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Asymmetric synthesis of the 6-cyanoindole derivatives as non-steroidal glucocorticoid receptor modulators using (+)- and (−)-*tert*-butyl 6-cyano-3-[3-ethoxy-1,1,1-trifluoro-2-hydroxy-3-oxopropan-2-yl]-1*H*-indole-1-carboxylate

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ABSTRACT

We have successfully synthesized enantiomerically pure (+)- and (−)-*tert*-butyl 6-cyano-3-[3-ethoxy-1,1,1-trifluoro-2-hydroxy-3-oxopropan-2-yl]-1*H*-indole-1-carboxylate (+)-**1** and (−)-**1**, which are key intermediates of non-steroidal glucocorticoid receptor modulators, by employing a cinchona alkaloid catalyzed addition of 6-cyanoindole to ethyl trifluoropyruvate. The optimized method can be applied to large-scale synthesis. Furthermore, using the key intermediates (+)-**1** and (−)-**1**, enantiomerically pure glucocorticoid receptor modulators (+)-**3** and (−)-**3** can be synthesized (>99% ee for both compounds). The glucocorticoid receptor binding affinity was influenced by the stereogenic center at the trifluoromethyl alcohol moiety; compound (−)-**3** showed a higher binding affinity compared to (+)-**3**.

1. Introduction

A number of non-steroidal glucocorticoid receptor modulators, containing the trifluoromethyl alcohol structure and possessing the anti-inflammatory effects of a glucocorticoid but with reduced adverse effects, have been explored as potential therapeutics for a variety of inflammatory diseases, such as asthma, rheumatoid arthritis, and allergic rhinitis.[1–3] Recently, we have also disclosed novel indole derivatives, such as **2** and **3**, which have the trifluoromethyl alcohol structure as glucocorticoid receptor modulators.[4] Moreover, it has been reported that the absolute configuration of the hydroxyl group in the trifluoromethyl alcohol structure greatly influences the anti-inflammatory effects of glucocorticoid receptor modulators.[3] These findings led us to prepare enantiomerically pure indole derivatives in our glucocorticoid receptor modulator program. In view of the retrosynthesis of our glucocorticoid receptor modulators, enantiomerically pure **1** was considered to be a key intermediate (Fig. 1). In order to obtain enantiomerically pure **1** from enantiomerically pure **4**, we conducted catalytic asymmetric synthesis, which involved the asymmetric construction of the quarternary carbon center in the trifluoromethyl alcohol moiety.

Catalytic asymmetric synthesis, which is one of the important methodologies in modern synthetic chemistry for the preparation of enantiomerically enriched compounds, has been developed by using metal catalysts or organocatalysts.[5] Organocatalytic asymmetric reactions have several significant advantages over the metal-catalyzed ones for the following reasons: (1) lack of sensitivity to moisture and oxygen; (2) low cost and low toxicity and (3) they are recyclable and reusable catalysts.[6–8] Therefore, organocatalysts are expected to be very useful in both the pharmaceutical and chemical industries.

Several researchers have reported the organocatalytic asymmetric addition of indole derivatives to ethyl trifluoropyruvate **6**.[9] Ma et al. reported the chiral Brønsted acid catalyzed reaction, which afforded the corresponding products with modest ee.[9g] Jørgensen et al. described their discovery of chiral sulfonamides, which provided the product with 23% ee.[9d] Török et al. reported that cinchona alkaloids used as organocatalysts gave products quantitatively with high enantioselectivity.[9c] Among them, cinchona alkaloids, which represent a class of natural products possessing useful features as asymmetric organocatalysts, are inexpensive and readily available for bulk-scale synthesis.[10]

From the aforementioned information, we selected cinchona alkaloids as organocatalysts and prepared enantiomerically pure **4** by using a cinchona alkaloid catalyzed asymmetric addition on the basis of the previous report by Török's. Herein we report an efficient and practical synthesis of enantiomerically pure **4** employing a cinchona alkaloid catalyzed asymmetric addition of 6-cyanoindole **5** to **6**. We also demonstrate that an efficient procedure for the preparation of enantiomerically pure **1** from enantiomerically pure **4**, which is appropriate for use in large-scale synthesis with simple manipulations. Additionally, we report the asymmetric synthesis of glucocorticoid receptor modulators (+)-**3** and (−)-**3** by using the corresponding enantiomerically pure **1** and present their comparative glucocorticoid receptor binding affinity.

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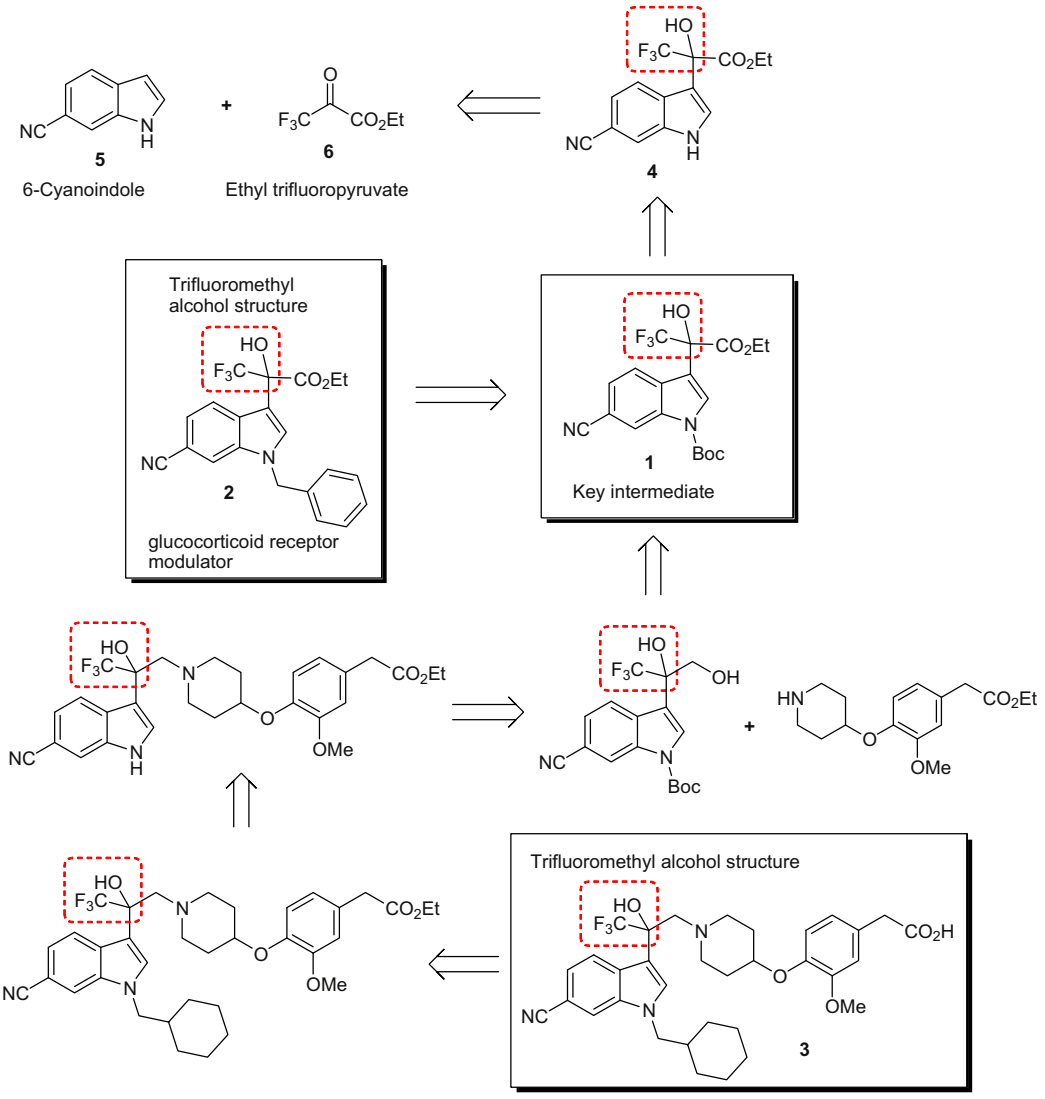
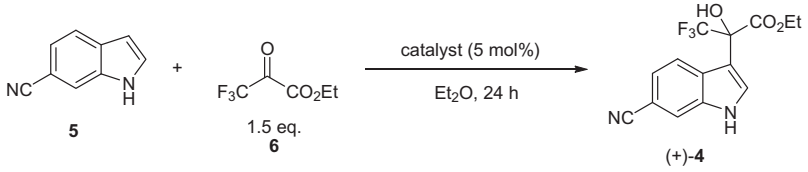


Figure 1. Retrosynthesis of glucocorticoid receptor modulators having the trifluoromethyl alcohol structure, such as **2** and **3**, via the key intermediate **1**.

Table 1
Effects of reaction temperature on cinchona alkaloids catalyzed asymmetric addition of **5** to **6**

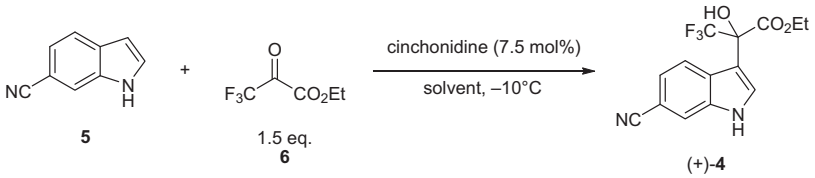


Entry	Catalyst	Temperature (°C)	Yield (%)	ee (%)
1	Cinchonidine	−10	88	90
2	Quinine	−10	81	87
3	Cinchonidine	−20	89	91
4	Cinchonidine	−40	71	94
5	Cinchonidine	−78	4	97

2. Results and discussion

Török et al. have reported the cinchona alkaloids catalyzed asymmetric addition of several indole derivatives to **6**. However, the reaction of **5** with **6** has not been included in that report.[9c] Thus, our initial efforts focused on investigating the effects of the cyano group at the C(6)-position of the indole ring by using cinchonidine under Török's experimental conditions (Table 1). As a result, the reaction of **5** with **6** in diethyl ether (Et_2O) afforded the product (+)-**4** with 90% ee in 88% yield (entry 1). These results suggest that

Table 2
Solvent screening for the cinchonidine catalyzed asymmetric addition of **5** to **6**



Entry	Solvent	Time (h)	Conversion[a] (%)		Yield (%)	ee (%)
			1 h	24 h		
1	Et_2O	24	65	95	89	89
2	Diisopropyl ether	24	64	97	93	90
3	Cyclopentyl methyl ether	24	61	97	90	88
4	MTBE	24	54	95	90	87
5	*n*-Hexane	24	4	41	29	56
6	*n*-Heptane	24	6	41	31	52
7	MeCN	24	43	70	59	70
8	EtOAc	24	49	94	88	80
9	Toluene	1	98	—	96	83

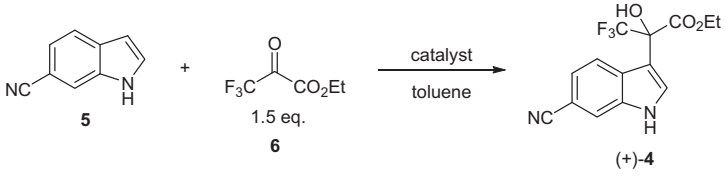
[a] Conversion was determined on the basis of area % by HPLC (254 nm).

the cyano group at the C(6)-position of the indole ring contributes to maintaining good yield and enantioselectivity. The reaction time of unsubstituted indole was 2 h,[9c] while that of 6-cyanoindole was 24 h. From these results, it was found that the low reactivity of the C(3)-position of the indole ring may be caused by the electron-withdrawing effect of the cyano group. Quinine, belonging to the cinchona alkaloids, also provided product (+)-**4** with 87% ee in 81% yield (entry 2). We then examined the effects of temperature on both the yield and enantioselectivity. Running the reaction at −20 °C resulted in both the yield and enantioselectivity being comparable to those at −10 °C (entries 1 and 3). Lower temperatures (<−20 °C) resulted in a decrease of the yield but an increase in enantioselectivity (entries 4 and 5).

As the reaction proceeded slowly at very low temperatures with decreased yield, we investigated the effects of solvents at −10 °C on the reaction outcome. The results of this investigation are summarized in Table 2. The reaction proceeded well in ethers, such as diethyl ether (Et_2O), diisopropyl ether, cyclopentyl methyl ether, and methyl *t*-butyl ether (MTBE) (entries 1–4), while both yield and enantioselectivity of the reaction were significantly decreased when *n*-hexane or *n*-heptane was used (entries 5 and 6). Acetonitrile (MeCN) proved unsuccessful in improving the reaction results, affording the product with 70% ee in 59% yield (entry 7). The yield of the reaction when using ethyl acetate (EtOAc) was equal to that of Et_2O, while the ee was slightly diminished (entry 8). Among the solvents tested, toluene clearly provided the best reaction rate and yield with 83% ee (entry 9).

On the basis of these findings, we selected toluene as the solvent and conducted further optimization of the reaction by examining the effect of the reaction temperature and the amount of catalyst (Table 3). Although the yield was maintained with increasing reaction temperature, the enantioselectivity decreased (entries 1–5). For example, carrying out the reaction at 40 °C for 1 h afforded the product in 92% yield with a significantly lower ee (71% ee). On the other hand, the use of 2.5 mol % of catalyst was comparable to 7.5 mol % of one in the yield and enantioselectivity (entries 3 and 6). When the amount of catalyst was reduced to 1 mol %, the yield and enantioselectivity decreased significantly to 53% and

Table 3
Optimization of reaction temperature and the amount of catalysts in toluene



Entry	Catalyst (mol %)	Temperature (°C)	Time (h)	Conversion[a] (%)		Yield (%)	ee (%)
				1 h	24 h		
1	Cinchonidine (7.5 mol %)	−40	24	24	99	95	86
2	Cinchonidine (7.5 mol %)	−10	1	98	—	96	83
3	Cinchonidine (7.5 mol %)	0	1	98	—	96	80
4	Cinchonidine (7.5 mol %)	25	1	99	—	96	76
5	Cinchonidine (7.5 mol %)	40	1	98	—	92	71
6	Cinchonidine (2.5 mol %)	0	3	92	—	93	81
7	Cinchonidine (1 mol %)	0	24	13	61	53	52
8	Cinchonine (7.5 mol %)	0	24	85	97	89	79[b]

[a] Conversion was determined on the basis of area % by HPLC (254 nm).
[b] The (−)-enantiomer was obtained as the major product.

52%, respectively (entry 7). Carrying out the reaction with cinchonine as catalyst afforded the corresponding product (−)-**4** with 79% ee, in 89% yield (entry 8).

We also found that the cinchonidine recovered from the reaction mixture following a simple procedure, as shown in Figure 2, gave almost the same result as the original one with 81% ee, in 95% yield (Scheme 1). The reaction mixture was extracted with aqueous 0.2 M HCl and the cinchonidine was separated into the aqueous layer. This was basified by aqueous 4 M NaOH at pH above 10, and the precipitate produced was filtered to recover cinchonidine in 96% yield (Fig. 2).

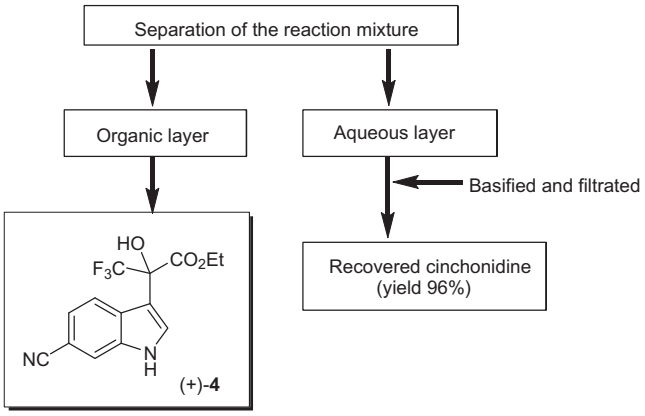
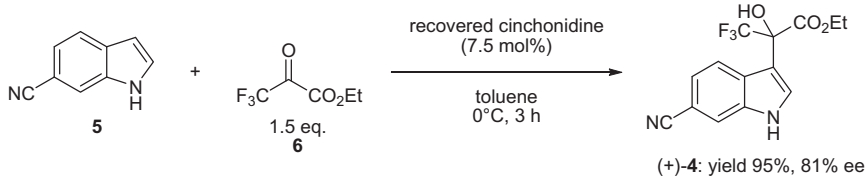


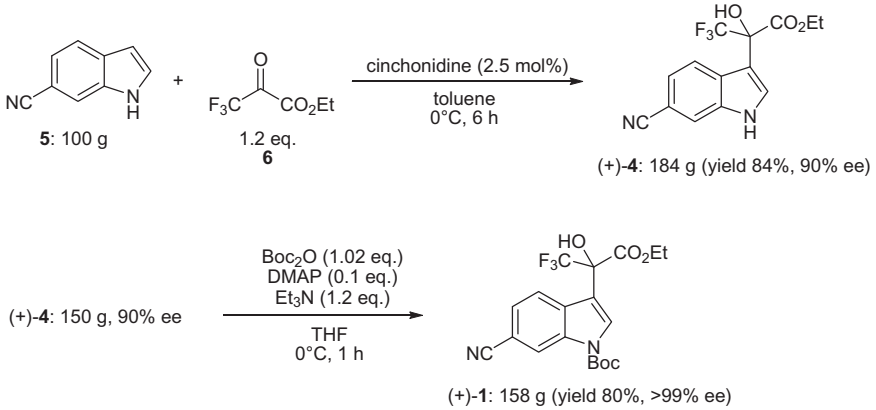
Figure 2. Procedure to recover cinchonidine.

Furthermore, we examined the large-scale synthesis of enantiomerically pure **1** and **4**. With the aforementioned findings in mind, toluene as solvent, 2.5 mol % catalyst, and 0 °C were chosen as the optimal conditions for the large-scale synthesis of enantiomerically pure **4**. To a mixture of **5** (100 g) and cinchonidine (5.18 g) in dry toluene (800 mL) that was allowed to stir at 0 °C for 1 h was slowly added **6** (132 g) in dry toluene (200 mL). At this stage, the reaction appeared as a suspension. The degree to which this suspension formed depended on the solubility of the product (+)-**4** in toluene (data not shown). The product (+)-**4** was obtained by simple filtration of the suspension with 90% ee, in 84% yield (Scheme 2). On the other hand, (+)-**4** in the filtrate showed a low degree of enantioselectivity (27% ee). The purification of (+)-**4** by filtration of the suspension system with 90% ee was superior to the result obtained by silica gel column chromatography with 81% ee (Table 3, entry 6). From these results, we considered that the reason for the high enantioselectivity obtained by this procedure was due to the crystallization of (+)-**4** in the suspension. The *N*-Boc protection of the nitrogen atom of (+)-**4** with Boc_2O followed by the purification using trituration with diisopropyl ether-*n*-hexane gave product (+)-**1** (158 g) with over 99% ee, in 80% yield. Using these simple manipulations, the large-scale synthesis of 100 g of the product was successfully achieved. The total yield (67%) was much better than using the chiral resolution method. Similarly to the procedure for (+)-**1**, *N*-Boc protection of the nitrogen atom of (−)-**4** provided enantiomerically pure (−)-**1** (>99% ee, 19.3 g, 73% yield). The total yield of (−)-**1** from **5** was 65%.

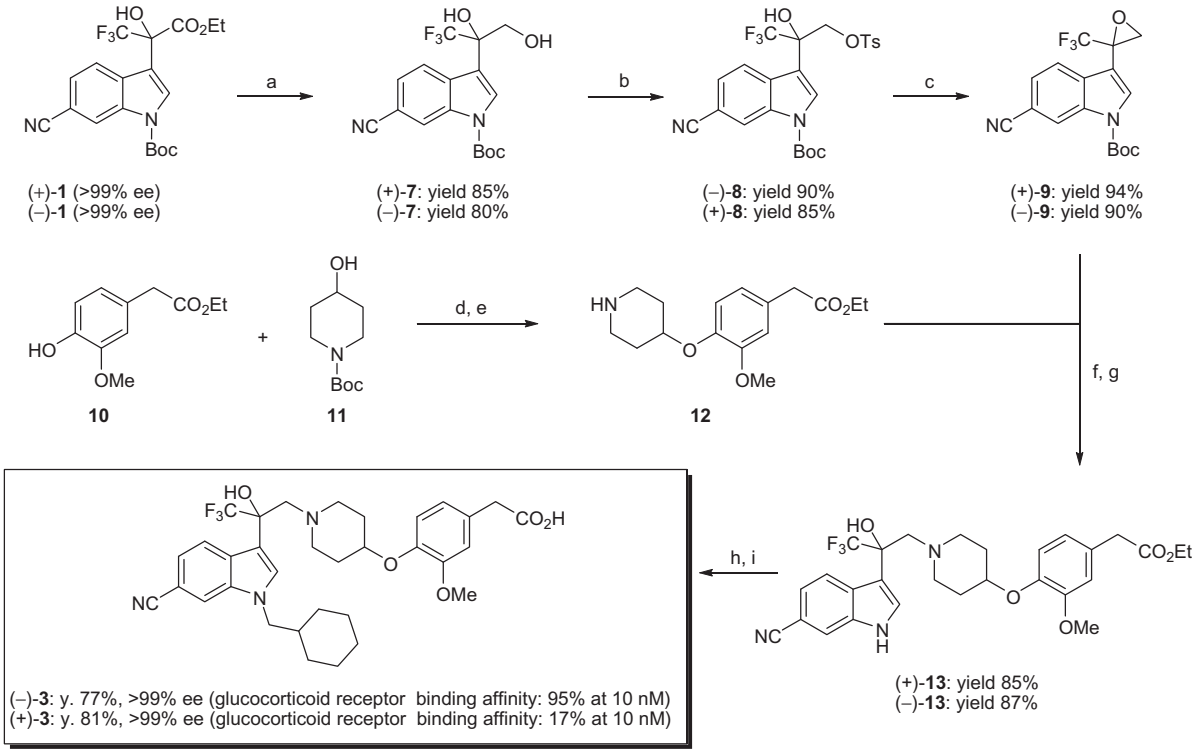
Finally, we conducted the asymmetric synthesis of the glucocorticoid receptor modulator **3** from enantiomerically pure (+)-**1** and (−)-**1** (Scheme 3). Reduction of ester (+)-**1** and (−)-**1** with $LiBH_4$ gave the corresponding alcohol (+)-**7** and (−)-**7**, respectively. Compounds (−)-**8** and (+)-**8** were prepared by tosylation of (+)-**7** and (−)-**7**, respectively. Epoxidation of (−)-**8** and (+)-**8** with aqueous 1 M NaOH in THF, respectively, yielded (+)-**9** and (−)-**9**. Mitsunobu reaction of **10** with **11** afforded phenoxy piperidine **12**. The ring-opening reaction of the corresponding (+)-**9** and (−)-**9** with **12** followed by deprotection of the Boc group provided (+)-**13** and (−)-**13**, respectively. Alkylation of (+)-**13** and (−)-**13** with cyclohexylmethyl bromide followed by hydrolysis of the corresponding esters gave enantiomerically pure (−)-**3** and (+)-**3** (>99% ee for both compounds). Racemization was not observed in all steps. The glucocorticoid receptor binding affinity for enantiomerically pure (+)-**3** and (−)-**3** was examined. The affinity of (−)-**3** was higher than that of (+)-**3** [(−)-**3**: 95% at 10 nM; (+)-**3**: 17% at 10 nM]. These results suggested that the glucocorticoid receptor



Scheme 1. Reaction using recovered cinchonidine.



Scheme 2. Large-scale synthesis of the enantiopure (+)-**1**.



Scheme 3. Synthesis of the glucocorticoid receptor modulators (−)-**3** and (+)-**3**. Reagents and conditions: (a) $LiBH_4$, THF, EtOH, 0 °C, 1 h; (b) TsCl, pyridine, rt, 20 h; (c) 1 M NaOH aq, THF, 0 °C, 10 min; (d) diisopropyl azodicarboxylate, PPh_3, THF, rt, 15 h; (e) 4 M HCl in 1,4-dioxane, $CHCl_3$, rt, 1 h; (f) Et_3N, 2-propanol, 70 °C, 14 h; (g) TFA, CH_2Cl_2, rt, 1 h; (h) cyclohexylmethyl bromide, K_2CO_3, DMF, 70 °C, 15 h; (i) 1 M NaOH aq, THF, MeOH, rt, 5 h.

binding affinity had a marked influence on the configuration at the trifluoromethyl alcohol moiety.

3. Conclusion

We have in this study optimized the asymmetric addition of 6-cyanoindole **5** to ethyl trifluoropyruvate **6** and developed an efficient synthesis of enantiomerically pure (+)-**1** (>99% ee) using easily available, recyclable, and inexpensive cinchona alkaloids as catalysts. All steps are operationally simple and applicable to 100 g scale synthesis. By using (+)-**1** and (−)-**1**, the corresponding glucocorticoid receptor modulators (−)-**3** and (+)-**3** have been successfully synthesized without racemization in all steps (>99% ee for both compounds). The glucocorticoid receptor binding affinities of (−)-**3** and (+)-**3** have been evaluated. Compound (−)-**3** showed a more potent binding affinity compared with (+)-**3**, indicating a stereochemical preference of the trifluoromethyl alcohol structure for glucocorticoid receptor binding affinity. At present, we are continuing our studies to obtain enantiomerically pure glucocorticoid receptor modulators using (+)-**1** as a key intermediate.

4. Experimental

4.1. General information

All reagents and solvents were used as obtained from commercial suppliers without further purification. All reactions were carried out under an atmosphere of N_2. Monitoring of reactions was carried out using a MERCK 60 F_{254} silica gel, glass-supported TLC plates, and visualization with UV light (254 nm). NMR spectra were recorded on a VARIAN Mercury-400 spectrometer at room temperature. Chemical shifts are given in δ values (ppm) using tetramethylsilane as the internal standard, and following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet and dq = double quartet. IR spectra were recorded as KBr pellets using a PerkinElmer Spectrum One. Optical rotations were recorded on a JASCO Polarimeter P-1020. Melting points were recorded on a Stanford Research Systems OptiMelt MPA100 without correction. Low-resolution mass spectra were recorded on a SHIMADZU LCMS-2010EV instrument under electron spray ionization (ESI) conditions. Elemental analyses were obtained on a CE Instruments EA1110. Reaction progress was monitored by HPLC at room temperature using a HITACHI L-7100 pump equipped with a HITACHI L-7400 UV detector with a KANTO Myghtysil RP-18 GP column (3 mm × 150 mm, 5 μm), eluted at 1.0 mL/min with a 30 min gradient (from 30% B to 95% B), where solvent A is water (0.05% TFA solution) and solvent B is acetonitrile (0.05% TFA solution). Enantiomeric excess was measured by chiral HPLC at 30 °C using a SHIMADZU LC-10AS pump equipped with a SHIMADZU SPD-10A UV detector with a DAICEL Chiralpak AD-H column (4.6 mm × 250 mm, 5 μm). The following abbreviations are used for reagents and solvents: TFA (trifluoroacetic acid), DMF (*N*,*N*-dimethylformamide), DMAP (4-dimethylaminopyridine), Boc_2O (di-*tert*-butyl dicarbonate), EtOAc (ethyl acetate), THF (tetrahydrofuran), diisopropyl ether.

4.2. (+)-Ethyl 2-(6-cyano-1*H*-indol-3-yl)-3,3,3-trifluoro-2-hydroxypropanoate (+)-4

To a mixture of 6-cyanoindole **5** (213 mg, 1.5 mmol) and cinchonidine (11.0 mg, 37.5 μmol) in dry toluene (7 mL) was added ethyl trifluoropyruvate **6** (298 μL, 2.25 mmol) in dry toluene (2 mL) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. The mixture was quenched with MeOH (20 mL) and DMF (2 mL) and stirred at room temperature over 30 min. The mixture was concentrated and the residue purified by silica gel chromatography (EtOAc/*n*-hexane = 1/2) to afford (+)-**4** (435 mg, 93%, 81% ee) as a pale purple solid; [Anal. Calcd for $C_{14}H_{11}F_3N_2O_3$: C, 53.85; H,

3.55; N, 8.97. Found: C, 53.91; H, 3.58; N, 9.06]; $[\alpha]_D^{25} = +1.2$ (*c* 1.98, $CHCl_3$); mp 127–129 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.94 (s, 1H, NH), 7.94 (dd, *J* = 1.6, 0.6 Hz, 1H), 7.88 (d, *J* = 8.6 Hz, 1H), 7.75 (d, *J* = 2.7 Hz, 1H), 7.65 (s, 1H, OH), 7.40 (dd, *J* = 8.6, 1.6 Hz, 1H), 4.32 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.27 (dq, *J* = 10.7, 7.1 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.2, 134.9, 129.0, 127.8, 123.8 (q, $^1J_{C-F}$ = 286 Hz), 121.7, 121.3, 119.9, 116.6, 109.0, 102.9, 76.3 (q, $^2J_{C-F}$ = 29.8 Hz), 62.1, 13.8; IR (KBr) ν 3439, 3366, 2230, 1750, 1459, 1348, 1283, 1231, 1178, 1115, 1019 cm^{-1}; MS (ESI) *m/z* 335 (M+Na)$^+$; Enantiomeric excess was determined by HPLC [Chiralpak AD-H, EtOH/*n*-hexane = 8/92, flow rate 1.0 mL/min, λ = 254 nm, retention times: (+)-isomer 16.2 min, (−)-isomer 28.7 min].

4.3. (−)-Ethyl 2-(6-cyano-1*H*-indol-3-yl)-3,3,3-trifluoro-2-hydroxypropanoate (−)-4

To a mixture of 6-cyanoindole **5** (213 mg, 1.5 mmol) and cinchonine (33.1 mg, 112 μmol) in dry toluene (7 mL) was added ethyl trifluoropyruvate **6** (298 μL, 2.25 mmol) in dry toluene (2 mL) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 24 h. The mixture was quenched with MeOH (20 mL) and DMF (2 mL) and stirred at room temperature over 30 min. The mixture was concentrated and the residue was purified by silica gel chromatography (EtOAc/*n*-hexane = 1/2) to afford (−)-**4** (418 mg, 89%, 79% ee) as a pale purple solid; [Anal. Calcd for $C_{14}H_{11}F_3N_2O_3$: C, 53.85; H, 3.55; N, 8.97. Found: C, 53.94; H, 3.58; N, 9.06]; $[\alpha]_D^{25} = -1.1$ (*c* 2.00, $CHCl_3$); mp 127–129 °C.

4.4. Procedure to recover the organocatalyst from the reaction mixture

To a mixture of 6-cyanoindole **5** (20.0 g, 141 mmol) and cinchonidine (3.11 g, 10.6 mmol) in dry toluene (700 mL) was added ethyl trifluoropyruvate **6** (35.9 g, 211 mmol) in dry toluene (140 mL) dropwise at 0 °C. The reaction mixture was quenched by 0.2 M HCl (100 mL) and extracted with EtOAc (200 mL). The aqueous layer was basified by 4 M NaOH to produce a pale yellow solid. The solid was filtered, washed with water (10 mL), and dried to give cinchonidine (3.0 g, 96%).

4.5. Large-scale synthesis of (+)-ethyl 2-(6-cyano-1*H*-indol-3-yl)-3,3,3-trifluoro-2-hydroxy-propanoate (+)-4

To a mixture of 6-cyanoindole **5** (100 g, 703 mmol) and cinchonidine (5.18 g, 17.6 mmol) in dry toluene (800 mL) was added ethyl trifluoropyruvate **6** (132 g, 774 mmol) in dry toluene (200 mL) dropwise at 0 °C. The mixture was stirred at 0 °C for 6 h. The reaction mixture was filtered. The solid was dried to give (+)-**4** (184 g, 84%, 90% ee).

4.6. Large-scale synthesis of (+)-*tert*-butyl 6-cyano-3-[3-ethoxy-1,1,1- trifluoro-2-hydroxy-3-oxopropan-2-yl]-1*H*-indole-1-carboxylate (+)-1

To a mixture of (+)-**4** (150 g, 480 mmol, 90% ee), Et_3N (58.3 g, 577 mmol) and DMAP (5.87 g, 48.0 mmol) in dry THF (720 mL) was added Boc_2O (107 g, 490 mmol) in dry THF (240 mL) dropwise at 0 °C. The mixture was stirred at 0 °C for 1 h. The reaction mixture was neutralized with 5% $KHSO_4$ solution (1500 mL). The mixture was extracted with EtOAc (1000 mL). The organic layer was washed with water (150 mL) and brine (150 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was triturated with diisopropyl ether (375 mL) and *n*-hexane (675 mL) at 0 °C. The mixture was filtered and the filtrate was concentrated. The residue was triturated with diisopropyl ether (100 mL) and *n*-hexane (500 mL) at 0 °C and filtered to give (+)-**1** (158 g, 80%, 99% ee) as a pale yellow solid; [Anal. Calcd for $C_{19}H_{19}F_3N_2O_5$: C, 55.34; H, 4.64; N, 6.79. Found: 55.11; H, 4.65; N, 6.74]; $[\alpha]_D^{25} = +1.6$ (*c* 2.02, $CHCl_3$); mp 77–79 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (s, 1H), 8.10 (s, 1H, OH), 7.98 (s, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.71 (dd, *J* = 8.4, 1.3 Hz, 1H), 4.34 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.31 (dq, *J* = 10.7, 7.1 Hz, 1H), 1.67 (s, 9H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.3, 147.5, 133.6, 130.2, 128.5, 125.7, 123.3 (q, $^1J_{C-F}$ = 286 Hz), 122.3, 119.0, 118.8, 114.2, 106.6, 85.7, 75.9 (q, $^2J_{C-F}$ = 30.0 Hz), 62.6, 27.4, 13.7; IR (KBr) ν 3414, 2229, 1750, 1443, 1377, 1278, 1243, 1148, 1089 cm^{-1}; MS (ESI) *m/z* 435 (M+Na)$^+$; Enantiomeric excess was determined by HPLC [Chiralpak AD-H, EtOH/*n*-hexane = 5/95, flow rate 1.0 mL/min, λ = 254 nm, retention times: (+)-isomer 6.8 min, (−)-isomer 10.3 min].

4.7. (−)-*tert*-Butyl 6-cyano-3-[3-ethoxy-1,1,1-trifluoro-2-hydroxy-3-oxopropan-2-yl]-1*H*-indole-1-carboxylate (−)-1

Compound (−)-**1** was prepared from (−)-**4** (20.0 g, 64.1 mmol, 79% ee) using a procedure similar to that described for (+)-**1**; pale yellow solid (19.3 g, 73%, 99% ee); [Anal. Calcd for $C_{19}H_{19}F_3N_2O_5$: C, 55.34; H, 4.64; N, 6.79. Found: 55.50; H, 4.66; N, 6.86]; $[\alpha]_D^{25} = -1.7$ (*c* 2.05, $CHCl_3$); mp 77–79 °C.

4.8. (+)-*tert*-Butyl 6-cyano-3-(1,1,1-trifluoro- 2,3-dihydroxypropan-2-yl)-1*H*-indole-1-carboxylate (+)-7

To a mixture of $LiBH_4$ (3.17 g, 146 mmol) in dry THF (120 mL) and EtOH (15 mL) was added (+)-**1** (15.0 g, 36.4 mmol, 99% ee) in dry THF (30 mL) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then quenched with 5% $KHSO_4$ solution. The mixture was extracted with EtOAc. The organic layer was washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography (EtOAc/*n*-hexane = 1/1) to afford (+)-**7** (11.5 g, 85%) as an amorphous solid; [Anal. Calcd for $C_{17}H_{17}F_3N_2O_4{\cdot}0.5H_2O$: C, 53.83; H, 4.78; N, 7.38. Found: 53.49; H, 4.49; N, 7.27]; $[\alpha]_D^{25} = +12.9$ (*c* 2.08, $CHCl_3$); mp 39–40 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 (s, 1H), 8.09 (d, *J* = 8.3 Hz, 1H), 8.00 (s, 1H), 7.62 (d, *J* = 8.3 Hz, 1H), 6.78 (s, 1H, OH), 5.33 (t, *J* = 5.6 Hz, 1H, OH), 4.15–3.83 (m, 2H), 1.64 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.3, 133.9, 132.1, 128.6, 125.6 (q, $^1J_{C-F}$ = 288 Hz), 125.5, 123.6, 119.5, 118.8, 117.3, 106.2, 85.4, 75.3 (q, $^2J_{C-F}$ = 27.0 Hz), 63.4, 27.5; IR (ATR) ν 3432, 2228, 1740, 1615, 1553, 1475, 1440, 1371, 1317, 1257, 1147, 1094, 1048 cm^{-1}; MS (ESI) *m/z* 393 (M+Na)$^+$.

4.9. (−)-*tert*-Butyl 6-cyano-3-(1,1,1-trifluoro-2,3-dihydroxy-propan-2-yl)-1*H*-indole-1-carboxylate (−)-7

Compound (−)-**7** was prepared from (−)-**1** (7.00 g, 17.0 mmol, 99% ee) using a procedure similar to that described for (+)-**7**; amorphous solid (5.03 g, 80%); $[\alpha]_D^{25} = -13.3$ (*c* 2.06, $CHCl_3$); mp 39–40 °C.

4.10. (−)-*tert*-Butyl 6-cyano-3-(1,1,1-trifluoro-2-hydroxy-3-{[(4-methylphenyl)sulfonyl]oxy}-propan-2-yl)-1*H*-indole-1-carboxylate (−)-8

To a solution of (+)-**7** (10.0 g, 27.0 mmol) in pyridine (80 mL) was added *p*-toluenesulfonyl chloride (25.7 g, 135 mmol) at room temperature. The reaction mixture was stirred at room temperature for 20 h and then concentrated. A toluene solution of the residue was washed with 1 M HCl, water and then concentrated. The crude product was purified by silica gel chromatography (EtOAc/*n*-hexane = 1/3) to afford (−)-**8** (12.7 g, 90%) as a white solid; [Anal.

Calcd for $C_{24}H_{23}F_3N_2O_6S$: C, 54.96; H, 4.42; N, 5.34. Found: 55.11; H, 4.37; N, 5.41]; $[\alpha]_D^{25} = -16.5$ (*c* 2.07, $CHCl_3$); mp 115–116 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (s, 1H), 7.89 (s, 1H), 7.83 (d, *J* = 8.3 Hz, 1H), 7.66–7.58 (m, 3H), 7.55 (d, *J* = 8.3 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 4.62 (d, *J* = 10.7 Hz, 1H), 4.51 (d, *J* = 10.7 Hz, 1H), 2.37 (s, 3H), 1.64 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.0, 145.1, 133.8, 131.3, 130.8, 129.8, 128.7, 127.5, 125.7, 124.5 (q, $^1J_{C-F}$ = 288 Hz), 122.8, 119.3, 118.9, 114.8, 106.5, 85.7, 73.8 (q, $^2J_{C-F}$ = 29.2 Hz), 69.3, 27.4, 21.1; IR (ATR) ν 3426, 2226, 1745, 1440, 1337, 1352, 1320, 1297, 1258, 1235, 1172, 1149, 1116, 1092 cm^{-1}; MS (ESI) *m/z* 547 (M+Na)$^+$.

4.11. (+)-*tert*-Butyl 6-cyano-3-(1,1,1-trifluoro-2-hydroxy-3-{[(4-methylphenyl)sulfonyl]oxy}-propan-2-yl)-1*H*-indole-1-carboxylate (+)-8

Compound (+)-**8** was prepared from (−)-**7** (4.80 g, 13.0 mmol) using a procedure similar to that described for (−)-**8**; white solid (5.78 g, 85%); $[\alpha]_D^{25} = +16.2$ (*c* 2.08, $CHCl_3$); mp 115–116 °C.

4.12. (+)-*tert*-Butyl 6-cyano-3-[2-(trifluoromethyl)oxiran-2-yl]-1*H*-indole-1-carboxylate (+)-9

To a solution of (−)-**8** (12.0 g, 22.9 mmol) in THF (115 mL) was added 1 M NaOH (22.9 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min. The reaction mixture was neutralized with saturated NH_4Cl solution and then extracted with EtOAc. The organic layer was washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated to afford (+)-**9** (7.6 g, 94%) as a white solid; [Anal. Calcd for $C_{17}H_{15}F_3N_2O_3$: C, 57.96; H, 4.29; N, 7.95. Found: 57.98; H, 4.23; N, 8.02]; $[\alpha]_D^{25} = +14.0$ (*c* 2.08, $CHCl_3$); mp 103–104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (br s, 1H), 7.95 (s, 1H), 7.80 (d, *J* = 8.3 Hz, 1H), 7.54 (dd, *J* = 8.3, 1.5 Hz, 1H), 3.50 (d, *J* = 5.2 Hz, 1H), 3.09 (dq, *J* = 5.2, 1.7 Hz, 1H), 1.70 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 134.3, 131.5, 130.0, 126.3, 123.1 (q, $^1J_{C-F}$ = 278 Hz), 121.1, 120.1, 120.0, 111.4, 108.3, 86.1, 53.7 (q, $^2J_{C-F}$ = 39.2 Hz), 50.0 (q, $^3J_{C-F}$ = 1.7 Hz), 28.1; IR (ATR) ν 2225, 1749, 1617, 1476, 1442, 1395, 1370, 1316, 1259, 1227, 1152, 1096, 1054 cm^{-1}; MS (ESI) *m/z* 375 (M+Na)$^+$.

4.13. (−)-*tert*-Butyl 6-cyano-3-[2-(trifluoromethyl)oxiran-2-yl]-1*H*-indole-1-carboxylate (−)-9

Compound (−)-**9** was prepared from (+)-**8** (5.00 g, 9.53 mmol) using a procedure similar to that described for (+)-**9**; white solid (3.03 g, 90%); $[\alpha]_D^{25} = -14.6$ (*c* 2.03, $CHCl_3$); mp 103–104 °C.

4.14. Ethyl [3-methoxy-4-(piperidin-4-yloxy)phenyl]acetate hydrochloride 12

To a solution of **10** (5.00 g, 23.8 mmol), **11** (6.22 g, 30.9 mmol) and PPh_3 (9.36 g, 35.7 mmol) in THF (79 mL) was added diisopropyl azodicarboxylate (7.52 mL, 35.7 mmol) at room temperature. The reaction mixture was stirred at room temperature for 15 h and then concentrated. The residue was purified by silica gel chromatography (EtOAc/*n*-hexane = 1/3) to afford a pale yellow oil. To a $CHCl_3$ (5 mL) solution of the oil was added 4 M HCl in 1,4-dioxane (50 mL) at room temperature. The reaction mixture was stirred at room temperature for 1 h and then concentrated. Trituration with Et_2O (40 mL) and filtration of the solid gave **12** (5.66 g, 72%) as a white solid; [Anal. Calcd for $C_{16}H_{24}ClNO_4$: C, 58.27; H, 7.33; N, 4.25. Found: 58.02; H, 7.14; N, 4.30]; mp 131–133 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.59 (br s, 2H, NH), 6.85 (d, *J* = 8.2 Hz, 1H), 6.85 (d, *J* = 1.7 Hz, 1H), 6.79 (dd, *J* = 8.2, 1.7 Hz, 1H), 4.61–4.51 (m, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 3.56 (s, 2H), 3.54–3.39 (m, 2H), 3.36–3.21 (m, 2H), 2.32–2.06 (m, 4H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.3, 150.9, 144.4, 129.0, 121.3, 118.3, 113.2, 70.1, 60.6, 55.5, 40.7, 39.5, 26.6, 13.9; IR (ATR) ν 2788, 1734, 1590, 1515, 1461, 1447, 1417, 1344, 1308, 1285, 1270, 1190, 1165, ,1137, 1124, 1036, 1023 cm^{-1}; MS (ESI) *m/z* 294 (M+H)$^+$.

4.15. (+)-Ethyl [4-({1-[2-(6-cyano-1*H*-indol-3-yl)-3,3,3-trifluoro-2-hydroxypropyl]piperidin-4-yl}oxy)-3-methoxyphenyl]acetate (+)-13

To a mixture of (+)-**9** (2.00 g, 5.68 mmol) and Et_3N (1.97 mL, 14.2 mmol) in 2-propanol (19 mL) was added **12** (2.06 g, 6.25 mmol) at room temperature. The reaction mixture was stirred at 70 °C for 14 h. The reaction mixture was neutralized with 5% $KHSO_4$ solution and then extracted with EtOAc. The organic layer was washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated. To a CH_2Cl_2 (10 mL) solution of the residue was added TFA (20 mL) at room temperature. The mixture was stirred at room temperature for 1 h and then concentrated. Next, an EtOAc solution of the residue was washed with saturated $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel chromatography (EtOAc/*n*-hexane = 1/1) to afford (+)-**13** (2.65 g, 86%) as an amorphous solid; [Anal. Calcd for $C_{28}H_{30}F_3N_3O_5$: C, 61.64; H, 5.54; N, 7.70. Found: 61.55; H, 5.48; N, 7.77]; $[\alpha]_D^{25} = +6.7$ (*c* 2.01, $CHCl_3$); mp 55–56 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.76 (br s, 1H, NH), 7.97 (d, *J* = 8.4 Hz, 1H), 7.88 (dd, *J* = 1.2, 0.8 Hz, 1H), 7.73 (s, 1H), 7.33 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.85 (d, *J* = 2.0 Hz, 1H) , 6.70 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.24 (s, 1H, OH), 4.18–4.10 (m, 1H), 4.08 (q, *J* = 7.2 Hz, 2H), 3.71 (s, 3H), 3.54 (s, 2H), 3.16 (d, *J* = 13.6 Hz, 1H), 3.03 (d, *J* = 13.6 Hz, 1H), 2.77–2.65 (m, 2H), 2.39–2.28 (m, 2H), 1.79–1.69 (m, 2H), 1.55–1.45 (m, 2H), 1.18 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.8, 149.5, 144.7, 134.8, 128.5, 128.4, 127.2, 125.8 (q, $^1J_{C-F}$ = 284 Hz), 122.0, 121.0, 120.9, 120.1, 116.2, 116.1, 113.5, 112.9, 102.1, 73.9 (q, $^2J_{C-F}$ = 27.3 Hz), 73.1, 59.9, 59.8, 55.4, 51.5, 39.7, 30.5, 14.0; IR (ATR) ν 3284, 2219, 1719, 1511, 1458, 1408, 1338, 1264, 1202, 1176, 1141, 1035 cm^{-1} cm^{-1}; MS (ESI) *m/z* 568 (M+Na)$^+$.

4.16. (−)-Ethyl [4-({1-[2-(6-cyano-1*H*-indol-3-yl)-3,3,3-trifluoro-2-hydroxypropyl]piperidin-4-yl}oxy)-3-methoxyphenyl]acetate (−)-13

Compound (−)-**13** was prepared from (−)-**9** (2.00 g, 5.67 mmol) using a procedure similar to that described for (+)-**13**; amorphous solid (2.70 g, 87%); $[\alpha]_D^{25} = -6.5$ (*c* 2.03, $CHCl_3$); mp 55–56 °C.

4.17. (−)-{4-[(1-{2-[6-Cyano-1-(cyclohexylmethyl)-1*H*-indol-3-yl]-3,3,3-trifluoro-2-hydroxy-propyl}piperidin-4-yl)oxy]-3-methoxyphenyl}acetic acid (−)-3

To a mixture of (+)-**13** (1.00 g, 1.83 mmol) and K_2CO_3 (1.52 g, 11.0 mmol) in DMF (18 mL) was added cyclohexylmethyl bromide (972 mg, 5.49 mmol) at room temperature. The reaction mixture was stirred at 70 °C for 15 h. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography (EtOAc/*n*-hexane = 1/3) to afford an amorphous solid. To a solution of the amorphous solid in THF (10 mL) and MeOH (10 mL) was added 1 M NaOH (5 mL) at room temperature. The reaction mixture was stirred at room temperature for 5 h and then neutralized with saturated NH_4Cl solution. The mixture was extracted with EtOAc. The organic layer was washed with water and brine. The organic layer was dried over Na_2SO_4 and

concentrated. The crude product was purified by silica gel chromatography (MeOH/$CHCl_3$ = 1/20) to afford (−)-**3** (862 mg, 77%, 99% ee) as an amorphous solid; [Anal. Calcd for $C_{33}H_{38}F_3N_3O_5{\cdot}0.75H_2O$: C, 63.20; H, 6.35; N, 6.70. Found: 62.89; H, 6.12; N, 6.67]; $[\alpha]_D^{25} = -6.2$ (*c* 2.08, $CHCl_3$); mp 104–106 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 (s, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.72 (s, 1H), 7.33 (d, *J* = 8.5 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.83 (d, *J* = 1.6 Hz, 1H), 6.68 (dd, *J* = 8.0, 1.6 Hz, 1H), 4.22–3.96 (m, 3H), 3.68 (s, 3H), 3.44 (s, 2H), 3.16 (d, *J* = 13.5 Hz, 1H), 2.95 (d, *J* = 13.5 Hz, 1H), 2.79–2.59 (m, 2H), 2.41–2.18 (m, 2H), 1.83–1.52 (m, 6H), 1.52–1.30 (m, 4H), 1.20–1.01 (m, 3H), 1.01–0.84 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.8, 150.0, 144.9, 135.4, 132.7, 129.1, 128.4, 126.1 (q, $^1J_{C-F}$ = 287 Hz), 122.5, 121.4, 121.3, 120.5, 116.7, 115.6, 114.0, 119.9, 102.5, 74.5 (q, $^2J_{C-F}$ = 27.3 Hz), 73.4, 59.9, 55.6, 51.8, 51.6, 40.2, 38.1, 30.7, 30.6, 29.9, 29.8, 25.9, 25.1; IR (ATR) ν 2221, 1721, 1586, 1509, 1450, 1387, 1265, 1224, 1152, 1035 cm^{-1}; MS (ESI) *m/z* 614 $(M+H)^+$. Enantiomeric excess was determined by HPLC [Chiralpak IC, 2-propanol/*n*-hexane/TFA/Et_2NH = 20/80/0.1/0.1, flow rate 1.0 mL/min, λ = 220 nm, retention times: (+)-isomer 25.5 min, (−)-isomer 32.7 min].

4.18. (+)-{4-[(1-{2-[6-Cyano-1-(cyclohexylmethyl)-1*H*-indol-3-yl]-3,3,3-trifluoro-2-hydroxy-propyl}piperidin-4-yl)oxy]-3-methoxyphenyl}acetic acid (+)-3

Compound (+)-**3** was prepared from (−)-**13** (200 mg, 0.367 mmol) using a procedure similar to that described for (−)-**3**; amorphous solid (183 mg, 81%, 99% ee); $[\alpha]_D^{25} = +6.1$ (*c* 2.01, $CHCl_3$); mp 104–106 °C.

4.19. Glucocorticoid receptor binding assay

The binding affinity was determined according to the previously reported protocol.[4]

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