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Synthesis of novel amino acid derivative of 7-AVCA

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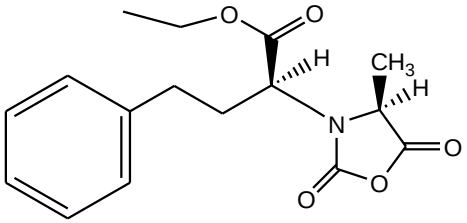
Abstract: *In this study, synthesis of novel β-Lactam derivative comprising of 7-AVCA and NEPA-NCA [(R)-ethyl 2-(((S)-4-methyl-2, 5-dioxo oxazolidin-3-yl)methyl)-4-phenylbutanoate] is disclosed. The synthesis of intended compound has been characterized and confirmed by 1H-NMR, 13C-NMR and Mass.*
Key words: *β-Lactam, NEPA-NCA, 7-AVCA*

I. Introduction

We have reported "Synthesis of novel β-Lactam derivative and it's application" in IOSR Journal of Applied Chemistry (IOSR-JAC) e-ISSN: 2278-5736.Volume 7, Issue 7 Ver. I. (July. 2014), PP 16-20 and subsequently two more novel amino acid derivatives of β-Lactam compounds have been also published in the same journal. In continuation of this research, one more novel β-Lactam derivative amino acid was synthesized.

NEPA-NCA (III) i.e. [(S)-ethyl-2-((S)-4-methyl-2, 5-dioxooxazolidin-3-yl)-4-phenylbutanoate], which is an important side chain moiety in field of medicinal chemistry and it is used in the synthesis of many Angiotensin-I converting enzyme (ACE) Inhibitors) i.e cardiovascular drugs. The significance of NEPA-NCA in synthesis of various ACE inhibitors, e.g.Ramipril, Trandolapril, Delapril, Imidapril, and Quinapril.HCl has been well demonstrated in literature justifying their potential as antihypertensive role. Several chemical substances have been reported where different amino acids have been condensed with NEPA-NCA to yield product of therapeutic use.



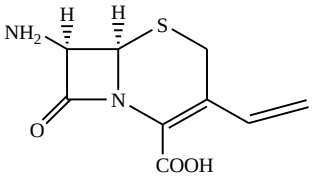
NEPA-NCA

$C_{17}H_{21}NO_5$
Mol. Wt.: 319.35

There is one more class of amino acids known as β-Lactam compound (beta-Lactam antibiotics). β-Lactam antibiotics are a particular class of antibiotics, including all antibiotic agents that contain a β-Lactam ring in their chemical structures.

7-AVCA i.e. (6R, 7R)-7-((S)-2-((S)-1-ethoxy-1-oxo-4-phenylbutan-2-ylamino)propanamido)-8-oxo-3-vinyl-5-thia-1-aza-bicyclo[4,2,0]oct-2-ene-2-carboxylic acid is a β-lactam compound and it is a key amino acid in the preparation of cephalosporin antibiotics and their intermediates. It is used in preparation of cefixime and cefdinir. All these are third generation cephalosporins. Third-generation cephalosporins are broad-spectrum antimicrobial agents which are useful in a variety of illness. Their proven record of clinical efficacy, favorable pharmacokinetics, and low frequency of adversarial effects make third-generation cephalosporins the preferred antibiotic in several clinical situations.

7-AVCA i.e. [(6R,7R)-7-amino-8-oxo-3-vinyl-5-thia-1-aza-bicyclo [4,2,0]oct-2-ene-2-carboxylic acid having the following structure;



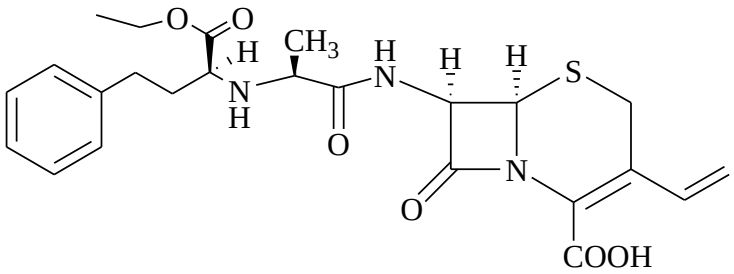
7-AVCA

$C_9H_{10}N_2O_3S$
Mol. Wt.: 226.25

(6*R*,7*R*)-7-amino-8-oxo-3-vinyl-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid

The role of NEPA-NCA has been well discovered in literature justifying their role as antihypertensive property. Similarly 7-AVCA has been also used as precursor of potential antibacterial drug. It was our interest to develop a protocol using to synthesize a novel β-Lactam derivative compound using NEPA-NCA & 7-AVCA, which may yield into the preparation of a novel β-Lactam derivative and may carry significant biological activity.

So, the molecule (Compound-C) (M.F. $C_{24}H_{29}N_3O_6S$), chemical name:[(6R,7R)-7-((S)-2-((S)-1-ethoxy-1-oxo-4-phenylbutan-2-ylamino)propanamido)-8-oxo-3-vinyl-5-thia-1-aza-bicyclo[4,2,0]oct-2-ene-2-carboxylic acid] has been synthesized by reaction of NEPA-NCA (III), chemical name: [(S)-ethyl-2-((S)-4-methyl-2,5-dioxooxazolidin-3-yl)-4-phenylbutanoate] (M.F. $C_{16}H_{19}NO_5$) with cephalosporin intermediate 7-AVCA (I), chemical name: [(6R,7R)-7-amino-8-oxo-3-vinyl-5-thia-1-aza-bicyclo[4,2,0]oct-2-ene-2-carboxylic acid] (M.F.$C_9H_{10}N_2O_3S$) in MDC (dichloromethane) as solvent. (Scheme-1)



Comp-C

$C_{24}H_{29}N_3O_6S$
Mol. Wt.: 487.57

II. Experimentation

A suspension of (6R,7R)-7-amino-8-oxo-3-vinyl-5-thia-1-aza-bicyclo [4,2,0]oct-2-ene-2-carboxylic acid i.e. 7-AVCA (I) (20 g; 88.4 milimoles) and dichloromethane (300 mL) was heated to reflux with 97.24 milimoles of hexamethyldisilazane (HMDS) and 35.36 milimoles of trimethylchlorosilane (TMCS) for 4-6 hours. The solution containing(6R,7R)-trimethylsilyl-8-oxo-7-(trimethylsilylamino)-3-vinyl-5-thia-1-aza-bicyclo[4,2,0]oct-2-ene-2-carboxylate (II) i.e. silylated 7-AVCA was gradually cooled to room temperature (20-30°C) and subsequently added 106.08 milimoles of compound (III) i.e. NEPA-NCA. The above mixture was stirred for 2-3 hours then added water (250 mL) and tetrahydrofuran (125 mL) over a period of 10-20 minutes. The mixture was stirred at the same temperature for 30 to 60 minutes to precipitate the product. Filtered the material and washed with dichloromethane (50 mL) followed by water (50 mL) twice. Material was dried under vacuum at 35-45°C for 4-6 hours (Yield 80% molar).

III. Result & Discussion

Spectral analysis was performed to characterize the compound-C. The characterization of spectral data confirms the structure of product compound-C. 1H-NMR (400 MHz), 13C-NMR (300 MHz) and Mass were carried out to confirm the structure of this compound.

The novel β-Lactam derivative (compound-C) exhibit distinct spectral properties as elucidated by 1H-NMR, 13C-NMR and Mass spectra. 1H-NMR, 13C-NMR, IR and MASS spectral data of compound (C) are in Table-1, 2 and 3 respectively.

The stability of compound-C was studied at 5±3°C under dry condition and found that Compound-C has substantial stability upon storage under dry condition at low temperature (2-8°C). However the product molecule is sensitive to moisture.

The above mentioned compound-C may possess antibacterial activity; the screening of this compound may confirm its antihypertensive property also.

Acknowledgements

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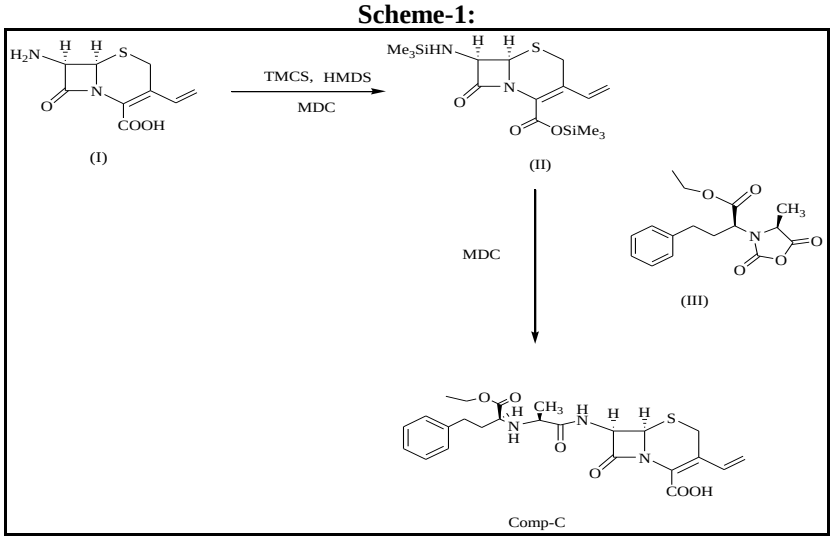
Scheme-1:



Chemical Structure:

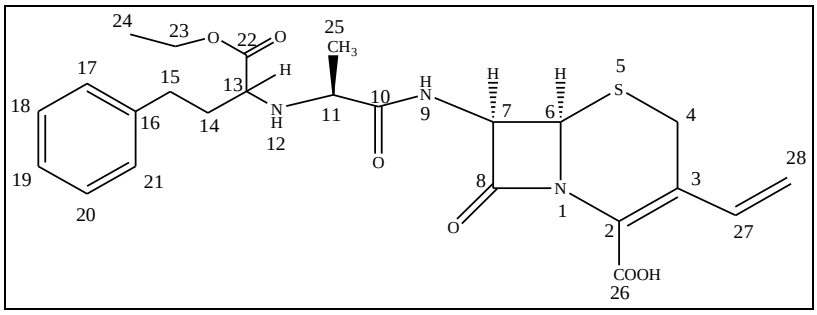


Table-1: 1H NMR: In D_2O

Chemical shift (δ ppm)	Assignments	
1.891-1.962	(d, 3H)	H-25
2.014 -2.123	(t, 3H)	H-24
2.391-2.412	(m,2H)	H-14
2.721 – 2.874	(t, 2H)	H-15
3.365-3.479	(d, 1H	H-4
3.612-3.723	(d, 1H)	
3.711-3.831	(t, 1H)	H-13
4.016-4.119	(q, 1H)	H-11
4.239-4.381	(q, 2H)	H-23
4.797– 4.921	(d, 1H)	H-6
5.017-5.224	(m, 2H)	H-28
5.293-5.397	(d, 1H)	H-7
5.402-5.412	(m, 1H)	H-27
5.418 - 5.460	(m, 1H)	H-19
5.931-6.021	(m, 2H)	H-17, H-21
6.141 - 6.259	(m, 2H)	H-18, H-20

Table-2: 13C NMR

Chemical shift (δ ppm)	Carbon assignment
19.14	C-24
23.68	C-25
53.38	C-4
57.86	C-15
59.25	C-14
62.12	C-11
62.51	C-13
62.92	C-6
63.69	C-7
66.13	C-23
114.21	C-28
117.29	C-2
124.60	C-19
128.15	C-17, C-21
130.32	C-18, C-20
131.18	C-3
134.58	C-16
135.75	C-27
167.21	C-26
169.15	C-8
170.88	C-22
174.56	C-10

Table-3: Mass: ESI mode, M.F. $C_{24}H_{29}N_3O_6S$: calculated: 487.57

m/z (amu)	Assignment
488.5	$[M+H]^+$