Enantioselective One-Pot Synthesis of 2-Amino-4-(indol-3-yl)-4*H*-Chromenes

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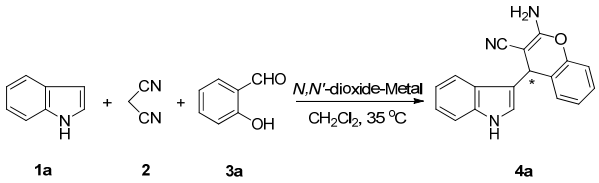
Contents:

1. General remarks

^{1}H NMR spectra were recorded on commercial instruments (400 or 600 MHz). Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, δ = 7.26; DMSO, δ = 2.49). Spectra were reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), integration and assignment. ^{13}C NMR spectra were collected on commercial instruments (100 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from the tetramethylsilane with the solvent resonance as internal standard ($CDCl_3$, δ = 77.0; DMSO, δ = 39.6). Melting points (m.p.) were measured on electrothermal digital melting point apparatus and were uncorrected. Enantiomeric excesses (ee) were determined by HPLC analysis using the corresponding commercial chiral column as stated in the experimental procedures at 23 ^{o}C. Optical rotations were reported as follows: $[\alpha]^{T}_{D}$ (c g/100 mL, in ethyl acetate). HRMS was recorded on a commercial apparatus (ESI Source). All catalytic reactions were run in dried glassware using standard techniques. CH_2Cl_2 was distilled over CaH_2. All salicyaldehydes, indoles and malononitrile were commercially available and used as purchased without further purification.

2. Extra information of the optimization of the reaction conditions

Table 1. Details of the couter ion screening. [a]



entry	ligand	metal	**L**/metal	yield (%)[b]	*ee* (%)[c]
1	**L1**	$ZnCl_2$	2:1	96	0
2	**L1**	$ZnSO_4{\cdot}7H_2O$	2:1	70	16
3	**L1**	$Zn(ClO_4)_2{\cdot}6H_2O$	2:1	62	60
4	**L1**	$Zn(OTf)_2$	2:1	84	62
5	**L1**	$Zn(BF_4)_2{\cdot}6H_2O$	2:1	69	47
6[d]	**L1**	$Zn(OTf)_2$	2:1	78	82
7[d]	**L1**	$Zn(ClO_4)_2{\cdot}6H_2O$	2:1	76	84
8[e]	**L1**	$Zn(ClO_4)_2{\cdot}6H_2O$	2:1	73	6

[a] Unless otherwise noted, reactions were carried out with 10 mol % of catalyst in CH_2Cl_2 (0.5 mL) at 35 °C for 26 h. [b] Isolated yield. [c] Determined by HPLC using chiral IB column. [d] 20 mol % of $NaBAr_F$ was added. [e] 20 mol % of sodium tetraphenylborate was added.

The effect of the counter ion of the central metal was investigated. It is interesting that the addition of $NaBAr_F$ to the reaction increased the ee value, whereas the addition $NaBPh_4$ dramatically decreased the ee of the reaction (84% ee vs. 6% ee, entry 7 vs. entry 8). It indicated both the Lewis basicity and the coordination capability of the counter ion have significant effect on the enantioselectivity of the reaction.

Under the optimized condition, other electron-rich substrates were also employed as Michael donor. When pyrrole was used instead of indole, the corresponding product was obtained in 5% *ee* with 92% yield. Other substrates, such as 3,4-dimethoxyphenol, 3-benzylindolin-2-one, diethyl phosphonate, were also tested, but only trace amounts of corresponding products were obtained.

3. X-ray structure of 4a

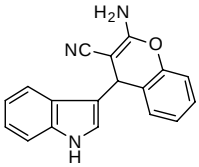
Single crystal of **4a** [$C_{18}H_{13}N_3O$] was obtained from the mixed solvents of petroleum ether and ethyl acetate. The absolute configuration is *S*. CCDC833191 contains the supplementary crystallographic data which can be obtained free of charge from The Cambrige Crystallographic Data Centere via www.ccdc.cam.ac.uk/data_request/cif.

Crystal data. $C_{18}H_{13}N_3O$, $M = 287.31$, orthorhombic, $a = 9.896(2)$, $b = 11.390(2)$, $c = 12.460(3)$ Å, $U = 1404.5(5)$ Å^3, $T = 173.0$ K, space group $P212121$, $Z = 4$.

4. Typical procedure for catalytic asymmetric Knoevenagel/Pinner/ Friedel–Crafts Alkylation

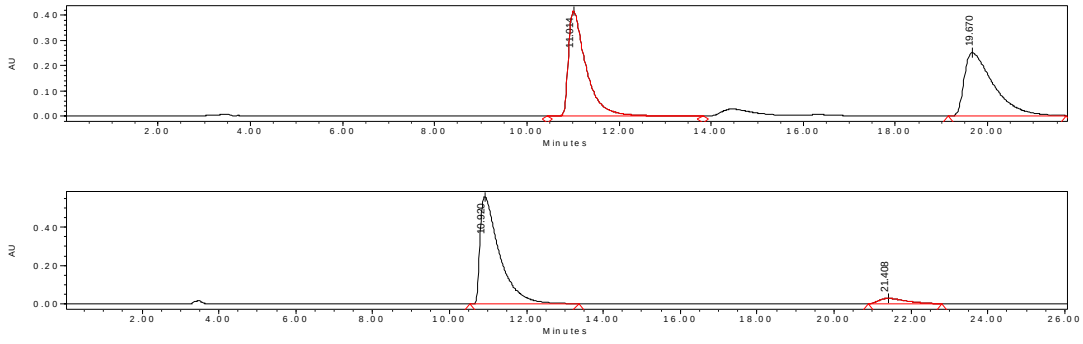
N,*N*'-dioxide **L1** (12.4 mg, 0.02 mmol), $Zn(ClO_4)_2{\cdot}6H_2O$ (3.7 mg, 0.01 mmol), $NaBAr_F$ (18.0 mg, 0.02 mmol) and malononitrile **2** (6.6 mg, 0.1 mmol) were stirred in CH_2Cl_2 (0.5 mL) at 35 °C for 0.5 h, then **3a** (10.2 μL, 0.1 mmol) was added. After 20 minutes, indole **1a** (12.8, 0.11 mmol) and 3 Å MS (20 mg) was added. The mixture was stirred at 35 °C for the time indicated. The reaction mixture was purified by flash chromatography (petroleum ether: ethyl acetate = 2:1) on silica gel to afford the desired product. [1]

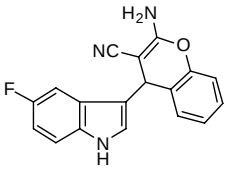
5. Characterization of the products



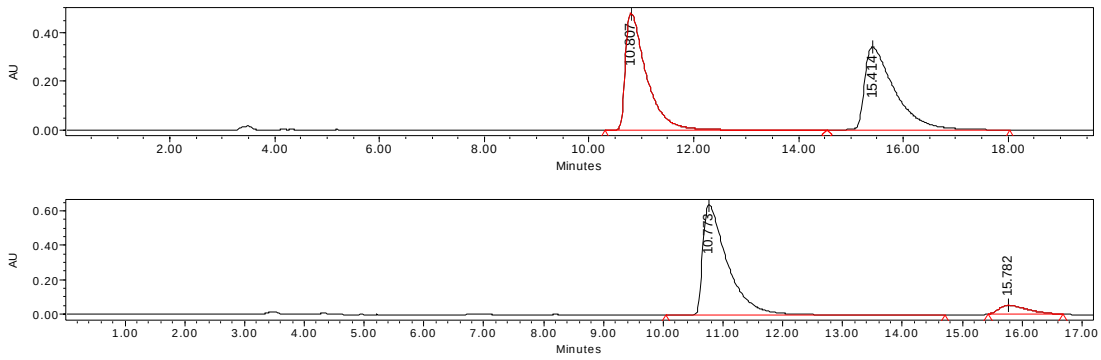
2-amino-4-(1H-indol-3-yl)-4H-chromene-3-carbonitrile 4a: Yellow solid in 87% yield (petroleum ether : EtOAc = 2 : 1); $[\alpha]^{26}_D$ = +35.7 (c 0.2, EtOAc); the ee was determined by HPLC analysis using a chiral IB column (*i*PrOH/hexane = 20/80, 1.0 mL/min, 254 nm), t_r (major) = 10.92 min, t_r (minor) = 21.41 min, 87% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.93 (1H, s), 7.34 (1H, d, *J* = 8.1 Hz), 7.30 (1H, d, *J* = 1.6 Hz), 7.25 – 7.17 (2H, m), 7.09 – 6.97 (4H, m), 6.87 (1H, t, *J* = 7.5 Hz), 6.82 (2H, s), 4.99 (1H, s) ppm; ^{13}C NMR (100 MHz, DMSO) δ = 160.54, 148.90, 137.39, 129.75, 128.30, 125.69, 124.81, 124.19, 123.51, 121.49, 121.30, 119.20, 118.97, 118.91, 116.22, 112.20, 56.79, 32.93 ppm; EI-HRMS: Calcd for $C_{18}H_{14}N_3O$ $[M+H]^+$ 288.1137, Found 288.1131.

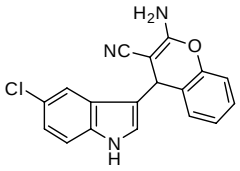
4r: 88% yield and 86% *ee*; $[\alpha]^{26}_D$ = -35.9 (c 0.4, EtOAc).





2-amino-4-(5-fluoro-1H-indol-3-yl)-4H-chromene-3-carbonitrile 4b: Yellow solid; M.P.: 44-46 °C; 81% yield (petroleum ether : EtOAc = 2 : 1); $[\alpha]^{26}_D$ = +22.8 (c 0.5, EtOAc); the ee was determined by HPLC analysis using a chiral IB column (*i*PrOH/hexane = 20/80, 1.0 mL/min, 254 nm), t_r (major) = 10.92 min, t_r (minor) = 15.78 min, 83% *ee*; ^{1}H NMR (600 MHz, DMSO) δ = 11.06 (1H, d, *J* = 1.6 Hz,), 7.38 (1H, d, *J* = 2.5 Hz,), 7.34 (1H, dd, *J* = 8.7, 4.6 Hz), 7.23 – 7.19 (1H, m), 7.08 (2H, t, *J* = 8.3 Hz), 7.01 (1H, t, *J* = 7.5 Hz), 6.92 – 6.88 (2H, m), 6.87 (2H, s), 4.99 (1H, s) ppm; ^{13}C NMR (150 MHz, DMSO) δ = 160.60, 157.68, 156.15, 148.85, 133.98, 129.71, 128.43, 125.79, 125.73, 125.63, 124.93, 123.91, 121.19, 119.51, 119.48, 116.26, 113.25, 113.18, 109.72, 109.55, 103.46, 103.31, 56.40, 32.68 ppm; EI-HRMS: Calcd for $C_{18}H_{13}FN_3O$ $[M+H]^+$ 306.1043, Found 306.1043.

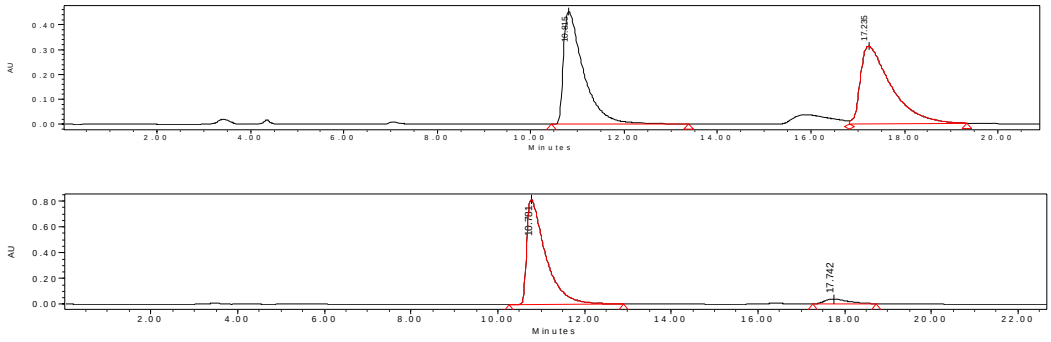


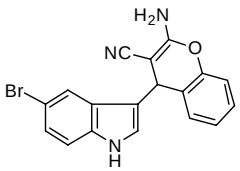


2-amino-4-(5-chloro-1H-indol-3-yl)-4H-chromene-3-carbonitrile 4c:

Yellow solid in 85% yield (petroleum ether : EtOAc = 2 : 1); $[\alpha]^{26}_{D}$ = +11.9 (c 0.4, EtOAc); the ee was determined by HPLC analysis using a chiral IB column (*i*PrOH/hexane = 20/80, 1.0 mL/min, 254 nm), t_r (major) = 10.78 min, t_r (minor) = 17.74 min, 88% *ee*; ^{1}H NMR (400 MHz, DMSO) δ = 11.17 (1H, s), 7.40 (1H, d, *J* = 2.2 Hz), 7.37 (1H, d, *J* = 8.6 Hz), 7.26 – 7.17 (2H, m), 7.11 – 6.97 (4H, m), 6.89 (2H, s), 5.01 (1H, s) ppm; ^{13}C NMR (100 MHz, DMSO) δ = 160.55, 148.84, 135.81, 129.72, 128.50, 126.73, 125.49, 124.96, 123.83, 123.58, 121.47, 121.14, 119.10, 117.99, 116.29, 113.80, 56.41, 32.62 ppm; EI-HRMS: Calcd for $C_{18}H_{13}ClN_3O$ $[M+H]^+$ 322.0747, Found 322.0741.

4s: 86% yield and 88% *ee*; $[\alpha]^{26}_{D}$ = -11.2 (c 0.5, EtOAc).

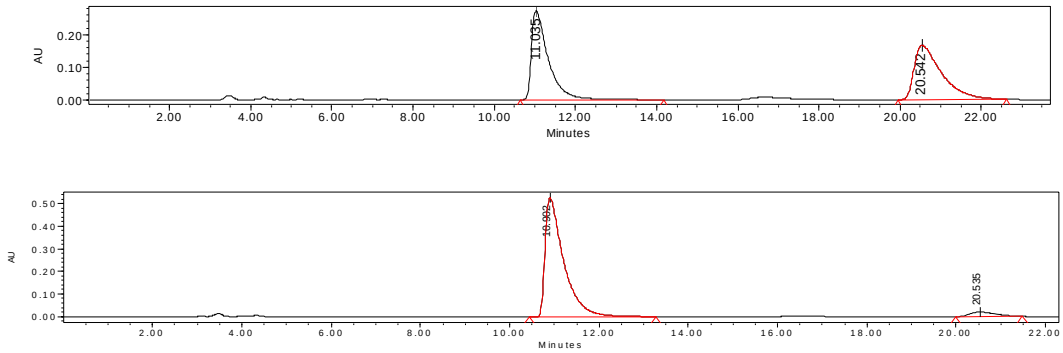


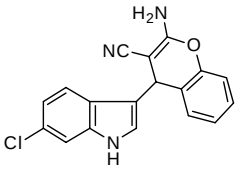


2-amino-4-(5-bromo-1H-indol-3-yl)-4H-chromene-3-carbonitrile 4d:

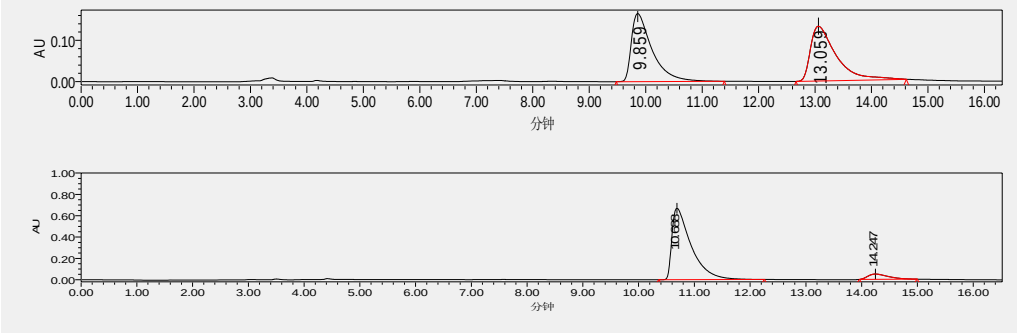
Yellow solid in 75% yield (petroleum ether : EtOAc = 2 : 1); $[\alpha]^{26}_{D}$ = +8.7 (c 0.5, EtOAc); the ee was determined by HPLC analysis using a chiral IB column (*i*PrOH/hexane = 20/80, 1.0 mL/min, 254 nm), t_r (major) = 10.90 min, t_r (minor) = 20.54 min, 90% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.30 (1H, s), 7.40 (1H, s), 7.25 – 7.15 (3H, m), 7.14 – 7.11 (1H, m), 7.06 – 6.96 (3H, m), 5.02 (1H, s), 4.68 (2H, s) ppm; ^{13}C NMR (100 MHz, DMSO) δ = 160.66, 148.95, 136.14, 129.83, 128.61, 127.59, 125.44, 125.07, 124.11, 123.93, 121.25, 121.17, 119.16, 116.40, 114.39, 111.76, 56.52, 32.73 ppm; EI-HRMS: Calcd for $C_{18}H_{13}BrN_3O$ $[M+H]^+$ 366.0242, Found 366.0240.

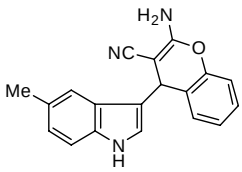
4t: 79% yield and 89% *ee*; $[\alpha]^{26}_{D}$ = -8.1 (c 0.5, EtOAc).



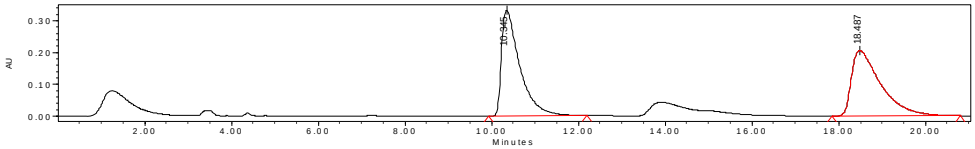


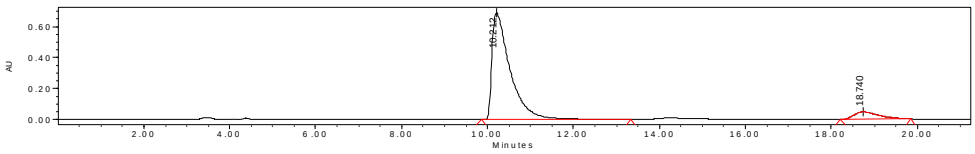
2-amino-4-(6-chloro-1H-indol-3-yl)-4H-chromene-3-carbonitrile 4e: Yellow solid; m.p. 76-78 °C ; 82% yield (petroleum ether : EtOAc = 2 : 1); $[\alpha]^{26}_{D}$ = +22.2 (c 0.4, EtOAc); the ee was determined by HPLC analysis using a chiral IB column (*i*PrOH/hexane = 20/80, 1.0 mL/min, 254 nm), t_r (major) = 10.68 min, t_r (minor) = 14.25 min, 85% *ee*; ^{1}H NMR (400 MHz, DMSO): δ = 11.09 (1H, s), 7.39 (1H, d, *J* = 1.4 Hz), 7.35 (1H, d, *J* = 2.2 Hz), 7.20 (2H, dd, *J* = 10.6, 4.8 Hz), 7.05 (2H, d, *J* = 7.9 Hz), 7.00 (1H, t, *J* = 7.4 Hz), 6.91 (1H, dd, *J* = 8.5, 1.7 Hz), 6.86 (2H, s), 5.00 (1H, s) ppm. ^{13}C NMR (100 MHz, DMSO) δ = 160.56, 148.87, 137.76, 129.66, 128.43, 126.37, 124.88, 124.79, 124.50, 123.91, 121.11, 120.13, 119.42, 119.33, 116.29, 111.82, 56.59, 32.70 ppm; EI-HRMS: Calcd for $C_{18}H_{13}ClN_3O$ $[M+H]^+$ 322.0747, Found 322.0741.

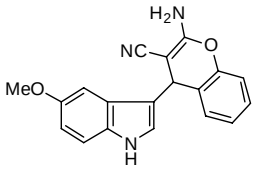




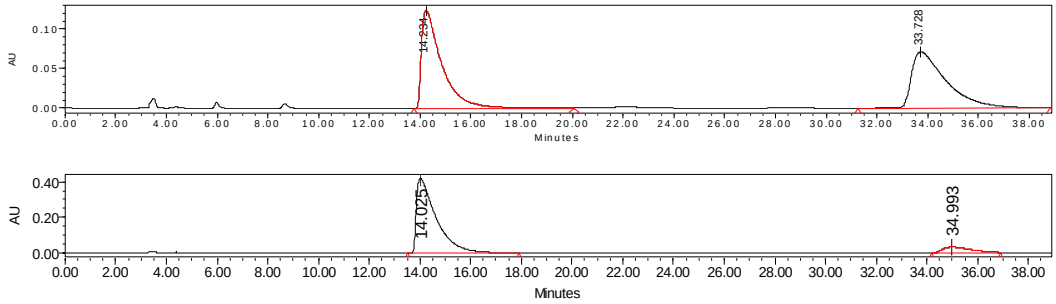
2-amino-4-(5-methyl-1H-indol-3-yl)-4H-chromene-3-carbonitrile 4f: Yellow solid; M.P.: 74–76 °C; 83% yield (petroleum ether : EtOAc = 2 : 1); $[\alpha]^{26}_{D}$ = +25.1 (c 0.4, EtOAc); the ee was determined by HPLC analysis using a chiral IB column (*i*PrOH/hexane = 20/80, 1.0 mL/min, 254 nm), t_r (major) = 10.24 min, t_r (minor) = 18.74 min, 83% *ee*; ^{1}H NMR (400 MHz, DMSO) δ = 10.78 (1H, s), 7.21 (3H, m), 7.08 – 7.01 (3H, m), 6.98 (1H, t, *J* = 7.4 Hz), 6.85 (1H, d, *J* = 8.3 Hz), 6.80 (2H, s), 4.95 (1H, s), 2.25 (3H, s) ppm; ^{13}C NMR (100 MHz, DMSO) δ = 160.53, 148.87, 135.72, 129.70, 128.26, 127.17, 125.95, 124.79, 124.31, 123.64, 123.08, 121.30, 118.67, 118.54, 116.19, 111.88, 56.78, 32.84, 21.92 ppm; EI-HRMS: Calcd for $C_{19}H_{16}N_3O$ $[M+H]^+$ 302.1293, Found 302.1299.

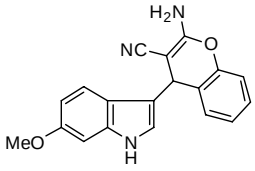




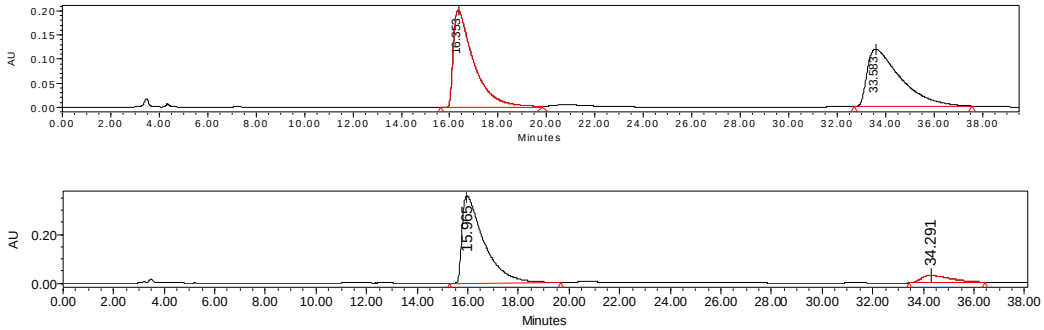


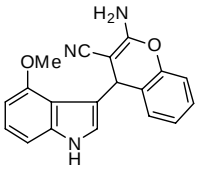
2-amino-4-(5-methoxy-1H-indol-3-yl)-4H-chromene-3-carbonitrile 4g: Yellow solid in 89% yield (petroleum ether : EtOAc = 2 : 1); $[\alpha]^{26}_{D}$ = +11.0 (c 0.5, EtOAc); the ee was determined by HPLC analysis using a chiral IB column (*i*PrOH/hexane = 20/80, 1.0 mL/min, 254 nm), t_r (major) = 14.03 min, t_r (minor) = 34.99 min, 80% *ee*; ^{1}H NMR (400 MHz, DMSO) δ = 10.75 (1H, s), 7.21 (3H, dd, *J* = 18.5, 8.4 Hz), 7.10 (1H, d, *J* = 7.4 Hz), 7.05 (1H, d, *J* = 8.1 Hz), 7.00 (1H, t, *J* = 7.4 Hz), 6.82 (2H, s), 6.75 (1H, s), 6.70 (1H, dd, *J* = 8.8, 1.9 Hz), 4.96 (1H, s), 3.64 (3H, s) ; ^{13}C NMR (100 MHz, DMSO) δ = 160.68, 153.24, 148.97, 132.51, 129.75, 128.27, 126.09, 124.85, 124.27, 124.04, 121.35, 119.08, 116.14, 112.71, 110.98, 101.36, 55.70, 55.62, 32.86 ppm; EI-HRMS: Calcd for $C_{19}H_{16}N_3O_2$ $[M+H]^+$ 318.1243, Found 318.1236.



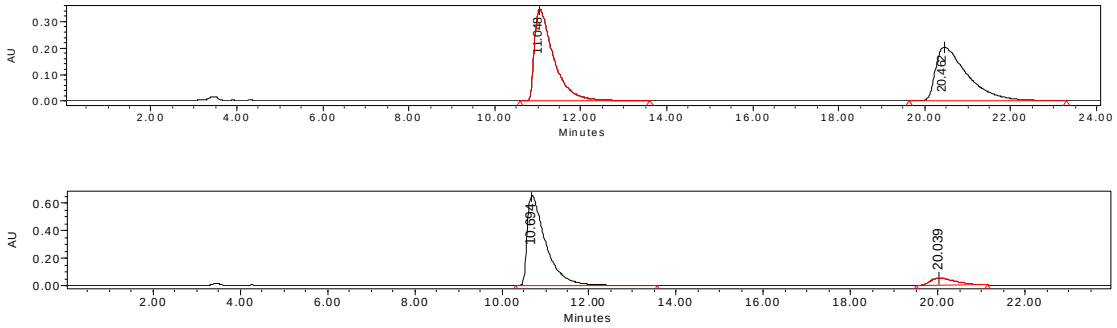


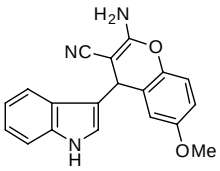
2-amino-4-(6-methoxy-1H-indol-3-yl)-4H-chromene-3-carbonitrile 4h: Yellow solid; M.P.: 210–212 °C;78% yield (petroleum ether : EtOAc = 2 : 1); $[\alpha]^{26}_{D}$ = +23.2 (c 0.5, EtOAc); the ee was determined by HPLC analysis using a chiral IB column (*i*PrOH/hexane = 20/80, 1.0 mL/min, 254 nm), t_r (major) = 15.67 min, t_r (minor) = 34.29 min, 80% *ee*; ^{1}H NMR (400 MHz, DMSO) δ = 10.70 (1H, s), 7.18 (1H, t, *J* = 7.6 Hz), 7.14 (1H, s), 7.09 – 7.01 (3H, m), 6.99 (1H, d, *J* = 7.4 Hz), 6.83 (1H, s), 6.79 (2H, s), 6.53 (1H, d, *J* = 8.7 Hz), 4.91 (1H, s), 3.70 (3H, s) ppm; ^{13}C NMR (100 MHz, DMSO): δ = 160.51, 155.95, 148.87, 138.13, 129.72, 128.27, 124.78, 124.23, 122.09, 121.28, 120.05, 119.42, 119.15, 116.20, 109.18, 95.31, 56.80, 55.63, 32.94 ppm; EI-HRMS: Calcd for $C_{19}H_{16}N_3O_2$ $[M+H]^+$ 318.1243, Found 318.1238.





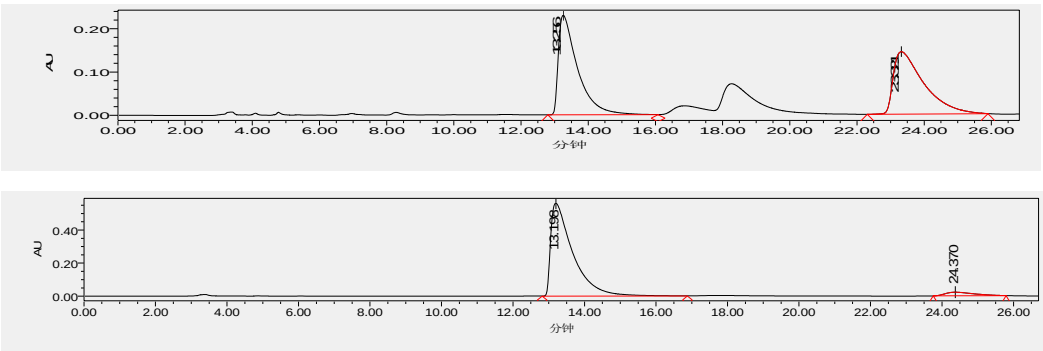
2-amino-4-(4-methoxy-1H-indol-3-yl)-4H-chromene-3-carbonitrile 4i: Yellow solid; M.P.: 102–104 °C; 81% yield (petroleum ether : EtOAc = 2 : 1); $[\alpha]^{26}_{D}$ = +100.9 (c 0.2, EtOAc); the ee was determined by HPLC analysis using a chiral IB column (*i*PrOH/hexane = 20/80, 1.0 mL/min, 254 nm), t_r (major) = 10.69 min, t_r (minor) = 20.04 min, 80% *ee*; ^{1}H NMR (600 MHz, DMSO) δ = 10.93 (1H, s), 7.16 – 7.09 (2H, m), 7.03 (1H, s,), 7.00 – 6.91 (4H, m), 6.70 (2H, s), 6.41 (1H, d, *J* = 7.4 Hz), 5.18 (1H, s), 3.75 (3H, s) ppm; ^{13}C NMR (150 MHz, DMSO) δ = 160.62, 154.12, 148.71, 138.75, 129.62, 127.72, 125.68, 124.43, 122.72, 122.43, 121.79, 120.31, 116.03, 115.98, 105.39, 99.61, 57.36, 55.21, 33.07 ppm; EI-HRMS: Calcd for $C_{19}H_{16}N_3O_2$ $[M+H]^+$ 318.1243, Found 318.1242.

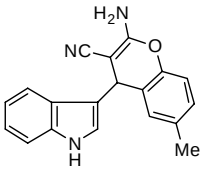




2-amino-4-(1H-indol-3-yl)-6-methoxy-4H-chromene-3-carbonitrile 4j: Yellow solid; M.P.: 70–72 °C; 85% yield (petroleum ether : EtOAc = 2 : 1); $[\alpha]^{26}_{D}$ = -28.9 (c 0.2, EtOAc); the ee was determined by HPLC analysis using a chiral IB column (*i*PrOH/hexane = 20/80, 1.0 mL/min, 254 nm), t_r (major) = 13.20 min, t_r (minor) = 24.37 min, 90% *ee*; ^{1}H NMR (400 MHz, DMSO) δ = 10.93 (1H, s), 7.35 (1H, d, *J* = 8.1 Hz), 7.30 (1H, d, *J* = 2.0 Hz), 7.27 (1H, d, *J* = 7.9 Hz), 7.03 (2H, m), 6.89 (1H, t, *J* = 7.5 Hz), 6.81 – 6.74 (3H, m), 6.61 (1H, d, *J* = 2.8 Hz), 4.96 (1H, s), 3.59 (3H, s) ppm; ^{13}C NMR (100 MHz, DMSO): δ = 160.81, 156.02, 142.97, 137.37, 125.64, 125.19, 123.45, 121.49, 121.43, 119.09, 118.96, 118.91, 117.11, 114.09, 113.75, 112.20, 56.27, 55.75, 33.36 ppm; EI-HRMS: Calcd for $C_{19}H_{16}N_3O_2$ $[M+H]^+$ 318.1243, Found 318.1234.

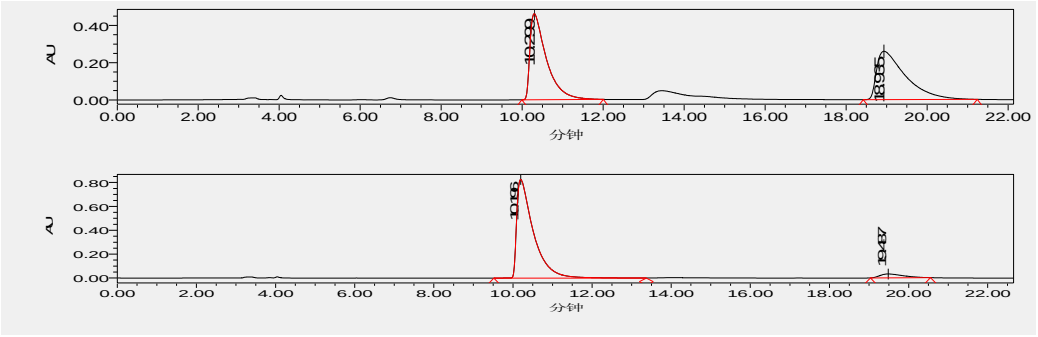
4u: 82 % yield and 89% *ee*; $[\alpha]^{26}_{D}$ =+27.8 (c 0.5, EtOAc).

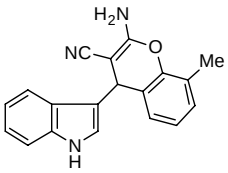




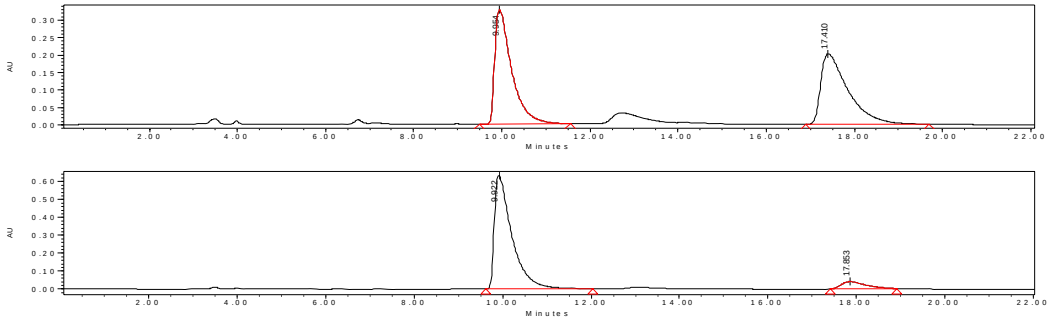
2-amino-4-(1H-indol-3-yl)-6-methyl-4H-chromene-3-carbonitrile 4k: Yellow solid; M.P.: 72–74 °C; 81% yield (petroleum ether : EtOAc = 2 : 1); $[\alpha]^{26}_{D}$ = -21.0 (c 0.4, EtOAc); the ee was determined by HPLC analysis using a chiral IB column

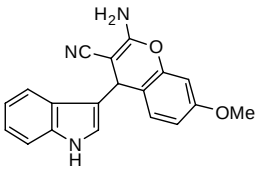
(*i*PrOH/hexane = 20/80, 1.0 mL/min, 254 nm), t_r (major) = 10.20 min, t_r (minor) = 19.49 min, 90% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.11 (1H, s), 7.32 (2H, m), 7.16 – 7.09 (2H, m), 7.03 – 6.93 (2H, m), 6.91 (1H, d, *J* = 8.3 Hz), 6.86 (1H, s), 4.99 (1H, s), 4.55 (2H, s), 2.14 (3H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.32, 146.62, 136.95, 134.51, 129.70, 128.72, 125.68, 122.43, 122.37, 122.14, 120.49, 119.61, 119.27, 119.22, 115.83, 111.42, 60.72, 32.74, 20.72 ppm; EI-HRMS: Calcd for $C_{19}H_{16}N_3O$ $[M+H]^+$ 302.1293, Found 302.1283.





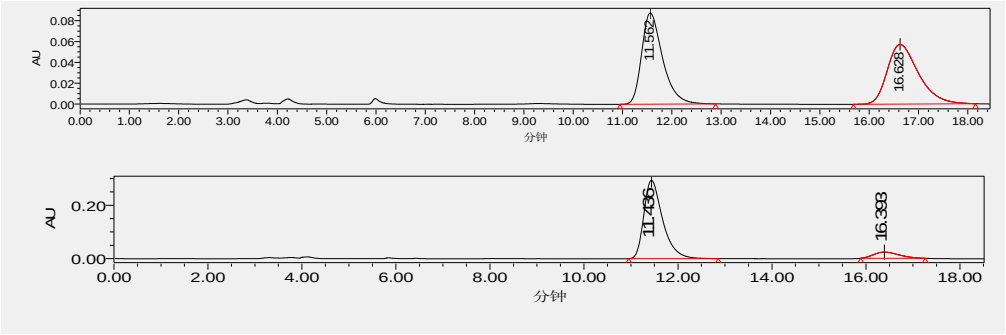
2-amino-4-(1H-indol-3-yl)-8-methyl-4H-chromene-3-carbonitrile 4l: Yellow solid; M.P.: 58-62 °C; 78% yield (petroleum ether : EtOAc = 2 : 1); $[\alpha]^{26}_D$ = +65.9 (0.4, EtOAc); the ee was determined by HPLC analysis using a chiral IB column (*i*PrOH/hexane = 20/80, 1.0 mL/min, 254 nm), t_r (major) = 9.92 min, t_r (minor) = 17.85 min, 84% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.08 (1H, s), 7.33 (2H, t, *J* = 8.5 Hz), 7.16 – 7.08 (2H, m), 7.00 (2H, t, *J* = 7.4 Hz), 6.92 (1H, d, *J* = 7.1 Hz), 6.86 (1H, t, *J* = 7.5 Hz), 5.05 (1H, s), 4.60 (2H, s), 2.33 (3H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.23, 147.02, 136.91, 129.43, 127.04, 125.70, 125.23, 124.38, 122.57, 122.46, 122.15, 120.39, 119.63, 119.41, 119.20, 111.41, 60.88, 32.79, 15.88 ppm; EI-HRMS: Calcd for $C_{19}H_{16}N_3O$ $[M+H]^+$ 302.1293, Found 302.1303.

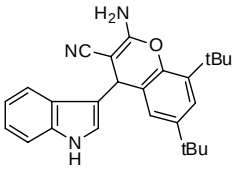




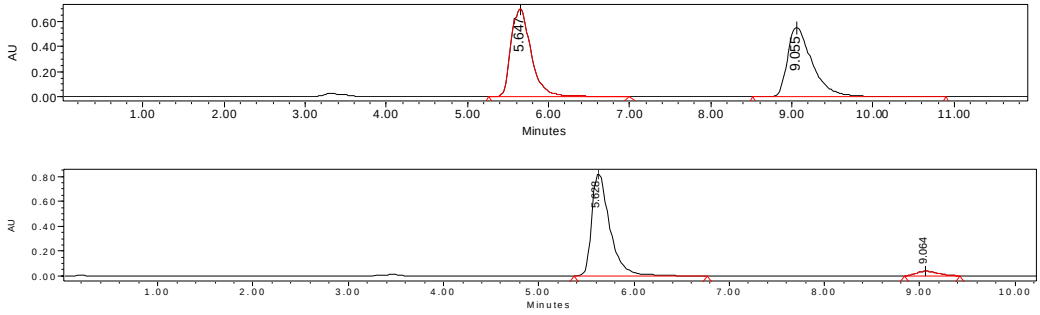
2-amino-4-(1H-indol-3-yl)-7-methoxy-4H-chromene-3-carbonitrile 4m: Viscous oil; 37% yield (petroleum ether : EtOAc = 2 : 1); $[\alpha]^{26}_D$ = +13.9 (c 0.2, EtOAc); the ee was determined by HPLC analysis using a chiral IC column (*i*PrOH/hexane = 20/80, 1.0 mL/min, 254 nm), t_r (major) = 11.44 min, t_r (minor) = 16.39 min, 81% *ee*; ^{1}H NMR (400 MHz, DMSO) δ = 10.90 (1H, s), 7.34 (1H, d, *J* = 8.1 Hz), 7.29 (1H, s), 7.21 (1H, d, *J* = 7.5 Hz), 7.03 (1H, t, *J* = 7.6 Hz), 6.95 (1H, d, *J* = 8.4 Hz,), 6.85 (1H, d, *J* = 7.2 Hz,), 6.78 (2H, s), 6.62 – 6.55 (2H, m), 4.91 (1H, s), 3.71 (3H, s) ppm; ^{13}C NMR (100 MHz, DMSO) δ = 160.36, 159.12, 149.43, 137.41, 130.41, 125.67, 123.42,

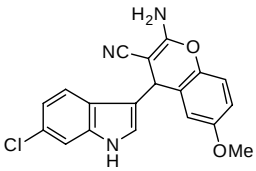
121.44, 121.32, 119.31, 118.95, 118.89, 116.04, 112.16, 111.43, 101.07, 57.09, 55.78, 32.40 ppm; EI-HRMS: Calcd for $C_{19}H_{16}N_3O_2$ $[M+H]^+$ 318.1243, Found 318.1231.



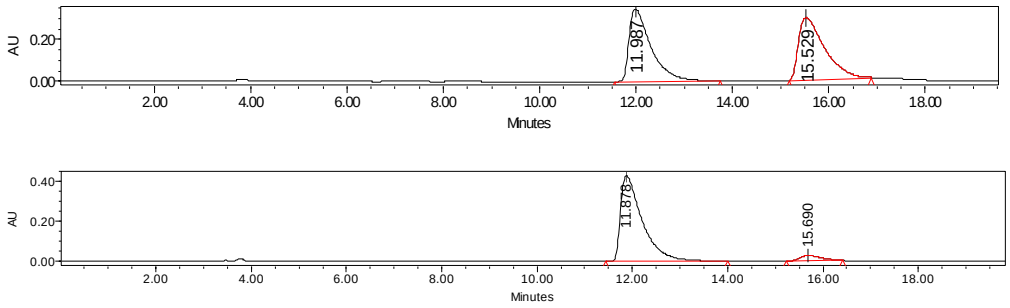


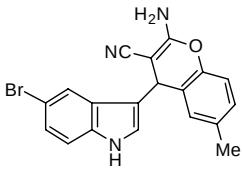
2-amino-6,8-di-tert-butyl-4-(1H-indol-3-yl)-4H-chromene-3-carbonitrile 4n: Yellow solid; M.P.: 52-54 °C; 41% yield (petroleum ether : EtOAc = 2 : 1); $[\alpha]^{26}_D$ = +1.3 (c 0.2, EtOAc); the ee was determined by HPLC analysis using a chiral IC column (*i*PrOH/hexane = 20/80, 1.0 mL/min, 254 nm), t_r (major) = 5.63 min, t_r (minor) = 9.06 min, 90% *ee*; ^{1}H NMR (400 MHz, DMSO) δ = 10.87 (1H, s), 7.38 (1H, d, *J* = 7.9 Hz), 7.34 (1H, d, *J* = 8.1 Hz), 7.21 (1H, d, *J* = 2.1 Hz), 7.12 (1H, d, *J* = 1.9 Hz), 7.07 – 7.01 (2H, m), 6.88 (1H, t, *J* = 7.5 Hz), 6.83 (2H, s), 4.91 (1H, s), 1.43 (9H, s), 1.14 (9H, s) ppm; ^{13}C NMR (100 MHz, DMSO) δ = 160.87, 145.93, 145.88, 137.37, 136.37, 125.67, 124.43, 124.06, 122.93, 121.95, 121.52, 121.44, 120.01, 119.11, 118.87, 112.16, 56.56, 35.06, 34.54, 33.84, 31.61, 30.56 ppm; EI-HRMS: Calcd for $C_{26}H_{30}N_3O$ $[M+H]^+$ 400.2389, Found 400.2385.



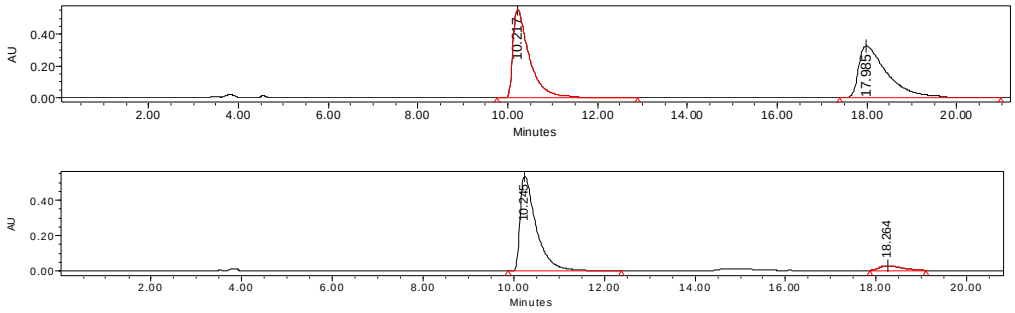


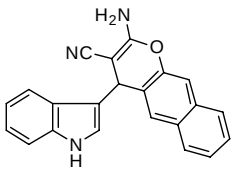
2-amino-4-(6-chloro-1H-indol-3-yl)-6-methoxy-4H-chromene-3-carbonitrile 4o: Yellow solid; M.P.: 144–146 °C; 68% yield (petroleum ether : EtOAc = 2 : 1); $[\alpha]^{26}_D$ = -44.3 (c 0.4, EtOAc); the ee was determined by HPLC analysis using a chiral IC column (*i*PrOH/hexane = 20/80, 1.0 mL/min, 254 nm), t_r (major) = 11.88 min, t_r (minor) = 15.69 min, 88% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.13 (1H, s), 7.31 (1H, s), 7.21 (1H, d, *J* = 8.5 Hz), 7.14 (1H, s), 6.99 – 6.94 (2H, m), 6.73 (1H, dd, *J* = 8.9, 2.7 Hz,), 6.53 (1H, d, *J* = 2.5 Hz,), 4.99 (1H, s), 4.57 (2H, s), 3.62 (3H, s) ppm.; ^{13}C NMR (100 MHz, DMSO) δ = 160.85, 156.10, 142.95, 137.76, 126.39, 124.89, 124.74, 124.47, 121.27, 120.14, 119.34, 117.20, 114.01, 113.93, 111.84, 56.12, 55.78, 33.15 ppm; EI-HRMS: Calcd for $C_{19}H_{15}ClN_3O_2$ $[M+H]^+$ 352.0853, Found 352.0847.



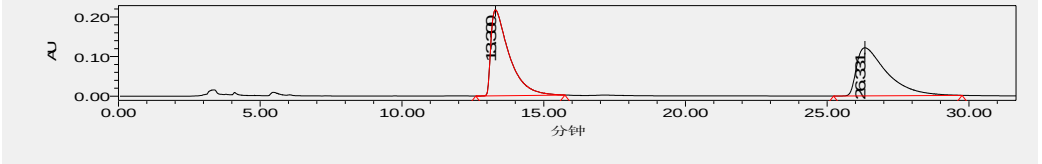


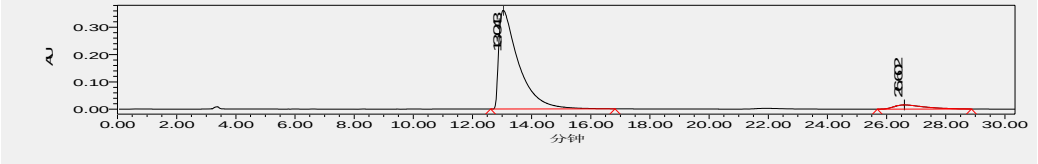
2-amino-4-(5-bromo-1H-indol-3-yl)-6-methyl-4H-chromene-3-carbonitrile 4p: Yellow solid; M.P.: 76–78 °C; 68% yield (petroleum ether : EtOAc = 2 : 1); $[\alpha]^{26}_{D}$ = -40.9 (c 0.5, EtOAc); the ee was determined by HPLC analysis using a chiral IB column (*i*PrOH/hexane = 20/80, 1.0 mL/min, 254 nm), t_r (major) = 10.25 min, t_r (minor) = 18.26 min, 89% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.24 (1H, s), 7.40 (1H, s), 7.22 – 7.16 (2H, m), 7.15 – 7.12 (1H, m), 6.98 (1H, d, *J* = 8.4 Hz), 6.92 (1H, d, *J* = 8.3 Hz), 6.80 (1H, s), 4.95 (1H, s), 4.62 (2H, s), 2.15 (3H, s) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.40, 146.49, 135.59, 134.66, 129.49, 128.98, 127.30, 125.08, 123.81, 121.83, 121.71, 120.47, 118.70, 116.00, 112.93, 112.91, 60.16, 32.55, 20.73 ppm; EI-HRMS: Calcd for $C_{19}H_{15}BrN_3O$ $[M+H]^+$ 380.0398, Found 380.0397.





2-amino-4-(1H-indol-3-yl)-4H-benzo[g]chromene-3-carbonitrile 4q: Yellow solid; M.P.: 267–269 °C; 70% yield (petroleum ether : EtOAc = 2 : 1); $[\alpha]^{26}_{D}$ = -2.4 (c 0.3, EtOAc); the ee was determined by HPLC analysis using a chiral IB column (*i*PrOH/hexane = 20/80, 1.0 mL/min, 254 nm), t_r (major) = 13.043 min, t_r (minor) = 26.602 min, 87% *ee*; ^{1}H NMR (400 MHz, DMSO) δ = 10.90 (1H, s), 8.12 (1H, d, *J* = 8.3 Hz), 7.88 (2H, t, *J* = 8.9 Hz), 7.45 – 7.34 (4H, m), 7.29 (1H, d, *J* = 8.1 Hz), 7.22 (1H, d, *J* = 8.0 Hz), 6.98 (1H, t, *J* = 7.5 Hz), 6.89 – 6.80 (3H, m), 5.58 (1H, s) ppm; ^{13}C NMR (100 MHz, DMSO) δ = 160.20, 146.91, 137.15, 131.25, 131.05, 129.59, 128.81, 127.21, 125.59, 125.20, 124.12, 123.49, 121.39, 121.36, 119.00, 118.97, 118.62, 117.13, 116.16, 112.18, 58.25, 30.89ppm; Calcd for $C_{22}H_{16}N_3O$ $[M+H]^+$ 338.1293, Found 338.1285.

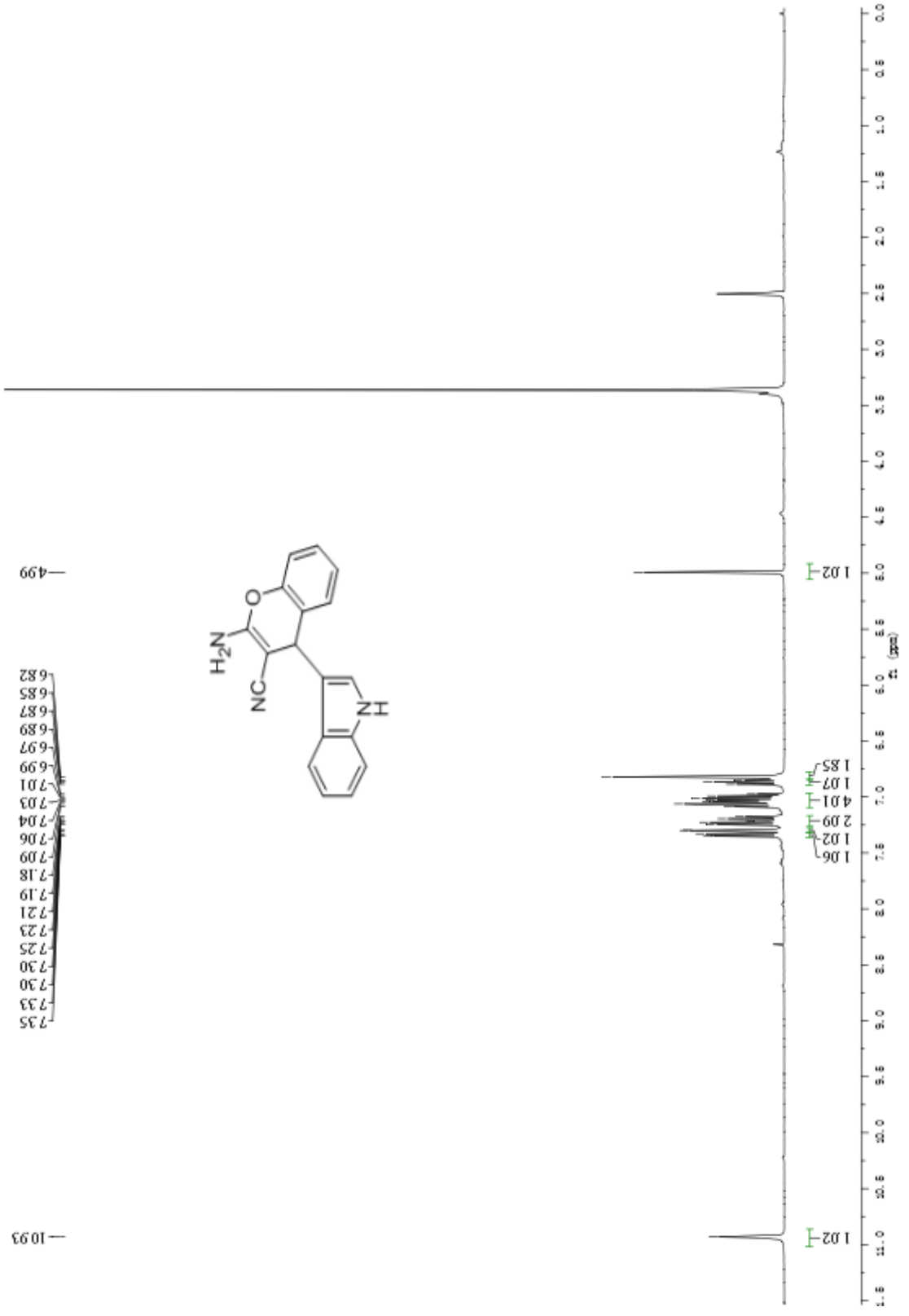




6. References

[1]. Shanthi, G.; Perumal, P. T. *Tetrahedron Lett.* **2007,** *48*, 6785.

7. Copy of ^{1}H NMR and ^{13}C NMR spectra for products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6.87
6.89
6.97
6.99
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7.03
7.04
7.06
7.09
7.18
7.19
7.21
7.23
7.25
7.30
7.30
7.33
7.35
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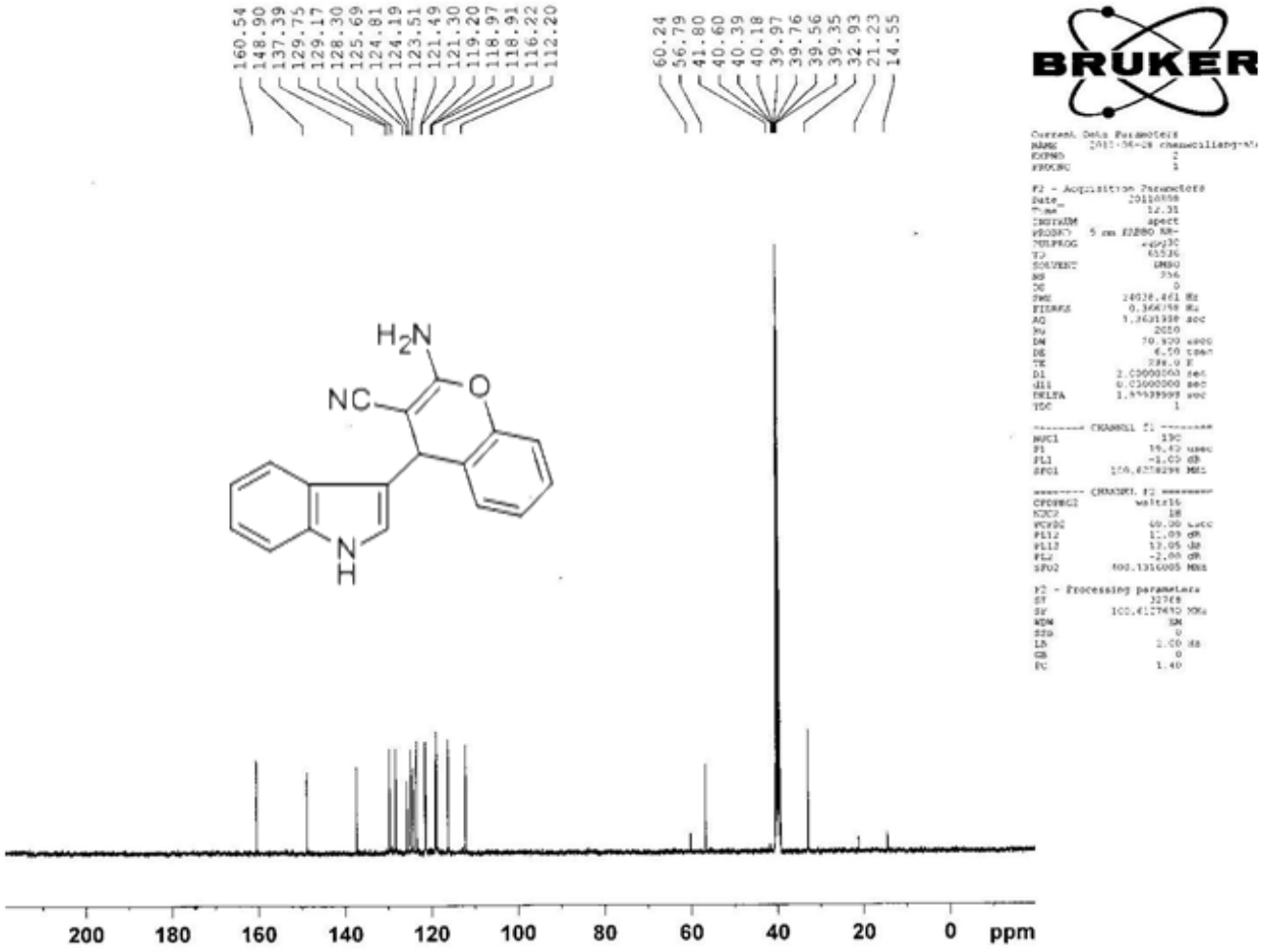
1.07
4.01
2.09
1.02
1.06
1.02
f1 (ppm)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118.97
118.91
116.22
112.20
60.24
56.79
41.80
40.60
40.39
40.18
39.97
39.76
39.56
39.35
32.93
21.23
14.55
BRUKER
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NC
O
N
H
200
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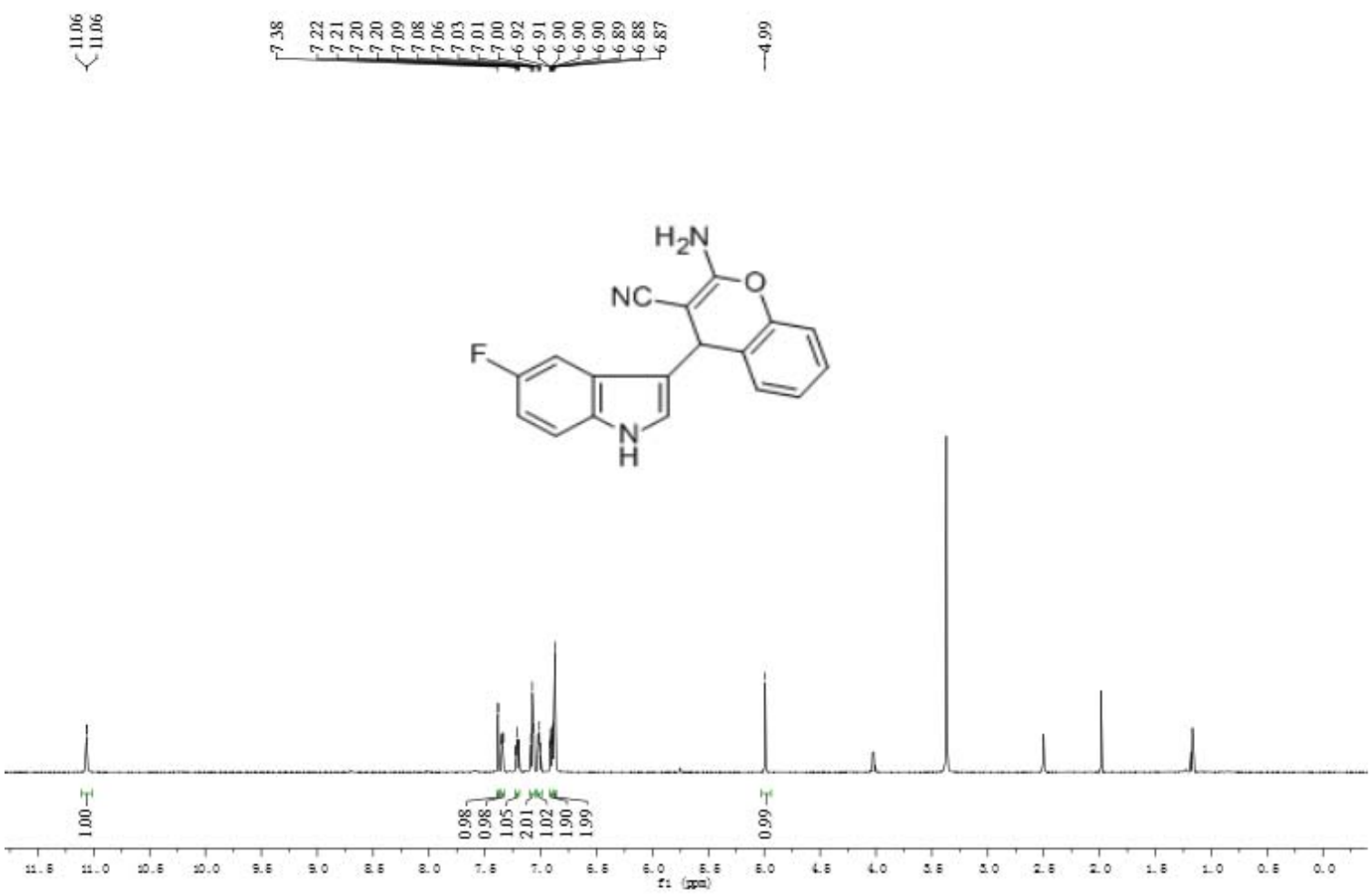
160
140
120
100
80
60
40
20
0
ppm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11.06
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7.21
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7.06
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6.91
6.90
6.90
6.90
6.89
6.88
6.87
4.99
H2N
O
NC
F
N
H
1.00
0.98
0.98
1.05
2.01
1.02
1.90
1.99
0.99
f1 (ppm)

32.68
36.40
103.31
103.46
109.55
109.72
113.18
116.26
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128.43
129.71
133.98
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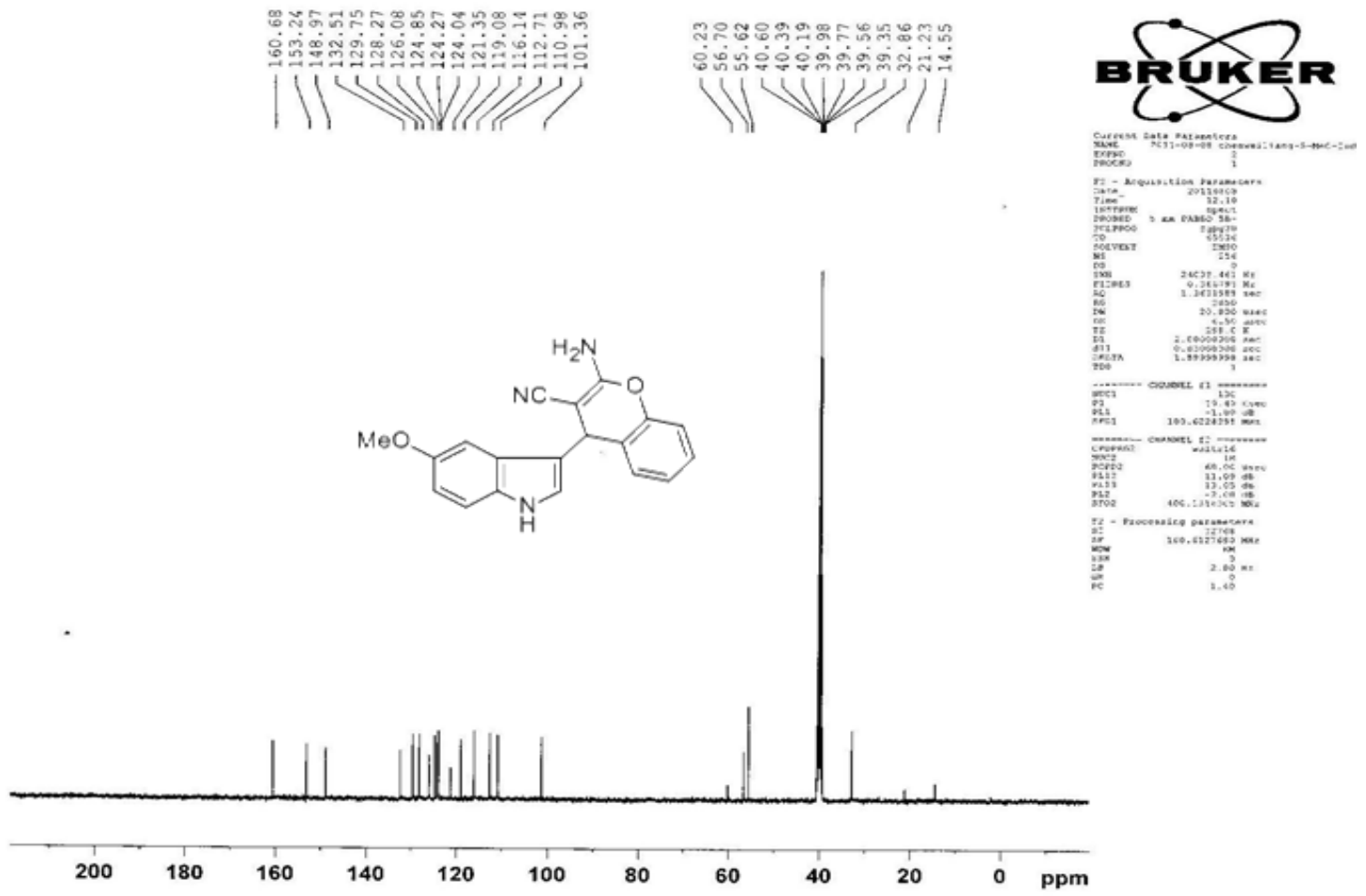
157.68
160.60
NC
H2N
O
NH
F

10.75
4.96
3.64
7.24
7.22
7.19
7.17
7.11
7.09
7.06
7.04
7.02
7.00
6.98
6.82
6.75
6.71
6.71
6.69
6.69
1.00
2.94
0.99
3.04
1.02
1.02
1.01
1.04
1.95
1.02
1.02
f1 (ppm)
H2N
NC
O
N
H
MeO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124.85
124.27
124.04
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56.70
55.62
40.60
40.39
40.19
39.98
39.77
39.56
39.35
32.86
21.23
14.55
BRUKER
H_2N
NC
O
MeO
N
H
200
180
160
140
120
100
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60
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20
0
ppm

10.78
4.95
2.25
7.22
7.22
7.21
7.20
7.07
7.05
7.03
7.00
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3.09
1.08
1.10
1.98
3.03
1.05
H2N
NC
O
NH
Me
f1 (ppm)

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121.30
118.54
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56.78
32.84
21.92
f1 (ppm)
O
H2N
NC
NH
Me

11.17
5.01
7.40
7.39
7.38
7.36
7.24
7.22
7.20
7.09
7.07
7.05
7.03
7.02
7.00
6.89
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O
NC
N
H
Cl
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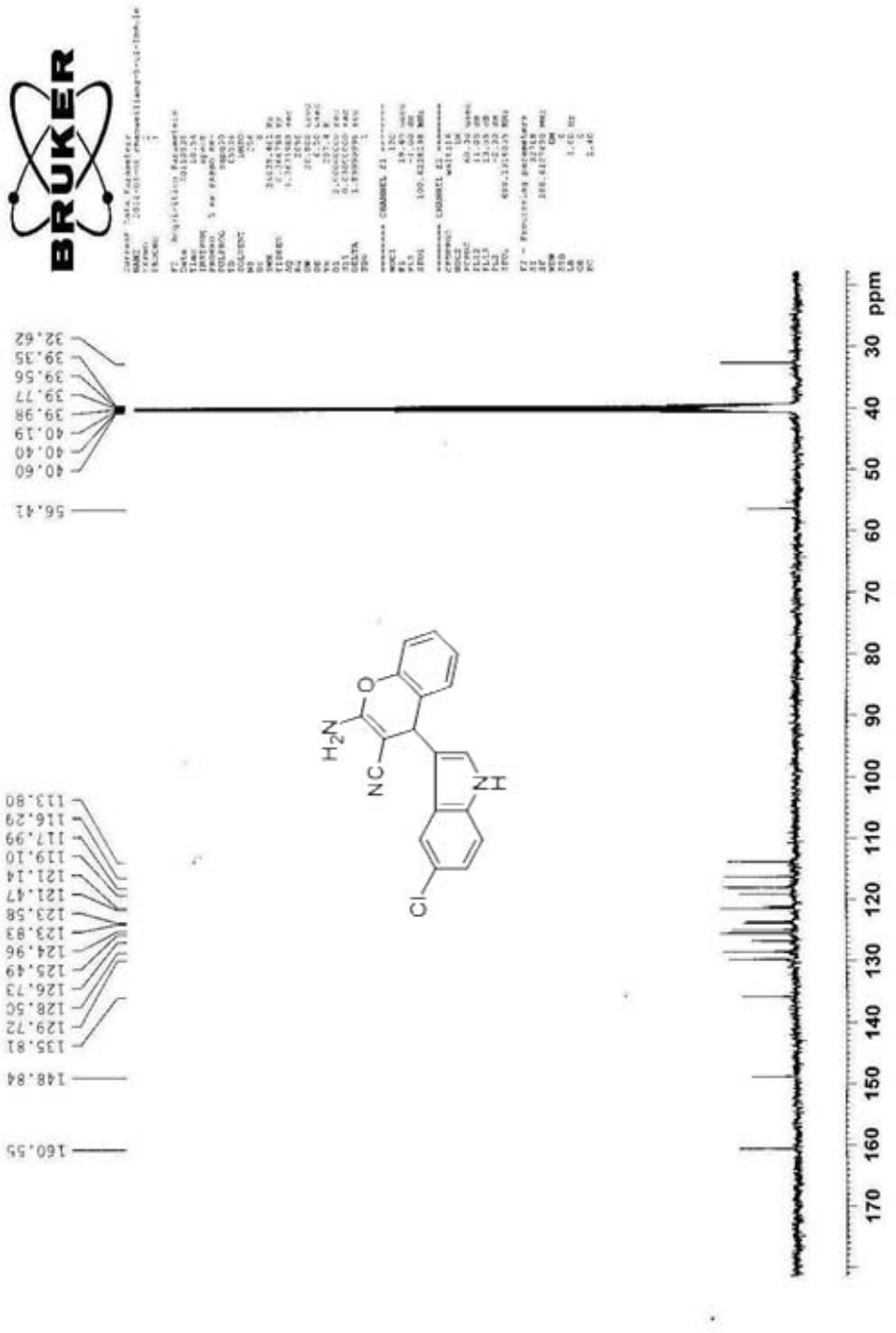
0.99
1.02
2.09
4.04
1.97
f1 (ppm)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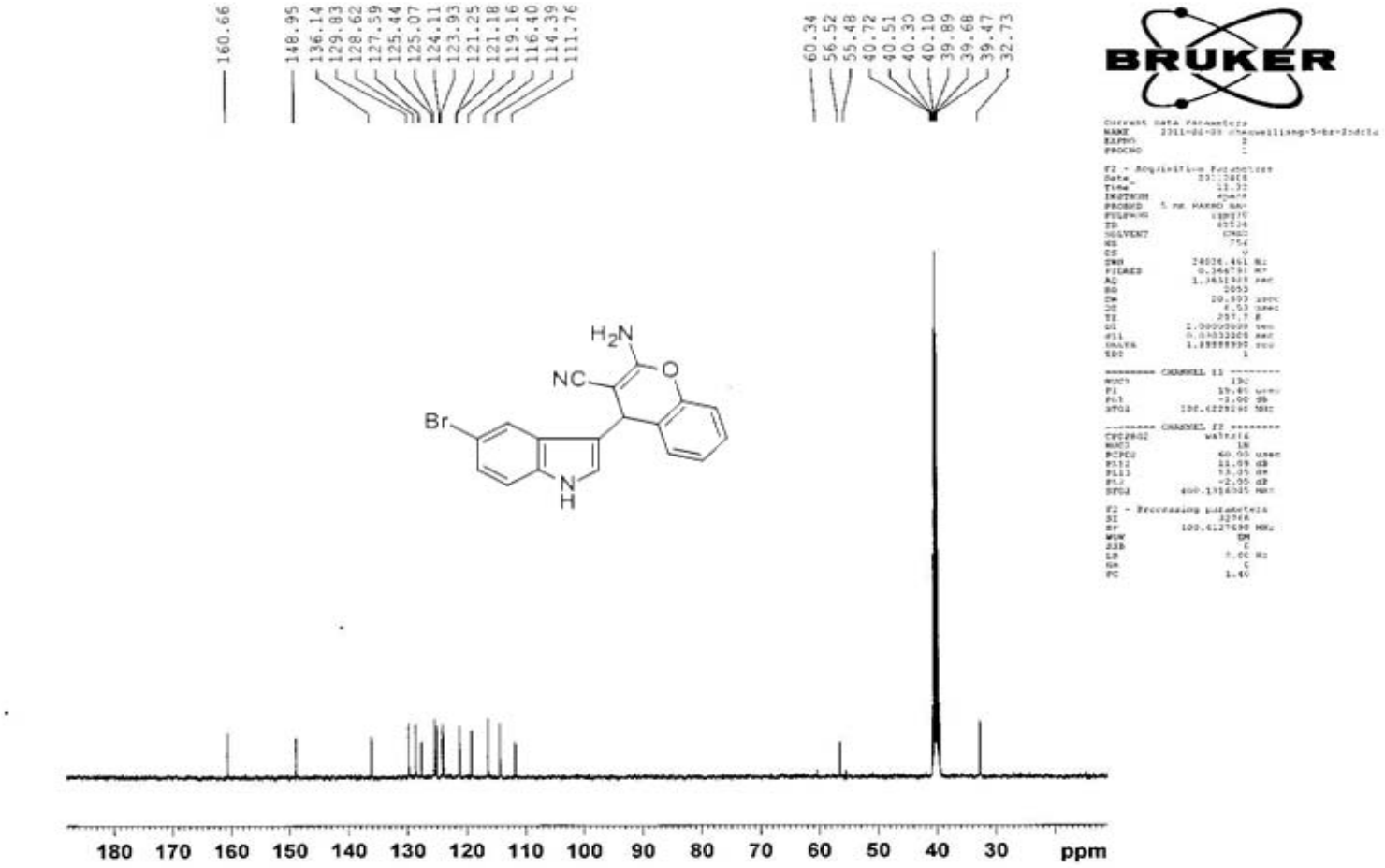
135.81
148.84
160.55
H2N
NC
O
NH
Cl
ppm

8.30
7.40
7.16
7.13
7.12
7.05
7.03
7.02
7.00
6.99
6.97
6.94
5.02
4.68
0.95
1.94
1.00
0.97
2.91
1.13
3.00
f1 (ppm)
NC
O
H_2N
NH
Br


160.66
148.95
136.14
129.83
128.62
127.59
125.44
125.07
124.11
123.93
121.25
121.18
119.16
116.40
114.39
111.76
60.34
56.52
55.48
40.72
40.51
40.30
40.10
39.89
39.68
39.47
32.73
BRUKER
H_2N
NC
O
Br
N
H
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 ppm

10.93
7.14
7.13
7.12
7.12
7.10
7.03
6.99
6.97
6.96
6.95
6.95
6.93
6.92
6.70
6.42
6.40
5.18
3.75
1.02
0.95
1.00
2.03
4.15
0.96
2.02
3.02
f1 (ppm)
H2N
O
NC
OMe
NH

33.07
55.21
57.36
99.61
105.39
115.98
116.03
120.31
121.79
122.43
122.72
124.43
125.68
127.72
138.75
148.71
154.12
160.62
O
H2N
NC
OMe
NH
f1 (ppm)

10.70
7.20
7.18
7.16
7.14
7.08
7.06
7.05
7.04
7.02
7.00
6.98
6.83
6.79
6.55
6.52
4.91
3.70
1.00
1.08
0.99
3.08
1.06
1.05
1.04
1.01
1.01
3.04
f1 (ppm)
O
H2N
NC
NH
MeO

32.94
55.63
56.80
95.31
109.18
116.20
119.15
120.05
124.78
128.27
129.72
138.13
148.87
155.95
160.51
f1 (ppm)
O
H2N
NC
NH
MeO

0.00
5.00
11.09
6.86
6.90
6.90
6.92
6.93
6.98
7.00
7.01
7.04
7.06
7.18
7.19
7.20
7.22
7.35
7.35
7.37
7.39
7.39
H2N
O
NC
NH
Cl
1.00
0.98
1.00
0.96
2.05
1.98
1.04
1.02
1.92
f1 (ppm)

32.70
56.59
111.82
116.29
119.33
123.91
124.50
124.79
124.88
128.43
137.76
148.87
160.56
f1 (ppm)
NC
H2N
O
NH
Cl

10.90
4.91
3.71
6.58
6.58
6.59
6.60
6.61
6.78
6.85
6.86
6.88
6.94
6.96
7.01
7.03
7.05
7.20
7.22
7.29
7.33
7.35
7.36
1.00
1.01
3.00
2.07
1.25
1.06
1.10
1.14
OMe
O
H_2N
NC
NH

160.36
159.12
149.43
137.41
130.41
123.42
119.31
118.95
118.89
116.04
112.16
111.43
101.07
57.09
55.28
32.40
OMe
O
H2N
NC
H
N
f1 (ppm)

10.93
7.36
7.34
7.30
7.30
7.28
7.26
7.02
6.89
6.87
6.80
6.79
6.77
6.61
6.60
4.96
3.59
1.00
1.03
1.02
1.09
2.09
1.07
3.04
1.06
1.04
3.07
f1 (ppm)
OMe
O
H2N
NC
N
H

160.81
156.02
142.97
137.37
121.49
121.43
119.09
118.96
118.91
117.11
114.09
113.75
112.20
56.27
55.75
33.36
OMe
O
H_2N
NC
N
H
f1 (ppm)

Me
H2N
NC
NH
8.08
7.35
7.33
7.31
7.10
7.09
7.02
7.00
6.98
6.93
6.91
6.88
6.86
6.84
5.05
4.60
2.33
0.93
2.05
2.06
2.04
1.03
1.04
1.00
1.97
3.05
f1 (ppm)

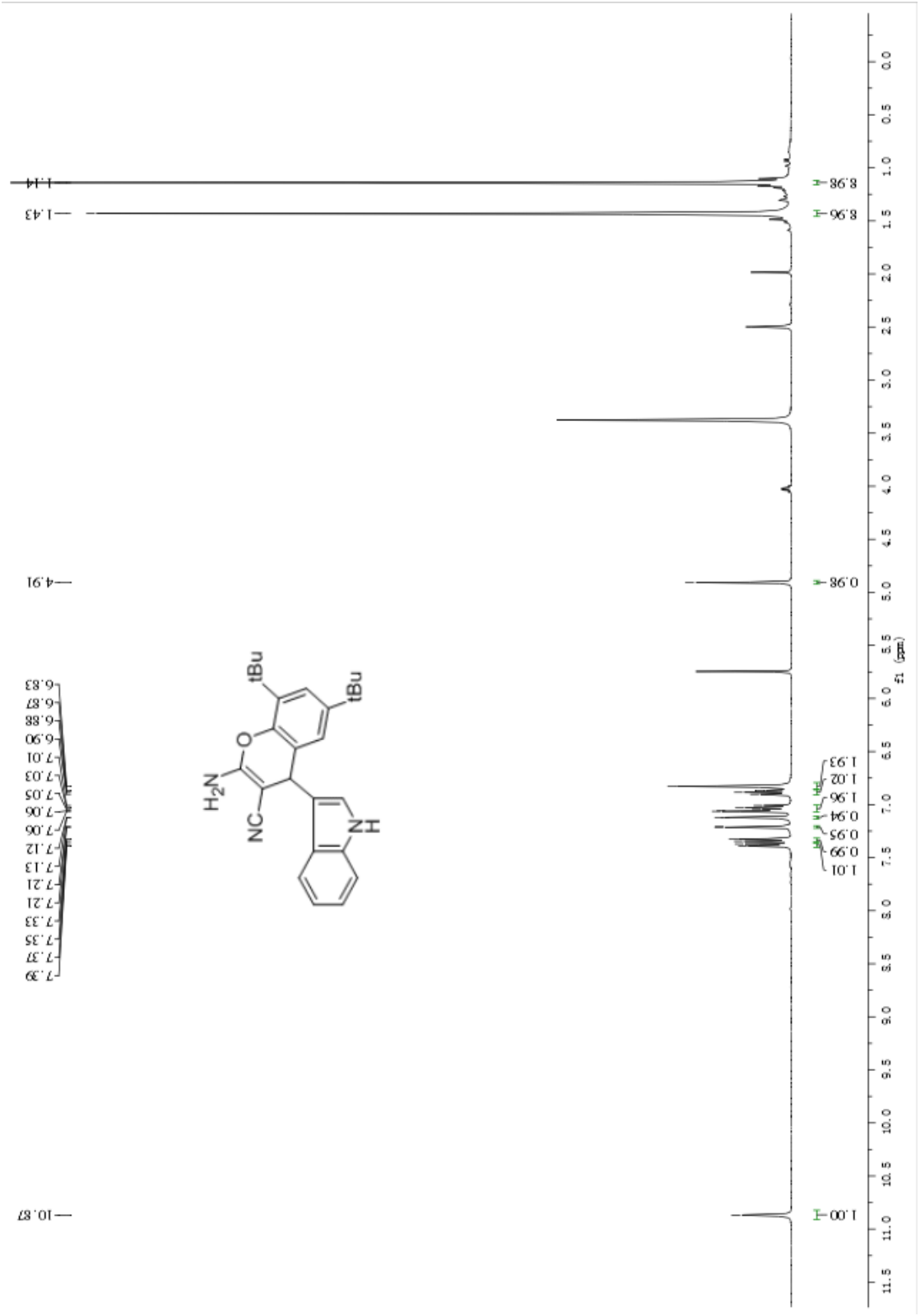
Me
O
H_2N
NC
NH
159.23
147.02
136.91
127.04
122.57
122.46
122.15
120.39
119.63
119.41
119.20
111.41
60.88
32.79
15.88
f1 (ppm)

8.13
7.31
7.22
7.20
7.17
7.14
6.96
6.72
6.54
6.53
4.99
4.57
3.62
H2N
NC
O
OMe
N
H
Cl
1.00
1.07
1.10
1.10
2.08
1.09
1.08
1.08
1.99
1.08
3.07
f1 (ppm)

160.85
156.10
142.95
137.76
126.39
124.89
124.74
124.47
120.14
117.20
114.01
113.93
111.84
56.12
55.78
33.15
f1 (ppm)

8.11
7.34
7.32
7.31
7.31
7.12
7.10
7.02
7.00
6.98
6.97
6.97
6.94
6.92
6.90
6.86
4.99
4.55
2.14
0.95
2.04
2.06
2.01
1.00
1.01
2.99
1.93
1.00
f1 (ppm)
Me
O
H_2N
NC
N
H

159.32
146.62
136.95
134.51
129.70
128.72
125.68
122.43
119.22
115.83
111.42
60.72
32.74
20.72
f1 (ppm)
Me
O
H2N
NC
NH


tBu
tBu
O
H2N
NC
N
H
10.87
7.39
7.37
7.35
7.33
7.21
7.21
7.13
7.12
7.06
7.06
7.05
7.03
7.01
6.90
6.88
6.87
6.83
4.91
1.43
1.14
1.00
0.98
8.96
8.98
1.01
0.99
0.95
0.94
1.96
1.02
1.93
f1 (ppm)

160.87
145.93
145.88
137.37
136.37
122.93
121.95
121.52
121.44
120.01
119.11
118.87
112.16
56.56
35.06
34.54
33.84
31.61
30.56
f1 (ppm)

8.24
7.40
7.13
6.99
6.97
6.94
6.91
6.80
4.95
4.62
2.15
0.96
0.93
1.96
1.06
1.03
1.00
1.99
1.04
3.01
f1 (ppm)
Me
Br
NC
H_2N
O
N
H

20.73
32.55
60.16
112.91
112.93
116.00
118.70
120.47
121.71
121.83
123.81
129.49
134.66
135.59
146.49
159.40
Me
O
H_2N
NC
N
H
Br
f1 (ppm)

10.90
8.13
8.11
7.88
7.86
7.38
7.30
7.21
6.98
6.96
6.86
6.83
6.81
5.58
1.00
1.01
2.04
4.08
1.02
1.02
1.04
3.01
1.03
f1 (ppm)
NC
O
H2N
N
H

160.20
146.91
137.15
127.21
125.20
124.12
123.49
121.39
189.86
116.16
112.18
58.25
30.89
H2N
NC
O
NH
f1 (ppm)