Supplementary material

Study on the properties and in vitro transdermal and cytotoxicity of drug-active ionic liquids with matrine as the cation

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1. Mass spectrum of anions and cations in ionic liquids

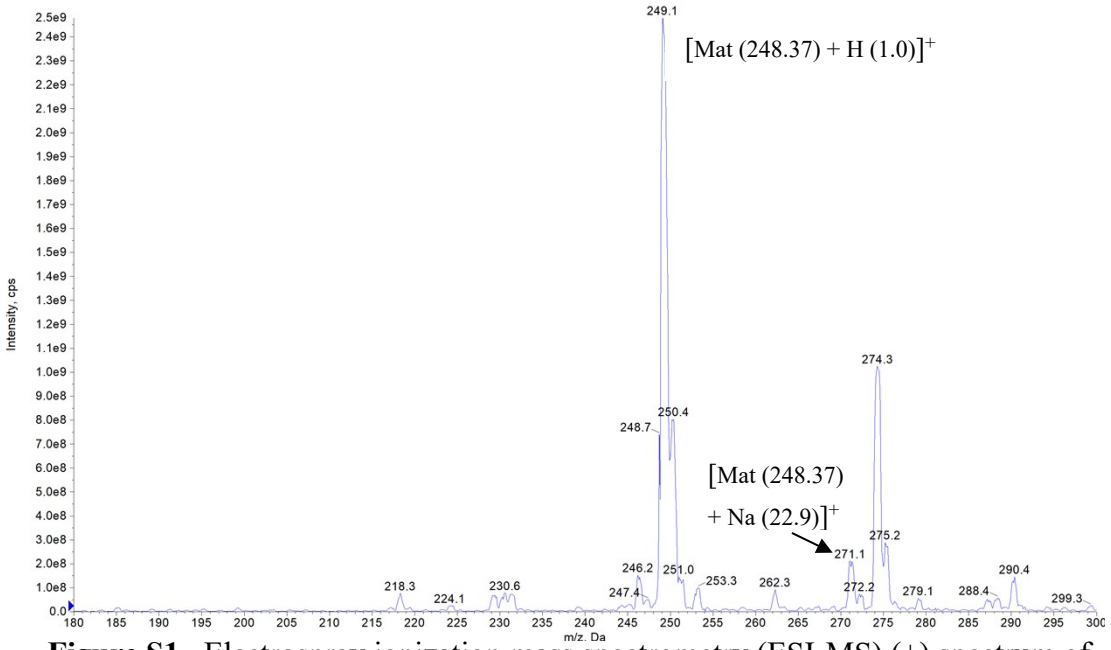

Figure S1. Electrospray ionization mass spectrometry (ESI-MS) (+) spectrum of matrine (Mat).

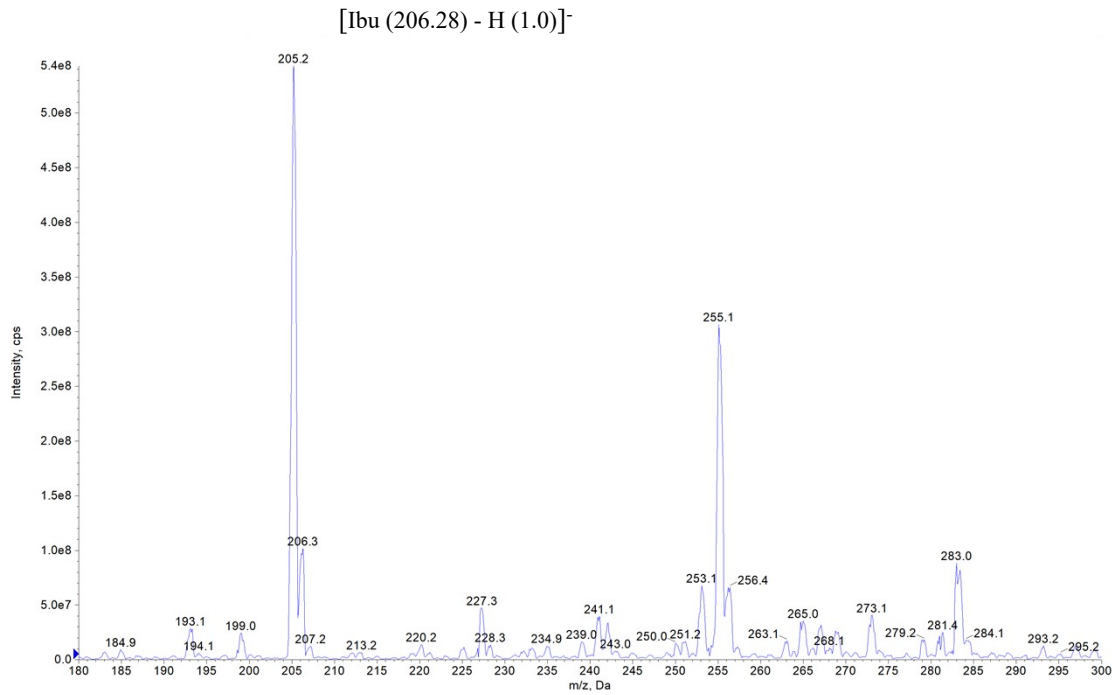

Figure S2. Electrospray ionization mass Spectrometry (ESI-MS) (-) spectrum of [Ibu] in [Mat][Ibu] ionic liquid.

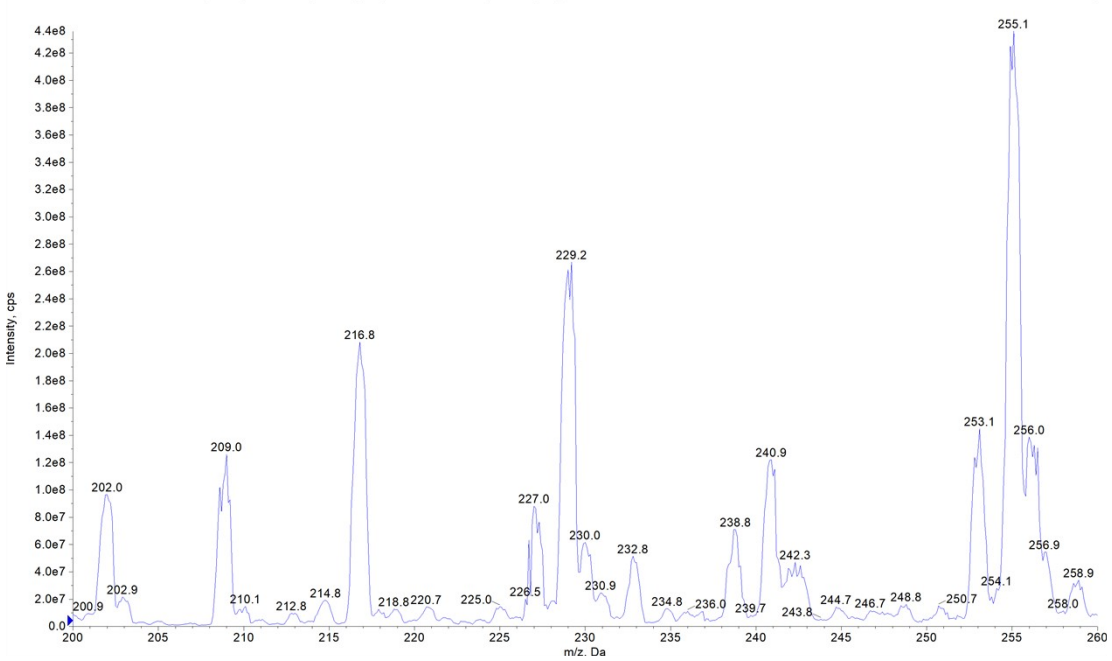

Figure S3. Electrospray ionization mass Spectrometry (ESI-MS) (-) spectrum of [Nap] in [Mat][Nap] ionic liquid.

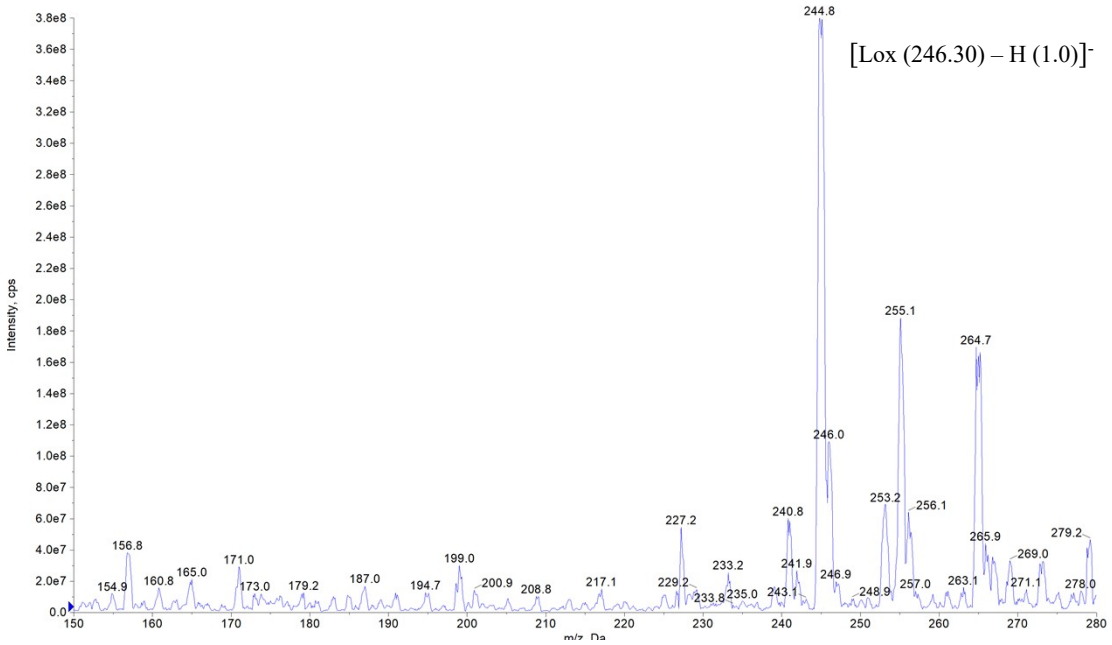

Figure S4. Electrospray ionization mass Spectrometry (ESI-MS) (-) spectrum of [Lox] in [Mat][Lox] ionic liquid.

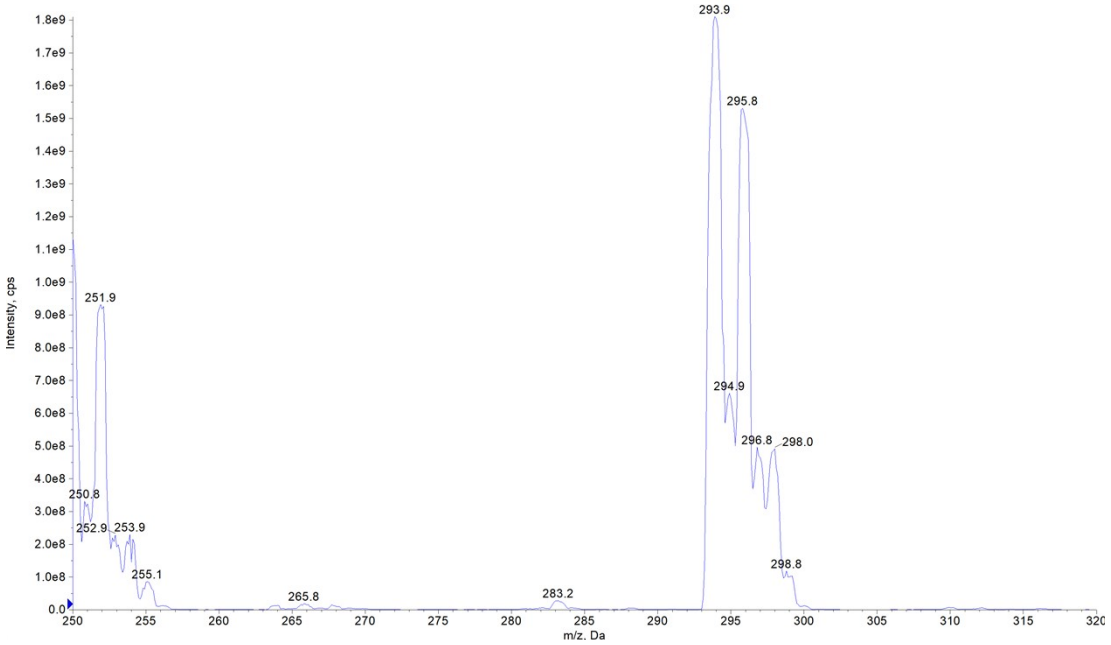

Figure S5. Electrospray ionization mass Spectrometry (ESI-MS) (-) spectrum of [Dic] in [Mat][Dic] ionic liquid.

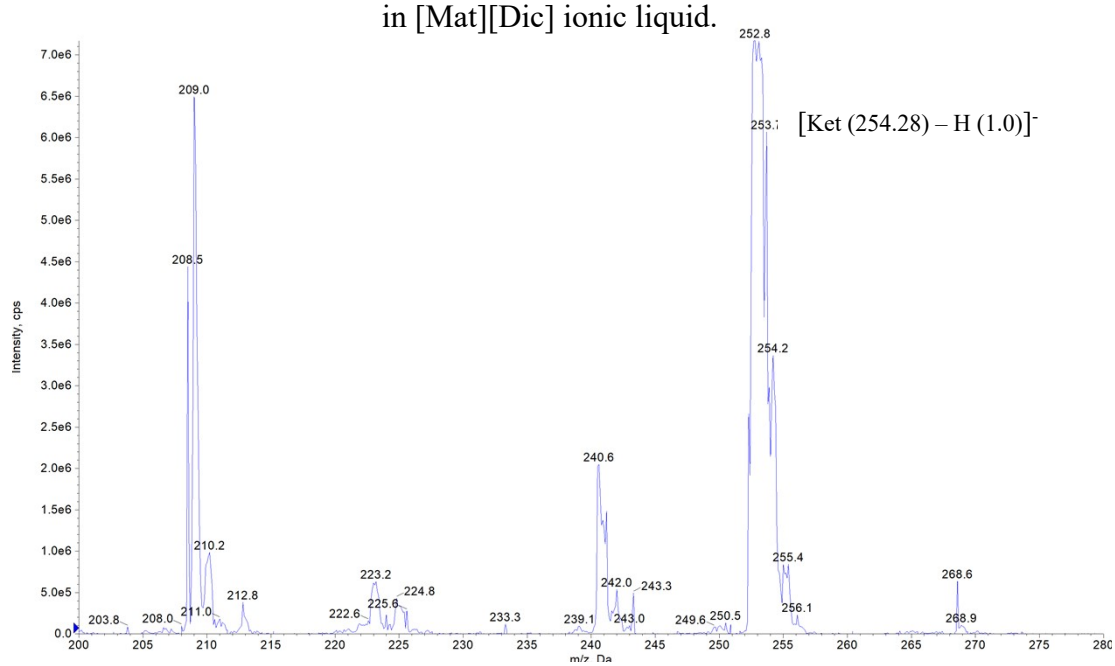

Figure S6. Electrospray ionization mass Spectrometry (ESI-MS) (-) spectrum of [Ket] in [Mat][Ket] ionic liquid.

2. Infrared spectrogram

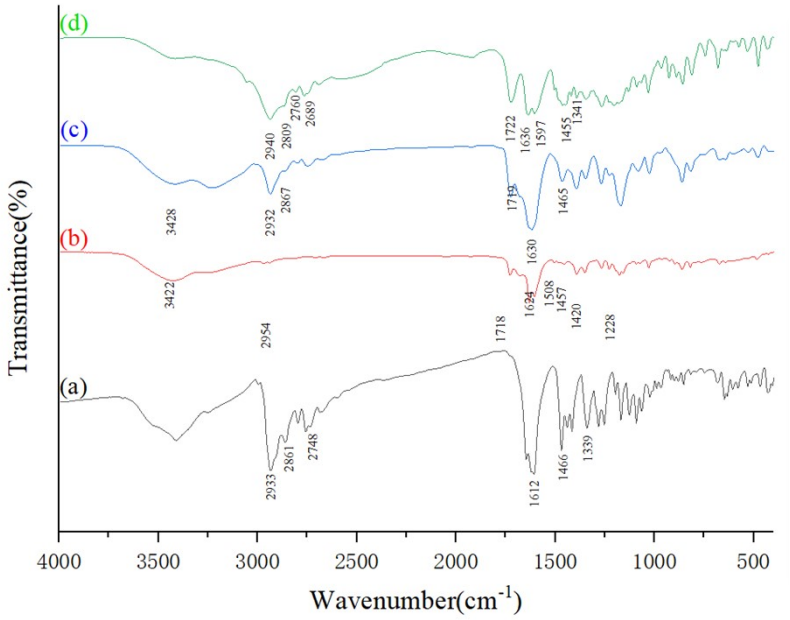

Figure S7. FT-IR spectra of pure drugs (a) Mat, (b) Ibu and their corresponding

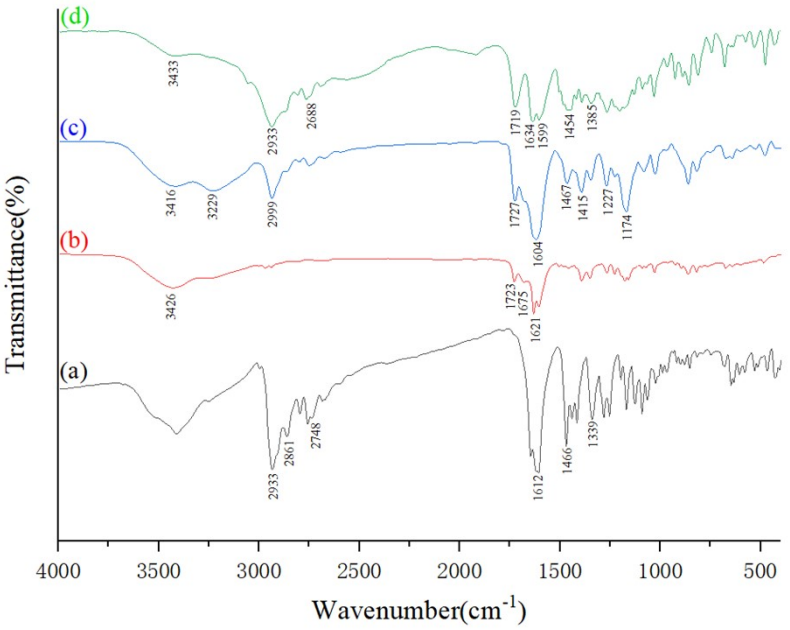

Figure S8. FT-IR spectra of pure drugs (a) Mat, (b) Nap and their corresponding physical mixtures (c) PM and (d) ionic liquids.

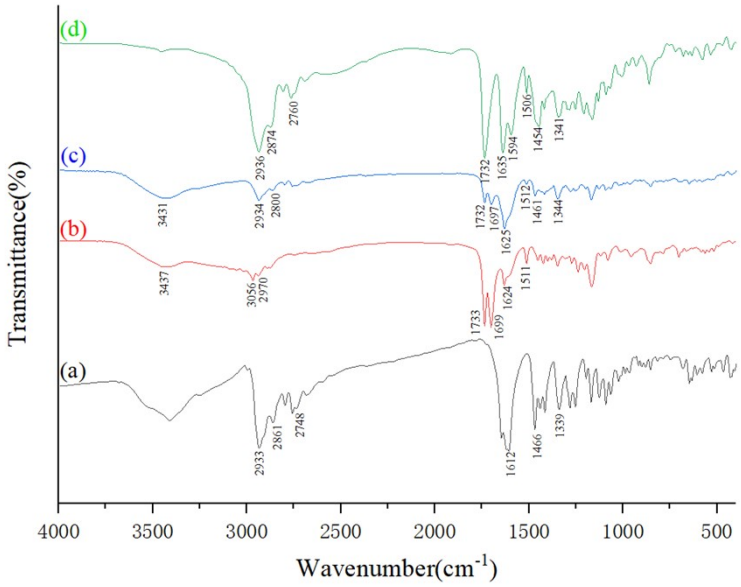

Figure S9. FT-IR spectra of pure drugs (a) Mat, (b) Lox and their corresponding physical mixtures (c) PM and (d) ionic liquids.

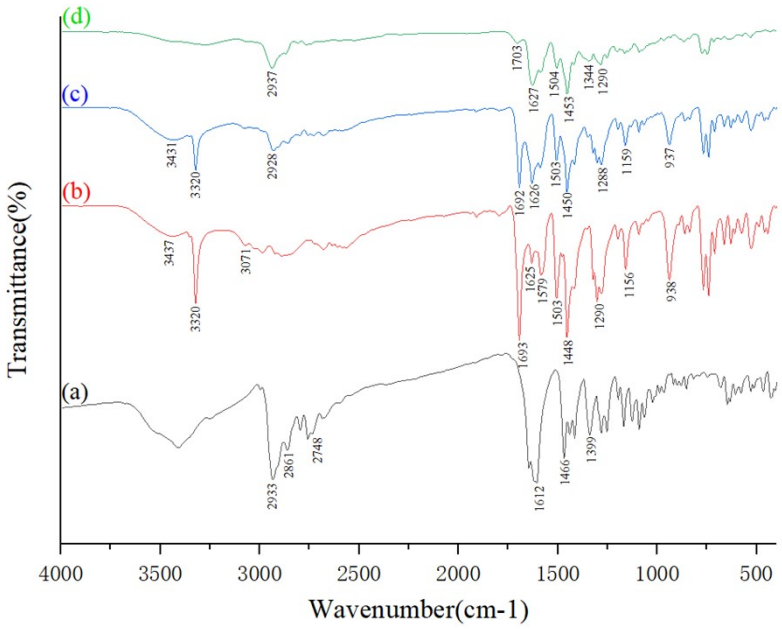

Figure S10. FT-IR spectra of pure drugs (a) Mat, (b) Dic and their corresponding physical mixtures (c) PM and (d) ionic liquids.

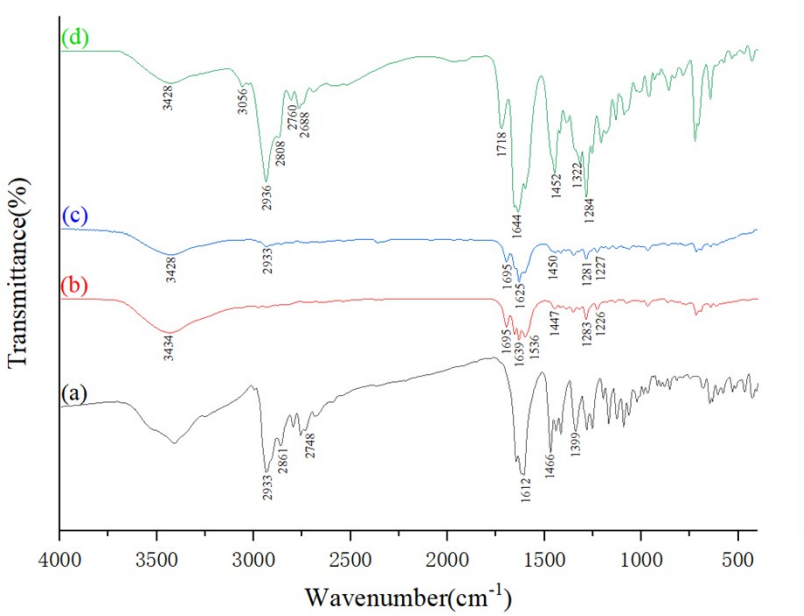

Figure S11. FT-IR spectra of pure drugs (a) Mat, (b) Ket and their corresponding physical mixtures (c) PM and (d) ionic liquids.

3. ^{1}H NMR and ^{13}C NMR data of raw materials and ionic liquids

1.1. ^{1}H NMR data

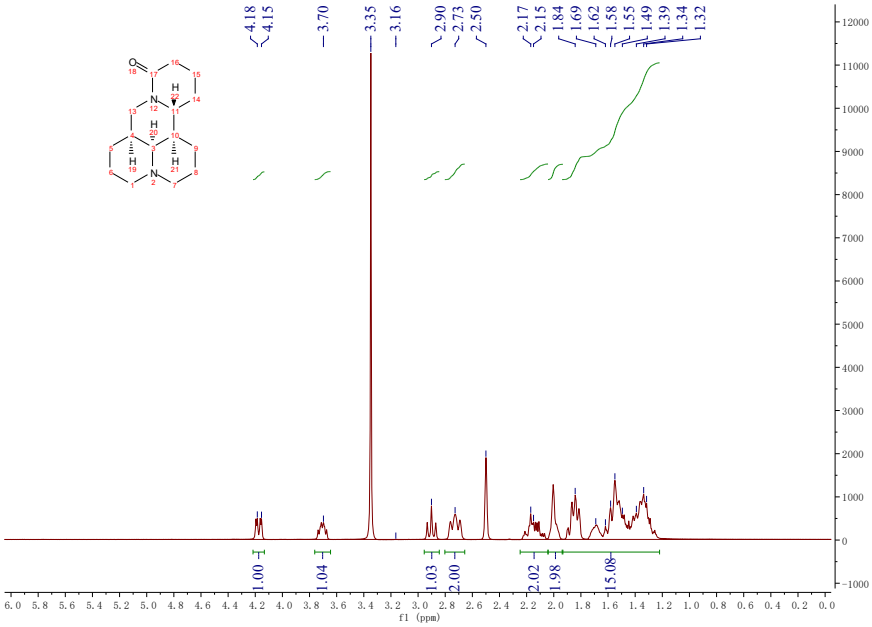

Figure S12. ^{1}H NMR (400MHz, DMSO-d6) Spectra of Mat.

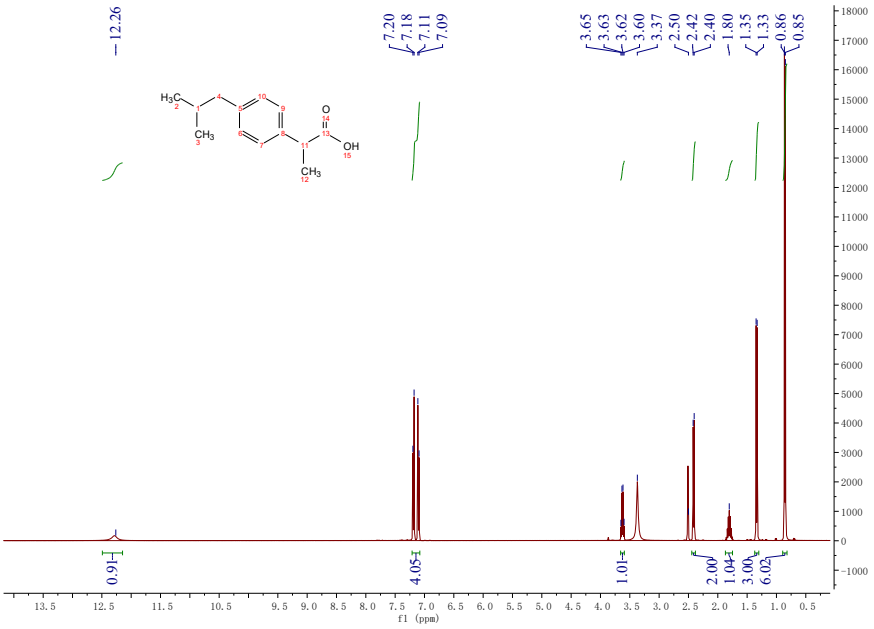

Figure S13. ^{1}H NMR (400MHz, DMSO-d6) Spectra of Ibu.

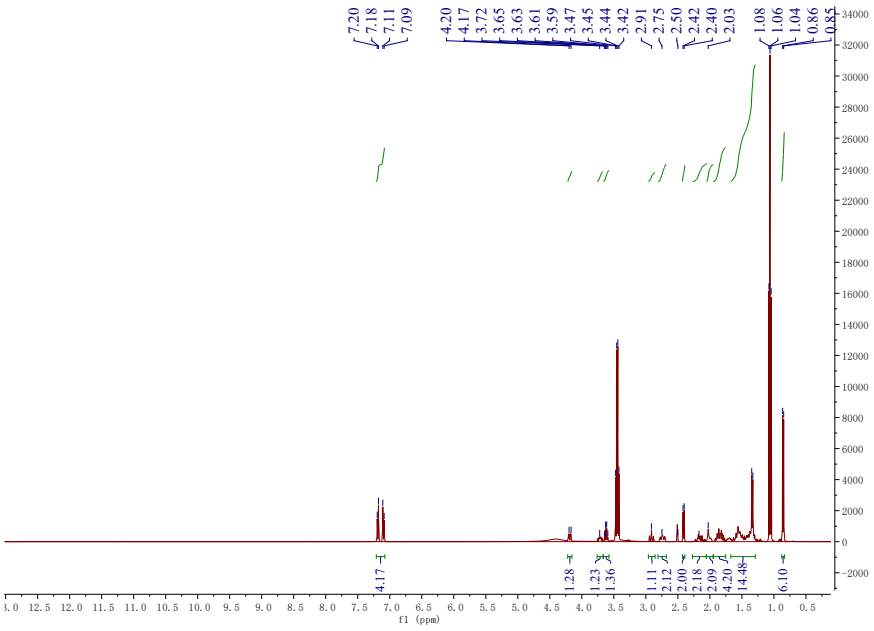

Figure S14. ^{1}H NMR (400MHz, DMSO-d6) Spectra of [Mat][Ibu].

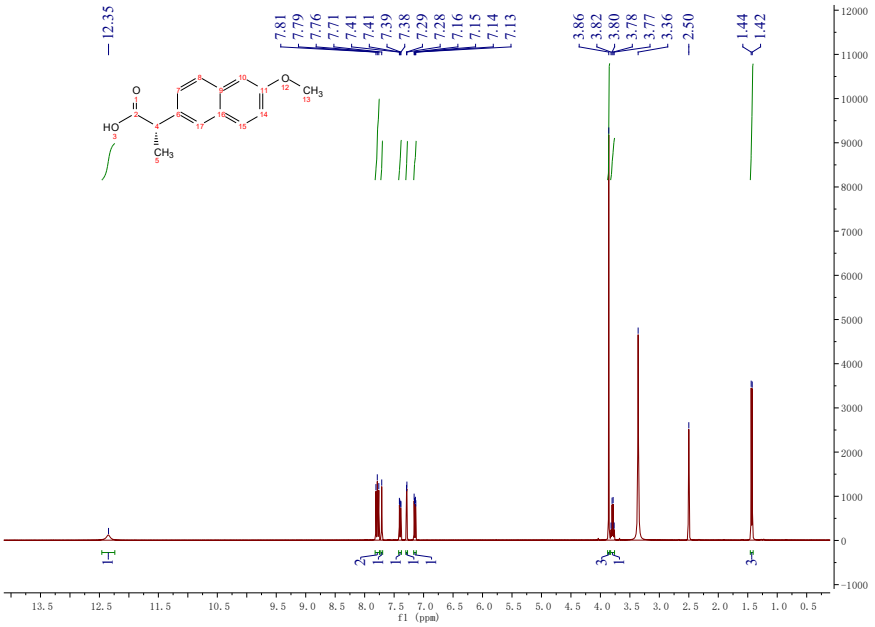

Figure S15. [1]H NMR (400MHz, DMSO-d6) Spectra of Nap.

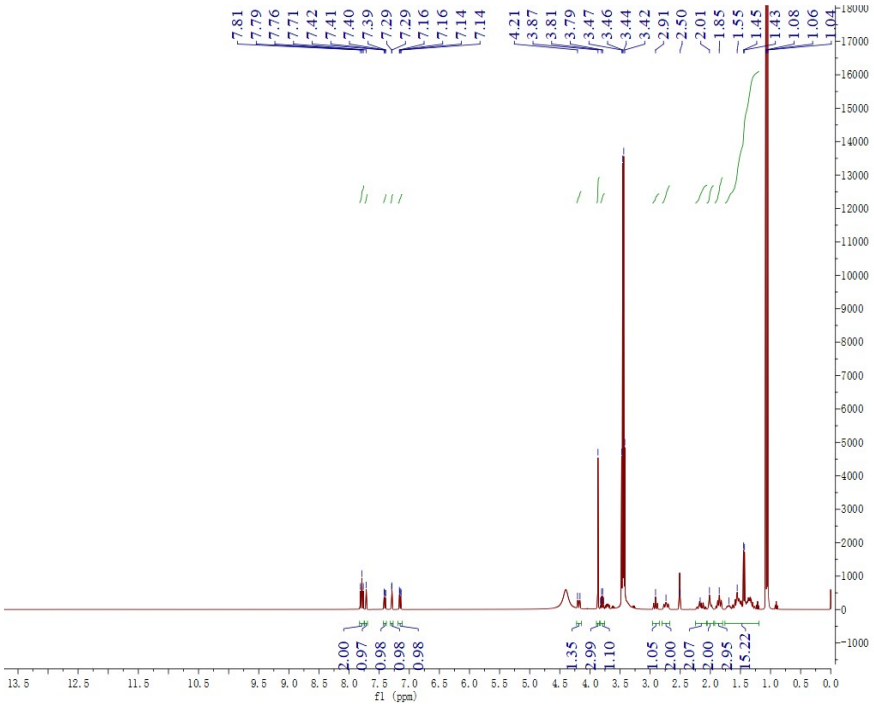

Figure S16. [1]H NMR (400MHz, DMSO-d6) Spectra of [Mat][Nap].

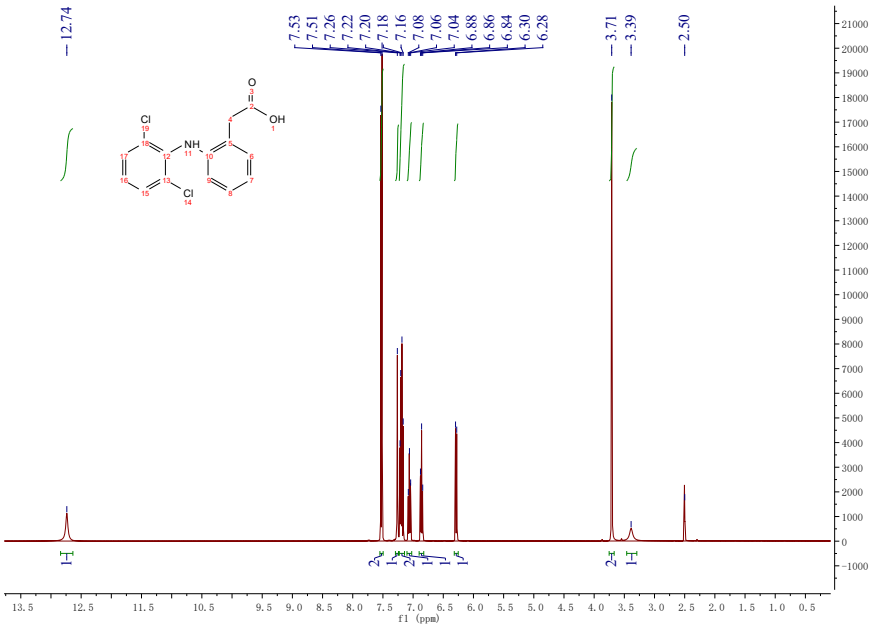

Figure S17. [1]H NMR (400MHz, DMSO-d6) Spectra of Dic.

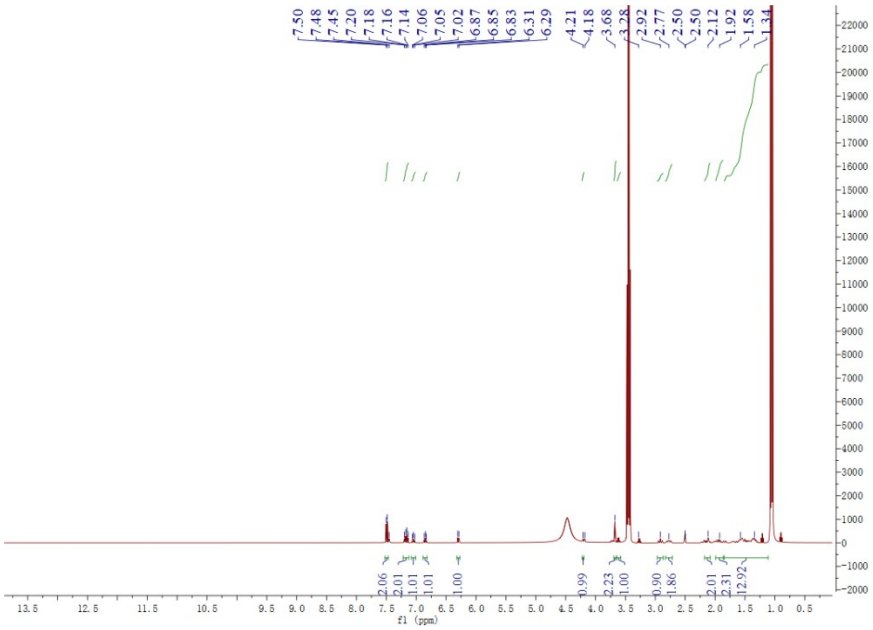

Figure S18. [1]H NMR (400MHz, DMSO-d6) Spectra of [Mat][Dic].

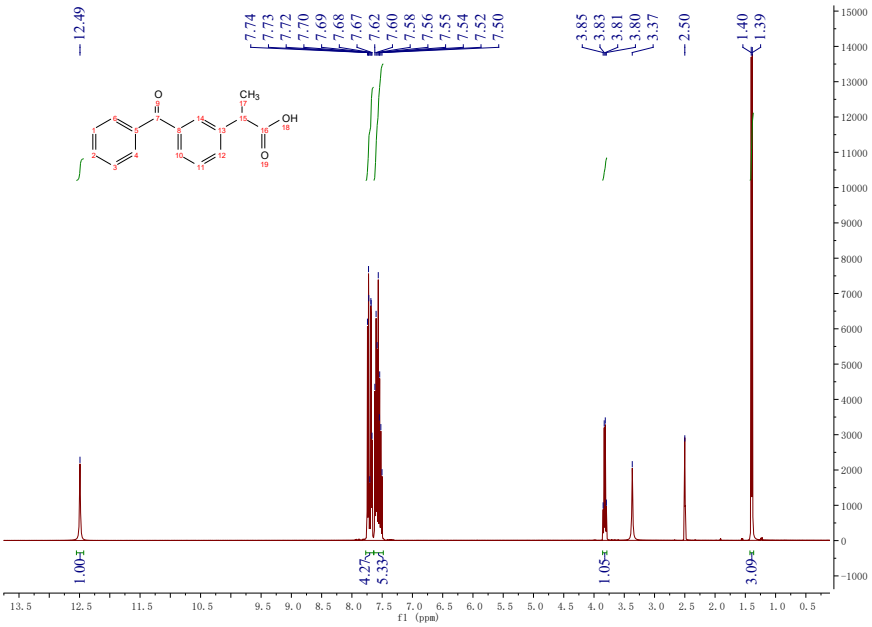

Figure S19. ^{1}H NMR (400MHz, DMSO-d6) Spectra of Ket.

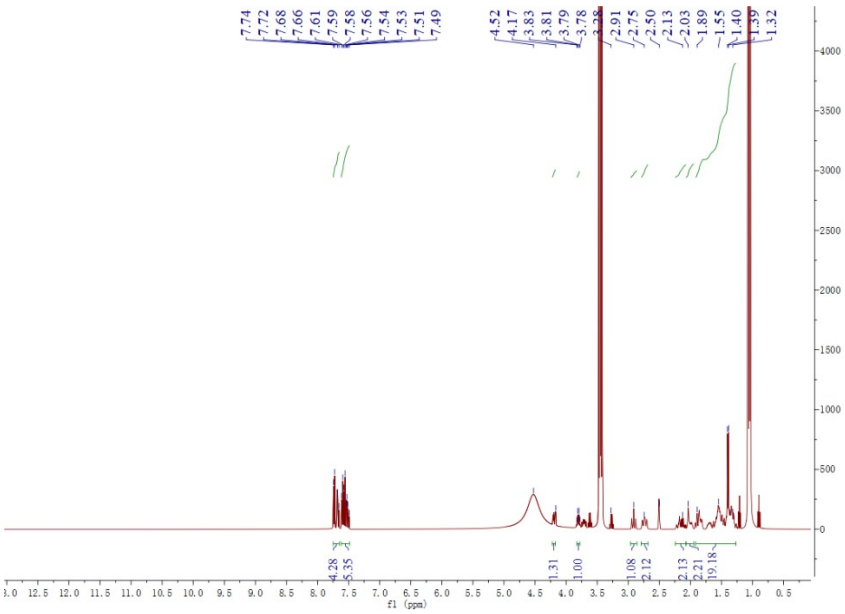

Figure S20. ^{1}H NMR (400MHz, DMSO-d6) Spectra of [Mat][Ket].

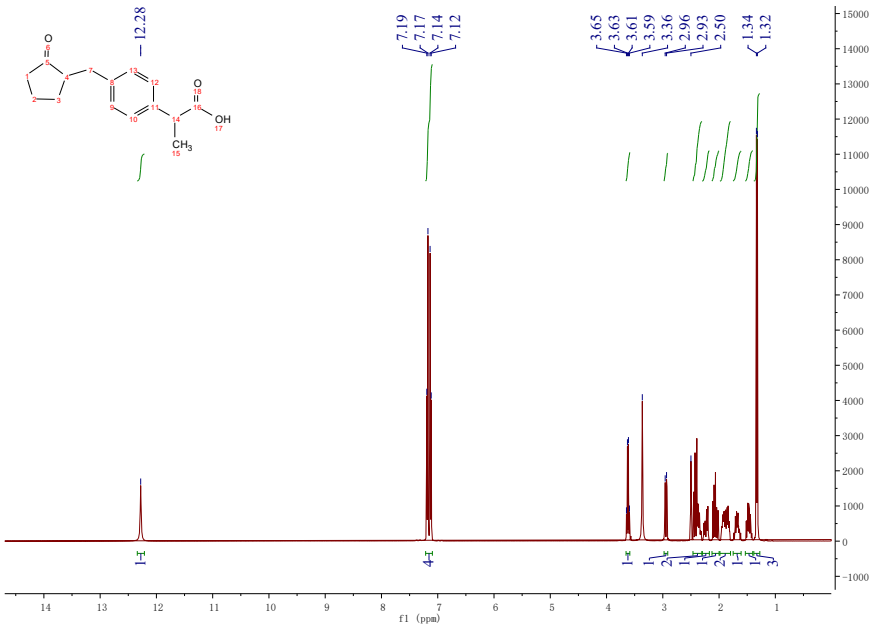

Figure S21. [1]H NMR (400MHz, DMSO-d6) Spectra of Lox.

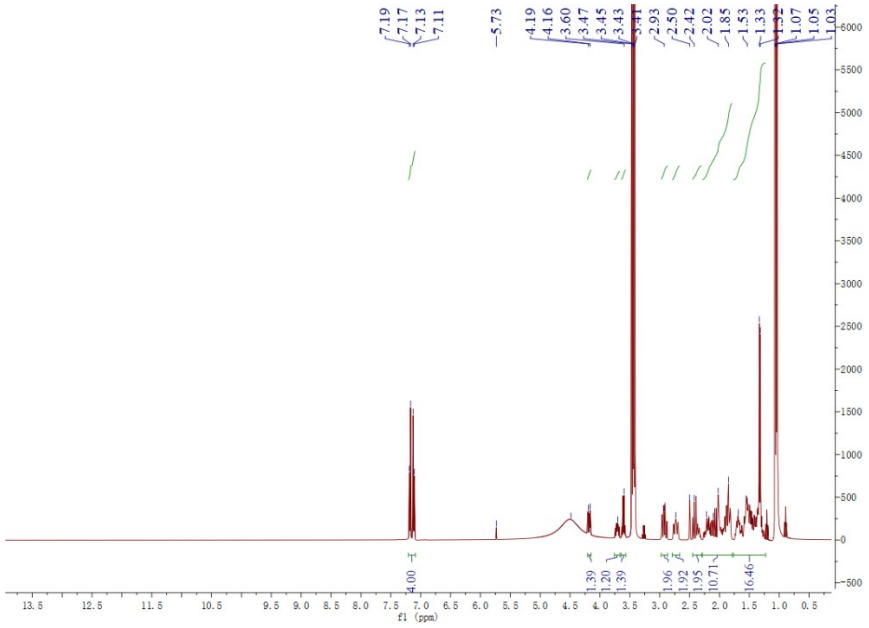

Figure S22. [1]H NMR (400MHz, DMSO-d6) Spectra of [Mat][Lox].

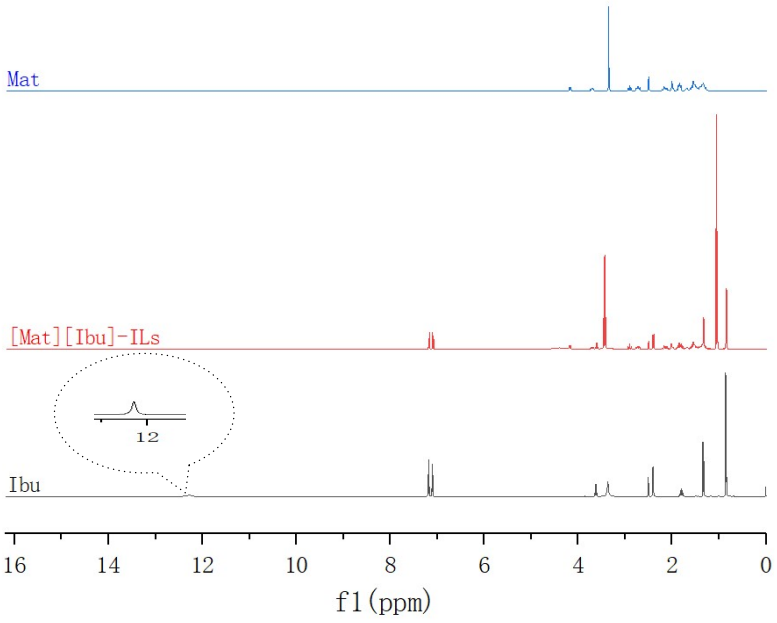

Figure S23. ^{1}H NMR (400MHz, DMSO-d6) Spectra of Pure Drug (Ibu, Mat) and ionic liquids (ILs).

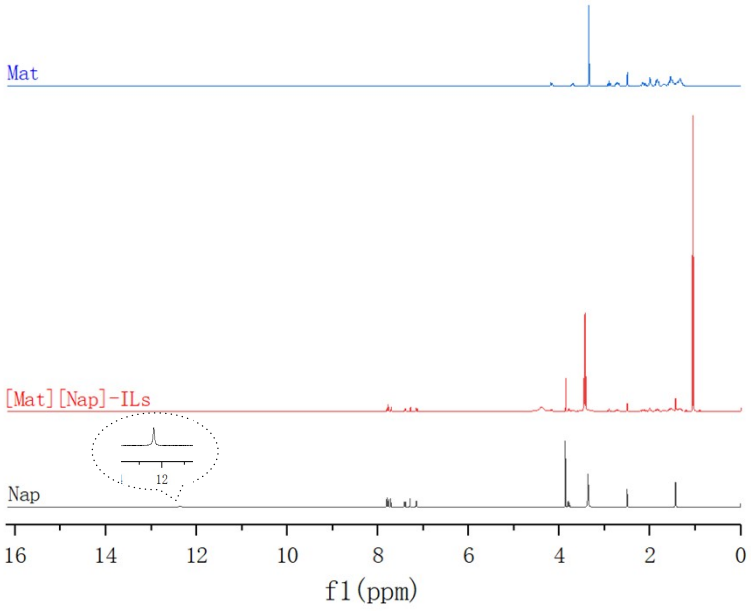

Figure S24. ^{1}H NMR (400MHz, DMSO-d6) Spectra of Pure Drug (Nap, Mat) and ionic liquids (ILs).

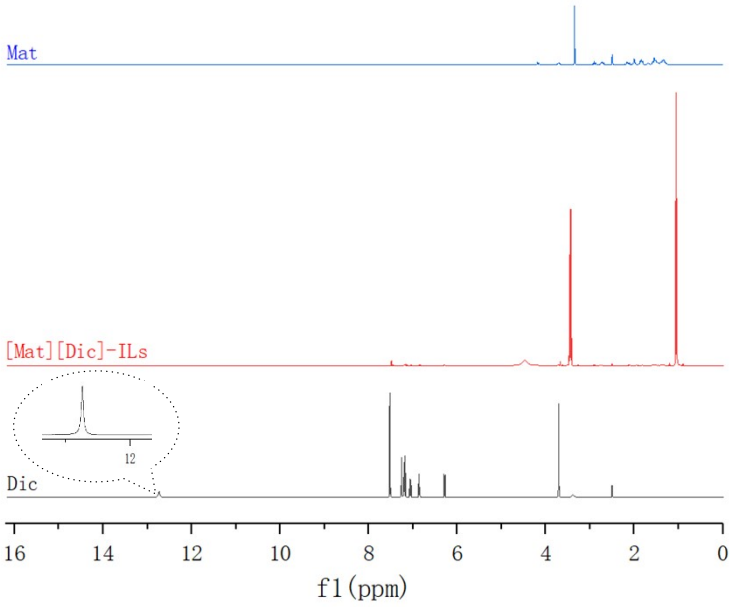

Figure S25. [1]H NMR (400MHz, DMSO-d6) Spectra of Pure Drug (Dic, Mat) and ionic liquids (ILs).

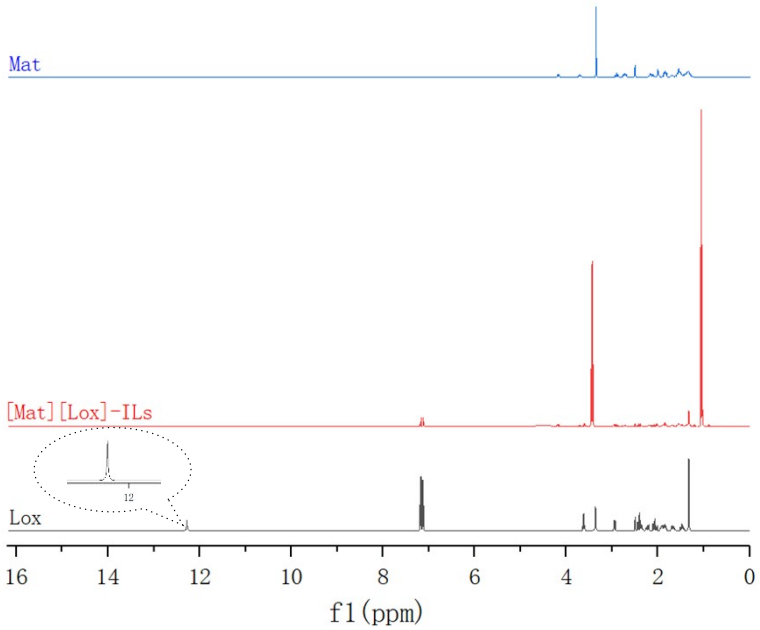

Figure S26. [1]H NMR (400MHz, DMSO-d6) Spectra of Pure Drug (Lox, Mat) and ionic liquids (ILs).

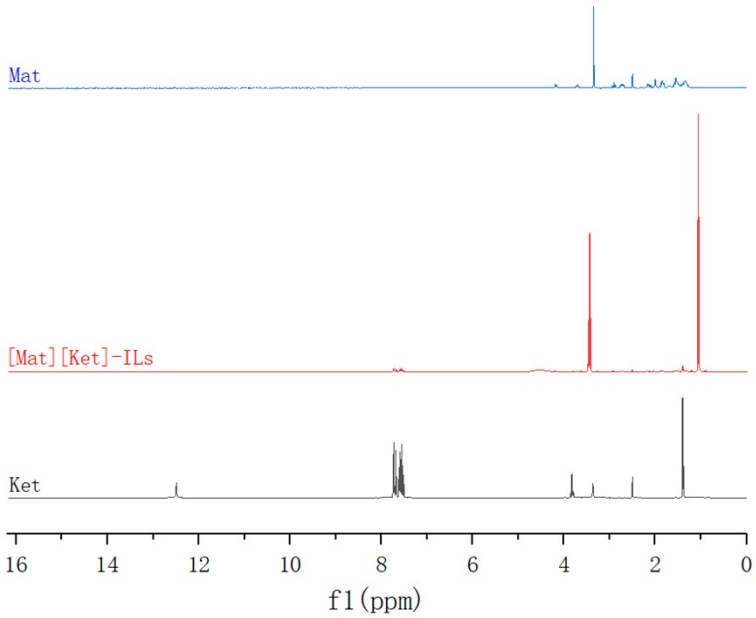

Figure S27. ^{1}H NMR (400MHz, DMSO-d6) Spectra of Pure Drug (Ket , Mat) and ionic liquids (ILs).

1.2. ^{13}C NMR data

(1) Mat

^{13}C-NMR (101MHz, DMSO-d6): δ168.08(s), 63.38(s), 56.91(s), 56.80(s), 52.84(s), 42.74(s), 41.03(s), 35.31(s), 32.68(s), 27.76(s), 26.61(s), 26.27(s), 20.96(s), 20.46(s), 18.73(s).

(2) Ibu

^{13}C-NMR (101MHz, DMSO-d6): δ175.71(s), 139.77(s), 138.69(s), 129.19(s), 127.32(s), 44.43(s), 29.86(s), 22.41(s), 18.76(s).

(3) [Mat][Ibu]

^{13}C-NMR (101MHz, DMSO-d6): δ175.80(s), 168.18(s), 139.76(s), 138.86(s), 129.18(s), 127.35(s), 63.45(s), 56.94(d, J=40Hz), 56.33(s), 52.88(s), 44.54(d, J=40Hz), 42.82(s), 41.06(s), 35.36(s), 32.71(s), 29.95(s), 27.78(s), 26.70(s), 26.28(s), 22.40(s), 20.99(s), 20.49(s), 18.78(s).

(4) Nap

^{13}C-NMR (101MHz, DMSO-d6): δ175.71(s), 157.30(s), 136.52(s), 133.44(s), 129.33(s), 128.60(s), 127.06(s), 126.63(s), 125.78(s), 118.93(s), 105.86(s), 55.37(s), 44.78(s), 18.67(s).

(5) [Mat][Nap]

^{13}C-NMR (101MHz, DMSO-d6): δ175.82(s), 168.23(s), 157.40(s), 136.69(s), 133.54(s), 129.35(s), 128.71(s), 127.09(s), 126.66(s), 125.83(s), 118.95(s),

105.88(s), 63.44(s), 56.95(s), 56.85(s), 56.35(s), 55.36(s), 52.89(s), 44.97(s), 42.83(s), 41.09(s), 35.38(s), 32.72(s), 27.79(s), 26.69(s), 26.28(s), 21.00(s), 20.50(s), 18.78(s).

(6) Lox

^{13}C-NMR (101MHz, DMSO-d6): δ175.68(s), 139.03(s), 138.78(s), 129.00(s), 127.54(s), 50.22(s), 44.48(s), 37.79(s), 34.75(s), 28.95(s), 20.24(s), 18.76(d, J=4Hz).

(7) [Mat][Lox]

^{13}C-NMR (101MHz, DMSO-d6): δ175.77(s), 168.26(s), 139.25(s), 138.81(s), 129.02(s), 127.59(s), 63.48(s), 56.98(s), 56.87(s), 56.36(s), 52.92(s), 50.32(s), 44.65(s), 42.86(s), 41.11(s), 37.82(s), 35.40(s), 34.85(s), 32.73(s), 29.03(s), 27.82(s), 26.71(s), 26.31(s), 21.02(s), 20.52(s), 20.30(s), 18.77(s).

(8) Dic

^{13}C-NMR (101MHz, DMSO-d6): δ173.63(s), 142.89(s), 137.32(s), 131.13(s), 130.27(s), 129.41(s), 127.75(s), 125.81(s), 124.10(s), 120.98(s), 116.16(s), 37.98(s).

(9) [Mat][Dic]

^{13}C-NMR (101MHz, DMSO-d6): δ173.99(s), 168.40(s), 143.04(s), 137.57(s), 131.12(s), 130.11(s), 129.44(s), 127.67(s), 125.58(s), 124.73(s), 121.12(s), 116.42(s), 63.49(s), 56.90(d, J=44Hz), 56.42(s), 52.91(s), 42.79(s), 41.07(s), 35.35(s), 32.75(s), 27.70(s), 26.75(s), 26.19(s), 20.93(s), 20.44(s), 18.76(s).

(10)Ket

^{13}C-NMR (101MHz, DMSO-d6): δ195.80(s), 175.31(s), 141.98(s), 137.26(s), 137.17(s), 132.97(s), 132.11(s), 129.84(s), 128.96(s), 128.82(s), 128.72(s), 128.60(s), 44.63(s), 18.72(s).

(11)[Mat][Ket]

^{13}C-NMR (101MHz, DMSO-d6): δ195.91(s), 175.50(s), 168.31(s), 142.19(s), 137.39(s), 137.30(s), 132.98(s), 132.15(s), 129.91(s), 128.95(s), 128.84(s), 128.60(s), 63.49(s), 56.97(d, J=44Hz), 56.87(s), 56.39(s), 56.20(s), 52.93(s), 44.89(s), 42.87(s), 41.12(s), 35.41(s), 32.74(s), 27.81(s), 26.73(s), 26.30(s) 21.01(s), 20.51(s), 18.76(s).

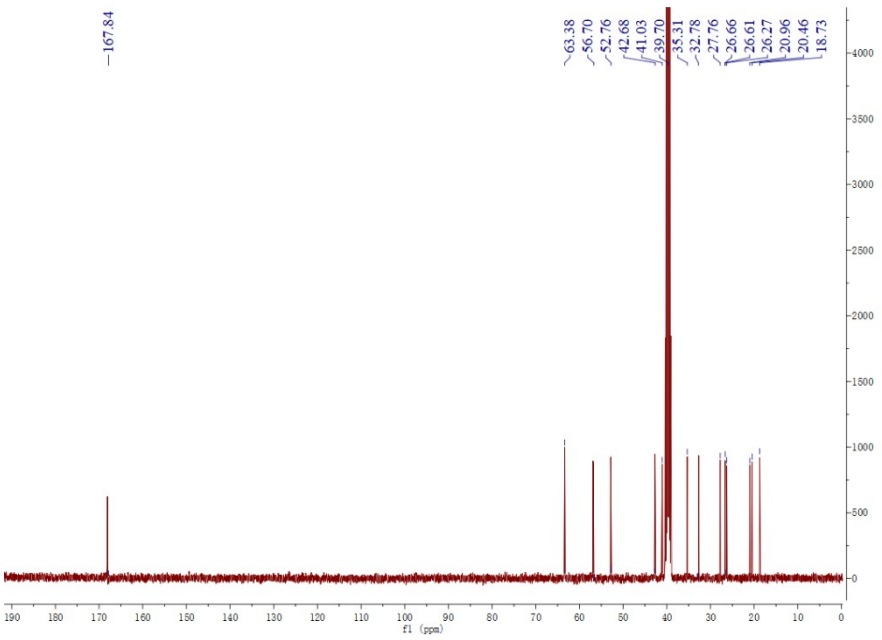

Figure S28. ^{13}C NMR (101MHz, DMSO-d6) Spectra of Mat.

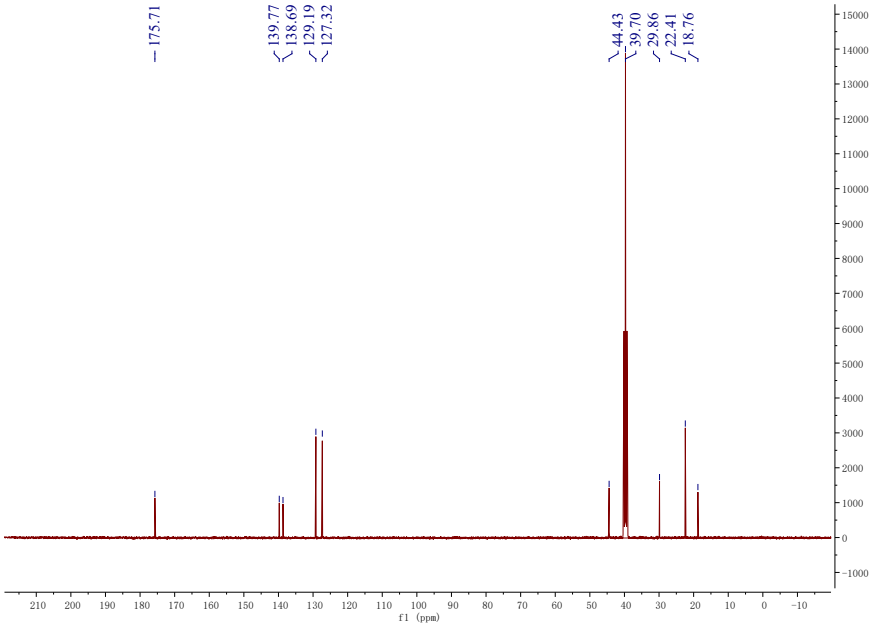

Figure S29. ^{13}C NMR (101MHz, DMSO-d6) Spectra of Ibu.

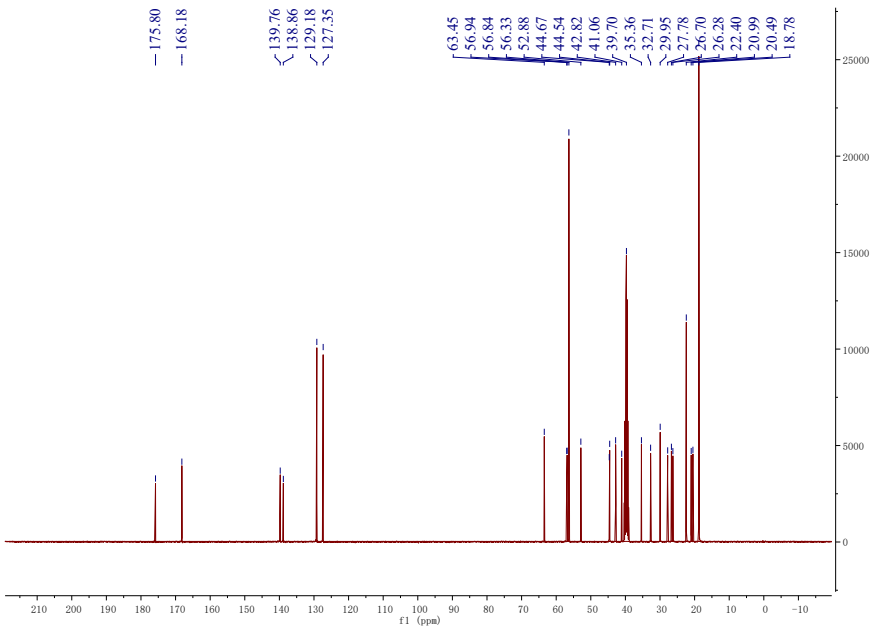

Figure S30. ^{13}C NMR (101MHz, DMSO-d6) Spectra of [Mat][Ibu].

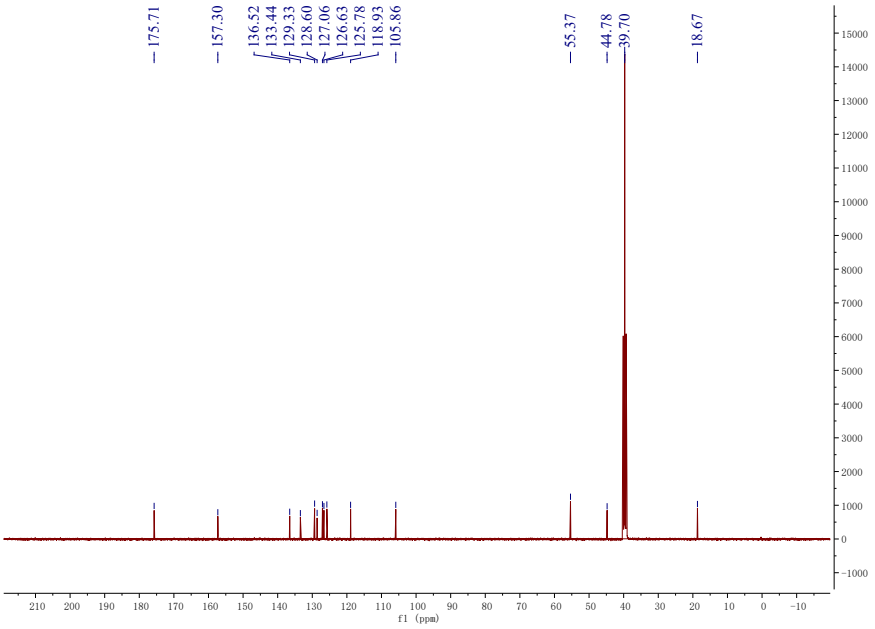

Figure S31. ^{13}C NMR (101MHz, DMSO-d6) Spectra of Nap.

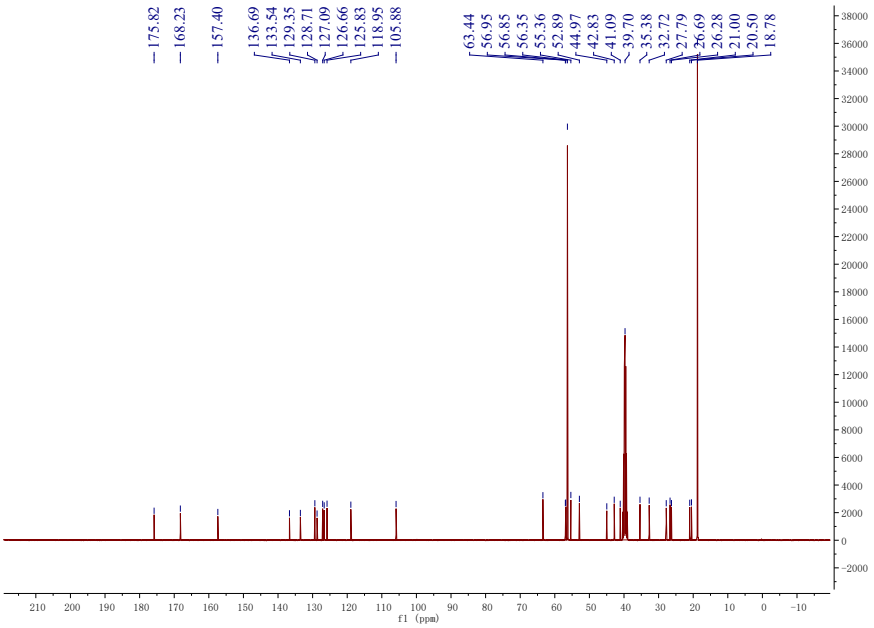

Figure S32. ^{13}C NMR (101MHz, DMSO-d6) Spectra of [Mat][Nap].

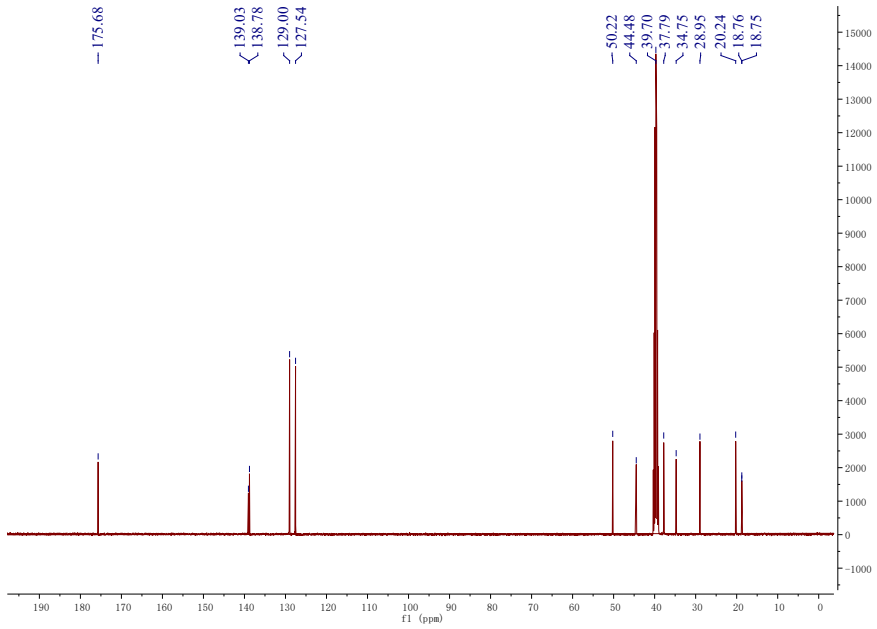

Figure S33. ^{13}C NMR (101MHz, DMSO-d6) Spectra of Lox.

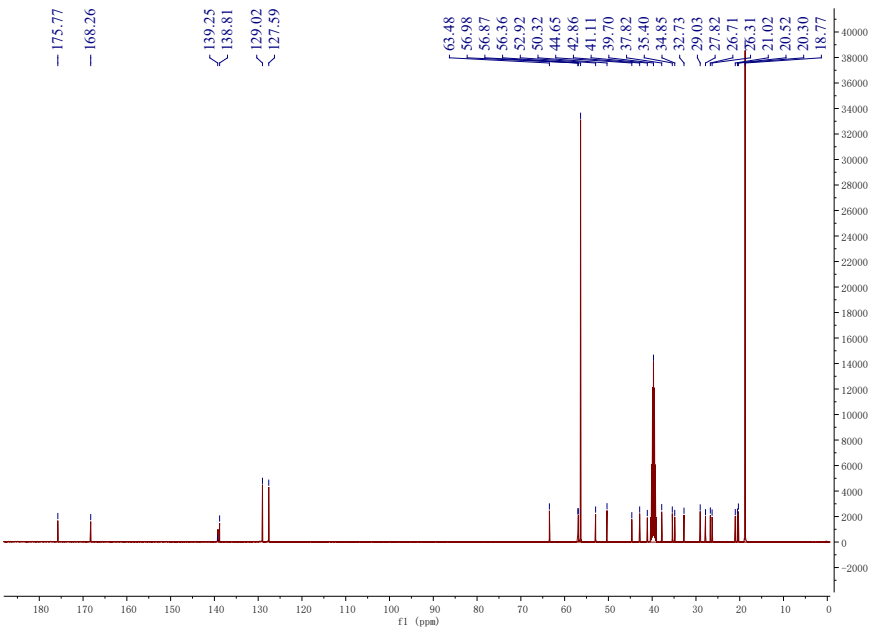

Figure S34. ^{13}C NMR (101MHz, DMSO-d6) Spectra of [Mat][Lox].

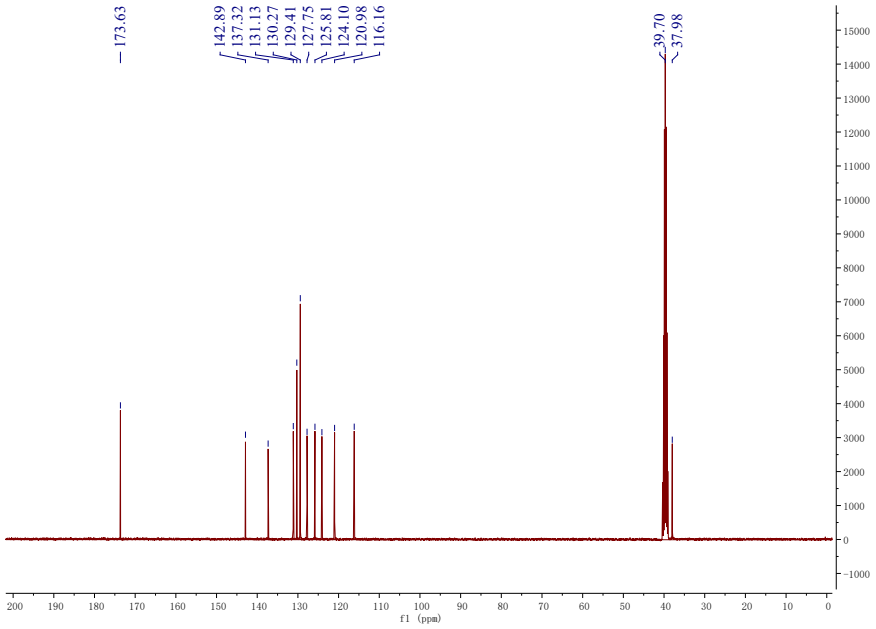

Figure S35. ^{13}C NMR (101MHz, DMSO-d6) Spectra of Dic.

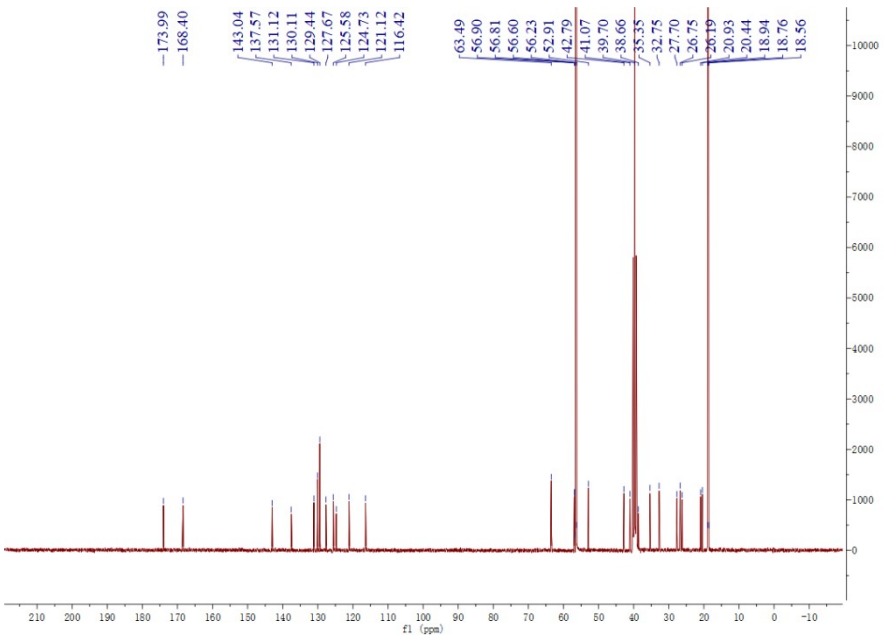

Figure S36. ^{13}C NMR (101MHz, DMSO-d6) Spectra of [Mat][Dic].

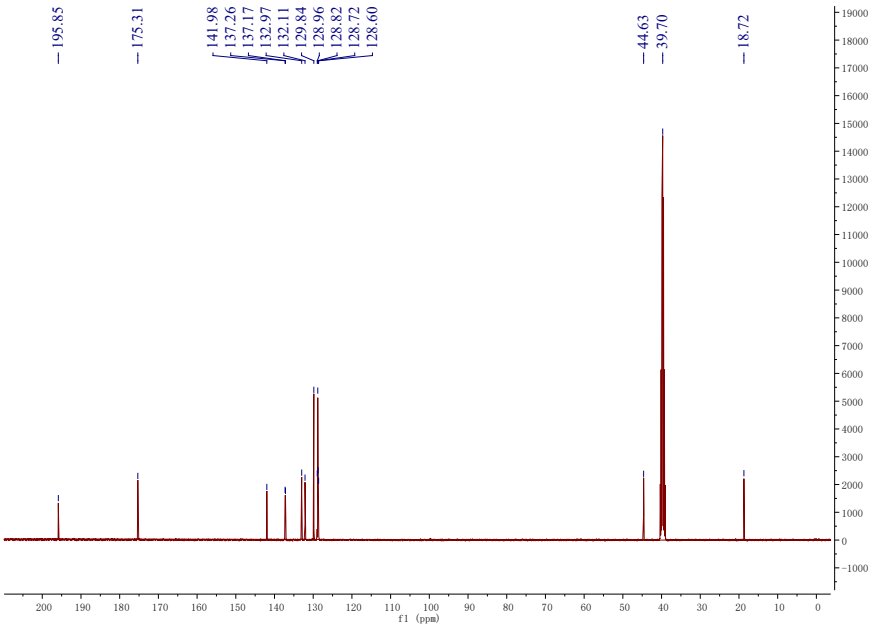

Figure S37. ^{13}C NMR (101MHz, DMSO-d6) Spectra of Ket.

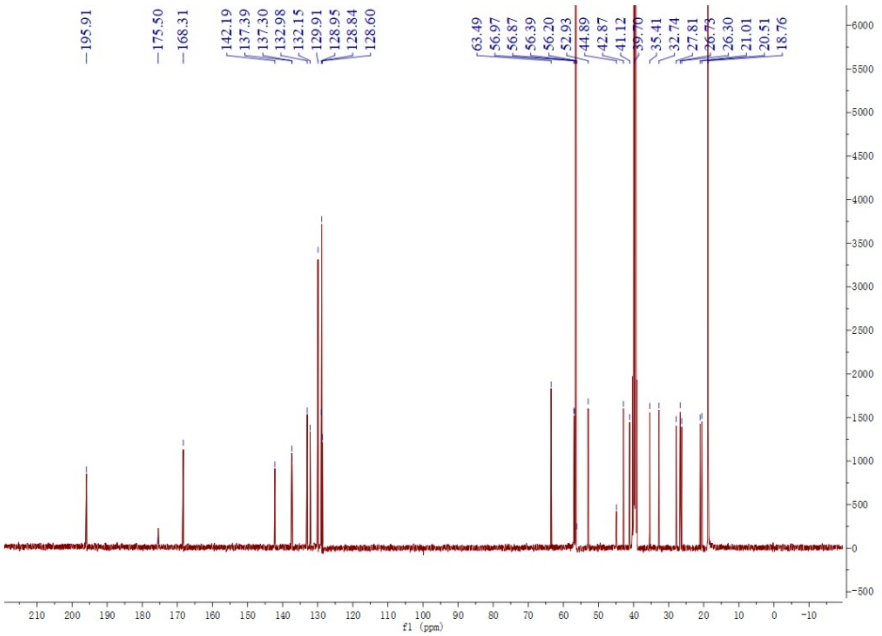

Figure S38. ^{13}C NMR (101MHz, DMSO-d6) Spectra of [Mat][Ket].

4. Determination of solubility

Table S1 Equilibrium solubility of Pure APIs and API-ILs at 37 ℃ pH 7.4 PBS.

Samples		Solubility(mg/mL)	Solubility increase/decrease
Pure APIs	Mat	55.65	
	Ibu	5.19	
	Nap	4.65	
	Lox	6.10	
	Dic	1.61	
	Ket	3.36	
API-ILs	[Mat][Ibu]-Mat	1088.33	increase 20-fold
	[Mat][Ibu]-Ibu	405	increase 78-fold
	[Mat][Nap]-Mat	835	increase 15-fold
	[Mat][Nap]-Nap	460	increase 99-fold
	[Mat][Lox]-Mat	1771	increase 20-fold
	[Mat][Lox]-Lox	1750	increase 287-fold
	[Mat][Dic]-Mat	735	increase 13-fold
	[Mat][Dic]-Dic	135.21	increase 95-fold
	[Mat][Ket]-Mat	2850	increase 51-fold
	[Mat][Ket]-Ket	742.50	increase 220-fold