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Synthesis and characterization of tetralones as intermediates for podophyllotoxin analogues

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ABSTRACT

Podophyllotoxin has captured the attention of chemists all over the world for its biological activity. It was isolated from many plants of *Podophyllum* species such as *Podophyllum emodi*, *Podophyllum peltatum* and others. It mainly exhibits anticancer, antimitotic, antimalarial, anti-aids and other activities. Its use is restricted due to its toxicity and unfavourable solubility. It was aimed to synthesize some new heterocyclic analogues of podophyllotoxin by changing the substituents by changing lactone ring with pyrazoline ring and substituents in ring C with hydrogen and methoxy group. Chalcones were prepared by Claisen-Schmidt reaction of 1,3-methylene dioxyacetophenone with benzaldehyde and *p*-anisaldehyde. The reaction of chalcone with trimethylsulphoxonium iodide in presence of sodium hydride gave cyclopropyl ketone. Intramolecular cyclization reaction of cyclopropyl ketone gave tetralone intermediates of podophyllotoxin. They are obtained in good yields. The structure of all the products was confirmed by spectral data.

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1. Introduction

Plants of genus *podophyllum* are rich sources of aryl tetralin type lignans. Podophyllotoxin is a cytotoxin lignan found in *Berberidaceae* plants such as *Podophyllum peltatum Linnaeus*, *Podophyllum emodi Wall* and *Podophyllum pleianthum* [1,2]. Extensive chemical investigation of *podophyllum* species revealed the presence of a number of compounds like podophyllotoxin, quercetin, 4-demethyl podophyllotoxin, podophyllotoxin glucoside, 4-demethyl podophyllotoxin glucoside, kempferol, picropodophyllin, deoxy podophyllotoxin, 4-demethyl deoxy podophyllotoxin, isopicropodophyllin, α-peltatin, β-peltatin. The lignan podophyllotoxin is highly valued as precursor for clinical use compounds. Extracts of *podophyllum* species have been used for diverse cultures since ancient times as antidotes against poisons and toxic, cathartic, purgative, antihelminthic and vesicant [3].

Podophyllotoxin is effective in the treatment of genital warts in children and against *Molluscum contagiosum* which is generally a self limiting benign skin disease that affects mostly children, young adults and HIV patients. In the modern system of medicine, the plant extracts has been successfully used for treatment of various disorders such as monocytoid leukemia, hodgkins lymphoma, bacterial and viral infections, veneral warts, rheumatoid arthralgia, associated with numbness of the limbs and pyogenic infection of skin tissues, AIDS associated with kaposis sarcoma and different cancers of brain, lungs and bladder. Antitumor activity is the outstanding property of podophyllotoxin [4].

Some of the derivatives and analogues of podophyllotoxin showed good anticancer activity. In view of these, it was decided to synthesize new tetralone intermediates of podophyllotoxin by chalcone route. The tetralones were synthesized by modifying lactone ring with pyrazoline ring and change the substituent in ring C with hydrogen and methoxy group to study structure activity relationship (Figure 1).

2. Experimental

2.1. Materials and methods

All the required reagents and chemicals were purchased from Merck. They were used without further purification. Melting points were taken in open capillary tubes and are uncorrected.

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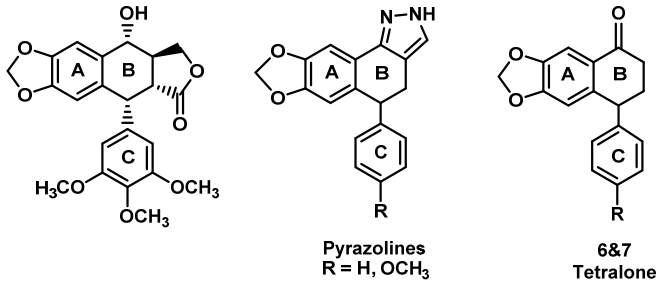
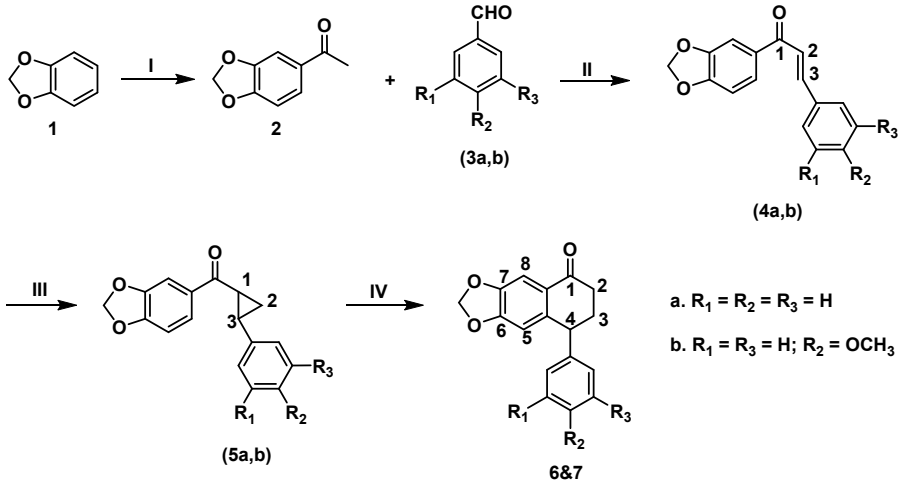


Figure 1. Podophyllotoxin.



Reagents and conditions:
I: Ac_2O, fused $ZnCl_2$, stirred at room temperature (29 °C) for 4 hours.
II: NaOH, H_2O, C_2H_5OH stirred at room temperature (29 °C) for 10 hours.
III: NaH, dry benzene, trimethyl sulphoxonium iodide, stirred for 5 hr and further at 50-60 °C for 1 hour.
IV: Anhydrous $SnCl_4$, Ac_2O, dry CH_2Cl_2. stirred at room temperature for 5 hours.

Scheme 1

Thin layer chromatography (TLC) is performed with Merck pre-coated silica gel plates ($60F_{254}$) with iodine as a developing agent. IR spectra in KBr were recorded on Perkin-Elmer model 683 spectrometers. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded using tetramethyl silane (TMS) as an internal reference on Bruker spectrometer. Elemental analyses were performed on a Perkin-Elmer 2400. Mass spectra were obtained by Hitachi RMU-61 spectrophotometer.

2.2. Synthesis

2.2.1. General procedure for the synthesis of 1-(benzo[d][1,3]dioxol-6-yl)ethanone (2)

1,3-Benzodioxole (10 g) in acetic anhydride (30 mL) containing fused zinc chloride (12 g) as catalyst was stirred at room temperature for 4 h. After the usual work up, thick brown solid product was obtained in 85% yield (9 g). The purity of the compound was checked by TLC in different solvent mixture (Scheme 1).

1-(Benzo[d][1, 3]dioxol-6-yl) ethanone (**2**): Color: Dark brown solid. Yield: 85%. M.p.: 95-97 °C. FT-IR (KBr, ν, cm^{-1}): 2917 (C-H), 1661 (C=O), 1603 (Ar, C=C). ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.52 (s, 3H, CH_3), 6.02 (s, 2H,-O-CH_2-O-), 6.84 (d, 1H, *J* = 3 Hz, Ar-H), 7.24 (s, 1H, Ar-H), 7.42 (d, 1H, *J* = 3 Hz, Ar-H).

2.2.2. General procedure for the synthesis of chalcones (4a, 4b)

Substituted benzaldehydes (3.5 mL) and substituted acetophenone (5 g) were stirred in water (25 mL) and ethanol (15 mL) mixture in the presence of sodium hydroxide (2 g) at room temperature for 6 h. The reaction mixture was kept overnight in an ice bath. The precipitated products were filtered and recrystallized from methanol (Scheme 1).

1-(Benzo[d][1,3] dioxol-6-yl)-3-phenylprop-2-en-1-one (**4a**): Color: Light yellow solid. Yield: 80%. M.p.: 194-196 °C. FT-IR (KBr, ν, cm^{-1}): 1653 (C=O), 1590 (C=C). ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 6.04 (s, 2H, -O-CH_2-O), 6.87 (d, 1H, *J* = 3 Hz, α-C-H), 7.76 (d, 1H, *J* = 3 Hz, β-C-H), 7.39-7.65 (m, 8H, Ar-H). MS (EI, *m/z*): 253, 231, 215, 198, 167, 149, 97, 58. Anal. calcd. or $C_{16}H_{12}O_3$: C, 76.18; H, 4.79. Found: C, 76.75; H, 4.83%.

1-(Benzo[d][1, 3] dioxol-6-yl)-3-(4 methoxyl phenyl) prop-2-en-1-one (**4b**): Color: Light yellow solid. Yield: 80%. M.p.: 241-243 °C. FT-IR (KBr, ν, cm^{-1}): 1646 (C=O), 1603 (C=C). ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.82 (s, 3H, OCH_3), 6.02 (s, 2H, -OCH_2O-), 6.85-7.24 (m, 4H, Ar-H, α-C-H), 7.32-7.82 (m, 5H, Ar-H). MS (EI, *m/z*): 283, 211, 144, 99. Anal. calcd. for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.34; H, 4.96%.

2.2.3. General procedure for the synthesis of cyclopropyl ketones (5a,b)

To the stirred suspensions of sodium hydride (0.9 g) in dry benzene (20 mL) the trimethy sulphoxonium iodide (7 g) was added. The reaction mixture was stirred for 20 minutes at 30 °C. Chalcone (8 g) in dry benzene (15 mL) was added dropwise to the above solution. The reaction mass was stirred at 28-29 °C for 6 hours and raised the temperature to 50-60 °C for 1 hour. The completion of the reaction was confirmed by thin layer chromatography and the cooled reaction mixture was poured into 5% hydrochloric acid solution (30 mL). The precipitated gummy residue was extracted into chloroform. The combined organic layer was washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. They were recrystallized from methanol (Scheme 1).

Benzo[d][1, 3]dioxol-5-yl (2-phenylcyclopropyl)methanone (**5a**): Color: Light yellow solid. Yield: 75 %. M.p.: 226-228 °C. FT-IR (KBr, ν, cm^{-1}): 1653 (C=O), 1604 (C-C of cyclopropyl), 1590 (Ar, C=C). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 6.01 (s, 2H, O-CH_2-O), 1.48-1.86 (t, 2H, *J* = 4 Hz, C_2-H), 2.64 (m, 1H, C_1-H), 2.79 (m, 1H, C_3-H), 6.81 (d, 1H, Ar-H), 7.15-7.61 (m, 7H, Ar-H). MS (EI, *m/z*): 267 (M+1), 167, 149. Anal. calcd. for $C_{17}H_{14}O_3$: C, 76.68; H, 5.30. Found: C, 76.7; H, 5.26%.

Benzo[d][1, 3]dioxol-5-yl (2-(4-methoxyphenyl)cyclopropyl) methanone (**5b**): Color: Light yellow solid. Yield: 81 %. M.p.: 276-279 °C. FT-IR (KBr, ν, cm^{-1}): 1647 (C=O), 1603 (C-C of cyclopropyl), 1580 (C=C, Ar). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.74 (s, 3H, OCH_3), 1.41-1.80 (t, 2H, *J* = 4 Hz,C_2-H), 2.59 (m, 1H, C_3-H), 2.69 (m, 1H, C_1-H). MS (EI, *m/z* (%)): 283 (M+1). Anal. calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.99; H, 5.42%.

2.2.4. General procedure for the synthesis of tetralones (6, 7)

Acetic anhydride (0.94 mL) and anhydrous stannic chloride (1 mL) were added to the cyclopropyl ketones (3 g) were dissolved in dry dichloromethane (20 mL) solution. The resultant reaction mixture was stirred at 28-29 °C for 6 hrs. The completion of reaction was known by thin layer chromatography. The reaction mixture was poured into 5% hydrochloric acid solution (40 mL), the product was extracted into chloroform. The organic layer was washed with water, dried over anhydrous Na_2SO_4 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) to give products in good yields. They were recrystallized from methanol (Scheme 1).

8-Phenyl-7, 8-dihydronaphtho[2, 3-d][1, 3]dioxol-5(6H)-one (**6**): Color: Dark brown gummy solid. Yield: 68%. M.p.: 256-258 °C. FT-IR (KBr, ν, cm^{-1}): 2922 (C-H), 1608 (C=C), 1677 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.62-2.68 (tt, 2H, C_2-H), 1.25-1.40 (m, 2H, C_3-H), 3.16 (t, 1H, C_4-H), 5.97 (s, 2H, O-CH_2-O-), 6.58 (s, 1H, Ar-H), 6.90-7.53 (m, 6H, Ar-H). MS (EI, *m/z* (%)): 267 (M+1). Anal. calcd. for $C_{17}H_{14}O_3$: C, 76.68; H, 5.30. Found: C, 76.93; H, 5.26%.

8-(4-Methoxyphenyl)-7,8-dihydronaphtho[2, 3-d][1,3]dioxol-5(6H)-one (**7**): Color: Dark brown gummy solid. Yield: 60 %. M.p.: 273-275 °C. FT-IR (KBr, ν, cm^{-1}): 1673 (C=O), 2922 (C-H), 1607 (Ar, C=C). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.78 (s, 3H, OCH_3), 5.84 (s, 2H, O-CH_2-O-), 2.53 (tt, 2H, C_2-H), 1.24 (m, 2H, C_3-H), 3.16 (m, 1H, C4-H), 6.40 (s, 1H, Ar-H), 6.84 (d, 2H, Ar-H), 7.01-7.52 (m, 3H, Ar-H). MS (EI, *m/z*): 297 (M+1). Anal. calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.93; H, 5.46%.

3. Results and discussion

1-(Benzo[*d*][1,3]dioxol-6-yl) ethanone (**2**) was prepared in excellent yield by Friedel-Crafts acylation reaction of 1,3-benzodioxole with acetic anhydride in presence of fused zinc chloride (Scheme 1). The structure of compound **2** was confirmed by FT-IR and ^{1}H NMR spectra. The chalcones (**4a**, **5b**) were prepared in good yields by the Claisen-Schmidt condensation of 1-(benzo[*d*][1,3]dioxol-6-yl) ethanone (**2**) with benzaldehydes (**3a**,**b**) separately in the presence of sodium hydroxide in ethanol-water mixture [5,6]. The cyclopropyl ketones (**5a**,**b**) were prepared in high yields by the reaction of chalcones (**4a**,**b**) with trimethyl sulphoxonium iodide in presence of sodium hydride in dry benzene [7-9]. The tetralones (**6** and **7**) were prepared in good yields by the intramolecular cyclization of cyclopropyl ketones (**5a**,**b**) in presence of anhydrous stannic chloride and acetic anhydride in dry dichloromethane [10,11]. The structure of all the synthesized compounds was confirmed by FT-IR, ^{1}H NMR, Mass spectra and elemental analysis. The ^{1}H NMR spectrum of compound **6** showed distinct singlets at δ 6.58 and 7.53 ppm assignable to aromatic C_5-H and C_8-H, respectively. The tetralone protons showed absorption peaks at δ 2.62-2.68 ppm (tt, 2H, C_2-H), 1.25-1.40 ppm (m, 2H, C_3-H), 3.16 ppm (t, 1H, C_4-H). IR spectrum of the carbonyl group stretching frequency of compound **6** appeared at 1677 cm^{-1}.

4. Conclusion

In summary, a convenient synthesis of tetralones as intermediates for podophyllotoxin analogues has been developed. We have used environmental friendly chemicals and conditions. The chalcone method gave good yields of tetralones. They are very useful for the synthesis of analogues of podophyllotoxin.

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