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DBU-Mediated Diastereoselective [3+2]-Cycloaddition of Isatin Ketonitrones and Coumarins to Construct Coumarin-Fused Spiropyrolidine Oxoindoles

Qing Yan [1,2,†], Lan Ma [1,†], Qian Zhong [1], Zixin Zhang [1], Ruyi Zhou [1], Chunyan Long [3], Wanbing Wu [3], Sicheng Li [1,4], Qiao He [1,5] and Guizhou Yue [1,*]

[1] College of Science, Sichuan Agricultural University, Ya'an, Sichuan, 625014, China
[2] Sichuan Tongsheng Biopharmaceutical Co., Ltd., Deyang, Sichuan, 618029, China
[3] Sichuan Jisheng Biopharmaceutical Co., Ltd., Leshan, Sichuan, 614000, China
[4] The Yingjing County Emergency Management Agency, Ya'an, Sichuan, 625200, China
[5] Agriculture and Rural Bureau of Daying Country, Suining, Sichuan, 629300, China
* Correspondence: yueguizhou@sicau.edu.cn
† These three authors contributed equally to this work and are joint first authors.

Abstract

The synthesis of novel dicyclic spiropyrrolidine oxoindole derivatives was reported, using [3+2]-cycloaddition of isatin ketonitrone 1,3-dipoles, generated from the condensation of various substituted isatins and arylhydroxylamines, with coumarins. The pentacyclic products bearing four consecutive stereocenters, including two quaternary carbon stereocenters fused in one ring structure, were smoothly acquired in moderate to high yields (22-98%) with high regio- (*α* and *exo* type) and diastereoselectivities (>20:1 *dr*). The synthesized compounds (>45 examples) were well characterized through different spectroscopic techniques, such as single crystal XRD, FTIR, NMR, and mass spectral analysis.

Keywords: cycloaddition; ketonitrone; coumarin; spirooindole

1. Introduction

Coumarins, a class of naturally occurring benzopyrone derivatives, are widely present in medicinal plants and isolated from 1820 [1–8]. Many of these compounds have demonstrated significantly high biological activities (anticancer, anti-HIV, antibacterial, anti-pathogen, anticoagulant and antispasmodic activities…) [9–25]. For examples, a famous compound warfarin (**II**), originated from dicoumarol (**I**) (Figure 1), exhibited an anticoagulant activity, and was subsequently used as a rodenticide and a drug for prevention of cerebral thrombosis [26,27]. Compounds **III-V** also displayed considerable chemotherapeutic efficacy against mammary cancer induced by polycyclic aromatic hydrocarbons, important soybean lipoxygenase (LOX) inhibitory activity, and significant anticancer activity against both bladder cancer and glioma, respectively [28–31]. In addition, versatile coumarin skeletons by facile chemical modification were served as key components in organic optical devices [32–35]. The chemical syntheses of coumarins have been well developed by various methods, including common condensations/lactonizations, transition-metal-catalyzed reactions, and photoinduced organocatalytic methods [36–44]. Meanwhile, as a kind of important synthons, coumarins could take part in various chemical reactions, which offered structurally more complex derivatives of coumarin [45–71]. Spirooxindoles, on the other hand, are a class of tricyclic organic molecules featuring multiple contiguous quaternary or tertiary stereocenters, commonly found in natural products and bioactive compounds [72–95]. Their unique structures and remarkable biological activities make them highly promising in the field of medicine, positioning them as one of the most potential drug candidates. For instance, the two compounds **VI** and **VII** inhibited an advanced glycation end (AGE) product formation activity (IC_{50}=11.37 nm) [96], and the α-amylase and α-glucosidase enzyme inhibitory activity (IC_{50}=0.28 and 0.31 mg mL^{-1}) [97], respectively. Furthermore, the tetrahydroisoquinolinyl oxindole **VIII** showed a highly effective and selective histone lysine-specific demethylase 1 (LDS1) inhibitory activity (IC_{50}= 42 nm) [98]. The spiropyrrolothiazolyl oxindole **IX** was discovered to exhibit in vitro activity against MCF-7 and K562-leukemia cancer cells, with IC_{50} values of 15.32 and 14.74 μM, respectively [99].

Among many spirooxindoles, sipropyrolidine ones are the most common type of compound, and possess the diverse and important biological activities, which have attracted widespread attention and considerable interest from organic chemists all over the world [100–125]. In the various synthetic approaches of spiropyrrolidine oxindoles, 1,3-dipolar cycloaddition of isatin-derived dipoles (azomethine ylide, azomethine imine and nitrone *etc*.) with dipolarophiles has been shown to be the most practical and simplest method for constructing pyrrolidine ring [126–179]. As a versatile synthon, nitrone was widely used in various organic reactions for constructing complex molecules [180–211]. Recently, we have developed a rapidly [3+2]-cycloaddition of isatin ketonitrone 1,3-dipoles with chalcones to afford novel dicyclic spiropyrrolidine oxindole derivatives in 18-98% yields and >20:1 *dr* values under *t*-BuOK (Scheme 1) [212]. Meanwhile, Michael adducts were obtained under DBU, with 18-83% yields and 1:1->20:1 *dr* values. As an extension of our work on 1,3-dipolar cycloaddition of isatin [126–179ketonitrones, we attempted to treat isatin ketonitrone **1a** using coumarin **2a** as a partner in the presence of base, which expected to give pentacyclic spiropyrolidine oxoindoles.

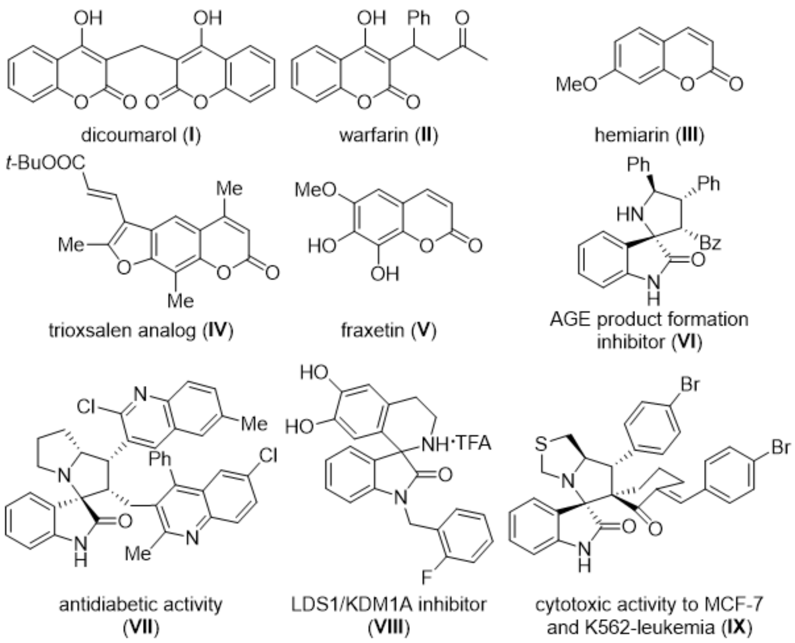
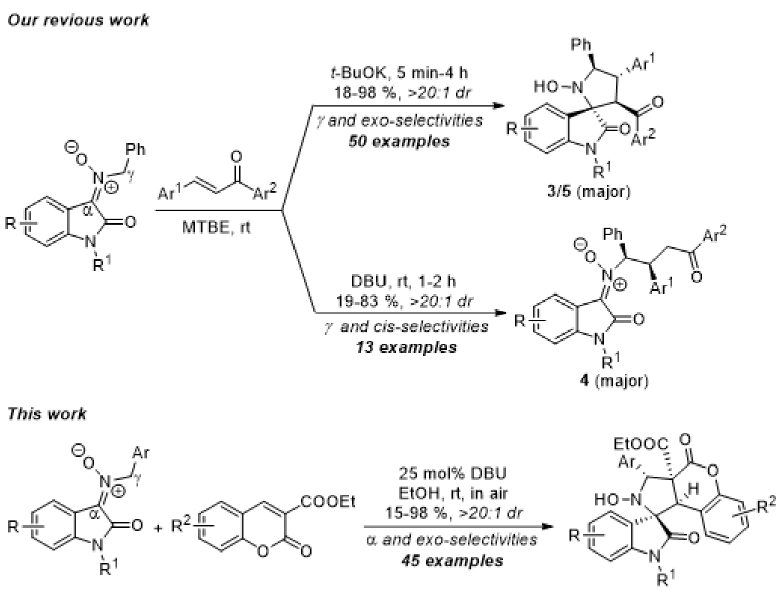


Figure 1. Representatives of natural and artificial coumarin and spirooxindole derivatives **(I-IX).**

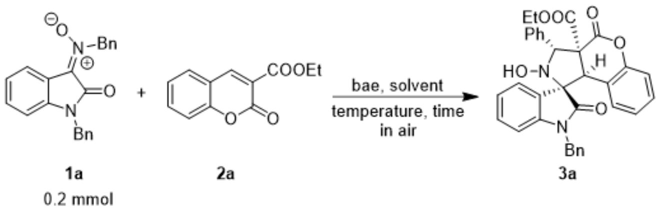


Scheme 1. [3+2]-Cycloaddition and Michael addition of isatin ketonitrones with dipolarophiles.

2. Results and Discussion

Prior to starting this research, *N*-Bn isatin ketonitrone **1a** and ethyl coumarin 3-carboxylate **2a** were selected as model substrates, as illustrated in Table 1. Initially, the reaction was performed in the presence of DBU (25 mol%) in some protic and aprotic solvents, such as H_2O, EtOH, MTBE, DMF, THF and DCM. The result demonstrated that above all aprotic solvents could not afford the desired cycloadduct **3a** at rt or under heating condition (entries 1-2). Fortunately, however, the protic polar solvent EtOH gave 70% yield of the desired product **3a** (entry 4). The ^{1}H NMR spectrum for **3a** showed that the shifts of two proton in pyrrolidine ring were 6.39 (singlet peak) and 4.70 (singlet peak) ppm, respectively, which could confirm *α*-C of isatin ketonitrone **1a** nucleophilically attacked the electrophilic site of the electron-efficient C=C bond in coumarin **2a**, to obtain *α*-selective cycloadduct. Furthermore, the stereochemistry (*exo*-configuration) of cycloadduct **3a** were indirectly proved by the single crystal X-ray diffraction of compound **3b** (Figure 3). Subsequently, various alcohols, for instance MeOH, IPA, *n*BuOH and *t*BuOH were screened for improving the yield of the reaction. Regrettably, the above all alcohols afford lower yields than one of ethanol. Next, other organic and inorganic bases were screened using ethanol as a solvent. The inorganic bases (for instance *t*BuOK, KOH, NaOH and $NaHCO_3$) did not work at all at rt and gave the complex results at heating or refluxing conditions. Although both EtONa and MeONa could smoothly proceed, the conversion rates of **1a** were too low. In organic bases, such as DMAP, DABCO and Ph_3P, the reactions were also discovered to be not take place, while in other secondary and tertiary amines (Et_2NH, Bn_2NH, TEA, Bn_3N, *n*Pr_3N, DIPEA, tri-*n*-amylamine and tri-*n*-octylamine), the conversion rates of **1a** were equally low, even if the reaction temperature was increased. Changing the amount of coumarin **2a** (2.1 equiv.), the yield was almost the same compared to 1.0 equivalent of **2a**. Finally, the amount of DBU and the concentration of the reaction were investigated. The higher concentration (0.2 M) could slightly increase the yield (74%). Considering the above factors, the optimal reaction condition for 1,3-dipolar cycloaddition was established as isatin ketonitrone **1a** (1 equiv.), maleimide **2a** (1.05 equiv.) and base DBU (0.25 equiv.) in EtOH at rt for 5 h (entry 14).

Table 1. The condition optimization of model reaction [a].



Entry	Reaction Condition	Yield (%)[b,c]
1	DBU, **2a**, DCM, 24 h	-[d]
2	DBU, **2a**, DMF, 24 h	complex
3	DBU, **2a**, MeOH, 4 h	58
4	DBU, **2a**, EtOH, 5 h	70
5	DBU, **2a**, IPA, 11 h	60
6	DBU, **2a**, *n*BuOH, 9 h	63
7	DBU, **2a**, *t*BuOH, 4 h	54
8	DABCO, **2a**, EtOH, 4 h	20[e]
9	DMAP, **2a**, EtOH, 8 h	24[e]
10	DBU, **2a**, dry EtOH, 6 h	62
11	DBU, 2.1 eq **2a**, EtOH, 14 h	71
12	50 mol% DBU, **2a**, EtOH, 2.5 h	51
13	100 mol% DBU, **2a**, EtOH, 2.5 h	36
14	**DBU, 2a, 1.0 mL, EtOH, 5 h**	**74**
15	DBU, **2a**, 4.0 mL, EtOH, 9 h	69

[a]Unless otherwise indicated, the reaction was performed at the 0.2 mmol scale in a solvent (2 mL) with base (25 mol%) at rt, and the molar ratio of **1a**:**2a** was 1:1.05. [b]Isolated yield. [c]The selectivity (*dr*>20:1 in all cases) was determined by ^{1}H NMR. [d]NR: no reaction. [e]The reaction was performed at reflux.

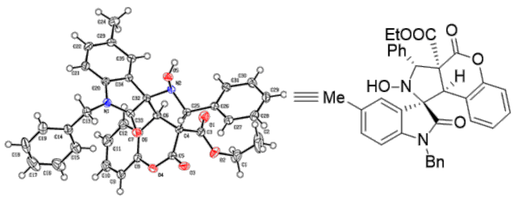
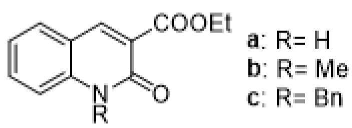


Figure 2. X-ray crystal structure of **3b** (CCDC: 2375731).



5

Figure 3. Other unsuccessful like-coumarins **5**.

After the optimal reaction conditions established, a wide range of different substituted isatin ketonitrones were explored for this 1,3-dipolar cycloaddition. As outlined in the Table 2, various substituent groups installed on isatin ketonitrones could be tolerated, which furnished the desired cycloadducts in 38-98% yields with >20:1 *dr* values, except for the cases of **3h-i**, **3o** and **3v**. It was worth noting that the cycloaddition for the synthesis of **3a** was scale up to 0.5 mmol or 5 mmol, which gave rise to the same yield. The substituent patterns on the benzene ring of isatin part of compounds **1** had a significant impact on the yields. All in all, the yields of the electron-donating groups were relative higher than that of the electron-withdrawing ones. For example, 5-methyl group installed on

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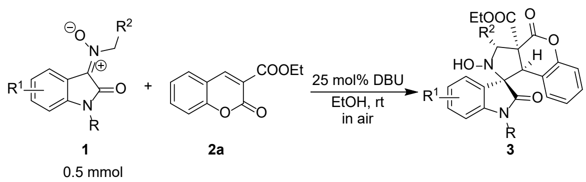
the benzene ring afforded the highest yield (98%) (entry 2), whereas, the strong electron-withdrawing groups (5-NO_2 and 7-CF_3) gave a complex mixture (entries 8 and 9). Changing the substituent groups (R= H, Me, Et, allyl and propargyl) on the nitrogen atom of isatin part of ketonitrones **1**, the corresponding cycloadducts were also rendered consistently in satisfactorily yields (59-85%). Subsequently, when R^2 group (R^2= Ph) was replaced by various substituent phenyl gourps, the products **3p-u** were generated smoothly with moderate to good yields as a single isomer. However, only a trace amount of **3o** was found when R^2 was a hydrogen atom possibly due to ketonitrone's difficulty to form the active intermediate C-N-C type 1,3-dipole in the presence of DBU, even EtONa (entry 15). The similar result was also discovered in the case of **3v** (entry 22). Next, in view of **3b** obtained in the highest yield, these reactions were investigated using substituent phenyl instead of phenyl at the site of R^2, when R^1 was 5-methyl group. The results demonstrated that their yields were analogous to these of **3p-u** (entries 23-29). Finally, the substrate bearing benzyl at nitrogen atom and aryl groups at the site of R^2 were also underwent the 1,3-dipolar cycloaddition, which afforded commonly the inferior outcomes to the above examples, in especial **3ad** and **3ae**. From the above results, the yields were seemingly irrelevant to the electronic effects of substituents at the site of R^2. However, when the steric bias existed on the substrate, the yield dynamically dropped off (entry 26).

Table 2. Synthesis of coumarin-fused spiropyrrolidine oxindoles **3** from isatin ketonitrones **1** and coumarins **2a** [a].



Entry	Compound	R	R^1	R^2	Yield (%)[b]
1	**3a**	Bn	H	Ph	74 (74)[c]
2	**3b**	Bn	5-Me	Ph	98
3	**3c**	Bn	5-OMe	Ph	82
4	**3d**	Bn	5-F	Ph	82
5	**3e**	Bn	5-Cl	Ph	74
6	**3f**	Bn	6-Br	Ph	58
7	**3g**	Bn	5-I	Ph	51
8	**3h**	Bn	5-NO_2	Ph	-[d]
9	**3i**	Bn	7-CF_3	Ph	-[d]
10	**3j**	H	H	Ph	76
11	**3k**	Me	H	Ph	80
12	**3l**	Et	H	Ph	78
13	**3m**	allyl	H	Ph	85
14	**3n**	propargyl	H	Ph	59
15	**3o**	H	H	H	-[e]
16	**3p**	H	H	4-MeC_6H_4	66
17	**3q**	H	H	4-$OMeC_6H_4$	54
18	**3r**	H	H	4-FC_6H_4	78
19	**3s**	H	H	4-ClC_6H_4	86
20	**3t**	H	H	4-BrC_6H_4	82
21	**3u**	H	H	4-$NO_2C_6H_4$	47
22	**3v**	Bn	5-Me	H	-[d]
23	**3w**	Bn	5-Me	4-MeC_6H_4	77
24	**3x**	Bn	5-Me	4-$OMeC_6H_4$	50
25	**3y**	Bn	5-Me	4-FC_6H_4	69

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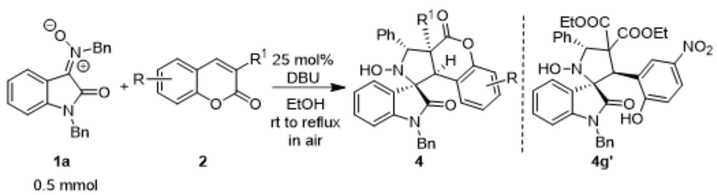
26	**3z**	Bn	5-Me	2-ClC6H4	48
27	**3aa**	Bn	5-Me	4-ClC6H4	85
28	**3ab**	Bn	5-Me	4-BrC6H4	66
29	**3ac**	Bn	5-Me	4-NO2C6H4	52
30	**3ad**	Bn	H	4-MeC6H4	46
31	**3ae**	Bn	H	4-OMeC6H4	38
32	**3af**	Bn	H	4-FC6H4	63[f]
33	**3ag**	Bn	H	4-ClC6H4	76
34	**3ah**	Bn	H	4-BrC6H4	68
35	**3ai**	Bn	H	4-NO2C6H4	60

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.525 mmol) and DBU (0.125 mmol), EtOH (2.5 mL), rt, 5-24h. [b]Isolated yield via column chromatography. [c]The reaction was scaled up to 5 mmol and the product **3a** was obtained with a quantity of 2.08g. [d]The reaction gave a complex. [e]Only a trace amount of the product was obtained. [f]The reaction was performed in *t*BuOH.

In order to further explore the generality of the cycloaddition reaction, various substituted coumarins were studied. All results were illuminated in Table 3. Firstly, coumarins bearing various groups on benzene ring were employed to react with **1a**, which showed that the electron effect and site of substituent played a critical impact on yields and diastereoselectivities of the reaction. For example, 8-ethoxyl coumarin could smoothly undergo the cycloaddition and obtain the yield of 86% with >20:1 *dr*, whereas, 7-methoxyl coumarin only gave the yield of 22%. Furthermore, when 7-methoxyl group was replaced by 7-diethylamino group, this reaction gave rise to a complex mixture. All coumarin bearing electron-withdrawing or electron-deficient group at 6-position afforded the desired products with yields of 67-82%. However, 6,8-dibromocoumarin only gave 30% yield, which was similar for the reaction result of 7-methoxylcoumarin. It was worth noting that 6-nitrocoumarin **2h** was subjected to the cycloaddition with **1a** in EtOH, and then the lactone ring of the cycloadduct was opened to yield the compound **4g'** with 24% yield. After many experiments, the reaction **2h** with **1a** was carried out in non-nucleophilic solvent *t*-BuOH, leading to the desired product **4g** with good yield. Next, other coumarin 3-carboxylic esters **2k-n** were investigated. Both *i*-propyl and *n*-butyl esters **2l-m** were treated with **1a**, leading to the same and slight low yield compared with **2a**, whereas benzyl esters **2n** could lead to a higher yield than **2a**. Surprisingly, the yield for the reaction of methyl ester **2k** sharply decreased, maybe because of the its unstability in the currently reactional condition. Thirdly, when the entire ethyl ester group of **2a** was replaced by other groups, such as H, CN, X, Ac, Bz, carboxyl and amide, all reactions were very messy. In addition, the analogue 2-quinolinones **5** was also applied in this reaction, though the attempts were unsuccessful.

Table 3. Synthesis of coumarin-fused spiropyrrolidine oxindoles **4** from istain ketonitrones **1a** and coumarin **2** [a].



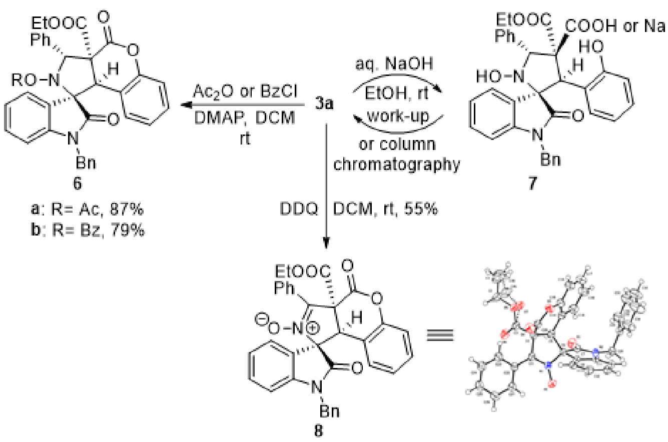
Entry	Compound	R	R1	Yield (%)[b]
1	**4a**	8-Me	COOEt	65
2	**4b**	7-OMe	COOEt	22
3	**4c**	8-OEt	COOEt	86
4	**4d**	6-F	COOEt	82
5	**4e**	6-Cl	COOEt	67

6	**4f**	6-Br	COOEt	67
7	**4g (4g′)**	6-NO_2	COOEt	75 (24)[c]
8	**4h**	6,8-*t*-Bu_2	COOEt	73
9	**4i**	7-Et_2N	COOEt	-[d]
10	**4j**	6,8-Br_2	COOEt	30
11	**4k**	H	COOMe	30[e]
12	**4l**	H	COO*i*-Pr	67
13	**4m**	H	COO*n*-Bu	67
14	**4n**	H	COOBn	89[e]
15	**4o**	H	H	-[d]
16	**4p**	H	Cl	-[d]
17	**4q**	H	Br	-[d]
18	**4r**	H	Bz	-[d]
19	**4s**	H	COOH	-[d]
20	**4t**	H	CN	-[d]
21	**4u**	H	Ac	-[d]
22	**4v**	H	CONH*n*-Bu	-[d]
23	**4w**	H	CON*n*-Bu_2	-[d]

[a]Reaction conditions: **1** (0.5 mmol), **2a** (0.525 mmol) and DBU (0.125 mmol), EtOH (2.5 mL), rt to reflux. [b]Isolated yield via column chromatography. [c]The reaction gave the lactone ring-opening product **4g′** at the standard condition, while the reaction could obtain the desired product **4g** using *t*BuOH as a solvent. [d]The reaction gave a complex. [e]The reaction was performed in *t*BuOH.

To achieve an asymmetric version of the present reaction, some chiral catalysts, such as quinine, quinidine, hydroquinidine, (*S*)-BINOL, (*R*)-BINAP, instead of DBU, were screened in the model reaction of **1a** and **2a** in EtOH at reflux. Unfortunately, all ligands were not suitable for this reaction (0–26% yields and 0% ee).

To show the synthetic utility of these spiropyrrolidine scaffolds, the derivatization of the model substrate **3a** was took place. As shown in scheme 2, the hydroxyl group of **3a** was protected by acetyl or benzoyl groups in the presence of DMAP, providing the compounds **6a** and **6b**, respectively, with 87% and 79% yields. Next, the saponification of **3a** in the presence of NaOH could gave smoothly the desired carboxylic acid **7**. Unexpectedly, the carboxylic acid was found to reconvert quickly into **3a** by TLC, even if sodium salt of **7** was not acidified, needless to say the isolation of **7** via column chromatography (by silica gel using 0.5% TEA of EtOAc/Petroleum ether as an eluent). Exposed to DDQ in DCM, **3a** was oxidized to the new nitrone **8** in 55% yield. The configuration of oxidation product **8** were undoubtedly proved by its single crystal X-ray diffraction.



Scheme 2. Transformation of **3a** and X-ray crystal structure of the compound **8** (CCDC: 2518523).

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3. Materials and Methods

3.1. General Methods

All reactions were carried out without strict water-free and oxygen-free conditions. All reagents were obtained from commercial suppliers unless otherwise stated. All solvents and reagents were directly used for reactions without further purification unless otherwise stated. When the reactions preformed at the condition of MeONa, EtONa and *t*BuONa, solvents (DCM, DCE, dioxane and MTBE) were pre-dried with CaH_2. Flash chromatography was performed using silica gel (200-300 mesh). Reactions were monitored by TLC or/and colour changes of reaction solution. Visualization was achieved under a UV lamp (254 nm and 365 nm), I_2 and by developing the plates with anisaldehyde. ^1H and ^{13}C NMR were recorded on 400 and 600 MHz NMR spectrometers with tetramethylsilane (TMS) as the internal standard and were calibrated using residual undeuterated solvent as an internal reference ($CHCl_3$: ^1H NMR= 7.26, ^{13}C NMR= 77.16; DMSO-d_6: ^1H NMR= 2.50, ^{13}C NMR= 39.52). IR spectra were acquired on an FT-IR spectrometer and are reported in wavenumbers (cm^{-1}). High-resolution mass spectra were obtained using electrospray ionization (ESI). The following abbreviations are used for the multiplicities: *s*: singlet, *d*: doublet, *t*: triplet, *sept*: septet, *m*: multiplet, *br s*: broad singlet for proton spectra. Coupling constants (*J*) are reported in Hertz (Hz).

3.2. Preparation of Intermediates

All *N*-substituted isatins were prepared by isatin (1.0 equiv.) and alkyl halides (1.5 equiv.) under NaH (2.0 equiv.) in DMF at 0°C-rt.[1] All *O*-substituted benzyl hydroxylamine hydrochlorides were prepared by two-step reactions, including the aldoxime reaction (1 equiv. aromatic aldehydes/1.2 equiv. hydroxylamine hydrochloride/2.0 equiv. NaOAc/1:1 EtOH:H_2O and the reduction of aldoxime (1.0 equiv. aromatic aldoxime/1.2 equiv. $NaBH_3CN$/10.0 equiv. con. HCl/MeOH/0°C-rt).[2] All isatin ketonitrones **1** were prepared by isatin or substituted isatins (1.0 equiv.) and *O*-benzyl or substituted benzyl hydroxylamine hydrochlorides (1.1 equiv.) in the condition of HOAc (2.0 equiv.) in MeOH at rt.[3]

All coumarins **2** to the equimolar mixture of salicyladehyde (1.0 equiv.) and malonate ester (3.2 equiv) in absolute ethanol or tetrahydrofuran was added catalytic amount of piperidine (0.35 equiv.) and resulting homogeneous mixture was refluxed for 5-8 h. Completion of the reaction was confirmed by TLC, whole reaction mixture was dispensed into crushed ice and the resulting precipitate was filtered, dried and recrystallized from methanol.[4] 2*H*-chromene-3 carbaldehydes **5** were prepared by salicyladehyde (1.0 equiv.) or acrolein (1.2 equiv.) under potassium carbonate (1.2 equiv.) in dioxane was refluxed. The mixture was stirred at rt for 27 h before it was quenched with a saturated NH_4Cl solution. The aqueous solution was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether: EtOAc = 100:1 to 50:1) to furnish **5**.[5]

3.3. General Procedure for Condition Optimization

A 10 mL tube was charged with isatin ketonitrone **1a** (0.2 mmol, 1.0 equiv.) coumarin **2a** (0.21-0.22 mmol, 1.05-1.1 equiv.), base (0.05-0.2 mmol, 25-100 mol%) and solvent (1-4 mL). After the reaction mixture is directly concentrated under vacuum. The residue was purified by flash silica gel chromatography eluated with EtOAc:PE (1:12 to 1:2, v/v) to afford the corresponding product **3a**.

3.4. General Procedure for Typical Procedure for Cycloaddition

A 25 mL tube was charged with isatin ketonitrone 1 (0.5 mmol, 1.0 equiv.), coumarin 2 (0.525 mmol, 1.05 equiv.), DBU (0.125 mmol, 25 mol%) and EtOH/*t*-BuOH (2.5 mL). The reaction mixture was stirred at rt and monitor by TLC plate. fter the reaction mixture is directly concentrated under

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vacuum.The residue was purified by flash silica gel chromatography eluated with EtOAc:PE (1:12 to 1:2, v/v) to afford the corresponding products **3**.

3.5. The Phenomenon of the Reaction and TLC

Figure 4 showed the phenmenon of the reaction for **1a** and **2a** under DBU and TLC of starting materials **1a**/**2a** and product **3a**.

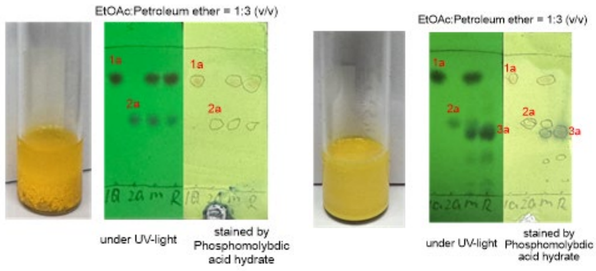


Figure 4. before adding DBU (left) and after adding DBU (right).

3.6. Deriverziation of 3a

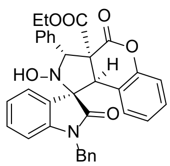
To a solution of **3a** (280 mg, 0.5 mmol, 1.0 equiv.) in DCM (3 mL) was added DMAP (18 mg, 0.15 mmol, 0.3 equiv.), Ac_2O (70 μL, 0.75 mmol, 1.5 equiv.) at rt. The mixture was stirred at rt for 18 h before it was quenched with a saturated $NaHCO_3$ solution (10 mL). The aqueous solution was extracted with EtOAc (3x10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether: EtOAc = 8:1 to 2:1) to provide the acetate **6a** in 87% yield.

To a solution of **3a** (280 mg, 0.5 mmol, 1.0 equiv.) in DCM (3 mL) was added DMAP (112 mg, 1.0 mmol, 2.0 equiv.), BzCl (145 μL, 1.25 mmol, 2.5 equiv.) at rt. The mixture was stirred at rt for21 h before it was quenched with a saturated $NaHCO_3$ solution (10 mL). The aqueous solution was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether: EtOAc = 8:1 to 6:1) to furnish the benzoate **6b** in 79% yield.

To a solution of **3a** (280 mg, 0.5 mmol, 1.0 equiv.) in DCM (5 mL) was added DDQ (170 mg, 0.75 mmol, 1.5 equiv.). The mixture was stirred at rt for 3 h before it was quenched with a saturated Na_2SO_3 solution (15 mL). The aqueous solution was extracted with DCM (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was washed with methanol to give the pure product **8** in 55% yield.

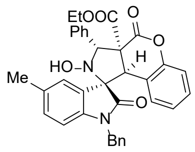
3.7. Data for All New Compounds

*(±)-ethyl (1R,3R,3aS,9bR)-1′-benzyl-2-hydroxy-2′,4-dioxo-3-phenyl-2,3-dihydro-4H-spiro[chromeno[3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**3a**)*



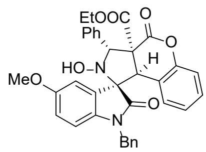
207.4 mg, 74%, a white solid, *>20:1 dr*, mp: 182.9-184.1°C; IR (thin film): ν_{max} 3470, 3061, 3032, 2977, 2911, 1760, 1732, 1615, 1491, 1369, 1228, 1212, 1179, 768, 732, 610, 532 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.54 (s, 1H), 7.82 (d, *J* = 6.8 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 2H), 7.40 (ψt, *J* = 7.4 Hz, 3H), 7.34-7.26 (m, 3H), 7.14-7.11 (m, 2H), 7.05 (ψt, *J* = 7.4 Hz, 2H), 6.90 (ψt, *J* = 7.4 Hz, 1H), 6.69 (d, *J* = 7.2 Hz, 1H), 6.53 (d, *J* = 7.2 Hz, 2H), 6.38 (d, *J* = 7.52 Hz, 1H), 5.76 (s, 1H), 4.88 (d, *J* = 16.4 Hz, 1H), 4.68 (s, 1H), 4.51 (d, *J* = 16.0 Hz, 1H), 3.61-3.49 (m, 2H), 0.65 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 175.1, 167.2, 164.6, 150.8, 144.1, 138.2, 135.7, 130.6, 128.9, 128.4, 128.2, 128.1, 127.4, 126.7, 126.4, 125.0, 124.9, 123.7, 117.5, 115.2, 109.9, 77.4, 72.4, 63.0, 59.3, 47.0, 42.6, 13.5; HRMS (ESI): *m/z* calcd for $C_{34}H_{28}N_2O_6Na$ [M+Na]$^+$ 583.1845, found 583.1836.

(±)-ethyl (1R,3R,3aS,9bR)-1′-benzyl-2-hydroxy-5′-methyl-2′,4-dioxo-3-phenyl-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate **(3b)**



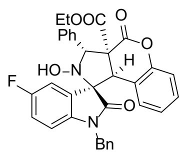
281.0mg, 98%, a white solid, *>20:1 dr*, mp: 185.3-186.6^{o}C; IR (thin film): ν_{max} 3479, 3377, 3065, 3032, 2982, 2919,1767, 1728, 1705, 1496, 1369, 1227, 1174, 808, 765, 527 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.84 (d, *J* = 7.8 Hz, 1H), 7.60 (s, 1H), 7.40 (ψt, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 6.8 Hz, 1H), 7.27 (t, *J* = 7.4 Hz, 1H), 7.11 (ψt, *J* = 7.2 Hz, 1H), 7.09–7.06 (m, 2H), 7.04 (ψt, *J* = 7.8 Hz, 2H), 6.80 (ψt, *J* = 7.4 Hz, 1H), 6.56 (d, *J* = 7.8 Hz, 2H), 6.44 (d, *J* = 7.8 Hz, 2H), 6.11 (s, 1H), 5.01 (d, *J* = 16.2 Hz, 1H), 4.78 (s, 1H), 4.72 (s, 1H), 4.35 (d, *J* = 15.6 Hz, 1H), 3.69-3.64 (m, 1H), 3.60-3.55 (m, 1H), 2.46 (s, 3H), 0.76 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-*d*$_6$): δ 174.4, 167.0, 164.6, 151.1, 141.8, 137.4, 135.0, 133.0, 130.8, 129.6, 128.9, 128.6, 128.2 (2C), 128.1, 127.2, 126.7, 125.8, 124.8, 124.2, 117.6, 114.9, 109.6, 72.51, 63.0, 59.1, 46.9, 43.4, 21.3, 13.3; HRMS (ESI): *m/z* calcd for $C_{35}H_{30}N_2O_6Na$ [M+Na]$^+$ 597.2002, found 597.1976.

(±)-ethyl (1R,3R,3aS,9bR)-1′-benzyl-2-hydroxy-5′-methoxy-2′,4-dioxo-3-phenyl-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate **(3c)**



242.6 mg, 82%, a white solid, *>20:1 dr*, mp: 176.3-177.9^{o}C; IR (thin film): ν_{max} 3476, 3067,3026, 2920, 2841, 1770, 1707, 1495, 1435, 1353, 1247, 1171, 1019, 1005, 763, 704 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.51 (s, 1H), 7.72 (d, *J* = 7.2 Hz, 2H), 7.40-7.38 (m, 4H), 7.31 (t, *J* = 7.0 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.05 (ψt, *J* = 7.2 Hz, 2H), 6.93 (ψt, *J* = 7.6 Hz, 1H), 6.88 (dd, *J* = 8.8, 1.6 Hz, 1H), 6.59 (d, *J* = 8.4 Hz, 1H), 6.51 (d, *J* = 7.6 Hz, 2H), 6.47 (d, *J* = 7.6 Hz, 1H), 5.74 (s, 1H), 4.85 (d, *J* = 16.0 Hz, 1H), 4.68 (s, 1H), 4.46 (d, *J* = 16.0 Hz, 1H), 3.85 (s, 3H), 3.62-3.46 (m, 2H), 0.65 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 174.8, 167.2, 164.6, 156.5, 150.8, 138.3, 137.4, 135.8, 130.6, 128.9, 128.8, 128.6, 128.2, 128.1, 127.7, 127.4, 126.7, 124.9, 117.4, 115.3, 114.9, 112.0, 110.4, 77.7, 72.4, 62.9, 59.3, 56.2, 47.0, 42.7, 13.5; HRMS (ESI): *m/z* calcd for $C_{35}H_{30}N_2O_7Na$ [M+Na]$^+$ 613.1951, found 613.1946.

*(±)-ethyl (1R,3R,3aS,9bR)-1′-benzyl-5′-fluoro-2-hydroxy-2′,4-dioxo-3-phenyl-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (***3d***)*



236.3 mg, 82%, a white solid, *>20:1 dr*, mp: 188.1-189.0^{o}C; IR (thin film): ν_{max} 3469, 3065, 3039, 2921, 1767, 1708, 1492, 1370, 1355, 1249, 1172, 767, 705, 609, 557 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.59 (s, 1H), 7.77-7.71 (m, 3H), 7.42-7.38 (m, 3H), 7.32 (t, *J* = 6.8 Hz, 1H), 7.20-7.12 (m, 3H), 7.05 (ψt, *J* = 7.4 Hz, 2H), 6.94 (ψt, *J* = 7.4 Hz, 1H), 6.68 (dd, *J* = 8.2, 3.8 Hz, 1H), 6.51 (d, *J* = 7.6 Hz, 3H), 5.73 (s, 1H), 4.88 (d, *J* = 16.4 Hz, 1H), 4.73 (s, 1H), 4.50 (d, *J* = 16.0 Hz, 1H), 3.62-3.48 (m, 2H), 0.65 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 175.0, 167.0, 164.6, 150.8, 140.3, 138.2, 135.5, 130.7, 128.9, 128.6, 128.4,

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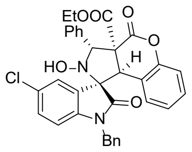
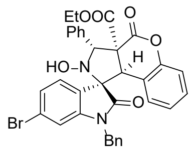
128.3, 128.2, 127.5, 126.7, 125.0, 117.5, 117.1, 116.8, 115.0, 113.4, 113.2, 110.8 (*J* = 31.6 Hz), 77.7 (*J* = 4.0 Hz), 72.4, 62.9, 59.3, 46.8, 42.7, 13.4; ^{19}F NMR (376 MHz, DMSO-d_6): -119.7; HRMS (ESI): *m*/*z* calcd for $C_{34}H_{27}N_2O_6FNa$ [M+Na]$^+$ 601.1751, found 601.1757.

*(±)-ethyl (1R,3R,3aS,9bR)-1′-benzyl-5′-chloro-2-hydroxy-2′,4-dioxo-3-phenyl-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**3e**)*



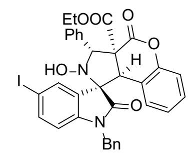
221.1 mg, 74%, a white solid, *>20:1 dr*, mp: 189.7-191.1°C; IR (thin film): ν_{max} 3469, 3067, 3037, 2985, 1765, 1734, 1486, 1354, 1256, 1170, 767, 704, 693, 550 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 (s, 1H), 7.91 (s, 1H), 7.91 (s, 1H), 7.20 (d, *J* = 7.2 Hz, 2H), 7.43-7.38 (m, 4H), 7.20 (d, *J* = 7.2 Hz, 2H), 7.32 (t, *J* = 7.2 Hz, 1H), 7.15-7.12 (m, 2H), 7.06 (ψt, *J* = 7.4 Hz, 2H), 6.96 (ψt, *J* = 7.4 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 6.50 (ψd, *J* = 6.8 Hz, 3H), 5.72 (s, 1H), 4.88 (d, *J* = 16.0 Hz, 1H), 4.75 (s, 1H), 4.51 (d, *J* = 16.4 Hz, 1H), 3.62-3.49 (m, 2H), 0.64 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.9, 167.0, 164.6, 150.8, 143.0, 138.1, 135.4, 130.7, 130.6, 128.9, 128.6, 128.5, 128.2, 127.9, 127.5, 126.7, 125.4, 125.0, 117.5, 115.0, 111.4, 77.6, 72.4, 63.0, 59.3, 46.8, 42.7, 13.5; HRMS (ESI): *m*/*z* calcd for $C_{34}H_{27}N_2O_6ClNa$ [M+Na]$^+$ 617.1455, found 617.1447.

*(±)-ethyl (1R,3R,3aS,9bR)-1′-benzyl-6′-bromo-2-hydroxy-2′,4-dioxo-3-phenyl-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**3f**)*



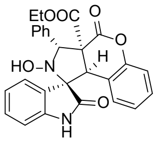
185.8 mg, 58%, a white solid, *>20:1 dr*, mp: 193.7-194.5°C; IR (thin film): ν_{max} 3367, 3067, 2924, 2995, 2852, 1754, 1716, 1615, 1491, 1454, 1228, 1183, 761, 701, 698, 651, 511 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.59 (s, 1H), 7.79 (d, *J* = 9.4 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 2H), 7.48 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.43-7.38 (m, 3H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 1H), 7.07 (ψt, *J* = 7.8 Hz, 2H), 6.98-6.95 (m, 2H), 6.53 (d, *J* = 7.8 Hz, 2H), 6.48 (d, *J* = 6.6 Hz, 1H), 5.71 (s, 1H), 4.87 (d, *J* = 16.2 Hz, 1H), 4.70 (s, 1H), 4.57 (d, *J* = 16.2 Hz, 1H), 3.60-3.45 (m, 2H), 0.65 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 175.1, 167.0, 164.6, 150.8, 145.7, 138.0, 135.4, 130.8, 129.0, 128.9, 128.5, 128.2, 127.6, 127.1, 126.7, 126.5, 125.7, 125.1, 123.4, 117.6, 114.9, 112.9, 77.2, 72.4, 63.0, 59.3, 46.7, 42.6, 13.5; δ HRMS (ESI): *m*/*z* calcd for $C_{34}H_{27}N_2O_6BrNa$ [M+Na]$^+$ 661.0950, found 661.0952.

*(±)-ethyl (1R,3R,3aS,9bR)-1′-benzyl-5′-iodo-2-hydroxy-2′,4-dioxo-3-phenyl-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**3g**)*



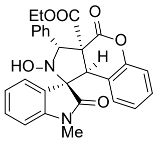
175.7 mg, 51%, a white solid, *>20:1 dr*, mp: 184.4-185.4°C; IR (thin film): ν_{max} 3413, 3067, 2983, 2929, 2852, 1754, 1613, 1351, 1262, 1228, 1169, 1029, 808, 767, 701, 608, 534 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.61 (s, 1H), 8.13 (d, *J* = 1.2 Hz, 1H), 7.72 (d, *J* = 7.2 Hz, 2H), 7.68 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.42 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.40 (ψt, *J* = 7.8 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.13 (t, *J* = 7.2 Hz, 1H), 7.05 (ψt, *J* = 7.5 Hz, 2H), 6.96 (td, *J* = 7.5, 0.9 Hz, 1H), 6.54 (d, *J* = 8.4 Hz, 1H), 6.50 (d, *J* = 7.2 Hz, 2H), 6.50 (ψt, *J* = 7.5 Hz, 1H), 5.72 (s, 1H), 4.87 (d, *J* = 16.2 Hz, 1H), 4.72 (s, 1H), 4.49 (d, *J* = 16.2 Hz, 1H), 3.59 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.53 (dq, *J* = 10.8, 7.2 Hz, 1H), 0.64 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.6, 167.0, 164.6, 150.8, 143.9, 139.2, 138.1, 135.3, 133.4, 130.7, 128.9, 128.8, 128.5, 128.2, 127.5, 126.7, 125.0, 117.5, 115.0, 112.3, 87.1, 77.4, 72.4, 63.0, 59.3, 46.8, 42.6, 13.5; HRMS (ESI): *m/z* calcd for $C_{34}H_{27}N_2O_6INa$ $[M+Na]^+$ 709.0811, found 709.0793.

*(±)-ethyl (1R,3R,3aS,9bR)-2-hydroxy-2′,4-dioxo-3-phenyl-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**3j**)*



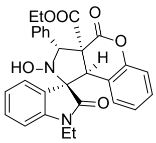
178.7 mg, 76%, a white solid, *>20:1 dr*, mp: 186.3-187.4°C; IR (thin film): ν_{max} 3367, 3283, 3057, 3043, 2995, 2935, 1778, 1714, 1620, 1498, 1351, 1257, 1228, 1181, 1019, 763, 741, 598, 567 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.27 (s, 1H), 8.40 (s, 1H), 7.71 (t, *J* = 8.8 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.40-7.21 (m, 6H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.88 (ψt, *J* = 7.4 Hz, 1H), 6.75 (d, *J* = 7.6 Hz, 1H), 6.36 (d, *J* = 7.6 Hz, 1H), 5.70 (s, 1H), 4.55 (s, 1H), 3.59-3.47 (m, 2H), 0.64 (t, *J* =7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 176.7, 167.3, 164.6, 150.8, 143.9, 138.4, 130.6, 130.3, 128.9, 128.2, 128.1, 128.0, 127.2, 125.0, 124.7, 122.9, 117.3, 115.6, 110.3, 77.5, 72.3, 62.9, 59.2, 47.0, 13.5; HRMS (ESI): *m/z* calcd for $C_{27}H_{22}N_2O_6Na$ $[M+Na]^+$ 493.1376, found 493.1339.

*(±)-ethyl (1R,3R,3aS,9bR)-2-hydroxy-1′-methyl-2′,4-dioxo-3-phenyl-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**3k**)*



193.1 mg, 80%, a white solid, *>20:1 dr*, mp: 172.1-172.8°C; IR (thin film): ν_{max} 3477, 3060, 3038, 2985, 2944, 1765, 1711, 1617, 1498, 1378, 1250, 1228, 1174, 1095, 771, 754, 699, 610, 540 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 (s, 1H), 7.79 (d, *J* = 7.2 Hz, 1H), 7.70 (d, *J* = 7.2 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.38 (ψt, *J* = 7.2 Hz, 2H), 7.32 (ψt, *J* = 7.4 Hz, 1H), 7.30 (ψt, *J* = 7.0 Hz, 1H), 7.24 (ψt, *J* = 7.6 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.85 (ψt, *J* = 7.4 Hz, 1H), 6.31 (d, *J* = 7.6 Hz, 1H), 5.70 (s, 1H), 4.60 (s, 1H), 3.59-3.47 (m, 2H), 2.82 (s, 3H), 0.64 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.8, 167.2, 164.6, 150.6, 145.3, 138.2, 130.7, 130.3, 128.9, 128.2, 128.1, 127.9, 126.4, 124.7, 124.6, 123.6, 117.4, 115.3, 109.2, 77.3, 72.3, 62.9, 59.2, 47.0, 26.0, 13.5; HRMS (ESI): *m/z* calcd for $C_{28}H_{24}N_2O_6Na$ $[M+Na]^+$ 507.1532, found 507.1527.

*(±)-ethyl (1R,3R,3aS,9bR)-1′-ethyl-2-hydroxy-2′,4-dioxo-3-phenyl-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**3l**)*



195.4 mg, 78%, a white solid, *>20:1 dr*, mp: 170.4-171.0°C; IR (thin film): ν_{max} 3449, 3063, 2981, 2931, 1764, 1732, 1711, 1616, 1491, 1468, 1455, 1373, 1258, 1229, 1178, 763, 750, 610, 551 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (s, 1H), 7.77 (d, *J* = 7.2 Hz, 1H), 7.71 (d, *J* = 7.2 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.39 (ψt, *J* = 7.4 Hz, 2H), 7.31 (ψt, *J* = 7.2 Hz, 2H), 7.24 (ψt, *J* = 7.6 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 7.00 (d, *J* = 7.6 Hz, 1H), 6.83 (ψt, *J* = 7.4 Hz, 1H), 6.22 (d, *J* = 7.6 Hz, 1H), 5.74 (s, 1H), 4.54 (s, 1H), 3.55-3.49 (m, 3H), 3.32-3.27 (m, 1H), 0.65 (t, *J* = 7.0 Hz, 3H), 0.49 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.6, 167.2, 164.6, 150.7, 144.0, 138.3, 130.7, 130.3, 128.9, 128.2, 128.1, 127.8, 126.7, 124.8, 124.5,

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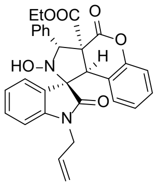
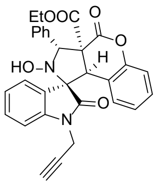
123.5, 117.1, 115.1, 109.3, 77.3, 72.5, 62.9, 59.2, 47.7, 34.0, 13.5, 12.0; HRMS (ESI): *m/z* calcd for $C_{29}H_{26}N_2O_6Na$ [M+Na]$^+$ 521.1689, found 521.1683.

*(±)-ethyl (1R,3R,3aS,9bR)-1′-allyl-2-hydroxy-2′,4-dioxo-3-phenyl-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**3m**)*



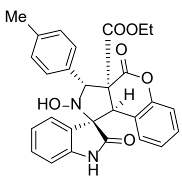
217.6 mg, 85%, a white solid, *>20:1 dr*, mp: 168.4-169.9°C; IR (thin film): ν_{max} 3448, 3092, 3059, 2982, 2915, 1762, 1734, 1715, 1618, 1492, 1469, 1369, 1257, 1234, 1181, 767, 749, 732, 702, 608, 527 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.48 (s, 1H), 7.80 (d, *J* = 6.8 Hz, 1H), 7.70 (d, *J* = 7.2 Hz, 2H), 7.41 (t, *J* = 8.2 Hz, 1H), 7.40 (ψt, *J* = 7.8 Hz, 2H), 7.31 (ψt, *J* = 6.8 Hz, 2H), 7.26 (ψt, *J* = 7.6 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.87 (d, *J* = 7.6 Hz, 1H), 6.85 (ψt, *J* = 7.6 Hz, 1H), 6.34 (d, *J* = 7.2 Hz, 1H), 5.72 (s, 1H), 5.38-5.29 (m, 1H), 4.70 (d, *J* = 10.0 Hz, 1H), 4.61 (s, 1H), 4.27 (d, *J* = 17.2 Hz, 1H), 4.15 (d, *J* = 16.4 Hz, 1H), 3.95(t, *J* = 17.2 Hz, 1H), 3.60-3.47 (m, 2H), 0.65 (t, *J* =7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 174.7, 167.2, 164.6, 150.8, 144.3, 138.3, 131.2, 130.6, 130.4, 128.9, 128.2, 128.1, 126.3, 124.8, 124.7, 123.6, 117.4, 115.9, 115.2, 109.2, 77.4, 72.4, 62.9, 59.2, 47.2, 41.3, 13.5; HRMS (ESI): *m/z* calcd for $C_{30}H_{26}N_2O_6Na$ [M+Na]$^+$ 533.1689, found 533.1686.

*(±)-ethyl (1R,3R,3aS,9bR)-2-hydroxy-2′,4-dioxo-3-phenyl-1′-(prop-2-yn-1-yl)-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**3n**)*



148.9 mg, 59%, a white solid, *>20:1 dr*, mp: 176.3-168.4°C; IR (thin film): ν_{max} 3270, 3067, 3041, 2975, 2923, 1775, 1730, 1711, 1615, 1491, 1369, 1245, 1226, 1163, 759, 700, 612,529 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (ψd, *J* = 7.8 Hz, 3H), 7.47 (td, *J* = 7.8, 0.9 Hz, 1H), 7.39 (ψt, *J* = 7.8 Hz, 2H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.31 (ψt, *J* = 7.2Hz, 1H), 7.16 (td, *J* = 7.1, 1.2 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 6.75 (ψt, *J* = 7.5 Hz, 1H), 6.32 (d, *J* = 7.8 Hz, 1H), 6.05 (s, 1H), 4.74 (s, 1H), 4.72 (s, 1H), 4.31 (dd, *J* = 17.4, 2.4 Hz, 1H), 4.12 (dd, *J* = 17.4, 2.4 Hz, 1H), 3.64 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.56 (dq, *J* = 10.8, 7.2 Hz, 1H), 1.92 (t, *J* = 2.4 Hz, 1H), 0.74 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5, 166.8, 164.5, 150.9, 143.2, 137.2, 130.5, 129.6, 128.8, 128.2, 128.1, 127.6, 125.9, 124.1, 124.0, 123.7, 117.5, 114.5, 109.7, 77.2, 76.1, 72.6, 71.8, 63.0, 58.0, 47.2, 28.8, 13.2; HRMS (ESI): *m/z* calcd for $C_{30}H_{24}N_2O_6Na$ [M+Na]$^+$ 531.1532, found 531.1511.

*(±)-ethyl (1R,3R,3aS,9bR)-2-hydroxy-2′,4-dioxo-3-(p-tolyl)-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**3p**)*



160.2 mg, 66%, a white solid, *>20:1 dr*, mp: 162.2-164.0°C; IR (thin film): ν_{max} 3384, 3098, 3032, 2981, 2921, 2851, 1763, 1736, 1713, 1621, 1491, 1458, 1350, 1228, 1170, 754, 641, 583 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.28 (s, 1H), 8.37 (s, 1H), 7.71 (d, *J* = 7.2 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.34 (t, *J* = 7.6

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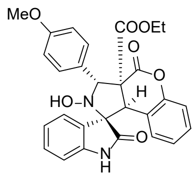
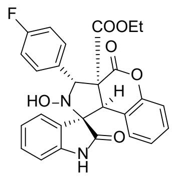
Hz, 1H), 7.27-7.17 (m, 4H), 7.06 (d, *J* = 8.4 Hz, 1H), 6.87 (ψt, *J* = 7.4 Hz, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 6.35 (d, *J* = 7.6 Hz, 1H), 5.65 (s, 1H), 4.53 (s, 1H), 3.58-3.51 (m, 2H), 2.30 (s, 3H), 0.65 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 176.9, 167.3, 164.6, 150.8, 143.9, 137.2, 135.3, 130.5, 130.2, 128.8, 128.7, 128.0, 127.3, 125.0, 124.6, 122.8, 117.3, 115.6, 110.3, 77.4, 72.0, 62.8, 59.1, 46.9, 21.2, 13.4; HRMS (ESI): *m/z* calcd for $C_{28}H_{24}N_2O_6Na$ [M+Na]$^+$ 507.1532, found 507.1521.

*(±)-ethyl (1R,3R,3aS,9bR)-2-hydroxy-3-(4-methoxyphenyl)-2′,4-dioxo-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**3q**)*



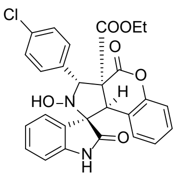
135.5 mg, 54%, a white solid, *>20:1 dr*, mp: 150.5-151.3°C; IR (thin film): ν_{max} 3422, 3189, 3086, 2917, 2848, 1778, 1736, 1716, 1619, 1512, 1471, 1247, 1166, 1026, 751, 637, 558 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 (s, 1H), 8.36 (s, 1H), 7.70 (d, *J* = 7.2 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.33 (ψt, *J* = 7.6 Hz, 1H), 7.27-7.19 (m, 2H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 2H), 6.87 (ψt, *J* = 7.4 Hz, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 6.34 (d, *J* = 7.6 Hz, 1H), 5.64 (s, 1H), 4.54 (s, 1H), 3.75 (s, 3H), 3.59-3.52 (m, 2H), 0.68 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 176.9, 167.3, 164.7, 159.4, 150.8, 143.8, 130.5, 130.2, 130.1, 130.0, 128.0, 127.3, 124.9, 124.6, 122.8, 117.3, 115.7, 113.6, 110.3, 77.4, 71.9, 62.9, 59.1, 55.6, 46.8, 13.5; HRMS (ESI): *m/z* calcd for $C_{28}H_{24}N_2O_7Na$ [M+Na]$^+$ 523.1481, found 523.10467.

*(±)-ethyl (1R,3R,3aS,9bR)-3-(4-fluorophenyl)-2-hydroxy-2′,4-dioxo-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**3r**)*



189.7 mg,78%, a white solid, *>20:1 dr*, mp: 205.6-206.3°C; IR (thin film): ν_{max} 3350, 3096, 2980, 2840, 1760, 1737, 1711, 1621, 1509, 1472, 1458, 1226, 1177, 1158, 756, 643, 509 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.31 (s, 1H), 8.47 (s, 1H), 7.72 (m, 3H), 7.34 (t, *J* = 7.4 Hz, 1H), 7.28-7.21 (m, 4H), 7.07 (d, *J* = 8.4 Hz, 1H), 6.88 (ψt, *J* = 7.2 Hz, 1H), 6.75 (d, *J* = 7.6 Hz, 1H), 6.35 (d, *J* = 8.0 Hz, 1H), 5.68 (s, 1H), 4.53 (s, 1H), 3.59 (q, *J* = 7.0 Hz, 2H), 0.69 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 176.8, 167.3, 164.7, 150.7, 143.9, 134.4 (d, *J*= 3.0 Hz), 130.9, 130.8 (d, *J*= 8.0 Hz), 130.6, 130.3, 128.0, 127.1, 125.0, 124.7, 122.9, 117.4, 115.5, 115.1, 114.9, 110.3, 77.4, 71.6, 63.0, 59.0, 46.9, 13.5; ^{19}F NMR (376 MHz, DMSO-d_6): -115.0; HRMS (ESI): *m/z* calcd for $C_{27}H_{21}N_2O_6FNa$ [M+Na]$^+$ 511.1281, found 511.1279.

*(±)-ethyl (1R,3R,3aS,9bR)-3-(4-chlorophenyl)-2-hydroxy-2′,4-dioxo-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**3s**)*



218.2 mg, 86%, a white solid, *>20:1 dr*, mp: 166.7-167.4°C; IR (thin film): ν_{max} 3368, 3088, 2983, 2836, 1766, 1736, 1709, 1621, 1490, 1457, 1227, 1177, 1017, 752, 670, 579 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.32 (s, 1H), 8.51 (s, 1H), 7.73-7.68 (m, 3H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.34 (ψt, *J* = 7.8 Hz, 1H), 7.26 (ψt, *J* = 7.6 Hz, 1H), 7.23 (ψt, *J* = 7.2 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 6.89 (ψt, *J* = 7.6 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 6.35 (d, *J* = 7.6 Hz, 1H), 5.67 (s, 1H), 4.52 (s, 1H), 3.61 (q, *J* = 7.0 Hz, 2H), 0.68 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 176.4, 167.3, 164.7, 150.7, 143.9, 137.3, 132.8, 130.7, 130.3, 128.2,

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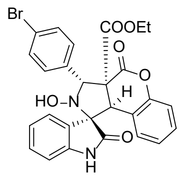
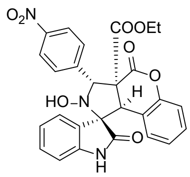
128.0, 127.0, 125.0, 124.7, 122.9, 117.4, 115.4, 110.3, 77.4, 71.5, 63.0, 59.0, 47.0, 13.5; HRMS (ESI): *m/z* calcd for $C_{27}H_{21}N_2O_6ClNa$ [M+Na]$^+$ 527.0986, found 527.0984.

*(±)-ethyl (1R,3R,3aS,9bR)-3-(4-bromophenyl)-2-hydroxy-2′,4-dioxo-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**3t**)*



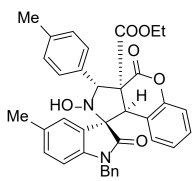
225.9 mg, 82%, a white solid, *>20:1 dr*, mp: 161.6-163.0°C; IR (thin film): ν_{max} 3513, 3282, 2859, 1784, 1714, 1688, 1487, 1247, 1226, 1178, 1010, 858, 748, 665, 570 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.32 (s, 1H), 8.51 (s, 1H), 7.72 (d, *J* = 7.2 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.34 (ψt, *J* = 7.6 Hz, 1H), 7.26 (ψt, *J* = 7.6 Hz, 1H), 7.22 (ψt, *J* = 7.6 Hz, 1H),7.08 (d, *J* = 8.0 Hz, 1H), 6.88 (ψt, *J* = 7.4 Hz, 1H), 6.75 (d, *J* = 7.2 Hz, 1H), 6.35 (d, *J* = 7.6 Hz, 1H), 5.66 (s, 1H), 4.52 (s, 1H), 3.61 (q, *J* = 7.1 Hz, 2H), 0.68 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 176.7, 167.3, 164.7, 150.7, 143.9, 137.7, 131.2, 131.0, 130.6, 130.3, 128.0, 126.9, 125.0, 124.7, 122.9, 121.3, 117.4, 115.4, 110.3, 77.4, 71.6, 63.0, 59.0, 47.0, 13.5; HRMS (ESI): *m/z* calcd for $C_{27}H_{21}N_2O_6BrNa$ [M+Na]$^+$ 571.0481, found 571.0471.

*(±)-ethyl (1R,3R,3aS,9bR)-2-hydroxy-3-(4-nitrophenyl)-2′,4-dioxo-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**3u**)*



122.1 mg, 47%, a white solid, *>20:1 dr*, mp: 170.4-171.8°C; IR (thin film): ν_{max} 3360, 3288, 2941, 2345, 1782, 1735, 1605, 1523, 1492, 1347, 1256, 1174, 1112, 1017, 856, 745, 608, 573 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.37 (s, 1H), 8.69 (s, 1H), 8.30 (d, *J* = 8.4 Hz, 2H), 7.97 (d, *J* = 8.4 Hz, 2H), 7.75 (d, *J* = 7.2 Hz, 1H), 7.36 (ψt, *J* = 7.5 Hz, 1H), 7.28 (ψt, *J* = 7.6 Hz, 1H), 7.25 (ψt, *J* = 7.2 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 6.90 (ψt, *J* = 7.4 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 6.37 (d, *J* = 7.2 Hz, 1H), 5.80 (s, 1H), 4.53 (s, 1H), 3.60 (q, *J* = 7.0 Hz, 2H), 0.66 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 176.6, 167.3, 164.7, 150.6, 147.6, 146.1, 143.9, 130.8, 130.4, 130.0, 128.1, 126.6, 125.2, 124.8, 123.5, 123.0, 117.4, 115.2, 110.4, 77.6, 71.5, 63.2, 59.1, 47.3, 13.5; HRMS (ESI): *m/z* calcd for $C_{27}H_{21}N_3O_8Na$ [M+Na]$^+$ 538.1226, found 538.1215.

*(±)-ethyl (1R,3R,3aS,9bR)-1′-benzyl-2-hydroxy-5′-methyl-2′,4-dioxo-3-(p-tolyl)-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**3w**)*



227.7 mg, 77%, a white solid, *>20:1 dr*, mp: 167.4-169.2°C; IR (thin film): ν_{max} 3369, 3037, 2975, 2915, 2851, 1757, 1741, 1709, 1609, 1498, 1369, 1271, 1248, 1178, 801, 769, 623, 565 cm^{-1};^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.47 (s, 1H), 7.63 (s, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.8 Hz, 1H), 7.11 (d, *J* = 6.8 Hz, 2H), 7.04 (ψt, *J* = 7.2 Hz, 2H), 6.91 (ψt, *J* = 7.2 Hz, 1H), 6.56 (d, *J* = 8.0 Hz, 1H), 6.50 (d, *J* = 7.2 Hz, 2H), 6.42 (d, *J* = 7.2 Hz, 1H), 5.70 (s, 1H), 4.85 (d, *J* = 16.4 Hz, 1H), 4.64 (s, 1H), 4.46 (d, *J* = 16.4 Hz, 1H), 3.64-3.51 (m, 2H), 2.42 (s, 3H), 2.31 (s, 3H), 0.66 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 175.0, 167.2, 164.7, 150.8, 141.8, 137.2, 135.8, 135.2, 132.8, 130.8, 130.5, 128.8, 128.7, 128.5, 127.4, 126.7, 126.5, 125.5, 124.9, 117.4, 115.3, 109.7, 77.4, 72.2, 62.9, 59.3, 46.9, 42.6, 21.3, 13.5; HRMS (ESI): *m/z* calcd for $C_{36}H_{32}N_2O_6Na$ [M+Na]$^+$ 611.2158, found.611.2137.

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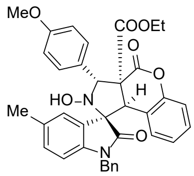
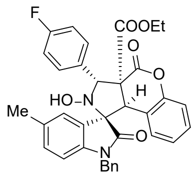
*(±)-ethyl (1R,3R,3aS,9bR)-1′-benzyl-2-hydroxy-3-(4-methoxyphenyl)-5′-methyl-2′,4-dioxo-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**3x**)*



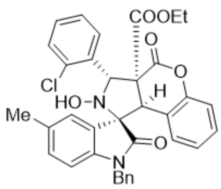
149.9 mg, 50%, a white solid, *>20:1 dr*, mp: 147.1-147.7°C; IR (thin film): ν_{max} 3440, 3069, 3032, 2983, 2935, 2836, 1776, 1736, 1694, 1612, 1514, 1498, 1370, 1244, 1163, 1134, 1022, 823, 754, 699, 567 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (s, 1H), 7.63 (s, 1H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.11 (ψd, *J* = 7.2 Hz, 3H), 7.04 (ψt, *J* = 7.4 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.90 (ψt, *J* = 7.6 Hz, 1H), 6.56 (d, *J* = 8.0 Hz, 1H), 6.50 (d, *J* = 7.2 Hz, 2H), 6.42 (d, *J* = 7.6 Hz, 1H), 5.69 (s, 1H), 4.85 (d, *J* = 16.2 Hz, 1H), 4.65 (s, 1H), 4.47 (d, *J* = 16.2 Hz, 1H), 3.76 (s, 3H), 3.66-3.53 (m, 2H), 2.42 (s, 3H), 0.69 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 175.0, 167.2, 164.7, 159.4, 150.8, 141.8, 135.8, 132.8, 130.8, 130.5, 130.1, 128.8, 128.5, 127.4, 126.7, 126.5, 125.5, 124.9, 117.4, 115.3, 113.6, 109.7, 77.4, 72.1, 62.9, 59.2, 55.6, 46.8, 42.6, 21.3, 13.5; HRMS (ESI): *m/z* calcd for $C_{36}H_{32}N_2O_7Na$ [M+Na]$^+$ 627.2107, found.627.2096.

*(±)-ethyl (1R,3R,3aS,9bR)-1′-benzyl-3-(4-fluorophenyl)-2-hydroxy-5′-methyl-2′,4-dioxo-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**3y**)*



205.6 mg, 69%, a white solid, *>20:1 dr*, mp: 185.6-186.5°C; IR (thin film): ν_{max} 3478, 2989, 2960, 2918, 1774, 1737, 1710, 1613, 1516, 1496, 1158, 812, 765, 610, 503 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (s, 1H), 7.74 (d, *J* = 7.2 Hz, 1H), 7.74 (d, *J* = 6.4 Hz, 1H), 7.65 (s, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.25 (ψt, *J* = 8.6 Hz, 2H), 7.12 (ψt, *J* = 7.2 Hz, 3H), 7.04 (ψt, *J* = 7.4 Hz, 2H), 6.92 (ψt, *J* = 7.6 Hz, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 6.50 (d, *J* = 7.6 Hz, 2H), 6.42 (d, *J* = 7.6 Hz, 1H), 5.73 (s, 1H), 4.85 (d, *J* = 16.4 Hz, 1H), 4.64 (s, 1H), 4.47 (d, *J* = 16.4 Hz, 1H), 3.68-3.55 (m, 2H), 2.42 (s, 3H), 0.70 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.9, 167.3, 164.7, 150.8, 141.8, 135.8, 134.3 (d, *J* = 2.8 Hz), 132.8, 130.9, 130.8, 130.6, 128.5, 127.4, 126.7, 126.3, 125.5, 124.9, 117.5, 115.2, 114.9, 109.7, 77.4, 71.8, 63.1, 59.2, 46.9, 42.7, 21.3, 13.5; ^{19}F NMR (376 MHz, DMSO-d_6): -114.9; HRMS (ESI): *m/z* calcd for $C_{35}H_{29}N_2O_6FNa$ [M+Na]$^+$ 615.1907, found 615.1904.

*(±)-ethyl (1R,3S,3aS,9bR)-1′-benzyl-3-(2-chlorophenyl)-2-hydroxy-5′-methyl-2′,4-dioxo-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**3z**)*



147.3 mg, 48%, a white solid, *>20:1 dr*, mp: 155.0-156.2°C; IR (thin film): ν_{max} 3447, 3069, 3030, 2979, 2921, 2867, 1782, 1717, 1605, 1497, 1457, 1370, 1259, 1226, 1152, 1007, 815, 756, 695, 532 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (s, 1H), 7.89 (d, *J* = 7.2 Hz, 1H), 7.79 (s, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.43-7.33 (m, 3H), 7.14-7.12 (m, 5H), 6.92 (ψt, *J* = 7.2 Hz, 1H), 6.52 (d, *J* = 8.0 Hz, 1H), 6.47 (ψd, *J* = 6.4 Hz, 3H), 6.20 (s, 1H), 4.87 (d, *J* = 16.2 Hz, 1H), 4.80 (s, 1H), 4.46 (d, *J* = 16.2 Hz, 1H), 3.69-3.61 (m, 1H), 3.48-3.40 (m, 1H), 2.41 (s, 1H), 0.63 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.9, 166.1, 162.4, 151.0, 141.7, 137.3, 135.8, 135.1, 132.8, 131.7, 130.8, 130.5, 130.0, 129.5, 128.9, 128.4, 127.4, 127.1,

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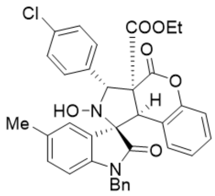
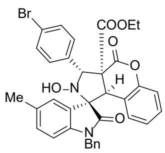
126.6, 126.5, 125.8, 124.7, 117.3, 115.5, 109.6, 77.4, 69.5, 63.1, 60.1, 46.9, 42.6, 21.1, 13.4; HRMS (ESI): *m/z* calcd for $C_{35}H_{29}N_2O_6ClNa$ [M+Na]$^+$ 631.1612, found 631.1602.

*(±)-ethyl (1R,3S,3aS,9bR)-1′-benzyl-3-(4-chlorophenyl)-2-hydroxy-5′-methyl-2′,4-dioxo-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**3aa**)*



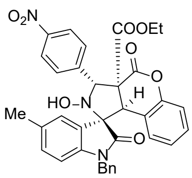
276.5 mg, 85%, a white solid, *>20:1 dr*, mp: 192.4-193.7°C; IR (thin film): ν_{max} 3454, 3067, 3018, 2983, 2925, 2859, 1774, 1729, 1705, 1607, 1497, 1455, 1374, 1349, 1262, 1225, 1165, 1015, 811, 755, 629, 544 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.65 (s, 1H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.13 (ψt, *J* = 7.8 Hz, 3H), 7.04 (ψt, *J* = 7.8 Hz, 2H), 6.92 (ψt, *J* = 7.4 Hz, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 6.50 (d, *J* = 7.2 Hz, 2H), 6.42 (d, *J* = 7.6 Hz, 1H), 5.72 (s, 1H), 4.85 (d, *J* = 16.0 Hz, 1H), 4.63 (s, 1H), 4.47 (d, *J* = 16.0 Hz, 1H), 3.70-3.58 (m, 2H), 2.42 (s, 3H), 0.70 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.9, 167.2, 164.7, 150.8, 141.8, 137.2, 135.7, 132.8, 130.9, 130.7, 128.8, 128.5, 128.3, 127.4, 126.7, 126.2, 125.6, 125.0, 117.5, 115.1, 109.7, 77.4, 71.4, 63.1, 59.1, 47.0, 42.7, 21.2, 13.5; HRMS (ESI): *m/z* calcd for $C_{35}H_{29}N_2O_6ClNa$ [M+Na]$^+$ 631.1612, found 631.1613.

*(±)-ethyl (1R,3S,3aS,9bR)-1′-benzyl-3-(4-bromophenyl)-2-hydroxy-5′-methyl-2′,4-dioxo-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**3ab**)*



204.7 mg, 66%, a white solid, *>20:1 dr*, mp: 193.1-194.8°C; IR (thin film): ν_{max} 3370, 3032, 2977, 2929, 2902, 1753, 1741, 1708, 1497, 1369, 1250, 1225, 1182, 1013, 770, 806, 770, 612, 536 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (s, 1H), 7.67-7.61 (m, 5H), 7.40 (t, *J* = 7.2 Hz, 1H), 7.12 (ψt, *J* = 7.4 Hz, 3H), 7.04 (ψt, *J* = 7.4 Hz, 2H), 6.92 (ψt, *J* = 7.6 Hz, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 6.51 (d, *J* = 7.6 Hz, 2H), 6.42 (d, *J* = 7.6 Hz, 1H), 5.71 (s, 1H), 4.84 (d, *J* = 16.0 Hz, 1H), 4.63 (s, 1H), 4.47 (d, *J* = 16.0 Hz, 1H), 3.70-3.59 (m, 2H), 2.42 (s, 3H), 0.70 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.9, 167.2, 164.7, 150.7, 141.8, 137.6, 135.7, 132.8, 131.2, 131.0, 130.9, 130.6, 128.8, 128.5, 127.4, 126.7, 126.2, 125.6, 125.0, 121.4, 117.5, 115.1, 109.7, 77.4, 71.8, 63.1, 59.1, 47.0, 42.6, 21.2, 13.5; HRMS (ESI): *m/z* calcd for $C_{35}H_{29}N_2O_6BrNa$ [M+Na]$^+$ 675.1107, found 675.1080.

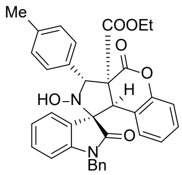
*(±)-ethyl (1R,3R,3aS,9bR)-1′-benzyl-2-hydroxy-5′-methyl-3-(4-nitrophenyl)-2′,4-dioxo-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**3ac**)*



157.8 mg, 52%, a white solid, *>20:1 dr*, mp: 194.1-195.5°C; IR (thin film): υ_{max} 3500, 3063, 3037, 2989, 2921, 1782, 1707, 1605, 1516, 1495, 1456, 1347, 1261, 1247, 1231, 1177, 765, 697, 544 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (s, 1H), 8.31 (d, *J* = 7.6 Hz, 2H), 7.99 (d, *J* = 8.4 Hz, 2H), 7.68 (s, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 1H), 7.12 (ψt, *J* = 7.2 Hz, 2H), 7.05 (ψt, *J* = 7.4 Hz, 2H), 6.94 (ψt, *J* = 7.2 Hz, 1H), 6.59 (d, *J* = 8.0 Hz, 1H), 6.51 (d, *J* = 7.2 Hz, 2H), 6.44 (d, *J* = 7.6 Hz, 1H), 5.84 (s, 1H), 4.86 (d, *J* = 16.2 Hz, 1H), 4.64 (s, 1H), 4.49 (d, *J* = 16.2 Hz, 1H), 3.67-3.59 (m, 2H), 2.43 (s, 3H), 0.67 (t, *J* = 7.0

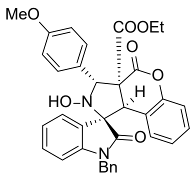
Hz, 3H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 174.8, 167.2, 164.7, 150.7, 147.6, 146.0, 141.8, 135.7, 132.9, 131.0, 130.7, 130.0, 128.9, 128.5, 127.4, 126.7, 125.9, 125.7, 125.1, 123.5, 117.6, 114.8, 109.8, 77.5, 71.7, 69.3, 59.2, 47.3, 42.7, 21.3, 13.5; HRMS (ESI): *m/z* calcd for $C_{35}H_{29}N_3O_8Na$ [M+Na]$^+$ 642.1852, found 642.1846.

*(±)- ethyl (1R,3R,3aS,9bR)-1′-benzyl-2-hydroxy-2′,4-dioxo-3-(p-tolyl)-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**3ad**)*



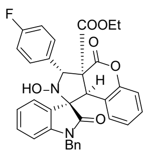
133.6 mg, 46%, a white solid, *>20:1 dr*, mp: 164.5-166.5°C; IR (thin film): ν_{max} 3852, 3678, 3649, 1712, 1460, 1369, 1231, 1176, 857, 738, 620, 554 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.48 (s, 1H), 7.81 (d, *J* = 6.8 Hz, 1H), 7.58 (d, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.32 (ψt, *J* = 7.2 Hz, 1H), 7.28 (ψt, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.05 (ψt, *J* = 7.4 Hz, 2H), 6.89 (ψt, *J* = 7.6 Hz, 1H), 6.68 (d, *J* = 7.6 Hz, 1H), 6.52 (d, *J* = 7.6 Hz, 2H), 6.37 (d, *J* = 7.6 Hz, 1H), 5.71 (s, 1H), 4.87 (d, *J* = 16.2 Hz, 1H), 4.66 (s, 1H), 4.50 (d, *J* = 16.2 Hz, 1H), 3.61-3.52 (m, 2H), 2.31 (s, 3H), 0.67 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 175.1, 167.2, 164.7, 150.8, 144.1, 137.3, 135.7, 135.2, 130.6, 128.9, 128.8, 128.7, 128.4, 127.4, 126.7, 126.5, 125.0, 124.9, 123.7, 117.5, 115.2, 109.9, 77.3, 72.4, 62.9, 59.3, 47.0, 42.6, 21.2, 13.5; HRMS (ESI): *m/z* calcd for $C_{35}H_{30}N_2O_6Na$ [M+Na]$^+$ 597.2002, found 597.2014.

*(±)-ethyl (1R,3R,3aS,9bR)-1′-benzyl-2-hydroxy-3-(4-methoxyphenyl)-2′,4-dioxo-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**3ae**)*



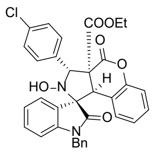
112.0 mg, 38%, a yellow solid, *>20:1 dr*, mp: 169.3-169.6°C; IR (thin film): ν_{max} 3853, 3669, 3629, 3565, 1779, 1703, 1611, 1462, 1234, 1171, 1019, 855, 757, 668, 602, 516 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.48 (s, 1H), 7.80 (d, *J* = 7.2 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.32 (ψt, *J* = 7.8 Hz, 1H), 7.28 (ψt, *J* = 7.4 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.05 (ψt, *J* = 7.6 Hz, 2H), 6.96 (d, *J* = 8.4 Hz, 2H), 6.88 (ψt, *J* = 7.6 Hz, 1H), 6.68 (d, *J* = 7.2 Hz, 1H), 6.52 (d, *J* = 7.6 Hz, 2H), 6.37 (d, *J* = 7.6 Hz, 1H), 5.70 (s, 1H), 4.87 (d, *J* = 16.4 Hz, 1H), 4.67 (s, 1H), 4.50 (d, *J* = 16.4 Hz, 1H), 3.76 (s, 3H), 3.65-3.54 (m, 2H), 0.70 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 175.1, 167.2, 164.7, 159.4, 150.8, 144.1, 135.7, 130.6, 130.1, 130.0, 128.9, 128.4, 126.7, 126.5, 124.9, 124.9, 123.7, 117.5, 115.3, 113.6, 109.9, 77.3, 72.1, 62.9, 59.3, 55.6, 46.8, 42.6, 13.5; HRMS (ESI): *m/z* calcd for $C_{35}H_{30}N_2O_7Na$ [M+Na]$^+$ 613.1951, found 613.1949.

*(±)-ethyl (1R,3R,3aS,9bR)-1′-benzyl-3-(4-fluorophenyl)-2-hydroxy-2′,4-dioxo-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**3af**)*



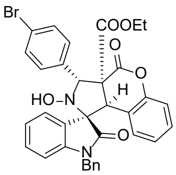
181.3 mg, 63%, a yellow solid, *>20:1 dr*, mp: 161.1-163.6°C; IR (thin film): ν_{max} 3852,3696, 3680, 3624, 3564, 3422, 1773, 1732, 1611, 1369, 1169, 858, 819, 757, 507 cm$^{-1;}$ ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.59 (s, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.74 (dd, *J* = 8.4, 6.0 Hz, 2H), 7.40 (td, *J* = 8.4, 1.0 Hz, 1H), 7.32 (td, *J* = 7.6, 1.2 Hz, 1H), 7.32 (ψt, *J* = 8.0 Hz, 1H), 7.32 (ψt, *J* = 8.8 Hz, 2H), 7.13 (ψt, *J* = 7.4 Hz, 2H), 7.05 (ψt, *J* = 7.4 Hz, 2H), 6.90 (ψt, *J* = 7.4 Hz, 1H), 6.69 (d, *J* = 7.6 Hz, 1H), 6.53 (d, *J* = 7.6 Hz, 2H), 6.38 (d, *J* = 7.6 Hz, 1H), 5.75 (s, 1H), 4.87 (d, *J* = 16.0 Hz, 1H), 4.66 (s, 1H), 4.51 (d, *J* = 16.0 Hz, 1H), 3.65-3.58 (m, 2 H), 0.71 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 175.0, 167.2, 164.7, 150.8, 144.2, 135.7, 134.3 (d, *J* = 2.7 Hz), 130.9, 130.8, 130.7, 128.9, 128.4, 127.5, 126.7, 126.3, 125.0 (2C), 123.7, 117.5, 115.2, 115.1, 115.0, 109,9, 77.3, 71.8, 63.1, 59.1, 47.0, 42.6, 13.5; ^{19}F NMR (376 MHz, DMSO-d_6): -114.9; HRMS (ESI): *m/z* calcd for $C_{34}H_{27}N_2O_6FNa$ [M+Na]$^+$ 601.1751, found 601.1740.

*(±)-ethyl (1R,3R,3aS,9bR)-1′-benzyl-3-(4-chlorophenyl)-2-hydroxy-2′,4-dioxo-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**3ag**)*



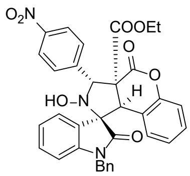
225.5mg, 76%, a white solid, *>20:1 dr*, mp: 183.1-184.2°C; IR (thin film): ν_{max} 3852, 3734, 3678, 3574, 3563, 2981, 2933, 1778, 1714, 1611, 1493, 1229,1165, 1009, 862, 754, 610, 544 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (s, 1H), 7.82 (d, *J* = 7.2 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.32 (ψt, *J* = 7.8 Hz, 1H), 7.28 (ψt, *J* = 7.2 Hz, 1H), 7.13 (ψt, *J* = 8.2 Hz, 1H), 7.05 (ψt, *J* = 7.6 Hz, 2H), 6.90 (ψt, *J* = 7.6 Hz, 1H), 6.69 (d, *J* = 7.2 Hz, 1H), 6.53 (d, *J* = 7.6 Hz, 2H), 6.38 (d, *J* = 7.6 Hz, 1H), 5.74 (s, 1H), 4.87 (d, *J* = 16.0 Hz, 1H), 4.65 (s, 1H), 4.51 (d, *J* = 16.0 Hz, 1H), 3.63 (q, *J* = 7.0 Hz, 2H), 0.71 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 175.0, 167.2, 164.7, 150.8, 144.1, 137.2, 135.7, 132.9, 130.7, 128.9, 128.4, 128.3, 127.5, 126.7, 126.2, 125.0 (2C), 123.7, 117.5, 115.0, 110.0, 77.3, 71.8, 63.1, 59.1, 47.0, 42.6, 13.5; HRMS (ESI): *m/z* calcd for $C_{34}H_{27}N_2O_6ClNa$ [M+Na]$^+$ 617.1455, found 617.1455.

*(±)-ethyl (1R,3R,3aS,9bR)-1′-benzyl-3-(4-bromophenyl)-2-hydroxy-2′,4-dioxo-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**3ah**)*



218.2 mg, 68%, a white solid; *>20:1 dr*, mp: 190.0-191.3°C; IR (thin film): ν_{max} 3854, 3729, 3668, 3633, 1740, 1712, 1617, 1498, 1376, 1232, 1180, 1004, 858, 804, 736, 620 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (s, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.32 (ψt, *J* = 7.6 Hz, 1H), 7.28 (ψt, *J* = 7.6 Hz, 1H), 7.13 (ψt, *J* = 8.4 Hz, 2H), 7.05 (t, *J* = 7.4 Hz, 2H), 6.90 (ψt, *J* = 7.0 Hz, 1H), 6.69 (d, *J* = 7.6 Hz, 1H), 6.52 (d, *J* = 6.8 Hz, 2H), 6.38 (d, *J* = 7.6 Hz, 1H), 5.72 (s, 1H), 4.87 (d, *J* = 16.2 Hz, 1H), 4.65 (s, 1H), 4.51 (d, *J* = 16.2 Hz, 1H), 3.64 (q, *J* = 7.0 Hz, 2H), 0.70 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 175.0, 167.2, 164.7, 150.8, 144.1, 137.6, 135.7, 131.2, 131.0, 130.7, 128.9, 128.4, 127.5, 126.7, 126.2, 125.0, 124.9, 123.7, 121.4, 117.5, 115.0, 109.9, 77.3, 71.8, 63.1, 59.1, 47.1, 42.7, 13.5; HRMS (ESI): *m/z* calcd for $C_{34}H_{27}N_2O_6BrNa$ [M+Na]$^+$ 661.0950, found 661.0924.

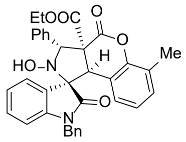
*(±)-ethyl (1R,3R,3aS,9bR)-1′-benzyl-2-hydroxy-3-(4-nitrophenyl)-2′,4-dioxo-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**3ai**)*



182.1 mg, 60%, a white solid, *>20:1 dr*, mp: 202.1-203.2°C; IR (thin film): ν_{max} 3854, 3736, 3639, 3612, 3396, 3070, 2987, 2931, 1728, 1610, 1348, 1235, 1178, 1009, 754, 699, 610, 551 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (s, 1H), 8.31 (d, *J* = 8.8 Hz, 2H), 8.00 (d, *J* = 8.8 Hz, 2H), 7.85 (d, *J* = 7.2 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 6.8 Hz, 1H), 7.06 (ψt, *J* = 7.4 Hz, 2H), 6.92 (ψt, *J* = 7.4 Hz, 1H), 6.71 (d, *J* = 7.6 Hz, 1H), 6.53 (d, *J* = 7.6

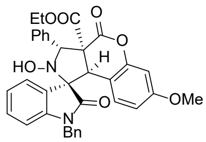
Hz, 2H), 6.40 (d, *J* = 7.6 Hz, 1H), 5.86 (s, 1H), 4.88 (d, *J* = 16.2 Hz, 1H), 4.66 (s, 1H), 4.53 (d, *J* = 16.2 Hz, 1H), 3.62 (q, *J* = 7.0 Hz, 2H), 0.69 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 175.0, 167.2, 164.7, 150.7, 147.6, 146.0, 144.2, 135.6, 130.8, 130.0, 128.9, 128.4 127.5, 126.7, 125.9, 125.1, 125.0, 123.8, 123.5, 117.6, 114.8, 110.0, 77.5, 71.8, 63.3, 59.2, 47.3, 42.7, 13.5; HRMS (ESI): *m/z* calcd for $C_{34}H_{27}N_3O_8Na$ $[M+Na]^+$ 628.1696, found 628.1690.

*(±)-ethyl (1R,3R,3aS,9bR)-1′-benzyl-2-hydroxy-6-methyl-2′,4-dioxo-3-phenyl-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**4a**)*



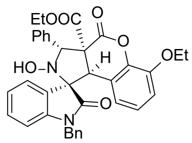
188.6 mg, 65%, a white solid; *>20:1 dr*, mp: 182.6-183.9°C; IR (thin film): ν_{max} 3460, 3061, 3035, 2981, 2915, 1755, 1733, 1615, 1468, 1366, 1273, 1207, 1184, 1031, 1006, 837, 782, 752, 631, 551, 530 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (s, 1H), 7.80 (d, *J* = 6.8 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 2H), 7.40 (ψt, *J* = 7.6 Hz, 2H), 7.34-7.23 (m, 4H), 7.13 (t, *J* = 7.4 Hz, 1H), 7.05 (ψt, *J* = 7.5 Hz, 2H), 6.76 (ψt, *J* = 7.4 Hz, 1H), 6.70 (d, *J* = 7.2 Hz, 1H), 6.53 (d, *J* = 7.6 Hz, 2H), 6.19 (d, *J* = 7.2 Hz, 1H), 5.77 (s, 1H), 4.87 (d, *J* = 16.2 Hz, 1H), 4.65 (s, 1H), 4.51 (d, *J* = 16.2 Hz, 1H), 3.60-3.48 (m, 2H), 2.22 (s, 3H), 0.65 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 175.1, 167.2, 164.6, 149.1, 144.2, 138.3, 135.8, 131.8, 130.6, 128.9, 128.8, 128.2, 128.1, 127.4, 126.7, 126.6, 126.1, 125.9, 124.9, 124.2, 123.6, 114.8, 109.8, 77.4, 72.5, 62.9, 59.2, 47.2, 42.7, 15.9, 13.5; HRMS (ESI): *m/z* calcd for $C_{35}H_{30}N_2O_6Na$ $[M+Na]^+$ 597.2002, found 597.2003.

*(±)-ethyl (1R,3R,3aS,9bR)-1′-benzyl-2-hydroxy-7-methoxy-2′,4-dioxo-3-phenyl-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**4b**)*



64.7 mg, 22%, a white solid, *>20:1 dr*, mp: 169.6-171.1°C; IR (thin film): ν_{max} 3478, 2958, 2924, 2853, 1770, 1710, 1613, 1493, 1467, 1361, 1194, 1081, 1013, 955, 856, 747, 595, 643 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 1H), 7.79 (d, *J* = 6.4 Hz, 1H), 7.71 (d, *J* = 7.2 Hz, 2H), 7.39 (ψt, *J* = 7.4 Hz, 2H), 7.33-7.25 (m, 3H), 7.15 (ψt, *J* = 7.2 Hz, 1H), 7.03 (t, *J* = 7.6 Hz, 2H), 6.74 (d, *J* = 2.0 Hz, 1H), 6.71 (d, *J* = 7.6 Hz, 1H), 6.57 (d, *J* = 7.6 Hz, 2H), 6.48 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.24 (d, *J* = 8.8 Hz, 1H), 5.75 (s, 1H), 4.91 (d, *J* = 16.0 Hz, 1H), 4.59 (s, 1 H), 4.51 (d, *J* = 16.0 Hz, 1H), 3.74 (s, 3H), 3.59-3.52 (m, 2H), 0.65 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 175.2, 167.2, 164.8, 160.9, 151.8, 144.1, 138.3, 135.8, 130.5, 129.1, 128.8, 128.6, 128.2, 128.1, 127.5, 126.8, 126.5, 124.9, 123.6, 111.6, 109.8, 106.8, 102.4, 77.4, 72.3, 62.9, 59.3, 56.0, 46.7, 42.6, 13.5; HRMS (ESI): *m/z* calcd for $C_{35}H_{30}N_2O_7Na$ $[M+Na]^+$ 613.1952, found 613.1949.

*(±)-ethyl (1R,3R,3aS,9bR)-1′-benzyl-6-ethoxy-2-hydroxy-2′,4-dioxo-3-phenyl-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**4c**)*



261.0 mg, 86%, a white solid, *>20:1 dr*, mp: 143.2-145.1°C; IR (thin film): ν_{max} 3471, 3068, 3039, 2981, 2927, 1774, 1715, 1615, 1587, 1369, 1243, 1181, 1069, 953, 866, 754, 700, 664, 604, 540 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (s, 1H), 7.80 (d, *J* = 6.8 Hz, 1H), 7.71 (d, *J* = 7.6 Hz, 2H), 7.40 (ψt, *J* = 7.6 Hz, 2H), 7.31 (ψt, *J* = 7.8 Hz, 2H), 7.27 (t, *J* = 7.6 Hz, 1H), 7.14 (ψt, *J* = 7.2 Hz, 1H), 7.12-7.05 (m, 3H), 6.81 (ψt, *J* = 8.0 Hz, 1H), 6.68 (d, *J* = 7.2 Hz, 1H), 6.54 (d, *J* = 7.6 Hz, 2H), 5.91 (d, *J* = 7.6 Hz, 1H), 5.74 (s, 1H),

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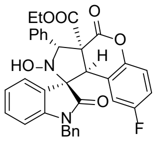
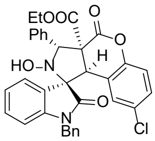
4.89 (d, *J* = 16.4 Hz, 1H), 4.67 (s, 1H), 4.52 (d, *J* = 16.4 Hz, 1H), 4.11-3.97 (m, 2H), 3.61-3.48 (m, 2H), 1.35 (t, *J* = 7.0 Hz, 3H), 0.65 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 175.1, 167.1, 164.4, 146.8, 144.2, 140.0, 138.3, 135.7, 130.6, 128.9, 128.8, 128.2, 128.1, 127.4, 126.6, 126.5, 124.9, 124.8, 123.7, 119.2, 115.9, 113.8, 109.9, 77.3, 72.5, 64.6, 63.0, 59.0, 47.1, 42.6, 15.0, 13.4; HRMS (ESI): *m/z* calcd for $C_{36}H_{32}N_2O_7Na$ [M+Na]$^+$ 627.2107, found 627.2110.

*(±)-ethyl (1R,3R,3aS,9bR)-1'-benzyl-8-fluoro-2-hydroxy-2',4-dioxo-3-phenyl-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3'-indoline]-3a(9bH)-carboxylate (**4d**)*



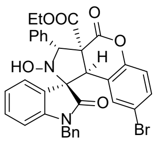
236.4 mg, 82%, a yellow solid, *>20:1 dr*, mp: 177.4-178.2°C; IR (thin film): ν_{max} 3471, 3068, 3018, 2977, 2909, 1770, 1731, 1615, 1495, 1467, 1369, 1250, 1183, 1007, 874, 753, 700, 623, 542 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (s, 1H), 7.82 (d, *J* = 7.2 Hz, 1H), 7.70 (d, *J* = 7.2 Hz, 2H), 7.40 (ψt, *J* = 7.4 Hz, 2H), 7.35-7.26 (m, 4H), 7.22 (dd, *J* = 8.8, 4.8 Hz, 1H), 7.16 (ψt, *J* = 7.2 Hz, 1H), 7.09 (ψt, *J* = 7.4 Hz, 2H), 6.76 (d, *J* = 7.6 Hz, 1H), 6.60 (d, *J* = 7.6 Hz, 2H), 6.06 (d, *J* = 8.0 Hz, 1H), 5.74 (s, 1H), 4.90 (d, *J* = 16.0 Hz, 1H), 4.69 (s, 1H), 4.53 (d, *J* = 16.0 Hz, 1H), 3.62-3.49 (m, 2H), 0.65 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 175.0, 167.0, 164.4, 147.2 (d, *J* = 2.0 Hz), 144.1, 138.1, 135.8, 130.8, 128.9, 128.2, 127.6, 126.8, 126.0, 125.1, 123.8, 119.5 (d, *J* = 9.6 Hz), 117.8, 117.6, 116.9, 116.8, 114.5, 114.2, 110.1, 77.3, 72.4, 63.0, 58.8, 46.8, 42.7, 13.4; ^{19}F NMR (376 MHz, DMSO-d_6): -118.0; HRMS (ESI): *m/z* calcd for $C_{34}H_{27}N_2O_6FNa$ [M+Na]$^+$ 601.1751, found 601.1754.

*(±)-ethyl (1R,3R,3aS,9bR)-1'-benzyl-8-chloro-2-hydroxy-2',4-dioxo-3-phenyl-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3'-indoline]-3a(9bH)-carboxylate (**4e**)*



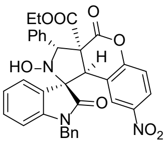
204.2 mg, 67%, a white solid, *>20:1 dr*, mp: 168.8-170.0°C; IR (thin film): ν_{max} 3448, 3098, 3059, 3022, 2977, 2913, 1774, 1725, 1707, 1489, 1468, 1381, 1255, 1255, 1161, 1138, 1007, 885, 750, 701, 615, 557, 534 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (s, 1H), 7.83 (d, *J* = 7.2 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 2H), 7.46 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.39 (ψt, *J* = 7.4 Hz, 2H), 7.36-7.24 (m, 3H), 7.19 (d, *J* = 8.8 Hz, 1H), 7.17 (ψt, *J* = 7.2 Hz, 1H), 7.10 (ψt, *J* = 7.6 Hz, 2H), 6.75 (d, *J* = 7.6 Hz, 1H), 6.58 (d, *J* = 7.6 Hz, 2H), 6.32 (d, *J* = 2.4 Hz, 1H), 5.73 (s, 1H), 4.91 (d, *J* = 16.0 Hz, 1H), 4.69 (s, 1H), 4.53 (d, *J* = 16.0 Hz, 1H), 3.62-3.50 (m, 2H), 0.66 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 175.0, 166.9, 164.2, 149.6, 144.1, 138.0, 135.7, 130.8, 130.6, 128.9, 128.8, 128.6, 128.2 (2C), 127.8, 127.6, 126.6, 125.9, 125.1, 123.8, 119.5, 117.2, 110.0, 77.3, 72.4, 63.1, 58.9, 46.6, 42.7, 13.4; HRMS (ESI): *m/z* calcd for $C_{34}H_{27}N_2O_6ClNa$ [M+Na]$^+$ 617.1455, found 617.1450.

*(±)-ethyl (1R,3R,3aS,9bR)-1'-benzyl-8-bromo-2-hydroxy-2',4-dioxo-3-phenyl-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3'-indoline]-3a(9bH)-carboxylate (**4f**)*



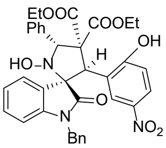
214.3 mg, 67%, a white solid, *>20:1 dr*, mp: 159.1-161.2°C; IR (thin film): ν_{max} 3453, 3064, 3026, 2983, 2930, 1776, 1725, 1615, 1467, 1227, 1163, 1075, 999, 824, 749, 700, 614, 535 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (s, 1H), 7.83 (d, *J* = 7.2 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 2H), 7.58 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.40 (ψt, *J* = 7.4 Hz, 2H), 7.37 (ψt, *J* = 8.0 Hz, 1H), 7.33-7.29 (m, 2 H), 7.17 (ψt, *J* = 7.2 Hz, 1H), 7.12 (s, 1 H), 7.11 (ψt, *J* = 7.2 Hz, 2H), 6.75 (d, *J* = 7.6 Hz, 1H), 6.57 (d, *J* = 7.6 Hz, 2H), 6.45 (d, *J* = 2.4 Hz, 1H), 5.73 (s, 1H), 4.91 (d, *J* = 16.0 Hz, 1H), 4.69 (s, 1H), 4.53 (d, *J* = 16.0 Hz, 1H), 3.62-3.50 (m, 2H), 0.66 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 175.0, 166.9, 164.2, 150.1, 144.1, 138.0, 135.7, 133.4, 130.8, 130.7, 128.9, 128.8, 128.2 (2C), 127.5, 126.5, 125.9, 125.1, 123.8, 119.8, 117.7, 116.5, 110.0, 77.3, 72.4, 63.1, 58.9, 46.6, 42.7, 13.4; HRMS (ESI): *m/z* calcd for $C_{34}H_{27}N_2O_6BrNa$ [M+Na]$^+$ 661.0950, found 661.0933.

*(±)-ethyl (1R,3R,3aS,9bR)-1′-benzyl-2-hydroxy-8-nitro-2′,4-dioxo-3-phenyl-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**4g**)*



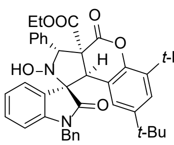
228.0 mg, 75%, a white solid, *>20:1 dr*, mp: 142.8-143.6°C; IR (thin film): ν_{max} 3904, 3740, 3079, 1784, 1714, 1613, 1528, 1343, 1246, 1149, 996, 844, 742, 699 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.66 (s, 1H), 8.23 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.89 (dd, *J* = 7.0, 1.0 Hz, 1H), 7.71 (d, *J* = 7.6 Hz, 2H), 7.44-7.31 (m, 6H), 7.14 (d, *J* = 2.4 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 7.02 (ψt, *J* = 7.6 Hz, 2H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.60 (d, *J* = 7.2 Hz, 2H), 5.76 (s, 1H), 4.85 (d, *J* = 16.0 Hz, 2H), 4.82 (s, 1 H), 4.51 (d, *J* = 16.0 Hz, 1H), 3.63-3.50 (m, 2H), 0.67 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 175.0, 166.6, 163.7, 155.3, 144.0, 143.5, 137.8, 135.9, 131.0, 128.9, 128.7, 128.3, 127.7, 127.0, 126.4, 125.5, 125.3, 124.0, 123.9, 119.0, 116.6, 110.2, 77.3, 72.5, 63.2, 58.7, 46.4, 42.8, 13.4; HRMS (ESI): *m/z* calcd for $C_{34}H_{27}N_3O_8Na$ [M+Na]$^+$ 628.1696, found 6281.1693.

*(±)-diethyl (3R,3′R,5′R)-1-benzyl-1′-hydroxy-3′-(2-hydroxy-5-nitrophenyl)-2-oxo-5′-phenylspiro[indoline-3,2′-pyrrolidine]-4′,4′-dicarboxylate (**4g′**)*



77.4 mg, 24%, a white solid, *>20:1 dr*, mp: 178.1-180.0°C; IR (thin film): ν_{max} 3852, 3732, 3676, 3649, 3622, 1725, 1618, 1496, 1339, 1289, 1195, 1098, 1020, 803, 753, 702, 611 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 11.02 (s, 1H), 8.32 (d, *J* = 2.8 Hz, 1H), 8.20 (s, 1H), 7.97 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.71 (dd, *J* = 5.8, 2.2 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 2H), 7.35 (ψt, *J* = 7.4 Hz, 2H), 7.28 (t, *J* = 7.2 Hz, 1H), 7.18-7.11 (m, 3H), 7.05 (ψt, *J* = 7.4 Hz, 2H), 6.84 (d, *J* = 7.6 Hz, 2H), 6.75 (d, *J* = 9.2 Hz, 1H), 6.60 (dd, *J* = 6.8, 1.6 Hz, 1H), 6.46 (s, 1H), 5.85 (s, 1H), 4.90 (d, *J* = 15.8 Hz, 1H), 4.55 (d, *J* = 15.8 Hz, 1H), 3.88-3.80 (m, 1H), 3.72-3.64 (m, 1H), 3.60-3.52 (m, 1H), 3.22-3.14 (m, 1H), 0.67 (t, *J* = 7.0 Hz, 3H), 0.59 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 174.8, 169.2, 168.4, 162.7, 143.7, 139.3, 138.6, 136.3, 129.8, 128.6, 128.5, 128.1, 128.0, 127.9, 127.6, 127.1, 125.4, 125.1, 122.9, 122.8, 115.6, 109.0, 76.9, 70.7, 65.6, 61.7, 61.2, 43.3, 42.6, 13.5, 13.4; HRMS (ESI): *m/z* calcd for $C_{36}H_{33}N_3O_9Na$ [M+Na]$^+$ 674.2114, found 674.2107.

*(±)-ethyl (1R,3R,3aS,9bR)-1′-benzyl-6,8-di-tert-butyl-2-hydroxy-2′,4-dioxo-3-phenyl-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**4h**)*



246.1 mg, 73%, a white solid, *>20:1 dr*, mp: 145.1-146.8°C; IR (thin film): ν_{max} 3065, 3035, 2962, 2907, 2867, 1774, 1720, 1615, 1468, 1365, 1225, 1163, 1124, 1007, 750, 699, 631, 546 cm^{-1}; ^{1}H NMR (400

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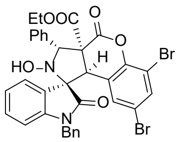
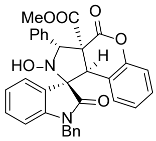
MHz, DMSO-d_6) δ 8.53 (s, 1H), 7.82 (d, *J* = 6.8 Hz, 1H), 7.73 (d, *J* = 7.6 Hz, 2H), 7.40 (ψt, *J* = 7.2 Hz, 2H), 7.36-7.29 (m, 3H), 7.24 (s, 1H), 7.14 (ψt, *J* = 7.4 Hz, 1H), 7.01 (ψt, *J* = 7.4 Hz, 2H), 6.74 (d, *J* = 7.2 Hz, 1H), 6.45 (d, *J* = 7.6 Hz, 2H), 6.12 (s, 1H), 5.83 (s, 1H), 4.94 (d, *J* = 16.0 Hz, 1H), 4.52 (s, 1H), 4.35 (d, *J* = 16.0 Hz, 1H), 3.63-3.50 (m, 2H), 1.36 (s, 9H), 0.73 (s, 9H), 0.68 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 175.0, 167.4, 126.6, 164.3, 147.1, 145.4, 144.3, 138.4, 136.4, 136.1, 130.4, 128.9, 128.7, 128.2, 128.0, 127.3, 126.7, 124.9, 124.0, 123.5, 123.3, 114.5, 109.6, 77.6, 72.4, 62.7, 58.6, 48.1, 42.9, 35.1, 34.1, 31.0, 30.0, 13.6; HRMS (ESI): *m/z* calcd for $C_{42}H_{44}N_2O_6Na$ [M+Na]$^+$ 695.3097, found 695.3082.

(±)-ethyl (1R,3R,3aS,9bR)-1′-benzyl-6,8-dibromo-2-hydroxy-2′,4-dioxo-3-phenyl-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (***4j***)



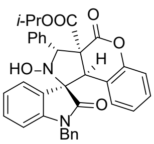
109.1 mg, 30%, a yellow solid; *>20:1 dr*, mp: 147.9-149.1°C; IR (thin film): υ_{max} 3472, 3070, 3035, 2983, 2940, 1789, 1714, 1614, 1495, 1369, 1238, 1155, 1125, 1000, 862, 752, 699, 546 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (s, 1H), 7.93 (d, *J* = 2.0 Hz, 1H), 7.83 (d, *J* = 7.2 Hz, 1H), 7.69 (d, *J* = 7.2 Hz, 2H), 7.40 (ψt, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.32 (ψt, *J* = 6.6 Hz, 1H), 7.31 (ψt, *J* = 7.0 Hz, 1H), 7.19 (ψt, *J* = 7.2 Hz, 1H), 7.13 (ψt, *J* = 7.4 Hz, 2H), 6.83 (d, *J* = 7.6 Hz, 1H), 6.76 (d, *J* = 7.2 Hz, 2H), 6.41 (d, *J* = 2.0 Hz, 1H), 5.73 (s, 1H), 4.91 (d, *J* = 16.0 Hz, 1H), 4.72 (s, 1H), 4.55 (d, *J* = 15.7 Hz, 1H), 3.63-3.50 (m, 2H), 0.66 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 175.0, 166.5, 163.5, 137.8, 136.0, 135.8, 130.9, 130.2, 128.9, 128.3, 127.7, 126.7, 125.6, 125.2, 123.9, 118.9, 116.5, 111.6, 110.1, 77.2, 72.5, 63.2, 58.9, 46.7, 42.8, 13.4; HRMS (ESI): *m/z* calcd for $C_{34}H_{26}N_2O_6Br_2Na$ [M+Na]$^+$ 741.0035, found 741.0034.

(±)-methyl (1R,3R,3aS,9bR)-1′-benzyl-2-hydroxy-2′,4-dioxo-3-phenyl-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (***4k***)



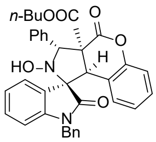
81.3 mg, 30%, a white solid, *>20:1 dr*, mp: 158.8-159.6°C; IR (thin film): ν_{max} 3854, 3555, 3474, 3185, 3068, 2915, 1744, 1709, 1610, 1491, 1460, 1253, 1178, 948, 756, 705, 604, 526 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (s, 1H), 7.83 (d, *J* = 6.6 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 2H), 7.40 (ψt, *J* = 7.4 Hz, 3H), 7.32 (ψt, *J* = 7.2 Hz, 2H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 7.12 (d, *J* = 7.2 Hz, 1H), 7.05 (ψt, *J* = 7.6 Hz, 2H), 6.90 (ψt, *J* = 7.6 Hz, 1H), 6.69 (d, *J* = 7.6 Hz, 1H), 6.53 (d, *J* = 7.6 Hz, 2H), 6.38 (d, *J* = 7.6 Hz, 1H), 5.76 (s, 1H), 4.88 (d, *J* = 16.0 Hz, 1H), 4.68 (s, 1H), 4.51 (d, *J* = 16.0 Hz, 1H), 3.07 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 175.1, 167.7, 164.5, 150.8, 144.1, 138.2, 135.7, 130.6, 128.9, 128.7, 128.4, 128.2, 128.1, 127.4, 126.7, 126.3, 125.0, 124.9, 123.7, 117.5, 115.1, 109.9, 77.4, 72.4, 59.5, 53.5, 46.9, 42.6; HRMS (ESI): *m/z* calcd for $C_{33}H_{26}N_2O_6Na$ [M+Na]$^+$ 569.1689, found 569.1700.

(±)-isopropyl (1R,3R,3aS,9bR)-1′-benzyl-2-hydroxy-2′,4-dioxo-3-phenyl-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (***4l***)



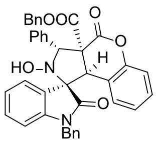
193.2 mg, 67%, a white solid, *>20:1 dr*, mp: 182.0-183.0°C; IR (thin film): ν_{max} 3474, 3065, 3030, 2989, 2907, 1748, 1731, 1617, 1492, 1371, 1261, 1230, 1261, 1181, 1100, 1004, 908, 753, 701, 610, 553 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.2 Hz, 2H), 7.79 (d, *J* = 6.6 Hz, 1H), 7.39 (ψt, *J* = 7.5 Hz, 2H), 7.31 (ψt, *J* = 7.2 Hz, 1H), 7.27 (td, *J* = 7.8, 1.2 Hz, 2H), 7.25 (td, *J* = 8.1, 0.9 Hz, 1H), 7.12 (ψt, *J* = 7.5 Hz, 1H), 7.09 (dd, *J* = 8.4, 0.6 Hz, 1H), 7.05 (ψt, *J* = 7.8 Hz, 2H), 6.79 (td, *J* = 7.5, 0.9 Hz, 1H), 6.58 (d, *J* = 7.2 Hz, 2H), 6.56 (dd, *J* = 7.2, 1.2 Hz, 1H), 6.42 (d, *J* = 7.2 Hz, 1H), 6.10 (s, 1H), 5.03 (d, *J* = 16.2 Hz, 1H), 4.80 (s, 1H), 4.72 (s, 1H), 4.46 (Sept, *J* = 6.0 Hz, 1H), 4.38 (d, *J* = 16.2 Hz, 1H), 0.95 (d, *J* = 6.0 Hz, 3H), 0.57 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 174.4, 166.4, 164.6, 151.1, 144.2, 137.3, 134.9, 130.4, 129.7, 129.1, 128.6, 128.2, 128.1, 127.2, 126.6, 126.0, 124.1, 124.0, 123.3, 117.6, 114.9, 109.8, 77.0, 72.4, 71.3, 59.0, 47.2, 43.4, 21.2, 20.5; HRMS (ESI): *m/z* calcd for $C_{35}H_{30}N_2O_6Na$ [M+Na]$^+$ 597.2002, found 597.1975.

*(±)-n-butyl (1R,3R,3aS,9bR)-1′-benzyl-2-hydroxy-2′,4-dioxo-3-phenyl-2,3-dihydro-4H-spiro[chromeno[3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**4m**)*



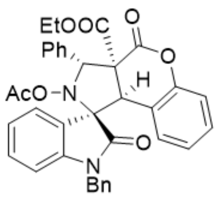
197.1 mg, 67%, a white solid, *>20:1 dr*, mp: 144.6-145.9^{o}C; IR (thin film): ν_{max} 3474, 3063, 3035, 2958, 2872, 1777, 1716, 1615, 1491, 1455, 1369, 1226, 1174, 1035, 753, 700, 610, 528 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.53 (s, 1H), 7.80 (d, *J* = 7.2 Hz, 1H), 7.42-7.37 (m, 3H), 7.34-7.27 (m, 3H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.13 (ψt, *J* = 7.2 Hz, 1H), 7.05 (ψt, *J* = 7.4 Hz, 2H), 6.90 (ψt, *J* = 7.4 Hz, 1H), 6.69 (d, *J* = 7.2 Hz, 1H), 6.53 (d, *J* = 7.2 Hz, 2H), 6.38 (d, *J* = 7.6 Hz, 1H), 5.76 (s, 1H), 4.88 (d, *J* = 16.4 Hz, 1H), 4.66 (s, 1H), 4.51 (d, *J* = 16.4 Hz, 1H), 3.57-3.51 (m, 1H), 3.47-3.41 (m, 1H), 1.10-0.99 (m, 4H), 0.73 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 175.1, 167.2, 164.7, 150.3, 144.1, 138.2, 135.7, 130.6, 128.9, 128.8, 128.3, 128.2, 128.1, 127.4, 126.7, 126.4, 124.9, 124.9, 123.7, 117.5, 115.1, 109.9, 77.4, 72.4, 66.5, 59.4, 47.2, 42.6, 29.8, 18.7, 13.9; HRMS (ESI): *m/z* calcd for $C_{36}H_{32}N_2O_6Na$ [M+Na]$^+$ 611.2158, found 611.2149.

*(±)-benzyl (1R,3R,3aS,9bR)-1′-benzyl-2-hydroxy-2′,4-dioxo-3-phenyl-2,3-dihydro-4H-spiro[chromeno[3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**4n**)*



276.9 mg, 89%, a white solid, *>20:1 dr*, mp: 131.9-132.5^{o}C; IR (thin film): ν_{max} 3648, 3415, 3063, 3020, 1968, 1742, 1708, 1613, 1461, 1374, 1217, 1175, 1004, 910, 739, 695, 608, 528 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.55 (s, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 7.2 Hz, 2H), 7.40 (t, *J* = 7.2 Hz, 1H), 7.37-7.30 (m, 4H), 7.29-7.27 (m, 4H), 7.13 (t, *J* = 8.4 Hz, 1H), 7.12 (t, *J* = 6.8 Hz, 1H), 7.05 (ψt, *J* = 7.6 Hz, 2H), 6.99-6.96 (m, 2H), 6.90 (ψt, *J* = 7.4 Hz, 1H), 6.69 (d, *J* = 7.6 Hz, 1H), 6.53 (d, *J* = 7.6 Hz, 2H), 6.39 (d, *J* = 7.6 Hz, 1H), 5.78 (s, 1H), 4.88 (d, *J* = 16.2 Hz, 1H), 4.70 (s, 1H), 4.64 (d, *J* = 12.4 Hz, 1H), 4.51 (d, *J* = 16.2 Hz, 1H), 4.37 (d, *J* = 12.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 175.1, 167.1, 164.6, 150.8, 144.1, 138.1, 135.7, 134.9, 130.7, 128.9, 128.8, 128.6, 128.4, 128.3, 128.2, 127.9, 127.4, 126.7, 126.3, 125.0, 124.9, 123.7, 117.5, 115.1, 109.9, 77.4, 72.5, 68.1, 59.4, 47.3, 42.6; HRMS (ESI): *m/z* calcd for $C_{39}H_{30}N_2O_6Na$ [M+Na]$^+$ 645.2002, found 645.1997.

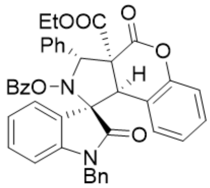
*(±)-ethyl (1R,3R,3aS,9bR)-2-acetoxy-1′-benzyl-2′,4-dioxo-3-phenyl-2,3-dihydro-4H-spiro[chromeno[3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**6a**)*



 doi:10.20944/preprints202603.0943.v1

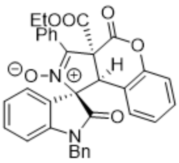
260.7 mg, 87%, a white solid, mp: 194.2-196.0°C; IR (thin film): ν_{max} 3523, 3445, 3210, 3059, 2931, 2859, 1773, 1737, 1707, 1610, 1492, 1367, 1165, 998, 758, 697, 596,495 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 7.90 (d, *J* = 6.4 Hz, 1H), 7.80 (d, *J* = 7.2 Hz, 1H), 7.43-7.31 (m, 5H),7.26 (t, *J* = 7.2 Hz, 1H), 7.17-7.08 (m, 4 H), 6.92 (td, *J* = 7.6, 0.8 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 6.63 (d, *J* = 7.2 Hz, 2H), 6.39 (d, *J* = 7.2 Hz, 1H), 6.03 (s, 1H), 4.86 (s, 1H), 4.84 (d, *J* = 16.0 Hz, 1H), 4.60 (d, *J* = 16.0 Hz, 1H), 3.64-3.50 (m, 2H), 1.53 (s, 3H), 0.67 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 173.5, 167.8, 166.5, 164.1, 150.8, 143.6, 136.0, 135.6, 131.4, 131.0, 129.0, 128.8, 128.4, 128.3, 127.7, 126.9, 126.5, 125.1, 123.9, 123.3, 117.7, 114.1, 110.2, 76.7, 71.3, 63.3, 59.2, 46.7, 42.8, 18.6, 13.4; HRMS (ESI): *m/z* calcd for $C_{36}H_{30}N_2O_7Na$ [M+Na]$^+$ 625.1951, found 625.1953.

*(±)-ethyl (1R,3R,3aS,9bR)-2-(benzoyloxy)-1′-benzyl-2′,4-dioxo-3-phenyl-2,3-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline]-3a(9bH)-carboxylate (**6b**)*



263.0 mg, 79%, a white solid, 10:1 *dr*, mp: 160.4-162.1°C; IR (thin film): ν_{max} 3847, 3648, 3567, 3511, 3237, 2975, 2929, 1766, 1715, 1610, 1459, 1233, 1167, 1017, 753, 701, 554 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 7.99 (dd, *J* = 6.4, 2.4 Hz, 1H), 7.89 (d, *J* = 7.2 Hz, 2H), 7.59-7.50 (m, 3H), 7.45-7.36 (m, 5H), 7.32-7.25 (m, 3H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.11 (ψt, *J* = 7.4 Hz, 1H), 6.98-6.92 (m, 3 H), 6.67 (dd, *J* = 5.6, 3.2 Hz, 1H), 6.57 (d, *J* = 7.2 Hz, 2H), 6.25 (s, 1H), 4.95 (s, 1H), 4.88 (d, *J* = 16.0 Hz, 1H), 4.57 (d, *J* = 16.0 Hz, 1H), 3.67-3.54 (m, 2H), 0.69 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 173.5, 166.5, 164.2, 163.3, 150.8, 143.5, 135.9, 135.4, 134.4, 131.4, 131.2, 129.5, 129.3, 129.0, 128.9, 128.5, 128.4, 127.6, 127.3, 126.8, 126.5, 125.1, 124.0, 123.3, 117.7, 114.0, 110.2, 76.9, 71.6, 63.4, 59.2, 46.9, 42.8, 13.4; HRMS (ESI): *m/z* calcd for $C_{41}H_{32}N_2O_7Na$ [M+Na]$^+$ 687.2107, found 687.2106.

*(±)-(1R,3aS,9bR)-1′-benzyl-3a-(ethoxycarbonyl)-2′,4-dioxo-3-phenyl-3a,9b-dihydro-4H-spiro[chromeno [3,4-c]pyrrole-1,3′-indoline] 2-oxide (**8**)*



154.0 mg, 55%, a white solid, 10:1 *dr*, mp: 295.1-295.8°C; IR (thin film): ν_{max} 3098, 3068, 2975, 2927, 1773, 1746, 1721, 1458, 1374, 1263, 1225, 1150, 1023, 990, 910, 860, 762, 697, 637, 544 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.43-8.40 (m, 2H), 7.76 (d, *J* = 7.2 Hz, 1H), 7.55-7.51 (m, 4H), 7.46 (t, *J* = 7.4 Hz, 1H), 7.32 (d, *J* = 7.2 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.17 (ψt, *J* = 7.2 Hz, 1H), 7.10 (ψt, *J* = 7.4 Hz, 1H), 7.06 (ψt, *J* = 7.2 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.57 (ψd, *J* = 7.2 Hz, 3H), 4.93 (s, 1H), 4.86 (d, *J* = 16.2 Hz, 1H), 4.59 (d, *J* = 16.2 Hz, 1H), 4.29-4.23 (m, 1H), 4.20-4.12 (m, 1H), 0.98 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 170.7, 167.9, 161.3, 150.9, 140.4, 135.1, 132.5, 131.6, 131.4, 129.0, 128.7, 128.4, 127.8, 126.8, 126.4, 125.6, 124.5, 122.8, 117.6, 113.2,110.8, 85.9, 64.3, 60.3, 47.6, 43.3, 13.9; HRMS (ESI): *m/z* calcd for $C_{34}H_{26}N_2O_6Na$ [M+Na]$^+$ 581.1689, found 581.1683.

4. Conclusions

This section is not mandatory but can be added to the manuscript if the discussion is unusually long or complex. In summary, we have developed a rapidly [3+2]-cycloaddition of isatin ketonitrone 1,3-dipoles generated in situ with coumarins to access novel dicyclic spiropyrrolidine oxindole derivatives (45 examples) in moderate to excellent yields (22-98%). The reaction proceeded under mild conditions and were found to be high regio- and diastereoselectivities (>20:1 *dr*). All the synthesized *exo*-type spirooxindole derivatives **3**/**4** were confirmed by using ^{1}H and ^{13}C NMR, IR and HMRS technologies. The relative stereochemistry of products was explained undoubtedly by the single crystal X-ray of **3b** and **8**. Additionally, the transformation of spiroxindole product was realized successfully, which exhibited their good value of synthetic applications. Further exploration and application of this reaction in organic synthesis is ongoing in our laboratory.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. Copes of NMR for all new compounds; Copes of HRMS for all new compounds; Copes of data of X-ray crystal structures for compounds **3**b and **8**.

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References

1. Sardari, S.; Nishibe, S.; Daneshtalab, M. Coumarins, the bioactive structures with antifungal property. in *Stud. Nat. Prod. Chem.*, Attaur, R., Ed. Elsevier: **2000**, vol. 23, pp. 335–393.
2. Estévez-Braun, A.; González, A. G. Coumarins. *Nat. Prod. Rep.* **1997**, *14*, 465–475.
3. Malikov, V. M.; Saidkhodzhaev, A. I.; Aripov, K. N. Coumarins: Plants, structure, properties. *Chem. Nat. Compd.* **1998**, *34*, 202–264.
4. Malikov, V. M.; Saidkhodzhaev, A. I. Coumarins. Plants, structure, properties. *Chem. Nat. Compd.* **1998**, *34*, 345–409.
5. Malikov, V. M.; Saidkhodzhaev, A. I. Coumarins: Plants, structures, properties. *Chem. Nat. Compd.* **1998**, *34*, 517–548.
6. Kong, L. Coumarin chemistry. Natural Product Chemistry Series, Chemical Industry Press, **2007** (in Chinese).
7. Nan, Z.-D.; Shang, Y.; Zhu, Y.-D.; Zhang, H.; Sun, R.-R.; Tian, J.-J.; Jiang, Z.-B.; Ma, X.-L.; Bai, C. Systematic review of natural coumarins in plants (2019–2024): chemical structures and pharmacological activities. *Phytochemistry* **2025**, *235*, 114480.
8. Zhang, A.; Su, M.; Yuan, Z.; Deng, S.; Yu L.; Wang, H. Research progress on the application of chemically synthesized coumarin derivatives. *Chem. Res. Appl.* 2026, **38**, 1–10 (in Chinese).
9. Barot, K. P.; Jain, S. V.; Kremer, L.; Singh, S.; Ghate, M. D., Recent advances and therapeutic journey of coumarins: current status and perspectives. *Med. Chem. Res.* **2015**, *24*, 2771–2798.
10. Sharifi-Rad, J.; Cruz-Martins, N.; López-Jornet, P.; Lopez, E. P.-F.; Harun, N.; Yeskaliyeva, B.; Beyatli, A.; Sytar, O.; Shaheen, S.; Sharopov, F.; Taheri, Y.; Docea, A. O.; Calina, D.; Cho, W. C., Natural coumarins exploring the pharmacological. *Oxid. Med. Cell. Longev.* **2021**, *2021*, 6492346.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 March 2026 doi:10.20944/preprints202603.0943.v1

11. M.; Croce, N.; Gallo, V.; Arienzo, A.; Salvatore, G.; Antonini, G. Coumarin-induced hepatotoxicity: a narrative review. *Molecules* **2022**, *27*, 9063.
12. Sharma, V.; Sharma, A.; Wadje, B. N.; Bharate, S. B. Benzopyrone, a privileged scaffold in drug discovery: an overview of FDA-approved drugs and clinical candidates. *Med. Chem. Res.* **2024**, *44*, 2035–2077.
13. Hussain, M. K.; Khatoon, S.; Khan, M. F.; Akhtar, M. S.; Ahamad, S.; Saquib, M. Coumarins as versatile therapeutic phytomolecules: a systematic review. *Phytomedicine* **2024**, *134*, 155972.
14. Zeki, N. M.; Mustafa, Y. F. 6,7-Coumarin-heterocyclic hybrids: A comprehensive review of their natural sources, synthetic approaches, and bioactivity. *J. Mol. Struct.* **2024**, *1303*, 137601.
15. Aqib, M.; Khatoon, S.; Ali, M.; Sajid, S.; Assiri, M. A.; Ahamad, S.; Saquib, M.; Hussain, M. K. Exploring the anticancer potential and mechanisms of action of natural coumarins and isocoumarins. *Eur. J. of Med. Chem.* **2025**, *282*, 117088.
16. Tariq, H.; Khan, S.; Miyan, K.; Qidwai, S. N.; Ahamad, S.; Saquib, M.; Hussain, M. K. Exploring natural coumarins in antiprotozoal drug discovery: a comprehensive review. *Chem. Biodiv.* **2025**, *22*, e01964.
17. Liu, W.; Wu, L.; Liu, W.; Tian, L.; Chen, H.; Wu, Z.; Wang, N.; Liu, X.; Qiu, J.; Feng, X.; Xu, Z.; Jiang, X.; Zhao, Q. Design, synthesis and biological evaluation of novel coumarin derivatives as multifunctional ligands for the treatment of Alzheimer's disease. *Eur. J. Med. Chem.* **2022**, *242*, 114689.
18. T.; Dang, W.; Zhou, Y.; Zhou, D.; Meng, Q.; Xu, L.; Chen, G.; Lin, B.; Qing, D.; Sun, Y.; Hou, Y.; Li, N. Sesquiterpene coumarins isolated from *Ferula bungeana* and their anti-neuroinflammatory activities. *Bioorg. Chem.* **2022,** *128*, 106102.
19. Zhang, Y.; Xu, Z.; Dou, M.; Xu, Y.; Fu, X.; Zhu, F.; Ye, H.; Zhang, J.; Feng, G. Design, synthesis, and bioactivity of novel coumarin-3-carboxylic acid derivatives containing a thioether quinoline moiety. *ACS Omega* **2024**, *9*, 50695–50704.
20. Szwaczko, K.; Strzyga-Łach, P.; Struga, M.; Kiernozek-Kalińska, E.; Szafrański, K.; Skiba, A.; Płazińska, A.; Skalicka-Woźniak, K.; Bielenica, A. Design, synthesis, structure–activity relationships, and preliminary anticancer properties of menthol-modified coumarin esters and 3,4-dihydrocoumarin derivatives. *ACS Omega*, **2025**, *10*, 46418–46434.
21. Tataringa, G.; Tuchilus, C.; Ahmed, M.; Ahmed, S.; Bhat, A. R.; Ben Hadda, T.; Zbancioc, A.-M.; Fahelelbom, K. M. Discovery of new molecular hybrid derivatives with coumarin scaffold bearing pyrazole/oxadiazole moieties: Molecular docking, POM analyses, in silico pharmacokinetics and in vitro antimicrobial evaluation with identification of potent antitumor pharmacophore sites. *Bioorg. Chem.* **2024**, 153, 107761.
22. Mortel, S. L. R.; Macalino, S. J. Y.; Wang, M.; Tie, J.-K. In silico and in vitro studies of potential novel vitamin K epoxide reductase (VKOR) inhibitors suggest an updated structure–activity relationship. *ACS Omega* **2025**, *10*, 26694–26704.
23. Zhao, Y.; Peng, Z.; Wang, G. Design, synthesis, kinetic analysis, molecular docking, and mechanistic studies of novel coumarin-oxadiazole derivatives as α-glucosidase and PTP1B inhibitors. *Bioorg. Med. Chem.* **2025**, *129*, 118321.
24. Khanna, A.; Narang, A.; Thakur, V.; Singh, K.; Kumar, N.; Kaur, R.; Megha; Raj, A.; Devi, M.; Jyoti; Rana, R.; Sharma, A.; Kaur, H.; Singh, P.; Kaur, S.; Bedi, P. M. S. Design, synthesis, antibacterial evaluation, and molecular modelling studies of 1,2,3-triazole-linked coumarin-vanillin hybrids as potential DNA gyrase and topoisomerase IV inhibitors. *Bioorg. Chem.* **2025**, *164*, 108815.
25. Zakaria, B. S.; Ewes, W. A.; El-Messery, S. M.; E.Goda, F. Synthesis and antiviral activity of new 4-substituted oxycoumarins against SARS and HSV-2 viruses: mechanistic and molecular modeling study. *Bioorg. Chem.* **2025**, *164*, 108845.
26. Beinema, M.; Brouwers, J. R.; Schalekamp, T.; Wilffert, B. Pharmacogenetic differences between warfarin, acenocoumarol and phenprocoumon. *Thromb. Haemost.* **2008**, *100* (6), 1052–1057.
27. Winter, Y.; Dodel, R.; Korchounov, A.; Grond, M.; Oertel, W. H.; Back, T. Clinical and pharmacological properties of new oral anticoagulants for the prevention of cerebral thromboembolism: Factor Xa and thrombin inhibitors. *World J. Neurosci.* **2012**, *2*, 7–14.
28. Pattanayak, S.; Bose, P. Herniarin, a natural coumarin, inhibits mammary carcinogenesis by modulating liver X receptor-α/β-PI3K-Akt-Maf1 Pathway in sprague-dawley rats. *Pharmacogn. Mag.* **2019**, *15*, 510.

29. D. Hadjipavlou-Litina, E. B. S, M. Militsopoulou, C. M. Athanassopoulos and D. Papaioannou, Hadjipavlou-Litina, D.; S, E. B.; Militsopoulou, M.; Athanassopoulos, C. M.; Papaioannou, D. Trioxsalen derivatives with lipoxygenase inhibitory activity. *J. Enzyme Inhib. Med. Chem.* **2009**, *24*, 1351–1356.
30. Weng, M.; Deng, Z.; Huang, S.; Lin, X.; Xu, N.; Sun, X.; Wu, W.; Lu, J.; Wang, D. Fraxetin inhibits proliferation and induces apoptosis of bladder cancer through the Akt pathway in vitro and in vivo. *J. Biochem. Mol. Toxicol.* **2024**, *38*, e23556.
31. Qu, L.; Lin, P.; Lin, M.; Ye, S.; Papa Akuetteh, P. D.; Zhou Y. Fraxetin Inhibits the Proliferation and Metastasis of Glioma Cells by Inactivating JAK2/STAT3 Signaling. *Evidence-Based Comple. Altern. Med.* **2021**, *2021*, 5540139.
32. Cui, D.; Zhang, L.; Zhang, J.; Li, W.; Chen, J.; Guo, Z.; Sun, C.; Wang, Y.; Wang, W.; Li, S.; Huang, W.; Zheng, C.; Chen, R. Hybrid local and charge-transfer material with ultralong room temperature phosphorescence for efficient organic afterglow Light-Emitting Diodes. *Angew. Chem. Int. Ed.* **2024,** *63*, e202411588.
33. Ueda, M.; Uehara, A.; Usui, K.; Hasegawa, M. A folded mechanochromic organic fluorophore based on thianthrene-fused coumarin. *Chem. Commun.* **2026**, *62*, 2208–2211.
34. Zhang, X.; Jiang, Y.; Wang, Y.; Li, Y.; Tang, H.; Shao, A.; Ni, J. Fluorescence monitoring of STING using a coumarin-based chemigenetic probe. *New J. Chem.* **2026**, *50*, 537–543.
35. Jiang, L.; Tang, L.; Mei, T.; Xiao, M.; Xiang, K.; Zhou, W.; Cai, Y.; Fan, M.; Jia, T.; Tao, Q.; Ye, L.; Bi, Z.; Zhou, C.; Wang, X.; Chen, J.; Lu, G.; Liu, Y.; Yang, R.; Su, W.; Ma, W.; Fan, Q. Coumarin-based volatile and non-volatile solid additives enable organic solar cells with 20.32% efficiency. *Angew. Chem. Int. Ed.* **2026**, *65*, e24002.
36. Kouznetsov, V. V.; Puerto-Galvis, C. E.; Villamizar, M. C. O.; Vargas-Mendez, L. Y. Insights into the metal-catalyzed alkyne hydroarylation reactions and related processes for the synthesis of coumarins. *Curr. Org. Chem.* **2017**, *21*, 949–963.
37. Lončarić, M.; Gašo-Sokač, D.; Jokić, S.; Molnar, M. Recent advances in the synthesis of coumarin derivatives from different starting materials. *Biomolecules* **2020**, *10*, 151.
38. Moghadam Farid, S.; Seifinoferest, B.; Gholamhosseyni, M.; Larijani, B.; Mahdavi, M. Modern metal-catalyzed and organocatalytic methods for synthesis of coumarin derivatives: a review. *Org. Biomol. Chem.* **2022**, *20*, 4846–4883.
39. Pitaro, M.; Croce, N.; Gallo, V.; Arienzo, A.; Salvatore, G.; Antonini, G. Coumarin-induced hepatotoxicity: a narrative review. *Molecules* **2022**, *27*, 9063.
40. Sharma, D.; Dhayalan, V.; Chatterjee, R.; Khatravath, M.; Dandela, R. Recent advances in the synthesis of coumarin and its derivatives by using aryl propiolates. *ChemistrySelect* **2022**, 7, e202104299.
41. Patra, S.; Patra, P.; Rout, D.; Adikari, S.; Mahanty, D. S. A short review on the synthesis of oxazolo/thiazolo/imidazolocoumarins and their biological activities. *Synth. Commun.* **2023**, 1–23.
42. Habibi, W.; Talbi, S.; Hamri, S.; Hafid, A.; Khouili, M. Coumarin derivatives: microwave synthesis and biological properties—a review. *J. Heterocycl. Chem.* **2024**, *61*, 2070–2096.
43. Firoz, H.; Ali, R.; Khan, F. A.; Kakkar, P.; Soni, R. K.; Assiri, M. A.; Ahamad, S.; Saquib, M.; Hussain, M. K. Coumarins as versatile scaffolds: innovative synthetic strategies for generating diverse heterocyclic libraries in drug discovery. *J. Mol. Struct.* **2026**, *1352*, 144426.
44. Abdel-Aziem, A.; Elsharabasy, S. A.; Sayed, M. T. Synthesis, reactions, and biological evaluation potential of coumarin derivatives: review. *J. Heterocycl. Chem.* **2026**, *63*, 169–194.
45. Nasab, N. H.; Azimian, F.; Kruger, H. G.; Kim, S. J. Acetylcoumarin in cyclic and heterocyclic-containing coumarins: synthesis and biological applications. *Tetrahedron* **2022**, *129*, 133158.
46. Hooshmand, S. E.; Alavioon, S. I.; Saeb, M.; Brahmachari, G.; Shiri, M. Decarboxylation and cross-coupling reactions of coumarin-3-carboxylic acid: a comprehensive review. *Tetrahedron* **2024**, *167*, 134238.
47. Langer, P. Adventures in coumarin chemistry. *Synlett* **2025**, *36*, 29–43.
48. Zuo, X.; Chen, S.; Xu, S.-W.; Chang, S.-Q.; Liu, X.-L.; Zhou, Y.; Yuan, W.-C. Highly efficient, catalyst-free, diastereoselective, diversity-oriented synthesis of dihydrocoumarin–pyrrolidine–spirooxindoles bearing three contiguous stereocenters. *Synthesis*, **2019**, *51*, 2339–2350.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 March 2026 doi:10.20944/preprints202603.0943.v1

49. Huang, Q.; Fu, J.; Chang, Z.; Gan, W.; YongjiangWang; Han, X. Diversity-oriented synthesis of coumarin-fused cyclopentanones via a nucleophilic phosphine controlled cascade reaction. *Synlett* **2022**, *33*, 1282–1286.
50. Dey, S.; Das, A.; Yadav, R. N.; Boruah, P. J.; Sarkar, K.; Paul, A.; Hossain, M. F. Electron donor-acceptor complex enabled photocascade strategy for synthesis of trans-dihydrofuro [3,2-c]chromen-4-one scaffolds via radical conjugate addition of pyridinium ylide. *Chem. Commun.* **2024**, *60*, 14384–14387.
51. Chandrasekar, L.; Yun-Zhen, H.; Hao-Tse, C.; Yu-Chen, H.; Liu, W.-M. Synthesis of alkynyl cyclopropa[c]coumarins via propargyl sulfonium salts as C1 synthon. *Org. Biomol. Chem.* **2024**, *22*, 9219–9230.
52. Li, Y.-J.; Wu, Z.-L.; Gu, Q.-S.; Fan, T.; Duan, M.-H.; Wu, L.; Wang, Y.-T.; Wu, J.-P.; Fu, F.-L.; Sang, F.; Peng, A.-T.; Jiang, Y.; Liu, X.-Y.; Lin, J.-S. Catalytic intermolecular asymmetric [2π+2σ] cycloadditions of bicyclo [1.1.0]butanes: practical synthesis of enantioenriched highly substituted bicyclo [2.1.1]hexanes. *J. Am. Chem. Soc.* **2024**, *146*, 34427–34441.
53. Voloshkin, V. A.; Villa, M.; Martynova, E. A.; Beliš, M.; Van Hecke, K.; Ceroni, P.; Nolan, S. P. Synthesis of cyclobutane-fused chromanones via gold-mediated photocatalysis. *Chem. Sci.* **2024**, *15*, 4571–4580.
54. Yi, Z.-Q.; Zhang, W.; Yi, B.; Liu, C.; Xie, Y.; Li, M.; Xiong, Y.; Wu, W.; Tan, J.-P. Stereoselective synthesis of biology-oriented pentacyclic pyrrolo [2,1-a]isoquinoline scaffolds by photoredox-induced radical annulations. *Org. Lett.* **2025**, *27*, 2197–2202.
55. Long, C.-H.; Zuo, Y.-P.; Kong, C.-C.; Cai, Z.-N.; Qin, H.-B., Visible-light-driven [2+2] cycloaddition of coumarins with diverse olefins using a 4CzIPN photosensitizer: application to the total synthesis of (±)-lindleyanin. *Org. Lett.* **2025**, *27*, 11038–11044.
56. Nachimuthu, K.; Nallasivam, J. L. Palladium-catalyzed formal [3+2] cycloadditions to access spirocyclopentane-2-oxindole fused chromanones, quinolinones, and thiochromones. *Chem. Asian J.* **2025**, *20*, e00550.
57. Xiang, M.; Liu, G.-Y.; Liu, H.-M.; Zhou, W.-Y.; Wang, G.; Fei, F.; Jia, Y.-Q.; Shen, L.-W. The [4+2] annulation of *o*-acylamino-aryl MBH carbonates with coumarins: facile access to tetrahydrochromeno [4,3-b]quinolin-6-ones. *New J. Chem.* **2025**, *49*, 683–686.
58. Kumari, P.; Tiwari, G.; Narayana, C.; Sagar, R. Stereoselective and regioselective synthesis of chiral dihydrofurocoumarins as glycohybrids. *Org. Lett.* **2025**, *27*, 12363–12367.
59. Alizadeh, A.; Hasanpour, H. The sequential one-pot reaction of isatylidene malononitriles and 4-hydrazinocoumarin: metal catalyst-free and efficient access to coumarin-fused spiro[diazepin-5,3′-oxindole]. *Synthesis* **2026**, in press.
60. Li, N.-B.; Liu, Y.-C.; Liu, L.-H.; Wei, W.-Y.; Zhang, D.; He, W.-M.; Jia, H.-Y.; Bian, W. Visible-light-induced annulation of 4-aminocoumarins to tetrahydropyrimidine-fused coumarins and evaluation of their antitumor activities. *Green Chem.* **2026**, *28*, 1601–1606.
61. Tripathi, K. N.; Singh, S.; Akhtar, N.; Manna, K.; Singh, R. P. Visible-light-driven site-selective alkylation of the benzo core of coumarins. *Chem. Commun*. **2022**, *58*, 9674–9677.
62. Singh, S.; Tripathi, K. N.; Singh, R. P. Redox activated amines in the organophotoinduced alkylation of coumarins. *Org. Biomol. Chem*. **2022**, *20*, 5716–5720.
63. Sun, B.; Wang, Y.; Wang, J.; Chen, M.; Zhong, Z.; Wang, J.; Jin, C. Photoredox-catalyzed redox-neutral decarboxylative C-H acylations of coumarins with alpha-keto acid. *Org. Lett.* **2023**, *25*, 2466–2470.
64. Patra, J.; Nair, A. M.; Volla, C. M. R. Expedient radical phosphonylations via ligand to metal charge transfer on bismuth. *Chem. Sci.* **2024**, *15*, 7136–7143.
65. Mritunjay; Sharma, S.; Singh, P.; Gupta, A.; Singh, V.; Singh, L.; Kumar, A. DBU-catalyzed vinylogous reaction of 3-cyano-4-methylcoumarins with 3-arylsulfonyl-3-indolyloxindoles. *ChemistrySelect* **2024**, *9*, e202402133.
66. Sharma, P.; Singh, T.; Rawat, N.; Singh, A. Visible-light-mediated, LMCT-enabled C(sp3)-H Bond alkylation of alkanes and silanes via C-4 functionalization of coumarins. *J. Org. Chem.* **2025**, *90*, 5574–5577.
67. Rawat, N.; Sharma, P.; Nasireddy, S. R.; Vilas, A.; Singh, A. Organophotocatalyzed radical hydrophosphonylation of acrylates, *α,β*-unsaturated ketones, coumarins, quinoxalinones, and *p*-quinone methides. *J. Org. Chem.* **2025**, *90*, 8703–8711.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 12 March 2026 doi:10.20944/preprints202603.0943.v1

68. Topolska, A.; Przydacz, A.; Sieroń, L.; Skrzyńska, A.; Fraile, A.; Alemán, J.; Albrecht, Ł. Aminocatalytic 1,6-addition of 2-benzyl-3-furaldehyde to 3-cyano-4-styrylcoumarins: a dearomative approach for the synthesis of furan–coumarin hybrids. *J. Org. Chem.* **2025**, *90*, 14931–14942.
69. Romaniszyn, M.; Gronowska, K.; Albrecht, Ł., Remote functionalization of 4-(alk-1-en-1-yl)-3-cyanocoumarins via the asymmetric organocatalytic 1,6-addition. *Adv. Synth. Catal.* **2021**, *363*, 5116–5121.
70. Jia, L.; Zhang, Z. Ru(II)-catalyzed C-H alkylation of indoles at the C-3 position with coumarin-3-carboxylic acids. *ChemistrySelect*. **2025**, *10*, e00281.
71. Hsu, C.-W.; Chen, Y.-J.; Huang, X.-R.; Shi, C.-J.; Lin, T.-I.; Yen, T.-C.; Nagare, Y. K.; Marri, G.; Chen, Y.-R.; Lin, W. Regiodivergent synthesis utilizing alkyl hex-5-en-2-ynoates and 3-homoacyl coumarins: phenol-mediated controllable phosphine-catalyzed michael and 1,7-umpolung addition. *Org. Lett.* **2025**, *27*, 12385–12390.
72. 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.
73. Panda, S. S.; Jones, R. A.; Bachawala, P.; Mohapatra, P. P. Spirooxindoles as potential pharmacophores. *Mini-Rev. Med. Chem.* **2017**, *17*, 1515–1536.
74. Bariwal, J.; Voskressensky, L. G.; Van der Eycken, E. V. Recent advances in spirocyclization of indole derivatives. *Chem. Soc. Rev.* **2018**, *47*, 3831–3848.
75. Deepthi, A.; Thomas, N. V.; Sathi, V. Green protocols for the synthesis of 3,3'-spirooxindoles – 2016- mid 2019. *Curr. Green Chem.* **2019**, *6*, 210–225.
76. Lin, Y.; Du, D. Recent advances in squaramide-catalyzed asymmetric cascade reactions for the synthesis of spirooxindoles. *Chin. J. Org. Chem.* **2020**, *40*, 3214–3236 (in Chinese).
77. Saeed, R.; Sakla, A. P.; Shankaraiah, N. An update on the progress of cycloaddition reactions of 3-methyleneindolinones in the past decade: versatile approaches to spirooxindoles. *Org. Biomol. Chem.* **2021**, *19*, 7768–7791.
78. Wang, Y.; Cobo, A. A.; Franz, A. K. Recent advances in organocatalytic asymmetric multicomponent cascade reactions for enantioselective synthesis of spirooxindoles. *Org. Chem. Front.* **2021**, *8*, 4315–4348.
79. Ganesh, M.; Suraj, S. Expeditious entry into carbocyclic and heterocyclic spirooxindoles. *Org. Biomol. Chem.* **2022**, *20*, 5651–5693.
80. Jana, M.; Mal, S. Recent update on synthesis of spiro-heterocycles in alcohol using malononitrile as a building block. *Arkivoc* **2022**, *2022*, 361–385.
81. Panda, S. S.; Aziz, M. N.; Stawinski, J.; Girgis, A. S. Azomethine ylides—versatile synthons for pyrrolidinyl-heterocyclic compounds. *Molecules* **2023**, *28*, 618.
82. Liandi, A. R.; Cahyana, A. H.; Alfariza, D. N.; Nuraini, R.; Sari, R. W.; Wendari, T. P. Spirooxindoles: recent report of green synthesis approach. *Green Synth. Catal.* **2023**, *5*, 1–13.
83. Asif, M.; Azaz, T.; Tiwari, B.; Nasibullah, M. Propagative isatin in organic synthesis of spirooxindoles through catalysis. *Tetrahedron* **2023**, *134*, 133308.
84. Pan, Y.-M.; He, M.-X.; Wang, Q.; Liu, H.-F.; Ren, S.-Y., Research advances in electrochemical synthesis of spirocyclic skeleton compounds. *Synthesis* **2023**, *55*, 2873–2895.
85. Borah, B.; Veeranagaiah, N. S.; Sharma, S.; Patat, M.; Prasad, M. S.; Pallepogu, R.; Chowhan, L. R. Stereoselective synthesis of CF_3-containing spirocyclic-oxindoles using *N*-2,2,2-trifluoroethylisatin ketimines: an update. *RSC Adv.* **2023**, *13*, 7063–7075.
86. Helal, M. H.; Owda, M. E.; Mogharbel, A. T.; Hamzah Alessa, A.; Omer, N.; Abdelaziz, M. A.; Ibrahim, I.; Eliwa, E. M. C3-Spirooxindoles: divergent chemical synthesis and bioactivities (2018–2023). *Bioorg. Chem.* **2024**, *143*, 107091.
87. Borah, B.; Patat, M.; Chowhan, L. R. Organocatalytic enantioselective assembly of dispiro-bisoxindoles with vicinal stereocenters. *Org. Biomol. Chem.* **2024**, *22*, 8365–8373.
88. Feng, J.; Wang, Y.; Li, E. Q.; Loh, T. P. Recent developments in copper-catalyzed annulations for synthesis of spirooxindoles. *Chem. Rec.* **2024**, *24*, e202400126.
89. Spirooxindole: chemistry, synthesis, characterization and biological significance, eds. Patel, G.; Shah, V. R.; Nguyen, T. A.; Deshmukh, K. Elsevier, **2024**.

90. Zhao, K.; Zhai, M.; Zhang, L.; Meng, X. Recent advances in the reaction of isatin-derived MBH carbonates, synthesis of spiro-oxindoles. *Org. Biomol. Chem.* **2025**, *23*, 1292–1308.
91. Hari, D. P.; Singha, T. Visible-light-mediated strain-release radical spirocyclizations: access to functionalized spirocyclobutanes. *Synlett* **2025**, *36*, 445–451.
92. Liu, Y.-Q.; Wu, Y.; Li, B.; Tang, X.; Chen, C. Recent advances in the organocatalytic synthesis of chiral C3-spiro-cyclopentaneoxindoles. *Org. Biomol. Chem.* **2025**, *23*, 757–773.
93. Fatima, H. N.; Ahmad, M.; Nazir, M. S.; Akram, S.; Aslam, S. Recent synthetic methodologies for pyrrolidine derivatives through multicomponent reactions. *Synth. Commun.* **2025**, *55*, 1201–1227.
94. Padavi, S. K.; Vasave, S. P.; Patil, D. B. Eco-friendly strategies for synthesizing spirooxindoles and pyranopyrazoles: a comprehensive review. *ChemistrySelect* **2026**, *11*, e04793.
95. Chen, R.; Zhang, L.; Zhao, X.; Fang, Z.; Zhang, L.; Zhang, Q.; Zhang, C.; Zhu, Y. Discovery, bioactivities and biosynthesis of spirooxindole alkaloids. *Nat. Prod. Rep.* **2026**, in press.
96. Kaur, A.; Singh, B.; Vyas, B.; Silakari, O. Synthesis and biological activity of 4-aryl-3-benzoyl-5-phenylspiro[pyrrolidine-2.3′-indolin]-2′-one derivatives as novel potent inhibitors of advanced glycation end product. *Eur. J. Med. Chem.* **2014**, *79*, 282–289.
97. Teja, C.; Babu, S. N.; Noor, A.; Daniel, J. A.; Devi, S. A.; Nawaz Khan, F. R. Cu/TEMPO catalyzed dehydrogenative 1,3-dipolar cycloaddition in the synthesis of spirooxindoles as potential antidiabetic agents. *RSC Adv.* **2020**, *10*, 12262–12271.
98. Yang, C.; Fang, Y.; Luo, X.; Teng, D.; Liu, Z.; Zhou, Y.; Liao, G. Discovery of natural product-like spirooxindole derivatives as highly potent and selective LSD1/KDM1A inhibitors for AML treatment. *Bioorg. Chem.* **2022**, *120*, 105596.
99. Lotfy, G.; Said, M. M.; El Ashry, E. S. H.; El Tamany, E. S. H.; Al-Dhfyan, A.; Abdel Aziz, Y. M.; Barakat, A. Synthesis of new spirooxindole-pyrrolothiazole derivatives: Anti-cancer activity and molecular docking. *Bioorg. Med. Chem.* **2017**, *25*, 1514–1523.
100. Liu, D.; Xu, H. C. Electrochemical rearrangement of indoles to spirooxindoles in continuous flow. *Eur. J. Org. Chem.* **2022**, *26*, e202200987.
101. Liu, J.; Mallick, S.; Xie, Y.; Grassin, C.; Lucas, B.; Scholermann, B.; Pahl, A.; Scheel, R.; Strohmann, C.; Protzel, C.; Berg, T.; Merten, C.; Ziegler, S.; Waldmann, H. Morphological profiling identifies the motor protein Eg5 as cellular target of spirooxindoles. *Angew. Chem. Int. Ed.* **2023**, *62*, e202301955.
102. Wang, Y.; Tian, X.; Zhang, Y.; Ren, W. Synthesis of functionalized 3,2′-pyrrolidinyl spirooxindoles via domino 1,6-addition/annulation reactions of *para*-quinone methides and 3-chlorooxindoles. *Org. Chem. Front.* **2022**, *9*, 615–626.
103. Li, T.-H.; Du, D.-M. Asymmetric synthesis of isoxazole and trifluoromethyl-containing 3,2′-pyrrolidinyl dispirooxindoles via squaramide-catalysed [3+2] cycloaddition reactions. *Org. Biomol. Chem.* **2022**, *20*, 817–823.
104. Li, X.-T.; Tian, H.-Z.; Sun, X.-W. Organocatalytic aza-Michael/Mannich cascade reaction: synthesis of enantioenriched 3,3′-spirooxindole γ-lactams. *J. Org. Chem.* **2023**, *88*, 7839–7843.
105. Leena, S. S.; Akhir, A.; Saxena, D.; Maitra, R.; Chopra, S.; Deepthi, A. Synthesis of tryptanthrin appended dispiropyrrolidine oxindoles and their antibacterial evaluation. *RSC Med. Chem.* **2023**, *14*, 1165–1171.
106. He, J.; Mei, H.; Escorihuela, J.; Han, J. Electrochemical multicomponent cascade radical process enabling synthesis of iodomethyl spiropyrrolidinyl-oxindoles. *Chin. J. Chem.* **2024**, *42*, 1691–1698.
107. Jia, B.; Sun, Z.; Miao, X.; Ma, S.; Dong, Y.; Dang, G.; Zhang, X.; Ma, Y., Copper-catalyzed enantioselective synthesis of spirohydroindoles by ethoxyformylmethylene oxindole and iminoester 1,3-dipole cycloaddition: an examination of associated biological activities. *ACS Omega* **2024**, *9*, 24406–24414.
108. Wei, F.; Zhang, Y. Palladium-catalyzed cascade distal C–H methylation and cyclization for the construction of spirooxindole skeletons. *Org. Lett.* **2024**, *26*, 9221–9226.
109. Li, C.; Wang, Y.; Hu, D.; Zhang, B.; Yin, H.; Li, Y.-L. A Base promoted [3+2] cycloaddition of benzothiazolium salts with isoindigos to synthesis *N*, *S*-polyheterocyclic 3, 3′-bispirooxindoles. *Asian J. Org. Chem.* **2024**, *13*, e202400478.

110. Kanchrana, M.; Krishna, G. R.; Dey, B.; Pandey, N.; Guru, S. K.; Sangolkar, A. A.; Pawar, R.; Basavoju, S. Ionic liquid assisted green synthesis of quinoxaline based bisspirooxindoles: anticancer evaluation and molecular dynamics. *ChemistrySelect* **2024**, *9*, e202403608.
111. Nichinde, C.; Bhati, M.; Girase, A.; Patil, B.; Chaudhari, S.; Gamidi, R. K.; Joshi, K.; Kinage, A. K. A sequential nitro-Michael addition and reductive cyclization cascade reaction for diastereoselective synthesis of multifunctionalized 3,3′-pyrrolidinyl-spirooxindoles. *Eur. J. Org. Chem.* **2024**, e202401121.
112. Tan, H.; Xiang, Y.; Huang, J.; Ren, S.; Lin, C.; Xu, Z.; Tang, D.; Chen, Z. Microwave-assisted synthesis of pyrrolidinyl-spirooxindoles via tandem 1,3-dipolar cycloaddition and oxidative dehydrogenation. *Tetrahedron* **2025**, *169*, 134379.
113. Bharani, S.; Ananda Rao, B.; Chowhan, L. R.; Pallepogu, R.; Prasad, M. S. Asymmetric synthesis of spiro[benzofuran-pyrrolidine]-indolinedione via bifunctional urea catalyzed [3 + 2]-annulation *Org. Biomol. Chem.* **2025**, *23*, 914–919.
114. Wang, Y.; Zheng, L.; Zi, R.; Niu, Y.; Yang, S.; Hu, D.; Dong, J.-W., Diastereoselective Three-Component 1,3-Dipolar Cycloaddition: Concise Synthesis of Functionalized Tetrahydrocarboline-fused Spirooxindoles, *Org. Biomol. Chem.*, **2025**, *23*, 2941–2953.
115. Lu, X.; Huang, A.; Jia, A.; Tang, S. Synthesis of 3,2′-pyrrolidinyl spirooxindole derivative via 2,3-rearrangement of ammonium ylide. *J. Org. Chem.* **2025**, *90*, 4216–4224.
116. Indira, M.; Reddy, P. V. G. Efficient synthesis of spirooxindole-pyrrolo [1,2-a]pyrazin-2-ones via ionic liquid-ultrasonication. *ChemistrySelect* **2025**, *10*, e202405095;
117. Pronina, Y.; Filatov, A.; Shmakov, S.; Selivanov, S.; Kryukova, M.; Spiridonova, D.; Ponyaev, A.; Stepakov, A.; Boitsov, V. Highly efficient synthesis of spiro [1-azabicyclo [3.2.0]heptane] frameworks via [3+2]-cycloaddition. *J. Org. Chem.* **2025**, *90*, 4926–4945.
118. Lavanya, M.; Sundararaj, R.; Mani, K. S.; Balu, K.; Durai, M.; Alam, P.; Sd, P.; Durai, M.; Ahn, Y. H. Computational design, synthesis, and biological assessment of some pyrrolo [3,4-c]pyrroles targeting mycobacterium tuberculosis. *ChemistrySelect* **2025**, *10*, e202405796.
119. Al-Jassas, R. M.; Islam, M. S.; Al-Majid, A. M.; Haukka, M.; Nafie, M. S.; Abu-Serie, M. M.; Teleb, M.; Shaaban, M. M.; Alayyaf, A. M. A.; Domingo, L. R.; Ashraf, S.; Ul-Haq, Z.; Abdel Aziz, Y. M.; Barakat, A. Marine-inspired spirooxindole PIM-1 kinase inhibitors endowed with concomitant TRKA/CDK2 inhibition for multifaceted NSCLC apoptotic induction. *ChemMedChem* **2025**, *20*, e202500028.
120. Hazra, A.; Maity, D.; Bhosale, S. S.; Hajra, S. Asymmetric synthesis of 3,3′-pyrrolidonyl spirooxindole-5′-carboxylic ester from l-tryptophan. *Synthesis* **2025**, *57*, 488–494.
121. Tan, H.; Xiang, Y.; Huang, J.; Ren, S.; Lin, C.; Xu, Z.; Tang, D.; Chen, Z. Microwave-assisted synthesis of pyrrolidinyl-spirooxindoles via tandem 1,3-dipolar cycloaddition and oxidative dehydrogenation. *Tetrahedron* **2025**, *169*, 134379.
122. Xuan, T.; Wang, X.; Wang, Y. Asymmetric [3+2] cycloannulation of benzoxazinones for the synthesis of imidazo [5,1-c]oxazinones *Org. Lett.* **2025**, *27*, 3134–3138.
123. Gao, H.; Yang, X.; Shi, L. Asymmetric oxidative rearrangement of indoles enabled by dual catalysis with in situ generated acyl hypoiodite and chiral phosphoric acid. *Org. Chem. Front.* **2025**, *12*, 3848–3855.
124. Zimnitskiy, N. S.; Korotaev, V. Y.; Ulitko, M. V.; Sosnovskikh, V. Y. 1-Styryl-1,3-diketones in the synthesis of spiro[oxindole-3,2′-pyrrolidines] with notable anticancer activity. *Mol. Diver.* **2025**, *29*, 5979–5992.
125. Cao, X.; Tao, P.; Yu, S.; Yang, S.; Li, S.-W. Asymmetric Michael-Mannich cascade reaction of azomethine ylides with isatin-derived trifluoromethyl acrylates catalyzed by a Cu(I) catalyst. *Org. Chem. Front.* **2026**, in press.
126. Lashgari, N.; Ziarani, G. M. Synthesis of heterocyclic compounds based on isatin through 1,3-dipolar cycloaddition reactions. *Arkivoc*. **2012**, *i*, 277–320.
127. Fokas, D.; Ryan, W. J.; Casebier, D. S.; Coffen, D. L. Solution-phase synthesis of a spiro[pyrrolidine-2,3′-oxindole] library via a three component 1,3-dipolar cycloaddition reaction. *Tetrahedron Lett.* **1998**, *39*, 2235–2238.
128. Shanmugam, P.; Viswambharan, B.; Madhavan, S. Synthesis of novel functionalized 3-spiropyrrolizidine and 3-spiropyrrolidine oxindoles from Baylis-Hillman adducts of isatin and heteroaldehydes with azomethine ylides via [3+2]-cycloaddition. *Org. Lett.* **2007**, *9*, 4095–4098.

 doi:10.20944/preprints202603.0943.v1

129. Mehrdad, M.; Faraji, L.; Jadidi, K.; Eslami, P.; Sureni, H. A regioselective and diastereoselective synthesis of new spiro-isoxazolidines via 1,3-dipolar cycloaddition of stable isatin ketonitrone and various dipolarophiles. *Monatsh. Chem.* **2011**, *142*, 917–921.
130. Liu, J.; Sun, H.; Liu, X.; Ouyang, L.; Kang, T.; Xie, Y.; Wang, X. Direct construction of novel *exo*′-selective spiropyrrolidine bisoxindoles via a three-component 1,3-dipolar cycloaddition reaction. *Tetrahedron Lett.* **2012**, *53*, 2336–2340.
131. Xiao, J.-A.; Liu, Q.; Ren, J.-W.; Liu, J.; Carter, R. G.; Chen, X.-Q.; Yang, H. Highly enantioselective construction of polycyclic spirooxindoles by organocatalytic 1,3-dipolar cycloaddition of 2-cyclohexenone catalyzed by proline-sulfonamide. *Eur. J. Org. Chem.* **2014**, *2014*, 5700–5704.
132. Revathy, K.; Lalitha, A. An efficient green chemistry protocol for the synthesis of novel spiropyrrolizidine compounds. *RSC Adv.* **2014**, *4*, 279–285.
133. Pavlovskaya, T. L.; Yaremenko, F. G.; Lipson, V. V.; Shishkina, S. V.; Shishkin, O. V.; Musatov, V. I.; Karpenko, A. S. The regioselective synthesis of spirooxindolo pyrrolidines and pyrrolizidines via three-component reactions of acrylamides and aroylacrylic acids with isatins and alpha-amino acids. *Beilstein J. Org. Chem.* **2014**, *10*, 117–126.
134. Dai, W.; Jiang, X.-L.; Wu, Q.; Shi, F.; Tu, S.-J. Diastereo- and enantioselective construction of 3,3′-pyrrolidinyldispirooxindole framework via catalytic asymmetric 1,3-dipolar cycloadditions. *J. Org. Chem.* **2015**, *80*, 5737–5744.
135. Haddad, S.; Boudriga, S.; Akhaja, T. N.; Raval, J. P.; Porzio, F.; Soldera, A.; Askri, M.; Knorr, M.; Rousselin, Y.; Kubicki, M. M.; Rajani, D. A strategic approach to the synthesis of functionalized spirooxindole pyrrolidine derivatives: in vitro antibacterial, antifungal, antimalarial and antitubercular studies. *New J. Chem.* **2015**, *39*, 520–528.
136. Uma Rani, G.; Vivek Kumar, S.; Bharkavi, C.; Menéndez, J. C.; Perumal, S. One-pot access to a library of dispiro oxindole-pyrrolidine/pyrrolothiazole-thiochromane hybrids via three-component 1,3-dipolar cycloaddition reactions. *ACS Comb. Sci.* **2016**, *18*, 337–342.
137. Du, Y.; Yu, A.; Jia, J.; Zhang, Y.; Meng, X. Direct N-H/alpha,alpha,beta,beta-C(sp^3)-H functionalization of piperidine via an azomethine ylide route: synthesis of spirooxindoles bearing 3-substituted oxindoles. *Chem. Commun.* **2017**, *53*, 1684–1687.
138. Lin, W.; Zhan, G.; Shi, M.; Du, W.; Chen, Y. [3 + 3] Formal cycloadditions of nitrones from isatins and azaoxyallyl cations for construction of spirooxindoles. *Chin. J. Chem.* **2017**, *35*, 857–860.
139. Huang, W.-J.; Chen, Q.; Lin, N.; Long, X.-W.; Pan, W.-G.; Xiong, Y.-S.; Weng, J.; Lu, G. Asymmetric synthesis of trifluoromethyl-substituted 3,3′-pyrrolidinyl-dispirooxindoles through organocatalytic 1,3-dipolar cycloaddition reactions. *Org. Chem. Front.* **2017**, *4*, 472–482.
140. Wu, P.; Gao, H.; Sun, J.; Yan, C.-G. 1,3-Dipolar cycloaddition reaction for diastereoselective synthesis of functionalized dihydrospiro[indoline-3,2′-pyrroles]. *Chin. Chem. Lett.* **2017**, *28*, 329–332.
141. Filatov, A. S.; Knyazev, N. A.; Molchanov, A. P.; Panikorovsky, T. L.; Kostikov, R. R.; Larina, A. G.; Boitsov, V. M.; Stepakov, A. V. Synthesis of functionalized 3-spiro[cyclopropa[a]pyrrolizine]- and 3-spiro [3-azabicyclo [3.1.0]hexane]oxindoles from cyclopropenes and azomethine ylides via [3+2]-cycloaddition. *J. Org. Chem.* **2017**, *82*, 959–975.
142. Lin, B.; Zhang, W.-H.; Wang, D.-D.; Gong, Y.; Wei, Q.-D.; Liu, X.-L.; Feng, T.-T.; Zhou, Y.; Yuan, W.-C. 3-Methyl-4-nitro-5-isatylidenyl-isoxazoles as 1,3-dipolarophiles for synthesis of polycyclic 3,3′-pyrrolidinyl-dispirooxindoles and their biological evaluation for anticancer activities. *Tetrahedron* **2017**, *73*, 5176–5188.
143. Yue, G.; Wu, Y.; Dou, Z.; Chen, H.; Yin, Z.; Song, X.; He, C.; Wang, X.; Feng, J.; Zhang, Z.; Zou, P.; Lu, C. Synthesis of spiropyrrolidine oxindoles via Ag-catalyzed stereo- and regioselective 1,3-diploar cycloaddition of indole-based azomethine ylides with chalcones. *New J. Chem.* **2018**, *42*, 20024–20031.
144. Ryu, H.; Seo, J.; Ko, H. M. Synthesis of spiro[oxindole-3,2′-pyrrolidine] derivatives from benzynes and azomethine ylides through 1,3-dipolar cycloaddition reactions. *J. Org. Chem.* **2018**, *83*, 14102–14109.
145. Zhao, H.-W.; Wang, L.-R.; Guo, J.-M.; Ding, W.-Q.; Song, X.-Q.; Wu, H.-H.; Tang, Z.; Fan, X.-Z.; Bi, X.-F. Formal [5+3] cycloaddition of vinylethylene carbonates with isatin-based α-(trifluoromethyl)imines for diastereoselective synthesis of medium-heterocycle-fused spirooxindoles. *Adv. Synth. Catal.* **2019**, *361*, 4761–4771.

146. Wu, W.-T.; Han, Y.; Sun, J.; Yan, C.-G. Efficient construction of pyrrolo [1′,2′:1,2]azocino [4,5-c]quinolines via cascade cycloaddition and annulation reaction. *Org. Chem. Front.* **2019**, *6*, 3530–3534.
147. Niu, B.; Wu, X. Y.; Wei, Y.; Shi, M. Palladium-catalyzed diastereoselective formal [5+3] cycloaddition for the construction of spirooxindoles fused with an eight-membered ring. *Org. Lett.* **2019**, *21*, 4859–4863.
148. Yang, G.; Li, S.; Wang, Q.; Chen, H.; Yang, C.; Yin, Z.; Song, X.; Zhang, L.; Lu, C.; Yue, G. K_2CO_3-Promoted formal [3+3]-cycloaddition of *N*-unsubstituted isatin *N,N′*-cyclic azomethine imine 1,3-dipoles with Knoevenagel adducts. *Molecules* **2023**, *28*, 1034.
149. Wang, X.; Yang, P.; Zhang, Y.; Tang, C.-Z.; Tian, F.; Peng, L.; Wang, L.-X. Isatin *N,N′*-cyclic azomethine imine 1,3-dipole and abnormal [3 + 2]-cycloaddition with maleimide in the presence of 1,4-diazabicyclo [2.2.2]octane. *Org. Lett.*, **2017**, *19*, 646-649.
150. Wang, X.; Wu, L.; Yang, P.; Song, X.-J.; Ren, H.-X.; Peng, L.; Wang, L.-X. Isatin *N,N′*-cyclic azomethine imine 1,3-dipole and base catalyzed Michael addition with *β*-nitrostyrene via C3 umpolung of oxindole. *Org. Lett.* **2017**, *19*, 3051–3054.
151. Jin, Q.; Zhang, J.; Jiang, C.; Zhang, D.; Gao, M.; Hu, S. Self [3+4] cycloadditions of isatin *N,N′*-cyclic azomethine imine 1,3-dipole with *N*-(*o*-chloromethyl)aryl amides. *J. Org. Chem.* **2018**, *83*, 8410–8416.
152. Hu, S.; Zhang, J.; Jin, Q. DMAP-catalyzed alkylation of isatin *N,N′*-cyclic azomethine imine 1,3-dipoles with Morita-Baylis-Hillman carbonates. *New J. Chem.* **2018**, *42*, 7025–7029.
153. Moghaddam, F. M.; Eslami, m.; Siahpoosh, A.; Hoda, G. S. A diastereoselective construction of functionalized dihydro-pyridazine based spirooxindole scaffold via C-3 umpolung of isatin *N,N′*-cyclic azomethine imine. *New J. Chem.* **2019**, *43*, 10318–10323.
154. Wang, Q.-H.; Zhu, Z.-X.; Huang, T.; Wu, M.-S. Base catalyzed unexpected rearrangement of isatin-derived *N,N′*-cyclic azomethine imines and Michael addition to hindered vinylidene bisphosphonates: access to 3,3-disubstituted oxindole-fused pyrazolidin-3-one derivatives containing bisphosphonates. *Tetrahedron* **2019**, *75*, 416–421.
155. Yue, G.; Dou, Z.; Zhou, Z.; Zhang, L.; Feng, J.; Chen, H.; Yin, Z.; Song, X.; Liang, X.; Wang, X.; Rao, H.; Lu, C. Rapid abnormal [3+2]-cycloaddition of isatin *N,N′*-cyclic azomethine imine 1,3-dipoles with chalcones. *New J. Chem.* **2020**, *44*, 8813–8817.
156. Meerakrishna, R. S.; Suresh, S. S.; Athira, M.; Choutipalli, V. S. K.; Shanmugam, P. Diverse reactivity of isatin based *N,N′*-cyclic azomethine imine dipoles with arynes: synthesis of 1′-methyl-2′-oxospiro [indene-1,3′-indolines] and 3-aryl-3-pyrazol-2-oxindoles. *New J. Chem.* **2020**, *44*, 11593–11601.
157. Shi, Y.; Wang, G.; Chen, Z.; Wu, M.; Wang, J.; Trigoura, L.; Guo, H.; Xing, Y.; Sun, S. Synthesis of spiro(indoline-3,1-pyrazolo [1,2-a]pyrazoles) by 1,3-dipolar cycloadditions of isatin *N,N′*-cyclic azomethine imines with alkynes. *J. Heterocycl. Chem.* **2020**, *57*, 2044–2047.
158. Jin, Q.; Zhang, D.; Zhang, J. A [3 + 2] cycloaddition/C-arylation of isatin *N,N′*-cyclic azomethine imine 1,3-dipole with arynes. *RSC Adv.* **2020**, *10*, 30620–30623.
159. Wang, Z.-Y.; Yang, T.; Chen, R.; Ma, X.; Liu, H.; Wang, K.-K. 1,3-Dipolar cycloaddition of isatin *N,N′*-cyclic azomethine imines with *α,β*-unsaturated aldehydes catalyzed by DBU in water. *RSC Adv.* **2020**, *10*, 24288–24292.
160. Kartikey, K. D. D.; Reddy, M. S.; Chowhan, L. R. Isatin *N,N′*-cyclic azomethine imine 1,3-dipole mediated regio and diastereoselective synthesis of isoxazole-containing spirooxindoles by an abnormal [3+2] cycloaddition. *Tetrahedron Lett.* 2020, **61**, 152664.
161. Fang, Q.-Y.; Jin, H.-S.; Wang, R.-B.; Zhao, L.-M. A role for isatin azomethine imines as a dipolarophile in cycloaddition reactions. *Org. Lett.* **2020**, *22*, 7358–7362.
162. Abdelmouna, K.; Laghchioua, F.; Paz, F. A. A.; Mendes, R. F.; Moura, N. M. M.; Faustino, M. A. F.; Cavaleiro, J. A. S.; Kandri Rodi, Y.; Rakib, E. M.; Neves, M. G. P. M. S. Development of catalyst-free approach to synthesize novel spiro[indoline-3,1′-pyrazolo [1,2-a]pyrazoles] via 1,3-dipolar cycloaddition. *J. Mol. Struct.* **2023**, *1272*, 134170.
163. Li, X.; Li, W.-S.; Fu, X.; Wan, W.-J.; Wang, L.-X. A novel [4 + 3] annulation between isatin *N,N′*-cyclic azomethine 1,3-dipole and in situ generated nitrosoalkene for direct preparation of seven-membered heterocyclic spirooxindoles. *Tetrahedron Lett.* **2024**, *146*, 155183.

164. Wang, Y.; Wei, X.; Qu, J.; Wang, B. Palladium-catalyzed umpolung allylation of isatin-derived azomethine imines with vinylcyclopropanes. *Eur. J. Org. Chem.* **2024**, *27*, e202400743.
165. Mehrdad, M.; Faraji, L.; Jadidi, K.; Eslami, P.; Sureni, H. A regioselective and diastereoselective synthesis of new spiro-isoxazolidines via 1,3-dipolar cycloaddition of stable isatin ketonitrone and various dipolarophiles. *Monatsh. Chem.* **2011**, *142*, 917–921.
166. Yang, H.-B.; Wei, Y.; Shi, M. Construction of spiro[indoline]oxindoles through one-pot thermal-induced [3+2] cycloaddition/silica gel-promoted fragmentation sequence between isatin ketonitrones and electron-deficient alkynes. *Tetrahedron* **2013**, *69*, 4088–4097.
167. Chen, Y. R.; Zhan, G.; Du, W.; Chen, Y. C. Regioselective asymmetric formal (3+2) cycloadditions of nitrone ylides from isatins and enals. *Adv. Synth. Catal.* **2016**, *358*, 3759-3764.
168. Zhan, G.; Shi, M. L.; Lin, W. J.; Ouyang, Q.; Du, W.; Chen, Y. C. Direct asymmetric aza-vinylogous-type Michael additions of nitrones from isatins to nitroalkenes. *Chem.–Eur. J.* **2017**, *23*, 6286–6289.
169. Lin, W.; Zhan, G.; Shi, M.; Du, W.; Chen, Y. 3 + 3] Formal cycloadditions of nitrones from isatins and azaoxyallyl cations for construction of spirooxindoles. *Chin. J. Chem.* **2017**, *35*, 857–860.
170. Shi, M.; Zhan, G.; Du, W.; Chen, Y. Direct asymmetric aza-vinylogous Mannich reaction of nitrones from isatins and ketimines. *Acta Chim. Sinica* **2017**, *75*, 998–1002 (in Chinese).
171. Maiuolo, L.; Merino, P.; Algieri, V.; Nardi, M.; Di Gioia, M. L.; Russo, B.; Delso, I.; Tallarida, M. A.; De Nino, A. Nitrones and nucleobase-containing spiro-isoxazolidines derived from isatin and indanone: solvent-free microwave-assisted stereoselective synthesis and theoretical calculations. *RSC Adv.* **2017**, *7*, 48980–48988.
172. Wu, S.-Y.; Chen, W.-L.; Ma, X.-P.; Cui Liang, G.-F. S.; Mo, D.-L. Copper-Catalyzed [3+2] cycloaddition and interrupted Fischer indolization to prepare polycyclic furo [2,3-b]indolines from *N*-aryl isatin nitrones and methylenecyclopropanes. *Adv. Synth. Catal.* **2019**, *361*, 965–970.
173. Cheng, X.; Fei, W.; Luo, Z.; Li, J.; Wang, Z.; Yao, W. DABCO-catalyzed *α*-regio- and diastereoselective (3+2) cycloadditions of nitrone ylides from isatins and activated alkenes. *Synthesis* **2020**, *52*, 3632–3639.
174. Yuan, H.; Lu, D.-L.; Liang, C.; Mo, D.-L. Synthesis of spirooxindole-benzo[d]oxazoles and dihydrobenzofurans through cycloaddition and rearrangement of *N*-vinyl nitrones and arynes. *Adv. Synth. Catal.* **2022**, *364*, 1409–1414.
175. Luo, Z.; Wang, Z.; Yao, W. DABCO-catalyzed [3+2] cycloaddition of isatin-derived nitrones and electron-deficient dienes via a 1,6-addition reaction. *Synthesis* **2022**, *54*, 4339–4346.
176. Luo, M.-L.; Hou, Q.; Liu, S.-J.; Zhao, Q.; Qin, R.; Peng, C.; Han, B.; Zhan, G. One-step synthesis of hydropyrrolo [3,2-b]indoles via cascade reactions of oxindole-derived nitrones with allenoates. *Org. Lett.* **2022**, *24*, 8493–8497.
177. Yuan, H.; Wu, Y.-Z.; Fang, Y.-H.; Chen, C.-H.; Liang, C.; Mo, D.-L. Synthesis of spirooxindole-1,2-oxazinan-5-ones through 2,2,2-trifluoroethanol promoted [3 + 3] cycloaddition of *N*-Vinyl oxindole nitrones and oxyallyl cations. *J. Org. Chem.* **2023**, *88*, 16155–16166.
178. Behera, K.; Mohapatra, S.; Nayak, S.; Mohapatra, S.; Parida, S. P.; Bhattacharya, D.; Rout, U. K.; Sahoo, C. R. Transition metal- and base-free [3+2] cycloaddition: design, synthesis, and antibacterial activity of isoxazolidine derivatives. *ChemistrySelect* **2024**, *9*, e202404850.
179. Zou, N.; Wu, Y.-Z.; Zhong, X.-Y.; Wei, C.; Liao, L.-M.; Mo, D.-L.; Zhou, W.-J. Asymmetric [3+3] cycloaddition of *N*-vinyl oxindole nitrones with 2-indolylmethanols to prepare spirooxindole [1,2]oxazines. *Adv. Synth. Catal.* **2024**, *366*, 4960–4965.
180. Hamer, J.; Macaluso, A., Nitrones. *Chem. Rev.* **1964**, *64*, 473–495.
181. Delpierre, G. R.; Lamchen, M. Nitrones. *Quart. Rev., Chem. Soc.* **1965**, *19*, 329–348.
182. Black, D. S. C.; Crozier, R. F.; Davis, V. C. 1,3-Dipolar cycloaddition reactions of nitrones. *Synthesis* **1975**, 205–221.
183. Confalone, P. N.; Huie, E. M. The [3+2] nitrone-olefin cycloaddition reaction, in *Organic Reactions*, ed. A. S. K. et. al., John Wiley & Sons, Inc., **1988**, vol. 36, p. 74.
184. Zhao, B. Application of nitrones in total synthesis of natural products. *Prog. Chem.* **2000**, *12*, 77–88 (in Chinese).
185. Osborn, H. M. I.; Gemmell, N.; Harwood, L. M. 1,3-dipolar cycloaddition reactions of carbohydrate derived nitrones and oximes. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2419–2438.

186. Hu, X.-F.; Feng, Y.-Q.; Li X.-F. Chiral Lewis acid-catalyzed 1,3-dipolar cycloadditions between nitrones and alkenes. *Chin. J. Org. Chem.* **2005**, *25*, 1–7 (in Chinese).
187. Rück-Braun, K.; Freysoldt, T. H. E.; Wierschem, F. 1,3-Dipolar cycloaddition on solid supports: nitrone approach towards isoxazolidines and isoxazolines and subsequent transformations. *Chem. Soc. Rev.* 2005, *34*, 507–516.
188. Yang, J. Recent developments in nitrone chemistry: some novel transformations. *Synlett* **2012**, *23*, 2293–2297.
189. Murahashi, S.-I.; Imada, Y. Synthesis and transformations of nitrones for organic synthesis. *Chem. Rev.* **2019**, *119*, 4684–4716.
190. Yue, G.; Liu B. Research progress on [3＋*n*] (*n*≥3) cycloaddition of 1,3-dipoles. *Chin. J. Org. Chem.* **2020**, *40*, 3132–3153 (in Chinese).
191. Thakur, S.; Das, A.; Das, T. 1,3-Dipolar cycloaddition of nitrones: synthesis of multisubstituted, diverse range of heterocyclic compounds. *New J. Chem.* **2021**, *45*, 11420–11456.
192. Akulov, A. A.; Varaksin, M. V.; Mampuys, P.; Charushin, V.; Chupakhin, O. N.; Maes, B. U. W. C(sp^2)–H functionalization in non-aromatic azomethine-based heterocycles. *Org. Biomol. Chem.* **2021**, *19*, 297–312.
193. Oudeyer, S.; Levacher, V.; Beucher, H.; Brière, J.-F. Recent advances in catalystic and technology-driven radic al addtion to *N*,*N*-disubsititued iminum species. *Molecules* **2023**, *28*, 1071.
194. Tamura, O. Exploration and development of nitrone chemistry. *Chem. Pharm. Bull.* **2024**, *72*, 731–746.
195. Tanaka, K. Recent advances in the direct N–C(sp^2) nitrone synthesis from oxime. *Eur. J. Org. Chem.* **2024**, *27*, e202400202.
196. Abdulla, M.; Hussain, M. K.; Ahamad, S. Trifluoromethylnitrone: a versatile building block for synthesizing trifluoromethyl-containing heterocyclic compounds. *Org. Biomol. Chem.* **2024**, *22*, 5242–5256.
197. Kobus, M.; Friedrich, T.; Zorn, E.; Burmeister, N.; Maison, W. Medicinal chemistry of drugs with *N*-oxide functionalities. *J. Med. Chem.* **2024**, *67*, 5168–5184.
198. Rozpara, I.; Marco-Contelles, J.; Piotrowska, D. G.; Głowacka, I. E. Phosphorylated nitrones—synthesis and applications. *Molecules* **2025**, *30*, 1333.
199. Yokoshima, S. Intramolecular cycloaddition of nitrones in total synthesis of natural products. *Nat. Prod. Rep.* **2025**, *42*, 1071–1090.
200. Stańska, B.; Dahyia, A.; Loska, R. Nitrones as directing groups in transition metal-catalysed C-H activation. *Org. Biomol. Chem.* **2026**, *24*, 11–37.
201. Mohapatra, S.; Prusty, K.; Bhol, S.; Panigrahi, G.; Nayak, S. Nitrone chemistry: a versatile gateway to diverse heterocycles. *RSC Adv.* **2026**, *16*, 292–331.
202. Zhu, Z.-Y.; Tian, P.; Chang, J.; Li, H.; Kang, Y.; Xie, P.; Yao, T.; Zhang, X. Photocatalytic (3+3) cycloaddition of arylaminocyclopropanes with nitrones: highly diastereoselective synthesis of 1,2-oxazinan-6-amine derivatives. *Chem. Commun.* **2025**, *61*, 18428–18431.
203. Zhang, M.; Kong, L.; Li, S.; Gao, S.; Li, X. Diastereoselective synthesis of 5,5-difluoroisoxazolidine via [3 + 2] cycloaddition between nitrones and difluoroacrylates. *Tetrahedron Lett.* **2025**, 167, 155647.
204. Zaika, Y. O.; Vashchenko, B. V.; Sosunovych, B. S.; Khutorianskyi, A. V.; Yasman, P.; Ogurok, V. M.; Brovarets, V. S.; Grygorenko, O. O. [3+2] Cycloadditions of *α*,*β*-unsaturated sultams. *Eur. J. Org. Chem.* **2025**, *28*, e202500093.
205. Xu, C.; Wang, Y.; Xiao, M.; Tian, R.; Duan, Z. A tandem route toward isoxazolidine fused phospholene skeleton involving dearomative [3+2] cycloaddition of P-heteroarenes and nitrones. *Chin. J. Chem.* **2025**, *43*, 1161–1165.
206. Wang, S.; Xie, W.; Jiang, C.; Guo, C.; Chang, J.; Zhu, B. Highly regio- and diastereoselective 1,3-DC reaction of BDAs and nitrones: synthesis of the spiro[benzofuran-2,5′-isoxazolidine] framework. *J. Org. Chem.* **2025**, *90*, 8531–8541.
207. Wang, J.; Luo, S.; Yuan, X.; Cheng, J.; Yang, Z.; Huang, Z. Enantioselective Zn-catalyzed hydrophosphinylation of nitrones: an efficient approach for constructing chiral *α*-hydroxyamino-phosphine oxides. *Chem. Sci.* **2025**, *16*, 7051–7056.
208. Salih, R. N.; Algso, M.; Mohammad-Salim, H. Mechanistic study of *N*-*t*-butyl nitrone and nitroethene (3 + 2) cycloaddition: a combined DFT, docking, and ADMET approach. *J. Heterocycl. Chem.* **2025**, *62*, 1328–1343.

doi:10.20944/preprints202603.0943.v1

209. Li, G.-X.; Xu, Z.-J.; Che, C.-M. Fe-BPsalan complex-catalyzed asymmetric 1,3-dipolar [3+2] cycloaddition of nitrones with α,β-unsaturated acyl imidazoles. *J. Org. Chem.* **2026**, *91*, 911–924.
210. Stanska, B.; Ostrowska, S.; Loska, R. Rhodium-catalyzed C–H annulation of aldonitrones with allyl methyl carbonate. *Synlett* **2026**, in press.
211. Toda, Y.; Soma, Y.; Horiba, N.; Koyama, M.; Iwakuma, F.; Matsumoto, S.; Sukegawa, K.; Kikuchi, A.; Suga, H. Chiral amine-urea mediated asymmetric inverse-electron-demand cycloadditions of cyclic nitrones with o-hydroxystyrenes. *Org. Biomol. Chem.* **2026**, *24*, 1006-1010.
212. Chen, S.; Ma, L.; Yue, C.; Du, B.; Lu, C.; Long, C.; Wu, W.; Li, S.; He, Q.; Yue, G. Base-controlled diastereoselective [3+2]-cycloaddition and Michael addition of isatin ketonitrones and chalcones to construct spiropyrrolidine oxoindoles and γ-substituted isatin ketonitrones. *New J. Chem.* **2025**, *49*, 16978–16988.