

Bis(indoline-2,3-diones): Versatile precursors for novel bis(2',6'-dimethyl-2-oxo-1'*H*-spiro[indoline-3,4'-pyridine]-3',5'-dicarbonitrile) derivatives

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Abstract

Reaction of 3-aminocrotononitrile with a series of bis(indoline-2,3-diones) afforded the corresponding bis(2',6'-dimethyl-2-oxo-1'*H*-spiro[indoline-3,4'-pyridine]-3',5'-dicarbonitrile) derivatives in good to excellent yields.

Keywords: Bis(indoline-2,3-diones), bis(spirooxindole), 1,4-dihydropyridine-3,5-dicarbonitrile, alkylation, condensation

Introduction

Spiroheterocycles are of considerable interest because the structural rigidity affects considerably their biological activity.¹ Among them, spirooxindoles,²⁻⁷ constitute the core structural element of many natural and biologically active molecules such as spirotryprostatin B **I**, pteropodine **II**,⁸ gelsemine **III**,⁹ and horsfiline **IV**¹⁰ (Fig. 1).

Moreover, the 1,4-dihydropyridine-3,5-dicarbonitrile scaffold represents a class of medicinally significant compounds, which has demonstrated a diverse range of biological activities dependent upon substitutions around the core pyridine ring.¹¹ Dihydropyridine drug molecules, as nifedipine **V** and nicardipine **VI** are clinically effective as calcium Ca²⁺ channel blockers for treatment of coronary heart diseases and for the treatment of hypertension.¹²⁻¹⁴ Furthermore, bis-heterocyclic compounds have been reported to possess interesting biological properties¹⁵⁻¹⁷ including antihypertensive,¹⁸ antiallergenic¹⁹ and antitumor activities.^{18,20}

As a part of an ongoing research program on bis-heterocycles,²¹⁻²⁷ as well as on the utility of enamines in organic synthesis,²⁸⁻³⁴ we report the results of our investigations concerning the reactivity patterns of bis-isatin derivatives towards 3-aminocrotononitrile aiming at synthesis of bis(spirooxindole) incorporating 1',4'-

dihydropyridine-3',5'-dicarbonitrile derivatives. It is anticipated that the combination of the two scaffolds in a single molecule can lead to the discovery of new active drugs.

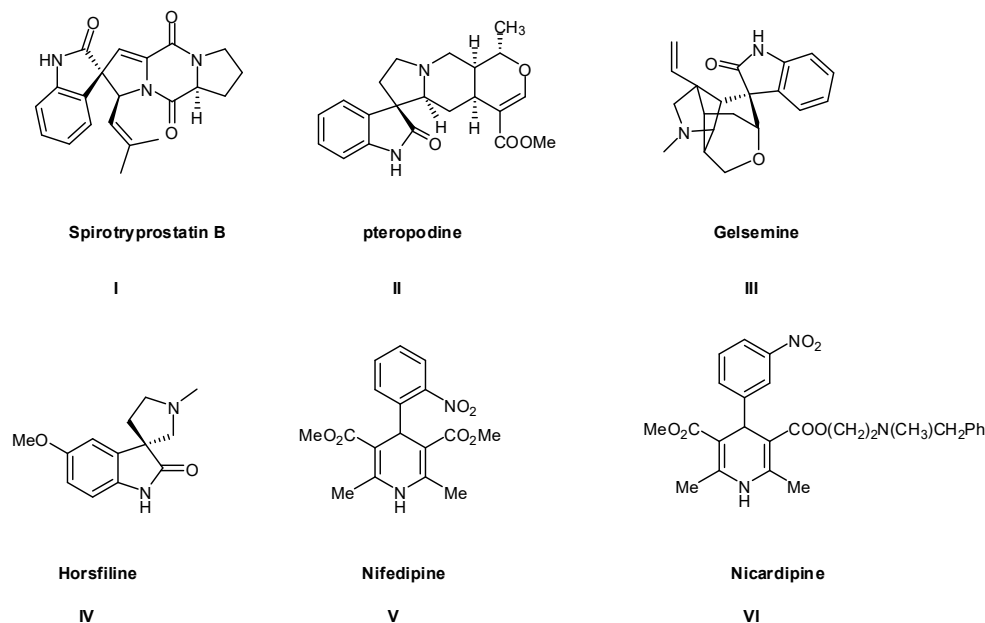
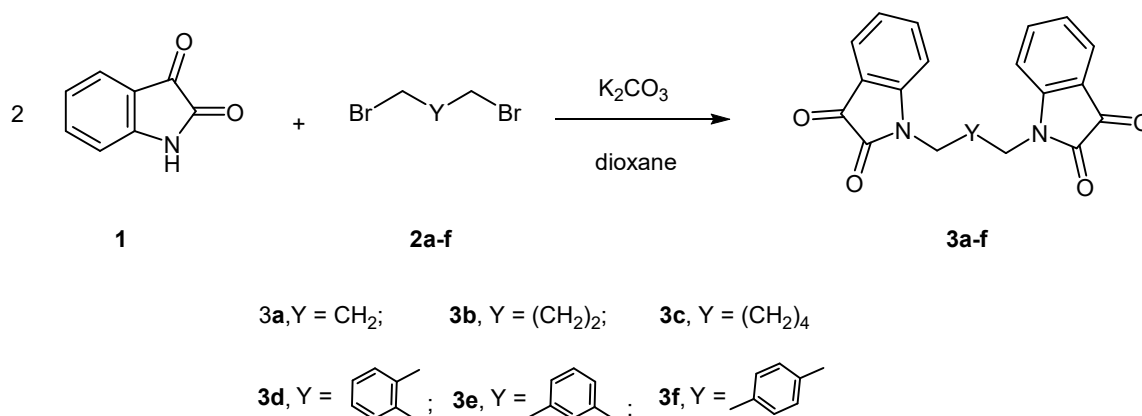


Figure 1

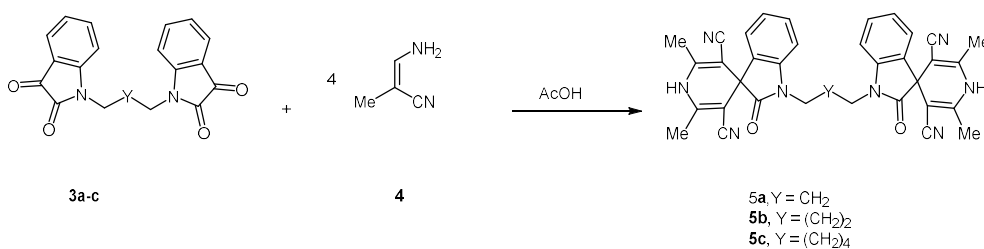
Results and Discussion

The bis(indoline-2,3-diones) **3a-f** were chosen as precursors to a variety of novel bis(spirooxindole) incorporating 1',4'-dihydropyridine-3',5'-dicarbonitrile derivatives. They can be prepared by the reaction of indoline-2,3-dione **1** with the appropriate dibromo compounds **2a-f** in the presence of anhydrous K₂CO₃ (Scheme 1).³⁵⁻³⁷

The reactivity of **3a-c** towards 3-aminocrotonitrile **4** was investigated. Thus, reaction of an AcOH solution of one equivalent of each of the bis(indoline-2,3-diones) **3a-c** with four equivalents of **4** afforded the respective bis(2',6'-dimethyl-2-oxo-1'*H*-spiro[indoline-3,4'-pyridine]-3',5'-dicarbonitriles) **5a-c** which are tethered to alkyl linkage (Scheme 2).



Scheme 1. Synthesis of bis(indoline-2,3-diones) **3a-f**. Reaction condition: isatin (25 mmol), dibromo derivatives **2a-f** (10 mmol), K₂CO₃ (30 mmol), dioxane (10 mL), reflux 30 min. Yields: 75-84%.



Scheme 2. Synthesis of compounds **5a-c**. Reaction condition: bis(indoline-2,3-diones) **3a-c** (10 mmol), 3-aminocrotononitrile (45 mmol), AcOH, reflux 1 h. Yields: 75-82%.

Encouraged by the above results, the bis(2,6'-dimethyl-2-oxo-1'*H*-spiro[indoline-3,4'-pyridine]-3',5'-dicarbonitriles) which are linked to xylyl linkage **5d-f** were prepared *via* the direct reaction of one equivalent of the bis(indoline-2,3-diones) **3d-f** with four moles of 3-aminocrotononitrile **4** (Fig. 2).

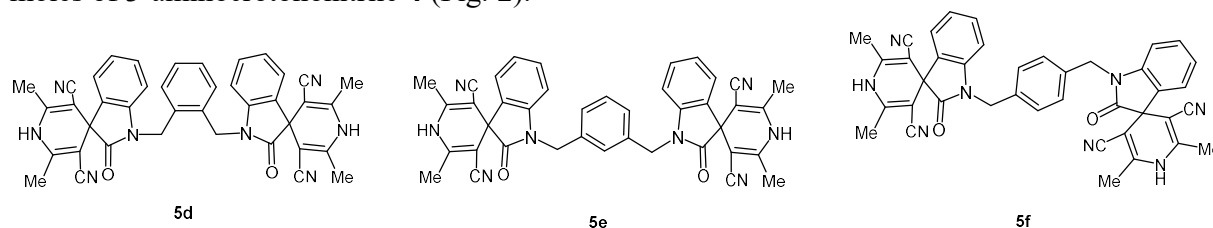
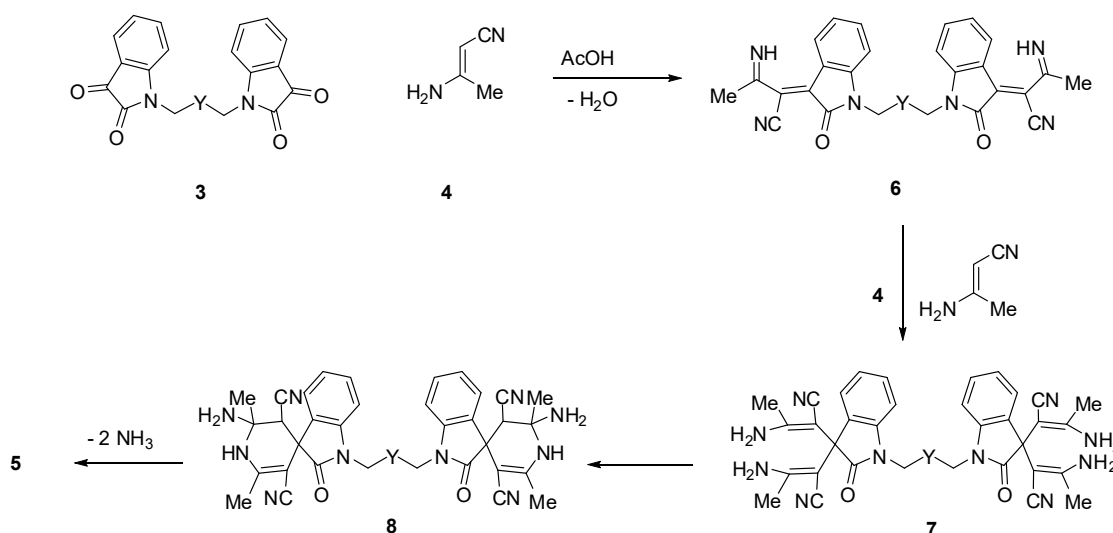


Figure 2. Bis(2,6'-dimethyl-2-oxo-1'*H*-spiro[indoline-3,4'-pyridine]-3',5'-dicarbonitrile) linked to xylyl linkage **5d-f**.

The structure of compounds **5a-f** was supported based on IR, NMR and mass spectral studies. Thus, the ¹H NMR spectrum of **5b** revealed characteristic multiplet at δ 1.68 ppm for -

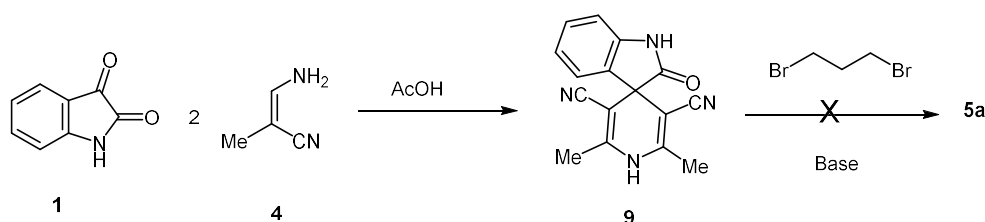
CH₂. It also showed singlet integrated by 12H at δ 2.12 ppm for the four methyl groups. It revealed multiplet signal at δ 3.73 ppm for NCH₂. In addition, the singlet signal at δ 9.98 is assigned to NH group. The aromatic protons appear at the expected position at δ 7.12-7.37 ppm. On the other hand, the ¹H-NMR spectrum of 1,1''-(1,4 phenylenebis(methylene))bis(2',6'-dimethyl-2-oxo-1'*H*-spiro[indoline-3,4'-pyridine]-3',5'-dicarbonitrile) **5f** exhibited three singlet signals at δ 2.13, 4.92 and 10.02 ppm assigned to CH₃, CH₂ and NH, respectively. Furthermore, ¹³C NMR spectrum of **5f** was found to be in agreement with proposed structure; it showed the methyl signal at δ 17.9 ppm and the spiro carbon at δ 42.8 ppm. It also featured a CN signal at δ = 117.2 ppm. The C=O group appeared at δ = 175.8 ppm. All other carbon signals appeared at their expected positions.

Apparently, the reaction pathway involves initial condensation of the bis(indoline-2,3-diones) **3** with two equivalents of the 3-aminocrotononitrile **4** to yield the unstable bis-ylidene derivatives **6**. The bis-ylidenes then react with another two moles of **4**, yielding the bis-diamines **7**, which cyclize into **8**. Finally the intermediates **8** lose two moles of NH₃ yielding the final isolable products **5** (Scheme 3).



Scheme 3: Proposed pathway for the synthesis of compounds **5a-f**

In search for another pathway for synthesis of compounds **5**, our attention focused on 2',6'-dimethyl-2-oxo-1'*H*-spiro[indoline-3,4'-pyridine]-3',5'-dicarbonitrile **9** as a precursor which should then undergo bis(alkylation) with the appropriate dibromoalkanes to give **5**. Unfortunately, repeated attempts to obtain the target compound **5a** through the direct alkylation reaction of **9** with the dibromopropane under different basic conditions were unsuccessful. Instead, the starting materials were recovered completely unreacted (Scheme 4).



Scheme 4: Attempted synthesis of bis(spirooxindole) **5a** by bis(alkylation) of spiro derivative **9**

Conclusions

We have developed an efficient synthetic strategy for novel bis(spirooxindoles) incorporating 1,4-dihydropyridine-3,5-dicarbonitrile derivatives using the bis(indoline-2,3-diones). The two dihydropyridine unites were tethered to isatin *via* alkyl or aryl groups. The newly synthesized compounds are interesting both in their own right as unusual molecules and for their promising pharmacological and biological activities.

Acknowledgements

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Experimental Section

General. Melting points were measured with a Stuart melting point apparatus and are uncorrected. The IR spectra were recorded using a FTIR Bruker–vector 22 spectrophotometer as KBr pellets. The ^1H NMR spectrum were recorded in $\text{DMSO}-d_6$ as solvent on Varian Gemini NMR spectrometer at 400 MHz using TMS as internal standard. Chemical shifts are reported as δ values in ppm. Mass spectra were recorded with a Shimadzu GCMS–QP–1000 EX mass spectrometer in EI (70 eV) model. The elemental analyses were performed at the Micro analytical center, Cairo University.

General method for synthesis of compounds 3a-f. Compounds **3a-f** were prepared according to the reported procedures.^{35–37} A mixture of isatin **1** (0.025 mol) and anhydrous K_2CO_3 (0.03 mol) was stirred at room temperature in dioxane (10 mL) for 15 min. A solution of the dibromo derivatives **2a-f** (0.01 mol) in dioxane (5 mL) was then added and the reaction was heated at reflux for 30 min. The reaction mixture was poured on iced water and the collected solid was crystallized from ethanol-dioxane mixture (1:1).

General method for synthesis of compounds 5a-f. A mixture of bis-isatin derivatives **3a-f** (1 mmol) and 3-aminocrotononitrile **4** (4.5 mmol) in AcOH (10 mL) was heated at reflux for 1 h. The collected precipitate was washed thoroughly with distilled water (25 mL), air-dried and crystallized from dioxane-DMF (5:1).

1,1''-(Propane-1,3-diyl)bis(2',6'-dimethyl-2-oxo-1'*H*-spiro[indoline-3,4'-pyridine]-3',5'-dicarbonitrile) (5a). Faint pink. Yield: 0.44 g (75%). mp > 300 °C. IR (KBr) 3302, 3232, 2205, 1707. ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.64 (m, 4H, 2CH₂), 2.10 (s, 12H, 4 Me), 3.69 (m, 4H, 2 NCH₂), 7.08-7.36 (m, 8H, arom.H), 9.96 (br s, 2H, 2NH); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 18.1, 25.1, 37.8, 50.8, 80.3, 108.8, 117.5, 123.5, 125.4, 129.9, 133.4, 140.9, 149.2, 175.8. MS (EI, 70 eV) *m/z* 592 [M⁺]. Anal. Calc. for C₃₅H₂₈N₈O₂ (592.66): C, 70.93; H, 4.76; N, 18.91. Found: C, 70.86; H, 4.61; N, 18.79.

1,1''-(Butane-1,4-diyl)bis(2',6'-dimethyl-2-oxo-1'*H*-spiro[indoline-3,4'-pyridine]-3',5'-dicarbonitrile) (5b). Faint pink. Yield: 0.48 g (80%). mp > 300 °C. IR (KBr) 3298, 3214, 2204, 1700. ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.68 (m, 4H, 2CH₂), 2.12 (s, 12H, 4 Me) 3.73 (m, 4H, 2NCH₂), 7.12-7.37 (m, 8H, arom.H), 9.98 (br s, 2H, 2NH); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 17.9, 24.1, 38.7, 50.8, 81.0, 109.2, 117.2, 123.3, 125.2, 130.0, 133.1, 141.3, 148.5, 175.7. MS (EI, 70 eV) *m/z* 606 [M⁺]. Anal. Calc. for C₃₆H₃₀N₈O₂ (606.69): C, 71.27; H, 4.98; N, 18.47. Found: C, 71.18; H, 4.85; N, 18.39.

1,1''-(Hexane-1,6-diyl)bis(2',6'-dimethyl-2-oxo-1'*H*-spiro[indoline-3,4'-pyridine]-3',5'-dicarbonitrile) (5c). Faint pink. Yield: 0.52 g (82%). mp > 300 °C. IR (KBr) 3295, 3220, 2203, 1702. ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.34 (m, 4H, 2CH₂), 1.56 (m, 4H, 2CH₂), 2.10 (s, 12H, 4 Me), 3.65 (m, 4H, 2NCH₂), 7.06-7.36 (m, 8H, arom.H), 9.95 (br s, 2H, 2NH); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 17.9, 25.6, 26.6, 38.7, 50.7, 81.0, 109.0, 117.1, 123.2, 125.3, 129.9, 133.2, 141.4, 148.4, 175.5. MS (EI, 70 eV) *m/z* 634 [M⁺]. Anal. Calc. for C₃₈H₃₄N₈O₂ (634.74): C, 71.91; H, 5.40; N, 17.65. Found: C, 71.83; H, 5.35; N, 17.55.

1,1''-(1,2-Phenylenebis(methylene))bis(2',6'-dimethyl-2-oxo-1'*H*-spiro[indoline-3,4'-pyridine]-3',5'-dicarbonitrile) (5d). Faint pink. Yield: 0.50 g (76%). mp > 300 °C. IR (KBr) 3293, 3223, 2205, 1701. ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.16 (s, 12 H, 4 Me), 5.20 (s, 4H, 4 CH₂), 6.96-7.47 (m, 12 H, arom.H), 10.07 (br s, 2H, 2 NH); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 18.0, 40.7, 51.1, 80.9, 109.8, 117.5, 123.8, 125.5, 127.0, 130.0, 132.4, 133.0, 141.3, 148.8, 176.0. MS (EI, 70 eV) *m/z* 654 [M⁺]. Anal. Calc. for C₄₀H₃₀N₈O₂ (654.73): C, 73.38; H, 4.62; N, 17.11. Found: C, 73.29; H, 4.55; N, 17.03.

1,1''-(1,3-Phenylenebis(methylene))bis(2',6'-dimethyl-2-oxo-1'*H*-spiro[indoline-3,4'-pyridine]-3',5'-dicarbonitrile) (5e). Faint pink. Yield: 0.51 g (78%). mp > 300 °C. IR (KBr) 3304, 3242, 2205, 1723. ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.15 (s, 12H, 4 Me), 4.91 (s, 4H, 4CH₂), 6.73-7.42 (m, 12H, arom.H), 10.05 (br s, 2H, 2NH); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 17.9, 42.8, 50.9, 80.9, 109.5, 117.4, 123.7, 125.4, 125.7, 125.8, 128.8, 129.9, 133.0, 135.8, 140.9, 148.7, 175.8. MS (EI, 70 eV) *m/z* 654 [M⁺]. Anal. Calc. for C₄₀H₃₀N₈O₂ (654.73): C, 73.38; H, 4.62; N, 17.11. Found: C, 73.31; H, 4.53; N, 16.99.

1,1''-(1,4-Phenylenebis(methylene))bis(2',6'-dimethyl-2-oxo-1'H-spiro[indoline-3,4'-pyridine]-3',5'-dicarbonitrile) (5f). Faint pink. Yield: 0.54 g (83%). mp > 300 °C. IR (KBr) 3305, 3228, 2202, 1705. ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.13 (s, 12H, 4Me), 4.92 (s, 4H, 2CH₂), 6.84-7.39 (m, 12H, arom.H), 10.02 (br s, 2H, 2NH); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 17.9, 42.8, 50.9, 80.9, 109.5, 117.2, 123.7, 125.3, 127.1, 129.9, 133.0, 134.7, 141.0, 148.6, 175.8. MS (EI, 70 eV) *m/z* 654 [M⁺]. Anal. Calc. for C₄₀H₃₀N₈O₂ (654.73): C, 73.38; H, 4.62; N, 17.11. Found: C, 73.33; H, 4.50; N, 17.15.

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