) and dried over anhydrous Na_2SO_4. The excess of solvent was concentrated using rotavapor to yield crude product **1**. Column chromatography on silica gel (100-200 mesh) was further performed for purification using diethyl ether and hexane (0.2 : 9.8) as eluent. Yield = 2.61 g, 71%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.72 (s, 1H), 4.07 (q, J = 5.69 Hz, 2H), 2.70 (t, J = 5.82 Hz, 2H), 2.36 (t, J = 5.64 Hz, 2H), 1.67-1.58 (m, 4H), 1.20 (t, J = 5.70 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 168.92, 166.82, 111.65, 59.32, 35.88, 32.55, 26.38, 25.45, 14.31 ppm.

(ESI-MS, *m/z)* = $[M]^+$ calculated for $C_9H_{14}O_2$ 154.0990; found 154.1419.



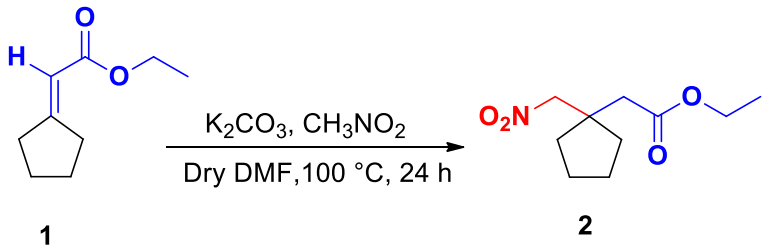
Scheme 1.1: Synthesis of compound **1**

3.2. Synthesis of Compound **2**

A condenser (without water circulation) was first set with a two neck R.B. flask. 2.82 g (20.47 mmol) of dry K_2CO_3 was transferred to the R.B. and immediately purged with argon gas. 60 mL of dry DMF was transferred to the RB and warmed at 100 °C for 2 h. After this, the mixture solution of 3.157 g (20.47 mmol) of compound **1** and 1.64 mL (30.70 mmol) of nitromethane was added dropwise using syringe about 20 min and the reaction mixture was stirred overnight at 100 ˚C. The reaction mixture was allowed to cool at 25 ℃ and then with ice water bath. Then it was acidified by concentrated hydrochloric acid once the reaction was completed. The combined layer extracted with hexane (3×50 mL) then washed with brine solution (2×30 mL) and parched over anhydrous Na_2SO_4. The excess of solvent was removed in rotavapor in to yield unpurified product **2**. Column chromatography on silica gel (100-200 mesh) was further performed for purification using diethyl ether and hexane (1: 9) as eluent. Yield = 3.34 g, 76%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.56 (s, 2H), 4.07 (q, J = 5.69 Hz, 2H), 2.48 (s, 2H), 1.64-1.55 (m, 8H), 1.19 (t, J = 5.71 Hz, 3H) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.43, 81.21, 60.45, 44.68, 40.45, 36.25, 24.06, 14.20 ppm.

(ESI-MS, *m/z)* = $[M + Na]^+$ determined for $C_{10}H_{17}NO_4Na$ 238.1050, found 238.1162.



Scheme 1.2: Synthesis of compound **2**

Generally, the precursor compound "Gababutin" can be synthesized from cyclopentanone as the starting material. It is treated with triethyl phosphonoacetate in presence of base KO^tBu, in presence of solvent THF. It undergoes reaction, to predominately produce *E*-alkene, thus it gives ethyl 2-cyclopentylideneacetate **1**. Compound **1** is treated with nitromethane in presence of base K_2CO_3 and solvent DMF, to yield ethyl 2-(1-(nitromethyl)cyclopentyl) acetate (**2**). Now, compound **2** will reacts with 10% Pd/C H_2 gas to give spiro lactam: 2-azaspiro[4.4] nonan-3-one **3**. Then compound **3** will be hydrolyzed by using 6 N HCl : 1,4-dioxane to give finally gababutin **4**. The resulting compound **4** will be treated with boc-anhydride in presence of 1N NaOH and 1,4-dioxane to give Boc-Gbn-OH **5**.

Chapter 4

Result and Discussion

4.1. Characterization

^{1}H and ^{13}C NMR spectral data

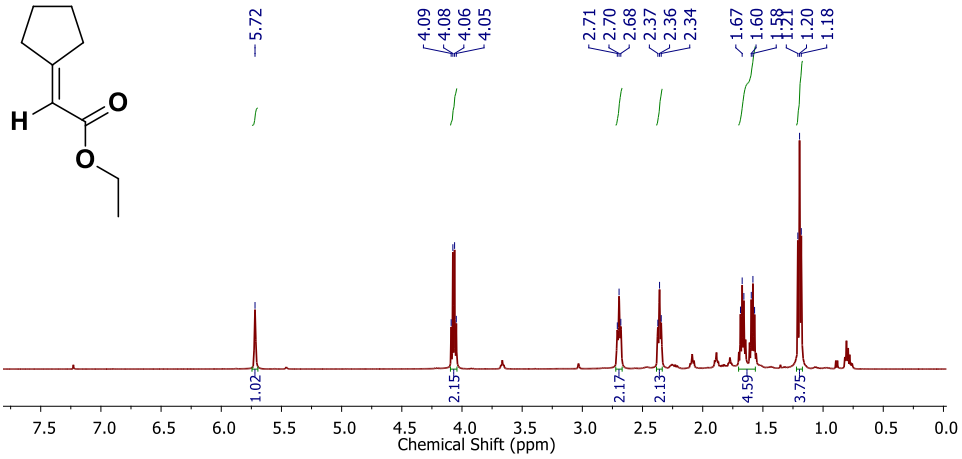


Fig.1. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **1**.

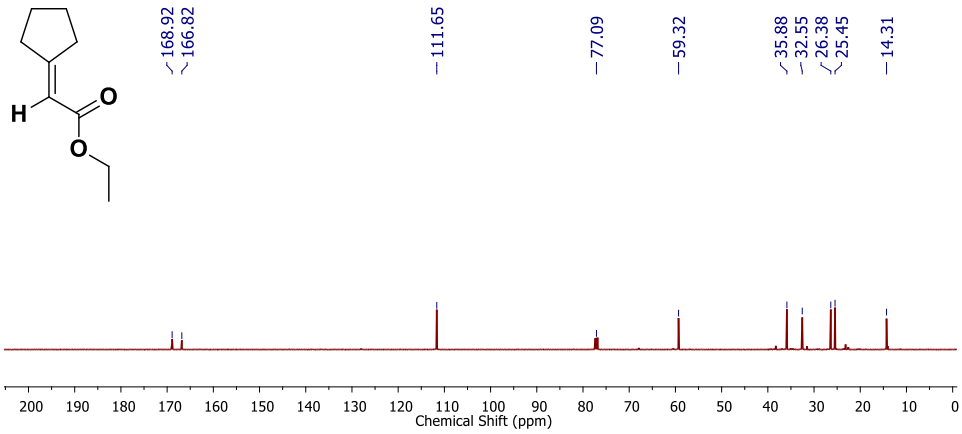


Fig. 2. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **1**.

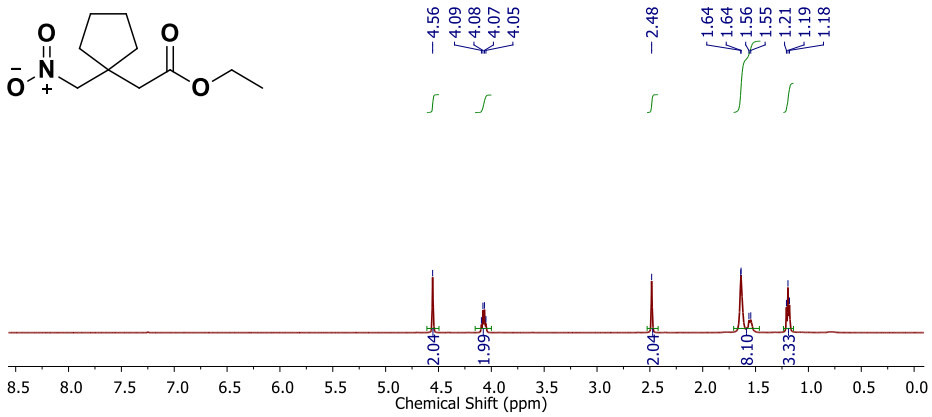


Fig. 3. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **2**.

Mass spectral data

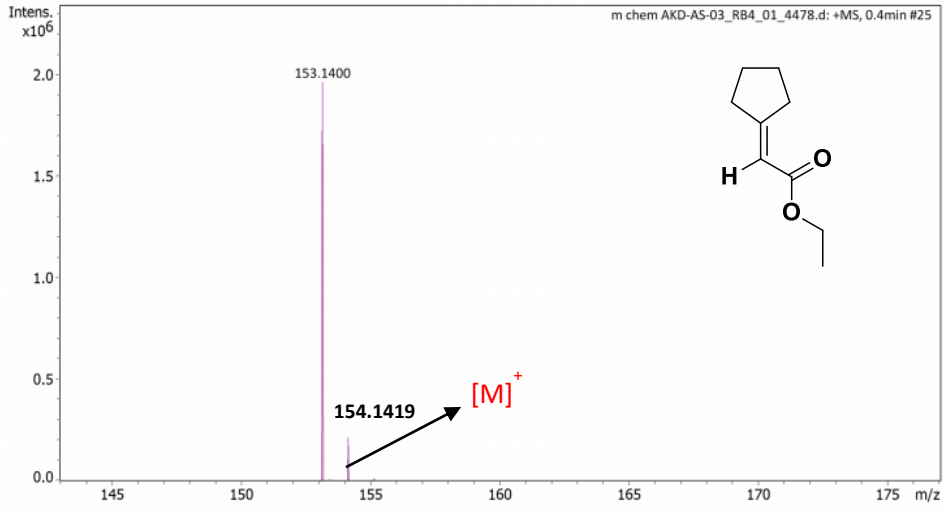


Fig. 4. Mass spectrum of compound **1;** determined for $C_9H_{14}O_2$ 154.0990; found 154.1419

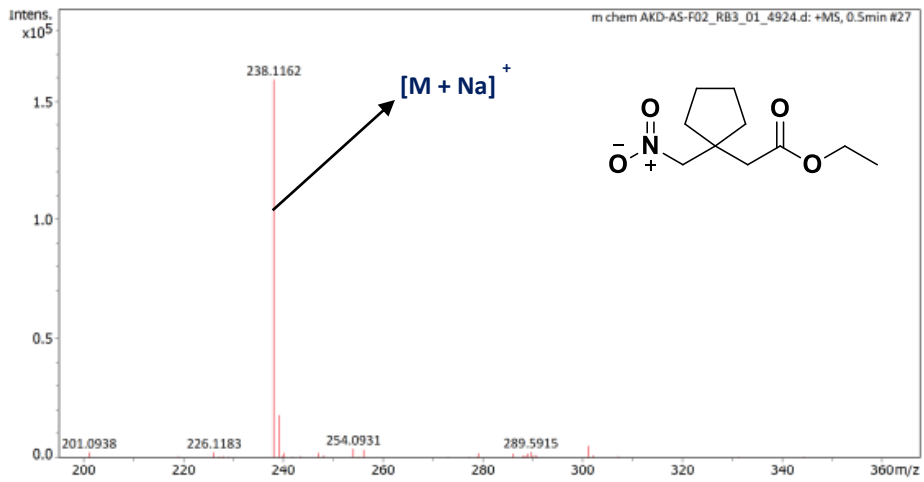


Fig. 5. Mass spectrum of compound **2;** determined for $C_{10}H_{17}NO_4Na$ 238.1050, found 238.1162

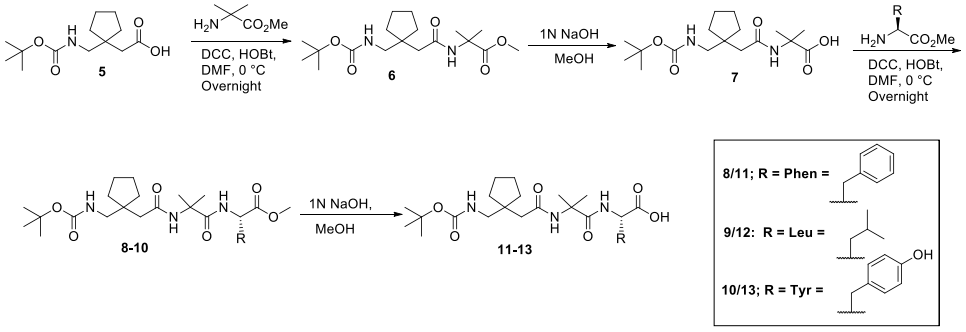
Chapter 5

5.1 Conclusion

I have successfully synthesized **1** and **2**. I have taken the precursor compound cyclopentanone and treated with triethyl phosphonoacetate, which gives yellowish ester that is resulted from Wittig modified reaction. The product is purified using column chromatography on silica gel (100-200 mesh) using diethyl ether and hexane (0.2: 9.8) as eluent and its yield is quite efficient, which is 71%. In the second step this above ester is treated with nitromethane, which undergoes 1,4-Michael addition reaction. A brownish nitro product is obtained, which is purified using column chromatography on silica gel (100-200 mesh using diethyl ether and hexane (1: 9) as eluent and yielding 76%. These above compounds were successfully synthesized and purified over column chromatography. NMR, and mass spectrometry was used for further characterization of these purified compounds.

5.2 Future Plans

In future I want to proceed with this unnatural amino acid to synthesized different form of unnatural amino acid Boc-Gbn-OH. Self-assembly pattern of this Boc-Gbn-OH based peptides will be investigated in both solution and solid state. I am going to study their supramolecular interactions both at solution and crystal phase.



Scheme 2: Synthetic scheme of gababutin based peptides.

After the synthesis of compound **4** (gababutin), I will proceed for the synthesis of hybrid tetrapeptides. In the very first step gababutin **4** will be neutralized by 1N NaOH. Then the N-terminal of the compound **4** will be protected with Boc by treating it with $(Boc)_2O$, it will thus results into the formation of Boc-Gbn-OH **5**. Then compound **5** will be used for the synthesis of peptides. Compound **5** will react with methyl ester of Aib, in presence of DCC, HOBt and solvent DMF, to give methyl protected peptide **6**. The hydrolysis of compound **6** with 2N NaOH and methanol will produce compound **7**. As the right end –COOH of peptide will be free, so it will react with methyl protected amino acids in presence of DCC, HOBt and DMF to produce dipeptide (**9-11**). Again compounds **8-10** will be hydrolyzed with 2N NaOH and will give compounds (**11-13**). Here we will study the self-assembled behavior for the three different R groups that is phenyl, leucine and tyrosine and will observed their self-aggregation at supramolecular level both at solid and solution state.

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