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Anti-diabetic Activity of Synthetic Aryltetalin Derivatives

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Abstract

The aryltetralin derivatives were extracted from plant and also synthesized using tetralone as a starting material. They were synthesized by replacing 1,3-methylene dioxy ring with dimethoxy, hydroxy, methyl, chlorine, hydrogen and methoxy group. The structure of the final compounds was confirmed by ^{1}H NMR, ^{13}C NMR, mass spectra and elemental analysis data and the analogues were screened for anti-diabetic activity. It is noteworthy all the synthesized derivatives exhibits good anti-diabetic activity with respect to extracted aryltetralin compound.

Keywords: Podophyllotoxin • Bromination • Reduction • Antidiabetic activity

Introduction

Lignans are a very interesting class of natural products due to their pharmacological properties, their great number of structural possibilities and the chemical approaches to their synthesis [1]. In these lignan family, the cytotoxic podophyllotoxin has been the most studied is a potent tubulin binding antimitotic agent and its derivative etoposide and Teniposide is currently used in cancer chemotherapy [2]. Although the natural podophyllin resin was used in folk medicine, it was not until the 1940s that its antitumor activity was confirmed and this triggered intense studies toward synthetic routes led mainly on synthetic, structural and mechanistic aspects of podophyllotoxin provided much of the basis for the synthetic studies that followed. All the reported synthetic routes to 1 produced racemic material or involved classical resolution techniques [3].

In view of the above facts, it was decided to modify the structure of podophyllotoxin (Figure 1). They were synthesized by replacing 1,3-methylene dioxy ring with dimethoxy, hydroxy, methyl, chlorine, hydrogen and methoxy group. The synthesized podophyllotoxin analogues were screened for their biological activity [4-10].

Materials and Methods

All the 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-254). Acme, India silica gel, 60-120 mesh is used for column chromatography. IR spectra in KBr were recorded on Perkin-Elmer model 683 spectrometers. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded $CDCl_3$ solvent containing Tetra Methyl Silane (TMS) as internal references were recorded on Bruker spectrometer; Elemental analyses were performed on a Perkin-Elmer 2400. Mass spectra were obtained by Water-Q-TOF ultima spectrometer.

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Synthesis

General procedure for the synthesis of α-bromo derivative of 1-tetralone 3(a-f): The starting material 2a-f (4 mmol) in acetonitrile (50 mL) and *p*-toluene sulphonic acid (1.14 g, 6 mmol) was heated at 65 °C, N-bromosuccinimide (0.71 g, 4 mmol) was added slowly in lots over a period of 1 hour and the reaction mixture was stirred for 4-5 h. After completion of the reaction, reaction mixture was diluted with ethyl acetate (100 mL) and washed with water (2 × 50mL). The ethyl acetate layer was separated and evaporated to get the crude product. The obtained product again recrystallized with ethanol to get a pure product.

2-bromo-6, 7-dimethoxy-4-(3, 4, 5-trimethoxyphenyl)-3, 4-dihydronaphthalen-1(2H)-one 3a:

Color: light brown solid; M.p 168 °C; Yield: 75.18%. ^{1}H NMR: 7.58-7.05 (2 H, s, Ar-H), 6.52(2 H, s, Ar-H), 4.93(1 H, t, CH-Br), 4.04 (1 H, t, J=4.7, CH), 3.80(15 H, s, OCH_3), 2.69-2.45 (2 H, m, J=6.4, CH_2); ^{13}C NMR: 186.1, 154.7, 153.4, 147.2, 137.3, 136.7, 133.8, 127.3, 110.5, 109.2, 106.6, 60.8, 56.1, 53.9, 42.1, 39.9; MS, *m/z*: 452.15 (M+).

Anal. Calcd. For $C_{21}H_{23}BrO_6$: C, 55.89; H, 5.14; Br 17.70; O, 21.26 Found: C, 55.87; H, 5.04; Br 17.71; O, 21.29%.

2-bromo-6-hydroxy-4-(3, 4, 5-trimethoxyphenyl)-3, 4-dihydronaphthalen-1(2H)-one 3b:

Color: dark brown solid; M.p 171 °C; Yield: 75.18%. ^{1}H NMR: 8.15 (1 H, d, Ar-H), 7.12(1 H, d, Ar-H), 6.60-6.52(3 H, m, Ar-H),5.35(1 H, t, OH), 4.93(1 H, t, CH-Br), 4.04 (1 H, t, J=4.7, CH), 3.80(12 H, s, OCH_3), 2.69-2.45 (2 H, m, J=6.4, CH_2); ^{13}C NMR: 186.1, 161.9, 153.4, 141.9, 137.3, 136.7, 130.7, 126.6, 120.6, 113.3, 106.6, 60.8, 56.1, 53.9, 42.1, 39.9;MS, *m/z*: 408.15 (M+).

Anal. Calcd. For $C_{19}H_{19}BrO_5$: C, 56.03; H, 4.70; Br 19.62; O, 19.64 Found: C, 56.07; H, 4.71; Br 19.62; O, 19.64%.

2-bromo-6-methyl-4-(3, 4, 5-trimethoxyphenyl)-3, 4-dihydronaphthalen-1(2H)-one 3c:

Color: dark brown solid. Yield: 65.18%. ^{1}H NMR: 7.80-7.13 (3 H, d, Ar-H), 6.52(2 H, s, Ar-H), 4.93(1 H, t, CH-Br), 4.04 (1 H, t, J=4.7, CH), 3.80(12 H, s, OCH_3), 2.69-2.45 (2 H, m, J=6.4, CH_2) 2.34 (3 H, s, CH_3); ^{13}C NMR: 186.1, 153.4, 143.3, 140.4, 137.3, 136.7, 131.0, 128.0, 126.4, 125.2, 106.6, 60.8, 56.1, 53.9, 42.1, 39.9; MS, *m/z*: 406.15 (M+).

Anal. Calcd. For $C_{20}H_{21}BrO_4$: C, 59.27; H, 5.22; Br 19.72; O, 15.79 Found: C, 59.28; H, 5.21; Br 19.76; O, 15.76%.

2-bromo-6-chloro-4-(3,4,5-trimethoxyphenyl)-3, 4-dihydronaphthalen-1(2H)-one 3d:

Color: light brown solid. Yield: 71.18%. ^{1}H NMR: 7.86-7.39 (3 H, q, Ar-H), 6.52(2 H, s, Ar-H), 4.93(1 H, t, CH-Br), 4.04 (1 H, t, J=4.7, CH), 3.80(12 H, s, OCH_3), 2.69-2.45 (2 H, m, J=6.4, CH_2); ^{13}C NMR: 186.1, 165.5, 153.4, 141.9, 139.2, 137.3, 136.7, 132.1, 130.7, 127.9, 126.2, 106.6, 60.8, 56.1, 53.9, 41.1, 39.9; MS, *m/z*: 426.15 (M+).

Anal. Calcd. For $C_{19}H_{18}BrClO_4$: C, 53.61; H, 4.26; Br 18.77; Cl, 8.33, O, 15.03 Found C, 53.60; H, 4.25; Br 18.79; Cl, 8.31, O, 15.07%.

2-bromo-4-(3,4,5-trimethoxyphenyl)-3, 4-dihydronaphthalen-1(2H)-one 3e:

Color: brown coloured solid. Yield: 67.78%. ^{1}H NMR: 7.95- 7.35 (6 H, m, Ar-H), 6.52(2 H, s, Ar-H), 4.93(1 H, t, CH-Br), 4.04 (1 H, t, J = 4.7, CH), 3.80(12 H, s, OCH_3), 2.69-2.45 (2 H, m, J=6.4, CH_2); ^{13}C NMR: 186.1, 153.4, 140.5, 137.3, 136.7, 134.0, 133.6, 128.1, 126.1, 106.6, 60.8, 56.1, 53.9, 41.8, 39.9; MS, *m/z*: 390.15 (M+).

Anal. Calcd. For $C_{19}H_{19}BrO_4$: C, 58.33; H, 4.89; Br 20.42; O, 16.36 Found: C, 58.34; H, 4.83; Br 20.45; O, 16.37%.

2-bromo-6-methoxy-4-(3,4,5-trimethoxyphenyl)-3,4-dihydronaphthalen-1(2H)-one 3f:

Color: dark brown solid. Yield: 69.98%. ^{1}H NMR: 8.25- 6.89 (3 H, s, Ar-H), 6.52(2 H, s, Ar-H), 4.93(1 H, t, CH-Br), 4.04 (1 H, t, J = 4.7, CH), 3.80(12 H, s, OCH_3), 2.69-2.45 (2 H, m, J=6.4, CH_2); ^{13}C NMR: 186.1, 165.5, 153.4, 147.2, 137.3, 136.7, 133.8, 127.3, 110.5, 109.2, 106.6, 60.8, 56.1, 53.9, 42.1, 39.9; MS, *m/z*: 422.15 (M+).

Anal. Calcd. For $C_{20}H_{21}BrO_5$: C, 57.09; H, 5.04; Br 18.97; O, 18.99 Found: C, 57.07; H, 5.01; Br 18.99; O, 18.97%.

General procedure for the preparation of 4-(3, 4, 5-trimethoxyphenyl) naphthalen-1(4h)-one 4(a-f): A mixture of 3a-f (3 mmol) and Sodium-tertiary-butoxide (0.317 g, 3.3 mmol) in THF (25 mL) was refluxed at room temperature under nitrogen atmosphere for 10 hours. The progress of the reaction was monitored by TLC which showed the absence of starting material in the reaction mixture. After completion of the reaction, reaction mixture was poured into water (100 mL) and extracted with ethyl acetate (50 mL). The evaporation of the ethyl acetate layer gave crude product. This was purified by ethyl acetate/hexane (90: 10 v/v) on silica gel to get pure product.

6, 7-dimethoxy-4-(3, 4, 5-trimethoxyphenyl) naphthalen-1(4H)-one 4a:

Color: pale yellow solid; M.p. 118OC; Yield: 70.18%. ^{1}H NMR: 7.21-7.09 (2 H, d, Ar-H), 6.88 (1 H, d,α-CH), 6.86 (1 H, d, ββ-CH), 6.46 (2 H, s, Ar-H), 4.74 (1 H, t, J = 4.7, CH), 3.89(15 H, s, OCH_3); ^{13}C NMR: 183.7, 156.1, 153.4, 147.8, 139.7, 136.7, 136.2, 134.6, 131.9, 126.3, 113.8, 106.7, 104.3, 60.8, 56.1, 47.4; MS, *m/z*: 372.15 (M+).

Anal. Calcd. For $C_{20}H_{22}O_6$: C, 68.10; H, 5.94; O, 25.99 Found: C, 68.07; H, 5.91; O, 25.97%.

6-hydroxy-4-(3, 4, 5-trimethoxyphenyl) naphthalen-1(4H)-one 4b:

Color: cream coloured solid; M.p. 128 OC; Yield: 65.08%. ^{1}H NMR: 7.61-7.10 (2 H, d, Ar-H), 6.86 (1 H, d,α-CH), 6.82(1 H, d, β-CH), 6.46(2 H, s, Ar-H), 6.79 (1 H, d, Ar-H), 5.30(1 H, s, OH), 4.79 (1 H, t, J=4.7, CH), 3.89(9 H, s, OCH_3); ^{13}C NMR: 183.7, 163.3, 153.4, 140.0, 139.7, 136.7, 136.2, 134.6, 130.2, 125.6, 114.4, 113.9, 104.3, 60.8, 56.1, 47.4; MS, *m/z*: 342.15 (M+).

Anal. Calcd. For $C_{18}H_{19}O_5$: C, 69.95; H, 5.57; O, 24.51 Found: C, 69.97; H, 5.56; O, 24.50%.

6-methyl-4-(3, 4, 5-trimethoxyphenyl) naphthalen-1(4H)-one 4c:

Color: cream coloured solid. Yield: 75.18%. ^{1}H NMR: 7.65-7.23 (3 H, m, Ar-H), 6.89 (1 H, d, α α-CH), 6.86(1 H, d, β β-CH), 6.46(2 H, s, Ar-H), 4.76 (1 H, t, J=4.7, CH), 3.89(9 H, s, OCH_3,), 2.35(3 H, s, CH_3); ^{13}C NMR: 183.7, 153.4, 144.7, 139.7, 138.5, 136.7, 136.2, 134.6, 130.6, 130.3, 130.0, 127.0, 104.3, 60.8, 56.1, 47.4, 21.6; MS, *m/z*: 324.15 (M+).

Anal. Calcd. For $C_{20}H_{20}O_4$: C, 74.07; H, 6.21; O, 19.73 Found: C, 74.09; H, 6.19; O, 19.75%.

6-chloro-4-(3, 4, 5-trimethoxyphenyl) naphthalen-1(4H)-one 4d:

Color: light yellow coloured solid. Yield: 75.18%. ^{1}H NMR: 7.71-7.49 (3 H, m, Ar-H), 6.89 (1 H, d, α-CH), 6.86(1 H, d, ββ-CH), 6.46(2 H, s, Ar-H), 4.86 (1 H, t, J=4.7, CH), 3.92(9 H, s, OCH_3); ^{13}C NMR: 183.7, 153.4, 140.7, 140.0, 139.7, 136.7, 136.2, 134.6, 131.8, 131.1, 128.5, 126.8, 104.3, 60.8, 56.1, 46.4; MS, *m/z*: 344.15 (M+).

Anal. Calcd. For $C_{19}H_{17}ClO_4$: C, 66.19; H, 4.97; Cl, 10.28; O, 18.56 Found: C, 66.17; H, 4.99; Cl, 10.26; O, 18.58%.

4-(3, 4, 5-trimethoxyphenyl) naphthalen-1(4H)-one 4e:

Color: cream coloured solid. Yield: 75.18%. ^{1}H NMR: 7.71-7.49 (3 H, m, Ar-H), 6.89 (1 H, d, α-CH), 6.86(1 H, d, β-CH), 6.46(2 H, s, Ar-H), 4.86 (1 H, t, J=4.7, CH), 3.92(9 H, s, OCH_3); ^{13}C NMR: 183.7, 153.4, 139.7, 138.6, 136.7, 136.2, 135.0, 134.6, 133.0, 128.7, 127.9, 126.7, 104.3, 60.8, 56.1, 47.4; MS, *m/z*: 311.15 (M+).

Anal. Calcd. For $C_{19}H_{18}O_4$: C, 73.54; H, 5.85; O, 20.62 Found: C, 73.53; H, 5.86; O, 20.64%.

6-methoxy-4-(3, 4, 5-trimethoxyphenyl) naphthalen-1(4H)-one 4f:

Color: Cream coloured solid. Yield: 75.18%. ^{1}H NMR: 7.61-7.20 (1 H, d, Ar-H), 6.99 (1H d Ar-H), 6.86 (1H, d, α -CH), 6.82(1 H, d, ββ -CH), 6.46(2 H, s, Ar-H), 4.70 (1 H, t, J = 4.7, CH), 3.79(12 H, s, OCH_3); ^{13}C NMR: 183.7, 166.9, 153.4, 139.7, 139.6, 136.7, 136.2, 134.6, 129.8, 125.3, 112.8, 112.3, 104.3, 60.8, 56.1, 47.4; MS, *m/z*: 342.15 (M+).

Anal. Calcd. For $C_{20}H_{20}O_5$: C, 70.57; H, 5.92; O, 23.50 Found: C, 70.58; H, 5.91; O, 23.52%.

General procedure for the preparation of 3-bromomethyl-4-oxo-1-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene-2-carbonitrile 5(a-f): Potassium cyanide (0.1625 g, 2.5 mmol) was added to the reaction mixture of compound 4a-f (2.5 mmol), tetra butyl ammonium bromide (0.08 g, 0.25 mmol) and dibromomethane (0.64 g, 3.75 mmol) which were stirred under nitrogen gas atmosphere at room temperature using dried THF solvent (25 mL) and refluxed for 5 hours at 60^{0}C. After completion of the reaction which was monitored by TLC, the reaction mixture was evaporated to dryness and extracted with water (100 mL) followed by Diethyl ether (50 mL). The organic layer was separated and was evaporated to dryness. The obtained solid compound was purified by column chromatography on silica gel using hexane/ethyl acetate (80:20 v/v).

3-(bromomethyl)-6, 7-dimethoxy-4-oxo-1-(3, 4, 5-trimethoxyphenyl)-1, 2, 3, 4-tetrahydronaphthalene-2-carbonitrile 5a: Color: yellowish solid; M.p 152 °C; Yield: 62.88%. ^{1}H NMR: 8.20 (1 H, d, Ar-H), 7.13 (2 H, s, Ar-H), 6.52-6.60 (2 H, t, Ar-H), 5.32(1 H, s OH), 4. 07 (1 H, d, J=4.0, CH), 3.83(9 H, s, OCH_3), 3.80(1 H, t, CH-CN), 3.58-3.33(3 H, m, CH_2-Br), 2.35(3 H, s, CH_3); ^{13}C NMR: 199.1, 161.9, 153.4, 141.9, 137.3, 136.7, 130.7, 126.6, 120.6, 119.2, 113.3, 106.6, 60.8, 56.1, 49.0, 36.7, 30.4, 26.8; MS, *m/z*: 492.15 (M+).

Anal. Calcd. For $C_{23}H_{24}BrNO_6$: C, 56.34; H, 4.93; Br, 16.30; N, 2.86; O, 19.58 Found: C, 56.38; H, 4.92; Br, 16.31; N, 2.15; O, 17.92%.

3-(bromomethyl)-7-hydroxy-4-oxo-1-(3, 4, 5-trimethoxyphenyl)-1, 2, 3, 4-tetrahydronaphthalene-2-carbonitrile 5b: Color: buff coloured solid; M.p. 164°C. Yield: 63.18%. ^{1}H NMR: 8.20 (1 H, d, Ar-H), 7.13 (2 H, s, Ar-H), 6.52-6.60 (2 H, t, Ar-H), 5.32(1 H, s OH), 4. 07 (1 H, d, J=4.0, CH), 3.83(9 H, s, OCH_3), 3.80(1 H, t, CH-CN), 3.58-3.33(3 H, m, CH_2-Br), 2.35(3 H, s, CH_3); ^{13}C NMR: 199.1, 161.9, 153.4, 141.9, 137.3, 136.7, 130.7, 126.6, 120.6, 119.2, 113.3, 106.6, 60.8, 56.1, 49.0, 36.7, 30.4, 26.8; MS, *m/z*: 447.15 (M+).

Anal. Calcd. For $C_{21}H_{20}BrNO_5$: C, 56.52; H, 4.52; Br, 17.90; N, 3.14; O, 17.97 Found: C, 56.58; H, 4.58; Br, 17.93; N, 3.15; O, 17.92%.

3-(bromomethyl)-7-methyl-4-oxo-1-(3, 4, 5-trimethoxyphenyl)-1, 2, 3, 4-tetrahydronaphthalene-2-carbonitrile 5c: Color: yellow coloured solid; M.p. 174 °C; Yield: 75.18%; ^{1}H NMR: 7.80 (1 H, d, Ar-H), 7.24-7.13 (2 H, d, Ar-H), 6.52 (2 H, s, Ar-H), 4. 05 (1 H, d, J=4.0, CH), 3.93(9 H, s, OCH_3), 3.80(1 H, t, CH-CN), 3.58-3.33(2 H, m, CH2-Br), 3.4(1 H, q, CH), 2.35(3 H, s, CH_3); ^{13}C NMR: 199.1, 153.4, 143.3, 140.4, 137.3, 136.7, 131.0, 128.0, 126.4, 125.2, 119.2, 106.6, 60.8, 56.1, 49.0, 36.7, 30.4, 26.8, 21.6; MS, *m/z*: 432.15 (M+).

Anal. Calcd. For $C_{22}H_{22}BrNO_4$: C, 59.47; H, 4.99; Br, 17.98; N, 3.16; O, 14.47 Found: C, 59.48; H, 4.98; Br, 17.99; N, 3.15; O, 14.40%.

3-(bromomethyl)-7-chloro-4-oxo-1-(3, 4, 5-trimethoxyphenyl)-1, 2, 3, 4-tetrahydronaphthalene-2-carbonitrile 5d:

Color: light yellow solid; M.p. 154 °C; Yield: 75.18%; ^{1}H NMR: 7.80 (1 H, d, Ar-H), 7.24-7.13 (2 H, d, Ar-H), 6.52 (2 H, s, Ar-H), 4. 05 (1 H, d, J=4.0, CH), 3.93(9 H, s, OCH_3), 3.80(1 H, t, CH-CN), 3.58-3.33(2 H, m, CH_2-Br), 3.4(1 H, q, CH), 2.35(3 H, s, CH_3); ^{13}C NMR: 199.1, 153.4, 143.3, 140.4, 137.3, 136.7, 131.0, 128.0, 126.4, 125.2, 119.2, 106.6, 60.8, 56.1, 49.0, 36.7, 30.4, 26.8, 21.6; MS, *m/z*: 432.15 (M+).

Anal. Calcd. For $C_{22}H_{22}BrNO_4$: C, 59.47; H, 4.99; Br, 17.98; N, 3.16; O, 14.47 Found: C, 59.48; H, 4.98; Br, 17.99; N, 3.15; O, 14.40%.

3-(bromomethyl)-4-oxo-1-(3, 4, 5-trimethoxyphenyl)-1, 2, 3, 4-tetrahydronaphthalene-2-carbonitrile 5e:

Color: dark yellow coloured solid; M.p. 169 °C; Yield: 75.18%; ^{1}H NMR: 7.92-7.35 (4 H, m, Ar-H), 6.56(2 H, s, Ar-H), 4. 0 (1 H, d, J=4.0, CH), 3.92(9 H, s, OCH_3), 3.78(1 H, t, CH-CN), 3.58-3.33(2 H, m, CH_2-Br), 3.4(1 H, q, CH); ^{13}C NMR: 199.1, 153.4, 140.5, 137.3, 136.7, 134.0, 133.6, 128.1, 126.1, 119.2, 106.6, 60.8, 56.1, 49.0, 36.4, 30.4, 26.8; MS, *m/z*: 432.15 (M+).

Anal. Calcd. For $C_{21}H_{20}BrNO_4$: C, 58.62; H, 4.68; Br, 18.57; N, 3.26; O, 14.87 Found: C, 58.65; H, 4.65; Br, 18.58; N, 3.25; O, 14.89%.

3-(bromomethyl)-7-methoxy-4-oxo-1-(3, 4, 5-trimethoxyphenyl)-1, 2, 3, 4-tetrahydronaphthalene-2-carbonitrile 5f: Color: dark yellow coloured solid; M.p. 179 °C; Yield: 75.18%; ^{1}H NMR: 7.88-7.39 (3 H, m, Ar-H), 6.58(2 H, s, Ar-H), 4. 08 (1 H, d, J=4.0, CH), 3.82(9 H, s, OCH_3), 3.76(1 H, t, CH-CN), 3.58-3.33(2 H, m, CH_2-Br), 3.45(1 H, m, CH); ^{13}C NMR: 199.1, 153.4, 141.9, 139.2, 137.3, 136.7, 132.1, 130.7, 127.9, 127.9, 119.2, 106.6, 60.8, 56.1, 49.0, 35.9, 30.4, 26.8; MS, *m/z*: 466.15 (M+).

Anal. Calcd. For $C_{21}H_{19}BrClNO_4$: C, 54.27; H, 4.12; Br, 17.19; Cl, 7.63; N, 3.01; O, 13.77 Found: C, 54.24; H, 4.11; Br, 17.18; Cl, 7.63; N, 3.05; O, 13.78%.

General procedure for the synthesis of 9-(3, 4, 5-trimethoxyphenyl)-3, 3a, 9, 9a-tetrahydronaphtho [2, 3-c] furan-1, 4-dione 6(a-f): To a stirred solution of compound 5a-f (0.980 g, 2 mmol) 20% sulphuric acid was added and refluxed at 90 °C for 15 hours. After completion of the reaction, the reaction mixture was poured into ice, extracted with ethyl acetate and then ethyl acetate was evaporated to get crude solid which was purified by column chromatography on silica gel using hexane/ethyl acetate (80: 20 v/v).

6,7-dimethoxy-9-(3,4,5-trimethoxyphenyl)-3, 3a, 9, 9a-tetrahydronaphtho[2,3-c]furan-1,4-dione 6a:

Color: white coloured solid; M.p. 151 °C; Yield: 68.98%; IR: 1635 cm^{-1}(benzylic C=O), 1755 cm^{-1} (lactone C=O);^{1}H NMR: 7.98-7.35 (4 H, m, Ar-H), 6.58(2 H, s, Ar-H), 4. 68 (2 H, d, J=4.0, CH), 3.83(9 H, s, OCH_3), 4.58-3.59 (6 H, t, CH_2); ^{13}C NMR: 193.3, 175.4, 153.4, 140.5, 136.7, 136.1, 133.6, 134.0, 128.1, 126.1, 106.6, 69.3, 60.8, 56.1, 47.0, 46.7, 43.5;MS, *m/z*: 369.15 (M+).

Anal. Calcd. For $C_{21}H_{20}O_6$: C, 68.47; H, 5.47; O, 26.06 Found: C, 68.49; H, 5.44; O, 26.08%.

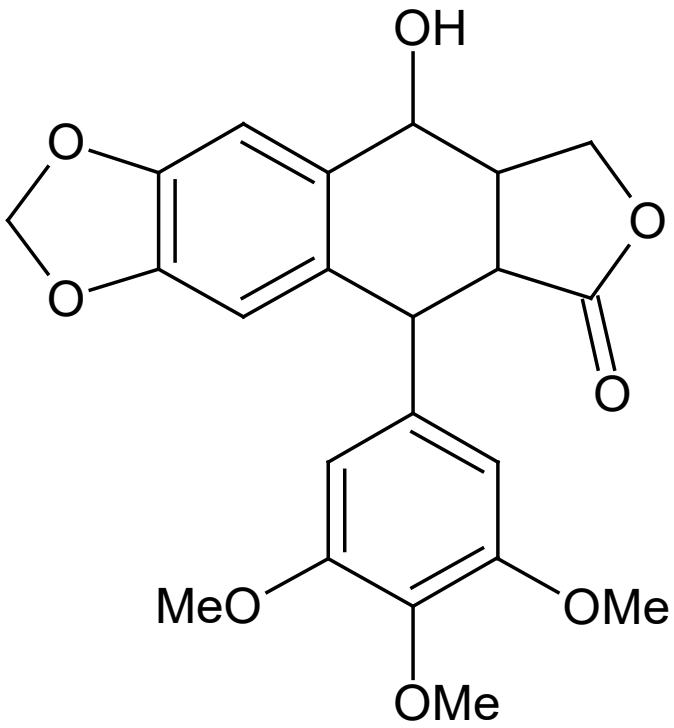

Figure 1. The structure of podophyllotoxin.

7-hydroxy-9-(3, 4, 5-trimethoxyphenyl)-3, 3a, 9, 9a-tetrahydronaphtho [2, 3-c] furan-1, 4-dione 6b:

Color: white coloured solid; M.p. 158 °C; Yield: 68.09%; IR: 1675 cm^{-1}(benzylic C=O), 1795 cm^{-1} (lactone C=O);^{1}H NMR: 7.98-7.35 (4 H, m, Ar-H), 6.58(2 H, s, Ar-H), 4. 68 (2 H, d, J=4.0, CH), 3.83(9 H, s, OCH_3), 4.58-3.59 (6 H, t, CH_2); ^{13}C NMR: 193.3, 175.4, 153.4, 140.5, 136.7, 136.1, 133.6, 134.0, 128.1, 126.1, 106.6, 69.3, 60.8, 56.1, 47.0, 46.7, 43.5; MS, *m/z*: 369.15 (M+).

Anal. Calcd. For $C_{21}H_{20}O_6$: C, 68.47; H, 5.47; O, 26.06 Found: C, 68.49; H, 5.44; O, 26.08%.

7-methyl-9-(3, 4, 5-trimethoxyphenyl)-3, 3a, 9, 9a-tetrahydronaphtho [2, 3-c] furan-1, 4-dione 6c:

Color: white coloured solid; M.p. 167 °C; Yield: 65.68%; IR: 1635 cm^{-1}(benzylic C=O), 1755 cm^{-1} (lactone C=O); ^{1}H NMR: 7.98-7.35 (4 H, m, Ar-H), 6.58(2 H, s, Ar-H), 4. 68 (2 H, d, J=4.0, CH), 3.83(9 H, s, OCH_3), 4.58-3.59 (6 H, t, CH_2); ^{13}C NMR: 193.3, 175.4, 153.4, 140.5, 136.7, 136.1, 133.6, 134.0, 128.1, 126.1, 106.6, 69.3, 60.8, 56.1, 47.0, 46.7, 43.5; MS, *m/z*: 369.15 (M+).

Anal. Calcd. For $C_{21}H_{20}O_6$: C, 68.47; H, 5.47; O, 26.06 Found: C, 68.49; H, 5.44; O, 26.08%.

7-chloro-9-(3, 4, 5-trimethoxyphenyl)-3, 3a, 9, 9a-tetrahydronaphtho [2, 3-c] furan-1, 4-dione 6d:

Color: white coloured solid; M.p. 161 °C; Yield: 86.78%; IR: 1635 cm^{-1}(benzylic C=O), 1755 cm^{-1} (lactone C=O); ^{1}H NMR: 7.98-7.35 (4 H, m, Ar-H), 6.58(2 H, s, Ar-H), 4. 68 (2 H, d, J=4.0, CH), 3.83(9 H, s, OCH_3), 4.58-3.59 (6 H, t, CH_2); ^{13}C NMR: 193.3, 175.4, 153.4, 140.5, 136.7, 136.1, 133.6, 134.0, 128.1, 126.1, 106.6, 69.3, 60.8, 56.1, 47.0, 46.7, 43.5; MS, *m/z*: 369.15 (M+).

Anal. Calcd. For $C_{21}H_{20}O_6$: C, 68.47; H, 5.47; O, 26.06 Found: C, 68.49; H, 5.44; O, 26.08%.

9-(3, 4, 5-trimethoxyphenyl)-3, 3a, 9, 9a-tetrahydronaphtho [2, 3-c] furan-1, 4-dione 6e:

Color: white coloured solid; M.p. 171 °C; Yield: 75.78%; IR: 1675 cm^{-1}(benzylic C=O), 1785 cm^{-1} (lactone C=O); ^{1}H NMR: 7.98-7.35 (4 H, m, Ar-H),

6.58(2 H, s, Ar-H), 4. 68 (2 H, d, J=4.0, CH), 3.83(9 H, s, OCH_3), 4.58-3.59 (6 H, t, CH_2); ^{13}C NMR: 193.3, 175.4, 153.4, 140.5, 136.7, 136.1, 133.6, 134.0, 128.1, 126.1, 106.6, 69.3, 60.8, 56.1, 47.0, 46.7, 43.5; MS, *m/z*: 369.15 (M+).

Anal. Calcd. For $C_{21}H_{20}O_6$: C, 68.47; H, 5.47; O, 26.06 Found: C, 68.49; H, 5.44; O, 26.08%.

7-methoxy-9-(3, 4, 5-trimethoxyphenyl)-3, 3a, 9, 9a-tetrahydronaphtho [2, 3-c] furan-1, 4-dione 6f:

Color: white coloured solid; M.p. 167 °C; Yield: 95.28%; IR: 1635 cm^{-1}(benzylic C=O), 1755 cm^{-1} (lactone C=O); ^1H NMR: 8.21-8.30 (1 H, d, Ar-H), 7.16(1 H, s, Ar-H), 7.05-7.07(1 H, d, Ar-H), 6.70(2 H, s, Ar-H), 4. 70-4.48 (4 H, m, Ar-CH), 3.83(12 H, s, OCH_3), 3.65-3.63 (4 H, t, CH_2); ^{13}C NMR: 193.7, 175.0, 165.5, 153.4, 149.3, 136.7, 136.1, 130.3, 126.3, 111.7, 106.6, 104.6, 69.3, 60.8, 56.1, 55.8, 46.7, 44.1, 43.5; MS, *m/z*: 398.45 (M+) (Figure 2).

Anal. Calcd. For $C_{22}H_{22}O_7$: C, 66.32; H, 5.57; O, 28.11 Found: C, 66.33; H, 5.59; O, 28.09%.

Results and Discussion

Synthesis

Bromination of the compound 2(a-f) was carried out in acetonitrile using N-bromo succinimide as the brominating agent. The conditions adopted are a modification of the reported procedure. The bromination happened selectively at the α-position to the carbonyl group of the tetralone. The selective bromination of the compound 2(a-f) was performed using N-bromosuccinimide in acidic medium by maintaining optimum temperature of 70 °C in acetonitrile solvent. Using of N-bromosuccinimide is to activate the *p*-toluene sulphonic acid at the carbonyl oxygen to facilitate the formation of bromonium ions that leads to the formation of α-bromo tetralones. Single time addition of NBS resulted in the formation of more dibromo derivative. An excess of NBS also resulted in the formation of dibromo derivative. Hence one equivalent of NBS was added slowly in lots. The progress of the reaction was monitored by TLC.

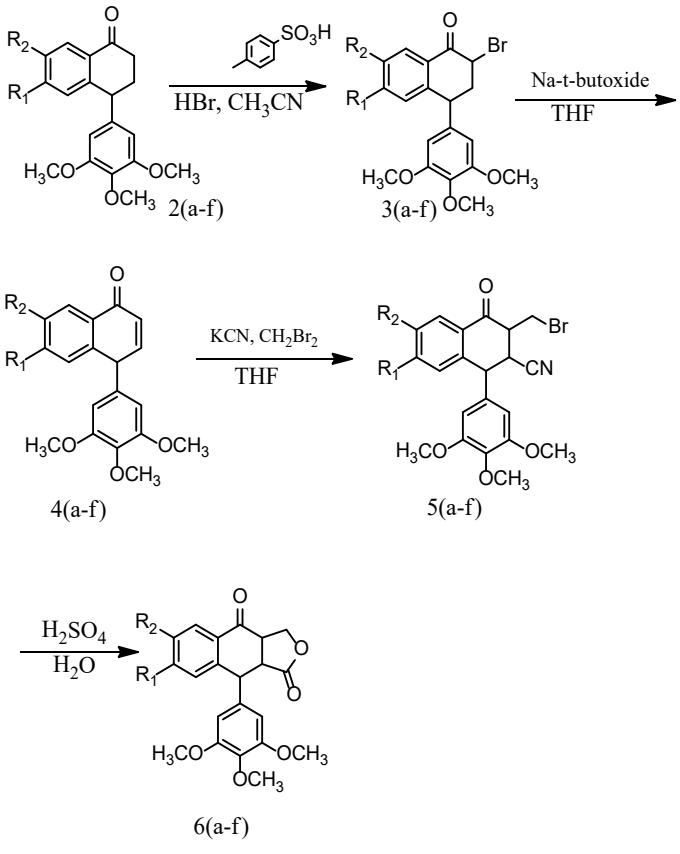

Figure 2. Protocol for the synthesis of podophyllotoxin analogues.

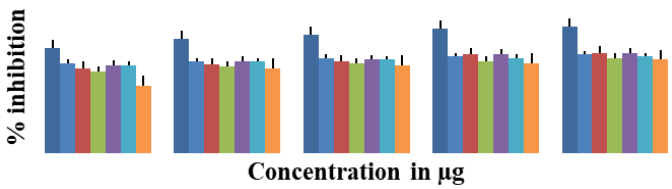

Figure 3. Pancreatic α-amylase inhibition of aryltetralin derivatives 6(a-f). The compounds were taken in micro molar concentration; the above said method is followed. The reference compound was treated as same without the compound treatment and taken as 100%.

Table 1. Pancreatic α-amylase inhibition of aryl tetralin derivatives 6(a-f).

Where	R_1	R_2
a	OCH_3	OCH_3
b	H	OH
c	H	CH_3
d	H	Cl
e	H	H
f	H	OCH_3

The impurities were removed during crystallization. The reaction mixture after the completion of the reaction was washed with water and extracted with ethyl acetate. The ethyl acetate layer was evaporated to get the product which was recrystallized from 10% ethanol in hexane to give the product. The products were identified using ^1H and ^{13}C-NMR. ^1H NMR showed characteristic triplet at δ 4.7-4.93 ppm for hydrogen at the carbon bearing the bromo group. The tertiary hydrogen at γ-carbon to the carbonyl showed a triplet δ 4.05-4.48 ppm. ^{13}C-NMR showed carbonyl carbon at δ 186.10 ppm. The mass spectrums of M-1, M+1 peak are observed in the ratio of 50.5: 49.5 indicating the presence of bromine atom in the compound.

The brominated tetralone was dehydrohalogenated to the compound 4(a-f). The reaction mixture was refluxed using sodium-tertiary-butoxide in THF as a solvent for 10 hour under nitrogen atmosphere. Use of milder bases like triethyl amine and sodium carbonate led to lesser yield and incomplete reaction. Slight excess of sodium-tertiary-butoxide caused faster reaction but lesser yield after purification, the optimum amount of base was critical for the reaction. Hence THF was found to be the ideal solvent for the reaction. The product was identified by ^1H-NMR and ^{13}C-NMR and mass spectra and IR spectra. Mass spectra showed absence of peaks associated with bromine atom. The ^1H-NMR showed signal at δ 6.8-7.1 ppm for the protons across the double bond. The absence of multiplet also at δ 2.6 ppm also confirms the formation of the product.

Potassium cyanide solution was added to the mixture of dibromomethane and tetra-n-butylammonium bromide in dry THF under nitrogen atmosphere which was kept at 60 °C. The progress of the reaction was monitored by TLC. The products were identified by ^1H-NMR and mass spectra. ^1H-NMR did not show signals at δ 6.8 ppm indicating the absence of double bond protons. It showed a doublet at δ 3.5 ppm for the protons on carbon bearing the bromine atom. ^{13}C-NMR shows signals at δ 119.3 ppm indicates the presence of the cyanide group. The carbonyl group is intact at δ 200.4 ppm.

The 3-bromomethyl-1-phenyl-1, 2, 3, 4-tetrahydronaphthalene-2-carbonitrile was added to 20% sulphuric acid and refluxed for 15 hours. The reaction mixture was poured into ice and extracted with ethyl acetate. The crude compound is purified by column chromatography on silica gel using ethyacetate/hexane (80:20). IR spectra showed two strong carbonyl absorptions, one at 1755 cm^{-1} attributed to the lactone ring and the other at 1635 cm^{-1} attributed to a benzylic carbonyl group. ^1H-NMR of the compound shows signals of doublet at δ 4.5 ppm and at δ 4.7 ppm indicating the protons at C-1 and C-9. Multiplets are seen at δ 3.5 ppm which indicates the protons on the carbon in the tetrahydro naphthalene ring system. ^{13}C-NMR shows signals as singlet at δ 176 ppm pertaining to the carbonyl group of the lactone moiety while the carbonyl on the tetralone ring shows as singlet at δ 200.7 ppm [11].

Anti-diabetic activity

The new synthetic analogues were screened for antidiabetic activity by determining the ability of compounds to inhibit alpha amylase by DNS method and by measuring the non-enzymatic albumin glycosilation. In this study, amylase activity for synthesized compounds was assayed according to Bernfeld method (Bernfeld). This assay is based on the oxidation of ketone functional group in synthesized compounds. The principal involved is the test for the presence of free carbonyl group (C=O), the so called reducing sugar. One mole of sugar will react with one mole of 3, 5- dinitrosalicylic acid. Simultaneously 3, 5-dinitrosalicylic acid (DNS) is reduced to 3-amino, 5- nitro salicylic acid under alkaline conditions [11].

The Pancreatic α-amylase inhibition of podophyllotoxin analogues 6(a-f) were studied in terms of oxidation of ketone functional group using DNS method (Figure 3). All the analogues inhibited α-amylase enzyme significantly with an IC_{50} values ranging between 23.25 µg/mL and 46.5 µg/mL compared to the reference compound acarbose with an IC_{50} value of 95.8 µg/mL (Table 1).

Conclusion

In conclusion, the new podophyllotoxin analogues has been synthesized successively in good yield and The structures of synthesized compounds were confirmed and characterized by analytical data's such as IR, ^{1}H NMR, ^{13}C NMR, Mass spectra and elemental analysis. They were screened for biological activity and showed good alpha amylase inhibition assay.

Acknowledgement

None.

Conflict of Interest

The authors declare no conflicts of interest.

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