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"Synthesis of novel amino acid [(6R, 7R)-7-((S)-2-((S)-1-ethoxy-1-oxo-4-phenylbutan-2-ylamino) propanamido)-3-methyl-8-oxo-5-thia-1-aza-bicyclo[4,2,0]oct-2-ene-2-carboxylicacid]"

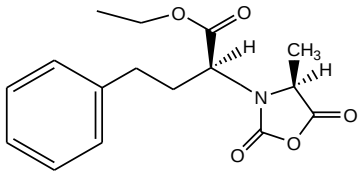
Dr. Sarita Shrivastava*, Amulya Ranjan, Niraj Kumar Tripathi
Dept. of Chemistry, Institute for Excellence in Higher Education (IEHE), Bhopal-M.P. (India)

Abstract: *In this study, synthesis of novel β-Lactam derivative comprising of 7-ADCA 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-ADCA*

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 "Novel β-Lactam derivative: Synthesis and application" in the same journal IOSR-JAC e-ISSN: 2278-5736. Volume 7, Issue 10 Ver. I. (Oct. 2014), PP 01-05. In continuation of this research another 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-phenyl butanoate], is an important side chain component used in the synthesis various cardiovascular drugs. NEPA-NCA, is a well-known chemical compound used in pharmaceutical industry, which plays a substantial role in synthesizing Angiotensin-I converting enzyme (ACE) Inhibitors e.g. delapril, enalapril, imidapril, indolapril, moexipril, quinapril, ramipril and trandolapril. There are so many chemical substances described where different amino acids have been condensed with NEPA-NCA to yield product of therapeutic use.

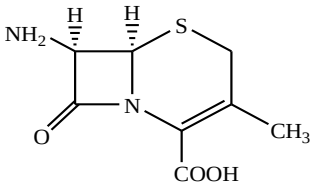


NEPA-NCA

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

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

7-ADCA i.e. [(6R,7R)-7-amino-3-methyl-8-oxo-5-thia-1-aza-bicyclo[4,2,0]oct-2-ene-2-carboxylicacid] is a β-lactam compound and it is a key intermediate for the synthesis of cephalosporins and their intermediates. It is used in preparation of Cephalexin, Cephradine and Cefadroxil. All these are first generation cephalosporins. They have good antimicrobial activity against gram-positive bacteria but limited activity against gram-negative species. The chemical structures of the first generation cephalosporins are fairly simple. As an example three drugs of this class (Cephalexin, Cephradine and Cefadroxil), all have a single methyl group at position C-3. The common side groups at C-3 for first class cephalosporins are small uncharged groups like methyl. The methyl group at position C-3 gives low affinity for common penicillin binding proteins (PBP) which can in part explain the relatively low activity of these first drugs. All of the first generation cephalosporins have α-amino group at position C-7. This structure makes them vulnerable to hydrolysis by β-lactamases. Position 3 of the dihydrothiazine ring alters pharmaco-kinetic properties and receptor binding affinity. 7-ADCA i.e. [(6R, 7R)-7-amino-3-methyl-8-oxo-5-thia-1-azabicyclo [4,2,0]oct-2-ene-2-carboxylic acid having the following structure.

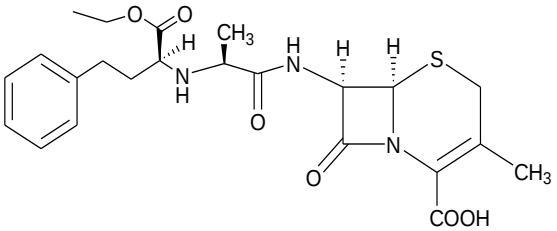


7-ADCA

$C_8H_{10}N_2O_3S$
Mol. Wt.: 214.24

The role of NEPA-NCA has been well validated in literature justifying their potential as antihypertensive property. Similarly 7-ADCA has been also used as precursor of potential antibacterial drug.

Therefore it exhilarated us to disclose a molecule comprising NEPA-NCA and β-Lactam compound like 7-ADCA which may yield into the preparation of a novel β-Lactam derivative amino acid compound and may possess significant biological activity. In the present work, the molecule (Compound-B) (M.F. $C_{23}H_{29}N_3O_6S$), chemical name: [(6R, 7R)-7-((S)-2-((S)-1-ethoxy-1-oxo-4-phenylbutan-2-ylamino)propanamido) -3-methyl-8-oxo-5-thia-1-aza-bicyclo[4,2,0]oct-2-ene-2-carboxylicacid] has been synthesized by reaction of NEPA-NCA (III) (M.F. $C_{16}H_{19}NO_5$) with cephalosporin intermediate 7-ADCA (I) (M.F. $C_8H_{10}N_2O_3S$) in dichloromethane as solvent. (Scheme-1).



Comp-B

$C_{23}H_{29}N_3O_6S$
Mol. Wt.: 475.56

II. Experimentation

A suspension of (6R,7R)-7-amino-3-methyl-8-oxo-5-thia-1-aza-bicyclo[4,2,0]oct-2-ene-2-carboxylic acid i.e. 7-ADCA (I) (20 g; 93.35 milimoles) and dichloromethane (300 mL) was heated to reflux with 102.68 milimoles of hexamethyldisilazane (HMDS) and 39.21 milimoles of trimethylchlorosilane (TMCS) for 4-6 hours. The solution containing (6R,7R)-trimethylsilyl-7-amino-3-methyl-8-oxo-5-thia-1-aza-bicyclo[4,2,0]oct-2-ene-2-carboxylate (II) i.e. silylated 7-ADCA was gradually cooled to room temperature (20-30°C) and subsequently added 112.02 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 to afford the product. Material was dried under vacuum at 35-45°C for 4-6 hours (Yield 85% molar).

III. Result & Discussion

Spectral analysis was performed to characterize the compound-B. The characterization of spectral data confirms the structure of product compound-B. 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-B) exhibit distinct spectral properties as evidenced by 1H-NMR, 13C-NMR and Mass spectra. 1H-NMR, 13C-NMR and MASS spectral data of compound-B are shown in Table-1, 2 and 3 respectively.

The stability of compound-B was studied at 5±3°C under dry condition and found that Compound-B 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-B may possess antibacterial activity; the screening of this compound may confirm its antihypertensive property also.

Acknowledgements

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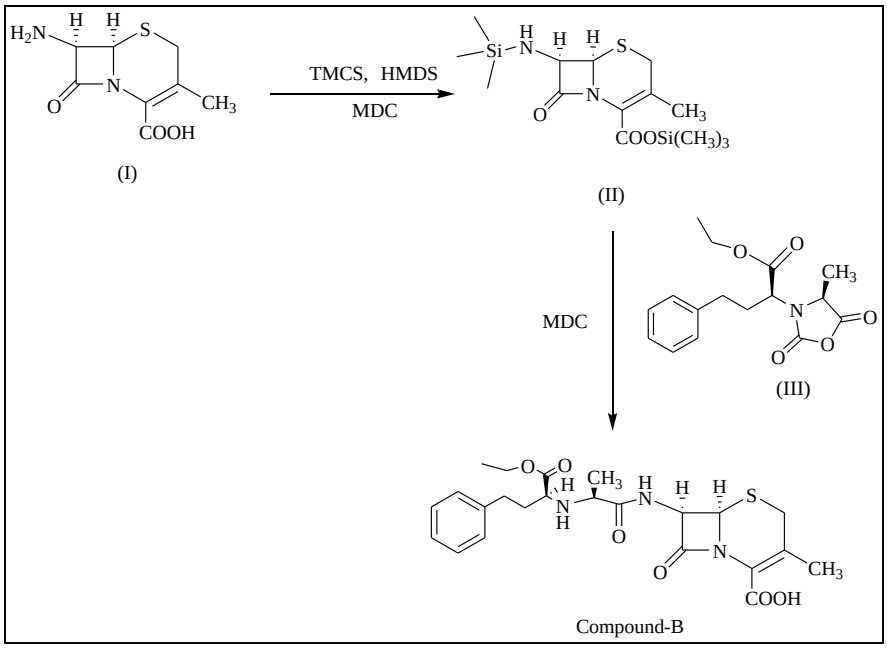
References

[1]. Shrivastava, Sarita; Ranjan, Amulya; Tripathi, Niraj Kumar; "Synthesis of novel β-Lactam derivative and it's application." IOSR Journal of Applied Chemistry (IOSR-JAC) Volume 7, Issue 7 Ver. I. (July. 2014), PP 16-20.
[2]. Mehta, Goverdhan; Singh, Vishwakarma in Chemical Society Reviews (2002), 31(6), 324-334
[3]. Singh, Girij Pal; Wani, Mukesh Jagannath; Lande, Hemraj Mahadeorao; Jain, Adinath Murlidhar; WO 2006085332 A1
[4]. Wang, Lixin; Li, Xianguo; Cai, Zegui; Wang, Wen; Tian, Fang; CN 101024630 A
[5]. Ku, Dae Ho; Baek, Yeong Chan; Shin, Yong Bong; KR 2010004315 A
[6]. Joshi, Narendra Shriram; Bhirud, Shekhar Bhaskar; Ramam, Buddhavarapu Pattabhi; Bodkhe, Arjun Rajaram; IN 2004MU01060 A
[7]. Tien, Mong-Jong; Liu, Yu-Liang; US 6541635 B1
[8]. Jackson, Bill Grinnell, Ger Offen (1970), DE 1942454 A
[9]. Bijev, A; Radev, I; Borisova,Y Pharmazie (2000), 55(8), 568-571
[10]. Gong, Denghuang; Ma, Yuxiu; Lv, Jian; Wu, Xianying; Gao, Li; Hao, Panjie; Sun, Huiqian; Method for preparation of intermediate of Cefozopran hydrochloride; CN 102443016 A
[11]. Manca, Antonio; Monguzzi, Riccardo; Zenoni, Maurizio; Marsili, Leonardo, US 20060100424 A1
[12]. Ishiyama, Tadashi; Ota, Kazumi; Ikeda, Shinya; Mitsutomo, Koichi; JP 2006096679 A
[13]. Gupta, Niranjan Lal; Prasad, Mohan; Trivedi, Anurag; Rane, Dnyandeo Ragho; IN 184842 A1
[14]. Lee, Chun Ho; Lee, Won Hee; KR 163211 B1
[15]. Moon, Soon-Koo; Lee, Kwan-Soon; Kim, Yong-Lip; Jang, Young-Kil; Kim, Maeng-Sub; Lee, Hyang Won; Chun, Jong-Pil; Lee, Jae-Hun; Yu, Seung-Won; Kil, Young-Hwan; KR 9611778 B1
[16]. Tsuge, Otohiko; Kanemasa, Shuji; Yamada, Toshiaki; Matsuda, Koyo; Journal of Organic Chemistry (1987), 52(12), 2523-30
[17]. Yoshida, Junichi; Itami, Kenichiro; Kajimoto, Okitsugu; JP 2004323436 A
[18]. Khazaei, Ardeshir; Rostami, Amin; Mantashlo, Fatemeh; Phosphorus, Sulfur and Silicon and the Related Elements (2009), 184(9), 2288-2296
[19]. Wong, Stanislaus S; Hemraj-Benny, Tirandai; US 20090060815 A1
[20]. Niu, Zhigang; Bai, Songming; Li, Zhigang; Yu, Shuling; CN 101696213 A
[21]. Prasada Rao, Korrapati V V; Dandala, Ramesh; Handa, Vijay K.; Subramanyeswara Kamat, Anand G; Rao, Inti V; Rani, Ananta; Naidu, Andra; Journal of heterocyclic chemistry, 2007, vol. 44, pp. 1513-1515
[22]. Takahashi, Satomi; Inoue, Kenji; Yanagida, Yoshifumi; Ohashi, Takehisa; Watanabe, Kiyoshi; Eur. Pat. Appl. (1987), EP 215335
[23]. Kalman, D; Barriere, SL; Review of the pharmacology, pharmacokinetics, and clinical use of cephalosporins;Texas Heart Institute journal, (1990), 17(3), 203-15.
[24]. Garcia-Rodriguez, J. A.; Bellido, J. L. Munoz; Sanchez, J. E. Garcia; Oral cephalosporins: current perspectives; International journal of antimicrobial agents (1995), 5 (4), 231-43.
[25]. Sader, H.; Historical overview of the cephalosporin spectrum: Four generations of structural evolution; Antimicrobic Newsletter, (1992), 8(12), 75–82.

Scheme-1:



Chemical Structure:

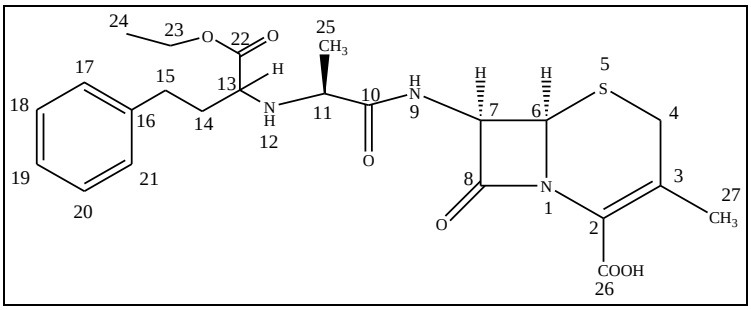


Table-1: 1H NMR: In D_2O

Chemical shift (δ ppm)	Proton Assignments	
1.857-1.935	(d, 3H)	H-25
2.018-2.117	(t, 3H)	H-24
1.702-1.712	(s, 3H)	H-27
2.389-2.412	(m,2H)	H-14
2.717–2.934	(t, 2H)	H-15
3.362 -3.474	(d, 1H)	H-4
3.683 -3.717	(d, 1H)	
3.731-3.841	(t, 1H)	H-13
4.021-4.118	(q, 1H)	H-11
4.241-4.383	(q, 2H)	H-23
4.795-4.911	(d, 1H)	H-6
5.282-5.390	(d, 1H)	H-7
5.414-5.462	(m, 1H)	H-19
5.942-6.035	(m, 2H)	H-17, H-21
6.214-6.250	(m, 2H)	H-18, H-20

Table-2: 13C NMR:

Chemical shift (δ ppm)	Carbon assignment
18.68	C-27
19.52	C-24
24.64	C-25
54.32	C-4
58.36	C-15
60.27	C-14
62.71	C-11
62.94	C-13
62.33	C-6
63.47	C-7
66.23	C-23
116.29	C-2
117.42	C-3
123.61	C-19
129.85	C-17, C-21
131.12	C-18, C-20
159.58	C-16
168.93	C-8
169.48	C-26
170.16	C-22
174.12	C-10

Table-3: Mass: ESI mode, M.F. $C_{23}H_{29}N_3O_6S$: calculated: 475.56

m/z (amu)	Assignment
476.5	$[M+H]^+$