

Supporting Information

Characterizing Fibril Morphological Changes by Spirooxindoles for Neurodegenerative Disease Application

Anthony Dahdah, Nilamuni H. de Silva, Subashani Maniam, Ewan W. Blanch*

School of Science, STEM College, RMIT University, 124 La Trobe Street, Melbourne, VIC, 3001,
Australia

*ewan.blanch@rmit.edu.au

General Experimental

The starting materials, reagents were purchased from Sigma Aldrich, Merck, AK Scientific, Alfa Aesar and were used without further purification. Reactions were monitored by TLC analysis using insert Merck pre-coated thin aluminium plate coated with silica gel and F254 indicator and visualized by the aid of UV light at 254 nm wavelength. Melting points were determined on an electro thermal melting point apparatus and are uncorrected. Heating and cooling rate of the instrument was set at 1°C per minute. Nuclear Magnetic Resonance spectra (¹H, and ¹³C) were recorded with 300 MHz (¹H) and 75 MHz (¹³C) (Bruker) NMR spectrometer, using TMS as an internal reference. The chemical shifts values are expressed in parts per million (ppm) relative to DMSO and coupling constants (*J*) in Hz. Splitting patterns of multiplicities are designated as: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublet; m, multiplets. High-resolution mass spectrometric data were obtained by using LC-TOF mass spectrometer (150 eV). Low-resolution mass spectrometric data were obtained a Bruker GC-TOF mass spectrometer.

Synthesis

2'-(2-hydroxybenzoyl)-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizin]-2-one (**Hd-74**)

A mixture of isatin (1.0 mmol), L-proline (1.1 mmol) and hydroxychalcone (1.0 mmol) dissolved in 3 mL of ethanol, were irradiated under microwave irradiation (200 W power) at 65 °C for 10 minutes. After completion of the reaction, formed product was filtered and washed with ethanol. The obtained product was dried overnight using a vacuumed to obtain the hydroxy tri-aromatic spirooxindole **Hd-74**. The NMR and mass spectra are consistent with the reported data from Prasad *et al.* 2011.¹ Pale white solid, yield 65.4%, Melting point: 196-198 °C, ¹H NMR (300 MHz, DMSO-*d*₆): δ 11.11 (s, 1H, NH), 10.27 (s, 1H, OH), 7.46-7.43 (m, 2H, Ar-H), 7.33-7.07 (m, 7H, Ar-H), 6.88 (t, *J*=7.5 Hz, 1H, Ar-H), 6.70-6.65 (m, 2H, Ar-H), 6.59 (d, *J*=7.7 Hz, 1H, Ar-H), 5.02 (d, *J*=10.3 Hz, 1H, pyrrolidine), 3.98-3.85 (m, 2H, pyrrolidine), 2.68 (q, *J*=8.0,7.9,7.0 Hz, pyrrolidine), 2.37-2.31 (m, 1H, pyrrolidine), 1.90-1.67 (m, 4H, pyrrolidine); ¹³C NMR (75 MHz, DMSO-*d*₆): δ 202.2, 179.7, 160.1, 142.8, 140.5, 136.0, 129.9, 129.7, 129.1, 128.2, 127.8, 127.2, 125.3, 122.3, 121.4, 119.3, 117.5, 110.1, 73.1, 71.6, 64.0, 52.7, 48.2, 29.6, 26.7; MS (ESI): *m/z* 425 [M+H]⁺. MS (ESI) calculated for C₂₇H₂₄N₂O₃ [M+H]⁺ 425.2; obtained: 425.2.

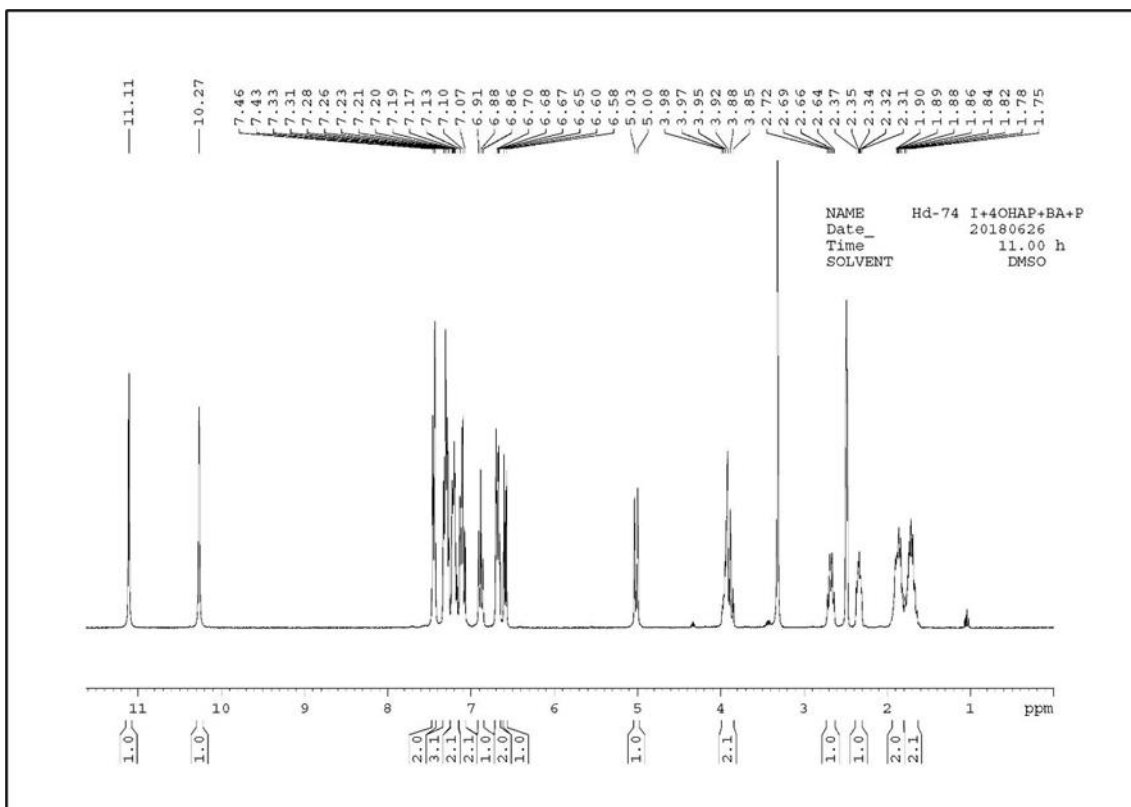


Figure S1. ^1H NMR (300 MHz, $\text{DMSO-}d_6$) spectrum of compound Hd-74.

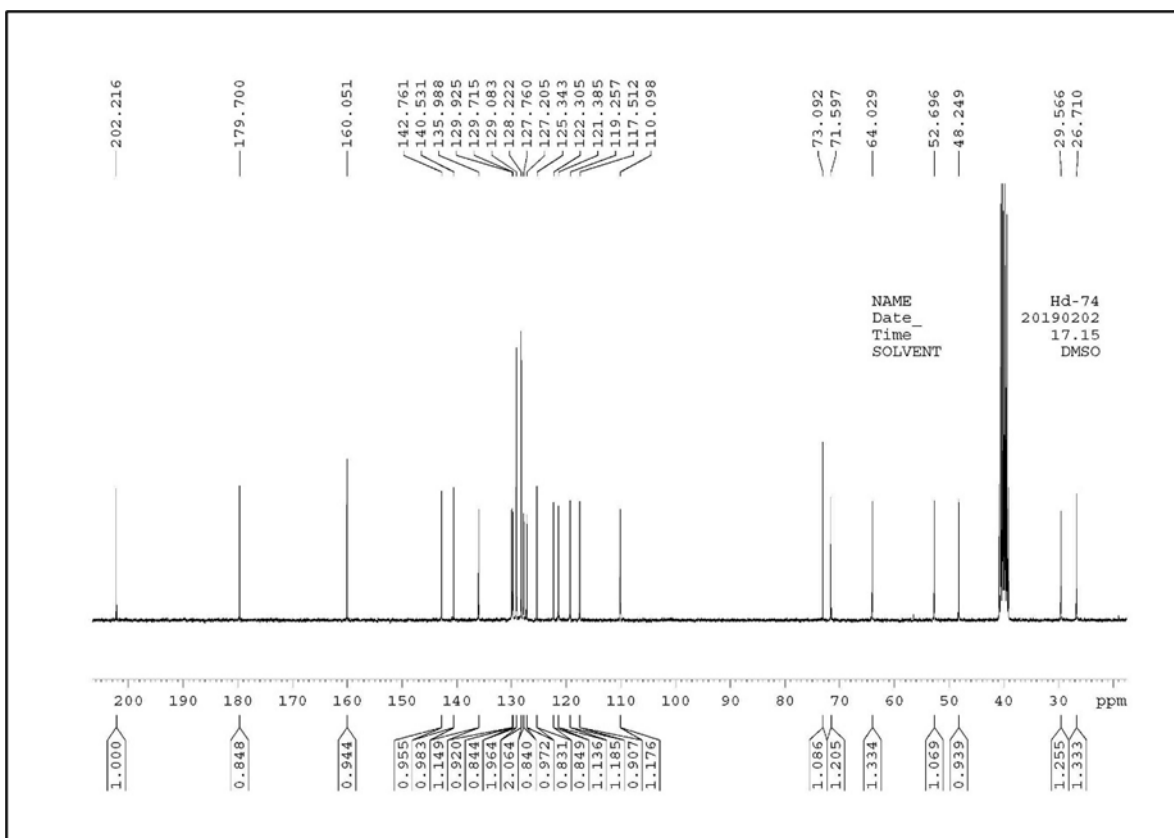


Figure S2. ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) spectrum of compound Hd-74.

CD Spectrum

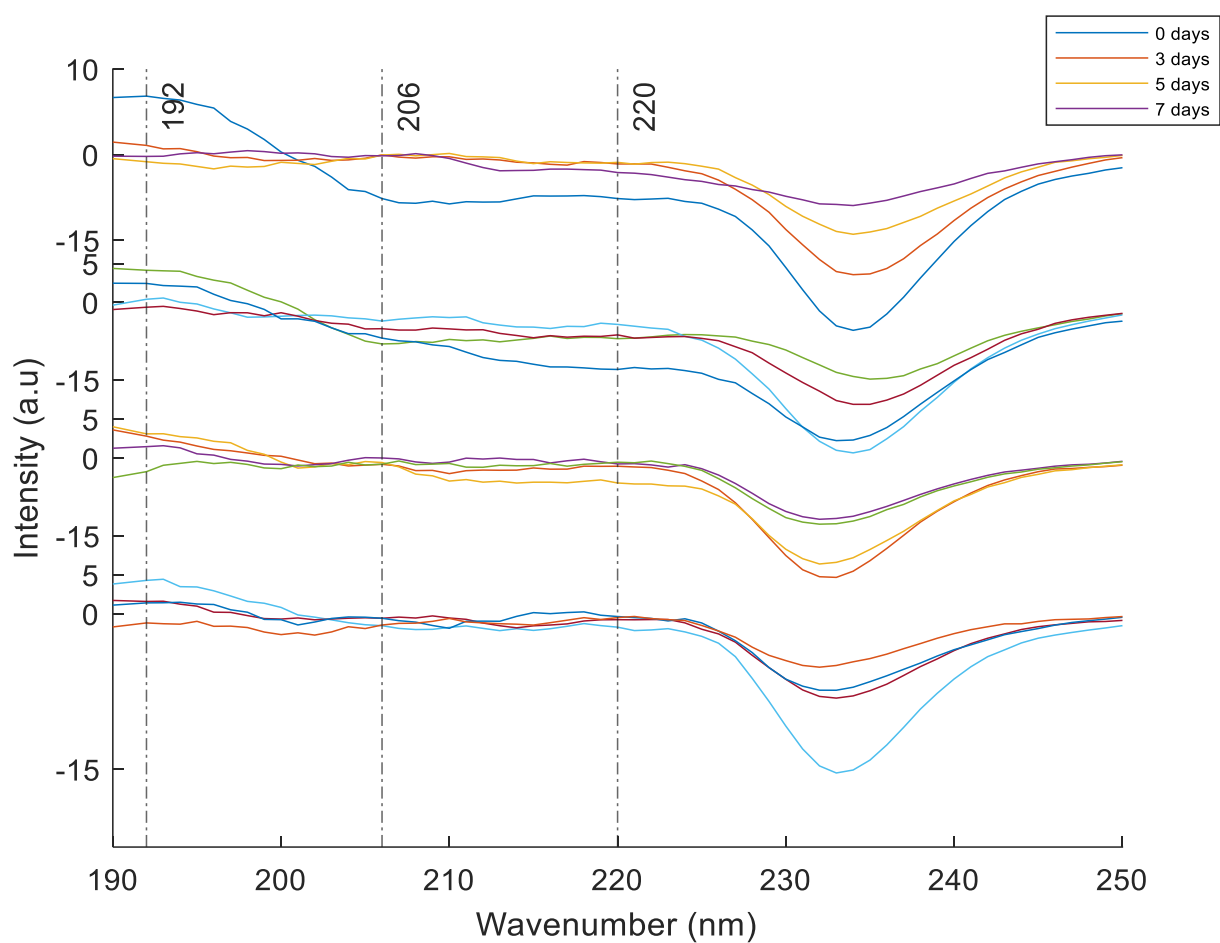


Figure S3. Circular dichroism spectra for (a) HEWL fibrils and HEWL exposed to 5 mM (b) **Hd-63**, (c) **Hd-66** and (d) **Hd-74**.

Reference

1. Prasad, T. A. A.; Vithiya, B. S. M.; Ignacimuthu, S., A facile and regioselective synthesis of Spiro pyrrolidines and pyrrolizines through 1, 3-dipolar cycloaddition protocol. *Der Pharma Chemica*, **2011**, 3(3):293-299.