

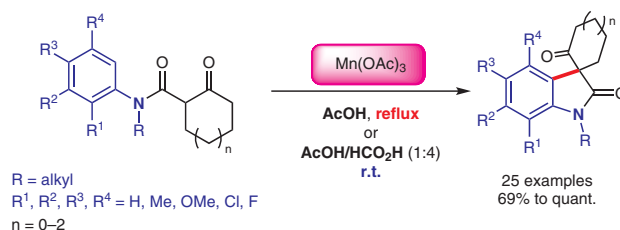
Manganese(III)-Based Oxidative Cyclization of *N*-Aryl-2-oxocycloalkane-1-carboxamides: Synthesis of Spiroindolinones

Shintaro Katayama

Hiroshi Nishino*

Department of Chemistry, Graduate School of Science,
Kumamoto University, Kurokami 2-39-1, Chûou-Ku,
Kumamoto 860-8555, Japan
nishino@kumamoto-u.ac.jp

This manuscript is dedicated to the late Professor Shô Ito,
Professor Emeritus of Tohoku University, Japan, who
showed Hiroshi Nishino the way as a chemist.



Received: 22.03.2019

Accepted after revision: 04.05.2019

Published online: 24.05.2019

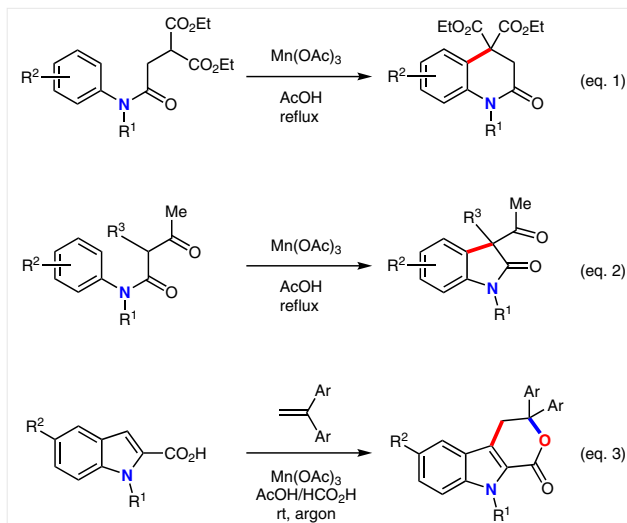
DOI: 10.1055/s-0037-1611563; Art ID: ss-2019-f0190-op

Abstract The Mn(III)-based oxidative cyclization of twenty-five *N*-aryl-2-oxocycloalkane-1-carboxamides is investigated. The reactions progress efficiently to give the desired spiro[cycloalkane-1,3'-indoline]-2,2'-diones in high to quantitative yields. The easy conversion of the carbonyl functional group of one of the indoline products, 1'-methylspiro[cyclohexane-1,3'-indoline]-2,2'-dione, is also demonstrated.

Key words spiro[cycloalkane-1,3'-indoline]-2,2'-diones, oxidative cyclization, 5-*exo* cyclization, radicals, heterocycles, spiro compounds, indolinones

Cyclization is one of the most important techniques to construct complex organic molecules,¹ and can be accomplished via ionic,² radical,³ and concerted techniques,⁴ and by ring-closing metathesis.⁵ From the standpoint of the cyclization reaction, we have been studying the oxidative radical cyclization using Mn(OAc)₃.⁶ For example, the oxidation of 2-[2-[alkyl(aryl)amino]-2-oxoethyl]malonates gave 1-alkyl-2-oxo-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylates (Scheme 1, eq. 1),⁷ which could be converted into quinolines. A similar reaction of *N*,2-dialkyl-*N*-aryl-3-oxobutanamides produced 3-acetyl-1,3-dialkylindolin-2-ones in quantitative yields (Scheme 1, eq. 2),⁸ which could be transformed into indoles. On the other hand, indole-2-carboxylic acids underwent oxidative trapping reactions with alkenes followed by cyclization to give indolelactones (Scheme 1, eq. 3).⁹ During the course of these studies, we communicated our preliminary results on the synthesis of spiro[cyclohexane-1,3'-indoline]-2,2'-diones via the oxidation of *N*-aryl-2-oxocyclohexane-1-carboxamides through a formal 5-*exo*-trig cyclization.¹⁰ Although the reaction was very simple and convenient and the product spiroindolinones are important for the total synthesis of some natural prod-

ucts, for example, satavaptan, as a selective vasopressin V₂ receptor antagonist^{11a,b} and gelsemine, as a highly toxic plant alkaloid,^{11c-e} the yields and the synthetic applications were not high enough. Recently, we developed the activation of Mn(OAc)₃ by adding HCO₂H to the reaction and dramatically changed the reaction time and temperature, which improved the product yields.¹² We then attempted to scrutinize the reactions of *N*-aryl-2-oxocycloalkane-1-carboxamides in order to develop the synthesis of spiroindolinone derivatives.



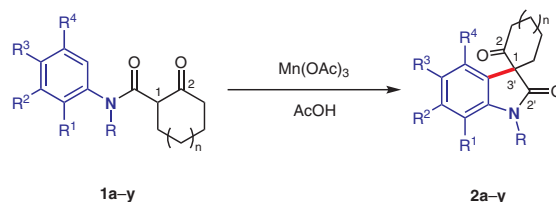
Scheme 1 Synthesis of heterocycles using Mn(III)-based oxidations

N-Aryl-2-oxocycloalkane-1-carboxamides **1a–y** were prepared by the condensation of ethyl 2-oxocycloalkane-carboxylates with the corresponding anilines (see the Supporting Information). The oxidation of *N*-methyl-2-oxo-*N*-phenylcyclohexane-1-carboxamide (**1a**) with Mn(OAc)₃ in AcOH gave 1'-methylspiro[cyclohexane-1,3'-indoline]-2,2'-

dione (**2a**) (Table 1, entries 1–3);¹⁰ however, the reaction took a long time in AcOH (2 days at r.t.), giving a low yield of **2a** (entry 1), elevating the temperature (reflux) in AcOH caused the retro-condensation of **1a** (entry 2), and the use of an excess amount of the oxidant led to **2a** in 55% yield (entry 3). Thus, we decided to explore the reaction under milder conditions in the presence of HCO₂H. The reaction in AcOH/HCO₂H (4:1 v/v) at room temperature afforded the spiroindolinone **2a** in 38% yield after 30 hours (entry 4). When the amount of HCO₂H was further increased, the yield of **2a** was higher, and a maximum yield of 88% was

achieved using AcOH/HCO₂H (1:4 v/v) (entry 7). However, the use of only HCO₂H as the solvent decreased the yield of **2a**, although the reaction time was shorter (entry 8). We thus considered the reaction conditions in entry 7 to be optimum, and other *N*-alkyl-2-oxo-*N*-phenylcyclohexane-1-carboxamides **1b–e** underwent the reaction to give the desired spiroindolinones **2b–e** in good yields (entries 9–12). These results indicated that the oxidative cyclization was not influenced by the *N*-alkyl group of the carboxamides **1a–e**, although the yield of **2d** was slightly lower than those of the 1'-alkylspiroindolinones **2a–c** and **2e**.

Table 1 Oxidation of *N*-Aryl-2-oxocycloalkane-1-carboxamides **1a–y** with Mn(OAc)₃^{a,b}



Entry		R	R ¹	R ²	R ³	R ⁴	n	1/Mn(OAc) ₃ ^c	AcOH/HCO ₂ H v/v	Temp	Time	Product (yield) ^d
1	1a	Me	H	H	H	H	1	1:2.5	5:0	r.t.	2 d	2a (15%)
2	1a	Me	H	H	H	H	1	1:2.5	5:0	reflux	4 min	2a (69%) ^e
3	1a	Me	H	H	H	H	1	1:3	5:0	reflux	5 min	2a (55%)
4	1a	Me	H	H	H	H	1	1:2.5	4:1	r.t.	30 h	2a (38%)
5	1a	Me	H	H	H	H	1	1:2.5	3:2	r.t.	24 h	2a (60%)
6	1a	Me	H	H	H	H	1	1:2.5	2:3	r.t.	24 h	2a (68%)
7	1a	Me	H	H	H	H	1	1:2.5	1:4	r.t.	24 h	2a (88%)
8	1a	Me	H	H	H	H	1	1:2.5	0:5	r.t.	18 h	2a (67%)
9	1b	Et	H	H	H	H	1	1:2.5	1:4	r.t.	24 h	2b (83%)
10	1c	<i>n</i> -Pr	H	H	H	H	1	1:2.5	1:4	r.t.	24 h	2c (90%)
11	1d	<i>i</i> -Pr	H	H	H	H	1	1:2.5	1:4	r.t.	24 h	2d (69%)
12	1e	<i>n</i> -Bu	H	H	H	H	1	1:2.5	1:4	r.t.	24 h	2e (87%)
13	1f	Me	H	H	Me	H	1	1:2.5	1:4	r.t.	24 h	2f (37%)
14	1f	Me	H	H	Me	H	1	1:2	5:0	reflux	1 min	2f (84%)
15	1g	Me	H	H	OMe	H	1	1:2	5:0	reflux	1 min	2g (86%)
16	1h	Me	H	H	Cl	H	1	1:2.5	5:0	reflux	1 min	2h (75%)
17	1i	Me	H	H	F	H	1	1:2.5	5:0	reflux	1 min	2i (90%)
18	1j	Me	Me	H	H	H	1	1:2	5:0	reflux	0.5 min	2j (96%)
19	1k	Me	OMe	H	H	H	1	1:2.5	5:0	reflux	1 min	2k (88%)
20	1l	Me	Cl	H	H	H	1	1:2.5	5:0	reflux	0.5 min	2l (93%)
21	1m	Me	H	Me	H	H	1	1:2.5	5:0	reflux	2 min	2m (92%) ^f
22	1n	Me	Me	Me	H	H	1	1:2.5	5:0	reflux	1 min	2n (95%)
23	1o	Me	H	Me	H	Me	1	1:2.5	5:0	reflux	1 min	2o (88%)
24	1p	Me	H	H	H	H	0	1:2.5	5:0	reflux	1 min	2p (87%)
25	1p	Me	H	H	H	H	0	1:2.5	1:4	r.t.	0.5 min	2p (84%)

Table 1 (continued)

Entry		R	R ¹	Carboxamide			n	1/Mn(OAc) ₃ ^c	AcOH/HCO ₂ H v/v	Temp	Time	Product (yield) ^d
				R ²	R ³	R ⁴						
26	1q	Et	H	H	H	H	0	1:2.5	1:4	r.t.	0.5 min	2q (quant.)
27	1r	<i>n</i> -Pr	H	H	H	H	0	1:2.5	1:4	r.t.	0.5 min	2r (quant.)
28	1s	<i>i</i> -Pr	H	H	H	H	0	1:2.5	1:4	r.t.	0.5 min	2s (98%)
29	1t	<i>n</i> -Bu	H	H	H	H	0	1:2.5	1:4	r.t.	0.5 min	2t (97%)
30	1u	Me	H	H	H	H	2	1:2.5	1:4	r.t.	48 h	2u (76%)
31	1u	Me	H	H	H	H	2	1:2.5	5:0	reflux	5 min	2u (90%)
32	1v	Me	H	H	Me	H	2	1:2.5	5:0	reflux	5 min	2v (86%)
33	1w	Me	H	H	Cl	H	2	1:2.5	5:0	reflux	6 min	2w (78%)
34	1x	Me	Me	H	H	H	2	1:2.5	5:0	reflux	3 min	2x (93%)
35	1y	Me	Cl	H	H	H	2	1:2.5	5:0	reflux	3 min	2y (74%)

^a The reactions of carboxamides **1** (0.5 mmol) were carried out in solvent (15 mL) under argon (entries 1–12).

^b The reactions of carboxamides **1** (0.3 mmol) were carried out in solvent (10 mL) under argon (entries 13–35).

^c Molar ratio.

^d Yield of isolated product **2**.

^e The retro-condensation of **1a** also occurred and no starting **1a** was recovered.

^f The regioisomers **2m** (R² = Me) and **2m'** (R⁴ = Me) were produced in a 2:1 regioisomeric ratio.

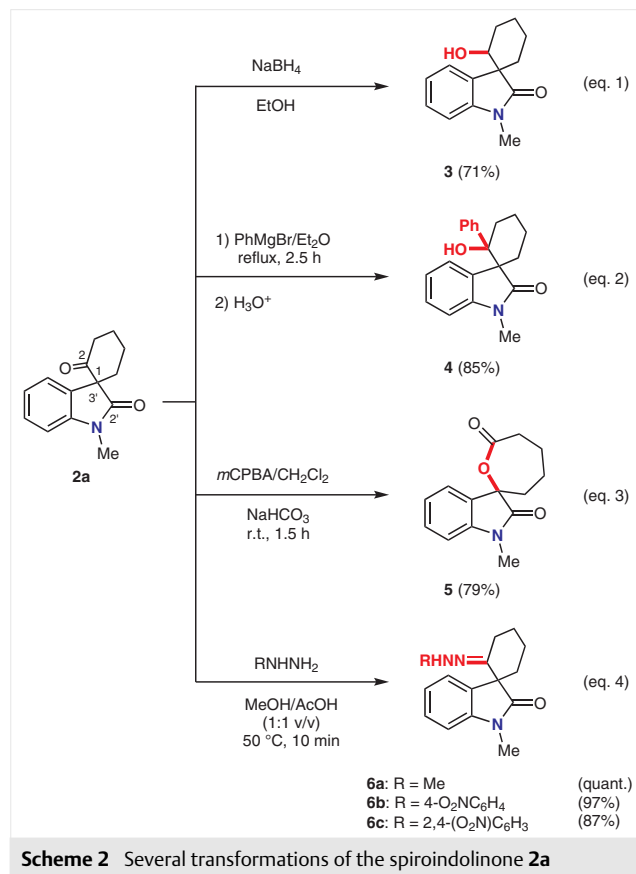
In order to investigate the influence of a substituent on the phenyl group, the reaction of *N*-4-methylphenylcyclohexane-1-carboxamide **1f** was carried out under the optimized conditions. Contrary to our expectation, the reaction still took 24 hours and the decomposition of **1f** occurred somewhat before the oxidative cyclization, resulting in the formation of product **2f** in a low yield (Table 1, entry 13). It was then necessary to activate the reaction and shorten the reaction time, so that the reaction could be conducted at reflux temperature. Gratifyingly, the reaction was complete within 1 minute and gave the desired spiroindolinone **2f** in 84% yield (entry 14). Methyl-, methoxy-, chloro-, and fluoro-substituted phenylcyclohexane-1-carboxamides **1g–o** also gave very good results under similar conditions (entries 15–23). The reaction of *N*-3-methylphenylcyclohexane-1-carboxamide **1m** produced two regioisomers, **2m** (R² = Me) and **2m'** (R⁴ = Me) in a 2:1 regioisomeric ratio, probably due to the steric hindrance of the methyl group (entry 21). In any event, the oxidative cyclization was not influenced by electron-donating and halo groups on the phenyl group.

We also compared the reactivity of a 2-oxocyclohexyl group to that of 2-oxocyclopentyl and 2-oxocycloheptyl groups. The oxidation of *N*-methyl-2-oxocyclopentanecarboxamide **1p** in boiling AcOH gave the desired spiroindolinone **2p** in a high yield as expected (Table 1, entry 24). Surprisingly, when a similar reaction was carried out in AcOH/HCO₂H (1:4 v/v) at room temperature, the oxidant was consumed in an extremely short reaction time and **2p** was obtained in a similar yield (entry 25). The reaction of other *N*-alkyl-2-oxocyclopentanecarboxamides **1q–t** also led to very good results, producing the corresponding

spiroindolinones **2q–t** in excellent to quantitative yields (entries 26–29). On the other hand, the reaction of *N*-methyl-2-oxocycloheptanecarboxamide **1u** at room temperature needed a long reaction time (48 h) to consume the oxidant, affording the corresponding spiroindolinone **2u** in 76% yield (entry 30). However, the reaction in AcOH at reflux temperature was complete within 5 minutes to produce **2u** in 90% yield (entry 31). The reactions of other substituted 2-oxocycloheptanecarboxamides **1v–y** were also carried out in boiling AcOH to give the desired spiroindolinones **2v–y** in high yields (entries 32–35). Accordingly, it was found that the trend in the reactivity decreased in the order: cyclopentanecarboxamides > cyclohexanecarboxamides > cycloheptanecarboxamides based on the reaction conditions described above.

Finally, in order to investigate the synthetic applications, 1'-methylspiro[cyclohexane-1,3'-indoline]-2,2'-dione (**2a**) was subjected to reduction, a Grignard reaction,¹³ Baeyer–Villiger oxidation,¹⁴ and to reactions with hydrazines (Scheme 2).¹⁵ The spiroindolinone **2a** underwent reduction with NaBH₄ in EtOH to afford the corresponding alcohol **3**, of which the diastereomer **3'** (3:4 dr) could be isolated by chromatographic separation (eq. 1). The Grignard reaction with phenylmagnesium bromide followed by hydrolysis gave 2-hydroxy-1'-methyl-2-phenylspiro[cyclohexane-1,3'-indolin]-2'-one (**4**) in 85% yield (eq. 2). The Baeyer–Villiger oxidation/rearrangement occurred effectively using *m*-chloroperbenzoic acid (*m*CPPA) in the presence of NaHCO₃ to produce the corresponding spiro[indoline-3,2'-oxepane]-2,7'-dione **5** in 79% yield (eq. 3). The reactions with methylhydrazine, 4-nitrophenylhydrazine, and 2,4-dinitrophenylhydrazine were carried out in

MeOH/AcOH at 50 °C. The reactions proceeded smoothly and the corresponding hydrazones **6a–c** were obtained in very good yields (eq. 4).



In summary, we have demonstrated the facile synthesis of spiroindolinones **2a–y** and subsequent synthetic applications. That is, the oxidation of *N*-alkyl-2-oxo-*N*-phenylcyclohexane-1-carboxamides **1a–e** and *N*-alkyl-2-oxo-*N*-phenylcyclopentane-1-carboxamides **1p–t** proceeded in AcOH/HCO₂H at room temperature, producing the corresponding spiroindolinones **2a–e** and **2p–t** in yields ranging from 69% to quantitative. 2-Oxocyclohexane-1-carboxamides **1f–o**, having substituents on the phenyl group, and the *N*-aryl-2-oxocycloheptane-1-carboxamides **1u–y** underwent the oxidation in boiling AcOH, giving the desired spiroindolinones **2f–o** and **2u–y** in high yields. The synthetic and work-up procedures were very simple and the corresponding spiroindolinones were obtained in high to quantitative yields. In addition, spiroindolinone **2a** was easily transformed into the alcohols **3** and **4**, the ring-expanded lactone **5**, and the hydrazones **6a–c**. The obtained spiroindolinones can be used as convenient starting materials for the synthesis of natural products,¹¹ and we believe this methodology could be widely used by the chemistry community.

The anilines, 2-oxocycloalkane-1-carboxylates, and solvents were commercially available and used as received. Manganese(III) acetate dihydrate [Mn(OAc)₃·2H₂O] was synthesized according to our modified method.⁸ The *N*-alkyl-*N*-aryl-2-oxocycloalkane-1-carboxamides **1a–y** were prepared by the condensation of *N*-alkylanilines with ethyl 2-oxocycloalkane-1-carboxylates (see the Supporting Information). Melting points were recorded using a MP-J3 Yanagimoto micromelting point apparatus and are uncorrected. IR spectra were measured neat or in CHCl₃ using an IRAffinity-1S spectrophotometer with a MIRacle 10 ATR accessory and are expressed in cm^{−1}. NMR spectra were recorded using a JNM ECX 500 spectrometer at 500 MHz for ¹H and at 125 MHz for ¹³C, with tetramethylsilane as the internal standard. The chemical shifts are reported as δ values (ppm) and the coupling constants in Hz. The following abbreviations are used for the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. High-resolution mass spectra were recorded using a JEOL JMS-700 MStation and were obtained at the Instrumental Analysis Center, Kumamoto University, Kumamoto, Japan. Elemental analyses were obtained using a J-Science Lab JM10 instrument.

Oxidation of 2-Oxocycloalkane-1-carboxamides **1a–y**; General Procedure

The general procedure for the oxidation of 2-oxocycloalkane-1-carboxamides **1a–f** and **1p–u** at room temperature was as follows. To cycloalkanecarboxamide **1** (0.3 mmol) dissolved in glacial AcOH (2 mL)/HCO₂H (8 mL) was added Mn(OAc)₃·2H₂O (0.75 mmol), and the resulting mixture was stirred at room temperature under an argon atmosphere until the brown-black color of the solution turned transparent pale yellow. After the Mn(III) oxidant was completely consumed (if needed, the presence of Mn(III) can be monitored using iodine–starch paper), the solvent was removed under reduced pressure. Following removal of the solvent, 2 M HCl (15 mL) was added to dissolve the solid residue and the obtained aqueous mixture was extracted with CHCl₃ (3 × 20 mL). The combined extracts were washed with a saturated aqueous solution of NaHCO₃ and H₂O, dried over anhydrous MgSO₄, then concentrated to dryness. The obtained residue was separated by silica gel column chromatography eluting with EtOAc/hexane (2:8 or 3:7 v/v) to give the desired spiro[cycloalkane-1,3'-indoline]-2,2'-diones **2a–f** and **2p–u** (see Table 1).

The oxidations of the 2-oxocycloalkane-1-carboxamides **1f–p** and **1u–y** at reflux temperature were as follows. To cycloalkanecarboxamide **1** (0.3 mmol) dissolved in glacial AcOH (10 mL) was added Mn(OAc)₃·2H₂O (0.75 mmol), and the mixture was quickly heated at reflux temperature using a pre-heated oil bath at 140 °C under an argon atmosphere until the brown color of Mn(III) turned transparent. After work-up as described above, the desired spiro[cycloalkane-1,3'-indoline]-2,2'-diones **2f–p** and **2u–y** were obtained (see Table 1). The solid products were further purified by recrystallization from appropriate solvents to prepare analytical samples. Specific details are given below.

1'-Methylspiro[cyclohexane-1,3'-indoline]-2,2'-dione (**2a**)^{11a}

Yield: 97.8 mg (88%); colorless microcrystals (from EtOH/hexane); mp 97–99 °C (Lit.¹⁶ 92–94 °C); *R*_f = 0.31 (EtOAc/hexane, 3:7).

IR (CHCl₃): 1690 (C=O) cm^{−1}.

¹H NMR (500 MHz, CDCl₃): δ = 7.31–7.28 (m, 2 H, arom H), 7.09 (dt, *J* = 7.6, 1.0 Hz, 1 H, arom H), 6.84 (dd, *J* = 8.0, 0.8 Hz, 1 H, arom H), 3.18 (s, 3 H, =N-Me), 3.05 (ddd, *J* = 14.3, 10.4, 5.6 Hz, 1 H, *H*-CH), 2.59 (dt, *J* =

14.3, 5.6 Hz, 1 H, *H*-CH), 2.45–2.37 (m, 1 H, *H*-CH), 2.26–2.21 (m, 1 H, *H*-CH), 2.20–2.13 (m, 1 H, *H*-CH), 2.09 (ddd, *J* = 14.1, 10.3, 4.1 Hz, 1 H, *H*-CH), 2.02–1.94 (m, 1 H, *H*-CH), 1.89–1.82 (m, 1 H, *H*-CH).

¹³C NMR (125 MHz, CDCl₃): δ = 204.9 (C=O), 174.0 (–N–C=O), 143.0 (C-7'a), 129.2 (C-3'a), 128.4, 124.3, 122.4, 108.2 (arom CH), 63.4 (C-1), 39.5, 37.0, 26.7 (CH₂), 26.2 (=N–Me), 20.1 (CH₂).

Anal. Calcd for C₁₄H₁₅NO₂: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.20; H, 6.87; N, 6.09.

1'-Ethylspiro[cyclohexane-1,3'-indoline]-2,2'-dione (2b)

Yield: 101.5 mg (83%); colorless microcrystals (from EtOH/hexane); mp 64–66 °C; *R*_f = 0.31 (EtOAc/hexane, 3:7).

IR (CHCl₃): 1694 (C=O) cm^{–1}.

¹H NMR (500 MHz, CDCl₃): δ = 7.31–7.27 (m, 2 H, arom H), 7.08 (t, *J* = 7.5 Hz, 1 H, arom H), 6.86 (d, *J* = 7.5 Hz, 1 H, arom H), 3.74 (q, *J* = 7.3 Hz, 2 H, –CH₂–CH₃), 3.06 (ddd, *J* = 16.5, 10.5, 6.0 Hz, 1 H, *H*-CH), 2.85 (dt, *J* = 14.0, 5.3 Hz, 1 H, *H*-CH), 2.49–2.39 (m, 1 H, *H*-CH), 2.25–2.21 (m, 1 H, *H*-CH), 2.19–2.17 (m, 1 H, *H*-CH), 2.11–2.15 (m, 1 H, *H*-CH), 2.02–1.93 (m, 1 H, *H*-CH), 1.89–1.82 (m, 1 H, *H*-CH), 1.24 (t, *J* = 7.25 Hz, 3 H, –CH₂–CH₃).

¹³C NMR (125 MHz, CDCl₃): δ = 205.1 (C=O), 173.7 (–N–C=O), 142.2 (C-7'a), 129.6 (C-3'a), 128.4, 124.6, 122.3, 108.4 (arom C), 63.4 (C-1), 39.6, 37.2 (CH₂), 34.8 (–CH₂–CH₃), 26.8, 20.2 (CH₂), 12.5 (–CH₂–CH₃).

FAB HRMS (acetone/NBA): *m/z* [M + H]⁺ calcd for C₁₅H₁₈NO₂: 244.1338; found: 244.1331.

1'-Propylspiro[cyclohexane-1,3'-indoline]-2,2'-dione (2c)

Yield: 109.1 mg (90%); colorless microcrystals (from EtOH/hexane); mp 51–53 °C; *R*_f = 0.34 (EtOAc/hexane, 3:7).

IR (CHCl₃): 1694 (C=O) cm^{–1}.

¹H NMR (500 MHz, CDCl₃): δ = 7.30–7.27 (m, 2 H, arom H), 7.08 (t, *J* = 7.8 Hz, 1 H, arom H), 6.85 (d, *J* = 8.5 Hz, 1 H, arom H), 3.66 (t, *J* = 7.3 Hz, 2 H, –CH₂–CH₂–CH₃), 3.06 (ddd, *J* = 16.0, 10.5, 5.5 Hz, 1 H, *H*-CH), 2.59 (dt, *J* = 13.5, 4.8 Hz, 1 H, *H*-CH), 2.46–2.38 (m, 1 H, *H*-CH), 2.26–2.16 (m, 2 H, CH₂), 2.12–2.07 (m, 1 H, *H*-CH), 2.02–1.94 (m, 1 H, *H*-CH), 1.88–1.84 (m, 1 H, *H*-CH), 1.73–1.69 (m, 2 H, –CH₂–CH₂–CH₃), 0.94 (t, *J* = 7.5 Hz, 3 H, –CH₂–CH₂–CH₃).

¹³C NMR (125 MHz, CDCl₃): δ = 205.1 (C=O), 174.2 (–N–C=O), 142.6 (C-7'a), 129.5 (C-3'a), 128.4, 124.6, 122.3, 108.6 (arom C), 63.4 (C-1), 41.6 (–CH₂–CH₂–CH₃), 39.6, 37.3, 26.7 (CH₂), 20.6 (–CH₂–CH₂–CH₃), 20.2 (CH₂), 11.2 (–CH₂–CH₂–CH₃).

FAB HRMS (acetone/NBA): *m/z* [M + H]⁺ calcd for C₁₆H₂₀NO₂: 258.1494; found: 258.1489.

1'-Isopropylspiro[cyclohexane-1,3'-indoline]-2,2'-dione (2d)

Yield: 88.5 mg (69%); yellow oil; *R*_f = 0.28 (EtOAc/hexane, 3:7).

IR (CHCl₃): 1692 (C=O) cm^{–1}.

¹H NMR (500 MHz, CDCl₃): δ = 7.28–7.26 (m, 2 H, arom H), 7.07 (t, *J* = 7.8 Hz, 1 H, arom H), 7.01 (d, *J* = 8.5 Hz, 1 H, arom H), 4.60 (hept, *J* = 6.9 Hz, 1 H, –CH(CH₃)₂), 3.11–3.05 (m, 1 H, *H*-CH), 2.60–2.55 (m, 1 H, *H*-CH), 2.47–2.40 (m, 1 H, *H*-CH), 2.22–2.17 (m, 2 H, CH₂), 2.11–2.05 (m, 1 H, *H*-CH), 1.99–1.92 (m, 1 H, *H*-CH), 1.86–1.82 (m, 1 H, *H*-CH), 1.47 (d, *J* = 7.0 Hz, 6 H, –CH(CH₃)₂).

¹³C NMR (125 MHz, CDCl₃): δ = 205.2 (C=O), 173.8 (–N–C=O), 141.8 (C-7'a), 129.9 (C-3'a), 128.2, 124.7, 122.0, 109.9 (arom C), 63.2 (C-1), 43.9 (–CH(CH₃)₂), 39.7, 37.5, 26.8, 20.2 (CH₂), 19.3 (–CH(CH₃)₂).

FAB HRMS (acetone/NBA): *m/z* [M + H]⁺ calcd for C₁₆H₂₀NO₂: 258.1494; found: 258.1489.

1'-Butylspiro[cyclohexane-1,3'-indoline]-2,2'-dione (2e)

Yield: 118.6 mg (87%); yellow oil; *R*_f = 0.28 (EtOAc/hexane, 3:7).

IR (CHCl₃): 1694 (C=O) cm^{–1}.

¹H NMR (500 MHz, CDCl₃): δ = 7.31–7.27 (m, 2 H, arom H), 7.08 (t, *J* = 7.8 Hz, 1 H, arom H), 6.85 (d, *J* = 8.0 Hz, 1 H, arom H), 3.69 (t, *J* = 7.5 Hz, 2 H, –CH₂–CH₂–CH₂–CH₃), 3.09–3.03 (m, 1 H, *H*-CH), 2.61–2.56 (m, 1 H, *H*-CH), 2.46–2.39 (m, 1 H, *H*-CH), 2.24–2.17 (m, 2 H, CH₂), 2.12–2.07 (m, 1 H, *H*-CH), 2.02–1.95 (m, 1 H, *H*-CH), 1.88–1.84 (m, 1 H, *H*-CH), 1.64 (quint, *J* = 7.5 Hz, 2 H, –CH₂–CH₂–CH₂–CH₃), 1.36 (sext, *J* = 7.4 Hz, 2 H, –CH₂–CH₂–CH₂–CH₃), 0.94 (t, *J* = 7.5 Hz, 3 H, –CH₂–CH₂–CH₂–CH₃).

¹³C NMR (125 MHz, CDCl₃): δ = 205.1 (C=O), 174.1 (–N–C=O), 142.6 (C-7'a), 129.5 (C-3'a), 128.4, 124.6, 122.3, 108.6 (arom C), 63.4 (C-1), 39.8 (CH₂), 39.6 (–CH₂–CH₂–CH₂–CH₃), 37.3 (CH₂), 29.3 (–CH₂–CH₂–CH₂–CH₃), 26.8, 20.2 (CH₂), 19.9 (–CH₂–CH₂–CH₂–CH₃), 13.6 (–CH₂–CH₂–CH₂–CH₃).

FAB HRMS (acetone/NBA): *m/z* [M + H]⁺ calcd for C₁₇H₂₂NO₂: 272.1651; found: 272.1654.

1',5'-Dimethylspiro[cyclohexane-1,3'-indoline]-2,2'-dione (2f)

Yield: 102.5 mg (84%); colorless microcrystals (from EtOH/hexane); mp 125–127 °C; *R*_f = 0.37 (EtOAc/hexane, 2:8).

IR (CHCl₃): 1690 (C=O) cm^{–1}.

¹H NMR (500 MHz, CDCl₃): δ = 7.12–7.10 (m, 2 H, arom H), 6.73 (d, *J* = 8.0 Hz, 1 H, arom H), 3.18 (s, 3 H, =N–Me), 3.07 (ddd, *J* = 16.0, 11.0, 6.0 Hz, 1 H, *H*-CH), 2.59 (dt, *J* = 14.0, 5.0 Hz, 1 H, *H*-CH), 2.44–2.40 (m, 1 H, *H*-CH), 2.36 (s, 3 H, Me), 2.25–2.27 (m, 2 H, *H*-CH), 2.08 (ddd, *J* = 13.5, 10.5, 4.0 Hz, 1 H, *H*-CH), 2.01–1.93 (m, 1 H, *H*-CH), 1.89–1.82 (m, 1 H, *H*-CH).

¹³C NMR (125 MHz, CDCl₃): δ = 205.3 (C=O), 174.1 (–N–C=O), 140.8 (C-7'a), 132.1 (C-5'), 129.4 (C-3'a), 128.9, 125.4, 108.1 (arom CH), 63.7 (C-1), 39.8, 37.3, 26.9 (CH₂), 26.4 (=N–Me), 21.2 (Me), 20.3 (CH₂).

FAB HRMS (acetone/NBA): *m/z* [M + H]⁺ calcd for C₁₅H₁₈NO₂: 244.1338; found: 244.1321.

5'-Methoxy-1'-methylspiro[cyclohexane-1,3'-indoline]-2,2'-dione (2g)

Yield: 111.0 mg (86%); colorless microcrystals (from EtOH/hexane); mp 111–113 °C; *R*_f = 0.38 (EtOAc/hexane, 2:8).

IR (CHCl₃): 1684 (C=O) cm^{–1}.

¹H NMR (500 MHz, CDCl₃): δ = 6.89 (d, *J* = 2.4 Hz, 1 H, arom H), 6.83 (dd, *J* = 8.5, 2.4 Hz, 1 H, arom H), 6.74 (d, *J* = 8.5 Hz, 1 H, arom H), 3.80 (s, 3 H, MeO), 3.17 (s, 3 H, =N–Me), 3.08 (ddd, *J* = 16.0, 11.0, 6.0 Hz, 1 H, *H*-CH), 2.57 (dt, *J* = 14.0, 5.0 Hz, 1 H, *H*-CH), 2.49–2.40 (m, 1 H, *H*-CH), 2.25–2.17 (m, 2 H, CH₂), 2.08 (ddd, *J* = 14.5, 11.0, 4.0 Hz, 1 H, *H*-CH), 2.01–1.92 (m, 1 H, *H*-CH), 1.87–1.81 (m, 1 H, *H*-CH).

¹³C NMR (125 MHz, CDCl₃): δ = 205.1 (C=O), 173.8 (–N–C=O), 155.9 (C-5'), 136.7 (C-7'a), 130.6 (C-3'a), 112.6, 112.3, 108.6 (arom CH), 64.0 (C-1), 55.8 (MeO), 39.7, 37.5, 26.9 (CH₂), 26.5 (=N–Me), 20.3 (CH₂).

FAB HRMS (acetone/NBA): *m/z* [M + H]⁺ calcd for C₁₅H₁₈NO₃: 260.1287; found: 260.1296.

5'-Chloro-1'-methylspiro[cyclohexane-1,3'-indoline]-2,2'-dione (2h)

Yield: 58.4 mg (75%); colorless microcrystals (from EtOH/hexane); mp 89–91 °C; R_f = 0.34 (EtOAc/hexane, 2:8).

IR (CHCl₃): 1694 (C=O) cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.29 (dd, J = 8.3, 2.0 Hz, 1 H, arom H), 7.25 (d, J = 2.0 Hz, 1 H, arom H), 6.76 (d, J = 8.3 Hz, 1 H, arom H), 3.18 (s, 3 H, =N-Me), 3.10 (ddd, J = 16.5, 11.5, 6.0 Hz, 1 H, *H*-CH), 2.57 (dt, J = 14.0, 5.0 Hz, 1 H, *H*-CH), 2.50–2.42 (m, 1 H, *H*-CH), 2.25–2.19 (m, 2 H, CH₂), 2.08 (ddd, J = 15.0, 11.5, 4.0 Hz, 1 H, *H*-CH), 2.00–1.91 (m, 1 H, *H*-CH), 1.86–1.80 (m, 1 H, *H*-CH).

¹³C NMR (125 MHz, CDCl₃): δ = 204.4 (C=O), 173.6 (–N–C=O), 141.7 (C-7'a), 130.9 (C-3'a), 128.5 (arom CH), 128.0 (C-5'), 125.2, 109.2 (arom CH), 63.7 (C-1), 39.6, 37.5, 26.9 (CH₂), 26.6 (=N-Me), 20.1 (CH₂).

FAB HRMS (acetone/NBA): m/z [M + H]⁺ calcd for C₁₄H₁₅ClNO₂: 264.0791; found: 264.0784.

5'-Fluoro-1'-methylspiro[cyclohexane-1,3'-indoline]-2,2'-dione (2i)

Yield: 66.4 mg (90%); colorless microcrystals (from EtOH/hexane); mp 76–78 °C; R_f = 0.27 (EtOAc/hexane, 2:8).

IR (CHCl₃): 1697 (C=O) cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.04–6.99 (m, 2 H, arom H), 6.77–6.75 (m, 1 H, arom H), 3.18 (s, 3 H, =N-Me), 3.12 (ddd, J = 17.0, 11.5, 5.5 Hz, 1 H, *H*-CH), 2.56 (dt, J = 13.5, 4.5 Hz, 1 H, *H*-CH), 2.52–2.43 (m, 1 H, *H*-CH), 2.25–2.19 (m, 2 H, CH₂), 2.08 (ddd, J = 15.5, 11.5, 4.0 Hz, 1 H, *H*-CH), 2.00–1.91 (m, 1 H, *H*-CH), 1.85–1.79 (m, 1 H, *H*-CH).

¹³C NMR (125 MHz, CDCl₃): δ = 204.5 (C=O), 173.7 (–N–C=O), 159.0 (d, J = 239 Hz, C-5'), 139.0 (d, J = 3 Hz, C-7'a), 130.7 (d, J = 9 Hz, C-3'a), 114.7 (d, J = 23 Hz, C-6'), 112.8 (d, J = 23 Hz, C-4'), 108.6 (d, J = 9 Hz, C-7'), 63.8 (d, J = 1 Hz, C-1), 39.5, 37.5, 26.9 (CH₂), 26.5 (=N-Me), 20.0 (CH₂).

FAB HRMS (acetone/NBA): m/z [M + H]⁺ calcd for C₁₄H₁₅FNO₂: 248.1087; found: 248.1091.

1',7'-Dimethylspiro[cyclohexane-1,3'-indoline]-2,2'-dione (2j)

Yield: 117.0 mg (96%); colorless microcrystals (from EtOH/hexane); mp 128–130 °C; R_f = 0.33 (EtOAc/hexane, 2:8).

IR (CHCl₃): 1684 (C=O) cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.09 (d, J = 7.2 Hz, 1 H, arom H), 7.03 (d, J = 7.6 Hz, 1 H, arom H), 6.99 (t, J = 7.6 Hz, 1 H, arom H), 3.47 (s, 3 H, =N-Me), 3.08 (ddd, J = 16.5, 11.5, 5.5 Hz, 1 H, *H*-CH), 2.59–2.57 (m, 1 H, *H*-CH), 2.56 (s, 3 H, Me), 2.48–2.41 (m, 1 H, *H*-CH), 2.21–2.18 (m, 2 H, CH₂), 2.07 (ddd, J = 14.0, 10.5, 4.0 Hz, 1 H, *H*-CH), 1.99–1.90 (m, 1 H, *H*-CH), 1.86–1.81 (m, 1 H, *H*-CH).

¹³C NMR (125 MHz, CDCl₃): δ = 205.4 (C=O), 174.8 (–N–C=O), 140.9 (C-7'a), 132.3 (arom CH), 130.0 (C-3'a), 122.5 (2 C, arom CH), 119.9 (C-7'), 63.0 (C-1), 39.7, 37.7 (CH₂), 29.8 (=N-Me), 26.9, 20.3 (CH₂), 19.1 (Me).

FAB HRMS (acetone/NBA): m/z [M + H]⁺ calcd for C₁₅H₁₈NO₂: 244.1338; found: 244.1326.

7'-Methoxy-1'-methylspiro[cyclohexane-1,3'-indoline]-2,2'-dione (2k)

Yield: 68.7 mg (88%); colorless microcrystals (from EtOH/hexane); mp 94–96 °C; R_f = 0.33 (EtOAc/hexane, 2:8).

IR (CHCl₃): 1684 (C=O) cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.04 (t, J = 7.9 Hz, 1 H, arom H), 6.88 (s, 1 H, arom H), 6.88 (d, J = 8.0 Hz, 1 H, arom H), 3.84 (s, 3 H, MeO), 3.46 (s, 3 H, =N-Me), 3.10 (ddd, J = 16.5, 11.0, 6.0 Hz, 1 H, *H*-CH), 2.56 (dt, J = 13.5, 4.8 Hz, 1 H, *H*-CH), 2.50–2.41 (m, 1 H, *H*-CH), 2.23–2.19 (m, 2 H, CH₂), 2.07 (ddd, J = 14.0, 10.0, 4.0 Hz, 1 H, *H*-CH), 1.98–1.89 (m, 1 H, *H*-CH), 1.85–1.80 (m, 1 H, *H*-CH).

¹³C NMR (125 MHz, CDCl₃): δ = 205.4 (C=O), 174.2 (–N–C=O), 145.3 (C-7'a), 131.1 (C-3'a), 130.9 (C-7'), 123.1, 117.2, 112.4 (arom CH), 63.6 (C-1), 55.9 (MeO), 39.6, 37.6 (CH₂), 29.7 (=N-Me), 26.8, 20.1 (CH₂).

FAB HRMS (acetone/NBA): m/z [M + H]⁺ calcd for C₁₅H₁₈NO₃: 260.1287; found: 260.1277.

7'-Chloro-1'-methylspiro[cyclohexane-1,3'-indoline]-2,2'-dione (2l)

Yield: 72.8 mg (93%); yellow oil; R_f = 0.35 (EtOAc/hexane, 2:8).

IR (neat): 1699 (C=O) cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.23 (dd, J = 8.2, 1.1 Hz, 1 H, arom H), 7.12 (dd, J = 7.4, 1.1 Hz, 1 H, arom H), 7.01 (t, J = 7.5 Hz, 1 H, arom H), 3.56 (s, 3 H, =N-Me), 3.13 (ddd, J = 18.0, 12.5, 6.0 Hz, 1 H, *H*-CH), 2.55 (dt, J = 13.5, 4.3 Hz, 1 H, *H*-CH), 2.52–2.45 (m, 1 H, *H*-CH), 2.25–2.18 (m, 2 H, CH₂), 2.08 (ddd, J = 15.5, 11.5, 4.0 Hz, 1 H, *H*-CH), 1.97–1.88 (m, 1 H, *H*-CH), 1.84–1.78 (m, 1 H, *H*-CH).

¹³C NMR (125 MHz, CDCl₃): δ = 204.5 (C=O), 174.1 (–N–C=O), 139.0 (C-7'a), 131.9 (C-3'a), 130.8, 123.4, 123.2 (arom CH), 115.5 (C-7'), 63.2 (C-1), 39.5, 37.9 (CH₂), 29.8 (=N-Me), 26.9, 20.0 (CH₂).

FAB HRMS (acetone/NBA): m/z [M + H]⁺ calcd for C₁₄H₁₅ClNO₂: 264.0791; found: 264.0777.

1',6'-Dimethylspiro[cyclohexane-1,3'-indoline]-2,2'-dione (2m)

Yield: 45.0 mg (61%); colorless microcrystals (from EtOH/hexane); mp 168–170 °C; R_f = (EtOAc/hexane, 2:8).

IR (neat): 1688 (C=O) cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.18 (d, J = 7.5 Hz, 1 H, arom H), 6.91 (d, J = 7.5 Hz, 1 H, arom H), 6.67 (s, 1 H, arom H), 3.17 (s, 3 H, =N-Me), 3.02 (ddd, J = 15.5, 9.5, 5.0 Hz, 1 H, *H*-CH), 2.59 (dt, J = 13.5, 5.3 Hz, 1 H, *H*-CH), 2.44–2.34 (m, 1 H, *H*-CH), 2.38 (s, 3 H, Me), 2.26–2.21 (m, 1 H, *H*-CH), 2.19–2.15 (m, 1 H, *H*-CH), 2.07 (ddd, J = 13.5, 9.5, 3.5 Hz, 1 H, *H*-CH), 2.02–1.94 (m, 1 H, *H*-CH), 1.89–1.83 (m, 1 H, *H*-CH).

¹³C NMR (125 MHz, CDCl₃): δ = 205.3 (C=O), 174.5 (–N–C=O), 143.2 (C-7'a), 138.8 (C-6'), 126.4 (C-3'a), 124.2, 123.1, 109.3 (arom C), 63.4 (C-1), 39.6, 37.1, 26.8 (CH₂), 26.3 (=N-Me), 21.7 (Me), 20.3 (CH₂).

FAB HRMS (acetone/NBA): m/z [M + H]⁺ calcd for C₁₅H₁₈NO₂: 244.1338; found: 244.1320.

1',4'-Dimethylspiro[cyclohexane-1,3'-indoline]-2,2'-dione (2m')

Yield: 22.6 mg (31%); colorless microcrystals (from EtOH/hexane); mp 81–83 °C; R_f = (EtOAc/hexane, 2:8).

IR (neat): 1695 (C=O) cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.21 (t, J = 8.0 Hz, 1 H, arom H), 6.90 (d, J = 8.0 Hz, 1 H, arom H), 6.67 (d, J = 8.0 Hz, 1 H, arom H), 3.20–3.13 (m, 1 H, *H*-CH), 3.16 (s, 3 H, =N-Me), 2.64–2.55 (m, 2 H, CH₂), 2.40 (dt, J = 14.0, 4.0 Hz, 1 H, *H*-CH), 2.28–2.23 (m, 1 H, *H*-CH), 2.22 (s, 3 H, Me), 2.05 (d, J = 14.0 Hz, 1 H, *H*-CH), 1.89–1.82 (m, 1 H, *H*-CH), 1.79–1.76 (m, 1 H, *H*-CH).

¹³C NMR (125 MHz, CDCl₃): δ = 204.5 (C=O), 173.6 (–N–C=O), 143.3 (C-7'a), 135.0 (C-4'), 128.5 (arom C), 127.7 (C-3'a), 125.4, 105.9 (arom C), 63.5 (C-1), 40.3, 34.8 (CH₂), 26.5 (=N-Me), 26.3, 20.0 (CH₂), 19.2 (Me).

FAB HRMS (acetone/NBA): m/z [M + H]⁺ calcd for C₁₅H₁₈NO₂: 244.1338; found: 244.1333.

1',6',7'-Trimethylspiro[cyclohexane-1,3'-indoline]-2,2'-dione (2n)

Yield: 74.2 mg (95%); colorless microcrystals (from EtOH/hexane); mp 132–134 °C; R_f = 0.37 (EtOAc/hexane, 2:8).

IR (CHCl₃): 1684 (C=O) cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 6.99 (d, J = 7.5 Hz, 1 H, arom H), 6.92 (d, J = 7.5 Hz, 1 H, arom H), 3.49 (s, 3 H, =N-Me), 3.07 (ddd, J = 16.5, 11.0, 5.5 Hz, 1 H, *H*-CH), 2.56 (dt, J = 14.5, 5.0 Hz, 1 H, *H*-CH), 2.47 (s, 3 H, Me-C-7'), 2.45–2.38 (m, 1 H, *H*-CH), 2.30 (s, 3 H, Me-C-6'), 2.21–2.17 (m, 2 H, CH₂), 2.11–2.02 (m, 1 H, *H*-CH), 1.98–1.89 (m, 1 H, *H*-CH), 1.86–1.79 (m, 1 H, *H*-CH).

¹³C NMR (125 MHz, CDCl₃): δ = 205.5 (C=O), 175.2 (-N-C=O), 141.2 (C-7'a), 138.4 (C-6'), 127.9 (C-3'a), 124.2, 121.7 (arom C), 119.1 (C-7'), 62.7 (C-1), 39.6, 37.6 (CH₂), 30.6 (=N-Me), 26.8 (CH₂), 20.8 (Me-C-7'a), 20.3 (CH₂), 14.1 (Me-C-6'a).

FAB HRMS (acetone/NBA): m/z [M + H]⁺ calcd for C₁₆H₂₀NO₂: 258.1494; found: 258.1505.

1',4',6'-Trimethylspiro[cyclohexane-1,3'-indoline]-2,2'-dione (2o)

Yield: 68.4 mg (88%); colorless microcrystals (from EtOH/hexane); mp 164–166 °C; R_f = 0.31 (EtOAc/hexane, 1:9).

IR (CHCl₃): 1686 (C=O) cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 6.72 (s, 1 H, arom H), 6.49 (s, 1 H, arom H), 3.19–3.15 (m, 1 H, *H*-CH), 3.13 (s, 3 H, =N-Me), 2.64–2.54 (m, 2 H, CH₂), 2.38 (dt, J = 13.8, 4.5 Hz, 1 H, *H*-CH), 2.33 (s, 3 H, Me-C-6'), 2.27–2.22 (m, 1 H, *H*-CH), 2.17 (s, 3 H, Me-C-4'), 2.05–2.01 (m, 1 H, *H*-CH), 1.87–1.79 (m, 1 H, *H*-CH), 1.78–1.74 (m, 1 H, *H*-CH).

¹³C NMR (125 MHz, CDCl₃): δ = 204.6 (C=O), 173.8 (-N-C=O), 143.4 (C-7'a), 138.6 (C-6'), 134.6 (C-4'), 125.9 (arom C), 124.7 (C-3'a), 125.9 (arom C), 63.3 (C-1), 40.3, 34.8, 26.4 (CH₂), 26.3 (=N-Me), 21.5 (Me-C-6'), 20.0 (CH₂), 19.0 (Me-C-4').

FAB HRMS (acetone/NBA): m/z [M + Na]⁺ calcd for C₁₆H₁₉NO₂Na: 280.1313; found: 280.1315.

1'-Methylspiro[cyclopentane-1,3'-indoline]-2,2'-dione (2p)

Yield: 54.4 mg (84%); colorless microcrystals (from EtOH/hexane); mp 123–125 °C; R_f = 0.28 (EtOAc/hexane, 2:8).

IR (neat): 1742 (-C=O), 1694 (-N-C=O) cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.21 (dd, J = 15.5, 8.0 Hz, 1 H, arom H), 7.02–6.95 (m, 2 H, arom H), 6.77 (d, J = 7.5 Hz, 1 H, arom H), 3.12 (s, 3 H, =N-Me), 2.62–2.52 (m, 2 H, CH₂), 2.49–2.39 (m, 2 H, CH₂), 2.29 (dt, J = 13.0, 7.5 Hz, 1 H, *H*-CH), 2.17–2.12 (m, 1 H, *H*-CH).

¹³C NMR (125 MHz, CDCl₃): δ = 212.7 (C=O), 175.0 (-N-C=O), 144.2 (C-7'a), 130.2 (C-3'a), 128.6, 122.8, 122.3, 108.4 (arom C), 62.8 (C-1), 38.2, 34.0 (CH₂), 26.4 (=N-Me), 20.1 (CH₂).

FAB HRMS (acetone/NBA): m/z [M + H]⁺ calcd for C₁₃H₁₄NO₂: 216.1025; found: 216.1005.

1'-Ethylspiro[cyclopentane-1,3'-indoline]-2,2'-dione (2q)

Yield: 69.9 mg (quant.); colorless microcrystals (from EtOH/hexane); mp 72–74 °C; R_f = 0.28 (EtOAc/hexane, 2:8).

IR (neat): 1747 (-C=O), 1695 (-N-C=O) cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.28 (t, J = 7.0 Hz, 1 H, arom H), 7.09 (d, J = 7.0 Hz, 1 H, arom H), 7.03 (t, J = 7.5 Hz, 1 H, arom H), 6.87 (d, 1 H, J = 8.0 Hz, arom H), 3.74 (q, J = 7.3 Hz, 2 H, -CH₂-CH₃), 2.70–2.59 (m, 2 H, CH₂), 2.55–2.46 (m, 2 H, CH₂), 2.36 (dt, J = 14.0, 7.0 Hz, 1 H, *H*-CH), 2.26–2.17 (m, 1 H, *H*-CH), 1.26 (t, J = 7.3 Hz, 3 H, -CH₂-CH₃).

¹³C NMR (125 MHz, CDCl₃): δ = 212.6 (C=O), 174.6 (-N-C=O), 143.4 (C-7'a), 130.5 (C-3'a), 128.5, 122.6, 122.5, 108.5 (arom C), 62.8 (C-1), 38.2 (CH₂), 34.9 (-CH₂-CH₃), 34.0, 20.1 (CH₂), 12.5 (-CH₂-CH₃).

FAB HRMS (acetone/NBA): m/z [M + H]⁺ calcd for C₁₄H₁₆NO₂: 230.1181; found: 230.1185.

1'-Propylspiro[cyclopentane-1,3'-indoline]-2,2'-dione (2r)

Yield: 76.0 mg (quant.); colorless microcrystals (from EtOH/hexane); mp 69–71 °C; R_f = 0.32 (EtOAc/hexane, 2:8).

IR (neat): 1748 (-C=O), 1695 (-N-C=O) cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.27 (t, J = 4.0 Hz, 1 H, arom H), 7.08 (d, J = 7.5 Hz, 1 H, arom H), 7.03 (t, J = 7.8 Hz, 1 H, arom H), 6.86 (d, J = 8.0 Hz, 1 H, arom H), 3.72–3.60 (m, 2 H, -CH₂-CH₂-CH₃), 2.70–2.60 (m, 2 H, CH₂), 2.55–2.47 (m, 2 H, CH₂), 2.36 (dt, J = 13.0, 7.0 Hz, 1 H, *H*-CH), 2.25–2.19 (m, 1 H, *H*-CH), 1.74–1.69 (m, 2 H, -CH₂-CH₂-CH₃), 0.95 (t, J = 7.3 Hz, 3 H, -N-CH₂-CH₂-CH₃).

¹³C NMR (125 MHz, CDCl₃): δ = 212.7 (C=O), 175.1 (-N-C=O), 143.8 (C-7'a), 130.5 (C-3'a), 128.5, 122.54, 122.49, 108.6 (arom C), 62.8 (C-1), 41.6 (-CH₂-CH₂-CH₃), 38.2, 34.0 (CH₂), 20.6 (-CH₂-CH₂-CH₃), 20.1 (CH₂), 11.1 (-CH₂-CH₂-CH₃).

FAB HRMS (acetone/NBA): m/z [M + H]⁺ calcd for C₁₅H₁₈NO₂: 244.1338; found: 244.1322.

1'-Isopropylspiro[cyclopentane-1,3'-indoline]-2,2'-dione (2s)

Yield: 71.1 mg (98%); colorless microcrystals (from EtOH/hexane); mp 61–63 °C; R_f = 0.36 (EtOAc/hexane, 2:8).

IR (neat): 1749 (-C=O), 1694 (-N-C=O) cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.26 (t, J = 7.8 Hz, 1 H, arom H), 7.08 (d, J = 6.0 Hz, 1 H, arom H), 7.03–7.00 (m, 2 H, arom H), 4.56 (hept, J = 7.3 Hz, 1 H, -CH-(CH₃)₂), 2.69–2.59 (m, 2 H, CH₂), 2.54–2.46 (m, 2 H, CH₂), 2.35 (dt, J = 14.0, 7.0 Hz, 1 H, *H*-CH), 2.24–2.16 (m, 1 H, *H*-CH), 1.48 (d, J = 7.3, 6 H, -CH-(CH₃)₂).

¹³C NMR (125 MHz, CDCl₃): δ = 212.6 (C=O), 174.8 (-N-C=O), 143.1 (C-7'a), 130.8 (C-3'a), 128.3, 122.6, 122.2, 109.9 (arom C), 62.7 (C-1), 41.2 (-CH-(CH₃)₂), 38.2, 34.0, 20.1 (CH₂), 19.4, 19.2 (-CH-(CH₃)₂).

FAB HRMS (acetone/NBA): m/z [M + H]⁺ calcd for C₁₅H₁₈NO₂: 244.1338; found: 244.1326.

1'-Butylspiro[cyclopentane-1,3'-indoline]-2,2'-dione (2t)

Yield: 75.0 mg (97%); colorless microcrystals (from EtOH/hexane); mp 42–44 °C; R_f = 0.37 (EtOAc/hexane, 2:8).

IR (neat): 1748 (-C=O), 1697 (-N-C=O) cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.28 (t, J = 7.8 Hz, 1 H, arom H), 7.08 (d, J = 7.5 Hz, 1 H, arom H), 7.03 (t, J = 7.8 Hz, 1 H, arom H), 6.87 (d, J = 8.0 Hz, 1 H, arom H), 3.75–3.63 (m, 2 H, -CH₂-CH₂-CH₂-CH₃), 2.69–2.60 (m, 2 H, CH₂), 2.55–2.47 (m, 2 H, CH₂), 2.36 (dt, J = 13.5, 7.0 Hz, 1 H, *H*-CH), 2.25–2.18 (m, 1 H, *H*-CH), 1.70–1.62 (m, 2 H, -CH₂-CH₂-CH₂-CH₃), 1.42–1.34 (m, 2 H, -CH₂-CH₂-CH₂-CH₃), 0.94 (t, J = 7.5 Hz, 3 H, -CH₂-CH₂-CH₂-CH₃).

¹³C NMR (125 MHz, CDCl₃): δ = 212.7 (C=O), 175.0 (-N-C=O), 143.7 (C-7'a), 130.5 (C-3'a), 128.5, 122.52, 122.47, 108.6 (arom C), 62.8 (C-1), 39.8 (-CH₂-CH₂-CH₂-CH₃), 38.2, 34.0 (CH₂), 29.3 (-CH₂-CH₂-CH₂-CH₃), 20.1 (CH₂), 19.9 (-CH₂-CH₂-CH₂-CH₃), 13.6 (-CH₂-CH₂-CH₂-CH₃).

FAB HRMS (acetone/NBA): m/z [M + H]⁺ calcd for C₁₆H₂₀NO₂: 258.1494; found: 258.1474.

1'-Methylspiro[cycloheptane-1,3'-indoline]-2,2'-dione (2u)

Yield: 65.6 mg (90%); colorless microcrystals (from EtOH/hexane); mp 113–115 °C (Lit.¹⁶ 104–107 °C); R_f = 0.32 (EtOAc/hexane, 2:8).

IR (neat): 1709 (–C=O), 1683 (–N–C=O) cm^{–1}.

¹H NMR (500 MHz, CDCl₃): δ = 7.30 (t, J = 7.8 Hz, 1 H, arom H), 7.26 (d, J = 7.5 Hz, 1 H, arom H), 7.07 (t, J = 7.3 Hz, 1 H, arom H), 6.85 (d, J = 8.0 Hz, 1 H, arom H), 3.19 (s, 3 H, =N–Me), 3.06 (t, J = 10.5 Hz, 1 H, *H*-CH), 2.73 (t, J = 9.3 Hz, 1 H, *H*-CH), 2.32 (dd, J = 14.0, 9.0 Hz, 1 H, *H*-CH), 2.16–2.12 (m, 1 H, *H*-CH), 2.02 (dd, J = 14.5, 9.5 Hz, 1 H, *H*-CH), 1.92–1.87 (m, 1 H, *H*-CH), 1.83–1.78 (m, 4 H, –CH₂–CH₂).

¹³C NMR (125 MHz, CDCl₃): δ = 207.4 (C=O), 175.1 (–N–C=O), 143.3 (C-7'a), 130.6 (C-3'a), 128.5, 123.4, 122.5, 108.4 (arom C), 65.3 (C-1), 42.1, 34.6, 30.7, 26.6 (CH₂), 26.3 (=N–Me), 25.2 (CH₂).

1',5'-Dimethylspiro[cycloheptane-1,3'-indoline]-2,2'-dione (2v)

Yield: 65.9 mg (86%); colorless microcrystals (from EtOH/hexane); mp 112–114 °C; R_f = 0.24 (EtOAc/hexane, 2:8).

IR (neat): 1707 (–C=O), 1690 (–N–C=O) cm^{–1}.

¹H NMR (500 MHz, CDCl₃): δ = 7.10 (d, J = 7.5 Hz, 1 H, arom H), 7.08 (s, 1 H, arom H), 6.73 (d, J = 8.0 Hz, 1 H, arom H), 3.17 (s, 3 H, =N–Me), 3.07 (t, J = 10.8 Hz, 1 H, *H*-CH), 2.72 (t, J = 9.8 Hz, 1 H, *H*-CH), 2.35 (s, 3 H, Me), 2.32–2.23 (m, 1 H, *H*-CH), 2.17–2.12 (m, 1 H, *H*-CH), 2.04–1.98 (m, 1 H, *H*-CH), 1.93–1.88 (m, 1 H, *H*-CH), 1.84–1.77 (m, 4 H, –CH₂–CH₂).

¹³C NMR (125 MHz, CDCl₃): δ = 207.6 (C=O), 175.1 (–N–C=O), 140.9 (C-7'a), 132.1 (C-3'a), 130.7 (C-5'), 128.8, 124.3, 108.1 (arom C), 65.5 (C-1), 42.2, 34.7, 30.8, 26.6 (CH₂), 26.4 (=N–Me), 25.3 (CH₂), 21.1 (Me).

FAB HRMS (acetone/NBA): m/z [M + H]⁺ calcd for C₁₆H₂₀NO₂: 258.1494; found: 258.1487.

5'-Chloro-1'-methylspiro[cycloheptane-1,3'-indoline]-2,2'-dione (2w)

Yield: 64.9 mg (78%); colorless microcrystals (from EtOH/hexane); mp 125–127 °C; R_f = 0.31 (EtOAc/hexane, 2:8).

IR (neat): 1713 (–C=O), 1688 (–N–C=O) cm^{–1}.

¹H NMR (500 MHz, CDCl₃): δ = 7.27 (d, J = 8.0 Hz, 1 H, arom H), 7.24 (s, 1 H, arom H), 6.77 (d, J = 8.0 Hz, 1 H, arom H), 3.18 (s, 3 H, =N–Me), 3.12 (t, J = 10.8 Hz, 1 H, *H*-CH), 2.67 (t, J = 9.3 Hz, 1 H, *H*-CH), 2.33 (dd, J = 14.5, 10.0 Hz, 1 H, *H*-CH), 2.18–2.12 (m, 1 H, *H*-CH), 2.00 (dd, J = 15.0, 9.0 Hz, 1 H, *H*-CH), 1.96–1.90 (m, 1 H, *H*-CH), 1.86–1.72 (m, 4 H, –CH₂–CH₂).

¹³C NMR (125 MHz, CDCl₃): δ = 206.7 (C=O), 174.4 (–N–C=O), 141.9 (C-7'a), 132.3 (C-3'a), 128.4 (arom C), 127.9 (C-5'), 124.2, 109.3 (arom C), 65.6 (C-1), 42.1, 34.7, 30.7, 26.6 (CH₂), 26.5 (=N–Me), 25.3 (CH₂).Cl

FAB HRMS (acetone/NBA): m/z [M + H]⁺ calcd for C₁₅H₁₇ClNO₂: 278.0948; found: 278.0940.

1',7'-Dimethylspiro[cycloheptane-1,3'-indoline]-2,2'-dione (2x)

Yield: 71.8 mg (93%); colorless microcrystals (from EtOH/hexane); mp 119–121 °C; R_f = 0.32 (EtOAc/hexane, 2:8).

IR (neat): 1713 (–C=O), 1686 (–N–C=O) cm^{–1}.

¹H NMR (500 MHz, CDCl₃): δ = 7.10 (d, J = 7.0 Hz, 1 H, arom H), 7.02 (d, J = 8.0 Hz, 1 H, arom H), 6.94 (t, J = 7.5 Hz, 1 H, arom H), 3.48 (s, 3 H, =N–Me), 3.02 (t, J = 10.3 Hz, 1 H, *H*-CH), 2.73 (t, J = 10.3 Hz, 1 H, *H*-CH),

2.55 (s, 3 H, Me), 2.28 (dd, J = 14.5, 9.0 Hz, 1 H, *H*-CH), 2.18–2.12 (m, 1 H, *H*-CH), 2.00 (dd, J = 14.5, 9.5 Hz, 1 H, *H*-CH), 1.88–1.76 (m, 5 H, *H*-CH-CH₂-CH₂).

¹³C NMR (125 MHz, CDCl₃): δ = 207.6 (C=O), 176.0 (–N–C=O), 141.1 (C-7'a), 132.3 (arom C), 131.1 (C-3'a), 122.4, 121.2 (arom C), 120.0 (C-7'), 64.7 (C-1), 42.3, 35.0, 30.8 (CH₂), 29.7 (=N–Me), 26.6, 25.2 (CH₂), 19.0 (Me).

FAB HRMS (acetone/NBA): m/z [M + H]⁺ calcd for C₁₆H₂₀NO₂: 258.1494; found: 258.1473.

7'-Chloro-1'-methylspiro[cycloheptane-1,3'-indoline]-2,2'-dione (2y)

Yield: 62.4 mg (74%); colorless microcrystals (from EtOH/hexane); mp 116–118 °C; R_f = 0.43 (EtOAc/hexane, 2:8).

IR (neat): 1726 (–C=O), 1688 (–N–C=O) cm^{–1}.

¹H NMR (500 MHz, CDCl₃): δ = 7.22 (t, J = 8.0 Hz, 1 H, arom H), 7.13 (d, J = 7.0 Hz, 1 H, arom H), 6.98 (t, J = 8.0 Hz, 1 H, arom H), 3.56 (s, 3 H, =N–Me), 3.09 (t, J = 10.5 Hz, 1 H, *H*-CH), 2.69 (t, J = 10.0 Hz, 1 H, *H*-CH), 2.31 (dd, J = 14.5, 9.5 Hz, 1 H, *H*-CH), 2.17–2.11 (m, 1 H, *H*-CH), 2.00 (dd, J = 15.0, 9.0 Hz, 1 H, *H*-CH), 1.93–1.88 (m, 1 H, *H*-CH), 1.84–1.74 (m, 4 H, –CH₂–CH₂).

¹³C NMR (125 MHz, CDCl₃): δ = 206.8 (C=O), 175.2 (–N–C=O), 139.2 (C-7'a), 133.3 (C-3'a), 130.8, 123.3, 122.1 (arom C), 115.7 (C-7'), 65.0 (C-1), 42.1, 35.0, 30.7 (CH₂), 29.8 (=N–Me), 26.6, 25.2 (CH₂).

FAB HRMS (acetone/NBA): m/z [M + H]⁺ calcd for C₁₅H₁₇ClNO₂: 278.0948; found: 278.0939.

2-Hydroxy-1'-methylspiro[cyclohexane-1,3'-indoline]-2'-one (3) and (3')

The spiroindolinone **2a** (69 mg, 0.3 mmol) and NaBH₄ (14 mg, 0.3 mmol) were dissolved in EtOH (5 mL) and the mixture was stirred at room temperature for 10 min. After removal of the solvent, H₂O (10 mL) was added and the aqueous mixture was extracted with CHCl₃ (3 × 10 mL). The combined extracts were washed with a saturated aqueous solution of NaHCO₃ and H₂O, dried over anhydrous MgSO₄, then concentrated to dryness. The obtained residue was separated by silica gel column chromatography eluting with EtOAc/hexane (1:1 v/v), affording the corresponding alcohol **3** and the diastereomer **3'**.

Compound 3

Yield: 21.0 mg (31%); colorless microcrystals (from EtOH/hexane); mp 145–146 °C; R_f = 0.31 (EtOAc/hexane, 5:5).

IR (neat): 3435 (OH), 1690 (–C=O) cm^{–1}.

¹H NMR (500 MHz, CDCl₃): δ = 7.36 (d, J = 7.0 Hz, 1 H, arom H), 7.32–7.29 (t, J = 7.8 Hz, 1 H, arom H), 7.09 (t, J = 6.5 Hz, 1 H, arom H), 6.86 (d, J = 8.0 Hz, 1 H, arom H), 3.85–3.84 (m, 1 H, *H*-C–OH), 3.21 (s, 3 H, =N–Me), 2.78 (s, 1 H, –OH), 2.24–2.17 (m, 1 H, *H*-CH), 2.02–1.96 (m, 3 H, *H*-CH/CH₂), 1.93–1.87 (m, 1 H, *H*-CH), 1.69–1.62 (m, 1 H, *H*-CH), 1.60–1.50 (m, 2 H, *H*-CH).

¹³C NMR (125 MHz, CDCl₃): δ = 179.1 (–N–C=O), 143.7 (C-7'a), 132.4 (C-3'a), 128.1, 123.3, 122.3, 108.0 (arom C), 72.3 (C-2), 52.3 (C-1), 31.4, 28.5 (CH₂), 26.0 (=N–Me), 22.1, 20.0 (CH₂).

FAB HRMS (acetone/NBA): m/z [M + H]⁺ calcd for C₁₄H₁₇NO₂: 231.1259; found: 231.1258.

Compound 3'

Yield: 27.8 mg (40%); colorless microcrystals (from EtOH/hexane); mp 153–156 °C; R_f = 0.19 (EtOAc/hexane, 5:5).

IR (neat): 3431 (–OH), 1682 (–C=O) cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 7.57 (d, J = 7.0 Hz, 1 H, arom H), 7.34 (t, J = 7.8 Hz, 1 H, arom H), 7.07 (t, J = 8.0 Hz, 1 H, arom H), 6.89 (d, J = 8.0 Hz, 1 H, arom H), 4.07–4.05 (m, 1 H, H -C–OH), 3.23 (s, 3 H, =N–Me), 2.06–1.97 (m, 2 H, CH_2), 1.93–1.86 (m, 1 H, H -CH), 1.84–1.78 (m, 1 H, H -CH), 1.75–1.70 (m, 2 H, CH_2), 1.64–1.58 (m, 2 H, CH_2), 1.25 (s, 1 H, –OH).

^{13}C NMR (125 MHz, CDCl_3): δ = 179.5 (–N–C=O), 144.4 (C-7'a), 130.2 (C-3'a), 128.2, 125.4, 121.8, 108.2 (arom C), 73.1 (C-2), 54.9 (C-1), 32.7, 30.9 (CH_2), 26.4 (=N–Me), 24.0, 20.5 (CH_2).

FAB HRMS (acetone/NBA): m/z [$M + H$] $^+$ calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_2$: 231.1259; found: 231.1259.

2-Hydroxy-1'-methyl-2-phenylspiro[cyclohexane-1,3'-indolin]-2'-one (4)

Bromobenzene (393 mg, 2.5 mmol) dissolved in dry Et_2O (2 mL) was added dropwise over 20 min to Mg turnings (61 mg, 2.5 mmol) in dry Et_2O (3 mL) in a 50 mL three-necked flask under an argon atmosphere, then the mixture was heated at 50 °C for 30 min. The spiroindolinone **2a** (112.4 mg, 0.5 mmol) in dry Et_2O (3 mL) was added dropwise over 30 min to the mixture, then the mixture was heated under reflux for 2 h. The reaction was quenched by adding crushed ice and the obtained aqueous solution was acidified with a saturated aqueous solution of NH_4Cl , then extracted with EtOAc (3 $\times$ 20 mL). The combined extracts were washed with a saturated aqueous solution of NaHCO_3 and H_2O , dried over anhydrous MgSO_4 , then concentrated to dryness. The obtained residue was separated by silica gel column chromatography, eluting with EtOAc /hexane (2:8 v/v), to give the corresponding alcohol **4**.

Yield: 127.5 mg (85%); colorless microcrystals (from EtOH /hexane); mp 137–139 °C; R_f = 0.26 (EtOAc /hexane, 1:9).

IR (neat): 3350 (OH), 1672 (–C=O) cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 7.83 (d, J = 7.5 Hz, 1 H, arom H), 7.20 (t, J = 7.8 Hz, 1 H, arom H), 7.10 (t, J = 7.5 Hz, 1 H, arom H), 6.98–6.93 (m, 5 H, arom H), 6.54 (d, J = 7.5 Hz, 1 H, arom H), 6.00 (s, 1 H, –OH), 2.88 (s, 3 H, =N–Me), 2.60–2.52 (m, 2 H, CH_2), 2.34–2.24 (m, 1 H, H -CH), 2.06–1.96 (m, 1 H, H -CH), 1.90–1.82 (m, 3 H, CH_2 / H -CH), 1.49–1.46 (m, 1 H, H -CH).

^{13}C NMR (125 MHz, CDCl_3): δ = 180.3 (–N–C=O), 143.7, 143.1, 131.6, 127.9 (arom C), 126.7 (2 C, arom C), 126.4, 125.7 (arom C), 125.5 (2 C, arom C), 122.1, 108.3 (arom C), 74.9 (C-2), 55.7 (C-1), 32.5, 29.8 (CH_2), 25.7 (=N–Me), 20.1, 19.9 (CH_2).

FAB HRMS (acetone/NBA): m/z [$M + H$] $^+$ calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_2$: 307.1572; found: 307.1591.

1-Methylspiro[indoline-3,2'-oxepane]-2,7'-dione (5)

To the spiroindolinone **2a** (69 mg, 0.3 mmol) in CH_2Cl_2 (4 mL) were added *m*-chloroperbenzoic acid (106 mg, 0.6 mmol) and NaHCO_3 (50 mg, 0.6 mmol). The mixture was stirred at room temperature for 1.5 h and the reaction was quenched by adding brine. The organic layer was separated, dried over anhydrous MgSO_4 , and concentrated to dryness. The obtained residue was separated by silica gel column chromatography, eluting with EtOAc /benzene (1:9 v/v), to give the corresponding lactone **5**.

Yield: 59.8 mg (79%); colorless microcrystals (from EtOH /hexane); mp 167–169 °C; R_f = 0.37 (EtOAc /benzene, 1:9).

IR (neat): 1714 (–C=O) cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 7.37 (d, J = 7.5 Hz, 1 H, arom H), 7.32 (t, J = 7.8 Hz, 1 H, arom H), 7.09 (t, J = 7.5 Hz, 1 H, arom H), 6.81 (d, J = 8.0 Hz, 1 H, arom H), 3.86 (m, 1 H, H -CH), 3.18 (s, 3 H, =N–Me), 2.86 (dd, J = 15.0, 6.5 Hz, 1 H, H -CH), 2.36–2.30 (m, 1 H, H -CH), 2.29–2.21 (m, 1 H, H -CH), 2.15–2.11 (m, 1 H, H -CH), 2.00–1.97 (m, 1 H, H -CH), 1.88–1.85 (m, 1 H, H -CH), 1.76–1.68 (m, 1 H, H -CH).

^{13}C NMR (125 MHz, CDCl_3): δ = 174.8 (–N–C=O), 173.3 (–C=O), 141.6 (C-7'a), 130.7 (C-3'a), 130.0, 123.4, 123.2, 108.4 (arom C), 81.5 (C-1), 37.2, 36.7 (CH_2), 26.3 (=N–Me), 23.0, 22.9 (CH_2).

FAB HRMS (acetone/NBA): m/z [M] $^+$ calcd for $\text{C}_{14}\text{H}_{15}\text{NO}_3$: 245.1052; found: 245.1062.

1'-Methyl-2-(2-methylhydrazineylidene)spiro[cyclohexane-1,3'-indolin]-2'-one (6a); Typical Procedure

A mixture of the spiroindolinone **2a** (45.9 mg, 0.2 mmol) and methylhydrazine (18.4 mg, 0.4 mmol) was heated at 50 °C in MeOH/AcOH (1:1 v/v, 4 mL) for 10 min. After removal of the solvent, H_2O (10 mL) was added and the aqueous solution was extracted with CHCl_3 (3 $\times$ 10 mL). The combined extracts were washed with a saturated aqueous solution of NaHCO_3 and H_2O , dried over anhydrous MgSO_4 , then concentrated to dryness. The obtained residue was separated by silica gel column chromatography, eluting with EtOAc /hexane (1:1 v/v), to give the corresponding methylhydrazone **6a**.

Yield: 54.0 mg (quant.); colorless microcrystals (from EtOH /hexane); mp 131–132 °C; R_f = 0.31 (EtOAc /hexane, 6:4).

IR (neat): 1664 (–N–C=O) cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 7.23 (d, J = 7.5 Hz, 1 H, arom H), 7.18 (t, J = 7.5 Hz, 1 H, arom H), 6.81 (t, J = 7.5 Hz, 1 H, arom H), 6.53 (d, J = 8.0 Hz, 1 H, arom H), 4.21 (s, 1 H, =NNH– CH_3), 3.03 (s, 3 H, =N– CH_3), 2.82 (s, 3 H, =NNH– CH_3), 2.20–2.18 (m, 1 H, H -CH), 2.09–2.04 (m, 1 H, H -CH), 1.69–1.63 (m, 2 H, CH_2), 1.49–1.29 (m, 4 H, CH_2 – CH_2).

^{13}C NMR (125 MHz, CDCl_3): δ = 173.3 (–N–C=O), 141.6 (C-7'a), 130.7 (C-3'a), 130.0, 123.4, 123.2, 108.4 (arom C), 81.5 (C-1), 37.2, 36.7 (CH_2), 26.3 (=N–Me), 23.0, 22.9 (CH_2).

Anal. Calcd for $\text{C}_{15}\text{H}_{19}\text{N}_3\text{O}$: C, 70.01; H, 7.44; N, 16.33. Found: C, 69.91; H, 7.64; N, 16.20.

1'-Methyl-2-[2-(4-nitrophenyl)hydrazineylidene]spiro[cyclohexane-1,3'-indolin]-2'-one (6b)

The reaction of **2a** (68.6 mg, 0.3 mmol) with 4-nitrophenylhydrazine (91.9 mg, 0.6 mmol) gave 4-nitrophenylhydrazone **6b**.

Yield: 112.6 mg (97%); orange microcrystals (from EtOH /hexane); mp 214–217 °C; R_f = 0.23 (EtOAc /hexane, 3:7).

IR (neat): 1697 (–N–C=O) cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 8.03 (d, J = 9.5 Hz, 2 H, arom H), 7.86 (s, 1 H, –N–H), 7.37–7.32 (m, 2 H, arom H), 7.13 (t, J = 8.0 Hz, 1 H, arom H), 6.89 (d, J = 7.5 Hz, 1 H, arom H), 6.76 (d, J = 9.0 Hz, 1 H, arom H), 3.24 (s, 3 H, =N–Me), 2.83–2.77 (m, 1 H, H -CH), 2.68–2.63 (m, 1 H, H -CH), 2.34–2.26 (m, 1 H, H -CH), 2.12–2.09 (m, 1 H, H -CH), 2.08–1.94 (m, 2 H, CH_2), 1.86–1.76 (m, 2 H, CH_2), 1.76–1.68 (m, 1 H, H -CH).

^{13}C NMR (125 MHz, CDCl_3): δ = 177.1 (–N–C=O), 150.5 (C-6), 150.1 (arom C), 142.6 (C-7'a), 139.6 (arom C), 132.3 (C-3'a), 128.0 (arom C), 125.8 (2 C, arom C), 124.5, 122.2 (arom C), 111.5 (2 C, arom C), 108.4 (arom C), 55.8 (C-1), 35.8 (CH_2), 26.3 (=N–Me), 24.7, 23.2, 20.1 (CH_2).

FAB HRMS (MeOH -NBA-Nal): m/z [$M + \text{Na}$] $^+$ calcd for $\text{C}_{20}\text{H}_{20}\text{N}_4\text{NaO}_3$: 387.1433; found 387.1489.

2-[2-(2,4-Dinitrophenyl)hydrazineylidene]-1'-methylspiro[cyclohexane-1,3'-indolin]-2'-one (6c)

The reaction of **2a** (45.5 mg, 0.2 mmol) with 2,4-dinitrophenylhydrazine (39.8 mg, 0.2 mmol) gave the desired 2,4-dinitrophenylhydrazine **6c**.

Yield: 70.3 mg (87%); orange microcrystals (from EtOH/hexane); mp 86–89 °C; R_f = 0.39 (EtOAc/hexane, 3:7).

IR (neat): 1699 (–N=C=O) cm^{-1} .

^1H NMR (500 MHz, CDCl_3): δ = 11.16 (s, 1 H, –N–H), 9.04 (d, J = 2.5 Hz, 1 H, arom H), 8.17 (dd, J = 10.0, 3.0 Hz, 1 H, arom H), 7.44 (d, J = 9.5 Hz, 1 H, arom H), 7.39–7.35 (m, 2 H, arom H), 7.15 (t, J = 7.3 Hz, 1 H, arom H), 6.92 (d, J = 8.0 Hz, 1 H, arom H), 3.26 (s, 3 H, =N–Me), 3.03–2.97 (m, 1 H, *H*–CH), 2.77 (dt, J = 16.5, 5.5 Hz, 1 H, *H*–CH), 2.37–2.30 (m, 1 H, *H*–CH), 2.19–2.08 (m, 2 H, CH_2), 2.05–1.99 (m, 1 H, *H*–CH), 1.94–1.87 (m, 2 H, CH_2).

^{13}C NMR (125 MHz, CDCl_3): δ = 176.1 (–N=C=O), 157.4 (C–6), 145.2 (arom C), 142.8 (C–7'a), 137.9 (arom C), 131.6 (C–3'a), 129.9, 129.2, 128.3, 124.4, 123.2, 122.3, 116.4, 108.5 (arom C), 56.1 (C–1), 36.0 (CH_2), 26.4 (=N–Me), 25.0, 24.6, 20.1 (CH_2).

FAB HRMS (MeOH–NBA–NaI): m/z [$M + \text{Na}$] $^+$ calcd for $\text{C}_{20}\text{H}_{19}\text{N}_5\text{NaO}_5$: 432.1284; found 432.1278.

Funding Information

This research was supported by the Japan Society for the Promotion of Science, Grant-in-Aid for Scientific Research (C) (No. 25410049 and 18K05109). We also acknowledge the Nissan Chemical Corporation for financial support.

Acknowledgment

H.N. thanks Mr. Daichi Hirata, Department of Science, Faculty of Science, Kumamoto University, Japan, for his technical assistance.

Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0037-1611563>.

References

- (1) (a) Habermas, K. L.; Denmark, S. E.; Jones, T. K. *Org. React.* **1994**, 45, 1. (b) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* **1996**, 48, 301. (c) Julia, M. *Acc. Chem. Res.* **1971**, 4, 386. (d) Iqbal, J.; Bhatia, B.; Nayyar, N. *Chem. Rev.* **1994**, 94, 519. (e) Tang, M.-C.; Zou, Y.; Watanabe, K.; Walsh, C. T.; Tang, Y. *Chem. Rev.* **2017**, 117, 5226.
- (2) (a) Rastetter, W. H.; Phillion, D. P. *J. Org. Chem.* **1981**, 46, 3209. (b) Wisner, J. A.; Beer, P. A.; Drew, M. G. B. *Angew. Chem. Int. Ed.* **2001**, 40, 3606. (c) Shorthill, B. J.; Granucci, R. G.; Powell, D. R.; Glass, T. E. *J. Org. Chem.* **2002**, 67, 904. (d) Pigge, F. C.; Ghasedi, F.; Rath, N. P. *J. Org. Chem.* **2002**, 67, 4547. (e) Miramon, M.-L.; Mignet, N.; Herscovici, J. *J. Org. Chem.* **2004**, 69, 6949. (f) Sierra, M. A.; Pellico, D.; Gómez-Gallego, M.; Manchenño, M. J.; Torres, R. *J. Org. Chem.* **2006**, 71, 8787. (g) Muthusamy, S.; Gnanaprakasam, B.; Suresh, E. *J. Org. Chem.* **2007**, 72, 1495. (h) Leon, F.; Rivera, D. G.; Wessjohann, L. A. *J. Org. Chem.* **2008**, 73, 1762. (i) Gibson, H. W.; Wang, H.; Bonrad, K.; Jones, J. W.; Slebodnick, C.; Zackharov, L. N.; Rheingold, A. L.; Habenicht, B.; Lobue, P.; Ratliff, A. E. *Org. Biomol. Chem.* **2005**, 3, 2114. (j) Pederson, A. M.-P.; Ward, E. M.; Schoonover, D. V.; Slebodnick, C.; Gibson, H. W. *J. Org. Chem.* **2008**, 73, 9094.
- (3) (a) de Klein, W. J. In *Organic Syntheses by Oxidation with Metal Compounds*; Mijis, W. J.; de Jonge, C. R. H. I., Ed.; Plenum Press: New York, **1986**, 261. (b) Snider, B. B. *Chem. Rev.* **1996**, 96, 339. (c) Melikyan, G. G. *Org. React.* **1997**, 49, 427. (d) *Radicals in Organic Synthesis*, Vol. 1; Renaud, P.; Sibi, M. P., Ed.; Wiley-VCH: New York, **2001**. (e) Zard, S. Z. *Radical Reactions in Organic Synthesis*; Oxford University Press: New York, **2003**. (f) Snider, B. B. *Tetrahedron* **2009**, 65, 10738. (g) Burton, J. W. In *Encyclopedia of Radicals in Chemistry, Biology and Materials*; Chatgililoglu, C.; Studer, A., Ed.; John Wiley & Sons: New York, **2012**, 901. (h) Krylov, I. B.; Terent'ev, A. O.; Timofeev, V. P.; Shelimov, B. N.; Novikov, R. A.; Merkulova, V. M.; Nikishin, G. I. *Adv. Synth. Catal.* **2014**, 356, 2266.
- (4) (a) Klotzel, M. C. *Org. React.* **1948**, 4, 1. (b) Holmes, H. L. *Org. React.* **1948**, 4, 60. (c) Butz, L. W.; Rytina, A. W. *Org. React.* **1949**, 5, 136. (d) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, 80, 63. (e) Takano, K.; Munakata, R.; Tadano, K. *Chem. Rev.* **2005**, 105, 4779. (f) Mackay, E. G.; Sherburn, M. S. *Synthesis* **2015**, 47, 1. (g) Yang, R.-Y.; Sun, J.; Yan, C.-G. *ACS Omega* **2018**, 3, 5406.
- (5) (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, 34, 18. (b) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, 104, 2199. (c) Monfette, S.; Fogg, D. E. *Chem. Rev.* **2009**, 109, 3783.
- (6) (a) Nishino, H. In *Topics in Heterocyclic Chemistry, Bioactive Heterocycles I*; Eguchi, S., Ed.; Springer: Berlin, **2006**, 39. (b) Asahi, K.; Nishino, H. *Tetrahedron* **2008**, 64, 1620. (c) Asahi, K.; Nishino, H. *Synthesis* **2009**, 409. (d) Cong, Z.-Q.; Miki, T.; Urakawa, O.; Nishino, H. *J. Org. Chem.* **2009**, 74, 3978. (e) Ito, Y.; Tomiyasu, Y.; Kawanabe, T.; Uemura, K.; Ushimizu, Y.; Nishino, H. *Org. Biomol. Chem.* **2011**, 9, 1491. (f) Maemura, Y.; Tanoue, Y.; Nishino, H. *Heterocycles* **2012**, 85, 2491. (g) Matsumoto, C.; Yasutake, K.; Nishino, H. *Tetrahedron* **2016**, 72, 6963. (h) Huynh, T.-T.; Nguyen, V.-H.; Nishino, H. *Tetrahedron Lett.* **2017**, 58, 3619. (i) Huynh, T.-T.; Yamakawa, H.; Nguyen, V.-H.; Nishino, H. *ChemistrySelect* **2018**, 3, 6414.
- (7) Tsubusaki, T.; Nishino, H. *Tetrahedron* **2009**, 65, 9448.
- (8) Kikue, N.; Takahashi, T.; Nishino, H. *Heterocycles* **2014**, 90, 540.
- (9) Inoue, T.; Nishino, H. *Heterocycles* **2018**, 97, 431.
- (10) (a) Takayanagi, J.; Nishino, H. *Abstracts of Papers, The 98th CSJ Annual Meeting*; Funabashi: Japan, 20–23.March.2018, 3PC-023. (b) Katayama, S.; Nishino, H. *Abstracts of Papers, The 99th CSJ Annual Meeting*; Kobe: Japan, 16–19.Mar.2019, 2PB-133.
- (11) (a) Hurst, T. E.; Gorman, R.; Drouhin, P.; Taylor, R. J. K. *Tetrahedron* **2018**, 74, 6485. (b) Venkatesan, H.; Davis, M. C.; Altas, Y.; Snyder, J. P.; Liotta, D. C. *J. Org. Chem.* **2001**, 66, 3653. (c) Flann, C. J.; Overman, L. E.; Sarkar, A. K. *Tetrahedron Lett.* **1991**, 32, 6993. (d) Atarashi, S.; Choi, J.-K.; Ha, D.-C.; Hart, D. J.; Kuzmich, D.; Lee, C.-S.; Ramesh, S. C.; Wu, S. C. *J. Am. Chem. Soc.* **1997**, 119, 6226. (e) Madin, A.; O'Donnell, C. J.; Oh, T.; Old, D. W.; Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **2005**, 127, 18054.
- (12) Matsumoto, R.; Nishino, H. *Synth. Commun.* **2015**, 45, 1807.
- (13) Yamada, T.; Iwahara, Y.; Nishino, H.; Kurosawa, K. *J. Chem Soc., Perkin Trans. 1* **1993**, 609.
- (14) (a) Renz, M.; Meunier, B. *Eur. J. Org. Chem.* **1999**, 737. (b) Brink, G.-J.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Rev.* **2004**, 104, 4105.
- (15) Ouyang, J.; Nishino, H.; Kurosawa, K. *J. Heterocycl. Chem.* **1996**, 33, 1291.
- (16) Wang, L.; Su, Y.; Xu, X.; Zhang, W. *Eur. J. Org. Chem.* **2012**, 33, 6606.