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Crystallization of the Racemic Conglomerate and Racemic Compound of Efonidipine

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***Abstract*—Efonidipine is a dual blocker of T-type and L-type calcium channels with 1, 4-dihydropyridine structure attached to a phosphonate skeleton. As a chiral compound, it has a special property that can exist as a racemic conglomerate or a racemic compound based on the different crystallization conditions. One racemic conglomerate and one racemic compound were disclosed and characterized in this research. Efonidipine conglomerate could obtain from its racemic solution when ethanol, methanol, tetrahydrofuran, ethyl acetate and acetonitrile were chosen as the crystallized solvent. While, racemic compound which existed as an acetone solvate could be prepared by crystallization from acetone only and the crystallization process must be keep stood without agitating. In order to confirm this conclusion, three single crystals of R-efonidipine, S-efonidipine and R/S- efonidipine acetone solvate have been prepared and determined.**

Keywords-efonidipine; crystallization; racemic conglomerate; racemic compound

I. INTRODUCTION

There are three different kinds of racemates: the racemic conglomerate or named conglomerate, racemic compound or called true racemate, and racemic solid solution (pseudoracemate) [1].

The racemic conglomerate consists of a physical mixture of pure crystals of the two isomers. There are only 5% to 10% probabilities of all organic compounds to form conglomerate when they crystallized from a racemic solution. Conglomerate-forming crystals molecular have a stronger affinity for the same isomers than for the two isomers or the counterpart crystallize separately. The formation of conglomerate provides a means to obtain pure enantiomers of organic compounds by direct crystallization separation which is simpler, greener and more cost-effective than any other methods [2].

The racemic compound is formed by a single crystal in which the two isomers pack against each other in a regular fashion with a 1:1 ratio. There are about 90% probabilities of all organic compounds to form racemic compound. In this crystals, molecular have a stronger affinity for the counterpart than for the same isomers [2].

In the pseudoracemate crystal, the isomers are in equal proportions but are packed in random fashion. There are rare probabilities of all organic compounds to form pseudoracemate crystals. In this crystals, molecular have no significant difference of the affinity for the same isomers or the counterparts [2].

Each racemic mode has its own physical characteristics, such as the structure, melting temperature, solubility, and density [3].

Efonidipine, (±)-2-[benzyl (phenyl) amino] ethyl 1,4-dihydro-2,6-dimethyl-5- (5,5-dimethyl - 2-oxo -1, 3, 2-dioxaphosphorinan-2-yl)-4-(3-nitrophenyl)-3-pyridine-car boxylate (Fig. 1a), is a dual blocker of T-type and L-type calcium channels with 1, 4-dihydropyridine structure attached to a phosphonate skeleton. Its hydrochloride monoethanolate is already being marketed in Japan by Shionogi & Co., Ltd. and ZERIA pharmaceutical Co., Ltd as an antihypertensive and antianginal drug. The drug exhibits a longer half-life, better hydrophilicity and bioavailability than existing Ca2+ antagonists and appears to have an ideal profile with organ-protective effects in heart and kidney.

Efonidipine exists as a racemate consists of R-enantiomer (Fig. 1b) and S-enantiomer (Fig. 1c) due to a chiral center in 1, 4-dihydropyridine. R-enantiomer and S-enantiomer exhibits completely different biological activities [4, 5] and have been used in different fields which is the case for most chiral drugs.

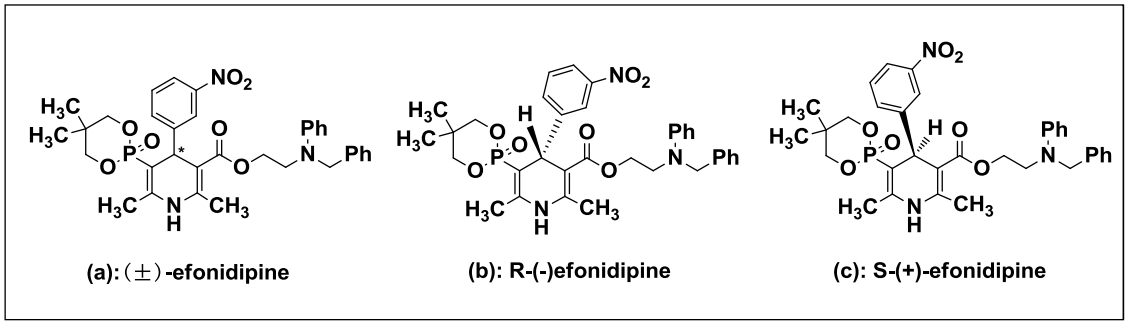


Figure 1. Chemical structure of Efonidipine

Asymmetric synthesis of S- efonidipine isomer and its crystal structure has been reported by R. Sakoda [6] in 1992. Recently, M. Otsuka group reported the stability and physicochemical characterization of efonidipine hydrochloride ethanolate [7]. But, the formation and characterization of the racemates of efonidipine has not been reported. Regarding the advantages of direct crystallization, the screen of all possible types of efonidipine racemates has a crucial significance. One racemic conglomerate and one racemic compound in the form of an acetone solvate were disclosed and characterized in this research. Efonidipine conglomerate could obtain from multiple crystallized solvent very easily. While, racemic compound which existed as an acetone solvate could be prepared by crystallization from acetone only and the crystallization process must be keep stood without agitating (Fig. 2).

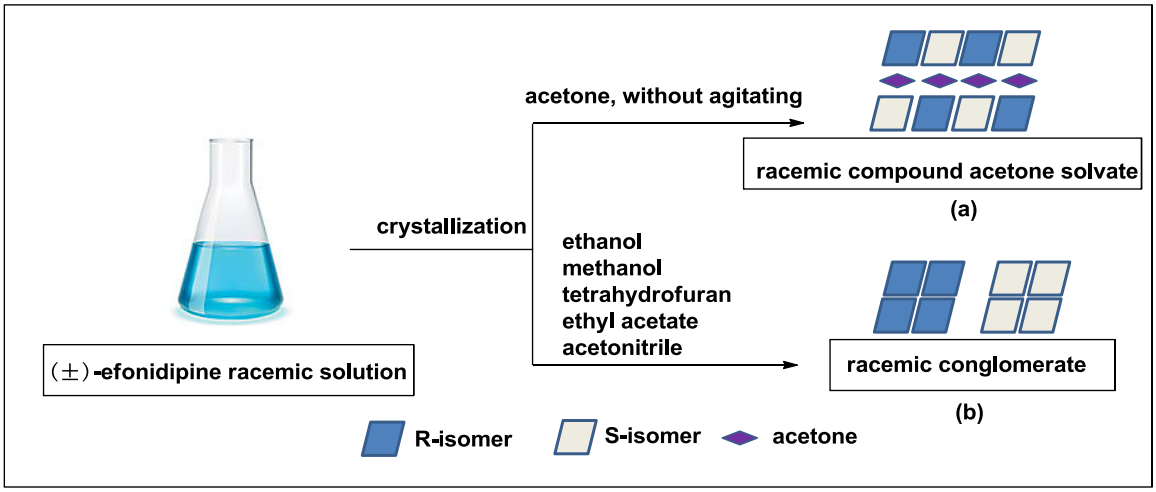


Figure 2. Different types of Efonidipine racemates

II. EXPERIMENTAL

A. *Materials:*

Efonidipine were supplied by Furen Pharmaceutical Technology Development Co., Ltd as a racemate. All other chemicals and reagents used were analytical reagent grade.

B. *Single Crystal Formation and X-Ray Diffraction Data Collection:*

Three single crystals of R-efonidipine, S-efonidipine and R/S- efonidipine acetone solvate have been prepared and determined in this study.

To prepare single crystal of R/S- efonidipine acetone solvate, efonidipine racemic powder was added to acetone, at approximately 55-65℃ to fully dissolve. The resulting solution was then left undisturbed at room temperature for three days and the crystallization process was keep stood

without agitating. The yellow-green prismatic shape crystals were collected by filtration.

To prepare R-efonidipine and S-efonidipine single crystal which existed as a racemic conglomerate, efonidipine racemic powder was added to ethanol, at approximately 70-75℃ to fully dissolve the compound. The resulting solution was then left undisturbed at room temperature for three days. The yellow prismatic shape crystals of R-efonidipine isomer and S- efonidipine isomer single crystals obtained by stochastically.

R-efonidipine and S-efonidipine single crystal which existed as a racemic conglomerate could be also formed when methanol, tetrahydrofuran, ethyl acetate and acetonitrile were chose as the crystallization solvents.

Single crystal X-ray diffraction data were collected at 291 K on a Rigaku Gemini E with monochromated CuK α radiation (λ = 1.54184 Å). The structures were solved by direct methods using ShelXS structure solution program and refined by the ShelXL refinement package.

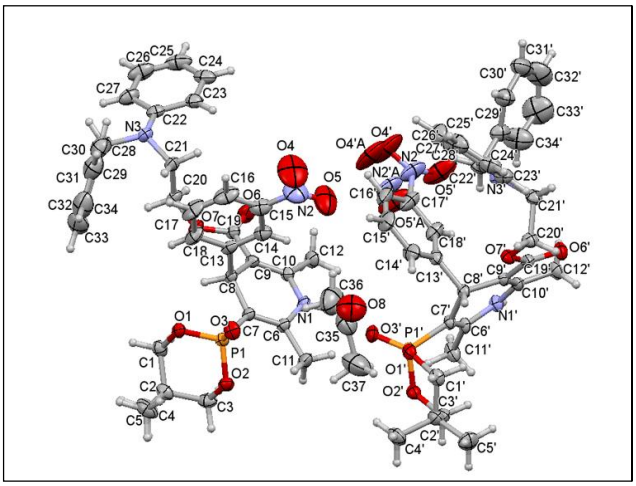
III. RESULTS AND DISCUSSION

C. The Single Crystal of Efonidipine Isomers

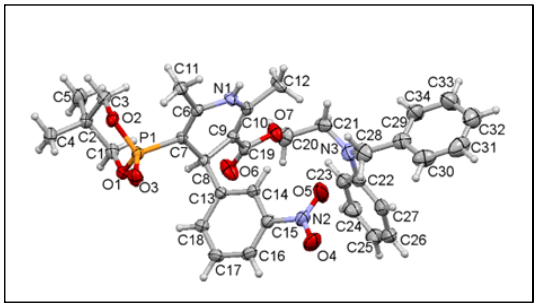
R/S- efonidipine acetone solvate, R-efonidipine and S-efonidipine single crystals (Fig. 3) were obtained from a racemate solution when the conditions of recrystallization were studied. The crystallographic parameters of our crystals are summarized in Table 1.

R/S- efonidipine acetone solvate single crystal was a novel structure which has not been reported by anyone. Its crystal structure belongs to triclinic, space group P-1.

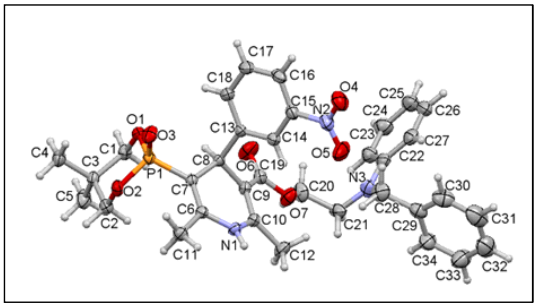
R-efonidipine and S-efonidipine single crystals were selected at the same crystal conditions through random screening and the crystallographic parameters were in accordance with previously reported values. Their crystal structures belong to monoclinic, space group P212121.



R/S- efonidipine acetone solvate (a)



R-efonidipine (b)



S-efonidipine (c)

Figure 3. Crystal structure of the R/S- efonidipine acetone solvate (a), R-efonidipine (b) and S-efonidipine (c)

TABLE I. CRYSTALLOGRAPHIC PARAMETERS OF R/S- EFONIDIPINE ACETONE SOLVATE, R-EFONIDIPINE AND S-EFONIDIPINE

	R/S- efonidipine acetone solvate	R-efonidipine	S-efonidipine
Molecular formula	$(C_{34}H_{38}N_3O_7P)_2.C_3H_6O$	$C_{34}H_{38}N_3O_7P$	$C_{34}H_{38}N_3O_7P$
Molecular weight	1321.39	631.64	631.64
Temperature (K)	293	291	293
Crystal color, habit	Yellow-green, Prism	Yellow, Prism	Yellow, Prism
Crystal system	triclinic	Orthorhombic	Orthorhombic
Space group	P-1	$P2_12_12_1$	$P2_12_12_1$
Lattice parameters (Å, ٩)			
a =	13.9972(6)	9.9571(3)	9.9690(3)
b =	17.2985(4)	13.1879(3)	13.1954(3)
c =	18.4787(6)	24.6117(7)	24.5856(6)
α=	63.723(3)	90.00	90.00
β=	68.593(3)	90.00	90.00
γ=	67.115(4)	90.00	90.00
Volume ($Å^3$)	3594.1(3)	3231.84(15)	3234.11(15)
Z	2	4	4
D_{calcd} ($Mg\ m^{-3}$)	1.221	1.298	1.297
Reflections collected	56083	12090	8060
Independent reflections	12829	6233	4960
R_{int}	0.0498	0.0309	0.0263
Absolute structure parameter	-	-0.059(17)	0.04(2)
Goodness-of-fit on F^2	1.053	1.046	1.040
Final R indices [$I > 2\sigma(I)$]	R_1=0.0592 W R_2=0.1774	R_1=0.0447 W R_2=0.1164	R_1=0.0447 W R_2=0.1052
R indices (all data)	R_1=0.0657 W R_2=0.1854	R_1=0.0490 W R_2=0.1211	R_1=0.0547 W R_2=0.1144

The analyses on crystal structures have verified that Efonidipine conglomerate could obtain from its racemic solution when ethanol was chosen as the crystallized solvent. The same results were got when ethanol solvent was substituted by another solvent such as methanol, tetrahydrofuran, ethyl acetate and acetonitrile. While, racemic compound which existed as an acetone solvate could be prepared by crystallization from acetone only and the crystallization process must be keep stood without agitating. The racemic compound unsolvate has not been obtained in this study.

IV. CONCLUSION

The types of Efonidipine racemates were explored by single crystals XRD in this research. The conditions of how to obtain racemic conglomerate and racemic compound of Efonidipine have been revealed. Unlike most organic compounds, this work finds that the preparation of Efonidipine conglomerate is very simple and convenient while the preparation of Efonidipine racemic compound is very difficult. It might be explained that the molecular affinity between the same isomers of Efonidipine are stronger than that between the different isomers. The favorable stability and the convenient preparation process of efonidipine conglomerate enhance the possibility of direct crystallization utilization.

V. ACKNOWLEDGEMENT

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