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One-Pot Enantioselective Synthesis of Functionalized Pyranocoumarins and 2-Amino-4*H*-chromenes: Discovery of a Type of Potent Antibacterial Agent

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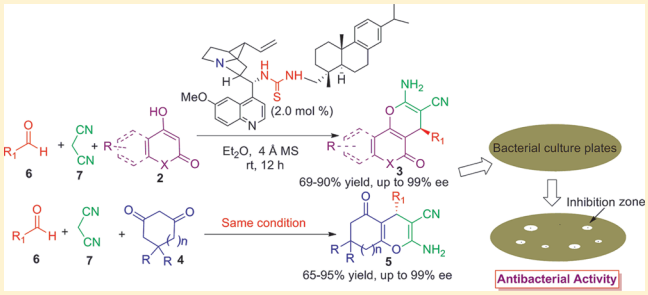
Supporting Information

ABSTRACT: Function-oriented design and synthesis of chiral small molecules with novel activity is a key goal in modern organic chemistry. As multiple antibiotic-resistant pathogens are emerging and causing serious diseases, the need for practical routes for the development of new types of antibacterial agents is very urgent. Herein, we present a highly efficient process for the synthesis of optically active pyranocoumarins and 2-amino-4*H*-chromenes through an organocatalytic Knoevenagel/Michael/cyclization sequence, and the preliminary biological studies of these new heterocyclic compounds revealed potent antibacterial activity. This study provides a novel strategy for further research and development of new types of antibacterial agents effective against human pathogens.



INTRODUCTION

Coumarins and pyrans are ubiquitous in many important biologically active molecules, synthetic drugs, and drug candidates (Figure 1),[1] which have shown biological and pharmacological activities.[2] Consequently, the incorporation of the two structural features into interesting motifs, such as pyranocoumarins and 2-amino-4*H*-chromenes, may have some significance to the design of new therapeutic agents.[3] However, to date, the asymmetric catalytic approaches to construct these privileged heterocycles in enantiomerically pure form are still surprisingly rare.[4] In particular, the evaluation of chiral pyranocoumarins and 2-amino-4*H*-chromenes for biological activities and studies on structure−activity relationships are scarce and remain a great challenge.

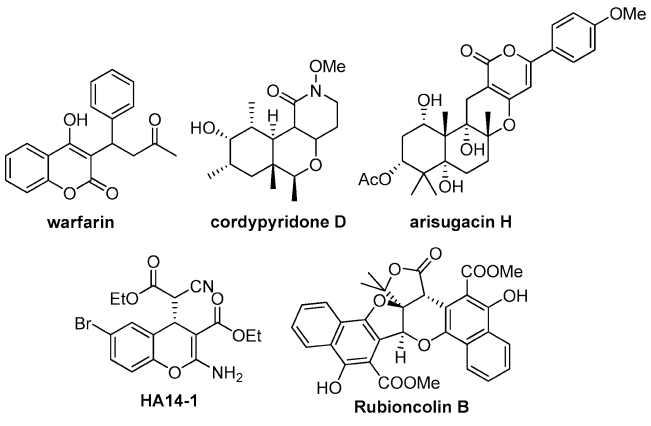


Figure 1. Natural products pyranocoumarins and 2-amino-4*H*-chromenes.

Recently, organocatalytic domino reactions[5] where multiple carbon−carbon bond formations are achieved in a single operation using simple experimental procedures have become one of the most powerful methods for the synthesis of useful organic molecules. As a result, significant advances have been made in this flourishing area by several groups. Significant progress has been made using α,β-unsaturated aldehydes, ketones, esters, imides, and nitroolefins as electrophiles.[6] In contrast, less progress has been made on α,α-dicyanoolefins, probably because of their high chemical reactivity.[7] Considering that α,α-dicyanoolefins could be readily prepared from a simple Knoevenagel condensation of aldehydes with malononitrile and that the nitrile group could be easily transformed to other important groups, research into a suitable catalytic system for α,α-dicyanoolefin addition is particularly appealing. On the other hand, as intramolecular domino reactions have become one of the most powerful methods for the construction of useful organic molecules, multiple-component intermolecular

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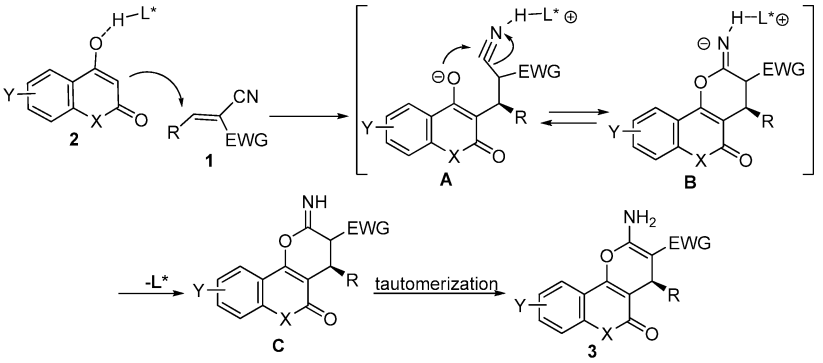
Scheme 1. Strategy for Synthesis of Chiral Pyranocoumarins by Chiral Tertiary Amines



domino reactions with highly enantioselectivity still remain elusive in current organic synthesis.[8]

RESULTS AND DISCUSSION

As part of our continuous interest in developing new methods for the synthesis of useful compounds,[9] we recently succeeded in developing a novel class of bifunctional thiourea catalysts based on abietic acid[10] and applied it to enantioselective synthesis.[9a−c] Encouraged by these successful efforts and aiming to demonstrate the efficiency and generality of this abietic-acid-derived thiourea bifunctional catalysis, we fixed our recent attention on employing this novel catalysis for the asymmetric synthesis of optically active pyranocoumarins and 2-amino-4*H*-chromenes prepared from simple and easily available starting materials under mild reaction conditions.

We envisioned that in the presence of a chiral tertiary amine-thiourea, 4-hydroxycoumarins **2** might be activated through a hydrogen bond between the nitrogen atom of the chiral tertiary amine-thiourea with the hydrogen of the hydroxyl.[11] Then the electron-rich α-carbon atom of **2** attacks the electron-deficient cyanoolefins **1** to generate the Micheal adducts **A**. Subsequently, intramolecular cyclization of **A** afforded the cyclized adducts **B**, and finally, tautomerization of **C** obtained the desired final product **3** (Scheme 1).

To explore the possibility of the proposed Michael addition/cyclization sequence, initially, we used the reaction of 2-benzylidenemalononitrile with 4-hydroxycoumarin as a model reaction, and a variety of bifunctional organocatalysts were screened at room temperature in toluene for the synthesis of the optically active pyranocoumarins (Figure 2, Table 1). The results showed that the bifunctional thiourea catalyst derived from quinine amine[12] based on abietic acid exhibited good activity and high enantioselectivity (Table 1, entry 6), while other thiourea catalysts derived from diaminocyclohexane (Table 1, entries 1−5), and cinchonine or quinine derivatives (Table 1, entries 7−11) provided disappointing results. Solvent optimization results showed that ether was a better solvent according to the enantioselectivity (up to 94% ee, Table 1, entry 13). Satisfactorily, little decrease in enantioselectivity or yield was observed when the loading of tertiary amine-thiourea **L6** was lowered to 2.0 mol % (Table 1, entry 15).

With optimal conditions established, we then examined the scope of the reaction for the construction of various optically active pyranocoumarins, and the results are summarized in Table 2. In general, the reaction proceeded smoothly to afford the desired products in good yields and excellent enantioselectivities. For the reaction with 4-hydroxycoumarin **2a**, a wide range of substituted aromatic α,α-dicyanoolefins **1** were

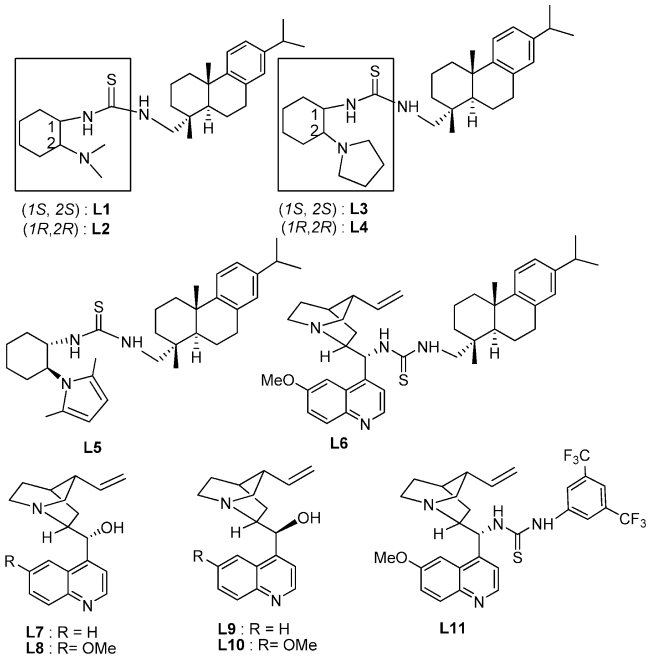


Figure 2. Organocatalysts used in this study.

examined (Table 2, entries 1−10). It was found that α,α-dicyanoolefins **1** with either electron-withdrawing or electron-donating groups on the phenyl ring provided good yields (75−90%) and excellent enantioselectivities (83−98% ee values). In addition, good results were also obtained by using 2-furyl, 3-thienyl, and *n*-hexyl as substituents of α,α-dicyanoolefins **1** (Table 2, entries 11−13). And various substituted 4-hydroxycoumarins are also suited under this system (Table 2, entries 14−16). Importantly, this efficient approach can also be utilized for the asymmetric synthesis of optically pure pyranone using the reaction of 4-hydroxy-6-methyl-2-pyrone **2e** with 2-benzylidenemalononitrile **1a** (Table 2, entry 17). Furthermore, cyanoacrylates are also suitable to afford the desirable products (Table 2, entries 18−19). The absolute configuration of products were determined to be *R* by using single crystal X-ray diffraction of **3f**.[13]

Encouraged by the results achieved above, we wished this effective catalysis system could be extended to the asymmetric synthesis of other useful organic molecules, such as 2-amino-4-*H*-chromenes. Considering their potential versatility as active-determining building blocks in some biologically active natural products,[14] to date, efficient protocols for construction of the optically pure form have not been achieved.[15] Satisfactorily, as

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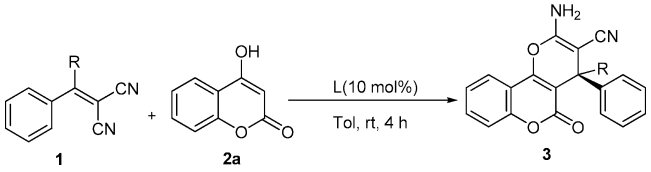
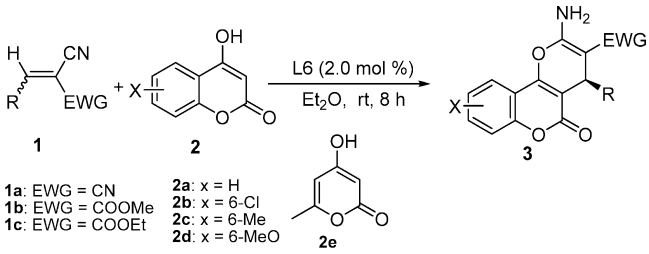
Table 1. Catalyst Screening and Optimization of Reaction Conditions[a]



entry	catalyst	R	yield[b] (%)	ee[c] (%)
1	**L1**	H	**3a**/77	44[d]
2	**L2**	H	**3a**/74	42
3	**L3**	H	**3a**/80	69[d]
4	**L4**	H	**3a**/82	70
5	**L5**	H	<10	n.d.[e]
6	**L6**	H	**3a**/92	87
7	**L7**	H	**3a**/81	39
8	**L8**	H	**3a**/76	35
9	**L9**	H	**3a**/74	53[d]
10	**L10**	H	**3a**/70	37[d]
11	**L11**	H	**3a**/75	38
12	**L6**	CH_3	<10	n.d.[e]
13[f]	**L6**	H	**3a**/90	94
14[f,g]	**L6**	H	**3a**/91	93
15[f,h]	**L6**	H	**3a**/90	93

[a]Unless otherwise specified, the reaction was carried out with **1a** (0.2 mmol) and **2a** (0.3 mmol) in the presence of an organocatalyst **L** (0.02 mmol) in toluene (2.0 mL) at rt for 4 h. [b]Isolated yield. [c]Determined by chiral HPLC on a Chiralpak OD column. [d]The opposite configuration. [e]Not determined. [f]The reaction was conducted in Et_2O (2.0 mL). [g]5.0 mol % of ligand loading for 6 h. [h]2.0 mol % of ligand loading for 8 h.

Table 2. Asymmetric Synthesis of 3,4-Dihydropyrano[c]chromenes via Two-Component Reactions[a]



entry	R	sm	yield[b] (%)	ee[c] (%)
1	Ph	**1a**/**2a**	**3a**/90	93
2	4-ClPh	**1a**/**2a**	**3b**/87	94
3	4-FPh	**1a**/**2a**	**3c**/83	98
4	4-BrPh	**1a**/**2a**	**3d**/89	96
5	3-ClPh	**1a**/**2a**	**3e**/81	87
6	3-BrPh	**1a**/**2a**	**3f**/75	90
7	3-MeOPh	**1a**/**2a**	**3g**/78	83
8	2-FPh	**1a**/**2a**	**3h**/87	93
9	2-BrPh	**1a**/**2a**	**3i**/80	88
10	2-MePh	**1a**/**2a**	**3j**/81	96
11	2-furyl	**1a**/**2a**	**3k**/72	99
12	3-thienyl	**1a**/**2a**	**3l**/88	95
13	*n*-hexyl	**1a**/**2a**	**3m**/69	77
14	Ph	**1a**/**2b**	**3n**/86	98
15	Ph	**1a**/**2c**	**3o**/82	96
16	Ph	**1a**/**2d**	**3p**/81	90
17	Ph	**1a**/**2e**	**3q**/82	93
18	Ph	**1b**/**2a**	**3r**/85	80
19	Ph	**1c**/**2a**	**3s**/83	92

[a]Unless otherwise specified, the reaction was carried out with **1** (0.2 mmol) and **2** (0.3 mmol) in the presence of an organocatalyst **L6** (0.02 mmol) and Et_2O (2.0 mL) at rt for 8 h. [b]Isolated yield. [c]Determined by HPLC on a Chiralpak AD or OD column, and the configuration was assigned by comparison of HPLC date and X-ray crystal data of **3f**.

shown in Table 3, in general, the reaction proceeded smoothly to afford various kinds of 2-amino-4-*H*-chromenes **5** in good yields (71−95%) and excellent enantioselectivities (up to 99% ee). More importantly, when cyclohexane-1,2-dione **4c** was used as nucleophile, the reaction could proceed well to give the desired product in good yield (67%) and moderate enantioselectivities (77% ee, Scheme 2). In addition, good results were also obtained by using naphthalen-1-ol **4d** and naphthalene-1,3-diol **4e** as substrates (up to 84% yield and 83% ee, Scheme 3).

More importantly, pyranocoumarins and 2-amino-4-*H*-chromenes could be readily obtained without any loss of enantioselectivies when the condition was extended to one-pot, three-component intermolecular domino reactions among aromatic aldehyde, malononitrile, and 4-hydroxycoumarin or cyclohexane-1,3-dione (Scheme 4).[16]

Coumarin and chromen derivatives have been reported to have various biological activities, such as anticoagulant, anticancer, anti-HIV, and apoptosis-inducing activities.[17] However, other biological activities, such as antibacterial activity, have not been successfully exploited. So in this study, some of the synthesized compounds **3a−s** and **5a−v** were tested for their antibacterial activities at concentrations of 3.125, 6.25, 12.5, 25.0, 50.0, 100.0, and 200.0 μg/mL using a standard broth microdilution method.[18] Antibacterial activity studies showed that the coumarin-based compounds, such as **3d**, **3g**, **3j**, **3n**, **3q**, and **3r**, were only very slightly active against standard reference strains of *Staphylococcus aureus* (CMCC 26003) and *Escherichia coli* (CMCC 44102). Interestingly, 2-amino-4*H*-chromene derivatives exhibited distinct antibacterial activity against *S. aureus* (CMCC 26003). As summarized in Table 4, optically active **5u** (MIC = 6.25 μg/mL) was 2 times more efficient than kanamycin sulfate (MIC = 15.625 μg/mL), a well-known antibiotic. And **5u** with a hydroxyl group at the 5-position was about 50-fold more active than the lead compound **5t** (MIC = 300.0 μg/mL) against *S. aureus*. This phenomenon suggests that the hydroxyl is a key functional group of 2-amino-4*H*-chromenes that enhances the inhibition effect on the growth of *S. aureus*. In addition, the optically active **5u** was 4 times more efficient than the racemic form (MIC = 25.0 μg/mL). The 4-chlorophenyl analogue **5v** (MIC = 6.25 μg/mL) was equally potent as **5u**.

Cytotoxicity tests for new a therapeutic agent are necessary before it can be declared as a potential medicine for any disease. Having identified a potential agent with antibacterial activity, the next question is whether this antibacterial agent has selectivity between bacteria and human cells. We chose a hemolysis experiment as a model to test the acute cytotoxicity of these compounds. And the acute cytotoxicity of **5u** (racemic), **5u**, and **5v** was examined as according to Ryan and co-workers with a little modification.[19] Blood specimens were freshly collected from mice and different adult human donors. Solutions of different concentrations were added to the erythrocytes and incubated for 60 min at 37 °C; 0.2% Triton-X

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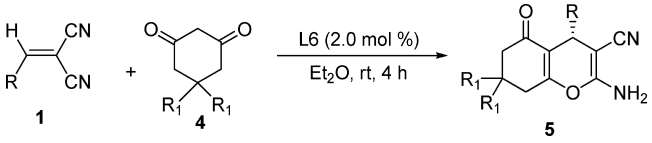
Table 3. Asymmetric Synthesis of 2-Amino-4*H*-chromenes via Two-Component Reactions[a]



1 4 5

entry	R	R_1	yield[b] (%)	ee[c] (%)
1	Ph	**4a**/H	**5a**/94	96
2	4-ClPh	**4a**/H	**5b**/90	95
3	4-BrPh	**4a**/H	**5c**/91	93
4	4-FPh	**4a**/H	**5d**/87	85
5	4-CNPh	**4a**/H	**5e**/95	80
6	4-MeOPh	**4a**/H	**5f**/89	79
7	3-ClPh	**4a**/H	**5g**/83	89
8	3-BrPh	**4a**/H	**5h**/86	97
9	3-MeOPh	**4a**/H	**5i**/90	94
10	3-MePh	**4a**/H	**5j**/85	89
11	2-BrPh	**4a**/H	**5k**87	99
12	2-FPh	**4a**/H	**5l**/91	97
13	2-MeOPh	**4a**/H	**5m**/93	80
14	2-furyl	**4a**/H	**5o**/84	75
15	*n*-hexyl	**4a**/H	**5p**/71	73
16	Ph	**4b**/Me	**5q**/83	68

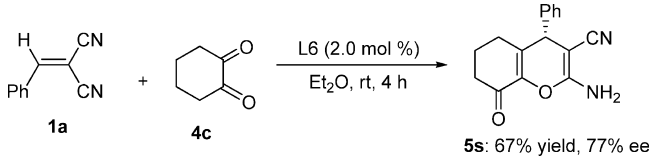
[a]Unless otherwise specified, the reaction was carried out with **1** (0.2 mmol) and **4** (0.3 mmol) in the presence of an organocatalyst **L6** (0.02 mmol) in Et_2O (2.0 mL) at rt for 4 h. [b]Isolated yield. [c]Determined by HPLC.

100 and PBS were used as the positive and the negative control, respectively. The data of these compounds against mice erythrocytes showed that the release of mice hemoglobin was less than 5% even at the concentration of 125 μg/mL, which is about 20 times of the MIC (Figure 3A). And the release of human hemoglobin was less than 5% even at the concentration of 250 μg/mL, which is about 40 times of the MIC (Figure 3B). Besides the acute cytotoxicity assay, the chronic cytotoxicity of these compounds against human cells was also assayed. Briefly, human Jurkat and Hela cells were inoculated into 96-well plates at 8×10^3 cells/well before treatment. After 24 h, the cells were treated with a range of concentrations of compounds, and PBS buffer was used as control. All the cells were incubated for 24 h at 37 °C and 5% CO_2. Then, MTT reagent solution was added, and the 96-well plate was incubated for 4 h at 37 °C. After that, the supernatant was discarded and the MTT formazan precipitate was dissolved in 150 μL of DMSO with gentle shaking. The absorbance was determined at 570 nm. IC_{50} values for each cell line were evaluated, representing the concentration at which human cell viability was reduced to 50% compared with PBS treated cells. The data of these compounds against human cells showed that the IC_{50} value of **5u** and **5v** was about 4 times the antibacterial MIC (Table 5). These results showed that these compounds show same selectivity against bacteria.

CONCLUSION

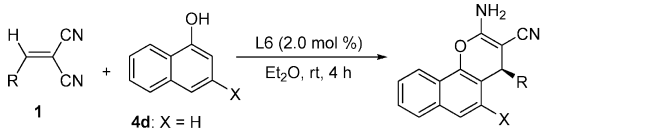
In conclusion, we have successfully developed a unique approach to asymmetric synthesis of various optically pure pyranocoumarins and 2-amino-4*H*-chromenes catalyzed by a novel tertiary amine-thiourea with low ligand loading under one-pot, two-component and three-component intermolecular domino reactions with high yield (up to 95%) and

Scheme 2. Asymmetric Synthesis of 2-Amino-4*H*-chromene 5s via Two-Component Reactions



1a 4c **5s**: 67% yield, 77% ee

Scheme 3. Asymmetric Synthesis of 2-Amino-4*H*-chromene 5t, 5u, and 5v via Two-Component Reactions



1 **4d**: X = H **4e**: X = OH

R = Ph, X = H, **5t,** 84% yield, 75% ee
R = Ph, X = OH, **5u,** 70% yield, 83% ee
R = 4-ClPh, X = OH, **5v,** 65% yield, 80% ee

enantioslectivities (up to 99% ee). Importantly, preliminary biological studies of these new heterocyclic compounds showed antibacterial activity against *S. aureus*, MIC = 6.25 μg/mL. This study discloses a novel type of antibacterial agent and may provide a practical strategy for further developing new types of potent antibiotics efficient against Gram-positive human pathogens. Further investigation on these new heterocyclic compounds is ongoing in our laboratories.

EXPERIMENTAL SECTION

All reactions were carried out under an argon atmospheric condition unless otherwise noted, and solvents were dried according to established procedures. Reactions were monitored by thin layer chromatography (TLC); column chromatography purifications were carried out using silica gel. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a 300 MHz spectrometer in $CDCl_3$ unless otherwise noted, and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on 300 MHz spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as internal standard unless otherwise noted. Data are presented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, cm = complex multiplet), and coupling constant in Hertz (Hz). Infrared (IR) spectra were recorded on a spectrometer. Optical rotations were recorded on a polarimeter. HR-MS was measured with a mass spectrometer. Melting points were measured on a melting point apparatus and were uncorrected. The ee value determination was carried out using chiral high-performance liquid chromatography (HPLC) with Daicel Chiracel AD-H column with a UV-detector.

General Procedure for Asymmetric Synthesis of L6. Carbon disulfide (15 mmol) and *N*,*N*′-dicyclohexylcarbodiimide (DCC, 10 mmol) were added to a solution of dehydroabietic amine (10 mmol) in dry ether (50 mL) at 0 °C. The reaction mixture was allowed to warm slowly to room temperature over a period of 3 h and then was stirred for a further 12 h at room temperature. After separation of the precipitated thiourea by filtration, the resulting mixture was concentrated under reduced pressure, and the residue was purified through column chromatography on silica gel (eluent, ethyl acetate/hexane 1:50) to give the isothiocyanate as a yellow oil (90% yield). And then the isothiocyanate (6.0 mmol) was added over a period of 1.5 h to a stirred solution of (*R*)-quininenamine (5 mmol, 1.14 g) in dry dichloromethane (30 mL). The reaction mixture was stirred overnight at room temperature. After the reaction was completed, the resulting mixture was concentrated under reduced pressure, and the residue was purified through column chromatography on silica gel

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Scheme 4. Asymmetric Synthesis of Pyranocoumarins and 2-Amino-4*H*-chromenes via One-Pot, Three-Component Domino Reaction

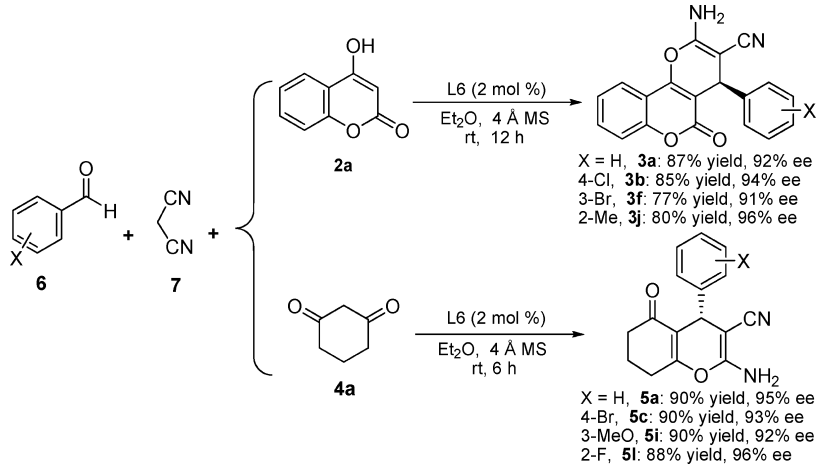

Table 4. Antibacterial Activity of Compounds 3 and 5[a]

	MIC (μg/mL)	
compounds	*S. aureus* (CMCC 26003)	*E. coli* (CMCC 44102)
3d	>100.0	>100.0
3g	>100.0	>100.0
3j	>100.0	>100.0
3n	>100.0	>100.0
3q	100.0	>100.0
3r	>100.0	>100.0
5i	>100.0	>100.0
5k	>100.0	>100.0
5r	>100.0	>100.0
5t	>100.0	>100.0
5u (racemic)	25.0	>100.0
5u	6.25	>100.0
5v	6.25	>100.0
kanamycin	15.625	62.5−125.0
vancomycin	1.0	>64.0

[a]MICs were determined by a standard broth microdilution method as recommended by the NCCLS. Serial 2-fold dilutions of each compound were made in appropriate broth, the plates were inoculated with 1×10^6 CFU mL^{-1} of each strain in a volume of 100 μL, and then the compounds of different concentrations were added in each well. Plates were incubated at 35 °C for 18 h, and then the MICs were scored.

(eluent, ethyl acetate) to give the isothiocyanate **L6** as a white solid (67% yield).

1-(((1*R*,4a*S*,10a*R*)-7-Isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yl)methyl)-3-((1*R*)-(6-methoxyquinolin-4-yl)(8-vinylquinuclidin-2-yl)-methyl)thiourea (L6). White solid: mp 133−134 °C; $[\alpha]^{20}_D = -70$ (c = 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 8.67 (s, 1 H), 7.89−7.92 (d, J = 5.1 Hz, 2 H), 7.37−7.44 (m, 2 H), 7.10−7.13 (d, J = 8.1 Hz, 1 H), 6.93−6.95 (d, J = 7.8 Hz, 1 H), 6.83 (s, 1 H), 5.72−5.83 (m, 2H), 4.87−4.98 (m, 2 H), 3.90 (s, 3 H), 3.55−3.58 (d, J = 10.5 Hz, 1 H), 3.04−3.14 (m, 4 H), 2.75−2.80 (t, J = 6.6 Hz, 3 H), 2.51−2.59 (m, 2 H), 2.22 (br, 2 H), 1.54 (br, 1 H), 1.38 (m, 7 H), 1.54−1.77 (m, 11 H), 1.09 (s, 3 H), 0.78 (s, 3 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 158.0, 148.5, 148.1, 145.9, 145.2, 142.9, 135.7, 132.2, 128.9, 127.4, 125.0, 124.5, 122.2, 115.2, 104.2, 56.6, 56.3, 45.1, 41.8, 39.0, 38.4, 37.9, 36.8, 33.9, 30.5, 28.4, 28.1, 26.6, 26.1, 25.1, 24.9, 21.8, 19.8, 19.6, 19.2 ppm; **IR** (neat) 3328, 3070, 2925, 2864, 1711, 1620, 1536, 1359, 1232, 1026, 726 cm^{-1}; **HRMS** (ESI) $C_{41}H_{54}N_4OS$ $[M + H]^+$ calcd 651.4091, found 651.4081.

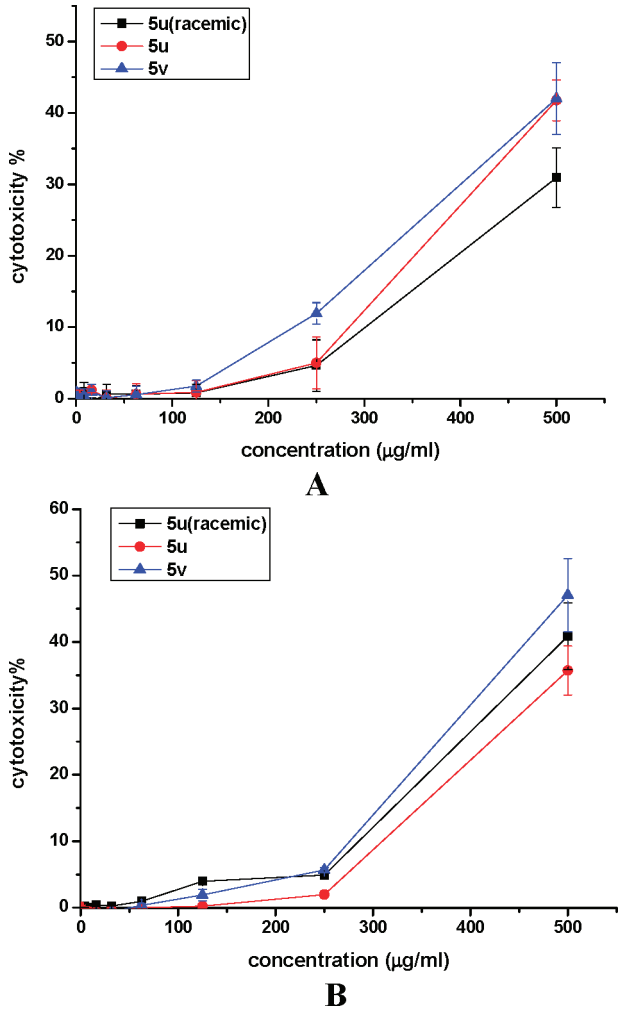

Figure 3. The acute cytotoxicity studies of **5u** (racemic), **5u**, and **5v** (A) against mice red blood cells and (B) against human red blood cells. (For experimental details, see the Supporting Information.)

General Procedure for Asymmetric Synthesis Pyranocoumarins. Typical experimental procedure: To a stirred solution of **L6** (0.004 mmol, 2.0 mol %) and 4-hydroxycoumarin **2a** or 4-hydroxy-6-methyl-2-pyrone **2b** or 4-hydroxy-1-methyl-1,2- dihydroquinolin-2-one **2c** (0.30 mmol) in dry ether (1.0 mL), a solution of α,β-unsaturated

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Table 5. Chronic Cytotoxicity of Compounds against Human Cells

compounds	IC_{50} (μg/mL)	
	Hela	Jurkat
5u (racemic)	25	25
5u	100	100
5v	25	27

nitriles (0.2 mmol) in dry ether (1.0 mL) was added over a period of 10 min. The solution was stirred at room temperature for 8 h. After the reaction was completed (monitored by TLC), the resulting mixture was concentrated under reduced pressure, and the residue was purified through column chromatography on silica gel (eluent, ethyl acetate/dichloromethane 1:25) to give the pure products. After filtration, the solvent was removed at reduced pressure to give the pure products.

(*R*)-2-Amino-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-c]-chromene-3-carbonitrile (3a). White solid: mp 264−265 °C; 90% yield; 93% *ee* determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254 nm, t_{major} = 20.52 min, t_{minor} = 27.81 min); $[\alpha]^{20}_D$ = +12 (*c* = 1.0, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.90−7.93 (d, *J* = 7.8 Hz, 1 H), 7.69−7.72 (t, *J* = 6.9 Hz, 1 H), 7.42−7.52 (m, 3 H), 7.25−7.33 (m, 5 H), 4.46 (s, 1 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 159.5, 157.9, 153.4, 152.1, 143.3, 132.9, 128.5, 127.6, 127.1, 124.6, 122.4, 119.2, 116.5, 112.9, 104.0, 57.9, 36.9 ppm; **IR** (neat) 3350, 3320, 2921, 2852, 2195, 1700, 1669, 1603, 1373, 1044, 759 cm^{-1}; **HRMS** (ESI) $C_{19}H_{12}N_2O_3$ $[M + H]^+$ calcd 317.0921, found 317.0926.

(*R*)-2-Amino-4-(4-chlorophenyl)-5-oxo-4,5-dihydropyrano-[3,2-c]chromene-3-carbonitrile (3b). White solid: mp 233−234 °C; 87% yield; 94% *ee* determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254 nm, t_{major} = 13.21 min, t_{minor} = 25.66 min); $[\alpha]^{20}_D$ = +13 (*c* = 1.0, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.90−7.93 (d, *J* = 7.5 Hz, 1 H), 7.70−7.75 (t, *J* = 7.5 Hz, 1 H), 7.45−7.53 (m, 3 H), 7.30−7.39 (dd, *J* = 8.4 Hz, 19.5 Hz, 4 H), 4.50 (s, 1 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 160.0, 158.4, 154.0, 152.6, 142.8, 133.5, 132.2, 130.1, 128.9, 125.1, 123.0, 119.5, 117.0, 113.4, 103.9, 58.0, 36.8 ppm; **IR** (neat) 3404, 2924, 2255, 2184, 2128, 1704, 1668, 1378, 1026, 1001, 763 cm^{-1}; **HRMS** (ESI) $C_{19}H_{11}ClN_2O_3$ $[M + NH_4]^+$ calcd 368.0796, found 368.0804.

(*R*)-2-Amino-4-(4-fluorophenyl)-5-oxo-4,5-dihydropyrano-[3,2-c]chromene-3-carbonitrile (3c). White solid: mp 243−244 °C; 83% yield; 98% *ee* determined by HPLC on a Chiralpak AD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254 nm, t_{major} = 11.10 min, t_{minor} = 7.53 min); $[\alpha]^{20}_D$ = +12 (*c* = 0.5, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.90−7.93 (d, *J* = 7.8 Hz, 1 H), 7.69−7.74 (t, *J* = 7.2 Hz, 1 H), 7.44−7.52 (m, 3 H), 7.32−7.36 (dd, *J* = 5.4 Hz, 8.4 Hz, 2 H), 7.12−7.18 (t, *J* = 9.0 Hz, 2 H), 4.50 (s, 1 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 162.8, 159.5 (d, *J* = 6.8 Hz), 157.8, 153.3, 152.1, 139.4, 132.9, 129.6 (d, *J* = 8.3 Hz), 124.6, 122.4, 119.1, 116.5, 115.1 (d, *J* = 21.8 Hz), 112.9, 103.7, 57.7, 36.2 ppm; **IR** (neat) 3378, 2922, 2852, 2254, 2191, 1714, 1673, 1376, 1025, 1000, 761 cm^{-1}; **HRMS** (ESI) $C_{19}H_{11}FN_2O_3$ $[M + H]^+$ calcd 335.0826, found 335.0834.

(*R*)-2-Amino-4-(4-bromophenyl)-5-oxo-4,5-dihydropyrano-[3,2-c]chromene-3-carbonitrile (3d). White solid: mp 228−229 °C; 89% yield; 96% *ee* determined by HPLC on a Chiralpak AD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254 nm, t_{major} = 12.76 min, t_{minor} = 8.46 min); $[\alpha]^{20}_D$ = +15 (*c* = 1.0, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.90−7.92 (d, *J* = 7.8 Hz, 1 H), 7.70−7.75 (t, *J* = 7.2 Hz, 1 H), 7.53 (s, 1 H), 7.46−7.50 (dd, *J* = 6.0 Hz, 7.5 Hz, 4 H), 7.24−7.27 (d, *J* = 8.4 Hz, 2 H), 4.48 (s, 1 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 160.0, 158.3, 154.0, 152.6, 143.2, 133.5, 131.8, 130.5, 125.1, 124.4, 123.0, 120.7, 117.0, 113.4, 103.9, 57.9, 36.9 ppm; **IR** (neat) 3414, 2925, 2854, 2255, 2193, 2128, 1673, 1378, 1027, 1002, 764 cm^{-1}; **HRMS** (ESI) $C_{19}H_{11}BrN_2O_3$ $[M + NH_4]^+$ calcd 412.0291, found 412.0287.

(*R*)-2-Amino-4-(3-chlorophenyl)-5-oxo-4,5-dihydropyrano-[3,2-c]chromene-3-carbonitrile (3e). White solid: mp 227−228 °C; 81% yield; 87% *ee* determined by HPLC on a Chiralpak AD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254 nm, t_{major} = 11.91 min, t_{minor} = 8.51 min); $[\alpha]^{20}_D$ = +13 (*c* = 1.0, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.91−7.93 (d, *J* = 7.8 Hz, 1 H), 7.70−7.75 (t, *J* = 7.5 Hz, 1 H), 7.45−7.52 (m, 3 H), 7.26−7.37 (m, 4 H), 4.53 (s, 1 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 160.0, 158.4, 154.2, 152.6, 146.2, 133.5, 133.4, 130.8, 128.0, 127.6, 127.0, 125.1, 123.0, 119.5, 117.0, 113.4, 103.6, 57.8, 37.1 ppm; **IR** (neat) 3350, 3185, 2923, 2854, 2196, 1725, 1672, 1603, 1371, 1025, 756 cm^{-1}; **HRMS** (ESI) $C_{19}H_{11}ClN_2O_3$ $[M + NH_4]^+$ calcd 368.0796, found 368.0802.

(*R*)-2-Amino-4-(3-bromophenyl)-5-oxo-4,5-dihydropyrano-[3,2-c]chromene-3-carbonitrile (3f). White solid: mp 247−248 °C; 75% yield; 90% *ee* determined by HPLC on a Chiralpak AD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254 nm, t_{major} = 12.76 min, t_{minor} = 9.11 min); $[\alpha]^{20}_D$ = +23 (*c* = 1.0, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.90−7.93 (dd, *J* = 1.2 Hz, 7.8 Hz, 1 H), 7.70−7.75 (t, *J* = 7.2 Hz, 1 H), 7.44−7.53 (m, 5 H), 7.29−7.31 (m, 2 H), 4.51 (s, 1 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 160.0, 158.4, 154.2, 152.6, 146.5, 133.5, 131.2, 130.9, 130.5, 127.4, 125.1, 123.0, 122.2, 119.5, 117.0, 113.4, 103.6, 57.8, 37.1 ppm; **IR** (neat) 3321, 3183, 2921, 2852, 2195, 1713, 1672, 1604, 1375, 1054, 761 cm^{-1}; **HRMS** (ESI) $C_{19}H_{11}BrN_2O_3$ $[M + H]^+$ calcd 395.0026, found 395.0036.

(*R*)-2-Amino-4-(3-methoxyphenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (3g). White solid: mp 233−234 °C; 78% yield; 83% *ee* determined by HPLC on a Chiralpak AD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254 nm, t_{major} = 14.62 min, t_{minor} = 10.83 min); $[\alpha]^{20}_D$ = +18 (*c* = 1.0, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.90−7.93 (d, *J* = 7.8 Hz, 1 H), 7.69−7.74 (t, *J* = 7.5 Hz, 1 H), 7.44−7.52 (m, 3 H), 7.23−7.28 (t, *J* = 8.4 Hz, 1 H), 6.85 (s, 1 H), 6.82 (s, 2 H), 4.45 (s, 1 H), 3.74 (s, 3 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 159.5, 159.2, 157.9, 153.4, 152.1, 144.8, 132.9, 129.6, 124.6, 122.4, 119.7, 119.1, 116.5, 113.8, 112.9, 111.9, 103.8, 57.8, 54.9, 36.8 ppm; **IR** (neat) 3364, 3313, 3177, 2920, 2850, 2189, 1710, 1668, 1371, 1051, 766 cm^{-1}; **HRMS** (ESI) $C_{20}H_{14}N_2O_4$ $[M + H]^+$ calcd 347.1026, found 347.1031.

(*R*)-2-Amino-4-(2-fluorophenyl)-5-oxo-4,5-dihydropyrano-[3,2-c]chromene-3-carbonitrile (3h). White solid: mp 205−206 °C; 87% yield; 93% *ee* determined by HPLC on a Chiralpak AD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254 nm, t_{major} = 16.56 min, t_{minor} = 9.73 min); $[\alpha]^{20}_D$ = +21 (*c* = 1.0, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.91−7.94 (d, *J* = 7.5 Hz, 1 H), 7.71−7.76 (t, *J* = 7.2 Hz, 1 H), 7.46−7.54 (dd, *J* = 7.8 Hz, 15.0 Hz, 3 H), 7.29−7.36 (m, 2 H), 7.14−7.27 (m, 2 H), 4.75 (s, 1 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 161.8, 159.4, 158.6, 158.2, 153.8, 152.1, 133.0, 130.2, 129.8 (d, *J* = 12.0 Hz), 129.2 (d, *J* = 8.3 Hz), 124.7, 122.4, 119.0, 116.6, 115.5 (d, *J* = 21.8 Hz), 112.8, 102.6, 56.3, 31.3 ppm; **IR** (neat) 3370, 2922, 2853, 2188, 1703, 1668, 1598, 1375, 1054, 1027, 749 cm^{-1}; **HRMS** (ESI) $C_{19}H_{11}FN_2O_3$ $[M + H]^+$ calcd 335.0826, found 335.0819.

(*R*)-2-Amino-4-(2-bromophenyl)-5-oxo-4,5-dihydropyrano-[3,2-c]chromene-3-carbonitrile (3i). White solid: mp 247−248 °C; 80% yield; 88% *ee* determined by HPLC on a Chiralpak AD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254 nm, t_{major} = 17.68 min, t_{minor} = 10.18 min); $[\alpha]^{20}_D$ = +14 (*c* = 1.0, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.91−7.93 (d, *J* = 7.5 Hz, 1 H), 7.71−7.76 (t, *J* = 7.5 Hz, 1 H), 7.58−7.61 (d, *J* = 7.8 Hz, 1 H), 7.46−7.54 (m, 3 H), 7.31 (s, 2 H), 7.19−7.21 (m, 1 H), 5.00 (s, 1 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 159.3, 157.9, 153.9, 152.2, 141.9, 133.0, 132.7, 130.6, 129.0, 128.3, 124.7, 122.9, 122.5, 118.6, 116.6, 112.8, 103.1, 56.6, 36.4 ppm; **IR** (neat) 3318, 3176, 2923, 2853, 2194, 1712, 1672, 1604, 1375, 1054, 751 cm^{-1}; **HRMS** (ESI) $C_{19}H_{11}BrN_2O_3$ $[M + H]^+$ calcd 395.0026, found 395.0035.

(*R*)-2-Amino-5-oxo-4-*o*-tolyl-4,5-dihydropyrano[3,2-c]-chromene-3-carbonitrile (3j). White solid: mp 210−211 °C; 81% yield; 96% *ee* determined by HPLC on a Chiralpak AD-H column

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(hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254 nm, t_{major} = 12.60 min, t_{minor} = 7.86 min); $[\alpha]^{20}_D$ = +19 (*c* = 1.0, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.91−7.94 (dd, *J* = 1.2 Hz, 7.8 Hz, 1 H), 7.72−7.74 (t, *J* = 8.4 Hz, 1 H), 7.45−7.53 (dd, *J* = 7.5 Hz, 15.9 Hz, 2 H), 7.38 (s, 1 H), 7.03−7.16 (m, 4 H), 4.76 (s, 1 H), 2.51 (s, 3 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 159.5, 157.7, 153.4, 152.0, 142.2, 135.2, 132.8, 130.0, 127.9, 126.7, 124.6, 122.4, 119.2, 116.5, 112.8, 104.6, 57.8, 32.4, 19.0 ppm; **IR** (neat) 3402, 2924, 2854, 2255, 2196, 2128, 1673, 1377, 1027, 1003, 764 cm^{-1}; **HRMS** (ESI) $C_{20}H_{14}N_2O_3$ $[M + NH_4]^+$ calcd 348.1343, found 348.1353.

(*R*)-2-Amino-4-(furan-2-yl)-5-oxo-4,5-dihydropyrano[3,2-c]-chromene-3-carbonitrile (3k). White solid: mp 268−269 °C; 72% yield; 99% *ee* determined by HPLC on a Chiralpak AD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254 nm, t_{major} = 11.96 min, t_{minor} = 9.62 min); $[\alpha]^{20}_D$ = +22 (*c* = 1.0, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.88−7.91 (d, *J* = 7.5 Hz, 1 H), 7.71−7.76 (t, *J* = 7.5 Hz, 1 H), 7.47−7.54 (m, 5 H), 6.38−6.40 (t, *J* = 3.0 Hz, 1 H), 6.28−6.29 (d, *J* = 3.0 Hz, 1 H), 4.63 (s, 1 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 159.3, 158.7, 154.1, 153.9, 152.1, 142.4, 133.1, 124.9, 124.7, 122.3, 116.6, 112.8, 110.6, 106.4, 101.5, 55.2, 30.5 ppm; **IR** (neat) 3380, 3192, 2923, 2853, 2200, 1704, 1669, 1607, 1376, 1052, 759 cm^{-1}; **HRMS** (ESI) $C_{17}H_{10}N_2O_4$ $[M + Na]^+$ calcd 329.0533, found 329.0542.

(*R*)-2-Amino-5-oxo-4-(thiophen-3-yl)-4,5-dihydropyrano-[3,2-c]chromene-3-carbonitrile (3l). White solid: mp 228−229 °C; 88% yield; 95% *ee* determined by HPLC on a Chiralpak AD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254 nm, t_{major} = 11.13 min, t_{minor} = 8.52 min); $[\alpha]^{20}_D$ = +31 (*c* = 1.0, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.88−7.90 (d, *J* = 7.8 Hz, 1 H), 7.68−7.74 (t, *J* = 7.8 Hz, 1 H), 7.43−7.541 (m, 4 H), 7.35 (s, 1 H), 7.02−7.04 (dd, *J* = 1.2 Hz, 7.8 Hz, 1 H), 4.60 (s, 1 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 160.1, 158.7, 153.7, 152.5, 144.3, 133.3, 127.5, 126.9, 125.1, 122.9, 122.6, 119.8, 117.0, 113.5, 104.4, 57.9, 32.4 ppm; **IR** (neat) 3394, 2922, 2853, 2253, 2195, 1707, 1666, 1375, 1024, 999, 759 cm^{-1}; **HRMS** (ESI) $C_{17}H_{10}N_2O_3S$ $[M + NH_4]$+ calcd 340.0750, found 340.0759.

(*R*)-2-Amino-5-oxo-4-hexyl-4,5-dihydropyrano[3,2-c]-chromene-3-carbonitrile (3m). White solid: mp 171−172 °C; 69% yield; 77% *ee* determined by HPLC on a Chiralpak AD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254 nm, t_{major} = 11.39 min, t_{minor} = 8.07 min); $[\alpha]^{20}_D$ = +11 (*c* = 1.0, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.80−7.83 (d, *J* = 8.1 Hz, 1 H), 7.68−7.74 (t, *J* = 8.7 Hz, 1 H), 7.44−7.49 (t, *J* = 8.1 Hz, 2 H), 7.33 (s, 1 H), 3.42−3.45 (dd, *J* = 3.9 Hz, 5.4 Hz, 1 H), 1.65−1.99 (m, 1 H), 1.49−1.60 (m, 1 H), 1.17−1.32 (m, 2 H), 0.84−0.89 (t, *J* = 6.9 Hz, 3 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 160.4, 159.8, 154.5, 152.5, 133.2, 125.0, 122.6, 120.1, 117.0, 113.4, 104.8, 55.6, 36.6, 31.2, 25.6, 14.3 ppm; **IR** (neat) 3310, 3190, 2925, 2191, 1703, 1667, 1606, 1390, 1313, 1036, 755 cm^{-1}; **HRMS** (ESI) $C_{16}H_{14}N_2O_3$ $[M + H]^+$ calcd 283.1077, found 283.1083.

(*R*)-2-Amino-9-chloro-5-oxo-4-phenyl-4,5-dihydropyrano-[3,2-c]chromene-3-carbonitrile (3n). White solid: mp 188−189 °C; 86% yield; 98% *ee* determined by HPLC on a Chiralpak AD-H column (hexane/2-propanol = 80/20, flow rate = 0.8 mL/min, 254 nm, t_{major} = 18.13 min, t_{minor} = 11.09 min); $[\alpha]^{20}_D$ = +29 (*c* = 1.0, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.94 (s, 1 H), 7.74−7.77 (d, *J* = 9.0 Hz, 1 H), 7.50−7.53 (d, *J* = 9.0 Hz, 1 H), 7.42 (s, 1 H), 7.26−7.32 (m, 6 H), 4.45 (s, 1 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 159.7, 158.3, 153.0, 151.3, 143.6, 133.1, 131.0, 130.1, 129.3, 128.2, 127.7, 122.4, 119.2, 115.1, 105.4, 58.4, 37.5 ppm; **IR** (neat) 3395, 3319, 3255, 3191, 2921, 2852, 2199, 1707, 1672, 1375, 1055 cm^{-1}; **HRMS** (ESI) $C_{19}H_{11Cl}N_2O_3$ $[M + H]^+$ calcd 351.0531, found 351.0536.

(*R*)-2-Amino-9-methyl-5-oxo-4-phenyl-4,5-dihydropyrano-[3,2-c]chromene-3-carbonitrile (3o). White solid: mp 229−230 °C; 82% yield; 96% *ee* determined by HPLC on a Chiralpak AD-H column (hexane/2-propanol = 70/30, flow rate = 1.0 mL/min, 254 nm, t_{major} = 9.76 min, t_{minor} = 6.57 min); $[\alpha]^{20}_D$ = +58 (*c* = 1.0, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.71 (s, 1 H), 7.50−7.52 (d, *J* = 8.4 Hz, 1 H), 7.42 (s, 1 H), 7.31−7.36 (m, 3 H), 7.25−7.27 (m, 3 H), 4.43 (s, 1 H), 2.43 (s, 3 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 159.6, 157.9, 157.8, 153.3, 150.2, 143.3, 134.0, 133.7, 128.5, 127.5, 127.1, 122.0, 116.2, 112.5, 103.8, 57.9, 36.9, 20.4 ppm; **IR** (neat) 3412, 3308, 3183, 2924, 2855, 2181, 1643, 1598, 1374, 1210, 998 cm^{-1}; **HRMS** (ESI) $C_{20}H_{14}N_2O_3$ $[M + H]^+$ calcd 331.1077, found 331.1067.

(*R*)-2-Amino-9-methoxy-5-oxo-4-phenyl-4,5-dihydropyrano-[3,2-c]chromene-3-carbonitrile (3p). White solid: mp 220−221 °C; 81% yield; 90% *ee* determined by HPLC on a Chiralpak AD-H column (hexane/2-propanol = 70/30, flow rate = 1.0 mL/min, 254 nm, t_{major} = 12.13 min, t_{minor} = 7.69 min); $[\alpha]^{20}_D$ = +37 (*c* = 1.0, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.40−7.43 (d, *J* = 8.7 Hz, 1 H), 7.37 (s, 1 H), 7.25−7.37 (m, 6 H), 4.45 (s, 1 H), 3.87 (s, 3 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 159.6, 157.9, 155.8, 153.1, 146.5, 143.3, 128.5, 127.5, 127.1, 120.3, 119.1, 117.7, 113.3, 104.8, 104.1, 57.8, 55.8, 36.9 ppm; **IR** (neat) 3425, 3295, 2923, 2853, 2205, 1705, 1673, 1457, 1374, 1235, 1020 cm^{-1}; **HRMS** (ESI) $C_{20}H_{14}N_2O_4$ $[M + H]^+$ calcd 347.1026, found 347.1019.

(*R*)-2-Amino-7-methyl-5-oxo-4-phenyl-4,5-dihydropyrano-[4,3-b]pyran-3-carbonitrile (3q). White solid: mp 234−235 °C; 82% yield; 93% *ee* determined by HPLC on a Chiralpak AD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254 nm, t_{major} = 17.70 min, t_{minor} = 9.96 min); $[\alpha]^{20}_D$= −17 (*c* = 1.0, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.29−7.34 (t, *J* = 7.5 Hz, 2 H), 7.17−7.25 (m, 4 H), 6.29 (s, 1 H), 4.28 (s, 1 H), 2.22 (s, 3 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 162.9, 161.3, 158.1, 158.0, 143.5, 128.4, 127.4, 126.9, 119.3, 100.7, 97.9, 57.8, 36.2, 19.2 ppm; **IR** (neat) 3399, 3323, 3203, 2923, 2198, 1711, 1675, 1644, 1382, 1260, 1138 cm^{-1}; **HRMS** (ESI) $C_{16}H_{12}N_2O_3$ $[M + H]^+$ calcd 281.0921, found 281.0914.

(*S*)-Methyl 2-Amino-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate (3r). White solid: mp 164−165 °C; 85% yield; 80% *ee* determined by HPLC on a Chiralpak AD-H column (hexane/2-propanol = 70/30, flow rate = 1.0 mL/min, 254 nm, t_{major} = 11.92 min, t_{minor} = 8.97 min); $[\alpha]^{20}_D$ = +15 (*c* = 1.0, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.97−8.00 (d, *J* = 7.2 Hz, 1 H), 7.87 (s, 2 H), 7.67−7.72 (t, *J* = 7.5 Hz, 1 H), 7.43−7.51 (dd, *J* = 7.5 Hz, 15.9 Hz, 2 H), 7.24−7.26 (d, *J* = 3.9 Hz, 4 H), 7.14−7.18 (m, 1 H), 4.72 (s, 1 H), 3.56 (s, 3 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 167.8, 159.8, 158.6, 153.1, 152.0, 144.8, 132.6, 128.1, 127.7, 126.4, 124.6, 122.4, 116.5, 113.1, 106.9, 76.9, 50.7, 35.0 ppm; **IR** (neat) 3410, 3305, 2951, 2924, 1719, 1693, 1657, 1374, 1196, 1049, 761 cm^{-1}; **HRMS** (ESI) $C_{20}H_{15}NO_5$ $[M + H]^+$ calcd 350.1023, found 350.1022.

(*S*)-Ethyl 2-Amino-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate (3s). White solid: mp 161−162 °C; 83% yield; 92% *ee* determined by HPLC on a Chiralpak AD-H column (hexane/2-propanol = 70/30, flow rate = 1.0 mL/min, 254 nm, t_{major} = 9.06 min, t_{minor} = 7.68 min); $[\alpha]^{20}_D$ = +18 (*c* = 1.0, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.98−8.00 (d, *J* = 7.2 Hz, 1 H), 7.87 (s, 2 H), 7.66−7.72 (t, *J* = 7.2 Hz, 1 H), 7.43−7.51 (dd, *J* = 7.5 Hz, 15.6 Hz, 2 H), 7.17−7.25 (m, 5 H), 4.71 (s, 1 H), 3.99−4.03 (dd, *J* = 6.6 Hz, 13.2 Hz, 2 H), 1.10−1.14 (t, *J* = 6.3 Hz, 1 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 167.5, 159.8, 158.5, 153.1, 152.0, 144.9, 132.6, 127.9, 126.4, 124.5, 122.4, 116.5, 113.1, 106.8, 77.0, 59.0, 35.2, 14.1 ppm; **IR** (neat) 3413, 3306, 2924, 2854, 1724, 1691, 1375, 1282, 1197, 1090, 762 cm^{-1}; **HRMS** (ESI) $C_{21}H_{17}NO_5$ $[M + H]^+$ calcd 364.1179, found 364.1172.

General Procedure for Asymmetric Synthesis of 2-Amino-4*H*-chromenes. Typical experimental procedure: To a stirred solution of **L6** (0.004 mmol, 2.0 mol %) and various carbonyl compounds **4a**−**4f** (0.30 mmol) in dry ether (1.0 mL), a solution of α,β-unsaturated nitriles (0.2 mmol) in dry ether (1.0 mL) was added over a period of 10 min. The solution was stirred at room temperature for 4.0 h. After the reaction was completed (monitored by TLC), the resulting mixture was concentrated under reduced pressure, and the residue was purified through column chromatography on silica gel (eluent, ethyl acetate/dichloromethane 1:25) to give the pure products. After filtration, the solvent was removed at reduced pressure to give the pure products.

(*R*)-2-Amino-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (5a). White solid: mp 211−212C; 94% yield;

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96% *ee* determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254 nm, t_{major} = 11.91 min, t_{minor} = 10.40 min); $[\alpha]^{20}_D$ = +16 (*c* = 1.0, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.25−7.30 (t, *J* = 7.5 Hz, 2 H), 7.14−7.17 (m, 3 H), 6.99 (s, 2 H), 4.19 (s, 1 H), 2.58−2.61 (m, 2 H), 2.20−2.31 (m, 2 H), 1.84−1.99 (m, 2 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 196.3, 164.9, 158.9, 145.2, 128.8, 127.6, 127.0, 120.2, 114.2, 58.7, 36.8, 35.9, 26.9, 20.3 ppm; **IR** (neat) 3326, 3208, 2923, 2855, 2187, 1678, 1645, 1601, 1361, 994, 692 cm^{-1}; **HRMS** (ESI) $C_{16}H_{14}N_2O_2$ [M + H]$^+$ calcd 267.1128, found 267.1131.

(*R*)-2-Amino-4-(4-chlorophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (5b). White solid: mp 239−240 °C; 90% yield; 95% *ee* determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254 nm, t_{major} = 11.00 min, t_{minor} = 9.41 min); $[\alpha]^{20}_D$ = +10 (*c* = 1.0, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.26−7.54 (dd, *J* = 1.8 Hz, 6.6 Hz, 2 H), 7.17−7.20 (dd, *J* = 1.8 Hz, 6.6 Hz, 2 H), 7.05 (s, 1 H), 4.20 (s, 1 H), 2.59−2.63 (m, 2 H), 2.21−2.31 (m, 2 H), 1.85−1.99 (m, 2 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 196.3, 165.1, 158.9, 144.2, 131.5, 129.5, 128.7, 120.0, 113.8, 58.1, 36.7, 35.4, 26.9, 20.2 ppm; **IR** (neat) 3413, 3334, 3215, 2918, 2194, 1682, 1653, 1365, 1131, 1005, 507 cm^{-1}; **HRMS** (ESI) $C_{16}H_{13}ClN_2O_2$ [M + H]$^+$ calcd 301.0738, found 301.0743.

(*R*)-2-Amino-4-(4-bromophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (5c). White solid: mp 241−242 °C; 91% yield; 93% *ee* determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254 nm, t_{major} = 11.81 min, t_{minor} = 10.03 min); $[\alpha]^{20}_D$ = +18 (*c* = 1.0, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.46−7.49 (d, *J* = 8.4 Hz, 2 H), 7.12−7.15 (d, *J* = 8.4 Hz, 2 H), 7.07 (s, 1 H), 4.20 (s, 1 H), 2.61−2.63 (m, 2 H), 2.24−2.31 (m, 2 H), 1.88−1.99 (m, 2 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 196.3, 165.1, 158.8, 144.7, 131.6, 130.0, 120.1, 113.7, 58.0, 36.7, 35.5, 26.9, 20.2 ppm; **IR** (neat) 3417, 3331, 3213, 2961, 2195, 1681, 1653, 1363, 1207, 1005, 504 cm^{-1}; **HRMS** (ESI) $C_{16}H_{13}BrN_2O_2$ [M + H]$^+$ calcd 345.0233, found 345.0243.

(*R*)-2-Amino-4-(4-fluorophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (5d). White solid: mp 209−210 °C; 87% yield; 85% *ee* determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254 nm, t_{major} = 11.34 min, t_{minor} = 9.64 min); $[\alpha]^{20}_D$ = +13 (*c* = 1.0, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.18−7.22 (m, 2 H), 7.07−7.13 (m, 2 H), 7.04 (s, 2 H), 4.21 (s, 1 H), 2.61−2.63 (m, 2 H), 2.27−2.28 (m, 2 H), 1.90−1.99 (m, 2 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 196.4, 165.0, 163.0, 159.7, 158.9, 141.4, 129.5 (d, *J* = 8.3 Hz), 120.1, 115.4 (d, *J* = 21.0 Hz), 114.1, 58.5, 36.7, 35.2, 26.9, 20.2 ppm; **IR** (neat) 3414, 3335, 3218, 2928, 2193, 1683, 1654, 1367, 1209, 1002, 533 cm^{-1}; **HRMS** (ESI) $C_{16}H_{13}FN_2O_2$ [M + H]$^+$ calcd 285.1034, found 285.1043.

(*R*)-2-Amino-4-(4-cyanophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (5e). White solid: mp 237−238 °C; 95% yield; 80% *ee* determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254 nm, t_{major} = 18.57 min, t_{minor} = 16.46 min); $[\alpha]^{20}_D$ = +19 (*c* = 1.0, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.75−7.78 (d, *J* = 8.4 Hz, 2 H), 7.36−7.39 (d, *J* = 8.1 Hz, 2 H), 7.13 (s, 2 H), 4.30 (s, 1 H), 2.60−2.63 (m, 2 H), 2.27−2.31 (m, 2 H), 194−1.99 (m, 2 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 196.3, 165.6, 159.0, 150.7, 132.8, 128.8, 119.8, 119.3, 113.2, 109.9, 57.5, 36.7, 36.2, 26.9, 20.2 ppm; **IR** (neat) 3419, 3332, 3215, 2921, 2198, 1681, 1653, 1365, 1207, 1004, 555 cm^{-1}; **HRMS** (ESI) $C_{17}H_{13}N_3O_2$ [M + H]$^+$ calcd 292.1081, found 292.1087.

(*R*)-2-Amino-4-(4-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (5f). White solid: mp 206−207 °C; 89% yield; 79% *ee* determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254 nm, t_{major} = 18.01 min, t_{minor} = 12.78 min); $[\alpha]^{20}_D$ = +16 (*c* = 1.0, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.05−7.08 (dd, *J* = 1.8 Hz, 6.6 Hz, 2 H), 6.95 (s, 1 H), 6.82−6.85 (dd, *J* = 2.1 Hz, 6.9 Hz, 2 H), 4.13 (s, 1 H), 3.71 (s, 3 H), 2.60−2.62 (m, 2 H), 2.24−2.30 (m, 2 H), 1.86−1.99 (m, 2 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 196.3, 164.6, 158.8, 158.4, 137.4, 128.6, 120.3, 114.5, 114.1, 58.9, 55.5, 36.8, 35.0, 26.9, 20.3 ppm; **IR** (neat) 3330, 3212, 3187, 2928, 2193, 1682, 1654, 1367, 1260, 1170, 535 cm^{-1}; **HRMS** (ESI) $C_{17}H_{16}N_2O_3$ [M + H]$^+$ calcd 297.1234, found 297.1232.

(*R*)-2-Amino-4-(3-chlorophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (5g). White solid: mp 223−224 °C; 83% yield; 89% *ee* determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254 nm, t_{major} = 12.38 min, t_{minor} = 9.89 min); $[\alpha]^{20}_D$ = +14 (*c* = 1.0, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.24−7.35 (m, 2 H), 7.12−7.19 (m.2 H), 7.08 (s, 2 H), 4.22 (s, 1 H), 2.59−2.63 (m, 2 H), 2.28−2.32 (m, 2 H), 1.86−1.99 (m, 2 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 196.4, 165.3, 158.9, 147.7, 133.4, 130.7, 127.5, 127.1, 126.4, 113.6, 58.0, 36.7, 35.7, 26.9, 20.2 ppm; **IR** (neat) 3448, 3313, 3154, 2924, 2196, 1682, 1644, 1367, 1212, 1001, 693 cm^{-1}; **HRMS** (ESI) $C_{16}H_{13}ClN_2O_2$ [M + H]$^+$ calcd 301.0738, found 301.0744.

(*R*)-2-Amino-4-(3-bromophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (5h). White solid: mp 193−194 °C; 86% yield; 97% *ee* determined by HPLC on a Chiralpak O−H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254 nm, t_{major} = 11.74 min, t_{minor} = 8.84 min); $[\alpha]^{20}_D$ = +6 (*c* = 1.0, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.38−7.40 (d, *J* = 7.8 Hz, 1 H), 7.33 (s, 1 H), 7.24−7.29 (t, *J* = 7.8 Hz, 1 H), 7.16−7.19 (d, *J* = 7,8 Hz, 1 H), 7.10 (s, 1 H), 4.21 (s, 1 H), 2.58−2.65 (m, 2 H), 2.26−2.32 (m, 2 H), 1.88−1.99 (m, 2 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 196.4, 165.3, 158.9, 148.0, 131.1, 130.3, 130.0, 126.8, 122.0, 120.0, 113.6, 57.9, 36.7, 35.7, 26.9, 20.2 ppm; **IR** (neat) 3324, 3209, 2954, 2922, 2854, 2190, 1674, 1652, 1363, 1206, 1002 cm^{-1}; **HRMS** (ESI) $C_{16}H_{13}BrN_2O_2$ [M + H]$^+$ calcd 345.0233, found 345.0225.

(*R*)-2-Amino-4-(3-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (5i). White solid: mp 195−196 °C; 90% yield; 94% *ee* determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254 nm, t_{major} = 17.15 min, t_{minor} = 13.53 min); $[\alpha]^{20}_D$ = +18 (*c* = 1.0, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.18−7.28 (t, *J* = 7.8 Hz, 1 H), 6.99 (s, 1 H), 6.66−6.78 (m, 3 H), 4.16 (s, 1 H), 3.72 (s, 3 H), 2.58−2.64 (m, 2 H), 2.26−2.31 (m, 2 H), 1.87−1.99 (m, 2 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 195.8, 164.5, 159.2, 158.4, 146.3, 129.4, 119.7, 119.2, 113.6, 113.2, 111.3, 58.0, 54.9, 36.3, 35.2, 26.4, 19.8 ppm; **IR** (neat) 3320, 3176, 2942, 2196, 1680, 1605, 1366, 1262, 1210, 1001, 537 cm^{-1}; **HRMS** (ESI) $C_{17}H_{16}N_2O_3$ [M + H]$^+$ calcd 297.1234, found 297.1230.

(*R*)-2-Amino-5-oxo-4-m-tolyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (5j). White solid: mp 211−212 °C; 85% yield; 89% *ee* determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254 nm, t_{major} = 11.90 min, t_{minor} = 9.33 min); $[\alpha]^{20}_D$ = +10 (*c* = 1.0, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.13−7.19 (t, *J* = 7.5 Hz, 1 H), 7.00 (s, 1 H), 6.92−6.98 (m, 3 H), 4.14 (s, 1 H), 2.58−2.64 (m, 2 H), 2.21−2.31 (m, 5 H), 1.84−1.99 (m, 2 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 196.3, 164.8, 158.8, 145.2, 137.8, 128.7, 128.1, 127.7, 124.7, 120.2, 114.3, 58.7, 36.8, 35.8, 26.9, 21.5, 20.3 ppm; **IR** (neat) 3319, 3259, 3165, 2924, 2195, 1681, 1648, 1366, 1208, 1001, 537 cm^{-1}; **HRMS** (ESI) $C_{17}H_{16}N_2O_2$ [M + H]$^+$ calcd 281.1285, found 281.1290.

(*R*)-2-Amino-4-(2-bromophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (5k). White solid: mp 208−209 °C; 87% yield; 99% *ee* determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254 nm, t_{major} = 21.92 min, t_{minor} = 17.36 min); $[\alpha]^{20}_D$ = +12 (*c* = 1.0, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.51−7.54 (d, *J* = 7.8 Hz, 1 H), 7.28−7.32 (t, *J* = 7.2 Hz, 1 H), 7.08−7.17 (m, 2 H), 7.03 (s, 2 H), 4.72 (s, 1 H), 2.60−2.62 (m, 2 H), 2.22−2.29 (m, 2 H), 1.94−1.99 (m, 2 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 196.2, 165.5, 158.9, 143.9, 133.0, 130.3, 128.8, 128.6, 123.2, 119.6, 113.6, 57.5, 36.8, 35.4, 26.9, 20.3 ppm; **IR** (neat) 3475, 3315, 3175, 2962, 2187, 1682, 1658, 1595, 1362, 1248, 756 cm^{-1}; **HRMS** (ESI) $C_{16}H_{13}BrN_2O_2$ [M + H]$^+$ calcd 345.0233, found 345.0239.

(*R*)-2-Amino-4-(2-fluorophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (5l). White solid: mp 217−218 °C; 91% yield; 97% *ee* determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254 nm, t_{major} = 13.59 min, t_{minor} = 11.76 min); $[\alpha]^{20}_D$ = +30 (*c* = 1.0, acetone); **^{1}H**

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NMR (300 MHz, DMSO-d_6) δ 7.08−7.24 (m, 4 H), 7.03 (s, 2 H), 4.47 (s, 1 H), 2.60−2.63 (m, 2 H), 2.20−2.33 (m, 2 H), 1.86−2.02 (m, 2 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 196.2, 165.5, 159.1 (d, J = 32.3 Hz), 158.7, 131.8 (d, J = 13.5 Hz), 129.9 (d, J = 3.8 Hz), 128.9 (d, J = 7.5 Hz), 124.9 (d, J = 3.8 Hz), 119.9, 115.8 (d, J = 21.8 Hz), 112.9, 57.2, 36.7, 29.9, 26.9, 20.3 ppm; **IR** (neat) 3324, 3257, 3173, 2928, 2190, 1685, 1646, 1370, 1211, 1167, 761 cm^{-1}; **HRMS** (ESI) $C_{16}H_{13}FN_2O_2$ [M + H]$^+$ calcd 285.1034, found 285.1030.

(*R*)-2-Amino-4-(2-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (5m). White solid: mp 191−192 °C; 93% yield; 80% *ee* determined by HPLC on a Chiralpak AD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254 nm, t_{major} = 8.45 min, t_{minor} = 14.17 min); $[\alpha]^{20}_D$ = +21 (c = 1.0, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.12−7.18 (m, 1 H), 6.94−6.99 (m, 2 H), 6.80−6.86 (m, 2 H), 4.54 (s, 1 H), 3.76 (s, 3 H), 2.61−2.63 (m, 2 H), 2.22−2.29 (m, 2 H), 1.88−1.99 (m, 2 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 196.2, 165.5, 159.3, 157.2, 133.0, 128.5, 128.2, 120.9, 120.2, 113.6, 112.1, 58.1, 56.1, 36.9, 30.0, 26.9, 20.4 ppm; **IR** (neat) 3373, 3323, 3182, 2929, 2184, 1682, 1646, 1369, 1206, 1001, 753 cm^{-1}; **HRMS** (ESI) $C_{17}H_{16}N_2O_3$ [M + Na]$^+$ calcd 319.1053, found 319.1046.

(*R*)-2-Amino-4-(furan-2-yl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (5o). White solid: mp 224−225 °C; 84% yield; 75% *ee* determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254 nm, t_{major} = 13.73 min, t_{minor} = 12.13 min); $[\alpha]^{20}_D$ = +15 (c = 0.2, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.48−7.49 (t, J = 0.9 Hz, 1 H), 7.08 (s, 1 H), 6.31−6.33 (dd, J = 2.1 Hz, 3.3 Hz, 1 H), 6.05−6.06 (d, J = 3.3 Hz, 1 H), 4.33 (s, 1 H), 2.57−2.61 (m, 2 H), 2.27−2.35 (m, 2 H), 1.85−1.99 (m, 2 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 195.6, 165.1, 159.2, 155.7, 141.7, 119.5, 111.4, 110.4, 105.1, 55.2, 36.1, 28.9, 26.4, 19.7 ppm; **IR** (neat) 3398, 3325, 3212, 2925, 2187, 1680, 1603, 1360, 1210, 1012, 536 cm^{-1}; **HRMS** (ESI) $C_{14}H_{12}N_2O_3$ [M + H]$^+$ calcd 257.0921, found 257.0926.

(*R*)-2-Amino-4-hexyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (5p). White solid: mp 165−166 °C; 71% yield; 73% *ee* determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254 nm, t_{major} = 13.21 min, t_{minor} = 11.72 min); $[\alpha]^{20}_D$ = +11 (c = 1.0, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 6.88 (s, 1 H), 3.14−3.17 (t, J = 4.2 Hz, 1 H), 2.30−2.47 (m, 2 H), 1.89−1.99 (m, 2 H), 1.74−1.87 (m, 2 H), 1.57−1.45 (m, 2 H), 1.21−1.33 (m, 2 H), 1.14−1.19 (t, J = 7.8 Hz, 3 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 196.9, 165.4, 160.2, 120.7, 114.4, 55.9, 37.8, 36.8, 29.5, 26.8, 20.4, 18.0, 14.4 ppm; **IR** (neat) 3394, 3319, 3195, 2922, 2853, 2194, 1700, 1666, 1455, 1375, 1055 cm^{-1}; **HRMS** (ESI) $C_{13}H_{16}N_2O_2$ [M + H]$^+$ calcd 233.1285, found 233.1291.

(*R*)-2-Amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (5q). White solid: mp 208−209 °C; 83% yield; 68% *ee* determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254 nm, t_{major} = 17.38 min, t_{minor} = 15.41 min); $[\alpha]^{20}_D$ = +13 (c = 1.0, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.26−7.31 (t, J = 4.2 Hz, 2 H), 7.13−7.20 (m, 3 H), 7.00 (s 2 H), 4.17 (s, 1 H), 2.51 (s, 2 H), 2.07−2.28 (dd, J = 15.9 Hz, 46.8 Hz, 2 H), 1.04 (s, 3 H), 0.95 (s, 3 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 196.1, 162.9, 158.9, 145.2, 128.8, 127.6, 127.0, 120.1, 113.2, 58.8, 55.3, 50.4, 36.0, 32.3, 28.8, 27.2 ppm; **IR** (neat) 3396, 3325, 3212, 2962, 2199, 1681, 1660, 1602, 1370, 1214, 698 cm^{-1}; **HRMS** (ESI) $C_{18}H_{18}N_2O_2$ [M + H]$^+$ calcd 295.1441, found 295.1443.

(*R*)-2-Amino-8-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (5s). White solid: mp 91−92 °C; 67% yield; 77% *ee* determined by HPLC on a Chiralpak AD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254 nm, t_{major} = 12.56 min, t_{minor} = 20.63 min); $[\alpha]^{20}_D$= −10 (c = 1.0, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.35−7.40 (t, J = 7.5 Hz, 2 H), 7.22−7.25 (m, 3 H), 6.90 (s, 1 H), 4.19 (s, 1 H), 2.25−2.42 (m, 2 H), 2.71−2.99 (m, 4 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 190.5, 160.0, 143.2, 140.1, 134.9, 129.3, 128.3, 127.9, 120.5, 55.5, 43.4, 37.9, 27.4, 21.8 ppm; **IR** (neat) 3425, 3332, 3192, 2930, 2192, 1670, 1633, 1598, 1409, 1557, 702 cm^{-1}; **HRMS** (ESI) $C_{16}H_{14}N_2O_2$ [M + H]$^+$ calcd 267.1128, found 267.1134.

(*S*)-2-Amino-4-phenyl-4*H*-benzo[h]chromene-3-carbonitrile (5t). White solid: mp 196−197 °C; 84% yield; 75% *ee* determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 90/10, flow rate = 1.0 mL/min, 254 nm, t_{major} = 27.39 min, t_{minor} = 24.92 min); $[\alpha]^{20}_D$ = +46 (c = 0.5, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 8.25−8.28 (d, J = 7.8 Hz, 1 H), 7.88−7.91 (d, J = 7.5 Hz, 1 H), 7.59−7.65 (t, J = 9.0 Hz, 3 H), 7.11−7.32 (m, 8 H), 4.91 (s, 1 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 160.6, 146.1, 143.2, 133.1, 129.2, 128.1, 127.4, 127.2, 127.1, 126.7, 124.4, 123.2, 121.2, 120.9, 118.4, 56.7, 41.3 ppm; **IR** (neat) 3385, 3323, 3210, 2920, 2195, 1663, 1616, 1399, 1368, 1097, 734 cm^{-1}; **HRMS** (ESI) $C_{20}H_{14}N_2O$ [M + H]$^+$ calcd 299.1179, found 299.1171.

(*S*)-2-Amino-5-hydroxy-4-phenyl-4*H*-benzo[h]chromene-3-carbonitrile (5u). White solid: mp 223−224 °C; 70% yield; 83% *ee* determined by HPLC on a Chiralpak AD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254 nm, t_{major} = 8.41 min, t_{minor} = 10.06 min); $[\alpha]^{20}_D$ = +18 (c = 1.0, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 8.10−8.13 (d, J = 8.1 Hz, 1 H), 7.67−7.69 (d, J = 8.1 Hz, 1 H), 7.43−7.47 (t, J = 6.9 Hz, 1 H), 7.35−7.40 (t, J = 7.5 Hz, 1 H), 7.24−7.29 (t, J = 7.2 Hz, 2 H), 7.13−7.19 (m, 5 H), 6.91 (s, 1 H), 4.75 (s, 1 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 160.3, 152.2, 145.4, 144.6, 133.4, 128.3, 127.1, 126.9, 126.4, 125.7, 123.1, 120.7, 120.5, 117.6, 111.3, 104.6, 57.3, 37.1 ppm; **IR** (neat) 3391, 3176, 2927, 2187, 1660, 1615, 1410, 1284, 1026, 1003, 760 cm^{-1}; **HRMS** (ESI) $C_{20}H_{14}N_2O_2$ [M + H]$^+$ calcd 315.1128, found 315.1122.

(*S*)-2-Amino-4-(4-chlorophenyl)-5-hydroxy-4*H*-benzo[h]-chromene-3-carbonitrile (5v). White solid: mp 166−167 °C; 65% yield; 80% *ee* determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, 254 nm, t_{major} = 20.24 min, t_{minor} = 16.54 min); $[\alpha]^{20}_D$ = +21 (c = 1.0, acetone); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 10.18 (br, 1 H), 8.09−8.11 (d, J = 8.4 Hz, 1 H), 7.65−7.68 (d, J = 8.1 Hz, 1 H), 7.41−7.46 (t, J = 7.2 Hz, 1 H), 7.33−7.38 (t, J = 7.5 Hz, 1 H), 7.30−7.33 (d, J = 8.4 Hz, 2 H), 7.13−7.16 (d, J = 8.7 Hz, 2 H), 7.04 (s, 2 H), 6.89 (s, 1 H), 4.76 (s, 1 H) ppm; **^{13}C NMR** (75 MHz, DMSO-d_6) δ 160.2, 152.2, 144.5, 133.5, 130.9, 129.0, 128.3, 126.9, 125.7, 123.1, 120.7, 120.4, 117.5, 110.7, 104.7, 56.8, 36.6 ppm; **IR** (neat) 3449, 3335, 3199, 2924, 2854, 2191, 1659, 1380, 1284, 1087, 835 cm^{-1}; **HRMS** (ESI) $C_{20}H_{13}ClN_2O_2$ [M + H]$^+$ calcd 349.0738, found 349.0734.

General Procedure for Antibacterial Activity of Pyranocoumarins and 2-Amino-4*H*-chromenes. Some of the synthesized compounds **3a−s** and **5a−v** were tested for their antibacterial activities at concentrations of 200.0, 100.0, 50.0, 25.0, 12.5, 6.25, and 3.125 μg/mL using standard broth microdilution methods. Briefly, a single colony of Gram negative or Gram positive bacteria was inoculated into culture medium (Luria−Bertani broth) and cultured overnight at 37 °C. An aliquot of this culture was transferred to 10 mL fresh culture medium and incubated for an additional 3−5 h at 37 °C to obtain midexponential phase organisms. Then, the bacteria were inoculated into 96-well microtiter plates (OD_{600} = 0.1). A 2-fold dilution series of compounds were added into each well, and then the plates were incubated at 37 °C for 16 h. Kanamycin sulfate, vancomycin, and PBS buffer were used as the positive and negative control, respectively. The *Staphylococcus aureus* (CMCC 26003) and *Escherichia coli* (CMCC 44102) were obtained from Gansu Food and Drug Administration. The antibacterial activity is expressed as minimal inhibitory concentration (MIC), and the MIC is defined as the minimal concentration that inhibits the microbial growth. The reported minimal inhibitory concentrations are the mean of triplicate measurements from three independent assays. The result of the antibacterial activities of pyranocoumarins and 2-amino-4*H*-chromenes is shown in Table 5.

General Procedure for Acute Cytotoxicity Testing of the Compounds. The acute cytotoxicity of these compounds was examined according to Ryan and co-workers with a little modification. Blood specimens were freshly collected from mice and different adult donors in heparinized tubes and centrifuged at 1000*g* for 3 min. The

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pellet was washed three times with cold PBS buffer gently and resuspended in the same buffer to a final erythrocyte concentration of 2%. The RBC suspension (100 μL) was added to a 96-well microtiter plate. The compound solutions of different concentrations were added to the erythrocytes and incubated for 60 min at 37 °C. 0.2% Triton-X 100 and PBS were used as the positive and the negative control, respectively. The release of hemoglobin of the supernatant was measured after centrifugation (1200g for 15 min) by a microplate reader (Bio-Rad 680) at 490 nm. The acute cytotoxicity of these compounds was calculated as the following formulation:

$$\text{acute cytotoxicity \%} = \frac{T - T_A}{T_B - T_A} \times 100\%$$

where T_A represents the negative control and T_B represents the positive control

General Procedure for Chronic Cytotoxicity Testing of the Compounds. The chronic cytotoxicity of these compounds was determined by the MTT (3-[4, 5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) assay with a little modification. Briefly, Human Jurkat and Hela cells were seeded in a 96-well plate at 8×10^3 cells/well 24 h before treatment. Then cells were treated with different concentrations of compounds for 24 h at 37 °C in a humidified atmosphere at 5% CO_2. Cells treated with phosphate buffered saline (PBS) buffer alone were the control. After that, 10 μL of 5 mg/mL MTT reagent solution was added into each well, and the 96-well plate was incubated for 4 h at 37 °C. Then, the supernatant was discarded, and the MTT formazan precipitate was dissolved in 150 μL of DMSO with gently shaking. The absorbance was determined by a microplate reader (Bio-Rad 680) at 570 nm. IC_{50} values for each cell line were evaluated, representing the concentration at which human cell viability was reduced to 50% compared with PBS-treated cells.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, compound characterization, and X-ray crystallographic data (CIF) for **3f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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