Journal of Molecular Structure 1137 (2017) 320–327

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: http://www.elsevier.com/locate/molstruc

Solvent effect on the self-assembly of salt solvates of an antihypertensive drug azilsartan and 2-methylimidazole

Xian-Rui Zhang, Lei Zhang*

School of Bioscience and Bioengineering, South China University of Technology, Guangzhou, 510006, PR China

ARTICLE INFO

Article history:
Received 28 October 2016
Received in revised form
24 January 2017
Accepted 15 February 2017
Available online 20 February 2017

Keywords:
Azilsartan
Self-assembly
2-Methylimidazole
Solvate
Salt
X-ray diffraction

ABSTRACT

Three salt solvates of azilsartan (AZ) with 2-methylimidazole (2MI) (namely AZ-2MI-H_2O, AZ-2MI-ACE and AZ-2MI-THF) and one azilsartan solvate (AZ-DIO, ACE = acetone, THF = tetrahydrofuran, and DIO = 1,4-dioxane) were manufactured by solvent-controlled self-assembly in aqueous-organic solutions. The experimental result of AZ-DIO shows that AZ is high affinity to DIO molecule, which has a unique ability to prevent salt formation between AZ and 2MI. Thermal studies of three salt solvates exhibit poor thermodynamic stability in environmental conditions. Solubility experiments show that AZ-2MI-ACE and AZ-2MI-THF are unstable and convert to AZ-2MI-H_2O in aqueous solution, and that AZ-2MI-H_2O exhibits increased solubility and retention stability in an aqueous medium compared with the commercial AZ-A crystalline form.

1. Introduction

In the past decade, the research on pharmaceutical salts and solvates has been a focus due to the potential ability to improve the solubilities and dissolution rates of poorly soluble active pharmaceutical ingredients (APIs) [1–6]. On the other hand, the US Food and Drug Administration (FDA) has indicated that different salt forms of the same active moiety are considered to be new drug entities [7]. Since multicomponent crystallization screening has begun to be routinely performed, polymorph and pseudopolymorph (solvate or hydrate) of salt formation have been a subject of intense interest in order to control polymorphic formation and to explore the formation mechanism [8–12]. A number of studies indicate that solvents often effect on the self-assembly of salt form and co-crystallization [13–15]. For example, solvents could also be in channels of crystal cells, an inclusion compound, or by encapsulation within pockets, an inclusion clathrate [16–18]. Meanwhile, this phenomenon has caused some discomfiture for the scientific classification of multicomponent crystals into solvate, cocrystal and salt. In order for the classification to be unambiguous, Grothe and Gelder have recently proposed a feasible classification system for all multicomponent crystallization: true solvate, true salt, true cocrystal, salt solvate, cocrystal solvate, cocrystal salt, and cocrystal salt solvate [19].

Azilsartan (AZ) is an angiotensin II receptor blocker which is used for the treatment of hypertension diseases (available in Japan) [20–22]. The crystal structure of AZ-A was disclosed in a CN patent, and some crystalline forms (solvate, salt or polymorph) were reported in the following literature [23–28]. 2-Methylimidazole (2MI) is a safe organic base with LD_{50} of 1500 mg/kg for oral rat [29]. Importantly, 2MI could be quickly eliminated without tissue accumulation in the human body, and the metabolism of 2MI was not affected by the dose or route of administration [30,31]. In the present work, we prepared three thermally stable salt solvates (AZ-2MI-H_2O, AZ-2MI-ACE and AZ-2MI-THF, ACE = acetone, THF = tetrahydrofuran, Scheme 1) and one azilsartan solvate (AZ-DIO, DIO = 1,4-dioxane) by a combination of AZ and 2MI in different conditions through solvent-controlled self-assembly, which are characterized by single crystal and powder X-ray diffractions, elemental analysis, thermogravimetric analysis and differential scanning calorimetry.

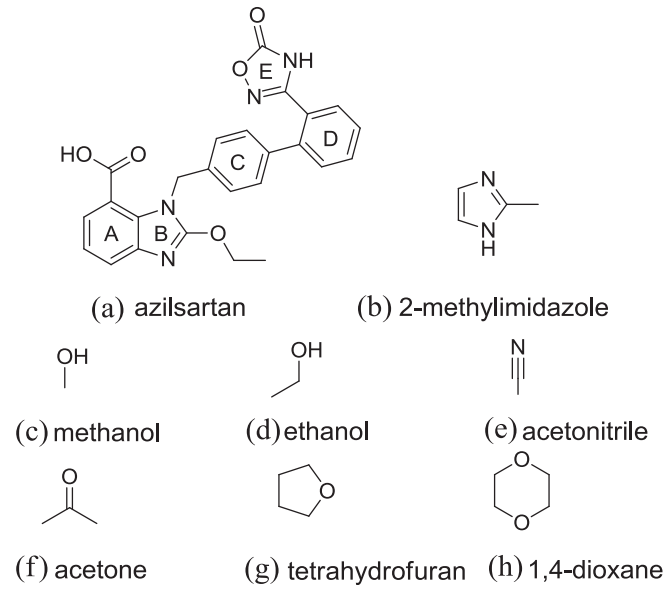
2. Experimental

2.1. Instrumentations and materials

All solvents and reagents (analytical grade) were obtained commercially and used as received unless otherwise mentioned.

* Corresponding author.
E-mail address: lzhangce@scut.edu.cn (L. Zhang).

http://dx.doi.org/10.1016/j.molstruc.2017.02.063
0022-2860/



Scheme 1. Molecular structures of AZ, 2MI, and the solvents used in this paper. Letters are the ring codes.

The C, H, and N microanalysis were carried out with a Vario EL cube elemental analyzer. Fourier infrared (FT-IR) spectra were performed on a Bruker Vector 33 in the 4000-400 cm^{-1} range. Thermogravimetric (TG) analysis experiments were carried out in Netzsch TG STA449-F5 equipment with the heating rate of 10 °C/min at a range of 30–500 °C under a nitrogen gas purge with a flow of 20 mL/min. Differential scanning calorimetry (DSC) studies were carried out using a Mettler Toledo DSC with a heating regime of 10 °C/min at a range of 30–250 °C under a nitrogen gas purge. Powder X-ray diffraction (PXRD) patterns were obtained with a RigakuSmartlab powder diffractometer coupled with a Cu Kα radiation tube (λ = 1.5418 Å, V = 40 kV and I = 30 mA) and 2θ scan in the 5–60° range.

2.2. Preparation of the compounds

2.2.1. AZ-A

AZ (40 mg) was dissolved in 14 mL of ethanol, and the resulting solution was stirred at room temperature for 2 h and left for slow evaporation. Colorless block crystals suitable for single crystal X-ray diffraction were obtained after 10 days. Yield: 23 mg (57%). The result is in good accordance with the literature [23,24]. Elemental Anal. Calcd for $C_{25}H_{20}N_4O_5$: C, 65.78%; H, 4.41%; N, 12.27%; found: C, 65.71%; H, 4.38%; N, 12.30%.

2.2.2. Salt solvate AZ-2MI-H_2O (1:0.5:1)

AZ-2MI-H_2O was obtained by dissolving AZ and 2MI (a total of 120 mg of a 1:1 or 2:1 stoichiometric ratio of AZ and 2MI) in 20 mL of methanol/water (4:1, v/v) [ethanol/water or acetonitrile/water], and stirred at room temperature for 2 h. The resulting solution was left for slow evaporation. Colorless block crystals suitable for single crystal X-ray diffraction were obtained after 20 days. Yield: 48 mg (40%). Calcd for $C_{27}H_{25}N_5O_6$: C, 62.91%; H, 4.88%; N, 13.59%; found: C, 62.88%; H, 4.83%; N, 13.62%.

2.2.3. Salt solvate AZ-2MI-ACE (1:1:1)

AZ-2MI-ACE was obtained by dissolving AZ and 2MI (a total of 200 mg of a 1:1 stoichiometric ratio of AZ and 2MI) in 20 mL of the acetone/water mixture (3:1, v/v), and stirring at room temperature for 2 h. The resulting solution was left for slow evaporation. Colorless block crystals suitable for single crystal X-ray diffraction were obtained after 7 days. Yield: 87 mg (44%). Calcd for $C_{32}H_{32}N_6O_6$: C, 64.42%; H, 5.41%; N, 14.09%; found: C, 64.39%; H, 5.35%; N, 14.02%.

2.2.4. Salt solvate AZ-2MI-THF (1:1:1)

AZ-2MI-THF was obtained by dissolving AZ and 2MI (a total of 200 mg of a 1:1 stoichiometric ratio of AZ and 2MI) in 20 mL of the tetrahydrofuran/water mixture (3:1, v/v), and stirring at room temperature for 2 h. The resulting solution was left for slow evaporation. Thick plate crystals suitable for single crystal X-ray diffraction were obtained after 7 days. Yield: 90 mg (45%). Calcd for $C_{33}H_{34}N_6O_6$: C, 64.91%; H, 5.61%; N, 13.76%; found: C, 64.87%; H,

Table 1
Crystallographic parameters of AZ, AZ salt solvates and AZ solvate.

	AZ-A	AZ-2MI-H_2O	AZ-2MI-ACE	AZ-2MI-THF	AZ-DIO
Chemical formula	$C_{25}H_{20}N_4O_5$	$C_{25}H_{19.5}N_4O_5$, 1/2$C_4H_7N_2$, H_2O	$C_{25}H_{19}N_4O_5$, $C_4H_7N_2$, C_3H_6O	$C_{25}H_{19}N_4O_5$, $C_4H_7N_2$, C_4H_8O	$C_{25}H_{20}N_4O_5$, 1/2$C_4H_8O_2$
formula sum	$C_{25}H_{20}N_4O_5$	$C_{27}H_{25}N_5O_6$	$C_{32}H_{32}N_6O_6$	$C_{33}H_{34}N_6O_6$	$C_{27}H_{24}N_4O_6$
formula weight	456.45	515.52	596.64	610.66	500.50
crystal system	monoclinic	triclinic	triclinic	triclinic	monoclinic
space group	$P2_1/c$	P-1	P-1	P-1	C 2/c
a [Å]	9.6485(17)	9.9221(7)	8.4545(14)	8.3994(7)	20.8764(18)
b [Å]	11.312(2)	11.0641(8)	9.0586(15)	9.0501(7)	14.2051(14)
c [Å]	19.984(4)	13.0650(9)	21.371(3)	21.0766(18)	16.1517(16)
α[°]	90	65.961(2)	80.905(3)	79.773(3)	90
β[°]	90.337(3)	68.288(2)	86.065(3)	85.575(3)	92.761(9)
γ[°]	90	83.972(2)	75.877(3)	75.618(2)	90
Z	4	2	2	2	8
V [$Å^3$]	2182.9(5)	1215.17(15)	1566.5(4)	1526.4(2)	4784.2(8)
D_{calc} [g cm^{-3}]	1.390	1.409	1.265	1.329	1.390
M [mm^{-1}]	0.099	0.102	0.089	0.093	0.100
reflns. collected	14474	11077	8662	11109	9172
unique reflns.	3844	3844	3943	4403	2845
observed reflns.	4994	5612	5490	5330	4192
R_1 [$I > 2\sigma(I)$]	0.0420	0.0633	0.0506	0.0587	0.0715
wR_2 (all data, F^2)	0.1029	0.1493	0.1427	0.1290	0.1765
GOF	1.038	0.995	1.052	1.072	1.084
largest diff. peak and hole [e·$Å^{-3}$]	0.297/−0.207	0.351/−0.409	0.339/−0.232	0.507/−0.395	0.769/−0.448
CCDC	1502250	1502251	1502252	1502253	1502254