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Asymmetric Synthesis of Spiro[4*H*-Chromene-3,3′-oxindoles] via a Squaramide-Organocatalysed Three-Component Cascade Knoevenagel/Michael/Cyclization Sequence

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Abstract: An efficient stereoselective three-component reaction for the synthesis of spiro[4*H*-chromene-3,3′-oxindole] derivatives was realized through an organocatalysed cascade Knoevenagel/Michael/cyclization reaction using a quinidine-derived squaramide as the catalyst. Under the optimized conditions, the reactions of isatins, malononitrile, and sesamol yield the desired spirooxindoles in good yields (75–87%) and moderate to high ee values (up to 90% ee). Two pairs of selected enantiomers were subjected to evaluation of their antiproliferative activities on three types of human cancer cell lines using the MTT assay. The results indicated that stereoselectivity and electrical effects had a significant impact on activity. Enantiomer *R*-**3f** exhibited optimal cytotoxic activity against the U_2O_S cell line, which was close to the inhibitory activity of the positive control, Adriamycin.

Keywords: enantioselective; cascade Knoevenagel/Michael/cyclization; quinidine- squaramide; spirooxindoles

1. Introduction

Chromenes are important core scaffolds in various natural products and pharmaceutical molecules that exhibit a wide spectrum of biological activities, such as anti-inflammatory, antitumour, antimicrobial, antitoxin and antimalarial properties [1–9]. Specifically, chromenes structure with chiral centres in numerous natural products have been proven to have diverse pharmacological effects (Figure 1) [10–12].

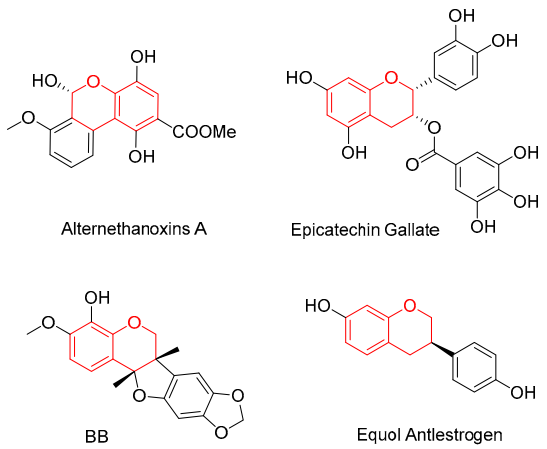

Figure 1. Examples of biologically active compounds containing chiral chromenes.

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In addition, optically active spirooxindole derivatives containing heterocyclic frameworks have attracted tremendous attention because of their prominent activities and wide utility as synthetic intermediates for alkaloids and clinical drugs [13–16]. Over past years, the significant progress has been made in the stereoselective construction of spirooxindole [17–26]. Considering the potential biological activity of both chromenes and spirooxindole structures, we think splicing two fragments into hybrid derivatives may result in a series of structurally and biologically significant new molecules. In recent years, various attempts have also been made for the synthesis of spirooxindoles with fused 4*H*-chromenes using different catalysts [27–32]. In 2012, Wang group developed a rosin thiourea catalysed reaction of coumarins with isatylidene malononitriles [28]. Afterwards, Zhao reported quinine-thiourea catalysed three-component cascade reactions of isatins, malononitrile, and 2-hydroxynaphthalene-1,4- diones [29]. In 2016, Khan et. al. disclosed the first enantioselective addition of naphthols and sesamol to indolylidene cyanoacetate derived from isatins organocatalysed by quinine -thiourea[30]. Additionally, Zhou [31] and Abdolmohammadi [32] respectively reported Knoevenagel/Michael/Cyclization of isatins, malononitrile, and sesamol, respectively. However, the methods reported in two studies did not involve asymmetric synthesis and resulted in racemic spirooxindoles. Despite the great developments, to the best of our knowledge, to date, the enantioselective one-pot, cascade reaction of isatins, malononitrile, and sesamol has not been explored.

We herein first reported the enantioselective domino Knoevenagel/Michael/ cyclization of isatins, malononitrile, and sesamol by employing the *cinchona* alkaloids, Takemoto's catalyst, proline, diphenyl aminoethanol and phosphoric acid derivatives **1a-1m** (Figure 2).

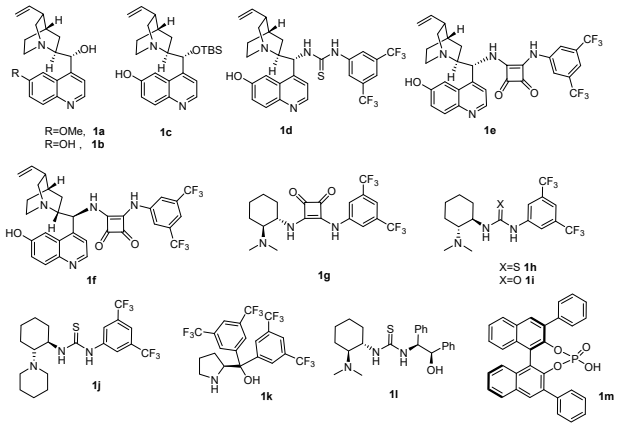
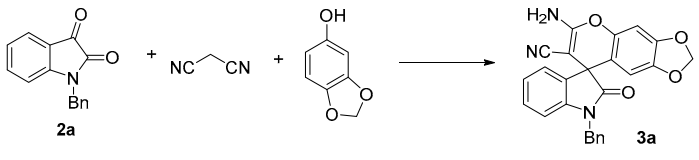


Figure 2. The structure of screened organocatalysts (**1a–1m**).

2. Results and Discussion

We first applied the catalysts **1a–1m** in the cascade reaction of *N*-benzylisatin(**2a**), malononitrile and sesamol to screen the optimal catalyst. The reaction was carried out with CH_2Cl_2 as a solvent in the presence of 10 mol% of catalysts at room temperature for 24 h (Table 1). Catalysts **1a-1l** preceded the reaction smoothly to give the desired product **3a** in 68-85% yields with 5-40% ees while phosphoric acid **1m** failed to catalyse the reaction (entry 13). Among of them, quinidine-squaramide **1f** was optimal in terms of the yield and enantioselectivity (entry 6) while Takemoto's catalysts and proline derivative showed poor asymmetric induction.

Table 1. Asymmetric Knoevenagel/Michael/cyclization reaction of isatin **2a**, malononitrile and sesamol catalysed by **1a-k** [a].



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Entry	Catalyst	Yield (%)[b]	%ee[c]
1	**1a**	78	10
2	**1b**	76	12
3	**1c**	80	10
4	**1d**	81	29
5	**1e**	83	38
6	**1f**	85	40
7	**1g**	82	26
8	**1h**	80	20
9	**1i**	68	5
10	**1j**	73	12
11	**1k**	74	12
12	**1l**	72	9
13	**1m**	-	-

[a]Reaction condition:*N*-benzylisatin (0.1 mmol) , malononitrile (0.1 mmol), sesamol (0.1 mmol) and catalyst **1f** (0.01 mmol) in CH_2Cl_2 (1.0 mL) at rt . [b]isolated yield. [c] Determined by HPLC analysis (Chiralpak AD).

To improve the enantioselectivity of the transformation, we investigated a variety of different reaction conditions (Table 2). The survey of solvents showed that $CHCl_3$ was optimal in terms of the yield and enantioselectivity (entry 2). The screening of catalyst loading showed that a 10 mol% equivalent of **1f** was optimal. Reduction of the catalyst loading to 5 mol% led to an obviously decrease in enantioselectivity and yield (entry 8 vs. entry 2), and 20 mol% loading offered no improvement in the asymmetric induction, albeit with a slightly improved yield (entry 9 vs. entry 2). When the reaction temperature was lowered from rt to 0 °C, the enantioselectivity of the product was improved to 58%, and the yield could be remained at the same level by prolonging the reaction time (entry 10). Next, a further temperature drop to −20 °C caused a significant decrease in both enantioselectivity (40% ee) and yield (68%). Furthermore, diluting the reaction concentration by half was detrimental to the yield and enantiocontrol (entry 12 vs. entry 10). Adding 4 Å molecular sieves (MS) led to a slightly higher ee value of 61% and increased yield (entry 13 vs. entry 10). Subsequently, the reaction was carried out in dry $CHCl_3$ under anaerobic conditions, and the ee value of the product was not improved (entry 14 vs. entry 13). Based on these experiments, the optimized conditions were determined to be $CHCl_3$ as the solvent with a 10 mol% loading of catalyst **1f** in the presence of 4 Å MS (200 mg) at 0 °C.

Table 2. Screening of reaction conditions for the asymmetric cascade reaction catalysed by **1f** [a].

Entry.	Solvent	Temperature	Catalyst. Amount (% mmol)	Yield (%)[b]	%ee[c]
1	CH_2Cl_2	rt	10	85	40
2	$CHCl_3$	rt	10	84	42
3	$(CH_2)_2Cl_2$	rt	10	76	28
4	Et_2O	rt	10	78	13
5	THF	rt	10	78	16
6	PhMe	rt	10	81	16
7	EtOAc	rt	10	75	10
8	$CHCl_3$	rt	5	71	35
9	$CHCl_3$	rt	20	88	36
10	$CHCl_3$	0	10	83	58
11	$CHCl_3$	-20	10	68	40
12[d]	$CHCl_3$	0	10	83	52
13[e]	$CHCl_3$	0	10	85	61
14[f]	$CHCl_3$	0	10	87	60

[a]Reaction condition:*N*-benzylisatin (0.10 mmol), sesamol (0.10 mmol), malononitrile (0.10 mmol) and **1f** in solvent (1 mL). [b]isolated yield. [c] Determined by HPLC analysis (ChiralpakAD). [d] 2 mL of solvent. [e] 4Å MS (about

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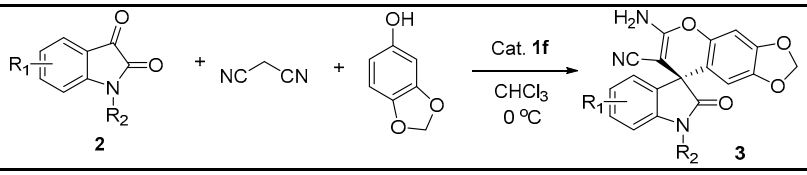
30 mg). [f] 4-methylbenzoic acid(0.01 mmol). [g] 4-nitrobenzoic acid(0.01 mmol). [f] with 4Å MS (about 30 mg) in anhydrous and anaerobic condition.

With the optimized conditions in hand, we explored the scope and general applicability of the protocol. A wide range of substituted isatins were evaluated, as shown in Table 3. A wide range of isatins bearing various substituents on the phenyl ring, such as halogens, methyl groups and methoxyl groups, were tolerated, giving the desired products in good yields (75-87%) with 45-90% ees, except 5-nitro substituted isatin, which produced **3i** with only 10% ee (entry 9). Therefore, the enantioselectivity was obviously affected by the substituted position on the phenyl ring of isatins. The reaction of 5-Br-substituted *N*-Bn-isatin afforded the optimal enantiomeric excess (90%ee, entry 6). Then, a 0.5 mmol scale asymmetric domino reaction of **2f** was conducted under the optimum conditions, and product **3f** was obtained in 82% yield with 85% ee (data in parentheses, entry 6). In the case of isatin and *N*-methylisatin as substrates, decreased ee values were obtained (entries 13, 14 vs. entry 1).

Table 3. Generality of the enantioselective Knoevenagel/Michael/cyclization reaction of isatins, malononitrile and sesamol [a].



2 3

Entry	R_1, R_2	Product	Yield (%)[b]	%ee[c]
1	H, Bn(**2a**)	**3a**	85	61
2	4-Cl, Bn(**2b**)	**3b**	83	65
3	4-Br, Bn(**2c**)	**3c**	77	50
4	5-F, Bn(**2d**)	**3d**	81	60
5	5-Cl, Bn(**2e**)	**3e**	85	50
6	5-Br, Bn(**2f**)	**3f**	87(82) [d]	90(85)[d]
7	5-Me, Bn(**2g**)	**3g**	81	70
8	5-OMe, Bn(**2h**)	**3h**	79	57
9	5-NO_2, Bn(**2i**)	**3i**	84	10
10	6-Cl, Bn(**2j**)	**3j**	82	55
11	7-Cl, Bn(**2k**)	**3k**	75	55
12	7-Br, Bn(**2l**)	**3l**	80	67
13	H, H(**2m**)	**3m**	79	45
14	H, Me(**2n**)	**3n**	78	50
15	5-Br, H(**2o**)	**3o**	83	72
16	5-Me, H(**2p**)	**3p**	81	59

[a]Reaction condition: isatins (0. 10 mmol), sesamol (0.10 mmol), malononitrile (0.10 mmol) and catalyst **1f** (0.01 mmol) in $CHCl_3$(1 mL) at 0 °C. [b]isolated yield. [c] Determined by HPLC analysis (Chiralpak AD). [d]The data in parentheses are the yield and ee value from reaction of 0.5 mmol scale.

The absolute configuration of spiro[4*H*-chromene-3,3′-oxindole] products **3** were unambiguously assigned as *R* according to the X-ray crystal structure analysis of **3f** (Figure 3) [33] .

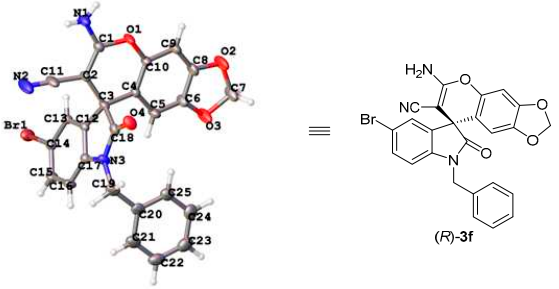


Figure 3. X-ray crystal structure of **3f.**

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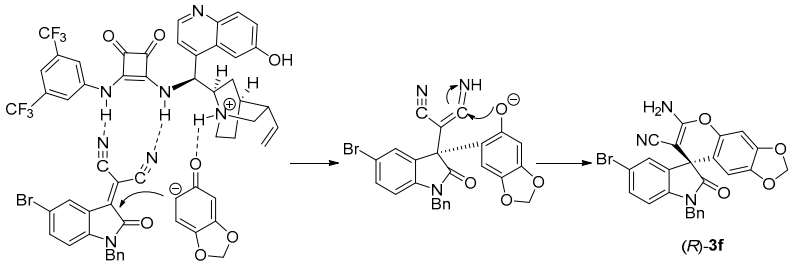
On the basis of the absolute stereochemistry of **3f**, a plausible transition state model is proposed. As shown in Scheme 1, isatin (**2a**) first reacts with malononitrile to yield the isatylidenemalononitrile intermediate, which is fixed and activated by the neighbouring two squaramide hydrogen atoms through double H-bonding, while sesamol is activated by an interaction between the tertiaryamine moiety of **1f** and the hydroxy group of sesamol. Then, *re*-face addition of the electron-rich sesamol to the electron-deficient isatylidenemalononitrile generates the Michael adduct intermediate, which is further transformed to the final *R*-**3f** through subsequent intramolecular cyclization and tautomerization.



Scheme 1. Proposed transition state for the formation of **3f.**

To broaden the scope of nucleophiles, electron-rich phenols (3,4-dimethoxy, 3,5-dimethoxy substituents), 1-naphthol and 4-hydroxyindole were reacted with *N*-benzylisatin and malononitrile under the screened catalyst conditions. Corresponding Spiro[4*H*-Chromene -3,3′-oxindoles] derivatives were smoothly obtained in good yields (Fig. 4). Among of them, 3,4-dimethoxy and 3,5-dimethoxy phenols have similar structures to sesamol. However, a moderate ee value (54%ee) was obtained in the reaction of 3,4-dimethoxy phenol as the nucleophile, while a low ee value (27%ee) was produced with 3,5-dimethoxy phenol as the reactant. Therefore, the substituted position of the OMe group had an important effect on the enantioselectivity. Furthermore, the reaction of 4-hydroxyindole obtained 56% enantioselectivity, while 1-naphthol as a nucleophile was unfavourable for the stereoselectivity of the reaction (17%ee).

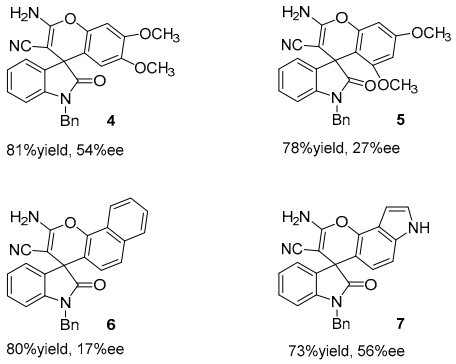


Figure 4. Expansion of the scope of nucleophiles

Considering the anticancer activity of various isatin derivatives [34–39], we plan to study the antiproliferative activities of the obtained products. Moreover, to investigate the impact of the chiral centre and electrical effect on activity, we chose 5-Br-1-Bn (electron-withdrawing) and 5-Me-1-Bn (electron-donating) isatin-derived products **3f** and **3g** with relatively high ee values for the activity test. Two pairs of enantiomers were catalysed by optical isomers **1e** and **1f** (as shown in Figure 2), and the racemic products were catalysed by DABCO. The structures of enantiomers and their ee vaules are shown in Figure 5.

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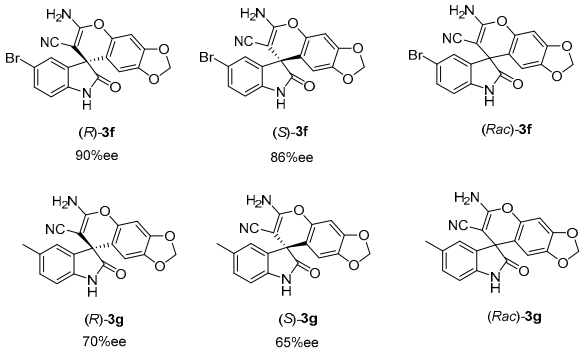

Figure 5. The structures of two pairs of enantiomers

The antiproliferative activities of selected compounds were evaluated on three types of human cancer cell lines, human prostate cancer cells (C_{42}), human cervical cancer cells (HeLa) and human osteosarcoma cells (U_2O_S) using the MTT [3-(4,5-dimethylthiazol-2-yl)- 2,5-diphenyl tetrazolium bromide] assay. It is evident from the results that most of the test compounds have shown cytotoxic activity on all tested cell lines in a concentration- dependent manner (Table 4).

Table 4. In vitro cytotoxicity of Spiro[4*H*-Chromene -3,3′- oxindoles] derivatives against C_{42}, HeLa & U_2O_S human cancer cells by MTT assay.

Entry	compounds	IC_{50} values[a] (μg/mL)		
		C_{42}	HeLa	U_2O_S
1	*R*-**3f**	11.57	16.32	6.73
2	*S*-**3f**	23.83	74.69	62.31
3	Racemic-**3f**	15.32	55.52	26.39
4	*R*-**3g**	12.22	47.97	17.98
5	*S*-**3g**	31.88	225.62	73.10
6	Racemic-**3g**	18.48	171.91	44.26
7	Adriamycin	6.02	1.48	4.72

[a] IC_{50} is defined as the concentration, which results in a 50% decrease in cell number as compared with that of the control cultures in the absence of an inhibitor and were calculated using the respective regression analysis. [b] Adriamycin was employed as positive control.

It is apparent from the results that these derivatives are found to be more potent on C_{42} and U_2O_S cell lines, followed by HeLa cells. Furthermore, the chiral factor showed an obvious impact on activity. *R*-configuration compounds were found to be more effective than *S*-configuration or racemic products (entry 1 vs entries 2 and 3 and entry 4 vs entries 5 and 6). In addition, the electrical effect exhibited a certain impact on the activity, and the 5-Br-substituted derivative was found to be more potent than the 5-CH_3-substituted product (entries 1, 2, and 3 vs entries 4, 5, and 6). From the screened compounds, compound *R*-**3f** exhibited excellent cytotoxic activity against the U_2O_S cell line (IC_{50}: 6.73 μg/mL), which was close to the inhibitory activity of the positive control (Adriamycin, IC_{50}: 4.72 μg/mL).

3. Conclusion

In summary, we have described the first enantioselective domino Michael/cyclization reaction of isatins, malononitrile, and sesamol organocatalysed by quinidine-derived squaramide to synthesize spiro [4*H*-chromene -3,3′-oxindole] derivatives in good yield with up to 90% enantioselectivity. The absolute configuration of compound **3f** was ascertained as an *R*-isomer on the

basis of X-ray crystallographic analysis. At present, the obtained ee values are not good, and further optimization of the catalyst and reaction conditions is underway. Two pairs of synthesized enantiomers were subjected to evaluation of their cytotoxic properties against different human cancer cell lines. The results indicated that stereoselectivity and electrical effects had obvious impacts on biological activity. Among of them, *R*-**3f** exhibited optimal cytotoxic activity against the U_2O_S cell line, which was close to the inhibitory activity of the positive control, Adriamycin. Therefore, spiro [4*H*-chromene-3,3′-oxindole] derivatives could be developed as antitumour candidate compounds after further research.

4. Materials and Methods

4.1. Chemistry

The ^{1}H NMR spectra were recorded on a 500 MHz for ^{1} H and at 125 MHz for ^{13} C NMR, using DMSO–d_6 as a solvent. The chemical shifts were reported in ppm, and the residual nondeuterated solvent (DMSO) as internal standard (2.5 and 39.52 ppm, respectively). The splitting patterns of the signals were reported as s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; and m, multiplet. High-resolution mass spectra (HRMS) were measured on a triple TOF 5600+ mass spectrometer equipped with an electrospray ionization (ESI) source in the negative-ion mode. The enantiomeric excess (ee) values of the products were determined by chiral HPLC, using Daicel Chiralpak AD columns (4.6 mm*250 mm). The reactions were monitored by thin layer chromatography (TLC). Purifications by column chromatography were conducted over silica gel (200–300 mesh). The organocatalysts **1a–1m** were purchased from Daicel chiral technologies (China) company, which almostly have purity of 98% and stereoselectivity of 99%.

4.2. General Procedure for the Enantioselective Knoevenagel/Michael/cyclization reaction of isatins, malononitrile and sesamol

To a tube, mixture of isatins (0.1 mmol), malononitrile (0.1 mmol), sesamol (0.1 mmol) and organocatalyst **1f** (0.01 mmol) in $CHCl_3$ (1.0 mL) was added 4 Å molecular sieves (30 mg). The resulting mixture was stirred at 0 °C for 24 hours. After the reaction was finished (monitored by TLC), the reaction directly poured into a column chromatography on silica gel with hexane/EtOAc (4:1) as eluent to afford the products **3a–p,** and **4-7**. Among of 20 products, there are 12 new compounds. The enantiomeric ratio was determined by HPLC analysis on a chiral ChiralPak AD column. Experimental data can be found in Supplementary Materials.

3a:whith solid, mp: 80.5-81.5 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.38 – 7.26 (m, 6H), 7.25 (d, *J* = 4.5 Hz, 2H), 7.14 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.07 (td, *J* = 7.5, 1.0 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.79 (s, 1H), 5.99 (dd, *J* = 13.5, 1.0 Hz, 2H), 5.82 (s, 1H), 5.01 (d, *J* = 16.0 Hz, 1H), 4.88 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 177.4, 161.5, 147.9, 144.5, 143.6, 142.3, 136.1, 133.6, 129.2, 128.6, 127.5, 127.2, 124.7, 123.5, 118.6, 112.1, 109.7, 104.4, 102.1, 98.2, 53.48, 50.3, 43.2. $[\alpha]_D^{25}$= +1 (c 0.50, MeOH)(61% ee); HPLC (Chiralpak AD, hexane:^{i}PrOH = 70:30, 1.0 mL/min, 254 nm), t_R= 10.7 min (major), 21.5 min (minor) .

3b: whith solid, mp: 235.5-236.6 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.43 – 7.35 (m, 2H), 7.35 – 7.25 (m, 6H), 7.05 (dd, *J* = 8.0, 0.5 Hz, 1H), 7.02 – 6.95 (m, 1H), 6.79 (s, 1H), 6.01 (dd, *J* = 3.5, 1.0 Hz, 2H), 6.00 (s, 1H), 5.08 (d, *J* = 16.0 Hz, 1H), 4.87 (d, *J* = 16.0 Hz, 1H);^{13}C NMR (126 MHz, DMSO-d_6) δ 176.5, 161.6, 147.9, 144.5, 144.0, 143.9, 135.6, 130.8, 130.2, 129.1, 128.5, 127.5, 127.1, 123.6, 118.2, 109.6, 108.7, 103.9, 102.0, 98.0, 51.5, 50.9, 43.5; HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{25}H_{16}ClN_3O_4Na$ 480.0727; found 480.0722; $[\alpha]_D^{25}$= -4 (c 0.61, MeOH)(65% ee); HPLC (Chiralpak AD, hexane:^{i}PrOH = 70:30, 1.0 mL/min, 254 nm), t_R= 15.3 min (major), 26.1 min (minor) .

3c: whith solid, mp: 263.7-264.6 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.38 (d, *J* = 7.0 Hz, 2H), 7.33 (t, *J* = 7.0 Hz, 2H), 7.30 – 7.25 (m, 3H), 7.25 – 7.18 (m, 2H), 7.02 (dd, *J* = 7.5, 1.0 Hz, 1H), 6.78 (s, 1H), 6.01 (s, 2H), 5.97 (s, 1H), 5.07 (d, *J* = 16.0 Hz, 1H), 4.87 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 176.7, 161.7, 148.0, 144.5, 144.2, 144.2, 135.7, 131.1, 130.6, 128.6, 127.6, 127.2, 126.8, 119.3, 118.4, 109.5, 109.3, 104.0, 102.1, 98.0, 52.0, 51.4, 43.4; HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{25}H_{16}BrN_3O_4Na$:

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524.0222; found: 524.0229; $[\alpha]_D^{25}$= -3 (c 0.55, MeOH)(50% ee); HPLC (Chiralpak AD, hexane:*i*PrOH = 70:30, 1.0 mL/min, 254 nm), t_R= 15.8 min (minor), 25.9 min (major) .

3d whith solid, mp: 192.7-193.3 °C ; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.46 – 7.22 (m, 7H), 7.13 (ddd, *J* = 10.5, 9.0, 2.5 Hz, 2H), 6.99 (dd, *J* = 8.5, 4.0 Hz, 1H), 6.80 (s, 1H), 6.00 (dd, *J* = 10.5, 1.0 Hz, 2H), 5.88 (s, 1H), 5.02 (d, *J* = 16.0 Hz, 1H), 4.87 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 177.4, 161.5, 160.1, 158.2, 148.0, 144.6, 143.6, 138.6, 135.9, 135.4, 135.3, 128.7, 127.6, 127.2, 118.6, 115.8, 115.6, 112.7, 112.5, 111.4, 110.9, 110.8, 104.4, 102.1, 98.3, 53.1, 50.7, 43.3; $[\alpha]_D^{25}$= +1 (c 0.58, MeOH)(60% ee); HPLC (Chiralpak AD, hexane:*i*PrOH = 70:30, 1.0 mL/min, 254 nm), t_R= 13.7 min (major), 23.8 min (minor) .

3e: whith solid, mp: 188.7-190.0 °C ; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.37-7.26 (m, 8H), 7.25 (d, *J* = 2.0 Hz, 1H), 7.01 (d, *J* = 8.5 Hz, 1H), 6.80 (s, 1H), 6.01 (dd, *J* = 13.5, 1.0 Hz, 2H), 5.91 (s, 1H), 5.04 (d, *J* = 16.0 Hz, 1H), 4.86 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 177.1, 161.4, 148.0, 144.6, 143.6, 141.2, 135.7, 135.6, 129.2, 128.6, 127.6, 127.1, 124.8, 118.5, 111.4, 111.1, 104.4, 102.1, 98.3, 52.9, 50.5, 43.3; HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{25}H_{16}ClN_3O_4Na$ 480.0727; found 480.0724; $[\alpha]_D^{25}$= -1 (c 0.52, MeOH)(50% ee); HPLC (Chiralpak AD, hexane:*i*PrOH = 70:30, 1.0 mL/min, 254 nm), t_R= 12.9 min (major), 21.1 min (minor) .

3f: whith solid, mp: 285.4-286.7 °C ;^{1}H NMR (500 MHz, DMSO-d_6) δ 7.48 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.40 – 7.22 (m, 8H), 6.95 (d, *J* = 8.5 Hz, 1H), 6.79 (s, 1H), 6.00 (d, *J* = 14.0 Hz, 2H), 5.91 (s, 1H), 5.03 (d, *J* = 16.0 Hz, 1H), 4.85 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 176.9, 161.3, 147.9, 144.5, 143.5, 141.6, 135.9, 135.6, 131.9, 128.5, 127.4, 127.3, 127.0, 118.3, 115.1, 111.7, 111.1, 104.3, 102.0, 98.2, 53.0, 50.4, 43.2; HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{25}H_{16}BrN_3O_4Na$: 524.0222; found : 524.0228; $[\alpha]_D^{25}$= -7 (c 0.65, MeOH)(90% ee); HPLC (Chiralpak AD, hexane:*i*PrOH = 70:30, 1.0 mL/min, 254 nm), t_R= 13.8 min (major), 22.8 min (minor).

3g: whith solid, mp: 130.4-131.2 °C ;^{1}H NMR (500 MHz, DMSO-d_6) δ 7.36 – 7.21 (m, 7H), 7.07 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.95 (s, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.78 (s, 1H), 5.98 (dd, *J* = 14.5, 1.0 Hz, 2H), 5.81 (s, 1H), 4.98 (d, *J* = 16.0 Hz, 1H), 4.84 (d, *J* = 16.0 Hz, 1H), 2.22 (s, 3H);^{13}C NMR (125 MHz, DMSO-d_6) δ 177.3, 161.4, 147.8, 144.5, 143.6, 139.9, 136.2, 133.8, 132.7, 129.5, 128.6, 127.5, 127.2, 125.1, 118.7, 112.2, 109.5, 104.5, 102.1, 98.2, 53.6, 50.3, 43.2, 20.5; $[\alpha]_D^{25}$= -5 (c 0.63, MeOH)(70% ee); HPLC (Chiralpak AD, hexane:*i*PrOH = 70:30, 1.0 mL/min, 254 nm), t_R= 13.7 min (major), 24.3 min (minor) .

3h: whith solid, mp: 191.8-192.5 °C ;^{1}H NMR (500 MHz, DMSO-d_6) δ 7.39 – 7.20 (m, 7H), 6.90 (d, *J* = 8.5 Hz, 1H), 6.85 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.78 (s, 1H), 6.74 (d, *J* = 2.5 Hz, 1H), 6.00 (dd, *J* = 9.0, 1.0 Hz, 2H), 5.82 (s, 1H), 4.97 (d, *J* = 16.0 Hz, 1H), 4.85 (d, *J* = 16.0 Hz, 1H), 3.67 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 177.1, 161.4, 156.2, 147.8, 144.5, 143.5, 136.1, 135.5, 134.8, 128.6, 127.4, 127.1, 118.6, 113.9, 112.0, 111.3, 110.3, 104.4, 102.0, 98.2, 55.5, 53.5, 50.7, 43.2; HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{26}H_{19}N_3O_5Na$ 476.1222; found 476.1227; $[\alpha]_D^{25}$= +1 (c 0.52, MeOH)(57% ee); HPLC (Chiralpak AD, hexane:*i*PrOH = 70:30, 1.0 mL/min, 254 nm), t_R= 19.5 min (major), 38.4 min (minor) .

3i: whith solid, mp: 148.7-150.1 °C ;^{1}H NMR (500 MHz, DMSO-d_6) δ 8.27 (dd, *J* = 8.5, 2.0 Hz, 1H), 8.01 (d, *J* = 2.0 Hz, 1H), 7.44 (s, 2H), 7.39 – 7.28 (m, 5H), 7.25 (d, *J* = 8.5 Hz, 1H), 6.83 (s, 1H), 6.06 (s, 1H), 6.00 (d, *J* = 13.5 Hz, 2H), 5.15 (d, *J* = 16.0 Hz, 1H), 4.95 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 177.8, 161.5, 148.3, 148.2, 144.6, 143.7, 143.6, 135.2, 134.5, 128.6, 127.6, 127.0, 126.3, 120.1, 118.2, 110.3, 110.2, 104.6, 102.1, 98.3, 52.5, 50.3, 43.6; HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{25}H_{16}N_4O_6Na$ 491.0968; found 491.0975; $[\alpha]_D^{25}$= -2 (c 0.59, MeOH)(10% ee); HPLC (Chiralpak AD, hexane:*i*PrOH = 70:30, 1.0 mL/min, 254 nm), t_R= 16.7 min (major), 34.6 min (minor) .

3j: whith solid, mp: 242.8-243.2 °C ;^{1}H NMR (500 MHz, DMSO-d_6) δ 7.41 – 7.25 (m, 7H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.11 (dt, *J* = 8.0, 1.5 Hz, 2H), 6.79 (s, 1H), 6.00 (dd, *J* = 10.0, 1.0 Hz, 2H), 5.92 (s, 1H), 5.03 (d, *J* = 16.0 Hz, 1H), 4.88 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 177.4, 148.0, 144.6, 143.9, 135.7, 132.3, 128.6, 127.6, 127.1, 126.2, 123.2, 111.4, 110.0, 104.5, 102.1, 98.2, 50.0, 43.2; HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{25}H_{16}ClN_3O_4Na$ 480.0727; found 480.0721; $[\alpha]_D^{25}$= +1 (c 0.60, MeOH)(55% ee); HPLC (Chiralpak AD, hexane:*i*PrOH = 70:30, 1.0 mL/min, 254 nm), t_R= 12.7 min (major), 17.9 min (minor) .

3k: whith solid, mp: 221.5-223.0 °C ;^{1}H NMR (500 MHz, DMSO-d_6) δ 7.37 – 7.24 (m, 8H), 7.16 (d, *J* = 7.0 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.80 (s, 1H), 6.13 (s, 1H), 6.01 (d, *J* = 6.0 Hz, 2H), 5.27 (s, 2H);^{13}C NMR (125 MHz, DMSO-d_6) δ 178.1, 161.4, 148.0, 144.7, 143.6, 138.5, 137.4, 136.8, 131.4, 128.5, 127.0,

126.0, 124.9, 124.1, 118.6, 114.7, 111.5, 104.9, 102.2, 98.2, 53.4, 50.5, 44.8; $[\alpha]_D^{25}$= +3 (c 0.48, MeOH)(55% ee); HPLC (Chiralpak AD, hexane:^{i}PrOH = 70:30, 0.8 mL/min, 254 nm), t_R= 17.5 min (major), 52.7 min (minor) .

3l: whith solid, mp: 256.5-257.3 ^{o}C ; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.48 (d, J = 8.0 Hz, 1H), 7.43 – 7.22 (m, 7H), 7.19 (d, J = 7.5 Hz, 1H), 7.04 (t, J = 7.5 Hz, 1H), 6.80 (s, 1H), 6.12 (s, 1H), 6.01 (d, J = 5.0 Hz, 2H), 5.37 (d, J = 17.0 Hz, 1H), 5.27 (d, J = 17.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 178.1, 161.3, 147.9, 144.6, 143.5, 139.8, 137.3, 137.0, 134.7, 128.3, 126.8, 125.9, 125.1, 124.5, 118.4, 111.5, 104.7, 102.0, 98.1, 53.5, 50.0, 44.4; HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{25}H_{16}BrN_3O_4Na$: 524.0222; found : 524.0226; $[\alpha]_D^{25}$= +1 (c 0.45, MeOH)(67% ee); HPLC (Chiralpak AD, hexane:^{i}PrOH = 80:20, 1.0 mL/min, 254 nm), t_R= 24.2 min (major), 87.6 min (minor) .

3m: whith solid, mp: 130.8-131.8 ^{o}C ; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.55 (s, 1H), 7.27 (td, J = 7.5, 1.5 Hz, 1H), 7.16 (s, 2H), 7.05 (d, J = 6.0 Hz, 1H), 7.01 (td, J = 7.5, 1.0 Hz, 1H), 6.93 (d, J = 7.5 Hz, 1H), 6.76 (s, 1H), 5.99 (dd, J = 7.5, 1.0 Hz, 2H), 5.88 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 178.4, 148.4, 146.6, 143.0, 139.4, 133.2, 128.6, 123.7, 121.1, 120.1, 109.0, 106.8, 100.7, 97.4, 75.1; $[\alpha]_D^{25}$= -2 (c 0.51, MeOH)(45% ee); HPLC (Chiralpak AD, hexane:^{i}PrOH = 70:30, 1.0 mL/min, 254 nm), t_R= 11.8 min (major), 15.7 min (minor) .

3n: whith solid, mp: 260.9-262.3 ^{o}C ;^{1}H NMR (500 MHz, DMSO) δ 7.38 (ddd, J = 8.0, 6.5, 2.5 Hz, 1H), 7.20 (s, 2H), 7.15 – 7.07 (m, 3H), 6.77 (s, 1H), 5.98 (dd, J = 4.5, 1.0 Hz, 2H), 5.91 (s, 1H), 3.19 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 177.1, 161.4, 147.7, 144.5, 143.6, 143.3, 133.6, 129.2, 124.4, 123.3, 118.5, 112.2, 109.1, 104.8, 102.0, 98.1, 53.6, 50.2, 26.4; $[\alpha]_D^{25}$= -2 (c 0.50, MeOH)(50% ee); HPLC (Chiralpak AS, hexane:^{i}PrOH = 90:10, 1.5 mL/min, 254 nm), t_R= 54.9 min (minor), 61.6 min (major) .

3o: whith solid, mp: 187.9-188.8 ^{o}C ;^{1}H NMR (500 MHz, DMSO-d_6) δ 10.70 (s, 1H), 7.46 (dd, J = 8.3, 2.1 Hz, 1H), 7.27 – 7.20 (m, 3H), 6.90 (d, J = 8.5 Hz, 1H), 6.76 (s, 1H), 6.00 (dd, J = 9.5, 1.0 Hz, 2H), 5.98 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 178.2, 161.2, 147.8, 144.5, 143.5, 141.1, 136.6, 131.9, 131.4, 128.5, 127.4, 118.3, 112.0, 111.4, 104.4, 101.9, 98.1, 53.3, 50.8; HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{18}H_{10}BrN_3O_4Na$: 433.9752; found: 433.9756; $[\alpha]_D^{25}$= -7 (c 0.62, MeOH)(72% ee); HPLC (Chiralpak AD, hexane:^{i}PrOH = 70:30, 1.0 mL/min, 254 nm), t_R= 9.6 min (major), 11.4 min (minor) .

3p: whith solid, mp: 260.7-261.2 ^{o}C ;^{1}H NMR (500 MHz, DMSO-d_6) δ 10.45 (s, 1H), 7.22 – 7.00 (m, 3H), 6.89-6.75 (m, 3H), 5.99 (d, J = 8.5 Hz, 2H), 5.88 (s, 1H), 2.23 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 178.8, 161.2, 147.7, 144.4, 143.5, 139.3, 134.6, 131.6, 129.4, 125.2, 118.6, 112.4, 109.8, 104.6, 102.0, 98.1, 53.9, 50.7, 20.6; $[\alpha]_D^{25}$= -5 (c 0.56, MeOH) (59% ee); HPLC (Chiralpak AD, hexane:^{i}PrOH = 70:30, 0.8 mL/min, 254 nm), t_R= 9.6 min (major), 11.4 min (minor) .

4: whith solid, mp: 191.5-192.8 ^{o}C ; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.41 – 7.25 (m, 7H), 7.23 (s, 2H), 7.13 (d, J = 7.0 Hz, 1H), 7.07 (t, J = 7.5 Hz, 2H), 6.71 (s, 1H), 5.73 (s, 1H), 4.96 (q, J = 15.5 Hz, 2H), 3.78 (s, 3H), 3.32 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 177.3, 161.5, 149.6, 145.9 142.9, 142.2, 136.2, 133.5, 129.1, 128.6, 128.5, 127.4, 127.2, 124.6, 123.4, 118.5, 110.8, 109.5, 108.3, 100.8, 55.8, 55.7, 53.7, 49.9, 43.0; HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{26}H_{20}N_3O_4Na$: 462.1430; found: 462.1437; $[\alpha]_D^{25}$= -5 (c 0.46, MeOH) (55% ee); HPLC (Chiralpak AD, hexane: ^{i}PrOH = 70:30, 1.0 mL/min, 254 nm), t_R= 17.3 min (major), 33.7 min (minor).

5: whith solid, mp: 288.3-288.5 ^{o}C ; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.41 – 7.25 (m, 7H), 7.23 (s, 2H), 7.13 (d, J = 7.0 Hz, 1H), 7.07 (t, J = 7.5 Hz, 2H), 6.71 (s, 1H), 5.73 (s, 1H), 4.96 (q, J = 15.5 Hz, 2H), 3.78 (s, 3H), 3.32 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 177.2, 160.5, 160.0, 157.4, 150.4, 142.4, 136.4, 134.7, 128.4, 128.0, 127.7, 127.3, 123.1, 122.6, 118.2, 108.6, 101.4, 95.6, 93.4, 56.0, 55.8, 55.6, 47.4, 43.4; HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{26}H_{20}N_3O_4Na$: 462.1430; found: 462.1438; $[\alpha]_D^{25}$= -4 (c 0.53, MeOH) (32% ee); HPLC (Chiralpak AS, hexane: ^{i}PrOH = 70:30, 1.0 mL/min, 254 nm), t_R= 11.0 min (major), 20.5 min (minor).

6: whith solid, mp: 247.5-248.8 ^{o}C ; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.30 (d, J = 8.5 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.73 – 7.68 (m, 1H), 7.66 – 7.62 (m, 1H), 7.60 – 7.52 (m, 3H), 7.39 (d, J = 7.5 Hz, 2H), 7.32 (ddd, J = 16.0, 12.0, 7.5 Hz, 4H), 7.18 (d, J = 7.0 Hz, 1H), 7.06 (dd, J = 14.0, 7.5 Hz, 2H), 6.48 (d, J = 8.5 Hz, 1H), 5.05 (d, J = 16.0 Hz, H), 4.95 (d, J = 16.0 Hz, H);^{13}C NMR (126 MHz, DMSO-d_6) δ 177.4, 161.2 143.7, 142.4, 136.0, 133.8, 133.1, 129.3, 128.6, 127.7, 127.5, 127.2, 125.0, 124.5, 123.6, 122.9, 120.8, 114.6, 109.7, 50.5, 43.2; HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{28}H_{19}N_3O_2Na$: 452.1375; found: 452.1371; $[\alpha]_D^{25}$=

-1 (c 0.49, MeOH) (20% ee); HPLC (Chiralpak AS, hexane: ^{i}PrOH = 70:30, 0.8 mL/min, 254 nm), t_R= 13.1 min (minor), 18.0 min (major).

7: whith solid, mp: 292.2-292.5 ^{o}C ; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.39 (s, 1H), 7.45 – 7.40 (m, 1H), 7.37 (d, *J* = 7.0 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.27 (ddd, *J* = 9.0, 6.5, 1.5 Hz, 4H), 7.11 (d, *J* = 6.5 Hz, 1H), 7.04 (t, *J* = 7.5 Hz, 2H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.51 (t, *J* = 2.0 Hz, 1H), 6.08 (d, *J* = 8.5 Hz, 1H), 4.96 (dd, *J* = 35.4, 16.0 Hz, 2H);^{13}C NMR (125 MHz, DMSO-d_6) δ 178.1, 161.6, 142.3, 141.5, 136.7, 136.2, 134.8, 128.9, 128.6, 127.5, 127.2, 126.2, 124.8, 123.4, 119.0, 118.7, 116.6, 109.5, 109.0, 108.7, 97.6, 54.3, 50.2, 43.0; $[\alpha]_D^{25}$= -1 (c 0.55, MeOH) (56% ee); HPLC (Chiralpak IA, hexane: ^{i}PrOH = 70:30, 1.5 mL/min, 254 nm), t_R= 8.0 min (minor), 15.2 min (major).

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org, Copies of ^{1}H and ^{13}C-NMR spectra and HPLC trace of products are available online at www.mdpi.com/xxx/s1. **Figure *S*1-*S*40**: NMR spectra of compounds **3a-3p** and **4-7; Figure S41-80**: HPLC trace of compounds **3a-3p** and **4-7.**

Author Contributions: Liming Wang and Hongwen Mu are co-first authors; they contributed equally to this work. They performed the experiments, acquired and analyzed the original data. Yuhong Sun conducted instrumental analysis. Y. Jin supervised the experiment, analyzed and checked all the data, wrote the draft and revised manuscript. Wei Zhang designed the research plan, provided funding supporting. All authors have given approval to the final version of the manuscript.

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References

1. Xiao, Z.-P.; Peng, Z.-Y.; Dong, J.-J.; He, J.; Ouyang, H.; Feng, Y.-T.; Lu, C.-L.; Lin, W.-Q.; Wang, J.-X.; Xiang, Y.-P.; Zhu, H.-L. Synthesis, Structure−Activity Relationship Analysis and Kinetics Study of Reductive Derivatives of Flavonoids as Helicobacter Pylori Urease Inhibitors. *Eur. J. Med. Chem.* **2013**, *63*, 685-695. doi.org/10.1016/j.ejmech.2013.03.016
2. Yee, E. M. H.; Pasquier, E.; Iskander, G.; Wood, K.; Black, D. S.; Kumar, N. Synthesis of Novel Isoflavene-Propranolol Hybrids as Anti-Tumor Agents. *Bioorg. Med. Chem.* **2013**, *21*, 1652-1660. doi.org/10.1016/j.bmc.2013.01.059
3. Eiffe, E.; Pasquier, E.; Kavallaris, M.; Herbert, C.; Black, D. S.; Kumar, N. Synthesis, Anticancer and Anti-Inflammatory Activity of Novel 2-Substituted Isoflavenes. *Bioorg. Med. Chem*. **2014**, 22, 5182- 5193. doi.org/10.1016/j.bmc.2014.08.010
4. Chen, Y.; Cass, S. L.; Kutty, S. K.; Yee, E. M. H.; Chan, D. S. H.; Gardner, C. R.; Vittorio, O.; Pasquier, E.; Black, D. S.; Kumar, N. Synthesis, Biological Evaluation and Structure−Activity Relationship Studies of Isoflavene Based Mannich Bases with Potent Anti-Cancer Activity. *Bioorg. Med. Chem. Lett*. **2015**, *25*, 5377-5383. doi.org/10.1016/j.bmcl.2015.09.027
5. Renko, D.; Provot, O.; Rasolofonjatovo, E.; Bignon, J.; Rodrigo, J.; Dubois, J.; Brion, J. D.; Hamze, A.; Alami, M. Rapid Synthesis of 4- Arylchromenes from Ortho-Substituted Alkynols: A Versatile Access to Restricted Isocombretastatin A-4 Analogues as Antitumor Agents. *Eur. J. Med. Chem.* **2015**, *90*, 834-844. doi.org/10.1016/j.ejmech.2014.12.024
6. Yee, E. M. H.; Brandl, M. B.; Black, D. S.; Vittorio, O.; Kumar, N. Synthesis of Isoflavene- Thiosemicarbazone Hybrids and Evaluation of Their Anti-Tumor Activity. *Bioorg. Med. Chem. Lett*. **2017**, *27*, 2454-2458. doi.org/10.1016/j.bmcl.2017.04.002
7. Malik, N.; Zhang, Z.; Erhardt, P. Total Synthesis of (±)-Glyceollin II and a Dihydro Derivative. *J. Nat. Prod.* **2015**, *78*, 2940-2947. doi.org/10.1021/acs.jnatprod.5b00607
8. Muharini, R.; Díaz, A.; Ebrahim, W.; Mandi, A.; Kurtan, T.; Rehberg, N.; Kalscheuer, R.; Hartmann, R.; Orfali, R. S.; Lin, W.; Liu, Z.; Proksch, P. Antibacterial and Cytotoxic Phenolic Metabolites from the Fruits of Amorpha Ruticosa. *J. Nat. Prod.* **2017**, *80*, 169-180. doi.org/10.1021/acs.jnatprod.6b00809
9. Rueda-Zubiaurre, A.; Yahiya, S.; Fischer, O. J.; Hu, X.; Saunders, C. N.; Sharma, S.; Straschil, U.; Shen, J.; Tate, E. W.; Delves, M. J.; Baum, J.; Barnard, A.; Fuchter, M. J. Structure−Activity Relationship Studies of a Novel Class of Transmission Blocking Antimalarials Targeting Male Gametes. *J. Med. Chem.* **2020**, *63*, 2240-2262. doi.org/10.1021/acs.jmedchem.9b00898
10. Chen, M,-S.; Yu, S.-J. Characterization of Lipophilized Monomeric and Oligomeric Grape Seed Flavan-3-ol Derivatives. *J. Agric. Food. Chem.* **2017**, 65, 8875-8883. doi.org/10.1021/acs.jafc.7b03530

11. Hu, B.; Liu, X.; Zhang, C.; Zeng, X. Food Macromolecule Based Nanodelivery Systems for Enhancing the Bioavailability of Polyphenols. *J. Food. Drug. Anal.* **2017**, *25*, 3-15. doi.org/10.1016/j.jfda.2016.11.004
12. Cheenpracha, S.; Karalai, C.; Ponglimanont, C.; Kanjana-Opas, A. Candenatenins, A. Phenolic Compounds from the Heartwood of Dalbergia Candenatensis. *J. Nat. Prod.* **2009**, *72*, 1395-1398. doi.org/10.1021/np900077h
13. Singh, G. S.; Desta, Z. Y. Isatins as Privileged Molecules in Design and Synthesis of Spiro Fused Cyclic Frameworks. *Chem. Rev.* **2012**, *112*, 6104–6155. doi.org/10.1021/cr300135y.
14. Williams, R. M.; Cox, R. J. Paraherquamides, Brevianamides, and Asperparalines:Laboratory Synthesis and Biosynthesis. An Interim Report. *Acc. Chem. Res.* **2003**, *36*, 127–139. doi.org/10.1021/ar020229e.
15. Yang, Y.-T.; Zhu, J.-F.; Liao, G.; Xu, H.-J.; Yu, B. The Development of Biologically Important Spirooxindoles as New Antimicrobial Agents. *Curr. Med. Chem*. **2018**, *25*, 2233–2244. doi.org/10.2174/0929867325666171129131311.
16. Panda, S. S.; Jones, R. A.; Bachawala, P.; Mohapatra, P. P. Spirooxindoles as Potential Pharmacophores. *Mini. Rev. Med. Chem.* **2017**, *17*, 1515–1536. doi.org/10.2174/ 1389557516666160624125108.
17. Chen, W.-B.; Wu, Z.-J.; Pei, Q.-L.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. Highly Enantioselective Construction Of Spiro, [4H-Pyran-3.30 -Oxindoles] Through a Domino Knoevenagel/Michael/Cyclization Sequence Catalyzed by Cupreine. *Org. Lett*. **2010**, *12*, 3132–3135. DOI: 10.1021/ol1009224.
18. Pellissier, H.; Recent Developments in Asymmetric Organocatalytic Domino Reactions. Recent Developments in Asymmetric Organocatalytic Domino Reactions. *Adv. Synth. Catal*. **2012**, *354*, 237–294. doi.org/10.1002/adsc.201100714.
19. Cheng, D.; Ishihara, Y.; Tan, B.; Barbas, C. F. Organocatalytic Asymmetric Assembly Reactions: Synthesis of Spirooxindoles via Organocascade Strategies. *ACS Catal*. **2014**, *4*, 743–762. doi.org/10.1021/cs401172r.
20. Santos, M. M. M. Recent Advances in the Synthesis of Biologically Active Spirooxindoles. *Tetrahedron* **2014**, *70*, 9735–9757. doi.org/10.1016/j.tet.2014.08.005.
21. Chauhan, P.; Mahajan, S.; Kaya, U.; Hack, D.; Enders, D. Bifunctional AmineSquaramides: Powerful Hydrogen-Bonding Organocatalysts for Asymmetric Domino/Cascade Reactions. *Adv. Synth. Catal.* **2015**, *357*, 253–281. doi.org/10.1002/adsc.201401003.
22. Ardkhean, R.; Caputo, D. F. J.; Morrow, S. M.; Shi, H.; Xiong, Y.; Anderson, E. A. Cascade Polycyclizations in Natural Product Synthesis. *Chem. Soc. Rev.* **2016**, *45*, 1557–1569. doi.org/ 10.1039/C5CS00105F.
23. Mei, G.-J.; Shi, F. Catalytic Asymmetric Synthesis of Spirooxindoles: Recent Developments. *Chem. Commun.* **2018**, *54*, 6607–6621. doi.org/10.1039/C8CC02364F.
24. Chanda, T.; Zhao, J. C.-G. Recent Progress in Organocatalytic Asymmetric Domino Transformations. *Adv. Synth. Catal.* **2018**, *360*, 2–79. doi.org/10.1002/adsc.201701059.
25. Mohammadi Ziarani, G.; Moradi, R.; Lashgari, N. Asymmetric Synthesis of Chiral Oxindoles Using Isatin as Starting Material. *Tetrahedron* **2018**, *74*, 1323–1353. doi.org/10. 1016/j.tet.2018.01.025.
26. Konda, S.; Jakkampudi,S.; Arman, H. D.; Zhao, J.C.-G. Enantioselective Synthesis of Spiro[4H- pyran-3,3-oxindole] Derivatives Catalyzed by Cinchona Alkaloid Thioureas: Significant Water Effects on the Enantioselectivity. *Synthetic Commun*. **2019**, *49*, 2971-2982. doi.org/10.1080/00397911.2019. 1651866
27. Tan, F.; Lu, L.-Q.; Yang, Q.-Q.; Guo, W.; Bian, Q.; Chen, J.-R.; Xiao, W.-J. Enantioselective Cascade Michael Addition/ Cyclization Reactions of 3-Nitro-2H-Chromenes with 3-Isothiocyanato Oxindoles: Efficient Synthesis of Functionalized Polycyclic Spirooxindoles. *Chem. Eur. J.* **2014**, *20*, 3415–3420. doi.org/10.1002/chem.201303583
28. Jiang, X.; Sun, Y.; Yao, J.; Cao, Y.; Kai, M.; He, N.; Zhang, X.; Wang Y.; Wang, R. Core Scaffold-Inspired Concise Synthesis of Chiral Spirooxindole-Pyranopyrimidines with Broad- Spectrum Anticancer Potency. *Adv. Synth. Catal*. **2012**, *354*, 917–925. doi.org/10.1002/adsc.201100792
29. Zhao, H.-W.; Li, B.; Tian, T.; Meng, W.; Yang, Z.; Song, X.-Q.; Chen X.-Q.; Pang, H.-L. Highly Enantioselective Synthesis of Chiral Pyranonaphthoquinone-Fused Spirooxindoles through Organocatalytic Three-Component Cascade Reactions. *Eur. J. Org. Chem.* **2015**, 2015, 3320–3326. doi.org/10.1002/ejoc.201500152
30. Kumari, P.; Nandi, S.; Kumar, G.; Khan,N. H.; Kureshy,R. I.; Abdi, S. H. R.; Eringathodi, S.; Bajaj, H. C. Construction of Highly Enantioselective Spiro-oxindole Derivatives with Fused Chromene via Organocascade Catalysis. *RSC Adv*. **2016**, *6*, 52384-52390. doi.org/10.1039/C6RA06812J.
31. Yang, C.; Yang, J.; Guo F. -M.; Zhao, Z.; Feng, T.-T.; Liu X. -L.; Zhou Y. Synthesis of Novel Spiro-Fused Pyranyl Benzo[*d*] [1,3]dioxol Oxindoles. *Chin. J. Synth. Chem.* **2015**, *23*, 599-602. doi.org/10.15952 /j.cnki.cjsc.10051511.2015.07.0599
32. Abdolmohammadi, S.; Rasouli Nasrabadi, S. R.; Dabiri, M. R.; Banihashemi Jozdani, S. M. TiO2 Nanoparticles Immobilized on Carbon Nanotubes: An Efficient Heterogeneous Catalyst in Cyclocondensation Reaction of Isatins with Malononitrile and 4-Hydroxycoumarin or 3, 4-Methylenedioxyphenol under Mild Reaction Conditions. *Appl Organometal Chem.* **2020**, e5462. doi.org/10.1002/aoc.5462

33. CCDC-2291478 (**3f**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif
34. Prathima, P. S.; Rajesh, P.; Rao, J. V.; Kailash, U. S.; Sridhar, B.; Rao, M. M. "On Water" Expedient Synthesis of 3-Indolyl- 3- Hydroxy Oxindole Derivatives and Their Anticancer Activity in Vitro. *Eur. J. Med. Chem*. **2014**, *84*, 155-159. doi.org/10.1016/j.ejmech.2014.07.004
35. Huong, T. T. L.; Dung,D.T. M.; Huan,N. V.; Cuong, L. V.; Hai, P. T.; Huong, L.T. T.; Kim, J.; Kim, Y. G.; Han,S. B.; Nam, N. H. Novel *N*-Hydroxybenzamides Incorporating 2-Oxoindoline with Unexpected Potent Histone Deacetylase Inhibitory Effects and Antitumor Cytotoxicity. *Bioorg. Chem*. **2017**, *71*, 160- 169. doi.org/10.1016/j.bioorg.2017.02.002
36. Kumar, S.; Saha, S. T.; Gu, L.; Palma, G.; Perumal, S.; Singh-Pillay, A.; Singh, P.; Anand, A.; Kaur, M.; Kumar, V 1H-1,2,3-Triazoletethered Nitroimidazole-Isatin Conjugates: Synthesis, Docking, and Anti-Proliferative Evaluation against Breast Cancer. *ACS Omega*, **2018**, *3*, 12106-12113. doi.org/10.1021/acsomega.8b01513
37. 37. Kumar, M. R.; Alagumuthu, M.; Dhayabaran, V. V. *N*-Substituted Hydroxynaphthalene Imino-oxindole Derivatives as New Class of PI3-Kinase Inhibitor and Breast Cancer Drug: Molecular Validation and Structure-Activity Relationship Studies. *Chem. Biol. Drug Des*. **2018**, 91, 277 -284. doi.org/10.1111/cbdd.13079
38. Diao, Q. -P.; Guo, H.; Wang, G. -Q. Design, Synthesis, and in Vitro Anticancer Activities of Diethylene Glycoltethered Isatin -1,2,3-Triazole-Coumarin Hybrids. *J Heterocycl Chem.* **2019**, *56*, 1667 -1671. doi.org/10.1002/jhet.3538
39. Shirai, F.; Mizutani, A.; Yashiroda, Y.; Tsumura, T.; Kano, Y.; Muramatsu, Y.; Chikada, T.; Yuki, H.; Niwa, H.; Sato, S.; Washizuka, K.; Koda, Y.; Mazaki, Y.; Jang, M. K.; Yoshida, H.; Nagamori, A.; Okue, M.; Watanabe, T.; Kitamura, K.; Shitara, E.; Honma, T.; Umehara,T.; Shirouzu, M.; Fukami, T.; Seimiya, H.; Yoshida, M.; Koyama, H. Design and Discovery of an Orally Efficacious Spiroindolinone-Based Tankyrase Inhibitor for the Treatment of Colon Cancer. *J. Med. Chem.* **2020**, *63*, 4183 -4204. doi.org/10.1021/acs.jmedchem.0c00045