Ionizable Cationic Lipids Featuring Schiff Base for Hepatic Delivery of siRNA

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ABSTRACT

Lipid nanoparticles (LNPs) have demonstrated their effectiveness as carriers for delivery of RNA therapeutics. As the core components of LNP system, ionizable cationic lipids (ICLs) are still the major focus of research in this field. Currently there is still a lack of sufficient knowledge about the structure-activity relationship (SAR) to facilitate the rational design of optimal lipids for different applications. In this study, we reported a class of novel ICLs featuring Schiff base. We generated a library of 50 ICLs, and *in vitro*/*in vivo* screening identified one lipid that was comparable to FDA approved Dlin-MC3-DMA lipid in siRNA LNPs-mediated gene silencing. Our work offers a novel approach to synthesize ICLs of new structural features, which may not only improve our understanding of SAR of ICLs but also lead to the development of improved LNPs for more effective delivery of nucleic acid therapeutics.

Methods

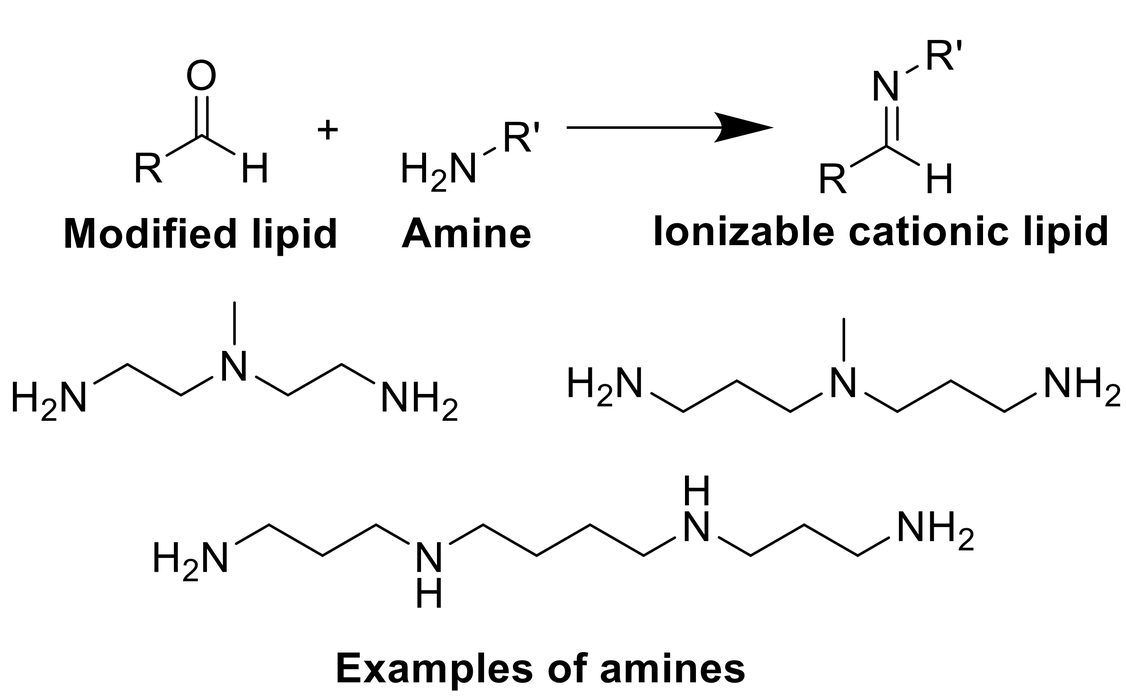

Fig 1: Synthesis of ionizable cationic lipids and scope of the library

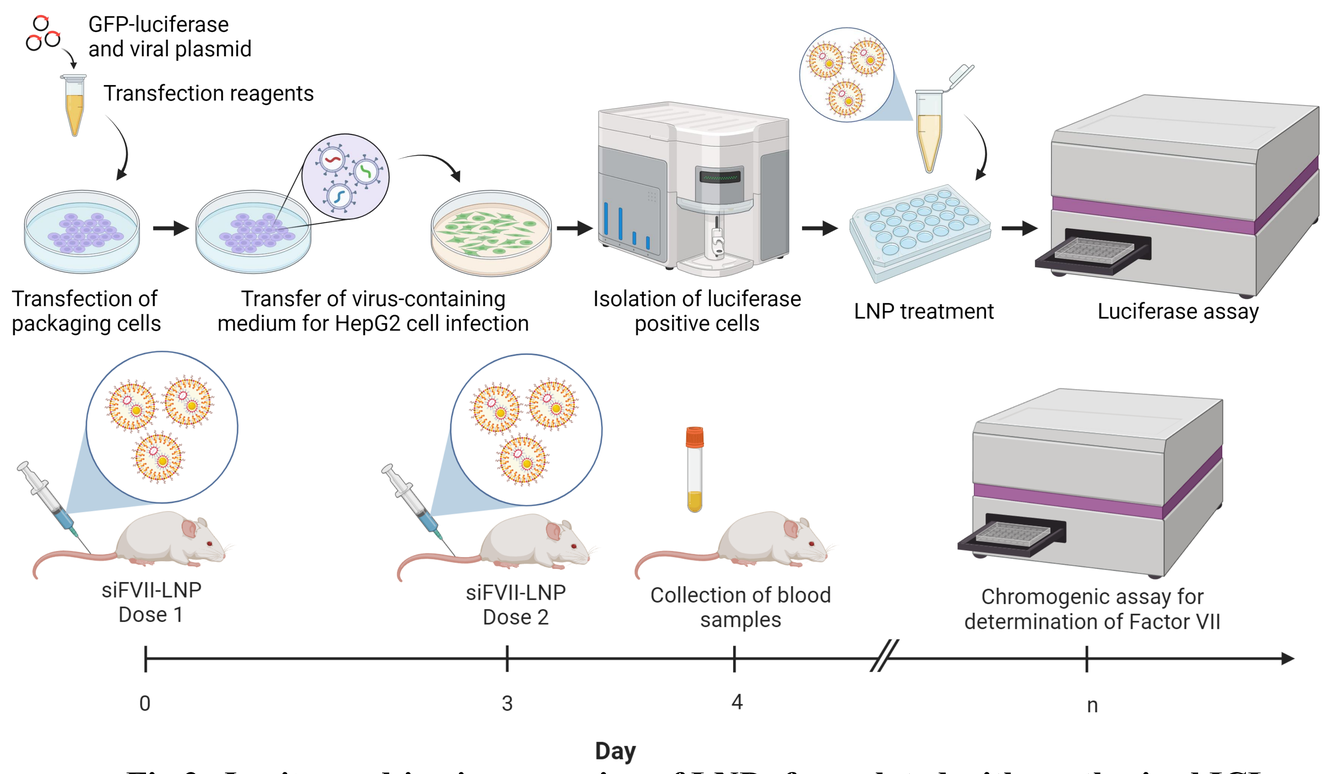

Fig 2: *In vitro* and *in vivo* screening of LNPs formulated with synthesized ICLs

RESULTS

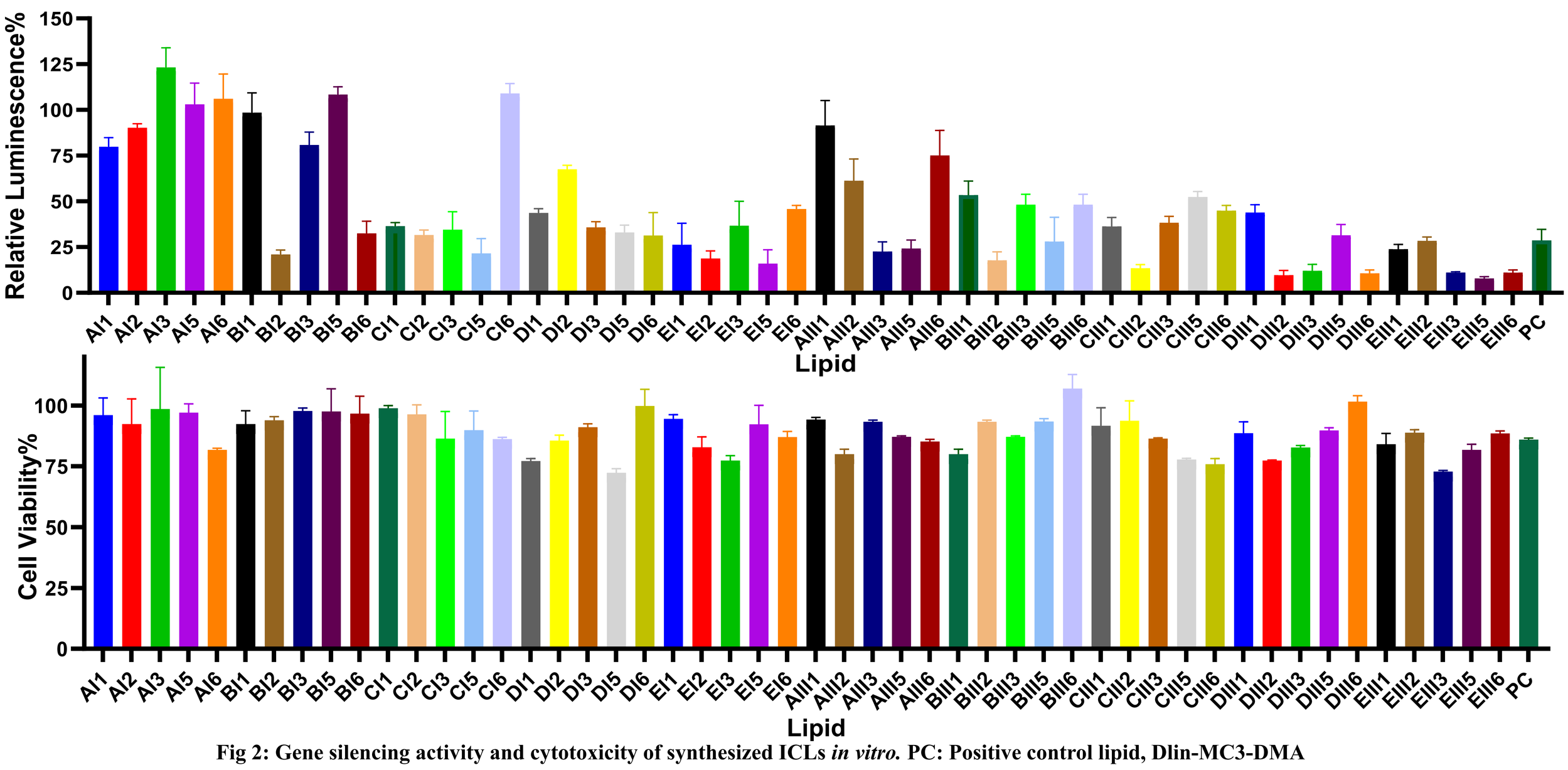

Fig 2: Gene silencing activity and cytotoxicity of synthesized ICLs *in vitro*. PC: Positive control lipid, Dlin-MC3-DMA

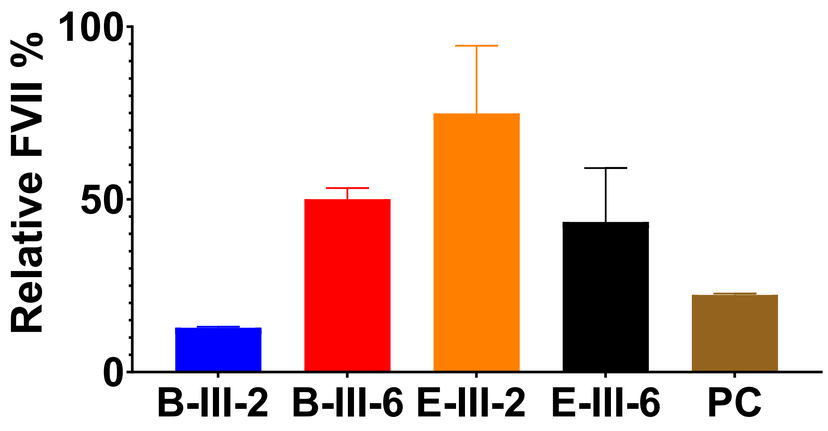

Fig 3: Hepatic FVII knockdown of ICLs *in vivo*. PC: Positive control lipid, Dlin-MC3-DMA

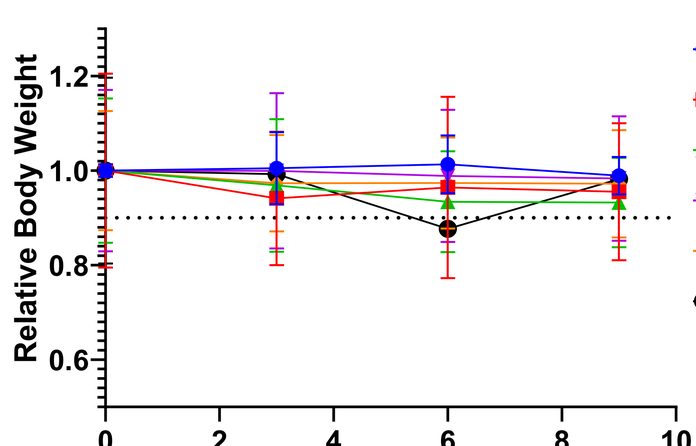

Fig. 4 Body weight of mice receiving LNPs in the dose-escalation toxicity study. CT: Non-treatment control; PC: Positive control lipid, Dlin-MC3-DMA

CONCLUSIONS

In conclusion, this study has demonstrated the feasibility of applying Schiff base in synthesis of ICLs in large quantities and in a short time. The availability of a library of ICLs of new structural features may further enrich our understanding of their SAR. It may also lead to the development of improved LNPs for more effective delivery of nucleic acids including siRNA.

ACKNOWLEDGEMENTS

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