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Synthesis and Study of Antimitotic Activities of Novel Analogues of Podophyllotoxin

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KEYWORDS

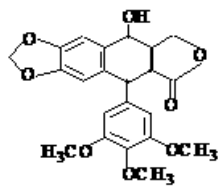
β-apopicropodophyllin, analogues, Tetralone esters, p-TsCl/py

ABSTRACT:

Podophyllotoxin derivatives and analogues show conspicuous antimitotic and other biological activities. The present study was concentrated on synthesis of novel analogues of podophyllotoxinande their study of antimitotic activities. β-apopicropodophyllin analogues, 1- Hydroxy-2-hydroxylmethyl-3-carboxy-4-(p-tolyl)-6, 7-dimethoxy - 1,2,3,4-tetrahydronaphthalene, 6-methoxy-7-methyl-9-p-tolyl naphtho [2.3-C] furan-1- (3H, 4H, 9H) one, 7-Chloro-6-methoxy-9-p-tolyl naphtho [2, 3-C] furan-1- (3H, 4H, 9H) one and 9-Cyclohexyl-6, 7-dimethoxy naphtho- [2,3-C] furan-1- (3H, 4H, 9H) one were synthesized using tetralone esters and its derivatives. The structures were confirmed by Proton NMR, IR,Massspectroscopy and C H analysis. ID_{50} 1.709x 10^{-6}M,1.862x 10^{-6} M, 1.587x 10^{-6} M and 1.784x 10^{-6} M were relatively lower to that of Podophyllotoxin (I) and ß-apopicropodophyllin having ID_{50} 4.290 x 10^{-6}M and 2.870 x 10^{-6}M shows more than 65%, a high inhibition activity to that parent compounds. Thus, new synthetic analogues find lot scopes in medicinal chemistry.

1. Introduction

Podophyllotoxin(**I**)[1]isa strong antimitotic agent, which has been extracted from two important medicinal plants named Podophyllum emodi an Indian species and Podophyllum peltatum a North American species that belong to the family of berbideracea[2]. The structure was confirmed by total synthesis of podophyllotoxin by Gensler[3]. Later it was synthesized by shorter routes [4, 5]. Number of asymmetric syntheses of podophyllotoxin has also been achieved recently [6, 7].



1

Podophyllotoxin(I) and several of its analogues show wide variety of biological activities such as cathartic, cytotoxic, antimitotic, anticancer, anti-tropical skin disease, antimalarial, virucidal, fungicidal[8, 9]etc. Podophyllotoxin derivatives and vinca alkaloids were the only drugs found markedly inhibit DNA ligases from normal cells [10]. Highly purified Podophyllotoxin (**1**) efficiently suppress in-vitro and in-vivo immune responses.

Podophyllotoxin(I) is found to have strong antimitotic activity, its wider use as the therapeutic agent in the treatment of neoplastic disease is restricted due to the toxic side effects, unfavourable solubility properties and its ready epimerization to picropodophyllin (**II**) which is not so active[11].β-Apopicropodophyllin (**III**),a dehydrated isomerised product of podophyllotoxin acts as a much stronger antimitotic agent[10]. The total

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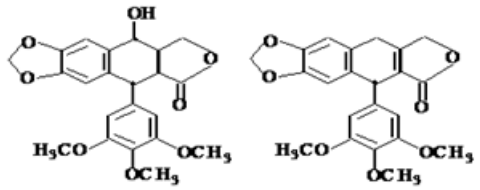
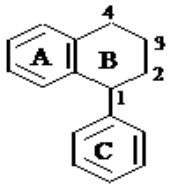
synthesis of β-apopicropodophyllin(**III**). The total synthesis of β-apopicropodophyllin (**III**)was carried out by Gensler et al [12, 13]. Very recently the asymmetric total synthesis of β-apopicropodophyllin (**III**)was prepared for the first time from podophyllotoxin(**I**)by a three-steps procedure by Schrecker and Hartwell[14]. Recently a convenient one step procedure for the preparation ofβ-apopicropodophyllin (**III**)frompodophyllotoxin(**I**)in excellent yield have been reported by Murthy and coworkers[15].



II III

The antimitotic activity, pharmacology and toxicity of these podophyllotoxin analogues have been reviewed [16]. The characteristic feature of podophyllotoxin molecule is the trans fused lactone ring imparting considerable rigidity to the geometry of the hydro aromatic ring. As a result, trimethoxy phenyl group takes an axial conformation that is very close to the neighbouring groups. The molecular model of podophyllotoxin also reveals that trans fused ring **B** is not only rigid but also strained. Where as in picropodophyllin (II) cis fused lactone ring allows considerable flexibility and trimethoxy phenyl ring can move into a less crowded space. These factors contribute more in promoting the ready base catalyzed epimerization of podophyllotoxin at its C_2 Position to a diastereomer picropodophyllin (II)

The strong antimitotic activity of podophyllotoxin and several of its analogueshas led to the investigation of structure activity relationship [17]. Schreir and coworkers have studied structure activity relationship of podophyllotoxin derivatives by modification of the lactone ring, ring **B** and change the substituents in ring **C**[18]. On the basis of the P-815 mastocytoma cell culture of the mouse, Schreier has summarized the structural requirements for biological activity among the podophyllotoxin analogues.



Gensler and coworkers[19] synthesized several non-lactone analogues of podophyllotoxin (**1**). These analogues showed strong antimitotic activity, but were less active than the parent compound (**I**).

Recently Murthy and coworkers have synthesized several derivatives and analogues of β-apopicropodophyllin (**III**) [20].After determining the antimitotic activity, some compounds are more active than the parent compound (**1**) and some are less active. It was further shown that functionalization of the hydro aromatic ring **B** of **III**with a group such as primary amino group or an epoxide ring (flanking the ring **B** and the lactone ring) or keto epoxide or diketone enhance the antimitotic activity of the parent compound (**I)**.The fact that some of the analogues retained their activity, despite the absence of lactone ring is contradictory to the hypothesis that biological activity involves acylation.The above studies of antimitotic activity of analogues of podophyllotoxin(**I**) or β-apopicropodophyllin (**II**) shows that the molecule possibly acts on a cell constituent not by covalent bond formation, but instead by non-covalent combination. There are evidences of neutral compounds like steroids binding to proteins by hydrophobic forces [21].

There has been growing evidence for the speculation that spindle poisons such as Colchicine, Vinblastine, and podophyllotoxin(**I**) are potent antimitotic agents and they act by destroying the function of microtubules, which constitute the spindle in the cell[22]. It has also been demonstrated that these spindle poisons bind non-covalently to the tubulin, the protein building block of microtubules, and that this binding inhibits mitosis in the cell. But still speculation has been made about β-apopicropodophyllin derivatives with substituents such as a nucleophylic amino group or an electrophylic epoxide ring might act through covalent bonding on some critical cell constituent[23]An interesting observation from Schreier and his coworkers is that tridemethoxy-β-apopicropodophyllin, a synthetic product, which act as a strong antimitotic agent [16-27].

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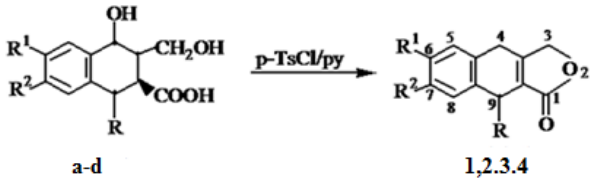
Hence it was decided to synthesize the analogues by replacing trimethoxy phenyl group with p-tolyl and cyclohexyl group, and methylenedioxy group with dimethoxy, methoxy methyl and chloro methoxy group respectively by Gensler'sand Chalcone methods.

2. Materials And Methods

Synthesis of β-apopicropodophyllin analogues 1, 2, 3 and 4

Compounds a-d were synthesized from 1- Hydroxy-2-hydroxylmethyl-3-carboxy-4-(p-tolyl)-6, 7-dimethoxy -1, 2, 3, 4-tetrahydronaphthalene which was synthesized usind Jensler's method as in our earlier research article.



1; a: $R^1 = R^2 = OCH_3$; R = p-tolyl

2; b: $R^1 = OCH_3$, $R^2 = CH_3$; R = p-tolyl

3; c: $R^1 = OH_3$, R^2=Cl; R = p-tolyl

4; d: $R^1 = R^2 = OCH_3$; R = cyclohexyl

Scheme

Synthesis of 6, 7-dimethoxy-9-p-tolyl naphtha [2, 3-C] furan-1- (3H, 4H, 9H) one (1)

A mixture of **a** (1.2g, 0.0322 moles), p-toluene sulfonyl chloride (3.5g, 0.0185 mole) and dry pyridine (30ml) in dry benzene (60 ml) was refluxed for 3h. The reaction mixture was cooled to room temperature, washed with 2N HCl (3x50ml) and then with water (2x40ml). The solvent was removed by distillation under reduced pressure gave thick brown residue. The crude product was column chromatographed over silica gel (10mx30) using chloroform as the eluant. The solvent was removed and evacuated at 50^0 C on a rotary evaporator gave orange red coloured crystalline solid in 72.02% yield (0.78g), m.p: 69-71^0C.

Synthesis of 6-methoxy-7-methyl-9-p-tolyl naphtho [2.3-C] furan-1- (3H, 4H, 9H) one (2)

Prepared from **b** (1.4g, 0.003928 moles), p-toluene sulfonyl chloride (4.2g, 0.02202mole) and dry pyridine (25ml) in dry benzene (60ml) as orange red coloured crystalline solid in 74.76% yield (0.937g), m.p: 72-74^0C.

Synthesis of 7-Chloro-6-methoxy-9-p-tolyl naphtho [2, 3-C] furan-1- (3H, 4H, 9H) one (3)

Prepared from **c** (1.5g, 0.0398 moles), p-toluene sulfonyl chloride (4.3g, 0.002216 mole) and dry pyridine (25ml) in dry benzene (60ml) as light yellow crystalline solid in 71.53% yield (0.978g), m.p: 78-80^0C.

Synthesis of 9-Cyclohexyl-6, 7-dimethoxy naphtho-[2,3-C] furan-1- (3H, 4H, 9H) one (4)

Prepared from **d** (0.5g, 0.0137 moles), p-toluene sulfonyl chloride (1.5g, 0.00786 mole) and dry pyridine (15ml) in dry benzene (40ml) as yellow crystalline solid in 70% yield (0.63g), m.p: 75-77^0C.

Anti-mitotic activity

The anti mitotic activities of the synthesized analogues of β- apopicropodophyllin were examined by the onion root tip method.

Assay:

The prepared slide was mounted for observation under a compound microscope. The total numbers of cells and the number of dividing cells were counted. The percent of the number of dividing cells compared to the control and the percent inhibition of mitosis by the test anti mitotic agent at a given concentration against a control were calculated.

3. Results And Discussion

Preparative analysis of dihydroxy acids a-d (Scheme)

6, 7-dimethoxy-9-p-tolyl naphtha [2, 3-C] furan-1- (3H, 4H, 9H) one (1)

IR (KBr): 1775 (lactone C=O), 1670 (shoulder tetra substituted C=C), 1595 (aromatic C=C) cm^{-1};

PMR ($CDCl_3$):δ 3.9-4.1 (s, 6H, OCH_3), δ 3.7 (s, 1H, C_9-H), δ7.2-7.4 (bm, 6H, Ar-H); δ 2.5 (s, 6H, CH_3), δ 3.8 (s, 2H, C_4-H), δ 4.9 (s, 2H, C_3-H);

Mass (m/z, % of abundance): 336 (M^+, 100), 334 (25), 245 (10), 244 (33), 299 (8), 91 (11);

Anal. Calcd: For $C_{21}H_{20}O_4$; C, 74.98; H, 5.99%;

Found: C, 74.96; H, 5.95%.

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6-methoxy-7-methyl-9-p-tolyl naphtho [2.3-C] furan-1-(3H, 4H, 9H) one (2)

IR (KBr): 1770 (lactone C=O), 1676 (shoulder tetra substituted C=C), 1590 (aromatic C=C) cm^{-1},

PMR ($CDCl_3$):δ 3.9-4.1 (s, 3H, OCH_3), δ 3.6 (s, 1H, C_9-H), δ 7.1-7.3 (bm, 6H, Ar-H); δ 2.4 (s, 6H, CH_3), δ 3.75 (s, 2H, C_4-H), δ 4.8 (s, 2H, C_3-H);

Mass (m/z, % abundance): 320 (M^+, 100), 318 (23), 299 (11), 228 (36), 213 (7), 91 (14);

Anal. Calcd: For $C_{21}H_{20}O_3$: C, 78.72; H, 6.29%;

Found: C, 78.69; H, 6.18%.

7-Chloro-6-methoxy-9-p-tolyl naphtho [2, 3-C] furan-1- (3H, 4H, 9H) one (3)

IR (KBr): 1770 (lactone C=O), 1687 (shoulder tetra substituted C=C), 1590 (aromatic C=C) cm^{-1};

PMR ($CDCl_3$):δ 4.0-4.2 (s, 3H, OCH_3), δ 3.8 (s, 1H, C_9-H), δ 7.1-7.3 (bm, 6H, Ar-H); δ 2.9-3.2 (m, 4H, C_8-H & C_9-H), δ 2.5 (s, 6H, CH_3), δ 3.85 (s, 2H, C_4-H), δ 4.9 (s, 2H, C_3-H);

Mass (m/z, % abundance): 340 (M^+, 98), 338 (20), 249 (13), 248 (34), 233 (9), 91 (13);

Anal. Calcd: For $C_{20}H_{17}O_3Cl$; C, 70.48; H, 5.99%;

Found: C, 70.46; H, 5.98%.

9-Cyclohexyl-6, 7-dimethoxy naphtho- [2,3-C] furan-1-(3H, 4H, 9H) one (4)

IR (KBr): 1770 (lactone C=O), 1663 (shoulder tetra substituted C=C), 1590 (aromatic C=C) cm^{-1},

PMR ($CDCl_3$): δ 1.0-2.0 (bm, 11H, cyclohexyl), δ 3.6 (d, J=6Hz, 1H, C_9-H), δ 3.8 (s, 2H, C_4-H), δ 4.8 (s, 2H, C_3-H), δ 7.0-7.2 (bm, 2H, Ar-H);

Mass (m/z, % abundance): 328 (M^+, 100), 326 (22), 245 (10), 244 (37), 229 (12), 83 (12);

Anal. Calcd: For $C_{20}H_{24}O_6$; C, 73.14; H, 7.36%;

Found: C, 73.09; H, 7.32%.

The IR spectrum of 1-hydroxy-2-hydroxy methyl-3-ethyl carboxy-4- (p-tolyl)-1, 2, 3,4-tetrahydro naphthalene **7** showed a broad absorption at the region 3500-3200cm^{-1} assigned to OH groups and a sharp absorption at 1730cm^{-1} assigned to ester carbonyl group. Compounds **8,9**, and **10** showed the IR spectra similar to that of **7**

Anti-mitotic activity

The inhibition study of the synthesizedproducts **1, 2, 3** and **4** was carried out for three different concentrations. The statistical data are recorded as shown in the Table1.

Table 1: Biological assay and anti-mitotic activity of compounds 1, 2, 3 and 4

Compound	Conc. In mol/l x 10^{-6}	Total No. of dividing cells	Total no. of cells	%. of dividing cells	Average	%. of dividing cells compare control	%. of inhibition compare to control	ID50M(($X10^{-6}$ mol/ l)
Control	-	19 18 20	104 93 88	18.269 19.354 22.727	20.116	100	0.0	-
Podophyllotoxin (I)	1.44	18 46 52	202 230 245	8.991 20.000 21.224	16.712	83.25	16.75	4.29
ß-apopicropodophyllin	1.51	23 34	209 183	11.005 18.579	14.792	73.53	26.47	2.87
1	1.19	6	126	4.761				

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Compound	Conc. In mol/l x 10^{-6}	Total No. of dividing cells	Total no. of cells	%. of dividing cells	Average	%. of dividing cells compare control	%. of inhibition compare to control	ID50M((X10^{-6} mol/ l)
	2.38 3.57	8 11	154 131	5.194 8.396	6.117	30.408	69.592	1.709
2	1.25 2.5 3.7	2 3 4	34 49 51	8.82 6.112 7.843	6.612	32.869	67.131	1.862
3	1.17 2.35 3.52	6 9 8	158 169 122	3.797 5.325 6.557	5.226	25.979	74.021	1.587
4	1.21 2.43 3.65	27 15 13	523 224 176	5.162 6.696 7.386	6.44	31.885	68.115	1.784

A bar graph of average concentration, versus percent inhibition for each test compound was drawn (Fig 1). The concentration needed for 50% inhibition (ID_{50}) was shown from the bar graph and ID_{50} values for the synthetic derivatives for antimitotic activity are tabulated. From the graph it is clear that the anti-mitotic activities of the newly synthesized analogues **1, 2, 3** and **4** showed an increased activity in compare to Control, Podophyllotoxin (1) and ß-apopicropodophyllin. The maximum activity for **1, 2, 3** and **4** with ID_{50}1.709x 10^{-6}M,1.862x 10^{-6} M, 1.587x 10^{-6} M and 1.784x 10^{-6}Mwere relatively lower to that of Podophyllotoxin (1) and ß-apopicropodophyllin having ID_{50} 4.290 x 10^{-6}M and 2.870 x 10^{-6}M. It is highly believed that the nucleophilic functional entities in the cell constituents might easily attack the electrophilic lactone ring moiety. The anti-mitotic activities of the newly synthesized compounds are mainly based on the size of the substituents attached to the aromatic rings

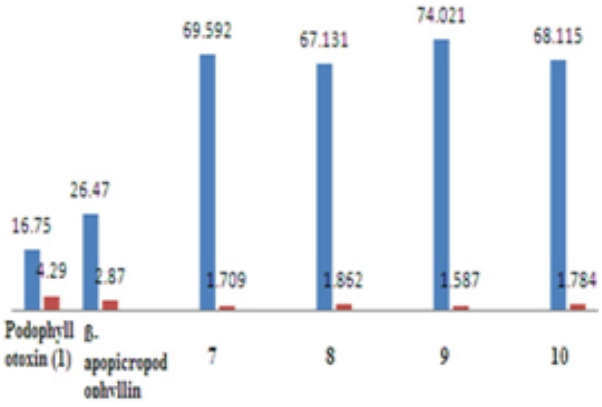

Fig. 1: Percent inhibition versus concentration

4. Conclusion

Tetralone esters were used as starting material to synthesis hydroxy methylene tetralone esters and hydroxy methylene tetralone acids as an intermediate compound to form tetra-substituted di-hydroxyl derivatives by Gensler's[13] and Chalcone methods. Hydroxy methylene tetralone esters under reduction with methanol 1- hydroxy–2–hydroxy methyl –3-ethyl carboxy-4- (tolyl)-6,7 dimethoxy-1, 2,3,4-tetrahydronaphthalene,1-Hydroxy-2-hydroxymethyl-3-ethyl caroxy-4- (P-tolyl)-7- methoxy-6-methyl-1, 2, 3, 4 –tetrahydronaphthalene, 1-Hydroxy-2-hydroxymethyl-3-ethyl carboxy-4- (p-tolyl)-6- chloro-7-methoxy-1, 2, 3,

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4 – tetrahydronaphthalene and 1-Hydroxy-2-hydroxylmethyl-3-ethyl carboxy-4-cyclohexyl- 6, 7-dimethoxy-1, 2, 3, 4 tetrahydronaphthalene were the stating compounds. The tetra-substituted di-hydroxyl derivatives of tetralone esters on dehydrating and cyclisation with p-TsCl/py results podophylloxin analogues 1- Hydroxy-2-hydroxylmethyl-3-carboxy-4-(p-tolyl)-6, 7-dimethoxy - 1,2,3,4-tetrahydronaphthalene, 6-methoxy-7-methyl-9-p-tolyl naphtho [2.3-C] furan-1- (3H, 4H, 9H) one, 7-Chloro-6-methoxy-9-p-tolyl naphtho [2, 3-C] furan-1- (3H, 4H, 9H) one and 9-Cyclohexyl-6, 7-dimethoxy naphtho-[2,3-C] furan-1- (3H, 4H, 9H) one. The structures were confirmed by Proton NMR, IR, Mass spectroscopy and analytical calculations. The anti-mitotic activities of the newly synthesized analogues **1, 2, 3** and **4** showed an increased activity in compare to Control, Podophyllotoxin (1) and ß-apopicropodophyllin. The maximum activity for **1, 2, 3** and **4** with ID_{50}1.709x 10^{-6}M,1.862x 10^{-6} M, 1.587x 10^{-6} M and 1.784x 10^{-6}Mwere relatively lower to that of Podophyllotoxin (1) and ß-apopicropodophyllin having ID_{50} 4.290 x 10^{-6}M and 2.870 x 10^{-6}M. All analogues show a conspicuously more than 65% inhibition compare to the parent compound.

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Conflict of interest

The authors declare no conflict of interest

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