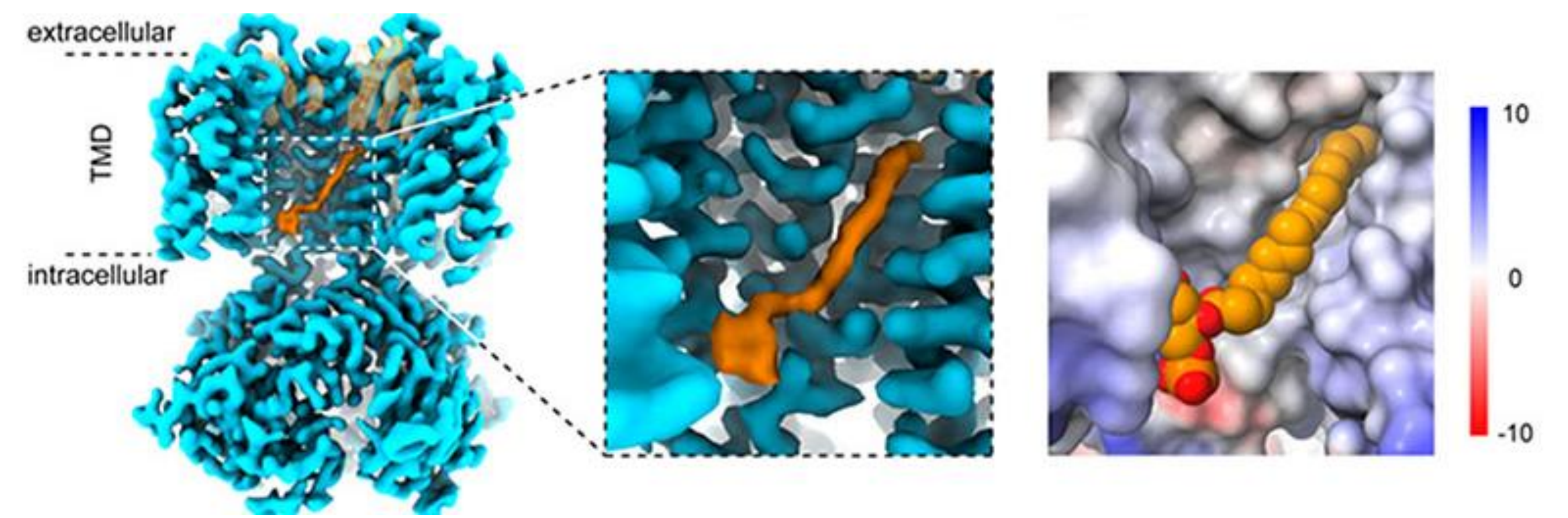


## Introduction

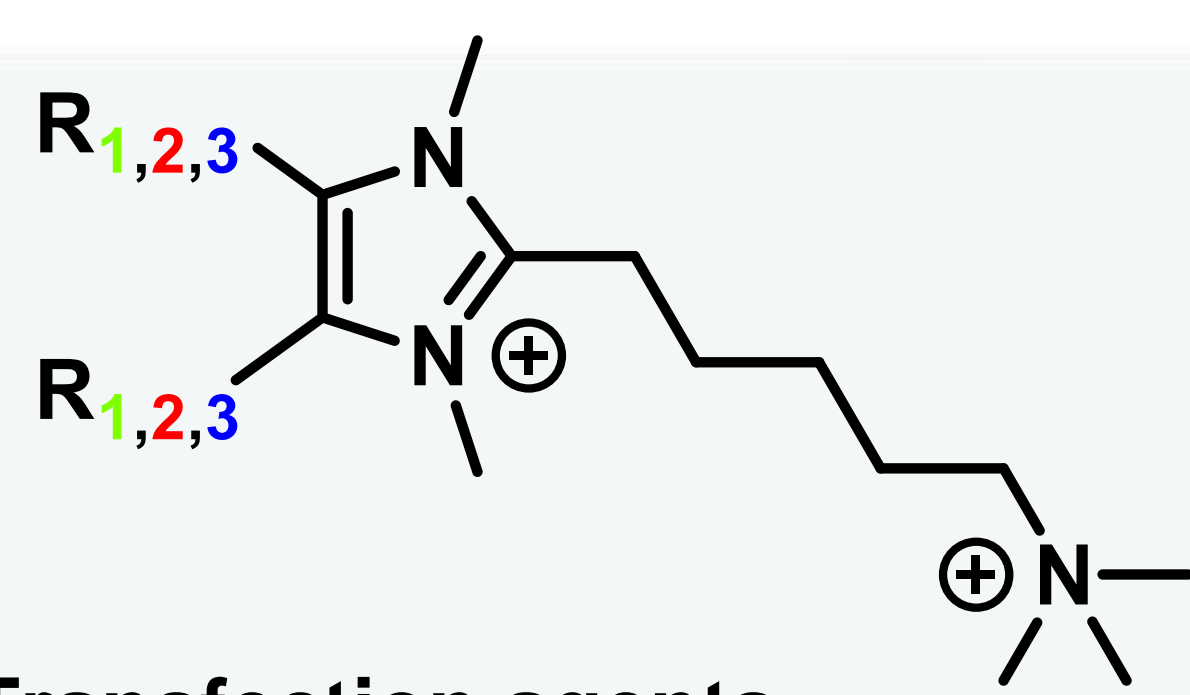
This research explores imidazol(ium)-based lipids as tools to improve gene delivery and their impact on HCN and Kv7 channels, crucial for heart and brain functions.<sup>[1]</sup> These lipids incorporate a functionalized alkyl moiety on C2 position, which is crucial for the interaction with genetic material and membranes, making them more effective and easier to synthesize.<sup>[2]</sup> A recent study found that lipid binding along the S6 helix disrupts a key salt bridge, affecting HCN channel stability.<sup>[1,3]</sup> Notably, natural PA can activate HCN2 channels by disrupting this bridge, unlike PIP2.

## HCN modulation



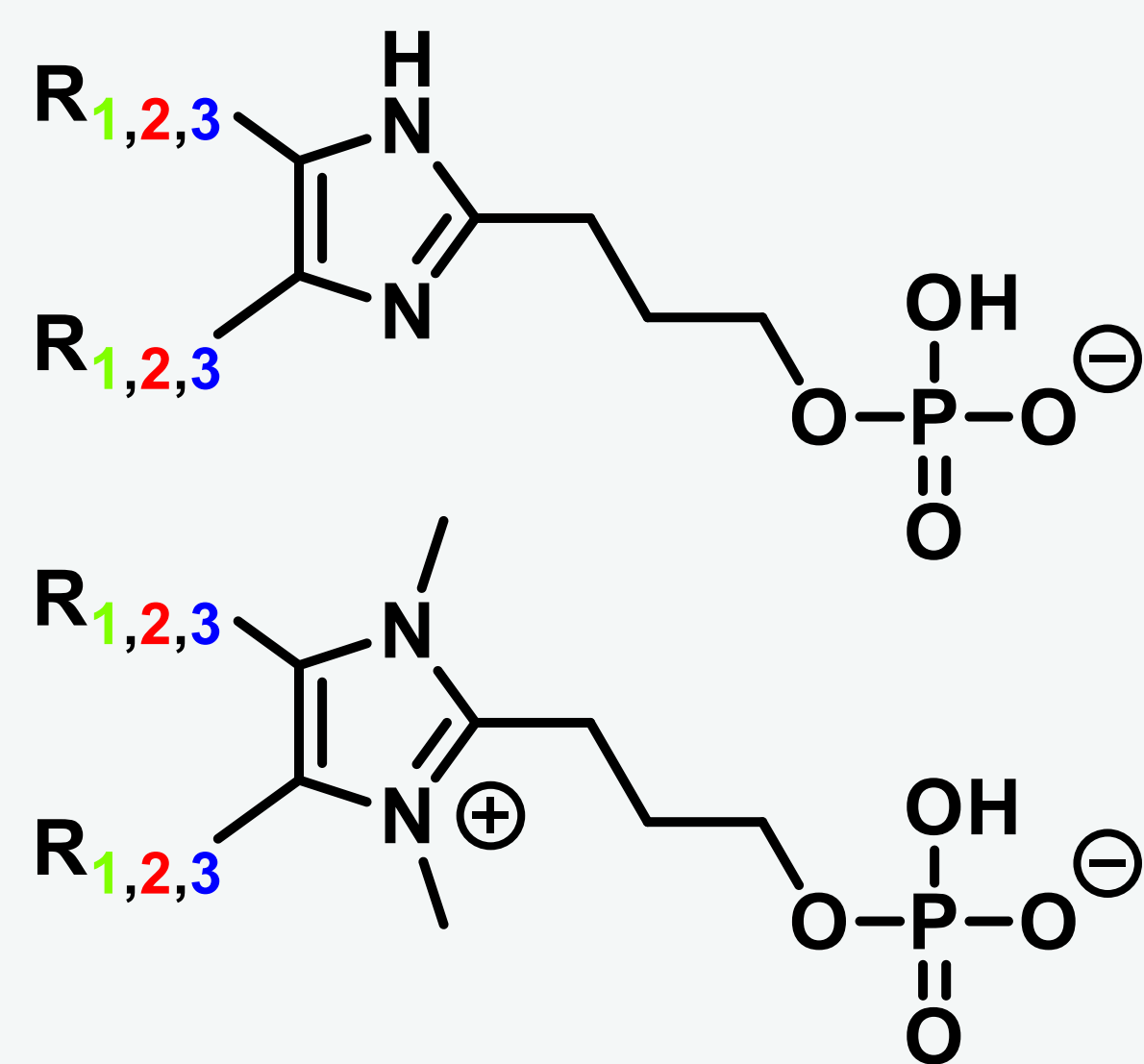
**Fig.1: SthK with POPA:** lipid interaction along S6, and Arg136-Asp226 salt bridge, absent in the open state. <sup>[1]</sup>

## Synthesis and applications of our imidazol(ium) lipid analogs



### Transfection agents

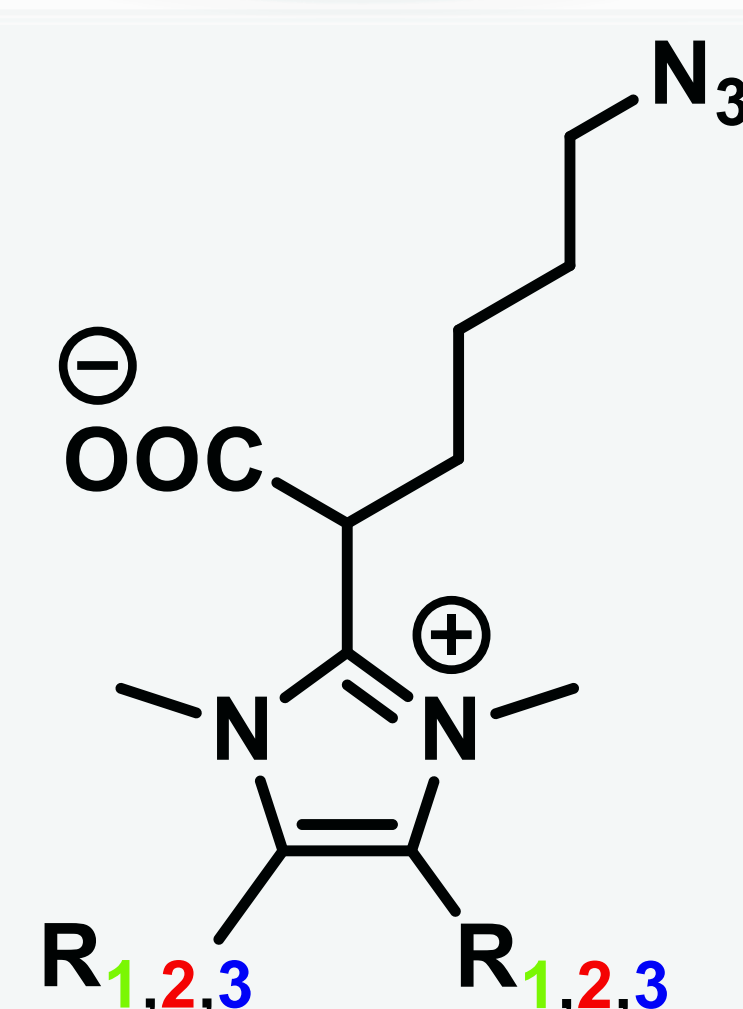
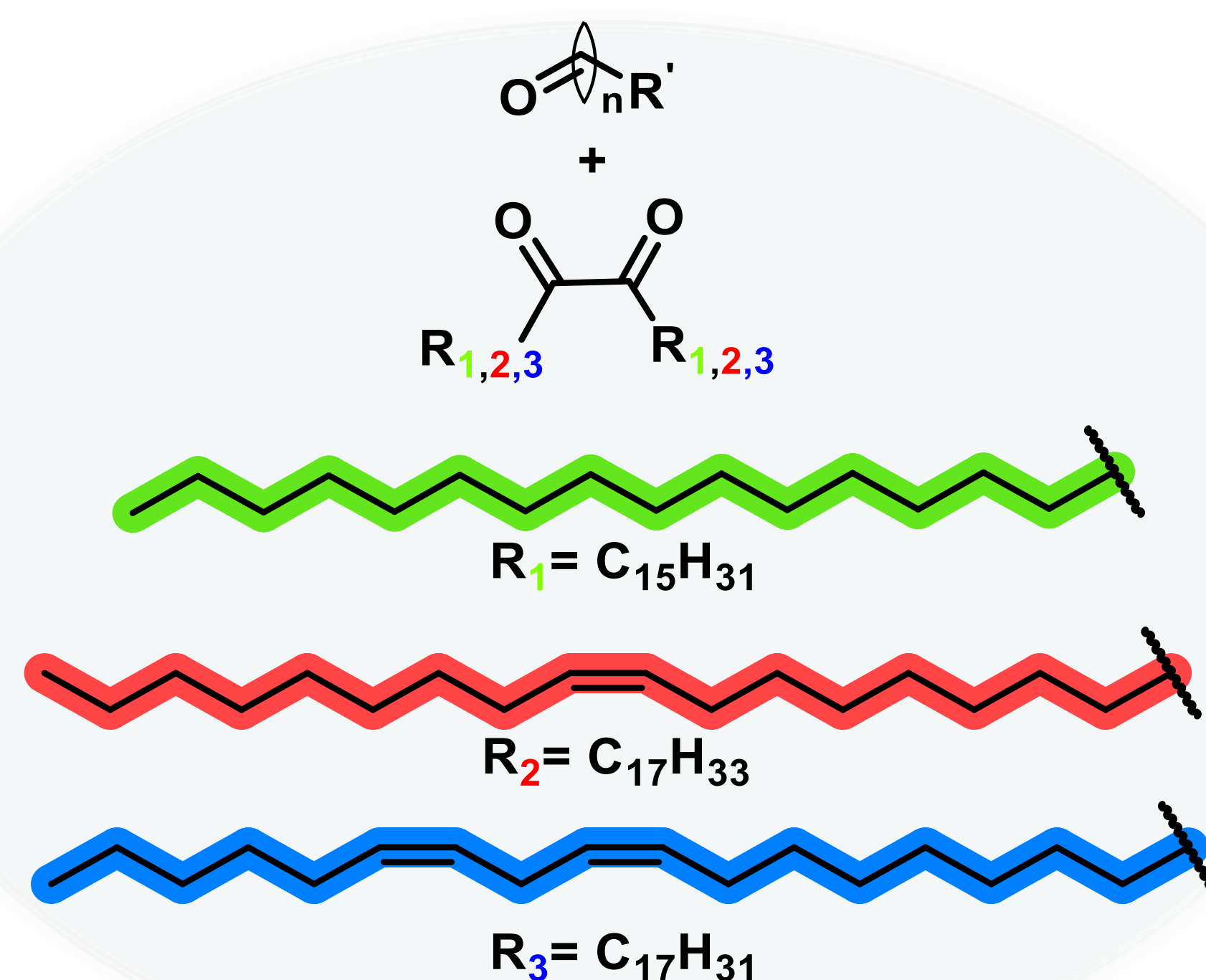
- Dicationic charges
- Results shown in Fig.3



### Anionic and Zwitterionic lipids

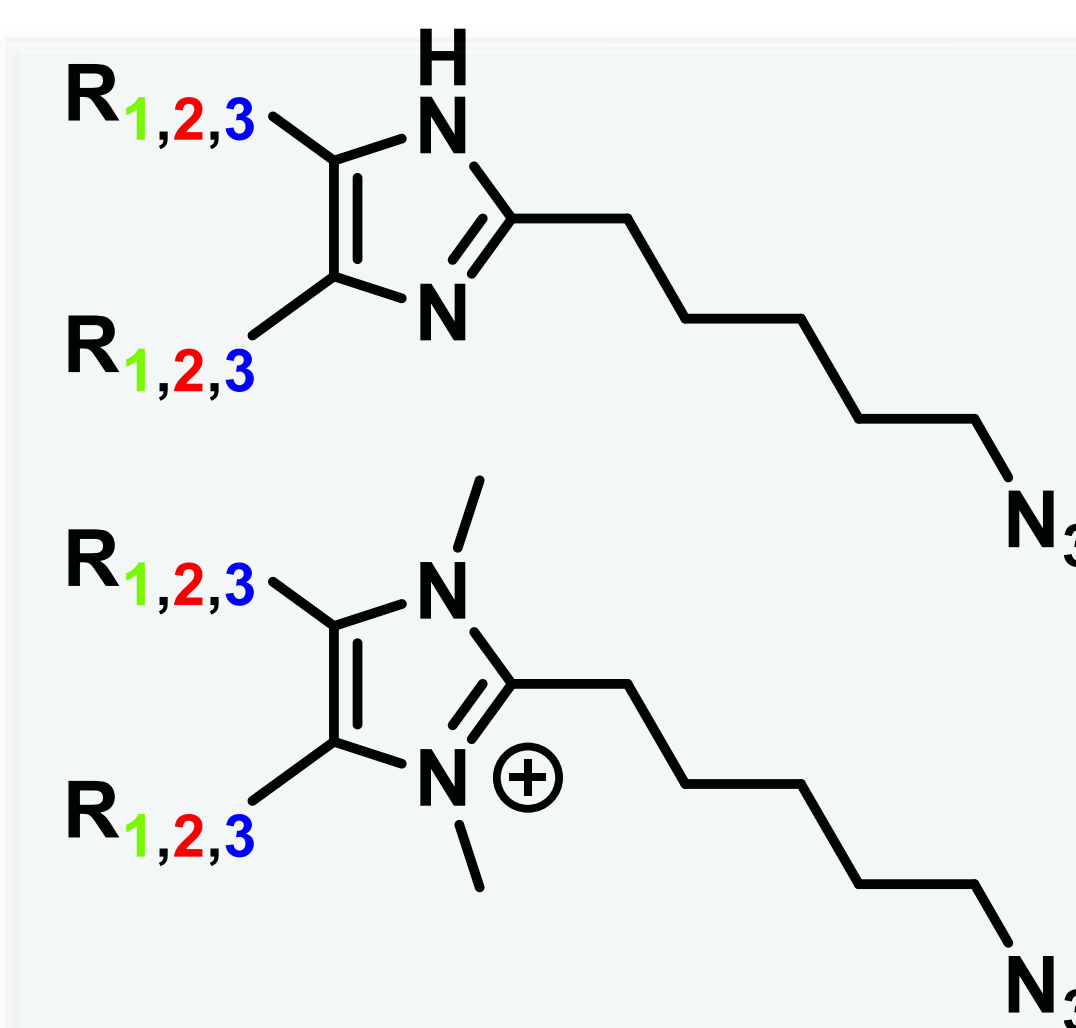
- Negatively charged headgroups
- For HCN and Kv7 modulation
- Other headgroups include, carboxylates and sulfonates

### Condensation reaction



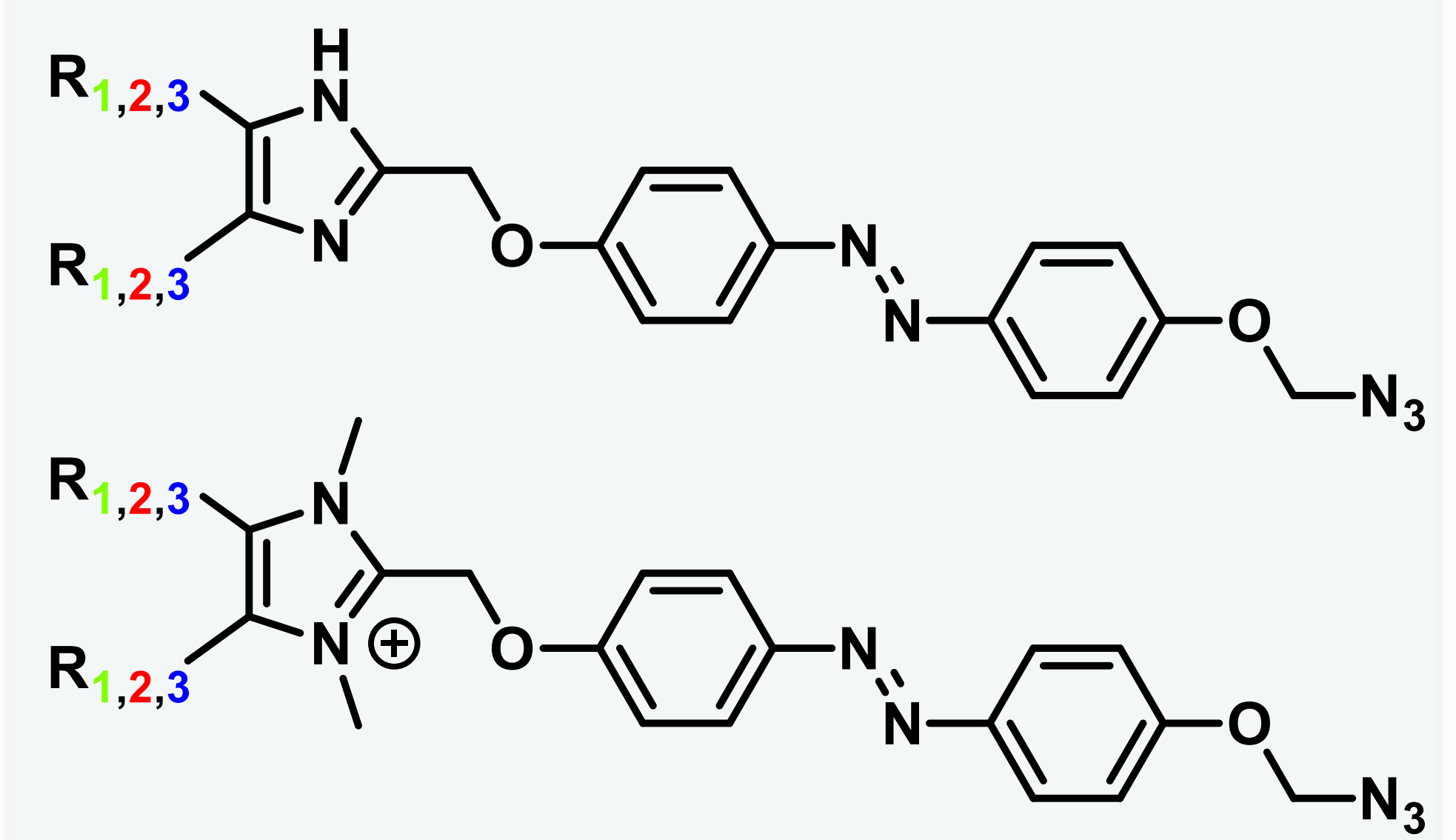
### Bifunctional lipids

- Stabilization of membrane with two different charges
- Clickable lipid



### Clickable lipids

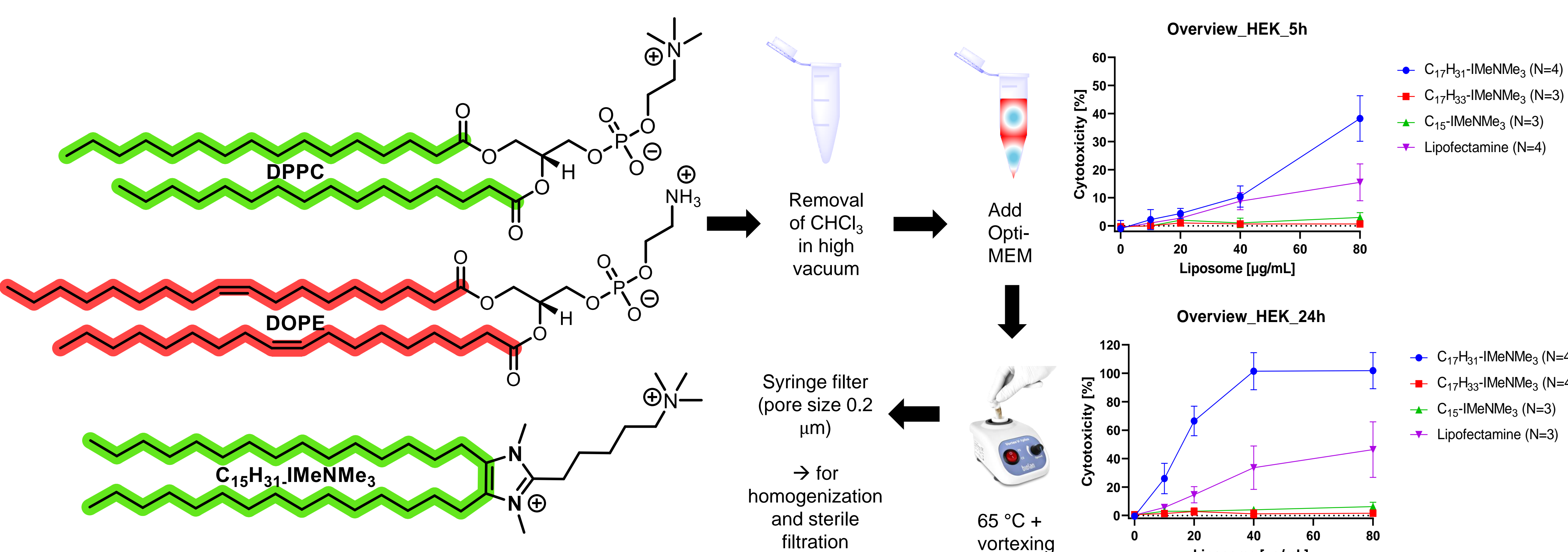
- Plant root growth
- Membrane visualization



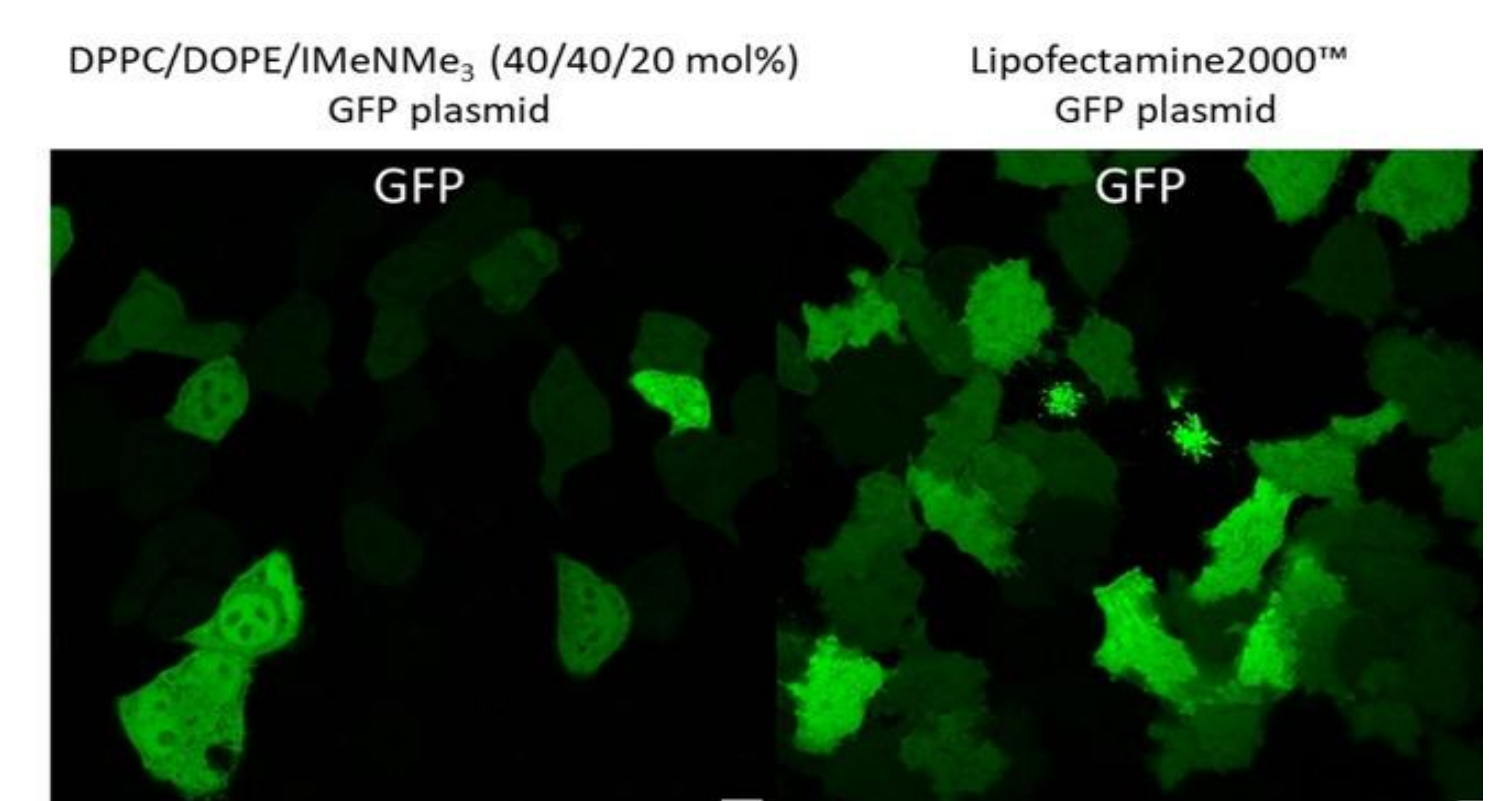
### Photo-switchable lipids

- Ion channels modulation
- Isomerization via switch on/off
- Membrane manipulation - click-chemistry
- Membrane curvature - backbone with photoswitch

## Method and results for transfection molecules



**Fig.2:** Liposome preparation using DPPC/DOPE/IMeNMe<sub>3</sub> 40/40/20 mol% and results for after 5 h and 24 h incubation. <sup>[2]</sup>



**Fig.3:** C<sub>15</sub>H<sub>31</sub>-IMeNMe<sub>3</sub> and Lipofectamin2000™ transfecting a GFP plasmid into HeLa cells, incubated overnight and GFP expression was then monitored by confocal fluorescence microscopy; scale bar 10 µm. <sup>[2]</sup>

### References:

- [1] Schmidpeter et al., *Nat Struct Mol Biol.*, 2022, 29,1092-1100.
- [2] Paulisch, T.O., Bornemann, S., Herzog, M et al., *Chem. Eur. J.*, 2020, 26,17176-17182.
- [3] Hansen, S. B., *Biochim Biophys Acta Mol Cell Biol Lipids.*, 2015,1851, 620-628.
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