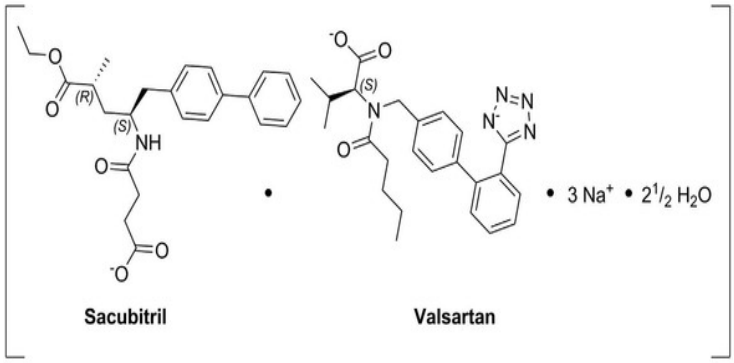
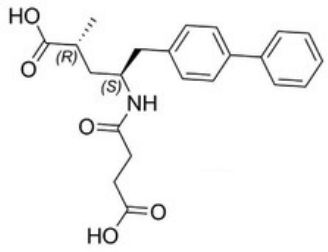
a)



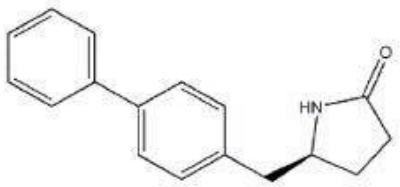
LCZ696

b)

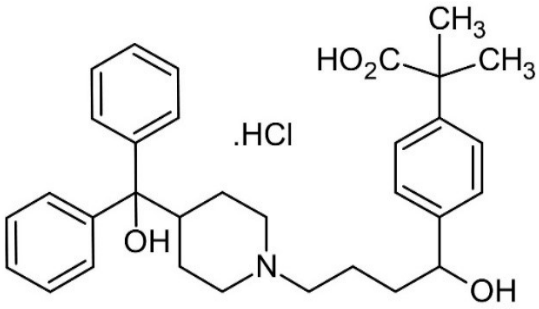


LBQ657
(Sacubitrilat)

c)

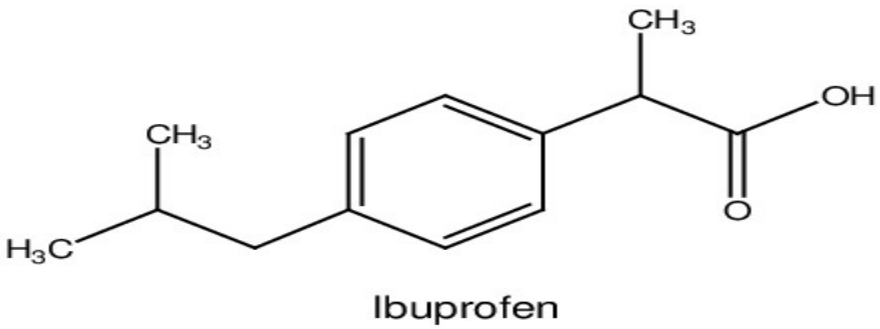


d)



Fexofenadine

e)



Ibuprofen

Figure S1: Structures of (a) LCZ696 supramolecular complex, (b) Sacubitrilat ,LBQ657, (c) Internal standard (IS) (d) Fexofenadine and (e)Ibuprofen.

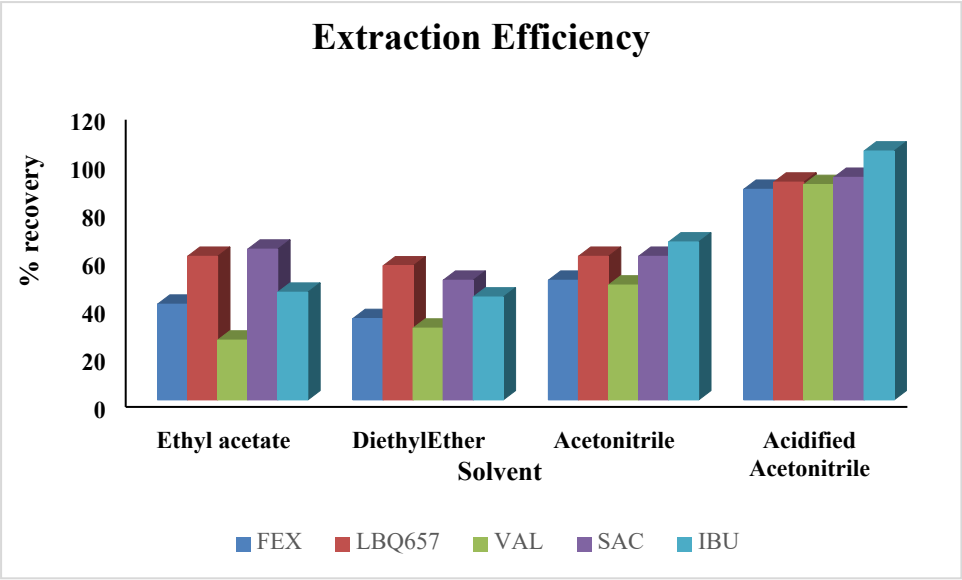
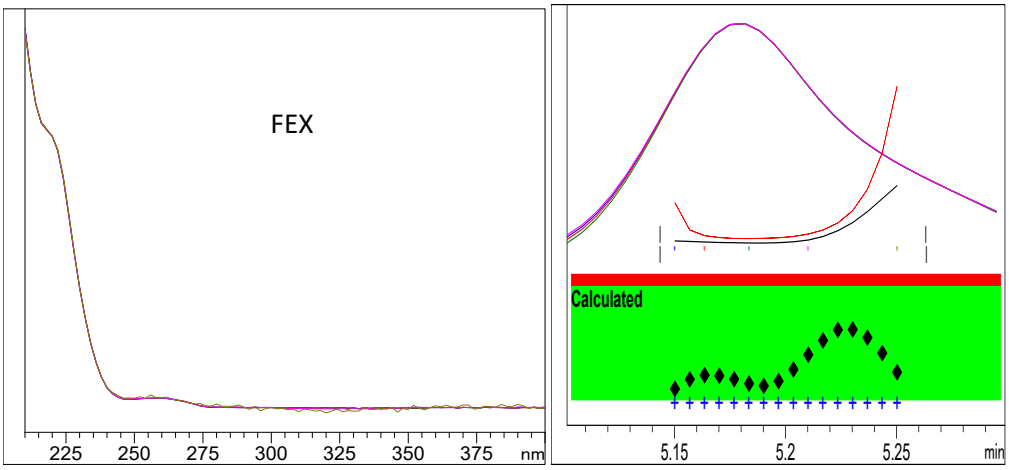
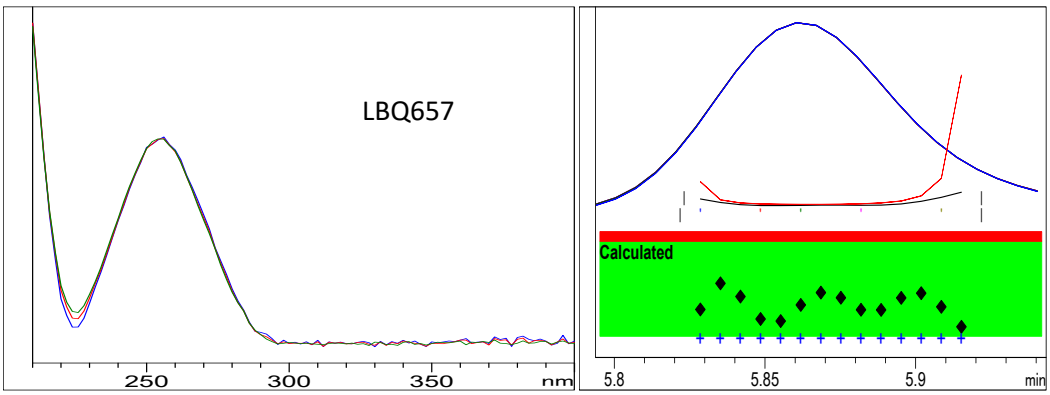


Figure S2: Effect of different solvents on extraction efficiency of FEX, LBQ657, VAL, SAC and IBU from plasma.

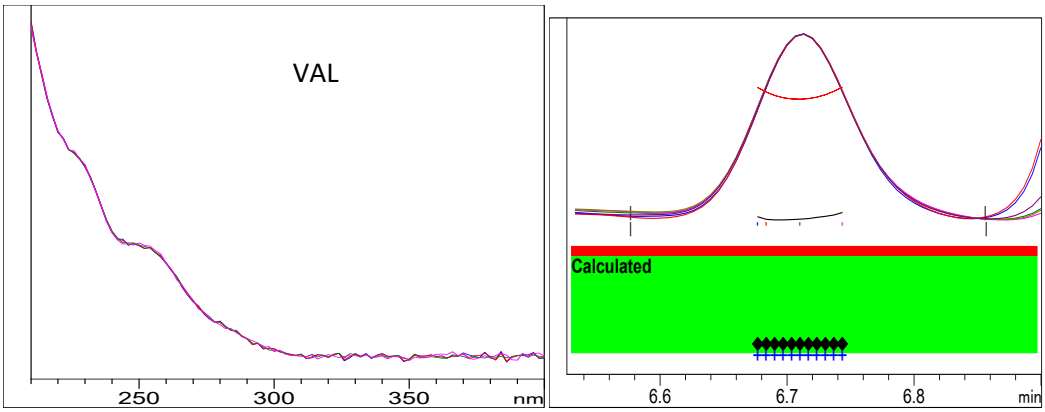
a)



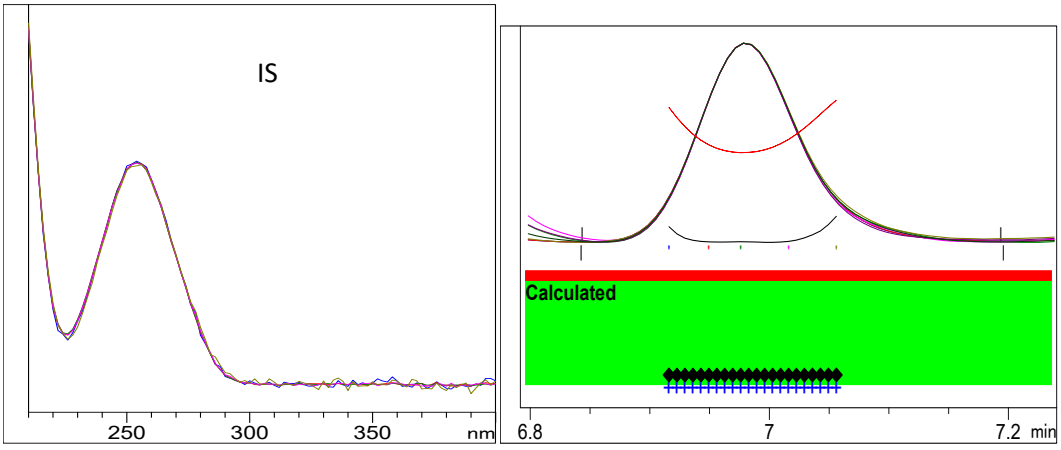
b)



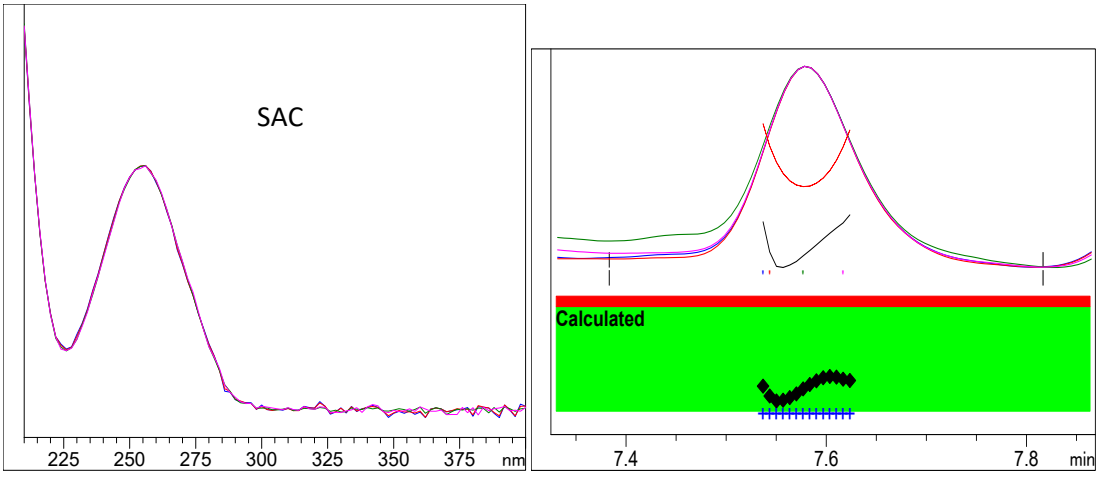
c)


VAL
250
300
350
nm
Calculated
6.6
6.7
6.8
min

d)


IS
250
300
350
nm
Calculated
6.8
7
7.2
min

e)



f)

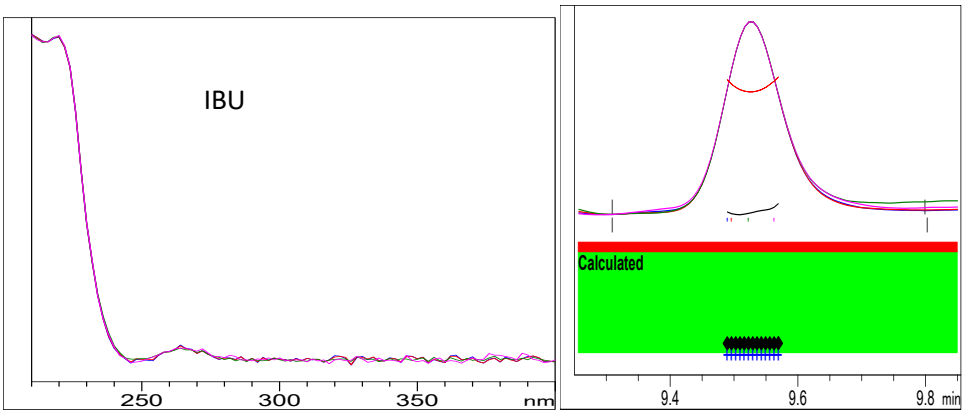
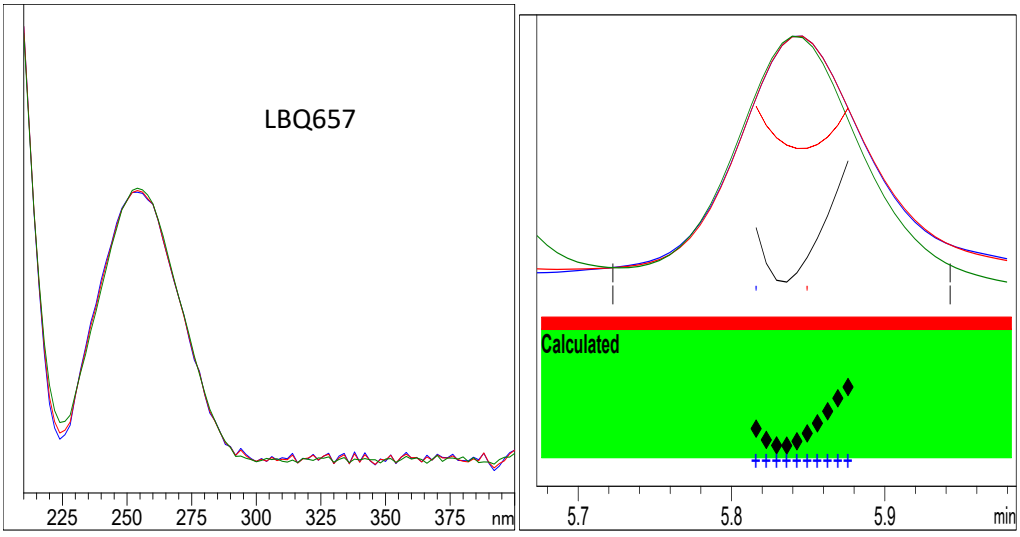


Figure S3: Superimposed absorption spectra and purity profile illustrating peak purity of (a)FEX, (b) LBQ657, (c) VAL, (d) IS, (e) SAC and (f) IBU obtained from spiked plasma with drugs and IS extracted from DAD.

a)



b)

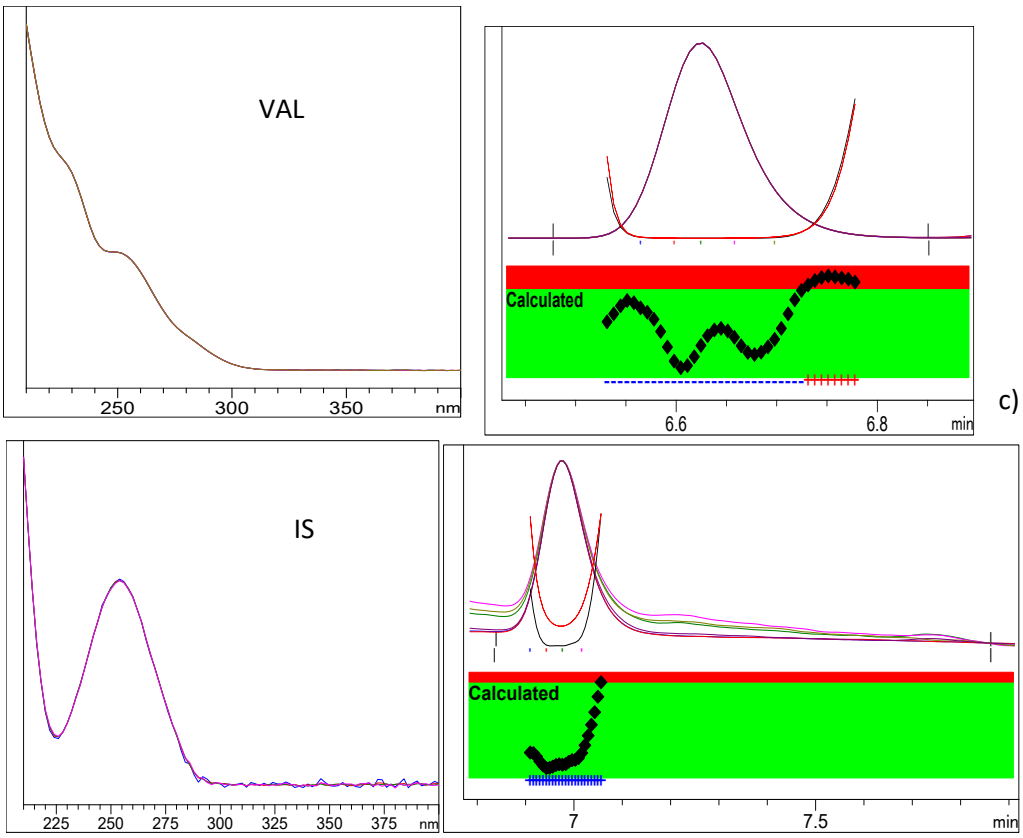


Figure S4: Representative example of Superimposed absorption spectra and purity profile illustrating peak purity of (a) LBQ657, (b)VAL and (c) IS obtained from real rat plasma at T_{max} after 15 min oral administration of Entresto ™ extracted from DAD.

Table S1: Gradient elution ratio and programmed wavelength for HPLC FLD.

HPLC/FLD gradient elution ratio			
Time (min)	**%A (phosphate buffer)**	**%B (ACN)**	**Flow rate (mL/min)**
0 → 1	60	40	1
1.3→8.5	30	70	0.8
8.6→10	30	70	1.1
HPLC FLD programmed wavelength			
Time (min)	**λ_{ex} nm**	**λ_{em} nm**	PMT
0	232	310	12
5.5	250	340	
8.5	232	310	

Table S2: Intra-day and inter-day precision and accuracy for the determination of LCZ696 analytes, FEX and IBU in spiked rat plasma samples using the proposed HPLC- FLD method.

Drug	Level	Concentration (µg/mL)	Accuracy		Precision	
			Mean % recovery [a]	E_r% [b]	Intra-day RSD%[c]	Inter-day RSD%[c]
FEX	LLOQ	2	100.08	0.08	0.96	1.12
	LQC	5	103.42	3.42	4.68	2.45
	MQC	10	100.51	0.51	7.22	1.67
	HQC	20	100.50	0.50	4.92	3.22
LBQ657	LLOQ	0.02	**94.32**	-5.68	4.56	6.21
	LQC	0.06	96.89	-3.11	5.09	3.22
	MQC	5	98.71	-1.29	3.21	2.04
	HQC	8	97.01	-2.99	4.56	3.90
VAL	LLOQ	0.025	**102.85**	2.85	6.67	2.33
	LQC	0.06	101.63	1.63	5.87	4.13
	MQC	5	95.49	-4.51	3.53	2.01
	HQC	10	99.83	-0.17	2.24	1.34
SAC	LLOQ	0.02	101.94	1.94	8.14	4.45
	LQC	0.06	99.73	-0.27	5.23	2.67
	MQC	5	95.98	-4.01	4.22	3.21
	HQC	8	98.97	-1.03	3.73	3.02
IBU	LLOQ	2	99.75	-0.25	5.30	4.12
	LQC	5	99.95	-0.04	3.40	2.10
	MQC	10	96.59	-3.41	0.58	3.90
	HQC	20	99.66	-0.34	2.16	2.66

[a]Mean % recovery for six determinations.

[b] % Relative error.

[c]% Relative standard deviation.

Table S3: Stability summary of the studied drugs in spiked rat plasma samples at two concentrations levels (LQC and HQC) using the proposed HPLC- FLD method (n = 6)

Stability conditions		FEX (µg mL $^{-1}$)		LBQ657 (µg mL $^{-1}$)		VAL (µg mL $^{-1}$)		SAC (µg mL $^{-1}$)		IBU (µg mL $^{-1}$)	
		5	**20**	**0.06**	**8**	**0.06**	**10**	**0.06**	**8**	**5**	**20**
Freeze and Thaw Stability	**Recovery %**	109.01	107.17	103.44	106.03	95.04	109.76	96.56	108.62	104.89	107.95
After 5 cycles at - 20°C	**RSD%**	3.45	1.57	2.05	6.09	6.01	4.11	2.02	4.45	3.11	7.84
Post preparative (5°C for 24 h)	**Recovery %**	106.67	88.44	105.55	103.51	106.71	97.52	106.32	100.28	107.01	89.57
	RSD%	5.78	6.57	4.32	2.87	4.52	2.09	3.11	1.27	2.02	3.31
Long-Term Stability	**Recovery %**	105.56	90.72	96.34	102.45	94.32	100.98	105.41	103.79	96.31	95.67
20 days at -20°C	**RSD%**	3.44	4.99	3.78	4.32	2.55	5.05	2.34	2.09	3.22	7.40
Bench-Top Stability(6h)	**Recovery %**	104.32	94.80	95.31	97.34	108.03	93.91	97.03	98.49	95.42	92.30
	RSD%	5.01	4.90	4.55	6.39	1.33	6.52	5.09	5.43	4.11	3.97