



Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

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

Ramesh Dhani

Department of Pharmaceutical Chemistry, Oil Technological Research Institute, Jawaharlal Nehru Technological University Anantapur, Andhra Pradesh, India.

ABSTRACT

Introduction of D-amino acids and N-methylation of amino acids like tyrosine, valine, alanine etc enhanced antimicrobial activity. Condensation of heterocyclic moieties viz nicotinic acid, thiazole, coumarin, quinoline, furan, imidazole etc. with amino acids and peptides resulted in compounds with potent biological activities. 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. The new threonine derivatives compounds are characterized by using IR, H^1 NMR and mass spectroscopy.

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

INTRODUCTION

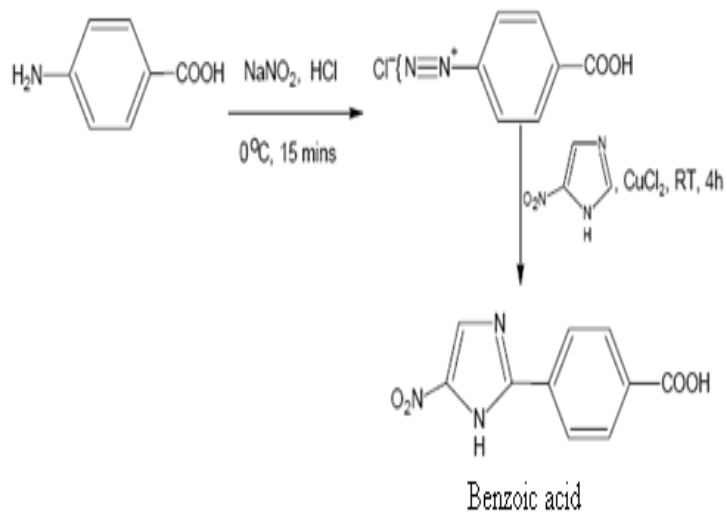
A great number of drugs are heterocyclic compounds, mostly are of synthetic origin, few have obtained from natural resources which include alkaloids, xanthenes, cardiac glycosides, vitamins and several antibiotics. Heterocyclic derivatives having two nitrogen atoms oriented in, 1-3 position are endowed 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. The N-methylated peptide antibiotics are found to possess enhanced activity as compared to the un methylated 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 [2, 4].

EXPERIMENTAL SECTION

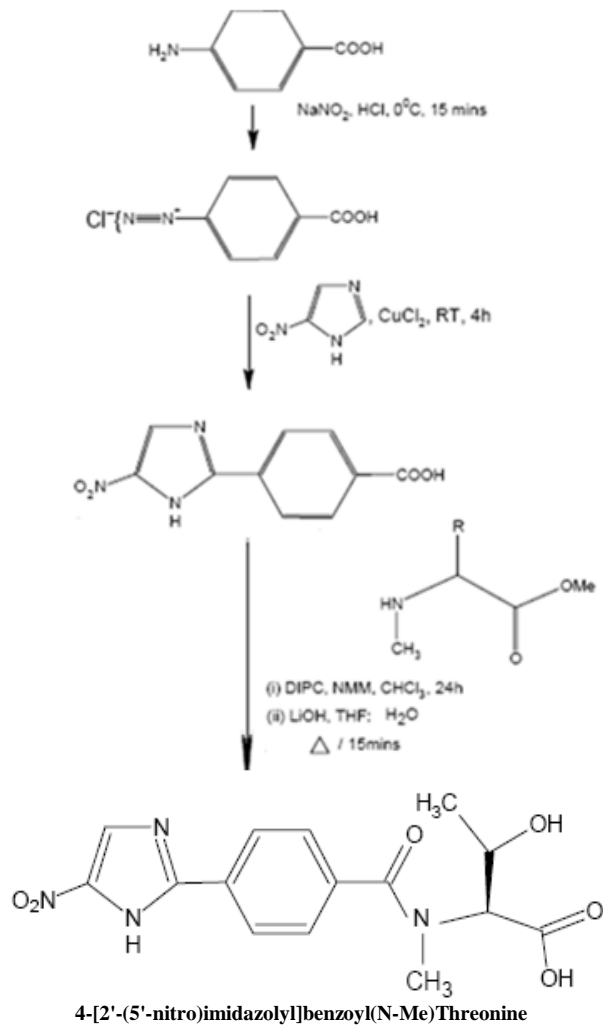
2.1 Synthesis of N-methyl amino acids methyl ester:

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 (Benion method) to get Boc-(N-Me) amino methyl ester [1, 5].

SCHEME-1



SCHEME-2



2.2 Preparation of 4-[2-(5-nitro)imidazolyl] 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, dilute 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 [3,6].

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 (1.631gms, 7.0 mmol.), DIPC, Et₃N (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 CHCl₃, washed with 10% NaHCO₃ (10ml) and 5% HCl (10ml), dried over anhydrous Na₂SO₄ and evaporated under vacuum to get the title compounds. The crude product was recrystallized from CHCl₃ 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 chromatograms 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 the purity 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

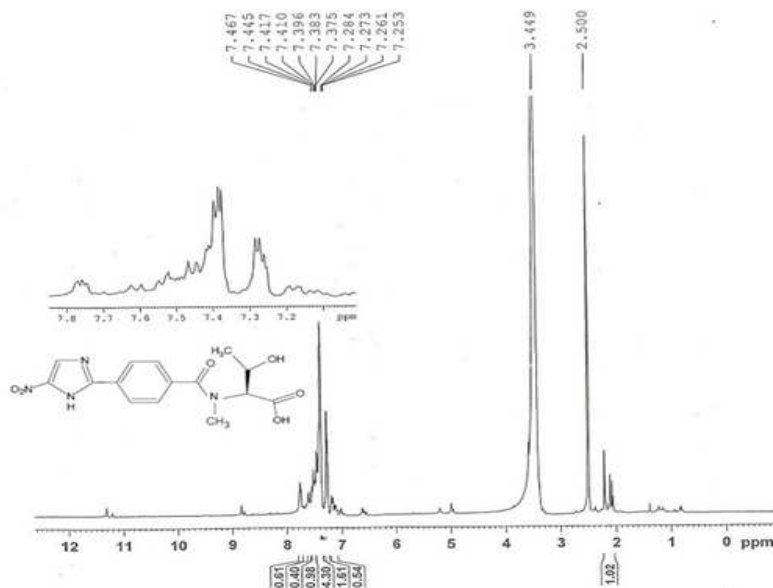
S.no	4-[2'-(5'-nitro)imidazolyl] benzoyl(N-Me)Phenyl alanine	
1.	Mol. Formula	C ₁₅ O ₆ N ₄ H ₁₈
2.	Mol. Weight	350
3.	Melting Point	173°C
4.	Physical state	Brown Solid
5.	R _f .Value	0.57
6.	Solvent System	CHCl ₃ : CH ₃ OH : H ₂ O (5:3:2)

RESULTS AND DISCUSSION

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

¹H NMR (300 MHz, CDCl₃) δ in ppm (Fig.no.1):

δ 7.6(1H, m, -NH), δ 7.4 (1H, m, Aromatic-H) δ 7.2 (2H, m, Aromatic-H), δ 6.9 (2H, m, Aromatic-H) δ 4.8 (1H, m, α-H), δ 3.8 (1H, s, COCH₃) δ 2.9 (1H, s, -N-CH₃) δ 1.4 (2H, d, β-CH₂), δ 1.2 (1H, m, γ -H), δ 0.95 (6H, d, CH₃ group) of threonine.

**IR (CHCl₃) in cm⁻¹ (Fig.no.2):**

Peak at 3565.22 corresponds to NH and Aromatic C-H stretching

Peak at 2818.14 corresponds to Aliphatic C-H stretching

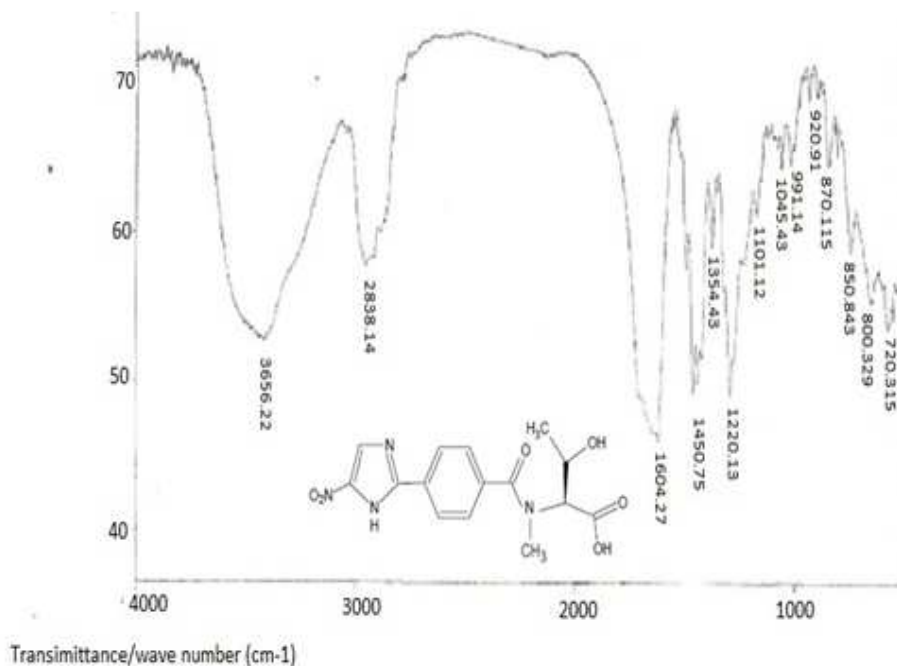
Peak at 1604.27 corresponds to Aliphatic C-H stretching

Peak at 1450.75 corresponds to C=O (carbonyl) stretching

Peak at 1354.43 corresponds to C=O (amide) stretching

Peak at 1220.13 corresponds to N-H bending

Peak at 1102.11 corresponds to C-H bending.



CONCLUSION

The new 4-[2'-(5'-nitro) imidazolyl] benzoyl (N-Me) amino acid derivatives was synthesized and 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) threonine was confirmed by physicochemical and spectral analysis.

Acknowledgement

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.

REFERENCES

- [1] Bansal RK., *Indian Journal Chemistry*, vol.12,Pg. no 34-36, **1996**.
- [2] Belagali SL, Harish K, Boja P., *Indian Journal Chemistry*, vol.6, pg no.378-387, **1998**.
- [3] Belagali SL and Himaja M, *Indian Journal Heterocycle Chemistry*, vol.22, pg no.8-11, **1998**.
- [4] Stanchev M, Tabakova S, Vedenov VG, Galovinsky E, Jung G, *Arch Pharm Wheinhein*, vol.19, pg no.332 – 292, **1999**.
- [5] Boja P, Belagali SL, Harish K, Holla BS and Gonsalves R., *Indian Journal Heterocycle Chemistry*, vol.3, pg no.263, **2000**.
- [6] Belagali SL, Mathew T, Himaja M, Kocienski P. *Indian Journal Chemistry*,vol 34, pg no 45-57, **1995**.
- [7] Benoiton NL, Akyusekli D, Chen. FM, *International Journal of Protein Research*,vol 45, pg no 466-470,**1995**.
- [8] Bauer AW, Kirby WM, Shersis JC, Turck M, *Indian Journal of chemistry*, vol 45,pg no493-496,**1996**.
- [9] Himaja M. Rajiv T, Geetha P, Harish K, Boja, *Boll Chim. Farmaceutico-Anno*, vol.13, pg.no168-175, **1999**.