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Liquid Co-crystals of Dual-Active Phenothiazine–NSAID Drugs: Synthesis, Spectroscopic, and Thermal Characterization

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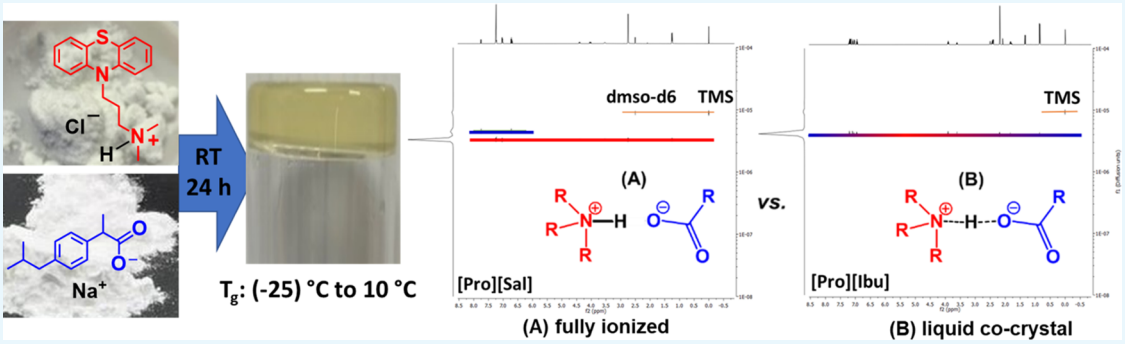

ABSTRACT: Four aliphatic phenothiazine cations (promazinium, promethazinium, chlorpromazinium, and triflupromazinium) were each paired with docusate anions and three different NSAID anions (ibuprofen, salicylate, and naproxen) to form fifteen glassy materials and one solid. The compounds were prepared *via* the metathesis reaction between the corresponding phenothiazine hydrochloride salts and sodium docusate or sodium NSAID salts and were obtained as liquid co-crystals with various degrees of ionization. The self-diffusion coefficients of several derivatives in 0.06 M DMSO-d_6 solutions were determined using DOSY NMR spectroscopy. The influence of the size, shape of the compounds, and intermolecular forces has been investigated by using the four promazine and the four ibuprofen co-crystals. The ion pairs (or aggregates) were found to be maintained in six out of the seven compounds examined. All fifteen glassy compounds showed reversible glass transitions in the −25 to 10 °C range with the docusate derivatives exhibiting the highest thermal stability (T_{onset} values being at least 40 °C higher than those of the corresponding phenothiazine hydrochlorides).

INTRODUCTION

Phenothiazine drugs, thiazine-based drugs used in pharma since 1950s, are known to have multiple biological effects (*e.g.*, anti-psychotic, antimalarial, antimicrobial, tranquilizers, anti-inflammatory, anti-psychotropic, and antitumor)[1] with the aliphatic derivatives (*e.g.*, promazine, chlorpromazine, trifluopromazine, and promethazine) having a moderate biological activity while the piperidine derivatives (*e.g.*, thioridazine) having a strong biological activity, and the piperazine derivatives (*e.g.*, trifluperazine and fluphenazine) having weak biological activity (Table 1).[1] As most pharmaceuticals, these drugs are administered as solid-state inorganic salts (*i.e.*, hydrochlorides), and they present all the solid-state disadvantages.[2−4] The existence of polymorphic structures (*i.e.*, different crystalline structures with different or no biological activity) is a major issue for the pharmaceutical industry as it can lead to potential legal ramifications;[5] multiple court cases addressed the polymorphic transformation of pharmaceuticals showing that, in USA, many solid forms of pharmaceuticals are different drugs altogether.[6] Research is currently focused on minimizing and/or eliminating this issue; numerous directions are investigated with the conversion of solid-state drugs into (a) liquid-state salts (*aka* ionic liquids, ILs, or salts that melt below 100 °C) and (b) co-crystals being two major approaches.[7] Conversion of pharmaceuticals into a liquid state was proven by numerous researchers[8−12] as a viable route for eliminating the solid-state disadvantages. For example, Hough et al. showed that Zantac (ranitidine hydrochloride), a drug included in court cases due to its polymorphic conversion, can readily convert into ranitidine docusate, a liquid form of the ranitidine drug obtained by pairing the ranitidine cation with the docusate anion.[13] Moreover, there is also an increased interest in bringing these liquid-state pharmaceuticals to market; for example, lidocaine etodolac is a dual-active liquid-state drug that completed phase III clinical

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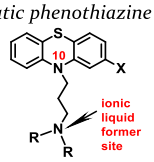
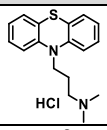
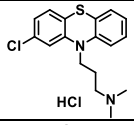
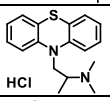
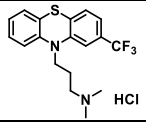
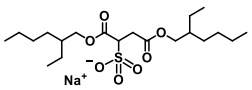
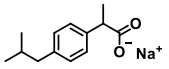
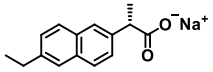
Table 1. Cation and Anion Precursors

	Name / Acronym	Structure	pKa
Cation Precursors: *Aliphatic phenothiazine drugs*  (moderate biological activity)	Promazine hydrochloride [Pro]Cl		9.40 [24]
	Chlorpromazine hydrochloride [CPro]Cl		9.30 [24]
	Promethazine hydrochloride [Prm]Cl		9.10 [24]
	Triflupromazine hydrochloride [FPro]Cl		9.20 [24]
Anion Precursor: *Sodium docusate*	Sodium docusate Na[Doc]		*
Anion precursors: *NSAIDs*	Sodium ibuprofenate Na[Ibu]		4.42** [25]
	Sodium salicylate Na[Sal]		2.97** [26]
	Sodium naproxenate Na[Nap]		4.18** [25]

[a]Sulfonic acids: very strong acids ($pK_a \sim -7$); e.g., methanesulfonic acid: $pK_a = -1.85$; ** pK_a of the conjugated acid.

trials with randomized testing being conducted on groups of up to 3000 patients.[14]

The ionic liquid strategy can be applied to organic compounds that contain ionizable groups; the most common groups used in ionic liquid synthesis are Bronsted precursors such as carboxylic acids ($R-CO_2H$) and carboxylates ($R-CO_2^-$ M^+) as anion sources and amines (1° $R-NH_2$, 2° R_2NH, or 3° R_3N) and quaternary ammonium salts (R_4N^+ aka QUATs) as cation sources. Depending on the anion and cation sources used, two types of liquid-state compounds can be obtained: (a) protic ionic liquids (PILs—obtained either through an acid−base reaction between a proton donor and a proton acceptor *OR* through a metathesis reaction between a carboxylate salt and a hydrochloride salt of an organic amine) and (b) aprotic ionic liquids (APILs—obtained through a metathesis reaction between a carboxylate salt and a QUAT). Although in the case of APILs, a liquid-state behavior is obtained due to the electrostatic interaction between the cation and the anion, in the case of PILs, the degree of ionization depends on if there is a full proton transfer from the Bronsted acid to the Bronsted base or not. Nuthakki et al.[15] suggested that a ΔpK_a [pK_a(conjugated acid)—pK_a(acid)] of at least 4 is needed for a liquid-state behavior to be obtained. However, a ΔpK_a value of at least 7−8 is needed to form PILs with an ionization degree higher than 99%. If the proton is shared between the anion and cation (*i.e.*, through a N···H−OOC hydrogen bonding rather than full proton transfer), the compounds are formed as liquid-state co-crystals (Figure 1)—according to Rogers et al., just sharing the hydrogen between the cation and anion can lead to a liquid-state behavior.[10,16] Furthermore, as in the case of solid-state co-crystals, the

Figure 1. (A) Fully ionized PILs (amminium derivatives) vs (B) liquid co-crystal PILs.

pharmaceutical activity of the constituent active ingredients from liquid co-crystals will not be affected while their physical properties (*e.g.*, solubility) will be improved.[17,18]

Phenothiazine drugs are sold as hydrochloride salts. Therefore, they are ideal cation precursors in the synthesis of dual-active PILs. Currently,[19] there are only three reports on liquid-state phenothiazine drugs (SciFinder search, "phenothiazine ionic liquids"); in a first report from 2007, Rogers et al.[20] reported on the synthesis of two double-salt ionic liquids where the anion is either the docusate or salicylate anion while the cation is a 1:1 mixture of promethazine and ephedrine cations held together through an intramolecular hydrogen bond. Second, in 2010, Dumitriu et al.[21] synthesized new liquid-state imidazolium-functionalized phenothiazine derivatives. Finally, Oh et al.[22] used N-substituted phenothiazines as pendant groups in polymeric ionic liquids. However, there is no report on investigating the synthesis of liquid-state dual-functional phenothiazine drugs. Because phenothiazine drugs do not have an analgesic effect, they are administered together with analgesics. For example, a combination of the prochlorperazine phenothiazine drug and an analgesic is required for the target therapy.[23] Here, we explore the possibility of converting aliphatic phenothiazine drugs into liquid-state dual-functional drugs by combining aliphatic

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phenothiazine cations with various organic anions such as docusate anions and NSAID carboxylates. The new compounds would potentially aid in drug administration (*i.e.*, single vs multiple administrations) while eliminating polymorphism.

RESULTS AND DISCUSSION

Synthesis. Four aliphatic phenothiazine drugs, promazine hydrochloride ([Pro]Cl), chlorpromazine hydrochloride ([CPro]Cl), promethazine hydrochloride ([Prm]Cl), and triflupromazine hydrochloride ([FPro]Cl), were used as cation precursors (Table 1) and were each reacted with sodium docusate (Na[Doc]) and three NSAIDs in their carboxylate form (*i.e.*, sodium ibuprofen, Na[Ibu]; sodium salicylate, Na[Sal]; and sodium naproxen, Na[Nap]) as anion precursors (Table 1) to potentially form dual functioning PILs with improved properties. The anion precursors were chosen based on the ΔpK_a between the phenothiazine hydrochloride salts and the anion-conjugated acids[24−26] while sodium docusate was chosen due to its known properties as a transdermal penetration enhancer and its ability to form liquid-state compounds when paired with various cations. The anion/cation molar ratio was kept the same as in the commercially available phenothiazine hydrochloride salts, allowing us to hypothesize that the biological properties of the cations will remain unaffected.

Sixteen new compounds were synthesized through a metathesis reaction between the cation (phenothiazine hydrochlorides) and anion precursors (sodium docusate or NSAID carboxylates) (Figure 2) as follows: a mixture of equimolar

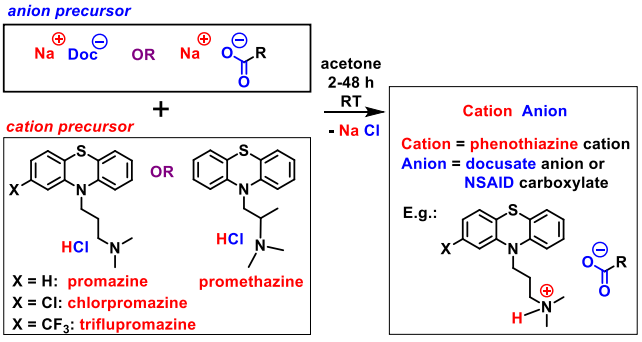

Figure 2. Formation of ILs with docusate anions and aliphatic phenothiazine drugs.

amounts of anion and cation precursors in acetone was stirred for 24 h at room temperature. The inorganic byproduct formed (NaCl) was filtered through a 0.2 μm syringe filter, and the removal of volatiles via rotary evaporation allowed the formation of fifteen highly viscous compounds and a solid ([Prm][Sal]) in high yields (>89%) and purity (Table S1, Supporting Information). All the obtained compounds were characterized using Fourier transform infrared (FT-IR) and nuclear magnetic resonance spectroscopy [one-dimensional (1D) and two-dimensional (2D) NMR].

FT-IR Spectroscopy. FT-IR spectra ranging between 650 and 3800 cm^{-1} (resolution of 1 cm^{-1}) were obtained for neat samples using a Perkin-Elmer attenuated total reflection (ATR)-IR Instrument. These spectra revealed that the position of the carboxylate stretches from the anions (labeled A in sodium salts and A′ in phenothiazine derivatives, Figure 3A1,A2) is shifted from ∼1550 cm^{-1} in sodium salts to ∼1730 cm^{-1} in the phenothiazine derivatives. For example, in the case of ibuprofen derivatives, the carboxylate stretch A appears at 1545 cm^{-1} in Na[Ibu], and it is shifted to 1730 cm^{-1} in [Pro][Ibu] and [CPro][Ibu] (Figure 3B1,B2), to 1708 cm^{-1} in [Prm][Ibu] (Figure 3B3), and to 1715 cm^{-1} in [FPro][Ibu] (Figure 3B4), these wavenumbers being similar to the carbonyl stretch from ibuprofen free acid (*i.e.*, H[Ibu], C═O at 1696 cm^{-1}). Moreover, the C−O stretch (labeled B in sodium salts and B′ in phenothiazine derivatives Figure 3A1, A2) is shifted from ∼1412 cm^{-1} in Na[Ibu] to 1448 cm^{-1} in [Pro][Ibu] and [CPro][Ibu], to 1462 cm^{-1} in [Prm][Ibu], and to 1456 cm^{-1} in [FPro][Ibu] (Figure 3B1−B4). Moreover, the N−H stretch from the cation present in all the phenothiazine hydrochlorides between 2300 and 2600 cm^{-1} seems to also be present in the synthesized compounds but with a lower intensity, further confirming the sharing of a hydrogen between the cation and anion (Figure S1, Supporting Information). The IR results can be explained by a decrease in the electron density around the carbonyl group from ibuprofen anions due to a decrease in the degree of ionization in the synthesized compounds. Similar results were observed for all the phenothiazine compounds synthesized (the full FT-IR spectra are shown in Figures S2−S5, Supporting Information). These observations are consistent with a "liquid co-crystal" behavior of all the synthesized compounds, where a hydrogen is shared between the cation and the anion (refer to Figure 2A2).

NMR Spectroscopy. The purity and formation of the compounds in a 1:1 stoichiometry were determined using NMR spectroscopy (purity: Table S1, Supporting Information; full NMR spectra: Figures S6−S21, Supporting Information). Furthermore, evidence of the co-crystal behavior of the synthesized compounds was seen through 1D and 2D NMR characterization. NMR spectra of 0.06 M DMSO-d_6 solutions were recorded using a Bruker 500 MHz spectrometer at 25 °C. NMR samples were prepared as follows: a pre-weighted amount of the compound was dissolved in 0.75 mL of DMSO-d_6 to obtain solutions of 0.06 M concentration. To ensure complete solvation of each compound, the samples were sonicated for 5 min before spectrum collection.

^{1}H-NMR Spectroscopy: Anion Comparison. Due to their vicinity to the most basic site from the cation precursor, the influence of the anion on the chemical shifts of the methyl and methylene groups from [Pro], [CPro], and [FPro] derivatives (Figure 4A1) and on the chemical shifts of the methyl and methine groups from [Prm] derivatives (Figure 4A2) was investigated. Figure 4B1 shows the stacked spectra for [Pro] derivatives. The methyl groups (highlighted in red) show as one singlet at 2.67 ppm in [Pro]Cl which is shifted downfield to 2.73 ppm in [Pro][Doc] and at 2.67 ppm in [Pro][Sal] and is shifted upfield to 2.29 ppm in [Pro][Ibu] and to 2.11 ppm in [Pro][Nap]. Similarly, the methylene group (highlighted in blue) shows as a triplet at 3.96 ppm in [Pro]Cl, has a similar chemical shift of 3.95 ppm in [Pro][Doc], and is slightly shifted downfield to 4.01 ppm in [Pro][Sal] and slightly shifted upfield to 3.91 ppm in [Pro][Ibu] and to 3.88 ppm in [Pro][Nap]. Similar trends were observed for the [CPro] and [FPro] derivatives; the chemical shifts differences for these compounds are shown in Table 2 and the corresponding stacked ^{1}H NMR spectra are presented in Figures S22 and S23 in Supporting Information.

Similarly, the methine group from the [Prm] derivatives (highlighted in blue, Figure 4B1) shows as a multiplet (triplet of quartets) at 3.53 ppm in [Prm]Cl and is slightly shifted downfield to 3.60 ppm in [Prm][Doc], has a similar chemical

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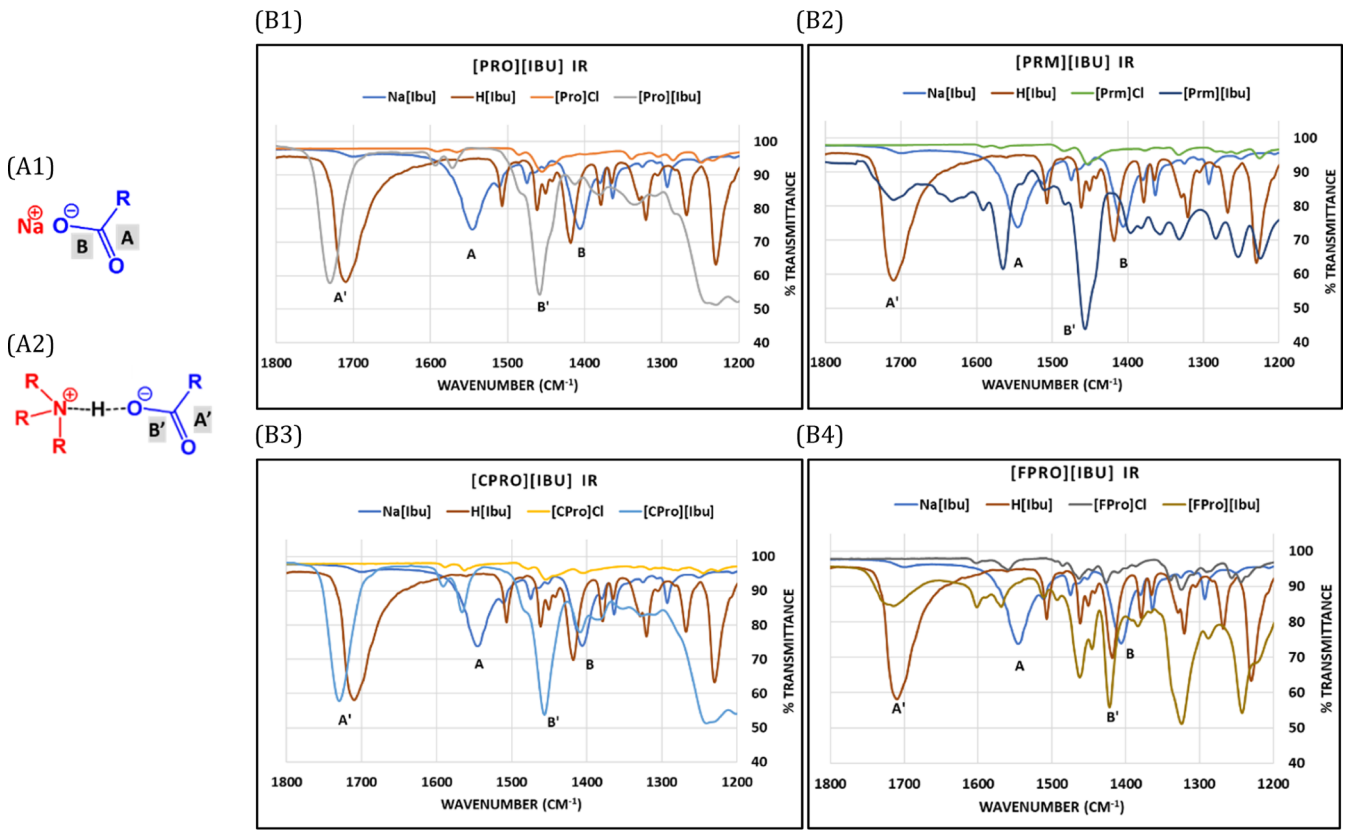

Figure 3. FT-IR spectra: carboxylate stretches in phenothiazine hydrochlorides and phenothiazine ILs; [Pro][Ibu], [CPro][Ibu], [Prm][Ibu], and [FPro][Ibu].

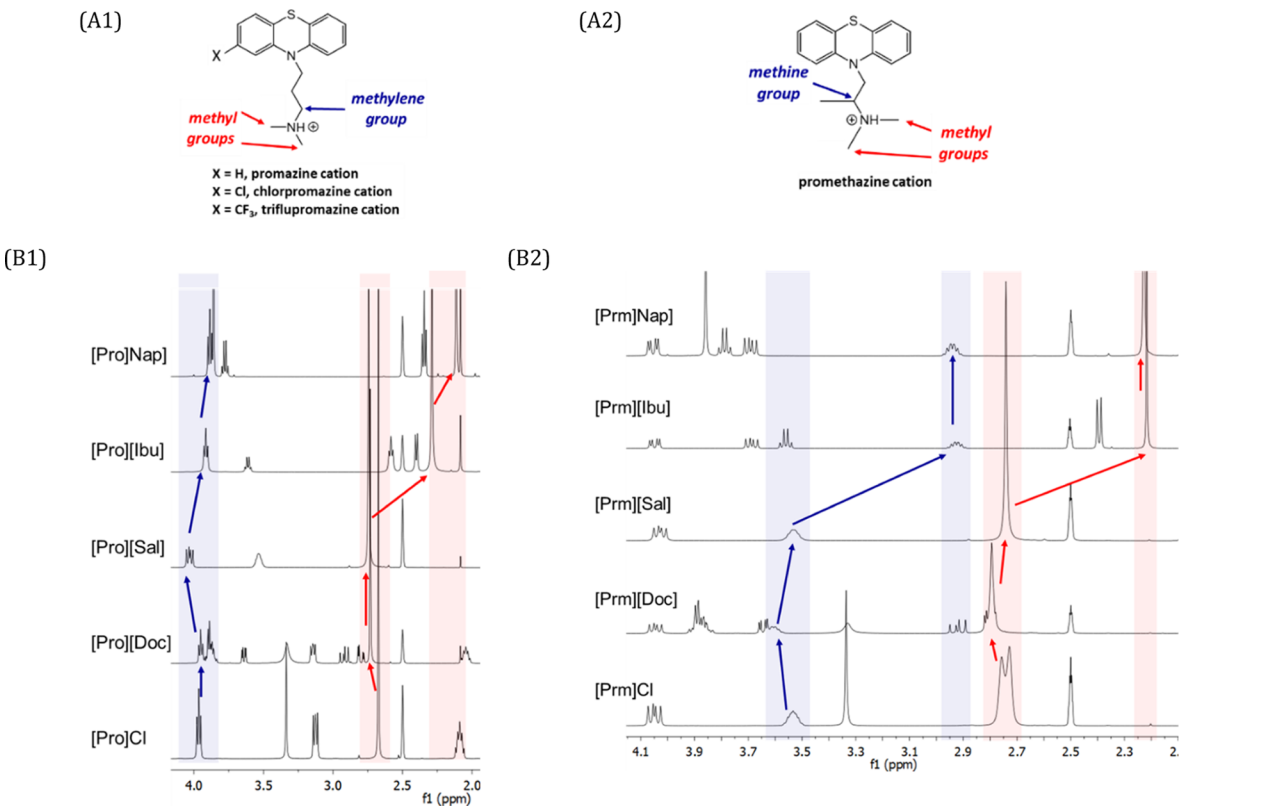

Figure 4. Structures for [Pro], [CPro], [FPro] (A1), and [Prm] (A2) cations and stacked ^{1}H NMR spectra for [Pro] (B1) and [Prm] (B2) derivatives.

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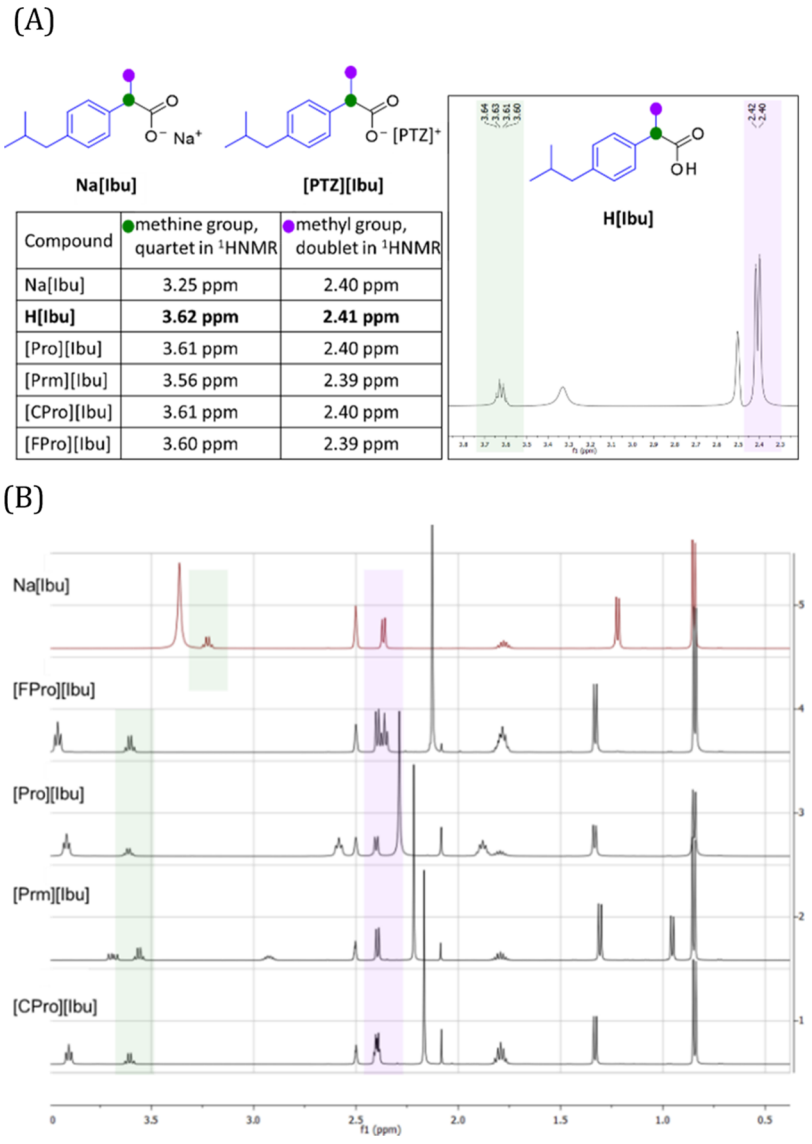
Table 2. Chemical Shift Values for Methyl, Methylene, and Methine Peaks Present in Promazine, Chlorpromazine, Trifluprom azine, and Promethazine Compounds

^{1}H NMR shifts (ppm) for methyl, CH_3, groups in [Pro], [CPro], [Prm] and [FPro] derivatives					
	[Cl]	[Doc]	[Ibu]	[Sal]	[Nap]
[Pro]	2.67	2.73	2.29	2.67	2.10
[CPro]	2.68	2.73	2.20	2.64	2.11
[Prm]	2.73	2.78	2.21	2.59	2.22
[FPro]	2.67	2.73	2.13	2.64	2.10
^{1}H NMR shifts (ppm) for methylene, CH_2, groups in [Pro], [CPro], and [FPro] derivatives					
	[Cl]	[Doc]	[Ibu]	[Sal]	[Nap]
[Pro]	3.96	3.95	4.01	3.91	3.88
[CPro]	3.98	3.96	3.96	3.90	3.89
[FPro]	4.06	4.03	4.04	3.95	3.95
^{1}H NMR shifts (ppm) for methine, CH, groups in [Prm] derivatives					
	[Cl]	[Doc]	[Ibu]	[Sal]	[Nap]
[Prm]	3.53	3.60	3.53	2.92	2.93

shift of 3.53 ppm in [Prm][Sal], and is shifted upfield to 2.92 ppm in [Prm][Ibu], and to 2.93 ppm in [Prm][Nap]. These results further confirm the co-crystal nature of the synthesized compounds with the hydrogen being shared between the cation and anion. Moreover, [Pro][Ibu] and [Pro][Nap] show a higher electron density while [Pro][Doc] and [Pro][Sal] show a lower electron density at the nitrogen site when compared to [Pro]Cl, further confirming a lower degree of ionization for [Pro][Ibu] and [Pro][Nap] and a higher degree of ionization for [Pro][Doc] and [Pro][Sal].

^{1}H NMR Spectroscopy: Cation Comparison. The cation influence on the anion's chemical shift differences further confirmed the co-crystal formation. This was analyzed by comparing the ^{1}H NMR spectra of the synthesized phenothiazine compounds with the spectra of the corresponding sodium salts and free acids of the anion precursors. For example, the chemical shifts of the methine and methyl groups adjacent to the carboxylate anion from [Pro][Ibu], [Prm]-[Ibu], [CPro][Ibu], and [FPro][Ibu] were compared to the chemical shifts of the same group from Na[Ibu] and ibuprofen



Compound	methine group, quartet in ^{1}HNMR	methyl group, doublet in ^{1}HNMR
Na[Ibu]	3.25 ppm	2.40 ppm
H[Ibu]	**3.62 ppm**	**2.41 ppm**
[Pro][Ibu]	3.61 ppm	2.40 ppm
[Prm][Ibu]	3.56 ppm	2.39 ppm
[CPro][Ibu]	3.61 ppm	2.40 ppm
[FPro][Ibu]	3.60 ppm	2.39 ppm

Figure 5. Cation influence on the 1H NMR chemical shifts of the methine and methyl groups in phenothiazine ibuprofen compounds ([PTZ][Ibu]): (A) chemical shift values and 1H NMR for H[Ibu] and (B) stacked ^{1}H NMR spectra for ibuprofen derivatives.

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free acid, H[Ibu] (Figure 5). A higher influence was obtained on the methine group: this group (highlighted in green in Figure 5), a quartet at 3.25 ppm in Na[Ibu], was shifted downfield to 3.61 ppm in [Pro][Ibu], 3.56 ppm in [Prm][Ibu], 3.61 ppm in [CPro][Ibu], and 3.60 ppm in [FPro][Ibu], respectively, chemical shifts that are similar to the methine group present in ibuprofen free acid, H[Ibu].

However, no significant influence is seen for the adjacent methyl group (highlighted in purple in Figure 5); this group shows as a doublet at 2.40 ppm in Na[Ibu] and at 2.41 ppm in[Pro][Ibu], 2.39 ppm in [Prm][Ibu], 2.40 ppm in [CPro]-[Ibu], and 2.39 ppm in [FPro][Ibu]. This is most likely due to a higher distance between this group and the basic site. The more downfield chemical shift values for the methine group in the synthesized phenothiazine ibuprofen compounds is consistent with a decrease in the electron density around the carboxylate anion, which further confirms their lower degree of ionization when compared to Na[Ibu] and therefore their existence as co-crystals.

Diffusion-Ordered (DOSY) NMR Spectroscopy. ^{1}H DOSY NMR is a powerful technique used to investigate the existence of individual species in a solution; in the case of ionic compounds, it can be used to determine if the cation and anion remain associated in solutions.[27] This can provide information on the transport properties and helps with the structural characterization of the compounds. The self-diffusion coefficients for the ion pair or the cation and anion present in the 0.06 M DMSO-d_6 solutions of each of the promazine derivatives ([Pro]Cl, [Pro][Doc], [Pro][Sal], [Pro][Ibu], and [Pro]Nap]) (Figures S24−S29, Supporting Information) and ibuprofen derivatives ([CPro][Ibu], [FPro][Ibu], and [Prm][Ibu]) (Table S4, Supporting Information) were determined by acquiring the corresponding ^{1}H DOSY NMR spectra at 298 K.

Self-diffusion coefficients are affected by the intermolecular interactions, size (*i.e.*, cross-sectional area Stokes Einstein equation), and shape of the compounds. As expected, the ^{1}H DOSY NMR spectrum of [Pro]Cl shows the presence of two different species, the [Pro] cation, and chloride anion (Cl) (Supporting Information, Figure S24A), with the [Pro] cation diffusion coefficient being 3.39×10^{-10} m^2/s (Figure 6). Only

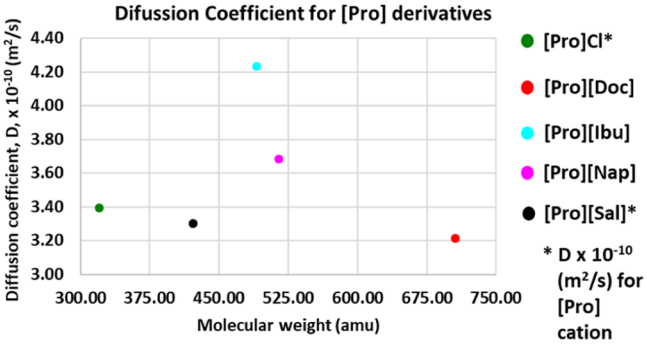

Figure 6. Diffusion coefficient data for [Pro] derivatives.

one species is seen in the 0.06 M [Pro][Doc], [Pro][Ibu], and [Pro][Nap] DMSO-d_6 solutions (Supporting Information, Figure S24B,C,E), consistent with their existence in an associated form (or a co-crystal form) with the cation and anion being held together through a low-barrier-type hydrogen bond. Moreover, the diffusion coefficient for these compounds increases with their decreasing size, with the lower-molecular weight compounds diffusing faster in the order: [Pro][Doc] ($D = 3.21 \times 10^{-10}$ m^2/s) < [Pro][Nap] ($D = 3.68 \times 10^{-10}$ m^2/s) < [Pro][Ibu] ($D = 4.23 \times 10^{-10}$ m^2/s) (Figure 6). These results confirm that the cation and anion in these compounds remain associated.

However, [Pro][Sal] exhibits a different behavior; two species with different diffusion rates are seen in the 0.06 M DMSO-d_6 [Pro][Sal] solution (Supporting Information, Figure S24D); these can be attributed to the existence of the [Pro] cation and [Sal] anion as individual species rather than in an associated form. Moreover, the obtained D value for the [Pro] cation (*i.e.*, $D = 3.39 \times 10^{-10}$ m^2/s) matches the one obtained for the cation in the ^{1}H DOSY spectrum for [Pro]Cl (*i.e.*, $D = 3.30 \times 10^{-10}$ m^2/s). This further confirms that [Pro][Sal] has a degree of ionization similar to [Pro]Cl.

The diffusion coefficients, D, for [Ibu] derivatives [Prm]-[Ibu], [CPro][Ibu], and [FPro][Ibu] was also determined using ^{1}H DOSY NMR (Supporting Information, Figures S24F−H). Each spectrum shows the presence of only one species consistent with the existence of the cation and anion from the [Ibu] derivatives in an associated form. Moreover, D values obtained for these derivatives show a similar trend as in the case of [Pro] derivatives: D increases with the decreasing size of the cation in the following order: [FPro][Ibu] ($D = 4.13 \times 10^{-10}$ m^2/s) < [CPro][Ibu] ($D = 4.18 \times 10^{-10}$ m^2/s) < [Pro][Ibu] ($D = 4.23 \times 10^{-10}$ m^2/s) (Figure 7).

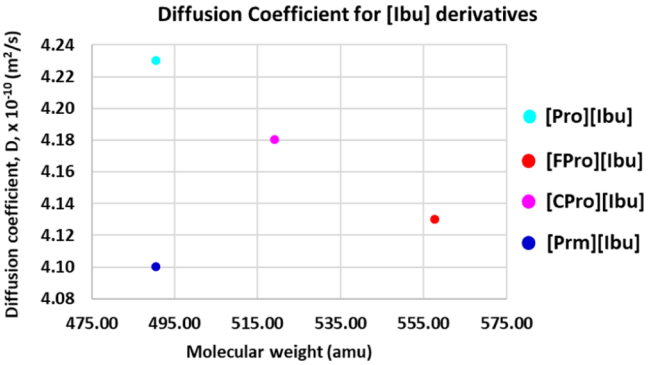

Figure 7. Diffusion coefficient data for [Ibu] derivatives.

The diffusion coefficient is also affected by the shape of the cation and therefore by the intermolecular forces between solute molecules; a lower D value (4.10×10^{-10} m^2/s) was obtained for [Prm][Ibu], a constitutional isomer of [Pro]-[Ibu], suggesting that molecules with weaker IMFs diffuse more slowly.

Thermal Characterization. The thermal behavior of the synthesized compounds was further investigated. Decomposition temperatures (T_{onset} and T_{endset}) were determined using thermogravimetric analysis (TGA) while phase transitions (glass transitions, T_g, solid−solid transitions, $T_{transition}$, and/or melting points, T_m) were determined using differential scanning calorimetry (DSC). The obtained T_{onset} and T_{endset} values are shown in Figure 8 and Table 3, the T_g values are shown in Table 3, while the full TGA and DSC graphs are shown in Figures S30−S37 from Supporting Information.

TGA. All the synthesized compounds but [Pro][Sal] underwent a one-step decomposition. The highest thermal stability was obtained for the docusate derivatives, where T_{onset} (°C) values were at least 40 °C higher than those of the

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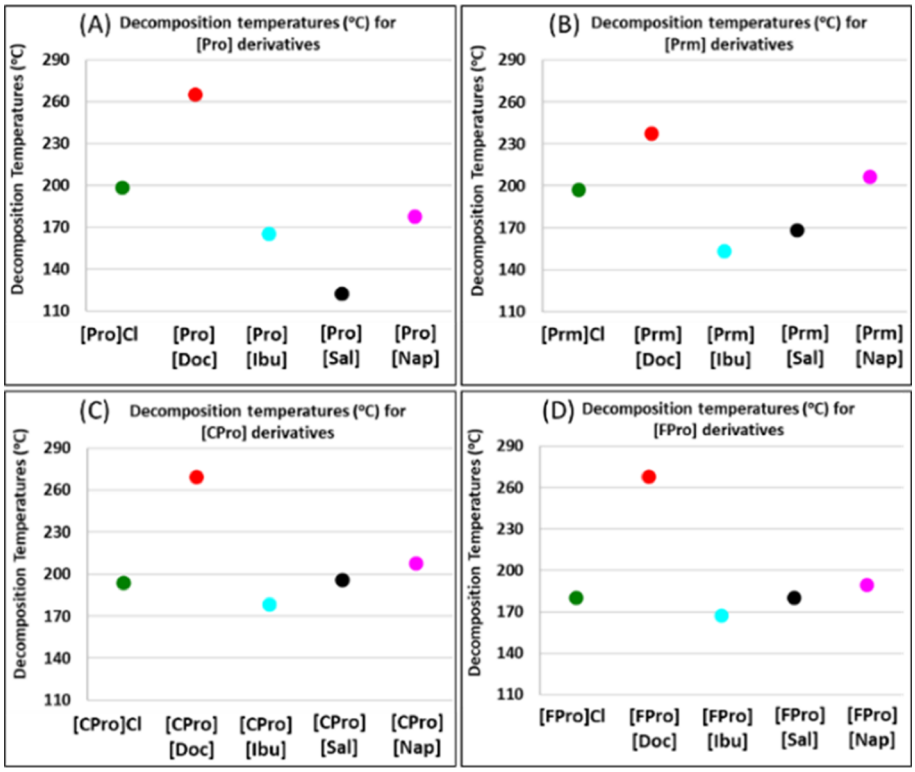

Figure 8. Thermal stability of (A) [Pro], (B) [Prm], (C) [CPro], and (D) [FPro] compounds: anion influence.

corresponding phenothiazine hydrochloride salts; the highest difference (~87 °C) was obtained for the [FPro] derivative (T_{onset} of 267.69 °C for [FPro][Doc] vs T_{onset} of 179.74 °C for [FPro]Cl).

Anion Influence on Thermal Stability (Figure 8). In the case of [Prm], [CPro], and [FPro] derivatives, the same thermal stability trend was observed with the decomposition temperatures increasing in the following order: [Ibu] < [Sal] < [Nap] < [Doc] derivatives. In the case of [Pro] derivatives, the [Pro][Ibu] (T_{onset} of 164.72 °C) showed a higher thermal stability than [Pro]Sal] (T_{onset} of 121.93 °C) while the higher-molecular weight compounds, [Pro][Doc] (T_{onset} of 265.04 °C) and [Pro]Nap] (T_{onset} of 177.23 °C), still showed the highest thermal stability.

Cation Influence on Thermal Stability (Figure 9). In the case of [Ibu] (cyan line in Figure 9) and [Doc] (red line in Figure 9) derivatives, the T_{onset} values for [Prm][Ibu] and [Prm][Doc] derivatives were observed to be lower than the corresponding T_{onset} values obtained for the less bulky constitutional isomers, [Pro][Ibu] and [Pro][Doc], respectively. For example, the T_{onset} for [Prm][Doc] was 237.24 °C while T_{onset} for [Pro][Doc] was 265.04 °C; this can be attributed to the higher degree of branching present in the carbon chain between the two nitrogen sites of the [Prm] cation (and therefore weaker intermolecular forces between identical molecules).

The corresponding [CPro] and [FPro] derivatives ([CPro]-[Ibu], [CPro][Doc], [FPro][Ibu], and [FPro][Doc]) showed similar or slightly higher thermal stability when compared to the corresponding [Pro][Ibu] and [Pro][Doc] derivatives, most likely due to the presence of stronger intermolecular forces between the cations, which can be attributed to the presence of −Cl and $-CF_3$ groups in their structures (*i.e.*, stronger dipole−dipole forces). However, in the case of [Sal] (black line in Figure 9) and [Nap] (magenta line in Figure 9) derivatives, the T_{onset} values for [Prm], [CPro], and [FPro] derivatives were observed to be higher than the T_{onset} values obtained for the corresponding [Pro] derivatives. This suggests a synergistic effect of the cation and anion on the thermal stability of these compounds.

Differential Scanning Calorimetry. Fifteen out of the sixteen prepared compounds were obtained as glassy materials. All compounds but [Prm][Sal] showed only a reversible glass transition, T_g, in the −90 to +90 °C range. This transition was present in all the three cycles of the DSC curve. For all the phenothiazine derivatives but [Pro] compounds (Figure 10), the lowest T_g value was obtained for the [Doc] derivative ([Prm][Doc], T_g = −15.44 °C; [CPro][Doc], T_g = −18.81 °C; and [FPro][Doc], T_g = −21.73 °C). In the case of [Pro] compounds, [Pro][Ibu] shows the lowest T_g of −21.54 °C. Similar trends were obtained for all the phenothiazine compounds with [Ibu], [Sal], and [Nap] derivatives showing higher T_g values compared to those of the corresponding [Doc] compounds. No significant trend could be identified when analyzing the cation influence on the T_g values of the investigated compounds (Figure 11). For example, the [CPro][Doc], [CPro[Nap], [FPro][Doc], and [FPro][Nap] compounds show lower T_g values compared to [Pro][Doc] and [Pro][Nap]. Opposite is obtained in the case of [Ibu] and [Sal] derivatives: the [CPro][Ibu], [CPro[Sal], [FPro][Ibu], and [FPro][Sal] compounds show higher T_g values compared to [Pro][Ibu] and [Pro][Sal]. [Prm][Ibu] and [Prm][Doc] show the highest T_g values when compared to those of the corresponding [Pro], [CPro], or [FPro] derivatives while [Prm][Sal] showed no glass transition or melting point in the investigated temperature range.

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Table 3. Thermal Analyses of Phenothiazine Co-crystals

Compound	Appearance	Thermogravimetric Analysis (TGA)			Differential Scanning Calorimetry (DSC)		
		T_{onset} (°C)	T_{endset} (°C)	Mass Loss after 30 min at 75 °C (%)	T_m (°C)	T_g on heating (°C)	T_g on cooling (°C)
[Pro]Cl		198.04	213.86	–	181[b]	–	–
[Pro][Doc]		265.04	278.61	1.90	ND[a]	-18.08	-22.35
[Pro][Ibu]		164.72	184.15	1.56	ND[a]	-21.54	-20.74
[Pro][Sal]		121.93 202.86	137.08 213.12	2.17	ND[a]	-9.14	-9.87
[Pro][Nap]		177.23	195.89	0.05	ND[a]	7.58	5.43
[Prm]Cl		197.05	212.16	–	227 – 230[b]	–	–
[Prm][Doc]		237.24	251.76	1.89	ND[a]	-15.44	-20.31
[Prm][Ibu]		152.86	169.49	0.54	ND[a]	-2.02	-3.88
[Prm][Sal]		167.73	183.41	0.05	ND[a]	ND[a]	ND[a]
[Prm][Nap]		206.20	227.49	1.99	ND[a]	2.16	5.89
[CPro]Cl		193.71	211.5	–	194 – 196[b]	–	–
[CPro][Doc]		269.20	285.13	1.62	ND[a]	-18.81	-22.04
[CPro][Ibu]		178.11	204.10	1.07	ND[a]	-13.08	-18.29
[CPro][Sal]		195.55	215.55	1.51	ND[a]	0.47	-3.57
[CPro][Nap]		207.32	228.94	1.92	ND[a]	4.39	3.82
[FPro]Cl		179.74	194.28	–	172 – 174[b]	–	–
[FPro][Doc]		267.69	285.89	1.80	ND[a]	-21.73	-23.84
[FPro][Ibu]		166.7	186.69	1.65	ND[a]	-19.11	-22.18
[FPro][Sal]		179.77	196.41	1.75	ND[a]	-0.76	-0.84
[FPro][Nap]		188.93	210.64	1.02	ND[a]	-7.55	-1.94

[a]ND—not detected in the (−90) to (+90) °C range. [b]Safety data sheet.

CONCLUSIONS

Phenothiazine drugs are known to have multiple pharmacological effects but no known analgesic effect. Therefore, these drugs are administered in combination with NSAIDs. Combining the two types of drugs into one single, liquid-state, compound would potentially aid with the drug administration while addressing other inherent solid-state issues such as polymorphism. The ΔpK_a difference between the pK_a of the conjugated acids and the acids used in this study (>5) suggests that a liquid-state behavior is indeed expected. In our search for new phenothiazine ionic liquids, we have found that aliphatic phenothiazine drugs (cation precursors) can be paired with various NSAIDs (anion precursors) to form dual functional PILs with various degrees of proton transfer between the cation and anion (*i.e.*, various degree of ionization), species also known as liquid co-crystals. According to various reports, co-crystal pharmaceuticals will keep the pharmacological properties of the component drugs. Therefore, the new liquid co-crystals reported here will not only benefit from dual functionality but will also show potential

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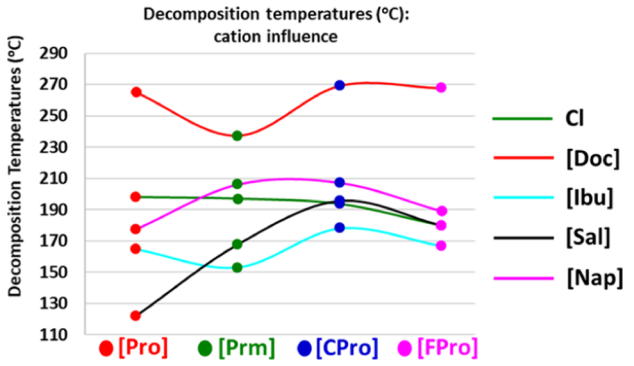

Figure 9. Thermal stability of Cl (green line), [Doc] (red line), [Ibu] (cyan line), [Sal] (black line), and [Nap] (magenta line) compounds: cation influence.

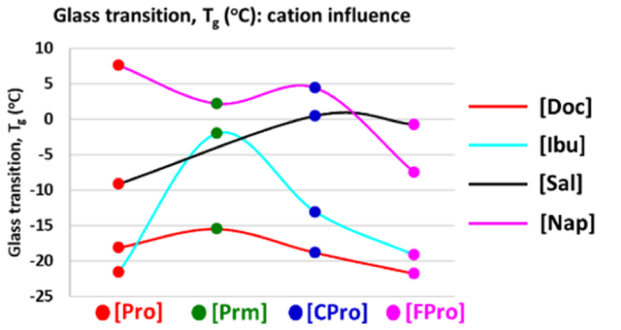

Figure 11. Glass transitions, T_g (°C), for [Doc] (red line), [Ibu] (cyan line), [Sal] (black line), and [Nap] (magenta line) compounds: cation influence.

synergistic effects (*i.e.*, similar to the dual-active lidocaine etodolac IL that completed phase III clinical trials). Moreover, the cation and anion remain associated in the 0.06 M DMSO-d_6 solutions (298 K) of the less-ionized compounds and not associated in a 0.06 M DMSO-d_6 solution (298 K) in the case of the highly ionized compounds. This information is the first step toward providing an insight into the transport properties of these compounds (*i.e.*, transdermal delivery): PILs have been shown to permeate through a skin-mimicking membrane faster than their corresponding ionic salts. Therefore, investigating the transdermal delivery of these compounds is currently on-going in our laboratory.

METHODS

Chemicals. All the cation precursors used in this study were purchased from Fisher Scientific (chlorpromazine hydrochloride 98% and triflupromazine hydrochloride 98%), TCI (promethazine hydrochloride 98%), and Aldrich (promazine hydrochloride 98%). The anion precursors were purchased from Acros Organics (sodium naproxen; 98%), Aldrich (sodium ibuprofen, 98%), and Fisher Scientific (sodium docusate, 99%). The compounds were used as received.

Characterization. *NMR Spectroscopy.* All the NMR spectra (^{1}H, ^{13}C, ^{19}F, and the ^{1}H−^{15}N HSQC) were acquired as follows: 0.06 M solutions of the investigated compounds in DMSO-d_6 were prepared, and the spectra were recorded at 25 °C using a Bruker 500 MHz spectrometer.

FT-IR Spectroscopy. FT-IR spectra ranging between 650 and 3800 cm^{-1} were obtained from neat aliquots of each API-IL by using a Perkin Elmer ATR-IR Instrument. The resolution for the spectra was of 1 cm^{-1}.

TGA. TGA experiments were performed on a Thermal Analysis Discovery TGA550 instrument. Samples (2−15 mg) were placed in 70 μL platinum pans and were analyzed as follows: the samples were heated under a flow of nitrogen from 25 to 800 °C in a dynamic heating regime by using a 5 °C/min heating ramp and an isotherm of 30 min at 75 °C.

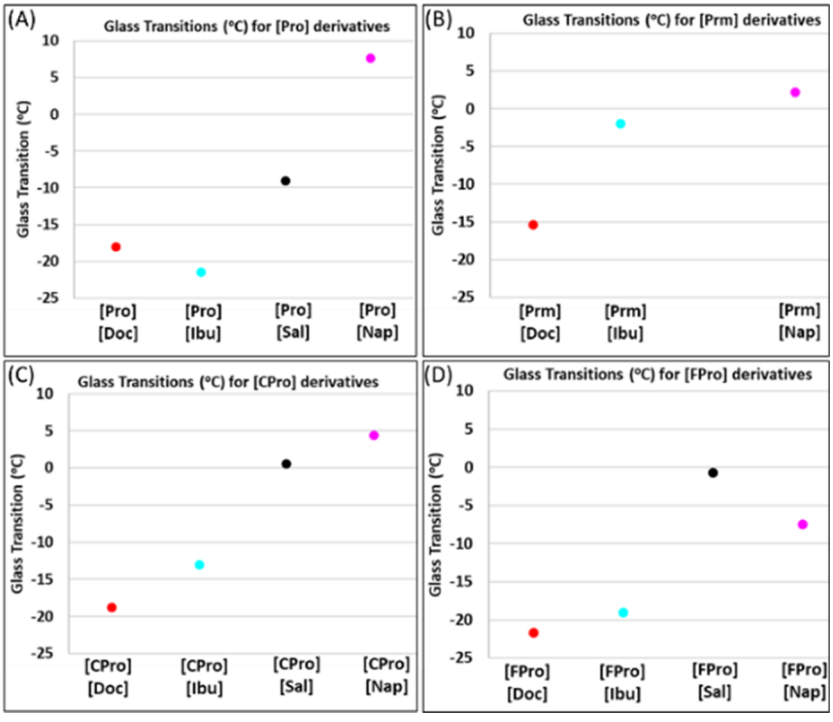

Figure 10. Glass transitions, T_g (°C), for (A) [Pro], (B) [Prm], (C) [CPro], and (D) [FPro] compounds: anion influence.

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DSC Analyses. DSC data were collected using a Thermal Analysis Discovery DSC250 instrument under a continuous flow of nitrogen. DSC samples were prepared by placing 2−15 mg of compound into sealed *T* Zero pans covered with hermetic Al lids and sealed using a *T*-Zero press. The data collection involved three cycles each consisting of four steps: (1) heating to 90 °C at a 5 °C/min heating rate; (2) a 5 min isotherm at 90 °C; (3) cooling at a 5 °C/min rate to −90 °C; and (4) a 5 min isotherm at −90 °C.

Syntheses. *General Synthesis of Phenothiazine Compounds.* Phenothiazine hydrochloride was suspended in anhydrous acetone, and an equimolar amount of anion precursor was added. The resulting suspension was stirred for 20−24 h at room temperature. The inorganic salt formed (NaCl) was removed by filtration through a 0.2 μm filter, and the solvent from the obtained solution was removed using a Buchi rotary evaporator under high vacuum (42 mbar and 50 °C), leaving behind highly viscous or glassy masses.

Promazine Hydrochloride, [Pro]Cl. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.26−7.14 (m, 2H), 7.09 (d, J = 8.3, 1.1 Hz, 1H), 6.97 (td, J = 7.5, 1.1 Hz, 1H), 3.97 (t, J = 7.2 Hz, 1H), 3.16−3.09 (m, 1H), 2.67 (s, 3H), 2.14−2.04 (m, 1H). ^{13}C NMR (126 MHz, DMSO): δ 144.50, 127.68, 127.22, 123.89, 122.75, 115.94, 54.27, 43.88, 41.95, 40.11, 39.91, 39.74, 39.57, 39.40, 39.23, 39.07, 21.48.

Promazine Docusate, [Pro][Doc]. 98.5% yield. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.33 (s, 1H), 7.27−7.16 (m, 4H), 7.08 (d, J = 8.1 Hz, 2H), 7.02−6.95 (m, 2H), 3.95 (t, J = 7.0 Hz, 2H), 3.94−3.81 (m, 4H), 3.18−3.11 (m, 2H), 2.80 (dd, J = 17.2, 3.6 Hz, 1H), 2.73 (s, 4H), 2.10−2.00 (m, 2H), 1.53−1.44 (m, 2H), 1.39−1.19 (m, 16H), 0.89−0.78 (m, 11H). ^{13}C NMR (126 MHz, DMSO): δ 171.02, 168.33, 144.46, 127.66, 127.26, 123.97, 122.78, 115.92, 66.17, 66.09, 66.07, 66.04, 54.59, 43.58, 42.40, 42.38, 39.52, 38.16, 38.12, 38.11, 38.08, 34.12, 29.73, 29.61, 29.55, 28.34, 28.33, 23.18, 23.15, 22.99, 22.97, 22.41, 22.38, 21.67, 13.91, 13.88, 13.87, 10.81, 10.78, 10.74, 10.72.

Promazine Ibuprofenate, [Pro][Ibu]. 90.4% yield. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.24−7.13 (m, 5H), 7.06 (dd, J = 22.3, 7.9 Hz, 3H), 6.95 (t, J = 7.4 Hz, 2H), 3.91 (t, J = 6.9 Hz, 2H), 2.58 (t, J = 7.2 Hz, 2H), 2.40 (d, J = 7.1 Hz, 1H), 2.29 (s, 6H), 1.93−1.74 (m, 3H), 1.33 (d, J = 7.1 Hz, 2H), 0.85 (d, J = 6.5 Hz, 4H). ^{13}C NMR (126 MHz, DMSO): δ 175.71, 144.85, 144.79, 139.63, 138.74, 129.10, 129.08, 127.78, 127.76, 127.32, 127.30, 127.26, 123.92, 123.90, 123.07, 122.72, 122.69, 116.05, 116.03, 55.79, 44.55, 44.45, 44.30, 44.26, 40.23, 40.07, 39.90, 39.73, 39.57, 39.40, 39.23, 30.85, 29.77, 23.62, 22.34, 22.28, 18.75, 18.71.

Promazine Salicylate, [Pro][Sal]. 98.8% yield. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.75 (dd, J = 7.6, 1.8 Hz, 1H), 7.27−7.19 (m, 7H), 7.06−6.97 (m, 2H), 6.75−6.66 (m, 2H), 4.40 (dd, J = 14.1, 4.5 Hz, 1H), 4.07−3.99 (m, 1H), 2.74 (s, 6H), 1.25 (d, J = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, DMSO): δ 173.13, 162.62, 145.05, 132.89, 130.70, 130.63, 128.38, 127.88, 125.39, 123.81, 123.54, 119.23, 117.45, 117.00, 116.94, 116.60, 116.53, 57.45, 47.80, 40.53, 40.36, 40.20, 40.03, 39.86, 39.69, 39.53, 12.16.

Promazine Naproxenate, [Pro][Nap]. 94.0% yield. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.77 (dd, J = 12.6, 8.7 Hz, 2H), 7.71 (s, 1H), 7.41 (dd, J = 8.4, 1.8 Hz, 1H), 7.28 (d, J = 2.5 Hz, 1H), 7.23−7.11 (m, 5H), 7.02 (dd, J = 8.2, 1.1 Hz, 2H), 6.94 (t, J = 7.5 Hz, 2H), 3.89 (t, 5H), 3.86 (s, 3H), 2.35 (t, J = 6.9 Hz, 2H), 2.12 (s, 7H), 1.79 (p, J = 7.0 Hz, 2H), 1.44 (d, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO): δ 175.64, 157.08, 144.80, 136.67, 133.22, 129.07, 129.04, 128.44, 127.56, 127.53, 127.10, 126.75, 126.46, 125.51, 125.47, 123.72, 122.44, 122.40, 118.62, 115.84, 115.80, 105.67, 56.13, 55.13, 45.00, 44.83, 40.06, 39.90, 39.73, 39.56, 39.40, 39.23, 39.06, 30.67, 24.26, 18.56.

Promethazine Hydrochloride, [Prm]Cl. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.43 (s, 1H), 7.37−7.31 (m, 2H), 7.30−7.22 (m, 4H), 7.03 (td, J = 7.4, 1.1 Hz, 2H), 4.54 (dd, J = 13.9, 4.1 Hz, 1H), 4.09−4.01 (m, 1H), 3.59−3.48 (m, 1H), 2.74 (d, J = 14.2 Hz, 6H), 1.27 (d, J = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, DMSO): δ 144.46, 127.88, 127.55, 124.89, 123.32, 123.29, 116.65, 116.61, 57.16, 46.97, 40.20, 40.03, 39.86, 39.69, 39.52, 39.35, 39.19, 39.02, 37.80, 11.29.

Promethazine Docusate, [Prm][Doc]. 88.5% yield. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.03 (s, 1H), 7.32−7.22 (m, 6H), 7.04 (td, J = 7.3, 1.6 Hz, 2H), 4.41 (dd, J = 14.2, 4.8 Hz, 1H), 4.05 (dd, J = 14.2, 8.6 Hz, 1H), 3.94−3.81 (m, 3H), 3.68−3.55 (m, 2H), 2.92 (dd, J = 17.2, 11.6 Hz, 1H), 2.79 (s, 6H), 1.54−1.43 (m, 2H), 1.39−1.19 (m, 16H), 0.89−0.78 (m, 9H). ^{13}C NMR (126 MHz, DMSO): δ 171.01, 168.32, 144.41, 127.88, 127.60, 124.99, 123.37, 116.51, 66.17, 66.10, 66.07, 66.03, 61.43, 57.50, 46.80, 39.52, 38.16, 38.12, 34.11, 30.67, 29.73, 29.54, 28.32, 23.18, 22.99, 22.40, 13.88, 13.87, 11.71, 11.70, 10.80, 10.77.

Promethazine Ibuprofenate, [Prm][Ibu]. 87.4% yield. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.25−7.14 (m, 6H), 7.11−7.03 (m, 4H), 6.95 (td, J = 7.5, 1.1 Hz, 2H), 4.05 (dd, J = 13.7, 4.8 Hz, 1H), 3.69 (dd, J = 13.8, 8.2 Hz, 1H), 3.57 (t, J = 7.1 Hz, 1H), 2.98−2.87 (m, 1H), 2.39 (d, J = 7.1 Hz, 2H), 2.22 (s, 5H), 1.85−1.73 (m, 1H), 1.31 (d, J = 7.1 Hz, 3H), 0.95 (d, J = 6.6 Hz, 3H), 0.85 (d, J = 6.6 Hz, 6H). ^{13}C NMR (126 MHz, DMSO): δ 175.92, 145.13, 139.53, 139.02, 128.71, 127.59, 127.28, 127.11, 124.37, 124.36, 122.58, 116.17, 55.42, 49.85, 45.13, 44.30, 40.61, 39.90, 39.77, 39.73, 39.57, 39.40, 39.23, 39.07, 29.62, 22.18, 18.91, 12.22.

Promethazine Salicylate, [Prm][Sal]. 91.7% yield. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.75 (dd, J = 7.7, 1.9 Hz, 1H), 7.27−7.19 (m, 7H), 7.06−6.98 (m, 2H), 6.75−6.66 (m, 2H), 4.39 (dd, J = 14.1, 4.5 Hz, 1H), 4.07−3.99 (m, 1H), 2.74 (s, 6H), 2.08 (s, 2H), 1.25 (d, J = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, DMSO): δ 173.07, 162.65, 145.05, 132.93, 130.69, 130.62, 128.37, 128.11, 125.39, 123.81, 119.24, 117.43, 117.00, 116.60, 57.50, 47.82, 40.53, 40.36, 40.32, 40.19, 40.03, 39.86, 39.69, 39.53, 31.18, 12.17.

Promethazine Naproxenate, [Prm][Nap]. 97.5% yield. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.78 (dd, J = 12.2, 8.7 Hz, 2H), 7.71 (s, 1H), 7.41 (dd, J = 8.5, 1.8 Hz, 1H), 7.28 (d, J = 2.5 Hz, 1H), 7.25−7.12 (m, 5H), 7.08 (dd, J = 8.2, 1.1 Hz, 2H), 6.96 (t, J = 6.9 Hz, 2H), 4.06 (dd, J = 13.8, 4.8 Hz, 1H), 3.79 (q, J = 7.1 Hz, 1H), 3.70 (dd, J = 13.8, 8.2 Hz, 1H), 3.00−2.89 (m, 1H), 2.23 (s, 6H), 2.09 (s, 1H), 1.44 (d, J = 7.1 Hz, 3H), 0.96 (d, J = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, DMSO): δ 175.57, 157.05, 145.11, 136.49, 133.19, 129.09, 128.39, 127.61, 127.30, 126.79, 126.44, 125.53, 124.39, 122.61, 118.64, 116.19, 105.68, 55.48, 55.14, 49.75, 44.74, 40.55, 39.53, 30.68, 18.52, 12.21.

Chlorpromazine Hydrochloride, [CPro]Cl. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.79 (s, 1H), 7.28−7.09 (m, 3H), 7.06−6.97 (m, 1H), 3.99 (t, J = 7.1 Hz, 1H), 3.16−3.09 (m, 1H), 2.68 (s, 3H), 2.12−2.02 (m, 1H). ^{13}C NMR (126 MHz, DMSO): δ 146.20, 143.70, 132.59, 128.22, 127.87, 127.35,

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123.73, 123.26, 122.97, 122.43, 116.45, 115.90, 54.21, 43.97, 41.96, 40.11, 39.91, 39.74, 39.57, 39.40, 39.23, 39.07, 21.50.

Chlorpromazine Docusate, [CPro][Doc]. 94.6% yield. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.39 (s, 1H), 7.29−7.17 (m, 3H), 7.15−7.07 (m, 2H), 7.06−6.98 (m, 2H), 3.97 (t, J = 7.0 Hz, 2H), 3.94−3.82 (m, 4H), 3.17−3.09 (m, 2H), 2.97−2.87 (m, 1H), 2.80 (dd, J = 17.2, 3.6 Hz, 1H), 2.73 (s, 5H), 2.10−1.98 (m, 3H), 1.53−1.44 (m, 2H), 1.38−1.17 (m, 15H), 0.89−0.78 (m, 11H). ^{13}C NMR (126 MHz, DMSO): δ 171.52, 168.84, 146.62, 144.23, 133.07, 128.80, 128.41, 127.93, 124.26, 123.84, 123.52, 123.00, 116.95, 116.44, 66.67, 66.59, 66.57, 66.53, 61.98, 55.05, 44.23, 40.53, 40.36, 40.32, 40.19, 40.03, 39.86, 39.69, 39.53, 38.67, 38.63, 38.61, 38.59, 34.63, 34.58, 31.16, 30.24, 30.11, 30.05, 28.85, 28.83, 23.68, 23.66, 23.50, 23.47, 22.91, 22.88, 22.22, 14.41, 11.35, 11.30.

Chlorpromazine Ibuprofenate, [CPro][Ibu]. 89.9% yield. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.25−7.12 (m, 3H), 7.11−7.02 (m, 2H), 7.03−6.93 (m, 1H), 3.90 (t, J = 6.9 Hz, 1H), 2.43−2.36 (m, 2H), 2.17 (s, 3H), 1.79 (hept, J = 6.7 Hz, 2H), 1.33 (d, J = 7.1 Hz, 1H), 0.84 (d, J = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, DMSO): δ 175.51, 146.25, 143.88, 139.44, 138.60, 132.43, 128.92, 128.90, 128.08, 128.06, 127.79, 127.77, 127.22, 127.20, 127.09, 127.07, 123.30, 122.99, 122.59, 122.09, 116.26, 115.74, 55.91, 44.84, 44.80, 44.55, 44.49, 44.40, 44.25, 40.06, 39.90, 39.73, 39.56, 39.40, 39.23, 39.06, 30.67, 29.60, 23.89, 22.20, 22.16, 18.58, 18.55.

Chlorpromazine Salicylate, [CPro][Sal]. 96.9% yield. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.69 (dd, J = 7.7, 1.8 Hz, 1H), 7.24−7.15 (m, 2H), 7.14−7.05 (m, 1H), 7.04−6.95 (m, 1H), 6.71−6.62 (m, 1H), 3.97 (t, J = 7.0 Hz, 1H), 3.12−3.04 (m, 1H), 2.68 (s, 3H), 2.04 (p, J = 7.3 Hz, 2H). ^{13}C NMR (126 MHz, DMSO): δ 172.36, 162.30, 146.13, 143.72, 132.57, 132.10, 130.14, 130.08, 128.24, 127.85, 127.38, 123.65, 123.26, 122.90, 122.43, 119.14, 116.62, 116.38, 115.98, 115.91, 115.88, 54.40, 43.90, 42.46, 40.02, 39.85, 39.81, 39.69, 39.52, 39.35, 39.19, 39.02, 30.68, 21.80.

Chlorpromazine Naproxenate, [CPro][Nap]. 95.2% yield. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.77 (dd, J = 12.4, 8.8 Hz, 2H), 7.71 (s, 1H), 7.41 (dd, J = 8.5, 1.8 Hz, 1H), 7.28 (d, J = 2.5 Hz, 1H), 7.25−7.11 (m, 4H), 7.10−7.02 (m, 2H), 7.02−6.93 (m, 2H), 3.90 (t, J = 6.9 Hz, 5H), 3.86 (s, 3H), 2.34 (t, J = 6.8 Hz, 2H), 2.12 (s, 7H), 1.77 (p, J = 6.9 Hz, 2H), 1.44 (d, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO): δ 175.61, 157.05, 146.27, 143.97, 136.59, 133.18, 132.43, 129.07, 128.39, 128.06, 127.78, 127.20, 126.75, 126.45, 125.51, 123.28, 122.96, 122.57, 122.05, 118.62, 116.24, 115.72, 105.67, 55.99, 55.13, 45.07, 44.81, 44.57, 39.52, 30.68, 24.10, 18.55.

Triflupromazine Hydrochloride, [FPro]Cl. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.79 (s, 1H), 7.41 (dd, J = 8.4, 0.9 Hz, 1H), 7.33−7.20 (m, 4H), 7.15 (d, J = 7.1 Hz, 1H), 7.03 (td, J = 7.5, 1.1 Hz, 1H), 4.06 (t, J = 7.1 Hz, 2H), 3.17−3.10 (m, 2H), 2.67 (s, 6H), 2.12−2.02 (m, 2H). ^{13}C NMR (126 MHz, DMSO): δ 145.49, 143.48, 129.66, 128.09, 127.91, 127.47, 123.50, 123.17, 123.11, 119.31, 119.28, 119.25, 116.63, 112.17, 112.14, 112.11, 54.19, 43.97, 41.93, 40.07, 39.90, 39.73, 39.57, 39.40, 39.23, 39.07, 21.47. ^{19}F NMR (471 MHz, DMSO): δ −60.80.

Triflupromazine Docusate, [FPro][Doc]. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.26 (s, 1H), 7.34−7.20 (m, 4H), 4.04 (t, J = 7.0 Hz, 2H), 3.94−3.82 (m, 4H), 3.64 (dd, J = 11.6, 3.5 Hz, 1H), 3.18−3.11 (m, 2H), 2.92 (dd, J = 17.2, 11.6 Hz, 1H), 2.80 (dd, J = 17.2, 3.6 Hz, 1H), 2.73 (s, 6H), 2.10−1.98 (m, 3H), 1.48 (ddq, J = 9.2, 6.1, 3.6 Hz, 2H), 1.38−1.18 (m, 18H), 0.91−0.78 (m, 12H). ^{13}C NMR (126 MHz, DMSO): δ 171.02, 168.34, 145.41, 143.51, 129.76, 128.57, 128.31, 128.07, 127.94, 125.23, 123.53, 123.21, 123.07, 119.35, 119.32, 119.29, 116.58, 66.15, 66.08, 66.06, 66.02, 61.42, 54.56, 43.71, 42.47, 42.43, 39.52, 38.16, 38.12, 38.11, 38.08, 34.11, 30.66, 29.60, 29.54, 28.33, 28.32, 28.29, 23.17, 23.15, 22.99, 22.96, 22.40, 22.37, 21.69, 13.90, 13.87, 10.79, 10.76, 10.72. ^{19}F NMR (471 MHz, DMSO): δ −60.85.

Triflupromazine Ibuprofenate, [FPro][Ibu]. 91.4% yield. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.35 (d, J = 7.9 Hz, 1H), 7.31−7.14 (m, 7H), 7.07 (t, J = 7.5 Hz, 3H), 6.99 (t, J = 7.5 Hz, 1H), 3.96 (t, J = 6.9 Hz, 2H), 2.42−2.33 (m, 4H), 2.13 (s, 6H), 1.79 (pd, J = 6.8, 3.8 Hz, 3H), 1.33 (d, J = 7.1 Hz, 3H), 0.84 (d, J = 6.6 Hz, 6H). ^{13}C NMR (126 MHz, DMSO): δ 175.56, 145.28, 143.77, 139.39, 138.57, 128.92, 128.25, 128.03, 127.72, 127.28, 127.09, 123.20, 122.53, 118.95, 118.92, 116.50, 116.35, 111.85, 111.81, 56.01, 44.98, 44.64, 44.41, 44.21, 40.07, 39.90, 39.73, 39.57, 39.40, 39.23, 39.06, 29.60, 24.00, 22.16, 18.58. ^{19}F NMR (471 MHz, DMSO): δ −60.99.

Triflupromazine Salicylate, [FPro][Sal]. 90.8% yield. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.68 (dd, J = 7.6, 1.8 Hz, 1H), 7.42−7.36 (m, 1H), 7.31−7.26 (m, 2H), 7.27−7.16 (m, 3H), 7.13−7.07 (m, 1H), 7.01 (td, J = 7.4, 1.1 Hz, 1H), 6.71−6.61 (m, 2H), 4.04 (t, J = 7.0 Hz, 2H), 3.12−3.05 (m, 2H), 2.67 (s, 6H), 2.05 (p, J = 7.2 Hz, 4H). ^{13}C NMR (126 MHz, DMSO): δ 172.40, 162.26, 145.39, 143.55, 132.14, 130.12, 129.64, 128.56, 128.31, 128.02, 127.88, 127.49, 125.22, 123.50, 123.09, 119.19, 119.05, 116.55, 116.49, 115.98, 115.92, 112.09, 112.06, 112.03, 54.38, 43.92, 42.42, 40.02, 39.85, 39.81, 39.69, 39.52, 39.35, 39.19, 39.02, 30.72, 21.77. ^{19}F NMR (471 MHz, DMSO): δ −60.87.

Triflupromazine Naproxenate, [FPro][Nap]. 99.0% yield. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.77 (dd, J = 12.3, 8.7 Hz, 2H), 7.70 (s, 1H), 7.40 (dd, J = 8.5, 1.8 Hz, 1H), 7.34 (d, J = 7.9 Hz, 1H), 7.28−7.11 (m, 6H), 7.06 (dd, J = 8.3, 1.2 Hz, 1H), 6.98 (t, J = 7.5 Hz, 1H), 3.95 (t, J = 6.9 Hz, 2H), 3.86 (s, 3H), 2.34 (t, J = 6.8 Hz, 2H), 2.11 (s, 7H), 1.77 (p, J = 6.9 Hz, 2H), 1.43 (d, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO): δ 175.59, 157.05, 145.33, 143.83, 136.55, 133.18, 129.07, 128.39, 128.01, 127.70, 127.27, 126.76, 126.44, 125.51, 123.17, 122.52, 118.94, 118.63, 116.32, 111.83, 111.80, 111.77, 105.67, 55.13, 45.03, 44.77, 44.66, 39.52, 30.67, 24.01, 18.52. ^{19}F NMR (471 MHz, DMSO): δ −60.99.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c07382.

Yields and purity, FT-IR, ^{1}H NMR, ^{13}C NMR, ^{1}H DOSY NMR spectra for all compounds, and TGA and DSC data (PDF)

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Notes

The authors declare no competing financial interest.

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