International Journal of Research and Development in Pharmacy and Life Sciences
Available online at http//www.ijrdpl.com
February - March, 2015, Vol. 4, No.2, pp 1422-1426
ISSN (P): 2393-932X, ISSN (E): 2278-0238

Research Article

CRYSTALLOGRAPHIC CHARACTERIZATION OF TRANS ESTERIFIED POTENTIAL IMPURITY OF CANDESARTAN

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(Received: December 09, 2014; **Accepted:** January 20, 2015**)**

ABSTRACT

The title compound (CDC II), $C_{28}H_{28}N_6O_3$, is a potential impurity found in commercial product candesartan cilexetil, consist of N- ethylation of tetrazole moiety attached to biphenyl ring, selectively at N-6 position. The Crystal structure held together by C–H···O intermolecular interactions. Crystal structure of the title compound was obtained by single crystal X-ray diffraction which was crystallizes in the monoclinic space group $P2_1/n$ with cell parameter a = 12.1574(12)Å, b = 13.9178(14)Å,c = 15.9742(19)Å and Z = 4.

Keywords: Candesartan - Impurity - Single Crystal - Intermolecular *N* - alkylation.

INTRODUCTION

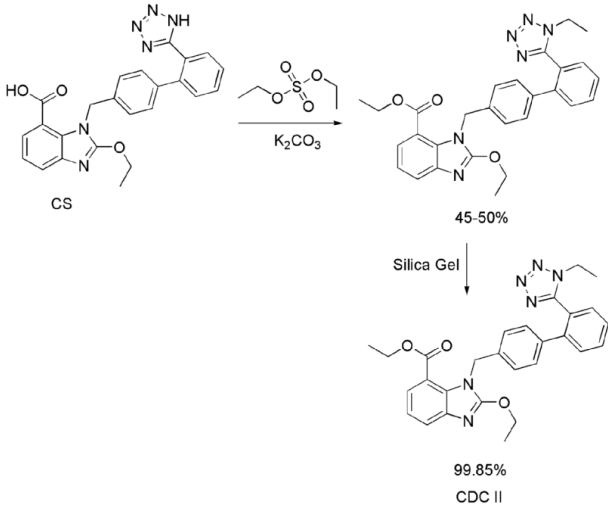
Analytical profile study is increasingly viewed as a valuable and essential part of quality requirements. Control of impurities is a key component of the overall quality of a pharmaceutical as their presence even in small amount may affect drug safety and efficacy. Impurity can be defined as any component of the drug substance which is not the chemical entity of the drug substance. [1] It can be also defined as any material that affects the purity of the material of interest like active ingredients or drug substance [2].Various regulatory authorities like the International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use (ICH) [3], United States of food and drug authority (USFDA) [4], European directorate of quality medicine (EDQM) [5] and other health agencies are emphasizing on the purity requirements and the identification of impurities in drug substance and products. As per ICH guidelines unknown impurities associated with bulk drug and dosage form, greater than the identification threshold should be identified. The title compound 2-ethoxy- 1-{[2'-(1-ethyl-1H-tetrazol-5-yl) biphenyl-4-yl] methyl}-1H-benzimid-azole-7-carboxylic acid ethyl ester is an impurity recently found in the drug substance candesartan cilexetil (CDS) which was identified and well characterized by our coauthors [6]. Candesartan (2-ethoxy-1-[[2_-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-1H-benzimidazole-7-carboxylic acid) is an active form of prodrug CDS which act as selective AT1 subtype anginotensin II receptor antagonists (AIIRAs) and used as a cardiovascular drug [7-9].

MATERIALS AND METHOD

Sample of candesartan (CS) was obtained from IPCA Laboratories Limited, Mumbai.

All the chemicals and solvents were obtained from Merck (LR grade) and were used without further purification. Melting points were taken in an open capillary tube and are uncorrected. DRIFT spectra were recorded on a Perkin Elmer spectrophotometer. 1H and 13C NMR Spectra were recorded in DMSO-d6 on a Brucker Avance II 400 MHz NMR spectrometer. Chemical shift of 1H and 13C spectra are reported in δ PPM downfield from tetramethyl silane. Mass spectra were recorded on water Micromass Q-T of Micro spectrometer equipped with an ESI source. The reactions were monitored on pre-coated TLC plates (Silica gel 60 F254, Merck), using iodine vapor as visualizing agent.

SYNTHESIS OF CDCII



Scheme 1 Synthesis of CDCII

To a solution of candesartan (5g, 12.13 mmol) acetone (250 mL, 50 vol.), potassium carbonate (2g, 14.5 mmol) and diethyl sulphate (1.86g, 12.13mmol) was added, stirred reaction mass for 5 h at 50-55OC, hot filtered through buckner under reduced pressure. Filtrate was concentrated and subjected to column chromatography purification. Yield=32 %, purity=99.85%.

1H-NMR (400 MHz, DMSO-d6): δ 7.69 (1H, m), 7.55 (1H, m), 7.55 (1H, m), 7.66 (1H, dd, J=7.92), 7.45 (1H, dd, J = 7.92), 7.16 (1H, t, J= 7.92), 6.97 (2H, d, J= 8.22), 5.49 (2H, s), 4.14 (2H, q, J = 7.31), 4.55 (2H, q, J = 7.01), 3.58 (2H, q), 1.35 (3H, t, J = 7.01), 0.76 (3H, t).

13C-NMR (100 MHz, DMSO-d6): δ 165.6, 158.3, 153.8, 141.6, 140.8, 131.7, 130.3, 130.9, 137.6, 136.9, 131.2,128.8, 128, 126.6, 122.4, 123.1, 121.6, 120.8, 115.7, 61, 66.6, 13.9, 14.3, 46.2, 42.1, 13.3

RESULTS AND DISCUSSION

The mechanism of formation of title compound as a process related impurity in commercial product CS was explained on the basis of trans esterification reaction [10-11].The title compound was synthesized by ethylation of candesartan using diethylsulphate in acetone under reflux condition (scheme 1). Reaction was monitored on HPLC equipped with Kromasil cyano column (250 mm × 4.6 mm, 5µm particle size), UV detection at 210 nm. Maximum conversion upto 45-50 % was obtained. The isolated product was purified to 99.85% using silica gel column chromatography. Without any further purification its spectral analysis was carried out. Proton NMR of CS and title compound was compared, chemical shift of all proton are in well agreement with that of CS, spectra of compound show two extra ethyl moiety and absence of –OH and –NH proton whose position were located by deuterium exchange experiment. The structure was further conformed by single crystal X-ray diffraction study. Position of ethyl group to tetrazole moiety was assigned by X-ray diffraction at N6 tautomeric position rather than N5 which was already characterized by 2D NOESY and HMBC experiments [6].

X-Ray structure determination

Crystals of CDC II suitable for single crystal X-ray diffraction were obtained by the slow evaporation of its saturated solution in chloroform and methanol (1:1 v/v) at 27 degree celcius. Data were collected on an Oxford Xcalibur Mova diffractometer [12] equipped with Eos CCD detector utilizing MoKα radiation (λ = 0.71073 Å). The structure was solved by direct methods and refined with full matrix least-squares technique by using ShelX [13]. All non-hydrogen atoms were refined anisotropically whereas the positions were geometrically fixed and refined isotropically for all the hydrogen atoms. All calculations were performed using PLATON [14] in the WinGX software package [15].

Compound CDCII crystallizes in a monoclinic system, space group P21/c with Z=4. The crystallographic and refinement details are given in table 1.CDCII adopts a nonplanar twisted conformation as shown in Figure 1. An intramolecular

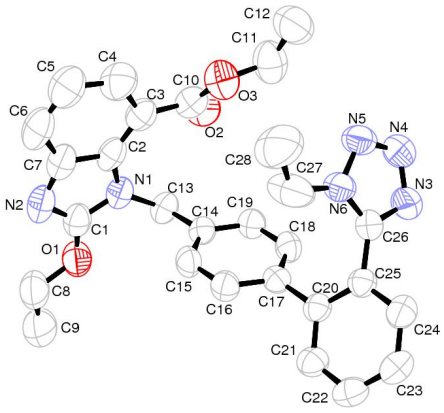


Figure 1 *ORTEP* diagram of CDCII drawn at 50% ellipsoidal probability for non-H atom.

C–H···O hydrogen bond (table 2) stabilizes this twisted conformation of the molecules which are further connected by the intermolecular C–H···O hydrogen bonds (figure2; table 2). The molecules are interlinked by various C–H···N hydrogen bonds generating a three-dimensional network. Also, intermolecular π···π interactions [d(Cg···Cg)=3.5680(15) Å] between the tetrazine rings provide an additional stability to the structure. Selected bond length and bond angle are given in table 3.

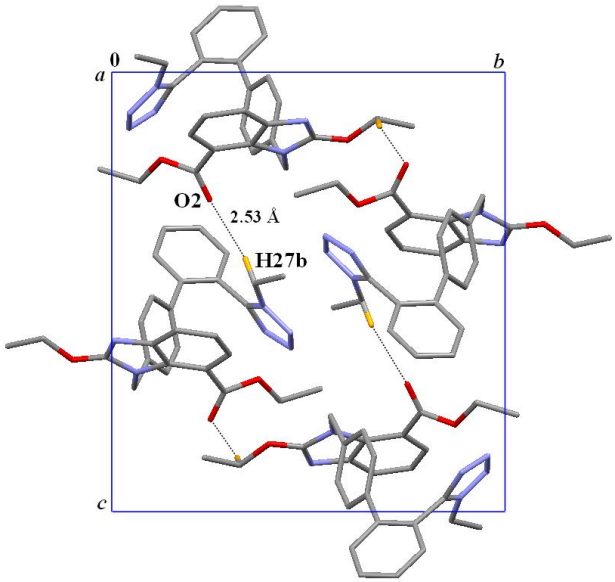


Figure 2 Packing diagram of CDCII viewed down the *a*-axis, C–H···O intermolecular interactions are shown by the dotted lines

Table 1 Crystal data and structure refinement for CDCII

DATA	CDCII
Formula	$C_{28}H_{28}N_6O_3$
Formula weight	496.6
Color	Colorless
Crystal morphology	Block
Temperature/K	295(1)
Radiation	Mo Kα
Wavelength/Å	0.71073
Crystal system	Monoclinic
Space group	$P2_1/c$
Crystal Dimension (mm)	0.40 × 0.40 × 0.30
a (Å)	12.1574(12)
b (Å)	13.9178(14)
c (Å)	15.9742(19)
β (°)	103.502(11)
Volume (Å^3)	2628.20(72)
Z	4
Index range	$-14 \le h \le 14, -17 \le k \le 17, -19 \le l \le 19$
Absorption correction	T_{min} = 0.9670, T_{max}=0.9751
Density (g/ml)	1.25
μ (1/mm)	0.084
F (000)	1047.8
θ (min, max)	2.4, 26.0
No. Unique Refln	5154
reflection with $I > 2\sigma(I)$	2863
No. of parameters	337
R_{int}	0.0606
*R*_obs, wR_2_obs	0.061, 0.186
$\Delta\rho_{min}$, $\Delta\rho_{max}$ (eÅ^{-3})	-0.343, 0.583
Goodness of fit on F^2	1.042
CCDC No	846820

REFINEMENT DETAILS

Refinement of F^2 against all reflections. The weighted R-factor wR and goodness of fit S are based on F^2, conventional R-factor are based on F, with F set to zero for negative F^2. The threshold expression of $F^2>2$ sigma (F^2) is used only for calculating R-factor(gt) etc. and is not relevant to the choice of reflections for refinement. R-factor based on F^2 are statistically about twice as large as those based on F, and r-factors based on all data will be even larger.

GEOMETRICAL DETAILS

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used

Table 2 Intramolecular and intermolecular interactions in CDCII

D–H···A	r(D–H)/Å	r(D–A)/Å	r(H···A)/Å	∠ D–H···A/º	Symmetry
C13–H13A···O2	0.97	2.960(3)	2.249(2)	129.3(1)	x,y,z
C15–H15···N2	0.93	3.357(3)	2.658(2)	132.5(2)	-x+1,-y+1,-z
C28–H28A···N3	0.96	3.679(5)	2.806(2)	151.5(3)	-x+2,-y,-z
C24–H24···N5	0.93	3.523(3)	2.705(2)	147.1(2)	-x+2,-y,-z
C27–H27B···O2	0.97	3.376(4)	2.531(2)	145.6(2)	x,-y+1/2,+z-1/2
C8–H8A···O2	0.97	3.646(5)	2.728(2)	158.1(2)	-x+1,+y+1/2,-z+1/2
C5–H5···N3	0.93	3.606(4)	2.750(2)	153.4(3)	x-1,+y,+z

Table 3 Selected Bond distance (Aº) and bond angle (º) of CDCII

Bond Distance		Bond angle	
O1 - C1	1.327(3)	C1- O1- C8	114.8(2)
O1 - C8	1.446(4)	C10 -O3- C11	117.0(2)
O3 - C10	1.326(3)	C26- N3- N4	106.0(2)
O3 - C11	1.450(4)	C1-N1- C2	105.0(2)
N3 - C26	1.317(3)	C1- N1- C13	124.0(2)
N3 - N4	1.353(3)	C2- N1- C13	129.8(2)
O2 - C10	1.200(3)	N4- N5- N6	106.3(2)
N1 - C1	1.372(3)	C26- N6- N5	108.5(2)
N1 - C2	1.401(3)	C26- N6- C27	130.3(2)
N1 - C13	1.465(3)	N5- N6- C27	121.2(2)
N5 - N4	1.290(3)	C21- C20- C25	117.7(2)
N5 - N6	1.348(3)	C21- C20- C17	119.6(2)
N6 - C26	1.327(3)	C25- C20- C17	122.7(2)
N6 - C27	1.470(4)	N5- N4- N3	110.7(2)
C17 - C16	1.382(3)	C1- N2- C7	103.8(3)
C17 - C18	1.393(3)	C19- C18- C17	121.0(2)
C17 - C20	1.482(3)	C19- C18- H18	119.5
C19 - C18	1.379(3)	C17- C18- H18	119.5
C19 - C14	1.389(3)	N3- C26- N6	108.5(2)
C20 - C21	1.389(3)	N3- C26- C25	125.6(2)
C20 - C25	1.400(3)	N6- C26- C25	125.8(2)
N2 - C1	1.294(3)	C3- C2- N1	134.3(2)
N2 - C7	1.379(4)	C3- C2- C7	121.4(3)
C25 - C24	1.380(3)	N1- C2- C7	104.3(3)
C25 - C26	1.480(3)	N1- C13- C14	112.69(19)
C13 - C14	1.509(3)	C15- C14- C13	120.9(2)
C21 - C22	1.371(3)	N2- C1- O1	127.4(3)
C15 - C16	1.374(3)	N2- C1- N1	115.5(3)
C15 - C14	1.374(3)	O1- C1- N1	117.1(3)
C23 - C24	1.376(4)	C15- C16- C17	122.0(2)
C23 - C22	1.382(4)	N2- C7- C6	128.0(3)
C7 - C6	1.384(4)	N2- C7- C2	111.3(3)
C3 - C4	1.395(4)	C6- C7- C2	120.8(3)
C3 - C10	1.478(4)	C2- C3- C10	124.8(2)
C6 - C5	1.376(5)	O2- C10- O3	123.3(3)
C27 - C28	1.385(5)	O3- C10- C3	111.9(2)
C4 - C5	1.384(5)	C28- C27- N6	118.9(3)
C8 - C9	1.458(5)	O1- C8- C9	107.8(3)
C11 - C12	1.478(5)	O3- C11- C12	108.0(3)

when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell is used for estimating esds involving l.s. planes.

Acknowledgement

The authors greatly acknowledge to Department of Science and Technology, India, for use of the CCD facility setup under the IRHPA-DST program at IISc, Bangalore and very thankful to Mr. Amol Dikundwar for his technical support.

Supplementary Data

Crystallographic data for the structure reported in this work including anisotropic displacement parameters, full bond lengths, bond angles and dihedral angles have been deposited with the Cambridge Crystallographic Data Center with CCDC No. 846820.Available free of charge at www.ccdc.cam.ac.uk/data_request/cif or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033.

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How to cite your article:

Kartik S. R., Ashok B. K., Deepa Y. P., Rakeshwar B., "Crystallographic characterization of trans esterified potential impurity of candesartan", Int. J. Res. Dev. Pharm. L. Sci., 2015, 4(2), pp. 1422-1426.

