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Synthesis and characterization of amino acid coupled benzimidazole based ligands

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ABSTRACT

New 'N,N,O' donor tridentate ligands have been synthesised by the condensation of 2-chloromethyl benzimidazole with amino acids, alanine, valine, leucine and phenylalanine in 1:1 stoichiometry and structurally characterized by FT-IR and HRMS.

Key words: Benzimidazole, Amino-acid and heterocyclic derivatives.

INTRODUCTION

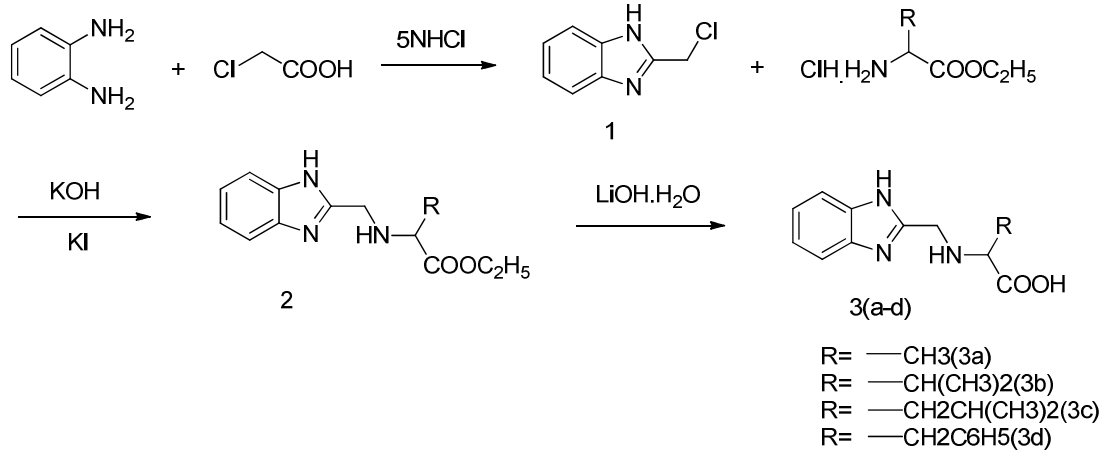
Benzimidazole is an aromatic bicyclic molecule ,where in benzene ring is fused to the 4,5 positions of the imidazole .It is found in many important group of substances [1-9] with applications in drug and ligand design[10,11]. It undergoes substitution reactions on benzene ring or on nitrogen atom to have functional groups like carboxylic, acyl , hydroxyl, thiol or sulfide groups in the molecule.Present work has been carriedout to synthesise a new class of benzimidazole derivatives by using most common amino acids . The both amine and carboxylic acid groups of amino-acid are retained in the resultant final molecule,These groups are beneficial for their applications in coordination chemistry as 'N,N,O' donor ligands.

MATERIALS AND METHODS

2.1 Materials :The chemicals, Chloroacetic acid (Aldrich), orthophenelinediamine (OPDA) Aldrich),L-Alanine methyl ester hydrochloride(Aldrich), L-Valine methyl ester hydrochloride(Aldrich), L-Leucine methyl ester hydrochloride(Aldrich), L-Phenylalanine methyl ester hydrochloride(Aldrich),hydrochloric acid (Merck), aqueous ammonia (Aldrich), potassium hydroxide (Sdfine), potassium iodide (Merck) and the solvents, methanol, ethylacetate, ethanol were of reagent grade.

2.2 Instrumental:
IR spectra were recorded on a JASCO FT-IR 5300 spectrometer and HRMS by MassLynx SCN781.

Synthetic Scheme:



Synthesis of 2-(((1H-benzo[d]imidazol-2-yl)methyl)amino)substituted acid derivatives:
Synthesis of 2-Chloromethyl-1H-benzimidazole (**1**)
In a 250 ml three necked flask, chloroacetic acid, 7.5 g (80.0 mmol) and o- phenylenediamine, 7.5 g (70.0 mmol) were dissolved in 60 ml of 5N HCl. The reaction mixture was refluxed for about 8 hrs at 100 °C with constant stirring[12] and the reaction was monitored by TLC. The reaction mixture was then cooled to 5 °C and neutralized with ammonium hydroxide solution.Light brown colour precipitate formed was filtered, washed with cold water to remove traces of hydrochloric acid and dried. It was re-crystallised from methanol to obtain pure compound **1**, 9.8g in 85% yield. MS(ESI): m/z 167 ($[M+H]^+$).

Synthesis of ethyl 2-(((1H-benzo[d]imidazol-2-yl)methyl)amino)substituted ester derivatives(**2a-d**):2-chloromethyl benzimidazole (30.0 mmol) and appropriate aminoacid methylester (30 mmol) were dissolved in 10vol of dry ethanol, to which potassium iodide (30.0 mmol) was added. The reaction mixture was refluxed at 80 °C with constant stirring for about 3h, to which potassium hydroxide (30.0 mmol) was added and continued for another 3h [13] .Reaction was monitored by TLC and the reaction mass was cooled to room temperature and poured into crushed ice.The gummy precipitate formed was extracted with ethylacetate. Extracted ethylacetate solution was evaporated completely under reduced pressure to get ethyl 2-(((1H-benzo[d]imidazol-2-yl)methyl)amino)substituted ester derivatives(**2 a-d**),in Quantitative Yield.

*Synthesis of 2-(((1H-benzo[d]imidazol-2-yl)methyl)amino)substituted acid derivatives(**3a-d**):* Compound, **2a-d** (32.0 mmol) was dissolved in 5vol methanol, to which $LiOH.H_2O$ (96.0 mmol) in 10ml water was added. Reaction mixture was stirred for about 12h .Reaction was monitored by TLC (chloroform : methanol (9:1)) for completion of the reaction. The reaction mixture was evaporated to 10 mL under reduced pressure,to which 20 mL of water was added and washed with ethyl acetate to remove impurities. Finally reaction mass pH was adjusted to neutral with 2N HCl. Compound (**3a-d)** precipitated out was filtered and dried.

2-(((1H-benzo[d]imidazol-2-yl)methyl)amino)propanoic acid(3a): Yield: 76%; mp 215–217 °C; HRMS: (*m*/*z*) 220.1081 (M + H).
2-(((1H-benzo[d]imidazol-2-yl)methyl)amino)-3-methylbutanoic acid(3b): Yield: 65%; mp 254–256 °C; HRMS: (*m*/*z*) 248.1402 (M + H).
2-(((1H-benzo[d]imidazol-2-yl)methyl)amino)-4-methylpentanoic acid(3c): Yield: 62%; mp 259–261 °C; HRMS: (*m*/*z*) 262.1555 (M + H).
2-(((1H-benzo[d]imidazol-2-yl)methyl)amino)-3-phenylpropanoic acid(3d): Yield: 71%; mp 244–246 °C; HRMS: (*m*/*z*) 296.1317 (M + H).

RESULTS AND DISSCUSSION

All the synthesized compounds were found to be stable in air and non-hygroscopic in nature. The complexes are insoluble in common organic solvents but are soluble in water, DMSO and DMF.

Structures:

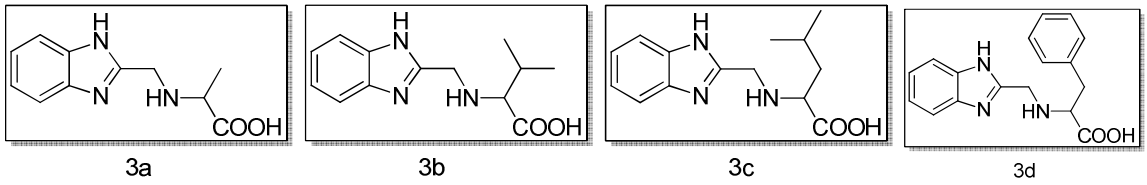
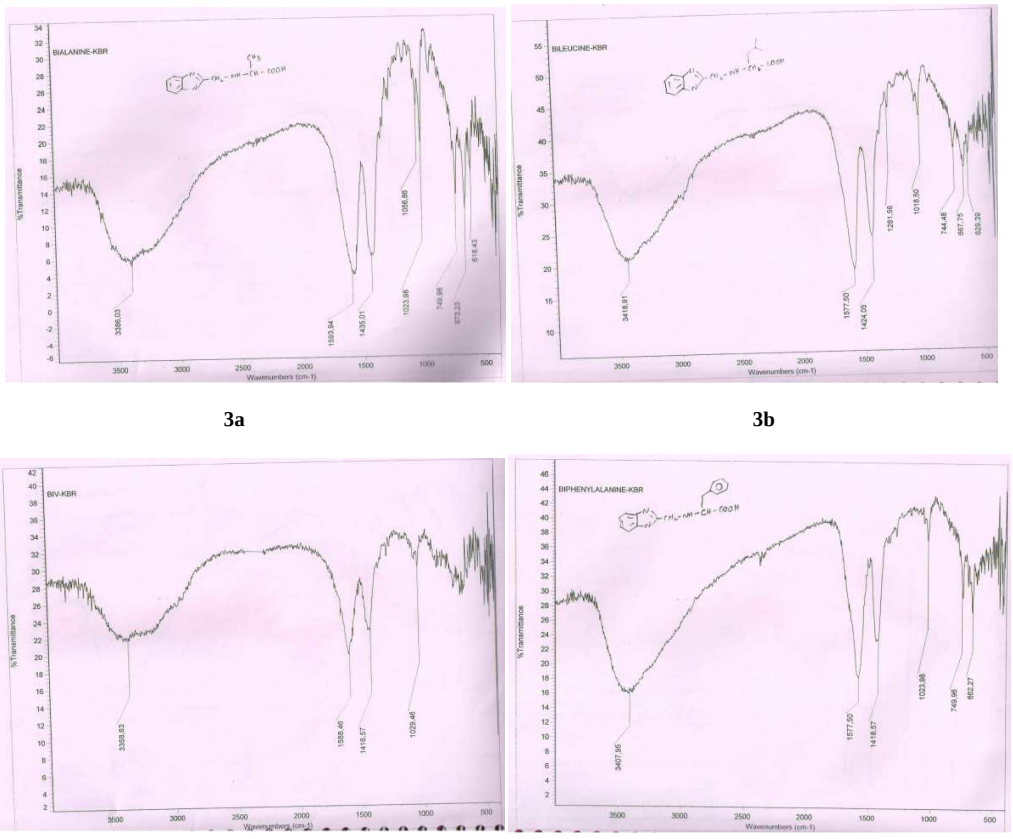


Fig.1.Structures of (a) 3a (b) 3b (c) 3c (d) 3d

3.1 Fourier Transform-Infrared (FT-IR) spectra:

Compound	ν(NH_2)	ν(C═N)	ν(C−N)	ν(COO^-)$_{as}$
3a	3386	1593	1023	1435
3b	3358	1593	1029	1418
3c	3418	1577	1018	1424
3d	3407	1577	1023	1418



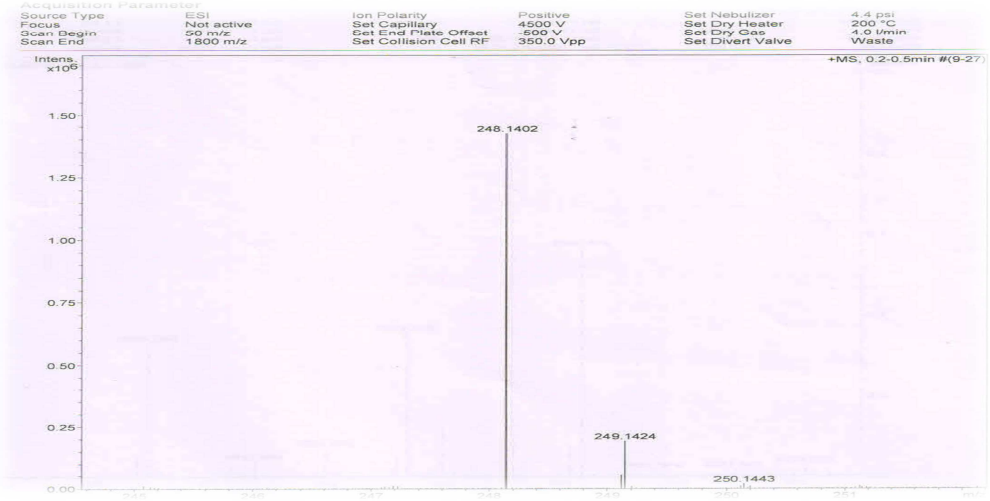
3a **3b**

3c **3d**

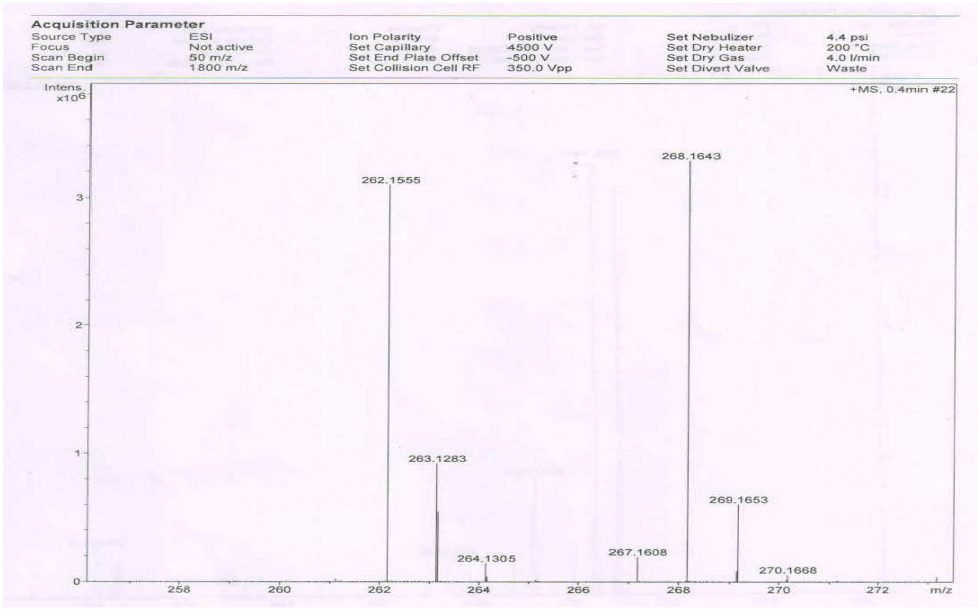
Fig.2.IR Spectrum of (a) 3a (b) 3b (c) 3c (d) 3d


Acquisition Parameter
Source Type ESI
Focus Not active
Scan Begin 50 m/z
Scan End 1500 m/z
Ion Polarity Positive
Set Capillary 4500 V
Set End Plate Offset -500 V
Set Collision Cell RF 350.0 Vpp
Set Nebulizer 4.4 psi
Set Dry Heater 180 °C
Set Dry Gas 4.0 L/min
Set Divert Valve Waste
Intens.
x10^4
+MS, 0.7min #38
220.1081
221.1112
218.0937
223.0944
224.1001
m/z

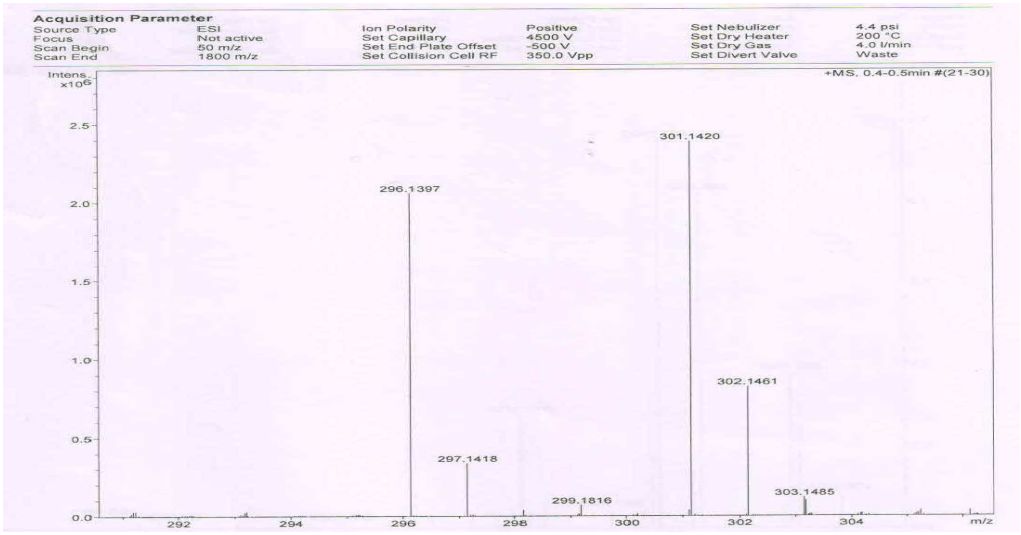
3a


Source Type ESI
Focus Not active
Scan Begin 50 m/z
Scan End 1800 m/z
Ion Polarity Positive
Set Capillary 4500 V
Set End Plate Offset -500 V
Set Collision Cell RF 350.0 Vpp
Set Nebulizer 4.4 psi
Set Dry Heater 200 °C
Set Dry Gas 4.0 L/min
Set Divert Valve Waste
Intens.
x10^5
+MS, 0.2-0.5min #(9-27)
248.1402
249.1424
250.1443

3b



3c



3d

Fig.3.HRMS of (a) 3a (b) 3b (c) 3c (d) 3d

CONCLUSION

This work represents a viable synthesis of 2-aminomethyl-benzimidazoles derivatives with overall yield 64-52% .This method follow mild reaction conditions and simple experimental technique under green conditions.The resultant compounds can act as tridentate 'N,N,O' donor ligands.

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