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Artificial Transmembrane Transport Nanopores Exhibiting V-Shaped Activity-ee Dependence

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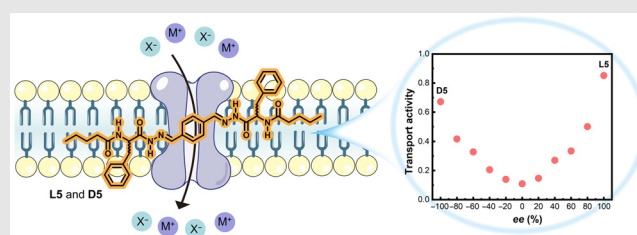
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The functional role of molecular chirality in transmembrane transport, a fundamental feature of biological channels, remains elusive. To address this, we employ artificial biomimetic systems as a well-defined investigative platform. We report a series of bilateral alkylamide phenylalanine hydrazone derivatives that self-assemble into ion-transporting nanopores within lipid membranes. Among these, the enantiomeric pair L5 and D5 exhibits the highest activity, with L5 consistently outperforming D5. This enantiomeric preference is attributed to the more efficient membrane insertion of L5 in chiral lipid environments. Remarkably, transport activity drops sharply in an equimolar mixture of L5 and D5. Systematic evaluation uncovers a distinct V-shaped dependence of activity on enantiomeric excess, enabling chirality-gated transport behavior. This regulation arises from heterochiral coassembly, which drives dense packing and closes the nanopores,

thereby inhibiting ion translocation. Our work elucidates a fundamental chirality-assembly-function relationship in transmembrane transport, provides a functional perspective on biological homochirality, and establishes a design strategy for biomimetic ion channels whose activity can be programmed and gated by enantiomeric composition.



Keywords: transmembrane transport, artificial nanopore, activity-ee dependence, chirality-gated transport, heterochiral coassembly

Introduction

Natural transmembrane channels are indispensable to living systems, where they regulate the transport of ions and molecules across lipid bilayers to maintain cellular homeostasis and enable signal transduction and energy

conversion.^{1–6} These channels are predominantly protein-based and inherently chiral, exhibiting a strong preference for homochiral architectures, as exemplified by the chiral organization of transmembrane helices in chloride channels,^{7,8} and the chirality-dependent tetrameric assembly of aquaporins (e.g. aquaporin 1).^{1,9} Despite their

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importance, the mechanisms by which chirality governs channel structure and transport function remain poorly understood, owing to their structural complexity and limited stability under *in vitro* conditions.

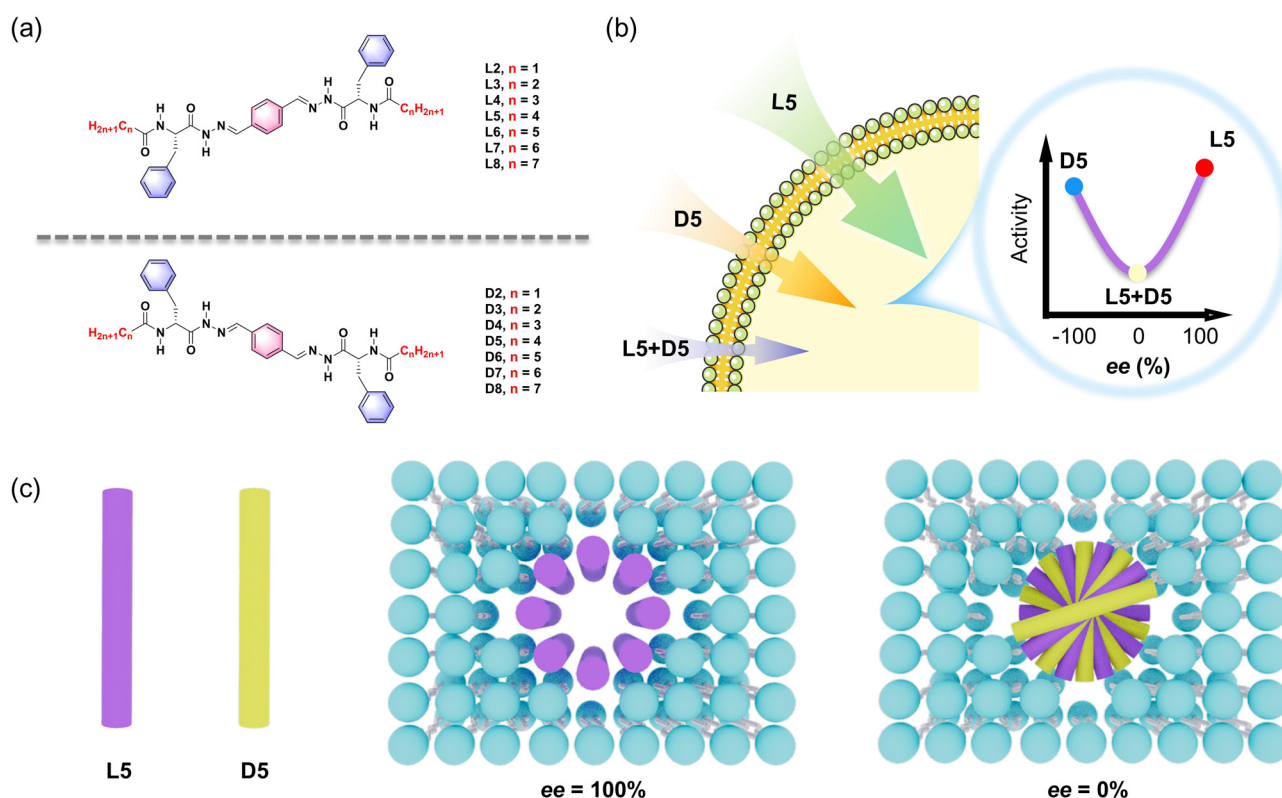
Artificial transmembrane transport systems have emerged as well-defined, stable, and tunable platforms that mimic natural channels, enabling systematic studies of structure-function relationships and offering potential biomedical applications.^{10–15} Such features make them particularly well suited for investigating how molecular chirality influences transmembrane transport.

In this context, several elegant studies have demonstrated that chirality can impart selectivity in artificial transport systems. For example, Hou and coworkers developed peptide-functionalized pillararene channels capable of enantioselective amino acid transport,¹⁶ while Liu and coworkers employed homochiral zirconium metal-organic cages to achieve enantioselective transmembrane permeation.¹⁷ In these cases, selectivity primarily arises from stereospecific host-guest interactions. Beyond molecular recognition, Shen and coworkers¹⁸ recently showed that the stereochemistry of *cis*- and *trans*-1,2-diaminocyclohexane-derived polyimides fundamentally alters ion-transport preference, leading to either Li⁺-selective or anion-selective channels. These studies illustrate that chirality can influence transport

behavior across multiple structural and organizational levels.

In parallel, supramolecular chiral assembly has increasingly attracted attention due to its relevance to the origin of biological homochirality and its applications in chiral recognition, asymmetric catalysis, and biomedicine.^{19–23} A defining characteristic of such assemblies is their pronounced sensitivity to the enantiomeric excess (ee) of the constituent building blocks.^{24,25} Relationships between circular dichroism (CD) intensity and ee have therefore been widely employed to diagnose chiral amplification or heterochiral assembly, with S-shaped or anti-S-shaped profiles serving as characteristic signatures.^{26–28} However, despite the widespread use of supramolecular pores and channels in biomimetic transmembrane transport,^{29–34} the influence of enantiomeric composition on transport efficiency has been scarcely explored,³⁵ and the underlying mechanisms remain largely unresolved.

We reasoned that systematic variation of the ee could provide direct insight into how chiral preference in membrane-confined self-assembly governs transmembrane transport function. Establishing a quantitative relationship between transport activity and ee would not only shed light on the functional advantages of homochirality in natural transmembrane channels but also enable the



Scheme 1 | (a) Molecular structures of the designed phenylalanine-based peptidomimetic hydrazone derivatives **L2–L8** and **D2–D8**. (b) Schematic illustration of the enantiomer-dependent transmembrane transport activity. (c) Schematic of the assemblies formed by **L5** and **D5** within the lipid bilayer at ee = 100% and 0%.

rational design of artificial transporters with programmable activity and chirality-gated transport behavior.^{36–38}

To test this hypothesis, we designed and synthesized a series of bilateral chiral alkylamide phenylalanine hydrazone derivatives as artificial transmembrane transporters (Scheme 1a). These molecules integrate multiple hydrogen-bonding motifs to promote supramolecular assembly with hydrophobic alkyl chains and phenylalanine residues to facilitate membrane insertion. Screening studies identified **L5/D5** and **L6/D6** as efficient transporters that self-assemble into nanopores within biomimetic membranes. Systematic investigation revealed pronounced enantiomer-dependent transport behavior: L-enantiomers consistently exhibited higher activity than their D-counterparts, attributable to more favorable interactions with chiral lipid bilayers. Remarkably, transport activity displayed a distinct V-shaped dependence on ee, with high activity for enantiopure systems but a dramatic minimum at ee = 0% (Scheme 1b). Mechanistic studies indicate that heterochiral coassembly leads to dense packing within the membrane, resulting in pore closure and suppression of ion transport (Scheme 1c). This work uncovers a previously unexplored activity, the ee relationship in artificial transmembrane channels, and elucidates how chirality governs transport through membrane-confined supramolecular assembly. These findings provide a conceptual framework for understanding the functional advantages of homochirality in natural channels and open new avenues for the design of intelligent, chirality-programmable, and gated biomimetic transport systems.

Results and Discussion

The phenylalanine-based peptidomimetic hydrazone derivatives **L2–L8** and **D2–D8** were readily synthesized in high yields through a concise synthetic sequence involving amide coupling, hydrazinolysis, and imine formation (Supporting Information Schemes S1 and S2). Their transmembrane ion-transport activities were first evaluated using the pH-sensitive fluorescent probe 8-hydroxypyrene-1,3,6-trisulfonic acid). In this assay, HPTS was encapsulated within large unilamellar vesicles (LUVs) composed of egg yolk phosphatidylcholine, with a transmembrane pH gradient established between the intravesicular (pH 7.0) and extravesicular (pH 8.0) solutions in the presence of 100 mM NaCl (Figure 1a).

Upon addition of the compounds at 0.5 μM , only **L5**, **D5**, **L6**, and **D6** induced pronounced increases in fluorescence (Supporting Information Figure S1 and Figure 1b), indicative of efficient ion transport, with **L5** exhibiting the highest activity (89% fluorescence change). In contrast, a series of control compounds (Supporting Information Schemes S3–S6) featuring modified amino acid residues (**L5A**, **L5V**, **L5L**, **L5T**),

altered central linkers (**4F–L5**, *meta*-**L5**, **2OH–L5**), or only one side (**L5–a**), showed markedly diminished activity (Supporting Information Figure S2 and Figure 1c). These results highlight the critical importance of the bilateral phenylalanine-based architecture for effective transmembrane transport. The transport activity of **L5** remained comparable when the extravesicular cations or anions were varied (Supporting Information Figures S3 and S4), indicating a lack of ion selectivity. This nonselective transport behavior is likely attributable to the formation of large nanopores that mediate transmembrane ion flow.

Dose-response curves obtained from the HPTS assay were analyzed using the Hill equation, affording EC_{50} values of 0.29 μM for **L5** and 0.41 μM for **D5** (Supporting Information Figure S5 and Table S1). The consistently higher activity of **L5** relative to its enantiomer suggests an intrinsic chirality-dependent transport behavior. This can be attributed to the greater membrane insertion efficiency of **L5**,³⁵ as indicated by absorbance measurements in buffer and LUV-containing buffer solutions (Supporting Information Figure S6), which reflect more favorable interactions between the L-enantiomer and the chiral lipid bilayer.³⁹ Regarding the control compounds (**L2/D2**, **L7/D7**, **L8/D8**), their transport activities do not always consistently follow the L-enantiomer > D-enantiomer trend at a fixed concentration (0.5 μM , Figure 1b). This is largely because their overall transport activities are weak at this concentration, and the signal fluctuations obscure the intrinsic enantiomeric preference. Nevertheless, EC_{50} values, which provide a more reliable comparison (Supporting Information Figure S5 and Table S1), indeed show that **L7** (1.95 μM) is more active than **D7** (3.03 μM), supporting the general trend that L-enantiomers outperform their D-counterparts when activities are measurable.

To further elucidate the role of chirality, we systematically investigated the transport activity of **L5/D5** mixtures at a fixed total concentration (0.5 μM) while varying the ee. Strikingly, the resulting activity-ee plot displayed a pronounced V-shaped profile (Figure 1d). While enantiopure samples (ee = $\pm 100\%$) exhibited high transport efficiency, the racemic mixture (ee = 0%) retained only $\sim 10\%$ of the maximal activity. An analogous enantiomeric dependence was observed for the **L6/D6** pair, which showed EC_{50} values of 0.50 μM (**L6**) and 1.09 μM (**D6**) (Supporting Information Figure S5 and Table S1), as well as a similar V-shaped activity-ee relationship (Figure 1e). These results reveal that transmembrane transport activity is exquisitely sensitive to enantiomeric composition.

Notably, the **L5/D5** racemate shows efficient membrane insertion performance (Supporting Information Figure S6), excluding inefficient membrane incorporation as the origin of the diminished activity. We therefore attribute the suppressed transport to heterochiral coassembly within the membrane, which gives rise to supramolecular structures with markedly reduced

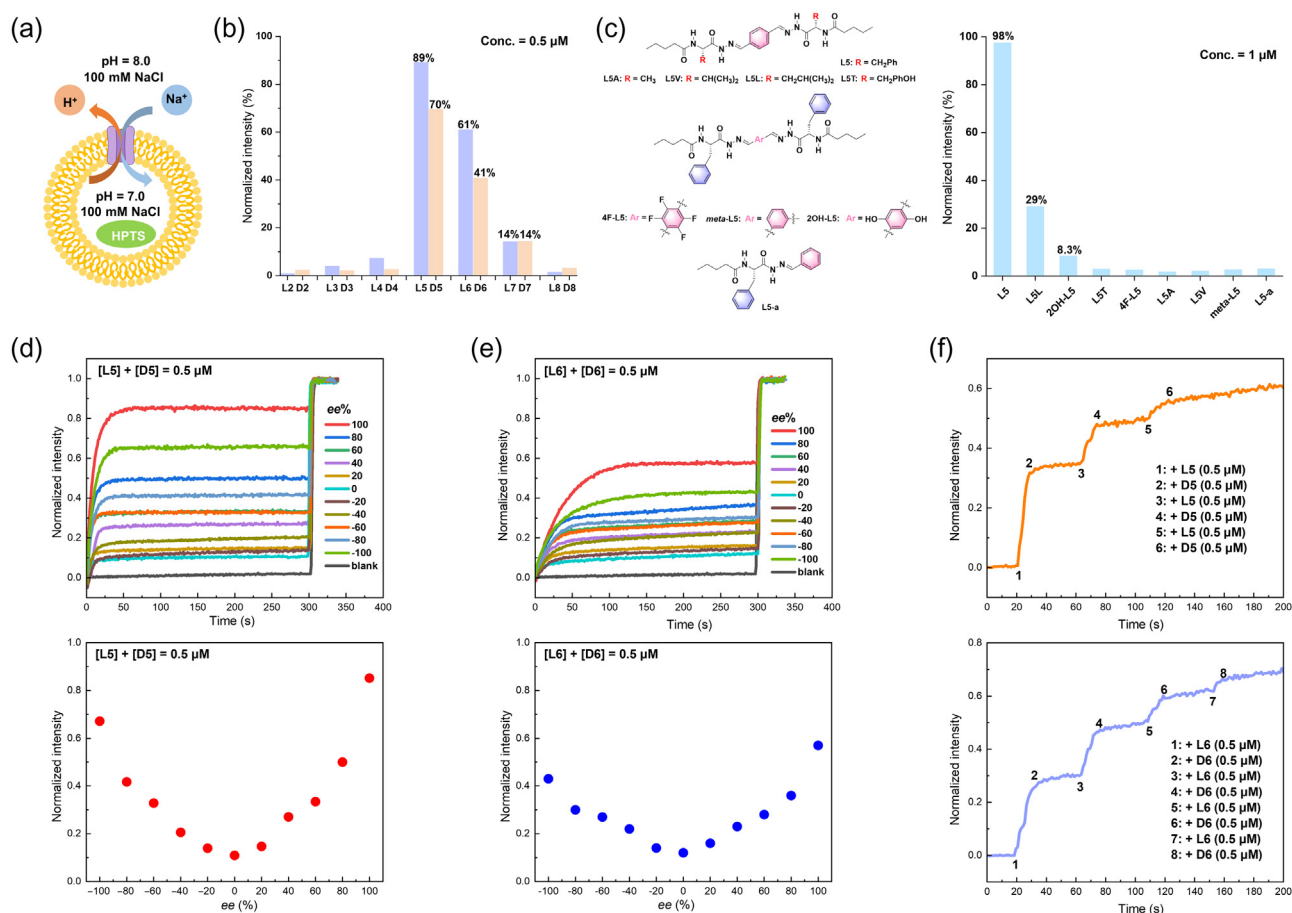


Figure 1 | (a) Schematic of the LUV-based HPTS assay. HPTS fluorescence increases with pH. (b) Comparative ion-transport activity of **L2-L8** and **D2-D8** at 0.5 μM. (c) Transport activity of control compounds at 1 μM. ee-dependent transport activity from the HPTS assay for the enantiomeric pairs (d) **L5/D5** and (e) **L6/D6**. (f) Transport activity from the HPTS assay upon alternating addition of **L5** (0.5 μM) and **D5** (0.5 μM), **L6** (0.5 μM) and **D6** (0.5 μM), demonstrating chirality-gated transport behavior.

conductivity. Motivated by this insight, we constructed a chirality-gated ion transport system by introducing the enantiomer **D5** during an ongoing **L5**-mediated transport process. After ion transport was initiated by 0.5 μM **L5**, **D5** was added at 10 s to modulate the transport behavior (Supporting Information Figures S7 and S8). Progressive addition of **D5** led to a gradual decrease in transport efficiency, with nearly complete inhibition observed upon addition of an equimolar amount of **D5** (0.5 μM). Further increasing the concentration of **D5** beyond that of **L5** partially restored transport activity, attributable to the intrinsic transport capability of excess **D5**. Finally, by alternately adding equimolar **L5** and **D5** or **L6** and **D6**, we established a sequential chirality-gated ion transport system (Figure 1f), demonstrating a novel gating mechanism controlled by molecular chirality.

To probe the transport mechanism, a 5(6)-carboxyfluorescein (CF) leakage assay was employed (Figure 2a). Consistent with the HPTS results, **L5**, **L6**, **D5**, and **D6** induced substantial CF leakage at 0.50 μM,

whereas the remaining derivatives were largely inactive (Figure 2b,c). Dynamic light-scattering measurements confirmed that the hydrodynamic size distribution of the LUVs remained unchanged upon addition of **L5**, **D5**, **L6**, **D6**, and the corresponding racemic mixtures of **L5/D5** and **L6/D6** (Figure 2d), indicating that vesicle integrity was preserved. Given the hydrodynamic diameter of CF (~1.0 nm), these results collectively support the formation of transmembrane nanopores rather than a carrier-mediated or disruptive mechanism.

Hill analysis of the CF leakage data yielded EC₅₀ values of 0.29 μM (**L5**), 0.34 μM (**L6**), 0.40 μM (**D5**), and 0.41 μM (**D6**) (Supporting Information Figure S9 and Table S2). Once again, the higher activity of the L-enantiomers correlates with their superior membrane insertion efficiency.³⁹ Importantly, the activity-ee relationships derived from the CF assay for both **L5/D5** and **L6/D6** pairs exhibited clear V-shaped profiles (Figure 2e,f), enabling the implementation of chirality-gated transmembrane transport (Supporting Information Figures

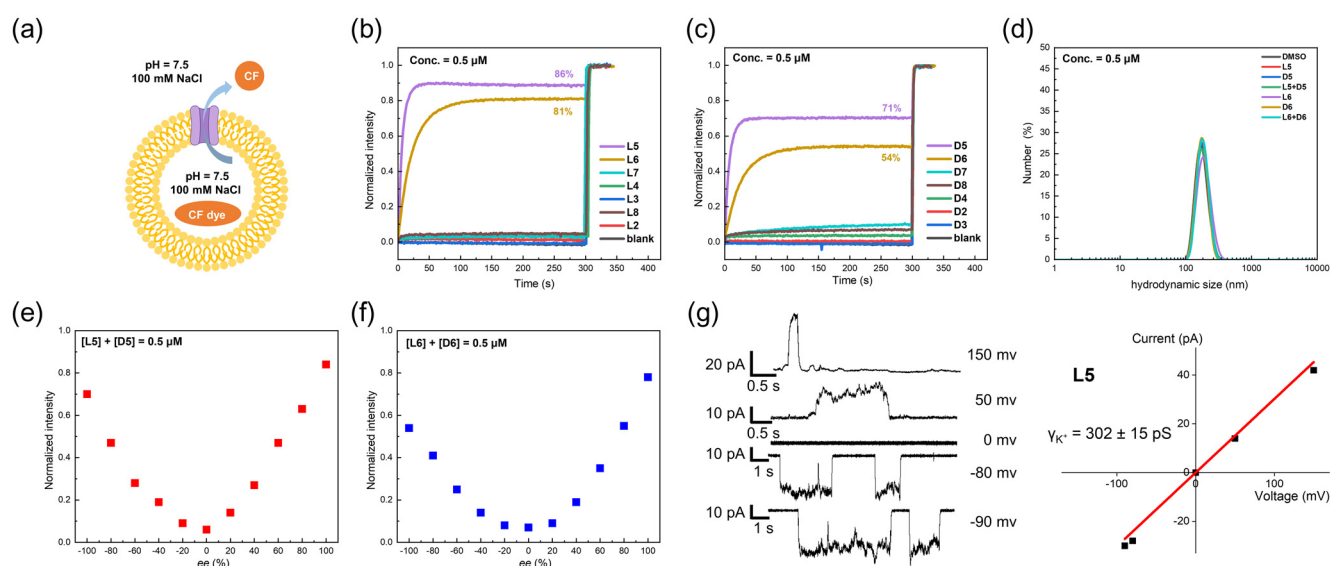


Figure 2 | (a) The CF dye leakage assay for qualitatively assessing the pore sizes of the formed channels by (b) **L2–L8** and (c) **D2–D8** at $0.5\ \mu\text{M}$. CF = 5(6)-carboxyfluorescein. (d) The hydrodynamic size distributions of LUVs before and after the incorporation of **L5**, **D5**, **L5+D5**, **L6**, **D6**, and **L6+D6**. ee-dependent transport activity from the CF assay for the enantiomeric pairs (e) **L5/D5** and (f) **L6/D6**. (g) Single-channel current traces and current–voltage (*I*–*V*) curve for **L5** recorded in symmetric baths (cis chamber = trans chamber = 1 M KCl) at a concentration of **L5**/DiPhyPC = 1/5000 in molar ratio, from which the ion conductance (γ) was determined to be $302 \pm 15\ \text{pS}$.

S10 and S11). These results align with the trends observed in the HPTS experiments, confirming that transport activity can be finely tuned through chirality control.

Planar lipid bilayer electrophysiology was subsequently employed to confirm nanopore formation at the single-channel level. Measurements were conducted using a DiPhyPC bilayer formed across a $200\ \mu\text{m}$ aperture, separating two chambers containing symmetric 1 M KCl solutions. Upon incorporation of **L5**, the compound with the highest transport activity, well-defined rectangular current traces characteristic of reversible channel opening and closing, were observed under an applied voltage. Analysis of the current–voltage relationship revealed a single-channel K^+ conductance of $302 \pm 15\ \text{pS}$ (Figure 2g). This high conductance provides direct evidence of discrete nanoscale pore formation.^{40–42} We also measured the single-channel conductance of **D5** and the **L5/D5** racemate, obtaining values of 168 ± 3 and $47 \pm 2\ \text{pS}$, respectively (Supporting Information Figure S12). The conductance trend (**L5** > **D5** > **L5/D5** racemate) is consistent with the transport activities determined by the HPTS assay (Figure 1d). For **L6**, **D6**, and the **L6/D6** racemate, a similar tendency was observed (Supporting Information Figure S13). Collectively, these results provide direct evidence for the nonlinear regulation of nanopore formation and ion transport by enantiomeric composition, corroborating the V-shaped activity–ee relationship and the chirality-gated mechanism.

To gain mechanistic insight into the origin of the ee-dependent transport behavior, we investigated the

supramolecular assembly of **L5** and **D5** in buffer solutions containing LUVs. Absorption spectra revealed distinct peaks at 325, 338, and 356 nm (Figure 3a), with both spectral profile and intensity varying as a function of ee. Compared with enantiopure **L5** or **D5** alone, their mixtures exhibited enhanced absorbance and more resolved spectral peaks. Plotting the absorbance at 356 nm as a function of ee yielded a bell-shaped profile (Figure 3b), consistent with the presence of heterochiral coassembly within the membrane environment.

Chiroptical properties were further examined by CD spectroscopy (Figure 3c). Unexpectedly, enantiopure **L5** and **D5** showed only weak CD signals, whereas decreasing the ee led to a gradual enhancement of CD intensity, with well-defined bisignate Cotton effects emerging at 360 and 320 nm and a crossover point at 338 nm, consistent with the absorption maximum (Figure 3a). This spectral profile is characteristic of an exciton-coupled Cotton effect, typically resulting from coupling between chromophores via π – π stacking. This observation suggests that enhanced π – π interactions between the central aromatic linkers facilitate heterochiral coassembly. The CD intensity reached a maximum at ee = $\pm 60\%$, followed by a sharp decrease to ee = 0%. The resulting CD–ee plot exhibited an unconventional Z-shaped dependence (Figure 3d).

This unconventional Z-shaped profile contrasts sharply with the classical “majority-rules”⁴³ or “sergeants-and-soldiers” effects⁴⁴ observed in chiral supramolecular polymers, where CD signals increase nonlinearly with ee

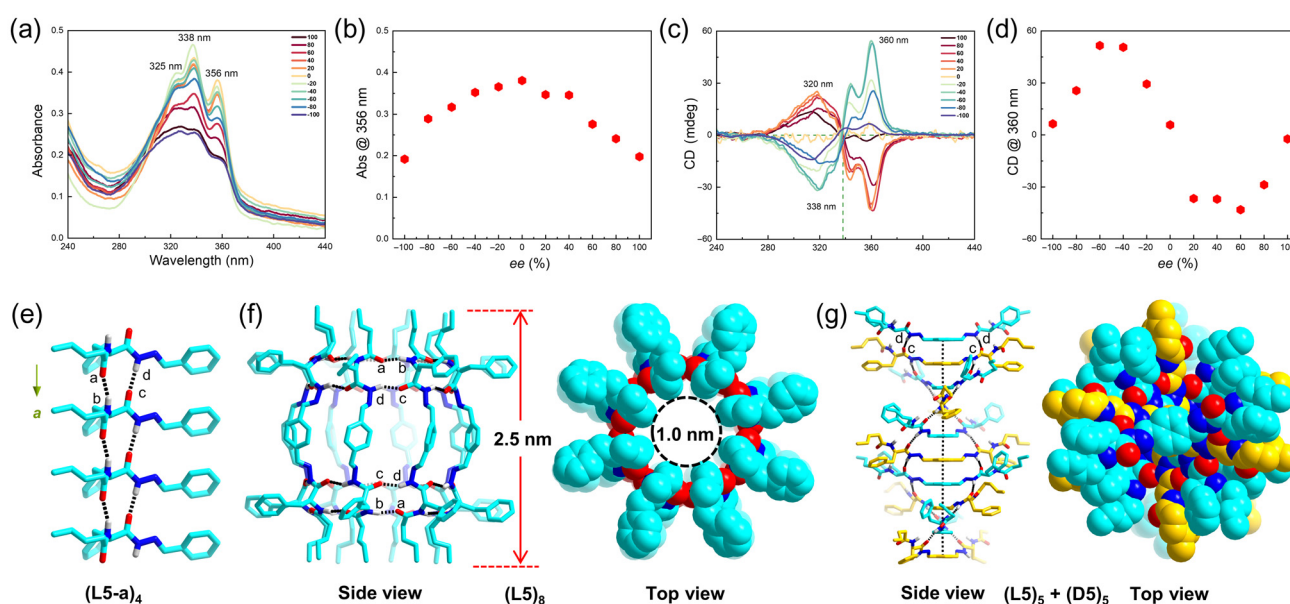


Figure 3 | (a) Absorption spectra of **L5/D5** at varying ee in LUV solutions. (b) Absorbance at 356 nm as a function of ee. (c) CD spectra of **L5/D5** at varying ee in LUV solutions. (d) CD signal at 360 nm as a function of ee. [**L5**] + [**D5**] = 10 μ M. (e) Hydrogen-bonding pattern observed in the crystal structure of **L5-a**. (f) Structural model of a hydrogen-bonded (**L5**)₈ assembly forming an open nanopore (2.5 nm in length, 1.0 nm in diameter), built by manual assembly in GaussView and Avogadro. (g) Structural model of a twisted stack formed by the racemic mixture (**L5**)₅ + (**D5**)₅, leading to a closed-pore structure, constructed analogously.

or the fraction of chiral species and peak at enantiopurity, reflecting chiral amplification.²⁶ Here, the maximum CD at ee = $\pm 60\%$ and the weak signal at ee = $\pm 100\%$ reveal a distinct regime in which moderate enantiomeric imbalance promotes heterochiral coassembly and enhances exciton coupling, rather than amplifying homochiral order. This unique behavior highlights the competition between homochiral and heterochiral interactions in membrane-confined assembly and suggests that variations in ee may induce fundamentally different supramolecular packing modes.

Indeed, related anomalous CD-ee relationships have previously been associated with packing-mode transitions in supramolecular assemblies, where enantiopure and racemic systems adopt fundamentally different morphologies such as flat nanostructures and twisted ribbons, respectively.⁴⁵ By analogy, we propose that enantiopure **L5** or **D5** molecules pack in a relatively flat arrangement within the membrane to form symmetric conductive nanopores with weak chiroptical responses, whereas heterochiral coassembly induces twisted packing that enhances CD signals but leads to pore closure and transport inhibition.

Consistent trends were also observed in buffer solutions in the absence of LUVs, where **L5** and **D5** displayed similar absorption and CD features, including the unconventional Z-shaped CD-ee dependence (Supporting

Information Figure S14). Scanning electron microscopy (SEM) further revealed that enantiopure **L5** and **D5** form fibrous aggregates, while the racemic mixture assembles into particulate morphologies, corroborating the strong preference for heterochiral coassembly (Supporting Information Figure S15). This preference was further confirmed in a nonpolar solvent (CHCl₃): a bell-shaped absorbance-ee profile (Supporting Information Figure S16) and distinct morphological differences between enantiopure and racemic samples (Supporting Information Figure S17) collectively support the occurrence of heterochiral coassembly.

We successfully crystallized the unilateral analogue of **L5**, that is, **L5-a** (Supporting Information Table S3). In the crystal lattice, molecules of **L5-a** engage with adjacent molecules through double N-H^b $\cdots$ O=C/N-H^d $\cdots$ O=C hydrogen bonds. This interaction drives a parallel packing arrangement along the *a*-axis, resulting in a one-dimensional supramolecular chain (Figure 3e). Informed by this hydrogen-bonding motif, we propose a plausible assembly mode for **L5** within LUV membranes. Four sets of the aforementioned N-H $\cdots$ O=C hydrogen bonds connect molecules into a linear chain. This chain is inferred to curve and close into a cyclic nanopore approximately 2.5 nm in length and 1.0 nm in diameter when eight **L5** molecules constitute the pore (Supporting Information Figure S18 and Figure 3f). The central cavity of

this pore facilitates the transport of ions and CF dye, while its highly symmetric conformation accounts for the observed weak CD signals.

By virtue of the nanopore structure established for **L5**, we next rationalized the pronounced transport differences among the synthesized compounds. For **L4** (shorter alkyl chains), strong exciton-coupled CD signals are observed in LUV-coining buffer (Supporting Information Figure S19), indicating extensive π - π stacking within the membrane that likely leads to nonporous aggregates and thus negligible transport activity. This behavior can be attributed to hydrophobic mismatch:⁴⁶ the shorter molecular length of **L4** relative to the hydrophobic core of the bilayer likely enforces a more vertical membrane orientation, promoting π - π stacking while disfavoring bending and cyclization into pore structures (Supporting Information Figure S20). In contrast, **L7** (longer alkyl chains) exhibits weak CD signals without obvious exciton-coupled features in LUV solutions (Supporting Information Figure S19), suggesting an assembly mode similar to that of **L5**. However, because the molecular length of **L7** exceeds the membrane hydrophobic thickness, the flexible terminal alkyl chains likely extend into the nanopore interior,⁴⁶ thereby reducing the effective pore size (Supporting Information Figure S20). Consistent with this model, **L7** shows moderate ion transport activity ($EC_{50} = 1.95 \mu\text{M}$; Supporting Information Figure S5 and Table S1) but negligible transport of the larger CF dye (Figure 2b). For **L5A** (altered amino acid residue) and **4F-L5** (modified central linker), exciton-coupled CD signals are likewise observed in LUV solutions (Supporting Information Figure S21), indicating that these derivatives fail to establish the hydrogen-bonding network required for nanopore formation. Instead, they preferentially undergo stacked assembly to generate pore-closed structures, consistent with their minimal transport activity (Figure 1c).

For the racemic **L5/D5** mixture, we propose that $\text{N-H}^{\text{d}} \cdots \text{O}=\text{C}$ hydrogen bonding, along with π - π interactions between heterochiral aromatic linkers, facilitates a twisted and dense coassembly (Supporting Information Figure S22 and Figure 3g). This assembly leads to a pore-closed structure that inhibits transport. The π - π interactions are evidenced by the exciton-coupled Cotton effect with a crossover at 338 nm (Figure 3a,c). Notably, when one enantiomer is in excess, this heterochiral twisted packing can develop a global preference in its handedness. This chiral bias gives rise to the pronounced CD signals and explains the unconventional Z-shaped CD-ee dependence (Figure 3d).⁴⁵ It should be noted, however, that the particulate morphologies observed by SEM (Supporting Information Figure S15) were obtained from an aqueous H_2O /dimethyl sulfoxide (99:1) solution of racemic **L5/D5** mixture after drying and may not represent the actual assembly structure within the lipid bilayer. Within the membrane, confinement and lipid

ordering likely direct the racemic mixture into a dense, pore-closed packing that differs from the macroscopic aggregates formed upon drying from bulk solution.

Whether the observed V-shaped activity-ee relationship represents a general feature of nanopore-forming systems remains an open question. We speculate that the activity-ee profile is governed by the balance between homochiral self-sorting and heterochiral coassembly within the membrane.⁴⁷ In the present system, heterochiral coassembly appears to generate densely packed, nonconductive structures that suppress ion transport, thereby producing the observed V-shaped dependence. By contrast, systems in which heterochiral assembly favors conductive channel formation exhibits inverted (bell-shaped) activity-ee profiles, whereas complete homochiral self-sorting would be expected to yield a near-linear dependence, as the two enantiomers would function independently without cooperative coassembly. Future studies on structurally distinct nanopore scaffolds will be required to determine the generality of these assembly-activity relationships. Nevertheless, our results establish the first ee-dependent gating mechanism in artificial ion channels and suggest a broader design principle whereby enantiomeric composition regulates supramolecular packing and transport function.

Conclusion

In conclusion, we report the design of chiral alkylamide phenylalanine hydrazone derivatives that self-assemble into functional nanopores within biomimetic phospholipid membranes, enabling efficient transmembrane ion transport. Chirality is shown to play a decisive role in regulating transport activity through membrane-confined supramolecular assembly. While **L** enantiomers consistently outperform their **D** counterparts, systematic variation of the ee in enantiomeric pairs (e.g., **L5/D5**) reveals a distinct V-shaped dependence of transport activity, uncovering for the first time a nonlinear regulatory mechanism of enantiomeric composition on channel performance. This is accompanied by an unconventional Z-shaped CD-ee relationship. These chiral effects originate from the more favorable membrane insertion of **L** enantiomers in chiral lipid environments, together with heterochiral coassembly that promotes dense packing, pore closure, and transport inhibition. Importantly, the resulting activity-ee relationship enables the construction of a chirality-gated transmembrane transport system, representing a previously unexplored mode of chirality-governed functional expression beyond classical CD-ee profiles. This work establishes a direct structure-function link between molecular chirality, supramolecular organization, and transmembrane transport. It provides a new design principle for chirality-programmable biomimetic ion channel systems.

Supporting Information

Supporting Information is available and includes detailed experimental procedures, additional figures and characterization data (Supporting Information Figures S23–S88). The supplementary crystallographic data for deposition were submitted to the Cambridge Crystallographic Data Centre [(CCDC) database # 2520886].

Conflict of Interest

There is no conflict of interest to report.

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References

1. Murata, K.; Mitsuoka, K.; Hirai, T.; Walz, T.; Agre, P.; Heymann, J. B.; Engel, A.; Fujiyoshi, Y. Structural Determinants of Water Permeation Through Aquaporin-1. *Nature* **2000**, *407*, 599–605.
2. Levin, E. J.; Cao, Y.; Enkavi, G.; Quick, M.; Pan, Y.; Tajkhorshid, E.; Zhou, M. Structure and Permeation Mechanism of a Mammalian Urea Transporter. *Proc. Natl. Acad. Sci. U.S.A.* **2012**, *109*, 11194–11199.
3. Wang, Q.-C.; Zheng, Q.; Tan, H.; Zhang, B.; Li, X.; Yang, Y.; Yu, J.; Liu, Y.; Chai, H.; Wang, X.; Sun, Z.; Wang, J.-Q.; Zhu, S.; Wang, F.; Yang, M.; Guo, C.; Wang, H.; Zheng, Q.; Li, Y.; Chen, Q.; Zhou, A.; Tang, T.-S. TMCO1 is an ER Ca²⁺ Load-Activated Ca²⁺ Channel. *Cell* **2016**, *165*, 1454–1466.
4. Lu, Y.; Yue, C.-X.; Zhang, L.; Yao, D.; Xia, Y.; Zhang, Q.; Zhang, X.; Li, S.; Shen, Y.; Cao, M.; Guo, C.-R.; Qin, A.; Zhao, J.; Zhou, L.; Yu, Y.; Cao, Y. Structural Basis for Inositol Pyrophosphate Gating of the Phosphate Channel XPR1. *Science* **2024**, *386*, eadp3252.
5. Thompson, M. J.; Tessier, C. J. G.; Ananchenko, A.; Hénault, C.; Emlaw, J. R.; Dehez, F.; Zarkadas, E.; daCosta, C. J. B.; Nury, H.; Baenziger, J. E. Asynchronous Subunit Transitions Prime Acetylcholine Receptor Activation. *Science* **2026**, *391*, eadw1264.
6. Doyle, D. A.; Morais Cabral, J.; Pfoetzner, R. A.; Kuo, A.; Gulbis, J. M.; Cohen, S. L.; Chait, B. T.; MacKinnon, R. The Structure of the Potassium Channel: Molecular Basis of K⁺ Conduction and Selectivity. *Science* **1998**, *280*, 69–77.
7. Dutzler, R.; Campbell, E. B.; MacKinnon, R. Gating the Selectivity Filter in CIC Chloride Channels. *Science* **2003**, *300*, 108–112.
8. Wang, K.; Preisler, S. S.; Zhang, L.; Cui, Y.; Missel, J. W.; Grønberg, C.; Gotfryd, K.; Lindahl, E.; Andersson, M.; Calloe, K.; Egea, P. F.; Klaerke, D. A.; Pusch, M.; Pedersen, P. A.; Zhou, Z. H.; Gourdon, P. Structure of the Human CIC-1 Chloride Channel. *PLoS Biol.* **2019**, *17*, e3000218.
9. Tajkhorshid, E.; Nollert, P.; Jensen, M. Ø.; Miercke, L. J. W.; O'Connell, J.; Stroud, R. M.; Schulten, K. Control of the Selectivity of the Aquaporin Water Channel Family by Global Orientational Tuning. *Science* **2002**, *296*, 525–530.
10. Tabushi, I.; Kuroda, Y.; Yokota, K. A,B,D,F-Tetrasubstituted β -Cyclodextrin as Artificial Channel Compound. *Tetrahedron Lett.* **1982**, *23*, 4601–4604.
11. Davis, J. T.; Gale, P. A.; Quesada, R. Advances in Anion Transport and Supramolecular Medicinal Chemistry. *Chem. Soc. Rev.* **2020**, *49*, 6056–6086.
12. Cataldo, A.; Norvaisa, K.; Halgreen, L.; Bodman, S. E.; Bartik, K.; Butler, S. J.; Valkenier, H. Transmembrane Transport of Inorganic Phosphate by a Strapped Calix[4]Pyrrole. *J. Am. Chem. Soc.* **2023**, *145*, 16310–16314.
13. Yan, T.; Liu, J. Transmembrane Ion Channels: From Natural to Artificial Systems. *Angew. Chem.* **2025**, *64*, e202416200.
14. Li, N.; Shen, J.; Ang, G. K.; Ye, R.; Zeng, H. Molecular Tetrahedrons as Selective and Efficient Ion Transporters via a Two-Station Swing-Relay Mechanism. *CCS Chem.* **2021**, *3*, 2269–2279.
15. Picci, G.; Marchesan, S.; Caltagirone, C. Ion Channels and Transporters as Therapeutic Agents: From Biomolecules to Supramolecular Medicinal Chemistry. *Biomedicines* **2022**, *10*, 885.
16. Chen, L.; Si, W.; Zhang, L.; Tang, G.; Li, Z.-T.; Hou, J.-L. Chiral Selective Transmembrane Transport of Amino Acids Through Artificial Channels. *J. Am. Chem. Soc.* **2013**, *135*, 2152–2155.
17. Li, Y.; Dong, J.; Gong, W.; Tang, X.; Liu, Y.; Cui, Y.; Liu, Y. Artificial Biomolecular Channels: Enantioselective Transmembrane Transport of Amino Acids Mediated by Homochiral Zirconium Metal-Organic Cages. *J. Am. Chem. Soc.* **2021**, *143*, 20939–20951.
18. Gou, F.; Yang, Z.; Wang, Q.; Chang, W.; Shen, J.; Zeng, H. Chirality-Induced Split Personality in Polymer with Intrinsic Microporosity-Based Artificial Ion Channels. *Angew. Chem.* **2025**, *64*, e202516573.
19. Liu, M.; Zhang, L.; Wang, T. Supramolecular Chirality in Self-Assembled Systems. *Chem. Rev.* **2015**, *115*, 7304–7397.

20. Yashima, E.; Ousaka, N.; Taura, D.; Shimomura, K.; Ikai, T.; Maeda, K. Supramolecular Helical Systems: Helical Assemblies of Small Molecules, Foldamers, and Polymers with Chiral Amplification and Their Functions. *Chem. Rev.* **2016**, *116*, 13752–13990.
21. Sang, Y.; Liu, M. Hierarchical Self-Assembly into Chiral Nanostructures. *Chem. Sci.* **2022**, *13*, 633–656.
22. García, F.; Gómez, R.; Sánchez, L. Chiral Supramolecular Polymers. *Chem. Soc. Rev.* **2023**, *52*, 7524–7548.
23. Cheng, L.; Liu, K.; Duan, Y.; Duan, H.; Li, Y.; Gao, M.; Cao, L. Adaptive Chirality of an Achiral Cage: Chirality Transfer, Induction, and Circularly Polarized Luminescence Through Aqueous Host–Guest Complexation. *CCS Chem.* **2021**, *3*, 2749–2763.
24. Shang, X.; Song, I.; Han, M.; Lee, J. H.; Ohtsu, H.; Choi, W.; Kim, J. C.; Ahn, J.; Kwak, S. K.; Oh, J. H. “Majority-Rules” Effect on Supramolecular Chirality and Optoelectronic Properties of Chiral Tetrachloro-Perylene Diimides. *Adv. Opt. Mater.* **2021**, *9*, 2001911.
25. Kumar, P.; Vo, T.; Cha, M.; Vishneratina, A.; Kim, J.-Y.; Xu, W.; Schwartz, J.; Simon, A.; Katz, D.; Nicu, V. P.; Marino, E.; Choi, W. J.; Veksler, M.; Chen, S.; Murray, C.; Hovden, R.; Glotzer, S.; Kotov, N. A. Photonically Active Bowtie Nanoassemblies with Chirality Continuum. *Nature* **2023**, *615*, 418–424.
26. Palmans, A. R. A.; Meijer, E. W. Amplification of Chirality in Dynamic Supramolecular Aggregates. *Angew. Chem.* **2007**, *46*, 8948–8968.
27. Yan, X.; Wang, Q.; Chen, X.; Jiang, Y.-B. Supramolecular Chiral Aggregates Exhibiting Nonlinear CD-ee Dependence. *Adv. Mater.* **2020**, *32*, e1905667.
28. Lin, X.-Y.; Shi, J.-L.; Wang, Q.; Yu, Y.-B.; Chen, X.-X.; Yan, X.; Wu, X.; Lin, J.-B.; Li, Z.; Jiang, Y.-B. Developing Chiral Aggregates Exhibiting Anti-S-Shaped CD-ee Dependence: Using a Meso-Isomer to Tune Dynamic Aggregates Induced by Enantiomers. *Chem. Commun.* **2025**, *61*, 1818–1821.
29. Kaucher, M. S.; Harrell, W. A.; Davis, J. T. A Unimolecular G-Quadruplex That Functions as a Synthetic Transmembrane Na⁺ Transporter. *J. Am. Chem. Soc.* **2006**, *128*, 38–39.
30. Si, W.; Xin, P.; Li, Z.-T.; Hou, J.-L. Tubular Unimolecular Transmembrane Channels: Construction Strategy and Transport Activities. *Acc. Chem. Res.* **2015**, *48*, 1612–1619.
31. Saha, T.; Gautam, A.; Mukherjee, A.; Lahiri, M.; Talukdar, P. Chloride Transport Through Supramolecular Barrel-Rosette Ion Channels: Lipophilic Control and Apoptosis-Inducing Activity. *J. Am. Chem. Soc.* **2016**, *138*, 16443–16451.
32. Ren, C.; Zeng, F.; Shen, J.; Chen, F.; Roy, A.; Zhou, S.; Ren, H.; Zeng, H. Pore-Forming Monopeptides as Exceptionally Active Anion Channels. *J. Am. Chem. Soc.* **2018**, *140*, 8817–8826.
33. Yan, T.; Liu, S.; Xu, J.; Sun, H.; Yu, S.; Liu, J. Unimolecular Helix-Based Transmembrane Nanochannel with a Smallest Luminal Cavity of 1 Å Expressing High Proton Selectivity and Transport Activity. *Nano Lett.* **2021**, *21*, 10462–10468.
34. Qi, S.; Tian, J.; Zhang, J.; Zhang, L.; Zhang, C.; Lin, Z.; Min, J.; Mao, S.; Dong, Z. Unimolecular Transmembrane Na⁺ Channels Constructed by Pore-Forming Helical Polymers with a 2.3 Å Aperture. *CCS Chem.* **2022**, *4*, 1850–1857.
35. Licsandru, E.; Kocsis, I.; Shen, Y.-X.; Murail, S.; Legrand, Y.-M.; van der Lee, A.; Tsai, D.; Baaden, M.; Kumar, M.; Barboiu, M. Salt-Excluding Artificial Water Channels Exhibiting Enhanced Dipolar Water and Proton Translocation. *J. Am. Chem. Soc.* **2016**, *138*, 5403–5409.
36. Bai, D.; Yan, T.; Wang, S.; Wang, Y.; Fu, J.; Fang, X.; Zhu, J.; Liu, J. Reversible Ligand-Gated Ion Channel via Interconversion Between Hollow Single Helix and Intertwined Double Helix. *Angew. Chem.* **2020**, *59*, 13602–13607.
37. Johnson, T. G.; Sadeghi-Kelishadi, A.; Langton, M. J. A Photo-Responsive Transmembrane Anion Transporter Relay. *J. Am. Chem. Soc.* **2022**, *144*, 10455–10461.
38. Yan, T.; Liu, S.; Li, C.; Xu, J.; Yu, S.; Wang, T.; Sun, H.; Liu, J. Flexible Single-Chain-Heteropolymer-Derived Transmembrane Ion Channels with High K⁺ Selectivity and Tunable pH-Gated Characteristics. *Angew. Chem.* **2022**, *61*, e202210214.
39. Hu, J.; Cochrane, W. G.; Jones, A. X.; Blackmond, D. G.; Paegel, B. M. Chiral Lipid Bilayers Are Enantioselectively Permeable. *Nat. Chem.* **2021**, *13*, 786–791.
40. Chen, Z.; Xie, X.; Jia, C.; Zhong, Q.; Zhang, Q.; Luo, D.; Cao, Y.; Mu, Y.; Ren, C. Concentration-Driven Evolution of Adaptive Artificial Ion Channels or Nanopores with Specific Anticancer Activities. *Angew. Chem.* **2024**, *63*, e202318811.
41. Zhang, L.; Tian, J.; Lin, Z.; Dong, Z. Efficient Sodium Transmembrane Permeation Through Helically Folded Nanopores with Natural Channel-Like Ion Selectivity. *J. Am. Chem. Soc.* **2024**, *146*, 8500–8507.
42. Chattopadhyay, S.; Banzal, K. V.; Talukdar, P. Photo-Activation of Tolane-Based Synthetic Ion Channel for Transmembrane Chloride Transport. *Angew. Chem.* **2025**, *64*, e202414354.
43. van Gestel, J.; Palmans, A. R. A.; Titulaer, B.; Vekemans, J. A. J. M.; Meijer, E. W. “Majority-Rules” Operative in Chiral Columnar Stacks of C₃-Symmetrical Molecules. *J. Am. Chem. Soc.* **2005**, *127*, 5490–5494.
44. Shi, L.; Tian, F.; Wang, S. “Sergeants-and-Soldiers” Effect and Modified Ising Model in Chiral Polymer Materials. *Sci. China Chem.* **2025**, *68*, 3429–3448.
45. Cao, H.; Zhu, X.; Liu, M. Self-Assembly of Racemic Alanine Derivatives: Unexpected Chiral Twist and Enhanced Capacity for the Discrimination of Chiral Species. *Angew. Chem.* **2013**, *52*, 4122–4126.
46. de Jesus, A. J.; Allen, T. W. The Determinants of Hydrophobic Mismatch Response for Transmembrane Helices. *Biochim. Biophys. Acta* **2013**, *1828*, 851–863.
47. Safont-Sempere, M. M.; Fernández, G.; Würthner, F. Self-Sorting Phenomena in Complex Supramolecular Systems. *Chem. Rev.* **2011**, *111*, 5784–5814.