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Enantioselective synthesis of 2-amino-5,6,7,8-tetrahydro-5-oxo-4*H*-chromene-3-carbonitriles using squaramide as the catalyst

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ABSTRACT

The organocatalyzed enantioselective synthesis of a series of chiral 2-amino-5,6,7,8-tetrahydro-5-oxo-4*H*-chromene-3-carbonitriles was achieved using bifunctional squaramides as the catalysts. The tandem Michael addition–cyclization reaction of cyclohexane-1,3-diones and benzylidenemalononitriles gave the corresponding products in excellent yields (up to 99%) and moderate to good enantioselectivities (up to 83% ee). This investigation provides an efficient and useful process for the synthesis of chiral 2-amino-4*H*-chromenes.

1. Introduction

Chromene derivatives, which occurred widely in natural compounds,[1] are one of the most important heterocyclic compounds. The chromene moiety frequently possesses efficient biological activities and pharmacological properties, such as spasmolytic, diuretic, anticoagulant, anticancer, and antianaphylactic activities.[2] Among the different types of chromene derivatives, 2-amino-4*H*-chromenes are popular compounds that exist in drugs. Some representative biologically active 2-amino-4*H*-chromene derivatives are listed in Figure 1.[3]

Due to their usefulness, methods for the synthesis of 2-amino-4*H*-chromenes have been developed.[4] The asymmetric synthesis of 4*H*-chromene derivatives has seen great improvements. To the best of our knowledge, there are two different types of methods for the asymmetric synthesis of 2-amino-4*H*-chromene scaffolds. The first type utilizes transition metal complexes as catalysts. For example, Feng et al. reported the asymmetric synthesis of 2-amino-4*H*-chromene derivatives with moderate to good yields and with high enantioselectivities.[5] The second type are organocatalyzed methods with bifunctional thioureas. Several reports using thiourea catalysts have been developed since 2008.[6] In 2009, Xie et al. reported the asymmetric synthesis of functionalized 2-amino-4*H*-chromene derivatives catalyzed by 9-amino-9-deoxyepiquinine in combination with (*R*)-1,1′-binaphth-2,2′-diylhydrogen phosphate.[7]

In recent years, thioureas[8,9] and squaramides[10,11] have emerged as important hydrogen-bonding organocatalysts for the preparation of enantiomerically enriched compounds. As part of our ongoing project on the synthesis and application of hydrogen-bonding

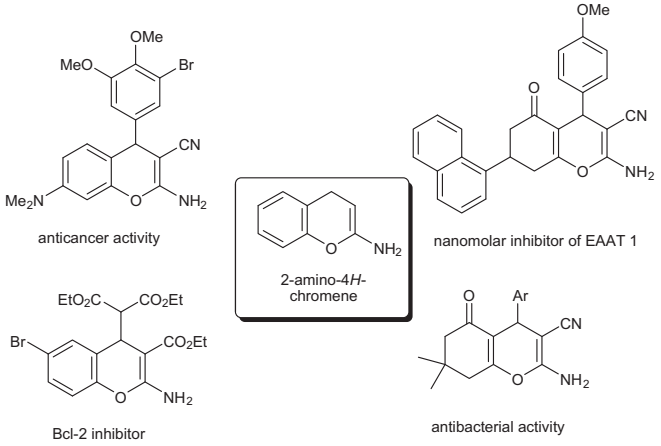

Figure 1. 2-Amino-4*H*-chromene and representative derivatives exhibiting biological activity.

thiourea and squaramide organocatalysts for the synthesis of functionalized chiral compounds, we have recently succeeded in developing an organocatalyzed enantioselective tandem Michael addition–cyclization of malononitrile to nitroalkenes for the direct synthesis of chiral 2-amino-4-(nitromethyl)-4*H*-chromene-3-carbonitriles.[12] To further extend this methodology for the synthesis of other chiral heterocyclic compounds, we want to develop a facile method for the asymmetric synthesis of 2-amino-5,6,7,8-tetrahydro-5-oxo-4*H*-chromene-3-carbonitriles catalyzed by these organocatalysts. During the preparation of our manuscript, Wang et al. reported a one-pot enantioselective synthesis of functionalized

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pyranocoumarins and 2-amino-4*H*-chromenes using tertiary amine-thioureas as the organocatalysts.[6e] Although the previous work has reported bifunctional thioureas can catalyze a tandem asymmetric Michael addition–cyclization reaction for the synthesis of chiral 2-amino-4*H*-chromenes, the asymmetric synthesis of these important chromenes is still lacking. Herein we report a bifunctional squaramide catalyzed Michael addition–cyclization sequence for the asymmetric synthesis of 2-amino-5,6,7,8-tetrahydro-5-oxo-4*H*-chromene-3-carbonitriles.

2. Results and discussion

Initially, we adopted the synthesis of 2-amino-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4*H*-chromene-3-carbonitrile **11a** from the tandem Michael addition–cyclization of 5,5-dimethylcyclohexane-1,3-dione **9** and benzylidenemalononitrile **10a** as the model reaction. Several thiourea and squaramide organocatalysts **1**–**8** (Fig. 2), which were readily prepared according to previous reports,[9a,c,11c,f,13] were first screened at room temperature. The results are presented in Table 1. In these catalysts, we found that the thiourea catalysts **1** and **2** gave very poor enantioselectivities (Table 1, entries 1 and 2). This result indicates that thiourea catalysts are not good for this reaction. Next, we tried to evaluate the catalytic performance of squaramide organocatalysts **3**–**8**. These squaramide catalysts performed much better than the thioureas. Catalyst **4** bearing a tertiary amine and a 3,5-bis(trifluoromethyl) group on the aromatic ring gave the best enantioselectivity, and the desired product was obtained in 93% yield and 53% ee at room temperature after 45 min (Table 1, entry 4). We next evaluated the effect of temperature and catalyst loading. When the reaction was carried out in CH_2Cl_2 at 0 °C for 5 h, product **11a** was obtained in a higher enantioselectivity and good yield (Table 1, entry 9). If the reaction temperature was decreased to −20 °C, the enantioselectivity decreased (Table 1, entry 10). No matter the loading of catalyst, whether it was decreased to 2 mmol % or increased to 10 mmol %, it did not give a better enantioselectivity (Table 1, entries 11 and 12).

For further optimization of the reaction condition, we next focused on the solvent effects. The screening results are summarized in Table 2. It was found that, besides CH_2Cl_2, similar yields could also be obtained in toluene, chlorobenzene, xylene, CH_3CN, THF, $ClCH_2CH_2Cl$, and $CHCl_3$ (Table 2, entries 2–8). Variation of the solvents had a pronounced effect on the enantioselectivity of the reaction. CH_3CN was the worst solvent for this reaction with 90% yield and 19% ee (Table 2, entry 5). THF was the best solvent, and the product was obtained in excellent yield and moderate enantioselectivity (Table 2, entry 6). Additionally, a slightly better enantioselectivity was obtained when 4 Å MS was added (Table 2, entry 9).

With the optimized reaction conditions in hand, we then screened the substrate scope of this reaction and the results are summarized in Table 3. A series of benzylidenemalononitrile derivatives **10** reacted with 5,5-dimethylcyclohexane-1,3-dione to afford the corresponding 2-amino-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4*H*-chromene-3-carbonitriles **11** in excellent yields with moderate to good enantioselectivities. As shown in Table 3, different substituted groups on the phenyl ring had pronounced effects on the enantioselectivity of this reaction: for *para*-bromobenzylidene-malononitrile, the enantioselectivity was 83% ee (Table 3, entry 4), and for *para*-nitrobenzylidene-malononitrile, the enantioselectivity was only 42% ee (Table 3, entry 6). The position of the substituent on

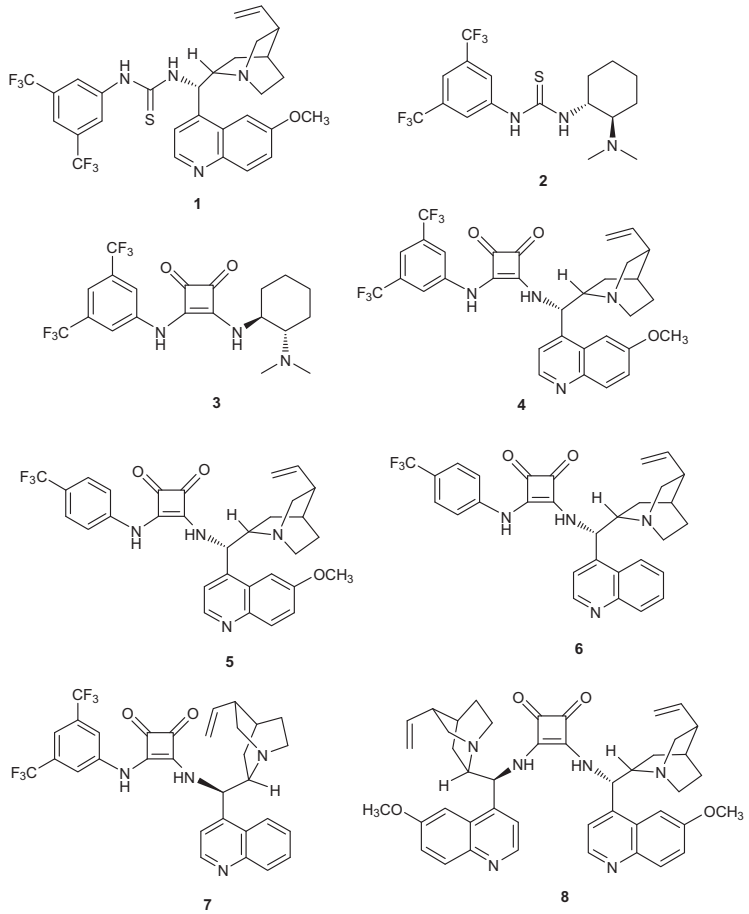
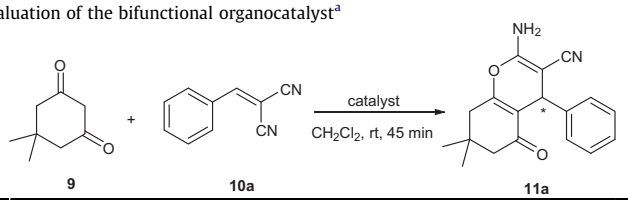


Figure 2. Thiourea and squaramide organcatalysts.

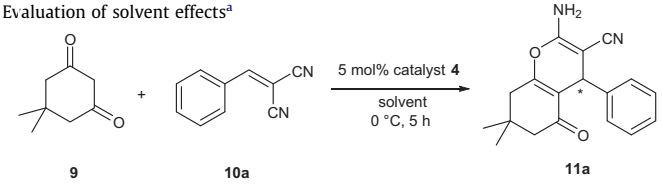
Table 1
Evaluation of the bifunctional organocatalyst[a]



Entry	Catalyst	Loading (mol %)	Yield[b] (%)	ee[c] (%)
1	**1**	5	97	18
2	**2**	5	99	−5
3	**3**	5	97	37
4	**4**	5	93	53
5	**5**	5	94	40
6	**6**	5	89	22
7	**7**	5	94	−40
8	**8**	5	97	22
9[d]	**4**	5	98	62
10[e]	**4**	5	95	52
11[d]	**4**	2	82	56
12[d]	**4**	10	99	47

[a] Unless noted otherwise, reactions were carried out with 5,5-dimethylcyclohexane-1,3-dione **9** (0.25 mmol) and benzylidenemalononitrile **10a** (0.25 mmol) in 2 mL of CH_2Cl_2 at room temperature.
[b] Isolated yields after silica gel chromatography.
[c] Determined by HPLC analysis on a Daicel Chiralpak IA column.
[d] Reactions were carried out at 0 °C for 5 h.
[e] Reactions were carried out at −20 °C for 24 h.

Table 2
Evaluation of solvent effects[a]



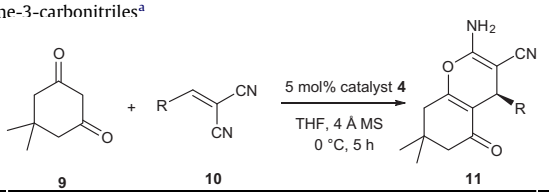
Entry	Solvent	Yield[b] (%)	ee[c] (%)
1	CH_2Cl_2	98	62
2	Toluene	88	48
3	Chlorobenzene	98	49
4	Xylene	87	51
5	CH_3CN	90	19
6	THF	98	65
7	$ClCH_2CH_2Cl$	95	53
8	$CHCl_3$	98	59
9[d]	THF	98	67

[a] Unless noted otherwise, reactions were carried out with 5,5-dimethylcyclohexane-1,3-dione **9** (0.25 mmol) and benzylidenemalononitrile **10a** (0.25 mmol) at 0 °C for 5 h.
[b] Isolated yields after silica gel chromatography.
[c] Determined by HPLC analysis on a Daicel Chiralpak IA column.
[d] 4 Å MS (30 mg) was used.

the phenyl ring also affected the enantioselectivity. The *ortho*-substituted compounds gave slightly lower enantioselectivities than the *para*-substituted compounds (Table 3, entry 7 vs entry 3, entry 8 vs entry 5). We tried several methods to synthesize alkyl-substituted methylenemalononitriles, but all trials were unsuccessful in giving the corresponding products. A commercially available ethoxymethylenemalononitrile was used as the substrate, but the Michael addition–cyclization reaction did not take place (Table 3 entry 11).

Encouraged by the above results, we investigated further the tandem Michael addition–cyclization of cyclohexane-1,3-dione **12** to benzylidenemalononitriles **10** catalyzed by catalyst **4** under the optimal conditions. The results are shown in Table 4. The same substrate scope was explored and the corresponding 2-amino-

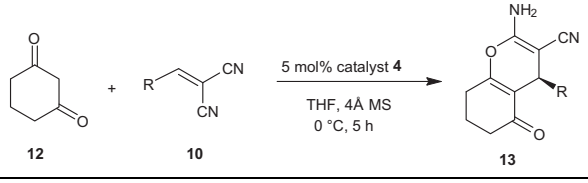
Table 3
Enantioselective synthesis of 2-amino-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4*H*-chromene-3-carbonitriles[a]



Entry	R	Product	Yield[b] (%)	ee[c] (%)
1	C_6H_5	**11a**	99	67
2	4-FC_6H_4	**11b**	95	58
3	4-ClC_6H_4	**11c**	97	55
4	4-BrC_6H_4	**11d**	96	83
5	4-MeC_6H_4	**11e**	97	68
6	4-$NO_2C_6H_4$	**11f**	94	42
7	2-ClC_6H_4	**11g**	99	51
8	2-MeC_6H_4	**11h**	98	65
9	3,4-$(MeO)_2C_6H_3$	**11i**	90	59
10	2-Naphthyl	**11j**	94	54
11	EtO	**11k**	—	—

[a] Unless noted otherwise, reactions were carried out with 5,5-dimethylcyclohexane-1,3-dione **9** (0.25 mmol), benzylidenemalononitrile **10** (0.25 mmol), and 30 mg 4 Å MS in THF at 0 °C for 5 h.
[b] Isolated yields after silica gel chromatography.
[c] Determined by HPLC analysis on a Daicel Chiralpak IA column.

Table 4
Enantioselective synthesis of 2-amino-5,6,7,8-tetrahydro-5-oxo-4*H*-chromene-3-carbonitriles[a]



Entry	R	Product	Yield[b] (%)	ee[c] (%)
1	C_6H_5	**13a**	84	55
2	4-FC_6H_4	**13b**	91	42
3	4-ClC_6H_4	**13c**	98	53
4	4-BrC_6H_4	**13d**	94	49
5	4-MeC_6H_4	**13e**	99	54
6	4-$NO_2C_6H_4$	**13f**	91	31
7	2-ClC_6H_4	**13g**	93	49
8	2-MeC_6H_4	**13h**	99	49
9	3,4-$(MeO)_2C_6H_3$	**13i**	94	52
10	2-Naphthyl	**13j**	99	46

[a] Unless noted otherwise, reactions were carried out with cyclohexane-1,3-dione **12** (0.25 mmol), benzylidenemalononitrile **10** (0.25 mmol), and 30 mg 4 Å MS in THF at 0 °C for 5 h.
[b] Isolated yields after silica gel chromatography.
[c] Determined by HPLC analysis on a Daicel Chiralpak IA column.

5,6,7,8-tetrahydro-5-oxo-4*H*-chromene-3-carbonitriles **13** were obtained in excellent yields with slightly lower enantioselectivities due to the lack of two methyl groups. As shown in Table 4, a similar tendency of the substituent effect on the enantioselectivities was observed.

On the basis of the experimental results described above, a catalytic activation mode for the asymmetric induction in this catalytic system is hypothesized and shown in Figure 3. We envision that the chiral squaramide **4** acts as a bifunctional catalyst. The cyclohexane-1,3-dione is deprotonated by the basic nitrogen atom of the tertiary amine. Meanwhile, the benzylidenemalononitrile is activated by the squaramide moiety via double hydrogen bonding between the NH groups and the CN group. The deprotonated cyclohexane-1,3-dione attacks the benzylidenemalononitrile from the *Si*-face to afford the (*R*)-configured stereocenter; the final product is formed after the following cyclization step.

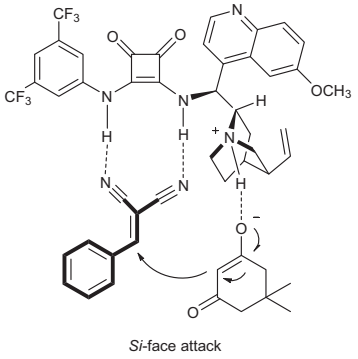
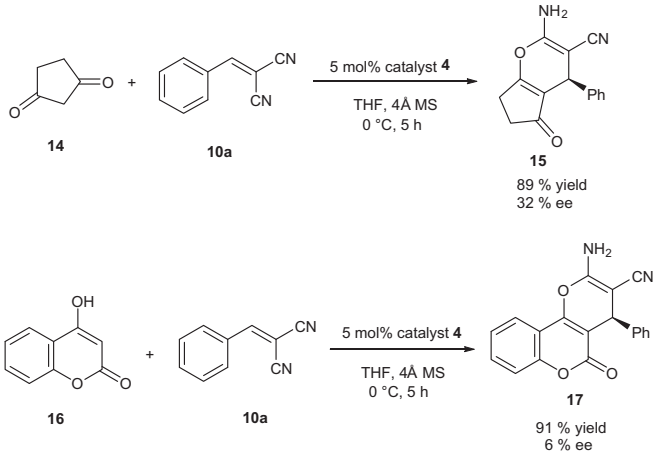


Figure 3. Proposed catalytic activation mode for the asymmetric induction.

In addition, we investigated the asymmetric Michael addition–cyclization of cyclopentane-1,3-dione and 4-hydroxycoumarin to benzylidenemalononitrile under the optimal conditions. The results are listed in Scheme 1. Comparable high yields were obtained in these two cases. 4-Hydroxycoumarin gave much lower enantioselectivity than cyclopentane-1,3-dione due to its higher reactivity.



Scheme 1. The asymmetric Michael addition–cyclization of cyclopentane-1,3-dione and 4-hydroxycoumarin with benzylidenemalononitrile. The asymmetric Michael addition–cyclization of cyclopentane-1,3-dione and 4-hydroxycoumarin with benzylidenemalononitrile.

3. Conclusion

We have developed an efficient organocatalyzed Michael addition–cyclization of cyclohexane-1,3-diones to benzylidenemalononitriles using a chiral bifunctional squaramide organocatalyst. The desired chiral 2-amino-5,6,7,8-tetrahydro-5-oxo-4*H*-chromene-3-carbonitriles were obtained with excellent yields (up to 99%) and moderate to good enantioselectivities (up to 83% ee) under mild conditions. This hydrogen-bonding squaramide organocatalysis route provides a facile method to access chiral functionalized chromene derivatives.

4. Experimental

4.1. General remarks

Commercially available compounds were used without further purification. Column chromatography was carried out with silica gel (200–300 mesh). Melting points were measured with a XT-4 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded with a Varian Mercury-plus 400 MHz spectrometer. ^{13}C NMR spectra were recorded at 100 MHz. Infrared spectra were obtained with a Perkin Elmer Spectrum One spectrometer. Optical rotations were measured with a WZZ-3 polarimeter at the indicated concentration with units of g/100 mL. The enantiomeric excesses of the products were determined by chiral HPLC using an Agilent 1200 LC instrument with Daicel Chiralpak IA column. The absolute configurations of the known products were assigned by HPLC and by comparison of the specific rotations with the reported data,[6e] and those of other products were assigned by analogy.

4.2. General procedure for the asymmetric synthesis of 2-amino-5,6,7,8-tetrahydro-5-oxo-4*H*-chromene-3-carbonitrile derivatives

To a solution of benzylidenemalononitrile **10** (0.25 mmol) and catalyst **4** (5 mmol %) in THF (2.0 mL) at 0 °C, 4 Å MS (30 mg) was added. Next, cyclohexane-1,3-dione **9** or **12** (0.25 mmol) was added. The reaction mixture was stirred for 5 h at 0 °C. After the reaction was complete, the solvent was removed under vacuum and the crude product was purified by column chromatography on silica gel to afford the corresponding products.

4.2.1. (*R*)-2-Amino-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4-phenyl-4*H*-chromene-3-carbonitrile 11a[6e]

Prepared according to the general procedure, the title compound was obtained as a white solid (72.6 mg, 99% yield); mp 207–208 °C. $[\alpha]_D^{25} = +35.5$ (*c* 0.53, acetone); HPLC (Daicel Chiralpak IA column, *n*-hexane/2-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R = 7.0 min, minor enantiomer t_R = 8.3 min, 67% ee. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.29 (t, *J* = 7.4 Hz, 2H, ArH), 7.13–7.20 (m, 3H, ArH), 7.02 (s, 2H, NH_2), 4.16 (s, 1H, CH), 2.52(AB quartet, *J* = 17.6 Hz, 2H, CH_2), 2.25 (d, *J* = 16.4 Hz, 1H, CH_2), 2.10 (d, *J* = 16.0 Hz, 1H, CH_2), 1.04 (s, 3H, CH_3), 0.95 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 195.5, 162.4, 158.4, 144.6, 128.2, 127.1, 126.5, 119.6, 112.7, 58.2, 49.9, 39.6, 35.5, 31.7, 28.3, 26.7 ppm.

4.2.2. (*R*)-2-Amino-4-(4-fluorophenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4*H*-chromene-3-carbonitrile 11b

Prepared according to the general procedure, the title compound was obtained as a white solid (74.1 mg, 95% yield); mp 193–194 °C (lit.[14] mp 191–193 °C racemic). $[\alpha]_D^{25} = +39.6$ (*c* 0.53, acetone); HPLC (Daicel Chiralpak IA column, *n*-hexane/2-propanol = 90:10, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R = 13.2 min, minor enantiomer t_R = 16.1 min, 58% ee. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.16–7.20 (m, 2H, ArH), 7.11 (t, *J* = 8.8 Hz, 2 H, ArH), 7.03 (s, 2H, NH_2), 4.20 (s, 1H, CH), 2.51 (s, 2H, CH_2), 2.25 (d, *J* = 16.0 Hz, 1H, CH_2), 2.11 (d, *J* = 16.0 Hz, 1H, CH_2), 1.04 (s, 3H, CH_3), 0.95 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 195.6, 162.4, 160.8 (d, $^1J_{CF}$ = 241.0 Hz), 158.4, 140.9, 129.0 (d, $^3J_{CF}$ = 8.0 Hz), 119.6, 114.9 (d, $^2J_{CF}$ = 21.2 Hz), 112.5, 58.1, 49.9, 39.6, 34.9, 31.7, 28.3, 26.8 ppm.

4.2.3. (*R*)-2-Amino-4-(4-chlorophenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4*H*-chromene-3-carbonitrile 11c

Prepared according to the general procedure, the title compound was obtained as a white solid (80.0 mg, 97% yield); mp 211–212 °C (lit.[14] mp 209–211 °C, racemic). $[\alpha]_D^{25} = +39.6$ (*c* 0.45, acetone); HPLC (Daicel Chiralpak IA column, *n*-hexane/2-propanol = 90:10, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R = 13.6 min, minor enantiomer t_R = 17.6 min, 55% ee. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.34 (d, *J* = 8.4 Hz, 2H, ArH), 7.16 (d, 2H, *J* = 8.0 Hz, ArH), 7.05 (s, 2H, NH_2), 4.19 (s, 1H, CH), 2.50 (s, 2H, CH_2), 2.24 (d, *J* = 16.0 Hz, 1H, CH_2), 2.10 (d,

J = 16.0 Hz, 1H, CH_2), 1.04 (s, 3H, CH_3), 0.95 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 195.5, 162.5, 158.4, 143.6, 131.0, 129.0, 128.2, 119.4, 112.3, 57.7, 49.9, 39.6, 35.0, 31.7, 28.2, 26.8 ppm.

4.2.4. (*R*)-2-Amino-4-(4-bromophenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4*H*-chromene-3-carbonitrile 11d

Prepared according to the general procedure, the title compound was obtained as a white solid (89.3 mg, 96% yield); mp 207–208 °C (lit.[14] mp 205–207 °C racemic). $[\alpha]_D^{25}$ = +39.2 (*c* 0.49, acetone); HPLC (Daicel Chiralpak IA column, *n*-hexane/2-propanol = 90:10, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R = 13.9 min, minor enantiomer t_R = 17.9 min, 83% ee. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.48 (d, J = 8.4 Hz, 2H, ArH), 7.11 (d, J = 8.4 Hz, 2H, ArH), 7.07 (s, 2H, NH_2), 4.18 (s, 1H, CH), 2.51 (s, 2H, CH_2), 2.25 (d, J = 16.0 Hz, 1H, CH_2), 2.10 (d, J = 16.4 Hz, 1H, CH_2), 1.03 (s, 3H, CH_3), 0.95 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 195.5, 162.5, 158.4, 144.1, 131.1, 129.4, 119.5, 112.2, 57.6, 49.8, 39.6, 35.1, 31.7, 28.2, 26.8 ppm.

4.2.5. (*R*)-2-Amino-5,6,7,8-tetrahydro-7,7-dimethyl-4-(4-methylphenyl)-5-oxo-4*H*-chromene-3-carbonitrile 11e

Prepared according to the general procedure, the title compound was obtained as a white solid (74.8 mg, 97% yield); mp 217–218 °C (lit.[15] mp 218–219 °C, racemic). $[\alpha]_D^{25}$ = +22.1 (*c* 0.97, acetone); HPLC (Daicel Chiralpak IA column, *n*-hexane/2-propanol = 90:10, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R = 11.9 min, minor enantiomer t_R = 15.4 min, 68% ee. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.08 (d, J = 8.0 Hz, 2H, ArH), 7.02 (d, J = 8.0 Hz, 2H, ArH), 6.96 (s, 2H, NH_2), 4.12 (s, 1H, CH), 2.50 (AB quartet, J = 17.2 Hz, 2H, CH_2), 2.22–2.26 (m, 3H, CH_2, CH_3), 2.08 (d, J = 16.4 Hz, 1H, CH_2), 1.03 (s, 3H, CH_3), 0.95 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 195.5, 162.2, 158.3, 141.7, 135.5, 128.8, 127.0, 119.6, 112.8, 58.4, 49.9, 39.6, 35.1, 31.7, 28.3, 26.7, 20.5 ppm.

4.2.6. (*R*)-2-Amino-5,6,7,8-tetrahydro-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-4*H*-chromene-3-carbonitrile 11f

Prepared according to the general procedure, the title compound was obtained as a white solid (79.3 mg, 94% yield); mp 175–176 °C (lit.[14] mp 179–180 °C, racemic). $[\alpha]_D^{25}$ = +25.0 (*c* 0.93, acetone); HPLC (Daicel Chiralpak IA column, *n*-hexane/2-propanol = 90:10, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R = 23.3 min, minor enantiomer t_R = 32.8 min, 42% ee. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.18 (d, J = 8.8 Hz, 2H, ArH), 7.45 (d, J = 8.8 Hz, 2H, ArH), 7.18 (s, 2H, NH_2), 4.37 (s, 1H, CH), 2.54 (s, 2H, CH_2), 2.27 (d, J = 16.0 Hz, 1H, CH_2), 2.12 (d, J = 16.4 Hz, 1H, CH_2), 1.05 (s, 3H, CH_3), 0.96 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 195.6, 163.0, 158.5, 152.2, 146.2, 128.5, 123.6, 119.2, 111.7, 56.9, 49.8, 39.6, 35.6, 31.7, 28.2, 26.8 ppm.

4.2.7. (*R*)-2-Amino-4-(2-chlorophenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4*H*-chromene-3-carbonitrile 11g

Prepared according to the general procedure, the title compound was obtained as a white solid (80.9 mg, 99% yield); mp 216–217 °C (lit.[14] mp 214–215 °C, racemic). $[\alpha]_D^{25}$ = +47.3 (*c* 0.77, acetone); HPLC (Daicel Chiralpak IA column, *n*-hexane/2-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R = 7.3 min, minor enantiomer t_R = 8.8 min, 51% ee. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.36 (d, J = 8.0 Hz, 1H, ArH), 7.27 (t, J = 6.8 Hz, 1H, ArH), 7.16–7.22 (m, 2H, ArH), 7.03 (s, 2H, NH_2), 4.70 (s, 1H, CH), 2.52 (AB quartet, J = 17.2 Hz, 2H, CH_2), 2.25 (d, J = 16.0 Hz, 1H, CH_2), 2.08 (d, J = 16.0 Hz, 1H, CH_2), 1.04 (s, 3H, CH_3), 0.98 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 195.4, 163.0, 158.6, 141.5, 132.0, 129.9, 129.3, 128.1, 127.3, 119.2, 111.7, 56.8, 49.9, 39.6, 32.8, 31.7, 28.3, 26.8 ppm.

4.2.8. (*R*)-2-Amino-5,6,7,8-tetrahydro-7,7-dimethyl-4-(2-methylphenyl)-5-oxo-4*H*-chromene-3-carbonitrile 11h

Prepared according to the general procedure, the title compound was obtained as a white solid (75.9 mg, 98% yield); mp 205–206 °C (lit.[14] mp 212–214 °C, racemic). $[\alpha]_D^{25}$ = +37.0 (*c* 0.74, acetone); HPLC (Daicel Chiralpak IA column, *n*-hexane/2-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R = 6.1 min, minor enantiomer t_R = 7.9 min, 65% ee. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.09–7.13 (m, 2H, ArH), 7.02–7.06 (m, 1H, ArH), 6.94 (s, 3H, ArH + NH_2), 4.47 (s, 1H, CH), 2.52 (s, 2H, CH_2), 2.46 (s, 3H, CH_3), 2.24 (d, J = 16.0 Hz, 1H, CH_2), 2.07 (d, J = 16.0 Hz, 1H, CH_2), 1.05 (s, 3H, CH_3), 0.96 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 195.6, 162.4, 158.2, 143.5, 134.7, 129.8, 127.2, 126.3, 126.1, 119.7, 113.4, 58.2, 49.9, 39.6, 31.8, 30.8, 28.4, 26.7, 19.0 ppm.

4.2.9. (*R*)-2-Amino-5,6,7,8-tetrahydro-7,7-dimethyl-4-(3,4-dimethoxyphenyl)-5-oxo-4*H*-chromene-3-carbonitrile 11i

Prepared according to the general procedure, the title compound was obtained as a white solid (79.6 mg, 90% yield); mp 194–195 °C (lit.[16] mp 191–193 °C, racemic). $[\alpha]_D^{25}$ = +21.1 (*c* 0.92, acetone); HPLC (Daicel Chiralpak IA column, *n*-hexane/2-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R = 11.0 min, minor enantiomer t_R = 14.1 min, 64% ee. ^1H NMR (400 MHz, DMSO-d_6): δ = 6.97 (s, 2H, NH_2), 6.86 (d, J = 8.0 Hz, ArH), 6.68 (s, 1H, ArH), 6.65 (dd, J_1 = 1.2 Hz, J_2 = 8.4 Hz, 1H, ArH), 4.12 (s, 1H, CH), 3.71 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 2.51 (AB quartet, J = 17.6 Hz, 2H, CH_2), 2.26 (d, J = 16.0 Hz, 1H, CH_2), 2.11(d, J = 16.0 Hz, 1H, CH_2), 1.04 (s, 3H, CH_3), 0.98 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 195.6, 162.2, 158.3, 148.4, 147.5, 137.3, 119.7, 119.1, 112.8, 111.7, 111.0, 58.5, 55.40, 55.37, 49.9, 39.6, 35.0, 31.7, 28.4, 26.6 ppm.

4.2.10. (*R*)-2-Amino-5,6,7,8-tetrahydro-7,7-dimethyl-4-(2-naphthyl)-5-oxo-4*H*-chromene-3-carbonitrile 11j

Prepared according to the general procedure, the title compound was obtained as a white solid (81.0 mg, 94% yield); mp 257–258 °C (lit.[17] mp 258–260 °C, racemic). $[\alpha]_D^{25}$ = +73.7 (*c* 0.92, acetone); HPLC (Daicel Chiralpak IA column, *n*-hexane/2-propanol = 90:10, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R = 19.2 min, minor enantiomer t_R = 24.6 min, 54% ee. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.37 (d, J = 8.0 Hz, 1H, ArH), 7.90–7.92 (m, 1H, ArH), 7.77 (d, J = 8.0 Hz, 1H, ArH), 7.43–7.58 (m, 3H, ArH), 7.24 (d, J = 7.2 Hz, 1H, ArH), 6.96 (s, 2H, NH_2), 5.14 (s, 1H, CH), 2.59 (s, 2H, CH_2), 2.24 (d, J = 16.0 Hz, 1H, CH_2), 2.06 (d, J = 16.0 Hz, 1H, CH_2), 1.05 (s, 3H, CH_3), 0.99 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 195.6, 162.7, 158.3, 133.2, 130.7, 128.3, 126.9, 125.7, 125.6, 125.5, 123.5, 119.5, 113.3, 58.8, 49.9, 39.6, 31.7, 28.3, 26.9 ppm.

4.2.11. (*R*)-2-Amino-5,6,7,8-tetrahydro-5-oxo-4-phenyl-4*H*-chromene-3-carbonitrile 13a[6e]

Prepared according to the general procedure, the title compound was obtained as a white solid (55.7 mg, 84% yield); mp 213–214 °C. $[\alpha]_D^{25}$ = +54.7 (*c* 0.74, acetone); HPLC (Daicel Chiralpak IA column, *n*-hexane/2-propanol = 90:10, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R = 16.1 min, minor enantiomer t_R = 19.8 min, 55% ee. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.28 (t, J = 7.2 Hz, 2H, ArH), 7.14–7.19 (m, 3H, ArH), 6.99 (s, 2H, NH_2), 4.19 (s, 1H, CH), 2.62 (s, 2H, CH_2), 2.21–2.31 (m, 2H, CH_2), 1.87–1.98 (m, 2H, CH_2) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 195.8, 164.4, 158.4, 144.7, 128.2, 127.0, 126.4, 119.7, 113.7, 58.2, 36.3, 35.4, 26.4, 19.7 ppm.

4.2.12. (*R*)-2-Amino-4-(4-fluorophenyl)-5,6,7,8-tetrahydro-5-oxo-4*H*-chromene-3-carbonitrile 13b[6e]

Prepared according to the general procedure, the title compound was obtained as a white solid (64.6 mg, 91% yield); mp 211–212 °C. $[\alpha]_D^{25} = +42.9$ (*c* 1.03, acetone); HPLC (Daicel Chiralpak IA column, *n*-hexane/2-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R = 7.6 min, minor enantiomer t_R = 8.6 min, 42% ee. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.20 (t, *J* = 6 Hz, 2H, ArH), 7.10 (t, *J* = 8.0 Hz, 2H, ArH), 7.02 (s, 2H, NH_2), 4.21 (s, 1H, CH), 2.61 (s, 2H, CH_2), 2.22–2.34 (m, 2H, CH_2), 1.88–1.98 (m, 2H, CH_2) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 195.8, 164.4, 160.8 (d, $^1J_{C\text{-}F}$ = 240.9 Hz), 158.4, 140.9, 128.9 ($^3J_{C\text{-}F}$ = 8.1 Hz), 119.6, 114.9 ($^2J_{C\text{-}F}$ = 21.2 Hz), 113.6, 58.0, 36.2, 34.7, 26.4, 19.7 ppm.

4.2.13. (*R*)-2-Amino-4-(4-chlorophenyl)-5,6,7,8-tetrahydro-5-oxo-4*H*-chromene-3-carbonitrile 13c[6e]

Prepared according to the general procedure, the title compound was obtained as a white solid (73.9 mg, 98% yield); mp 227–228 °C. $[\alpha]_D^{25} = +24.7$ (*c* 0.85, acetone); HPLC (Daicel Chiralpak IA column, *n*-hexane/2-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R = 7.7 min, minor enantiomer t_R = 9.1 min, 53% ee. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.34 (d, *J* = 8.0 Hz, 2H, ArH), 7.19 (d, *J* = 8.0 Hz, 2H, ArH), 7.05 (s, 2H, NH_2), 4.20 (s, 1H, CH), 2.61 (s, 2H, CH_2), 2.22–2.34 (m, 2H, CH_2), 1.88–1.96 (m, 2H, CH_2) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 195.7, 164.5, 158.4, 143.7, 131.0, 129.0, 128.2, 119.5, 113.3, 57.6, 36.2, 34.9, 26.4, 19.7 ppm.

4.2.14. (*R*)-2-Amino-4-(4-bromophenyl)-5,6,7,8-tetrahydro-5-oxo-4*H*-chromene-3-carbonitrile 13d[6e]

Prepared according to the general procedure, the title compound was obtained as a white solid (81.5 mg, 94% yield); mp 234–235 °C. $[\alpha]_D^{25} = +29.5$ (*c* 0.80, acetone); HPLC (Daicel Chiralpak IA column, *n*-hexane/2-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R = 8.0 min, minor enantiomer t_R = 9.6 min, 49% ee. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.47 (d, *J* = 8.0 Hz, 2H, ArH), 7.13 (d, *J* = 8.0 Hz, 2H, ArH), 7.05 (s, 2H, NH_2), 4.19 (s, 1H, CH), 2.61 (s, 2H, CH_2), 2.22–2.33 (m, 2H, CH_2), 1.88–1.96 (m, 2H, CH_2) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 195.7, 164.5, 158.4, 144.1, 131.1, 129.4, 119.5, 113.2, 57.5, 36.2, 35.0, 26.4, 19.7 ppm.

4.2.15. (*R*)-2-Amino-5,6,7,8-tetrahydro-4-(4-methylphenyl)-5-oxo-4*H*-chromene-3-carbonitrile 13e

Prepared according to the general procedure, the title compound was obtained as a white solid (69.6 mg, 99% yield); mp 225–226 °C (lit.[18] mp 214–216 °C, racemic). $[\alpha]_D^{25} = +36.0$ (*c* 0.85, acetone); HPLC (Daicel Chiralpak IA column, *n*-hexane/2-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R = 6.7 min, minor enantiomer t_R = 7.9 min, 54% ee. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.07 (d, *J* = 7.8 Hz, 2H, ArH), 7.03 (d, *J* = 8.0 Hz, 2H, ArH), 6.95 (s, 2H, NH_2), 4.14 (s, 1H, CH), 2.60 (s, 2H, CH_2), 2.20–2.32 (m, 5H, CH_2 + CH_3), 1.86–1.95 (m, 2H, CH_2) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 195.7, 164.1, 158.4, 141.8, 135.5, 128.8, 126.8, 127.0, 113.9, 58.3, 36.3, 35.0, 26.4, 20.5, 19.7 ppm.

4.2.16. (*R*)-2-Amino-5,6,7,8-tetrahydro-4-(4-nitrophenyl)-5-oxo-4*H*-chromene-3-carbonitrile 13f

Prepared according to the general procedure, the title compound was obtained as a white solid (76.8 mg, 99% yield); mp 233–234 °C (lit.[18] mp 235–236 °C, racemic). $[\alpha]_D^{25} = +42.2$ (*c* 1.02, acetone); HPLC (Daicel Chiralpak IA column, *n*-hexane/2-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R = 12.3 min, minor enantiomer t_R = 18.0 min, 31% ee. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.16 (d, *J* = 8.4 Hz, 2H, ArH), 7.47 (d, *J* = 8.4 Hz, 2H, ArH), 7.18 (s, 2H, NH_2), 4.37 (s, 1H, CH), 2.64 (s, 2H, CH_2), 2.23–2.37 (m, 2H, CH_2), 1.91–1.99 (m, 2H, CH_2) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 195.8, 165.0, 158.5, 152.2, 146.1, 128.5, 123.5, 119.3, 112.7, 56.9, 36.1, 35.5, 26.5, 19.7 ppm.

4.2.17. (*R*)-2-Amino-4-(2-chlorophenyl)-5,6,7,8-tetrahydro-5-oxo-4*H*-chromene-3-carbonitrile 13g

Prepared according to the general procedure, the title compound was obtained as a white solid (70.0 mg, 93% yield); mp 213–214 °C (lit.[18] mp 212–214 °C, racemic). $[\alpha]_D^{25} = +33.2$ (*c* 0.86, acetone); HPLC (Daicel Chiralpak IA column, *n*-hexane/2-propanol = 90:10, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R = 20.0 min, minor enantiomer t_R = 23.0 min, 34% ee. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.36 (d, *J* = 7.2 Hz, 1H, ArH), 7.26 (t, 1H, *J* = 7.0 Hz, 1H, ArH), 7.19 (t, *J* = 6.8 Hz, 2H, ArH), 7.01 (s, 2H, NH_2), 4.71 (s, 1H, CH), 2.55–2.67 (m, 2H, CH_2), 2.19–2.32 (m, 2H, CH_2), 1.90–1.97 (m, 2H,CH_2) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 195.6, 165.0, 158.5, 141.7, 132.0, 129.7, 129.2, 128.0, 127.4, 119.2, 112.8, 56.8, 36.2, 32.6, 26.4, 19.8 ppm.

4.2.18. (*R*)-2-Amino-5,6,7,8-tetrahydro-4-(2-methylphenyl)-5-oxo-4*H*-chromene-3-carbonitrile 13h

Prepared according to the general procedure, the title compound was obtained as a white solid (69.4 mg, 99% yield); mp 195–196 °C. $[\alpha]_D^{25} = +32.7$ (*c* 1.12, acetone); HPLC (Daicel Chiralpak IA column, *n*-hexane/2-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R = 7.0 min, minor enantiomer t_R = 7.8 min, 49% ee. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.02–7.13 (m, 3H, ArH), 6.96 (d, *J* = 7.2 Hz, 1H, ArH), 6.93 (s, 2H, NH_2), 4.47 (s, 1H, CH), 2.60–2.67 (m, 2H, CH_2), 2.46 (s, 3H, CH_3), 2.18–2.31 (m, 2H, CH_2), 1.88–1.98 (m, 2H, CH_2) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 195.8, 164.3, 158.1, 143.6, 134.7, 129.7, 127.3, 126.4, 126.1, 119.7, 114.5, 58.1, 36.2, 31.0, 26.3, 19.8, 19.0 ppm. HRMS (ESI): *m*/*z* calculated for $C_{17}H_{17}N_2O_2$ $[M+H]^+$ 281.12845, found 281.12791.

4.2.19. (*R*)-2-Amino-5,6,7,8-tetrahydro-4-(3,4-dimethoxyphenyl)-5-oxo-4*H*-chromene-3-carbonitrile 13i

Prepared according to the general procedure, the title compound was obtained as a white solid (76.9 mg, 94% yield); mp 227–228 °C (lit.[16] mp 227–229 °C, racemic). $[\alpha]_D^{25} = +24.9$ (*c* 0.85, acetone); HPLC (Daicel Chiralpak IA column, *n*-hexane/2-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R = 10.8 min, minor enantiomer t_R = 15.2 min, 53% ee. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.94 (s, 2H, NH_2), 6.85 (d, *J* = 8.4 Hz, 1H, ArH), 6.72 (s, 1H, ArH), 6.63–6.65 (m, 1H, ArH), 4.15 (s, 1H, CH), 3.72 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 2.61 (s, 2H, CH_2), 2.28 (s, 2H, CH_2), 1.87–1.98 (m, 2H, CH_2) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 195.8, 164.1, 158.3, 148.4, 147.5, 137.3, 119.8, 118.9, 113.9, 111.8, 111.1, 58.3, 55.45, 55.40, 36.3, 34.8, 26.4, 19.8 ppm.

4.2.20. (*R*)-2-Amino-5,6,7,8-tetrahydro-4-(2-naphthyl)-5-oxo-4*H*-chromene-3-carbonitrile 13j

Prepared according to the general procedure, the title compound was obtained as a white solid (66.1 mg, 99% yield); mp 254–255 °C (lit.[17] mp 254–255 °C, racemic). $[\alpha]_D^{25} = +61.5$ (*c* 0.78, acetone); HPLC (Daicel Chiralpak IA column, *n*-hexane/2-propanol = 90:10, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R = 26.1 min, minor enantiomer t_R = 28.6 min, 45% ee. ^{1}H NMR (400 MHz, DMSO-d_6-d_6): δ = 8.39 (d, *J* = 8.0 Hz, 1H, ArH), 7.91 (d, *J* = 7.6 Hz, 1H, ArH), 7.77 (d, *J* = 8.0 Hz, 1H, ArH), 7.51–7.58 (m, 2H, ArH), 7.44 (t, *J* = 7.2 Hz, 1H, ArH), 7.25 (d, *J* = 6.8 Hz, 1H, ArH), 6.94 (s, 2H, NH_2), 5.15 (s, 1H, CH), 2.62–2.75

(m, 2H, CH_2), 2.18–2.32 (m, 2H, CH_2), 1.91–2.01 (m, 2H, CH_2) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 195.8, 164.7, 158.4, 141.9, 133.2, 130.7, 128.3, 126.8, 125.7, 125.5, 124.9, 123.6, 119.6, 114.4, 58.7, 36.3, 30.0, 26.5, 19.8 ppm.

4.2.21. (*R*)-2-Amino-4,5,6,7-tetrahydro-5-oxo-4-phenyl-cyclopenta[*b*]pyran-3-carbonitrile 15

Prepared according to the general procedure, the title compound was obtained as a white solid (56.3 mg, 89% yield); mp 187–188 °C (lit.[19] mp 192–194 °C, racemic). $[\alpha]_D^{25} = +6.9$ (*c* 1.15, acetone); HPLC (Daicel Chiralpak IA column, *n*-hexane/2-propanol = 90:10, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R = 20.1 min, minor enantiomer t_R = 24.4 min, 32% ee. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.30 (t, *J* = 7.2 Hz, 2H, ArH), 7.18–7.23 (m, 3H, ArH), 7.20 (s, 2H, NH_2), 4.19 (s, 1H, CH), 2.68–2.82 (m, 2H, CH_2), 2.36–2.38 (m, 2H, CH_2) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 201.0, 176.2, 159.4, 142.6, 128.3, 127.6, 126.8, 119.7, 116.8, 57.5, 35.5, 33.4, 24.5 ppm.

4.2.22. (*R*)-2-Amino-5-oxo-4-phenyl-4*H*,5*H*-pyrano[3,2-*c*]chromene-3-carbonitrile 17[6e]

Prepared according to the general procedure, the title compound was obtained as a white solid (72.6 mg, 99% yield); mp 256–257 °C. $[\alpha]_D^{25} = +1.1$ (*c* 0.75, acetone); HPLC (Daicel Chiralpak IA column, *n*-hexane/2-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm): major enantiomer t_R = 8.1 min, minor enantiomer t_R = 8.8 min, 6% ee. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.90 (d, *J* = 8.0 Hz, 1H, ArH), 7.71 (t, *J* = 7.8 Hz, 1H, ArH), 7.41–7.51 (m, 4H, ArH), 7.25–7.33 (m, 5H, ArH + NH_2) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.4, 157.9, 153.3, 152.0, 143.3, 132.8, 128.4, 127.6, 127.0, 124.6, 122.4, 119.2, 116.5, 112.9, 103.9, 57.9, 36.9 ppm.

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