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Research Article

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Synthesis and Characterization of 4-[2'-(5'-Nitro) Imidazolyl] Benzoyl (N-Me) Leucine

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ABSTRACT

In the past two decades, a wide variety of bioactive peptides have been discovered. Many of the heterocyclic found to exhibit antifungal, antibacterial, cytotoxic, antineoplastic, insecticidal, anti-inflammatory, tyrosinase inhibitory and melanin production inhibitory activities.Imidazole has been drawn as promising structural units in the field of medicinal chemistry. Introduction of D-amino acids and N-methylation of amino acids like tyrosine, valine, alanine etc enhanced antimicrobial activity. Hence an attempt is made towards the sythesis of 5-nitroimidazolyl-benzoic acid derivative of N-methyl amino acids and peptide using solution phase technique of peptide synthesis.

Key words: Tyrosine, Valine, Alanine, Benzoic Acid, Imidazole

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INTRODUCTION

A great number of drugs are heterocyclic compounds, mostly are of synthetic origin, few have obtained from natural resources which include alkaloids, xanthines, cardiac glycosides, vitamins and several antibiotics. Heterocyclic derivatives having two nitrogen atoms oriented in, 1-3 position are endowed with wide spectrum of biological activities. Number of organo-sulphur and nitrogen containing compounds are present in living and non living system. Nitroimidazole derivatives were developed not only because of their novelty to structure but also because of novelty to action [1, 2].

N-methylated amino acids are commonly found in naturally occurring peptide antibiotics. The methylation of N-atom and the hydrogen bonding pattern of peptide containing these amino acids are different from that of unmethylated peptide. The N-methylated peptide antibiotics are found to possess enhanced activity ascompared to the unmethylated forms.Therefore, an attempt is made to synthesize a new bioactive series of 5-nitroimidazole derivatives of amino acids and peptides. Biological activity studies performed on these synthetic compounds proved to give good results [3, 4].

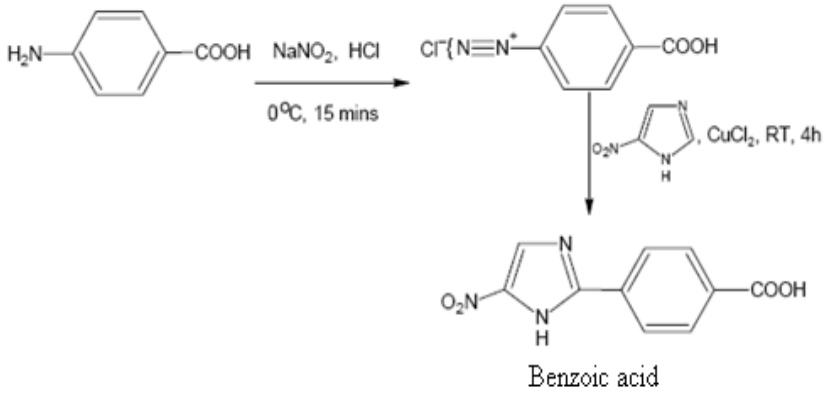
EXPERIMENTAL SECTION

2.1 Synthesis of N-methyl amino acids methyl ester:

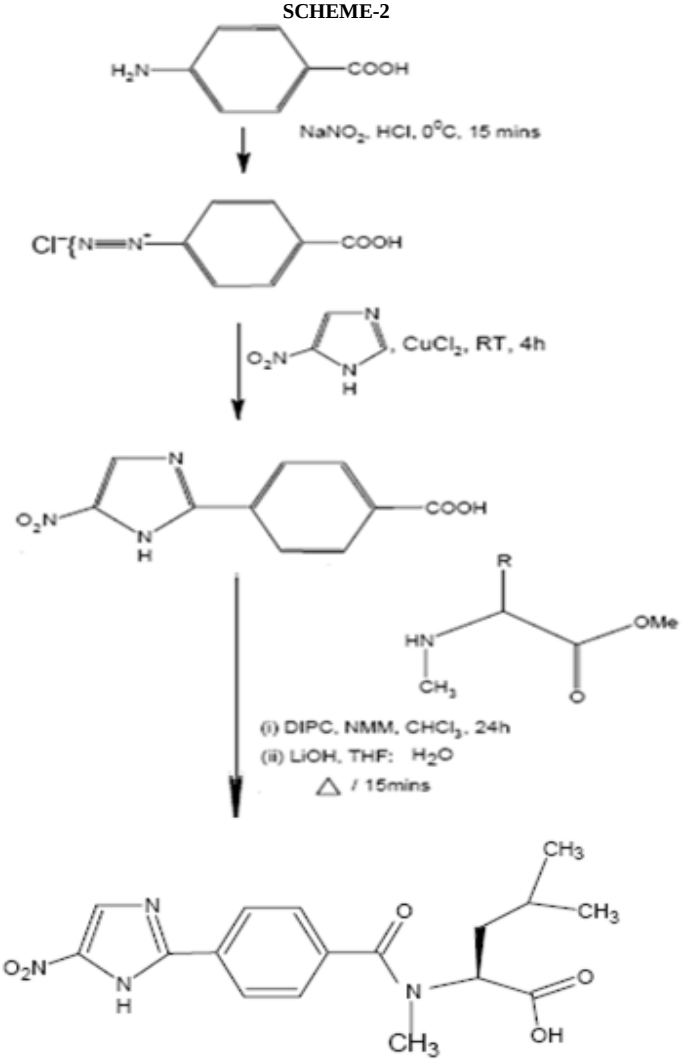
Amino acids were converted into the corresponding methyl ester hydrochloride using thionyl chloride and methanol. The amino end was then protected by introducing Boc-group using ditertiary butylpyrocarbonate and triethylamine to get Boc-L-amino methyl ester. N-methylation of this compound was done by treating with methyl iodide and

sodium hydride (Benoition method) to get Boc-(N-Me) amino methyl ester [5].

SCHEME-1



SCHEME-2



4-[2'-(5'-Nitro) Imidazolyl] Benzoyl (N-Me)Leucine

2.2 Preparation of4-[2-(5-nitro)imidzolyl] benzoic acid :
A mixture of p-amino benzoic acid (34.25 gms, 250 mmol), dilute hydrochloric acid (15%, 120ml) and water (150ml) was heated to get a clear solution**.** The solution was cooled to RT and diazotized by the addition of sodium nitrite solution (30%, 48ml)**.** The diazonium salt solution was filtered and to the filtrate, dilutes HCl (100ml) and nitroimidazole (250 mmol) and aqueous cupric chloride (5gms in 20ml of water) were added with stirring**.** Stirring was continued for 6 hrs and kept overnight in the refrigerator**.** The separated solid was collected by filtration and washed with water**.** The crude compound was crystallized from acetone to obtain pure of 4 [2-(5-nitro)imidazolyl] benzoic acid[6].

2.3 Preparation of 4-[2'-(5'-nitro) imidazolyl]benzoyl(N-Me)-Amino acid
To the (N-Me) amino acid methylester (7**.**0 mmol.) THF (20ml), added 4-[2'-(5'-nitro) imidazolyl]benzoic acid acid (1.631gms, 7**.**0 mmol.), DIPC, Et_3N (2.8ml) and stirred at room temp.for 24hr. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure, residue was dissolved in $CHCl_3$, washed with 10% $NaHCO_3$ (10ml) and 5% HCl (10ml), dried over anhydrous Na_2SO_4 and evaporated under vacuum to get the title compounds**.** The crude product was recrystallized from $CHCl_3$ and n-hexane [8, 9]**.**

2.4 Preliminary Analysis of the sample:
Thin-layer chromatography (TLC) was commonly used in the qualitative description of the complexity and composition of chemical mixtures.

Application of sample on TLC plates:
- The sample was applied to the chromatogram by repeated "spotting" above 1-2 cm from one end of the plate with a capillary tube.
- The most important precaution was not to apply spots below the level of the top of the solvent system in developing chamber

Developing solvent systems:
Development chamber was used for developing chromatogram. Chloroform: Methanol: Water 5:3:2 was the solvent system used for running TLC of these compounds.

Visualization of chromatogram:
After developing, the TLC plates were dried and then exposed to iodine vapours in a chamber, since chromalograms of many synthetic products were frequently observed by iodine vapors. R_f value was noted down. Purity of all the synthesized compounds including intermediates was checked by TLC on silica gel G plates. All compounds have shown only single spot indicating the completion of the reaction and thepurity of the product obtained.

$$R_f \text{ value} = \frac{\text{Distance traveled by solute front}}{\text{Distance traveled by solvent front}}$$

Table.1 Physical data of 4-[2'-(5' nitro) imidazolyl] benzoic acid

S.no	Product Name	Physical state	M.P(^{0}C)	% yield
1.	4-[2'-(5' nitro) imidazolyl]benzoic acid	Pale brown solid	256	21.49

Physicochemical analysis Table.2

S. no	**4-[2'-(5'-nitro)imidazolyl]benzoyl(N-Me)Leucine**	
1.	Mol. Formula	$C_{17}O_5N_4H_{20}$
2.	Mol. Weight	360
3.	Melting Point	268^{o}C
4.	Physical state	Light Brown
5.	R_f.Value	0.52
6.	Solvent System	$CHCl_3$: CH_3OH : H_2O (5:3:2)

RESULTS AND DISCUSSION

The synthesized new amino acid derivatives further studied for characterization of IR, NMR and Mass. To study the structure-activity relationship and to optimize the structure.

^{1}HNMR (300 MHz $COCl_3$) δ in ppm (fig. no 1):

δ 7.9 (1H, m, - NH), δ 7.7 (1H, m, Aromatic-H) δ 7.4 (2H, m, Aromatic-H) δ 6.9 (2H, m, Aromatic-H) δ, 4.8 (1H, m, α-H),δ3.8 (1H, s, $COCH_3$), δ2.9 (1H, s, -N-CH_3),δ1.4 (2H, d, β-CH_2 of Leucine),δ1.2 (1H, m, γ -H) δ0.95 (6H, d, CH_3 group of Leucine

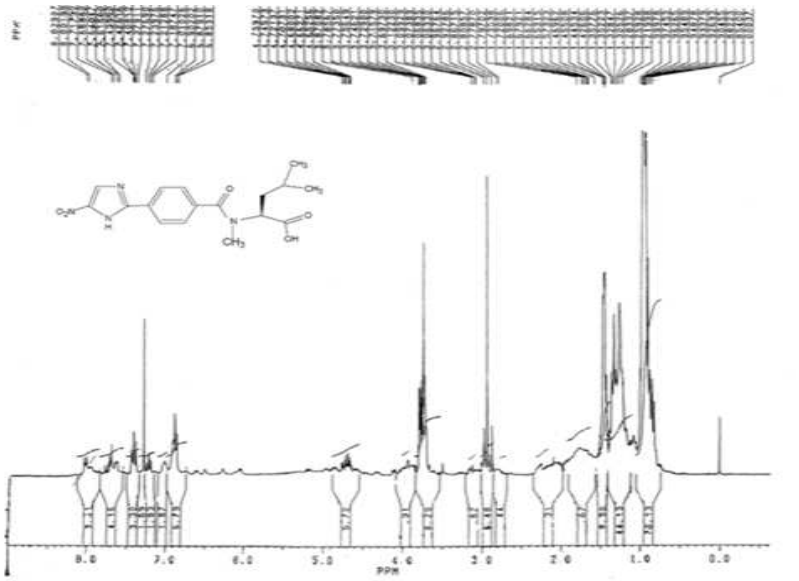


Fig.no 1 : 1HNMR of 4-[2'-(5'-nitro)imidazolyl]benzoyl(N-Me)Leucine

IR spectrum ($CHCl_3$) in cm-1(fig.no. 2)

Peak at 3305.5 corresponds to NH and Aromatic C-H stretching.
Peak at 2930.9 corresponds to Aliphatic C-H stretching.
Peak at 2870.1 corresponds to Aliphatic C-H stretching.
Peak at 1707.3 corresponds to C=O (carbonyl) stretching.
Peak at 1609.0 corresponds to C=O (amide) stretching.
Peak at 1544.7 corresponds to N-H bending.
Peakat1508.2 corresponds to C-H bending.

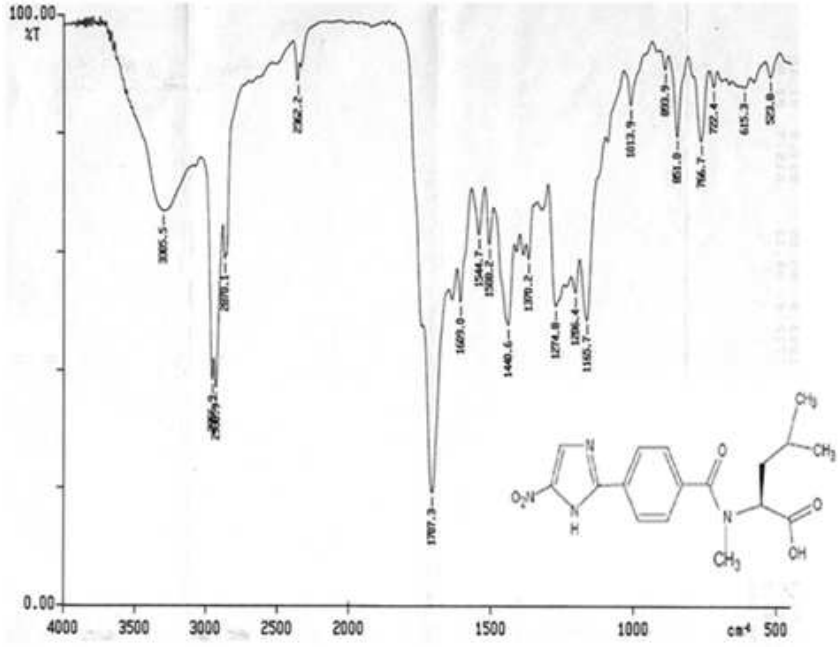


Fig.no 2 IR spectrum of 4-[2'-(5'-nitro)imidazolyl]benzoyl(N-Me)Leucine

Mass spectrum in m/z (fig.no 5):
(m/z): 375 correspond to molecular ion peak

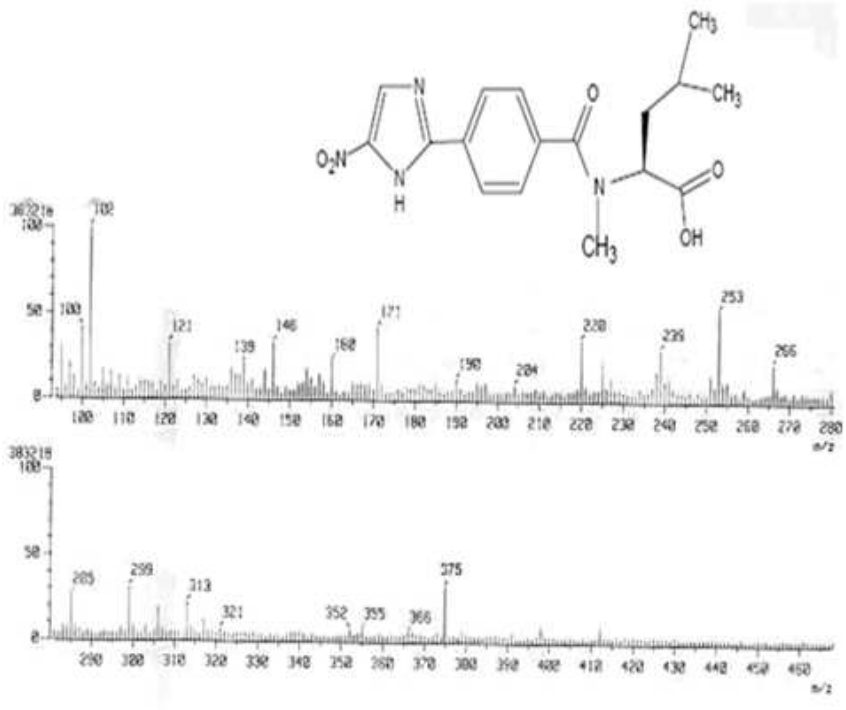


Fig.no 3 Mass spectrum of 4-[2'-(5'-nitro)imidazolyl]benzoyl(N-Me)Leucine

CONCLUSION

The synthesized 4-[2'-(5'-nitro)imidazolyl] benzoyl(N-Me) amino acid derivative was characterized by IR, NMR and Mass spectral data. By this studies find the structure- activity relationship and to optimize the structure. The synthesized amino acid derivative i.e., 4-[2'-(5'-Nitro) imidazolyl] benzoyl N-Me) leucine was to be confirmed by spectral analysis.

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I am indebted to my parents for their inspiration and encouragement given to me during this work with deep appreciation for their determination and enthusiasm at each and every front of my life to transform my dreams into reality. I am very thankful and prevail age to my deep sense of gratitude to Dr. Abdul Mohammed Bari, M.pharm., Ph.D, Director of Bright laboratories, Hyderabad.

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