Supporting Information

1. Solubility of Istradefylline in Twelve Different Solvents

The solubility data and the relative deviations of Istradefylline in seven single-solvents and five mixed-solvents in the range of 293.15 K to 333.15 K were recorded in Table S1.

Table S1. Solubility of Istradefylline in Twelve Different Solvents from 293.15 K to 333.15 K

solvent	T / K	x	x^{calc}	100δ	Solubility (mg/mL)	equilibrium crystal form of Istradefylline
methanol	293.15	$6.0102\cdot10^{-5}$	$5.9562\cdot10^{-5}$	0.899	0.6308	form II
	303.15	$1.4165\cdot10^{-4}$	$1.4584\cdot10^{-4}$	2.961	0.9521	
	313.15	$3.4118\cdot10^{-4}$	$3.3726\cdot10^{-4}$	1.150	1.4868	
	323.15	$7.3909\cdot10^{-4}$	$7.4041\cdot10^{-4}$	0.179	2.2726	
	333.15	$1.5504\cdot10^{-3}$	$1.5504\cdot10^{-3}$	0.024	3.5819	
ethanol	293.15	$9.7065\cdot10^{-5}$	$1.1608\cdot10^{-4}$	19.595	0.7061	form I
	303.15	$2.6974\cdot10^{-4}$	$2.5357\cdot10^{-4}$	5.995	1.9625	
	313.15	$5.6205\cdot10^{-4}$	$5.2695\cdot10^{-4}$	6.245	4.0904	
	323.15	$1.0077\cdot10^{-3}$	$1.0467\cdot10^{-3}$	3.633	7.3371	
	333.15	$2.0067\cdot10^{-3}$	$1.9955\cdot10^{-3}$	0.721	14.6255	
ethyl acetate	293.15	$1.8223\cdot10^{-3}$	$1.6380\cdot10^{-3}$	9.998	7.9374	form I
	303.15	$2.5023\cdot10^{-3}$	$2.4449\cdot10^{-3}$	2.205	9.9952	
	313.15	$3.3527\cdot10^{-3}$	$3.5650\cdot10^{-3}$	6.417	14.0693	
	323.15	$5.0619\cdot10^{-3}$	$5.0931\cdot10^{-3}$	0.654	22.1199	
	333.15	$7.2279\cdot10^{-3}$	$7.1484\cdot10^{-3}$	1.129	31.6541	
n-propanol	293.15	$2.0195\cdot10^{-4}$	$2.5122\cdot10^{-4}$	24.395	1.1470	form I
	303.15	$3.5509\cdot10^{-4}$	$4.4287\cdot10^{-4}$	24.720	2.0172	
	313.15	$8.7513\cdot10^{-4}$	$7.5357\cdot10^{-4}$	13.891	5.1910	
	323.15	$1.2359\cdot10^{-3}$	$1.2422\cdot10^{-3}$	0.178	7.0270	
	333.15	$1.9753\cdot10^{-3}$	$1.9906\cdot10^{-3}$	0.536	16.8872	
isopropanol	293.15	$2.2444\cdot10^{-4}$	$2.4557\cdot10^{-4}$	9.416	1.154	form I
	303.15	$3.5486\cdot10^{-4}$	$3.8601\cdot10^{-4}$	8.779	1.825	
	313.15	$6.5393\cdot10^{-4}$	$5.9059\cdot10^{-4}$	9.687	3.364	
	323.15	$8.6390\cdot10^{-4}$	$8.8232\cdot10^{-4}$	2.132	4.444	
	333.15	$1.2872\cdot10^{-3}$	$1.2911\cdot10^{-3}$	0.083	6.625	
n-butanol	293.15	$5.8994\cdot10^{-4}$	$5.1872\cdot10^{-4}$	12.073	2.479	form I
	303.15	$9.0924\cdot10^{-4}$	$9.3497\cdot10^{-4}$	2.830	3.822	
	313.15	$1.6551\cdot10^{-3}$	$1.6238\cdot10^{-3}$	2.180	6.964	
	323.15	$2.6569\cdot10^{-3}$	$2.7275\cdot10^{-3}$	2.537	11.189	
	333.15	$4.4749\cdot10^{-3}$	$4.4458\cdot10^{-3}$	0.540	18.88	
acetonitrile	293.15	$7.8859\cdot10^{-4}$	$6.0665\cdot10^{-4}$	23.071	5.820	form III
	303.15	$1.3033\cdot10^{-3}$	$1.2294\cdot10^{-3}$	5.431	9.623	

	313.15	$2.4173\cdot10^{-3}$	$2.3810\cdot10^{-3}$	1.612	17.868	
	323.15	$4.2078\cdot10^{-3}$	$4.4248\cdot10^{-3}$	5.101	31.161	
	333.15	$8.0031\cdot10^{-3}$	$7.9176\cdot10^{-3}$	1.030	62.49	
methanol/water (30/70,v/v)	293.15	$8.3539\cdot10^{-6}$	$8.6558\cdot10^{-6}$	3.614	0.1423	form II
	303.15	$1.5214\cdot10^{-5}$	$1.5374\cdot10^{-5}$	1.053	0.1682	
	313.15	$2.5667\cdot10^{-5}$	$2.6347\cdot10^{-5}$	2.648	0.2592	
	323.15	$4.3010\cdot10^{-5}$	$4.3727\cdot10^{-5}$	1.668	0.3133	
	333.15	$6.9422\cdot10^{-5}$	$7.0535\cdot10^{-5}$	1.604	0.4372	
ethanol/water (24/76,v/v)	293.15	$3.0766\cdot10^{-5}$	$2.6858\cdot10^{-5}$	12.703	0.4746	form I
	303.15	$6.1580\cdot10^{-5}$	$5.7309\cdot10^{-5}$	6.935	0.9674	
	313.15	$1.0523\cdot10^{-4}$	$1.1653\cdot10^{-4}$	10.741	1.4420	
	323.15	$2.3337\cdot10^{-4}$	$2.2686\cdot10^{-4}$	2.790	3.6616	
	333.15	4.2340·10-^{4}	$4.2458\cdot10^{-4}$	0.280	6.5132	
ethanol/water (55/45,v/v)	293.15	$1.2637\cdot10^{-4}$	$2.4088\cdot10^{-4}$	90.613	1.206	form I
	303.15	$3.9262\cdot10^{-4}$	$4.3874\cdot10^{-4}$	11.747	3.746	
	313.15	$7.0763\cdot10^{-4}$	$7.6957\cdot10^{-4}$	8.753	6.754	
	323.15	$1.5223\cdot10^{-3}$	$1.3049\cdot10^{-3}$	14.151	14.54	
	333.15	$2.0561\cdot10^{-3}$	$2.1465\cdot10^{-3}$	4.200	19.65	
acetonitrile/ Water (25/75,v/v)	293.15	$1.7171\cdot10^{-5}$	$2.3907\cdot10^{-5}$	39.227	0.247	form III
	303.15	$2.7358\cdot10^{-5}$	$3.7662\cdot10^{-5}$	37.663	0.393	
	313.15	$6.2272\cdot10^{-5}$	$5.7744\cdot10^{-5}$	7.272	0.895	
	323.15	$9.3962\cdot10^{-5}$	$8.6444\cdot10^{-5}$	8.001	1.350	
	333.15	$1.1693\cdot10^{-4}$	$1.2675\cdot10^{-4}$	8.395	1.680	
acetonitrile/ Water (58/42,v/v)	293.15	$2.2758\cdot10^{-4}$	$3.0125\cdot10^{-4}$	32.371	2.315	form III
	303.15	$5.8639\cdot10^{-4}$	$5.2035\cdot10^{-4}$	11.262	5.968	
	313.15	$8.3927\cdot10^{-4}$	$8.6877\cdot10^{-4}$	3.515	8.545	
	323.15	$1.4348\cdot10^{-3}$	$1.4071\cdot10^{-3}$	1.603	14.615	
	333.15	$2.2051\cdot10^{-3}$	$2.2182\cdot10^{-3}$	0.369	22.480	

2. Single crystal structure

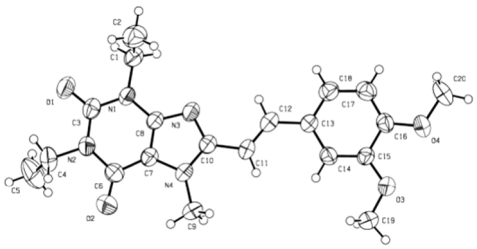


Figure S1. ORTEP view with labeling scheme for Istradefylline in ethanol.

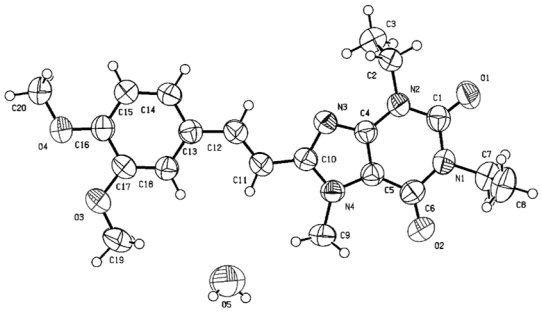


Figure S2. ORTEP view with labeling scheme for Istradefylline in methanol.

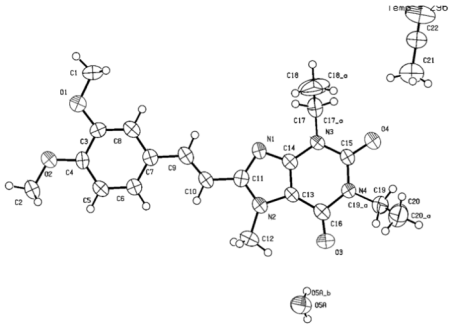


Figure S3. ORTEP view with labeling scheme for Istradefylline in acetonitrile.

Table S2. Bond Lengths for Istradefylline

1. Bond Lengths for Istradefylline in ethanol			
Bond	Length/Å	Bond	Length/Å
O3-C15	1.359(5)	C13-C18	1.386(7)
O3-C19	1.418(6)	C15-C14	1.377(7)
O1-C3	1.225(7)	C12-H12	0.93
O2-C6	1.224(6)	C12-C11	1.327(8)
O4-C16	1.367(7)	C7-C6	1.423(8)
O4-C20	1.429(8)	C14-H14	0.931
N4-C10	1.349(7)	C1-H1A	0.969
N4-C7	1.391(7)	C1-H1B	0.971
N4-C9	1.460(6)	C1-C2	1.499(6)
N3-C8	1.353(7)	C11-H11	0.93
N3-C10	1.347(6)	C9-H9A	0.96
N2-C3	1.395(6)	C9-H9B	0.96
N2-C6	1.405(7)	C9-H9C	0.96
N2-C4	1.480(8)	C18-H18	0.93
N1-C8	1.369(6)	C18-C17	1.386(9)
N1-C3	1.385(7)	C17-H17	0.93
N1-C1	1.463(6)	C4-H4A	0.97
C8-C7	1.360(7)	C4-H4B	0.97
C10-C11	1.445(7)	C4-C5	1.496(8)
C16-C15	1.410(7)	C19-H19	0.96
C16-C17	1.372(7)	C2-H2	0.959
C13-C12	1.460(7)	C5-H5	0.96

C13-C14	1.399(6)	C20-H20	0.96

2. Bond Lengths for Istradefylline in methanol

Bond	Length/Å	Bond	Length/Å
O1-C1	1.222(5)	C5-C6	1.415(5)
O2-C6	1.236(5)	C7-H7	0.990
O3-C17	1.375(4)	C7-C8	1.513(6)
O3-C19	1.408(7)	C8-H8	0.93
O4-C16	1.343(4)	C9-H9	0.980
O4-C20	1.428(5)	C10-C11	1.437(5)
N1-C1	1.405(5)	C11-C11	1.338(5)
N1-C6	1.404(5)	C12-C13	1.447(5)
N1-C7	1.473(5)	C13-C14	1.381(5)
N2-C1	1.368(4)	C13-C18	1.405(5)
N2-C2	1.480(5)	C14-H14	0.950
N2-C4	1.373(4)	C15-H15	0.949
N3-C4	1.339(4)	C14-C15	1.387(5)
N3-C10	1.351(4)	C15-C16	1.383(5)
N4-C5	1.386(4)	C16-C17	1.414(5)
N4-C9	1.461(4)	C17-C18	1.373(5)
N4-C10	1.363(4)	C18-H19	0.979
C2-C3	1.519(6)	O1-C1	1.222(5)
C4-C5	1.382(5)	O2-C6	1.236(5)
C2-H2	0.93	O3-C17	1.375(4)
C2-C3	1.399(4)	N1-C1	1.405(5)
C4-C5	1.382(5)	C1-C6	1.404(5)

3. Bond Lengths for Istradefylline in acetonitrile

Bond	Length/Å	Bond	Length/Å
O1 C3	1.366	H17A-C18	1.03
O2-C2	1.421	H17B-C18	1.01
O2-C4	1.368	C18-H18A	0.96
O3-C16	1.207	C18-H18B	0.96
O4-C15	1.232	C18-H18C	0.96
N1-C11	1.362	C18-H17A	1.03
N1-C14	1.341	C18-H17B	1.01
N2-C12	1.438	C19-H19A	0.97
N2-C13	1.382	C19-H19B	0.97
N3-C15	1.369	C19-H20B	1.238
N3-C17	1.504	C19-H20C	1.303
N3-C17	1.504	H19A-C20	1.14
N4-C15	1.373	H19B-C20	1.029
N4-C16	1.408	C20-H20A	0.96
N4-C19	1.517	C20-H19B	1.029
N4-C19	1.517	H20B-C19	1.238
C1-H1A	0.96	H20C-C19	1.303

C1-H1B	0.96	C17-H17A	0.969
C2-H2A	0.961	C17-H17B	0.97
C2-H2B	0.96	C18-H18A	0.96
C3-C4	1.4	C19-H19A	0.97
C3-C8	1.379	C19-H19B	0.97
C4-C5	1.388	C20-H20A	0.96
C5-H5	0.93	N5-C22	1.055
C5-C6	1.374	C21-H21A	0.961
C6-H6	0.93	C21-H21B	0.96
C6-C7	1.384	C21-H21C	0.959
C7-C8	1.386	C21-C22	1.391
C7-C9	1.458	C21-H21A	0.961
C8-H8	0.93	C21-H21B	0.96
C9-H9	0.93	C12-H12C	0.96
C9-C10	1.298	C12-H12A	0.96
C10-H10	0.931	C12-H12B	0.959
C10-C11	1.447	C12-H12C	0.96
C12-H12A	0.96	C13-C14	1.353
C12-H12B	0.959	C13-C16	1.425
C17-H17B	0.97	C17-H17A	0.969

4. Torsion Angles for Istradefylline in ethanol

Atom-Atom-Atom	Angle/°	Atom-Atom-Atom	Angle/°
C15-O3-C19	116.4(4)	O1-C3-N2	122.2(5)
C16-O4-C20	116.7(4)	O1-C3-N1	120.7(5)
C10-N4-C7	106.3(4)	N2-C3-N1	117.1(4)
C10-N4-C9	127.6(4)	N4-C7-C8	105.0(4)
C7-N4-C9	126.1(4)	N4-C7-C6	131.9(4)
C8-N3-C10	103.7(4)	C8-C7-C6	123.1(5)
C3-N2-C6	126.6(4)	C13-C14-C15	121.4(4)
C3-N2-C4	116.7(4)	C13-C14-H14	119.3
C6-N2-C4	116.7(4)	C15-C14-H14	119.3
C8-N1-C3	119.2(4)	N1-C1-H1A	109.1
C8-N1-C1	121.5(4)	N1-C1-H1B	109
C3-N1-C1	119.3(4)	N1-C1-C2	112.9(4)
N3-C8-N1	125.3(4)	H1A-C1-H1B	107.8
N3-C8-C7	112.6(4)	H1A-C1-C2	109
N1-C8-C7	122.2(4)	H1B-C1-C2	109
N4-C10-N3	112.5(4)	C10-C11-C12	122.2(5)
N4-C10-C11	123.0(4)	C10-C11-H11	118.9
N3-C10-C11	124.5(4)	C12-C11-H11	118.9
O4-C16-C15	114.5(4)	N4-C9-H9A	109.5
O4-C16-C17	125.8(5)	N4-C9-H9B	109.5
C15-C16-C17	119.7(5)	N4-C9-H9C	109.5
C12-C13-C14	122.3(4)	H9A-C9-H9B	109.5

C12-C13-C18	119.6(5)	H9A-C9-H9C	109.4
C14-C13-C18	118.0(5)	C16-C15-C14	119.3(4)
O3-C15-C16	115.5(4)	C13-C12-H12	116.2
O3-C15-C14	125.2(4)	C13-C12-C11	127.4(5)
		H12-C12-C11	116.4

5. Torsion Angles for Istradefylline in methanol

Atom-Atom-Atom	Angle/°	Atom-Atom-Atom	Angle/°
C16-O4-C20	116.6(3)	N4-C5-C6	132.7(3)
C1-N1-C6	126.8(3)	C4-C5-C6	123.0(3)
C1-N1-C7	115.4(3)	O2-C6-N1	120.8(3)
C6-N1-C7	117.7(3)	O2-C6-C5	127.4(3)
C1-N1-C2	119.8(3)	N1-C6-C5	111.9(3)
C1-N2-C4	120.4(3)	N1-C7-H7A	109.4
C2-N2-C4	119.7(3)	N1-C7-H7B	109.4
C4-N3-C10	103.9(3)	N1-C7-C8	111.3(4)
C5-N4-C9	125.8(3)	H7B -C7-H7A	108
C5-N4-C10	106.7(3)	H7A -C7-C8	109.3
C9-N4-C10	127.4(3)	H7B -C7-C8	109.4
O1-C1-N1	120.9(3)	C7-C8-H8A	109.5
O1-C1-N2	122.4(3)	C7-C8-H8B	109.4
N1-C1-N2	116.6(3)	C7-C8-H8C	109.4
N2-C2-H2	109.3	O4-C8-H8A	109.5
N2-C2-C3	111.7(3)	H8A-C8-H8B	109.6
H2A-C2-H2B	107.9	H8A-C8-H8C	109.5
H2-C2-C3	109.3	H8B-C8-H8C	109.4
C2-C3-H3A	109.3	N4-C9-H9A	109.5
C2-C3-H3B	109.5	N4-C9-H9B	109.5
C2-C3-H3C	109.5	N4-C9-H9C	109.5
H3A-C3-H3B	109.5	H9A-C9- H9B	109.5
H3A-C3-H3C	109.5	H9B-C9- H9C	109.5
H3B-C3-H3C	109.5	N3-C10-N4	112.0(3)
N2-C4-N3	125.8(3)	N4-C10-C11	123.4(3)
N2-C4-C5	121.1(3)	C10-C11-H11	119.1
N3-C4-C5	113.0(3)	C10-C11-C12	121.8(3)
N4-C5-N4	104.2(3)	H114-C11-C12	119.1

6. Torsion Angles for Istradefylline in acetonitrile

Atom-Atom-Atom	Angle/°	Atom-Atom-Atom	Angle/°
C1-O1-C3	117.1	O1-C1-H1B	109.5
C2-O2-C4	117.9	O1-C1-H1B	109.5
C11-N1-C14	102.8	H1A-C1-H1B	109.5
C11-N2-C12	128.1	H1A-C1-H1B	109.5
C11-N2-C13	106.5	H1B-C1-H1B	109.5
C12-N2-C13	125.4	O2-C2-H2A	109.4
C14-N3-C15	119.3	H2A-C2-H2B	109.4

C14-N3-C17	119.7	O1-C3-C4	115.2
C14-N3-C17	119.7	O1-C3-C8	126
C15-N3-C17	118.5	C4-C3-C8	118.8
C15-N3-C17	118.5	O2-C4-C3	116.1
C17-N3-C17	31.5	O2-C4-C5	124.3
C15-N4-C16	126.6	C3-C4-C5	119.6
C15-N4-C19	114.9	C4-C5-H5	120
C15-N4-C19	114.9	C5-C6-H6	119.1
C16-N4-C19	115	C5-C6-C7	121.6
C16-N4-C19	115	H6-C6-C7	119.3
C19-N4-C19	40	C6-C7-C8	117.8
O1-C1-H1A	109.4	C6-C7-C9	121.5
H9-C9-C10	116.6	C8-C7-C9	120.7
C9-C10-H10	116.2	C3-C8-C7	122.2
C9-C10-C11	127.4	C3-C8-H8	118.9
H10-C10-C11	116.3	C7-C8-H8	119
N1-C11-N2	112.5	C7-C9-H9	116.5
N1-C11-C10	125.1	C7-C9-C10	126.9
N2-C11-C10	122.4		

3. Preparation of three kinds of crystal istradefylline tablets

3.1 Materials

Lactose (Lactose Anhydrous), model: NF DTHV, batch number (Lot): B590000698, manufacturer: Kerry Inc-Rothschild, production date: 2019.09.09, valid until: 2022.09.08.

Microcrystalline Cellulose (MCC, Microcrystalline Cellulose), trademark: VIVAPUR®, model: PH 102, batch number (Batch No.): 56102193215, manufacturer: J. Rettenmaier & Sohne GmbH + Co. KG, production date: 2019.04, valid until: 2024.04.

Crospovidone (PVPP), trademark: Kollidon®, model:CL-F, batch number (Lot): 60547747G0, manufacturer: BASF SE, production date: 2019.03, valid until: 2022.03.

Magnesium Stearate, Trademark: LIGAMED®, Model: MF-2-V, Batch No.: C024748, Manufacturer: Peter Greven Nederland CV, Production Date: 2020.02, Valid until: 2024.02 .

To prepare the istradefylline tablets, prescribed amount of istradefylline and lactose was weighed and grinded in a mortar for 5 min (The median particle size of crystal form I/II/III is 5.6um, 5.2um, 7.1um respectively).

3.2 specific surface area

crystal I

superficial area	BET specific surface area of single point is 0.20000 at P/Po:	4.667	(m2/g)
	BET specific surface area of multipoint:	5.081	(m2/g)
	Surface area of micropores by T - diagram method:	0.000	(m2/g)
	External surface areabyT - diagram method:	5.081	(m2/g)

pore volume			
	Total volume of micropores (<2nm) by T-graph method:	0.000	(cm3/g)

crystal II

superficial area	BET specific surface area of single point is 0.20000 at P/Po:	4.73746	(m2/g)
	BET specific surface area of multipoint:	5.50915	(m2/g)

crystal III

superficial area	BET specific surface area of single point is 0.20000 at P/Po:	4.71559	(m2/g)
	BET specific surface area of multipoint:	5.18539	(m2/g)

BET equation
(P/Po)/[V(1-P/Po)] = (C-1)/(Vm*C) * P/Po + 1/(Vm*C)
(the N2) Sw = 4.35 * Vm / Mass
Single point BET equation(C>>1)
Vm = V * (1 - P/Po)

Figure S4. The surface area of three crystal forms

4.Thermogravimetric analysis (TGA) curves and IR

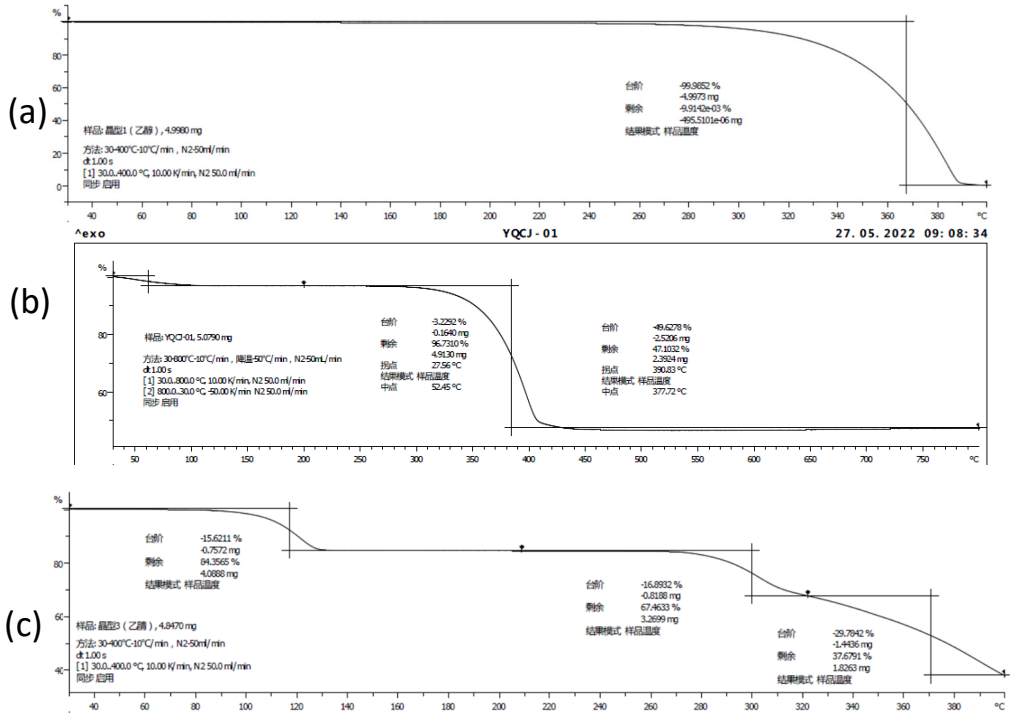
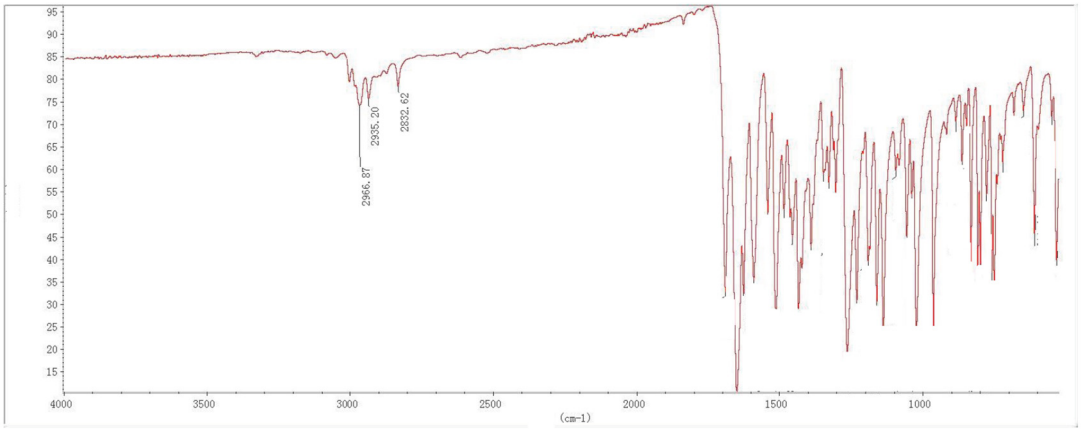
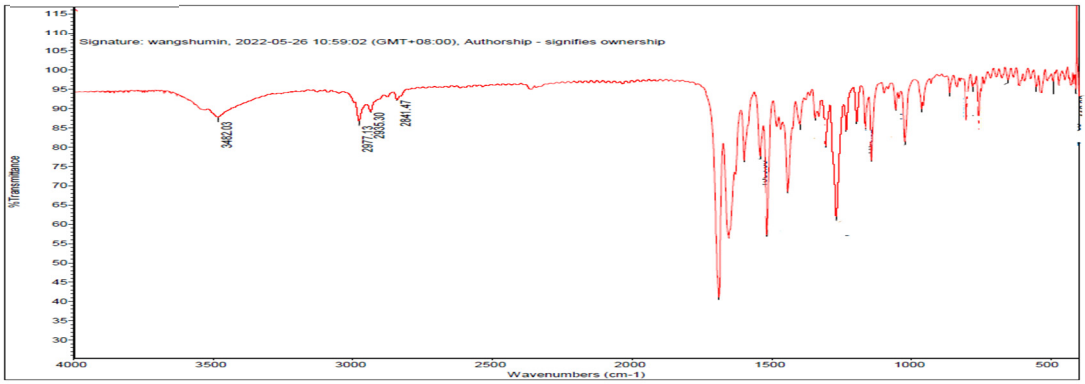


Figure S5. (a) The TGA curves of From I, **(b)** The TGA curves of From II and **(c)** The TGA curves of From III.

From I



From II



From III

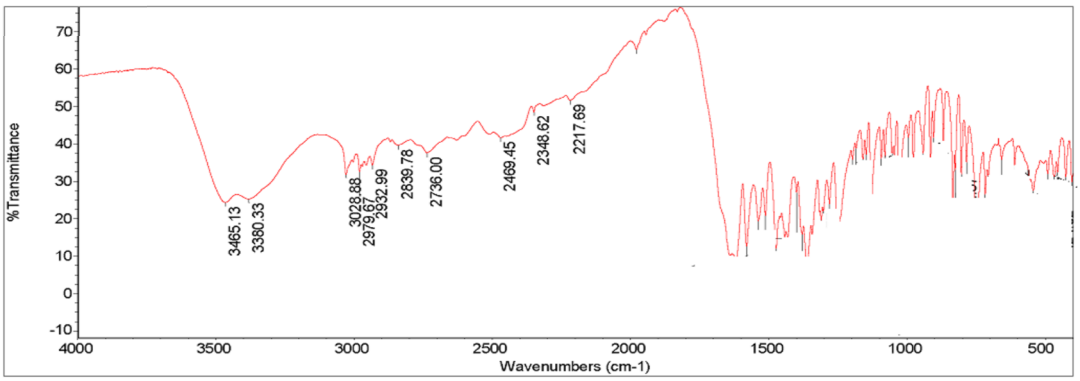


Figure S6. The IR of From I, The IR of From II and The IR of From III.

5. Stability data

Table S3. Stability data of Istradefylline (Form I of istradefylline)

Packaging Configuration: The packaging of the stability study samples is simulate to the market package. The samples is contained in two-layer PE bags. Fiber drums are used for external packages, sealed with plastic sealing.

Temperature: 25±2℃ Humidity: 60±5% Samples are packed under simulated market container

Batch No.	Detection time	Storage time	Appearance	Loss on Drying (%)	Assay (on dry basis ,%)	Related substance(%)						
						Impurity A	Impurity C	Impurity E	Impurity Z	4-Desmethyl istradefylline	Other individual impurities	Total impurities
			Light yellow to yellowish green crystalline powder	≤0.5	98.0-102.0	≤0.1	≤0.4	≤0.1	≤0.1	≤0.1	≤0.1	≤1.0
1608002	2016.8.16	0month	Yellowish green crystalline powder	0.03	99.9	0.01	not detected	not detected	0.006	not detected	0.02	0.05
	2017.2.9	3month	Yellowish green crystalline powder	0.03	100.0	0.1	not detected	not detected	0.1	not detected	0.03	0.3
1608003	2016.11.8	0month	Yellowish green crystalline powder	0.04	99.7	0.01	not detected	not detected	not detected	not detected	0.02	0.05
	2017.2.9	3month	Yellowish green crystalline powder	0.03	99.9	0.1	not detected	not detected	0.2	not detected	0.03	0.4
1608004	2016.11.8	0month	Yellowish green crystalline powder	0.03	99.6	0.02	not detected	not detected	not detected	not detected	0.02	0.05
	2017.2.9	3month	Yellowish green crystalline powder	0.03	100.1	0.09	not detected	not detected	0.1	not detected	0.03	0.3