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Aqueous Phase Supramolecular Synthesis of 3′-spirocyclic oxindoles Catalyzed by β-cyclodextrin

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Abstract

A high yielding green protocol is described for the synthesis of 3′-spirocyclic oxindoles by [3+2] cycloaddition reaction of azomethine ylides to the Δ^{12} double bond of andrographolide (a natural product isolated from Andrographis paniculata Nees) in water catalyzed by β-cyclodextrin.

Keywords: 3′-Spirocyclic oxindole; β-cyclodextrin; andrographolide; [3+2] cycloaddition reaction; azomethine ylide; reactions in water.

Introduction

In recent years considerable interest has been noticed among the synthetic organic chemists to perform organic reactions in water because it is cheap, non-toxic, non-inflammable and safe. Moreover, the unique physical and chemical properties of water often increase the reactivity as well as selectivity which is unattainable in common organic solvents[1] and the product may be easily isolated by simple filtration or recrystallization. But most of the organic compounds are hydrophobic in nature and their limited solubility in water is the prime obstacle in performing reactions in aqueous media. The strategy that has contributed to some extent to overcome this obstacle is the introduction of supramolecular catalysts, as for example β-cyclodextrin. β-Cyclodextrin(β-CD) are torus-shaped cyclic oligosaccharides and they have considerable hydrophobic cavities, which bind substrates selectively and catalyze chemical reactions by a supramolecular interaction[2,3]. Due to these unique structural properties β-CDs have been widely used in food and cosmetics industries[4], as well as pharmaceutical chemistry[5,6].

As a part of our concerted research for establishing novel methodologies for the synthesis of bioactive heterocycles in water[6-8]. We were intrigued by the unique characteristics of β-CDs and contemplated to utilize β-CD as catalyst for the synthesis of 3′-spirocyclic oxindoles which have a wide range of biological activities[9,10]. 3-spirocyclic oxindole ring systems are found in a number of bioactive alkaloid like horsifiline, spirotryprostatin A and B, elacomine and so on.

The varied biological activities of 3′-spirocyclic oxindole derivatives have attracted the attention of organic chemists and a number of synthetic methodologies have been developed for the preparation of them[11-13]. Recently N.B. Mondal et. al. reported a method for the synthesis of 3′-spirocyclic oxindoles by [3+2] cycloaddition reaction of azomethine ylide to the conjugated double bond of andrographolide[14]. However, their methodology had some shortcomings, like poor yields of the products (50-60%), long reaction time (22 h) and use of environmentally hazardous different organic solvents and lenghthy usual work up to get pure final product. To overcome these problems we have now successfully develop a truly green protocol for the synthesis of 3′-spirocyclic oxindoles with excellent yields in short reaction time using β-cyclodextrin (β-CD) as catalyst in aqueous media, without the use of any organic solvent and clean cut pure compounds.

Material and Methods

Experimental: Melting points were determined with a capillary melting point apparatus. IR spectra were recorded on a JASCO FTIR (model 410) in KBr pellets. ESI-MS (positive) was conducted using LC-ESI-Q-TOF micro Mass spectrometer. ^{1}H and ^{13}C NMR spectra were taken on a Bruker 600 MHz DPX spectrometer at 600 and 150 MHz respectively, with tetramethylsilane (TMS) as internal standard and the chemical shifts are reported in δ units. Andrographolide was isolated from the leaves of *Andrographis paniculata Nees* by the method described in the literature. Isatin derivatives, proline and sarcosine were purchased from Aldrich Chemical Ltd (USA).

General procedure for the synthesis of 3′-spirocyclic oxindoles: β-cyclodextrin (1 mmole) was dissolved in water (20 ml) by warming to 60 ºC until a clear solution was formed. Then, isatin derivative (1mmole) was added portion wise with constant stirring followed by L-proline/sarcosine (1 mmole) and andrographolide (1 mmole); the mixture was stirred at 80 ºC until the reaction was complete (monitored by TLC). After completion of the reaction (monitored by TLC), the contents of the reaction mixture were poured into a separating funnel and extracted with ethyl acetate (3x25 ml). The organic layer was washed thoroughly with hot water until free from β-cyclodextrin, dried over sodium sulfate, and evaporated to

dryness in a rotary evaporator under reduced pressure. The residue was chromatographed over a column of silica gel (100-200 mesh) eluting with a mixture of hexane and ethyl acetate in different ratios, to yield the 3′-spirocyclic oxindoles.

Spectral characterization of the compounds: Compound3a: Colourless needles, m.p. 182-184ºC (lit.[14] 180-182ºC); IR (KBr, ν_{max}) 3353, 2938, 2873, 1766, 1698, 1620, 1472 cm^{-1}; ^1H NMR (CD_3OD) δ 7.36 (1H, dd, *J*=1.2, 7.8Hz), 7.17 (2H, m), 6.98 (1H, d, *J*=7.8 Hz), 4.81 (1H, t, *J*=8.4 Hz), 4.61 (1H, t, *J*=8.4 Hz), 4.52 (1H, s), 4.15 (1H, m) 3.99 (1H, d, *J*=10.8 Hz), 3.94 (1H, t, *J*=9 Hz), 3.61 (1H, s), 3.35 (2H, dd, *J*=3.0, 11.4 Hz), 3.25 (1H, d, *J*=10.8 Hz), 2.86 (1H, m), 2.69 (1H, m), 2.22 (1H, m), 1.92 (1H, m), 1.71(9H, m), 1.26 (1H, m), 1.19 (1H, m), 1.16 (1H, m), 1.14 (3H, s), 1.00 (2H, m), 0.45 (3H, s); ^{13}C NMR (CD_3OD) δ 15.1 (CH_3), 20.8 (CH_2), 23.5 (CH_3), 25.7 (CH_2), 26.4 (CH_2), 29.1 (CH_2), 29.7 (CH_2), 38.3 (CH_2), 39.4 (CH_2), 40.7 (C), 43.8 (C), 49.6 (CH), 50.2 (CH_2), 54.0 (CH), 56.8 (CH), 57.6 (C), 65.0 (CH_2), 66.3 (CH), 68.4 (CH), 70.4 (CH_2), 77.8 (C), 80.9 (CH), 107.3 (CH_2), 112.1 (CH), 124.0 (CH), 127.8 (CH), 129.0 (C), 131.4 (CH), 143.8 (C), 148.2 (C), 179.7 (C), 183.9 (C); MS (ESI-MS, positive ion) m/z 551 $[M+H]^+$, 573 $[M+Na]^+$; HRMS m/z 573.2940 $[M+Na]^+$ [calcd. 573 .2941].

Compound3b: Colourless prisms, m.p. 180-182ºC (lit.[14] 182-184ºC); IR (KBr, ν_{max}) 3352, 2941, 1775, 1698, 1617, 1474 cm^{-1}; ^1H NMR (CD_3OD) δ 7.53 (1H, dd, *J*=1.8Hz, 7.8Hz), 7.29 (1H, d, *J*=1.8Hz), 6.92 (1H, d, *J*=7.8Hz), 4.80 (1H, m), 4.60 (2H, m), 4.17 (1H, m), 3.99 (1H, d, *J*=10.8Hz), 3.93 (1H, t, *J*=9Hz), 3.64 (1H, s), 3.35 (1H, m), 3.28 (2H, m), 2.82 (1H, m), 2.71 (1H, m), 2.25 (1H, m), 1.92 (1H, m), 1.69 (9H, m), 1.26 (1H, d, *J*=11.4Hz), 1.17 (5H, m), 1.15 (3H, s), 1.14 (1H, m), 1.01 (2H, m), 0.46 (3H, s); ^{13}C NMR (CD_3OD) δ 15.1 (CH_3), 20.9 (CH_2), 23.5 (CH_3), 25.7 (CH_2), 26.5 (CH_2), 29.1 (CH_2), 29.6 (CH_2), 38.3 (CH_2), 39.4 (CH_2), 40.7 (C), 43.8 (C), 49.7 (CH), 50.1 (CH_2), 54.0 (CH), 56.9 (CH), 57.8 (C), 65.0 (CH_2), 66.2 (CH), 68.4 (CH), 70.5 (CH_2), 77.7 (C), 80.9 (CH), 106.9 (CH_2), 113.8 (CH), 116.4 (C), 130.7 (CH), 131.5 (C), 134.3 (CH), 143.1 (C), 148.5 (C), 179.6 (C), 183.3 (C); MS (ESI-MS, positive ion) m/z 629 $[M+H]^+$, 631 $[(M+2)+H]^+$, 651 $[M+Na]^+$, 653 $[(M+2)+Na]^+$; HRMS m/z 651.2007 $[M+Na]^+$ [calcd. 651.2046].

Compound 3c: Colourless needles, m.p. 208-210ºC (lit.[14] 208-210ºC); IR (KBr, ν_{max}) 3321, 2950, 2885, 1771, 1700, 1610, 1469 cm^{-1}; ^1H NMR (CD_3OD) δ 7.47 (1H, m), 7.25 (2H, m), 7.10 (1H, d, *J*=7.8 Hz), 4.82 (1H, dd, *J*=8.4, 9Hz), 4.61 (1H, t, *J*=7.8 Hz), 4.53 (1H, s), 4.17 (1H, dd, *J*=6.6, 9Hz), 3.97 (1H, d, *J*=11.4 Hz), 3.94 (1H, t, *J*=9 Hz), 3.69 (1H, s), 3.37 (1H, dd, *J*=4.2, 10.2 Hz), 3.32 (1H, m), 3.24 (1H, d, *J*=11.4 Hz), 3.19 (3H, s), 2.83 (1H, m), 2.66 (1H, m), 2.19 (1H, m), 1.93 (1H, m), 1.71 (7H, m), 1.57 (2H, m), 1.20 (1H, m), 1.15 (1H, m), 1.13 (1H, m), 1.12 (3H, s), 0.99 (1H, m), 0.93 (1H, dd, *J*=2.4, 12.6 Hz), 0.43 (3H, s); ^{13}C NMR (CD_3OD) δ 15.0 (CH_3), 21.1 (CH_2), 23.5 (CH_3), 25.6 (CH_2), 26.3 (CH_2), 26.8 (CH_3), 29.0 (CH_2), 29.6 (CH_2), 38.1 (CH_2), 39.3 (CH_2), 40.8 (C), 43.7 (C), 49.8 (CH), 50.2 (CH_2), 53.9 (CH), 56.9 (CH), 58.0 (C), 65.0 (CH_2), 66.1 (CH), 68.5 (CH), 70.5 (CH_2), 77.2 (C), 80.9 (CH), 107.1 (CH_2), 110.9 (CH), 124.5 (CH), 127.4 (CH), 128.7 (C), 131.5 (CH), 145.6 (C), 148.5 (C), 179.6 (C), 181.6 (C); MS (ESI-MS, positive ion) m/z 565 $[M+H]^+$, 587 $[M+Na]^+$; HRMS m/z 565.3285 $[M+H]^+$ [calcd 565.3278], 587.3078 $[M+Na]^+$ [calcd. 587.3097].

Compound3d: Colourless needles, m.p. 180-182ºC (lit.[14] 181-183ºC); IR (KBr, ν_{max}) 3376, 2937, 1769, 1694, 1624, 1491 cm^{-1}; ^1H NMR (CD_3OD) δ 7.18 (1H, dd, *J*=0.6, 8.4 Hz), 6.99 (1H, s), 6.87 (1H, d, *J*=7.8 Hz), 4.80 (1H, dd, *J*=8.4, 9.0 Hz), 4.60 (1H, t, *J*=7.8 Hz), 4.53 (1H, s), 4.17 (1H, m), 3.99 (1H, d, *J*=11.4 Hz), 3.93 (1H, t, *J*=9.0 Hz), 3.61 (1H, s), 3.32 (2H, m), 3.25 (1H, d, *J*=11.4Hz), 2.88 (1H, m), 2.69 (1H, m), 2.37 (3H, s), 2.23 (1H, m), 1.92 (1H, m), 1.71 (10H, m), 1.26 (1H, m), 1.14 (4H, m), 1.00 (2H, m), 0.45 (3H, s); ^{13}C NMR (CD_3OD) δ 15.1 (CH_3), 20.8 (CH_2), 21.4 (CH_3), 23.5 (CH_3), 25.7 (CH_2), 26.4 (CH_2), 29.1 (CH_2), 29.7 (CH_2), 38.3 (CH_2), 39.4 (CH_2), 40.7 (C), 43.8 (C), 49.7 (CH), 50.2 (CH_2), 54.0 (CH), 56.9 (CH), 57.8 (C), 65.0 (CH_2), 66.2 (CH), 68.4 (CH), 70.4 (CH_2), 77.9 (C), 80.9 (CH), 107.1 (CH_2), 111.9 (CH), 128.4 (CH), 129.1 (C), 131.6 (CH), 133.8 (C), 141.3 (C), 148.3 (C), 179.8 (C), 183.8 (C); MS (ESI-MS, positive ion) m/z 565 $[M+H]^+$, 587 $[M+Na]^+$; HRMS m/z 565.3283 $[M+H]^+$ [calcd 565.3278], 587.3094 $[M+Na]^+$ [calcd. 587.3097].

Compound3e: Colourless needles, m.p. 181-183ºC (lit.[14] 180-182ºC); IR (KBr, ν_{max}) 3347, 2938, 1767, 1695, 1490 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.69 (1H, s, -NH), 6.93 (1H, dd, *J*=2.4, 9.0 Hz), 6.87 (1H, d, *J*=8.4 Hz), 6.68 (1H, s), 6.60 (1H, d, *J*=2.4 Hz), 5.04 (1H, d, *J*=4.8 Hz), 4.62 (2H, m), 4.48 (1H, s), 4.06 (1H, m), 3.99 (1H, m), 3.84 (1H, t, *J*=8.4 Hz), 3.75 (3H, s), 3.72 (1H, d, *J*=9.6 Hz), 3.51 (1H, s), 3.15 (3H, m), 2.69 (1H, m), 2.56 (1H, m), 2.15 (1H, m), 1.83 (1H, m), 1.58 (8H, m), 1.46 (1H, m), 1.17 (2H, m), 1.10 (1H, m), 1.00 (3H, s), 0.90 (1H, dd, J=1.8, 12.6 Hz), 0.83 (1H, m), 0.36 (3H, s); ^{13}C NMR (DMSO-d_6) δ 14.1 (CH_3), 18.9 (CH_2), 23.0 (CH_3), 24.3 (CH_2), 25.1 (CH_2), 27.8 (CH_2), 28.1 (CH_2), 36.4 (CH_2), 37.8 (CH_2), 42.2 (C), 47.5 (CH), 48.3 (CH_2), 51.7 (CH), 54.8 (CH), 55.4 (C), 55.8 (CH_3, C) 62.6 (CH_2), 64.5 (CH), 66.4 (CH), 68.6 (CH2), 76.1 (C), 78.2 (CH), 105.4 (CH_2), 111.3 (CH), 112.4 (CH), 114.9 (CH), 128.8 (C), 135.4 (C), 147.0 (C), 155.3 (C), 177.1 (C), 181.5 (C); MS (ESI-MS, positive ion) m/z 581 $[M+H]^+$, 603 $[M+Na]^+$; HRMS m/z 603.2988 $[M+Na]^+$ [calcd. 603.3046].

Compound3f: Colourless needles, m.p. 180-182ºC (lit.[14] 179-181ºC); IR (KBr, ν_{max}) 3374, 2938, 1767, 1700, 1630, 1486 cm^{-1}; ^1H NMR (CD_3OD) δ 7.13 (1H, dt, *J*=2.4, 9.0 Hz), 6.97 (2H, m), 4.81 (1H, dd, *J*=7.8, 9.0 Hz), 4.61 (1H, t, *J*=7.8 Hz), 4.58 (1H, s), 4.15 (1H, dd, *J*=5.4, 9.6 Hz), 3.99 (1H, d, *J*=11.4Hz), 3.94 (1H, t, *J*=9Hz), 3.63 (1H, s), 3.35 (1H, dd, *J*=3.6, 11.4 Hz), 3.27 (2H, m), 2.83 (1H, m), 2.72 (1H, m), 2.24 (1H, m), 1.93 (1H, m), 1.76 (3H, m), 1.71 (3H, m), 1.63 (1H, m), 1.27 (1H, d, *J*=11.4 Hz), 1.19 (5H, m), 1.01 (2H, m), 0.46 (3H, s); ^{13}C NMR (CD_3OD) δ 15.1 (CH_3), 20.8 (CH_2), 23.5 (CH_3), 25.7 (CH_2), 26.4 (CH_2), 29.1 (CH_2), 29.6 (CH_2), 38.3 (CH_2), 39.4 (CH_2), 40.7 (C), 43.8 (C), 49.7 (CH), 50.0 (CH_2), 54.0 (CH), 56.8 (CH), 57.6 (C), 65.0 (CH_2), 66.4 (CH), 68.4 (CH), 70.4 (CH_2),

78.1 (C), 80.9 (CH), 106.9 (CH_2), 113.0 (CH, $^3J_{C-F}$ 7.5 Hz), 115.2 (CH, $^2J_{C-F}$ 25.5 Hz), 117.7 (CH,$^2J_{C-F}$ 24 Hz), 131.0 (C, $^3J_{C-F}$ 7.5 Hz), 139.8 (C), 148.4 (C), 160.64 (C, $^1J_{C-F}$ 238.5 Hz), 179.6 (C), 183.8 (C); MS (ESI-MS, positive ion) m/z 569 $[M+H]^+$, 591 $[M+Na]^+$; HRMS m/z 569.3010 $[M+H]^+$ [calcd 569.3027], 591.2856 $[M+Na]^+$ [calcd. 591.2846].

Compound3g: Colourless needles, m.p. 179-181ºC (lit.[14] 178-180ºC); IR (KBr, ν_{max}) 3346, 2940, 1773, 1699, 1619, 1477 cm^{-1}; ^1H NMR (CD_3OD) δ 7.39 (1H, dd, *J*=2.4, 8.4 Hz), 7.16 (1H, d, *J*=2.4 Hz), 6.97 (1H, d, *J*=8.4 Hz), 4.80 (1H, dd, *J*=8.4, 9 Hz), 4.61 (1H, t, *J*=8.4 Hz), 4.58 (1H, s), 4.17 (1H, dd, *J*=6.0, 10.2 Hz), 3.99 (1H, d, *J*=10.8 Hz), 3.93 (1H, t, *J*=9 Hz), 3.63 (1H, s), 3.35 (1H, dd, *J*=3.6, 11.4 Hz), 3.27 (2H, m), 2.82 (1H, m), 2.71 (1H, m), 2.25 (1H, m), 1.93 (1H, m), 1.76 (5H, m), 1.65 (4H, m), 1.27 (1H, d, J=11.4 Hz), 1.20 (1H, dt, *J*=4.8, 12.6 Hz), 1.15 (4H, m), 1.00 (2H, m), 0.46 (3H, s); ^{13}C NMR (CD_3OD) δ 15.1 (CH_3), 20.9 (CH_2), 23.5 (CH_3), 25.7 (CH_2), 26.4 (CH_2), 29.1 (CH_2), 29.6 (CH_2), 38.3 (CH_2), 39.4 (CH_2), 40.7 (C), 43.8 (C), 49.7 (CH), 50.1 (CH_2), 54.0 (CH), 56.9 (CH), 57.7 (C), 65.0 (CH_2), 66.3 (CH), 68.4 (CH), 70.5 (CH_2), 77.7 (C), 80.9 (CH), 106.9 (CH_2), 113.4 (CH), 127.9 (CH), 129.4 (C), 131.1 (C), 131.3 (CH), 142.6 (C), 148.5 (C), 179.6 (C), 183.5 (C); MS (ESI-MS, positive ion) m/z 585 $[M+H]^+$, 587 $[(M+2)+H]^+$ 607 $[M+Na]^+$, 609 $[(M+2)+Na]^+$; HRMS m/z 607.2518 $[M+Na]^+$ [calcd. 607.2551].

Compound3h: Colourless needles, m.p. 184-186ºC (lit.[14] 184-186ºC); IR (KBr, ν_{max}) 3406, 2938, 1766, 1703, 1613, 1472 cm^{-1}; ^1H NMR (CD_3OD) δ 7.72 (1H, dd, *J*=1.2, 8.4 Hz), 7.46 (1H, d, *J*=1.2 Hz), 6.81 (1H, d, *J*=8.4 Hz), 4.79 (1H, dd, *J*=7.8, 9 Hz), 4.60 (3H, m), 4.17 (1H, dd, *J*=5.4, 9.6 Hz), 3.99 (1H, d, *J*=11.4 Hz), 3.93 (1H, t, *J*=9 Hz), 3.66 (1H, s), 3.36 (1H, m), 3.27 (2H, m), 2.81 (1H, m), 2.70 (1H, m), 2.25 (1H, m), 1.91 (1H, m), 1.73 (6H, m), 1.61 (2H, m), 1.26 (1H, d, *J*=10.8Hz), 1.20 (1H, m), 1.14 (4H, m), 1.02 (2H, m), 0.46 (3H, s); ^{13}C NMR (CD_3OD) δ 15.1 (CH_3), 21.0 (CH_2), 23.5 (CH_3), 25.7 (CH_2), 26.5 (CH_2), 29.1 (CH_2), 29.6 (CH_2), 38.2 (CH_2), 39.4 (CH_2), 40.7 (C), 43.8 (C), 49.7 (CH), 50.2 (CH_2), 54.0 (CH), 56.9 (CH), 57.8 (C), 65.0 (CH_2), 66.2 (CH), 68.4 (CH), 70.5 (CH_2), 77.4 (C), 80.9 (CH), 85.7 (C), 107.0 (CH_2), 114.2 (CH), 131.8 (C), 136.6 (CH), 140.3 (CH), 143.6 (C), 148.5 (C), 179.6 (C), 183.0 (C); MS (ESI-MS, positive ion) m/z 677 $[M+H]^+$, 699 $[M+Na]^+$; HRMS m/z 677.2083 $[M+H]^+$ [calcd 677.2088].

Compound4a: Colourless needles, m.p. 232-234ºC (lit.[14] 234-236ºC); IR (KBr, ν_{max}) 3374, 2938, 2851, 1724, 1619, 1471 cm^{-1}; ^1H NMR (CD_3OD) δ 7.30 (1H, dt, *J*=1.2, 7.8 Hz), 7.14 (1H, d, *J*=7.2 Hz), 7.01 (1H, dt, *J*=0.6, 7.8 Hz), 6.85 (1H, d, *J*=7.8 Hz), 4.82 (2H, d, *J*=12 Hz), 4.43 (1H, d, *J*=2.4 Hz), 4.13 (1H, d, *J*=11.4 Hz), 3.76 (1H, d, *J*=10.2 Hz), 3.41 (2H, m), 3.35 (1H, m), 3.18 (1H, dd, *J*=2.4, 10.2 Hz), 3.03 (1H, dd, *J*=6.0, 9.0 Hz), 2.90 (1H, m), 2.53 (1H, m), 2.41 (1H, m), 2.26 (1H, t, *J*=12.6 Hz), 2.04 (1H, m), 2.01 (1H, m), 1.97 (3H, s), 1.82 (3H, m), 1.56 (1H, d, *J*=11.4 Hz), 1.34 (1H, m), 1.28 (2H, m), 1.22 (3H, s), 0.69 (3H, s); ^{13}C NMR (CD_3OD) δ 15.9 (CH_3), 23.6 (CH_3), 25.6 (CH_2), 26.3 (CH_2), 29.3 (CH_2), 35.7 (CH_3), 38.6 (CH_2), 39.7 (CH_2), 40.4 (CH), 40.5 (C), 43.9 (C), 56.3 (CH), 57.0 (CH), 61.1 (CH_2), 65.3 (CH_2), 66.7 (C), 73.3 (CH), 75.4 (CH_2), 76.8 (C), 81.4 (CH), 108.6 (CH_2), 111.0 (CH), 123.9 (CH), 126.9 (CH), 127.0 (C), 131.5 (CH), 144.2 (C), 148.7 (C), 179.1 (CO), 180.7 (CO); MS (ESI-MS, positive ion) m/z 525 $[M+H]^+$, 547 $[M+Na]^+$; HRMS m/z 525.2943 $[M+H]^+$ [calcd. 525.2965].

Compound4b: Colourless needles, m.p. 208-210ºC (lit.[14] 209-211ºC); IR (KBr, ν_{max}) 3398, 2941, 2850, 1760, 1725, 1617, 1472 cm^{-1}; ^1H NMR (CD_3OD) δ 7.46 (1H, dd, *J*=2.4, 8.4 Hz), 7.24 (1H, d, *J*=1.8 Hz), 6.79 (1H, d, *J*=8.4 Hz), 4.82 (2H, d, *J*=10.2 Hz), 4.61 (1H, s), 4.42 (1H, m), 4.13 (1H, d, *J*=10.8 Hz), 3.82 (1H, d, *J*=10.2 Hz), 3.41 (2H, m), 3.34 (1H, d, *J*=10.8 Hz), 3.23 (1H, dd, *J*=2.4, 10.2 Hz), 3.00 (1H, m), 2.90 (1H, m) 2.51 (1H, m), 2.40 (1H, m), 2.24 (1H, m), 1.98 (3H, s), 1.96 (1H, m), 1.82 (5H, m), 1.56 (1H, d, *J*=11.4 Hz), 1.33 (1H, m), 1.26 (2H, m), 1.22 (3H, s), 0.69 (3H, s); ^{13}C NMR (CD_3OD) δ 15.9 (CH_3), 23.6 (CH_3), 25.6 (CH_2), 26.3 (CH_2), 29.3 (CH_2), 35.7 (CH_3), 38.6 (CH_2), 39.7 (CH_2), 40.3 (CH), 40.5 (C), 43.9 (C), 56.3 (CH), 57.0 (CH), 61.2 (CH_2), 65.3 (CH_2), 66.9 (C), 73.1 (CH), 75.5 (CH_2), 76.6 (C), 81.4 (CH), 108.6 (CH_2), 112.7 (CH), 116.3 (C), 129.5 (C), 130.0 (CH), 134.4 (CH), 143.5 (C), 148.7 (C), 178.6 (CO), 180.3 (CO); MS (ESI-MS, positive ion) m/z 603 $[M+H]^+$, 605 $[(M+2)+H]^+$, 625 $[M+Na]^+$, 627 $[(M+2)+Na]^+$; HRMS m/z 625.1905 [M+Na]+ [calcd. 625.1889].

Compound 4c: Colourless needles, m.p. 230-232ºC (lit.[14] 231-233ºC); IR (KBr, ν_{max}) 3430, 2942, 2855, 1770, 1698, 1625 cm^{-1}; ^1H NMR (CD3OD) δ 7.11 (1H, d, *J*=7.8 Hz), 6.98 (1H, s), 6.74 (1H, d, *J*=8.4 Hz), 4.82 (2H, d, *J*=9 Hz), 4.42 (1H, d, *J*=1.8 Hz), 4.13 (1H, d, *J*=10.8 Hz), 3.76 (1H, d, *J*=10.2 Hz), 3.41 (2H, m), 3.34 (1H, d, *J*=11.4 Hz), 3.19 (1H, dd, *J*=2.4, 10.2 Hz), 3.02 (1H, dd, *J*=6.0, 8.4 Hz), 2.89 (1H, m), 2.53 (1H, m), 2.41 (1H, m), 2.27 (3H, s), 2.23 (1H, d, *J*=12.6 Hz), 2.00 (2H, m), 1.96 (3H, s), 1.81 (3H, m), 1.56 (1H, d, *J*=11.4 Hz), 1.31 (3H, m), 1.22 (3H, s), 0.69 (3H, s); ^{13}C NMR (CD_3OD) δ 15.9 (CH_3), 21.3 (CH_3), 23.6 (CH_3), 25.6 (CH_2), 26.3 (CH_2), 29.3 (CH_2), 35.7 (CH_3), 38.6 (CH_2), 39.7 (CH_2), 40.3 (CH), 40.4 (C), 43.9 (C), 56.3 (CH), 57.0 (CH), 61.2 (CH_2), 65.3 (CH_2), 66.7 (C), 73.3 (CH), 75.5 (CH_2), 76.9 (C), 81.4 (CH), 108.6 (CH_2), 110.8 (CH), 127.1 (C), 127.5 (CH), 131.8 (CH), 133.7 (C), 141.7 (C), 148.7 (C), 179.1 (CO), 180.7 (CO); MS (ESI-MS, positive ion) m/z 539 $[M+H]^+$, 561 $[M+Na]^+$; HRMS m/z 539.3111 $[M+H]^+$ [calcd. 539.3121].

Compound4d: Colourless needles, m.p. 226-228ºC (lit.[14] 224-226ºC); IR (KBr, ν_{max}) 3462, 2944, 2854, 1750, 1706, 1642, 1491 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.40 (1H, s, -NH), 6.84 (1H, dd, *J*=2.4, 8.4 Hz), 6.73 (1H, d, *J*=8.4 Hz), 6.57 (1H, d, *J*=3 Hz), 5.77 (1H, d, *J*=4.2 Hz, 14-OH), 5.08 (1H, d, *J*=4.8 Hz, 3-OH), 4.75 (2H, d, *J*=10.8 Hz), 4.29 (1H, m), 4.13 (1H, dd, *J*=2.4, 7.8 Hz, 19-OH), 3.86 (1H, dd, *J*=2.4, 10.8 Hz), 3.72 (1H, d, *J*=10.2 Hz), 3.66 (3H, s), 3.29 (1H, t, *J*=8.4 Hz), 3.26 (1H, dd, *J*=4.2, 10.2 Hz), 3.22 (1H, m), 3.01 (1H, m), 2.85 (1H, dd, *J*=6, 8.4 Hz), 2.63 (1H, qn, *J*=6 Hz), 2.36 (1H, t, *J*=11.4 Hz), 2.31 (1H, d, *J*=12.6 Hz), 2.14 (1H, t, *J*=12.6 Hz), 1.90 (1H, m), 1.85 (4H, m), 1.73 (1H, m), 1.66 (2H, m), 1.45 (1H, d, *J*=11.4 Hz), 1.29 (1H, m), 1.15 (2H, m), 1.09 (3H, s), 0.59 (3H, s); ^{13}C

NMR (DMSO-d_6) δ 14.9 (CH_3), 23.1 (CH_3), 24.1 (CH_2), 24.5 (CH_2), 28.0 (CH_2), 34.9 (CH_3), 36.8 (CH_2), 38.0 (CH_2), 38.5 (CH), 38.8 (C), 42.3 (C), 54.4 (CH), 54.8 (CH), 55.3 (CH_3), 59.7 (CH_2), 62.8 (CH_2), 64.9 (C), 71.1 (CH), 73.4 (CH_2), 74.6 (C), 78.6 (CH), 107.4 (CH_2), 109.9 (CH), 112.1 (CH), 114.3 (CH), 127.0 (C), 136.1 (C), 147.6 (C), 154.7 (C), 176.5 (CO), 177.7 (CO); MS (ESI-MS, positive ion) m/z 555 $[M+H]^+$, 577 $[M+Na]^+$; HRMS m/z 577.2880 $[M+Na]^+$ [calcd. 577.2890].

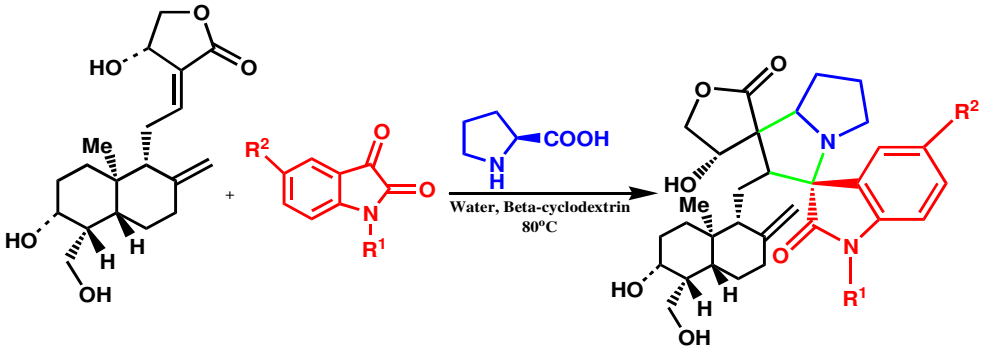
Compound4e: Colourless needles, m.p. 210-212ºC (lit.[14] 210-212ºC); IR (KBr, ν_{max}) 3400, 2941, 2852, 1762, 1715, 1634, 1486 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.63 (1H, s, -NH), 7.13 (1H, m), 6.82 (1H, dd, *J*=4.8, 8.4 Hz), 6.72 (1H, dd, *J*=2.4, 8.4 Hz), 5.84 (1H, d, *J*=3.6 Hz, 14-OH), 5.08 (1H, d, *J*=4.8 Hz, 3-OH), 4.75 (2H, d, *J*=10.2 Hz), 4.30 (1H, dd, *J*=2.4, 3.6 Hz), 4.13 (1H, m, 19-OH), 3.85 (1H, dd, *J*=2.4, 10.8 Hz), 3.76 (1H, d, *J*=9.6 Hz), 3.31 (1H, t, *J*=8.4 Hz), 3.25 (2H, m), 3.03 (1H, dd, *J*=2.4, 10.2 Hz), 2.85 (1H, dd, *J*=6, 8.4 Hz), 2.63 (1H, m), 2.36 (1H, m), 2.31 (1H, m), 2.13 (1H, t, *J*=12.6 Hz), 1.90 (1H, dd, *J*=4.2, 12.6 Hz), 1.87 (3H, s), 1.84 (1H, m), 1.73 (1H, m), 1.66 (2H, m), 1.45 (1H, d, *J*=10.8 Hz), 1.30 (1H, m), 1.15 (2H, m), 1.09 (3H, s), 0.60 (3H, s); ^{13}C NMR (DMSO-d_6) δ 14.9 (CH_3), 23.1 (CH_3), 24.1 (CH_2), 24.4 (CH_2), 28.0 (CH_2), 34.9 (CH_3), 36.8 (CH_2), 38.0 (CH_2), 38.5 (CH), 38.8 (C), 42.3 (C), 54.3 (CH), 54.8 (CH), 59.6 (CH_2), 62.8 (CH_2), 65.0 (C), 70.9 (CH), 73.5 (CH_2), 74.4 (C), 78.6 (CH), 107.3 (CH_2), 110.5 (CH, $^3J_{C\text{-}F}$ 7.5 Hz), 112.6 (CH, $^2J_{C\text{-}F}$ 24 Hz), 116.5 (CH, $^2J_{C\text{-}F}$ 22.5 Hz), 127.5 (C, $^3J_{C\text{-}F}$ 7.5 Hz), 139.2 (C), 147.6 (C), 157.8 (C, $^1J_{C\text{-}F}$ 23.7 Hz), 176.6 (CO), 177.6 (CO); MS (ESI-MS, positive ion) m/z 543 $[M+H]^+$, 565 $[M+Na]^+$; HRMS m/z 543.2888 $[M+H]^+$ [calcd. 543.2870].

Compound4f: Colourless needles, m.p. 210-212ºC (lit.[14] 211-213ºC); IR (KBr, ν_{max}) 3402, 2940, 2851, 1757, 1720, 1620, 1474 cm^{-1}; ^1H NMR (CD_3OD) δ 7.31 (1H, dd, *J*=2.4, 7.8 Hz), 7.11 (1H, d, *J*=2.4 Hz), 6.84 (1H, d, *J*=7.8 Hz), 4.82 (2H, d, *J*=10.8 Hz), 4.61 (1H, s), 4.42 (1H, d, *J*=1.8 Hz), 4.13 (1H, d, *J*=11.4 Hz), 3.82 (1H, d, *J*=10.2 Hz), 3.41 (2H, m), 3.35 (1H, m), 3.23 (1H, dd, *J*=1.8, 10.2 Hz), 3.00 (1H, dd, *J*=6.0, 7.8 Hz), 2.88 (1H, m), 2.51 (1H, m), 2.41 (1H, m), 2.24 (1H, t, *J*=12.6 Hz), 2.03 (1H, m), 1.98 (3H, s), 1.82 (3H, m), 1.56 (1H, d, *J*=11.4 Hz), 1.33 (1H, m), 1.27 (2H, m), 1.22 (3H, s), 0.69 (3H, s); ^{13}C NMR (CD_3OD) δ 15.9 (CH_3), 23.6 (CH_3), 25.6 (CH_2), 26.3 (CH_2), 29.3 (CH_2), 35.7 (CH_3), 38.6 (CH_2), 39.7 (CH_2), 40.3 (CH), 40.5 (C), 43.9 (C), 56.3 (CH), 57.0 (CH), 61.2 (CH_2), 65.3 (CH_2), 66.9 (C), 73.1 (CH), 75.5 (CH_2), 76.7 (C), 81.4 (CH), 108.6 (CH_2), 112.3 (CH), 127.2 (CH), 129.1 (C), 129.3 (C), 131.5 (CH), 143.0 (C), 148.7 (C), 178.7 (CO), 180.3 (CO); MS (ESI-MS, positive ion) m/z 559 $[M+H]^+$, 581 $[M+Na]^+$; 583 $[(M+2)+H]^+$ HRMS m/z 559.2580 $[M+H]^+$ [calcd. 559.2575].

Compound 4g: Colourless needles, m.p. 212-214ºC (lit.[14] 213-215ºC); IR (KBr, ν_{max}) 3412, 2940, 2855, 1722, 1614, 1470 cm^{-1}; ^1H NMR (CD_3OD) δ 7.65 (1H, dd, *J*=1.8, 8.4 Hz), 7.41 (1H, d, *J*=1.8 Hz), 6.68 (1H, d, *J*=8.4 Hz), 4.82 (2H, d, *J*=9.0 Hz), 4.61 (2H, s), 4.41 (1H, d, *J*=2.4 Hz), 4.13 (1H, d, *J*=11.4 Hz), 3.82 (1H, d, *J*=10.2 Hz), 3.38 (3H, m), 3.22 (1H, dd, *J*=1.8, 10.2 Hz), 2.99 (1H, m), 2.87 (1H, m), 2.51 (1H, m), 2.40 (1H, m), 2.23 (1H, t, *J*=12.6 Hz), 2.01 (1H, m), 1.98 (3H, s), 1.82 (2H, m), 1.56 (1H, d, *J*=11.4 Hz), 1.29 (3H, m), 1.22 (3H, s), 0.69 (3H, s); ^{13}C NMR (CD_3OD) δ 15.9 (CH_3), 23.6 (CH_3), 25.6 (CH_2), 26.3 (CH_2), 29.3 (CH_2), 35.7 (CH_3), 38.6 (CH_2), 39.7 (CH_2), 40.3 (CH), 40.5 (C), 43.9 (C), 56.3 (CH), 57.0 (CH), 61.2 (CH_2), 65.3 (CH_2), 66.9 (C), 73.1 (CH), 75.5 (CH_2), 76.4 (C), 81.4 (CH), 85.8 (C), 108.6 (CH_2), 113.1 (CH), 129.7 (C), 135.8 (CH), 140.4 (CH), 144.1 (C), 148.7 (C), 178.3 (CO), 180.3 (CO); MS (ESI-MS, positive ion) m/z 651 $[M+H]^+$, 673 $[M+Na]^+$; HRMS m/z 651.1926 $[M+H]^+$ [calcd. 651.1931].

Results and Discussion

Initially, we attempted the synthesis of 3′-spirocyclic oxindole 3a in order to optimize the reaction conditions (table-1). The reaction was carried out by forming the β-CD complex of isatin (2a) in water at 60 ºC, followed by the addition of L-proline and andrographolide (1) with constant stirring at 80 ºC

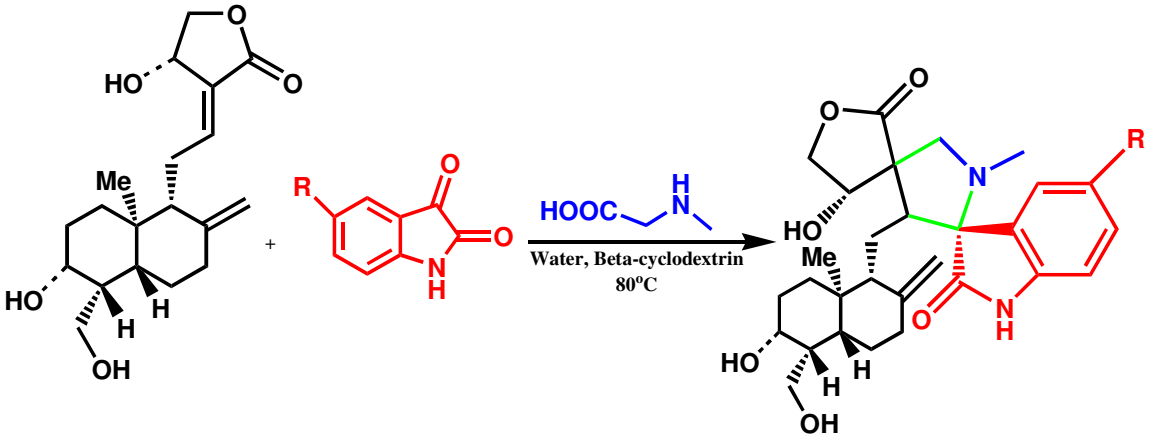


1 **2a-h** **3a-h**

Where **2a, 3a** : $R^1 = R^2 = H$; **2b, 3b**: $R^1 = H$, $R^2 = Br$; **2c, 3c**: $R^1 = Me$, $R^2 = H$; **2d, 3d**: $R^1 = H$, $R^2 = Me$; **2e, 3e**: $R^1 = H$, $R^2 = OMe$; **2f, 3f**: $R^1 = H$, $R^2 = F$; **2g, 3g**: $R^1 = H$, $R^2 = Cl$; **2h, 3h**: $R^1 = H$, $R^2 = I$;

Figure-1

β-CD catalyzed synthesis of dispiropyrrolizidinooxindoles (3a-h) in water



1 **2a-h** **4a-g**

Where **2a, 4a** : R = H; **2b, 4b** : R = Br; **2c, 4c** : R = Me; **2d, 4d** : R = OMe; **2e, 4e** : R = F; **2f, 4f** : R = Cl; **2g, 4g** : R = I;

Figure-2
β-CD catalyzed synthesis of di-spiropyrrolidino-oxindoles (4a-g) in water

After several attempts (varying the catalyst loading and time period), it was revealed that the reaction yielded maximum amount of 3′-spirocyclic oxindole 3a within 65 minutes with the mole ratio 1:1:1:1 of β-CD, isatin, L-proline and andrographolide respectively (table-1, entry 8). With lesser amount of catalyst, the yield was lower, however, higher yield was not obtained even when higher amount of catalyst was employed and with longer reaction time (table-1, entry 11). It is noteworthy that without β-CD (table-1, entry 1), the reaction was unsuccessful even after conducting the reaction for a long period. On the other hand the reaction also did not proceed when it was carried out below 80 ºC (table-1, entry 12). The structure of the final product was confirmed by IR, NMR, and Mass spectroscopy which clearly indicated that the product was a dispiropyrrolizidino-oxindole adduct of andrographolide[9].

Table-1
Optimization of catalysis content and reaction time

Entry	β-CD (equiv.)	T (°C)	Time (min)	Yields (%)[a]
1	0	80	240	NR[b]
2	0.25	80	120	42
3	0.25	80	240	44
4	0.50	80	80	53
5	0.50	80	160	56
6	0.75	80	75	60
7	0.75	80	150	62
8	1	80	65	96
9	1	80	100	96
10	1.5	80	60	96
11	5	100	100	96
12	5	70	240	NR[b]

[a]Isolated yields of pure products, [b]No reaction

In order to establish the generality and scope of this new methodology, we used different derivatives of isatin (2b-h). The results were summarized in table-2. All the reactions proceeded very cleanly at optimum temperature to afford dispiropyrrolizidino-oxindole adduct of andrographolide (3a-h) with high yield and no undesirable side product was obtained.

Table-2
β-CD catalyzed synthesis of 3′-spirocyclic oxindoles (3a-h) in water

Entry[a]	Isatin	Product	Time (min)	Yields (%)[b]
1	2a	3a	65	96
2	2b	3b	68	90
3	2c	3c	65	92
4	2d	3d	65	94
5	2e	3e	70	95
6	2f	3f	68	94
7	2g	3g	65	95
8	2h	3h	65	92

[a]All the reactions were performed using β-CD (1 mmol), isatin (1 mmol), L-proline (1mmol) and andrographolide (1mmol) at 80 ºC in water. [b]Isolated yield of pure products.

Next we attempted the synthesis of 3′-spirocyclic oxindole by using isatin (2a), sarcosine (as a source of amino acid) and andrographolide (1), following the above reaction protocol (figure-2). Gratifyingly, in this case also the reaction proceeded cleanly to yield dispiropyrrolidino-oxindole adduct of andrographolide[9] (confirmed by IR, NMR and Mass spectroscopy).

The above reaction was then performed with different isatin derivatives (2b-g) in order to observe the effect of substituent (table-3). In these cases also the reactions proceeded with high yield to afford dispiropyrrolidino-oxindole adducts of

andrographolide (4a-g). The possibility of using recycled β-CD was studied in the synthesis of 3a. After completion of the reaction the product was isolated by filtration in hot condition. The aqueous filtrate was cooled to 5 ^{o}C to crystallize out the catalyst which was recovered by filtration. This catalyst was recycled several times without noticeable change in yield of 3a.

Table-3
β-cyclodextrin catalyzed synthesis of 3′-spirocyclic oxindoles (4a-j) in water

Entry[a]	Isatin	Product	Time (min)	Yields (%)[b]
1	2a	4a	65	96
2	2b	4b	68	92
3	2c	4c	65	96
4	2d	4d	65	96
5	2e	4e	70	95
6	2f	4f	68	94
7	2g	4g	65	92

[a]All the reactions were performed using β-cyclodextrin (1 mmol), isatin (1 mmol), sarcosin (1mmol) and andrographolide (1mmol) at 80 ºC in water. [b] Isolated yield of pure products.

A plausible reaction mechanism for the formation of 3′-spirocyclic oxindole 3a is depicted in figure-3. It is presumed that isatin dissolved in water after forming an inclusion complex with β-CD from its secondary side[15]. Now an oxazolidinone intermediate A was formed, by the reaction of isatin and L-proline, which undergoes loss of CO_2 forming the azomethine ylide intermediate B[16]. The dienophile also dissolved in water by forming an inclusion complex with β-CD[17]. So, both azomethine ylide intermediate B and andrographolide came in close proximity in the β-CD cavity facilitating the 1,3-dipolar cycloaddition to the desired 3′-spirocyclic oxindole 3a.

Conclusion

In summary, we have developed a green protocol for the synthesis of 3′-spirocyclic oxindoles with excellent yields using β-cyclodextrin as supramolecular catalyst in aqueous medium. The study demonstrates minimization of reaction time with maximization of yields of the products. This high yielding process can be considered as a green protocol, as it fulfils many required criteria of green chemistry e.g., the use of an environmentally friendly solvent (water), reusability of catalyst, minimum chemical waste and minimization of reaction time.

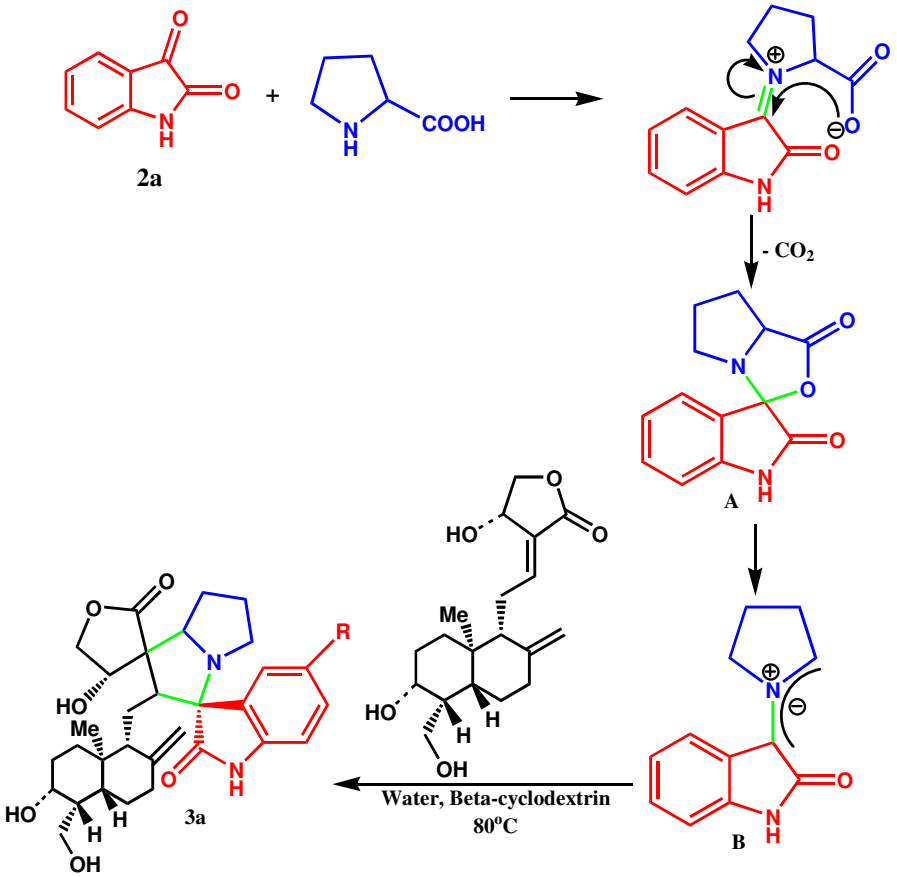


Figure-3
Plausible pathway for the formation of 3′-spirocyclic oxindole3a

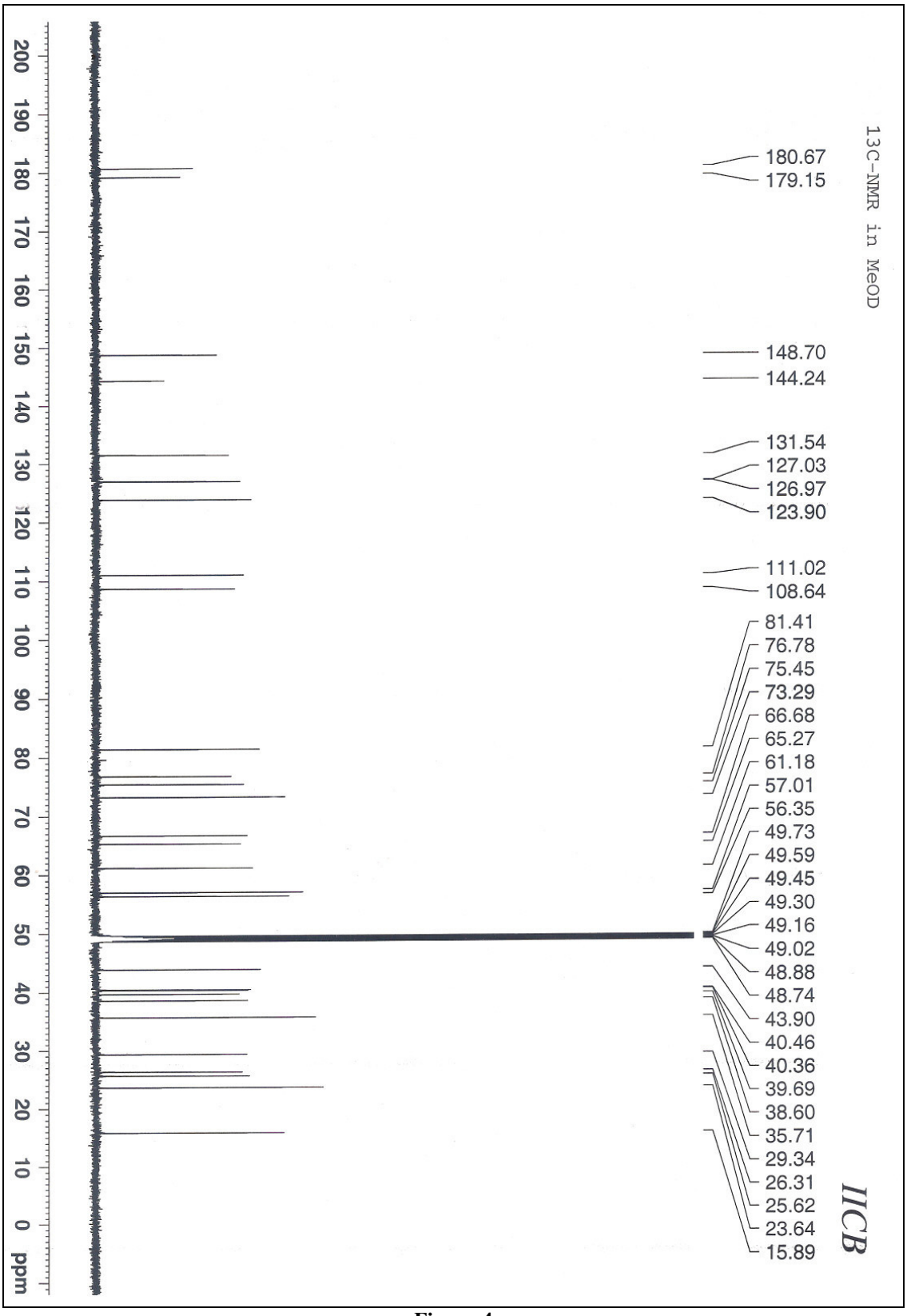


Figure-4
^{13}CNMR of Compound-4a in MeOD

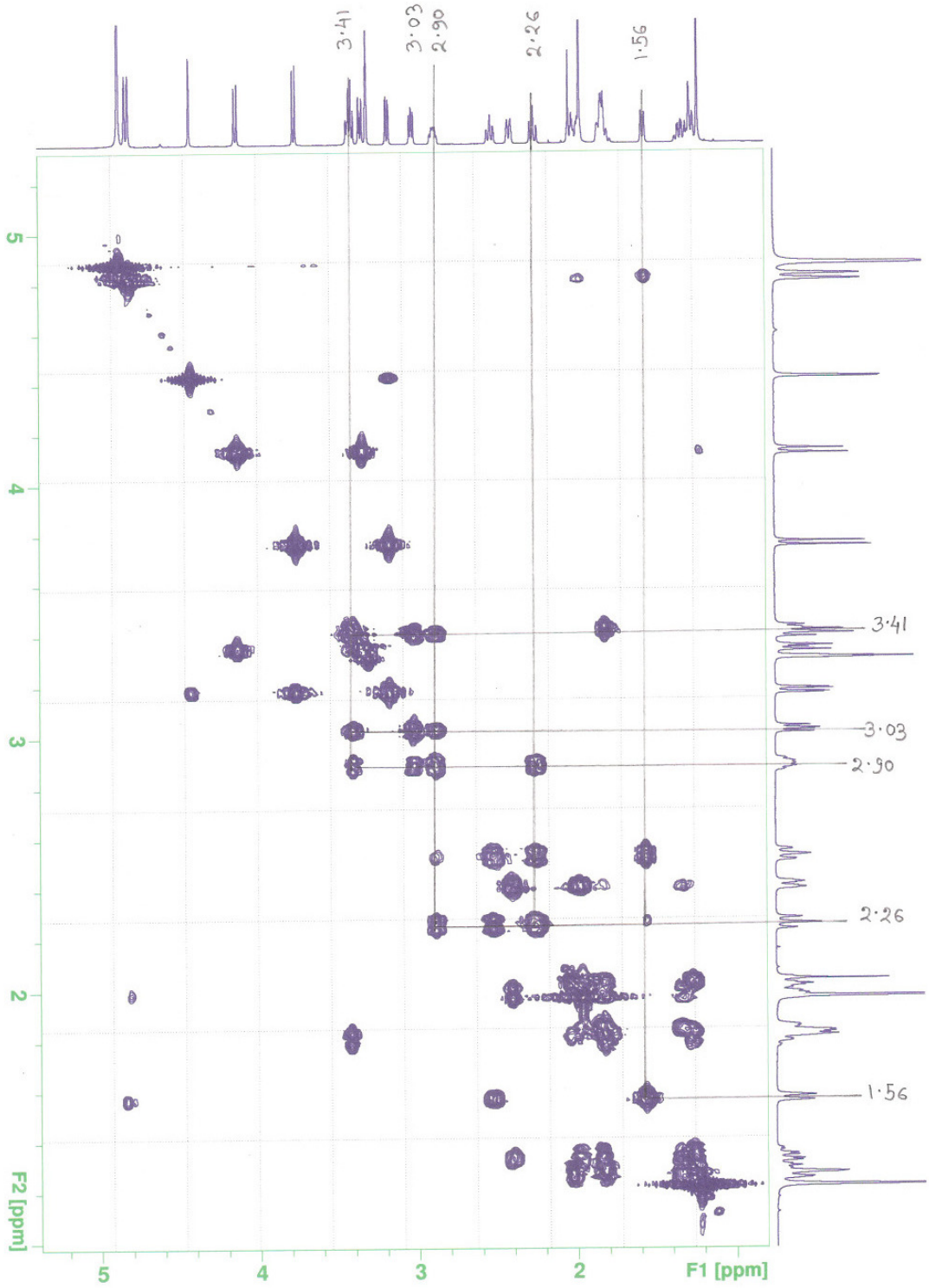


Figure-5
COSY of Compound-4a

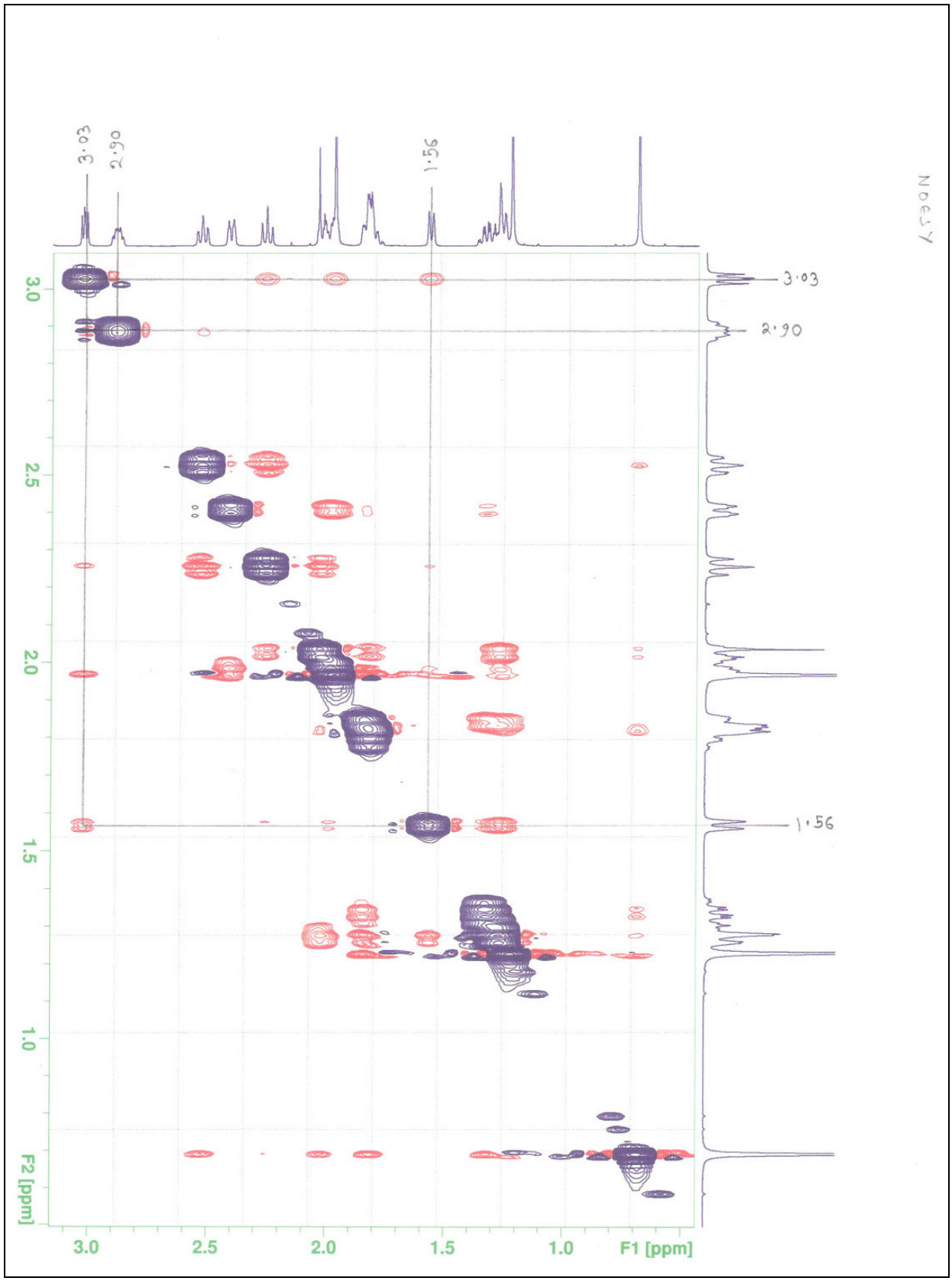


Figure-6
NOESY of Compound-4a

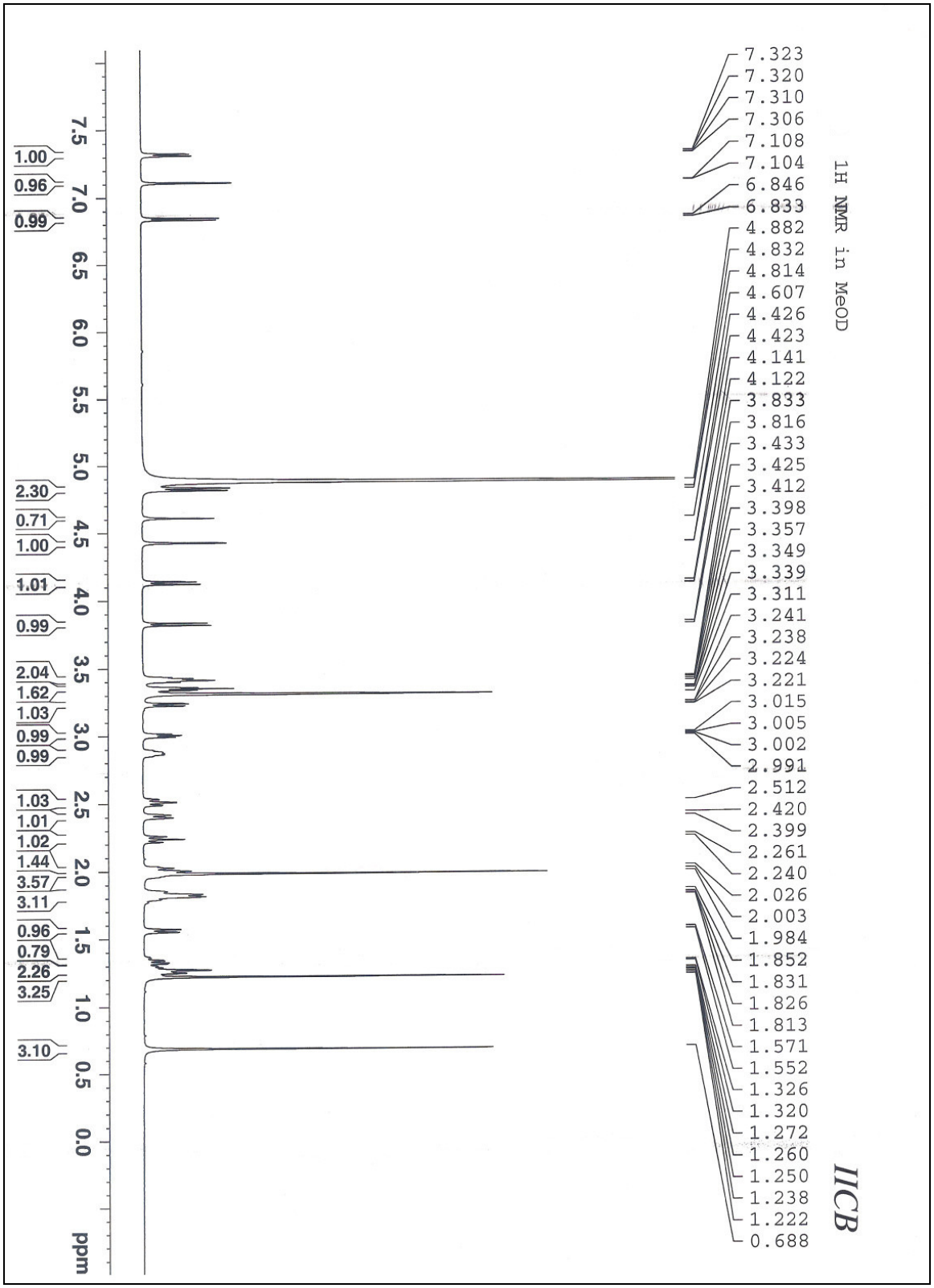


Figure-7
[1]HNMR of Compound-3a in MeOD

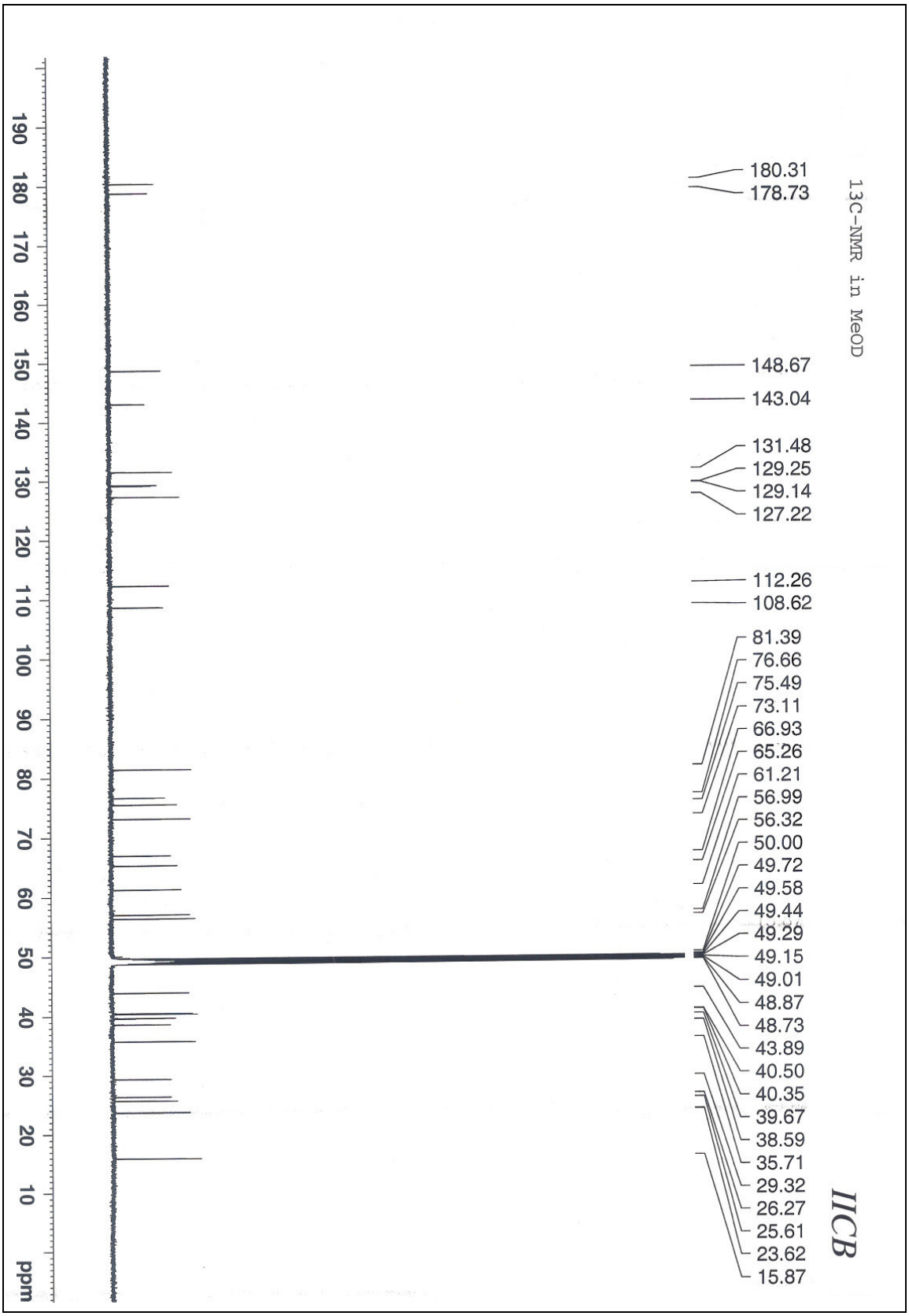


Figure-8
^{13}CNMR of Compound-3a in MeOD

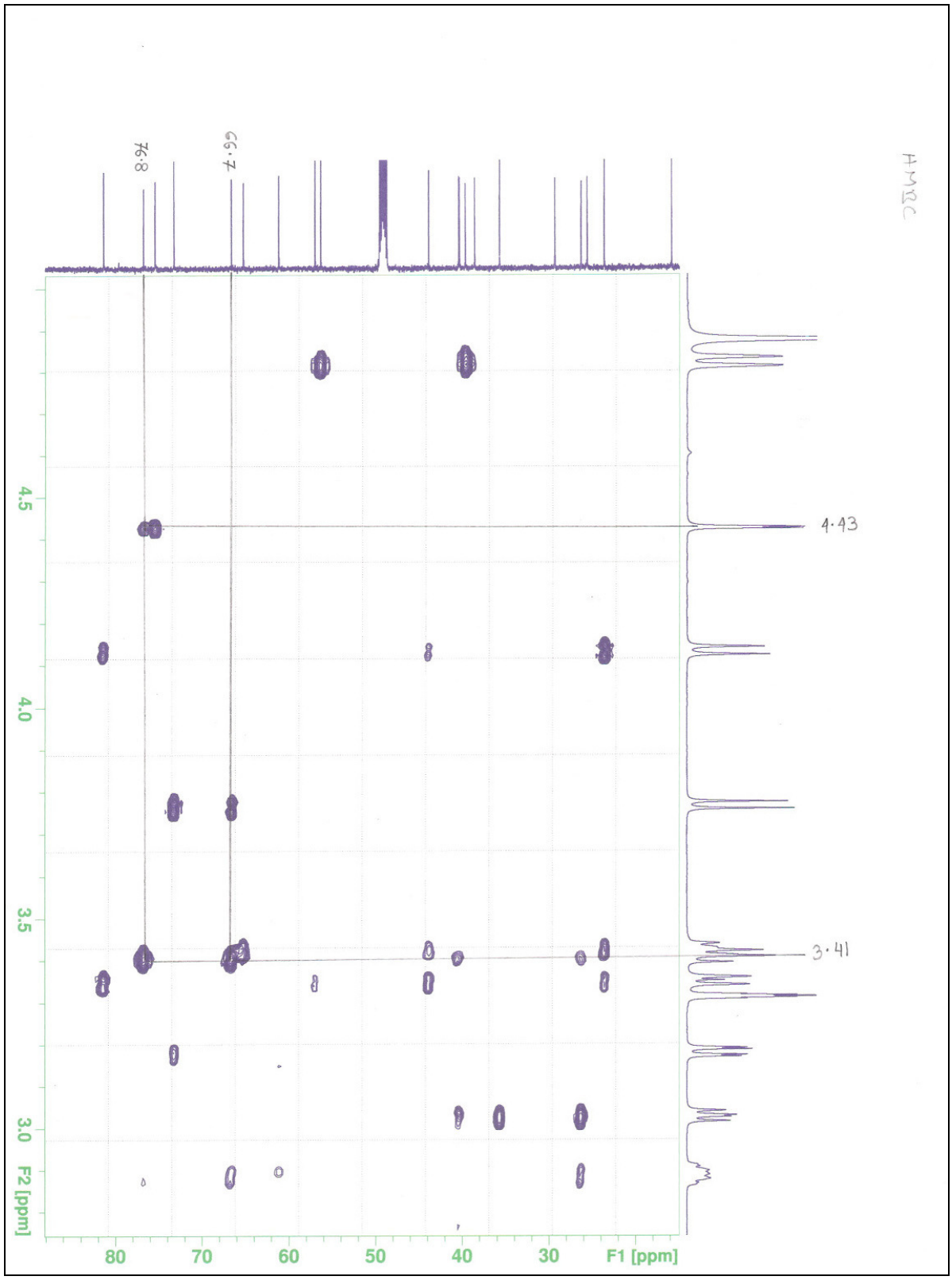


Figure-9
HMBC of Compound 3a

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