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Research Article

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Comparative studies for the cyclisation reactions of 2-alkynylaniline derivatives to generate the indole ring systems on polystyrene solid supports

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ABSTRACT

Generation of indole ring systems based on cyclisation of 2-alkynylaniline moieties on solid supports have been investigated. The cyclisation reactions were studied in 3 different conditions: (i) iodonium-mediated cyclisation (iodo-cyclisation) (ii) base-promoted cyclisation, and (iii) palladium (II)-mediated cyclisation. Only the latter with palladium dichloride gave satisfactory results on polystyrene resin solid supports.

Keywords Synthesis of indole, solid-phase synthesis, polystyrene, cyclisation of 2-alkynylaniline

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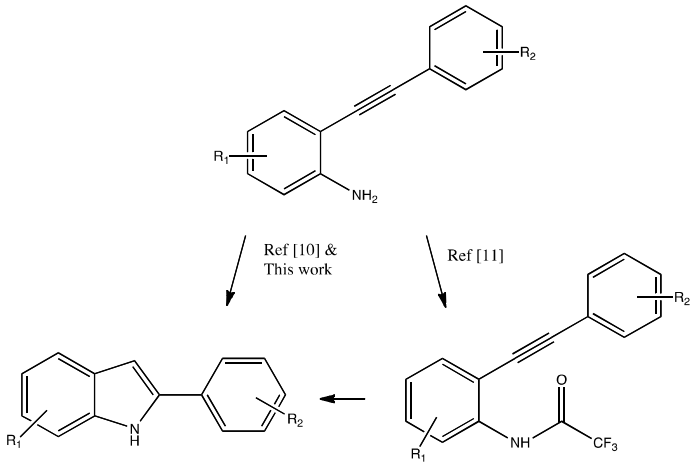
INTRODUCTION

The indole ring system is regarded as a privileged set of structures used in medicinal chemistry as it has been found in many natural products [1] as well as pharmaceutical agents [2-4] to have a remarkable range of biological activities. Various synthetic routes have been developed in solution phase chemistry to obtain the heterocyclic indole rings, including Fischer's pathway [5], based on the coupling reactions of hydrazine with aldedyde or ketone, Wittig's indole synthesis between phosphonium salt of benzylamides [6], Nenitzescu's synthesis of indoles [7], gold-mediated condensation reactions between N-arylhydroxylamines and alkynes [8], etc. Among them, cyclisation of 2-alkynylaniline derivatives [9] with or without the presence of palladium as a catalyst has attracted our attention for a number of reasons: (i) The starting materials 2-alkynylanilines are readily derived from 2-iodoanilines via Sonogashira coupling reactions with a wide range of alkynes [10, 11] (ii) It has been established that the amino groups adjacent to the alkyne functional groups can undergo an intramolecular cyclisation in the presence of iodonium reagents (iodo-cyclisation process) [9] and (iii) Simplicity of the base-promoted cyclisations of 2-alkynylanilines has also been thoroughly investigated in solution-phase [12] and the reaction conditions have been carried out in the presence of strong bases such as potassium hydride, potassium *t*-butoxides [13] etc. However, for both solution and solid-phase synthesis of indoles, the amino group of 2-alkynylanilnes required to be protected with trifluoroacetic acid [13] and the following cyclisation condition occurred with concomitant loss of the TFA group to generate the indole rings (Scheme 1). In addition, cyclisation of unprotected 2-alkynylanilines has not been fully investigated in solid-phase chemistry. This reason prompted us to investigate the solid-phase synthesis of indole ring systems from 2-alkynylanilines using three common reaction conditions: (i) iodonium-mediated cyclisation (iodocyclisation) (ii) base-promoted cyclisation, and (iii) palladium (II)-mediated cyclisation reactions.



Scheme 1: Cyclisation of 2-alkynylanilines with and without protection of amine moieties.

EXPERIMENTAL SECTION

Solvents and fine chemicals were purchased from Aldrich chemical company (Castle Hill, Australia) and used as supplied. Polystyrene resins derivatized with Fmoc-protected Rink Amide linker were purchased from Novabiochem (100 – 200 mesh, loading capacity: 0.47 mmol/g).

LC-MS analysis: LC analysis was conducted with a Phenomenex C18- (20 x 4.00 mm) column, using isocratic mobile-phase containing 10 % acetonitrile, 89.9 % water and 0.1 % of formic acid solution. Detection was measured at 214 nm and a flow rate was constant at 0.5 ml/min. MS analysis was conducted with Finnigan LCQ Avantage Max system.

Proton (^{1}H) and Carbon (^{13}C) NMR spectra were recorded with Bruker-300 spectrometer operating at 300 MHz for proton. All spectra were recorded in DMSO-d_6 or MeOD-d_4 at 25 ^{o}C.

Solid-phase reactions were carried out in 10-ml screw-cap vials (Wheaton vials, Aldrich). The reaction vials were incubated in a heat block and gently shaken at specified temperatures. After cleavage (20 % TFA in DCM) the residue was dried under a stream of N_2 gas. The residue was resuspended in ethyl acetate, passed through a plug of silica and the eluent was concentrated and submitted for LC-MS & NMR analysis without any further purification.
Preparation of resin **1**:

Rink amide resin (1 g, polystyrene, 100 – 200 mesh, Novabiochem, 0.55 mmol/g) was suspended in 10 ml of 20 % piperidine in DMF for 30 min (Fmoc-deprotection) and carefully washed with DMF (3 x 5 mL) and DCM (3 x 5 mL). The resulting resin was gently mixed on a shaker with a mixture of 2-amino-3-iodobenzoic acid (0.26 g, 1.0 mmol), HOBt (0.135g, 1.0 mmol) and 1,3-diisopropylcarbodiimide (0.126 g, 1 mmol) in DCM/DMF (1:1, 10 mL) at 40 ^{o}C for 16h. The resins were carefully washed with DCM/DMF (1:1, 3 x 5 mL) and DCM (3 x 5 mL) and dried under reduced pressure for 2-3 hours to afford **1**.

Preparation of resin **2:**
Resins **1** (0.5 g, 0.27 mmol) were incubated with a mixture of 4-methylphenylacetylene (115 mg, 1 mmol), $PdCl_2(PPh_3)_2$ (60 mg, 0.084 mmol) and CuI (10 mg, 0.10 mmol) in piperidine/ THF (1:1, 4 mL) at 60 ^{o}C for 16 h. The resulting resins were filtered and carefully washed with DMF (3 x 5 mL), methanol (5 mL) and DCM (3 x 5 mL) and dried under reduced pressure for 30 minutes to afford **2**.

Preparation of resin **3:**
Resins **2** (0.5 g, 0.27 mmol) were incubated with $PdCl_2$ (3.4 mg, 0.02 mmol) in acetonitrile (2 mL) at 60 ^{o}C for 1-2 hours. The resulting resins were filtered and carefully washed with DMF (3 x 5 mL), methanol (3 x 5 mL) and DCM (3 x 5 mL) and dried under reduced pressure for 30 minutes to afford **3.**

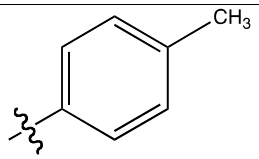
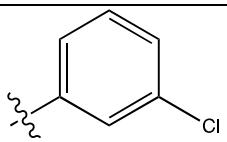
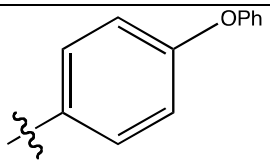
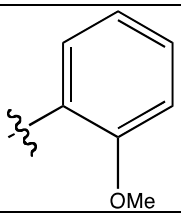
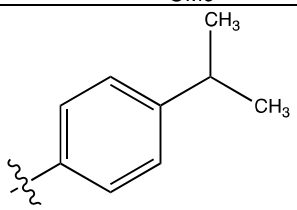
Compound **4a**: Resins **3** were finally incubated with 20 % TFA in DCM for 1 h. The cleavage solution was separated and dried under a stream of N_2 gas (15 min). The resulting crude products were dissolved in ethyl acetate (0.2 ml) and filtered through a plug of silica and the filtrate was concentrated and subjected to LC-MS and ^{1}H & ^{13}C-NMR analysis to confirm structure of the desired product **4a**.

4a. R_t = 5.93 min. by LC; MS: m/z = 251.0 $[M + H]^+$. ^{1}H-NMR (300 MHz, DMSO-d_6): 8.12 (s, 1H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.66 (d, *J* = 8.8 Hz, 1H), 7.40 (d, *J* = 8.6 Hz 1H), 7.29 (d, J = 8.6 Hz, 2H), 6.92 (s, 1H), 2.4 (s, 3H). ^{13}C-NMR (75 MHz, DMSO-d_6): 169.41, 139.54, 139.05, 137.57, 129.95, 129.56, 128.51, 125.51, 121.72, 120.51, 110.97, 99.40, 21.27.

4b. R_t = 5.0 min. by LC; MS: m/z = 271.2 $[M + H]^+$. ^{1}H-NMR (300 MHz, DMSO-d_6): 8.15 (s, 1H), 8.06 (s, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.50 (t, *J* = 8.3 Hz 1H), 7.6-7.3 (m, 2H), 7.12 (s, 1H). ^{13}C-NMR (75 MHz, DMSO-d_6):169.30, 139.32, 137.75, 134.48, 134.30, 131.24, 128.23, 127.74, 126.40, 125.08, 124.21, 122.37, 120.93, 111.30, 101.26.

4c. R_t = 5.28 min. by LC; MS: m/z = 329.5 $[M + H]^+$. ^{1}H-NMR (300 MHz, DMSO-d_6): 8.14 (s, 1H), 7.91 (d, *J* = 9.2 Hz, 2H), 7.68 (d, *J* = 9.2 Hz, 1H), 7.46-7.38 (m, 2H), 7.18 (t, *J* = 6.4 Hz, 1H), 7.1 - 6.5 (m, 5H), 6.93 (s, 1H). ^{13}C-NMR (75 MHz, DMSO-d_6): 169.42, 156.89, 156.82, 139.14, 138.98, 130.59, 128.54, 127.72, 127.36, 126.22, 124.16, 121.79, 120.54, 119.40, 119.30, 111.01, 99.56.

Table 2: LC-MS Analysis of the Compounds 4a-e

Compounds	R	% Purity	Rt (min)	LC-MS [M+H] found	LC-MS [M+H] Expected
4a		99	4.94	251.0	251.1
4b		98	5.00	271.2	271.1
4c		99	5.28	329.5	329.1
4d		99	4.83	267.7	267.5
4e		99	5.23	279.6	279.5

4d. R_t = 4.83 min. by LC; MS: m/z = 267.7 $[M + H]^+$. ^{1}H-NMR (300 MHz, MeOD-d_4): 8.17 (s, 1H), 7.78 (d, *J* = 7.5 Hz, 1H), 7.68 (d, *J* = 8.9 Hz, 1H), 7.49 (d, *J* = 8.4 Hz 1H), 7.31 (t, J = 7.2 Hz, 1H), 7.11 (s, 1H), 7.04 (t, J = 8.2 Hz,

1H), 6.98 (s, 1H), 3.97 (3H, s). ^{13}C-NMR (75 MHz, MeOD-d_4): 172.69, 156.40, 138.69, 137.02, 128.67, 128.02, 127.83, 124.22, 120.70, 120.66, 120.55, 120.19, 111.50, 110.49, 101.38, 54.67.

4e. R_t = 5.23 min. by LC; MS: m/z = 279.6 $[M + H]^+$. ^{1}H-NMR (300 MHz, MeOD-d_4): 8.16 (s, 1H), 7.73 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 8.6 Hz, 1H), 7.44 (d, *J* = 7.8 Hz 1H), 7.32 (t, J = 7.5 Hz, 2H), 6.86 (s, 1H), 3.85 – 3.0 (m, 1H), 1.28 (d, J = 7.1, 6H). ^{13}C-NMR (75 MHz, MeOD-d_4): 172.62, 148.51, 139.93, 139.42, 129.83, 128.81, 126.56, 124.96, 124.41, 120.77, 120.23, 110.34, 98.76, 33.76, 22.91.

RESULTS AND DISCUSSION

Scheme 2 outlines our solid-phase synthesis of a small group of 2-substituted indoles, using polystyrene resin as a solid support. Firstly, resin bound Rink amide linker was derivatized with 2-amino-3-iodobenzoic acid under standard coupling conditions (HOBt/DIC). The resulting resin was allowed to react with acetylene via Sonogashira coupling reaction to afford the substrate **2**. The resin **2** was subjected to a series of optimizing conditions (Table 1) for the cyclisation reactions. These conditions have proven to be effective in solution phase but they have not been analysed on solid supports. At first, the intramolecular cyclisation process mediated with iodonium or bromonium (TBAB) were carried out (entries 1 & 2, Table 1). This work followed the published procedure of cyclisation where the *N*-protected amine reacted rapidly with acetylenes, (either with methyl group [9] or TFA moiety [13]). However, no product was observed on solid-phase synthesis with unprotected amino groups in this study. Alternative methods using strong bases (potassium *t*-butoxide or NaH) were subsequently applied to the cyclisation reactions, but did not produce the desired result either (entries 3 & 4, table 1). It should be noted that the previously published reaction conditions [12] on Rink-MBHA-resins was not suitable for Rink-polystyrene-resins in this study. In fact, the polystyrene did not swell sufficiently in toluene, possibly explaining the poor yield in entry 3 (table 1) Surprisingly, Palladium-mediated cyclisation reactions with $PdCl_2$ as a catalyst worked well under very mild conditions (60 ^{o}C for less than 2 hours). It is notable that the reaction worked much better in acetonitrile than other solvents like dichloromethane or DMF as palladium formed a complex with acetonitrile, making it soluble under solid-phase conditions. Finally, cleavage by 20% TFA in DCM released target **4**, which was subjected to LC-MS analysis without further purification. The proton NMR of the compound **4** confirmed a single peak at around 6.9 ppm as the typical C-3 proton of indole ring. The reaction conditions were applied to several acetylenes and all were obtained in high yield (yield > 85%) and purity (Table 2).

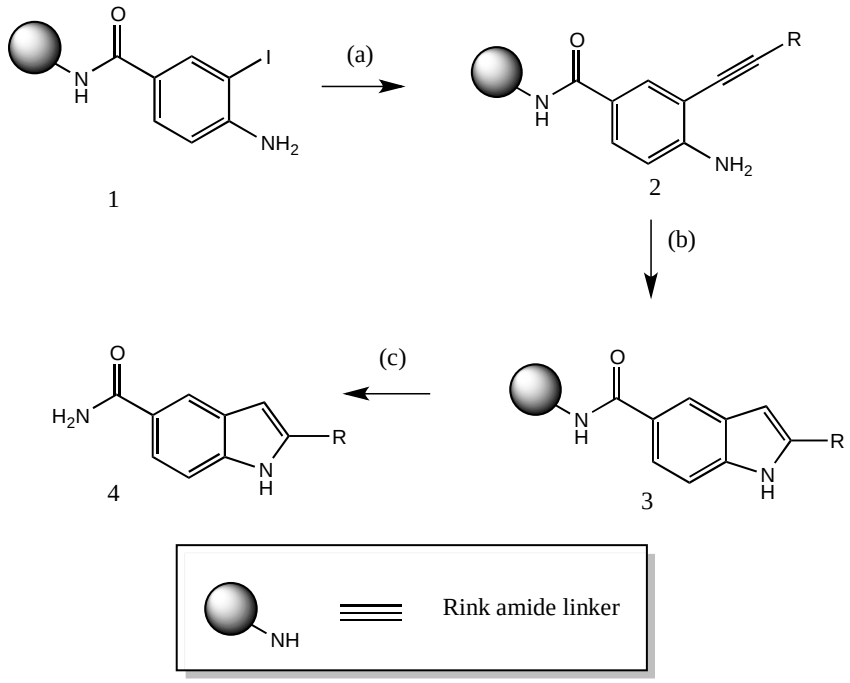


Figure 2: Solid-phase synthesis of 2-substituted indoles (R = substituted phenyl rings)

Table 1: Cyclisation Reactions of 2-Alkynylaniline Derivatives on Polystyrene Resin

Entry	R	Reaction conditions	% Purity	% Yield
1	4-Me-Ph	TBAB/THF/ 60 ^{o}C /12h	-	NR
2	4-Me-Ph	I_2 in DCM/60 ^{o}C /4h	-	NR
3	4-Me-Ph	K^{+}*t*-BuO^{-}/NMP/toluene or DCM/ 25 ^{o}C 4h then 60 ^{o}C /12h	-	<10
4	4-Me-Ph	NaH/NMP/toluene or DCM/60 ^{o}C /12h	-	NR
5	4-Me-Ph	$PdCl_2$/AcCN/ 60 ^{o}C/2h	99	95

CONCLUSION

This study focuses on the preparation of 2-substituted indoles, which has never been fully investigated on polystyrene resin solid supports so far. Here, we reported the successful conditions for cyclisation reaction of 2-alkynylaniline derivatives in the presence of $PdCl_2$ catalyst/acetonitrile solvent.

Acknowledgement
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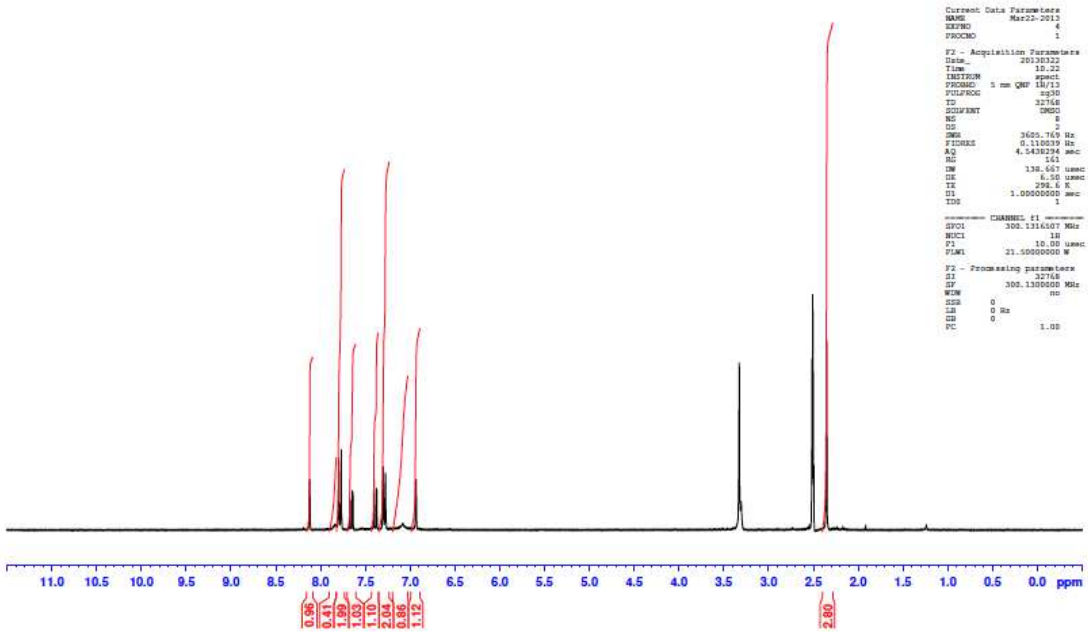
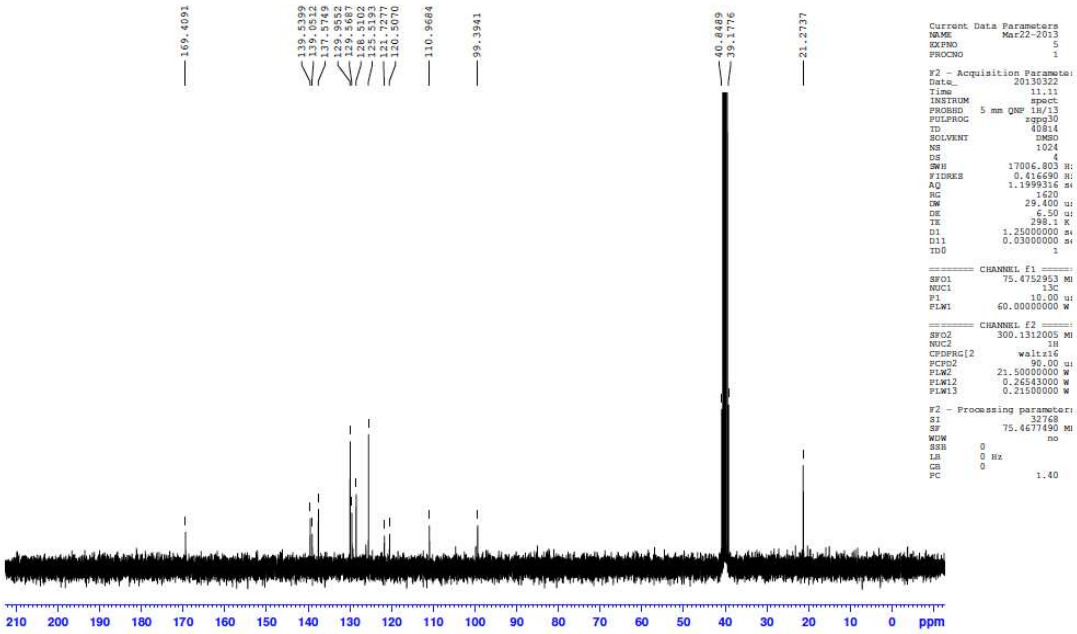


[1]HNMR spectrum of 4a



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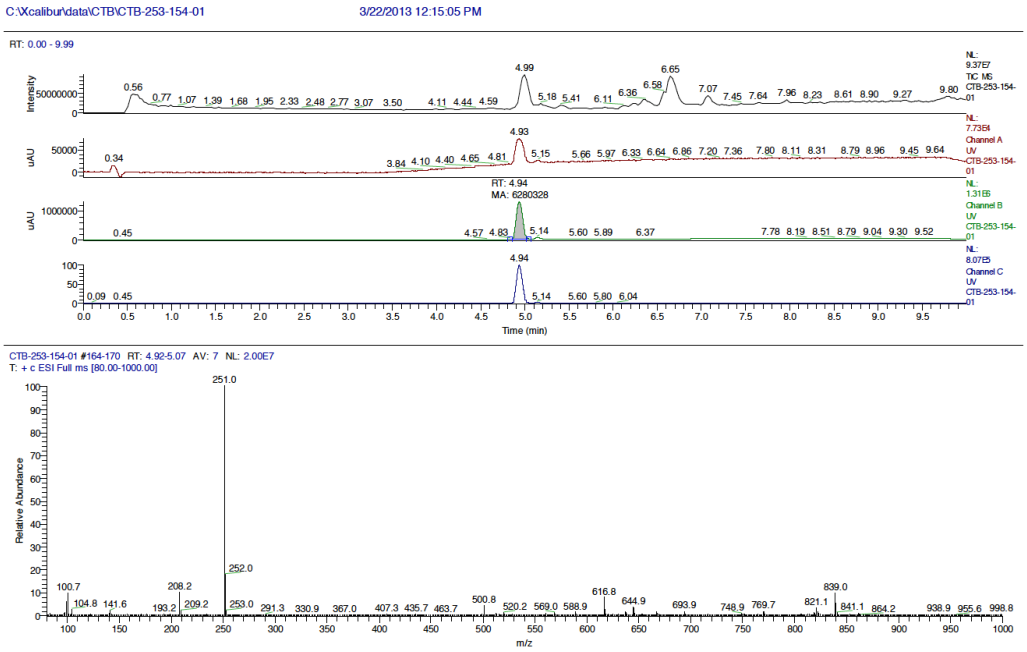

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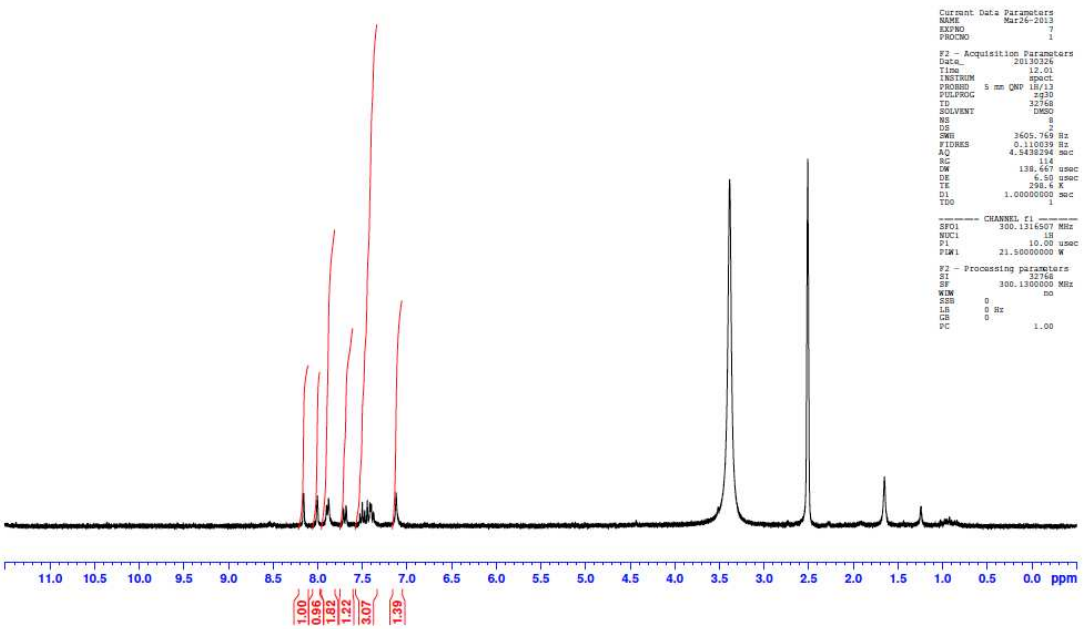
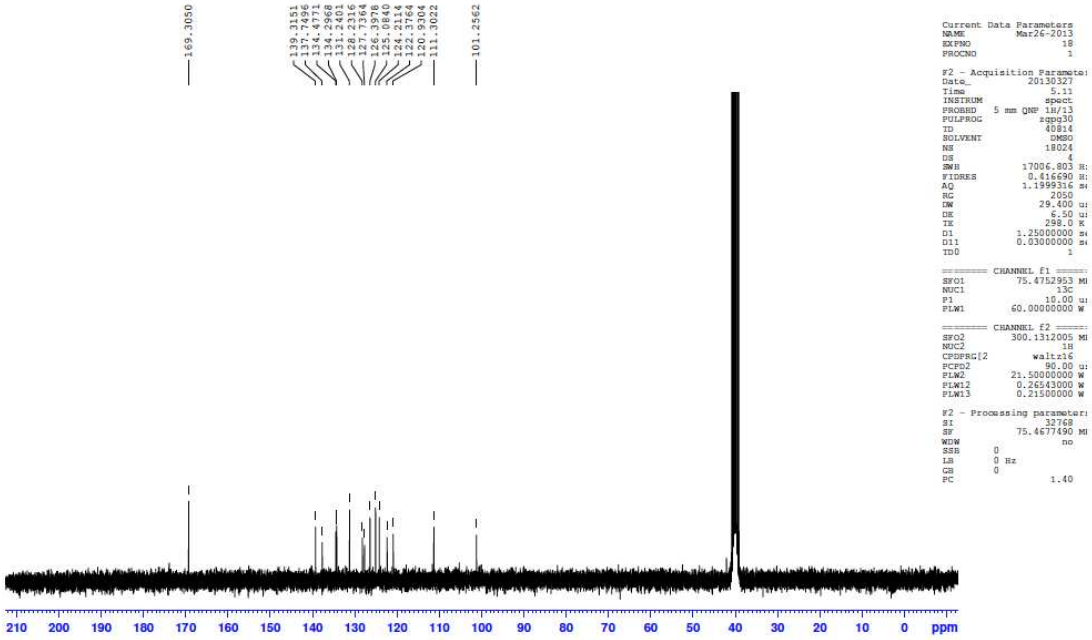
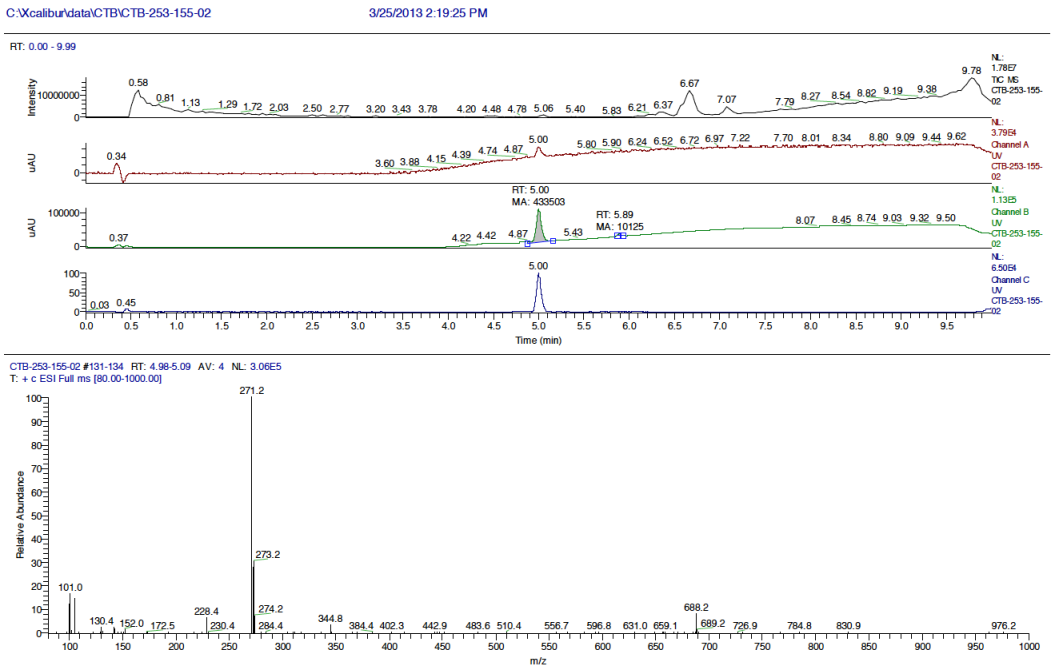
LC-MS Data of 4a



[1]HNMR spectrum of 4b



^{13}CNMR spectrum of 4b



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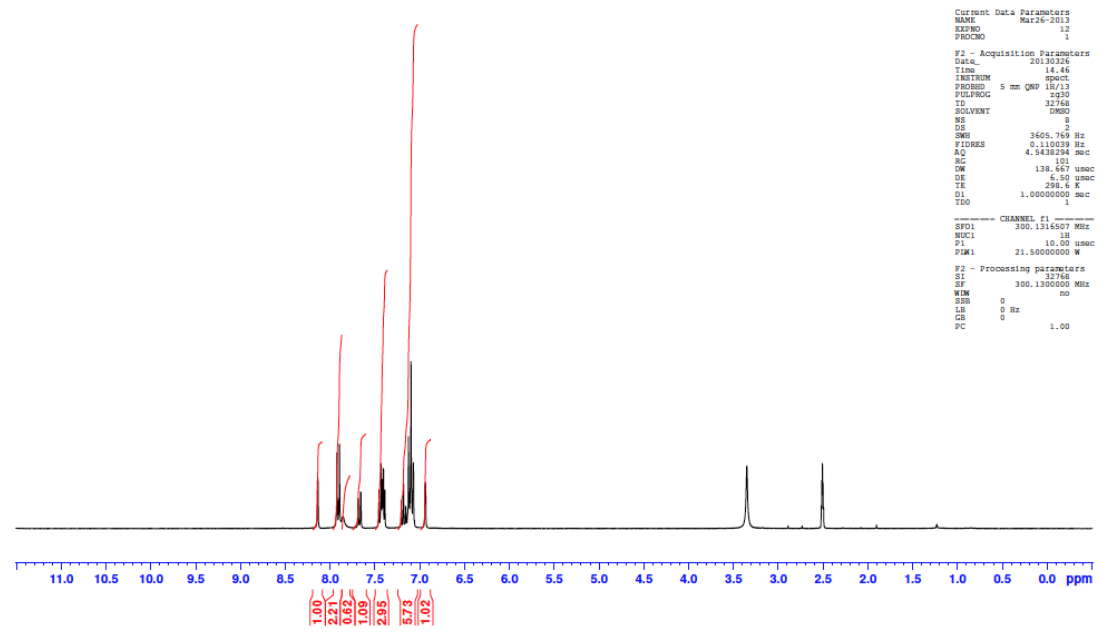

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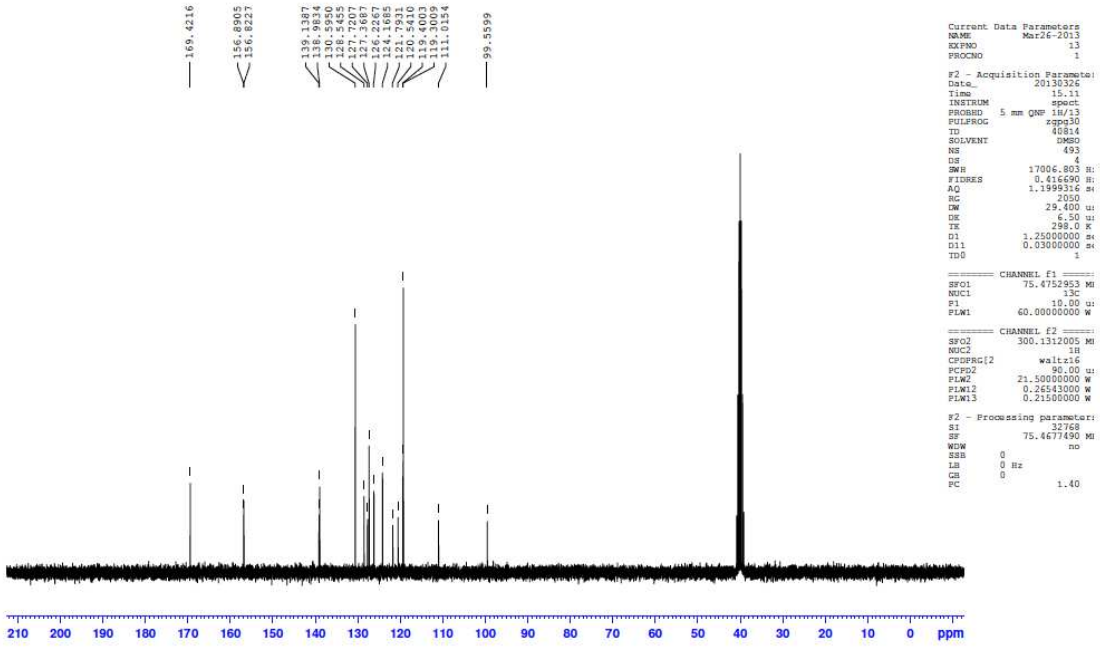
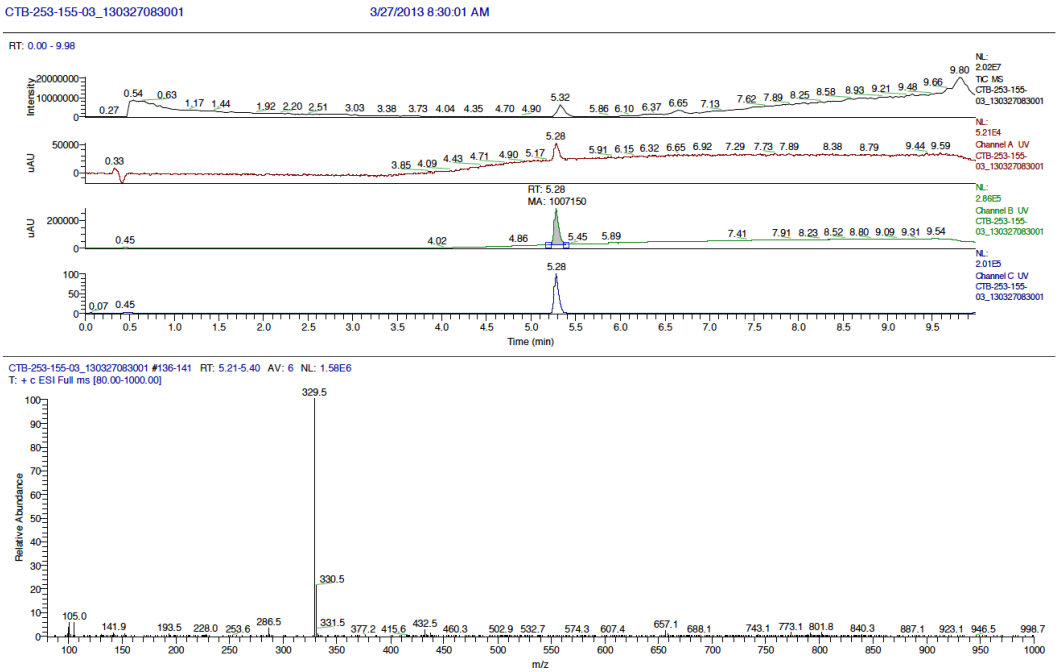


[13]CNMR spectrum of 4c



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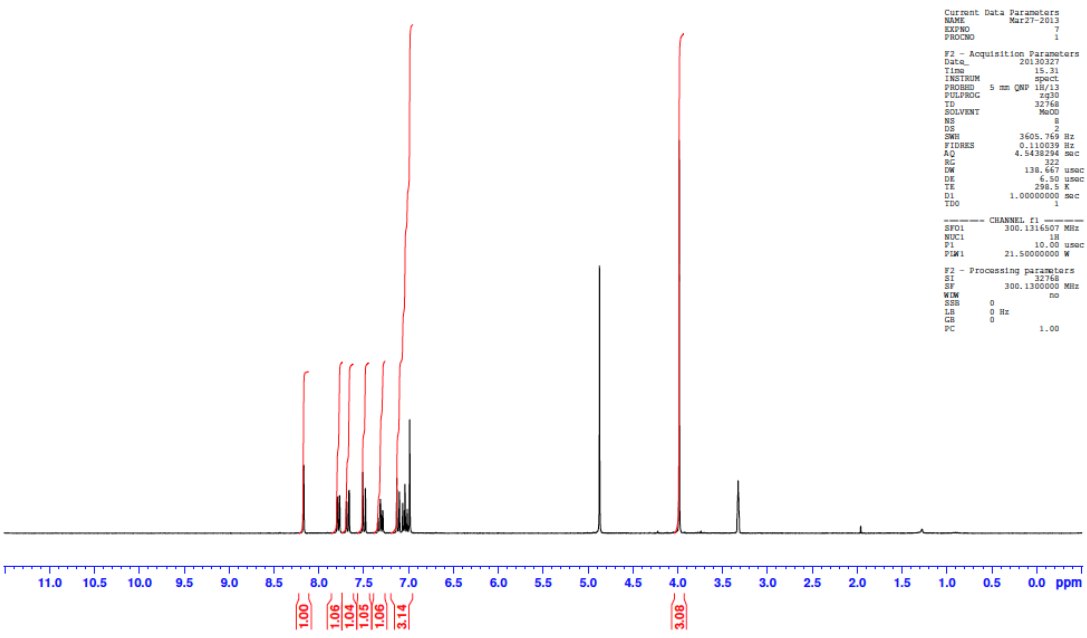

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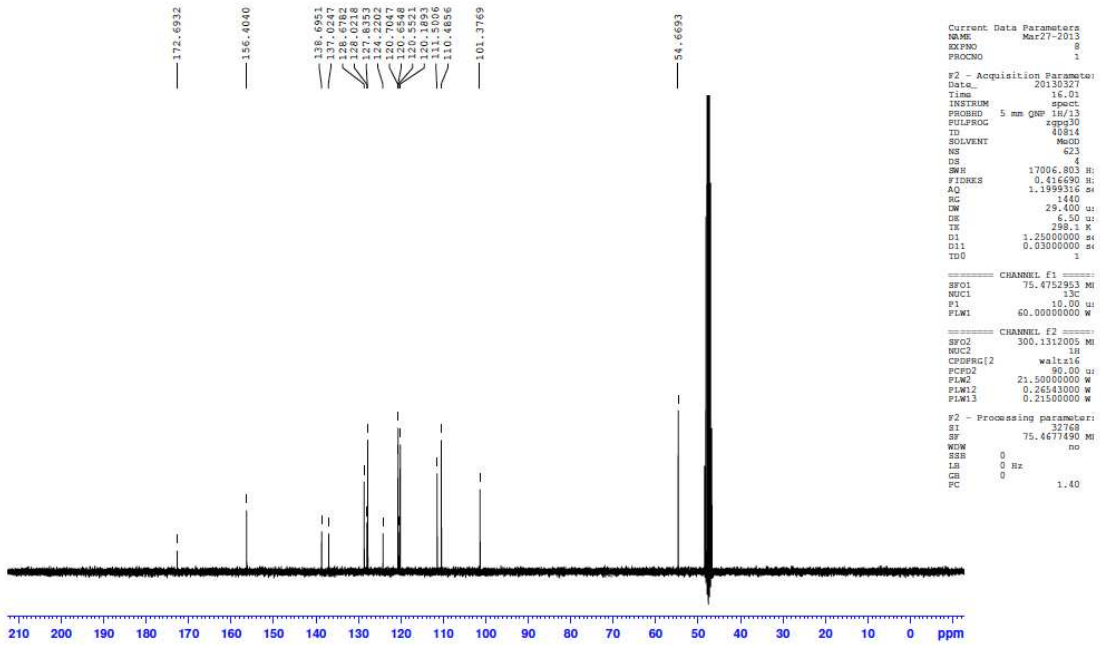
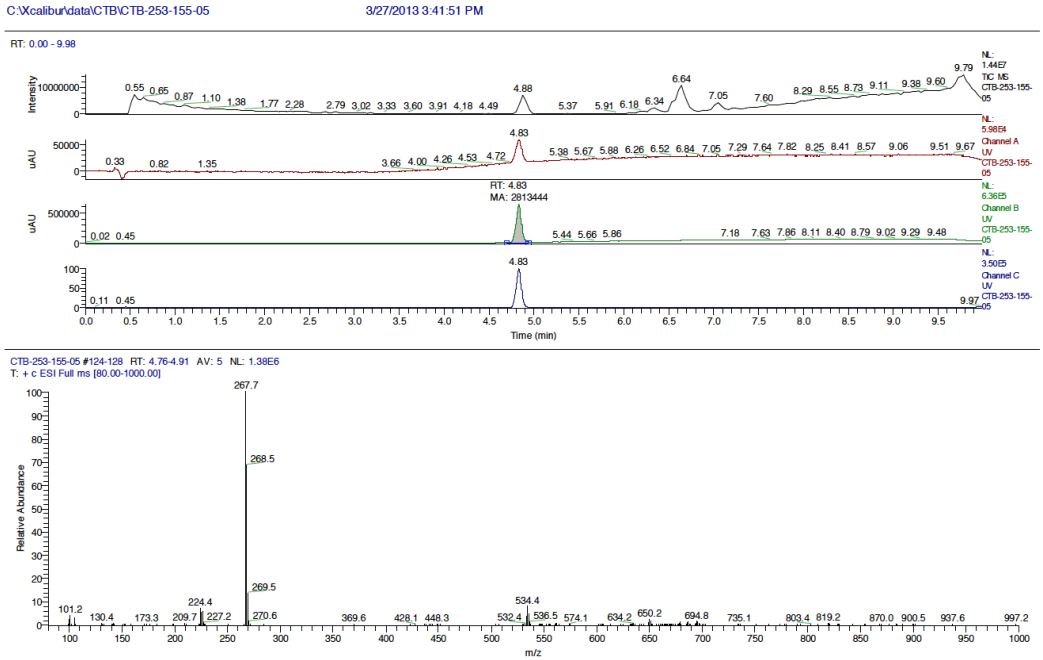


^{13}CNMR spectrum of 4d



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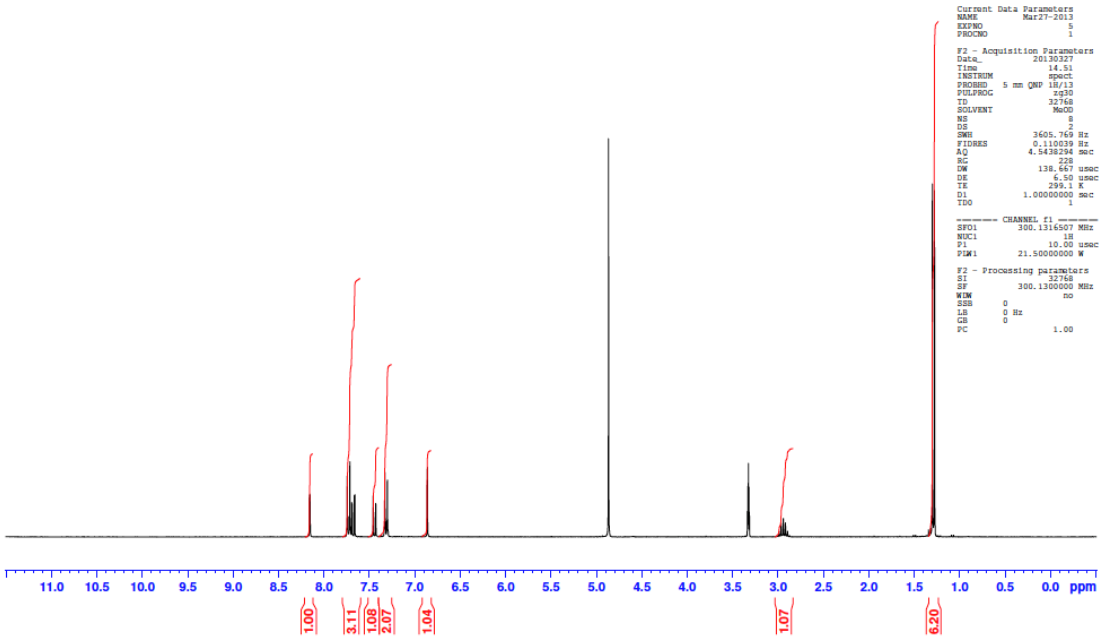

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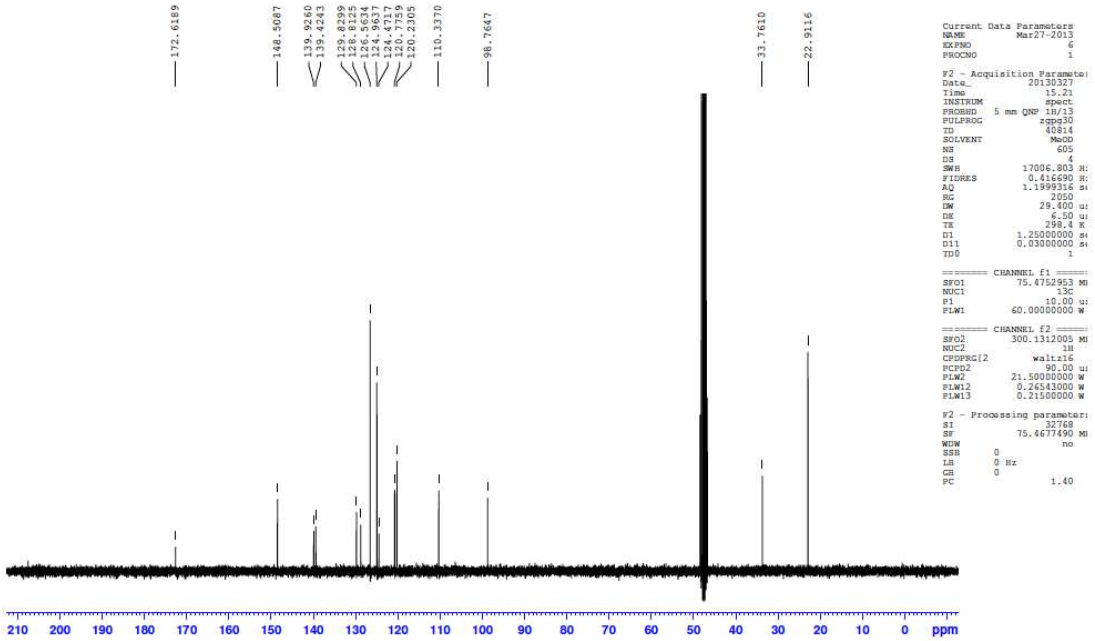

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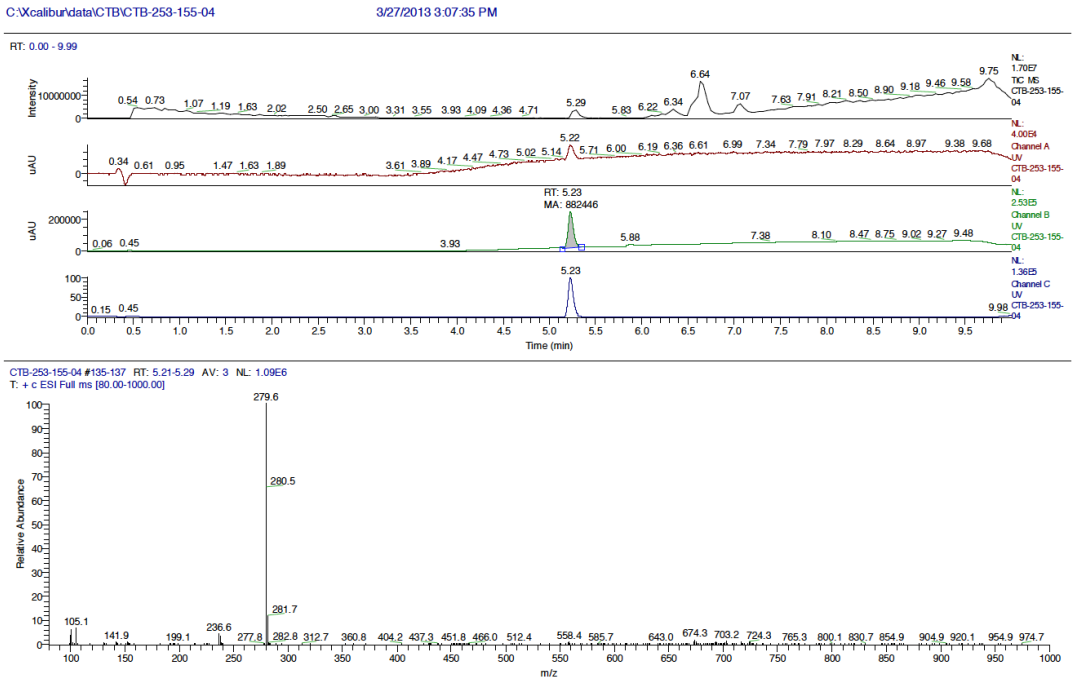

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LC-MS Data of 4e