

**Polyethylene Glycol Derivatization of the Non-active Ion in Active Pharmaceutical Ingredient Ionic Liquids Enhances Transdermal Delivery**

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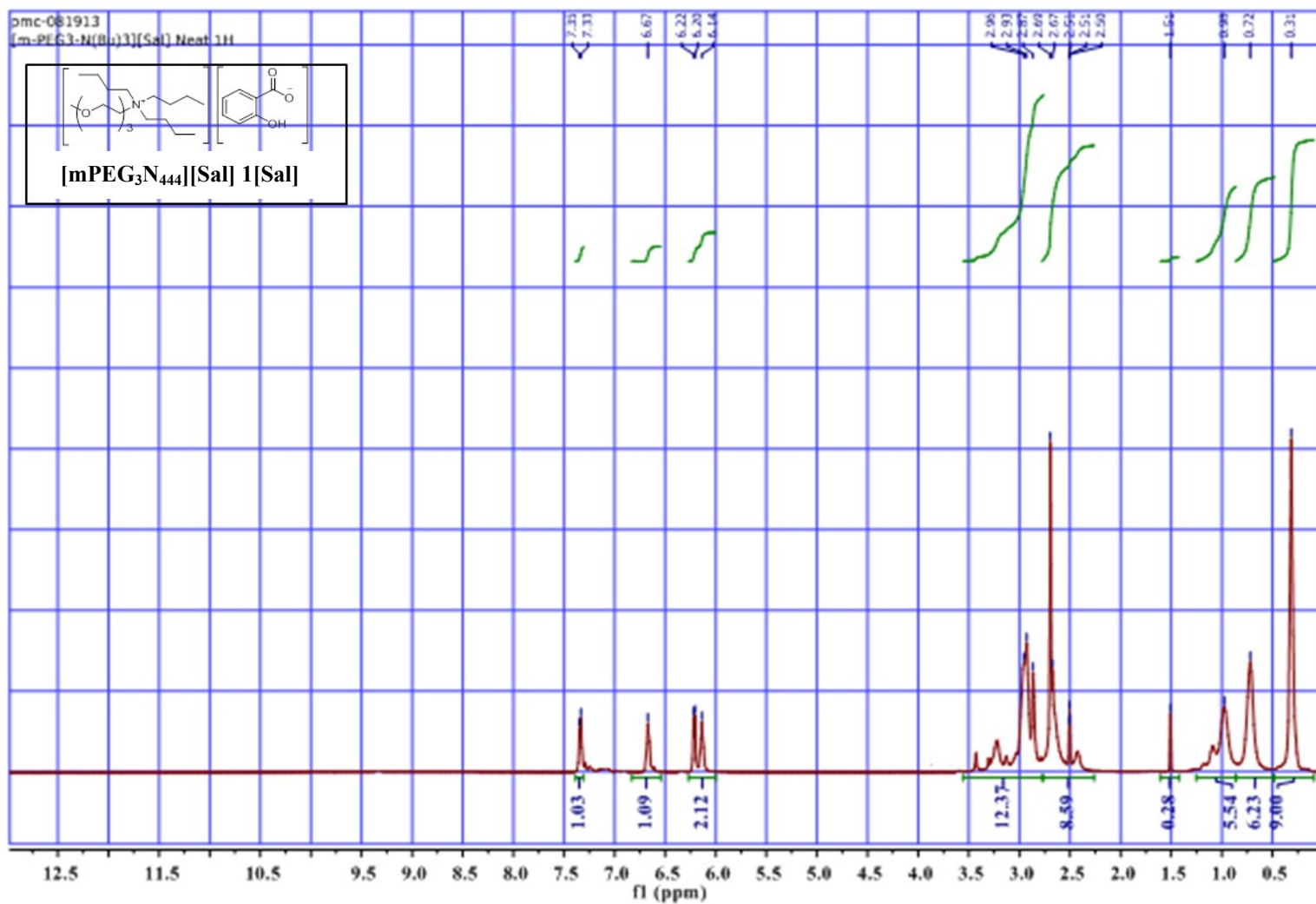
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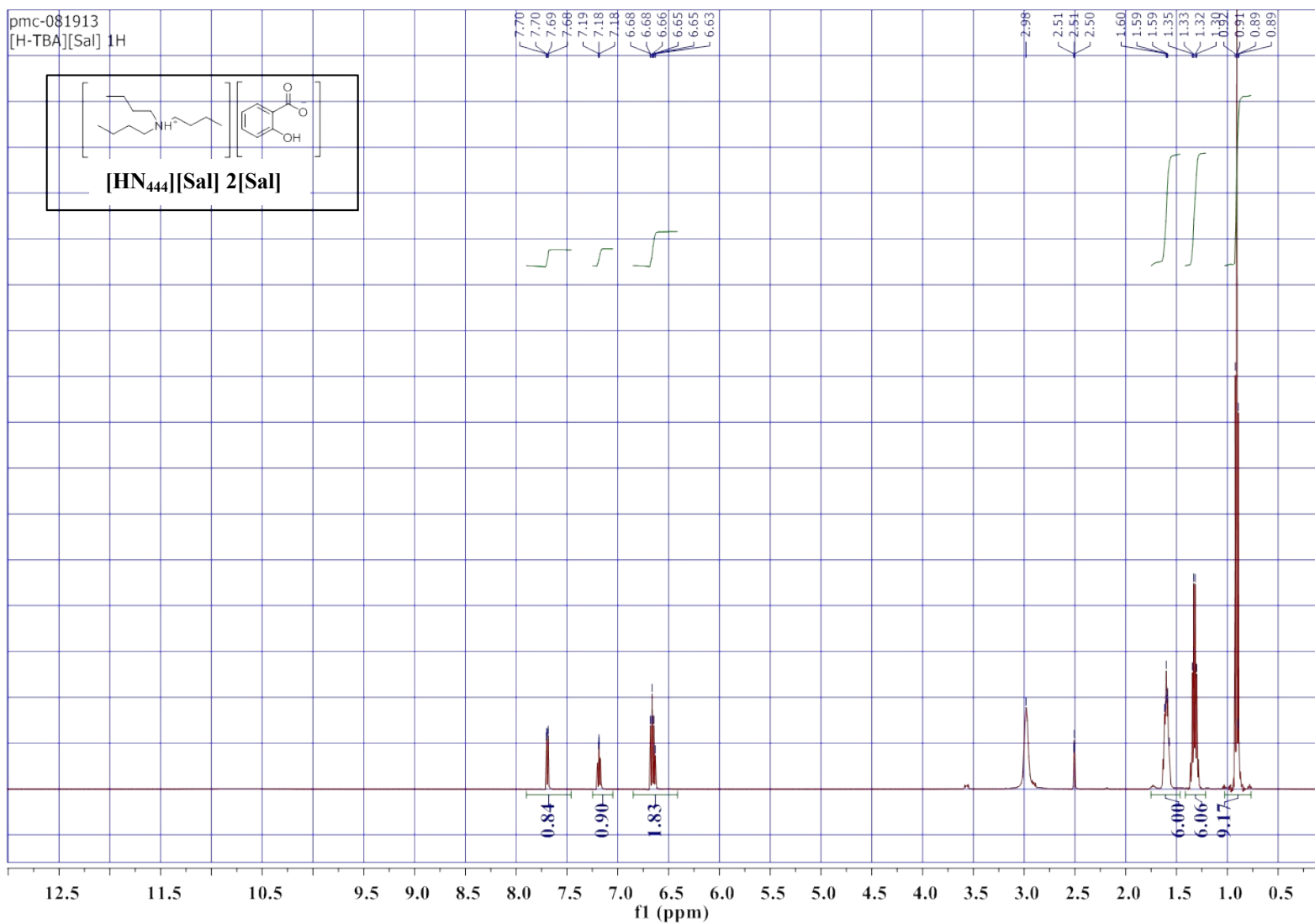
**SUPPORTING INFORMATION**

- |   |                   |
|---|-------------------|
| 1. Spectra of Synthesized Compounds <b>1[Sal]</b> – <b>4[Sal]</b> | <b>p. S2-S9</b>   |
| 2. SXR D data   | <b>p. S10-S11</b> |
| 3. TGA spectra  | <b>p. S12</b>     |
| 4. FT-IR spectra  | <b>p. S13-S14</b> |
| 5. Franz diffusion cell   | <b>p. S15</b>     |

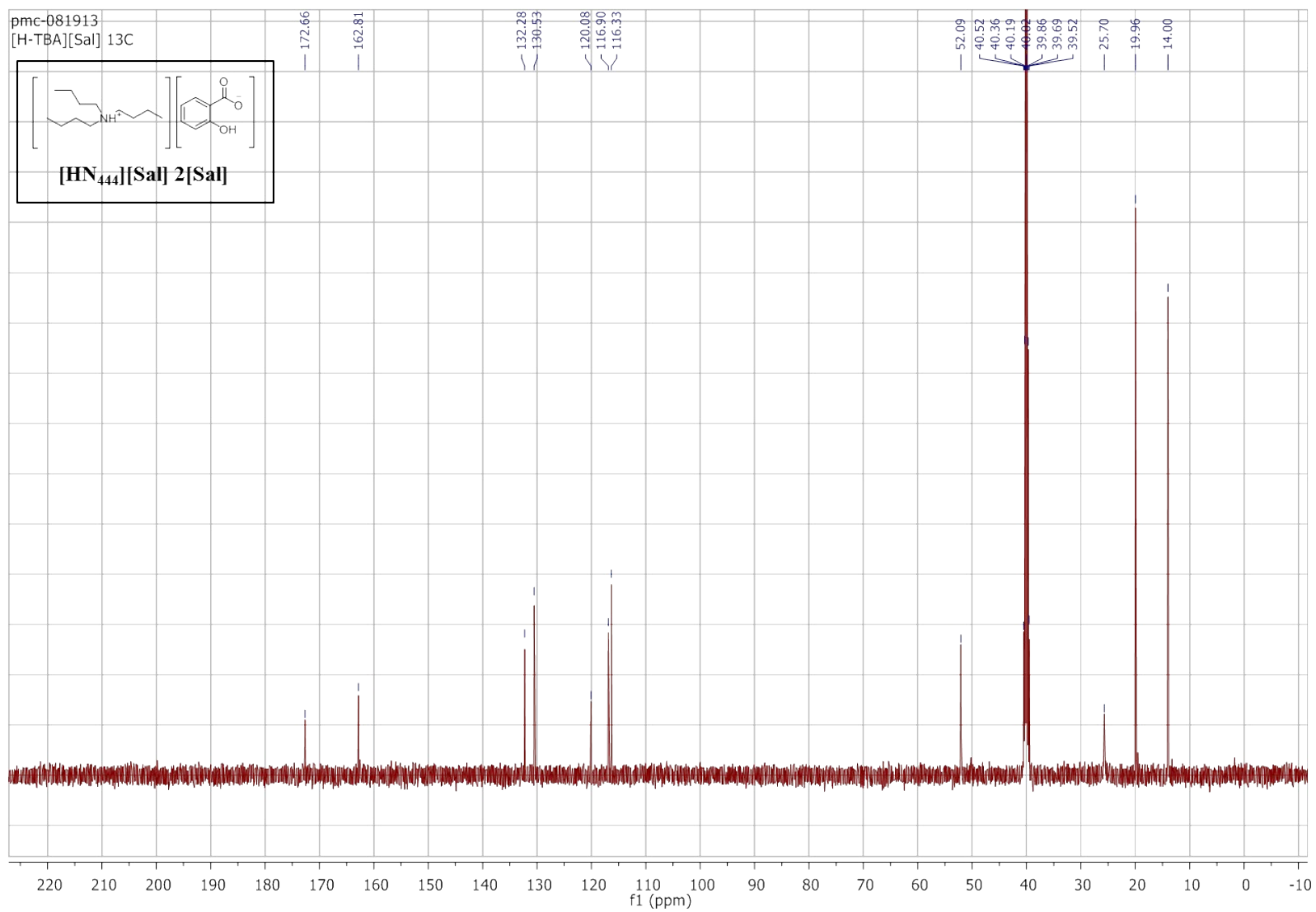


**Figure S1.** <sup>1</sup>H NMR (neat) of [mPEG<sub>3</sub>N<sub>444</sub>][Sal] (**1[Sal]**)  $\delta$  ppm: 7.34 (d, 1H, <sup>3</sup>J<sub>HH</sub> = 6.7 Hz), 6.68-6.66 (m, 1H), 6.21 (d, 1H, <sup>3</sup>J<sub>HH</sub> = 7.8 Hz), 6.14 (t, 1H, <sup>3</sup>J<sub>HH</sub> = 6.1 Hz), 3.22-2.69 (m, 23H), 0.98 (dt, 6H, <sup>3</sup>J<sub>HH</sub> = 0.97 Hz, 0.49), 0.71 (m, 6H), 0.31 (app t, 9H).

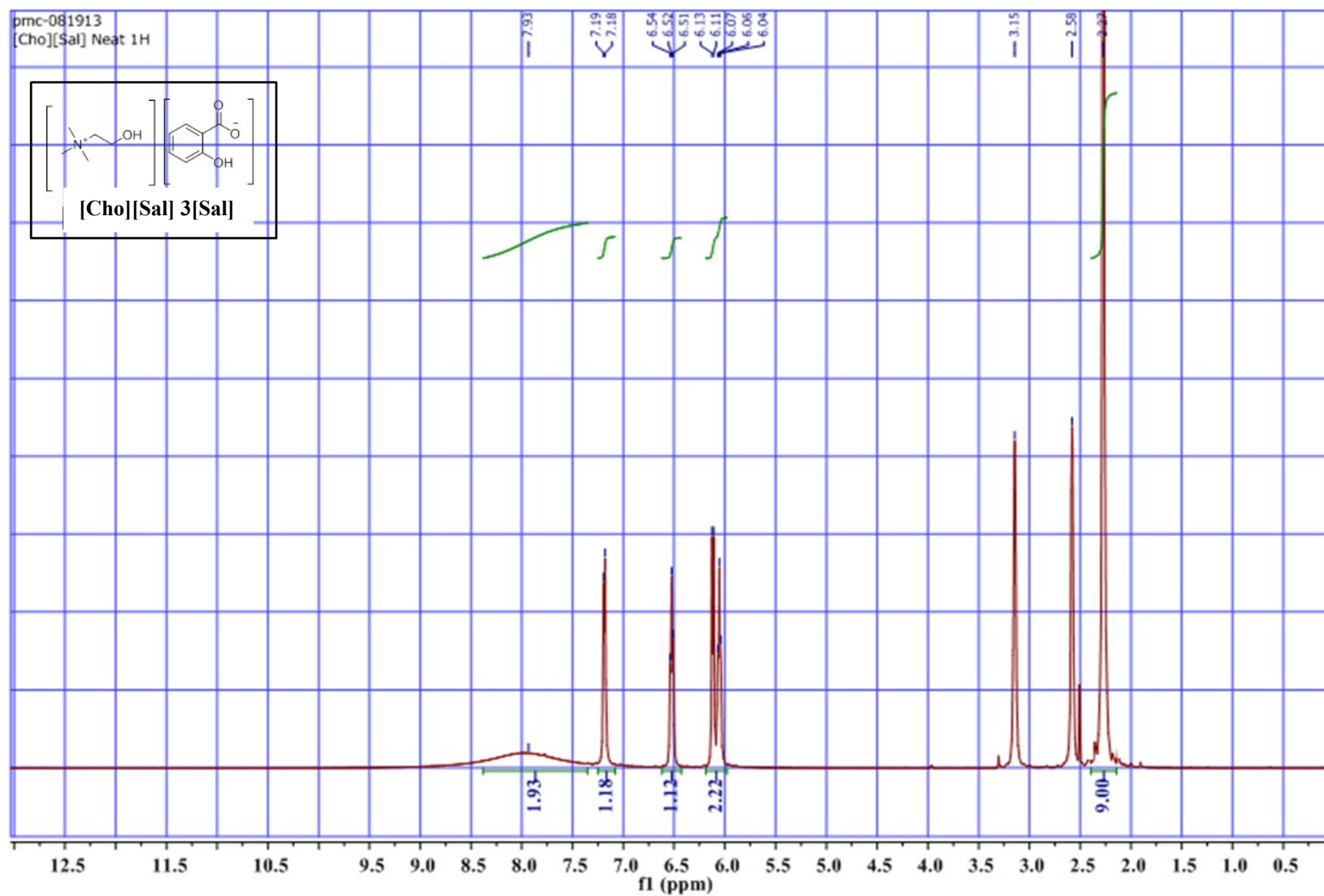




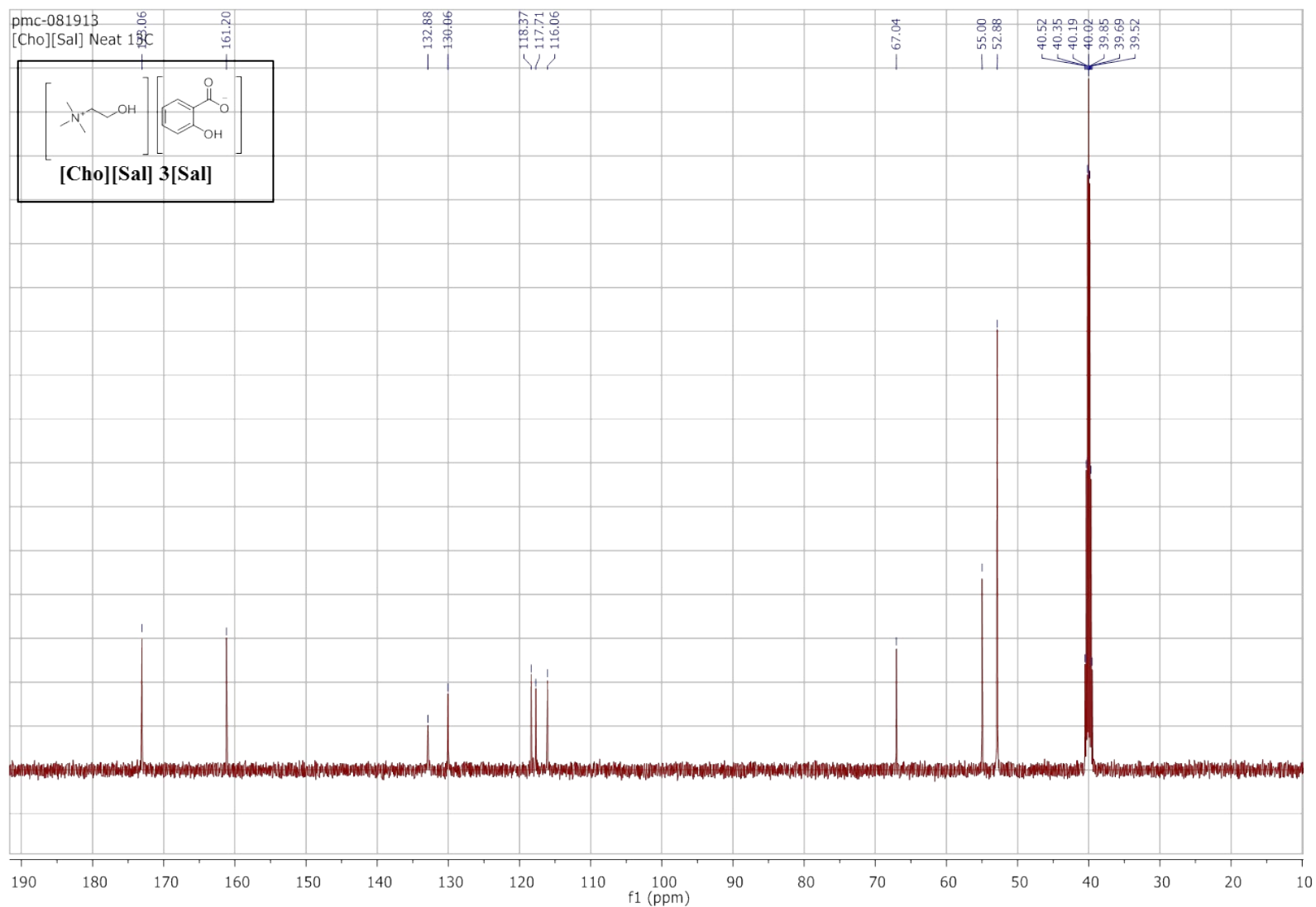
**Figure S3.** <sup>1</sup>H NMR (neat) of [HN<sub>444</sub>][Sal] (**2[Sal]**) δ ppm: 7.69 (dd, 1H, <sup>3</sup>J<sub>HH</sub> = 7.1 Hz, <sup>4</sup>J<sub>HH</sub> = 1.9 Hz), 7.19-7.16 (m, 1H), 6.67-6.62 (m, 2H), 2.98 (app t, 6H), 1.63-1.56 (m, 6H), 1.32 (sextet, 6H, <sup>3</sup>J<sub>HH</sub> = 7.4 Hz), 0.91 (t, <sup>3</sup>J<sub>HH</sub> = 7.1 Hz, 9H).



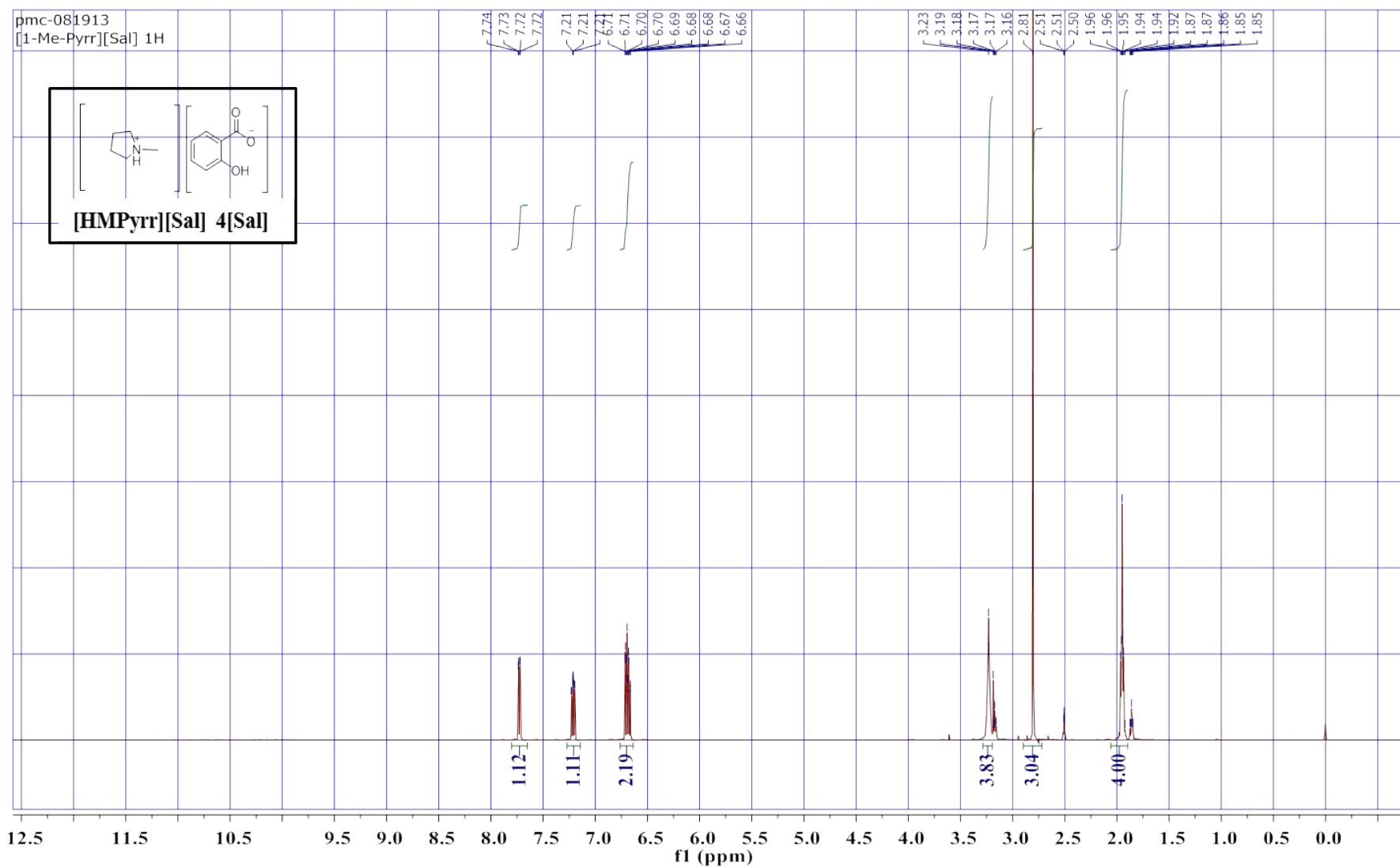
**Figure S4.**  $^{13}\text{C}$  NMR of  $[\text{HN}_{444}][\text{Sal}]$  ( $2[\text{Sal}]$ ) (126 MHz, DMSO)  $\delta$  172.66, 162.81, 132.28, 130.53, 120.08, 116.90, 116.33, 52.09, 25.70, 19.96, 14.00.



**Figure S5.** <sup>1</sup>H NMR (neat) of [Cho][Sal] (**3[Sal]**) δ ppm: 7.98 (bs), 7.18 (d, 1H, <sup>3</sup>J<sub>HH</sub> = 7.1 Hz), 6.52 (t, 1H, <sup>3</sup>J<sub>HH</sub> = 7.3 Hz), 6.11 (d, 1H, <sup>3</sup>J<sub>HH</sub> = 8.0 Hz), 6.05 (t, 1H, <sup>3</sup>J<sub>HH</sub> = 7.0 Hz), 3.14 (s, 2H), 2.57 (s, 2H), 2.25 (s, 9H)

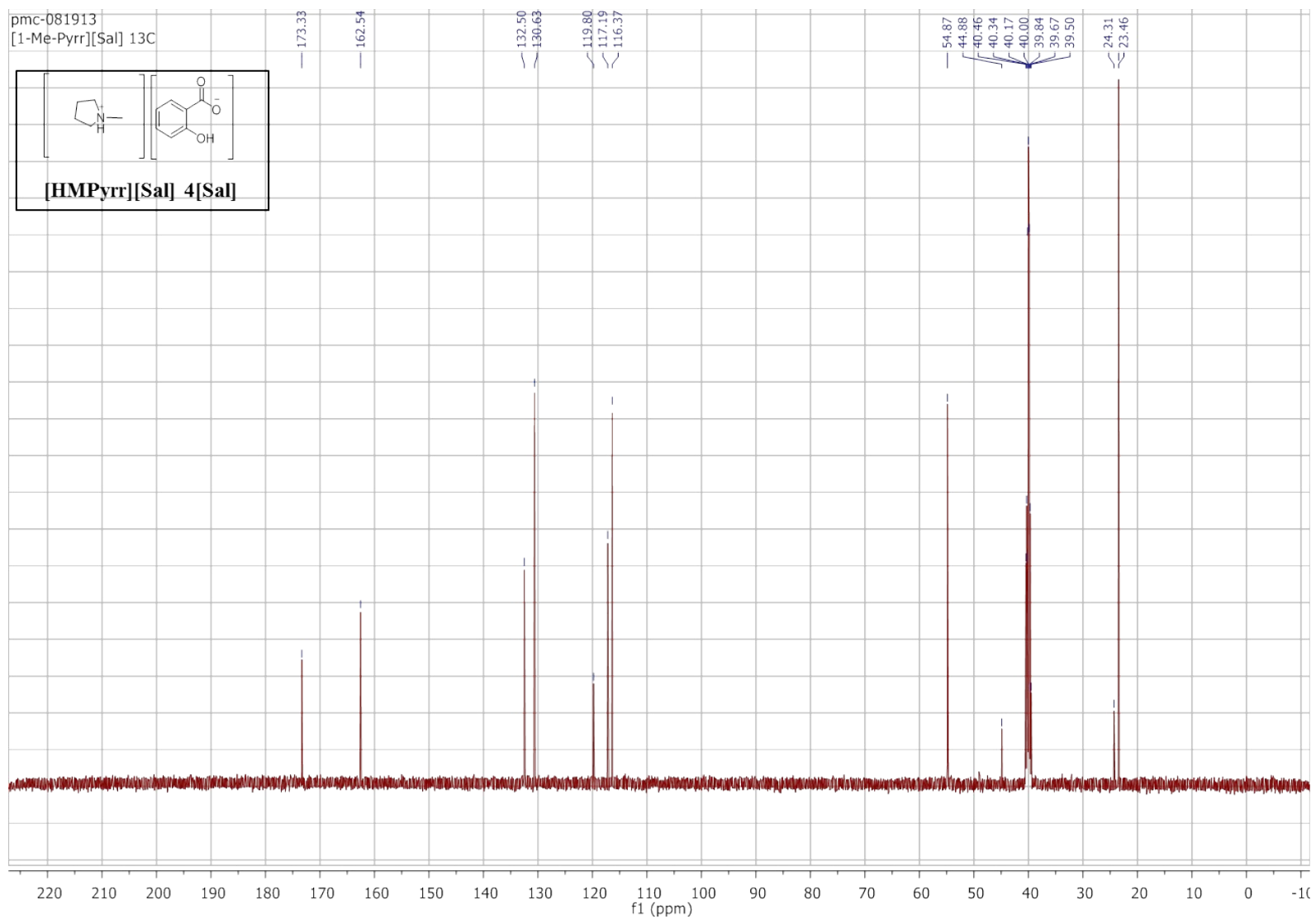


**Figure S6.** <sup>13</sup>C NMR of [Cho][Sal] (**3[Sal]**) (126 MHz, DMSO) 173.06, 161.20, 132.88, 130.06, 118.37, 117.71, 116.06, 67.04, 55.00, 52.88, 40.52, 40.35, 40.19, 40.02, 39.85, 39.69, 39.52.

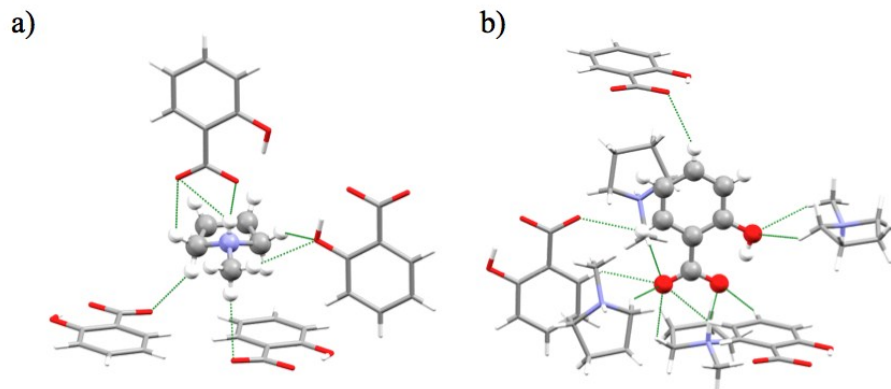


**Figure S7.**  $^1\text{H}$  NMR (500 MHz, DMSO) of [MPyrr][Sal] (**4[Sal]**)  $\delta$  ppm: 7.73 (dd,  $J = 7.6, 1.8$  Hz, 1H), 7.21 (ddd,  $J = 8.2, 7.2, 1.9$  Hz, 1H), 6.76 – 6.64 (m, 2H), 3.23 (s, 4H), 2.81 (s, 3H), 2.06 – 1.90 (m, 4H)

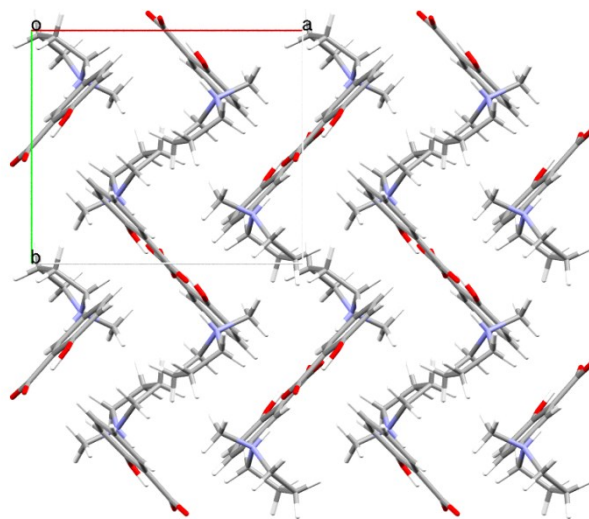




**Figure S8.**  $^{13}\text{C}$  NMR of [MPyrr][Sal] (**4[Sal]**) (126 MHz, DMSO)  $\delta$  173.33, 162.54, 132.50, 130.63, 119.80, 117.19, 116.37, 54.87, 44.88, 24.31, 23.46.



**Figure S9.** The environment surrounding the anion (a) and cation (b) in the crystal structure of [MPyrr][Sal] (**4[Sal]**).

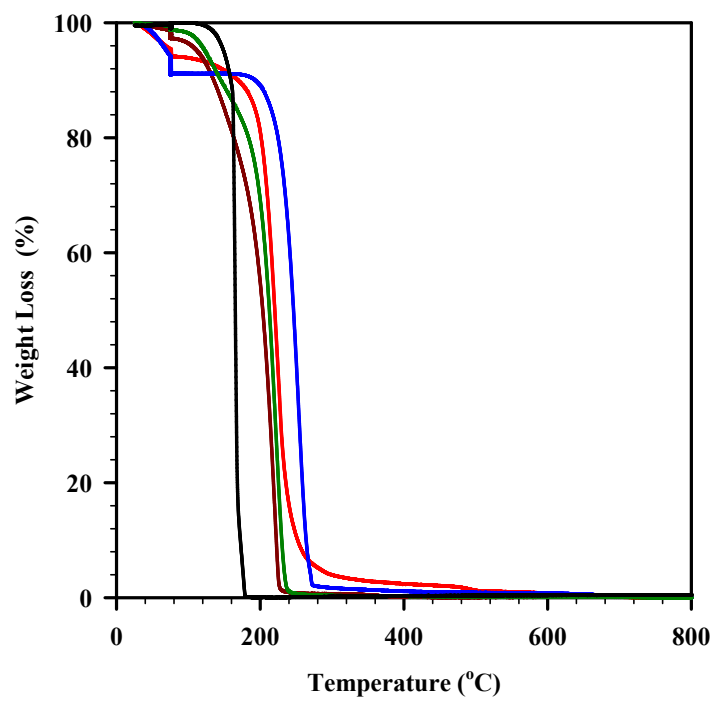


**Figure S10.** The crystal packing of [MPyrr][Sal] (**4[Sal]**).

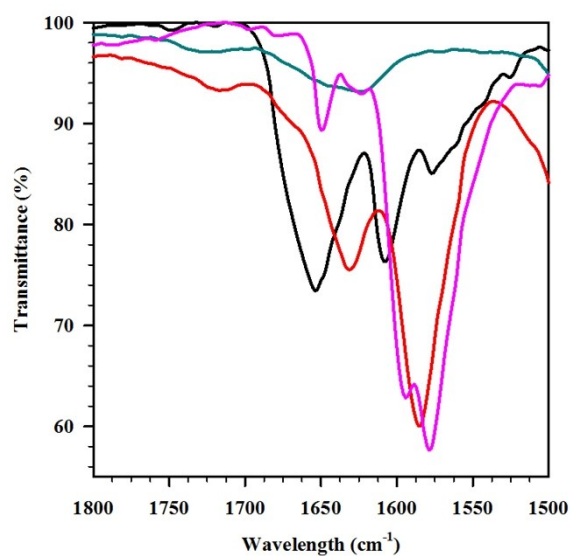
**Table S1:** Hydrogen bonding distances in [MPyrr][Sal] (**4[Sal]**)<sup>a</sup>

<b>D-H...A</b>	<b>d(D-H)/Å</b>	<b>d(H-A)/Å</b>	<b>d(D-A)/Å</b>	<b>D-H-A/°</b>
N1-H1...O14	0.94(1)	2.57(1)	3.245(1)	130(1)
N1-H1...O15	0.94(1)	1.77(1)	2.697(1)	168(1)
C2-H1A...O14	0.99	2.54	3.198(2)	124
C2-H1B...O14 <sup>1</sup>	0.99	2.34	3.215(2)	146
C6-H6A...O16 <sup>2</sup>	0.98	2.58	3.464(2)	150
C6-H6B...O14 <sup>3</sup>	0.98	2.53	3.461(2)	158
O16-H16...O15	0.89(2)	1.71(2)	2.528(1)	151(2)

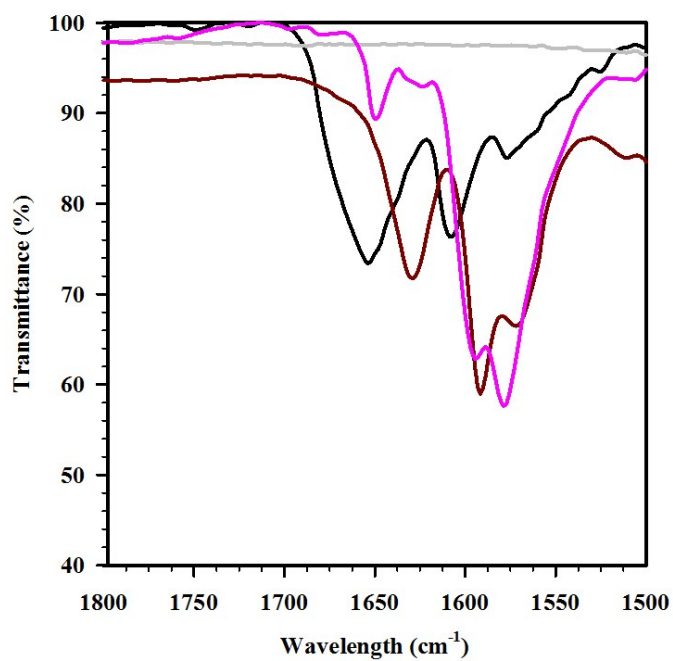
<sup>a</sup>The hydrogen bond donors were found from the difference maps and their coordinates were refined freely. All other hydrogen atoms involved in close contacts were placed in calculated positions and allowed to ride on the bonded atoms. Symmetry transformations used to generate equivalent atoms: (1) 3/2-x, 1/2+y, 1/2-z; (2) 2-x, 1-y, -z; (3) -1/2+x, 3/2-y, -1/2+z.



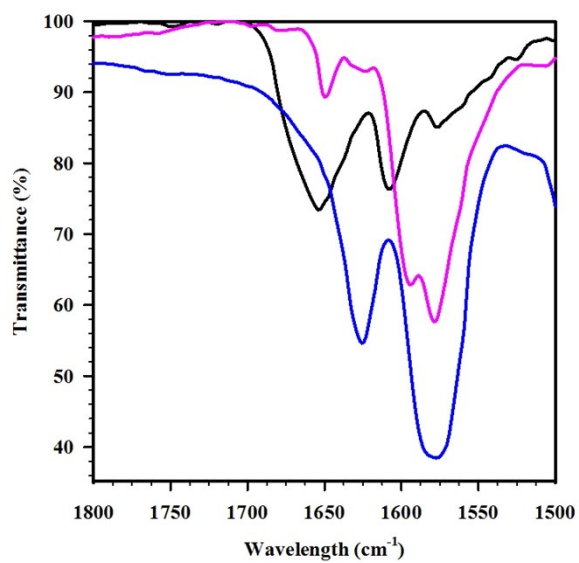
**Figure S11.** Thermogravimetric analysis curves of [mPEG<sub>3</sub>N<sub>444</sub>][Sal] **1[Sal]** (red), [HN<sub>444</sub>][Sal] **2[Sal]** (dark red), [Cho][Sal] **3[Sal]** (blue), [HMPyrr][Sal] **4[Sal]** (dark green), and HSal (black).



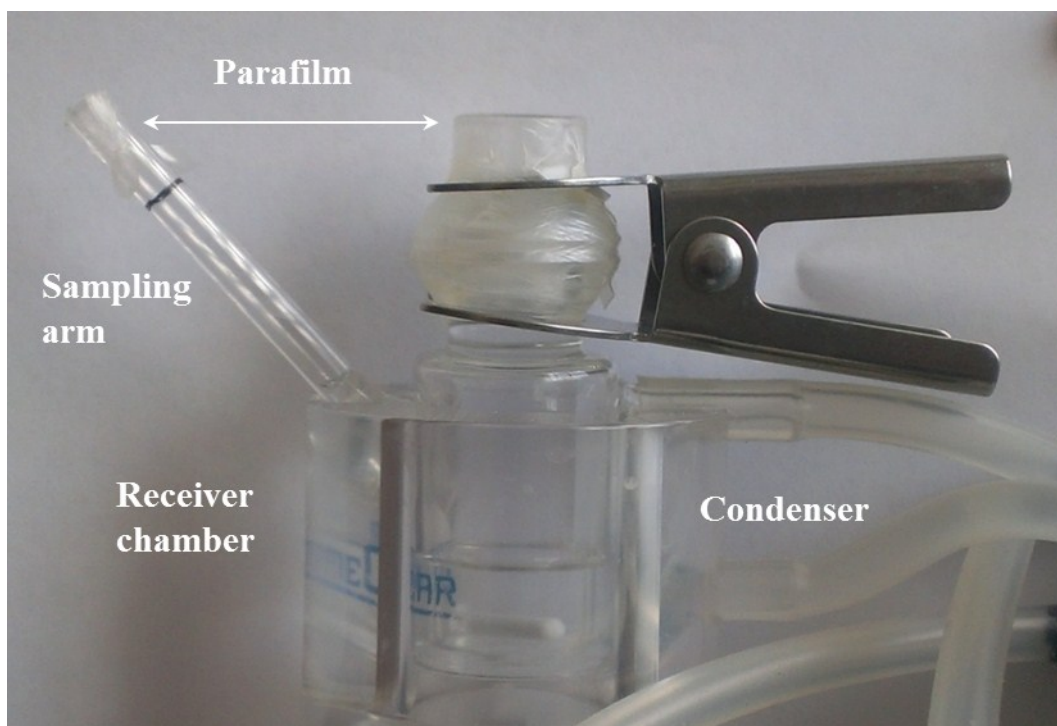
**Figure S12.** FT-IR spectrum of salicylic acid HSal (black), sodium salicylate Na[Sal] (pink), [mPEG<sub>3</sub>N<sub>444</sub>][Br] **1[Br]** (dark cyan), and [mPEG<sub>3</sub>N<sub>444</sub>][Sal] **1[Sal]** (red).



**Figure S13.** FT-IR spectrum of salicylic acid HSal (black), sodium salicylate Na[Sal] (pink), tributylamine N<sub>444</sub> **2** (gray), and [HN<sub>444</sub>][Sal] **2[Sal]** (dark red).



**Figure S14.** FT-IR spectrum of salicylic acid HSal (black), sodium salicylate Na[Sal] (pink), and [Cho][Sal] **3**[Sal] (blue). Here [Cho][OH], **3** is not shown as it is sold as a solution in methanol, resulting in an abundant O-H peak.



**Figure S15.** Assembled Franz diffusion cell for membrane transport.