A sustainable and novel LC-TQ-MS/MS method for quantifying mutagenic Ketoconazole-NDSRIs aligned with green and white analytical chemistry principles

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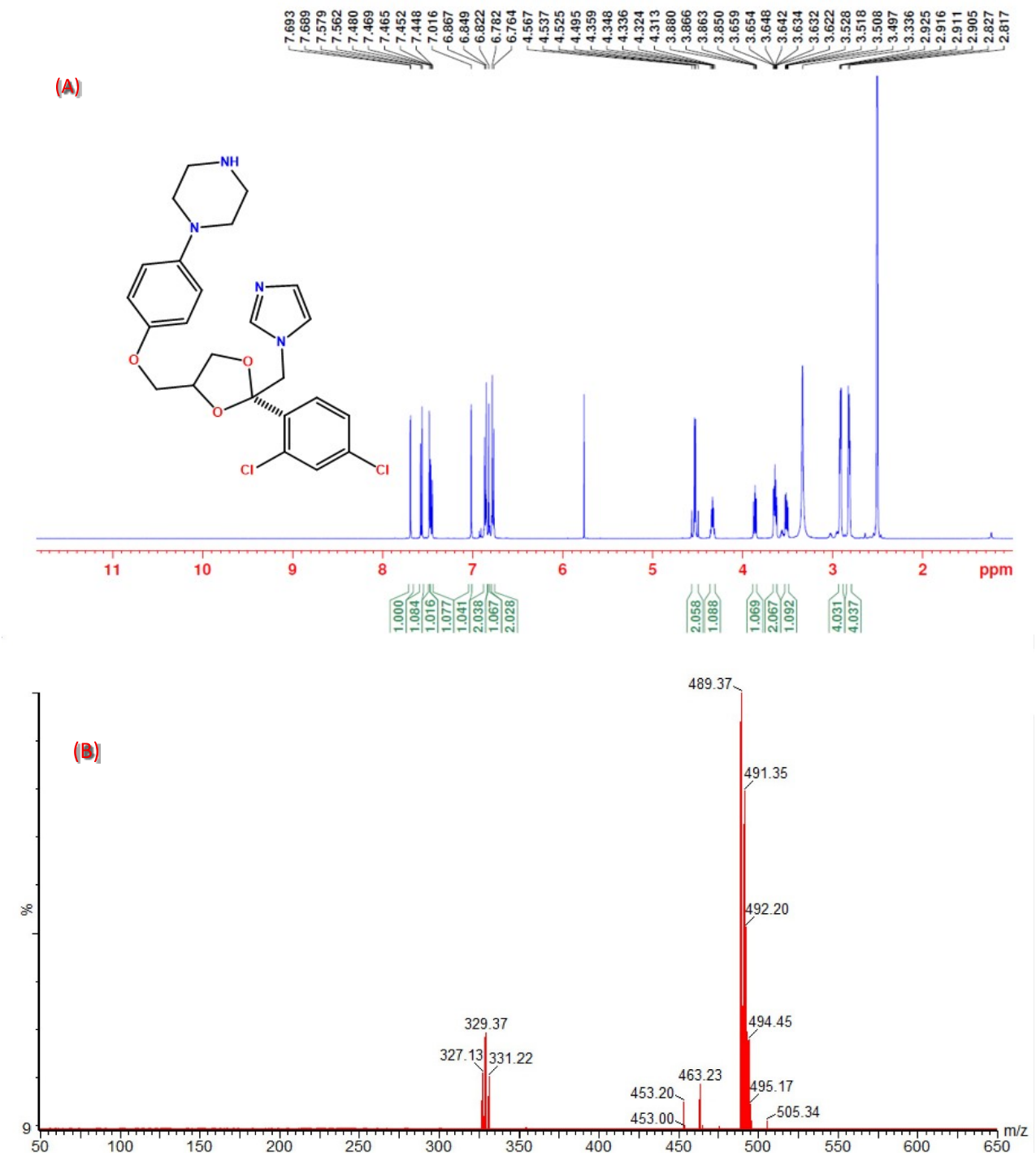

Fig. S1. (A) ^{1}H-NMR, and (B) mass spectra of KCZ degradant

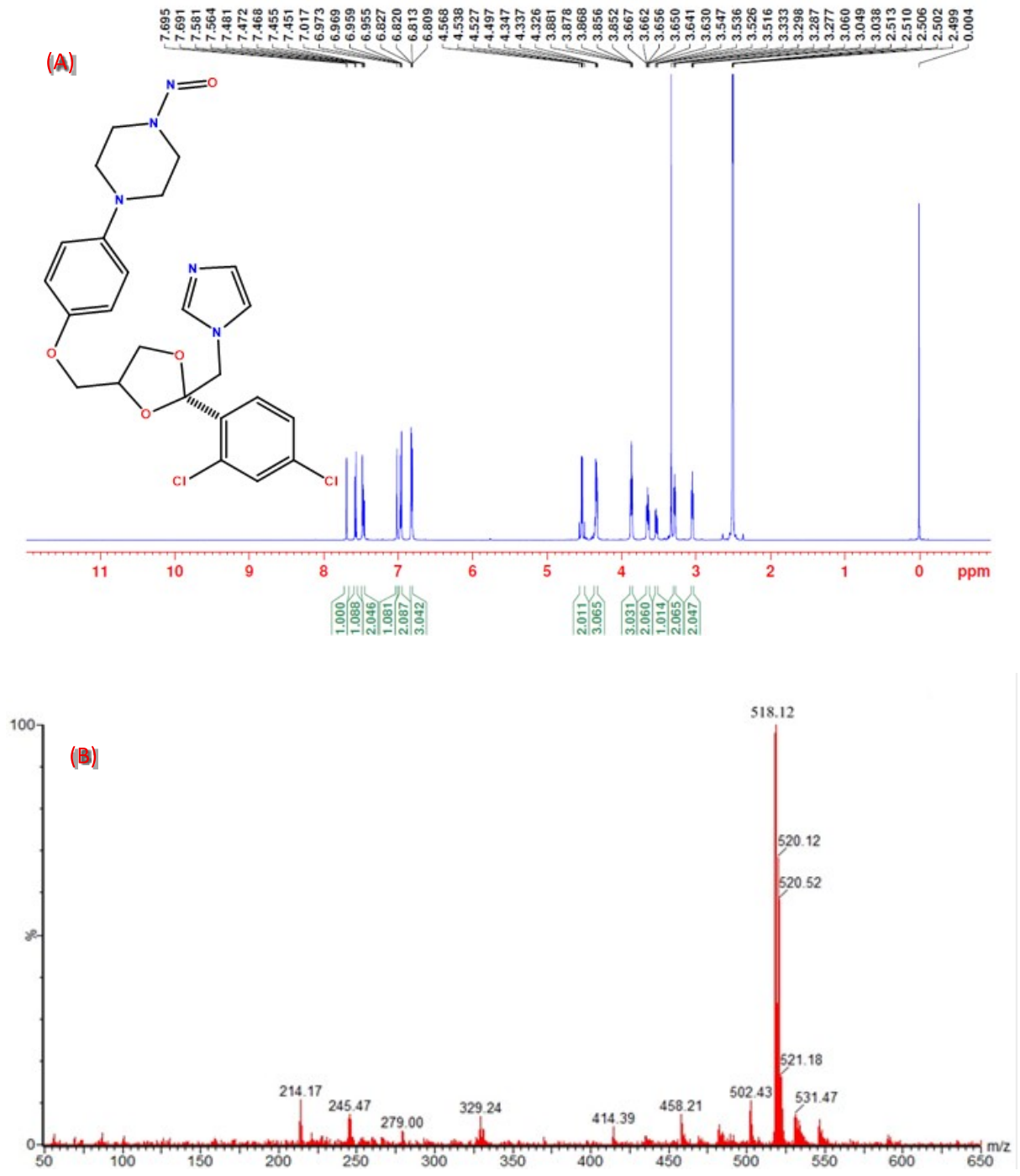

Fig. S2. (A) ^{1}H-NMR, and (B) mass spectra of KCZ degradant-NDSRI

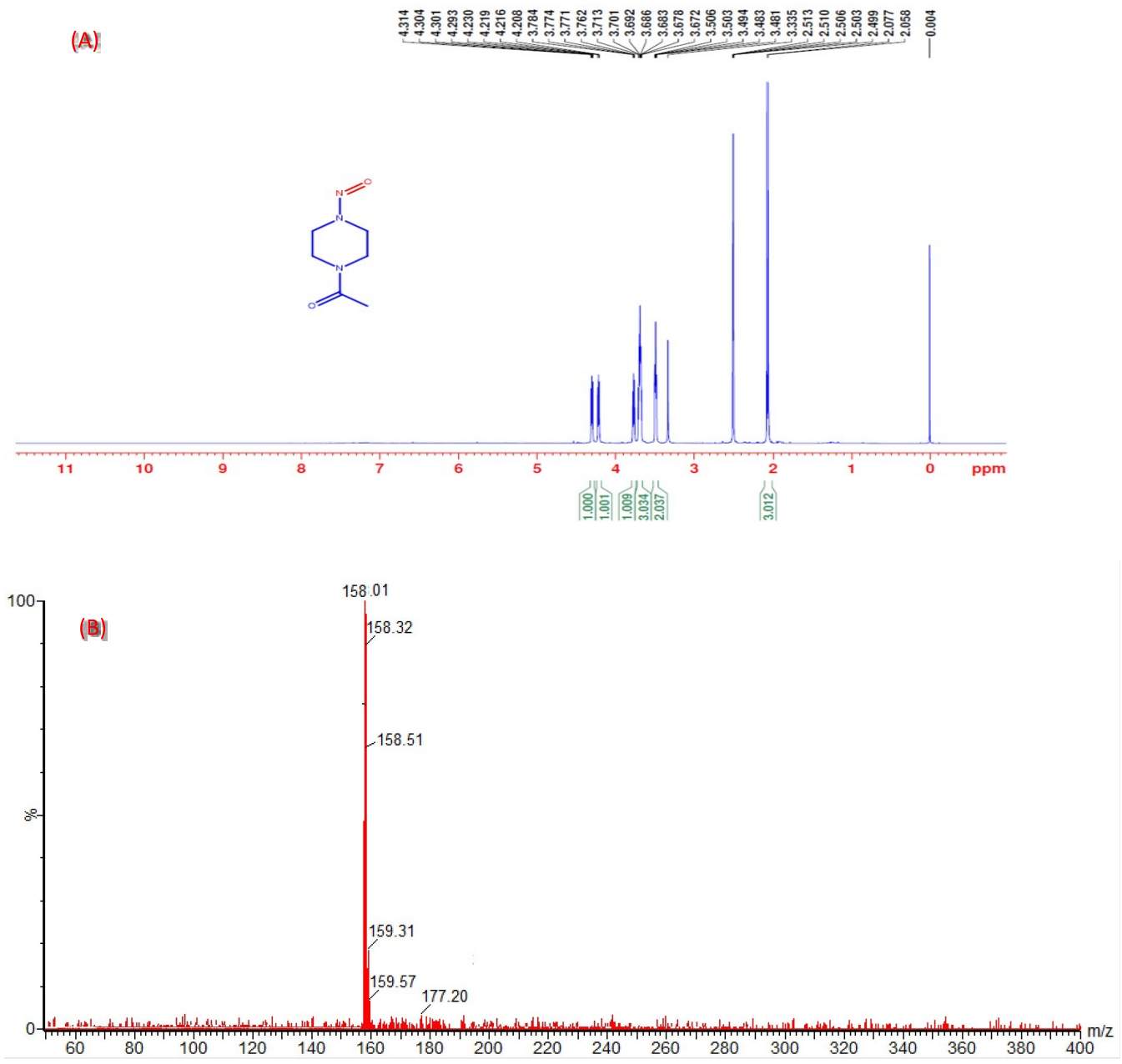

Fig. S3. (A) ^{1}H-NMR, and (B) mass spectra of N-NAP

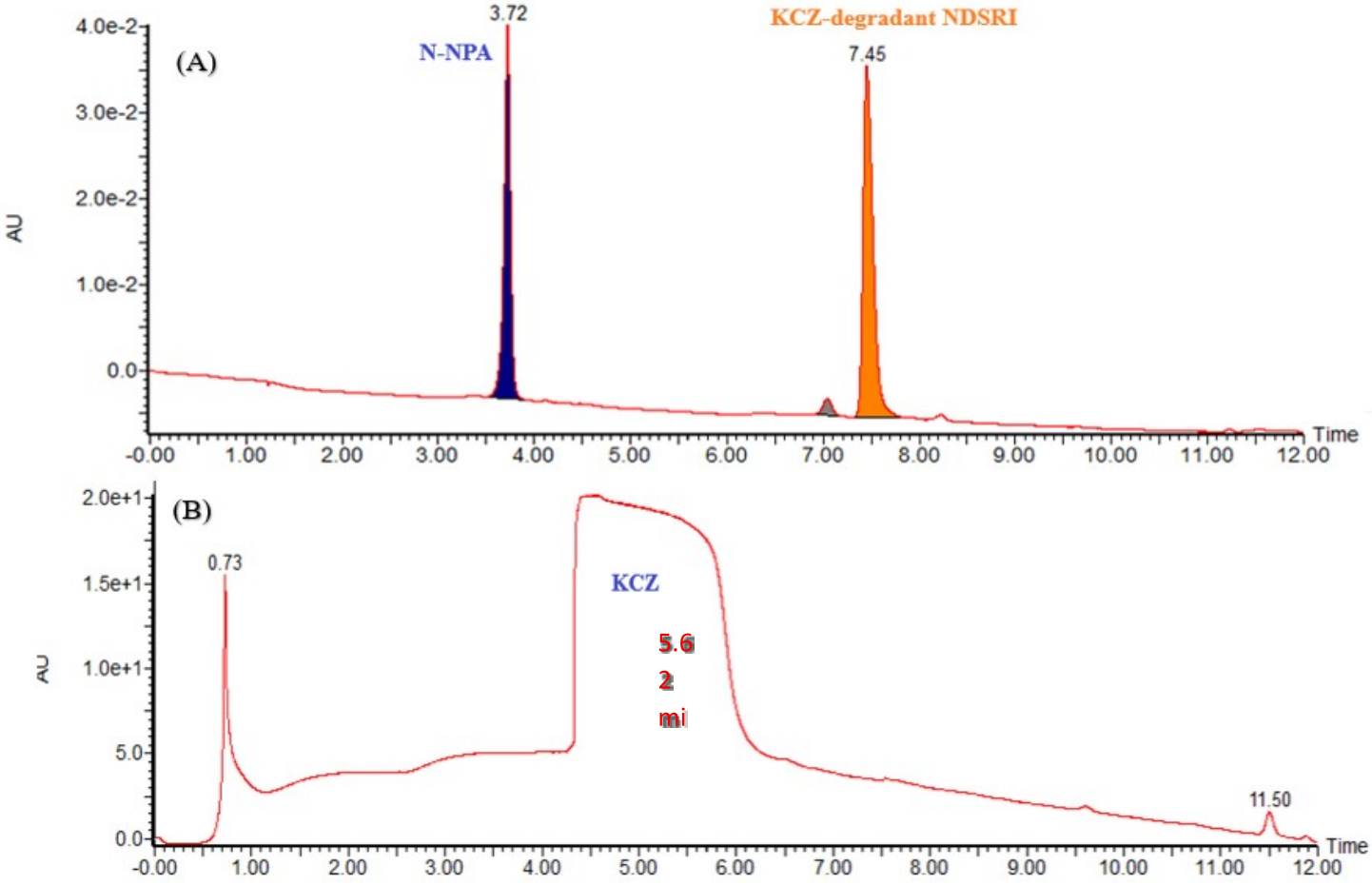

Fig. S4. Typical overlay UV chromatogram of (A) KCZ-NDSRIs, and (B) KCZ at 10 mg/mL solution

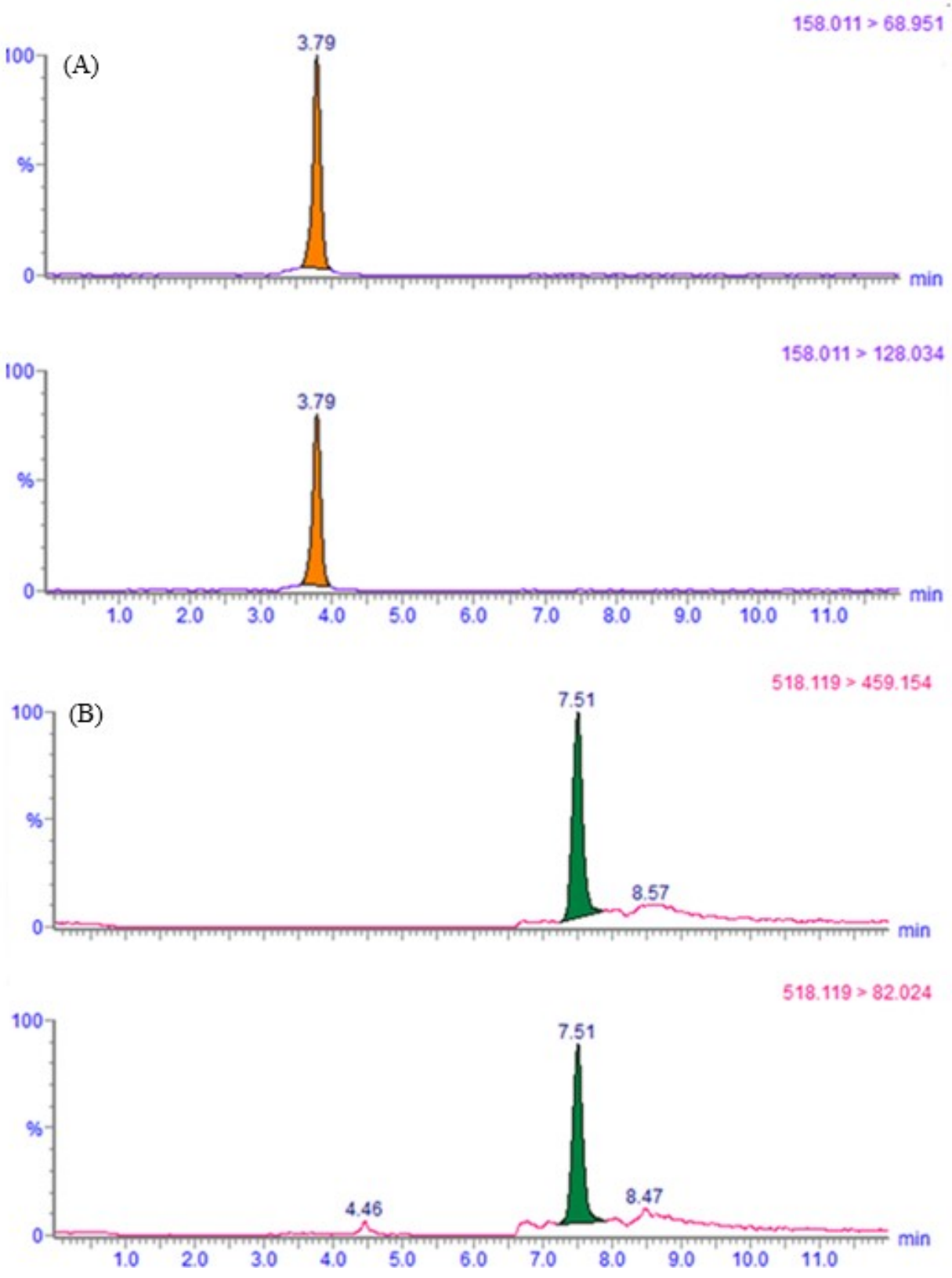

Fig. S5. Quantifier-qualifier MRM chromatograms of (A) KCZ degradant, and (B) KCZ-degradant NDSRI

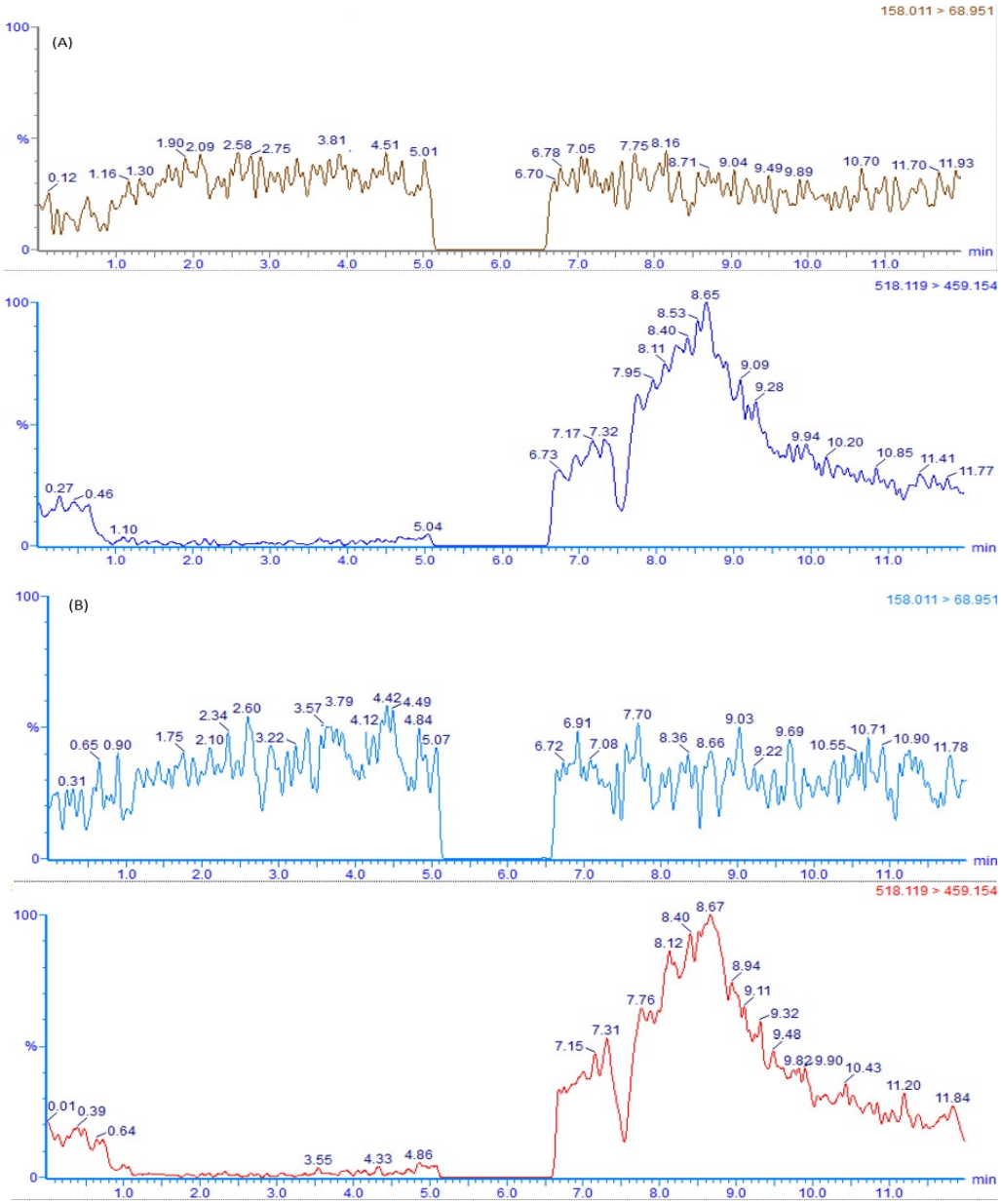

Fig. S6. MRM chromatograms of (A) KCZ-tablet formulation sample concentration at 10 mg mL^{-1} , and (B) KCZ-cream formulation sample concentration at 10 mg mL^{-1}

Table S1 Summarized results of the robustness study

Parameter	Change	Content (µg g^{-1})		% absolute difference with respect to the nominal condition	
		N-NPA	KCZ-degradant NDSRI	N-NPA	KCZ-degradant NDSRI
Flow rate (mL/min)	0.35	1.09	1.06	3.80	2.91
	0.40	1.05	1.03	-	-
	0.45	1.03	1.04	1.90	0.97
Column temp. (°C)	38	1.07	1.01	1.90	1.94
	40	1.05	1.03	-	-
	42	1.03	1.04	1.90	0.97
DT (°C)	400	1.04	1.05	0.95	1.94
	450	1.05	1.03	-	-
	500	1.05	1.04	0.0	0.97
DGF (L/Hr)	850	1.03	1.06	1.90	2.91
	900	1.05	1.03	-	-
	950	1.04	1.06	0.95	2.91
CE (V)	16	1.01	1.07	3.80	3.88
	18	1.05	1.03	-	-
	20	1.02	1.01	2.85	1.94

Table S2 MoGAPI and AGREE principles, method conditions, and score values

MoGAPI			AGREE		
Pictogram Name	Sub Part no and name	Method Condition	Principle	Method Condition	Principle Score
Sample sourcing	1. Collection	Off-Line	1. Sample treatment	Off-line analysis	0.48
	2. Preservation	None	2. Sample Amount	0.5 g	0.98
	3. Transport	None	3. Device Positioning	Off-line	0.0
	4. Storage	Normal Condition	4. Sample Prep. Stages	3 or fewer	1.0
Method type	5. Direct/Indirect	Simple Preparation	5. Automation, miniaturization	Automatic, none or miniaturized	1.0
Sample preparation	6. Scale of extraction	Nano	6. Derivatization	NA	1.0
	7. Solvents/Reagents	Non- Green	7. Waste	15 mL	0.32
	8. Additional treatments	None	8. Analysis Throughput	2	0.62
Reagents and chemicals used	9. Amount	<10 mL	9. Energy consumption	LC-MS	0.36
	10. NFPA health hazard value	Acetonitrile:2, Formic acid:2	10. Source of reagents	No reagents	1.0
	11. NFPA flammability value	Acetonitrile:3, Formic acid:3	11. Toxicity	10 mL	0.2
Instrumentation	12. Energy usage	<1.5 KWh per sample	12. Operator safety	Highly flammable	0.8
	13. Occupational hazard	Hermetic sealing of analytical procedure	**Method AGREE Score**		**0.65**
	14. Waste	>10 mL			
	15.	Degradation, passivation			
Symbol	O-Present	Qualitative and Quantitative			