



Synthesis of 3-acyl, methylene and epoxy substituted isoindolinone derivatives via the ortho-lithiation/cyclization procedures of aromatic imines with carbon monoxide

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ABSTRACT

A simple and convenient one-pot synthesis of 3-acyl, methylene and epoxy isoindolinone derivatives via the reaction of *o*-lithiated aromatic imines with carbon monoxide followed with acyl chlorides or $\text{PhCO}(\text{CH}_2)_n\text{Br}$ ($n = 1$ or 3) under mild reaction conditions has been developed. Preliminary *in vitro* tests for fungicidal activity of these isoindolinone derivatives indicated that most of them exhibit good fungicidal activity against *Sclerotinia sclerotiorum*.

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1. Introduction

The isoindolinone skeleton has been found to present in numerous natural products and synthetic pharmaceuticals with a wide range of biological activities (Fig. 1).¹ For example, pagoclone shows anxiolytic activity,² indoprofen is a non-steroidal anti-inflammatory drug,³ and BMCI shows Kv1.5 activity.^{1a} On the other hand, simple isoindolinones are versatile synthetic intermediates, and have been used as building blocks in various organic transformations to form important and more complex organic molecules.⁴ Therefore, a variety of synthetic approaches to isoindolinones have been developed in the literature,⁵ which are generally summed up in eight synthetic methods⁶ or two categories.⁷ The first category is based on phthalimides⁸ or phthalimides⁹ as the starting materials. The second one is the construction of the lactam ring through cyclization reactions of various functionalized aromatic compounds, such as the amination reaction of 2-halomethyl^{1b} or 2-acylbenzoate ester,^{1c} 2-carboxybenzaldehyde^{1a,10} and 2-alkynylbenzaldehyde,¹¹ as well as the *o*-lithiation/cyclization of benzamides.^{6,12} In consideration of the structural diversity and the structure-activity relationship of

isoindolinones, other synthetic approaches have been explored in recent years. Transition metal-catalyzed carbonylation¹³ and C–H functionalization,¹⁴ Diels–Alder¹⁵ and inverse-electron demand Diels–Alder,¹⁶ aza-Wittig¹⁷ and radical cyclization¹⁸ reactions as well as organocatalytic reactions^{10a,19} have been used to build the fundamental isoindolinone skeleton. In spite of all these achievements, the substrates were not readily available in many of above-mentioned cases, which were usually obtained by multistep reactions. Thus, the development of new efficient synthetic methods for isoindolinone derivatives from simple and readily available starting materials is highly desirable. Our recent investigations showed that isoindolinone derivatives were easily obtained by the reaction of *o*-lithiated aromatic imines with carbon monoxide, followed with alkyl halides under mild conditions.²⁰ As an extension of this work, herein we report the synthesis of 3-acyl, methylene and epoxy substituted isoindolinone derivatives through similar reactions, employing acyl chloride and $\text{PhCO}(\text{CH}_2)_n\text{Br}$ ($n = 1$ or 3) as the electrophiles instead of alkyl halides.

2. Results and discussion

2.1. Synthesis of 3-acyl and methylene substituted isoindolinones

Previous work has demonstrated that reaction of *o*-lithiated

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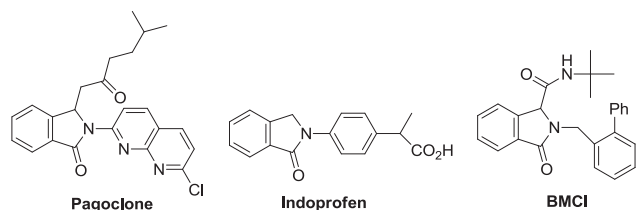
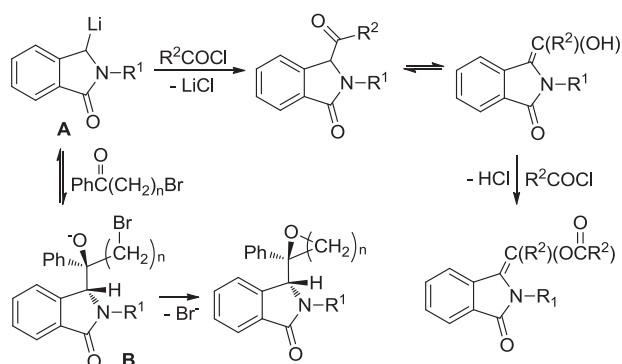


Fig. 1. Representative isoindolinone derivatives with bioactivity.

aromatic imines with carbon monoxide underwent a cyclization process to form a carbanion intermediate **A** at the 3-position of isoindolinone (Scheme 1).^{20,21} We found that in situ treatment of this intermediate with one equivalent of acyl chlorides afforded 3-acyl isoindolinones (**1a–4a**) and 3-methylene isoindolinones (**1b–4b**) (Table 1, entries 1–4) when an ethyl group was attached to the nitrogen atom. The formation of the methylene isoindolinone derivatives was greatly influenced by the steric hindrance of the substituents on the nitrogen atom (Table 2, entries 1–21). With the increase of the steric hindrance of the substituents, no similar methylene isoindolinone derivatives were isolated, and the yields of 3-acyl isoindolinones were improved evidently (Table 2, entries 1–11). Moreover, even the bulky 2,6-dimethylphenyl group on the nitrogen atom was tolerable, while the corresponding 3-acyl isoindolinones were also obtained in good yields (Table 2, entries 17 and 18). On the other hand, the properties of the substituents at acyl chlorides had relatively little effect on the formation of 3-acyl isoindolinones when the N-substituent was simple aliphatic group. For example, 2-*tert*-butyl-3-ferrocenylformylisoindolin-1-one (**15**) could be obtained in an excellent yield upon *N*-*tert*-butyl-2-bromobenzaldimine as the starting material, and ferrocene-carbonyl chloride as the final electrophile (Table 2, entry 11). However, bulky electrophiles such as ferrocenecarbonyl chloride might impair the reaction when the N-substituent was rigid, such as in the case of 2,6-Me₂C₆H₃ (Table 2, entry 21) in which the protonated product²⁰ of the intermediate **A** (*ca.* 20%) was obtained together with **25**, and the repulsion between substituents could not be alleviated by rotation or compression of the substituent. In addition, pyrrolo[3,4-*b*]pyridine-7-ones (**26** and **27**) were obtained together with some other byproducts of unknown structures when the substrate was expanded to 2-bromo-3-pyridinecarboxaldimine (Table 2, entries 22 and 23). The yields were relatively low compared with those of **11** and **13** probably because the corresponding acyl lithium intermediate partially resonated to pyridyl nitrogen anion instead of similar pyridyl substituted intermediated **A**,²⁰ and led to other competing reactions.

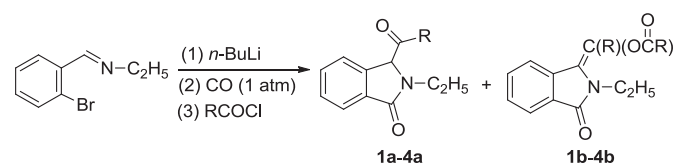
The formation of **1b–4b** should originate from the enolization



Scheme 1. Formation pathways of 3-acyl, methylene and epoxy substituted isoindolinones.

Table 1

Synthesis of 3-acyl and methylene substituted isoindolinones.

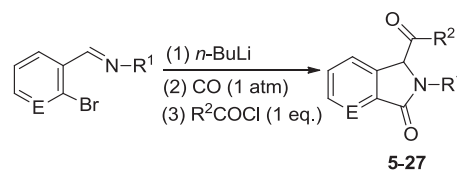


Entry	R	Isolated yield (%)
1	Me	1a (50)
2	Ph	2a (28)
3	<i>p</i> -FC ₆ H ₄	3a (27)
4	<i>n</i> -Pr	4a (49)
5 ^a	Me	1a (73)
6 ^a	Ph	2a (38)
7 ^a	<i>n</i> -Pr	4a (74)

^a Two equivalents of acyl chlorides were used.

Table 2

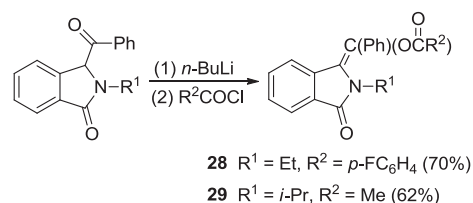
Synthesis of 3-acyl isoindolinones.



Entry	Comp.	E	R ¹	R ²	Yield (%) ^a
1	5	CH	Et	Ferrocenyl	48
2	6	CH	<i>i</i> -Pr	Me	71
3	7	CH	<i>i</i> -Pr	<i>n</i> -Pr	75
4	8	CH	<i>i</i> -Pr	Ph	73
5	9	CH	<i>i</i> -Pr	<i>p</i> -FC ₆ H ₄	67
6	10	CH	<i>i</i> -Pr	Ferrocenyl	85
7	11	CH	<i>t</i> -Bu	Me	89
8	12	CH	<i>t</i> -Bu	<i>n</i> -Pr	94
9	13	CH	<i>t</i> -Bu	Ph	73
10	14	CH	<i>t</i> -Bu	<i>p</i> -FC ₆ H ₄	94
11	15	CH	<i>t</i> -Bu	Ferrocenyl	94
12	16	CH	Cyclo-C ₆ H ₁₁	Me	71
13	17	CH	Cyclo-C ₆ H ₁₁	<i>n</i> -Pr	87
14	18	CH	Cyclo-C ₆ H ₁₁	Ph	88
15	19	CH	Cyclo-C ₆ H ₁₁	<i>p</i> -FC ₆ H ₄	71
16	20	CH	Cyclo-C ₆ H ₁₁	Ferrocenyl	58
17	21	CH	2,6-Me ₂ C ₆ H ₃	Me	74
18	22	CH	2,6-Me ₂ C ₆ H ₃	<i>n</i> -Pr	75
19	23	CH	2,6-Me ₂ C ₆ H ₃	Ph	55
20	24	CH	2,6-Me ₂ C ₆ H ₃	<i>p</i> -FC ₆ H ₄	46
21	25	CH	2,6-Me ₂ C ₆ H ₃	Ferrocenyl	22
22	26	N	<i>t</i> -Bu	Me	43
23	27	N	<i>t</i> -Bu	Ph	39

^a Isolated yields.

and subsequent esterification reaction of **1a–4a** (Scheme 1), which was supported by treatment of **2a** or **8** with a base and followed



Scheme 2. Reaction of 3-acyl isoindolinones.

with acyl chloride to afford analogous 3-methylene isoindolinone derivatives in good yields (**28** and **29**, Scheme 2). Thus, we proposed that the yields of **1b–4b** were possibly improved when the amount of acyl chloride was increased. However, the yields of 3-methylene derivatives decreased, and the yields of 3-acyl derivatives were clearly increased when two equivalents of alkylacyl chlorides were used (Table 1, entries 5 and 7). The enolization of 3-alkylacyl derivatives is possibly a slow process, and an excess of acyl chloride is beneficial to better conversion of the 3-lithiation intermediates to isoindolinones in these cases. Being different from the cases of alkylacyl chlorides, the yields of 3-methylene derivatives were higher than those of 3-acyl derivatives no matter one or two equivalents of aryl chlorides were used (Table 1, entries 2, 3 and 6). The faster enolization rate of 3-aryl derivatives led by the conjugation effect of the aryl group should be responsible for these results. Compounds **1–29** have been characterized by ^1H and ^{13}C NMR spectra, among which the new compounds have been also characterized by HRMS. Additionally, the structure of **5** has been confirmed by X-ray single crystal diffraction, which is shown in Fig. 2. The ^1H and ^{13}C NMR spectra of **1b**, **3b**, **4b** and **28** displayed two sets of proton and carbon signals, indicating the presence of isomers. The assignment of isomers was based on the NOE experiments (Fig. 3) and the X-ray crystal structure determination of Z-isomer of **3b** (**3b-Z**, Fig. 4), which was obtained through crystallization of the mixture from CH_2Cl_2 and hexane. The strong correlation was observed in the NOESY spectrum of Z isomer of **3b** between the $N\text{-CH}_2$ protons at 4.01 ppm and the aromatic proton at 8.15 ppm which should be the *meta* proton of fluorine atom. Despite of partial overlapping of the ^1H NMR signals of Z and E isomers of **4b**, two sets of signals with a ratio of ca. 75:25 were clearly integrated in nonoverlapping regions. The signals at 2.80 and 2.48 ppm were assigned to the allylic protons and the α -protons of the carbonyl group according to HMBC and HMQC experiments, respectively. Moreover, the signals set with larger integrals were attributed to the Z-isomer on the basis of NOE correlations between the protons at 2.80 ppm with the aromatic proton at 7.65 ppm and between the protons at 2.48 ppm with the $N\text{-CH}_2$ protons at 3.93 ppm. The NOE signals of E-isomer of **4b** have also been observed between the allylic protons and the $N\text{-CH}_2$ protons as well as between the α -protons of the carbonyl and the aromatic proton (Fig. 3, **4b-E**).

2.2. Synthesis of 3-epoxy substituted isoindolinones

We initially anticipated that 3-(acylmethyl) functionalized isoindolinone derivatives were obtained upon treatment with $\text{PhCO}(\text{CH}_2)_n\text{Br}$ ($n = 1$ or 3) as the final electrophiles after the

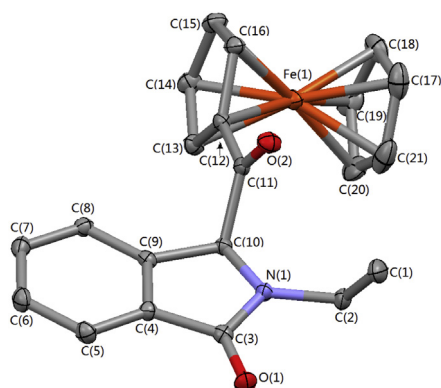


Fig. 2. The molecular structure of **5**.

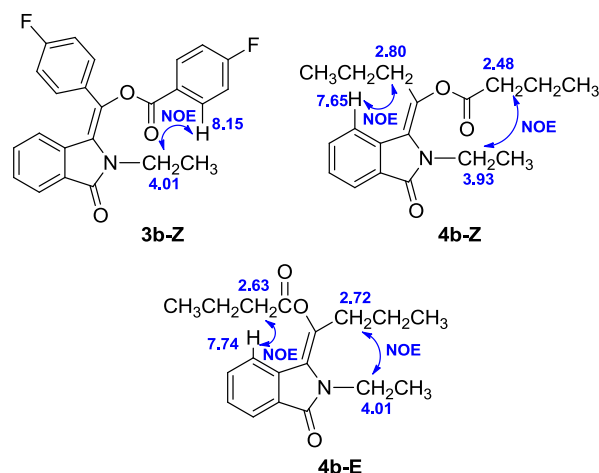


Fig. 3. The NOE corrections of **3b-Z** and **4b**.

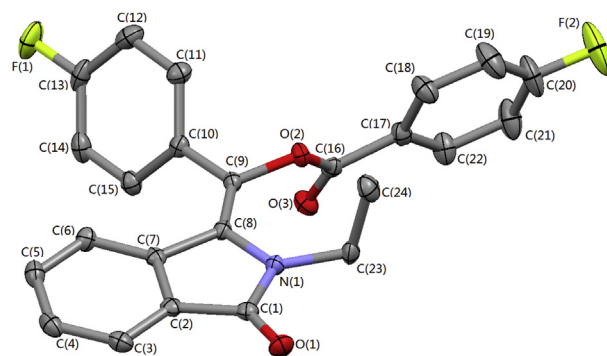
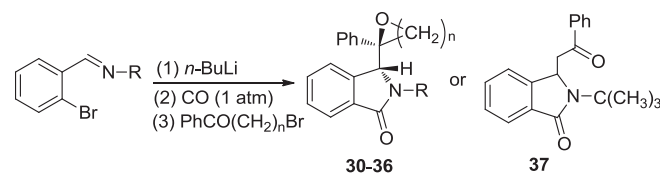


Fig. 4. The molecular structure of **3b-Z**.

complete lithiation of bromobenzaldimine, but in fact 3-epoxy substituted isoindolinones were formed in moderate to good yields except for **37** (Table 3). The 3-lithiation intermediate **A** of isoindolinones firstly attacked the carbonyl carbon of bromoketones (Scheme 1) instead of the replacement of bromide, like the reaction of alkyl bromide.²⁰ The resulting alkoxy anion **B** subsequently underwent an $\text{S}_{\text{N}}1$ reaction to form the epoxide ring. The

Table 3
Synthesis of 3-epoxy substituted isoindolinones.



Entry	Comp.	n	R	dr ^a	Yield (%) ^b
1	30	1	Et	—	56
2	31	1	<i>i</i> -Pr	16:1	71
3	32	1	<i>Cyclo</i> -C ₆ H ₁₁	25:1	75
4	33	3	Et	4.3:1	75
5	34	3	<i>i</i> -Pr	5.0:1	70
6	35	3	<i>Cyclo</i> -C ₆ H ₁₁	17:1	64
7	36	3	<i>t</i> -Bu	>25:1	63
8	37	1	<i>t</i> -Bu	—	57

^a The dr value was obtained by ^1H NMR spectra.

^b Isolated yields.

formation of **37** should be the combined results of the steric hindrance and short carbon chain. The S_N1 reaction of the *N*-*tert*-butyl alkoxy anion **B** with shorter carbon chain becomes difficult owing to the steric congestion in the final epoxy product. On the other hand, its reverse reaction back to **A** possibly occurs,²² which leads to the substitution reaction of bromide in PhCOCH_2Br to form **37** to be dominant. ^1H NMR analysis of the crude reaction mixture of **30** also revealed the presence of small amount of substitution products, which shows that there is actually an equilibrium competition between the S_N1 reaction and the direct substitution reaction of bromide.

It is known that the epoxide ring possesses high reaction activity toward various nucleophiles. Thus, compounds **30–32** maybe can be exploited as important intermediates in future work for other azaheterocyclic compounds through the ring-opening reaction of epoxides.^{4b} The dr value of **30** could not be obtained owing to the completely overlapping of ^1H NMR signals of diastereomers. Additionally, the dr values of other epoxides remarkably increase as the steric hindrance of the substituents on the nitrogen atom increases (Table 3, entries 3 and 7). Compounds **30–37** were fully identified by ^1H and ^{13}C NMR spectra as well as HRMS, and the structures of **31** and **35** were further confirmed by the X-ray crystal structure determination. The structure of **31** is depicted in Fig. 5, and that of **35** is shown in Supporting information.

2.3. Fungicidal activity

The preliminary *in vitro* antifungal activities of some compounds were assessed at 50 $\mu\text{g/mL}$, and results are listed in Table 4. The most striking feature is that compound **17** displayed good fungicidal activities against all the tested fungi, and most of the tested compounds showed better activity against *Sclerotinia sclerotiorum*, a fungal pathogen causing disease in a wide range of plants.²³ The inhibition percentage of **17** and **19** for this fungus is 100%, similar to that of azoxystrobin. Compounds **17** and **34** also showed better efficacy against *Alternaria solani* than azoxystrobin, supported by their higher inhibition percentage than that of azoxystrobin. Compound **25** showed moderate activities against *Gibberella zeae*, *Macrophoma kuwatsukai* and *Rhizoctonia cerealis* besides excellent activity against *Sclerotinia sclerotiorum*. In addition, most of these 3-acyl isoindolinones seem to be more active against *Sclerotinia sclerotiorum* than similar 3-alkyl derivatives.²⁰

In summary, a simple and convenient synthesis of 3-acyl, methylene and epoxy isoindolinone derivatives from readily available starting materials under mild reaction conditions has been developed. Preliminary *in vitro* tests for fungicidal activity of these isoindolinone derivatives indicate that most of them exhibit

good fungicidal activity against *Sclerotinia sclerotiorum*.

3. Experimental

3.1. General

All reactions were carried out under an argon atmosphere. Solvents were dried by standard methods and freshly distilled prior to use. NMR (^1H and ^{13}C) were recorded on a Bruker 400 spectrometer using CDCl_3 as the solvent, and the chemical shifts were reported in ppm with respect to the reference (internal SiMe_4 for ^1H and ^{13}C NMR spectra). HR mass spectra were obtained on a Varian QFT-ESI spectrometer. Melting points were measured with an X-4 digital micro melting-point apparatus and were uncorrected. The imines were prepared by the condensation reaction of 2-bromobenzaldehyde and 2-bromo-3-pyridinecarboxaldehyde with the corresponding amine according to the published methods.²⁴ Preliminary *in vitro* tests for fungicidal activity of compounds have been carried out by the fungi growth inhibition method.²⁵

3.2. Typical procedure for the synthesis of **1–27**

A hexane solution of *n*-BuLi (1.6 M, 1.25 mL, 2 mmol) was added to the solution of aromatic imine (2 mmol) in THF (30 mL) at -78°C . After the resulting mixture was stirred for 30 min, carbon monoxide was bubbled through the solution. The carbon monoxide atmosphere was kept with a balloon at the exit. After the reaction mixture was continuously stirred at -78°C for 30 min, acyl chloride (2 or 4 mmol) was added dropwise. The resulting mixture was stirred at -78°C for 30 min, allowed to reach room temperature slowly and stirred for overnight. The solvent was removed under reduced pressure, and the residue was isolated by column chromatography on silica with ethyl acetate/petroleum ether (V/V = 1:4) as the eluent to give the products.

3.2.1. 2-Ethyl-3-acylisoindolin-1-one (**1a**)

Oil; ^1H NMR δ 1.21 (t, J = 7.3 Hz, 3H), 1.87 (s, 3H), 3.17 (dq, J = 7.2 Hz, J = 14.3 Hz, 1H), 4.07 (dq, J = 7.4 Hz, J = 14.5 Hz, 1H), 4.99 (s, 1H), 7.39–7.41 (m, 1H), 7.49–7.56 (m, 2H), 7.84–7.86 (m, 1H); ^{13}C NMR δ 13.3, 23.8, 36.7, 69.8, 122.6, 124.2, 129.5, 132.2, 132.3, 138.7, 168.9, 204.9; HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{14}\text{NO}_2$ [$\text{M}+\text{H}$] $^+$: 204.1025, found: 204.1019.

3.2.2. (2,3-Dihydro-2-ethyl-3-oxo-1H-isoindol-1-ylidene)(methyl methyl acetate (**1b**))

White solid; mp: 91–93 $^\circ\text{C}$; The ^1H NMR spectrum showed a Z:E ratio of 95:5. ^1H NMR δ 1.25 (t, J = 7.1 Hz, 3H), 2.27 (s, 2.86H), 2.38 (s, 0.14H), 2.43 (s, 0.14H), 2.48 (s, 2.86H), 3.99 (q, J = 7.1 Hz, 2H), 7.46 (t, J = 7.4 Hz, 1H), 7.54–7.59 (m, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.88 (d, J = 7.5 Hz, 1H); ^{13}C NMR of major isomer δ 14.8, 19.9, 21.0, 37.1, 122.7, 123.6, 125.0, 128.3, 129.6, 130.7, 131.8, 135.2, 166.6, 168.6; ^{13}C NMR of minor isomer δ 18.5, 21.3, 36.2, 123.3, 123.5, 128.6, 132.2; other signals were overlapped with those of major isomer; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{16}\text{NO}_3$ [$\text{M}+\text{H}$] $^+$: 246.1130, found: 246.1130.

3.2.3. 2-Ethyl-3-benzoylisoindolin-1-one (**2a**)^{13f}

White solid; ^1H NMR δ 1.23 (t, J = 7.3 Hz, 3H), 3.16–3.25 (m, 1H), 4.06–4.16 (m, 1H), 6.06 (s, 1H), 7.20–7.23 (m, 1H), 7.40–7.55 (m, 4H), 7.67 (t, J = 7.4 Hz, 1H), 7.89–7.95 (m, 3H); ^{13}C NMR δ 13.4, 36.4, 65.6, 122.6, 124.3, 128.8, 129.1, 129.2, 131.7, 132.4, 134.3, 135.4, 139.5, 168.8, 193.9.

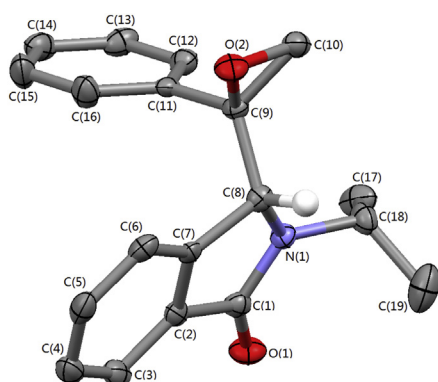


Fig. 5. The molecular structure of **31**.

Table 4Antifungal activity of **1–37** and azoxystrobin (Percent inhibition, 50 µg/mL in DMF).

Compound	<i>Alternaria solani</i>	<i>Botrytis cinerea</i>	<i>Cercospora arachidicola</i>	<i>Gibberella zeae</i>	<i>Macrophoma kuwatsukai</i>	<i>Phytophthora infestans</i>	<i>Rhizoctonia cerealis</i>	<i>Sclerotinia sclerotiorum</i>	<i>Thanatephorus cucumeris</i> (Frank) Domk
1a	22	9	12	21	23	15	0	29	8
2a	10	25	9	25	27	16	21	93	21
3a	24	22	24	13	26	19	12	63	18
4a	30	13	10	28	11	8	16	42	0
5	22	11	14	22	15	10	8	89	13
6	33	22	21	22	15	19	20	82	13
7	33	30	17	28	21	19	12	76	23
8	17	32	16	64	27	3	25	98	24
9	26	40	19	54	15	10	23	98	19
10	20	19	12	24	16	6	2	82	8
11	15	5	5	12	9	16	12	21	17
12	23	14	17	7	17	16	12	29	19
13	20	5	5	35	9	7	7	25	13
14	30	13	12	27	5	17	16	92	13
15	10	24	16	22	8	7	11	95	11
16	20	29	19	12	9	24	40	21	19
17	66	65	61	62	64	67	81	100	67
18	20	20	26	42	28	27	4	95	27
19	30	33	26	31	21	23	22	100	17
20	14	26	16	37	8	10	15	95	16
21	20	7	14	18	15	10	0	71	10
22	24	19	14	9	16	15	12	71	13
23	41	33	24	39	28	17	20	95	27
24	35	24	24	35	33	31	31	75	42
25	31	18	13	59	52	24	55	98	41
26	20	7	14	7	9	16	14	21	13
27	14	28	19	26	12	9	19	95	15
30	37	19	17	22	21	19	20	87	23
31	25	21	24	2	13	27	24	61	17
32	12	29	0	30	15	7	19	95	17
33	38	46	27	36	23	3	4	54	11
34	56	35	29	22	33	29	16	92	30
35	30	17	29	16	17	29	24	21	31
36	37	33	5	28	39	42	28	95	27
37	30	28	28	34	31	17	16	79	13
azoxystrobin	47	79	68	100	91	100	100	100	84

3.2.4. (2,3-Dihydro-2-ethyl-3-oxo-1H-isoindol-1-ylidene)(phenyl) methyl benzoate (2b)

White solid; mp: 158–160 °C; ^1H NMR δ 1.28 (t, J = 7.1 Hz, 3H), 4.03 (q, J = 7.1 Hz, 2H), 6.53 (d, J = 8.0 Hz, 1H), 7.21 (t, J = 7.7 Hz, 1H), 7.38 (t, J = 7.5 Hz, 1H), 7.47–7.53 (m, 5H), 7.63–7.70 (m, 3H), 7.84 (d, J = 7.5 Hz, 1H), 8.14 (d, J = 7.3 Hz, 2H); ^{13}C NMR δ 14.5, 37.4, 122.6, 123.2, 126.8, 128.7, 128.8, 128.9, 129.0, 129.4, 130.0, 130.2, 131.0, 131.4, 131.9, 134.1, 134.7, 135.7, 164.6, 167.2; HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{20}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 370.1443, found: 370.1439.

3.2.5. 2-Ethyl-3-p-fluorobenzoylisoindolin-1-one (3a)

Oil; ^1H NMR δ 1.22 (t, J = 7.2 Hz, 3H), 3.15–3.24 (m, 1H), 4.05–4.12 (m, 1H), 6.01 (s, 1H), 7.20 (t, J = 8.6 Hz, 2H), 7.23 (d, J = 7.1 Hz, 1H), 7.45 (dt, J = 1.3 Hz, J = 7.5 Hz, 1H), 7.50 (t, J = 7.4 Hz, 1H), 7.90 (d, J = 7.1 Hz, 1H), 7.96–8.00 (m, 2H); ^{13}C NMR δ 13.3, 36.4, 65.6, 116.4 (d, $J_{\text{F-C}}$ = 22.0 Hz), 122.5, 124.4, 129.2, 131.5, 131.6, 131.8, 132.3, 139.4, 166.3 (d, $J_{\text{F-C}}$ = 257.5 Hz), 168.7, 192.4. HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{15}\text{FNO}_2$ $[\text{M}+\text{H}]^+$: 284.1087, found: 284.1084.

3.2.6. (2,3-Dihydro-2-ethyl-3-oxo-1H-isoindol-1-ylidene)(p-fluorophenyl)methyl p-fluorobenzoate (3b)

White solid; mp: 119–121 °C; The ^1H NMR spectrum showed a Z:E ratio of 90:10. The pure Z-isomer was obtained through crystallization from the mixture solvent of CH_2Cl_2 and hexane. ^1H NMR of major Z-isomer δ 1.27 (t, J = 7.1 Hz, 2.7 H), 4.01 (q, J = 7.2 Hz, 1.8H), 6.49 (d, J = 7.5 Hz, 0.9H), 7.17–7.25 (m, 4.5H), 7.40 (t, J = 7.7 Hz, 0.9H), 7.65–7.69 (m, 1.8H), 7.86 (d, J = 7.5 Hz, 0.9H), 8.11–8.17 (m, 1.8H); ^1H NMR of minor E-isomer δ 0.86 (t, J = 7.0 Hz, 0.3H), 3.54 (q, J = 7.2 Hz, 0.2H), 6.86–6.91 (m, 0.1H), 7.12–7.15 (m,

0.5H), 7.44–7.48 (m, 0.2H), 7.62–7.65 (m, 0.1H), 7.89–7.91 (m, 0.1H), 8.23–8.26 (m, 0.2H); ^{13}C NMR δ 14.8, 37.2, 115.6, 115.8, 116.2 (d, $J_{\text{F-C}}$ = 4.9 Hz), 116.4 (d, $J_{\text{F-C}}$ = 4.6 Hz), 122.5, 123.5, 125.0, 127.2, 129.0, 129.4, 130.5, 130.6, 130.7, 131.6, 132.8, 132.9, 133.0, 133.1, 133.2, 135.5, 163.6 (d, $J_{\text{F-C}}$ = 251.3 Hz), 163.7, 166.5 (d, $J_{\text{F-C}}$ = 256.9 Hz), 167.2; HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{18}\text{F}_2\text{NO}_3$ $[\text{M}+\text{H}]^+$: 406.1255, found: 406.1251.

3.2.7. 2-Ethyl-3-propionylisoindolin-1-one (4a)

White solid; mp: 47–49 °C; ^1H NMR δ 0.43 (t, J = 7.4 Hz, 3H), 0.94 (t, J = 7.2 Hz, 3H), 1.10–1.22 (m, 2H), 1.73–1.81 (m, 1H), 1.90–1.98 (m, 1H), 2.82–1.91 (m, 1H), 3.79–3.85 (m, 1H), 4.75 (s, 1H), 7.12 (d, J = 7.1 Hz, 1H), 7.21–7.28 (m, 2H), 7.58 (q, J = 6.5 Hz, 1H); ^{13}C NMR δ 13.3, 13.4, 16.6, 36.7, 38.0, 69.5, 122.5, 124.1, 129.3, 132.0, 132.3, 138.9, 168.9, 206.8; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{18}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 232.1338, found: 232.1333.

3.2.8. (2,3-Dihydro-2-ethyl-3-oxo-1H-isoindol-1-ylidene)(propyl) methyl butyrate (4b)

Oil; The ^1H NMR spectrum showed a Z:E ratio of ca. 75:25. ^1H NMR of major isomer δ 1.02 (t, J = 7.5 Hz, 4.5H), 1.21 (t, J = 7.1 Hz, 2.25H), 2.48 (t, J = 7.4 Hz, 1.5H), 2.80 (t, J = 7.6 Hz, 1.5H), 3.93 (q, J = 7.1 Hz, 1.5H), 7.42–7.46 (m, 0.75H), 7.53–7.57 (m, 0.75H), 7.65 (d, J = 8.0 Hz, 0.75H), 7.87 (d, J = 7.4 Hz, 0.75H); ^1H NMR of minor isomer δ 0.95 (t, J = 7.4 Hz, 1.5H), 1.29 (t, J = 7.1 Hz, 0.75), 2.63 (t, J = 7.4 Hz, 0.5H), 2.72 (t, J = 7.5 Hz, 0.5H), 4.01 (q, J = 7.1 Hz, 0.5H), 7.39–7.41 (m, 0.25H), 7.49–7.51 (m, 0.25H), 7.74 (d, J = 7.8 Hz, 0.25H), 7.83 (d, J = 7.7 Hz, 0.25H); other signals of two isomers were overlapped at 1.64–1.80 (m, 4H) ppm; ^{13}C NMR of major isomer

δ 13.7, 13.9, 14.8, 18.2, 20.7, 34.0, 36.2, 37.2, 122.6, 123.4, 123.6, 123.8, 128.4, 131.9, 135.2, 135.7, 166.7, 171.6; ^{13}C NMR of minor isomer δ 13.6, 14.5, 18.2, 18.3, 21.1, 33.1, 35.7, 36.5, 125.5, 128.6, 129.8, 132.2, 172.0; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{24}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 302.1756, found: 302.1755.

3.2.9. 2-Ethyl-3-ferrocenylformylisindolin-1-one (**5**)

Red solid; mp: 163–165 °C; ^1H NMR δ 1.27 (t, J = 7.3 Hz, 3H), 3.14–3.23 (m, 1H), 4.01 (s, 5H), 4.13–4.22 (m, 1H), 4.56 (s, br, 1H), 4.61–4.63 (m, 2H), 5.00–5.02 (m, 1H), 5.48 (s, 1H), 7.50–7.56 (m, 3H), 7.93 (d, J = 6.3 Hz, 1H); ^{13}C NMR δ 13.4, 36.5, 67.6, 69.1, 70.1, 71.0, 72.9, 73.3, 122.8, 124.0, 129.1, 131.6, 132.1, 140.4, 168.8, 199.5; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{20}\text{FeNO}_2$ $[\text{M}+\text{H}]^+$: 374.0843, found: 374.0840.

3.2.10. 2-Isopropyl-3-acylisindolin-1-one (**6**)

White solid; mp: 70–72 °C; ^1H NMR δ 1.31 (d, J = 6.9 Hz, 3H), 1.33 (d, J = 6.8 Hz, 3H), 1.87 (s, 3H), 4.55–4.62 (m, 1H), 5.04 (s, 1H), 7.39 (d, J = 7.1 Hz, 1H), 7.54–7.61 (m, 2H), 7.91 (d, J = 6.9 Hz, 1H); ^{13}C NMR δ 20.4, 20.5, 23.0, 45.0, 68.4, 122.3, 123.9, 129.3, 132.1, 132.6, 139.2, 169.1, 205.5; HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{16}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 218.1181, found: 218.1180.

3.2.11. 2-Isopropyl-3-propionylisindolin-1-one (**7**)

Oil; ^1H NMR δ 0.72 (t, J = 7.4 Hz, 3H), 1.28 (d, J = 6.9 Hz, 3H), 1.33 (d, J = 6.8 Hz, 3H), 1.37–1.43 (m, 2H), 1.92–1.98 (m, 1H), 2.25–2.33 (m, 1H), 4.45–4.55 (m, 1H), 5.04 (s, 1H), 7.32–7.34 (m, 1H), 7.48–7.54 (m, 2H), 7.85–7.87 (m, 1H); ^{13}C NMR δ 13.5, 17.1, 20.7, 20.8, 37.2, 45.3, 68.5, 122.5, 124.2, 129.4, 132.1, 132.8, 139.5, 169.6, 208.2; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{20}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 246.1494, found: 246.1483.

3.2.12. 2-Isopropyl-3-benzoylisindolin-1-one (**8**)^{13f}

Yellow solid; ^1H NMR δ 1.19 (d, J = 6.9 Hz, 3H), 1.35 (d, J = 6.8 Hz, 3H), 4.43–4.52 (m, 1H), 5.96 (s, 1H), 7.22 (d, J = 7.4 Hz, 1H), 7.42–7.54 (m, 4H), 7.62 (d, J = 7.4 Hz, 1H), 7.86 (d, J = 7.5 Hz, 2H), 7.92 (d, J = 7.4 Hz, 1H); ^{13}C NMR δ 20.7, 21.1, 45.5, 65.3, 122.3, 124.3, 128.9, 129.1, 129.2, 131.8, 132.7, 134.1, 135.2, 140.3, 169.2, 195.3; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{18}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 280.1338, found: 280.1338.

3.2.13. 2-Isopropyl-3-*p*-fluorobenzoylisindolin-1-one (**9**)

White solid; mp: 121–123 °C; ^1H NMR δ 1.17 (d, J = 6.8 Hz, 3H), 1.34 (d, J = 6.8 Hz, 3H), 4.46–4.53 (m, 1H), 5.89 (s, 1H), 7.13 (t, J = 8.6 Hz, 2H), 7.23 (d, J = 6.9 Hz, 1H), 7.45–7.54 (m, 2H), 7.87–7.94 (m, 3H); ^{13}C NMR δ 20.7, 21.1, 45.5, 65.6, 116.3 (d, $J_{\text{F-C}}$ = 21.9 Hz), 122.3, 124.4, 129.3, 131.4 (d, $J_{\text{F-C}}$ = 3.0 Hz), 131.6 (d, $J_{\text{F-C}}$ = 9.2 Hz), 132.0, 132.5, 140.2, 166.1 (d, $J_{\text{F-C}}$ = 257.3 Hz), 169.2, 193.9; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{17}\text{FNO}_2$ $[\text{M}+\text{H}]^+$: 298.1243, found: 298.1234.

3.2.14. 2-Isopropyl-3-ferrocenylformylisindolin-1-one (**10**)

Red solid; mp: 136–138 °C; ^1H NMR δ 1.16 (d, J = 6.8 Hz, 3H), 1.33 (d, J = 6.7 Hz, 3H), 3.89 (s, 5H), 4.35–4.42 (m, 2H), 4.45 (s, 1H), 4.55 (s, 1H), 5.00 (s, 1H), 5.38 (s, 1H), 7.53–7.62 (m, 3H), 7.95 (d, J = 7.2 Hz, 1H); ^{13}C NMR δ 20.71, 20.73, 45.6, 68.1, 68.6, 70.2, 71.6, 72.1, 72.8, 122.8, 124.0, 129.1, 131.6, 132.7, 141.0, 169.3, 194.5; HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{22}\text{FeNO}_2$ $[\text{M}+\text{H}]^+$: 388.1000, found: 388.0996.

3.2.15. 2-*tert*-Butyl-3-acylisindolin-1-one (**11**)

White solid; mp: 104–106 °C; ^1H NMR δ 1.56 (s, 9H), 1.93 (s, 3H), 5.16 (s, 1H), 7.34–7.36 (m, 1H), 7.51–7.57 (m, 2H), 7.83–7.85 (m, 1H); ^{13}C NMR δ 23.1, 28.2, 56.0, 70.5, 122.2, 123.8, 129.4, 132.1, 133.6, 138.5, 170.1, 206.2; HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{18}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 232.1338, found: 232.1337.

3.2.16. 2-*tert*-Butyl-3-propionylisindolin-1-one (**12**)

Oil; ^1H NMR δ 0.71 (t, J = 7.4 Hz, 3H), 1.37–1.49 (m, 2H), 1.55 (s, 9H), 2.01–2.09 (m, 1H), 2.33–2.45 (m, 1H), 5.18 (s, 1H), 7.32–7.35 (m, 1H), 7.48–7.55 (m, 2H), 7.83–7.85 (m, 1H); ^{13}C NMR δ 13.4, 17.0, 28.3, 37.2, 56.0, 70.5, 122.3, 123.8, 129.3, 131.9, 133.6, 138.7, 170.3, 208.2; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{22}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 260.1651, found: 260.1650.

3.2.17. 2-*tert*-Butyl-3-benzoylisindolin-1-one (**13**)

White solid; mp: 160–161 °C; ^1H NMR δ 1.51 (s, 9H), 6.16 (s, 1H), 7.15 (d, J = 6.5 Hz, 1H), 7.38–7.41 (m, 1H), 7.44–7.53 (m, 3H), 7.62–7.66 (m, 1H), 7.85–7.92 (m, 3H); ^{13}C NMR δ 28.0, 55.6, 66.4, 122.0, 123.9, 128.9, 129.0, 129.2, 131.5, 133.6, 134.1, 135.1, 139.4, 169.6, 195.4; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{20}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 294.1494, found: 294.1495.

3.2.18. 2-*tert*-Butyl-3-*p*-fluorobenzoylisindolin-1-one (**14**)

White solid; mp: 157–159 °C; ^1H NMR δ 1.57 (s, 9H), 6.15 (s, 1H), 7.22–7.31 (m, 3H), 7.47–7.56 (m, 2H), 7.94 (d, J = 7.2 Hz, 1H), 8.01–8.08 (m, 2H); ^{13}C NMR δ 28.0, 55.8, 66.8, 116.4 (d, $J_{\text{F-C}}$ = 21.9 Hz), 122.0, 124.1, 129.2, 131.4 (d, $J_{\text{F-C}}$ = 3.0 Hz), 131.6 (d, $J_{\text{F-C}}$ = 9.2 Hz), 131.7, 133.5, 139.3, 166.1 (d, $J_{\text{F-C}}$ = 256.9 Hz), 169.7, 194.0; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{19}\text{FNO}_2$ $[\text{M}+\text{H}]^+$: 312.1400, found: 312.1395.

3.2.19. 2-*tert*-Butyl-3-ferrocenylformylisindolin-1-one (**15**)

Red solid; mp: 157–159 °C; ^1H NMR δ 1.47 (s, 9H), 3.79 (s, 5H), 4.38–4.46 (m, 2H), 4.52 (s, 1H), 5.01–5.03 (m, 1H), 5.46 (s, 1H), 7.53–7.58 (m, 3H), 7.92 (d, J = 7.3 Hz, 1H); ^{13}C NMR δ 28.1, 56.1, 68.7, 70.4, 71.8, 72.1, 72.3, 122.5, 123.7, 129.0, 131.5, 133.3, 140.5, 170.1, 201.2; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{24}\text{FeNO}_2$ $[\text{M}+\text{H}]^+$: 402.1156, found: 402.1151.

3.2.20. 2-Cyclohexyl-3-acylisindolin-1-one (**16**)

White solid; mp: 89–91 °C; ^1H NMR δ 1.11–1.20 (m, 1H), 1.37–1.47 (m, 3H), 1.52–1.60 (m, 1H), 1.67–1.71 (m, 1H), 1.83–1.94 (m, 7H), 4.19–4.24 (m, 1H), 5.03 (s, 1H), 7.36–7.38 (m, 1H), 7.53–7.59 (m, 2H), 7.90–7.92 (m, 1H); ^{13}C NMR δ 22.9, 25.2, 25.6, 25.8, 31.1, 31.3, 53.0, 68.9, 122.5, 124.2, 129.5, 132.2, 132.7, 139.3, 169.4, 206.3; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{20}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 258.1494, found: 258.1492.

3.2.21. 2-Cyclohexyl-3-propionylisindolin-1-one (**17**)

White solid; mp: 82–84 °C; ^1H NMR δ 0.70 (t, J = 7.4 Hz, 3H), 1.09–1.20 (m, 1H), 1.36–1.44 (m, 5H), 1.55–1.70 (m, 2H), 1.82–1.97 (m, 5H), 2.27–2.35 (m, 1H), 4.14–4.21 (m, 1H), 5.05 (s, 1H), 7.34–7.36 (m, 1H), 7.51–7.57 (m, 2H), 7.89–7.91 (m, 1H); ^{13}C NMR δ 13.5, 17.2, 25.3, 25.7, 25.8, 31.1, 31.3, 37.1, 53.1, 68.8, 122.5, 124.2, 129.3, 132.0, 132.7, 139.6, 169.6, 208.4; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{24}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 286.1807, found: 286.1803.

3.2.22. 2-Cyclohexyl-3-benzoylisindolin-1-one (**18**)

White solid; mp: 145–147 °C; ^1H NMR δ 0.86–1.12 (m, 1H), 1.25–1.42 (m, 3H), 1.55–1.94 (m, 6H), 4.11–4.16 (m, 1H), 6.00 (s, 1H), 7.19 (d, J = 7.4 Hz, 1H), 7.40–7.49 (m, 4H), 7.62 (d, J = 7.3 Hz, 1H), 7.87–8.14 (m, 3H); ^{13}C NMR δ 25.4, 25.8 (2 C), 31.1, 31.5, 53.4, 65.4, 122.3, 124.3, 128.9, 129.1 (2 C), 131.7, 132.6, 134.1, 135.2, 140.4, 169.2, 195.2; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{22}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 320.1651, found: 320.1645.

3.2.23. 2-Cyclohexyl-3-*p*-fluorobenzoylisindolin-1-one (**19**)

Oil; ^1H NMR δ 0.89–1.14 (m, 1H), 1.25–1.44 (m, 3H), 1.58–1.93 (m, 6H), 4.14–4.19 (m, 1H), 5.86 (s, 1H), 7.12 (t, J = 8.0 Hz, 2H), 7.24 (d, J = 7.3 Hz, 1H), 7.45–7.54 (m, 2H), 7.85–7.88 (m, 2H), 7.94 (d, J = 7.3 Hz, 1H); ^{13}C NMR δ 25.3, 25.8 (2 C), 31.2, 31.6, 53.3, 66.1, 116.2

(d, $J_{F-C} = 21.9$ Hz), 122.3, 124.5, 129.3, 131.6, 131.7, 131.9, 132.5, 140.4, 166.1 (d, $J_{F-C} = 257.5$ Hz), 169.2, 194.1; HRMS (ESI) calcd for $C_{21}H_{21}FNO_2$ $[M+H]^+$: 338.1556, found: 338.1549.

3.2.24. 2-Cyclohexyl-3-ferrocenylformylisoindolin-1-one (20)

Red solid; mp: 169–171 °C; 1H NMR δ 1.06–1.16 (m, 1H), 1.23–1.42 (m, 3H), 1.61–1.91 (m, 6H), 3.89 (s, 5H), 4.03–4.09 (m, 1H), 4.40 (s, 1H), 4.45 (s, 1H), 4.56 (s, 1H), 5.00 (s, 1H), 5.40 (s, 1H), 7.53–7.61 (m, 3H), 7.96 (d, $J = 7.1$ Hz, 1H); ^{13}C NMR δ 25.4, 25.8, 25.9, 31.0, 31.1, 53.5, 68.8, 70.3, 71.5, 72.1, 72.8, 122.7, 124.0, 129.1, 131.6, 132.6, 141.1, 169.3; HRMS (ESI) calcd for $C_{25}H_{26}FeNO_2$ $[M+H]^+$: 428.1313, found: 428.1303.

3.2.25. 2-(2,6-Dimethylphenyl)-3-acylisoindolin-1-one (21)

Oil; 1H NMR δ 2.08 (s, 3H), 2.13 (s, 3H), 2.35 (s, 3H), 5.49 (s, 1H), 7.09–7.20 (m, 3H), 7.51 (d, $J = 7.4$ Hz, 1H), 7.57–7.67 (m, 2H), 7.99 (d, $J = 7.4$ Hz, 1H); ^{13}C NMR δ 18.7, 19.0, 27.4, 70.9, 122.8, 124.9, 128.6, 129.1, 129.2, 129.6, 131.5, 132.7, 134.3, 135.4, 138.0, 140.0, 168.3, 202.4; HRMS (ESI) calcd for $C_{18}H_{18}NO_2$ $[M+H]^+$: 280.1338, found: 280.1331.

3.2.26. 2-(2,6-Dimethylphenyl)-3-propionylisoindolin-1-one (22)

Oil; 1H NMR δ 0.76 (t, $J = 7.4$ Hz, 3H), 1.45–1.50 (m, 2H), 2.16 (s, 3H), 2.27–2.33 (m, 1H), 2.37 (s, 3H), 2.44–2.52 (m, 1H), 5.57 (s, 1H), 7.09–7.18 (m, 3H), 7.48 (d, $J = 7.4$ Hz, 1H), 7.55–7.64 (m, 2H), 7.98 (d, $J = 7.3$ Hz, 1H); ^{13}C NMR δ 13.4, 16.8, 18.8, 19.0, 42.9, 70.0, 122.6, 124.8, 128.4, 129.0, 129.2, 129.4, 131.6, 132.4, 134.4, 135.2, 138.1, 140.2, 168.0, 204.5; HRMS (ESI) calcd for $C_{20}H_{22}NO_2$ $[M+H]^+$: 308.1651, found: 308.1650.

3.2.27. 2-(2,6-Dimethylphenyl)-3-benzoylisoindolin-1-one (23)

White solid; mp: 131–133 °C; 1H NMR δ 2.30 (s, 3H), 2.40 (s, 3H), 6.60 (s, 1H), 7.07–7.15 (m, 3H), 7.21 (d, $J = 7.4$ Hz, 1H), 7.46–7.54 (m, 4H), 7.63 (t, $J = 7.4$ Hz, 1H), 7.88 (d, $J = 7.9$ Hz, 2H), 8.02 (d, $J = 7.3$ Hz, 1H); ^{13}C NMR δ 18.85, 18.89, 65.8, 122.7, 124.9, 128.4, 128.6, 128.9, 129.1, 129.2, 129.3, 131.6, 132.2, 134.3, 134.5, 134.9, 136.1, 139.1, 140.8, 168.1, 193.4; HRMS (ESI) calcd for $C_{23}H_{20}NO_2$ $[M+H]^+$: 342.1494, found: 342.1490.

3.2.28. 2-(2,6-Dimethylphenyl)-3-p-fluorobenzoylisoindolin-1-one (24)

Oil; 1H NMR δ 2.28 (s, 3H), 2.34 (s, 3H), 6.50 (s, 1H), 7.09–7.16 (m, 5H), 7.23 (d, $J = 7.3$ Hz, 1H), 7.52–7.60 (m, 2H), 7.87–7.90 (m, 2H), 8.02 (d, $J = 6.8$ Hz, 1H); ^{13}C NMR δ 18.76, 18.80, 65.7, 116.3 (d, $J_{F-C} = 21.6$ Hz), 122.7, 125.0, 128.5, 128.6, 129.3, 129.4, 131.5, 131.6, 132.3, 132.5 (d, $J_{F-C} = 3.2$ Hz), 134.4, 135.0, 139.0, 140.8, 166.3 (d, $J_{F-C} = 257.6$ Hz), 168.0, 192.0; HRMS (ESI) calcd for $C_{23}H_{19}FNO_2$ $[M+H]^+$: 360.1400, found: 360.1391.

3.2.29. 2-(2,6-Dimethylphenyl)-3-ferrocenylformylisoindolin-1-one (25)

Red solid; mp: 273–275 °C; 1H NMR δ 2.39 (s, 3H), 2.64 (s, 3H), 3.84 (s, 5H), 4.67–4.70 (m, 2H), 4.87 (s, 1H), 4.93 (s, 1H), 6.09 (s, 1H), 7.16–7.25 (m, 3H), 7.38–7.40 (m, 1H), 7.50–7.56 (m, 2H), 7.99–8.01 (m, 1H); ^{13}C NMR δ 19.00, 19.02, 66.9, 69.6, 69.9, 70.0, 73.5, 73.9, 122.5, 124.7, 128.6, 128.7, 129.0, 129.6, 131.4, 131.9, 134.7, 134.9, 139.8, 141.1, 168.1, 196.2; HRMS (ESI) calcd for $C_{27}H_{24}FeNO_2$ $[M+H]^+$: 450.1156, found: 450.1150.

3.2.30. 5-Acetyl-6-tert-butyl-5,6-dihydro-7H-pyrrolo[3,4-b]pyridin-7-one (26)

White solid; mp: 183–185 °C; 1H NMR δ 1.59 (s, 9H), 1.98 (s, 3H), 5.18 (s, 1H), 7.44–7.47 (m, 1H), 7.74 (d, $J = 7.8$ Hz, 1H), 8.85 (d, $J = 4.5$ Hz, 1H); ^{13}C NMR δ 23.4, 28.1, 56.7, 68.1, 125.8, 130.7, 132.7, 151.2, 152.3, 167.6, 205.3; HRMS (ESI) calcd for $C_{13}H_{17}N_2O_2$

$[M+H]^+$: 233.1290, found: 233.1286.

3.2.31. 5-Benzoyl-6-tert-butyl-5,6-dihydro-7H-pyrrolo[3,4-b]pyridin-7-one (27)

White solid; mp: 209–211 °C; 1H NMR δ 1.55 (s, 9H), 6.25 (s, 1H), 7.28–7.30 (m, 1H), 7.48 (d, $J = 7.7$ Hz, 1H), 7.56 (t, $J = 7.7$ Hz, 2H), 7.70 (t, $J = 7.4$ Hz, 1H), 7.98 (d, $J = 7.6$ Hz, 2H), 8.77 (d, $J = 3.9$ Hz, 1H); ^{13}C NMR δ 27.8, 56.2, 63.9, 125.1, 128.9, 129.4, 130.2, 133.6, 134.5, 134.7, 151.3, 151.7, 167.2, 194.3; HRMS (ESI) calcd for $C_{18}H_{19}N_2O_2$ $[M+H]^+$: 295.1447, found: 295.1448.

3.3. Reaction of 2a and 8

A hexane solution of *n*-BuLi (1.6 M, 0.63 mL, 1 mmol) was added to the solution of **2a** or **8** (1 mmol) in THF (15 mL) at -78 °C. After the resulting mixture was stirred for 30 min, *p*-FC₆H₄COCl or CH₃COCl (1 mmol) was added. The reaction mixture was continuously stirred at -78 °C for 30 min, allowed to reach room temperature slowly and stirred for overnight. The solvent was removed under reduced pressure, and the residue was isolated by column chromatography on silica with ethyl acetate/petroleum ether (V/V = 1:4) as the eluent to give the products.

3.3.1. (2,3-Dihydro-2-ethyl-3-oxo-1H-isoindol-1-ylidene)(phenyl)methyl *p*-fluorobenzoate (28)

This compound was obtained using **2a** and *p*-FC₆H₄COCl. White solid; mp: 153–155 °C; The 1H NMR spectrum showed a Z:E ratio of 92:8. The pure Z-isomer was obtained by crystallization of the mixture from CH₂Cl₂ and hexane. 1H NMR of Z-isomer δ 1.28 (t, $J = 7.1$ Hz, 3H), 4.02 (q, $J = 7.0$ Hz, 2H), 6.52 (d, $J = 8.0$ Hz, 1H), 7.15–7.22 (m, 3H), 7.37 (t, $J = 7.5$ Hz, 1H), 7.46–7.50 (m, 3H), 7.67–7.69 (m, 2H), 7.84 (d, $J = 7.5$ Hz, 1H), 8.14–8.18 (m, 2H); 1H NMR of E-isomer δ 1.06 (t, $J = 7.3$ Hz), 3.84 (q, $J = 7.1$ Hz), 7.76–7.79 (m), 8.04–8.08 (m); other signals were overlapped with those of Z-isomer; ^{13}C NMR of Z-isomer δ 14.9, 37.2, 116.2 (d, $J_{F-C} = 22.1$ Hz), 122.6, 123.3, 125.1, 126.9, 128.8, 129.0, 129.4, 130.1, 130.9, 131.5, 131.6, 132.8, 132.9, 134.6, 135.7, 163.6, 166.1 (d, $J_{F-C} = 256.3$ Hz), 167.2; HRMS (ESI) calcd for $C_{24}H_{19}FNO_3$ $[M+H]^+$: 388.1349, found: 388.1341.

3.3.2. (2,3-Dihydro-2-isopropyl-3-oxo-1H-isoindol-1-ylidene)(phenyl)methyl acetate (29)

This compound was obtained using **8** and CH₃COCl. White solid; mp: 112–114 °C; 1H NMR δ 1.65 (d, $J = 6.9$ Hz, 6H), 2.22 (s, 3H), 4.62–4.69 (m, 1H), 6.31 (d, $J = 8.0$ Hz, 1H), 7.13 (t, $J = 7.7$ Hz, 1H), 7.32 (t, $J = 7.4$ Hz, 1H), 7.47–7.51 (m, 3H), 7.56–7.58 (m, 2H), 7.76 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR δ 20.7, 21.2, 48.1, 122.4, 122.8, 127.7, 128.6, 129.0, 129.9, 130.0, 130.9, 131.3, 131.5, 135.1, 136.0, 168.1, 168.6; HRMS (ESI) calcd for $C_{20}H_{20}NO_3$ $[M+H]^+$: 322.1443, found: 322.1440.

3.4. Synthesis of 30–37

These compounds were obtained through similar procedure mentioned above for synthesis of **1–27**, using PhCO(CH₂)_nBr (*n* = 1 or 3) as the electrophile instead of acyl chloride.

3.4.1. 2-Ethyl-3-(2-phenyl-2-oxiranyl)isoindolin-1-one (30)

Yellow solid; mp: 147–149 °C; 1H NMR δ 1.29 (t, $J = 7.2$ Hz, 3H), 3.05 (d, $J = 5.0$ Hz, 1H), 3.22 (d, $J = 5.0$ Hz, 1H), 3.41–3.50 (m, 1H), 4.20–4.29 (m, 1H), 4.42 (s, 1H), 7.03–7.11 (m, 5H), 7.36 (t, $J = 7.4$ Hz, 1H), 7.48 (t, $J = 7.5$ Hz, 1H), 7.65 (t, $J = 7.1$ Hz, 2H); ^{13}C NMR δ 13.5, 36.0, 53.0, 60.0, 64.3, 123.4, 123.7, 127.1, 128.0, 128.4, 128.7, 131.4, 132.4, 134.3, 142.3, 168.6; HRMS (ESI) calcd for $C_{18}H_{18}NO_2$ $[M+H]^+$: 280.1338, found: 280.1333.

3.4.2. 2-Isopropyl-3-(2-phenyl-2-oxiranyl)isoindolin-1-one (31)

White solid; mp: 137–139 °C; The ^1H NMR spectrum showed a mixture of diastereoisomers. ^1H NMR of major isomer δ 1.47 (d, $J = 6.8$ Hz, 2.82H), 1.55 (d, $J = 6.9$ Hz, 2.82H), 3.10 (d, $J = 4.9$ Hz, 0.94H), 3.19 (d, $J = 4.9$ Hz, 0.94H), 4.23–4.35 (m, 1H), 4.49 (s, 0.94H), 7.12–7.21 (m, 4.76H), 7.39 (t, $J = 7.4$ Hz, 0.94H), 7.46 (t, $J = 7.4$ Hz, 0.94H), 7.52–7.56 (m, 1H), 7.68 (d, $J = 7.4$ Hz, 0.94H); ^1H NMR of minor isomer δ 1.26 (d, $J = 6.7$ Hz, 0.18H), 1.30 (d, $J = 6.9$ Hz, 0.18H), 2.99 (d, $J = 5.1$ Hz, 0.06H), 3.50 (d, $J = 5.1$ Hz, 0.06H), 4.41 (s, 0.06H), 6.76 (d, $J = 7.5$ Hz, 0.12H), 7.06 (t, $J = 7.4$ Hz, 0.12H), 7.58–7.61 (m, 0.12H), 7.84 (d, $J = 7.4$ Hz, 0.06H); other signals at 4.23–4.35, 7.12–7.21 and 7.52–7.56 ppm were overlapped with those of major isomer; ^{13}C NMR δ 20.5, 20.6, 47.0, 53.3, 60.8, 64.7, 123.3, 123.8, 127.7, 128.1, 128.5, 128.7, 131.5, 133.0, 135.0, 142.9, 169.8; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{20}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 294.1494, found: 294.1492.

3.4.3. 2-Cyclohexyl-3-(2-phenyl-2-oxiranyl)isoindolin-1-one (32)

Yellow solid; mp: 92–94 °C; The ^1H NMR spectrum showed a mixture of diastereoisomers. ^1H NMR δ 1.20–1.42 (m, 4H), 1.70–1.73 (m, 1H), 1.87–1.98 (m, 4H), 2.12–2.22 (m, 1H), 3.11 (d, $J = 4.9$ Hz, 1H), 3.23 (d, $J = 4.9$ Hz, 0.96H), 3.39 (d, $J = 11.0$ Hz, 0.04H), 3.90–3.96 (m, 1H), 4.51 (s, 1H), 7.14–7.18 (m, 5H), 7.39 (t, $J = 7.3$ Hz, 1H), 7.46 (t, $J = 7.4$ Hz, 1H), 7.55 (d, $J = 7.5$ Hz, 1H), 7.68 (d, $J = 7.4$ Hz, 1H); ^{13}C NMR δ 25.6, 26.2, 26.4, 30.7, 30.9, 53.7, 55.2, 60.8, 64.6, 123.3, 123.7, 127.6, 128.0, 128.4, 128.7, 131.4, 132.9, 135.1, 143.0, 169.8; HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{24}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 334.1807, found: 334.1804.

3.4.4. 2-Ethyl-3-(tetrahydro-2-phenyl-2-furanyl)isoindolin-1-one (33)

Yellow solid; mp: 87–89 °C; The ^1H NMR spectrum showed a mixture of diastereoisomers. ^1H NMR of major isomer δ 1.31 (t, $J = 7.1$ Hz, 2.43H), 1.64–2.01 (m, 2.62H), 2.17–2.22 (m, 0.81H), 3.59–3.68 (m, 1H), 3.72–3.77 (m, 0.81H), 3.95–4.02 (m, 1H), 4.28–4.37 (m, 0.81H), 4.90 (s, 0.81), 6.68 (d, $J = 7.5$ Hz, 0.81H), 7.02–7.11 (m, 0.81H), 7.26–7.34 (m, 4.62H), 7.63–7.67 (m, 1H); ^1H NMR of minor isomer δ 1.16 (t, $J = 7.1$ Hz, 0.57H), 2.27–2.45 (m, 0.38H), 2.55–2.60 (m, 0.19H), 4.05–4.09 (m, 0.19H), 4.12–4.16 (m, 0.19H), 4.86 (s, 0.19H), 6.83 (d, $J = 7.1$ Hz, 0.38H), 7.44 (t, $J = 7.4$ Hz, 0.19H), 7.56 (t, $J = 7.3$ Hz, 0.19H), 7.75 (d, $J = 7.6$ Hz, 0.19H); other signals were overlapped with those of major isomer; ^{13}C NMR of major isomer δ 13.5, 25.2, 30.7, 37.3, 65.7, 66.5, 89.0, 123.0, 124.7, 126.9, 127.8, 127.9, 128.1, 130.3, 132.9, 140.7, 142.8, 169.7; ^{13}C NMR of minor isomer δ 13.2, 24.4, 36.5, 36.8, 67.3, 67.5, 90.1, 123.3, 123.4, 125.8, 127.4, 127.5, 128.5, 130.8, 134.1, 139.2, 142.5, 168.4; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{22}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 308.1651, found: 308.1647.

3.4.5. 2-Isopropyl-3-(tetrahydro-2-phenyl-2-furanyl)isoindolin-1-one (34)

Yellow solid; mp: 44–46 °C; The ^1H NMR spectrum showed a mixture of diastereoisomers. The major isomer could be obtained by crystallization of the mixture from CH_2Cl_2 and hexane. ^1H NMR of major isomer δ 1.42 (d, $J = 6.8$ Hz, 2.49H), 1.71 (d, $J = 6.9$ Hz, 2.49H), 1.73–1.80 (m, 1.83H), 1.89–1.96 (m, 2.17H), 3.56–3.61 (m, 0.83H), 3.94–4.00 (m, 1H), 4.33–4.44 (m, 0.83H), 4.87 (s, 0.83H), 6.20 (d, $J = 7.7$ Hz, 0.83H), 7.17 (dt, $J = 7.6$ and 1.1 Hz, 0.83H), 7.30–7.43 (m, 4.98H), 7.69 (d, $J = 7.5$ Hz, 0.83H); ^1H NMR of minor isomer δ 1.52 (d, $J = 6.8$ Hz, 0.51H), 2.26–2.36 (m, 0.34H), 2.51–2.57 (m, 0.17H), 4.01–4.07 (m, 0.34H), 4.72 (s, 0.17H), 6.93 (d, $J = 7.6$ Hz, 0.34H), 7.05–7.11 (m, 0.51H), 7.50–7.55 (m, 0.34H), 7.64 (d, $J = 7.2$ Hz, 0.17H), 7.73–7.76 (m, 0.17H); other signals were overlapped with those of major isomer; ^{13}C NMR of major isomer δ 19.8, 20.7, 24.2, 27.1, 49.8, 66.2, 67.5, 89.3, 122.9, 124.0, 127.4, 127.5, 128.1, 128.2, 130.1, 134.0, 141.2, 142.9, 170.6; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{24}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 322.1807, found: 322.1805.

3.4.6. 2-Cyclohexyl-3-(tetrahydro-2-phenyl-2-furanyl)isoindolin-1-one (35)

White solid; mp: 136–138 °C; The ^1H NMR spectrum showed a mixture of diastereoisomers. The major isomer could be obtained by crystallization of the mixture from CH_2Cl_2 and hexane. ^1H NMR of major isomer δ 1.28–1.30 (m, 3H), 1.69–2.00 (m, 8.82H), 2.13–2.21 (m, 1.12H), 2.64–2.74 (m, 0.94H), 3.58–3.63 (m, 0.94H), 3.90–4.04 (m, 2.06H), 4.89 (s, 0.94H), 6.19 (d, $J = 7.7$ Hz, 0.94H), 7.18 (t, $J = 7.5$ Hz, 0.94H), 7.33 (t, $J = 7.5$ Hz, 0.94H), 7.36–7.42 (m, 4.7H), 7.70 (d, $J = 7.5$ Hz, 0.94H); ^1H NMR of minor isomer δ 2.46–2.52 (m, 0.12H), 4.75 (s, 0.06H), 7.02–7.04 (m, 0.12H), 7.10–7.12 (m, 0.12H), 7.49–7.53 (m, 0.18H), 7.65 (d, $J = 7.6$ Hz, 0.12H); other signals were overlapped with those of major isomer; ^{13}C NMR of major isomer δ 24.3, 25.6, 26.3, 26.7, 27.2, 29.3, 30.6, 58.3, 66.3, 67.6, 89.5, 122.9, 124.0, 127.4, 127.6, 128.1, 128.2, 130.1, 134.1, 141.2, 142.9, 170.4; HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{28}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 362.2120, found: 362.2119.

3.4.7. 2-tert-Butyl-3-(tetrahydro-2-phenyl-2-furanyl)isoindolin-1-one (36)

White solid; mp: 107–109 °C; ^1H NMR δ 1.41–1.56 (m, 2H), 1.59–1.63 (m, 1H), 1.70 (s, 9H), 1.76–1.86 (m, 1H), 3.44–3.50 (m, 1H), 3.90–3.95 (m, 1H), 5.17 (s, 1H), 5.98 (d, $J = 7.5$ Hz, 1H), 7.12 (t, $J = 7.4$ Hz, 1H), 7.29–7.33 (m, 1H), 7.38–7.40 (m, 5H), 7.72 (d, $J = 7.4$ Hz, 1H); ^{13}C NMR δ 23.2, 25.9, 28.8, 56.7, 66.0, 66.3, 89.4, 122.8, 123.3, 127.7, 127.9, 128.1, 128.3, 129.5, 134.5, 141.9, 143.6, 170.7; HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{26}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 336.1964, found: 336.1959.

3.4.8. 2-tert-Butyl-3-(2-oxo-2-phenylethyl)isoindolin-1-one (37)

Red solid; mp: 100–102 °C; ^1H NMR δ 1.63 (s, 9H), 3.17–3.24 (m, 1H), 3.76–3.81 (m, 1H), 5.54–5.56 (m, 1H), 7.31–7.40 (m, 3H), 7.46–7.49 (m, 2H), 7.58–7.61 (m, 1H), 7.75–7.77 (m, 1H), 7.91 (d, $J = 7.7$ Hz, 2H); ^{13}C NMR δ 28.8, 45.6, 55.2, 56.3, 122.3, 123.2, 128.1, 128.2, 128.9, 131.5, 132.8, 133.8, 136.5, 146.8, 169.2, 197.4; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{22}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 308.1651, found: 308.1651.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.tet.2017.11.001>.

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