

## Synthesis and characterization of diaza analogues of podophyllotoxin

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### ABSTRACT

In an attempt to synthesize the novel diaza analogues of podophyllotoxin (7a-d) in five step reactions. The synthesis of title compounds has been achieved from tetralones, which were formulated with ethylformate; prepared via cyclization with hydrazine hydrate. Furthermore, these newly synthesized compounds were characterized by spectral and elemental analysis data.

### 1. Introduction

In the recent years, efforts have been made to synthesize novel analogues of podophyllotoxin that may bear antibacterial, antiviral, anticancer and antimetabolic activity [1]. Aryltetrahydronaphthalene-type lignans as podophyllotoxin and its derivatives are important natural products in the armamentarium of antineoplastic agents. The biological assessment of podophyllotoxin was followed by discovery of its mode of action and culminated in the synthesis of the anticancer drugs etoposide and teniposide [2]. Hence, current research is focused on synthesizing novel compounds and to study their structure activity relationship [3].

There exist a class of natural products called lignans, derived from the plants of the podophyllum species [4,5]. Podophyllotoxin is an important member of this class and it has received considerable attention for its remarkable biological applications (Figure 1). Since it is having toxic properties and solubility problem in water, it cannot be directly applied for the clinical use, instead certain extensive structural modifications have to be done [6]. As a result of these modifications, some of the semisynthetic analogues of podophyllotoxin have been synthesized, namely etoposide and teniposide are now in clinical use [7-11]. So it is necessary to study their structural activity relationship, hence several podophyllotoxin analogues have been synthesized [12]. In view of the above facts, it was decided to modify the structure of podophyllotoxin to synthesize novel diaza analogues of podophyllotoxin.

### 2. Experimental

#### 2.1. Materials and methods

All reagents and chemicals were purchased from Merck Chemicals used without further purification. Melting points were taken in open capillary tubes and are uncorrected. TLC is performed with E. Merck precoated silica gel plates (60F<sub>254</sub>)

with iodine as a developing agent. Acme, India silica gel, 60-120 mesh for column chromatography is used. IR spectra in KBr were recorded on Perkin-Elmer model 683 or 1310 spectrometers. <sup>1</sup>H NMR (400 MHz) and <sup>13</sup>C NMR (100 MHz) spectra using trimethyl silane (TMS) as an internal reference were recorded on Bruker spectrometer, Elemental analyses were performed on a Perkin-Elmer 2400, Elemental analyzer and the mass spectra were obtained on CEC-21-100B, Finnigan Mat 1210 or Micro mass 7070 spectrometers operating at 70eV using a direct inlet system.

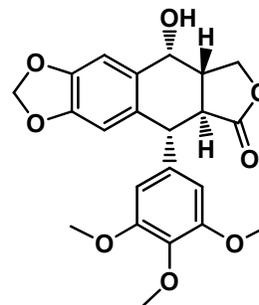
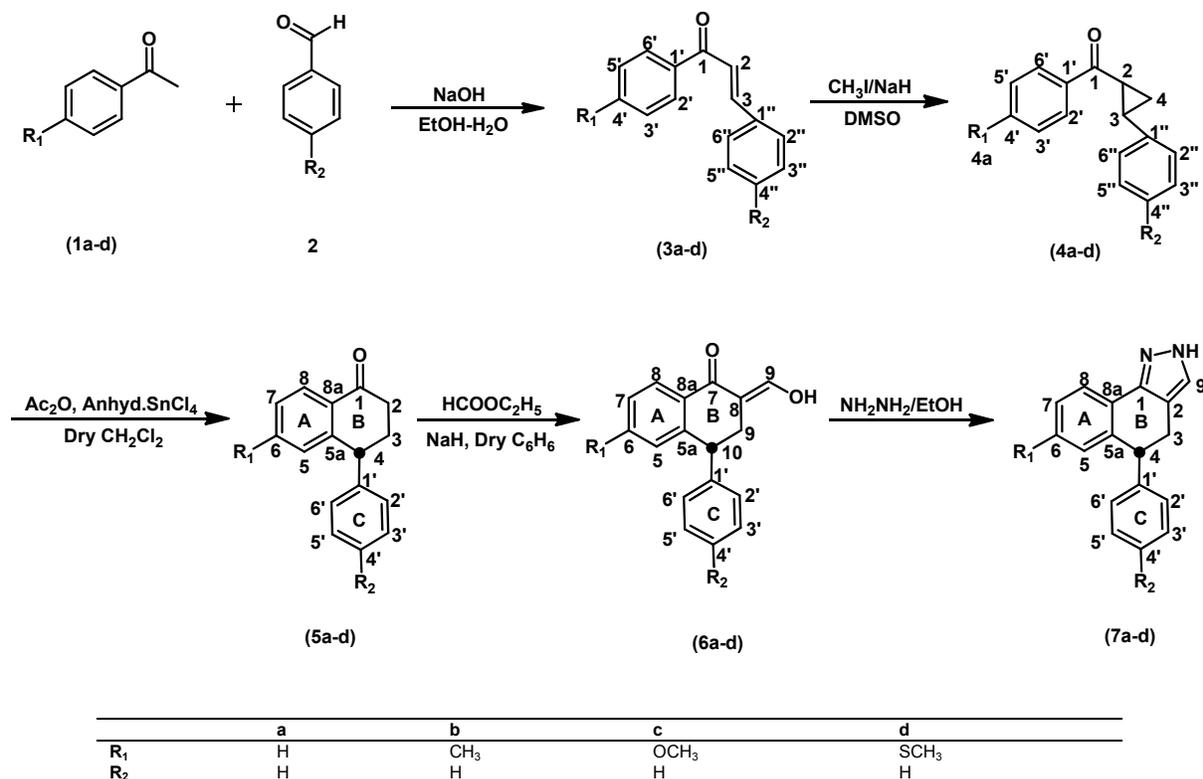


Figure 1. The structure of podophyllotoxin.

#### 2.2. Synthesis

##### 2.2.1. General procedure for the synthesis of chalcones (3a-d)

Substituted acetophenones (0.0487 mol) and benzaldehyde (5.2 g, 0.0487 mol) were stirred in water (40 mL) and ethanol (25 mL) mixture in the presence of sodium hydroxide (1.9 g, 0.0487 mol) at 15-30 °C for 4h. The reaction mixture was kept overnight in an ice bath. The precipitated products were filtered and recrystallized from ethanol (Scheme 1).



Scheme 1

**(E)-1,3-Diphenyl-2-propen-1-one (3a):** Color: Light yellow solid. Yield: 89.32%. M.p.: 91-93 °C. IR (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ): 3091, 2973 (Ar-CH), 1663 (C=O), 1589 (C=C).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 8.06 (d, 1H,  $J = 8.3$  Hz,  $\beta$ -CH), 7.89-7.30 (m, 10H, Ar-H), 7.55 (d, 1H,  $J = 8.0$  Hz,  $\alpha$ -CH).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 189.5 (C-1), 145.0 (C-3), 137.8 (C-1'), 135.4 (C-1''), 134.7 (C-4'), 129.2 (C-3', C-5'), 128.6 (C-3'', C-5''), 128.1 (C-2', C-6', C-2''), 127.5 (C-4''), 121.3 (C-2). MS (ESI,  $m/z$ ): 208.08 ( $M^+$ ). Anal. calcd. for  $\text{C}_{15}\text{H}_{12}\text{O}$ : C, 86.51; H, 5.81. Found: C, 86.48; H, 5.85%.

**(E)-3-Phenyl-1-p-tolylprop-2-en-1-one (3b):** Color: Light yellow solid. Yield: 66.35%. M.p.: 110-112 °C. IR (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ): 3128, 2965 (Ar-CH), 1670 (C=O), 1603 (C=C).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 8.10 (d, 1H,  $J = 8.0$  Hz,  $\beta$ -CH), 7.84-7.33 (m, 9H, Ar-H), 7.58 (d, 1H,  $J = 8.0$  Hz,  $\alpha$ -CH), 2.34 (s, 3H, CH<sub>3</sub>).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 189.5 (C-1), 145.3 (C-3), 144.0 (C-4'), 135.2 (C-1''), 134.8 (C-1'), 129.8 (C-2', C-6'), 129.5 (C-3', C-5'), 128.4 (C-3'', C-5''), 128.0 (C-2'', C-6''), 127.9 (C-4''), 121.3 (C-2), 21.2 (-CH<sub>3</sub>). MS (ESI,  $m/z$ ): 222.10 ( $M^+$ ). Anal. calcd. for  $\text{C}_{16}\text{H}_{14}\text{O}$ : C, 86.45; H, 6.35. Found: C, 86.42; H, 6.33%.

**(E)-1-(4-Methoxyphenyl)-3-phenylprop-2-en-1-one (3c):** Color: Light yellow solid. Yield: 71.88%. M.p.: 128-130 °C. IR (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ): 3135, 2973 (Ar-CH), 1667 (C=O), 1588 (C=C).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 8.09 (d, 1H,  $J = 7.5$  Hz,  $\beta$ -CH), 7.88-7.28 (m, 9H, Ar-H), 7.61 (d, 1H,  $J = 7.9$  Hz,  $\alpha$ -CH), 3.83 (s, 3H, OCH<sub>3</sub>).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 189.3 (C-1), 166.4 (C-4'), 145.6 (C-3), 135.2 (C-1''), 131.0 (C-2', C-6'), 130.2 (C-1'), 128.5 (C-3'', C-5''), 128.2 (C-2'', C-6''), 127.8 (C-4''), 121.3 (C-2), 114.8 (C-3', C-5'), 55.8 (-OCH<sub>3</sub>). MS (ESI,  $m/z$ ): 238.10 ( $M^+$ ). Anal. calcd. for  $\text{C}_{16}\text{H}_{14}\text{O}_2$ : C, 80.65; H, 5.92. Found: C, 80.62; H, 5.88%.

**(E)-1-(4-(Methylthio)phenyl)-3-phenylprop-2-en-1-one (3d):** Color: Light yellow solid. Yield: 73.50%. M.p.: 95-97 °C. IR (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ): 3142, 2985 (Ar-CH), 1673 (C=O), 1591 (C=C).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 8.00 (d, 1H,  $J = 7.3$  Hz,  $\beta$ -CH),

7.89-7.25 (m, 9H, Ar-H), 7.55 (d, 1H,  $J = 8.2$  Hz,  $\alpha$ -CH), 2.55 (s, 3H, SCH<sub>3</sub>).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 189.5 (C-1), 145.0 (C-4'), 145.0 (C-3), 135.2 (C-1''), 134.3 (C-1'), 128.9 (C-2', C-6'), 128.6 (C-3'', C-5''), 128.3 (C-2'', C-6''), 127.9 (C-4''), 127.3 (C-3', C-5'), 121.3 (C-2), 14.5 (-SCH<sub>3</sub>). MS (ESI,  $m/z$ ): 254.07 ( $M^+$ ). Anal. calcd. for  $\text{C}_{16}\text{H}_{14}\text{OS}$ : C, 75.55; H, 5.55. Found: C, 75.51; H, 5.53%.

### 2.2.2. General procedure for the synthesis of cyclopropyl ketones analogues (4a-d)

Sodium hydride (0.3 g, 0.0130 mol) was added in portions to the stirred suspensions of trimethylsulfoxonium iodide (2.8 g, 0.0130 mol) in dry DMSO (20 mL) under nitrogen gas atmosphere. The reaction mixture was stirred for 10 min. at 25-30 °C (until the evaluation of the H<sub>2</sub> gas ceased). Chalcones (0.0130 mol) in dry DMSO (15 mL) were added drop wise during 30min. to the above solution. The reaction mass was stirred at 26-28 °C for 2h. and raised the temperature to 50-60 °C for 1h. The completion of the reaction was confirmed by TLC and the reaction mixture was poured into water (20 mL). The precipitated gummy residue was extracted into chloroform. The combined organic layer was washed with water, dried over anhyd. Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The products were recrystallized from ethanol (Scheme 1).

**Phenyl (2-phenylcyclopropyl)methanone (4a):** Color: Dark brown semisolid. Yield: 77.63%. IR (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ): 3160, 2953 (Ar-CH), 1671 (C=O).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 7.95-7.25 (m, 10H, Ar-H), 2.10-2.02 (m, 2H, cyclopro-CH), 0.78 (d, 2H, C<sub>4</sub>-CH<sub>2</sub>).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 192.2 (C-1), 141.7 (C-1''), 136.3 (C-1'), 133.0 (C-4'), 128.9 (C-2', C-6', C-2''), 128.6 (C-3', C-5'), 128.3 (C-3'', C-5''), 125.1 (C-4''), 27.0 (C-2), 25.4 (C-3), 12.4 (C-4). MS (ESI,  $m/z$ ): 222.11 ( $M^+$ ). Anal. calcd. for  $\text{C}_{16}\text{H}_{14}\text{O}$ : C, 86.45; H, 6.35. Found: C, 86.43; H, 6.32%.

(2-Phenylcyclopropyl)(p-tolyl)methanone (**4b**): Color: Dark brown semisolid. Yield: 88.55%. IR (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ): 3155, 2948 (Ar-CH), 1677 (C=O).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 8.01-7.28 (m, 9H, Ar-H), 2.34 (s, 3H, CH<sub>3</sub>), 2.18-2.00 (m, 2H, cyclopro-CH), 0.81 (d, 2H, C<sub>4</sub>-CH<sub>2</sub>).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 192.3 (C-1), 142.7 (C-4'), 141.9 (C-1''), 133.8 (C-1'), 128.9 (C-3', C-5'), 128.6 (C-2', C-6'), 128.3 (C-3'', C-5''), 125.3 (C-4''), 125.0 (C-2''), 27.2 (C-2), 25.4 (C-3), 21.5 (-CH<sub>3</sub>), 14.8 (C-4). MS (ESI,  $m/z$ ): 236.12 (M<sup>+</sup>). Anal. calcd. for C<sub>17</sub>H<sub>16</sub>O: C, 86.40; H, 6.82. Found: C, 86.41; H, 6.79%.

(4-Methoxyphenyl)(2-phenylcyclopropyl)methanone (**4c**): Color: Dark brown semisolid. Yield: 74.30%. IR (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ): 3163, 2955 (Ar-CH), 1676 (C=O).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 7.95-7.31 (m, 9H, Ar-H), 3.85 (s, 3H, OCH<sub>3</sub>), 2.20-2.03 (m, 2H, cyclopro-CH), 0.80 (d, 2H, C<sub>4</sub>-CH<sub>2</sub>).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 192.0 (C-1), 165.2 (C-4'), 141.7 (C-4''), 129.9 (C-2', C-6'), 129.3 (C-1'), 128.3 (C-3'', C-5''), 125.4 (C-2'', C-6''), 121.0 (C-4''), 114.5 (C-3', C-5'), 55.7 (-OCH<sub>3</sub>), 27.3 (C-2), 25.5 (C-3), 14.4 (C-4). MS (ESI,  $m/z$ ): 252.14 (M<sup>+</sup>). Anal. calcd. for C<sub>17</sub>H<sub>16</sub>O<sub>2</sub>: C, 80.93; H, 6.39. Found: C, 80.90; H, 6.35%.

(4-(Methylthio)phenyl)(2-phenylcyclopropyl)methanone (**4d**): Color: Dark brown semisolid. Yield: 71.80%. IR (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ): 3178, 2965 (Ar-CH), 1687 (C=O).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 7.97-7.26 (m, 9H, Ar-H), 2.53 (s, 3H, SCH<sub>3</sub>), 2.21-2.05 (m, 2H, cyclopro-CH), 0.83 (d, 2H, C<sub>4</sub>-CH<sub>2</sub>).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 192.3 (C-1), 143.9 (C-4'), 141.7 (C-1''), 133.3 (C-1'), 132.0 (C-2', C-6'), 128.5 (C-3'', C-5''), 126.3 (C-3', C-5'), 125.2 (C-4''), 125.0 (C-2'', C-6''), 27.3 (C-2), 25.4 (C-3), -14.5 (-SCH<sub>3</sub>), 14.1 (C-4). MS (ESI,  $m/z$ ): 268.13 (M<sup>+</sup>). Anal. calcd. for C<sub>17</sub>H<sub>16</sub>OS: C, 76.08; H, 6.01. Found: C, 76.05; H, 6.03%.

### 2.2.3. General procedure for the synthesis of tetralones (5a-d)

Cyclopropyl ketones (0.0080 mol) were dissolved in dry dichloromethane (50 mL). Acetic anhydride (0.8 g, 0.0080 mol) and anhydrous stannic chloride (0.8 g, 0.0080 mol) were added under nitrogen gas atmosphere. The resultant reaction mixture was stirred at 25-28 °C for 3h. The completion of reaction was known by TLC. The reaction mixture was poured into 5% NaOH solution (20 mL). The product was extracted into dichloromethane. The organic layer was washed with water, dried over anhyd. Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum using a rotary evaporator to give brown residue. The product was purified by column chromatography using silica gel (60-120 mesh) as adsorbent and benzene as eluent. The benzene solution was concentrated to a small volume (20 mL) and hexane (100 mL) was added drop wise to give products in good yields. They were recrystallized from ethanol (Scheme 1).

4-Phenyl-3,4-dihydronaphthalen-1(2H)-one (**5a**): Color: Dark semisolid. Yield: 75.56%. IR (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ): 3112, 2934 (Ar-CH), 1685 (C=O).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 7.81-7.22 (m, 9H, Ar-H), 4.05 (t, 1H, CH), 2.65-2.21 (m, 4H, CH<sub>2</sub>).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 198.3 (C-1), 145.3 (C-1'), 140.5 (C-5a), 134.1 (C-8a), 133.8 (C-6), 129.5 (C-3', C-5'), 128.1 (C-2', C-6'), 128.0 (C-5, C-8), 126.5 (C-7), 126.2 (C-4'), 45.0 (C-4), 37.3 (C-2), 31.6 (C-3). MS (ESI,  $m/z$ ): 222.00 (M<sup>+</sup>). Anal. calcd. for C<sub>16</sub>H<sub>14</sub>O: C, 86.45; H, 6.35. Found: C, 86.41; H, 6.33%.

6-Methyl-4-phenyl-3,4-dihydronaphthalen-1(2H)-one (**5b**): Color: Dark semisolid. Yield: 66.14%. IR (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ): 3124-2943 (Ar-CH), 1694 (C=O).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 7.85-7.20 (m, 8H, Ar-H), 4.10 (t, 1H, CH), 2.63-2.20 (m, 4H, CH<sub>2</sub>), 2.31 (s, 3H, CH<sub>3</sub>).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 198.0 (C-1), 145.3 (C-1'), 143.5 (C-6), 140.2 (C-5a), 131.0 (C-8a), 129.5 (C-3', C-5'), 128.1 (C-2', C-6'), 128.0 (C-5), 126.5 (C-7), 126.1 (C-4'), 125.6 (C-8), 45.1 (C-4), 37.1 (C-2), 31.5 (C-3), 21.5 (-CH<sub>3</sub>). MS (ESI,  $m/z$ ): 236.09 (M<sup>+</sup>). Anal. calcd. for C<sub>17</sub>H<sub>16</sub>O: C, 86.40; H, 6.82. Found: C, 86.39; H, 6.85%.

6-Methoxy-4-phenyl-3,4-dihydronaphthalen-1(2H)-one (**5c**): Color: Dark semisolid. Yield: 81.61%. IR (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ): 3125, 2946 (Ar-CH), 1705 (C=O).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 7.90-7.18 (m, 8H, Ar-H), 4.02 (t, 1H, CH), 3.84 (s, 3H, OCH<sub>3</sub>), 2.60-2.18 (m, 4H, CH<sub>2</sub>).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 198.1 (C-1), 165.3 (C-6), 145.8 (C-1'), 141.9 (C-5a), 130.5 (C-8), 129.7 (C-3', C-5'), 128.0 (C-2', C-6'), 126.5 (C-8a), 126.0 (C-4'), 111.6 (C-7), 104.9 (C-5), 55.3 (-OCH<sub>3</sub>), 45.6 (C-4), 37.9 (C-2), 31.5 (C-3). MS (ESI,  $m/z$ ): 252.13 (M<sup>+</sup>). Anal. calcd. for C<sub>17</sub>H<sub>16</sub>O<sub>2</sub>: C, 80.93; H, 6.39. Found: C, 80.90; H, 6.41%.

6-(Methylthio)-4-phenyl-3,4-dihydronaphthalen-1(2H)-one (**5d**): Color: Dark semisolid. Yield: 93.40%. IR (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ): 3133, 2965 (Ar-CH), 1687 (C=O).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 7.87-7.12 (m, 8H, Ar-H), 4.00 (t, 1H, CH), 2.65-2.21 (m, 4H, CH<sub>2</sub>), 2.53 (s, 3H, SCH<sub>3</sub>).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 198.3 (C-1), 145.9 (C-1'), 143.8 (C-6), 140.7 (C-5a), 130.6 (C-8a), 129.5 (C-8), 129.2 (C-3', C-5'), 128.4 (C-2', C-6'), 126.3 (C-4'), 124.2 (C-7), 123.1 (C-5), 44.1 (C-4), 37.5 (C-2), 31.9 (C-3), 14.6 (-SCH<sub>3</sub>). MS (ESI,  $m/z$ ): 268.15 (M<sup>+</sup>). Anal. calcd. for C<sub>17</sub>H<sub>16</sub>OS: C, 76.08; H, 6.01. Found: C, 76.05; H, 6.05%.

### 2.2.4. General procedure for the synthesis of substituted hydroxyl methylene tetralones (6a-d)

Sodium hydride (1.2 g, 0.0508 mol) was added to a mixture of absolute ethanol (10 mL) and dry benzene (150 mL) and stirred for 1h. Ethyle formate (10 mL) was added dropwise to the above reaction mixture and stirred for another 1h, followed by dropwise addition of tetralones (5.1 g, 0.0138 mol), in dry benzene (100 mL) over a period of 1h. After stirring the red coloured mixture at room temperature for 2h, it was poured into 2N H<sub>2</sub>SO<sub>4</sub> (100 mL) in ice. The separated organic layer was washed with water (3x50 mL) and extracted into saturated sodium bicarbonate solution (3x50 mL), followed by 1% sodium hydroxide solution (3x50 mL). The sodium hydroxide extract was acidified with 2N H<sub>2</sub>SO<sub>4</sub> gave products in good yields. They were recrystallized from ethanol (Scheme 1).

Z)-2-(Hydroxymethylene)-4-phenyl-3,4-dihydronaphthalen-1(2H)-one (**6a**): Color: Dark brown solid. Yield: 79.09%. M.p.: 135-137 °C. Yield: 79.80%. IR (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ): 3255 (O-H), 3154, 2952 (Ar-CH), 1690 (C=O).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 5.7 (s, 1H, OH vinyl), 7.75-7.22 (m, 9H, Ar-H), 5.53 (s, 1H, CHOH), 4.10 (t, 1H, CH), 2.71 (d, 2H, CH<sub>2</sub>).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 183.6 (C-1), 172.9 (C-9), 143.4 (C-1'), 141.9 (C-5a), 135.2 (C-6), 133.0 (C-8a), 129.4 (C-3', C-5'), 128.9 (C-5), 128.5 (C-2', C-6'), 127.8 (C-8), 126.9 (C-7), 126.4 (C-4'), 117.3 (C-2), 42.9 (C-4), 29.7 (C-3). MS (ESI,  $m/z$ ): 250.13 (M<sup>+</sup>). Anal. calcd. for C<sub>17</sub>H<sub>14</sub>O<sub>2</sub>: C, 81.58; H, 5.64. Found: C, 81.56; H, 5.61%.

Z)-2-(Hydroxymethylene)-6-methyl-4-phenyl-3,4-dihydronaphthalen-1(2H)-one (**6b**): Color: Dark brown solid. Yield: 89.08%. M.p.: 129-131 °C. IR (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ): 3253 (O-H), 3152, 2951 (Ar-CH), 1690 (C=O).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 5.6 (s, 1H, OH, vinyl), 7.76-7.22 (m, 8H, Ar-H), 5.51 (s, 1H, CHOH), 4.15 (t, 1H, CH), 2.86 (s, 3H, CH<sub>3</sub>), 2.74 (d, 2H, CH<sub>2</sub>).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 183.5 (C-1), 173.6 (C-9), 144.5 (C-6), 143.1 (C-1'), 141.9 (C-5a), 130.5 (C-8), 130.1 (C-8a), 129.9 (C-3', C-5'), 128.6 (C-5), 128.4 (C-2', C-6'), 127.0 (C-7), 126.4 (C-4'), 117.9 (C-2), 42.5 (C-4), 29.8 (C-3), 29.5 (-CH<sub>3</sub>). MS (ESI,  $m/z$ ): 264.12 (M<sup>+</sup>). Anal. calcd. for C<sub>18</sub>H<sub>16</sub>O<sub>2</sub>: C, 81.79; H, 6.10. Found: C, 81.75; H, 6.13%.

Z)-2-(Hydroxymethylene)-6-methoxy-4-phenyl-3,4-dihydronaphthalen-1(2H)-one (**6c**): Color: Dark brown solid. Yield: 65.32%. M.p.: 140-142 °C. IR (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ): 3251 (O-H), 3156, 2958 (Ar-CH), 1672 (C=O).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 5.8 (s, 1H, OH vinyl), 7.79-7.26 (m, 8H, Ar-H), 5.51 (s, 1H, CHOH), 4.11 (t, 1H, CH), 3.87 (s, 3H, OCH<sub>3</sub>), 2.76 (d, 2H, CH<sub>2</sub>).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 183.4 (C-1), 172.6 (C-9), 166.7 (C-6), 143.3 (C-1'), 142.4 (C-5a), 129.9 (C-8), 129.4 (C-3', C-5'), 128.7 (C-2', C-6'), 126.4 (C-4'), 125.9 (C-8a), 117.3 (C-2), 112.5 (C-7), 105.8 (C-5), -55.9 (-OCH<sub>3</sub>), 42.8 (C-4), 29.4 (C-3).

MS (ESI,  $m/z$ ): 280.14 ( $M^+$ ). Anal. calcd. for  $C_{18}H_{16}O_3$ : C, 77.12; H, 5.75. Found: C, 77.15; H, 5.72%.

(*Z*)-2-(Hydroxymethylene)-6-(methylthio)-4-phenyl-3,4-dihydronaphthalen-1(2*H*)-one (**6d**): Color: Dark brown solid. Yield: 55.40%. M.p.: 145-147 °C. IR (KBr,  $\nu$ ,  $cm^{-1}$ ): 3258 (O-H), 3159-2952 (Ar-CH), 1678 (C=O).  $^1H$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 5.6 (s, 1H, OH vinyl), 7.75-7.27 (m, 8H, Ar-H), 5.49 (s, 1H, CHOH), 4.09 (t, 1H, CH), 2.61 (s, 3H, SCH<sub>3</sub>), 2.78 (d, 2H, CH<sub>2</sub>).  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 183.6 (C-1), 172.5 (C-9), 145.9 (C-6), 143.3 (C-1'), 141.9 (C-5a), 130.7 (C-8), 129.6 (C-8a), 129.2 (C-3', C-5'), 128.7 (C-2', C-6'), 126.7 (C-4'), 124.8 (C-7), 123.9 (C-5), 117.4 (C-2), 42.3 (C-4), 29.4 (C-3), 14.8 (-SCH<sub>3</sub>). MS (ESI,  $m/z$ ): 296.07 ( $M^+$ ). Anal. calcd. for  $C_{18}H_{16}O_2S$ : C, 72.94; H, 5.44. Found: C, 72.91; H, 5.42%.

### 2.2.5. General procedure for the synthesis of novel diaza analogues of podophyllotoxin (7a-d)

A mixture of hydroxymethylene tetralones (0.0145 mol) and hydrazine hydrate (0.5 g, 0.0145 mol) in absolute ethanol was refluxed for 3h. The excess of solvent was removed under reduced pressure. The solid thus obtained were collected and recrystallized from ethanol (Scheme 1).

5-Phenyl-4,5-dihydro-2*H*-benzo[*g*]indazole (**7a**): Color: Dark brown solid. Yield: 77.36%. M.p.: 151-153 °C. IR (KBr,  $\nu$ ,  $cm^{-1}$ ): 3269 (N-H), 3144, 2969 (Ar-CH).  $^1H$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 12.60 (s, 1H, NH), 7.65-7.23 (m, 9H, Ar-H), 7.53 (s, 1H, pyrazole-CH), 4.42 (t, 1H, CH), 3.29 (d,d, 2H, CH<sub>2</sub>).  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 144.5 (C-1), 143.2 (C-1'), 140.9 (C-5a), 133.5 (C-9), 129.3 (C-3', C-5'), 128.9 (C-8a), 128.4 (C-2', C-6'), 126.7 (C-4'), 126.5 (C-7), 126.1 (C-6), 123.1 (C-8), 120.0 (C-5a), 114.9 (C-2), 45.8 (C-4), 37.3 (C-3). MS (ESI,  $m/z$ ): 246.09 ( $M^+$ ). Anal. calcd. for  $C_{17}H_{14}N_2$ : C, 82.90; H, 5.73; N, 11.37. Found: C, 82.86; H, 5.70; N, 11.35%.

7-Methyl-5-phenyl-4,5-dihydro-2*H*-benzo[*g*]indazole (**7b**): Color: Dark brown solid. Yield: 82.65%. M.p.: 148-150 °C. IR (KBr,  $\nu$ ,  $cm^{-1}$ ): 3265 (N-H), 3142, 2968 (Ar-CH).  $^1H$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 12.64 (s, 1H, NH), 7.64-7.26 (m, 8H, Ar-H), 7.52 (s, 1H, pyrazole-CH), 4.44 (t, 1H, CH), 3.25 (d,d, 2H, CH<sub>2</sub>), 2.82 (s, 3H, CH<sub>3</sub>).  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 144.2 (C-1), 143.2 (C-1'), 140.6 (C-5a), 138.7 (C-6), 133.5 (C-9), 130.9 (C-5), 129.2 (C-3', C-5'), 128.6 (C-2', C-6'), 127.8 (C-8), 127.1 (C-7), 126.2 (C-4'), 125.6 (C-8a), 114.6 (C-2), 46.8 (C-4), 37.5 (C-3), 21.64 (-CH<sub>3</sub>). MS (ESI,  $m/z$ ): 260.14 ( $M^+$ ). Anal. calcd. for  $C_{18}H_{16}N_2$ : C, 83.04; H, 6.19; N, 10.76. Found: C, 83.00; H, 6.20; N, 10.79%.

7-Methoxy-5-phenyl-4,5-dihydro-2*H*-benzo[*g*]indazole (**7c**): Color: Dark brown solid. Yield: 68.83%. M.p.: 135-137 °C. IR (KBr,  $\nu$ ,  $cm^{-1}$ ): 3269 (N-H), 3147, 2969 (Ar-CH).  $^1H$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 12.59 (s, 1H, NH), 7.68-7.25 (m, 8H, Ar-H), 7.55 (s, 1H, pyrazole-CH), 4.39 (t, 1H, CH), 3.26 (d,d, 2H, CH<sub>2</sub>), 3.81 (s, 3H, OCH<sub>3</sub>).  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 161.3 (C-6), 144.6 (C-1), 143.7 (C-1'), 141.9 (C-5a), 133.5 (C-9), 129.3 (C-3', C-5'), 129.0 (C-8), 128.4 (C-2', C-6'), 126.5 (C-4'), 121.3 (C-8a), 114.6 (C-2), 112.5 (C-5), 112.4 (C-7), 55.6 (-OCH<sub>3</sub>), 46.7 (C-4), 37.1 (C-3). MS (ESI,  $m/z$ ): 276.13 ( $M^+$ ). Anal. calcd. for  $C_{18}H_{16}N_2O$ : C, 78.24; H, 5.84; N, 10.14. Found: C, 78.22; H, 5.85; N, 10.11%.

7-(Methylthio)-5-phenyl-4,5-dihydro-2*H*-benzo[*g*]indazole (**7d**): Color: Dark brown solid. Yield: 63.90%. M.p.: 145-147 °C. IR (KBr,  $\nu$ ,  $cm^{-1}$ ): 3265 (N-H), 3143, 2968 (Ar-CH).  $^1H$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 12.55 (s, 1H, NH), 7.61-7.29 (m, 8H, Ar-H), 7.51 (s, 1H, pyrazole-CH), 4.35 (t, 1H, CH), 3.21 (d,d, 2H, CH<sub>2</sub>), 2.49 (s, 3H, SCH<sub>3</sub>).  $^{13}C$  NMR (100 MHz, DMSO- $d_6$ ,  $\delta$ , ppm): 144.3 (C-1), 143.2 (C-1'), 140.9 (C-5a), 139.5 (C-6), 133.6 (C-9), 129.4 (C-3', C-5'), 128.4 (C-8), 128.3 (C-2', C-6'), 126.5 (C-4'), 125.5 (C-8a), 124.4 (C-7), 123.9 (C-5), 114.7 (C-2), 45.5 (C-4), 37.6 (C-3), 14.7 (-SCH<sub>3</sub>). MS (ESI,  $m/z$ ): 292.11 ( $M^+$ ). Anal. calcd. for  $C_{18}H_{16}N_2S$ : C, 73.94; H, 5.52; N, 9.58. Found: C, 73.93; H, 5.50; N, 9.55%.

## 3. Results and discussion

The synthesis of novel diaza analogues of podophyllotoxin has been carried out by chalcone route (Scheme 1). The benzylideneacetophenones (chalcones) (**3a-d**) were prepared in high yields by Claisen-Schmidt reaction of acetophenones (**1a-d**) with benzaldehyde (**2**) in the presence of sodium hydroxide in water-ethanol mixture [13,14]. The structures of the chalcones were confirmed by IR and  $^1H$  NMR spectral studies. IR spectra of compounds (**3a-d**) showed the C=C stretching frequency in the range 1626-1613  $cm^{-1}$  and  $^1H$  NMR showed the absence of aldehyde proton at 9.83 ppm. The cyclopropyl ketones (**4a-d**) were prepared in good yields by the reaction of chalcones (**3a-d**) with trimethylsulfoxonium iodide in the presence of sodium hydride in dry DMSO [15,16]. The sodium hydride acts as a base which abstracts a proton from the methyl group in trimethylsulfoxonium iodide to form a dimethylsulfoxonium methylide. It attacks nucleophilically the  $\beta$ -carbonyl atom of the chalcone which acts as Michael receptors to form an enolate ion, which undergoes nucleophilic attack on the methylene carbon atom bearing the dimethylsulfoxonium cation intramolecularly finally to form the desired cyclopropyl ketone. The structure of compounds (**4a-d**) was confirmed by IR spectra. In its IR spectra exhibited C=O stretching band in the range 1687-1671  $cm^{-1}$  and  $^1H$  NMR showed the cyclopropane CH<sub>2</sub> and CH peak at the range 2.21-2.00 and 0.83-0.78 ppm respectively. Tetralones (**5a-d**) were prepared in good yields by the Friedel-Craft's intramolecular cyclization reaction of cyclopropyl ketones (**4a-d**) in the presence of anhyd. stannic chloride and acetic anhydride in dry dichloromethane [17]. The cyclopropyl ketones undergoes electrophilic ring opening in the presence of Lewis acid to give benzylcarbocationic intermediate which is intramolecularly attacked by aryl ring  $\pi$ -electrons resulting in the formation of a six membered ring with a pendant carbocation. This readily gives up proton to form tetralones. Acetic anhydride which facilitates the formation of desired tetralones. In its IR spectra appeared absorption bands in the range 3133-2934  $cm^{-1}$  and 1705-1685  $cm^{-1}$  corresponds to aromatic and C=O stretching frequencies and  $^1H$  NMR of the ring B proton appears in the range 2.65-2.18 ppm. They are key intermediates for the preparation of the novel diaza analogues of podophyllotoxin. The tetralones on formylation to give substituted hydroxyl-methylene tetralones (**6a-d**) [18]. Formation of the presently synthesized tetralones with ethyl formate using sodium hydride as the base at room temperature gave single products in good yields.

The  $\beta$ -dicarbonyl compound, which exist in the enol form show the carbonyl absorption in the region 1640-1610  $cm^{-1}$ . Generally 1,3-diketones absorption peak with high intensity at 1715  $cm^{-1}$ . Enols containing this grouping, but the shift that occurs in these compounds is attributed to the intramolecular hydrogen bonding (Figure 2).

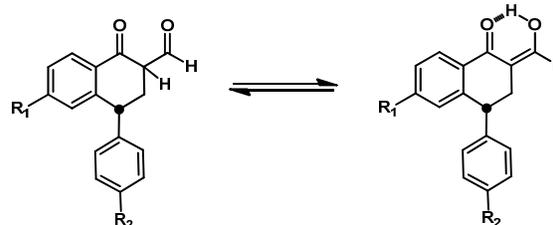


Figure 2.  $\beta$ -Dicarbonyl compound which exist in the enol form.

At the same time, the true alcoholic hydroxyl band near 3700  $cm^{-1}$  is absent in enols, but there is a band near 3258-3251  $cm^{-1}$  (s) which is attributed to the chelated hydroxyl group.  $^1H$  NMR showed the vinylic proton absorption at 5.80-5.60 ppm. The diaza analogues of podophyllotoxin (**7a-d**) were

synthesized in high yields by the condensation of hydroxymethylene tetralones and hydrazine hydrate in absolute ethanol [19]. The products were purified by column chromatography by using benzene-ethyl acetate mixture as eluent and silica gel as an adsorbent or recrystallization from ethanol. The compounds (**7a-d**) exhibited NH stretching band at 3269-3265  $\text{cm}^{-1}$  and proton NMR showed singlet NH peak at 12.64-12.55 ppm. Based on this, the synthesized compounds were confirmed.

#### 4. Conclusion

In summary, a convenient synthesis of novel diaza analogues of podophyllotoxin has been developed. This procedure provides good yields of podophyllotoxin analogues. This constitutes one of the synthetic methods by doing structural modifications to podophyllotoxin for novel diaza analogues of podophyllotoxin.

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