ACCOUNTS of chemical research

pubs.acs.org/accounts Article

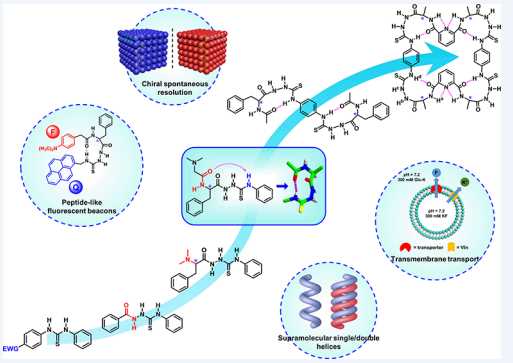
N-Acylamino Acid Amidothiourea: A Versatile Chiral Helical Building Block

Qian Wang, Si-Yi Liu, and Yun-Bao Jiang*

Cite This: *Acc. Chem. Res.* 2025, 58, 3046−3059 Read Online

ACCESS | Metrics & More | Article Recommendations

CONSPECTUS: Thioureas represent an important class of molecular frameworks, distinguished by their hydrogen-bonding capabilities. This feature has enabled the development of a variety of synthetic anion receptors and advanced molecular technologies with applications in analysis, catalysis, and therapeutics. Over the past three decades, our lab has focused on establishing *N*-acylamino acid amidothiourea platforms to revolutionize the thiourea-based supramolecular functionality, particularly in anion recognition, chirality transfer, spontaneous resolution, and macrocyclization synthesis. This Account highlights representative studies from our lab and describes our exploration of the relationship between *N*-acylamino acid amidothiourea conformation, folding, and emerging material properties.



The design of thiourea-based anion receptors usually involves enhancing the hydrogen-bonding propensity of the thioureido −NH proton(s). Conventional strategies employ electron-withdrawing groups to increase the acidity of −NH(s), although this risks deprotonation of −NH when they are too acidic or encounter highly basic anions. Our lab developed an alternative strategy for this goal that circumvents this limitation. By incorporating electron-donating amide groups to generate *N*-amidothioureas and exploiting molecular allostery to drive intramolecular charge transfer (ICT), we achieved a dramatic enhancement in anion binding affinity by orders of magnitude. The *N*-amidothioureas also serve as dynamic regulators of intramolecular chirality transfer via N−N bond conformational switching from twisted to planar states. Notably, *N*-acylamino acid amidothioureas exhibit a pronounced template effect due to the folded β-turn structure, enabling efficient macrocyclization syntheses that were previously unattainable. This breakthrough has facilitated the construction of macrocycle-based nanopores for transmembrane transport. Furthermore, by integrating intermolecular binding sites, we achieved helicity propagation of the helical β-turn structure through self-assembly, yielding supramolecular double helices with a linear CD-*ee* dependence. It presents a critical step toward spontaneous resolution for practical applications.

Given the expanding interest in thiourea and its derivatives, our chiral helical building blocks provide a versatile platform for advancing functional thiourea-based materials.

KEY REFERENCES

- Nie, L.; Li, Z.; Han, J.; Zhang, X.; Yang, R.; Liu, W.-X.; Wu, F.-Y.; Xie, J.-W.; Zhao, Y.-F.; Jiang, Y.-B. Development of *N*-Benzamidothioureas as a New Generation of Thiourea-Based Receptors for Anion Recognition and Sensing. *J. Org. Chem.* **2004**, *69* (19), 6449−6454.[1] Anion binding induces a conformation change in the *N*-amidothiourea receptor, strengthening its electron donor. This switches on the ICT, enhancing anion binding. The key is introducing an electron-donating amide group, RC(O)NH−, which produces a twisted N−N linkage to thiourea.
- Yan, X.-S.; Wu, K.; Yuan, Y.; Zhan, Y.; Wang, J.-H.; Li, Z.; Jiang, Y.-B. β-Turn structure in glycinylphenylalanine dipeptide based *N*-amidothioureas *Chem. Commun.* **2013**, *49* (79), 8943−8945.[2] Our first article reporting the β-turn structure in *N*-acylamino acid-based amidothiourea, in which the thiourea moiety, with its two −NH bonds in the *trans,cis*-conformation, is included within and thus experiences a chiral environment.
- Yan, X.-S.; Zou, K.-S.; Cao, J.-L.; Li, X.-R.; Zhao, Z.-X.; Li, Z.; Wu, A.-A.; Liang, W.-Z.; Mo, Y.-R.; Jiang, Y.-B. Single-handed supramolecular double helix of homochiral bis(*N*-amidothiourea) supported by double crossed C−I···S halogen bonds. *Nat. Commun.* **2019**, *10*, 3610.[3] A double helix was created thought self-assembly of helical fragments via crossed double C−I···S

Received: July 14, 2025
Revised: September 3, 2025
Accepted: September 5, 2025
Published: September 13, 2025

https://doi.org/10.1021/acs.accounts.5c00490
Acc. Chem. Res. 2025, 58, 3046−3059

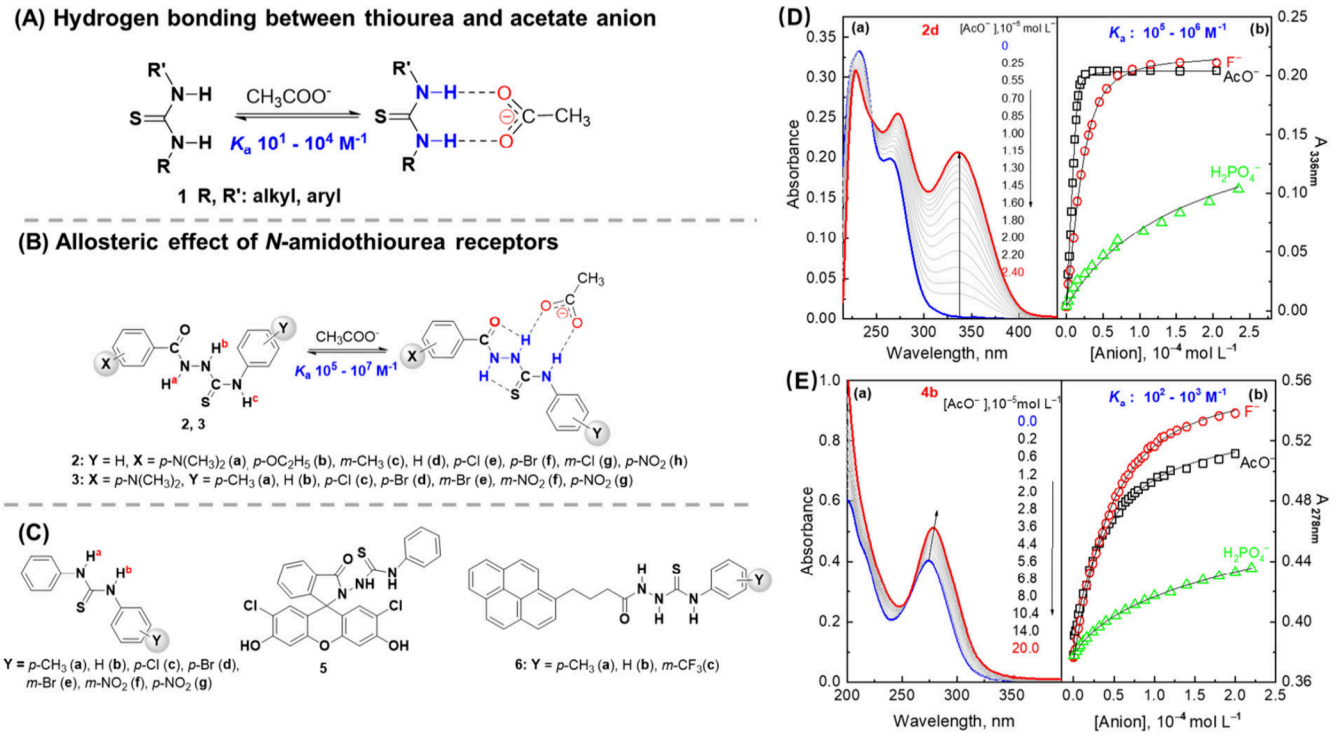


Figure 1. (A) Hydrogen bonding of thiourea with AcO^-. Binding constants (K_a) have been reported 10^1 and 10^4 M^{-1}. (B) Allosteric binding of *N*-amidothioureas to AcO^-. K_a values are 10^5 to 10^7 M^{-1}, 1−3 orders of magnitude higher than those of the simple thiourea anion receptors. (C) Structures of **4**−**6**. (D, E) Absorption spectra of **2d** and **4b** upon titration by AcO^- and plots of absorbance against anion concentration. Reproduced with permission from ref 1. Copyright 2004 American Chemical Society.

bonding. This process exhibits a linear CD-*ee* dependence, indicative of molecular self-sorting and spontaneous resolution when the chiral species is structurally modified into such helical building blocks.

- Lin, X.; Kou, B.-H.; Cao, J.-L.; Weng, P.-M.; Yan, X.-S.; Li, Z.; Jiang, Y.-B. Spontaneous Resolution of Helical Building Blocks through the Formation of Homochiral Helices in Two Dimensions. *Angew. Chem., Int. Ed.* **2022**, *61* (34), e202205914.[4] Halogenated (I, Br, Cl) *N*-acetylalanine amidothioureas featuring helical *β*-turns utilize intermolecular hydrogen- and halogen-bonding to form 2D supramolecular homochiral helices. Spontaneous resolution is achieved, providing a prototype for spontaneous resolution of chiral amino acid species.
- Gou, F.; Shi, D.; Kou, B.-H.; Li, Z.; Yan, X.-S.; Wu, X.; Jiang, Y.-B. One-Pot Cyclization to Large Peptidomimetic Macrocycles by In Situ-Generated *β*-Turn-Enforced Folding. *J. Am. Chem. Soc.* **2023**, *145* (17), 9530−9539.[5] Using the *β*-turn structure in the formed *N*-amidothiourea intermediate as a template, peptidomimetic macrocycles containing four amino acid residues are synthesized in high yields. This templating reaction can be applied to macrocycles with varied amino acid residues and/or aromatic arms.

1. INTRODUCTION

Thioureas[6] are essential building blocks for supramolecular materials and biomedical research with a wide range of applications in ion recognition,[7−9] organocatalysis,[10] and functional materials.[11,12] Recently, the design of biologically and pharmacologically active thiourea derivatives has garnered attention for facilitating transmembrane transport[13−17] and therapeutic applications including antitubercular, antimalarial, and antitumor effects.[18−20] Thiourea compounds at low concentrations have also been used as bioregulators to integrate redox signaling in plants.[21]

The value of thioureas was again recognized about 30 years ago, owing to the hydrogen bonding of their −NH(s) with the substrate to facilitate organocatalysis.[22,23] In principle, the higher acidity of the −NH(s) enhances hydrogen bonding with an electron-rich acceptor, making it preferable. One straightforward way to achieve this is by introducing an electron-withdrawing group to the −NH group. Deprotonation could happen when the −NH protons are too acidic or encounter a basic anion such as F^-, allowing colorimetric/fluorescence sensing of anions in aqueous solution.[24,25] Furthermore, formation of solvent-filled 3D channels by intermolecular interactions can be achieved.[26] It should be noted that the anion binding and deprotonation processes could be made reversible simply by the progressive addition of water.[27,28] Inspired by the character of the N−O bond in *α*-aminoxy acids, in which it twists due to the electrostatic repulsion between N and O atoms,[29] we proposed developing *N*-amidothioureas, i.e., introducing an electron-donating amide group, RC(O)NH−, next to −NH in thiourea, via the twisted N−N bond. A conformation change is expected to occur around the N−N bond when the anion binds to the thiourea moiety, forming a hydrogen-bonding network including the "−NH−NH−" motif so that thiourea together with the hydrogen-bonded anion join the amide −NH as electron donors. The latter is much strengthened such that an intramolecular charge transfer (ICT) occurs in the anion binding complex and a positive charge is generated in the thiourea moiety that provides an additional electrostatic

https://doi.org/10.1021/acs.accounts.5c00490
Acc. Chem. Res. 2025, 58, 3046−3059

interaction with the anion. The acidity of the thiourea −NH(s) in amidothioureas is not greater, yet the anion binding constants are orders of magnitude higher. Our group and the teams of Gale,[7,30] Gunnlaugsson,[25,31−33] and Das[34−36] confirm the superior binding of amidothioureas toward a variety of anions such as AcO^- and F^-. Note that in the chiral amidothiourea organocatalysts pioneered by Jacobsen et al.,[37−41] the thiourea moiety is linked to the amide group at the carboxylic acid side, i.e. $-C^*HR^1C(O)NR^2R^3$ ("C*" is a chiral carbon) via a N−C bond, different from the amidothioureas discussed here.

The next progress in our lab was to make the amide from a chiral carboxylic acid, the amino acid, in the forms of *N,N*-dimethylamino acid and *N*-acylamino acid. Importantly, in *N*-acylamino acid amidothioureas, chirality transfer occurs from the chiral center to *N*′-phenylthiourea moiety despite the twisted N−N linkage. This led to the identification of a β-turn maintained by a ten-membered intramolecular hydrogen bond (IHB). The β-turn structure is versatile in that it is able to generate peptide-like fluorescent beacons and template macrocyclization reactions and form supramolecular helices. Of significance is the linear CD-*ee* dependence for the double helix, suggesting a way to spontaneous resolution. This route was confirmed for alanine and phenylalanine, establishing a rational protocol for the challenging subject of spontaneous resolution.

2. STRONG ANION BINDING OF *N*-AMIDOTHIOUREAS

Thiourea is an important motif for building anion receptors via double hydrogen bonding interactions.[42] As a model system, binding of acetate anion to a thiourea-based receptor is illustrated in Figure 1A. When designing such receptors, three factors should be considered: (i) strength of the hydrogen bonding, (ii) conformations of the two N−H bonds versus the C═S bond, and (iii) location of the thiourea binding site in the receptor.[9] One straightforward approach to increase the anion binding affinity is increasing the acidity of the −NH protons (thiourea pK_a 21.1 in DMSO[43]) by introducing electron-withdrawing substituents. Contrary to this classic strategy, we introduced an electron-donating amide group, RC(O)NH−, next to the −NH group via an N−N bond.[44] This endeavor was inspired by the role of an N−O bond in α-aminoxy acid, twisted due to electrostatic repulsion between the N and O atoms.[29] The N−N bond would function similarly, yet the protons of "−NH−NH−" in the amidothiourea moiety can participate in intramolecular hydrogen bonding to network the structural framework. Another reason is that the amide C−N bond is only polar since the amide −NH is not very electron-donating. It can become more electron-donating when the thiourea moiety and the hydrogen-bonded anion are engaged. This leads to a charge transfer, in which the thiourea is within the electron donor to bear a positive charge, providing an additional electrostatic interaction with the anion beyond the existing hydrogen-bonding interaction.

The twist nature of the N−N bond was probed in *N*-amidothiourea receptors **2** and **3** (Figure 1B),[1,45] by following effects of substituents **X** and **Y** that were placed respectively at the two sides of the bond. **X** in the *N*-benzamide moiety of **2** affects the chemical shift of amide $-NH^a$, but not the thioureido $-NH^b$ and $-NH^c$ in the *N*′-phenylthiourea moiety. Conversely, **Y** in *N*′-phenylthiourea of **3** influences the chemical shifts of $-NH^b$ and $-NH^c$, but not $-NH^a$ (Table 1). The electronic communication between thiourea and benzamide moieties is blocked by the N−N bond. It is a twisted conformation, as evidenced by the crystal structure of **12**, which shows a −H−N−N−H dihedral angle of 106° (Figure 3A).

Table 1. Dependence on Hammett Constant σ of Chemical Shifts δ_{-NH} in 2−4 and Binding Constant K_a of 2−4 with AcO^- in CH_3CN

	δ_{-NH} (ppm) versus σ	K_a (M^{-1}) of AcO^- versus σ	ref.
2a−h	$\delta_{-NH}{}^a = 0.463\sigma_X + 10.5$, $\gamma^2 = 0.9821$	$K_{a(abs)} = 2.97 \times 10^5$ to 1.21×10^7	1
	$\delta_{-NH}{}^b = 0.128\sigma_X + 9.69$, $\gamma^2 = 0.9140$	K_a irrespective of σ_X	
	$\delta_{-NH}{}^c = 0.0977\sigma_X + 9.80$, $\gamma^2 = 0.9173$		
3a−g	$\delta_{-NH}{}^a = 0.125\sigma_Y + 10.14$, $\gamma^2 = 0.9876$	$K_{a(flu)} = 7.1 \times 10^4$ to 4.3×10^7	45
	$\delta_{-NH}{}^b = 0.467\sigma_Y + 9.69$, $\gamma^2 = 0.9754$	$K_{a(abs)} = 9.7 \times 10^3$ to 1.9×10^8	
	$\delta_{-NH}{}^c = 0.523\sigma_Y + 9.58$, $\gamma^2 = 0.9850$	$\ln K_{a(flu)} = 13.44 + 8.74\sigma_Y$, $\gamma^2 = 0.9238$	
		$\ln K_{a(abs)} = 12.07 + 10.57\sigma_Y$, $\gamma^2 = 0.9493$	
4a−g	$\delta_{-NH}{}^a = 0.693\sigma_Y + 9.75$, $\gamma^2 = 0.9689$	$K_{a(abs)} = 10^3$ to 10^4	45
	$\delta_{-NH}{}^b = 0.546\sigma_Y + 9.77$, $\gamma^2 = 0.9806$	$\ln K_{a(abs)} = 10.36 + 2.52\sigma_Y$, $\gamma^2 = 0.8474$	

The acidities of thioureido −NHs in **2** and **3** are lower than that of **4** (Figure 1B, C), as their chemical shifts are lower than those of $-NH^a$ and $-NH^b$ of **4** (Table 1), yet the binding constants of **2** and **3** with AcO^-, determined by nonlinear fitting of the absorbance of new absorption band against concentration of anion, in CH_3CN are 1−3 orders of magnitude higher. The substituent effects on the AcO^- binding constants of **2** and **3** in CH_3CN differ: that of **Y** in **3** is stronger than the classic *N*′-phenylthioureas **4** (Table 1), while **X** at *N*-benzamide of **2** does not have much influence on the anion binding affinity. The effect of substituent **Y** in **3** is amplified.

Ground-state ICT occurs in **2a−h** when binding to an anion, as a strong red-shift in the absorption occurs from 270 nm to 330−435 nm. This red-shift is much larger than that observed for **4** of less than 10 nm (Figure 1D, E). The absorption energy of the anion-binding complex of **2** depends linearly on the Hammett constant of **X** (**2a−g**: $h\upsilon^{max} = 3.67 - 0.337\sigma_X$). The red-shift is larger when **X** is more electron-withdrawing, **X** at the *N*-benzamide moiety of **2** being in electron acceptor, while the thiourea moiety is in the donor. The electron donor in **2**, the amide NH, is therefore substantially strengthened in its anion binding complex. The communication is established between the *N*-benzamide and *N*′-phenylthiourea moieties, so that **X** influences the absorption of the complex but not that of **2** itself because of the twisted N−N linkage.[36] It was therefore concluded that the conformation of the N−N bond changes to planar in the anion binding complex. The ICT in the complex generates a positive charge in the thiourea moiety, which reinforces binding to the hydrogen-bonded anion. This explains the amplified effect of **Y** in **3** on the anion affinity compare to that in **4**. In the anion binding complex, a hydrogen-bonding network is formed that the electron donor becomes an aminothiourea-anion block, which is strong to

https://doi.org/10.1021/acs.accounts.5c00490
Acc. Chem. Res. 2025, 58, 3046−3059

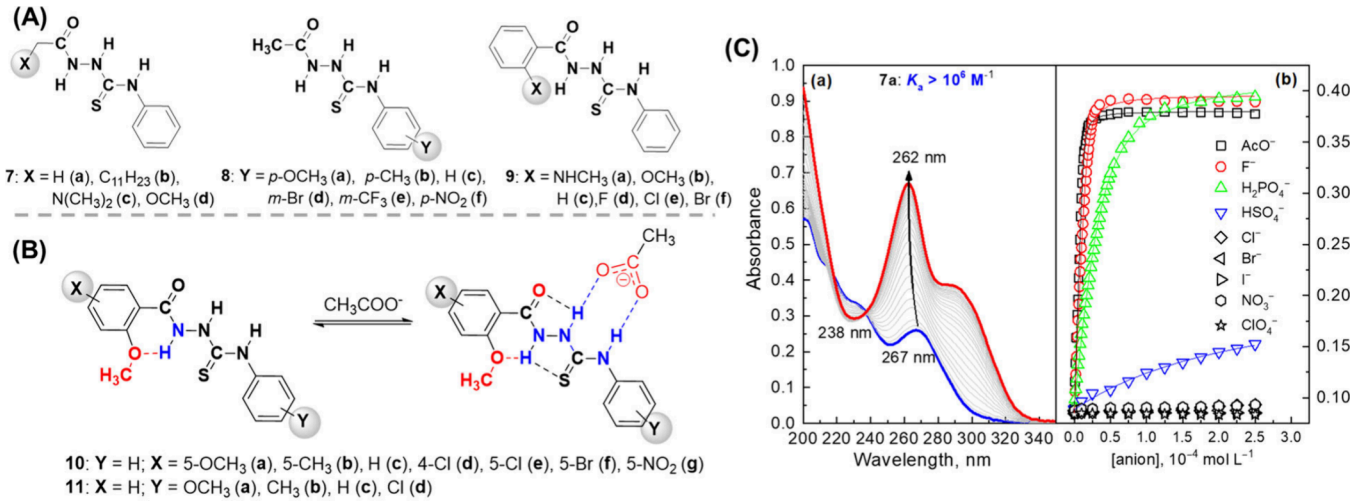


Figure 2. (A) Structures of *N*-amidothioureas **7**–**9** with aliphatic and aromatic amides and (B) **10** and **11** containing an IHB in the *N*-benzamide moiety. (C) (a) Absorption spectra of **7a** in CH_3CN in the presence of AcO^- and (b) plots of absorbance at 290 nm versus anion concentration. Reproduced with permission from ref 55. Copyright 2009 Royal Society of Chemistry.

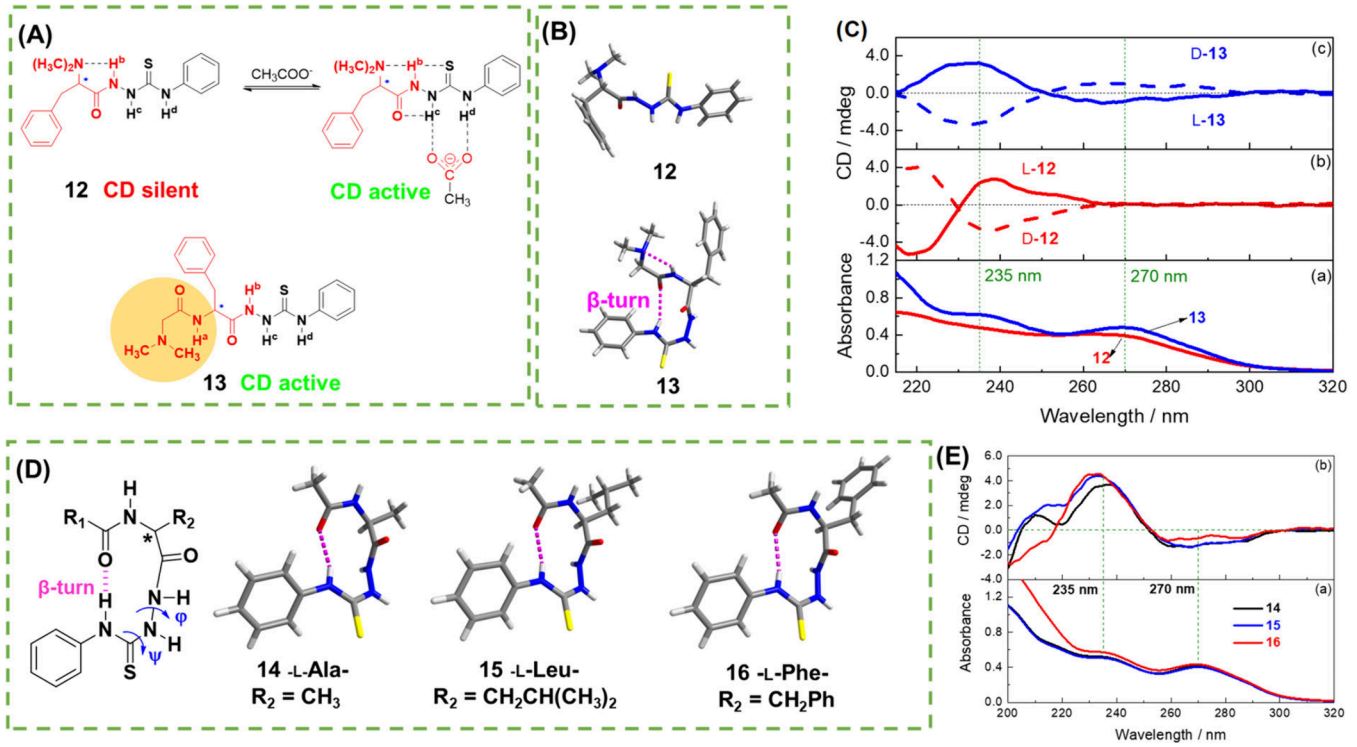


Figure 3. (A) Chemical and (B) crystal structures of **12** (CCDC 1859089) and **13**. (C) (a) Absorption and (b, c) CD spectra of **12** and **13** in CH_3CN. Reproduced with permission from ref 2. Copyright 2013 Royal Society of Chemistry. (D) *β*-Turn shown in the crystal structures of **14**–**16** ($R_1 = CH_3$). (E) (a) Absorption and (b) CD spectra of **14**–**16** in CH_3CN. Reproduced from ref 59. Available under a CC-BY license. Copyright Authors.

switch on the ICT (Figure 1B right). The necessity of amide −NH in this hydrogen-bonding network was supported by the lack of spectral response toward anions in CH_3CN from a rhodamine lactam derivative of *N*-amidothiourea (**5**, Figure 1C), which has no amide −NH proton.[46]

Gunnlaugsson et al.[47,48] established the capability of the thiourea motif as a binding site in anion receptors following the signaling mechanism of photoinduced electron transfer (PET),[49] which was proposed and encoded by de Silva and Gunnlaugsson et al.[50] The thiourea motif was linked to a fluorophore via a CH_2 spacer, which facilitates folding to bring the donor and acceptor in close proximity and an effective PET confirmed by quenched fluorescence. This provided a solid foundation for understanding the change in the electron-donating ability of *N*-amidothiourea upon binding to an anion. In the neutral PET receptors **6** (Figure 1C),[51] despite a longer spacer $(CH_2)_3$, anion binding induced a stronger quenching of fluorescence, indicating a larger drop in E_{ox} of the electron donor upon anion binding to the thiourea moiety. This finding corroborates our previous conclusion, based on the substantial red-shift in the absorption of **2** (Figure 1B, D).[1] The binding constants of **6** with anions such as F^- and AcO^- in CH_3CN at

https://doi.org/10.1021/acs.accounts.5c00490
Acc. Chem. Res. 2025, 58, 3046−3059

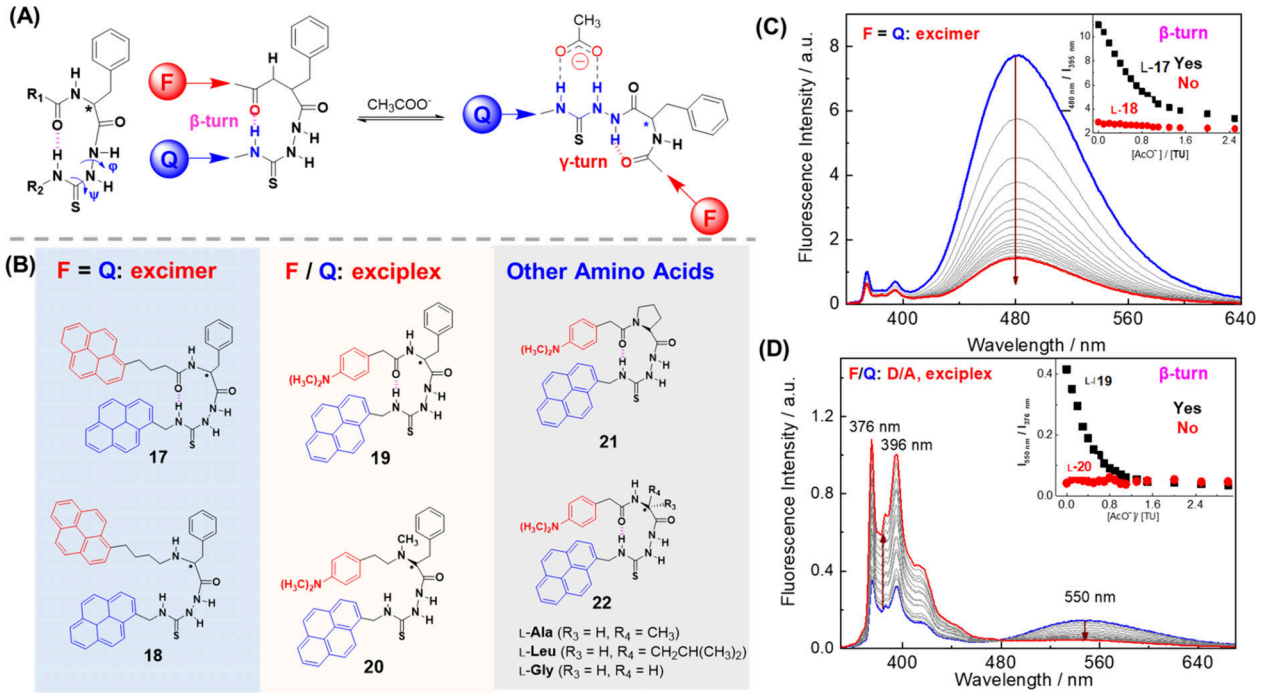


Figure 4. (A) Peptide-like fluorescent beacons for anions built on the *β*-turn structure in *N*-amidothiourea. "F" represents fluorophore and "Q" the quencher, while thiourea is the anion binding site. (B) Structures of **17**−**22**, in which **18** and **20** are control compounds without a *β*-turn. (C, D) Fluorescence spectra of **17** (C) and **19** (D) in the presence of AcO^-; insets show ratiometric fluorescence response of **17** and **19** and control compounds **18** and **20** toward AcO^- in CH_3CN. Reproduced with permission from ref 60. Copyright 2017 Royal Society of Chemistry.

10^5 to 10^7 M^{-1} are 2−4 orders of magnitude higher than those of simple thioureas and close to those of **2** and **3** (Figure 1B).[1,45] *N*-Amidothiourea was also employed to build PET sensors containing BODIPY or an acridinedione fluorophore in the amide moiety for sensing F^- and Hg^{2+}.[52,53] By introducing the *N*-amidothiourea motif into C-17 side-chain of a chiral cholic acid scaffold bearing two axial −OH groups at C-7/C-12 as second binding-site, PET sensors were developed for enantioselective recognition of amino acids.[54]

N-Acetamidothioureas **7** and **8** (Figure 2A) were next developed,[55] in which the amide is made from aliphatic carboxylic acid. The acidities of the thioureido −NH groups in **7** and **8** are lower than those in **2** and **3**, yet the binding affinities for AcO^- in CH_3CN (10^6 − 10^7 M^{-1}, Figure 2C) are similar. Thus, it was confirmed that *N*-amidothioureas from both *N*-aliphatic and *N*-aromatic amides function similarly as efficient anion receptors.

In view of the hydrogen-bonding network in the anion-binding complexes of **2** and **3** (Figure 1B right), *N*-(*ortho*-substituted-benzamido)thiourea counterparts (**9**, Figure 2A), which have an IHB in the *N*-benzamide moiety, were examined.[56] IHB in **9b** between *o*-OCH_3 and amide −NH was confirmed by crystal structure, in which the N−N single bond is less twisted. **9b** and its *N*-benzamido or *N*′-phenyl substituted derivatives **10** and **11** (Figure 2B) exhibit a new absorption around 341 nm from their AcO^- binding complexes in CH_3CN (Figure 2C). This gives anion binding constants over 10^7 M^{-1}, which are larger than that of **2d** around 10^5 M^{-1},[1] suggesting that the IHB in the *N*-benzamide moiety further enhances the anion binding. The effect of *ortho*-**X** in **9** on the absorption of its anion binding complex is opposite to that of *para*- or *meta*-**X** in **2** (Figure 1B).[36] The absorption energy of the AcO^--**10** complex similarly exhibits a linear dependence on Hammett constant of the *para*- or *meta*-**X**, $h\nu = 3.60-0.28\sigma_X$. The magnitudes of the slope and intercept are both smaller than those of **2** without *o*-OCH_3 ($h\nu = 3.67-0.34\sigma_X$).[36] The IHB in the *N*-benzamide moiety of **10** appears to buffer the effect of **X**. The anion binding constant of **10** remains independent of **X**, as with **2** (Figure 1B). The effect of **Y** of **11** on the anion binding constant is amplified compared to **4** (Figure 1C), but to a lesser extent than that observed for **3** having no such IHB (Figure 1B). Less change in the conformation around the N−N bond in **10** and **11** upon anion binding is likely responsible because of the extended hydrogen-bonding network in the *N*-benzamide moiety. This again supports the critical role of the twisted N−N bond, which undergoes a conformation change to enhance anion binding.

3. *β*-TURN IN *N*-ACYLAMINO ACID AMIDOTHIOUREAS

The strengthened anion binding affinity of *N*-amidothioureas inspired our exploration of chirality transfer. The amide was thus made from a chiral carboxylic acid, the amino acid. With the amine-dimethylated phenylalanine based L/D-**12** (Figure 3A),[57] no CD signal was observed in the absorption window of the *N*′-phenylthiourea chromophore (Figure 3Ca,b). This means no chiral communication from the chiral residue to the thiourea moiety, consistent with the twisted N−N linkage. When AcO^- anion binds to L/D-**12**, the absorption shifts to 296 nm together with an induced CD signal,[57] meaning that the chirality is transferred to the chromophore in anion-binding complex. The 5-membered IHB of amide $-NH^b$ with *α*-$N(CH_3)_2$ in **12** (Figure 3A, B), together with the hydrogen bonding network shown in the anion binding complexes of **2** and **3** (Figure 2B right), explains this chiral communication from chiral center to *N*′-phenylthiourea chromophore in **12** in the extended hydrogen-bonding network (Figure 3A).

https://doi.org/10.1021/acs.accounts.5c00490
Acc. Chem. Res. 2025, 58, 3046−3059

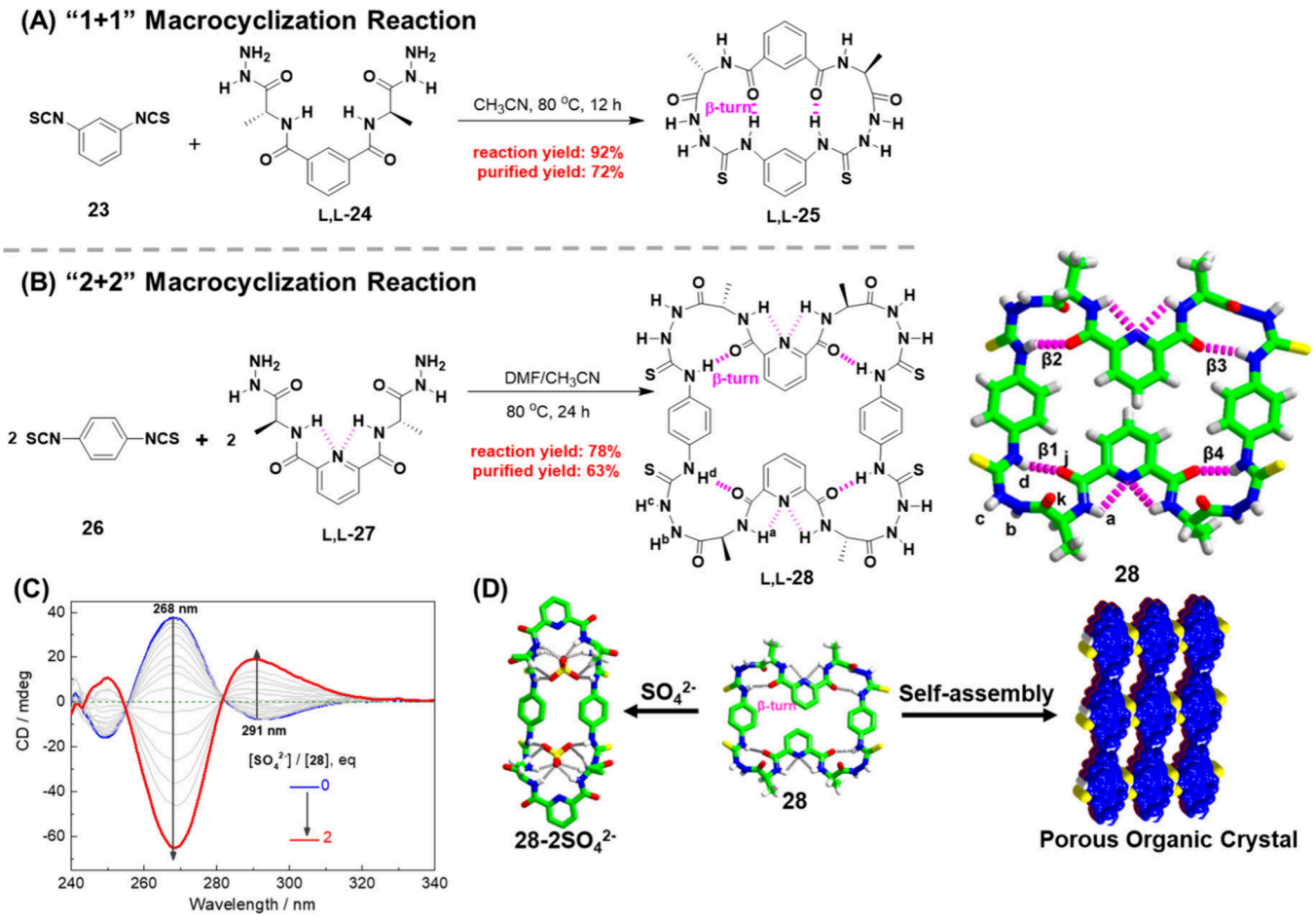


Figure 5. (A, B) β-Turn templated "1 + 1" and "2 + 2" macrocyclization to **25** and **28**. Crystal structure of L,L-**28** shows networked hydrogen bonds highlighted in pink dashed lines. (C) CD spectra of L,L-**28** in 99.5:0.5 (v/v) CH_3CN/DMSO in the presence of SO_4^{2-} at [**28**] = 5 μM. (D) Crystal structures of **28** and the **28**-2SO_4^{2-} complex and the 3D supramolecular porous structure of L,L-**28**. Reproduced with permission from ref 5. Copyright 2023 American Chemical Society.

The next evolution of *N*-amidothioureas was converting the amino acid residue from *N*,*N*-dimethylamino acid to *N*-acylamino acid. The resultant *N*-glycinylphenylalanine amidothioureas, which were obtained by introducing only an achiral *N*-acyl group, L/D-**13** (Figure 3A, B), are CD active at 270 nm (Figure 3Cc).[2] This means that chiral communication is established between the chiral carbon and *N*′-phenylthiourea chromophore despite the twisted N−N linkage. X-ray crystallography and ^{1}H NMR show a β-turn structure that bridges *N*-acyl C═O and −NH^d of *N*′-phenylthiourea by a 10-membered IHB (Figure 3B). This β-turn structure brings the achiral *N*′-phenylthiourea chromophore into a hydrogen-bonding network including the chiral center, explaining the CD output. The β-turn structure also brings its two termini into close proximity, an important characteristic that makes the turn structure a useful building block. **13**−**16** (Figure 3D) all contain a β-turn structure,[58,59] exhibiting a CD signal at 270 nm from the *N*′-phenylthiourea chromophore (Figure 3E), the CD reporter of the β-turn structure.

4. β-TURN STRUCTURE: A VERSATILE CHIRAL HELICAL BUILDING BLOCK

4.1. Peptide-like Fluorescent Beacons

The β-turn structure not only brings its two terminal groups into close proximity but also locks the two thioureido N−H bonds in a *trans,cis*-conformation (Figure 3B, D). This differs from the *trans,trans*-one required for anion binding via double hydrogen bonds. Anion binding to thiourea in this β-turn structure would lead to a conformational change, resulting in an extended structure in which the two terminal groups are separated (Figure 4A). This transformation is similar to that in classic nucleic acid beacons when binding a complementary sequence.[60] The two termini of the β-turn were equipped with two fluorophores or an electron donor/acceptor pair (Figure 4B). It exhibits enhanced excimer (**17**, Figure 4C) or exciplex (**19**, Figure 4D) emission. A sensitive ratiometric fluorescence response toward an anion takes place because of the weakened formation of excimer or exciplex. **18** and **20** (Figure 4B) bearing no such turn structure show very weak excimer or exciplex emission and, more importantly, the dual emission is not sensitive to the added anion (Figure 4C, D insets). Such peptide-like fluorescence beacons can be built from amino acid residues such as Pro, Ala, Leu, and Gly (**21** and **22**, Figure 4B).

4.2. Templated Synthesis of Peptidomacrocycle

The proximity of the two termini in the β-turn structure is similar to that led by a template used to promote the macrocyclization reactions, such as the role of K^+ in the synthesis of 18-crown-6.[61] The β-turn structure in *N*-acylamino acid amidothiourea was therefore applied as a template for macrocyclization. This was first tested, with

https://doi.org/10.1021/acs.accounts.5c00490
Acc. Chem. Res. 2025, 58, 3046−3059

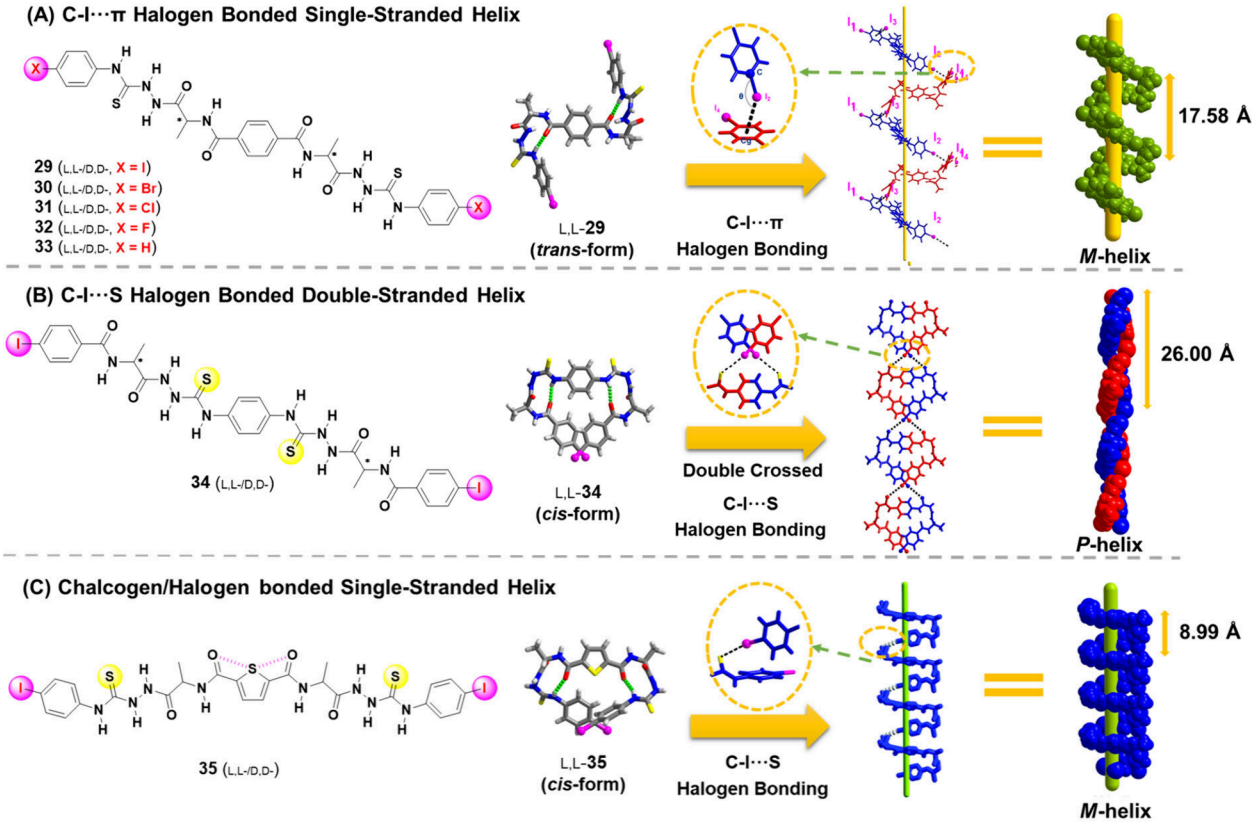


Figure 6. (A) Structures of **29**−**33** with halogen substituents and crystal structure of the single-stranded *M*-helix of L,L-**29** in the *trans*-conformation. "X" highlighted in a pink ball represents an equipped interaction group. Reproduced with permission from ref 64. Copyright 2017 American Chemical Society. (B) Molecular and crystal structure of **34** and crystal structure of the supramolecular double helix of L,L-**34** in the *cis*-conformation. Reproduced from ref 3. Available under a CC-BY license. Copyright Authors. (C) Molecular and crystal structure of **35** and crystal structure of the C−I···S halogen-bonding driven supramolecular single helix of L,L-**35** in the *cis*-conformation. Reproduced with permission from ref 69. Copyright 2022 Royal Society of Chemistry.

success, in the synthesis of macrocycle **25** from a "1 + 1" reaction of 1 molecule of *m*-benzenediisothiocyanate (**23**) and 1 molecule of bilateral *N*-acylamino acid hydrazide (**24**) (Figure 5A).[62] Next, this templating strategy was applied to a more challenging "2 + 2" macrocyclization, which led to the 46-membered peptidomacrocycles **28** (Figure 5B right).[5] Those macrocycles were obtained in a one-pot reaction of 2 molecules of **26** with 2 molecules of **27** in 1:1 (v/v) DMF/CH_3CN in high yields (63% isolated) after an easy filtration (Figure 5B). Three other peptidomacrocycles containing respectively D-alanine, L-phenylalanine, and achiral Aib residues were similarly obtained. HRMS spectra were taken during the reaction, revealing that the final peptidomacrocycle is formed in a stepwise manner. L,L-**28**, which contains 4 networked *β*-turn structures, shows a strong and selective binding to SO_4^{2-}, which otherwise binds weakly. A structural change occurs in the macrocycle when binding SO_4^{2-} leads to a reverse in the CD signals (Figure 5C), which suggests an inside-out conformation change. This is confirmed in the crystal structure of **28**-2SO_4^{2-} versus that of **28** (Figure 5D). The strong binding to SO_4^{2-} was also seen in a slow-exchange profile of the NMR signals in the anion binding complex. This profile has been observed in many other macrocycles, which are now made available in our laboratory. Another structural character of the peptidomacrocycles is their abundance of both intra- and intermolecular hydrogen-bonding sites, which afford interesting chirality communication within the cyclic backbone and between the cyclic structures. The macrocycles stack into hydrogen-bonded frameworks with nanometer-scale chiral channels (Figure 5D right) and stable structures of needle-and-rod morphology on the macroscopic scale. Our extension of using the *β*-turn structure as a template appears feasible so that a variety of macrocycles containing varying amino acid residues and arms can be made.

4.3. Formation of Supramolecular Helix

The *β*-turn structure is helical. When linked through intermolecular interactions between equipped groups, propagation of the helicity of this structure[63] would direct the formation of A supramolecular helix. Using halogen-substituted bilateral *N*-acylamino acid amidothioureas as the helical building blocks, halogen-bonded supramolecular single- and double-stranded helices were successfully built in both THE solid state and dilute solution in CH_3CN. With I-substituted L,L- or D,D-**29** (Figure 6A), intermolecular head-to-tail C−I···*π* halogen bonding results in A single-stranded supramolecular *M*- or *P*-helix, in which two *β*-turns exist in the thermodynamically favorable *trans*-form.[64] The helix that forms even in a highly diluted solution of CH_3CN at the *μ*M level is indicative of the strong intermolecular interactions. It exhibited strong CD signals, with a high anisotropic factor *g* of -3×10^{-3} at 272 nm. An S-shaped CD-*ee* dependence was observed in the solutions of L,L/D,D-**29** of varying enantiomeric excess (*ee*), indicating a chiral amplification.[65] In contrast, **30**−**32** that contain Br, Cl, or F of lower halogen-bonding ability, or **33** without a halogen atom, remain in the monomeric form

https://doi.org/10.1021/acs.accounts.5c00490
Acc. Chem. Res. 2025, 58, 3046−3059

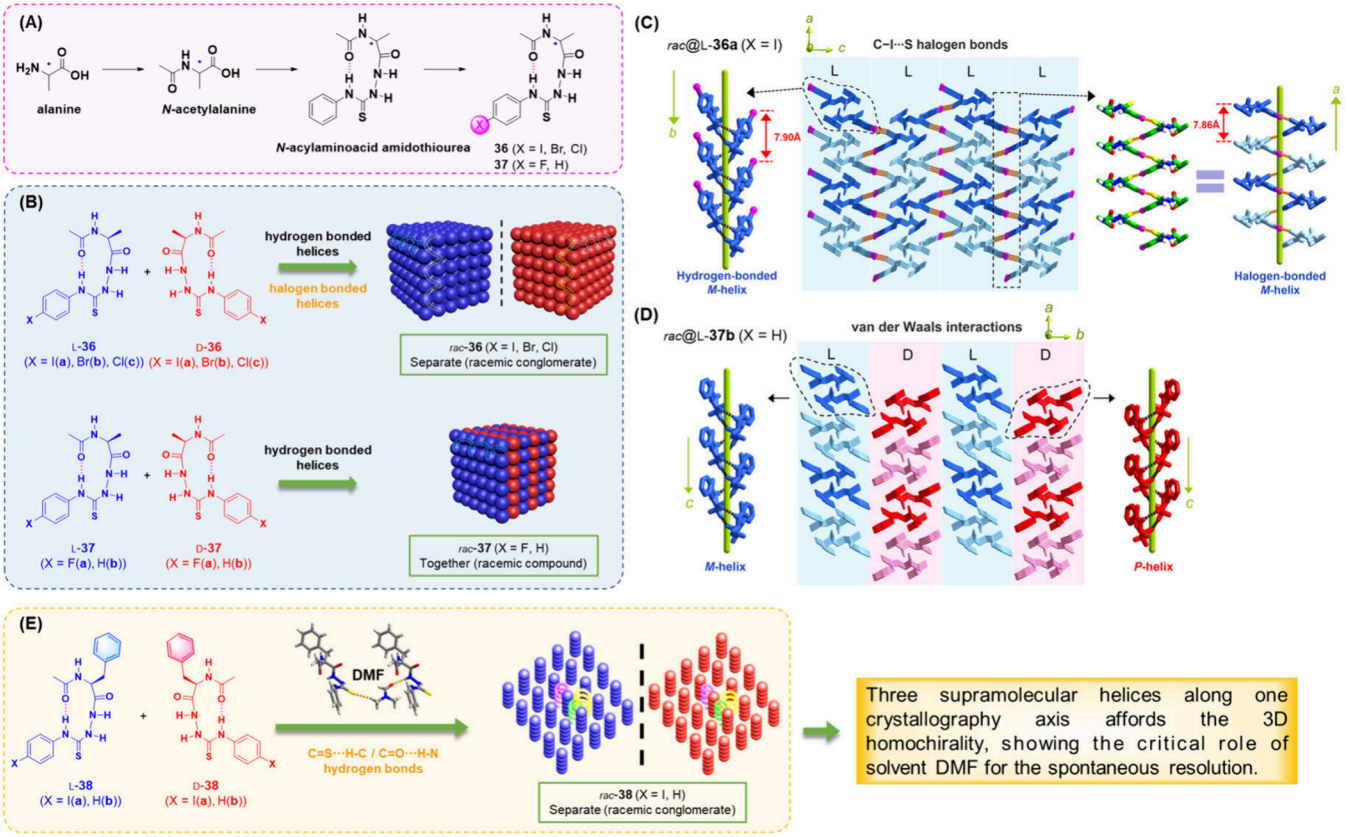


Figure 7. (A) Derivation of alanine into halogen-substituted helical building blocks **36** and **37**. (B) Schemes of racemic conglomerates in crystals of *rac*-**36** and racemic compounds in the crystals of *rac*-**37**. (C) X-ray 3D superstructure of L-**36a**. Homochiral 2D layers from hydrogen-bonded *M*-helices of L-**36a** are linked by C–I···S halogen bonds along the *c*-axis, leading to halogen-bonded *M*-helices. (D) 3D superstructure of *rac*-**37b** in the crystal structure. Homochiral 2D layers of *rac*@L-**37b** consisting of *M*-helices and those of *rac*@D-**37b** made up of *P*-helices are stacked alternatively via van der Waals interactions along the *b*-axis, leading to racemic 3D crystals. Reproduced with permission from ref 4 for **36** and **37**. Copyright 2022 Wiley-VCH. (E) Scheme of racemic conglomerates in crystals of *rac*-**38**, in which solvent DMF bridges the neighboring two helices of the same handedness. Reproduced from ref 72. Available under a CC-BY-NC-ND license. Copyright Authors.

in CH_3CN. A strong halogen-bonding interaction is necessary. Despite the widespread use of halogen bonds in crystal engineering,[66] this was the first report on building supramolecular helices in the solution phase. Recently, several other reports have appeared on the construction of supramolecular helices using halogen bonding interactions.[67,68]

Supramolecular double helices were similarly built from bilateral *N*-(*p*-iodobenzoyl)alanine amidothioureas **34** (Figure 6B left and middle), in which the C–I and C=S binding groups were moved to the central part of the molecule to allow the crossed double C–I···S halogen bonding.[3] Intermolecular halogen-bonding leads to two crossed noncovalent supramolecular chains, which are bridged by covalent spacers, *p*-phenylenediamine (Figure 6B right). Double helices form both in the solid state and in an extremely dilute CH_3CN solution. Again, the *β*-turn helical structure cooperates with the double-crossed C–I···S halogen bonding such that the helicity of the building blocks is propagated along the helix. This leads to a high *g* of −0.016 at 291 nm, an extremely low critical aggregation concentration of 0.08 *μ*M, and a high thermal stability. The strong intermolecular interactions not only pay the penalty of the unfavored *cis*-conformation of **34** in the helix but also well stabilize the helix. An important discovery is the linear CD-*ee* dependence in CH_3CN, which suggests the potential for spontaneous resolution of the chiral building blocks. Since the intermolecular interactions such as halogen bonding here can be solvent-dependent, the choice of solvents is important for the formation of the supramolecular helix in the solution phase.

As a thiophene derivative of **29**, **35** forms single-strand helix in its unfavored *cis*-conformation (Figure 6C),[69] similar to **34** in the double helix. The intramolecular double C=O···S···O=C chalcogen bonds in **35** appears to assist the intermolecular C–I···S halogen bonding in stabilizing this *cis*-conformation. The single-strand helix of **35** exhibits a much shorter pitch of 8.99 Å and a much higher *g* of −0.014 at 347 nm in CH_3CN than those of **29** (Figure 6A).[64] An almost linear CD-*ee* dependence was observed in this single-stranded helix of **35**, similar to that seen in the double helix of **34** (Figure 6B),[3] which exhibits a high *g* of −0.016 at 291 nm. It appears that a large *g* value might be an index of homochiral self-sorting. Recently, Liu et al.[70] reported a binary system composed of chiral histidine and alanine derivatives, which forms double helical *π*-aggregates with exceptionally strong circularly polarized luminescence. This opens an avenue to functional supramolecular helices from small-molecule building blocks.

4.4. Spontaneous Resolution via Formation of Multiple Supramolecular Helices

The linear CD-*ee* dependence observed in the supramolecular double-stranded helices in CH_3CN suggests the possibility of self-sorting via formation of homochiral supramolecular double

https://doi.org/10.1021/acs.accounts.5c00490
Acc. Chem. Res. 2025, 58, 3046−3059

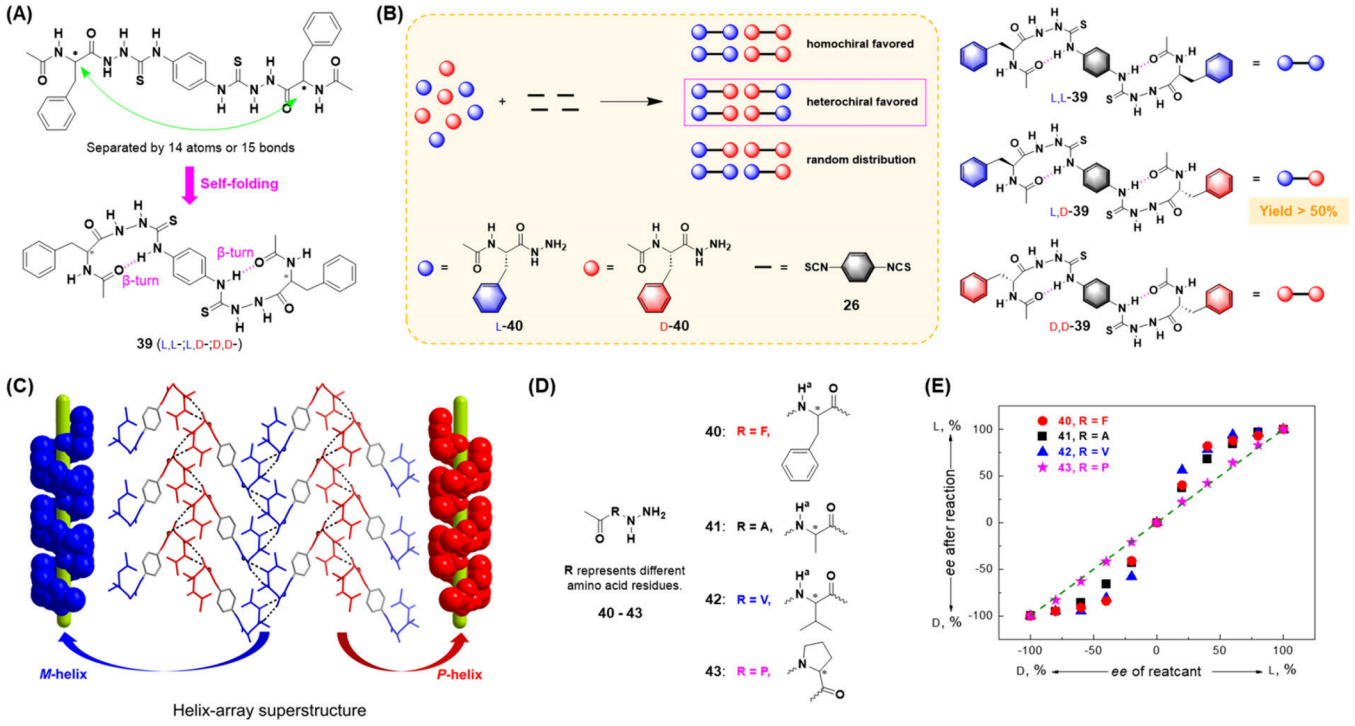


Figure 8. (A) Bilateral *N*-acylphenylalanine azapeptides L,L/L,D/D,D-**39** containing two *β*-turns. (B) Three fates of bilateral products from the reaction of L/D-**40** with **26**. (c) 2D helices array superstructure of L,D-**39** within the *bc*-plane, with stacking via N−H···S═C and N−H···O═C hydrogen bonds that lead to alternative *M*- and *P*-helices. The blue and red ones represent the sides of the molecule containing L- and D-phenylalanine residues, respectively. (D) Hydrazides **40**−**43**. (E) *ee*'s of **40**−**43** before and after their reaction with **26**. Reproduced from ref 73. Available under a CC-BY-NC-ND license. Copyright Authors.

helices.[3] When double helices are formed in two dimensions, homochirality is established in two-dimensions, ensuring the global 3D-homochirality required for spontaneous resolution.[71]

As the first proof-of-concept, alanine was derived into such helical chiral building blocks **36** and **37** capable of intermolecular hydrogen- and halogen-bonding (Figure 7A, B).[4] Spontaneous resolution was successful with **36** (X = I, Br, Cl) with strong halogen bonding ability (Figure 7C), but not **37** (X = F, H) with weak or no halogen bonding (Figure 7D). Crystal structures of *rac*-**36** show homochiral supramolecular helices formed in two dimensions, supported by hydrogen- and halogen-bonding, respectively, across the *β*-turn structure. This eventually ensures global 3D homochirality and spontaneous resolution (Figure 7C). The structural parameters of the hydrogen-bonded helix are not influenced by the halogen identity (X = I, Br, or Cl), indicating that the two helices are orthogonal. It is of significance to point out that in the crystals of *rac*-**36**, despite the coexistence of L- and D-**36**, the formed supramolecular helices consist of either L- or D-**36**, supporting the importance of propagation of the helicity in dictating the homochirality of the helix. *rac*-**37** crystallizes as a racemic compound (Figure 7D) where the hydrogen-bonded helix forms in only one dimension. These hydrogen-bonded helices form a homochiral 2D layer structure similar to the 2D-layer formed in **36**, but the layers in **37** stack in an alternative L- and D-manner, resulting in racemic crystals. The interactions between molecules of **36** that lead to the helices are strong, and no solvent molecules are included in the crystals. This may explain why spontaneous resolution of **36** was successful in several solvents. This however does not mean that solvent plays no role, since solvent−solute interactions can be of significance in facilitating crystallization.

The indispensable role of solvent was confirmed when we applied the spontaneous resolution strategy to phenylalanine (Phe), a more complicated amino acid that has additional $\pi\cdots\pi$ interactions between Phe-residues. Phe was converted to **38** (X = I, H. Figure 7E) and crystallization of the racemates was carried out in hydrogen bonding solvents, DMF, and 1:1:1 (v/v/v) DMF/CH_3CN/CH_3OH.[72] Spontaneous resolution succeeded in both solvents. Interestingly, only DMF molecules were found in the crystals that bridged neighboring helices of the same handedness by hydrogen bonds. Spontaneous resolution fails in other hydrogen-bonding solvents such as CH_3OH and CH_3CN. The distance between hydrogen-bonding donor and acceptor in DMF, which is comparable to the size of the benzyl substituent in Phe, is assumed responsible for the spontaneous resolution. The bridging of solvent DMF molecules between neighboring homochiral helices appears critical in dictating the intermolecular interactions between the helical building blocks since both **38a** (X = I) and **38b** (X = H) undergo spontaneous resolution (Figure 7E). The outputs of the attempts for spontaneous resolution of I-substituted **36a** (No) and **38a** (Yes) in CH_3CN or CH_3OH and nonsubstituted **38b** (Yes) and **37b** (No) in DMF[4,72] suggest that the substituent in the amino acid residue and the solvent are both important and they interplay. It appears that rigid helices of higher *g* values may favor the spontaneous resolution, which, however, needs to be clarified in more systems.

The chiral helical building blocks prefer to form homochiral supramolecular helices (**36**−**38**, Figure 7), suggesting that there could be chiral preference in the coupling products **39**

https://doi.org/10.1021/acs.accounts.5c00490
Acc. Chem. Res. 2025, 58, 3046−3059

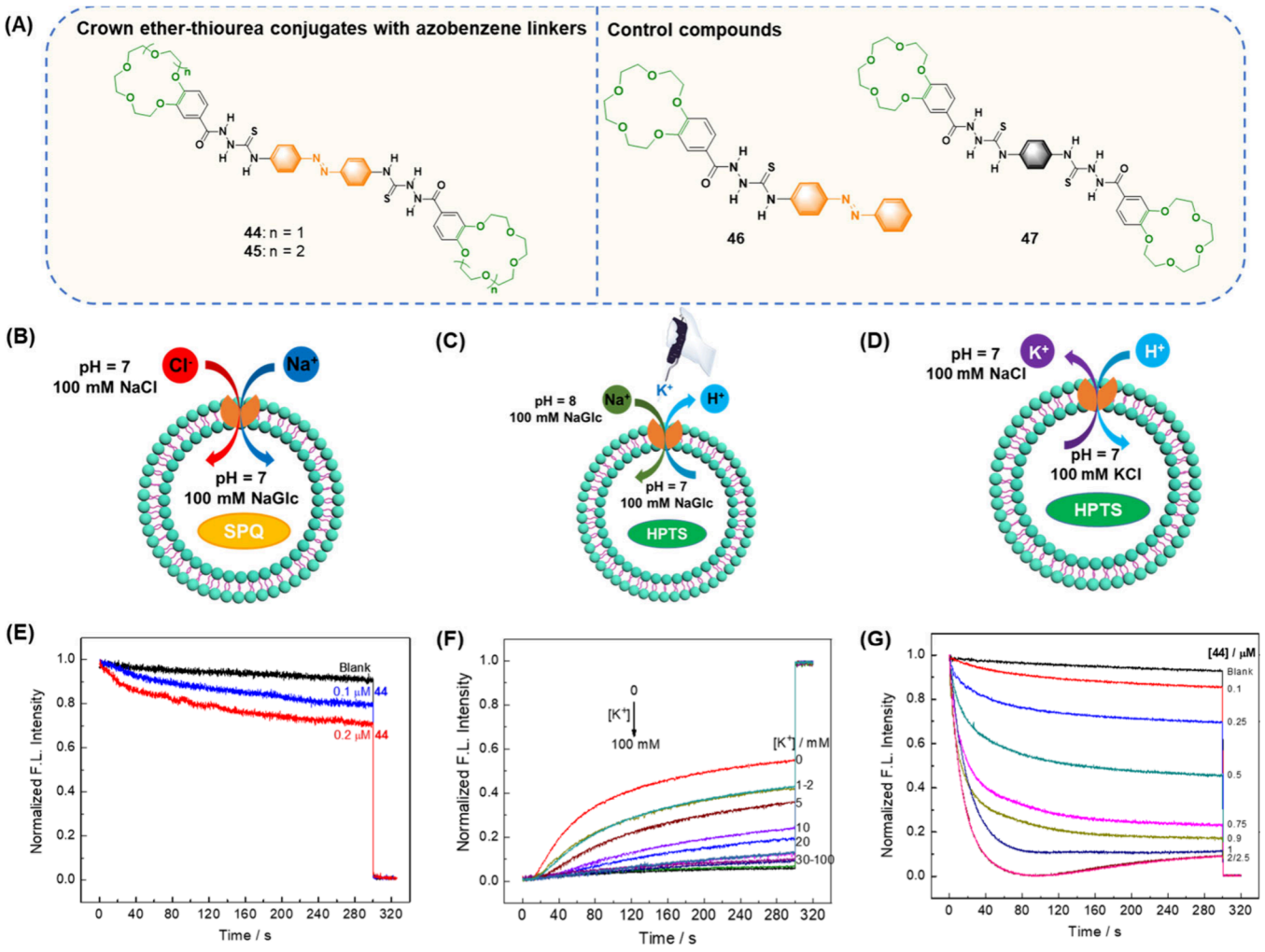


Figure 9. (A) Transporters **44** and **45** and control compounds **46** and **47**. (B–D) Schemes for membrane transport assays using Cl^--sensitive dye SPQ and pH-sensitive dye HPTS, showing transport conditions for Na^+, Cl^-, and K^+ by **44** or **45**. (E) Normalized fluorescence intensity upon addition of **44** (0–0.2 μM). (F) Normalized fluorescence intensity in the presence of **44** (0.3 μM) after externally adding KCl. (G) Normalized fluorescence intensity upon the addition of **44** (0–2.5 μM). Reproduced with permission from ref 74. Copyright 2022 Springer Nature.

that contain two β-turns (Figure 8A).[73] The reaction of racemic *N*-acylamino acid hydrazides (**40**) with **26** in CH_3CN (Figure 8B) led to **39** containing 56% (reaction at 25 °C) to 84% (100 °C) heterochiral L,D-**39**, both higher than its statistical percentage (50%). The heterochirality is more pronounced at higher reaction temperatures and in aprotic solvents, suggesting the role of strong hydrogen bonding. The crystal structure confirms that L,D-**39** features a helical-like superstructure, usch that the β-turns on two sides of the molecule form respectively a homochiral *M*-helix and *P*-helix via interturn hydrogen bonding, which alternatively arrange to stabilize each other (Figure 8C), similar to the alternative homochiral 2D layers of **37** consisting of L-**37** or D-**37** helices (Figure 7A).[4] The helical-like superstructure of L,D-**39** is more favorable than the β-sheet-like superstructure of homochiral L,L- or D,D-**39**. This heterochiral coupling leads to chiral amplification of the hydrazides when treated with achiral **26**, leaving unreacted hydrazides of higher *ee* or enantiopurity (Figure 8D, E). These results might be relevant to the origin of homochirality in nature. Meanwhile, a good understanding of the antiparallel stacking of supramolecular helices of opposite handedness would be helpful for achieving spontaneous resolution, which requires parallel stacking of the helices of the same handedness.

4.5. *N*-Amidothiourea-based Transmembrane Transporters

The strong binding to anions of *N*-amidothioureas inspired explorations of transmembrane transport. A crown ether motif was introduced to enable cation binding, and the crown ether-azobenzene-thiourea conjugates (**44**, **45**, Figure 9A) were found good cation/anion symporters.[74] The transmembrane transport experiments are carried out by using differences in the types of ions or pH values of the buffer solutions inside and outside the phospholipid bilayer of vesicles to form a gradient. When transporter molecules are added, the gradient difference gradually decreases. As a result, the fluorescence intensity of specific dyes or the scattering intensity of the buffer system changes in real time. **44** and **45** can transport both Na^+ and Cl^- across lipid bilayers (Figure 9B, E), while control compounds **46** and **47** do not, necessitating the bilateral structure and lipophilic azobenzene linker. **45** exhibits a significantly reduced transport activity for Na^+ compared to **44** but a better activity for Cl^-, presumably due to its too large cavity of 18-crown-6 for Na^+ while having higher Cl^- affinity. The Na^+/Cl^- transport activities of **44** and **45** are diminished

https://doi.org/10.1021/acs.accounts.5c00490
Acc. Chem. Res. 2025, 58, 3046–3059

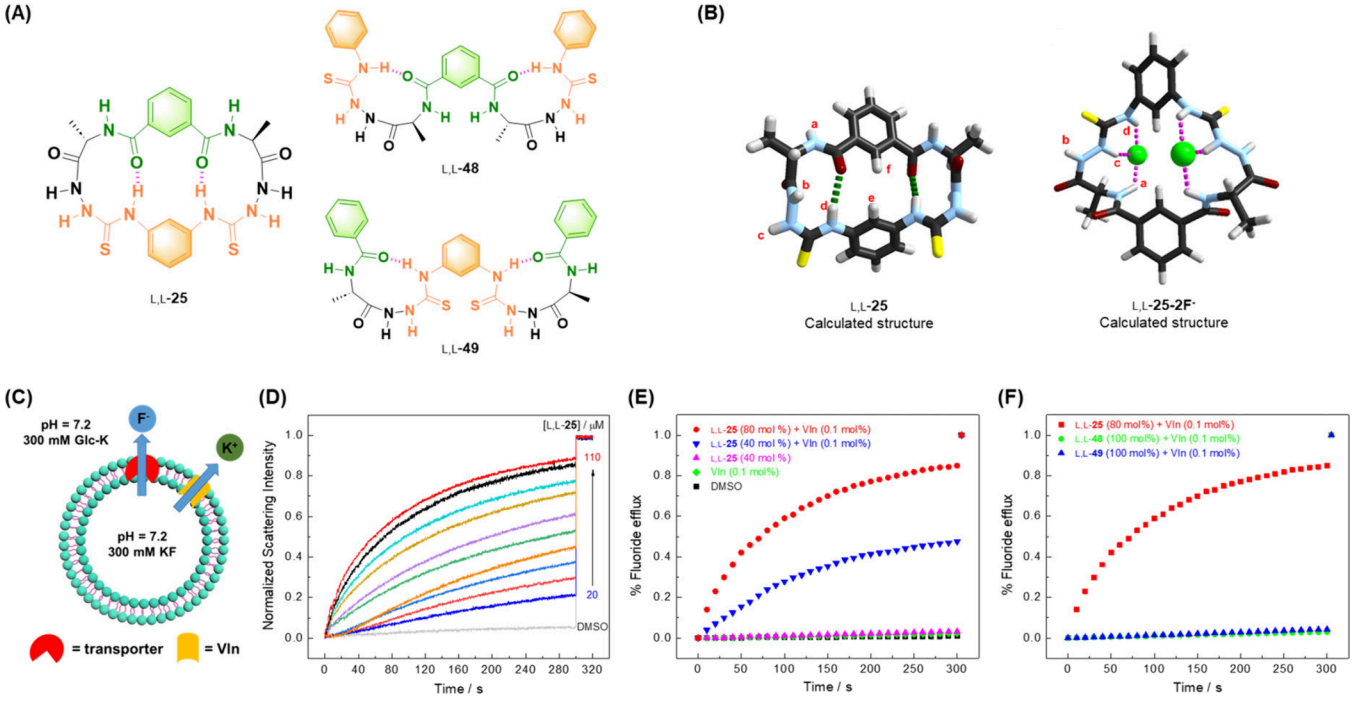


Figure 10. (A) Cyclic L,L-**25** and acyclic control compounds L,L-**48** and L,L-**49**. (B) Optimized structures of L,L-**25** and the $2F^-$-**25** complex at the B3LYP-D3(BJ)/6−311G level. (C) Osmotic response assay for F^- transport under a F^- concentration gradient. (D) Normalized scattering intensity of vesicles upon the addition of L,L-**25** (20−110 μM, 4−22 mol %) in the presence of Vln (0.1 mol %). (E) Normalized F^- efflux of the ISE assay obtained by the addition of L,L-**25** (40 or 80 mol %) in the presence of Vln (0, 0.1 mol %). (F) Normalized F^- efflux of the ISE assay upon the addition of L,L-**25** (80 mol %), L,L-**48** (100 mol %), and L,L-**49** (100 mol %) in the presence of 0.1 mol % Vln. Reproduced from ref 62. Available under a CC-BY license. Copyright Authors.

when K^+ ions are present outside the vesicles (Figure 9C, F), while facilitated K^+ efflux was observed when K^+ was put inside the LUVs (Figure 9D, G), demonstrating the carrier nature of the transporters. The transport selectivity of the transporters is instructive for their biological applications and insightful for new structural design.

Peptidomacrocycle L,L-**25** (Figure 10A) selectively transports F^- as 2:1 F^-/**25** complex (Figure 10B),[62] but not the larger Cl^-, Br^- ,and I^-. Despite being capable of binding F^-, acyclic L,L-**48** and L,L-**49** (Figure 10A) do not exhibit F^- transport activity, showing the necessity of cyclic structure (Figure 10C, D). The influence of valinomycin (Vln), a macrocyclic K^+ carrier, on the transport activity of L,L-**25** suggests an electrogenic anion-transport mechanism (Figure 10E, F). Cyclic L,L-**25** and acyclic L,L-**48** and L,L-**49** are all inactive in transporting larger Cl^-, demonstrating the critical role of the cavity size in ion transport. With the "2 + 2" version larger macrocycles, for example, **28** (Figure 5A), preliminary results are encouraging in transporting hydrophilic neutral species. Diverse thiourea-based anion transporters have been developed,[75−79] most of which are short-chain-like or multidentate ligands focusing on transporting Cl^- of biomedical significance. Gale's group has demonstrated the advantages of acylthioureas as anion transporters, mainly via intramolecular hydrogen bonding.[80] Those observations have encouraged our explorations of anion binding and transportation of *N*-amidothioureas that are rich in hydrogen-bonding sites.

5. CONCLUSIONS AND PERSPECTIVES

In this Account, we describe our efforts to develop the *N*-acylamino acid amidothiourea motif, a versatile helical chiral building block. The introduction of an amide motif, RC(O)-NH−, next to a thiourea −NH group has first led to *N*-amidothioureas bearing a twisted N−N bond that undergoes a conformational change when binding an anion. The anion binding affinities are much higher despite the lower acidities of the thioureido −NHs. An ICT in the anion binding complex that generates a positive charge in the thiourea moiety results in an allosteric effect to reinforce binding to the anion. Making an amide from a chiral amino acid yields *N*-acylamino acid amidothiourea, which bears a β-turn structure. This represents the basic helical chiral building block with its two termini in close proximity. It is able to build peptide-like fluorescent beacons, template macrocyclization reactions, and form supramolecular helices. The formed helix is homochiral and the double helix exhibits a linear CD-*ee* dependence. The latter suggests the potential of spontaneous resolution, and we confirmed it by deriving alanine and phenylalanine into such helical derivatives that form multiple homochiral helices.

Developing new functions of this building block, by means of structural design, is a subject of future efforts. The four parts in the turn structure can be modified. First, the factors that influence the *trans,cis*-conformation of two N−H bonds in thiourea deserve further study. Second, the *N*′-alkylthiourea counterparts could be examined such that they might be introduced into the peptide backbone to tune peptide folding. Third, the amino acid residue could be derived to provide functional groups. Fourth, the *N*-acyl group could be explored in its influences on turn structure and interblock interactions.

The functions of forming multiple supramolecular helices warrant further efforts, e.g., for spontaneous resolution of other amino acids and beyond. Formation of helices via coordination and/or dynamic covalent bonding,[81] might be another avenue. Chiral sensing via helix formation is a new subject, with likely

https://doi.org/10.1021/acs.accounts.5c00490
Acc. Chem. Res. 2025, 58, 3046−3059

enhanced performance because of the cooperativity between interblock interactions and propagation of helicity. The supramolecular helices also hold promise as chiro-optic, chiro-electronic, and chiro-magnetic materials, among which chirality-induced spin selectivity (CISS) is a subject of current interest.[82] In this regard, the peptide-like fluorescent beacons forming exciplex would provide diverse structural frameworks, in view of the effect of chirality on the excited-state electron transfer under a magnetic field, important model systems for understanding CISS.[83]

The use of the helical chiral building block to template macrocyclization shall be extended to a great variety of macrocycles and cages that consist of a flexible turn motif and rigid arylamide motif. These hybrid macrocycles have abundant hydrogen-bonding sites, which would assemble into nanochannels and porous materials, capable of molecular encapsulation,[5] recognition, and transport[62] of guest species. The propagation of helicity can guide the hierarchical assembly of supramolecular helices and macrocycles into larger chiral frameworks with defined porosity and chirality. Incorporating photoactive, redox-active, or catalytically active units into the macrocyclic structure could lead to functional nanomaterials for optoelectronics, catalysis, or drug delivery. The potential of the chiral helical block, as a component of asymmetric organocatalysts could be explored, as encouraged by the preliminary investigations[51] and its capability of long-distance chirality transfer.[60]

AUTHOR INFORMATION

Corresponding Author

Yun-Bao Jiang − *College of Chemistry and Chemical Engineering and the MOE Key Laboratory of Spectrochemical Analysis and Instrumentation, Xiamen University, Xiamen 361005, China;* orcid.org/0000-0001-6912-8721; Email: ybjiang@xmu.edu.cn

Authors

Qian Wang − *College of Chemistry and Chemical Engineering and the MOE Key Laboratory of Spectrochemical Analysis and Instrumentation, Xiamen University, Xiamen 361005, China*

Si-Yi Liu − *College of Chemistry and Chemical Engineering and the MOE Key Laboratory of Spectrochemical Analysis and Instrumentation, Xiamen University, Xiamen 361005, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.accounts.5c00490

Notes

The authors declare no competing financial interest.

Biographies

Qian Wang received her Ph.D. in 2016 from Xiamen University under the supervision of Prof. Yun-Bao Jiang. She was as a joint Ph.D. student during 2010−2012 in Bowling Green State University with Prof. Peter Lu. Since 2016, Dr. Wang has worked as an engineer at Xiamen University, interested in the aggregation and gelation of peptides.

Si-Yi Liu is currently a Ph.D. student with Prof. Yun-Bao Jiang. Si-Yi received her bachelor degree from East China University of Science and Technology in 2021 and then started to pursue her Ph.D. at Xiamen University. Her research focuses on synthesis and applications of peptidomacrocycles.

Yun-Bao Jiang earned a Ph.D. in chemistry from Xiamen University, where he is now a professor. He has been a Humboldt fellow at the Max Planck Institute for Biophysical Chemistry and a university postdoc at the University of Hong Kong. Research in his group focuses on photophysics of electron/proton transfer and spectral sensing and molecular recognition.

ACKNOWLEDGMENTS

The work from our laboratories described here has lasted for ca. 30 years, during which many students and colleagues, whose names can be found in the cited references, have contributed a lot. Professors Tao Jiang, Xin Wu, and Liuyin Jiang are thanked for reading the draft. The research has been supported by the National Science Foundation of China (grants 92356308, 22241503, 21820102006, 91856118, 21435003, and 21521004) and by the Ministry of Education, the Ministry of Science and Technology of China and Fujian Provincial Natural Science Foundation of China (2024J08007 to QW).

REFERENCES

(1) Nie, L.; Li, Z.; Han, J.; Zhang, X.; Yang, R.; Liu, W.-X.; Wu, F.-Y.; Xie, J.-W.; Zhao, Y.-F.; Jiang, Y.-B. Development of *N*-Benzamidothioureas as a New Generation of Thiourea-Based Receptors for Anion Recognition and Sensing. *J. Org. Chem.* **2004**, *69* (19), 6449−6454.

(2) Yan, X.-S.; Wu, K.; Yuan, Y.; Zhan, Y.; Wang, J.-H.; Li, Z.; Jiang, Y.-B. *β*-Turn structure in glycinylphenylalanine dipeptide based *N*-amidothioureas. *Chem. Commun.* **2013**, *49* (79), 8943−8945.

(3) Yan, X.-S.; Zou, K.-S.; Cao, J.-L.; Li, X.-R.; Zhao, Z.-X.; Li, Z.; Wu, A.-A.; Liang, W.-Z.; Mo, Y.-R.; Jiang, Y.-B. Single-handed supramolecular double helix of homochiral bis(*N*-amidothiourea) supported by double crossed C−I···S halogen bonds. *Nat. Commun.* **2019**, *10*, 3610.

(4) Lin, X.; Kou, B.-H.; Cao, J.-L.; Weng, P.-M.; Yan, X.-S.; Li, Z.; Jiang, Y.-B. Spontaneous Resolution of Helical Building Blocks through the Formation of Homochiral Helices in Two Dimensions. *Angew. Chem., Int. Ed.* **2022**, *61* (34), No. e202205914.

(5) Gou, F.; Shi, D.; Kou, B.-H.; Li, Z.; Yan, X.-S.; Wu, X.; Jiang, Y.-B. One-Pot Cyclization to Large Peptidomimetic Macrocycles by In Situ-Generated *β*-Turn-Enforced Folding. *J. Am. Chem. Soc.* **2023**, *145* (17), 9530−9539.

(6) Favre, H. A.; Powell, W. H. *Nomenclature of Organic Chemistry*; The Royal Society of Chemistry, 2013.

(7) Gale, P. A. From Anion Receptors to Transporters. *Acc. Chem. Res.* **2011**, *44* (3), 216−226.

(8) Wang, Q.-Q. Anion Recognition-Directed Supramolecular Catalysis with Functional Macrocycles and Molecular Cages. *Acc. Chem. Res.* **2024**, *57* (21), 3227−3240.

(9) Li, A.-F.; Wang, J.-H.; Wang, F.; Jiang, Y.-B. Anion complexation and sensing using modified urea and thiourea-based receptors. *Chem. Soc. Rev.* **2010**, *39* (10), 3729−3745.

(10) Ovian, J. M.; Jacobsen, E. N. A catalytic one-two punch. *Science* **2019**, *366* (6468), 948−949.

(11) Sentürk, B.; Butschke, B.; Eisenreich, F. Thiosemicarbazones as versatile photoswitches with light-controllable supramolecular activity. *Chem. Sci.* **2025**, *16* (7), 3130−3140.

(12) Kikkawa, K.; Sumiya, Y.; Okazawa, K.; Yoshizawa, K.; Itoh, Y.; Aida, T. Thiourea as a "Polar Hydrophobic" Hydrogen-Bonding Motif: Application to Highly Durable All-Underwater Adhesion. *J. Am. Chem. Soc.* **2024**, *146* (30), 21168−21175.

(13) Wezenberg, S. J.; Chen, L.-J.; Bos, J. E.; Feringa, B. L.; Howe, E. N. W.; Wu, X.; Siegler, M. A.; Gale, P. A. Photomodulation of

Transmembrane Transport and Potential by Stiff-Stilbene Based Bis(thio)ureas. *J. Am. Chem. Soc.* **2022**, *144* (1), 331−338.
(14) Berry, S. N.; Soto-Cerrato, V.; Howe, E. N. W.; Clarke, H. J.; Mistry, I.; Tavassoli, A.; Chang, Y.-T.; Pérez-Tomás, R.; Gale, P. A. Fluorescent transmembrane anion transporters: shedding light on anionophoric activity in cells. *Chem. Sci.* **2016**, *7* (8), 5069−5077.
(15) Valkenier, H.; Dias, C. M.; Porter Goff, K. L.; Jurček, O.; Puttreddy, R.; Rissanen, K.; Davis, A. P. Sterically geared tris-thioureas; transmembrane chloride transporters with unusual activity and accessibility. *Chem. Commun.* **2015**, *51* (75), 14235−14238.
(16) Valkenier, H.; Judd, L. W.; Li, H.; Hussain, S.; Sheppard, D. N.; Davis, A. P. Preorganized Bis-Thioureas as Powerful Anion Carriers: Chloride Transport by Single Molecules in Large Unilamellar Vesicles. *J. Am. Chem. Soc.* **2014**, *136* (35), 12507−12512.
(17) Johnson, T. G.; Sadeghi-Kelishadi, A.; Langton, M. J. A Photo-responsive Transmembrane Anion Transporter Relay. *J. Am. Chem. Soc.* **2022**, *144* (23), 10455−10461.
(18) Mishra, A.; Batra, S. Thiourea and Guanidine Derivatives as Antimalarial and Antimicrobial Agents. *Curr. Top. Med. Chem.* **2013**, *13* (16), 2011−2025.
(19) Arshad, N.; Parveen, U.; Channar, P. A.; Saeed, A.; Saeed, W. S.; Perveen, F.; Javed, A.; Ismail, H.; Mir, M. I.; Ahmed, A.; Azad, B.; Khan, I. Investigation of Newly Synthesized Bis-Acyl-Thiourea Derivatives of 4-Nitrobenzene-1,2-Diamine for Their DNA Binding, Urease Inhibition, and Anti-Brain-Tumor Activities. *Molecules* **2023**, *28* (6), 2707.
(20) Rahman, F. U.; Bibi, M.; Altaf, A. A.; Tahir, M. N.; Ullah, F.; Zia-Ur-Rehman; Khan, E. Zn, Cd and Hg complexes with unsymmetric thiourea derivatives; syntheses, free radical scavenging and enzyme inhibition essay. *J. Mol. Struct.* **2020**, *1211*, 128096.
(21) Srivastava, A. K.; Pasala, R.; Minhas, P. S.; Suprasanna, P. Chapter Four - Plant Bioregulators for Sustainable Agriculture: Integrating Redox Signaling as a Possible Unifying Mechanism. *Adv. Agron.* **2016**, *137*, 237−278.
(22) Mahlau, M.; List, B. Asymmetric counteranion-directed catalysis: concept, definition, and applications. *Angew. Chem., Int. Ed.* **2013**, *52* (2), 518−533.
(23) Brak, K.; Jacobsen, E. N. Asymmetric Ion-Pairing Catalysis. *Angew. Chem., Int. Ed.* **2013**, *52* (2), 534−561.
(24) Bonizzoni, M.; Fabbrizzi, L.; Taglietti, A.; Tiengo, F. Benzylideneamino)thioureas − Chromogenic Interactions with Anions and N−H Deprotonation. *Eur. J. Org. Chem.* **2006**, *2006* (16), 3567−3574.
(25) Duke, R. M.; Gunnlaugsson, T. Fluorescent sensing of anions using a bis-quinoxaline amidothiourea based supramolecular cleft; an example of an anion-induced deprotonation event. *Tetrahedron Lett.* **2010**, *51* (41), 5402−5405.
(26) Gunnlaugsson, T.; Kruger, P. E.; Jensen, P.; Tierney, J.; Ali, H. D. P.; Hussey, G. M. Colorimetric "Naked Eye" Sensing of Anions in Aqueous Solution. *J. Org. Chem.* **2005**, *70* (26), 10875−10878.
(27) Esteban-Gómez, D.; Fabbrizzi, L.; Licchelli, M. Why, on Interaction of Urea-Based Receptors with Fluoride, Beautiful Colors Develop. *J. Org. Chem.* **2005**, *70* (14), 5717−5720.
(28) Amendola, V.; Esteban-Gómez, D.; Fabbrizzi, L.; Licchelli, M. What Anions Do to N−H-Containing Receptors. *Acc. Chem. Res.* **2006**, *39* (5), 343−353.
(29) Yang, D.; Ng, F.-F.; Li, Z.-J.; Wu, Y.-D.; Chan, K. W. K.; Wang, D.-P. An Unusual Turn Structure in Peptides Containing α-Aminoxy Acids. *J. Am. Chem. Soc.* **1996**, *118* (40), 9794−9795.
(30) Gale, P. A.; Howe, E. N. W.; Wu, X. Anion Receptor Chemistry. *Chem.* **2016**, *1* (3), 351−422.
(31) Duke, R. M.; O'Brien, J. E.; McCabe, T.; Gunnlaugsson, T. Colorimetric sensing of anions in aqueous solution using a charge neutral, cleft-like, amidothiourea receptor: tilting the balance between hydrogen bonding and deprotonation in anion recognition. *Org. Biomol. Chem.* **2008**, *6* (22), 4089−4092.
(32) Duke, R. M.; McCabe, T.; Schmitt, W.; Gunnlaugsson, T. Recognition and Sensing of Biologically Relevant Anions in Alcohol and Mixed Alcohol−Aqueous Solutions Using Charge Neutral Cleft-Like Glycol-Derived Pyridyl−Amidothiourea Receptors. *J. Org. Chem.* **2012**, *77* (7), 3115−3126.
(33) Lincheneau, C.; Duke, R. M.; Gunnlaugsson, T. Formation of luminescent terbium(iii) self-assemblies from pyridyl bis-amidothioureas based ligands in MeOH and in water−DMSO solutions and their use in anion sensing application. *Org. Biomol. Chem.* **2012**, *10* (30), 6069−6073.
(34) Basu, A.; Das, G. Amidothiourea as a potential receptor for organic bases by resonance assisted low barrier hydrogen bond formation: Structure and Hirshfeld surface analysis. *CrystEngComm* **2012**, *14* (9), 3306−3314.
(35) Basu, A.; Dey, S. K.; Das, G. Amidothiourea based colorimetric receptors for basic anions: evidence of anion induced deprotonation of amide −NH proton and hydroxide induced anion···π interaction with the deprotonated receptors. *RSC Adv.* **2013**, *3* (18), 6596−6605.
(36) Basu, A.; Das, G. Neutral Acyclic Anion Receptor with Thiadiazole Spacer: Halide Binding Study and Halide-Directed Self-Assembly in the Solid State. *Inorg. Chem.* **2012**, *51* (2), 882−889.
(37) Lehnherr, D.; Ford, D. D.; Bendelsmith, A. J.; Kennedy, C. R.; Jacobsen, E. N. Conformational Control of Chiral Amido-Thiourea Catalysts Enables Improved Activity and Enantioselectivity. *Org. Lett.* **2016**, *18* (13), 3214−3217.
(38) Zuend, S. J.; Coughlin, M. P.; Lalonde, M. P.; Jacobsen, E. N. Scaleable catalytic asymmetric Strecker syntheses of unnatural α-amino acids. *Nature* **2009**, *461* (7266), 968−970.
(39) Lin, S.; Jacobsen, E. N. Thiourea-catalysed ring opening of episulfonium ions with indole derivatives by means of stabilizing non-covalent interactions. *Nat. Chem.* **2012**, *4* (10), 817−824.
(40) Wang, B.; Fan, S.; Zhang, C.; Sun, J. Catalytic Enantioselective α-Fluorination of Ketones with CsF. *J. Am. Chem. Soc.* **2025**, *147* (12), 10059−10065.
(41) Lovinger, G. J.; Sak, M. H.; Jacobsen, E. N. Catalysis of an SN2 pathway by geometric preorganization. *Nature* **2024**, *632* (8027), 1052−1059.
(42) Etter, M. C. Encoding and decoding hydrogen-bond patterns of organic compounds. *Acc. Chem. Res.* **1990**, *23* (4), 120−126.
(43) Bordwell, F. G. Equilibrium acidities in dimethyl sulfoxide solution. *Acc. Chem. Res.* **1988**, *21* (12), 456−463.
(44) Wu, F.-Y.; Li, Z.; Wen, Z.-C.; Zhou, N.; Zhao, Y.-F.; Jiang, Y.-B. A Novel Thiourea-Based Dual Fluorescent Anion Receptor with a Rigid Hydrazine Spacer. *Org. Lett.* **2002**, *4* (19), 3203−3205.
(45) Wu, F.-Y.; Li, Z.; Guo, L.; Wang, X.; Lin, M.-H.; Zhao, Y.-F.; Jiang, Y.-B. A unique NH-spacer for *N*-benzamidothiourea based anion sensors. Substituent effect on anion sensing of the ICT dual fluorescent *N*-(*p*-dimethylaminobenzamido)-*N*′-arylthioureas. *Org. Biomol. Chem.* **2006**, *4* (4), 624−630.
(46) Yang, R.; Liu, W.-X.; Shen, H.; Huang, H.-H.; Jiang, Y.-B. Anion Binding in Aqueous Solutions by *N*-(Isonicotinamido)-*N*′-phenylthiourea-Based Simple Synthetic Neutral Receptors. Role of the Hydrophobic Microenvironment of the Receptor Molecule. *J. Phys. Chem. B* **2008**, *112* (16), 5105−5110.
(47) Gunnlaugsson, T.; Davis, A. P.; Hussey, G. M.; Tierney, J.; Glynn, M. Design, synthesis and photophysical studies of simple fluorescent anion PET sensors using charge neutral thiourea receptors. *Org. Biomol. Chem.* **2004**, *2* (13), 1856−1863.
(48) Gunnlaugsson, T.; Davis, A. P.; Glynn, M. Fluorescent photoinduced electron transfer (PET) sensing of anions using charge neutral chemosensors. *Chem. Commun.* **2001**, *24*, 2556−2557.
(49) Weller, A. Electron-transfer and complex formation in the excited state. *Pure Appl. Chem.* **1968**, *16* (1), 115−124.
(50) de Silva, A. P.; Gunaratne, H. Q. N.; Gunnlaugsson, T.; Huxley, A. J. M.; McCoy, C. P.; Rademacher, J. T.; Rice, T. E. Signaling Recognition Events with Fluorescent Sensors and Switches. *Chem. Rev.* **1997**, *97* (5), 1515−1566.
(51) Liu, W.-X.; Jiang, Y.-B. *N*-Amidothiourea based PET chemosensors for anions. *Org. Biomol. Chem.* **2007**, *5* (11), 1771−1775.
(52) Ashokkumar, P.; Weißhoff, H.; Kraus, W.; Rurack, K. Test-Strip-Based Fluorometric Detection of Fluoride in Aqueous Media

https://doi.org/10.1021/acs.accounts.5c00490
Acc. Chem. Res. 2025, 58, 3046−3059

with a BODIPY-Linked Hydrogen-Bonding Receptor. *Angew. Chem., Int. Ed.* **2014**, *53* (8), 2225−2229.
(53) Koteeswari, R.; Ashokkumar, P.; Malar, E. J. P.; Ramakrishnan, V. T.; Ramamurthy, P. Highly selective, sensitive and quantitative detection of Hg^{2+} in aqueous medium under broad pH range. *Chem. Commun.* **2011**, *47* (27), 7695−7697.
(54) Wang, H.; Chan, W.-H.; Lee, A. W. M. Cholic acid-based fluorescent probes for enantioselective recognition of trifunctional amino acids. *Org. Biomol. Chem.* **2008**, *6* (5), 929−934.
(55) Liu, W.-X.; Yang, R.; Li, A.-F.; Li, Z.; Gao, Y.-F.; Luo, X.-X.; Ruan, Y.-B.; Jiang, Y.-B. *N*-(Acetamido)thiourea based simple neutral hydrogen-bonding receptors for anions. *Org. Biomol. Chem.* **2009**, *7* (19), 4021−4028.
(56) Jiang, Q.-Q.; Darhkijav, B.; Liu, H.; Wang, F.; Li, Z.; Jiang, Y.-B. Anion Binding of *N*-(*o*-Methoxybenzamido)thioureas: Contribution of the Intramolecular Hydrogen Bond in the *N*-Benzamide Moiety. *Chem.-Asian J.* **2010**, *5* (3), 543−549.
(57) Wang, F.; He, W.-B.; Wang, J.-H.; Yan, X.-S.; Zhan, Y.; Ma, Y.-Y.; Ye, L.-C.; Yang, R.; Cai, F.; Li, Z.; Jiang, Y.-B. Amino acid based chiral *N*-amidothioureas. Acetate anion binding induced chirality transfer. *Chem. Commun.* **2011**, *47* (42), 11784−11786.
(58) Zhang, Y.-H.; Yan, X.-S.; Cao, J.-L.; Weng, P.-M.; Miao, D.-Y.; Li, Z.; Jiang, Y.-B. Turn Conformation of β-Amino Acid-Based Short Peptides Promoted by an Amidothiourea Moiety at C-Terminus. *J. Org. Chem.* **2020**, *85* (15), 9844−9849.
(59) Yan, X.-S.; Luo, H.; Zou, K.-S.; Cao, J.-L.; Li, Z.; Jiang, Y.-B. Short Azapeptides of Folded Structures in Aqueous Solutions. *ACS Omega* **2018**, *3* (5), 4786−4790.
(60) Yuan, Y.; Yan, X.-S.; Li, X.-R.; Cao, J.-L.; Li, Z.; Jiang, Y.-B. Folded short azapeptide for conformation switching-based fluorescence sensing. *Chem. Commun.* **2017**, *53* (98), 13137−13140.
(61) Nishino, N.; Xu, M.; Mihara, H.; Fujimoto, T.; Ueno, Y.; Kumagai, H. Sequence dependence in solid-phase-synthesis-cyclization-cleavage for Cyclo(-arginyl-glycyl-aspartyl-phenylglycyl-). *Tetrahedron Lett.* **1992**, *33* (11), 1479−1482.
(62) Zhao, Z.-X.; Zhang, M.-M.; Tang, B.-L.; Weng, P.-M.; Zhang, Y.-Y.; Yan, X.-S.; Li, Z.; Jiang, Y.-B. Transmembrane Fluoride Transport by a Cyclic Azapeptide With Two β-Turns. *Front. Chem.* **2021**, *8*, 621323.
(63) Yan, X.-S.; Weng, P.-M.; Shi, D.; Jiang, Y.-B. Supramolecular helices from helical building blocks via head-to-tail intermolecular interactions. *Chem. Commun.* **2021**, *57* (94), 12562−12574.
(64) Cao, J.-L.; Yan, X.-S.; He, W.-B.; Li, X.-R.; Li, Z.; Mo, Y.-R.; Liu, M.-L.; Jiang, Y.-B. C−I···π Halogen Bonding Driven Supramolecular Helix of Bilateral *N*-Amidothioureas Bearing β-Turns. *J. Am. Chem. Soc.* **2017**, *139* (19), 6605−6610.
(65) Yan, X.; Wang, Q.; Chen, X.; Jiang, Y.-B. Supramolecular Chiral Aggregates Exhibiting Nonlinear CD−ee Dependence. *Adv. Mater.* **2020**, *32* (41), 1905667.
(66) Mukherjee, A.; Tothadi, S.; Desiraju, G. R. Halogen Bonds in Crystal Engineering: Like Hydrogen Bonds yet Different. *Acc. Chem. Res.* **2014**, *47* (8), 2514−2524.
(67) Xia, Y.; Hao, A.; Xing, P. Chalcogen and Pnictogen Bonding-Modulated Multiple-Constituent Chiral Self-Assemblies. *ACS Nano* **2023**, *17* (21), 21993−22003.
(68) Hu, Z.-Y.; Du, M.; Li, W.; Huang, X.; Ma, R.; Li, Y.; Shen, R.-Z.; Wang, T.; Liu, C.-Z.; Li, Z.-T. Selective Self-Assembly of Supramolecular Helices and Macrocycles Directed by Halogen Bonding. *Chem.-Eur. J.* **2025**, *31* (7), No. e202403821.
(69) Weng, P.-M.; Yan, X.-S.; Cao, J.-L.; Li, Z.; Jiang, Y.-B. Intramolecular chalcogen bonding to tune the molecular conformation of helical building blocks for a supramolecular helix. *Chem. Commun.* **2022**, *58* (44), 6461−6464.
(70) Wang, Y.; Niu, D.; Ouyang, G.; Liu, M. Double helical π-aggregate nanoarchitectonics for amplified circularly polarized luminescence. *Nat. Commun.* **2022**, *13*, 1710.
(71) Weng, P.-M.; Yan, X.-S.; Jiang, Y.-B. Formation of Multiple Supramolecular Helices for Spontaneous Resolution. *ChemSystemsChem.* **2023**, *5* (4), No. e202200043.
(72) Weng, P.; Lin, X.; Cai, Y.-L.; Yan, X.; Cao, J.; Li, Z.; Jiang, Y.-B. Role of solvent in the spontaneous resolution of amino acids via formation of supramolecular helices. *Cell Rep. Phys. Sci.* **2025**, *6* (4), 102521.
(73) Yan, X.-S.; Cao, J.-L.; Luo, H.; Li, Z.; Cao, Z.-X.; Mo, Y.-R.; Jiang, Y.-B. Heterochiral coupling to bilateral β-turn structured azapeptides bearing two remote chiral centers. *Nat. Commun.* **2024**, *15*, 9271.
(74) Zhao, Z.-X.; Tang, B.-L.; Yan, X.-S.; Wu, X.; Li, Z.; Gale, P. A.; Jiang, Y.-B. Crown ether-thiourea conjugates as ion transporters. *Front. Chem. Sci. Eng.* **2022**, *16* (1), 81−91.
(75) Busschaert, N.; Gale, P. A.; Haynes, C. J. E.; Light, M. E.; Moore, S. J.; Tong, C. C.; Davis, J. T.; Harrell, W. A., Jr. Tripodal transmembrane transporters for bicarbonate. *Chem. Commun.* **2010**, *46* (34), 6252−6254.
(76) Busschaert, N.; Wenzel, M.; Light, M. E.; Iglesias-Hernández, P.; Pérez-Tomás, R.; Gale, P. A. Structure−Activity Relationships in Tripodal Transmembrane Anion Transporters: The Effect of Fluorination. *J. Am. Chem. Soc.* **2011**, *133* (35), 14136−14148.
(77) Wenzel, M.; Light, M. E.; Davis, A. P.; Gale, P. A. Thiourea isosteres as anion receptors and transmembrane transporters. *Chem. Commun.* **2011**, *47* (27), 7641−7643.
(78) Busschaert, N.; Karagiannidis, L. E.; Wenzel, M.; Haynes, C. J. E.; Wells, N. J.; Young, P. G.; Makuc, D.; Plavec, J.; Jolliffe, K. A.; Gale, P. A. Synthetic transporters for sulfate: a new method for the direct detection of lipid bilayer sulfate transport. *Chem. Sci.* **2014**, *5* (3), 1118−1127.
(79) Valkenier, H.; Haynes, C. J. E.; Herniman, J.; Gale, P. A.; Davis, A. P. Lipophilic balance − a new design principle for transmembrane anion carriers. *Chem. Sci.* **2014**, *5* (3), 1128−1134.
(80) Haynes, C. J. E.; Busschaert, N.; Kirby, I. L.; Herniman, J.; Light, M. E.; Wells, N. J.; Marques, I.; Félix, V.; Gale, P. A. Acylthioureas as anion transporters: the effect of intramolecular hydrogen bonding. *Org. Biomol. Chem.* **2014**, *12* (1), 62−72.
(81) Yu, Y.; Shen, S.-H.; Chen, J.-B.; Ding, Q.-R.; Zhang, H.-X.; Zhang, J. Homochiral Single Crystals of Helical Polymer Nanotubes: Synthesis and Application. *J. Am. Chem. Soc.* **2025**, *147*, 20770−20777.
(82) Bloom, B. P.; Paltiel, Y.; Naaman, R.; Waldeck, D. H. Chiral Induced Spin Selectivity. *Chem. Rev.* **2024**, *124* (4), 1950−1991.
(83) Eckvahl, H. J.; Copley, G.; Young, R. M.; Krzyaniak, M. D.; Wasielewski, M. R. Detecting Chirality-Induced Spin Selectivity in Randomly Oriented Radical Pairs Photogenerated by Hole Transfer. *J. Am. Chem. Soc.* **2024**, *146* (34), 24125−24132.

https://doi.org/10.1021/acs.accounts.5c00490
Acc. Chem. Res. 2025, 58, 3046−3059