SUPPLEMENTARY MATERIAL

Semi-synthesis of A Novel Hybrid Isoxazolidino Withaferin via Chemoselective and Diastereoselective 1,3-Dipolar Nitrone Cycloaddition Reaction

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Abstract: A facile, atom-economic synthesis of isoxazolidino withaferin, a novel hybrid of withaferin A, has been accomplished via two-step reaction of nitrone synthesis followed by nitrone 1,3-dipolar cycloaddition. The reaction is highly chemoselective (preferential reaction only on one of the two double bonds present on withaferin A) and diastereoselective affording exclusively the cis-fused products. The structure was determined by detailed analysis of 1D, 2D NMR and mass spectral data.

Keywords: Withaferin A; Nitrone-cycloaddition; Semi-synthesis; Isoxazolidine; 2D NMR (HSQC, HMBC, COSY, NOESY);
Figure S1: $^1$H NMR of Withaferin A
Figure S2: $^1$H NMR of Withaferin A
Figure S3: $^1$H NMR of Withaferin A
Figure S4: $^1$H NMR of Withaferin A
Figure S5: $^1$H NMR of Withaferin A
Figure S6: $^{13}$C NMR of Withaferin A
Figure S7: $^{13}$C NMR, DEPT 90, 135 of Withaferin A
Figure S8: HPLC Profile of Compound 3A
Figure S9: Mass Spectra of Compound 3A

*ESI Scan (rt: 0.592 min) Frag=175.0V NO2-N-2.d

Counts vs. Mass-to-Charge (m/z)

- 735.3257
- 122.0962
- 242.2836
- 349.2344
- 522.5961

10
Figure S10: $^1$H NMR of Compound 3A
Figure S11: $^1$H NMR of Compound 3A
Figure S12: $^1$H NMR of Compound 3A
Figure S13: $^{13}$C NMR of Compound 3A
Figure S14: $^{13}$C NMR of Compound 3A
Figure S15: DEPT 135 of Compound 3A
Figure S16: COSY of Compound 3A
Figure S17: NOESY of Compound 3A
Figure S18: HMBC of Compound 3A
Figure S19: HMBC of Compound 3A
Figure S20: HSQC of Compound 3A
Figure S21: HPLC Profile of Compound 3B

<Sample Information>
Sample Name: BRN
Sample ID: BRN
Data Filename: BRN1.lcd
Method Filename: BASELINE.lcm
Batch Filename: 
Vial #: 1-2
Injection Volume: 10 uL
Date Acquired: 2/6/2018 3:33:06 PM
Date Processed: 2/6/2018 3:53:09 PM
Sample Type: Unknown
Acquired by: user
Processed by: user

<Chromatogram>

<Peak Table>
PDA Ch1 254nm

| Peak# | Ret. Time | Area   | Height | Area%  | Height% |
|-------|-----------|--------|--------|--------|---------|
| 1     | 3.963     | 11436622 | 1351555 | 100.000 | 100.000 |
| Total |           | 11436622 | 1351555 | 100.000 | 100.000 |
Figure S22: Mass Spectra of Compound 3B

+ESI Scan (rt: 1.817 min) Freq=175.0V BR-N-1C.d

Counts vs. Mass-to-Charge (m/z)

- Masses: 768.2510, 770.2496, 769.2538, 771.2524, 772.2545, 773.2567
Figure S23: $^1$H NMR of Compound 3B
Figure S24: $^1$H NMR of Compound 3B
Figure S25: $^1$H NMR of Compound 3B
Figure S26: $^1$H NMR of Compound 3B
Figure S2: $^{13}$C NMR of Compound 3B
Figure S28: DEPT 90 of Compound 3B
Figure S29: DEPT 135 of Compound 3B
Figure S30: HPLC Profile of Compound 3C

Analysis Report

Sample Information:
- Sample Name: CL N3
- Sample ID: CL N3
- Data Filename: CL N3.lcd
- Method Filename: WASHING.lcm
- Batch Filename:
- Vial #: 1-5
- Injection Volume: 20 μL
- Date Acquired: 2/27/2018 1:32:51 PM
- Date Processed: 2/27/2018 2:12:34 PM
- Sample Type: Unknown
- Acquired by: user
- Processed by: user

Chromatogram:

Peak Table:

| Peak# | Ret. Time | Area   | Height  | Area% | Height% |
|-------|-----------|--------|---------|-------|---------|
| 1     | 3.741     | 8473843| 855558  | 100.00| 100.00  |
| Total |           | 8473843| 855558  | 100.00| 100.00  |
Figure S31: Mass Spectra of Compound 3C

+ESI Scan (rt: 2.269 min) Frag=175.0V CL-N-1A-r002.d
Figure S32: $^1$H NMR of Compound 3C
Figure S33: $^{13}$C NMR of Compound 3C
Figure S34: DEPT 90 of Compound 3C
Figure S35: DEPT 135 of Compound 3C
Figure S36: Mass Spectra of Withaferin-Dinitrone Adduct 5

* Scan (rt 3.495 min) N-2A1.d

* 1181.6342

590.3128

288.2903

Counts vs. Mass-to-Charge (m/z)
Figure S37: \(^1\)H NMR Spectra of Withaferin-Dinitrone Adduct 5
Figure S38: $^1$H NMR Spectra of Withaferin-Dinitrone Adduct 5
Figure S39: $^1$H NMR Spectra of Withaferin-Dinitrone Adduct 5
Figure S40: $^1$H NMR Spectra of Withaferin-Dinitrone Adduct 5
Figure S41: $^{13}$C NMR Spectra of Withaferin-Dinitrone Adduct 5
Figure S42: DEPT 90 of Withaferin-Dinitrone Adduct 5
Figure S43: DEPT 135 of Withaferin-Dinitrone Adduct 5
Figure S44: COSY of Withaferin-Dinitrone Adduct 5
Figure S45: NOESY of Withaferin-Dinitrone Adduct 5
Figure S46: NOESY of Withaferin-Dinitrone Adduct 5
Figure S47: HMBC of Withaferin-Dinitrone Adduct 5
Figure S48: HSQC of Withaferin-Dinitrone Adduct 5